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RHODIUM-CATALYZED ASYMMETRIC 1,4-ADDITION OF 3-THIOPHENEBORONIC ACID TO α,β-UNSATURATED CARBONYL COMPOUNDS

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Abstract - Asymmetric 1,4-addition of 3-thiopheneboronic acid to α,β-unsaturated carbonyl compounds proceeded with high enantioselectivity in the presence of 3 mol% (Rh) of $[Rh(OH)((S)\text{-binap})]_2$ in dioxane/H_2O (10/1) at 40 °C to give the corresponding optically active β-(3-thienyl) carbonyl compounds of over 94% ee.

Asymmetric 1,4-addition of organometallic reagents to α,β-unsaturated carbonyl compounds is a useful process giving enantiomerically enriched β-substituted carbonyl compounds.[1] As one of the most promising methods for the asymmetric 1,4-addition, the addition of aryl- and alkenylboronic acids under catalysis by chiral phosphine-rhodium complexes has been rapidly developed.[2-4] However, to our best knowledge, heteroaromatic groups have not been introduced enantioselectively by the rhodium-catalyzed asymmetric 1,4-addition,[5] probably due to the instability of the corresponding boronic acids under the reaction conditions, the reactions typically being carried out with Rh(acac)((*S*)-binap) as a catalyst in dioxane/H_2O at 100 °C.[2] During our recent studies on the catalytic cycle of the rhodium-catalyzed asymmetric 1,4-addition,[6] we found that $[Rh(OH)((S)\text{-binap})]_2$ is much more catalytically active, which

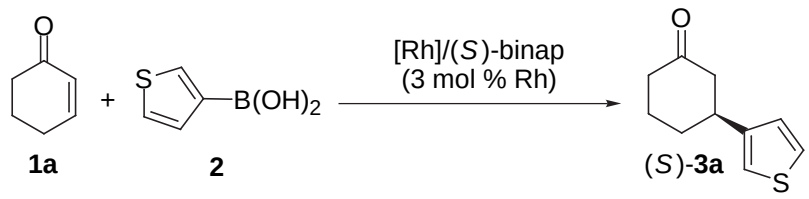
† Dedicated to Professor Yuichi Kanaoka on the occasion of his 75th birthday.

catalyzes the asymmetric 1,4-addition at a lower temperature with higher enantioselectivity. Here we wish to report that 3-thienyl group can be introduced on to the β-position of a variety of α,β-unsaturated carbonyl compounds with high enantioselectivity by use of the new catalyst [Rh(OH)((*S*)-binap)]$_2$ for the reaction of 3-thiopheneboronic acid.

RESULTS AND DISCUSSION

As a first set of experiment, several reaction conditions were examined for the addition of 3-thiopheneboronic acid (**2**) to 2-cyclohexenone (**1a**) (Scheme 1). Under our standard conditions used previously for the reaction of α,β-unsaturated ketones with phenylboronic acid,[2] that is, 3 mol % of the rhodium catalyst generated from Rh(acac)(C_2H_4)$_2$ with (*S*)-binap[7] in dioxane/H_2O (10/1) at 100 °C for 5 h, the reaction of 2-cyclohexenone (**1a**) with 3-thiopheneboronic acid (**2**) (3 equiv to **1a**) gave only a poor yield (30%) of the 1,4-addition product, 3-thiophen-3-ylcyclohexanone (**3a**), whose enantiomeric purity is 97% (entry 1 in Table 1). Considering that the reaction of enone (**1a**) with phenylboronic acid gave a high yield (>90%) of the phenylation product under the same reaction conditions,[2] the low yield is ascribed to the use of 3-thiopheneboronic acid (**2**). In the reactions at this high temperature (100 °C), it has been sometimes observed[2,6] that the hydrolysis of arylboronic acids (ArB(OH)$_2$) giving arenes (ArH) is the main side reaction which is responsible for the low yields of the 1,4-addition products. The reaction carried out at 40 °C did not improve the yield of **3a** though the enantioselectivity was higher (99% ee) (entry 2). A higher yield of the 1,4-addition product (**3a**) was obtained by use of [Rh(OH)((*S*)-binap)]$_2$ as a catalyst. Thus, the reaction of **1a** with thiopheneboronic acid (**2**) (5 equiv.) in THF/H_2O (10/1) in the presence of 3 mol % of [Rh(OH)((*S*)-binap)]$_2$ at 40 °C for 24 h gave 78% yield of (*S*)-3-thiophen-3-ylcyclohexanone (**3a**) with 99% ee (entry 3).

Scheme 1



Under similar reaction conditions, cyclic α,β-unsaturated ketones, 2-cyclopentenone (**1b**) and 2-cycloheptenone (**1c**), gave the corresponding thienylation products in 78% and 81% yields, respectively

Table 1. Asymmetric 1,4-Addition of 3-Thiopheneboronic Acid (**2**) to α,β-Unsaturated Carbonyl Compounds (**1**) Catalyzed by [Rh(OH)((*S*)-binap)]$_2$[a]

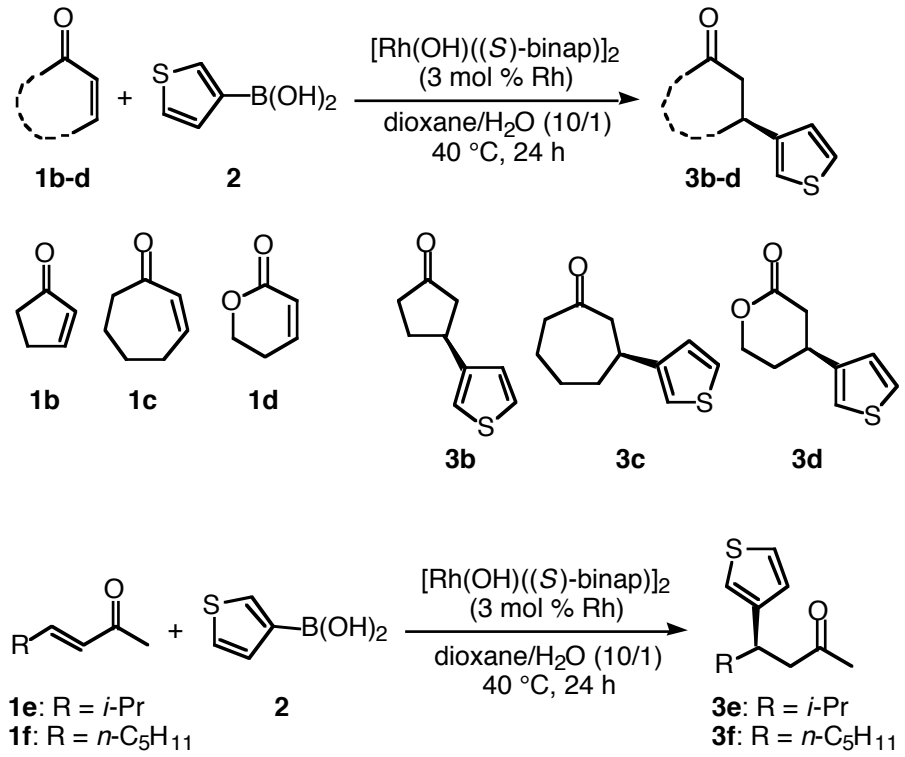
entry	enone **1**	reaction conditions	product **3** yield (%)[d]	% ee of **3**[b] (config)	$[\alpha]_D^{20}$[c] of **3**
1[e]	**1a**	100 °C 5 h	**3a** 30	97 (*S*)	
2[e]	**1a**	40 °C 24 h	**3a** 40	99 (*S*)	
3[f]	**1a**	40 °C 24 h	**3a** 78	99 (*S*)	
4	**1a**	40 °C 24 h	**3a** 67	99 (*S*)	+11.1°
5	**1b**	40 °C 24 h	**3b** 78	97 (*S*)	-63.1°
6	**1c**	40 °C 24 h	**3c** 81	99 (*S*)	-34.7°
7	**1d**	40 °C 24 h	**3d** 79	99 (*S*)	+19.8°
8	**1e**	40 °C 24 h	**3e** 75	99 (*S*)	-25.8°
9	**1f**	40 °C 24 h	**3f** 82	94 (*R*)	-17.4°

[a] The rhodium-catalyzed 1,4-addition was carried out with substrate (**1**) (0.20 mmol) and 3-thiopheneboronic acid (**2**) (0.60 mmol) in 0.55 mL of dioxane/H_2O (10/1) in the presence of 3 mol % (Rh) of [Rh(OH)((*S*)-binap)]$_2$ unless otherwise noted. [b] Determined by HPLC analysis of ketone (**3**) with chiral stationary phase columns (Chiralcel OD-H (**3a**, **3d**, **3e**, **3f**) and AD (**3b**, **3c**)). The configurations were assigned by consideration of the stereochemical reaction pathway (ref. 2a). [c] (*c* 1.00, chloroform). [d] Isolated yield by silica gel chromatography. [e] Reaction with 3 mol % of a rhodium catalyst generated from Rh(acac)(C_2H_4)$_2$ and (*S*)-binap. [f] With 1.00 mmol of **2** in THF/H_2O (10/1).

(entries 5 and 6). The asymmetric thienylation of α,β-unsaturated ester, 5,6-dihydro-2*H*-pyran-2-one (**1d**), was also successful giving 79% yield of **3d** (entry 7). The enantiomeric excesses of **3b**, **3c**, and **3d** are all very high, ranging between 97% and 99% ee. The configurations of the 1,4-addition products (**3a-d**) are assigned to be *S* by consideration of the stereochemical reaction pathway.[2a] The asymmetric 1,4-addition of thiopheneboronic acid also proceeded with high enantioselectivity for linear α,β-unsaturated ketones (**1e**) and (**1f**) (entries 8 and 9).

In summary, asymmetric 1,4-addition of 3-thiopheneboronic acid (**2**) to α,β-unsaturated carbonyl compounds (**1**) proceeded with high enantioselectivity in high yields by use of [Rh(OH)((*S*)-binap)]$_2$ as a catalyst. The enantiomerically enriched products substituted with thienyl group at the stereogenic carbon center are expected to be converted into a variety of useful compounds by further transformation.[8]

Scheme 2



EXPERIMENTAL SECTION

General. All anaerobic and/or moisture sensitive manipulations were carried out with standard Schlenk technique under predried nitrogen. Tetrahydrofuran and 1,4-dioxane were distilled from benzophenone-ketyl under nitrogen prior to use. Rhodium complex, [Rh(OH)((*S*)-binap)]$_2$ was prepared according to the reported procedure.[6] 2-Cyclohexenone (**1a**), 2-cyclopentenone (**1b**), and 2-cycloheptenone (**1c**) were distilled before use. 5,6-Dihydro-2*H*-pyran-2-one (**1d**), 5-methyl-3-hexen-2-one (**1e**), 3-nonen-2-one (**1f**), and 3-thiopheneboronic acid (**2**) were used as received without further purification. NMR spectra were recorded on a JEOL JNM LA-500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard for ^{1}H NMR and chloroform-*d* (δ 77.05) for ^{13}C NMR. Optical rotations were measured on a JASCO DIP-370 polarimeter.

Rhodium-Catalyzed Asymmetric 1,4-Addition of 3-Thiopheneboronic Acid (2) to α,β-Unsaturated Carbonyl Compounds (1): General Procedure. To a solution of [Rh(OH)((*S*)-binap)]$_2$ (4.4 mg, 3.0 μmol) and 3-thiopheneboronic acid (**2**) (76.8 mg, 0.600 mmol) in dioxane (0.5 mL) was added α,β-unsaturated carbonyl compound (**1**) (0.200 mmol) and water (0.05 mL) at rt under nitrogen. The flask was immersed in a bath maintained at 40 °C for 24 h. The resulting mixture was extracted with ethyl acetate and the extract was washed with saturated sodium bicarbonate, before it was

dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by PTLC on silica gel to give the desired 1,4-addition product (**3**). The results are summarized in Table 1. Spectroscopic data of the products are shown below: **3-Thiophen-3-ylcyclohexanone (3a):** colorless liquid, purified by PTLC (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$): δ 1.73-1.86 (m, 2H), 2.06-2.12 (m, 1H), 2.13-2.20 (m, 1H), 2.32-2.39 (m, 1H), 2.41-2.47 (m, 1H), 2.50 (ddd, *J* = 14.1, 11.8, 1.3 Hz, 1H), 2.68 (ddt, *J* = 14.1, 4.1, 1.9 Hz, 1H), 3.16 (tt, *J* = 11.0, 4.1 Hz, 1H), 6.98-6.99 (m, 2H), 7.29 (dd, *J* = 4.7, 3.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 25.04, 32.40, 39.85, 41.26, 48.52, 119.51, 125.95, 126.44, 145.41, 210.78. $[\alpha]^{20}_D$ +11.1° (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{10}H_{12}OS$: C, 66.63; H, 6.71. Found: C, 66.62; H, 6.69. **3-Thiophen-3-ylcyclopentanone (3b):** white solid, purified by PTLC (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$): δ 1.94-2.04 (m, 1H), 2.24-2.34 (m, 2H), 2.39-2.48 (m, 2H), 2.66 (dd, *J* = 18.3, 7.7 Hz, 1H), 3.49 (tt, *J* = 10.2, 7.1 Hz, 1H), 7.00-7.02 (m, 2H), 7.31 (t, *J* = 3.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 30.79, 37.71, 38.45, 45.68, 119.59, 126.18, 126.59, 144.28, 218.15. $[\alpha]^{20}_D$ - 63.1° (*c* 1.00, $CHCl_3$). mp 33-35 °C. Anal. Calcd for $C_9H_{10}OS$: C, 65.02; H, 6.06. Found: C, 65.14; H, 5.98. **3-Thiophen-3-ylcycloheptanone (3c):** colorless liquid, purified by PTLC (hexane/AcOEt = 4/1); ^{1}H NMR ($CDCl_3$): δ 1.47-1.55 (m, 1H), 1.65-1.78 (m, 2H), 1.92-2.05 (m, 2H), 2.12-2.18 (m, 1H), 2.54-2.57 (m, 2H), 2.71 (ddd, *J* = 14.6, 2.7, 1.8 Hz, 1H), 2.87 (dd, *J* = 14.5, 11.5 Hz, 1H), 3.07 (tt, *J* = 11.2, 2.6 Hz, 1H), 6.95-6.97 (m, 2H), 7.26 (dd, *J* = 4.9, 3.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 24.09, 28.82, 37.78, 38.50, 43.95, 50.85, 118.92, 125.80, 126.53, 147.05, 213.27. $[\alpha]^{20}_D$ - 34.7° (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{11}H_{14}OS$: C, 68.00; H, 7.26. Found: C, 68.08; H, 7.34. **4-Thiophen-3-yltetrahydropyran-2-one (3d):** white solid, purified by PTLC (hexane/AcOEt = 1/2); ^{1}H NMR ($CDCl_3$): δ 2.00 (dtd, *J* =14.9, 10.0, 4.9 Hz, 1H), 2.23 (dqd, *J* = 14.2, 4.3, 1.6 Hz, 1H), 2.64 (dd, *J* = 17.6, 10.2 Hz, 1H), 2.96 (ddd, *J* = 17.6, 6.0, 1.6 Hz, 1H), 3.36 (tt, *J* = 10.3, 5.4 Hz, 1H), 4.38 (ddd, *J* = 11.5, 10.0, 3.8 Hz, 1H), 4.47 (dt, *J* = 11.5, 4.8 Hz, 1H), 6.98 (dd, *J* = 5.1, 1.4 Hz, 1H), 7.03-7.04 (m, 1H), 7.34 (dd, *J* = 5.0, 2.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 30.08, 32.92, 37.15, 68.39, 119.99, 126.00, 126.75, 143.65, 170.34. $[\alpha]^{20}_D$ + 19.8° (*c* 1.00, $CHCl_3$). mp 49-51 °C. Anal. Calcd for $C_9H_{10}O_2S$: C, 59.32; H, 5.53. Found: C, 59.54; H, 5.61. **5-Methyl-4-thiophene-3-ylhexan-2-one (3e):** colorless liquid, purified by PTLC (hexane/AcOEt = 8/1); ^{1}H NMR ($CDCl_3$): δ 0.78 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 1.82 (octet, *J* = 6.7 Hz, 1H), 2.00 (s, 3H), 2.74 (d, *J* = 7.3 Hz, 2H), 3.12 (q, *J* = 7.4 Hz, 1H), 6.90-6.92 (m, 2H), 7.23 (dd, *J* = 4.5, 3.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 19.87, 20.65, 30.47, 32.94, 43.23, 47.53, 120.84, 125.08, 127.44, 143.71, 208.30. $[\alpha]^{20}_D$ - 25.8° (*c*

1.00, $CHCl_3$). Anal. Calcd for $C_{11}H_{16}OS$: C, 67.30; H, 8.22. Found: C, 67.31; H, 8.03. **4-Thiophen-3-ylnonan-2-one (3f):** colorless liquid, purified by PTLC (hexane/AcOEt = 8/1); ^1H NMR ($CDCl_3$): δ 0.84 (t, *J* = 7.1 Hz, 3H), 1.13-1.27 (m, 6H), 1.47-1.62 (m, 2H), 2.02 (s, 3H), 2.66 (dd, *J* = 16.1, 6.9 Hz, 1H), 2.69 (dd, *J* = 16.1, 7.5 Hz, 1H), 3.27 (dddd, *J* = 8.2, 7.5, 6.9, 6.4 Hz, 1H), 6.93-6.94 (m, 2H), 7.24 (dd, *J* = 4.8, 3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 14.01, 22.50, 26.97, 30.56, 31.70, 36.25, 36.59, 50.66, 120.15, 125.53, 126.55, 145.42, 207.98. $[\alpha]^{20}_D$ -17.4° (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{13}H_{20}OS$: C, 69.59; H, 8.98. Found: C, 69.45; H, 8.78.

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