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Copper-Catalyzed Oxidative Heck Reactions between Alkyltrifluoroborates and Vinyl Arenes

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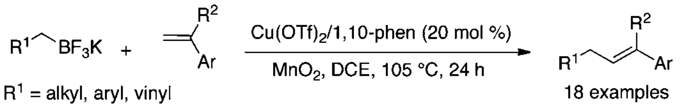
ABSTRACT



We report herein that potassium alkyltrifluoroborates can be utilized in oxidative Heck-type reactions with vinyl arenes. The reaction is catalyzed by a Cu(OTf)$_2$/1,10-phenanthroline with MnO$_2$ as the stoichiometric oxidant. In addition to the alkyl Heck, amination, esterification, and dimerization reactions of alkyltrifluoroborates are demonstrated under analogous reaction conditions. Evidence for an alkyl radical intermediate is presented.

Carbon−carbon bond formation via alkene C−H functionalization is a direct and atom-economical method for the synthesis of more highly substituted alkenes and analogues thereof.[1] The Mizoroki−Heck reaction[2] enables the cross-coupling of aryl and vinyl halides with alkenes. Although Heck reactions with alkyl halides present a challenge due to their potential to undergo β-hydride elimination under palladium catalysis, a number of methods that enable the use of alkyl halides in Heck-type reactions have recently appeared.[3]

The oxidative Heck reaction between organometallic compounds and alkenes is a halide-free alternative to the Mizoroki−Heck reaction.[2i] In recent years, aryl and vinylboronates have emerged as generally useful reagents for the oxidative Heck reaction of alkenes[2j−m] and related arene C−H functionalizations.[4] To date, however, no oxidative alkyl-Heck-type reactions using alkylborates have been reported, likely due to the complicating β-hydride

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(1) Recent examples: (a) Ilies, L.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 7672. (b) Schomaker, J. M.; Boyd, W. C.; Stewart, I. C.; Toste, F. D.; Bergman, R. G. *J. Am. Chem. Soc.* **2008**, *130*, 3777. (c) Tsai, A. S.; Brasse, M.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 540. (d) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350. (e) Shi, B.-F.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 460. (f) Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2004**, *6*, 4623. (g) Xu, Y.-H.; Lu, J.; Loh, T.-P. *J. Am. Chem. Soc.* **2009**, *131*, 1372. (h) Yu, H.; Jin, W.; Sun, C.; Chen, J.; Du, W.; He, S.; Yu, Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 5792. (i) Lee, D. H.; Kwon, K. H.; Yi, C. S. *Science* **2011**, *333*, 1613.

(2) Selected reviews: (a) *The Mizoroki−Heck Reaction*; Oestreich, M., Ed.; John Wiley & Sons: West Sussex, UK, 2009. (b) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146. (c) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (d) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. Cu-catalyzed Heck-type reactions: (e) Iyer, S.; Ramesh, C.; Sarkar, A.; Wadgaonkar, P. P. *Tetrahedron Lett.* **1997**, *38*, 8113. (f) Li, J.-H.; Wang, D.-P.; Xie, Y.-X. *Tetrahedron Lett.* **2005**, *46*, 4941. (g) Peng, Y.; Chen, J.; Liu, M.; Gao, W.; Wu, H. *Synthesis* **2011**, 213. (h) Phipps, R. J.; McMurray, L.; Ritter, S.; Duong, H. A.; Gaunt, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 10773. (i) Review of oxidative Heck reactions: Karimi, B.; Behzadnia, H.; Elhamifar, D.; Akhavan, P. F.; Esfahani, F. K.; Zamani, A. *Synthesis* **2010**, 1399. Oxidative Heck reaction using potassium aryltrifluoroborates: (j) Martinez, R. M.; Voica, F.; Genet, J.-P.; Darses, S. *Org. Lett.* **2007**, *9*, 3213. (k) Savmarker, J.; Lindh, J.; Nilsson, P.; Sjoberg, P. J. R.; Larhed, M. *ChemistryOpen* **2012**, *1*, 140. (l) Heck reaction with arylboronic acids and styrenes: Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martin-Matute, B. *J. Am. Chem. Soc.* **2001**, *123*, 5358. (m) Amengual, R.; Michelet, V.; Genet, J.-P. *Tetrahedron Lett.* **2002**, *43*, 5905.

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10.1021/ol401220b

elimination process. Herein we report successful oxidative Heck reactions of alkyltrifluoroborates with vinyl arenes.

Since the pioneering work of Vedejs and co-workers on the facile synthesis of organotrifluoroborates,[5] these reagents have seen an explosion in their use in cross-coupling reactions. They are more stable, easily handled, inert, and robust in comparison to the corresponding boronic acids. The majority of applications of organotrifluoroborates are as boronic acid surrogates in Suzuki–Miyara cross-coupling reactions.[6] Recently, additional synthetic transformations that demonstrated the versatility of these reagents have emerged. For example, Fensterbank and co-workers reported that stoichiometric amounts of various copper(II) salts can react with potassium alkyltrifluoroborates, enabling them to participate in coupling reactions with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl radical (TEMPO), presumably via generation of alkyl radical intermediates (vide infra, Scheme 1).[7] Molander and co-workers subsequently disclosed a $Mn(OAc)_3$-promoted C–H alkylation of heteroarenes using alkyltrifluoroborates.[8] More recently, Sanford and co-workers presented a Pd-catalyzed C–H alkylation of arenes utilizing potassium alkyltrifluoroborates.[9]

Taking these examples into account and based on our experience in copper catalysis,[10] we sought to demonstrate for the first time the use of these reagents in alkyl-Heck-type cross-coupling reactions (vide infra). We hypothesized that generation of an alkyl radical in the presence of an excellent radical acceptor (e.g., vinyl arenes) under oxidizing conditions should provide a formal alkyl-Heck-type product.[10]

We first explored the oxidative coupling of potassium benzyltrifluoroborate **1a** and 1,1-diphenylethylene (DPE) (Table 1). We found that when 20 mol % of Cu(2-ethylhexanoate)$_2$ was used with MnO_2 (3 equiv) as the terminal oxidant, trisubstituted alkene **2a** was formed in 57% yield (entry 1). After a short screen of copper salts and ligands, Cu(OTf)$_2$/1,10-phenanthroline (20 mol %) was identified as the best catalyst, giving 85% isolated yield of **2a** (entry 4). After screening other possible oxidants (entries 7–12), it was determined that MnO_2 (3 equiv) was most effective. It was interesting to note, however, that when $Mn(OAc)_3$ (2.5 equiv) was used as the sole promoter, **2a** was isolated in 53% yield.

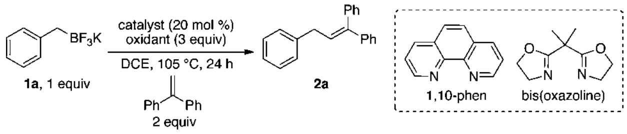
The coupling of borate **1a** was carried out with various vinyl arenes (Table 2). DPE[11] and other 1,1-disubstituted alkenes were highly reactive and gave yields from 62 to 85% (Table 2, entries 1, 3, and 8–10). Styrene, *p*-methylstyrene and *p*-methoxystyrene underwent the coupling reaction in moderate yields and with good *E*-selectivity (Table 2, entries 2, 4, and 5). *p*-Methoxystyrene gave an addition product involving styrene dimerization (see Supporting Information). *p*-Nitrostyrene was unreactive (not shown).

Ketone **2f** was obtained in moderate yield from the reaction of **1a** with α-pivaloxystyrene (Table 2, entry 5). The product most likely arises from the in situ elimination of the pivaloyl fragment.[12] Phenylbutadiene was also a competent coupling partner but gave a 1.7:1 mixture of (*E*,*E*) and (*Z*,*E*) isomers (Table 2, entry 6).

Exocyclic 1,1-disubstituted vinyl arenes (Table 2, entries 7–9) favored the allylic alkylation products **2h**, **2i**, and **2j**, where the alkene had migrated to an endocyclic position. Alkenes with only alkyl substituents were unreactive.

The scope of the alkylborate was next explored (Table 3). Potassium phenethyltrifluoroborate gave alkene **3a** in 81% yield (entry 1). Phenethyl boronic acid also provided alkene **3a** (67% yield, Table 3, entry 2). The skipped diene **3b** can be formed by reaction of allyltrifluoroborate with DPE (Table 3, entry 3). Cyclopentyltrifluoroborate was also reactive (Table 3, entry 4). Incorporating polar functional groups on the organoborate was tolerated; *tert*-butoxy ester and

Table 1. Optimization of Reaction Conditions



entry	catalyst	oxidant	yield (%)[a]
1[b]	Cu(eh)$_2$	MnO_2	57
2[c]	Cu(eh)$_2$		60
3	Cu(OTf)$_2$/bis(oxazoline)	MnO_2	78
4	Cu(OTf)$_2$/1,10-phen	MnO_2	85
5[d]	Cu(OTf)$_2$/1,10-phen	MnO_2	72
6[e]	Cu(OTf)$_2$/1,10-phen	MnO_2	40
7[f]	Cu(OTf)$_2$/1,10-phen	MnO_2/O_2	54
8	Cu(OTf)$_2$/1,10-phen	$NaNO_2$	32
9[g]	Cu(OTf)$_2$/1,10-phen	$NaNO_2/O_2$	37
10	Cu(OTf)$_2$/1,10-phen	oxone	26
11[h]	$Mn(OAc)_3$		53
12	Cu(OTf)$_2$/1,10-phen	(*t*-BuO)$_2$	30[i]

[a] Isolated yield. [b] Cu(eh)$_2$ = Cu(2-ethylhexanoate)$_2$. [c] 1.2 equiv of Cu(eh)$_2$. [d] 15 mol % of catalyst. [e] Reaction run at 80 °C. [f] 20 mol % of MnO_2 and O_2 (1 atm, balloon). [g] 20 mol % of $NaNO_2$ and O_2 (1 atm, balloon). [h] 2.5 equiv of $Mn(OAc)_3$. [i] Percent conversion based on remaining alkene. Multiple other products were observed. DCE = 1,2-dichloroethane.

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(6) Selected reviews: (a) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288and references therein. (b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275. (c) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623.

(7) (a) Sorin, G.; Martinez Mallorquin, R.; Contie, Y.; Baralle, A.; Malacria, M.; Goddard, J.-P.; Fensterbank, L. *Angew. Chem., Int. Ed.* **2010**, *49*, 8721. (b) Review of the role of organic radicals in reactions of trialkylboranes: Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415.

(8) (a) Molander, G. A.; Colombel, V.; Braz, V. A. *Org. Lett.* **2011**, *13*, 1852. (b) Presset, M.; Fleury-Bregeot, N.; Oehlrich, D.; Rombouts, F.; Molander, G. A. *J. Org. Chem.* **2013**, *78*, 4615.

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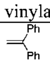
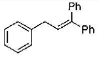
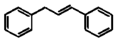
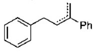
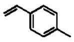
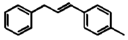
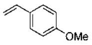
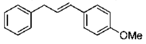
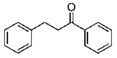
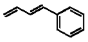
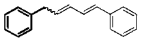
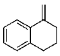
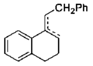
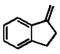
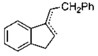
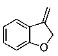
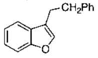
(10) Liwosz, T. W.; Chemler, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 2020.

(11) (a) Choi, J.; Tang, L.; Norton, J. R. *J. Am. Chem. Soc.* **2007**, *129*, 234. (b) Fischer, H.; Radom, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 1340.

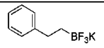
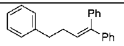
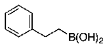
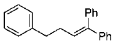
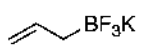
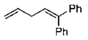
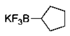
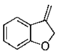
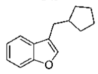
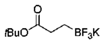
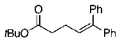
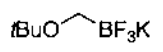
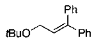
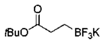
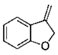
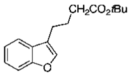
(12) Song, C.-X.; Cai, G.-X.; Farrell, T. R.; Jiang, Z.-P.; Li, H.; Gan, L.-B.; Shi, Z.-J. *Chem. Commun.* **2009**, 6002.

Table 2. Scope of the Cu-Catalyzed Coupling of Potassium Benzyltrifluoroborate with Vinylarenes[a]

entry	vinylarene	product	yield (%)[b]
1	 (DPE)	 **2a**	85
2		 **2b** (*E*:*Z* = 20:1)	43
3		 **2c** (1:1 terminal:internal)	62
4		 **2d** (*E*:*Z* = 20:1)	50
5		 **2e** (*E*:*Z* >20:1)	45
6		 **2f**	40
7		 **2g** [(*E*,*E*):(*Z*,*E*) = 1.7:1]	60
8		 **2h** (6:1 endo:exo)	76
9		 **2i** (2.5:1 endo:exo)[c]	82
10[d]		 **2j**	80

[a] The same conditions as Table 1, entry 4, were used in these reactions. [b] Isolated yield. [c] The exo isomer is a 1:1 *E*/*Z* mixture. [d] 1 equiv of alkene used.

Table 3. Scope of the Alkyltrifluoroborates[a]

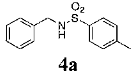
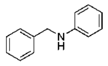
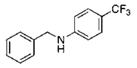
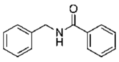
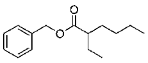
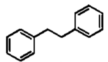
entry	organoboron	alkene	product	yield (%)[b]
1		 (DPE)	 **3a**	81
2		DPE	 **3a**	67
3		DPE	 **3b**	40[c]
4			 **3c**	60
5[d]		DPE	 **3d**	51
6[d]		DPE	 **3e**	46
7[d]			 **3f**	73

[a] The same conditions as Table1, entry 4, were used in these reactions unless otherwise noted. [b] Isolated yield. [c] Estimated yield; see Supporting Information. [d] Reactions were run in toluene at 120 °C.

tert-butoxy-substituted organoborates gave the alkenes **3d** and **3e** in 51 and 46%, respectively (Table 3, entries 5 and 6). When the *tert*-butoxy ester borate was used with 3-methylene-2,3-dihydrobenzofuran, the 3-substituted benzofuran **3f** was isolated in 73% yield (Table 3, entry 7). Reactions with these organoborates required a higher temperature for optimal conversion. Attempts to extend the scope of the reaction to aryl or vinyltrifluoroborates failed (not shown).[2i]

Further examination of the reactions of potassium benzyltrifluoroborate (**1a**) in other coupling reactions was briefly examined (Table 4). The reaction of **1a** and *p*-toluenesulfonamide gave the Chan-Lam coupling product,[13] sulfonamide **4a**, in an 83% yield (Table 4, entry 1). While several copper-catalyzed etherification and amination reactions of aryl and alkenyltrifluoroborates have been reported,[6a] copper-catalyzed reactions of alkylboron reagents and amines are rare.[13,14] Aniline and *p*-trifluoromethylaniline gave amines **4b** and **4c** in 30 and 70% yield, respectively (Table 4, entries 2 and 3). The more electron-rich aniline may provide a lower yield due to some catalyst inactivation.

Table 4. Additional Oxidative Couplings with Potassium Benzyltrifluoroborate[a]

entry	coupling partner	product	yield (%)[b]
1	$TsNH_2$	 **4a**	83
2	$PhNH_2$	 **4b**	30
3	*p*-$CF_3C_6H_4NH_2$	 **4c**	70
4	PhC(O)NH_2	 **4d**	66
5[c]	None	 **4e**	73
6	None	 **4f**	90

[a] The same conditions as Table 1, entry 4, were used in these reactions except 1.2 equiv of the coupling partner was used. [b] Isolated yield. [c] 1.2 equiv of $Cu(eh)_2$ used instead of $Cu(OTf)_2$/1,10-phen and MnO_2.

Benzamide was also a successful coupling partner, furnishing amide **4d** in 66% yield (Table 4, entry 4). In the absence of an external coupling partner and under stoichiometric amounts of $Cu(eh)_2$, ester **4e** was isolated in 73% yield (Table 4, entry 5). In the absence of an additional coupling partner, trifluoroborate **1a** smoothly dimerized under the copper-catalyzed reaction conditions to give dibenzyl **4f** in 90% yield (Table 4, entry 6).

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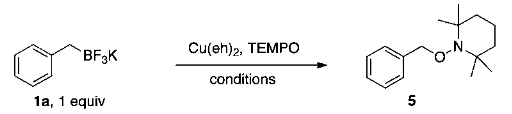
The TEMPO trapping reaction reported by Fensterbank and co-workers[7] utilized a stoichiometric amount of copper(2-ethylhexanoate)$_2$ [Cu(eh)$_2$] to convert **1a** to **5** (Scheme 1). We have reported amino-oxygenation reactions that involve carbon radical intermediates, where catalytic amounts of copper are employed in TEMPO couplings by using O_2 as the terminal oxidant.[15] Thus, we found that employing 20 mol % of Cu(eh)$_2$ under an oxygen atmosphere (1 atm, balloon), we were able to isolate TEMPO adduct **5** in 75% yield, thereby rendering Fensterbank's reaction catalytic in Cu(eh)$_2$.

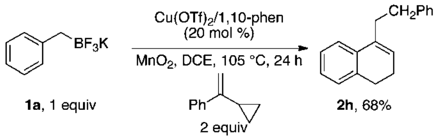
Scheme 1. Stoichiometric[7] and Catalytic TEMPO Capture Reactions



Fensterbank's conditions: Cu(eh)$_2$ (1.2 equiv), TEMPO, DMSO, 120 °C, 20 h (73% yield).

Our conditions: Cu(eh)$_2$ (20 mol %), TEMPO, O_2 (1 atm), DCE, 105 °C, 24 h (77% yield).

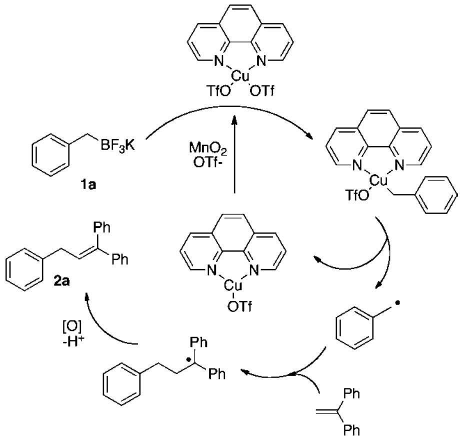
The intermediacy of an alkyl radical is strongly implicated in our reactions as well as those previously reported by Fensterbank and Molander.[7,8] To test this hypothesis further, the reaction of **1a** with 1-phenylvinylcyclopropane, which is known to participate in radical rearrangements,[16] was conducted (eq 1). This reaction gave a ring expansion product **2h** in a 68% yield, supporting the addition of a carbon radical to the alkene.



(1)

The mechanism of carbon radical generation is less clear. For their TEMPO capture reaction, Fensterbank and coworkers proposed an outer-sphere oxidation of the potassium alkyltrifluoroborate salt by copper(II), followed by homolytic cleavage of the C−B bond.[7] Molander also proposed homolytic cleavage of the C−B bond, facilitated by Mn(III), in his alkylation of heteroarenes with potassium alkyltrifluoroborates.[7,8] Conversely, Kuninobu and Sueki recently reported a copper-catalyzed Chan-Lam coupling of alkylboronate esters and amines that they proposed involves transmetalation of organoboron with copper(II).[14b] Taking these reactions and proposed mechanisms into account as well as our own results in the Heck-type and amination reactions above, we propose that our reaction feasibly occurs by (1) transmetalation of the organotrifluoroborate with copper(II); (2) homolysis of the C(sp^3)−Cu(II) bond as previously observed in our related reactions;[17] and (3) addition of the alkyl radical to the alkene followed by oxidation of the resulting benzylic radical to the alkene product by MnO_2 or Cu(II) (Scheme 2).

Scheme 2. Proposed Mechanism



The catalytic Chan-Lam-type couplings shown in Table 4, entries 1−4, most likely proceed via Cu(III) species, formed by addition of the carbon radical to Cu(II) with subsequent or prior Cu−NR$_2$ bond formation; the C−N bond is then formed via reductive elimination.[18] The ester product (Table 4, entry 5) is formed through a similar pathway, but in this case, one of the ethylhexanoate ligands of the Cu(III) intermediate is transferred to the product.[18b] Finally, the dimerization product (Table 4, entry 6) can be formed by direct combination of two benzyl radicals.

In summary, we have identified neutral reaction conditions for oxidative couplings of alkyltrifluoroborates with vinyl arenes and various other coupling partners. The Heck-type coupling can serve as a *B*-alkyl Suzuki reaction[19] surrogate, where the need for a β-halo styrene coupling partner can be replaced with the parent vinyl arene in some instances, and its success with a secondary alkyltrifluoroborate (Table 3, entry 4) is noteworthy in this respect.[6b] We anticipate that this new method shall prove useful to organic synthesis.

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Supporting Information Available. Experimental procedures and characterization data of new compounds. 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.