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ARTICLE

Cobalt Catalyzed Carbonylation of Unactivated C(sp^3)-H bonds

Nagaraju Barsu,[a] Shyam Kumar Bolli,[a] Basker Sundararaju[a,]*

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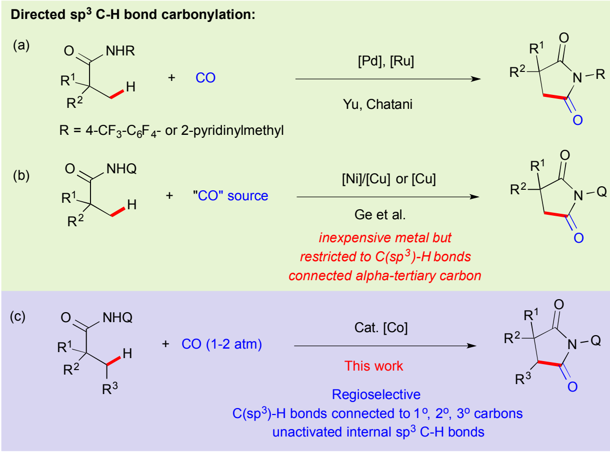
A, general efficient, regioselective cobalt catalyzed carbonylation of unactivated C(sp^3)-H bond of aliphatic amide was demonstrated using atmospheric (1-2 atm) carbon monoxide as a C1 source. This straightforward approach provides access to α-spiral succinimide regioselectively in good yield. Cobalt catalyzed sp^3 C-H bond carbonylation is reported for the first time including the functionalization of (β)-C-H bonds of α-1°, 2°, 3° carbons and even internal (β)-C-H bonds. Our initial mechanistic investigation reveals that the C-H activation step is irreversible and will possibly be the rate determining step.

Introduction

Catalytic carbonylation is one of the most straightforward processes for the production of carbonyl compounds both in academia and Industry.[1] Insertion of CO into the carbon-hydrogen bonds became even more interesting provided that the catalyst has the ability to activate both inert C-H bonds and to bind π-acidic carbon monoxide.[2] In this regard, Shunsuke Murahashi reported the first effective catalytic C-H carbonylation of benzaldimine in 1955 using low valent cobalt (0) complex.[3] Since then, several reports were documented for catalytic C(sp^2)-H bond carbonylation.[4] However the corresponding extension to carbonylation of C(sp^3)-H bond is rare and only a handful of examples were reported in the literature.[5] After pioneering work of Tanaka et al. for photo catalytic carbonylation of alkanes,[6] Chatani reported the directing group assisted C-H carbonylation of α-C(sp^3)-H bonds adjacent to nitrogen.[7] In 2010-11, Yu and Chatani independently reported the site-selective C(sp^3)-H carbonylation of aliphatic amide using Pd and Ru based catalysts, while the former used oxidative conditions, the later proceeded through a metal-hydride pathway (Scheme 1a).[8,9,10] We assumed that it would be more rational to choose a metal abundantly present in nature compared to precious metals in terms of cost effectiveness and unexploited inherent properties exhibited by them.[11] Utilization of 8-aminoquinoline as a bidentate auxiliary for C-H bond functionalization was first reported by Daugulis,[12] later developed by Chatani[13] and others[14] for several profitable applications using first row late transition metal precursors.

Using this approach, Ge et. al. reported recently the carbonylation of unactivated C(sp^3)-H bonds with Ni-Cu/Cu as a catalyst using DMF and nitromethane as a carbonyl sources.[15] But presented Nickel-Copper / Copper catalyzed carbonylation limited to β-C(sp^3)-H bonds connected to α-tertiary carbon (Scheme 1b). On the other hand, cobalt seems to be a very promising alternative metal catalyst for various C(sp^2)-H bond functionalization.[11a-b,16] Very recently Ge and Zhang independently reported cobalt catalyzed intramolecular cyclization through activation of directed C(sp^3)-H bonds.[17] Daugulis reported lately, cobalt catalyzed *o*-C(sp^2)-H bond carbonylation of benzamides at room temperature.[16n] We have previously demonstrated the activation of C(sp^3)-H bonds using Cp*Co(III) for C-H alkenation with alkynes and C-H amidation with oxazolone.[18] Inspired by these results and based on our continuous efforts on the development of cobalt catalyzed C-H bond functionalization,[19] we report herein the first regio- and site-selective cobalt catalyzed carbonylation of unactivated C(sp^3)-H bonds including terminal and internal C-H bond connected α-1°, 2° and 3° carbons (Scheme 1c).

Scheme 1: Carbonylation of Unactivated C(sp^3)-H bonds



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[a] Fine Chemical Laboratory, Department of Chemistry,
Indian Institute of Technology Kanpur, Kanpur, Uttar Pradesh, India.

† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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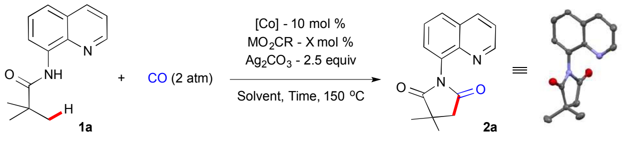
Results and discussion

We began our investigation using aliphatic amide **1a** and 2 atm CO gas as a C1 source with catalytic amount of simple $Co(OAc)_2$, metal carboxylate and silver carbonate as an oxidant at 150°C for 36 h in chlorobenzene (0.5 mL) and the optimization results are summarized in Table 1. Initial screening of different metal carboxylate revealed that good yield of **2a** was obtained with sodium benzoate (50 mol%) as an additive, which is also an optimal reaction parameter for intramolecular β-sp^3 C-H bond amidation[17a] (Table 1, entry 1-4). Lowering the reaction concentration did not provide any further improvement (entry 5). Small amount of sodium benzoate turned out to be crucial for high product formation with cobalt(II) (entry 6-7).

Table 1: Optimization studies and control experiments[a]



Entry	[Co]	MCO_2R (mol %)	Oxidant	Yield[b]
1	$Co(OAc)_2$	NaOPiv (50)	Ag_2CO_3	27
2	$Co(OAc)_2$	$Mn(OAc)_3$ (50)	Ag_2CO_3	n.r.
3	$Co(OAc)_2$	NaO_2CPh (50)	Ag_2CO_3	67
4	$Co(OAc)_2$	NaO_2CMes (50)	Ag_2CO_3	49
5	$Co(OAc)_2$	NaO_2CPh (50)	Ag_2CO_3	53[c]
6	$Co(OAc)_2$	NaO_2CPh (100)	Ag_2CO_3	43
7	$Co(OAc)_2$	NaO_2CPh (20)	Ag_2CO_3	76
8	$Co(OAc)_2$	NaO_2CPh (20)	Ag_2CO_3	70[d]
9	$Co(OAc)_2$	NaO_2CPh (20)	Ag_2CO_3	79[d,e]
10	$Co(OAc)_2$	NaO_2CPh (20)	Ag_2CO_3	87[d,f]
11	$Co(acac)_2$	NaO_2CPh (20)	Ag_2CO_3	86[d,f]
12	$Co(acac)_3$	NaO_2CPh (20)	Ag_2CO_3	87[d,f]
13	$Co_2(CO)_8$	NaO_2CPh (20)	Ag_2CO_3	68[d,f]
14	$CoBr_2$	NaO_2CPh (20)	Ag_2CO_3	61[d]
15	$Co(acac)_2$	NaO_2CPh (20)	Ag_2CO_3	95[d,g]
16	$[Co(Piv)_2]_2$	-	Ag_2CO_3	55[d,g]
17	$Co(acac)_3$	-	Ag_2CO_3	92[d,g]

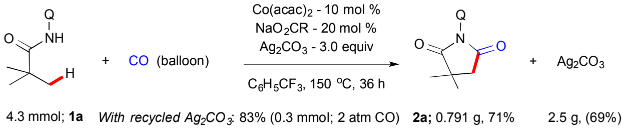
[a] All reactions reagents were added under argon atmosphere unless otherwise stated using **1a/**$[Co]/NaO_2CR/Ag_2CO_3$ in 0.2/0.02/0.02-0.05/0.5 mmol using chlorobenzene (0.5 mL) as solvent at room temperature and then pressurized with CO (2 atm) at 150 °C for 36 h. [b] Isolated yield [c] 1 mL of PhCl was used. [d] Reaction performed for 24 h. [e] 20 mol % of [Co] was used. [f] 3 equiv. of Ag_2CO_3 was used. [g] TFT (0.5 mL) was used as a solvent.

There was no significant change in yield when the reaction time was reduced to 24 h or by increasing the catalyst loading to 20 mol% (entries 8-9). To our delight, small increment in the silver carbonate gave excellent product formation after 24 h (entry 10). Next, we examined the various cobalt sources from different oxidations states. It was revealed that Co(II) and Co(III) gave excellent yields whereas Co (0) and $Co(II)Br_2$ gave moderate yield (entries 11-14). After brief solvent screening,[20] we found out that α, α, α-trifluorotoluene (TFT) was the best solvent, which provided 95 % of the succinimide **2a** under our optimized reaction parameters (entry 15). Well-defined, isolated cobalt-pivalate dimer[21] was used as a catalyst without any additive resulted in 55% yield (entry 16). We further confirmed that the direct use of Co(III) precursor in the absence of the sodium benzoate provide **2a** in 92% yield and structure of **2a** was confirmed by X-ray (entry 17).[22]

Prior to the scope of the reaction, we examined the scalability of the reaction. A gram scale reaction was performed with **1a** using atmospheric CO gas provides succinimide **2a** in 71% yield after 36 h (Scheme 2) and silver carbonate was regenerated from the residue in 69% (2.5 g) yield using the known literature procedure.[16e, 23] The recycled silver carbonate was used for C-H carbonylation resulted in 83% of **2a** under standard conditions (Scheme 2).

With the optimized conditions in hand, we next investigated the scope of the aliphatic amide and the results are depicted in scheme 3. Architecturally interesting spiral succinimide possessing 4-, 5-, 6-membered ring on the backbone was achieved in good yields (**2b-d**). Replacing one of the methyl group from **1a** by benzyl, 4-OMe-benzyl, cyclopentyl, isopropyl and alkyl chain at α-tertiary center gave desired succinimide in high yields (**2e-j**). Phenyl, ester, -Br substituents on the backbone were tolerated (**2k-m**). Next, the reactivity difference between $C(sp^2)$-H and $C(sp^3)$-H bond was investigated for cyclocarbonylation. It was found out that carbonylation of unactivated $C(sp^3)$-H bond was favoured over $C(sp^2)$-H bond (**2n-o**) and only **2o’** was obtained in 15% yield in addition to the **2o** (50%). This may be due to the fact that the former proceeds via facile 5-membered cyclocobaltation while the later proceeds through 6-membered metallocycle. Further, we explore the possibility of activating β-$C(sp^3)$-H bonds next to α-secondary and primary carbon center, which is much more challenging (not explored before for carbonylation using first row transition metals) than C-H bond next to α-tertiary carbon. Gratifyingly, propanamide (**1p**) and α -methylpropanamide (**1q**) underwent cyclocarbonylation albeit in moderate yield (**2p, 2q**) but the mass of the product can be improved if we prolong the reaction to 36 h with 20 mol% cobalt catalyst.

Scheme 2: Gram Scale synthesis of succinimide



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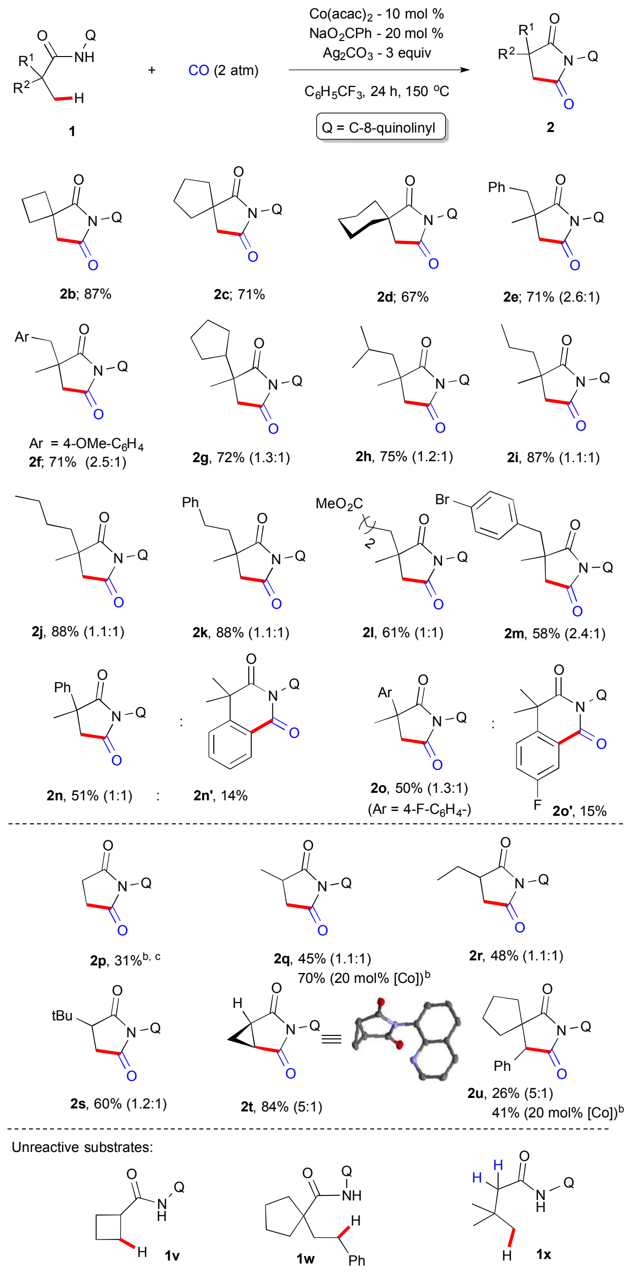
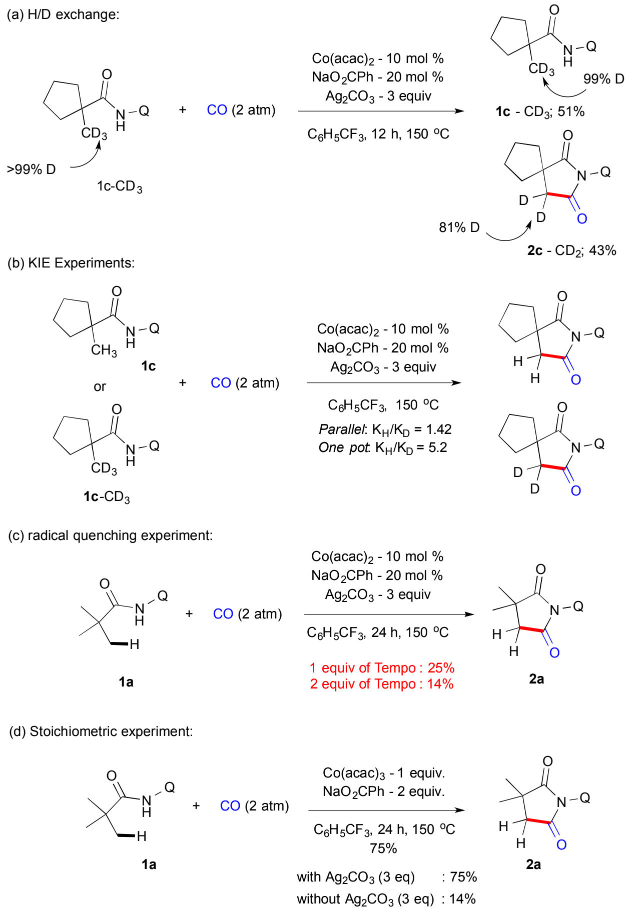
Systematic increase of bulkiness by incorporating -Et and -^{t}Bu group did not significantly alter the isomeric ratio (**2r-s**). Further to our delight, internal C(sp^3)-H bond was carbonylated in the case of **1t** and **1u**, it resulted in the formation of substituted and structurally strained succinimide (**2t** & **2u**) and X-ray further confirmed structure of **2t**.[22] The reactivity of **1u** was documented for the first time via internal β-C(sp^3)-H carbonylation. To understand the reaction mechanism, several experiments were carried out as displayed in Scheme 4.

Scheme 3: Scope and limitation



^{a}number in parenthesis is the ratio of diastereomer. ^{b}36 h instead of 24 h. ^{c} PhCl as a solvent



Scheme 4: H/D exchange, KIE and Control experiments

1c-CD$_3$ employed under our reaction conditions gave the corresponding carbonylation product **2c-CD$_2$** (43%) along with recovered starting material **1c**-CD$_3$ (51%) after 12 h (Scheme 4a). Analysis of the isolated compound revealed that **1c**-CD$_3$ did not have any H/D exchange, which indicates that the C-H activation step is irreversible. KIE value of 1.42 and 5.2 were determined from parallel and one-pot experiments using **1c**-CH$_3$ and **1c**-CD$_3$ (Scheme 4b). This value possibly suggests that the cleavage of C-H bond is the rate-determining step. Next, we have performed a series of control experiments. e.g. addition of stoichiometric amount radical scavenger such as of TEMPO (1eq), which drastically reduces the yield of **2a**, which further reduced to 14% when 2 equiv. of TEMPO was employed (Scheme 4c). Although there is no adduct possible to isolate from the mixture, the present result suggests that the possibility of SET pathway may also to be considered. In addition, we have also carried out the reaction with stoichiometric amount of Co(III) to gain insight into the possibility of Co(III) or Co(IV) intermediate involved in the catalytic cycle with and without Ag$_2$CO$_3$. In line with radical experiments, 1 eq of Co^{III}(acac)$_3$ without silver carbonate gave 14% of **2a** compared to 75% mass of **2a** was isolated with silver carbonate. Theses results indicate that the Co(IV) involved in reductive elimination than Co(III) (scheme 4d).

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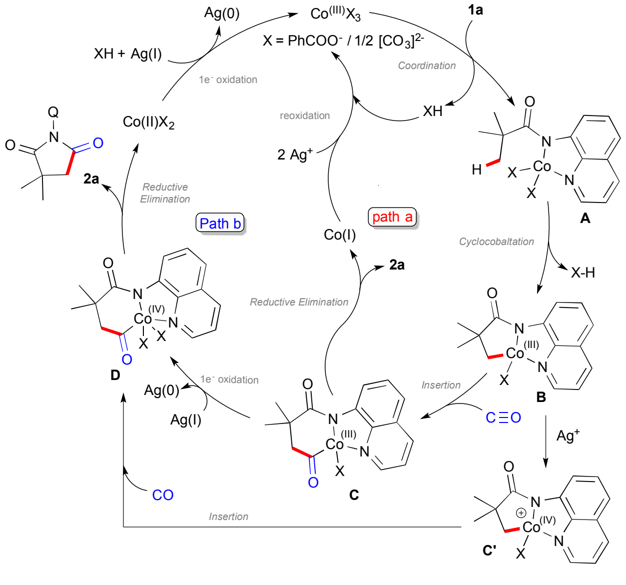
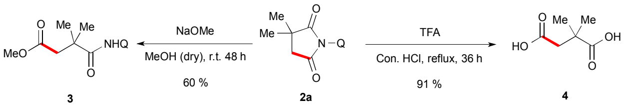


Scheme 5: Proposed Mechanism

Based on the control experiments and previous reports on β-C(sp^3)-H bond activation,[17] we propose the plausible mechanism as shown in scheme 5. Initial oxidation of Co(II) to Co(III) instigated by Ag^+ (confirmed by UV-Vis spectra),[20] which subsequently coordinated with **1a** via N, N-coordination (initial deprotonation possibly by silver carbonate) led to intermediate **A.** Then, carboxylate/carbonate assisted deprotonation provides cobaltacycle **B**. Co(III) intermediate **B** coordinates with CO followed by insertion into the C-Co(III), gave the intermediate **C**, which may either go for reductive elimination to Co(I) and reoxidized by silver to active Co(III) speicies as depicted in path a.[16a-g] Alternatively, intermediate **C** will undergo one electron oxidation to Co(IV), which will go for reductive elimination to **2a** and regenerate Co(II) (path b). At the same time, one may also consider intermediate **B** will undergo one electron oxidation to **C'** which then subsequently insert CO between Co-C led to **D** (path c), that further go for reductive elimination. Although final solution cannot be given for mechanism at this stage, control experiments suggest that path b or c may favour over path a.

To validate the synthetic utility of this method, we have performed two ring opening reaction with **1a** to obtain 1,4-dicarbonyl compound **3** and 1,4-dicarboxylicacid **4** in good yield under the standard reaction conditions (Scheme 6).

Scheme 6: Synthetic applications



Conclusions

We have developed new protocol for cobalt catalyzed site-selective carbonylation of unactivated C(sp^3)-H bond under atmospheric CO pressure to access to various succinimide derivatives that are active against seizures (anticonvulsantethosuximide). Our initial mechanistic investigation reveals that the involvement one electron process operated in the catalytic cycle and reaction may proceed through Co(IV) to Co(II) (Scheme 5, path b or c). Studies to further extend this new reactivity to develop new medicinal compounds and materials are currently underway. Further understanding of the mechanism including SET process, isolation of stoichiometric intermediate is presently on going in our laboratory.

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Notes and references

‡ CCDC 1507203 (**2t**) & 1507204 (**2a**) contains 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. The Supporting Information also provides additional information.

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22 See Notes for more information.

23 Catalytic carbonylation was performed using recycled silver carbonate, which resulted in 83% isolated yield of succinimide **2a** under the standard reaction conditions.

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