

Transition-Metal-Catalyzed Carboxylation of C–H Bonds**

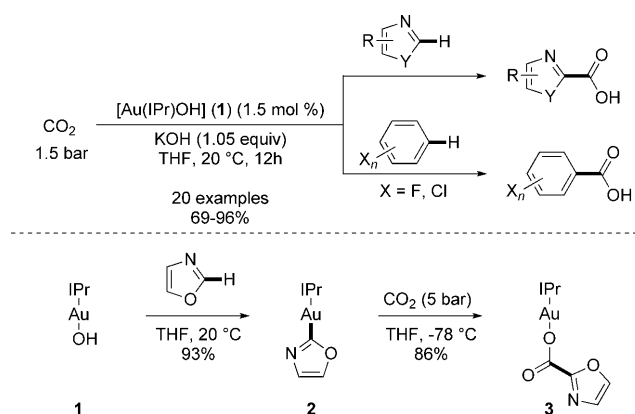
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C–H activation · carbon dioxide · copper · homogeneous catalysis · gold

Carbon dioxide (CO₂) gas is the most abundant carbon source in the Earth's atmosphere, and the anthropogenic CO₂ emission is estimated to be approximately 29 billion tons per year.^[1] The steadily increasing CO₂ concentration contributes to a trapping of heat radiating from the Earth's surface, which represents a major reason for global warming. In addition to an improved efficiency of known energy technologies, as well as a fast transfer to alternative energy sources, two main strategies are in the focus of scientific attention, namely carbon capture and storage (CCS), and carbon capture and reuse (CCR). While it is obvious that the utilization of CO₂ to generate chemical products does not allow for a significant overall reduction of CO₂ emission, it constitutes an ecologically sound contribution to an integrated carbon management strategy. Moreover, the use of CO₂ for chemical synthesis gives access to valuable polymers or complex organic molecules from an inexpensive, abundant, and non-toxic C1 source. Particularly, the prevalence of (hetero)aromatic carboxylic acid derivatives among biologically active compounds has sparked recent interest in the development of methods for their direct preparation from thermodynamically stable CO₂. Traditionally, the challenge of CO₂ fixation has been addressed through the use of strongly nucleophilic organometallic compounds, such as Grignard reagents.^[1,2] On the contrary, the more functional group tolerant, yet less reactive zinc- or boron-based reagents usually call for the use of stoichiometric or catalytic amounts of (transition)metals as additives.^[2–4] Unfortunately, these protocols rely on initial stoichiometric prefunctionalization prior to the subsequent key C–C bond-forming event. A more sustainable synthesis of carboxylic acids constitutes the direct carboxylation of C–H bonds, with an early example for a base-mediated carboxylation being represented by the Kolbe–Schmitt synthesis of salicylic acid from sodium phenolate, albeit under harsh reaction conditions. During recent years, transition-

metal catalysis has set the stage for efficient direct C–C bond-forming reactions to proceed under exceedingly mild reaction conditions,^[5] and they were extended to include site-selective direct carboxylation of C–H bonds in 2010.

On the basis of the stoichiometric auration of C–H acidic (hetero)arenes,^[6] Boogaerts and Nolan found that the gold complex [Au(IPr)OH] (**1**; IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) enabled efficient, direct carboxylation of (hetero)arenes at ambient temperature, provided that KOH is present as a stoichiometric base.^[7] Key to the success was the remarkably high basicity of N-heterocyclic carbene (NHC) gold complex **1** (pK_a^{DMSO} of 30.3), which allowed the functionalization of heteroarenes and arenes bearing moderately acidic^[8] C–H bonds. Stoichiometric experiments with well-defined gold complexes led to the isolation of the catalytically competent key intermediates **2** and **3** (Scheme 1), and thereby provided strong support for a deprotonative reaction mechanism.^[7]



Scheme 1. Gold(I)-catalyzed direct carboxylation of (hetero)arenes.^[7] THF = tetrahydrofuran.

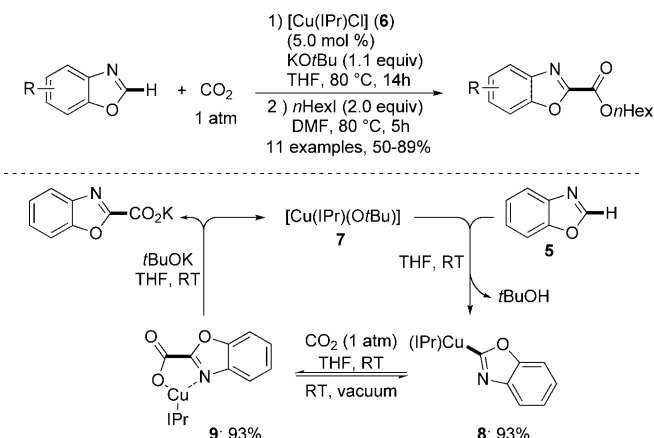
Interestingly, Boogaerts and Nolan also noted in their early contribution that the copper complex [Cu(IPr)X] (X = OH (**4**), X = Cl (**6**)) catalyzed the direct carboxylation of oxazole in 89% yield. Independent reports by Hou and co-workers,^[9] as well as Cazin, Nolan, and co-workers^[10] provided insight into the scope and mechanism of direct carboxylation reactions using inexpensive copper(I) complexes. Thus, Hou and co-workers tested copper catalysts derived from various

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[**] Support from the Ministry for Science and Culture of Lower Saxony within the CaSuS (Catalysis for Sustainable Synthesis) program is gratefully acknowledged.

ligands for the direct functionalization of benzoxazole (**5**).^[9] Most satisfactory results were obtained with complexes generated from sterically demanding NHCs and using KO^tBu as the base, whereas tertiary phosphines or nitrogen ligands generated significantly less effective catalysts. Interestingly, both isolated complex [Cu(IPr)Cl] (**6**) as well as the in situ generated NHC/copper complexes proved to be viable catalytic systems. Contrarily, only traces of the desired product were formed in the absence of a copper catalyst.^[9,11] Direct carboxylation of the more acidic benzoxazole (**5**) ($pK_a = 24.8$) and its derivatives proceeded efficiently (Scheme 2). Yet, less acidic heteroarenes, such as benzofuran

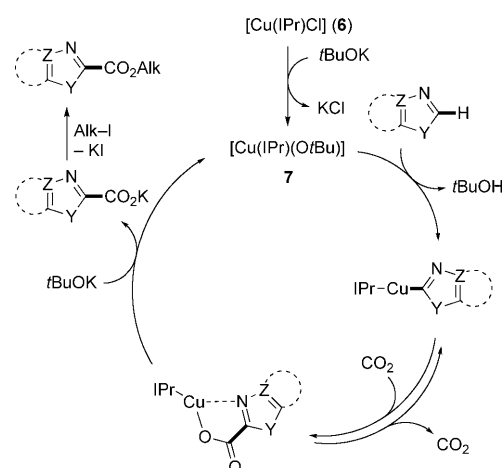


Scheme 2. Copper-catalyzed direct carboxylation of benzoxazoles.^[9] DMF = *N,N*-dimethylformamide, Hex = hexyl.

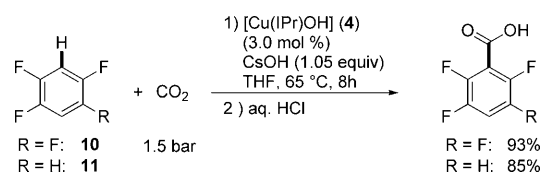
($pK_a = 33.2$) or benzothiazole ($pK_a = 27.3$), gave only traces of the desired products. Since the carboxylic acids underwent slow uncatalyzed decomposition, the products were isolated as their corresponding esters. As to the catalysts working mode, previous stoichiometric experiments revealed that precursor **6** reacted with KO^tBu to deliver complex **7**,^[3b] which in turn was shown to deprotonate azole **5** at ambient temperature.^[9] The well-defined complex **8** underwent a facile reversible stoichiometric insertion reaction with CO₂ under mild reaction conditions, thus delivering intermediate **9**.

Importantly, the fully characterized intermediates **8** and **9** were found to be catalytically competent, which resulted in the proposed catalytic cycle for the direct heteroarene carboxylation depicted in Scheme 3.

In an independent report, Cazin, Nolan, and co-workers accomplished direct carboxylation of N–H or C–H bonds through the use of [Cu(IPr)OH] (**4**) and CsOH as the stoichiometric base.^[10] The pK_{aDMSO} of complex **4** was determined to be 27.7. Based on the deprotonation mode of the postulated mechanism, substrates displaying C–H acidic sites having a pK_a value of less than 27.7 proved to be viable starting materials for direct carboxylation reactions; the substrates included oligofluoroarenes **10** and **11** (pK_a values are 23.1 and 26.1, respectively; Scheme 4), as well as benzoxazole (**5**, 90% yield), oxazole (77% yield), and benzothiazole (82% yield).^[8,10]



Scheme 3. Proposed mechanism of copper-catalyzed direct carboxylation.^[9]



Scheme 4. Copper-catalyzed direct carboxylation of electron-deficient oligofluoroarenes **10** and **11**.^[10]

In summary, direct carboxylation of (hetero)arenes have been accomplished under remarkably mild reaction conditions through the use of highly basic gold or copper NHC complexes, in combination with a stoichiometric potassium or cesium base. While these findings constitute an important breakthrough in the area of CO₂ fixation, a limitation of these protocols is represented by their restriction to moderately acidic C–H bonds with pK_a values of less than 32.3 (with complex [Au(IPr)OH]) and less than 27.7. Therefore, additional challenges are represented by direct carboxylation of less acidic substrates and unactivated C_{sp}–H bonds, as well as the use of milder stoichiometric bases. Considering the importance of efficient C–H bond functionalizations, along with the topical interest in the fixation of CO₂, more exciting developments are expected in this research area.

Received: December 14, 2011

Published online: March 22, 2011

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