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Palladium-Catalyzed Dehydrogenative β′-Arylation of β-Keto Esters under Aerobic Conditions: Interplay of Metal and Brønsted Acids

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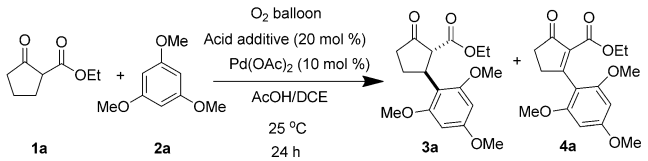
In chemical synthesis, methods that enable the rapid build up of complexity from simple precursors are highly valuable from an atom and redox economic point of view. In this regard, catalytic dehydrogenative cross-couplings between two different molecules are particularly attractive, since they do not require any pre-functionalization of the substrate.[1,2] The challenges associated with such processes are formidable—the catalysts will need to activate both components chemo- and regioselectively, while avoiding potential homocoupling reactions between either of the two coupling partners. For example, electron-rich arenes and phenols are known to undergo oxidative homocoupling reactions under catalytic oxidative conditions.[3,4] Another serious problem associated with these reactions is the potential for further oxidation of the product, especially when prolonged reaction times and/or forcing conditions, such as heating, are required to promote the reactions.

Here we show that by a careful choice of Pd catalyst and a Brønsted acid co-catalyst,[5] electron-rich arenes and a variety of phenols can undergo a highly regioselective cross-dehydrogenative coupling at room temperature with β-keto esters in the β′-position, overcoming problems associated with the overoxidation or degradation of the product. Previously, regioselective arylation in the β-position of esters has been successful only with prefunctionalized aryl halides.[6]

In contrast to our recently reported cross-dehydrogenative β′-functionalization of β-keto esters with indoles,[7] in our initial screens with electron-rich arenes we encountered significant challenges associated with expanding the scope of the reaction, including the generally lower reactivity of arenes compared to indoles, and the competing overoxidation or degradation of the product. In our initial screens with 1,3,5-trimethoxybenzene (**2a**) and β-keto ester **1a** (Table 1), the reaction was feasible only at elevated temperatures (80 °C) when *tert*-butyl perbenzoate (*t*BuOOBz) was used as the oxidant. Owing to the inherent hazards associated with prolonged heating of high concentrations of peroxides, we turned to oxygen gas as a mild alternative.[8] Although [Pd(tfa)$_2$] (tfa = trifluoroacetate) was an active catalyst at 50 °C, its use also resulted in significant overoxidation to enones **4a** and also **6a** (enone derived from **1a**) when O_2 was used as the terminal oxidant.

Table 1. Screen of Brønsted acid additive and solvent.[a]



Entry	Brønsted acid	p$K_{a(H_2O)}$[b]	Yield [%] of **3a**[c]	Yield [%] of **4a**[c]
1[d]	–	–	8	0
2[e,f,g]	–	–	44	29
3[f,h]	TFA (excess)	−0.3	17	15
4[h]	TFA (excess)	−0.3	40	15
5[d]	$TsOH\cdot H_2O$	ca. −3	complex mixture	
6[e]	Cl_3CCOOH	0.7	42	0
7[e]	HIO_3	0.8	37	<3
8[d]	$(PhO)_2P(O)OH$	ca. 1	82 (87)[i]	5 (3)[i]
9[e]	$Cl_2CHCOOH$	1.3	74	5
10[e]	*o*-NO_2-BzOH	2.2	13	<3
11[e]	$ClCH_2COOH$	2.9	19	6
12[d]	*p*-NO_2-BzOH	3.4	N.D.[j]	<3
13[e]	IBX	2.4	complex mixture	

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.4 mmol), acid additive (0.08 mmol), $Pd(OAc)_2$ (0.04 mmol) in 0.5 mL solvent under an oxygen-filled balloon at 25 °C for 24 h. [b] For a comparison of pK_a values, see Supporting Information. [c] Determined by ^{1}H NMR spectroscopy using an internal standard. [d] 4:1 AcOH/DCE. [e] 1:1 AcOH/DCE. [f] 10 mol % of [Pd(tfa)$_2$] were used instead of $Pd(OAc)_2$. [g] At 50 °C. [h] TFA/DCE (4:1) as solvent. [i] Isolated yield; 50 mol % diphenyl phosphate used. [j] N.D. = not detected.

Instead of trying to control the reaction by limiting the oxygen supply, we observed that the activity of a milder catalyst, $Pd(OAc)_2$, could be boosted by the addition of catalytic amounts of acids,[9] especially when acetic acid was also used as a co-solvent.[10] A survey of different acid co-catalysts revealed that diphenyl phosphate was particularly effective, affording the desired product **3a** in 82 % yield and minimizing the formation of overoxidation product **4a** (entry 8). When 50 mol % diphenyl phosphate was used, **3a** was isolated in 87 % yield. The rate of β-arylation in the presence of 50 mol % $(PhO)_2P(O)OH$ was approximately 14-fold faster when compared to the rate without the acid additive (Scheme 1).

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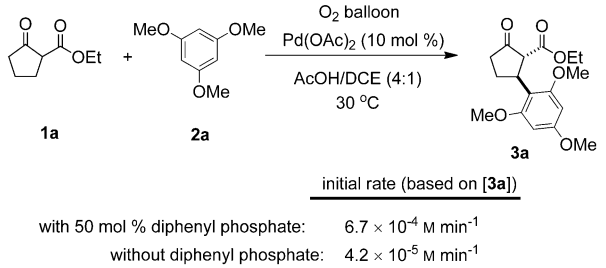
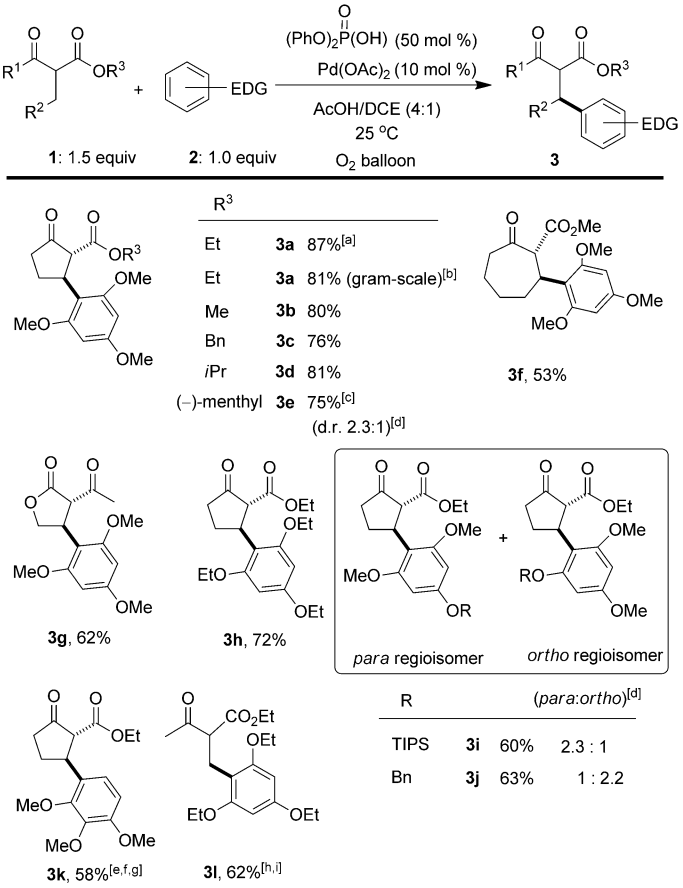


Scheme 1. Diphenyl phosphate accelerated Pd^{II}-catalyzed dehydrogenative coupling.

With the optimized conditions in hand, the scope of the coupling between different arenes and β-keto esters was then explored (Scheme 2). Among cyclic β-keto esters explored, 5-membered cyclic β-keto esters system furnishes coupling products (**3a**–**e**) with **2a** in high yields (75–87%) regardless of the steric bulkiness of ester group. Even a moderately diastereoselective arylation (**3e** of d.r. 2.3:1) can be achieved by (−)-menthyl ester. Seven-membered rings (**3f**) and γ-lactones (**3g**) are also viable partners for the β-arylation, and variations in substituent and substitution pattern of the aryl component can also be tolerated. For example, coupling of **1a** with triethoxylated arene yielded **3h** in 72% yield. Interestingly, some regioselectivity in the arylation process can be achieved by altering the arene substituent. For instance, a bulky TIPS-substituted arene led to selective formation of *para*-regioisomer of **3i** of 2.3:1 ratio, while the use of benzylated arene resulted in the reverse ratio in the formation of **3j** (*para*/*ortho* = 1:2.2). Furthermore, the coupling of **1a** with 1,2,3-trimethoxybenzene, under modified conditions, afforded **3k** as the exclusive isomer. Finally, acyclic β-keto ester-derived products can also be obtained by slow addition of the β-keto ester (**3l**).

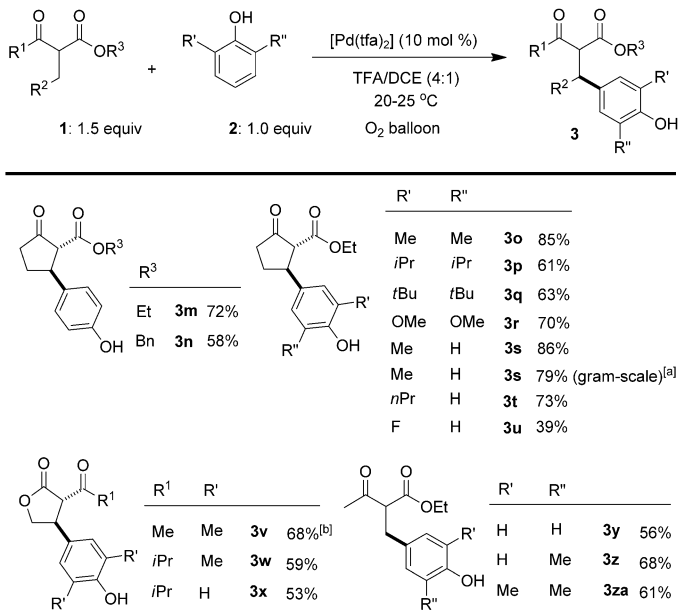
Although arenes bearing two donor groups, such as 1,3-dimethoxybenzene, were insufficiently reactive, we were delighted to find that unprotected phenols can be successfully used as the reaction partners when the reaction is conducted under modified conditions.[10] The scope of these reactions is summarized in Scheme 3. In general, β-arylation reactions are highly *para*-selective to phenolic systems, even in the case of simple phenol (**3m** and **3n**), which is known to be reactive at both *para*- and *ortho*-positions.[11] In addition, the reactions are remarkably tolerant to the steric crowding from the substitution(s) at the *ortho*-position(s) (**3o**–**u**). In particular, product **3q** can be efficiently obtained from the coupling with 2,6-di-*tert*-butylphenol. An electronically deactivated phenol can also be used, although with somewhat reduced yield (**3u**). Besides the cyclic β-keto esters, phenols are also capable of β-coupling to a β-keto lactone system (**3v**–**x**) without a competitive ring opening. Finally, successful dehydrogenative coupling between an α-methyl-β-keto ester and either an electron-rich arene (to give **3l** in Scheme 2) or unprotected phenols (to give **3y**–**3za** in Scheme 3) demonstrates that oxidative coupling can be used as an alternative disconnection to the conventional benzylation of β-keto esters.



Scheme 2. Scope of diphenyl phosphate/Pd^{II} co-catalyzed dehydrogenative coupling of **1** with different aromatics. Yields of isolated products are reported. Reaction conditions, unless otherwise indicated: **1** (0.6 mmol, 1.5 equiv), **2** (0.4 mmol, 1.0 equiv), diphenyl phosphate (50 mol%), $Pd(OAc)_2$ (10 mol%), AcOH/DCE (DCE = dichloroethane; 4:1, 0.5 mL) under an oxygen-filled balloon at 25 °C. [a] X-ray structure of **3a** is available [CCDC 879905], see the Supporting Information.[17] [b] **1** (1.33 g, 1.4 equiv), **2** (1.00 g, 1.0 equiv), diphenyl phosphate (25 mol%), $Pd(OAc)_2$ (5 mol%), AcOH/DCE (4:1, 15 mL) under an oxygen-filled balloon at 25 °C. [c] 1.2 equiv of **1e** used. [d] Isomeric ratio determined by ^1H NMR spectroscopy from a crude mixture. [e] Single regioisomer obtained exclusively. [f] 10 mol% of $[Pd(tfa)_2]$ in TFA/DCE (4:1, 0.5 mL) were used instead of $Pd(OAc)_2$ in AcOH/DCE. [g] In the absence of diphenyl phosphate. [h] 10 mol% of $[Pd(tfa)_2]$ were used instead of $Pd(OAc)_2$. [i] Slow addition of β-keto ester **1** over 10 h.

The practicability of dehydrogenative β′-arylation was also demonstrated by the gram-scale syntheses of **3a** (Scheme 2) and **3s** (Scheme 3) with a reduced loading (5 mol%) of Pd^{II} catalyst and oxygen gas as the sole oxidant.

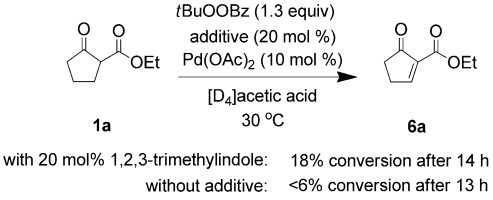
In line with the previously reported β′-arylation of β-keto esters with indoles,[7] two major mechanistic pathways for the reaction can be presented (Scheme 4): an "early-arylation" pathway in which the arene is palladated prior to its engagement with the β-keto ester, and a "late-arylation" pathway in which the β-keto ester is first oxidized to an enone species and then undergoes a conjugate addition-type process with the arene. The early arene pathway might involve migratory insertion to give **D-1**/**D-2** and subsequent



Scheme 3. Scope of Pd^{II}-catalyzed dehydrogenative coupling of **1** with different phenols. Yields of isolated products are reported. Reaction conditions: **1** (0.6 mmol, 1.5 equiv), **2** (0.4 mmol, 1.0 equiv), $[Pd(tfa)_2]$ (10 mol%), TFA/DCE (4:1, 0.5 mL) under an oxygen-filled balloon at 20–25 °C. [a] **1** (2.34 g, 1.4 equiv), **2** (1.08 g, 1.0 equiv), $[Pd(tfa)_2]$ (5 mol%), TFA/DCE (4:1, 12.5 mL) under an oxygen-filled balloon at 20 °C. [b] X-ray structure of **3v** is available [CCDC 880392], see the Supporting Information.[17]

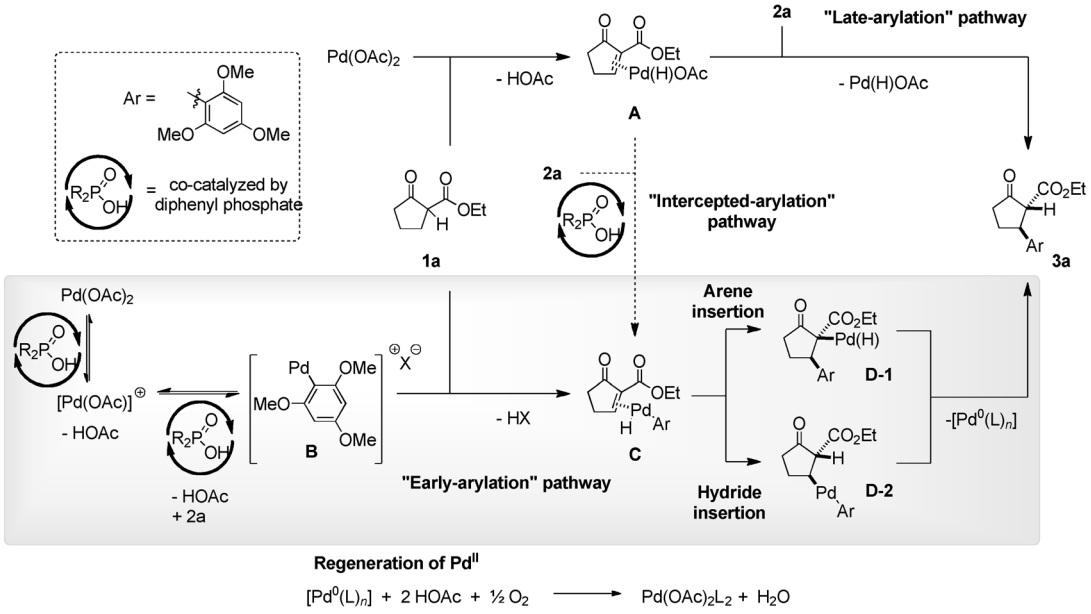
reductive elimination that results in the formation of the C–C bond at the β′-position.

In control experiments with *t*BuOOBz (130 mol%) and $Pd(OAc)_2$ (10 mol%) but without arene **2a**, the enone **6a** derived from β-keto ester **1a** is generated only very slowly (4.3×10^{-5} M min^{-1}; <6% conversion to enone **6a** after 13 h).[12] Conducting the same experiment in the presence of 50 mol% $(PhO)_2P(O)OH$ reveals that the rate of formation of enone is similarly slow (6.6×10^{-5} M min^{-1}; 2% conversion to enone **6a** after 3.5 h, after which time the concentration of **6a** remains essentially constant). However, control experiments with preformed enone **6b** and arene **2a** indicate that conversion to the product **3b** is essentially complete in 30 min with diphenyl phosphate (50 mol%), and the rate is independent of the presence of 10 mol% $Pd(OAc)_2$. As such, although the "late-arylation" pathway is feasible if enough enone is available, the slow formation of enone may limit the overall reaction rate.[13] The higher observed rate of the overall reaction (6.7×10^{-4} M min^{-1}, Scheme 1)[14] may be more consistent with the "early-arylation" pathway in which the dehydrogenation of the β-keto ester **1a** takes place with the involvement of the aryl–Pd species **B**. Importantly, our preliminary studies revealed that Pd^{II}-catalyzed dehydrogenation of **1a** can be accelerated by the presence of electron-rich carbon ligands [Eq. (1)],[15] pointing towards early involvement of the electron-rich arene in the reaction pathway.



(1)

In view of the above, the role of acid co-catalyst (diaryl phosphate) in these reactions most likely is to promote the formation of the arylpalladium species **B**. Previously, Fujiwara and co-workers have reported the use of acids, such as

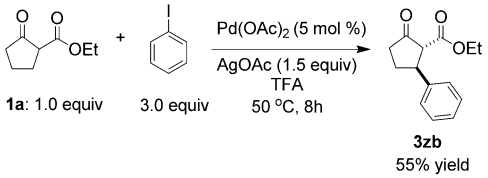


Scheme 4. Plausible reaction mechanism of dehydrogenative β-arylation of **1a** with **2a**.

trifluoroacetic acid as solvent in promoting electrophilic palladation of arenes at room temperature.[9] Alternatively, the acid co-catalyst might promote the conjugate addition step in the "late-arylation" scenario. However, no enantioselectivity could be obtained when a variety of sterically bulky chiral diaryl phosphates were screened instead of diphenyl phosphate.[10] Of course, such a result does not completely rule out the "late-arylation" pathway, since the stereochemistry could already be set in the planar-chiral complex **A** before the C–C bond formation. In the "early-arylation" scenario, the chiral Brønsted acid might be dissociated before the engagement of **1a** to generate complex **C**, thus leading to racemic product.

Although we cannot fully exclude either mechanism with these experiments, we have nevertheless obtained additional indirect evidence for the feasibility of the "early-arylation" pathway in a control experiment with iodobenzene.[16] The reaction proceeds with the use of AgOAc as the iodide scavenger to give direct β-arylation product **3zb** in 55% yield under acidic and phosphine-free conditions [Eq. (2)].

In conclusion, we have developed a Pd^{II}/Brønsted acid co-



(2)

catalyzed dehydrogenative β′-arylation of β-keto esters with arenes and phenols at room temperature using molecular oxygen (1 atm) as the sole oxidant. Notable features of the reaction include 1) mild, ambient reaction conditions, 2) tolerance of different substituent patterns, and 3) high regioselectivity. A possible mechanism involving acid-assisted palladation of arene and subsequent engagement of the β-keto ester is proposed on the basis of control experiments. The tunability and cooperativity of Pd^{II}/Brønsted acid system should play a pivotal role to broaden the scope of this transformation even further.

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Keywords: arylation · Brønsted acids · C–H functionalization · oxidation · palladium catalysis

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[12] See Supporting Information for details.

[13] It should be noted that the "early- and late-arylation" pathways are not necessarily exclusive.

[14] Due to the instability of enone derived from **1a** and the proton–deuterium exchange of arene **2a** in $[D_4]$acetic acid, the kinetics of enone formation experiments and dehydrogenative couplings were studied under slightly different, but comparable conditions.

[15] Detailed studies and the mechanistic implications of the accelerated effect of dehydrogenation of **1a** will be reported in due course.

[16] These reactions would take place via oxidative addition pathways, as in reference [6].

[17] CCDC-879905 (**3a**) and CCDC-880392 (**3v**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Arylation

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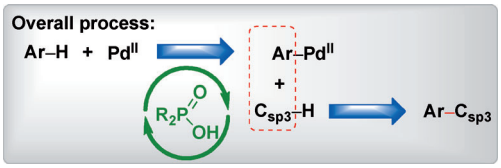
Palladium-Catalyzed Dehydrogenative β′-Arylation of β-Keto Esters under Aerobic Conditions: Interplay of Metal and Brønsted Acids



The Brønsted aids: The first dehydrogenative arylation of β-keto esters with arenes under ambient aerobic conditions was described (see scheme). Under a Pd^{II}/Brønsted acid co-catalytic system, regioselective arylations with alkoxylated arenes and phenols were achieved in good yields, even in gram-scale conditions.