Organic Letters

Letter

pubs.acs.org/OrgLett

Palladium-Catalyzed Acetylation of Arenes

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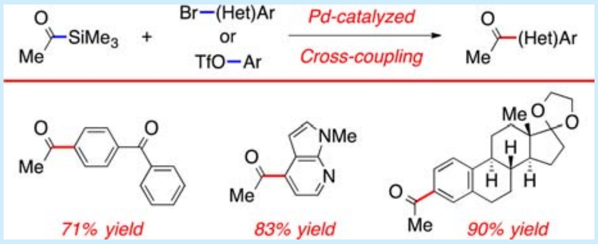
Ⓢ *Supporting Information*

ABSTRACT: A simple method for the preparation of aryl methyl ketones is reported. The transformation involves the Pd-catalyzed coupling of an acyl anion equivalent, acetyltrimethylsilane, with aryl bromides to afford the corresponding acetylated arenes in synthetically useful yields. The methodology is tolerant of heterocycles and provides a new method for arene functionalization.



Palladium-catalyzed cross-couplings remain indispensable tools for the assembly of carbon–carbon (C–C) bonds.[1] Whereas most C–C bond-forming methodologies allow for aryl–aryl or aryl–alkene couplings to proceed, fewer methods are available to introduce aryl-carbonyl linkages from standard electrophilic cross-coupling partners (Figure 1). Catalytic couplings of aryl electrophiles to generate aryl carbonyl derivatives typically involve the use of CO or CO_2,[2] which can be undesirable because of safety and practical considerations.[3]

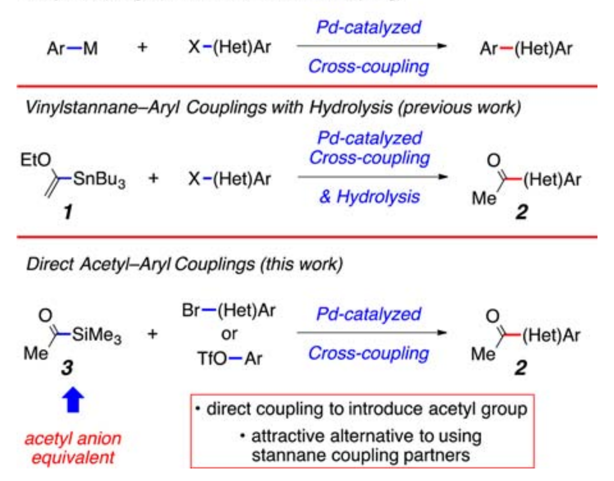


Figure 1. Known couplings and our approach to aryl and hetaryl methyl ketones **2**.

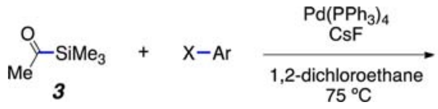
Aryl methyl ketones are an integral class of carbonyl derivatives, which serve as versatile synthetic building blocks. Not only do aryl methyl ketones participate as precursors to heterocycles, fragrances, and resins,[4] they have also been used as intermediates in the syntheses of a variety of drug candidates.[5] Several cross-coupling approaches to aryl methyl ketones have been reported, including carbonylative cross-couplings,[6,7] Heck reactions of enol ethers with subsequent hydrolysis,[8] and cross-coupling of α-alkoxyvinyl metal reagents with ensuing hydrolysis.[9,10] The most commonly used of these cross-couplings is highlighted in Figure 1. Stannane **1** can be coupled to aryl electrophiles to give ketone products **2** after hydrolysis of the intermediate coupling adduct.[5,10]

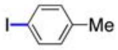
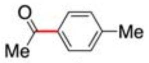
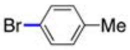
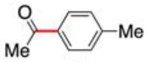
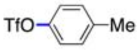
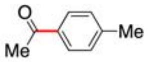
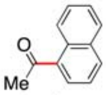
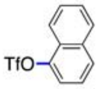
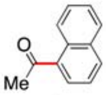
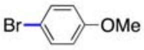
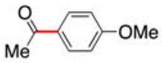
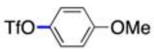
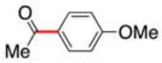
We envisioned an alternative approach that would employ commercially available acetyltrimethylsilane (**3**).[11] Acyl silanes, which are stable acyl anion precursors,[12] exhibit umpolung reactivity of typical carbonyl moieties and have seen limited use in Pd-catalyzed cross-couplings.[13,14] For instance, Schmink and Krska employed arylsilylketones for the synthesis of biaryl ketones,[14] whereas others have studied the reaction of acyl silanes with allylic and benzylic substrates.[15] Herein, we demonstrate that acylsilane **3** readily undergoes Pd-catalyzed cross-coupling with a variety of aryl and hetaryl bromides to efficiently deliver aryl and hetaryl methyl ketones.

We began our study by exploring the cross-coupling between acylsilane **3** and *p*-substituted toluene electrophiles.[16,17] An extensive survey of reaction parameters (*e.g.*, palladium complexes, ligands, solvents, bases, temperature, additives, substrates) led to the identification of reaction conditions that facilitated the desired acetylation. Although yields were modest using *p*-iodotoluene as the substrate (Table 1, entry 1), treatment of *p*-bromotoluene with acetyltrimethylsilane (**3**) in the presence of catalytic $Pd(PPh_3)_4$ and CsF, in 1,2-dichloroethane at 75 °C for 6 h, afforded the desired acylated arene **4** in 79% yield (entry 2). The use of the corresponding triflate also gave **4** in good yield (entry 3). With promising optimized conditions in hand, we tested additional bromide and triflate substrates. In the case of naphthyl derivatives, coupling took place to deliver ketone **5** (entries 4 and 5). The corresponding coupling of *p*-bromomethoxybenzene proceeded smoothly (entry 6), whereas lower yields of **6** were obtained for the coupling of the corresponding triflate (entry 7). As the aryl bromides generally performed best, we elected to focus our subsequent efforts on their cross-coupling with acylsilane **3**.

Received: December 10, 2013
Published: January 9, 2014

Table 1. Initial Survey of the Reaction Scope[a]



entry	X–Ar	product	yield[b]
1		 **4**	9%
2		 **4**	79%
3		 **4**	79%
4		 **5**	85%
5		 **5**	83%
6		 **6**	70%
7		 **6**	50%

[a]Conditions: $Pd(PPh_3)_4$ (5 mol %), substrate (1 equiv), acylsilane **3** (2 equiv), CsF (4 equiv), trimethoxybenzene (0.1 equiv), 6 h. [b]Yield of product was determined by ^1H NMR analysis of crude reaction mixtures using trimethoxybenzene as an internal standard.

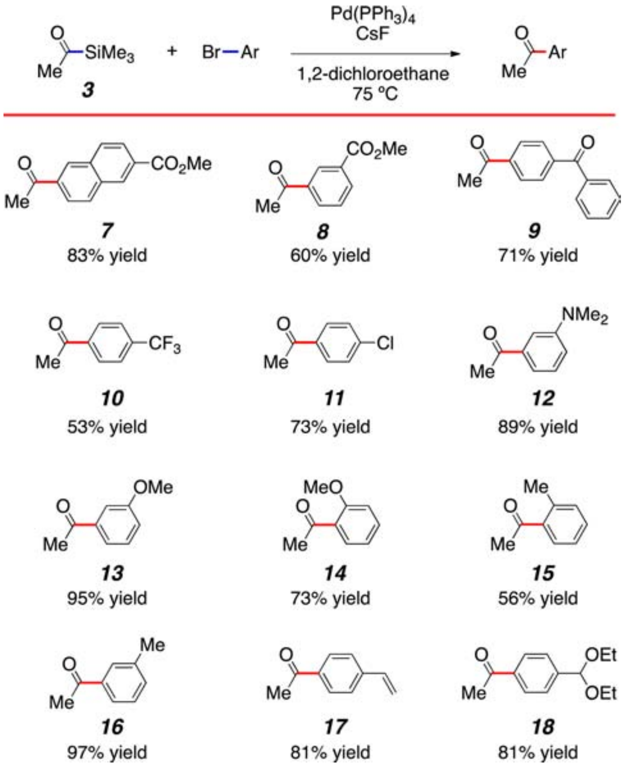


Figure 2. Scope of acetylation using aryl bromide coupling partners. Conditions: $Pd(PPh_3)_4$ (5 mol %), substrate (1 equiv), **3** (2 equiv), CsF (4 equiv), trimethoxybenzene (0.1 equiv), 6 h. The yield of the product was determined by ^1H NMR analysis of crude reaction mixtures using trimethoxybenzene as an internal standard. For **7**, $Pd(PPh_3)_4$ (10 mol %) was used.

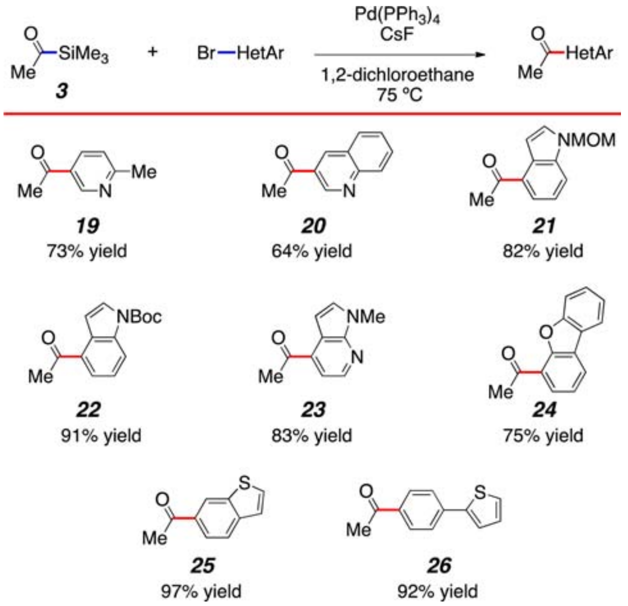


Figure 3. Scope of acetylation using hetaryl bromide coupling partners. Conditions: $Pd(PPh_3)_4$ (5 mol %), substrate (1 equiv), **3** (2 equiv), CsF (4 equiv), trimethoxybenzene (0.1 equiv), 6 h. The yield of the product was determined by ^1H NMR analysis of crude reaction mixtures using trimethoxybenzene as an internal standard. For **19**, **20**, and **24**, $Pd(PPh_3)_4$ (10 mol %) was used.

As shown in Figure 2, the methodology is tolerant of a variety of functional groups on bromoaromatic substrates. Electron-deficient substrates containing ester or ketone functional groups underwent the desired coupling to give ketone-containing products **7**–**9**. Additionally, trifluoromethyl and chloride bearing substrates were successfully employed, as demonstrated by the formation of coupled products **10** and **11**, respectively. We also examined substrates bearing amine and methoxy substituents and found that products **12**–**14** could be obtained without event. Although the formation of **14** demonstrates that *ortho* substituents are tolerated, we further validated this notion by coupling *o*-bromotoluene to give **15** in 56% yield. Additional products obtained include **16**–**18**, which show that the *m*-methyl group is tolerated, in addition to vinyl and acetal functional groups. It should be noted that several of the compounds obtained would likely be challenging to synthesize through standard Friedel–Crafts acylation chemistry (e.g., **9**, **10**, and **13**).[18]

We also examined a variety of heterocyclic substrates, which proved to be excellent cross-coupling partners (Figure 3). Pyridine[19] and quinoline substrates were tolerated, as judged by the formation of ketones **19** and **20**. Indoles and aza-derivatives could also be employed in this methodology to afford **21**–**23**. We also tested *O*- and *S*-containing heterocycles and found that products **24**–**26** were formed in good to excellent yields.

To further probe the scope and utility of the acetylation methodology, estrone derivatives **27** and **29** were independently subjected to the coupling conditions (Figure 4). We were delighted to find that the acetylation proceeded in both cases to furnish **28** in 58% and 90% isolated yields, respectively. The ability to access **28** demonstrates that the acetylation methodology may prove useful in complex settings and for the derivatization of biologically relevant compounds.

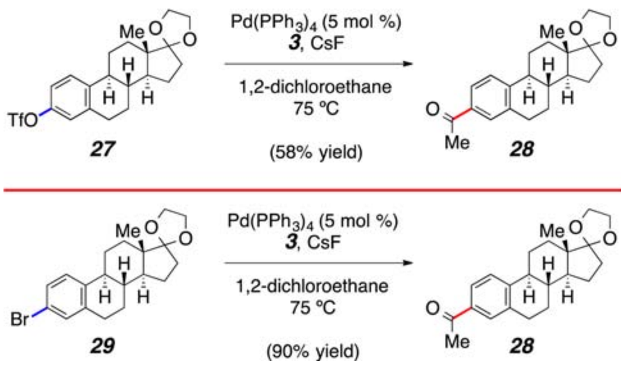


Figure 4. Acetylation of estrone derivatives **27** and **29**.

In summary, we have developed an efficient and simple method for the synthesis of aryl methyl ketones. The transformation relies on the Pd-catalyzed coupling of aryl bromides with the commercially available reagent acetyltrimethylsilane (**3**) to furnish the desired cross-coupled products in good or excellent yields. The methodology is tolerant of a variety of functional groups, in addition to *N*-, *O*-, and *S*-containing heterocycles. We expect this methodology will prove useful for arene functionalization in the complex settings encountered in natural product and drug synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Liana Hie (UCLA) for helpful discussions. The authors are grateful to Boehringer Ingelheim, DuPont, Eli Lilly, Amgen, AstraZeneca, Roche, Bristol-Myers Squibb, the Camille and Henry Dreyfus Foundation, the A. P. Sloan Foundation, the S. T. Li Foundation, and the University of California, Los Angeles for financial support. S.D.R. thanks the Foote Family and the UCLA Graduate Division's Dissertation Year Fellowship Program for support of his graduate studies. These studies were supported by shared instrumentation grants from the NSF (CHE-1048804) and the National Center for Research Resources (S10RR025631).

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(11) Acetyltrimethylsilane (**3**) is commerically available from Aldrich Chemical Co., Inc. (CAS #13411-48-8) at a current approximate cost of $1.65 USD/mmol.

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(16) Coupling was not observed when the corresponding aryl chloride or tosylate substrates were employed.

(17) Although not the focus of this study, it should be noted that the use of phenyltrimethylsilyl ketone as the acyl anion equivalent gave low yields of product.

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(19) Although chlorides were not tolerated when using non-heterocyclic substrates, it should be noted that exposure of 2-chloropyridine to our optimal reaction conditions delivered the corresponding methyl ketone product, albeit in a modest 23% yield.