

Palladium-Catalyzed Mono- α -arylation of Acetone with Aryl Halides and Tosylates

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 Supporting Information

ABSTRACT: We report the first example of selective Pd-catalyzed mono- α -arylation of acetone employing aryl chlorides, bromides, iodides, and tosylates. The use of appropriately designed P,N-ligands proved to be the key to controlling the reactivity and selectivity. The reaction affords good yields with substrates containing a range of functional groups at modest Pd loadings using Cs₂CO₃ as the base and employing acetone as both a reagent and the solvent.

Transition-metal-catalyzed α -arylation of carbonyl and related compounds has emerged as a useful and powerful strategy for the formation of sp³–sp² carbon–carbon bonds.¹ Despite considerable progress in the field, most notably from the groups of Hartwig,² Buchwald,³ among others,⁴ the identification of catalysts capable of the selective monoarylation of enolates employing a broad range of unbiased aryl halides has remained a persistent challenge. The monoarylation of enolates derived from acetate esters,⁵ methyl aryl ketones,^{2a,3a,c,5a,6} acetonitrile,⁷ and dimethylacetamide^{2b} with unbiased reaction partners has been established; however, the analogous selectivity with acetone, the simplest ketone substrate, still represents a significant challenge that has not been addressed to date.⁸

Key obstacles to the selective monoarylation of acetone include the fact that the α -aryl methyl ketone products still possess several reactive C–H bonds that can undergo further C–C bond-forming reactions, thus leading to mixtures of polyarylated products, even when acetone is employed in excess.⁹ Moreover, the ketone products following the initial arylation reaction are inherently more reactive toward subsequent arylation chemistry because of the increased acidity of the remaining α -C–H bonds, thereby resulting in more facile enolate formation. Additionally, reductive elimination from the key Pd(II)aryl(enolate) species has been demonstrated to be slower when less sterically demanding ketone substrates are employed.¹⁰ Although the challenges posed by acetone in α -arylation chemistry have been circumvented through the use of preformed stannyl or silyl acetone enolates (Figure 1 A,B),¹¹ such strategies employing acetone equivalents are not ideal from efficiency or economic standpoints, given the requirement of extra synthetic steps and the use of stoichiometric tin or zinc reagents. Alternatively, similar α -aryl methyl ketones have recently been prepared using a CuI-mediated arylation/C–C bond cleavage process that involves the reaction of β -diketones with aryl bromides and iodides (Figure 1C).¹² In this regard, the use of acetone as a

reagent for the selective synthesis of α -aryl methyl ketones (Figure 1D) represents an unmet challenge in metal-mediated α -arylation catalysis. Herein we report a Pd catalyst system and reaction conditions that allow, for the first time, the direct arylation of acetone with a diverse range of aryl halides and tosylates with excellent monoarylation selectivity.

Our initial efforts focused on the identification of suitable reaction conditions for the Pd-catalyzed selective monoarylation of acetone with 4-chlorotoluene (**1a**) using a catalyst system that we previously showed to display good monoarylation reactivity with small amines (Table 1).¹³ The use of [Pd(cinnamyl)Cl]₂, **L1** (Mor-DalPhos), and a 1:1 acetone/Cs₂CO₃ mixture (in 4-fold excess relative to **1a**) in 1,4-dioxane provided the desired monoarylated methyl ketone product (**2a**) in 37% yield (Table 1, entry 1). Further investigation into the reaction parameters revealed that both the catalytic activity and monoselectivity were highly sensitive to the components of the catalyst system.¹⁴ The choice of palladium source proved to be quite significant, as replacement of [Pd(cinnamyl)Cl]₂ with either Pd(OAc)₂ or Pd(dba)₂ resulted in <5% conversion of **1a** after 4 h. The ratio of **1a** to acetone and Cs₂CO₃ had a significant impact on both the rate and selectivity of this catalysis. Although the use of a 2-fold excess of base relative to acetone resulted in faster conversions of **1a**, more significant yields of diarylation products were observed (Table 1, entry 3). Further optimization revealed that superior yields of **2a** were achieved when an excess of acetone (10 equiv or neat) was used in the presence of 2 equiv of Cs₂CO₃ (relative to **1a**) for 5 h at 90 °C, whereby quantitative conversion of **1a** with excellent monoselectivity was observed (Table 1, entry 4). While quantitative conversion of **1a** was still observed, the use of lower Pd loadings (0.5 mol % Pd) for longer reaction times (48 h) resulted in diminished selectivity for **2a** (Table 1, entry 5). Notably, the reaction temperature could also be lowered to 50 °C with preserved monoarylation selectivity (Table 1, entry 6).

With 1 mol % [Pd(cinnamyl)Cl]₂ and 4 mol % ligand as a precatalyst mixture for the addition of **1a** to acetone (10 equiv) in the presence of Cs₂CO₃ (2 equiv) at 90 °C as the standard conditions, a series of structurally diverse phosphine and N-heterocyclic carbene ligands, which have found success in alternative α -arylation reactions, were screened to assess the importance of the ligand arylation chemistry (Table 1, entries 7–16). Replacement of (1-Ad)₂P– by Cy₂P– (**L2**) or the morpholino moiety by Me₂N– (**L3**) resulted in a loss of selectivity or activity, respectively. Most electron-rich monophosphines or carbenes, including tBu-DavePhos (**L5**), P(tBu)₃

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Previous Metal-Catalyzed Selective Cross-Coupling of Acetone Equivalents

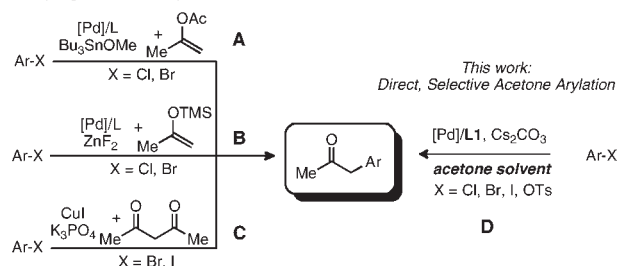


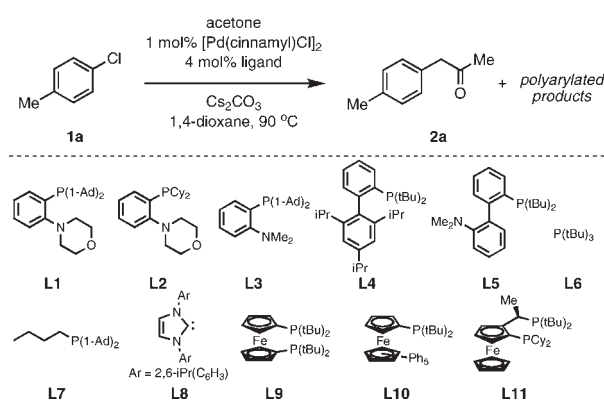
Figure 1. Comparison of (A–C) previous metal-catalyzed methods for the selective synthesis of α -aryl methyl ketones from acetone equivalents and (D) the method described in the present work.

(L6), cataCXium-A (L7), and IPr (L8), as well as the bisphosphine Josiphos (L11) gave comparatively poor results, with low conversions of the starting aryl chloride to mainly polyarylated products. Although the use of *t*Bu-XPhos (L4), bis(*di-tert*-butylphosphino)ferrocene (DTBPFF) (L9), or QPhos (L10) provided modest conversions of **1a** under our standard conditions, the poor selectivity observed for the desired monoarylation product further highlights the utility of L1 for the selective synthesis of α -aryl methyl ketone **2a**.

Having defined a highly effective catalyst system and reaction conditions for the selective monoarylation of acetone with 4-chlorotoluene, we sought to explore the scope of the reaction for other aryl (pseudo)halides (Table 2). The α -arylation of acetone with electron-rich and electron-neutral aryl chloride substrates proceeded to the corresponding monoarylated methyl ketone products **2b–e** in good to excellent yields (78–98%) when 2–3 mol % Pd (1–1.5 mol % [Pd(cinnamyl)Cl]₂) was employed in neat acetone at 90 °C.¹⁵ Electron-poor aryl chlorides, such as 4-chlorobenzotrifluoride, could also be employed successfully (**2f**, 70%). Substrates featuring benzyl-protected (**2h**) or free alcohol (**2i**) functional groups as well as those with geminally disubstituted olefin (**2j**) or tertiary amine (**2k**) groups also provided the desired ketone products with excellent mono-selectivity. Aryl chlorides containing N-heterocycles, such as pyridine (**2l**), pyrrole (**2m**), or *N*-benzylindole (**2n**), were also readily converted into the corresponding ketones in good to excellent yields (72–96%). Furthermore, aryl chloride substrates featuring alternative enolizable sites, such as benzyl and homobenzyl esters (**2o** and **2p**) or an acetanilide group (**2q**), were employed successfully in the chemoselective monoarylation of acetone with useful yields (66–84%).

Aryl bromides and iodides were also found to be suitable substrates for the selective monoarylation of acetone employing [Pd(cinnamyl)Cl]₂ and L1 (Table 2). Though electron-rich (**2r**) and sterically crowded (**2s**) aryl bromides were readily converted to the corresponding α -aryl methyl ketones (88 and 72%, respectively), the use of electron-poor aryl bromides, such as 4-bromobenzonitrile, surprisingly proved to be much more problematic (**2t**, 33%). A benzylic nitrile substrate, which features an alternative enolizable site, was chemoselectively converted to the desired ketone **2u**. Heteroaromatic substrates, such as 3-bromothiophene, 2-bromo-*N*-benzylpyrrole, 5-bromo-*N*-benzylindole, and 4-bromo-*N*-Boc-indole, were also suitable reaction partners (**2v–y**). This protocol was also shown to be amenable to large-scale reactions, as a 67% yield (1.2 g) of **2z** was obtained after reduction of the product ketone by NaBH₄ when the reaction was

Table 1. Optimization of the Pd-Catalyzed Monoselective α -Arylation of Acetone with 4-Chlorotoluene^a



entry	ligand	acetone:base ^b	<i>t</i> (h)	conv. (%)	yield of 2a (%)
1	L1	4:4	2	45	37
2 ^c	L1	4:4	2	77	48
3	L1	4:8	2	85	52
4	L1	10:2	5	>99	89 ^d
5 ^e	L1	10:2	48	>99	61
6 ^f	L1	10:2	48	78	71
7	L2	10:2	5	90	60
8	L3	10:2	5	47	44
9	L4	10:2	5	56	12
10	L5	10:2	5	38	11
11	L6	10:2	5	38	6
12	L7	10:2	5	<2	<2
13 ^g	L8	10:2	5	10	7
14 ^g	L9	10:2	5	59	14
15	L10	10:2	5	60	20
16 ^g	L11	10:2	5	35	23

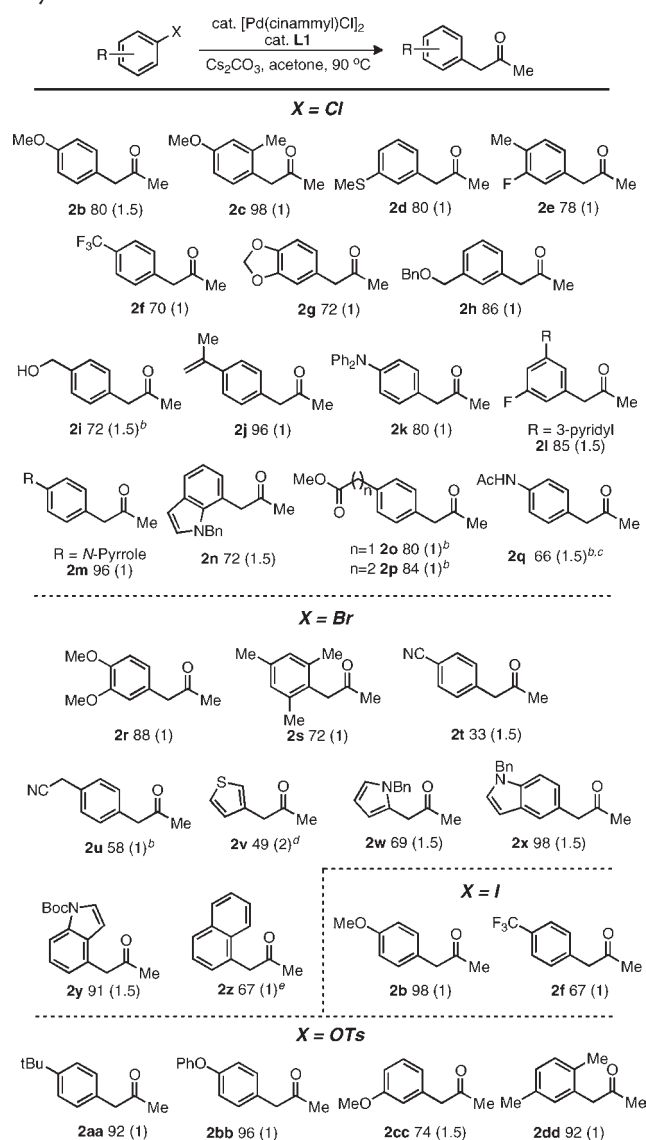
^a Conditions: 0.25 mmol ArCl scale in 0.5 mL of 1,4-dioxane. Conversions and yields were determined by GC using dodecane as an internal standard. ^b Relative to **1a**. ^c Using K₃PO₄ as the base. ^d Trace diarylation products were observed by GC. ^e Using 0.5 mol % Pd. ^f Reaction was conducted at 50 °C using 5 mol % Pd. ^g Using 2 mol % ligand.

conducted on a 10 mmol scale. Both electron-rich and electron-poor aryl iodides proved to be compatible substrates, as demonstrated by the synthesis of 4-methoxy and 4-trifluoromethyl α -aryl methyl ketones **2b** and **2f**.

While preliminary studies with aryl triflates and mesylates were not successful, aryl tosylates, which are easily prepared from inexpensive and readily available phenols, were also shown to be suitable reaction partners for the monoarylation of acetone (Table 2). Reactions of electron-rich and sterically congested aryl tosylates proceeded selectively with good to excellent yields (**2aa–dd**, 74–96%).¹⁶

The major limitation identified in the substrate scope survey featured in Table 2 is that the use of electron-poor aryl halides provided lower yields of the corresponding α -aryl methyl ketone products than did the use of electron-rich or neutral substrates. In order to provide insight into this limitation, competition experiments were conducted in conjunction with studies of the initial rates of reaction for a series of aryl chlorides. With 1 mol %

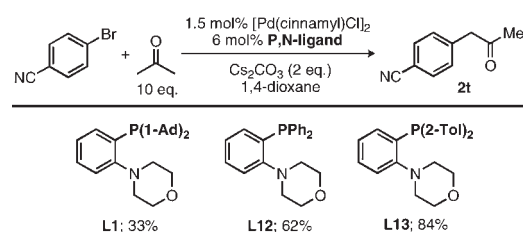
Table 2. Scope of the Palladium-Catalyzed α -Arylation of Acetone with Aryl Chlorides, Bromides, Iodides, and Tosylates^a



^a Conditions: 0.5 M ArX in acetone at 90 °C for 4–16 h, ArCl:Cs₂CO₃ = 1:2, [Pd]:L1 = 1:2. Yields are of isolated material. The [Pd(cinnamyl)Cl]₂ loading (mol %) is indicated in parentheses. ^b ArCl:Cs₂CO₃ = 1:3, [ArCl] = 0.25 M. ^c ¹H NMR yield relative to 1,4-bis(trifluoromethyl)benzene as an internal standard. ^d Isolated in a combined 70% yield with the direct arylation product (4.6:1). ^e Yield of corresponding alcohol after reduction with NaBH₄, performed on a 10 mmol scale.

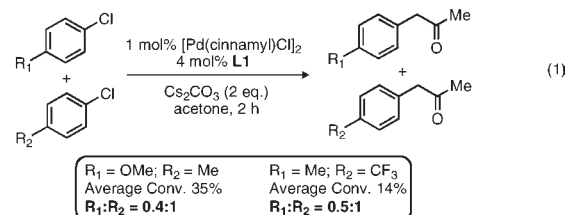
[Pd(cinnamyl)Cl]₂ and 4 mol % L1 along with 2 equiv of Cs₂CO₃ and 10 equiv of acetone (relative to the aryl chloride), the initial rates of reaction for 4-chloroanisole, 4-chlorotoluene, and 4-chlorobenzotrifluoride were monitored.¹⁷ The results from this study were consistent with those from the scope study: the use of more electron-rich aryl chloride substrates provided higher rates of catalysis. This trend also translated to competition reactions involving combinations of different aryl chlorides (eq 1), where it was observed that mixtures of more electron-rich aryl chlorides

Table 3. Ligand Screening for the Palladium-Catalyzed α -Arylation of Acetone with Electron-Deficient 4-Bromobenzonitrile^a



^a Reaction conditions: 0.5 M ArBr in acetone at 90 °C for 16 h, ArBr:Cs₂CO₃ = 1:2. Yields are of isolated material.

proceeded to higher average conversions (R₁ = OMe, R₂ = Me; 35% after 2 h) than those of electron-poor substrates (R₁ = Me, R₂ = CF₃; 14% after 2 h). Moreover, the favored product in each competition experiment was the α -aryl methyl ketone derived from the more electron-deficient aryl chloride, despite the fact that the electron-rich substrates reacted to form product more rapidly in the individual rate studies. The presence of electron-poor aryl chlorides appears to inhibit the α -arylation of more electron-rich substrates; presumably, this is a result of more facile oxidative addition of the electron-poor aryl chloride followed by a low rate of reductive elimination, effectively inhibiting the catalyst from reacting with electron-rich arenes. Collectively, these results suggest that the reactivity issues with electron-deficient substrates must arise in either the transmetalation or reductive elimination steps of the catalytic cycle.^{1c}



On the basis of the hypothesis that C–C reductive elimination of electron-deficient arenes with the acetone enolate from an [(L1)Pd(CH₂COCH₃)(Ar)] intermediate may be slowed as a result of the heightened basicity of palladium, as suggested by the mechanistic studies of Culkin and Hartwig,¹⁰ less electron-rich P, N-ligands were pursued in hopes of effecting these challenging transformations (Table 3). Substitution of the electron-rich di-1-adamantylphosphino moiety for less basic diphenylphosphino (L12) and di-2-tolylphosphino (L13) groups facilitated increasingly significant improvements with regard to the isolated yield of 2t (from 33 to 62 and 84% yield, respectively) from 4-bromobenzonitrile. We propose that the combined electronic and steric properties of L13 help to promote the presumably difficult reductive elimination between electron-poor arenes and acetone enolates. Notably, the use of L13 under similar conditions for the α -arylation of acetone with electron-deficient aryl chlorides was not successful, because of the more challenging Ar–Cl oxidative addition reaction when such triarylphosphine ligands are employed.¹⁸

Through the use of catalytic mixtures consisting of [Pd(cinnamyl)Cl]₂ and L13, a selection of electron-deficient aryl bromides were shown to be suitable reaction partners for the selective

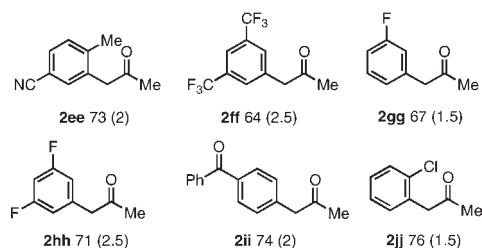


Figure 2. Expanded scope for palladium-catalyzed α -arylation of acetone using electron-deficient aryl bromides. Reaction conditions: 0.5 M ArBr in acetone at 90 °C, ArBr:Cs₂CO₃ = 1:2, [Pd]/L13 = 1:2. Yields are of isolated material, and the [Pd(cinnamyl)Cl]₂ loading (mol %) is indicated in parentheses. **2ff** and **2hh** were isolated as the corresponding alcohols following reduction using NaBH₄.

monoarylation of acetone (Figure 2). The use of sterically hindered electron-deficient aryl bromides (affording **2ee**) as well as those containing one or more electron-withdrawing groups, such as fluoride, trifluoromethyl, or acyl (affording **2ff–ii**), proceeded selectively to the α -aryl methyl ketone products in good yield (64–74%). The reactivity pattern of Pd/L13 mixtures was exploited in the selective cross-coupling of 2-chlorobromobenzene to generate the corresponding chloro-substituted ketone, thereby providing an opportunity for subsequent Pd(0)-mediated coupling chemistry of the remaining aryl chloride (**2jj**).¹⁹

In summary, we have described the first example of the selective, Pd-catalyzed mono- α -arylation of acetone with aryl chlorides, bromides, iodides, and tosylates. The reaction makes direct use of a simple and abundant three-carbon feedstock without the requirement of stoichiometric additives or preformed enolates to generate α -aryl methyl ketones. In view of the excellent selectivity and functional group tolerance, the ease of conducting such reactions, and the relative mildness of the reaction conditions, we expect this protocol to be widely adapted in synthetic chemistry.

ASSOCIATED CONTENT

S Supporting Information. Full experimental details and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (9) For the diarylation of acetone en route to oxime esters, see the Supporting Information for the following article: Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676.

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- (14) K₂CO₃ and Na₂CO₃ proved to be unsuccessful in promoting the reaction, and LiHMDS and NaOtBu provided intractable product mixtures in which negligible amounts of **2a** were observed by use of GC.

- (15) In neat acetone, L11 also provided good results for arylation with **1a** (94% conv., 93% yield at 60 °C in 19 h).

- (16) The use of 3-(trifluoromethyl)phenyl tosylate resulted in the formation the corresponding phenol as the major product under the standard conditions.

- (17) See the Supporting Information.

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- (19) Preliminary studies also showed that L13 was capable of cross-coupling electron-rich aryl bromides (4-bromotoluene and 4-bromoanisole) under similar conditions.