Carboxylic Acid Synthesis

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Catalytic Hydrocarboxylation of Alkenes and Alkynes with CO_2**

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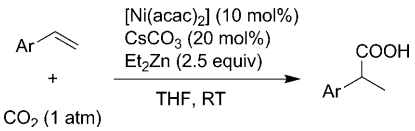
carbon dioxide · homogeneous catalysis · hydrocarboxylation · synthetic methods · transition metals

The use of carbon dioxide as a renewable and environmentally friendly source of carbon has attracted increasing attention.[1] Although CO_2 is used in many well-established reactions, attractive and straightforward procedures for the direct carboxylation of carbon nucleophiles with CO_2 as the electrophile remain largely underdeveloped.[2] The formation of a thermodynamically and kinetically stable C–C bond is the most desirable form of CO_2 fixation. The insertion of CO_2 into metal–carbon bonds of various of organometallic reagents with or without catalysts has been well documented.[1,2] Catalytic reactions involving the insertion of CO_2 into various intermediates with a metal–carbon bond have also been designed and explored.[1–3] Nickel is well known to be able to couple with an alkyne in an atmosphere of carbon dioxide to form an oxonickelacycle.[4] The use of such reaction intermediates has been applied to the hydrocarboxylation of alkynes, enynes, and diynes to form the respective α,β-unsaturated carboxylic acids.[5–7] Catalytic ring-closing carboxylation processes with a nickel catalyst and a bis-1,3-diene or a diyne substrate have also been developed.[8] In these reactions, an organozinc reagent was typically used for the transmetalation step in the catalytic cycle. Iwasawa and co-workers have also reported the hydrocarboxylation of allenes and 1,3-dienes with a silyl pincer-type palladium complex.[9] The reactions, carried out at ambient temperature under CO_2 (1 atm), enabled the facile and regioselective synthesis of β,γ-unsaturated carboxylic acids. However, recent breakthroughs in the catalytic hydrocarboxylation of styrene[10] and single alkynes[11,12] with CO_2 went beyond the limitation of substrates with an extensive π system. The catalytic CO_2 hydrocarboxylation of these simple unsaturated substrates is a significant advance and will prove to be a powerful synthetic approach.

The first direct hydrocarboxylation of a single alkene was reported by Rovis and co-workers, who developed a nickel-catalyzed hydrocarboxylation of styrenes with CO_2.[10] The reaction was conducted under very mild conditions with a nickel catalyst ([Ni(cod)$_2$] or [Ni(acac)$_2$]; 10 mol%), a base additive (20 mol%), and an organozinc reagent (2.5 equiv) in THF at room temperature under CO_2 at ambient pressure (Scheme 1; acac = acetylacetonate, cod = 1,5-cyclooctadiene). The reaction was developed for a variety of styrene



Scheme 1. Nickel-catalyzed hydrocarboxylation of styrene derivatives with CO_2.

analogues with electron-deficient and neutral substituents and was compatible with various functional groups, such as aryl chlorides, esters, ketones, and nitriles. A single regioisomer of the corresponding α-carboxylated product was generated in good yield. The suggested mechanism involved a nickel hydride active catalyst, instead of a typical Hoberg-type nickelacycle.[4] This metal-hydride intermediate is the common key intermediate for catalytic hydrocarboxylation reactions.[9] The insertion of the styrene moiety into the nickel–hydride bond afforded a benzyl nickel species, which then underwent direct carboxylation or carbozincation followed by carboxylation. Subsequent transmetalation of the reaction intermediate with Et_2Zn yielded the hydrocarboxylation product and released the precatalyst.

More recently, Ma and co-workers reported a nickel-catalyzed hydrocarboxylation of alkynes with diethyl zinc and CO_2.[11] In a typical reaction, an internal alkyne was converted into an *E* 2,3-disubstituted acrylic acid in the presence of the catalyst [Ni(cod)$_2$] (1–3 mol%), the additive CsF (1.0 equiv), $ZnEt_2$ (3 equiv), and CO_2 (1 atm; Scheme 2a). The products of a *syn* hydrocarboxylation were formed with high regio- and stereoselectivity in good to excellent yields. Symmetrical electron-rich aryl alkynes, alkyl alkynes, and unsymmetrical aryl/alkyl alkynes are suitable substrates.

The alkenyl metal species generated in situ in this reaction would be less active toward CO_2 insertion than the benzyl nickel intermediate in the styrene hydrocarboxylation de-

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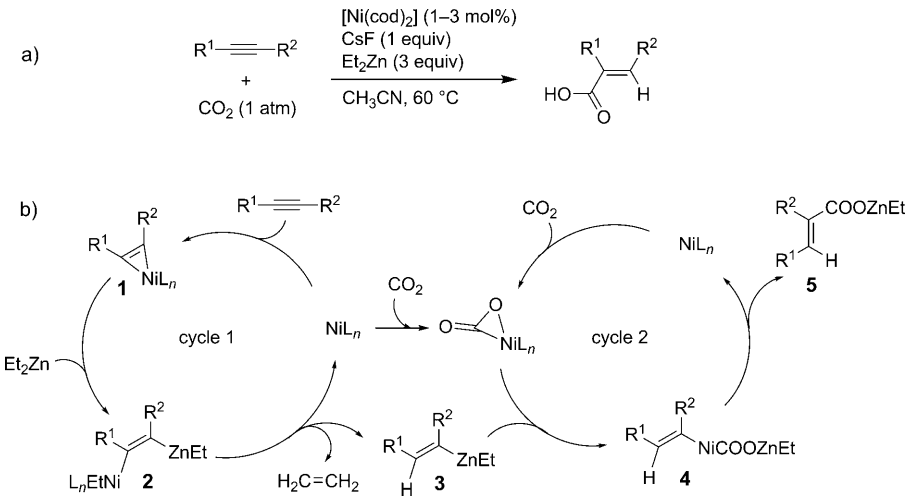
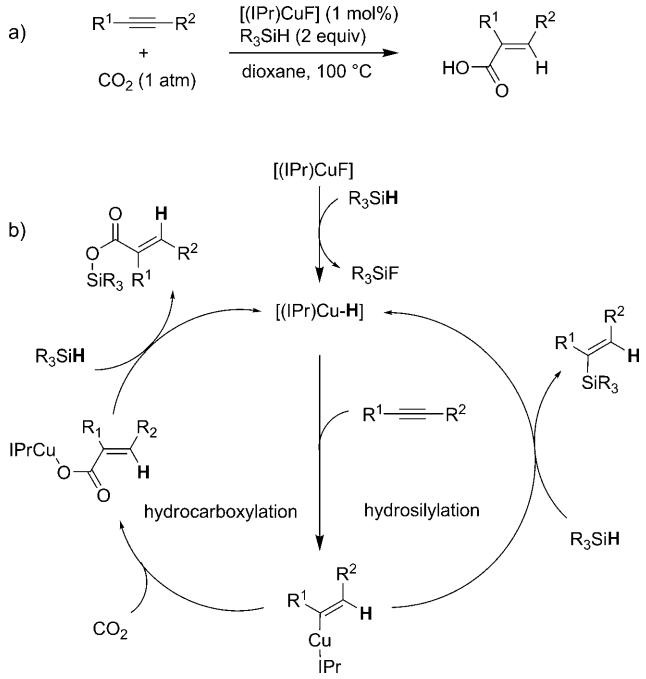


Scheme 2. a) Nickel-catalyzed hydrocarboxylation of alkynes with CO_2 and b) the proposed reaction mechanism.

scribed by Rovis and co-workers. A different reaction pathway involving two nickel catalytic cycles was proposed (Scheme 2b): Following initial activation of the alkyne by Ni^0, carbozincation leads to intermediate **2**. A β-hydride elimination and subsequent reductive elimination of ethane generates the *E* alkenyl zinc intermediate **3** and releases Ni^0. The second cycle involves the activation of CO_2 by Ni^0 to form an Aresta complex,[13] which would react with less active alkenyl zinc species **3** to form a zinc carboxylate product **5** and regenerate the Ni catalyst.

Parallel to the development of this reaction, Tsuji and co-workers developed a copper-catalyzed hydrocarboxylation of alkynes with CO_2 and hydrosilanes (Scheme 3a).[12] Organocopper reagents are unique in that the metal–carbon bond is of moderate polarity and is more susceptible to CO_2 insertion under ambient conditions.[14,15] The copper-catalyzed hydrosilylation of alkenes and alkynes is a well-documented reaction, and a species containing a Cu–C bond is the commonly accepted intermediate.[16] In this case, an intermediate with a Cu–C bond was designed and used in a catalytic hydrocarboxylation with CO_2. The reaction described by Tsuji and co-workers provided an elegant and useful method for the synthesis of α,β-unsaturated carboxylic acids by the hydrocarboxylation of alkynes with a catalyst and reagents that are mild and easy to handle. In comparison with the procedure of Ma and co-workers, the reaction has broad substrate scope: suitable substrates include symmetrical electron-rich and electron-deficient aryl alkynes, alkyl alkynes, unsymmetrical aryl/alkyl alkynes, and terminal alkynes. The reaction is also compatible with various functional groups, such as aryl halides, esters, ethers, and nitriles.



Scheme 3. a) Copper-catalyzed hydrocarboxylation of alkynes with CO_2 and b) the proposed two competitive reaction cycles. IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

The hydrocarboxylation developed by Tsuji and co-workers involves the addition of a copper(I) hydride containing an N-heterocyclic carbene ligand to an alkyne to afford an alkenyl copper intermediate. The insertion of CO_2 into the copper–carbon bond gives a copper carboxylate, and subsequent metathesis with the hydrosilane affords the corresponding silyl ester product. The challenge in this reaction is the possibility of competitive catalytic cycles (Scheme 3b):[17] the copper species could also catalyze direct hydrosilylation of the alkyne. The copper or NHC present in the system could also catalyze the hydrosilylation of CO_2.[18] Remarkably, under the optimized reaction conditions, side reactions of this system were successfully suppressed, and the desired product was obtained in high yield. Furthermore, the use of cheap and easy-to-handle hydrosilanes makes this reaction particularly attractive.

In conclusion, the new methodologies developed by the research groups of Rovis, Ma, and Tsuji for the hydrocarboxylation of alkenes and alkynes with carbon dioxide have twofold significance. First, these reactions demonstrate great possibilities for the use of CO_2 as a renewable and environmentally friendly source of carbon in organic synthesis. Further understanding of the reaction mechanisms could promote the development of new synthetic methodologies involving CO_2. Second, these reactions provide versatile methods for carboxylic acid synthesis. Further improvements in these hydrocarboxylation protocols could be made, especially in terms of the use of cheap and clean reducing reagents and the expansion of their scope with respect to possible substrates.

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