Efficient Access to Alanine Derivatives by 1,4-Additions of Potassium Trifluoro(organo)borates

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Potassium trifluoro(organo)borates, highly stable and easily prepared organoboron derivatives, were able to react with a great variety of dehydroamino esters. This reaction, catalyzed by rhodium complexes, allowed the formation of alanine derivatives bearing a great variety of amino protecting groups in good to high yields.

Introduction

α-Amino acids are important building blocks, particularly for combinatorial chemistry and drug discovery. A wide range of approaches is available for the synthesis of such compounds,[1] the most important being the amination of α-halo acids, the Strecker synthesis, multicomponent Ugi or Petasis condensations and catalytic hydrogenations of dehydroamino acids. Despite the great variety of well-known and tried methods, the development of new general synthetic protocols for α-amino acids is still an active field.

The synthesis of α-amino acids involving carbon−carbon bond formation by Michael addition to dehydroamino acid derivatives is an alternative that has only been explored to limited extent.[2,3] Real improvements in this strategy have recently been achieved with the 1,4-addition of soft organometallic reagents catalyzed by rhodium(I).[4] Li et al. first reported the use of organostannanes[5] and an example of the use of an organosilane[6] in the carbometallation of α-phthalimidoacrylate derivatives. Organoboronic acids have also proven to be suitable for this reaction[7] avoiding the use of toxic tin reagents. Two examples of an asymmetric version have recently been developed by Reetz[8] and Frost.[9] With the exception of the latter, all the reported reactions concerned the carbometallation of electron-deficient α-phthalimidoacrylate derivatives.

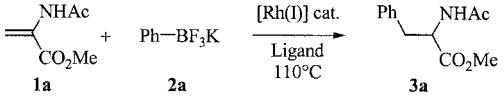
We have been involved for several years in the development of potassium trifluoro(organo)borates[10] in transition metal-catalyzed reactions, mainly with respect to cross-coupling reactions in the presence of palladium complexes[11] and asymmetric 1,4-additions catalyzed by chiral rhodium complexes.[12] These boron ate complexes offer several advantages over trivalent organoboronic acids and their derivatives: higher stability towards air and water, ease of preparation and purification, and generally higher reactivity in many processes.[10]

In this paper, we wish to report the development of a highly effective 1,4-addition of potassium trifluoro(organo)-borates to various dehydroamino esters.

Results and Discussion

Initially, we examined the 1,4-addition, catalyzed by rhodium complexes, of potassium trifluoro(phenyl)borate with dehydroamino ester **1a**, which is known to be a poor Michael acceptor (Table 1). As a rhodium source, cationic $[Rh(cod)_2]PF_6$ was selected because it has proven to be highly effective in carbometallation processes of potassium trifluoro(organo)borates with enones[12] and esters.[13]

Table 1. Optimization of the reaction conditions[a]



1a 2a 3a

Entry	Solvent	Ligand (3 mol %)	Time [h]	Conversion[b]
1	water	–	18	100 (40)
2	toluene/H_2O[c]	–	18	50
3	dioxane/H_2O[c]	–	18	50
4	toluene/H_2O[c]	PPh_3	1	23
5	toluene/H_2O[c]	PCy_3	1	40
6	toluene/H_2O[c]	dppp	1	100 (94)
7	toluene/H_2O[c]	dppf	1	80
8	toluene/H_2O[c]	dppb	1	80

[a] Reactions were conducted with 0.5 mmol of dehydroamino ester and 2 equiv. of RBF_3K, in the presence of 3 mol % of $[Rh(cod)_2]PF_6$/dppp at 110 °C. [b] Determined by GC analysis. Between parentheses, isolated yields. [c] Volumetric proportions 20:1.

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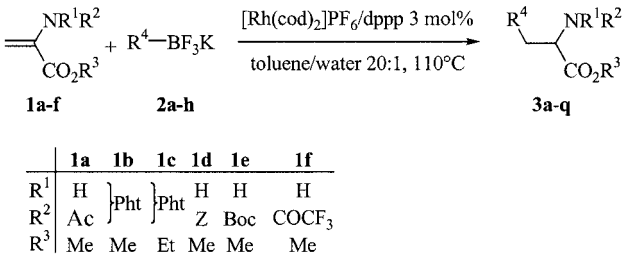
When the dehydroamino ester **1a** was allowed to react with potassium trifluoro(phenyl)borate **2a** in the presence of a catalytic amount of $[Rh(cod)_2][PF_6]$ (3 mol %) without additional ligands under refluxing conditions in water (Table 1, entry 1), the Michael addition adduct **3a** was isolated in 40 % yield. Although complete consumption of the starting material was observed, yields were low due to decomposition of the substrate. The use of a cosolvent in the reaction medium did not greatly improve the yields (entries 2 and 3). No reaction was observed without the catalyst, but the combination of rhodium(I) and a phosphane ligand resulted in an acceleration of the conjugate addition. Different ligands were tested (entries 4 to 8) and monophosphanes like triphenylphosphane and tricyclohexylphosphane resulted in incomplete reactions: hydrodeboration of potassium trifluoro(organo)borates was the major byproduct. In contrast, diphosphanes ligands (entries 6 to 8) gave higher conversions, the most efficient ligand being diphenylphosphanylpropane (entry 6). Under these conditions, the 1,4-addition adduct **3a** was obtained with complete conversion of the starting material and isolated in a 94 % yield.

Various organoboron reagents and dehydroamino esters were then examined under these optimized reaction conditions (Scheme 1).

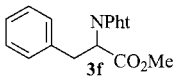
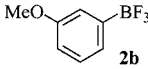
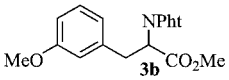
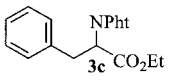
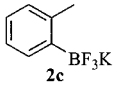
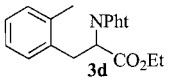
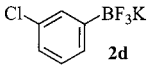
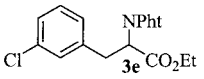
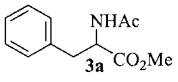
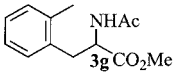
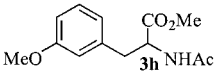
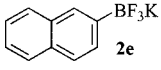
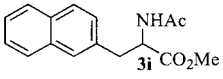
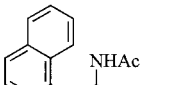
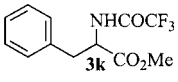
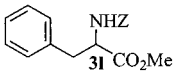
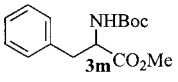
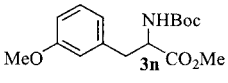


Scheme 1. The synthesis of arylalanine derivatives from 1,4-additions of potassium trifluoro(organo)borates

The generality of these optimized conditions was first tested on the very reactive α-phthalimidoacrylate derivative **1b** by varying the substituent on the potassium trifluoro(organo)borate. The synthesis of substrate **1b** was realized by the Trost α-addition reaction[14] of acetylenic carboxylic acid derivatives. As shown in the table (Table 2, entries 1 to 5), a great variety of potassium aryltrifluoroborates were able to carbometallate this type of dehydroamino ester, with good to high efficiency. The nature of the substituents (electron-deficient or -releasing) does not seem to influence the course of the Michael addition greatly. Reaction times were largely below one hour, even with the *ortho*-substituted organoborate derivative **2c** (entry 4). These results compete with and even surpass previously reported 1,4-additions on this substrate in terms of higher yields and shorter reaction times.[7,8,11]

The scope of this carbometallation was further extended by varying the nature of the amino protecting group (entries 6 to 14). Thus the standard protecting groups used in peptide synthesis such as acetyl (Ac), *tert*-butyloxycarbonyl (Boc), benzyloxycarbonyl (Z), or trifluoroacetyl ($COCF_3$), were tested under our conditions. To the best of our knowledge, this is the first time that these protecting groups have been tested in such catalytic 1,4-addition of organometallic reagents on this class of substrate, perhaps because of their lower reactivity than α-phthalimidoacrylate derivatives **1b** (Table 2). We were pleased to find that the various protecting groups were not only tolerated under these reaction conditions but allowed access to a large variety of α-amino esters in good yields. Particularly, Boc and Z protecting groups were not removed under these conditions allowing

Table 2. Arylalanine derivatives by rhodium-catalyzed conjugated additions[a]

Entry	Substrate	R-BF_3K	Product	Yield (%)
1	**1b**	**2a**	 **3f**	94
2	**1b**	 **2b**	 **3b**	90
3	**1c**	**2a**	 **3c**	95
4	**1c**	 **2c**	 **3d**	98
5	**1c**	 **2d**	 **3e**	75
6	**1a**	**2a**	 **3a**	94
7	**1a**	**2c**	 **3g**	85
8	**1a**	**2b**	 **3h**	78
9	**1a**	 **2e**	 **3i**	82
10	**1a**	 **2f**	 **3j**	74
11	**1f**	**2a**	 **3k**	94
12	**1d**	**2a**	 **3l**	78
13	**1e**	**2a**	 **3m**	70
14	**1e**	**2b**	 **3n**	76

[a] Reactions were conducted with 0.5 mmol of dehydroamino ester **1** and 2 equiv. of RBF_3K **2**, in the presence of 3 mol % of $[Rh(cod)_2]PF_6$/dppp, in toluene/water, 20:1, at 110 °C.

the formation of protected α-amino acids that are attractive for synthesis. Methyl *N*-(trifluoroacetylamino)acrylate (**1f**) was very reactive (with a reactivity similar to that of **1b**) and allowed the formation of adduct **3k** in a high yield (94 %). Once again, this reaction was very efficient as evident from the short reaction time, proving the high reactivity of potassium trifluoro(organo)borates in carbometallative processes catalyzed by rhodium.

We were also interested in testing the readily available, air and water stable, potassium alken-1-yltrifluoroborate under identical conditions. Preliminary results are summarized in Table 3.

Table 3. The Michael addition of potassium alken-1-yltrifluoroborate derivatives[a]

Entry	Substrate	R-BF_3K	Product	Yield (%)
1	**1a**	**2g**	**3o**	63
2	**1b**	**2g**	**3p**	63[b]
3	**1a**	**2h**	**3q**	55[c]

[a] Reactions were conducted with 0.5 mmol of dehydroamino ester **1** and 4 equiv. of RBF_3K **2**, in the presence of 3 mol % of $[Rh(cod)_2]PF_6$/dppp, in toluene/water, 20:1, at 110 °C. [b] Along with 32 % of 3,4-isomer. [c] Along with 30 % of 3,4-isomer.

Even if the carbometallation of potassium (alken-1-yl)trifluoroborates was not as efficient as that using aryl derivatives, potassium trifluoro[(*E*)-2-(4-methylphenyl)ethenyl]-borate (**2g**) added smoothly to dehydroamino ester derivatives affording alkenyl-substituted alanine derivatives in reasonable yields (entries 1−2). More particularly, potassium trifluoro(vinyl)borate (**2h**), a highly stable vinylating agent,[11b,11c] was able to add to methyl *N*-acetylaminoacrylate (**1a**) affording methyl 2-(acetylamino)pent-4-enoate (**3q**) in 55 % yield (entry 3), together with an isomerization product (26 %). Lower yields obtained with (alken-1-yl)trifluoroborates may be attributed to their higher tendency to be reduced under these reaction conditions, but also to the presence of isomers, due to the migration of the double bond. Further improvements to carbometallate potassium alken-1-yltrifluoroborate derivatives cleanly are underway.

The reactivities of phenylboronic acid and potassium trifluoro(phenyl)borate were also compared under these conditions for their 1,4-addition to dehydroamino ester **1a** (Figure 1). Under identical conditions, higher initial rates were observed for the 1,4-addition of phenylboronic acid, but the reaction stopped rapidly because of the competitive hydrodeboration of the boron reagent. On the other hand, using potassium trifluoro(phenyl)borate (**2a**), an induction period of around twenty minutes is observed before the formation of the conjugated adduct. After this initial period, potassium trifluoro(phenyl)borate reacted smoothly and quantitatively to afford *N*-acetylphenylalanine (**3a**) in a high yield. In this respect, the reactivity of potassium trifluoro(organo)borate is unusual and further studies are underway to understand this difference in reactivity observed with these two boron species. The first step in this carbometallation process is believed to be the transmetallation of the organometallic partner with the rhodium(I) precursor,[15] the presence of an inductive period using potassium trifluoro(organo)borate may be due to the slow transmetallation of the boron reagent with the cationic rhodium catalyst. Furthermore, this period presumably corresponds to the generation of either a more reactive boron reagent or another active catalyst precursor. We are currently working on this process in order to identify the active species.

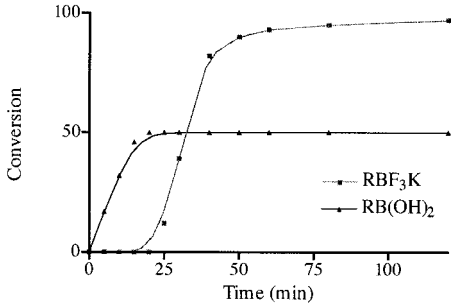


Figure 1. A comparison of the reactivity of $PhBF_3K$ and $PhB(OH)_2$ with **1a**

Conclusion

We have shown that potassium trifluoro(organo)borates were able to carbometallate dehydroamino esters with high efficiency in the presence of a rhodium catalyst. This reaction allowed the formation of various alanine derivatives in good to high yields (up to 98 %). In contrast to similar reactions previously described, a variety of amino acid protecting groups are tolerated under the reaction conditions used. Thanks to their high reactivity in transition metal-catalyzed reactions and greater stability than other organometallic reagents, potassium trifluoro(organo)borate appears to be a promising alternative as reagent for various reactions. We are currently working on an asymmetric version of this reaction.

Experimental Section

General Remarks: ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 200 or Avance 400 instruments; chemical shifts (δ) are reported in ppm relative to Me_4Si; coupling constants (*J*) are reported in Hz and refer to apparent peak multiplicities. ^{11}B and ^{19}F NMR spectra were recorded on a Bruker Avance 400 instrument at 128 and 376 MHz respectively using $BF_3{\cdot}Et_2O$ (^{11}B NMR spectra) and $CFCl_3$ (^{19}F NMR spectra) as an internal reference. Mass spectra were determined on a Ribermag instrument. High resolution mass spectra were performed on a Varian MAT311 at the Université Pierre et Marie Curie (Paris). Elemental analyses were done at the Regional Service of Microanalysis (Université Pierre et Marie Curie). Thin layer chromatography was carried out

on silica-gel plates (Merck F_{254}), spots were detected with UV light and revealed with $KMnO_4$ solution.
GC analyses were performed on a Hewlett−Packard instrument equipped with a J&W Scientific DB-1701 capillary column (15 m, ϕ = 0.25 μm), using an ionization flame detector: program A: 70 °C for 1 min then 20 °C/min up to 210 °C, program B: 150 °C for 1 min then 20 °C/min up to 250 °C, program C: isotherm 250 °C. $[Rh(cod)_2]PF_6$ was prepared according to published procedures.[16] Toluene was distilled from CaH_2.

Typical Procedure for the 1,4-Addition of Potassium Aryl- and Alken-1-yltrifluoroborates to Dehydroamino Esters: A mixture of dehydroamino ester (0.5 mmol), potassium trifluoro(organo)borate (2 equiv.), $[Rh(cod)_2]PF_6$ (7.0 mg, 3 mol %), and dppp (6.2 mg, 3 mol %) were charged into a flask under argon, followed by addition of a degassed toluene/water mixture (2 mL/0.1 mL) at room temperature. The flask was placed in a preheated oil bath at 110−115 °C and the mixture was stirred until completion of the reaction (followed by GC analysis). Purification by silica gel chromatography (eluent: cyclohexane/ethyl acetate) afforded analytically pure products. Compounds **3a**,[17] **3c**,[18] **3f**,[19] **3g**,[20] **3h**,[21] **3i**,[22] **3j**,[22] **3k**,[23] **3l**,[24] **3m**,[25] and **3q**[26] show identical physical data to that previously reported in the literature.

Methyl 3-(3-Methoxyphenyl)-2-phthalimidopropanoate (3b): A yellow solid obtained in a 90 % yield (153 mg) according to the general procedure. R_f = 0.42 (cyclohexane/ethyl acetate, 4:1). m.p. 83 °C. CPG: t_R = 15.0 min (A). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.54 (dd, ^2J = 10.5, ^3J = 5.7 Hz, 1 H), 3.60 (dd, ^2J = 10.6, ^3J = 5.7 Hz, 1 H), 3.66 (s, 3 H), 3.77 (s, 3 H), 5.16 (dd, ^3J = 10.3, ^3J = 6.2 Hz, 1 H), 6.57−6.69 (m, 3 H), 7.07 (td, ^3J = 7.6, ^4J = 1.1 Hz, 3 H), 7.66−7.72 (m, 2 H), 7.73−7.80 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.6, 52.9, 53.1, 55.0, 112.7, 114.1, 121.1, 123.4, 129.5, 131.6, 134.1, 138.2, 159.6, 167.4, 169.3 ppm. MS (70 eV): *m*/*z* (%) = 339 (11) [$M^{+\cdot}$], 192 (100). $C_{19}H_{17}NO_5$ (339.34): calcd. C 67.25, H 5.05, N 4.13; found C 66.44, H 5.00, N 4.04.

Ethyl 3-(2-Methylphenyl)-2-phthalimidopropanoate (3d): A yellow solid obtained in a 98 % yield (165 mg) according to the general procedure. R_f = 0.30 (cyclohexane/ethyl acetate, 9:1). m.p. 72 °C. CPG: t_R = 12.3 min (B). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.26 (t, ^3J = 7.1 Hz, 3 H), 2.39 (s, 3 H), 3.50 (dd, ^2J = 14.5, ^3J = 11.1 Hz, 1 H), 3.64 (dd, ^2J = 14.5, ^3J = 5.2 Hz, 1 H), 4.25 (q, ^3J = 7.1 Hz, 2 H), 5.15 (dd, ^3J = 11.1, ^3J = 5.2 Hz, 1 H), 6.95−7.08 (m, 4 H), 7.66−7.72 (m, 2 H), 7.73−7.80 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 19.2, 32.3, 51.7, 62.0, 123.4, 125.9, 127.0, 129.6, 130.5, 131.6, 134.0, 134.9, 136.5, 167.4, 168.9 ppm. MS (70 eV): *m*/*z* (%) = 337 (6) [$M^{+\cdot}$], 190 (57), 144 (100). $C_{20}H_{19}NO_4$ (337.37): calcd. C 71.20, H 5.68, N 4.15; found C 71.29, H 5.71, N 4.04.

Ethyl 3-(3-Chlorophenyl)-2-phthalimidopropanoate (3e): A yellow solid was obtained in a 75 % yield (134 mg) according to the general procedure. R_f = 0.20 (cyclohexane/ethyl acetate, 9:1). m.p. 68 °C. CPG: t_R = 14.6 min (A). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.26 (t, ^3J = 7.1 Hz, 3 H), 3.50 (dd, ^2J = 14.5, ^3J = 10.6 Hz, 1 H), 3.55 (dd, ^2J = 14.5, ^3J = 5.8 Hz, 1 H), 4.25 (q, ^3J = 7.2 Hz, 2 H), 5.11 (dd, ^3J = 10.6, ^3J = 5.8 Hz, 1 H), 7.06−7.17 (m, 4 H), 7.67−7.72 (m, 2 H), 7.73−7.82 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 34.4, 54.1, 62.2, 123.6, 127.0, 127.1, 129.8, 131.6, 134.2, 138.9, 167.3, 168.5 ppm. MS (70 eV): *m*/*z* (%) = 357 (6) [$M^{+\cdot}$], 210 (100). $C_{19}H_{16}ClNO_4$ (357.79): calcd. C 63.78, H 4.51, N 3.91; found C 63.61, H 4.51, N 4.00.

Methyl 2-(*tert*-Butyloxycarbonylamino)-3-(3-methoxyphenyl)propanoate (3n): A colorless liquid was obtained in a 76 % yield (118 mg) according to the general procedure. R_f = 0.18 (cyclohexane/ethyl acetate, 9:1). t_R = 14.4 min (A). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 3.03 (dd, ^2J = 13.8, ^3J = 6.2 Hz, 1 H), 3.09 (dd, ^2J = 13.8, ^3J = 5.7 Hz, 2 H), 3.72 (s, 3 H), 3.78 (s, 3 H), 4.55−4.60 (m, 1 H), 4.97 (br. d, ^3J = 7.8 Hz, 1 H), 6.67 (d, ^4J = 1.7 Hz, 1 H), 6.71 (d, ^3J = 7.5 Hz, 1 H), 6.78 (dd, ^3J = 8.2, ^4J = 1.7 Hz, 1 H), 7.20 (app. t, ^3J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.2, 38.3, 52.2, 54.3, 55.1, 79.9, 112.4, 114.9, 121.6, 129.5, 137.5, 155.0, 159.6, 172.3 ppm. MS (CI: NH_3) = 327 [M + NH_4]$^+$, 310 [M + H]$^+$, 271 [M − C_4H_8 + NH_4]$^+$, [M − C_4H_8 + H]$^+$. HRMS calcd. for $C_{16}H_{24}NO_5$: 310.1654; found 310.1650.

Methyl 2-Acetylamino-5-(*p*-tolyl)pent-4-enoate (3o): A colorless liquid was obtained in a 63 % yield (82 mg) according to the general procedure. R_f = 0.46 (cyclohexane/ethyl acetate, 2:3). t_R = 12.4 min (A). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.01 (s, 3 H), 2.33 (s, 3 H), 2.64−2.73 (m, 2 H), 3.75 (s, 3 H), 4.73 (td, ^3J = 7.8, ^3J = 5.6 Hz, 1 H), 5.99 (dt, ^3J = 15.8, ^3J = 7.8 Hz, 1 H), 6.10 (d, ^3J = 5.8 Hz, 1 H), 6.42 (d, ^3J = 15.8 Hz, 1 H), 7.10 (d, ^3J = 8.1 Hz, 2 H), 7.22 (d, ^3J = 8.1 Hz, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.1, 23.1, 35.8, 52.0, 52.4, 122.3, 126.1, 129.2, 134.0, 137.4, 1 69.7, 172.3 ppm. MS (70 eV): *m*/*z* (%) = 261 (4) [$M^{+\cdot}$], 202 (75), 143 (100). HRMS calcd. for $C_{15}H_{20}NO_3$: 262.1443; found 262.1437.

Methyl 2-Phthalimido-5-(*p*-tolyl)pent-4-enoate (3p): A colorless liquid obtained in a 45 % yield (59 mg) according to the general procedure. R_f = 0.40 (cyclohexane/ethyl acetate, 4:1). t_R = 16.1 min (C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.27 (s, 3 H), 3.12−3.17 (m, 2 H), 3.77 (s, 3 H), 5.01 (dd, ^3J = 9.0, ^3J = 6.8 Hz, 1 H), 6.04 (dt, ^2J = 15.8, ^3J = 7.4 Hz, 1 H), 6.38 (d, ^3J = 15.8 Hz, 1 H), 7.03 (d, ^3J = 8.1 Hz, 2 H), 7.12 (d, ^3J = 8.1 Hz, 2 H), 7.70−7.82 (m, 2 H), 7.83−7.89 (m, 2 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.2, 32.7, 49.4, 51.9, 123.6 (3 C), 126.1 (2 C), 129.2 (2 C), 131.7, 133.5, 134.2 (2 C), 134.7, 137.3, 167.3, 169.4 ppm. MS (70 eV): *m*/*z* (%) = 261 (4) [$M^{+\cdot}$], 202 (75), 143 (100). HRMS calcd. for $C_{21}H_{20}NO_4$: 350.1392; found 350.1390.

Typical Procedure for the Preparation of Potassium Trifluoro(organo)borates: A solution of the Grignard reagent [prepared from the aryl bromide (200 mmol) and magnesium (200 mmol) in anhydrous THF or diethyl ether (150 mL)] was added dropwise (keeping the internal temperature below −60 °C) to a mechanically stirred solution of trimethoxyborane (34.3 mL, 300 mmol, 1.5 equiv.) in anhydrous THF (150 mL). The solution was placed at room temperature (ca. 25°C) until the internal temperature reached 0 °C and the resulting suspension was poured into a saturated solution of KHF_2 (85.9 g, 1.1 mol, 5.5 equiv.; ***Caution***: use a Teflon vessel!) in water (concentration of nearly 5 M). After 5 min of stirring at room temperature the solvent was removed under vacuum (bath temperature: 50 °C) and the resulting solid was thoroughly dried under high vacuum (0.1 Torr; the solid has to be completely dried). It was then extracted four times with acetone (100 mL each time), the solution was filtered, and the solvents evaporated (if the solid is not completely dried, this procedure has to be repeated to avoid the presence of impurities). The powder was dissolved in a minimum amount of acetone, the solution was filtered and precipitation of the salt was accomplished by the addition of diethyl ether (using 3 to 5 times the amount of acetone). The white solid was filtered, washed thoroughly with diethyl ether, and dried under vacuum. In the ^{13}C NMR spectrum, the signal corresponding to the carbon atom in the α-position of the tetravalent boron atom was generally not observed. Potassium trifluoro(organo)borates **2a**,[27,11c]

2f,[27,11c] **2g**,[11b,11c] and **2h**[28] were prepared according to published procedures.

Potassium Trifluoro(3-methoxyphenyl)borate (2b):[29] A white solid was obtained from 1-bromo-3-methoxybenzene (200 mmol) according to the general procedure in an 85 % yield (35.6 g), m.p. 188 °C (acetone/diethyl ether).

Potassium Trifluoro(2-methylphenyl)borate (2c):[29] A white solid was obtained from 1-bromo-3-methoxybenzene (200 mmol) according to the general procedure in a 78 % yield (31.0 g), m.p. 232 °C (acetone/diethyl ether).

Potassium (3-Chlorophenyl)trifluoroborate (2d): A white solid was obtained from 1-bromo-3-chlorobenzene (200 mmol) according to the general procedure in a 73 % yield (32.0 g), m.p. 176 °C (acetone/diethyl ether). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 7.04−7.13 (m, 2 H), 7.37−7.43 (m, 2 H) ppm. ^{13}C NMR (50 MHz, [D$_6$]acetone): δ = 125.9, 129.0, 130.7, 132.2, 133, 1 ppm. ^{11}B NMR (128 MHz, [D$_6$]acetone): δ = 6.5 (q, J = 52 Hz) ppm. ^{19}F NMR (376 MHz, [D$_6$]acetone): δ = −145.5 (br. q, $J \approx$ 56 Hz).

Potassium Trifluoro(naphth-2-yl)borate (2e): A white solid was obtained from 2-bromonaphthalene (121 mmol) according to the general procedure in a 71 % yield (20.1 g), m.p. > 260 °C (acetone/diethyl ether). ^{1}H NMR (200 MHz, [D$_6$]acetone): δ = 7.33−7.45 (m, 2 H), 7.67−7.86 (m, 4 H), 8.11 (s, 1 H) ppm. ^{13}C NMR (50 MHz, [D$_6$]acetone): δ = 125.1, 125.4, 126.3, 128.2, 128.8, 131.2, 131.6, 133.8, 134.4 ppm. ^{11}B NMR (128 MHz, [D$_6$]acetone): δ = 7.41 (br) ppm. ^{19}F NMR (376 MHz, [D$_6$]acetone): δ = −142.1 (br. q) ppm.

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[1] For reviews on the synthesis of α-amino acids see: [1a] R. M. Williams, *Synthesis of Optically Active α-Amino Acids*, Pergamon Press, Oxford, **1989**. [1b]R. O. Duthaler, *Tetrahedron* **1994**, *50*, 1539−1650. [1c] D. Seebach, A. R. Sting, M. Hoffmann, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2708−2748. [1d] C. Cativiela, M. D. Diaz-de-Villegas, *Tetrahedron: Asymmetry* **1998**, *9*, 3517−3599. [1e] K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013−3028.

[2] For some examples of 1,4-additions of Grignard reagents see: [2a] C. Cardellichio, V. Fiandanese, G. Marchese, F. Naso, L. Ronzini, *Tetrahedron Lett.* **1985**, *26*, 4387−4390. [2b] C. Cativiela, M. D. Diaz-de-Villegas, J. A. Galvez, *Can. J. Chem.* **1992**, *70*, 2325−2328. [2c] P. A. Lander, L. S. Hegedus, *J. Am. Chem. Soc.* **1994**, *116*, 8126−8132. [2d] G. Cardillo, L. Gentilucci, A. Tolomelli, C. Tomasini, *Tetrahedron* **1999**, *55*, 6231−6242.

[3] For examples of conjugate radical additions see: [3a] K. Goodall, A. F. Parsons, *Tetrahedron* **1996**, *52*, 6739−6758. [3b] K. Goodall, A. F. Parsons, *Tetrahedron Lett.* **1997**, *38*, 491−494. [3c] S. R. Baker, A. F. Paesons, M. Wilson, *Tetrahedron Lett.* **1998**, *39*, 2815−2818. [3d] R. SanMartin, B. Tavassoli, K. E. Walsh, D. S. Walter, T. Gallagher, *Org. Lett.* **2000**, *2*, 4051−4054. [3e] M. P. Sibi, Y. Asano, J. B. Sausker, *Angew. Chem. Int. Ed.* **2001**, *40*, 1293−1296. [3f] R. C. F. Jones, D. J. C. Berthelot, J. N. Iley, *Tetrahedron* **2001**, *57*, 6539−6555.

[4] For reviews on asymmetric 1,4-additions catalyzed by rhodium complexes see: [4a] T. Hayashi, *Synlett* **2001**, 879−887. [4b] T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829−2844.

[5] T. S. Huang, C. Li, *Org. Lett.* **2001**, *3*, 2037−2039.

[6] T. S. Huang, C. Li, *Chem. Commun.* **2001**, 2348−2349.

[7] C. J. Chapman, C. G. Frost, *Adv. Synth. Catal.* **2003**, *345*, 353−355.

[8] M. T. Reetz, D. Moulin, A. Gosberg, *Org. Lett.* **2001**, *3*, 4083−4085.

[9] C. J. Cristopher, K. J. Wadswoth, C. G. Frost, *J. Organomet. Chem.* **2003**, *680*, 206−211.

[10] Review: S. Darses, J. P. Genet, *Eur. J. Org. Chem.* **2003**, 4313−4327.

[11] [11a] S. Darses, J. P. Genet, J. L. Brayer, J. P. Demoute, *Tetrahedron Lett.* **1997**, *38*, 4393−4395. [11b] S. Darses, G. Michaud, J. P. Genet, *Tetrahedron Lett.* **1998**, *39*, 5045−5048. [11c] S. Darses, G. Michaud, J. P. Genet, *Eur. J. Org. Chem.* **1999**, 1875−1883. See also: [11d] R. A. Batey, T. D. Quach, *Tetrahedron Lett.* **2001**, *42*, 9099−9103. [11e] G. A. Molander, B. W. Katona, F. Machrouki, *J. Org. Chem.* **2002**, *67*, 8416−8423. [11f] G. A Molander, C.-S. Yun, M. Ribagorda, B. Biolatto, *J. Org. Chem.* **2003**, *68*, 5534−5539. [11g] G. A. Molander, B. Biolatto, *J. Org. Chem.* **2003**, *68*, 4302−4314.

[12] [12a] M. Pucheault, S. Darses, J. P. Genet, *Tetrahedron Lett.* **2002**, *43*, 6155−6157. [12b] M. Pucheault, S. Darses, J. P. Genet, *Eur. J. Org. Chem.* **2002**, 3552−3557.

[13] Unpublished results from our laboratory.

[14] B. M. Trost, G. R. Dake, *J. Am. Chem. Soc.* **1997**, *119*, 7595−7596.

[15] T. Hayashi, M. Takahashi, Y. Takaya, M. Ogasawara, *J. Am. Chem. Soc.* **2002**, *124*, 5052−5058.

[16] [16a] R. R. Schrock, J. A. Osborn, *J. Am. Chem. Soc.* **1971**, *93*, 2397−2407. [16b] R. R. Schrock, J. A. Osborn, *J. Am. Chem. Soc.* **1971**, *93*, 3089−3090.

[17] N. Agular, A. Moyano, M. A. Pericàs, A. Riera, *Synthesis* **1998**, 313−316.

[18] W. J. Greenlee, E. D. Thorsett, *J. Org. Chem.* **1981**, *46*, 5351−5353.

[19] R. D. Larsen, R. A. Reamer, E. G. Corley, P. Davis, E. J. J. Grabowski, P. J. Reider, I. Shinkai, *J. Org. Chem.* **1991**, *56*, 6034−6038.

[20] C. Cardellicchio, V. Fiandanese, G. Marchese, F. Naso, L. Ronzini, *Tetrahedron Lett.* **1985**, *26*, 4387−4390.

[21] T. V. RajanBabu, T. A. Ayers, G. A. Halliday, K. K. You, J. C. Calabrese, *J. Org. Chem.* **1997**, *62*, 6012−6028.

[22] M. J. Burk, J. E. Feaster, W. A. Nugent, R. L. Harlow, *J. Am. Chem. Soc.* **1993**, *115*, 10125−10138.

[23] M. G. Constantino, P. Losco, *J. Org. Chem.* **1989**, *54*, 681−683.

[24] M. Ambazhagan, T. T. Reddy, S. Rajappa, *J. Chem. Soc., Perkin Trans. 1* **1997**, *11*, 1623−1628.

[25] P. Lopez-Serrano, M. A. Wegman, F. Rantwijk, R. A. Sheldon, *Tetrahedron: Asymmetry* **2001**, *12*, 235−240.

[26] N. J. Turner, G. M. Whitesides, *J. Am. Chem. Soc.* **1989**, *111*, 624−627.

[27] E. Vedejs, S. C. Fields, R. Hayashi, S. R. Hitchcock, D. R. Powell, M. R. Schrimpf, *J. Am. Chem. Soc.* **1999**, *121*, 2460−2470.

[28] N. A. Petasis, A. K. Yudin, I. A. Zavialov, G. K. S. Prakash, G. A. Olah, *Synlett* **1997**, 606−608.

[29] G. A. Molander, B. Biolatto, *Org. Lett.* **2002**, *4*, 1867−1870.

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