Sustainability Metric Case Study on Biaryl Bond Formation

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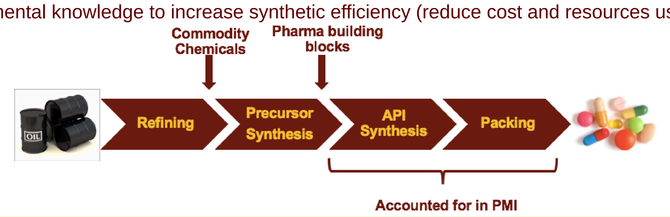
Abstract

The most common metric used to measure chemical processes is yield, which does not take into account all inputs. A more holistic view of chemical reactions is needed and a metric based analysis could be used to systematically focus methodological improvements. This project looks at the synthetic efficiency of an industrially relevant bond forming reaction, biaryl formation, and attempts to inventory all inputs used in this reaction.

The formation of phenylnaphthalene was studied as a model system to compare carbon-carbon bond formation reactions. The reactions were analyzed based on method, reaction conditions, catalyst composition, reagent loading, and other inputs (energy and solvent). The reactions were classified based on eight possible coupling permutations. The methods included reactions between nucleophilic or electrophilic naphthalene and phenyl derivatives as well as C-H bonds. Via this holistic metric based analysis, reactions with many dissimilar variables will be compared.

Introduction

Pharmaceuticals are incredibly important molecules with the power to alleviate suffering and to cure disease. While pharmaceuticals are a keystone of modern medicine, they are frequently very expensive and resource intensive to produce. In 2008, the cost to manufacture pharmaceuticals could be estimated at ~30% of the ~700 billion dollars in sales (*J. Pharma. Innovation.* 2008 *3*, 30) This is in excess of the rising cost to conduct R&D (~10%) and indicates that significant savings and resource minimization could be gained through synthetic optimization. Currently, pharmaceuticals are essentially arduously refined crude oil and are the end product of a very long and very complicated supply chain. The goal of this work is to gain a fundamental insight into the chemistry that connects the links in this supply chain and use that fundamental knowledge to increase synthetic efficiency (reduce cost and resources used).



Current Metrics of Synthesis

The classical metric used for chemical synthesis is yield, which is based solely on the "limiting reagent" and does not consider other inputs. Yield is defined as the percent (on a mole basis) of the starting material that is obtained as product. Yield does not account for other resources used such as reagents, catalysts, solvent, or infrastructure.

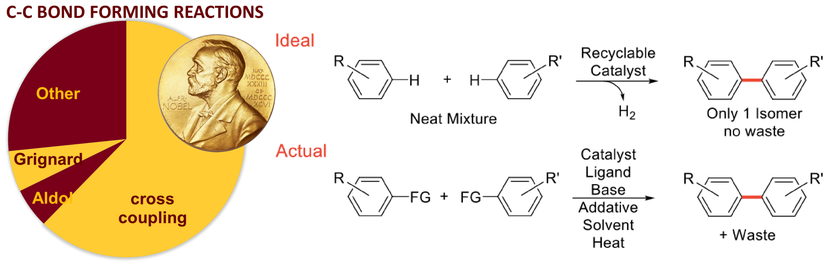
Recognizing the limitations inherent in yield, other metrics have been proposed. The standard metric used by the pharmaceutical industry to measure synthetic efficiency is Process Mass Intensity (PMI), which is more holistic than yield. The units on PMI are kg of materials used (including solvents and other reagents) per kg of product synthesized (pharmaceutical). While commodity chemicals typically have a PMI ranging from 1.1 to 2 (ideal PMI = 1), typical PMI in pharmaceutical production ranges from ~50 to >10,000. PMI has the attribute of being simple to track and is a readily informative when comparing two or more synthetic routes or procedures. Process chemists regularly reduce the PMI of a synthesis by >75% as part of optimization! While PMI is a terrific measure, it is still not truly holistic. PMI starts with "readily available precursors" by definition and is strictly based on mass. But, the same weight of two different substances can lead to very different life cycle impacts. For instance, in a hydrogenation reaction, the weight of a palladium catalyst may contribute < 1% to PMI but may contribute > 20% to LCA. While PMI is an excellent first approximation, more holistic life cycle analysis are needed.

Unfortunately, the complex nature of pharmaceuticals makes life cycle analyses difficult to complete partially because "life cycle inventory data are rarely available for pharmaceutical processes mainly due to the use of fine chemicals with complex molecular structures stemming from long production chains." (*ChemSusChem* 2014, *7*, 3521) or "Obtaining data for an LCA in the pharmaceutical industry is not a simple endeavor … it may involve 20, 50, or more chemicals … each of which will require their own inventory data…" *(Green Chem.* 2014 *16*, 3392)

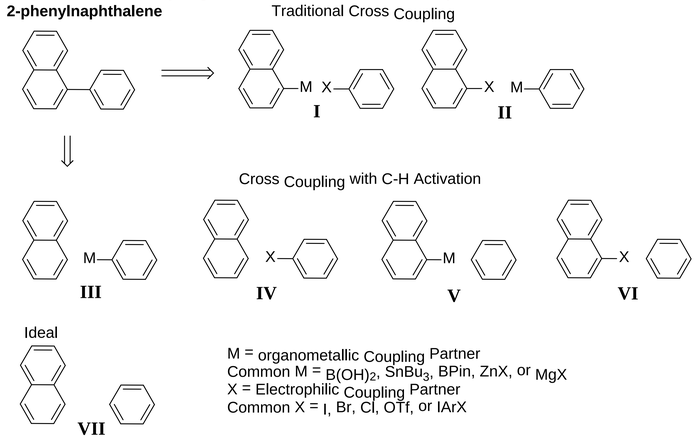
This work aims to partially address these issues by studying the life cycle inventory of a simple molecule 2-phenylnaphthalene as a surrogate for cross coupling. The carbon-carbon biaryl bond present in 2-phenylnaphthalene reflects the "functional unit" under study.

Relevance of Cross Coupling

The principle operation in organic synthesis is the formation of carbon-carbon bonds enroute to the target molecule. One of the most powerful methods for the formation of carbon-carbon bonds is the cross coupling reaction. In a recent survey of carbon-carbon bond forming reactions used by medicinal chemists, > 70% where cross couplings (*J. Med. Chem*. 2011, 54, 3451) The ubiquity and generality of this reaction are responsible for the 2010 Nobel prize in chemistry being awarded to the inventors of cross coupling.



While it is relatively straightforward to postulate what the ideal cross coupling would consist of, the reality is far from the ideal. This leads to a wide variety of cross coupling methods which use wildly varying reagents, additives, solvents, and catalysts. Because each of these components reflects varying production chains of varying lengths and life cycle impacts, a direct comparison of cross coupling is impractical. As such, a model system containing the functional carbon-carbon bond is needed. An ideal model system would 1) contain the C-C bond of interest, 2) require the use of cross coupling (over homo-coupling), 3) have a short supply chain from initial feedstocks, and 4) be well studied using various cross coupling technologies. 2-phenylnaphthalene possesses these characteristics and is reported in over 1,000 papers. Synthetic methods exist to form 2-phenylnaphthalene by eight different combinations of precursors:

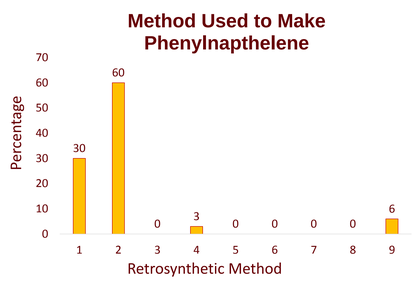


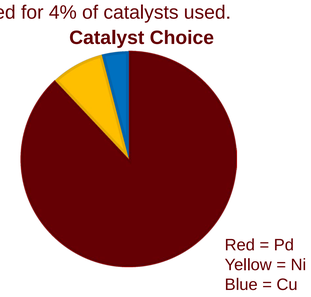
Method

A data set of over 1,000 papers describing 2-phenylnapthelene was obtained from SciFinder search engine. The reactions were classified based on the nucleophilic and electrophilic components of the reaction. In the possible methods, M is the nucleophilic component of the reaction and X is the electrophilic component of the reaction. The methods covered all combinations of nucleophilic, electrophilic, or C-H. An extra "other" category was added to account for reactions not included in the scope of the previous methods. Reaction information taken from the papers included: method of the coupling, electrophile used, equivalents of electrophile, nucleophile used, and the equivalents of nucleophile. The catalyst information taken from the papers included: metal used, catalyst complex, catalyst ligands, and the mole percent loading. The reaction conditions taken from the papers included: temperature, time, solvent, base, equivalents of base, additive, equivalents of additive, and if any other additives were used. The reaction results taken from the papers included catalyst turn over number and yield of product.

Results

The results below are a summary of a sub-sample of the data set pertaining to 2-phenyl naphthalene. The method most often used in the biaryl bond formation or the functional unit was Method 2. Method 2 was used in 60% of the reactions, Method 1 was used in 30% of the reactions. This indicates that the more ideal C-H couplings are still not common. Method 4 was used in only 3% of the reactions. Method 9 (Other) was used 6% of the time. The catalyst most often used was palladium. Palladium accounted for 88% of catalysts used, nickel accounted for 8% of catalysts used, and copper accounted for 4% of catalysts used.





The average mole percent of catalyst used was 2.9%. The average equivalent electrophile used was 1.3, and the average equivalent nucleophile used was 2.9. The average equivalent base used was 1.6, and the average equivalent additive used was 0.2. The turnover number (TON) varied wieldly. The minimum TON was 6 and the maximum TON was 800,000; both the minimum and maximum used palladium as a catalyst. A full inventory for the reagents and catalysts is provided below:

Catalysts	Bases	Additives	Electrophiles	Nucleophiles
CuI	CsF	KHMDS	Napth-Br	butyl vinyl ether
$NiCl_2(PPh_3)_2$	K_2CO_3	LiCl	Napth-Cl	Napthelene
$Pd(OAc)_2$	K_3PO_4	$N(n\text{-}Bu)_4Br$	Napth-I	Napth-B(OH)
$Pd(PPh_3)_4$	$NaCO_3$	PTSA	Napth-N_2BF_4	$Napth_3BPhH$
$PdCl_2(PPh_3)_2$	TBAF	TBAB	Napth-OP(O)$(OEt)_2$	Napth-MgBr
Pd_2dba_3	tBuOK	$ZnCl_2$	Napth-OTf	$PhBi(OEt)_2$
Na_2PdCl_4	TEA	TBAT	o-ethynylphenyl ketone	$PhBi(OMe)_2$
$[PdClAllyl]_2$	$W(CO)_5THF$		Ph-Br	$PhBi(OPr)_2$
	Cs_2CO_3		Ph-Cl	$PhB(OH)_2$
			$Ph_2I^+BF_4^-$	PhBpin
			PhI(OH)Ots	Ph-MgBr
			Ph_2ITFA	$PhSi(OEt_3)$
				$PhSn(C_6F_{13}CH_2CH_3)_3$

Summary

Method 2 was the most commonly used method, and palladium was the most commonly used catalyst. Turnover numbers ranged from 6 to 800,000 could be achieved with palladium. A wide number of electrophiles and nucleophiles were used, and many reactions included the use of a base and an additive.

Future Work

The data resented here represents a first attempt at quantifying the life cycle impacts of various cross coupling techniques. The model system 2-phenylnaphthalene is a simple enough structure that in principle a full life cycle inventory should be accomplishable. At present, the key cross coupling step has been investigated. Future work will focus on completing the inventory of the reagents and catalysts used in a cross coupling.