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Potassium Alkenyl- and Aryltrifluoroborates: Stable and Efficient Agents for Rhodium-Catalyzed Addition to Aldehydes and Enones

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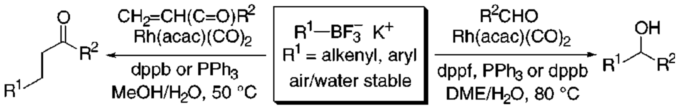
ABSTRACT



Potassium alkenyl- and aryltrifluoroborates undergo addition to enones and aldehydes in the presence of Rh(I) catalysts to give *β*-functionalized ketones and allylic/benzylic alcohols, respectively. Reaction proceeds more rapidly than with the corresponding boronic acids, and the choice of phosphine ligand does not signifcantly influence the overall efficiency of addition.

The use of organometallics as nucleophilic reagents is arguably the most important method for the formation of C−C bonds.[1] Two of the most widely used reactions are additions to carbonyl groups and conjugate additions to α,β-unsaturated carbonyls by organolithium/Grignard and organocopper/zinc reagents, respectively. A variety of other organometallic reagents have also been employed for these transformations. Recently, Miyaura and co-workers extended the scope of reagents to include organoboron compounds, demonstrating the rhodium(I)-catalyzed addition of aryl- and alkenylboronic acids to aldehydes[2] and enones.[3] A catalytic asymmetric 1,4-addition to enones has also been reported by the same authors.[3b] A major advantage over existing methods is the relative stability of boronic acids to air and moisture. As part of an ongoing program in organoboron research,[4] we have also been developing nucleophilic addition reactions of organoboron compounds, including the use of stable potassium allyl- and crotyltrifluoroborate salts as efficient reagents for allylation and crotylation of aldehydes and pyruvates,[4a] and the addition of alkenyl- and arylboronates to *N*-acyliminium ions.[4b] We now report the Rh(I)-catalyzed addition of air- and moisture-stable potassium alkenyl- and aryltrifluoroborates **1** to enones and aldehydes.

One strategy to improve the conditions under which Rh(I)-catalyzed nucleophilic additions of C−B reagents can occur, is to utilize more reactive boron reagents. Such reagents would also be useful for optimization studies, new catalyst development, asymmetric variants, and applications to combinatorial library synthesis. Organotrifluoroborate salts (RBF_3M, M = alkali metal) have only recently been applied in organic synthesis.[4a,5] Advantages of these reagents compared to the corresponding boronic acids, are their greater stability to air/water,[4a,5f,h] their ease of isolation, and the avoidance of trimer formation that can occur with boronic acids. With these potential advantages in mind, we decided

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(1) For reviews, see: (a) Devant, R. M.; Radunz, H.-E. In *Houben-Weyl, Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag Stuttgart: Stuttgart, Germany, 1995; Vol. E21, pp 1151−1334. (b) Yamamoto, Y. In *Houben-Weyl, Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Schaumann, E., Eds.; Georg Thieme Verlag Stuttgart: Stuttgart, Germany, 1995; Vol. E21, pp 2041−2067.

(2) Sakai, M.; Euda, M.; Miyaura, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 3279−3281.

(3) (a) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229−4331. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 3379−3380. (c) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8479−8482.

(4) (a) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Tetrahedron Lett.* **1999**, *40*, 4289−4292. (b) Batey, R. A.; MacKay, D. B.; Santhakumar, V. *J. Am. Chem. Soc.* **1999**, *121*, 5075−5076. (c) Batey, R. A.; Thadani, A. N.; Lough, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 450−451. (d) Batey, R. A.; Smil, D. V. *Angew. Chem., Int. Ed.* **1999**, *38*, 1798−1800. (e) Batey, R. A.; Thadani, A. N.; Lough, A. J. *Chem. Commun.* **1999**, 475−476.

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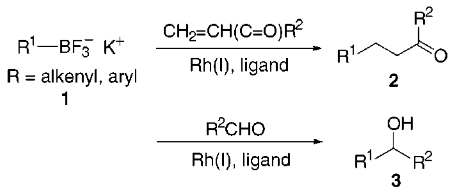
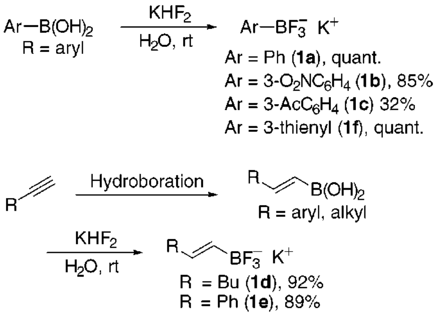
to explore the utility of organotrifluoroborates as nucleophiles in the aforementioned Rh(I)-catalyzed reactions to extend the scope of this useful transformation (Scheme 1).

Scheme 1



The formation of the potassium alkenyl- and aryltrifluoroborates **1** was achieved via the corresponding boronic acids as first described by Vedejs and co-workers.[5a] The requisite boronic acids were either commercially available or readily prepared by standard hydroboration methodology (Scheme 2).

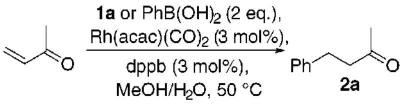
Scheme 2



To focus upon the effect of the boron-based reagent on conjugate additions to enones, we elected to use the same catalyst and reaction conditions as those reported by Miyaura and co-workers.[3a] Potassium phenyltrifluoroborate **1a** and methyl vinyl ketone (MVK) were chosen as representative substrates. By using 2 equiv of **1a** in the presence of $Rh(acac)(CO)_2$ (3 mol %) and 1,4-bis(diphenylphosphino)-butane (dppb) (3 mol %), reaction proceeded to full conversion after 16 h in MeOH/water (6:1) at 50 °C. The relative rate of reaction for **1a** was greater than that for phenylboronic acid under otherwise identical conditions, as determined at 1, 4, 8, and 16 h (Table 1).

The reaction was also effective using triphenylphosphine as a ligand (2 equivalents), with the isolated yield of **2a** dropping slightly to 84% after 16 h. Reaction with Wilkinson's catalyst (Aldrich Chemicals, 3 mol %) resulted in a 42% isolated yield of **2a** after 16 h. Reduction of the amount of trifluoroborate salt **1a** to 1.1 equiv resulted in a modest drop in the isolated product yield to 82%. When the reaction was conducted in dry DME or with just 10 equiv of water, the reaction was slower, with product to starting material ratios at 16 h of 25:75 and 80:20, respectively.

Table 1. Comparative Efficiency of Conjugate Addition of Potassium Phenyltrifluoroborate and Phenylboronic Acid to Methyl Vinyl Ketone

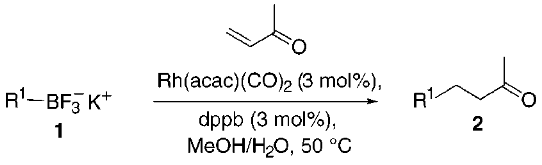


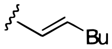
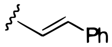
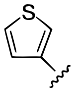
t (h)	yield (%) of **2a**[a]	
	$PhBF_3^-K^+$ (**1a**)	$PhB(OH)_2$
1	16	11
4	52	39
8	79	56
16	91	82[b]

[a] Isolated Yields. [b] 99% GC yield reported in ref 3a.

Other potassium alkenyl- and aryltrifluoroborates **1** also reacted with MVK using the standard protocol, giving comparable isolated yields of the products **2** (Table 2).

Table 2. Conjugate Arylation and Alkenylation of MVK with Potassium Aryl- and Alkenyltrifluoroborates



Reagent	R¹	Ketone	Yield [%]
1a	Ph	**2a**	85
1b	$3\text{-}O_2NC_6H_4$	**2b**	59
1c	$3\text{-}AcC_6H_4$	**2c**	98
1d	 Bu	**2d**	90
1e	 Ph	**2e**	quant.
1f	 S	**2f**	quant.

Particularly noteworthy is the addition of the electron-deficient trifluoroborate **1b** to MVK. We determined that the corresponding 3-nitrophenylboronic acid *does not add*

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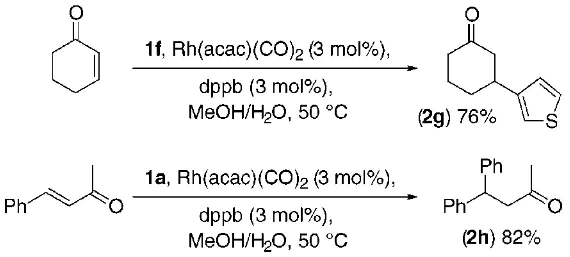
(5) (a) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020−3027, and references therein. (b) Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460−2470. (c) Petasis, N. A.; Yudin, A. K.; Zavialov, I. A.; Prakash, G. K. S.; Olah, G. A. *Synlett* **1997**, 606−608. (d) Darses, S.; Genêt, J.-P. *Tetrahedron Lett.* **1997**, *38*, 4393−4396. (e) Darses, S.; Michaud, G.; Genêt, J.-P. *Tetrahedron Lett.* **1998**, *39*, 5045−5048. (f) Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* **1999**, *5*, 1875−1883. (g) Xia, M.; Chen, Z.-C. *Synth. Commun.* **1999**, *29*, 2457−2465. (h) Chambers, R. D.; Clark, H. C.; Willis, C. J. *J. Am. Chem. Soc.* **1960**, *82*, 5298−5301.

under otherwise identical conditions, demonstrating the greater reactivity of the tetracoordinate trifluoroborate salts for the conjugate additions.

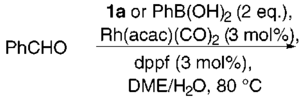
Having established the feasibility of Rh(I)-catalyzed conjugate addition of **1** to MVK, we briefly studied the scope of the process with terminally monosubstituted and cyclic enones as substrates. Under the optimized conditions, cyclohexenone and (*E*)-4-phenyl-3-buten-2-one reacted with **1f** and **1a**, respectively, to furnish the substituted ketones **2g** and **2h** in high yield (Scheme 3).

Scheme 3



The potassium trifluoroborate salts **1** were also useful reagents for nucleophilic additions to aldehydes. For initial studies we again opted to adapt the conditions developed by Miyaura and co-workers for the alkenylation and arylation of aldehydes.[2] Reaction of benzaldehyde with 2 equiv of **1a** with Rh(acac)(CO)$_2$ (3 mol %) and 1,1′-bis(diphenylphosphino)ferrocene (dppf) (3 mol %) resulted in the formation of **3a**. The reaction proceeded to full conversion after 16 h in DME/water (1:1) at 80 °C. The trifluoroborate salt **1a** is again more reactive than phenylboronic acid (Table 3). When **1a** was used, conversion was almost complete after 8 h, whereas less than half of the aldehyde had undergone reaction with phenylboronic acid.

Table 3. Comparative Efficiency of Potassium Phenyltrifluoroborate and Phenylboronic Acid Addition to Benzaldehyde

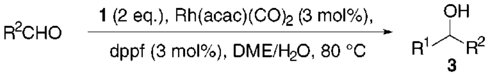


	conversion (%)[a]	
t (h)	$PhBF_3^-K^+$	$PhB(OH)_2$
1	20	<10
4	75	20
8	90	45
16	>99	>98

[a] Determined by ^{1}H NMR of the crude reaction mixture.

A variety of aldehydes were functionalized in this manner to give the corresponding allylic and benzylic alcohols **3** (Table 4).[6] The use of 2 equiv of the trifluoroborate salt was again found to be optimal, with the isolated yields of **3a** dropping to 69% and 28% with 1.5 and 1.1 equiv of **1a** respectively. Nitro-substituted aldehydes that reacted efficiently in our studies were found to be unreactive when the corresponding boronic acids were used under otherwise identical conditions.[2]

Table 4. Arylation and Alkenylation of Aldehydes with Potassium Aryl- and Alkenyltrifluoroborates



entry	$R^1BF_3^-K^+$	R^2	yield (%) (aldehyde)
1	**1a**	Ph	79 (**3a**)
2	**1a**	4-$O_2NC_6H_4$	85 (**3b**)
3	**1e**	4-$O_2NC_6H_4$	82 (**3c**)
4	**1a**	3-$O_2NC_6H_4$	88 (**3d**)
5	**1a**	2-$O_2NC_6H_4$	85 (**3e**)
6	**1d**	2-$O_2NC_6H_4$	88 (**3f**)
7	**1a**	4-NCC_6H_4	87 (**3g**)
8	**1d**	4-NCC_6H_4	85 (**3h**)
9	**1f**	4-NCC_6H_4	80 (**3i**)
10	**1a**	4-$MeOOCC_6H_4$	71 (**3j**)
11	**1e**	4-$MeOOCC_6H_4$	71 (**3k**)
12	**1a**	C_6H_{11}	86 (**3l**)

Finally, we briefly studied the effect of the ligand upon the reaction of phenyltrifluoroborate **1a** with 4-nitrobenzaldehyde. Significantly, the ligands dppb (1 equiv) and triphenylphosphine (2 equiv) were found to be effective in the reaction, with yields dropping from 85% with dppf to 83% with PPh$_3$ and 76% with dppb. This is in sharp contrast to the results obtained in the addition of phenylboronic acid to aldehydes, in which no reaction occurs with PPh$_3$ as a ligand.[2] This suggests that the P−Rh−P angle does not significantly affect catalyst activity under our conditions, an observation which may be useful in the design of more active or asymmetric catalysts for the reaction.

The greater effectiveness of the potassium trifluoroborate salts in the Rh(I) catalyzed additions to enones and aldehydes, compared to the boronic acids, presumably reflects more facile transmetalation to form the active Rh−C species. Although a full mechanistic study is required to confirm this hypothesis, other *tetracoordinate* boron compounds may offer a similar improvement in reactivity.

In conclusion, we have successfully demonstrated the viability of alkenyl- and aryltrifluoroborates as air- and

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(6) **Representative Procedure.** A suspension of potassium 3-thiophenetrifluoroborate **1f** (323 mg, 2.00 mmol) and 4-cyanobenzaldehyde (131 mg, 1.00 mmol), Rh(acac)(CO)$_2$ (8 mg, 0.03 mmol), and dppf (17 mg, 0.03 mmol) in a 1:1 mixture of DME/water (6 mL) was stirred at 80 °C for 16 h. The reaction mixture was then diluted with benzene (20 mL), and the layers were separated. The aqueous layer was extracted with benzene (3 × 5 mL). The combined organic extracts were dried (MgSO$_4$), filtered, and concentrated in vacuo to afford a brown oil. Silica gel chromatography (20% EtOAc/80% hexanes) afforded **3i** as a clear, colorless oil (172 mg, 80%).

moisture-stable agents for nucleophilic additions to enones and aldehydes. This is a significant practical improvement over existing conditions, expanding the scope of substrates which can be applied in the reaction, and further validating the utility of this very important transition metal-catalyzed reaction. We are currently working toward establishing the nature of the active intermediates within the catalytic cycle and the development of asymmetric variants for the additions to aldehydes. Extensions of this methodology to other substrates, and its application in combinatorial synthesis will also be reported in due course.

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Supporting Information Available: Preparation procedures and characterization data for **1b**−**d**, **1f**, **2a**−**f**, and **3a**−**l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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