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Cu-Catalysed carboxylation of aryl boronic acids with CO₂[†]Onkar S. Nayal,^a Junting Hong,^a Yang Yang^b and Fanyang Mo^b*^{a,c}

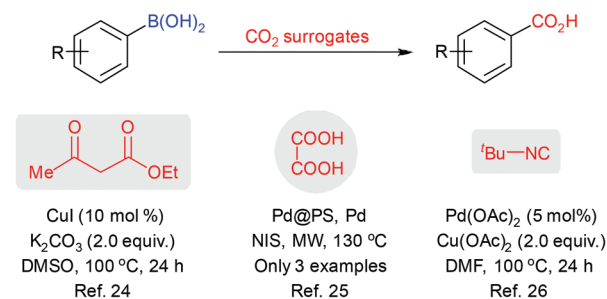
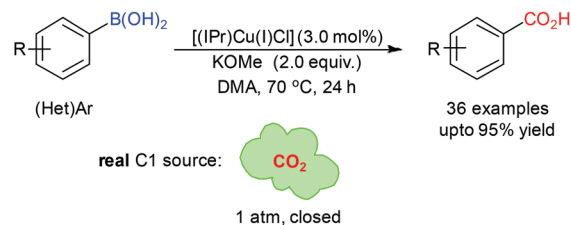
A copper/N-heterocyclic carbene (NHC) catalysed carboxylation of aryl boronic acids under one atmospheric pressure of CO₂ has been developed. A wide range of aryl boronic acids was transformed into benzoic acid derivatives in moderate to high yields. The carboxylation method shows excellent functional group compatibility, and sensitive functional groups such as carbonyls, esters, and nitriles were tolerated. Mechanistic studies revealed the vital role of the base in promoting the transmetalation step for this copper-catalysed carboxylation.

Introduction

The efficient conversion and utilisation of carbon dioxide (CO₂), the primary component of greenhouse gases, is of pivotal importance to combat global warming.^{1–3} In this context, the catalytic carboxylation of organic molecules with carbon dioxide represents a green and sustainable alternative for the synthesis of value-added chemicals.⁴ In recent years, CO₂ has been used as the C1 source in various organic transformations.⁵ Among these processes, synthesis of carboxylic acids with CO₂ through C–C bond formation is particularly attractive,^{6–8} in part due to the ubiquity of carboxylic acids in various bioactive natural products,⁹ agrochemicals¹⁰ and pharmaceuticals.^{11–13} Owing to the kinetic inertness and thermodynamic stability of carbon dioxide, highly reactive and air-sensitive organometallic reagents were usually used as the starting materials for nucleophilic carboxylation in previously developed approaches.³ However, the relatively low functional group tolerance of these organometallic species hampers their widespread application.

To overcome these challenges, in the past decades, organoboron reagents have been applied as the precursor to carboxylic acids due to their ease of handling, broad availability and functional group compatibility.¹⁴ In this regard, Iwasawa,^{15,16} Hou,^{17,18} Zhang and Lu,¹⁹ Nolan²⁰ and Riss groups²¹ have reported efficient protocols for the synthesis of

carboxylic acids from aryl and alkenyl boronic esters with CO₂. Despite these recent advances, the carboxylation of organoboronic acids, which constitute the simplest and most broadly available class of organoboron reagents,²² still remain underdeveloped.²³ Previous efforts^{24–26} in engaging arylboronic acids for the transition-metal-catalysed carboxylation have relied on various carbon dioxide surrogates including oxalic acid, acetyl acetate, and isocyanide (Scheme 1a). To date, the direct use of the most desirable C1 source for carboxylation,

a) Previous approaches: carboxylation reactions with CO₂ surrogatesb) This Work: Utilization of CO₂ as a real C1 source

Scheme 1 a) Previous strategies for the carboxylation reaction with various CO₂ surrogates. (b) This work: Utilization of CO₂ as a real C1 source for carboxylation reaction.

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namely carbon dioxide, has remained unsuccessful. Herein, we report an efficient and economical approach to utilise CO₂ for the synthesis of benzoic acids from boronic acids using an NHC-supported copper catalyst.

We started our investigation by evaluating a series of catalysts, bases, solvents and reaction temperature to facilitate the conversion of boronic acid (**1ah**) to carboxylic acid (**2ah**). After an extensive survey of reaction parameters (for details, see ESI Tables S1–4[†]), 82% yield of the desired product was obtained using 3.0 mol% [(IPr)Cu(I)Cl] and 2.0 equiv. of KOMe in DMA at 70 °C (Table 1, entry 1). The use of other alkoxide bases provided low yields of desired product due to incomplete conversion (Table 1, entries 2 and 3). Further evaluation of base stoichiometry revealed that 2.0 equiv. of KOMe to be optimal (Table 1 entries 1, 4 and 5 and see ESI, Table S4[†]). In addition, lowering the reaction temperature from 70 °C to 50 °C resulted in sluggish reaction (Table 1, entry 6), although the yield of the desired product could not be further improved by increasing the temperature (Table 1, entry 7). Moreover, control experiments show that both the catalyst and the base are critical to this transformation (Table 1, entries 8 and 9). Furthermore, trace quantities of water resulted in the undesired protodeboronation (Table 1, entries 10–12). Among all the solvents studied, DMA was found to be the best for this carboxylation (Table 1, entries 13–15 and see ESI, Table S3[†]).

We next examined the substrate scope of aryl boronic acids under these reaction conditions (Scheme 2). Electron-deficient substrates were successfully converted to the corresponding carboxylic acids (**2a–2l**). Halogen-substituted aryl boronic acids were also compatible under optimized reaction conditions (Scheme 2, **2a–2g**). A range of sensitive functional

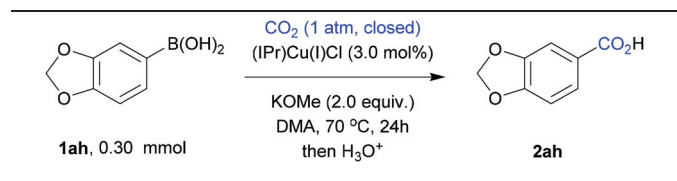
groups such as carbonyls, esters, nitriles and carboxylic acids were compatible with our protocol (Scheme 1, **2h–2k**). Furthermore, 1,4-phenylenediboronic acid also provided the corresponding dicarboxylated product in excellent yield (Scheme 1, **2l**).

Aryl boronic acids possessing an electron-donating group were also excellent substrates for this transformation. Amine substituted aryl boronic acids could be effectively converted to the desired products (Scheme 2, **2m–2n**), although free amines were not compatible (see ESI[†]). Up to 73% yield of the desired carboxylated product was obtained for substrates bearing unprotected phenols and alcohols (Scheme 2, **2o–2p**). Moreover, other electron-rich aryl boronic acids with a thioether and ether substituent converted smoothly into respective products with good yields (Scheme 2, **2q–2u**). The use of THF as the solvent was found to be important for the effective carboxylation of electron-neutral boronic acids (Scheme 2, **2v–2ag**). Finally, oxygen and nitrogen-containing heteroaromatic aryl boronic acids were tolerated and gave the corresponding carboxylated products **2ah**, **2ai**, and **2aj** in 80%, 53%, and 59% isolated yields, respectively. Unfortunately, no product was observed in the case of 2-pyridylboronic acid, presumably due to the rapid protodeborylation (Scheme 2, **2ak**).²⁷

To gain further insights into the mechanism of this Cu-catalysed carboxylation of aryl boronic acid with CO₂, stoichiometric studies were carried out. Initially, to find out the role of base in this transformation, we carried out the reaction between the catalyst [(IPr)Cu(I)Cl] and base KOMe in THF at room temperature. This reaction provided 93% yield of the copper alkoxide complex [(IPr)Cu(I)(OMe)] (Scheme 3a, **4** and see ESI[†] for more details).²⁸ We next carried out the carboxylation reaction of phenylboronic acid using a catalytic amount of [(IPr)Cu(I)(OMe)]. Although no desired product was obtained in the absence of KOMe (see ESI,† mechanistic study, page no. 28 and 29), the benzoic acid formed in 50% yield using a stoichiometric amount of base (Scheme 3b, **2ae**). These results indicate the key role of the base in promoting the carboxylation. Furthermore, the reaction between [(IPr)Cu(I)(OMe)] complex and phenylboronic acid in the presence of KOMe at room temperature afforded 70% yield of the NHC-ligated aryl-copper complex (Scheme 3c, **5** and for more details see ESI,† mechanistic study, page no. 30–32).²⁹ Stoichiometric reaction using this aryl copper(I) complex and carbon dioxide afforded 80% yield of the carboxylic acid (Scheme 3d, **2ae**).

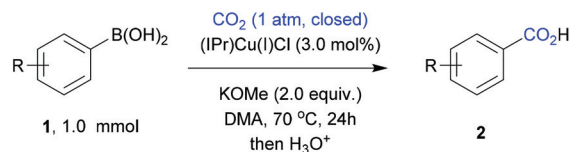
On the basis of these results and previous studies,^{15–21} a catalytic cycle for the carboxylation of aryl boronic with CO₂ is proposed in Scheme 4. Initially, the ligand exchange between [(IPr)Cu(I)Cl] and KOMe generates the copper alkoxide [(IPr)Cu(I)(OMe)] (**4**), which undergoes transmetalation with phenylboronic acid to form the arylcopper(I) complex [(IPr)Cu(I)Ph] (**5**). Nucleophilic addition of [(IPr)Cu(I)Ph] to CO₂ provides carboxylate [(IPr)Cu(I)(OOCPh)] (**6**). σ -Metathesis with KOMe generates PhCOOK (**7**) and regenerate [(IPr)Cu(I)(OMe)] (**4**), thereby completing the catalytic cycle. The hydrolysis of PhCOOK (**7**) finally furnishes the desired product.

Table 1 Optimization of the reaction conditions^a

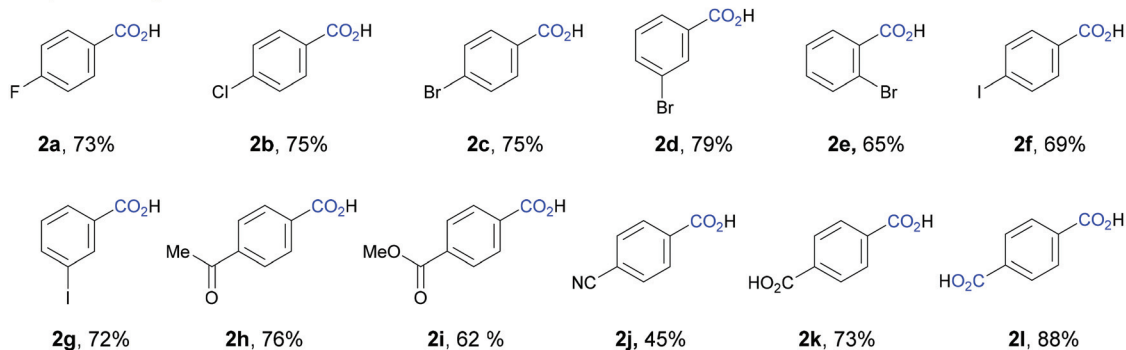


Entry	Variation from standard conditions	Yield ^b (%)
1	None	82
2	KO ^t Bu instead of KOMe in THF	9
3	LiOMe instead of KOMe	Trace
4	With 1.5 equiv. KOMe	75
5	With 1.0 equiv. KOMe	67
6	Reaction at 50 °C	45
7	Reaction at 100 °C	83
8	Without base	NR
9	Without [(IPr)Cu(I)Cl]	NR
10	Without anhydrous DMA	60
11	With 0.5 mmol of H ₂ O as an additive	58
12	With 1.0 mmol of H ₂ O as an additive	43
13	DMF instead of DMA	38
14	DMSO instead of DMA	33
15	MeCN instead of DMA	23

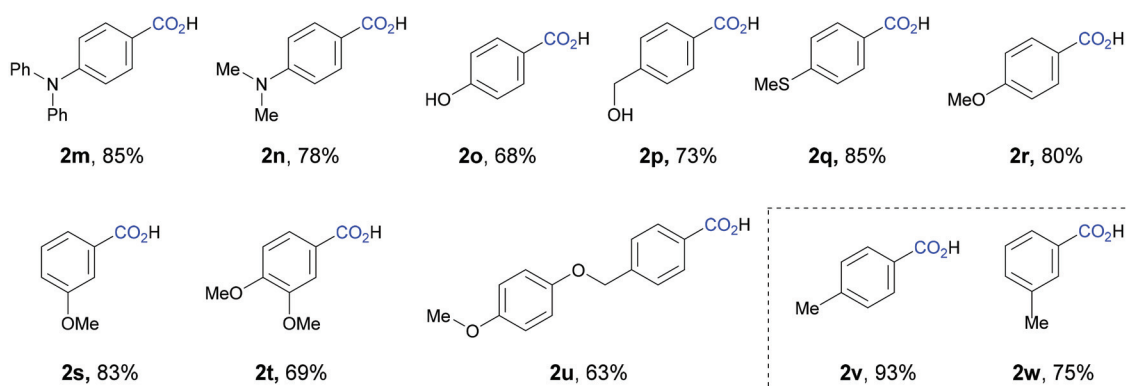
^a Reaction performed on 0.3 mmol scales. ^b Yields were determined by ¹H NMR with benzyl alcohol as an internal standard.



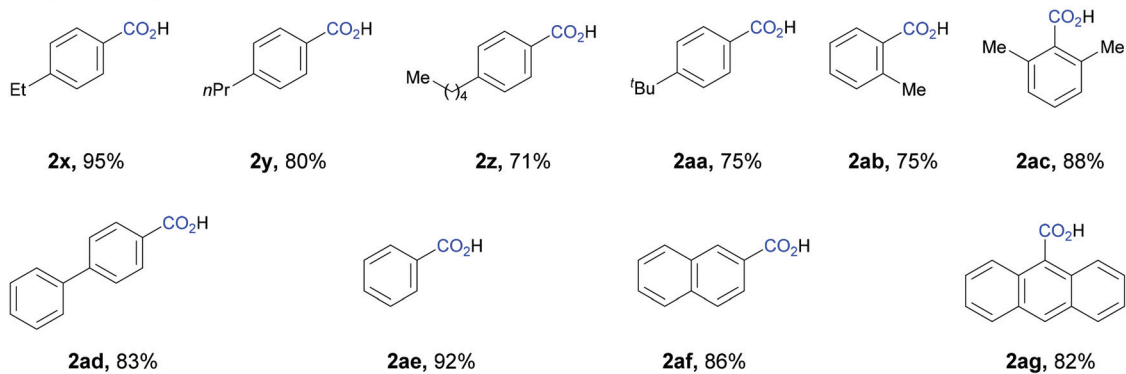
Scope with respect to electron-deficient arene boronic acids



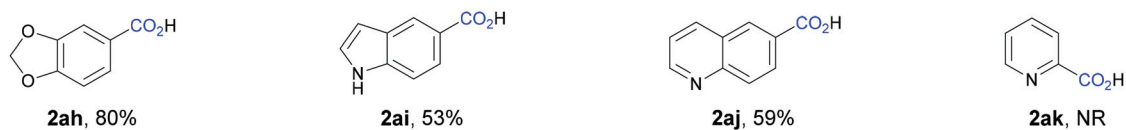
Scope with respect to electron rich arene boronic acids



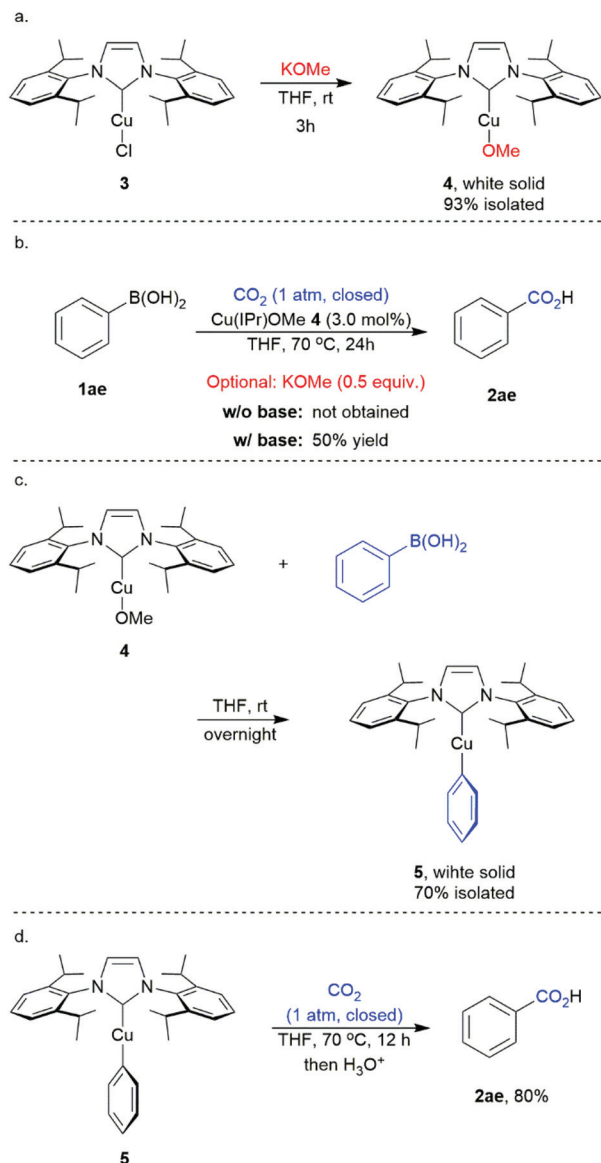
Scope with respect to neutral arene boronic acids



Scope with respect to hetero-atom containing arene boronic acid



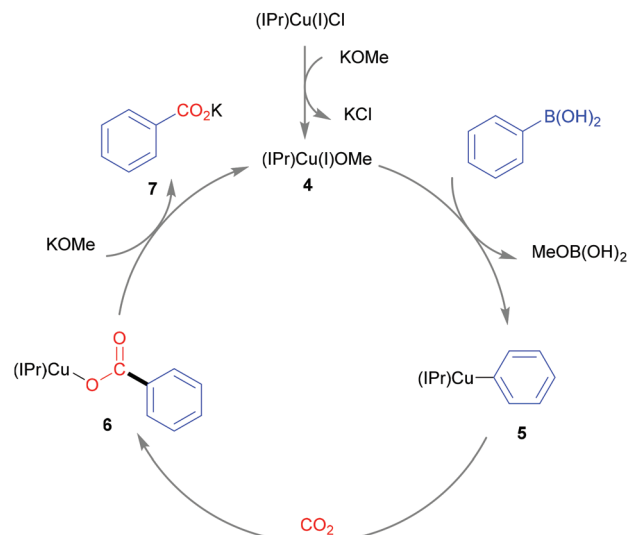
Scheme 2 The substrate scope of aryl boronic acids. Reactions were carried out by using aryl boronic acid (1.0 mmol), cat. $[(\text{IPr})\text{Cu}(\text{I})\text{Cl}]$ (3.0 mol%), base KOMe (2.0 equiv.) in DMA at 70 °C for 24 h under 1 atm CO_2 . Isolated yields were reported. For substrates **1v–1ag**, THF was used as solvent.



Scheme 3 Control experiments for mechanistic study.

Conclusions

In summary, we have developed a mild and efficient Cu-catalysed protocol for the synthesis of aryl carboxylic acid using aryl boronic acids and CO_2 . A wide range of aryl boronic acids were effectively transformed into benzoic acid derivatives. The developed carboxylation method showed excellent functional group tolerance, and a range of sensitive functional groups such as carbonyls, esters, and nitriles were compatible. In addition, stoichiometric studies indicated that the alkoxy copper(I) [(IPr)Cu(I)(OMe)] (4) and the arylcopper(I) species (5) are involved in this transformation. Further studies on the incorporation of CO_2 into other classes of organic molecules are currently underway in our laboratory.



Scheme 4 Proposed mechanistic pathway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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