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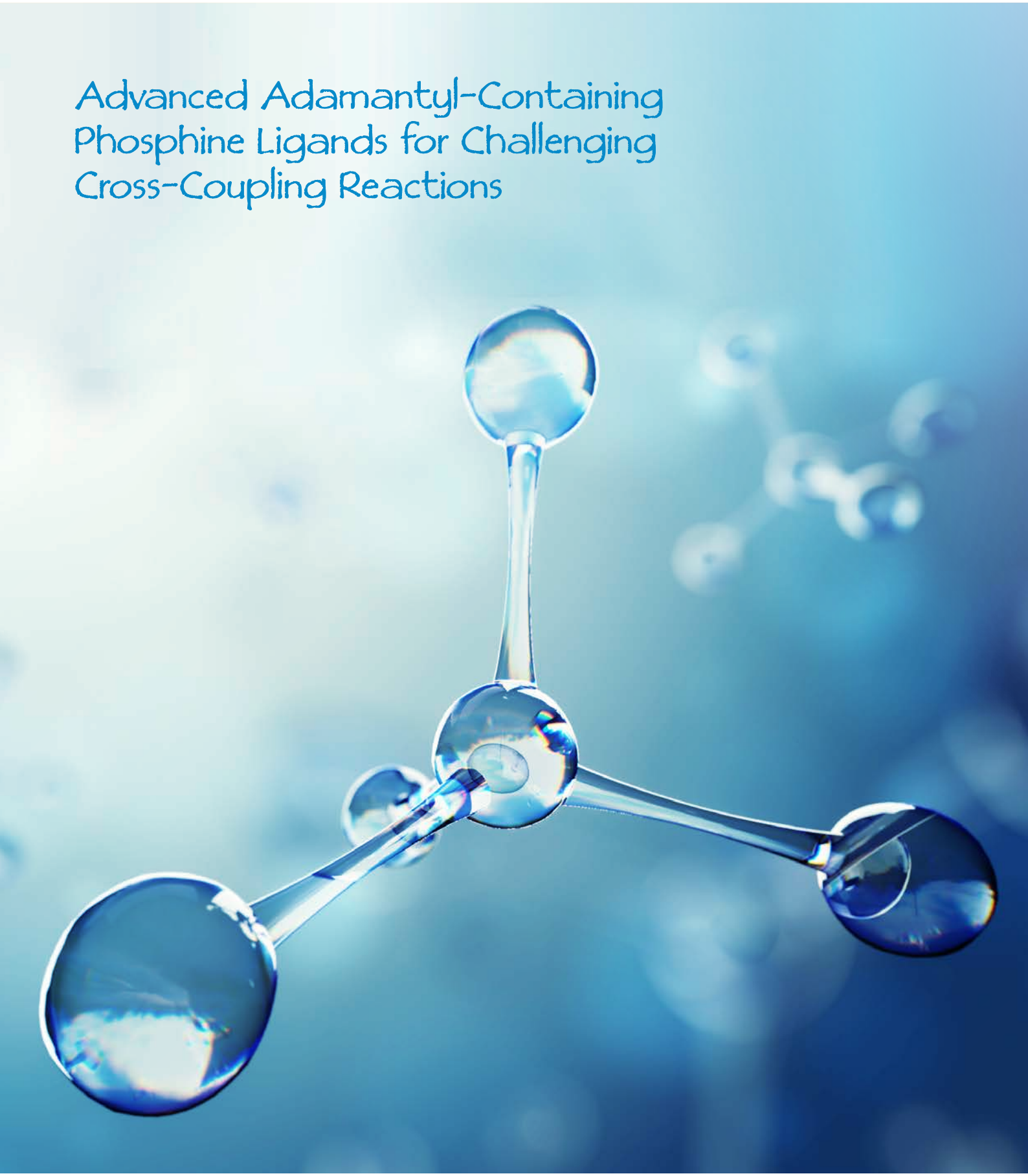
Advanced Adamantyl-Containing Phosphine Ligands for Challenging Cross-Coupling Reactions



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Foreword

The ability to tune the reactivity properties of metal complexes through the coordination of appropriate ancillary ligands is a well-established feature of organometallic chemistry that can be exploited in the development of new and synthetically useful catalytic reactivity. Indeed, the remarkable evolution of cross-coupling catalysis over the past twenty years can be attributed largely to advances in ancillary ligand design. During this evolution, adamantyl-containing phosphine ligands have emerged as offering unique and useful properties ranging from ease of handling to novel reactivity. This review documents prominent classes of adamantyl-based phosphine ligands, and discusses their suitability for industrial applications.

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Photo credit: Danny Abriel, Dalhousie University

Professor Mark Stradiotto is the Alexander McLeod Professor of Chemical Research and the Arthur B. McDonald Research Chair at Dalhousie University (Halifax, Canada). Professor Stradiotto has received multiple honours in recognition of his excellence in research and teaching, including the Chemical Institute of Canada 2021 Rio Tinto Award, which recognizes the novelty and interdisciplinary impact of his now-commercialized 'DalPhos' family of ligands and catalysts that are employed internationally in both academia and industry.

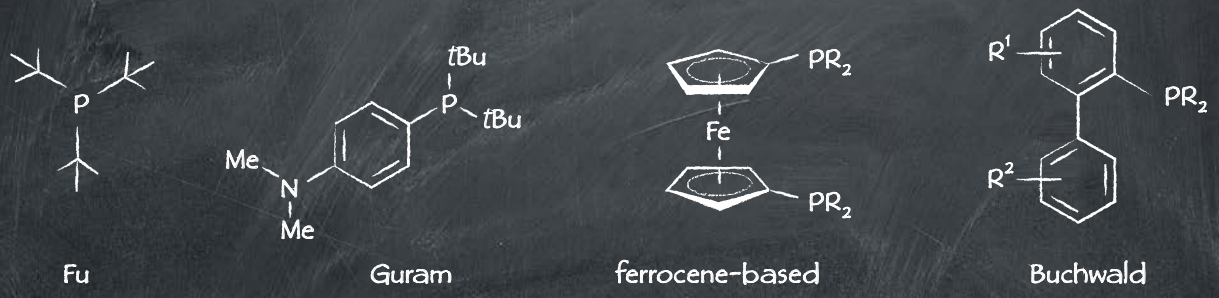
The Rise of the Bulky Adamantyl-Containing Phosphine Ligands

Countless review and research articles over the years have emphasised the importance of bulky and electron-rich phosphine ligands as a potential "make or break" factor for the success of particularly challenging palladium-catalysed cross-coupling reactions.[1] Thanks to academic research and advances in pharmaceutical chemistry, over the last two decades the field of Pd-catalyzed C-C and C-X bond formation reactions have witnessed remarkable progress. For example, nowadays Suzuki-Miyaura reaction alongside aromatic nucleophilic substitutions are two of the most frequently used synthetic tools to produce materials for drug discovery programmes.[2] N-Heterocyclic carbenes (NHCs) have emerged as alternatives to the more traditional phosphine ligands but have not yet reached the same level of applications in industry.[3] This mini-review article will focus on Pd catalysts containing phosphine ligands with the extremely bulky adamantane substituents. Our aim is not to provide an exhaustive account of the literature concerning these ligands, but only to provide a snapshot and highlight applications where adamantyl-containing ligands have excelled.

What factors can stop a catalyst or ligand from being qualified for a production process?

In addition to the obvious chemistry challenge of making a reaction work, the process chemist also needs to consider several other aspects in order to develop a production route. In the pharmaceutical industry the process to manufacture the API or drug will often, but not always, be different to the medicinal chemistry or drug discovery route. The process eventually chosen to carry out a particular step towards the synthesis of an API or other commercially relevant molecule has to satisfy on a number of points: 1) It should ideally be free of IP that belongs to another institution 2) All the reagents have to be readily available in bulk to ensure that the supply chain is secure even when the process is further scaled up 3) The cost needs to be minimised, although may not be a deterrent if a particular process is very efficient based on other parameters such as E-factor (sustainability), chemo- and/or stereoselectivity etc.

FIGURE 1: Structure of selected privileged phosphine ligands.



There is no such thing as a Universal Catalyst.

The importance of ligands for the eventual success of a certain cross-coupling reaction was recognised early. Since then, hundreds of different ligands have been developed and evaluated. Among these, there are a few that can be considered so-called privileged structures (Figure 1). The privileged ligands tend to provide a high chance of success in giving at least a small amount of any desired cross-coupling product and are therefore generally a good starting point.[4]

However, it is particularly important to recognise that there is no such thing as a universal catalyst. If time is invested into finding the optimum catalyst/ligand and reaction conditions for a specific reaction, it is very unlikely to find the exact same catalyst/ligand and conditions come up as the best one for different reactions and/or substrate combinations. As with any living beings – no two ones are exactly the same.

New ligands are always needed...

There is a plethora of new ligands continuously reported in the literature, of which only a very small percentage will survive the process of elimination and eventually make it to commercial scale. For this to happen, there needs to be collaboration and communication between academia and several players in the pharma-, agro and fine chemicals space. Ligand and catalyst manufacturers play a crucial role here in enabling the new technologies developed at small scale to become a viable option for manufacturing.

....but which ones will make it to commercial scale?

The selection process for which ligands and/or catalysts are continued to larger scale production is complex, with many factors to consider. Is there a demand from, for example, pharmaceutical companies for a particular ligand or catalyst? If the answer is yes – is there a supplier for this ligand to secure the supply chain even when ramping up production? If there is not – is any catalyst/ligand manufacturer able to develop it into a product? When developed, can it be supplied at a cost that makes the eventual process for its application commercially viable?

Bearing all this in mind – what are the chances of adamantyl-containing ligands eventually entering the manufacturing arena? We believe - very high...

Cone angles and electron-donating substituents...

As a rule of thumb, the more sterically hindered the ligand and the more electron-rich the P atom, the more active the resulting catalyst. For the class of ligand with phosphorus(III) donor atom of general structure PR_3, the most commonly used method for quantifying the steric properties is calculating Tolman cone angles (θ), defined as the apex angle of a cone emanating from the metal centre towards the van der Waals radii of the outermost ligand atoms (Figure 2).[5] [a]Although steric parameterization based on experimental or computational results has been studied for several decades, the link between this parameter and catalytic performance was not drawn until Osborn and co-workers found that optimal catalytic activity of Pd-phosphine complexes towards the carbonylation of dichloromethane and chlorobenzene was only observed where the cone angle ≥160° and the pKa exceeded 6.7.[6]

...make the adamantyl-containing phosphines very attractive from a ligand point of view

Based on the hypothesis that due to the favourable properties of the adamantane scaffold, ligands containing this motif may be able to contribute by affecting reactions that have not previously been efficiently achieved. Through the work of many research groups, this has indeed proven to be the case.

One representative example is PAd_3, which was developed by Carrow and co-workers in 2016.[5b] Investigations revealed that a PAd_3-palladacycle catalyzes Suzuki-Miyaura coupling of chloro(hetero) arenes with exceptional TOF and high TON that exceeds other alkylphosphines (Figure 3). The result, as well as the correlation between Tolman electronic and Taft σ_α parameter support the hypothesis that access to phosphine ligands with steric or electronic properties beyond previously investigated limits can enable unique reactivity in catalysis.[5b]

FIGURE 2: Tolman cone angle of monodentate phosphine ligand with general structure PR_3. The M-P bond length is set to 2.8 Å by default.

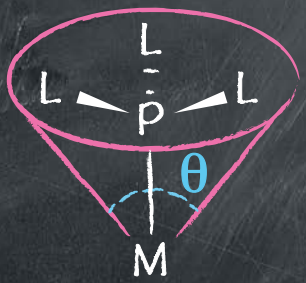
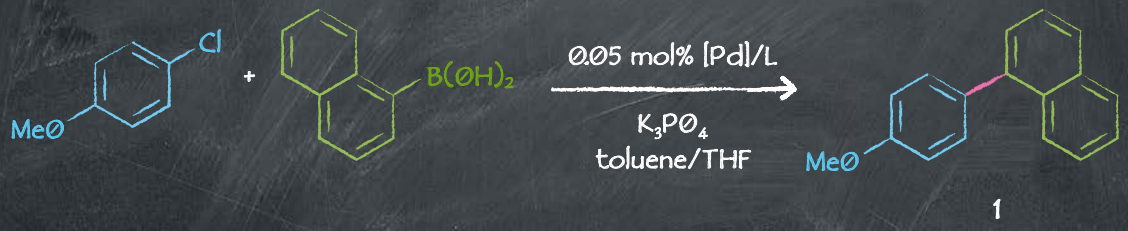


TABLE 1: Comparison of the Tolman cone angles and pK_a values of various commonly used phosphine ligands.[5]

Ligand	Tolman Cone Angle (θ)	pK_a values
PPh_3	145[5a]	2.73[5c]
$P(tBu)_3$	182[5a]	10.7[5d]
PAd_3	179[5b]	11.6[5b]
PCy_3	170[5a]	9.7[5a]

FIGURE 3: Yield of 1 with [Pd]/L = 1 in the cases of various alkylphosphines.

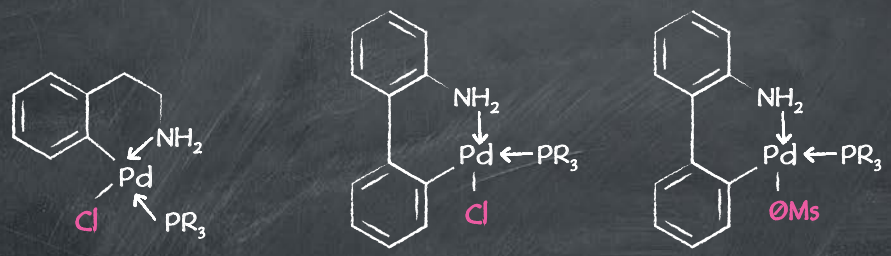


L	Time (h)	Yield of 1 (%)
PAd_3	4	99
$P(tBu)_3$	4	<10
Ad_2PnBu	4	<10
PCy_3	4	<10

In general, use of a Pd-G source and phosphine ligands of the type PR_3 as catalyst system (Figure 4) was found advantageous for Suzuki-Miyaura and C–N Cross-Coupling reactions. The identification of the optimal ligand was particularly significant with respect to achieving low catalyst loading. This highlights the importance of catalyst and ligand screening in order to explore the chemical space in its entirety.

Since the adamantane-containing ligand and catalysts was exhaustively reviewed by Williams and co-workers in 2016,[7] and a variety of commercially accessible ligands for palladium catalyzed cross-coupling reactions was also summarized by Spindler,[8] in this article we are limiting the discussions to selected adamantyl-containing ligands and their preformed Pd catalysts and highlighting applications where these ligands have excelled in recent years.

FIGURE 4: Structures of supporting ligands and palladium precatalysts encountered in this review.

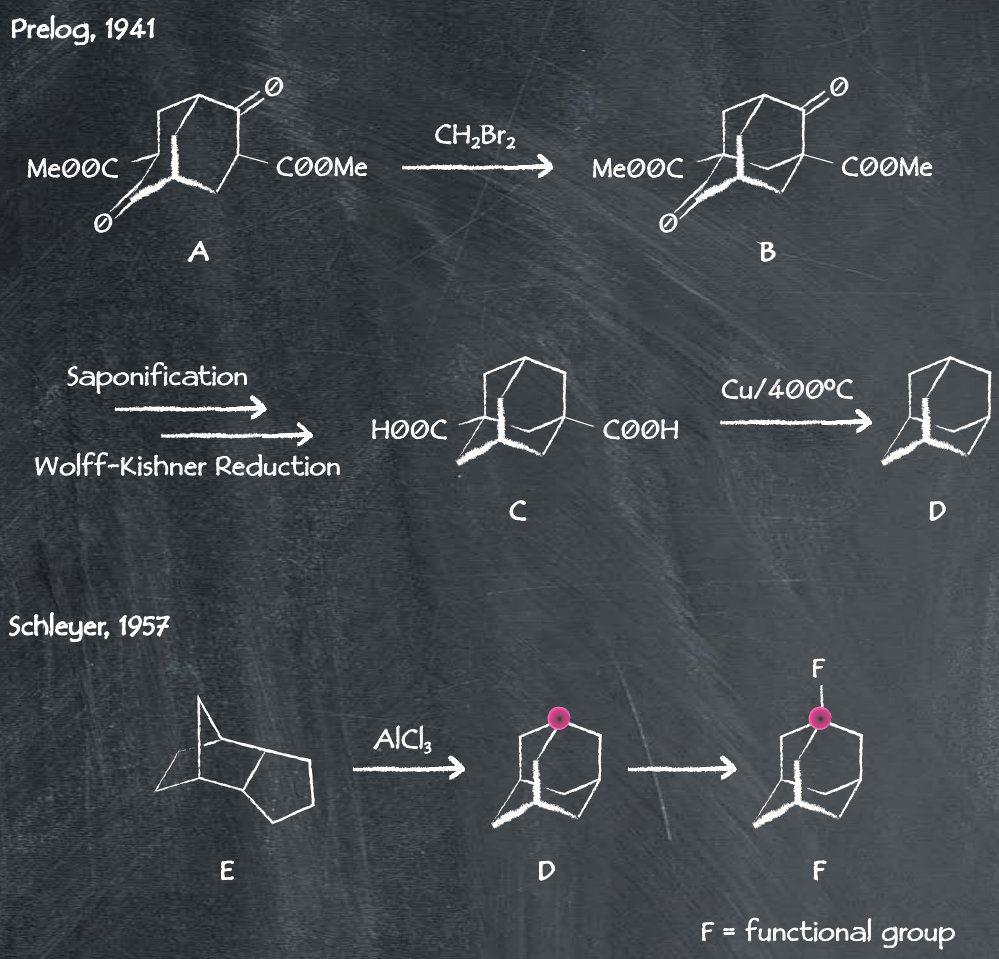


PR_3 Pd G1 complex PR_3 Pd G2 complex PR_3 Pd G3 complex

The idea of investigating adamantyl-containing phosphine in catalysis required an improved synthesis of this scaffold.

Adamantane has a carbon framework that consists of a single cage-shaped structure. As a natural constituent of fossil fuel, the first total synthesis of adamantane **D** was accomplished by Prelog and co-workers in 1941 (Scheme 1) taking advantage of the key Wolff-Kishner reduction step from the starting material **A**.[9] However, the cumbersome steps limited the overall yield of this compound and therefore also any subsequent interest of the synthetic organic chemist. In 1957, an alternative method was developed by Schleyer, using Lewis acid-catalyzed isomerization of endo-trimethylenenorbornane **E** (Scheme 1).[10] The acceptable yield as well as the ease of manipulations that contains only one step, together with feasible functionalization of adamantane, opened the door to the exploration of applications of the adamantane scaffold. The improved preparation protocols and modifications methodologies of adamantane functionalization have enabled the subsequent synthesis of various adamantyl-containing compounds. Adamantane is now a relatively cheap and readily available starting material.

SCHEME 1: Total synthesis of adamantane **D** by Prelog and Schleyer as well as the functionalized product **F**.



Catalysis applications featuring adamantyl-containing ligands include many named reactions...

Over the past decade, the number of literature examples of successful catalysts featuring the adamantyl moiety has certainly increased in the academic field. The current reaction portfolio includes C-C, C-N, C-heteroatom, and C-halogen bond formation. Even though these adamantyl-containing ligands have been utilized broadly for the synthesis of a variety of molecules, in this mini-review, we are restricting the scope to the ligands that have been used for the synthesis of pharmaceutically relevant molecules. Adamantyl-containing phosphine ligands included in this review are shown in Figure 5.

...C-C Bond Formation...

Suzuki-Miyaura reactions

While catalyst systems with Ad_2PnBu and transition metals such as Ir[11] and Ag[12] have been widely investigated in academia, the most common methodology in industry using this ligand is Pd-catalyzed Suzuki-Miyaura (S-M) cross-coupling reactions. Culminating in Prof. Suzuki being joint recipient, alongside Prof. Negishi and Prof. Heck, of the 2010 Nobel Prize in chemistry for his work in the cross-coupling area, this reaction has played an important role in synthesizing pharmaceutical motifs in recent years, and will no doubt continue to do so for the foreseeable future.

FIGURE 5: Ad-containing phosphine ligands in this review.

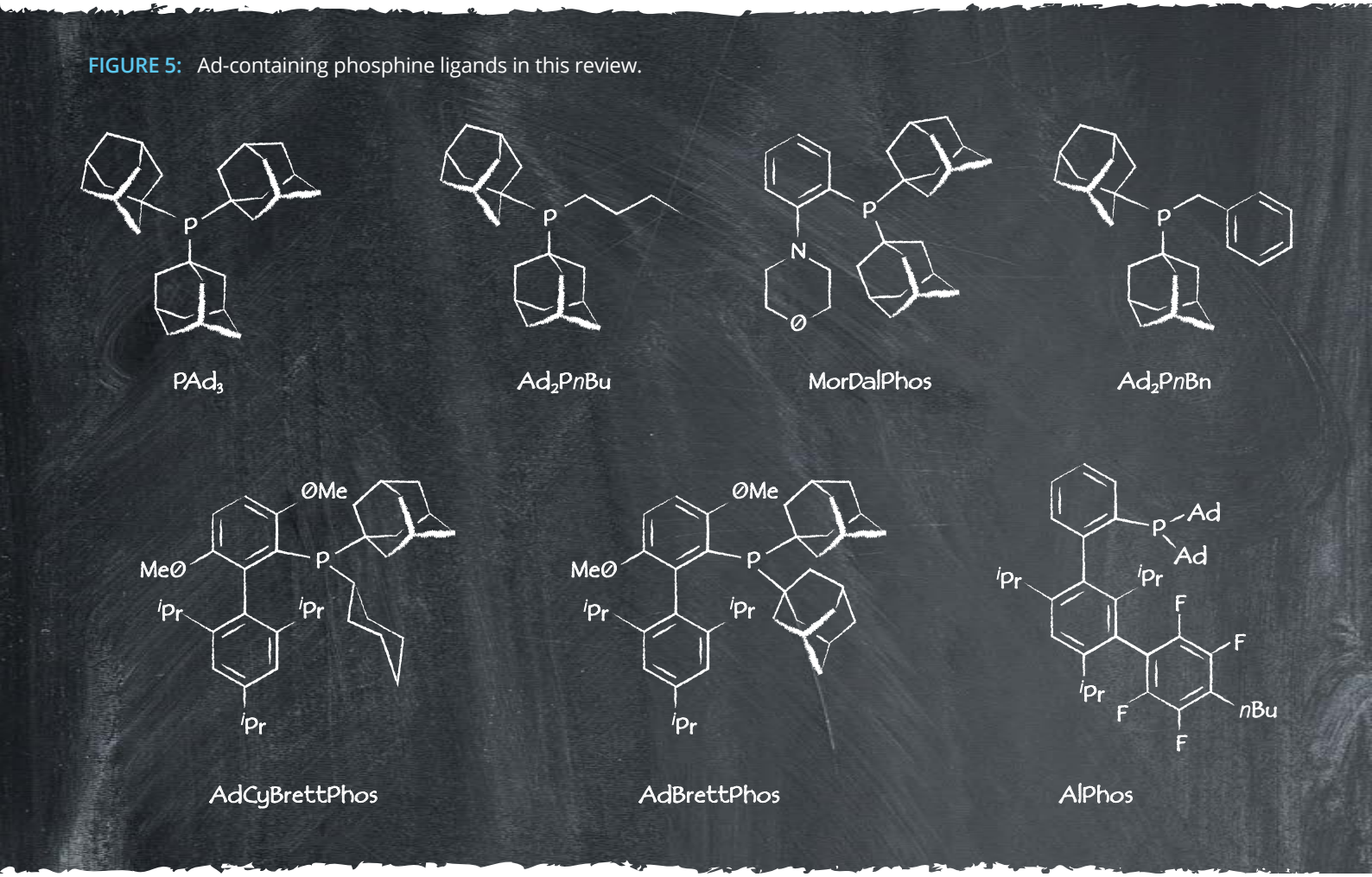
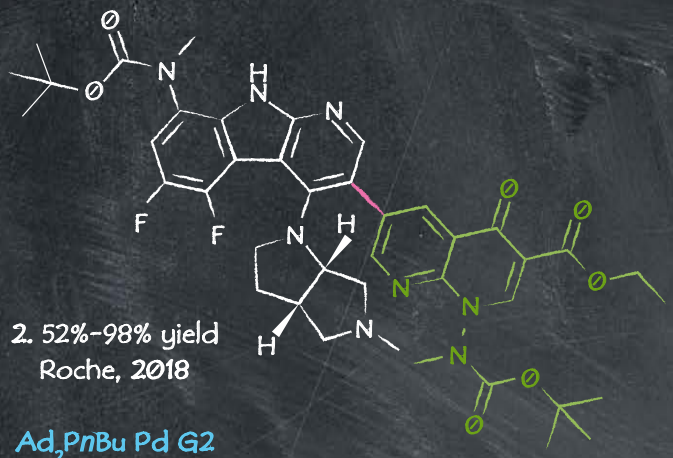
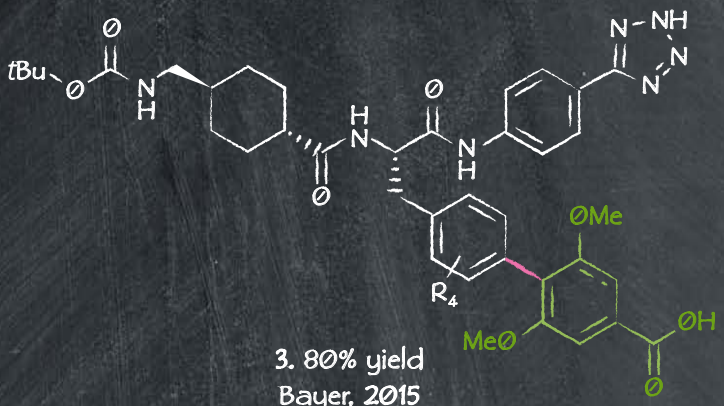


FIGURE 6: C-C bond formed using Palladium and Ad_2PnBu catalyst system is highlighted in red.



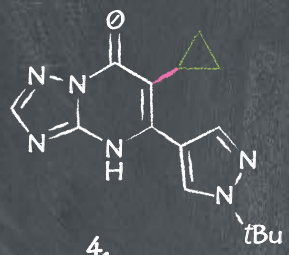
2. 52%-98% yield
Roche, 2018

Ad_2PnBu Pd G2



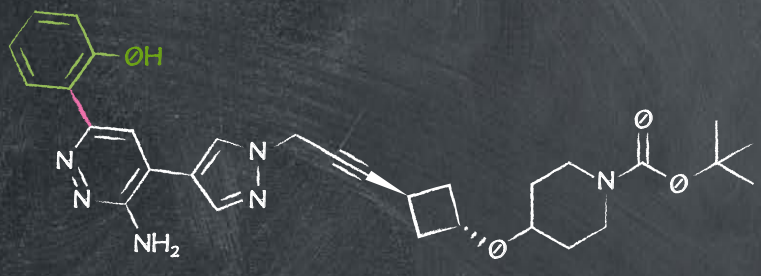
3. 80% yield
Bayer, 2015

Ad_2PnBu Pd G3



4.
Merck, 2018

Ad_2PnBu Pd G3



5. 78% yield
Genetech, 2019

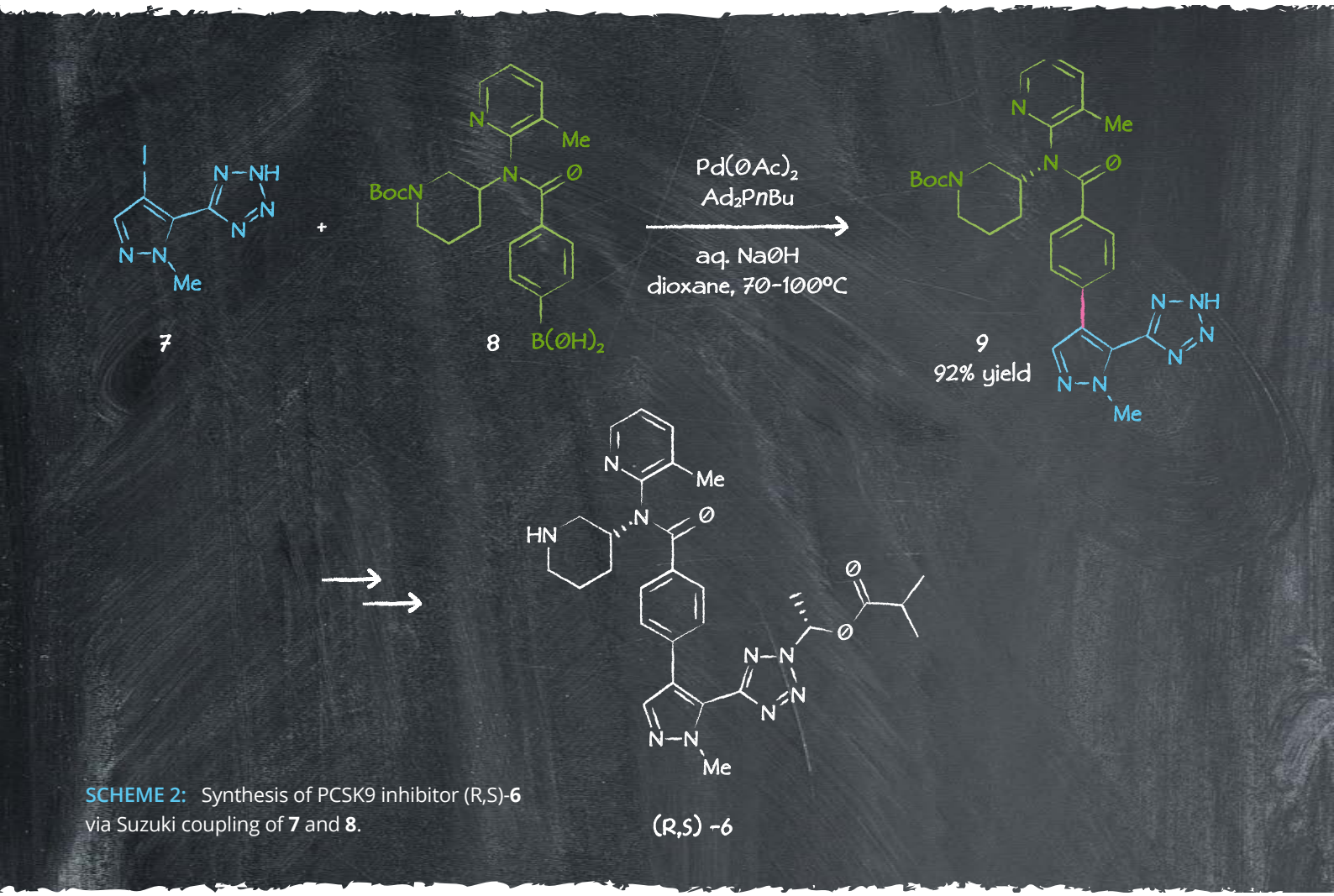
Ad_2PnBu Pd G3

Among the myriad of S-M reactions reported in the literature, we have cherry-picked a few of our favourite cross-couplings featuring adamantyl-containing ligands.

The first example was reported by researchers at Roche, in the synthesis of anti-bacterial agent **2** (Figure 6). The cross-coupling to form the core bi-pyridyl motif in a range of novel pyrido[2,3-b] indole compounds was successfully achieved using Ad_2PnBu Pd G2 as a catalyst.[13] Another example describes the gram-scale synthesis of the biphenyl block of substituted phenylalanine derivatives **3**. These compounds have been developed by Bayer for the treatment of cardiovascular diseases.[14] In this case Ad_2PnBu Pd G3 was employed as the catalyst.

This has also been the catalyst of choice for a number of other challenging S-M cross-coupling, as evidenced by Merck's synthesis of KDM5 inhibitors **4**[15] and Genentech's preparation of bifunctional PROTAC compounds **5**.[16] It is noteworthy that the Ad_2PnBu Pd G3 system shows high reactivity in the cases of electron-deficient substrates.

The synthesis of multigram quantities of small molecule PCSK9 inhibitor (R,S)-**6** was described by Pfizer.[17] An optimized set of conditions using $Pd(OAc)_2$ in combination with Ad_2PnBu as the catalyst system and elevated temperature of 100 °C in dioxane allowed for facile coupling of **7** with boronic acid **8** on a 1g scale to provide tetrazole intermediate **9** in 92% isolated yield (Scheme 2).



SCHEME 2: Synthesis of PCSK9 inhibitor (R,S)-**6** via Suzuki coupling of **7** and **8**.

Another multigram synthesis example reported by Merck involves the synthesis of the intermediate of biaryl chroman agoPAMs that shows superior efficacy to partial agonists.[18] As demonstrated in Figure 7, an improved S-M cross-coupling employing Ad_2PnBu Pd G3 was devised, utilizing vinyl tosylate and 3-benzyloxyphenyl boronic acid as substrates, to obtain the cinnamate derivate **10** in 89% yield. Moreover, the catalyst combination of $Pd(OAc)_2$ and Ad_2PnBu was also industrially applied for the S-M cross-coupling reactions. Taking advantage of this system, GSK and AstraZeneca disclosed the protocol of synthesis of the ATAD2 inhibitors.[19] Coupling reaction between (5-Methylpyridin-3-yl) boronic acid and the heteroaryl bromide fragment led to formation of the framework **11** of ATAD2 inhibitor in moderate yield.

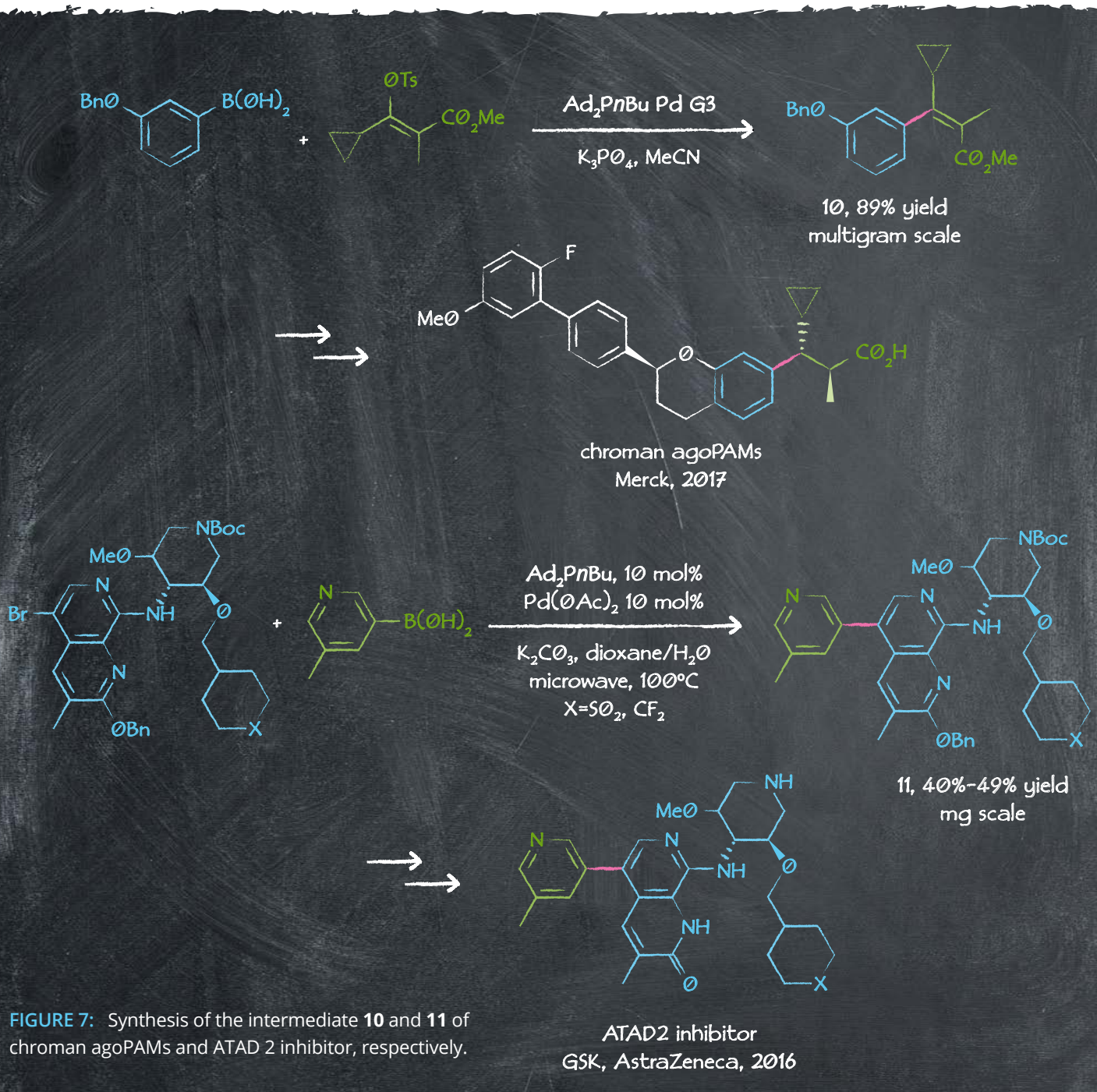
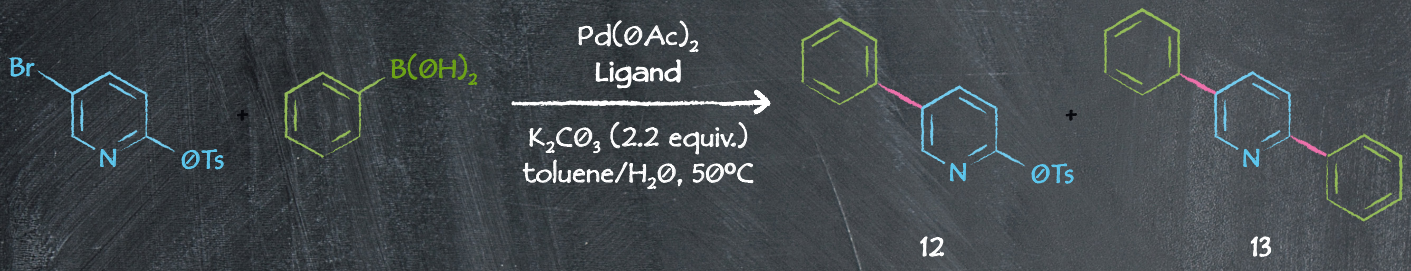


FIGURE 7: Synthesis of the intermediate **10** and **11** of chroman agoPAMs and ATAD 2 inhibitor, respectively.

Chemoselective Suzuki-Miyaura and α-arylation reactions

Selective mono-functionalisation of di-halide or pseudo-halide motifs is traditionally challenging to achieve. Often, a mixture of products is obtained which may require purification by chromatography. However, careful process optimisation may result in successful mono-functionalisation, avoiding tedious purification. We will highlight how this has been achieved purely by evaluating different phosphine ligands.

Pharmaceutically important unsymmetrical diarylpyridines were accessed via a mild chemoselective S-M coupling approach starting from bromo-2-sulfonyloxypyridines (Scheme 3).[20] When XPhos, SPhos, or RuPhos was used as the ligand, desired product **12** was afforded in moderate to good yields along with the symmetrical diarylated product **13**. Switching to trialkyl phosphine $P(Cy)_3$ improved the yield of **12** to 88 %. However, use of Ad_2PnBn as the ligand led to the highest isolated yield (99 %) of **12** in 20 min.[20a]



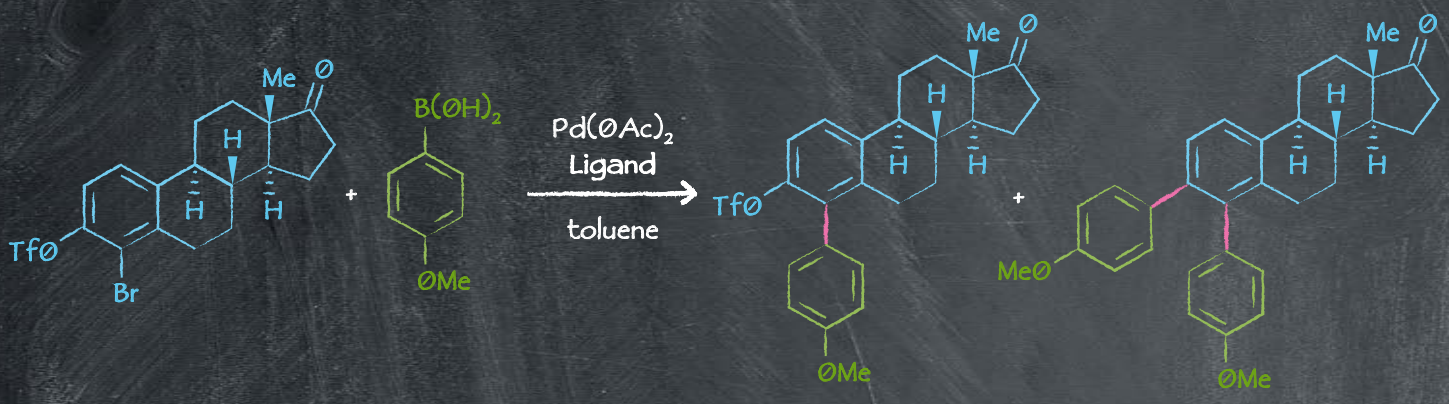
SCHEME 3: Optimization of the chemoselective S-M reaction employing bromo-2-sulfonyloxypyridines.

Ligand	Time (min)	Yield 12 (%)	Yield 13 (%)
XPhos	30	76	23
SPhos	30	81	18
RuPhos	40	63	36
$P(Cy)_3$	30	88	-
Ad_2PnBn	20	99	-

Further functionalization of the remaining tosyl (or triflate) group can afford novel and biologically relevant unsymmetrically substituted pyridine derivatives.[20]

Another example was the mono-arylation of the bromo aryl triflates of estrone derivatives using $Pd(OAc)_2$ and Ad_2PnBu system (Scheme 4). [21]

Interestingly, SPhos proved to be the ligand of choice for bisarylation, providing product **15** in 88 % yield. The use of Ad_2PnBu resulted in selective S-M coupling of the bromide over the triflate to afford desired product **14** in 98 % yield.[21b] The chemoselectivity could originate from the inherent steric hindrance of Ad_2PnBu, which might be too sterically encumbered for a second substitution.



SCHEME 4: Optimization of the chemoselective S-M reaction.

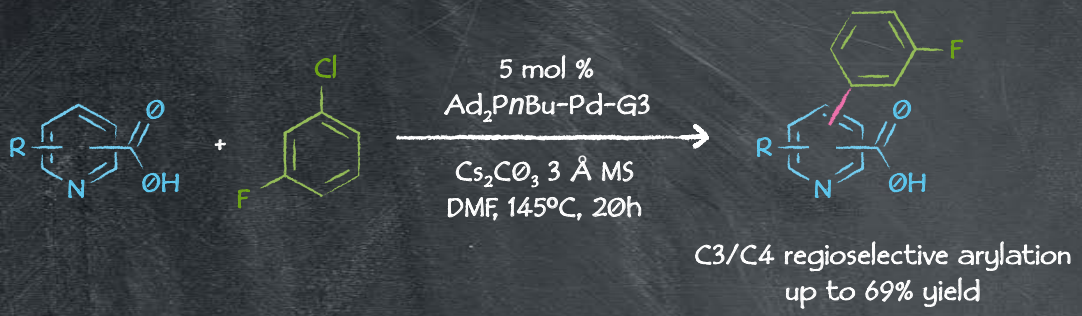
Ligand	Equiv. of $B(OH)_2$	Yield 14 (%)	Yield 15 (%)
$P(Cy)_3$	3.0	92	0
Ad_2PnBu	3.0	98	0
Ad_2PnBu	1.5	98	0
SPhos	3.0	12	88

Due to the high Lewis basicity of the sp^2 nitrogen, direct arylations of pyridines are challenging transformations in organic synthesis. The use of a Ad_2PnBu Pd G3 catalytic system and carboxylates as directing groups facilitated the C-H arylation of this difficult class of substrates (Scheme 5). This methodology allows for regioselective C3/C4 arylation without the need to use solvent quantities of the pyridine and using low-cost chloro- and bromoarenes as coupling partners.[22]

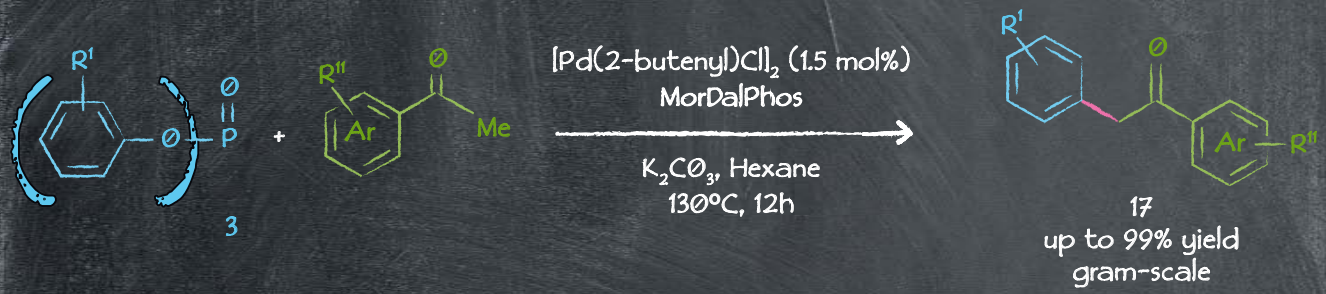
Another reaction class that has met with difficulties is the selective mono-arylation of aryl methyl ketones. One solution to this employed the adamantane-containing catalyst MorDalPhos. The catalyst system consisting of $[Pd(2\text{-butenyl})Cl]_2$ and MorDalPhos exhibited high catalytic reactivity toward the reaction of aryl and heteroaryl ketones with aryl phosphates, producing mono-α-arylation products **17** (Scheme 6).[23]

The reaction between triphenyl phosphate and acetophenone was carried out on gram-scale, clearly demonstrating the feasibility for scale-up of this methodology.

SCHEME 5: Arylation of pyridinecarboxylic acids with chloroarene.



SCHEME 6: α-Arylation of aryl and heteroaryl ketones with aryl phosphates

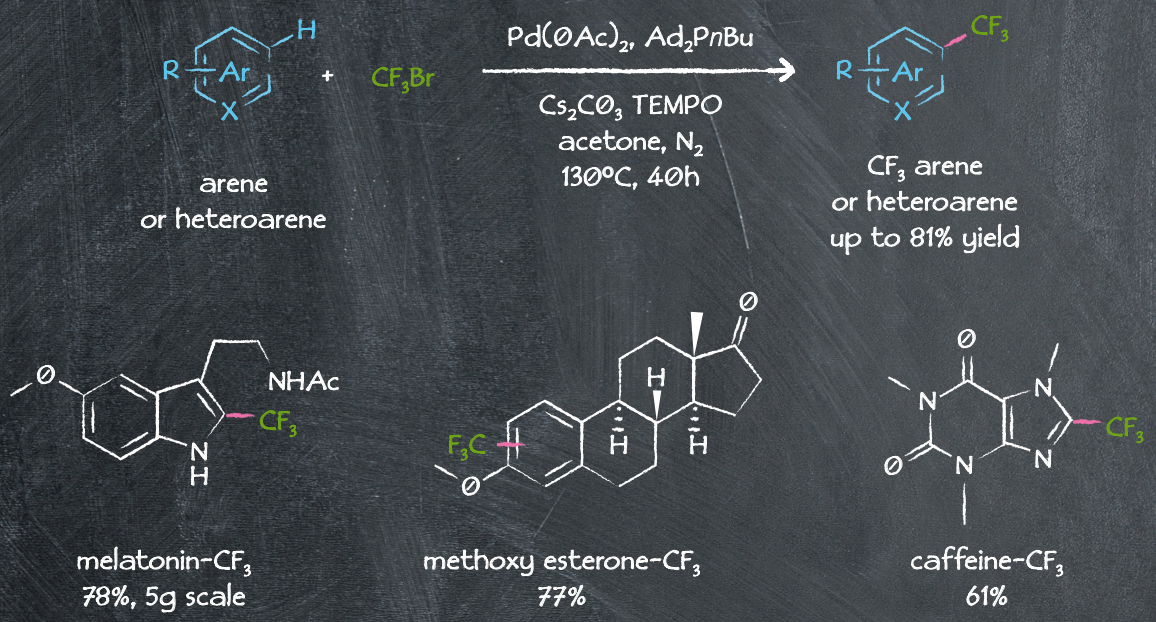


Trifluoromethylation

Fluorine-containing pharmaceuticals have attracted attention for the past 50 years, and it is estimated that 20 % of marketed drugs now contain fluorine.[24] Therefore, much effort has gone into the development of methodology that allows for the introduction of fluorine-containing moieties into drug-like molecules. One way of achieving this is Pd-catalyzed trifluoromethylation of pre- or non-functionalized arenes.

For this purpose, Beller and co-workers have demonstrated the homogeneous catalytic system of $Pd(OAc)_2$ and Ad_2PnBu to be effective in C-H functionalization reactions to produce several trifluoromethyl-substituted (hetero) arenes **18**.[25] As shown in Scheme 7, this novel methodology proceeds under comparably mild reaction conditions with good regio- and chemoselectivity. Substrate scope studies showed that trifluoromethylations of biologically important molecules, such as melatonin, caffeine, and methoxy esterone are viable from mg to multigram scale.[25a]

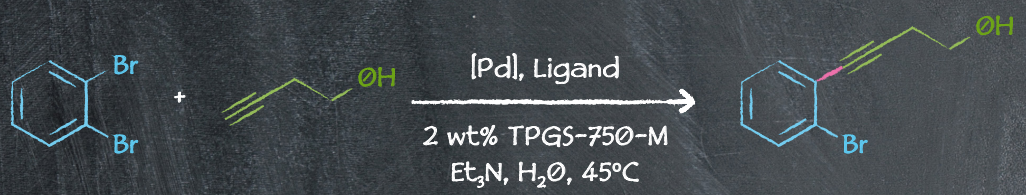
SCHEME 7: Palladium-catalyzed trifluoromethylation of (hetero)arenes.



Copper-free Sonogashira cross coupling

Another C-C bond formation reaction that is widely applied in industry is the Sonogashira cross-coupling, which forges a bond between a sp^2 and a sp carbon. Traditionally, a Cu salt is used as co-catalyst in this transformation, but recently research efforts have focused on the Cu-free variant, otherwise known as the Heck alkynylation reaction.[26]

Ad_2PnBu-based catalysts have also met with success in this reaction class. Researchers at Novartis recently developed a robust and general protocol for a sustainable copper-free Sonogashira cross coupling under micellar aqueous reaction conditions.[27] In this case, the result using the Ad_2PnBu Pd G3 catalyst in a representative copper-free Sonogashira reaction under micellar reaction conditions indicated the significance of ligand structure variation to modulate the reactivity. Catalyst systems based on the cBRIDP and the dppf ligands provided very low yields of the desired product. As shown in Scheme 8, although the HandaPhos ligand was known to be effective for other copper-free Sonogashira reactions under micellar conditions,[28] it was less reactive in this case with only 8% yield of desired product **19** being observed. Use of $Pd(DPEPhos)Cl_2$ or *t*BuXPhos Pd G3 resulted in moderately improved yield of **19**, although still not satisfactory. A shift of catalyst to Ad_2PnBu Pd G3 not only provided an improved yield in the cross-coupling reaction, but also enabled a reduction in catalyst loading from 3 to 1 mol% whilst maintaining the good yield (53 %).



SCHEME 8: Comparison of catalysts for the micellar Sonogashira reaction.

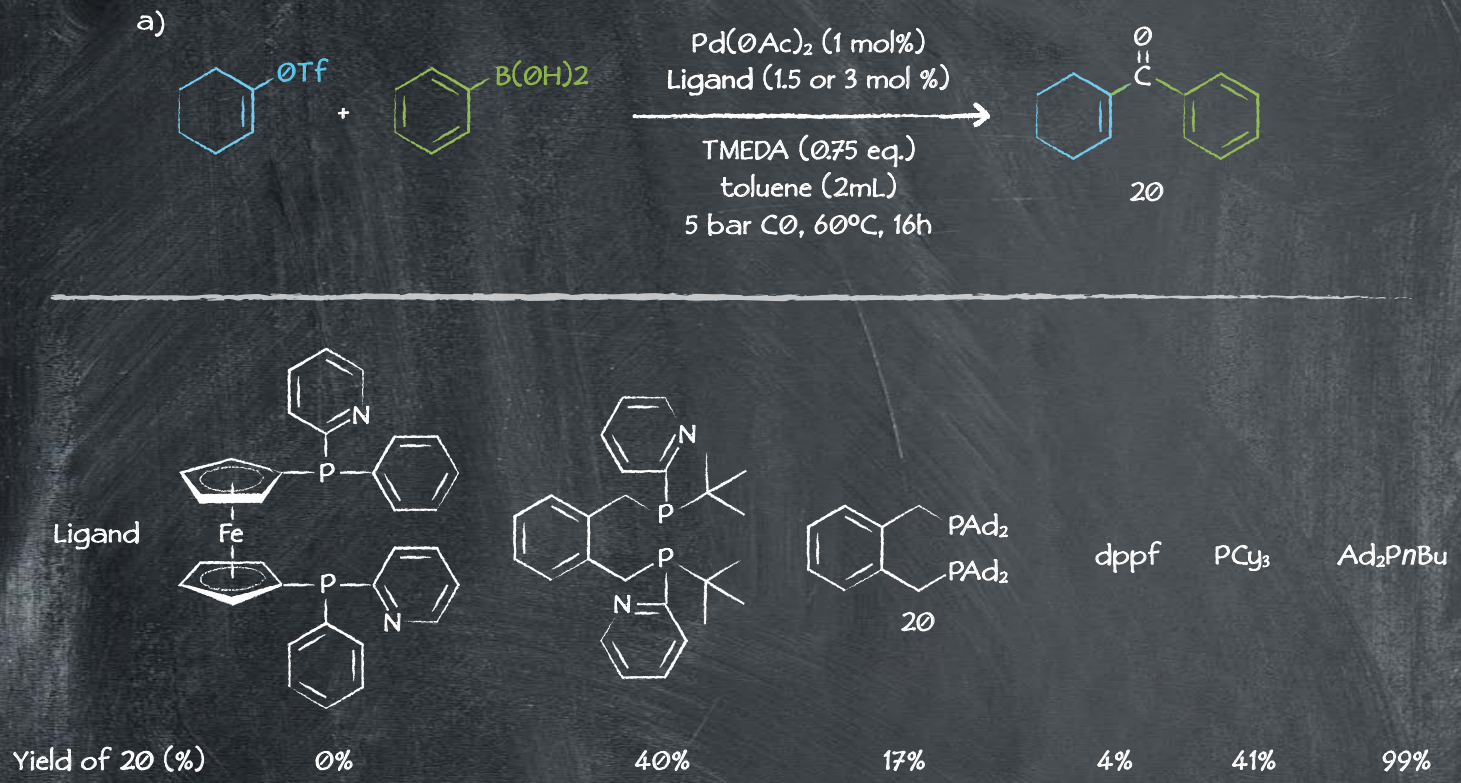
[Pd]/Ligand	Cat. Loading	Yield (%)
cBRIDP, $Pd(OAc)_2$	3.00 mol-%	16
$Pd(dppf)Cl_2$	3.00 mol-%	38
HandaPhos, $Pd(OAc)_2$	1.00 mol-%	8
*t*BuXPhos	1.00 mol-%	28
$Pd(DPEPhos)Cl_2$	1.00 mol-%	27
Ad_2PnBu Pd G3	3.00 mol-%	52
Ad_2PnBu Pd G3	1.00 mol-%	53

Carbonylation

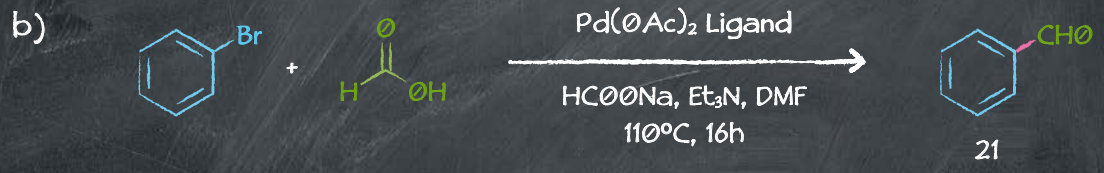
Metal-catalyzed carbonylation reactions are widely applied in the production of both bulk and fine chemicals.[29] One of the most important processes (by scale) is alkene hydroformylation,[30] of which the aryl and heteroaryl aldehydes are important intermediates in biologically active product synthesis.

It is therefore no surprise that adamantyl-containing catalysts have been evaluated also for the purpose of carbonylation reactions. As demonstrated in Scheme 9 (a), initial investigations by Beller and co-workers indicated that monophosphine ligands with steric hindrance provided by adamantyl substituent generally provided superior chemoselectivity to other bisphosphine ligands in the Pd-catalyzed carbonylation of vinyl triflates and nonaflates to 1-cyclohexenyl phenyl ketone **20**.[31] The same trend was also observed in the gas-free palladium-catalyzed reductive carbonylation of aryl and heteroaryl bromides, as demonstrated by Xu and co-workers.[32] It showed that the reactions with monodentate ligands resulted in much improved results. The desired product **21** was obtained in 68% yield using PCy_3 as the ligand, compared to 12% with DPPE (Scheme 9, b). Ultimately, the Ad_2PnBu ligand gave the highest yield of the product (83 %).

SCHEME 9: Pd-catalyzed synthesis of **20** and **21**.



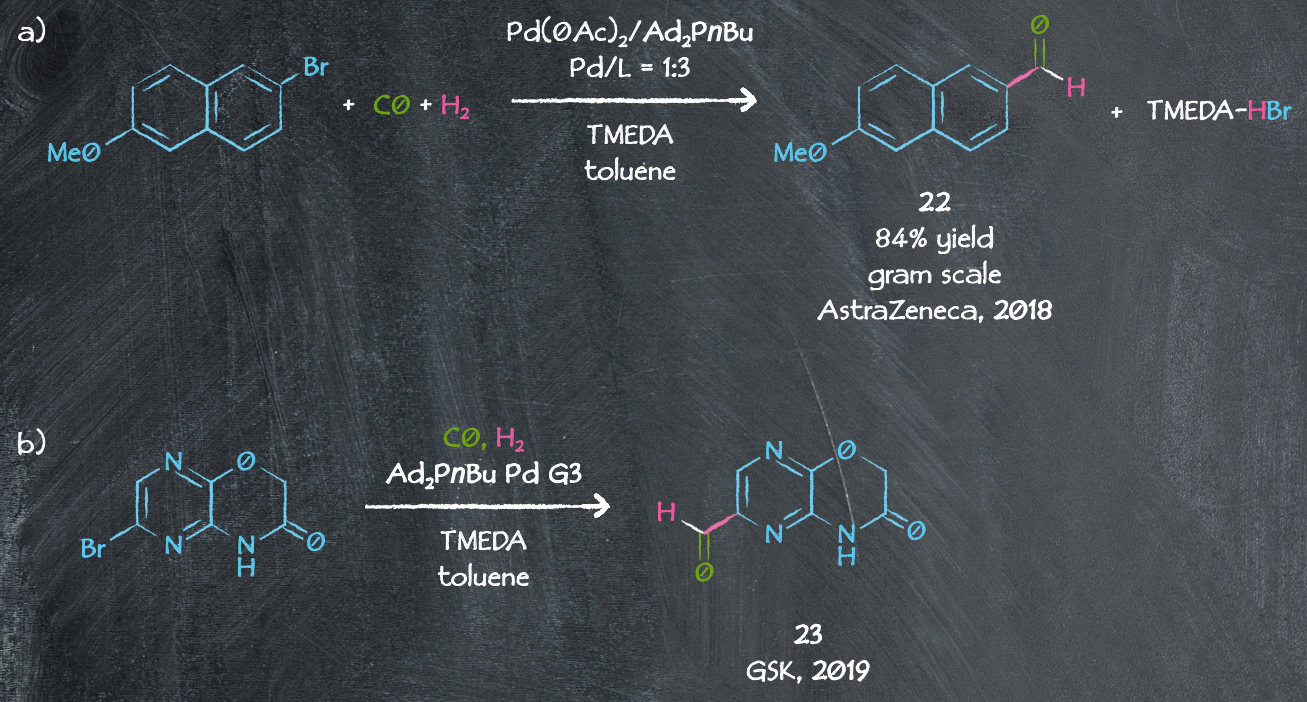
SCHEME 9: Pd-catalyzed synthesis of **20** and **21** continued...



Ligand	PPh_3	PCy_3	DPPE	Xantphos	BINAP	Ad_2PnBu
Yield of 21 (%)	46	68	12	0	0	83

Moreover, the palladium and Ad_2PnBu catalytic system has also been used in a continuous-flow protocol for the synthesis of (hetero)aryl aldehydes (Scheme 10, a).[33] The reaction proceeds with low catalyst and ligand loadings: $Pd(OAc)_2$ (1 mol% or below) and Ad_2PnBu (3 mol% or below). Notably, the protocol was successfully used in the scaled-up reductive carbonylation of 2-bromo-6-methoxynaphthalene to produce multigram quantities of 6-methoxy-2-naphthaldehyde **22** in 85% isolated yield. In addition, in GSK's patented method of synthesis of bicyclic heteroaromatic aldehydes **23** (Scheme 10, b), Ad_2PnBu Pd G3 was also identified as the potential catalyst, although the reported product yield was low (19% yield).[34]

SCHEME 10: Synthesis of aryl and heteroaryl aldehydes.



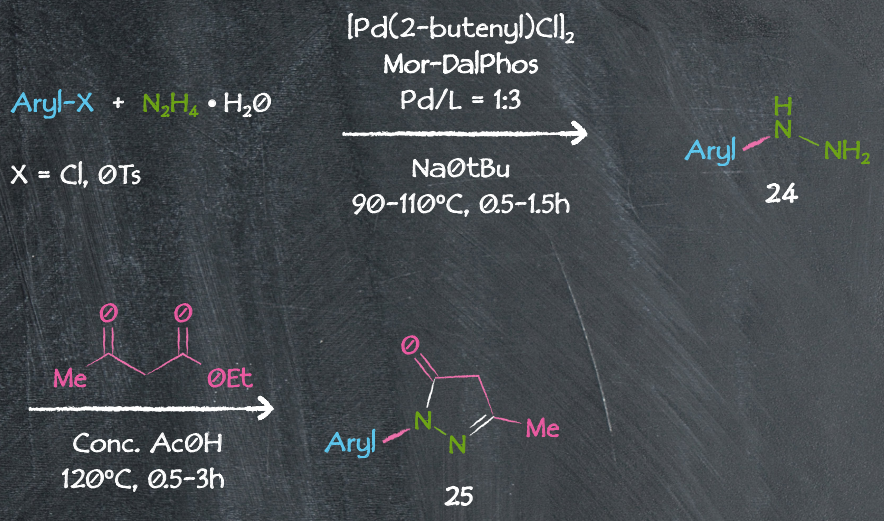
...C-N Bond Formation...

While Ad_2PnBu has been established as the dominant adamantyl-containing ligand in C-C bond formation reactions, other ligands containing this motif have appeared in the literature over the past 10 years in order to address gaps mainly in the C-heteroatom bond formation area.

One such notable ligand, namely MorDalPhos, has been applied in an increasing number of applications for the purpose of C-N bond formation. In recent years there have been examples not only from academic but also from industrial applications. Since the MorDalPhos ligand was developed by Stradiotto in 2010,[35] its outstanding performance in chemoselective arylations of amines has gradually been established. The applications of MorDalPhos in challenging Pd-catalyzed mono-arylation reactions were nicely summarised by Stradiotto in 2012.[36]

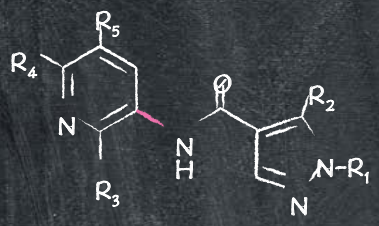
In 2016, Stradiotto reported the protocol using $[Pd(2\text{-butenyl})Cl]_2$ and MorDalPhos system to catalyse hydrazine monoarylation reaction, yielding N-aryl intermediate **24** (Scheme 11).[37] The protocol was then developed as an efficient means of preparing a focused library of 21 edaravone derivatives **25** featuring varied N-aryl substitutions. Moreover, a combination of MorDalPhos with $[Pd(\pi\text{-cinnamyl})Cl]_2$ enabled the first N-arylation of amines using aryl phosphates on gram-scale,[38] and common functional groups such as ether, keto, ester, and nitrile show an excellent compatibility with the mild reaction conditions.

SCHEME 11: Synthetic route to N-aryl product **24** and related edaravone derivatives **25**.



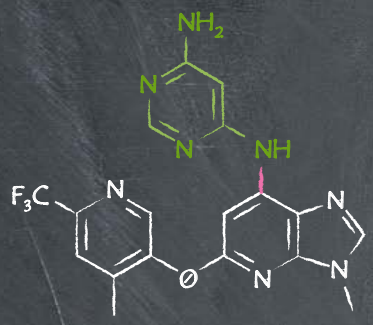
As shown in Figure 8, the palladium and MorDalPhos combination has in recent years also been employed in the synthesis of specific pharmaceutically relevant molecules, such as a range of MALT 1 inhibitors **26**. Here, the C-N bond formation was achieved using a $[Pd(cinnamyl)Cl]_2$/MorDalPhos catalyst system.[39] Taking advantage of MorDalPhos Pd G3, researchers at Galapagos demonstrated a C-N cross-coupling to form novel compounds for the treatment of inflammatory disorders (**27**).[40] Similarly, the above catalyst system was adopted by researchers at Merck to construct the C-N bond between alkyl amines and aryl halides.[41] The triazolo derivative **28** was applied in the treatment of central nervous system disorders[41a] and aryl monobactam **29** was used to deal with bacterial infection.[41b]

FIGURE 8: Pharmaceutically relevant molecules where the C-N bonds, constructed by a Pd/MorDalPhos catalyst system, have been highlighted in red.



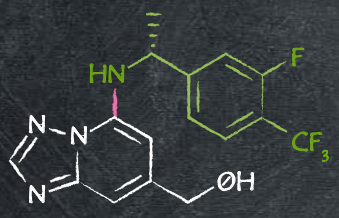
26, 75-100% yield
Janssen, 2019

$[Pd(cinnamyl)Cl]_2$
MorDalPhos



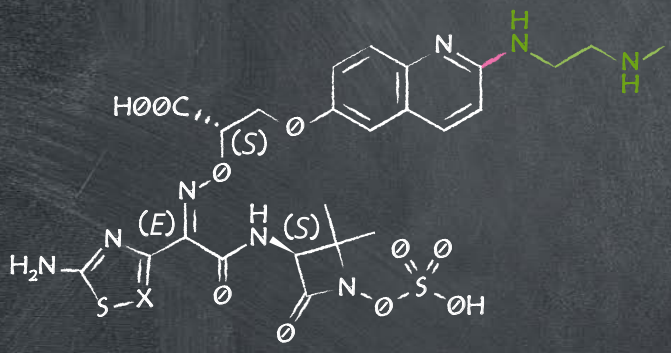
27, Galapagos NV, 2019

MorDalPhos Pd G3



28, Merck, 2017

MorDalPhos Pd G3



29, Merck, 2017

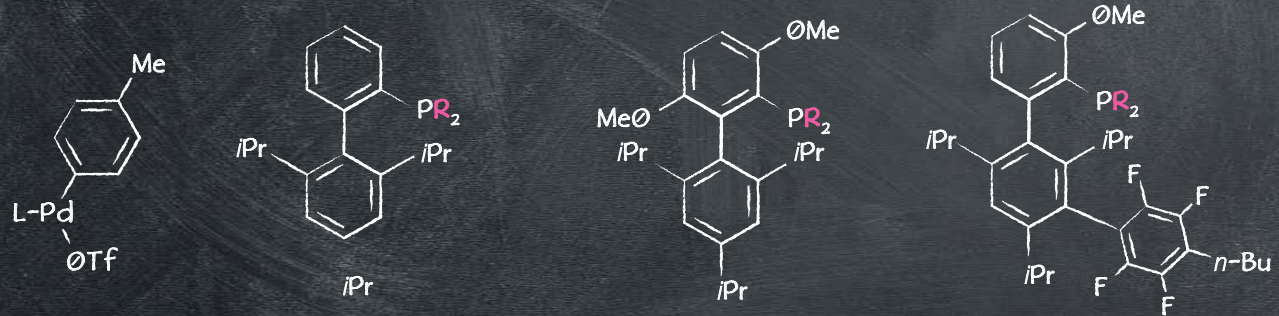
MorDalPhos Pd G3

Due to the low intrinsic acidity of amines, palladium-catalyzed C-N cross-coupling reactions generally require the use of a strong inorganic, or insoluble, base. This can lead to complications on scale-up because of the resulting heterogeneous nature of the reactions. Recently, the potential decomposition of one commonly employed type of base, sodium alkoxides, was highlighted, which can also contribute to reproducibility and scale-up issues.[42]

To address these issues, researchers have turned their attention to the development of protocols that enable the use of milder, soluble, organic bases. Buchwald and co-workers reported a AlPhos-supported palladium catalyst,[43] which enabled the amination reaction to proceed under mild reaction conditions with the organic base DBU. Ligand screening study revealed that adamantyl-containing phosphine ligands showed superior catalytic reactivity to other commonly used Buchwald ligands. As shown in Scheme 12,[43] precatalyst **P6** bearing **L6** (AlPhos) and **P5** (AdBrettPhos) provided nearly quantitative yield of the cross-coupling product **30** at room temperature. *t*-Butyl-based catalysts **P2** (t-BuXPhos) and **P4** (t-BuBrettPhos) provided the desired product in moderate yields only, and ligands bearing cyclohexyl (Cy) groups on the phosphine, including **P3** (BrettPhos) and **P1** (XPhos), failed to yield any of the desired product.

SCHEME 12: Comparison of ligands in Pd-catalyzed amination facilitated by DBU.

Precatalyst	Time	Yield (%)
P1	20 min	0
P2	20 min	30
P3	20 min	0
P4	20 min	61
P5	20 min	99
P6	20 min	99



P1-P6

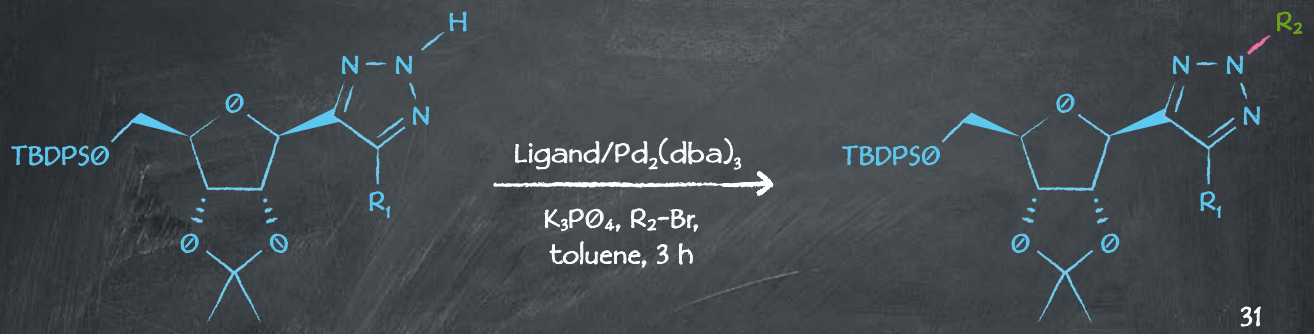
L1, R = Cy, XPhos
L2, R = *t*Bu, *t*BuXPhos

L3, R = Cy, BrettPhos
L4, R = *t*BuBrettPhos
L5, R = AdBrettPhos

L6, R = Ad, AlPhos

Another challenging C-N bond formation reaction is the selective N-arylation of heterocycles. In the regioselective synthesis of the C-nucleoside derivative N2-aryl-1,2,3-triazole **31** (Scheme 13), the catalyst system (Me*t*BuXPhos/$Pd_2(dba)_3$) generally utilized in C-N coupling reaction only provided moderate yield.[44] Among other biaryl phosphine ligands screened with $Pd_2(dba)_3$, only AdBrettPhos increased the yield to 73%. This is another example show-casing the high potential of adamantyl-containing ligands in palladium-catalyzed C-N cross-coupling reactions.

SCHEME 13: Screening ligands for N2 selective arylation.



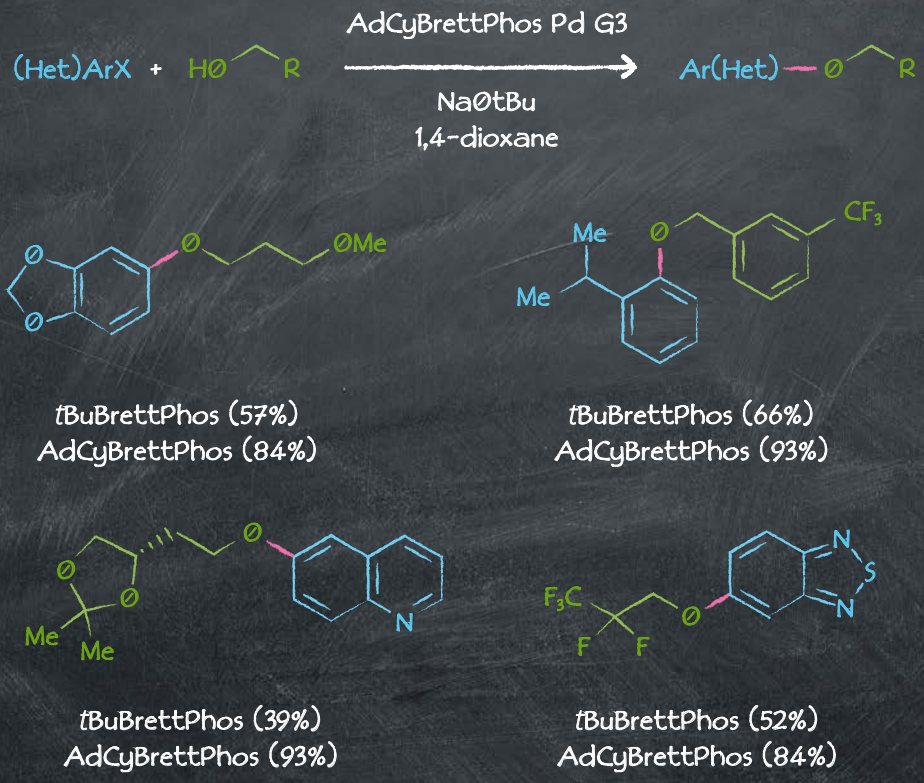
Ligand	Yield
MetBuXPhos	43
*t*BuXPhos	nr
*t*BuBrettPhos	traces
AdBrettPhos	73

C-Heteroatom Bond Formation

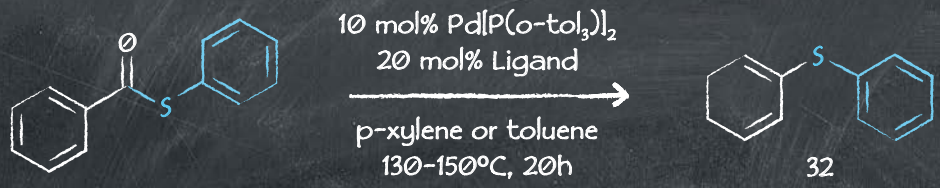
The reaction between an alcohol nucleophile and an aryl halide to form an ether is notoriously difficult, and although a number of publications on this topic has been produced in recent years, the lack of a solid general methodology for this transformation remains.

The C-O bond formation can in some cases be achieved by a Pd-based catalyst in combination with a ligand such as *t*BuBrettPhos.[45] However, in certain instances, e.g. when the substrate is an electron-rich aryl halide, the above catalyst system does not generally work. The solution here can be to switch to the AdCyBrettPhos ligand, which can promote efficient coupling in the case of unactivated electrophiles, so as to improve the yield of these challenging C-O bond-forming reactions (Scheme 14).[46]

SCHEME 14: Yield of Pd-catalyzed C–O cross-coupling reactions of unactivated substrates.



Adamantyl-containing ligands have also proved successful in the decarbonylative thioetherification of thioesters to form thioethers (Figure 9).[47] Several ligands were evaluated in this transformation; dppe, dppf and *t*-BuXantPhos all resulted in low to moderate yield of the desired thioether **32** (15-61%). BrettPhos provided a similar yield to dppf (58%), whereas adamantyl-based catalysts formed from $Pd[P(o\text{-}tol)_3]_2$ and Ad_2PnBu or Ad_2PnBn resulted in an improved yield of **32** (67 and 78% respectively).



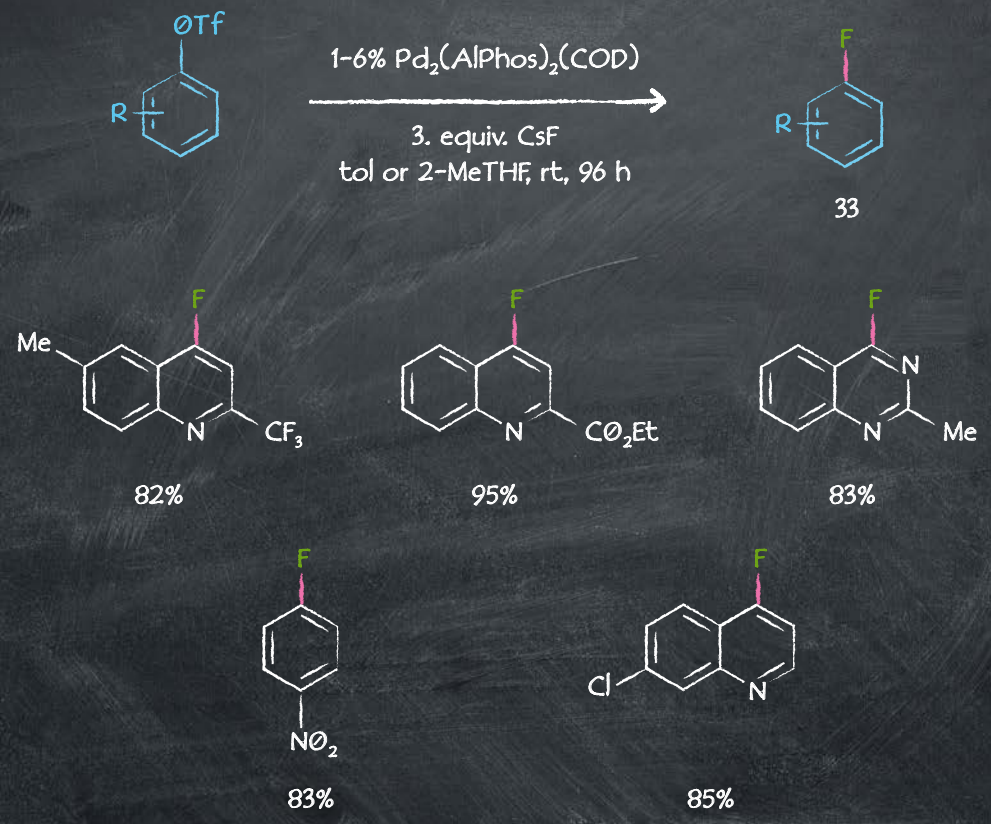
Ligand (mol%)	Yield
dppe (10)	19
dppf (20)	61
tBuXantphos (20)	15
Brettphos (10)	58
Ad_2PnBu (20)	67
PAd_2Bn (20)	78

FIGURE 9:
Pd-catalyzed decarbonylative thioetherification of thioesters.

...and C-Halogen Bond Formation.

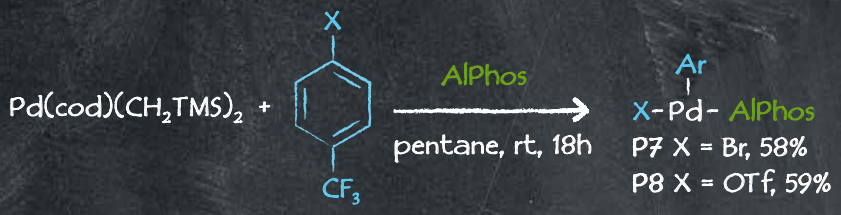
As previously mentioned, fluorine-containing molecules are of great importance in both pharmaceutical and agrochemical industries,[24] whereas the preparation of such compounds selectively under mild and general reaction conditions remains a challenge. In 2015, the biaryl monophosphine ligand AlPhos was developed by Buchwald and co-workers. With fluorines at pendant 4-(*n*-Bu)Ph group, AlPhos allows for the room-temperature Pd-catalyzed fluorination of a variety of activated (hetero)aryl triflates (Scheme 15).[48] Furthermore, aryl triflates and bromides that are prone to give mixtures of regioisomeric aryl fluorides with Pd-catalysis can now be converted to the desired aryl fluorides **33** with high regioselectivity.

SCHEME 15: Room-temperature fluorination of aryl triflates.

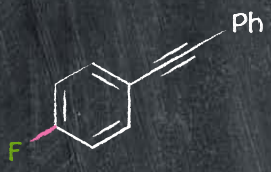


Taking advantage of the AlPhos ligand, Buchwald's team also developed the palladium-based oxidative addition complexes **P7** and **P8** (OACs, Scheme 16), which are themselves effective precatalysts for the construction of C-F bonds of aryl triflates and bromides, respectively, resulting in the corresponding aryl fluorides **34**.[49] Notably, these precatalysts **P7-8** are easily prepared in moderate isolated yield (ca. 58%) and stable to long-term storage under air.

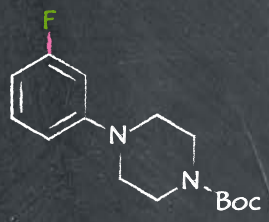
SCHEME 16: Synthesis of OACs and fluorination of aryl bromides and triflates with **P7** or **P8**.



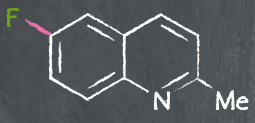
34



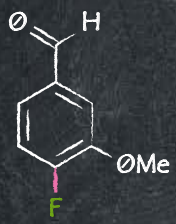
70%
4 mol% P7, 2 mol% cod
X = Br



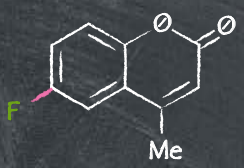
90%
4 mol% P7, 2 mol% cod
X = Br



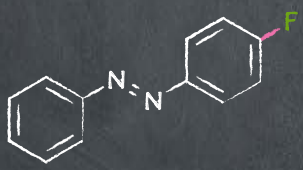
92%
1.5 mol% P7, 0.75 mol% cod
X = Br



82%
2 mol% P8
X = OTf



87%
2 mol% P8
X = OTf



82%
2 mol% P8
X = OTf

What is next...?

To date, adamantyl-containing phosphine ligands have been applied in a large number of C-C and C-X bond formation reactions. Whilst these ligands are well established for drug development purposes and in academic settings, the number of reported large-scale applications are easily counted on the fingers of one hand. Some possible reasons for this may be the existence of ligand IP protection in some cases, combined with the perceived difficult synthesis of this type of ligands. However, as the reaction scope for the adamantyl-phosphine based catalysts continue to be expanded by research groups (academic as well as industrial) across the globe, and their favourable properties are better documented and understood, we predict a rise in the number of applications also for the requirement of production of larger quantities of for example APIs. This can only be achieved by good communication and close collaboration between academia, research groups in the pharmaceutical (and to a certain extent agro) industry and catalyst and ligand manufacturers. The time investment of catalyst/ligand manufacturers is particularly important in overcoming the synthesis challenges and making adamantyl-containing ligands readily available and a commercially viable option for the pharmaceutical industry.

We believe that this process is already well underway, and the valuable adamantyl-containing ligands are at a stage where they can make an impact and start playing a vital role also in process development R&D and production.

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Dr Hui Zhao received her M. Sc. in organic chemistry from Hangzhou Normal University in 2014. She joined Prof. David Scheschkewitz's group for her Ph.D. at Saarland University in Germany where her research focused on the synthesis and application of low-valent silicon compounds. In 2020, she joined the product development division of Sinocompound in Jiangsu, China, where she is working on the technical support of novel ligands and homogeneous metal catalysts.

Dr Carin Seechurn

Dr Carin Seechurn undertook her MChem with French studies at U.M.I.S.T (University of Manchester Institute of Science and Technology) and graduated in 2003. She subsequently moved to University of Cambridge for her PhD studies in synthetic organic chemistry followed by a post-doctoral research associate position, both under supervision of Prof. Gaunt. After 12 years as a research scientist in the homogeneous catalysis group at Johnson Matthey, she joined Sinocompound as Technical Advisor in 2020. Using her extensive homogeneous catalysis knowledge, she is providing technical support to customers and is instrumental in executing technical marketing strategies.

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