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Potassium organotrifluoroborates: new partners in catalytic enantioselective conjugate additions to enones

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Abstract—Potassium organotrifluoroborates, highly stable organoboron derivatives and easily accessible from organolithiated reagents, can achieve rhodium(I)-catalyzed asymmetric 1,4-additions to enones using binap as chiral ligand. This reaction proceeds in nearly quantitative yields to afford β-functionalized ketones with e.e. up to 98%. © 2002 Elsevier Science Ltd. All rights reserved.

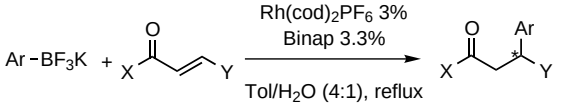
The 1,4-conjugate addition of organometallic reagents to unsaturated compounds bearing electron-withdrawing group is one of the most versatile reactions in organic synthesis. Although Michael addition is a key step in many synthetic approaches to natural products, the scope of this carbon–carbon bond formation can be enlarged by the development of catalytic and asymmetric approaches. During the last 10 years, the asymmetric 1,4-addition of organozinc or magnesium compounds catalyzed by copper(I) has been widely developed,[1] but was generally limited to the introduction of alkyl substituents.

In 1997, Miyaura et al.[2] reported a catalytic approach for the addition of arylboronic acids to enones. Following this communication, rhodium(I) catalyzed asymmetric addition of boron reagents to other substrates[3], including ketones[4], esters[5], amides[6], phosphonates[7], or nitroalkenes[8] using atropoisomeric diphosphines as ligands has been developed both by Hayashi and Miyaura. One major advantage of using boron reagents compared to other organometallic reagents lies in their high tolerance towards functional groups and low toxicity of reaction by-products. However, in this reaction, depending on the Michael type substrates, different organoboronic acid derivatives must be employed (boroxins, benzodioxaboroles, borates) in order to achieve high yields. Moreover, addition of specified equivalents of water had to be strictly controlled. Thus, it appeared interesting to search for other organoboron reagents which could transmetallate to rhodium(I) more easily. We,[9] then others[10] have shown that potassium organotrifluoroborates were efficient partners in palladium-catalyzed cross-coupling reactions and offered good alternatives to boronic acids because of their higher stability, ease of preparation and purification.[9c,11] Batey et al.[12] have reported that these species could be used in rhodium-catalyzed 1,4-additions and 1,2-additions to enones and aldehydes, but no asymmetric version was reported.

Having established a general access to potassium alkenyl- and aryltrifluoroborates,[9c] we now wish to report our preliminary results concerning the use of potassium organotrifluoroborates as reagents in enantioselective conjugate addition to enones (Scheme 1, Table 1).

Conditions for carrying out the 1,4-addition to enones were optimized using potassium phenyltrifluoroborate **1a** and cyclohexenone **2a**.

We found that the addition of potassium phenyltrifluoroborate **1a** to cyclohexenone **2a** was efficiently catalyzed by a rhodium complex generated in situ by



Scheme 1. Rhodium-catalyzed asymmetric 1,4-addition of potassium organotrifluoroborate to enones.

Keywords: organotrifluoroborates; asymmetric catalysis; 1,4-addition; rhodium catalyst.

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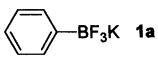
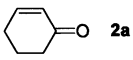
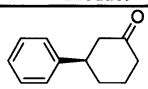
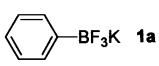
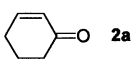
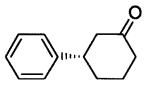
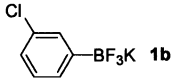
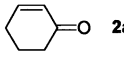
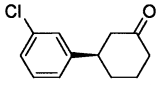
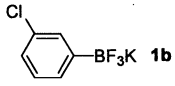
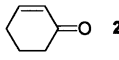
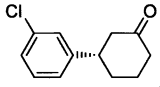
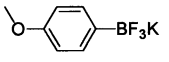
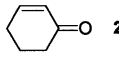
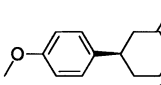
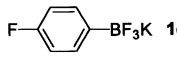
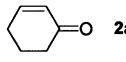
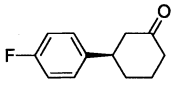
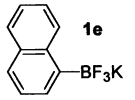
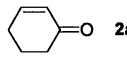
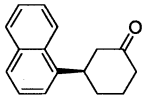
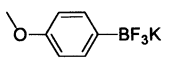
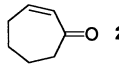
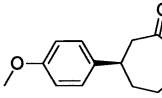
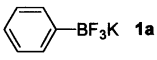
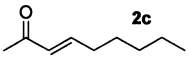
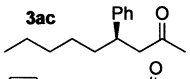
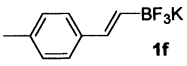
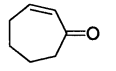
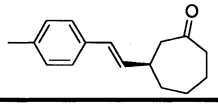
Table 1. Rhodium-catalyzed enantioselective 1,4-additions of organotrifluoroborates to enones

Entry	RBF_3K[a]	Enone	Ligand	Time	Product	Yield[b]	% e.e.[c]
1	 **1a**	 **2a**	(*R*)-Binap	1h	 **3aa**	99%	98%[d]
2	 **1a**	 **2a**	(*S*)-Binap	1h	 **3aa**	99%	98%[d]
3	 **1b**	 **2a**	(*R*)-Binap	20h 3h[g]	 **3ba**	89% 96%	- 97%[d]
4	 **1b**	 **2a**	(*S*)-Binap	3h[g]	 **3ba**	95%	97%[d]
5	 **1c**	 **2a**	(*R*)-Binap	6h[g]	 **3ca**	97%	90%[e]
6	 **1d**	 **2a**	(*R*)-Binap	2h 2h[i]	 **3da**	41% 95%	- 98%[f]
7	 **1e**	 **2a**	(*R*)-Binap	20h 20h[i]	 **3ea**	53% 90%	- 98%[d]
8	 **1c**	 **2b**	(*R*)-Binap	3h	 **3cb**	75%	94%[d]
9	 **1a**	 **2c**	(*R*)-Binap	1h	 **3ac**	99%	92%[e]
10	 **1f**	 **2b**	(*R*)-Binap	1h	 **3fb**	70%	95%[d]

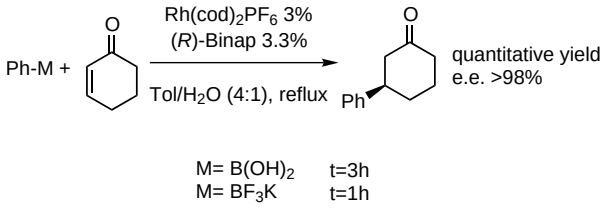
[a] Prepared according to ref 9c. [b] Isolated yield after silica gel chromatography. [c] Determined by HPLC analysis using chiral stationary phase column. [d] Daicel Chiralcel OD-H. [e] Daicel Chiralcel OJ. [f] Daicel Chiralcel AD. [g] 3 equivalents of aryltrifluoroborate were used. [h] 4 equivalents of aryltrifluoroborate were used. [i] 5 equivalents of aryltrifluoroborate were used.

mixing $Rh(cod)_2PF_6$ with 1.1 equiv. of binap[13] in refluxing toluene/water (4:1).[14] Under such conditions, compound (*R*)-**3aa** was obtained in quantitative yield and high enantiomeric excess (98%) using (*R*)-binap as ligand (entry 1)[15] and the use of (*S*)-binap lead to the opposite configuration (entry 2) with the same level of enantioselection. Other potassium aryltrifluoroborates also afforded 1,4-addition adduct very efficiently (entries 3–7) giving crude 3-arylsubstituted cyclohexanones with high purities. Moreover, reactions were generally complete within a few hours. In some cases, reduction of potassium aryltrifluoroborate into arene was found to be a competitive process. Increasing the amount of the organoboron reagent allowed the reaction to go to completion (entries 6 and 7).

Different cyclic and acyclic α,β-unsaturated ketones can be used as partners in this conjugate addition. Reactions of aryltrifluoroborates on cyclohept-2-enone **2b** or non-2-enone **2c** were complete in 1 hour (entries 8 and 9) and gave Michael adducts with high yields and enantiomeric excesses.

Next, we examined the reactivity of potassium alkenyltrifluoroborates toward 1,4-addition. In the previous conditions, 3-(2-(4-methylphenyl)vinyl)cycloheptanone **3fb** was obtained in 70% yield and a good enantiomeric excess (95% e.e.), using 2-(4-methylphenyl)vinyltrifluoroborate **1f** and cylohepten-2-one as substrates.

Compared reactivity of organotrifluoroborates and boronic acids was estimated using the same reaction conditions. In the presence of 3% of $Rh(cod)_2PF_6$ and 3.3% of (*R*)-binap, it was found that phenylboronic acid **4** undergoes 1,4-addition with the same yield and enantiomeric excess but reaction time was longer (conversion after 1 hour reaction was only 50%). This seems to confirm the higher reactivity of potassium organotrifluoroborates compared to boronic acids in transmetallation processes[9c,12] (Scheme 2).



Scheme 2. Compared reactivity of boronic acids and potassium organotrifluoroborates.

In conclusion, we have shown that potassium organotrifluoroborates proved to be a good alternative in enantioselective rhodium(I)-catalyzed conjugate additions of boron reagents to α,β-unsaturated ketone with useful levels of enantioselectivity. These reagents, which are more stable and easier to prepare, seemed to be more reactive than their boronic acids analogues. Extension of this reaction to other Michael acceptors is currently in progress and will be reported in due course.

Acknowledgements

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References

1. For reviews on enantioselective conjugate addition see: (a) Perlmutter, P. *Conjugate Addition in Organic Synthesis*; Pergamon Press: Oxford, 1992; (b) Schmalz, H.-G. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds; Pergamon: Oxford, 1991; Vol. 4, Chapters 1–5; (c) Rossiter, B. E.; Swingle, N. M. *Chem. Rev*. **1992**, *92*, 771–806; (d) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033–8061; (d) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171–196.
2. Miyaura, N.; Hayashi, H.; Sakai, M. *Organometallics* **1997**, *16*, 4229–4231.
3. Hayashi, T. *Synlett* **2001**, 879–887.
4. (a) Hayashi, T.; Ogasawara, M.; Takaya, Y. *J. Am. Chem. Soc*. **1998**, *120*, 5579–5580; (b) Hayashi, T.; Ogasawara, M.; Takaya, Y. *Tetrahedron Lett*. **1998**, *39*, 8479–8482; (c) Reetz, M. T.; Moulin, D.; Gosberg, A. *Org. Lett*. **2001**, *3*, 4083–4085.
5. (a) Hayashi, T.; Ogasawara, M.; Kurushima, H.; Senda, T.; Takaya, Y. *Tetrahedron: Asymmetry* **1999**, *10*, 4047–4056; (b) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem*. **2000**, *65*, 5951–5955.
6. (a) Hayashi, T.; Ogasawara, M.; Senda, T. *J. Org. Chem*. **2001**, *66*, 6852–6856; (b) Miyaura, N.; Sukuma, S. *J. Org. Chem*. **2001**, *66*, 8944–8946.
7. Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc*. **1999**, *121*, 11591–11592.
8. Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc*. **2000**, *122*, 10716–10717.
9. (a) Darses, S.; Genet, J. P.; Brayer, J. L.; Demoute, J. P. *Tetrahedron Lett*. **1997**, *38*, 4393–4396; (b) Darses, S.; Michaud, G.; Genet, J. P. *Tetrahedron Lett*. **1998**, *39*, 5045–5048; (c) Darses, S.; Michaud, G.; Genet, J. P. *Eur. J. Org. Chem*. **1999**, 1875–1883.
10. (a) Molander, A. G.; Rodriguez Rivero, M. *Org. Lett*. **2002**, *4*, 107–109; (b) Molander, A. G.; Ito, T. *Org. Lett*. **2001**, *3*, 393–396; (c) Puentener, K.; Scalone, M. *European Patent* no. 1 057 831 A2, **2000**.
11. Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf *J. Org. Chem*. **1995**, *60*, 3020–3027.
12. Batey, R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett*. **1999**, *1*, 1683–1686.
13. (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley and Sons: New York, 1994; (b) Okhuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed; New York; 2000; pp. 1–110.
14. To a mixture of **1a** (184 mg, 1 mmol, 2 equiv.), $Rh(cod)_2PF_6$ (7.0 mg, 3 mol%), and (*R*)-binap (10.3 mg, 3.3 mol%) in degazed toluene/water (2 mL/0.5 mL) was added cyclohexenone **2a** (48 mg, 0.5 mmol) and the mixture was stirred at 105–110°C for 75 min. After filtration on celite eluting with CH_2Cl_2, the solvent was removed under reduce pressure. Chromatography purification over silica gel (cyclohexane/AcOEt = 9/1) afforded 86 mg (99% yield) of (*R*)-3-phenylcylohexanone (**3aa**) as colourless oil with 98% e.e. (determined by HPLC analysis: Daicel Chiralcel OD-H, hexane/2-propanol = 98/2). $[\alpha]_D$ +21 (*c* 0.98, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.75–2.0 (2H, m), 2.15–2.25 (2H, m), 2.40–2.65 (4H, m), 3.1–3.3 (1H, m), 7.2–7.4 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.4, 32.6, 41.1, 44.6, 48.8, 126.5, 126.6, 128.6, 144.3, 210.9.
15. Absolute configuration was determined by comparison with $[\alpha]_D$ given in the literature, and enantiomeric excesses by HPLC analysis using chiral phase stationary column.