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Digest paper

# Recent advances in C($sp^3$)—H bond carbonylation by first row transition metals

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ABSTRACT

Carbonylation is one of the most valuable processes both in academia and industry. Direct functionalization of inert C($sp^2$)—H bond into C($sp^2$)-carbonyl derivatives was actively pursued over decades using noble metals. But the corresponding C($sp^3$)—H bond carbonylation is a challenging area and only few examples were known till now. Utilization of first row transition metals as an alternative to their noble partners is more sustainable. In this context, use of first row transition metals for direct C($sp^3$)—H bond functionalization is burgeoning as an exciting area. This digest review covers some of the recent achievements in this regard especially using Ni, Co and Cu as first row transition metals. The reported approaches are categorized in two types: directed and non-directed activation/functionalization of C($sp^3$)—H bonds using carbon monoxide gas or its surrogates as a C1 source.

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## Introduction

Carbonylation reactions using carbon monoxide as C1 source and catalyzed by transition metals have long been practiced and are, one of the most widely employed processes both in the academia and industry.[1] Since the pioneering work of Heck,[2] carbonylative coupling of aryl halides into various carbonyl derivatives are well documented and broadly applied in the targeted synthesis. But the requirement of prefunctionalization of C—H bond into polarized C—X bond limits this process. Recently, direct activation and functionalization of C—H bond catalyzed by transition metals have been developed as emerging tool for sustainable transformations.[3] Incidentally, the first catalytic C—H carbonylative coupling was achieved by Shunsuke Murahashi in 1955 using low-valent Co(0)-carbonyl complex.[4] To achieve such a process, the catalyst should have the inherent ability to bind with $\pi$-acidic carbon monoxide in addition to activate inert C—H bond. Inspired by the pioneering work on C($sp^2$)-H bond carbonylation, recent achievements in C—H bond activation[5] led to develop various methods for direct carbonylation of C($sp^2$)—H bonds using various transition metals. But the corresponding catalytic carbonylation of C($sp^3$)—H bond of alkanes into carbonyl compounds using carbon monoxide or its surrogates as C1 source is very rare, only few reports are documented using noble metals.[6] In this regard, the first effective catalytic carbonylation of C($sp^3$)—H bond was achieved by Tanaka and co-workers using a rhodium complex under photo-irradiative conditions.[7] Later, Chatani and co-workers reported the chelate

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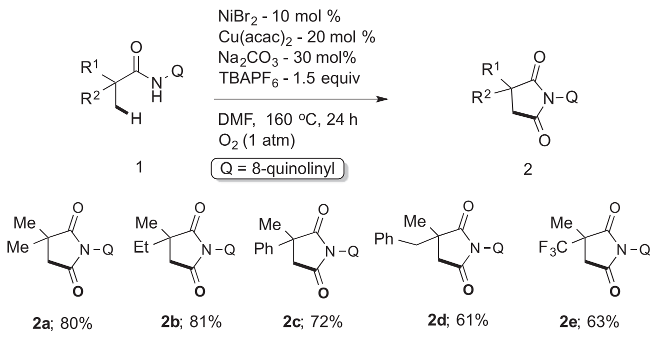
assisted α-C—H carbonylation of cyclic aliphatic amine using Rh-carbonyl complex in the presence of olefin as hydrogen acceptor.[8] Recently, Yu[9a] and Chatani[9b,c] independently reported the carbonylation of unactivated C($sp^3$)—H bonds using Pd(II) and Ru (0) catalysts. Though both reactions have shown excellent control over regio-selectivity, the operative mechanism is very different as the former proceeded under oxidative conditions and the latter proceeded through a metal-hydride pathway. Few years later, C($sp^3$)—H bond carbonylation[10] of aliphatic amines under atmospheric pressure of carbon monoxide was reported by Gaunt and co-workers.[11] It is noteworthy that the reaction did not require any additional directing group. Replacement of noble metal by less expensive, earth-abundant and non-toxic first row transition metal is essential due to sustainablity.[12] In this regard, several examples of carbonylative coupling of C($sp^2$)—H bonds were recently reported using first row transition metals.[13] However, challenging carbonylation of C($sp^3$)—H bonds is extremely rare and only few reports were documented. In this review, we provide an overview of recent achievements on C($sp^3$)—H bond carbonylation starting from alkyl derivatives and catalyzed by first row transition metals (Ni, Co and Cu) using carbon monoxide or its surrogates as C1 source.

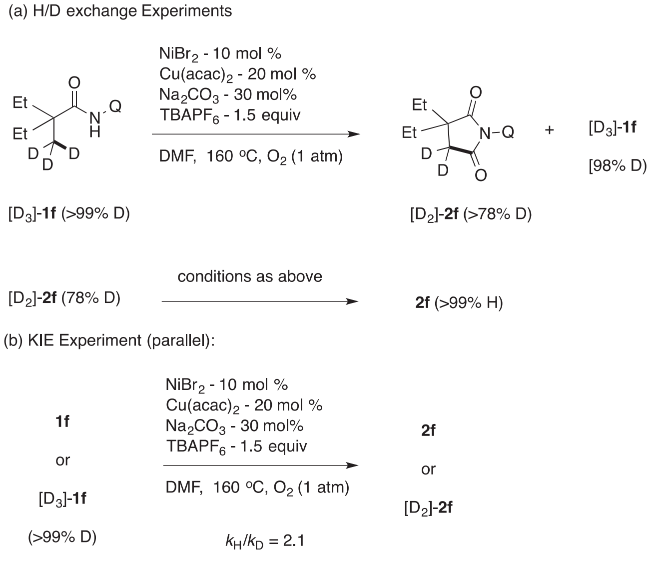
## Directing group-assisted catalytic carbonylation of unactivated $sp^3$ CH bonds

### *Carbonylation using "CO" surrogates with nickel and copper*

The serendipitous discovery of $Ni(CO)_4$ during the purification of metallic nickel in industry propagated the isolation and use of this low valent metal complex for various fundamental study and applications.[14] Since then, nickel is one of the mostly used metal salts for carbonylation process. Especially, the use of nickel for C—H bond functionalization was advanced when Chatani and others explored the field with the bidentate chelate[15]-assisted C—H bond activation.[16] Although carbonylation is a simple and powerful strategy to produce carbonyl-containing derivatives, the synthetic application is restricted due to the requirement of high-pressure, toxicity and cumbersome procedures that are associated with the use of carbon monoxide. Alternatively, surrogates that are known to produce 'CO' *in situ* have been utilized to replace toxic carbon monoxide.[17] In the view of increased interest on the use of inexpensive and environmentally benign catalysts that are based on first row transition metals, Ge and co-workers have recently demonstrated the carbonylative cyclization of aliphatic amides using dimethylformamide (DMF) as carbonyl surrogates.[18] This method involves the direct β-C($sp^3$)—H carbonylation of aliphatic amides using 8-aminoquinoline as directing group and DMF as the carbonyl source under Ni(II)/Cu(II) synergistic catalytic conditions (Scheme 1). The use of DMF as the alternative carbon source along with atmospheric oxygen instead of hazardous carbon monoxide gas is one of the remarkable factor that makes this protocol more user friendly. It is essential to use both Ni(II) and Cu (II) along with ammonium salt ($TBAPF_6$) to achieve high productivity. Various α,α-disubstituted propanamides were effectively carbonylated into corresponding succinimides but amides containing α-methylene, β- and γ-methyl groups were not transformed under the reported conditions.



**Scheme 1.** Ni(II)/Cu(II)-catalyzed carbonylation of C($sp^3$)—H bonds.



**Scheme 2.** Deuterium-labeling experiments.

As the reaction conditions utilized DMF as carbonyl source, CO may arise either from the carbonyl group or the methyl group of DMF. In order to evaluate these possibilities, $^{13}C$ labeled DMF ($^{13}C{=}O$) was used as the solvent under optimized conditions and only trace amount of $^{13}C$ incorporated product was observed. Various control experiments with *N*-containing solvents suggested that incorporation of CO arose from the methyl group and not from the carbonyl group of DMF. Deuterium labeling experiments suggested that the rate-determining step involved the cyclometallation step and apparent H/D exchange was observed in the product (Scheme 2b). These results indicate that the detected H/D exchange of the product [$D_2$]-**2f** is mainly due to the formation of an enolate ion followed by protonation (Scheme 2).

Based on the experimental observations, a plausible mechanism was proposed as shown in Scheme 3. Initial coordination of amide by ligand exchange followed by irreversible C($sp^3$)—H cleavage assisted by base led to the cyclometallated intermediate **B**. Simultaneously, DMF was converted into an *N*-methyl-*N*-methylenemethanaminium species **C** *via* sequential decarbonylation. Then, nucleophilic addition of M—C bond in intermediate **B** to the iminium **C** formed **D** and elimination process under copper catalysis in the presence of oxygen as sole oxidant took place to give intermediate **F**. Further sequential transformations led to the expected carbonylated product **2** as depicted in the Scheme 3.

The same group further continued to explore different catalysts as well as carbonyl surrogates for C($sp^3$)—H bond carbonylation using first row transition metals. They very recently reported the C—H bond carbonylation of aliphatic amide using nitromethane as carbonyl surrogates.[19] In fact, according to the authors, this serendipity discovery was achieved when C($sp^3$)—C($sp^3$) dehydrogenative coupling was attempted between aliphatic amide and nitromethane under oxidative conditions. In contrast to the expected dehydrogenative coupling, the reaction progressed through the copper-mediated C—H activation and a subsequent Nef type reaction (see Scheme 4).