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Palladium-Catalyzed Preparation of Weinreb Amides from Boronic Acids and *N*-Methyl-*N*-methoxycarbamoyl Chloride

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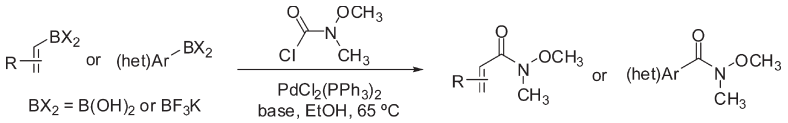

A simple protocol for the synthesis of Weinreb benzamides and α,β-unsaturated Weinreb amides through a palladium-catalyzed cross-coupling reaction between organoboronic acids and *N*-methoxy-*N*-methylcarbamoyl chloride has been developed. The method is also applicable to the use of potassium organotrifluoroborates.

Introduction

The use of *N*-methoxy-*N*-methylamides (Weinreb amides) as synthetic precursors to ketones and aldehydes has become a much-exploited strategy in organic synthesis since its original description by Nahm and Weinreb in 1981.[1,2] The remarkable ability of these building blocks to undergo a single substitution reaction in the presence of excess organometal reagents with minimal byproduct formation is key to their popularity as acylating agents for laboratory syntheses as well as for industrial scale processes.

Over the intervening years, many synthetic methods have been developed for the preparation of *N*-methoxy-*N*-methylamides of both benzoic and aliphatic acids, with the most widespread approach based on the condensation of carboxylic acids with *N*,*O*-dimethylhydroxylamine.[3] Among the alternative tactics for Weinreb amide preparation include the palladium-catalyzed aminocarboxylation of aryl bromides[4] and lactam/lactone-derived vinyl triflates[5] with *N*,*O*-dimethylhydroxylamine in a carbon monoxide atmosphere (Scheme 1, eq 1) and the Stille-type cross-coupling reaction between aryl and vinyl stannanes and *N*-methoxy-*N*-methylcarbamoyl chloride (**2**) developed by Murakami and co-workers (Scheme 1, eq 2).[6,7] We were particularly intrigued by this latter process and set out to examine whether we could develop a general cross-coupling method to prepare Weinreb amides by replacing the organotin component with the less toxic and more widely available boronic acid building blocks (eq 3, Scheme 1).

We were encouraged by the work of Duan and Deng,[8] who showed that di-*n*-butylcarbamoyl chloride could be cross-coupled with simple arylboronic acids under palladium/copper cocatalysis, and by Kristensen and co-workers,[9] who used neopentylglycol arylboronic esters to prepare benzamides from carbamoyl chlorides with palladium

(1) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(2) For reviews, see: (a) Balasubramaniam, S.; Aidhen, I. S. *Synthesis* **2008**, *23*, 3707. (b) Khlestkin, V. K.; Mazhukin, D. G. *Curr. Org. Chem.* **2003**, *7*, 967. (c) Singh, J.; Satyamurthi, N.; Aidhen, I. S. *J. Prakt. Chem.* **2000**, *342*, 340. (d) Mentzel, M.; Hoffmann, H. M. R. *J. Prakt. Chem.* **1997**, *339*, 517. (e) Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15.
(3) For examples, see: (a) Woo, J. C. S.; Fenster, E.; Dake, G. R. *J. Org. Chem.* **2004**, *69*, 8984. (b) Hioki, K.; Kobayashi, H.; Ohkihara, R.; Tani, S.; Kunishima, M. *Chem. Pharm. Bull.* **2004**, *52*, 470. (c) Kim, M.; Lee, H.; Han, K.-J.; Kay, K.-Y. *Synth. Commun.* **2003**, *33*, 4013. (d) Colobert, F. C.; Des Mazery, R.; Solladié, G.; Carreño, M. C. *Org. Lett.* **2002**, *4*, 1723. (e) De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 2534. (f) Bailén, M. A.; Chinchilla, R.; Dodsworth, D. J.; Nájera, C. *Tetrahedron Lett.* **2001**, *42*, 5013. (g) Banwell, M.; Smith, J. *Synth. Commun.* **2001**, *31*, 2011. (h) Tunoori, A. R.; White, J. M.; Georg, G. I. *Org. Lett.* **2000**, *2*, 4091. (i) Gibson, C. L.; Hanada, S. *Tetrahedron: Asymmetry* **1996**, *7*, 1281. (j) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461. (k) Einhorn, J.; Einhorn, C.; Luche, J.-L. *Synth. Commun.* **1990**, *20*, 1105.
(4) (a) Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7102. (b) Martinelli, J. R.; Freckmann, D. M. M.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 4843. (c) Zhuang, L.; Wai, J. S.; Embrey, M. W.; Fisher, T. E.; Egbertson, M. S.; Payne, L. S.; Guare, J. P. Jr.; Vacca, J. P.; Hazuda, D. J.; Felock, P. J.; Wolfe, A. L.; Stillmock, K. A.; Witmer, M. V.; Moyer, G.; Schleif, W. A.; Gabryelski, L. J.; Leonard, Y. M.; Lynch, J. J. Jr.; Michelson, S. R.; Young, S. D. *J. Med. Chem.* **2003**, *46*, 453.
(5) (a) Deagostino, A.; Larini, P.; Occhiato, E. G.; Pizzuto, L.; Prandi, C.; Venturello, P. *J. Org. Chem.* **2008**, *73*, 1941. (b) Aungst, R. A.; Funk, R. L. *J. Am. Chem. Soc.* **2001**, *123*, 9455.
(6) Murakami, M.; Hoshino, Y.; Ito, H.; Ito, Y. *Chem. Lett.* **1998**, *2*, 163.
(7) For preparations of Weinreb amides reacting *N*-methoxy-*N*-methylcarbamoyl chloride with organolithium or organomagnesium reagents, see: (a) Lee, J. I. *Bull. Korean Chem. Soc.* **2007**, *28*, 695. (b) Lee, J. I.; Jung, H. *J. Korean Chem. Soc.* **2005**, *49*, 609. (c) Lee, J. I.; Park, H. *Bull. Korean Chem. Soc.* **2002**, *23*, 521. (d) Tius, M. A.; Busch-Petersen, J.; Yamashita, M. *Tetrahedron Lett.* **1998**, *39*, 4219.
(8) Duan, Y.-Z.; Deng, M.-Z. *Synlett* **2005**, *2*, 355.
(9) Lysén, M.; Kelleher, S.; Begtrup, M.; Kristensen, J. L. *J. Org. Chem.* **2005**, *70*, 5342.

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SCHEME 1. Palladium-Catalyzed Preparation of Alkenyl and Aryl Weinreb Amides

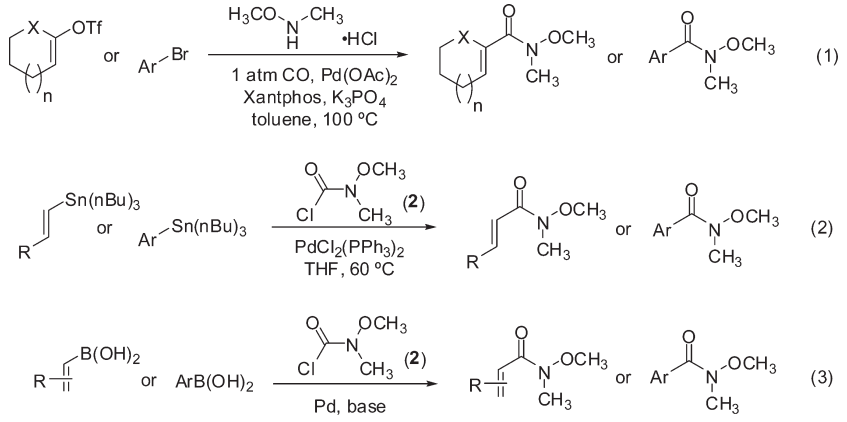
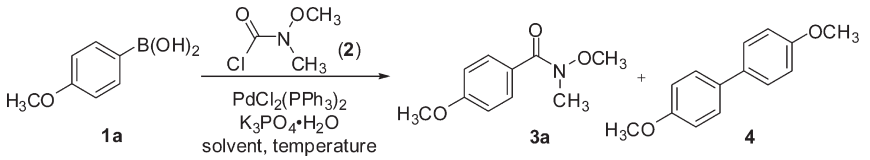


TABLE 1. Conditions To Optimize Cross-Coupling of 4-Methoxyphenylboronic Acid (1a) with *N*-Methyl-*N*-methoxycarbamoyl Chloride (2)



entry	reaction conditions[a]	equiv of **2**	equiv of $K_3PO_4 \cdot H_2O$	yield of **3a** (%)	yield of **4** (%)
1	toluene, 100 °C, 2 h	2.0	2.0	39	7
2	toluene, 80 °C, 2 h	2.0	2.0	54	7
3	toluene, 80 °C, 2 h	1.5	2.0	47	18
4	toluene, 80 °C, 4 h	1.5	2.5	39	20
5	toluene, 80 °C, 2 h	2.0	3.0	53	6
6	toluene, 60 °C, 1 h	2.0	2.0	57	7
7	toluene, 60 °C, 1 h	3.0	2.0	62	14
8	toluene, 40 °C, 2 h	2.0	2.0	32	13
9	THF, 65 °C, 2 h	2.0	2.0	62	11
10	THF, 65 °C, 5 h	3.0	2.0	27	5
11	THF, 40 °C, 8 h	2.0	2.0	43	12
12	dioxane, 80 °C, 9 h	2.0	2.0	21	3
13	dioxane, 65 °C, 4 h	2.0	2.0	7	10
14	dioxane, 40 °C, 6 h	2.0	2.0	9	8
15	ethanol, 80 °C, 1 h	2.0	2.0	38	19
16	ethanol, 65 °C, 2 h	2.0	2.0	89	4
17	ethanol, 65 °C, 2 h	3.0	2.0	92	3
18	ethanol, 40 °C, 4 h	2.0	2.0	72	12

[a]Reactions were run on 1 mmol scale and utilized 5 mol % of $PdCl_2(Ph_3P)_2$ in 5 mL of anhydrous solvent. The reaction times are shown. Isolated yields are based on arylboronic acid **1a**.

catalysis. Herein we report a simple, efficient procedure for the preparation of Weinreb amides through the palladium-catalyzed cross-coupling of commercially available *N*-methoxy-*N*-methylcarbamoyl chloride (**2**) with both (hetero)aryl and alkenyl organoboronic acids.

Results and Discussion

We began our investigation by screening various reaction conditions for the cross-coupling of *N*-methoxy-*N*-methylcarbamoyl chloride (**2**)[10] with 4-methoxyphenylboronic acid (**1a**) as shown in Table 1. On the basis of the literature precedents for similar systems,[9] we decided to use 5 mol % of bis(triphenylphosphine)dichloropalladium(II) as catalyst, which ultimately worked very well for the method. Early in the investigation we found that the zerovalent catalyst tetrakis(triphenylphosphine)palladium(0) did not work as well, and in fact led to minor amounts of a byproduct in which the *N*-methoxy functionality of **3a** was removed, similar to an observation made by Larhed and co-workers in a palladium(0)-catalyzed aminocarboxylation reaction.[11a] We also made a brief investigation into any effect played by copper as an additive,[8] but largely without success. Again, small amounts of a byproduct in which the formed Weinreb amide **3a** underwent heterolytic cleavage of the nitrogen−oxygen bond

(10) For other examples of metal-catalyzed cross-coupling reactions utilizing *N*-methoxy-*N*-methylcarbamoyl chloride, see ref 5 and: (a) Sato, Y.; Tamura, T.; Kinbara, A.; Miwako, M. *Adv. Synth. Catal.* **2007**, *349*, 647. (b) Sato, Y.; Tamura, T.; Mori, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2436.

(11) For instances involving heterolytic cleavage of *N*-alkoxyamide nitrogen−oxygen bonds of Weinreb amides under some cross-coupling conditions, see: (a) Odell, L. R.; Sävmarker, J.; Larhed, M. *Tetrahedron Lett.* **2008**, *49*, 6115. (b) Zhang, Z.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2008**, *10*, 3005.

was observed, similar to an observation by Zhang and Liebeskind in which copper salts were shown to lead to heterolytic cleavage of *N*-alkoxyamides under some cross-coupling conditions.[11b]

Of the inorganic bases surveyed (in toluene at 80 °C, not shown), potassium phosphate monohydrate was found to be the most successful, leading to the best reproducible yields of Weinreb benzamide **3a** and with minimal hydrolysis of the carbamoyl chloride reagent **2**. Interestingly, the use of anhydrous potassium phosphate failed to provide sufficient amounts of the benzamide, analogous to reports that hydrated potassium phosphate is preferable as a base in some types of palladium-catalyzed reactions.[12]

Examination of solvent and temperature parameters on the cross-coupling reaction is summarized in Table 1. In each case, small amounts of the aryl homocoupling byproduct **4** were observed. Reactions at higher temperatures resulted in significant decreases in isolated yields, presumably in part due to greater thermal instability of carbamoyl chloride **2** in the basic media. Interestingly, increasing the amount of **2** to 3 equiv did not significantly increase the yield of **3a** (entries 6 vs. 7, 9 vs. 10 and 16 vs. 17), so 2 equiv was chosen for use as a general method.

We applied the best conditions to other arylboronic acid and heteroarylboronic acid substrates **1** and found that the protocol worked quite well as a general method to effect the preparation of *N*-methyl-*N*-methoxybenzamides and heterocyclic congeners **3** (Table 2).

The optimized conditions of ethanol at 65 °C transformed both electron-rich arylboronic acids **1a**,**b** (entries 1 and 2) as well as electron-poor substrates **1d**−**g** (entries 4−7) and conjugated aromatics **1h**,**i** (entries 8 and 9) to the corresponding Weinreb benzamides **3a**−**i** equally well. Heterocyclic substrates also provided heteroaryl Weinreb amides in good yields and included a benzofuran **3j** (entry 10), (benzo)thiophenes **3k** and **3*l*** (entries 11 and 12), indoles **3m** and **3n** (entries 13 and 14), pyridazine **3o** (entry 15), and quinoline **3p** (entry 16). In several of these cases, the best conditions for three different solvents were examined head-to-head with the same substrate, in every case showcasing superior yields with anhydrous ethanol. It should be noted that none of the bis-amide byproduct arising from addition of *N*-methoxy-*N*-methylamine (formed by decomposition of **2** in situ) to the carboxyethyl moiety of product **3f** was observed. It should be noted that none of the byproduct arising from the *N*-acylation of the indole product **3n** by excess *N*-methoxy-*N*-methylcarbamoyl chloride was observed. The exceptions to the generality of this transformation were seen in the use of 2-methoxyphenylboronic acid (**1c**, entry 3) and pyridine-3-boronic acid (**1q**, entry 17). In the former case, the use of **1c** failed to provide useful amounts of the corresponding amide **3c**, although in any set of conditions tried the starting materials were completely consumed. Presumably the greater energy required to overcome the steric bulkiness at the reactive site (longer reaction times and higher temperatures examined, not shown) results in the destruction of the reagents before the cross-coupling can take place. Preliminary attempts to modify the procedure for 1c, such as employed by Buchwald and co-workers to overcome the reduced reactivity of ortho-substituted substrates in their palladium-catalyzed aminocarbonylation method (Scheme 1),[4a,b] showed some initial promise, and will be reported to address this substrate limitation in due course. With the use of pyridine-3-boronic acid (**1q**), none of the conditions examined provided any reasonable amounts of the corresponding product **3q**, even at prolonged reaction times, which is consistent with observations from the literature that pyridine-derived 3-boronic acids usually do not readily participate in many cross-coupling reactions.[13] Nevertheless, given the overall generality of our cross-coupling procedure for **2** with arylboronic acids, we were pleased to find a method for preparing Weinreb benzamides equivalent in yields with the palladium-catalyzed aminocarboxylation of aryl bromide substrates reported by the Buchwald group (for example, compare to literature yields of 89% for **3a**, 87% for **3c**, 87% for **3g**, 94% for **3h**, and 91% for 3k).[4] In our case we cite several more examples of heteroaryl-derived Weinreb benzamide products in addition to the development of reaction conditions that avoid the use of carbon monoxide as a reagent.

We next turned our attention to the preparation of α,β-unsaturated *N*-methoxy-*N*-methylamides **6** from the corresponding olefinic boronic acids **5** (Table 3).

As before, we examined several solvents and reaction temperatures in order to optimize the transformation from (*E*)-styrylboronic acid (**5a**) to the corresponding cinnamyl Weinreb amide **6a** (best results shown in Table 3). While we were ultimately successful in establishing that our protocol in anhydrous ethanol did indeed reproducibly provide a general route to preparing the requisite vinylic Weinreb amides **6**, the isolated yields ranged from only very modest to satisfactory. Even so, we were pleased to provide the first examples of α,β-unsaturated Weinreb amides generated from linear and branched vinylboronic acids, differing from the palladium-catalyzed methods[5] in which only vinyl triflates derived from (thio)lactones or lactams were found to undergo aminocarboxylation to provide Weinreb amides of cyclic olefins.[14] It should also be noted that no byproducts arising from a Michael-type 1,4 addition of *N*-methoxy-*N*-methylamine (formed by decomposition of **2** in situ) to the α,β-unsaturated amide moiety of products **6** were observed.

We subsequently focused our attention to the application of the method to cross-coupling using potassium organotrifluoroborates **7** and **8** as coupling partners for Weinreb amide formation, given the rising interest in these air-stable and increasingly available reagents in metal-catalyzed cross-coupling reactions (Table 4).[15]

When developing the methods for this cross-coupling, however, we found that the use sodium carbonate as a base

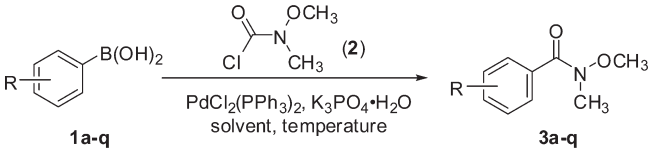
(12) (a) Urawa, Y.; Ogura, K. *Tetrahedron Lett*. **2003**, *44*, 271. (b) Urawa, Y.; Naka, H.; Miyazawa, M.; Souda, S.; Ogura, K. *J. Organomet. Chem*. **2002**, *653*, 269.

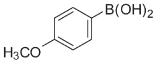
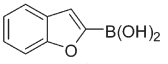
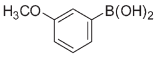
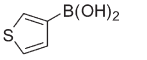
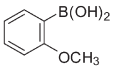
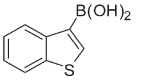
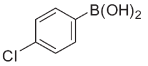
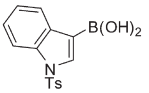
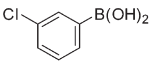
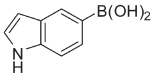
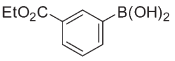
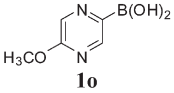
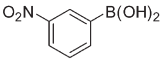
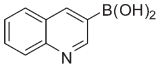
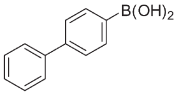
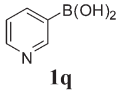
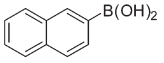
(13) Fu, X.-L.; Wu, L.-L.; Fu, H.-Y.; Chen, H.; Li, R.-X. *Eur. J. Org. Chem*. **2009**, 2051 and references cited therein.

(14) A report recently appeared describing the palladium(II)-catalyzed addition of two arylboronic acids to alkynyl Weinreb amides to provide trisubstituted α,β-unsaturated Weinreb amide products: Bush, A. G.; Jiang, J. L.; Payne, P. R.; Ogilvie, W. W. *Tetrahedron* **2009**, *65*, 8502.

(15) For articles and reviews citing work with potassium organotrifluoroborates, see: (a) Molander, G. A.; Canturk, B.; Kennedy, L. E. *J. Org. Chem*. **2009**, *74*, 973. (b) Darses, S.; Genet, J.-P. *Chem. Rev*. **2008**, *108*, 288. (c) Stefani, H. A.; Cella, R.; Adriano, S. *Tetrahedron* **2007**, *63*, 3623. (d) Molander, G. A.; Ellis, N. *Acc. Chem. Res*. **2007**, *40*, 275.

TABLE 2. Cross-Coupling of Aryl- and Heteroarylboronic Acids 1 with 2



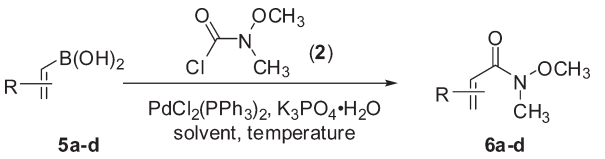
entry	substrate **1**	yield of **3**[a] (conditions)	entry	substrate **1**	yield of **3**[a] (conditions)
1	 **1a**	57% (A, 1 h) 62% (B, 2 h) 53% (B, 4 h)[b] 89% (C, 2 h)	10	 **1j**	82% (C, 2 h)
2	 **1b**	37% (A, 2 h) 37% (B, 5 h) 91% (C, 1.5 h)	11	 **1k**	80% (A, 5 h) 67% (B, 4 h) 54% (B, 4 h)[b] 86% (C, 1 h)
3	 **1c**	<5% (C, 7 h)	12	 **1l**	65% (C, 1 h)
4	 **1c**	43% (A, 2 h) 55% (B, 2.5 h) 87% (C, 1 h)	13	 **1m**	5% (A, 15 h) 10% (B, 5 h) 72% (C, 4 h)
5	 **1e**	29% (A, 5 h) 35% (A, 3 h)[b] 37% (B, 15 h) 89% (C, 1 h)	14	 **1n**	78% (C, 1 h)
6	 **1f**	62% (A, 5 h) 57% (B, 5 h) 87% (C, 1 h)	15	 **1o**	87% (C, 3 h)
7	 **1g**	89% (C, 1 h)	16	 **1p**	52% (C, 1 h)
8	 **1h**	49% (A, 2 h) 22% (B, 6 h) 95% (C, 1.5 h)	17	 **1q**	<5% (C, 5 h)
9	 **1i**	90% (C, 1 h)			

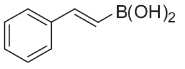
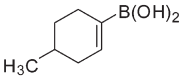
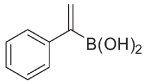
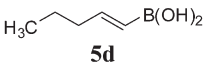
[a]Isolated yields based on (hetero)arylboronic acids **1**. Unless noted otherwise, reactions were run on 1 mmol scale and utilized 5 mol % of $PdCl_2(Ph_3P)_2$, 2.0 equiv of carbamoyl chloride **2**, and 2.0 equiv of $K_3PO_4 \cdot H_2O$ in 5 mL of solvent. Conditions A: toluene, 60 °C. Conditions B: THF, 65 °C. Conditions C: EtOH, 65 °C. The reaction times are shown. [b]This reaction substituted 2.0 equiv of CsF in place of $K_3PO_4 \cdot H_2O$.

in place of potassium phosphate was more reliable. Thus, subjection of electron-rich potassium aryltrifluoroborate **7a** to the optimized reaction conditions with carbamoyl chloride **2** provided the corresponding 4-methoxybenzamide **3a** in good yields that were also very comparable to the method using the corresponding boronic acid **1a** (compare Table 4, entry 1 with Table 2, entry 1). Likewise, the less-activated substrate **7b** provided a good isolated yield of the corresponding Weinreb benzamide **3d** when run in anhydrous ethanol, and again comparable to the method using boronic acid **1d** (compare entry 2 with Table 2, entry 4). Thiophene-derived 2-potassium trifluoroboronate substrate **7c** underwent cross-coupling to provide **3r** in good yield (entry 3), as did the use of thiophene-derived 3-potassium trifluoroboronate substrate **7d** to provide **3k**, comparable to the method using the analogous heteroaryl boronic acid **1j** (compare entry 4 with Table 2, entry 11). Furthermore, two potassium alkenyltrifluoroborates **8a**,**b** underwent cross-coupling with **2** under these conditions to provide useful amounts of the corresponding α,β-unsaturated Weinreb amides **6a** and **6e**. In the former example, this yield is on par with the method using the corresponding alkenylboronic acid **5a** (compare entry 5 with Table 3, entry 1).

In summary, we have demonstrated a mild palladium-catalyzed cross-coupling reaction of (hetero)arylboronic acids **1** and alkenylboronic acids **5** with commercially available *N*-methoxy-*N*-methylcarbamoyl chloride (**2**) to afford Weinreb (hetero)benzamides **3** and α,β-unsaturated

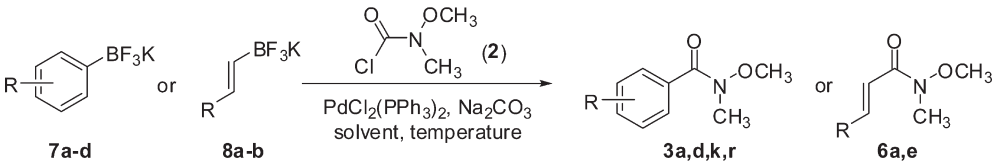
TABLE 3. Coupling of Alkenyl Boronic Acids 5 with Carbamoyl Chloride 2

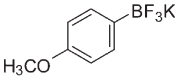
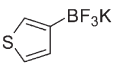
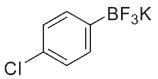
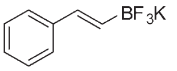
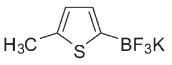
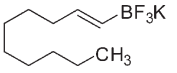


entry	substrate **5**	yield of **6**[a] (conditions)	entry	substrate **5**	yield of **6**[a] (conditions)
1	 **5a**	68% (A, 4 h) 54% (B, 3 h) 76% (C, 1 h)	3	 **5c**	56% (C, 1 h)
2	 **5b**	36% (C, 1.5 h)	4	 **5d**	81% (C, 3 h)[b]

[a]Isolated yields based on vinylboronic acids **5**. See Table 2 footnote for reaction details. [b]Reaction run at 60 °C.

TABLE 4. Coupling of Potassium Organotrifluoroborates 7 and 8 with Carbamoyl Chloride 2



entry	substrate **7** or **8**	yield of **3** or **6**[a] (conditions)	entry	substrate **7** or **8**	yield of **3** or **6**[a] (conditions)
1	 **7a**	58% (A, 5 h) 66% (B, 9 h) 87% (C, 2 h)	4	 **7d**	81% (C, 2 h)
2	 **7b**	89% (C, 2 h)	5	 **8a**	79% (C, 2 h)
3	 **7c**	84% (C, 2 h)	6	 **8b**	72% (C, 2 h)

[a]Isolated yields based on potassium (hetero)aryltrifluoroborates **7** or potassium vinyltrifluoroborates **8**. Unless noted otherwise, reactions were run on 1 mmol scale and utilized 5 mol % of $PdCl_2(Ph_3P)_2$, 2.0 equiv of carbamoyl chloride **2**, and 5.0 equiv of Na_2CO_3 in 5 mL of solvent. Conditions A: toluene, 60 °C. Conditions B: THF, 65 °C. Conditions C: EtOH, 65 °C. The reaction times are shown.

Weinreb amides **6**, respectively, in good to excellent isolated yields. The use of potassium phosphate monohydrate as a base is key to the process as is the use of anhydrous ethanol as a solvent. The method was also extended to the preparation of Weinreb amides **3** and **6** by the analogous cross-coupling reaction of *N*-methoxy-*N*-methylcarbamoyl chloride with potassium (hetero)aryltrifluoroborates **7** and potassium alkenyltrifluoroborates **8** in comparable isolated yields. While in each case presented in this study a commercially available reagent was utilized to define the method, this protocol should be an improvement upon existing methods for the preparation of Weinreb amides in cases where other precursors are not commercially available or difficult to prepare, including nontraditional preparations with metal-catalyzed cross-coupling conditions in which the use of carbon monoxide is to be avoided.

Experimental Section

General Experimental. All nonaqueous reactions were performed under an atmosphere of dry nitrogen unless otherwise specified. Commercial grade reagents and anhydrous solvents were used as received from vendors and no attempts were made to purify or dry these components further. Removal of solvents under reduced pressure was accomplished with a rotary evaporator using a Teflon-lined KNF vacuum pump. Flash column chromatography was performed by using an automated medium-pressure chromatography system using normal-phase disposable prepacked silica gel columns. Melting points are uncorrected. Data for proton NMR spectra were obtained at 300 or 500 MHz and are reported in ppm δ values, using tetramethylsilane as an internal reference. Low-resolution mass spectroscopic analyses were performed on a single quadrupole mass spectrometer utilizing electrospray ionization (ESI). High-resolution mass spectroscopic analyses were performed on a time-of-flight mass spectrometer utilizing electrospray ionization (ESI).

Representative Procedure A: Preparation of *N*,4-Dimethoxy-*N*-methylbenzamide (3a, Table 2) from 4-Methoxyphenylboronic Acid.[4a,16] A suspension of commercially available 4-methoxyphenylboronic acid (**1a**, 200 mg, 1.3 mmol, 1.0 equiv), commercially available *N*-methoxy-*N*-methylcarbamoyl chloride (**2**, 325 mg, 2.6 mmol, 2.0 equiv), dichlorobis(triphenylphosphine)-palladium(II) (46 mg, 5 mol %), and potassium phosphate monohydrate (606 mg, 2.6 mmol, 2.0 equiv) in anhydrous ethanol (5.0 mL) was heated at 65 °C under nitrogen for 2 h. The cooled mixture was filtered through a pad of silica gel, eluting with ethyl acetate, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (gradient of 2:8 to 6:4), to provide *N*,4-dimethoxy-*N*-methylbenzamide (**3a**) as a yellow oil (229 mg, 89%): TLC R_f 0.50 (1:1 hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (dd, J = 6.6, 1.8 Hz, 2H), 6.88 (dd, J = 6.6, 1.8 Hz, 2H), 3.85 (s, 3H), 3.56 (s, 3H), 3.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 161.8, 130.8, 126.3, 113.5, 61.2, 55.6, 34.2; MS (ESI) m/z 196.1 $[M + H]^+$.

a. *N*,3-Dimethoxy-*N*-methylbenzamide (3b, Table 2).[16b] Using representative procedure A with commercially available 3-methoxyphenylboronic acid (**1b**), the product was obtained as a yellow oil (235 mg, 91%): TLC R_f 0.50 (1:1 hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.20 (m 3H), 7.01−6.97 (m, 1H), 3.83 (s, 3H), 3.58 (s, 3H), 3.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 159.5, 135.8, 129.4, 120.7, 116.9, 113.7, 61.4, 55.7, 34.2; MS (ESI) m/z 196.1 $[M + H]^+$.

b. 4-Chloro-*N*-methoxy-*N*-methylbenzamide (3d, Table 2).[4a,b,16c,17a,18] Using representative procedure A with commercially available 4-chlorophenylboronic acid (**1d**), the product was obtained as a yellow oil (222 mg, 87%): TLC R_f 0.45 (1:1 hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, J = 6.3, 1.5 Hz, 2H), 7.37 (dd, J = 6.6, 1.8 Hz, 2H), 3.54 (s, 3H), 3.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 137.1, 132.6, 130.2, 130.1, 128.6, 61.4, 33.9; MS (ESI) m/z 199.8 $[M]^+$.

c. 3-Chloro-*N*-methoxy-*N*-methylbenzamide (3e, Table 2).[19] Using representative procedure A with commercially available 3-chlorophenylboronic acid (**1e**), the product was obtained as a yellow oil (228 mg, 89%): TLC R_f 0.50 (1:1 hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.44 (dd, J = 8.1, 0.9 Hz, 1H), 7.36−7.31 (m, 1H), 3.54 (s, 3H), 3.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 136.1, 134.3, 131.0, 129.7, 128.7, 126.7, 61.5, 33.9; MS (ESI) m/z 199.8 $[M]^+$.

d. Ethyl 3-(methoxy(methyl)carbamoyl)benzoate (3f, Table 2). Using representative procedure A with commercially available 3-(ethoxycarbonyl)phenylboronic acid (**1f**), the product was obtained as a colorless oil (213 mg, 87%): TLC R_f 0.40 (1:1 hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.15 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.50 (t, J = 7.8, 7.5 Hz, 1H), 4.41 (q, J = 7.2 Hz, 2H), 3.56 (s, 3H), 3.38 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 166.2, 134.7, 132.7, 131.8, 130.8, 129.6, 128.5, 61.5, 61.4, 33.8, 14.6; HRMS (ESI) m/z 238.1076 $[M + H]^+$ (238.1079 calcd for $C_{12}H_{15}NO_4$ + H).

e. *N*-Methoxy-*N*-methyl-3-nitrobenzamide (3g, Table 2).[4a,18] Using representative procedure A with commercially available 3-nitrophenylboronic acid (**1g**), the product was obtained as a yellow solid (223 mg, 89%): mp 39−41 °C; TLC R_f 0.45 (1:1 hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.33−8.30 (m, 1H), 8.05 (d, J = 7.8 Hz, 1H), 7.61 (dd, J = 8.1, 7.8 Hz, 1H), 3.56 (s, 3H), 3.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 148.1, 135.8, 134.7, 129.5, 125.6, 123.9, 61.7, 33.6; MS (ESI) m/z 211.0 $[M + H]^+$.

f. *N*-Methoxy-*N*-methylbiphenyl-4-carboxamide (3h, Table 2).[4b] Using representative procedure A with commercially available biphenyl-4-ylboronic acid (**1h**), the product was obtained as a off-white solid (230 mg, 95%): mp 78−80 °C; TLC R_f 0.60 (1:1 hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4 Hz, 2H), 7.65−7.61 (m, 4H), 7.48−7.35 (m, 3H), 3.59 (s, 3H), 3.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 143.7, 140.6, 133.1, 129.2, 129.1, 128.2, 127.5, 127.0, 61.4, 34.1; MS (ESI) m/z 242.1 $[M + H]^+$.

g. *N*-Methoxy-*N*-methyl-2-naphthamide (3i, Table 2).[20] Using representative procedure A with commercially available naphthalen-2-ylboronic acid (**1i**), the product was obtained as a yellow oil (225 mg, 90%): TLC R_f 0.55 (1:1 hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.92−7.85 (m, 3H), 7.76 (dd, J = 8.7, 1.5 Hz, 1H), 7.58−7.49 (m, 2H), 3.56 (s, 3H), 3.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 134.6, 132.8, 131.8, 129.2, 129.0, 128.0, 127.9, 127.7, 126.8, 125.4, 61.4, 34.2; MS (ESI) m/z 216.1 $[M + H]^+$.

h. *N*-Methoxy-*N*-methylbenzofuran-2-carboxamide (3j, Table 2). Using representative procedure A with commercially available benzofuran-2-ylboronic acid (**1j**), the product was obtained as a colorless oil (207 mg, 82%): TLC R_f 0.55 (1:1 hexanes/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.50 (s, 1H), 7.42 (dt, J = 7.5, 1.0 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 3.83 (s, 3H), 3.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 155.2, 146.9, 127.7, 127.4, 123.8, 123.0, 113.5, 112.5, 61.9, 33.7; HRMS (ESI) m/z 206.0818 $[M + H]^+$ (206.0817 calcd for $C_{11}H_{11}NO_3$ + H).

i. *N*-Methoxy-*N*-methylthiophene-3-carboxamide (3k, Table 2).[4a,b] Using representative procedure A with commercially available thiophene-3-boronic acid (**1k**), the product was obtained as a yellow oil (230 mg, 86%): TLC R_f 0.50 (1:1 hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, J = 3.0, 0.9 Hz, 1H), 7.58 (dd, J = 5.1, 1.8 Hz, 1H), 7.30 (dd, J = 5.1, 3.0 Hz 1H), 3.66 (s, 3H), 3.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 134.8, 131.2, 129.4, 125.1, 61.5, 33.6; MS (ESI) m/z 171.9 $[M + H]^+$.

j. *N*-Methoxy-*N*-methylbenzo[*b*]thiophene-3-carboxamide (3l, Table 2). Using representative procedure A with commercially available benzo[*b*]thiophen-3-ylboronic acid (**1l**), the product was obtained as a yellow oil (144 mg, 65%): TLC R_f 0.55 (1:1 hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, J = 8.1 Hz, 1H), 8.05 (s, 1H), 7.88 (d, J = 7.5 Hz, 1H), 7.44−7.37 (m, 2H), 3.60 (s, 3H), 3.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 139.6, 138.2, 131.0, 129.0, 125.3, 125.2,

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124.7, 122.6, 61.7, 33.9; HRMS (ESI) m/z 222.0595 $[M + H]^+$ (222.0589 calcd for $C_{11}H_{11}NO_2S + H$).

k. *N*-Methoxy-*N*-methyl-1-tosyl-1*H*-indole-3-carboxamide (3m, Table 2). Using representative procedure A with commercially available 1-tosyl-1*H*-indol-3-ylboronic acid (**1m**), the product was obtained as a yellow oil (58 mg, 72%): TLC R_f 0.50 (1:1 hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.27 (dd, J = 7.2, 1.8 Hz, 1H), 7.98 (dd, J = 7.2, 1.5 Hz, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.36−7.31 (m, 2H), 7.26 (d, J = 9.3 Hz, 2H), 3.71 (s, 3H), 3.40 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 145.9, 135.1, 134.4, 130.4, 130.3, 130.0, 127.3, 125.5, 124.5, 123.2, 113.9, 113.3, 61.4, 33.3, 21.9; HRMS (ESI) m/z 359.1064 $[M + H]^+$ (359.1066 calcd for $C_{18}H_{18}N_2O_4S + H$).

l. *N*-Methoxy-*N*-methyl-1*H*-indole-5-carboxamide (3n, Table 2). Using representative procedure A with commercially available 1*H*-indol-5-ylboronic acid (**1n**), the product was obtained as an off-white solid (199 mg, 78%): mp 136−138 °C; TLC R_f 0.45 (1:1 hexanes/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.06 (d, J = 1.5 Hz, 1H), 7.55 (dd, J = 8.5, 1.5 Hz, 1H), 7.35 (d, J = 8.5 Hz, 1H), 7.22 (t, J = 3.0 Hz, 1H), 6.59−6.58 (m, 1H), 3.59 (s, 3H), 3.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 137.4, 127.4, 125.7, 125.6, 122.7, 122.2, 110.9, 103.6, 61.2, 35.0; HRMS (ESI) m/z 205.0982 $[M + H]^+$ (205.0977 calcd for $C_{11}H_{12}N_2O_2 + H$).

m. *N*,5-Dimethoxy-*N*-methylpyrazine-2-carboxamide (3o, Table 2). Using representative procedure A with commercially available 5-methoxypyrazin-2-ylboronic acid (**1o**), the product was obtained as a colorless oil (107 mg, 84%): TLC R_f 0.30 (1:1 hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.97 (s, 2H), 4.08 (s, 3H), 3.61 (s, 3H), 3.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 165.1, 160.6, 121.6, 61.6, 55.7, 33.3; HRMS (ESI) m/z 198.0876 $[M + H]^+$ (198.0879 calcd for $C_8H_{11}N_3O_3 + H$).

n. *N*-Methoxy-*N*-methylquinoline-3-carboxamide (3p, Table 2). Using representative procedure A with commercially available quinolin-3-ylboronic acid (**1p**), the product was obtained as a yellow oil (131 mg, 52%): TLC R_f 0.40 (1:1 hexanes/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.56 (s, 1H), 8.14 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.78 (t, J = 8.0, 7.0 Hz, 1H), 7.59 (t, J = 7.5 Hz, 1H), 3.56 (s, 3H), 3.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 149.7, 148.9, 137.3, 131.3, 129.6, 128.9, 127.5, 127.2, 127.2, 61.6, 33.5; HRMS (ESI) m/z 217.0983 $[M + H]^+$ (217.0977 calcd for $C_{12}H_{12}N_2O_2 + H$).

o. (*E*)-*N*-Methoxy-*N*-methylcinnamamide (6a, Table 3).[17a,21] Using representative procedure A with commercially available (*E*)-styrylboronic acid (**5a**), the product was obtained as a yellow oil (197 mg, 76%): TLC R_f 0.55 (1:1 hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 15.6 Hz, 1H), 7.59−7.56 (m, 2H), 7.40−7.37 (m, 3H), 7.06 (d, J = 15.6 Hz, 1H), 3.77 (s, 3H), 3.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 143.7, 135.5, 130.1, 129.1, 128.3, 116.1, 62.2, 32.8; MS (ESI) m/z 192.1 $[M + H]^+$.

p. *N*-Methoxy-*N*-methyl-2-phenylacrylamide (6b, Table 3). Using representative procedure A with commercially available 1-phenylvinylboronic acid (**5b**), the product was obtained as a yellow oil (93 mg, 36%): TLC R_f 0.50 (1:1 hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.31 (m, 5H), 5.70 (s, 1H), 5.50 (s, 1H), 3.45 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 136.5, 128.9, 128.7, 126.2, 115.8, 61.3; HRMS (ESI) m/z 192.1021 $[M + H]^+$ (192.1025 calcd for $C_{11}H_{13}NO_2 + H$).

q. (±)-*N*-Methoxy-*N*,4-dimethylcyclohex-1-enecarboxamide (6c, Table 3). Using representative procedure A with commercially available (±)-4-methylcyclohex-1-enylboronic acid (**5c**), the product was obtained as a colorless oil (76 mg, 58%): TLC R_f 0.55 (1:1 hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14−6.13 (m, 1H), 3.65 (s, 3H), 3.23 (s, 3H), 2.32−2.17 (m, 3H), 1.79−1.59 (m, 3H), 1.33−1.20 (m, 1H), 0.99 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 133.8, 130.9, 61.3, 34.1, 33.9, 30.7, 28.0, 25.9, 21.9; HRMS (ESI) m/z 184.1341 $[M + H]^+$ (184.1338 calcd for $C_{10}H_{17}NO_2 + H$).

r. (*E*)-*N*-Methoxy-*N*-methylhex-2-enamide (6d, Table 3).[22] Using representative procedure A with commercially available (*E*)-pent-1-enylboronic acid (**5d**), the product was obtained as a colorless oil (223 mg, 81%): TLC R_f 0.55 (1:1 hexanes/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99−6.93 (m, 1H), 6.40 (d, J = 15.5 Hz, 1H), 3.69 (s, 3H), 3.22 (s, 3H), 2.23−2.18 (m, 2H), 1.51−1.47 (m, 2H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 148.0, 119.1, 61.9, 34.8, 32.7, 21.9, 14.0; MS (ESI) m/z 158.1 $[M + H]^+$.

Representative Procedure B: Preparation of *N*,4-Dimethoxy-*N*-methylbenzamide (3a, Table 4) from Potassium 4-Methoxyphenyltrifluoroborate (7a). A suspension of commercially available potassium 4-methoxyphenyltrifluoroborate (**7a**, 100 mg, 0.47 mmol, 1.0 equiv), commercially available *N*-methoxy-*N*-methylcarbamoyl chloride (**2**, 325 mg, 0.94 mmol, 2.0 equiv), dichlorobis(triphenylphosphine)palladium(II) (17 mg, 5 mol %), and sodium carbonate (249 mg, 2.35 mmol, 5.0 equiv) in anhydrous ethanol (5.0 mL) was heated at 65 °C under nitrogen for 2 h. The cooled mixture was filtered through a pad of silica gel, eluting with ethyl acetate, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (gradient of 2:8 to 6:4), to provide *N*,4-dimethoxy-*N*-methylbenzamide (**3a**) as a yellow oil (79 mg, 87%): see data listed above.

a. 4-Chloro-*N*-methoxy-*N*-methylbenzamide (3d, Table 4). Using representative procedure B with commercially available potassium (4-chlorophenyl)trifluoroborate (**7b**), the product was obtained as a yellow oil (163 mg, 89%): see data listed above.

b. *N*-Methoxy-*N*,5-dimethylthiophene-2-carboxamide (3r, Table 4).[23] Using representative procedure B with commercially available potassium 5-methyl-2-thiophenetrifluoroborate (**7c**), the product was obtained as a yellow oil (152 mg, 84%): TLC R_f 0.65 (1:1 hexanes/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 4.0 Hz, 1H), 6.77 (d, J = 3.5 Hz, 1H), 3.76 (s, 3H), 3.34 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 147.7, 135.1, 130.9, 125.7, 61.8, 33.3, 15.6; MS (ESI) m/z 186.1 $[M + H]^+$.

c. *N*-Methoxy-*N*-methylthiophene-3-carboxamide (3k, Table 4). Using representative procedure B with commercially available potassium 3-thiophenetrifluoroborate (**7d**), the product was obtained as a yellow oil (145 mg, 81%): see data listed above.

d. (*E*)-*N*-Methoxy-*N*-methylcinnamamide (6a, Table 4). Using representative procedure B with commercially available potassium (*E*)-styryltrifluoroborate (**8a**), the product was obtained as a yellow oil (145 mg, 79%): see data listed above.

e. (*E*)-*N*-Methoxy-*N*-methylundec-2-enamide (6e, Table 4). Using representative procedure B with commercially available potassium (*E*)-1-decenyltrifluoroborate (**7e**), the product was obtained as a colorless oil (166 mg, 72%): TLC R_f 0.60 (1:1 hexanes/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99−6.94 (m, 1H), 6.40 (d, J = 15.5 Hz, 1H), 3.69 (s, 3H), 3.23 (s, 3H), 2.25−2.20 (m 2H), 1.47−1.44 (m, 2H), 1.33−1.26 (m, 10H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 148.4, 118.9, 61.9, 32.8, 32.7, 32.1, 29.7, 29.5 (2), 28.6,

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22.9, 14.4; HRMS (ESI) m/z 228.1969 $[M + H]^+$ (228.1963 calcd for $C_{13}H_{25}NO_2 + H$).

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Supporting Information Available: Proton and carbon NMR spectra for all compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.