

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

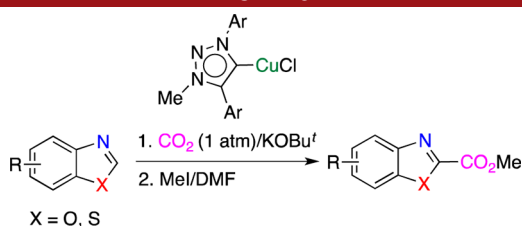
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ABSTRACT



1,2,3-Triazol-5-ylidene copper(I) complexes (*tzn*HCu) efficiently catalyzed the direct C—H carboxylation of benzoxazole and benzothiazole derivatives with CO₂ to give the corresponding esters in excellent yields after treatment with alkyl iodide. The *tzn*HCu 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 (CO₂) is of current interest in organic synthesis as a useful C1 source because it is an abundantly available, inexpensive, innocuous, and promising renewable resource.¹ As a result, CO₂ fixation has been intensively studied academically and industrially. However, organometallic reagents should be employed in C—C bond-forming reactions with CO₂ due to its high thermodynamic stability and low reactivity. Traditionally, the

challenge of CO₂ 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 *tzNHC* 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 *tzNHC* 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 *tzNHC* ligands and their metal complexes to various synthetic reactions, we have applied the *tzNHC*-copper(I) complex to the C–H carboxylation of heteroaryl compounds with CO₂. We report here that the *tzNHC*-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., (*tzNHC*)CuCl, were prepared by our previous method.⁷ The abbreviations used in this paper for these *tzNHC* 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

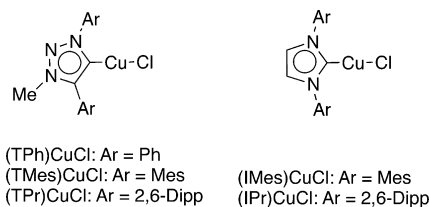


Figure 1. 1,2,3-Triazol-5-ylidene copper and imidazol-2-ylidene copper complexes.

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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 CO₂. 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, CO₂ 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 CO₂ 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}

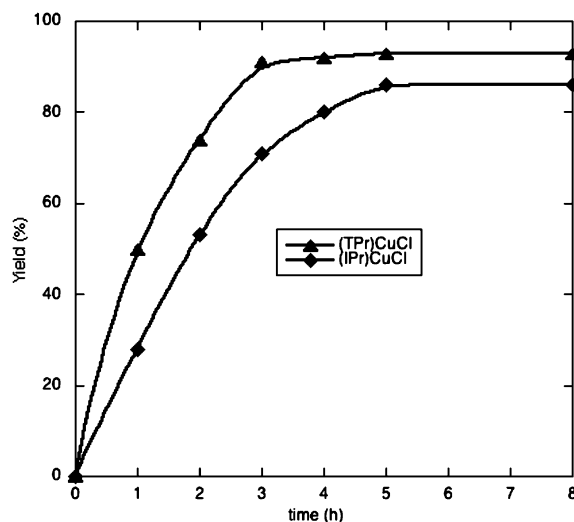
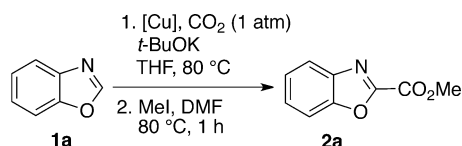


Figure 2. Time vs yield (%) plot for (TPr)CuCl-catalyzed direct carboxylation of benzoxazole: (▲) (TPr)CuCl; (◆) (IPr)CuCl.

(8) (a) For a review, see: Crowley, J. D.; Lee, A.-L.; Kilpin, K. L. *Aust. J. Chem.* **2011**, *64*, 1118. (b) Mathew, P.; Neels, A.; Albrecht, M. *J. Am. Chem. Soc.* **2008**, *130*, 13534. (c) Guisado-Barrios, G.; Bouffard, J.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 4759.

The catalytic activities of the other *tz*NHC-copper(I) complexes [(TMe)₃CuCl], (TPh)₃CuCl and the imidazol-2-ylidene copper(I) complex [(IMes)₃CuCl] 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)₃CuCl and (IPr)₃CuCl and required a longer reaction time (14 h) to obtain reasonable yields, albeit lower than those achieved with (TPr)₃CuCl and (IPr)₃CuCl. 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)₃CuCl was the least active catalyst. However, (TPh)₃CuCl 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)₃CuCl. 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 CO₂^a



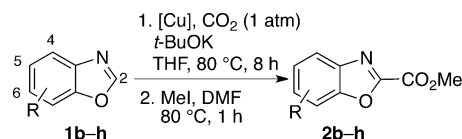
entry	[Cu]	time (h)	yield (%) ^b
1	(TPr) ₃ CuCl	8	86
2	(IPr) ₃ CuCl	8	84
3	(TMe) ₃ CuCl	14	77
4	(IMes) ₃ CuCl	14	71
5	(TPh) ₃ CuCl	14	75
6	TPr·HBF ₄	14	0

^a Benzoxazole (1.0 mmol), *t*-BuOK (1.2 mmol), [Cu] (0.05 mmol); THF (5 mL), CO₂ (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)₃CuCl 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)₃CuCl (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)₃CuCl (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)₃CuCl catalyst was used instead of (TPr)₃CuCl, the yield was improved up to 77% (entry 8). For sterically demanding substrates, the less hindered (TPh)₃CuCl may be suitable as a catalyst.

Table 2. Direct Carboxylation with Substituted Benzoxazoles^a



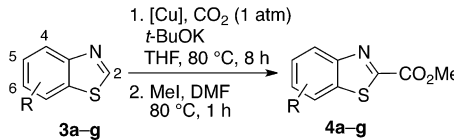
entry	R	product, yield (%) ^b
1	1b , 5-Me	2b , 79
2	1c , 6-Me	2c , 68
3	1d , 5-Ph	2d , 88
4	1e , 5-NO ₂	2e , 41
5	1f , 5-Cl	2f , 69
6	1g , 5-Br	2g , 86
7	1h , 4-Me	2h , 42
8 ^c	1h , 4-Me	2h , 77

^a **1b–h** (1.0 mmol), *t*-BuOK (1.2 mmol), (TPr)₃CuCl (0.05 mmol); THF (5 mL), CO₂ (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)₃CuCl was used as a catalyst.

Next, the (TPr)₃CuCl 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)₃CuCl afforded the carboxylation product of benzothiazole in good yield (75%) considering that (IPr)₃CuCl 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)₃CuCl 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)₃CuOH complex is reported to be an effective catalyst for a direct C–H carboxylation of benzothiazole, we planned to prepare (TPr)₃CuOH.^{4b} However, a recent report shows that transmetalation of *tz*NHCsCuCl with CsOH gives *tz*NHC oxide, not copper hydroxide. Petronilho, A.; Müller-Bunz, H.; Albrecht, M. *Chem. Commun.* **2012**, 48, 6499.

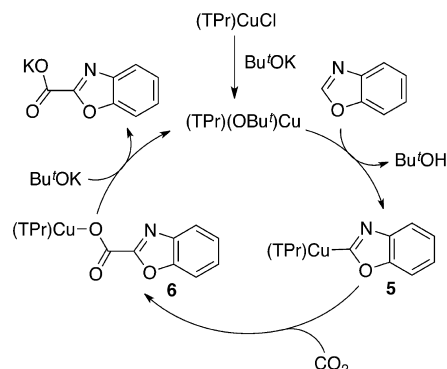
Table 3. Direct Carboxylation with Substituted Benzothiazoles^a


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), CO₂ (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 ¹³C 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 CO₂ into the Cu–C bond yields the copper carboxylate **6**, which leads to the potassium carboxylate by metal ex-

Scheme 1. Plausible Reaction Mechanism

change with *t*-BuOK, during which time the copper alkoxide regenerates.

In conclusion, we have prepared 1,2,3-triazol-5-ylidene 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 ¹³C 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.