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Palladium-Catalyzed Mono-α-arylation of Acetone at Room Temperature

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Abstract: The first examples of acetone mono-α-arylation at room temperature are described, enabled by use of a $[Pd(cinnamyl)Cl]_2$/JosiPhos catalyst system. (Hetero)aryl chloride, bromide, and iodide electrophiles featuring or lacking *ortho*-substitution, and comprising a range of functionalities (e.g., alkoxy, cyano, fluoro, trifluoromethyl, or alkenyl) and heteroaryl motifs (e.g., pyrrole, pyridine, isoquinoline, quinoline, quinaldine, (benzo)thiophene, benzothiazole, or benzodioxole) were successfully accommodated. Proof-of-principle experiments confirm that other (hetero)aryl methyl ketones can also be employed in such room temperature mono-α-arylations. The established substrate scope is the most extensive reported to date for acetone mono-α-arylation under any conditions, and more generally represents the first room temperature ketone mono-α-arylations employing a structurally diverse set of (hetero)aryl chlorides.

The development of palladium-catalyzed C–C cross-coupling reactions has transformed the way in which chemists approach organic synthesis on benchtop and industrial scales.[1] Following the Nobel Prize-winning contributions by Heck,[2] Negishi,[3] and Suzuki,[4] a range of alternative C–C bond-forming protocols have been developed.[5] Among these, the mono-α-arylation of carbonyl (and related) compounds has emerged as an effective Csp^2–Csp^3 bond-forming methodology that does not require pre-formation of an organometallic reaction partner.[6] The synthetic potential of such protocols is underscored by the prevalence of the α-aryl carbonyl moiety in key synthetic intermediates as well as target molecules of biological and medicinal interest.[7]

Prior to the development of modern palladium-catalyzed methods, the α-arylation of carbonyl compounds typically required the use of activated aryl halides in combination with pre-formed enolate nucleophiles, resulting in low substrate scope, poor functional group tolerance given the harsh reaction conditions employed, and the required use of air-sensitive and/or toxic reagents. However, recent advances in catalyst development, including optimization of the base, palladium source, and ancillary ligand design,[8] has enabled a range of reaction partners to be accommodated in the palladium-catalyzed mono-α-arylation of carbonyl compounds.[6a–d,9] Noteworthy reports on related copper- and nickel-catalyzed[10,11] transformations have also appeared recently.

Notwithstanding such progress, a number of important challenges remain. The development of catalysts that exhibit high levels of selectivity with sterically unbiased (hetero)aryl electrophile/carbonyl compound pairings has proven to be difficult. This is due in part to the fact that the initially formed mono-α-arylation product features α-CH protons that are more acidic than those in the starting carbonyl compound, resulting in more facile enolate formation and uncontrolled polyarylation. These and other factors make the use of acetone, the most structurally simple ketone, a formidable challenge for most catalyst systems,[12] despite the fact that the palladium-catalyzed mono-α-arylation of alternative methyl carbonyl compounds was established during the initial development of the field nearly twenty years ago.[13]

The selective mono-α-arylation of acetone was first reported by our group in 2011,[14] employing a $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos[15] catalyst system (X = Cl, Br, I, tosylate, mesylate); a selection of other palladium catalysts featuring either closely related *ortho*-phenylene P,N-ligands (X = Cl, Br),[16] or XantPhos (X = imidazolylsulfonate),[17] have subsequently proven capable of promoting such transformations (Figure 1). Very recently we demonstrated that the mono-α-arylation of acetone using the $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos catalyst system can be incorpo-

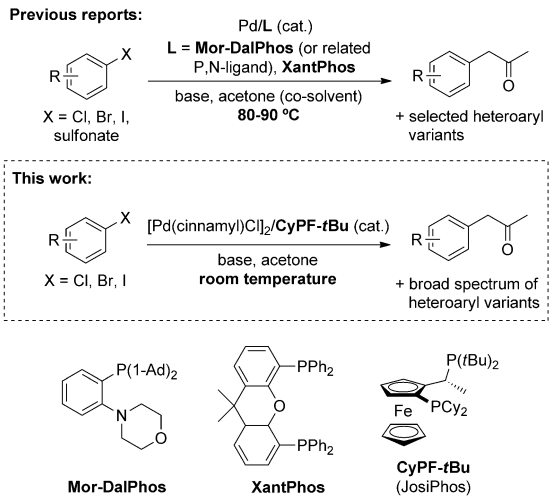

Figure 1. Palladium-catalyzed mono-α-arylation of acetone.

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rated into the one-pot, multicomponent synthesis of 2-methylindoles, a core structure found within Indomethacin (non-steroidal anti-inflammatory), Oxypertine (antipsychotic), and Panobinostat (anti-cancer).[18] The carbonylative mono-α-arylation of acetone has also been achieved.[19]

Whereas the use of acetone as both the ketone reactant and solvent is attractive in the synthesis of 1-(hetero)aryl-propan-2-one derivatives, each of the catalyst systems reported thus far for acetone mono-α-arylation employ reaction temperatures (≥80 °C, in some cases using a co-solvent) that exceed the boiling point of acetone (56 °C). As such, the identification of alternative catalysts that are capable of promoting such transformations at room temperature would represent an important advance. Indeed, it is worthy of mention that while progress has been made with regard to the development of myriad palladium-catalyzed room temperature transformations using relatively inexpensive and abundant (hetero)aryl chloride reaction partners,[15,20] related examples of room temperature ketone mono-α-arylation chemistry are limited to four table entries involving (IPr)Pd-catalyzed transformations of propriophenone (41–75%).[21] Herein, we report the first examples of acetone mono-α-arylation chemistry conducted at room temperature, which is achieved through use of a palladium catalyst system featuring the JosiPhos[22] ligand variant CyPF-*t*Bu depicted in Figure 1.

Our initial efforts to identify a catalyst system for the palladium-catalyzed mono-α-arylation of acetone at room temperature focused on the use of [Pd(cinnamyl)Cl]$_2$/Mor-DalPhos under conditions similar to those that we employed with success at 90 °C,[14a] with the exception of using higher catalyst loadings and a longer reaction time (Figure 2). Poor results were obtained in the test reaction with 4-biphenyl bromide, affording **1** in 12% isolated yield. Similarly poor results were obtained when using BrettPhos (16%), a ligand developed by the Buchwald group that has proven to be effective in other classes of challenging monoarylation reactions conducted at room temperature.[23] Reports from the Hartwig group have established the utility of the Solvias CyPF-*t*Bu JosiPhos ligand variant in otherwise difficult palladium-catalyzed ammonia monoarylation reactions conducted at elevated temperatures,[24] as well as in room temperature C–S cross-couplings.[20f] Given the similar conceptual challenges presented by acetone mono-α-arylation chemistry, we sought to evaluate the utility of [Pd(cinnamyl)Cl]$_2$/CyPF-*t*Bu mixtures in room-temperature reactions of acetone. We were pleased to observe that the use of this catalyst system enabled the formation of **1** in 57% isolated yield under the conditions outlined in Figure 2. Extending the reaction time from 24 to 48 h while employing 7.5 mol% Pd (both unoptimized parameters) allowed for the isolation of **1** in 87% yield from 4-biphenyl bromide. Notably, the use of alternative bases under analogous conditions resulted in negligible consumption of 4-biphenyl bromide (K_2CO_3), incomplete consumption (<50%) of 4-biphenyl bromide and conversion to **1** (K_3PO_4), or complete consumption of 4-biphenyl bromide with formation of multiple unidentified products and negligible conversion to **1** (NaO*t*Bu or NaN(SiMe$_3$)$_2$).

Having identified the [Pd(cinnamyl)Cl]$_2$/CyPF-*t*Bu catalyst system as being effective for the room temperature mono-α-arylation of acetone with 4-biphenyl bromide (7.5 mol% Pd), we turned our attention to exploring the scope of reactivity with substituted aryl chlorides, bromides, and iodides (Figure 3). Employing 4-biphenyl chloride as a coupling partner under analogous conditions afforded **1** in 88% isolated yield. A selection of *para*-substituted 4-chlorobiphenyl derivatives featuring methyl, trifluoromethyl, methoxy, or cyano substituents was also accommodated under these conditions (**2**–**5**, 50–69%), although increased catalyst loadings proved beneficial (10 mol% Pd; **3**–**5**, 71–86%). A series of *ortho*-, *meta*-, and *para*-substituted halogenated anisoles proved to be effective substrates (**6**–**8**, 64–83%), as did 4-chloro-3-methylanisole (**9**, 78%) and 2-bromobiphenyl (**10**, 70%). Halogenated xylene (**11**, 60%; **12**, 80%), fluorobenzene (**13**, 62%), styrene (**14**, 64%), and napthyl (**15**, 57%; **16**, 77%) derivatives were also accommodated.

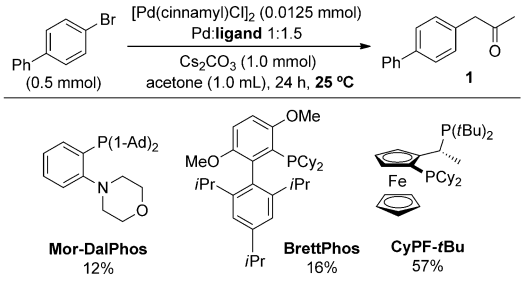

Figure 2. Ligand screen for the palladium-catalyzed mono-α-arylation of acetone at room temperature (yields of isolated **1** reported).

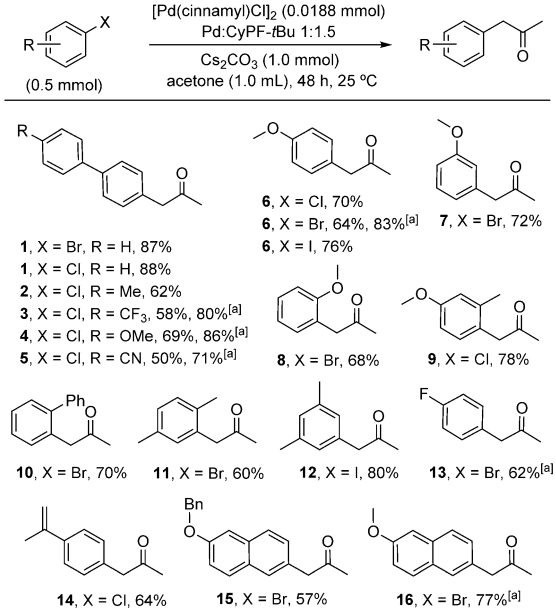

Figure 3. Scope of palladium-catalyzed mono-α-arylation of acetone employing substituted aryl halides (yields of isolated products reported). [a] Using 0.025 mmol [Pd(cinnamyl)Cl]$_2$.

Given the ubiquity of heterocyclic motifs in medicinal, biological, and natural products chemistry, we sought to evaluate the compatibility of electrophilic coupling partners featuring such functionality in the mono-α-arylation of acetone at room temperature using the [Pd(cinnamyl)Cl]$_2$/CyPF-*t*Bu catalyst system (Figure 4). It is worthy of mention that while selected

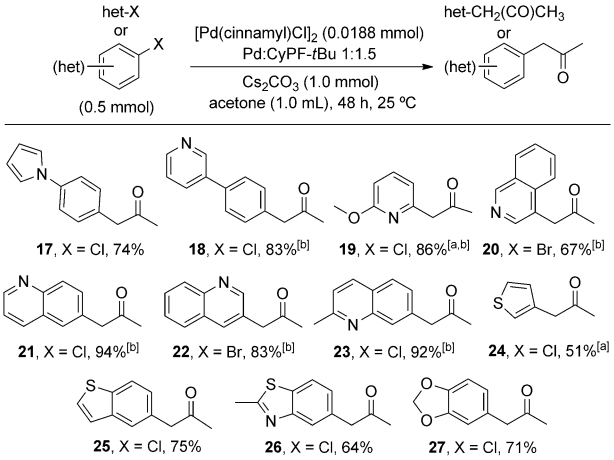

Figure 4. Scope of palladium-catalyzed mono-α-arylation of acetone employing aryl halides featuring heterocyclic functionality (yields of isolated products reported). [a] Using 0.025 mmol [Pd(cinnamyl)Cl]$_2$. [b] Isolated as the hydrochloride salt.

transformations of heterocycle-containing substrates have been featured in past reports on palladium-catalyzed acetone mono-α-arylation conducted at elevated temperature,[14,16–18] such coupling partners have for the most part been overlooked in this chemistry. In this context we were pleased to observe that substituted pyrrole (**17**), pyridine (**18**, **19**), isoquinoline (**20**), quinoline (**21**, **22**), quinaldine (**23**), (benzo)thiophene (**24**, **25**), benzothiazole (**26**), and benzodioxole (**27**) coupling partners functioned well in our newly developed room temperature acetone mono-α-arylation chemistry (Figure 4, 51–94%).

Though the room-temperature mono-α-arylation chemistry that we describe above was conducted exclusively using acetone as the nucleophilic reaction partner, proof-of-principle experiments confirmed that other (hetero)aryl methyl ketone substrates can also be employed (Figure 5). In test cross-couplings with acetophenone, heteroaryl chlorides featuring benzothiophene (**28**, 67%), benzothiazole (**29**, 95%), and quinoline (**30**, 88%) core structures each proved to be suitable substrates. The incorporation of heterocyclic functionality into both of the reaction partners also proved to be feasible, as evidenced by the successful room temperature cross-coupling of 5-chloro-benzo[*b*]thiophene with each of 2-acetylthiophene and 2-acetylfuran to afford **31** (82%) and **32** (53%), respectively.

In conclusion, we have identified a [Pd(cinnamyl)Cl]$_2$/JosiPhos catalyst system that has enabled the first example of acetone mono-α-arylation chemistry conducted at room temperature. The established substrate scope encompasses (hetero)aryl

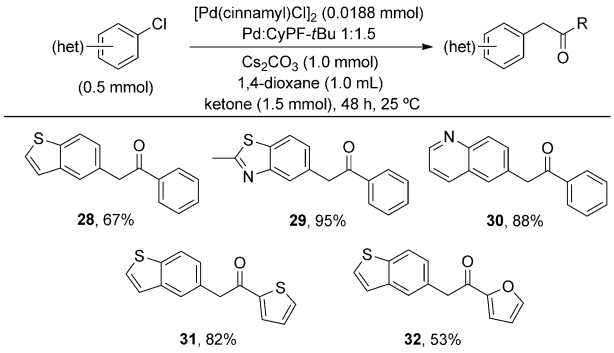

Figure 5. Palladium-catalyzed mono-α-arylations of alternative (hetero)aryl methyl ketone substrates (yields of isolated products reported).

chlorides, bromides, and iodides featuring or lacking *ortho*-substitution, and comprising a range of substituents (e.g., alkoxy, cyano, fluoro, trifluoromethyl, alkenyl) and heterocyclic structures (e.g., pyrrole, pyridine, isoquinoline, quinoline, quinaldine, (benzo)thiophene, benzothiazole, benzodioxole). Preliminary experimentation confirmed that other (hetero)aryl methyl ketones can also be accommodated in such room temperature mono-α-arylation chemistry. The established substrate scope is notable in that it is the most extensive reported to date for the mono-α-arylation of acetone under any reaction conditions, and represents the first room temperature ketone mono-α-arylations employing a structurally diverse set of (hetero)aryl chlorides. Future research efforts will be directed toward developing increasingly effective catalysts for room temperature mono-α-arylation chemistry, as well as in the application of such transformations in the construction of useful target molecules.

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Keywords: arylation · cross-coupling · Josiphos · palladium · room temperature

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