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Efficient access to chiral β-arylamides via asymmetric 1,4-additions of potassium trifluoro(organo)borates

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Abstract—This paper describes an efficient enantioselective conjugate addition of highly stable potassium trifluoro(organo)borates to α,β-unsaturated amides. This reaction, catalyzed by chiral rhodium(I) complexes affords Michael adducts with high yields and enantiomeric excesses up to 95%.

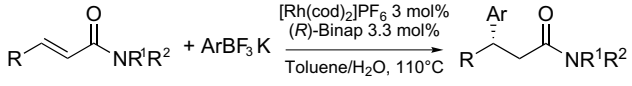
During the last decade, developments of enantioselective catalyzed 1,4-additions of organometallics contributed to the synthesis of many pharmaceutical targets.[1] Among the pairs catalytic systems and organometallic reagents developed, 1,4-addition of organozinc compounds catalyzed by chiral copper(I) complexes was the first to emerge as an efficient way to introduce alkyl substituents on unsaturated substrates.[2] Later, Miyaura and Hayashi developed an enantioselective 1,4-addition of boronic acids to enones catalyzed by chiral rhodium(I) complexes.[3] Aryl or alkenyl groups could then be introduced successfully on various electron-deficient olefins.[4,5]

However, enamides turned out to be the less reactive Michael acceptors and reported examples are scarce. Strong organometallic reagents such as organolithium or Grignard have been shown to react with enamides but reactions were limited to diastereoselective pathways.[6] Recently, it has been reported that arylboronic acids reacted with α,β-unsaturated amides in the presence of a chiral rhodium(I) catalyst, allowing a straightforward access to β-substituted amides with ee up to 93%.[7,8] However, described examples are rather limited and the reaction generally requires a large excess of boron derivatives (up to 5 equiv). Moreover, the use of moisture sensitive boroxine[8] or a base in conjunction with boronic acids[7] is needed in order to achieve moderate yields. Indeed, there is still a need for a general and efficient carbometallation process allowing an enantioselective addition of organometallic reagents to enamides.

Recently, we reported that potassium trifluoro(organo)borates, easily prepared and highly stable reagents,[9] participated in rhodium-catalyzed enantioselective 1,4-additions to enones,[10] unsaturated esters,[11] dehydroaminoesters,[12] and Baylis–Hilmann adducts[13] with high efficiency. We envisioned that these boron reagents would be good candidates in asymmetric 1,4-additions to enamides.

We were pleased to find that using our previously described conditions,[10] high yields and enantiomeric excesses were achieved in the formation of chiral β-arylamides (Scheme 1).

Indeed, when potassium trifluoro(phenyl)borate **1a** was allowed to react with *N*-benzylcrotonamide **2a** in refluxing toluene/water (20:1) in the presence of a chiral



Scheme 1. Rhodium-catalyzed enantioselective 1,4-addition of potassium aryltrifluoroborates to enamides.

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

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Table 1. Effect of additives on the asymmetric 1,4-addition of $PhBF_3K$ to *N*-benzylcrotonamide

Entry	Additive	Conv.[a] (%)	Ee[b] (%)
1	None	100	93
2	$KHCO_3$ 10%	98	48
3	K_2CO_3 10%	99	92
4	KF 10%	99	64

[a] Conversion determined by GC.
[b] Determined by HPLC using chiral stationary phase column.

catalyst, generated in situ from 3 mol% $[Rh(cod)_2]PF_6$ and 3.3 mol% (*R*)-Binap, the addition proceeded to completion within 1 h to afford the desired product **3aa** in 87% yield and 93% ee (Table 1, entry 1).[14]

In rhodium-catalyzed 1,4-addition of arylboronic acids to enamides, Sakuma and Miyaura.[7] underlined a great influence upon addition of a base: the latter allowing the reaction to go to completion; low yields being obtained in its absence. In the present reaction, addition of bases did not show any influence on conversions (Table 1, entries 2–4) whereas it generally resulted in a dramatic decrease of the enantioselectivities (entries 2 and 4). Such diminution of the ee was not observed with boronic acids and we do not know at present the origin of such profound effect. Intrigued by this difference of reactivity between phenylboronic acid and potassium trifluoro(phenyl)borate, we evaluated the behavior of these organoboron compounds in the 1,4-addition to enamides under identical conditions (Fig. 1).

In the presence of 3 mol% of $[Rh(cod)_2]PF_6$ and 3.3 mol% of (*R*)-Binap, the addition of phenylboron derivatives (2 equiv) to *N*-benzylcrotonamide was followed by GC analysis. When the reaction was conducted with potassium trifluoro(phenyl)borate, an induction time of 10 min was observed but the reaction

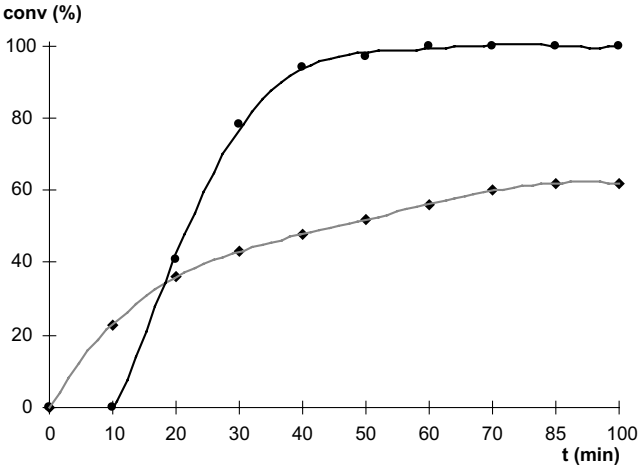


Figure 1. Compared reactivity of phenylboronic acid (◆) and potassium trifluoro(phenyl)borate (●) in 1,4-addition to enamide **2a**.

went to completion in less than one hour. In comparison, when phenylboronic acid was used, the conversion reached a maximum of 62%. In both cases, *N*-benzyl-3-phenylbutanamide was obtained with identical optical purities (93% ee). This result may explain the use of higher number of equivalents of boronic acids compared to trifluoroborates in this reaction.

The induction period observed in the presence of potassium trifluoroborate derivatives might correspond to the in situ formation of either another more active rhodium catalyst or a different boron species, as already observed in other reactions with trifluoro(organo)-borates.[12a]

We tested the generality of the reaction by a variation of the Michael acceptors and potassium trifluoro(organo)borates (Table 2). Under optimized conditions

Table 2. 1,4-Addition of potassium aryltrifluoroborates to enamides

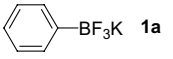
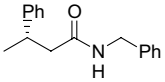
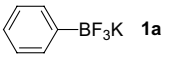
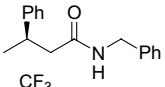
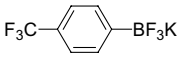
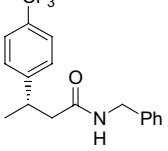
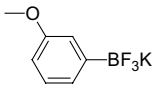
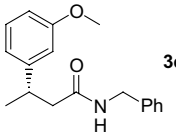
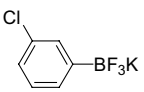
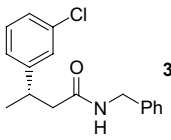
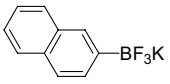
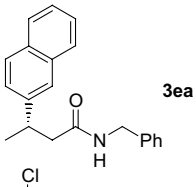
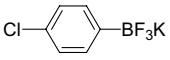
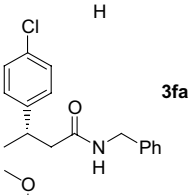
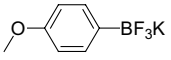
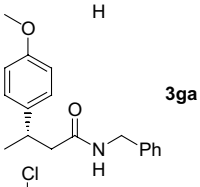
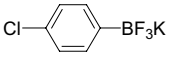
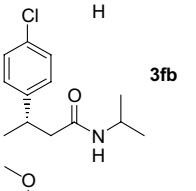
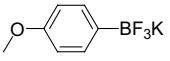
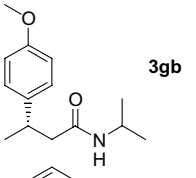
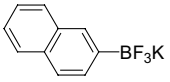
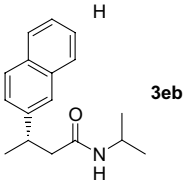
Entry	RBF_3K	Product	Yield[a] (%)	Ee[b] (%)
1	 **1a**	 **3aa**	86	93
2	 **1a**	 **3aa**	87	93[c]
3	 **1b**	 **3ba**	100[d]	91
4	 **1c**	 **3ca**	93	86
5	 **1d**	 **3da**	81	93

Table 2 (*continued*)

Entry	RBF_3K	Product	Yield[a] (%)	Ee[b] (%)
6	 **1e**	 **3ea**	100[d]	88
7	 **1f**	 **3fa**	91	94
8	 **1g**	 **3ga**	94	95
9	 **1f**	 **3fb**	97	92
10	 **1g**	 **3gb**	87	94
11	 **1e**	 **3eb**	100	95

[a] Isolated yield.
[b] Determined by HPLC using a chiral phase stationary column.
[c] Using (*S*)-Binap as chiral ligand.
[d] Reaction conducted with 3 equiv of aryltrifluoroborate.

several aryltrifluoroborates added with high efficiency on *N*-benzylcrotonamide **2a** affording 1,4-adducts with ee up to 95% (entries 1–8). From these results, it appeared that either electron withdrawing (entry 3) or even releasing substituents (entries 4 and 8) on the aryltrifluoroborate moiety are tolerated and seemed to have no influence on the enantioselectivity of this reaction. These results are in sharp constrast with those observed by Sakuma and Miyaura[7] where electron rich arylboronic acids reacted with low efficiency: the reaction between 4-methoxyphenylboronic acid and *N*-benzylcrotonamide **2a** affords only 50% yield of 1,4-adduct with low ee (77%).[7] *N*-Isopropylcrotonamide **2b** reacted equally well (entries 9–11). For example, reaction of trifluoro(4-methoxyphenyl)borate **1g** with *N*-isopropylcrotonamide **2b** afforded the 1,4-addition adduct **3gb** in 87% yield and an enantiomeric excess of 95%.

From these preliminary results, potassium trifluoro(organo)borates appear to be very efficient partners in rhodium-catalyzed enantioselective 1,4-additions to enamides. These highly stable and easily prepared boron derivatives seem to be more reactive than the boronic acid analogues. It is also noteworthy that the reaction proceeds without the addition of a base with nearly quantitative yields and good to excellent enantiomeric excesses whatever the electronic properties of the aryltrifluoroborate. Indeed the use of potassium trifluoro(organo)borates in such carbometallation processes proved to be superior than boronic acids. Further studies are underway to extend this reaction to other substrates and mechanistic investigations are in progress.

Acknowledgements

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14. General procedure for the 1,4-addition of potassium trifluoro(organo)borates on α,β-unsaturated amides (entry 4): A mixture of potassium trifluoro(3-methoxyphenyl)borate (198 mg, 1 mmol), *N*-benzylbut-2-enamide (87.5 mg, 0.5 mmol), $Rh(cod)_2PF_6$ (7.0 mg, 3 mol%) and (*R*)-Binap (10.3 mg, 3.3 mol%) were charged in a flask then a degassed toluene/water mixture (2:0.5 mL) was added at room temperature. The flask was placed in a preheated oil bath at 105–110 °C until completion of the reaction (followed by GC analysis). Direct purification by silica gel chromatography afforded **3ca** as a white solid (104 mg, 93% yield). Mp = 76 °C. R_f (cyclohexane/ethyl acetate: 3/2) = 0.30. ^{1}H NMR (200 MHz, $CDCl_3$, δ) 1.33 (3H, d, $J = 7.0$ Hz, CH_3), 2.47 (2H, d, $J = 7.6$ Hz, CH_2CO), 3.32 (1H, app hex, $J = 7.0$ Hz, CHAr), 3.79 (3H, s, OCH_3), 4.29 (1H, dd, $J = 5.8$ Hz, $J = 14.8$ Hz, NCH_2), 4.41 (1H, dd, $J = 5.8$ Hz, $J = 14.8$ Hz, NCH_2), 5.56 (1H, br s, NH), 6.75–6.86 (3H, m, H_{Ar}), 7.06 (2H, dd, $J = 7.0$ Hz, $J = 2.6$ Hz, H_{Ar}), 7.19–7.31 (4H, m, H_{Ar}). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 21.8, 37.1, 43.4, 45.7, 55.1, 111.6, 112.8, 119.1, 127.3, 127.5, 128.6, 129.6, 138.1, 147.5, 159.8, 171.4. MS (IE, m/z): 283 (43%, $M^{+\cdot}$), 148 (100%), 91 (48%). $[\alpha]_D^{28}$ +35.3 (*c* 0.8, $CHCl_3$). HPLC (Chiralcel OD-H, *n*-hexane/propan-2-ol: 95/5, 1 mL min^{-1}): $t_1 = 54.5$ min, $t_2 = 59.9$ min. $C_{18}H_{21}NO_2$ calcd: C: 76.29; H: 7.47; N: 4.94; found: C: 76.17; H: 7.51; N: 4.87.