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Potassium trifluoro(organo)borates in rhodium-catalyzed 1,4-additions to α,β-unsaturated esters

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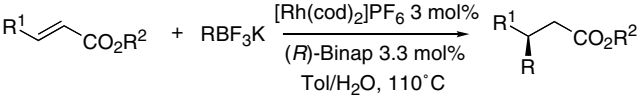
Abstract—This letter describes an efficient and enantioselective conjugate addition of highly stable potassium trifluoro(organo)borates to α,β-unsaturated esters. This reaction, catalyzed by chiral rhodium(I) complexes, affords Michael adducts with high yields and enantiomeric excesses up to 96%.

Rhodium-catalyzed carbon–carbon bond forming reactions using organometallic reagents has recently emerged as a powerful tool in organic synthesis.[1] Particularly, the asymmetric 1,4-addition of organometallics allowed the introduction of a β-substituent to a Michael acceptor with concomitant enantioselective control of the newly created carbon–carbon bond.[2] Among the various organometallics, organoboronic acids have shown to add efficiently to various activated olefins like enones,[2,3] α,β-unsaturated esters,[4,5] amides,[2] phosphonates,[2] sulfones,[6] or nitroalkenes[2] in the so-called Miyaura–Hayashi reaction.

Among these Michael acceptors, unsaturated ketones have proven to be the most reactive and consequently the most studied substrates. On the other hand, α,β-unsaturated esters have shown to be less reactive and reports of 1,4-addition of organometallic reagents to these substrates using rhodium catalyst are very scarce.[4,5] Even if organoboron derivatives have proven to be suited in this reaction, large excesses of reagents are needed to obtain moderate yields of Michael adducts.[5] Higher yields have been achieved using in situ prepared lithium borates $ArB(OMe)_3Li$ with careful control of the amount of added water.[4] These conditions proved to be suited for acyclic substrates, but for cyclic ones, again a large excess of boronic acid was more adapted.[4]

As alternate organoboron derivatives, we have shown that potassium trifluoro(organo)borates[7] were highly suitable either in palladium-catalyzed cross-coupling reactions[8] or in rhodium-catalyzed reactions and developed efficient protocols for asymmetric 1,4-addition to enones[9] and enamides[10] where low amounts of organoboron derivatives had to be employed compared to trivalent organoboron species.[2,3c,11] These stable and easily prepared tetravalent boron species allowed the development of new reactions such as an efficient access to chiral amino acids via 1,4-addition/enantioselective protonation[12] or a direct access to ketones from aldehydes via a Heck-type reaction.[13] Herein we want to report for the first time the use of potassium trifluoro(organo)borates in rhodium-catalyzed asymmetric 1,4-addition to α,β-unsaturated esters, extending the scope of previously described reactions (Scheme 1).[9,10]

Indeed, under standard conditions,[9,10] that is, using cationic rhodium complex as catalyst precursor in the presence of Binap as chiral ligand, we were



Scheme 1. Rh-catalyzed 1,4-additon of RBF_3K to α,β-unsaturated esters.

Keywords: Borates; Asymmetric catalysis; 1,4-Addition; Rhodium; Esters.

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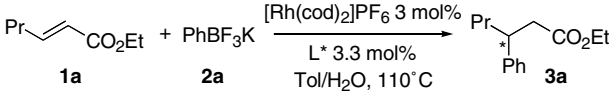
pleased to find that the 1,4-addition of potassium trifluoro(phenyl)-borate (**2a**) to ethyl hex-2-enoate (**1a**) occurred smoothly affording the expected adduct **3a** in 95% yield and 90% ee (Table 1, entry 1). In order to further improve the enantioselectivity of the reaction, other bidentate chiral ligands were evaluated in this reaction model under standard conditions. However, despite several attempts (see Table 1 for some selected examples), the enantioselectivity could not be improved and the highest enantiomeric excesses were obtained using Binap. MeOBiphep chiral ligand derivatives[14] show lower level of enantioselectivity (entry 2) and in many cases no chiral induction was observed (entries 3–5). It is unclear at present if formation of racemic products results from unfavorable steric interactions of the substrate with the chiral rhodium complex or from a 1,4-addition catalyzed by achiral rhodium complex because of incomplete complexation of the chiral ligand. Using ferrocenyl chiral Josiphos derivatives,[15] slower reactions and modest chiral induction were observed. Further optimizations of the reaction parameters such as the solvent or temperature did not result in any improved reactivity nor enantioselectivity. Thus, it appeared, at present, that reaction conditions optimized for the 1,4-addition of potassium trifluoro(organo)borates to enones[9] or α,β-unsaturated amides[10] also proved to be optimal for α,β-unsaturated esters.

Indeed, in the presence of cationic $[Rh(cod)_2]PF_6$ in combination with (*R*) or (*S*)-Binap, 1,4-addition of potassium aryltrifluoroborates to α,β-unsaturated esters

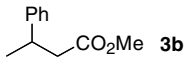
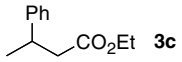
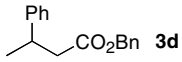
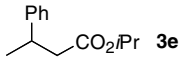
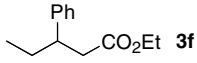
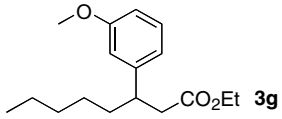
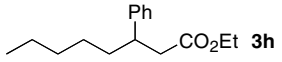
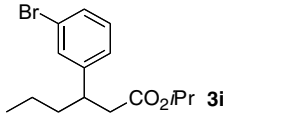
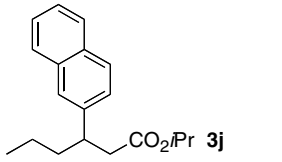
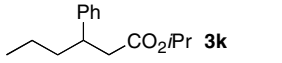
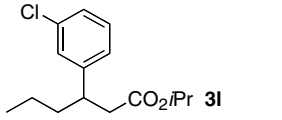
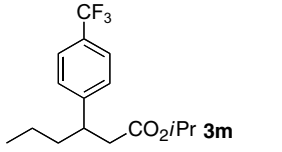
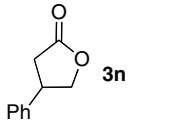
Table 1. Influence of the chiral bidentate ligand on the enantioselectivity of the 1,4-addition[a]



Entry	Ligand (L*)	Yield[b]	ee[c] (%)
1	(*S*)-Binap	95	90 (*S*)
2	(*S*)-MeOBiphep	100	72 (*S*)
3	(*S*)-*p*DMA-MeOBiphep[d]	100	0
4	(*R*)-2-Furyl-MeOBiphep[e]	91	0
5	(*R*)-3,5-*t*Bu-MeOBiphep[f]	23	0
6	(*R*,*S*)-Josiphos	30	31 (*R*)
7	(*S*,*R*)-Cy_2PF-PPh_2[g]	33	21 (*R*)
8	(*R*,*S*)-Cy_2PF-PCy_2[h]	<5	52 (*R*)

[a] Reactions conducted using 0.5 mmol of **1a**, 2 equiv of **2a** with 3 mol % of $[Rh(cod)_2][PF_6]$ and 3.3 mol % L* at 110 °C in 2 ml toluene/water 20:1.
[b] Isolated yield of 1,4-addition adduct **3a**.
[c] Determined by HPLC using Daicel Chiralcel OD-H column (hexane/*i*PrOH 99:1, 0.5 ml/min).
[d] *p*DMA-MeObiphep: 6,6′-dimethoxy-2,2′-bis[di(4-dimethylaminophenyl)-phosphanyl)-1,1′-biphenyl.
[e] 2-furylMeObiphep: 6,6′-dimethoxy-2,2′-bis[di(2-furyl)phosphanyl)-1,1′-biphenyl.
[f] 3,5-*t*Bu-MeOBiphep: 6,6′-dimethoxy-2,2′-bis[di(3,5-di-*tert*-butylphenyl)-phosphanyl)-1,1′-biphenyl.
[g] Cy_2PF-PPh_2: 1-[2-(dicyclohexylphosphanyl)ferrocenyl]-ethyldiphenylphosphane.
[h] Cy_2PF-PCy_2: 1-[2-(dicyclohexylphosphanyl)ferrocenyl]-ethyldicyclohexylphosphane.

Table 2. Asymmetric 1,4-addition of RBF_3K to α,β-unsaturated esters[a]

Entry	Product	Yield[b]	ee[c]
1	 **3b**	96	84 (*R*)[d]
2	 **3c**	98	86 (*R*)[d]
3	 **3d**	91	85 (*S*)
4	 **3e**	93	93 (*S*)
5	 **3f**	96	86 (*S*)
6	 **3g**	88	87 (*S*)
7	 **3h**	95	86 (*S*)
8	 **3i**	50	91 (*S*)
9	 **3j**	75	90 (*S*)
10	 **3k**	87	96 (*S*)
11	 **3l**	66	90 (*S*)
12	 **3m**	54	89 (*S*)
13	 **3n**	55[e]	93 (*R*)

[a] Reactions conducted using 0.5 mmol of **1**, 2 equiv of **2** with 3 mol % of $[Rh(cod)_2][PF_6]$ and 3.3 mol % (*R*)-Binap at 110 °C in 2 ml toluene/water 20:1.
[b] Isolated yields of 1,4-addition adducts **3**.
[c] Determined by HPLC using Daicel Chiralcel OD-H column excepted **3j** (Chiralcel OJ) and **3n** (Chiralpak AS-H). Absolute configuration of the adducts was established by comparison of the sign of optical rotation or chiral HPLC retention time with that of configurationally assigned compounds.
[d] Using (*S*)-Binap as chiral ligand.
[e] Reaction conducted with 4 equiv of aryltrifluoroborate.

occurred smoothly in a biphasic solvent (toluene/water) at 110 °C (Table 2).[16] The influence of the ester moiety on either reactivity or enantioselectivity was evaluated using several crotonic esters derivatives (entries 1–4). From these results, it appeared that increasing steric hindrance at the ester moiety resulted in an increase of the enantiomeric excesses without affecting the yields. Among these esters, isopropyl derivatives seemed to be the most adapted affording the 1,4-addition adduct **3e** in 93% yields and 93% ee.[17]

Other potassium aryltrifluoroborates also added efficiently to different unsaturated esters (Table 2). Once again, from these results it appeared that the levels of enantioselectivity using ethyl esters (entries 5–7, ee = 86–87%) were always slightly lower than those observed with isopropyl esters (entries 8–12, ee >89%). Concerning the potassium aryltrifluoroborate partner, it seems that the electronic nature of the substituents does not greatly influence their reactivity: either electron-withdrawing (entry 12) or releasing groups (entry 6) were tolerated on the aromatic ring. α,β-unsaturated lactones showed lower reactivity under these conditions, as observed in the addition of boronic acids,[4] but a 55% yield was obtained in the 1,4-addition of potassium trifluoro(phenyl)trifluoroborate to 2(*5H*)-furanone (**3n**) with 93% enantiomeric excess.

In order to get further insight on the reaction pathway, the reactivity of trifluoroborates and boronic acids was evaluated under our conditions (see Fig. 1). The 1,4-addition of phenylboronic acid and potassium trifluoro(phenyl)borate (**2a**) to ethyl oct-2-enoate (**1h**), in the presence of 3 mol % $[Rh(cod)_2]PF_6$ and 3.3 mol % (*R*)-Binap in toluene/water at 110 °C was analyzed by GC/MS. The main feature of these kinetics revealed a great difference of reactivity between these organoboron derivatives: reaction with phenylboronic acid takes place instantaneously whereas an induction period is observed with potassium trifluoro(phenyl) borate.[10] These results indicate that transmetallation of boronic acids is fast to the Rhodium/Binap precursor whereas it did not happen or to a lesser extend with trifluoroborate derivatives. This fast transmetallation of boronic acids resulted in an accumulation of phenyl-rhodium species which are very proned to hydrolysis, a competitive process with the insertion of the carbon–carbon double bond[2] (Scheme 2).

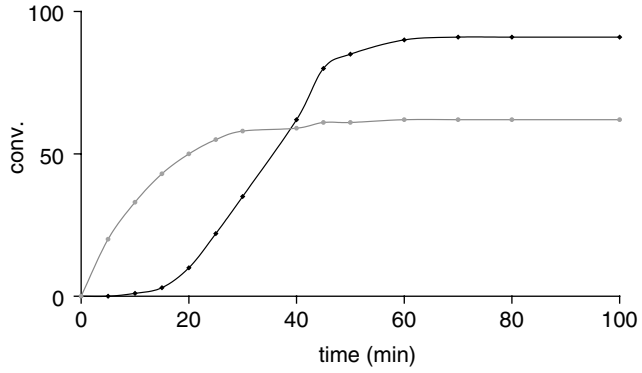
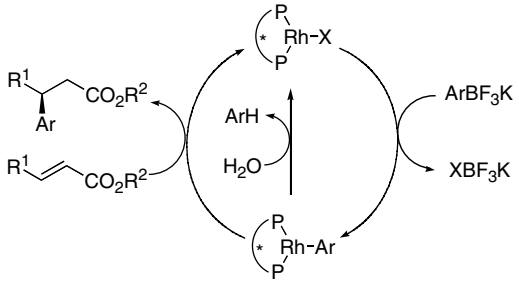


Figure 1. Compared reactivity of $PhBF_3K$ **2a** (◆) and $PhB(OH)_2$ (●) in rhodium-catalyzed 1,4-addition to ethyl oct-2-enoate (**1h**).



Scheme 2. Proposed simplified mechanism.

These results may explain that larger amounts of organoboronic acids are needed in such carbometallation processes compared to potassium trifluoro(organo)borates, because the importance of hydrolysis may be correlated with their fast transmetallation rate. Indeed, using two equivalents of organoboron derivatives, lower yields of 1,4-addition adduct were observed using boronic acids (Fig. 1). On the other hand, with potassium trifluoro(organo)borates, transmetallation seems to be rate determining, preventing accumulation of aryl-rhodium species and their hydrolysis. Further studies are underway to elucidate this difference of reactivity.

From these preliminary results, potassium trifluoro(organo)borates appear to be very efficient partners in rhodium-catalyzed enantioselective 1,4-additions to α,β-unsaturated esters. These highly stable and easily prepared boron derivatives seem to be more suited than the boronic acid analogues in such reaction. It is also noteworthy that the reaction proceeds with high yields and good to excellent enantiomeric excesses whatever the electronic properties of the aryltrifluoroborates, providing a useful tool in organic synthesis. Indeed, the use of potassium trifluoro(organo)borates in such carbometallation processes proved to be superior to boronic acids.

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16. General procedure for the 1,4-addition of potassium trifluoro(organo)borates on α,β-unsaturated esters: A septum-capped vial equipped with a magnetic stirring bar was charged with potassium (naphth-2-yl)trifluoroborate (2 equiv, 1 mmol, 234.1 mg), $[Rh(cod)_2][PF_6]$ (3 mol %, 6.9 mg), (*R*)-Binap (3.3 mol %, 10.3 mg). The vial was closed and evacuated under vacuum and placed under an argon atmosphere. Degassed toluene (2 ml) and water (100 μl) followed by isopropyl hex-2-enoate (0.5 mmol, 72 μl) were added and the mixture was stirred in a preheated oil bath at 110 until completion of the reaction (GC). After cooling the vessel at room temperature, the reaction mixture was purified by silica gel chromatography (ethyl acetate/cyclohexane 20:1) to afford **3j** as a colorless oil (106.8 mg, 75% yield). $[\alpha]_D^{25}$ +14.5 (*c* 0.94, $CHCl_3$), lit.[4] $[\alpha]_D^{25}$ −16 (*c* 0.94, $CHCl_3$). HPLC (Daicel Chiralcel OJ, hexane/propan-2-ol 99:1, 1 ml/min, 215 nm) t_R = 10.0 (*S*) and 12.1 min (*R*).
17. *tert*-Butylester derivatives which are not easily available were not tested.