Potassium Organotrifluoroborates in Rhodium-Catalyzed Asymmetric 1,4-Additions to Enones

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Dedicated to Professor Marc Julia on the occasion of his 80th birthday

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Potassium organotrifluoroborates, highly stable organoboron derivatives, participate in asymmetric 1,4-additions to enones. This reaction, catalyzed by cationic rhodium(I) complexes chelated with binap, MeO-biphep or josiphos ligand, affords 1,4-adducts with high yields and enantioselectivities of up to 99%. Careful study of the reaction parameters shows the high sensitivity of the reaction to temperature, solvent and the amount of water cosolvent.

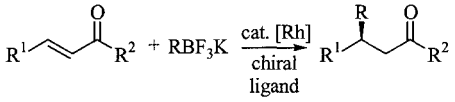
Introduction

The transition-metal catalyzed asymmetric Michael addition is a new synthetic tool in organic synthesis for making carbon-carbon bonds.[1] This reaction has become increasingly important with the recent development of the catalytic conjugate addition of organometallic reagents. One major advance is the use of organozinc compounds in the addition to α,β-unsaturated substrates. This reaction is efficiently catalyzed by copper(I) complexes containing chiral ligands. In particular, the addition of diethylzinc to enones has provided an opportunity for the development of a large variety of chiral ligands. These systems generally allow the efficient and enantioselective transfer of an alkyl group to the Michael acceptor, although the introduction of an sp^2 center is still a challenge.

In 1997, Miyaura et al.[2] showed that arylboronic acids can add efficiently to Michael acceptors in the presence of a rhodium(I) catalyst and water as cosolvent. With the use of a binap chiral ligand associated with rhodium(I), the Hayashi and Miyaura groups[3] have developed an asymmetric version of the Michael addition of organoboron compounds. Extensions of this reaction[4] include the 1,4-addition of aryl- and alkenylboronic acids or boroxines to enones,[3,5] α,β-unsaturated esters,[6] amides,[7] phosphonates[8] and nitroalkenes.[9] The use of other chiral ligands like amidomonophosphanes[10] or binol-based diphosphonites[11] has also been reported. Another interesting feature of this reaction is that it can be conducted very efficiently in water as the only solvent.[12,13] However, one drawback is the use of large excesses of boronic acids (generally 5 equiv.) to achieve high yields[3,4,14] because of undesirable reduction of the organoboron partner. Moreover, the preparation and purification of some boronic acids is tremendously difficult[15] and many of them are air and moisture sensitive. Thus, it appeared attractive to use other boron reagents in the asymmetric 1,4-addition to Michael acceptors.

We, and others, have recently shown that potassium organotrifluoroborates (RBF_3K) are efficient reagents in palladium-catalyzed cross-coupling reactions with arenediazonium salts,[16] iodonium salts[17] and aryl halides and triflates.[18] Moreover, Batey et al.[19] have shown that these reagents participate in achiral rhodium-catalyzed 1,4- and 1,2-additions to enones and aldehydes. Potassium organotrifluoroborates present major advantages over other organoboron derivatives: they are readily prepared in high yields and purities,[16c,20] (isolation of boronic acid is not necessary), very easily purified and can be stored indefinitely without any precaution.

In this paper, we wish to report the development of a catalytic and asymmetric version of the 1,4-addition of the valuable aryl- and alkenyltrifluoroborates to enones[21] (Scheme 1).



Scheme 1

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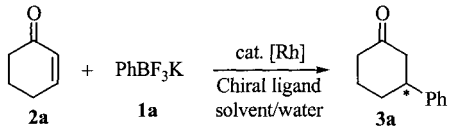
Results and Discussion

In order to achieve high yields and enantioselectivities in this reaction, we studied various parameters: catalyst precursor, solvent, chiral ligand, presence of water and temperature. As a reaction model, the 1,4-addition of potassium phenyltrifluoroborate (**1a**) to cyclohexenone (**2a**) was chosen (Scheme 2).



Scheme 2

First of all, using the conditions described by Miyaura and Hayashi[3] for the enantioselective 1,4-addition of organoboronic acids to enones (dioxane/H_2O, [Rh(acac)(C_2H_4)$_2$], Binap, 100 °C), only traces of the adduct **3a** were observed (Table 1, entry 1). Another neutral rhodium(I) complex showed similar behavior (entry 2). It was only when cationic rhodium(I) complexes were used that quantitative conversions were achieved (entries 3−6) although the enantioselectivities, as determined by chiral-phase HPLC (Daicel Chiralcel AS-H), were rather poor, ranging from 15 to 34%.

Table 1. Effect of the catalyst precursor[a]

Entry	Catalyst	Time (h)	Conv.[b] (%)	*e.e.*[c] (%)
1	[Rh(acac)(C_2H_4)$_2$]	24	1	–
2	[RhCl(cod)]$_2$	24	3	–
3	[Rh(cod)$_2$][OTf]	4	100	15
4	[Rh(cod)$_2$][BF_4]	1−2	100	20
5	[Rh(cod)$_2$][PF_6]	1−2	100	31
6	[Rh(cod)$_2$][ClO_4]	1−2	100	34

[a] Reaction conducted with 0.5 mmol of **2a** and 2 equiv. of **1a** in dioxane/water (10:1), in the presence of 3 mol % catalyst and 3.3 mol % (*R*)-binap at 105−110 °C. [b] Conversion determined by GC. [c] Determined by HPLC: Chiralcel AS-H; (*R*) configuration.

Such an influence of the catalyst precursor was not observed in the Miyaura−Hayashi reaction, where neutral and cationic catalyst precursors gave similar results in terms of yields and enantioselectivities.[3,6b,7b] In order to increase the optical purity of phenylcyclohexanone (**3a**), a screening of solvents was conducted using [Rh(cod)$_2$][PF_6] as catalyst precursor in the presence of water (Table 2).

As we can see from this table the solvent has a major influence on the enantioselectivities, with conversions being generally quantitative. Very low *ee*'s were obtained in polar solvents (entries 4 and 5) or in protic ones (entries 2 and 3). Higher enantioselectivities were achieved in aprotic and non-chelating solvents like toluene or heptane. In the former, very high *ee*'s were observed (98%). In solvents such as dioxane or chlorobenzene optical purities were quite low.

Table 2. Influence of the solvent[a]

Entry	Solvent	Time (h)	Conv.[b] (%)	*ee*[c] (%)
1	Dioxane	2	100	31
2	MeOH	4	80	13
3	*i*PrOH	20	100	50
4	CH_3CN	20	100	10
5	DMF	1	100	2
6	Toluene	2	100	98
7	Heptane	4	85	69
8	PhCl	1	100	35

[a] Reaction conducted with 0.5 mmol of **2a** and 2 equiv. of **1a** in solvent/water (10:1), in the presence of 3 mol % [Rh(cod)$_2$][PF_6] and 3.3 mol % (*R*)-binap at 105−110 °C. [b] Conversion determined by GC. [c] Determined by HPLC: Chiralcel AS-H; (*R*) configuration.

The presence of water is also crucial for this reaction: in its absence the reaction is very slow and the asymmetric induction too (Figure 1). An increase in the amount of water is accompanied by an increase of the *ee*, and the 1,4-addition adduct is formed in quantitative yields. This influence of the water content of the reaction medium is very different from Miyaura−Hayashi 1,4-additions of organoboronic acids, where water only influences the yields and not the enantiomeric excesses.[4]

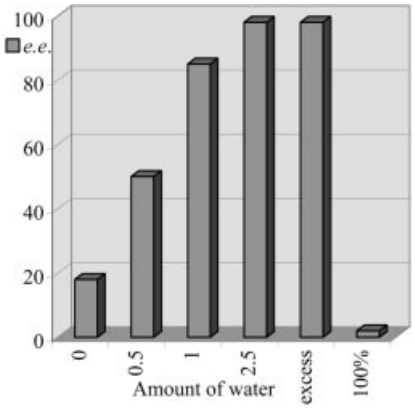
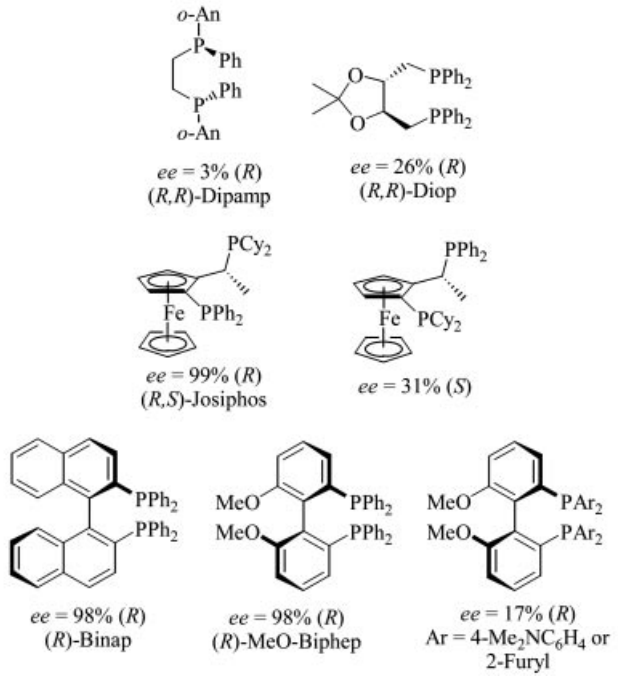


Figure 1. Influence of the amount of water

Using strictly one equivalent of water per boron, we observed large variations of the enantioselectivities (from 80 to 98%) in different systems. This can be explained by the azeotrope mixture formed between water and toluene which results in a rapid diminution of the water content in the medium before the completion of the 1,4-addition. Thus, the value of one equivalent of water per boron is critical for the process but is difficult to maintain during the reaction. For practical purposes one should therefore use an excess of water compared to boron reagent, typically a 10:1 mixture of toluene/water. It is noteworthy that excess water

slows the reaction down and in pure water no asymmetric induction was observed.

We next turned our attention to the influence of the chiral diphosphane ligand in the present 1,4-addition of potassium phenyltrifluoroborate (**1a)** to cyclohexenone (**2b**; Scheme 3). All reactions were conducted in the presence of $[Rh(cod)_2][PF_6]$ with different bidentate ligands in toluene/water at 100 °C. In all cases quantitative conversions were observed within 1 or 2 hours.



Scheme 3. Influence of the chiral ligand in the 1,4-addition of **1a** to **2a**

Many tested ligands that are currently and efficiently used in asymmetric hydrogenations or other asymmetric reactions, such as diop[22] or dipamp,[23] resulted in poor enantiofacial discriminations. However, the use of atropisomeric ligands like binap[24] or MeO-biphep[25] afforded 1,4-adduct **3a** with high and similar enantiomeric excesses (98%). Concerning MeO-biphep derivatives, it is interesting to note that the electronic properties of the aryl substituent on the phosphorous atom play a crucial role in the enantiofacial recognition: low *ee*'s were obtained with 4-dimethylaminophenyl or 2-furyl derivatives. Ferrocenyl ligands also show interesting levels of enantioselectivity; in particular, with josiphos[26] as ligand very high *ee*'s were achieved.

Finally, the reaction temperature is also very important: 1,4-additions conducted below 100 °C (bath temperature) only afford the racemic product. Thus, it appears that high yields and enantiomeric excesses can be achieved in the Michael addition of potassium phenyltrifluoroborate (**1a**) to cyclohexenone (**2a**) using $[Rh(cod)_2][PF_6]$[27] chelated with atropisomeric ligands like binap and MeO-biphep, or chiral planar ligands like josiphos, as catalytic system, in a toluene/water mixture as solvent, conducting the reaction at temperatures above 100 °C. These optimized conditions[28] were applied to various enones and potassium aryl- and alkenyltrifluoroborates, using binap as chiral ligand (Table 3).

Under standard conditions, potassium phenyltrifluoroborate **1a** adds very efficiently to different enones (Table 3, entries 1−6) affording the 1,4-adducts in quantitative yields and with high enantiomeric excesses. The size of the ring of cyclic enones does not seem to have any influence on the reactivity or on the asymmetric induction (entries 1−4), and linear enones react equally well (entries 5 and 6). Each time very short reaction times were observed (below 1 hour). Under the present conditions, phenylboronic acid reacts slower (reaction time of 3 hours compared with 1 hour using RBF_3K) with enone **2a**, although similar yields and *ee*'s are obtained. This confirms the higher reactivity of potassium organotrifluoroborates compared to organoboronic acids, as reported previously.[18,19] Using (*R*)- or (*S*)-binap allowed the selective formation of (*R*)- or (*S*)-1,4-addition adducts with the same sense of induction (entries 1 and 2).

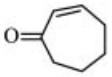
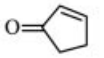
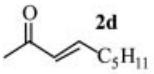
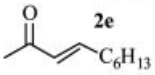
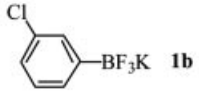
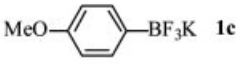
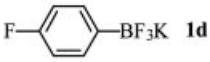
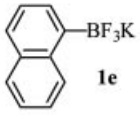
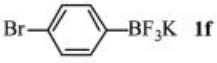
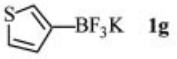
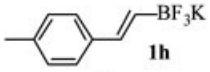
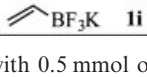
Other potassium aryltrifluoroborates reacted equally well with cyclohexenone (entries 7−15) and other linear and cyclic enones (entries 16−18). Almost quantitative yields and high levels of enantioselectivity were generally observed. Under the same conditions, potassium alkenyltrifluoroborates also participated in this Michael-type addition with comparable reactivity (entries 19−21) and enantiomeric excesses of over 92%. In particular, introduction of the vinyl moiety was highly efficient (entry 21) and good levels of enantioselectivity were obtained using potassium vinyltrifluoroborate (**1i**), which is easily accessible on a large scale from vinylmagnesium chloride.[16]

A lower catalyst loading can be used in this reaction (Scheme 4). For example, the 1,4-addition of potassium phenyltrifluoroborate (**1a**) to cyclohexenone (**2a**), in the presence of 0.05 mol % catalyst, afforded high yields of **3a** with lower enantioselectivities.

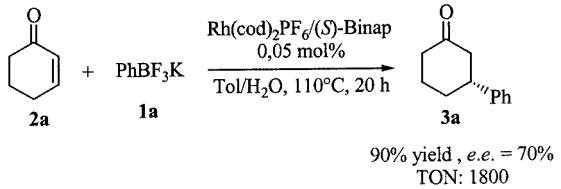
Conclusion

We have developed an efficient method to effect asymmetric 1,4-additions of potassium organotrifluoroborates to enones. This reaction, catalyzed by cationic rhodium(I) complexes chelated with chiral diphosphane ligands, occurs in a toluene/water mixture, to afford Michael adducts with good levels of enantioselectivity (up to 99%). Compared to Miyaura−Hayashi conditions, using organoboronic acid derivatives, this reaction generally requires less of the organometallic reagent. Moreover, potassium organotrifluoroborates present several advantages over their boronic acid counterparts: they are easily accessible using classical organoboron synthesis[29] followed by in situ treatment by potassium hydrogen difluoride,[16,20] and can be obtained with high purities by simple filtration. Moreover, all these compounds shows exceptional stabilities compared to other organoboron derivatives. The extension of this reaction to other Michael acceptors is currently been developed and will be reported in due course.

Table 3. Asymmetric 1,4-addition of potassium organotrifluoroborates to enones[a]

Entry	RBF_3K	Enone	Time (h)	Product	Yield (%)	*ee*[b] (%)	$[\alpha]_D^{20}$ (*c* in $CHCl_3$)
1	**1a**	**2a**	1	**3aa**	99	98 (*R*)	+21.0 (0.98)
2			1		99	99 (*S*)[d]	
3	**1a**	 **2b**	1	**3ab**	98	95	+55.6 (0.48)
4	**1a**	 **2c**	1	**3ac**	99	95	+93.8 (0.84)
5	**1a**	 **2d**	1	**3ad**	99	92	+16.9 (0.48)
6	**1a**	 **2e**	1	**3ae**	95	95	+12.2 (0.4)
7	 **1b**	**2a**	20	**3be**	89	96 (*R*)	+10.0 (1.0)
8			3[e]		96	97 (*R*)	
9			3[e]		95	97 (*S*)[d]	
10	 **1c**	**2a**	6[e]	**3ca**	97	90	+15.0 (2.2)
11	 **1d**	**2a**	2	**3da**	46	nd	+14.3 (1.2)
12			2[g]		95	98	
13	 **1e**	**2a**	20	**3ea**	53	87	+45.8 (1.5)
14			20[g]		90	98	
15	 **1f**	**2a**	6	**3fa**	90	96	+6.0 (1.1)
16	**1c**	**2b**	3	**3cb**	75	94	+16.9 (0.81)
17	 **1g**	**2d**	2	**3gd**	84	90[d]	−13.0 (0.4)
18	**1b**	**2e**	2	**3be**	73	87[d]	−7.8 (1.9)
19	 **1h**	**2a**	7[e]	**3ha**	93	95	−9.2 (1.3)
20	**1h**	**2b**	1	**3hb**	70	95	−8.2 (0.45)
21	 **1i**	**2a**	2[f]	**3ia**	99	92	+18.1 (0.7)
22			2[h]		83	89	

[a] Reactions were conducted with 0.5 mmol of enone and 2 equiv. of RBF_3K, in the presence of 3 mol % of $[Rh(cod)_2][PF_6]$/(*R*)-binap in toluene/water 4:1 at 105−110 °C. [b] Determined by HPLC analysis using Daicel Chiralcel chiral stationary phase column. [c] In $CHCl_3$ as solvent. [d] Using (*S*)-binap as chiral ligand. [e] 3 equiv. of RBF_3K were used. [f] 4 equiv. of RBF_3K were used. [g] 5 equiv. of RBF_3K were used. [h] Using (*R*)-MeObiphep as chiral ligand.



Scheme 4. Catalyst loading

Experimental Section

General Remarks: ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 200 at 200 and 50 MHz respectively; chemical shifts (δ) are reported in ppm relative to Me_4Si; coupling constants (*J*) are reported in Hz and refer to apparent peak multiplicities. Mass spectra were determined on a Ribermag instrument. Elementary 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}) and spots were detected with UV light.

GC analyses were performed on a Hewlett−Packard 5890 instrument equipped with a J&W Scientific DB-1701 capillary column (15 m, Ø = 0.25 μm), using an ionisation flame detector. Chiral HPLC analysis were conducted with Waters 600 system, using Daicel Chiralcel chiral stationary phase columns: OD-H hexane/2-propanol 98:2 (**3ba**, **3bd**, **3hb**), OD-H hexane/2-propanol 90:10 (**3ad**, **3cb**), OJ hexane/2-propanol 90:10 (**3ca**), OJ hexane/2-propanol 98:2 (**3ab**), AD hexane/2-propanol 98:2 (**3da**), AD hexane/2-propanol 95:5 (**3ea**), AS-H hexane/2-propanol 98:2 (**3aa**, **3ac**, **3ae**, **3fa**, **3gd**, **3ha**), AS-H hexane/2-propanol 90:10 (**3ec**). Enantiomeric excesses of compound **3ia** were determined by chiral GC analysis: Hydrodex®-β-6-TBDM column (25 m, Ø = 0.25 mm), at 90 °C and 1.3 mL·min^{-1}.

Potassium organotrifluoroborates[16c] and $[Rh(cod)_2][PF_6]$[27] were prepared according to published procedures. Toluene was freshly distilled from CaH_2.

Typical Procedure for the 1,4-Addition of Potassium Aryl- and Alkenyltrifluoroborates to Enones: A mixture of potassium organotrifluoroborate (number of equivalents indicated in the table), $[Rh(cod)_2][PF_6]$ (7.0 mg, 3 mol %), and (*R*)- or (*S*)-binap (10.3 mg, 3.3 mol %) were placed in a flask and then a degassed toluene/water mixture (2 mL/0.5 mL) was added at room temperature followed by the enone (0.5 mmol). The flask was heated in a preheated oil bath at 105−110 °C and the mixture was stirred until completion of the reaction (followed by GC analysis). After filtration through celite (eluting with CH_2Cl_2), the solvent was removed under reduced pressure. Purification by chromatography through silica gel afforded analytically pure product.

(*R*)-3-Phenyldecan-2-one (3ae): Light yellow oil (111 mg) obtained from **1a** (0.5 mmol) and **2e** (1 mmol) in 95% yield according to the general procedure. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.7−1 (m, 4 H), 1.1−1.4 (m, 9 H), 2.03 (s, 3 H), 2.73 (d, *J* = 7.2 Hz, 2 H), 7.1−7.4 (m, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 22.5, 27.2, 29.1, 30.5, 31.6, 36.4, 41.2, 50.8, 126.2, 127.4, 128.3, 144.5, 207.9 ppm. MS (70 eV): *m*/*z* (%) = 232 (2) [M$^{+\cdot}$], 174 (18), 43 (100).

(*R*)-4-Thiophen-3-ylnonan-2-one (3gd): Light yellow oil (94 mg) obtained from **1g** (0.5 mmol) and **2d** (1 mmol) in 84% yield according to the general procedure. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.7−0.9 (m, 3 H), 1.1−1.4 (m, 6 H), 1.4−1.7 (m, 2 H), 2.03 (s, 3 H), 2.68 (d, *J* = 14.1 Hz, 2 H), 3.28 (m, 1 H), 6.90−6.97 (m, 2 H), 7.23−7.3 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.8, 22.3, 26.7, 30.3, 31.5, 36.0, 36.3, 50.4, 119.9, 125.3, 126.3, 145.2, 207.8 ppm. MS (70 eV): *m*/*z* (%) = 224 (20) [M$^{+\cdot}$], 181 (26), 125 (40), 43 (100).

(*S*)-3-(3-Chlorophenyl)decan-2-one (3be): Colourless oil (126 mg) obtained from **1b** (0.5 mmol) and **2e** (1 mmol) in 95% yield according to the general procedure. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.7−0.9 (m, 3 H), 1.1−1.4 (m, 8 H), 1.4−1.8 (m, 2 H), 2.05 (s, 3 H), 2.72 (d, *J* = 14.2 Hz, 2 H), 3.12 (m, 1 H), 7.0−7.4 (m, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.8, 22.3, 27.0, 28.9, 30.4, 31.4, 36.1, 40.6, 50.3, 125.6, 126.3, 127.3, 129.4, 134.0, 146.7, 207.0 ppm. MS (70 eV): *m*/*z* (%) = 266 (3) [M$^{+\cdot}$], 208 (35), 43 (100).

(*R*)-3-[2-(4-Methylphenyl)vinyl]cyclohexanone (3ha): White solid (100 mg) obtained from **1h** (0.5 mmol) and **2a** (1.5 mmol) in 93% yield according to the general procedure. m.p. 94−95 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.5−2.8 (m, 12 H), 6.1 (dd, *J* = 15.9 Hz and 6.6 Hz, 1 H), 6.39 (d, *J* = 15.9 Hz, 1 H), 7.12 (d, *J* = 8 Hz, 2 H), 7.25 (d, *J* = 8 Hz, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.0, 24.9, 31.4, 41.2, 41.8, 47.4, 125.9, 128.8, 129.2, 131.8, 134.2, 137.0, 210.8 ppm. MS (70 eV): *m*/*z* (%) = 214 (19) [M$^{+\cdot}$], 105 (100).

(*R*)-3-[2-(4-Methylphenyl)vinyl]cycloheptanone (3hb): Colourless oil (85 mg) obtained from **1h** (0.5 mmol) and **2b** (1 mmol) in 74% yield according to the general procedure. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.4−2.8 (m, 14 H), 6.10 (dd, *J* = 15.9 Hz and 6.7 Hz, 1 H), 6.37 (d, *J* = 15.9 Hz, 1 H), 7.11 (d, *J* = 8 Hz, 2 H), 7.21 (d, *J* = 8 Hz, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.0, 24.0, 28.3, 37.1, 39.3, 44.0, 49.4, 125.9, 128.2, 129.1, 133.2, 134.4, 136.9, 213.5 ppm. MS (70 eV): *m*/*z* (%) = 228 (23) [M$^{+\cdot}$], 129 (62), 118 (65), 105 (100).

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[28] A mixture of potassium organotrifluoroborate (number of equivalents indicated in the table), $[Rh(cod)_2][PF_6]$ (7.0 mg, 3 mol %), and (*R*)-binap or (*S*)-binap (10.3 mg, 3.3 mol %) were placed in a flask and then a degassed toluene/water mixture (2 mL/0.5 mL) was added at room temperature followed by the enone (0.5 mmol). The flask was heated in a preheated oil bath at 105−110 °C and the mixture was stirred until completion of the reaction (followed by GC analysis). After filtration through celite (eluting with CH_2Cl_2), the solvent was removed under reduced pressure. Purification by chromatography over silica gel afforded analytically pure product.
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