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Direct β-Alkylation of Ketones and Aldehydes via Pd-Catalyzed Redox Cascade

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Supporting Information

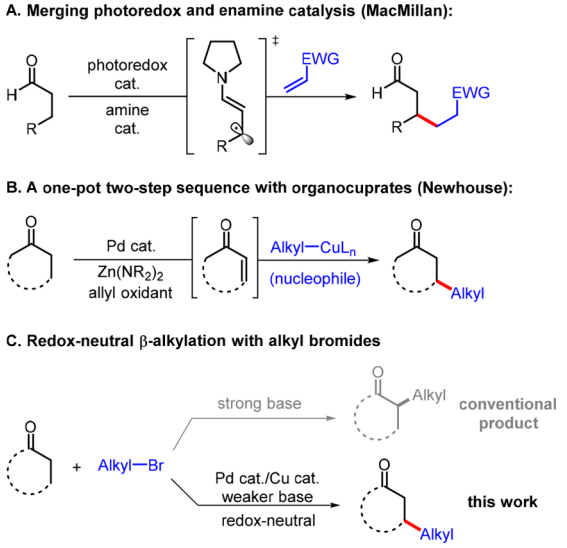
ABSTRACT: We report a direct β-alkylation of ketones and aldehydes with simple alkyl bromides through a Pd-catalyzed redox-cascade strategy. The use of a Cu cocatalyst is important for improved efficiency. The reaction is redox-neutral, without the need for strong acids or bases. Both cyclic and acyclic ketones, as well as α-branched aldehydes, are suitable substrates for coupling with secondary and tertiary alkyl bromides. Concise formal synthesis of Zanapezil is achieved using this β-alkylation method.

Alkylation of carbonyl compounds has been an important and fundamental approach to form carbon−carbon bonds.[1] Conventionally, treatment of ketones with strong bases followed by addition of alkyl halides provides α-alkylated products. In contrast, direct alkylation at the unactivated β-position is much more challenging.[2] While the powerful directing group approach enables β-C−H functionalization of various carbonyl compounds,[3] β-alkylation[4] of ketones and aldehydes remains difficult; in addition, the β-positions of cyclic ketones are generally inaccessible via a directing mode. Recently, MacMillan and co-workers disclosed an elegant approach for β-alkylation via merging enamine and photoredox catalysis, in which Michael acceptors, or ketones/imines were employed as the alkyl source (Scheme 1A).[5,6] More recently, an efficient one-pot β-alkylation protocol was developed by Newhouse and co-workers through a sequence of Pd-catalyzed ketone dehydrogenation followed by conjugate addition of an organocuprate nucleophile (Scheme 1B).[7,8] We were motivated by the convenience of using readily available simple alkyl halides as the alkyl source, which could possibly enable a direct β-alkylation of saturated carbonyl compounds in the absence of stoichiometric oxidants or reductants. Herein, we describe our initial efforts toward the development of a redox-neutral β-alkylation of ketones and certain aldehydes with a weaker base and simple alkyl bromides utilizing a palladium-catalyzed redox-cascade strategy (Scheme 1C).

Our laboratory has been engaged in systematic development of a Pd-redox-cascade approach for β-functionalization of ketones[9] and amides.[10] This strategy starts with Pd(II)-enolate formation between a Pd(II) precatalyst and the carbonyl substrate, followed by β-hydrogen elimination to give an unsaturated carbonyl intermediate.[11] The resulting Pd(0) species then undergoes oxidative addition with the electrophile, e.g., an aryl halide, to give an aryl-Pd(II) intermediate, which upon migratory insertion and protonation of the new Pd(II)-enolate provides the β-product and regenerates the Pd(II) catalyst. As a result, the electrophile serves as both the oxidant for carbonyl desaturation and the carbon source for β-functionalization. However, to extend this Pd-redox-cascade strategy to β-alkylation, the use of alkyl halides as the electrophile constitutes significant difficulties. First, oxidative addition of Pd(0) to alkyl halides is generally more difficult than to aryl halides.[12] Second, the resulting alkyl-Pd(II) species are prone to β-hydrogen elimination rather than migratory insertion.[13] The seminal work by Firmansjah and Fu shows that such an issue could be addressed using a bulky NHC ligand, but it remains challenging to use secondary or tertiary alkyl halides.[14] Alternatively, besides a two-electron oxidative addition, electron-rich Pd(0) is also known to undergo a one-electron pathway, in which Pd(0) can abstract the halogen atom from an alkyl halide to give a Pd(I)-X species and an alkyl radical.[15] This process has appeared in several Pd-catalyzed atom-transfer, cross coupling, and carbonylative reactions using alkyl halides as the substrate.[16] For example, Alexanian,[17] Zhou,[18] Gevorgyan[19] and Fu[20] recently demonstrated this concept in elegant alkyl-Heck reactions with attractive scopes and synthetic applications.

For the proposed β-alkylation pathway (Scheme 2), it is possible to trigger the same radical formation from an alkyl halide with the electron-rich Pd(0) species, which could be followed by

Scheme 1. β-Alkylation of Aldehydes and Ketones



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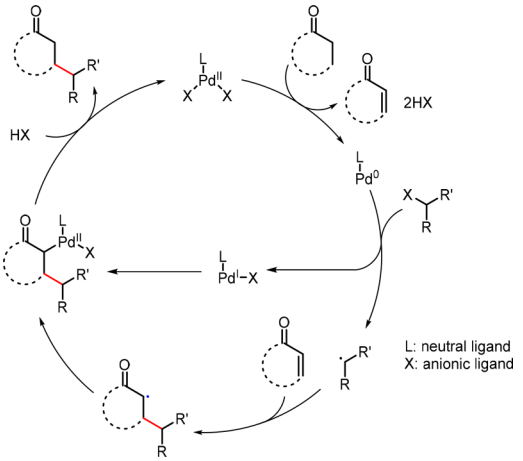
Scheme 2. Proposed Strategy

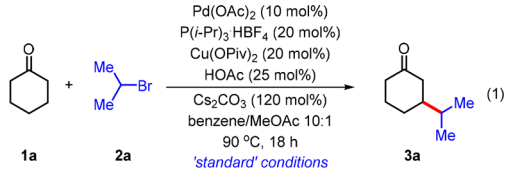


a radical relay with the enone intermediate and then recombination of the α-radical with the Pd(I)-X to generate the β-alkylated Pd(II) enolate. However, the key difference between this proposed reaction and the Pd(I)-mediated alkyl-Heck reaction is that at any given time only a catalytic amount of enone exists in this system. As a consequence, if the generated unstabilized alkyl radical species cannot react with the enone in a timely fashion, many side reactions would occur, e.g., C−H abstraction and dimerization. Moreover, whether the Pd-catalyzed two-electron dehydrogenation process would be compatible in the presence of reactive radical species could be another concern.

We anticipated that the main issue of the proposed catalytic cycle (Scheme 2) should come from the instability of the alkyl radical generated, thus hypothesized that, by adding an additional catalyst, e.g., a Cu salt, that can reversibly generate the alkyl radical,[21] the lifetime of the alkyl radical could be significantly extended. In addition, the α-radical generated after conjugate addition could possibly recombine with Cu(I) (instead of Pd(I)) to give a Cu(II) enolate, which may minimize potential undesired β-hydrogen elimination prior to the enolate protonation; the Pd(I) species could then be oxidized by Cu(II) to regenerate the Pd(II) catalyst. To test the hypothesis, cyclohexanone (**1a**) and 2-bromopropane (**2a**) were employed as the model substrates; gratifyingly, the desired β-alkylation product (**3a**) was obtained in 65% yield (Table 1, entry 1) using $Pd(OAc)_2$/$P(i\text{-}Pr)_3$/$Cu(OPiv)_2$ as the catalysts. In this reaction, no α-alkylation product was observed. The overdehydrogenation product (3-isopropyl-2-cyclohexenone), generated via further β-hydrogen elimination of the β-alkylated Pd-enolate, was only observed in a small amount (<3%) in this case. A high concentration of the ketone substrate appeared to be necessary to maintain fast dehydrogenation; when the ketone and the alkyl bromide were used in a 1:1 ratio, lower efficiency was observed under the current conditions (Table 1, entry 2).

A number of control experiments were then conducted to understand the role of each reactant (Tables 1 and S1). First, a comparable yield was obtained when the reaction was performed in the dark (Table 1, entry 3), suggesting that light is not needed for the radical generation in this reaction. Both alkyl iodides and chlorides were less efficient than the corresponding alkyl bromide (Table 1, entries 4 and 5). Unsurprisingly, no product was detected without palladium (Table 1, entry 6), and the ligand played a pivotal role in this transformation (Table 1, entries 7−10). $P(i\text{-}Pr)_3$ was optimal due to its electronic richness and

Table 1. Selected Optimization of Reaction Conditions[a]



Entry	Variations from the "standard" conditions	Yield of **3a**[b]
1	none	65%
2	0.4 mmol of **1a** was used instead	34%[c]
3	performed in the dark	63%
4	*i*-Pr-I instead of *i*-Pr-Br	40%
5	*i*-Pr-Cl instead of *i*-Pr-Br	1%
6	without $Pd(OAc)_2$	0%
7	without $P(i\text{-}Pr)_3{\cdot}HBF_4$	2%
8	$PCy_3{\cdot}HBF_4$ instead of $P(i\text{-}Pr)_3{\cdot}HBF_4$	48%
9	$P(t\text{-}Bu)_3{\cdot}HBF_4$ instead of $P(i\text{-}Pr)_3{\cdot}HBF_4$	1%
10	PPh_3 instead of $P(i\text{-}Pr)_3{\cdot}HBF_4$	5%
11	without $Cu(OPiv)_2$	20%
12	$Cu(OPiv)_2$ 10 mol % instead of 20 mol %	61%
13	$Cu(OAc)_2$ instead of $Cu(OPiv)_2$	61%
14	CuOAc instead of $Cu(OPiv)_2$	59%

[a]Unless otherwise noted, all the reactions were run with **1a** (1.0 mmol) and **2a** (0.4 mmol) in 0.44 mL solvent for 18 h. [b]NMR yield determined using 1,1,2,2-tetrachloroethane as the internal standard. [c]3,5-Dialkylation and overdehydrogenation products were observed in 9% and 4% yields, respectively.

proper steric bulkiness. Though PCy_3 was still effective, bulkier $P(t\text{-}Bu)_3$ or less electron-rich PPh_3 gave much lower yields. In addition, bidentate ligands were not efficient (Table S1, entries 2 and 3). Adding $Cu(OPiv)_2$ cocatalyst was found to significantly improve the yield from 20% to 65% (Table 1, entry 11).[22] Meanwhile, lowering the Cu loading, using $Cu(OAc)_2$ instead, or switching to Cu(I) precatalyst only slightly reduced the yield (Table 1, entries 12−14). A mixed solvent between benzene and MeOAc proved to be optimal, though benzene alone or 1,4-dioxane also gave similar yields (Table S1, entries 4−8). The role of Cs_2CO_3 was proposed to first neutralize the HBr generated in the reaction and second serve as a halide scavenger due to the low solubility of CsBr, while other bases were less effective (Table S1, entries 9−11). Finally, it is interesting to note that a catalytic amount of HOAc was also crucial, though the exact reason is unclear (Table S1, entries 12 and 13).

The scope of alkyl halides was first investigated with cyclohexanone and propiophenone (Scheme 3).[23] A wide range of secondary and tertiary alkyl bromides were suitable substrates for this transformation.[24] Besides isopropyl bromide (**3a**, **3i**), cyclic alkyl bromides, ranging from 4- to 8-membered rings, smoothly delivered the desired products in moderate to good yields (**3b**−**3g**). Attributed to the near-neutral reaction conditions, acid- or base-reactive functional groups were well tolerated, including ethers (**3e**), Boc-protected amines (**3j**), esters (**3l**−**3p**), nitriles (**3o**), cyclopropane moieties (**3p**), benzoyl-, TBS- and MOM-protected alcohols (**3l**, **3q**, **3r**), amides (**3w**), electron-rich olefins (**3u**) and ketones (**3v**).[25] 2-Bromonorbornane gave the alkylation at the *exo* face of norbornane (**3k**), which was confirmed by X-ray crystallography. Tertiary alkyl bromides also worked well for both cyclic and linear ketones (**3h**, **3s**, **3t**), but the overdehydrogenation became somewhat competitive. A one-pot hydrogenation protocol could be adopted to ease the isolation. Alkyl bromides derived from

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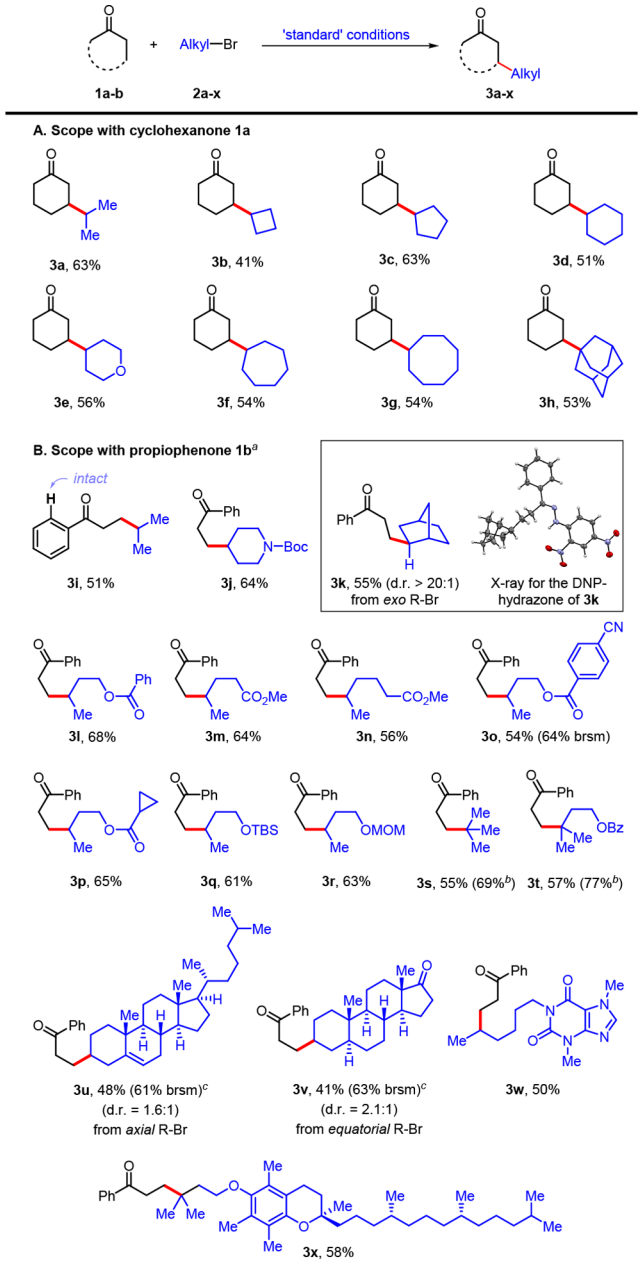
Scheme 3. Substrate Scope of Alkyl Bromides

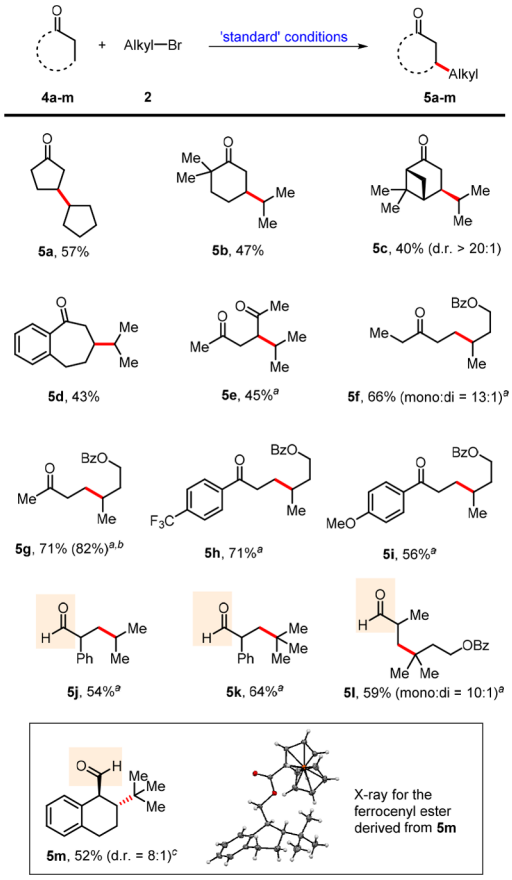


[a]In these cases, 5 equiv of **1b** was used. [b]Yield in the parentheses was obtained when a one-pot hydrogenation was conducted after the reaction. [c]15 mol % $Pd(OAc)_2$, 30 mol % $P(i\text{-}Pr)_3{\cdot}HBF_4$ and 30 mol % $Cu(OPiv)_2$ were used.

bioactive natural products, such as cholesterol (**3u**), androsterone (**3v**), pentoxyphylline (**3w**), and α-tocopherol (**3x**), also smoothly afforded the desired coupling products. Interestingly, when propiophenone was used as substrates (Scheme 3B), the *ortho* C−H bonds on the aryl group remained intact. It is noteworthy that the reductive debromination of alkyl bromides was found to be the major side reaction that accounts for the mass balance of this transformation (see Table S2 for details).

The scope of the carbonyl substrates was further explored (Scheme 4). Cyclic ketones, such as cyclopentanone (**5a**), poly substituted cyclohexanones (**5b** and **5c**), and benzocycloheptanone (**5d**), were competent substrates. The 1,4-diketone also yielded the desired product (**5e**). Simple linear ketones, e.g., 3-

Scheme 4. Substrate Scope of Ketones and Aldehydes

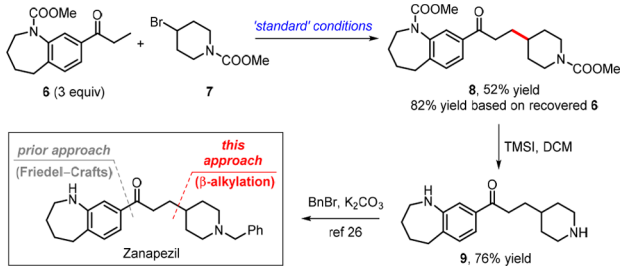


[a]In these cases, 5 equiv of ketone or aldehyde was used. [b]Yield in the parentheses was obtained when a one-pot hydrogenation was conducted after the reaction. [c]The product was isolated as an alcohol after $NaBH_4$ reduction.

pentanone (**5f**) and 2-butanone (**5g**), exhibited higher reactivity. In addition, propiophenones with trifluoromethyl or methoxy substituents at the *para* position afforded the desired β-alkylation products in good yields (**5h**, **5i**). Intriguingly, aldehydes with α-branches were also feasible substrates under the identical reaction conditions (**5j**−**5m**). The α-substituents were important to prevent self-aldol condensation reactions. Nevertheless, both secondary and tertiary alkyl bromides could effectively couple with α-aryl- or alkyl-substituted aldehydes. In particular, the aldehyde containing a cyclic structure gave predominately the *trans*-product (**5m**).

The synthetic utility of this method is illustrated in a concise formal synthesis of Zanapezil, a selective acetylcholinesterase inhibitor (Scheme 5).[26] Employing ketone **6** and bromide **7** as

Scheme 5. Formal Synthesis of Zanapezil



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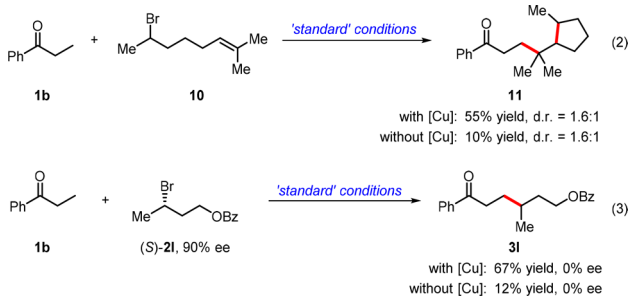
the coupling partners, a convergent synthesis was achieved through β-alkylation. While 3 equiv of ketone **6** was used for higher efficiency, most unreacted ketones can be easily recovered. Overall, this method offers a new bond disconnection strategy for the synthesis of Zanapezil.

Finally, to probe the radical participation in this reaction, a radical clock experiment was conducted (eq 2). When alkyl



bromide **10** with a tethered trisubstituted olefin was subjected to the reaction conditions with or without Cu cocatalyst, ketone **11** was obtained as the only product in which the 5-*exo* cyclization proceeded prior to the 1,4-addition.[27] This observation is consistent with the proposed radical-involved mechanism, as the cyclization would be sluggish for the alternative oxidative addition/migratory insertion pathway due to the steric hindrance of the olefin. Additionally, an enantioenriched alkyl bromide (*S*)-**2l** with 90% *ee* delivered the racemic alkylation product, which also indicates alkyl radicals to be reasonable intermediates (eq 3).

In summary, we have developed a new method for direct β-alkylation of simple ketones and α-branched aldehydes via Pd-catalyzed redox cascade. Different from existing β-functionalization methods, this strategy permits the use of simple, readily available alkyl bromides as the alkylation source. Considering the relatively broad substrate scope, the redox-neutral feature, and high functional group tolerance, this approach should find use in complex molecule synthesis. In addition, merging a radical process with Pd-catalyzed desaturation should also have implications beyond this work. Efforts on further improving the reaction efficiency and enabling enantioselective transformations are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b03530.

Experimental procedures; spectral data (PDF)
Data for $C_{22}H_{24}N_4O_4$ (CIF)
Data for $C_{26}H_{30}FeO_2$ (CIF)

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Notes

The authors declare no competing financial interest.

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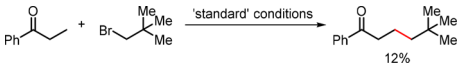
(23) The overdehydrogenation byproduct formation for linear ketones was easier due to the higher propensity of β-hydrogen elimination caused by the flexibility of the skeleton, but fortunately, the product/byproduct ratio was greater than 10:1 for most cases.

(24) Primary alkyl bromides are potentially viable substrates, but they suffer from low reaction rates and undesired S_N2 reactions with acetate or pivalate salts. The following reaction delivered the desired product in 12% yield.



(25) For **3v**, a small amount of dehydrogenation product of the cyclopentanone moiety was observed (<5%).

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