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Asymmetric 1,4-addition of alkenylzirconium reagents to α,β-unsaturated ketones catalyzed by chiral rhodium complexes

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Abstract—Highly enantioselective 1,4-addition of alkenylzirconocene chlorides to α,β-enones was found to be catalyzed by a chiral rhodium complex generated from $[Rh(cod)(MeCN)_2]BF_4$ and (*S*)-BINAP. The reaction can be applied to either cyclic or acyclic enones and the optical yield was up to 99% ee. The reaction mechanism would involve the transmetalation between the alkenylzirconocene chloride and the rhodium complex to give the alkenylrhodium species as a key intermediate.

The hydrometalation of alkenes and alkynes is one of the most versatile and direct pathways for the formation of organometallic reagents for organic synthesis. Alkenylzirconocene chlorides can be prepared easily and regio- and stereoelectively through the hydrozirconation of alkynes with Schwartz reagent (Cp_2ZrHCl),[1] and are recognized to be convenient and useful organometallic reagents as donors of the alkenyl groups in transition metal-catalyzed C–C bond formation reactions.[2] Schwartz and co-workers demonstrated the 1,4-addition of these alkenylzirconium reagents to α,β-unsaturated ketones mediated by copper salts[3] or catalyzed by $Ni(acac)_2$,[4] which are successfully applied to the prostaglandin synthesis. However, asymmetric version of the catalytic 1,4-addition of the alkenylzirconium reagents has not yet been reported to date.

Considerable attention has been paid to the rhodium-catalyzed addition of various organometallic reagents to carbonyl compounds.[5] Noteworthy is the highly enantioselective 1,4-addition of organometallic reagents, such as boron,[6] silicon,[7] tin,[8] and titanium,[9] to α,β-unsaturated carbonyl compounds. Recently, Hanzawa and co-workers reported the rhodium-catalyzed addition of alkenylzirconocene chlorides to aldimines[10] and 1,4-addition to α,β-unsaturated carbonyl compounds.[11]

During our continuous study of rhodium-catalyzed addition reaction of organometallic compounds,[12] we found independently that the highly enantioselective 1,4-addition of alkenylzirconocene chlorides to α,β-unsaturated ketones can be achieved by use of the rhodium(I) complexes modified by (*S*)-BINAP as the catalysts. Compared with the previously reported asymmetric 1,4-addition of alkenylboron or -silicon reagents,[6,7] the present reaction can be performed under neutral, anhydrous, and extremely mild reaction conditions. This new methodology provides a facile and useful synthetic route to optically active β-(E)-alkenylketones from α,β-unsaturated ketones with alkynes.

We examined first the reaction of (*E*)-1-octenylzirconocene chloride (**2a**), prepared from 1-octyne (**1a**) with Schwartz reagent, with cyclohexenone (**3a**) in the presence of a catalytic amount (5 mol%) of rhodium(I) complex ($[Rh(cod)(MeCN)_2]BF_4$) and various chiral phosphine ligands (Table 1, entries 1–6). Although (*R*,*R*)-Chiraphos (**5**), (*S*)-(*R*)-BPPFA (**6**), (*R*,*R*)-MeDuphos (**7**), and (*R*,*R*)-DIOP (**8**) were not effective in the present asymmetric 1,4-addition, the reactions with both (*S*)-BINAP (**9**) and (*S*)-TolBINAP (**10**) gave the 1,4-adduct **4aa** in good yields of 97% and 96%, respectively, with an excellent ee of 96%. The reactions using other transition metal catalysts with (*S*)-BINAP were then examined (Table 1, entries 7–13). The cationic rhodium(I) complex with cyclooctadiene ($[Rh(cod)_2]BF_4$) and the chloride-coordinated neutral rhodium(I) dimer complex ($[RhCl(cod)]_2$) also exhibited good catalytic activity and enantioselectivity (entries 7 and 8),

Keywords: Asymmetric 1,4-addition; Alkenylzirconium; Rhodium catalyst; α,β-Enone.
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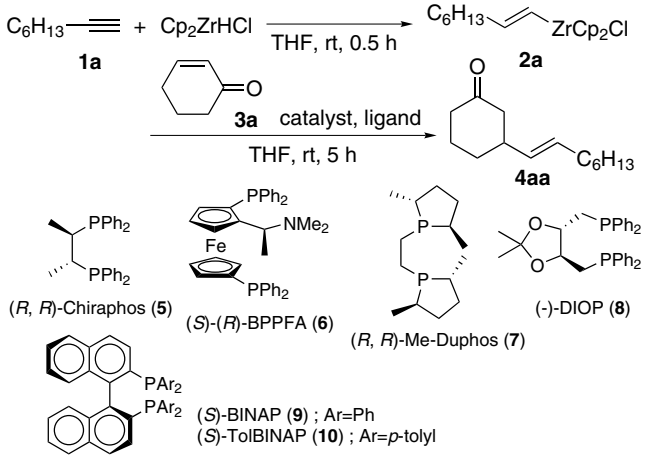
Table 1. Asymmetric 1,4-addition of (*E*)-1-octenylzirconocene chloride (**2a**) to cyclohexenone (**3a**) catalyzed by various rhodium complexes[a]



Entry	Catalyst	Ligand	Yield[b] (%)	Ee[c] (%)
1	$[Rh(cod)(MeCN)_2]BF_4$	**5**	57	31 (*R*)
2	$[Rh(cod)(MeCN)_2]BF_4$	**6**	Trace	
3	$[Rh(cod)(MeCN)_2]BF_4$	**7**	83	25 (*R*)
4	$[Rh(cod)(MeCN)_2]BF_4$	**8**	Trace	
5	$[Rh(cod)(MeCN)_2]BF_4$	**9**	97	96 (*S*)
6	$[Rh(cod)(MeCN)_2]BF_4$	**10**	96	96 (*S*)
7	$[Rh(cod)_2]BF_4$	**9**	83	96 (*S*)
8	$[RhCl(cod)]_2$	**9**	96	96 (*S*)
9	$Rh(acac)(C_2H_4)_2$	**9**	14	91 (*S*)
10	$Ni(acac)_2$	None	86	
11	$Ni(acac)_2$	**9**	31	0
12	$Pd_2(dba)_3{\cdot}CHCl_3$	None	90	
13	$Pd_2(dba)_3{\cdot}CHCl_3$	**9**	0	

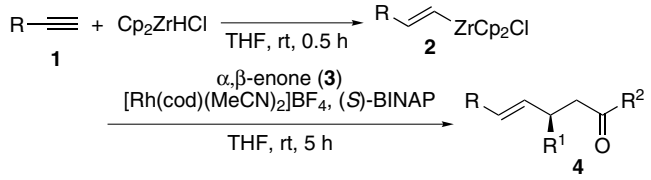
[a] Common reaction conditions: **1a** (1.2 mmol), **3a** (1.0 mmol), catalyst (0.05 mmol), ligand (0.06 mmol), 6 mL of THF, rt, 5 h, N_2 atmosphere.
[b] Isolated yield.
[c] See Ref. 13.

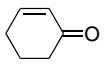
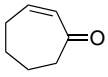
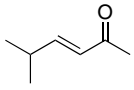
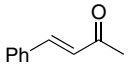
while acetylacetonato complex ($Rh(acac)(C_2H_4)_2$) gave poor yield with slightly lower enantioselectivity (entry 9). As was reported by Schwartz et al., the reaction using $Ni(acac)_2$ as the catalyst without BINAP gave the product in good yield (entry 10). However, when the reaction was performed in the presence of (*S*)-BINAP, the yield decreased to 30% and no enantioselectivity was observed (entry 11). Although the palladium(0) complex ($Pd_2(dba)_3{\cdot}CHCl_3$) without BINAP was also found to catalyze the present 1,4-addition reaction, addition of (*S*)-BINAP completely inhibited the reaction (entries 12 and 13). These results clearly show the advantage of the rhodium complexes as the catalyst for the asymmetric 1,4-addition of the alkenylzirconium reagents.

With the optimized reaction conditions (Table 1, entry 5), asymmetric 1,4-addition of various alkenylzirconocene chlorides **2** prepared from corresponding alkynes **1** to α,β-enones **3** were examined.[13] The results are summarized in Table 2. The reactions of linear alkenylzirconocenes **2b** and **2c** with cyclohexenone (**3a**) afforded the corresponding 1,4-adducts **4ba** and **4ca** in good yields of 83% and 96% with excellent ees of 96% and 99%, respectively (entries 1 and 2). The yield and enantioselectivity decreased in the reaction of 3,3-dimethyl-1-butenylzirconocene (**2d**) with **3a**, which gave the product **4da** in 49% yield with 79% ee (entry 3). In the reaction of styrylzirconocene (**2e**) with **3a**, the enantioselectivity was high, however, the yield was low (entry 4). The reactions of linear alkenylzirconocenes **2a** and **2b** with cyclopentenone (**3b**) afforded the corresponding 1,4-adducts **4ab** and **4bb** in excellent yields of 99% and 93%, respectively, with a good ee of 86% (entries 5 and 6). The reactions of **2a** and **2b** with cycloheptenone (**3c**) proceeded highly enantioselectively, affording the products **4ac** and **4bc** in good yield with excellent ees of 97% and 95%, respectively (entries 7 and 8). The 1,4-addition of alkenylzirconocene chlorides **2a** and **2b** to acyclic α,β-enones also proceeded enantioselectively. They added to 5-methyl-3-hexen-2-one (**3d**) to give the products **4ad** and **4bd** in good yield with 72% ee and 71% ee, respectively (entries 9 and 10). Similarly, the addition to 4-phenyl-3-buten-2-one (**3e**) gave **4ae** and **4be** in good ees of 79% ee and 80% ee (entries 11 and 12).

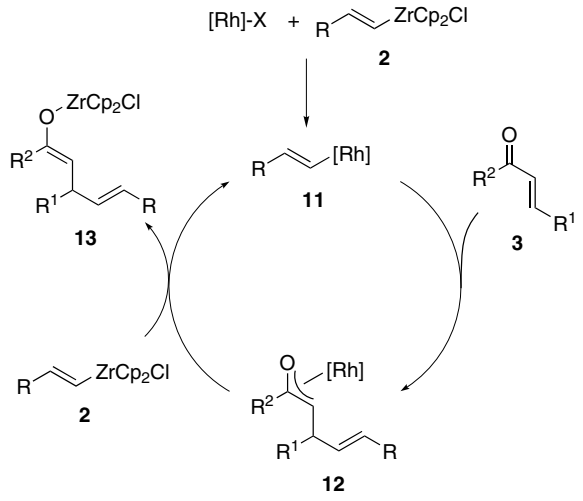
The reaction mechanism (Scheme 1) probably involves the generation of an alkenylrhodium intermediate **11** by the transmetalation between the alkenylzirconocene chloride **2** and the rhodium complex. Such reaction pathway was proposed generally in the rhodium-catalyzed 1,4-addition of various organometallic reagents.[6–9,11,12e] Alkenylrhodium **11** would then add to the α,β-enone **3** to give the oxa-π-allylrhodium **12**, which then reacts with alkenylzirconocene chloride **2** to give

Table 2. Asymmetric 1,4-addition of alkenylzirconocene chlorides **2** to α,β-enone **3** catalyzed by the rhodium-(*S*)-BINAP complexes[a]



Entry	R in **2**	α,β-enone **3**	Yield[b] (%)	Ee[c] (%)
1	C_4H_9 (**2b**)		83 (**4ba**)	96
2	C_5H_{11} (**2c**)	**3a**	96 (**4ca**)	99
3	*tert*-C_4H_9 (**2d**)	**3a**	49 (**4da**)	79
4	Ph (**2e**)	**3a**	20 (**4ea**)	95
5	C_6H_{13} (**2a**)		99 (**4ab**)	86 (*S*)
6	C_4H_9 (**2b**)	**3b**	93 (**4bb**)	86
7	C_6H_{13} (**2a**)		87 (**4ac**)	97
8	C_4H_9 (**2b**)	**3c**	63 (**4bc**)	95
9	C_6H_{13} (**2a**)		85 (**4ad**)	72
10	C_4H_9 (**2b**)	**3d**	82 (**4bd**)	71
11	C_6H_{13} (**2a**)		62 (**4ae**)	79 (*R*)
12	C_4H_9 (**2b**)	**3e**	52 (**4be**)	80

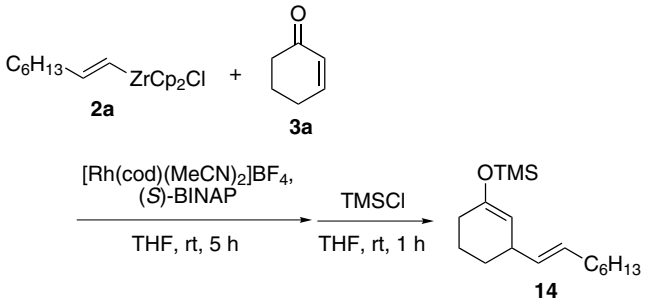
[a] Common reaction conditions: **1** (1.2 mmol), **3** (1.0 mmol), $[Rh(cod)(MeCN)_2]BF_4$ (0.05 mmol), (*S*)-BINAP (0.06 mmol), 6 mL of THF, rt, 5 h, N_2 atmosphere.
[b] Isolated yield.
[c] See Ref. 13.



Scheme 1.

the alkenylrhodium intermediate **11** and zirconium enolate **13**. Actually, when the reaction mixture of **2a** with **3a** was quenched by trimethylsilyl chloride instead of water, the formation of silyl enol ether **14** was observed by GC–Mass (Scheme 2). The stereochemical pathway of the addition of the Rh–C bond to the enones would be similar to those in the asymmetric 1,4-addition of organoboron or organotitanium reagents reported previously.[6c,9]

In conclusion, highly enantioselective 1,4-addition of alkenylzirconocene chlorides to α,β-enones was catalyzed by a chiral rhodium complex generated from $[Rh(cod)(MeCN)_2]BF_4$ and (*S*)-BINAP. (*E*)-1-Alkenyl groups can be introduced easily and enantioselectively



Scheme 2.

into β-position of a variety of ketones. Further studies to expand the scope and to clarify mechanistic details are underway.

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13. Representative procedure for (*S*)-**4aa**. To a suspension of Cp_2ZrHCl (309 mg, 1.2 mmol) in THF (4 mL), octyne (132 mg, 1.2 mmol) was added and the mixture was stirred at room temperature for 0.5 h under N_2 to give a solution of 1-octenylzirconocene chloride. In another flask, $[Rh(cod)(MeCN)_2]BF_4$ (19.0 mg, 0.05 mmol) and (*S*)-BINAP (37.4 mg, 0.06 mmol) was mixed in THF (2 mL) and stirred at room temperature for 0.5 h under N_2. To the solution of rhodium catalyst, cyclohexenone (96.1 mg, 1.0 mmol) and the solution of 1-octenylzirconocene chloride were added and the mixture was stirred at room temperature for 5 h under N_2. The reaction was quenched by adding a few drops of 2 N NH_4Cl aq and then stirred for 1 h. Et_2O (20 mL) was added to the reaction mixture and the resulting precipitate was removed by filtration. After the solvent was removed in vacuo, the residue was purified by flash chromatography (hexane/AcOEt = 10/1) to give the product (*S*)-**4aa** (202 mg, 0.97 mmol) in 97% yield. The optical yield was determined by HPLC using a chiral stationary phase column (Daicel Chiralpak AS-H, hexane/2-PrOH = 98/2). $[\alpha]_D^{30}$ −14 (*c* 1.04, $CHCl_3$) 96% ee (*S*). The absolute configuration was determined to be (*S*)-(−) according to the literature procedure.[6d] **4ba**: The optical yield was determined by HPLC (Daicel Chiralpak AS-H, hexane/2-PrOH = 98/2). $[\alpha]_D^{29}$ −18 (*c* 1.00, $CHCl_3$) 96% ee. (*S*)-**4ca**: The optical yield was determined by HPLC (Daicel Chiralpak AS-H, hexane/2-PrOH = 98/2). $[\alpha]_D^{31}$ −17 (*c* 1.04, $CHCl_3$) 99% ee (*S*) (lit.[6d] $[\alpha]_D^{20}$ −16 (*c* 0.91, $CHCl_3$), 96% ee (*S*)). **4da**: The optical yield was determined by HPLC (Daicel Chiralpak AS-H, hexane/2-PrOH = 98/2). $[\alpha]_D^{21}$ −16 (*c* 0.96, $CHCl_3$) 79% ee (lit.[6d] $[\alpha]_D^{20}$ −20 (*c* 1.31, $CHCl_3$), 91% ee). (*S*)-**4ea**: The optical yield was determined by HPLC (Daicel Chiralcel OD-H, hexane/2-PrOH = 95/5). $[\alpha]_D^{20}$ +9.1 (*c* 1.00, $CHCl_3$) 95% ee (*S*) (lit.[6d] $[\alpha]_D^{20}$ +7.6 (*c* 0.86, $CHCl_3$), 92% ee (*S*)). (*S*)-**4ab**: The optical yield was determined by HPLC (Daicel Chiralpak AS-H, hexane/2-PrOH = 98/2). $[\alpha]_D^{30}$ −65 (*c* 1.02, $CHCl_3$) 86% ee (*S*). The absolute configuration was determined to be (*S*)-(−) by correlation with (*S*)-(−)-3-carboxycyclopentanone according to the same procedure as **4aa**. (*S*)-(−)-3-carboxycyclopentanone: $[\alpha]_D^{25}$ −18 (*c* 0.58, MeOH) (lit.[14] $[\alpha]_D^{20}$ −21.8 (*c* 1.90, MeOH), 98% ee (*S*)). **4bb**: The optical yield was determined by HPLC (Daicel Chiralpak AS-H, hexane/2-PrOH = 98/2). $[\alpha]_D^{30}$ −79 (*c* 1.00, $CHCl_3$) 86% ee. **4ac**: ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 0.88 (t, $J = 7.1$ Hz, 3H), 1.23–1.37 (m, 8H), 1.36–1.49 (m, 2H), 1.56–1.67 (m, 1H), 1.83–1.99 (m, 5H), 2.30–2.37 (m, 1H), 2.47–2.57 (m, 4H), 5.35 (dd, $J = 15.4$ and 6.8 Hz, 1H), 5.41 (dt, $J = 15.4$ and 6.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 14.10, 22.65, 24.13, 28.45, 28.78, 29.45, 31.73, 32.48, 37.49, 39.07, 44.09, 49.91, 129.23, 134.23, 214.00. IR (neat): 1701 cm^{-1}. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.61; H, 11.42. The optical yield was determined by HPLC (Daicel Chiralpak AS-H, hexane/2-PrOH = 98/2). $[\alpha]_D^{26}$ −31 (*c* 1.07, $CHCl_3$) 97% ee. **4bc**: ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 0.88 (t, $J = 2.1$ Hz, 3H), 1.24–1.38 (m, 4H), 1.38–1.50 (m, 2H), 1.58–1.67 (m, 1H), 1.82–2.18 (m, 5H), 2.29–2.41 (m, 1H), 2.42–2.60 (m, 4H), 5.35 (dd, $J = 15.4$ and 6.8 Hz, 1H), 5.41 (dt, $J = 15.4$ and 6.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 13.97, 22.16, 24.14, 28.47, 31.66, 32.18, 37.51, 39.10, 44.11, 49.94, 129.20, 134.25, 214.15. Anal. Calcd for $C_{15}H_{26}O$: C, 80.35; H, 11.41. Found: C, 79.97; H, 11.56. The optical yield was determined by HPLC (Daicel Chiralpak AS-H, hexane/2-PrOH = 98/2). $[\alpha]_D^{15}$ −34 (*c* 1.04, $CHCl_3$) 95% ee. **4ad**: ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 0.83 (d, $J = 6.8$ Hz, 3H), 0.87 (d, $J = 6.9$ Hz, 3H), 0.88 (t, $J = 6.9$ Hz, 3H), 1.20–1.36 (m, 8H), 1.52–1.64 (m, 1H), 1.94–2.00 (m, 2H), 2.10 (s, 3H), 2.30–2.48 (m, 3H), 5.20 (ddt, $J = 15.3$, 8.4, and 1.3 Hz, 1H), 5.38 (dt, $J = 15.3$ and 6.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 14.09, 18.87, 20.46, 22.66, 28.79, 29.52, 30.54, 31.72, 31.92,

32.61, 45.08, 47.15, 130.22, 132.43, 208.99. IR (neat): 1716 cm^{-1}. Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.07; H, 12.73. The optical yield was determined by HPLC (Daicel Chiralpak AS-H, hexane/2-PrOH = 98/2). $[\alpha]_D^{26}$ −4.1 (*c* 1.02, $CHCl_3$) 72% ee. **4bd**: ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 0.84 (d, $J = 6.8$ Hz, 3H), 0.87 (d, $J = 6.9$ Hz, 3H), 0.88 (t, $J = 7.1$ Hz, 3H), 1.24–1.36 (m, 4H), 1.53–1.64 (m, 1H), 1.94–2.01 (m, 2H), 2.09 (s, 3H), 2.30–2.48 (m, 3H), 5.20 (ddt, $J = 15.2$, 8.5, and 1.2 Hz, 1H), 5.38 (dt, $J = 15.3$ and 6.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 13.88, 18.84, 20.43, 22.12, 30.49, 31.72, 31.88, 32.25, 45.06, 47.11, 130.23, 132.33, 208.87. The optical yield was determined by HPLC (Daicel Chiralpak AS-H, hexane/2-PrOH = 98/2). $[\alpha]_D^{18}$ −0.4 (*c* 1.02, $CHCl_3$) 71% ee. (*R*)-**4ae**: ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 0.91 (t, $J = 8.8$ Hz, 3H), 1.22–1.43 (m, 8H), 2.03 (q, $J = 8.7$ Hz, 2H), 2.12 (s, 3H), 2.78 (dd, $J = 7.1$ and 6.4 Hz, 1H), 2.81 (dd, $J = 7.2$ and 7.8 Hz, 1H), 3.88 (q, $J = 9$ Hz, 1H), 5.48 (dt, $J = 19.5$ and 8.0 Hz, 1H), 5.58 (dd, $J = 19.5$ and 8.8 Hz, 1H), 7.20–7.30 (m, 3H), 7.32–7.40 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 14.11, 22.65, 28.84, 29.33, 30.72, 31.71, 32.52, 43.98, 49.89, 126.43, 127.50, 128.58, 131.15, 132.10, 143.83, 207.43. IR (neat): 1710 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14. Found: C, 83.62; H, 10.42. The optical yield was determined by HPLC (Daicel Chiralpak AS-H, hexane/2-PrOH = 98/2). $[\alpha]_D^{27}$ −1.4 (*c* 1.04, $CHCl_3$) 79% ee (*R*). The absolute configuration was determined to be (*R*)-(−) by correlation with (*S*)-(+)-4-oxo-2-phenylpentanoic acid methyl ester according to the same procedure as **4aa**. (*S*)-(+)-4-oxo-2-phenylpentanoic acid methyl ester: $[\alpha]_D^{26}$ +121 (*c* 1.02, $CHCl_3$) (lit.[15] $[\alpha]_D^{20}$ −108.76 (*c* 0.79, $CHCl_3$), 71% ee (*R*)). **4be**: The optical yield was determined by HPLC (Daicel Chiralpak AS-H, hexane/2-PrOH = 98/2). $[\alpha]_D^{21}$ −3.1 (*c* 1.03, $CHCl_3$) 80% ee.

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