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Palladium-Catalyzed Dehydrogenative β′-Functionalization of β-Keto Esters with Indoles at Room Temperature

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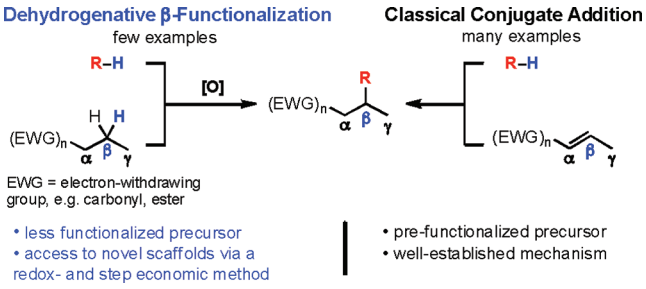
Supporting Information

ABSTRACT: The dehydrogenative β′-functionalization of α-substituted β-keto esters with indoles proceeds with high regioselectivities (C3-selective for the indole partner and β′-selective for the β-keto ester) and good yields under mild palladium catalysis at room temperature with a variety of oxidants. Two possible mechanisms involving either late or early involvement of indole are presented.

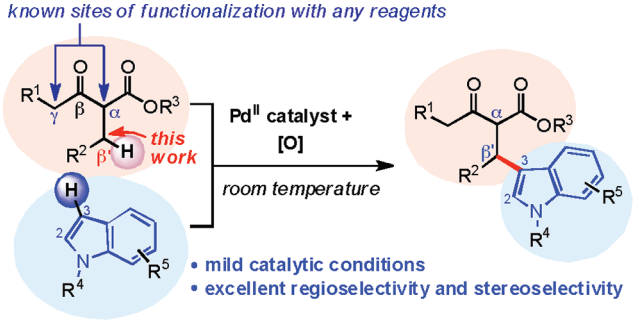
Direct cross-coupling reactions where new carbon−carbon bonds are generated via the oxidation of C−H bonds are highly desirable transformations from the atom-economic point of view. It is therefore not surprising that these reactions, also called cross-dehydrogenative coupling (CDC) reactions, have attracted significant attention in the past few years.[1] The selectivity challenges associated with such processes are formidable, since the C−H functionalization could potentially take place at several different sites.[2] As an example, regioselective coupling at the β-position of carbonyl compounds would be a desirable alternative to the classical conjugate addition reactions[3] (Scheme 1) since saturated, less functionalized precursors would be required. However, dehydrogenative β-functionalization reactions of carbonyl compounds[4] are rare and typically involve the use of directing groups[5] or auxiliary amine catalysts.[6] In the case of esters, amides, and β-dicarbonyl compounds, CDCs afford products functionalized at the α-position instead of the β-position.[7]

Scheme 1. Roadmap of β-Functionalization of Carbonyl Derivatives



Because of the central place of heterocycles, especially indoles, in medicinal chemistry, we recently initiated a program directed toward oxidative functionalizations of indoles and β-keto esters. Indole is the third most popular ring system found bioactive molecules[8] and a common core of over 3000 natural products.[9] Known dehydrogenative coupling methods currently allow the union of indoles with tertiary amines, alkenes, arenes, and heteroarenes.[9,10] Herein we describe a simple protocol for the oxidative coupling of α-substituted β-keto esters and indoles at the remote β′ position of the β-keto ester (Scheme 2).

Scheme 2. Regioselective Functionalization of β-Keto Esters with Indoles



We initiated our screen by examining the reaction of *N*-methylindole (**2a**) with cyclic β-keto ester **1a** (Table 1). With $Mn(OAc)_2$ and *t*-BuOOH as the oxidant, we obtained the α-coupled product **4a** in poor yield, and similar results were obtained with $Cu(OAc)_2$. However, the use of $Pd(OAc)_2$ gave a significantly improved yield, and more importantly, the site of the coupling had switched to the β′ position to give **3a**. Further screens indicated that $Pd(TFA)_2$ was a more active catalyst than $Pd(OAc)_2$ and that dioxane as well as the mixed solvent 2-propanol/AcOH were optimal solvents. With the *i*-PrOH/AcOH solvent system,[11] the undesired side reaction, homocoupling of **1a**,[12] could be minimized. Although a wide variety of oxidants gave reasonable conversions at room temperature, *tert*-butyl perbenzoate (*t*-BuOOBz) afforded superior results (entry 18), and these conditions were then selected for further exploration. It should be noted that in addition to peroxide oxidants, MnO_2, AgOAc, and oxygen were also synthetically useful oxidants (entries 6, 9, and 12). Significantly, the regioselectivity was excellent on both coupling partners, and no **4a** or no indole regioisomers could be detected in reactions with Pd^{II} catalysts.

Schemes 3 and 4 summarize the results obtained with a range of indoles and β-keto esters. Both unsubstituted as well as *N*-substituted indoles give good product yields (**3a**−**h**), and the reaction is highly tolerant of substituents with different

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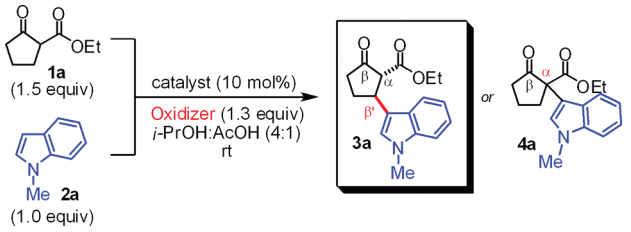
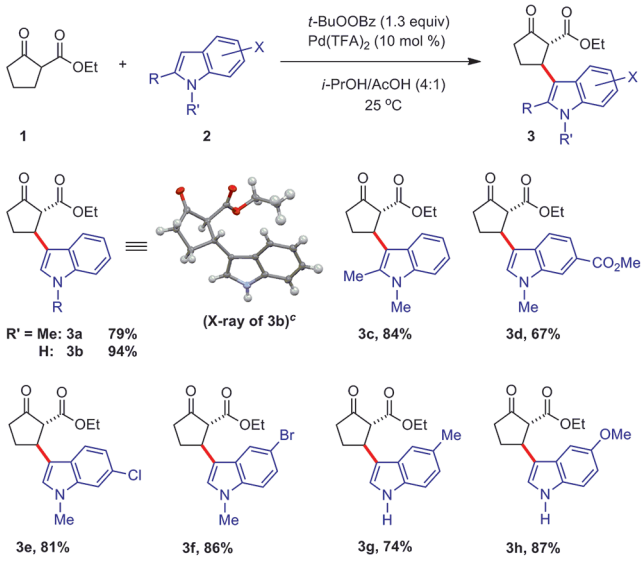
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	oxidizer	product (%)[b]
1[c]	$Mn(OAc)_2$	*t*-BuOOH[d]	**4a** (<10)
2[c]	$Cu(OAc)_2$	*t*-BuOOH[d]	**4a** (12)
3	$Pd(OAc)_2$	*t*-BuOOH	**3a** (43)
4	**$Pd(TFA)_2$**	***t*-BuOOH**	**3a (67)**
5	$Pd(TFA)_2$	H_2O_2	**3a** (46)
6	$Pd(TFA)_2$	O_2 (1 atm)	**3a** (64)
7	$Pd(TFA)_2$	DDQ	**3a** (<2)
8	$Pd(TFA)_2$	oxone	**3a** (35)
9	$Pd(TFA)_2$	AgOAc	**3a** (42)
10	$Pd(TFA)_2$	$Na_2S_2O_8$	**3a** (45)
11	$Pd(TFA)_2$	$K_2S_2O_8$	**3a** (59)
12	$Pd(TFA)_2$	MnO_2	**3a** (58)
13	$Pd(TFA)_2$	*t*-BuOO*t*-Bu	**3a** (26)
14	$Pd(TFA)_2$	$PhCMe_2OOH$	**3a** (57)
15	$Pd(TFA)_2$	$(PhCMe_2O)_2$	**3a** (34)
16	$Pd(TFA)_2$	*t*-BuOOAc	**3a** (72)
17	$Pd(TFA)_2$	BzOOBz	**3a** (37)
18	**$Pd(TFA)_2$**	***t*-BuOOBz**	**3a (82)**
19	$Pd(TFA)_2$	*t*-BuOOBz	**3a** (66)[e]

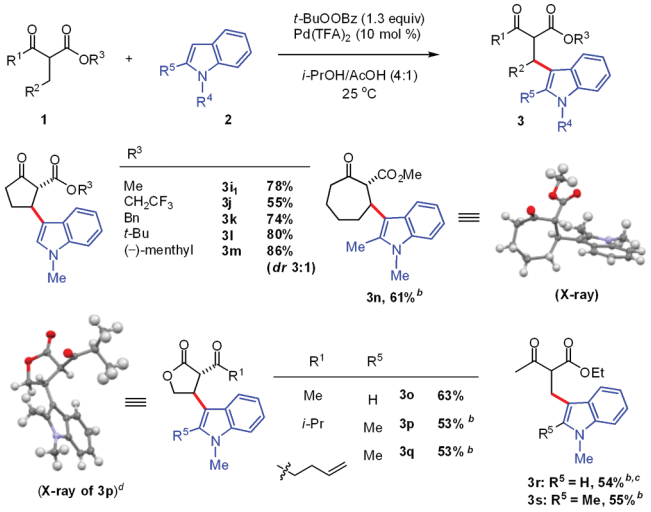
[a]Unless otherwise indicated, reactions were carried out with 0.4 mmol scale of **2a** for 15−18 h. [b]Determined by ^1H NMR analysis using dibenzyl ether as the internal standard. [c]Neat at 70 °C. [d]5.3 M in *iso*-octane. Addition of a polar cosolvent inhibited the reaction completely (see the Supporting Information for further solvent screens). [e]In 20% $AcOH/H_2O$.

Scheme 3. Scope of Dehydrogenative Coupling with Different Indoles[a]



[a]Isolated yields of pure products are reported. Conditions, unless otherwise indicated: **1** (1.5 equiv), **2** (0.4 mmol, 1.0 equiv), *t*-BuOOBz (1.3 equiv), $Pd(TFA)_2$ (0.1 equiv), *i*-PrOH/AcOH (4:1, 0.5 mL) at 25 °C. [b]Opposite enantiomer shown.

Scheme 4. Scope of Dehydrogenative Coupling with Different β-Keto Esters[a]



[a]Isolated yields of pure products are reported. Conditions, unless otherwise indicated: β-keto ester (1.5 equiv), indole (0.4 mmol, 1.0 equiv), *t*-BuOOBz (1.3 equiv), $Pd(TFA)_2$ (0.1 equiv), *i*-PrOH/AcOH (4:1, 0.5 mL) at 25 °C. [b]Slow addition of indole over 10 h. [c]4.5 equiv of **1r** was used. [d]Opposite enantiomer shown.

electronic properties in the indole nucleus (**3d−h**) (Scheme 3), allowing further opportunities for synthetic transformations. Furthermore, β-keto esters with different steric demands (see products **3i−l**) are readily engaged in the coupling reaction (Scheme 4). All cyclic products exhibited trans stereochemistry,[13] and the use of an enantiopure menthyl-derived ester enables the β-functionalization in a diastereoselective fashion (**3m**, dr = 3:1 for the two trans isomers). Other β-keto ester scaffolds, including cycloheptanone (**3n**) and γ-butyrolactone (**3o−p**) systems, are also compatible. Notably, a pendant olefinic unit in **3q** remains intact, reflecting the mildness of the reaction conditions and the orthogonal reactivity to Heck-type reactions.[14] In addition, acyclic β-keto esters can also be β-functionalized (**3r** and **3s**).[15]

Mechanistically, the β-arylation is likely to proceed via a Pd^0/Pd^{II} catalytic manifold instead of the oxidant-dependent Pd^{II}/Pd^{IV} cycle[16] because (1) the reaction could proceed with a variety of oxidants (Table 1) and (2) a reasonable product yield (66%) was obtained when the reaction was performed with a stoichiometric amount of $Pd(TFA)_2$ in the absence of an external oxidant under an argon atmosphere.

To provide insight into the reaction mechanism, the following kinetic experiments were performed. The rate of the dehydrogenative coupling between **1a** and **2a** displays a saturation dependence on β-keto ester **1a**.[17] The effect of indole **2a** is more complex (Figure 1): at low [**2a**], the rate exhibits a pseudo-first-order dependence (the rate rises to maximum at 1 equiv of **2a**), while inhibition kinetics appears when [**2a**] is increased from 1 to 8 equiv.[17] Furthermore, the reaction rate is not dependent on the oxidant concentration, and the reaction is 0.7th order with respect to $[Pd(TFA)_2]$.[17]

At least two different mechanistic scenarios are consistent with the above data (Scheme 5). The first scenario involves a Saegusa oxidation[18] of **1a** to enone intermediate **A** followed by a Friedel−Crafts-type or Pd-catalyzed conjugate addition of indole **2a**. In this "late indole" mechanism, the pseudo-first-order kinetics at low concentrations of **2a** could be rationalized

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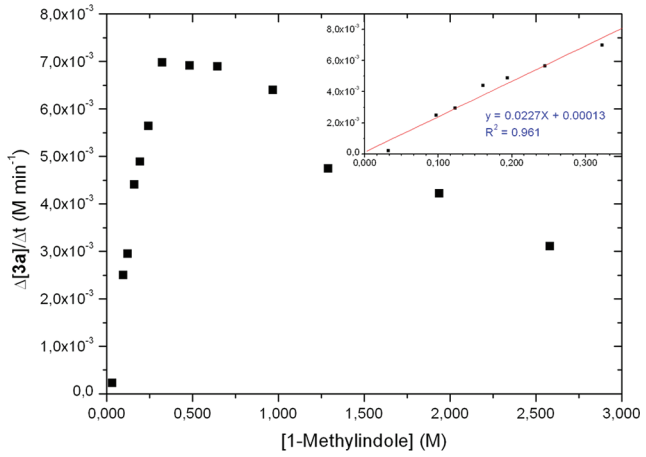
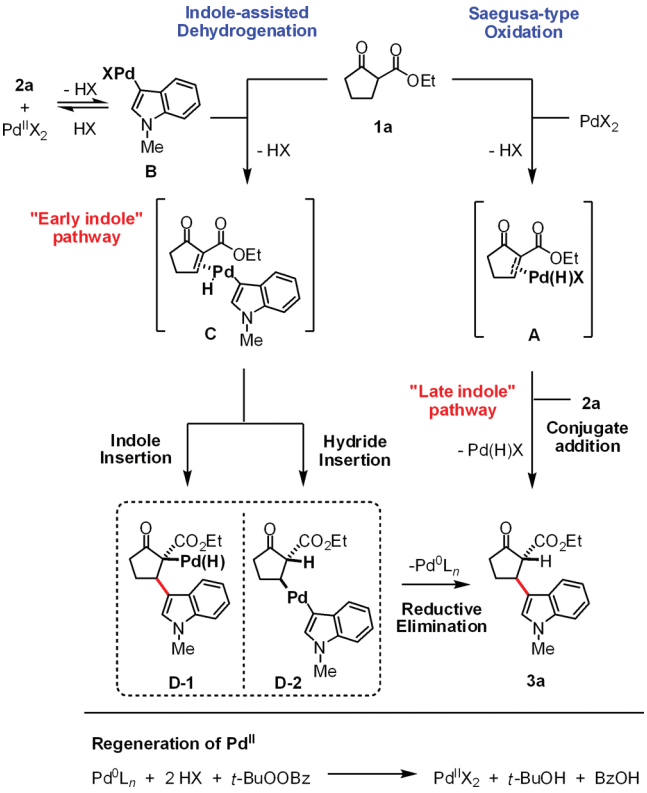


Figure 1. Plot of the initial rate of dehydrogenative coupling of β-keto ester **1a** with varying concentrations of 1-methylindole **2a**: [**1a**] = 0.484 M, [**2a**] = 0.0323–2.583 M, [$Pd(TFA)_2$] = 0.032 M, [*t*-BuOOBz] = 0.424 M at 25 °C. The inset displays a linear least-squares fit for [**2a**] ranging from 0.0323 to 0.323 M.

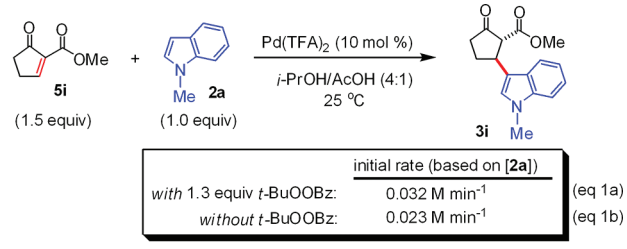
Scheme 5. Plausible Mechanisms for Pd^{II}-Catalyzed Dehydrogenative β'-Functionalization of β-Keto Esters

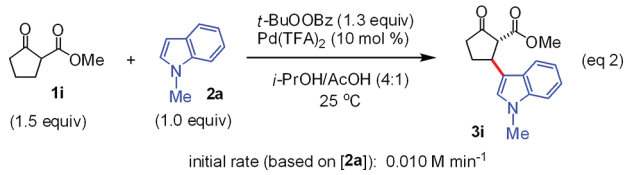


if the Saegusa oxidation is faster than the conjugate addition at low [**2a**]. The catalytic cycle would be completed by the regeneration of Pd^{II} from Pd^0 in the presence of *tert*-butyl perbenzoate.[19]

Alternatively, an "early indole" scenario in which a palladated indole species **B** is involved in the dehydrogenation step could also be envisioned. The reaction might then proceed via intermediates **C** and **D-1** or **D-2**. This mechanism would also be consistent with the kinetic behavior of indole if the rate is suppressed at high [**2a**] by the formation of $Pd(indole)_2$ species. Literature precedents supporting this mechanistic alternative include the following: (a) indoles are known to be palladated and homocoupled at C3;[12] (b) α-arylpalladium species derived from β-dicarbonyl compounds are known to undergo slow reductive eliminations, suppressing the competing α-arylation;[20] and (c) a similar mechanism for the β-arylations of preformed ester enolates with heteroaryl and aryl halides was recently proposed on the basis of kinetic and computational studies.[21]

Further kinetic experiments with preformed enone **5i** or β-ketoester **1i** did not fully resolve the issue. Under the standard conditions, the reaction between **5i** and **2a** (eq 1a or 1b) was





ca. 2–3 times faster than the standard reaction between **1i** and **2a** (eq 2). Under acid catalysis (20 mol % TFA) or with 4:1 *i*-PrOH/AcOH alone, the reaction between **5i** and **2a** was significantly slower (initial rate of 0.003 or 0.001 M min^{-1}, respectively).[17] These data suggest that if **5i** is an intermediate (Saegusa pathway), the conjugate addition step is unlikely to be acid-catalyzed. Interestingly, in a control experiment with **1a** but without indole **2a**, only very slow formation of enone was observed (12% conversion to **5a** after 14 h, rate of formation of **5a** = 0.00025 M min^{-1}).[17] Therefore, although neither mechanistic pathway can be completely ruled out at present, in practice the reaction appears to require the presence of indole to engage the β-keto ester partner fully.

In summary, we have presented a novel dehydrogenative coupling method for constructing $C(sp^2)$–$C(sp^3)$ bonds by connecting the C3 position of indoles and the β'-position of β-keto esters under mild reaction conditions and with excellent regioselectivities. Two possible mechanisms have been presented: a Saegusa-type mechanism ("late indole") and an indole-assisted dehydrogenation mechanism ("early indole"). Efforts to advance the understanding of the reaction mechanism and generalize the concept of dehydrogenative β'-functionalization are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data for new compounds. 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.

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