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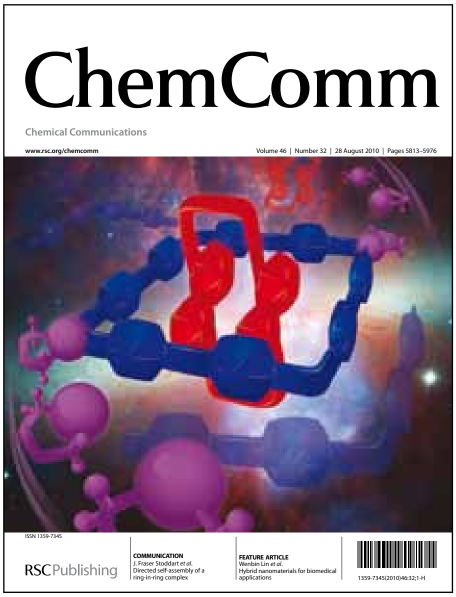

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ARTICLE TYPE

Palladium-Catalyzed Oxidative Direct C-H/C-H Cross Coupling of Anilides with *β*-Keto Esters

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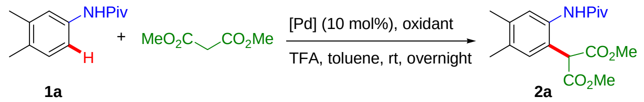
A Pd(II)-catalyzed oxidative direct C(sp^2)-H/C(sp^3)-H cross coupling of anilides with *α*-dicarbonyl compounds with Mn(OAc)$_3$·2H$_2$O as oxidant is reported and this protocol provides a facile access to *α*-aryl malonates and *β*-keto esters in good yields and regioselectivity.

Transition metal-catalyzed oxidative cross coupling reactions for C-C bond formation via twofold direct C-H activation (termed cross dehydrogenative coupling, CDC) are attracting extensive investigation.[1] With the coupling of unfunctionalized hydrocarbons, the CDC reaction is a promising approach for the design of highly atom-economical transformations. In this regard, palladium has been the catalyst of choice for many investigations. Since the pioneering works by Fujiwara and co-workers on the Pd-catalyzed oxidative aromatic C-H alkenylation,[2] remarkable advances have been made by many research groups on dehydrogenative C(sp^2)-H/C(sp^2)-H cross-coupling of (hetero)arenes with alkenes[3] or arenes[4] via Pd(II)/Pd(0) catalysis. However, the analogous examples of structurally different hydrocarbons involving C(sp^2)-H/C(sp^3)-H bond cross coupling are sparse in the literature.[5]

Recently, we[6] and others[7] reported the Pd-catalyzed oxidative arene acylations based on cross coupling of arenes with aldehydes with *tert*-butyl hydroperoxide (TBHP) as oxidant. The acylation reactions should involve two distinct C-H activation processes: (1) arene C-H palladation to form arylpalladium(II) complexes, and (2) oxyradical-mediated hydrogen atom abstraction of the aldehyde C-H bond to form acyl radicals. The subsequent coupling of the acyl radicals with the arylpalladium complexes should bring about the C-C bond formation. Inspired by these results, we envisioned that the analogous cross coupling reaction of arylpalladium(II) complex with a *α*-dicarbonylalkyl radical [•CH(COR)$_2$] would lead to the formation of *α*-aryl dicarbonyl compounds.[8] Herein we report a mild Pd(II)-catalyzed direct *α*-arylation of 1,3-dicarbonyls with anilides by cross dehydrogenative coupling reaction using Mn(OAc)$_3$·2H$_2$O as stoichiometric oxidant.

At the outset, we examined the reaction of 3,4-dimethyl-*N*-pivalanilide (**1a**, 0.2 mmol) and dimethyl malonate (6 equiv.) in the presence of Pd(OAc)$_2$ (10 mol%), trifluoroacetic acid (TFA) (0.5 equiv.) and TBHP (2 equiv.) as oxidant with dioxane or toluene as solvent. No significant product formation was observed despite standing the mixture for overnight at room temperature or at 80 °C (Table 1, entries 1 – 2). Gratifyingly, when Mn(OAc)$_3$·2H$_2$O (1 equiv.) was employed as oxidant, the "**1a** + dimethyl malonate" reaction at room temperature furnished the arylmalonate **2a** in 17% yield (entry 3). The molecular structure of a di-*tert*-butyl arylmalonate derivative **2c** has been established by X-ray crystallography (see Figure S44 in ESI). Other palladium catalysts such as Pd(TFA)$_2$ and Pd(OTs)$_2$(MeCN)$_2$ did not give significant improvement (entries 4 – 5). After several trials, we found that employing 2 equiv. of TFA would improve the product yield to 41% (entry 6). In order to achieve a sustained supply of the malonate radicals over the reaction time, reagents were added to the reaction mixture in a batchwise fashion. Thus, when **1a** was treated with dimethyl malonate (3 × 3 equiv./4 h), Pd(OAc)$_2$ (10 mol%), Mn(OAc)$_3$·2H$_2$O (3 × 50 mol%/4 h) and TFA (3 × 3 equiv./4 h) in toluene (1.5 mL) at room temperature, **2a** was obtained in 85% yield (entry 9). Notably, no **2a** formation was observed in the absence of the Pd catalyst (entry 10).

Table 1 Reaction Optimizations[a]

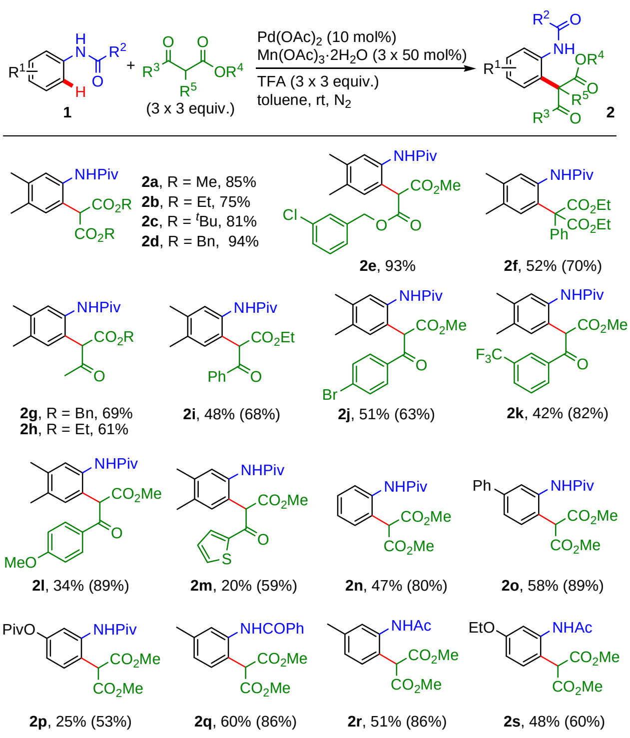


Entry	Pd catalyst	Malonate (equiv.)	Oxidant (equiv.)	TFA (equiv.)	Yield[b] (%)
1[c]	Pd(OAc)$_2$	6	TBHP (2)	0.5	0
2[d]	Pd(OAc)$_2$	6	TBHP (2)	0.5	0
3	Pd(OAc)$_2$	6	Mn(OAc)$_3$ (1)	0.5	17
4	Pd(TFA)$_2$	6	Mn(OAc)$_3$ (1)	0.5	18
5	Pd(OTs)$_2$(MeCN)$_2$	6	Mn(OAc)$_3$ (1)	0.5	16
6	Pd(OAc)$_2$	3	Mn(OAc)$_3$ (1)	2	41
7[e]	Pd(OAc)$_2$	2 × 3 equiv.	[Mn] (2 × 50 mol%)	2 × 3 equiv.	72
8[e]	Pd(OAc)$_2$	2 × 3 equiv.	[Mn] (2 × 50 mol%)	2 × 3 equiv.	80
9[e,f]	Pd(OAc)$_2$	3 × 3 equiv.	[Mn] (3 × 50 mol%)	2 × 3 equiv.	85
10[e]	none	3 × 3 equiv.	[Mn] (3 × 50 mol%)	2 × 3 equiv.	0

[a] Reaction conditions: **1a** (0.2 mmol), dimethyl malonate, Pd catalyst (10 mol%), TBHP or Mn(OAc)$_3$·2H$_2$O as oxidant, TFA, toluene (1.5 mL) at room temperature under N$_2$ for overnight. [b] Yields are determined by ^{1}H NMR. [c] Dioxane was used as solvent. [d] 80 °C instead of rt. [e] Batchwise addition interval 4 h. [f] Isolated yield.

With the optimized conditions in hand, various malonates and keto esters were examined for the Pd-catalyzed direct C-H arylation (Table 2). A series of dialkyl malonates such as ethyl, *tert*-butyl malonates would successfully transform **1a** to the corresponding arylmalonates **2b** and **2c** in good yields. When malonates bearing more sterically hindered benzyl group were used as coupling partner, **2d** and **2e** were obtained in 93–94% yields. Notably, diethyl phenylmalonate was also effective for the coupling reaction**,** and α,α-biarylmalonate **2f** bearing a quaternary carbon was obtained in 52% yield. Based on their smaller pKa's comparing to the malonates,[9] β-keto esters should be effective coupling partners. Notwithstanding, the corresponding coupling with **1a** produced **2g**–**2m** in 20–69% yields. The lower anilide conversion was attributed to the incompatibility of the rate of arene C-H palladation and the Mn-mediated radical generation.

Table 2 Substrate scope study[a,b]



[a] Reaction conditions: **1** (0.2 mmol), 1,3-dicarbonyls (3 × 3 equiv. / 4 h), $Pd(OAc)_2$ (10 mol%), $Mn(OAc)_3\cdot 2H_2O$ (3 × 50 mol% / 4 h), TFA (3 × 3 equiv. / 4 h), toluene (1.5 mL) at room temperature under N_2 for overnight. [b] Isolated yields; percentage yield based on anilide conversion is given in parentheses.

The scope of the anilides was also investigated, and the Pd-catalyzed direct C-H activation was found to be sensitive to the substituent effects. For example, pivalanilides bearing other *meta*-substituents (H, Ph and OPiv) reacted with dimethyl malonate to give **2n**–**2p** in 25–58% yields. As anticipated, benzamido and acetamido are capable directing groups for the *ortho* C-H coupling reactions to give **2q**–**2s** in 48–60% yields.

Next, we sought to apply this coupling reaction for the synthesis of indoles. For instance, treating **2g** and **2h** (0.2 mmol) with concentrated HCl (0.1 mL) and EtOH (5 mL) under reflux for 0.5 h afforded the unprotected indole **3g** and **3h** in 73 and 69% yield, respectively (Scheme 1).

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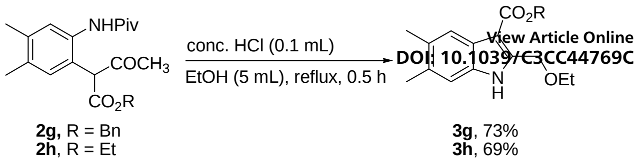
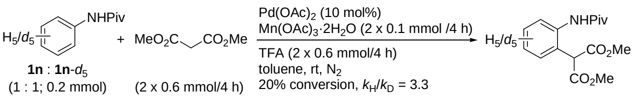
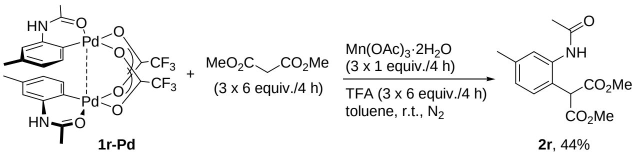


Scheme 1 Synthesis of unprotected indole **3g** and **3h**.

The Pd-catalyzed oxidative coupling reaction exhibits a primary KIE (k_H/k_D) of 3.3 based on the competitive experiments using an equimolar amount of **1n** and **1n**-d_5 (Scheme 2).[10] In addition, a cyclopalladated complex **Pd-1r** was prepared according to the literature.[4g] In this work, the stoichiometric reaction of **Pd-1r** and dimethyl malonate in presence of $Mn(OAc)_3\cdot 2H_2O$ and TFA in toluene at room temperature produced the corresponding product **2r** in 44% yield (Scheme 3). This result suggested that the Pd-catalyzed coupling reaction is likely to proceed via the cyclopalladated complex, which is formed by the rate-limiting arene C-H activation.



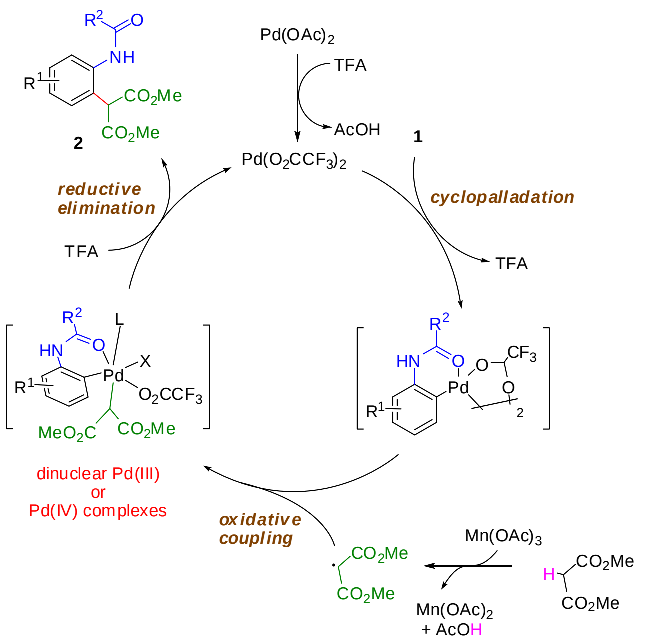
Scheme 2 Kinetic isotope effect study.



Scheme 3 Stoichiometric reaction of **Pd-1r** with dimethyl malonate.

Scheme 4 depicts a plausible mechanism for the Pd-catalyzed direct C-H α-arylation of the 1,3-dicarbonyl compounds. In the presence of an excess amount of TFA, $Pd(OAc)_2$ should undergo ligand exchange to form $Pd(TFA)_2$. Coordination of **1** with $Pd(TFA)_2$, followed by the rate-limiting C-H activation, afforded the six-membered palladacycle with the elimination of TFA. Since oxidation of dicarbonyl compounds by $Mn(OAc)_3\cdot 2H_2O$ is known to generate enolate radicals,[11] we hypothesized that the enolate radicals would couple with the palladacycle to give some either the dinuclear Pd(III)[12] or Pd(IV)[13] complexes. Reductive elimination of the high valent Pd species would give the desired arylmalonate.

In conclusion, we have described a Pd-catalyzed direct C-H/C-H cross coupling of 1,3-dicarbonyl compounds and anilides. With $Mn(OAc)_3\cdot 2H_2O$ as oxidant, arylmalonates were obtained in good yields and regioselectivity. A mechanism involving the coupling of cyclopalladated complex with carboradical is proposed. The reaction can be performed under mild conditions without addition of base and provides a easy route to α-aryl carbonyl compounds. Comprehensive mechanistic studies are underway.



Scheme 4 Proposed mechanism.

Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedure, ^{1}H and ^{13}C NMR spectra and analytical data for all the compounds; crystallographic data for **2c**. CCDC 946973. For ESI and crystallographic in CIF and other electronic format see DOI: 10.1039/b000000x/

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