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Direct C−H Carboxylation with Carbon Dioxide Using 1,2,3-Triazol-5-ylidene Copper(I) Complexes

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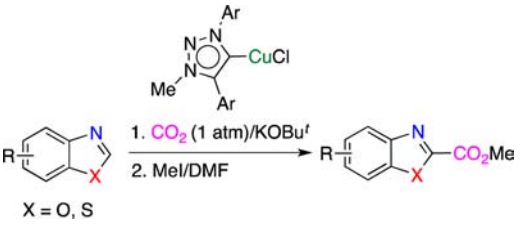
ABSTRACT



1,2,3-Triazol-5-ylidene copper(I) complexes (*tz*NHC-Cu) efficiently catalyzed the direct C−H carboxylation of benzoxazole and benzothiazole derivatives with CO_2 to give the corresponding esters in excellent yields after treatment with alkyl iodide. The *tz*NHC copper(I) complex, i.e., [(TPr)CuCl], worked somewhat more effectively than the corresponding imidazol-2-ylidene copper(I) complex [(IPr)CuCl] to give the carboxylation product in higher yields.

Carbon dioxide (CO_2) is of current interest in organic synthesis as a useful C1 source because it is an abundantly available, inexpensive, innoxious, and promising renewable resource.[1] As a result, CO_2 fixation has been intensively studied academically and industrially. However, organometallic reagents should be employed in C−C bond-forming reactions with CO_2 due to its high thermodynamic stability and low reactivity. Traditionally, the challenge of CO_2 fixation has been addressed through the use of strongly nucleophilic organometallic compounds, such as Grignard reagents.[2]

Other preactivated substrates such as organic halides have served as alternatives to carboxylation.[3] A more desirable synthesis of carboxylic acids would be the direct carboxylation of C−H bonds.[4] In recent years, Hou and Nolan's research groups independently succeeded in the C−H carboxylation of aromatic compounds using *N*-heterocyclic carbene (NHC) metal complexes as catalysts under mild reaction conditions.[4a−c] The NHC metal complexes provide an effective method for the synthesis of heteroaryl carboxylic acid derivatives, which are biologically active compounds.[5]

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We recently have shown that the 1,2,3-triazol-5-ylidene (*this type of carbene is abbreviated as tzNHC to distinguish it from conventional NHCs*)[6] copper(I) complex is a more active catalyst for the copper-catalyzed azide alkyne cycloaddition (CuAAC) reaction than the corresponding imidazol-2-ylidene NHC copper analogue.[7] The *tz*NHC copper(I) successfully catalyzed the reaction between a sterically crowded alkyne and a sterically crowded azide to give a highly sterically crowded 1,2,3-triazole in a reasonable yield. The efficiency of the *tz*NHC copper(I) complex may be attributed to the stronger donor property of the 1,2,3-triazol-5-ylidene ligand.[8] In order to extend the *tz*NHC ligands and their metal complexes to various synthetic reactions, we have applied the *tz*NHC-copper(I) complex to the C−H carboxylation of heteroaryl compounds with CO_2. We report here that the *tz*NHC-copper complex catalyzed direct C−H carboxylation effectively, not only with benzoxazole but also with benzothiazole derivatives.

1,4-Diaryl-3-methyl-1,2,3-triazol-5-ylidene-copper(I) complexes, i.e., (*tz*NHC)CuCl, were prepared by our previous method.[7] The abbreviations used in this paper for these *tz*NHC ligands are as follows: TPh, Ar = Ph; TMes, Ar = mesityl (2,4,6-trimethylphenyl); TPr, Ar = 2,6-diisopropylphenyl (shown in Figure 1). (TPr)CuCl was first prepared in this work, and (TPh)CuCl and (TMes)CuCl were prepared previously.We first evaluated the activity of (TPr)CuCl by carrying out a time-dependent monitoring of the reaction of benzoxazole **1a** with CO_2. The yield vs time graphs of (TPr)CuCl and the corresponding imidazol-2-ylidene copper(I) complex, i.e., (IPr)CuCl, for comparison are shown in Figure 2. A typical reaction was carried out as follows. To a Schlenk tube were added 1.2 equiv of *t*-BuOK (with respect to benzoxazole) and copper complex (5 mol %) in THF. Next, CO_2 gas was introduced into the tube followed by the addition of benzoxazole. The tube was sealed and heated at 80 °C under 1 atm of CO_2 for the prescribed times. THF was removed under vacuum, MeI (2 equiv to benzoxazole) in DMF was added to the tube, and the solution was heated at 80 °C for 1 h. No decomposition of the catalysts or precipitation of metallic copper was observed during the reaction. The product benzoxazole carboxylic acid was thus transformed to its methyl ester, and yields were determined by GC using biphenyl as an internal standard. As seen in the graph, (TPr)CuCl catalyzed the reaction faster than (IPr)CuCl, and the yield of the product reached 91% after 3 h. The reaction with (TPr)CuCl was nearly complete after 5 h to give the product in 93% yield, while the reaction with (IPr)CuCl gave the product in 86% yield. The yield was constant after 8 h for the reactions with both (TPr)CuCl and (IPr)CuCl, showing that the reaction was terminated within 8 h, although the C−H carboxylation catalyzed by (IPr)CuCl was carried out for 14 h in the original work by Hou's research group.[4a]

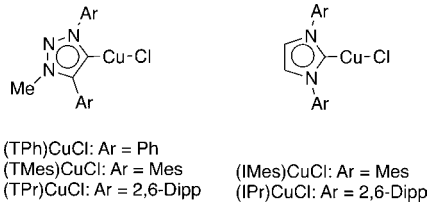

Figure 1. 1,2,3-Triazol-5-ylidene copper and imidazol-2-ylidene copper complexes.

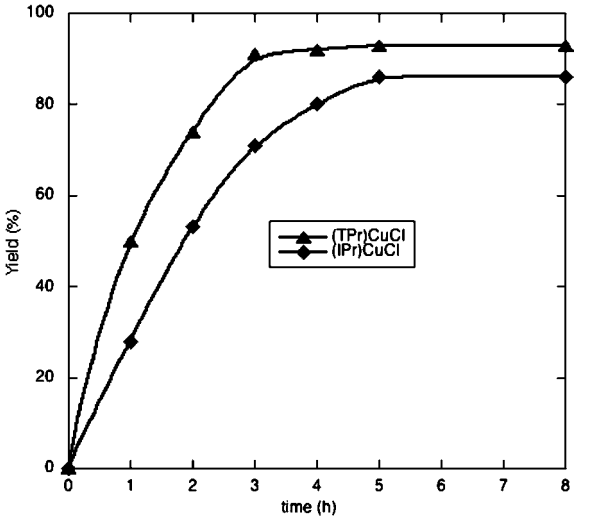

Figure 2. Time vs yield (%) plot for (TPr)CuCl-catalyzed direct carboxylation of benzoxazole: (▲) (TPr)CuCl; (◆) (IPr)CuCl.

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(7) (a) Nakamura, T.; Terashima, T.; Ogata, K.; Fukuzawa, S.-i. *Org. Lett.* **2011**, *13*, 620. Related recent papers on *tz*NHCs: (b) Nakamura, T.; Ogata, K.; Fukuzawa, S.-i. *Chem. Lett.* **2010**, *39*, 920. (c) Inomata, S.; Hiroki, H.; Terashima, T.; Ogata, K.; Fukuzawa, S.-i. *Tetrahedron* **2011**, *67*, 7263. (d) Terashima, T.; Inomata, S.; Ogata, K.; Fukuzawa, S.-i. *Eur. J. Inorg. Chem.* **2012**, 1387.

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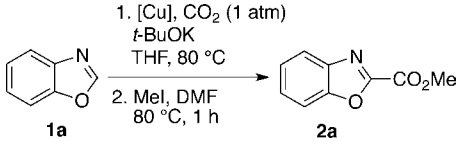
The catalytic activities of the other *tz*NHC-copper(I) complexes [(TMes)CuCl, (TPh)CuCl] and the imidazol-2-ylidene copper(I) complex [(IMes)CuCl] were also examined under the same conditions. The results are summarized in Table 1 where isolated yields by PTLC were shown. These complexes catalyzed the reaction slower than (TPr)CuCl and (IPr)CuCl and required a longer reaction time (14 h) to obtain reasonable yields, albeit lower than those achieved with (TPr)CuCl and (IPr)CuCl. From these experiments, *tz*NHC-copper(I) complexes showed somewhat higher catalytic activities than their corresponding NHC-copper(I) complexes; however, both of them gave almost the same product yields after a long reaction time. The more sterically hindered and more electron-rich ligands made the catalyst more active, whereas (TPh)CuCl was the least active catalyst. However, (TPh)CuCl can still be used practically as a catalyst considering the accessibility of its precursor (1,4-diphenyl-1,2,3-triazole) by the click reaction and gives a moderate but higher yield (75%) than (IMes)CuCl. It must be noted that 1,2,3-triazolium salt (carbene precursor) alone hardly catalyzed the reaction (Table 1, entry 6).

Table 1. Optimization of the Copper-Catalyzed Direct Carboxylation of Benzoxazole with CO_2[a]

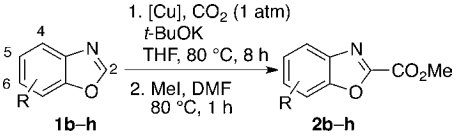


entry	[Cu]	time (h)	yield (%)[b]
1	(TPr)CuCl	8	86
2	(IPr)CuCl	8	84
3	(TMes)CuCl	14	77
4	(IMes)CuCl	14	71
5	(TPh)CuCl	14	75
6	TPr·HBF_4	14	0

[a] Benzoxazole (1.0 mmol), *t*-BuOK (1.2 mmol), [Cu] (0.05 mmol); THF (5 mL), CO_2 (1 atm), 80 °C, then evaporation of THF under vacuum, DMF (5 mL), MeI (2.0 mmol), 80 °C, 1 h. [b] Isolated yield.

The carboxylation of various substituted benzoxazoles **1b**–**h** was examined using the most effective (TPr)CuCl catalyst under the same conditions. The product carboxylic acids were isolated as their methyl esters after alkylation with MeI as the prescribed method. The results are summarized in Table 2. The reaction with 5- and 6-methylbenzoxazoles afforded the products in good yields (entries 1–2). The reaction with 5-phenylbenzoxazole also gave a high yield (88%) (entry 3). The reaction with 5-nitrobenzoxazole gave a low yield (41%) which was on the same order as (IPr)CuCl (entry 4). 5-Halogenated (R = Cl, Br) benzoxazoles tolerated the reaction, with carboxylation occurring only at the 2-oxazole carbon to give the corresponding esters in good yields (entries 5–6); carboxylation at the C-halogen position was hardly observed. For the reaction with 4-methylbenzoxazole, the product was obtained in low yield (entry 7) as with (IPr)CuCl (50%),[4a] perhaps due to steric repulsion between the substituent at the 4-position and the ligand of the complex. When the less hindered (TPh)CuCl catalyst was used instead of (TPr)CuCl, the yield was improved up to 77% (entry 8). For sterically demanding substrates, the less hindered (TPh)CuCl may be suitable as a catalyst.

Table 2. Direct Carboxylation with Substituted Benzoxazoles[a]



entry	R	product, yield (%)[b]
1	**1b**, 5-Me	**2b**, 79
2	**1c**, 6-Me	**2c**, 68
3	**1d**, 5-Ph	**2d**, 88
4	**1e**, 5-NO_2	**2e**, 41
5	**1f**, 5-Cl	**2f**, 69
6	**1g**, 5-Br	**2g**, 86
7	**1h**, 4-Me	**2h**, 42
8[c]	**1h**, 4-Me	**2h**, 77

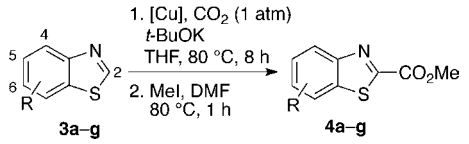
[a] **1b**–**h** (1.0 mmol), *t*-BuOK (1.2 mmol), (TPr)CuCl (0.05 mmol); THF (5 mL), CO_2 (1 atm), 80 °C, then evaporation of THF under vacuum, DMF (5 mL), MeI (2.0 mmol), 80 °C, 1 h. [b] Isolated yield. [c] (TPh)CuCl was used as a catalyst.

Next, the (TPr)CuCl catalyst was applied to the reaction with other azoles such as benzothiazole and *N*-methylbenzimidazole under the same conditions. For the reaction with benzothiazole, the corresponding methyl ester was obtained in 75% yield after methylation of the carboxylic acid, while a trace amount of carboxylation product was obtained from *N*-methylbenzimidazole. It is amazing that (TPr)CuCl afforded the carboxylation product of benzothiazole in good yield (75%) considering that (IPr)CuCl only gives a trace amount of the product.[9] The substrate scope of various substituted benzothiazoles **3a**–**g** was examined, and the results are summarized in Table 3. Electron-donating substituents at the 6-position gave yields comparable to that with an electron-neutral substrate (entries 1–3), while electron-withdrawing substituents gave lower yields of products (entries 4–5). The reactions with 4-substituted benzothiazoles gave trace amounts of products, and the use of (TPh)CuCl gave products in low yields (entries 6–7).

We attempted to isolate the intermediate of the reaction to elucidate the reaction mechanism. Thus, when benzoxazole was treated with a stoichiometric amount of

(9) Since the (IPr)CuOH complex is reported to be an effective catalyst for a direct C–H carboxylation of benzothiazole, we planned to prepare (TPr)CuOH.[4b] However, a recent report shows that transmetallation of *tz*NHCsCuCl with CsOH gives *tz*NHC oxide, not copper hydroxide. Petronilho, A.; Müller-Bunz, H.; Albrecht, M. *Chem. Commun.* **2012**, *48*, 6499.

Table 3. Direct Carboxylation with Substituted Benzothiazoles[a]



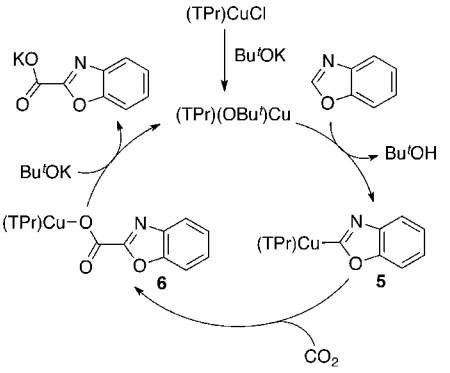
entry	R	product, yield (%)[b]
1	**3a**, H	**4a**, 75
2	**3b**, 6-Me	**4b**, 79
3	**3c**, 6-MeO	**4c**, 72
4	**3d**, 6-Cl	**4d**, 66
5	**3e**, 6-Br	**4e**, 44
6[c]	**3f**, 4-Me	**4f**, 33
7[c]	**3g**, 4-Cl	**4g**, 34

[a] **3a**–**g** (1.0 mmol), *t*-BuOK (1.2 mmol), (TPr)CuCl (0.05 mmol); THF (5 mL), CO_2 (1 atm), 80 °C, then evaporation of THF under vacuum, DMF (5 mL), MeI (2.0 mmol), 80 °C, 1 h. [b] Isolated yield. [c] (TPh)CuCl was used as a catalyst.

(TPr)CuCl and *t*-BuOK, the benzoxazole copper complex **5** was isolated in 49% yield. In the ^{13}C NMR spectrum (THF-d_8), distinctive signals were observed at 171.5 and 196.0 ppm. The former signal is readily assigned to the carbene carbon of 1,2,3-triazol-5-ylidene, and the latter signal can be assigned as the oxazole *C*-Cu since the signal of *C*-Cu is observed at a similar position (195.8 ppm) in the corresponding imidazol-2-ylidene copper complex, (IPr)(benzoxazole)Cu. It is reasonable to identify the copper complex as the (TPr)(benzoxazole)Cu complex. We can assume the reaction mechanism is similar to that proposed for the (IPr)CuCl-catalyzed reaction.[4a,10]

In the first step, (TPr)Cu(OBu^t) is generated by the metal exchange reaction of (TPr)CuCl with *t*-BuOK, and then the copper alkoxide reacts with benzoxazole to afford (TPr)(benzoxazole)Cu by deprotonation (C−H activation) of the benzoxazole C−H bond (Scheme 1). Insertion of CO_2 into the Cu−C bond yields the copper carboxylate **6**, which leads to the potassium carboxylate by metal exchange with *t*-BuOK, during which time the copper alkoxide regenerates.

Scheme 1. Plausible Reaction Mechanism



In conclusion, we have prepared 1,2,3-triazol-5-yidene based copper complexes that catalyzed the direct C−H carboxylation of heteroaromatic compounds effectively to give the corresponding carboxylic acids and esters. The complexes promoted the reaction somewhat more effectively than the corresponding imidazol-2-ylidene copper complexes. (TPr)CuCl was the most effective catalyst, but readily accessible (TPh)CuCl could be used practically as well.

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Supporting Information Available. Full experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra (PDF) for all products; crystallographic data for (TPr)CuCl in a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.