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Pd(II)-Catalyzed Carbonylation of C(sp^3)−H Bonds: A New Entry to 1,4-Dicarbonyl Compounds

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Abstract: Pd(II)-catalyzed β-C(sp^3)−H carbonylation of *N*-arylamides under CO (1 atm) has been achieved. Following amide-directed C(sp^3)−H cleavage and insertion of CO into the resulting [Pd(II)−C(sp^3)] bond, intramolecular C−N reductive elimination gave the corresponding succinimides, which could be readily converted to 1,4-dicarbonyl compounds. This method was found to be effective with substrates containing α-hydrogen atoms and could be applied to effect methylene C(sp^3)−H carbonylation of cyclopropanes.

The development of diverse transformations using Pd catalysis to functionalize unactivated β-C(sp^3)−H bonds in aliphatic acids and their amide derivatives could offer a new strategy for synthesizing molecules with complex tertiary and quaternary carbon centers.[1−3] To broaden the scope of this approach, we have reported a variety of novel C−C and C−heteroatom bond-forming reactions.[1,3b] We envisioned that a reaction to effect β-carbonylation of C(sp^3)−H bonds would be a highly desirable addition to our collection of transformations because replacement of C−H bonds by a highly oxidized carbonyl group installs a versatile handle for further structural elaboration. For example, β-carbonylation of aliphatic acids would provide a novel route to synthetically important 1,4-dicarbonyl compounds[4,5] that are widespread in biologically important natural products (Figure 1).[6]

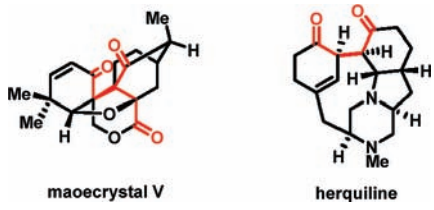
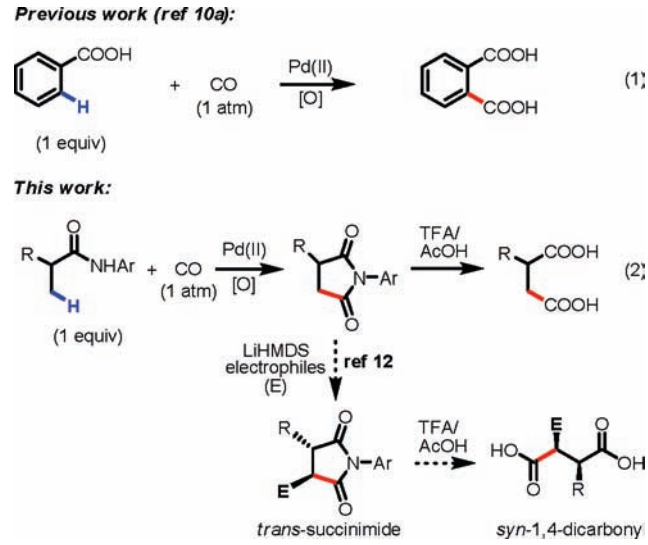


Figure 1. Natural products that contain 1,4-dicarbonyl moiety.

Despite landmark developments in Pd(0)-catalyzed carbonylation of aryl halides, triflates, and tosylates[7] and recent progress on Pd(II)-catalyzed carbonylation of aryl C(sp^2)−H bonds (eq 1),[8−11] Pd(II)-catalyzed C(sp^3)−H carbonylation reactions that use the substrate as a limiting reagent have yet to be reported. Herein, we disclose a protocol for Pd(II)-catalyzed β-C(sp^3)−H carbonylation of aliphatic amides to give succinimides which are readily hydrolyzed to afford broadly useful 1,4-dicarbonyl compounds (eq 2). The succinimide intermediates are also well-established synthons for preparation of *syn*-disubstituted 1,4-dicarbonyl compounds through regioselective and diastereoselective enolate chemistry (eq 2).[12] TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) was found to be a crucial co-oxidant for efficient reoxidation of Pd(0) to Pd(II) in the presence of CO.



Early reports by Fujiwara described a Pd-catalyzed C(sp^3)−H carbonylation reaction of alkanes (used in excess) under CO (20 to 50 atm) using $K_2S_2O_8$ as the reoxidant in TFA at 80 °C, which gave a regioisomeric mixture of the corresponding carboxylic acid products.[13] The use of excess substrate and the lack of regioselectivity limited the usefulness of this chemistry for synthetic applications. Although regioselective C(sp^2)−H carbonylation using 1 equiv of substrate under CO (1 atm) has been accomplished[8−11] through the use of proximate directing groups, extending this approach to C(sp^3)−H carbonylation represents a significant challenge. One major obstacle is that excess CO inhibits the activation of the inert C(sp^3)−H bonds by competitively occupying coordination sites on the Pd(II) center, thereby preventing the requisite C−H agostic interaction. In addition, both the insertion of CO into a [Pd(II)−C(sp^3)] cyclopalladated intermediate and reductive elimination from Pd involving a C(sp^3)−CO moiety have a limited number of precedents.[14]

With these considerations in mind, we initiated our investigation of Pd-catalyzed C(sp^3)−H carbonylation by first identifying a highly efficient directing group for facile C(sp^3)−H activation. Recently, our group established that acidic amides are superior directing groups for promoting C−H activation reactions with both Pd(0)/PR_3 and Pd(II) catalysts.[1c,d] We therefore focused our efforts on using acidic amide substrates for our exploratory studies (Table 1).

Gratifyingly, we observed that **1a** could be transformed into the desired carbonylation product **2a** in 30% yield (based on ^{1}H NMR), using $Pd(OAc)_2$ (10 mol %) as the catalyst, AgOAc (2 equiv) as the oxidant, and KH_2PO_4 as the base, under CO (1 atm) in *n*-hexane at 130 °C (Table 1, entry 4). Following 1,1-migratory insertion to forge the C(sp^3)−CO bond, the Pd intermediate undergoes Pd-

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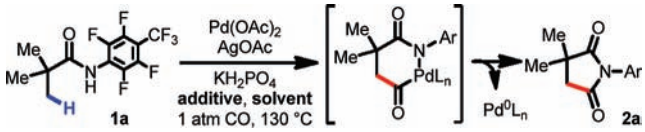
Table 1. Optimization of Reaction Conditions for Pd-Catalyzed C(sp^3)−H Carbonylation[a]



entry	additive	solvent	yield (%)[b]	entry	additive	solvent	yield (%)[b]
1	none	DMF	<1	6	$Cu(OAc)_2$	*n*-hexane	4
2	none	toluene	7	7	DMF	*n*-hexane	54
3	none	C_6F_6	8	8	PivOH	*n*-hexane	50
4	none	*n*-hexane	30	9	TEMPO[c]	*n*-hexane	80
5	BQ	*n*-hexane	13	10	TEMPO	*n*-hexane	95

[a] Reaction conditions: **1a** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (2.0 equiv), KH_2PO_4 (2.0 equiv), additive (2.0 equiv), solvent (1 mL), CO (1 atm), 130 °C, 18 h. [b] The yield was determined by ^{1}H NMR analysis of the crude product using 1,1,2,2-tetrachloroethane as an internal standard. [c] TEMPO (0.2 equiv).

mediated C−N reductive elimination to give the corresponding succinimide products.

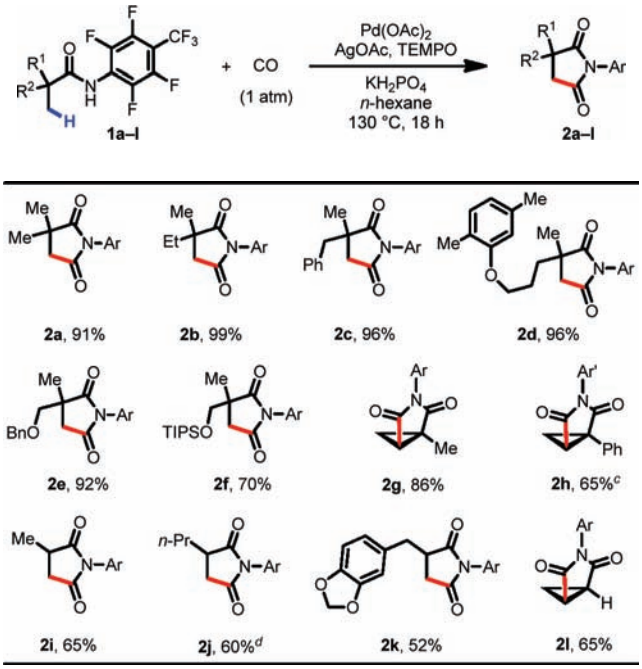
After surveying a wide array of organic solvents, we observed that *n*-hexane gave the best reactivity. This finding was unexpected, as *n*-hexane has rarely been an effective solvent in our previous C−H activation reactions.[1] Several additives that are known to positively influence Pd-catalyzed C−H functionalization reactions (e.g., 1,4-benzoquinone and $Cu(OAc)_2$) were tested; however, they proved to be incompatible with the reaction conditions (entries 5 and 6). Among the other additives tested, DMF (2 equiv) increased conversion to 54% (entry 7), and pivalic acid improved the yield to 50% (entry 8). Further screening of the additives revealed that the addition of a catalytic amount of TEMPO (0.2 equiv) as a co-oxidant with AgOAc dramatically improved the conversion to over 80% (entry 9). Although the precise role of TEMPO remains to be elucidated, one plausible explanation is that oxoammonium salt[15] (the oxidized form of TEMPO) reoxidizes Pd(0) to Pd(II) more efficiently than solely AgOAc. A stoichiometric amount of both TEMPO and AgOAc is required to achieve full conversion; using 2.0 equiv of TEMPO and AgOAc increased the yield to 95% (entry 10), while using 2.0 equiv of TEMPO gave only 12% conversion (see Supporting Information (SI)).

Notably, other directing groups that have previously been utilized in our laboratory for C(sp^3)−H activation, such as carboxylic acids, hydroxamic acids, oxazolines, and pyridines, were unreactive under these conditions. An analogous acidic directing group *N*-toluenesulfonyl amide (CONHTs),[16] however, gives a corresponding product in lower yield (63%, see SI).

With the optimized conditions in hand, we converted a range of commercial aliphatic acids into the corresponding CONHAr amides to examine the scope of this carbonylation protocol (Table 2). Substrates with a quaternary α-carbon atom gave good to excellent yields of the succinimide products (**2a**−**h**). Products containing ether groups (**2d**−**f** and **2k**) could also be obtained in good yields. The benzyl moiety proved to be a better protecting group than the TIPS group for *β*-hydroxyl substrates (**1e** and **1f**), while TBS-protected substrates gave none of the desired product. Notably, this method was also effective for the carbonylation of methylene C−H bonds in cyclopropane substrates (**2g**, **2h**, and **2l**). Intriguingly, cyclopropyl C(sp^3)−H bonds could be selectively carbonylated over a methyl C(sp^3)−H bond (in **1g**) and an *ortho* aryl C(sp^2)−H bond (in **1h**).

In our early efforts to develop C(sp^3)−H functionalization reactions with aliphatic carboxylic acids and their derivatives, substrates containing α-hydrogen atoms were often unreactive,

Table 2. Substrate Scope for C(sp^3)−H Carbonylation[a,b]

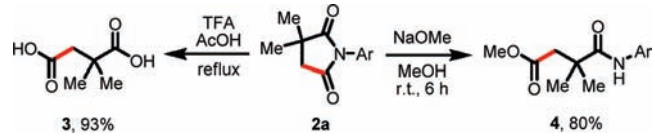


[a] Reaction conditions: amide substrate **1** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), TEMPO (2.0 equiv), AgOAc (2.0 equiv), KH_2PO_4 (2.0 equiv), *n*-hexane (1 mL), CO (1 atm), 130 °C, 18 h. [b] Isolated yield. [c] Ar′ = C_6F_5. [d] $Pd(OAc)_2$ (20 mol %).

restricting the substrate scope to those containing quaternary α-carbon atoms. We were pleased to find that, in the present study, carbonylated products **2i**−**l** could be obtained in acceptable yields from substrates containing α-hydrogen atoms. These types of products are highly valuable synthons for the preparation of 1,4-dicarbonyl compounds.[4−6]

To demonstrate the synthetic utility of this reaction, succinimide product **2a** was subjected to two different ring-opening conditions to obtain either 1,4-dicarboxylic acid **3** or 1,4-dicarbonyl molecule **4** (Scheme 1). Upon treatment of **2a** with TFA/AcOH under reflux, hydrolysis occurs to give 2,2-dimethylsuccinic acid **3** in 93% isolated yield. Similarly, treatment of **2a** with NaOMe in methanol at room temperature gave 80% of the ester product **4** without concomitant hydrolysis of the amide moiety; thus this group could potentially be used to direct further elaboration of the *gem*-dimethyl unit *via* Pd-catalyzed C−H functionalization.

Scheme 1. Ring-Opening of Succinimides



In summary, we have developed a novel protocol to effect carbonylation of C(sp^3)−H bonds under CO (1 atm). Studies to expand the scope of the reaction to simple carboxylic acid substrates and to develop an enantioselective variant for substrates containing *gem*-dimethyl or cyclopropyl groups are currently underway in our laboratory.

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Research Foundation of Korea Grant funded by the Korean Government (NRF-2009-352-C00077). We also thank Bristol Myers Squibb for a predoctoral fellowship (M.W.).

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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