Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Supporting Information

Making Better Decisions During Synthetic Route Design: Leveraging Prediction to Achieve Greenness-by-Design

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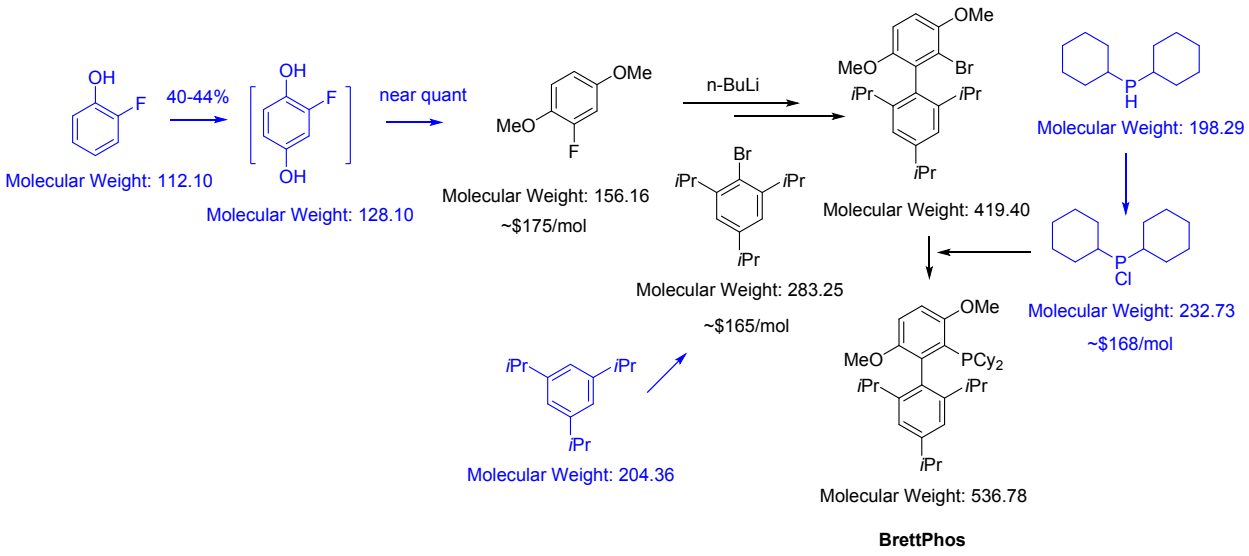
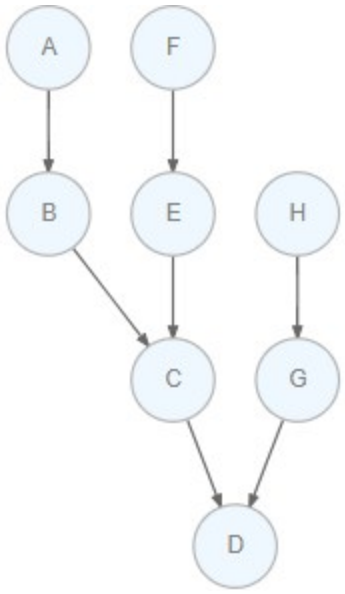
One of the very useful applications of the PMI web app is that it allows assessment of the probable PMI distribution for a known synthesis where actual process details are not known. This situation can be quite common, especially when trying to apply the $100/mol criteria for starting material when assessing overall sustainability, as proposed by Roschangar et al.[i] Here we would like to show an example of leveraging PMI prediction to estimate the cumulative on-scale PMI for the synthesis of a phosphine ligand, based on the route to the compound literature. Brettphos is one of the popular phosphines developed by Buchwald group. Its large-scale synthesis has been revealed previously.[ii] The synthesis included a telescoped process from 1,4-dimethoxy-2-fluorobenzene and 2,4,6-triisopropylbromobenzene, followed by reacting with chlorodicyclohexylphosphine. The two step processes showed 63% yield with step PMI 158 and last step with 80% yield and step PMI 92. All those starting materials are currently above the $100/mol threshold (based on the lowest listed bulk price available on Scifinder for illustration purpose). The 1,4-dimethoxy-2-fluorobenzene is prepared by oxidation, followed by methylation using ortho-fluorophenol.[iii] The yield for the telescoped process was reported as being around 45%. Based on these info, we can use our PMI app to estimate the cPMI for Brettphos – using prediction for the sections highlighted in blue.



Scheme S1. BrettPhos Synthesis



PMI Calculator | 1. Define Process | 2. PMI Values | 3. Results

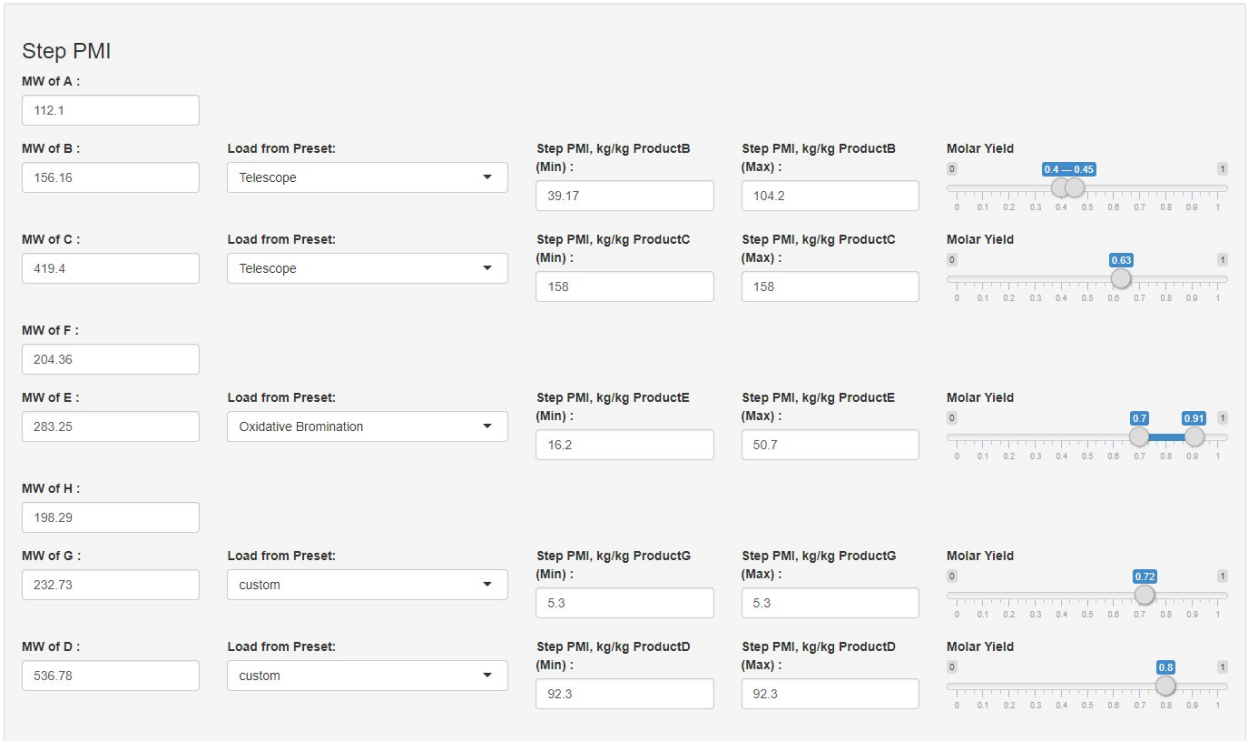
Process

Define each step in the process here, specifying the input, yield, and output of each step

Stoichiometry Range: Low	Stoichiometry Range: High	Input Name	Output Name
1	1	A	B
1	1	B	C
1	1	C	D
1	1	F	E
2	2	E	C
1	1	H	G
1.09	1.09	G	D

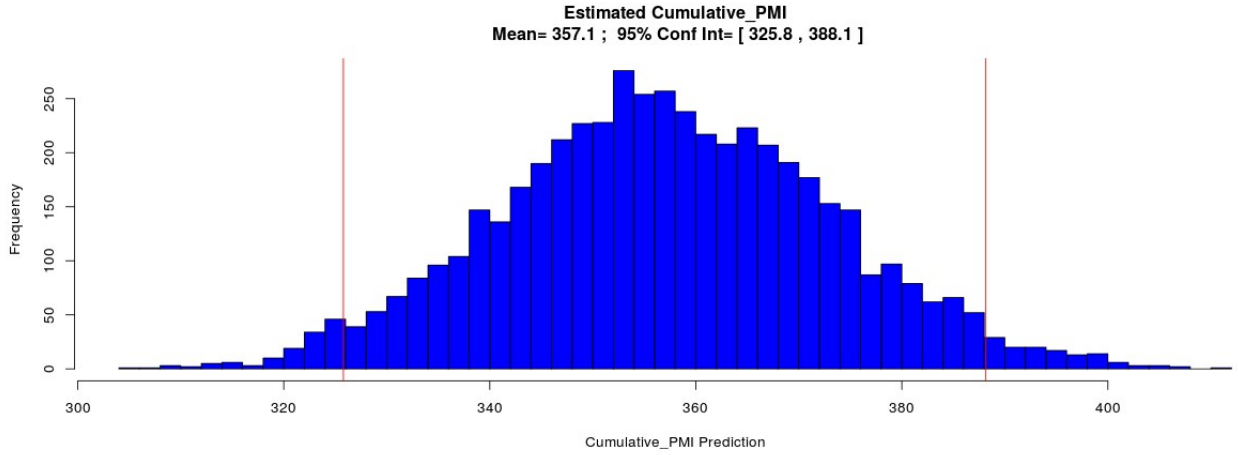
Add Row | Remove Row

First, we will codify the whole reaction using A to H as the labels. Then we will establish the reaction sequence using the 1st tab selecting starting material and product from each of the reaction. On this tab we can also provide the stoichiometric information. For example, we knew that using the Buchwald groups procedure, two equivalent of 2,4,6-triisopropylbromobenzene, labelled as E will be used. (The range of the stoichiometric ratio can be provided as well, such as 1.5 to 2 equivalent, for demo purpose here, we will use 2 eq only). In the same fashion, we knew chlorodicyclohexylphosphine, G, was introduced as 1.09 eq, we can provide the number in the stoichiometry cell here. Once the "Define Process" tab is filled, we can click the "PMI value" tab where a reaction network will be automatically generated as a DAG-like network graph. We can fill out the molecular weights for each nodes, followed by selecting the reaction type from the database, the range of the step PMI and yields will be autofilled. At this point, if one has the actual step PMI and yield info, or only has yield range, we can select the ranges accordingly. For example, for the 1st two steps, assuming a telescoped process to make 1,4-dimethoxy-2-fluorobenzene based on the literature, we would select observed 40~45% yield range and using the generic step PMI range from the telescope type unless one has updated info. For the next telescoped step to make biphenyl compound, C, one can choose either existing process info (step PMI 158/ yield 63%) as fixed single number or using any other anticipated ranges. For demo purpose, we used actual process info for some of the later steps.

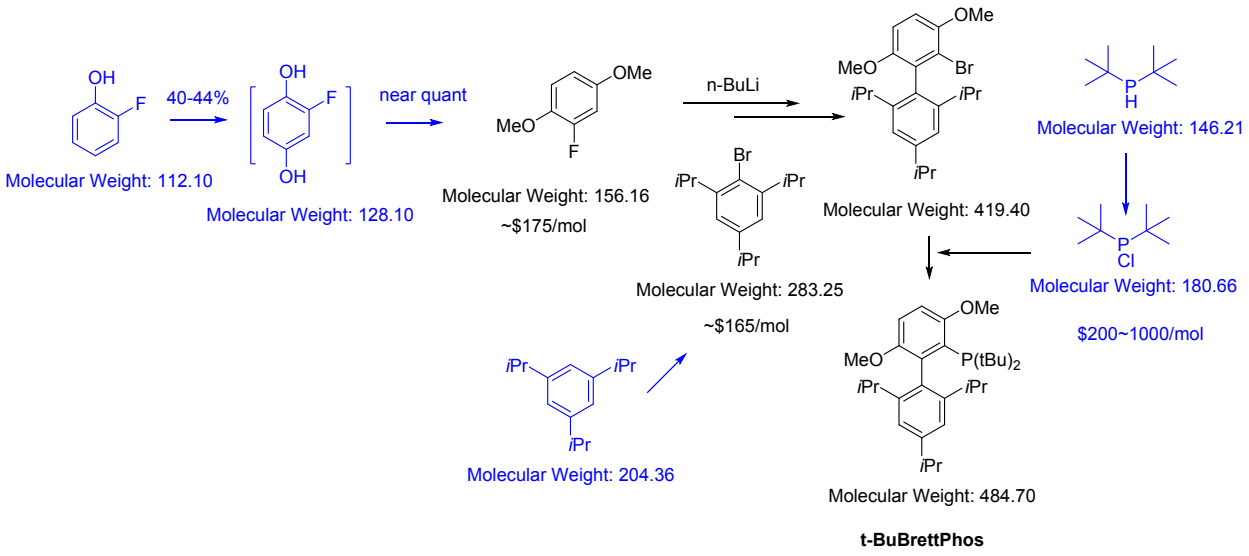


The next step is to click on the results tab and click "calculate" button to initiate the monte carlo simulation. The cumulative PMI results will be presented as histogram with average cPMI showing 357 and 95% CI

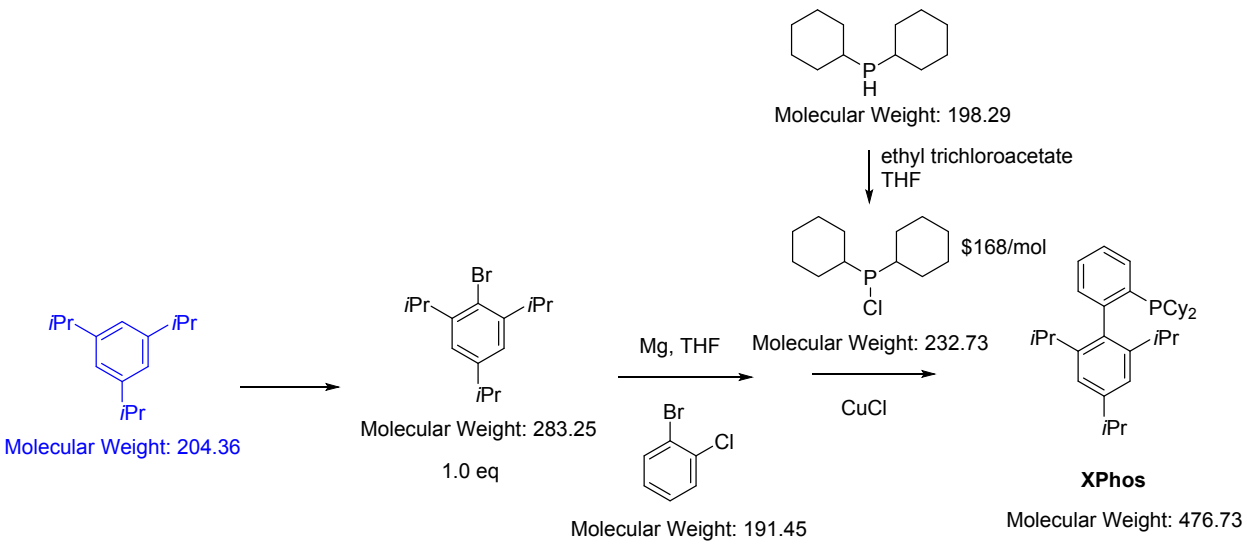
[326,388]. Please note that the main portion of the 2-step synthesis reported in the Buchwald paper without including the three side chain synthesis gave cPMI 247. The $100/mol threshold made the whole ligand synthesis 45% larger!



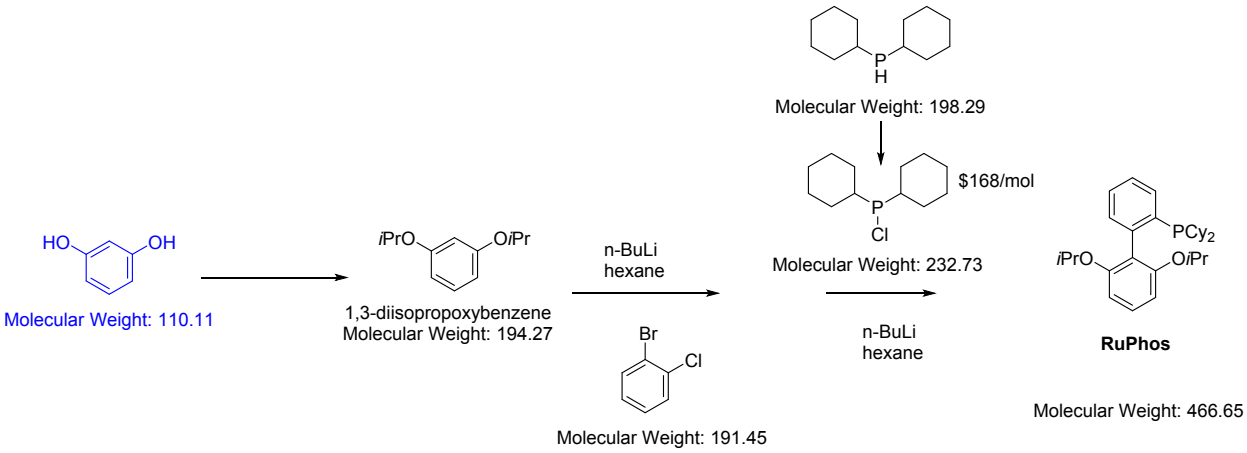
We evaluated the cPMI for rest of the phosphine ligands used in the illustration. The synthetic schemes area as follows for t-Bu-Brettphos, Xphos, Ruphos, BINAP, and Xantphos.



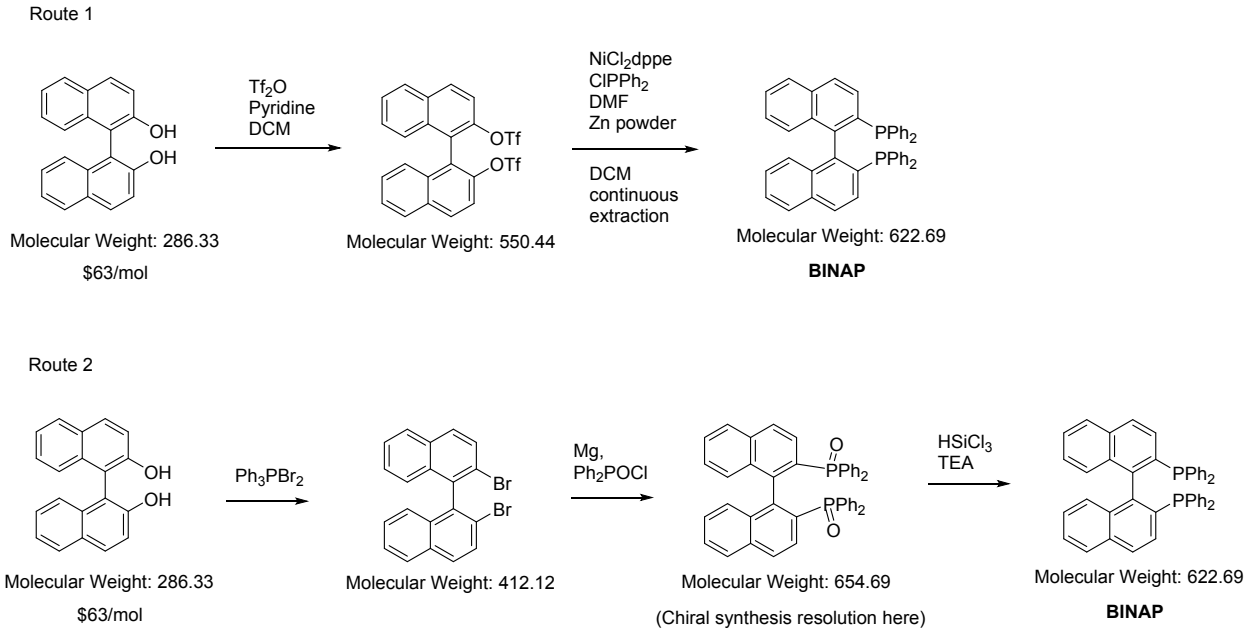
Scheme S2. tert-Bu-BrettPhos Synthesis



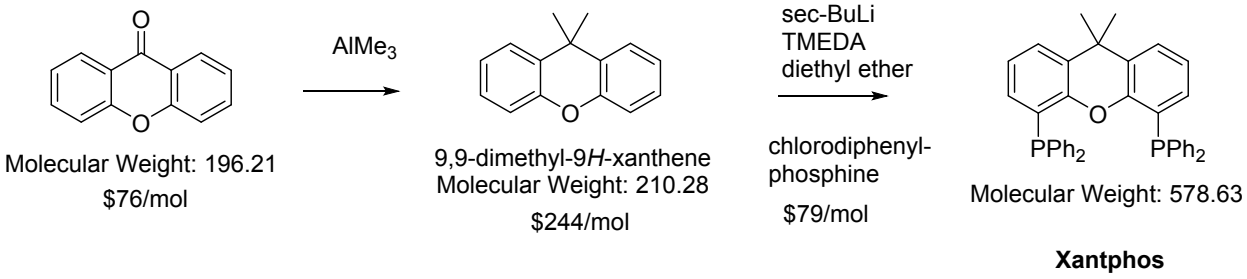
Scheme S3. XPhos Synthesis



Scheme S4. RuPhos Synthesis



Scheme S5.rac-BINAP Synthesis



Scheme S6.Xantphos Synthesis

The cPMI and corresponding overall yield from designated starting material on the longest linear sequence were calculated based on the reported literatures as well as step PMI/yield from reaction types collected in the aggregated ACS GCI dataset in case no detailed procedure was available as a reasonable estimates. The table below includes the result.

Ligand (Mw)	cPMI (avg)	Overall yield	Starting material from LLS (Mw)
Brettphos (536.78)	357	21%	o-fluorophenol (112.10)
tBu-Brettphos (484.70)	325	23%	o-fluorophenol (112.10)
XPhos (476.73)	54	45%	Trisisopropylbenzene (204.36)
RuPhos (466.65)	134	57%	Resorcinol (110.11)
BINAP (622.69)	82 (route1) 180 (route2)	52% (route1) 39% (route2)	BINOL (286.33)
Xantphos (578.63)	104	72%	Xanthone (196.21)

i F. Roschangar, et al. *Green Chem.*, 2018, **20**, 2206-2211

ii N. Hoshiyaa, S. L. Buchwald, *Adv. Synth. Catal*. 2012, **354**, 2031 – 2037.

iii (a) A. E. Feiring et al *J. Org. Chem*. 1975, **40**, 2543. (b) R. A. Glennon et al *J. Med. Chem.* 1982, **25**, 1163.