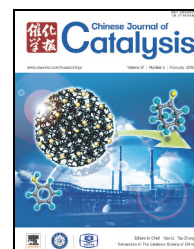




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## Highlight

# Ni-catalyzed direct carboxylation of unactivated alkyl electrophiles with carbon dioxide

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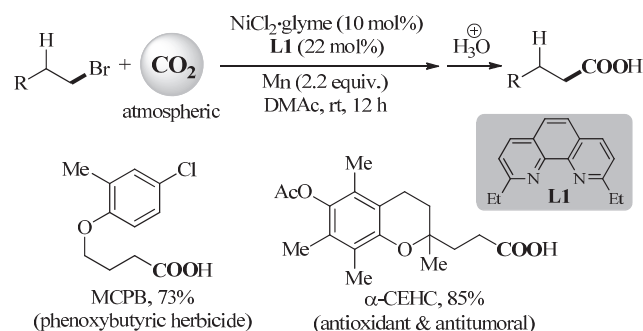


Carbon dioxide is a cheap, abundant and renewable C1 building block. Over the last two decades, considerable research efforts have been devoted to developing new reactions for the efficient incorporation of carbon dioxide into a broad range of compounds for the production of value-added materials [1]. Notably, these efforts have culminated in the development of several transition-metal-catalyzed methods capable of providing access to numerous synthetically important carboxylic acids and derivatives using carbon dioxide as a carboxylative reagent [2]. In most of these cases, carbon dioxide acts as an electrophile or cycloaddition partner, which can react with a broad range of nucleophiles and unsaturated compounds [3]. In addition to these traditional cross-coupling reactions, there have been several recent reports describing the development of a transition-metal-catalyzed reaction for the reductive cross-coupling of two different electrophiles. This new reaction represents a more straightforward approach for the construction of carbon–carbon bonds, because it avoids the many tedious and expensive pre-activation steps required by the traditional processes described above for the preparation of air- and/or moisture-sensitive organometallic reagents [4–6]. For this reason, the direct reductive carboxylation of (pseudo)halide electrophiles with carbon dioxide represents a more attractive and environmentally friendly method for the synthesis of functional carboxylic acids [7].

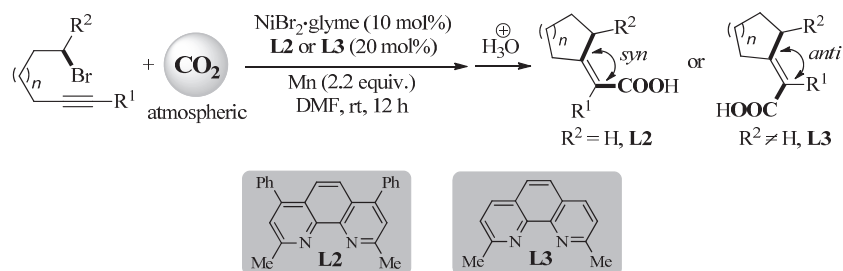
In 2009, Martin and co-workers [8] reported the first catalytic reductive carboxylation of an electrophile with carbon dioxide, where an aryl bromide was successfully carboxylated under 1 MPa of carbon dioxide pressure using a palladium/*t*Bu-XPhos catalyst and two equivalent of ZnEt<sub>2</sub> as a reducing agent. Tsuji and co-workers [9] subsequently reported the development of an elegant nickel-based catalytic system for the direct carboxylation of aryl and vinyl chlorides under atmospheric carbon dioxide at room temperature using Mn/Et<sub>4</sub>Ni as a reducing agent, which was easy to handle. Notably, mechanistic studies revealed that a Ni(I) species was formed as a key intermediate during this catalytic carboxylation cycle [9]. Further studies by Martin's group demonstrated that this nickel-catalyzed reductive carboxylation could be applied to a vari-

ety of different electrophiles, including benzyl halides [10], aryl and benzyl esters [11], and allyl esters [12] using carbon dioxide. However, the direct carboxylation of unactivated alkyl electrophiles bearing a β-hydrogen remains a challenging area of research, because substrates of this type are reluctant to undergo the oxidative addition step required to initiate the reaction. Moreover, the alkylmetal intermediates formed in situ from these substrates are prone to competitive side reaction, including β-hydride elimination and homodimerization reactions.

Martin's group [13] recently reported an important breakthrough in this area when they achieved the direct carboxylation of a series of unactivated primary alkyl bromides and sulfonates bearing β-hydrogens with carbon dioxide (Scheme 1). Notably, this reaction required the presence of a nickel catalyst, as well as a 1,10-phenanthroline-type ligand. Furthermore, a series of screening experiments revealed that the optimal catalytic system for this reaction was NiCl<sub>2</sub>·glyme/2,9-diethyl-1,10-phenanthroline (**L1**, Scheme 1), which not only allowed for the direct carboxylation of these challenging substrates, but also suppressed the unwanted side reactions. It is noteworthy that the other nickel/phosphine catalyst systems previously reported for the carboxylation of other electrophiles were found to be inefficient in this case. Furthermore, the electronic and steric properties of the 1,10-phenanthroline ligand were found to have a profound effect on the product selectivity of this



**Scheme 1.** Ni-catalyzed direct carboxylation of unactivated alkyl bromide with carbon dioxide.



**Scheme 2.** Ni-catalyzed cascade reductive cyclization/carboxylation of unactivated alkyl bromides with carbon dioxide.

transformation. For example, subtle changes in the structure of the ligand backbone led to a pronounced decrease in the yield or the complete failure of the reaction.

This nickel catalyst system allowed for the direct carboxylation of a wide variety of unactivated primary alkyl bromides bearing  $\beta$ -hydrogen to give the corresponding carboxylic acids in good yields using Mn as reducing agent under an atmosphere of carbon dioxide at room temperature. Notably, this catalyst system exhibited good functional group compatibility, with ester, nitrile, acetal, amide, carbamate, ketone, aldehyde, alcohol, phenol, and aryltin groups being well tolerated. Furthermore, substrates containing an aryl chloride, tosylate, or pivalate group, which had been previously evaluated under similar Ni-catalyzed conditions, reacted exclusively at the bromide sites. Although unactivated primary alkyl chlorides and iodides, secondary alkyl bromides, and phenethyl electrophiles proved to be unsuitable substrates for the present catalytic system, unactivated alkyl sulfonates reacted smoothly using a  $\text{NiBr}_2 \cdot \text{glyme} / 2,9\text{-dimethyl-}1,10\text{-phenanthroline}$  catalyst at elevated temperatures. Based on its high catalytic efficiency and operational simplicity, this protocol represents an extremely useful process for practical organic synthesis. This process was also successfully applied to the concise synthesis of two biologically active compounds, namely MCPB and  $\alpha$ -CEHC, to highlight its synthetic utility (Scheme 1).

Mechanistic studies ruled out the possibility of the alkene generated by the  $\beta$ -hydride elimination of the substrate undergoing a hydrocarboxylation reaction or the involvement of an organomanganese species. Based on the results of a cleverly-designed diastereoisomer experiment and several radical clock reactions, the authors suggested that the catalytic cycle involved several SET processes and proceeded via a Ni(I) species.

Based on the nickel/nitrogen ligand catalytic system described above, Martin's group [14] recently reported the cascade reductive cyclization/carboxylation of unactivated alkyl bromides bearing an internal alkyne group under an atmosphere of carbon dioxide. Notably, this reaction provided facile access to a series of carbocyclic carboxylic acids in good yields (Scheme 2). Remarkably, the *syn/anti* selectivity of this reaction could be readily modulated by the substrate selection and/or ligand backbone.

In summary, Martin and co-workers have successfully developed an efficient catalytic system for the nickel-catalyzed direct reductive carboxylation of unactivated primary alkyl

bromides bearing  $\beta$ -hydrogens with carbon dioxide under mild reaction conditions. This reaction represents an attractive and operationally simple approach for the synthesis of valuable carboxylic acids from readily available alkyl bromides and carbon dioxide. Furthermore, this unique process for the combination of unactivated primary alkyl bromides with carbon dioxide has considerably expanded the substrate scope for the reductive coupling of alkyl electrophiles. It is therefore envisaged that this new catalytic system and its associated mechanistic insights will provide a platform for the development of novel and more efficient direct carboxylation reactions using alkyl electrophiles and carbon dioxide.

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