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# Preparation of Imides via the Palladium-Catalyzed Coupling Reaction of Organoborons with Methyl *N*-[Methoxy(methylthio)methylene]-carbamate as a One-Carbon Elongation Reaction

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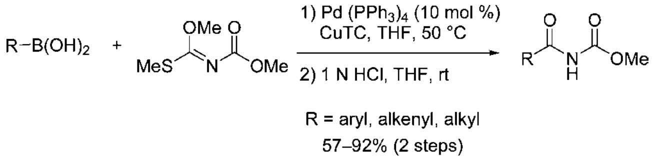
## ABSTRACT

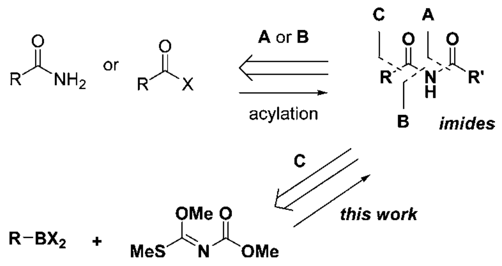


**The preparation of imides via the palladium-catalyzed coupling reaction as a one-carbon elongation reaction is described. The palladium-catalyzed coupling reaction of aryl-, alkyl-, and alkenylborons with *N*-[methoxy(methylthio)methylene]carbamate in the presence of Cu(I) thiophene-2-carboxylate (CuTC) affords imino ethers that are converted to the corresponding imides by acidic hydrolysis in high yield. The imino ethers are also useful for preparing the corresponding ester without using carbon monoxide.**

Imides are diacyl derivatives of ammonia or primary amines or, in a broad sense, functional groups consisting of two carbonyl groups bound to nitrogen. Recently, imides have been utilized in the catalytic asymmetric conjugate additions of hydrazoic acid,[1a] cyanide,[1b] amine,[1c] malononitrile,[1d] oxime,[1e] arylthiol,[1f] and activated methylene compounds[1g,h] along with their transformations,[1] suggesting their potential utility in organic synthesis.

Usually, imides are prepared by condensation reactions of amides with acylating reagents (**A**)[2] or by reaction of activated carboxylic acid derivatives with amides (**B**).[3] Therefore, these methods require the corresponding carboxylic acids or their derivatives as starting materials, thereby limiting the variation of their syntheses.

**Scheme 1**



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(1) (a) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959. (b) Sammis, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442. (c) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204. (d) Sibi, M. P.; Prabagaran, N.; Ghorpade, S. G.; Jasperse, C. P. *J. Am. Chem. Soc.* **2003**, *125*, 11796. (e) Vanderwal, C. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 14724. (f) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603. (g) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4032. (h) Inokuma, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 9413.

(2) For example, see: Yao, L.; Pitta, B.; Ravikumar, P. C.; Purzycki, M.; Fleming, F. F. *J. Org. Chem.* **2012**, *77*, 3651.

(3) For example, see: DeNinno, M. P.; Eller, C.; Etienne, J. B. *J. Org. Chem.* **2001**, *66*, 6988.

10.1021/ol303062a

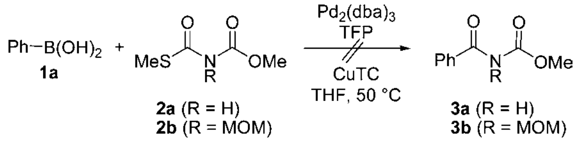
Liebeskind and Srogl reported a palladium-catalyzed C−C cross-coupling reaction of thioesters with boronic acids in the presence of Cu(I) thiophene-2-carboxylate (CuTC) that affords ketones under neutral conditions.[4] This C−C bond-forming reaction has been extended to the cross-coupling reactions between a variety of organosulfur and organometallic reagents. Most boronic acids and organosulfur compounds are air- and moisture-stable and have low toxicity. Therefore, the cross-coupling reactions with these reagents are highly attractive and useful for the organic syntheses of complex natural products.

Palladium-catalyzed one-carbon elongation reactions of organoborons have been reported.[5] However, most of the reactions use toxic carbon monoxide, and to the best of our knowledge, the preparation of imides via the Pd-catalyzed coupling reaction has not yet been reported. We herein report a preparation method of imides via the Pd-catalyzed coupling reactions of organoboranes (**C**, Scheme 1).

We first attempted the Pd-catalyzed coupling reaction of phenylboronic acid **1a** with imide **2a** (Scheme 2) because this reaction was thought to provide straightforward access to imides. The reaction was carried out under the conditions that have been used in the Liebeskind−Srogl coupling reaction.

However, the coupled product **3a** was not obtained and only **2a** was consumed. This result suggested the possibility of the occurrence of *β*-elimination of the acylpalladium intermediate that was formed by the reaction of **2a** with palladium(0). Therefore, we attempted the reaction of **1a** with **2b**, which has a MOM group on the nitrogen atom, but no reactions occurred.

**Scheme 2**



We next examined the coupling reaction of **1a** with methyl *N*-[methoxy(methylthio)methylene]carbamate (**4**) because **4** has a methylthio group attached at the $sp^2$ carbon of a C−N double bond and no H-atom on the nitrogen. Compound **4** was prepared in a one-pot manner according to the known procedure[6] as shown in Scheme 3. That is, the reaction of methyl chloroformate with potassium isothiocyanate was carried out in THF to afford isothiocyanate, which was subjected to the reaction with methanol, followed by *S*-methylation with dimethyl sulfate to afford **4** as a white crystal.

**Scheme 3**

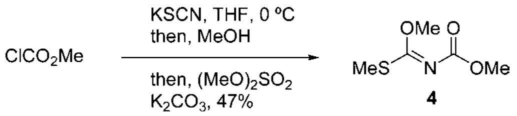
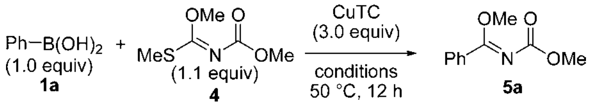


**Table 1.** Optimization of the Pd-Catalyzed Coupling Reaction of Phenylboronic Acid **1a** with **4**



| entry | solvent | Pd (10 mol %) | ligand (mol %) | yield (%)[a] |
|---|---|---|---|---|
| 1 | THF | $Pd(PPh_3)_4$ | – | 91 |
| 2 | 1,4-dioxane | $Pd(PPh_3)_4$ | – | 80 |
| 3 | DMF | $Pd(PPh_3)_4$ | – | 69 |
| 4 | $CH_3CN$ | $Pd(PPh_3)_4$ | – | 50 |
| 5 | toluene | $Pd(PPh_3)_4$ | – | 42 |
| 6 | $(CH_2Cl)_2$ | $Pd(PPh_3)_4$ | – | 42 |
| 7 | THF | $Pd(OAc)_2$ | $PPh_3$ (20) | 70 |
| 8 | THF | $Pd(OAc)_2$ | $PPh_3$ (30) | 76 |
| 9 | THF | $Pd(OAc)_2$ | TFP[b] (30) | 81 |
| 10 | THF | $Pd_2(dba)_3$ | $AsPh_3$ (30) | 70 |

[a] Isolated yields. [b] TFP = tris(2-furyl)phosphine.

With **4** in hand, its Pd-catalyzed coupling reaction with arylboronic acid **1a** was examined (Table 1). Because the coupling reaction did not proceed at rt, all the reactions (entries 1−10) were carried out at 50 °C using **4** (1.1 equiv) in the presence of CuTC (copper(I) thiophene-2-carboxylate) (3.0 equiv), which is the additive usually used in the Liebeskind−Srogl coupling reaction. The reaction with a catalytic amount of $Pd(PPh_3)_4$ in THF afforded the coupled product **5a** in 91% yield. The same reaction was carried out in different solvents, but the yield was not improved (entries 2−6). Palladium catalysts other than $Pd(PPh_3)_4$ were also examined (entries 7−10); however, the best results were obtained when using $Pd(PPh_3)_4$.

The negatively charged boronate under the basic conditions can undergo the addition−elimination sequence to form the same product without palladium. However, the reaction of **1a** in the absence of a Pd reagent afforded no products, suggesting that this coupling reaction is a Pd-catalyzed reaction.

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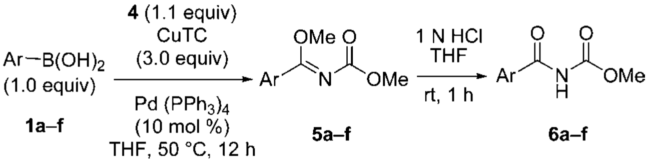
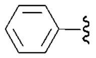
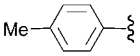
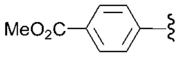
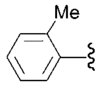
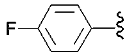
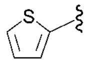
(4) (a) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260. (b) Yu, Y.; Liebeskind, L. S. *J. Org. Chem.* **2004**, *69*, 3554. (c) Prokopcov, H.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2009**, *48*, 2276.

(5) (a) Miyaura, N.; Suzuki, A. *Chem. Lett.* **1981**, 879. (b) Satoh, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1986**, 1329. (c) Ohe, T.; Ohe, K.; Uemura, S.; Sugita, N. *J. Organomet. Chem.* **1988**, *344*, C5. (d) Cho, C. S.; Ohe, T.; Uemura, S. *J. Organomet. Chem.* **1995**, *496*, 221. (e) Duan, Y.-Z.; Deng, M.-Z. *Synlett* **2005**, 355. (f) Yamamoto, Y.; Hattori, K.; Ishii, J.-I.; Nishiyama, H.; Itoh, K. *Chem. Commun.* **2005**, 4438. (g) Yamamoto, Y. *Adv. Synth. Catal.* **2010**, *352*, 478. (h) Liu, Q.; Li, G.; He, J.; Liu, J.; Li, P.; Lei, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 3371. (i) Li, M.; Wang, C.; Fang, P.; Ge, H. *Chem. Commun.* **2011**, *47*, 6587. For the transition-metal-catalyzed carboxylation of organoborons with carbon-dioxide, see: Rh: (j) Ukai, K.; Aoki, M.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2006**, *128*, 8706. (k) Takaya, J.; Tadami, S.; Ukai, K.; Iwasawa, N. *Org. Lett.* **2008**, *10*, 2697. Cu: (l) Ohishi, T.; Nishiura, M.; Hou, Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 5792.

(6) Cohen, F.; Overman, L. E. *J. Am. Chem. Soc.* **2006**, *128*, 2594.

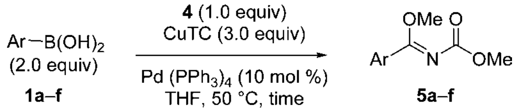
**Table 2.** Preparation of Imides **6a**–**f** via the Pd-Catalyzed Coupling Reactions of Arylboronic Acids **1a**–**f** (1.0 equiv) with **4** (1.1 equiv)

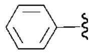
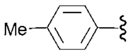
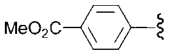
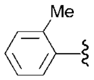
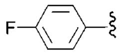
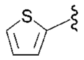


| entry | Ar– | yield (%)[a] of **5** | yield (%)[a] of **6** |
|---|---|---|---|
| 1 |  | 91 (**5a**) | 97 (**6a**) |
| 2 |  | 97 (**5b**) | 95 (**6b**) |
| 3 |  | 81 (**5c**) | 97 (**6c**) |
| 4 |  | 88 (**5d**) | 93 (**6d**) |
| 5 |  | 77 (**5e**) | 91 (**6e**) |
| 6 |  | 60 (**5f**) | 95 (**6f**) |

[a] Isolated yields.

**Table 3.** Pd-Catalyzed Coupling Reactions of Phenylboronic Acids **1a**–**f** (2.0 equiv) with **4** (1.0 equiv)



| entry | Ar– | time (h) | yield (%)[a] of **5** |
|---|---|---|---|
| 1 |  | 27 | 90 (**5a**) |
| 2 |  | 24 | 98 (**5b**) |
| 3 |  | 24 | 77 (**5c**) |
| 4 |  | 24 | 98 (**5d**) |
| 5 |  | 19 | 74 (**5e**) |
| 6 |  | 20 | 76 (**5f**) |

[a] Isolated yields.

Hydrolysis of **5a** under acidic conditions easily afforded imide **6a** in 97% yield (Table 2, entry 1). Hence, the coupling reaction of other arylboronic acids **1b**–**f** with **4** and the following hydrolysis were examined next (Table 2). The coupling reaction of *p*-tolylboronic acid **1b** with **4** afforded **5b** in 97% yield, and its acidic hydrolysis gave **6b** in 95% yield (entry 2). The yields of the coupling reactions of phenylboronic acids bearing an ester (entry 3) or a fluoride (entry 5) were slightly lower, probably because the electron-withdrawing groups on the phenyl group could reduce the reactivity of the arylboronic acids. The yield of the reaction of *o*-tolylboronic acid (entry 4) was also reduced, possibly owing to the steric bulkiness of the methyl group at the ortho position. The yield of the reaction of 2-thienylboronic acid (entry 6) was marginal, which could be attributed to the deactivation of palladium or copper by the coordination of the thienyl group.

The Pd-catalyzed coupling reactions of arylboronic acids **1a**–**f** (2.0 equiv) with **4** (1.0 equiv) were also examined (Table 3). The yields of all the reactions were comparable (entries 1–3 and 5) to those in Table 2 or better (entries 4 and 6). Notably, all the reactions required a prolonged reaction time for completion, though the reason is unknown.

The Pd-catalyzed coupling reactions of *B*-alkyl 9-BBN reagents with thioesters reported by Liebeskind[4b] and the successful results above encouraged us to examine the Pd-catalyzed coupling reaction of *B*-alkyl 9-BBN reagents with **4** (Table 4). *B*-alkyl 9-BBN reagents are easily prepared by hydroboration of the corresponding alkenes with 9-BBN. Therefore, the Pd-catalyzed coupling reactions of some *B*-alkyl 9-BBN reagents with **4** were carried out. That is, alkenes **7a**–**e** were subjected to the reaction with 9-BBN (1.0 equiv) to form *B*-alkyl 9-BBN reagents, which were used for the coupling reactions with **4** (1.1 equiv) in the presence of CuTC (3.0 equiv), Pd(PPh$_3$)$_4$ (10 mol %), and cesium carbonate (5.0 equiv).

Use of cesium carbonate was necessary in the reaction of *B*-alkyl 9-BBN reagents to attain good yields.[4,7] The overall yields of the three steps, hydroboration of alkenes **7a**–**e** with 9-BBN, the palladium-catalyzed coupling reaction of *B*-alkyl 9-BBN reagents with **4**, and subsequent acid hydrolysis, are all summarized in Table 4. All alkenes (**7a**–**e**) were successfully converted to the corresponding imides via the three steps (Table 4, entries 1–5). The overall yield is high, ranging from 76% to 83%. Thus, the average yield per step is over 90%, indicating that the three-step sequence could be a practical protocol for preparing alkyl imides.

The Pd-catalyzed coupling reactions of alkenylboronic acids **9a** and **9b** (1.0 equiv) with **4** (1.1 equiv) also afforded the corresponding imides under the optimized conditions in Table 1 (Table 5). Although the coupling reaction of **9a** required 12 h for completion (entry 1), the acid hydrolysis following the coupling reactions of **9a** and **9b** afforded imides **10a** and **10b**, respectively, in excellent yields, indicating that the protocol developed by us would also be useful for the preparation of α,*β*-unsaturated imides.

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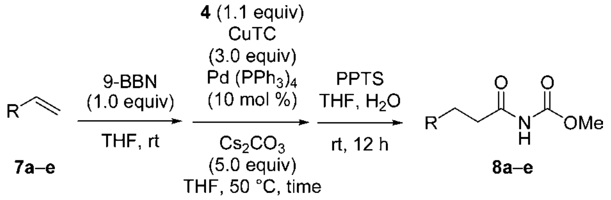
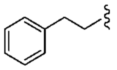
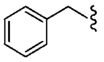
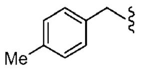
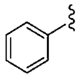
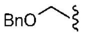
(7) (a) Miyaura, N.; Ishiyama, T.; Ishikawa, M.; Suzuki, A. *Tetrahedron Lett.* **1986**, *27*, 6369. (b) Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405. (c) Oh-e, T.; Miyayra, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201.

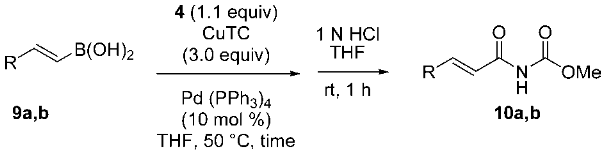
**Table 4.** Preparation of Imides **8a**−**e** via the Pd-Catalyzed Coupling Reactions of Prepared *B*-Alkyl 9-BBN Reagents **7a**−**e** with **4**

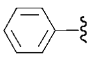


| entry | R– | time (h) | yield (%) (3 steps)$^a$ |
|---|---|---|---|
| 1 |  | 3 | 83 (**8a**) |
| 2 |  | 3 | 82 (**8b**) |
| 3 |  | 3 | 80 (**8c**) |
| 4 |  | 3 | 76 (**8d**) |
| 5 |  | 6 | 80 (**8e**) |

$^a$ Isolated yields.

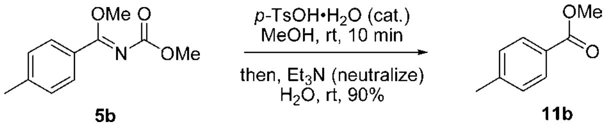
**Table 5.** Preparation of Imides **10** via the Pd-Catalyzed Coupling Reactions of Alkenylboronic Acids **9a** and **9b** with **4**



| entry | R– | time (h) | yield (%)$^a$ of **10** |
|---|---|---|---|
| 1 |  | 12 | 93 (**10a**) |
| 2 | $n$-C$_5$H$_{11}$– | 1 | 91 (**10b**) |

$^a$ Isolated yields.

**Scheme 4**



Imino ethers are known to be precursors of esters. For example, imide **5b** was converted to the corresponding methyl ester **11b** in 90% yield (Scheme 4). Hence, the Pd-catalyzed coupling reaction of organoborons with **4** could be utilized for the preparation of esters.

In summary, we have developed a new preparation method of imides via the Pd-catalyzed coupling reaction of organoborons with methyl *N*-[methoxy(methylthio)methylene]carbamate. The method is widely applicable to aryl-, alkyl-, and alkenylborons, enabling access to a variety of imides in high to excellent yields. The imino ethers formed by the Pd-catalyzed coupling reaction are easily converted to the corresponding imides or esters under mild acidic conditions. The developed preparation method comprises a one-carbon elongation that does not use toxic carbon monoxide. The same Pd-catalyzed reaction of organostannanes with methyl *N*-[methoxy(methylthio)methylene]carbamate is surmised to give the same results; hence, it is now under investigation, and the results will be reported in due course.

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**Supporting Information Available.** Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.