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Palladium-Catalyzed Mono-α-Arylation of Acetone with Aryl Imidazolylsulfonates

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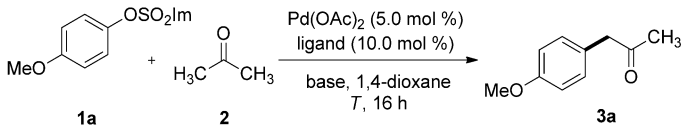
Palladium-catalyzed arylations of α-C–H acidic compounds have emerged as reliable tools for the formation of $C(sp^3)$–$C(sp^2)$ bonds.[1,2] In particular, pioneering studies by the groups of Miura,[3] Buchwald,[4] and Hartwig[5] have set the stage for broadly applicable α-arylations of various carbonyl compounds.[1,6,7] Despite this remarkable progress,[6] generally applicable mono-α-arylations of the simplest ketone, acetone, have until very recently proven elusive.[8] This is largely because the monoarylated acetone derivatives are inherently more reactive than acetone itself, which can lead to mixtures of oligo- and polyarylated products that are difficult to separate. Stradiotto and co-workers' elegantly designed DalPhos P,N ligands[9] were very recently found to be the key to controlling the chemoselectivity and reactivity of challenging mono-α-arylations of acetone.[10] In recent years, the focus on transition-metal-catalyzed arylations has shifted to the use of phenol-derived, fluorine-free[11] electrophiles as arylating reagents because these electrophiles are readily accessible and can be easily utilized as directing groups in versatile arene functionalization strategies.[12] In this context, air- and moisture-stable aryl imidazolylsulfonates **1** are particularly attractive because of the self-destructive, and thus nongenotoxic properties, of the byproduct imidazolylsulfonic acid.[13] Within our research program on the use of phenol-based electrophiles for metal-catalyzed C–H bond[14,15] arylations,[16,17] we became interested in employing user-friendly imidazolylsulfonates for α-arylations of ketones, with a particular focus on the use of acetone (**2**), which we wish to report herein.

Our optimization studies were initiated by probing a set of ligands for the difficult mono-α-arylation of acetone (**2**) with aryl imidazolylsulfonate **1a** in 1,4-dioxane as the solvent (Table 1 and Table S1 in the Supporting Information). Interestingly, although monodentate phosphine ligands only provided unsatisfactory results, chemoselective and efficient catalysis was accomplished with bisphosphines 1,1′-bis(diphenylphosphino)ferrocene (dppf)[18] and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos)[19] (Table 1, entries 1–3). Among a variety of bases, Cs_2CO_3 proved to be optimal, whereas NaO*t*Bu led to an undesired decomposition of the organic electrophile **1a** (Table 1, entry 6). Reactions proceeded most satisfactorily in 1,4-dioxane as the solvent, with transformations performed in THF, toluene, or MeCN being less successful. Different palladium(II) compounds served as viable precatalysts; the most efficient catalysis was achieved by employing inexpensive $Pd(OAc)_2$ which ensured high catalytic efficacy even at a significantly lower reaction temperature (Table 1, entries 7–17).[20] It is worth noting that in a previous study the inexpensive precursor $Pd(OAc)_2$ led to a low conversion of acetone (**2**) (< 5%).[10a]

Table 1. Optimization studies on the mono-α-arylation of acetone (**2**) with aryl imidazolylsulfonate **1a**.[a]



1a **2** **3a**

Entry	Ligand	Base	*T* [°C]	Yield [%]
1	PCy_3	Cs_2CO_3	110	–[b]
2	dppf	Cs_2CO_3	110	50
3	XantPhos	Cs_2CO_3	110	>98 (79)
4	XantPhos	K_2CO_3	110	–[b]
5	XantPhos	$K_3PO_4 \cdot H_2O$	110	35
6	XantPhos	NaO*t*Bu	110	–
7[c]	XantPhos	Cs_2CO_3	80	>98 (31)
8[d]	XantPhos	Cs_2CO_3	80	–[b]
9	XantPhos	Cs_2CO_3	60	80 (62)
10	$(t\text{Bu})_3\text{P}\cdot\text{HBF}_4$	Cs_2CO_3	80	–[b]
11	X-Phos	Cs_2CO_3	80	15
12	HIMesCl	Cs_2CO_3	80	–[b]
13	dppe	Cs_2CO_3	80	–[b]
14	dppb	Cs_2CO_3	80	–[b]
15	*rac*-BINAP	Cs_2CO_3	80	80 (38)
16	DPE-Phos	Cs_2CO_3	80	>98 (69)
17	**XantPhos**	**Cs_2CO_3**	**80**	**>98 (84)**

[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.5 mL), $Pd(OAc)_2$ (5.0 mol%), ligand (10.0 mol%), base (1.0 mmol), 1,4-dioxane (2.0 mL); conversion was determined by GC; isolated yields are given in parentheses; Im = imidazolyl, Cy = cyclohexyl, *t*Bu = *tert*-butyl, X-Phos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, IMesH = 1,3-bis(2,4,6-trimethylphenyl)imidazolium, dppe = 1,2-bis(diphenylphosphino)ethane, dppb = 1,4-bis(diphenylphosphino)butane, *rac*-BINAP = racemic 2,2′-bis-(diphenylphosphino)-1,1′-binaphthalene, DPE-Phos = bis(2-diphenylphosphinophenyl)ether. [b] Only unreacted **1a** observed by GC/MS analysis. [c] [{(cinnamyl)PdCl}$_2$] (2.5 mol%). [d] [Pd_2dba_3] (2.5 mol%); dba = dibenzylideneacetone.

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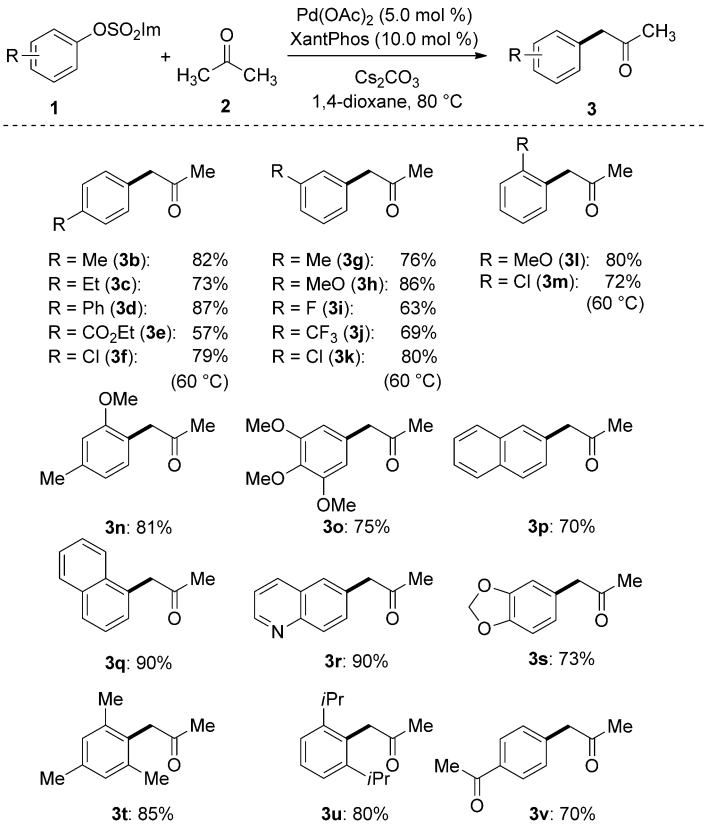
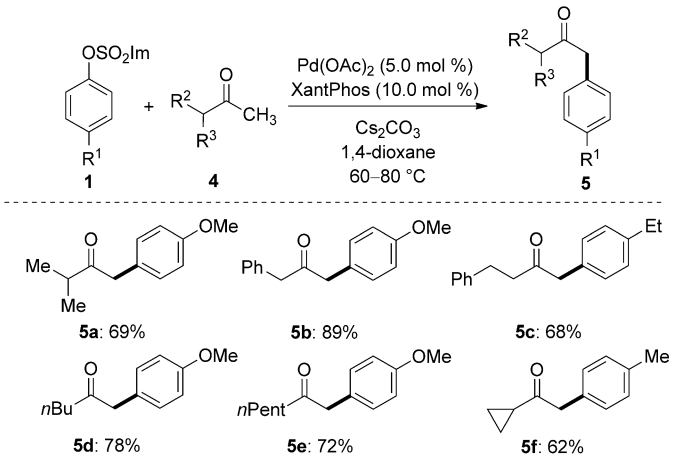


Scheme 1. Palladium-catalyzed mono-α-arylation of acetone (**2**).

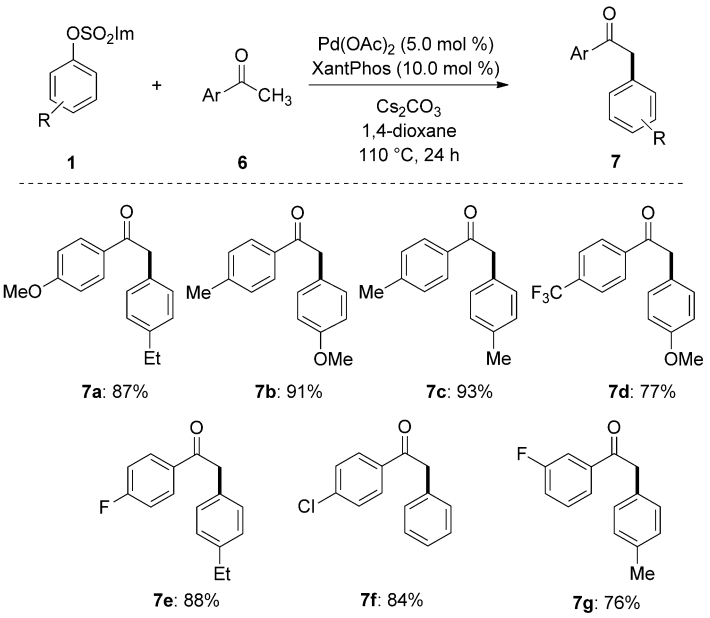
We tested the scope of the optimized catalytic system using the mono-α-arylation of acetone (**2**) (Scheme 1). A variety of aryl imidazolylsulfonates **1**, with *para*, *meta* or *ortho* substituents, furnished the desired products **3b**–**3s** with excellent chemoselectivities. The catalytic system proved to be broadly applicable and was found to be tolerant of valuable electrophilic functional groups such as fluoro, chloro or ester substituents as well as heterocyclic moieties. Furthermore, sterically shielded di-*ortho*-substituted electrophiles **1t** and **1u** were converted with high catalytic efficacy to the desired mono-arylated products **3t** and **3u**, respectively. Importantly, acetophenone derivative **1v** delivered the mono-α-arylation product **3v** of acetone **2** as the only product of a competition experiment, which is a strong testament for the excellent chemoselectivity of the palladium catalyst (see below).

The optimized catalytic system was not restricted to the α-arylation of acetone (**2**), but also enabled the efficient functionalization of alkyl methyl ketones **4** with aryl imidazolylsulfonates **1**, including a cyclopropane derivative, to give monoarylated products **5** (Scheme 2). Notably, the palladium-catalyzed functionalization occurred with excellent site- and monoselectivity at the sterically less congested methyl substituent of ketones **4**.

Furthermore, acetophenones **6** provided the desired monoarylated products **7** with high yields of isolated products, again through a chemoselective transformation of the methyl group of ketones **6** (Scheme 3).



Scheme 2. Mono-α-arylation of alkyl methyl ketones **4** (*n*Pent = *n*-pentyl).

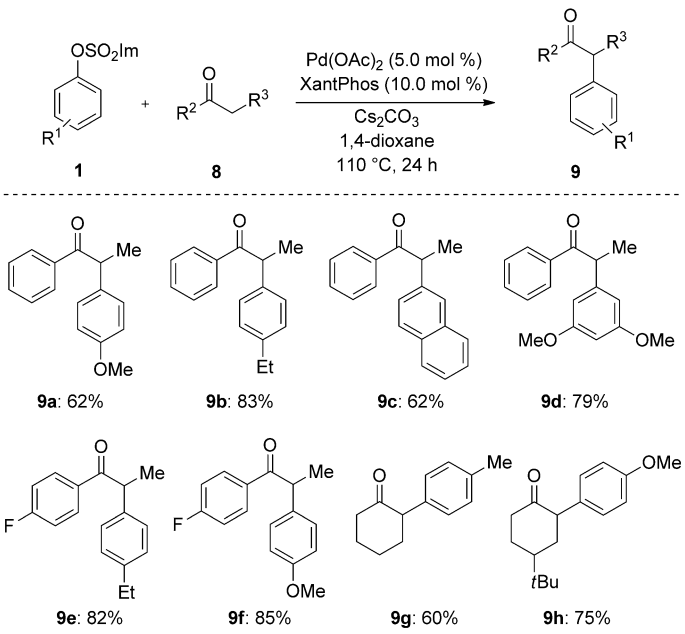


Scheme 3. Chemoselective mono-α-arylation of aryl methyl ketones **6**.

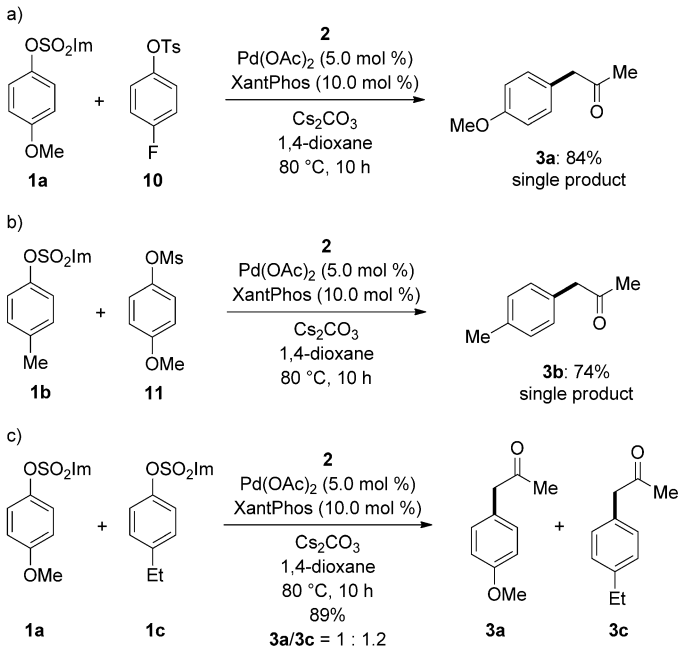
However, the protocol for α-arylations with imidazolylsulfonates **1** was not limited to methyl ketones. Indeed, the optimized catalytic system allowed for effective α-arylations of diversely substituted alkyl ketones **8**, including cyclic substrates (Scheme 4).

Given the remarkable chemoselectivity exerted by the optimized palladium catalyst in mono-α-arylations with imidazolylsulfonates **1**, we became interested in probing its mode of action. Intermolecular competition experiments revealed that aryl imidazolylsulfonates **1** are significantly more reactive than aryl tosylates **10** or mesylates **11**, even when they are electronically deactivated (Scheme 5).

In summary, we have reported the first α-arylations of carbonyl compounds with user-friendly aryl imidazolylsulfo-



Scheme 4. α-Arylation of alkyl ketones **8** with imidazolylsulfonates **1**.



Scheme 5. Competition experiments with different electrophiles.

nates as electrophiles. A catalytic system derived from bidentate phosphine XantPhos and inexpensive $Pd(OAc)_2$ proved widely applicable, and allowed for the challenging mono-α-arylation of acetone with ample scope.

Acknowledgements

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Keywords: arylation · C–H activation · C–O activation · imidazolylsulfonate · palladium · phosphane ligands

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[20] The use of 2.5 mol% of the palladium catalyst resulted in an unsatisfactorily low yield of the desired product **3a** (see Table S1 in the Supporting Information).

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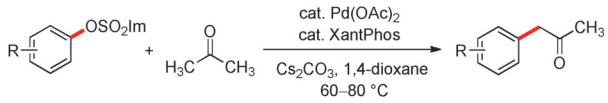

Set the ace(tone): A palladium catalyst derived from the bidentate XantPhos ligand and $Pd(OAc)_2$ has enabled broadly applicable mono-α-arylations of acetone to be performed with air- and moisture-stable aryl imidazolylsulfonates as most user-friendly electrophiles (see scheme).

C–O Activation

L. Ackermann, V. P. Mehta* ▮▮▮▮–▮▮▮▮

Palladium-Catalyzed Mono-α-Arylation of Acetone with Aryl Imidazolylsulfonates