Organic LETTERS
Letter
pubs.acs.org/OrgLett

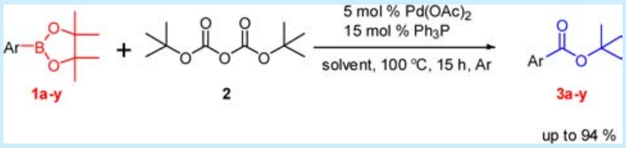
Preparation of *tert*-Butyl Esters via Pd-Catalyzed *tert*-Butoxycarbonylation of (Hetero)aryl Boronic Acid Derivatives

Xinjian Li,[†] Dapeng Zou,[†] Helong Zhu,[†] Yaping Wang,[†] Jingya Li,[‡] Yangjie Wu,*[,†] and Yusheng Wu*[,‡]

[†]The College of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou, Henan 450001, PR China
[‡]Tetranov International, Inc., 100 Jersey Avenue, Suite A340, New Brunswick, New Jersey 08901, United States

S *Supporting Information*

ABSTRACT: A novel protocol to synthesize *tert*-butyl esters from boronic acids or boronic acid pinacol esters and di-*t*-butyl dicarbonate has been successfully achieved. The cross-coupling reactions can produce up to 94% yields by using palladium acetate and triphenylphosphine as catalyst system, dioxane as a solvent. Moreover, a wide range of substrates including benzenes, pyridines, and quinolines boronic acids or boronic acid pinacol esters can fit with this system as well.

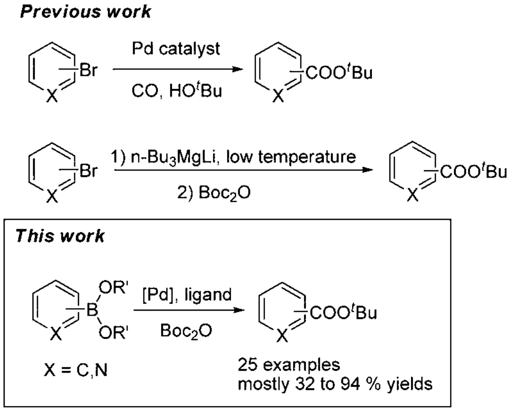


Derivatives of aryl (heteroaryl) esters are among the most important structural motifs and are found in bioactive compounds, synthetic materials, protecting groups[1] and as an important source of carboxylic acid.[2]

Several paths of alkoxycarbonylation of aryl (heteroaryl) derivatives have been reported, but most of the methods are based on the reaction of Grignard or lithium reagent with alkylchloroformate, dimethyl carbonate, or other carbonylation reagent, which required cryogenic conditions and afforded products with variable yields.[3,4] Recently Skrydstrup et al. developed excellent procedures for the preparation of tertiary esters by palladium-catalyzed *tert*-butyloxycarbonylation of aryl bromides with carbon monoxide.[5] However, one of the raw materials for the *tert*-butyloxycarbonylation reaction still is toxic carbon monoxide. Despite numerous protocols reported in the literature, the formation of tertiary esters remains a persistent challenge under friendly conditions.

Since Suzuki first reported the palladium(0)-catalyzed cross-coupling reaction of aryl boronate derivatives,[6] the exciting breakthroughs have been achieved as an important C−C bond-forming reaction extensively used in the synthesis of natural products and pharmaceutical compounds. As the substrate of a powerful alternative to the conventional organometallic building blocks, organoboron reagents represent a kind of stable and easily obtained structure. In 2001, Goossen and co-workers synthesized aryl ketones from boronic acids and carboxylic acids or anhydrides.[7] However, the protocol to synthesize *tert*-butyl esters from boronic acid or boronic acid pinacol esters has not been reported as an alternative method of *tert*-butyloxycarbonylation reaction without carbon monoxide. Although di-*t*-butyl dicarbonate was widely known as a useful stable raw material for the protection of amines and amine derivatives,[8] there have been no reports of alkoxycarbonylation reaction using di-*t*-butyl dicarbonate. Herein, our target was to develop a convenient preparation of *tert*-butyl esters directly from boronic acids or boronic acid pinacol esters and di-*t*-butyl dicarbonate under mild nontoxic conditions and with minimal waste production (Scheme 1).

Scheme 1. Preparation of Aryl Esters via Alkoxycarbonylation

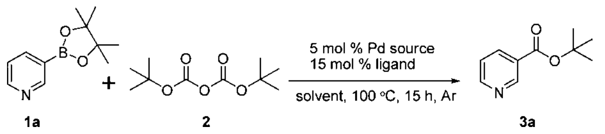


First, the reaction of 3-pyridineboronic acid pinacol ester (**1a**) with di-*t*-butyl dicarbonate (**2**) was chosen as model reaction to screen several palladium catalysts and ligands under various conditions.

As shown in Table 1, various Pd source (5 mol % loading) and ligands were investigated (Table 1, entries 1−7). The products were analyzed by GC−MS and GC. When palladium acetate was used as catalyst in the presence of triphenylphosphine, the desired product was obtained in 94% yield (Table 1, entry 3). Obviously, the palladium acetate and triphenylphosphine were more effective than other Pd source/ligand couples in this reaction (Table 1, entries 1−7).

Received: November 16, 2013
Published: March 21, 2014

Table 1. Investigation of the Reaction Parameters[a]



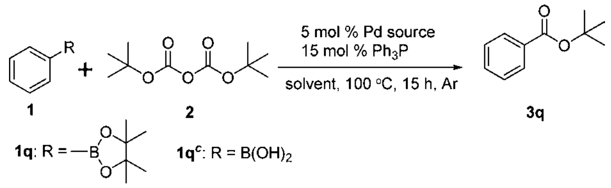
entry	Pd source	ligand	base	solvent	yield[b,c] [%]
1	$PdCl_2$	Ph_3P	–	dioxane	33
2	$Pd_2(dba)_3$	Ph_3P	–	dioxane	62
3	***$Pd(OAc)_2$***	***Ph_3P***	–	***dioxane***	***94***, 82[i]
4	$Pd(TFA)_2$	Ph_3P	–	dioxane	77
5	$Pd(Ph_3P)_4$	–	–	dioxane	68
6	$Pd(OAc)_2$	PCy_3	–	dioxane	trace
7	$Pd(OAc)_2$	L1-L10	–	dioxane	13–62
8	$Pd(OAc)_2$	Ph_3P	K_2CO_3	dioxane	65
9	$Pd(OAc)_2$	Ph_3P	K_3PO_4	dioxane	70
10	$Pd(OAc)_2$	Ph_3P	KOAc	dioxane	42
11	$Pd(OAc)_2$	Ph_3P	Na_2CO_3	dioxane	85
12	$Pd(OAc)_2$	Ph_3P	CsF	dioxane	42
13	$Pd(OAc)_2$	Ph_3P	*t*-BuOK	dioxane	no
14	$Pd(OAc)_2$	Ph_3P	–	dioxane	10,[d] 30[e]
15	$Pd(OAc)_2$	Ph_3P	–	DMF	trace
16	$Pd(OAc)_2$	Ph_3P	–	NMP	11
17	$Pd(OAc)_2$	Ph_3P	–	toluene	59
18	$Pd(OAc)_2$	Ph_3P	–	toluene	79[f]
19	$Pd(OAc)_2$	Ph_3P	–	DME	60[g]
20	$Pd(OAc)_2$	Ph_3P	–	dioxane	85[g]
21	$Pd(OAc)_2$	Ph_3P	–	THF	56[h]
22	$Pd(OAc)_2$	Ph_3P	–	EtOAc	61[h]

[a] Reaction conditions: 0.6 mmol **1a**, 1.2 mmol **2**, 5 mol % catalyst, 15 mol % ligand, 3 mL of solvent, 100 °C, 15 h, 1.8 mmol base, argon atmosphere. [b] The yields were determined by using GC. [c] Isolated yields based on **1a**. [d] Reaction performed in the presence of H_2O (2.4 mmol, 4 equiv). [e] Reaction performed in the presence of H_2O (1.2 mmol, 2 equiv). [f] The reaction temperature was 110 °C. [g] The reaction temperature was 80 °C. [h] The reaction temperature was 65 °C. [i] Oxygen atmosphere.

Second, bases are very important in transition-metal-catalyzed organic reactions to promote the catalytic reaction efficiency and increase the yields of products.[9] The influence of various bases for this transformation was studied in the discovered optimized catalytic condition. Na_2CO_3 and K_3PO_4 were found to give reasonable yields of the desired product (Table 1 entries 8–13), but it is important to point out that the base does not play a critical role for this reaction. The desired product was obtained in a higher yield in the absence of base (Table 1, entry 3). Because the external base is not required, we speculated that oxidative addition of the Pd catalyst into di-*t*-butyl dicarbonate leads to the formation of an equivalent of *tert*-butoxide, which may be serving as the base for trans-metalation.[10−12] It is thus that the reaction does not require external base. The decreased yields with external bases added could be due to base-promoted decomposition of di-*t*-butyl dicarbonate at high temperatures. We also tested oxygen atmosphere[13] in the reaction of using 3-pyridineboronic acid or 3-pyridineboronic acid ester as raw materials, and the yield was less than the result under argon atmosphere (Table 1, entry 3[i]). The solvents were found having significant effect on the reaction outcome (Table 1, entries 14–22). Dioxane gave the best yield at 100 °C, whereas using other polar aprotic solvents or changing the reaction temperature from 110 to 65 °C all resulted in much poorer yields of the desired product (Table 1, entries 15–22). It was also found the yield was lower in the presence of a certain amount of water (Table 1, entry 14[d,e]). Finally, the optimum reaction condition was determined as the combination of 5 mol % $Pd(OAc)_2$, 15 mol % Ph_3P, in anhydrous dioxane at 100 °C.

We expanded the scope of *t*-butoxycarbonylation of (hetero)aryl boronic acid pinacol ester in the optimized conditions, It is found that the lower yield was obtained using phenylboronic acid pinacol ester as substrate (Table 2, entry 1). After 15 h, almost all of phenylboronic acid pinacol ester was monitored by GC–MS. So, we tried using Cu(I) or Ag(I) as additives (Table 2, entries 2–5). Unfortunately, no corresponding product was found except homocoupling product. However, to our delight, 70% phenyl *tert*-butyl ester was obtained when phenylboronic acid was used as the main raw material under the optimized reaction conditions (Table 2, entry 6).

Table 2. Screen of the Additive and Base for the Reaction of Phenylboronic Acid Pinacol Ester or Phenylboronic Acid with Di-*t*-butyl Dicarbonate[a]

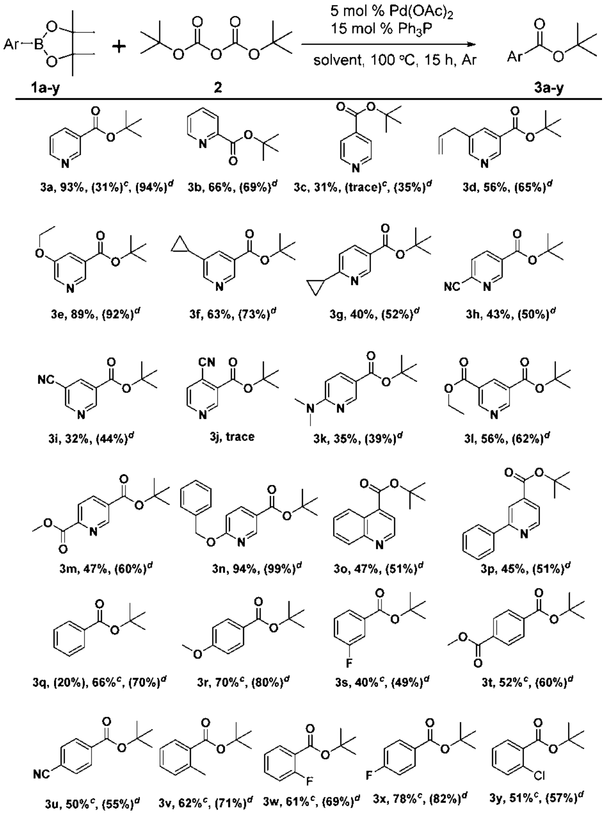


entry	S.M.	base	additive	yield[b] [%]
1	**1q**	–	–	20
2	**1q**	–	CuI	0
3	**1q**	–	Cu_2O	0
4	**1q**	–	Ag_2CO_3	trace
5	**1q**	Na_2CO_3	Ag_2CO_3	0
6	***1q***^{c}	–	–	***70***
7	**1q**^{c}	Na_2CO_3	–	54
8	**1q**^{c}	Na_2CO_3	Ag_2CO_3	trace
9	**1q**^{c}	–	Ag_2CO_3	trace
10	**1q**^{c}	–	CuI	0

[a] Reaction conditions: 0.6 mmol **1**, 1.2 mmol **2**, 5 mol % $Pd(OAc)_2$, 15 mol % Ph_3P, 3 mL of dioxane, 100 °C, 15 h, 1.8 mmol base, 20 mol % additive, argon atmosphere. [b] The yields were determined by using GC or GC–MS.

Continuing to investigate the reaction scope, we explored various arylboronic acid pinacol esters for this process under the optimized reaction conditions (Scheme 2). It was found that both electron-rich and electron-poor pyridine boronic acid pinacol esters could be successfully converted to the corresponding products in moderate to good yields. As shown in Scheme 2, the reaction conditions could be compatible with a wide range of functional groups such as ethers, alkyl, vinyl, esters, nitriles and amino groups. Furthermore, the position of functional groups in pyridine boronic acid pinacol esters had a weak effect on product yields (Scheme 2, **3e**, **3n**; **3l**, **3m**; **3f**, **3g**). But for nitrile-substituted pyridines, steric hindrance of pyridine boronic acid pinacol esters was the main factor effecting product yields (Scheme 2, **3h**, **3i**, **3j**). In addition, the position of boronic acid pinacol esters of pyridine had some noticeable impact on product yields (Scheme 2, **3a**, **3b**, **3c**): α-pyridine boronic acid pinacol esters and β-pyridine boronic acid pinacol esters gave the desired products in moderate to good yields, but γ-position of boronic

Scheme 2. Palladium-Catalyzed *tert*-Butyloxycarbonylation Reactions of Boronic Acid Derivatives with Di-*tert*-butyl Dicarbonate[a,b]



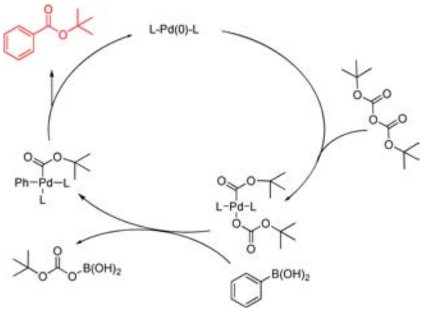
[a]Reaction conditions: 0.6 mmol **1**, 1.2 mmol **2**, 5 mol % $Pd(OAc)_2$, 15 mol % Ph_3P, 3 mL of dioxane, 100 °C, 15 h, argon atmosphere. [b]Isolated yields based on **1**. [c]Using boronic acid as substrate. [d]The yields were determined by using GC.

acid pinacol of pyridine only gave the desired product in 31% yield (Scheme 2, **3c**).

Because the yield of the *tert*-butyloxycarbonylation from phenylboronic acid was higher than the yields from phenylboronic acid pinacol esters, other substituent phenylboronic acids were used, also leading to moderate to good yields. (Scheme 2, **3r**, **3s**, **3t**, **3u**, **3v**, **3w**, **3x**, **3y**). We proceeded to study the reactions of 3-, 4-pyridine boronic acid with di-*t*-butyl dicarbonate under the optimized reaction conditions. But both 3- and 4-pyridine boronic acids afforded the corresponding products **3a** and **3c** separately in only 31% and trace yields (Scheme 2, **3a**[c], **3c**[c]). So, the phenyl boronic acid or pyridineboronic acid ester both can afford the corresponding *tert*-butyloxycarbonylation product smoothly.

Because of the fact that the phenyl boronic acid could afford the corresponding *tert*-butyloxycarbonylation product, and when using phenyl boronic acid ester as raw a large number of substrates was monitored by GC−MS after reaction, and the base from decomposition of di-*t*-butyl dicarbonate existed, we speculated the transmetalation was the rate-determining step and presumed a simplified reaction mechanism analogous to that of other palladium-catalyzed cross-coupling reactions[10,13] to explain some of these findings. We also tested oxygen atmosphere in the reaction of using 3-pyridineboronic acid or 3-pyridineboronic acid ester as raw materials and found the yield was lower.[13] So we conjectured some of these findings as the cycle in Scheme 3 similar to the mechanism proposed by Goossen and co-workers,[11,12] instead of mechanism of oxidation coupling.[10,13]

Scheme 3. Possible Mechanism of *tert*-Butyloxycarbonylation



In conclusion, a more direct, convenient and novel route to aryl (heteroaryl) *tert*-butyl esters in one pot was discovered and developed *via* the palladium-catalyzed cross-coupling reactions of boronic acid or boronic acid pinacol esters with di-*tert*-butyl dicarbonate. In this reaction, an efficient and generally applicable catalytic system has been developed. Both the catalyst and ligand are commercially available. By contrast, cheaper, greener, and nontoxic di-*tert*-butyl dicarbonate has been used compared with traditional *tert*-butyloxycarbonylation method. We believe that the process combined with the condition would be attractive and beneficial for its further development. Further exploration of this reaction is currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and copies of ^1H and ^{13}C NMR spectra for all the coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yusheng.wu@tetranovglobal.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the Natural Science Foundation of China (20772114, 21172200), the Innovation Fund for Outstanding Scholar of Henan Province (0621001100) and Research Program of Fundamental and Advanced Technology of Henan Province (122300413203) for financial support.

■ REFERENCES

(1) (a) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Wiley: New York, 1989; p 1266. (b) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; VCH: New York, 1989; p 881. (c) Carmo, A. C.; Souza de, L. K. C.; Costa de, C. E. F.; Longo, E.; Zamian, J. R.; Rocha Filha da, G. N. *Fuel* **2009**, *88*, 461. (d) Nishikubo, T.; Kameyama, A.; Yamada, Y.; Yoshida, Y. *J. Polym. Sci., Part A: Polym. Chem.* **1996**, *34*, 3531. (e) Ansari, H. R.; Curtis, A. J. *J. Soc. Cosmet. Chem.* **1974**, *25*, 203.

(2) (a) Li, B.; Berliner, M.; Buzon, R.; Chiu, C. K.-F.; Colgan, S. T.; Kaneko, T.; Keene, N.; Kissel, W.; Le, T.; Leeman, K. R.; Marquez, B.; Morris, R.; Newell, L.; Wunderwald, S.; Witt, M.; Weaver, J.; Zhang, Z.; Zhang, Z. *J. Org. Chem.* **2006**, *71*, 9045. (b) Filali, E.; Lloyd-Jones, G. C.; Sale, D. A. *Synlett* **2009**, 205. (c) Marcantoni, E.; Massaccesi, M.; Torregiani, E.; Bartoli, G.; Bosco, M.; Sambri, L. *J. Org. Chem.* **2001**, *66*, 4430.

(3) (a) Ghera, E.; Bendavid, Y. *J. Org. Chem.* **1988**, *53*, 2972. (b) Rausch, D.; Lambert, C. *Org. Lett.* **2006**, *8*, 5037. (c) Bratton, L. D.; Huh, H.; Bartsch, R. A. *J. Heterocycl. Chem.* **2000**, *37*, 815.

(4) (a) Li, H.; Balsells, J. *Tetrahedron Lett.* **2008**, *49*, 2034. (b) Amedio, J. C. J.; Lee, G. T.; Prasad, K.; Repic, O. *Synth. Commun.* **1995**, *25*, 2599. (c) Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 2nd ed.; John Wiley & Sons: New York, 1999.

(5) Xin, Z.; Gøgsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. *Org. Lett.* **2012**, *14*, 284.

(6) (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437. (b) Miyaura, N.; Suzuki, A. *Chem. Commun.* **1979**, *19*, 866.

(7) Goossen, L. J.; Ghosh, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 3458.

(8) (a) Greene, T. W.; Wuts, P. G. M. *Protecting Group in Organic Synthesis*; John Wiley and Sons: New York, 1999. (b) Kocienski, P. J. *Protecting Groups*; Georg Thieme: New York, 2000. (c) Shirini, F.; Mamaghani, M.; Atghia, S. V. *Catal. Commun.* **2011**, *12*, 1088.

(9) Ouyang, K.; Xi, Z. *Acta Chim. Sin.* **2013**, *71*, 13.

(10) (a) Kakino, R.; Narahashi, H.; Shimizu, I.; Yamamoto, A. *Chem. Lett.* **2001**, 1242. (b) Kakino, R.; Yasumi, S.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 137.

(11) Goossen, L. J.; Ghosh, K. *Eur. J. Org. Chem.* **2002**, 3254.

(12) Goossen, L. J.; Koley, D.; Hermann, H. L.; Thiel, W. *J. Am. Chem. Soc.* **2005**, *127*, 11102.

(13) Yoo, K. S.; Yoon, C. H.; Jung, K. W. *J. Am. Chem. Soc.* **2006**, *128*, 16384.