Transition Metals/Lewis Acids Co-catalyzed Intra-/Intermolecular Aminocyanation of Alkenes/Alkynes via N–CN Bond Activation

And

Synthetic and Characteristic Studies on Dibenzo[*g*,*s*]rubicenes and Naphtho[2,3-*a*]aceanthrylenes

A DISSERTATION

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Dedication

To my beloved parents, Wang Wei and Zhang Xiaofen

To my beloved soulmate, Dr. Zhi Bo

Abstract

This thesis is composed of two parts: in Chapter 1, 2 and 3, the development of transition metals/Lewis acids co-catalyzed aminocyanation of unsaturated C–C bonds via N–CN bond activation was described and discussed. In Chapter 4 and 5, a new synthetic route to cyclopenta-fused polycyclic aromatic hydrocarbons (CP-PAHs) was explored, followed by the studies on optical and electrochemical properties of synthesized rubicene derivatives.

Chapter 1 briefly introduces catalytic difunctionalization of unsaturated C–C bonds via addition reactions and cyanofunctionalization of multiple bonds via C–CN bond activation. Chapter 2 and 3 describe our recent reported intramolecular aminocyanation of alkenes via N–CN bond activation by palladium/Lewis acid cooperative catalysis, and an ongoing project: intermolecular aminocyanation of unsaturated C–C bonds via N–CN bond activation, in order to readily prepare heterocycles with quaternary centers and regioselective β-amino acids.

Chapter 4 summarizes the physical properties and synthetic methods of CP-PAHs, as well as rubicene, as a member of CP-PAHs. Chapter 5 concludes our recent work on development of a new synthetic route to naphtho[2,3-*a*]aceanthrylenes and dibenzo[*g*,*s*]rubicenes, using a tandem Sonogashira cross-coupling and tetra-dehydro-Diels−Alder cycloaddition cascade, which provides a facile fine-tuning method for the optical and electrochemical properties of potential electron acceptors.

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List of Abbreviations

(R)-BINAP	(R)-(+)-(1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)
(R)-Tol-BINAP	(R)-(+)-2,2′-bis(di-p-tolylphosphino)-1,1′-binaphthyl
(R,R)-Bicp	(1R,1'R,2R,2'R)-(−)2,2'-Diphenylphosphino-1,1'-Bicyclopentyl
(R,R)-Et-DUPHOS	1,2-Bis[(2R,5R)-2,5-diethylphospholano]benzene
(R,R)-Et-FerroTANE	1,1'-Bis[(2R,4R)-2,4-diethyl-1-phosphetanyl]ferrocene
(R,R)-Me-BPE	(2R,5R)-1-[2-[(2R,5R)-2,5-dimethylphospholan-1-yl]ethyl]-2,5-dimethylphospholane
(R,R)-Me-DUPHOS	1,2-Bis[(2R,5R)-2,5-dimethylphospholano]benzene
(R,R)-SIPHOS-PE	N-di[(R)-1-phenylethyl]-[(R)-1,1′-spirobiindane-7,7′-diyl]-phosphoramidite
(R,R,R)-(+)-Ph-SKP	(+)-1,13-Bis(diphenyl)phosphino-(5aR,8aR,14aR)-5a,6,7,8,8a,9-hexahydro-5H-[1]benzopyrano [3,2-d]xanthene
(R,R,R)-(+)-Tol-SKP	(+)-1,13-bis[di(4-methylphenyl)phosphino]-(5aR,8aR,14aR)-5a,6,7,8,8a,9-hexahydro-5H-[1]benzopyrano[3,2-d]xanthene
(S)-BINAP	(S)-(−)-(1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)
(S,S)-BDPP	((2*R*,4*R*)-pentane-2,4-diyl)bis(diphenylphosphane)
Ac	acetyl
Ac_2O	Acetic Anhydride
acac	acetylacetonyl
AcOH	Acetic Acid
Ar	aryl
BDE	bond dissociation energy
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bpy	2,2'-bipyridine
cod	1,5-cyclooctadiene
conv.	conversion
Cp	cyclopentadienyl
CP-PAH	Cyclopenta-fused polycyclic aromatic hydrocarbons
Cy	cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DavePhos	2-Dicyclohexylphosphino-2′-(N,N-dimethylamino)biphenyl

dba	dibenzylideneacetone
DBFPhos	4,6-Bis(diphenylphosphino) dibenzofuran
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
decalin	decahydronaphthalene
DFT	Density Functional Theory
DMAP	4-(dimethylamino)pyridine
dmdba	3,5,3’,5’-dimethoxydibenzylideneacetone
DMF	*N*,*N*-dimethylformamide
DMPU	*N,N'-dimethylpropylene urea*
DMSO	Dimethylsulfoxide
DPEphos	bis[(2-diphenylphosphino)phenyl] ether
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1′-ferrocenediyl-bis(diphenylphosphine)
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
DTBMP	2,6-di-tert-butyl-4-methylpyridine
E^+	electrophile
ee	enantiomeric excess
ESI	Electrospray Ionization
Et	ethyl
EtOAc	Ethyl Acetate
FG	functional group
Fmoc-Osu	9-Fluorenylmethyl N-succinimidyl carbonate
FVP	Flash vacuum pyrolysis
GC	Gas Chromatography
Hex	hexanes
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HOMO	Highest Occupied Molecular Orbital
HPLC	high performance liquid chromatography
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
IMes	1,3-Dimesitylimidazol-2-ylidene
IPA	isopropanol
IPr	1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene
iPr	Isopropyl
IR	Infrared
JohnPhos	(2-Biphenyl)di-tert-butylphosphine
LA	Lewis acid

LDA	Lithium Diisopropyl Amide
LDI	Laser Desorption Ionization
LRMS	Low Resolution Mass Spectrometry
LUMO	Lowest Unoccupied Molecular Orbital
M	Molar
MALDI	Matrix-assisted Laser Desorption Ionization
Me	Methyl
MeOH	Methanol
mL	Milliliters
mm	Millimeters
mpt	Melting Point
MS	Mass Spectrometry
naph	Naphthalene
nBuLi	n-Butyl Lithium
NCTS	N-cyano-N-phenyl-p-toluenesulfonamide
NFSI	*N*-fluorobenzenesulfonimide
NHC	*N*-Heterocyclic Carbene
NiXantphos	4,6-Bis(diphenylphosphino)-10H-phenoxazine
nm	Nanometers
NMR	Nuclear Magentic Resonance
NPhth	phthalimide
Ns	para-nitrobenzenesulfonyl
Nu or Nu^-	nucleophile
OFAT	one-factor-at-a-time
OFET	Organic Field-Effect Transistor
OLED	Organic Light-Emitting Diode
OPV	Organic Photovoltaic
OTf	Triflate
o-Tol	ortho-Tolyl
PAH	Polycyclic Aromatic Hydrocarbon
PEG	polyethylene glycol
PEPPSI™-IPr	[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
PG	Protecting group
Ph	Phenyl
PhMe	toluene
pin	pinacolato
PMP	para-methoxyphenyl
PPG	polypropylene glycol
ppm	Parts Per Million
p-Tol	para-Tolyl
PTSA	para-Toluene Sulfonic Acid
Py	Pyridinyl
pyr	pyridine

rac.	racemic
rt	room temperature
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
SIMes	1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene
SIPr	1,3-Bis(2,6-diisopropylphenyl)imidazolidene
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
TASF	Tris(dimethylamino)sulfonium Difluorotrimethylsilicate
TBAF	Tetrabutylammonium Fluoride
TBS	tert-butyldimethylsilyl
t-Bu	tert-Butyl
TEA	Triethylamine
TES	Triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic Anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMS	trimethylsilyl
TMSA	(Trimethylsilyl)acetylene
TMSCl	Chlorotrimethylsilane
TMSCN	Trimethylsilyl cyanide
Tol	Toluene
TS	Transition state
Ts	para-toluenesulfonyl
TsOH	p-Toluenesulfonic acid
UV-Vis	Ultraviolet–visible spectroscopy
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
X-Phos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
xylenes	Dimethylbenzene mixture

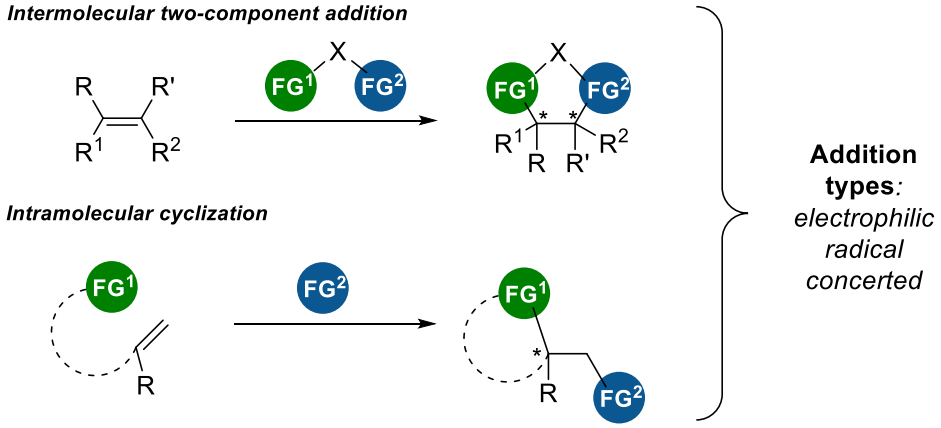
Chapter 1 Introduction to catalytic difunctionalization of unsaturated C−C bonds

1.1 Overview of catalytic difunctionalization reactions of unsaturated C−C bonds

Addition to unsaturated C−C bonds is a type of classical and essential reaction allow two vicinal groups installed across an unsaturated C−C bonds with the formation of two new bonds. Traditionally, addition reactions can be classified into three categories: electrophilic, radical and concerted.[1] On the merits of chiral catalysts or reagents, the high control of regioselectivity and stereoselectivity on addition step would achieve, i.e., the Sharpless dihydroxylation of alkenes.[2] Hence, due to the ubiquity of alkenes/alkynes obtained from feedstocks and the rapid construction of molecular complexity, catalytic difunctionalization of unsaturated C−C bonds via addition reactions have been extensively investigated in order to improve the efficiency on organic syntheses and large-scale production in the chemical industry.[3–5] Numerous difunctionalization strategies have been developed and employed in synthesis of natural products, design of novel pharmaceuticals and construction of molecular architectures. Typical difunctionalization methods generally involve dioxylation(dihydroxylation),[2,6–9] dihalogenation/halofunctionalization,[10–13] diamination,[9,14–16] carbofunctionalization,[17–21] aminofunctionalization,[3,4,22–30] oxyfunctionalization,[3,4,26,27,29,31,32] etc.

Difunctionalization of alkenes is a convenient method to directly construct stereogenoic centers in one step. Compared with classic intermolecular three-component

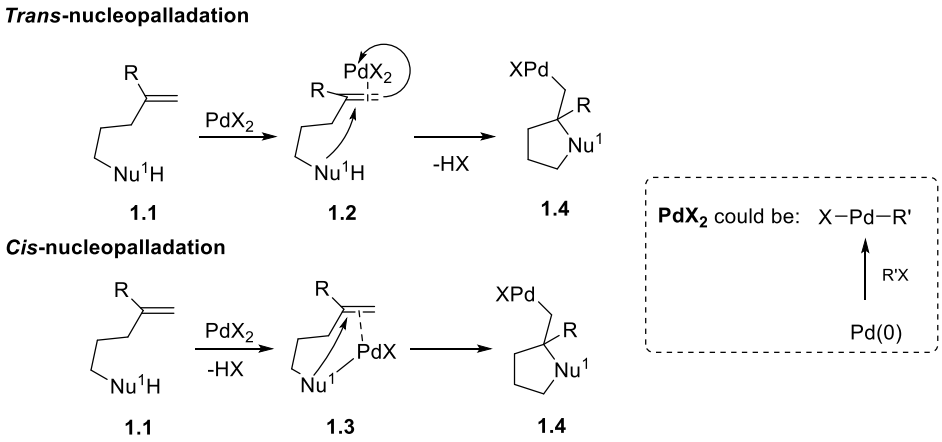
difunctionalization of alkenes, difunctionalization of alkenes via catalytic intramolecular cyclization or intermolecular two-component alkene addition, now attract more attentions from chemists due to the feasibility of cyclic compound construction with the formation of quaternary stereocenters, which is traditionally challenging.[33–35] (**Scheme 1-1**) Among all established catalytic intramolecular cyclization of unsaturated C−C bonds, palladium-catalyzed cyclizations should be highlighted because they are now widespread in synthesis of heterocycles,[26,36] such as lactones and lactams that are served as precursors or intermediates for drug molecules. The corresponding mechanisms and geometrical models are both well-constructed for Pd-mediated cyclization of alkenes/alkynes.[4,37,38]



Scheme 1-1 Difunctionalization of alkenes to construct cyclic compounds with stereocenters

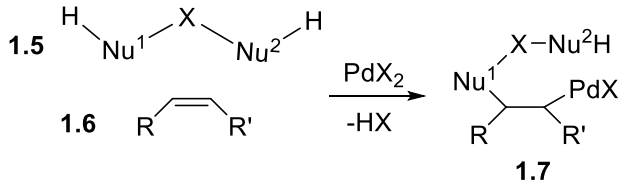
The Pd-mediated intramolecular cyclization process could achieve via *trans*- or *cis*-nucleopalladation.[3,4] (**Scheme 1-2**) Both Pd(0) and Pd(II) catalysts can be utilized in the reactions, but Pd(0) needs to be oxidized first by additive oxidants, or via oxidative addition of reagents with the desired functional group that would be introduced later.

Trans-nucleopalladation starts from the initial "activation" of unsaturated C−C bond by the π-coordination to palladium catalyst, followed by attack of nucleophile on the double bond. *Cis*-nucleopalladation requires the coordination of intramolecular nucleophile to the metal center first, followed by *syn*-addition of Nu–Pd bond to the alkene. The ring formation both completes simultaneously during introduction of the first functional group to afford the same cyclic product **1.4**.



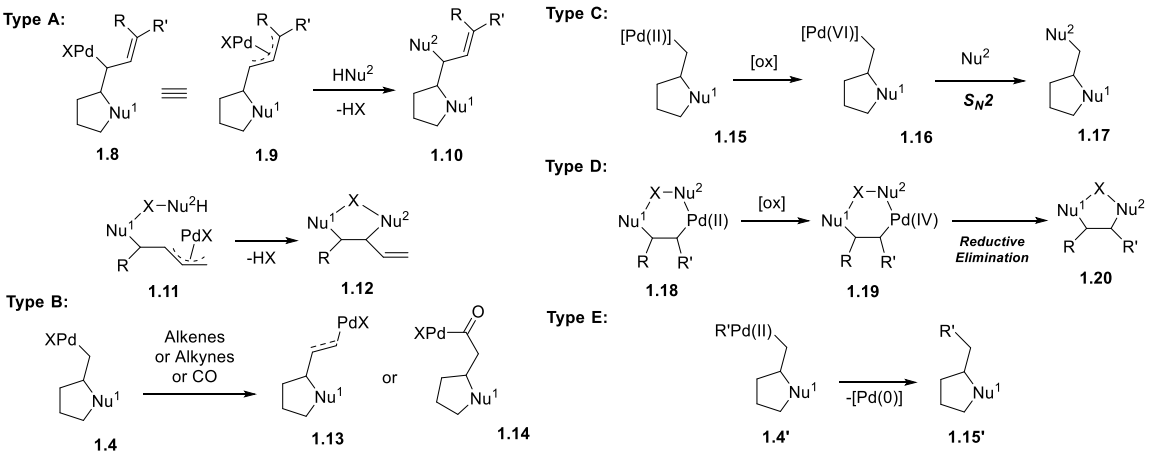
Scheme 1-2 Two types of nucleopalladation

The Pd-catalyzed intermolecular two-component alkene addition generally occurs between alkenes and nucleophiles with two available nucleophilic sites, such as ureas, β-amino alcohols and α-amino acids, etc. The reaction is initiated by a nucleopalladation on the alkene to link the two components together, giving the intermediate **1.7**. Both *cis*- and *trans*-nucleopalladation were observed in related mechanistic studies.[39] (**Scheme 1-3**)



Scheme 1-3 Nucleopalladation in intermolecular difunctionalization of alkenes

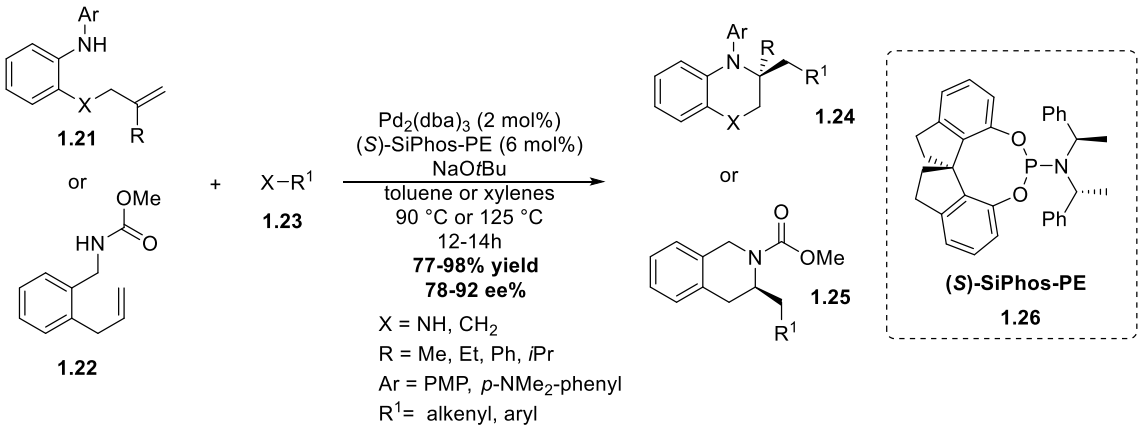
Once the cyclic intermediates **1.4** and branched intermediate **1.7** obtained, the second functionalization could be introduced via the following pathways:[3] (**Scheme 1-4**) (a) nucleophilic substitution or reductive elimination of π-allyl palladium complex when conjugated dienes served as substrates,[39–42] (b) new multiple bond insertion into C−Pd bond,[17,43–46] (c) S_N2-type nucleophilic substitution of high-valence palladium(IV),[47–52] (d) reductive elimination of oxidized palladium(IV) to form new C−Nu bond, [52–56] (e) direct reductive elimination from Pd(II) species **1.4'**.[4,27]



Scheme 1-4 Different pathways toward the second functionalization on alkenes

Utilizing the strategy discussed above, a large variety of heterocycles bearing oxygen and nitrogen are rapidly prepared in one-pot manner, with high regioselectivity and

stereoselectivity in the presence of chiral ligands that afford asymmetric catalyst complex, or existing stereocenters in the substrates. For instance, in 2014, the first asymmetric Pd-catalyzed alkene-carboamination reactions were reported by Wolfe et. al.,[57] successfully affording benzo-fused six-membered including tetrahydroquinolines, tetrahydroquinoxalines and tetrahydroisoquinolines bearing a quaternary center in high yields as well as enantioselectivities. (**Scheme 1-5**) The high enantioselectivity could be attributed to the stereocontrol of chiral ligand (*S*)-Siphos-PE during the *syn*-aminopalladation step.



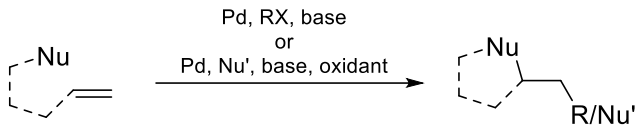
Scheme 1-5 The first reported asymmetric Pd-catalyzed carboamination of alkenes

However, all methods mentioned above rely on the introduction of exogenous reagents to furnish difunctionalization of unsaturated C−C bonds, possibly make existing substituents intolerable under harsh conditions such as strong oxidants, bases. In addition, stoichiometric or excess reagents are required, also leading to a lower atom-economy.[58–60] During the incorporation of second functional group on metal center via ligand exchange,

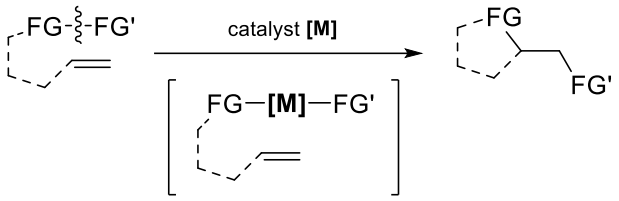
the generation of metal salts and other byproducts would also increase undesired waste[61,62] that may make purification more challenging.

Hence, a direct addition of two functional groups on unsaturated C−C bonds is an alternative strategy to access difunctionalization, relying upon oxidative addition of the bond between both required functional groups to the metal center before nucleometallation.[63–65] The intramolecular cyclization achieves via the insertion of multiple bond into carbo or hetero–Pd bond, generally in accordance with Baldwin's rule. The second functional group then could be installed on alkenes/alkynes via the direct reductive elimination. Unlike exogenous introduction of functional groups, the direct addition displays in a fully-intramolecular manner, obviating from any unnecessary byproducts and unfavored additional treatments.

Nucleopalladation with exogenous reagents

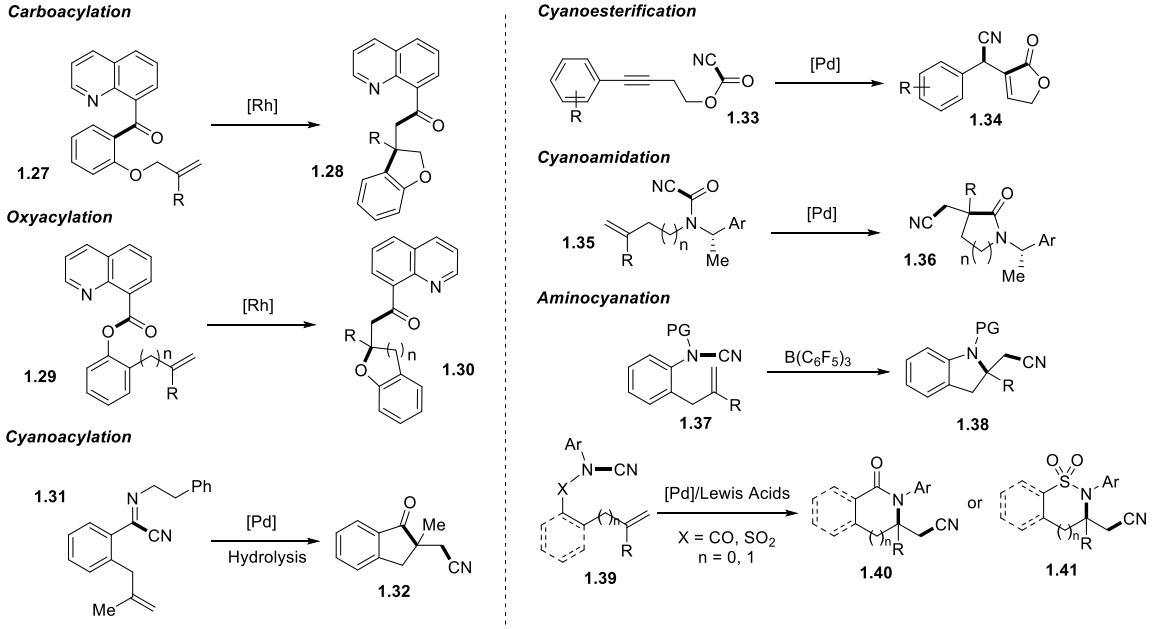


Intramolecular difunctionalization via bond activation



Scheme 1-6 Direct addition of alkenes with bond activation and cyclization

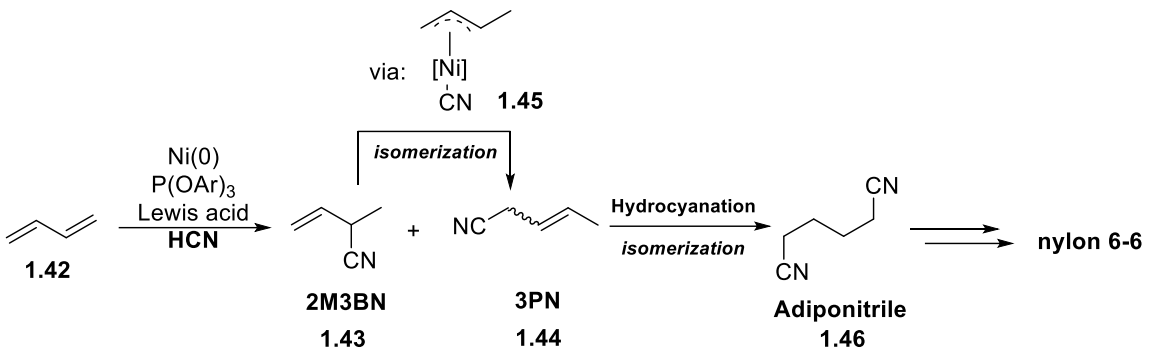
Over the past decades, transition-metal-catalyzed bond activation has been emerged as an increasingly powerful tool in organic synthesis.[65–68] Our group is mainly focusing on the activation of C−C bonds and other "inert" bonds such as C−O, C−CN and N−CN. We have successfully disclosed that the utility of inert bond activation for alkene/alkyne carboacylation,[64,69,70] oxyacylation,[71] cyanoacylation,[72] cyanoesterification,[73] cyanoamidation[74] and aminocyanation.[75,76] Following the previous success on difunctionalization via bond activation, recently we devote our efforts to aminocyanation in both intramolecular and intermolecular manner, aiming at developing new synthetic routes to valuable heterocycles and amino acids.



Scheme 1-7 Reported transition-metal-catalyzed difunctionalization of alkenes/alkynes with bond activation in Douglas lab

1.2 Overview of catalytic cyanofunctionalization of unsaturated C−C bonds

Cyano group is one of the most versatile functional groups in organic synthesis, owing to its direct transformation into various moieties, including carboxylic acids, amides, amines, esters, etc. Nitriles are also widely utilized in the field of agrochemistry, pharmaceuticals and organic electronic materials.[77,78] To minimize the environmental hazards such as metal cyanides used or generated in the traditional cyanation reactions, recent research interests are directed to catalytic cyanation with nonmetallic cyanating reagents. A classic example in industrial application is the DuPont adiponitrile process, which is used to prepare the starting materials of nylon 6-6.[79] (**Scheme 1-8**) In the presence of nickel catalyst, catalytic hydrocyanation of butadiene proceeds smoothly with hydrogen cyanide, affording a pair of regioisomers: 2-methyl-3-butenenitrile (2M3BN) and 3-pentenenitrile (3PN). A key step in the process is the isomerization of 2M3BN to 3PN, the desired intermediate of final product adiponitrile.[80–82] With the assistance of Lewis acid, nickel metal center can cleave the C−CN bond in 2M3BN via oxidative addition, giving the linear product 3PN. Further hydrocyanation and isomerization deliver adiponitrile at the end. Detailed mechanistic studies support the isomerization via C−CN bond activation is more favored rather than C−H cleavage. The bite angle and electronic effects of bidentate phosphine ligands are essential to inhibit the generation of branched side product 2M3BN.[83,84]

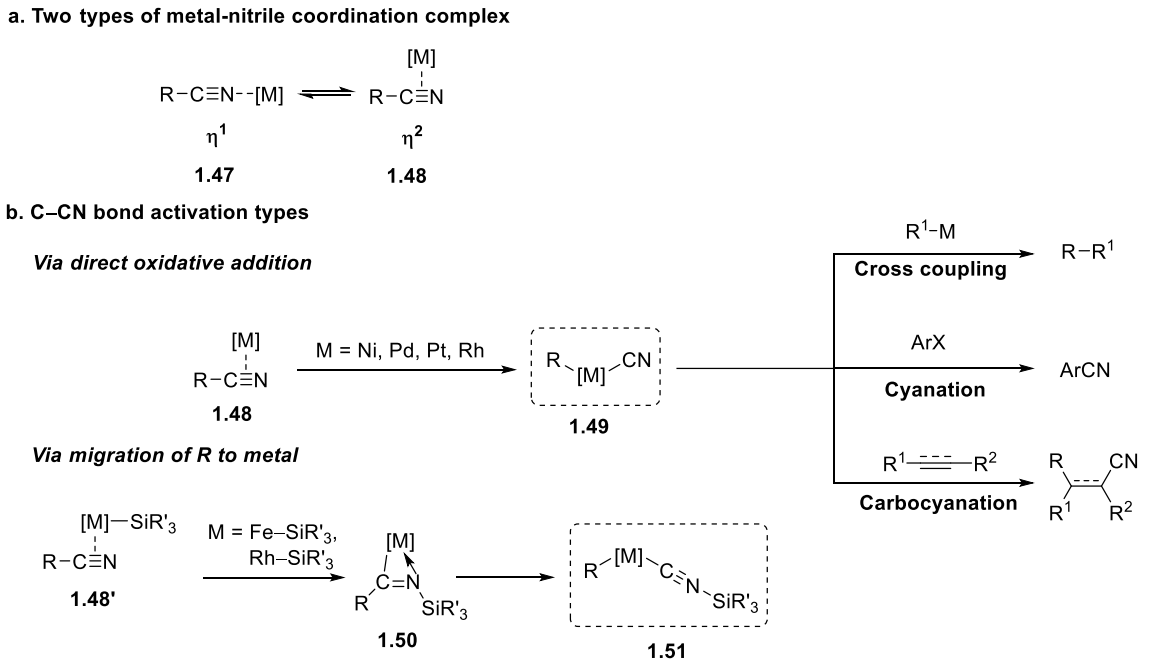


Scheme 1-8 The DuPont adiponitrile process

Taking the advantages of bond activation, direct of nonpolar C−C multiple bonds has been a powerful strategy for synthesis of functionalized nitriles. Herein, catalytic cyanofunctionalization of alkenes or alkynes via C−CN or heteroatom−CN bond activation will be briefly summarized.

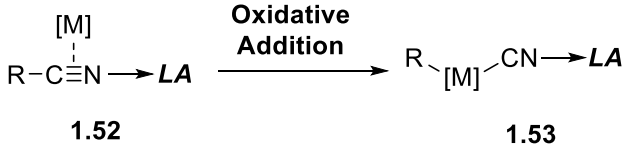
C−CN bond activation has been well investigated for several decades. C−CN bonds are generally regarded as "inert" bonds due to their relative high bond dissociation energies (over 100 kcal/mol)[85] but can be still cleaved by a variety of low-valence metal complexes. Before the cleavage step, cyano groups coordinate to the metal center in either end-on (η^1) or side-on (η^2) manner. Low-valence metal complexes typically prefer η^2-coordination via π-back donation of cyano triple bond.[86] Starting from η^2-coordination, the cleavage of C−CN bonds can undergo into two pathways: direct oxidative addition to a metal center only, or insertion of cyano group into a metal−Si bond first followed by C−CN bond activation, giving a silylisonitrile moiety on metal center.[87,88] (**Scheme 1-9**) Based on preliminary studies on stoichiometric C−CN bond activation, the utility of catalytic C−CN bond activation in synthetic application has been emerged in recent years. Till now, three

types of reactions can be achieved via C−CN bond activation: cross-coupling,[89,90] cyanation of aryl halides[91,92] and carbocyanation of unsaturated bonds.[89]



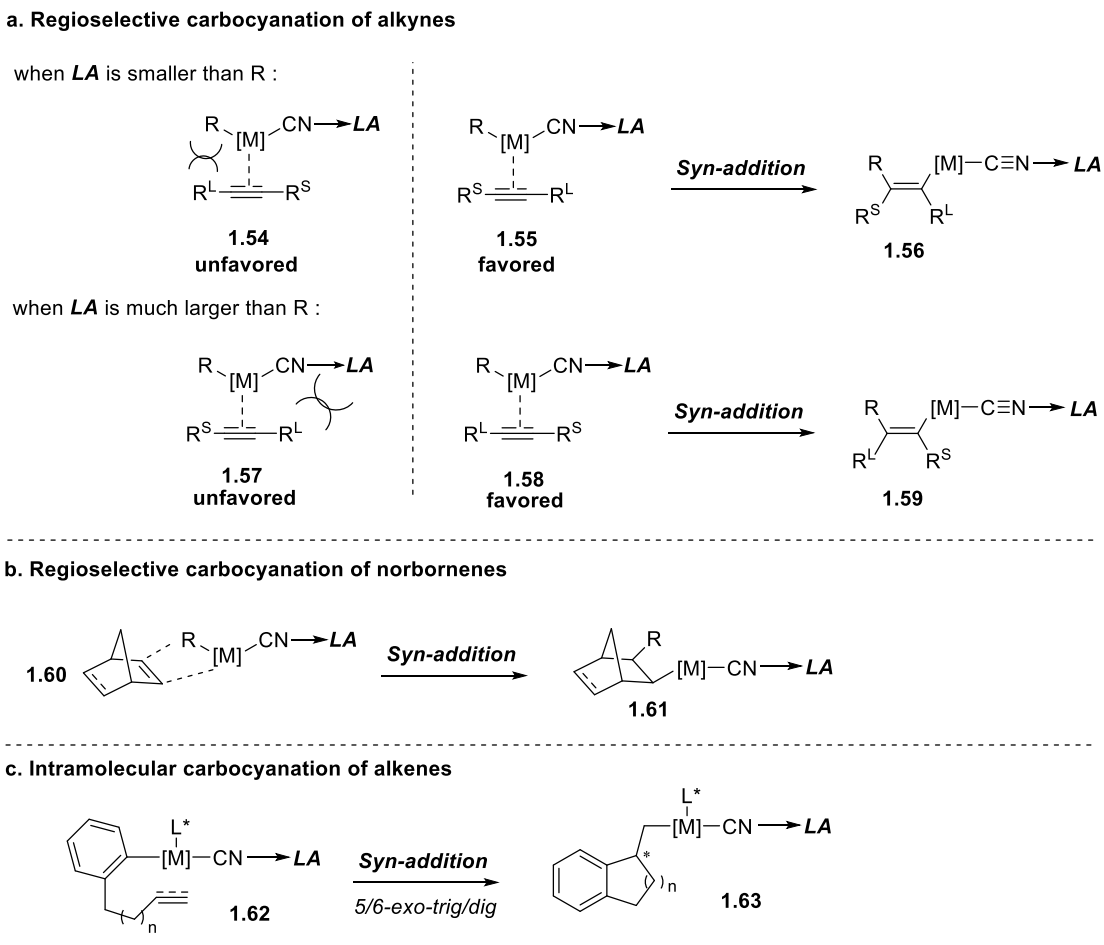
Scheme 1-9 C−CN bond activation: mechanism and applications

Carbocyanation of unsaturated bonds requires oxidative addition of C−CN bond in nitriles to metal center, followed by migratory insertion of multiple bonds into C–metal bond and subsequent reductive elimination to form a new C–CN bond. The common metal species used as catalysts here are palladium and nickel.



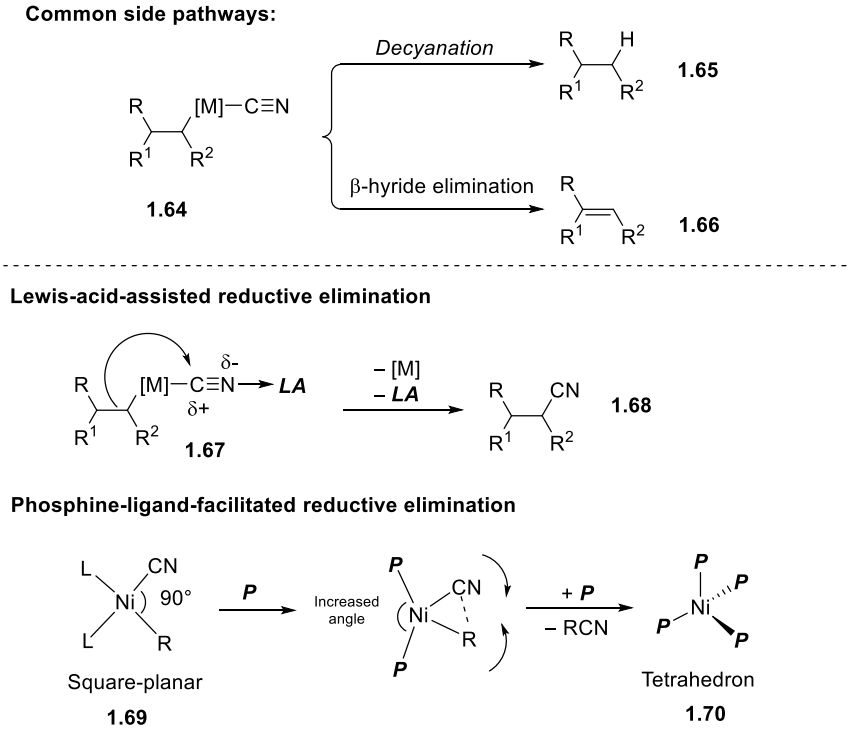
Scheme 1-10 Lewis-acid-assisted oxidative addition

The cleavage of C−CN bond can be promoted by Lewis acids. (**Scheme 1-10**) Recent studies revealed the role of Lewis acids: they can not only suppress the coordination of terminal nitrogen on cyano group to the metal center, but also weaken the C−CN bond via inductive effect, leading to the acceleration of oxidative addition step. The presence of Lewis acids also makes the bond cleavage step irreversible and stabilize the resultant complex bearing M−CN bond. [83,84,93]



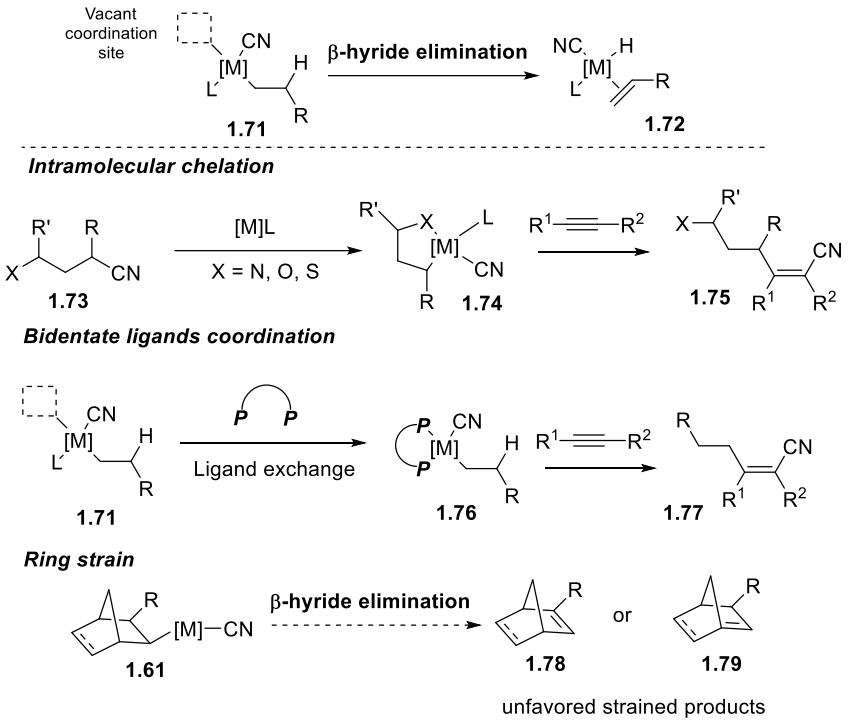
Scheme 1-11 Regioselective carbocyanation of alkenes/alkynes

Generally, the *syn*-addition of R−M bond to unsaturated bonds is prominent during the migratory insertion step. (**Scheme 1-11**) Thus, the regioselectivity of intermolecular carbocyanation is controllable.[78,94] For instance, the bulky R group on metal center prefers to add on the less sterically hindered side of unsymmetrical alkynes, unless much bulkier Lewis acid attached to the cyano moiety that leads to the reversed regioselectivity. Similarly, carbocyanation of norbornene and norbornadiene affords *exo-cis* adducts exclusively. Intramolecular carbocyanation favors a 5/6-exo-trig/dig fashion, according to Baldwin's rule. Due to the construction of quaternary centers, asymmetric intramolecular carbocyanation of alkenes can be mediated by the chiral catalyst complex.[95]



Scheme 1-12 The methods to enhance reductive elimination

Reductive elimination is crucial to cyanofunctionalization reactions. The sluggish formation of new C−CN bond would lead to undesired decyanation pathway or competitive β-hydride elimination.[78] The reductive elimination of R and cyano group can be enhanced significantly by both Lewis acids and bidentate ligands. (**Scheme 1-12**) The rate acceleration correlates directly with Lewis acid strength, due to the generation of more electrophilic nitrile carbon induced by stronger Lewis acids that facilitate nucleophilic attack of R group.[96] Recent studies about ligand bite angle effect on hydrocyanation[97] revealed that reductive elimination step is the rate-determining step, starting from a square-planar Ni(II) species. Phosphine ligands with appropriate cone angles or bite angles, such as Xantphos with a bite angle around 114˚, can destabilize the square-planar Ni(II) species leading to the bond formation between R and cyano group, and stabilize the resultant tetrahedral Ni(0) complex, in order to accelerate the reductive elimination and the overall catalysis.[98–100]

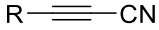
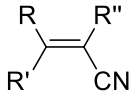
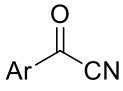
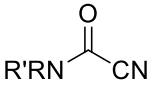


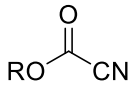
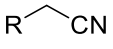
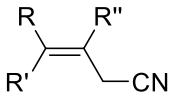
Scheme 1-13 The methods to suppress β-hydride elimination

Compared with the broad scope of intermolecular carbocyanation of alkynes, intermolecular reactions across alkenes are still limited possibly due to the readily β-hydride elimination giving undesired Heck-type products. Generally, this side pathway can be suppressed by occupying the vacant coordination site in metal center, using bidentate ligands or intramolecular coordination the heteroatoms in substrates.[101] (**Scheme 1-13**) The formation of C(sp^3)–CN bond can be also promoted by the structure design of substrates, which affords unfavored β-hydride elimination products that increase ring strain and even violate Bredt's rule.[102] Intramolecular carbocyanation of alkenes generally obviate from β-hydride elimination owing to the construction of quaternary centers from 1,1-disubstituted alkenes.

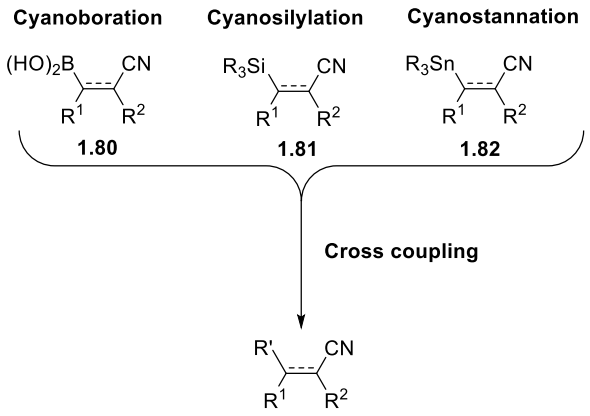
Up till now, carbocyanation of unsaturated C–C bonds has been extended to a broader scope of multiple-bond substrates and carbocyanating reagents. The explored π-reactants include internal and terminal alkynes, 1,1- or 1,2-disubstituted (strained) alkenes and 1,2-dienes. The C–CN bond activation can be further divided into three types: (1) C(sp)–CN bond cleavage of alkynyl cyanides, (2) C(sp^2)–CN bond cleavage of aryl, alkenyl, aroyl, carbamoyl cyanides and alkyl carbonocyanidate, (3) C(sp^3)–CN bond cleavage of alkyl and allyl cyanides. (**Scheme 1-14**) More details for each type of carbocyanation can be found in recent reported reviews.[78,103–105]

Table 1-1 Carbocyanations with a variety of nitriles

C–CN bond type	Nitriles	Reaction names
C(sp)–CN		Alkynylcyanation
C(sp^2)–CN	ArCN	Arylcyanation
		Alkenylcyanation
		Cyanoacylation
		Cyanoamidation

		Cyanoesterification
$C(sp^3)$–CN		Alkylcyanation
		Allylcyanation

Based on the achievements of well-developed carbocyanation via C–CN bond activation, the same core concept, "cut and sew",[65] was directly extended to catalytic cyanofunctionalization of unactivatd multiple bonds via heteroatom–CN σ bonds,[106] involving B–CN,[107–109] Si–CN,[110–112] Ge–CN,[113,114] Sn–CN,[115] Br–CN,[116] S–CN,[117–119] O–CN,[120,121] N–CN.[75,76,120] The resultant cyanofunctionalized adducts can further serve as precursors of cross coupling reactions such as Suzuki couplings (organoboranes), Hiyama couplings (organosilanes), Stille couplings (organostannanes) and all organohalide-related metal catalyzed couplings, which expand the synthetic utility of these methodologies. Except carbo-, oxy- and aminocyanation, the rest of cyanofunctionalization mentioned above were reported feasible for alkyne substrates only.[78]



Scheme 1-14 Synthetic utility of cyanofunctionalization products

In the following two chapters, new aminocyanation reactions of alkenes and alkynes developed by our group will be discussed in detail, as well as mechanistic studies and synthetic applications.

Chapter 2 Intramolecular aminocyanation of alkenes via Palladium/Lewis acid catalyzed N−CN bond activation

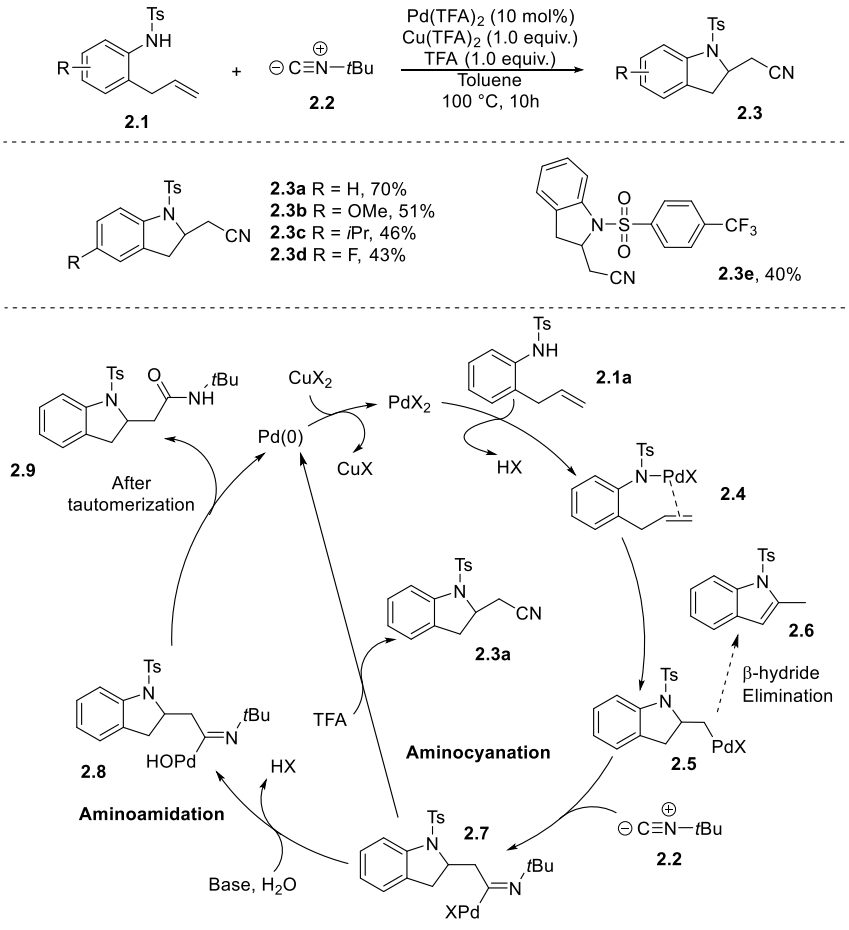
2.1 Overview of intramolecular aminocyanation of unsaturated C−C bonds

Though significant progress has been made on cyano-[1,2] and aminofunctionalization[3] of unsaturated C−C bonds, yet scope on direct aminocyanation of unsaturated C−C bonds is comparatively limited, perhaps due to the selection of amino and cyano sources.

The first copper-catalyzed aminocyanation of alkenes was achieved by Zhang et al.[4] in 2013, using N-fluorobenzenesulfonimide as amino source, and TMSCN as cyano source. Such intermolecular reaction provides a novel method towards β-aminonitriles, via the metal-coordinated nitrogen-centered radical intermediate. (More details can be found in Chapter 3)

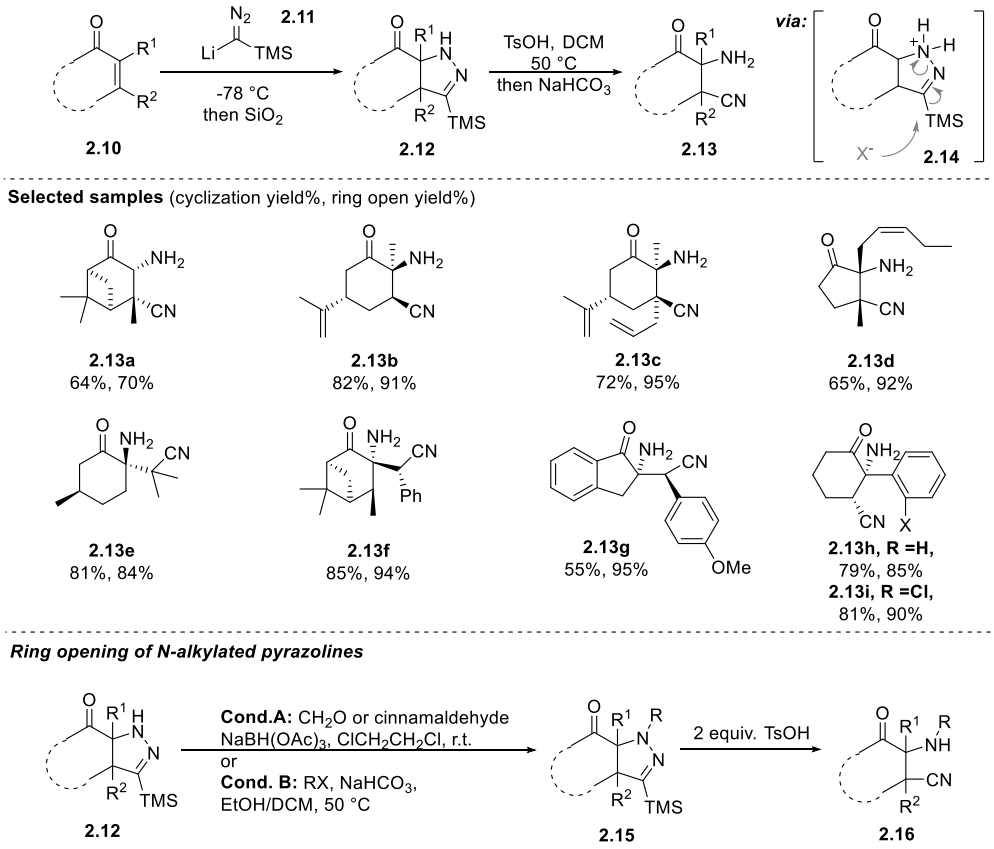
Later, Jiang et al.[5] reported a palladium-catalyzed intramolecular aminative cyclization, followed by isonitrile insertion to achieve aminocyanation of alkenes (**Scheme 2-1**). Based on well-established intramolecular aminopalladation of alkenes, nitrogen heterocycles can be constructed while using *t*-butyl isocyanide **2.2** as exogenous cyano source to afford cyclic β-aminonitriles, in the presence of TFA. The authors also expanded the scope of substrates to *para*-substituted sulfonamides. Interestingly, when TFA was replaced with a base (DABCO) and water, the reaction underwent aminoamidation pathway instead of aminocyanation. A proposed mechanism rationalized these two

aminofunctionalizations: first, the alkylpalladium species **2.5** generates from intramolecular aminopalladation of the alkene. Subsequent migratory insertion of *t*-butyl isocyanide into N−Pd bond affords the imine species **2.7**. Then the mechanism diverges into two paths: TFA-promoted β-*t*-butyl-elimination towards the aminocyanation product and base-participated hydroxylation followed by tautomerization towards the aminoamidation product (**Scheme 2-1**).



Scheme 2-1 Pd-catalyzed aminocyanation via intramolecular aminative cyclization

Lee et al.[6] reported a stepwise formal aminocyanation of α, β-unsaturated cyclic enones via formal dipolar cycloaddition followed by N−N bond cleavage (**Scheme 2-2**). They utilized lithium trimethylsilyldiazomethane **2.11** to provide Δ^2-pyrazoline **2.12** through a selective 1,4-addition-cyclization, due to a steric repulsion between the bulky TMS group in **2.11** and the α-methylene moiety in the enone, which disfavors 1,2-addition. To demonstrate the synthetic utility of the method, a series of tri- and tetrasubstituted natural product derivatives with cyclic enone backbones were examined for cyclization first. Spiro-bicyclic products **2.12e**, **2.12f** and **2.12g** can be also formed in good yields from enones bearing an exocyclic C−C double bond. Then, with Brønsted-acid-induction, the corresponding pyrazolines **2.12** succeeded in delivering α-amino-β-cyano ketones by breaking N−N bonds. Furthermore, under the conditions of either reductive amination or direct alkylation with alkyl halides and base, *N*-alkyl pyrazolines **2.15** and α-alkylamino-β-cyano ketones **2.16** were also affordable.

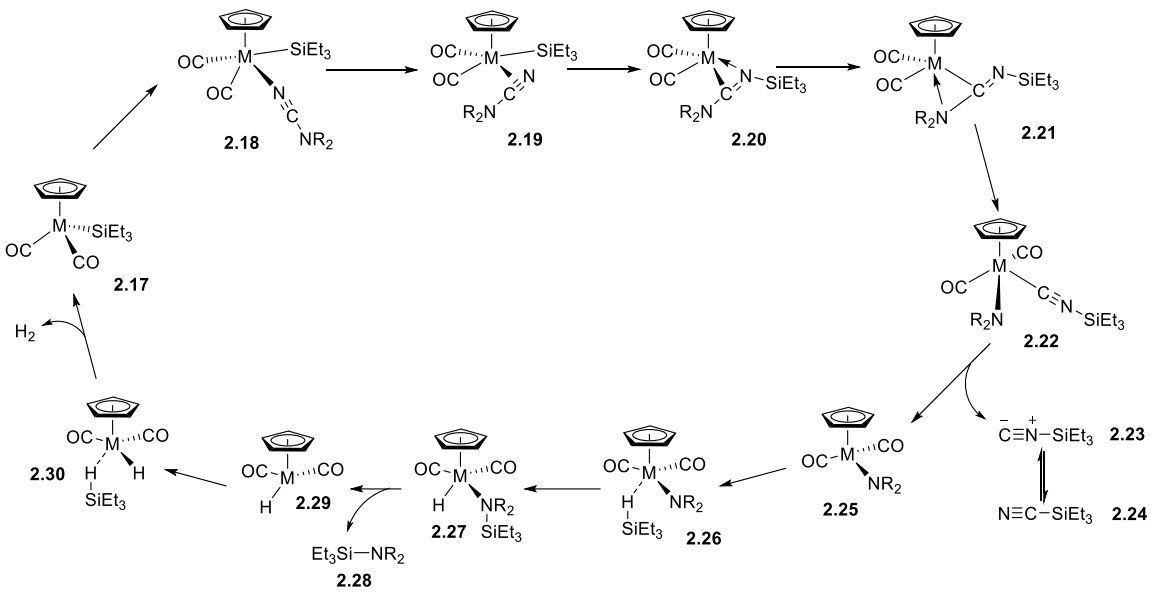


Scheme 2-2 Formal aminocyanation of α, β-unsaturated cyclic enones

An alternative method is the use of cyanamides via N−CN bond cleavage to realize aminocyanation of unsaturated C−C bonds. Though cyanamides have been extensively studied and utilized in organic synthesis,[7] N−CN bond activation remain challenging due to its high bond dissociation energy with partially double bond character.[8]

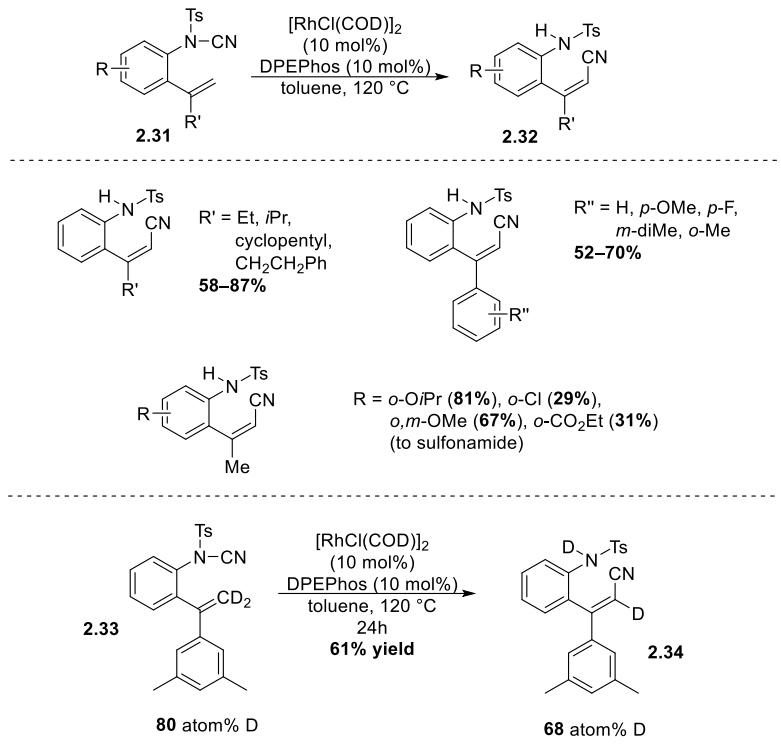
The first transition-metal-mediated N−CN bond cleavage was reported by Nakazawa et al. in 2009.[9] The catalytic bond activation was attained by either a silyl-iron/molybdenum complexes. Later, based on hybrid DFT calculations with the B3LYP functional,[10] the proposed bond cleavage process can be separated into 5 steps (**Scheme 2-**

3): (1) coordination of nitrogen in cyano group (N_{CN}) to the metal center, giving an end-on complex, (2) isomerization to side-on π-complex (coordination of π-electrons of cyano triple bond to the metal) , (3) migration of TES group to afford *N*-silylated η^2-amidino complex **2.20** (which can be isolated), including the formation of metal−C_{CN} σ-bond and metal−N_{CN} dative bond, (4) dissociation of N_{CN} followed by coordination of N_{NR2} to the metal center, (5) cleavage of R_2N−C σ-bond to give a silylisocyanide complex. To regenerate the active catalyst, the siylisocyanide falls from the metal center, leading to an amido complex **2.25**. Then the complex **2.25** reacts with triethylsilane to produce R_2N−TES species and metal hydride complex. Finally, via σ-metathesis, the silyl-metal catalyst is regenerated with the loss of H_2. This study supports that aminocyanation of unsaturated C−C bonds is feasible through N−CN bond cleavage.



Scheme 2-3 Proposed process for metal-mediated N−CN bond cleavage

Wang and Falck[11] later also discovered the N−CN bond cleavage in the presence of rhodium catalyst and diphosphine ligand to achieve intramolecular cyanation of a styrene (**Scheme 2-4**). Besides the optimal combination: $[Rh(COD)Cl]_2$ and DPEPhos, other rhodium or palladium species with phosphine ligands are still able to afford the desired product in modest yields. Decyanation product was also observed even using the optimal conditions. The reactivity of substrates with various olefinic and aromatic substituents was then examined. Most of them can give moderate to good yields, except substrates with electron-deficient arenes bearing chlorine and ethyl ester moiety. To gain more insight into the mechanism, the authors employed a deuterium labeling experiment, suggesting that the intramolecular reaction exists. However, the detailed mechanism including N−CN bond cleavage and cyano-transfer process is still unsolved.

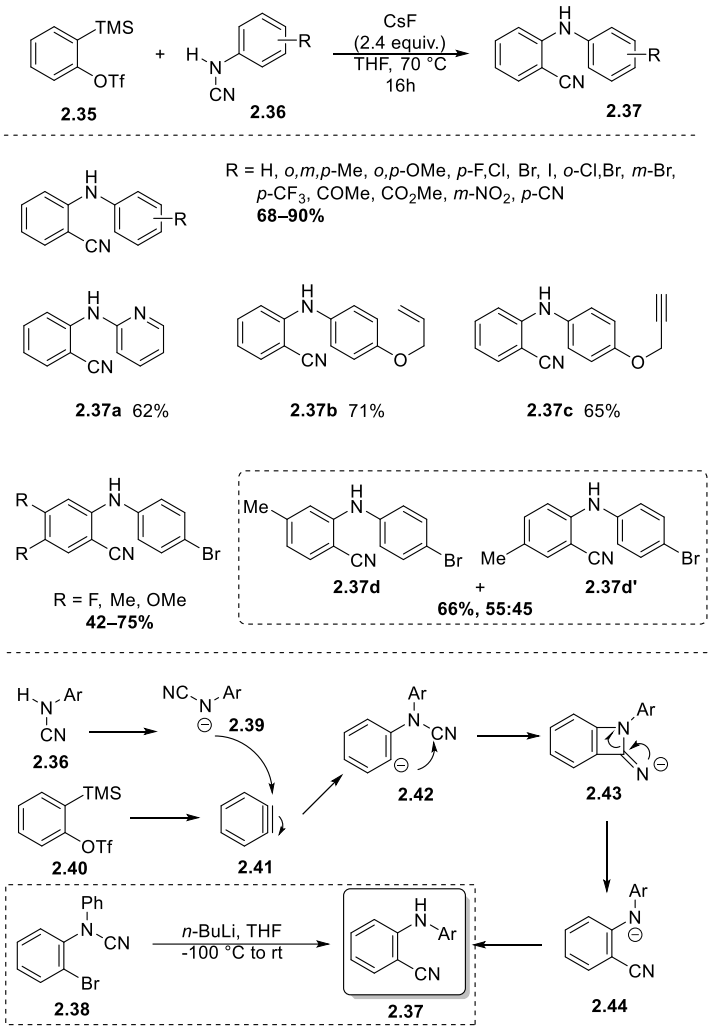


Scheme 2-4 Rh-catalyzed cyano group transfer via N−CN bond cleavage

In recent years, several studies were published on aminocyanation of unsaturated C−C bonds via N−CN bond activation. Herein, the following paragraphs will briefly summarize the developments of this methodology, including our own contribution to this field.

Zeng et al.[12] utilized the well-established 1,2 difunctionalization of arenes via direct addition of σ-bond across arynes,[13] to realize aminocyanation of benzynes. (**Scheme 2-5**) Treating 2-(trimethylsilyl)phenyl trifluoromethanesulfonate as the benzyne precursor, with *N*-aryl cyanamides as amino/cyano sources, a variety of 2-aminobenzonitriles bearing

electron-neutral, -donating and -withdrawing groups, can be all obtained in good yields. Though the side product, the N−H adduct was detected in the reaction of *N*-(4-bromophenyl)cyanamide, the chemoselectivity is still satisfying when lower concentration of substrates was used in THF. The fluoride sources and solvent species also impact on the conversion and chemoselectivity of the reaction. The proposed mechanism includes nucleophilic attack of the deprotonated cyanamide to a benzyne, followed by nucleophilic attack of the resulting phenyl anion to cyano group to form a 4-membered ring, ring opening due to the ring strain and protonation. The product of the reaction between *N*-(2-bromophenyl)-*N*-phenylcyanamide with *n*-BuLi followed by quenching with protons, supports that a phenyl anion is involved in the process of N−CN bond cleavage.



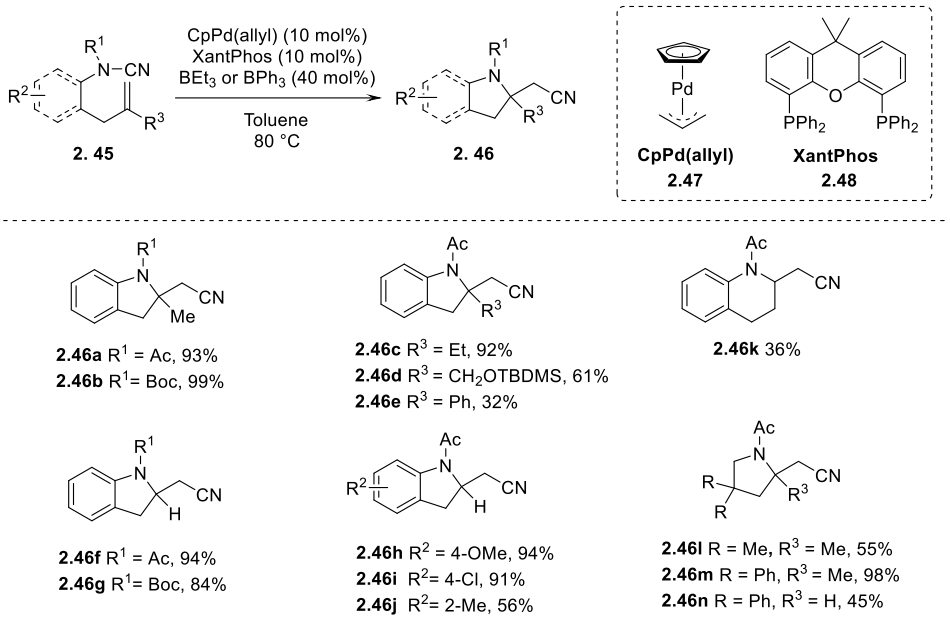
Scheme 2-5 Aminocyanation of arenes via direct addition of σ-bond across arynes

In 2014, Nakao *et al.* discovered an intramolecular aminocyanation of alkene via N−CN bond activation.[14] (**Scheme 2-6**) Based on their previous research on nickel/Lewis acid cooperative catalyzed carbocyanation[15] and palladium catalyzed oxycyanation[16] reactions, they also succeeded in applying a palladium/triorganoboron cooperative catalysis to activate N−CN bond in acyl cyanamides, followed by the intramolecular

insertion of the double bond into the N−CN bond in a 5-exo-trig manner, to prepare *N*-acetyl indolines bearing an aza-quaternary stereocenter and a cyano group.

During the optimization of conditions, the authors demonstrated that the combination of CpPd(allyl) and Lewis acids BEt_3/BPh_3 is crucial to the reactions. Other transition metals and Lewis acids such as perfluorotriphenylborane and triethylaluminium were far less effective. XantPhos also performed a better reactivity than other mono- or bidentate phosphine ligands, possibly due to its appropriate bite angle. Surprisingly, when $B(C_6F_5)_3$ was added to the reaction without any metal catalysts, **2.46a** was still obtained in 11% yield, at a higher temperature with prolonged reaction time.

The reactivity of both *N*-acetyl and *N*-tert-butyloxycarbonyl (Boc) cyanamides with various substituents were examined under the optimized conditions. Substituents on alkene moiety including methyl, ethyl and (tert-butyldimethylsilyloxy)methyl were tolerated, while phenyl led to a sluggish reaction with decyanation. More importantly, the mono-substituted alkene substrate **2.46f** can also smoothly deliver the corresponding product in 94% yield without β-hydride elimination. 4-Methoxy-, 4-chloro-, and 2-methyl-substituted indolines, as well as 2-substituted tetrahydroquinoline, were all successfully obtained. Pyrrolidines can be prepared from the cyanamides with aliphatic skeletons in modest to good yields.



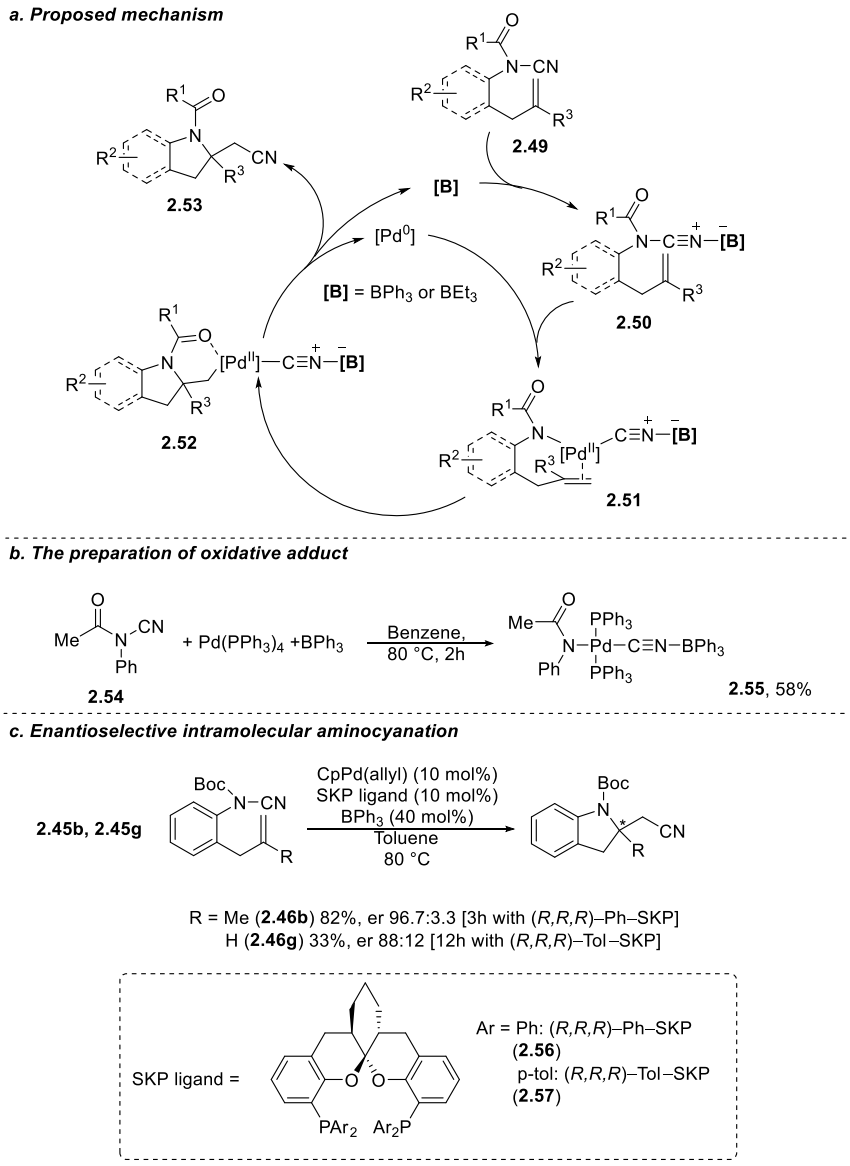
Scheme 2-6 Intramolecular aminocyanation of alkene via N−CN bond activation using acyl cyanamides

A plausible catalytic cycle was proposed in **Scheme 2-7**: First, the N−CN bond of cyanamide is cleaved via oxidative addition to palladium(0) center, with the aid of borane Lewis acid by binding to the terminal nitrogen of cyano group, to lower the target bond's energy. Through *syn*-aminopalladation[17,18], a five-membered heterocycle is constructed in a 5-exo-trig manner. Finally, the boron-bound product is formed by reductive elimination, with C−CN bond formation. The boron catalyst then falls from the product and then attaches to another unreacted substrate molecule to start a new cycle again. However, it is still possible that the aminocarbonyl group in **2.49** coordinates to a boron catalyst in the catalytic cycle.

To verify their hypotheses, the oxidative adduct intermediate **2.55** was examined by ^{1}H NMR spectroscopy and X-ray crystallography, which were prepared from a

stoichiometric reaction (**Scheme 2-7, part b**). The N−CN bond activation didn't occur in the absence of Lewis acid. Hence, the structure of **2.55** suggests that the boron Lewis acid induces the cleavage of N−CN bond when it adheres to the cyano group. In addition, the coordination of the aminocarbonyl to a palladium center is likely to form a six-membered ring intermediate, in order to suppress β-hydride elimination when R^3=H (**2.52**). It is noteworthy that the reductive elimination, which gives a new C(sp^3)−CN bond formation, can be affected both by the coordination of a cyano group to the Lewis acid[19] and the bidentate phosphine ligands with a large bite-angle.[20]

Furthermore, the first example of an enantioselective aminocyanation reaction was achieved in the presence of chiral ligands, (*R*,*R*,*R*)-Ph-SKP and (*R*,*R*,*R*)-Tol-SKP (**Scheme 2-7, part c**), instead of XantPhos. The reaction of substrate **2.45b** can afford an optically active cyclized product in good yield and high ee. When R=H (substrate **2.45g**), the desired chiral product is also obtained, though in a lower yield and ee.

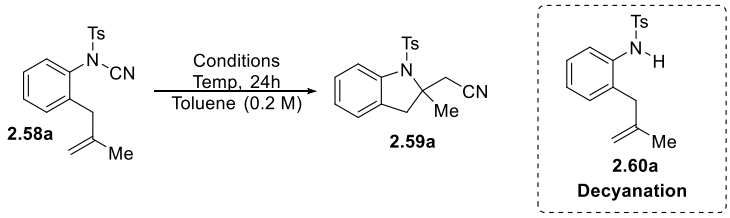


Scheme 2-7 Mechanistic studies and enantioselective intramolecular aminocyanation

In the same year, our group also disclosed intramolecular aminocyanation of alkenes via N−CN bond activation in *N*-tosyl cyanamides, to prepare *N*-tosyl indolines (**Scheme 2-8**).[21] The highlight of our work is the metal-free, Lewis-acid-only conditions with full intramolecularity.

N-cyano-*N*-phenyl-*p*-toluene sulfonamide (NCTS) was chosen as our target cyanamide due to the presence of strong electron-withdrawing tosyl group, which can assist to weaken the N−CN bond. We started screening of conditions for aminocyanation of NCTS cyanamide **2.58a** with a series of transition metals and Lewis acids, based on some previous successful examples on C−CN,[15] O−CN[16] and N−CN[11] bond activation. (**Table 2-1**) The combination of rhodium catalysts and borane Lewis acids can afford the desired product in modest yields with the decyanation byproduct. Surprisingly, when 1 equivalent of $B(C_6F_5)_3$ was used in the absence of metal catalyst, the optimal yield still achieved. Hence, we investigated all available Lewis acids in our lab to see if they can also promote the aminocyanation reaction. $BF_3{\cdot}OEt_2$, $AlCl_3$, and Me_2AlCl were able to afford the product **2.59a** but $B(C_6F_5)_3$ was still the best promoter here. Unfortunately, even at 150 °C, the substrate **2.58a** still remained in the presence of triphenylborane.

Table 2-1 Optimization of intramolecular aminocyanation of *N*-tosyl cyanamides



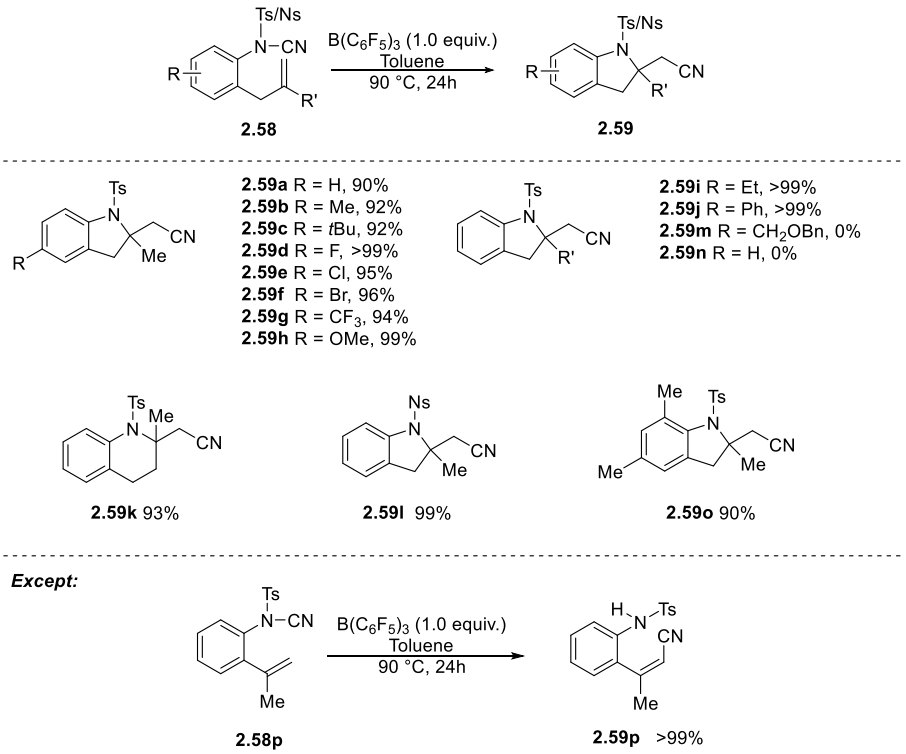
Entry	Selected Conditions (Metal +Lewis acid)	Temp (°C)	Yield (%)
1	$[Rh(C_2H_4)Cl]_2$ (5 mol%) + BPh_3 (1.2 equiv)	110	49 [b]
2	$[Rh(C_2H_4)Cl]_2$ (5 mol%) + $B(C_6F_5)_3$ (1 equiv)	90	89 [b]
3	$B(C_6F_5)_3$ (1 equiv)	90	90 [b]
4	$BF_3{\cdot}OEt_2$(1 equiv)	90	31 [b]
5	$AlCl_3$ (1 equiv)	90	52 [b]
6	Me_2AlCl (1 equiv)	90	11 [a]

7	BPh_3 (1 equiv)	150	No product

[a] Determined by ^1H NMR analysis using *p*-methoxyacetophenone as the internal standard. [b] Yield after column chromatography.

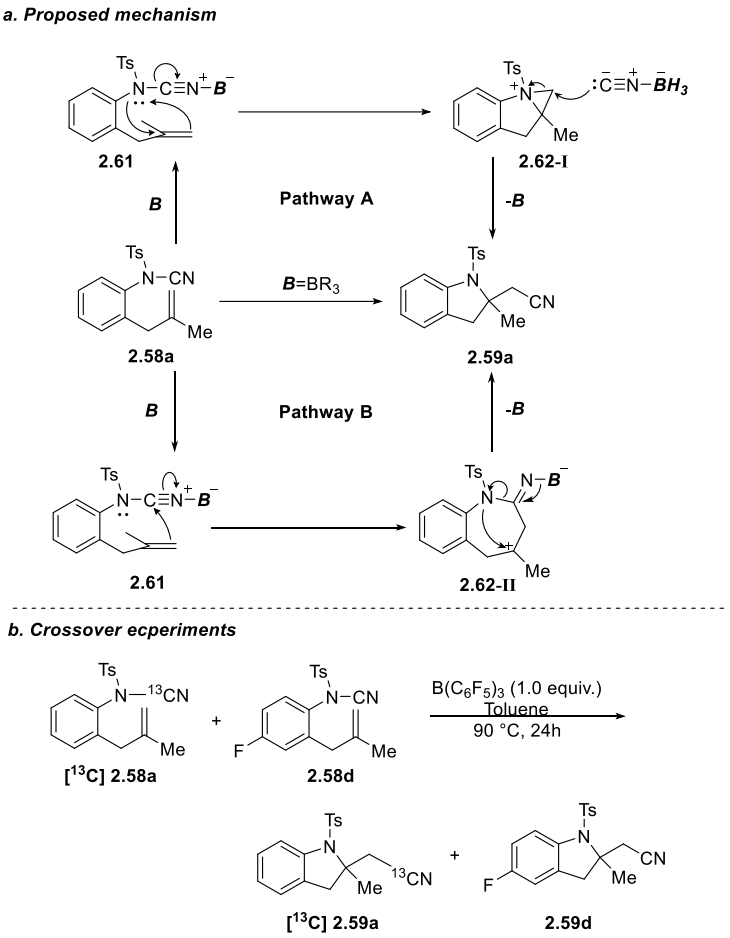
Later, the scope of NCTS-type cyanamides were examined under the optimal conditions. (**Scheme 2-8**) Substrates **2.58b–2.58h**, bearing mono-substituents *para* to the cyanamide moiety or bi-substituents **2.58o**, all delivered corresponding indolines in excellent yields. Substrates with alkene substituents other than methyl (ethyl, phenyl) provided the desired products in almost quantitative yields. However, mono-substituted alkene and benzyloxymethyl-substituted alkene failed to afford their products. Tetrahydroquinoline **2.59k** and nosyl-protected indoline **2.59l** can be both obtained in good yields.

Interestingly, the reaction of the *o*-isopropenylsubstituted cyanamide **2.58p** afforded an alkenyl nitrile **2.59p** in quantitative yield, instead of the expected cyclization product, a four-membered benzazetidine. (**Scheme 2-8,** the bottom). Such type of cyano transfer reaction was also reported by Wang and Falck,[11] suggesting that the rhodium catalyst is not actually crucial. Future work will explore the mechanistic consequence of this observation for aminocyanation.



Scheme 2-8 Non-metal-catalyzed intramolecular aminocyanation of alkenes

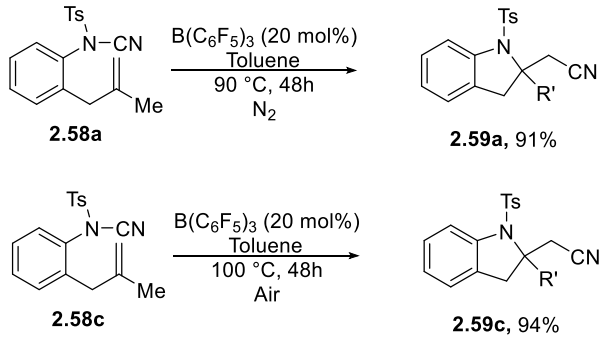
We hypothesized the catalytic cycle begins from the adduct **2.61** (**Scheme 2-9**), then two possible pathways are possible to afford the desired product: In Pathway A, the N−CN bond is cleaved through the formation of aziridinium ion with the loss of cyano group, promoted by Lewis acid.[22] Then nucleophilic attack of dissociated boron-bound cyanide opens the three-membered ring to afford the product. In Pathway B, a seven-membered carbocation intermediate is formed by nucleophilic attack of the alkene at the carbon of cyano group, which is the typical site of nucleophilic attack on cyanamides. Then, the medium ring contracts to give a smaller five-membered-ring, with simultaneous N−CN bond cleavage.



Scheme 2-9 Mechanistic studies on intramolecular aminocyanation of alkenes

However, Pathway A was ruled out based on the results of the crossover experiments. [^{13}C] 2.58a and **2.58d** were mixed in equal amounts under the optimal condition (1.0 equiv. of $B(C_6F_5)_3$ in toluene at 90 ˚C) only afforded the non-crossover products [^{13}C] **2.59a** and **2.59d** (**Scheme 2-9, part b**). It supported that the studied aminocyanation of alkenes here is a fully-intramolecular reaction, without intermolecular exchange of cyano groups.

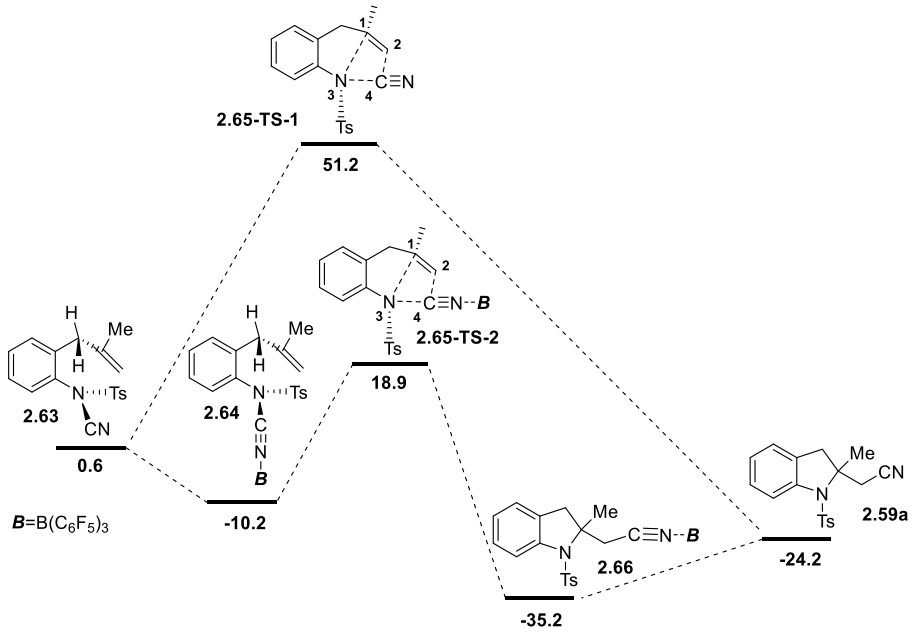
Based on the proposed mechanism above, it seems that Lewis acid can serve as a catalyst. (**Scheme 2-10**) To verify this hypothesis, an aminocyanation of **2.58a** was performed with 20 mol% $B(C_6F_5)_3$ in toluene and heated at 90 ˚C for an elongated reaction time (48 h), finally giving the corresponding product **2.59a** was obtained in 91% yield. The results indicate that the coordination of cyano group to $B(C_6F_5)_3$ is flexible, which allows the boron Lewis acid to return the catalytic cycle. Remarkably, aminocyanation of **2.58c** was still successful under air on a larger scale, with 20 mol% $B(C_6F_5)_3$ and heating at 100 ˚C for 48 hours. Hence, our intramolecular aminocyanation can also achieve in a catalytic manner, which saves the cost of expensive commercial-available $B(C_6F_5)_3$ reagent.



Scheme 2-10 Lewis-acid-catalyzed intramolecular aminocyanation

Recently, Zhao et al.[23] investigated our Lewis-acid-catalyzed intramolecular aminocayanation of alkenes by DFT calculations and proposed a novel concerted and asynchronous mechanism (**Scheme 2-11**).[24–26] The key step (aminocyanation on the alkene) can be divided two stages: in the first stage, the formation of the C2−C4 bond and the cleavage of the N3−C4 complete simultaneously, Then, in the second stage, the C1−N3 bond is constructed to afford the final product. However, under mild conditions, the free

energy of a 4-memebered cyclic transition state **2.65**-TS-1 is as high as 51.2 kcal/mol, indicating that the alkene addition step can hardly occur without any Lewis acid.

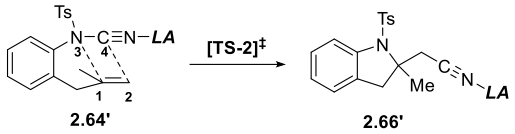


Scheme 2-11 DFT calculated Gibbs free energy diagram for intramolecular aminocyanation

In the presence of $B(C_6F_5)_3$, the adduct **2.64** is formed exothermically by the coordination of cyano group to borane center. Then **2.64** can deliver the corresponding cyclic product **2.66** via **2.65**-TS-2 with lower energy barrier (18.9 kcal/mol), suggesting that the Lewis acid is indispensable to the aminocyanation of alkenes. Besides $B(C_6F_5)_3$, the authors also examined other two Lewis acids (Lewis acidity order: BPh_3<$SnCl_4$< $B(C_6F_5)_3$) to check if the Lewis acidity impact on the reactivity. The calculated activation barrier is lower when stronger Lewis acid exists in the reaction, which is consistent with experimental results (**Table 2-2**). The variations in bond lengths (C1–N3, C2–C4 and N3–

C4) from **2.64** to **2.66** along the intrinsic reaction coordinate also show that the reaction is concerted and asynchronous.

Table 2-2 Calculated and experimental results for intramolecular aminocyanation with Lewis acids



2.64' 2.66'

Lewis acids	The calculated hydride affinities (kcal/mol)	The calculated free energy barrier (kcal/mol)	Experimental yield (%)
BPh_3	-91.6	36.8	0
$SnCl_4$	-123.3	32.7	49
$B(C_6F_5)_3$	-130.6	29.1	90

In addition, the key seven-membered ring intermediate in our previous proposed stepwise mechanism (**Scheme 2-9, part a, pathway b**), cannot be located on the potential energy surface.

Based on the calculation of the activation free energy of the rate-determining step, the effect of substituents at the N3 atom and alkene moiety on the reactivity of intramolecular aminocyanation may be significant. A series of substrates with different substituents (tosyl, acyl chloride, acetyl and methyl) on the N3 atom were investigated first. The magnitudes of the reaction barriers increase with the decline of electron-withdrawing ability. It suggests that the stronger electron−withdrawing substituent attached to N3 atom, the more readily the reaction can happen.

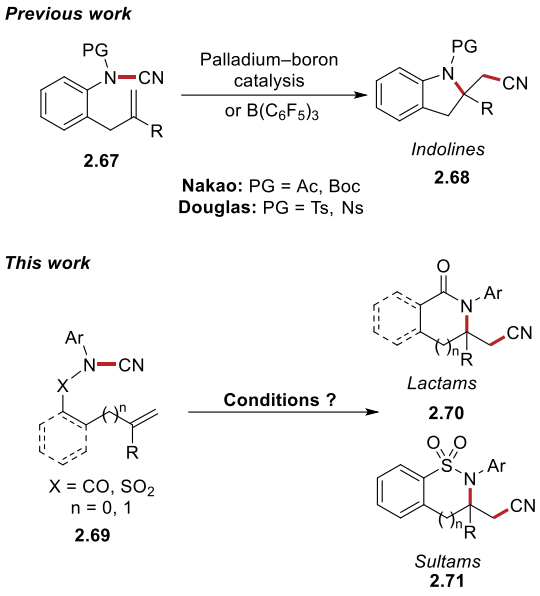
The free energy barriers of substituents at the alkene are also examined. When methyl is replaced by phenyl, the barrier decreases from 29.1 to 24.5 kcal/mol, whereas if methyl is replaced by hydrogen it increases from 29.1 to 39.4 kcal/mol. It indicates that a conjugated substituent can lower the activation barrier by strengthening the nucleophilicity of the alkene to accelerate the reaction.

2.2 Development on intramolecular aminocyanation via N−CN bond activation: free from rigid tethers

As discussed above, intramolecular aminocyanation of unsaturated C−C bonds is an efficient method to directly introduce two versatile functional groups in one step, especially construct *N*-heterocycles with quaternary centers in highly atom-economic fashion. Such valuable method for building molecular complexity motivates us to explore its synthetic application more. We also found that, both Nakao's and our alkene aminocyanation methods are mainly limited to benzo-fused products. To expand the scope of substrates, we designed two new series of *N*-acyl and *N*-sulfonyl cyanamides, which obviates the requirement of rigid aromatic tethers, as well as remains the connection feature of "breakable" N−CN bonds, in order to afford lactams and sultams bearing a nitrogen-substituted quaternary stereocenter and cyano group.

To realize the cyclization of *N*-acyl cyanamides with flexible alkyl tether, we utilized the Thorpe-Ingold (gem-disubstituent)[27] effect, which install α,α'-disubstituents to

the carbonyl group. Moreover, a stereoselective cyanofunctionalization may be feasible with a pre-existing stereocenter on the alkyl tether, which has been rarely examined. (**Scheme 2-12**)



Scheme 2-12 Design for new intramolecular aminocyanation of alkenes

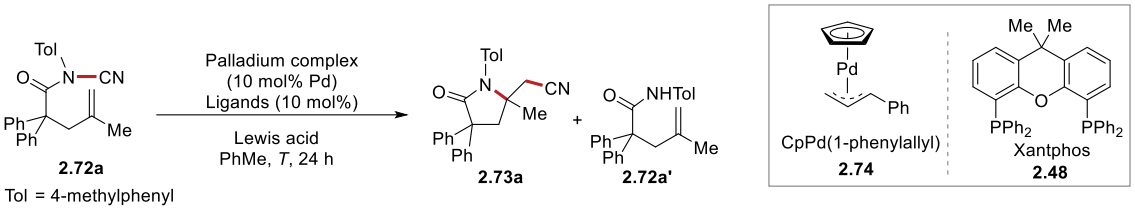
2.2.1 Reaction optimization of aminocyanation of N-acyl cyanamide 2.72a

N-acyl cyanamide **2.72a** were prepared from diphenylacetic acid, β-methallyl chloride, and *p*-Toluidine in just 3 total steps. We initiated the investigation of conditions with a boron Lewis acid (BPh_3 or $B(C_6F_5)_3$) alone, but only observed unconsumed starting material **2.72a** and byproduct **2.72a'**, the product of reductive decyanation (**Table 2-3**, entries 1 and 2). Aminocyanation of **2.72a** with $AlCl_3$ still led to decomposition (entry 3) with unidentified products.

Luckily, the palladium/Lewis acid-cocatalyst conditions developed by Nakao's group were also efficient to an alkyl-tethered cyanamide substrate. In the presence of CpPd(1-phenylallyl) (10 mol %), BPh_3 (40 mol %), and Xantphos (10 mol %), aminocyanation of **2.72a** afforded the desired **2.73a** in 87% yield and a trace amount of **2.72a'** (entry 4).

Remarkably, using $Pd(PPh_3)_4$ and BPh_3 (entry 5), the reaction still afforded **2.73a** in a slightly lower yield of than the Xantphos/CpPd(1-phenylallyl) system (81% versus 87%), offering a simple and affordable alternative catalytic system. Other palladium sources, such as $Pd(OAc)_2$ or Pd_2dba_3, resulted in an less effective reaction (entries 6 and 7). Bidentate phosphine ligands with different bite angles were also examined (entries 8–14). Generally, ligands with a larger bite angle afforded a higher yield of product, and Xantphos reached the summit (entry 12). However, further expansion of the bite angle led to the decrease of yield, even shut down the reaction (entry 13 and 14). A control reaction without BPh_3 gave a small amount of **2.73a** along with unidentified byproducts (entry 15). Finally, aminocyanation of **2.72a** under the optimized conditions, including CpPd(1-phenylallyl) (10 mol %), Xantphos (10 mol %), and a boron Lewis acid (40 mol %) in toluene at 80 °C, delivered the desired **2.73a** in 89% and 99% isolated yield with BPh_3 and BEt_3, respectively (entries 16 and 17).

Table 2-3 Optimization of aminocyanation of N-acyl cyanamide **2.72a**



Entry	Palladium	Ligand	Lewis acid (equiv.)	*T* (°C)	Yield (%)[a]
1	–	–	BPh_3 (0.5)	100	0[b]
2	–	–	$B(C_6F_5)_3$ (0.5)	80	0[b]
3	–	–	$AlCl_3$ (0.5)	80	0[c]
4	CpPd(1-phenylallyl)	Xantphos	BPh_3 (0.5)	90	87
5	$Pd(PPh_3)_4$	–	BPh_3 (0.5)	90	81
6	$Pd(OAc)_2$	Xantphos	BPh_3 (0.5)	90	67
7	Pd_2dba_3	Xantphos	BPh_3 (0.5)	90	69
8	CpPd(1-phenylallyl)	dppe[d]	BPh_3 (0.4)	80	0[b]
9	CpPd(1-phenylallyl)	dppp	BPh_3 (0.4)	80	23
10	CpPd(1-phenylallyl)	dppb	BPh_3 (0.4)	80	49
11	CpPd(1-phenylallyl)	DPEphos	BPh_3 (0.4)	80	72
12	CpPd(1-phenylallyl)	Xantphos	BPh_3 (0.4)	80	93
13	CpPd(1-phenylallyl)	Nixantphos	BPh_3 (0.4)	80	81
14	CpPd(1-phenylallyl)	DBFphos	BPh_3 (0.4)	80	0[b]
15	CpPd(1-phenylallyl)	Xantphos	–	80	< 20[e]
16[g]	CpPd(1-phenylallyl)	Xantphos	BPh_3 (0.4)	80	89[f]
17[g]	CpPd(1-phenylallyl)	Xantphos	BEt_3 (0.4)	80	99[f]

[a] Determined by ^{1}H NMR analysis using *p*-methoxyacetophenone as the internal standard. [b] Only **2.72a** and **2.72a'** detected by NMR spectroscopy. [c] Decomposition of **2.72a**. [d]Bite-angle values: dppe 85°; dppp 91°; dppb 98°; DPEphos 102°; Xantphos 111°; Nixantphos 114°; DBFphos 131°. [e] Complex reaction mixture. [f] Yield after column chromatography. [g] Conditions applied to further substrate scope study.

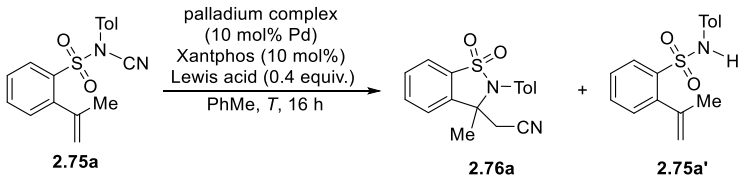
2.2.2 Reaction optimization of aminocyanation of N-Sulfonyl cyanamide 2.75a

Based on successful metal-free aminocyanation of *N*-tosyl cyanamides, we are motivated to design new substrates that contain electron-withdrawing *N*-sulfonyl moiety

to facilitate N−CN cleavage. Hence, *N*-sulfonyl cyanamide **2.75a** were prepared and examined the reaction conditions to access biologically active sultam **2.76a** (**Table 2-4**).

With our previous success in mind, we started heating of **2.75a** with metal-free aminocyanation conditions (1.0 equivalent of $B(C_6F_5)_3$ alone in toluene) but failed to observe any desired **2.76a** (**Table 2-4**, entry 1). Lewis acid catalyst like BF_3•OEt_2 or BPh_3 didn't provide the product either (entries 2 and 3). Under palladium/Lewis acid co-catalysis, aminocyanation of **2.75a** succeeded in affording **2.76a** along with a small amount of reductive decyanation by-product **2.75a'** (entry 4). After screening a series of palladium sources (entries 5–7) and reaction temperatures (entries 8–10), the optimal catalytic system finally afforded **2.76a** in almost quantitative yield, in the presence of Pd_2dba_3 (5 mol %), Xantphos (10 mol %), and BPh_3 (40 mol %) in toluene at 80 °C (entry 9). Only unconsumed starting material was detected in a control experiment performed without BPh_3 (entry 11).

Table 2-4 optimization of aminocyanation of N-Sulfonyl cyanamide **2.75a**



2.75a **2.76a** **2.75a'**

Entry	Palladium	Lewis acid	*T* (°C)	Yield (%)[a]
1[b]	–	$B(C_6F_5)_3$[c]	100	0[d]
2[b]	–	BF_3•OEt_2[c]	100	0[d]
3[b]	–	BPh_3	100	0[d]
4	$Pd(OAc)_2$	BPh_3	100	69

5	$Pd(TFA)_2$	BPh_3	100	63
6	CpPd(1-phenylallyl)	BPh_3	100	81
7	Pd_2dba_3	BPh_3	100	85
8	Pd_2dba_3	BPh_3	90	95
9	Pd_2dba_3	BPh_3	80	99[e]
10	Pd_2dba_3	BPh_3	70	82
11	Pd_2dba_3	–	100	0[d]

[a] Determined by ^1H NMR analysis using DMSO-d_6 as the solvent and *p*-methoxyacetophenone as the internal standard. [b] Without Xantphos. [c] 1.0 equivalent. [d] Unconsumed starting material. [e] Yield after column chromatography.

2.3 Scope and Synthetic application of intramolecular aminocyanation of alkenes

2.3.1 Scope of aminocyanation of *N*-acyl cyanamides

The substrate scope of aminocyanation reactions was then extensively explored. From commercial-available anilines, a variety of *N*-acyl cyanamides bearing aryl substituents can be readily prepared. (**Table 2-5**).

N-phenyl cyanamide **2.72b** and substrates bearing tert-butyl, fluoro, chloro, methoxy, and acetoxy groups *para* to the cyanamide moiety provided the corresponding pyrrolidones in good to excellent yields (**2.73b–2.73g**). The cyclic products containing an electron-withdrawing aryl substituent (**2.73h–2.73k**, R = Ac, Cl, CF_3, CO_2Me) were obtained along with reductive decyanation byproducts. The decyanation pathway can be

inhibited by increasing the amount of Lewis acid and lowering reaction temperature with satisfactory yields (67–92%). Products **2.73l** and **2.73m**, bearing one or two *m*-OMe substituents were isolated in good yield. However, substrate with two *o*-methyl substituents resulted in a modest yield even increasing the loading of both catalysts, possibly due to steric hindrance. A pendant olefin (**2.73o**) and a pyridine ring (**2.73p**) were tolerated to the reaction conditions, demonstrating the compatibility of these typical coordinating-functional-groups.

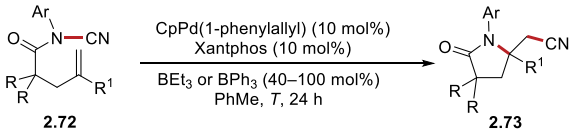
We then turned our attention to groups α to the acyl cyanamide carbonyl. Besides geminal phenyl groups in the substrates we discussed before, pyrrolidones containing geminal methyl (**2.73q** and **2.73r**) and benzyl groups (**2.73s**) α to the carbonyl, as well as spirocyclic products (**2.73t**–**2.73v**) were all afforded via aminocyanation-cyclization in good yields. Conversely, the yield of **2.73w** (33%) dropped dramatically in the absence of α substituents, indicating that the Thorpe-Ingold effect contributes to cyclization step in aminocyanation.

Next, we moved to focusing on alkene substitution. Substrates with alkyl substituents other than methyl performed with comparable yield (**2.73x** and **2.73y**). Aminocyanation of substrate bearing allylic benzyloxymethyl group (**2.73z**) was less fruitful, even after raising the catalyst loading to 20 mol % of Pd. The sluggish cyclization of a styrenyl double bond can be promoted by slightly higher catalyst loading (**2.73aa**, 85%, 15 mol % Pd used). In spite of possible *β*-hydride elimination, which is a common competitive pathway for the palladium-mediated addition across a monosubstituted alkene,

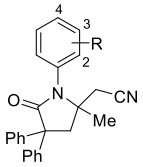
the aminocyanation still succeeded in affording the corresponding pyrrolidone **2.73ab** in 47% yield. Additionally, alkyl group (benzyl), instead of aryl groups, attached to the amide nitrogen made the N–CN bond much more inert to be activated and only 29% yield of **2.73ac** was obtained.

The aminocyanation of cyanamides with styrenyl alkenes and aromatic tethers smoothly delivered corresponding isoindolinones (**2.73ad**–**2.73af**, 59–99% yield). Six-membered lactams **2.73ag** (94% yield) and **2.73ah** (49% yield) were successfully constructed with a higher catalyst loading. In addition, we identified several incompatible substrates under the aminocyanation conditions. Substrates bearing an electron-deficient alkene (**2.72ai**) or an aryl C–Br bond (**2.72aj**) failed to provide any detectable amount of products (**2.73ai** or **2.73aj**), possibly due to a reluctant alkene insertion and competitive C–Br bond activation. An *N*-acetyl substituent on the aryl ring (**2.72ak**) rendered the N–CN bond unreactive with our optimized catalyst, even at 120 °C. Perhaps the coordination of nitrogen in *N*-acetyl to palladium center hampered the oxidative addition of N–CN bond.

Table 2-5 Scope of aminocyanation of *N*-acyl cyanamides



2.72 **2.73**



2.73b, R = H, 96%
(40 mol% BEt_3, 80 °C)

2.73c, R = 4-*t*Bu, 93%
(40 mol% BEt_3, 80 °C)

2.73d, R = 4-F, 90%
(40 mol% BEt_3, 80 °C)

2.73e, R = 4-Cl, 86%
(60 mol% BPh_3, 80 °C)

2.73f, R = 4-OMe, 95%
(40 mol% BEt_3, 80 °C)

2.73g, R = 4-OAc, 90%
(40 mol% BEt_3, 80 °C)

2.73h, R = 4-Ac, 67%[b]
(100 mol% BEt_3, 70 °C)

2.73i, R = 3-Cl, 76%
(80 mol% BEt_3, 70 °C)

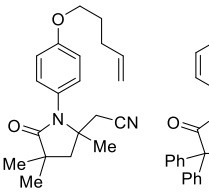
2.73j, R = 3-CF_3, 86%
(60 mol% BEt_3, 70 °C)

2.73k, R = 3-CO_2Me, 92%
(60 mol% BEt_3, 70 °C)

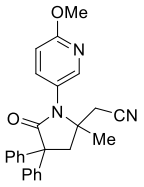
2.73l, R = 3-OMe, 84%
(40 mol% BEt_3, 80 °C)

2.73m, R = 3,5-$(OMe)_2$, 87%
(40 mol% BEt_3, 70 °C)

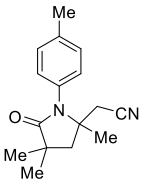
2.73n, R = 2,4-$(Me)_2$, 43%[b]
(100 mol% BEt_3, 70 °C)



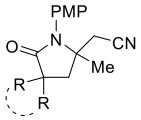
2.73o, 84%
(40 mol% BEt_3, 80 °C)



2.73p, 96%
(80 mol% BEt_3, 80 °C)



2.73q, 93%
(40 mol% BEt_3, 80 °C)



2.73r, R = Me, 88%
(40 mol% BEt_3, 80 °C)

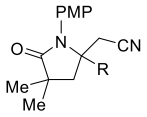
2.73s, R = Bn, 82%
(80 mol% BEt_3, 70 °C)

2.73t, R = *c*-$(CH_2)_3$, 93%
(60 mol% BEt_3, 70 °C)

2.73u, R = *c*-$(CH_2)_4$, 96%
(100 mol% BEt_3, 80 °C)

2.73v, R = *c*-$(CH_2)_2O(CH_2)_2$, 85%
(60 mol% BEt_3, 80 °C)

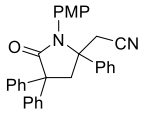
2.73w, R = H, 33%[b]
(40 mol% BPh_3, 120 °C)



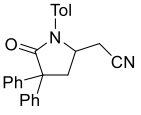
2.73x, R = *n*Bu, 90%
(60 mol% BEt_3, 80 °C)

2.73y, R = CH_2CH_2Ph, 80%
(100 mol% BEt_3, 70 °C)

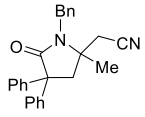
2.73z, R = CH_2OBn, 37%[d]
(100 mol% BEt_3, 90 °C)



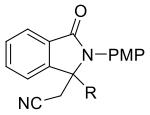
2.73aa, 85%[b]
(100 mol% BEt_3, 80 °C)



2.73ab, 47%
(60 mol% BEt_3, 70 °C)



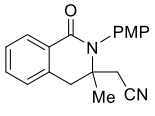
2.73ac, 29%[b,c]
(50 mol% BPh_3, 120 °C)



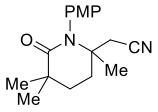
2.73ad, R = Me, 99%
(60 mol% BEt_3, 80 °C)

2.73ae, R = Ph, 99%
(60 mol% BEt_3, 80 °C)

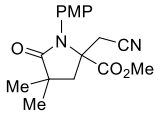
2.73af, R = H, 59%
(60 mol% BEt_3, 70 °C)



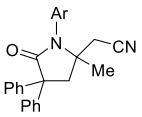
2.73ag, 94%[c]
(100 mol% BEt_3, 80 °C)



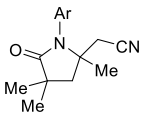
2.73ah, 49%[d]
(100 mol% BEt_3, 70 °C)



2.73ai, 0%[e]



Ar = *p*-Br-C_6H_4
2.73aj, 0%[e]



Ar = *p*-NHAc-C_6H_4
2.73ak, 0%[e]

[a]Reaction conditions: CpPd(1-phenylallyl) (10 mol %), Xantphos (10 mol %), BPh_3 or BEt_3, PhMe (1.0 mL). Reaction time: 30 h (2h, 2m); 36 h (2u, 2y, 2aa); 48 h (2n, 2s, 2ab, 2ah); 24 h (all other entries). All yields are isolated yields.
[b]Run with 15 mol % Pd/Xantphos.
[c]Run in m-xylene.
[d]Run with 20 mol % Pd/Xantphos.
[e]Unconsumed staring material.

2.3.2 Scope of aminocyanation of *N*-sulfonyl cyanamides

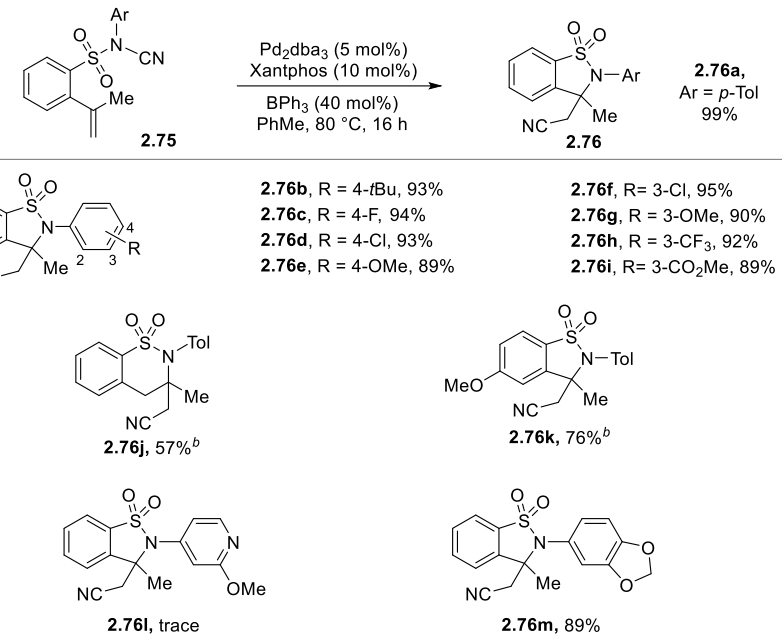
N-sulfonyl cyanamides can be readily obtained via the condensation between sulfonyl chlorides and *N*-aryl cyanamides, which are prepared from various commercial-available anilines.

N-sulfonyl cyanamides, prepared from *N*-aryl cyanamides bearing various aryl subsitutents, including -*t*Bu, -F, -Cl, -OMe, -CF_3, and -CO_2Me groups *para* or *meta* to the nitrogen atom, all smoothly converted to the corresponding sultams in consistently high yields (**Table 2-6, 2.76b–2.76i**, 89–95% yield). The formation of a six-membered sultam (**2.76j**, 57% yield) was also successful via aminocyanation. Sultams with a OMe substituent para to the sulfonyl group (**2.76k** 76% yield), or an acetal on *N*-aryl group (**2.76m**, 89% yield) were all isolated in good yields under aminocyanation conditions.

However, only a trace amount of product (**2.76l**) bearing 2-methoxypyridine under our optimized conditions for sultam formation. The mass balance consisted mainly of the starting material. In contrast, as discussed above, the preparation of **2.73p** was fruitful, which also contains a 2-methoxypyridine. Taken together, aminocyanation is still possible when basic heteroatoms are present, but likely requires further additional optimization on a case-by-case basis.

In conclusion, our results show that a variety of functional groups are compatible with sultam-forming aminocyanation reactions.

Table 2-6 Scope of aminocyanation of N-sulfonyl cyanamides



[a]Reaction conditions: Pd_2dba_3 (5 mol %), Xantphos (10 mol %), BPh_3 (40 mol %), PhMe, 80 °C, 16 h. All yields are isolated yields. [b]Run for 24 h.

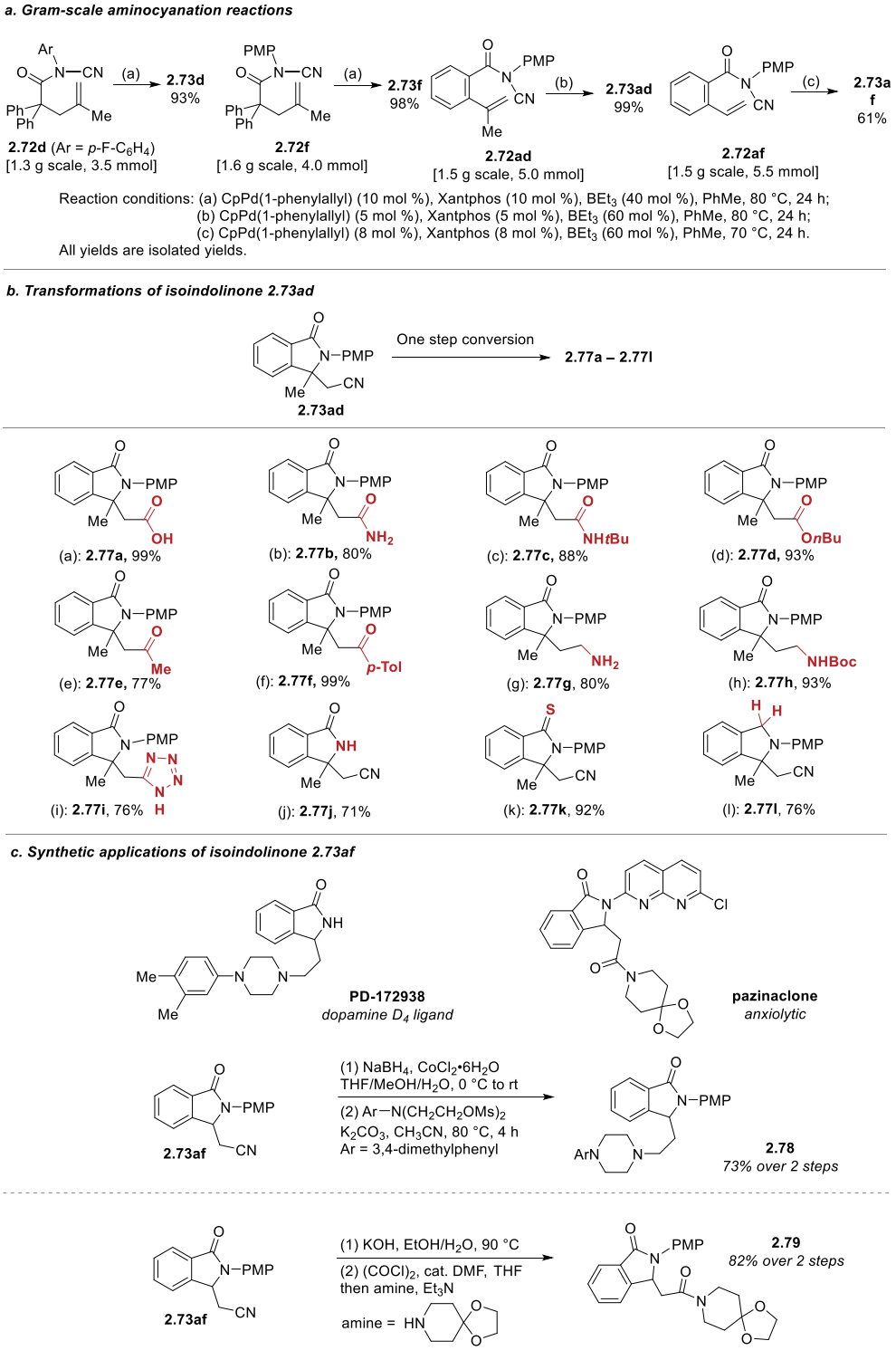
2.3.3 Synthetic application of aminocyanation products

To demonstrate the synthetic utility of aminocyanation, we first directed to large-scale synthesis. Aminocyanation of cyanamides **2.72d** and **2.72f** can readily afford the corresponding pyrrolidones **2.73d** and **2.73f** in excellent yields on a gram scale (**Scheme 2-13, a**). Cyclization of **2.72ad** and **2.72af** also proceeded smoothly to the corresponding isoindolinones **2.73ad** and **2.73af** with reduced catalyst loading (5 mol % and 8 mol % of Pd/Xantphos, respectively). The results indicate the aminocyanation is a potential method for mass production of common drug-related molecules, such as pyrrolidones and isoindolinones.

Next, the versatility of aminocyanation products in synthesis was also investigated. The aminocyanation product of *N*-acyl cyanamide, isoindolinone **2.73ad** was subjected to a variety of chemical transformations (**Scheme 2-13, b**). **2.73ad** was hydrolyzed under basic conditions to give either carboxylic acid **2.77a** or primary amide **2.77b** in good yield depending on the reaction time. *N*-*tert*-Butyl amide **2.77c** was obtained from **2.73ad** in 88% yield via a Ritter reaction. Ester **2.77d** was isolated in 93% yield via the nucleophilic attack of *n*-butanol to **2.73ad** in the presence of *p*-TsOH. A nickel-catalyzed methylation of the nitrile using $AlMe_3$ provided methyl ketone **2.77e** in 77% yield.[28] A palladium-catalyzed arylation reaction with *p*-tolylboronic acid quantitatively produced aryl ketone **2.77f**.[29] Reduction of the nitrile employing a $NaBH_4$–$CoCl_2{\cdot}6H_2O$ system generated amine **2.77g** in high chemoselectivity. By further protection of amino group in **2.77g** with $(Boc)_2O$, the corresponding *N*-Boc carbamate **2.77h** was obtained in good yield. Dibutyltin oxide-mediated cycloaddition of nitrile **2.73ad** with trimethylsilyl azide gave tetrazole **2.77i** in 76% yield.[30] Chemoselective deprotection of the *N*-PMP group with cerium (IV) ammonium nitrate afforded free isoindolinone **2.77j** in 71% yield. Thioamide **2.77k** was obtained in excellent yield by treating **2.73ad** with Lawesson's reagent. Chemoselective reduction of the amide moiety was also achieved using Hantzsch ester under mild conditions, furnishing isoindoline **2.77l** in 76% yield.[31]

The transformations of aminocyanation product **2.73af** applied to the preparation of synthetic intermediates and analogs of biologically active isoindolinones were also exemplified (**Scheme 2-13, c**). Chemoselective reduction of the nitrile, followed by base-

mediated cyclization of the piperazine ring, afforded isoindolinone **2.78** in 73% yield over two steps, which served as an advanced intermediate to PD-172938, a potent dopamine D_4 ligand.[32] In addition, hydrolysis of **2.73af** to carboxylic acid, followed by subsequent amide coupling reaction furnished amide **2.79** in 82% yield as a structural analogue to the anxiolytic drug pazinaclone.[33]



Scheme 2-13 Synthetic applications of aminocyanation products

All yields are of isolated material. Reaction conditions for **Scheme 2-13, b**: (a) KOH, EtOH/H_2O, 90 °C, 40 h; (b) KOH, MeOH/H_2O, 90 °C, 2 h; (c) H_2SO_4 (1.2 equiv), *t*BuOH, 80 °C, 12 h; (d) TsOH·H_2O (2 equiv), *n*BuOH, 120 °C, 20 h; (e) Ni(acac)$_2$ (10 mol %), $AlMe_3$ (3 equiv), benzene, 50 °C, 5 h; (f) Pd(OAc)$_2$ (10 mol %), *p*-tolylboronic acid (2 equiv), 2,2′-bipyridyl (20 mol %), CF_3CO_2H (10 equiv), THF/H_2O, 90 °C, 28 h; (g) $NaBH_4$ (4 equiv), $CoCl_2·6H_2O$ (1.5 equiv), MeOH, 0 °C, 2 h; (h) $(Boc)_2O$ (2.5 equiv), $NaBH_4$ (4 equiv), $CoCl_2·6H_2O$ (1.5 equiv), MeOH, 0 °C, 3 h; (i) $TMSN_3$ (3 equiv), *n*$Bu_2Sn(O)$ (0.5 equiv), PhMe, 100 °C, 48 h; (j) cerium (IV) ammonium nitrate (6 equiv), CH_3CN/H_2O, rt, 2 h; (k) Lawesson's reagent (1 equiv), PhMe, 100 °C, 2.5 h; (l) Tf_2O (1.2 equiv), CH_2Cl_2, 0 °C to rt, 30 min, then Hantzsch ester (3 equiv), rt, 4 h. acac = acetylacetonyl; PMP = 4-methoxyphenyl.

2.4 Mechanistic considerations

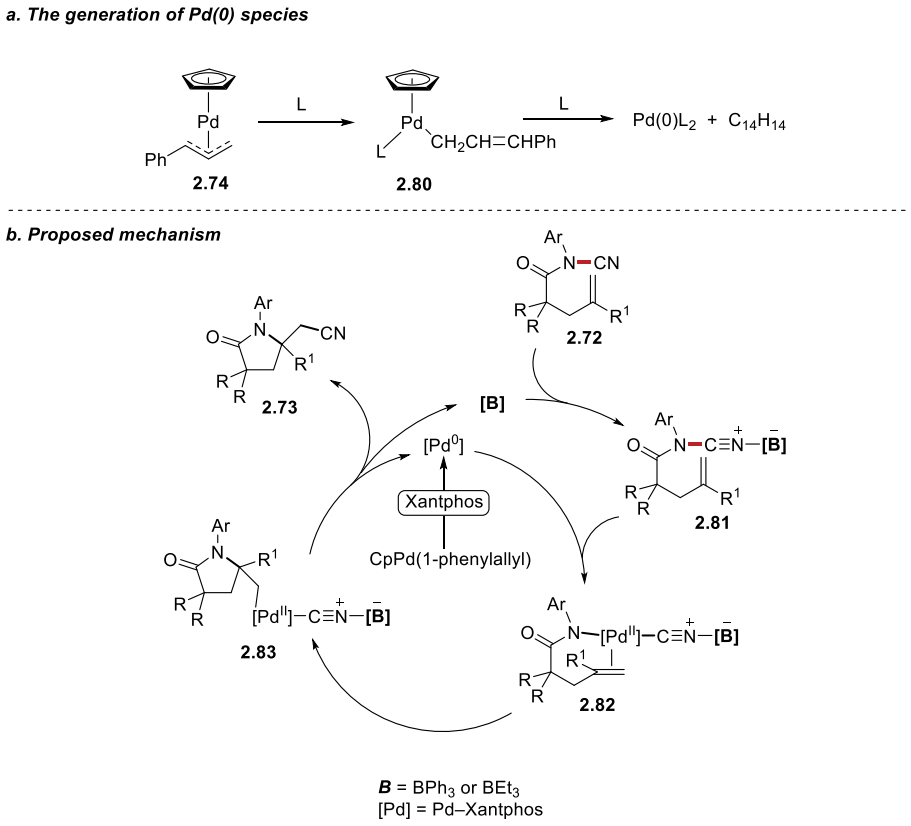
2.4.1 Proposed mechanism and confirmation of the intramolecularity

Due to the utilization of palladium/Lewis acid co-catalysis system, we propose a catalytic cycle consistent with the Nakao group's previous study.[14]

The proposed mechanism is shown in **Scheme 2-14, b**. We hypothesized the reaction undergoes a Pd(0)/Pd(II) catalytic cycle. The Pd(0) species Pd_2dba_3 can directly enter the cycle, whereas the Pd(II) species, CpPd(1-phenylallyl) complex need to be *in situ* converted to an active Pd(0) complex initially. Recently, Baird et al.[34,35] discovered that the resulting reduced palladium(0)/phosphine complex, via facile reductive elimination upon reacting with phosphine ligands (**Scheme 2-14, a**), performed much better in cross coupling reactions than the catalyst systems consisting of Pd(0) or Pd(II) catalyst precursors and the same phosphines. Such conclusion presumably rationalizes the remarkable reactivity of CpPd(1-phenylallyl) complex towards N–CN bond activation in *N*-acyl cyanamides. In addition, the less active Pd_2dba_3 fits for *N*-sulfonyl cyanamides

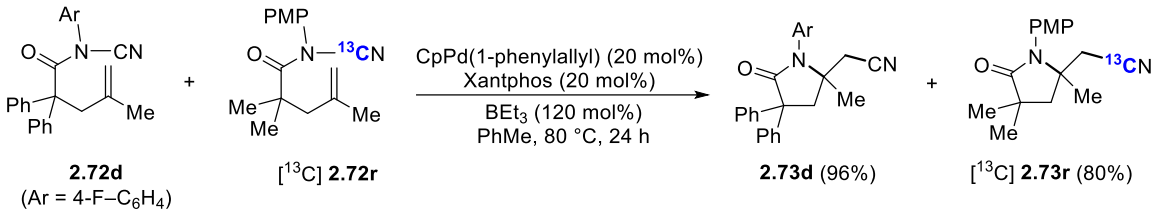
better possibly due to their weaker N–CN bonds. We also observed that the conditions using CpPd(1-phenylallyl) gave more decyanation product, which supports the assumption.

In the presence of Pd(0) catalyst, the Lewis acid catalyst is coordinated by nitrogen in cyano group, which promotes the N–CN bond cleavage. Amidopalladium(II) cyanide complex **2.82** then generates via the oxidative addition to the Pd(0) center. Intramolecular addition of the N–Pd bond across the alkene double bond provides alkylpalladium(II) cyanide complex **2.83**, followed by reductive elimination to construct C–CN bond and regeneration of the active palladium catalyst. Finally, the product is released with the dissociation of Lewis acid to start a new turn of catalytic cycle. The substrate scope study revealed that Thorpe–Ingold effect is essential to the ring formation.



Scheme 2-14 Proposed mechanism of intramolecular aminocyanation

To support the proposed mechanism above, we need to verify the intramolecularity of the reactions first. A double cross-over experiment was performed to probe intramolecularity in Pd/Lewis acid catalyzed aminocyanation (**Scheme 2-15**). *N*-acyl cyanamide **2.72d** and ^{13}C-lableled **2.72r** ([^{13}C]**2.72r**) were both subjected to the optimized aminocyanation conditions in 1:1 ratio, affording the corresponding non-crossover products **2.73d** and [^{13}C]**2.73r**. The lack of detectable crossover products indicates that the cyano group is not exchangeable, even the possible dissociation of Pd–CN bond occurs in the proposed catalytic cycle. These results are consistent with the fully intramolecular mechanism and proposed intermediates **2.82** and **2.83** in **Scheme 2-14**, part b.



Scheme 2-15 A double cross-over experiment for intramolecular aminocyanation

2.4.2 Discovery on diastereoselective intramolecular aminocyanation

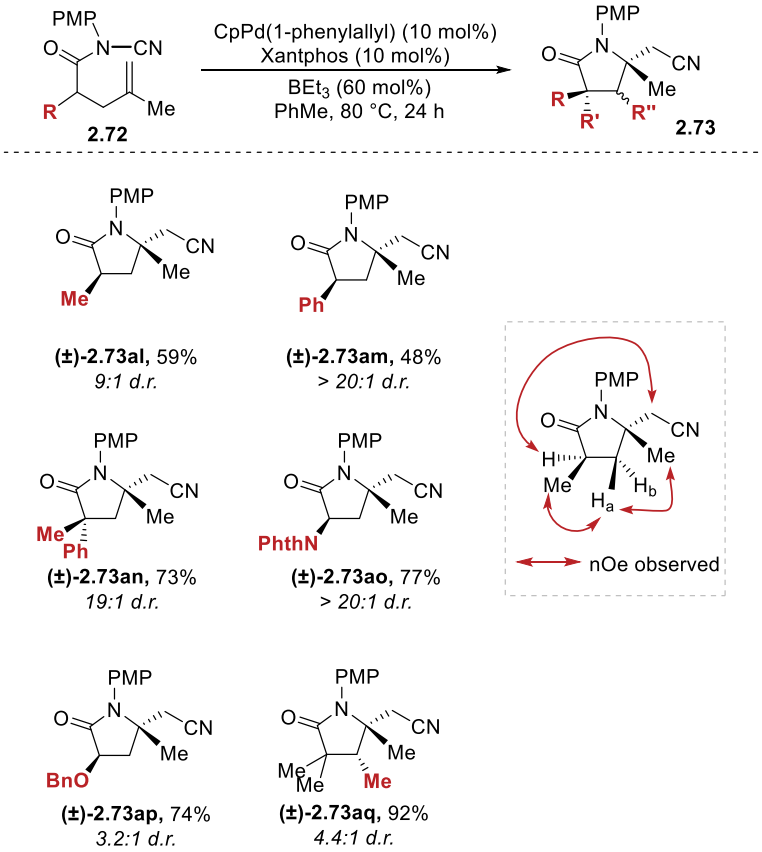
Due to the use of flexible alkyl chain tether and proposed *syn*-aminopalladation, we expected to achieve a diastereoselective cyclization if a pre-existing stereocenter has been constructed.

To examine the diastereoselectivity of the alkene addition step, we prepared substrates **2.72al–2.72aq** bearing an existing stereogenic center α to the carbonyl via alkylation reactions of enolates (dianions of carboxylic acids) (**Scheme 2-16**).

We started the investigation by the cyclization of α-methyl-substituted cyanamide **2.72al**. Gratifyingly the corresponding lactams **2.73al** was obtained in 9:1 d.r and 59% yield. The *syn*-relationship of the two methyl groups was determined by 1D nOe experiments. Similarly, substrate substituted with a phenyl group α to the carbonyl (**2.72am**) yielded the corresponding lactam **2.73am** in moderate yield (48%), but with excellent selectivity (> 20:1 d.r.), presumably due to its larger steric bulkiness.

Encouraged by these results, we further extended the scope of diastereoselective aminocyanation reactions to access functionalized lactams bearing an all-carbon stereocenter (**2.73an**), an *N*-phthalimide group (**2.73ao**), or a benzyloxy group (**2.73ap**) α

to the carbonyl, resulting in generally good yield. The d.r. was excellent when either of the α-substituents was in a larger steric size, as in **2.73an** (19:1 d.r.) and **2.73ao** 20:1 d.r.), but lower when the bulky moiety was far from the α-quaternary center (**2.73ap**, 3.2:1). Furthermore, cyclization of an alkene with an allylic stereogenic center (with a β-substituent) proceeded cleanly to provide densely substituted lactam **2.73aq** in 92% yield and 4.4:1 d.r.

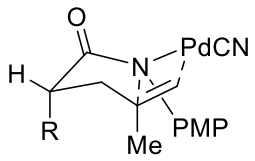


Scheme 2-16 Diastereoselective intramolecular aminocyanation of alkenes

2.4.3 Studies on the origin of diastereoselectivity

To rationalize the diastereoselectivity of aminocyanation reactions, we were driven to build a preliminary model for the step of coordination of alkene to the palladium center, prior to migratory insertion (Scheme). Initially, we hypothesized a chair-like geometry to maximize the transition-state stability during the formation of 5-membered ring, which is a common model of intramolecular aminopalladation.[14,15,33,34]

Generally, substituents with large A-value prefer to reside in the equatorial position over the axial to obviate steric repulsions in the cyclohexane skeleton. However, in our case, if the substituent α to the carbonyl stays in an (pseudo)equatorial orientation, the corresponding stereochemistry is not consistent what we observed in the major diastereomers (with its enantiomers). When the substituent aligns in the axial orientation, the pronounced 1,3-diaxial interactions also increase with the methyl group in the alkene moiety. (**Figure 2-1**)

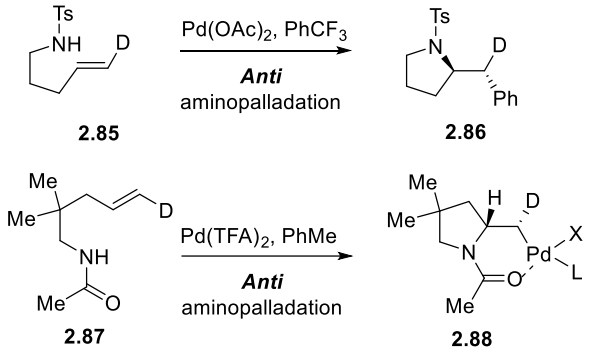


2.84

Figure 2-1 Chair-like transition state model

Before we determine the final optimal model, we still need to confirm a prerequisite: the alkene aminopalldation step is syn, anti, or a mixture of the two? A possible mode for anti-addition is through dissociation of N–Pd bond possibly induced by the Lewis acid, to

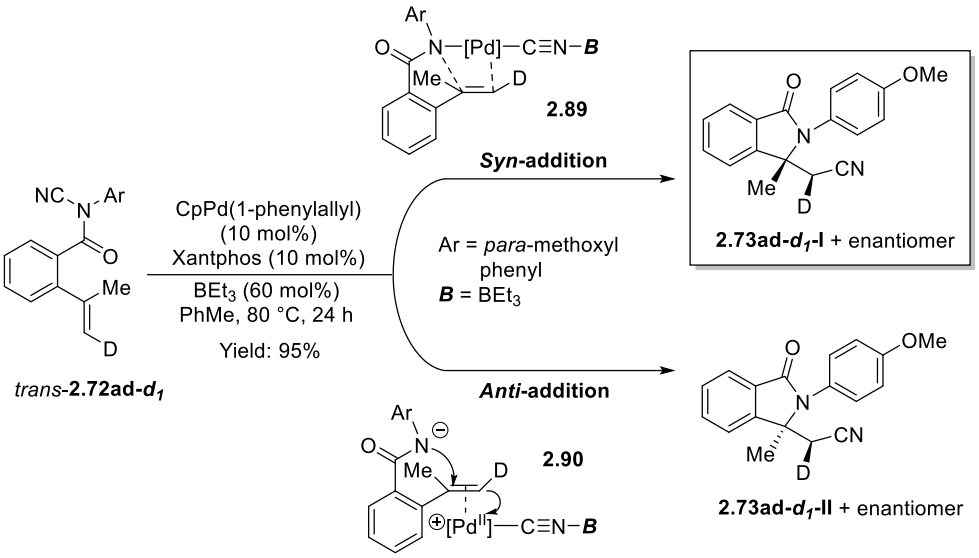
form an alkene complex, followed by attack of nitrogen on the alkene. This would be consistent with our null observation on cyano group crossover, if it occurred by the formation of a tight ion pair (**Scheme 2-17**). Anti-aminopalladation was also discovered in the case of Pd-catalyzed alkene carboamination reactions of *N*-tosyl-pent-4-enylamines[17] and *N*-acyl-pent-4-enylamines.[37,38] The mix of syn- and anti-addition is still possible: Stahl has illustrated that alkene aminopalladation of Pd(II)–sulfonamidate complexes are reversible,[39] and Wolfe et al. also found that electron-withdrawing N-substituents can slow the rate of syn-aminopalladation process.[17,40]



Scheme 2-17 Examples for anti-aminopalladation

To gain the further insight into the diastereoselectivity of the aminocyanation reactions, we studied the stereochemistry of the alkene addition step. (**Scheme 2-18**) We designed a terminal mono-deuterated substrate (*trans*-**2.72ad-*d*$_1$**) to examine how the N–Pd bond inserts into the alkene. **2.72ad** was chosen as the target due to its quantitative yield and rigid structure, which may help to directly obtain the stereochemistry without any further chemo-decoration, possibly leading to an inversion of the configuration at the deuterated carbon center. The mono-deuterated terminal alkene can be obtained via

zirconium-mediated methylalumination of alkyne,[41] followed by quenching with D_2O, to give 97% D.



Scheme 2-18 Studies on aminopalladation of *trans*-**2.72ad-*d*$_1$**

The structures of the possible products (**2.73ad-*d*$_1$-I** and 2**.73ad-*d*$_1$-II**) are shown in Scheme 5. Aminocyanation of *trans*-**2.72ad-*d*$_1$** yielded a single diastereomer, however, assigning the position of deuterium in **2.73ad-*d*$_1$** was challenging due to the exocyclic stereogenic center. The ^{1}H-NMR spectrum of unlabeled **2.73ad** showed the diastereotopic protons (Atom 13 and 31 in **Figure 2-2**[42]) as well-resolved signals (δ = 2.89, 2.70 ppm), showing that the two protons are in distinct electronic environments. Thus, we hypothesized that the two diastereotopic protons could be assigned by 1D nOe experiments. As expected, the downfield diastereotopic proton in **2.73ad** shows the through-space interactions with aromatic proton 24 on the isoindoline and 32/35 on the *para*-methoxyphenyl group. The upfield diastereotopic proton is only observed to enhance the

signal of proton 32/35 on the *para*-methoxyphenyl group. We also ran an nOe experiment for the only proton α to the nitrile (δ= 2.88 ppm) in the ^{1}H-NMR of **2.73ad-*d*$_1$**, and we observed nOe for aromatic proton 24 and 32/35. These data support the assignment of our labeled product as **2.73ad-*d*$_1$-I**, assuming a conformation where the methyl and nitrile groups are *anti*. This assumption seemed reasonable, but we sought additional data to confirm our assignment.

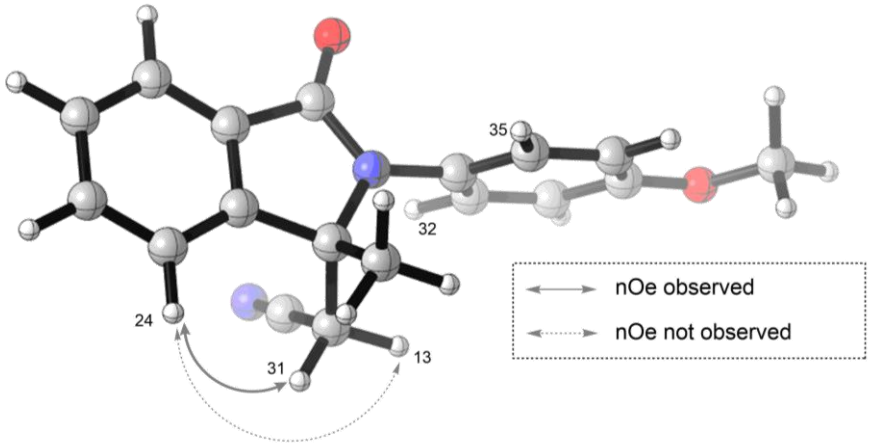
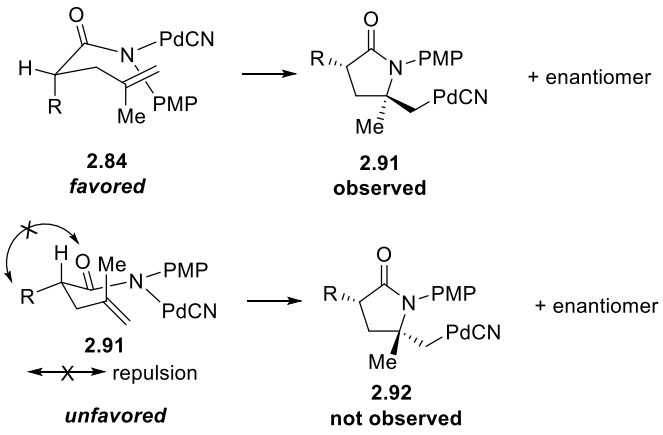


Figure 2-2 Optimal geometry of **2.73ad** and nOe results

To bolster our assignment of **2.73ad-*d*$_1$**, we utilized computational methods[43] to predict the chemical shifts of the diastereotopic protons in **2.73ad**. Conformational minimization *in silico* confirmed our assumptions about the *anti*-orientation of the nitrile and methyl group in the dominant conformers. The diastereotopic protons (labeled as 31 and 13 in **Figure 2-2**) were respectively predicted at δ = 2.80 and 2.62 ppm (Δδ = 0.18 ppm), while the experimental chemical shifts are δ = 2.89, 2.70 ppm (Δδ = 0.19 ppm) in the ^{1}H-NMR of **2.73ad**. Compared with the spectrum of **2.73ad-*d*$_1$**, the more upfield peak

around 2.70 ppm is not observed, confirming that proton 13 is the one labeled as deuterium. Combined with nOe results, we assign **2.73ad-d_1-I** as the diastereomer produced by of aminocyanation of *trans*-**2.72ad-d_1**. These results are consistent with the alkene addition proceeding via a *syn*-addition pathway.



Scheme 2-19 Proposed model for the diastereoselectivity

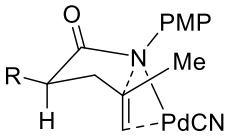
Based on *syn*-aminopalladation, we proposed a model (shown in **Scheme 2-19**) to elucidate the origin of the diastereoselectivity. During the ring-forming step, the molecule may adopt a chair-like conformation. The alkene needs to be aligned parallel to the N–Pd bond, in order to facilitate the following migratory insertion. Meanwhile, the larger substituent adjacent to the carbonyl prefers to be oriented in a pseudoaxial position to minimize $A_{1,3}$-strain between the R-group and the carbonyl. Hence, the cyclization reactions afforded the diastereomers we observed (**2.73al–2.73ap**). Similar model with pseudoaxial substituents in chair conformation was also reported by Wolfe et al.[44]

We recently revised the proposed chair-like model above, using the more favorable half-chair geometry for cyclopentanones (**Figure 2-3**).[45] Based on Hammond postulate,[46] if the cyclization is an endothermic reaction, the structure of transition state more closely resembles the product. Hence, the α-substituent to the carbonyl now lies in a favorable pseudo-equatorial orientation. To obviate 1,3-diaxial interaction with the axial proton, the aryl group on nitrogen prefers to reside in pseudo-equatorial as well. However, we still need more computational studies on the energy of the cyclic product support the hypothesis.

2.93 ***Favored*** **2.94** ***Unfavored***

Figure 2-3 Half-chair transition state models

In addition, we also initially proposed a boat-like transition state. Due to the less stability than chair-like conformers, there are only a few reports[40,47] adopting the boat-like geometry as the favored transition state in the generation of 6-membered rings. Moreover, $A_{1,3}$-strain between the R-group and the carbonyl still exists in the boat-like model. (**Figure 2-4**)



2.95

Figure 2-4 Boat-like transition state model

2.5 Conclusion and Future work

In summary, we developed an intramolecular aminocyanation of alkenes by N–CN bond activation of *N*-acyl and *N*-sulfonyl cyanamides, accessing a broad range of nitrogen-containing heterocycles, including pyrrolidones, piperidinones, isoindolinones, and sultams. The synthetic utility of the method was demonstrated in a variety of transformations of the resulting lactam heterocycles, including those leading to medicinally relevant intermediates. Additionally, diastereoselective aminocyanation reactions, previously underdeveloped, were successfully applied to the formation of densely substituted pyrrolidones. We have shown through isotope labeling experiments that the reaction proceeds via a *syn*-addition pathway and that the cyclization is intramolecular due to the lack of cross-over in cyanide labeled experiments. These data add clarity to the mechanistic picture for the N–CN bond activation and functionalization promoted by palladium and Lewis acid catalysts.

2.6 Experimental Section

2.6.1 General details

Unless otherwise noted, all reactions were carried out using oven-dried glassware under a nitrogen atmosphere. Dichloromethane (CH_2Cl_2) and toluene were distilled from CaH_2 prior to use. Tetrahydrofuran (THF) was distilled from Na/benzophenone prior to use. *m*-Xylene and toluene were further degassed by bubbling a stream of argon through

the liquid in a Strauss flask and then stored in a nitrogen-filled glove box. Acetonitrile (CH_3CN), benzene, methanol (MeOH), anhydrous *N*,*N*-dimethylformamide (DMF) and anhydrous diethyl ether (Et_2O) were purchased from Sigma-Aldrich and Alfa Aesar, and used without further purification. Unless otherwise noted, all chemicals were purchased from commercial sources and used as received. All transition-metal complexes, except for CpPd(1-phenylallyl), were purchased from Sigma-Aldrich or Strem and used as received. CpPd(1-phenylallyl) was synthesized following a known procedure.[35] Triphenylborane (BPh_3) was purchased from Strem and recrystallized from anhydrous heptanes under nitrogen.[48] Tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] was purchased from Strem and used as received.

Analytical thin-layer chromatography (TLC) and preparative thin-layer chromatography were carried out using 250 μm and 1000 μm silica plates (SiliCycle), respectively. Eluted plates were visualized first with a UV lamp (254 nm) and then stained with potassium permanganate, iodine, or bromocresol green. Flash column chromatography was performed using 230–400 mesh (particle size 40–63 μm) silica gel purchased from SiliCycle.

^{1}H NMR (400 and 500 MHz), ^{13}C NMR (75 and 125 MHz), and ^{19}F NMR (375 and 470 MHz) spectra were obtained on Varian Inova and Bruker Avance instruments. ^{1}H NMR spectra data were reported as δ values in ppm relative to TMS (δ 0.00) or chloroform (7.26) if collected in $CDCl_3$, or dimethyl sulfoxide (δ 2.50) if collected in DMSO-d_6. ^{13}C NMR spectra data were reported as δ values in ppm relative to chloroform (δ 77.00) if

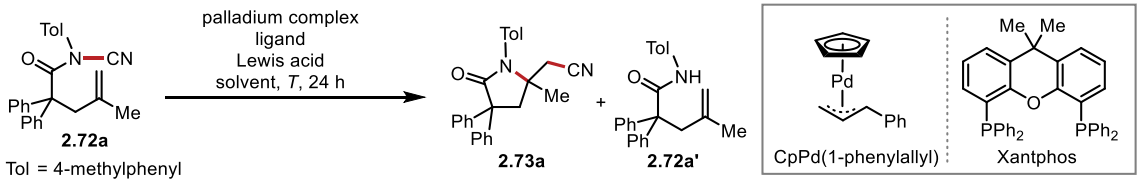
collected in $CDCl_3$ or dimethyl sulfoxide (δ 39.50) if collected in DMSO-d_6. ^{19}F NMR spectra data were reported as δ values in ppm using instrument standard. ^1H NMR coupling constants were reported in Hz, and multiplicity was indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); quint (quintet); m (multiplet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dddd (doublet of doublet of doublet of doublets); dt (doublet of triplets); td (triplet of doublets); ddt (doublet of doublet of triplets); dq (doublet of quartets); app (apparent); br (broad). Raw NMR data files or processed NMR data files, referred to as ".mnova files" in the tables below, are available from the corresponding author upon request. Infrared (IR) spectra were obtained on a MIDAC FT-IR spectrometer. A thin-film of sample was prepared by evaporating solvent (CH_2Cl_2 or $CDCl_3$) on NaCl plates. High-resolution mass spectra (HRMS) in electrospray ionization (ESI) experiments were performed on a Bruker BioTOF II (Time-of-flight) instrument using PEG-300, PEG-400 or PPG-400 as an internal standard.

2.6.2 Optimization of aminocyanation conditions

A general procedure: In a nitrogen-filled glove box, a one-dram vial was charged with a magnetic stirring bar, substrate **2.72a** (38.1 mg, 0.1 mmol), BPh_3 (9.7 mg, 0.04 mmol), Xantphos (5.8 mg, 0.01 mmol), and a solution of CpPd(1-phenylallyl) in toluene (0.02 M, 0.5 mL, 0.01 mmol). The reaction mixture was sealed with a PTFE lined cap, removed from the glove box, and heated in an aluminum heating block for 24 h. The resulting mixture was allowed to cool to room temperature and a stock solution of *p*-methoxyacetophenone (0.1 M in toluene, 0.3 mL, 0.03 mmol) was added as the internal

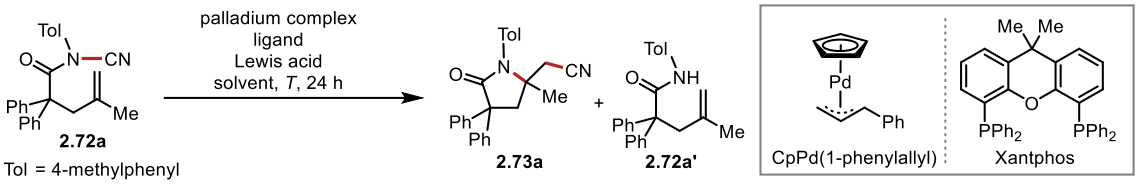
NMR-standard. The resulting mixture was concentrated in vacuo and the yield of **2.73a** was determined by ^{1}H NMR analysis. The isolated yield was obtained by concentrating the crude mixture onto Celite, followed by flash column chromatography.

Table 2-7 Optimization of aminocyanation of N-acyl cyanamide **2.72a**



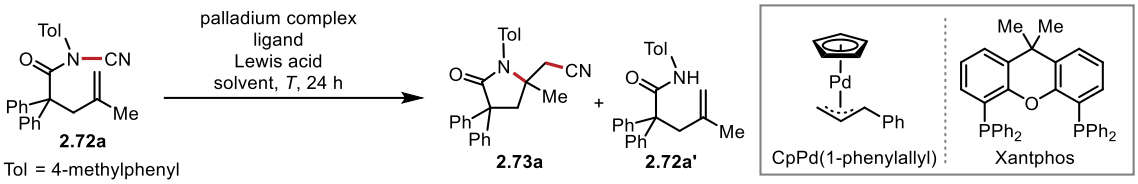
Entry	Palladium[a]	Ligand[b]	Lewis acid (equiv.)	Solvent	*T* (°C)	Yield of 2.73a (%)[c]
1	CpPd(1-phenylallyl)	Xantphos	BPh_3 (0.5)	PhMe	90	87[d]
2	$Pd(OAc)_2$	Xantphos	BPh_3 (0.5)	PhMe	90	67
3	$Pd(TFA)_2$	Xantphos	BPh_3 (0.5)	PhMe	90	17
4	$[Pd(allyl)Cl]_2$	Xantphos	BPh_3 (0.4)	PhMe	100	0[e]
5	Pd_2dba_3	Xantphos	BPh_3 (0.5)	PhMe	90	69
6	$Pd(PPh_3)_4$	–	BPh_3 (0.5)	PhMe	90	81
7	CpPd(1-phenylallyl)	Xantphos[f]	$B(C_6F_5)_3$ (0.5)	PhMe	100	0[e]
8	CpPd(1-phenylallyl)	Xantphos[f]	$AlMe_2Cl$ (0.5)	PhMe	100	0[e]
9	CpPd(1-phenylallyl)	Xantphos[f]	$AlCl_3$ (0.5)	PhMe	100	0[e]
10	CpPd(1-phenylallyl)	Xantphos[f]	$ZnCl_2$ (0.5)	PhMe	100	0[g]
11	CpPd(1-phenylallyl)	Xantphos[f]	$Zn(OTf)_2$ (0.5)	PhMe	100	0[g]
12	CpPd(1-phenylallyl)	dppe	BPh_3 (0.4)	PhMe	80	0[e]

Table 2-7 Optimization of aminocyanation of N-acyl cyanamide **2.72a**



Entry	Palladium[a]	Ligand[b]	Lewis acid (equiv.)	Solvent	*T* (°C)	Yield of 2.73a (%)[c]
13	CpPd(1-phenylallyl)	dppp	BPh_3 (0.4)	PhMe	80	23
14	CpPd(1-phenylallyl)	dppb	BPh_3 (0.4)	PhMe	80	49
15	CpPd(1-phenylallyl)	DPEphos	BPh_3 (0.4)	PhMe	80	72
16	CpPd(1-phenylallyl)	Xantphos	BPh_3 (0.4)	PhMe	80	93
17	CpPd(1-phenylallyl)	Nixantphos	BPh_3 (0.4)	PhMe	80	81
18	CpPd(1-phenylallyl)	DBFphos	BPh_3 (0.4)	PhMe	80	0[e]
19	CpPd(1-phenylallyl)	Xantphos[f]	BPh_3 (0.4)	THF	80	26
20	CpPd(1-phenylallyl)	Xantphos[f]	BPh_3 (0.4)	$PhCF_3$	80	0[g]
21	CpPd(1-phenylallyl)	Xantphos[f]	BPh_3 (0.4)	dioxane	80	20
22	CpPd(1-phenylallyl)	Xantphos[f]	BPh_3 (0.4)	1,2-DCE	80	0[e]
23	CpPd(1-phenylallyl)	Xantphos[f]	BPh_3 (0.4)	DMF	80	0[g]
24	CpPd(1-phenylallyl)	Xantphos[f]	BPh_3 (0.4)	cyclohexane	80	85
25	CpPd(1-phenylallyl)	Xantphos	–	PhMe	80	< 20[h]
26	–	–	BPh_3 (0.5)	PhMe	100	0[e]

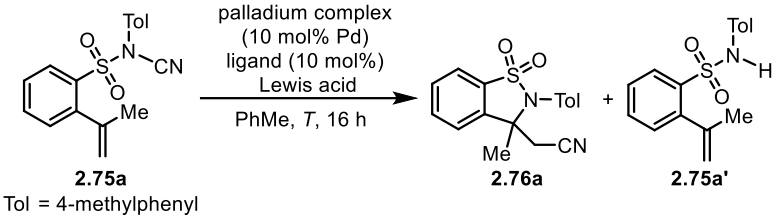
Table 2-7 Optimization of aminocyanation of N-acyl cyanamide **2.72a**



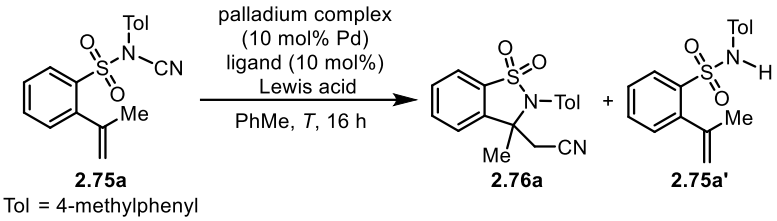
Entry	Palladium[a]	Ligand[b]	Lewis acid (equiv.)	Solvent	*T* (°C)	Yield of 2.73a (%)[c]
27	–	–	$B(C_6F_5)_3$ (0.5)	PhMe	80	0[e]
28	–	–	$AlCl_3$ (0.5)	PhMe	80	0[h]
29	CpPd(1-phenylallyl)	Xantphos	BPh_3 (0.4)	PhMe	80	89
30	CpPd(1-phenylallyl)	Xantphos	BEt_3 (0.4)	PhMe	80	99

[a]10mol% palladium complex. [b]10 mol% ligand. [c]Determined by ^{1}H NMR analysis using *p*-methoxyacetophenone as the internal standard. [d]Isolated yiled after column chromatography. [e]Only **2.72a** and **2.72a'** detected by NMR spectroscopy. [f]15mol% Xantphos. [g]Unconsumed **2.72a**. [h]Complex reaction mixture.

Table 2-8 Optimization of aminocyanation of N-acyl cyanamide **2.75a**



Entry	Palladium	Ligand	Lewis acid (equiv.)	*T* (°C)	Yield of 2.76a (%)[a]
1	–	–	$B(C_6F_5)_3$ (1.0)	100	0[b]
2	–	–	BF_3•OEt_2 (1.0)	100	0[b]
3	–	–	BPh_3 (0.4)	100	0[b]
4	$Pd(OAc)_2$	Xantphos	BPh_3 (0.4)	100	69
5	$Pd(PPh_3)_4$	Xantphos	BPh_3 (0.4)	100	32
6	$Pd(TFA)_2$	Xantphos	BPh_3 (0.4)	100	63
7	Pd_2dba_3	Xantphos	BPh_3 (0.4)	100	85

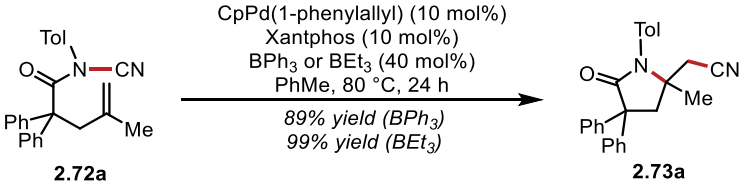


2.75a Tol = 4-methylphenyl **2.76a** **2.75a'**

Entry	Palladium	Ligand	Lewis acid (equiv.)	*T* (°C)	Yield of 2.76a (%)[a]
8	Pd_2dba_3	Xantphos	BPh_3 (0.4)	90	95
9	Pd_2dba_3	Xantphos	BPh_3 (0.4)	80	99[c]
10	Pd_2dba_3	Xantphos	BPh_3 (0.4)	70	78
11	Pd_2dba_3	Xantphos	–	100	0[b]

[a]Determined by ^1H NMR analysis using DMSO-d_6 as the solvent and *p*-methoxyacetophenone as the internal standard. [b]Unconsumed starting material. [c]Isolated yield after column chromatography.

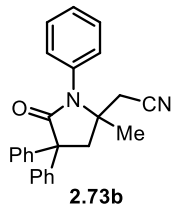
2.6.3 Results of aminocyanation reactions



2.72a **2.73a**

Aminocyanation of 2.72a as a representative example: In a nitrogen-filled glove box, a one-dram vial was charged with a magnetic stirring bar, cyanamide **2.72a** (76.2 mg, 0.2 mmol), BPh_3 or BEt_3 (BPh_3: 19.4 mg, 0.08 mmol; BEt_3: 1.0 M in Hex, 80 µL, 0.08 mmol), Xantphos (11.6 mg, 0.02 mmol), and a solution of CpPd(1-phenylallyl) in toluene (0.02 M, 1.0 mL, 0.02 mmol). The reaction mixture was sealed with a PTFE lined cap, removed from the glove box, and heated at 80 °C in an aluminum heating block for 24 h. The resulting mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 (5

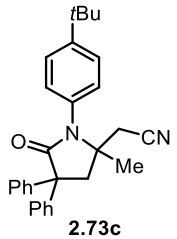
mL), and concentrated onto Celite. The crude product was purified by gradient flash column chromatography (1:9 → 15:85 EtOAc/Hex) to afford **2.73a** as a pale yellow foam (0.198 mmol, 99% yield with BEt_3). R_f = 0.32 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.7 Hz, 2H), 7.46 (d, *J* = 7.7 Hz, 2H), 7.35 (dt, *J* = 13.2, 7.6 Hz, 4H), 7.29 – 7.22 (m, 4H), 7.03 (d, *J* = 7.8 Hz, 2H), 3.33 (d, *J* = 13.7 Hz, 1H), 3.00 (d, *J* = 13.7 Hz, 1H), 2.42 (d, *J* = 16.6 Hz, 1H), 2.37 (s, 3H), 2.33 (d, *J* = 16.5 Hz, 1H), 1.33 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.9, 142.9, 142.8, 138.9, 132.2, 130.3, 129.2, 128.8, 128.5, 127.7, 127.6, 127.2, 127.0, 116.8, 59.8, 56.9, 46.7, 29.3, 26.5, 21.1; **HRMS** (ESI) calcd for $[C_{26}H_{24}N_2O + Na]^+$ 403.1781, found 403.1786; **IR** (thin film) 2247, 1697, 1513, 1373.



2.73b

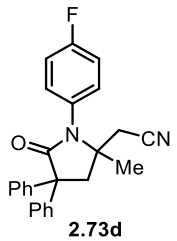
Prepared from **2.72b** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (40 mol%) in toluene at 80 °C for 24 h. **2.73b** was purified by gradient flash column chromatography (1:9 → 15:85 EtOAc/Hex) as an off-white foam (0.192 mmol, 96% yield). R_f = 0.24 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 – 7.49 (m, 2H), 7.50 – 7.31 (m, 9H), 7.28 (td, *J* = 7.7, 7.1, 1.7 Hz, 2H), 7.20 – 7.14 (m, 2H), 3.36 (d, *J* = 13.8 Hz, 1H), 3.03 (d, *J* = 13.7 Hz, 1H), 2.44 (d, *J* = 16.5 Hz, 1H), 2.36 (d, *J* = 16.6 Hz, 1H), 1.36 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.0, 142.9, 142.7,

135.0, 129.7, 129.5, 128.9, 128.8, 128.6, 127.7, 127.6, 127.3, 127.1, 116.8, 59.9, 56.9, 46.8, 29.4, 26.6; **HRMS** (ESI) calcd for $[C_{25}H_{22}N_2O + Na]^+$ 389.1624, found 389.1625; **IR** (thin film) 2247, 1697, 1493, 1371.



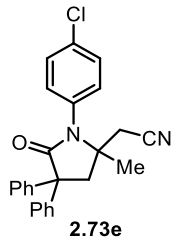
2.73c

Prepared from **2.72c** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (40 mol%) in toluene at 80 °C for 24 h. **2.73c** was purified by gradient flash column chromatography (1:9 → 1:4 EtOAc/Hex) as a pale yellow foam (0.186 mmol, 93% yield). R_f = 0.51 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.1 Hz, 2H), 7.46 (ddd, *J* = 8.3, 3.8, 1.3 Hz, 4H), 7.39 – 7.23 (m, 6H), 7.08 (d, *J* = 7.1 Hz, 2H), 3.34 (d, *J* = 1.2 Hz, 1H), 3.02 (d, *J* = 1.1 Hz, 1H), 2.43 (d, *J* = 1.1 Hz, 1H), 2.36 (d, *J* = 16.5 Hz, 1H), 1.36 (d, *J* = 1.2 Hz, 3H), 1.33 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.0, 151.9, 143.0, 142.7, 132.1, 128.9, 128.8, 128.5, 127.7, 127.6, 127.3, 127.0, 126.7, 116.9, 59.9, 56.9, 46.7, 34.7, 31.2, 29.3, 26.6; **HRMS** (ESI) calcd for $[C_{29}H_{30}N_2O + Na]^+$ 445.2250, found 445.2244; **IR** (thin film) 2247, 1696, 1510, 1372.



2.73d

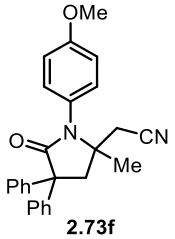
Prepared from **2.72d** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (40 mol%) in toluene at 80 °C for 24 h. **2.73d** was purified by flash column chromatography (1:9 → 1:4 EtOAc/Hex) as a pale yellow foam (0.180 mmol, 90% yield). R_f = 0.29 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.7 Hz, 2H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.36 (dt, *J* = 10.6, 7.6 Hz, 4H), 7.28 (t, *J* = 7.1 Hz, 2H), 7.15 (d, *J* = 6.6 Hz, 4H), 3.34 (d, *J* = 13.7 Hz, 1H), 3.03 (d, *J* = 13.7 Hz, 1H), 2.43 (d, *J* = 16.6 Hz, 1H), 2.35 (d, *J* = 16.6 Hz, 1H), 1.34 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.2, 162.6 (d, $^1J_{F-C}$ = 249.2 Hz), 142.7, 142.6, 131.4 (d, $^3J_{F-C}$ = 8.7 Hz), 130.9 (d, $^4J_{F-C}$ = 3.2 Hz), 128.9, 128.6, 127.7, 127.6, 127.4, 127.2, 116.8 (d, $^2J_{F-C}$ = 22.8 Hz), 116.6, 59.9, 56.9, 46.7, 29.4, 26.5; **^{19}F NMR** (470 MHz, $CDCl_3$) δ –111.9; **HRMS** (ESI) calcd for $[C_{25}H_{21}FN_2O + Na]^+$ 407.1530, found 407.1536; **IR** (thin film) 2247, 1698, 1509, 1374, 1221.



2.73e

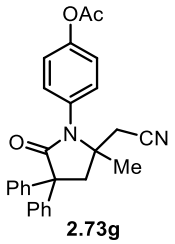
Prepared from **2.72e** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BPh_3 (60 mol%) in toluene at 80 °C for 24 h. **2.73e** was purified by flash column chromatography (1:9 → 15:85 EtOAc/Hex) as an off-white foam (0.172 mmol, 86% yield). R_f = 0.32 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 – 7.41 (m, 6H), 7.36 (dt, *J* = 10.3, 7.6 Hz, 4H), 7.30 – 7.26 (m, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 3.34

(d, *J* = 13.7 Hz, 1H), 3.02 (d, *J* = 13.7 Hz, 1H), 2.42 (d, *J* = 16.6 Hz, 1H), 2.34 (d, *J* = 16.5 Hz, 1H), 1.33 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.0, 142.6, 142.5, 135.0, 133.6, 130.8, 130.0, 128.9, 128.6, 127.6, 127.5, 127.4, 127.2, 116.6, 59.9, 56.9, 46.7, 29.4, 26.6; **HRMS** (ESI) calcd for $[C_{25}H_{21}ClN_2O + Na]^+$ 423.1235, found 423.1236; **IR** (thin film) 2247, 1698, 1493, 1371.



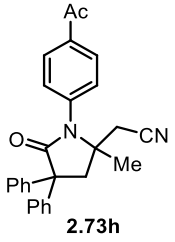
2.73f

Prepared from **2.72f** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (40 mol%) in toluene at 80 °C for 24 h. **2.73f** was purified by flash column chromatography (1:3 EtOAc/Hex) as a pale yellow oil (0.190 mmol, 95% yield). R_f = 0.32 (3:7 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.35 (dt, *J* = 12.5, 7.6 Hz, 4H), 7.30 – 7.24 (m, 2H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H), 3.33 (d, *J* = 13.7 Hz, 1H), 3.00 (d, *J* = 13.7 Hz, 1H), 2.42 (d, *J* = 16.6 Hz, 1H), 2.34 (d, *J* = 16.6 Hz, 1H), 1.33 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.1, 159.7, 143.0, 142.8, 130.6, 128.8, 128.5, 127.7, 127.6, 127.4, 127.2, 127.0, 116.9, 114.9, 59.8, 56.8, 55.5, 46.6, 29.3, 26.5; **HRMS** (ESI) calcd for $[C_{26}H_{24}N_2O_2 + Na]^+$ 419.1730, found 419.1736; **IR** (thin film) 2247, 1696, 1512, 1375, 1251.



2.73g

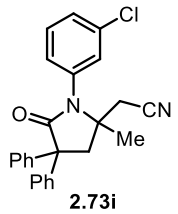
Prepared from **2.72g** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (40 mol%) in toluene at 80 °C for 24 h. **2.73g** was purified by flash column chromatography (1:3 → 45:55 EtOAc/Hex) as an off-white foam (0.180 mmol, 90% yield). R_f = 0.59 (1:1 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.7 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.39 – 7.32 (m, 4H), 7.30 – 7.26 (m, 2H), 7.23 – 7.15 (m, 4H), 3.36 (d, *J* = 13.8 Hz, 1H), 3.03 (d, *J* = 13.7 Hz, 1H), 2.45 (d, *J* = 16.5 Hz, 1H), 2.37 (d, *J* = 16.6 Hz, 1H), 2.31 (s, 3H), 1.34 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.1, 169.0, 150.8, 142.7, 142.6, 132.4, 130.6, 128.8, 128.6, 127.7, 127.6, 127.3, 127.1, 122.9, 116.7, 60.0, 57.0, 46.7, 29.4, 26.6, 21.1; **HRMS** (ESI) calcd for $[C_{27}H_{24}N_2O_3 + Na]^+$ 447.1679, found 447.1682; **IR** (thin film) 2247, 1755, 1698, 1507, 1371, 1196.



2.73h

Prepared from **2.72h** on a 0.2 mmol scale with CpPd(1-phenylallyl) (15 mol%), Xantphos (15 mol%), and BEt_3 (100 mol%) in toluene at 70 °C for 30 h. **2.73h** was purified by flash column chromatography (1:4 → 3:7 EtOAc/Hex) as a pale yellow foam (0.134

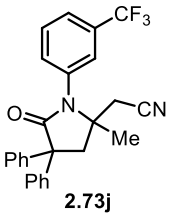
mmol, 67% yield). R_f = 0.36 (4:6 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.37 (dt, *J* = 11.6, 7.7 Hz, 4H), 7.29 (t, *J* = 7.6 Hz, 4H), 3.38 (d, *J* = 13.8 Hz, 1H), 3.06 (d, *J* = 13.7 Hz, 1H), 2.62 (s, 3H), 2.46 (d, *J* = 16.6 Hz, 1H), 2.38 (d, *J* = 16.6 Hz, 1H), 1.38 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.0, 175.0, 142.5, 142.4, 139.6, 137.1, 129.7, 129.6, 128.9, 128.7, 127.6, 127.5, 127.4, 127.2, 116.5, 60.2, 57.0, 46.9, 29.5, 26.8, 26.7; **HRMS** (ESI) calcd for $[C_{27}H_{24}N_2O_2 + Na]^+$ 431.1730, found 431.1733; **IR** (thin film) 2247, 1687, 1600, 1367, 1266.



2.73i

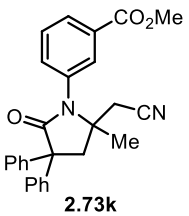
Prepared from **2.72i** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (80 mol%) in toluene at 70 °C for 24 h. **2.73i** was purified by flash column chromatography (1:9 → 15:85 EtOAc/Hex) as a white foam (0.152 mmol, 76% yield). R_f = 0.31 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.7 Hz, 2H), 7.46 – 7.32 (m, 8H), 7.31 – 7.26 (m, 2H), 7.17 (t, *J* = 1.3 Hz, 1H), 7.12 – 7.07 (m, 1H), 3.36 (d, *J* = 13.7 Hz, 1H), 3.03 (d, *J* = 13.7 Hz, 1H), 2.44 (d, *J* = 16.6 Hz, 1H), 2.36 (d, *J* = 16.6 Hz, 1H), 1.36 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.0, 142.6, 142.4, 136.3, 135.2, 130.7, 129.7, 129.3, 128.9, 128.6, 127.9, 127.6, 127.5, 127.4, 127.2, 116.5,

60.0, 56.9, 46.8, 29.4, 26.6; **HRMS** (ESI) calcd for $[C_{25}H_{21}ClN_2O + Na]^+$ 423.1235, found 423.1234; **IR** (thin film) 2248, 1699, 1478, 1368.



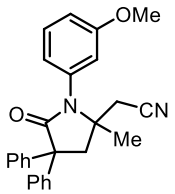
2.73j

Prepared from **2.72j** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (60 mol%) in toluene at 70 °C for 24 h. **2.73j** was purified by flash column chromatography (1:9 → 1:4 EtOAc/Hex) as a pale yellow foam (0.172 mmol, 86% yield). R_f = 0.29 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.9 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 2H), 7.47 – 7.33 (m, 8H), 7.29 (dd, *J* = 8.8, 7.2 Hz, 2H), 3.37 (d, *J* = 13.8 Hz, 1H), 3.05 (d, *J* = 13.7 Hz, 1H), 2.43 (d, *J* = 16.6 Hz, 1H), 2.36 (d, *J* = 16.6 Hz, 1H), 1.37 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.1, 142.5, 142.4, 135.8, 133.2, 132.2 (q, $^2J_{F–C}$ = 33.0 Hz), 130.4, 128.9, 128.7, 127.6, 127.51, 127.46, 127.3, 126.2 (q, $^3J_{F–C}$ = 3.7 Hz), 125.8 (q, $^3J_{F–C}$ = 3.8 Hz), 122.4 (q, $^1J_{F–C}$ = 270.9 Hz), 116.4, 60.1, 57.0, 46.8, 29.5, 26.7; **^{19}F NMR** (470 MHz, $CDCl_3$) δ –62.6; **HRMS** (ESI) calcd for $[C_{26}H_{21}F_3N_2O + Na]^+$ 457.1498, found 457.1502; **IR** (thin film) 2249, 1700, 1328, 1129.



2.73k

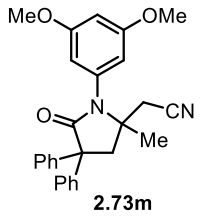
Prepared from **2.72k** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (60 mol%) in toluene at 70 °C for 24 h. **2.73k** was purified by flash column chromatography (15:85 → 3:7 EtOAc/Hex) as a pale yellow foam (0.184 mmol, 92% yield). R_f = 0.39 (3:7 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.10 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.81 (t, *J* = 1.9 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.47 – 7.42 (m, 2H), 7.42 – 7.33 (m, 5H), 7.32 – 7.26 (m, 2H), 3.92 (s, 3H), 3.38 (d, *J* = 13.8 Hz, 1H), 3.04 (d, *J* = 13.7 Hz, 1H), 2.45 (d, *J* = 16.5 Hz, 1H), 2.39 (d, *J* = 16.5 Hz, 1H), 1.39 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.0, 165.9, 142.7, 142.4, 135.4, 134.2, 131.9, 130.3, 130.0, 129.9, 128.9, 128.6, 127.6, 127.5, 127.4, 127.1, 116.5, 60.0, 56.9, 52.4, 46.9, 29.4, 26.7; **HRMS** (ESI) calcd for $[C_{27}H_{24}N_2O_3 + Na]^+$ 447.1679, found 447.1683; **IR** (thin film) 2250, 1723, 1699, 1370, 1291.



2.73l

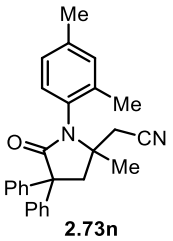
Prepared from **2.72l** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (40 mol%) in toluene at 80 °C for 24 h. **2.73l** was purified by flash column chromatography (15:85 → 1:4 EtOAc/Hex) as a yellow oil (0.168 mmol, 84% yield). R_f = 0.19 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 – 7.49 (m, 2H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.38 – 7.32 (m, 5H), 7.31 – 7.22 (m, 2H), 6.95 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.74 (dd, *J* = 7.7, 1.8 Hz, 1H), 6.71 (d, *J* = 2.3 Hz, 1H), 3.81 (s, 3H), 3.35 (d,

J = 13.7 Hz, 1H), 3.01 (d, *J* = 13.7 Hz, 1H), 2.45 (d, *J* = 16.6 Hz, 1H), 2.35 (d, *J* = 16.6 Hz, 1H), 1.34 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.8, 160.4, 142.8, 142.7, 136.1, 130.3, 128.8, 128.5, 127.7, 127.6, 127.3, 127.1, 121.5, 116.8, 115.6, 114.2, 59.9, 56.9, 55.4, 46.7, 29.4, 26.6; **HRMS** (ESI) calcd for $[C_{26}H_{24}N_2O_2 + Na]^+$ 419.1730, found 419.1732; **IR** (thin film) 2248, 1697, 1491, 1372, 1287, 1267.



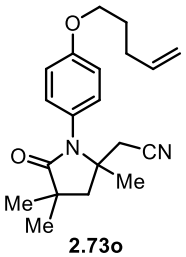
2.73m

Prepared from **2.72m** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (40 mol%) in toluene at 70 °C for 30 h. **2.73m** was purified by flash column chromatography (1:4 → 1:3 EtOAc/Hex) as a pale yellow foam (0.174 mmol, 87% yield). R_f = 0.36 (3:7 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.4 Hz, 2H), 7.46 (d, *J* = 7.5 Hz, 2H), 7.35 (dt, *J* = 9.7, 7.6 Hz, 4H), 7.30 – 7.24 (m, 2H), 6.50 (t, *J* = 2.3 Hz, 1H), 6.30 (d, *J* = 2.1 Hz, 2H), 3.79 (s, 6H), 3.35 (d, *J* = 13.7 Hz, 1H), 3.01 (d, *J* = 13.7 Hz, 1H), 2.49 (d, *J* = 16.6 Hz, 1H), 2.36 (d, *J* = 16.6 Hz, 1H), 1.34 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.6, 161.3, 142.8, 142.7, 136.6, 128.8, 128.6, 127.7, 127.6, 127.3, 127.1, 116.9, 107.8, 100.6, 59.9, 56.9, 55.5, 46.8, 29.4, 26.6; **HRMS** (ESI) calcd for $[C_{27}H_{26}N_2O_3 + Na]^+$ 449.1836, found 449.1837; **IR** (thin film) 2248, 1698, 1206, 1157.



2.73n

Prepared from **2.72n** on a 0.2 mmol scale with CpPd(1-phenylallyl) (15 mol%), Xantphos (15 mol%), and BEt_3 (100 mol%) in toluene at 70 °C for 48 h. **2.73n** was purified by flash column chromatography twice (first: 1:9 EtOAc/Hex; second: CH_2Cl_2) as a colorless oil (0.086 mmol, 43% yield). R_f = 0.49 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.42 – 7.33 (m, 4H), 7.31 – 7.26 (m, 2H), 6.97 (s, 1H), 6.95 (d, *J* = 1.1 Hz, 2H), 3.29 (d, *J* = 13.9 Hz, 1H), 3.05 (d, *J* = 13.9 Hz, 1H), 2.54 (d, *J* = 16.7 Hz, 1H), 2.49 (d, *J* = 16.7 Hz, 1H), 2.28 (s, 3H), 2.11 (s, 3H), 1.41 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.8, 143.3, 143.3, 142.8, 133.0, 130.9, 129.8, 128.7, 128.4, 128.0, 127.9, 127.4, 127.2, 126.5, 120.7, 116.4, 81.1, 58.6, 48.7, 30.2, 26.9, 20.9, 18.4; **HRMS** (ESI) calcd for $[C_{27}H_{26}N_2O + Na]^+$ 417.1937, found 417.1941; **IR** (thin film) 2253, 1698, 1494, 1125.

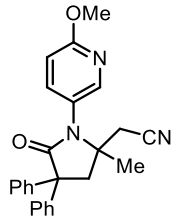


2.73o

Prepared from **2.72o** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (40 mol%) in toluene at 80 °C for 24 h. **2.73o** was purified

by flash column chromatography (1:4 → 2:3 EtOAc/Hex) as a colorless oil (0.168 mmol, 84% yield).* R_f = 0.31 (2:3 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.11 – 7.04 (m, 2H), 6.97 – 6.91 (m, 2H), 5.85 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.07 (dq, *J* = 17.1, 1.7 Hz, 1H), 5.01 (dq, *J* = 10.2, 1.4 Hz, 1H), 3.97 (t, *J* = 6.4 Hz, 2H), 2.48 (s, 2H), 2.32 (d, *J* = 13.7 Hz, 1H), 2.28 – 2.20 (m, 2H), 2.11 (d, *J* = 13.7 Hz, 1H), 1.94 – 1.84 (m, 2H), 1.43 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 179.6, 159.1, 137.6, 130.6, 127.3, 117.1, 115.33, 115.27, 67.3, 59.6, 46.5, 39.6, 30.8, 30.0, 28.3, 28.2, 27.8, 27.0; **HRMS** (ESI) calcd for $[C_{20}H_{26}N_2O_2 + Na]^+$ 349.1886, found 349.1881; **IR** (thin film) 2248, 1691, 1511, 1394, 1249.

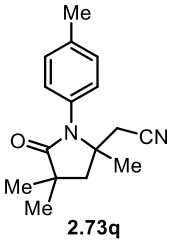
* Note: Product contained a small amount of impurity (ca. 5%) presumably resulting from olefin isomerization.



2.73p

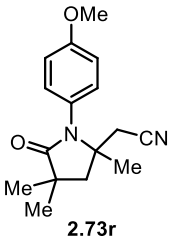
Prepared from **2.72p** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (80 mol%) in toluene at 80 °C for 24 h. **2.73p** was purified by flash column chromatography (15:85 → 3:7 EtOAc/Hex) as a pale yellow oil (0.192 mmol, 96% yield). R_f = 0.35 (3:7 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 (d, *J*

= 2.6 Hz, 1H), 7.49 – 7.46 (m, 2H), 7.45 – 7.43 (m, 2H), 7.41 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.36 (ddd, *J* = 11.2, 8.6, 7.0 Hz, 4H), 7.31 – 7.25 (m, 2H), 6.83 (d, *J* = 8.7 Hz, 1H), 3.95 (s, 3H), 3.34 (d, *J* = 13.7 Hz, 1H), 3.03 (d, *J* = 13.7 Hz, 1H), 2.41 (d, *J* = 16.6 Hz, 1H), 2.33 (d, *J* = 16.6 Hz, 1H), 1.33 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.5, 163.9, 147.3, 142.5, 142.5, 139.9, 128.9, 128.6, 127.6, 127.5, 127.4, 127.2, 125.1, 116.5, 111.9, 59.8, 56.9, 53.8, 46.6, 29.3, 26.4; **HRMS** (ESI) calcd for $[C_{25}H_{23}N_3O_2 + Na]^+$ 420.1682, found 420.1690; **IR** (thin film) 2248, 1698, 1494, 1385, 1285.



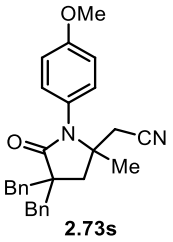
2.73q

Prepared from **2.72q** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (40 mol%) in toluene at 80 °C for 24 h. **2.73q** was purified by flash column chromatography (1:4 → 1:1 EtOAc/Hex) as pale yellow oil (0.186 mmol, 93% yield). R_f = 0.43 (1:1 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 2H), 7.09 – 7.04 (m, 2H), 2.49 (d, *J* = 1.5 Hz, 2H), 2.38 (s, 3H), 2.34 (d, *J* = 13.7 Hz, 1H), 2.12 (d, *J* = 13.7 Hz, 1H), 1.44 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 179.5, 138.7, 132.4, 130.3, 129.4, 117.1, 59.6, 46.7, 39.7, 30.9, 28.3, 27.8, 27.1, 21.1; **HRMS** (ESI) calcd for $[C_{16}H_{20}N_2O + Na]^+$ 279.1468, found 279.1467; **IR** (thin film) 2248, 1694, 1514, 1393.



2.73r

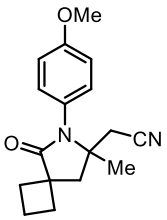
Prepared from **2.72r** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (40 mol%) in toluene at 80 °C for 24 h. **2.73r** was purified by flash column chromatography (30:70:0 → 30:70:0.5 EtOAc/Hex/MeOH) as a thick tan oil (0.176 mmol, 88% yield). R_f = 0.25 (1:1 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 3.82 (s, 3H), 2.48 (app s, 2H), 2.32 (d, *J* = 13.7 Hz, 1H), 2.11 (d, *J* = 13.7 Hz, 1H), 1.43 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 179.6, 159.6, 130.7, 127.5, 117.1, 114.8, 59.6, 55.4, 46.5, 39.6, 30.8, 28.2, 27.8, 27.0; **HRMS** (ESI) calcd for $[C_{16}H_{20}N_2O_2 + Na]^+$ 295.1417, found 295.1413; **IR** (thin film) 2247, 1693, 1513, 1394, 1251.



2.73s

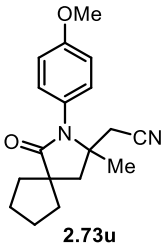
Prepared from **2.72s** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (80 mol%) in toluene at 70 °C for 48 h. **2.73s** was purified by flash column chromatography (1:9 → 3:7 EtOAc/Hex) as a pale yellow oil (0.164 mmol, 82% yield). R_f = 0.32 (3:7 EtOAc/Hex); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.26 (m,

10H), 6.89 – 6.82 (m, 2H), 6.58 – 6.51 (m, 2H), 3.77 (s, 3H), 3.49 (d, *J* = 13.0 Hz, 2H), 2.64 (d, *J* = 11.6 Hz, 1H), 2.61 (d, *J* = 11.6Hz, 1H), 2.31 (d, *J* = 14.5 Hz, 1H), 2.12 (d, *J* = 14.5 Hz, 1H), 1.56 (d, *J* = 16.0 Hz, 1H), 0.43 (d, *J* = 16.1 Hz, 1H), 0.36 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.7, 159.6, 137.9, 137.5, 130.91, 130.89, 130.5, 128.6, 128.3, 127.4, 127.2, 127.1, 117.0, 114.7, 58.9, 55.4, 51.9, 44.9, 44.8, 36.2, 29.2, 25.9; **HRMS** (ESI) calcd for $[C_{28}H_{28}N_2O_2 + Na]^+$ 447.2043, found 447.2036; **IR** (thin film) 2250, 1689, 1512, 1249.



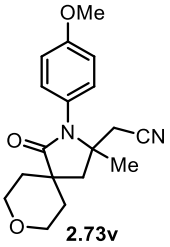
2.73t

Prepared from **2.72t** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (60 mol%) in toluene at 70 °C for 24 h. **2.73t** was purified by flash column chromatography (30:70:0.5 → 30:70:1 EtOAc/Hex/MeOH) as a pale yellow oil (0.186 mmol, 93% yield). R_f = 0.19 (30:70:0.5 EtOAc/Hex/MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.08 – 7.02 (m, 2H), 6.98 – 6.92 (m, 2H), 3.82 (s, 3H), 2.70 – 2.57 (m, 2H), 2.51 (d, *J* = 13.4 Hz, 1H), 2.48 (d, *J* = 16.7 Hz, 1H), 2.43 (d, *J* = 16.7 Hz, 1H), 2.33 (d, *J* = 13.4 Hz, 1H), 2.21 – 2.12 (m, 1H), 2.12 – 1.97 (m, 3H), 1.37 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 178.5, 159.5, 130.6, 127.5, 116.8, 114.8, 60.5, 55.4, 46.4, 44.6, 32.3, 31.6, 29.6, 26.8, 16.5; **HRMS** (ESI) calcd for $[C_{17}H_{20}N_2O_2 + Na]^+$ 307.1417, found 307.1415; **IR** (thin film) 2248, 1692, 1512, 1386, 1250.



2.73u

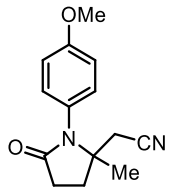
Prepared from **2.72u** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (100 mol%) in toluene at 80 °C for 36 h. **2.73u** was purified by flash column chromatography (20:80:1 → 20:80:2 EtOAc/Hex/MeOH) as a pale yellow oil (0.192 mmol, 96% yield). R_f = 0.16 (20:80:1 EtOAc/Hex/MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.12 – 7.04 (m, 2H), 6.98 – 6.92 (m, 2H), 3.82 (s, 3H), 2.52 (d, *J* = 16.5 Hz, 1H), 2.48 (d, *J* = 16.5 Hz, 1H), 2.34 (d, *J* = 13.4 Hz, 1H), 2.25 – 2.10 (m, 3H), 1.94 – 1.83 (m, 2H), 1.77 – 1.68 (m, 4H), 1.43 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 179.8, 159.5, 130.7, 127.6, 117.0, 114.8, 60.1, 55.4, 49.7, 47.1, 39.7, 39.2, 30.3, 27.5, 25.54, 25.46; **HRMS** (ESI) calcd for $[C_{18}H_{22}N_2O_2 + Na]^+$ 321.1573, found 321.1570; **IR** (thin film) 2246, 1691, 1513, 1387, 1250.



2.73v

Prepared from **2.72v** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (60 mol%) in toluene at 80 °C for 24 h. **2.73v** was purified by flash column chromatography (40:60:0 → 50:50:2 EtOAc/Hex/MeOH) as a colorless

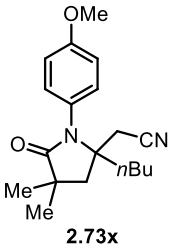
oil (0.170 mmol, 85% yield). R_f = 0.21 (50:50:1 EtOAc/Hex/MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.14 – 7.06 (m, 2H), 7.00 – 6.92 (m, 2H), 4.05 (ddt, *J* = 13.8, 11.7, 4.1 Hz, 2H), 3.83 (s, 3H), 3.58 (dddd, *J* = 16.4, 11.6, 10.6, 2.7 Hz, 2H), 2.52 (d, *J* = 16.8 Hz, 1H), 2.47 (d, *J* = 16.8 Hz, 1H), 2.37 (d, *J* = 13.9 Hz, 1H), 2.26 (d, *J* = 14.0 Hz, 1H), 2.24 – 2.13 (m, 2H), 1.63 (ddt, *J* = 13.6, 4.5, 2.4 Hz, 1H), 1.52 (ddt, *J* = 13.5, 4.5, 2.4 Hz, 1H), 1.44 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 177.8, 159.7, 130.7, 127.1, 117.1, 114.9, 64.1, 63.9, 60.1, 55.5, 43.3, 41.4, 35.4, 35.0, 30.9, 28.9; **HRMS** (ESI) calcd for $[C_{18}H_{22}N_2O_3 + Na]^+$ 337.1523, found 337.1521; **IR** (thin film) 2249, 1687, 1513, 1384, 1251.



2.73w

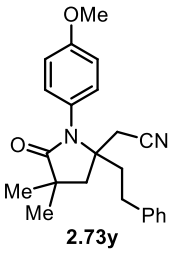
Prepared from **2.72w** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BPh_3 (40 mol%) in *m*-xylene at 120 °C for 24 h. **2.73w** was purified by flash column chromatography (25:75:0 → 40:60:0 → 60:40:5 EtOAc/Hex/MeOH) as a pale yellow oil (0.066 mmol, 33% yield). R_f = 0.45 (5:95 MeOH/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.12 – 7.07 (m, 2H), 6.99 – 6.93 (m, 2H), 3.82 (s, 3H), 2.74 (ddd, *J* = 16.9, 9.9, 6.6 Hz, 1H), 2.63 (ddd, *J* = 17.5, 9.9, 6.3 Hz, 1H), 2.53 (d, *J* = 16.8 Hz, 1H), 2.48 (d, *J* = 16.8 Hz, 1H), 2.40 (ddd, *J* = 13.3, 9.9, 6.3 Hz, 1H), 2.18 (ddd, *J* = 13.3, 9.9, 6.6 Hz, 1H), 1.40 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.7, 159.8, 130.6, 127.1, 116.8, 115.0, 62.5, 55.5, 31.7, 29.4, 29.2, 26.7; **HRMS** (ESI) calcd for

$[C_{14}H_{16}N_2O_2 + Na]^+$ 267.1104, found 267.1105; **IR** (thin film) 2244, 1693, 1513, 1387, 1251.



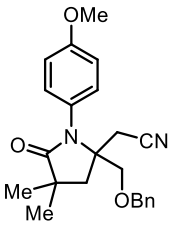
2.73x

Prepared from **2.72x** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (60 mol%) in toluene at 80 °C for 24 h. **2.73x** was purified by flash column chromatography (20:80:0 → 30:70:1 EtOAc/Hex/MeOH) as a pale yellow oil (0.180 mmol, 90% yield). R_f = 0.16 (3:7 EtOAc/Hex); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16 – 7.06 (m, 2H), 7.00 – 6.92 (m, 2H), 3.82 (s, 3H), 2.52 (d, *J* = 16.8 Hz, 1H), 2.42 (d, *J* = 16.8 Hz, 1H), 2.21 (d, *J* = 14.1 Hz, 1H), 2.14 (d, *J* = 14.1 Hz, 1H), 1.71 – 1.60 (m, 1H), 1.53 (ddd, *J* = 13.9, 11.6, 3.1 Hz, 1H), 1.41 (s, 3H), 1.33 (s, 3H), 1.45 – 1.22 (m, 4H), 0.93 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 180.0, 159.5, 130.5, 127.7, 117.5, 114.8, 62.8, 55.4, 42.8, 39.3, 39.3, 29.7, 27.7, 27.5, 26.4, 22.7, 13.9; **HRMS** (ESI) calcd for $[C_{19}H_{26}N_2O_2 + Na]^+$ 337.1886, found 337.1892; **IR** (thin film) 2246, 1694, 1513, 1395, 1252.



2.73y

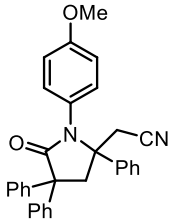
Prepared from **2.72y** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (100 mol%) in toluene at 70 °C for 36 h. **2.73y** was purified by flash column chromatography (20:80:0 → 30:70:1 EtOAc/Hex/MeOH) as a pale yellow oil (0.160 mmol, 80% yield). R_f = 0.14 (3:7 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.24 – 7.20 (m, 1H), 7.19 – 7.10 (m, 4H), 7.00 – 6.89 (m, 2H), 3.81 (s, 3H), 2.74 (td, *J* = 12.6, 12.2, 4.3 Hz, 1H), 2.66 – 2.55 (m, 2H), 2.50 (d, *J* = 16.9 Hz, 1H), 2.34 (d, *J* = 14.2 Hz, 1H), 2.24 (d, *J* = 14.1 Hz, 1H), 1.98 (ddd, *J* = 14.1, 12.2, 5.6 Hz, 1H), 1.89 (ddd, *J* = 14.1, 12.1, 4.3 Hz, 1H), 1.45 (s, 3H), 1.39 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 180.0, 159.6, 139.9, 130.5, 128.8, 128.1, 127.5, 126.5, 117.3, 114.9, 62.6, 55.4, 42.9, 41.4, 39.3, 30.6, 29.8, 27.61, 27.57; **HRMS** (ESI) calcd for $[C_{23}H_{26}N_2O_2 + Na]^+$ 385.1886, found 385.1888; **IR** (thin film) 2244, 1693, 1512, 1395, 1252.



2.73z

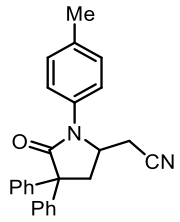
Prepared from **2.72z** on a 0.2 mmol scale with CpPd(1-phenylallyl) (20 mol%), Xantphos (20 mol%), and BEt_3 (100 mol%) in toluene at 90 °C for 24 h. **2.73z** was purified by preparative thin-layer chromatography (30:70:3 EtOAc/Hex/MeOH) as a thick colorless oil (0.074 mmol, 37% yield). R_f = 0.29 (3:7 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 7.15 – 7.05 (m, 2H), 6.96 – 6.86 (m, 2H), 4.53 (s, 2H), 3.81 (s, 3H), 3.36 (d, *J* = 9.2 Hz, 1H), 3.30 (d, *J* = 9.3 Hz, 1H), 2.59 (d, *J* = 16.9 Hz, 1H), 2.42 (d, *J* =

16.9 Hz, 1H), 2.36 (d, *J* = 13.9 Hz, 1H), 2.13 (d, *J* = 14.0 Hz, 1H), 1.39 (s, 3H), 1.31 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 180.6, 159.6, 136.8, 130.7, 128.6, 128.1, 127.9, 127.5, 116.9, 114.8, 73.5, 73.1, 62.4, 55.5, 42.2, 39.4, 27.8, 27.1, 26.8; **HRMS** (ESI) calcd for $[C_{23}H_{26}N_2O_3 + Na]^+$ 401.1836, found 401.1829; **IR** (thin film) 2253, 1692, 1512, 1396, 1251.



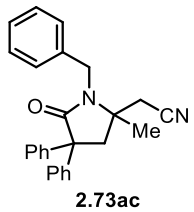
2.73aa

Prepared from **2.72aa** on a 0.2 mmol scale with CpPd(1-phenylallyl) (15 mol%), Xantphos (15 mol%), and BEt_3 (100 mol%) in toluene at 80 °C for 36 h. **2.73aa** was purified by flash column chromatography (15:85 → 3:7 EtOAc/Hex) as a thick pale yellow oil (0.170 mmol, 85% yield). R_f = 0.42 (3:7 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 – 7.44 (m, 2H), 7.38 (dd, *J* = 8.6, 7.0 Hz, 2H), 7.35 – 7.32 (m, 2H), 7.31 – 7.26 (m, 1H), 7.24 – 7.16 (m, 8H), 7.07 – 6.96 (m, 2H), 6.83 – 6.70 (m, 2H), 3.74 (s, 3H), 3.51 (d, *J* = 14.1 Hz, 1H), 3.46 (d, *J* = 14.1 Hz, 1H), 3.19 (d, *J* = 16.9 Hz, 1H), 2.83 (d, *J* = 16.9 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.5, 158.6, 144.0, 141.0, 140.7, 128.8, 128.53 (two overlapped peaks), 128.46, 128.2 (two overlapped peaks), 127.8, 127.7, 127.2, 127.0, 126.5, 116.8, 114.3, 65.6, 56.9, 55.3, 49.1, 27.3; **HRMS** (ESI) calcd for $[C_{31}H_{26}N_2O_2 + Na]^+$ 481.1886, found 481.1895; **IR** (thin film) 2250, 1694, 1511, 1361, 1252.



2.73ab

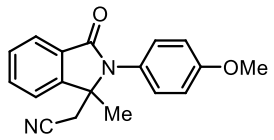
Prepared from **2.72ab** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (60 mol%) in toluene at 70 °C for 48 h. **2.73ab** was purified by flash column chromatography (12:88:0 → 20:80:1 EtOAc/Hex/MeOH) as a colorless oil (0.094 mmol, 47% yield). R_f = 0.32 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H), 7.39 – 7.26 (m, 8H), 7.23 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 4.26 (dddd, *J* = 11.4, 9.0, 6.8, 3.3 Hz, 1H), 3.22 (dd, *J* = 13.1, 5.9 Hz, 1H), 2.83 (dd, *J* = 13.0, 8.3 Hz, 1H), 2.66 (dd, *J* = 17.0, 3.3 Hz, 1H), 2.47 (dd, *J* = 16.9, 7.4 Hz, 1H), 2.36 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.4, 142.7, 141.1, 137.3, 133.3, 130.1, 128.7, 128.5, 127.9, 127.6, 127.4, 127.2, 124.9, 115.9, 57.8, 52.4, 40.1, 22.3, 21.1; **HRMS** (ESI) calcd for $[C_{25}H_{22}N_2O + Na]^+$ 389.1624, found 389.1623; **IR** (thin film) 2251, 1699, 1514, 1385, 1298.



2.73ac

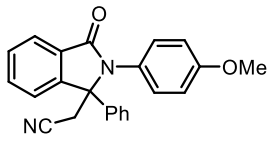
Prepared from **2.72ac** on a 0.2 mmol scale with CpPd(1-phenylallyl) (15 mol%), Xantphos (15 mol%), and BPh_3 (50 mol%) in *m*-xylene at 120 °C for 24 h. **2.73ac** was

purified by flash column chromatography (1:9 → 1:4 EtOAc/Hex) as a thick pale yellow oil (0.058 mmol, 29% yield). R_f = 0.35 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 – 7.48 (m, 2H), 7.41 – 7.18 (m, 13H), 4.85 (d, *J* = 15.3 Hz, 1H), 4.39 (d, *J* = 15.3 Hz, 1H), 3.19 (d, *J* = 13.8 Hz, 1H), 2.84 – 2.71 (m, 1H), 2.11 (d, *J* = 16.7 Hz, 1H), 1.96 (d, *J* = 16.6 Hz, 1H), 1.39 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.0, 143.3, 142.2, 137.6, 128.90, 128.88, 128.4, 127.9, 127.8, 127.6, 127.5, 127.4, 126.9, 116.8, 59.0, 56.6, 47.1, 43.6, 28.8, 25.7; **HRMS** (ESI) calcd for $[C_{26}H_{24}N_2O + Na]^+$ 403.1781, found 403.1782; **IR** (thin film) 2250, 1689, 1495, 1398.



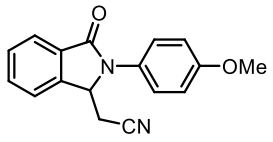
2.73ad

Prepared from **2.72ad** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (60 mol%) in toluene at 80 °C for 24 h. **2.73ad** was purified by flash column chromatography (0.6:100 → 1:100 MeOH/CH_2Cl_2) as a pale yellow foam (0.198 mmol, 99% yield). R_f = 0.29 (2:100 MeOH/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.72 – 7.62 (m, 2H), 7.57 (td, *J* = 7.3, 1.2 Hz, 1H), 7.25 – 7.18 (m, 2H), 7.06 – 7.00 (m, 2H), 3.85 (s, 3H), 2.90 (d, *J* = 16.6 Hz, 1H), 2.70 (d, *J* = 16.7 Hz, 1H), 1.67 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.6, 159.9, 147.1, 132.7, 130.9, 130.8, 129.4, 126.6, 124.6, 121.2, 115.9, 115.2, 63.7, 55.5, 28.5, 24.8; **HRMS** (ESI) calcd for $[C_{18}H_{16}N_2O_2 + Na]^+$ 315.1104, found 315.1101; **IR** (thin film) 2247, 1697, 1513, 1377, 1249.



2.73ae

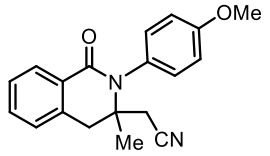
Prepared from **2.72ae** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (60 mol%) in toluene at 80 °C for 24 h. **2.73ae** was purified by flash column chromatography (1:100 MeOH/CH_2Cl_2) as a yellow foam (0.198 mmol, 99% yield). R_f = 0.33 (2:100 MeOH/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 – 7.95 (m, 1H), 7.71 – 7.54 (m, 2H), 7.41 – 7.28 (m, 4H), 7.11 – 7.03 (m, 2H), 6.83 – 6.71 (m, 4H), 3.76 (s, 3H), 3.49 (d, *J* = 16.4 Hz, 1H), 3.20 (d, *J* = 16.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.8, 159.3, 147.6, 137.7, 133.1, 131.4, 129.61, 129.60, 129.1, 129.0, 127.0, 126.7, 124.6, 122.5, 115.6, 114.6, 68.8, 55.4, 25.8; **HRMS** (ESI) calcd for $[C_{23}H_{18}N_2O_2 + Na]^+$ 377.1260, found 377.1269; **IR** (thin film) 2252, 1698, 1513, 1366, 1250.



2.73af

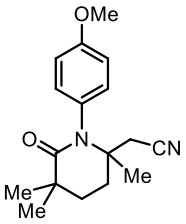
Prepared from **2.72af** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (60 mol%) in toluene at 70 °C for 24 h. **2.73af** was purified by flash column chromatography (1:4 → 1:1 EtOAc/Hex) as a pale yellow foam (0.118 mmol, 59% yield). R_f = 0.36 (1:4 → 1:1 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.5 Hz, 1H), 7.74 – 7.66 (m, 2H), 7.61 (td, *J* = 7.4, 1.3 Hz, 1H), 7.43 – 7.36 (m, 2H),

7.06 – 6.98 (m, 2H), 5.24 (dd, *J* = 7.4, 3.4 Hz, 1H), 3.85 (s, 3H), 3.00 (dd, *J* = 16.8, 3.5 Hz, 1H), 2.67 (dd, *J* = 16.8, 7.4 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.7, 158.4, 141.7, 132.6, 132.0, 129.8, 128.2, 126.2, 124.6, 122.3, 115.4, 114.9, 57.2, 55.5, 22.0; **HRMS** (ESI) calcd for $[C_{17}H_{14}N_2O_2 + Na]^+$ 301.0947, found 301.0942; **IR** (thin film) 2250, 1695, 1514, 1249.



2.73ag

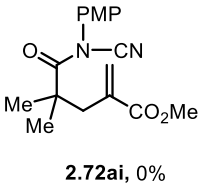
Prepared from **2.72ag** on a 0.2 mmol scale with CpPd(1-phenylallyl) (15 mol%), Xantphos (15 mol%), and BEt_3 (100 mol%) in toluene at 80 °C for 24 h. **2.73ag** was purified by preparative thin-layer chromatography (2:100 MeOH/CH_2Cl_2) as an yellow foam (0.188 mmol, 94% yield). R_f = 0.48 (2:100 MeOH/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.53 (td, *J* = 7.5, 1.4 Hz, 1H), 7.41 (td, *J* = 7.6, 1.2 Hz, 1H), 7.32 – 7.26 (m, 1H), 7.14 – 7.08 (m, 2H), 7.00 – 6.92 (m, 2H), 3.84 (s, 3H), 3.40 (d, *J* = 15.9 Hz, 1H), 3.28 (d, *J* = 15.9 Hz, 1H), 2.69 (d, *J* = 16.6 Hz, 1H), 2.62 (dd, *J* = 16.5, 0.9 Hz, 1H), 1.41 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.8, 159.4, 134.7, 132.8, 131.1, 130.44, 130.37, 128.9, 128.3, 127.8, 127.6, 116.6, 115.0, 114.6, 58.6, 55.5, 40.3, 28.5, 26.2; **HRMS** (ESI) calcd for $[C_{19}H_{18}N_2O_2 + Na]^+$ 329.1260, found 329.1262; **IR** (thin film) 2247, 1656, 1511, 1372, 1250.



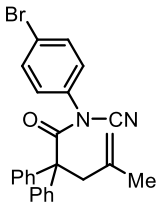
2.73ah

Prepared from **2.72ah** on a 0.2 mmol scale with CpPd(1-phenylallyl) (20 mol%), Xantphos (20 mol%), and BEt_3 (100 mol%) in toluene at 70 °C for 48 h. **2.73ah** was purified by preparative thin-layer chromatography (40:60:4 EtOAc/Hex/MeOH) as a pale yellow oil (0.098 mmol, 49% yield). R_f = 0.48 (40:60:4 EtOAc/Hex/MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.13 – 6.85 (m, 4H), 3.81 (s, 3H), 2.54 (d, *J* = 16.7 Hz, 1H), 2.44 (d, *J* = 16.7 Hz, 1H), 2.37 (ddd, *J* = 13.8, 9.7, 4.0 Hz, 1H), 2.06 – 1.81 (m, 3H), 1.39 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.4, 159.0, 131.2 (br), 130.7, 117.1, 114.5, 59.2, 55.4, 38.4, 31.6, 31.5, 30.5, 27.9, 27.7, 27.5; **HRMS** (ESI) calcd for $[C_{17}H_{22}N_2O_2 + Na]^+$ 309.1573, found 309.1565; **IR** (thin film) 2241, 1645, 1511, 1390, 1249.

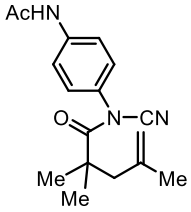
unsuccessful substrates



2.72ai, 0%

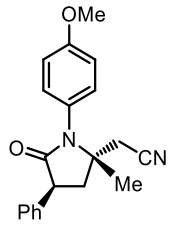


2.72aj, 0%



2.72ak, 0%

The aminocyanation reactions of these substrates resulted in unconsumed starting material. No desired product was detected in the crude reaction mixture.



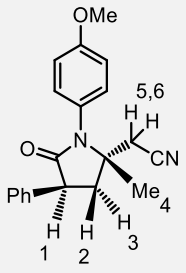
(±)-2.73al

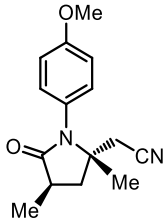
Prepared from **2.72al** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (100 mol%) in toluene at 80 °C for 24 h. **2.73al** was purified by flash column chromatography (1:4:0 → 3:7:0.1 EtOAc/Hex/MeOH) as a pale yellow oil (0.096 mmol, 48% yield). R_f = 0.14 (3:7 EtOAc/Hex); > 20:1 d.r. based on ^{1}H NMR spectroscopy. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 – 7.21 (m, 5H), 7.16 – 7.09 (m, 2H), 7.00 – 6.91 (m, 2H), 4.13 (app t, *J* = 9.7 Hz, 1H), 3.82 (s, 3H), 2.91 (dd, *J* = 13.7, 9.6 Hz, 1H), 2.61 (d, *J* = 16.8 Hz, 1H), 2.53 (d, *J* = 16.7 Hz, 1H), 2.26 (dd, *J* = 13.7, 9.8 Hz, 1H), 1.42 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.5, 159.7, 138.9, 130.7, 128.8, 128.0, 127.3, 127.2, 117.0, 114.9, 60.8, 55.4, 46.3, 41.5, 28.5, 28.1; **HRMS** (ESI) calcd for $[C_{20}H_{20}N_2O_2 + Na]^+$ 343.1417, found 343.1416; **IR** (thin film) 2244, 1695, 1512, 1387, 1251.

Assignment of stereochemistry of (±)-2.73al by nOe NMR experiments

Conclusion: **H1** and **H4** are *anti*; Ph group and **H4** are *syn*.

Assigned Structure	Key ^{1}H NMR Signals	Irradiation	Key nOe Results	Associate File
	H1: 4.13 (app t, *J* = 9.7 Hz, 1H) **H2:** 2.26 (dd, *J* = 13.7, 9.8 Hz, 1H) **H3:** 2.91 (dd, *J* = 13.7, 9.6 Hz, 1H)	**H4**	nOe observed: **H2, H5,6** nOe not observed: **H1**	2.73al-nOe-exp1.mnova

 **(±)-2.73al** *> 20:1 d.r.*	**H4:** 1.42 (s, 3H) **H5,6:** 2.61 (d, *J* = 16.8 Hz, 1H), 2.53 (d, *J* = 16.7 Hz, 1H)	**H1**	nOe observed: **H3, H5,6** nOe not observed: **H4**	2.73al-nOe-exp2.mnova



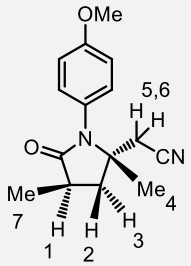
(±)-2.73am

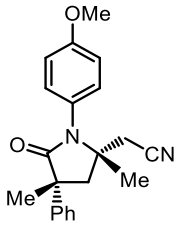
Prepared from **2.72am** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (60 mol%) in toluene at 80 °C for 24 h. **2.73am** was purified by flash column chromatography (4:6:0 → 5:5:0.15 EtOAc/Hex/MeOH) as a pale yellow oil (0.118 mmol, 59% yield). R_f = 0.21 (1:1 EtOAc/Hex); 9:1 d.r. based on ^{1}H NMR spectroscopy. *Major diastereomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.10 – 7.02 (m, 2H), 6.99 – 6.92 (m, 2H), 3.82 (s, 3H), 2.98 – 2.83 (m, 1H), 2.66 (dd, *J* = 13.4, 9.1 Hz, 1H), 2.54 (d, *J* = 16.7 Hz, 1H), 2.47 (d, *J* = 16.5 Hz, 1H), 1.78 (dd, *J* = 13.4, 9.8 Hz, 1H), 1.38 (s, 3H), 1.32 (d, *J* = 7.1 Hz, 3H); *Major diastereomer:* **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.2, 159.6, 130.6, 127.4, 117.1, 114.9, 60.7, 55.4, 40.9, 35.0, 28.3, 28.1, 16.7; **HRMS** (ESI) calcd for $[C_{15}H_{18}N_2O_2 + Na]^+$ 281.1260, found 281.1267; **IR** (thin film) 2244, 1694, 1513, 1390, 1251.

Assignment of stereochemistry of (±)-2.73am (major diastereomer) by nOe NMR experiments

Conclusion: **H4** and **H7** are *syn*.

Assigned Structure	Key ^{1}H NMR Signals	Irradiation	Key nOe Results	Associate File

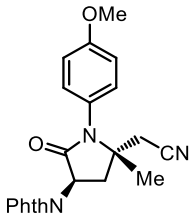
 **(±)-2.73am** *9:1 d.r. major diasteromer*	**H1:** 2.98 – 2.83 (m, 1H) **H2:** 1.78 (dd, *J* = 13.4, 9.8 Hz, 1H) **H3:** 2.66 (dd, *J* = 13.4, 9.1 Hz, 1H) **H4:** 1.38 (s, 3H) **H5,6:** 2.54 (d, *J* = 16.7 Hz, 1H), 2.47 (d, *J* = 16.5 Hz, 1H) **H7:** 1.32 (d, *J* = 7.1 Hz, 3H)	**H2**	nOe observed: **H3, H4, H7** nOe not observed: **H1, H5,6**	2.73am-nOe-exp1.mnova



(±)-2.73an

Prepared from **2.72an** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (60 mol%) in toluene at 80 °C for 24 h. **2.73an** was purified by flash column chromatography (1:4 → 3:7 EtOAc/Hex) to yield a mixture of diastereomers as an off-white solid (0.146 mmol, 73% yield). R_f = 0.25 (2:3 EtOAc/Hex); 19:1 d.r. based on ^{1}H NMR spectroscopy. The major and minor diastereomers could be separated as a saturated solution in 1:1 isopropanol:hexanes via HPLC using an Agilent Eclipse XDB-CN column, with an injection volume of 50 μL, flow rate of 5 mL/min., and eluting with an isocratic 15:85 isopropanol:hexanes solvent system. R_t major diastereomer = 6.93 min; R_t minor diastereomer = 9.36 min. *Major diastereomer:* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 – 7.51 (m, 2H), 7.40 (dd, *J* = 8.4, 7.2 Hz, 2H), 7.33 – 7.25 (m, 1H), 7.07 – 7.00 (m, 2H), 7.00 – 6.93 (m, 2H), 3.83 (s, 3H), 3.07 (d, *J* = 13.7 Hz, 1H), 2.31 (app t, *J* =

15.5 Hz, 2H), 2.18 (d, *J* = 16.4 Hz, 1H), 1.64 (s, 3H), 1.45 (s, 3H); *Major diastereomer:* **^{13}C NMR** (125 MHz, $CDCl_3$) δ 177.0, 159.7, 144.0, 130.7, 129.2, 127.4, 127.2, 125.9, 116.9, 114.9, 59.8, 55.5, 48.5, 47.4, 28.4, 28.2, 27.3; *Major diastereomer*: **^{1}H-NMR** (500 MHz; CD_3CN): δ 7.54-7.53 (m, 2H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.31-7.29 (m, 1H), 7.16-7.14 (m, 2H), 7.03-7.02 (m, 2H), 3.83 (s, 3H), 2.80 (d, *J* = 13.8 Hz, 1H), 2.51 (d, *J* = 16.9 Hz, 1H), 2.40 (d, *J* = 13.8 Hz, 1H), 2.33 (d, *J* = 16.9 Hz, 1H), 1.62 (s, 3H), 1.41 (s, 3H).; *Minor diastereomer*: **^{1}H-NMR** (500 MHz; CD_3CN): δ 7.49-7.48 (m, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.17-7.15 (m, 1H), 7.04-7.02 (m, 1H), 3.83 (s, 1H), 2.70 (d, *J* = 13.7 Hz, 1H), 2.62 (d, *J* = 16.9 Hz, 1H), 2.59 (d, *J* = 17.1 Hz, 1H), 2.51 (d, *J* = 13.7 Hz, 1H), 1.60 (s, 1H), 1.11 (s, 1H). **HRMS** (ESI) calcd for $[C_{21}H_{22}N_2O_2 + Na]^+$ 357.1573, found 357.1595; **IR** (thin film) 2235, 1688, 1513, 1452, 1388, 1250.



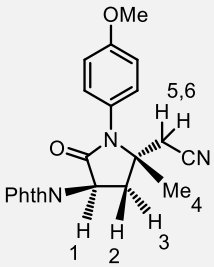
(±)-2.73ao

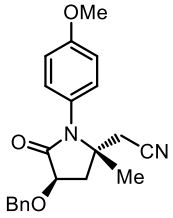
Prepared from **2.72ao** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (60 mol%) in toluene at 80 °C for 24 h. **2.73ao** was purified by flash column chromatography (4:6:0 → 5:5:0.2 EtOAc/Hex/MeOH) as a pale yellow foam (0.286 mmol, 77% yield). R_f = 0.22 (1:1 EtOAc/Hex); > 20:1 d.r. based on ^{1}H NMR spectroscopy. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.24 – 7.17 (m, 2H), 7.03 – 6.95 (m, 2H), 5.34 (dd, *J* = 10.3, 9.3 Hz, 1H),

3.83 (s, 3H), 2.85 (dd, *J* = 13.7, 10.3 Hz, 1H), 2.70 (d, *J* = 16.8 Hz, 1H), 2.61 (d, *J* = 16.8 Hz, 1H), 2.51 (dd, *J* = 13.7, 9.3 Hz, 1H), 1.49 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.5, 167.3, 159.9, 134.3, 131.8, 130.5, 126.8, 123.5, 116.8, 115.0, 60.6, 55.5, 48.3, 36.8, 29.7, 27.3; **HRMS** (ESI) calcd for $[C_{22}H_{19}N_3O_4 + Na]^+$ 412.1268, found 412.1277; **IR** (thin film) 2252, 1776, 1714, 1512, 1390, 1251.

Assignment of stereochemistry of (±)-2.73ao by nOe NMR experiments

Conclusion: **H1** and **H4** are *anti*; NPhth group and **H4** are *syn*.

Assigned Structure	Key ^{1}H NMR Signals	Irradiation	Key nOe Results	Associate File
 **(±)-2.73ao** *> 20:1 d.r.*	**H1:** 5.34 (dd, *J* = 10.3, 9.3 Hz, 1H) **H2:** 2.51 (dd, *J* = 13.7, 9.3 Hz, 1H) **H3:** 2.85 (dd, *J* = 13.7, 10.3 Hz, 1H) **H4:** 1.49 (s, 3H) **H5,6:** 2.70 (d, *J* = 16.8 Hz, 1H), 2.61 (d, *J* = 16.8 Hz, 1H)	**H1**	nOe observed: **H2, H3, H5,6** nOe not observed: **H4**	2.73ao-nOe-exp1.mnova
		H4	nOe observed: **H2, H5,6** nOe not observed: **H1**	2.73ao-nOe-exp2.mnova



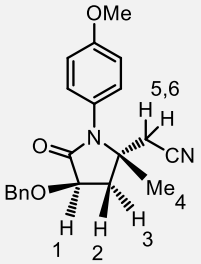
(±)-2.73ap

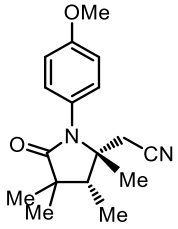
Prepared from **2.72ap** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (60 mol%) in toluene at 70 °C for 24 h. **2.73ap** was purified by flash column chromatography (2:8:0 → 3:7:0.15 EtOAc/Hex/MeOH) as a yellow oil

(0.148 mmol, 74% yield). R_f = 0.10 (3:7 EtOAc/Hex); 3.2:1 d.r. based on ^{1}H NMR spectroscopy. *Major diastereomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 7.14 – 7.07 (m, 2H), 7.00 – 6.93 (m, 2H), 5.07 (d, *J* = 11.7 Hz, 1H), 4.77 (d, *J* = 11.7 Hz, 1H), 4.43 (dd, *J* = 8.2, 5.6 Hz, 1H), 3.81 (s, 3H), 2.63 (dd, *J* = 14.0, 8.3 Hz, 1H), 2.46 (app s, 2H), 2.17 (dd, *J* = 13.9, 5.6 Hz, 1H), 1.42 (s, 3H); *Major diastereomer:* **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.7, 159.8, 137.6, 130.4, 128.4, 128.0, 127.8, 126.6, 116.8, 115.0, 74.2, 72.5, 60.9, 55.4, 39.6, 29.3, 27.7; **HRMS** (ESI) calcd for $[C_{21}H_{22}N_2O_3 + Na]^+$ 373.1523, found 373.1536; **IR** (thin film) 2247, 1702, 1512, 1388, 1251.

Assignment of stereochemistry of (±)-2.73ap (major diastereomer) by nOe NMR experiments

Conclusion: **H1** and **H4** are *anti*; OBn group and **H4** are *syn*.

Assigned Structure	Key ^{1}H NMR Signals	Irradiation	Key nOe Results	Associate File
 **(±)-2.73ap** *3.2:1 d.r. major diastereomer*	**H1:** 4.43 (dd, *J* = 8.2, 5.6 Hz, 1H) **H2:** 2.17 (dd, *J* = 13.9, 5.6 Hz, 1H) **H3:** 2.63 (dd, *J* = 14.0, 8.3 Hz, 1H) **H4:** 1.42 (s, 3H) **H5,6:** 2.46 (app s, 2H)	**H1**	nOe observed: **H3, H5,6** nOe not observed: **H4**	2.73ap-nOe-exp1.mnova

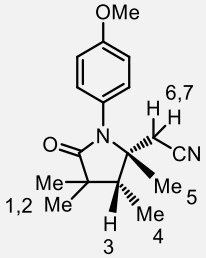


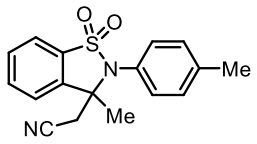
(±)-2.73aq

Prepared from **2.72aq** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (60 mol%) in toluene at 80 °C for 24 h. **2.73aq** was purified by flash column chromatography (30:70:0 → 30:70:0.5 EtOAc/Hex/MeOH) as a pale yellow oil (0.184mmol, 92% yield). R_f = 0.27 (1:1 EtOAc/Hex); 4.4:1 d.r. based on ^{1}H NMR spectroscopy. *Major diastereomer:* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.08 – 7.02 (m, 2H), 6.99 – 6.93 (m, 2H), 3.82 (s, 3H), 2.54 (app s, 2H), 2.20 (q, *J* = 7.4 Hz, 1H), 1.44 (s, 3H), 1.25 (d, *J* = 8.0 Hz, 3H), 1.24 (s, 3H), 1.22 (s, 3H); *Major diastereomer:* **^{13}C NMR** (125 MHz, $CDCl_3$) δ 179.8, 159.6, 130.9, 127.5, 117.3, 114.8, 62.9, 55.4, 49.1, 42.2, 27.9, 26.6, 24.4, 21.2, 9.6; **HRMS** (ESI) calcd for $[C_{17}H_{22}N_2O_2 + Na]^+$ 309.1573, found 309.1578; **IR** (thin film) 2245, 1694, 1513, 1398, 1250.

Assignment of stereochemistry of (±)-2.73aq (major diastereomer) by nOe NMR experiments

Conclusion: **H3** and **H5** are *syn*; **H5** and **H4** are *anti*.

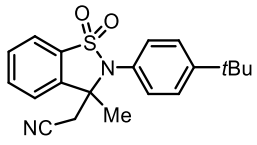
Assigned Structure	Key ^{1}H NMR Signals	Irradiation	Key nOe Results	Associate File
 **(±)-2.73aq** *4.4:1 d.r. major diastereomer*	**H1,2:** 1.24 (s, 3H), 1.22 (s, 3H) **H3:** 2.20 (q, *J* = 7.4 Hz, 1H) **H4:** 1.25 (d, *J* = 8.0 Hz, 3H) **H5:** 1.44 (s, 3H) **H6,7:** 2.54 (app s, 2H)	**H3**	nOe observed: **H5, H4** nOe not observed: **H6,7**	2.73aq-nOe-exp1.mnova
		H5	nOe observed: **H3, H6,**7 nOe not observed: **H4**	2.73aq-nOe-exp2.mnova



2.76a

Prepared from **2.75a** on a 0.2 mmol scale with Pd_2dba_3 (5 mol%), Xantphos (10 mol%), and BPh_3 (40 mol%) in toluene at 80 °C for 16 h. **2.76a** was purified by flash column chromatography (15:85:1 EtOAc/Hex/MeOH → 3:100 MeOH/CH_2Cl_2) as an amorphous pale yellow solid (0.198 mmol, 99% yield). R_f = 0.50 (1:1 EtOAc/Hex); **^{1}H NMR** (400 MHz, $CDCl_3$)* δ 7.98 – 7.87 (m, 1H), 7.79 – 7.70 (m, 2H), 7.67 (ddd, *J* = 7.7, 5.9, 2.6 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 2.91 (d, *J* = 16.7 Hz, 1H), 2.85 (d, *J* = 16.7 Hz, 1H), 2.43 (s, 3H), 1.72 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.8, 139.0, 134.3, 133.4, 132.8, 130.7, 130.3, 127.0, 123.3, 121.9, 116.0, 63.4, 29.2, 25.2, 21.3; **HRMS** (ESI) calcd for $[C_{17}H_{16}N_2O_2S + Na]^+$ 335.0825, found 335.0831; **IR** (thin film) 2254, 1508, 1180.

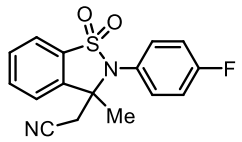
*Note: Sulfonamides **2.76a–2.76k** were only partially soluble in $CDCl_3$. For consistency, the corresponding ^{1}H and ^{13}C NMR spectra were still collected in $CDCl_3$.



2.76b

Prepared from **2.75b** on a 0.2 mmol scale with Pd_2dba_3 (5 mol%), Xantphos (10 mol%), and BPh_3 (40 mol%) in toluene at 80 °C for 16 h. **2.76b** was purified by flash

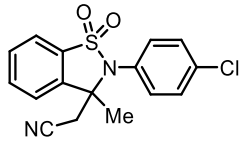
column chromatography (15:85:1 EtOAc/Hex/MeOH → 3:100 MeOH/CH_2Cl_2) as an amorphous pale yellow solid (0.186 mmol, 93% yield). R_f = 0.57 (1:1 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.8 Hz, 1H), 7.76 – 7.71 (m, 2H), 7.65 (ddd, *J* = 8.3, 5.0, 3.4 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 2.92 (d, *J* = 16.7 Hz, 1H), 2.84 (d, *J* = 16.7 Hz, 1H), 1.71 (s, 3H), 1.35 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.5, 139.0, 134.1, 133.3, 132.5, 130.2, 127.0, 126.8, 123.3, 121.7, 116.0, 63.6, 34.8, 31.2, 29.1, 25.2; **HRMS** (ESI) calcd for $[C_{20}H_{22}N_2O_2S + Na]^+$ 377.1294, found 377.1296; **IR** (thin film) 2253, 1511, 1297, 1178, 1151.



2.76c

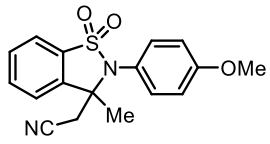
Prepared from **2.75c** on a 0.2 mmol scale with Pd_2dba_3 (5 mol%), Xantphos (10 mol%), and BPh_3 (40 mol%) in toluene at 80 °C for 16 h. **2.76c** was purified by flash column chromatography (15:85:1 EtOAc/Hex/MeOH → 3:100 MeOH/CH_2Cl_2) as an amorphous pale yellow solid (0.188 mmol, 94% yield). R_f = 0.46 (1:1 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.7 Hz, 1H), 7.82 – 7.63 (m, 3H), 7.52 (dd, *J* = 8.7, 4.9 Hz, 2H), 7.32 – 7.20 (m, 2H), 2.90 (d, *J* = 16.7 Hz, 1H), 2.84 (d, *J* = 16.8 Hz, 1H), 1.71 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.7 (d, $^1J_{F–C}$ = 251.7 Hz), 138.7, 135.0 (d, $^3J_{F–C}$ = 9.1 Hz), 134.0, 133.6, 130.4, 125.7 (d, $^4J_{F–C}$ = 3.3 Hz), 123.3, 121.9, 117.2 (d, $^2J_{F–C}$ = 22.7 Hz), 115.7, 63.6, 29.3, 25.3; **^{19}F NMR** (470 MHz, $CDCl_3$) δ –109.3; **HRMS** (ESI)

calcd for $[C_{16}H_{13}FN_2O_2S + Na]^+$ 339.0574, found 339.0579; **IR** (thin film) 2253, 1505, 1302, 1291, 1178, 1152.



2.76d

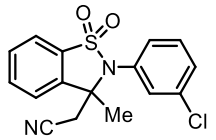
Prepared from **2.75d** on a 0.2 mmol scale with Pd_2dba_3 (5 mol%), Xantphos (10 mol%), and BPh_3 (40 mol%) in toluene at 80 °C for 16 h. **2.76d** was purified by flash column chromatography (15:85:1 EtOAc/Hex/MeOH → 3:100 MeOH/CH_2Cl_2) as an amorphous pale yellow solid (0.186 mmol, 93% yield). R_f = 0.49 (1:1 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.77 (td, *J* = 7.6, 1.2 Hz, 1H), 7.73 – 7.64 (m, 2H), 7.54 – 7.50 (m, 2H), 7.47 (dt, *J* = 8.9, 2.1 Hz, 2H), 2.90 (d, *J* = 16.7 Hz, 1H), 2.83 (d, *J* = 16.8 Hz, 1H), 1.71 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.7, 136.9, 134.3, 134.0, 133.6, 130.5, 130.4, 128.5, 123.3, 121.9, 115.7, 63.7, 29.3, 25.3; **HRMS** (ESI) calcd for $[C_{16}H_{13}ClN_2O_2S + Na]^+$ 355.0278, found 355.0281; **IR** (thin film) 2253, 1490, 1302, 1177.



2.76e

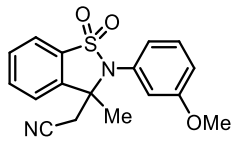
Prepared from **2.75e** on a 0.2 mmol scale with Pd_2dba_3 (5 mol%), Xantphos (10 mol%), and BPh_3 (40 mol%) in toluene at 80 °C for 16 h. **2.76e** was purified by flash

column chromatography (15:85:1 EtOAc/Hex/MeOH → 3:100 MeOH/CH_2Cl_2) as an amorphous white solid (0.178 mmol, 89% yield). R_f = 0.32 (1:1 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.8 Hz, 1H), 7.78 – 7.61 (m, 3H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 3.86 (s, 3H), 2.90 (d, *J* = 16.8 Hz, 1H), 2.83 (d, *J* = 16.7 Hz, 1H), 1.70 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.0, 139.0, 134.3, 134.2, 133.4, 130.3, 123.3, 121.9, 121.6, 116.0, 115.3, 63.5, 55.6, 29.2, 25.2; **HRMS** (ESI) calcd for $[C_{17}H_{16}N_2O_3S + Na]^+$ 351.0774, found 351.0763; **IR** (thin film) 2253, 1507, 1265, 1177.



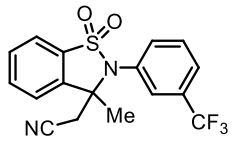
2.76f

Prepared from **2.75f** on a 0.2 mmol scale with Pd_2dba_3 (5 mol%), Xantphos (10 mol%), and BPh_3 (40 mol%) in toluene at 80 °C for 16 h. **2.76f** was purified by flash column chromatography (15:85:1 EtOAc/Hex/MeOH → 3:100 MeOH/CH_2Cl_2) as a tan foam (0.190 mmol, 95% yield). R_f = 0.43 (1:1 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.7 Hz, 1H), 7.77 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.69 (td, *J* = 7.5, 1.2 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.45 (dt, *J* = 7.8, 1.6 Hz, 1H), 2.91 (d, *J* = 16.7 Hz, 1H), 2.86 (d, *J* = 16.7 Hz, 1H), 1.74 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.7, 135.6, 133.9, 133.6, 133.1, 131.33, 131.30, 130.9, 130.8, 130.5, 123.3, 121.9, 115.6, 63.8, 29.4, 25.3; **HRMS** (ESI) calcd for $[C_{16}H_{13}ClN_2O_2S + Na]^+$ 355.0278, found 355.0287; **IR** (thin film) 2254, 1588, 1471, 1180.



2.76g

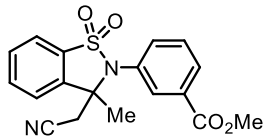
Prepared from **2.75g** on a 0.2 mmol scale with Pd_2dba_3 (5 mol%), Xantphos (10 mol%), and BPh_3 (40 mol%) in toluene at 80 °C for 16 h. **2.76g** was purified by flash column chromatography (15:85:1 EtOAc/Hex/MeOH → 3:100 MeOH/CH_2Cl_2) as an amorphous pale yellow solid (0.180 mmol, 90% yield). R_f = 0.46 (1:1 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.7 Hz, 1H), 7.79 – 7.69 (m, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 8.1 Hz, 1H), 7.16 – 7.02 (m, 3H), 3.84 (s, 3H), 2.94 (d, *J* = 16.8 Hz, 1H), 2.85 (d, *J* = 16.8 Hz, 1H), 1.72 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 160.6, 138.9, 134.2, 133.4, 130.9, 130.5, 130.3, 124.9, 123.3, 121.7, 118.6, 116.1, 115.9, 63.7, 55.5, 29.2, 25.3; **HRMS** (ESI) calcd for $[C_{17}H_{16}N_2O_3S + Na]^+$ 351.0774, found 351.0782; **IR** (thin film) 2253, 1600, 1486, 1297, 1178.



2.76h

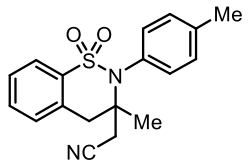
Prepared from **2.75h** on a 0.2 mmol scale with Pd_2dba_3 (5 mol%), Xantphos (10 mol%), and BPh_3 (40 mol%) in toluene at 80 °C for 16 h. **2.76h** was purified by flash column chromatography (15:85:1 EtOAc/Hex/MeOH → 3:100 MeOH/CH_2Cl_2) as an amorphous pale yellow solid (0.184 mmol, 92% yield). R_f = 0.47 (1:1 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.7 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.80 – 7.63

(m, 6H), 2.91 (d, J = 16.8 Hz, 1H), 2.85 (d, J = 16.8 Hz, 1H), 1.73 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.6, 136.5, 133.80, 133.75, 132.7 (q, $^2J_{F–C}$ = 33.2 Hz), 131.0, 130.8, 130.6, 129.9 (q, $^3J_{F–C}$ = 3.8 Hz), 127.3 (q, $^3J_{F–C}$ = 3.6 Hz), 123.3, 123.2 (q, $^1J_{F–C}$ = 271.1 Hz), 121.9, 115.5, 63.9, 29.4, 25.3; **^{19}F NMR** (470 MHz, $CDCl_3$) δ –62.6; **HRMS** (ESI) calcd for $[C_{17}H_{13}F_3N_2O_2S + Na]^+$ 389.0542, found 389.0549; **IR** (thin film) 2255, 1332, 1179, 1151.



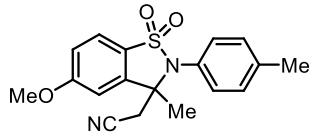
2.76i

Prepared from **2.75i** on a 0.2 mmol scale with Pd_2dba_3 (5 mol%), Xantphos (10 mol%), and BPh_3 (40 mol%) in toluene at 80 °C for 16 h. **2.76i** was purified by flash column chromatography (15:85:1 EtOAc/Hex/MeOH → 3:100 MeOH/CH_2Cl_2) as pale yellow foam (0.178 mmol, 89% yield). R_f = 0.24 (1:1 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.24 (dt, J = 7.8, 1.4 Hz, 1H), 8.16 (t, J = 1.9 Hz, 1H), 7.95 (dt, J = 7.8, 0.9 Hz, 1H), 7.81 – 7.73 (m, 3H), 7.70 (ddd, J = 7.6, 6.9, 1.5 Hz, 1H), 7.64 (t, J = 7.9 Hz, 1H), 3.95 (s, 3H), 2.92 (d, J = 17.0 Hz, 1H), 2.88 (d, J = 17.0 Hz, 1H), 1.76 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 165.7, 138.8, 137.5, 134.1, 134.0, 133.6, 132.4, 131.5, 130.5, 130.4, 130.2, 123.4, 121.9, 115.7, 63.7, 52.5, 29.5, 25.2; **HRMS** (ESI) calcd for $[C_{18}H_{16}N_2O_4S + Na]^+$ 379.0723, found 379.0714; **IR** (thin film) 2255, 1724, 1296, 1180.



2.76j

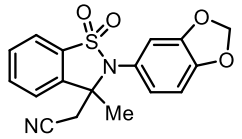
Prepared from **2.75j** on a 0.2 mmol scale with Pd_2dba_3 (5 mol%), Xantphos (10 mol%), and BPh_3 (40 mol%) in toluene at 80 °C for 24 h. **2.76j** was purified by preparative thin-layer chromatography (35:65 EtOAc/Hex) as a yellow foam (0.116 mmol, 58% yield). R_f = 0.37 (3:7 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.59 (td, *J* = 7.6, 1.4 Hz, 1H), 7.48 (td, *J* = 7.7, 1.2 Hz, 1H), 7.43 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.21 – 6.85 (br m 4H), 3.61 (d, *J* = 15.2 Hz, 1H), 3.53 (d, *J* = 15.2 Hz, 1H), 2.76 (d, *J* = 16.5 Hz, 1H), 2.71 (d, *J* = 16.5 Hz, 1H), 2.36 (s, 3H), 1.37 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 139.7, 139.5, 133.0, 132.7, 131.8 (br), 131.3, 130.2, 129.2, 127.8, 122.3, 116.5, 60.7, 39.0, 30.5, 26.3, 21.1; **HRMS** (ESI) calcd for $[C_{18}H_{18}N_2O_2S + Na]^+$ 349.0981, found 349.0952; **IR** (thin film) 2253, 1508, 1325, 1174.



2.76k

Prepared from **2.75k** on a 0.2 mmol scale with Pd_2dba_3 (5 mol%), Xantphos (10 mol%), and BPh_3 (40 mol%) in toluene at 80 °C for 24 h. **2.76k** was purified by flash column chromatography (1:4 → 1:1 EtOAc/Hex) as an pale yellow foam (0.152 mmol, 76% yield). R_f = 0.18 (3:7 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.5 Hz, 1H),

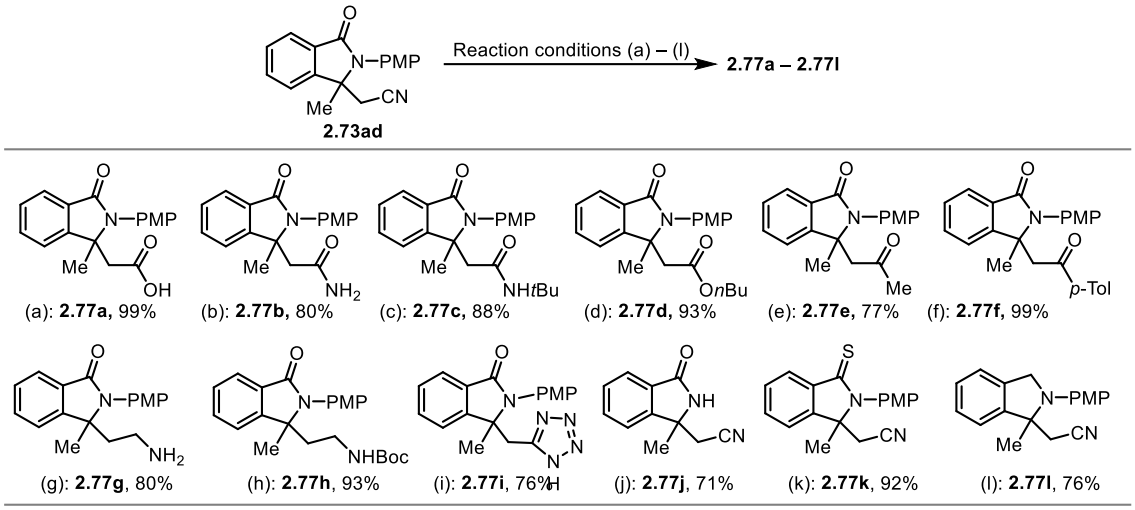
7.38 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 3.92 (s, 3H), 2.88 (d, *J* = 16.7 Hz, 1H), 2.82 (d, *J* = 16.7 Hz, 1H), 2.42 (s, 3H), 1.69 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.6, 141.4, 140.6, 132.9, 130.6, 127.1, 126.1, 123.3, 116.6, 116.1, 108.0, 63.2, 56.0, 29.2, 25.2, 21.2; **HRMS** (ESI) calcd for $[C_{18}H_{18}N_2O_3S + Na]^+$ 365.0930, found 365.0938; **IR** (thin film) 2254, 1597, 1293, 1172.



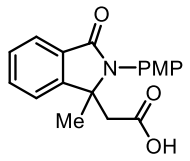
2.76m

Prepared from **2.75m** on a 0.2 mmol scale with Pd_2dba_3 (5 mol%), Xantphos (10 mol%), and BPh_3 (40 mol%) in toluene at 80 °C for 16 h. **2.76m** was purified by flash column chromatography (15:85:1 EtOAc/Hex/MeOH → 2:100 MeOH/CH_2Cl_2) as an amorphous white solid (0.178 mmol, 89% yield). R_f = 0.46 (1:1 EtOAc/Hex); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 – 7.91 (m, 1H), 7.78 – 7.70 (m, 2H), 7.67 (ddd, *J* = 7.7, 6.7, 1.8 Hz, 1H), 7.01 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.96 (d, *J* = 2.0 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.07 (d, *J* = 1.1 Hz, 2H), 2.93 (d, *J* = 16.6 Hz, 1H), 2.84 (d, *J* = 16.6 Hz, 1H), 1.73 (s, 3H);**^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.5, 148.7, 138.9, 134.1, 133.5, 130.4, 127.3, 123.4, 122.7, 121.9, 115.9, 113.3, 109.0, 102.2, 63.6, 29.2, 25.2; **HRMS** (ESI) calcd for $[C_{17}H_{14}N_2O_4S + Na]^+$ 365.0566, found 365.0557; **IR** (thin film) 2139, 1482, 1295, 1177.

2.6.4 Transformations of aminocyanation products 2.73ad and 2.73af

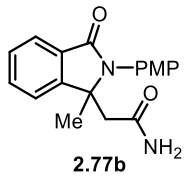


Reaction conditions: (a) KOH, EtOH/H_2O, 90 °C, 40 h; (b) KOH, MeOH/H_2O, 90 °C, 2 h; (c) H_2SO_4 (1.2 equiv), *t*BuOH, 80 °C, 12 h; (d) $TsOH \cdot H_2O$ (2 equiv), *n*BuOH, 120 °C, 20 h; (e) $Ni(acac)_2$ (10 mol%), $AlMe_3$ (3 equiv), benzene, 50 °C, 5 h; (f) $Pd(OAc)_2$ (10 mol%), *p*-tolylboronic acid (2 equiv), 2,2′-bipyridyl (20 mol%), CF_3CO_2H (10 equiv), THF/H_2O, 90 °C, 28 h; (g) $NaBH_4$ (4 equiv), $CoCl_2 \cdot 6H_2O$ (1.5 equiv), MeOH, 0 °C, 2 h; (h) $(Boc)_2O$ (2.5 equiv), $NaBH_4$ (4 equiv), $CoCl_2 \cdot 6H_2O$ (1.5 equiv), MeOH, 0 °C, 3 h; (i) $TMSN_3$ (3 equiv), $nBu_2Sn(O)$ (0.5 equiv), PhMe, 100 °C, 48 h; (j) cerium (IV) ammonium nitrate (6 equiv), CH_3CN/H_2O, rt, 2 h; (k) Lawesson's reagent (1 equiv), PhMe, 100 °C, 2.5 h; (l) Tf_2O (1.2 equiv), CH_2Cl_2, 0 °C to rt, 30 min, then Hantzsch ester (3 equiv), rt, 4 h. acac = acetylacetonyl; PMP = 4-methoxyphenyl.



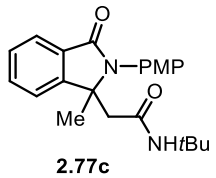
2.77a

Synthesis of 2.77a: In a one-dram reaction vial, **2.73ad** (58.5 mg, 0.2 mmol) was heated with KOH (224 mg, 4 mmol) in EtOH (0.6 mL) and H_2O (0.6 mL) at 90 °C for 40 h. The reaction was cooled to room temperature, acidified with 1 M HCl (10 mL), and extracted with EtOAc (15 mL × 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. Analytically pure **2.77a** was obtained as a pale brown powder without further purification (0.2 mmol, quant. yield). R_f = 0.35 (5:95 MeOH/CH_2Cl_2); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.08 (br s, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.9 Hz, 2H), 3.81 (s, 3H), 3.01 (d, *J* = 15.9 Hz, 1H), 2.62 (d, *J* = 15.9 Hz, 1H), 1.48 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 170.3, 167.2, 158.8, 149.3, 131.8, 131.2, 130.9, 128.03, 128.00, 122.8, 122.1, 114.4, 64.3, 55.3, 41.0, 26.3; **HRMS** (ESI) calcd for $[C_{18}H_{17}NO_4 + Na]^+$ 334.1050, found 334.1058; **IR** (thin film) 1712, 1651, 1513, 1246, 1185.



2.77b

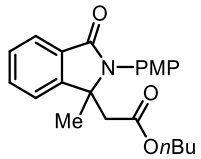
Synthesis of 2.77b: In a one-dram reaction vial, **2.73ad** (58.5 mg, 0.2 mmol) was heated with KOH (224 mg, 4 mmol) in MeOH (1.0 mL) and H_2O (1.0 mL) at 90 °C for 2 h. The reaction was cooled to room temperature, acidified with 1 M HCl (10 mL), and extracted with EtOAc (15 mL × 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting mixture was purified by flash column chromatography (4:96 → 5:95 MeOH/CH_2Cl_2) to give **2.77b** as a white foam (0.160 mmol, 80% yield). R_f = 0.24 (2:100 MeOH/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.5 Hz, 1H), 7.63 – 7.56 (m, 2H), 7.48 (td, *J* = 7.1, 1.7 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 5.64 (s, 1H), 5.42 (s, 1H), 3.82 (s, 3H), 2.74 (d, *J* = 14.6 Hz, 1H), 2.54 (d, *J* = 14.6 Hz, 1H), 1.63 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.8, 168.1, 159.4, 148.9, 132.2, 131.0, 130.9, 128.6, 127.5, 124.1, 122.0, 114.8, 65.3, 55.4, 44.1, 25.8; **HRMS** (ESI) calcd for $[C_{18}H_{18}N_2O_3 + Na]^+$ 333.1210, found 333.1214; **IR** (thin film) 3327, 3191, 1670, 1615, 1513, 1387, 1248.



2.77c

Synthesis of 2.77c: To a one-dram reaction vial was added **2.73ad** (58.5 mg, 0.2 mmol), *tert*-butyl alcohol (0.40 mL), and conc. H_2SO_4 (3 drops via glass pipiet, ca. 60 mg, 0.6 mmol). The reaction was heated at 80 °C for 24 h. The reaction was cooled to room temperature, diluted with CH_2Cl_2 (3 mL), and washed with saturated aqueous $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 mL × 3). The combined organic

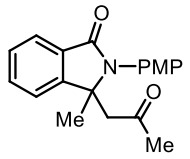
extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting mixture was purified by flash column chromatography (1:1 EtOAc/Hex) to afford **2.77c** as a white foam (0.176 mmol, 88% yield). R_f = 0.16 (1:1 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.63 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.59 – 7.49 (m, 2H), 7.37 – 7.31 (m, 2H), 7.04 – 6.97 (m, 2H), 4.77 (s, 1H), 3.85 (s, 3H), 2.70 (d, *J* = 14.3 Hz, 1H), 2.56 (d, *J* = 14.4 Hz, 1H), 1.59 (s, 3H), 1.06 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.4, 159.4, 149.0, 132.1, 131.6, 131.0, 128.7, 127.8, 124.9, 124.5, 121.7, 114.8, 65.7, 55.5, 51.1, 46.4, 28.3, 26.1; **HRMS** (ESI) calcd for $[C_{22}H_{26}N_2O_3 + Na]^+$ 389.1836, found 389.1845; **IR** (thin film) 3330, 1680, 1656, 1512, 1391, 1247.



2.77d

Synthesis of 2.77d: 2.73ad (0.2 mmol) was heated with $TsOH{\cdot}H_2O$ (76.1 mg, 0.4 mmol) and *n*BuOH (0.2 mL, 2.2 mmol) in a HPLC vial at 120 °C for 20 h. The reaction mixture was cooled to room temperature, concentrated onto Celite, and purified by flash column chromatography (1.5:100 MeOH/CH_2Cl_2) to afford **2.77d** as a colorless oil (0.186 mmol, 93% yield). R_f = 0.31 (2:100 MeOH/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.62 – 7.56 (m, 1H), 7.52 – 7.47 (m, 2H), 7.33 – 7.27 (m, 2H), 7.05 – 6.95 (m, 2H), 3.85 (s, 3H), 3.82 (t, *J* = 6.7 Hz, 2H), 2.86 (d, *J* = 15.0 Hz, 1H), 2.79 (d, *J* = 15.0 Hz, 1H), 1.60 (s, 3H), 1.37 – 1.24 (m, 2H), 1.20 – 1.08 (m, 2H), 0.82 (t, *J* =

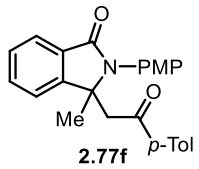
7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.0, 168.1, 159.4, 148.6, 131.8, 131.4, 131.0, 128.4, 127.8, 124.0, 121.6, 114.8, 64.8, 64.5, 55.4, 42.5, 30.2, 26.5, 18.9, 13.5; **HRMS** (ESI) calcd for $[C_{22}H_{25}NO_4 + Na]^+$ 390.1676, found 390.1679; **IR** (thin film) 1730, 1696, 1513, 1377, 1248.



2.77e

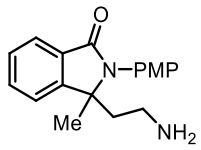
Synthesis of 2.77e:[28] Under N_2, $AlMe_3$ (2 M Hex, 0.6 mL, 1.2 mmol) was added dropwise to a solution of **2.73ad** (117 mg, 0.4 mmol) and $Ni(acac)_2$ (10.4 mmol, 0.04 mmol) in benzene (0.4 mL) at room temperature. The reaction was heated at 50 °C for 5 h and was allowed to cool to room temperature and stir overnight. The reaction was cooled to 0 °C and quenched by careful addition of water (2 mL), which was then taken up to 1 M HCl (10 mL) and extracted with EtOAc (20 mL × 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting mixture was purified by flash column chromatography (1.5:100 MeOH/CH_2Cl_2) to give **2.77e** as pale yellow oil (0.308 mmol, 77% yield). R_f = 0.27 (2:100 MeOH/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 – 7.90 (m, 1H), 7.58 (td, *J* = 7.4, 1.1 Hz, 1H), 7.54 (d, *J* = 7.1 Hz, 1H), 7.49 (td, *J* = 7.4, 1.2 Hz, 1H), 7.24 – 7.19 (m, 2H), 7.03 – 6.96 (m, 2H), 3.85 (s, 3H), 3.00 (d, *J* = 16.5 Hz, 1H), 2.80 (d, *J* = 16.6 Hz, 1H), 1.89 (s, 3H), 1.64 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 204.4, 168.0, 159.4, 148.9, 131.9, 131.4, 130.8, 128.3,

127.9, 124.1, 121.6, 114.7, 64.9, 55.4, 50.0, 31.4, 26.3; **HRMS** (ESI) calcd for $[C_{19}H_{19}NO_3 + Na]^+$ 332.1257, found 332.1262; **IR** (thin film) 1689, 1613, 1513, 1379, 1247.



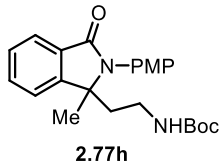
2.77f

Synthesis of 2.77f:[29] To a one-dram reaction vial was added **2.73ad** (58.5 mg, 0.2 mmol), *p*-tolylboronic acid (54.4 mg, 0.4 mmol), 2,2′-bipyridyl (6.2 mg, 0.04 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), CF_3CO_2H (150 μL, 2.0 mmol), THF (0.5 mL), and H_2O (0.1 mL). The reaction vessel was briefly purged with N_2 for ca. 1 min and then heated at 90 °C for 28 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL), and washed with 1 M HCl (5 mL). The aqueous phase was extracted with EtOAc (10 mL × 2). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting mixture was purified by flash column chromatography (1.5:100 MeOH/CH_2Cl_2) to give **2.77f** as an off-white powder (0.201 mmol, quant. yield). R_f = 0.28 (2:100 MeOH/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (dt, *J* = 6.3, 1.5 Hz, 1H), 7.70 – 7.56 (m, 2H), 7.52 – 7.38 (m, 3H), 7.23 – 7.09 (m, 4H), 7.03 – 6.86 (m, 2H), 3.81 (s, 3H), 3.50 (d, *J* = 16.8 Hz, 1H), 3.31 (d, *J* = 16.8 Hz, 1H), 2.36 (s, 3H), 1.73 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.5, 168.3, 159.4, 149.3, 144.0, 134.7, 131.7, 131.5, 130.9, 129.2, 128.1, 128.0, 127.9, 124.0, 121.7, 114.8, 65.1, 55.4, 44.5, 26.5, 21.5; **HRMS** (ESI) calcd for $[C_{25}H_{23}NO_3 + Na]^+$ 408.1570, found 408.1562; **IR** (thin film) 1687, 1606, 1513, 1380, 1247.



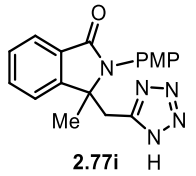
2.77g

Synthesis of 2.77g: To a solution of **2.73ad** (58.5 mg, 0.2 mmol) and $CoCl_2 \cdot 6H_2O$ (71.4 mg, 0.3 mmol) in MeOH (1.5 mL) was added $NaBH_4$ (30.3 mg, 0.8 mmol) in one portion at 0 °C. The resulting mixture was stirred at 0 °C for 2 h and quenched with saturated aqueous NH_4Cl (ca. 2 mL), which was then taken up to 1 N NaOH (10 mL) and extracted with EtOAc (15 mL × 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting mixture was purified by flash column chromatography (5:95:0.5 → 7:93:0.1 MeOH/CH_2Cl_2/Et_3N) to give **2.77g** as a tan oil (0.160 mmol, 80% yield). R_f = 0.26 (5:95:0.5 MeOH/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.5 Hz, 1H), 7.59 (td, *J* = 7.5, 1.2 Hz, 1H), 7.51 – 7.41 (m, 2H), 7.22 – 7.16 (m, 2H), 7.03 – 6.96 (m, 2H), 3.82 (s, 3H), 2.86 (br s, 2H), 2.62 (ddd, *J* = 12.0, 10.4, 4.8 Hz, 1H), 2.27 – 1.98 (m, 3H), 1.48 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.3, 159.3, 149.2, 132.2, 131.1, 130.2, 128.3, 127.9, 124.2, 121.2, 114.9, 66.4, 55.4, 40.1, 36.7, 26.6; **HRMS** (ESI) calcd for $[C_{18}H_{20}N_2O_2 + Na]^+$ 319.1417, found 319.1417; **IR** (thin film) 3367, 1683, 1513, 1380, 1248.



2.77h

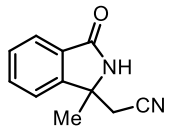
Synthesis of 2.77h: To a solution of **2.73ad** (58.5 mg, 0.2 mmol), Boc_2O (109 mg, 0.5 mmol), and $CoCl_2 \cdot 6H_2O$ (71.4 mg, 0.3 mmol) in MeOH (1.5 mL) was added $NaBH_4$ (30.3 mg, 0.8 mmol) in one portion at 0 °C. The resulting mixture was stirred at 0 °C for 3 h and quenched with saturated aqueous NH_4Cl (ca. 2 mL), which was then taken up to 1 N NaOH (10 mL) and extracted with EtOAc (15 mL × 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting mixture was purified by flash column chromatography (0.6:100 → 1:100 MeOH/CH_2Cl_2) to give **2.77h** as a white foam (0.186 mmol, 93% yield). R_f = 0.15 (1:100 MeOH/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.5 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.53 – 7.41 (m, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.02 – 6.93 (m, 2H), 4.28 (br s, 1H), 3.84 (s, 3H), 3.02 – 2.95 (br m 1H), 2.73 – 2.60 (br m 1H), 2.23 – 2.13 (br m 1H), 2.05 – 1.97 (br m 1H), 1.49 (s, 3H), 1.39 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.3, 159.2, 155.6, 149.0, 132.3, 131.1, 130.3, 128.3, 128.0, 124.4, 121.3, 114.8, 66.2, 55.4, 37.8, 36.0, 28.3, 26.7; **HRMS** (ESI) calcd for $[C_{23}H_{28}N_2O_4 + Na]^+$ 419.1941, found 419.1961; **IR** (thin film) 1683, 1513, 1382, 1249, 1173.



2.77i

Synthesis of 2.77i:[30] $TMSN_3$ (81 μL, 0.6 mmol) was added to a mixture of **2.73ad** (58.5 mg, 0.2 mmol) and *n*$Bu_2Sn(O)$ (24.9 mg, 0.1 mmol) in toluene (1.0 mL) at room temperature in a one-dram reaction vial. The resulting mixture was heated at 100 °C for 48

h. Upon cooling to room temperature, the reaction mixture was co-concentrated with MeOH (2 mL × 3 cycles). The residue was concentrated onto Celite and purified by flash column chromatography (3:100 → 5:100 MeOH/CH_2Cl_2) to give **2.77i** as an off-white solid (0.146 mmol, 73% yield). R_f = 0.20 (5:95 MeOH/CH_2Cl_2); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.65 – 7.53 (m, 3H), 7.53 – 7.47 (m, 2H), 7.43 (td, *J* = 7.2, 1.4 Hz, 1H), 7.13 – 7.03 (m, 2H), 3.82 (s, 3H), 3.55 (d, *J* = 15.2 Hz, 1H), 3.32 (d, *J* = 15.2 Hz, 1H), 1.63 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.9, 158.9, 152.5 (br), 147.9, 132.0, 131.5, 130.7, 128.4, 127.8, 122.9, 122.3, 114.4, 65.5, 55.3, 31.6, 25.5; **LRMS** (ESI) calcd for $[C_{18}H_{17}N_5O_2 - H]^-$ 334.1, found 334.1; **IR** (thin film) 1654, 1514.

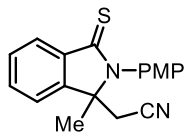


2.77j

Synthesis of 2.77j: Cerium (IV) ammonium nitrate (658 mg, 1.2 mmol) was added in one portion to a solution of **2.73ad** (58.5 mg, 0.2 mmol) in CH_3CN (1.6 mL) and H_2O (0.6 mL) at room temperature in a one-dram reaction vial. The resulting mixture was stirred for 2 h and diluted with water (10 mL), which was then extracted with EtOAc (15 mL × 3). Without further treatment,[1] the combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting mixture was purified by flash column chromatography (2:100 → 4:100 MeOH/CH_2Cl_2) to give **2.77j** as

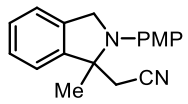
[1] Washing the organic extracts with a reducing agent, such as aqueous $NaHSO_3$ solution, reduced 1,4-benzoquinone by-product to hydroquinone. Hydroquinone coeluted with 2.77j during chromatography.

a pale yellow oil (0.142 mmol, 71% yield). R_f = 0.14 (2:100 MeOH/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (br s, 1H), 7.87 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.65 (td, *J* = 7.5, 1.2 Hz, 1H), 7.61 – 7.49 (m, 2H), 2.91 (d, *J* = 16.6 Hz, 1H), 2.84 (d, *J* = 16.6 Hz, 1H), 1.76 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.8, 148.9, 132.8, 130.7, 129.4, 124.3, 121.2, 116.3, 58.9, 30.2, 25.2; **HRMS** (ESI) calcd for $[C_{11}H_{10}N_2O + Na]^+$ 209.0685, found 209.0683; **IR** (thin film) 2251, 1699, 1470.



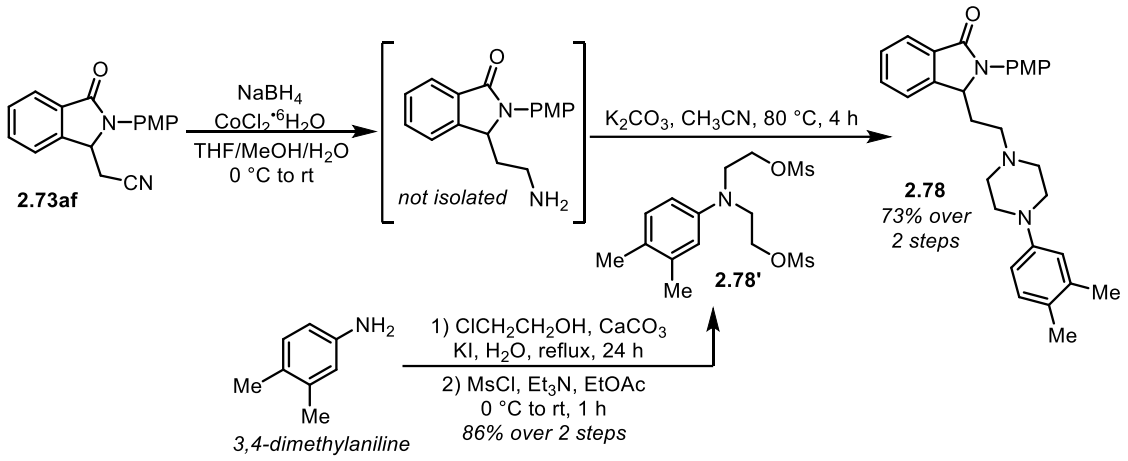
2.77k

Synthesis of 2.77k: 2.73ad (58.5 mg, 0.2 mmol) was heated with Lawesson's reagent (80.8 mg, 0.2 mmol) in toluene (0.8 mL) at 100 °C for 2.5 h in a one-dram reaction vial. The reaction mixture was cooled to room temperature, concentrated onto Celite, and purified by flash column chromatography (0:100 → 0.6:100 MeOH/CH_2Cl_2) to afford **2.77k** as a bright yellow foam (0.184 mmol, 92% yield). R_f = 0.58 (1:100 MeOH/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.70 (td, *J* = 7.5, 1.2 Hz, 1H), 7.65 – 7.55 (m, 2H), 7.25 – 7.19 (m, 2H), 7.13 – 7.06 (m, 2H), 3.87 (s, 3H), 2.95 (d, *J* = 16.6 Hz, 1H), 2.75 (d, *J* = 16.6 Hz, 1H), 1.72 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.8, 160.2, 145.0, 137.4, 132.6, 130.6, 129.8, 128.7, 126.5, 120.9, 115.5, 115.4, 55.5, 28.0, 24.0; **HRMS** (ESI) calcd for $[C_{18}H_{16}N_2OS+ Na]^+$ 331.0876, found 331.0883; **IR** (thin film) 2252, 1609, 1512, 1388, 1318, 1251.



2.77l

Synthesis of 2.77l:[31] Tf_2O (40.4 μL, 0.24 mmol) was added dropwise to a solution of **2.73ad** (58.5 mg, 0.2 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C under N_2. The reaction was stirred for 5 min at 0 °C, then it was allowed to warm to room temperature and stir for additional 30 min, whereupon Hantzsch ester (152 mg, 0.6 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 4 h, then it was directly concentrated onto Celite and purified by flash column chromatography (CH_2Cl_2) to afford **2.77l** as a colorless oil (0.152 mmol, 76% yield). **2.77l** appeared to be unstable upon extended exposure to air (> 5 h), but it can still be handled and characterized without special precautions. R_f = 0.56 (CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 4H), 7.02 – 6.95 (m, 2H), 6.95 – 6.90 (m, 2H), 4.76 (d, *J* = 13.0 Hz, 1H), 4.60 (d, *J* = 13.1 Hz, 1H), 3.80 (s, 3H), 2.95 (d, *J* = 16.7 Hz, 1H), 2.90 (d, *J* = 16.7 Hz, 1H), 1.80 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.4, 144.6, 138.3, 136.7, 128.3, 127.7, 122.5, 121.7, 118.8, 117.5, 114.9, 67.1, 55.7, 55.1, 27.8, 26.2; **HRMS** (ESI) calcd for $[C_{18}H_{18}N_2O + Na]^+$ 301.1311, found 301.1314; **IR** (thin film) 2248, 1513, 1246.



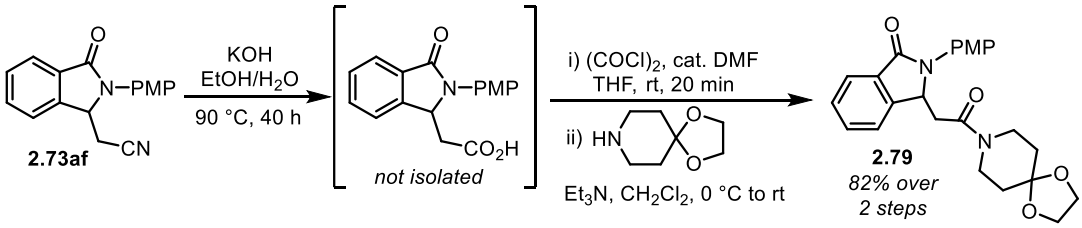
Synthesis of dimesylate 2.78':[49] A suspension of 3,4-dimethylaniline (606 mg, 5 mmol), 2-chloroethanol (1.7 mL, 25 mmol), $CaCO_3$ (1300 mg, 13 mmol), and KI (83 mg, 0.5 mmol) in water (5 mL) was heated to reflux (oil bath temperature 110 °C) for 24 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (50 mL) and water (10 mL), filtered through a pad of Celite, and separated. The organic phase was washed with water (10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting diol product was used for next step without further purification. Next, the above obtained diol (5 mmol theoretical) was dissolved in EtOAc (15 mL) and cooled to 0 °C. Et_3N (2.8 mL, 20 mmol), followed by a solution of MsCl (1718 mg, 15 mmol) in EtOAc (5 mL) was added dropwise at 0 °C. The resulting mixture was allowed to warm to room temperature and stir for 1 h. Upon completion, the reaction was diluted with Et_2O (30 mL), filtered through a pad of Celite, washed with 1 M HCl (20 mL), and separated. The organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting mixture was

purified by flash column chromatography (2:3 → 3:2 EtOAc/Hex) to afford dimesylate **2.78'** as a pale yellow oil (4.3 mmol, 86% yield over 2 steps). R_f = 0.44 (2:100 MeOH/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.3 Hz, 1H), 6.55 (d, *J* = 2.8 Hz, 1H), 6.49 (dd, *J* = 8.3, 2.9 Hz, 1H), 4.34 (t, *J* = 5.9 Hz, 4H), 3.72 (t, *J* = 5.9 Hz, 4H), 2.97 (s, 6H), 2.23 (s, 3H), 2.17 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 144.3, 137.9, 130.7, 126.6, 114.7, 110.6, 66.7, 51.0, 37.4, 20.3, 18.5.

Synthesis of piperazine 2.78: To a solution of **2.73af** (167 mg, 0.6 mmol) and $CoCl_2 \cdot 6H_2O$ (214 mg, 0.9 mmol) in THF/MeOH/H_2O (4.0, 0.5, 2.0 mL, respectively) was added $NaBH_4$ (182 mg, 4.8 mmol) in one portion at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (ca. 5 mL), which was then taken up to 1 N NaOH (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting amine product was used for next step without further purification. Next, the above obtained amine (0.6 mmol theoretical) was heated with dimesylate **6'** (146 mg, 0.4 mmol)[2] and K_2CO_3 (220 mg, 1.6 mmol) in CH_3CN (2 mL) at 80 °C for 4 h. The reaction was cooled to room temperature, diluted with EtOAc (30 mL), washed with water (5 mL), and separated. The organic phase was washed with brine (10 mL), dried over anhydrous $MgSO_4$, and

[2] It was difficult to separate product 6 from the residual dimesylate 6' during column chromatography. Thus 6' was tentatively used as the limiting reactant.

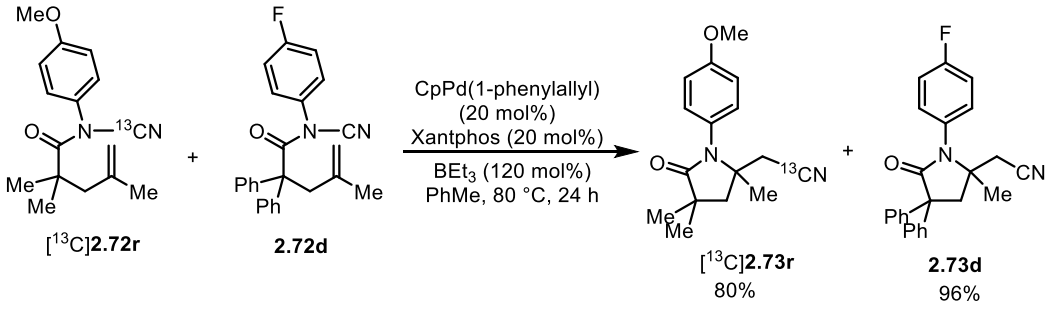
concentrated in vacuo. The resulting mixture was purified by flash column chromatography (4:6:0 → 5:5:0.15 EtOAc/Hex/MeOH) to afford **2.78** as a pale yellow oil (0.29 mmol, 73% yield over 2 steps based on **6'**). R_f = 0.30 (5:5:0.1 EtOAc/Hex/MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.92 (dt, *J* = 7.6, 1.1 Hz, 1H), 7.59 (td, *J* = 7.5, 1.2 Hz, 1H), 7.54 – 7.44 (m, 4H), 7.03 – 6.92 (m, 3H), 6.69 (d, *J* = 2.6 Hz, 1H), 6.62 (dd, *J* = 8.2, 2.7 Hz, 1H), 5.30 (dd, *J* = 6.0, 2.7 Hz, 1H), 3.84 (s, 3H), 3.06 – 2.98 (m, 4H), 2.41 – 2.34 (m, 4H), 2.20 (s, 3H), 2.19 – 1.96 (m, 7H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.1, 157.4, 149.4, 144.6, 137.0, 132.4, 131.8, 130.1, 129.8, 128.3, 128.0, 125.4, 124.1, 122.1, 118.0, 114.4, 113.7, 59.6, 55.5, 53.2, 52.4, 49.5, 28.2, 20.1, 18.7; **HRMS** (ESI) calcd for $[C_{29}H_{33}N_3O_2 + H]^+$ 456.2646, found 456.2652; **IR** (thin film)1690, 1513, 1389, 1248.



Synthesis of amide 2.79: 2.73af (111 mg, 0.4 mmol) was heated with KOH (448 mg, 8 mmol) in EtOH (1 mL) and H_2O (1 mL) at 90 °C for 40 h. The reaction was cooled to room temperature, acidified with 1 M HCl (15 mL), and extracted with EtOAc (20 mL × 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting carboxylic acid product was used for next step without further purification. Next, to a suspension of the above obtained

carboxylic acid (0.4 mmol theoretical) in THF (1 mL) was added one drop of DMF via glass pipet, followed by addition of $(COCl)_2$ (2.5 M solution in CH_2Cl_2, 0.32 mL, 0.8 mmol) at room temperature. The reaction mixture was stirred for 20 min, whereupon gas evolution ceased. The mixture was concentrated in vacuo at room temperature to afford the crude acid chloride, which was redissolved in THF (2 mL) and cooled to 0 °C. To this solution was added Et_3N (112 μL, 0.6 mmol), followed by a solution of 1,4-dioxa-8-azaspiro[4.5]decane (86 mg, 0.6 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C. The reaction was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was diluted with EtOAc (30 mL), washed with 0.5 M HCl (10 mL), and separated. The organic phase was washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting mixture was purified by flash column chromatography (3:2 → 7:3 EtOAc/Hex) to afford amide **2.79** as a pale yellow oil (0.33 mmol, 82% yield over 2 steps based on **2.73af**). R_f = 0.36 (7:3 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.3 Hz, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.56 (td, *J* = 7.4, 1.3 Hz, 1H), 7.54 – 7.48 (m, 3H), 7.04 – 6.87 (m, 2H), 5.79 (dd, *J* = 9.3, 3.7 Hz, 1H), 4.00 – 3.90 (m, 4H), 3.83 (s, 4H), 3.79 – 3.73(m, 1H), 3.72 – 3.66 (m, 1H), 3.36 – 3.26 (m, 2H), 2.88 (dd, *J* = 15.9, 3.7 Hz, 1H), 2.43 (dd, *J* = 16.0, 9.4 Hz, 1H), 1.71 – 1.62 (m, 2H), 1.50 (t, *J* = 5.8 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.9, 166.7, 157.4, 145.3, 132.1, 131.8, 129.4, 128.6, 125.1, 123.9, 123.2, 114.5, 106.5, 64.4, 58.3, 55.4, 43.5, 39.9, 36.3, 35.3, 34.7; **HRMS** (ESI) calcd for $[C_{24}H_{26}N_2O_5 + Na]^+$ 445.1734, found 445.1749; **IR** (thin film) 1694, 1633, 1514, 1361, 1248.

2.6.5 Double cross-over experiment



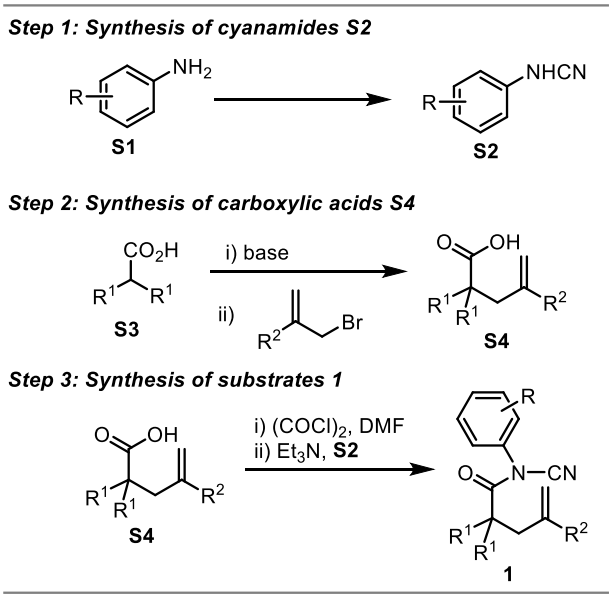
[^{13}C]**2.72r** was prepared in the same manner as **2.72r**, from cyanamide [^{13}C]**S2g** and carboxylic acid **S4b**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.22 – 7.14 (m, 2H), 6.98 – 6.90 (m, 2H), 4.99 – 4.89 (m, 1H), 4.87 (app s, 1H), 3.82 (s, 3H), 2.75 (s, 2H), 1.81 (s, 3H), 1.50 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.2 (d, $^{2}J_{C–C}$ = 4.5 Hz), 159.9, 141.4, 128.8, 127.7, 114.9, 114.8, 111.1 (^{13}CN), 55.5, 46.9, 44.9, 26.2, 23.9.

Double cross-over experiment: In a nitrogen-filled glove box, a one-dram vial was charged with a magnetic stirring bar, [^{13}C]**2.72r** (27.3 mg, 0.1 mmol), **2.72d** (38.4 mg, 0.1 mmol), BEt_3 (1.0 M in Hex, 120 µL, 0.12 mmol), Xantphos (11.6 mg, 0.02 mmol), and a solution of CpPd(1-phenylallyl) in toluene (0.02 M, 1.0 mL, 0.02 mmol). The reaction mixture was sealed with a PTFE lined cap, removed from the glove box, and heated at 80 °C in an aluminum heating block for 24 h. The resulting mixture was allowed to cool to room temperature, concentrated onto Celite, and purified by flash column chromatography (1:4 → 1:1 EtOAc/Hex) to give an inseparable mixture of [^{13}C]**2.73r** and **2.73d**. The yields were determined by integration of ^{1}H NMR spectrum of product mixture. **2.73d** showed

no detectable enrichment in ^{13}C by analysis of the ^{1}H and ^{13}C NMR spectra, or the HRMS data for the mixture.

2.6.6 Synthesis of substrates: N-acyl cyanamides

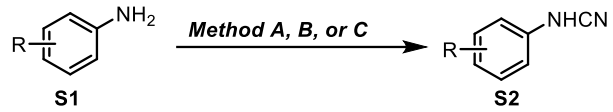
All *N*-acyl cyanamide substrates **1** are synthesized in 3 steps. Step 1 synthesizes aryl cyanamides **S2** from the corresponding anilines **S1**. Step 2 synthesizes carboxylic acids **S4**. Step 3 synthesizes substrates **1** by coupling cyanamides **S2** with acids **S4**.



2.6.6.1 Synthesis of cyanamides S2 (Step 1)

CAUTION! *Cyanogen bromide (BrCN) is highly toxic and hydrolyzes readily to release hydrogen cyanide. The related preparation must be carried out in a well-ventilated fume hood. Excess BrCN should be destroyed with aqueous NaOH solution and the resulting aqueous solution should be disposed of properly.*

Step 1. Synthesis of cyanamides S2

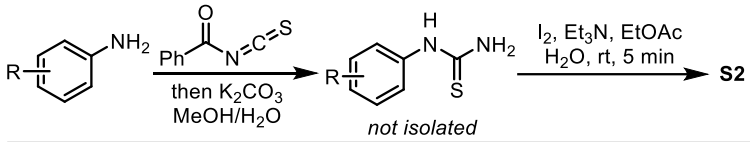


S1 **S2**

Method A: BrCN (0.6 equiv), Et_2O, 0 °C to rt, 24 h

Method B: BrCN (1.2 equiv), NaOAc (3.0 equiv), MeOH, 0 °C to rt, 24 h

Method C:



Method A: A solution of BrCN (1271 mg, 12 mmol) in Et_2O (10 mL) was slowly added to aniline **S1** (20 mmol) in Et_2O (20 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stir for 24 h. Upon completion, the mixture was diluted with Et_2O (40 mL) and filtered through a pad of Celite. The filtrate was washed with 1 M HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), and were dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography or precipitated from Et_2O/Hex or CH_2Cl_2/Hex at 0 °C.

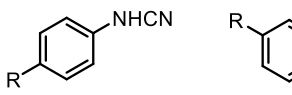
Method B: A solution of BrCN (2542 mg, 24 mmol) in MeOH (30 mL) was slowly added to a mixture of aniline (20 mmol) and NaOAc (60 mmol) in MeOH (30 mL) at 0 °C. The reaction mixture was stirred for 1 h, then was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was neutralized with saturated aqueous

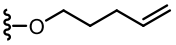
$NaHCO_3$ (20 mL) and concentrated to a small volume. The residue was taken up to water (50 mL) and extracted with CH_2Cl_2 (30 mL × 3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography.

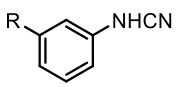
Method C: To a solution of aniline **S1** (10 mmol) in THF (15 mL) was added benzoyl isothiocyanate (1.48 mL, 11 mmol) in THF (10 mL) at room temperature. The resulting solution was stirred for 2–3 h. Upon completion, the reaction was concentrated, and the residue was suspended in MeOH (30 mL) and treated with a solution of K_2CO_3 (30 mmol) in H_2O (10 mL). The reaction was stirred overnight and concentrated, which was then taken up to water (100 mL). The resulting thiourea product was precipitated and collected by filtration, and was used without further purification. Next, to a suspension of the above obtained thiourea (10 mmol theoretical) in EtOAc (30 mL) was added H_2O (2 mL) and Et_3N (2.8 mL, 20 mmol), followed by addition of I_2 (2792 mg, 11 mol) in 6–7 batches at room temperature. Upon complete addition of I_2, the reaction was stirred for additional 5 min and quenched by addition of saturated aqueous $NaHSO_3$ (2 mL). The resulting mixture was diluted with EtOAc (50 mL) and filtered through a pad of Celite. The filtrate was washed with H_2O (10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography.

Method D: A solution of BrCN (2542 mg, 8 mmol) in toluene (4 mL) was slowly added to a mixture of aniline (4 mmol) and $NaHCO_3$ (14 mmol) in toluene (4 mL) at room temperature. The reaction mixture was stirred for overnight. Upon completion, the reaction was neutralized with saturated aqueous $NaHCO_3$ (5 mL) and taken up to water (20 mL). The crude product was collected by filtration and dissolved in DCM followed by water wash. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to afford solid product.

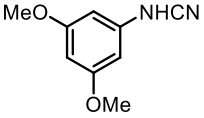
Synthesized cyanamides S2



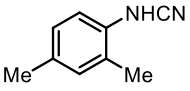
S2a, R = Me
S2b, R = H
S2c, R = *t*Bu
S2d, R = F
S2e, R = Cl
S2f, R = Br
S2g, R = OMe
S2h, R = OAc
S2i, R = NHAc
S2j, R = COMe
S2k, R = 



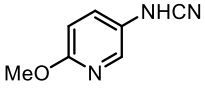
S2l, R = Cl
S2m, R = CF_3
S2n, R = CO_2Me
S2o, R = OMe



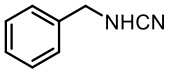
S2p



S2q

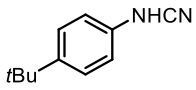


S2r



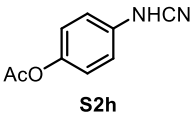
S2s

S2a, **S2b**, **S2d–S2g**, **S2o**, and **S2s** were known compounds and were prepared following reported procedures.[12,50–52]



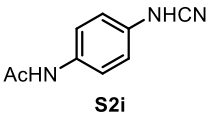
S2c

Prepared from 4-(*tert*-butyl)aniline on a 20.0 mmol scale using method A. **S2c** was purified by flash column chromatography (2:100 MeOH/CH_2Cl_2) as an off-white solid (9.36 mmol, 94% yield). R_f = 0.44 (5:95 MeOH/CH_2Cl_2); mp 86–88 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H), 7.00 – 6.90 (m, 2H), 6.10 (br s, 1H), 1.30 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 146.8, 134.4, 126.6, 115.1, 111.3, 34.3, 31.3; **HRMS** (ESI) calcd for $[C_{11}H_{14}N_2 + Na]^+$ 197.1049, found 197.1047; **IR** (thin film) 3159, 2227, 1517, 1253.



S2h

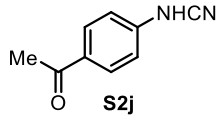
Prepared from 4-aminophenyl acetate[53] on a 9.7 mmol scale using method B. **S2h** was purified by precipitation (CH_2Cl_2/Hex) as an off-white solid (8.2 mmol, 85% yield). R_f = 0.54 (1:1 EtOAc/Hex); mp 95–97 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.04 (dd, *J* = 8.8, 1.1 Hz, 2H), 6.97 – 6.90 (m, 2H), 2.31 (d, *J* = 1.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.2, 146.3, 135.1, 122.8, 116.3, 111.0, 21.1; **HRMS** (ESI) calcd for $[C_9H_8N_2O_2 + Na]^+$ 199.0478, found 199.0505; **IR** (thin film) 3183, 2237, 1757, 1510, 1221, 1195.



S2i

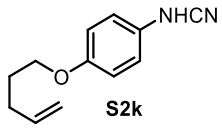
Prepared from *N*-(4-aminophenyl)acetamide on a 10 mmol scale using method B. **S2i** was purified by precipitation (MeOH/H_2O) as a tacky white solid. R_f = 0.48 (1:9 MeOH/CH_2Cl_2); **^{1}H NMR** (500 MHz, DMSO-d_6) δ 9.88 (s, 1H), 7.54 (d, *J* = 8.6 Hz, 2H),

6.88 (d, J = 8.5 Hz, 2H), 2.01 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ 167.9, 134.4, 133.7, 120.5, 115.2, 112.5, 23.8; **HRMS** (ESI) calcd for $[C_9H_9N_3O + Na]^+$ 198.0638, found 198.0649; **IR** (thin film) 2227, 1670, 1449.



S2j

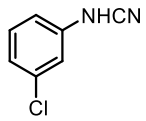
Prepared from 1-(4-aminophenyl)ethan-1-one on a 10.0 mmol scale using method C. **S2j** was purified by flash column chromatography (2:100 MeOH/CH_2Cl_2) as a pale yellow solid (6.2 mmol, 62% yield). R_f = 0.45 (5:95 MeOH/CH_2Cl_2); mp 110–112 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ 10.73 (s, 1H), 7.96 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 2.51 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ 196.2, 143.2, 131.5, 130.5, 114.7, 111.2, 26.4; **HRMS** (ESI) calcd for $[C_9H_8N_2O - H]^-$ 159.0564, found 159.0526; **IR** (thin film) 3188, 2229, 1740, 1272.



S2k

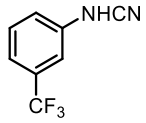
Prepared from 4-(pent-4-en-1-yloxy)aniline[54] on a 7.3 mmol scale using method B. **S2k** was purified by flash column chromatography (1:100 → 2:100 MeOH/CH_2Cl_2) as an oily purple solid (4.96 mmol, 68% yield). R_f = 0.28 (1:100 MeOH/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.97 – 6.91 (m, 2H), 6.90 – 6.85 (m, 2H), 6.11 (br s, 1H), 5.85 (ddt, J = 16.8, 10.1, 6.6 Hz, 1H), 5.06 (dt, J = 17.1, 1.5 Hz, 1H), 5.00 (dt, J = 10.2, 1.5 Hz, 1H), 3.93 (t, J = 6.6 Hz, 2H), 2.30 – 2.17 (m, 2H), 1.94 – 1.81 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$)

δ 155.6, 137.7, 130.0, 116.8, 115.7, 115.2, 111.8, 67.6, 30.0, 28.3. **HRMS** (ESI) calcd for $[C_{12}H_{14}N_2O + Na]^+$ 225.0998, found 225.0998; **IR** (thin film) 2218, 1640, 1510, 1233.



S2l

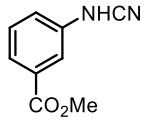
Prepared from 3-chloroaniline on a 15.0 mmol scale using method C. **S2l** was purified by flash column chromatography (2:100 MeOH/CH_2Cl_2) as a pale yellow solid (10.51 mmol, 71% yield). R_f = 0.48 (5:95 MeOH/CH_2Cl_2); mp 68–70 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 1H), 7.07 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.04 (t, *J* = 2.2 Hz, 1H), 6.92 (dd, *J* = 8.2, 2.3 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.3, 135.5, 130.8, 123.9, 115.7, 113.6, 110.7; **HRMS** (ESI) calcd for $[C_7H_5ClN_2 - H]^-$ 151.0068, found 151.0060; **IR** (thin film) 3396, 2237, 1600.



S2m

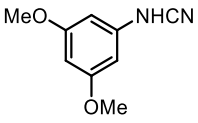
Prepared from 3-(trifluoromethyl)aniline on a 20.0 mmol scale using method C. **S2m** was purified by flash column chromatography (2:100 MeOH/CH_2Cl_2) as a pale yellow solid (16.8 mmol, 84% yield). R_f = 0.46 (5:95 MeOH/CH_2Cl_2); mp 85–87 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 (t, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 2.0 Hz, 1H), 7.23 (dd, *J* = 8.2, 2.3 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 137.9, 132.3 (q, $^2J_{F–C}$ = 32.8 Hz), 130.5, 123.4 (q, $^1J_{F–C}$ = 270.8 Hz), 120.5 (q, $^3J_{F–C}$ = 3.8 Hz), 118.6,

112.3 (q, $^{3}J_{F–C}$ = 3.9 Hz), 110.7; **^{19}F NMR** (470 MHz, $CDCl_3$) δ –63.0; **LRMS** (ESI) calcd for $[C_8H_5F_3O_2 – H]^-$ 185.0, found 185.1; **IR** (thin film) 3110, 2242, 1331. The NMR data is consistent with a literature report.[55]



S2n

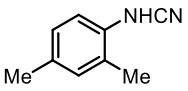
Prepared from methyl 3-aminobenzoate on a 15.0 mmol scale using method C. **S2n** was purified by flash column chromatography (1:100 → 2:100 MeOH/CH_2Cl_2) as a pale yellow solid (13.5 mmol, 90% yield). R_f = 0.46 (5:95 MeOH/CH_2Cl_2); mp 88–91 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.71 (app s, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.28 (dd, *J* = 8.1, 2.6 Hz, 1H), 3.94 (d, *J* = 1.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.6, 137.8, 131.5, 130.0, 124.6, 119.6, 116.4, 110.8, 52.6; **HRMS** (ESI) calcd for $[C_9H_8N_2O_2 + Na]^+$ 199.0478, found 199.0478; **IR** (thin film) 3152, 2227, 1594, 1251.



S2p

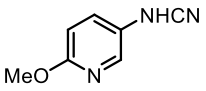
Prepared from 3,5-dimethoxyaniline on a 10.0 mmol scale using method B. **S2p** was purified by flash column chromatography (3:100 MeOH/CH_2Cl_2) as a white solid (5.2 mmol, 52% yield). R_f = 0.44 (5:95 MeOH/CH_2Cl_2); mp 138–140 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26 (s, 1H), 6.19 (d, *J* = 2.1 Hz, 1H), 6.16 (d, *J* = 2.1 Hz, 2H), 3.78 (s, 6H); **^{13}C**

NMR (125 MHz, $CDCl_3$) δ 161.9, 138.8, 110.4, 95.8, 94.0, 55.5; **HRMS** (ESI) calcd for $[C_9H_{10}N_2O_2 - H]^-$ 177.0670, found 177.0689. **IR** (thin film) 2946, 2242, 1114, 1028.



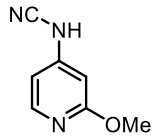
S2q

Prepared from 2,4-dimethylaniline on a 10.0 mmol scale using method A. **S2q** was purified by precipitation (Et_2O/Hex) as an off-white solid (8.4 mmol, 84% yield). R_f = 0.46 (5:95 MeOH/CH_2Cl_2); mp 102–104 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.1 Hz, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.96 (app s, 1H), 6.06 (br s, 1H), 2.28 (s, 3H), 2.20 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 133.3, 132.9, 131.6, 127.9, 124.1, 115.6, 111.9, 20.6, 16.9; **HRMS** (ESI) calcd for $[C_9H_{10}N_2 + Na]^+$ 169.0736, found 169.0740; **IR** (thin film) 3184, 2220, 1514.



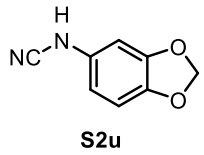
S2r

Prepared from 6-methoxypyridin-3-amine on a 10.0 mmol scale using method C. **S2r** was purified by flash column chromatography (3:97 → 5:95 MeOH/CH_2Cl_2) as a brick red solid (6.75 mmol, 68% yield). R_f = 0.44 (5:95 MeOH/CH_2Cl_2); mp 105–107 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ 10.11 (br s, 1H), 7.84 (dd, *J* = 3.0, 0.7 Hz, 1H), 7.36 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.84 (dd, *J* = 8.8, 0.7 Hz, 1H), 3.80 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ 159.6, 133.0, 129.6, 127.3, 112.1, 111.3, 53.3; **HRMS** (ESI) calcd for $[C_7H_7N_3O + H]^+$ 150.0662, found 150.0654; **IR** (thin film) 3054, 2210, 1495.



S2t

Prepared from 6-methoxypyridin-4-amine on a 4.0 mmol scale using method C. **S2t** was purified by flash column chromatography (4:100 → 5:100 MeOH/CH_2Cl_2) as a white solid (2.76 mmol, 69% yield). R_f = 0.44 (5:100 MeOH/CH_2Cl_2); mp 171–174 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.47 (s, 1H), 7.88 (d, *J* = 5.7 Hz, 1H), 6.53 (d, *J* = 5.1 Hz, 1H), 6.21 (d, *J* = 1.7 Hz, 1H), 3.86 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 163.5, 156.9, 144.4, 114.1, 107.2, 94.6, 54.9; **HRMS** (ESI) calcd for $[C_7H_7N_3O + Na]^+$ 172.0481, found 172.0510; **IR** (thin film) 2138, 1631, 1595, 1494.



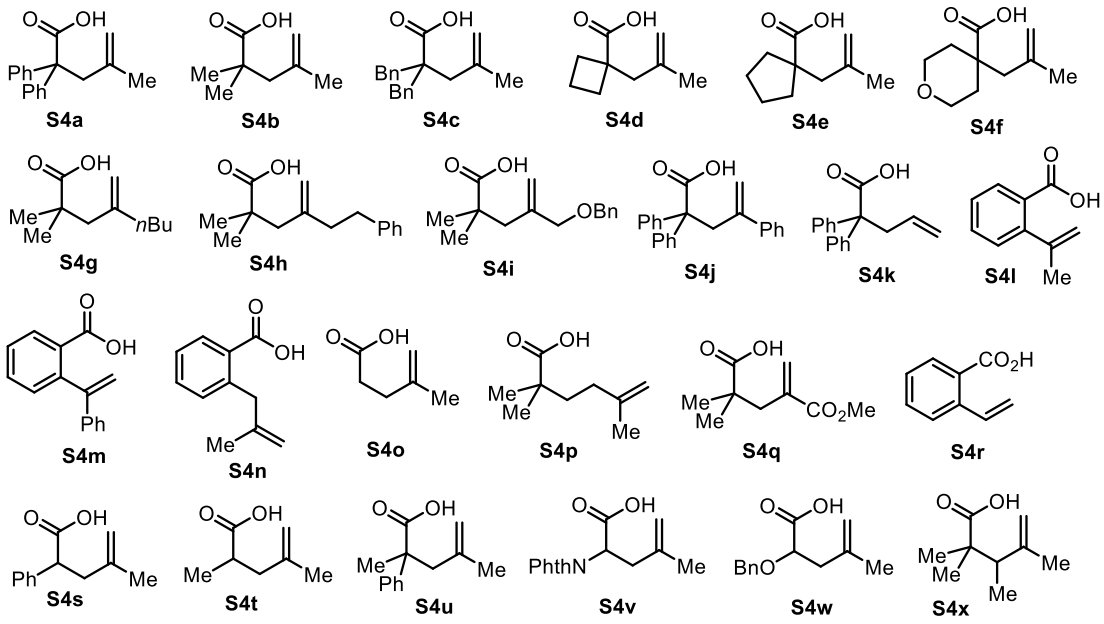
S2u

Prepared from benzo[d][1,3]dioxol-5-amine on a 4.0 mmol scale using method D. **S2u** was collected as a white solid (0.13 mmol, 33% yield).). R_f = 0.51 (5:100 MeOH/CH_2Cl_2); mp 83–85 °C;**^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.75 (d, *J* = 8.4 Hz, 1H), 6.57 (s, 1H), 6.45 (d, *J* = 8.2 Hz, 1H), 5.97 (s, 2H), 5.61 (br s, 1H); **^{13}C NMR** (125 MHz,

$CDCl_3$) δ 148.7, 144.2, 131.6, 111.6, 108.7, 108.0, 101.6, 98.1; **HRMS** (ESI) calcd for $[C_8H_6N_2O_2 + Na]^+$ 185.0321, found 185.0304; **IR** (thin film) 2222, 1637, 1485, 1199.

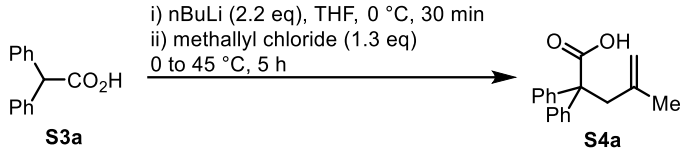
2.6.6.2 Synthesis of carboxylic acids S4 (Step 2)

Synthesized carboxylic acids S4

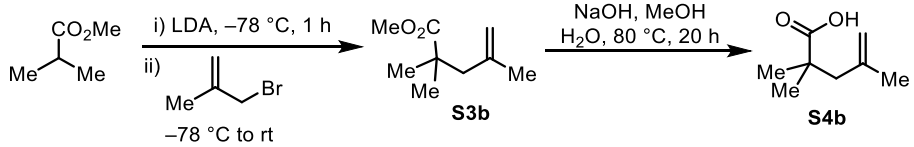


S4j–S4o, S4r, and **S4s** were known compounds and were prepared following known procedures.[3]

[3] **S4j**: Zhang, Z.; Liu, F. *Org. Biomol. Chem.* **2015**, *13*, 6690. **S4k**: Marion Merrell Dow Inc. Patent: US5039691 A1, 1991. **S4l–S4o**: Nicolai, S.; Erard, S.; González, D. F.; Waser, J. *Org. Lett.* **2010**, *12*, 384. **S4r**: Bunescu, A.; Wang, Q.; Zhu, J. *Chem. Euro. J.* **2014**, *20*, 14633. **S4s**: Barczak, N. T.; Jarvo, E. R. *Chem. Euro. J.* **2011**, *17*, 12912.



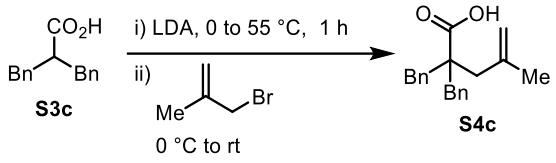
Synthesis of S4a: To a solution of diphenylacetic acid **S3a** (10.610g, 50 mmol) in THF (100 mL) was slowly added *n*BuLi (2.5 M Hex, 44 mL, 110 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min, followed by slow addition of methally chloride (7.04 mL, 65 mmol). The reaction was heated to 45 °C for 5 hours, which was then cooled in an ice bath, acidified with 2 N HCl to pH < 2, and separated. The aqueous phase was extracted with Et_2O (30 mL × 3). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated to a small volume, whereupon acid **S4a** began to precipitate. Cold hexanes (ca. 80 mL) was added to allow further precipitation of **S4a**, which was collected by vacuum filtration as a white crystalline solid (8.65g, 32.5 mmol, 65% yield). R_f = 0.32 (1:4 EA/Hex); mp 117–118 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 4H), 7.31 – 7.21 (m, 6H), 4.71 (t, *J* = 1.7 Hz, 1H), 4.55 (app s, 1H), 3.18 (s, 2H), 1.33 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 180.1, 142.6, 141.8, 129.0, 127.8, 126.9, 115.6, 60.1, 45.6, 24.3; **IR** (thin film) 3059, 1699, 1495, 1215. The NMR data is consistent with a literature report.[56]



Synthesis of S3b: To a solution of *i*Pr_2NH (3.36 mL, 24 mmol) in THF (15 mL) was dropwise added *n*BuLi (2.5 M Hex, 9.2 mL, 23 mmol) at –78 °C. The resulting solution was stirred at –78 °C for 40 min, then a solution of methyl isobutyrate (2043 mg, 20 mmol) in THF (10 mL) was dropwise added. The reaction mixture was stirred at –78 °C for additional 1 h, followed by slow addition of methallyl bromide (2.62 mL, 26 mmol) at the same temperature. The resulting mixture was allowed to warm to room temperature and stir overnight, which was then quenched with saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (20 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The resulting mixture was purified by flash column chromatography (2:98 → 1:9 Et_2O/Hex) to give ester **S3b** as a colorless oil (2340 mg, 15 mmol, 75% yield). R_f = 0.44 (5:95 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.81 – 4.74 (m, 1H), 4.62 – 4.60 (m, 1H), 3.64 (s, 3H), 2.28 (s, 2H), 1.62 (s, 3H), 1.16 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 178.3, 142.4, 114.1, 51.6, 48.5, 42.0, 25.5, 23.4; **IR** (thin film) 1734, 1643, 1199, 1131.

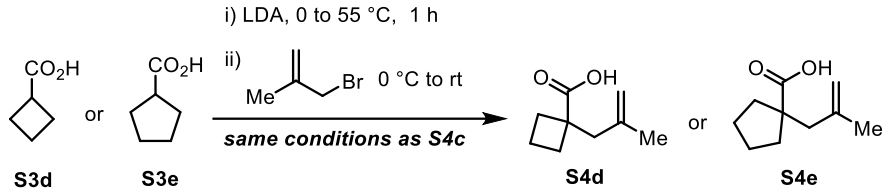
Synthesis of S4b: A mixture of **S3b** (1562 mg, 10 mmol), NaOH (800 mg, 20 mmol), MeOH (10 mL), and H_2O (10 mL) was heated at 80 °C for 20 h. The reaction was cooled to 0 °C, acidified with 2 N HCl to pH ≤ 2, and extracted with Et_2O (20 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give **S4b** as a bright yellow oil (1390 mg, 9.8 mmol, 98% crude yield). **S4b** was co-concentrated with benzene (5 mL × 3 cycles) and was used without further

purification. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.84 – 4.82 (m, 1H), 4.71 – 4.69 (m, 1H), 2.34 (s, 2H), 1.71 (s, 3H), 1.21 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 185.2, 142.2, 114.4, 48.2, 42.0, 25.3, 23.6. The NMR data is consistent with a known report.[57]



Synthesis of S4c: To a solution of *i*Pr_2NH (1.05 mL, 7.5 mmol) in THF (6 mL) was dropwise added *n*BuLi (2.5 M Hex, 2.9 mL, 7.2 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 10 min, then a solution of 2-benzyl-3-phenylpropanoic acid **S3c**[58] (721 mg, 3.0 mmol) in THF (3 mL) was slowly added. The reaction mixture was heated at 55 °C for 1 h, then was cooled back to 0 °C and added methallyl bromide (0.43 mL, 4.2 mmol). The reaction was allowed to warm to room temperature and stir overnight, then it was acidified with 2 N HCl to pH ≤ 2 and extracted with Et_2O (20 mL × 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated. The resulting mixture was purified by flash column chromatography (1:4 → 3:7 Et_2O/Hex) to give acid **S4c** as a pale yellow oil (795 mg, 2.7 mmol, 90% yield). R_f = 0.39 (3:7 Et_2O/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 – 7.16 (m, 10H), 5.02 (app s, 1H), 4.87 (app s, 1H), 3.10 (d, *J* = 14.0 Hz, 2H), 3.05 (d, *J* = 14.0 Hz, 2H), 2.26 (s, 2H), 1.73 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 182.6, 142.1, 137.1, 130.4, 128.0, 126.6, 113.1, 50.5,

41.1, 40.9, 25.1; **HRMS** (ESI) calcd for $[C_{20}H_{22}O_2 - H]^-$ 293.1547, found 293.1536; **IR** (thin film) 1700, 1454, 1265.

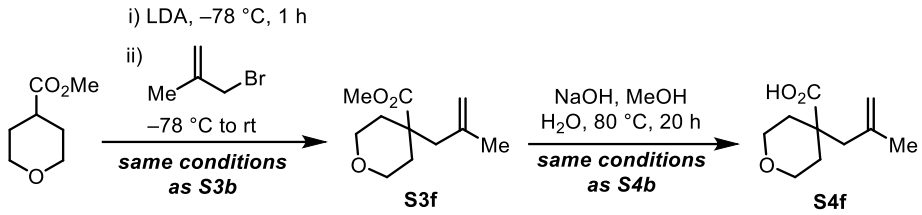


S4d and **S4e** were synthesized in the manner as **S4c**.

S4d was synthesized from cyclobutanecarboxylic acid **S3d** on a 5 mmol scale. **S4d** was purified by flash column chromatography (1:9 → 15:85 EtOAc/Hex) as a colorless oil (648 mg, 4.2 mmol, 84% yield). R_f = 0.52 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.76 (app s, 1H), 4.60 (app s, 1H), 2.56 (s, 2H), 2.55 – 2.47 (m, 2H), 2.06 – 1.98 (m, 2H), 1.98 – 1.90 (m, 2H), 1.69 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 183.7, 142.3, 112.1, 47.0, 45.4, 30.5, 23.3, 15.8; **LRMS** (ESI) calcd for $[C_9H_{14}O_2 - H]^-$ 153.1, found 153.1; **IR** (thin film) 3076, 1698, 1650, 1256, 1225.

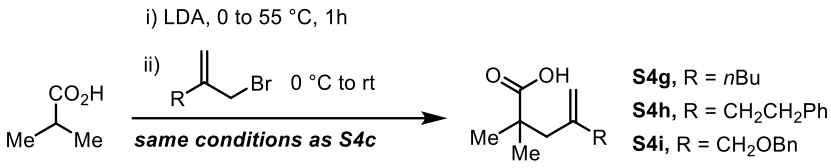
S4e was synthesized from cyclopentanecarboxylic acid **S3e** on a 15 mmol scale. **S4e** was purified by flash column chromatography (1:4 → 1:3 Et_2O/Hex) as a pale yellow oil (1796 mg, 10.68 mmol, 71% yield). R_f = 0.32 (3:7 Et_2O/Hex); **^{1}H NMR** (500 MHz,

$CDCl_3$) δ 4.78 – 4.77 (m, 1H), 4.67 (d, *J* = 1.1 Hz, 1H), 2.42 (s, 2H), 2.19 – 2.11 (m, 2H), 1.70 (s, 3H), 1.68 – 1.50 (m, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 184.6, 142.8, 113.2, 53.3, 46.4, 36.2, 24.8, 23.3; **HRMS** (ESI) calcd for $[C_{10}H_{16}O_2 - H]^-$ 167.1078, found 167.1049; **IR** (thin film) 3075, 1697, 1650, 1453, 1223.



S3f was synthesized in the same manner as **S3b**, starting from methyl tetrahydro-2*H*-pyran-4-carboxylate on a 7.3 mmol scale. **S3f** was purified by flash column chromatography (1:9 → 15:85 Et_2O/Hex) as a pale yellow oil (1230 mg, 6.2 mmol, 85% yield). R_f = 0.42 (1:9 Et_2O/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.84 – 4.83 (m, 1H), 4.66 (dd, *J* = 2.1, 1.0 Hz, 1H), 3.82 (dt, *J* = 11.9, 3.8 Hz, 2H), 3.71 (s, 3H), 3.45 (td, *J* = 11.6, 2.3 Hz, 2H), 2.31 (s, 2H), 2.09 (dd, *J* = 13.9, 2.7 Hz, 2H), 1.67 (s, 3H), 1.55 (ddd, *J* = 13.8, 11.2, 4.4 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.0, 140.9, 114.9, 65.3, 51.6, 48.7, 45.0, 34.6, 23.7; **HRMS** (ESI) calcd for $[C_{11}H_{18}O_3 + Na]^+$ 221.1148, found 221.1168; **IR** (thin film) 1730, 1647, 1194, 1134.

S4f was synthesized in the same manner as **S4b**, from the hydrolysis of **S3f** on a 10.0 mmol scale. **S4f** was obtained as a white solid (1784 mg, 9.7 mmol, 97% crude yield) and was used without further purification. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.88 – 4.83 (m, 1H), 4.72 (app s, 1H), 3.86 (dt, *J* = 12.0, 3.8 Hz, 2H), 3.53 (td, *J* = 11.7, 2.3 Hz, 2H), 2.35 (s, 2H), 2.09 (dd, *J* = 13.9, 2.6 Hz, 2H), 1.73 (s, 3H), 1.59 (ddd, *J* = 13.8, 11.2, 4.5 Hz, 2H).



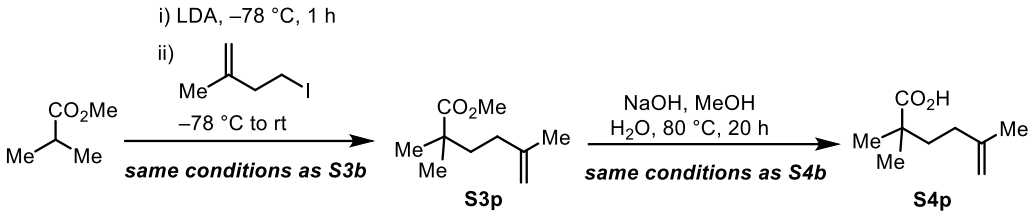
S4g–S4i were synthesized in the same manner as **S4c** by quenching the dianion of isobutyric acid with the corresponding substituted allyl bromide.

S4g was synthesized from isobutyric acid on a 8.0 mmol scale, using 2-(bromomethyl)hex-1-ene[59] as the quenching electrophile. **S4g** was purified by flash column chromatography (5:95 → 1:9 EtOAc/Hex) as a colorless oil (1066 mg, 5.78 mmol, 72% yield). R_f = 0.60 (1:4 EtOAc/Hex); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.84 (q, *J* = 1.5 Hz, 1H), 4.73 (app s, 1H), 2.33 (s, 2H), 1.97 (t, *J* = 7.3 Hz, 2H), 1.45 – 1.35 (m, 2H), 1.34 – 1.23 (m, 2H), 1.21 (s, 6H), 0.89 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.9,

146.3, 112.9, 46.2, 42.2, 36.7, 30.1, 25.4, 22.4, 13.9; **LRMS** (ESI) calcd for $[C_{11}H_{20}O_2 - H]^-$ 183.1, found 183.2; **IR** (thin film) 3053, 1699, 1640, 1474.

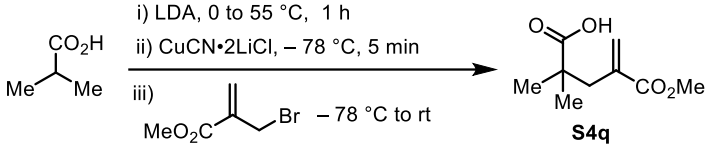
S4h was synthesized from isobutyric acid on a 6.0 mmol scale, using 2(3-(bromomethyl)but-3-en-1-yl)benzene[60] as the quenching electrophile. **S4h** was purified by flash column chromatography (5:95 → 1:9 EtOAc/Hex) as a pale yellow oil (981 mg, 4.22 mmol, 70% yield). R_f = 0.41 (15:85 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 2H), 7.20 – 7.12 (m, 3H), 4.88 (q, *J* = 1.5 Hz, 1H), 4.78 (app s, 1H), 2.79 – 2.69 (m, 2H), 2.37 (s, 2H), 2.33 – 2.22 (m, 2H), 1.22 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 184.8, 145.5, 142.0, 128.3, 128.3, 125.7, 113.8, 46.1, 42.2, 38.9, 34.6, 25.4; **HRMS** (ESI) calcd for $[C_{15}H_{20}O_2 - H]^-$ 231.1391, found 231.1375; **IR** (thin film) 3064, 1697, 1641, 1474, 1219.

S4i was synthesized from isobutyric acid on a 8.0 mmol scale, using 2(((2-(bromomethyl)allyl)oxy)methyl)benzene[61] as the quenching electrophile (performed at – 78 °C instead of 0 °C). Unfortunately, several attempts to purify **S4i** by flash column chromatography were unsuccessful. **S4i** was thus taken to the next step without further treatment.

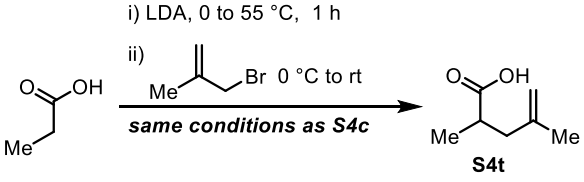


S3p was synthesized in the same manner as **S3b**, starting from methyl isobutyrate on a 20 mmol scale and using 4-iodo-2-methylbut-1-ene[62] as the quenching electrophile. **S3p** was purified by flash column chromatography (5:95 Et_2O/Hex) as a colorless oil (2348 mg, 13.8 mmol, 69% yield). R_f = 0.48 (5:95 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.69 (app s, 1H), 4.67 (app s, 1H), 3.67 (s, 3H), 1.96 – 1.88 (m, 2H), 1.72 (s, 3H), 1.68 – 1.63 (m, 2H), 1.19 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 178.3, 145.7, 109.7, 51.6, 42.1, 38.8, 33.1, 25.1, 22.6; **IR** (thin film) 1734, 1650, 1194, 1133.

S4p was synthesized in the same manner as **S4b**, from the hydrolysis of **S3p** on a 13.8 mmol scale. **S4p** was obtained as a pale yellow oil (2051 mg, 13.1 mmol, 95% crude yield), and was used without further purification. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.71 – 4.69 (m, 1H), 4.69 – 4.68 (m, 1H), 2.05 – 1.93 (m, 2H), 1.74 (s, 3H), 1.72 – 1.64 (m, 2H), 1.22 (s, 6H).



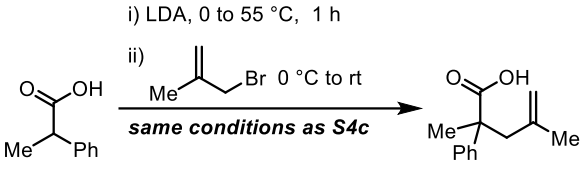
Synthesis of S4q: To a solution of *i*Pr_2NH (1.9 mL, 13.5 mmol) in THF (10 mL) was dropwise added *n*BuLi (2.5 M Hex, 5.2 mL, 13.0 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 10 min, followed by addition of isobutyric acid (475 mg, 5.4 mmol) in THF (5 mL). The reaction was heated at 55 °C for 1 h, which was then cooled back to –78 °C and was added CuCN•2LiCl (1 M THF solution, 6.4 mL, 6.4 mmol). The resulting mixture was stirred at –78 °C for 5 min, whereupon methyl 2-(bromomethyl)acrylate[61] (1353 mg, 7.56 mmol) was added. The reaction was allowed to warm to room temperature and stir overnight, then it was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (20 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The resulting mixture was purified by flash column chromatography (2:100 → 5:100 MeOH/CH_2Cl_2) to give **S4q** as a pale yellow oil (376 mg, 2.02 mmol, 37% yield). R_f = 0.54 (5:95 MeOH/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.26 (d, *J* = 1.5 Hz, 1H), 5.61 (d, *J* = 1.3 Hz, 1H), 3.73 (s, 3H), 2.66 (d, *J* = 1.0 Hz, 2H), 1.19 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 183.6, 167.9, 137.0, 128.3, 51.9, 42.8, 40.7, 24.6; **IR** (thin film) 1705, 1701, 1440, 1299, 1199, 1168.



S4t

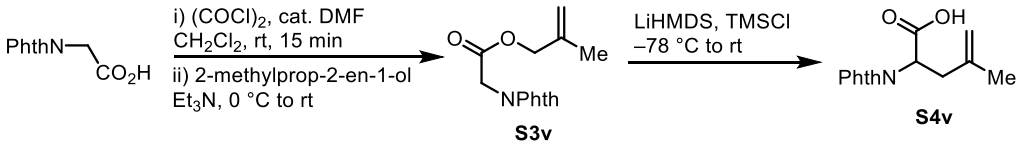
S4t was synthesized in the same manner as **S4c** by quenching the dianion of propionic acid with methallyl bromide. **S4t** obtained as a pale yellow oil, which was

sufficiently pure without column chromatography purification (95% yield). R_f = 0.35 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.80 (app s, 1H), 4.74 (d, *J* = 1.0 Hz, 1H), 2.67 (sextet, *J* = 7.1 Hz, 1H), 2.45 (ddd, *J* = 14.2, 7.1, 1.2 Hz, 1H), 2.10 (ddd, *J* = 14.1, 7.8, 1.1 Hz, 1H), 1.72 (s, 3H), 1.17 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.9, 142.5, 112.5, 41.5, 37.6, 22.1, 16.5. The NMR data is consistent with a literature report.[63]



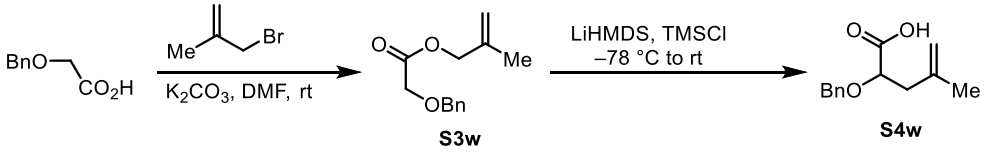
S4u

S4u was synthesized in the same manner as **S4c** by quenching the dianion of 2-phenylpropanoic acid[64] with methallyl bromide. **S4u** was purified by flash column chromatography (1:9 EtOAc/Hex) as a pale yellow oil (68% yield). R_f = 0.35 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 – 7.37 (m, 2H), 7.33 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.29 – 7.22 (m, 1H), 4.85 – 4.79 (m, 1H), 4.66 (d, *J* = 1.2 Hz, 1H), 2.94 (d, *J* = 13.5 Hz, 1H), 2.65 (d, *J* = 13.5 Hz, 1H), 1.57 (s, 3H), 1.47 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 182.4, 142.9, 141.9, 128.4, 127.1, 126.2, 115.4, 49.2, 46.8, 23.8, 21.7; **LRMS** (ESI) calcd for $[(C_{13}H_{15}O_2)_2 + Na]^-$ 429.2, found 429.2. **IR** (thin film) 2941, 1690, 1449, 1408, 1375, 1320, 1274.



Synthesis of S3v: To a solution of *N*-phthaloylglycine (2462 mg, 12 mmol) in CH_2Cl_2 (20 mL) was added 4 drops of DMF via glass pipet, followed by addition of $(COCl)_2$ (2.5 M solution in CH_2Cl_2, 4.4 mL, 11 mmol) at room temperature. The reaction mixture was stirred for 15 min, whereupon gas evolution ceased, and it was cooled to 0 °C. To this solution was added Et_3N (3.34 mL, 24 mmol), followed by a solution of 2-methylprop-2-en-1-ol (721 mg, 10 mmol) in CH_2Cl_2 (6 mL) at 0 °C. The reaction was allowed to warm to room temperature and stir for 1.5 h. The reaction was diluted with CH_2Cl_2 (30 mL), washed with 1 M HCl (20 mL), and separated. The organic phase was washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting mixture was purified by flash column chromatography (1:4 EtOAc/Hex) to afford **S3v** as a white foam (2182 mg, 8.4 mmol, 84% yield). R_f = 0.36 (1:4 EtOAc/Hex); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.1 Hz, 2H), 4.98 (t, *J* = 1.2 Hz, 1H), 4.95 (dd, *J* = 1.6, 0.8 Hz, 1H), 4.59 (s, 2H), 4.49 (s, 2H), 1.75 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.4, 167.0, 139.0, 134.2, 132.0, 123.6, 113.7, 69.0, 38.8, 19.4; **HRMS** (ESI) calcd for $[C_{14}H_{13}NO_4 + Na]^+$ 282.0737, found 282.0744; **IR** (thin film) 1752, 1724, 1416, 1193.

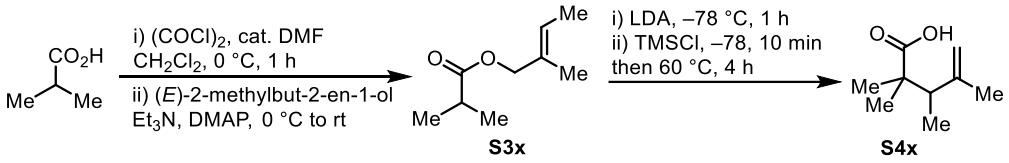
Synthesis of S4v: To a solution of hexamethyldisilazane (2.2 mL, 10.4 mmol) in THF (4 mL) was dropwise added *n*BuLi (2.5 M Hex, 3.8 mL, 9.6 mmol) at 0 °C. The resulting LiHMDS solution was allowed to warm to room temperature and stirred for 20 min, which was then dropwise added to a solution of **S3v** (2074 mg, 8 mmol) and TMSCl (1.32 mL, 10.4 mmol) in THF (12 mL) at –78 °C. The reaction was stirred at –78 °C for 10 min and was allowed to warm to room temperature and stir overnight. 1 M HCl (20 mL) was added and the resulting mixture was stirred at room temperature for 30 min and extracted with EtOAc (20 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The resulting mixture was purified by flash column chromatography (1:100:1 → 2:100:0.5 MeOH/CH_2Cl_2/AcOH) to give **S4v** as a yellow foam (520 mg, 2.0 mmol, 25% yield). R_f = 0.44 (2:100:0.1 MeOH/CH_2Cl_2/AcOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 5.14 (dd, *J* = 12.2, 4.2 Hz, 1H), 4.70 (t, *J* = 1.7 Hz, 1H), 4.66 (d, *J* = 1.9 Hz, 1H), 3.13 (dd, *J* = 14.4, 12.1 Hz, 1H), 2.83 (dd, *J* = 14.4, 4.1 Hz, 1H), 1.75 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.8, 167.4, 140.4, 134.2, 131.6, 123.6, 114.5, 50.1, 36.7, 21.4; **LRMS** (ESI) calcd for $[C_{14}H_{13}NO_4 - H]^-$ 258.1, found 258.2; **IR** (thin film) 1775, 1714, 1391.



Synthesis of S3w: 2-(benzyloxy)acetic acid[65] (2493 mg, 15 mmol) was stirred with methallyl bromide (2228 mg, 16.5 mmol) and K_2CO_3 (3105 mg, 22.5 mmol) in DMF (30 mL) at room temperature for 24 h. The reaction was taken up to water (150 mL) and extracted with Et_2O (30 mL × 3). The combined organic extracts were washed with 2 M LiCl (10 mL × 2) and brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated. The resulting mixture was purified by flash column chromatography (5:95 EtOAc/Hex) to give **S3w** as a colorless oil (2766 mg, 12.6 mmol, 84% yield). R_f = 0.32 (5:95 EtOAc/Hex); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.27 (m, 5H), 4.99 (t, *J* = 1.2 Hz, 1H), 4.96 – 4.92 (m, 1H), 4.65 (s, 2H), 4.59 (s, 2H), 4.14 (s, 2H), 1.76 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.0, 139.4, 137.0, 128.4, 128.00, 127.97, 113.4, 73.3, 67.9, 67.1, 19.4; **HRMS** (ESI) calcd for $[C_{13}H_{16}O_3 + Na]^+$ 243.0992, found 243.0996; **IR** (thin film) 1758, 1454, 1193, 1129.

Synthesis of S4w: To a solution of hexamethyldisilazane (2.9 mL, 14 mmol) in THF (5 mL) was dropwise added *n*BuLi (2.5 M Hex, 5.2 mL, 13 mmol) at 0 °C. The resulting LiHMDS solution was allowed to warm to room temperature and stirred for 20 min, which was then dropwise added to a solution of **S3w** (2203 mg, 10 mmol) and TMSCl (1.9 mL, 15 mmol) in THF (25 mL) at –78 °C. The reaction was stirred at –78 °C for 40 min and was allowed to warm to room temperature and stir for additional 2 h. 1 M NaOH (10 mL) was added and the resulting mixture was stirred at room temperature for 30 min, which was then diluted with water (50 mL), washed with Et_2O (10 mL × 2), and separated.

The aqueous phase was acidified with concentrated HCl to pH < 2 and extracted with Et_2O (30 mL × 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated. The resulting mixture was purified by flash column chromatography (3:100 MeOH/CH_2Cl_2) to give **S4w** as a tan oil (1734 mg, 7.87 mmol, 79% yield). R_f = 0.42 (5:95 MeOH/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.85 (br s, 1H), 7.43 – 7.26 (m, 5H), 4.87 (t, *J* = 1.7 Hz, 1H), 4.83 (app s, 1H), 4.74 (d, *J* = 11.6 Hz, 1H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.14 (t, *J* = 6.4 Hz, 1H), 2.54 (dd, *J* = 6.5, 1.0 Hz, 2H), 1.74 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.8, 140.6, 136.9, 128.4, 128.04, 128.02, 114.0, 76.6, 72.6, 40.8, 22.5; **HRMS** (ESI) calcd for $[C_{13}H_{16}O_3 + Na]^+$ 243.0992, found 243.1000; **IR** (thin film) 1717, 1455, 1207, 1107.



Synthesis of S3x: To a solution of isobutyric acid (1489 mg, 16.9 mmol) in CH_2Cl_2 (13 mL) was added 6 drops of DMF via glass pipet, followed by addition of $(COCl)_2$ (2 M solution in CH_2Cl_2, 7.8 mL, 15.6 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, whereupon a solution of (*E*)-2-methylbut-2-en-1-ol[66] (1119 mg, 13 mmol) in CH_2Cl_2 (10 mL) was added, followed by addition of Et_3N (4.5 mL, 33 mmol) and DMAP (159 mg, 1.3 mmol). The reaction was allowed to warm to room temperature and stir overnight. The reaction was diluted with CH_2Cl_2 (40 mL), washed with 1 M HCl (30 mL),

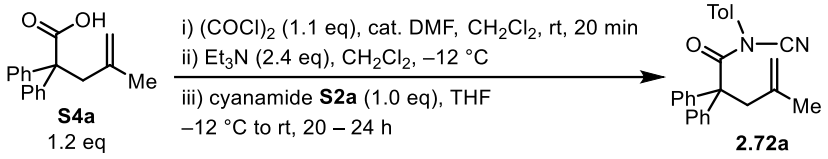
followed by saturated aqueous $NaHCO_3$ (20 mL) and brine, and separated. The organic phase was washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford **S3x** as a colorless oil (1137 mg, 7.3 mmol, 56% crude yield). **S3x** was used for next step without further purification. R_f = 0.76 (1:9 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.58 – 5.51 (m, 1H), 4.46 (d, *J* = 0.9 Hz, 2H), 2.57 (hept, *J* = 7.2 Hz, 1H), 1.68 – 1.59 (m, 6H), 1.19 (d, *J* = 0.7 Hz, 3H), 1.17 (d, *J* = 0.7 Hz, 3H); **IR** (thin film) 1737, 1471, 1191, 1155.

Synthesis of S4x: To a solution of *i*Pr_2NH (1.47 mL, 10.5 mmol) in THF (10 mL) was dropwise added *n*BuLi (2.5 M Hex, 4 mL, 10 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 10 min then it was cooled to –78 °C and was added a solution of **S3x** (781 mg, 5 mmol) in THF (5 mL). The reaction was stirred at –78 °C for additional 1 h, followed by addition of TMSCl (1.27 mL, 10 mmol) at the same temperature. The resulting mixture was stirred at –78 °C for 10 min, then it was allowed to warm to room temperature over 30 min and heated at 60 °C for 4 h. The reaction was cooled to room temperature, stirred with 2 M HCl (15 mL) for 1 h, and extracted with Et_2O (20 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated. Unfortunately, attempts to purify **S4x** by flash column chromatography were unsuccessful. **S4x** was thus taken to the next step without further treatment. R_f = 0.44 (15:85 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.86 (t, *J* = 1.7 Hz, 1H), 4.77 – 4.74 (m, 1H), 2.60 (q, *J* = 7.2 Hz, 1H), 1.73 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H), 1.06 (d, *J* = 7.2

Hz, 3H); **LRMS** (ESI) calcd for $[C_9H_{16}O_2 - H]^-$ 155.1, found 155.2; **IR** (thin film) 1699, 1461, 1255.

2.6.6.3 Synthesis of substrates 2.72 (Step 3)

Step 3: synthesis of substrates 1, standard conditions

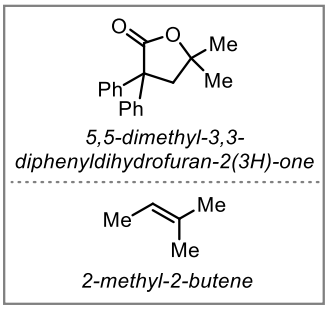


Modified conditions:
2-methyl-2-butene (8–10 eq) *was added at step i) under otherwise identical conditions.*

Synthesis of substrate 2.72a as a representative example, standard conditions:

To a suspension of acid **S4a** (1598 mg, 6.0 mmol) in CH_2Cl_2 (5.0 mL) was added DMF (3 drops via glass pipet), followed by dropwise addition of $(COCl)_2$ (2.0 M in CH_2Cl_2, 2.8 mL, 5.5 mmol) at room temperature. The mixture was stirred for 15–20 minutes, whereupon gas evolution ceased, and all acid dissolved. The reaction flask was cooled to –12 °C in an ethylene glycol/dry ice bath and a solution of Et_3N (1.67 mL, 12.0 mmol) in CH_2Cl_2 (4.0 mL) was dropwise added. Thereafter, a solution of *N*-(*p*-tolyl)cyanamide **S2a** (661 mg, 5.0 mmol) in CH_2Cl_2/THF (3.0 and 1.0 mL, respectively) was slowly added at the same temperature. The resulting mixture was allowed to warm up to room temperature

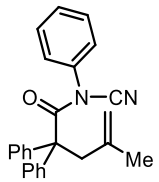
and stir for 20 h. Et_2O (30 mL) was added to allow precipitation of triethylamine hydrochloride, which was filtrated through a short Celite column. Without further treatment,[4] the filtrate was concentrated in vacuo and the resulting oily residue was purified by flash column chromatography to afford substrate **2.72a** as a white powder (1.79 mmol, 36% yield). R_f = 0.49 (1:9 EtOAc/Hex); mp 108–110 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 (dt, *J* = 6.2, 1.3 Hz, 4H), 7.40 (dd, *J* = 8.6, 6.8 Hz, 4H), 7.36 – 7.30 (m, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.10 – 7.03 (m, 2H), 4.77 (app s, 1H), 4.48 (app s, 1H), 3.42 (s, 2H), 2.35 (s, 3H), 1.42 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.0, 141.0, 139.4, 139.2, 133.7, 130.2, 128.8, 128.3, 127.6, 125.9, 116.5, 109.3, 62.1, 47.1, 24.5, 21.1; **HRMS** (ESI) calcd for $[C_{26}H_{24}N_2O + Na]^+$ 403.1781, found 403.1778; **IR** (thin film) 2230, 1725, 1508, 1203.



Modified conditions: In step i), 5,5-dimethyl-3,3-diphenyldihydrofuran-2(3*H*)-one was formed as a by-product. This compound frequently coeluted with product **1** during column chromatography. It was found that the addition of 2-methyl-2-butene (8–10

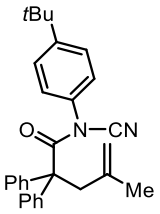
[4] Washing the organic extracts with water or aqueous solutions (e.g., 1 M HCl) led to a heavy emulsion.

equivalents) at step i) significantly reduced the amount of this by-product in the crude reaction mixture. Under such conditions, most substrates were readily purified after one column chromatography and were obtained as thick oil or tacky solid. Some substrates were further precipitated from CH_2Cl_2/Hex or CH_2Cl_2/pentane and were converted to crystalline solid.



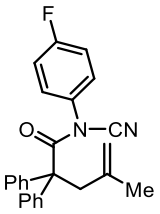
2.72b

Prepared from acid **S4a** and cyanamide **S2b** on a 5.0 mmol scale under standard conditions. **2.72b** was purified by flash column chromatography (2:3 → 1:1 CH_2Cl_2/Hex) as a white powder (1.96 mmol, 39% yield). R_f = 0.53 (15:85 EtOAc/Hex); mp 101–103 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.7 Hz, 4H), 7.44 – 7.31 (m, 9H), 7.20 (d, *J* = 7.6 Hz, 2H), 4.78 (app s, 1H), 4.49 (app s, 1H), 3.43 (s, 2H), 1.43 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.9, 141.0, 139.1, 136.3, 129.6, 129.1, 128.8, 128.4, 127.7, 126.1, 116.6, 109.2, 62.2, 47.1, 24.5; **HRMS** (ESI) calcd for $[C_{25}H_{22}N_2O + Na]^+$ 389.1624, found 389.1622; **IR** (thin film) 2231, 1725, 1491, 1204.



2.72c

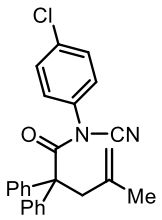
Prepared from acid **S4a** and cyanamide **S2c** on a 5.0 mmol scale under standard conditions. **2.72c** was purified by flash column chromatography (3:7 → 2:3 CH_2Cl_2/Hex) as a white solid (2.28 mmol, 46% yield). R_f = 0.68 (1:1 CH_2Cl_2/Hex); mp 118–121 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.5 Hz, 4H), 7.44 – 7.38 (m, 6H), 7.36 – 7.30 (m, 2H), 7.12 (dd, *J* = 8.6, 1.0 Hz, 2H), 4.78 (d, *J* = 1.6 Hz, 1H), 4.49 (app s, 1H), 3.43 (s, 2H), 1.42 (s, 3H), 1.30 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.1, 152.4, 141.1, 139.2, 133.6, 128.8, 128.3, 127.6, 126.6, 125.5, 116.6, 109.3, 62.2, 47.1, 34.7, 31.2, 24.5; **HRMS** (ESI) calcd for $[C_{29}H_{30}N_2O + Na]^+$ 445.2250, found 445.2256; **IR** (thin film) 2231, 1725, 1510, 1205.



2.72d

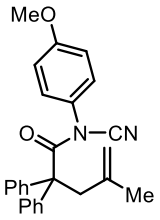
Prepared from acid **S4a** and cyanamide **S2d** on a 5.0 mmol scale under standard conditions. **2.72d** was purified by flash column chromatography (3:7 → 1:1 CH_2Cl_2/Hex), and further precipitated (CH_2Cl_2/pentane, 1:40 v/v) as a white powder (2.21 mmol, 44% yield). R_f = 0.48 (1:1 CH_2Cl_2/Hex); mp 110–112 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52

(d, J = 7.8 Hz, 4H), 7.41 (dd, J = 8.5, 6.9 Hz, 4H), 7.34 (t, J = 7.3 Hz, 2H), 7.20 – 7.14 (m, 2H), 7.10 (t, J = 8.5 Hz, 2H), 4.78 (app s, 1H), 4.49 (app s, 1H), 3.42 (s, 2H), 1.42 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.0, 162.4 (d, $^1J_{F–C}$ = 250.1 Hz), 141.0, 139.0, 132.2 (d, $^4J_{F–C}$ = 3.2 Hz), 128.7, 128.4, 128.2 (d, $^3J_{F–C}$ = 9.0 Hz), 127.8, 116.7 (d, $^2J_{F–C}$ = 23.3 Hz), 116.58, 109.0, 62.2, 47.1, 24.5; **^{19}F NMR** (470 MHz, $CDCl_3$) δ –111.0; **HRMS** (ESI) calcd for $[C_{25}H_{21}FN_2O + Na]^+$ 407.1530, found 407.1530; **IR** (thin film) 2233, 1727, 1506, 1202.



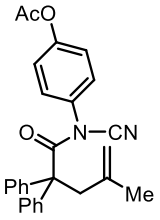
2.72e

Prepared from acid **S4a** and cyanamide **S2e** on a 5.0 mmol scale under standard conditions. **2.72e** was purified by flash column chromatography (35:65 → 2:3 CH_2Cl_2/Hex), and further precipitated (CH_2Cl_2/Hex, 1:40 v/v) as a white powder (2.30 mmol, 46% yield). R_f = 0.38 (1:1 CH_2Cl_2/Hex); mp 116–118 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 – 7.47 (m, 4H), 7.44 – 7.36 (m, 6H), 7.36 – 7.30 (m, 2H), 7.14 (d, J = 8.7 Hz, 2H), 4.78 (app s, 1H), 4.48 (app s, 1H), 3.42 (s, 2H), 1.41 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.8, 141.0, 138.9, 135.1, 134.7, 129.8, 128.7, 128.4, 127.8, 127.4, 116.6, 108.8, 62.2, 47.1, 24.5; **HRMS** (ESI) calcd for $[C_{25}H_{21}ClN_2O + Na]^+$ 423.1235, found 423.1242; **IR** (thin film) 2232, 1727, 1488, 1191.



2.72f

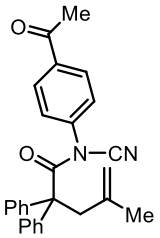
Prepared from acid **S4a** and cyanamide **S2g** on a 5.0 mmol scale under standard conditions. **2.72f** was purified by flash column chromatography (3:7 → 1:1 CH_2Cl_2/Hex) as a white solid (2.37 mmol, 47% yield). R_f = 0.42 (1:1 CH_2Cl_2/Hex); mp 90–92 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.3 Hz, 4H), 7.40 (t, *J* = 7.7 Hz, 4H), 7.37 (t, *J* = 7.1 Hz, 2H), 7.10 – 7.06 (m, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.77 (d, *J* = 1.4 Hz, 1H), 4.48 (app s, 1H), 3.79 (s, 3H), 3.42 (s, 2H), 1.42 (d, *J* = 1.4 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.2, 159.9, 141.1, 139.2, 128.9, 128.8, 128.3, 127.6, 127.5, 116.5, 114.8, 109.4, 62.1, 55.5, 47.1, 24.5; **HRMS** (ESI) calcd for $[C_{26}H_{24}N_2O_2 + Na]^+$ 419.1730, found 419.1736; **IR** (thin film) 2230, 1725, 1508, 1249.



2.72g

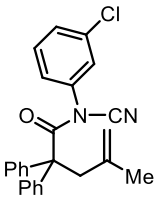
Prepared from acid **S4a** and cyanamide **S2h** on a 5.0 mmol scale under standard conditions. **2.72g** was purified by flash column chromatography (1:1 CH_2Cl_2/Hex → 15:85 EtOAc/Hex), and further precipitated (CH_2Cl_2/Hex, 1:40 v/v) as a white powder (1.34 mmol, 27% yield). R_f = 0.35 (1:4 EtOAc/Hex); mp 120–121 °C; **^{1}H NMR** (500 MHz,

$CDCl_3$) δ 7.51 (d, *J* = 8.3 Hz, 4H), 7.40 (t, *J* = 7.3 Hz, 4H), 7.33 (d, *J* = 7.6 Hz, 2H), 7.23 – 7.19 (m, 2H), 7.18 – 7.12 (m, 2H), 4.78 (d, *J* = 1.5 Hz, 1H), 4.48 (app s, 1H), 3.42 (s, 2H), 2.29 (d, *J* = 0.9 Hz, 3H), 1.42 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.8, 168.8, 150.7, 141.0, 139.0, 133.5, 128.7, 128.4, 127.7, 127.2, 122.8, 116.6, 109.0, 62.2, 47.1, 24.5, 21.1; **HRMS** (ESI) calcd for $[C_{27}H_{24}N_2O_3 + Na]^+$ 447.1679, found 447.1676; **IR** (thin film) 2232, 1765, 1726, 1503, 1190.



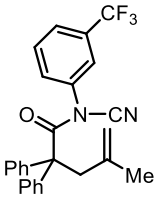
2.72h

Prepared from acid **S4a** and cyanamide **S2j** on a 4.0 mmol scale under standard conditions. **2.72h** was purified by flash column chromatography (1:9 acetone/Hex) as a thick yellow oil (1.04 mmol, 26% yield). R_f = 0.37 (1:4 acetone/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.5 Hz, 2H), 7.53 (m, *J* = 7.5 Hz, 4H), 7.42 (t, *J* = 8.5 Hz, 4H), 7.35 (td, *J* = 8.5, 1.6 Hz, 4H), 4.79 (t, *J* = 1.8 Hz, 1H), 4.49 (app s, 1H), 3.43 (s, 2H), 2.60 (s, 3H), 1.41 (d, *J* = 1.4 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 196.5, 172.6, 140.9, 140.1, 138.8, 137.1, 129.6, 128.7, 128.5, 127.8, 126.0, 116.7, 108.6, 62.4, 47.1, 26.7, 24.5; **HRMS** (ESI) calcd for $[C_{27}H_{24}N_2O_2 + Na]^+$ 431.1730, found 431.1721; **IR** (thin film) 2232, 1728, 1688, 1600, 1178.



2.72i

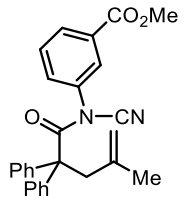
Prepared from acid **S4a** and cyanamide **S2l** on a 5.0 mmol scale under standard conditions. **2.72i** was purified by flash column chromatography (3:7 → 4:6 CH_2Cl_2/Hex), and further precipitated (CH_2Cl_2/Hex, 1:40 v/v) as a white powder (2.27 mmol, 45% yield). R_f = 0.44 (1:9 EtOAc/Hex); mp 114–116 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.7 Hz, 4H), 7.42 (t, *J* = 7.7 Hz, 4H), 7.38 – 7.32 (m, 4H), 7.22 (d, *J* = 2.1 Hz, 1H), 7.11 (dd, *J* = 6.1, 2.7 Hz, 1H), 4.79 (app s, 1H), 4.48 (app s, 1H), 3.42 (s, 2H), 1.41 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.7, 140.9, 138.9, 137.2, 135.1, 130.5, 129.4, 128.7, 128.5, 127.8, 126.5, 124.3, 116.7, 108.7, 62.3, 47.1, 24.5; **HRMS** (ESI) calcd for $[C_{25}H_{21}ClN_2O + Na]^+$ 423.1235, found 423.1238; **IR** (thin film) 2232, 1729, 1589, 1190.



2.72j

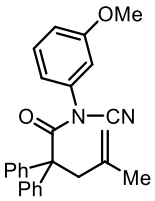
Prepared from acid **S4a** and cyanamide **S2m** on a 5.0 mmol scale under standard conditions. **2.72j** was purified by flash column chromatography (3:7 → 4:6 CH_2Cl_2/Hex) as a white solid (2.31 mmol, 46% yield). R_f = 0.57 (1:1 CH_2Cl_2/Hex); mp 111–112 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.8 Hz, 1H), 7.59 – 7.50 (m, 5H), 7.48 (app s, 1H),

7.45 – 7.38 (m, 5H), 7.38 – 7.32 (m, 2H), 4.80 (app s, 1H), 4.50 (app s, 1H), 3.44 (s, 2H), 1.42 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.8, 140.9, 138.8, 136.8, 132.2 (q, $^2J_{F–C}$ = 33.5 Hz), 130.3, 129.4, 128.7, 128.5, 127.9, 126.0 (q, $^3J_{F–C}$ = 3.7 Hz), 123.3 (q, $^3J_{F–C}$ = 3.8 Hz), 123.1 (q, $^1J_{F–C}$ = 271.0 Hz), 116.7, 108.6, 62.3, 47.1, 24.5; **^{19}F NMR** (470 MHz, $CDCl_3$) δ –62.7; **HRMS** (ESI) calcd for $[C_{26}H_{21}F_3N_2O + Na]^+$ 457.1498, found 457.1501; **IR** (thin film) 2233, 1728, 1328, 1177.



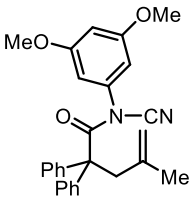
2.72k

Prepared from acid **S4a** and cyanamide **S2n** on a 5.0 mmol scale under standard conditions. **2.72k** was purified by flash column chromatography (3:7 → 6:4 CH_2Cl_2/Hex) as a tacky white solid (3.07 mmol, 61% yield). R_f = 0.32 (1:1 CH_2Cl_2/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.90 (d, *J* = 1.8 Hz, 1H), 7.54 (dt, *J* = 8.2, 1.3 Hz, 4H), 7.50 (td, *J* = 7.9, 1.0 Hz, 1H), 7.42 (dd, *J* = 8.2, 6.8 Hz, 4H), 7.39 – 7.32 (m, 3H), 4.79 (app s, 1H), 4.50 (app s, 1H), 3.93 (s, 3H), 3.43 (s, 2H), 1.42 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.8, 165.5, 141.0, 138.9, 136.5, 131.9, 130.5, 130.2, 129.7, 128.8, 128.5, 127.8, 127.3, 116.7, 108.8, 62.3, 52.5, 47.1, 24.5; **HRMS** (ESI) calcd for $[C_{27}H_{24}N_2O_3 + Na]^+$ 447.1679, found 447.1684; **IR** (thin film) 2233, 1727, 1289.



2.72l

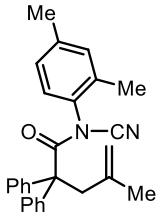
Prepared from acid **S4a** and cyanamide **S2o** on a 5.0 mmol scale under standard conditions. **2.72l** was purified by flash column chromatography (5:95 → 1:9 EtOAc/Hex) as a white solid (1.84 mmol, 37% yield). R_f = 0.42 (15:85 EtOAc/Hex); mp 80–83 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.8 Hz, 4H), 7.40 (t, *J* = 7.7 Hz, 4H), 7.36 – 7.27 (m, 3H), 6.90 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.78 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.70 (t, *J* = 2.3 Hz, 1H), 4.78 (app s, 1H), 4.49 (app s, 1H), 3.76 (s, 3H), 3.42 (s, 2H), 1.42 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.9, 160.3, 141.0, 139.1, 137.2, 130.2, 128.8, 128.3, 127.6, 118.2, 116.5, 114.7, 112.1, 109.1, 62.2, 55.5, 47.1, 24.5; **HRMS** (ESI) calcd for $[C_{26}H_{24}N_2O_2 + Na]^+$ 419.1730, found 419.1725; **IR** (thin film) 2231, 1727, 1606, 1490, 1204.



2.72m

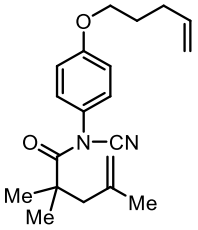
Prepared from acid **S4a** and cyanamide **S2p** on a 4.5 mmol scale under standard conditions. **2.72m** was purified by flash column chromatography twice (8:92 → 12:88 acetone/Hex) as a thick colorless oil (1.96 mmol, 44% yield). R_f = 0.23 (1:9 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.6 Hz, 4H), 7.40 (t, *J* = 7.6 Hz, 4H), 7.36 –

7.30 (m, 2H), 6.44 (t, *J* = 2.3 Hz, 1H), 6.30 (d, *J* = 2.3 Hz, 2H), 4.77 (app s, 1H), 4.47 (app s, 1H), 3.75 (s, 6H), 3.41 (s, 2H), 1.41 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.8, 161.2, 141.1, 139.1, 137.7, 128.8, 128.4, 127.7, 116.6, 109.1, 104.6, 101.1, 62.3, 55.5, 47.2, 24.5; **HRMS** (ESI) calcd for $[C_{27}H_{26}N_2O_3 + Na]^+$ 449.1836, found 449.1828; **IR** (thin film) 2231, 1728, 1206, 1158.



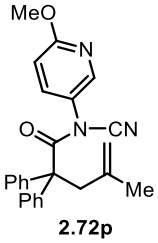
2.72n

Prepared from acid **S4a** and cyanamide **S2q** on a 5.0 mmol scale under standard conditions. **2.72n** was purified by flash column chromatography (3:7 → 1:1 CH_2Cl_2/Hex), and further precipitated (pentane) as a white powder (0.46 mmol, 9% yield). R_f = 0.44 (1:9 EtOAc/Hex); mp 108–110 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73 – 7.30 (m, 10H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 7.9 Hz, 1H), 4.69 (app s, 1H), 4.40 (app s, 1H), 3.41 (app s, 1H), 3.35 (app s, 1H), 2.30 (s, 3H), 1.87 (s, 3H), 1.31 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.8, 141.0, 140.0, 135.5, 132.6, 132.2, 129.4, 128.9, 128.4, 128.3, 128.0, 127.8, 127.0, 116.7, 108.9, 62.5, 47.8, 24.5, 21.1, 16.8; **HRMS** (ESI) calcd for $[C_{27}H_{26}N_2O + Na]^+$ 417.1937, found 417.1944; **IR** (thin film) 2230, 1721, 1499, 1209.



2.72o

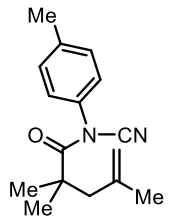
Prepared from acid **S4b** and cyanamide **S2k** on a 3.0 mmol scale under standard conditions. **2.72o** was purified by flash column chromatography (4:96 → 8:92 EtOAc/Hex) as a colorless oil (2.07 mmol, 69% yield). R_f = 0.49 (1:9 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.20 – 7.12 (m, 2H), 6.93 (d, *J* = 9.1 Hz, 2H), 5.84 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.06 (dt, *J* = 17.1, 1.5 Hz, 1H), 5.01 (d, *J* = 10.1 Hz, 1H), 4.94 (app s, 1H), 4.86 (app s, 1H), 3.97 (t, *J* = 6.5 Hz, 2H), 2.75 (s, 2H), 2.26 – 2.21 (app q, 2H), 1.89 (p, *J* = 6.8 Hz, 2H), 1.81 (s, 3H), 1.49 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.2, 159.4, 141.4, 137.5, 128.6, 127.7, 115.4 (two overlapped peaks), 114.8, 111.1, 67.4, 46.9, 44.8, 30.0, 28.2, 26.2, 23.9; **HRMS** (ESI) calcd for $[C_{20}H_{26}N_2O_2 + Na]^+$ 349.1886, found 349.1870; **IR** (thin film) 2227, 1508, 1249, 1190.



2.72p

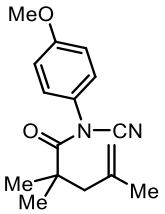
Prepared from acid **S4a** and cyanamide **S2r** on a 4.0 mmol scale under modified conditions. **2.72p** was purified by flash column chromatography (1:9 → 15:85 EtOAc/Hex) as a tacky white solid (3.22 mmol, 81% yield). R_f = 0.62 (1:4 EtOAc/Hex); **^{1}H NMR** (500

MHz, $CDCl_3$) δ 8.01 (d, *J* = 2.7 Hz, 1H), 7.51 (dd, *J* = 8.5, 1.3 Hz, 4H), 7.40 (dd, *J* = 8.6, 6.8 Hz, 4H), 7.37 – 7.31 (m, 3H), 6.76 (d, *J* = 8.9 Hz, 1H), 4.79 (t, *J* = 1.7 Hz, 1H), 4.53 – 4.46 (m, 1H), 3.93 (s, 3H), 3.43 (s, 2H), 1.42 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.2, 164.0, 144.7, 140.9, 139.0, 136.6, 128.7, 128.4, 127.8, 127.0, 116.6, 111.7, 108.9, 62.1, 54.0, 46.9, 24.4; **HRMS** (ESI) calcd for $[C_{25}H_{23}N_3O_2 + Na]^+$ 420.1682, found 420.1694; **IR** (thin film) 2233, 1728, 1492, 1388, 1202.



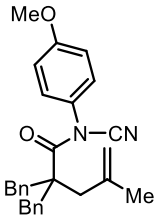
2.72q

Prepared from acid **S4b** and cyanamide **S2a** on a 5.0 mmol scale under standard conditions. **2.72q** was purified by flash column chromatography (2:98 → 5:95 EtOAc/Hex) as a pale yellow oil (4.39 mmol, 88% yield). R_f = 0.53 (1:9 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 – 7.22 (m, 2H), 7.18 – 7.11 (m, 2H), 4.94 (d, *J* = 1.6 Hz, 1H), 4.87 (t, *J* = 1.0 Hz, 1H), 2.75 (s, 2H), 2.37 (s, 3H), 1.81 (s, 3H), 1.50 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.0, 141.4, 139.3, 133.6, 130.2, 126.1, 114.8, 111.0, 46.9, 44.9, 26.1, 23.8, 21.1; **HRMS** (ESI) calcd for $[C_{16}H_{20}N_2O + Na]^+$ 279.1468, found 279.1478; **IR** (thin film) 2228, 1725, 1509, 1190.



2.72r

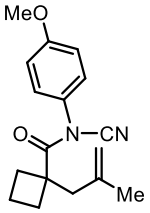
Prepared from acid **S4b** and cyanamide **S2g** on a 5.0 mmol scale under standard conditions. **2.72r** was purified by flash column chromatography (3:7 → 1:1 CH_2Cl_2/Hex) as a colorless oil (3.61 mmol, 72% yield). R_f = 0.36 (1:9 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.20 – 7.17 (m, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.94 (d, *J* = 4.5 Hz, 1H), 4.87 (app s, 1H), 3.82 (s, 3H), 2.75 (s, 2H), 1.81 (s, 3H), 1.50 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.2, 159.9, 141.4, 128.8, 127.7, 114.9, 114.8, 111.1, 55.5, 46.9, 44.8, 26.2, 23.8; **HRMS** (ESI) calcd for $[C_{16}H_{20}N_2O_2 + Na]^+$ 295.1417, found 295.1411; **IR** (thin film) 2228, 1724, 1509, 1250, 1189.



2.72s

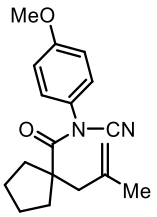
Prepared from acid **S4c** and cyanamide **S2g** on a 4.0 mmol scale under standard conditions. **2.72s** was purified by flash column chromatography twice (first: 3:7 → 1:1 CH_2Cl_2/Hex; second: 3:97 → 1:9 EtOAc/Hex) as a thick colorless oil (1.28 mmol, 32% yield). R_f = 0.56 (1:1 CH_2Cl_2/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 10H), 6.87 (app s, 4H), 5.09 (app s, 1H), 4.91 (app s, 1H), 3.79 (s, 3H), 3.36 (d, *J* = 14.7 Hz, 2H),

3.32 (d, J = 14.8 Hz, 2H), 2.74 (s, 2H), 1.85 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.9, 159.9, 141.9, 136.5, 130.5, 128.8, 128.4, 127.7, 127.1, 114.8, 112.5, 110.7, 55.5, 52.6, 41.1, 40.2, 25.1; **HRMS** (ESI) calcd for $[C_{28}H_{28}N_2O_2 + Na]^+$ 447.2043, found 447.2050; **IR** (thin film) 2228, 1723, 1508, 1250, 1181.



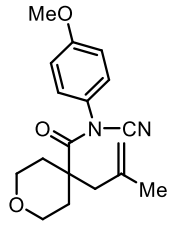
2.72t

Prepared from acid **S4d** and cyanamide **S2g** on a 4.0 mmol scale under modified conditions. **2.72t** was purified by flash column chromatography (5:95 → 1:9 EtOAc/Hex) as a colorless oil (3.51 mmol, 88% yield). R_f = 0.36 (1:9 EtOAc/Hex); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20 (dt, J = 9.1, 2.2 Hz, 2H), 6.94 (dt, J = 9.1, 2.2 Hz, 2H), 4.90 – 4.88 (m, 1H), 4.87 (t, J = 1.7 Hz, 1H), 3.82 (s, 3H), 2.96 (s, 2H), 2.84 – 2.73 (m, 2H), 2.32 – 2.21 (m, 2H), 2.12 – 1.99 (m, 1H), 1.96 – 1.83 (m, 1H), 1.75 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.6, 159.8, 142.1, 127.9, 127.4, 114.8, 114.3, 110.4, 55.5, 49.4, 45.1, 31.4, 23.0, 15.2; **HRMS** (ESI) calcd for $[C_{17}H_{20}N_2O_2 + Na]^+$ 307.1417, found 307.1430; **IR** (thin film) 2230, 1728, 1509, 1251, 1188.



2.72u

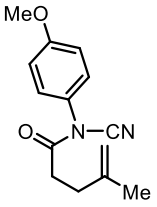
Prepared from acid **S4e** and cyanamide **S2g** on a 4.0 mmol scale under modified conditions. **2.72u** was purified by flash column chromatography (5:95 → 15:85 EtOAc/Hex) as a pale yellow oil (3.27 mmol, 82% yield). R_f = 0.39 (1:9 EtOAc/Hex); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 (dt, *J* = 9.0, 2.1 Hz, 2H), 6.94 (dt, *J* = 9.0, 2.1 Hz, 2H), 4.93 – 4.92 (m, 1H), 4.91 (t, *J* = 1.6 Hz, 1H), 3.82 (s, 3H), 2.82 (d, *J* = 1.1 Hz, 2H), 2.48 (dddd, *J* = 13.5, 6.8, 3.7, 1.6 Hz, 2H), 1.87 (dddd, *J* = 13.2, 7.6, 5.2, 1.8 Hz, 2H), 1.79 (s, 3H), 1.76 – 1.64 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.1, 159.8, 142.2, 128.7, 127.6, 114.8, 114.4, 111.0, 55.7, 55.5, 46.1, 37.1, 25.1, 23.5; **HRMS** (ESI) calcd for $[C_{18}H_{22}N_2O_2 + Na]^+$ 321.1573, found 321.1575; **IR** (thin film) 2228, 1724, 1509, 1250, 1184.



2.72v

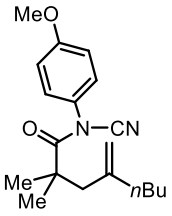
Prepared from acid **S4f** and cyanamide **S2g** on a 4.0 mmol scale under modified conditions. **2.72v** was purified by flash column chromatography twice (1:9 → 1:4 EtOAc/Hex) as a thick pale yellow oil (2.05 mmol, 51% yield). R_f = 0.34 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.18 (dt, *J* = 9.0, 2.1 Hz, 2H), 6.97 (dt, *J* = 8.9, 2.4 Hz, 2H), 4.98 – 4.97 (m, 1H), 4.97 – 4.96 (m, 1H), 3.89 (dt, *J* = 12.2, 4.0 Hz, 2H), 3.83 (s, 3H), 3.59 (ddd, *J* = 12.5, 10.5, 2.4 Hz, 2H), 2.81 (s, 2H), 2.54 – 2.48 (m, 2H), 1.89 – 1.77 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.2, 160.1, 140.3, 128.4, 127.8, 115.8, 115.0, 110.8, 64.8,

55.6, 47.3, 46.1, 34.8, 23.9; **HRMS** (ESI) calcd for $[C_{18}H_{22}N_2O_3 + Na]^+$ 337.1523, found 337.1518; **IR** (thin film) 2227, 1723, 1509, 1250, 1185, 1114.



2.72w

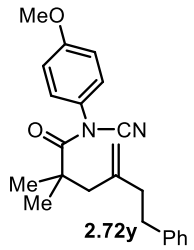
Prepared from acid **S4o** and cyanamide **S2g** on a 3.0 mmol scale under standard conditions. **2.72w**was purified by flash column chromatography (1:9 → 1:4 EtOAc/Hex) as a pale yellow oil (1.79 mmol, 60% yield). R_f = 0.21 (1:9 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.96 (dd, *J* = 9.0, 0.8 Hz, 2H), 4.81 (app s, 1H), 4.74 (app s, 1H), 3.83 (s, 3H), 2.87 (br app s, 2H), 2.45 (t, *J* = 7.6 Hz, 2H), 1.77 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.7, 160.0, 143.0, 127.3, 127.0, 115.0, 111.3, 110.0, 55.6, 32.7, 32.0, 22.4; **HRMS** (ESI) calcd for $[C_{14}H_{16}N_2O_2 + Na]^+$ 267.1104, found 267.1106; **IR** (thin film) 2233, 1735, 1509, 1251.



2.72x

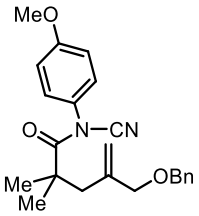
Prepared from acid **S4g** and cyanamide **S2g** on a 4.0 mmol scale under modified conditions. **2.72x** was purified by flash column chromatography (2:3 → 3:2 CH_2Cl_2/Hex) as a colorless oil (2.72 mmol, 68% yield). R_f = 0.44 (1:1 CH_2Cl_2/Hex); **^{1}H NMR** (500 MHz,

$CDCl_3$) δ 7.18 (dt, *J* = 9.0, 2.0 Hz, 2H), 6.95 (dt, *J* = 9.0, 2.4 Hz, 2H), 4.94 (d, *J* = 1.5 Hz, 1H), 4.87 (d, *J* = 1.4 Hz, 1H), 3.82 (s, 3H), 2.74 (s, 2H), 2.08 – 2.02 (m, 2H), 1.52 – 1.42 (m, 8H), 1.39 – 1.28 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.2, 159.9, 145.6, 128.8, 127.7, 114.9, 113.0, 111.1, 55.5, 45.1, 45.0, 36.9, 30.1, 26.2, 22.4, 14.0; **HRMS** (ESI) calcd for $[C_{19}H_{26}N_2O_2 + Na]^+$ 337.1886, found 337.1875; **IR** (thin film) 2230, 1724, 1509.



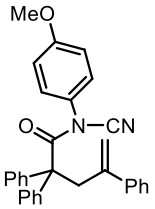
2.72y

Prepared from acid **S4h** and cyanamide **S2g** on a 3.5 mmol scale under modified conditions. **2.72y** was purified by flash column chromatography (5:95 → 1:9 EtOAc/Hex) as a pale yellow oil (2.55 mmol, 73% yield). R_f = 0.32 (1:9 EtOAc/Hex); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.23 – 7.17 (m, 3H), 7.10 – 7.05 (m, 2H), 6.91 – 6.85 (m, 2H), 5.00 (d, *J* = 1.4 Hz, 1H), 4.93 (app s, 1H), 3.80 (s, 3H), 2.87 – 2.75 (m, 4H), 2.36 (dd, *J* = 8.9, 7.4 Hz, 2H), 1.50 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.2, 159.9, 144.8, 141.6, 128.7, 128.37, 128.35, 127.7, 125.9, 114.8, 113.7, 111.1, 55.5, 45.5, 45.0, 38.9, 34.4, 26.2; **HRMS** (ESI) calcd for $[C_{23}H_{26}N_2O_2 + Na]^+$ 385.1886, found 385.1892; **IR** (thin film) 2227, 1724, 1508, 1250, 1183.



2.72z

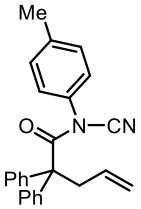
Prepared from acid **S4i** and cyanamide **S2g** on a 3.4 mmol scale under modified conditions. **2.72z** was purified by flash column chromatography (5:95 → 15:85 EtOAc/Hex) as a colorless oil (1.72 mmol, 51% yield). R_f = 0.42 (15:85 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 4H), 7.30 – 7.27 (m, 1H), 7.18 – 7.13 (m, 2H), 6.93 – 6.88 (m, 2H), 5.25 (d, *J* = 1.5 Hz, 1H), 5.12 (d, *J* = 1.3 Hz, 1H), 4.50 (s, 2H), 3.98 (s, 2H), 3.81 (s, 3H), 2.83 (d, *J* = 1.1 Hz, 2H), 1.50 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.2, 159.9, 142.2, 138.0, 128.8, 128.4, 127.8, 127.8, 127.6, 116.3, 114.8, 111.1, 73.1, 71.8, 55.5, 44.7, 42.2, 26.1; **HRMS** (ESI) calcd for $[C_{23}H_{26}N_2O_3 + Na]^+$ 401.1836, found 401.1833; **IR** (thin film) 2230, 1723, 1509, 1250, 1182.



2.72aa

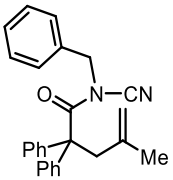
Prepared from acid **S4j** and cyanamide **S2g** on a 4.0 mmol scale under modified conditions. **2.72aa** was purified by flash column chromatography twice (first: 1:4 → 1:1 CH_2Cl_2/Hex; second: 8:92 → 1:4 Et_2O/Hex) as a white foam (2.46 mmol, 61% yield). R_f = 0.24 (1:9 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 4H), 7.35 – 7.16

(m, 11H), 6.83 – 6.78 (m, 2H), 6.73 – 6.68 (m, 2H), 5.18 (d, *J* = 1.4 Hz, 1H), 4.70 (d, *J* = 1.3 Hz, 1H), 3.93 (s, 2H), 3.76 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.6, 159.8, 143.9, 142.3, 139.4, 129.3, 128.7, 128.1, 128.0, 127.6, 127.4, 127.2, 126.7, 120.1, 114.6, 109.5, 62.0, 55.5, 44.1; **HRMS** (ESI) calcd for $[C_{31}H_{26}N_2O_2 + Na]^+$ 481.1886, found 481.1894; **IR** (thin film) 2230, 1725, 1508, 1249, 1202.



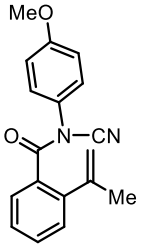
2.72ab

Prepared from acid **S4k** and cyanamide **S2a** on a 5.0 mmol scale under standard conditions. **2.72ab** was purified by flash column chromatography (3:7 → 1:1 CH_2Cl_2/Hex), and further precipitated (CH_2Cl_2/Hex, 1:40 v/v) as a white powder (2.58 mmol, 52% yield). R_f = 0.54 (15:85 EtOAc/Hex); mp 99–100 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 – 7.39 (m, 8H), 7.39 – 7.31 (m, 2H), 7.24 – 7.18 (m, 2H), 7.12 – 7.05 (m, 2H), 5.65 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.05 (ddd, *J* = 17.1, 3.4, 1.5 Hz, 1H), 5.01 – 4.98 (m, 1H), 3.36 (d, *J* = 7.0 Hz, 2H), 2.36 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.0, 139.4, 138.9, 133.6, 133.2, 130.2, 128.8, 128.5, 127.8, 126.0, 119.2, 109.2, 62.1, 44.8, 21.1; **HRMS** (ESI) calcd for $[C_{25}H_{22}N_2O + Na]^+$ 389.1624, found 389.1626; **IR** (thin film) 2231, 1725, 1508, 1206.



2.72ac

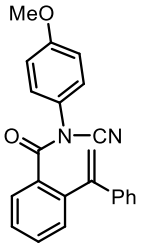
Prepared from acid **S4a** and cyanamide **S2s** on a 5.0 mmol scale under standard conditions. **2.72ac** was purified by flash column chromatography (3:7 → 1:1 CH_2Cl_2/Hex) as a colorless oil (3.98 mmol, 80% yield). R_f = 0.55 (15:85 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 13H), 7.18 (dd, *J* = 7.4, 1.8 Hz, 2H), 4.72 (s, 2H), 4.63 (d, *J* = 1.9 Hz, 1H), 4.30 (app s, 1H), 3.30 (s, 2H), 1.31 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.8, 140.9, 138.9, 133.8, 128.9, 128.70, 128.65, 128.6, 128.2, 127.5, 116.4, 109.9, 62.0, 52.7, 47.1, 24.4; **HRMS** (ESI) calcd for $[C_{26}H_{24}N_2O + Na]^+$ 403.1781, found 403.1781; **IR** (thin film) 2231, 1710, 1496, 1193.



2.72ad

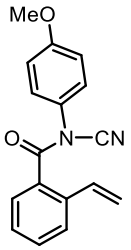
Prepared from acid **S4l** and cyanamide **S2g** on a 5.0 mmol scale under modified conditions. **2.72ad** was purified by flash column chromatography (2:3 → 3:2 CH_2Cl_2/Hex) as an oily solid (2.68 mmol, 54% yield). R_f = 0.20 (1:9 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 – 7.48 (m, 2H), 7.42 – 7.37 (m, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 5.34 (app s, 1H), 5.13 (app s, 1H), 3.83 (s, 3H), 2.22 (s, 3H); **^{13}C NMR** (125

MHz, $CDCl_3$) δ 170.0, 159.8, 143.2, 141.7, 131.4, 130.7, 128.1, 127.6, 127.5, 127.4, 126.8, 117.2, 114.8, 110.0, 55.6, 23.2; **HRMS** (ESI) calcd for $[C_{18}H_{16}N_2O_2 + Na]^+$ 315.1104, found 315.1116; **IR** (thin film) 2235, 1723, 1509, 1250.



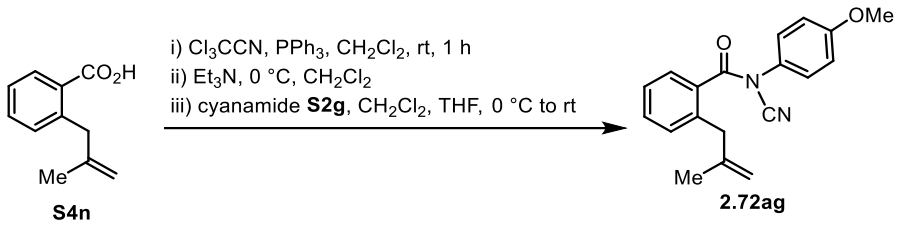
2.72ae

Prepared from acid **S4m** and cyanamide **S2g** on a 4.8 mmol scale under modified conditions. **2.72ae** was purified by flash column chromatography (1:9 → 1:4 EtOAc/Hex), and further precipitated (CH_2Cl_2/pentane, 1:40 v/v) as a white powder (3.02 mmol, 63% yield). R_f = 0.43 (1:4 EtOAc/Hex); mp 103–105 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.58 (td, *J* = 7.6, 1.4 Hz, 1H), 7.52 – 7.46 (m, 2H), 7.39 – 7.30 (m, 5H), 6.82 (dt, *J* = 9.1, 2.1 Hz, 2H), 6.78 (dt, *J* = 9.2, 2.1 Hz, 2H), 5.74 (app s, 1H), 5.49 (app s, 1H), 3.78 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.5, 159.7, 147.6, 141.2, 140.3, 131.9, 131.5, 131.2, 128.5, 128.3, 127.95, 127.89, 127.8, 127.0, 126.8, 117.4, 114.6, 110.0, 55.5; **HRMS** (ESI) calcd for $[C_{23}H_{18}N_2O_2 + Na]^+$ 377.1260, found 377.1268; **IR** (thin film) 2253, 1726, 1509.



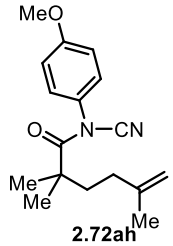
2.72af

Prepared from acid **S4r** and cyanamide **S2a** on a 3.2 mmol scale under modified conditions. **2.72af** was purified by flash column chromatography (5:95 → 1:4 EtOAc/Hex) as a waxy solid (1.33 mmol, 41% yield). R_f = 0.37 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 – 7.57 (m, 1H), 7.51 – 7.47 (m, 2H), 7.36 (td, *J* = 7.6, 1.2 Hz, 1H), 7.33 – 7.29 (m, 2H), 7.00 – 6.88 (m, 3H), 5.79 (d, *J* = 17.4 Hz, 1H), 5.48 (d, *J* = 11.0 Hz, 1H), 3.82 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 169.1, 159.9, 136.5, 132.9, 131.7, 130.2, 127.7, 127.6, 127.4, 127.0, 126.7, 118.8, 114.9, 109.6, 55.6; **HRMS** (ESI) calcd for $[C_{17}H_{14}N_2O_2 + Na]^+$ 301.0947, found 301.0947; **IR** (thin film) 2238, 1719, 1509, 1251.



S4n **2.72ag**

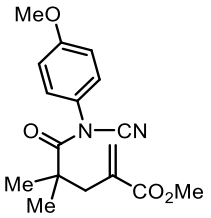
Synthesis of 2.72ag following a different procedure:[5] To a solution of acid **S4n** (1057 mg, 6.0 mmol) and Cl_3CCN (1733 mg, 12.0 mmol) in CH_2Cl_2 (6.0 mL) was added PPh_3 (3147 mg, 12 mmol) in CH_2Cl_2 (6.0 mL) at room temperature. The resulting mixture was stirred for 1 h and cooled to 0 °C, whereupon a solution of Et_3N (1.0 mL, 7.5 mmol) in CH_2Cl_2 (3.0 mL) was added, followed by cyanamide **S2g** (741 mg, 5.0 mmol) in CH_2Cl_2–THF (4 mL, 3:1 v/v). The resulting mixture was allowed to warm to room temperature and stir overnight, which was then diluted with Et_2O (30 mL), filtered through a short Celite column, concentrated, and purified by flash column chromatography (1:9 → 15:85 EtOAc/Hex) to afford **2.72ag** as an oily yellow solid (4.57 mmol, 91% yield). R_f = 0.42 (15:85 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.3 Hz, 1H), 7.47 (td, *J* = 7.6, 1.4 Hz, 1H), 7.36 – 7.29 (m, 4H), 6.97 (d, *J* = 8.9 Hz, 2H), 4.93 (app s, 1H), 4.70 (app s, 1H), 3.84 (s, 3H), 3.53 (s, 2H), 1.73 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 169.0, 159.9, 144.3, 138.7, 131.7, 131.6, 131.3, 127.7, 127.4, 127.0, 126.4, 114.9, 113.1, 110.0, 55.6, 41.4, 22.4; **HRMS** (ESI) calcd for $[C_{19}H_{18}N_2O_2 + Na]^+$ 329.1260, found 329.1269; **IR** (thin film) 2236, 1721, 1509, 1252.



2.72ah

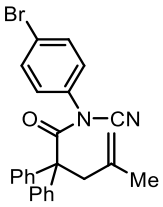
[5] **S4n** cyclized completely to the lactone by-product under the standard conditions. This procedure was modified based on a known report: Jang, D. O.; Park, D. J.; Kim, J. *Tetrahedron Lett.* **1999**, *40*, 5323.

Prepared from acid **S4p** and cyanamide **S2g** on a 4.0 mmol scale under modified conditions. **2.72ah** was purified by flash column chromatography (5:95 → 15:85 EtOAc/Hex) as a colorless oil (3.29 mmol, 82% yield). R_f = 0.51 (1:1 CH_2Cl_2/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.19 (dt, *J* = 9.2, 2.4 Hz 2H), 6.95 (dt, *J* = 8.9, 2.1 Hz 2H), 4.77 (m, 1H), 4.76 (app s, 1H), 3.82 (s, 3H), 2.07 (app s, 4H), 1.80 (s, 3H), 1.49 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.1, 159.9, 144.7, 128.7, 127.7, 114.9, 110.8, 110.7, 55.5, 44.9, 37.6, 33.1, 25.2, 22.5; **HRMS** (ESI) calcd for $[C_{17}H_{22}N_2O_2 + Na]^+$ 309.1573, found 309.1569; **IR** (thin film) 2228, 1725, 1509, 1250.



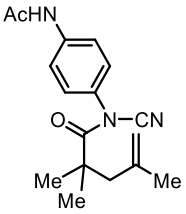
2.72ai

Prepared from acid **S4q** and cyanamide **S2a** on a 2.6 mmol scale under modified conditions. **2.72ai** was purified by flash column chromatography (3:2 CH_2Cl_2/Hex → CH_2Cl_2) as a colorless oil (1.57 mmol, 61% yield). R_f = 0.61 (CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 6.97 – 6.93 (m, 2H), 6.31 (d, *J* = 1.3 Hz, 1H), 5.70 (d, *J* = 1.2 Hz, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 3.03 (d, *J* = 1.0 Hz, 2H), 1.46 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.5, 167.4, 159.9, 136.3, 129.1, 129.0, 127.9, 114.8, 111.3, 55.5, 52.1, 44.8, 40.9, 25.5; **HRMS** (ESI) calcd for $[C_{17}H_{20}N_2O_4 + Na]^+$ 339.1315, found 339.1318; **IR** (thin film) 2230, 1721, 1509, 1250.



2.72aj

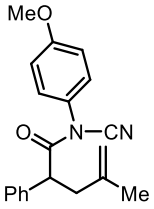
Prepared from acid **S4a** and cyanamide **S2f** on a 5.0 mmol scale under standard conditions. **2.72aj** was purified by flash column chromatography (3:7 → 1:1 CH_2Cl_2/Hex) as a white solid (1.77 mmol, 35% yield). R_f = 0.33 (1:1 CH_2Cl_2/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.59 – 7.47 (m, 6H), 7.41 (t, *J* = 7.6 Hz, 4H), 7.37 – 7.30 (m, 2H), 7.08 (d, *J* = 8.6 Hz, 2H), 4.78 (d, *J* = 1.2 Hz, 1H), 4.48 (app s, 1H), 3.42 (s, 2H), 1.41 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.7, 141.0, 138.9, 135.3, 132.8, 128.7, 128.4, 127.8, 127.7, 123.1, 116.6, 108.7, 62.3, 47.1, 24.5; **HRMS** (ESI) calcd for $[C_{25}H_{21}BrN_2O + Na]^+$ 467.0729, found 467.0729; **IR** (thin film) 2232, 1727, 1486, 1189.



2.72ak

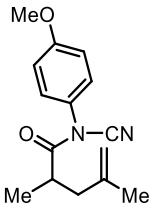
Prepared from acid **S4b** and cyanamide **S2i** on a 5.0 mmol scale under standard conditions. **2.72ak** was purified by flash column chromatography twice (first: 1:20 MeOH/CH_2Cl_2; second: Et_2O) as a pale yellow oil (3.31 mmol, 66% yield). R_f = 0.47 (5:95 MeOH/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.78 (br s, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 4.95 (app s, 1H), 4.86 (app s, 1H), 2.75 (s, 2H), 2.15 (s, 3H), 1.81

(s, 3H), 1.50 (d, J = 1.4 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.2, 168.6, 141.3, 138.8, 131.5, 127.0, 120.5, 114.9, 110.8, 46.9, 45.0, 26.1, 24.5, 23.9; **HRMS** (ESI) calcd for $[C_{17}H_{21}N_3O_2 + Na]^+$ 322.1526, found 322.1526; **IR** (thin film) 2229, 1725, 1676, 1509, 1257, 1189.



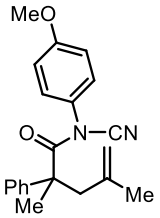
2.72al

Prepared from acid **S4s** and cyanamide **S2g** on a 4.0 mmol scale under modified conditions. **2.72al** was purified by flash column chromatography (5:95 → 15:85 EtOAc/Hex) as a pale yellow oil (2.42 mmol, 61% yield). R_f = 0.31 (1:9 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.28 (m, 5H), 7.11 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 9.2 Hz, 2H), 4.83 (app s, 1H), 4.74 (app s, 1H), 4.51 (br m, 1H), 3.81 (s, 3H), 2.94 (dd, J = 14.7, 9.2 Hz, 1H), 2.50 – 2.34 (br m, 1H), 1.75 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.3 (br), 160.1 (br), 142.0, 136.7, 129.0, 128.1, 128.0, 127.5 (br), 127.1, 114.8, 112.7, 110.0 (br), 55.6, 48.6 (br), 42.0, 22.8; **HRMS** (ESI) calcd for $[C_{20}H_{20}N_2O_2 + Na]^+$ 343.1417, found 343.1423; **IR** (thin film) 2233, 1734, 1508, 1251.



2.72am

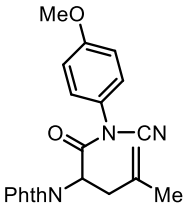
Prepared from acid **S4t** and cyanamide **S2g** on a 3.0 mmol scale under modified conditions. **2.72am** was purified by flash column chromatography (1:9 EtOAc/Hex) as a pale yellow oil (1.47 mmol, 49% yield). R_f = 0.56 (3:7 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26 – 7.20 (m, 2H), 6.99 – 6.88 (m, 2H), 4.88 – 4.82 (m, 1H), 4.77 (app s, 1H), 3.82 (s, 3H), 3.35 (br app s, 1H), 2.55 (dd, *J* = 14.0, 7.6 Hz, 1H), 2.17 (dd, *J* = 14.0, 6.9 Hz, 1H), 1.77 (s, 3H), 1.28 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.5, 160.0, 141.9, 127.3, 127.1, 114.9, 113.2, 110.1, 55.5, 41.8, 36.6 (br), 22.3, 17.0; **HRMS** (ESI) calcd for $[C_{15}H_{18}N_2O_2 + Na]^+$ 281.1260, found 281.1266; **IR** (thin film) 2231, 1736, 1509, 1251, 1180.



2.72an

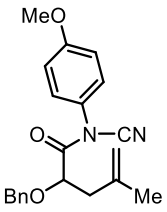
Prepared from acid **S4u** and cyanamide **S2g** on a 2.0 mmol scale under modified conditions. **2.72an** was purified by flash column chromatography (1:9 EtOAc/Hex) as an off-white tacky solid (0.72 mmol, 36% yield). R_f = 0.42 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 2H), 7.39 – 7.31 (m, 3H), 7.16 – 7.10 (m, 2H), 6.96 – 6.87 (m, 2H), 4.95 (t, *J* = 1.8 Hz, 1H), 4.80 (dd, *J* = 2.1, 1.0 Hz, 1H), 3.81 (s, 3H), 3.19 (d, *J* = 14.0 Hz, 1H), 2.79 (d, *J* = 13.7 Hz, 1H), 1.80 (s, 3H), 1.48 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.3, 159.9, 141.6, 141.0, 129.0, 128.6, 127.8, 127.5, 126.4, 116.6, 114.8, 109.5,

100.0, 55.6, 52.2, 46.3, 24.1; **HRMS** (ESI) calcd for $[C_{21}H_{22}N_2O_2 + Na]^+$ 357.1573, found 357.1578; **IR** (thin film) 2229, 1719, 1507, 1245, 1220.



2.72ao

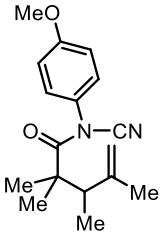
Prepared from acid **S4v** and cyanamide **S2g** on a 1.67 mmol scale under modified conditions. **2.72ao** was purified by flash column chromatography (3:7 EtOAc/Hex) as a white foam (0.56 mmol, 33% yield). R_f = 0.38 (3:7 EtOAc/Hex); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.33 – 7.19 (m, 2H), 6.97 – 6.86 (m, 2H), 5.42 (dd, *J* = 11.0, 4.3 Hz, 1H), 4.74 (app s, 1H), 4.66 (app s, 1H), 3.80 (s, 3H), 3.05 (dd, *J* = 14.0, 11.0 Hz, 1H), 2.84 (dd, *J* = 14.1, 4.3 Hz, 1H), 1.80 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.5, 166.8, 160.2, 139.9, 134.5, 131.3, 127.2, 127.1, 123.8, 115.6, 115.0, 108.9, 55.6, 50.6, 37.4, 21.6; **HRMS** (ESI) calcd for $[C_{22}H_{19}N_3O_4 + Na]^+$ 412.1268, found 412.1273; **IR** (thin film) 2233, 1777, 1717, 1508, 1384, 1251.



2.72ap

Prepared from acid **S4w** and cyanamide **S2g** on a 5.0 mmol scale under modified conditions. **2.72ap** was purified by flash column chromatography (15:85 EtOAc/Hex) as a

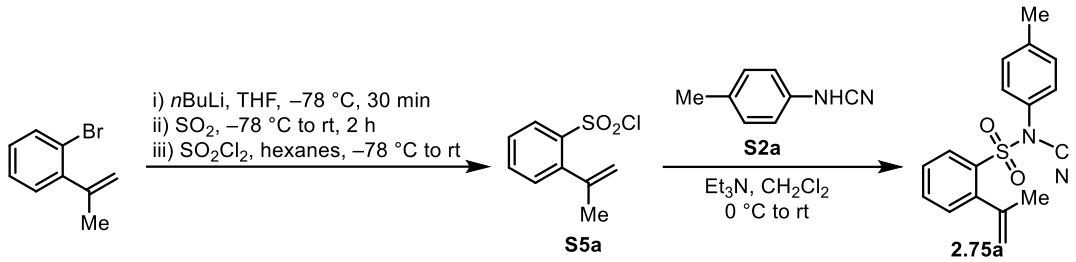
pale yellow oil (4.63 mmol, 93% yield). R_f = 0.23 (1:9 EtOAc/Hex); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.28 (m, 5H), 7.16 – 7.08 (m, 2H), 6.96 – 6.86 (m, 2H), 4.92 (app s, 1H), 4.88 (app s, 1H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.66 (br t, 1H), 4.60 (d, *J* = 11.5 Hz, 1H), 3.81 (s, 3H), 2.65 (d, *J* = 6.7 Hz, 2H), 1.78 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.2, 160.0, 140.0, 136.5, 128.5, 128.3, 128.2, 127.2, 126.8, 114.9, 114.7, 109.3, 72.9, 55.5, 40.6, 22.5 (one peak overlapped by $CDCl_3$); **HRMS** (ESI) calcd for $[C_{21}H_{22}N_2O_3 + Na]^+$ 373.1523, found 373.1538; **IR** (thin film) 2232, 1745, 1509, 1251, 1183.



2.72aq

Prepared from acid **S4x** and cyanamide **S2g** on a 4.0 mmol scale under modified conditions. **2.72aq** was purified by flash column chromatography (3:97 → 1:9 EtOAc/Hex) as a colorless oil (2.93 mmol, 73% yield). R_f = 0.35 (1:9 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.22 – 7.10 (m, 2H), 6.99 – 6.91 (m, 2H), 5.05 – 5.01 (m, 1H), 4.96 (t, *J* = 1.6 Hz, 1H), 3.82 (s, 3H), 3.36 (q, *J* = 7.1 Hz, 1H), 1.80 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H), 1.14 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.4, 159.9, 146.1, 129.0, 127.8, 114.8, 114.4, 111.2, 55.5, 48.6, 45.0, 23.1, 22.2, 21.5, 14.7; **HRMS** (ESI) calcd for $[C_{17}H_{22}N_2O_2 + Na]^+$ 309.1573, found 309.1568; **IR** (thin film) 2227, 1723, 1509, 1250, 1179.

2.6.7 Synthesis of substrates: N-sulfonyl cyanamides



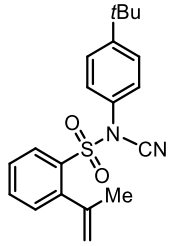
Synthesis of substrate 2.75a as a representative example: To a solution of 1-bromo-2-(prop-1-en-2-yl)benzene[67] (8672 mg, 44 mmol) in THF (40 mL) was dropwise added *n*BuLi (2.5 M Hex, 16 mL, 40 mmol) at –78 °C. The reaction was stirred at –78 °C for 30 min, whereupon a stock solution of SO_2 (ca. 2.3 M THF, 34.8 mL, 80 mmol)[6] was dropwise added. The reaction was allowed to warm to room temperature and stirred for additional 2 h. The reaction was concentrated to dryness to afford the lithium sulfinate as a white solid, which was triturated with pentane (20 mL × 2) to remove the residual 1-bromo-2-(prop-1-en-2-yl)benzene, followed by suspended in hexanes (150 mL) and cooled to –78 °C. To this suspension was slowly added SO_2Cl_2 (2.92 mL, 36 mmol) in hexanes (40 mL). The resulting mixture was vigorously stirred at –78 °C for 20 min, which was then allowed to warm to room temperature and stir for additional 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL), diluted with H_2O (20 mL), and extracted with Et_2O (30 mL × 3). The combined organic extracts were washed with water

[6] Prepared by bubbling $CaCl_2$-dried SO_2 gas through THF in a Schlenk flask at 0 °C following a similar report: Li, W.; Beller, M.; Wu, X. *Chem. Commun.* **2014**, *50*, 9513. The concentration of SO_2 was estimated by measuring the mass of dissolved SO_2 against the total volume of the resulting solution.

(20 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated. The resulting mixture was purified by flash column chromatography (5:95 EtOAc/Hex) to afford sulfonyl chloride **S5a** as a pale yellow oil (6684 mg, 30.8 mmol, 86% yield over 2 steps based on SO_2Cl_2). R_f = 0.59 (1:9 EtOAc/Hex). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.68 (td, *J* = 7.6, 1.3 Hz, 1H), 7.50 (ddd, *J* = 8.7, 7.6, 1.4 Hz, 1H), 7.35 (dd, *J* = 7.6, 1.4 Hz, 1H), 5.38 (t, *J* = 1.5 Hz, 1H), 5.08 (t, *J* = 1.2 Hz, 1H), 2.17 (t, *J* = 1.2 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 144.0, 142.3, 141.9, 135.0, 131.5, 128.8, 127.9, 117.6, 25.1.

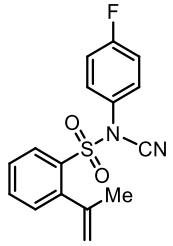
Next, the above obtained sulfonyl chloride **S5a** (520 mg, 2.4 mmol) was dissolved in CH_2Cl_2 (2.0 mL) and added to a solution of cyanamide **S2a** (2.0 mmol) and Et_3N (0.42 mL, 3.0 mmol) in CH_2Cl_2 (4.0 mL) at 0 °C. The reaction was allowed to warm to room temperature and stir for 4–6 h until TLC indicated the complete consumption of staring material. The mixture was then diluted with CH_2Cl_2 (30 mL), washed with 1 M HCl (10 mL), and separated. The organic phase was washed with brine (10 mL), dried over $MgSO_4$, and concentrated. The resulting mixture was purified by flash column chromatography (Hex → 1:9 EtOAc/Hex) to afford substrate **2.75a** as a pale yellow oil (1.72 mmol, 86% yield). R_f = 0.51 (1:4 EtOAc/Hex). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.64 (td, *J* = 7.6, 1.3 Hz, 1H), 7.40 (ddd, *J* = 8.5, 7.5, 1.4 Hz, 1H), 7.33 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 2H), 7.09 – 7.03 (m, 2H), 5.30 (t, *J* = 1.5 Hz, 1H), 4.76 (t, *J* = 1.1 Hz, 1H), 2.34 (s, 3H), 2.10 (t, *J* = 1.3 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 145.2, 143.0, 140.2, 134.8, 134.0, 131.6, 131.4, 130.9, 130.4, 127.6, 126.1, 117.2, 108.1,

25.4, 21.1; **HRMS** (ESI) calcd for $[C_{17}H_{16}N_2O_2S + Na]^+$ 335.0825, found 335.0818; **IR** (thin film) 2236, 1505, 1380, 1181.



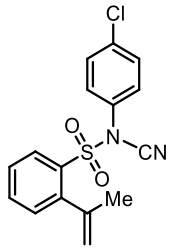
2.75b

Prepared from sulfonyl chloride **S5a** and cyanamide **S2c** on a 2.0 mmol scale. **3b** was purified by flash column chromatography (2:98 → 1:9 EtOAc/Hex) as a white solid (1.70 mmol, 85% yield). R_f = 0.55 (1:4 EtOAc/Hex). mp 84–86 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.65 (d, *J* = 1.4 Hz, 1H), 7.43 (d, *J* = 1.3 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.31 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 2H), 5.24 (app s, 1H), 4.64 (app s, 1H), 2.07 (s, 3H), 1.28 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.3, 145.2, 143.0, 134.8, 134.1, 131.5, 131.4, 130.8, 127.7, 126.8, 125.8, 117.0, 108.2, 34.8, 31.1, 25.4; **HRMS** (ESI) calcd for $[C_{20}H_{22}N_2O_2S + Na]^+$ 377.1294, found 377.1306; **IR** (thin film) 2233, 1504, 1381, 1182.



2.75c

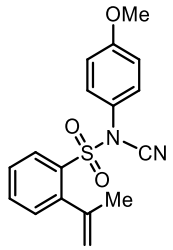
Prepared from sulfonyl chloride **S5a** and cyanamide **S2d** on a 2.0 mmol scale. **2.75c** was purified by flash column chromatography (Hex → 1:9 EtOAc/Hex) as a yellow oil (1.68 mmol, 84% yield). R_f = 0.53 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.66 (td, *J* = 7.5, 1.3 Hz, 1H), 7.45 – 7.39 (m, 1H), 7.34 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.23 – 7.16 (m, 2H), 7.05 (dd, *J* = 9.1, 7.9 Hz, 2H), 5.30 (app s, 1H), 4.74 (app s, 1H), 2.11 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.0 (d, $^1J_{F–C}$ = 251.7 Hz), 145.3, 143.1, 135.1, 133.7, 131.6, 131.0, 130.1 (d, $^4J_{F–C}$ =3.2 Hz), 128.6 (d, $^3J_{F–C}$ = 9.1 Hz), 127.8, 117.2, 117.0 (d, $^2J_{F–C}$ = 23.3 Hz), 107.9, 25.5; **^{19}F NMR** (470 MHz, $CDCl_3$) δ –109.4; **HRMS** (ESI) calcd for $[C_{16}H_{13}FN_2O_2S + Na]^+$ 339.0574, found 339.0565; **IR** (thin film) 2237, 1503, 1383, 1181.



2.75d

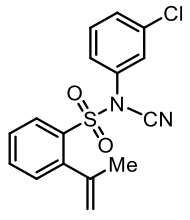
Prepared from sulfonyl chloride **S5a** and cyanamide **S2e** on a 2.0 mmol scale. **2.75d** was purified by flash column chromatography (5:95 → 1:9 EtOAc/Hex) as a white solid (1.78 mmol, 89% yield). R_f = 0.49 (1:4 EtOAc/Hex); mp 68–70 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.66 (td, *J* = 7.5, 1.3 Hz, 1H), 7.43 (ddd, *J* = 8.6, 7.6, 1.4 Hz, 1H), 7.36 – 7.32 (m, 3H), 7.16 (dt, *J* = 8.8, 2.2 Hz, 2H), 5.31 (app s, 1H), 4.75 (app s, 1H), 2.11 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 145.2, 143.0, 135.8, 135.2, 133.7,

132.8, 131.6, 131.0, 130.1, 127.8, 127.2, 117.3, 107.6, 25.4; **HRMS** (ESI) calcd for $[C_{16}H_{13}ClN_2O_2S + Na]^+$ 355.0278, found 355.0275; **IR** (thin film) 2253, 2239, 1486, 1184.



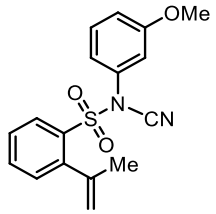
2.75e

Prepared from sulfonyl chloride **S5a** and cyanamide **S2g** on a 2.0 mmol scale. **2.75e** was purified by flash column chromatography (1:9 → 1:4 EtOAc/Hex) as a colorless oil (1.78 mmol, 89% yield). R_f = 0.30 (1:4 EtOAc/Hex); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.64 (td, *J* = 7.6, 1.3 Hz, 1H), 7.39 (ddd, *J* = 8.0, 7.5, 1.4 Hz, 1H), 7.34 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.12 – 7.03 (m, 2H), 6.87 – 6.77 (m, 2H), 5.31 (t, *J* = 1.5 Hz, 1H), 4.78 (t, *J* = 1.1 Hz, 1H), 3.79 (s, 3H), 2.11 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.7, 145.2, 143.1, 134.8, 133.9, 131.4, 131.0, 128.3, 127.6, 126.5, 117.1, 114.9, 108.2, 55.6, 25.5; **HRMS** (ESI) calcd for $[C_{17}H_{16}N_2O_3S + Na]^+$ 351.0774, found 351.0781; **IR** (thin film) 2253, 1507, 1383, 1265, 1182.



2.75f

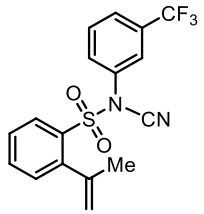
Prepared from sulfonyl chloride **S5a** and cyanamide **S2l** on a 2.0 mmol scale. **2.75f** was purified by flash column chromatography (1:9 → 1:4 EtOAc/Hex) as a white solid (1.62 mmol, 81% yield). mp 58–61 °C; R_f = 0.43 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.67 (td, *J* = 7.5, 1.3 Hz, 1H), 7.45 (ddd, *J* = 8.7, 7.5, 1.4 Hz, 1H), 7.40 – 7.33 (m, 2H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.26 (dd, *J* = 3.9, 1.8 Hz, 1H), 7.13 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 5.30 (app s, 1H), 4.73 (app s, 1H), 2.11 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 145.3, 143.0, 135.4, 135.3, 135.2, 133.7, 131.6, 131.0, 130.7, 129.8, 127.8, 125.7, 123.5, 117.3, 107.4, 25.4; **HRMS** (ESI) calcd for $[C_{16}H_{13}ClN_2O_2S + Na]^+$ 355.0278, found 355.0284; **IR** (thin film) 2230, 1589, 1383, 1182.



2.75g

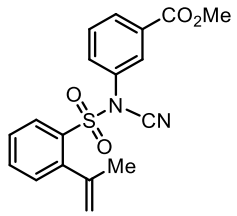
Prepared from sulfonyl chloride **S5a** and cyanamide **S2o** on a 2.0 mmol scale. **2.75g** was purified by flash column chromatography (8:92 → 1:9 EtOAc/Hex) as a yellow solid (1.43 mmol, 71% yield). R_f = 0.38 (1:4 EtOAc/Hex); mp 85–87 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.64 (td, *J* = 7.6, 1.3 Hz, 1H), 7.42 (ddd, *J* = 8.1, 7.4, 1.4 Hz, 1H), 7.33 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.23 (t, *J* = 8.5 Hz, 1H), 6.89 (ddd, *J* = 8.5, 2.3, 1.1 Hz, 1H), 6.79 – 6.72 (m, 2H), 5.32 (app s, 1H), 4.77 (app s, 1H), 3.74 (s, 3H), 2.11 (d, *J* = 1.2 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 160.4, 145.2, 142.9, 135.2, 134.9, 134.1, 131.5, 131.0, 130.4, 127.7, 117.6, 117.3, 115.6, 111.3, 107.8, 55.5, 25.4; **HRMS**

(ESI) calcd for $[C_{17}H_{16}N_2O_3S + Na]^+$ 351.0774, found 351.0785; **IR** (thin film) 2253, 2234, 1606, 1183.



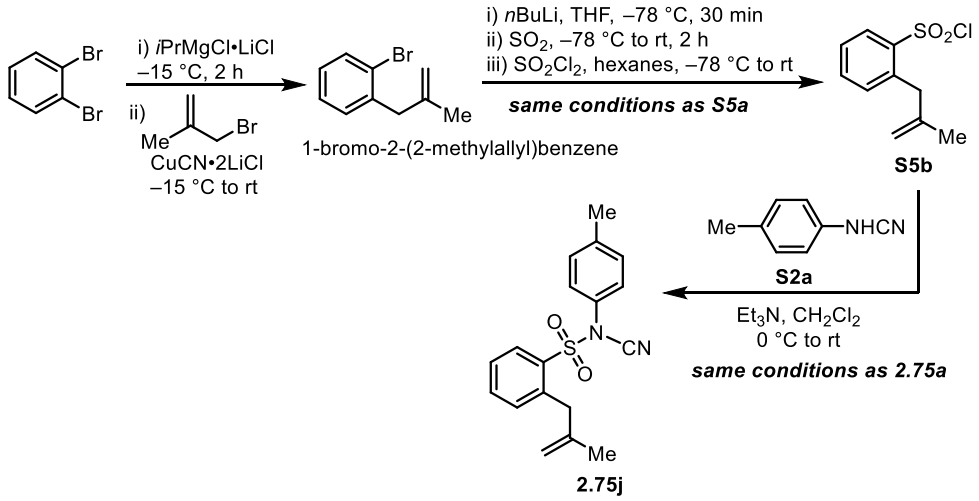
2.75h

Prepared from sulfonyl chloride **S5a** and cyanamide **S2m** on a 2.0 mmol scale. **2.75h** was purified by flash column chromatography (5:95 → 1:9 EtOAc/Hex) as a thick pale yellow oil (1.62 mmol, 81% yield). R_f = 0.49 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.68 (td, *J* = 7.6, 1.3 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 7.49 – 7.42 (m, 3H), 7.35 (dd, *J* = 7.6, 1.3 Hz, 1H), 5.27 (app s, 1H), 4.67 (app s, 1H), 2.10 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 145.3, 143.0, 135.4, 135.0, 133.5, 132.5 (q, $^2J_{F–C}$ = 33.5 Hz), 131.7, 131.0, 130.6, 128.7, 127.9, 126.2 (q, $^3J_{F–C}$ = 3.7 Hz), 122.9 (q, $^1J_{F–C}$ = 271.0 Hz), 122.5 (q, $^3J_{F–C}$ = 3.9 Hz), 117.2, 107.3, 25.4; **^{19}F NMR** (470 MHz, $CDCl_3$) δ –63.0; **HRMS** (ESI) calcd for $[C_{17}H_{13}F_3N_2O_2S + Na]^+$ 389.0542, found 389.0539; **IR** (thin film) 2253, 1386, 1328, 1183, 1139.



2.75i

Prepared from sulfonyl chloride **S5a** and cyanamide **S2n** on a 2.0 mmol scale. **2.75i** was purified by flash column chromatography (1:9 → 1:4 EtOAc/Hex) as a pale yellow oil (1.69 mmol, 85% yield). R_f = 0.31 (1:4 EtOAc/Hex); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 – 8.01 (m, 1H), 7.92 – 7.85 (m, 2H), 7.67 (td, *J* = 7.6, 1.3 Hz, 1H), 7.51 – 7.40 (m, 3H), 7.35 (dd, *J* = 7.6, 1.3 Hz, 1H), 5.30 (app s, 1H), 4.75 (app s, 1H), 3.91 (s, 3H), 2.11 (d, *J* = 0.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.2, 145.2, 143.0, 135.2, 134.7, 133.8, 132.1, 131.6, 131.0, 130.5, 130.0, 129.8, 127.8, 126.6, 117.4, 107.6, 52.6, 25.4; **HRMS** (ESI) calcd for $[C_{18}H_{16}N_2O_4S + Na]^+$ 379.0723, found 379.0729; **IR** (thin film) 2254, 1727, 1265, 1184.



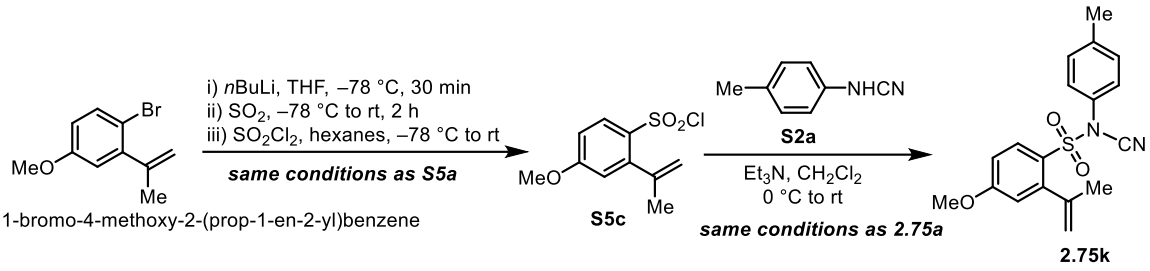
Synthesis of 1-bromo-2-(2-methylallyl)benzene: To a solution of *i*PrMgCl·LiCl (0.77 M in THF, 14.3 mL, 11 mmol) was slowly added 1,2-dibromobenzene (1.23 mL, 10 mmol) at –15 °C. The resulting solution was stirred at –15 °C for 2 h, whereupon methallyl bromide (1.21 mL, 12 mmol) and CuCN·2LiCl (1.0 M in THF, 1.0 mL, 1.0 mmol) were

sequentially added. The reaction was allowed to warm to room temperature and stir overnight, which was then quenched with saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (20 mL × 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated to afford 1-bromo-2-(2-methylallyl)benzene as a pale yellow oil (1972 mg, 9.3 mmol, 93% crude yield), which was taken to the next step without further purification. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.28 – 7.20 (m, 2H), 7.07 (ddd, *J* = 7.9, 6.7, 2.3 Hz, 1H), 4.86 (app s, 1H), 4.59 (app s, 1H), 3.46 (s, 2H), 1.76 (s, 3H). The NMR data is consistent with a literature report.[68]

Synthesis of sulfonyl chloride S5b: Sulfonyl chloride **S5b** was prepared in the same manner as **S5a**, starting from 1-bromo-2-(2-methylallyl)benzene on a 2.5 mmol scale. **S5b** was purified by flash column chromatography (1:9 Et_2O/Hex) as a colorless oil (1.9 mmol, 76% yield). R_f = 0.63 (1:9 EtOAc/Hex); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.66 (td, *J* = 7.6, 1.4 Hz, 1H), 7.50 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.45 (td, *J* = 7.8, 1.4 Hz, 1H), 4.98 (t, *J* = 1.5 Hz, 1H), 4.68 – 4.57 (m, 1H), 3.89 (s, 2H), 1.78 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.3, 142.9, 139.5, 135.0, 132.5, 128.9, 127.1, 114.1, 40.1, 22.5.

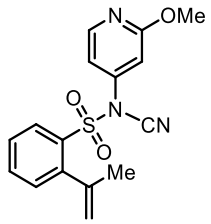
Synthesis of substrate 2.75j: 2.75j was prepared in the same manner as **2.75a**, starting from sulfonyl chloride **S5b** and cyanamide **S2a** on a 2.0 mmol scale. **2.75j** was

purified by flash column chromatography (1:9 → 1:4 EtOAc/Hex) as a colorless oil (1.17 mmol, 83% yield). R_f = 0.30 (1:9 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.62 (td, *J* = 7.5, 1.4 Hz, 1H), 7.45 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.35 (td, *J* = 7.7, 1.3 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 2H), 7.10 – 7.04 (m, 2H), 4.90 (app s, 1H), 4.48 (d, *J* = 0.7 Hz, 1H), 3.63 (s, 2H), 2.35 (s, 3H), 1.73 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.7, 140.6, 140.5, 134.9, 134.4, 132.6, 131.55, 131.53, 130.4, 127.1, 126.4, 113.6, 108.4, 40.7, 22.6, 21.1; **HRMS** (ESI) calcd for $[C_{18}H_{18}N_2O_2S + Na]^+$ 349.0981, found 349.0993; **IR** (thin film) 2235, 1505, 1378, 1179.



Synthesis of sulfonyl chloride S5c: Sulfonyl chloride **S5c** was prepared in the same manner as **S5a**, starting from 1-bromo-4-methoxy-2-(prop-1-en-2-yl)benzene[69] on a 7.2 mmol scale. **S5c** was purified by flash column chromatography (1:9 EtOAc/Hex) as an oily yellow solid (4.8 mmol, 67% yield). R_f = 0.38 (1:9 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 9.1 Hz, 1H), 6.93 (dd, *J* = 9.1, 2.7 Hz, 1H), 6.78 (d, *J* = 2.7 Hz, 1H), 5.39 – 5.32 (m, 1H), 5.13 – 5.02 (m, 1H), 3.91 (s, 3H), 2.16 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.4, 146.6, 142.4, 133.8, 131.7, 117.2, 116.4, 112.8, 55.9, 25.0.

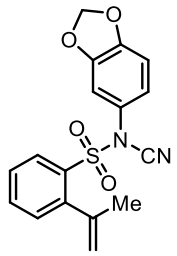
Synthesis of substrate 2.75k: 2.75k was prepared in the same manner as **2.75a**, starting from sulfonyl chloride **S5c** and cyanamide **S2a** on a 2.0 mmol scale. **2.75k** was purified by flash column chromatography (1:9 → 1:4 EtOAc/Hex) as a white solid (1.74 mmol, 87% yield). R_f = 0.30 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 9.0 Hz, 1H), 7.17 – 7.13 (m, 2H), 7.11 – 7.05 (m, 2H), 6.84 (dd, *J* = 9.0, 2.7 Hz, 1H), 6.77 (d, *J* = 2.7 Hz, 1H), 5.27 (app s, 1H), 4.76 (app s, 1H), 3.89 (s, 3H), 2.34 (s, 3H), 2.10 (d, *J* = 0.5 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.2, 147.7, 143.1, 140.0, 133.7, 131.8, 130.4, 126.1, 125.3, 116.8, 116.5, 112.7, 108.4, 55.8, 25.3, 21.1; **HRMS** (ESI) calcd for $[C_{18}H_{18}N_2O_3S + Na]^+$ 365.0930, found 365.0941; **IR** (thin film) 2235, 1590, 1369, 1242, 1176.



2.75l

Prepared from sulfonyl chloride **S5a** and cyanamide **S2t** on a 1.0 mmol scale. **2.75l** was purified by flash column chromatography (15:85 → 20:80 EtOAc/Hex) as a yellow gel (0.54 mmol, 54 % yield). R_f = 0.18 (1:4 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 5.8 Hz, 1H), 8.06 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.67 (td, *J* = 7.5, 1.2 Hz, 1H), 7.53 – 7.46 (m, 1H), 7.33 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.84 (dd, *J* = 5.8, 2.1 Hz, 1H), 6.67 (d, *J* = 2.1 Hz, 1H), 5.40 (s, 1H), 4.81 (s, 1H), 3.90 (s, 3H), 2.14 (s, 3H).**^{13}C NMR** (125 MHz, $CDCl_3$) δ 165.3, 148.7, 145.2, 144.1, 142.4, 135.5, 134.0, 131.7, 131.2, 127.9, 118.2, 108.9,

105.9, 102.6, 54.0, 25.2. **HRMS** (ESI) calcd for $[C_{16}H_{15}N_3O_3S + Na]^+$ 352.0726, found 352.0749; **IR** (thin film) 2230, 1594, 1481, 1381.

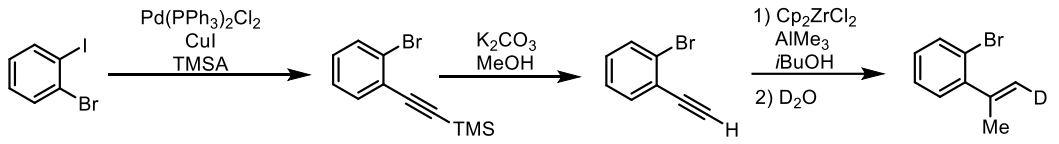


2.75m

Prepared from sulfonyl chloride **S5a** and cyanamide **S2u** on a 1.0 mmol scale. **2.75m** was purified by flash column chromatography (1:4 EtOAc/Hex) as a yellow gel (0.65 mmol, 65% yield). R_f = 0.45 (1:4 EtOAc/Hex); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.65 (td, *J* = 7.5, 1.3 Hz, 1H), 7.42 (td, *J* = 7.8, 1.4 Hz, 1H), 7.35 (dd, *J* = 7.6, 1.4 Hz, 1H), 6.71 (d, *J* = 8.3 Hz, 1H), 6.68 (d, *J* = 2.2 Hz, 1H), 6.61 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.02 (s, 2H), 5.34 (s, 1H), 4.82 (s, 1H), 2.12 (s, 3H)..**^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.0, 148.5, 145.3, 143.2, 135.0, 133.9, 131.5, 131.1, 127.7, 127.6, 121.0, 117.3, 108.5, 108.1, 108.0, 102.3, 77.3, 77.0, 76.7, 25.5.**HRMS** (ESI) calcd for $[C_{17}H_{14}N_2O_4S + Na]^+$ 365.0566, found 365.0574; **IR** (thin film) 2229, 1607, 1505, 1482, 1180.

2.6.8 Study towards the stereochemistry of alkene addition step

Synthesis of mono-deuterated substrate *trans*-2.72ad-d_1



S5

The precursor of **S5** (2-bromo-1-ethynylbenzene) was prepared from 2-bromoiodobenzene in 2 steps based on the reported procedures.[70]

(*E*)-1-bromo-2-(prop-1-en-2-yl-1-d)benzene (S5): The preparation of **S5** was performed according to a literature reference.[71] To a flame dried, N_2 purged, 25 mL round bottomed flask, bis(cyclopentadienyl)zirconium dichloride (73 mg, 0.25 mmol, 5.0 mol %) and Me_3Al (3.75 mL, 7.5 mmol, 1.5 equiv, 2.0 M solution in toluene) were added at 0 °C. Then isobutanol (0.05 mL, 0.5 mmol, 10 mol %) was added at the same temperature, while a white fume can be observed over the reaction mixture in the flask. After 10 minutes, 2-bromo-1-ethynylbenzene (905 mg, 5.0 mmol, 1 equiv.) was added. The mixture was stirred at room temperature overnight. D_2O (10 mL) was dropwise added to the mixture at 0 °C (*Caution!* Gas evolution, reaction vessel must be vented.) The aqueous phase was extracted with petroleum ether and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuum. The crude product **S5** (815 mg) with 97% D-labeling was obtained as a dark orange oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.19 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.11 (td, *J* = 7.9, 1.9 Hz, 1H), 5.23 – 5.22 (m, 0.03H), 4.92 (s, 1H), 2.10 (d, *J* = 0.8 Hz, 3H).

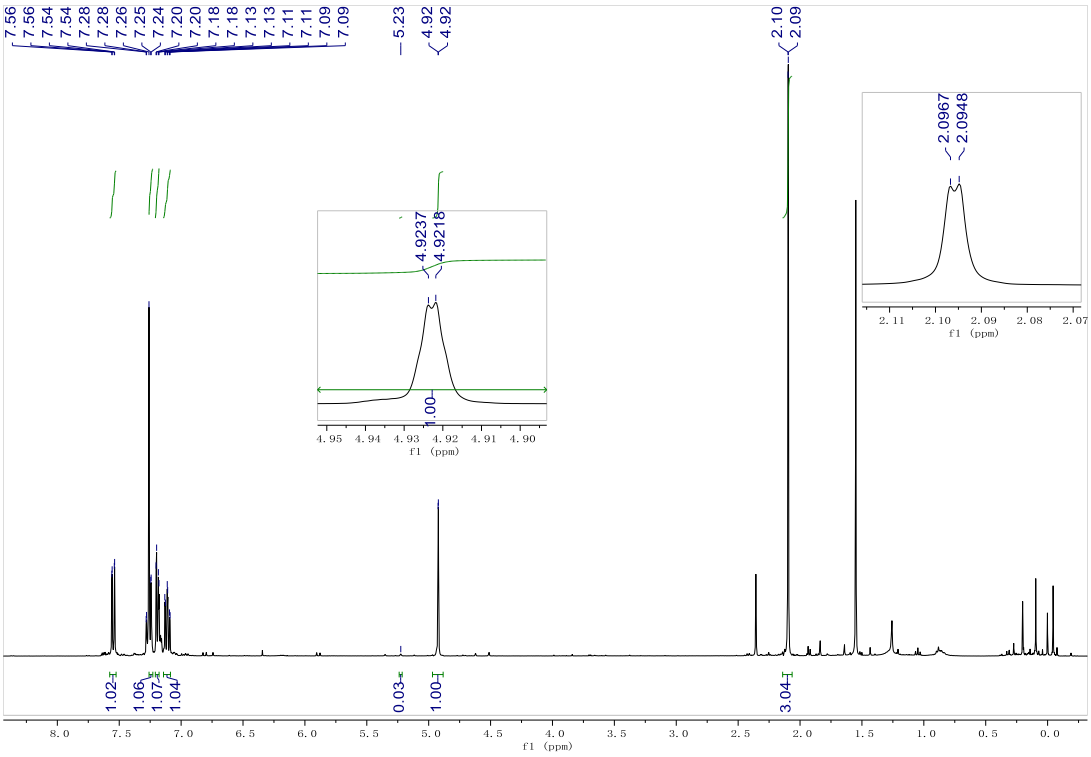
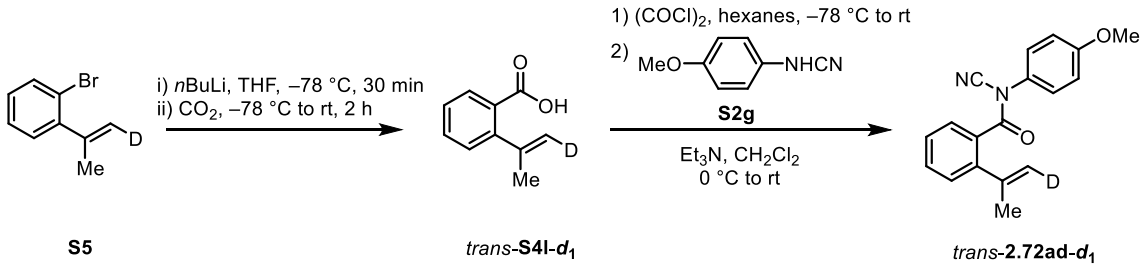


Figure 2-5 The ^{1}H-NMR spectrum of crude S5



***trans*-S4l-d_1:** To a solution of **S5** (815mg, crude mass) in anhydrous THF (4 mL), nBuLi (1.5 mL, 2.5 M solution in hexanes) was added dropwise at -78 °C. After 30 minutes, CO_2 gas was bubbled into the flask for 10 minutes (CO_2 gas was introduced by warming

dry ice and passing the vapor through an anhydrous $CaSO_4$ column prior to entering the reaction vessel). The resulting mixture was allowed to warm up to room temperature and stir overnight. The reaction was quenched with sat. $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with diethyl ether (10 mL). The aqueous portion was then acidified with 1M HCl until pH=1 (as indicated by pH paper). The resulting milky-white aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo to afford the crude *trans*-**S4l-*d*$_1$** as a pale-yellow solid (495 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.94 (s, 1H), 7.98 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.53 (td, *J* = 7.5, 1.4 Hz, 1H), 7.38 (td, *J* = 7.7, 1.4 Hz, 1H), 7.30 – 7.26 (m, 1H), 5.38 (s, 0.07H), 4.91 (d, *J* = 0.9 Hz, 1H), 2.14 (d, *J* = 0.9 Hz, 3H).

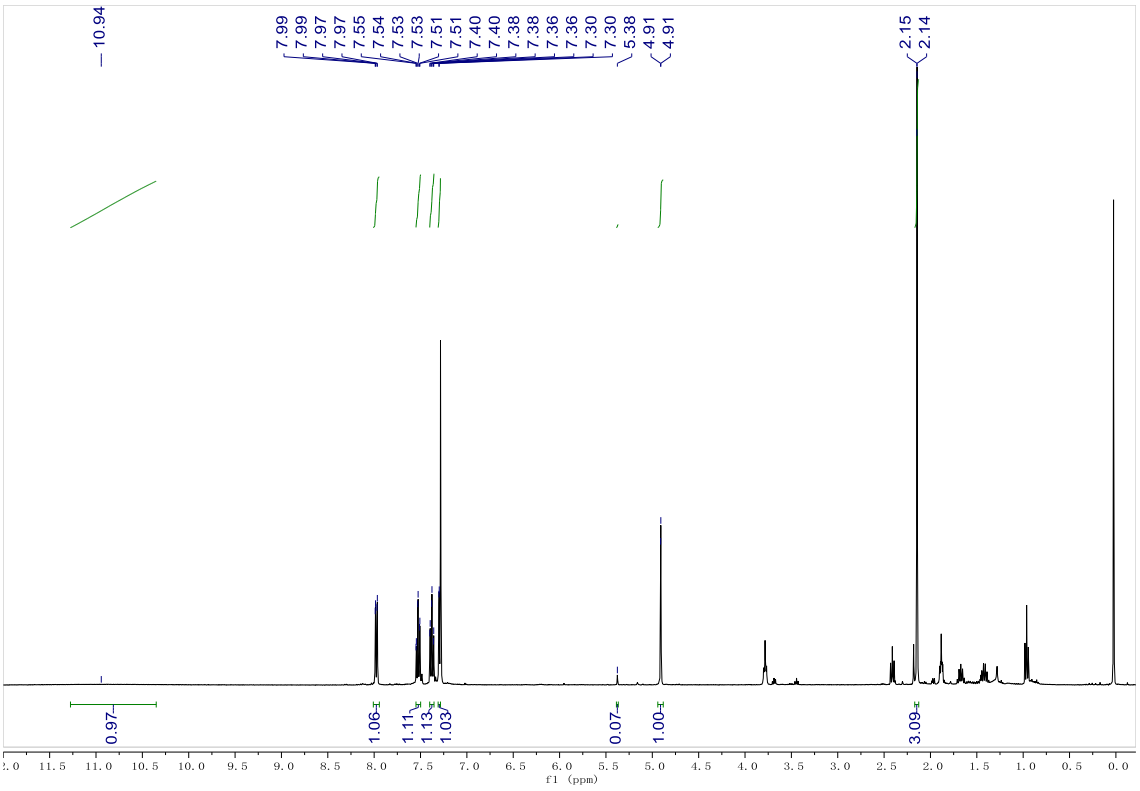
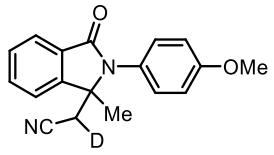


Figure 2-6 The ^{1}H-NMR spectrum of crude *trans*-S4l-d_1

***trans*-2.72ad-d_1**: The preparation of *trans*-**2.72ad-d_1** was performed based on standard conditions (See 6.3 synthesis of substrate **2.72ad**) with modifications. To a suspension of acid ***trans*-S4l-d_1** (495 mg, crude mass) in CH_2Cl_2 (3 mL) was added DMF (1 drop via glass pipet) and isoamylene (6.3 mL, 60 mmol), followed by dropwise addition of $(COCl)_2$ (2.0 M in CH_2Cl_2, 1.5 mL, 3.0 mmol) at room temperature. The mixture was stirred for 30 minutes, whereupon gas evolution ceased and all ***trans*-S4l-d_1** dissolved. The reaction flask was cooled to –12 °C in an ethylene glycol/dry ice bath and a solution of Et_3N (0.82 mL, 6.0 mmol) in CH_2Cl_2 (2.0 mL) was added dropwise. Thereafter, a solution of cyanamide **S2g** (445 mg, 3.0 mmol) in CH_2Cl_2/THF (1.5 and 0.5 mL, respectively) was

slowly added at the same temperature. The resulting mixture was allowed to warm up to room temperature and stir for 20 h. Et_2O (20 mL) was added to precipitate triethylamine hydrochloride, which was filtrated through a short Celite® column. Without further treatment, the filtrate was concentrated in vacuo and the resulting oily residue was purified by flash column chromatography to afford ***trans*-2.72ad-*d*$_1$** as a sticky white wax (2.0 mmol, 67 % yield). R_f = 0.20 (1:9 EtOAc/Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 – 7.48 (m, 2H), 7.43 – 7.36 (m, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 5.34 (app s, 0.01H), 5.13 (app s, 1H), 3.83 (s, 3H), 2.22 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.1, 159.9, 143.1, 141.8, 131.5, 130.7, 128.2, 127.6, 127.52, 127.46, 126.9, 116.9 (t, *J* = 24.4 Hz), 114.9, 110.1, 55.6, 23.2; **HRMS** (ESI) calcd for $[C_{18}H_{15}DN_2O_2 + Na]^+$ 316.1104, found 316.1116; **IR** (thin film) 2230, 1712, 1607, 1506, 1244.

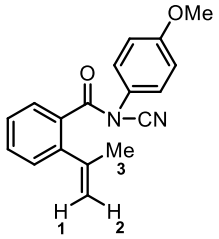


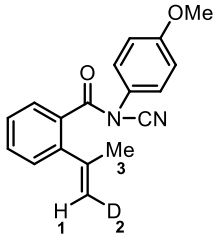
2.73ad-*d*$_1$

Prepared from ***trans*-2.72ad-*d*$_1$** on a 0.2 mmol scale with CpPd(1-phenylallyl) (10 mol%), Xantphos (10 mol%), and BEt_3 (60 mol%) in toluene at 80 °C for 24 h. **2.73ad-*d*$_1$** was purified by flash column chromatography (0.6:100 → 1:100 MeOH/CH_2Cl_2) as a pale yellow foam (0.19 mmol, 95% yield). R_f = 0.29 (2:100 MeOH/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.5 Hz, 1H), 7.70 – 7.62 (m, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.22 (d, J = 7.8 Hz, 2H), 7.03 (d, J = 7.8 Hz, 2H), 3.85 (s, 3H), 2.88 (s, 1H), 1.67 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.7, 160.0, 147.1, 132.7, 131.0, 130.9, 129.5, 126.7, 124.7,

121.3, 116.0, 115.3, 63.7, 55.6, 28.4 (t, J = 20.5 Hz), 24.9; **HRMS** (ESI) calcd for $[C_{18}H_{15}DN_2O_2 + Na]^+$ 316.1167, found 316.1151; **IR** (thin film) 2246, 1691, 1609, 1511, 1370, 1246.

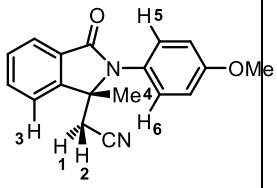
Assignment of stereochemistry of *trans*-2.72ad-d_1 by nOe NMR experiments

Assigned Structure	Key ^{1}H NMR Signals	Irradiation	Key nOe Results	Associate File
 **2.72ad**	**H1:** 5.15 (s, 1H) **H2:** 5.35 (s, 1H) **H3:** 2.23 (s, 3H)	**H1**	nOe observed: **H2** nOe not observed: **H3**	2.72ad-nOe-exp1.mnova
		H3	Strong nOe: **H2** Weak nOe: **H1**	2.72ad-nOe-exp2.mnova

Assigned Structure	Key ^{1}H NMR Signals	Irradiation	Key nOe Results	Associate File
 ***trans*-2.72ad-d_1**	**H1:**5.14 (s, 1H) **H3:**2.23 (s, 3H)	**H1**	nOe not observed: **H3**	2.72ad-D-nOe-exp1.mnova

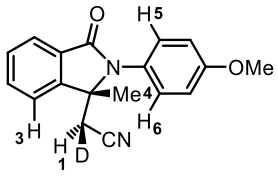
Conclusion: The proton and methyl group are *trans*.

Assignment of stereochemistry of (±)-2.73ad by nOe NMR experiments

Assigned Structure	Key ^{1}H NMR Signals	Irradiation	Key nOe Results	Associate File
 **(±)-2.73ad**	**H1:** 2.89 (d, J = 16.7 Hz, 1H) **H2:** 2.70 (d, J = 16.7 Hz, 1H) **H3:** 7.66 – 7.63 (m, 1H) **H4:** 1.68 (s, 3H) **H5,6:** 7.22 (d, J = 8.9 Hz, 2H)	**H1**	nOe observed: **H2, H3, H4, H5,6**	2.73ad-nOe-exp1.mnova
		H2	nOe observed:	2.73ad-nOe-exp2.mnova

			H1, H4, H5,6 nOe not observed: **H3**	

Assignment of stereochemistry of (±)-2.73ad-d_1 by nOe NMR experiments

Assigned Structure	Key ^{1}H NMR Signals	Irradiation	Key nOe Results	Associate File
 **(±)-2.73ad-d_1-I**	**H1:** 2.88 (s, 1H) **H3:** 7.66 – 7.63 (m, 1H) **H4:** 1.68 (s, 3H) **H5,6:** 7.22 (d, J = 8.9 Hz, 2H)	**H1**	nOe observed: **H3, H4, H5,6**	2.73ad-D-nOe-exp1.mnova

2.6.9 Computation of ^{1}H-NMR chemical shifts of 2.73ad

The protocol of computational prediction was provided by Hoye et al.[43] The studied molecule (**2.73ad**) was initially subjected to a Monte Carlo conformational search using MacroModel (version 11.0, MMFF forcefield) and Maestro (version 10.4.017), implemented in the Schrödinger software suite. Then each geometry of **2.73ad** was optimized at the M062X/6-31+G(d,p) level of theory with CPCM(chloroform) solvation model. The nature of each optimized geometry was verified by frequency calculation (298K, at the same level of theory). The relative free energies obtained from the frequency calculation were used to determine the Boltzmann weighting factors for each conformer. NMR calculation was performed for each conformer at the b3lyp/6-311+G(2d,p) level of theory. We used the scaling parameters for this protocol [b3lyp/6-311+G(2d,p)//M06-

2X/6-31+G(d,p)] created by Tantillo et al.[72] The Boltzmann weighting factors were applied to the computed NMR shielding tensors for each nucleus of each individual conformer.

Table 2-9 Electronic Energies and Boltzmann Factor of 2.73ad Conformers 1-7

Conformer	***Energy (a.u.)***	***Energy (kcal/mol)***	***Relative Energy (kcal/mol)***	***Boltzmann Factor***	***Equilibrium Mole Fraction***
2.73ad-conf-1	-954.920767	-599221.749	0.837097528	0.243064839	0.071029052
2.73ad-conf-2	-954.920985	-599221.8858	0.70030048	0.306271354	0.089499428
2.73ad-conf-3	-954.91905	-599220.6715	1.914531152	0.039362362	0.011502574
2.73ad-conf-4	-954.919157	-599220.7387	1.847387647	0.04409124	0.012884459
2.73ad-conf-5	-954.921925	-599222.4756	0.110441653	0.8297664	0.242476539
2.73ad-conf-6	-954.922062	-599222.5616	0.024472866	0.959491986	0.280385294
2.73ad-conf-7	-954.922101	-599222.5861	0	1	0.292222654

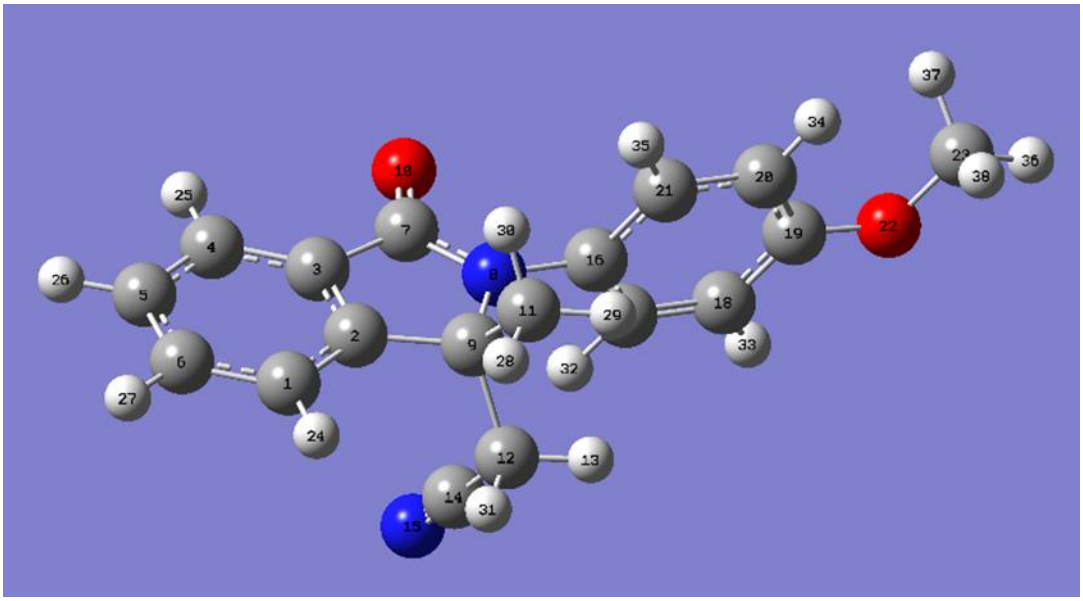


Figure 2-7 The labeling number of the atoms in **2.73ad**

Table 2-10 Predicted and experimental chemical shifts in ^{1}H-NMR of **2.73ad**

Gaussian atom numbers	*Predicted chemical shift (ppm)*	*Experimental Chemical Shift (ppm)*	$\delta_{Exp\text{-}comp}$ *(ppm)*
13	2.60	2.70	0.10
24	7.49	7.64	0.15
25	7.77	7.97	0.20
26	7.44	7.58	0.14
27	7.54	7.68	0.14
28	1.79		
29	1.69	1.68	0.09*
30	1.30		
31	2.82	2.89	0.07
32	7.32	7.22	-0.10
33	6.93	7.03	0.10
34	6.93	7.03	0.10
35	7.22	7.22	0.00
36	3.91		
37	3.65	3.86	0.12*
38	3.65		

***** For methyl protons, $\delta_{Exp\text{-}comp} = \delta_{Exp} - \overline{\delta_{comp}}$

Cartesian Coordinates

2.73ad-Conformer 1				**2.73ad-Conformer 2**			
C	3.737329	0.579261	0.279851	C	3.712518	0.566566	0.463941
C	2.463073	0.034384	0.160862	C	2.44949	0.028563	0.239676
C	2.297299	-1.31028	-0.1492	C	2.302273	-1.31697	-0.07611
C	3.376156	-2.15922	-0.36279	C	3.389874	-2.17339	-0.1927
C	4.65559	-1.61645	-0.25519	C	4.659024	-1.63752	0.020398
C	4.830163	-0.2643	0.063973	C	4.814323	-0.28466	0.346307
C	0.844815	-1.62392	-0.17997	C	0.855765	-1.62257	-0.2273
N	0.199055	-0.44851	0.13218	N	0.193198	-0.44208	0.023576
C	1.108507	0.694388	0.336138	C	1.088972	0.69716	0.296729
O	0.310465	-2.6945	-0.42094	O	0.336562	-2.69166	-0.50527
C	0.941824	1.322889	1.719484	C	0.810244	1.33374	1.658186
C	0.827263	1.728933	-0.78467	C	0.908835	1.727349	-0.84858
H	0.970864	1.260107	-1.76392	H	1.131096	1.253104	-1.81038
C	1.69505	2.905647	-0.69811	C	1.773788	2.899297	-0.69457
N	2.384317	3.830472	-0.61598	N	2.45992	3.82001	-0.5581
C	-1.22148	-0.33323	0.168427	C	-1.2245	-0.31898	-0.06288

C	-1.94182	-0.19927	-1.01487	C	-1.84188	-0.17978	-1.31185
C	-3.33246	-0.08765	-0.99715	C	-3.21895	-0.0582	-1.4014
C	-4.00491	-0.11003	0.228025	C	-4.00121	-0.07511	-0.23807
C	-3.28445	-0.25394	1.42171	C	-3.39392	-0.2251	1.011575
C	-1.90394	-0.37062	1.389717	C	-2.00602	-0.35162	1.08749
O	-5.35086	-0.00506	0.361395	O	-5.33839	0.055659	-0.42559
C	-6.12599	0.122259	-0.81871	C	-6.17415	0.027779	0.719098
H	3.891698	1.62496	0.531858	H	3.851462	1.612785	0.722673
H	3.215609	-3.20709	-0.60054	H	3.243536	-3.22165	-0.43784
H	5.526453	-2.24521	-0.41445	H	5.536294	-2.27226	-0.06086
H	5.835772	0.13748	0.148806	H	5.811627	0.111662	0.514374
H	1.679719	2.117278	1.862605	H	1.538269	2.124595	1.859492
H	-0.05747	1.754698	1.830717	H	-0.19233	1.771457	1.682316
H	1.09262	0.564011	2.491259	H	0.890731	0.57773	2.443239
H	-0.21321	2.067118	-0.7143	H	-0.13168	2.072251	-0.86753
H	-1.41166	-0.19456	-1.96416	H	-1.23208	-0.17967	-2.21202
H	-3.86756	0.010217	-1.93437	H	-3.71462	0.046951	-2.36151
H	-3.83048	-0.28228	2.359566	H	-3.9781	-0.25456	1.923694
H	-1.34495	-0.50359	2.311786	H	-1.52888	-0.48819	2.053972
H	-7.16253	0.185884	-0.49112	H	-7.19202	0.143508	0.349899
H	-5.85858	1.031697	-1.36818	H	-6.08227	-0.92667	1.24908
H	-5.99897	-0.7512	-1.46773	H	-5.9351	0.852041	1.400253

2.73ad-Conformer 3

C	3.842344	1.095638	0.222044
C	2.654309	0.37692	0.158159
C	2.67003	-1.00004	-0.01891
C	3.855071	-1.71537	-0.14152
C	5.050082	-1.00023	-0.08131
C	5.040903	0.388837	0.098214
C	1.269062	-1.49603	-0.048
N	0.471752	-0.39238	0.157381
C	1.224649	0.871555	0.269632
O	0.881574	-2.64107	-0.21725
C	0.973271	1.577298	1.603216
C	0.917299	1.80829	-0.92655
H	1.670547	2.603164	-0.95901
C	-0.39615	2.460683	-0.85064
N	-1.41089	3.011561	-0.78623

2.73ad-Conformer 4

C	3.858588	1.069385	-0.00633
C	2.662098	0.364319	0.051061
C	2.649736	-1.01864	-0.07061
C	3.814594	-1.75377	-0.25384
C	5.01794	-1.05266	-0.31465
C	5.036781	0.342513	-0.1926
C	1.245369	-1.49681	0.027089
N	0.478191	-0.37489	0.247551
C	1.250866	0.881852	0.252901
O	0.835059	-2.64267	-0.06631
C	1.11079	1.641581	1.573083
C	0.860709	1.776854	-0.95093
H	1.616605	2.560572	-1.07182
C	-0.43684	2.447152	-0.79697
N	-1.43877	3.010781	-0.67119

C	-0.9494	-0.44337	0.053011	C	-0.94699	-0.40712	0.2683
C	-1.54649	-0.61548	-1.20131	C	-1.6516	-0.61056	-0.91407
C	-2.92544	-0.63259	-1.32121	C	-3.04575	-0.61072	-0.92303
C	-3.72944	-0.47132	-0.18413	C	-3.73709	-0.39647	0.272745
C	-3.14087	-0.31647	1.073531	C	-3.03082	-0.20844	1.468331
C	-1.74942	-0.31281	1.18239	C	-1.6453	-0.2234	1.466007
O	-5.06868	-0.48792	-0.40278	O	-5.08983	-0.36437	0.376607
C	-5.92357	-0.3178	0.71451	C	-5.84876	-0.54066	-0.80719
H	3.852218	2.173879	0.365102	H	3.890092	2.152251	0.091508
H	3.838185	-2.79301	-0.27864	H	3.776595	-2.83575	-0.3446
H	5.99855	-1.52093	-0.17291	H	5.951242	-1.58925	-0.45647
H	5.983736	0.92633	0.143612	H	5.985678	0.868868	-0.24205
H	1.596529	2.474191	1.67185	H	1.746969	2.531924	1.557854
H	-0.07367	1.879564	1.693721	H	0.077434	1.961584	1.732595
H	1.228133	0.908521	2.428936	H	1.422247	1.00207	2.402566
H	0.983484	1.246644	-1.86426	H	0.848003	1.179613	-1.86864
H	-0.91811	-0.73838	-2.08004	H	-1.10469	-0.77241	-1.83979
H	-3.40647	-0.76236	-2.28566	H	-3.56935	-0.77016	-1.85815
H	-3.74141	-0.20588	1.968586	H	-3.59093	-0.06068	2.38642
H	-1.28612	-0.21378	2.159839	H	-1.0965	-0.09908	2.395029
H	-6.93918	-0.34942	0.322751	H	-6.89324	-0.47061	-0.50701
H	-5.78597	-1.12586	1.441634	H	-5.62339	0.243801	-1.53813
H	-5.74713	0.648574	1.199818	H	-5.66045	-1.52416	-1.25203

2.73ad-Conformer 5

2.73ad-Conformer 6

C	3.747511	-0.79175	-0.77006	C	3.705682	-0.68375	-0.98915
C	2.517382	-0.22118	-0.46688	C	2.487364	-0.16654	-0.56617
C	2.442322	0.941221	0.288972	C	2.43819	0.968025	0.233033
C	3.577081	1.58115	0.771505	C	3.588005	1.633068	0.640241
C	4.814707	1.013252	0.472722	C	4.813937	1.120241	0.21879
C	4.896306	-0.15933	-0.2887	C	4.869534	-0.02504	-0.5853
C	1.01249	1.31488	0.456757	C	1.015939	1.284643	0.532086
N	0.291547	0.361898	-0.22984	N	0.271304	0.332601	-0.12985
C	1.125382	-0.68857	-0.83967	C	1.084877	-0.67086	-0.83833
O	0.549204	2.26691	1.06246	O	0.573604	2.196673	1.210693
C	0.931866	-0.77656	-2.35454	C	0.768183	-0.72195	-2.33404
C	0.79958	-2.06567	-0.21309	C	0.856763	-2.07533	-0.22909
H	-0.24121	-2.33308	-0.4298	H	-0.19034	-2.37105	-0.36296
C	0.987334	-2.06813	1.240123	C	1.171645	-2.11209	1.201557

N	1.133019	-2.04609	2.386873	N	1.417518	-2.11607	2.331275
C	-1.13354	0.324986	-0.23736	C	-1.14709	0.243789	-0.01567
C	-1.82435	-0.11634	0.887929	C	-1.96806	0.677908	-1.05149
C	-3.21891	-0.16315	0.895537	C	-3.35704	0.580283	-0.95058
C	-3.92478	0.235491	-0.24304	C	-3.92382	0.051547	0.212112
C	-3.23326	0.691065	-1.37368	C	-3.10046	-0.36983	1.265533
C	-1.84819	0.7413	-1.36641	C	-1.72311	-0.27467	1.150939
O	-5.27802	0.222734	-0.34541	O	-5.25834	-0.08805	0.415567
C	-6.02299	-0.2097	0.780458	C	-6.13413	0.344353	-0.61132
H	3.826116	-1.7024	-1.35958	H	3.764146	-1.57277	-1.61302
H	3.490655	2.488597	1.362514	H	3.522068	2.518136	1.266742
H	5.726199	1.480346	0.833348	H	5.736647	1.609329	0.516236
H	5.871193	-0.58513	-0.50817	H	5.835846	-0.40835	-0.90022
H	1.626397	-1.50805	-2.7775	H	1.446099	-1.41854	-2.83559
H	-0.08839	-1.08643	-2.59881	H	-0.25947	-1.05728	-2.50177
H	1.129873	0.196704	-2.81025	H	0.898281	0.269841	-2.7739
H	1.444588	-2.83384	-0.65203	H	1.483955	-2.80932	-0.74549
H	-1.26737	-0.41525	1.772396	H	-1.522	1.110334	-1.94275
H	-3.73078	-0.50585	1.787065	H	-3.97257	0.927213	-1.77213
H	-3.8039	1.011556	-2.23983	H	-3.56432	-0.76453	2.164222
H	-1.31133	1.118287	-2.23233	H	-1.08118	-0.58897	1.970038
H	-7.07069	-0.13694	0.492502	H	-7.142	0.149928	-0.24764
H	-5.78371	-1.24829	1.034676	H	-6.01412	1.416134	-0.80443
H	-5.83468	0.434002	1.64673	H	-5.96337	-0.2177	-1.53635

2.73ad-Conformer 7

C	3.707261	0.597209	1.036411	H	1.505084	2.750928	0.946287
C	2.486688	0.119987	0.574804	H	-1.09116	0.792289	-1.90191
C	2.43173	-0.95656	-0.30075	H	-3.57594	0.976142	-2.07307
C	3.578059	-1.60085	-0.74899	H	-3.96795	-1.09138	1.681422
C	4.806344	-1.12757	-0.28955	H	-1.51552	-1.27725	1.830033
C	4.86763	-0.04107	0.591963	H	-7.14437	-0.20172	0.235641
C	1.008005	-1.24114	-0.6247	H	-6.00298	-1.50591	0.662345
N	0.269218	-0.32642	0.093712	H	-5.97085	0.045178	1.557279
C	1.087264	0.615493	0.876898				
O	0.560503	-2.10471	-1.36098				
C	0.761886	0.558406	2.370384				
C	0.874598	2.063434	0.373019				
H	-0.17057	2.357967	0.523472				

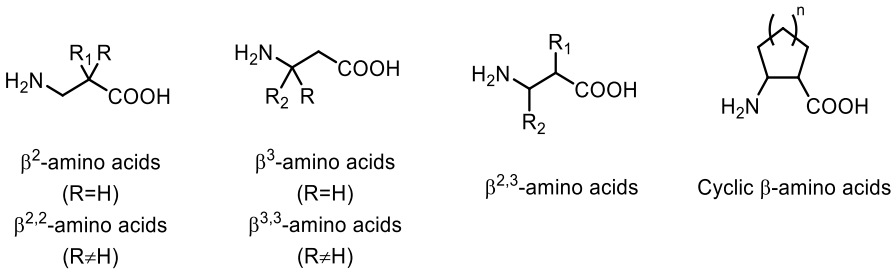
C	1.198158	2.204706	-1.04913
N	1.450531	2.292686	-2.17399
C	-1.14958	-0.2286	-0.00608
C	-1.73009	0.398644	-1.11534
C	-3.10821	0.498653	-1.21757
C	-3.92723	-0.02792	-0.2091
C	-3.35559	-0.66402	0.896205
C	-1.96611	-0.76409	0.984994
O	-5.26289	0.122813	-0.39648
C	-6.13473	-0.42139	0.579447
H	3.76981	1.440582	1.720414
H	3.507991	-2.44003	-1.43532
H	5.726455	-1.60198	-0.61723
H	5.835611	0.31219	0.935643
H	1.439614	1.212882	2.925967
H	-0.26555	0.885074	2.555925
H	0.884632	-0.4636	2.737166

Chapter 3 Intermolecular aminocyanation of unsaturated C−C bonds via N−CN bond activation

3.1 Synthetic strategies toward β-amino acids

β-amino acids abundantly exist in peptides and natural products as fundamental subunits. In recent years, β-amino acids are gaining considerable interests due to their impressive biological activity, pharmaceutical and agrochemical properties.[1–3] In addition, taking the advantages of diverse conformational structures, β-peptides (oligomers composed of β-amino acids) show a better stability than their α-counterparts. [4–7] Hence, to extend the understanding of protein structure and the design of novel medicines, synthetic approaches toward β-amino acids are studied intensively, especially on the installation of various substituents and controlment of stereochemistry.

Based on the position of substituents on at the 3-aminopropionic acid core, the family of β-amino acids can be divided into these categories: α-substituted (β^2- & $\beta^{2,2}$-), β-substituted (β^3- & $\beta^{3,3}$-) and α, β-multi-substituted β-amino acids ($\beta^{2,3}$-, $\beta^{2,2,3}$-, $\beta^{2,3,3}$- & $\beta^{2,2,3,3}$-) (**Scheme 3-1**). [8,9] Besides linear strictures, cyclic β-amino acids are also attractive synthetic targets. Herein, this chapter will briefly summarize general synthetic methods for β-amino acids with different backbones.



Scheme 3-1 General structure types of β-amino acids

3.1.1 Synthetic methods for α-substituted β-amino acids

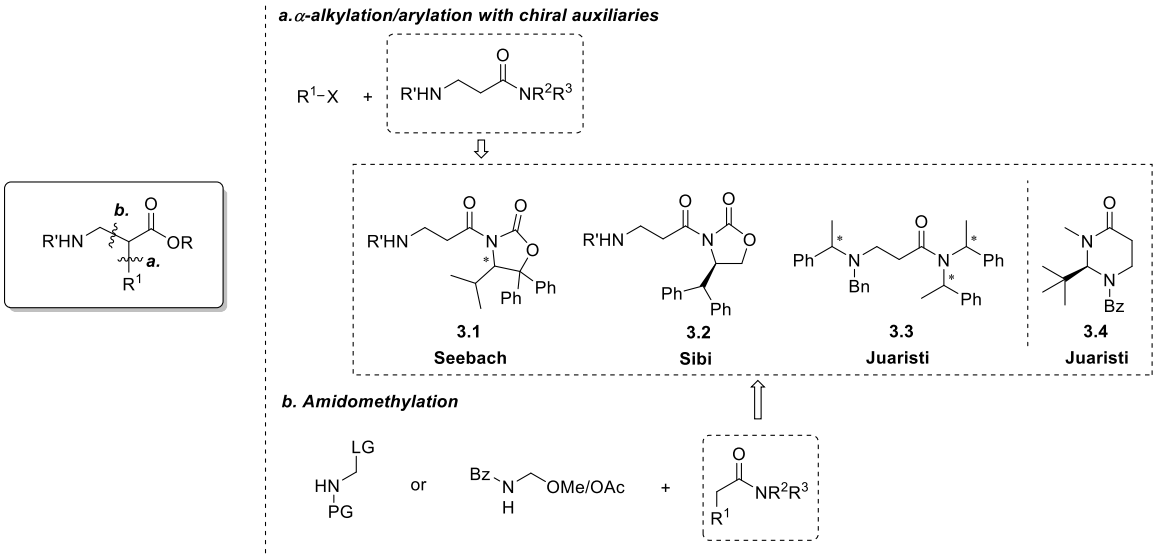
The presence of β^2-amino acids makes β-peptides more stable against proteolytic degradation and less liable to metabolic process.[5,6] However, β^2-amino acids are not readily available, compared with their β^3-counterparts. Several reviews have concluded synthetic methods to prepare α-substituted β-amino acids.[3,6,9] Generally speaking, β^2-amino acids can be synthesized through the following types of reactions: (1) nucleophilic attack of enolates, (2) Conjugate addition of amines, (3) hydrogenation of α,β-unsaturated nitrile and ester derivatives, (4) Curtius degradation of monosubstituted succinates, (5) hydrolysis of 5-substituted dihydrouracils. These reactions can be further modified to prepare enantiopure β^2-amino acids using chiral auxiliaries or ligands.

(1) Nucleophilic attack of enolates

Based on the species of nucleophiles, the skeleton of β^2-amino acids can be constructed into two ways (**Scheme 3-2**). The first method is direct introduction of α-substituents (electrophiles).[9] Starting from β-homoglycine derivatives, in the presence of oxazolidinone (**Scheme 3-2, 3.1**&**3.2)** (Evans Auxiliary)[10–12] or α-phenethyl group[13]

(**Scheme 3-2, 3.3**) as the chiral inductor, diastereoselective α-alkylation can be efficiently achieved. Further hydrolysis steps can remove the auxiliary moiety to generate β^2-amino acids with α-substituents. Similarly, Juaristi et al.[9,14,15] utilized enantiomerically pure 2-tertbutylperhydropyrimidin-4-one derivatives (**3.4**) to afford 1,4-trans-alkylation product, due to the axial-oriented *t*-butyl group. In addition, 1,4-cis diastereomer can be obtained by reforming the enolate, followed by protonation from the face opposite to the *t*-butyl group.

The other method is introduction of amidomethylene moiety at α-position.[6] The previous strategy (diastereoselective α-alkylation to enolates with chiral auxiliaries) is still feasible for α-amidomethylation, using electrophiles such as *N*-chloromethylbenzamide[16,17] or *N*-acetoxy[18]/methoxy[11,19] methyl benzyl carbamate (Mannich-type reactions) to obtain β^2-amino acids.

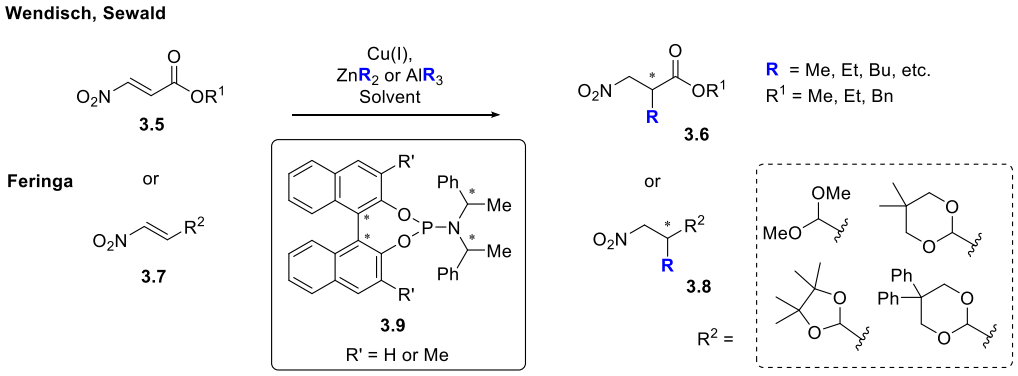


Scheme 3-2 Two disconnections toward β^2-amino acids via nucleophilic attack of enolates

(2) Conjugate addition of amines

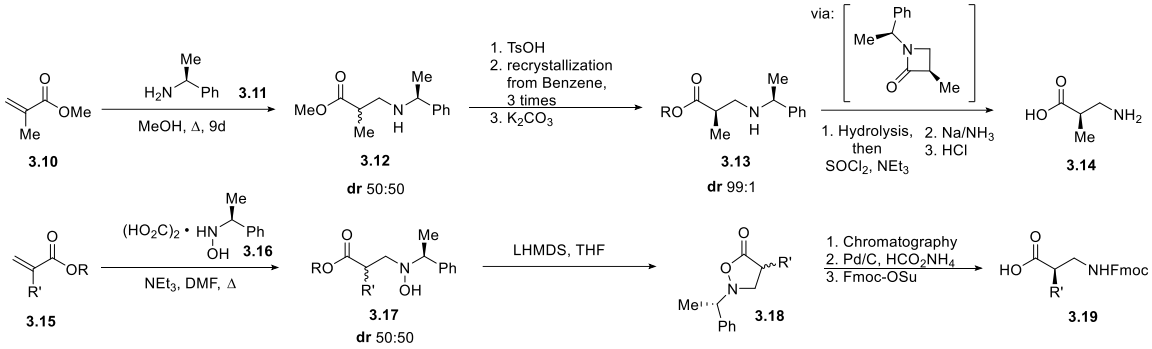
Conjugate addition to α, β-unsaturated carboxylic acid derivatives is one of the most versatile methods to prepare functionalized β-amino acids.[20] β-amino acids with multi-substituents can be readily obtained, depending on the skeleton structure of substrates. Asymmetric syntheses of α-substituted β -amino acids are also well developed.

Michael-type conjugate addition is a classical route to β^2-amino acids. Wendisch[21,22] and Sewald[23] have demonstrated that Cu(I)-mediated conjugate addition of alkyl zinc/aluminum reagents to β-nitroesters (**3.5)** provided both regioselectivity and enantioselectivity (50-96% es) with chiral BINOL-based P, N ligands (**Scheme 3-3**). Meanwhile, Feringa[24] also applied similar conditions to nitropropene (**3.7**) acetals and achieved better enantioselectivity (95-99% es) with (*S,R,R*)-Ligand **3.9**. Nitro groups can be then selectively reduced to amino groups via catalytic hydrogenation with ammonium formate.



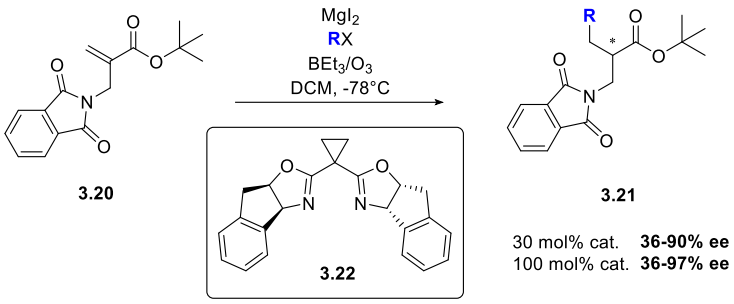
Scheme 3-3 Enantioselective conjugate addition of β-nitroesters and nitroproenes

Aza-Michael addition is an alternative synthetic method when ammonia equivalents and α-alkylacrylate esters served as Michael donors and acceptors respectively. Moreover, when chiral amine nucleophiles are applied (such as α-methylbenzylamine **3.11**[25] and hydroxylamine **3.16**[26]), (**Scheme 3-4**) the corresponding diastereomeric products can be separated via recrystallization, or further converted into a chromatography-separable mixture of diastereomeric cyclized products (isoxazolidinones **3.18**). The ring-opening and amino-protection steps are followed to deliver the desired β^2-amino acids.



Scheme 3-4 Aza-Michael additions using chiral amines

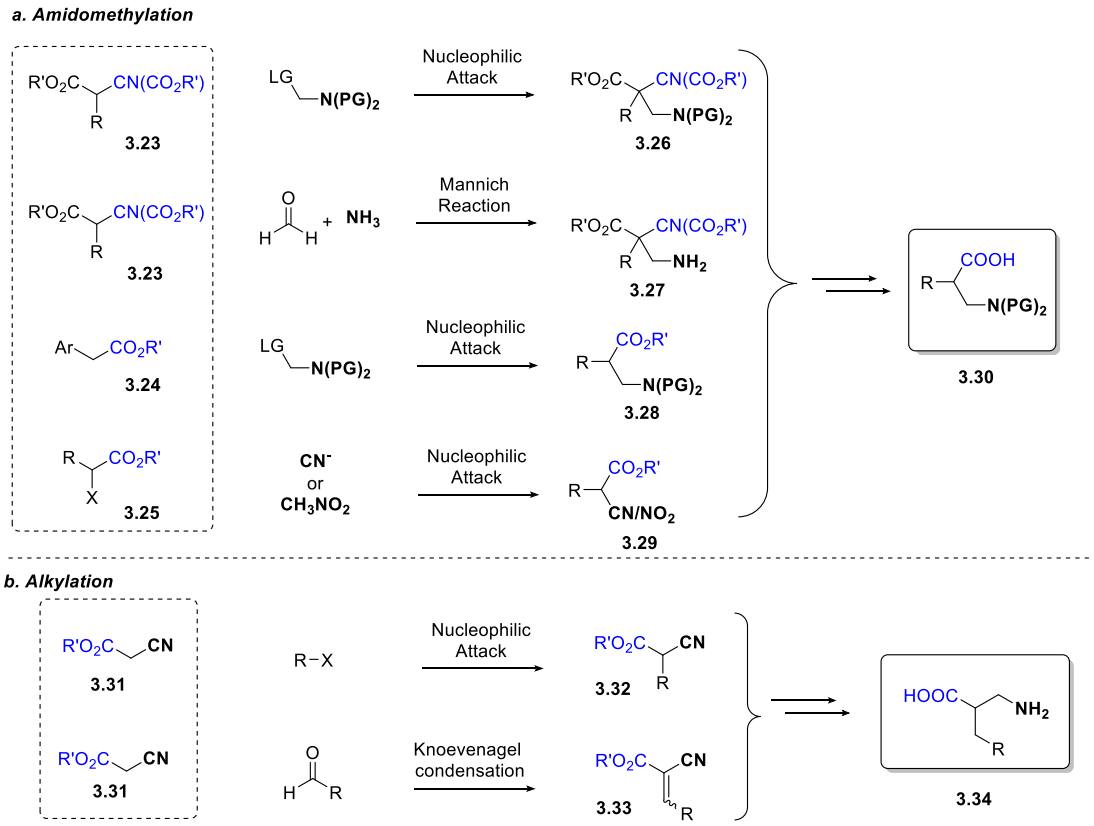
Sibi and Patil[27] discovered a radical conjugate addition to acrylates **3.20**, followed by asymmetric hydrogen atom transfer (**Scheme 3-5**). The use of MgI_2 catalyst and chiral ligand **3.22** gave modest to good enantioselectivity, especially for tertiary and cyclic radicals.



Scheme 3-5 Magnesium-mediated enantioselective conjugate additions

(3) Hydrogenation/reduction of nitrile and ester derivatives

Cyano group is one of the most versatile building blocks, which can be readily transformed into amines, carboxylic acids and esters. Hence, amino acids can be prepared from nitrile (as well as ester) derivatives with introduction of exogenous amino or carboxyl sources.

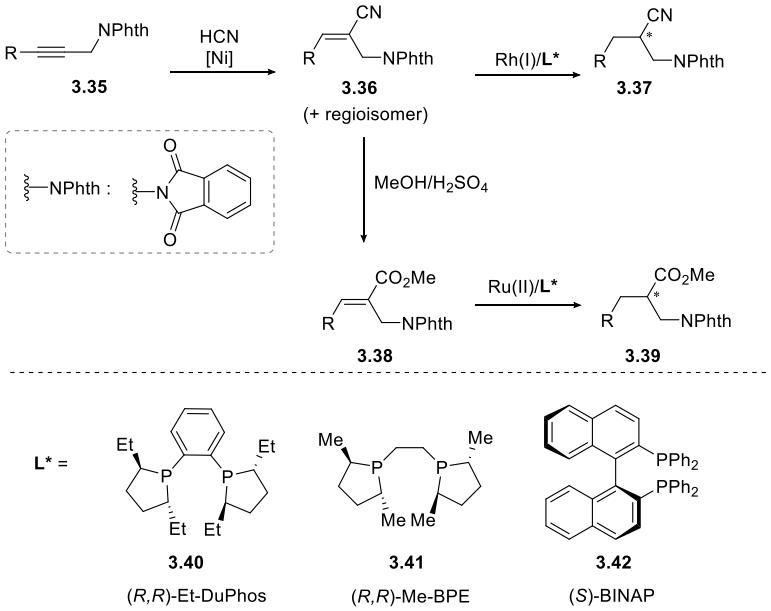


Scheme 3-6 Routes to β^2-amino acids from nitrile and ester derivatives

Amidomethylation on mono-substituted malonic/cyanoacetic esters **3.23** or aryl acetic esters **3.24** via nucleophilic substitution[28,29] or Mannich-type reaction[30] (**Scheme 3-6**) is one of classical synthetic strategies. Herein, cyano group (or ester) is served as the mask of carboxyl groups. Decarboxylation can remove the redundant ester moiety to provide the desired amino acid products. In addition, nucleophilic substitution of α-haloesters **3.25**, using cyanides or nitromethanes as nucleophiles, can also introduce the amino moiety.

Alkylation of cyanoacetic esters is an alternative method. Besides the direct nucleophilic attack on alkyl halides, Knoevenagel condensation[31] is another feasible approach. The products, α, β-unsaturated nitrile/ester derivatives **3.31**, can be further converted into β^2-amino acids via hydrogenation or complete reduction.

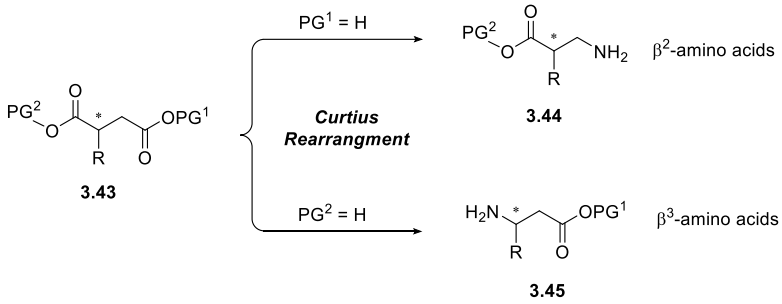
Moreover, α, β-unsaturated nitrile and ester derivatives, such as **3.36** and **3.38**, are the precursors for the preparation of enantiopure β^2-amino acids by means of asymmetric hydrogenation. Jackson and co-workers[32] have demonstrated that Rh/Ru-catalyzed enantioselective hydrogenation can afford β^2-amino acids in good yields and with es ranging from 50 to 92%.(**Scheme 3-7**)



Scheme 3-7 Enantioselective hydrogenation of α, β-unsaturated nitrile and ester derivatives

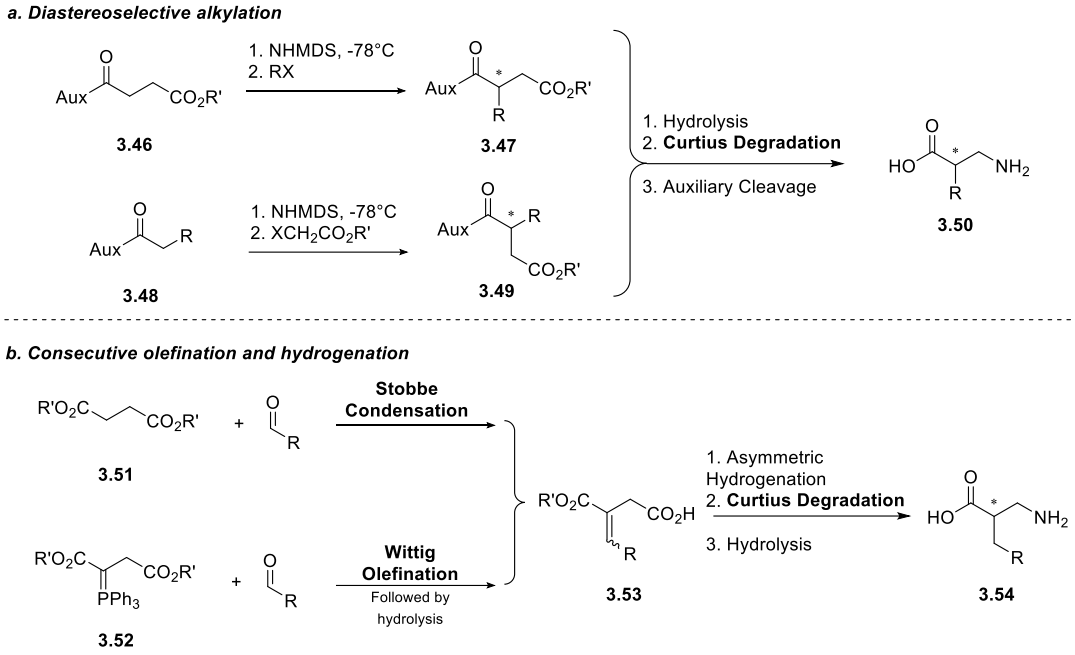
(4) Curtius degradation of monosubstituted succinates

Curtius rearrangement is a protocol for the synthesis of both β^2- and β^3-amino acids from mono-substituted succinates **3.43**, depending on the transformation of either of carboxyl groups (**Scheme 3-8**).



Scheme 3-8 Divergence of Curtius rearrangement to prepare either β^2- or β^3-amino acids

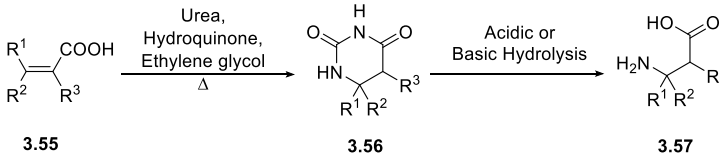
Moreover, the starting materials, chiral monosubstituted succinates, can be obtained from two pathways: diastereoselective alkylation of chiral succinyloxazolidinones[12,33] or acyloxazolidinones[11,33,34], and asymmetric hydrogenation of 3-enoic acids which are prepared from succinic esters via Stobbe condensation[35,36] or Wittig olefination[37]. (**Scheme 3-9**)



Scheme 3-9 Syntheses of β^2-amino acids through Curtius rearrangement

(5) Hydrolysis of 5-substituted dihydrouracils

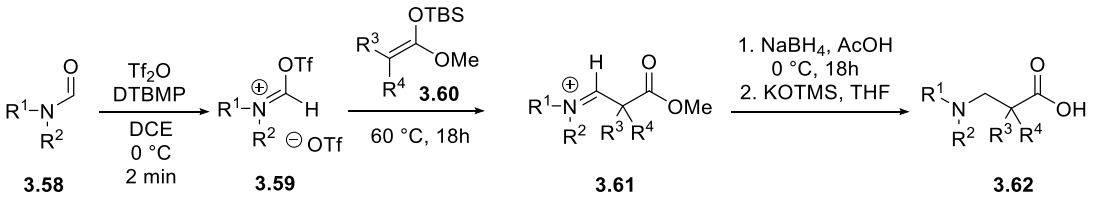
Dihydrouracils are a general source of β^2-amino acids due to their commercial availability and simple preparation from urea and acrylic acids[38]. (**Scheme 3-10**)Hydrolysis of dihydrouracils **3.56**[39,40] can also afford $\beta^{3,3}$- and $\beta^{2,3,3}$-amino acids, depending on the substituents on the backbones.



Scheme 3-10 Hydrolysis of substituted dihydrouracils

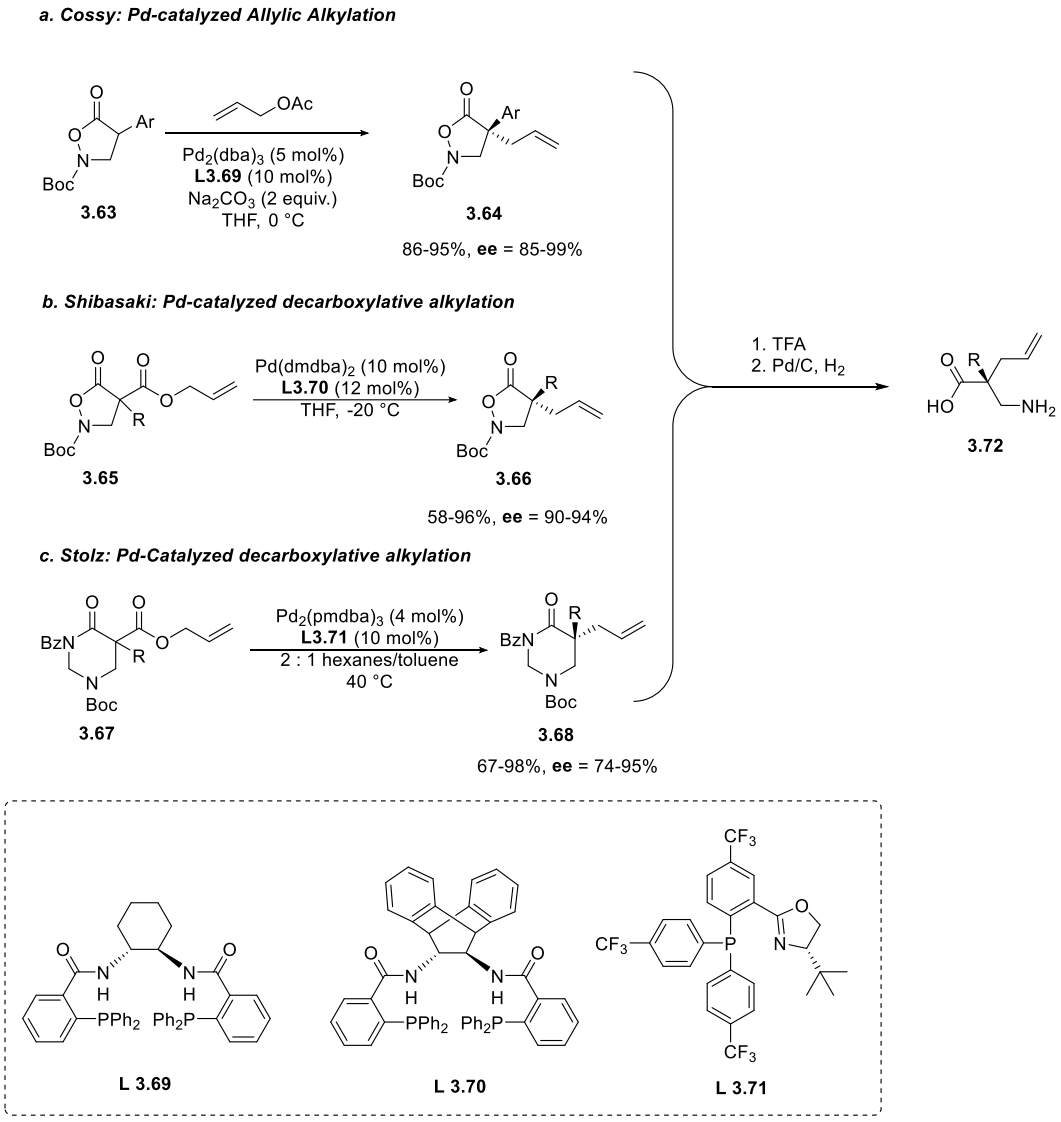
α, α-Disubstituted β-amino acids are achievable via most of the methods mentioned above, such as enolate dialkylation and Mannich reaction.[41] In the past few years, some unique methods also succeed in affording gem-disubstituted β-amino acids.

In 2014, Romanens and Bélanger reported a new approach to prepare $\beta^{2,2}$-amino acids, employing Vilsmeier−Haack reaction and nucleophilic attack of silyl enol ethers **3.60**.[42] (**Scheme 3-11**)When formamide **3.58** is replaced with other *N*-acylamides, this method can be also used for the synthesis of $\beta^{2,2,3}$-amino acids.



Scheme 3-11 Preparation of $\beta^{2,2}$-amino acids using Vilsmeier−Haack reaction

Recently, Cossy[43] and Shibasaki[44] demonstrated that Pd-catalyzed asymmetric allylic alkylation of 4-substituted isoxazolidin-5-ones (**3.63**, **3.65**) can afford chiral $\beta^{2,2}$-amino acids after ring-opening steps (**Scheme 3-12**). Stoltz[45] and co-workkers discovered that tetrahydropyrimidin-2-ones (**3.67**) can be also served as the precursors in Pd-catalyzed decarboxylative allylic alkylation.



Scheme 3-12 Preparation of the precursors of β²-amino acids via stereoselective Pd-catalyzed allylation

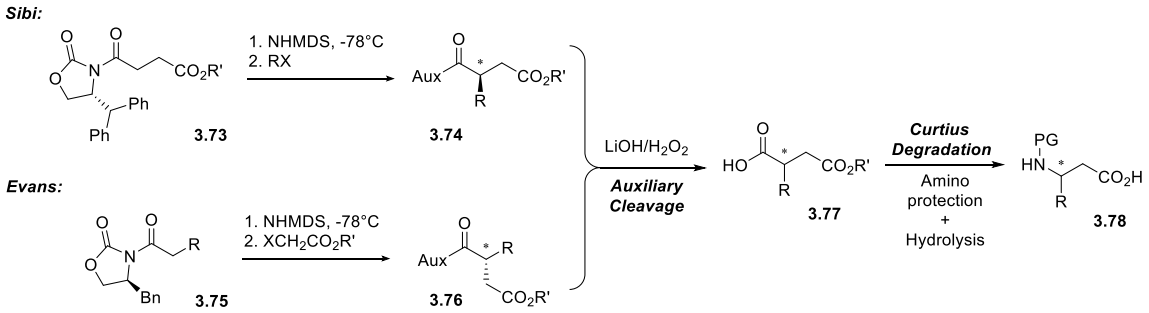
3.1.2 Synthetic methods for β-substituted β-amino acids

Generally, the synthetic methodologies of β²-amino acids are also viable for β³-amino acids. In addition, β³-amino acids can be directly prepared from natural α-amino

acids, which make them more commercially-available. Other versatile routes to β^3-amino acids will be also discussed in this section.

(1) Alkylation of enolates followed by Curtius rearrangement

As discussed above, Curtius protocol can afford both β^2- and β^3- amino acids from oxazolidinone derivatives. The difference is the sequence of treatments after diastereoselective alkylation (**Scheme 3-13**). When chiral auxiliaries are removed first, followed by Curtius reaction and hydrolysis of esters, β^3-amino acid derivatives are achieved. Conversely, hydrolysis of esters first will lead to β^2-amino acids instead. Sibi[12] and Evans[46] both manifested the feasibility of this synthetic strategy towards chiral β-substituted amino acids.



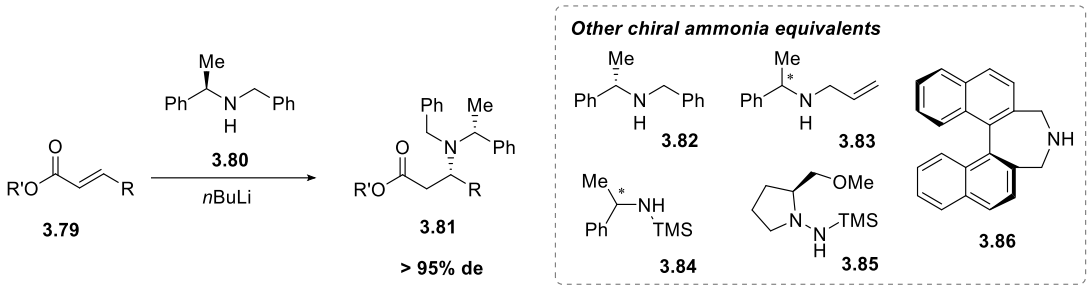
Scheme 3-13 Diastereoselective enolate alkylations followed by Curtius reactions

(2) Conjugate addition

Michael-type conjugate addition on α, β-unsaturated carbonyl derivatives is a straightforward and versatile method to β-substituted β-amino acids. To construct the chiral

centers in amino acids, generally there are three options: utilization of chiral amido nucleophiles, Michael acceptors with chiral auxiliaries and asymmetric catalysis.[1]

A series of lithium amides (**Scheme 3-14**) can be used as chiral amino source to give stereoselective conjugate addition with high dr. However, the deprotection conditions of benzylamide **3.80** (hydrogenolysis) is usually not compatible with some functional groups. Hence, Davis and co-workers applied allylamides **3.83** instead to diastereoselective conjugate additions, which can undergo an efficient deprotection (deallylation) in the presence of alkene moiety.[47,48] In addition, silylated amides such as TMS-SAMP **3.85** [49] and *N*-(1-phenylethyl)-(trimethylsilyl)amine **3.84** [50] were also explored as chiral ammonia equivalents to suppress competing 1,2-addition. TMS group is readily removable in acidic conditions.



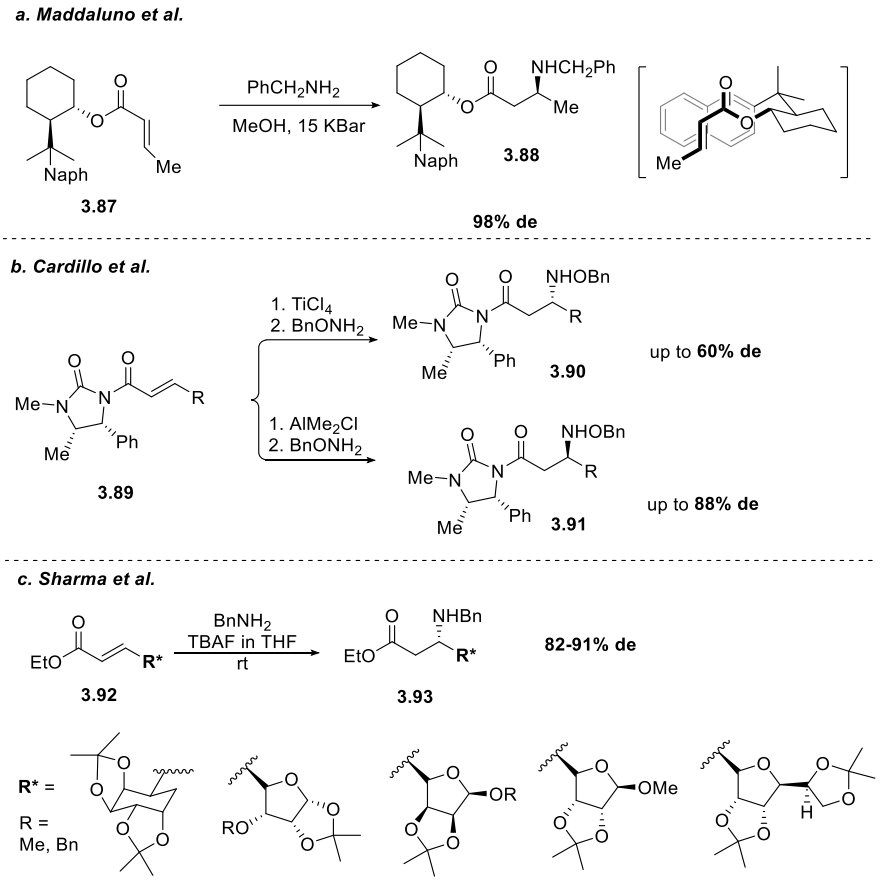
Scheme 3-14 Conjugate addition using chiral amino nucleophiles

Chiral auxiliary strategy is widely applied to stereoselective 1,4-additions. Several types of chiral auxiliaries have been investigated by recent reports. Maddaluno et al. succeeded in achieving high stereocontrol of the addition to crotonate substrate **3.87**.[51] Due

to the shielding originated from π-stacking model, (**Scheme 3-15, a**) the nucleophile prefers to attack the less hindered side of the acceptor.

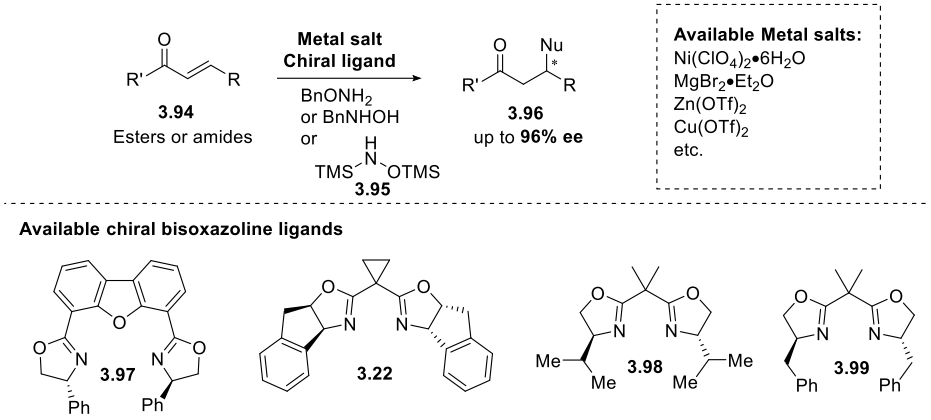
Chiral oxazolidinone moieties are also examined by Cardillo et al.[52] They also discovered that the use of Lewis acids can promote the diastereoselectivity of conjugate additions (**Scheme 3-15, b**). The Lewis acids are not able to control the rotamers population, but also to enhance the reactivity of the substrate. In particular, an inversion of newly-constructed stereocenter was observed when $TiCl_4$ was replaced with $AlMe_2Cl$.

Sugar-based acetals can be served as chiral auxiliaries as well, where locate at β-carbon of α, β- unsaturated ester substrates. Sharma et al. [53] utilized sugar derived γ-alkoxy α,β -unsaturated esters **3.92** as chiral substrates in the presence of TBAF to afford diastereoselective adducts (**Scheme 3-15, c**). TBAF can improve the reactivity of amine nucleophiles and suppress possible 1,2-addition pathway.



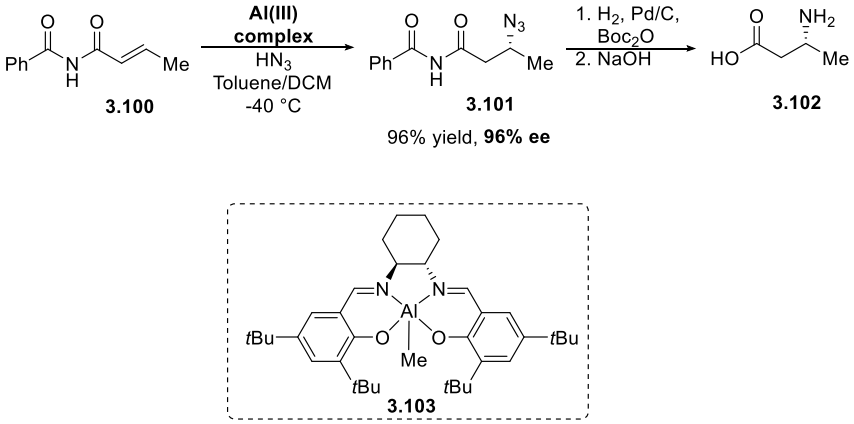
Scheme 3-15 Diastereoselective conjugate additions using chiral auxiliaries

Asymmetric catalysis is the third method to access enantiomerically-pure β^3-amino acids via conjugate addition. Among numerous published reports, the catalysts prepared from metal salts such as Ni(II)[54], Mg(II)[55], Zn(II),[56,57] and Cu(II)[58] with chiral ligand bisoxazoline derivatives(**3.22, 3.97-3.99**) shows a better performance to afford enantioselective adducts from achiral substrates. (**Scheme 3-16**)



Scheme 3-16 Metal-mediated enantioselective conjugate addition

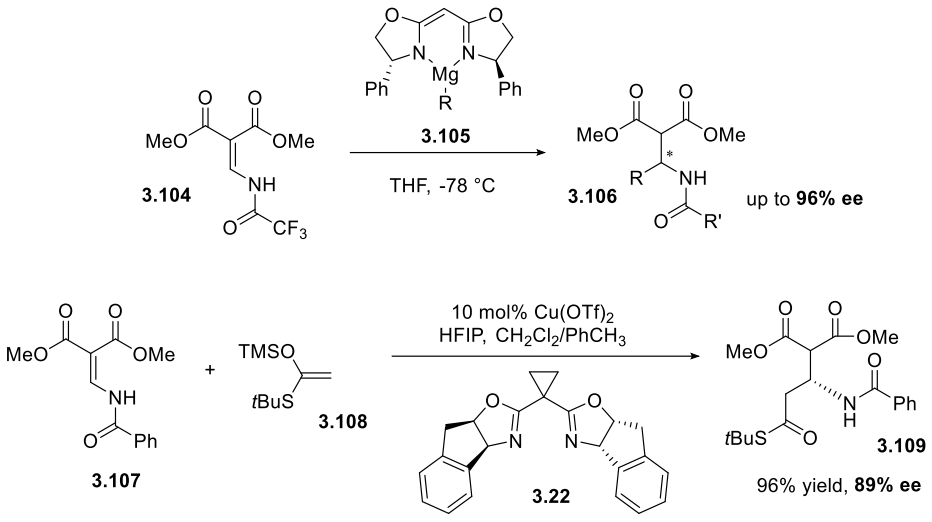
In addition, Al(III) complex catalysts can also give a high stereoselectivity (**Scheme 3-17**). Myers and Jacobsen[59] developed a new conjugation addition of hydrazoic acid to unsaturated amides **3.100** with readily available chiral (salen) Al(III) complex **3.103**. Both high yield and enantioselectivity were achieved.



Scheme 3-17 Introduction of an amino group via aluminum-catalyzed conjugate addition

Besides aza-Michael additions, conjugate additions of carbon-based nucleophiles to α, β-unsaturated enamide substrates (**3.104** and **3.107**) is an alternative route (**Scheme**

3-18). Organomagnesium reagents[60] **3.105** and silyl enol ether [61] **3.108** can be both served as nucleophiles here.



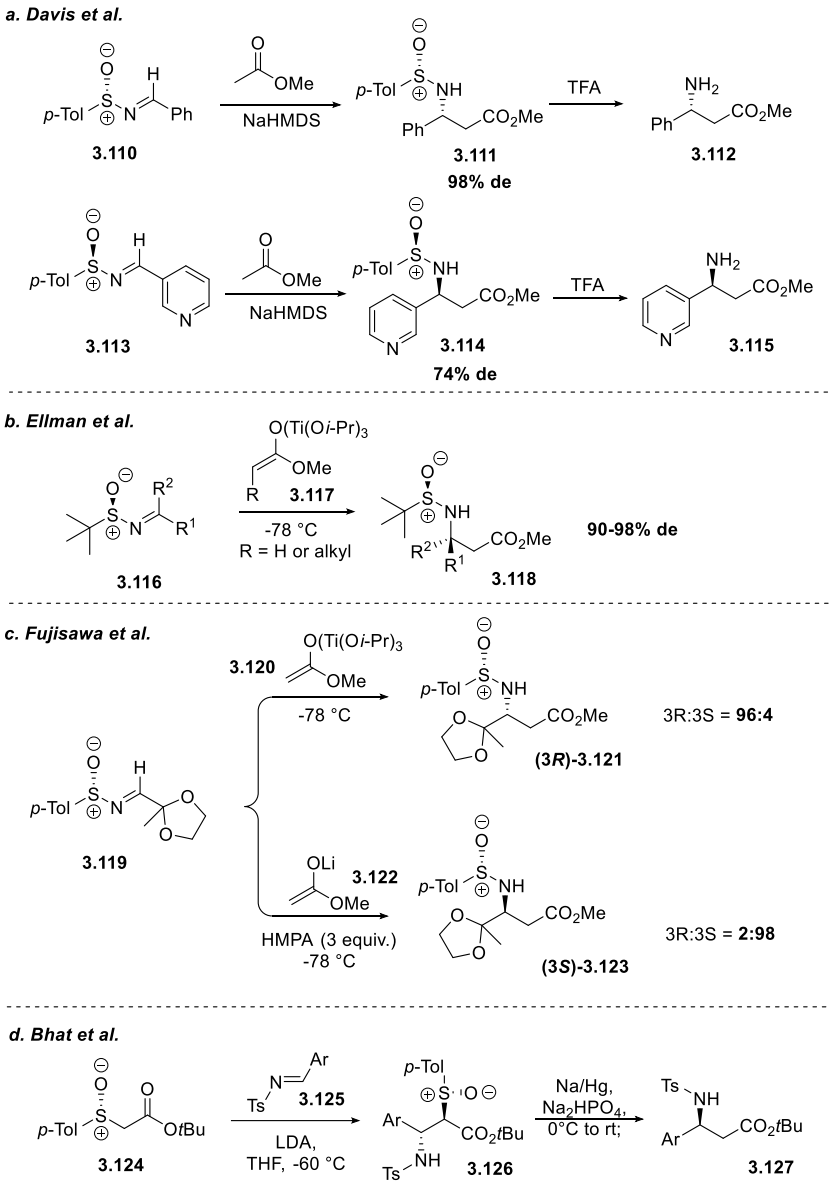
Scheme 3-18 Enantioselective β-alkylation via metal-mediated conjugate additions

(3) Mannich-type reactions

Mannich reaction is a convergent route to β-amino acids via a new C–C bond formation between two components ester enolate equivalents and imines. Various chiral auxiliaries and catalysts are explored to enhance the stereoselectivity while increase the reactivity of imines. To synthesize β^3- or $\beta^{3,3}$-amino acids, aldimines and ketimines are used for the starting materials, respectively.

The family of sulfoxides, which are served as chiral auxiliaries in imines, gains more attention in recent years.[62] The chiral sulfoxides can not only make the corresponding sulfinimines (**3.110, 3.113, 3.116, 3.119, 3.124**) as strong Michael acceptors, but also enhance the diastereoselectivity of Mannich reactions between sulfinimines and silyl enol

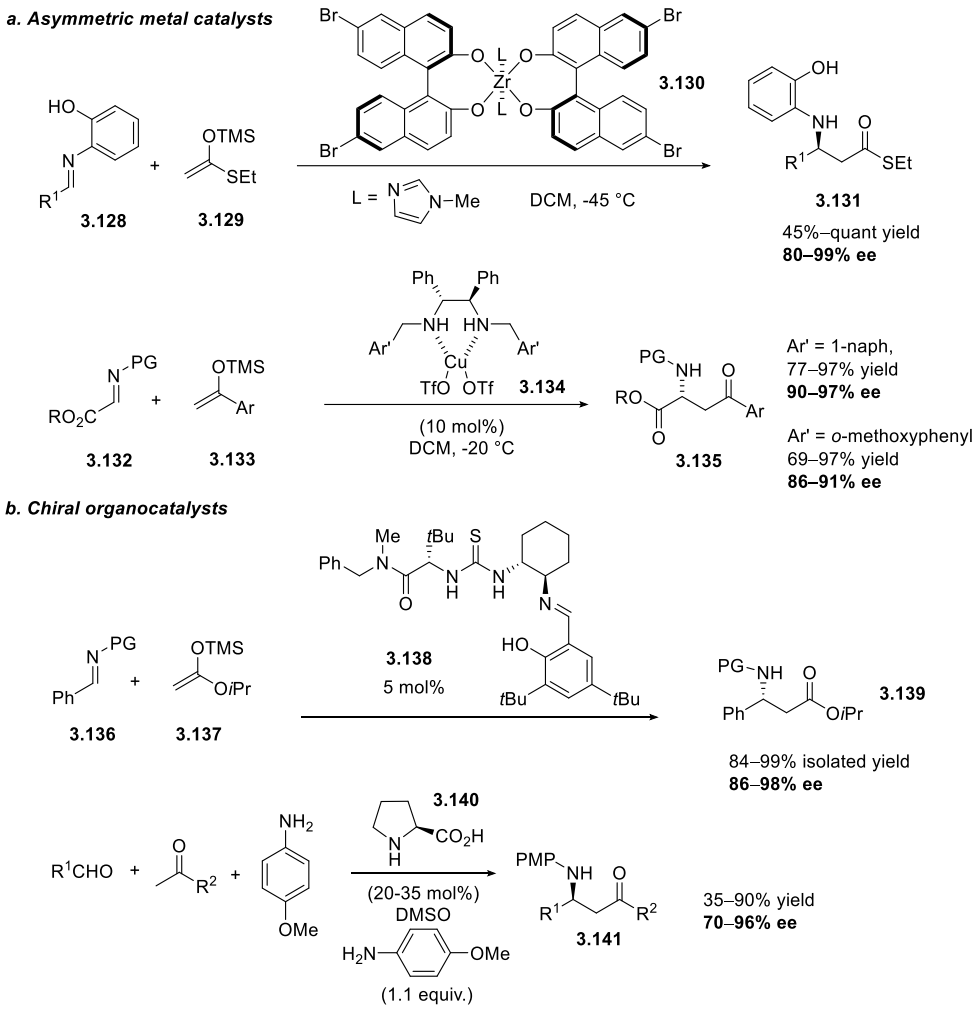
ethers. More importantly, sulfoxides can be readily removed without epimerization. Davis,[63] Ellman[64] and Fujisawa[65] contributed a lot to the application in asymmetric synthesis of β^3- and $\beta^{3,3}$-amino acids from chiral sulfinimines (**Scheme 3-19, a, b, c**). In addition, the chiral sulfoxides can be attached to enolate components as well to control the stereoselectivity.[66](**Scheme 3-19, d**)



Scheme 3-19 Mannich reactions using sulfoxides as chiral auxiliaries

Compared with chiral auxiliary strategy, catalytic enantioselective Mannich reactions have their own advantages: (1) obviation from tedious removal steps of auxiliaries, and (2) high atom economy due to the use of asymmetric catalysts instead of stochiometric amounts of chiral auxiliaries.[67] Metal catalysts such as Zr,[68,69] Cu,[70–72] etc.

are well investigated. Meanwhile, organocatalysts, like thiourea derivatives[73] **3.138** and prolines[74,75] **3.140**, also performed well in enantioselectivity (**Scheme 3-20**).

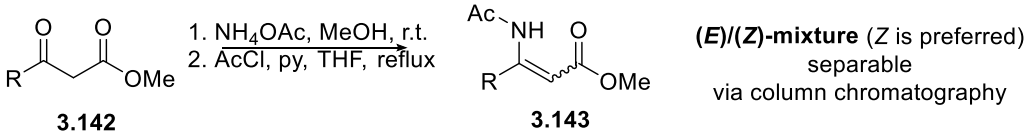


Scheme 3-20 Catalytic enantioselective Mannich reactions

(4) Hydrogenation of unsaturated nitrile and ester derivatives

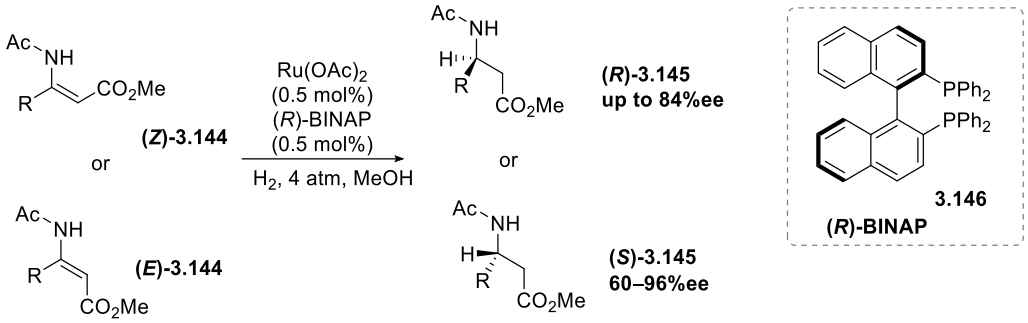
Asymmetric hydrogenation is an attractive and promising strategy in recent years due to its several advantages: broader substrate scope, higher reactivity and selectivity, and

less by-products and wastes.[76] The straightforward preparation of the starting materials, prochiral (*E*) or (*Z*)-enamine esters, makes asymmetric hydrogenation more extensively investigated in the synthesis of β-substituted β-amino acids, compared with α-substituted β-amino acids. An alternative way is condensation of primary amides with β-ketoesters **3.142** to afford (*Z*)-β-(acylamino)acrylates **3.143** (**Scheme 3-21**). [77]



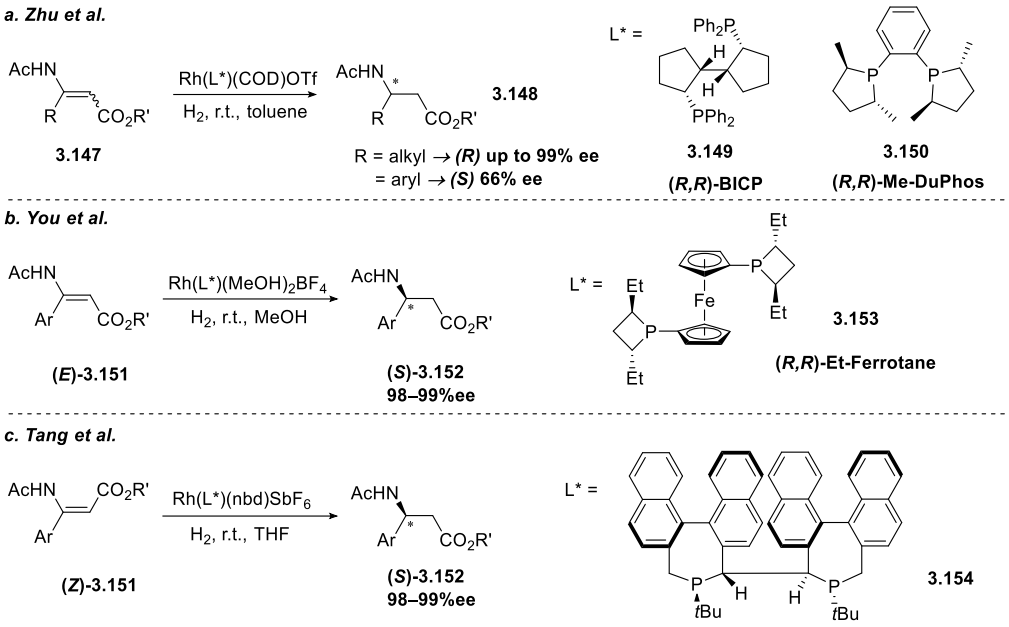
Scheme 3-21 Preparation of *N*-acyl-β-(amino)acrylates

Generally, Ruthenium or Rhodium, coupled with chiral ligands such as phosphines are used for enantioselective hydrogenation of enamido esters.[78] In 1991, Noyori and co-worker[79] discovered the first asymmetric hydrogenation of *N*-acyl-β-(amino)acrylates, using BINAP-Ru(lI) diacetate complex as the catalyst. Moderate to good enantioselectivities are obtained for hydrogenation of (*E*)-**3.144**, while (*Z*)-**3.144** achieved lower enantioselectivities. In addition, the two isomers afforded opposite absolute configuration in major enantiomers, except aryl substituted substrates, which both isomers provided identical (*R*)-configuration. (**Scheme 3-22**)



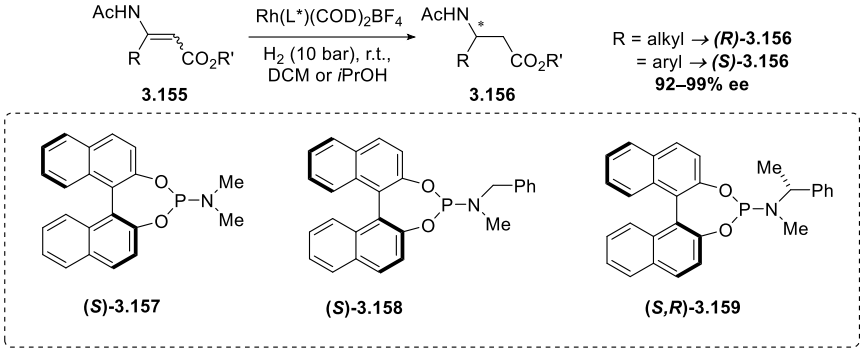
Scheme 3-22 Ruthenium-catalyzed asymmetric hydrogenation of *N*-acyl-β-(amino)acrylates

A series of bidentate phosphine ligand with rhodium complexes are then well screened to improve the enantioselectivity of hydrogenation.[78] Zhang,[80,81] You,[82] and Tang[83] et al. elucidated the chiral catalysts shown in **Scheme 3-23** afforded highly enantioselective hydrogenated products. Later, Heller and co-workers[84] reported a kinetic study on the first order rate constants and enantioselectivities observed in the hydrogenation of (*E*)- and (*Z*)-methyl β-*N*-acetylamidobutenoates. The behaviors of feasible bidentate ligands in asymmetric hydrogenation are summarized.



Scheme 3-23 Rhodium-catalyzed asymmetric hydrogenation using bidentate phosphine ligands

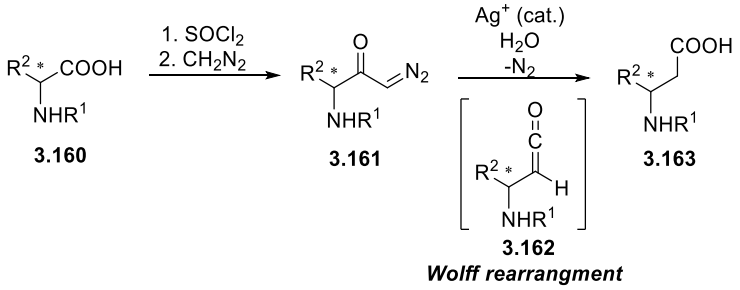
Alternatively, monodentate phosphine ligands also demonstrated their high stereocontrol ability. For example, Feringa et al.[85] reported three monodentate phosphoramidites that are feasible for enantioselective hydrogenation with 92–99% ee range (**Scheme 3-24**).



Scheme 3-24 Rhodium-catalyzed asymmetric hydrogenation using monodentate phosphine ligands

(5) Homologation of α-amino acids

Arndt-Eistert reaction is a popular method for synthesis of β^3-amino acids (**Scheme 3-25**).[86] It allows the direct homologation from low-cost natural α-amino acids in abundant supply. The classical procedure is as follows: First, the starting materials need to be converted to acyl chlorides (activation step), followed by the addition of diazomethane to prepare corresponding α-amino acid-derived diazoketones. Then a Wolff rearrangement occurs in the presence of silver salts to deliver the elongated product by one CH_2 unit. This process also allows the retention of the existing chiral centers from enantiomeric-pure amino acids. However, traditional Arndt-Eistert conditions have some limitations: (1) activation using acid chlorides may lead to racemization of substrates, (2) diazomethane is poisonous and explosive, (3) the cost of silver salts is not economical for large-scale reactions, though usually only catalytic amount is used here.

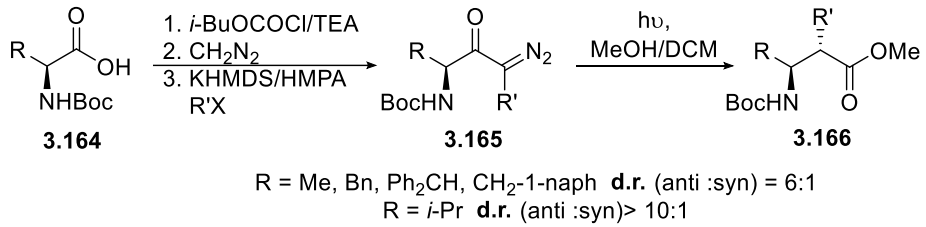


Scheme 3-25 Arndt-Eistert reactions

Hence, a variety of modifications are well developed. Instead of acyl chloride, the amino acids are transformed into anhydrides (i.e. using $Et_3N/ClCO_2Et$[87]) to obviate the

racemization. TMS-CHN_2 is recommended as a common substitute for diazomethane.[88] Photochemical[87] and thermal conditions[89] are also applied to Wolff rearrangement.

α, β-disubstituted β-amino acids can be also prepared via Arndt-Eistert reactions.[90] The precursors of Wolff rearrangement, C-1-alkylated diazoketones, are prepared from general diazoketones via anionic alkylation with potassium hexamethyldisilazide (KHMDS)/alkyl halides. The UV-induced rearrangement would deliver the corresponding stereoselective products in favor of the anti-isomer. (**Scheme 3-26**)



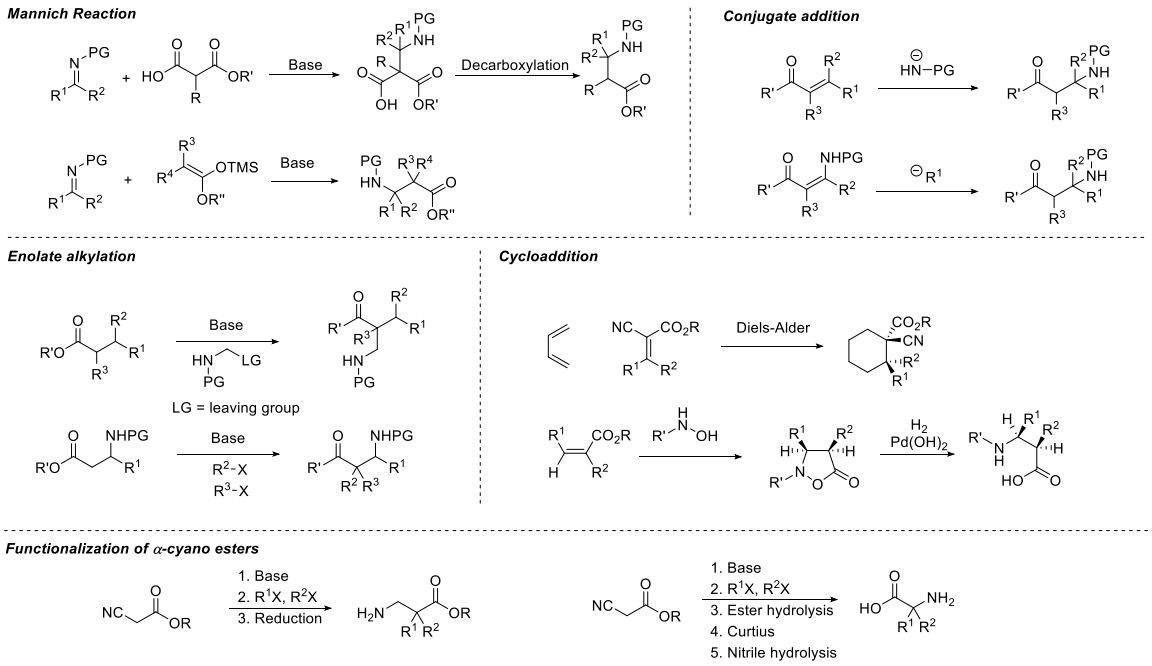
Scheme 3-26 Diastereoselective preparation of α, β-disubstituted β-amino acids via Arndt-Eistert reactions

3.1.3 Synthetic methods for multi-substituted β-amino acids

Generally, synthesis of multi-substituted β-amino acids ($\beta^{2,2}$-, $\beta^{3,3}$-, $\beta^{2,3}$-, $\beta^{2,2,3}$-, $\beta^{2,3,3}$- & $\beta^{2,2,3,3}$-) can be achieved via the methods discussed above, or further functionalization based on mono-substituted ones.

Common routes involve: (1) Mannich-type reactions, using disubstituted silyl ketene acetals or anionic malonic esters, coupled with secondary ketimines,[8,67] (2) Conjugate addition on multi-substituted unsaturated esters or amides,[91,92] (3) α-Difunctionalization of enolates,[93,94] (4) Cycloaddition, including direct synthesis of cyclic

amino acids[95] and acyclic ones with ring-opening step,[96] (5) Functionalization of α-cyano esters followed by reduction or Curtius degradation.[12] Other miscellaneous methods can be found in Seebach's review. [41] **Scheme 3-27** shows the general patterns of the routes listed above.

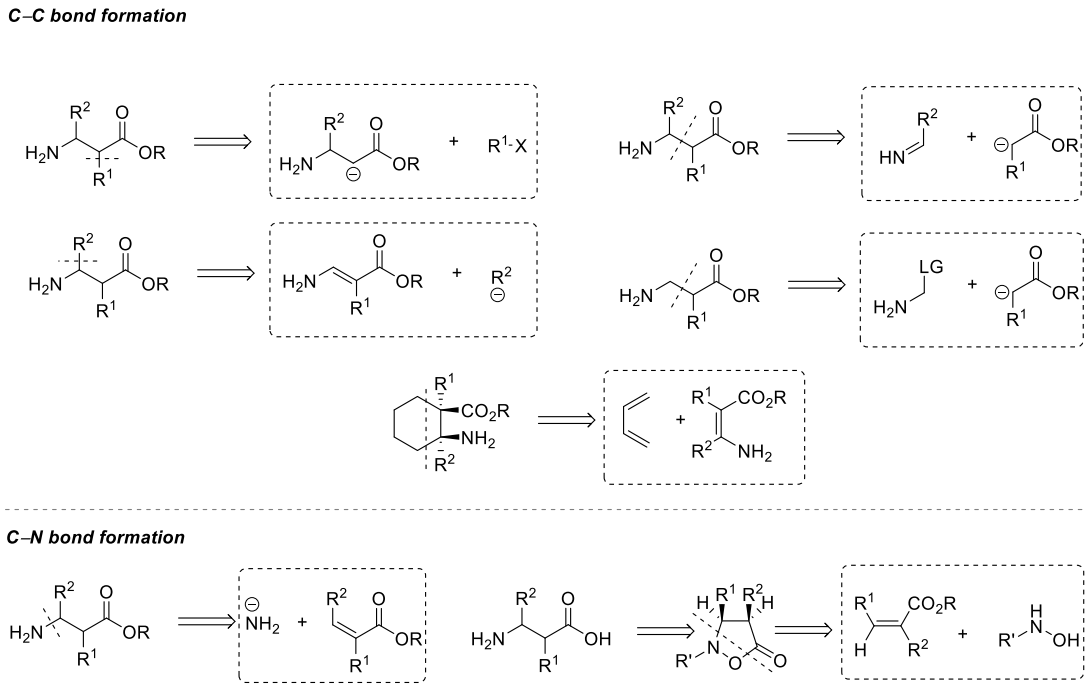


Scheme 3-27 Summaries of common synthetic routes to multi-substituted β-amino acids

3.2 Research proposal

In summary, to synthesize β-amino acids, the skeleton disconnections can be classified as follows. (**Scheme 3-28**) However, there are some disadvantages: First, preparation of desired acyclic branched substrates may be tedious and low-productive, especially for multi-substituted β-amino acids. Second, Homologation or repetitive alkylation steps may lead to racemization of chiral starting materials, in the presence of

strong bases or acids. Third, the compatibility of functional groups is a potential problem, caused by some harsh conditions. Lastly, though high diastereoselectivity can be achieved, the cleavage of chiral auxiliaries would result in low atom economy. But cycloaddition route is an exception, since it can simultaneously form two bonds and set up multi-stereocenters, when asymmetric Lewis acid catalysts are used.



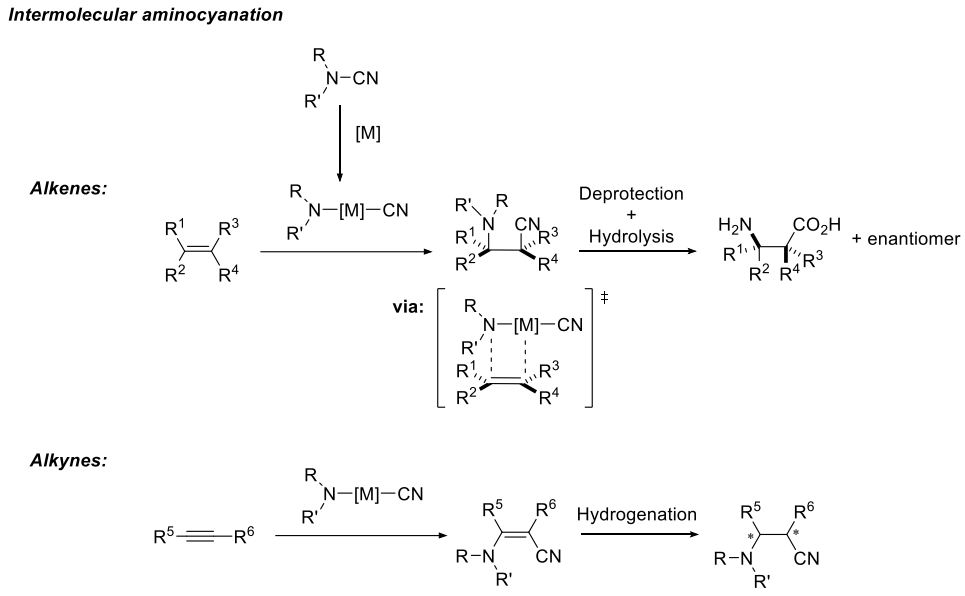
Scheme 3-28 Bond disconnections for multi-substituted β-amino acids

Based on the discussion above, a new strategy for synthesis of β-amino acids should be (1) a highly efficient and direct synthetic route for installation of substituents, (2) using asymmetric catalysts with mild conditions to achieve stereoselectivity. Recently, difunctionalization of unsaturated C–C bonds gains more attention due to high atom economy, abundant supply of alkenes/alkynes and well-studied stereochemistry. Based on

our previous intramolecular aminocyanation studies,[97,98] to simplify and unify the synthesis of β-amino acids, herein the intermolecular aminocyanation strategy is proposed.

Intermolecular aminocyanation strategy is to directly add amino (protected) and cyano groups (precursor of carboxyl) across pre-designed alkenes or alkynes, via catalytic N–CN bond activation of cyanamides (**Scheme 3-29**). This new route will allow the formation of new C–CN and C–N bonds with syn addition pathway (if using similar catalytic conditions as we reported before). Moreover, enantioselectivity of aminocyanation may be achieved if appropriate chiral ligands are discovered.

The substrates, alkenes and alkynes are ubiquitous and commercially-available since most of them are general industrial products. The more complicated skeletons (with specific substituents) can be traced back to corresponding alkenes and alkynes prepared from a variety of synthetic methods, such as Wittig reaction,[99] McMurry reaction[100] and olefin[101,102]/alkyne[103] metathesis. By means of asymmetric hydrogenation, the aminocyanation products of alkynes will be further converted to β^2-, β^3-, and $\beta^{2,3}$-amino acids with stereocenters.



Scheme 3-29 Preparation of multi-substituted β-amino acids via intermolecular aminocyanation

However, some potential challenges need to be envisioned: (1) suitable cyanamide for intermolecular aminocyanation, whose N–CN bond is not strong as normal, allows bond cleavage (activation), (2) efficient catalyst(s) for bond activation, with high enantioselectivity if possible, (3) regioselectivity of addition step, (4) tolerance of functional groups during aminocyanation, (5) removable protecting group(s) of amino moiety.

Based on intramolecular aminocyanation of alkenes, we found that electron-withdrawing *N*-acyl or *N*-sulfonyl groups can make the N–CN bond activation. Then, after we explored a series of known protecting groups, phthalimides come in our sight. The phthalimide has some unique characters: the structure with two acyl groups bonded to one nitrogen, which may facilitate the cleavage of N–CN bond. The planar geometry can

decrease the hinderance on addition process but still lead to possible regioselectivity due to modest steric repulsion between the larger substituents in alkenes/alkynes and the phenyl group of phthalimide. Finally, the deprotection conditions of phthalimides is mild. Some reports have demonstrated that phthalimide can be removed with hydrazine in the presence of carboxyl group.[104,105] Therefore, *N*-cyanophthalimide is selected as the aminocyanating reagent first.

Before examining the reactivity of *N*-cyanophthalimide and optimization of conditions, some recent publications on intermolecular aminocyanation are briefly introduced in Section 3.3.

3.3 Recent studies on intermolecular aminocyanation of alkenes and alkynes

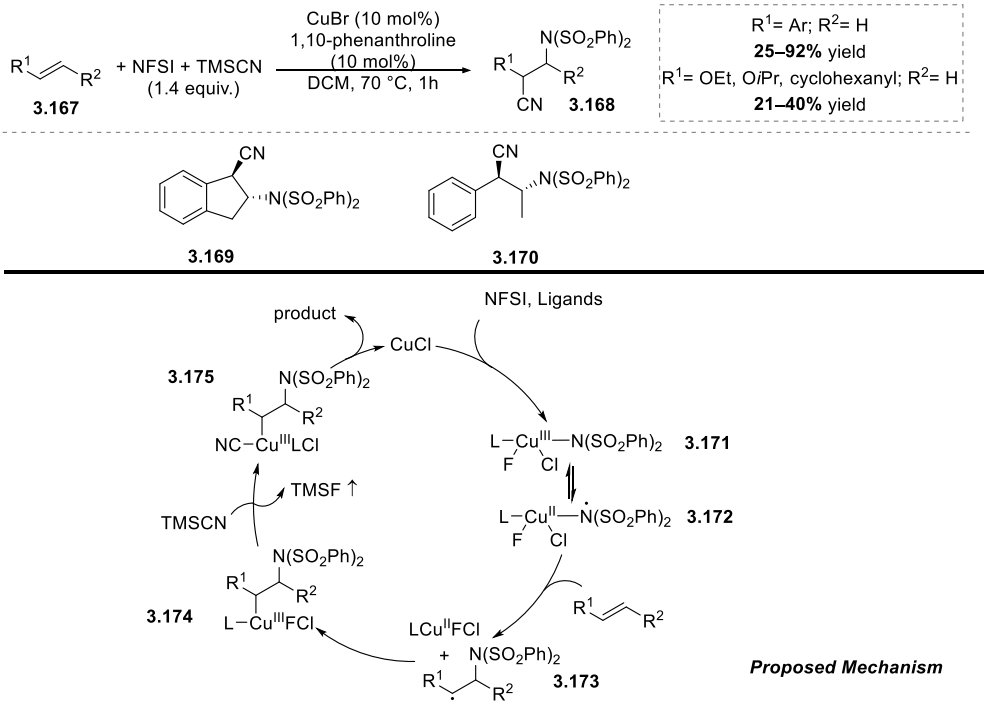
Only a few intermolecular aminocyanation of alkenes and alkynes are reported in recent years. Till now, none of those reports utilize N–CN bond activation to realize intermolecular aminocyanation.

In 2013, Zhang et al.[106] reported the first copper-catalyzed intermolecular aminocyanation of alkenes using *N*-fluorobenzenesulfonimide (NFSI) and trimethylsilyl cyanide (TMSCN) with high regioselectivity (**Scheme 3-30**). The reaction is initiated by the oxidation of Cu(I) catalyst with NFSI, in order to generate a stable Cu(II)-coordinated aminyl radical complex. Then the aminyl radical adds on the alkene to afford benzylic radical **3.173**. The released Cu(II) species subsequently binds to the radical and give Cu(III) species **3.174**. After ligand exchange and reductive elimination, the desired

aminocyanation product was obtained followed by the regeneration of Cu(I) catalyst. In addition, the yield fell dramatically when treated with metal cyanides like $Zn(CN)_2$ or CuCN. The reason may be the higher affinity between TMS and fluoride that facilitate the release of gaseous by-product TMSF, which can drive the reaction forward.

The high regioselectivity originates from the stability of radicals, which may explain the lower yield of non-activated aliphatic alkenes. Remarkably, based on X-ray crystallography results of aminocyanation product of either (E)- or (Z)-prop-1-enylbenzene, only the trans-addition product **3.170** was obtained. However, the authors didn't discuss on the removal of sulfonyl groups on nitrogen.

In conclusion, this protocol allows low loading of the catalyst, mild reaction conditions, and compatibility with a wide variety of functional groups

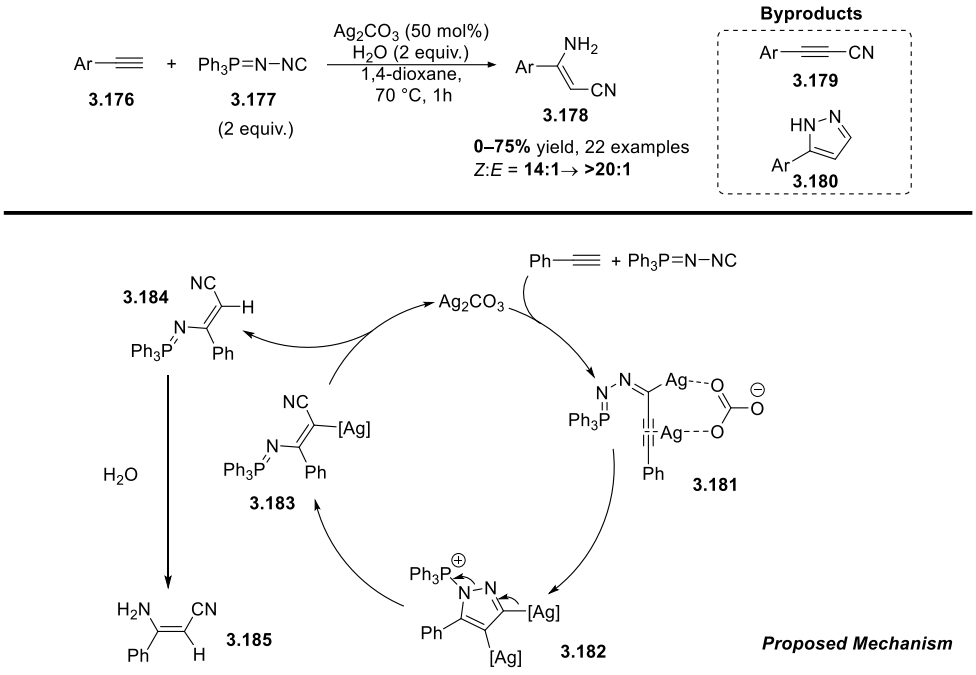


Scheme 3-30 Copper-catalyzed intermolecular aminocyanation of alkenes

Just a few months ago, the first silver-promoted formal intermolecular aminocyanation of alkynes was reported by Chen et al (**Scheme 3-31**).[107] They utilized *N*–isocyanoiminotriphenylphosphorane (NIITP) **3.177** served as a source of both amino and nitrile components. Under the optimal conditions, the syn-addition alkyne product, (*Z*)-β-aminoacrylonitrile, can be obtained up to 75% yield, with byproducts involving anti-addition isomers, 3-(*p*-tolyl)propiolonitrile and 3-*p*-tolyl-1H-pyrazole. In this paper, the scope of substrates is limited to arylacetylenes. The synthetic applications including large scale synthesis and chemical transformations of β-aminoacrylonitrile are explored as well.

The proposed mechanism supported by DFT calculations is shown in **Scheme 3-31**. From the beginning, the isocyano group in NIITP is attacked by the activated alkyne,

whose terminal proton is removed by silver acetate. Subsequently, a stable five-membered pyrazole intermediate **3.182** was formed via 5-endo-*dig* cyclization. Then the ring opens with N–N bond cleavage and cyano formation. Finally, the desired product is obtained after protonation and hydrolysis of the iminophosphorane **3.184**. The pathway is supported by the generation of byproduct pyrazole species, but it doesn't explain the formation of (*E*)-type products.



Scheme 3-31 Silver-promoted formal intermolecular aminocyanation of alkynes

3.4 Preliminary results and discussion

3.4.1 Preparation of aminocyanating reagent

The aminocyanating reagent, *N*-cyanophthalimide is bench-stable and less toxic. It is also readily prepared from phthalimide and cyanogen bromide, reported by previous

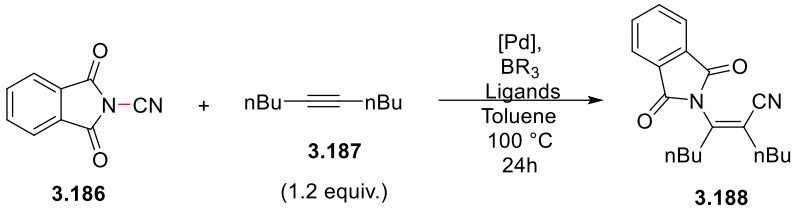
related studies.[108] However, the reported synthetic route still need to be modified, in order to remove any halogen residue and possible byproduct *N*,*N*-diethylcyanamide. Longer reaction time (2 hours instead of 15 minutes) helps to obtain a higher conversion. Due to the lack of charcoal for decoloring, the final product was further purified by column chromatography in 62% yield. More details are in Experimental Section 3.6.

3.4.2 Discovery of aminocyanation of 5-decyne

To develop a new intermolecular aminocyanation for general alkenes and alkynes, the non-activated, non-hinderance alkyne, 5-decyne was chosen to test the feasibility of the reaction, with *N*-cyanophthalimide. The preliminary attempts still focused on Lewis acids only or metal/Lewis acid co-catalysis system, using toluene as a solvent. First of all, the standard conditions for intramolecular aminocyanation were examined (**Table 3-1**, Entry 1–5). However, none of them can afford the desired product, only unconsumed starting material and decyanation product (phthalimide) was obtained. Then, a series of palladium(II) catalysts were screened, but only decyanation and undefined byproducts were detected with low consumption of cyanamide (less than 50%). To our delight, when 1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene (IPr) was used as the ligand, the desired aminocyanation product was observed in both Entry 12 and 13, though the cyanamide and decyanation were found on ^{1}H NMR spectrum. (the ratio for cyanamide, phthalimide and product = 1 : 1.8 : 2.2.) The scale-up reaction still provided the same components' ratio (Entry 14). The desired product **3.188** was isolated via column chromatography in 22% yield. The structure was then determined as (Z)-configuration by

1D nOe experiment, which supports the syn-addition pathway we discussed above. However, besides the unreacted cyanamide and decyanation product, an unidentified aliphatic impurity was isolated as well.

Table 3-1 Investigation of intermolecular aminocyanation of 5-decyne



Entry[a]	[Pd] (mol%)	BR_3 (mol%)	Ligands (mol%)	Toluene (mL)
1	/	BPh_3 (40)	/	1
2	Pd_2dba_3 (5)	BPh_3 (40)	XantPhos (10)	1
3[b]	CpPd(1-allylphenyl) (10)	BPh_3 (40)	XantPhos (10)	1
4	/	$B(C_6F_5)_3$ (100)	/	0.5
5	/	$B(C_6F_5)_3$ (50)	/	0.5
6	$Pd(OAc)_2$ (10)	BPh_3 (40)	XantPhos (10)	0.5
7	$Pd(OAc)_2$ (10)	$B(C_6F_5)_3$ (50)	XantPhos (10)	0.5
8	$Pd(PPh_3)_4$ (10)	BPh_3 (40)	/	0.5
9	$Pd(PPh_3)_2Cl_2$ (10)	BPh_3 (40)	XantPhos (10)	0.5
10	Pd(dppf)Cl_2 (10)	BPh_3 (40)	XantPhos (10)	0.5
11	$Ni(COD)_2$ (10)	$B(C_6F_5)_3$ (50)	IPr (10)	0.5
12	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	IPr (10)	0.5
13	CpPd(1-allylphenyl) (10)	$B(C_6F_5)_3$ (50)	IPr (10)	0.5
14[c]	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	IPr (10)	0.5

[a]0.1 mmol of *N*-cyanophthalimide, 0.12 mmol of 5-decyne were used for all entries, unless otherwise mentioned. All results are estimated by ^{1}H NMR analysis of the crude product mixture. [b]5 equivalents of 5-decyne were used. [c]The reaction performed on 0.3 mmol scale.

3.4.3 Optimization of conditions for aminocyanation of 5-decyne

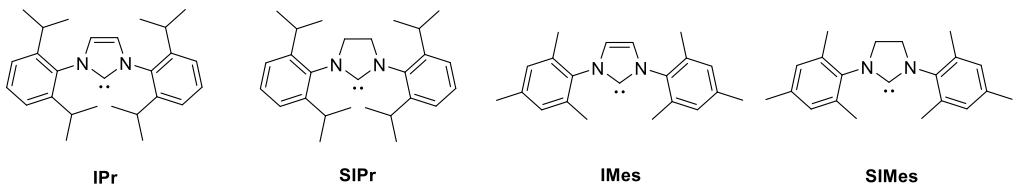
Encouraged by preliminary results, we then moved to optimize all reaction parameters, including metal catalyst species, Lewis acids, ligands, solvents, and temperatures, based on the one-factor-at-a-time (OFAT) method. Some problems need to be solved in the following optimizations: (1) the remaining cyanamide means the N–CN bond activation is not fully complete, (2) the observed decyanation indicates the inefficiency of alkyne addition step, (3) the aliphatic impurities may be from the isomerization of 5-decyne.

Hence, we started modifying the species and loading of boron Lewis acids, aiming at inhibiting the decyanation. (**Table 3-2**, Entry 1–4) Based on our previous studies, the stronger Lewis acid binds to the terminal of cyano group, the easier N–CN bond cleavage can achieve. In addition, the loading of Lewis acid can also facilitate the bond activation. However, either triphenylborane or triethylborane failed to give the product, though somehow broke the N–CN bond leading to decyanation. (The Lewis acidity order: BEt_3> $B(C_6F_5)_3$ > BPh_3, determined by Gutmann-Beckett methods, in toluene-d_8.[109]) One equivalent of perfluorotriphenylborane was able to consume all cyanamide, but still afforded more phthalimide. Comparatively, less loading of Lewis acid gave lower conversion of cyanamide.

Next, we focused on the effect of concentration and temperature. (**Table 3-2**, Entry 5–8) Increasing the concentration of cyanamide from 0.2 mol/L to 1 mol/L, didn't give the

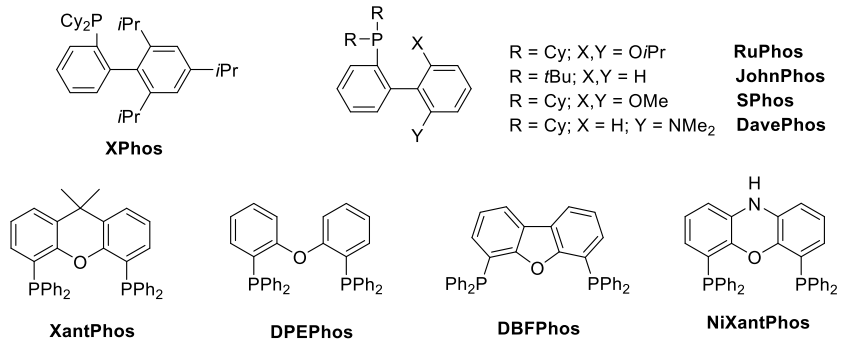
satisfying results. Lower temperature seemed to inhibit the decyanation better but make less cyanamide consumed. Higher temperature didn't improve the product ratio a lot either.

Then, we moved to screen other *N*-Heterocyclic Carbene (NHC) ligands (**Table 3-2**, Entry 10–12) due to the efficiency we found when IPr was used. Compared with bidentate phosphine ligands, NHC ligands have these advantages[110]: (1) stronger σ-donors than phosphines that facilitate oxidative additions (bond activation), (2) strong metal–carbenic bond tends to inhibit ligand dissociation, (3) sterically bulky groups on the heterocycles can promote reductive elimination. The Huynh's electronic parameter (HEP)[111] suggests that the donor ability for these four NHC ligands is: IMes (177.2) < IPr (177.5) <SIMes=SIPr (177.6). However, it seems that the steric factor impacted on reactivity more than the electronic. Both IPr and SIPr gave similar ratio for the decyanation and product, while IMes and SIMes provided less products. Moreover, the loading of NHC ligands did not change the conversion and yield. (**Table 3-2**, Entry 9)



Scheme 3-32 Structures of NHC ligands

Meanwhile, both mono- and bidentate phosphine ligands were investigated. (Table 3-2, Entry 13–23) Unfortunately, only few of them can afford the desired product. Some new aromatic compounds possibly generated but failed to be separated by prepTLC to be further analyzed.



Scheme 3-33 Structures of phosphine ligands

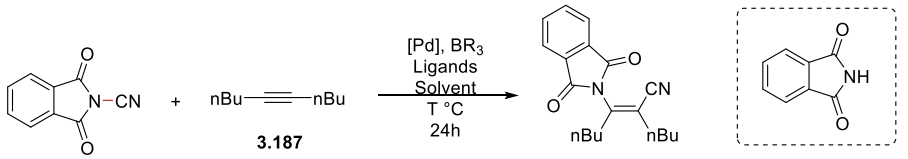
Due to the strong donor ability of NHC ligands and good electron acceptor boron Lewis acid, we proposed that Frustrated Lewis pair (FLP) may generate *in situ* which could activate the bond. Frustrated Lewis pair is a pair of Lewis acid and base combination, whose inherent reactivity to form stable donor-acceptor adducts is suppressed by steric factors. IPr–$B(C_6F_5)_3$ has been demonstrated as a reactive FLP to activate a series bonds including H–H, N–H and C–H bonds. [112] Hence, we set up a contrast experiment to verify our hypothesis (Table 3-2, Entry 24). Without palladium species, the reaction is non-productive at all, but still a trace amount of phthalimide was detected. Then, we prepared a solution of palladium catalyst with IPr ligand in toluene first, aiming at forcing IPr to bind to metal center before the addition of Lewis acid. The rest of reagents were added to the solution after 48-hour stirring. The results showed that lower conversion was obtained. Further study is still in progress.

Finally, we went back to investigate more metal catalysts and solvents, to check their effects on the reaction. (Table 3-2, Entry 26–38) None of them can provide any

inspiring results. We also found that the longer reaction time helps to obtain better conversion, but cyanamides was still not fully consumed after 48 hours. (Entry 39,40)

Besides 5-decyne, we also applied the "optimal" conditions (Table 3-2, Entry 0) for other substrates, including norbornene, styrene and cyclohexene. Unfortunately, none of their corresponding products were detected.

Table 3-2 Optimization of intermolecular aminocyanation conditions



Cyanamide **3.186** + **3.187** → **Product** **3.188** + Decyanation product **Phthalimide** **3.189**

Entry[a]	**[Pd] (mol%)**	**BR_3 (mol%)**	**Ligands (mol%)**	**Solvent**	**Temp. (°C)**	**Results**[b]
0	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	IPr (10)	Toluene	100	1 : 1.8 : 2.2
1	Pd_2dba_3 (5)	BPh_3 (50)	IPr (10)	Toluene	100	1 : 0.2 : 0
2	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (20)	IPr (10)	Toluene	100	1 : 0.3 : 0.15
3	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (100)	IPr (10)	Toluene	100	0 : 1 : 0.1
4	Pd_2dba_3 (5)	BEt_3 (50)	IPr (10)	Hexanes[c]	100	1 : 0.35 : 0
5	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	IPr (10)	Toluene[d]	100	1 : 2.4 :0.4
6	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	IPr (10)	Toluene[d]	80	1 : 3 : 0.8
7	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	IPr (10)	Toluene	80	1 : 0.7 : 0.6
8	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	IPr (10)	Toluene	120	1 : 1.5 : 2.5
9	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	IPr (20)	Toluene	120	1 : 1.8 : 2.2

10	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	SIPr (10)	Toluene	100	1 : 1.8 : 2
11	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	IMes (10)	Toluene	100	1 : 1.1 : 0.75
12	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	SIMes (10)	Toluene	100	1 : 1.9 : 1.6
13	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	PCy_3 (20)	Toluene	100	1 : 3.2: 0.8
14	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	P(o-Tol)$_3$ (20)	Toluene	100	1 : 1 : 0
15	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	P(t-Bu)$_3$ (20)	Toluene	100	1 : 1.5 : 0
16	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	DPEPhos (10)	Toluene	100	n.d.
17	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	DBFPhos (10)	Toluene	100	1 : 1.2 : 0
18	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	NiXantPhos (10)	Toluene	100	1 : 1.3 : 0
19	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	XPhos (10)	Toluene	100	1 : 1.16 : 0
20	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	RuPhos (10)	Toluene	100	1 : 1.45 : 0.25
21	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	JohnPhos (10)	Toluene	100	1 : 1 : 0.07
22	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	SPhos (10)	Toluene	100	1 : 1.44 : 0.25
23	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	DavePhos (10)	Toluene	100	1 : 1.47 : 0.41
24	/	$B(C_6F_5)_3$ (50)	IPr (10)	Toluene	100	1 : 0.05 : 0
25[e]	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	IPr (10)	Toluene	100	1 : 0.8 : 0.4
26	$Pd(PPh_3)_4$ (10)	$B(C_6F_5)_3$ (50)	IPr (10)	Toluene	100	1 : 0.6 : 0
27	$Pd(OAc)_2$ (10)	$B(C_6F_5)_3$ (50)	IPr (10)	Toluene	100	1 :0.2 : 0
28[f]	$Ni(COD)_2$ (10)	$B(C_6F_5)_3$ (50)	PCy_3 (20)	Toluene	100	No product
29[f]	$Ni(COD)_2$ (10)	$B(C_6F_5)_3$ (50)	PCy_2Ph (20)	Toluene	100	No product
30[f]	$Ni(COD)_2$ (10)	$B(C_6F_5)_3$ (50)	XantPhos (10)	Toluene	100	No product
31[f]	$Ni(COD)_2$ (10)	$B(C_6F_5)_3$ (50)	P(4-OMe-Ph)$_3$ (20)	Toluene	100	No product

32 [f]	$Ni(COD)_2$ (10)	$B(C_6F_5)_3$ (50)	PCy_2Ph (20)	Toluene	100	No product
33	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	IPr (10)	$PhCF_3$	100	1 : 2.9 : 1.7
34	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	IPr (10)	Methylcycl-ohexane	100	1 : 2.59 : 1.17
35	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	IPr (10)	1,4-dioxane	100	1 : 2.21 : 1.04
36	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	IPr (10)	Mesitylene	100	1 : 1.49 : 0.85
37	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	IPr (10)	DMAC	100	1 : 0.13 : 0
38	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	IPr (10)	Decalin	100	1 : 0.8 : 0.4
39 [g]	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	IPr (10)	Toluene	100	1 : 6 : 3.25
40 [g]	Pd_2dba_3 (5)	$B(C_6F_5)_3$ (50)	IPr (10)	Toluene	100	1 : 0.86 : 0.46

[a] 0.1 mmol of *N*-cyanophthalimide, 0.12 mmol of 5-decyne, 0.5 mL solvents were used for all entries, unless otherwise mentioned. All results are estimated by ^1H NMR analysis of the crude product mixture. [b] All results' ratio is cyanamide : phthalimide : product. [c] The triethylborane used here is a stock solution in hexanes. [d] 0.1 mL toluene was used. [e] Palladium reagent and IPr were mixed in toluene and stirred for 48 hours before the reaction began. [f] All nickel-containing results were analyzed by prepTLC. [g] Reactione time for Entry 39: 48 hours; for Entry 40, 6 hours.

3.5 Conclusion and future work

In summary, we discovered a new intermolecular aminocyanation of alkynes via palladium/Lewis acid co-catalyzed N–CN bind activation and succeeded in identifying the desired product. Though the best yield is only 22% and the optimization of conditions is still ongoing. Future work will focus on new design of aminocyanating reagent, expand the scope of substrates to both alkene and alkyne series, and explore the synthetic utility of the products.

3.6 Experimental Section

3.6.1 General details

Unless otherwise noted, all reactions were carried out using oven-dried glassware under a nitrogen atmosphere. Toluene was distilled from CaH_2 prior to use. Trifluorotoluene ($PhCF_3$) was distilled from K_2CO_3 prior to use. Toluene and $PhCF_3$ were further degassed by bubbling a stream of argon through the liquid in a Strauss flask and then stored in a nitrogen-filled glove box. Methylcyclohexane, mesitylene, 1,4-dioxane, *N*,*N*-dimethyl acetamide(DMAC), decalin were purchased and used as received.

Unless otherwise noted, all chemicals were purchased from commercial sources and used as received. All transition-metal complexes, phosphine ligands and NHC ligands were purchased from Sigma-Aldrich or Strem and used as received, except CpPd(1-phenylallyl). CpPd(1-phenylallyl) was synthesized following a known procedure.[7] Cyanogen bromide, 5-decyne, norbornene, styrene and cyclohexene were purchased from commercial sources and used as received. Phthalimide was prepared from neutralization of commercial-available phthalimide potassium salt.

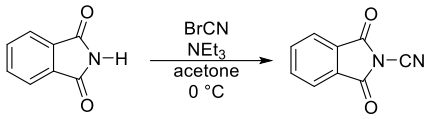
Triphenylborane (BPh_3), Triethylborane (BEt_3) and tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] was purchased from Strem and used as received. All $B(C_6F_5)_3$-promoted or palladium-catalyzed aminocyanation reactions were carried out in a Vacuum Atmospheres nitrogen-filled glove box in 1 dram vials (Chemglass) with PTFE lined caps and heating was applied by aluminum block heaters.

[7] Fraser, A. W.; Besaw, J. E.; Hull, L. E.; Baird, M. C. *Organometallics* **2012**, *31*, 2470.

Analytical thin-layer chromatography (TLC) and preparative thin-layer chromatography were carried out using 250 μm and 1000 μm silica plates (SiliCycle), respectively. Eluted plates were visualized first with a UV lamp (254 nm) and then stained with potassium permanganate or *p*-anisaldehyde, followed by heating. Flash column chromatography was performed using 230 – 400 mesh (particle size 40 – 63 μm) silica gel purchased from SiliCycle.

^{1}H NMR (300, 400 and 500 MHz) and ^{13}C NMR (75, 100 and 125 MHz) spectra were obtained on Varian Inova and Bruker Avance instruments. ^{1}H NMR spectra data were reported as δ values in ppm relative to chloroform (δ 7.26) if collected in $CDCl_3$. ^{13}C NMR spectra data were reported as δ values in ppm relative to chloroform (δ 77.0) if collected in $CDCl_3$. ^{1}H NMR coupling constants were reported in Hz, and multiplicity was indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); quint (quintet); m (multiplet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dddd (doublet of doublet of doublet of doublets); dt (doublet of triplets); td (triplet of doublets); ddt (doublet of doublet of triplets); dq (doublet of quartets); app (apparent); br (broad). High-resolution mass spectra (HRMS) were performed using either electrospray ionization (ESI) or GC/MS. ESI methods were performed on a Bruker BioTOF II (Time-of-flight) instrument using PEG-300, PEG-400 or PPG-400 as an internal standard.

3.6.2 Synthesis of N-cyanophthalimide



3.189 3.186

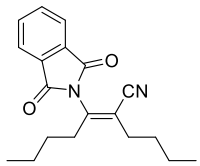
Phthalimide (735 mg, 5 mmol) and cyanogen bromide (635 mg, 6 mmol) were placed in dry and argon flushed 25 mL round-bottomed flask, followed by the addition of 10 mL of acetone at 0 °C. Next, Et_3N (0.9 mL, 6.4 mmol) was added dropwise over 3 min and kept stirring at same temperature. After 2 hours, it was allowed to warm up to room temperature and partitioned between ethyl acetate (15 mL) and water (10 mL). The water layer was extracted twice with ethyl acetate (2 x 10 mL). Combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. Later, the crude product was recrystallized from ethyl acetate and pentane at 0 °C, then purified by flash column chromatography (1:4 → 1:1 EtOAc/Hex) to give the *N*-cyanophthalimide in 55% (490 mg) yield as white crystalline solid. The NMR data is consistent with a literature report.[8]

3.6.3 Optimization of conditions for aminocyanation of 5-decyne

A general procedure: In a nitrogen-filled glove box, a one-dram vial was charged with a magnetic stirring bar, *N*-cyanophthalimide (17.2 mg, 0.1 mmol), Lewis acid (0.05 mmol), Ligands (0.01 mmol or 0.02 mmol), catalyst (0.01 mmol), and a solution of 5-Decyne in toluene (0.24 M, 0.5 mL, 0.12 mmol). The reaction mixture was sealed with a PTFE lined cap, removed from the glovebox, and heated in an aluminum heating block for

[8] Anbarasan, P.; Neumann, H.; Beller, M. *Chem.: Eur. J.* **2010**, *16* (16), 4725–4728.

24 h. The resulting mixture was allowed to cool to room temperature. The resulting mixture was concentrated in vacuo. The relative ratio for cyanamide, phthalimide and the product was determined by ^{1}H NMR analysis. The isolated yield was obtained by concentrating the crude mixture onto Celite, followed by flash column chromatography.

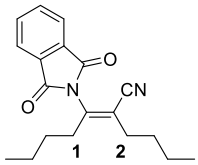


3.190

3.190: Purified by flash column chromatography (1:9 → 1:1 EtOAc/Hex) as a yellow oil (205 mg, 0.66 mmol, 22 % yield). R_f = 0.46 (1:1 EtOAc/Hex); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.0 Hz, 2H), 2.57 (t, *J* = 7.3 Hz, 2H), 2.43 (t, *J* = 7.6 Hz, 2H), 1.66 (p, *J* = 7.4 Hz, 2H), 1.46 (h, *J* = 7.4 Hz, 2H), 1.40 – 1.25 (m, 4H), 0.98 (t, *J* = 7.3 Hz, 3H), 0.87 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.0, 145.9, 134.6, 131.6, 124.1, 117.2, 116.8, 30.7, 30.2, 29.4, 28.7, 22.4, 22.0, 13.81, 13.76; **HRMS** (ESI) calcd for $[C_{19}H_{22}N_2O_2 + Na]^+$ 333.1573, found 333.1582;

Assignment of stereochemistry of 3.190 by nOe NMR experiments

Assigned Structure	Key ^{1}H NMR Signals	Irradiation	Key nOe Results
		H1	**H2**

	**H1**: 2.57 (t, *J* = 7.3 Hz, 2H), **H2**: 2.43 (t, *J* = 7.6 Hz, 2H).	**H2**	**H1**

Chapter 4 Introduction to cyclopenta-polycyclic aromatic hydrocarbons and rubicenes

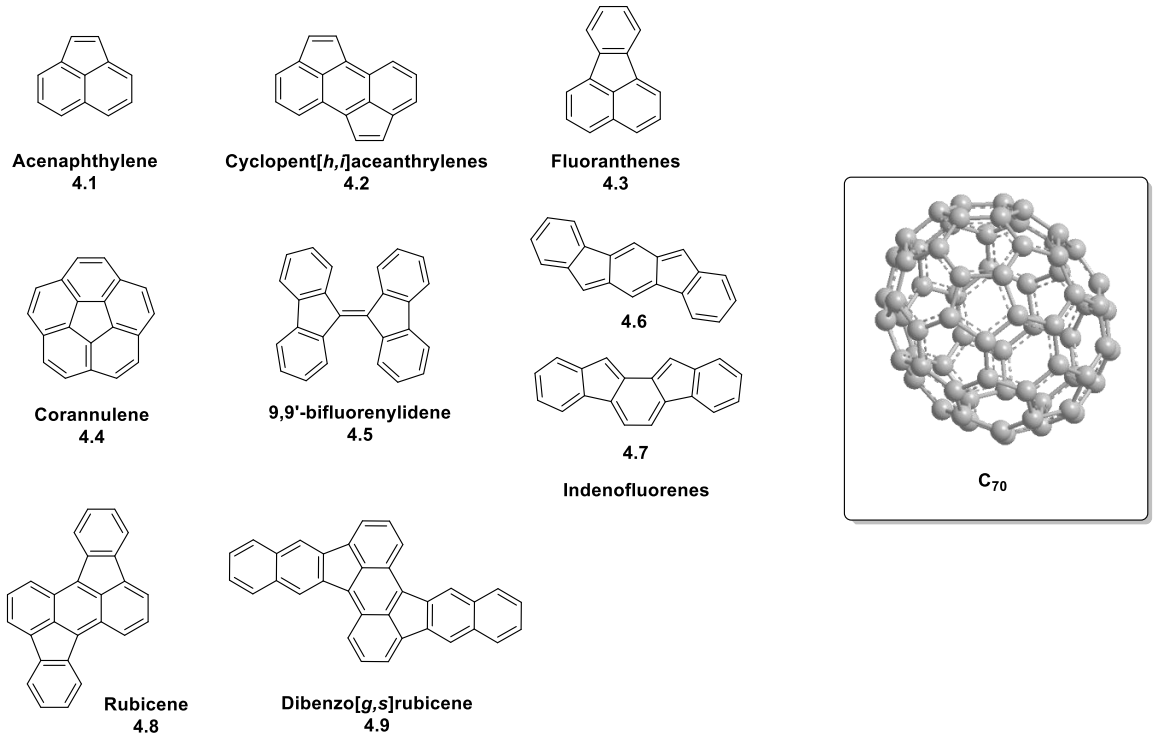
4.1 Overview of cyclopenta-fused polycyclic aromatic hydrocarbons (CP-PAHs)

Cyclopenta-fused polycyclic aromatic hydrocarbons (CP-PAHs) are a variety of aromatic systems embedded with 5-membered rings. They have been investigated for several decades due to the controversy about their aromaticities according to Hückel's rule, and unique geometrical structures as building blocks of complicated geodesic polyarenes, i.e. fullerenes C_{60} and C_{70}.

In recent years , fullerenes gain more attentions because of their ubiquitous high electron affinity and efficiency on transportation of charges.[1] Hence, fullerenes and their derivatives are widely employed as n-type semiconductors in organic photovoltaics (OPVs). However, the harsh preparation conditions, challenging purification and comparatively low solubility of fullerene derivatives somehow restrict their utilities in the field of solar cells research.[2] Moreover, to match with the desired electron donors better, potential organic opto-electronics still require further fine adjustments to promote their properties. However, the control of HOMO-LUMO gaps and LUMO levels of fullerene derivatives is not flexible as demanded due to limited chemical modification methods that mostly rely on addition reactions, which means no approach can access to the extended conjugation between the fullerene core and substituents. In other words, herein resonance effect (expansion of π-conjugation) cannot be utilized in the post-synthetic modifications,

only inductive effect is able to adjust the energy of frontier molecular orbitals (FMOs), which is not strong enough and falls off exponentially with distance.[2–4]

Generally, small CP-PAHs such as acenaphthylenes (**4.1**), cyclopent[*h,i*]aceanthrylenes (**4.2**), fluoranthenes (**4.3**), corannulenes (**4.4**), bifluorenylidenes (**4.5**), indenofluorenes (**4.6 & 4.7**), rubicenes (**4.8**) and dibenzo[*g,s*]rubicenes (**4.9**) can be all found on fullerenes as structural fragments. Most of them are synthetic accessible and readily functionalized. Hence, to gain more insights into the structure-property relationships in fullerenes and design novel organic opto-electronics with flexible energy-tuning, CP-PAHs are now promising research targets towards potential electron acceptors, depending on their photochemical and electrochemical properties.



Scheme 4-1 The structure of CP-PAHs as fragments of C_{70}

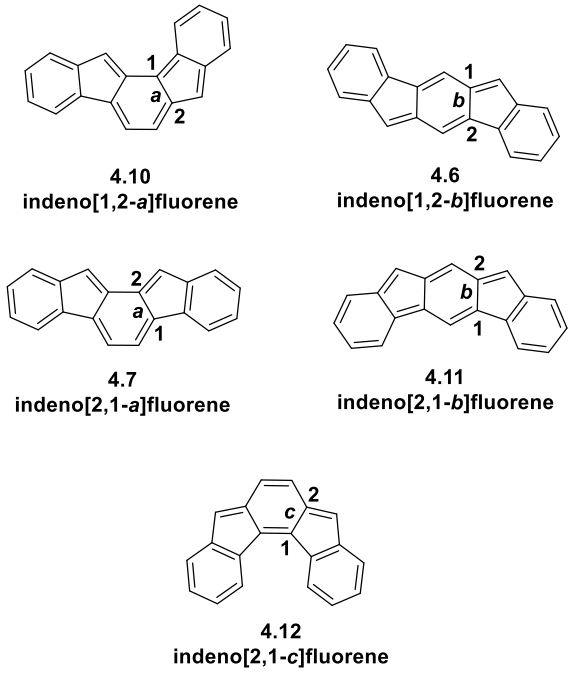
CP-PAHs with 4n π-systems are considered as anti-aromatic molecules based on Hückel's [4n+2] rule, thus these molecules are prone to accept extra pair of electrons to fulfill the requirement of aromaticity with [4n+2] π-electrons. Recent electrochemical studies[5,6] show that CP-PAHs are readily reduced and the incorporation of peripheral pentagons to an alternate-PAH can enhance the electron affinity, which contribute to their low-lying LUMOs. In addition, the computed Hückel bond orders and Hückel charge densities provided the evidence for the formation of 6π-electron cyclopentadienide sub-structures in the radical anions and the dianions of all mono- and bis-CP-PAHs.[6] Moreover, further experimental and computational work[5,7–9] elucidated that the peripheral cyclopenta-rings of the mono- and bis-CP-PAHs serve as electron-withdrawing substituents in the

neutral ground state. Hence, the incoming new electrons mainly locate in the peripheral pentagons of CP-PAHs. This conclusion is also confirmed by DFT calculations of extended CP-PAHs,[4,10–12] whose LUMOs prevalently distribute on the inner CP-PAH cores where the dianionic cyclopentadienyl character is located.

Besides the low-lying LUMOs, the band gaps between HOMO and LUMO of reported CP-PAHs are generally narrower than those of benzenoid PAHs, according to optical measurements, cyclic voltammograms and TD-DFT calculations.[13,14] The extension of π-conjugation system in CP-PAHs[4,15–18] (i.e. the polymerization of CP-PAH monomers[19]) can even possess band gaps lower than 1.5 eV. Compared with the band gap of C_{60} (1.86 eV) and C_{70} (1.57 eV)[20], the results demonstrate the utility of CP-PAHs as n-type materials in OPVs and organic field-effect transistors.

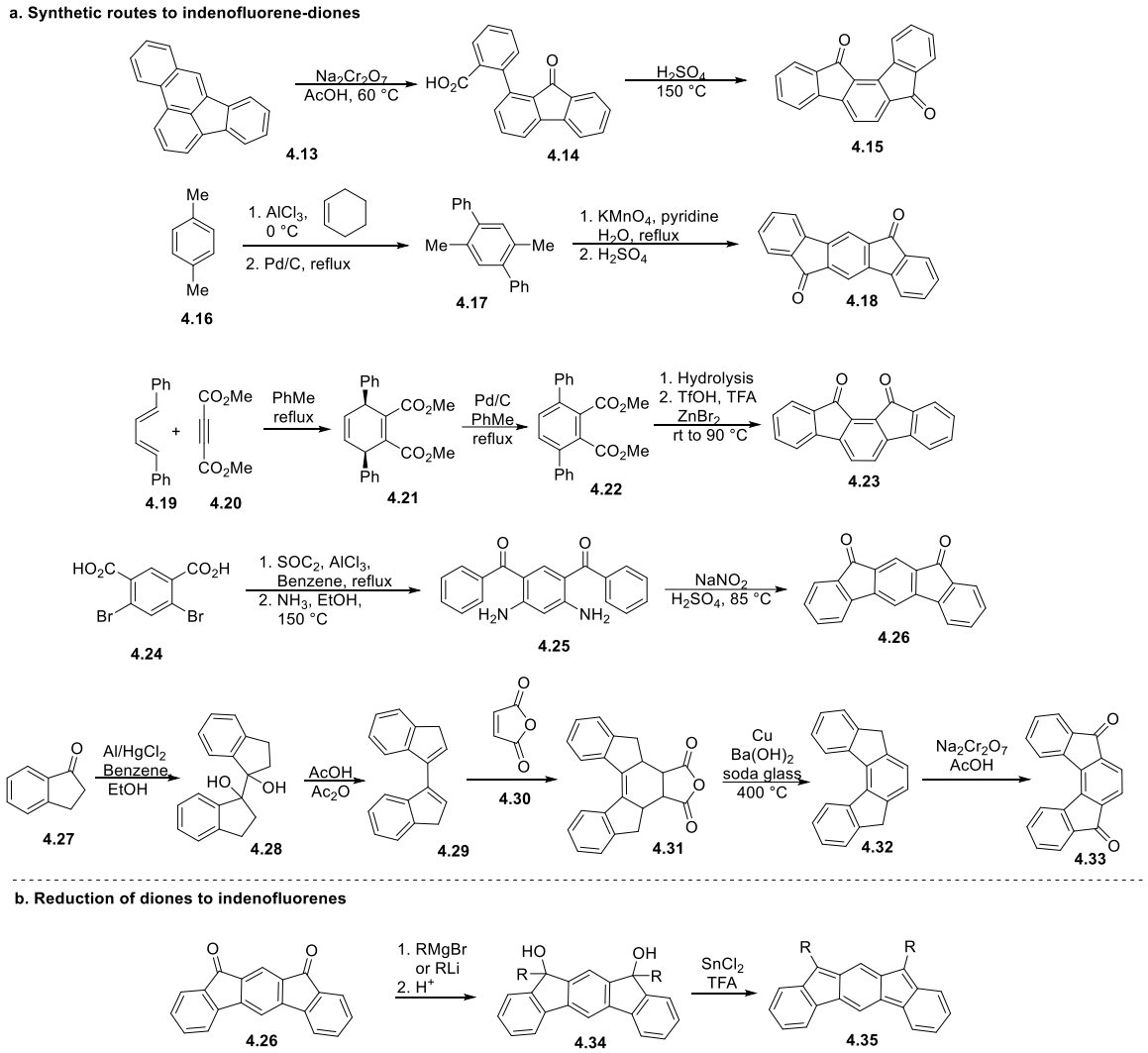
4.2 Synthetic methods toward CP-PAHs

In general, synthetic methods to introduce five-membered rings into conjugated systems involve: (a) aromatization of cyclopenta-diones, which are widely utilized in the synthesis of *ortho*-fused PAHs, such as indenofluorenes, (b) intramolecular cross-coupling reactions of halogenated arenes via C−H functionalization or Friedel–Crafts reaction, (c) intramolecular oxidative coupling of arenes (Scholl cyclization).



Scheme 4-2 Regioisomers of indenofluorenes

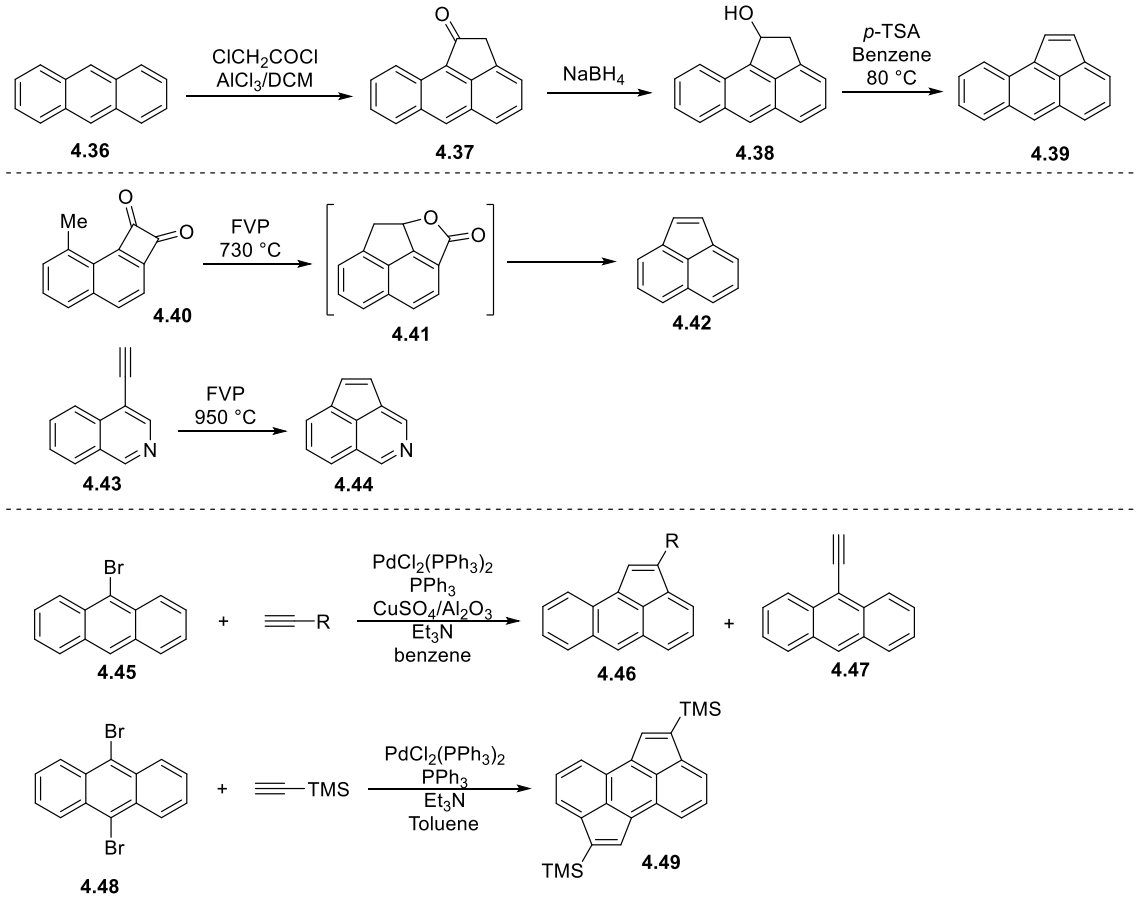
Depending on the connecting types of indene and fluorene, indenofluorenes have 5 regioisomers: [1,2-*a*], [1,2-*b*], [2,1-*a*], [2,1-*b*] and [2,1-*c*] (**Scheme 4-2**). [21] Several selected synthetic routes[22–24] to each dione scaffold are shown in **Scheme 4-3**. Generally, the formation of cyclopenta-rings can achieve via electrophilic aromatic substitutions, including Friedel–Crafts acylation and Pschorr reaction.[25] Diels-Alder reactions are useful for the construction of middle phenyl core in dione **4.23** and **4.33**. The final desired indenofluorenes are obtained via aromatization of cyclopenta-rings, involving reduction of diones via 1,2-addition using carbon-based nucleophiles such as Grignard reagents, and subsequent reduction of resulting diols with anhydrous $SnCl_2$.[18,26,27] The non-substituted indenofluorenes are unavailable due to their instability.



Scheme 4-3 Synthetic routes to indenofluorenes

Non-alternant PAHs (or *ortho*- and *peri*-fused PAHs[28]) with peripheral cyclopenta-rings, such as aceanthrylene, can be prepared via peri-cyclopentenelation of alternant PAHs backbones. Reported methods of direct cyclopentenelation include: (**Scheme 4-4**) (1) reduction of the cyclopentanone precursor followed by dehydration,[29] (2) flash vacuum

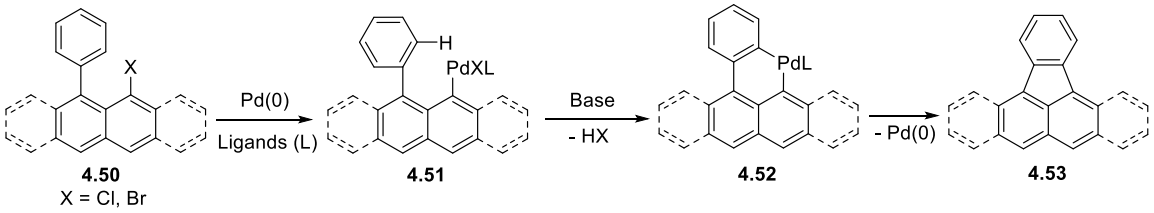
pyrolysis (FVP) of dione **4.40**[30] or 4-ethynylisoquinoline **4.43**,[31] (3) palladium-catalyzed cascade Sonogashira cross-coupling/ C–H activation.[15,32]



Scheme 4-4 Synthetic routes to CP-PAHs with non-alternant PAH backbones

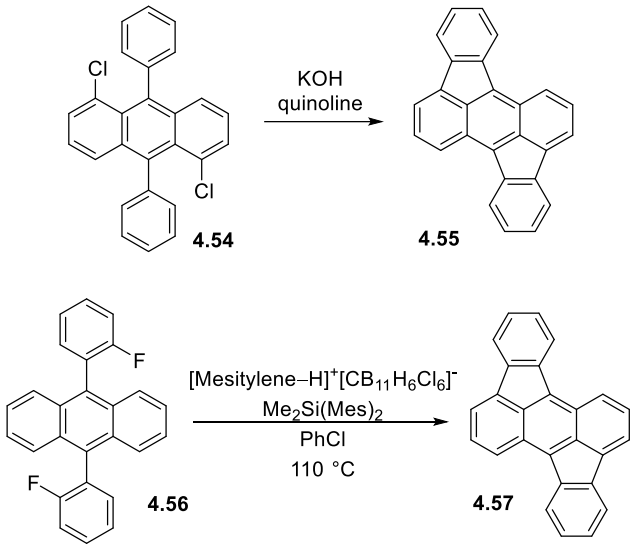
The cyclopenta-rings embedded in non-alternant PAHs, are constructed mostly relying on intramolecular transition-metal-catalyzed aryl-aryl coupling via cleavage of C–H bond. [33–37] Generally, the cross coupling occurs between an aryl halide and an arene. The metal center initially inserts into C–halide bond via oxidative addition, then the proximity C–H bond is activated by the palladium with the assistance of base to form a new Pd–C

bond. Finally, the ring closure achieves through reductive elimination and the palladium (0) returns to the catalytic cycle.



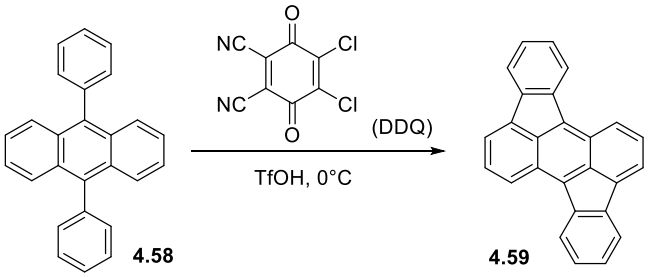
Scheme 4-5 Pd-catalyzed aryl-aryl coupling via cleavage of C–H bond

Interestingly, the halogenated substrates, which are similar to **4.50**, also succeeded in affording corresponding CP-PAHs (including rubicenes) under the conditions with strong base, [38] or with mesitylenium carborane (a strong Brønsted acid) and silane reagents.[39]



Scheme 4-6 Cyclization using strong acid/base conditions

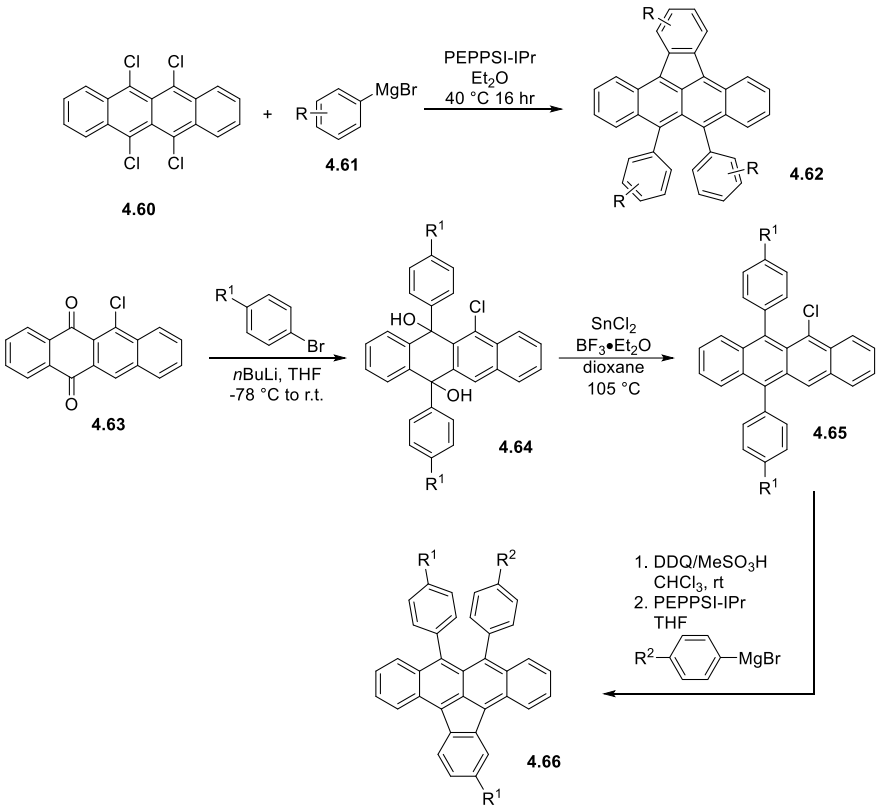
In the absence of halides, intramolecular oxidative coupling of arenes (Scholl cyclization) can realize the ring closure as well.[40] Traditional conditions involve Lewis acid catalysts such as $AlCl_3$, $FeCl_3$, etc.[41] Recently, DDQ or other oxidants with proton sources are widely used in the couplings of electron-rich arenes.[42–44]



Scheme 4-7 Cyclization via oxidative coupling (Scholl reactions)

In the past few years, our group also explored two new synthetic routes to CP-PAHs using cross coupling and cyclization cascades. We prepared symmetric-substituted diarylindeno-[1,2,3-*f,g*]tetracene, which were proven to be a novel type of donor material with high open-circuit voltage and power conversion efficiencies, from 5,6,11,12-tetrachlorotetracenes.[45] The synthesis starts from Kumada–Tamao–Corriu cross coupling with Grignard reagents to install aryl side-substituents, followed by *in situ* annulation via PEPPSI-IPR catalyzed C–H activation. The cross-coupling step allows aryls with various substituents to attach to the tetracene core, in order to tune the electronic properties of resulting products depending on the inductive effects from electron-withdrawing/donating groups. To obtain asymmetric diaryl-substituted indenotetracenes, we then developed an alternative synthetic route: starting from 1,2-addition of aryllithium reagent to halogenated dione **4.63**, the resulting diol was obtained. Upon reductive aromatization with

tin(II)dichloride, followed by Scholl penta-annulation, the resulting cyclized products further couple up with a new aryl moiety via Kumada–Tamao–Corriu reactions to afford desired asymmetric substituted indenotetracenes. Such late-stage diversification allows fine-tuning of electronic properties with more combinations of multi-substituents on aryls.



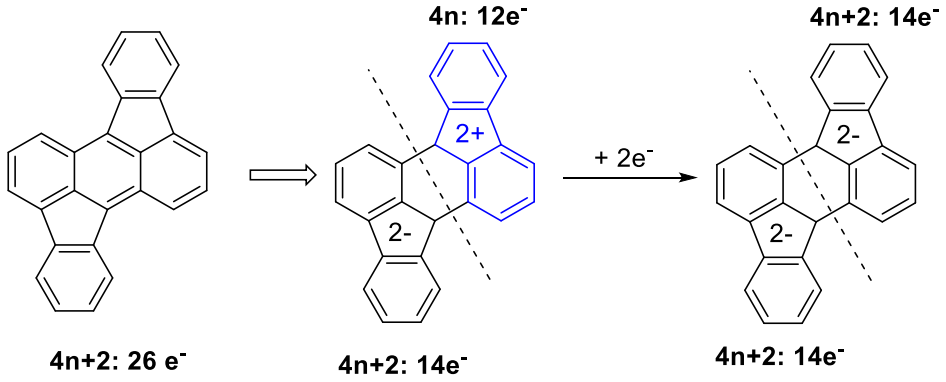
Scheme 4-8 Synthetic routes to diarylindeno-[1,2,3-*f*,*g*]tetracenes

4.3 Overview of Rubicenes: physical properties and synthetic methods

As a fragment of fullerene C_{70}, rubicenes are also potential organic semiconductor materials due to their electronic characteristics. The following paragraphs will simply

introduce physical properties of rubicenes and some reported derivatives, to rationalize why they are promising candidates in the field of opto-photovoltaics.

The structure of rubicene is shown in Scheme 4-9. The π-conjugation of rubicene consists of 26 electrons, which meets the requirement of Hückel's 4n+2 aromaticity. But rubicene still is prone to accept 2 more electrons, in order to form a more stable charged molecule with two Hückel's aromatic moieties.[19,46,47] The pentagonal rings in CP-PAHs may be the location where the new electrons reside, due to their antiaromatic character. Recent experiments and calculations support this hypothesis, indicating that the presence of cyclopenta-rings contributes to the better electron affinity of rubicenes and other CP-PAHs.[6,42,43,48]



Scheme 4-9 The aromaticity of rubicene

Compared with other curved or bowl-like fragments such as corannulene, rubicenes are planar molecules with parallel π-orbitals that promote more intermolecular electronic coupling, taking the advantage of better crystal packing. Based on its X-ray single crystal structure, the C_2h symmetric planar structure of rubicene crystallizes in a monoclinic $P2_1/n$

space group with unit cell parameters of: *a*: 16.291 Å, *b*: 5.144 Å, *c*:19.056 Å, *α*: 90.00°, *β*: 97.02°, *γ*: 90.00°.[49] The rubicenes are π-stacked into two arrays when viewed along the *c*-axis, and the angle between the molecular planes of each array is 84°, nearly perpendicular to each other, which is attributed to the C–H/π hydrogen bonds.[50] Meanwhile, the molecules in the same stack are tilted about 47° away from the stacking axis, causing the "staircase" structure of each stack. Moreover, the distance between two adjacent parallel molecules is 3.38 Å. Such short interplanar distance leads to a more efficient pathway for charge transport.[51]

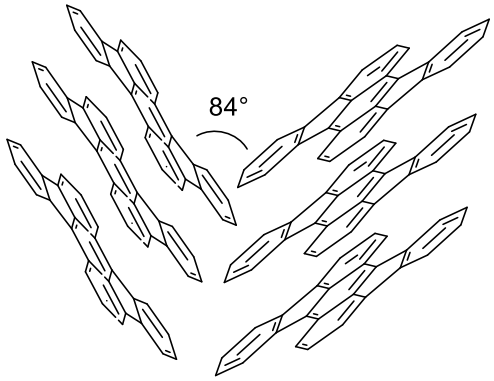


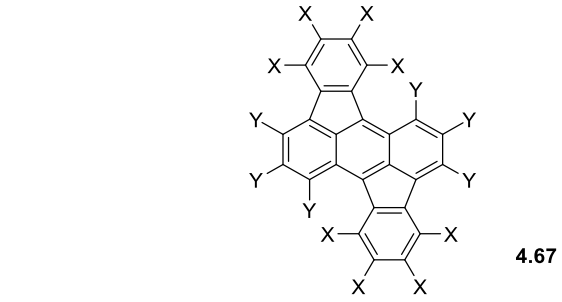
Figure 4-1 X-ray single crystal structure of rubicene

Lee et al. investigated the electronic characteristics of rubicene in organic field-effect transistors (OFETs).[49] A saturation hole mobility of 0.20 $cm^2/V{\cdot}s$ and a current on/off ratio (I_{on}/I_{off}) of 1.0×10^4 were detected when rubicene was used in bottom-gate/bottom-contact polycrystalline thin-film OFETs. The device performance can be further improved with a mobility of 0.32 $cm^2/V{\cdot}s$ and I_{on}/I_{off} of 2.5×10^4 with pentafluorobenzenethiol (PFBT) self-assembled monolayer (SAM) treatment on Au

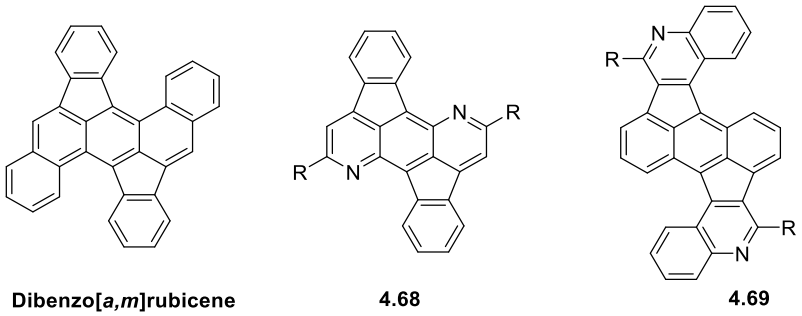
electrodes. The high hole mobility can be attributed to the fully-delocalized HOMO level and good π-stacking. In addition, the DFT calculations suggest the energy levels of fully-delocalized HOMO/LUMO orbitals are at -5.29 and -2.54 eV, respectively, which are lower the conventional p-type semiconductors, such as tetracene (-2.09 and -4.87 eV), pentacene (-2.40 and -4.61 eV) and rubrene (-2.09 and -4.69 eV), at the same calculation level, possibly due to the electron-withdrawing cyclopenta-rings. The evaluated ionization energy of rubicene is 5.57 eV, obtained by ultraviolet photoelectron spectroscopy (UPS), indicating that rubicene can be a potential material for ambipolar charge transport in OFETs or OPVs.

To achieve better electronic performance of rubicenes, people then devoted efforts to the extension of π-conjugation, introduction of heteroatoms, and installation of various electron-donating/withdrawing substituents. Moral[52] et al. theoretically studied a series of electronic properties of halogenated, cyanated and dibenzo-fused rubicenes based on DFT calculations. The results suggest that the presence of halogens and cyano groups can lower the energy of HOMO/LUMO orbitals to make substituted rubicenes display more p-type semiconductor character than unsubstituted rubicene. The dibenzo[*a, m*]rubicene shows the similar properties, supported by experimental results as well.[53] Interestingly, both hexa- and octa-halogen-substituted rubicenes and dibenzo[a, m]rubicene are found as twisted, nonplanar conjugated backbones, but the charge mobility are not impaired. Additionally, Park et al.[37] succeeded in preparing nitrogen-embedded rubicenes. These two new

heteroatom-containing rubicenes also possess lower HOMO/LUMO energy levels, confirmed by both CV and DFT calculations.



4.67

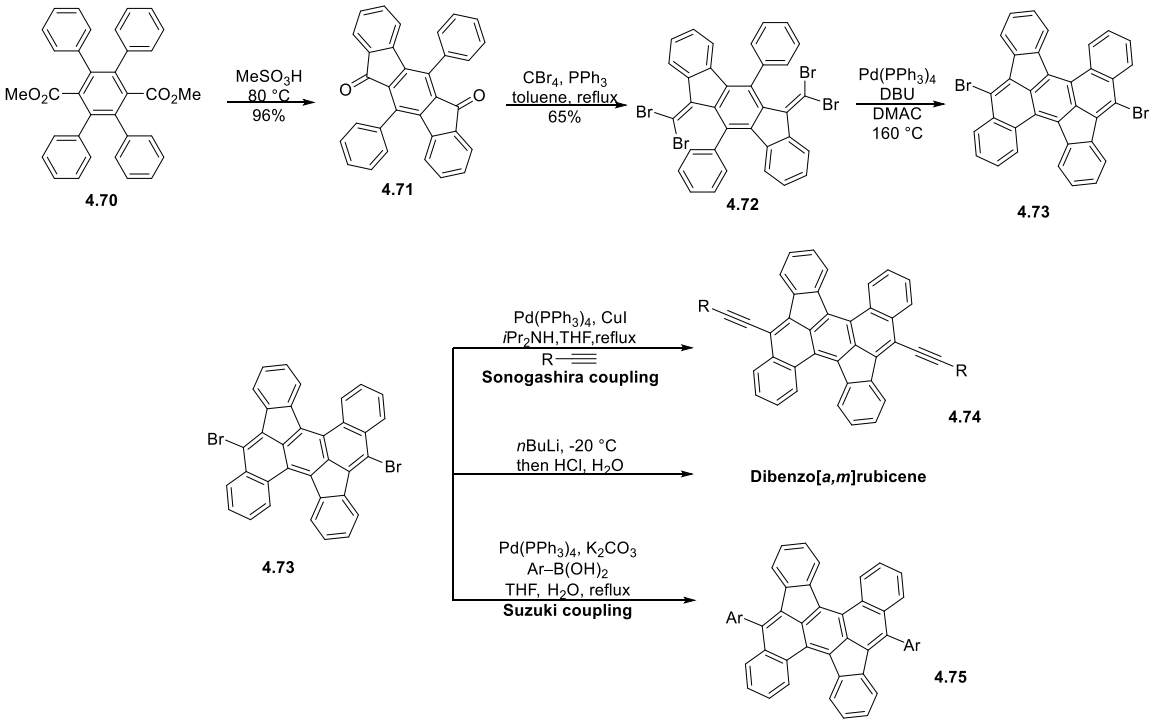


Dibenzo[*a,m*]rubicene **4.68** **4.69**

Scheme 4-10 Reported rubicene derivatives

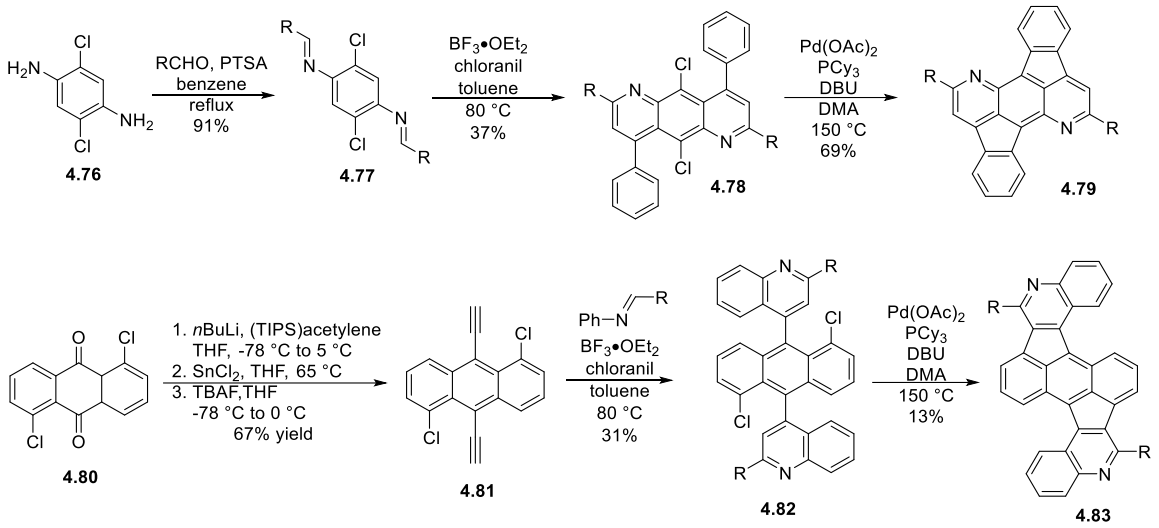
The synthetic methods for CP-PAHs are introduced in Section 4.2, which are still available for most of rubicenes. Two typical synthetic routes to dibenzo-fused rubicenes are shown in Scheme 4-11 and 4-12. The synthesis of dibenzorubicene derivatives[53] involves the preparation of indenofluorenedione and intramolecular C–H activation/ cross coupling cascade. More interestingly, the halogenated dibenzorubicene can be further diverged into three products: dibenzo[*a, m*]rubicene via dehalogenation,

diethynyldibenzo[*a, m*]rubicene via Sonogashira coupling, diaryl dibenzo[*a, m*]rubicene via Suzuki coupling.



Scheme 4-11 Syntheses of dibenzo[*a, m*]rubicene derivatives

1,8-diazarubicene and diquinolinerubicene are synthesized via the pathways in Scheme 4-12.[37] The nitrogen-containing aromatic rings are formed by Diels–Alder reactions, though the yields are just moderate. The penta-annulation step can afford the desired products, however the yield of **4.83** is low due to the less reactive C–H bond in quinoline moiety.



Scheme 4-12 Syntheses of nitrogen-embedded rubicenes

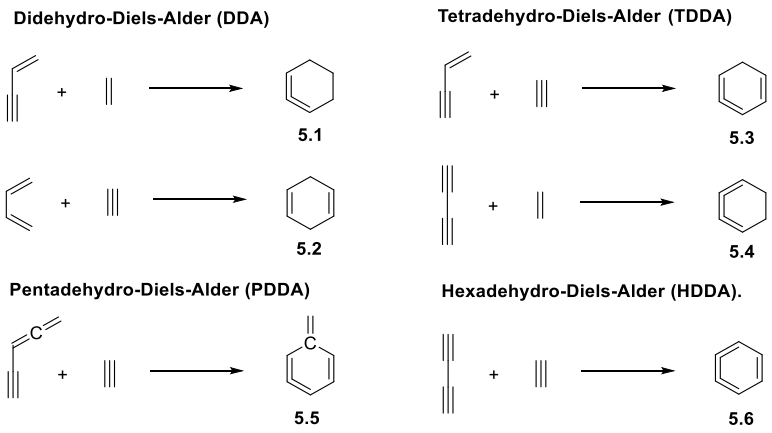
In conclusion, rubicene, as a member of CP-PAHs family, displays excellent electronic characteristics and potential as a promising organic semiconductor material. Further chemical modifications can improve its performance in OFETs and OPVs. However, the existing methods for fine-tuning on rubicenes are generally tedious and introducing substituents may not be tolerated under harsh conditions in some reported routes. Hence, our group are motivated to develop a new synthetic route to a broader range of rubicene derivatives and investigate the properties on these new rubicene-related molecules. More details will be then discussed in Chapter 5.

Chapter 5 Synthetic and characteristic studies on dibenzo[*g,s*]rubicenes and naphtho[2,3-a]aceanthrylenes

5.1 Overview of tetra-dehydro-Diels−Alder (TDDA) reactions

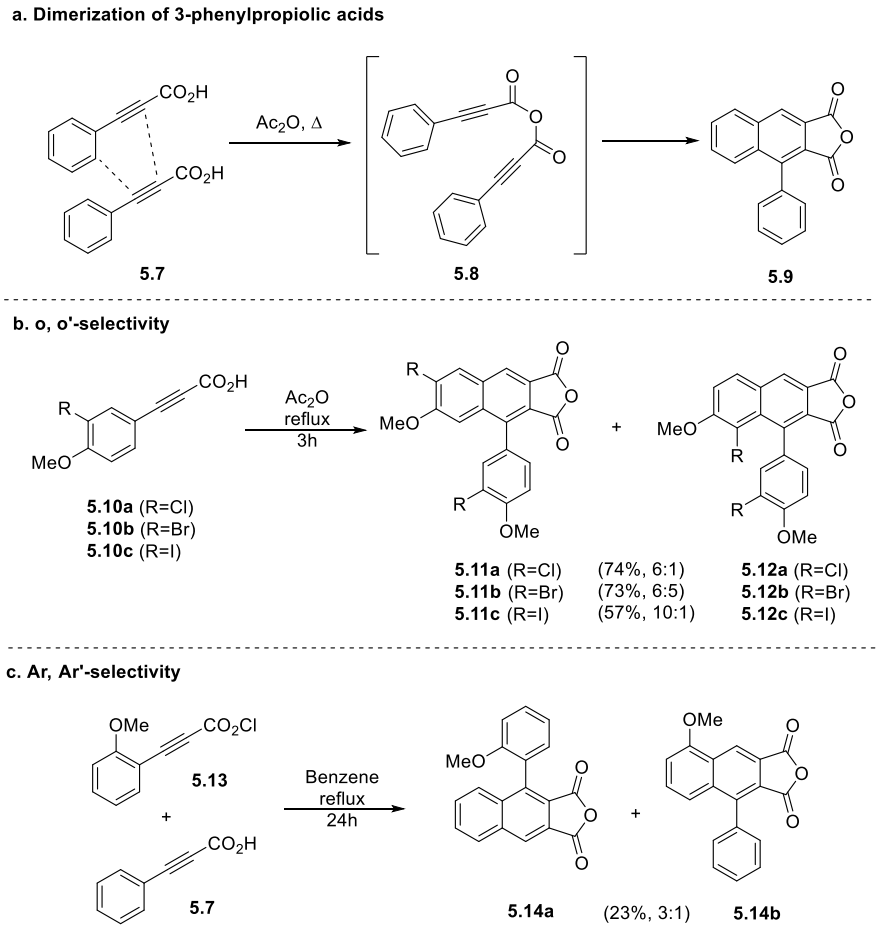
Diels–Alder reaction, a [4π+2π] cycloaadition reaction between a couple of diene and dienophile, is one of the most classical and prominent cyclization reactions due to its efficiency on the ring formation and rapid construction of multi-stereocenters.[1–4] In the past decades, Diels–Alder reactions were further developed into the cyclizations between triple-bond reactants, including enynes and diynes served as diene components, and alkyne used as dienophiles. Such Diels-Alder cycloadditions with incremental unsaturation of reactants are so-called dehydro Diels–Alder reactions.[5] Depending on the number of hydrogens that are removed from traditional dienes and dienophiles, the dehydro Diels–Alder reactions can be classified as didehydro-Diels–Alder(DDA),[6] tetradehydro-Diels–Alder (TDDA),[6,7] pentadehydro-Diels–Alder (PDDA),[7] and hexadehydro-Diels–Alder (HDDA).[8] (Scheme 5-1)

Tetradehydro-Diels–Alder (TDDA) reactions, generally can take place between enynes and alkynes or between diynes and alkenes, giving the corresponding intermediates **5.3** and **5.4**, respectively.[5,9] The intermediate **3.3** can further deliver the product, benzene, via hydride-shift. The detailed mechanism will be discussed in the following paragraphs.



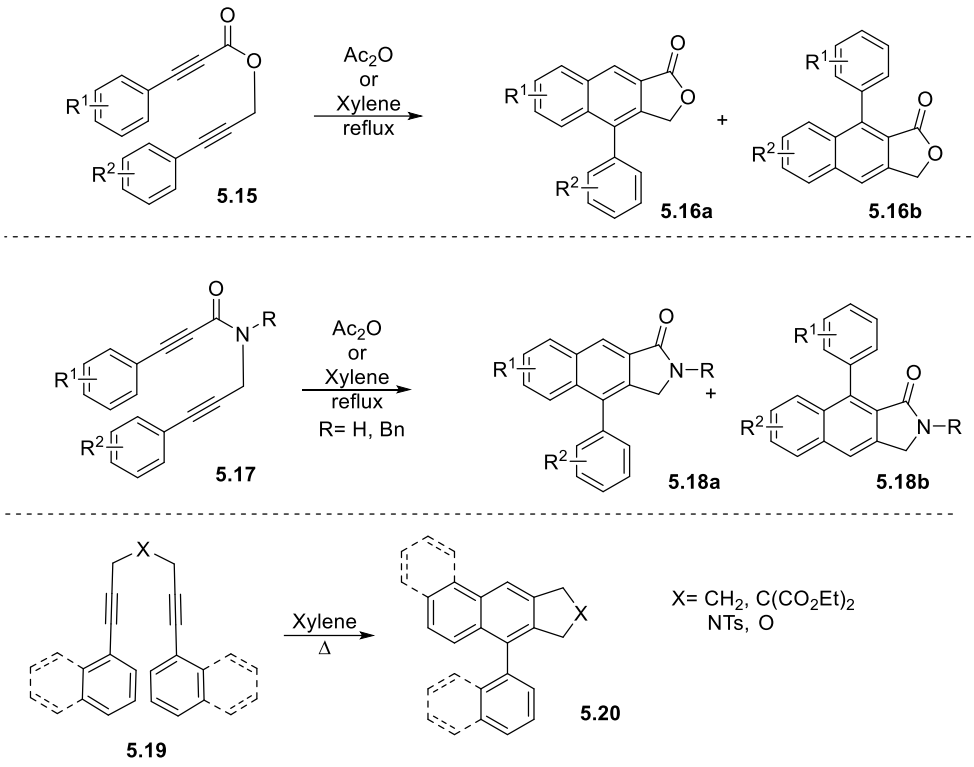
Scheme 5-1 Various types of dehydro-Diels–Alder reactions

TDDA has a more than 120-year history that can trace back to the dimerization of 3-phenylpropiolic acids, discovered by Michael and Bucher.[10] Later, further studies found that the reactants **5.7** condensed into an anhydride **5.8** (served as a linker to bind two molecules) before the cyclization step.[11] Moreover, two regioselectivity phenomena present in such type of DDA reactions, *o*, *o*′-selectivity and Ar, Ar′-selectivity. *o*, *o*′-selectivity usually occurs in the dimerization of *meta*- and *para*-disubstituted phenylacetylene moieties.[5,12] (**Scheme 5-2, b**) The TDDA reactions preferred to give the products with less steric hinderance between the aromatic rings. Ar, Ar′-selectivity is generally used to describe the regioselectivity for the DDA reactions between phenylacetylene derivatives with different substituents. For instance, the ortho-substituted compound **5.13** reacted with carboxylic acid **5.7** to afford two regio isomers in 23% yield (**Scheme 5-2, c**). The steric repulsion in the favored product between the methoxy group and proximity aromatic proton may rationalized the low yield.



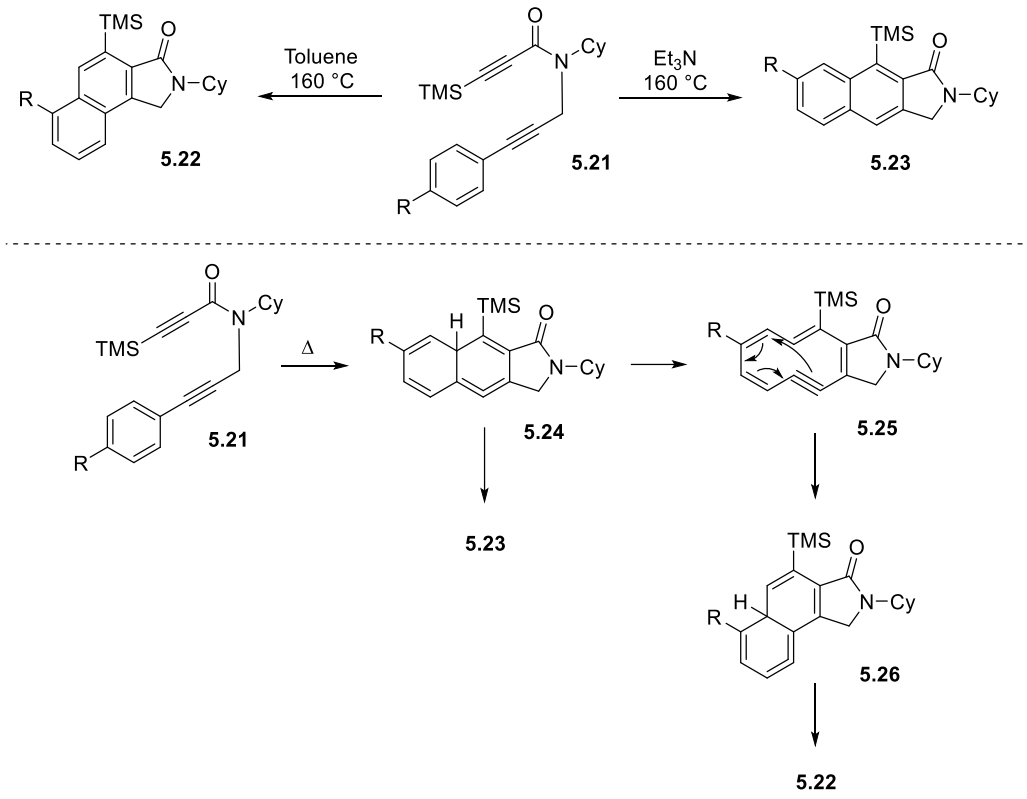
Scheme 5-2 Regioselectivity of TDDA reactions

As the discussion above, TDDA reactions need a linker to facilitate the cyclization process. Hence, the scope of linkers is then further expanded to esters,[13–18] amides,[18,19] ethers[20] etc. (**Scheme 5-3**)



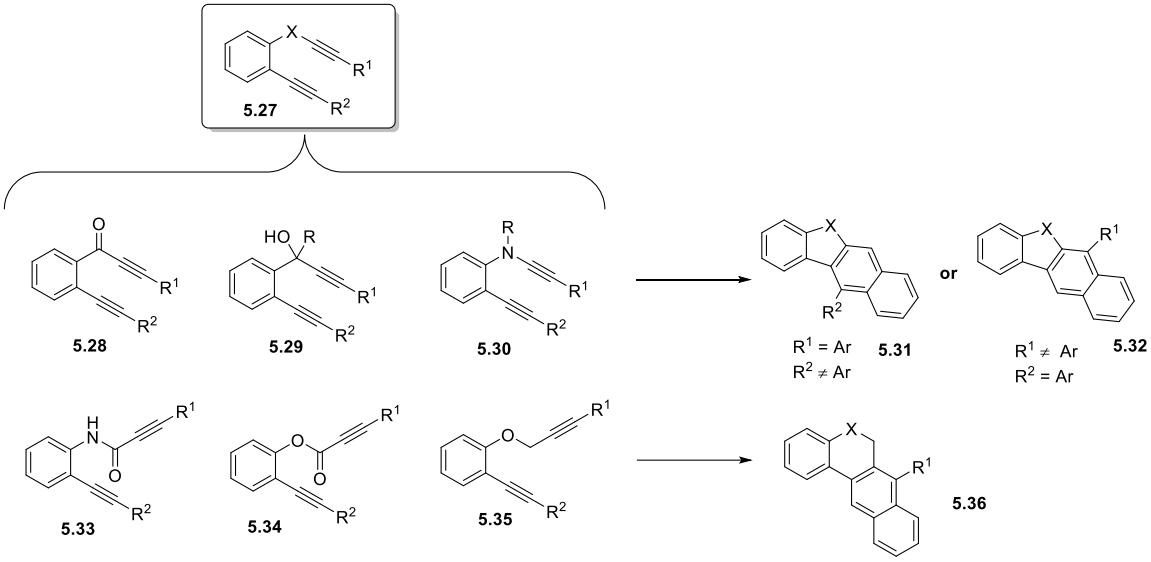
Scheme 5-3 Various linkers in intramolecular TDDA reactions

Interestingly, when one of the phenyl moieties is replaced with H or TMS group, a rearrangement byproduct was also obtained from a 10-membered ring enyne intermediate (such as **5.25**) via the retro–Diels–Alder reaction of cycloallene intermediate **5.24**.[21] (**Scheme 5-4**) Later, Saá and co-workers[22] also found that the use of triethylamine is able to accelerate the deprotononation-protonation step from the initially-formed cycloallene **5.24**, in order to suppresses the rearrangement pathway observed in toluene. Similar results were also reported by *Shibata* and co-workers upon heating of di-(3-phenylpropargyl)ether (**5.19, Scheme 5-3)** in xylene.[20]



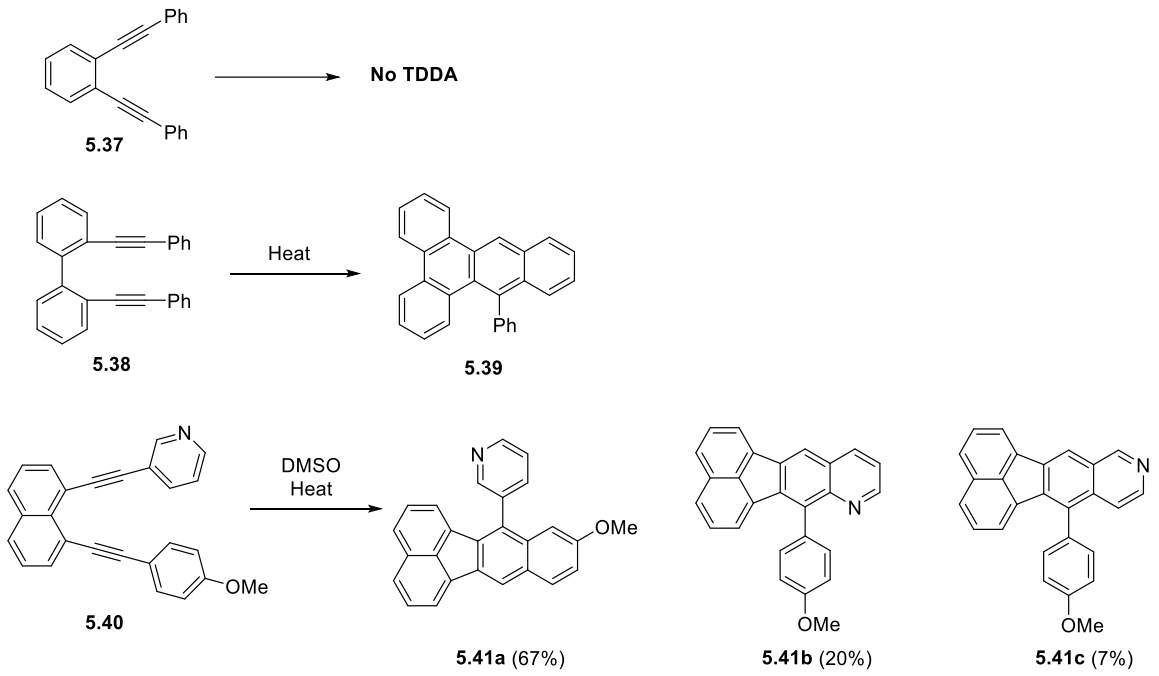
Scheme 5-4 Retro–Diels–Alder pathway in TDDA reactions

Besides heteroatoms with acyclic chains, aromatic rings can be also used as tethers in TDDA reactions. There are two types of aromatic tethers. The first type still needs to introduce a functional moiety to link the aromatic ring and alkyne to achieve the formation of cyclopenta- or cylcohexa-rings. (**Scheme 5-5**) The "X" functional moiety here could be a carbonyl group[23–25] (**5.28**), a quaternary carbon center[26–28] (**5.29**, a secondary or tertiary alcohol), a protected nitrogen[29] (**5.30**)to give 5-membered rings, or an amide[30] (**5.33**), an ester[30] (**5.34**), and an OCH_2 (**5.35**)[30] linkage to give 6-membered rings.



Scheme 5-5 Aromatic tethers of TDDA reactions: Type-I

The second type of aromatic tethers consists of an entire aromatic skeleton, which can directly synthesize polyaromatic hydrocarbons. The proximity of enyne and alkyne components is crucial to the initiation of TDDA reaction. (**Scheme 5-6**) For example, the TDDA pathway is not observed upon heating or photolysis of 1,2-bis(phenylethynyl)benzene **5.37**, only dimerization and Bergman cyclization products were detected,[31,32] presumably due to the long distance that inhibits the bond formation between terminal ene and alkyne. Conversely, the TDDA reaction underwent smoothly in **5.38**.[33] Moreover, the alkyne moieties can be also installed on naphthalenes, bearing heterocycles and a variety of substituents.[34–37]

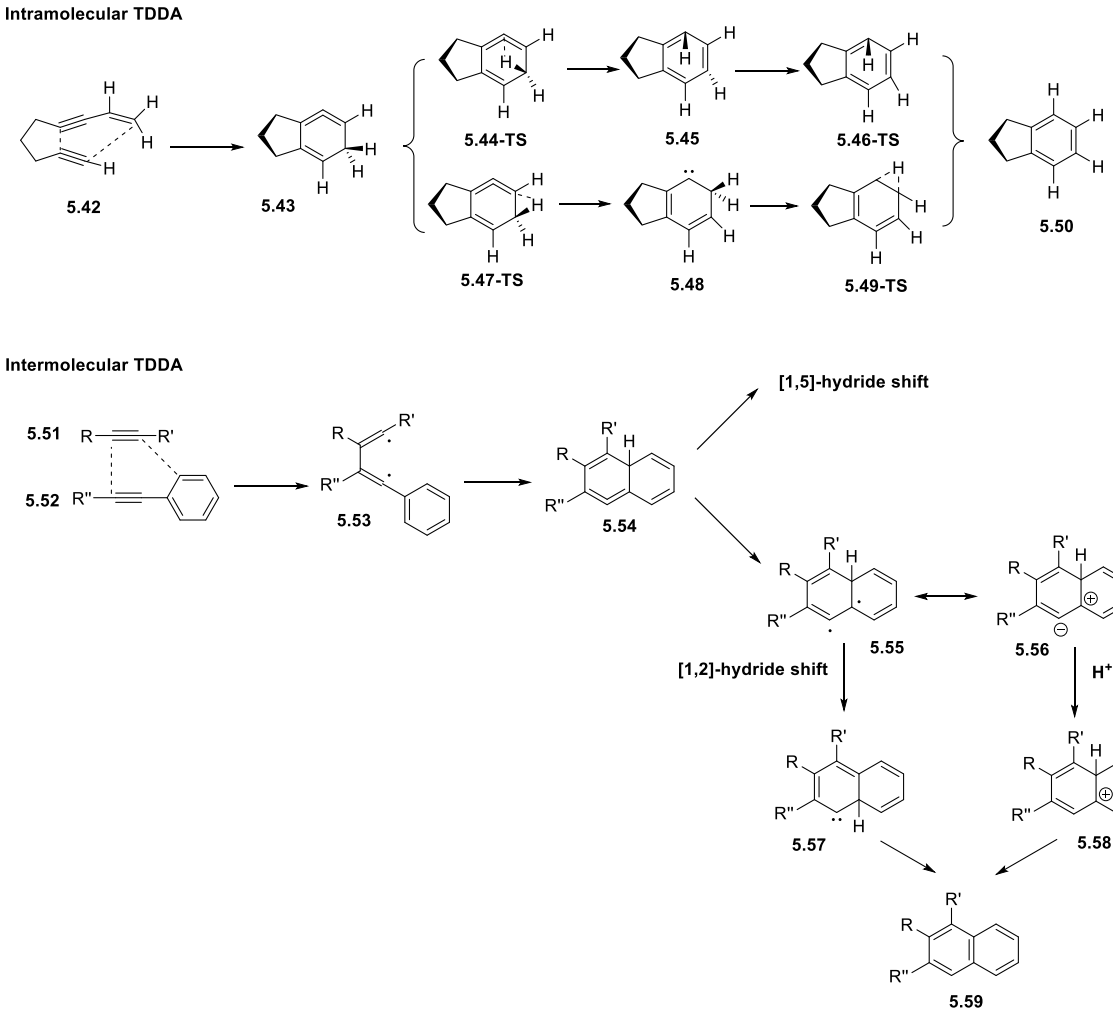


Scheme 5-6 Aromatic tethers of TDDA reactions: Type-II

In recent years, the mechanism of inter- and intramolecular thermal TDDA reactions were well investigated by theoretical and experimental tools.[38,39] The stepwise mechanism is shown in **Scheme 5-7**. Both intermolecular and intramolecular reactions proceed through a six-membered allene as an intermediate, but the activation free energy for intermolecular reaction is much higher than intramolecular one. The result also reasons that intramolecular TDDA is more productive than intermolecular reactions, possibly attributed to its lower activation entropy.

Both inter/intramolecular TDDA reactions can undergo into two pathways: [1,5]-hydride shift or consecutive [1,2]-hydride shifts. (**Scheme 5-7**) According to the calculated results, the barriers of [1,5]-hydride shift is higher than the first [1,2]-hydride shift in both

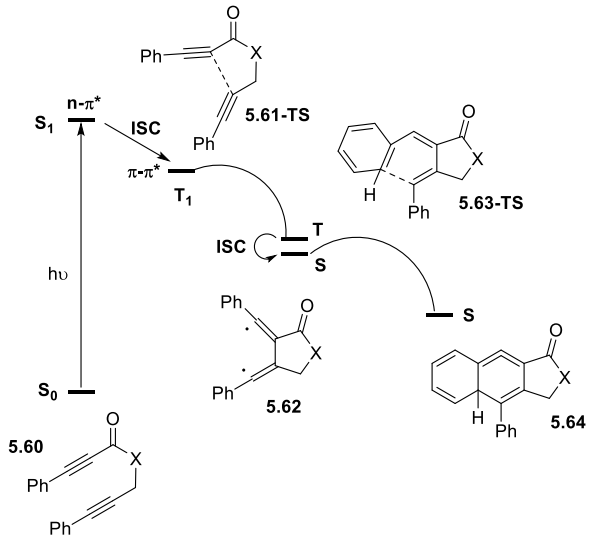
cases. Due to the large skeletal angle bending, the formation of **5.44**-TS shows a higher steric demand. Moreover, the second [1,2]-H shift proceeds nearly barrierless. The presence of carbene intermediate **5.48** in [1,2]-hydride shift pathway was also supported by experimental findings.[38,40] All results above support that the two subsequent [1,2]-hydride shifts pathway is more favorable in TDDA reaction. Remarkably, the cycloallenes **5.43** and **5.54** are still prone to convert into dehydro[10]annulenes (**Scheme 5-4**) in aprotic solvents, because [1,2]-hydride shift is slower than the ring-opening process. Isotope-labeling experiment[27] showed that, in the presence of protons, the zwitterion **5.56** is protonated first followed by deprotonation to give the final aromatic ring, which suppresses the rearrangement process discussed in **Scheme 5-4.**



Scheme 5-7 Proposed mechanisms of TDDA reactions

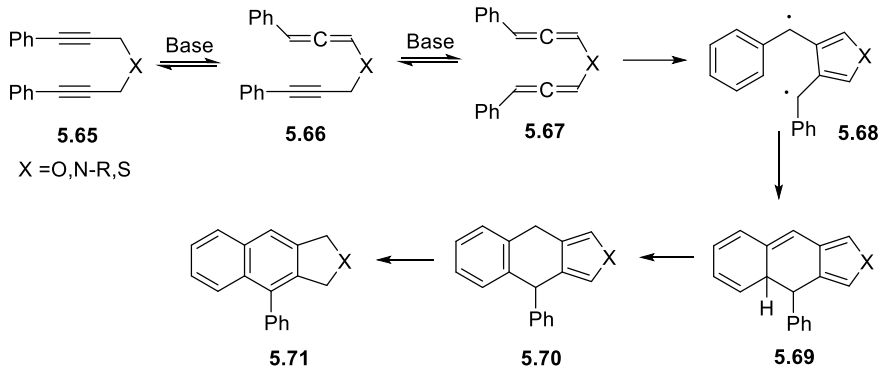
Besides thermal conditions, TDDA reactions can also occur via photolysis, transition-metal-catalysis and base-catalysis.[5] Though the concerted Diels-Alder reaction is a photochemically forbidden process, based on Woodward-Hoffmann rules related to orbital symmetry considerations,[41] the stepwise radical mechanism can rationalize the photo-initiated TDDA reactions at room temperature, supported by quantum chemical calculations and photophysical investigations.[42,43] (**Scheme 5-8**) It should be mentioned

that, the barrier of [1,2]-hydride shift is quite high at room temperature, thus the intermediate cycloallene **5.64** requires protic solvents to undergo protonation-deprotonation process, which is common for photo-initiated TDDA reactions.



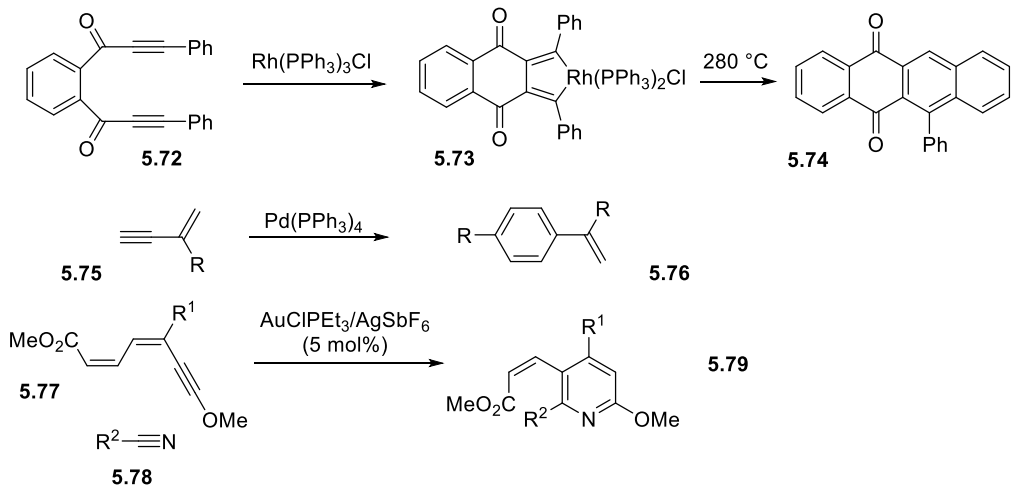
Scheme 5-8 Jablonski diagram of photo-initiated TDDA reactions

Base-catalyzed TDDA reactions generally occur among substrates with two propargyl moieties, which are linked with an electronegative atom such as O, N and S. (**Scheme 5-9**) The substrates convert to corresponding bis-allenes, then transform into diradicals **5.68** bearing aromatic heterocycles. Finally, the diradicals further provide the final cyclized TDDA products via proton-transfers.[44,45]



Scheme 5-9 Base-catalyzed TDDA reactions

Transition-metal catalyzed TDDA cyclizations are reported more recently. Some typical examples are shown in **Scheme 5-10.** Rhodium,[46] palladium[47] and gold[48] are common catalysts used in TDDAs.



Scheme 5-10 Transition-metal-mediated TDDA reactions

5.2 Research proposal

As discussed in Chapter 4, rubicene (**5.80**) and dibenzo[*g*,*s*]rubicene (**5.81**) are planar fragments of fullerene C_{70} (**Figure 5-1**). Due to the excellent performance of

fullerene family in organic photovoltaics (OPVs), studying the fragments of fullerenes and their planar analogs could help us further understand structure−property relationships and inspire people to design novel organic electronic materials. Herein, we selected rubicene and its derivatives as research targets.

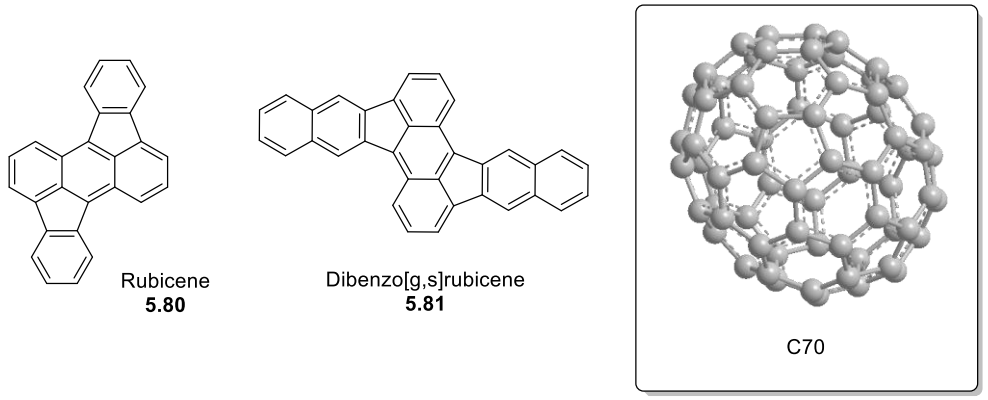


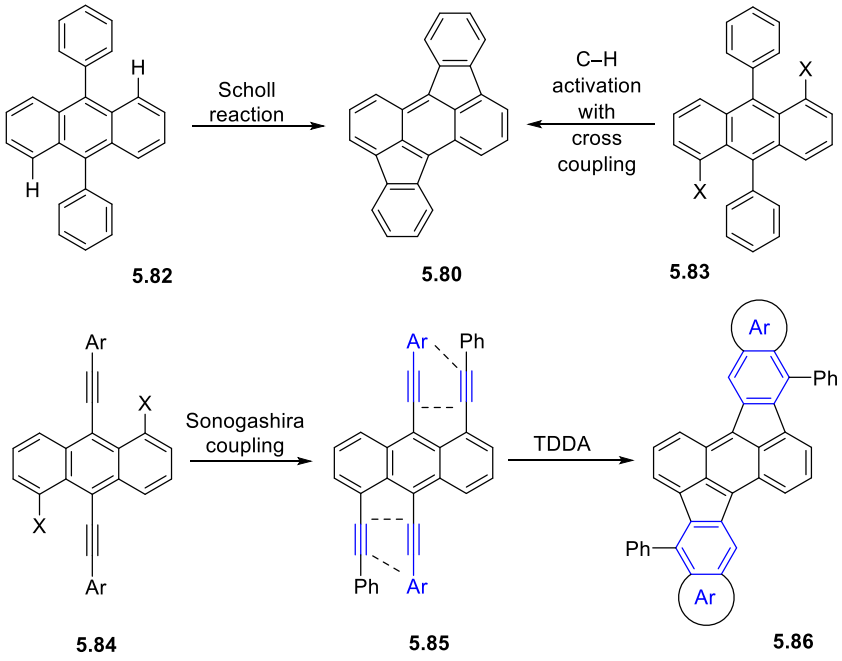
Figure 5-1 Structure of rubicene and dibenzo[*g*,*s*]rubicene

Several studies are reported on the semiconductive properties of rubicene and its analogs.[49,50] Generally, chemical/structural modifications to aromatic core structures can create new materials with unique properties and better device performance. However, the scope of rubicene-based derivatives was still limited by the lack of direct and efficient synthetic routes to extend the number of valuable candidates in rubicene family. Hence, a convenient synthetic approach needs to be developed, in order to fine-tune the photochemical and electronical properties of rubicene derivatives with diverse substituents and extensive conjugation system, which would allow systematic study of these molecules.

To explore new synthetic routes to rubicene derivatives, one of the challenges is how to achieve the formation of cyclopenta-rings. General methods are summarized in

Chapter 4, which involve (a) aromatization of cyclopentanones, (b) intramolecular C−H functionalization and cross-coupling cascades and (c) intramolecular oxidative dehydrogenative coupling of carefully designed precursors (Scholl reactions). However, the methods above can only afford one (type of) ring per reaction, leading to low efficiency on the construction of polycyclic skeletons over tedious steps. Moreover, the newly introduced substituents may be not tolerable under some harsh conditions including strong acids/bases and extremely high temperature. Either two-directional synthesis or multiple-ring formation in one-step during the cycloaddition of non-aromatic units would be the solution to improve the cyclization efficiency. Using catalytic cross coupling with mild conditions may also allow the presence of most functional groups and facilitate the introduction of various moieties with inductive effects.

From the perspectives above, dehydro-Diels−Alder (DDA) reactions attract our attentions. Specifically, based on the summary in Section 5.1, tetra-dehydro-Diels−Alder (TDDA) reactions between enyne and alkyne attached to naphthalene core can produce a benzene ring as well as a peripheral pentagon under mild thermal conditions. Herein, we report our work on the synthesis of dibenzo[*g*,*s*]rubicene derivatives. Our approach features a one-pot cascade combining a Sonogashira cross-coupling reaction with a tetra-dehydro-Diels−Alder reaction (**Scheme 5-11**).



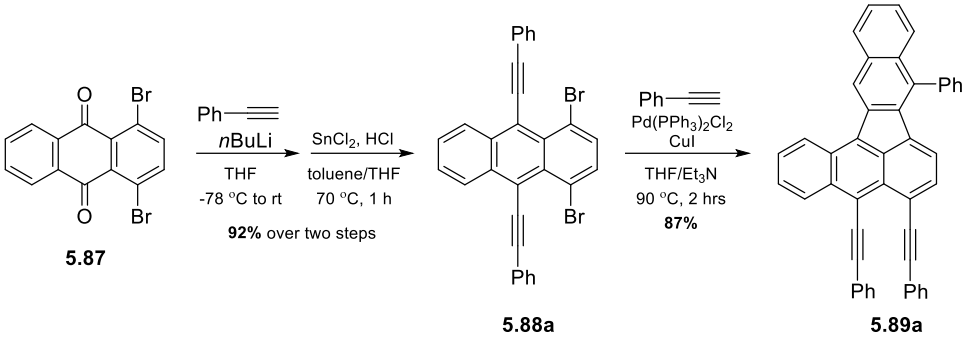
Scheme 5-11 Proposed synthetic route to rubicene derivatives via TDDA

5.3 Results and discussion

5.3.1 Synthesis and scope of naphtho[2,3-a]aceanthrylenes and dibenzo[g,s]rubicenes

We initially explored our approach on 1,4-dibromo-9,10-bis(phenylethynyl)anthracene **5.88a** (**Scheme 5-12**), which is prepared from anthracenedione core via tin-mediated aromatization, aiming at the completion of double-side TDDA towards benzo[*a*]indeno[1,2,3-*fg*]aceanthrylene. When **5.88a** and phenylacetylene were heated under common Sonogashira cross-coupling conditions, a polycyclic structure **5.89a** was formed via single-side annulation, presumably transformed from intermediate **5.90** (**Scheme 5-13**), yet not observed in the resulting crude by ^{1}H NMR.

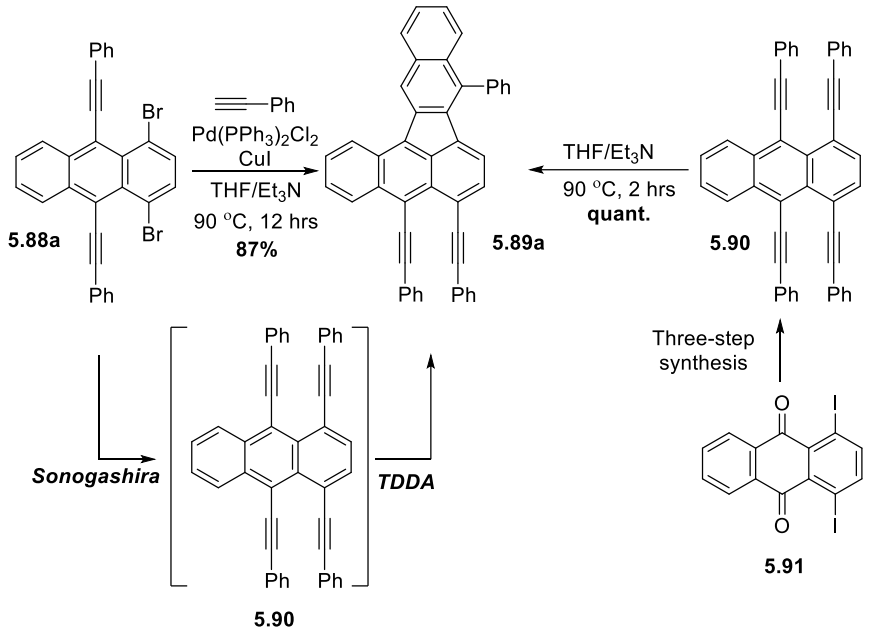
The structure of **5.89a** was further confirmed by X-ray crystallography. After the optimization of conditions, the product **5.89a** can be obtained in 87% yield when the reaction was heated at 90 °C in THF/TEA solvent pair for 2 hours, in the presence of $Pd(PPh_3)_4$ (2.5 mol%) and copper iodide (1 mol%).



Scheme 5-12 Synthesis of naphtho[2,3-a]aceanthrylene **5.89a**

As mentioned above, TDDA reactions can occur under both thermal and transition-metal-catalyzed conditions. We hypothesized that the TDDA event in **Scheme 5-13** was thermally promoted, rather than transition metal mediated. Hence, we investigated TDDA cyclization of the supposed intermediate tetrayne **5.90** independently. To obtain the separable tetrayne **5.90**, we still utilized Sonogashira coupling reaction but using 1,4-diiodo-9,10-anthracenedione **5.91** as the starting material, due to the better reactivity of aryliodide substrates at lower temperature, in order to suppress the subsequent TDDA event. Then tetrayne **5.90** was subjected to the non-metal TDDA conditions involving THF and TEA only. As hypothesized, after two-hour heating at 90 °C, the mono-cyclized product **5.89a** was formed in almost quantitative yield. Taken all results together, we infer that

transformation from **5.88a** to **5.89a** is a one-pot cascade containing Sonogashira cross-coupling reaction and a *in situ* thermally promoted TDDA event.

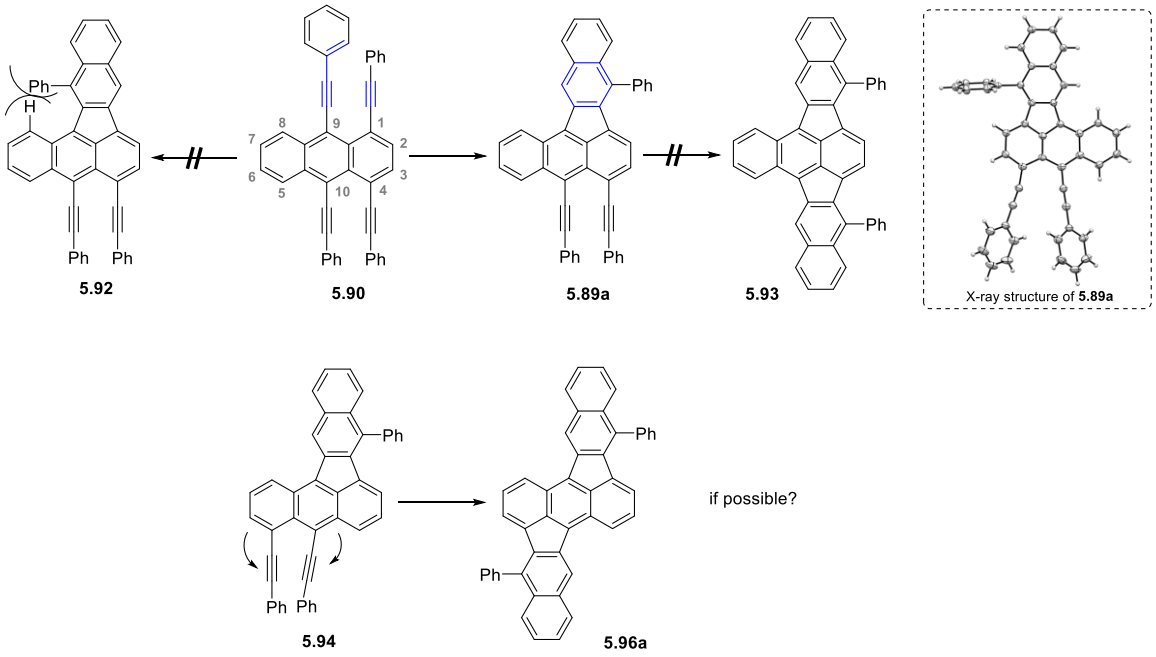


Scheme 5-13 Examination of TDDA cyclization step

Examining the crystal structure of **5.89a** obtained by X-ray crystallography (**Scheme 5-14**), we also discovered that the middle phenylethynyl moiety only serves as enyne component in the TDDA event, though the other regioisomer can be generated via TDDA in theory. The absence of **5.92** may be caused by the steric repulsion between the phenyl and C−H bond at C_8, which retards the ring formation step.

Then we moved to elucidate the origin of single-side annulation instead of double-side ones. We noticed that the unreacted phenylacetylene groups swing out at a wide angle (124°) instead of expected parallel geometry, presumably due to the steric repulsion between the phenylethynyl groups and the back-clamping effect of benzoindenyl ring at

the opposite peri-positions.[51,52] The distorted structure of **5.89a** makes the enyne and alkyne too far to undergo a TDDA cyclization. In addition, we supposed that the back-clamping effect may push the phenylethynyl moieties at C_5 and C_{10} much closer, that facilitate the second TDDA event to afford the desired double-annulation.

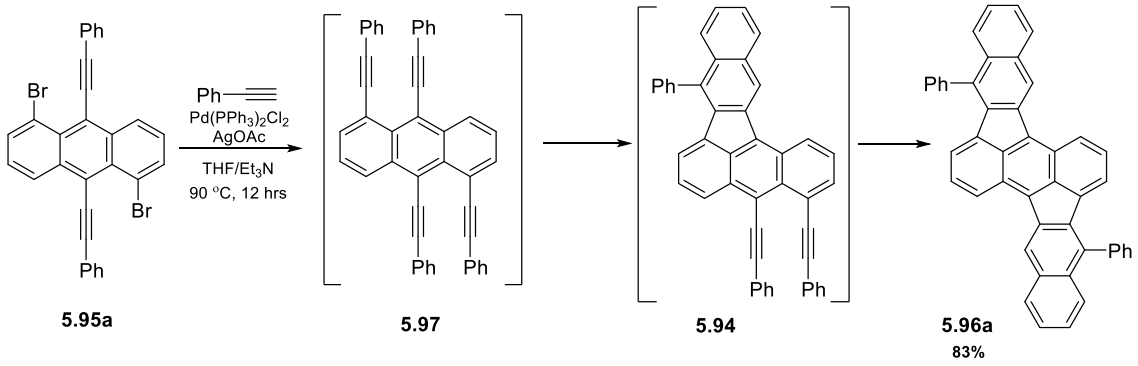


Scheme 5-14 Structural investigation of **5.89a**

To verify our hypothesis, we prepared 1,5-dibromo-9,10-bis(phenylethynyl)anthracene anthracene **5.95a** from corresponding 1,5-dibromoanthraquinone (**Scheme 5-15**). Then **5.95a** was subjected to the optimized conditions of mono-TDDA reaction, dibenzo[*g*,*s*]rubicene product **5.96a** was obtained and identified by ^{1}H NMR. Unexpectedly, we also found side products including uncyclized tetrayne and single-side TDDA product **5.94** in the resulting crude mixture. The discovery of the desired double TDDA cyclization as well as byproducts **5.94** and **5.97** supports our

previous hypothesis that the generation of dibenzo[*g*,*s*]rubicene proceeds via stepwise annulations, and the formation of peripheral pentagon in intermediate **5.94** can somehow facilitate the second TDDA annulation.

Hence, the promising results encouraged us to improve the yield of the dibenzo[*g*,*s*]rubicene product **5.96a** with the investigation of better conditions. We still focused on a one-pot reaction to obviate any unnecessary isolation. Based on previous studies, TDDA reactions can be promoted by transition metals,[42] though the previous experiment, heating of tetrayne, confirmed that TDDA proceeded under thermal conditions well in **Scheme 5-13**. Additionally, alkyne substrates generally can be activated in cycloaddition reactions by some "soft" metals, such as silver,[53] due to the π-binding effect. Thus, we planned to use a transition metal that would facilitate the ring closure step. We screened a variety of silver(I) and copper(I) salts, and finally silver acetate performed best in the TDDA event to afford the double-side cyclization product **5.96a** in a yield of 83%.



Scheme 5-15 Synthesis of dibenzo[*g*,*s*]rubicene **5.96a**

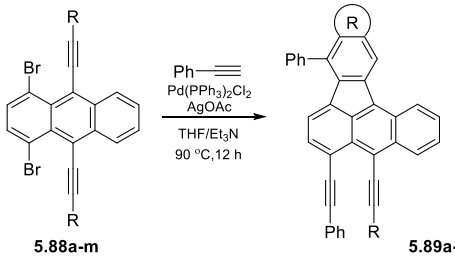
Upon the optimal conditions in hand, we explored the scope of naphtho[2,3-*a*]aceanthrylene **5.89b**−**m** and dibenzo[*g*,*s*]rubicene analogs **5.96b**−**l** (**Table 5-1 & 5-2**). We initially started screening the substrates whose ethynyl moieties at the 9,10-anthracene positions are attached to various aryl or vinyl functionalities. To increase the solubility of products in organic solvents, we designed a series of substrates containing aryl groups substituted with alkyl groups **5.89b**−**f**, **5.96b**−**f**. All of them can smoothly converted into corresponding products in high yields. Interestingly, only one type of regioisomers **5.89b** and **5.96b** were obtained in the reactions of reactants **5.88b** and **5.95b** with ortho-methyl substitution, indicating that the TDDA occurs on the less substituted side of enynes. In addition, the solubility of *n*-butyl substituted products is much better than others, as we expected.

Next, the substrates bearing electron-donating/withdrawing groups were examined, in order to further observe how electronic effects impact on the physical characteristics of synthesized materials. The electron-rich substrates with alkyloxy groups still afforded their products in excellent yields (**5.89g, 5.89h**, **5.96g**), while the substrates with the electron-withdrawing groups led to lower yields (**5.96h**, 42%; **5.89i**, 72%), due to the deactivation of enynes by trifluoromethyl group. We then moved to the substrates with 1-cyclohexenylacetylene moieties and obtained the desired cyclized products **5.89k** and **5.96j** in 98% and 83% yields, respectively. The results suggested that either aromatic ring or simple alkene can be incorporated to form the enyne. Similarly, the reaction of substrates

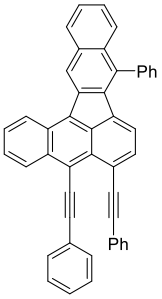
with naphthyl groups also performed efficiently to deliver the corresponding products. (**5.89j**, 97%; **5.96i**, 94%).

We are also interested in sulfur-containing CP-PAHs due to their impressive performance in the field of organic semiconductor and organic photovoltaics.[54–57] Hence, we prepared the substrates with thiophene rings substituted at two different sites. The reactions are still successful to give desired products with regiospecificity on cyclization, which can be rationalized by the more double-bond character of b-bonds rather than c-bonds in thiophene rings. (**5.89&5.96 l, m**)

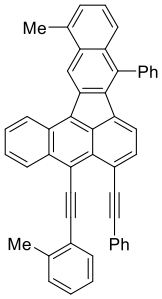
Table 5-1 Synthesis of naphtho[2,3-*a*]aceanthrylene **5.89a**–**m**



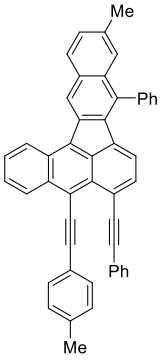
5.88a-m **5.89a-m**



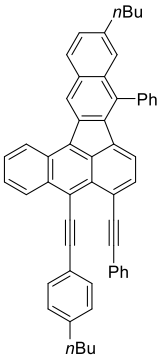
5.89a, 87%



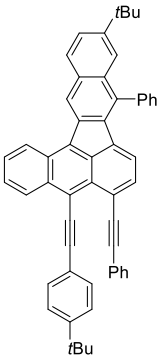
5.89b, 92%



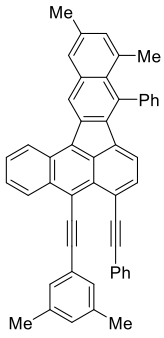
5.89c, 95%



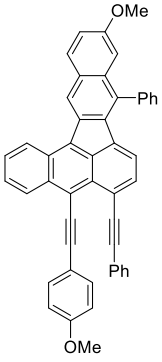
5.89d, 98%



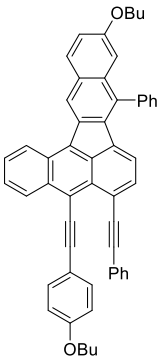
5.89e, 98%



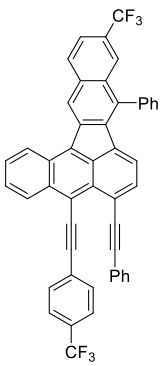
5.89f, quant.



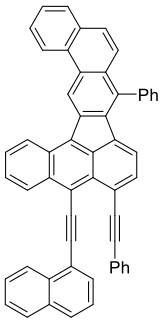
5.89g, 98%



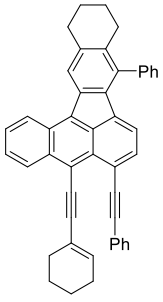
5.89h, 99%



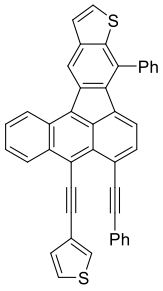
5.89i, 72%



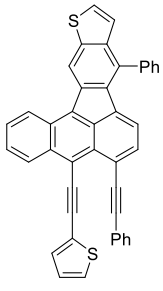
5.89j, 97%



5.89k, 98%

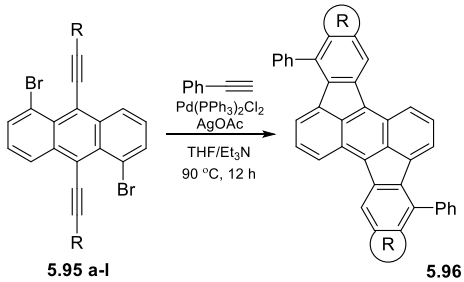


5.89l, 96%

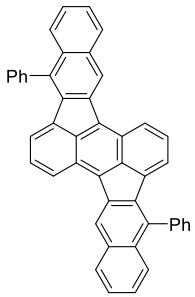


5.89m, 93%

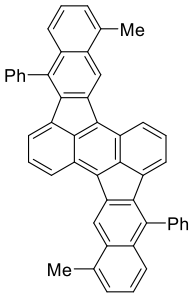
Table 5-2 Synthesis of dibenzo[*g*,*s*]rubicene analogs **5.96b**–**l**



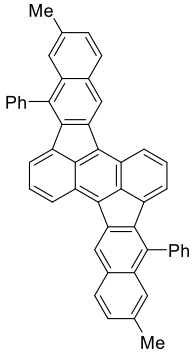
5.95 a-l **5.96 a-l**



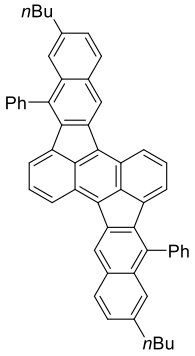
5.96a, 83%



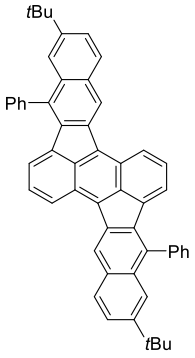
5.96b, 83%



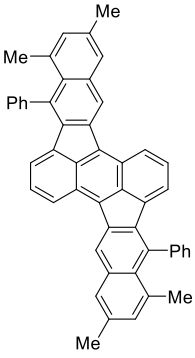
5.96c, 90%



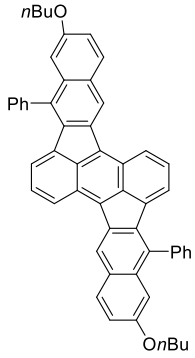
5.96d, 90%



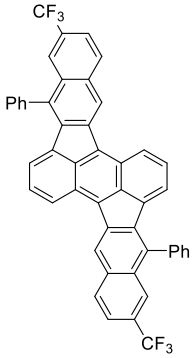
5.96e, 70%



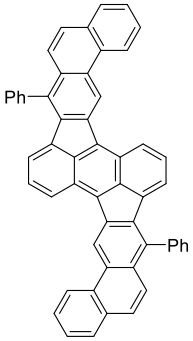
5.96f, 90%



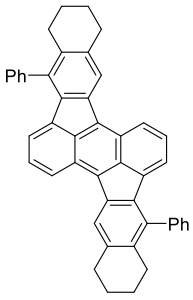
5.96g, 89%



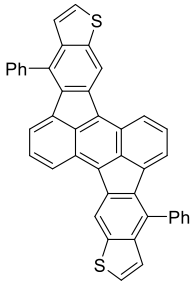
5.96h, 42%



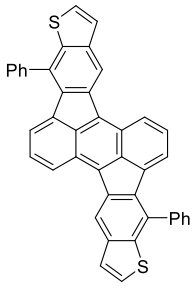
5.96i, 94%



5.96j, 83%



5.96k, 97%



5.96l, 92%

5.3.2 Optical and electrochemical properties of naphtho[2,3-a]aceanthrylenes and dibenzo[g,s]rubicenes

The optical properties of our synthesized CP-PAHs were initially characterized with ultraviolet-visible (UV-Vis) spectroscopy. All absorption spectra of the compounds were measured in THF solutions at the concentration of 1×10^{-5} mol/L. The featured absorption bands of the measured compounds mostly locate in the visible region. The charge-transfer absorption peaks centered in the range from 450 to 600 nm are characteristic of the acene family.

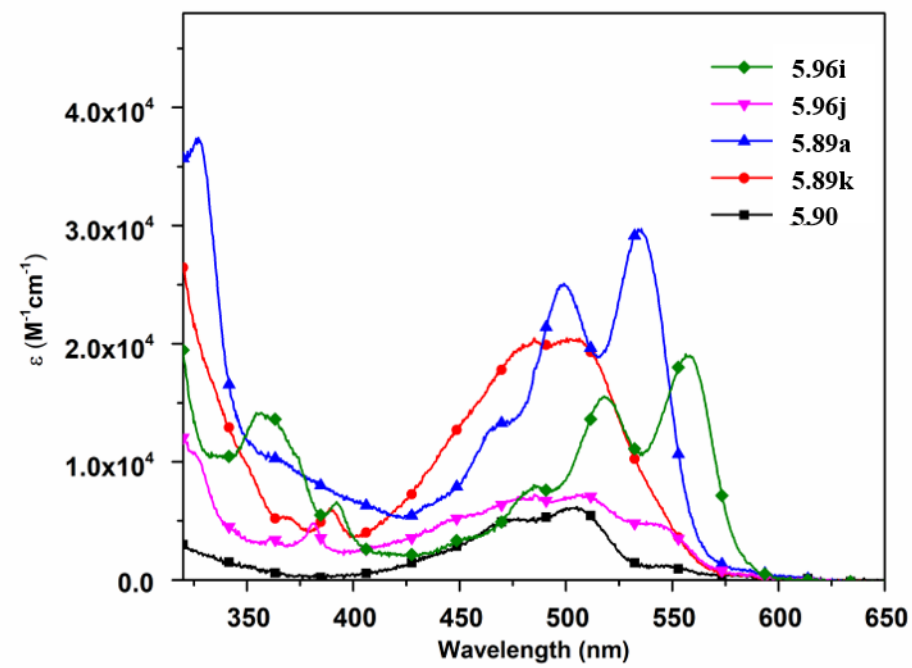


Figure 5-2 Absorption spectra of selected CP-PAHs and tetrayne

In Figure 5-2, the impact of the conjugation pattern was investigated based on the absorption spectra of compound **5.96i, 5.96j**, **5.89a** and **5.89k**. The uncyclized tetrayne

intermediate **5.90** had the lowest extinction coefficient among all the compounds. The dibenzo[*g*,*s*]rubicene derivatives possessed three sets of characteristic absorption bands, which were bathochromically shifted, compared with naphtho[2,3-*a*]aceanthrylene derivatives. The larger onset wavelengths of compound **5.96i** and **5.96j** indicated their decreased bandgaps due to extended π-conjugation. Compounds **5.89a** and **5.96i** displayed more pronounced vibrational structures, attributed to their more rigid π-scaffold.

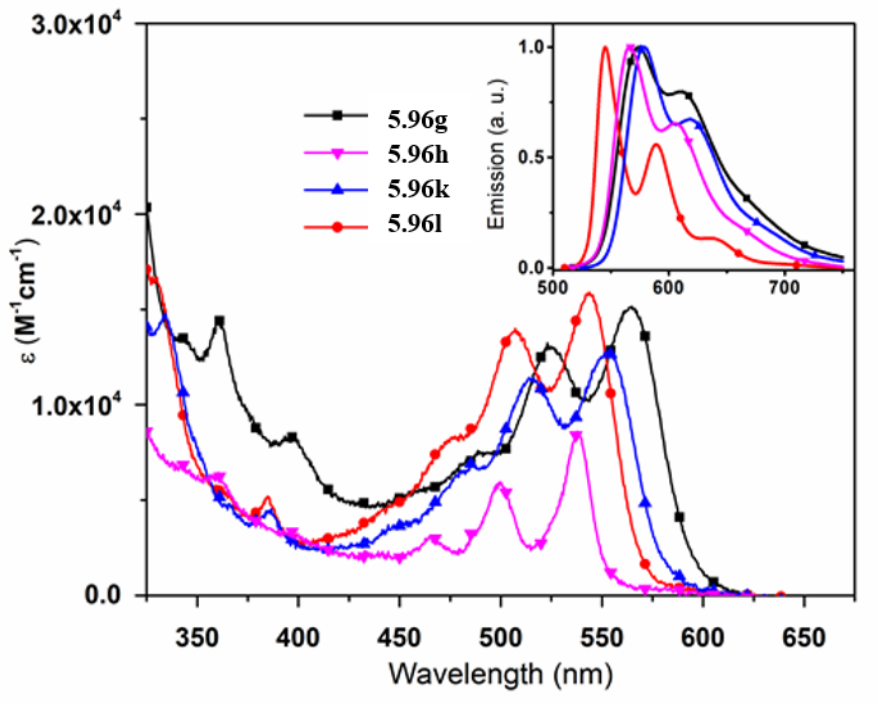


Figure 5-3 Absorption spectra of **5.96g,h,k,l**

In Figure 5-3, the absorption properties of dibenzo[*g*,*s*]rubicene derivatives containing EDG/EWG and heteroatoms were examined. Similar prominent absorption features were found with three sets of absorption bands ranging between 475 nm and 600 nm. The longest wavelength transition of electron-rich compound **5.96g** was more

bathochromic with higher absorption intensity, rather than the electron-deficient compound **5.96h**. Interestingly, a noticeable discrepancy was observed between the most red-shift absorption bands of regioisomers **5.96k** and **5.96l**, whose sulfur atom reside at different positions. The results suggested that chemical modification with various substituents can fine-tune the optical properties of these conjugated systems. In addition, the bandgaps of dibenzo[*g*,*s*]rubicenes range from 2.07−2.23 eV, calculated by the absorbance onset wavelengths.

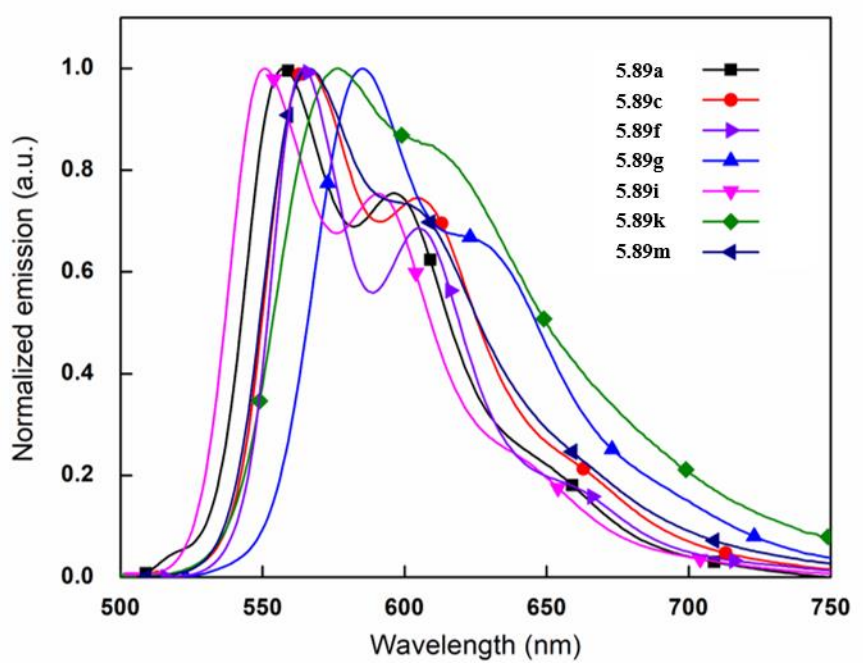


Figure 5-4 Emission spectra of naphtho[2,3-*a*]aceanthrylene derivatives

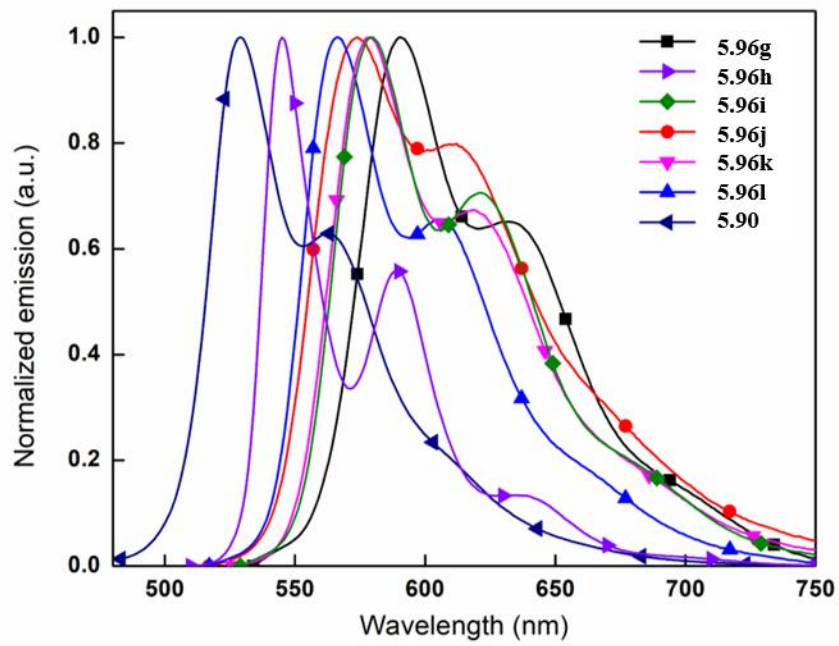


Figure 5-5 Emission spectra of dibenzo[*g*,*s*]rubicene derivatives

The emission properties of prepared CP-PAHs were then characterized by fluorescence spectroscopy (**Figure 5-4, 5-5**). Quantum yields of selected compounds are listed in **Table 5-3.** The emission spectra of both dibenzo[*g*,*s*]rubicene and naphtho[2,3-*a*]aceanthrylene derivatives were highly similar to the mirror image of their absorption spectra, indicating their absorptions and emissions both favor the same transition process. The quantum yields of more rigid rubicene derivatives (**5.96g,h,i**) with extended conjugation were much higher than the one with flexible backbone (**5.96j**, 28%). Lower quantum yields were unsurprisingly observed for sulfur-containing rubicene derivatives, presumably due to the alternate relaxation pathways made possible by sulfur.

Table 5-3 Optical properties of dibenzo[*g,s*]rubicenes

Compound	***Absorption*** λ_{max} ***(nm)***	***Emission*** λ_{max} ***(nm)***	***Optical*** E_g ***(eV)***	***Quantum Yield***
5.96g	523, 563	590, 633	2.07	66%
5.96h	500, 537	545, 589, 634	2.23	75%
5.96i	484, 517, 556	578, 621	2.12	79%
5.96j	477, 505, 535	573, 612,	2.18	28%
5.96k	515, 554	578, 619	2.12	30%
5.96l	507, 542	566, 606	2.18	17%

The electrochemical properties were studied by cyclic voltammetry in THF solvent at the concentration of 1 mmol/L (**Figure 5-6**). The dibenzo[*g,s*]rubicene derivatives showed two-electron reduction features, consistent with the electron-accepting behavior of cyclopenta-rings. Oxidation waves were not observed within the THF solvent window, suggesting that the difficulty of electron-loss process. Herein, HOMO levels were calculated from the measured LUMO levels and the optical bandgap from the absorption spectra. LUMO energies were calculated according to the first quasi-reversible reduction waves, using ferrocene as an internal reference with the assumed ionization potential as −4.8 eV for the ferrocene/ferricenium (Fc/Fc^+) redox system. The calculated results are shown in **Table 5-4**. The HOMO level of **5.96g** is the highest one among all selected samples, owing to the most electron-donating group (alkyloxy group) and the lowest LUMO level of **5.96h** is attributed to the most electron-deficient group.

The measured LUMO levels of the dibenzo[*g*,*s*]rubicene derivatives are generally lower than the common benzenoid PAHs (anthracene −2.25 eV, tetracene −2.61 eV and perylene −2.55 eV), in the range from −3.22 to −3.47 eV, indicating the stronger electron affinity of dibenzo[*g*,*s*]rubicene derivatives without the introduction of electron-withdrawing groups. However, the LUMO levels are close to the reported values for rubicene,[58] even with the extended conjugation system.

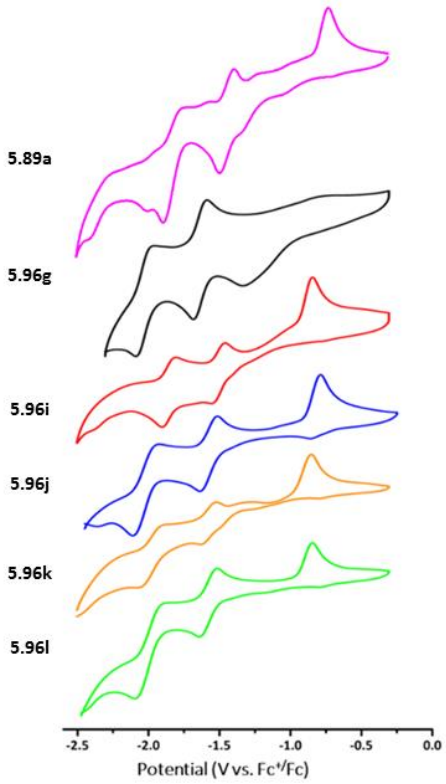


Figure 5-6 Cyclic voltammograms of newly synthesized CP-PAHs

Table 5-4 Electrochemical results of dibenzo[*g*,*s*]rubicenes

Compound	E_{r1} *(V)*	E_{r2} *(V)*	*Optical* E_g *(eV)*	*LUMO (eV)*	*HOMO (eV)*
5.96g	-1.64	-2.03	2.07	-3.22	-5.29
5.96h	-1.43	--	2.23	-3.47	-5.70
5.96i	-1.51	-1.87	2.12	-3.34	-5.46
5.96j	-1.63	-2.08	2.18	-3.24	-5.42
5.96k	-1.58	-1.98	2.12	-3.30	-5.42
5.96l	-1.58	-2.00	2.18	-3.28	-5.46

To gain more insights into the electronic structures of dibenzo[*g*,*s*]rubicene derivatives, density functional theory (DFT) calculations were carried out using the B3LYP functional and 6-31+G(d, p) basis set. The geometry and energy level of HOMOs and LUMOs were obtained and shown in **Figure 5-6** and experimental section 5.6. The HOMO/LUMO contours of **5.96a** show that the delocalized character considerably extends from the rubicene core to the peripheral benzene moieties but does not reach the phenyl ring whose plane is perpendicular to the main conjugation plane. In **5.89a**, both HOMO/LUMO orbitals distribute over the CP-PAH core and the uncyclized phenylacetylene units. This orbital models (See experimental section) of the selected dibenzo[*g*,*s*]rubicenes are similar to **5.96a**, possessing the HOMO/LUMO orbitals over the whole π-conjugation involving both cyclopenta-rings, which explain the low FMO energy levels of benzo-fused rubicene species. In addition, the FMO patterns of regioisomers **5.96k** and **5.96l** have some subtle differences on the thiophene moieties, presumably leading to their discrepancy on absorption behaviors. The bandgaps obtained from TD-

DFT calculations matched well with the measured optical band gap within 0.13 eV difference. (**Table 5-5**)

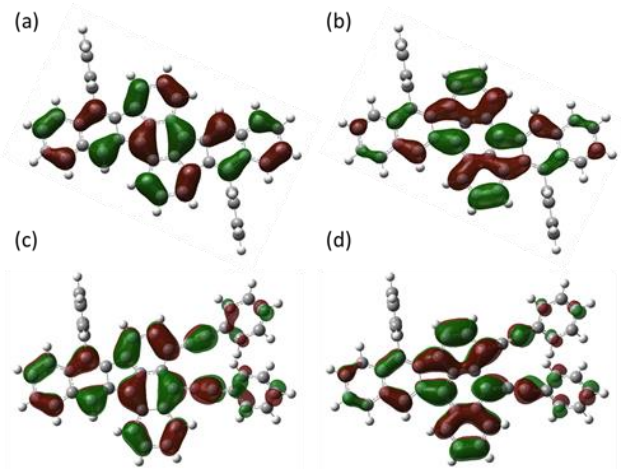


Figure 5-7 DFT calculated molecular orbitals: (a) HOMO of **5.96a**, (b) LUMO of **5.96a**, (c) HOMO of **5.89a**, (d) LUMO of **5.89a**. See the experimental section for more calculated HOMO/LUMO figures of dibenzo[g,s]rubicene derivatives.

Table 5-5 DFT calculated results for HOMO-LUMO gaps

Compound	***Optical*** E_g ***(eV)***	***DFT*** E_g ***(eV)***
5.96g	2.07	2.22
5.96h	2.23	2.38
5.96i	2.12	2.26
5.96j	2.18	2.42
5.96k	2.12	2.32
5.96l	2.18	2.38

As discussed before, the cyclopenta-rings in CP-PAHs display antiaromaticity and may trap the new electrons during reductions. Hence, to further understand and verify the

aromatic features of the prepared CP-PAHs, nucleus-independent chemical shift (NICS) calculations were performed on **5.89a** and **5.96a**.

The definition of aromaticity is a manifestation of electron delocalization in closed circuits, either in two or in three dimensions.[59] The ring currents of π-electrons in aromatic rings can be impacted by external magnetic field to generate an induced magnetic field. Hence, to observe the absolute magnetic shielding caused by the induced magnetic field is an available approach for the aromaticity evaluation.

NICS calculation is a method to predict the NMR chemical shift of a "ghost" atom, generally placed in the center axis of a studied ring system.[60] Consistent with the NMR chemical shift convention, the signs of the computed values are reversed: aromaticity is characterized by negative NICS values, while antiaromaticity by positive NICS values. It is noteworthy that the size of the NICS does not provide an absolute measure of aromaticity.[61]

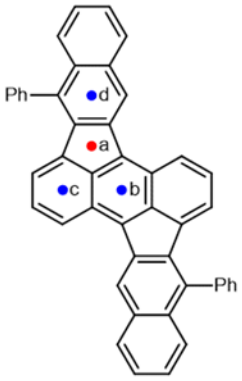
We then set the "observation points" at the center of pentagon (NICS(0)), 1 Å above ring centers (NICS(1)) as well as its neighboring benzenoid rings in compound **5.96a**. As shown in **Figure 5-6**, values obtained via NICS(0) and NICS(1) were both positive numbers at the center of pentagons, indicating an antiaromatic character of the cyclopenta-rings. However, based on recent studies, in order to evaluate the π-aromaticity more accurately, we need to remove the local contributions of σ framework and focus more on just the contributions arising from the zz component of the shielding tensor. Thus NICS(1)zz was later performed to verify the previous conclusion. The cyclopenta-rings

were still regarded as antiaromatic, and the all benzenoid rings remain aromatic characters. The results of NICS calculations for **5.89a** are similar. The calculated NICS data is consistent with other work on CP-PAHs[62,63] and confirmed the antiaromatic character of cyclopenta-rings that contributes to better electron affinity and narrower bandgaps.

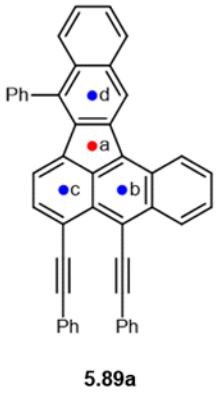
Table 5-6 NICS results for **5.96a**

Position	*NICS(0)*	*NICS(1)*	*NICS(1)zz*
a	5.59	1.12	10.99
b	−7.40	-9.16	-21.09
c	−5.86	-8.02	-18.77
d	−5.34	-7.32	-17.82

Table 5-7 NICS(1) and NICS(1)zz results for **5.89a** and **5.96a**



5.96a



5.89a

5.96a	NICS(1)	$NICS(1)_{zz}$
a	1.12	10.99
b	-9.16	-21.09
c	-8.02	-18.77
d	-7.32	-17.82

5.89a	NICS(1)	$NICS(1)_{zz}$
a	0.76	10.21
b	-9.73	-22.88
c	-8.09	-17.71
d	-7.52	-18.11

5.4 Conclusion and future

In conclusion, a new method involving tandem Sonogashira cross-coupling and tetra-dehydro-Diels−Alder cycloaddition cascade was developed to readily construct rubicene-based polycyclic aromatic structures. A series of dibenzo[*g*,*s*]rubicene and

naphtho[2,3-*a*]aceanthrylene derivatives were successfully obtained with various functional groups and heterocycles. The synthesized new CP-PAHs possess narrow bandgaps low-lying LUMO levels and unique optical/electronic characteristics, due to cyclopenta-ring structures and extended conjugation system. NICS calculations elucidated the antiaromatic character of the embedded five-membered rings as electron acceptors. All results above demonstrate the potential of the prepared products as novel optoelectronic materials.

In the future, the reactions can be expanded to more alkyne components such as trimethylsilylacetylene (TMSA), which can be further converted into halides to achieve the homocoupling reaction of dibenzo[*g,s*]rubicenes. Additionally, pyridines, pyrroles and quinolines can be also incorporated into the conjugation, rather than thiophenes.

5.5 Experimental Section

5.5.1 General details

Unless otherwise noted, all reactions were carried out using oven-dried glassware under a nitrogen atmosphere. Dichloromethane (CH_2Cl_2), Acetonitrile (CH_3CN) and toluene were distilled from CaH_2 prior to use. Tetrahydrofuran (THF) was distilled from Na/benzophenone prior to use. Dichloromethane and toluene were further degassed by bubbling a stream of argon through the liquid in a Strauss flask and then stored in a nitrogen-filled glove box. Anhydrous diethyl ether (Et_2O) was purchased from Sigma-Aldrich and used without further purification. Unless otherwise noted, all chemicals were

purchased from commercial sources and used as received. Palladium and copper salts were purchased from Sigma-Aldrich or Strem and used as received. 1-Butyl-4-eth-1-ynylbenzene, 3-ethynylthiophene, 1-ethynyl-4-methoxybenezne, 4-(trifluoromethyl)phenylacetylene, 4-tert-butylphenylacetylene and 1-ethynylcyclohexene were purchased from commercial sources and used as received. The commercially available 2-ethynylthiophene, 1-ethynyl-4-methoxybenzene, 4-ethynyltoluene, 1-butoxy-4-ethynylbenezne, 1-ethynylnaphthalene, 2-ethynylnaphthalene, 1-ethynyl-3,5-dimethylbenzene and 2-ethynyltoluene were prepared via the desilylation of the Sonagashira coupling products of the corresponding aryl bromides or iodides with trimethylsilylacetylene.

Analytical thin-layer chromatography (TLC) and preparative thin-layer chromatography were carried out using 250 μm and 1000 μm silica plates (SiliCycle), respectively. Eluted plates were visualized first with a UV lamp (254 nm) and then stained with potassium permanganate or p-anisaldehyde, followed by heating. Flash column chromatography was performed using 230 – 400 mesh (particle size 40 – 63 μm) silica gel purchased from SiliCycle.

^{1}H NMR (300, 400 and 500 MHz) and ^{13}C NMR (75, 100 and 125 MHz) spectra were obtained on Varian Inova and Bruker Avance instruments. 1H NMR spectra data were reported as δ values in ppm relative to chloroform (δ 7.26) if collected in $CDCl_3$ or THF (δ 3.58, 1.72) if collected in THF-d_8. ^{13}C NMR spectra data were reported as δ values in ppm relative to chloroform (δ 77.0) if collected in CDCl3 or THF (δ 25.31, 67.21) if

collected in THF- d_8. Note: Due to their extremely poor solubility, the ^{13}C NMR spectra of rubicene derivatives were not collected. ^{19}F NMR spectra data were reported as δ values in ppm relative to hexafluorobenzene (δ −164.9). ^{1}H NMR coupling constants were reported in Hz, and multiplicity was indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); quint (quintet); m (multiplet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dddd (doublet of doublet of doublet of doublets); dt (doublet of triplets); td (triplet of doublets); ddt (doublet of doublet of triplets); dq (doublet of quartets); app (apparent); br (broad). IR spectra were obtained with an ATR source using a Nicolet iS5 FT-IR spectrometer. High-resolution mass spectra (HRMS) were performed using either electrospray ionization (ESI) or GC/MS. ESI methods were performed on a Bruker BioTOF II (Time-of-flight) instrument using PEG-300, PEG-400 or PPG-400 as an internal standard. GC/MS were collected on an Agilent 7200 GC/QTOF-MS instrument using a direct solid probe method in which the samples were heated to 325 °C. Low-resolution mass spectra (LRMS) were performed using laser desorption ionization (LDI) methods on AB-Sciex 5800 MALDI/TOF-MS. Note: Many of the new compounds reported in this manuscript lack HRMS data due to extremely poor solubility in polar solvents (methanol or acetonitrile), which make ionization of such hydrocarbons very challenging. Attempts to obtain HRMS data were unsuccessful due to the low signal for the compounds relative to the internal standard at all concentrations attempted.

UV-vis extinction spectra were obtained using a Mikropack DH-2000 UV-Vis-NIR spectrometer. Equipped with a K-Sphere “Petite” integrating sphere, a PTI

QuantaMaster™ 400 fluorescence spectrofluorometer was used to determine steady state fluorescence emission and quantum yield (QY). To be more specific, the integrating sphere used the "direct excitation" method to measure the absolute QY, and the measurement for each sample was completed in four individual scans, namely the excitation scattering and the emission for both the solvent and the sample. The integral of each scan was calculated by the fluorometer software, PTI Felix GX, and so was the value of absolute QY, which can be expressed as follows:

$$\mathrm{QY}(\%) = \frac{I_{smpl\ em} - I_{sol\ em}}{I_{smpl\ ex} - I_{sol\ ex}} \times 100\%$$

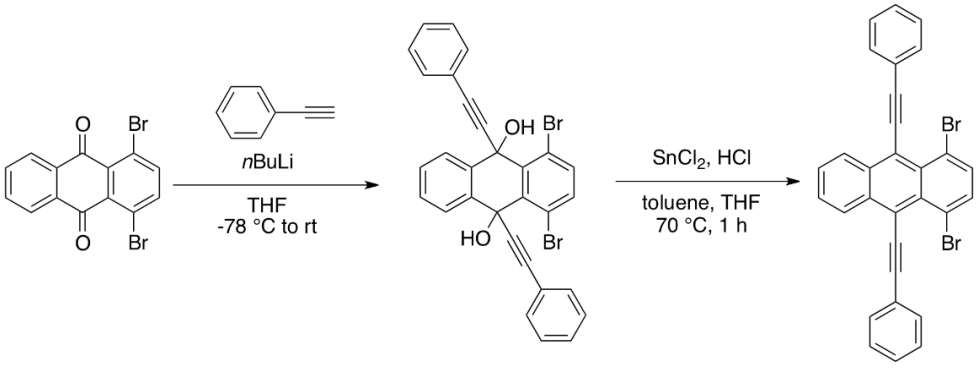
Where $I_{smpl\ em}$ is the integral of the emission of the sample solution, and $I_{sol\ em}$ is the integral of the emission of the solvent; correspondingly, $I_{smpl\ ex}$ is the integral of the excitation scattering of the sample solution, $I_{sol\ ex}$ and is the integral of the excitation scattering of the solvent.

Cyclic voltammograms were recorded on a CHI600C potentiostat. A gold electrode was used as the working electrode, a platinum wire as the counter electrode, and an Ag wire in 10 mM $AgNO_3$/0.1M $TBAClO_4$ in acetonitrile as the reference electrode. The gold electrode was polished with aqueous dispersions of alumina (0.3 and 0.05 μm). Then, the electrode was cleaned in water and ethanol by ultrasonication and dried with nitrogen flow. The scan speed was 50 mV/s. The potential in THF solution was measured with tetrabutylammonium hexafluorophosphate ($TBAPF_6$, 0.1 M) employed as supporting electrolyte. The energy level of Fc/Fc^+ is assumed to be −4.8 eV below the vacuum level.

5.5.2 Synthetic procedures

Procedure I

*Synthesis of 1,4-dibromo-9,10-bis(phenylethynyl)anthracene **5.88a***



To a 100 mL flame-dried round bottom flask were added phenylacetylene (0.70 mL, 6.4 mmol), and dry THF (16 mL) under N_2. The mixture was cooled to -78 °C and *n*BuLi (2.5 M in hexanes, 2.4 mL, 6.0 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 1h before the addition of quinone (732 mg, 2.0 mmol) in one portion. The mixture was allowed to warm up to room temperature and stirred overnight. To the mixture was added toluene (16 mL), followed by a solution of $SnCl_2$ (2.28 g, 12 mmol) in 4M HCl (8 mL). The resulting mixture was stirred at 60 °C for 1h before cooling to room temperature. The volatiles were removed *in vacuo*. The residue filtered and washed with H_2O (50 mL) and MeOH (50 mL). The crude product was purified by column chromatography on silica gel (20 mm x 250 mm, CH_2Cl_2/hexanes 1:20 to 1:10) to afford the product as an orange-red solid (988 mg, 92%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.88 (dd, *J* = 6.5, 3.5 Hz, 2H), 7.76-7.70 (m, 8H), 7.48-7.42 (m, 6H).

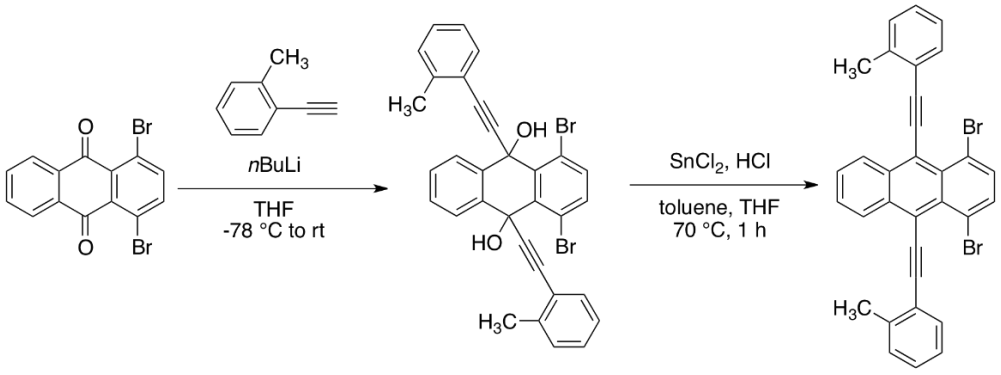
^{13}C NMR ($CDCl_3$, 125 MHz) δ 133.7, 133.6, 131.2, 130.9, 128.9, 128.6, 128.2, 127.4, 123.8, 120.9, 119.5, 109.8, 88.0.

IR (neat, cm^{-1}) 3079, 2193, 1488, 1385.

LRMS (LDI) *m*/*z*, 535.8 [M^+].

mp: 171–172 °C.

Synthesis of 1,4-dibromo-9,10-bis(o-tolylethynyl)anthracene ***5.88b***



Prepared from 2.0 mmol of quinone according to Procedure I; 92% yield; orange-red solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.91 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.70 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.70 (s, 2H), 7.33-7.31 (m, 4H), 7.29-7.26 (m, 2H), 2.69 (s, 6H).

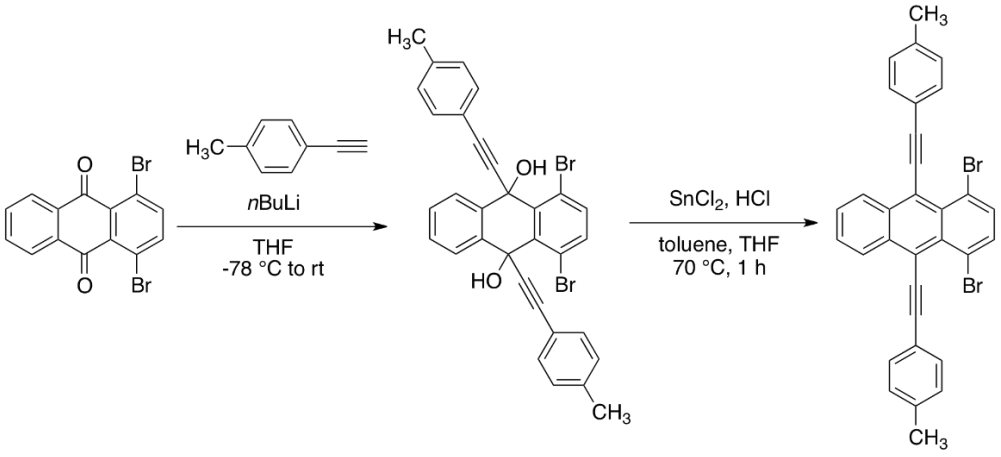
^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.1, 133.7, 133.5, 131.4, 131.1, 129.8, 128.8, 128.1, 127.5, 125.8, 123.6, 120.8, 119.7, 109.2, 91.5, 21.3.

IR (neat, cm^{-1}) 3066, 2177, 1576, 1485, 1456, 1385, 1375.

HRMS (GC/MS solid probe) cacld for $C_{32}H_{20}Br_2$ [M^+] *m*/*z* 563.9911, found [M^+] 563.9967.

mp: 145–149 °C.

Synthesis of 1,4-dibromo-9,10-bis(p-tolylethynyl)anthracene ***5.88c***



Prepared from 3.0 mmol of quinone according to Procedure I; 92% yield; orangish red solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.87 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.70 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.69 (s, 2H), 7.64 (d, *J* = 8.0 Hz, 4H), 7.26 (d, *J* = 8.0 Hz, 2H), 2.43 (s, 6H).

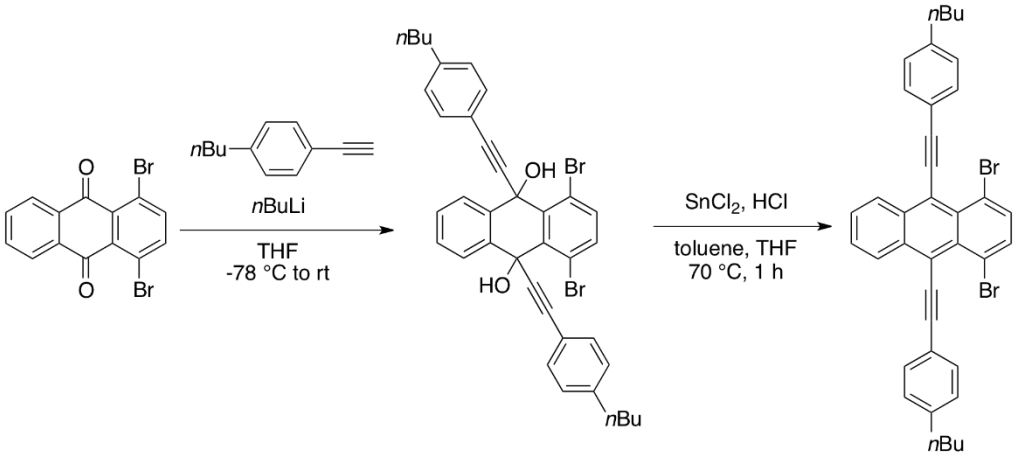
^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.1, 133.50, 133.48, 131.1, 130.8, 129.3, 128.1, 127.4, 120.9, 120.8, 119.5, 110.0, 87.6, 21.7.

IR (neat, cm^{-1}) 3071, 3026, 2186, 1507, 1393.

HRMS (ESI) cacld for $C_{32}H_{20}Br_2$ [M^+] *m*/*z* 563.9911, found [M^+] 563.9894.

mp: 167–171 °C.

Synthesis of 1,4-dibromo-9,10-bis((4-butylphenyl)ethynyl)anthracene ***5.88d***



Prepared from 4.0 mmol of quinone according to Procedure I; 89% yield; orangish red solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.87 (dd, *J* = 7.0, 3.0 Hz, 2H), 7.70 (dd, *J* = 7.0, 3.0 Hz, 2H), 7.68 (s, 2H), 7.66 (d, *J* = 8.0 Hz, 4H), 7.26 (d, *J* = 8.0 Hz, 2H), 2.67 (t, *J* = 7.5 Hz, 4H), 1.66-1.62 (m, 4H), 1.42-1.36 (m, 4H), 0.95 (t, *J* = 7.5 Hz, 6H).

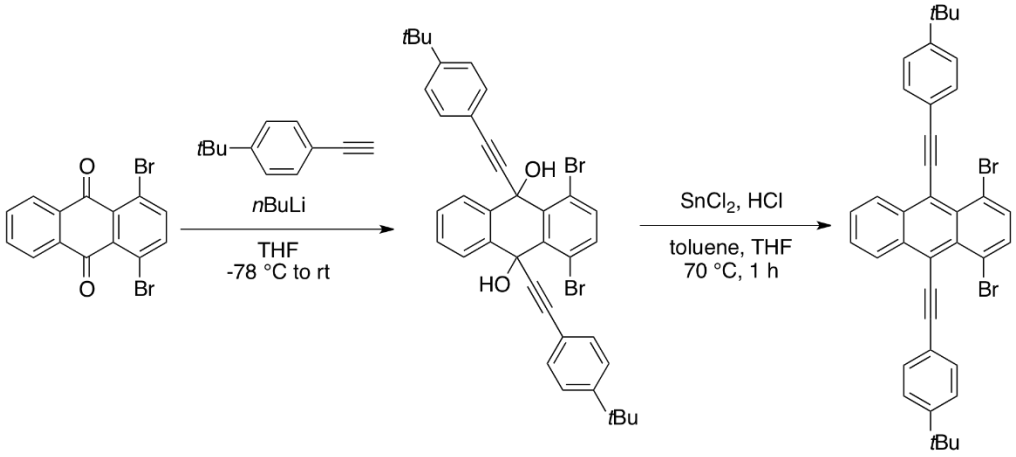
^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.1, 133.505, 133.500, 131.1, 130.8, 128.7, 128.1, 127.42, 121.0, 120.9, 119.5, 110.1, 87.6, 35.7, 33.4, 22.3, 14.0.

IR (neat, cm^{-1}) 3031, 2957, 2927, 2857, 2185, 1511, 1504, 1390.

LRMS (LDI) *m*/*z*, 647.9 [M^+].

mp: 107–112 °C.

Synthesis of 1,4-dibromo-9,10-bis((4-(tert-butyl)phenyl)ethynyl)anthracene ***5.88e***



Prepared from 2.0 mmol of quinone according to Procedure I; 92% yield; orangish yellow solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.87 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.71-7.67 (m, 8H), 7.48 (dd, *J* = 6.5, 2.0 Hz, 4H), 1.37 (s, 18H).

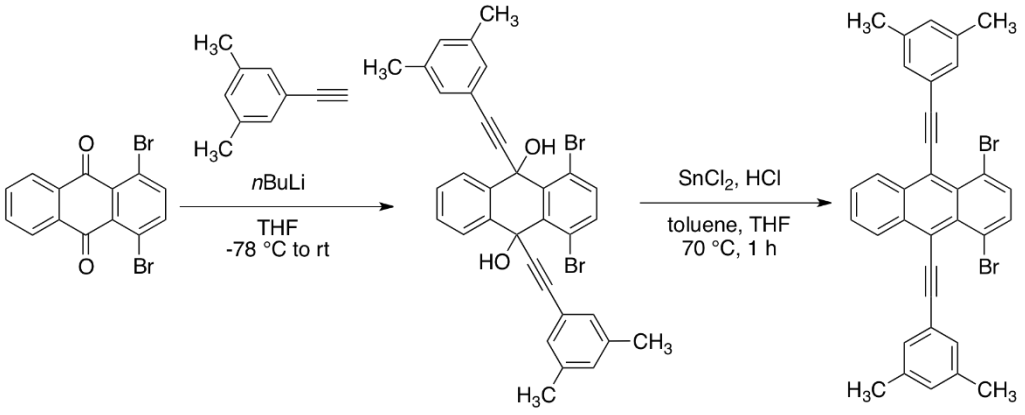
^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.2, 133.54, 133.51, 131.1, 130.7, 128.1, 127.4, 125.6, 120.9, 120.8, 119.5, 110.0, 87.5, 34.9, 31.2.

IR (neat, cm^{-1}) 3060, 2963, 2195, 1502, 1390.

HRMS (ESI) cacld for $C_{38}H_{32}Br_2$ [M^+] *m/z* 648.0850, found [M^+] 648.0825.

mp: 188–196 °C.

Synthesis of 1,4-dibromo-9,10-bis((3,5-dimethylphenyl)ethynyl)anthracene ***5.88f***



Prepared from 2.0 mmol of, 88% yield quinone according to Procedure I; orangish red solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.86 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.71 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.69 (s, 2H), 7.37 (s, 4H), 7.06 (s, 2H), 2.39 (s, 12H).

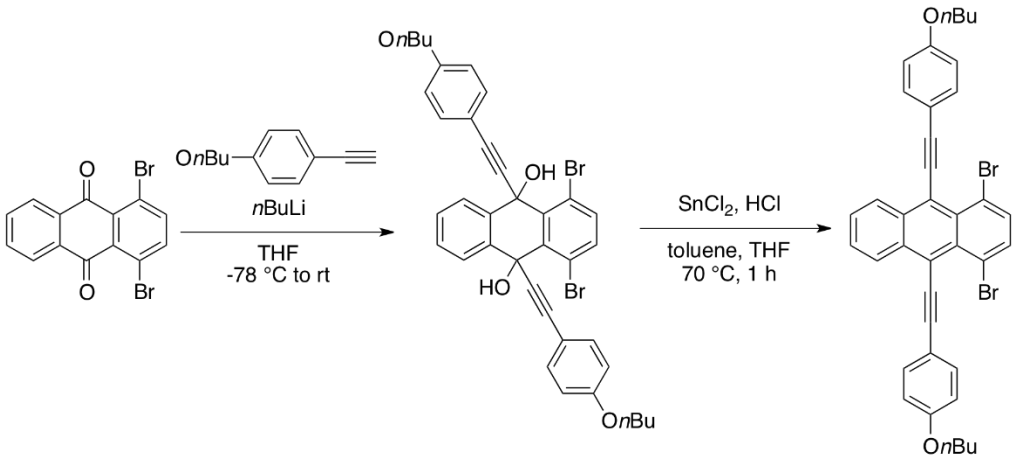
^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.1, 133.6, 133.5, 131.1, 130.8, 128.5, 128.1, 127.4, 123.5, 120.9, 119.5, 110.2, 87.4, 21.2.

IR (neat, cm^{-1}) 2914, 2859, 2184, 1709, 1595, 1393, 1374.

HRMS (ESI) cacld for $C_{34}H_{24}Br_2$ [M^+] *m*/*z* 595.0224, found [M^+] 592.0172.

mp: 171–178 °C.

Synthesis of 1,4-dibromo-9,10-bis((4-butoxyphenyl)ethynyl)anthracene ***5.88h***



Prepared from 2.0 mmol of quinone according to Procedure I; 96% yield; orangish red solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.85 (dd, *J* = 6.7, 3.3 Hz, 2H), 7.74-7.61 (m, 8H), 7.00-6.90 (m, 4H), 4.02 (t, *J* = 6.5 Hz, 4H), 1.84-1.77 (m, 4H), 1.59-1.45 (m, 4H), 1.00 (t, *J* = 7.4 Hz, 6H).

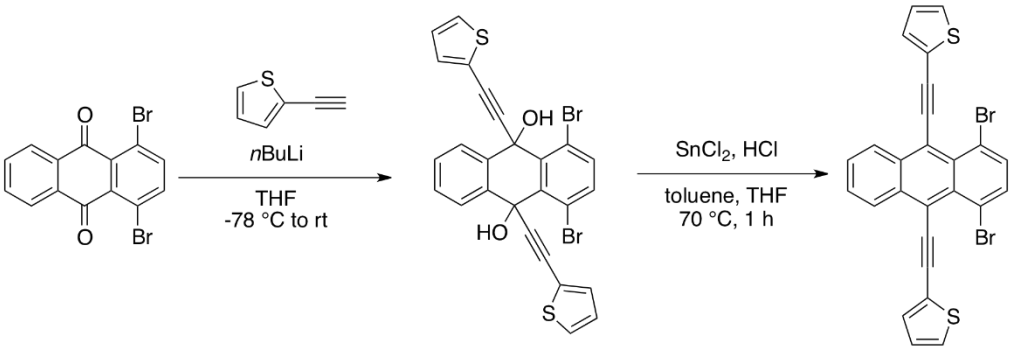
^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.8, 133.42, 133.41, 132.4, 131.0, 128.0, 127.5, 120.9, 119.4, 115.8, 114.8, 110.1, 87.1, 67.8, 31.2, 19.2, 13.9.

IR (neat, cm^{-1}) 3069, 2956, 2928, 2868, 2183, 1601, 1508, 1463, 1249.

HRMS (ESI) cacld for $C_{38}H_{32}Br_2O_2$ [M^+] *m*/*z* 680.0749, found [M^+] 680.0748.

mp: 140–143 °C.

Synthesis of 2,2'-((1,4-dibromoanthracene-9,10-diyl)bis(ethyne-2,1-diyl))dithiophene ***5.88l***



Prepared from 2.0 mmol of quinone according to Procedure I; 66% yield; dark red solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.76 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.70 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.69 (s, 2H), 7.48 (d, *J* = 3.5 Hz, 2H), 7.43 (d, *J* = 5.0 Hz, 2H), 7.13 (dd, *J* = 5.0, 3.5 Hz, 2H).

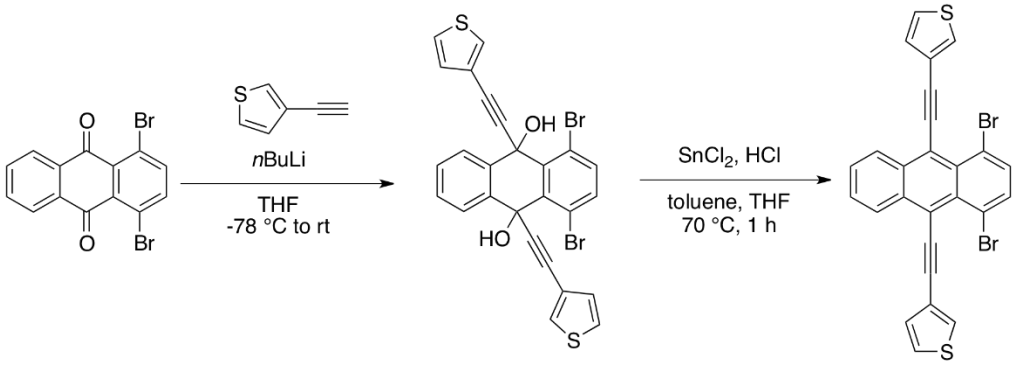
^{13}C NMR ($CDCl_3$, 100 MHz) δ 133.7, 133.1, 131.6, 131.1, 128.4, 128.3, 127.4, 127.3, 123.8, 120.9, 119.1, 103.7, 92.2.

IR (neat, cm^{-1}) 3106, 2171, 1578, 1520.

LRMS (LDI) *m*/*z*, 547.7 [M^+].

mp: 138–143 °C.

Synthesis of 3,3'-((1,4-dibromoanthracene-9,10-diyl)bis(ethyne-2,1-diyl))dithiophene ***5.88m***



Prepared from 2.0 mmol of quinone according to Procedure I; 79% yield; orangish red solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.82 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.74 (dd, *J* = 2.5, 1.5 Hz, 2H), 7.70 (dd, *J* = 7.0, 3.5 Hz, 2H), 7.69 (s, 2H), 7.42-7.40 (m, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ 133.6, 133.4, 131.1, 129.0, 128.6, 128.2, 127.3, 125.8, 123.0, 120.6, 119.3, 105.4, 87.5.

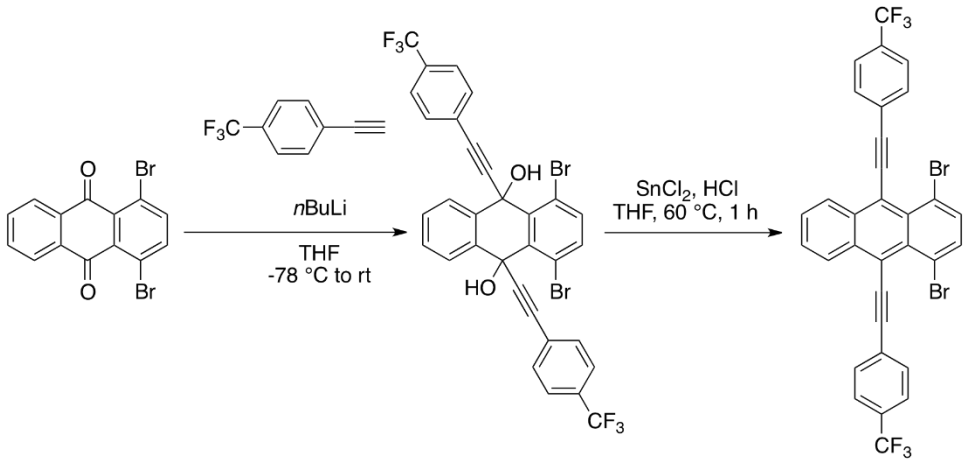
IR (neat, cm^{-1}) 3107, 2916, 2849, 2191, 1579, 1361.

LRMS (LDI) *m*/*z*, 547.7 [M^+].

mp: 144–149 °C.

Procedure II

Synthesis of 1,4-dibromo-9,10-bis((4-(trifluoromethyl)phenyl)ethynyl)-anthracene ***5.88i***



To a 250 mL flame-dried round bottom flask were added 4-(trifluoromethyl)phenylacetylene (2.18 g, 12.8 mmol), and dry THF (40 mL) under N_2. The mixture was cooled to -78 °C and *n*BuLi (2.5 M in hexanes, 4.8 mL, 12.0 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 1h before the addition of quinone (1.464 g, 4.0 mmol)in one portion. The mixture was allowed to warm up to room temperature and stirred overnight. NH_4Cl (sat. aq. 10 mL) was added to the flask. A solution of $SnCl_2$ (7.6 g, 40 mmol) in 4M HCl (40 mL) was added to the above mixture. The resulting mixture was stirred at 60 °C for 1h before cooling to room temperature. The volatiles were removed *in vacuo*. The residue filtered and washed with H_2O (50 mL) and MeOH (50 mL). The crude product was purified by column chromatography on silica gel (20 mm x 250 mm, CH_2Cl_2/hexanes 1:5 to 1:2 to 1:1) to afford the product as an orangish red solid (2.47 g, 92%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.84 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.84 (d, *J* = 7.5 Hz, 4H), 7.75 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.74 (s, 2H) 7.71 (d, *J* = 7.5 Hz, 4H)

^{13}C NMR ($CDCl_3$, 126 MHz) δ 134.0, 133.6, 131.4, 131.1, 130.5 (q, *J* = 33 Hz), 128.6, 127.3, 127.2, 125.6 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 274.7 Hz), 120.8, 119.3, 108.2, 89.9.

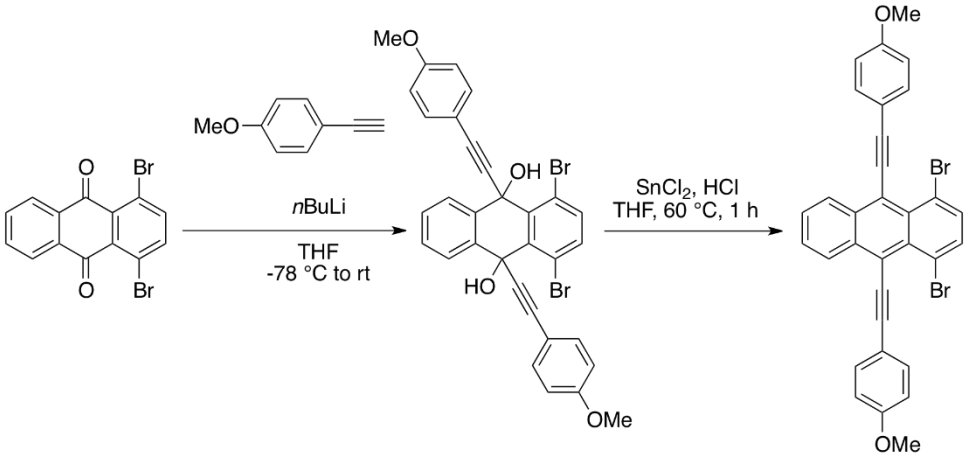
^{19}F NMR ($CDCl_3$, 470 MHz) δ -65.97

IR (neat, cm^{-1}) 2926, 1608, 1315.

HRMS (GC/MS solid probe) cacld for $C_{32}H_{14}Br_2F_6$ [M^+] *m*/*z* 671.9346, found [M^+] 671.9349.

mp: 190–194 °C.

Synthesis of 1,4-dibromo-9,10-bis((4-methoxyphenyl)ethynyl)anthracene ***5.88g***



Prepared from 4.0 mmol of quinone according to Procedure II; 93% yield; orangish red solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.86 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.76-7.71 (m, 8H), 6.98 (dd, *J* = 6.5, 1.5 Hz, 2H), 3.88 (s, 6H).

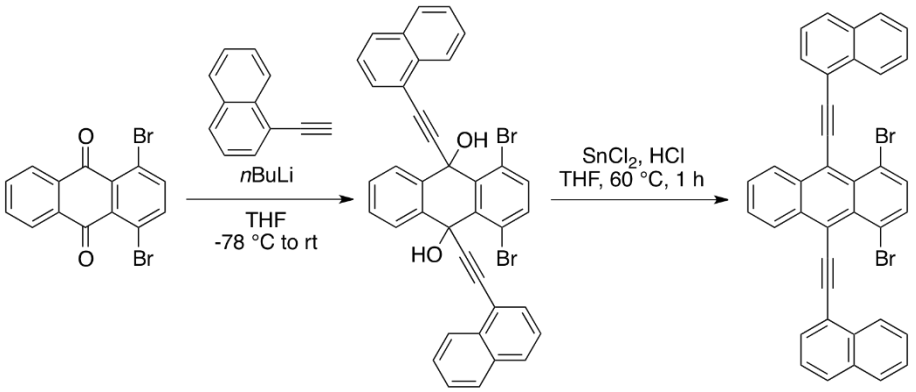
^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.2, 133.4, 132.4, 131.0, 128.0, 127.5, 120.9, 119.4, 116.0, 114.3, 109.9, 87.1, 55.4.

IR (neat, cm^{-1}) 3071, 3006, 2967, 2926, 2833, 2183,1601, 1505, 1454, 1435, 1287, 1249.

HRMS (ESI) cacld for $C_{32}H_{20}Br_2O_2$ [M^+] *m*/*z* 595.9810, found [M^+] 595.9792.

mp: 201–205 °C.

Synthesis of 1,4-dibromo-9,10-bis(naphthalen-1-ylethynyl)anthracene ***5.88j***



Prepared from 4.0 mmol of quinone according to Procedure II; 92% yield; orangish red solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.04 (dd, *J* = 6.7, 3.3 Hz, 2H), 8.65 (d, *J* = 8.3, 2H), 8.00 (dd, *J* = 7.1, 1.2 Hz, 2H), 7.93 (d, *J* = 8.2, 4H), 7.77-7.73 (m, 4H), 7.67-7.62 (m, 2H), 7.60-7.54 (m, 4H).

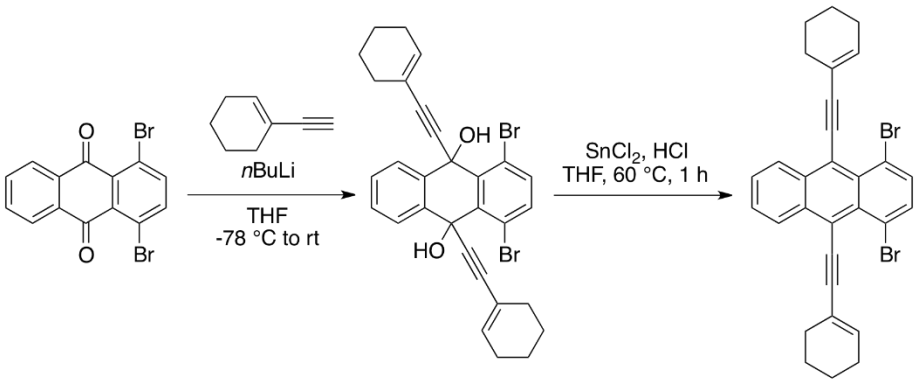
^{13}C NMR ($CDCl_3$, 125 MHz) δ 133.9, 133.7, 133.4, 133.2, 131.3, 130.1, 129.3, 128.43, 128. 38, 127.6, 127.1, 126.6, 126.5, 125.5, 121.5, 120.9, 119.8, 108.7, 92.4.

IR (neat, cm^{-1}) 3043, 2189, 1581, 1504, 1408, 1333.

LRMS (LDI) *m*/*z*, 635.8 [M^+].

mp: 171–176 °C.

Synthesis of 1,4-dibromo-9,10-bis(cyclohex-1-en-1-ylethynyl)anthracene ***5.88k***



Prepared from 4.0 mmol of quinone according to Procedure II; 92% yield; orangish red solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.70 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.63 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.61 (s, 2H), 6.46-6.43 (m, 2H), 2.45-2.40 (m, 4H), 2.27-2.22 (m, 4H), 1.79-1.74 (m, 4H), 1.72-1.66 (m, 4H).

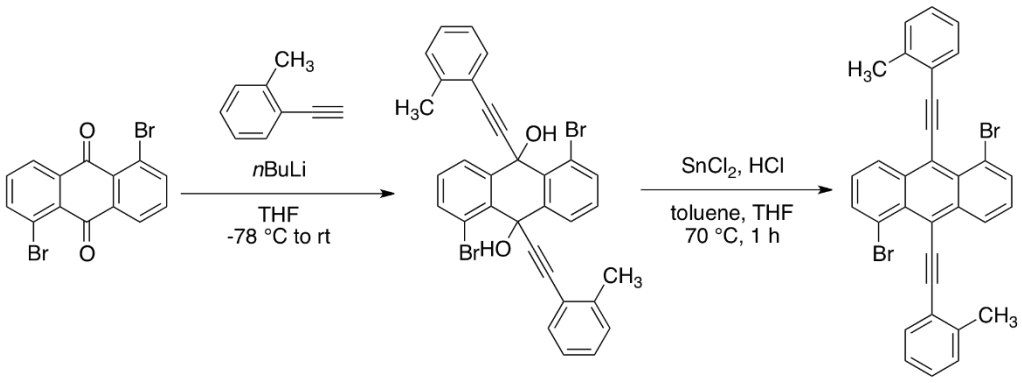
^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.6, 133.4, 133.2, 130.9, 127.8, 127.4, 121.8, 121.0, 119.5, 111.8, 85.7, 28.2, 26.0, 22.3, 21.3.

IR (neat, cm^{-1}) 3067, 2927, 2857, 2184, 1579, 1394.

HRMS (GC/MS solid probe) cacld for $C_{30}H_{24}Br_2$ [M^+] *m*/*z* 544.0224, found [M^+] 544.0303.

mp: 168–172 °C.

Synthesis of 1,5-dibromo-9,10-bis(o-tolylethynyl)anthracene ***5.95b***



Prepared from 2.0 mmol of quinone according to Procedure I; 90% yield; orangish red solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.01 (dd, *J* = 9.0, 1.0 Hz, 2H), 7.98 (dd, *J* = 7.5, 1.0 Hz, 2H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.40 (dd, *J* = 9.0, 7.5 Hz, 2H), 7.33-7.31 (m, 4H), 7.29-7.26 (m, 2H), 2.68 (s, 6H).

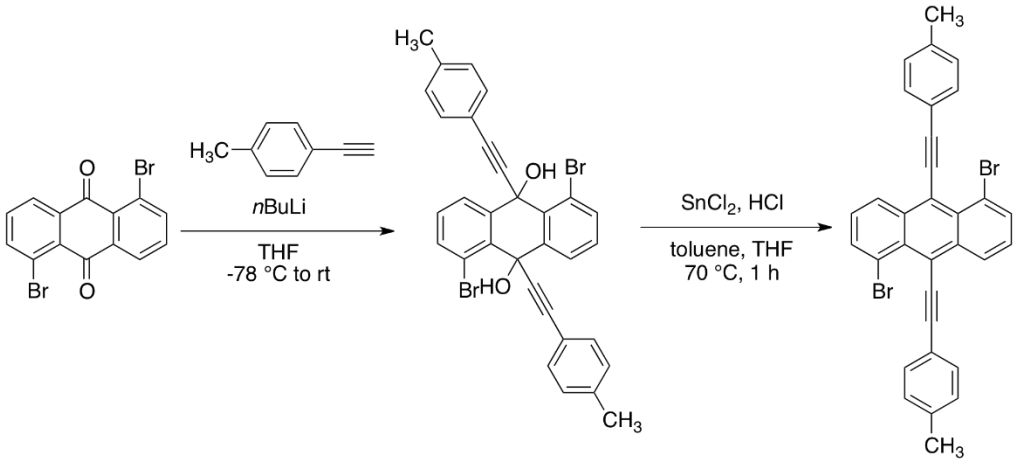
^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.1, 135.8, 135.0, 131.4, 129.8, 129.6, 128.9, 128.1, 126.9, 125.8, 123.6, 120.6, 119.6, 108.7, 91.8, 21.3.

IR (neat, cm^{-1}) 3068, 3018, 2972, 2920, 2181,1608, 1486, 1456, 1386, 1376.

HRMS (GC/MS solid probe) cacld for $C_{32}H_{20}Br_2$ [M^+] *m*/*z* 563.9911, found [M^+] 563.9905.

mp: 110–116 °C.

Synthesis of 1,5-dibromo-9,10-bis(p-tolylethynyl)anthracene ***5.95c***



Prepared from 2.0 mmol of quinone according to Procedure I; 96% yield; orangish red solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.97 (dd, *J* = 9.0, 1.5 Hz, 2H), 7.98 (dd, *J* = 7.5, 1.0 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 4H), 7.40 (dd, *J* = 9.0, 7.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H).

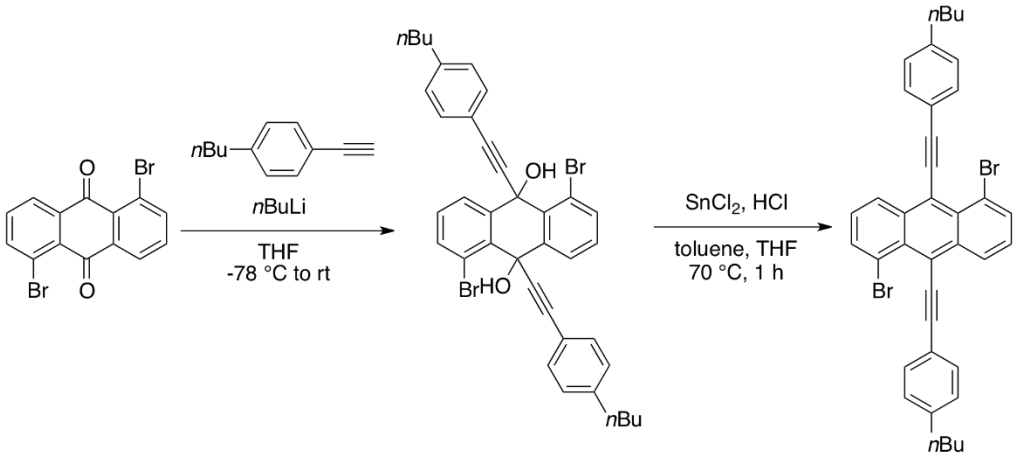
^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.2, 135.6, 135.0, 130.8, 129.6, 129.4, 128.2, 126.9, 120.7, 120.6, 119.3, 109.4, 87.9, 21.7.

IR (neat, cm^{-1}) 3039, 2914, 2190, 1606, 1506, 1392, 1376.

HRMS (GC/MS solid probe) cacld for $C_{32}H_{20}Br_2$ [M^+] *m*/*z* 563.9911, found [M^+] 563.9864.

mp: 211–215 °C.

Synthesis of 1,5-dibromo-9,10-bis((4-butylphenyl)ethynyl)anthracene ***5.95d***



Prepared from 2.0 mmol of quinone according to Procedure I; 90% yield; orangish red solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.97 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.98 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.66 (dd, *J* = 6.5, 1.5 Hz, 4H), 7.40 (dd, *J* = 8.5, 6.5 Hz, 2H), 7.26 (d, *J* = 6.5 Hz, 4H), 2.67 (t, *J* = 7.5 Hz, 4H), 1.67-1.60 (m, 4H), 1.41-1.36 (m, 4H), 0.95 (t, *J* = 7.5 Hz, 6H).

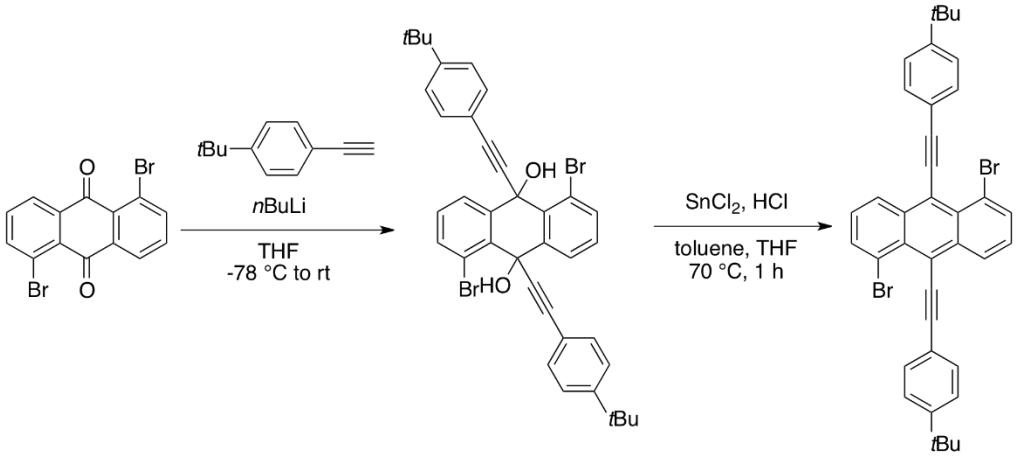
^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.2, 135.6, 135.0, 130.8, 129.5, 128.7, 128.2, 126.9, 120.9, 120.6, 119.3, 109.5, 88.0, 35.7, 33.4, 22.3, 14.0.

IR (neat, cm^{-1}) 3086, 3037, 2955, 2928, 2858, 1505, 1393, 1376.

LRMS (LDI) *m*/*z*, 647.9 [M^+].

mp: 120–124 °C.

Synthesis of 1,5-dibromo-9,10-bis((4-(tert-butyl)phenyl)ethynyl)anthracene ***5.95e***



Prepared from 2.0 mmol of quinone according to Procedure I; 91% yield; orangish red solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.97 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.98 (dd, *J* = 7.5, 1.0 Hz, 2H), 7.68 (dd, *J* = 6.5, 2.0 Hz, 4H), 7.47 (dd, *J* = 6.5, 2.0 Hz, 4H), 7.40 (dd, *J* = 9.0, 7.5 Hz, 2H), 1.37 (s, 18H).

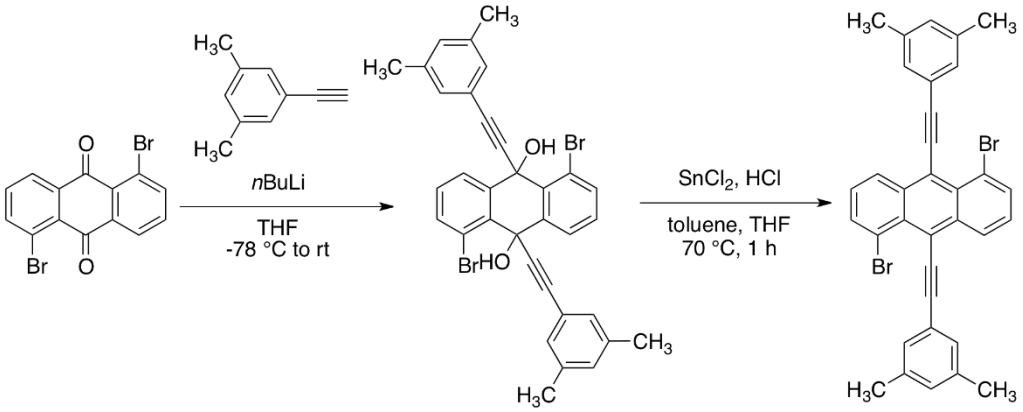
^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.3, 135.6, 135.0, 130.7, 129.6, 128.2, 126.9, 125.6, 120.7, 120.7, 119.3, 109.4, 87.9, 34.9, 31.2.

IR (neat, cm^{-1}) 3089, 2961, 2866, 2186, 1502, 1392, 1376, 1360, 1273.

LRMS (LDI) *m*/*z*, 647.9 [M^+].

mp: 218–223 °C.

Synthesis of 1,5-dibromo-9,10-bis((3,5-dimethylphenyl)ethynyl)anthracene ***5.95f***



Prepared from 2.0 mmol of quinone according to Procedure I; 78% yield; orangish red solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.01 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.98 (dd, *J* = 7.0, 1.5 Hz, 2H), 7.42 (dd, *J* = 8.5, 7.0 Hz, 2H), 7.37 (s, 4H), 7.06 (s, 2H), 2.38 (s, 12H).

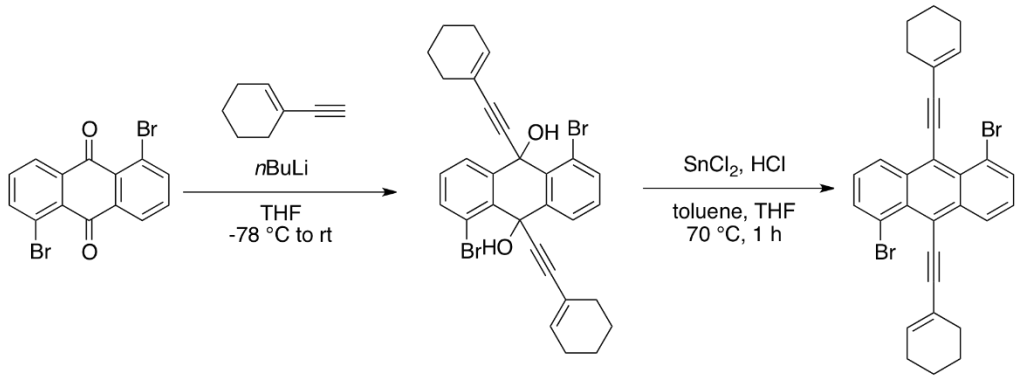
^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.2, 135.7, 135.0, 130.9, 129.6, 128.5, 128.2, 126.9, 123.4, 120.7, 119.3, 109.6, 87.8, 21.2.

IR (neat, cm^{-1}) 3033, 2913, 2858, 2187, 1607, 1596, 1471, 1395, 1383, 1294.

HRMS (GC/MS solid probe) cacld for $C_{34}H_{24}Br_2$ [M^+] *m*/*z* 592.0224, found [M^+] 592.0202.

mp: 215–222 °C.

Synthesis of 1,5-dibromo-9,10-bis(cyclohex-1-en-1-ylethynyl)anthracene ***5.95j***



Prepared from 2.0 mmol of quinone according to Procedure I; 91% yield; orangish red solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.80 (dd, *J* = 8.8, 1.2 Hz, 2H), 7.90 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.32 (dd, *J* = 8.8, 7.2 Hz, 2H), 6.49-6.39 (m, 2H), 2.46-2.39 (m, 4H), 2.28-2.20 (m, 4H), 1.80-1.73 (m, 4H), 1.73-1.65 (m, 4H).

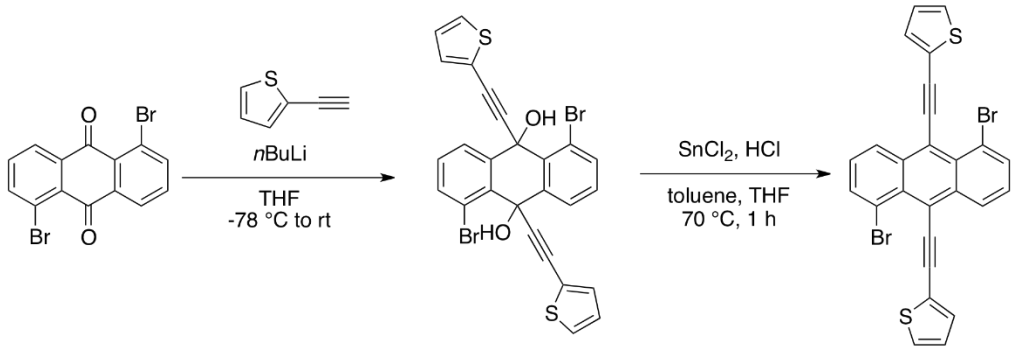
^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.7, 135.5, 134.7, 129.4, 128.2, 126.6, 121.8, 120.7, 119.3, 111.2, 86.2, 28.2, 26.0, 22.3, 21.6.

IR (neat, cm^{-1}) 2925, 2857, 2825, 2181, 1605, 1444, 1432, 1395, 1346.

HRMS (GC/MS solid probe) cacld for $C_{30}H_{24}Br_2$ [M^+] *m*/*z* 544.0224, found [M^+] 544.0222.

mp: 181–185 °C.

Synthesis of 2,2'-((1,5-dibromoanthracene-9,10-diyl)bis(ethyne-2,1-diyl))dithiophene ***5.95k***



Prepared from 2.0 mmol of quinone according to Procedure I; 95% yield; dark red solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.89 (dd, *J* = 8.8, 1.2 Hz, 2H), 7.99 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.49 (dd, *J* = 3.7, 1.1 Hz, 2H), 7.46-7.38 (m, 4H), 7.13 (dd, *J* = 5.1, 3.6 Hz, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 135.3, 135.2, 131.7, 129.5, 128.3, 128.0, 127.4, 127.1, 123.7, 120.7, 119.0, 103.2, 92.6.

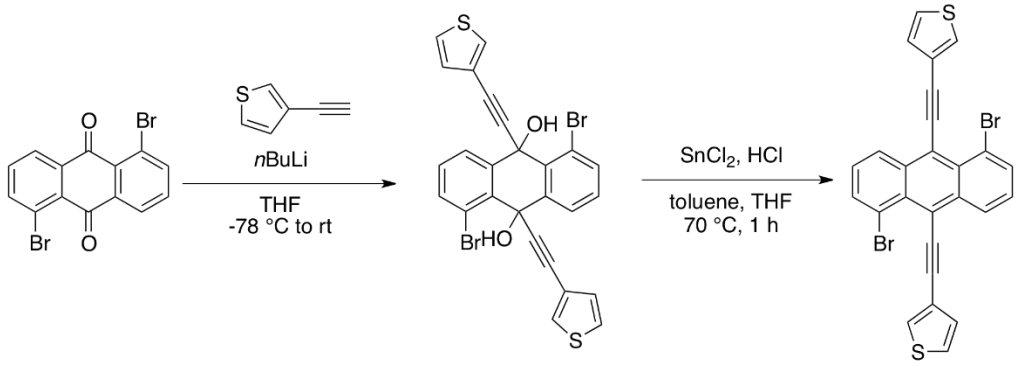
IR (neat, cm^{-1}) 3090, 2170, 1604, 1505, 1434, 1378, 1333, 1219.

LRMS (LDI) *m*/*z*, 547.7 [M^+].

mp: 198–203 °C.

Procedure III

Synthesis of 3,3'-((1,5-dibromoanthracene-9,10-diyl)bis(ethyne-2,1-diyl))dithiophene ***5.95l***



To a 100 mL flame-dried round bottom flask were added 3-ethynylthiophene (691 mg, 6.4 mmol), and dry THF (16 mL) under N_2. The mixture was cooled to -78 °C and *n*BuLi (2.5 M in hexanes, 2.4 mL, 6.0 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 1h before the addition of quinone (732 mg, 2.0 mmol) in one portion. The mixture was allowed to warm up to room temperature and stirred overnight. To the mixture was added toluene (16 mL). A solution of $SnCl_2$ (2.28 g, 12 mmol) in 4M HCl (8 mL) was added to the above mixture. The resulting mixture was stirred at 60 °C for 1h before cooling to room temperature. The volatiles were removed *in vacuo*. The residue filtered and washed with H_2O (50 mL), MeOH (50 mL), CH_2Cl_2 (20 mL) and MeOH (20 mL) to afford the product as an orangish red solid (956 mg, 87%)

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.98 (dd, *J* = 9.0, 1.0 Hz, 2H), 7.99 (dd, *J* = 7.5, 1.0 Hz, 2H), 7.75 (t, *J* = 2.0 Hz, 2H), 7.43-7.39 (m, 6H).

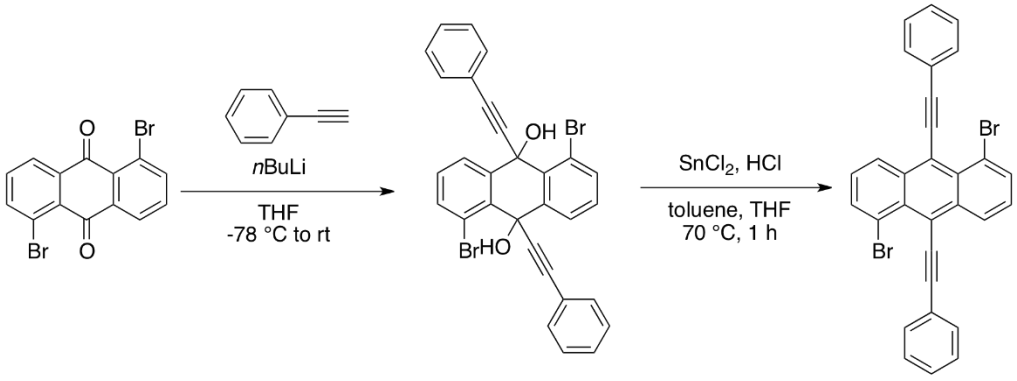
^{13}C NMR ($CDCl_3$, 126 MHz) δ 135.1, 129.7, 129.1, 128.7, 128.2, 128.2, 127.5, 127.0, 125.8, 122.9, 120.6. Not all carbon signals were observed due to poor solubility.

IR (neat, cm^{-1}) 3100, 3043, 2189, 1607, 1584, 1505, 1410, 1377, 1361, 1336, 1214.

LRMS (LDI) *m*/*z*, 547.7 [M^+].

mp: 224–229 °C.

Synthesis of 1,5-dibromo-9,10-bis(phenylethynyl)anthracene ***5.95a***



Prepared from 2.0 mmol of quinone according to Procedure I; 94% yield; orangish red solid;

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.98 (dd, *J* = 9.0, 1.5 Hz, 2H), 8.00 (dd, *J* = 7.0, 1.0 Hz, 2H), 7.76-7.74 (m, 4H), 7.48-7.40 (m, 8H).

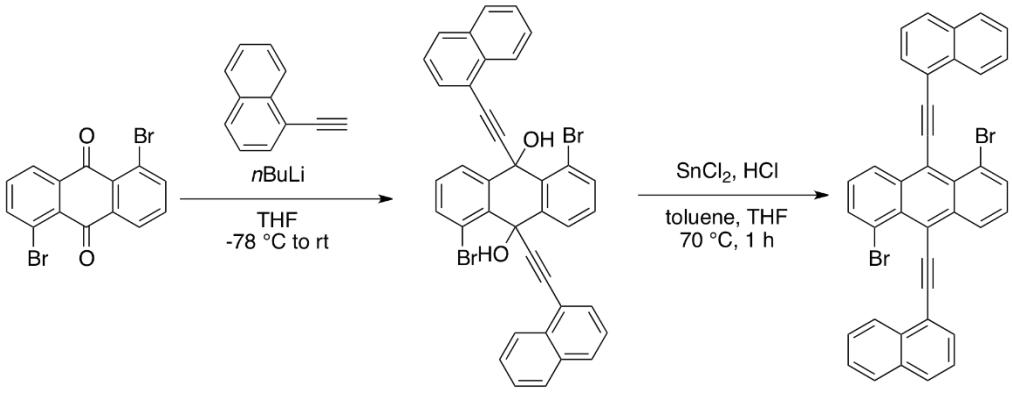
^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.7, 135.1, 130.9, 129.7, 128.9, 128.6, 128.1, 127.0, 123.7, 120.6, 119.3, 109.2, 88.4.

IR (neat, cm^{-1}) 3053, 2926, 2192, 1606, 1593, 1489, 1438, 1391, 1376.

LRMS (LDI) *m*/*z*, 535.8 [M^+].

mp: 213–218 °C.

Synthesis of 1,5-dibromo-9,10-bis(naphthalen-1-ylethynyl)anthracene ***5.95i***



Prepared from 2.0 mmol of quinone according to Procedure III; 88% yield; orangish red solid;

^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.16 (d, *J* = 8.5 Hz, 2H), 8.64 (d, *J* = 8.5 Hz, 2H), 8.04 (d, *J* = 7.0 Hz, 2H), 8.00 (d, *J* = 6.5 Hz, 2H), 7.94-7.92 (m, 4H), 7.73-7.67 (m, 2H), 7.61-7.55 (m, 4H), 7.47 (dd, *J* = 9.0, 7.0 Hz, 2H).

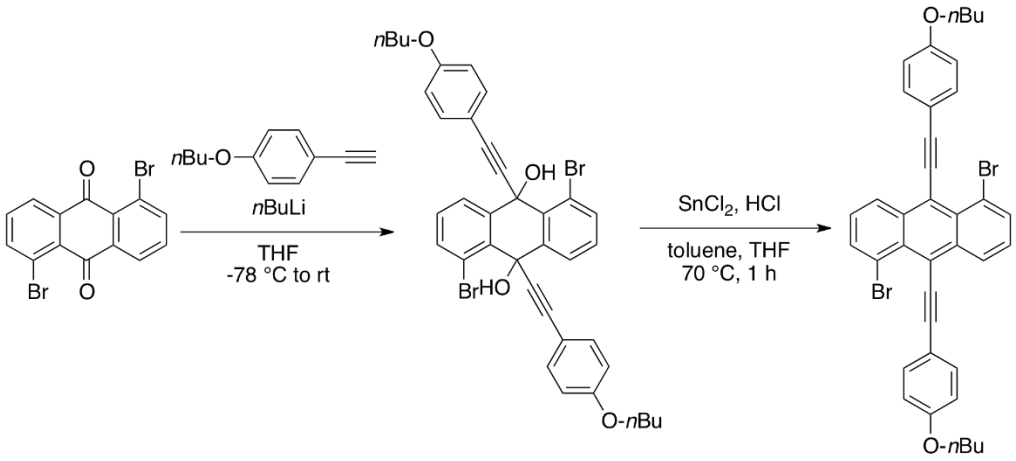
^{13}C NMR ($CDCl_3$, 126 MHz) δ 136.0, 135.2, 133.4, 133.2, 130.2, 129.3, 128.5, 128.3, 127.2, 127.1, 126.6, 126.5, 125.5, 121.5, 120.8, 119.7, 108.2, 92.8. Not all carbon signals were found (one aromatic carbon signal missing).

IR (neat, cm^{-1}) 3042, 2188, 1608, 1584, 1575, 1505, 1462, 1409, 1377, 1214.

LRMS (LDI) *m*/*z*, 635.8 [M^+].

mp: 209–213 °C.

Synthesis of 1,5-dibromo-9,10-bis((4-butoxyphenyl)ethynyl)anthracene ***5.95g***



Prepared from 2.0 mmol of quinone according to Procedure I; 93% yield; orangish red solid;

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.97 (dd, *J* = 9.0, 1.0 Hz, 2H), 7.97 (dd, *J* = 7.5, 1.0 Hz, 2H), 7.67 (dd, *J* = 7.5, 2.0 Hz, 4H), 7.40 (dd, *J* = 9.0, 7.5 Hz, 2H), 6.96 (dd, *J* = 7.0,

2.0 Hz, 4H), 4.03 (t, *J* = 6.5 Hz, 4H), 1.83-1.79 (m, 4H), 1.55-1.49 (m, 6H), 1.00 (t, *J* = 7.5 Hz, 6H).

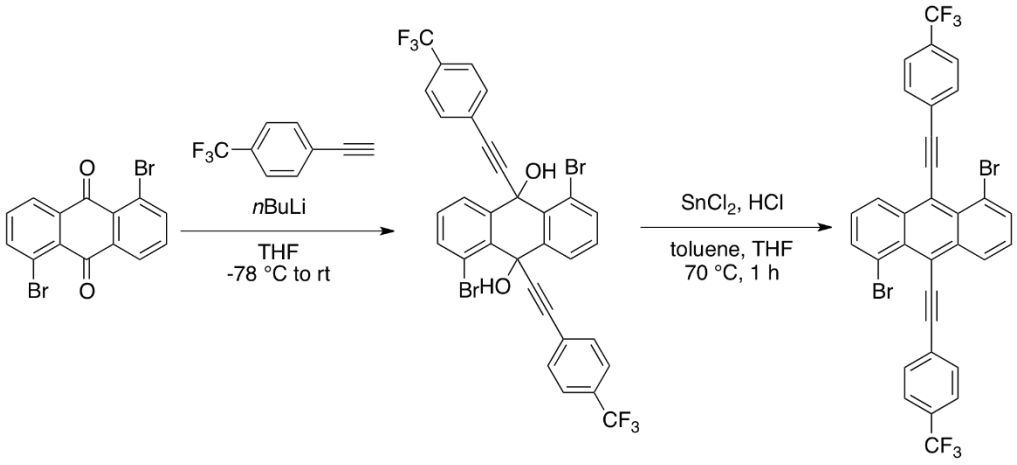
^{13}C NMR ($CDCl_3$, 126 MHz) δ 159.8, 135.6, 134.9, 132.4, 129.5, 128.2, 126.8, 120.7, 119.3, 115.7, 114.8, 109.5, 87.5, 67.9, 31.3, 19.3, 13.9.

IR (neat, cm^{-1}) 3091, 3063, 2953, 2868, 2189, 1601, 1507, 1448, 1395, 1375, 1288, 1246.

LRMS (LDI) *m*/*z*, 680.0 [M^+].

mp: 180–186 °C.

Synthesis of 1,5-dibromo-9,10-bis((4-(trifluoromethyl)phenyl)ethynyl)anthracene ***5.95h***



Prepared from 2.0 mmol of quinone according to Procedure III; 82% yield; orangish red solid;

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.94 (dd, *J* = 9.0, 1.5 Hz, 2H), 8.03 (dd, *J* = 7.5, 1.0 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 4H), 7.71 (*J* = 8.0 Hz, 4H), 7.46 (dd, *J* = 9.0, 7.5 Hz, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 135.7, 135.5, 131.1, 130.7, 129.9, 127.9, 127.4, 125.6, 120.5, 119.2. Not all carbon signals were observed due to poor signal to noise ratio.

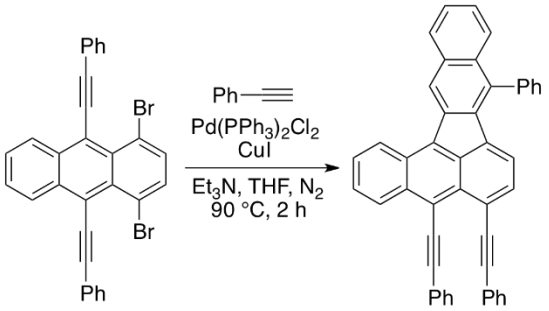
^{19}F NMR ($CDCl_3$, 470 MHz) δ -65.99.

IR (neat, cm^{-1}) 3095, 2925, 2191, 1608, 1568, 1405, 1393, 1318.

HRMS (GC/MS solid probe) cacld for $C_{32}H_{14}Br_2F_6$ [M^+] *m*/*z* 671.9346, found [M^+] 671.9349.

mp: 243–247 °C.

Synthesis of 9-phenyl-5,6-bis(phenylethynyl)naphtho[2,3-a]aceanthrylene ***5.88a***



A 100 mL flame-dried Schlenk flask was evacuated and backfilled with N_2 three times. Dibromide (2107 mg, 0.2 mmol), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol), CuI (1 mg, 0.005 mmol), phenylacetylene (53 µL, 0.48 mmol), dry THF (2 mL) and dry Et_3N (2 mL) were added under N_2. The flask was sealed and the mixture was stirred at 90 °C for 2h before cooling to room temperature. The volatiles were removed *in vacuo*. The residue was purified by column chromatography on silica gel (25 mm x 200 mm, CH_2Cl_2/hexanes 1:6 to 1:5 to 1:2) to afford the product as a red solid (101 mg, 87%)

^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.05 (d, *J* = 8.5 Hz, 1H), 8.99 (d, *J* = 8.5 Hz, 1H), 8.87 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.82 (t, *J* = 7.5 Hz, 1H), 7.74-7.64 (m, 5H), 7.60-7.52 (m, 6H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.35-7.32 (m, 2H), 7.28-7.22 (m, 2H), 7.21-7.17 (m, 2H), 7.15-7.11 (m, 2H), 6.55 (d, *J* = 7.0 Hz, 1H).

^{13}C NMR (THF-*d*8, 125 MHz) δ 139.5, 138.6, 138.4, 137.3, 137.13, 137.09, 135.0, 134.8, 134.4, 134.3, 133.5, 132.9, 132.54, 132.51, 132.5, 130.7, 130.21, 130.17, 129.5, 129.23, 129.20, 129.0, 128.84, 128.81, 128.4, 127.7, 127.5, 127.3, 127.2, 125.6, 124.8, 124.6, 124.4, 122.5, 121.0, 119.0, 106.1, 98.1, 91.0, 88.7.

IR (neat, cm^{-1}) 3052, 2197, 1595, 1440, 1428, 1405.

HRMS (EI) cacld for $C_{46}H_{26}$ [M^+] *m*/*z* 578.2035, found [M^+] 578.2061.

mp: 230–238 °C.

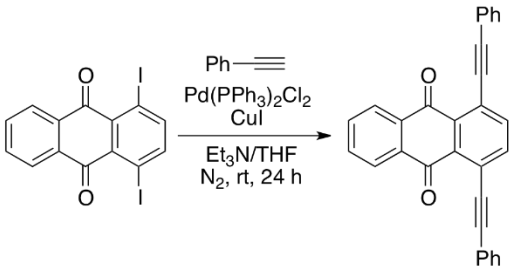
Synthesis of 1,4-diiodoanthracene-9,10-dione ***5.91***

To a 500 mL flame-dried round bottom flask were added dibromide (2.928 g, 8.0 mmol), CuI (15.24 g, 80 mmol), KI (39.84 g, 240 mmol) and dry 1,3-dimethyl-2-imidazolidinone (32 mL) under N_2. The mixture was stirred at 150 °C overnight under N_2. After cooling to room temperature, CH_2Cl_2 (160 mL) and brine (80 mL) was added to the mixture. After filtration via a Buchner funnel, the organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (40 mm x 250 mm, CH_2Cl_2/hexanes 1:3 to 1:2 to 1:1 to 2:1). The resulting solid was washed with hexanes to remove remaining DMI to afford the product as a yellow solid (2.23 g, 61%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.26 (dd, *J* = 6.0, 3.0 Hz, 2H), 7.99 (s, 2H), 7.80 (dd, *J* = 6.0, 3.0 Hz, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ 181.0, 147.9, 134.5, 134.3, 133.1, 127.1, 94.0.

Synthesis of 1,4-bis(phenylethynyl)anthracene-9,10-dione ***5.91'***

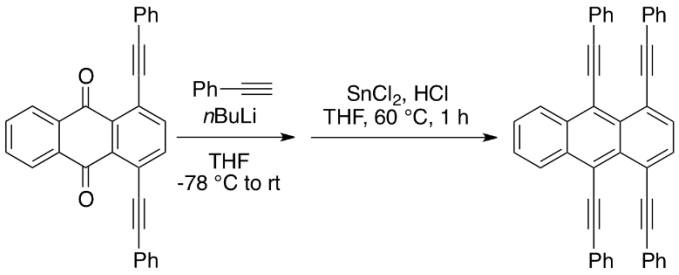


To a 250 mL flame-dried round bottom flask were added diiodide (2.30 g, 5.0 mmol), $Pd(PPh_3)_2Cl_2$ (176 mg, 0.25 mmol), CuI (48 mg, 0.25 mmol), dry THF (100 mL), dry Et_3N (25 mL) and phenylacetylene (1.32 mL, 12 mmol) under N_2. The mixture was stirred at room temperature for 24 h under N_2. The volatiles were removed *in vacuo*. The residue was purified by column chromatography (1st column on silica gel, 40 mm x 250 mm, CH_2Cl_2/hexanes 1:2 to 1:1; 2nd column on neutral Al_2O_3, 40 mm x 150 mm, CH_2Cl_2/hexanes 1:1) to afford the product as a yellow solid (1.49 g, 73%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.33 (dd, *J* = 6.0, 3.0 Hz, 2H), 7.91 (s, 2H), 7.80 (dd, *J* = 6.0, 3.0 Hz, 2H), 7.74-7.72 (m, 4H), 7.44-7.40 (m, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ 181.9, 138.7, 134.4, 133.9, 133.3, 132.2, 129.0, 128.4, 127.1, 123.4, 123.1, 97.5, 89.5.

Synthesis of 1,4,9,10-tetrakis(phenylethynyl)anthracene ***5.90***



To a 50 mL flame-dried round bottom flask were added phenylacetylene (0.34 mL, 3.1 mmol), and dry THF (6 mL) under N_2. The mixture was cooled to -78 °C and *n*BuLi (2.5 M in hexanes, 1.2 mL, 3.0 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 1h before the addition of quinone (241 mg, 0.59 mmol) in one portion. The mixture was allowed to warm up to room temperature and stirred overnight. NH_4Cl (sat. aq. 6 mL) was added to the mixture. The volatiles were removed *in vacuo*. The residue was partitioned between CH_2Cl_2 (12 mL) and H_2O (6 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (20 mm x 250 mm, CH_2Cl_2/hexanes 1:1 to 2:1 to 4:1) to afford the diols (249 mg, 0.407 mmol) that were used in the next step.

To the 50 mL round bottom flask containing the purified diols (249 mg, 0.407 mmol) was added THF (5 mL). A solution of $SnCl_2$ (1.88 g, 3.3 mmol) in 6M HCl (5 mL) was added to the above mixture. The resulting mixture was stirred at 60 °C for 1h before cooling to room temperature. H_2O (66 mL) was added to the mixture. After filtration, the crude product was dissolved in CH_2Cl_2, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (20 mm x 250 mm,

CH_2Cl_2/hexanes 1:10 to 1:8 to 1:4) to afford the product as a dark red solid (188 mg, 55% over two steps)

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.86 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.88 (s, 2H), 7.69 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.54-7.52 (m, 4H), 7.38-7.36 (m, 4H), 7.28-7.13 (m, 12H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ 134.4, 133.5, 131.6, 131.5, 130.9, 128.3, 128.1, 128.0, 127.9, 127.6, 127.4, 123.7, 123.6, 122.1, 119.1, 107.4, 99.9, 90.9, 88.2.

IR (neat, cm^{-1}) 3052, 2927, 2190, 1595, 1441, 1399.

LRMS (LDI) *m*/*z*, 578.1 [M^+].

Procedure IV

General synthetic procedures for one-pot Sonogashira cross-coupling

The reactions were performed in a N_2-filled glovebox following the general procedure described below. To a 4-mL reaction vial was added dibromide substrate (0.1 mmol), $Pd(PPh_3)_2Cl_2$ (2.8 mg, 0.004 mmol), AgOAc (0.7 mg, 0.004 mmol), phenylacetylene (25 mg, 0.24 mmol), freshly distilled THF (2 mL) and Et_3N (1 mL). The vial was then sealed and heated to 90 °C for 12 hours before cooling to room temperature. The crude solution was mixed with 10 mL of methanol and was sonicated for 2 minutes. The resulting mixture was then vacuum filtered and washed with methanol (10 mL × 2) and diethyl ether (5 mL × 2). The product was collected as dark red solid with good purity.

Further purification methods such as recrystallization and column chromatography were not applied unless otherwise noted.

13-methyl-9-phenyl-6-(phenylethynyl)-5-(o-tolylethynyl)naphtho[2,3-a]aceanthrylene ***5.89b***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a red solid (92%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.05−9.00 (m, 3H), 7.86−7.80 (m, 1H), 7.73−7.61 (m, 5H), 7.59−7.49 (m, 4H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.41 (d, *J* = 6.8 Hz, 1H), 7.32 (dd, *J*= 8.2 Hz, 7.0 Hz, 1H), 7.23−7.11 (m, 5H), 7.07−7.01 (m, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.3, 138.8, 137.6, 136.7, 136.5, 136.1, 135.2, 133.83, 133.76, 132.6, 132.3, 132.1, 131.5, 129.8, 129.4, 129.2, 129.1, 128.5, 128.4, 128.3, 128.1, 127.81, 127.78, 127.5, 126.6, 125.9, 125.41, 125.38, 124.4, 123.70, 123.65, 121.7, 120.3, 120.1, 119.2, 118.5, 104.1, 97.4, 91.4, 90.5, 21.0, 20.2.

IR (neat, cm^{-1}) 3054, 2920, 1595, 1489, 1440.

LRMS (LDI) *m*/*z*, 606.1 [M^+].

11-methyl-9-phenyl-6-(phenylethynyl)-5-(p-tolylethynyl)naphtho[2,3-a]aceanthrylene ***5.89c***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a red solid (95%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.98 (d, *J* = 9.2 Hz, 1H), 8.95 (d, *J* = 9.2 Hz, 1H), 8.76 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.79−7.73 (m, 1H), 7.71−7.61 (m, 5H), 7.51 (dd, *J*= 7.6 Hz, 1.2 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.39−7.30 (m, 4H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.19−7.11 (m, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.47 (d, *J* = 7.2 Hz, 1H), 2.44 (s, 3H), 2.34 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.6, 138.4, 137.7, 137.0, 136.5, 136.3, 136.1, 135.5, 134.3, 133.6, 132.6, 131.83, 131.78, 131.70, 131.65, 129.9, 129.3, 129.0, 128.9, 128.8, 128.5, 128.2, 128.0, 127.9, 127.7, 127.60, 127.56, 126.5, 125.9, 124.5, 123.9, 122.9, 121.6, 120.6, 119.9, 118.1, 105.3, 97.0, 90.5, 87.5, 22.0, 21.5.

IR (neat, cm^{-1}) 3048, 2916, 1596, 1509, 1491, 1441, 1403, 1364.

LRMS (LDI) *m*/*z*, 606.1 [M^+].

11-butyl-5-((4-butylphenyl)ethynyl)-9-phenyl-6-(phenylethynyl)naphtho[2,3-a]aceanthrylene ***5.89d***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a red solid (98%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.02 (d, *J* = 8.8 Hz, 1H), 8.97 (d, *J* = 8.4 Hz, 1H), 8.81 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.79 (dd, *J* = 8.0, 6.8 Hz, 1H), 7.73−7.61 (m, 4H), 7.53 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.49−7.30 (m, 7H), 7.23−7.17 (m, 1H), 7.15−7.10 (m, 1H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.49 (d, *J* = 8.0 Hz, 1H), 2.69 (t, *J* = 8.0 Hz, 2H), 2.59 (t, *J* = 8.0 Hz, 2H), 1.69−1.48 (m, 4H), 1.36 (sext, *J* = 7.2 Hz, 4H), 0.96 (t, *J* = 7.6 Hz, 3H), 0.91 (t, *J* = 7.6 Hz, 3H).

IR (neat, cm^{-1}) 3050, 2955, 2925, 2854, 1440.

LRMS (LDI) *m*/*z*, 690.2 [M^+].

mp: 161–167 °C.

11-(tert-butyl)-5-((4-(tert-butyl)phenyl)ethynyl)-9-phenyl-6-(phenylethynyl)naphtho[2,3-a]aceanthrylene ***5.89e***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a red solid (98%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.04 (d, *J* = 8.6 Hz, 1H), 8.97 (d, *J* = 8.9 Hz, 1H), 8.82 (s, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.82 (d, *J* = 1.3 Hz, 1H), 7.72 – 7.60 (m, 7H), 7.56 – 7.51 (m, 2H), 7.49 – 7.45 (m, 2H), 7.32 – 7.28 (m, 2H), 7.23 – 7.15 (m, 3H), 7.11 – 7.06 (m, 2H), 6.54 (d, *J* = 7.3 Hz, 1H), 1.31 (s, 18H).

IR (neat, cm^{-1}) 3055, 2959, 2865, 1597, 1505, 1491.

LRMS (LDI) *m*/*z*, 690.2 [M^+].

mp: 220–225 °C.

5-((3,5-dimethylphenyl)ethynyl)-10,12-dimethyl-9-phenyl-6-(phenylethynyl)naphtho[2,3-a]aceanthrylene ***5.89f***

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.03–8.95 (m, 2H), 8.76 (s, 1H), 7.82–7.67 (m, 3H), 7.58 (m, 6H), 7.39 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.24−7.22 (m, 1H), 7.19–7.13 (m, 4H), 7.07 (s, 1H), 6.89 (s, 1H), 6.01 (d, *J* = 7.4 Hz, 1H), 2.51 (s, 3H), 2.13 (s, 6H), 2.07 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.6, 138.4, 137.6, 137.0, 136.8, 136.7, 136.5, 136.0, 135.7, 135.4, 135.1, 133.7, 132.9, 131.7, 131.3, 130.2, 129.9, 129.5, 128.83, 128.79, 128.6, 128.4, 128.2, 128.1, 127.9, 127.8, 127.51, 127.47, 126.4, 124.5, 124.0, 123.9, 123.2, 121.8, 119.6, 118.1, 105.6, 96.9, 90.5, 87.5, 25.2, 21.2, 21.0.

IR (neat, cm^{-1}) 3024, 2914, 2863, 1596, 1442.

LRMS (LDI) *m*/*z*, 634.1 [M^+].

mp: 168–174 °C.

11-methoxy-5-((4-methoxyphenyl)ethynyl)-9-phenyl-6-(phenylethynyl)naphtho[2,3-a]aceanthrylene ***5.89g***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a dark red solid (98%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.98 (d, *J* = 8.8 Hz, 1H), 8.95 (d, *J* = 8.8 Hz, 1H), 8.76 (s, 1H), 7.97 (d, *J* = 8.9 Hz, 1H), 7.80 – 7.74 (m, 1H), 7.70 – 7.61 (m, 5H), 7.54 – 7.50 (m, 2H), 7.47 – 7.43 (m, 2H), 7.38 – 7.33 (m, 2H), 7.24 – 7.12 (m, 4H), 6.88 (d, *J* = 2.5 Hz, 1H), 6.73 – 6.68 (m, 2H), 6.50 (d, *J* = 7.3 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.6, 158.2, 138.5, 137.7, 136.4, 135.8, 135.0, 134.7, 133.7, 133.3, 133.2, 131.8, 131.7, 130.6, 129.8, 129.4, 128.88, 128.87, 128.1, 127.98, 127.95, 127.8, 127.6, 127.5, 126.4, 124.5, 123.9, 122.9, 121.7, 120.0, 118.00, 117.95, 113.7, 106.2, 105.1, 97.0, 90.5, 87.0, 55.3, 55.2.

IR (neat, cm^{-1}) 3058, 2950, 2926, 2830, 1614, 1604, 1507, 1462, 1430.

LRMS (LDI) *m*/*z*, 638.1 [M^{+}].

11-butoxy-5-((4-butoxyphenyl)ethynyl)-9-phenyl-6-(phenylethynyl)naphtho[2,3-a]aceanthrylene ***5.89h***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a red solid (99%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.93 (s, 1H), 8.91 (s, 1H), 8.69 (s, 1H), 7.92 (d, *J* = 8.9 Hz, 1H), 7.74 – 7.69 (m, 1H), 7.68−7.59 (m, 5H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.42 (d, *J* =

8.7 Hz, 2H), 7.36 (d, *J* = 6.9 Hz, 2H), 7.21 (d, *J* = 7.3 Hz, 2H), 7.19−7.11 (m, 3H), 6.85 (d, *J* = 2.3 Hz, 1H), 6.68 (d, *J* = 8.7 Hz, 2H), 6.46 (d, *J* = 7.3 Hz, 1H), 3.93 (t, *J* = 6.5 Hz, 2H), 3.87 (t, *J* = 6.4 Hz, 2H), 1.82−1.66 (m, 4H), 1.57−1.38 (m, 4H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.3, 157.7, 138.6, 137.7, 136.4, 136.1, 135.7, 134.9, 134.7, 133.8, 133.3, 133.2, 131.8, 131.7, 130.6, 129.8, 129.4, 128.9,128.8, 128.1, 128.1, 128.0, 127.8, 127.5, 127., 126.40, 124.5, 124.0, 122.9, 121.6, 120.0, 118.2, 118.0, 115.7, 114.3, 107.1, 105.2, 97.0, 90.6, 86.9, 67.8, 67.6, 31.25, 31.22, 19.29, 19.25, 13.89, 13.88.

IR (neat, cm^{-1}) 3056, 2953, 2927, 2871, 2189, 1603, 1491, 1440, 1244, 1218.

LRMS (LDI) *m*/*z*, 722.2 [M^+].

9-phenyl-6-(phenylethynyl)-11-(trifluoromethyl)-5-((4-(trifluoromethyl)phenyl)ethynyl)naphtho-[2,3-a]aceanthrylene ***5.89i***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a red solid (72%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.99 (d, *J* = 8.6 Hz, 1H), 8.91 (d, *J* = 8.7 Hz, 1H), 8.86 (s, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.88 (s, 1H), 7.83 (t, *J* = 7.1 Hz, 1H), 7.75 – 7.69 (m,

6H), 7.58 (d, *J* = 8.1 Hz, 2H), 7.53 (dd, *J* = 7.2, 2.1 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.33 – 7.30 (m, 2H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 2H), 6.56 (d, *J* = 7.3 Hz, 1H).

IR (neat, cm^{-1}) 3066, 2923, 2851, 1613, 1490, 1322, 1106.

LRMS (LDI) *m*/*z*, 714.1 [M^+].

9-phenyl-6-(phenylethynyl)-5-(thiophen-2-ylethynyl)benzo[5,6]fluorantheno[8,9-b]thiophene ***5.89l***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a red solid (96%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.91−8.87 (m, 3H), 7.79 – 7.75 (m, 1H), 7.70 – 7.66 (m, 2H), 7.64 – 7.57 (m, 5H), 7.43 – 7.39 (m, 3H), 7.25 – 7.18 (m, 4H), 7.11 (dd, *J* = 3.6, 1.0 Hz, 1H), 7.07 (d, *J* = 5.4 Hz, 1H), 6.88 (dd, *J* = 5.4, 3.6 Hz, 1H), 6.80 (d, *J* = 7.3 Hz, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 139.9, 139.1, 138.6, 137.4, 137.3, 136.3, 136.2, 134.0, 133.0, 132.4, 132.1, 132.0, 131.7, 129.3, 129.1, 128.9, 128.3, 128.2, 128.0, 127.94, 127.88, 127.7, 127.5, 127.0, 126.7, 126.7, 124.4, 124.0, 123.8, 123.7, 121.8, 120.1, 117.8, 117.4, 98.3, 97.3, 91.8, 90.1.

IR (neat, cm^{-1}) 3052, 2182, 1594, 1490.

LRMS (LDI) *m*/*z*, 590.0 [M^+].

5-(cyclohex-1-en-1-ylethynyl)-9-phenyl-6-(phenylethynyl)-10,11,12,13-tetrahydronaphtho[2,3-a]aceanthrylene ***5.89k***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a red solid (98%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.80 (dd, *J* = 8.6, 4.5 Hz, 2H), 8.10 (s, 1H), 7.69 (ddd, *J* = 8.5, 6.6, 1.3 Hz, 1H), 7.63 – 7.54 (m, 6H), 7.54 – 7.49 (m, 1H), 7.39 – 7.29 (m, 5H), 6.31 (d, *J* = 7.2 Hz, 1H), 6.19 (tt, *J* = 4.1, 1.8 Hz, 1H), 3.05 (t, *J* = 6.3 Hz, 2H), 2.50 (t, *J* = 6.3 Hz, 2H), 2.25 – 2.16 (m, 2H), 2.00 – 1.93 (m, 2H), 1.91 – 1.83 (m, 2H), 1.83 – 1.73 (m, 2H), 1.53 – 1.44 (m, 4H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 139.8, 138.6, 137.9, 137.6, 137.4, 136.0, 135.9, 135.8, 134.5, 134.3, 131.8, 131.5, 130.8, 129.1, 129.0, 128.9, 128.6, 128.0, 127.9, 127.49, 127.45, 127.3, 126.1, 124.4, 124.29, 124.28, 122.0, 121.3, 120.0, 118.9, 107.1, 96.6, 90.5, 85.4, 31.0, 29.1, 27.9, 25.8, 23.4, 23.1, 22.2, 21.4.

IR (neat, cm^{-1}) 3053, 2925, 2855, 2184, 1596, 1491, 1442.

LRMS (LDI) *m*/*z*, 586.2 [M^+].

mp: 282–290 °C.

9-phenyl-6-(phenylethynyl)-5-(thiophen-3-ylethynyl)benzo[1,2]fluoranthe no[8,9-b]thiophene ***5.89m***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a red solid (93%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.96−8.84 (m, 2H), 8.76 (s, 1H), 7.79−7.58 (m, 8H), 7.54 (d, *J* = 4.8 Hz, 1H), 7.48 (d, *J* = 4.8 Hz, 1H), 7.43−7.32 (m, 4H), 7.25−7.12 (m, 4H), 6.84 (d, *J* = 7.2 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.9, 139.5, 138.0, 137.2, 136.2, 131.6, 130.0, 129.4, 129.0, 129.0, 128.9, 128.7, 128.3, 128.1, 128.0, 127.7, 126.5, 126.5, 125.2, 124.4, 123.8, 122.8, 121.7, 120.1, 118.3, 105.1, 100.2, 90.4, 87.4. Not all the carbon signals were observed due to low solubility.

IR (neat, cm^{-1}) 3053, 1490, 1442, 1364.

LRMS (LDI) *m*/*z*, 590.0 [M^+].

5-(naphthalen-1-ylethynyl)-9-phenyl-6-(phenylethynyl)phenanthro[3,2-a]aceanthrylene ***5.89j***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a red solid (97%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.73 (s, 1H), 9.14 (d, *J* = 8.7 Hz, 1H), 9.10 (d, *J* = 8.7 Hz, 1H), 8.98 (d, *J* = 8.4 Hz, 1H), 8.66 (d, *J* = 7.5 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.89−7.76 (m, 5H), 7.73−7.64 (m, 7H), 7.57−7.45 (m, 5H), 7.29−7.25 (m, 1H), 7.08−7.03 (m, 2H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.84 (t, *J* = 7.7 Hz, 2H), 6.56 (d, *J* = 7.3 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.8, 138.2, 137.4, 136.6, 136.5, 136.3, 134.9, 133.3, 133.2, 133.0, 132.2, 132.1, 131.3, 130.8, 130.8, 130.5, 130.1, 129.9, 129.3, 129.1, 128.8, 128.7, 128.6, 128.11, 128.07, 128.0, 127.7, 127.6, 127.5, 127.0, 126.9, 126.8, 126.7, 126.3, 125.1, 125.0, 124.5, 123.5, 122.9, 122.3, 121.4, 120.5, 118.6, 117.7, 103.4, 97.5, 92.5, 90.3. Not all the carbon signals were resolved.

IR (neat, cm^{-1}) 3058, 1613, 1600, 1582, 1413.

LRMS (LDI) *m*/*z*, 678.1 [M^+].

4,13-diphenyldibenzo[g,s]rubicene ***5.96a***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a red solid (83%).

^{1}H NMR (THF-d_8, 400 MHz) δ 8.98 (s, 2H), 8.87 (d, *J* = 8.6 Hz, 2H) 8.12 (d, *J* = 7.9 Hz, 2H), 7.74−7.47 (m, 12H), 7.42−7.36 (m, 2H), 6.74 (d, *J* = 7.0 Hz, 2H).

IR (neat, cm^{-1}) 3048, 1597, 1443.

LRMS (LDI) *m*/*z*, 578.0 [M^+].

8,17-dimethyl-4,13-diphenyldibenzo[g,s]rubicene ***5.96b***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a red solid (70%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.97 (s, 2H), 8.71 (d, *J* = 8.8 Hz, 2H), 7.75−7.64 (m, 6H), 7.61−7.54 (m, 6H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* =7.2 Hz, 2H), 7.36−7.28 (m, 2H), 6.69 (d, *J* = 7.2 Hz, 2H), 2.97 (s, 6H).

IR (neat, cm^{-1}) 3034, 2920, 2850, 1441, 1373, 1329.

LRMS (LDI) *m*/*z*, 606.1 [M^+].

6,15-dimethyl-4,13-diphenyldibenzo[g,s]rubicene ***5.96c***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a red solid (89%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.75 (s, 2H), 8.72 (d, *J* = 8.4 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.74−7.62 (m, 6H), 7.59−7.53 (m, 6H), 7.39−7.32 (m, 4H), 6.64 (d, *J* = 7.2 Hz, 2H).

IR (neat, cm^{-1}) 3055, 3038, 2972, 2945, 2859, 1612, 1600, 1448, 1361, 1325, 1286.

LRMS (LDI) *m*/*z*, 606.1 [M^+].

6,15-dibutyl-4,13-diphenyldibenzo[g,s]rubicene ***5.96d***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a purple solid (90%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.74 (s, 2H), 8.71 (d, *J* = 8.4 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 2H), 7.74−7.63 (m, 6H), 7.60−7.49 (m, 6H), 7.39 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.33 (s, 2H), 6.64 (d, *J* = 7.2 Hz, 2H), 2.68 (t, *J* = 8.0 Hz, 4H), 1.66−1.56 (m, 4H), 1.36 (sext, *J* = 7.6 Hz, 4H), 0.91 (t, *J* = 7.2 Hz, 6H).

IR (neat, cm^{-1}) 3052, 2954, 2923, 2869, 2855, 1614, 1450, 1359, 1328.

LRMS (LDI) *m*/*z*, 690.1 [M^+].

mp: 348–356 °C.

6,15-di-tert-butyl-4,13-diphenyldibenzo[g,s]rubicene ***5.96e***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a red solid (86%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.74 (s, 2H), 8.72 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J* = 8.8 Hz, 2H), 7.72−7.51 (m, 16H), 6.69 (d, *J* = 6.8 Hz, 2H), 1.31 (s, 18H).

IR (neat, cm^{-1}) 3048, 2961, 2867, 1611, 1463, 1367, 1325, 1288, 1251.

LRMS (LDI) *m*/*z*, 690.1 [M^+].

5,7,14,16-tetramethyl-4,13-diphenyldibenzo[g,s]rubicene ***5.96f***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a red solid (89%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.68 (s, 2H), 8.64 (d, *J* = 8.8 Hz , 2H), 7.72 (s, 2H), 7.64−7.56 (m, 10H), 7.44 (dd, *J* = 8.4, 7.2 Hz, 2H), 7.05 (s, 2H), 6.16 (d, *J* = 6.8 Hz, 2H), 2.49 (s, 6H), 2.07 (s, 6H).

IR (neat, cm^{-1}) 3025, 2966, 2923, 2862, 1620, 1607, 1573, 1435, 1337, 1293.

LRMS (LDI) *m*/*z*, 634.1 [M^+].

6,15-dibutoxy-4,13-diphenyldibenzo[g,s]rubicene ***5.96g***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a red solid (89%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.70 (s, 2H), 8.69 (d, *J* = 8.8 Hz, 3H), 7.94 (d, *J* = 8.8 Hz, 2H), 7.72 – 7.61 (m, 6H), 7.56 (dd, *J* = 8.2, 1.8 Hz, 4H), 7.53 – 7.48 (m, 2H), 7.19 (dd, *J* = 8.8, 2.5 Hz, 2H), 6.89 (d, *J* = 2.5 Hz, 2H), 6.65 (d, *J* = 6.9 Hz, 2H), 3.90 (t, *J* = 6.4 Hz, 4H), 1.78 – 1.70 (m, 4H), 1.51 – 1.41 (m, 4H), 0.95 (t, *J* = 7.4 Hz, 6H).

IR (neat, cm^{-1}) 3056, 2956, 2929, 2868, 2183, 1612, 1506, 1446, 1210, 1174.

HRMS (ESI) cacld for $C_{54}H_{42}O_2$ [M^+] *m*/*z* 722.3185, found [M^+] 722.3186.

mp: 353–362 °C.

4,13-diphenyl-6,15-bis(trifluoromethyl)dibenzo[g,s]rubicene ***5.96h***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the crude product was purified via column chromatography (3:1 Hexanes/CH_2Cl_2) to afford the desired product as a red solid (42%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.82 (s, 2H), 8.74 (d, *J* = 8.8 Hz, 2H), 8.14 (d, *J* = 8.4 Hz, 2H), 7.87 (s, 2H), 7.76−7.67 (m, 8H), 7.60 (dd, *J* = 8.4, 7.2 Hz, 2H), 7.59−7.53 (m, 4H), 6.74 (d, *J* = 6.8 Hz, 2H).

^{19}F NMR ($CDCl_3$, 471 MHz) δ −65.27.

IR (neat, cm^{-1}) 3064, 1625, 1585, 1437, 1424, 1382, 1333, 1311, 1271.

HRMS (GC/MS solid probe) cacld for $C_{48}H_{24}F_6$ [M^+] *m*/*z* 714.1782, found [M^+] 714.1747.

4,12-diphenylrubiceno[6,5-b:13,12-b']dithiophene ***5.96k***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a dark red solid (97%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.81 (s, 2H), 8.61 (d, *J* = 8.4 Hz, 2H), 7.68 – 7.57 (m, 10H), 7.52 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.39 (d, *J* = 5.5 Hz, 2H), 7.07 (d, *J* = 5.4 Hz, 2H), 6.93 (d, *J* = 6.9 Hz, 2H).

IR (neat, cm^{-1}) 3056, 2597, 2162, 1591, 1438, 1369.

LRMS (LDI) *m*/*z*, 590.0 [M^+].

4,12-diphenylrubiceno[5,6-b:12,13-b']dithiophene ***5.96l***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a dark red solid (92%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.76 (s, 2H), 8.66 (d, *J* = 8.6 Hz, 2H), 7.71–7.62 (m, 8H), 7.55–7.52 (m, 4H), 7.50–7.46 (m, 4H), 6.99 (d, *J* = 6.9 Hz, 2H).

IR (neat, cm^{-1}) 3099, 3068, 2181, 2162, 1598, 1440, 1360, 1259.

LRMS (LDI) *m*/*z*, 590.0 [M^+].

4,13-diphenyl-5,6,7,8,14,15,16,17-octahydrodibenzo[g,s]rubicene ***5.96j***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a red solid (83%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.50 (d, *J* = 8.5 Hz, 2H), 8.06 (s, 2H), 7.65 – 7.49 (m, 8H), 7.47 – 7.32 (m, 8H), 6.44 (d, *J* = 6.8 Hz, 2H), 3.04 (t, *J* = 6.2 Hz, 4H), 2.50 (t, *J* = 6.3 Hz, 4H), 1.91 – 1.75 (m, 8H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 140.1, 138.6, 138.4, 137.6, 137.1, 135.0, 134.2, 133.5, 132.6, 129.1, 129.0, 128.7, 127.4, 125.1, 123.9, 123.6, 122.4, 30.9, 28.0, 23.5, 23.1.

IR (neat, cm^{-1}) 3051, 2929, 2856, 2182, 1598, 1442.

LRMS (LDI) *m*/*z*, 586.1 [M^+].

4,15-diphenyldinaphtho[2,1-g:2',1'-s]rubicene ***5.96i***

Prepared from 0.1 mmol of dibromide according to Procedure IV, the desired product was obtained as a red solid (94%).

^{1}H NMR (THF-d_8, 400 MHz) δ 9.89 (s, 2H), 9.20 (d, *J* = 8.3 Hz, 2H), 9.13 (d, *J* = 8.6 Hz, 2H), 7.93 (d, *J* = 7.9 Hz, 2H), 7.77–7.61 (m, 18H), 7.56 (d, *J* = 9.1 Hz, 2H), 6.80 (d, *J* = 6.9 Hz, 2H).

IR (neat, cm^{-1}) 3051, 2918, 2162, 1978, 1599, 1436, 1347.

LRMS (LDI) *m*/*z*, 678.1 [M^+].

5.5.3 DFT and NICS calculation of dibenzo[g,s]rubicene derivatives

All calculations were conducted in Gaussian 09. The geometry of each studied molecule was optimized at the B3LYP[9]/6-31+G(d,p) level of theory in the gas phase. HOMO/LUMO energy levels and bandgaps of each studied molecule were then performed using TD-DFT method at the same level of theory. Nucleus-Independent chemical shift (NICS) calculations were performed using a GIAO procedure at the same level of theory.[10]

[9] P. J. Stephens, F. J. Devlin, C. F. Chabalowski, and M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623
[10] H. Fallah-Bagher-Shaidaei, C. S.Wannere, C. Corminboeuf, and P. v. R. Schleyer, *Org. Lett.* **2006**, *8*, 863.

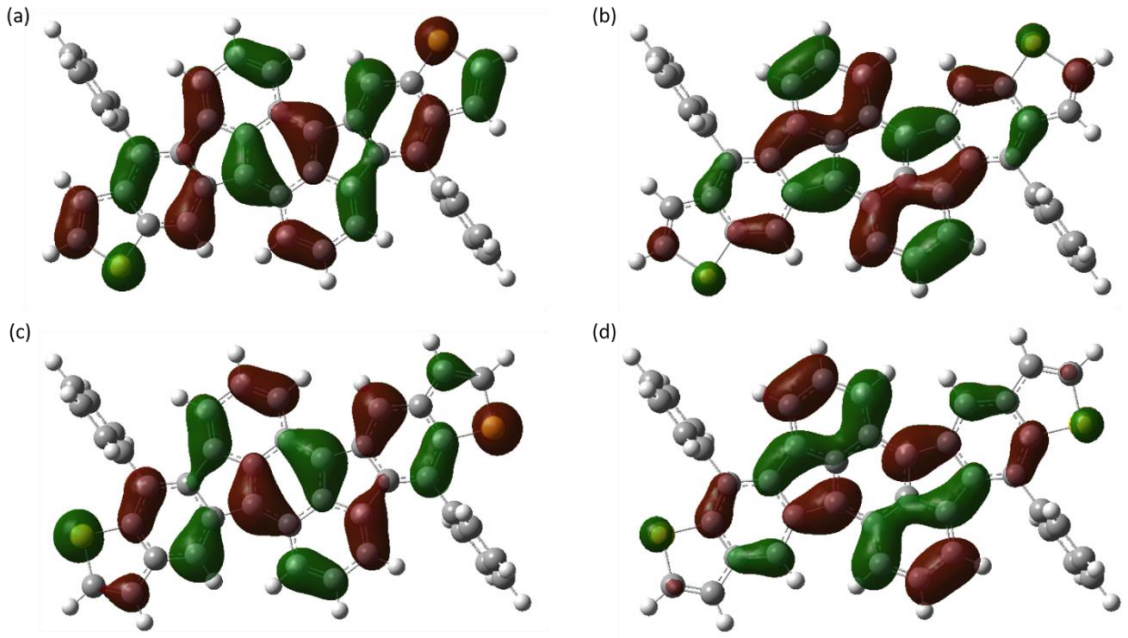


Figure 5-8 The calculated frontier molecular orbital diagrams of (a) HOMO of **5.96k**, (b) LUMO of **5.96k**, (c) HOMO of **5.96l**, (d) LUMO of **5.96l**.

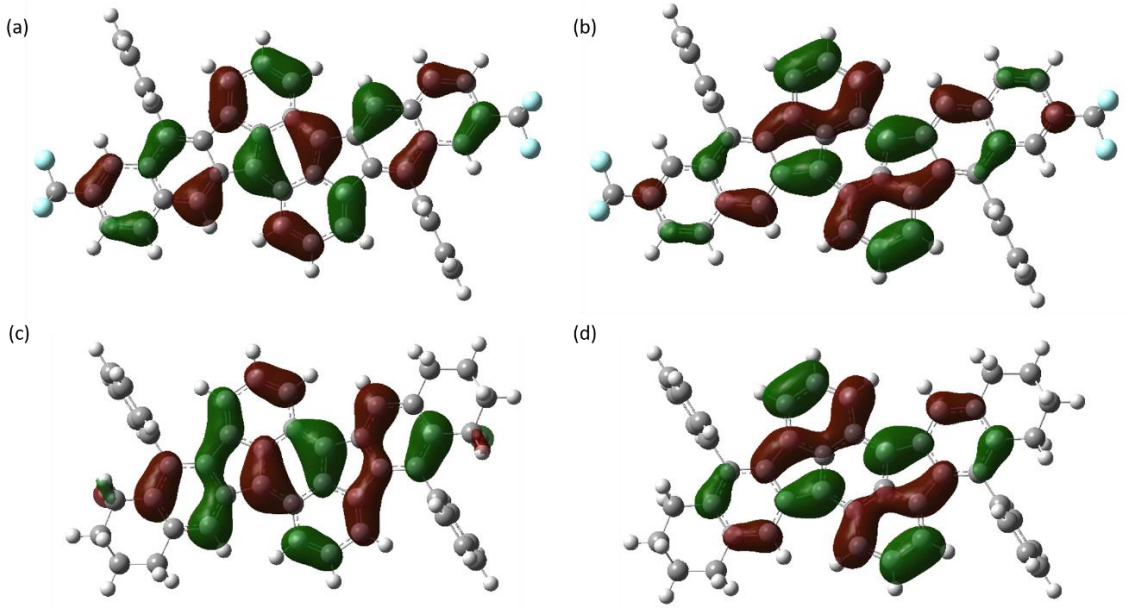


Figure 5-9 The calculated frontier molecular orbital diagrams of (a) HOMO of **5.96h**, (b) LUMO of **5.96h**, (c) HOMO of **5.96j**, (d) LUMO of **5.96j**.

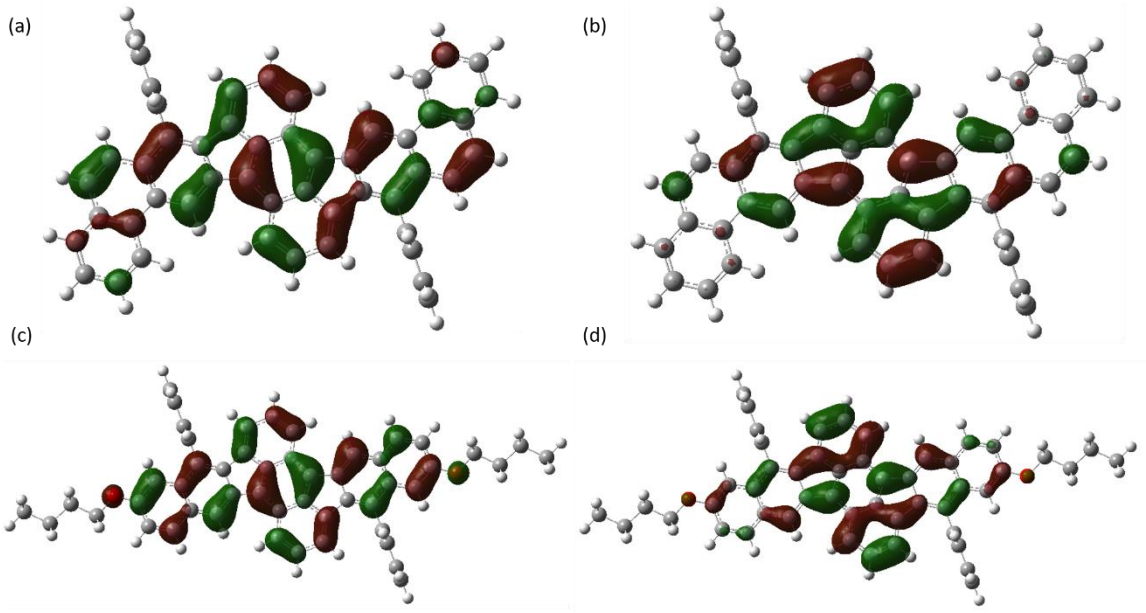


Figure 5-10 The calculated frontier molecular orbital diagrams of (a) HOMO of **5.96i**, (b) LUMO of **5.96i**, (c) HOMO of **5.96g**, (d) LUMO of **5.96g**.

Cartesian Coordinates

5.89a

C	-0.83786	2.841876	0.338244
C	0.604277	2.712771	0.262681
C	1.240828	1.43401	0.093831
C	0.448948	0.252042	0.057194
C	-0.95907	0.430017	0.076513
C	-1.61408	1.669857	0.198158
C	0.911658	-1.1221	-0.003142
C	-0.03118	-2.14669	-0.126752
C	-1.42825	-1.929	-0.157767
C	-1.9022	-0.63967	-0.036725
C	-1.39222	4.143245	0.536307
C	-0.59619	5.257761	0.6371
C	0.813829	5.135933	0.540063
C	1.388746	3.901979	0.357378

C	-3.06247	1.398665	0.147677
C	-3.24119	-0.0349	0.004342
C	-4.49845	-0.60544	-0.079447
C	-5.65424	0.2497	-0.024697
C	-5.47726	1.668158	0.108613
C	-4.16714	2.218875	0.190924
C	-6.97941	-0.2596	-0.102228
C	-8.07354	0.581851	-0.053334
C	-7.89653	1.978967	0.075613
C	-6.62383	2.505614	0.154379
C	-4.67536	-2.08403	-0.227893
C	-4.77329	-2.90951	0.90291
C	-4.93363	-4.29089	0.764549
C	-5.00054	-4.86606	-0.50778
C	-4.90947	-4.0517	-1.640333
C	-4.74946	-2.6705	-1.500778
C	2.646058	1.407183	-0.112036
C	2.269758	-1.52202	0.148358
C	3.836532	1.500666	-0.359335
C	3.360951	-2.02947	0.343735
H	0.337106	-3.16636	-0.171663
H	-2.09242	-2.77922	-0.252688
H	-2.46428	4.252515	0.621511
H	-1.04652	6.233818	0.792676
H	1.440097	6.01992	0.615989
H	2.466208	3.813047	0.289973
H	-4.08317	3.295443	0.27669
H	-7.12698	-1.32942	-0.201651
H	-9.07594	0.168143	-0.114519
H	-8.76191	2.634186	0.11259
H	-6.47977	3.57866	0.253668
H	-4.71908	-2.46484	1.892726
H	-5.00537	-4.916	1.650118
H	-5.124	-5.93978	-0.615852
H	-4.96241	-4.49014	-2.632884
H	-4.67708	-2.03963	-2.382335
C	5.223059	1.567501	-0.681307
C	4.642896	-2.59731	0.600044
C	5.806309	0.60185	-1.52926
C	7.158361	0.678217	-1.857095
C	7.952802	1.710966	-1.348352

C	4.937279	-3.91494	0.188326
C	6.185225	-4.47566	0.453862
C	7.159922	-3.73813	1.134094
C	7.385099	2.672073	-0.505269
C	6.033239	2.605482	-0.173141
H	5.188231	-0.19926	-1.920395
H	7.594098	-0.07205	-2.51043
H	9.006204	1.766482	-1.606714
H	7.996866	3.476089	-0.106325
H	5.592504	3.35042	0.481937
C	6.877975	-2.43177	1.546884
C	5.633846	-1.86169	1.284222
H	4.179134	-4.48659	-0.337625
H	6.397263	-5.49086	0.130843
H	8.130988	-4.17807	1.341511
H	7.630847	-1.85358	2.074726
H	5.414739	-0.84811	1.602161

5.96k

C	0.020931	1.464992	-0.012516
C	1.187069	0.644012	-0.008818
C	1.211499	-0.7692	-0.011928
C	-0.02093	-1.46499	-0.012516
C	-1.18707	-0.64401	-0.008818
C	-1.2115	0.769196	-0.011928
C	-0.24683	-2.87695	-0.017589
C	-1.53098	-3.38204	-0.020373
C	-2.68525	-2.54439	-0.015132
C	-2.5146	-1.17659	-0.0069
C	0.246827	2.876953	-0.01759
C	1.530978	3.382037	-0.020374
C	2.685248	2.544386	-0.015133
C	2.514598	1.176585	-0.0069
C	-2.62556	1.172649	-0.014262
C	-3.43486	-0.02213	-0.004376
C	-4.82498	0.038934	-0.000988
C	-5.43124	1.325312	-0.016114
C	-4.61862	2.487635	-0.030112
C	-3.21882	2.429047	-0.027456
C	3.434856	0.022133	-0.004376
C	2.625556	-1.17265	-0.014261
C	4.824979	-0.03893	-0.000987

5.96l

C	0.056392	1.463351	-0.0147
C	1.202169	0.613704	-0.01033
C	1.192451	-0.79869	-0.01375
C	-0.05639	-1.46335	-0.0147
C	-1.20217	-0.6137	-0.01033
C	-1.19245	0.798688	-0.01375
C	-0.31707	-2.86954	-0.02154
C	-1.61322	-3.3432	-0.02568
C	-2.74683	-2.47785	-0.0196
C	-2.54275	-1.11441	-0.00904
C	0.317072	2.869535	-0.02154
C	1.613218	3.343198	-0.02568
C	2.74683	2.477853	-0.0196
C	2.542745	1.114412	-0.00904
C	-2.59816	1.238021	-0.01681
C	-3.43299	0.061186	-0.00624
C	-4.82483	0.153605	-0.0036
C	-5.36984	1.45474	-0.02278
C	-4.56813	2.624629	-0.03664
C	-3.163	2.504504	-0.03185
C	3.432987	-0.06119	-0.00624
C	2.598158	-1.23802	-0.01681
C	4.824833	-0.15361	-0.0036

C	5.431244	-1.32531	-0.016112	C	5.369843	-1.45474	-0.02278
C	4.618617	-2.48764	-0.03011	C	4.568132	-2.62463	-0.03664
C	3.218822	-2.42905	-0.027455	C	3.163001	-2.5045	-0.03186
C	-5.68753	-1.18257	0.02477	C	-5.72374	-1.04076	0.026676
C	5.687534	1.182569	0.024771	C	5.723739	1.040761	0.026675
C	-6.00514	-1.80494	1.242064	C	-6.02804	-1.67128	1.243224
C	-6.81832	-2.94092	1.269974	C	-6.87444	-2.78206	1.275222
C	-7.32707	-3.4699	0.080186	C	-7.42805	-3.27713	0.090831
C	-7.02075	-2.85427	-1.136703	C	-7.1342	-2.65315	-1.12466
C	-6.20845	-1.71725	-1.163778	C	-6.28917	-1.54068	-1.15644
C	6.208452	1.717253	-1.163777	C	6.289168	1.540682	-1.15644
C	7.020753	2.854271	-1.136703	C	7.134196	2.653154	-1.12466
C	7.327074	3.469896	0.080186	C	7.428045	3.277129	0.090831
C	6.818322	2.94092	1.269974	C	6.874439	2.782057	1.275222
C	6.005137	1.804939	1.242064	C	6.028039	1.671276	1.243224
C	-6.83413	1.654159	-0.01409	S	-7.08003	1.861946	-0.02008
C	-7.06656	2.995393	-0.028749	C	-6.70335	3.569369	-0.04107
C	6.834125	-1.65416	-0.014088	S	7.080027	-1.86195	-0.02008
C	7.066556	-2.99539	-0.028747	C	6.703354	-3.56937	-0.04107
S	-5.59786	3.944775	-0.043829	C	-5.36616	3.823054	-0.04805
S	5.597863	-3.94478	-0.043827	C	5.366164	-3.82305	-0.04805
H	0.589864	-3.56477	-0.020011	H	0.5034	-3.57663	-0.0246
H	-1.6739	-4.45895	-0.026059	H	-1.78247	-4.41631	-0.03312
H	-3.66979	-2.99696	-0.017946	H	-3.74223	-2.90606	-0.0235
H	-0.58986	3.564769	-0.020012	H	-0.5034	3.576633	-0.0246
H	1.673901	4.458954	-0.02606	H	1.782469	4.416305	-0.03312
H	3.669786	2.996959	-0.017946	H	3.742225	2.906061	-0.02349
H	-2.63445	3.341073	-0.036531	H	-2.55653	3.402886	-0.04069
H	2.634454	-3.34107	-0.036529	H	2.556529	-3.40289	-0.04069
H	-5.60867	-1.39682	2.167533	H	-5.59675	-1.28844	2.163813
H	-7.05364	-3.41143	2.220477	H	-7.10114	-3.25919	2.224438
H	-7.95847	-4.35348	0.101387	H	-8.08552	-4.1414	0.115446
H	-7.41303	-3.25789	-2.065916	H	-7.5621	-3.03059	-2.04903
H	-5.96951	-1.24222	-2.111195	H	-6.06037	-1.05795	-2.10231
H	5.969509	1.242216	-2.111194	H	6.060373	1.057953	-2.10231
H	7.413033	3.257884	-2.065916	H	7.562102	3.030588	-2.04903
H	7.958472	4.353484	0.101386	H	8.085516	4.141402	0.115446
H	7.053635	3.411428	2.220477	H	7.10114	3.259192	2.224438
H	5.608668	1.396821	2.167533	H	5.596751	1.28844	2.163813
H	-7.62336	0.91232	-0.001975	H	-7.51231	4.287895	-0.04766
H	-8.02303	3.500818	-0.0312	H	7.512305	-4.2879	-0.04766

H	7.623364	-0.91232	-0.001973	H	-4.94608	4.822829	-0.06049
H	8.023029	-3.50082	-0.031197	H	4.946081	-4.82283	-0.06049

5.96h

C	-0.19917	-1.45227	0.000026
C	1.077988	-0.81619	0.000016
C	1.311313	0.577794	0.000001
C	0.19917	1.452267	0.000016
C	-1.07799	0.816186	0.000014
C	-1.31131	-0.57779	0.000006
C	0.190125	2.881324	0.000044
C	-1.00273	3.575459	0.000062
C	-2.27027	2.92329	0.000053
C	-2.30905	1.544901	0.000028
C	-0.19013	-2.88132	0.000065
C	1.002733	-3.57546	0.000086
C	2.27027	-2.92329	0.000069
C	2.30905	-1.5449	0.000032
C	-2.76895	-0.76661	-0.000006
C	-3.39305	0.543435	0.000017
C	-4.76756	0.686295	0.000007
C	-5.58431	-0.49924	-0.000030
C	-4.96421	-1.79349	-0.000070
C	-3.54664	-1.90202	-0.000058
C	-7.00297	-0.42941	-0.000033
C	-7.76992	-1.5769	-0.000085
C	-7.15997	-2.85654	-0.000131
C	-5.78775	-2.95247	-0.000123
C	3.393045	-0.54344	0.000013
C	2.768952	0.766606	-0.000014
C	4.767559	-0.6863	0.000003
C	5.584313	0.499242	-0.000037
C	4.964214	1.793493	-0.000077
C	3.546639	1.902015	-0.000066
C	7.002973	0.42941	-0.000042
C	7.769922	1.5769	-0.000096
C	7.159968	2.856542	-0.000141
C	5.78775	2.952469	-0.000131
C	-5.41285	2.036494	0.000032
C	5.412845	-2.03649	0.000028
C	-5.72042	2.680525	-1.208320

5.96j

C	-0.00824	-1.4638	-0.01225
C	1.173978	-0.66692	-0.00853
C	1.226102	0.744664	-0.00935
C	0.008242	1.463799	-0.01225
C	-1.17398	0.666922	-0.00853
C	-1.2261	-0.74466	-0.00935
C	-0.1883	2.880853	-0.01992
C	-1.46213	3.410229	-0.02554
C	-2.63404	2.59497	-0.01966
C	-2.49285	1.224094	-0.00762
C	0.188304	-2.88085	-0.01992
C	1.462127	-3.41023	-0.02555
C	2.634038	-2.59497	-0.01966
C	2.492853	-1.22409	-0.00762
C	-2.6512	-1.116	-0.00518
C	-3.43046	0.081235	0.000824
C	-4.82621	0.020565	0.007532
C	-5.47018	-1.24661	0.009434
C	-4.69713	-2.4239	-0.00448
C	-3.29377	-2.34762	-0.01189
C	-6.99141	-1.31484	-0.00275
C	-7.55553	-2.69167	0.369402
C	-5.33902	-3.80305	0.017175
C	3.430464	-0.08124	0.000824
C	2.651196	1.116	-0.00518
C	4.826212	-0.02057	0.007533
C	5.470184	1.246609	0.009435
C	4.697129	2.423904	-0.00448
C	3.293766	2.347616	-0.01189
C	6.991409	1.314836	-0.00275
C	7.555533	2.691674	0.369404
C	6.816919	3.799374	-0.38612
C	5.339023	3.803054	0.017176
C	-5.63905	1.279418	0.012687
C	5.639054	-1.27942	0.012687
C	-6.10959	1.834678	-1.18717
C	-6.85826	3.014928	-1.18351

C	-6.31678	3.944279	-1.208498	C	-7.15071	3.657423	0.022861
C	-6.6148	4.580138	0.000070	C	-6.68958	3.111911	1.224564
C	-6.31672	3.94427	1.208618	C	-5.93977	1.932685	1.218302
C	-5.72036	2.680516	1.208402	C	5.939766	-1.93269	1.218302
C	5.72039	-2.6805	1.208397	C	6.689579	-3.11191	1.224564
C	6.316748	-3.94426	1.208614	C	7.150712	-3.65742	0.022862
C	6.614794	-4.58014	0.000065	C	6.858264	-3.01493	-1.1835
C	6.316748	-3.94429	-1.208503	C	6.109595	-1.83468	-1.18717
C	5.720392	-2.68054	-1.208324	H	0.664173	3.549404	-0.02298
C	-9.27159	-1.5014	-0.000021	H	-1.5849	4.489743	-0.03389
C	9.271588	1.5014	-0.000034	H	-3.60821	3.069341	-0.02492
H	1.121828	3.43338	0.000062	H	-0.66417	-3.5494	-0.02299
H	-0.98078	4.661453	0.000086	H	1.584904	-4.48974	-0.03389
H	-3.17425	3.520221	0.000070	H	3.608211	-3.06934	-0.02493
H	-1.12183	-3.43338	0.000091	H	-2.72768	-3.27373	-0.02397
H	0.980783	-4.66145	0.000121	H	-7.40088	-0.54971	0.665068
H	3.174251	-3.52022	0.000088	H	-7.34915	-1.04386	-1.00739
H	-3.1103	-2.89443	-0.000102	H	-7.44563	-2.85813	1.450368
H	-7.48591	0.5397	-0.000002	C	-6.81692	-3.79937	-0.38612
H	-7.77497	-3.75053	-0.000181	H	2.72768	3.273734	-0.02397
H	-5.31233	-3.9295	-0.000161	H	7.349149	1.043858	-1.00738
H	3.110302	2.894432	-0.000111	H	7.400882	0.549712	0.665069
H	7.485912	-0.5397	-0.000013	H	7.26231	4.780126	-0.18213
H	7.77497	3.750526	-0.000191	H	6.908332	3.626546	-1.46767
H	5.312329	3.929496	-0.000170	H	-5.87867	1.34203	-2.1278
H	-5.48773	2.189435	-2.149111	H	-7.21063	3.432281	-2.12271
H	-6.54886	4.429804	-2.152016	H	-7.73272	4.574573	0.02665
H	-7.07913	5.561926	0.000084	H	-6.91094	3.604578	2.16729
H	-6.54875	4.429788	2.152152	H	-5.57639	1.515357	2.153477
H	-5.48762	2.189421	2.149179	H	5.576382	-1.51536	2.153478
H	5.487675	-2.1894	2.149175	H	6.91094	-3.60458	2.167291
H	6.548801	-4.42976	2.152147	H	7.73272	-4.57457	0.026651
H	7.079132	-5.56193	0.000080	H	7.21063	-3.43228	-2.12271
H	6.548803	-4.42983	-2.152021	H	5.87867	-1.34203	-2.1278
H	5.487678	-2.18946	-2.149115	H	-5.25083	-4.21506	1.034053
F	-9.73918	-0.23122	-0.000407	H	-4.76572	-4.47768	-0.63055
F	-9.80923	-2.12016	1.087754	H	-8.63018	-2.71735	0.154199
F	-9.80936	-2.12088	-1.087317	H	8.630176	2.71735	0.154202
F	9.739177	0.231217	-0.000428	H	7.445633	2.858129	1.45037
F	9.809226	2.120149	1.087745	H	5.250828	4.215055	1.034054
F	9.809354	2.120884	-1.087326	H	4.765723	4.477682	-0.63055

					H	-6.90833	-3.62655	-1.46767
					H	-7.26231	-4.78013	-0.18213
5.96i				**5.96g**				
	C	-0.36995	1.417464	0.000029	C	0.315895	-1.43007	0.001109
	C	0.973315	0.937312	0.000019	C	-1.00912	-0.90009	0.001046
	C	1.3726	-0.41875	0.000013	C	-1.35596	0.47026	0.000933
	C	0.36995	-1.41746	0.000025	C	-0.3159	1.430072	0.001002
	C	-0.97332	-0.93731	0.000018	C	1.00912	0.90009	0.001047
	C	-1.3726	0.418747	0.000016	C	1.355964	-0.47026	0.001039
	C	0.529091	-2.83822	0.000051	C	-0.42276	2.855077	0.001044
	C	-0.57331	-3.66825	0.000064	C	0.709709	3.644483	0.001111
	C	-1.90924	-3.16979	0.000051	C	2.025937	3.097636	0.001129
	C	-2.1106	-1.80588	0.000027	C	2.177409	1.726692	0.001091
	C	-0.52909	2.838222	0.000061	C	0.422759	-2.85508	0.001249
	C	0.573311	3.668254	0.000075	C	-0.70971	-3.64448	0.001298
	C	1.90924	3.16979	0.000058	C	-2.02594	-3.09763	0.001204
	C	2.110601	1.805881	0.000028	C	-2.17741	-1.72669	0.001075
	C	-2.84351	0.429084	0.000013	C	2.82313	-0.54099	0.000959
	C	-3.30297	-0.93596	0.000018	C	3.340522	0.816891	0.001042
	C	-4.65758	-1.2262	0.000005	C	4.697408	1.07366	0.000981
	C	-5.60131	-0.14565	-0.000005	C	5.616798	-0.03882	0.000747
	C	-5.14791	1.211068	-0.000008	C	5.098974	-1.37979	0.000565
	C	-3.7542	1.467352	-0.000007	C	3.693756	-1.60517	0.00071
	C	-7.01257	-0.40859	-0.000021	C	7.018152	0.148682	0.000592
	C	-7.92706	0.602622	-0.000039	C	7.890159	-0.93069	0.000211
	C	-7.51932	1.975331	-0.000036	C	7.384246	-2.25399	-8E-06
	C	-6.12705	2.292555	-0.000016	C	6.017597	-2.45734	0.000188
	C	3.30297	0.935955	0.000016	C	-3.34052	-0.81689	0.000906
	C	2.843514	-0.42908	0.000009	C	-2.82313	0.54099	0.000769
	C	4.657578	1.226197	0.000003	C	-4.69741	-1.07366	0.000785
	C	5.601306	0.145649	-0.000009	C	-5.6168	0.038816	0.000431
	C	5.147906	-1.21107	-0.000012	C	-5.09897	1.379791	0.00021
	C	3.754197	-1.46735	-0.000011	C	-3.69376	1.605167	0.000417
	C	7.012572	0.408587	-0.000027	C	-7.01815	-0.14868	0.000221
	C	7.927063	-0.60262	-0.000045	C	-7.89016	0.930692	-0.00025
	C	7.519323	-1.97533	-0.000041	C	-7.38425	2.253985	-0.00051
	C	6.127052	-2.29256	-0.00002	C	-6.0176	2.457336	-0.00026
	C	-5.13987	-2.64381	0.000001	C	5.229441	2.472187	0.001102
	C	5.139869	2.643812	-0.000001	C	-5.22944	-2.47219	0.000979
	C	-5.36831	-3.32137	1.207676	C	5.486014	3.139776	1.208723
	C	-5.80918	-4.64746	1.208329	C	5.978772	4.447414	1.209574

C	-6.02969	-5.31484	-0.000011	C	6.225028	5.105841	0.001331
C	-5.80911	-4.64747	-1.208345	C	5.978984	4.447543	-1.20703
C	-5.36824	-3.32138	-1.20768	C	5.486231	3.139904	-1.2064
C	5.36823	3.321381	-1.207683	C	-5.48623	-3.13997	-1.20649
C	5.809098	4.647477	-1.208348	C	-5.97898	-4.44761	-1.20704
C	6.02969	5.31484	-0.000014	C	-6.22503	-5.10584	0.001356
C	5.809189	4.647458	1.208326	C	-5.97878	-4.44735	1.209563
C	5.368322	3.321361	1.207673	C	-5.48602	-3.13971	1.208638
H	1.519595	-3.27617	0.000071	O	9.223653	-0.6268	0.000173
H	-0.42354	-4.74424	0.000087	C	10.18674	-1.68288	-0.00192
H	-2.73628	-3.8695	0.000061	C	11.57168	-1.05026	-0.00263
H	-1.5196	3.276167	0.000084	C	12.69634	-2.094	-0.00537
H	0.423536	4.744239	0.000103	C	14.09325	-1.4623	-0.00593
H	2.736277	3.869496	0.000069	O	-9.22365	0.626797	-0.0004
H	-3.40288	2.489378	-0.000033	C	-10.1867	1.682882	-0.00193
H	-7.34972	-1.43879	-0.000021	C	-11.5717	1.050253	-0.00239
H	-8.99042	0.377555	-0.000055	C	-12.6963	2.093997	-0.00445
C	-8.47921	3.017081	-0.000048	C	-14.0933	1.462296	-0.00479
C	-8.09331	4.343471	-0.000039	H	-1.39702	3.328429	0.001055
H	3.40288	-2.48938	-0.000038	H	0.599315	4.725312	0.001155
H	7.349719	1.438785	-0.000028	H	2.87818	3.766273	0.001176
H	8.990415	-0.37756	-0.000063	H	1.397021	-3.32843	0.00135
C	8.479214	-3.01708	-0.000053	H	-0.59931	-4.72531	0.001417
C	8.093307	-4.34347	-0.000043	H	-2.87818	-3.76627	0.001242
H	-5.19587	-2.80553	2.148187	H	3.341833	-2.63112	0.000558
H	-5.9798	-5.15769	2.152131	H	7.437648	1.147805	0.000724
H	-6.37206	-6.34566	-0.000015	H	8.051915	-3.10685	-0.0003
H	-5.97969	-5.15771	-2.152151	H	5.629701	-3.47295	0.000038
H	-5.19575	-2.80555	-2.148187	H	-3.34183	2.63112	0.00023
H	5.195727	2.805558	-2.148189	H	-7.43765	-1.1478	0.000386
H	5.979664	5.157715	-2.152155	H	-8.05192	3.106845	-0.00088
H	6.372058	6.345656	-0.000019	H	-5.6297	3.472955	-0.00044
H	5.979826	5.15768	2.152128	H	5.293594	2.630709	2.149021
H	5.195891	2.805524	2.148185	H	6.169746	4.95038	2.153416
C	-6.72092	4.66504	-0.000013	H	6.607311	6.122579	0.001418
C	-5.76575	3.663251	-0.000001	H	6.170121	4.950613	-2.15078
H	-9.53344	2.751866	-0.000064	H	5.293981	2.630937	-2.14679
H	-8.83896	5.132981	-0.000049	H	-5.29398	-2.63106	-2.1469
H	-6.40811	5.705191	-0.000001	H	-6.17012	-4.95074	-2.15076
H	-4.72079	3.950871	0.000025	H	-6.60731	-6.12258	0.0015
C	6.72092	-4.66504	-0.000016	H	-6.16975	-4.95026	2.153433

C	5.765754	-3.66325	-0.000004
H	9.533438	-2.75187	-0.00007
H	8.838955	-5.13298	-0.000053
H	6.408109	-5.70519	-0.000003
H	4.720788	-3.95087	0.000023

H	-5.2936	-2.63059	2.148907
H	10.05018	-2.3143	0.88804
H	10.04832	-2.31237	-0.89296
H	11.66046	-0.40014	-0.88218
H	11.6625	-0.40257	0.878494
H	12.59338	-2.74681	0.872488
H	12.59149	-2.7442	-0.88492
H	14.8759	-2.22827	-0.00777
H	14.24168	-0.8312	-0.88981
H	14.24347	-0.8336	0.879355
H	-10.0499	2.314064	0.888158
H	-10.0486	2.312604	-0.89284
H	-11.6607	0.400404	-0.8821
H	-11.6622	0.402294	0.87857
H	-12.5931	2.746517	0.873588
H	-12.5918	2.744479	-0.88383
H	-14.8759	2.228258	-0.00618
H	-14.2419	0.831442	-0.88881
H	-14.2432	0.833336	0.880359

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Appendix

All NMR spectra are shown in Appendix volume.