

Selective Monoarylation of Acetate Esters and Aryl Methyl Ketones Using Aryl Chlorides

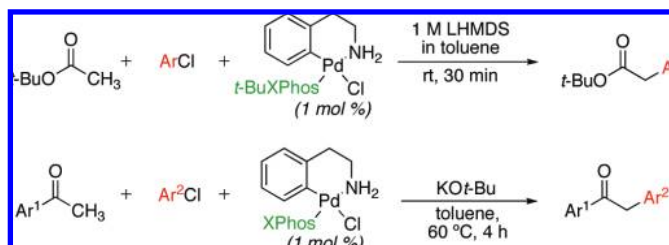
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ABSTRACT



Simple, efficient procedures for the monoarylation of acetate esters and aryl methyl ketones using aryl chlorides are presented. Previously, no general method was available to ensure the highly selective monoarylation of these classes of substrates using aryl chlorides. Using palladium precatalysts recently reported by our group, these reactions are easily accomplished under mild conditions that tolerate a wide array of heterocyclic substrates.

It has been well demonstrated that the use of Pd-catalyzed α -substitution reactions of carbonyl compounds can be an effective strategy to achieve the arylation and vinylation of enolates,^{1,2} often with excellent enantiomeric control.³ However, there are very few reported examples of the selective monoarylation of enolates from acetate esters and

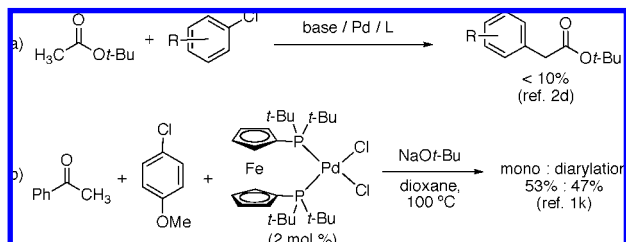
methyl ketones using aryl halides or sulfonates where the enolate is not biased toward monoarylation by the presence of an ortho substituent on the aryl halide or by the presence of a pre-existing α -substituent on the enolate. Such α -arylation reactions are typically unsuccessful as a result of the instability of alkali ester enolates^{2d} or the formation of significant amounts of diarylated side products. To the best of our knowledge, the few examples of the monoarylation of *tert*-butyl acetate that have been demonstrated separately by Hartwig^{2b,c} and our group^{2a} using aryl bromides constitute the only examples of the direct monoarylation of acetate esters. In one recent report, when alkali metal enolates of acetate esters were employed with aryl chlorides, less than 10% of the desired α -arylated ester was observed (Scheme 1a).^{2d} The corresponding zinc enolates were employed in an attempt to circumvent this problem, but the only reported examples utilized chlorobenzene and electron-deficient aryl

(1) For ketones, see: (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382. (c) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1740. (d) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (e) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360. (f) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818. (g) Culkun, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (h) Viciu, M. S.; Kelly, R. A.; Stevens, E. D.; Naud, F.; Studer, M.; Nolan, S. P. *Org. Lett.* **2003**, *5*, 1479. (i) Navarro, O.; Marion, N.; Oonishi, Y.; Kelly, R. A.; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 685. (j) Huang, J.; Bunel, E.; Faul, M. M. *Org. Lett.* **2007**, *9*, 4343. (k) Grasa, G. A.; Colacot, T. J. *Org. Process Res. Dev.* **2008**, *12*, 522. (l) Marion, N.; Ecarnot, E. C.; Navarro, O.; Amoroso, D.; Bell, A.; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 3816. (m) Carril, M.; SanMartin, R.; Dominguez, E.; Tellitu, I. *Tetrahedron* **2007**, *63*, 690.

(2) For esters, see: (a) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996. (b) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410. (c) Hama, T.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 1545. (d) Hama, T.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 1549.

(3) (a) Chieffi, A.; Kamikawa, K.; Ahman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897. (b) Hamada, T.; Chieffi, A.; Ahman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261. (c) Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195.

Scheme 1



chlorides as substrates. With regards to the monoarylation of aryl methyl ketones, there exist only a few reported examples that employ aryl halides lacking an ortho substituent.^{1e,i} A recent report highlighted the difficulty of preventing the formation of undesired diarylated products when the enolates of methyl aryl ketones are employed in cross-coupling reactions using aryl halides (Scheme 1b).^{1k}

Previously, we reported a new class of palladium precatalyst for C–N cross-coupling reactions that is easily activated without the need for exogenous additives and ensures the formation of the corresponding monoligated active complex of Pd(0) (Figure 1).⁴ These biarylmonophosphine-ligated

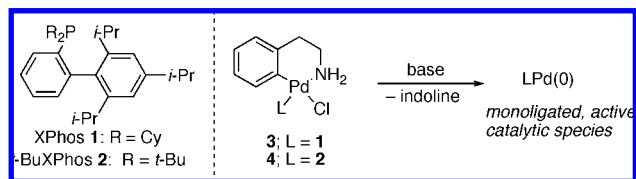


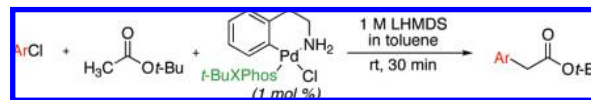
Figure 1. Formation of $L_1Pd(0)$ complexes bearing biarylphosphines.

precatalysts intercept a competent catalytic cycle for C–N bond formation at the amine complex and are activated after deprotonation by the base intrinsically necessary for the cross-coupling reaction. Since base is also required for the α -arylation of carbonyl enolates, we have begun to investigate the use of these precatalysts as convenient Pd sources for conducting such C–C cross-coupling reactions under mild conditions.⁵ Herein we report simple, efficient procedures to effect the α -arylation of acetate esters and aryl methyl ketones with aryl chlorides using precatalysts bearing biarylmonophosphine ligands. We believe that the success of these reactions results largely from the high activity of the $L_1Pd(0)$ species generated by our precatalysts and the related ability to conduct the reactions under very mild conditions.

We have found that precatalysts bearing bulky biarylmonophosphine ligands **1** and **2** (**3** and **4**, respectively) can

efficiently promote the α -arylation of *tert*-butyl acetate. Although **3** and **4** can both promote the α -arylation reaction, the use of **4** is necessary to obtain selective monoarylation of the acetate ester. Table 1 displays a series of monoarylated

Table 1. Selective Monoarylation of *tert*-Butyl Acetate Using Aryl and Heteroaryl Chlorides^a



entry	product	yield ^b (%)	entry	product	yield ^b (%)
1		95	6		90
2		90	7		87 ^c
3		90	8		88
4		95	9		92 ^d
5		92 ^c	10		85 ^e

^a Reaction conditions: aryl chloride (0.5 mmol), *tert*-butyl acetate (0.75 mmol), 1 M LHMDS (1.5 mL, 1.5 mmol) at rt for 30 min. ^b Isolated yields (average of two runs). ^c Reaction conducted at 0 °C. ^d 4 h reaction time. ^e 14 h reaction time.

tert-butyl acetates that were prepared from the direct α -arylation of *tert*-butyl acetate. These reactions occur efficiently using aryl and heteroaryl chlorides and *tert*-butyl acetate at room temperature with 1 mol % **4** and a commercially available solution of 1 M LHMDS in toluene. No solvent other than that from the LHMDS solution is necessary. In general, these reactions are complete in less than 30 min. However, more difficult aryl chlorides (entries 9 and 10) require longer reaction times. The electronic nature of the aryl chloride had little effect on the success of the cross-coupling reaction; reactions involving 4-chlorotoluene (entry 1) and 4-chlorodimethylaniline (entry 3) each proceeded efficiently in less than 30 min. For reactions involving highly reactive aryl chlorides (entries 5 and 7), the temperature had to be reduced to 0 °C to preclude the formation of bisarylated products. Even at 0 °C, these reactions were complete in

(4) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686.

(5) (a) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552. (b) Martin, R.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 4561.

(6) A water-mediated preactivation protocol that we recently reported could also be used to access an active $L_1Pd(0)$ complex for use at room temperature. See: Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505.

approximately 30 min. Because our precatalysts are easily activated well below 0 °C, they constitute powerful palladium sources for such low-temperature cross-coupling reactions.⁶

We propose that our ability to monoarylate the lithium enolate of *tert*-butyl acetate arises from a combination of three factors: (1) the use of a bulky ligand that retards subsequent bisarylation of the monoarylated product; (2) the use of a precatalyst that rapidly forms a highly active L₁Pd(0) complex and results in the rapid conversion of the starting material, preventing competitive background Claisen reactions and the decomposition of potentially unstable metal enolates;^{2d} and (3) the use of low temperatures, which favors monoarylation in these cross-coupling reactions. All three of these reaction properties are readily accessed through the use of precatalyst **4** as the palladium/ligand source. At present, monodentate ligands provide better results than those obtained with bidentate ones. However, it is possible that bidentate ligands whose use provides similar (or better) results may be discovered.

Although the use of *t*-BuXPhos (**2**) was required to achieve the selective monoarylation of *tert*-butyl acetate using aryl chlorides, XPhos (**1**) proved to be the optimal ligand for the monoarylation of aryl methyl ketones (Table 2). Using precatalyst **3** and KO*t*-Bu⁷ in toluene at 60 °C, the monoarylation reactions are complete in less than 4 h. The reaction tolerates a variety of heterocyclic moieties in both the aryl chloride and the aryl methyl ketone. Previously, there have been few reported examples of analogous Pd-catalyzed α -arylation reactions that employ either heteroaryl methyl ketones (entries 2, 3, 5, 10) or heteroaryl halides (entry 6). With this protocol, various acetyl furans, acetyl thiophenes, and acetyl pyridines can be successfully monoarylated. Using precatalyst **3**,⁸ monoarylation products can also be obtained in good yields where both heteroaryl acetyls and heteroaryl chlorides are employed together (entries 7–9, 11). Efforts to arylate heteroaryl methyl ketones whose heteroaryl groups possess two or more heteroatoms (e.g., thiazoles, imidazoles, pyrazines, and triazoles) were largely unsuccessful. When the α -arylation of an aryl methyl ketone is conducted in the presence of an acetamide group, complete selectivity for the arylation of the ketone enolate is observed over the amide enolate (entry 12). Again, the use of a bulky, biarylphosphine ligand permits selective monoarylation, and the use of a highly active Pd source permits the cross-coupling reactions to be conducted under mild conditions.

In summary, we have developed operationally simple, efficient methods for the selective monoarylation of acetate esters and aryl methyl ketones. These methods employ readily activated precatalysts bearing bulky biarylmonophosphine ligands in order to effect monoarylation under mild conditions. In each case, the reactions largely tolerate the presence of heteroaromatic substituents. The success of these reactions further demonstrates the advantages of conducting Pd-catalyzed cross-coupling reactions using metallacyclic

Table 2. Selective Monoarylation of Aryl and Heteroaryl Acetyls Using Aryl and Heteroaryl Chlorides^a

entry	product	yield ^b (%)	entry	product	yield ^b (%)
1		89	7		76
2		88	8		85
3		81	9		79
4		97	10		84
5		90	11		82
6		90	12		86

^a See Supporting Information for general procedures. ^b Isolated yields (average of two runs).

precatalysts such as **3** and **4**. Such precatalysts permit Pd activation under mild reaction conditions and in the absence of competitive residual ligands such as dba or PPh₃ that are typically used to stabilize Pd(0) precursors.

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Supporting Information Available: Experimental procedures and spectral data for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(7) It was found empirically that the use of NaO*t*-Bu resulted in the formation of significantly greater amounts of diarylated products.

(8) Precatalyst **3** is currently available from Strem (item 46-0268). We expect **4** to be available in the near future.