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Catalytic Direct β-Arylation of Simple Ketones with Aryl Iodides

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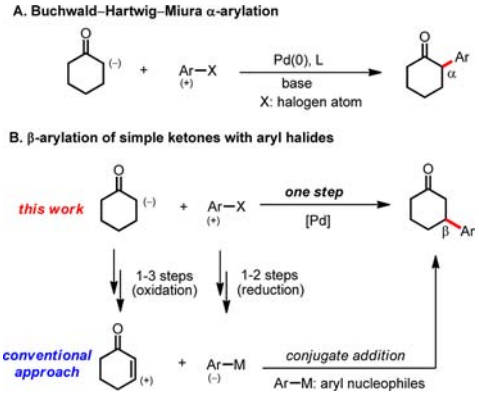
Supporting Information

ABSTRACT: Herein we report a direct β-arylation of simple ketones with widely available aryl iodides, combining palladium-catalyzed ketone oxidation, aryl-halide activation, and conjugate addition through a single catalytic cycle. Simple cyclic ketones with different ring-sizes, as well as acyclic ketones, can be directly arylated at the β-position with complete site-selectivity and excellent functional group tolerance.

Functionalization and transformation of carbonyl compounds are essential to organic synthesis. While the α-position of the carbonyl group can be readily functionalized through enolate chemistry, the corresponding β-C−H bonds are typically not reactive. As an important class of carbonyl compound-functionalization, arylation has been achieved at the α-position through Pd-catalyzed couplings of carbonyl compounds and aryl halides[1] (Scheme 1A, pioneered by Buchwald, Hartwig, and Miura), preparing structural motifs frequently found in pharmaceutical, material and agrochemical products.[2] The practicality and wide applicability of the α-arylation reactions are likely attributed to the use of readily available starting materials (simple carbonyl compounds, aryl halides), the efficient and tunable Pd catalysts, the scalable reaction conditions and high functional group tolerance. However, the corresponding β-arylation, while equally important, has remained largely underdeveloped.

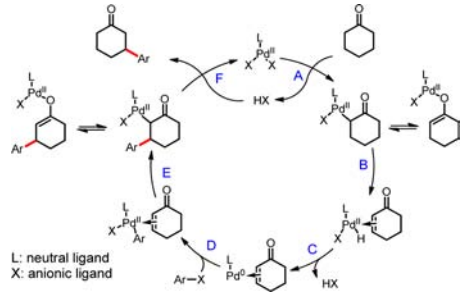
Scheme 1. α- and β-Arylation of Ketones



Conventionally, β-aryl-substituted carbonyl compounds are synthesized through conjugate addition of aryl (often metal-based) nucleophiles to α,β-unsaturated compounds (Scheme 1B);[3] however, both reactants require additional steps and redox processes to prepare. For example, conjugated enones are usually prepared in 1−3 steps from the corresponding saturated ketones via direct or indirect dehydrogenation (an oxidation process),[4] and most aryl nucleophiles (e.g., organocuprate or boron reagents) ultimately come from the corresponding aryl halides through metalation (a reduction process).[5] To circumvent this drawback, elegant directing group (DG)-based strategies were developed enabling the direct β-arylation, albeit limited to linear amide substrates;[6] β-arylation of linear esters has also been developed.[7] Recently, MacMillan and co-workers reported a photoredox-based β-arylation of aldehydes and ketones, using electron-deficient arylnitriles as the coupling partner.[8] A general solution to the β-arylation problem possessing the broadly applicable feature of Buchwald−Hartwig−Miura α-arylation, which includes direct use of readily accessible substrates, high functional group compatibility and scalability, would be transformative but remains to be discovered. Herein, we disclose a catalytic coupling between simple ketones and widely available aryl halides, a process that is formally similar to the Buchwald-Hartwig−Miura α-arylation, but exhibits complete site-selectivity at the β-position of ketones.

Our strategy aims to couple ketone dehydrogenation, aryl-halide activation, and conjugate addition by taking advantage of different reactive modes of Pd-complexes (Scheme 2). Pd-mediated ketone dehydrogenation is known to provide a straightforward route to activate the C−H bond β to the carbonyl,[9−12] which follows a sequence of Pd(II)-enolate formation, β-H elimination and reductive elimination of an acid (HX) to give an enone and a Pd(0) species (Steps A−C, Scheme 2). For example, an efficient catalytic process was recently reported by Stahl and Diao, employing oxygen gas to oxidize the Pd(0) intermediate to generate active Pd(II)

Scheme 2. Proposed Strategy[a]



[a]A "two catalytic cycle" mechanism involving Pd-catalyzed ketone dehydrogenation and reductive Heck cannot be excluded.

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catalyst.[12f] We hypothesized that aromatic halides could serve as the stoichiometric oxidant to promote ketone oxidation to conjugated enones as the oxidative addition of Pd(0) into aryl-halide bonds to give Pd(II) is a well-established process (Step D).[5] We also hypothesized that the resulting aryl-Pd(II) species would undergo migratory insertion into the conjugated enone olefin to provide a Pd(II)-enolate[3b,13] (Step E), which upon protonation by HX would give the β-arylated product and regenerate the Pd(II) catalyst (Step F). A key feature of this proposed strategy is that ketone oxidation and conjugate addition are incorporated into a single catalytic cycle by using aryl halides as both the oxidant and aryl source. Comparing to the conventional 1,4-addition approach (Scheme 1B), this strategy would significantly streamline the synthesis by reducing the number of steps and minimizing the oxidation/reduction operations.[14−16]

The success of this strategy relies on addressing the following key challenges: First, an electrophilic Pd complex is generally required for ketone oxidation[12i] (Steps A and B) while oxidative addition into carbon−halide bonds (Step D) prefers electron-rich catalysts.[5] Thus, developing a catalyst system that is able to accommodate both needs during the catalytic cycle is nontrivial. Second, dimerization of aryl halides[17] and overoxidations to phenols and/or to β-aryl enones,[18] which are known side reactions, must be inhibited. Third, given that the Pd-mediated dehydrogenation works most efficiently with carboxylate ligands,[10,12i] a suitable promoter must be found to extract halides from the Pd and deliver carboxylate anions to restore the active catalyst.

To examine the feasibility of the proposed strategy, cyclohexanone (**1a**) and iodobenzene (**2a**) were used as the model substrates. A variety of Pd precatalysts, ligands, solvents and additives were examined (Table S1). Ultimately, we discovered that use of palladium trifluoroacetate/P(*i*-Pr)$_3$ as the precatalyst/ligand and silver trifluoroacetate as the promoter in 1,4-dioxane/hexafluoroisopropanol (HFIP) as mixed-solvents afforded the desired β-arylation product (3-phenyl-cyclohexanone, **3a**) in a 76% yield, along with 10% of biphenyl formed through the dimerization of PhI (eq 1). Interestingly, neither overoxidation to 3-phenyl-cyclohexenone nor the α-arylation product was observed.[19] Note that the combination of electron-rich phosphine-Pd complexes and aryl halides has been extensively employed in the ketone α-arylation reactions;[2] however, while a similar combination is employed here, this reaction proceeded with complete site-selectivity for the β-position. This can likely be explained that the Buchwald−Hartwig−Miura arylation typically uses stoichiometric bases to generate the corresponding enolates, but our reaction operates under acidic conditions, which triggered a different activation mode (Scheme 2).

A set of control experiments were consequently conducted (Table 1). In the absence of Pd, no product was obtained, suggesting the pivotal position of Pd in the catalytic cycle (entry 1). Electron-rich ligands were uncommon for the Pd-catalyzed dehydrogenation reactions.[12d,20,21] However, for this β-arylation reaction, electron-rich phosphines play an important role in inhibiting the aryl dimerization and promoting formation of the desired product, though the exact reason is unclear (entries 2−8). In the absence of P(*i*-Pr)$_3$ or use of triisopropyl phosphine oxide, biphenyl was observed as the major product with only a trace amount of the β-arylated ketone formed (entries 2 and 8). Other electron-rich phosphines, such as PMe_3 and PCy_3, also proved to be efficient (entries 3 and 4). In contrast, use of less electron-rich PPh_3 or sterically hindered P(*t*-Bu)$_3$ led to

Table 1. Selected Optimization of Reaction Conditions[a]

entry	variations from the 'standard' conditions	yield of **3a** (%)[b]	yield of Ph-Ph (%)[b]
1	w/o $Pd(TFA)_2$	0	0
2	w/o P(*i*-Pr)$_3$	4	56
3	PMe_3 instead of P(*i*-Pr)$_3$	56	9
4	PCy_3 instead of P(*i*-Pr)$_3$	51	8
5	PPh_3 instead of P(*i*-Pr)$_3$	30	25
6	P(*t*-Bu)$_3$ instead of P(*i*-Pr)$_3$	4	48
7	BINAP instead of P(*i*-Pr)$_3$	2	16
8	(*i*-Pr)$_3$P=0 instead of P(*i*-Pr)$_3$	3	47
9	w/o AgTFA	0	0
10	AgOAc instead of AgTFA	56	20
11	$Pd(OAc)_2$/AgOAc instead of $Pd(TFA)_2$/AgTFA	51	11
12	NaO*t*-Bu instead of AgTFA[c]	0	0
13	1,4-dioxane only, no HFIP	66	21
14	*t*-BuOH instead of HFIP	65	15
15	TFA instead of HFIP	23	7
16	toluene instead of 1,4-dioxane	19	6
17	Ph-I:cyclohexanone = 1:1	67	17

[a]Reaction conditions: all the reactions were run on a 0.2 mmol scale with 1.0 mL solvents in 12 h. [b]GC yield determined using dodecane as the internal standard. [c]HFIP was not added.

formation of a considerable amount of biphenyl (entries 5 and 6). Bidentate phosphine ligands (entry 7) and nitrogen-based ligands were found much less effective (Table S1). Silver salts were utilized to facilitate iodide-carboxylate exchange,[22] which is expected to be crucial for regenerating the active Pd(II) catalyst (entry 9). Replacing the trifluoroacetate counterion of the silver salts with acetate resulted in decreased yields (entries 10 and 11). Interestingly, substitution of the Ag salt with strong bases, such as NaO*t*Bu, gave a complex reaction mixture without forming any β-or α-arylation product (entry 12). Solvent effects were also surveyed (entries 13−16): while 1,4-dioxane is most suitable for this transformation, addition of mildly acidic HFIP (pK_a 9.3 in H_2O) is beneficial likely because it accelerates the protonation of Pd-enolates to regenerate the Pd(II) catalysts (Step F, Scheme 2), which in turn should diminish side reactions, e.g., overoxidations. On the other hand, HFIP is not acidic enough to protonate phosphine ligands, whereas using stronger acids, such as trifluoroacetic acid (TFA), as a cosolvent was found detrimental. Finally, when **1a** and PhI were added in an equimolar ratio, the desired 3-phenyl-cyclohexanone was still provided in 67% yield (entry 17).

With the optimized conditions in hand, the substrate scope was then investigated (Table 2). Aryl iodides containing arenes with different electronic properties (electron-rich and -poor) all participated to give the corresponding β-arylated ketones (**3a**−**3m**).[23] In addition, substitutions on the aryl group at the ortho, meta, or para positions are all tolerated. Furthermore, a broad range of functional groups, including aryl ethers, cyanides, aryl chlorides, fluorides, naphthalene, protected indoles, carboxylic esters, nitro group, and sulfonamides, are compatible under the reaction conditions. These features indicate that this Pd-catalyzed direct β-arylation exhibits comparable reactivity and scope as the aryl-conjugate additions but using fewer steps.

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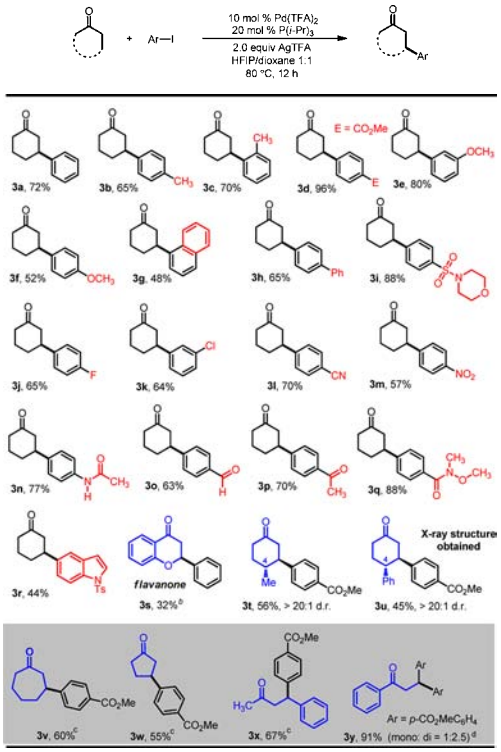
Table 2. Substrate Scope[a]



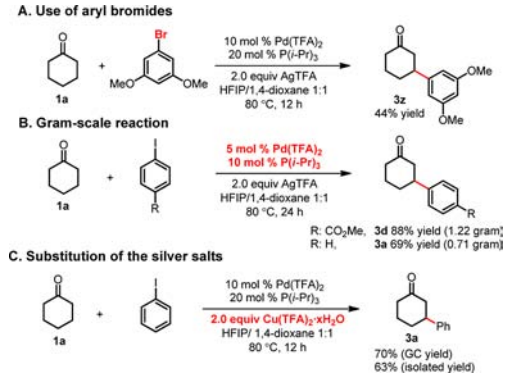
[a]Reaction conditions: aryl iodide (0.4 mmol), ketone (1.0 mmol), $Pd(TFA)_2$ (0.04 mmol), $P(i\text{-}Pr)_3$ (0.08 mmol), AgTFA (0.8 mmol), HFIP (1 mL), dioxane (1 mL), 80 °C, 12 h. [b]1.0 equiv of the ketone and 2.5 equiv of iodobenzene were used. [c]5.0 equiv of the ketone was used. [d]10.0 equiv of the ketone was used.

Perhaps, it is more encouraging to note that products that are more difficult to prepare via conventional 1,4-additions, such as arenes that contain base- or nucleophile-sensitive groups (e.g., amide protons **3n**, ketones with enolizable hydrogens **3p**, aldehydes **3o**, Weinreb amide **3q**), can also be accessed using this method. The high chemoselectivity is likely due to the mild reaction conditions (base-free) as well as the absence of stoichiometric aryl-metal nucleophiles.

The scope of the ketone component was also examined. The β-arylation of ketones bearing a stereocenter at the C4 position proceeded with excellent diastereoselectivity (>20:1) giving the trans products (**3t**, **3u**). Besides the 6-membered ring ketones, cyclopentanone and cycloheptanone also provided the desired β-arylation products (**3v**, **3w**). Acyclic ketones also proved to be suitable substrates (**3x**, **3y**). Given the broad substrate scope, this approach is clearly complementary to the previous DG-based[6] and photoredox[8] β-arylation methods. Interestingly, when propiophenone was employed, a mixture of mono- and diarylated products was isolated in 91% yield with a 1:2.5 ratio. The tendency of propiophenone to give diarylation products is likely due to its flexible conformation permitting free bond rotation, which in turn, results in a second ketone dehydrogenation via β-H elimination.

It is known that aryl bromides are less reactive than aryl iodides in the Pd-mediated oxidative additions;[5] nevertheless, our preliminary studies indicate that aryl bromides still hold great promise as suitable substrates (Scheme 3A). Further optimizing the reaction conditions and expanding the substrate scope will be executed in our future endeavors. In addition, this β-arylation method proved to be readily scalable; on a gram scale, the β-

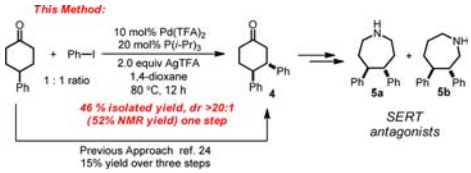
Scheme 3. Further Exploration



arylation product was isolated in 88% yield using methyl 4-iodobenzoate and 69% yield using phenyl iodide with a lower catalyst loading (Scheme 3B). Finally, efforts have also been set forth to examine whether the silver promoter can be substituted with more economically viable reagents. It is encouraging to note that replacement of silver trifluoroacetate with copper(II) trifluoroacetate only slightly reduced the yield (Scheme 3C).

Finally, application of this Pd-catalyzed direct β-arylation in the synthesis of a key intermediate (**4**) for SERT antagonist **5a**/**b** (serotonin reuptake inhibitors) is illustrated in Scheme 4. The

Scheme 4. Synthesis of Intermediate 4 for SERT Antagonist



previous approach,[24] using classical dehydrogenation and 1,4-addition, required three steps and provided a 15% overall yield. With this β-arylation method, ketone **4** was obtained in one single step with a 3-fold increase in yield from the same ketone material and just one equiv of PhI.

In summary, this Pd-catalyzed direct β-arylation of simple ketones overcomes several limitations and complements the scope of β-functionalization of carbonyl compounds. It has significant advantages over the conventional 1,4-additions, because this approach not only circumvents use of conjugated enones and aryl nucleophiles, which need additional steps and redox procedures to prepare, but also tolerates base/nucleophile-sensitive moieties. It is distinct from the amide/ester-based C−H activation strategy[6,7] by allowing both linear and cyclic ketones to react; direct coupling of the readily available aryl halides also distinguishes this work from the photoredox strategy.[8] Furthermore, this methodology is scalable and chemoselective. Although still in its infancy, this approach has shown great potential to streamline complex-molecule synthesis. Finally, the unique tandem Pd-redox system discovered here is expected to shed lights on developing other β-functionalization transformations. Efforts on improving the catalyst activity through systematic understanding of the reaction mechanism are ongoing.

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■ ASSOCIATED CONTENT

Supporting Information

Procedures, characterization and X-ray crystallography data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): A provisional patent based on this technology has been filed.

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