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Copper-Catalyzed Coupling of Arylboronic Acids with Potassium Cyanate: A New Approach to the Synthesis of Aryl Carbamates

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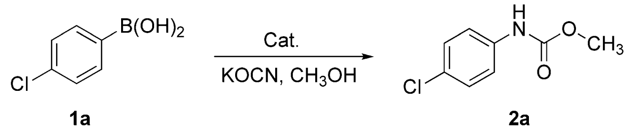
Abstract: The copper-catalyzed coupling of aromatic boronic acids with potassium cyanate in the presence of an alcohol has been employed for the synthesis of arylcarbamates. This simple and highly efficient approach can be carried out in air at room temperature and, importantly, no base, ligand, or additive is required.

Keywords: arylboronic acids; carbamates; cross-coupling; homogeneous catalysis

Carbamates show remarkable biological activities. They are known to have pesticide, insecticide, antibiotic, fungicide, herbicide and other pharmacological properties.[1] They are also of considerable importance because of their application as intermediates for the synthesis of polyurethane-based polymers and as protecting groups[2] of amines in peptide synthesis. Because of their importance, the synthesis of carbamates has become a focus of synthetic organic chemistry and several efforts have been made for the preparation of the title compounds. Initially carbamates were almost exclusively synthesized by the reaction of amines with phosgene or its derivatives such as chloroformate,[2a,3] dialkyl carbonates[4] or reaction of alcohols with isocyanates.[5] These procedures had several drawbacks, notably the extreme toxicity of reagents and generation of by-products. Numerous methods have been described to avoid such drawbacks, such as reductive carbonylation of aromatic nitro compounds[6] and oxidative carbonylation of amines catalyzed by various transition metal complexes.[7] However, the former route suffers from a lack of economical viability while the latter suffers from hazards in the handling of carbon monoxide and oxygen under high pressures. Carbamate synthesis has been accomplished by Hofmann rearrangement from amides,[8] Cs_2CO_3-induced reaction of amines with alkyl halides and CO_2,[9] reaction of azides and chloroformates in the presence of trimethylphosphine,[10] 1,1-carbonyldiimidazole-promoted reaction between alcohols and amines[11] and reaction of tetraethylammonium hydrogen carbonate with amines.[12] The other methods employed to prepare carbamates are carbonylation of amines[13] and alcoholysis of urea.[14] Transition metal-catalyzed cross-coupling reactions are now recognized as extremely powerful strategies for the formation of carbon-heteroatom bonds. The pioneering studies of Buchwald and Hartwig established palladium complexes as efficient catalysts for these reactions.[15] These studies provided the impetus to evaluate other transition metal catalysts and have led to a renaissance in copper-based couplings.[16] Copper catalysis enables the use of a wide scope of reagents as aryl sources such as aryl halogenides, arylsiloxanes, aryltrialkylstannes, diaryliodonium salts, triarylbismuthanes, or aryllead triacetates.[17] Independently reported by the groups of Chan, Evans, and Lam in 1998, this cross-coupling procedure resolved the long-standing problem of the simple and mild formation of C-heteroatom bonds using an arylboronic acid as the aryl donor. The method has proven to have a wide range of nucleophilic reaction partners including phenols, amines, *N*-hydroxyphthalimides and N-heterocycles to give the corresponding N- or O-arylated products.[18] Arylboronic acids have also been widely used as precursors in other synthetic organic transformations such as cyanation, trifluoromethylation, halogenations, alkynylation and carboxylation.[19] To the best of our knowledge there is no example for the conversion of arylboronic acids to carbamates. Herein we report this methodology by which carbamates were prepared by a copper-catalyzed reaction of arylboronic acids with potassium cyanate in the presence of an alcohol.

Initially, 4-chlorobenzeneboronic acid was chosen as the model substrate. To optimize the reaction con-

Table 1. Optimization of the reaction conditions.



Entry	Catalyst	Solvent	*T* [°C]	*t* [h]	**2a** [%]
1	$Cu(OAc)_2 \cdot H_2O$	MeOH	r.t.	24	43
2	$CuBr_2$	MeOH	r.t.	24	49
3	$CuSO_4 \cdot 5H_2O$	MeOH	r.t.	24	38
4	$Cu(OAc)_2 \cdot H_2O$	MeOH	60	20	69
5	$CuBr_2$	MeOH	60	20	75
6	$CuSO_4 \cdot 5H_2O$	MeOH	60	20	63
7	$CuCO_3$	MeOH	60	25	47
8	$CuCl_2 \cdot 2H_2O$	MeOH	60	22	72
9	Cu_2O	MeOH	60	25	40
10	CuI	MeOH	60	25	44
11	$CuBr_2$[a]	MeOH	60	48	57
12	$CuBr_2$[b]	MeOH	60	20	76
13	$CuBr_2$[c]	MeOH	60	20	–
14	–	MeOH	60	24	–

[a] $CuBr_2$ (5 mol%).

[b] $CuBr_2$ (20 mol%).

[c] The reaction was carried out under a nitrogen atmosphere.

ditions, catalysts, solvents and temperatures of the reaction were investigated. As shown in Table 1, the best activity was shown at 60 °C. The reaction provided a lower conversion at room temperature. (Table 1, entries 1–3) Different Cu sources were tested using potassium cyanate in methanol. We observed that, in open air (without bubbling air), all tested Cu(I) salts and $CuCO_3$ showed relatively lower catalytic activity. (Table 1, entries 7, 9, 10). All the other tested Cu(II) salts gave better results and the best conversion was observed with $CuBr_2$. (Table 1, entry 5) No desired product was observed in the absence of air (in a nitrogen atmosphere, Table 1, entry 13) which indicated that an oxidative process was involved in the formation of the products. The reaction was also monitored with different catalyst loadings and the results showed that 10 mol% of $CuBr_2$ (relative to the aromatic boronic acid) was the best choice for completing the reaction. At a lower catalyst loading the reaction took longer and was not complete even after stirring for several days. (compare Table 1, entry 5 with Table 1, entries 11 and 12). No reaction occurred in the absence of a copper catalyst. (Table 1, entry 14) Since the reaction is catalyzed by Cu(II), the effect of different ligands such as 1,10-phenanthroline, 2,2′-bipyridine, PPh_3 and *S*-proline was investigated under the reaction conditions and no improvement was observed in reaction efficiency.

When ethanol and allyl alcohol were used as the solvent the corresponding carbamates were obtained under the optimized reaction conditions. (Table 2, entries 14 and 18)

Therefore our optimal reaction conditions for most of the conversions of 4-chlorobenzeneboronic acid to the titled product are as follows: 10 mol% of $CuBr_2$ as the catalyst, alcohol as the solvent and alkoxy source of products, and the reaction is carried out in air at 60 °C.

Next we investigated the scope of the copper-catalyzed reaction with respect to the arylboronic acid and alcohol. As shown in Table 2, most of the arylboronic acids examined under the standard reaction conditions provided moderate to good yields of the products. The aromatic boronic acids substituted with halogen and electron-deficient CF_3 groups gave the corresponding carbamates in good yields. Arylboronic acids with electron-donating alkyl, alkoxy and phenoxy groups led to relatively lower yields of aryl carbamates under the optimized reaction conditions. 2,5-Dimethoxybenzeneboronic acid, with high steric hindrance, led to the protolytic deboronation under the reaction conditions. (Table 2, entry 13) Ethanol, propanol, 2-propanol and allyl alcohol led to the formation of the corresponding products. (Table 2, entries 14–19)

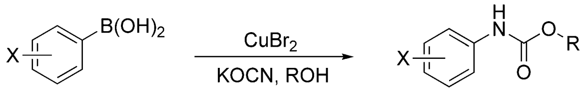
To broaden the scope of substrate used, we carried out the reaction of 4-chlorobenzeneboronic acid ester with potassium cyanate and methanol under the standard conditions and the corresponding product was afforded in moderate yield. (Table 2, entry 12)

Although the mechanism for the coupling of organoboranes with the cyanate ion is not clear at this moment, a possible catalytic cycle is shown in Scheme 1.

The proposed mechanism involves rapid coordination/ligand exchange of the Cu(II) salt by a cyanate ion to form the intermediate OCNCu(II)Br. The second step involves transmetallation of the arylboronic acid with OCNCu(II)Br to give the intermediate ArCu(II)NCO complex. ArCu(II)NCO may undergo reductive elimination to give the product ArNCO. Alternatively, ArCu(II)NCO may undergo air oxidation to yield the corresponding higher oxidation-state copper(III) complex ArCu(III)NCO, which can more efficiently reductively eliminate to afford the product ArNCO. The copper(I) formed can then be easily oxidized by oxygen to copper(II) to complete the catalytic cycle. Subsequent reaction of the aryl isocyanate with the alcohol affords the corresponding carbamate.

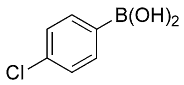
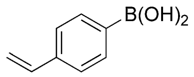
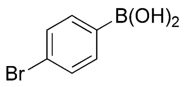
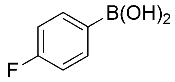
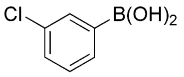
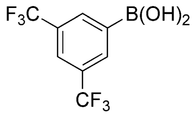
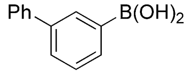
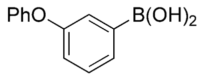
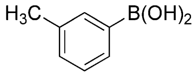
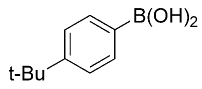
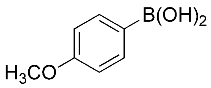
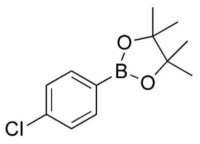
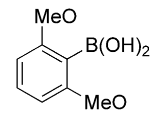
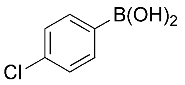
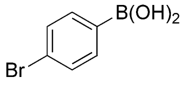
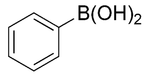
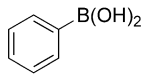
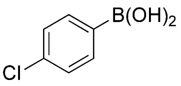
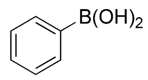
In summary, a simple and efficient copper-catalyzed method for the synthesis of carbamates by coupling of aromatic boronic acids with potassium cyanate has been developed. The coupling reactions were performed in air, without the need for sealed reaction vessels and neither a base, ligand nor additive was necessary.

Table 2. Copper-catalyzed reaction of arylboronic acids with ptassium cyanate in the presence of an alcohol at 60 °C.



1

2 (R = Me)
3 (R = Et)
4 (R = Pr)
5 (R = 2-Pr)
6 (R = allyl)

Entry		ArB(OH)$_2$	ROH	2–6	Yield [%][b]
1	**1a**		MeOH	**2a**	75
2	**1b**			**2b**	80
3	**1c**			**2c**	76
4	**1d**			**2d**	69
5	**1e**			**2e**	71
6	**1f**			**2f**	58
7	**1g**			**2g**	54
8	**1h**			**2h**	51
9	**1i**			**2i**	51[a]
10	**1j**			**2j**	54[a]
11	**1k**			**2k**	48
12	**1l**			**2l**	48
13	**1m**			–	–
14			EtOH	**3a**	79
15				**3c**	73
16	**1n**		Pr-OH	**4n**	66[a]
17			2-Pr-OH	**5n**	61[a]
18			Allyl-OH	**6a**	76
19				**6n**	69[a]

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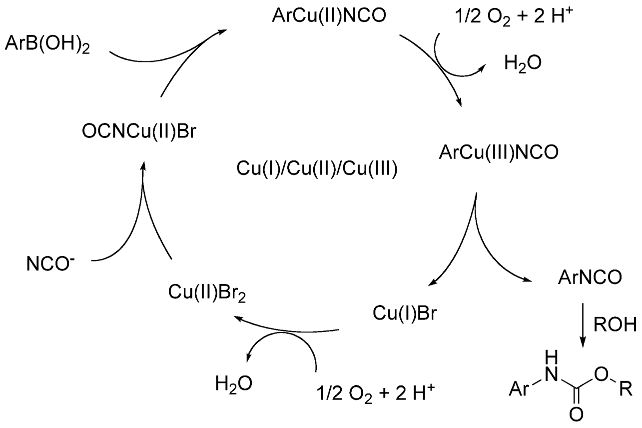
[a] The corresponding carbamoylcarbamate was obtained as the by-product.
[b] Isolated yield.



Scheme 1. Plausible mechanism.

Experimental Section

Typical Procedure for Conversion of Arylboronic Acids to Arylcarbamates

To a solution of arylboronic acid (1.0 equiv.) or arylboronic ester (1.0 equiv-) in methanol, potassium cyanate (1.5 equiv.) and $CuBr_2$ (10 mol%) were added and the mixture was stirred at 60 °C for 24 h. The reaction progress was monitored by TLC. Work-up of the reaction involved evaporating the solvent under reduced pressure, then extraction with dichloromethane. The solvent was removed under vacuum and the product was purified by column chromatography (silica gel, Merck 230–400 mesh) using dichloromethane-ethyl acetate (9:1) as eluent.

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