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Cu(OTf)$_2$-Mediated Chan-Lam Reaction of Carboxylic Acids to Access Phenolic Esters

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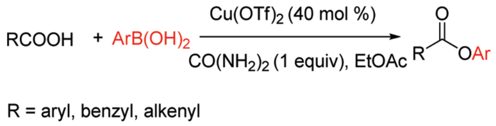
Received August 9, 2010



A Cu(OTf)$_2$-mediated Chan-Lam reaction of carboxylic acids with arylboronic acids is described. It represents a facile and practical methodology to access phenolic esters in moderate to good yields. The procedure tolerates a series of functional groups, such as methoxycarbonyl, acetoxy, free phenolic hydroxyl, vinyl, nitro, trifluoromethyl, methoxyl, bromo, chloro, iodo, and acetyl groups.

The construction of carbon−oxygen bonds is a central theme in organic synthesis. Among these, the transition-metal-catalyzed reaction of ArX and alcohols or phenols is one of the most powerful methods for the forming of C−O bonds.[1] However, the employing of a strong base, such as KO^{t}Bu and NaOMe, as well as the elevated reaction temperature, would diminish the functional compatibility and the reaction practicality. Alternative transformation involves the copper-catalyzed Chan-Lam reaction of arylboronic acids with alcohols or phenols,[2] which may run under room temperature. However, to the best of our knowledge, the employing of carboxylic acids as an O-donor in Chan-Lam reaction has never been studied or reported before. The formed benzoate derivatives are important building blocks in the synthesis of natural and pharmacological compounds.[3] However, the direct esterification of benzoic acid and phenol[4] as well as transesterification reactions[5] were often conducted under strongly acidic or basic conditions, which might limit the scope of functional groups and cause side reactions, such as carbonization, oxidation, etc.[6] The Baeyer−Villiger oxidation[7] reaction may suffer from low regioselectivity. From the synthetic point of view, it is a highly desirable goal to develop a versatile approach to the synthesis of phenolic esters in a simple and mild way. Very recently, we reported a copper-catalyzed esterification of carboxylic acids or anhydrides with aryl and alkenyl trimethoxysilane.[8] However, 3 equiv of expensive AgF are required for the aforementioned transformations. Herein, we report a Cu(OTf)$_2$-mediated Chan-Lam reaction of carboxylic acids with boronic acids.

We initiated our investigation by examining the reaction of benzoic acid and phenylboronic acid (Table 1). During the survey of additives, to our delight, phenyl benzoate was produced in 25% yield in the presence of 1 equiv of urea as an additive in ethyl acetate (entry 2, Table 1). Benzamide was also effective for this transformation, while thiourea and acetamide inhibited the reaction. The influence of copper catalysts was investigated, and Cu(OTf)$_2$ turned out to be the best (entries 6−9, Table 1). Several solvents, such as toluene, THF, MeNO$_2$, and MeCN, were also examined. No product was formed in the absence of copper (entry 14, Table 1). Compatible yield was gained when the reaction was conducted under oxygen. We believed the urea may at least act

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(1) (a) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395. (b) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333. (c) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6787. (d) Mann, G.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 5413.

(2) For selected references, please see: (a) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winteres, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933. (b) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937. (c) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 1381. (d) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett.* **2003**, *44*, 4927. (e) Chan, D. M. T.; Monaco, K. L.; Li, R.; Bonne, D.; Clark, C. G.; Lam, P. Y. S. *Tetrahedron Lett.* **2003**, *44*, 3863. (f) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415. (g) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560.

(3) (a) Moretto, A.; Nicolli, A.; Lotti, M. *Toxicol. Appl. Pharmacol.* **2007**, *219*, 196. (b) Beginn, U.; Zipp, G.; Moller, M. *Chem.—Eur. J.* **2000**, *6*, 2016. (c) Barratt, M. D.; Basketter, D. A; Roberts, D. W. *Toxicol. in Vitro* **1994**, *8*, 823. (d) Child, J. J.; Oka, T.; Simpson, F. J.; Krishnamurty, H. G. *Can. J. Microbiol.* **1971**, *17*, 1455. (e) Berndt, M. C.; Bowles, M. R.; King, G. J.; Zerner, B. *Biochim. Biophys. Acta* **1996**, *1298*, 159. (f) James, C.; Snieckus, V. *J. Org. Chem.* **2009**, *74*, 4080. (g) Nagamitsu, T.; Marumoto, K.; Nagayasu, A.; Fukuda, T.; Arima, S.; Uchida, R.; Ohshiro, T.; Harigaya, Y.; Tomoda, H.; Omura, S. *J. Antibiot.* **2009**, *62*, 69.

(4) (a) Konwar, D.; Gogoi, P. K.; Gogoi, P.; Borah, G.; Baruah, R.; Hazarika, N.; Borgohain, R. *Indian J. Chem. Technol.* **2008**, *15*, 75. (b) Vijayakumar, B.; Iyengar, P.; Nagendrappa, G.; Prakash, B. S. J. *J. Ind. Chem. Soc.* **2005**, *82*, 922. (c) Lee, C. K.; Yu, J. S.; Lee, H.-J. *J. Heterocycl. Chem.* **2002**, *39*, 1207. (d) Eshghi, H.; Rafei, M.; Karimi, M. H. *Synth. Commun.* **2001**, *31*, 771. (e) Ueda, M.; Mori, H. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1636. (f) Ueda, M.; Oikawa, H. *J. Org. Chem.* **1985**, *50*, 760. (g) Keshavamurthy, K. S.; Vankar, Y. D.; Dhar, D. N. *Synthesis* **1982**, 506. (h) Lowrance, W. W., Jr. *Tetrahedron Lett.* **1971**, *12*, 3453. (i) Kankanala, K.; Reddy, V.; Mukkanti, K.; Pal, S. *J. Fluorine Chem.* **2009**, *130*, 505. (j) Won, J.; Kim, H.; Kim, J.; Yim, H.; Kim, M.; Kang, S.; Chung, H.; Lee, S.; Yoon, Y. *Tetrahedron* **2007**, *63*, 12720.

(5) (a) Khalfina, I. A.; Vlasov, V. M. *Russ. J. Org. Chem.* **2008**, *44*, 1619. (b) Oohashi, Y.; Fukumoto, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1508. (c) Degani, I.; Dughera, S.; Fochi, R.; Serra, E. *Synthesis* **1999**, 1200. (d) Karimi Zarchi, M.; Mirjalili, B.; Acal, A. *J. Appl. Polym. Sci.* **2010**, *115*, 237.

(6) (a) Fischer, E. *Ber.* **1895**, *28*, 3254. (b) Jewel, P.; Butts, J. *J. Am. Chem. Soc.* **1931**, *53*, 3560. (c) Shokrolahi, A.; Zali, A.; Pouretedal, H. R.; Mahdavi, M. *Catal. Commun.* **2008**, *9*, 859.

(7) (a) Olah, G. A.; Wang, Q.; Trivedi, N. J.; Prakash, G. K. S. *Synthesis* **1991**, 739. (b) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Narsaiah, A. V. *Chem. Lett.* **2004**, *33*, 248. (c) Kotsuki, H.; Arimura, K.; Araki, T.; Shinohara, T. *Synlett* **1999**, 462. (d) Toda, F.; Yagi, M.; Kiyoshige, K. *J. Chem. Soc., Chem. Commun.* **1988**, 958. (e) Ghazanfari, D.; Hashemi, M. M.; Shahidi-Zandi, M. *Synth. Commun.* **2008**, *38*, 2037. (f) Gaikwad, D. D.; Dake, S. A.; Kulkarni, R. S.; Jadhav, W. N.; Kakde, S. B.; Pawar, R. P. *Synth. Commun.* **2007**, *37*, 4093.

(8) (a) Luo, F.; Pan, C.; Qian, P.; Cheng, J. *Synthesis* **2010**, 2005. (b) Luo, F.; Pan, C.; Qian, P.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 5379.

DOI: 10.1021/jo101558s

TABLE 1. Selected Results for Optimal Reaction Conditions[a]

$$\underset{\mathbf{1a}}{\mathrm{PhCOOH}} + \underset{\mathbf{2a}}{\mathrm{PhB(OH)_2}} \longrightarrow \underset{\mathbf{3aa}}{\mathrm{PhCOOPh}}$$

entry	catalyst	additive	solvent	yield (%)
1	$Cu(OAc)_2$		EtOAc	< 5
2	$Cu(OAc)_2$	NH_2CONH_2	EtOAc	25
3	$Cu(OAc)_2$	$PhCONH_2$	EtOAc	15
4	$Cu(OAc)_2$	NH_2CSNH_2	EtOAc	< 5
5	$Cu(OAc)_2$	CH_3CONH_2	EtOAc	< 5
6	$Cu(OTf)_2$	NH_2CONH_2	EtOAc	95
7	$Cu(acac)_2$	NH_2CONH_2	EtOAc	33
8	Cu_2O	NH_2CONH_2	EtOAc	7
9	CuI	NH_2CONH_2	EtOAc	< 5
10	$Cu(OTf)_2$	NH_2CONH_2	toluene	< 5
11	$Cu(OTf)_2$	NH_2CONH_2	THF	90
12	$Cu(OTf)_2$	NH_2CONH_2	CH_3NO_2	56
13	$Cu(OTf)_2$	NH_2CONH_2	MeCN	20
14		NH_2CONH_2	EtOAc	< 5

[a] Reaction conditions: benzoic acid (0.2 mmol), phenylboronic acid (0.6 mmol), Cu source (40 mol %), and additive (1.0 equiv) in solvent (2 mL), 60 °C; 12 h under air.

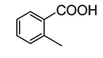
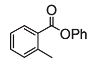
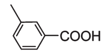
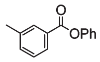
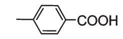
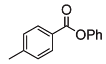
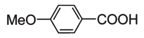
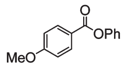
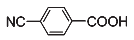
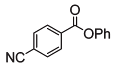
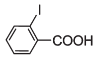
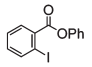
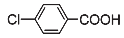
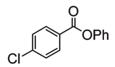
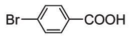
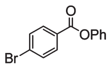
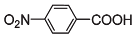
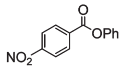
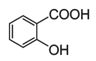
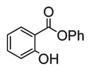
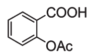
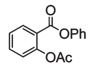
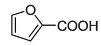
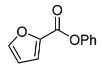
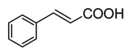
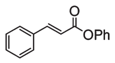
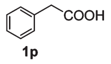
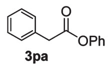
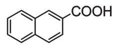
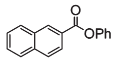
as a ligand to copper under this transformation. The reaction conducted on a 2 mmol scale formed the product in an acceptable 65% yield.

Finally, the optimized conditions were found as following: under air, $Cu(OTf)_2$ (40 mol %) as the catalyst, and urea (1 equiv) in ethyl acetate at 60 °C.

With the established optimal parameters, we turned our attention to investigate the scope of carboxylic acids. The results were summarized in Table 2. The electronic property of the groups on the phenyl ring of carboxylic acids had some effect on the reaction. Generally, the carboxylic acids possessing electron releasing groups produced the phenolic esters with higher yields (e.g., entries 1, 11, and 15, Table 2). The procedure tolerated a range of functional groups, such as iodo, chloro, bromo, nitro, free phenolic hydroxyl, and acetyloxy groups. The compatible of halo groups is synthetically useful since the products could be easily further modifiable. The hindrance on the phenyl ring of carboxylic acids had a limited effect on the reaction. For example, **1b** and **1g** produced the products **3ba** and **3ga** in 94 and 78% yields, respectively (entries 1 and 6, Table 2). Salicylic acid **1k** delivered the phenolic ester **3ka** in moderate yield, however, when the phenolic hydroxyl was masked with acetyl, the esterification yield dramatically increased to 88% (entries 10 and 11, Table 2). Notably, the hetero aromatic carboxylic acid, such as furan-2-carboxylic acid **1n**, cinnamic acid **1o**, and 2-phenylacetic acid **1p** ran smoothly under the standard conditions, producing the esters in 95, 96, and 98% yields, respectively (entries 12, 13 and 14, Table 2). The yield decreased to 50 and 70% under the presence of molecular sieves or using the dry EtOAc as solvents, respectively. This transformation is very practical, as it could be conducted under air, and the rigorous exclusion of air/moisture is not required either.

TABLE 2. Reaction of Carboxylic Acids with Phenylboronic Acid[a]

$$\underset{\mathbf{1}}{\mathrm{ArCOOH}} + \underset{\mathbf{2a}}{\mathrm{PhB(OH)_2}} \longrightarrow \underset{\mathbf{3}}{\mathrm{ArCOOPh}}$$

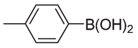
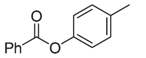
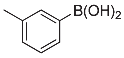
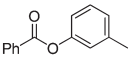
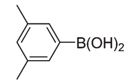
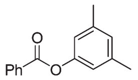
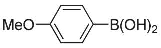
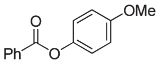
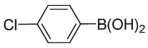
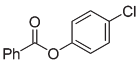
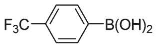
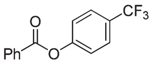
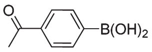
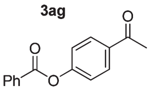
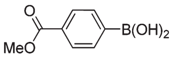
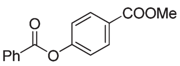
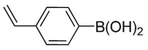
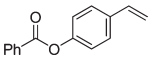
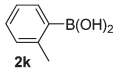
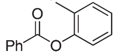
entry	carboxylic acid **1**	product **3**	yield (%)
1	 **1b**	 **3ba**	94
2	 **1c**	 **3ca**	71
3	 **1d**	 **3da**	88
4	 **1e**	 **3ea**	64
5	 **1f**	 **3fa**	60
6	 **1g**	 **3ga**	78
7	 **1h**	 **3ha**	86
8	 **1i**	 **3ia**	78
9	 **1j**	 **3ja**	63
10	 **1k**	 **3ka**	51
11	 **1m**	 **3ma**	88
12	 **1n**	 **3na**	95
13	 **1o**	 **3oa**	96
14	 **1p**	 **3pa**	98
15	 **1q**	 **3qa**	89

[a] Reaction conditions: carboxylic acid (0.2 mmol), phenylboronic acid (73 mg, 0.6 mmol), $Cu(OTf)_2$ (29 mg, 40 mol %), urea (12 mg, 1.0 equiv) in EtOAc (2 mL), 60 °C, 12 h under air.

Next, the esterification of benzoic acid with several arylboronic acids was investigated (Table 3). We found 24 h was required to complete the reaction. For example, the reaction of benzoic acid and 4-vinylphenyl boronic acid afforded the products in 65 and 90% at 12 and 24 h, respectively. As expected, the groups on the phenyl ring of arylboronic acids, such as chloro, trifluoromethyl, acetyl, and methoxycarbonyl were well compatible under the standard procedure. Notably, vinyl in **2j** survived under the reaction procedure, producing **3aj** in 90% yield (entry 9, Table 3). 2-Methylphenylboronic acid delivered the ester in 38% yield. Disappointingly, 4-hydroxyphenylboronic acid and other *ortho*-substituted

TABLE 3. Reaction of Benzoic Acid with Arylboronic Acids[a]

$$\underset{\mathbf{1a}}{PhCOOH} + \underset{\mathbf{2}}{ArB(OH)_2} \longrightarrow \underset{\mathbf{3}}{PhCOOAr}$$

entry	arylboronic acid **2**	product **3**	yield (%)
1	 **2b**	 **3ab**	70
2	 **2c**	 **3ac**	90
3	 **2d**	 **3ad**	83
4	 **2e**	 **3ae**	38
5	 **2f**	 **3af**	50
6	 **2g**	 **3ag**	51
7	 **2h**	 **3ah**	90
8	 **2i**	 **3ai**	43
9	 **2j**	 **3aj**	90
10	 **2k**	 **3ak**	38

[a] Reaction conditions: benzoic acid (24 mg, 0.2 mmol), arylboronic acid (0.6 mmol), Cu(OTf)$_2$ (29 mg, 40 mol %), urea (12 mg, 1.0 equiv) in EtOAc (2 mL), 60 °C, 24 h, under air.

phenylboronic such as 2-chlorophenylboronic, 2-methoxyphenylboronic, and naphthaleneboronic acid failed to deliver the desired esters.

The phenol was detected as a byproduct during the procedure. However, when benzoic acid and phenol were subjected to the standard reaction condition in the absence or presence of phenylboronic acid (10 and 20 mol %, respectively), a trace of ester (< 1%) was formed. This result ruled out the possibility of a hydroxylation of boronic acids[9]/esterification pathway.

In conclusion, we have developed a Cu(OTf)$_2$-mediated Chan-Lam reaction of carboxylic acid and arylboronic acids, affording the phenolic esters in moderate to good yields. The reaction showed remarkably broad substrate scope and good functional group tolerance.

Experimental Section

Typical Experimental Procedure for the Reaction of Arylboronic Acids with Carboxylic Acids to Esters. Under air, a reaction tube was charged with carboxylic acid (0.2 mmol), arylboronic acid (0.6 mmol), Cu(OTf)$_2$ (29 mg, 40 mol %), urea (0.2 mmol), and ethyl acetate (2 mL). The mixture was stirred at 60 °C. After the mixture was kept stirring for 12 or 24 h, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the product.

Phenyl 2-Acetoxybenzoate (3ma). Compound **3ma** is a white solid; ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.15 (d, J = 7.9 Hz, 1H), 7.58−7.54 (m, 1H), 7.36−7.31 (m, 3H), 7.21−7.17 (m, 1H), 7.11−7.09 (m, 3H), 2.23 (s, 3H). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 169.7, 162.9, 151.2, 150.6, 134.5, 132.2, 129.5, 126.1, 126.0, 124.0, 121.7, 21.0. IR (prism, cm^{-1}): 3058, 1739, 1694, 1483, 1188, 740. MS (EI) 256 (M$^+$); HRMS Calcd for $C_{15}H_{12}O_4$ (M$^+$), 256.0736; found, 256.0730.

Acknowledgment. We thank the National Natural Science Foundation of China (No. 20972115), the Key Project of Chinese Ministry of Education (No. 209054), and State Key Laboratory of Coordination Chemistry of Nanjing University for financial support.

Supporting Information Available: Experimental procedures along with copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] The transition-metal catalyzed hydroxylation of boronic acids, please see: (a) Xu, J.; Wang, X.; Shao, C.; Su, D.; Cheng, G.; Hu, Y. *Org. Lett.* **2010**, *12*, 1964. (b) Kianmehr, E.; Yahyaee, M.; Tabatabai, K. *Tetrahedron Lett.* **2007**, *48*, 2713. (c) Maleczka, R. E.; Shi, F.; Holmes, D.; Smith, M. R., III. *J. Am. Chem. Soc.* **2003**, *125*, 7792. (d) Benjamin, R.; Travis, B. R.; Ciaramitaro, B. P.; Borhan, B. *Eur. J. Org. Chem.* **2002**, 3429. (e) Simon, J.; Salzbrunn, S.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *J. Org. Chem.* **2001**, *66*, 633.