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

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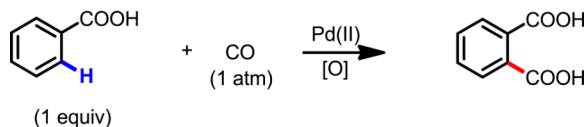
Abstract

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 reductive amination 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 wide spread in biologically important natural products (Figure 1).⁶

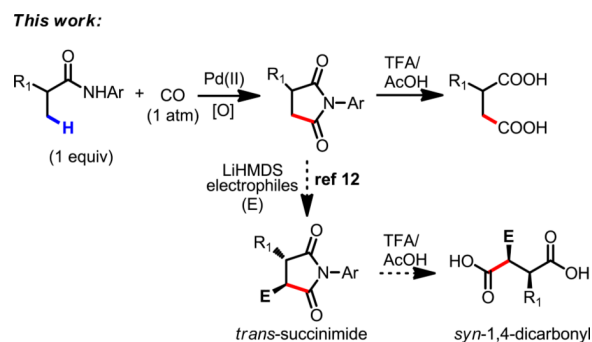
Despite landmark developments in Pd(0)-catalyzed carbonylation of aryl halides, triflates and tosylates⁷ and recent progress on Pd(II)-catalyzed carbonylation of aryl C(sp^2)–H bonds (eq 1),^{8–11} Pd(II)-catalyzed C(sp^3)–H carbonylation reactions that use the substrate as limiting reagent have yet 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 was found to be a crucial co-oxidant for efficient reoxidation of Pd(0) to Pd(II) in the presence of CO.

Previous work (ref 10a):



(1)

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(2)

Early reports by Fujiwara described a Pd-catalyzed $C(sp^3)$ -H carbonylation reaction of gaseous 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 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 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 group for promoting C-H activation reactions with both Pd(0)/ PR_3 and Pd(II) catalysts.^{1c,1d} 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 1H 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 intermediate undergoes Pd-mediated reductive amination 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 (2,2,6,6-Tetramethylpiperidine-1-oxyl) (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 salt¹⁵ (the oxidized form of TEMPO) reoxidizes Pd(0) to Pd(II) more efficiently than solely AgOAc. Stoichiometric amount of both TEMPO and AgOAc is required to achieve full conversion; using 2.0 equiv of TEMPO and AgOAc increased yield to 95% (entry 10), while using 2.0 equiv of TEMPO gave only 12 % conversion (see Supporting Information).

Notably, other directing groups that have previously been utilized in our laboratory for C(sp³)-H activation, such as carboxylic acids, hydroxamic acids, oxazolines, and pyridines, were unreactive under these optimized conditions. An analogous acidic directing group *N*-toluenesulfonyl amide (CONHTs), however, gives 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. 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 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(sp³)-H bonds could be selectively carbonylated over a methyl C(sp³)-H bond (in **1g**) and an *ortho* aryl C(sp²)-H bond (in **1h**).

In our early efforts to develop C(sp³)-H functionalization reactions with aliphatic carboxylic acids and their derivatives, substrates containing α -hydrogen atoms were often unreactive, 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 preparation of 1,4-dicarbonyl compounds.⁴⁻⁶

To demonstrate the synthetic utility of this reaction, succinimide product **2a** was subjected to 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.

In summary, we have developed a novel protocol to effect carbonylation of C(sp³)-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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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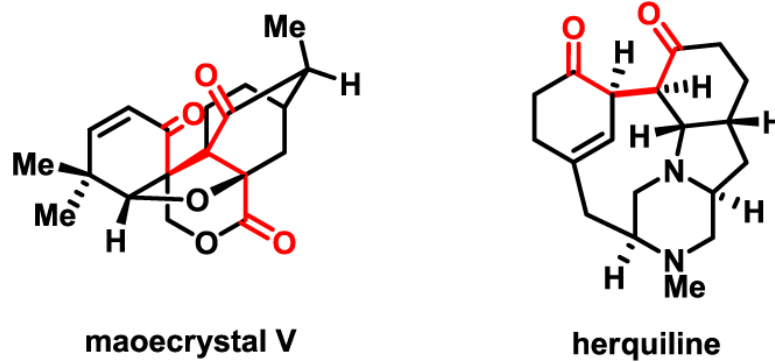
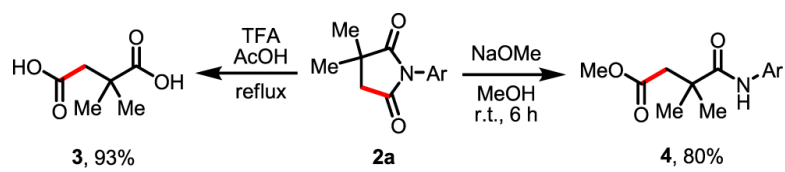
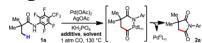


Figure 1.
Natural products that contain 1,4-dicarbonyl moieties.



Scheme 1.
Ring Opening of Succinimides

Table 1Optimization of Reaction Conditions for Pd-Catalyzed C(sp³)-H Carbonylation^a

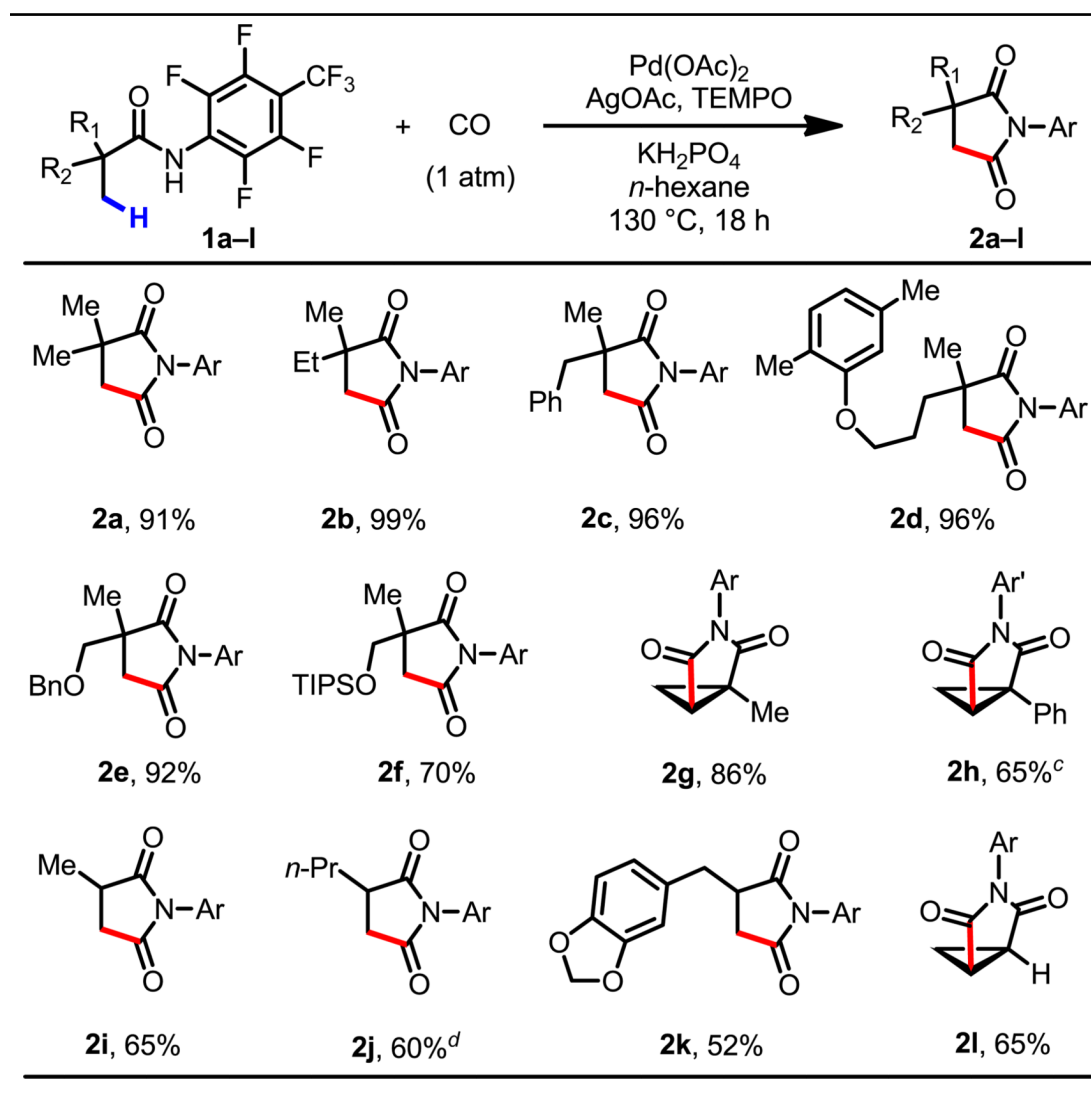
entry	additive	solvent	yield (%) ^b
1	none	DMF	<1
2	none	toluene	7
3	none	C ₆ F ₆	8
4	none	<i>n</i> -hexane	30
5	BQ	<i>n</i> -hexane	13
6	Cu(OAc) ₂	<i>n</i> -hexane	4
7	DMF	<i>n</i> -hexane	54
8	PivOH	<i>n</i> -hexane	50
9	TEMPO ^c	<i>n</i> -hexane	80
10	TEMPO	<i>n</i> -hexane	95

^aReaction conditions: **1a** (0.1 mmol), Pd(OAc)₂ (10 mol %), AgOAc (2.0 equiv), KH₂PO₄ (2.0 equiv), additive (2.0 equiv), solvent (1 mL), CO (1 atm), 130 °C, 18 h.

^bThe yield was determined by ¹H NMR analysis of the crude product using 1,1,2,2-tetrachloroethane as an internal standard.

^cTEMPO (0.2 equiv).

Table 2

Substrate Scope for C(sp³)-H Carbonylation^{a,b}

^aReaction conditions: amide substrate **1** (0.1 mmol), Pd(OAc)₂ (10 mol %), TEMPO (2.0 equiv), AgOAc (2.0 equiv), KH₂PO₄ (2.0 equiv), *n*-hexane (1 mL), CO (1 atm), 130 °C, 18 h.

^bIsolated yield.

^cAr' = C₆F₅.

^dPd(OAc)₂ (20 mol %).