C–H/N–H Bond Functionalization

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Carboxylation of N–H/C–H Bonds Using N-Heterocyclic Carbene Copper(I) Complexes**

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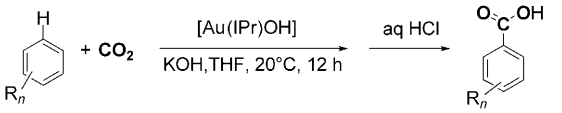
Transition-metal-mediated carboxylation of N–H and C–H bonds represents a nascent area in organic chemistry, because these reactions enable the efficient construction of valuable synthons.[1] Palladium-catalyzed N-carbonylation–oxidation sequences are well-documented, but they often require high catalyst loadings and the use of either gaseous carbon monoxide or Group VI metal–carbonyl complexes.[2] An analogous transformation sequence is also promoted by molybdenum and tungsten carbonyl amine species under forcing temperatures.[3] Important advances in C-carboxylation reactions have been made using ruthenium[1a] and nickel complexes;[4] however, examples under mild conditions are elusive. The carboxylation of allylstannanes,[5] organozincs,[6] and organoboronic esters[7,8] have been described as a new method to improve functional group tolerance, but the stoichiometric consumption of an organometallic reagent remains a disadvantage. The reactivity of allylstannanes and organozinc compounds necessitates handling under an inert atmosphere, while organoboronic esters are expensive. A protocol has recently been developed for the C-carboxylation of simple aromatic groups under very mild reaction conditions. In this case the strongly basic [Au(IPr)(OH)][9] (IPr=1,3-bis(diisopropyl)phenylimidazol-2-ylidene[10]) complex ($pK_{aDMSO} = 30.3(2)$) was used,[11] which contains an N-heterocyclic carbene (NHC) ligand [Eq. (1)].



(1)

As the initial C–H activation proceeds through a simple protonolysis mechanism,[12] simple Brønsted/Lowry acid/base theory was used as an effective method to predict the feasibility and site selectivity of such a C–H bond functionalization. In this earlier report, an alternative to the use of the well-defined [Au(IPr)(OH)] was devised, which made use of its synthetic precursor, namely [Au(IPr)Cl], in the presence of KOH to generate [Au(IPr)(OH)] in situ. The possibility to perform this exact C–H bond functionalization with [Cu(IPr)Cl][13] was also demonstrated.[11]

We have recently developed the synthetically versatile analogue [Cu(IPr)(OH)] (**1**),[14] for which a pK_{aDMSO} value of 27.7(2) was determined by potentiometric titrimetry.[15] As the pK_a value for **1** was found to be inferior to that of [Au(IPr)(OH)], we suspected on the basis of this simple acid/base reactivity prediction method that the scope of the C–H bond carboxylation might be more limited. However, in view of the straightforward synthetic access to the precursor to **1**, we deemed the exploration of such a powerful and simple functionalization protocol worthy of exploration. Herein, we show that **1** is a highly regioselective catalyst for the carboxylation of N–H and C–H bonds that possess a pK_{aDMSO} value of less than 27.7.[16]

As 2-substituted *N*-carbamoylimidazoles represent an important motif in natural product chemistry,[17] 2-methyl-1*H*-imidazole (**2a**) was selected as the model substrate ($pK_{aDMSO} = 19.2$). A rudimentary screening of the reaction parameters defined the optimized catalyst system as 3 mol% of [Cu(IPr)(OH)] and 1.1 equivalents of CsOH in THF (Table 1, entry 1). This solution was heated to 40°C under 1.5 bar of CO_2 for 12 hours, then quenched with iodomethane

Table 1: N-carboxylation of 2-methyl-*1H*-imidazole with NHC–copper(I) catalysts.[a]

2a **3a**

Entry	[Cu]	Loading (mol%)	Base	Yield [%][b]
1	[Cu(IPr)(OH)] (**1**)	3.0	CsOH	94
2	–	–	CsOH	0
3	[Cu(IPr)(OH)] (**1**)	3.0	–	0
4	[Cu(IPr)(OH)] (**1**)	1.5	CsOH	88
5	[Cu(IPr)Cl]	3.0	NaOH	72
6	[Cu(IPr)Cl]	3.0	KOH	84
7	[Cu(IPr)Cl]	3.0	CsOH	91
8	[Cu(IPr)Cl]	1.5	CsOH	69
9	[Cu(SIPr)Cl]	1.5	CsOH	28
10	[Cu(IMes)Cl]	1.5	CsOH	16
11	[Cu(SIMes)Cl]	1.5	CsOH	23

[a] Conditions: 1 mmol **2a**, 1.1 mmol base, $p(CO_2) = 1.5$ bar, 40°C, 20 Hz, 2 mL THF, $t = 8$ h. [b] Yield of isolated product.

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to afford the stable *N*-methyl-2-methylimidazole carboxylate (**3a**) in quantitative yield.

The parent acid was isolated as a white solid in 88% yield after acid hydrolysis of the solution containing the catalyst, but underwent spontaneous decarboxylation (28% in 3 h at 22°C). Under otherwise analogous reaction conditions, no conversion of **2a** was observed in the absence of [Cu(IPr)(OH)], and no catalyst turnover was observed in the absence of CsOH. Traces of oxygen led to the decomposition of **1** within one hour and must therefore be stringently excluded during loading. Catalyst loading could be decreased to 1.5 mol% with a slight erosion of the yield (Table 1, entry 4). Treatment of [Cu(IPr)Cl] in situ with alternative alkali metal hydroxide reagents could also mediate the N-carboxylation of **2a** (Table 1, entries 5–7). The effect of the base was evaluated and reaction plots indicate that although NaOH and KOH are effective bases, CsOH is most effective in generating the active species when carboxylation reactions are conducted at 40°C.[15] In reactions where the active species is generated in situ, catalyst turnover was only observed after approximately three hours and the profiles of CO_2 consumption in time suggest that the kinetics of the carboxylation reaction are relatively independent of the IPr–copper(I) source beyond the induction time (Figure 1).

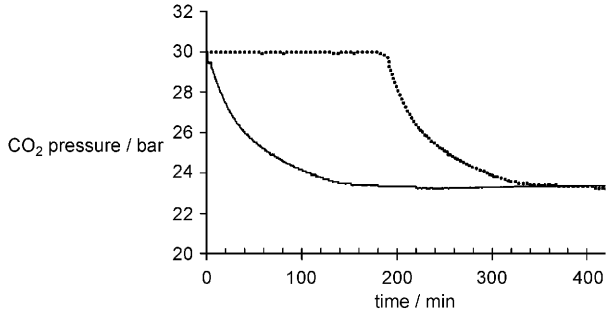


Figure 1. Reaction profiles for the N-carboxylation of 2-methyl-1*H*-imidazole with **1** at 40°C: well-defined complex (bottom, ——), complex generated in situ (top, -----).

The use of other NHC ligands (Figure 2) gave significantly lower yields of **3a** under analogous reaction conditions (Table 1, entries 9–11). The IPr ligand appears optimum at this stage.

The scope of N-carboxylation under the optimized reaction conditions is outlined in Table 2. The imidazole, indole, and pyrazole derivatives were transformed cleanly and quantitatively to the corresponding methyl esters (Table 2, entries 1–3). No further purification step had to be used after the simple work-up (extraction, separation, and conversion into ester).[15] Competitive O and C reactivity has been reported to render regioselective carbamoylation of indolinones and pyrrolones problematic.[18] It was, therefore, gratifying to observe **3e** as the only product (Table 2, entry 4). Substrates possessing N–H bonds with pK_a values above 27.7 fail to undergo carboxylation, thereby supporting the usefulness of the prediction based on the pK_a value. This method was then extrapolated to the carboxylation of C–H

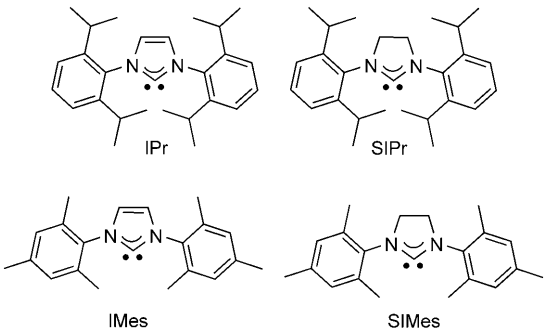
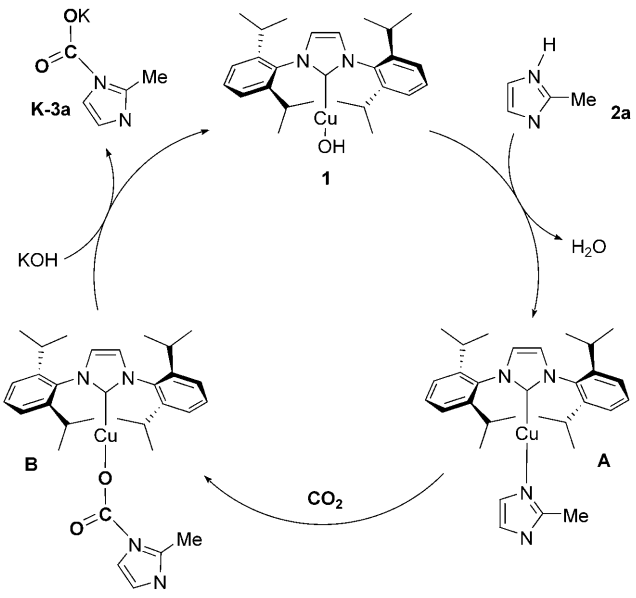


Figure 2. NHC ligands used in this study. IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, SIMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene.

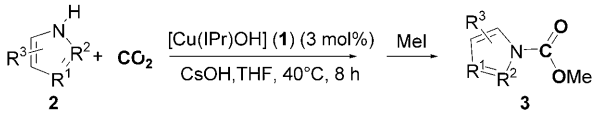
bonds (Table 3). Gas chromatography analysis showed that the conversion of heteroaromatic compounds **4a–4c** under the aforementioned reaction conditions was lethargic (16–29%). However, simply increasing the temperature to 65°C significantly improved the catalyst turnover to afford **5a–5c** in quantitative yields (Table 3, entries 1–3). It is worth noting that the C2-selective carboxylation of **4c** is distinct from the Friedel–Crafts mechanism, which promotes C3 selectivity,[20] thus highlighting the complementarily of this method to the classical transformation. Polyfluorinated arenes **4d–4e** were also found to undergo clean conversion into the corresponding carboxylic acids under these reaction conditions (Table 3, entries 4 and 5). Moreover, the presence of two activated C–H bonds in **4e** allowed facile synthesis of the symmetrical terephthalic acid **5f** when 2.2 equivalents of CsOH were employed (Table 3, entry 6).

Preliminary mechanistic studies suggest that the catalytic cycle is very similar to the one proposed for the gold-catalyzed carboxylation reaction[11] (Scheme 1), where protonolysis of 2-methyl-1*H*-imidazole (**2a**) by

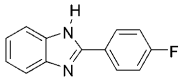
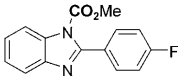
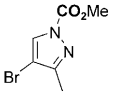
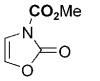
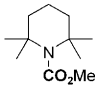


Scheme 1. Proposed catalytic cycle for the N-carboxylation of 2-methyl-1*H*-imidazole with [Cu(IPr)(OH)] (**1**).

Table 2: N–H-carboxylation of N-heterocycles with [(Cu(IPr)(OH)].

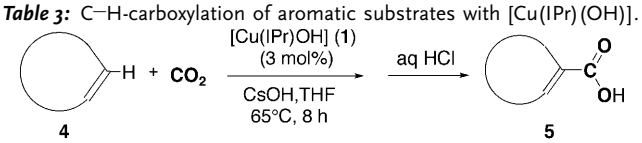


2 3

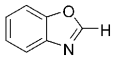
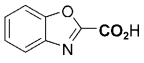
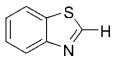
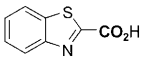
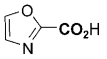
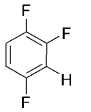
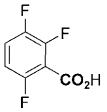
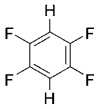
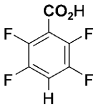
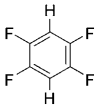
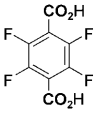
Entry	Substrate		pK_a[a] (N–H)	Product (Yield [%])[b]		TOF [h^{-1}][c]
1		**2b**	18.6		**3b** (88)	17.5
2		**2c**	16.4		**3c** (93)	19.1
3		**2d**	19.8		**3d** (85)	16.6
4		**2e**	15.0		**3e** (90)	20.3
5		**2f**	37.0		**3f** (0)	–
6		**2g**	30.6		**3g** (0)	–

[a] pK_a values taken from Ref. [16]. [b] Yields of the isolated product are the average of three runs. [c] Turnover frequency determined after 1 h, defined as mol of ester per mol of Cu per hour.

Table 3: C–H-carboxylation of aromatic substrates with [Cu(IPr)(OH)].



4 5

Entry	Substrate		pK_a[a](C–H)	Product (Yield [%])[b]	
1		**4a**	24.8		**5a** (90)
2[c]		**4b**	27.3		**5b** (82)
3		**4c**	27.7		**5c** (77)
4		**4d**	26.1		**5d** (85)
5		**4e**	23.1		**5e** (93)
6		**4e**	23.1		**5f** (80)[d]

[a] pK_a values taken from Ref. [16]. [b] Yields of the isolated product are the average of three runs. [c] See Ref. [19]. [d] Catalysis conducted with 2.2 equiv of CsOH.

[Cu(IPr)(OH)] (**1**) generates the copper(I)-imidazole species **A**. Nucleophilic addition of the imidazole ligand to the electron-deficient carbon atom of CO_2 effects insertion to give the corresponding carboxylate complex **B**. The cycle proceeds with a salt metathesis involving KOH to regenerate **1**, with concurrent precipitation of potassium 2-methyl-1*H*-imidazole-1-carboxylate (**K-3a**).

In summary, we have demonstrated the ability of NHC copper(I) hydroxide complexes to enable the regioselective carboxylation of N–H and C–H bonds that are predicted to be suitably acidic by Brønsted/Lowry theory. The copper-based system permits a significant range of N–H and C–H carboxylation reactions. Current efforts are focused on understanding how variation in the composition of the catalyst can influence this potentially quite powerful transformation.

Experimental Section

Representative general procedure for the catalytic carboxylation with NHC-Cu^I complexes: A reaction tube was charged with a solution of [Cu(IPr)(OH)] (14.0 mg, 0.03 mmol), CsOH (164.9 mg, 1.1 mmol), and tetradecane (0.1 mL, 0.19 mmol) in THF (1.7 mL) under 1.5 bar of CO_2. The mixture was incubated for about 15 min at 40 °C with vigorous stirring (1450 rpm). A solution of the aromatic substrate (1 mmol) in THF (0.3 mL) was introduced through a CO_2-flushed syringe. The reaction was run at 40 °C for 12 h, then quenched with iodomethane (62 μL, 1 mmol; or 1 mmol HCl in the case of carboxylic acid formation). The product mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (6 mL), washed with 15 % aqueous NaCl (3 × 4 mL), and dried over Na_2SO_4. Volatiles were removed under reduced pressure to afford the methyl carboxylate.

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