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A Copper-Catalyzed Petasis Reaction for the Synthesis of Tertiary Amines and Amino Esters

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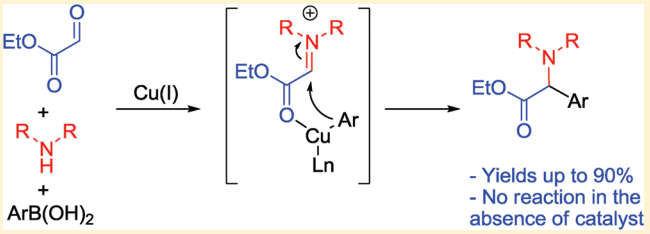
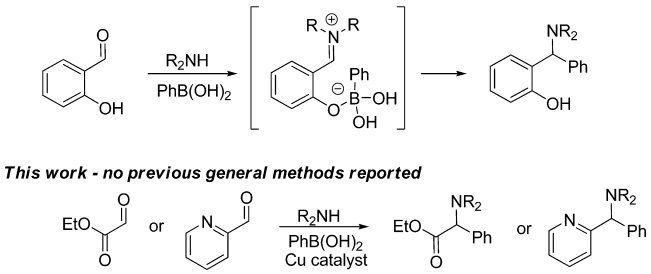
Supporting Information

ABSTRACT: We have developed a copper-catalyzed process for the coupling of aldehydes, amines, and boronic acids. This allows greater reactivity with simple aryl boronic acids and allows coupling reactions to proceed that previously failed. Initial mechanistic studies support a process involving transmetalation from boron to copper.



The three component coupling of an amine, aldehyde, and boronic acid (known as the Petasis reaction) is a convenient route to the synthesis of highly functionalized tertiary amines.[1] In general, the reaction tends to proceed exceptionally well when there is a free hydroxy group on the aldehyde fragment, allowing the formation of an activated boronate salt (see Scheme 1).[2] Other heteroatoms may also fulfill this role, but reactivity is invariably reduced; in general without a hydroxy group on the aldehyde, unactivated aryl boronic acids give little or no product, and the more reactive vinyl boronic acids, or trifluoroalkenyl boronates activated with Lewis acids, are required.[2−4]

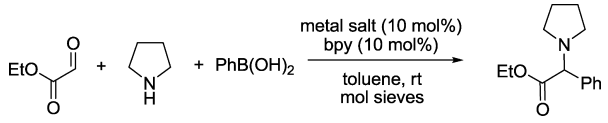
Scheme 1. Expansion of Scope of Petasis Reaction



Some catalytic variants of the Petasis reaction have been developed. Notably an enantioselective organocatalytic variant was reported by Schaus and co-workers, using allyl boronate esters and chiral diols[5,6] and another organocatalytic system by Yuan and co-workers using salicylaldehydes.[7] Catalytic variants have also been developed for Petasis-type reactions such as the addition of organoboron compounds to *N*-acyl quinolinium ions,[8−10] *N*,*O*-aminals,[11] and very recently the three component coupling of imines, acid chlorides, and tetraaryl boron compounds, catalyzed by copper salts and a Lewis base.[12]

In an attempt to increase the reactivity of aryl boronic acids, we investigated the use of palladium salts as catalysts. Our initial hope was to form a more reactive aryl palladium species capable of arylating the transient iminium intermediate, in a similar manner to the arylation of *N*-tosyl imines by boronic acids and palladium (see Scheme 2).[13−17] Unfortunately, these attempts were uniformly unsuccessful, and no product was observed. We next attempted to use copper(I) bromide. This had previously proven effective for the addition of terminal alkynes to iminium salts[18] as well as activating boronic acids in the Suzuki coupling.[19] To our delight, this allowed the reaction to proceed, albeit with a 9% yield. To ensure this was due to the presence of copper, we repeated the reaction with no catalyst, and again no product was observed.

Scheme 2. Initial Attempts at Catalysis



With this result in hand, we set about trying to increase the yield of amino ester obtained. A solvent screen indicated that DMF was the optimal solvent out of those tested, giving an improved yield of 48%. This increased to 63% upon increasing the temperature to 70 °C, but no product was observed at 100 °C (possibly because of the volatility of the amine employed).

Next, the effect of the copper salt was examined (see Table 1). Copper(I) halides all worked in roughly comparable yields, although copper(I) acetate gave a dramatically reduced amount of product. Copper(II) salts were in general ineffective, and no trace of product was observed. The only exception to this was copper(II) acetate, which to our surprise gave the desired compound in 50% yield. The reason for this discrepancy is currently being investigated. Finally, in order to test the sensitivity of the reaction to oxygen and moisture, we ran it

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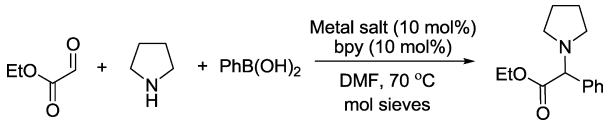
Table 1. Effect of Various Metal Salts on Reaction Yield



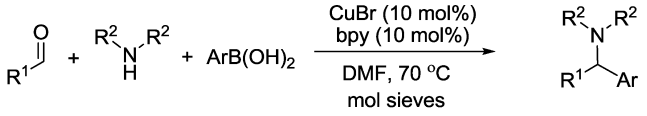
entry	metal salt	yield (%)[a]
1	CuBr	63
2	CuCl	54
3	CuI	64
4	CuOAc	4
5	$CuBr_2$	0
6	$CuCl_2$	0
7	$CuSO_4$	0
8	$Cu(OTf)_2$	0
9	$Cu(OAc)_2$	50
10[b]	CuBr	42

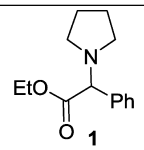
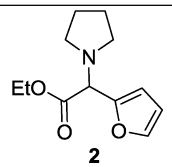
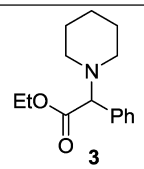
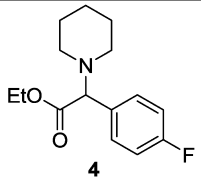
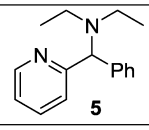
Reaction times 24 h. [a]Determined by ^{1}H NMR spectroscopy. [b]Reaction run under a noninert atmosphere.

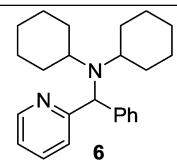
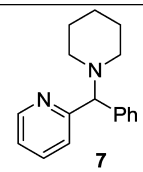
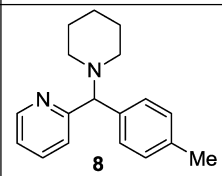
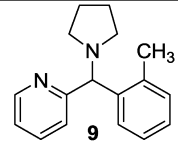
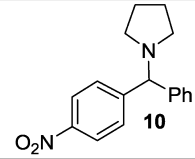
under a noninert atmosphere. In this case, we observed a significant drop in yield (Table 1, entry 10), indicating the importance of excluding oxygen and moisture.

Next, we examined the generality of the reaction by altering the amine, boronic acid, and aldehyde (see Table 2). First, after observing the need to maintain an oxygen-free atmosphere (see above), we noticed that yield increased dramatically after degassing the DMF prior to use and finely powdering the molecular sieves. With regard to the amine component, pyrrolidine worked better than piperidine or diethylamine, presumably because of its smaller steric profile. The reaction could tolerate both electron-rich and electron-poor boronic acids, with perhaps a slight increase in yields observed with more electron poor substrates (Table 2, entry 1 vs 2, entry 3 vs 4, entry 7 vs 8). In common with all Petasis couplings, it was necessary to use aldehydes with coordinating groups. In our case, pyridine-2-carboxaldehyde gave higher yields than ethyl glyoxalate (Table 2, entry 3 vs entry 7). With regard to sterics, while heterocylic and secondary amines with primary alkyl groups gave product, changing to dicyclohexylamine shut down the reaction (Table 2, entry 6), as did use of ortho-substituents on the aryl boronic acid (Table 2, entry 9) (of course, these reactions also failed to provide any product in the uncatalyzed reaction). Finally, to confirm that some coordinating group was necessary on the aldehyde, we repeated the reaction using 2-nitrobenzaldehyde (Table 2, entry 10). Because this would be approximately as electron-poor (and hence electrophilic) as

Table 2. Substrate Scope



Entry[a]	Product	Yield (%)
1	 **1**	90
2	 **2**	79
3	 **3**	51
4	 **4**	57
5	 **5**	43

Entry[a]	Product	Yield (%)
6	 **6**	0
7	 **7**	76
8	 **8**	74
9	 **9**	<5
10	 **10**	0

Reaction times 24 h. [a]DMF degassed prior to use.

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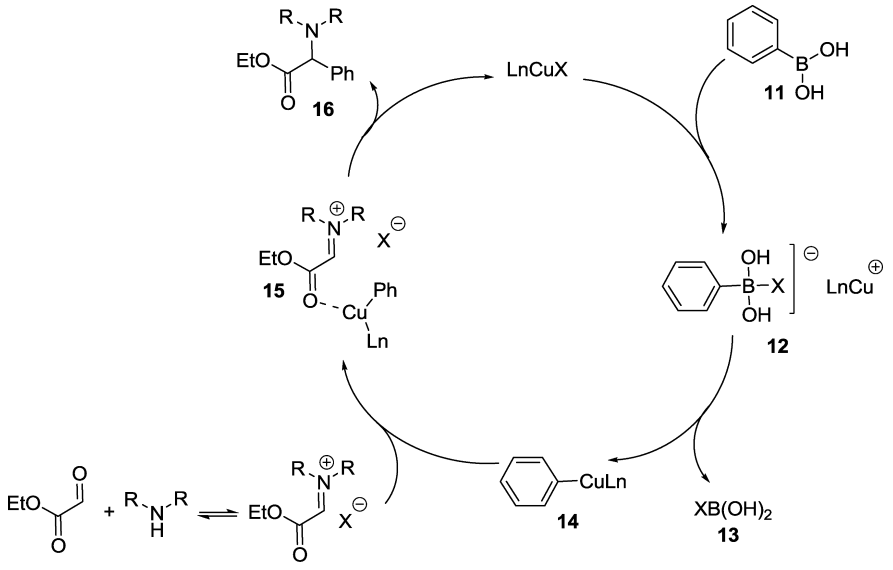

Figure 1. Proposed mechanism for copper catalysis.

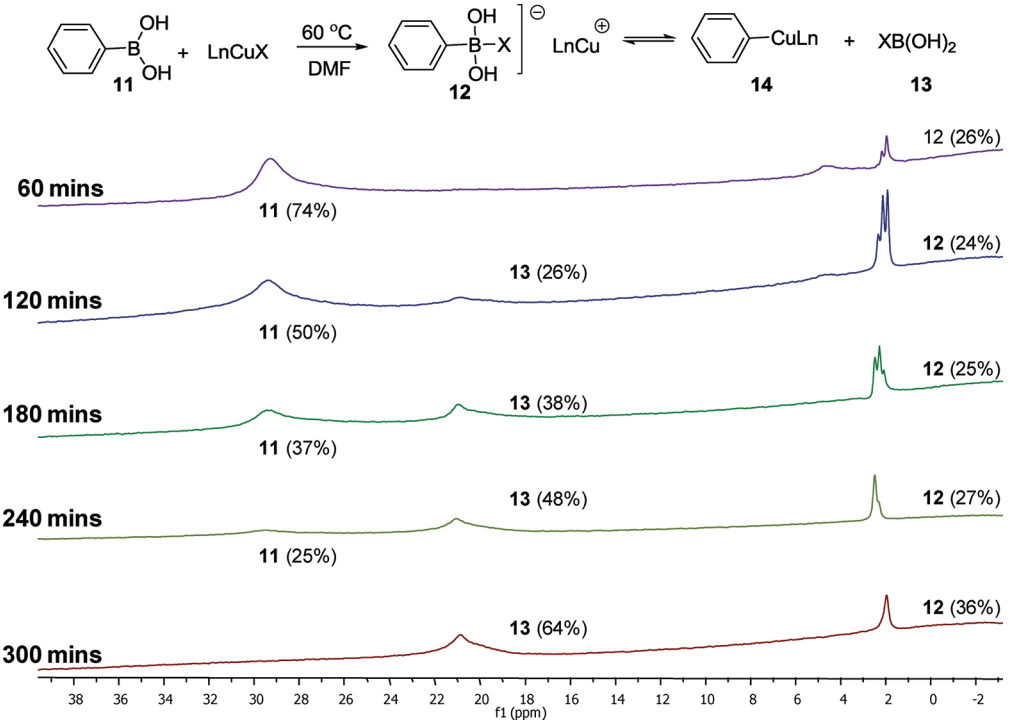

Figure 2. ^{11}B NMR analysis of phenyl boronic acid with copper salts in DMF.

pyridine-2-carboxaldehyde, but without any suitable site for coordination, it would allow us to examine these two requirements separately. As expected, no product was formed, indicating the importance of some coordinating functionality on the aldehyde component.

These results led us to tentatively assign a mechanism for the process (see Figure 1). We postulated the initial formation of a boronate salt through the interaction of the boronic acid **8** with the counterion of the copper salt. This activated species (**12**) could then transmetallate copper, leading to the formation of an organocuprate (**14**) along with byproduct **13**. Carbon–carbon bond formation could then occur through nucleophilic attack at any iminium ions in solution. The requirement of a coordinating atom on the aldehyde fragment would seem to imply that there is a coordination event, activating the cuprate and bringing it in close proximity to the electrophilic center. This then allows the regeneration of the copper salt.

If the above mechanism is broadly correct, it would be expected to see three major boron-containing compounds in solution: **11**, **12**, and **13**. To examine this, we monitored a 1:1 ratio of bpy/CuBr with phenyl boronic acid (see Figure 2). Pleasingly, we observed 3 main peaks by ^{11}B NMR, with shifts corresponding to those expected for compounds **11**, **12**, and **13** (on the basis of literature values for related compounds[20]). Phenyl boronic acid appears at 29.3 ppm. Upon addition of CuBr, we observe first the formation of a boron-containing species at 2.0 ppm. We postulate that this is the boronate salt **12** (where X is bromide or hydroxide). The shift broadly

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corresponds to that observed for the related reaction with alkenyl boronate esters[20] (to the best of our knowledge, there have been no previously reported shifts for such compounds derived from aryl boronic acids). As the reaction progresses, a third species appears, which we assigned as **13**. The concentration of this side product should correspond to the total amount of aryl copper species **14** produced. Within 4 h, the starting phenyl boronic acid is completely consumed, and **13** is the major species observed, presumably in equilibrium with salt **12**.

In order to confirm the identity of **12**, we heated phenyl boronic acid with NaOAc in DMF. This would be expected to show only two peaks by ^{11}B NMR: boronic acid **11** and a boronate salt **12** (transmetalation, and hence the formation of **13**, would not be possible without copper). Again, this is what was observed: some phenyl boronic acid was consumed, but this then stayed constant throughout the duration of the experiment (4 h). The only other boron-containing species in solution was salt **12**.

To show that our active nucleophile was generated by the interaction of copper salt with the boronic acid, we repeated the experiment, again monitoring the process by ^{11}B NMR. Once the phenyl boronic acid was completely consumed, we added the solution to a mixture of ethyl glyoxalate and piperidine under our standard conditions: the desired compound was formed rapidly in essentially quantitative yield.[21]

Finally, to examine the cause for a complete lack of reactivity with a number of Cu(II) salts, we monitored a solution containing $CuBr_2$ and phenyl boronic acid. No change was observed by NMR, indicating that in these cases, it is the absence of any interaction between the boronic acid and the metal salt that results in no formation of product.

In conclusion, we have developed a copper-catalyzed process for the coupling of an amine, aldehyde, and boronic acid. This allows a much greater flexibility in the choice of reagents in the Petasis reaction, thereby removing a significant limitation with the original process. The catalytic system is convenient and inexpensive, and a likely mechanism of action has been described.

EXPERIMENTAL SECTION

General Methods. Ethyl glyoxalate was purchased as a 50% solution in toluene and freshly distilled before use. DMF was dried over calcium hydride and degassed by successive freeze−pump−thaw cycles. Molecular sieves were powdered and activated by heating under vacuum prior to use. All reactions were carried out in oven-dried glassware.

General Procedure for the Catalyzed Petasis Reaction. Dry, degassed DMF (12 mL) was added to a mixture of copper salt (0.142 mmol) and 2,2′-bipyridine (26.4 mg, 0.17 mmol) under nitrogen, and the solution was stirred at 60 °C for 1 h. After this time, aldehyde (1.42 mmol), amine (1.42 mmol), and boronic acid (2.84 mmol) were charged to the flask along with powdered 3 Å molecular sieves. The solution was stirred at 70 °C for 24 h and subsequently filtered on a short silica pad. After evaporation of the solvent, the residue was purified by column chromatography on silica gel.

Compound **1**.[22] Isolated as a yellow oil after column chromatography (CH_2Cl_2/EtOAc/MeOH 90:9:1): ^{1}H NMR (400 Hz, $CDCl_3$) δ 7.50 (d, 2H, J = 7.6 Hz), 7.40−7.30 (m, 3H), 4.27−4.08 (m, 2H), 3.93 (s, 1H), 2.68−2.54 (m, 2H), 2.52−2.40 (m, 2H), 1.91−1.72 (m, 4H), 1.22 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 Hz, $CDCl_3$) δ 171.8 (q), 137.5 (q), 128.5, 128.4, 128.2, 74.1, 60.9, 52.5, 23.3, 14.1; IR (NaCl disk) ν_{max}/cm^{-1} 2968, 2791, 1743 (s, C═O), 1153, 1024; HRMS calcd for $C_{14}H_{20}NO_2$ [M + H]$^+$ 234.1494, found 234.1496.

Compound **2**. Isolated as a yellow oil after column chromatography (CH_2Cl_2/EtOAc 98:2): ^{1}H NMR (400 Hz, $CDCl_3$) δ 7.40 (dd, 1H, J = 1.9, 0.9 Hz), 6.41−6.33 (m, 2H), 4.31−4.17 (m, 3H), 2.74−2.47 (m, 4H), 1.89−1.74 (m, 4H), 1.27 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 Hz, $CDCl_3$) δ 169.6 (q), 150.0 (q), 142.6, 110.3, 109.0, 65.4 (CH), 61.3, 51.6, 23.4, 14.2 (CH_3); IR (NaCl disk) ν_{max}/cm^{-1} 2966, 2809, 1736 (s, C═O), 1150, 1012; HRMS calcd for $C_{12}H_{18}NO_3$ [M + H]$^+$ 224.1287, found 224.1285.

Compound **3**.[23] Isolated as an orange oil after column chromatography (CH_2Cl_2/EtOAc 92:8): ^{1}H NMR (400 Hz, $CDCl_3$) δ 7.50−7.43 (m, 2H), 7.40−7.31 (m, 3H), 4.28−4.09 (m, 2H), 3.98 (s, 1H), 2.47−2.37 (m, 4H), 1.67−1.56 (m, 4H), 1.52−1.41 (m, 2H), 1.23 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 Hz, $CDCl_3$) δ 171.9 (q), 136.4 (q), 128.8, 128.4, 128.1, 75.0, 60.7, 52.4, 25.8, 24.4, 14.2; IR (NaCl disk) ν_{max}/cm^{-1} 2933, 2853, 2300, 1741 (s, C═O), 1261, 1155, 1122, 801, 696; HRMS calcd for $C_{15}H_{22}NO_2$ [M + H]$^+$ 248.1651, found 248.1660.

Compound **4**. Isolated as a yellow oil after column chromatography (CH_2Cl_2/EtOAc 90:10): ^{1}H NMR (400 Hz, $CDCl_3$) δ 7.51−7.37 (m, 2H), 7.12−6.96 (m, 2H), 4.30−4.06 (m, 2H), 3.94 (s, 1H), 2.46−2.30 (m, 4H), 1.69−1.53 (m, 4H), 1.52−1.41 (m, 2H), 1.23 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 Hz, $CDCl_3$) δ 171.7 (q), 162.6 (d, J = 246.4 Hz, q), 132.2 (q), 130.4 (d, J = 8.0 Hz), 115.3 (d, J = 21.5 Hz), 74.2, 60.8 (CH_2), 52.3 (CH_2), 25.8 (CH_2), 24.3 (CH_2), 14.2; IR (NaCl disk) ν_{max}/cm^{-1} 2934, 1733 (s, C═O), 1604, 1507, 1223, 1150, 805; HRMS calcd for $C_{15}H_{21}FNO_2$ [M + H]$^+$ 266.1556, found 266.1566.

Compound **5**. Isolated as an amorphous green solid after column chromatography (hexane/EtOAc/Et_3N 94:1:5): ^{1}H NMR (400 Hz, $CDCl_3$) δ 8.52 (d, 1H, J = 4.8 Hz), 7.68−7.58 (m, 2H), 7.53 (d, 2H, J = 7.5 Hz), 7.34−7.27 (m, 2H), 7.21 (apt t, 1H), 7.15−7.05 (m, 1H), 4.90 (s, 1H), 2.63 (q, 4H, J = 7.0 Hz), 1.01 (t, 6H, J = 7.0 Hz); ^{13}C NMR (100 Hz, $CDCl_3$) δ 163.2 (q), 149.0, 142.1 (q), 136.4, 128.4, 128.3, 127.0, 121.8, 73.6, 42.8 (CH_2), 10.6; IR (NaCl disk) ν_{max}/cm^{-1} 2969, 2933, 1588, 1432, 746, 730, 699; HRMS calcd for $C_{16}H_{21}N_2$ [M + H]$^+$ 241.1705, found 241.1712.

Compound **7**. Isolated as an amorphous green solid after column chromatography (hexane/EtOAc/Et_3N 80:15:5): ^{1}H NMR (400 Hz, $CDCl_3$) δ 8.51 (d, 1H, J = 5.1 Hz), 7.70−7.58 (m, 2H), 7.50 (d, 2H, J = 7.3 Hz), 7.36−7.26 (m, 2H), 7.25−7.17 (m, 1H), 7.15−7.05 (m, 1H), 4.42 (s, 1H), 2.61−2.26 (m, 4H), 1.70−1.55 (m, 4H), 1.53−1.40 (m, 2H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 162.9 (q), 149.0, 141.8 (q), 136.5, 128.4, 128.3, 127.0, 122.1, 121.8, 78.7, 53.3 (CH_2), 26.1 (CH_2), 24.6 (CH_2); IR (NaCl disk) ν_{max}/cm^{-1} 2931, 2753, 1587, 1431, 746, 699; HRMS calcd for $C_{17}H_{21}N_2$ [M + H]$^+$ 253.1705, found 253.1713.

Compound **8**. Isolated as an amorphous green solid after column chromatography (hexane/EtOAc/Et_3N 80:15:5): ^{1}H NMR (400 Hz, $CDCl_3$) δ 8.48 (d, 1H, J = 4.6 Hz), 7.65−7.52 (m, 2H), 7.35 (d, 2H, J = 7.7 Hz), 7.15−7.00 (m, 3H), 4.34 (s, 1H), 2.56−2.10 (m, 7H), 1.63−1.53 (m, 4H), 1.48−1.40 (m, 2H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 163.1 (q), 149.0, 138.8 (q), 136.6 (q), 136.5, 129.1, 128.2, 122.0, 121.7, 78.4, 53.3 (CH_2), 26.1 (CH_2), 24.6 (CH_2), 21.1; IR (NaCl disk) ν_{max}/cm^{-1} 2930, 2855, 1587, 1432, 797, 753; HRMS calcd for $C_{18}H_{23}N_2$ [M + H]$^+$ 267.1861, found 267.1871.

ASSOCIATED CONTENT

Supporting Information

NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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