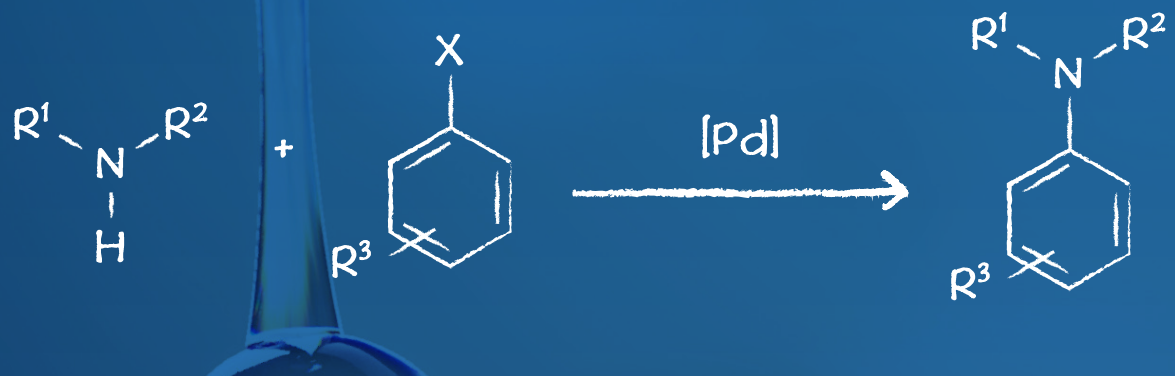
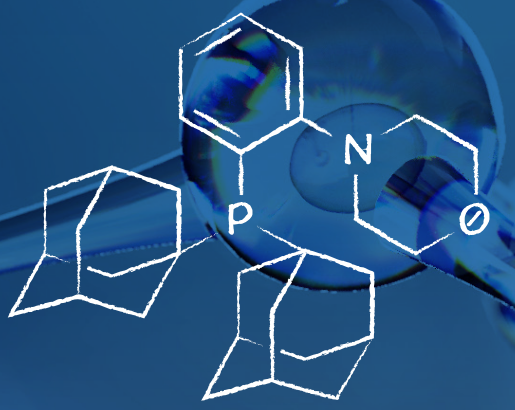
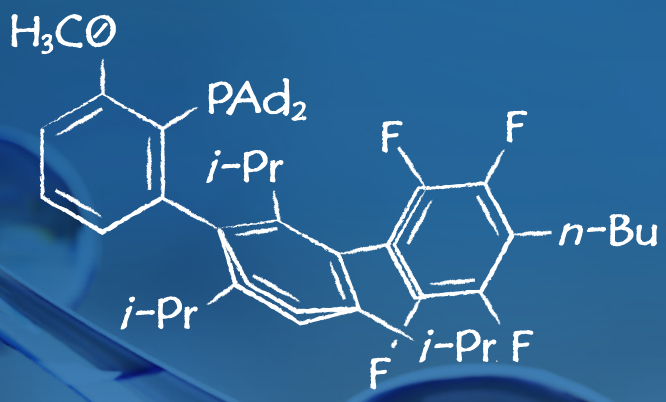
SC SNAPSHOT

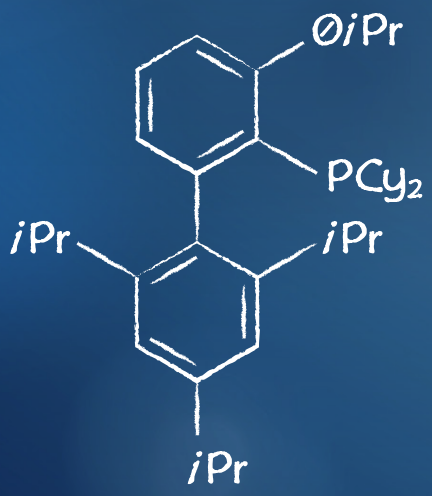
Pd-CATALYSED C-N BOND FORMATION:

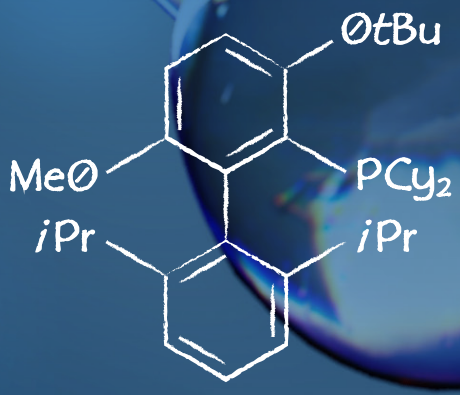
SOME OPTIONS TO ACHIEVE CHALLENGING TRANSFORMATIONS











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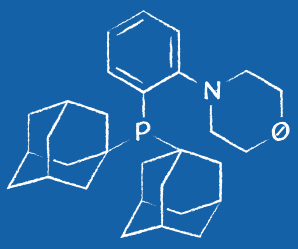
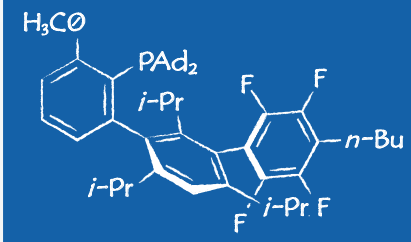
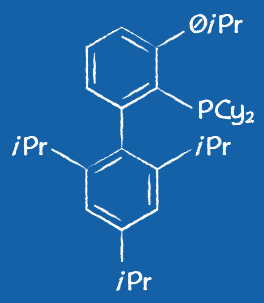
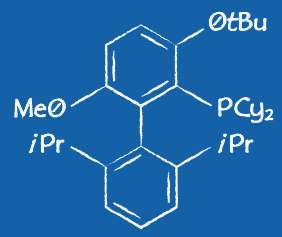
C-N Bond Formation Mini-Cheat Sheet

Ligand	Product code	Noteworthy points	References
 MorDalPhos	SC-4199	Versatile ligand: - Selective mono-arylation (ammonia, hydrazine, acetone) - Useful in arylation of heteroaryl - and alkylamines as well as amides	[5, 6a-c]
 AlPhos	SC-5023	Enables use of soluble organic bases.	[11, 12]
 EPhos	SC-4484	Enables use of mild bases such as NaOPh and K_2CO_3.	[13]
 GPhos	SC-5110	Enables reaction at ambient temperature.	[14]

43%
of the five most frequently used reaction types to produce compounds in drug discovery programs are C-N bond formation reactions, among which N-arylation accounts for 21%.[1]

Pd-catalysed C-N bond formation reactions

How do you know which catalyst or ligand to use? The million-dollar question for any R&D chemist who is trying to forge a new bond, whether for drug discovery or process development purposes. Based on experience and literature searches, it is possible to short-list catalyst or ligand candidates that are likely to work in a given transformation. But there is only one place where you will find the true answer – in the lab.

The large number of ligands and catalysts that have been developed for Pd-catalysed C-N bond formation reactions reflect the fact that this is one of the most widely applied technologies in industry. 43% of the five most frequently used reaction types to produce compounds in drug discovery programs are C-N bond formation reactions, among which N-arylation accounts for 21%.[1]

Starting with the widely applied bidentate ligands, such as BINAP[2] and Xantphos,[3] as well as monodentate tertiary phosphines, such as *t*-Bu_3P,[4] in recent years a number of more advanced ligands that have demonstrated high activity particularly in challenging C-N bond formation reactions have appeared in the literature. Some of these will be discussed in this Snapshot article, which is not designed to be a review of this area but will merely provide a few highlights of the choices available to the synthetic chemist.

The first product highlight is MorDalPhos, a dialkylaryl-phosphine ligand developed by Prof. Mark Stradiotto.[5] This ligand has been applied in combination with Pd in an increasing number of applications for the synthesis of pharmaceutically relevant molecules. As shown in Figure 1, taking advantage of MorDalPhos Pd G3, researchers at Galapagos demonstrated a C-N cross-coupling to form novel compounds **1** for the treatment of inflammatory disorders.[6a] Similarly, the above catalyst system was adopted by researchers at Merck to construct the C-N bond in triazolo derivative **2**[4b] that was applied in the treatment of central nervous system disorders. The C-N coupling of a range of MALT 1 inhibitors **3** was achieved by [Pd(cinnamyl)Cl]$_2$/ MorDalPhos catalyst system.[4c]

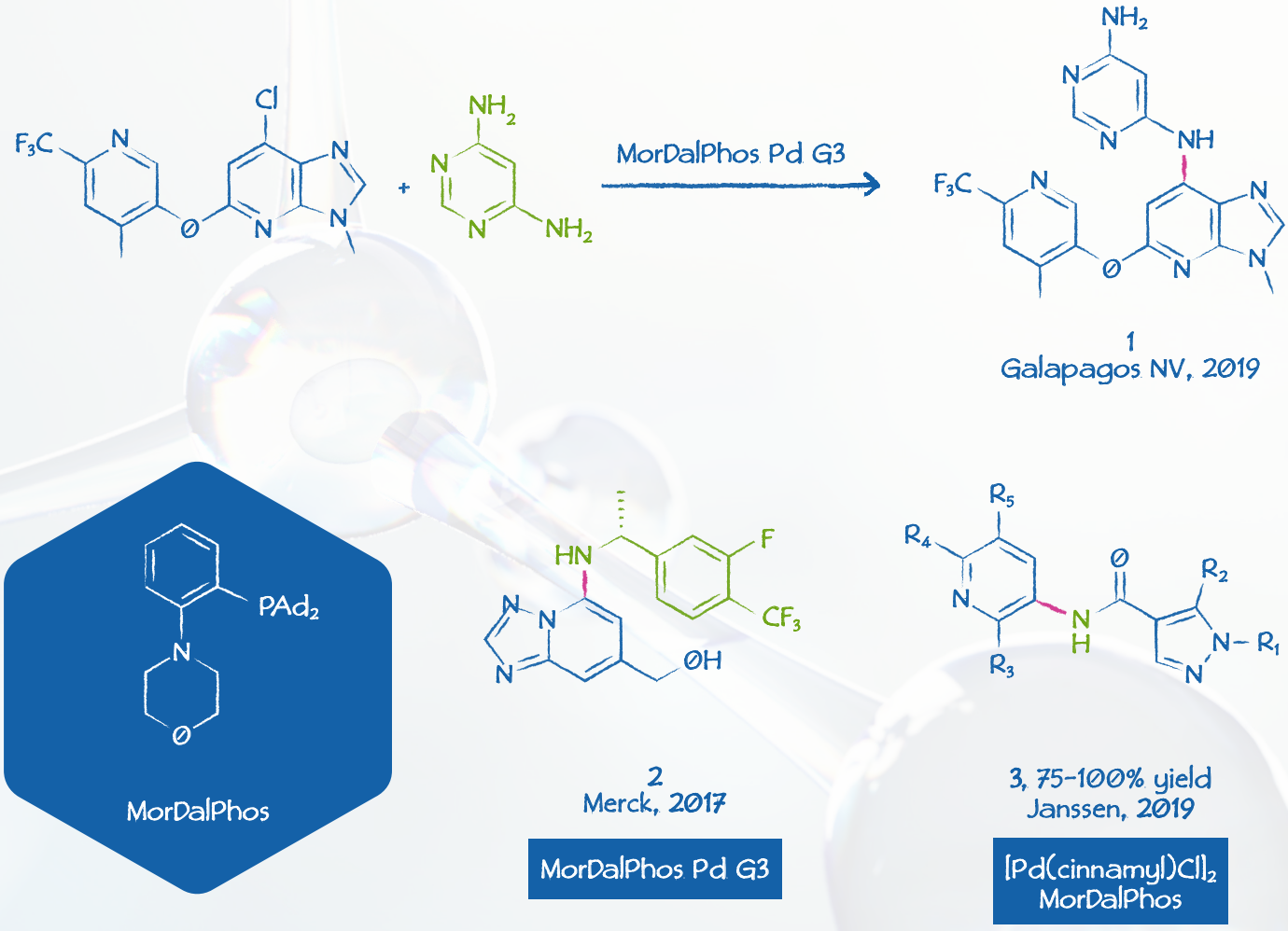


Figure 1. C-N bond formed using [Pd]/MorDalPhos catalyst system

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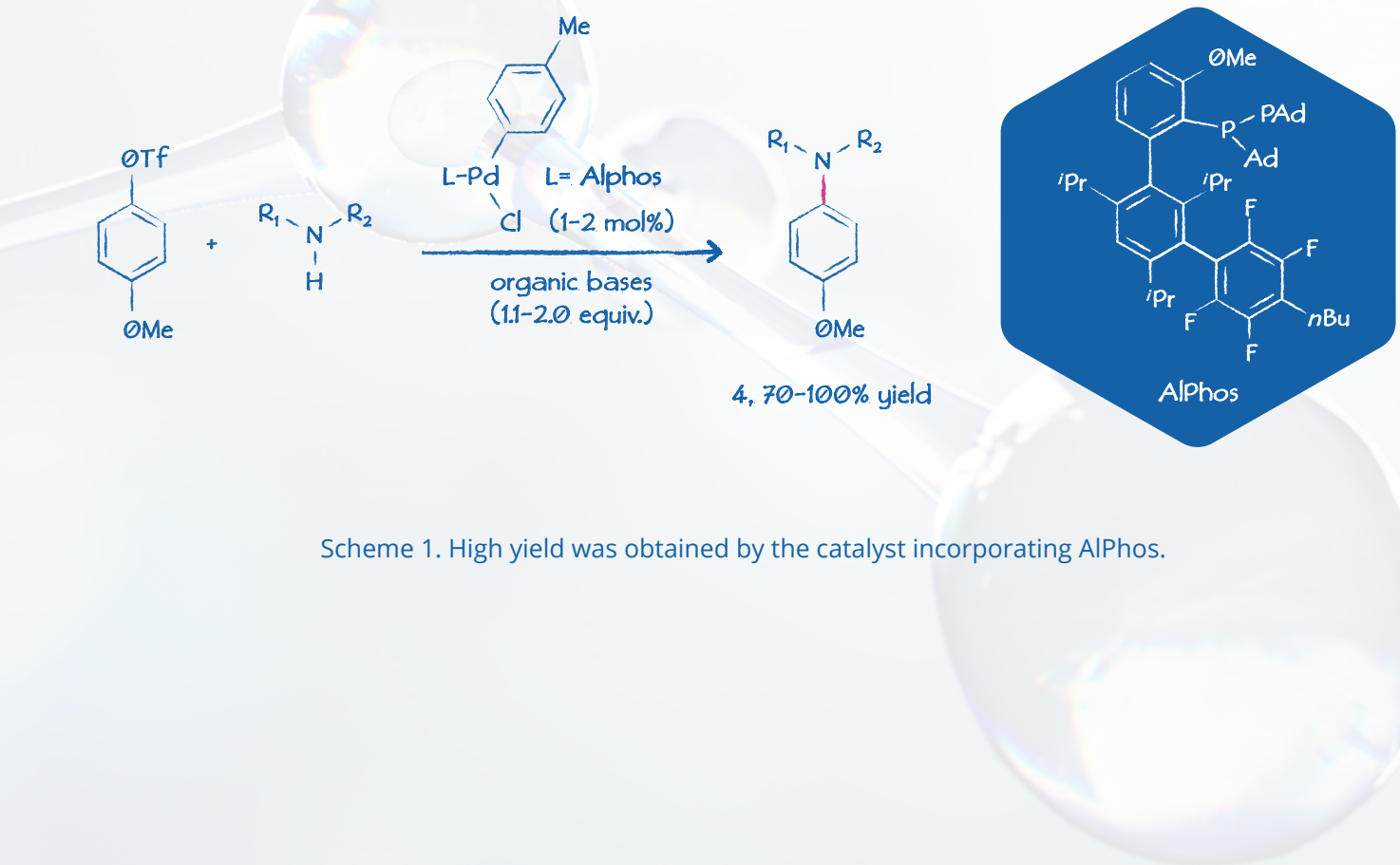
The remainder of the products that will be highlighted here belong to the family of dialkylbiarylphosphine ligands developed by Prof. Stephen Buchwald.[7] Due to their structural variability, Buchwald ligands can be tuned to promote the desired reactivity or selectivity in any specific transformation.

The two most established Buchwald ligands for C-N bond formation reactions are BrettPhos[8] and RuPhos.[9] Another novel Buchwald ligand is AlPhos that was developed in 2015.[10] The incorporation of AlPhos in a Pd-catalysed system enabled the utilization of a weak organic base (DBU) in the C-N coupling reactions.[11] The use of a soluble base resulted in a fully homogeneous nature of the reaction mixture and therefore suggests high potential of this catalyst system in advanced manufacturing methods such as continuous flow chemistry. Indeed, using automated microfluidic platform, researchers at MIT investigated the C-N coupling reaction between aryl triflate and amines. The result showed that the catalyst incorporating AlPhos was the most efficient compared to other dialkylbiarylphosphine ligands (Scheme 1).[12]



Scheme 1. High yield was obtained by the catalyst incorporating AlPhos.

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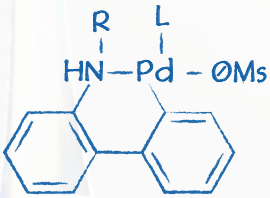
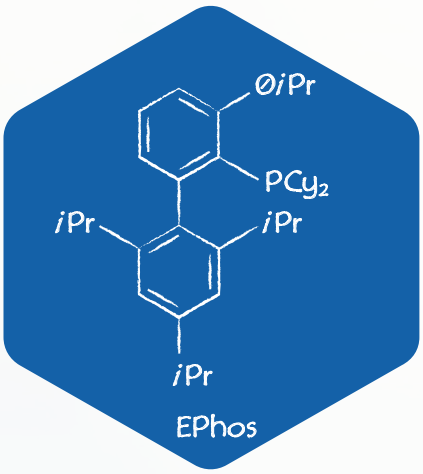
Recently, two updated Buchwald ligands, namely, EPhos[13] and GPhos[14] were developed. In both molecules, the bulky alkoxy substituent favours the formation of C-bound Pd^{II} isomer, which might account for the different efficiency between BrettPhos and EPhos in Pd-catalyzed C-N cross-couplings.[13] Catalyst screening (Scheme 2 and Table 1) demonstrated palladium precatalysts supported by EPhos are capable of promoting highly efficient coupling between aryl halide and primary amine using a mild base such as K_2CO_3 or NaOPh. Progressing the ligand evolution further, the catalyst system derived from GPhos enabled room-temperature C-N coupling reactions with high levels of efficiency in terms of both catalyst loading required and reaction time (Scheme 3).[14]



P1: L = BrettPhos, R = Me
P2: L = tBuBrettPhos, R = H
P3: L = EPhos, R = Me
P4: L = XPhos, R = Me



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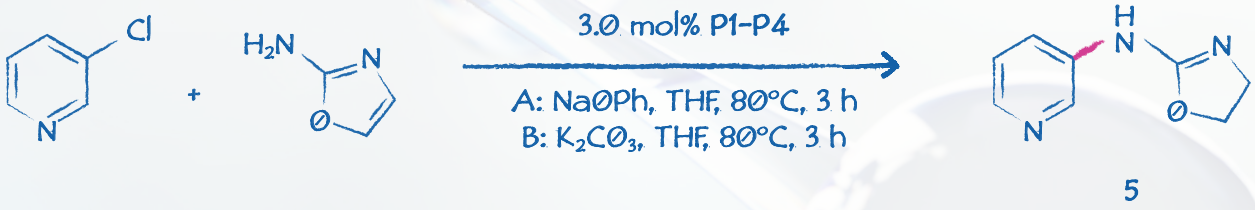

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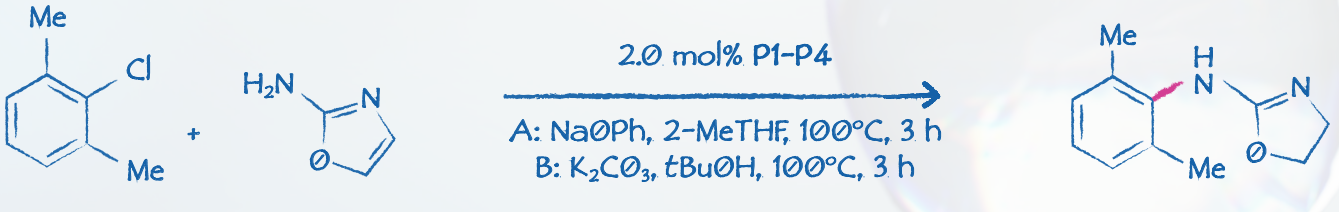
b)



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Scheme 2. C-N coupling between aryl halide and primary amine.

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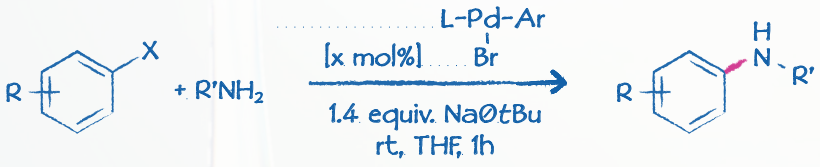
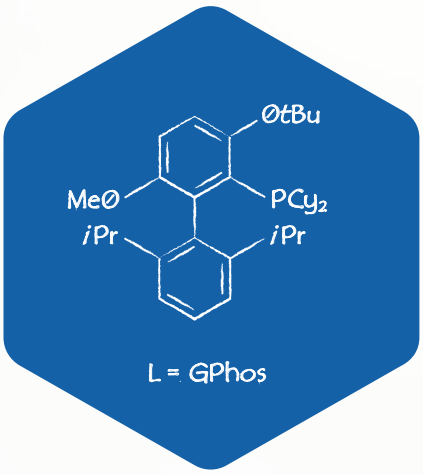
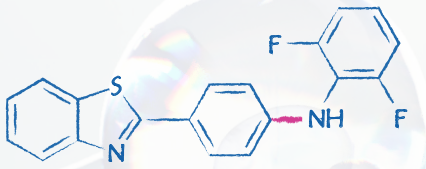
Table 1.
Yields of **5** and **6** under different conditions

	Equation (a)		Equation (b)	
	Yield of 5 (%)		Yield of 6 (%)	
	A	B	A	B
P1	54	25	/	38
P2	50	36	0	0
P3	78	/	85	92
P4	0	0	0	0

Scheme 3. Examples demonstrating high efficiency of catalyst system with GPhos.

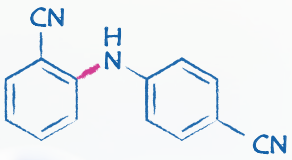






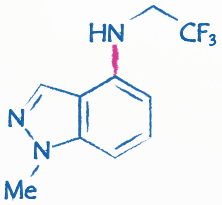
X = Br
[0.2 mol%], 95%

Previous: 3.0%
[Pd]/3.0%L, rt, 24 h



X = Cl
[0.5 mol%], 97%

Previous: 1.5%
[Pd]/3.0%BrettPhos, 110°C, 14 h



X = Br
[0.2 mol%], 95%

Previous: 0.1-1.5%
[Pd]/0.2-3.0% AdBippyPhos, 110°C, 6 h

To conclude, a combination of reaction mechanisms-guided ligand design and careful optimisation of reaction conditions is continuing to expand the potential applications of C-N bond formation reactions in the fine chemical space.

The final choice of catalyst system will depend on the priority requirements for your C-N bond formation process, after having assessed the chemistry performance. Factors to consider can be the overall process costs, base- or temperature sensitive functional groups in your substrates, as low metal loading as possible to avoid Pd contamination of your product, or indeed commercial availability of the catalyst and/or ligand.

We believe that having identified the best catalyst/ligand for your process, the commercial availability should not be a factor that stops this process from being scaled-up. We can work with you to ensure that the catalyst or ligand you need is available at the scale you require and to the timeline you require it.

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