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Design of an Indolylphosphine Ligand for Reductive Elimination-Demanding Monoarylation of Acetone Using Aryl Chlorides

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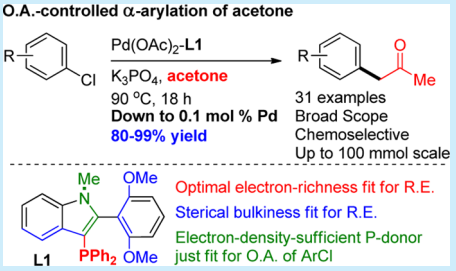
Supporting Information

ABSTRACT: The rational design of a phosphine ligand for the reductive elimination-demanding Pd-catalyzed mono-α-arylation of acetone is demonstrated and reported. The catalyst is tolerant of previously proven challenging electron-deficient aryl chlorides and provides excellent product yields with down to 0.1 mol % Pd. Preliminary investigations suggest that the rate-limiting step for the proposed system is the oxidative addition of aryl chlorides, in which it contradicts previous findings regarding the α-arylation of acetone with aryl halides.



Direct α-arylation of carbonyl compounds such as methyl aryl ketones, alkyl esters, amides, and acetonitrile with aryl halides and sulfonates assisted by transition-metal complexes have empowered chemists to construct $C(sp^2)-C(sp^3)$ bonds that are useful in the synthesis of pharmaceuticals.[1] In particular, products generated from α-arylation of the simplest acetone are key functionalities in many biologically active and medicinally valuable compounds (Figure 1).[2]

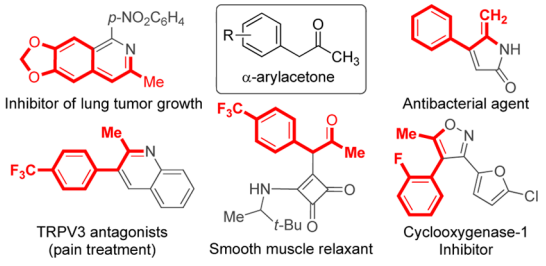


Figure 1. Biologically active compounds and their potential applications.

Despite the high attractiveness of this protocol, the selective acetone mono-α-arylation has yet to realize its potential as undesirable further arylation reaction occurs.[3] Indeed, the more reactive benzylic protons lead to a mixture of multiple arylation byproducts.[4] In addition to the problem arising from the more reactive C−H protons, the C−C reductive elimination of the aryl palladium enolate species has been reported to be slower when less sterically congested ketone substrates are used.[5] In 2011, Stradiotto reported the first palladium-catalyzed direct mono-α-arylation of acetone with aryl halides using $-PAd_2$-containing (Ad = 1-adamantyl) P,N-type Mor-DalPhos as the ligand.[6] Later, $-PCy_2$-containing P,N-type Zheda-phos[7] and P,N-type di(ferrocenyl)-2-morpholinophenylphosphine[8] and bidentate Xantphos[9] were also found to promote this reaction. During the completion of our experimental works, a report appeared that Josiphos-type ligand (CyPF-*t*-Bu) could make this reaction viable at room temperature using 7.5−10 mol % of Pd for 48 h.[10] In fact, the appropriate ligand coordinating number and electronic and steric balance of ligand have been shown to be critical for achieving monoselective α-arylation.[11] Despite the application of optimal ligands, the scope of the coupling partners may not be general.[12] Recently, Walsh showed that indolyl-backbone phosphines were effective in promoting Pd-catalyzed monoarylation of α-acidic C−H bonds.[13] It is to our persisting and great interest to use indolylphosphines[14] in Pd-catalyzed cross couplings and direct arylation of acidic C−H bonds.[15] Herein, we demonstrate and report the rational design of a new indolylphosphine ligand to address the challenges that arose from the Pd-catalyzed mono-α-arylation of acetone with aryl chlorides.

In addition to the aforementioned alkylphosphines in acetone monoarylation, we envisioned that ligands having a usual $-PR_{(alkyl)2}$ group, where R = Cy, *t*-Bu, 1-Ad, etc., are generally active toward cross-coupling of aryl chlorides.[16] Nevertheless, the inherent properties of high electron-richness and steric bulkiness of the alkyl substituent at the $-PR_{(alkyl)2}$ moiety cannot be managed individually, and thus the $-PR_{(alkyl)2}$ group may not be complementary best fit to the reductive elimination process.[17] We were intrigued to investigate the reductive elimination-demanding process by considering these two factors independently in a single ligand. To tackle the reductive elimination electronically, our rational design of ligand focuses on the less electron-rich phosphorus donor, for instance the $-PPh_2$ group (Figure 2), where this group attached to the C3-indole position would enjoy essentially sufficient electron-richness for oxidative addition of the $C_{(Ar)}-$

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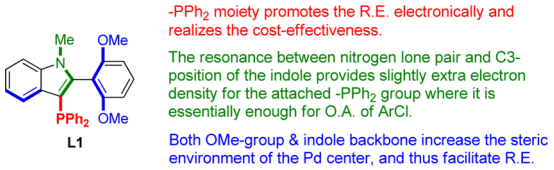
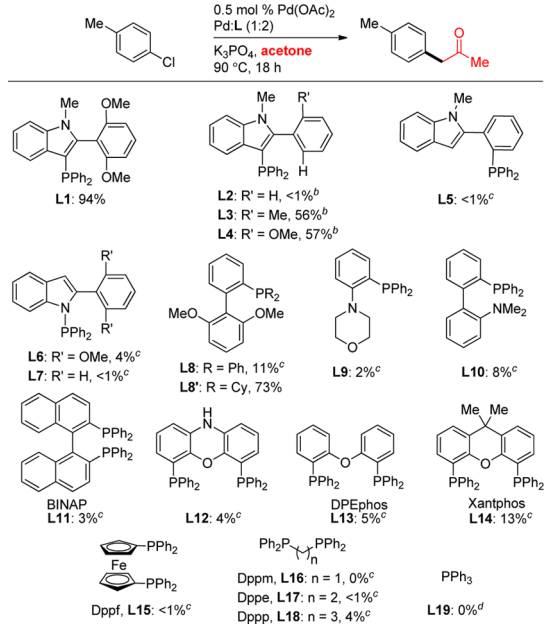


Figure 2. Rational design of an indolylphosphine ligand suitable for mono-α-arylation of acetone with aryl chlorides.

Cl bond[18] but also can facilitate the reductive elimination (i.e., too electron-rich phosphines, e.g., Ar-PCy_2 or Ar-P-*t*-Bu_2, would slow the RE process).[19] In addition to studying the electronic nature of the phosphorus donor, we wanted to prepare a ligand with large remote bulky groups for promoting reductive elimination (Figure 2).[20]

To investigate our postulation, a series of structurally similar $-PPh_2$-containing ligands were tested for the acetone monoarylation (Scheme 1). Ligand **L1** was found to have

Scheme 1. Evaluation of Ligand Efficacy of Ligand Bearing the Diphenylphosphino Moiety[a]



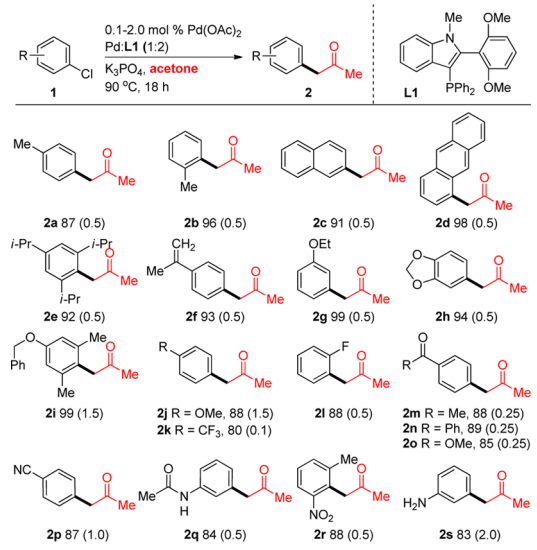
[a]Reaction conditions: *p*-chlorotoluene (0.5 mmol), K_3PO_4 (1.25 mmol), acetone (1.7 mL, 0.30 M), $Pd(OAc)_2$/L = 1:2, (0.0025 mol, 0.5 mol % Pd) under nitrogen at 90 °C for 18 h under N_2, calibrated GC yields were reported. [b]1.0 mol % $Pd(OAc)_2$, M:L = 1:2. [c]5.0 mol % $Pd(OAc)_2$, M:L = 1:2. [d]20 mol % $Pd(OAc)_2$, M:L = 1:2.

sufficient electronic richness for activating the Ar−Cl bond and necessary electronic/steric bulkiness to enhance the reductive elimination of the Ar−Pd-enolate species. It was found that the product yields were generally improved along with the increasing size of the substituted group at the *ortho*-position of the 2-aryl ring (H < Me ≈ OMe < 2,6-di-OMe) (**L2**-**L4** vs **L1**). Ligand **L5** with a phosphino group at the relatively less electron-rich 2′-position of the aryl ring was found to be inferior. Structurally comparable ligand **L6**, where the $-PPh_2$ moiety was bound to the indole nitrogen position, resulted in a loss of activity (**L6** vs **L1**). Presumably, the N−PPh_2 ligand does not activate the Ar−Cl bond since >95% of *p*-chlorotoluene remains unreacted as judged by GC−FID analysis. The $-PPh_2$ versions of the state-of-the-art ligand skeletons (**L8**, **L9**, and **L10**) were also examined. They only partially promoted this process, presumably due to the insufficient electron-richness for cleavage of the Ar−Cl bond. A list of well-documented bidentate phosphine ligands, e.g., BINAP and Xantphos, which were successful in promoting other α-arylation reactions, were further surveyed to illustrate the importance of the ligand skeleton in acetone arylation chemistry (**L11**−**L18**). Nevertheless, even the catalyst loading was increased to 5 mol % Pd, and no obvious improvement to the desired product yields was observed. It should be noted that for all of the low yield entries aryl chlorides remained unreacted and no other arylated side products were observed.

Having identified the best ligand, other reaction conditions were investigated (see the Supporting Information, Table S1). K_3PO_4 proved to be the best base of choice for this system. For the metal source investigation, $Pd(OAc)_2$ and $[PdCl(cinnamyl)]_2$ gave the best results among other Pd precursors screened. The more available and less expensive $Pd(OAc)_2$ was chosen for further study.

With the optimized reaction conditions in hand, we next evaluated the efficacy of this catalyst system in the arylation of acetone using aryl chlorides (Scheme 2). In general, 0.5 mol %

Scheme 2. Pd-Catalyzed Mono-α-arylation of Acetone with ArCl[a]



[a]Reaction conditions: Pd:**L1** = 1:2, ArCl (0.5 mmol), K_3PO_4 (1.25 mmol), acetone (1.7 mL, 0.30 M); 90 °C for 18 h under N_2. Isolated yields were reported. Catalyst loading was reported in parentheses as mol % of Pd with respect to ArCl. Reaction times were not optimized for each substrate.

of Pd could satisfy the coupling of a wide range of aryl chlorides with no diarylated side product formation. Highly sterically congested aryl chlorides (Scheme 2, **2e**) were converted to the corresponding products in excellent yield.[21] Deactivated aryl chlorides were found to be feasible coupling partners (Scheme 2, **2i,j**). Particularly noteworthy is that electron-deficient aryl chlorides, which were previously reported as challenging substrates, were smoothly transformed to the desired products in high yields under low catalyst loading (0.1−0.5 mol % Pd, Scheme 2, **2k**−**o**). Substrates featuring alternative enolizable sites afforded chemoselective monoarylation of acetone in good yield (Scheme 2, **2m**). Slightly higher catalyst loading was required to afford **2p** probably due to the competitive nitrile

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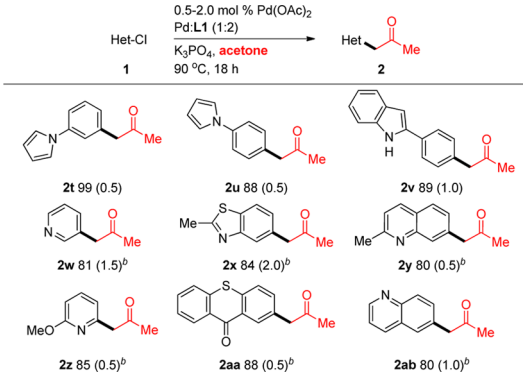
coordination.[22] In general, common functional groups, such as keto, ester, nitrile, amido, nitro, and free amino groups, were compatible under these reaction conditions (Scheme 2, **2m–s**).

Apart from a variety of aryl chlorides, heteroaryl chlorides were also examined (Scheme 3). Under the new catalyst system, pyrrolyl and unprotected indole substrates could give the coupling product in good yields (Scheme 3, **2t–v**).[23] For particular coordinating heteroaryl substrates, $Pd(dba)_2$ was found to be a better metal source. Pyridyl, benzothiazolyl, quinolinyl, and thioxanthenyl chlorides were coupled with acetone enolate efficiently (Scheme 3, **2w–ab**).

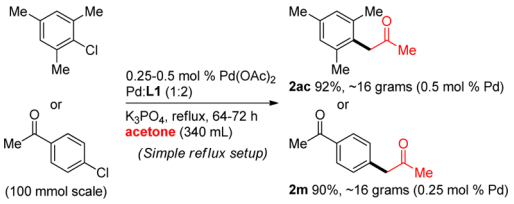
Scheme 3. Scope of Heteroaryl Chlorides[a]



[a]Reaction conditions: Pd:**L1** = 1:2, Het-Cl (0.5 mmol), K_3PO_4 (1.25 mmol), acetone (1.7 mL, 0.30 M); 90 °C for 18 h under N_2. Isolated yields were reported. Catalyst loading was reported in parentheses as mol % of Pd with respect to ArCl. Reaction times were not optimized for each substrate. [b]$Pd(dba)_2$ was used as the Pd metal source.

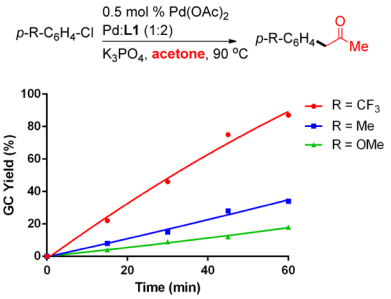
Scaling up the microscale experiment always encountered practical problems, for instance, from use of a nonhandy apparatus to process safety concerns.[24] To realize the amenability of the Pd–**L1** system for a large-scale reaction (100 mmol scale), we avoided the use of undesirable large-size Schlenk glassware,[25] while we simply employed the traditional reflux setup to conduct the catalysis.[26] With 0.25–0.5 mol % of Pd at a reaction temperature of ~60 °C,[27] the coupling catalysis proceeded smoothly (Scheme 4).

Scheme 4. Large-Scale Synthesis of Mono-α-aryl Acetones



In order to have more mechanistic insight toward the arylation reaction under the newly developed Pd–**L1** system, competition experiments were conducted (Scheme 5). *p*-Chloroanisole, *p*-chlorotoluene, and *p*-chlorobenzotrifluororide were selected to probe the electronic effect with respect to the rate of acetone monoarylation. Electron-deficient *p*-chlorobenzotrifluoride was found to proceed at the fastest reaction rate, while the electron-rich *p*-chloroanisole showed the slowest rate among the aryl chlorides studied (Scheme 5). It is worth noting that inverted results were observed with reference to the reported literature, which employed Mor-DalPhos (bearing an electron rich $-PAd_2$ moiety) as the ligand.[28] Our results suggested that the rate-limiting step of acetone monoarylation is highly subjective to the change of ligand electronic properties. As suggested, the oxidative addition of aryl chlorides became the rate-limiting step for the Pd–**L1** system while the demanding reductive elimination proceeded smoothly.

Scheme 5. Reaction Rate Study of Electronically Different ArCl in Acetone Arylation (Average of Four Independent Runs)



In summary, we have rationally designed a ligand which is principally fit for the mono-α-arylation of acetone using aryl chlorides. The optimal balance between the affordable oxidative addition of the Ar–Cl bond by **L1** and effective facilitation to the highly demanding reductive elimination of aryl palladium acetone enolate species is the key to success for this catalysis. Under the newly developed Pd–**L1** catalyst system, a wide spectrum of aryl chlorides having keto, amido, ester, nitrile, nitro, unprotected indole, free amino, and heterocyclic functionalities, as well as the previously reported difficult electron-deficient aryl chlorides, have been found to be applicable substrates for this reaction. We believe these ligand characteristics are a useful basis for future phosphine ligand design and provide another viewpoint to look into difficult α-arylation of small carbonyl compounds. With features of relatively low catalyst loading and the ease of scale-up synthesis, we anticipate this inexpensive ligand[29] will be useful in routine synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02344.

Experimental procedures, ^1H, ^{13}C, ^{31}P, ^{19}F NMR spectra, and characterization data of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(17) In general, the increase of the steric bulkiness of the alkyl group (e.g., from Cy to *t*-Bu group) would also increase the electron richness of the $-PR_2$ group. The first steric factor certainly favors the RE process, but the second electronic factor would slow the RE. These two aspects cannot be handled separately from a single $-PR_2$ group.

(18) The indicated C-3 position of indole is estimated to be 10^{13} times more reactive than benzene for electrophilic attack; see: Laws, A. P.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, 591.

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(21) Example **2e** represents the most sterically bulky ArCl substrate for monoarylation of acetone.

(22) To investigate the possible influence of nitrile group coordination in this catalysis, an additional experiment was conducted. When 1 equiv of PhCN (0.5 mmol) was added to the acetone arylation of **2a** (Scheme 2), the product yield was dropped from 87% to 23%, with 70% ArCl unreacted (as judged by calibrated GC–FID analysis).

(23) Previous literature reported the benzyl-protected indole for the α-arylation process. See ref 6a.

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(25) It is preferable to use a Schlenk tube in small-scale reactions. However, when the scale is increased, problems will be generated. On a 100 mmol scale, a 4 L Schlenk flask is required for this synthesis.

(26) A three-necked round-bottom flask equipped with thermometer, rubber septum, and water condenser was used as the vessel for this acetone monoarylation reaction.

(27) The reaction temperature was measured to be about 60 °C.

(28) Stradiotto reported the RE is the rate-limiting step. For the initial rate study using a Pd/Mor-DalPhos system, see the Supporting Information of ref 6a.

(29) Ligand cost and catalyst loading become two of the most important factors in production-scale catalysis; see: Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599. In view of cost-effectiveness, the new ligand **L1** features the use of the inexpensive $-PPh_2$ group (precludes the incorporation of relatively expensive $-PR_{(alkyl)2}$ group). According to the 2014 Aldrich catalog, $ClPPh_2$ (337.5 USD/500g) is approximately 80 times less expensive than $ClPCy_2$ (271.5 USD/5g) and 378 times cheaper than $ClPAd_2$ (255.5 USD/g). Chlorodiferrocenylphosphine is not commercially available.

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