Synlett J. Richardson et al. Letter

An Efficient Palladium-Catalyzed α-Arylation of Acetone Below its Boiling Point

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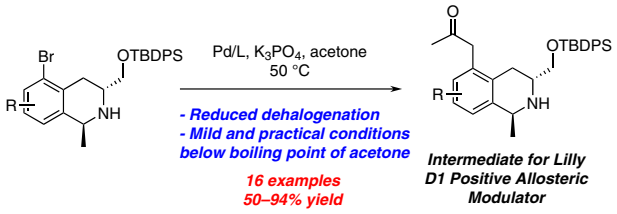

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Abstract The monoarylation of acetone is a powerful transformation, but is typically performed at temperatures significantly in excess of its boiling point. Conditions described for performing the reaction at ambient temperatures led to significant dehalogenation when applied to a complex aryl halide. We describe our attempts to overcome both issues in the context of our drug-discovery program.

Key words arylation, cross-coupling, drugs, ketones, medicinal chemistry, palladium

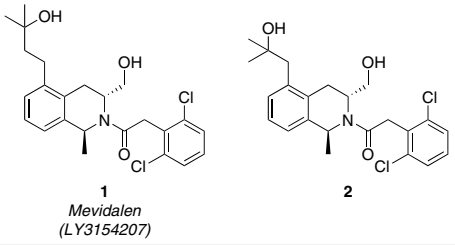

Figure 1 Lilly D1 positive allosteric modulators

It has been considered that activation of the D1 receptor holds significant promise for the treatment of several neurological disorders. The positive allosteric modulation approach to increasing D1 receptor activity holds significant promise because binding at an allosteric site of the D1 receptor potentially addresses pharmacological selectivity issues associated with the orthosteric agonism, as well as chemical stability issues of some known D1 agonists, by requiring a different pharmacophore. Additionally, the physiologically more-relevant mode of action of a D1 PAM might result in a lower propensity for overstimulation and tolerance development, as well as a potentially better safety profile.[1] We recently discovered an orally available D1 positive allosteric modulator, Mevidalen (LY3154207, **1**), that is currently in Phase 2 development for the treatment of Lewy body dementia (PRESENCE, NCT03305809).[2]

During the discovery of **1**, a number of structurally related compounds were prepared and studied, including **2** (Figure 1).[1]

Early efforts to prepare **2** and structurally related compounds involved a long and inefficient procedure (5 steps; 35% yield) to arrive at ketone **5** (Scheme 1) and so a more efficient and direct installation of this group was sought. Ultimately the arylation of the in situ generated tin enolate worked very efficiently and was used to deliver **2** and structurally related compounds on a multigram scale. Ultimately, as our desire to better profile these molecules in an in vivo setting increased, it became increasingly important to control the levels of tin in the active pharmaceutical ingredient. We therefore sought to avoid the use of tin altogether, and were attracted to the direct arylation of acetone.

The direct monoarylation of acetone was first reported by Stradiotto and co-workers in 2011,[3] and a number of reports on the use of modified ligands and on expansions of the scope of the aryl halide partner have subsequently appeared.[4–10] We began by exploring several of the previously reported methods for the direct arylation of **3** (Table 1), and we found that, although this reaction was possible under the reported conditions, two major issues were encountered that would present a challenge when working at scale. First, a major limitation of several of the reported methods is that the reactions are typically conducted at temperatures above 80 °C, which are significantly above the boiling point of acetone (56 °C). Importantly, Stradiotto and co-workers have demonstrated that this transformation can be achieved at 25 °C by using the Josiphos variant ligand

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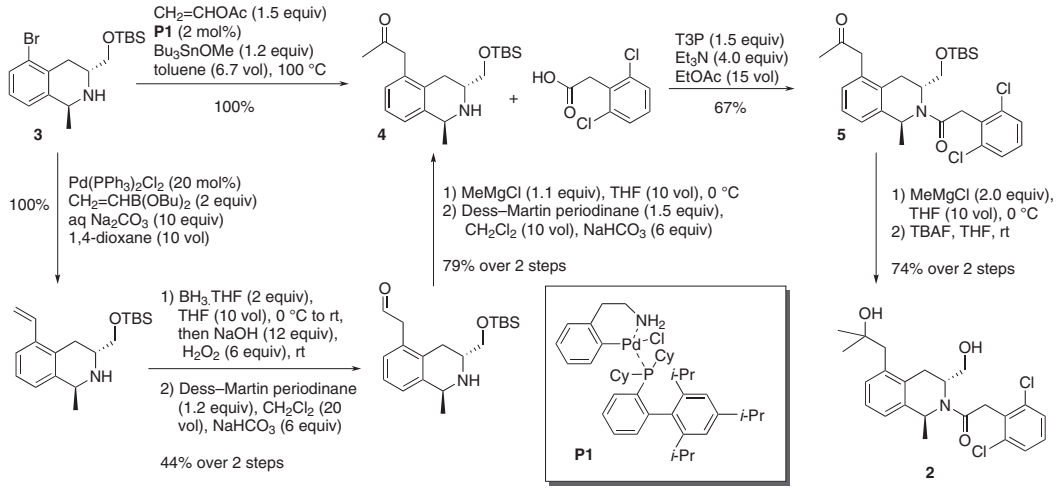
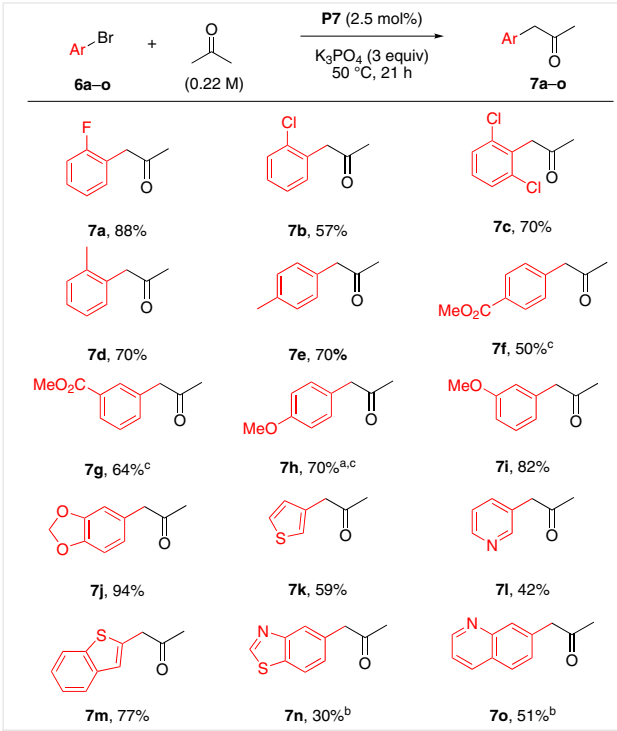


Scheme 1 Synthetic routes to compound **2**

cyPF-tBu (**L1**). Unfortunately, while this permits operation in a convenient temperature range, we found that dehalogenation of **3** led to a major byproduct (Table 1, entry 1), resulting in reduced yields and difficult separations. The literature conditions that were typically performed at higher temperatures gave complete conversion, but inherently suffered from the issues of heating significantly above the boiling point of the solvent. As such, we investigated these reactions at 50 °C to examine the effect that this would have on the reaction outcome (entries 2–4). In all cases the conversion was reduced; however, it was found that the MePhos ligand (**L4**) performed quite well at this temperature (entry 7) in THF as a co-solvent.[11] Interestingly, the use of potassium phosphate instead of cesium chloride led to an increase in conversion (entries 7 and 8), suggesting that the latter base should be used in subsequent studies with this ligand; however, cesium carbonate might be worthy of further evaluation in future studies.

This study also demonstrated that it might be possible, by varying the nature of the ligand, to achieve better conversion and, possibly, improved dehalogenation. A screen of 16 ligands was therefore performed using, where possible, preformed palladium complexes where the formation of the active Pd(0)L complex is robust and well-studied (Table 2).[12–14] This screen showed that the ligand structure had a strong effect on the outcome of the reaction, both in terms of the overall conversion and the extent to which dehalogenation of **3** occurred. Generally, the Buchwald monodentate biaryl ligand class of ligands performed well (entries 1, 2, and 5–8), with the exception of those where steric hindrance at phosphorus is significant (entries 3 and 4). Most other ligands performed poorly, although the performance of 2-Tol-MorDalPhos (**L5**) was improved by increasing the temperature and changing the solvent and base (entry 16). Since XPhos (**L7**) showed the best performance among these ligands, and was available to us in bulk quantities, we selected this ligand for further exploration of the conditions.

Having selected XPhos (**L7**) as ligand for palladium, we explored some of the other reaction conditions (Table 3). Changing the co-solvent from THF to toluene was possible but offered little advantage. Indeed, it was possible to elim-



Scheme 2 Scope of acetone arylation conditions. Isolated yields are reported. [a] Reaction performed for 24 h. [b] Reaction performed for 72 h. [c] The product was impure, so the yield was adjusted by using maleic acid as an internal standard.

inate the co-solvent entirely (Table 3, entries 1–3). The use of an additional ligand was unnecessary (entry 4), and under these conditions, the reaction performed well at a 2.5 mol% loading of Pd (entry 5). An exploration of some common bases showed that changing to other bases had a strongly negative impact on the outcome of the reaction (entries 6–10).

With these conditions in hand, we sought to better understand their general applicability. A range of (het)aryl bromides **6a–o** were subjected to these conditions without optimization to form the corresponding α-aryl acetones **7a–o** in moderate to good yield for a range of substrates (Scheme 2).

Ortho-substitution was broadly tolerated, as were electron-donating and electron-withdrawing groups, although the latter were less well tolerated. Several substrates failed to deliver any desired product at all, and these tended to be strongly electron deficient (Figure 2). These findings are consistent with those for other methods for acetone arylation,[6,10] but the present method benefits from additional convenience, especially for larger-scale work, where operation below the boiling point simplifies the equipment required; moreover, it eliminates the significant dehalogenation observed under the previously reported ambient-temperature conditions with a Josiphos-type ligand.

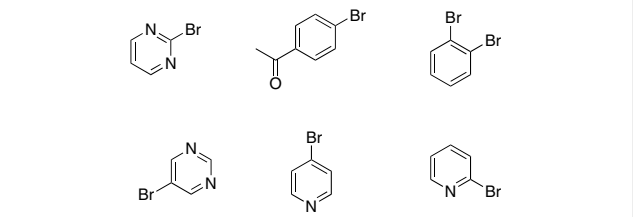
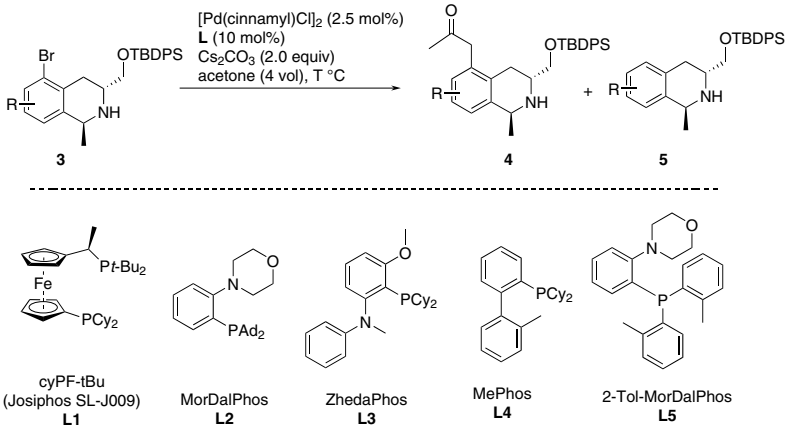


Figure 2 Failed substrates

We have developed an alternative set of conditions for the monoarylation of acetone avoiding significant dehalogenation in a complex substrate.[15] The procedure is operationally simple and displays reasonable generality across a diverse set of (het)aryl halides.

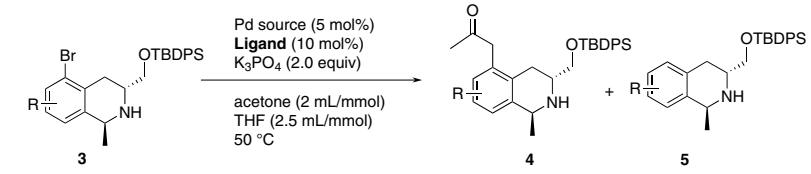
Table 1 Survey of Reported Conditions and Close Variants Thereof[a]

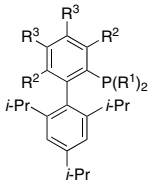


Entry	Ligand	Temp (°C)	Time (h)	**4**/**5**/**3**[b]	Ref.
1	**L1**	25	72	53:20:27	9
2	**L2**	90	19	95:5:0	3
3	**L3**	90	19	95:5:0	8
4[c,d]	**L4**	70	19	95:5:0	11
5	**L2**	50	19	49:3:48	
6	**L3**	50	19	12:0:88	
7[c,d]	**L4**	50	19	76:7:17	
8[c]	**L4**	50	19	27:5:68	
9	**L5**	50	19	67:10:23	3

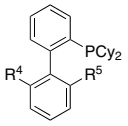
[a] Reaction conditions: $[Pd(cinnamyl)Cl]_2$ (5 mol%), ligand (15 mol%).
[b] Determined by LC/MS.
[c] In 2:1 THF–acetone as solvent and with tris(dibenzylideneacetone)dipalladium(0) $[Pd_2(dba)_3]$ as the Pd source.
[d] With K_3PO_4 as the base.

Table 2 Ligand Screening for the Arylation Reaction

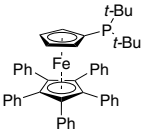




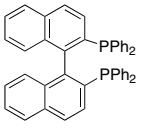
BrettPhos **L6**; R^1 = Cy, R^2 = OMe, R^3 = H
XPhos **L7**; R^1 = Cy, R^2 = R^3 = H
tBuBrettPhos **L8**; R^1 = *t*-Bu, R^2 = OMe, R^3 = H
tBuXPhos **L9**; R^1 = *t*-Bu, R^2 = R^3 = H



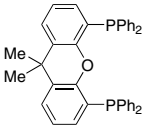
SPhos **L10**; R^4 = R^5 = OMe
RuPhos **L11**; R^4 = R^5 = O*i*-Pr
CPhos **L12**; R^4 = R^5 = NMe_2
DavePhos **L13**; R^4 = NMe_2, R^5 = H



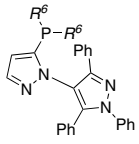
QPhos **L14**



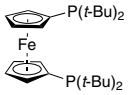
BINAP **L15**



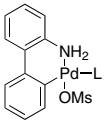
XantPhos **L16**



BippyPhos **L17**; R^6 = *t*-Bu
AdBippyPhos **L18**; R^6 = 1-Ad

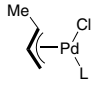


dtbpf **L19**

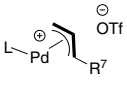


P12: L = **L12** (CPhos)
P13: L = **L13** (DavePhos)
P19: L = **L19** (dtbpf)
P20: L = **L1**

P15: L = **L15** (BINAP)
P16: L = **L16** (XantPhos)



P7: L = **L7** (XPhos)
P10: L = **L10** (SPhos)
P11: L = **L11** (RuPhos)
P14: L = **L4** (QPhos)

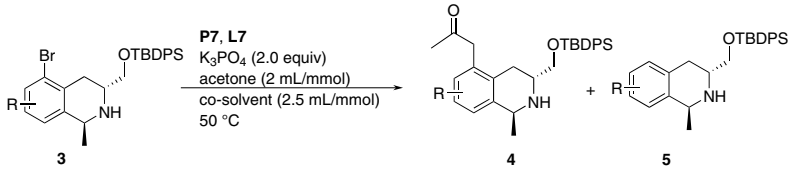


P6: R^7 = Me, L = **L6** (BrettPhos)
P8: R^7 = H, L = **L8** (tBuBrettPhos)
P9: R^7 = H, L = **L9** (tBuXPhos)
P17: R^7 = H, L = **L17** (BippyPhos)
P18: R^7 = H, L = **L18** (AdBippyPhos)

Entry	Pd source	Ligand	Ratio **4**/**5**/**3**[a]
1	**P6**	**L6**	66:7:27
2	**P7**	**L7**	90:10:0
3	**P8**	**L9**	12:12:76
4	**P9**	**L9**	19:9:72
5	**P10**	**L10**	76:7:1
6	**P11**	**L11**	78:5:1
7	**P12**	**L12**	73:7:1
8	**P13**	**L13**	53:11:36
9	**P14**	**L14**	37:16:47
10	**P15**	–	6:6:88
11	**P16**	–	32:3:65
12	**P17**	**L17**	3:1:96
13	**P18**	**L18**	6:6:88
14	**P19**	–	23:14:63
15	**P20**	–	11:11:78
16	**[Pd(cinnamyl)Cl]$_2$**	**L5**	89:9:2

[a] Determined by LC/MS.

Table 3 Further Optimization of the Monoarylation



Entry	Co-solvent	**P7** loading (mol%)	**L7** loading (mol%)	Base	**4**/**5**/**3**[b]
1	THF	5	5	K_3PO_4	90:10:0
2	toluene	5	5	K_3PO_4	90:8:2
3	–	5	5	K_3PO_4	93:7:0
4	–	5	5	K_3PO_4	92:6:2
5	–	2.5	–	K_3PO_4	91:7:2
6	–	2.5	–	KH_2PO_4	0:0:100
7	–	2.5	–	K_2HPO_4	0:0:100
8	–	2.5	–	K_2CO_3	9:1:90
9	–	2.5	–	DBU	0:0:100
10	–	2.5	–	*t*-BuOK	–[b]

[a] Determined by LC/MS.
[b] Complex mixture of products.

Acknowledgment

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(15) **1-Arylacetones 7a–o; General Method**
A 20 mL vial equipped with a stirrer bar and rubber seal was charged with the appropriate (het)aryl bromide **6** (2.4 mmol), K_3PO_4 (3 equiv), and **P7** (2.5 mol%). The vial was sealed and degassed by using three vacuum/N_2 cycles before acetone (10.8 mL) was added and the resulting mixture was heated to 50 °C for the appropriate time (Scheme 2). The mixture was then cooled to rt, diluted with EtOAc, and filtered through Celite, washing with additional EtOAc. The filtrate was evaporated to dryness and purified by chromatography (silica gel).
1-(2-Methylphenyl)propan-2-one (7d)
Synthesized according to the general procedure from 2-bromotoluene (286 μL, 2.38 mmol) as a colorless oil; yield: 245 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.12 (m, 4 H), 3.72 (s, 2 H), 2.25 (s, 3 H), 2.14 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.8, 29.4, 49.3, 126.7, 127.5, 130.5, 130.6, 133.3, 137.0, 206.6.

