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# Rhodium-catalyzed asymmetric 1,4-addition of arylboron compounds generated *in situ* from aryl bromides

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## Abstract

Rhodium-catalyzed asymmetric 1,4-addition to α,β-unsaturated ketones is effected by use of arylborates, generated *in situ* by lithiation of aryl bromides followed by treatment with trimethoxyborane, to give the corresponding β-aryl ketones of up to 99% ee in high yields. The addition of 1 equiv. (to arylborate) of water is essential for high chemical yields.

Rhodium(I)-catalyzed 1,4-addition of aryl- and alkenylboronic acids to α,β-unsaturated ketones reported by Miyaura in 1997 opened a new synthetic route to β-substituted ketones.[1] Very recently, we have succeeded in applying the rhodium-catalyzed reaction to catalytic asymmetric synthesis by carrying out the reaction in the presence of Rh(acac)$(C_2H_4)_2$/(*S*)-binap as a catalyst in dioxane/$H_2O$ (10/1) at 100°C.[2] We have also reported the successful use of 2-alkenyl-1,3-2-benzodioxaboroles, readily accessible by hydroboration of alkynes with catecholborane, for the catalytic asymmetric 1,4-addition.[3] Arylboronic acids are usually obtained by acidic hydrolysis of their esters, but the procedures for their isolation and purification are not always easy.[4] If some arylboron species generated from readily accessible compounds were applicable to the catalytic asymmetric reaction without isolation, it would be much more practically useful. Here we report that arylborates readily generated *in situ* by treatment of aryl bromides with butyllithium and trimethoxyborane can be used for the catalytic asymmetric 1,4-addition. The chemical yields here are higher than those obtained under the previously reported[2] reaction conditions.

In the first set of experiments, we studied the asymmetric arylation of 2-cyclohexenone (**1a**) with lithium trimethyl 4-methoxyphenylborate[4c] generated by lithiation of 4-methoxyphenyl bromide (**2m**) with butyllithium followed by treatment of the resulting aryllithium with trimethoxyborane (Scheme 1, Table 1). It should be noted that, under the reaction conditions previously reported[2] where 4-methoxyphenylboronic acid is used in dioxane/$H_2O$ (10/1), 3-(4-methoxyphenyl)cyclohexanone (**3am**)

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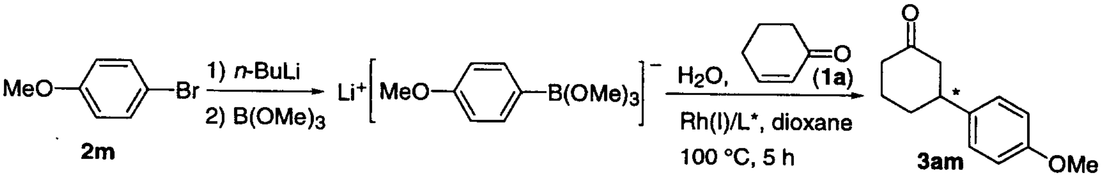
is not produced due to competing hydrolysis of the boronic acid giving methoxybenzene. The results summarized in Table 1 show that 1,4-addition product **3am** is obtained on addition of water to the rhodium-catalyzed reaction and the yield of **3am** is strongly dependent on the amount of water added. The highest yield was obtained in the reaction carried out in the presence of one equiv. (to **2m**) of water (entry 3). Thus, the reaction of **1a** (0.40 mmol) with lithium trimethyl arylborate (1.00 mmol, 2.5 equiv. to **1a**) in the presence of Rh(I)/(*S*)-binap catalyst (3 mol%) and one equiv. (to arylborate) of water (18 mg, 1.00 mmol) gave 80% yield of (*S*)-**3am**[5] which is 98% enantiomerically pure. In the reaction with 5 equiv. of arylborate, the yield was a little higher (86%) (entry 6). Addition of excess water lowered the yield though the enantioselectivity was kept constant, the yield of **3am** on addition of 10 equiv. and 2 equiv. of water being 19% and 52%, respectively (entries 1 and 2). In the absence of water, the reaction is very sluggish giving only 4% yield of **3am** (entry 5). It seems that the addition of water is essential for the present rhodium-catalyzed 1,4-addition and too much water disturbs the reaction by acceleration of the hydrolysis of the aryl–boron bond.



Rh(I)/L* = Rh(acac)($C_2H_4$)$_2$/(*S*)-binap (3 mol %)

Scheme 1.

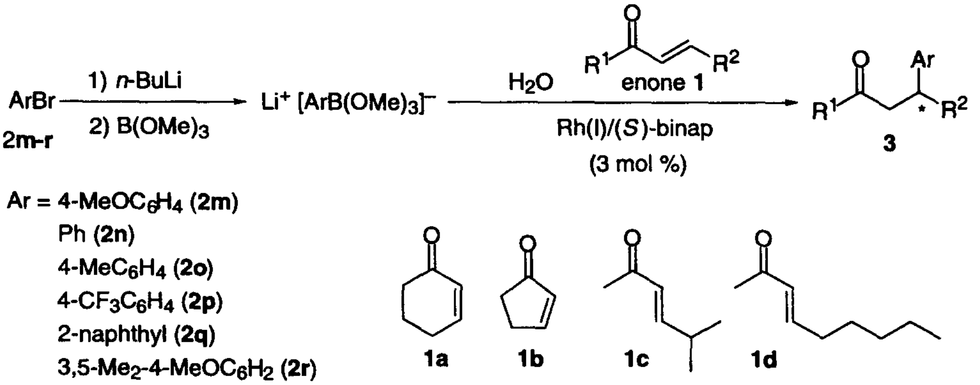
Several aryl groups, phenyl (**2n**), 4-$MeC_6H_4$ (**2o**), 4-$CF_3C_6H_4$ (**2p**), 2-naphthyl (**2q**), 3,5-$Me_2$-4-$MeOC_6H_2$ (**2r**), were also introduced into α,β-unsaturated ketones **1a–d** with high enantioselectivity in high yields by the reaction with arylborates in the presence of one equiv. of water (Scheme 2, Table 2).[6,7] We succeeded in reducing the amount of the catalyst under the present reaction conditions (entries 3, 6 and 8). For a typical example, the reaction of **1a** with a boron reagent derived from **2q** gave 96% yield of product **3aq** in 99% ee even in the presence of 0.1 mol% of the rhodium catalyst, the enantioselectivity

Table 1
Effects of amount of water in rhodium-catalyzed asymmetric arylation of 2-cyclohexenone (**1a**) with an arylborate derived from 4-bromoanisole (**2m**)[a]

| entry | equiv of **2m** | $H_2O$ (equiv to **2m**) | yield (%)[b] | % ee[c] |
|---|---|---|---|---|
| 1 | 2.5 | 10.0 | 19 | 98 |
| 2 | 2.5 | 2.0 | 51 | 98 |
| 3 | 2.5 | 1.0 | 80 | 98 |
| 4 | 2.5 | 0.5 | 74 | 98 |
| 5 | 2.5 | none | 4 | 97 |
| 6 | 5.0 | 1.0 | 86 | 98 |
| 7 | 1.3 | 1.0 | 52 | 98 |
| 8[d] | 5.0[d] | – | 0 | – |

[a] The reaction was carried out in dioxane at 100 °C for 5 h in the presence of 3 mol % of the catalyst generated from Rh(acac)($C_2H_4$)$_2$ and (*S*)-binap. [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis with a chiral stationary phase column (Daicel Chiralcel OD-H, hexane/2-propanol = 98/2). [d] Reaction of 4-methoxyphenylboronic acid in dioxane/$H_2O$ (10/1).

being the same as that observed with 3 mol% of the catalyst (entries 7 and 8). Thus, the present 'one-pot synthesis' method is superior to that previously reported[2] with arylboronic acids both in higher catalytic activity resulting in higher chemical yields and in easier manipulation avoiding isolation of arylboronic acids.



Scheme 2.

Table 2

Rhodium-catalyzed asymmetric arylation of α,β-unsaturated ketones **1** with arylborates derived from aryl bromides **2**[a]

| entry | enone **1** | aryl bromide **2** | yield (%)[b] of **3** | % ee[c] of **3** | $[\alpha]_D^{20}$ (*c* in $CHCl_3$) |
|---|---|---|---|---|---|
| 1 | **1a** | **2m** | 80 (**3am**) | 98 (*S*) | −15 (0.94) |
| 2 | **1a** | **2n** | >99 (**3an**) | 99 (*S*) | −22 (1.01) |
| 3[d] | **1a** | **2n** | 71 (**3an**) | 99 (*S*) | |
| 4 | **1a** | **2o** | 95 (**3ao**) | 99 (*S*) | −17 (0.95) |
| 5 | **1a** | **2p** | >99 (**3ap**) | 99 (*S*) | −11 (0.92) |
| 6[d] | **1a** | **2p** | 73 (**3ap**) | 98 (*S*) | |
| 7 | **1a** | **2q** | >99 (**3aq**) | 99 (*S*) | −8.3 (0.89) |
| 8[d] | **1a** | **2q** | 96 (**3aq**) | 99 (*S*) | |
| 9 | **1a** | **2r** | 93 (**3ar**) | 99 (*S*) | −15 (1.23) |
| 10 | **1b** | **2m** | 84 (**3bm**) | 92 (*S*) | −66 (0.96) |
| 11 | **1b** | **2n** | >99 (**3bn**) | 97 (*S*) | −92 (0.84) |
| 12 | **1b** | **2o** | 95 (**3bo**) | 93 (*S*) | −81 (1.16) |
| 13 | **1b** | **2p** | >99 (**3bp**) | 93 (*S*) | −57 (1.02) |
| 14 | **1b** | **2q** | >99 (**3bq**) | 94 (*S*) | −56 (0.78) |
| 15 | **1c** | **2n** | 75 (**3cn**) | 97 | −33 (1.05) |
| 16 | **1d** | **2n** | >99 (**3dn**) | 91 | −17 (1.26) |

[a] The reaction was carried out in dioxane at 100 °C for 5 h with arylborates formed *in situ* in the presence of 1 equiv (to **2**) of $H_2O$ and 3 mol % of the catalyst generated from $Rh(acac)(C_2H_4)_2$ and (*S*)-binap, unless otherwise noted. [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis with chiral stationary phase columns: Daicel Chiralcel OD-H (**3am**, **3an**, **3ap**, **3aq**, **3cn**, **3dn**), AD (**3ao**), AS (**3ar**), OB-H (**3bn**, **3bo**, **3bp**) (eluent, hexane/2-propanol = 98/2), and OB-H (**3bm**, **3bq**) (eluent, hexane/2-propanol = 90/10). For the absolute configuration, see ref. 2. [d] In the presence of 0.1 mol % of the catalyst.

It is assumed that lithium phenylborate Li[PhB$(OMe)_3$] undergoes hydrolysis with one equivalent of $H_2O$ to give Li[PhB$(OMe)_2$(OH)] or PhB(OMe)(OLi) together with methanol.[8] The rhodium-catalyzed reaction of PhB$(OMe)_2$[9] (1.00 mmol) with 2-cyclohexenone (**1a**, 0.40 mmol) did not proceed at all, while the reaction gave a quantitative yield of 3-phenylcyclohexanone (**3an**) in 99% ee on addition of 1 equiv. (to PhB$(OMe)_2$) of lithium hydroxide. The results may support that Li[PhB$(OMe)_2$(OH)] or PhB(OMe)(OLi) is a reactive species for the present asymmetric 1,4-addition.

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5. The absolute configuration of the arylation product obtained with (*S*)-binap ligand is expected to be (*S*) according to an empirical rule shown in Ref. 2.
6. Compound **3am**: $^1$H NMR ($CDCl_3$) δ 1.71–1.85 (m, 2H), 2.04–2.07 (m, 1H), 2.11–2.16 (m, 1H), 2.33–2.59 (m, 4H), 2.96 (tt, *J*=11.7 and 3.9 Hz, 1H), 3.79 (s, 3H), 6.87 (d, *J*=8.8 Hz, 2H), 7.14 (d, *J*=8.8 Hz, 2H); $^{13}$C NMR ($CDCl_3$) δ 25.49, 33.00, 41.18, 43.97, 49.24, 55.27, 114.01, 127.49, 136.57, 158.26, 211.23. Anal. calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.34; H, 8.05. Compound **3aq**: $^1$H NMR ($CDCl_3$) δ 1.75–1.85 (m, 1H), 1.89–1.97 (m, 1H), 2.12–2.18 (m, 2H), 2.36–2.49 (m, 2H), 2.59–2.69 (m, 2H), 3.16 (tt, *J*=12.0 and 3.9 Hz, 1H), 7.34 (dd, *J*=8.6 and 1.8 Hz, 1H), 7.42–7.48 (m, 2H), 7.62 (s, 1H), 7.78–7.81 (m, 3H); $^{13}$C NMR ($CDCl_3$) δ 25.51, 32.68, 41.22, 44.77, 48.82, 124.72, 125.30, 125.63, 126.18, 127.60, 127.67, 128.34, 132.37, 133.54, 141.73, 210.91. Anal. calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.72; H, 7.28. Compound **3ar**: $^1$H NMR ($CDCl_3$) δ 1.70–1.84 (m, 2H), 2.01–2.06 (m, 1H), 2.11–2.16 (m, 1H), 2.27 (s, 6H), 2.32–2.57 (m, 4H), 2.89 (tt, *J*=12.0 and 4.1 Hz, 1H), 3.71 (s, 3H), 6.85 (s, 2H); $^{13}$C NMR ($CDCl_3$) δ 16.12, 25.54, 32.92, 41.14, 44.18, 49.10, 59.61, 126.80, 130.85, 139.63, 155.50, 211.11. Anal. calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.33; H, 8.75. Compound **3bm**: $^1$H NMR ($CDCl_3$) δ 1.90–1.99 (m, 1H), 2.25–2.33 (m, 2H), 2.39–2.48 (m, 2H), 2.64 (dd, *J*=18.1 and 7.6 Hz, 1H), 3.37 (tt, *J*=10.5 and 6.8 Hz, 1H), 3.80 (s, 3H), 6.88 (d, *J*=8.8 Hz, 2H), 7.17 (d, *J*=8.8 Hz, 2H); $^{13}$C NMR ($CDCl_3$) δ 31.41, 38.91, 41.49, 46.04, 55.32, 114.06, 127.65, 135.13, 158.37, 218.62. Anal calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.48; H, 7.46. Compound **3bo**: $^1$H NMR ($CDCl_3$) δ 1.92–2.01 (m, 1H), 2.25–2.37 (m, 2H), 2.34 (s, 3H), 2.39–2.48 (m, 2H), 2.65 (dd, *J*=18.1 and 7.3 Hz, 1H), 3.38 (tt, *J*=11.0 and 7.3 Hz, 1H), 7.15 (s, 4H); $^{13}$C NMR ($CDCl_3$) δ 21.00, 31.32, 38.92, 41.89, 45.94, 126.62, 129.36, 136.35, 140.06, 218.63. Anal calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.66; H, 8.25. Compound **3bp**: $^1$H NMR ($CDCl_3$) δ 1.96–2.04 (m, 1H), 2.30–2.37 (m, 2H), 2.46–2.52 (m, 2H), 2.70 (dd, *J*=17.8 and 7.3 Hz, 1H), 3.49 (tt, *J*=11.0 and 7.1 Hz, 1H), 7.38 (d, *J*=8.1 Hz, 2H), 7.60 (d, *J*=8.1 Hz, 2H); $^{13}$C NMR ($CDCl_3$) δ 31.00, 38.72, 42.05, 45.48, 124.16 (q, *J*=271.8 Hz), 125.67 (q, *J*=4.1 Hz), 127.16, 129.14 (q, *J*=33.1 Hz), 147.13, 217.34. Anal. calcd for $C_{12}H_{11}F_3O$: C, 63.16; H, 4.86; F, 24.97. Found: C, 63.34; H, 4.92; F, 24.95. Compound **3bq**: $^1$H NMR ($CDCl_3$) δ 2.05–2.14 (m, 1H), 2.32–2.39 (m, 1H), 2.44–2.55 (m, 3H), 2.75 (dd, *J*=18.3 and 7.8 Hz, 1H), 3.59 (tt, *J*=10.7 and 7.1 Hz, 1H), 7.39 (dd, *J*=8.3 and 1.7 Hz, 1H), 7.44–7.50 (m, 2H), 7.67 (s, 1H), 7.80–7.85 (m, 3H); $^{13}$C NMR ($CDCl_3$) δ 31.08, 38.80, 42.31, 45.70, 124.85, 125.34, 125.68, 126.28, 127.62, 128.40, 132.38, 133.47, 140.44, 218.29. Anal. calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.75; H, 6.83. For **3an**, **3ao**, **3ap**, **3bn**, **3cn**, and **3dn**, see Ref. 2.
7. For a typical example (entry 2 in Table 2), a hexane solution of butyllithium (650 μL, 1.00 mmol) was added to bromobenzene (**2n**, 157 mg, 1.00 mmol) in $Et_2O$ (0.5 mL) at 0°C. The mixture was stirred at room temperature for 1

h and cooled to –78°C. Trimethoxyborane (104 mg, 1.00 mmol) was added to the reaction mixture. The mixture was stirred at –78°C for 30 min and at room temperature for 1 h. To the mixture, were added $H_2O$ (18 mg, 1.00 mmol), 2-cyclohexenone (**1a**, 39 mg, 0.40 mmol) and a solution of $Rh(acac)(C_2H_4)_2$ (3.1 mg, 12 μmol) and (*S*)-binap (9.0 mg, 14 μmol) in dioxane (2 mL). The whole mixture was heated at 100°C for 5 h. Addition of saturated aqueous sodium hydrogen carbonate followed by ethyl acetate extraction and silica gel chromatography (hexane/ethyl acetate=5/1) gave 70 mg (>99% yield) of (*S*)-3-phenylcyclohexanone (**3an**), whose enantiomeric purity was determined to be 99% ee by HPLC analysis with a chiral stationary phase column.

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