CO_2 Fixation

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Copper-Catalyzed Direct Carboxylation of C–H Bonds with Carbon Dioxide**

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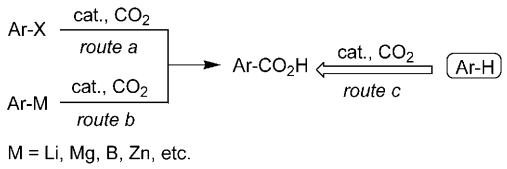
The use of carbon dioxide (CO_2) as a C1 building block for chemical synthesis has recently attracted much interest because of its abundance, low cost, nontoxicity, and high potential as a renewable source.[1] However, the high thermodynamic stability and low reactivity of CO_2 means that its use in C–C bond-forming reactions usually requires organometallic reagents or other preactivated substrates such as organic halides (Scheme 1, routes a and b).[2,3] Although the reaction of C–H bonds with CO_2 would be the most attractive and atom-economic route for the synthesis of carboxylic acids (Scheme 1, route c), the direct carboxylation of a C–H bond with CO_2 has remained a challenge.[4]

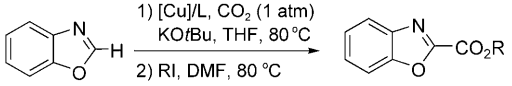


Scheme 1. Carboxylation reactions with CO_2.

We recently reported the carboxylation of organoboronic esters with CO_2 by using N-heterocyclic carbene (NHC) copper complexes.[3d] In this study, we explored the potential of the copper catalysts for the carboxylation of C–H bonds. Herein we report that the NHC-copper complexes can serve as excellent catalysts for the direct carboxylation of aromatic heterocyclic C–H bonds with CO_2 to afford the corresponding carboxylic esters after treatment with an alkyl iodide. Heterocyclic carboxylic acids and derivatives are important structural motifs that are often found in medicinally important molecules and synthetically useful fine chemicals.[5] Although the C–H activation and functionalization (such as arylation, alkynylation, and amination) of aromatic heterocycles by copper catalysts have been reported,[6,7] the carboxylation of C–H bonds of heterocyclic compounds with CO_2 has remained almost unexplored.

We first chose the NHC-copper(I) complex [Cu(IPr)Cl] (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene),[8] which had previously shown excellent activity for the carboxylation of organoboronic esters,[3d] as a catalyst for the reaction of benzoxazole ($pK_a = 24.8$) with CO_2. The reaction was carried out in the presence of 5 mol% of [Cu(IPr)Cl] and 1.1 equivalents of KO*t*Bu (with respect to benzoxazole) under 1 atm of CO_2 in THF at 80°C for 14 hours. The formation of the potassium benzoxazole-2-carboxylate salt was observed by ^1H and ^{13}C NMR spectroscopic analyses of the crude product. However, in an attempt to obtain the carboxylic acid by acidification, aqueous HCl was added, which resulted in rapid decarboxylation taking place to give a complicated mixture of unidentified products.[9] The addition of MeI (2.0 mmol) to a solution of the crude product mixture in *N*,*N*-dimethylformamide (DMF) prior to hydrolysis, led to the ester derivative—methyl benzoxazole-2-carboxylate—being isolated in 76% yield after stirring at 80°C for 5 hours (Table 1, entry 1). The use of EtI and *n*-$C_6H_{13}I$ instead of MeI afforded the correspond-

Table 1: Copper-catalyzed direct carboxylation of benzoxazole with carbon dioxide.[a]



Entry	[Cu]	Ligand	RI	Yield [%][b]
1	[Cu(IPr)Cl]	–	MeI	76[c]
2	[Cu(IPr)Cl]	–	EtI	74[c]
3	[Cu(IPr)Cl]	–	$C_6H_{13}I$	80[c]
4	$Cu(OAc)_2$	IPr·HCl	$C_6H_{13}I$	53
5	$Cu(OTf)_2$	IPr·HCl	$C_6H_{13}I$	50
6	$CuCl_2$	IPr·HCl	$C_6H_{13}I$	56
7	CuI	IPr·HCl	$C_6H_{13}I$	45
8	CuBr	IPr·HCl	$C_6H_{13}I$	70
9	CuCl	IPr·HCl	$C_6H_{13}I$	69
10	CuCl	SIPr·HCl	$C_6H_{13}I$	70
11	CuCl	IMes·HCl	$C_6H_{13}I$	62
12	CuCl	SIMes·HCl	$C_6H_{13}I$	70
13	CuCl	PPh_3	$C_6H_{13}I$	7
14	CuCl	1,10-phen[d]	$C_6H_{13}I$	21
15	CuCl	L-proline	$C_6H_{13}I$	5
16	CuCl	TMEDA	$C_6H_{13}I$	trace
17	–	–	$C_6H_{13}I$	trace
18	–	SIPr·HCl	$C_6H_{13}I$	trace
19	CuCl	–	$C_6H_{13}I$	8

[a] Reaction conditions: [Cu] (10 mol%), L (10 mol%), benzoxazole (1.0 mmol), KO*t*Bu (1.1 mmol), CO_2 (1 atm), THF (5 mL), 80°C, 14 h, then the THF was evaporated, DMF (5 mL), RI (2.0 mmol), 80°C, 5 h, unless otherwise noted. [b] Yield of the isolated product. [c] [Cu(IPr)Cl] (5 mol%). [d] 1,10-phenanthroline.

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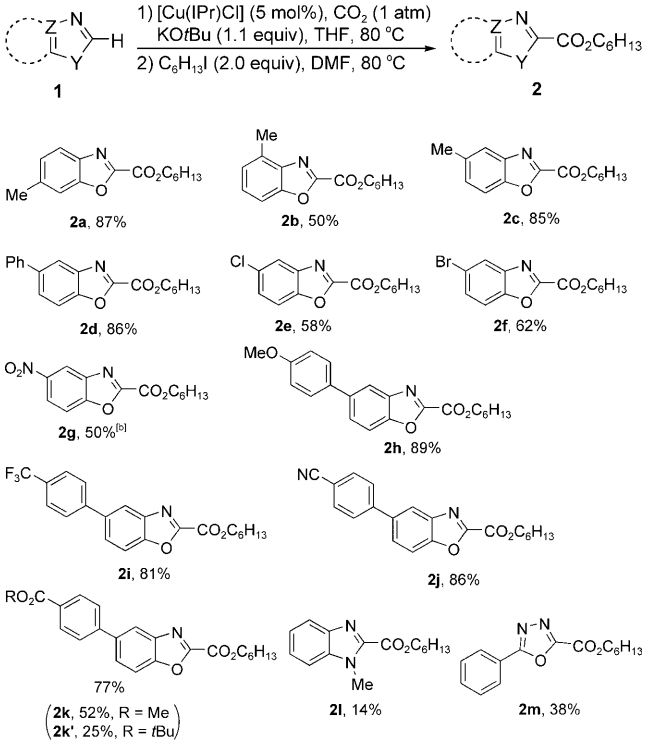
ing ethyl and hexyl ester derivatives, respectively (Table 1, entries 2 and 3). In a similar manner, the combination of the Cu^{II} compounds $Cu(OAc)_2$, $Cu(OTf)_2$, and $CuCl_2$ or Cu^{I} halides CuX (X = I, Br, Cl) with N-heterocyclic carbene ligands such as IPr·HCl, SIPr·HCl (SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene), IMes·HCl (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene), or SIMes·HCl (SIMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene) were also effective for the carboxylation of benzoxazole, with CuCl and CuBr seeming to give the most efficient reactions (Table 1, entries 4–12). Other ligands such as PPh_3, 1,10-phenanthroline, L-proline, and tetramethylethylenediamine (TMEDA) were less effective (Table 1, entries 9–16). In the absence of a copper source, only a trace amount of the carboxylation product was observed under the same reaction conditions (Table 1, entries 17 and 18). The use of CuCl alone afforded the expected product in only 8% yield (Table 1, entry 19). Of the catalysts surveyed, [Cu(IPr)Cl] proved to be the best. In addition to KO*t*Bu, other bases such as K_2CO_3, K_3PO_4, LiO*t*Bu, and NaO*t*Bu were also examined, but these were less effective. The use of THF and toluene as solvent gave better results than DMF, dioxane, or acetonitrile.

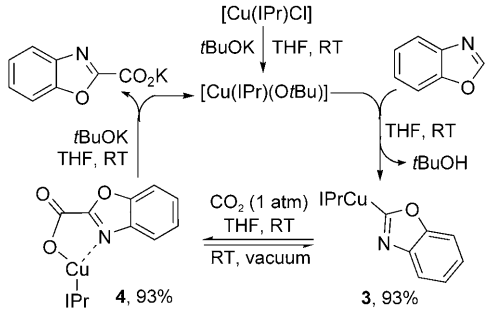
The carboxylation of other heterocyclic compounds was then examined by using [Cu(IPr)Cl] as the catalyst and *n*-$C_6H_{13}I$ as an alkylating agent. Some representative results are summarized in Scheme 2. The reactions of 6- and 5-methylbenzoxazoles with CO_2 took place smoothly to give the corresponding hexyl esters **2a** and **2c**, which were isolated in 87% and 85% yield, respectively. The reaction of 4-methylbenzoxazole under the same conditions gave a lower yield of the corresponding ester **2b** (50%), probably because of the steric influence of the methyl group on the heterocyclic ring.

Various 5-arylated benzoxazole derivatives bearing either electron-donating (e.g., OMe) or electron-withdrawing (e.g., CF_3 and CN) functional groups at the aryl unit could be used in the carboxylation reaction to give the corresponding functionalized esters, such as **2h**, **2i**, and **2j**, selectively and in high yields. In the case of 5-(methylbenzoate)-substituted benzoxazole, the expected straightforward reaction product **2k** was isolated in 52% yield, along with a by-product **2k'** (25%), which was formed by transesterification with the *t*BuOH generated in situ. Chloride, bromide, and nitro groups could survive the reaction conditions to give the corresponding functionalized ester products such as **2e**, **2f**, and **2g**. In comparison with benzoxazoles, *N*-methylbenzoimidazole ($pK_a = 32.5$) afforded the corresponding ester **2l** in 14% yield, while 1,3,4-oxadiazole afforded the expected product **2m** in 38% yield; the low yield of these products is probably due to their weaker acidity.[10] Similarly, only a trace amount of the carboxylation products was observed in the reactions of substrates with higher pK_a values such as benzothiazole ($pK_a = 27.3$), 4-phenyloxazole, and benzofuran ($pK_a = 33.2$).

Several stoichiometric reactions were examined to elucidate the mechanism of the current catalytic process, (Scheme 3). As reported previously,[3d,11] the alkoxide Cu complex [Cu(IPr)(O*t*Bu)] could be easily obtained by the reaction of [Cu(IPr)Cl] with *t*BuOK. The reaction of [Cu(IPr)(O*t*Bu)] with 1.0 equivalent of benzoxazole gave the benzoxazolylcopper complex **3**, which was isolated in 93% yield. Colorless single crystals of **3** were obtained by recrystallization from THF/toluene (1:1). X-ray crystallographic analysis revealed that the benzoxazolyl group is bound to the Cu atom in an η^1 fashion, with an almost linear C(1)-Cu(1)-C(2) configuration ($\sphericalangle$C(1)-Cu(1)-C(2) = 174.4(2)°; Figure 1). The carboxylate complex **4** was isolated in 93% yield after exposure of **3** to 1 atm of CO_2 in THF at room temperature. X-ray crystallographic analysis established that the benzoxazolylcarboxylate unit in **4** is bound to the Cu atom in a chelating fashion through a carboxylate oxygen atom and the nitrogen atom to form a five-membered



Scheme 2. Copper-catalyzed carboxylation of aromatic heterocycles with carbon dioxide. Reaction conditions: [Cu(IPr)Cl] (5 mol%), substrate (1.0 mmol), KO*t*Bu (1.1 mmol), CO_2 (1 atm), THF (5 mL), 80°C, 14 h, then THF was evaporated, DMF (5 mL), RI (2.0 mmol), 80°C, 5 h. Yield of the isolated product. THF = tetrahydrofuran.



Scheme 3. Stoichiometric reactions of copper complexes.

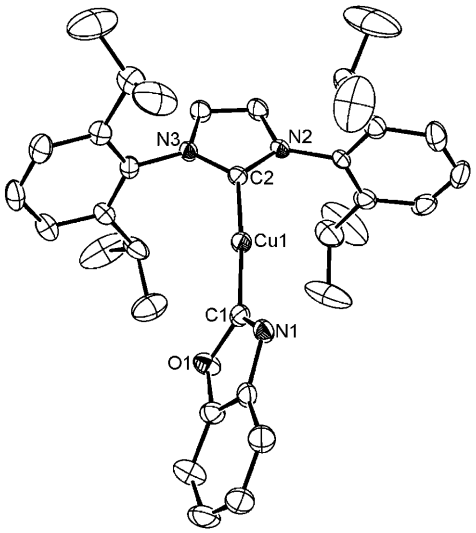


Figure 1. ORTEP structure of **3**. Thermal ellipsoids are set at 30% probability. Hydrogen atoms have been omitted for clarity. Selected bond lengths [Å] and angles [°]: Cu(1)-C(1) 1.905(4), Cu(1)-C(2) 1.903(4); C(1)-Cu(1)-C(2) 174.4(2).

ring (Figure 2). When **4** was kept under vacuum overnight or under a nitrogen atmosphere for one week at room temperature, decarboxylation took place to give **3** almost quantitatively. However, the reaction of the carboxylate complex **4** with one equivalent of *t*BuOK in THF afforded the potassium carboxylate salt and the copper alkoxide [Cu(IPr)(O*t*Bu)] quantitatively. It is also noteworthy that complexes **3**, **4**, and [Cu(IPr)(O*t*Bu)] all showed high catalytic activity in the carboxylation of benzoxazole under similar reaction conditions to afford the corresponding ester products, which were isolated in 78–83% yield.

On the basis of the above experimental observations, a possible mechanism for the copper-catalyzed carboxylation of heterocycles with CO_2 is proposed (Scheme 4). The initial metathesis reaction between [Cu(IPr)Cl] and *t*BuOK affords the copper alkoxide complex [Cu(IPr)(O*t*Bu)], which subsequently reacts with a heterocyclic compound to give the organocopper species **5** through activation (deprotonation) of the heterocyclic C–H bond. Insertion of CO_2 into the Cu–C bond in **5** furnishes the carboxylate **6**, which could release CO_2 to regenerate **5**. Further reaction of **6** with *t*BuOK would regenerate the copper alkoxide [Cu(IPr)(O*t*Bu)] and release the potassium carboxylate, which after reaction with alkyl iodide affords the ester product **2**.

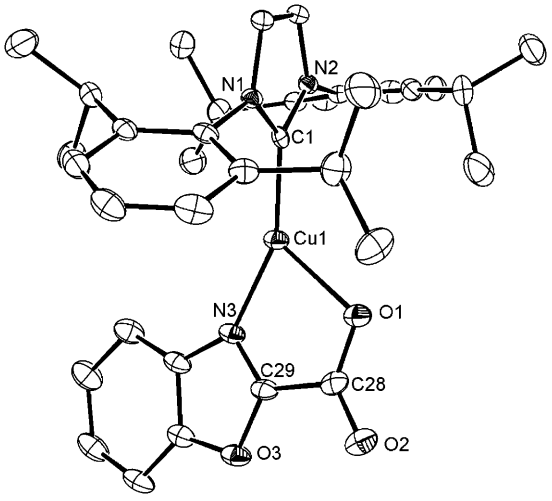
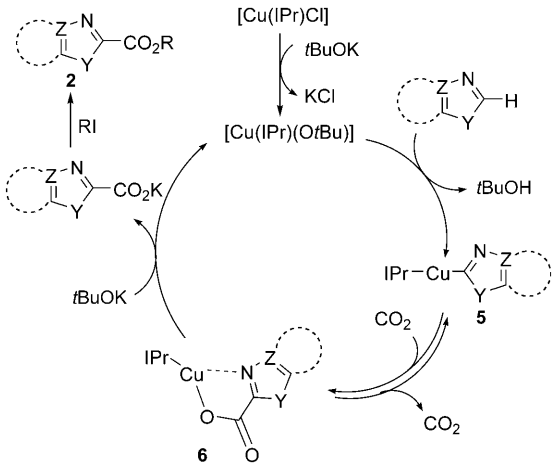


Figure 2. ORTEP structure of **4**. Thermal ellipsoids are set at 30% probability. Hydrogen atoms have been omitted for clarity. Selected bond lengths [Å] and angles [°]: Cu(1)-C(1) 1.872(3), Cu(1)-N(3) 1.957(2), Cu(1)-O(1) 2.183(2), O(1)-C(28) 1.257(3); C(1)-Cu(1)-N(3) 156.68(11), C(1)-Cu(1)-O(1) 121.46(10), N(3)-Cu(1)-O(1) 80.50(9).



Scheme 4. A possible mechanism for the direct carboxylation of aromatic heterocycles with carbon dioxide.

In summary, we have identified a novel protocol for the direct carboxylation of aromatic heterocyclic C–H bonds. This method has the unique advantages of employing CO_2 as a C1 source, simple heterocycles as substrates (no need to prepare preactivated substrates), and relatively cheap copper complexes as catalysts. Thus, this method constitutes an economical and environmentally benign process for the synthesis of heterocyclic carboxylic esters. Moreover, some key reaction intermediates such as the benzoxazolylcopper complex **3** and the carboxylate complex **4** have been isolated and structurally characterized, thus providing important insight into the mechanistic details of this reaction.

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[12] CCDC 782839 (**3**) and CCDC 782840 (**4**) contain 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.

