

Reversed-Polarity Synthesis of Diaryl Ketones via Palladium-Catalyzed Cross-Coupling of Acylsilanes

Jason R. Schmink[†] and Shane W. Krska^{*,§}

[†]Penn/Merck Laboratory for High-Throughput Experimentation, Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States

[§]Department of Process Chemistry, Merck Research Laboratories, Rahway, New Jersey 07065, United States

 Supporting Information

ABSTRACT: Acylsilanes serve as acyl anion equivalents in a palladium-catalyzed cross-coupling reaction with aryl bromides to give unsymmetrical diaryl ketones. Water plays a unique and crucial activating role in these reactions. High-throughput experimentation techniques provided successful reaction conditions initially involving phosphites as ligands. Ultimately, 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxo-6-phosphaadamantane was identified as giving a longer-lived catalyst with higher turnover numbers. Its use, in conjunction with a palladacycle precatalyst, led to optimal reaction rates and yields. Scope and limitations of this novel method are presented along with initial mechanistic insight.

Palladium-catalyzed cross-coupling reactions possess tremendous versatility and functional group compatibility, and are one of the most powerful tools for C–C bond formation.¹ Accordingly, Pd catalysis has been used extensively in the formation of aryl aryl, alkyl aryl, and alkyl alkyl ketones. Numerous reports describe the formation of ketones by coupling activated carboxylic acid derivatives with various transmetalating reagents² (Figure 1A) or via carbonylative coupling of an aryl halide with an organometallic species³ (Figure 1B).

Although these approaches have been thoroughly examined, a third, polarity-reversed disconnection strategy has received limited attention. To date, only a handful of reports have described the cross-coupling of acyl anion equivalents with appropriate electrophiles to generate ketones (Figure 1C).

The majority of these protocols have involved the direct arylation of aldehydes or activated derivatives such as imines or hydrazones with aryl halides⁴ or organometallic species,⁵ or have utilized vinyl ethers or metalated analogues thereof which reveal the alkyl aryl ketone upon acidic hydrolysis of the reaction product.⁶ Taken together, these reports cover a limited synthetic scope with a patchwork of diverse reagents and conditions. If general conditions could be identified, this reversed-polarity approach would provide a useful alternative to the traditional methods, and would prove especially valuable for medicinal chemists for late-stage introduction of versatile ketone moieties into complex scaffolds for diversity-oriented synthetic strategies.

The use of organometallic acyl compounds potentially offers a general solution to the polarity-reversed synthesis of ketones, although their use in cross-coupling chemistry has been explored only to a limited degree. Reports have described the cross-coupling of acylstannanes,⁷ -silanes,⁸ and -zirconocenes⁹ with allylic halides and esters, affording β,γ -unsaturated ketones



Figure 1. Cross-coupling approaches to ketone synthesis.

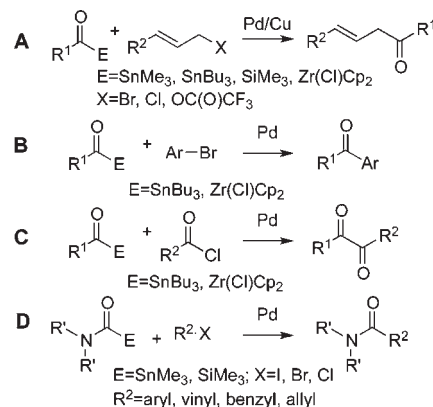


Figure 2. Examples of cross-coupling of acyl organometallics (Cp = η^5 -cyclopentadienyl anion).

(Figure 2A). Two of these reports also gave one example each of low-yielding cross-coupling of acylstannane or -zirconocene reagents with halobenzenes to give ketones (Figure 2B).^{7a,9a} Acyltin and -zirconocene reagents also couple with acyl chlorides, giving unsymmetrical α,α -diketones (Figure 2C).^{7a,9a,10} Finally, carbamoylsilanes¹¹ and -stannanes¹² under Pd catalysis effect the direct carbamoylation of aryl, vinyl, benzyl, and allyl halides to give the corresponding amides (Figure 2D).

Assessing the range of potential organometallic acyl anion equivalents, we decided to focus our attention on silicon. The use of silicon as competent metalloid in transition metal-catalyzed

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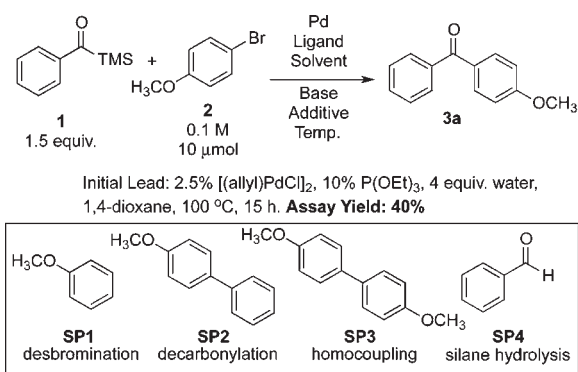


Figure 3. Initial HTE screening lead and reaction impurity profile.

cross-coupling has been widely demonstrated,¹³ and acylsilanes are stable, isolable compounds with a high functional group tolerance. Furthermore, acylsilanes do not have the toxicity problems associated with tin and are more accessible and easily handled than the corresponding acylzirconocenes.¹⁴ Indeed, there has been a recent renaissance in the use of acylsilanes as acyl anion equivalents in addition reactions to active electrophiles such as aldehydes,¹⁵ ketones,¹⁶ Michael acceptors,¹⁷ imines,^{17d,18} and nitrones¹⁹ catalyzed by Lewis bases such as fluoride, cyanide, N-heterocyclic carbenes (NHCs), or metallophosphites. Herein we report the successful development of a Pd-catalyzed cross-coupling between arylacylsilanes and aryl bromides to afford the corresponding unsymmetrical diaryl ketones.²⁰

To begin our investigations, we utilized a high-throughput experimentation (HTE)²¹ platform to assess a wide range of conditions (Figure 3). The initial screen sought to cross-couple 4-bromoanisole **1** with phenyl trimethylsilyl ketone **2**. In general, the reaction performed best in ethereal solvents (THF, 2-MeTHF, 1,4-dioxane); [(allyl)PdCl]₂ was found to be the best Pd source, and both K₃PO₄ and Cs₂CO₃ were found to be capable bases, although all others screened show little or no desired reactivity. With respect to ligand, though a few bulky, electron-rich phosphine ligands showed some desired reactivity,²² all gave significant amounts of the desbromination of **1** (Figure 3, SP1). Phosphites such as triethylphosphite gave the highest levels of desired product.²³ Although reactions with phosphite ligand tended not to form desbromination byproduct SP1, other byproducts were observed, including decarbonylated biphenyl SP2, symmetric biphenyl SP3, and benzaldehyde SP4 arising from the hydrolysis of acylsilane. Surprisingly, the most crucial component for the success of the reaction was found to be water. Of all other potential activators screened—including alcohols, tertiary amines, pyridines, NHCs, and numerous fluoride sources—*none* showed any desired product formation. Currently, the desired reaction only proceeds in the presence of water.^{13c} Intrigued, we sought to probe this reaction in more detail to gain some insight into its dynamics.

Kinetic studies showed that the reaction exhibited a significant induction period when using 2.5% [(allyl)PdCl]₂ and 10% P(OEt)₃, i.e., 1:2 Pd:L stoichiometry.²² However, upon moving to a 1:1 Pd:L ratio the reaction initiated immediately, suggesting that the active catalyst might be an L₁Pd complex.²⁴ In both cases the desired reaction stalled after about 3 h at ~40% yield. These observations suggested the phosphite ligand was undergoing hydrolysis under the reaction conditions, thus truncating the useful catalyst lifetime and hampering desired product yield. Hoping to attenuate the rate of ligand hydrolysis, we screened a

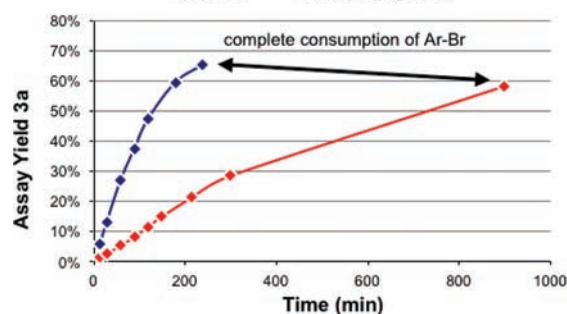
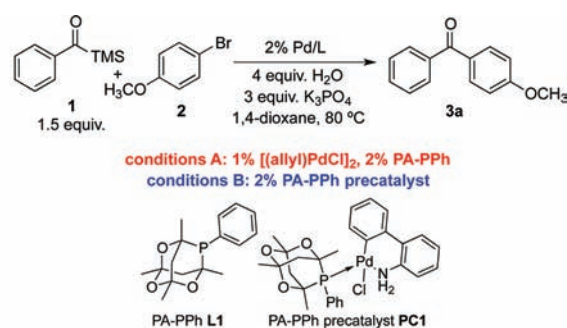


Figure 4. Comparison of reactivity using conditions A (red) vs B (blue).

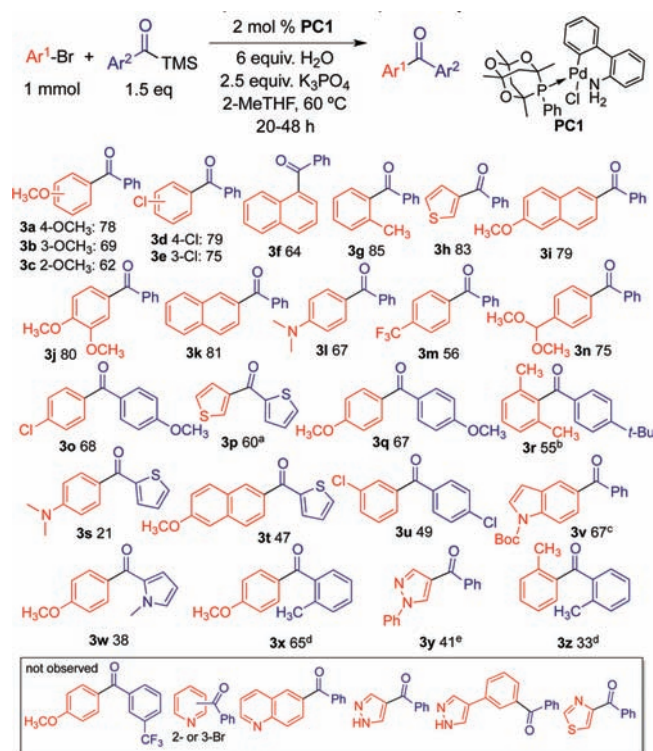
range of phosphite analogues.²⁵ Only P(Oi-Pr)₃ showed modest overall improvement (assay yield of 52%), and still with significant side-product formation. Similarly, all attempts to dose additional ligand or additional Pd/ligand complex over time proved unproductive, and impeded rather than augmented product formation.

Confronted with the conflicting roles of water in enabling the desired catalytic cycle though ultimately deactivating the catalyst, we returned to the screening platform in search of a ligand that was tolerant of water, yet mimicked the activity of the phosphite ligands. Gratifyingly, this second screen of 72 phosphine ligands returned the bulky 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxo-6-phosphaadamantane ligand (PA-PPh; Figure 4, L1)²⁶ that performed nearly on par (38% yield by assay at 100 °C) with the phosphite ligands. Additionally, this new system showed desired reactivity at lower temperatures (80 °C, 57% yield by assay), raising the prospect that side product formation could be attenuated at lower temperatures while maintaining reasonable reaction times.

Recently, the design²⁷ of aminobiphenyl palladacycle compounds and their subsequent exploitation as a platform to generate active Pd(0)–ligand complexes under mild conditions²⁸ has shown some promise in terms of increased reactivity at lower temperatures, prompting us to explore their use in this system. Here too, substituting the aminobiphenyl palladacycle precatalyst PC1 in place of the in situ combination of [(allyl)PdCl]₂ and free ligand L1 led to a significant increase in catalytic activity at 80 °C (Figure 4).²⁹ This increased reactivity ultimately allowed the reaction temperature to be lowered to 60 °C and provided a cleaner reaction profile. Final optimization led to a general set of conditions: 2% of PC1, 6 equiv of H₂O, 2.5 equiv of K₃PO₄, and 1.5 equiv of the acylsilane in 2-MeTHF for 18–20 h at 60 °C. Using these conditions, product **3a** was isolated in 78% yield after column chromatography.

These optimized reaction conditions were applied to various aryl bromides and arylacylsilanes, providing moderate to good yields for the synthesis of a range of unsymmetrical benzophenones (Table 1). Aryl chlorides were tolerated (**3d**, **3e**), as were heterocycles (**3h**, **3p**, **3s**, **3t**, **3v**, **3w**, **3y**). As the system became more sterically demanding in the series 1-bromonaphthalene (**3f**), 2-bromoanisole (**3c**),

Table 1. Substrate Scope with Isolated Product Yields



^a Isolated as inseparable 92:8 mixture with hydrolyzed acylsilane (aldehyde). ^b Reaction time = 3 d, isolated as inseparable 95:5 mixture with the dimerized acylsilane (1,2-diketone). ^c Reaction time = 2 d, 80 °C. ^d Reaction temp = 67 °C. ^e Reaction temp = 67 °C; time = 91 h.

2-bromotoluene (**3g**), and 2,6-dimethylbromobenzene (**3r**), reaction times had to be extended to fully consume the aryl bromide (e.g., **3r**, 3 days), though eventually each was isolated in modest to good yield.

Although electron-withdrawing groups were tolerated as part of the aryl bromide (**3m**), the attempted coupling between 3-(trifluoromethyl)phenyl trimethylsilyl ketone and 4-bromoanisole provided none of the desired benzophenone, presumably due to the attenuated nucleophilicity and decreased hydrolytic stability of the former. Similarly, substrates with strongly Lewis basic sites inhibited the reaction, and heterocycles with acidic sites (e.g., pyrazoles) rapidly decomposed the acylsilanes. However, protection of the nitrogen allowed these substrates to engage in the desired coupling (**3v**, **3w**, **3y**). Our initial attempts to cross-couple alkanoylsilanes have been met with some success and will be reported in due course.²²

Preliminary mechanistic studies indicate these reactions exhibit overall first-order kinetics across a range of electronically diverse aryl bromides. The results of a small Hammett study (Figure 5) suggest the buildup of positive charge during the rate-determining step ($\rho = -0.53$).³⁰ Though exhaustive mechanistic studies are yet to be completed, our initial qualitative and quantitative observations allow us to propose a putative reaction mechanism for this transformation (Figure 6).

We speculate that traditional oxidative insertion of mono-ligated Pd(0) complex **I** into bromoanisole **2** leads to Pd(II) aryl bromide complex **II**. Because it is widely believed that electron-withdrawing groups facilitate the oxidative insertion step in Pd-catalyzed cross-coupling reactions, and given the results of the Hammett study, we believe oxidative insertion is unlikely to be

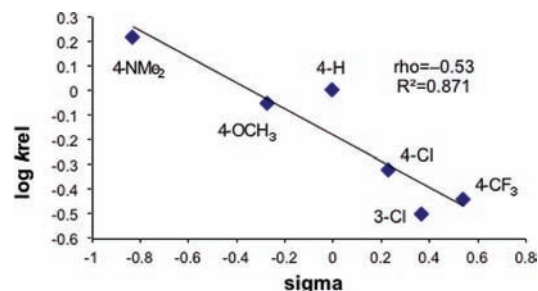


Figure 5. Hammett plot with negative slope (ρ) indicating positive charge buildup on rate-determining step.

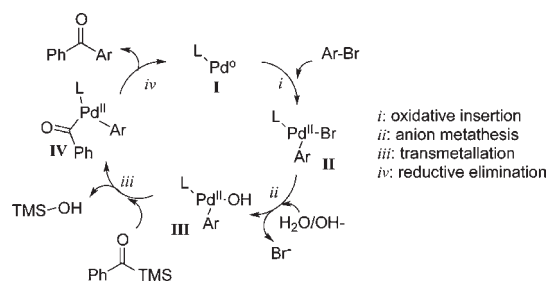


Figure 6. Putative mechanism.

the rate-determining step.³¹ Next, on the basis of our observations of the crucial role of water as an activator and because fluoride ion provided *no desired product*, we propose anion metathesis and formation of the palladium hydroxo intermediate **III** in our putative mechanism. It should be noted that recent work by both Jutand and Hartwig as well as early work by Miyaura³² similarly suggests an intermediate palladium hydroxo complex that then undergoes transmetalation in the Suzuki–Miyaura reaction under certain conditions. After transmetalation to **IV**, reductive elimination yields the title benzophenone and regenerates the PdL₁ catalyst **I**. It is reasonable to speculate that the buildup of positive charge indicated by the Hammett study could manifest itself in the transition states of any one of the remaining three steps, i.e., *ii*, *iii*, or *iv*. As such, at this time no reasonable speculation can be made as to which subsequent step after oxidative insertion is the rate-determining step.³³

In conclusion, we have disclosed an effective new strategy for the polarity-reversed synthesis of diaryl ketones via a Pd-catalyzed cross-coupling between aryl halides and arylacylsilanes. Use of HTE techniques and in-depth investigations revealed the crucial role water played in enabling this reaction and identified the bulky phosphadmantyl ligand–palladacycle precatalyst **PC1** combination which gave enhanced reactivity and yield. Continued mechanistic studies and methodology extension are underway and will be reported in due course.

■ ASSOCIATED CONTENT

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

■ AUTHOR INFORMATION

Corresponding Author

shane_krska@merck.com

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