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Stereoselective Reactions. Part 31:[1] Catalytic Asymmetric Alkylation of Achiral Lithium Enolates Using a Chiral Tetradentate Amine in the Presence of an Achiral Bidentate Amine

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Abstract—Catalytic asymmetric alkylation of achiral lithium enolates of 1-tetralone and cyclohexanone with reactive alkyl halides was realized by using a combination of a chiral tetradentate amine (~0.05 equiv.) and an achiral bidentate amine (2 equiv.).

Introduction

Lithium enolates play a central role in organic synthesis, because they react with various electrophiles to undergo many synthetically important reactions, such as alkylation, acylation, aldolization, protonation, etc.[2] It is also known that the lithium enolate prepared from a carbonyl compound and a lithium amide forms a complex in solution with the amine coming from the lithium amide employed.[3] It is therefore reasonable to assume that the achiral lithium enolate prepared by using a chiral lithium amide forms a complex with the chiral amine coming from the chiral lithium amide employed, where the symmetrical π-system of the enolate is expected to exist in a chiral environment, and reacts with electrophiles enantioselectively.

Based on this strategy, we have previously reported enantioselective alkylation of achiral lithium enolates of six-membered cyclic ketones using a stoichiometric amount of a chiral tetradentate amine in the presence of lithium bromide (LiBr) in toluene.[1,4] It is suggested that the formation of a ternary complex comprising lithium enolate, chiral tetradentate amine, and LiBr is responsible for high asymmetric induction. It is also shown that the rate of the alkylation reaction of the lithium enolate of 1-tetralone is slow in the absence and in the presence of a bidentate amine, but is enhanced significantly in the presence of a tetradentate amine.[1,5] Expecting the fast exchange of two kinds of ligands to the lithium in situ,[6] efforts were made to achieve a catalytic version of this enantioselective alkylation reaction using a catalytic amount of a tetradentate amine ((*R*)-**1**) in the presence of 2 equiv. of an achiral bidentate amine as an additive.[7]

Results and Discussion

As shown in Scheme 1, the trimethylsilyl enol ether (**2**) of 1-tetralone was treated with 1.0 equiv. of MeLi–LiBr in ether to give the corresponding lithium enolate (**3**) containing LiBr. After addition of (*R*)-**1** and an achiral additive in a given solvent, benzyl bromide (10 equiv.) was added and the whole was stirred at −45°C for 18 h. Some results using *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), an achiral bidentate amine, as an additive are summarized in Table 1.

First, the reaction was examined in toluene. Without (*R*)-**1** and TMEDA, the reaction practically did not proceed (run 1) with 86% recovery of 1-tetralone, while in the presence of 2 equiv. of TMEDA, racemic **4a** was obtained in 12% yield (run 2). In the presence of 1 equiv. of (*R*)-**1**, (*R*)-**4a** was obtained with 97% ee in 56% isolated yield (run 3). These results demonstrate that (*R*)-**1** accelerates the reaction of **3**, presumably due to the deaggregation of the lithium enolate and formation of the complex with (*R*)-**1** and LiBr. However, on reducing the amount of (*R*)-**1** to a substoichiometric amount (0.2 equiv.), the product was obtained in less than 1% yield with 87% recovery of 1-tetralone (run 4). We assumed that this result might come from the deactivation of (*R*)-**1** by complexation with LiBr, because of the presence of LiBr in a large excess relative to (*R*)-**1** at the beginning of

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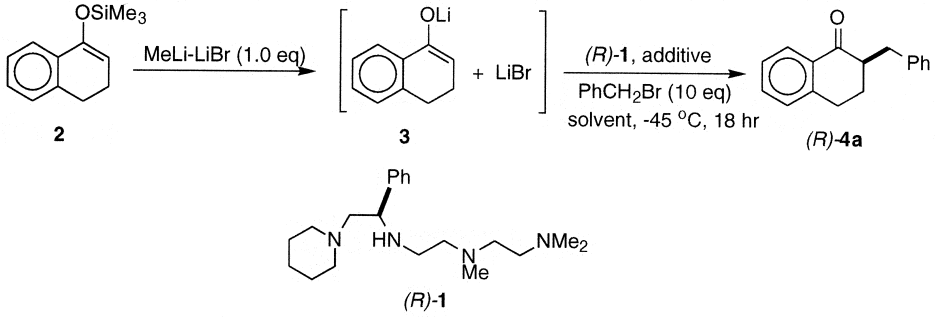


Scheme 1.

Table 1. Benzylation of **3** using (*R*)-**1** in the absence and in the presence of TMEDA (typical procedures are described in the experimental section)

Run	(*R*)-**1** (equiv.)	TMEDA (equiv.)	Solvent	Product ((*R*)-**4a**)	
				Isolated yield (%)	ee (%)
1	0	0	Toluene	<1	–
2	0	2.0	Toluene	12	–
3	1.0	0	Toluene	56	97
4	0.2	0	Toluene	<1	52
5	0.2	1.0	Toluene	68	87
6	0.2	2.0	Toluene	89	86
7[a]	0.2	2.0	Toluene	90	78
8	0.2	3.0	Toluene	87	87
9	0.2	4.0	Toluene	80	79
10	0.2	8.0	Toluene	37	52
11	0	0	DME	28	–
12	0	2.0	DME	32	–
13	1.0	0	DME	92	94
14	0.2	0	DME	82	82
15	0.2	2.0	DME	79	92
16	0.2	2.0	Cyclopentane	38	50
17	0.2	2.0	Ether	40	78
18	0.2	2.0	THF	42	77

[a] The result using a halide-free solution of MeLi in ether for the generation of **3**.

the reaction. Therefore, TMEDA was added as an additive with the intention of trapping LiBr. Both the chemical yield and ee were then increased greatly (runs 5–10). The best result was obtained by using 2.0 or 3.0 equiv. of TMEDA (runs 6 and 8). As was observed previously,[4a] the ee of the product decreased when LiBr was absent at the beginning of the reaction (run 7).

The situation is somewhat different in DME. Thus, without (*R*)-**1** and TMEDA, the product was obtained in 28% yield (run 11), which is higher than that obtained in toluene (run 1). This result suggests that the lithium enolate is deaggregated to some extent in DME. In the presence of 2 equiv. of TMEDA, the chemical yield of the product was not improved (run 12). However, in the presence of 1.0 equiv. of (*R*)-**1**, (*R*)-**4a** was obtained in reasonably good chemical and optical yields (run 13). Contrary to the reaction in toluene, reducing the amount of (*R*)-**1** to 0.2 equiv. gave (*R*)-**4a** in still higher chemical and optical yields (run 14), but a better result was obtained in the presence of 0.2 equiv. of (*R*)-**1** and 2.0 equiv. of TMEDA (run 15). It is reasonable to assume that DME can work, to some extent, to trap LiBr. The chemical yield and ee of the product were found to be dependent on the solvent used (runs 6, 15–18). Among the solvents examined, toluene and DME were most effective for the present catalytic asymmetric benzylation.

The effect of various achiral additives (2.0 equiv.) on the benzylation of **3** using 0.2 equiv. of (*R*)-**1** was then examined in toluene. The results are shown in Table 2. Of linear terminal diamines (runs 1–7), TMEDA and *N*,*N*,*N*′,*N*′-tetramethylpropylenediamine (**5**) were found to be excellent additives with respect to both chemical and optical yields of the product (runs 2 and 3), probably

Table 2. Effect of additives (2 equiv.) on the benzylation of **3** using 0.2 equiv. of (*R*)-**1** in toluene (a typical procedure is described in the experimental section)

Run	Additive	Product ((*R*)-**4a**)	
		Isolated yield (%)	ee (%)
1	$Me_2N–CH_2–NMe_2$	<3	83
2	$Me_2N–(CH_2)_2–NMe_2$ (TMEDA)	89	86
3	$Me_2N–(CH_2)_3–NMe_2$ (**5**)	83	92
4	$Me_2N–(CH_2)_4–NMe_2$	42	93
5	$(CH_2)_5N–(CH_2)_2–N(CH_2)_5$	63	86
6	$(CH_2)_5N–(CH_2)_3–N(CH_2)_5$	38	96
7	$H_2N–(CH_2)_2–NH_2$	30	88
8	$MeO–(CH_2)_2–OMe$ (DME)	15	86
9	$Me_2N–CH_2CH_3$	9	95
10[a]	$Me_2N–CH_2CH_3$	9	95
11	$Me_2N–(CH_2)_2–N(Me)–(CH_2)_2–NMe_2$	87	47

[a] The result using 4.0 equiv. of an additive.

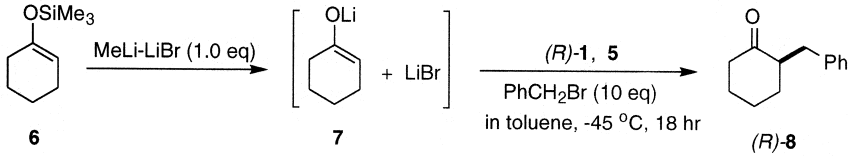
because they trap LiBr effectively by the formation of a five- or six-membered chelated structure. Changing the two terminal dimethylamino groups to the more hindered piperidino groups (runs 5 and 6), or to the less hindered amino groups (run 7) and methoxy groups (run 8) gave poorer yields, while the ee of the product remained high. The results using monodentate and tridentate ligands (runs 9–11) suggest that the bidentate ligands function more effectively.

Selecting **5** as an achiral bidentate additive in the present catalytic asymmetric benzylation reaction using (*R*)-**1**, the effect of decreasing the amount of (*R*)-**1** was examined. The results obtained with 2.0 equiv. of **5** in toluene and in DME are summarized in Table 3. In both toluene (runs 1–6) and DME (runs 7–10), good chemical and optical yields were retained, up to 0.05 equiv. of (*R*)-**1**. It is generally recognized that chemical yields are a little higher in DME, while the ees of the product are a little higher in toluene under the present catalytic conditions.

Table 3. Benzylation of **3** with catalytic amount of (*R*)-**1** in the presence of **5** (2.0 equiv.) (typical procedures are described in the experimental section)

Run	(*R*)-**1** (equiv.)	Solvent	Product ((*R*)-**4a**)	
			Isolated yield (%)	ee (%)
1	0.2	Toluene	83	92
2	0.1	Toluene	78	95
3	0.05	Toluene	76	96
4	0.05	Toluene[a]	82	95
5	0.025	Toluene	69	97
6	0.01	Toluene	29	89
7	0.2	DME	86	92
8	0.1	DME	91	93
9	0.05	DME	91	90
10	0.01	DME	55	48

[a] In toluene containing DME (32 equiv.).



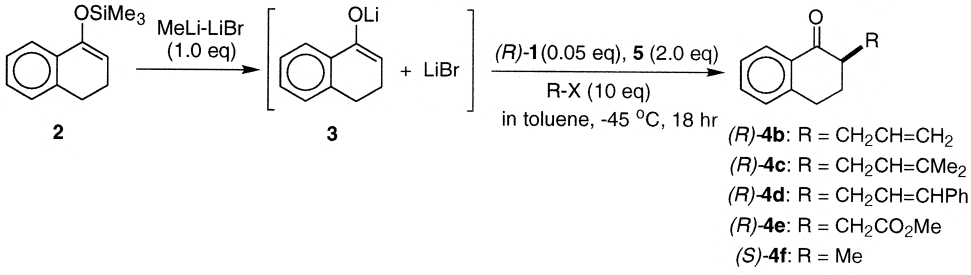
Scheme 2.

Benzylation reaction of the lithium enolate (**7**) of cyclohexanone was also examined using (*R*)-**1** and **5** in toluene. The results are shown in Table 4. These results demonstrate that (*R*)-**1** also functions as a catalyst for the benzylation of **7** (Scheme 2).

Table 4. Benzylation of **7** using (*R*)-**1** and **5** in toluene (a typical procedure is described in the experimental section)

Run	(*R*)-**1** (equiv.)	**5** (equiv.)	Product ((*R*)-**8**)	
			Isolated yield (%)	ee (%)
1[a]	1.0	0	43	91
2	0.2	2.0	52	92
3	0.1	2.0	52	90
4	0.05	2.0	47	75

[a] Data taken from Ref. 1.



Scheme 3.

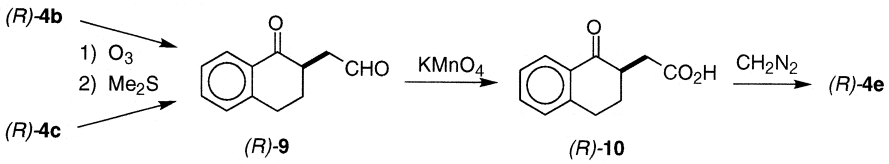
Based on these data, catalytic asymmetric alkylation of **3** with reactive alkyl halides was examined in toluene using 0.05 equiv. of (*R*)-**1** and 2.0 equiv. of **5**. The results are summarized in Table 5. It is again shown that chiral (*R*)-**1** turns over efficiently by addition of achiral **5** (Scheme 3).

The absolute configurations of (*R*)-**4a**,[4a] (*R*)-**4d**,[4a] (*S*)-**4f**,[8] and (*R*)-**8**[8] are already known. As shown in Scheme 4, (*R*)-**4b** and (*R*)-**4c** were chemically correlated to (*R*)-**4e**, whose absolute configuration was determined by circular dichroism.[4a,9,10]

Table 5. Catalytic asymmetric alkylation of **3**

Run	R–X	Product		
		4	Isolated yield (%)	ee (%)
1	CH_2=CH–CH_2Br	(*R*)-**4b**	69	96
2	Me_2C=CH–CH_2Br	(*R*)-**4c**	62	97
3	PhCH=CHCH_2Br	(*R*)-**4d**	69	91
4[a]	MeO_2C–CH_2Br	(*R*)-**4e**	84	81
5	MeI	(*S*)-**4f**	28	77

[a] Alkylation time was 40.5 h.



Scheme 4.

Conclusion

Catalytic asymmetric alkylation of the lithium enolates of 1-tetralone and cyclohexanone with reactive alkyl halides in the presence of LiBr was realized by the turnover of a chiral tetradentate amine ((*R*)-**1**) (~0.05 equiv.) by addition of an achiral bidentate amine (**5**) (2.0 equiv.) as an additive. It is assumed that **5** works to prevent deactivation of (*R*)-**1** by trapping LiBr, which exists in a large excess relative to (*R*)-**1** at the beginning of the reaction. Since the reactions of lithium enolates with electrophiles constitute the most fundamental and widely used processes in synthesis, the method mentioned here should provide a useful strategy for catalytic asymmetric reactions of achiral lithium enolates.

Experimental

General

IR spectra were recorded on a JASCO Report-100 spectrometer. ^{1}H NMR (270 MHz) and ^{13}C NMR (67.80 MHz) spectra were recorded in $CDCl_3$ on a JEOL EX-270 spectrometer. Chemical shifts are given in δ (ppm) using tetramethylsilane as an internal standard. Coupling constants (*J*) are given in hertz. Mass spectra (MS, HRMS) were recorded on a JEOL JMS-D 300 or JEOL JMS-SX 102 spectrometer. Optical rotations were measured by a Jasco DIP-370 polarimeter. For anhydrous solvents, toluene, ether, THF, DME, and cyclopentane were distilled from sodium/benzophenone ketyl under argon atmosphere. (*R*)-**1**,[11] **2**,[1] and **6**[1] were prepared as reported.

(*R*)-2-Benzyl-1-tetralone ((*R*)-4a). (a) (Table 1, run 3) Under argon atmosphere, a solution of MeLi–LiBr in ether (1.17N, 0.89 mL, 1.05 mmol) was added to **2** (228.2 mg, 1.05 mmol), and the whole was stirred at room temperature for 1.5 h. After addition of toluene (7 mL) at −20°C, a solution of (*R*)-**1** (347.5 mg, 1.05 mmol) in toluene (5 mL) was added, and the whole was stirred at −20°C for 30 min. A solution of benzyl bromide (1.24 mL, 10.5 mmol) in toluene (2 mL) was added at −78°C, and the whole was stirred at −45°C for 18 h. After the reaction mixture was cooled to −78°C, 10% aqueous citric acid (10 mL) was added, and the whole was allowed to warm to room temperature. The reaction mixture was extracted with ether (20 mL) twice, and the ethereal extracts were combined and washed with satd. aqueous $NaHCO_3$ (20 mL) and brine (20 mL). After drying ($MgSO_4$), the solvent was evaporated to dryness to give a residue, which was purified by column chromatography (silica gel, hexane/ether=50/1) to give (*R*)-**4a** (137.2 mg, 56%, 97% ee by HPLC analysis (Waters Opti-Pak TA, hexane/2-propanol=9/1)) as a colorless oil. $[\alpha]_D^{25}$ +18.1 (*c*=1.81, MeOH). Spectral data (IR, ^{1}H NMR) were identical to those reported previously.[1]

(b) (Table 1, run 4) Under argon atmosphere, a solution of MeLi–LiBr in ether (1.17N, 0.87 mL, 1.02 mmol) was added to **2** (223.0 mg, 1.02 mmol), and the whole was stirred at room temperature for 1.5 h. After addition of toluene (7 mL) at −20°C, a solution of (*R*)-**1** (68.0 mg, 0.20 mmol) in toluene (5 mL) was added, and the whole was stirred at −20°C for 30 min. A solution of benzyl bromide (1.21 mL, 10.2 mmol) in toluene (2 mL) was added at −78°C, and the whole was treated as in (a) above to give a residue after evaporation of the dried ethereal extracts. This residue was subjected to column chromatography (silica gel, hexane/ether=50/1) to give (*R*)-**4a** (1.0 mg, 0.4%, 52% ee by HPLC analysis) as a colorless oil. Further elution using hexane/ether (10/1) gave 1-tetralone (130.3 mg, 87%) as a colorless oil.

(c) (Table 1, run 6) Under argon atmosphere, a solution of MeLi–LiBr in ether (1.17N, 0.83 mL, 0.97 mmol) was added to **2** (212.8 mg, 0.97 mmol), and the whole was stirred at room temperature for 1.5 h. After addition of toluene (7 mL) at −20°C, a solution of (*R*)-**1** (65.4 mg, 0.20 mmol) in toluene (5 mL) and then TMEDA (0.29 mL, 1.95 mmol) were added, and the whole was stirred at −20°C for 30 min. A solution of benzyl bromide (1.16 mL, 9.7 mmol) in toluene (2 mL) was added at −78°C, and the whole was treated as in (a) above to give a residue after evaporation of the dried ethereal extracts. The residue was subjected to column chromatography (silica gel, hexane/ether=50/1) to give (*R*)-**4a** (203.8 mg, 89%, 86% ee by HPLC analysis) as a colorless oil.

(d) (Table 1, run 15) Under argon atmosphere, a solution of MeLi–LiBr in ether (1.16N, 0.93 mL, 1.07 mmol) was added to **2** (234.7 mg, 1.07 mmol), and the whole was stirred at room temperature for 1.5 h. After addition of DME (7 mL) at −20°C, a solution of (*R*)-**1** (70.9 mg, 0.21 mmol) in DME (5 mL) and then TMEDA (0.32 mL, 2.15 mmol) were added, and the whole was stirred at −20°C for 30 min. A solution of benzyl bromide (1.28 mL, 10.7 mmol) in DME (2 mL) was added at −78°C, and the whole was treated as in (a) above to give a residue after evaporation of the dried ethereal extracts. The residue was subjected to column chromatography (silica gel, hexane/ether=60/1) to give (*R*)-**4a** (200.6 mg, 79%, 92% ee by HPLC analysis) as a colorless oil. Further elution using hexane/ether (10/1) gave 1-tetralone (14.9 mg, 9%) as a colorless oil.

(e) (Table 2, run 3) Under argon atmosphere, a solution of MeLi–LiBr in ether (1.17N, 0.86 mL, 1.00 mmol) was

added to **2** (218.9 mg, 1.00 mmol), and the whole was stirred at room temperature for 1.5 h. After addition of toluene (7 mL) at −20°C, a solution of (*R*)-**1** (66.7 mg, 0.20 mmol) in toluene (5 mL) and then **5** (0.34 mL, 2.0 mmol) were added, and the whole was stirred at −20°C for 30 min. A solution of benzyl bromide (1.19 mL, 10.0 mmol) in toluene (2 mL) was added at −78°C, and the whole was treated as in (a) above to give a residue after evaporation of the dried ethereal extracts. The residue was subjected to column chromatography (silica gel, hexane/ether=50/1) to give (*R*)-**4a** (196.5 mg, 83%, 92% ee by HPLC analysis) as a colorless oil.

(f) (Table 3, run 3) Under argon atmosphere, a solution of MeLi–LiBr in ether (1.16N, 0.88 mL, 1.02 mmol) was added to **2** (222.4 mg, 1.02 mmol), and the whole was stirred at room temperature for 1.5 h. After addition of toluene (7 mL) at −20°C, a solution of (*R*)-**1** (17.1 mg, 0.051 mmol) in toluene (5 mL) and then **5** (0.34 mL, 2.0 mmol) were added, and the whole was stirred at −20°C for 30 min. A solution of benzyl bromide (1.21 mL, 10.2 mmol) in toluene (2 mL) was added at −78°C, and the whole was treated as in (a) above to give a residue after evaporation of the dried ethereal extracts. The residue was subjected to column chromatography (silica gel, hexane/ether=60/1) to give (*R*)-**4a** (182.3 mg, 76%, 96% ee by HPLC analysis) as a colorless oil. Further elution using hexane/ether (10/1) gave 1-tetralone (20.7 mg, 14%) as a colorless oil.

(*R*)-2-Benzylcyclohexanone ((*R*)-8). (Table 4, run 3) Under argon atmosphere, a solution of MeLi–LiBr in ether (1.16N, 0.94 mL, 1.09 mmol) was added to **6** (185.1 mg, 1.09 mmol), and the whole was stirred at room temperature for 1.5 h. After addition of toluene (7 mL) at −20°C, a solution of (*R*)-**1** (36.6 mg, 0.11 mmol) in toluene (5 mL) and then **5** (0.36 mL, 2.2 mmol) were added, and the whole was stirred at −20°C for 30 min. A solution of benzyl bromide (1.29 mL, 10.9 mmol) in toluene (2 mL) was added at −78°C, and the whole was treated as in (a) for the synthesis of (*R*)-**4a** above to give a residue after evaporation of the dried ethereal extracts. The residue was subjected to column chromatography (silica gel, hexane/ether=20/1) to give (*R*)-**8** (107.0 mg, 52%, 90% ee by HPLC analysis (Waters Opti-Pak TA, hexane/2-propanol=300/1)) as a colorless oil. Spectral data (IR, ^{1}H NMR) were identical to those reported previously.[1]

(*R*)-2-Allyl-1-tetralone ((*R*)-4b). Under argon atmosphere, a solution of MeLi–LiBr in ether (1.16N, 0.82 mL, 0.95 mmol) was added to **2** (207.7 mg, 0.95 mmol), and the whole was stirred at room temperature for 1.5 h. After addition of toluene (7 mL) at −20°C, a solution of (*R*)-**1** (16.2 mg, 0.048 mmol) in toluene (5 mL) and then **5** (0.32 mL, 1.9 mmol) were added, and the whole was stirred at −20°C for 30 min. A solution of allyl bromide (0.82 mL, 9.51 mmol) in toluene (2 mL) was added at −78°C, and the whole was treated as in (a) for the synthesis of (*R*)-**4a** above to give a residue after evaporation of the dried ethereal extracts. The residue was subjected to column chromatography (silica gel, hexane/ether=60/1) to give (*R*)-**4b** (122.3 mg, 69%, 96% ee by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol=2000/1)) as a colorless oil. $[\alpha]_D^{25}$ −29.9 (c = 1.29, MeOH). IR (neat) cm^{-1}: 1675, 1635, 1600. ^{1}H NMR: 1.78–1.95 (1H, m, CH_2–CH*H*–CH), 2.18–2.82 (4H, m, CH_2–C*H*H–C*H*, CH_2–CH=CH), 3.0 (2H, m, Ar-CH_2), 5.07 (1H, d, J=9.9, –CH=CH*H*), 5.11 (1H, d, J=11.9, –CH=C*H*H), 5.77–5.93 (1H, m, –C*H*=CH_2), 7.15–7.35 (2H, m, Ar*H*), 7.46 (1H, t, J=11,9, Ar*H*), 8.04 (1H, J=7.9, Ar*H*). Racemic **4b** is reported.[12]

(*R*)-2-Prenyl-1-tetralone ((*R*)-4c). Under argon atmosphere, a solution of MeLi–LiBr in ether (1.07N, 0.95 mL, 1.02 mmol) was added to **2** (224.4 mg, 1.02 mmol), and the whole was stirred at room temperature for 1.5 h. After addition of toluene (7 mL), a solution of (*R*)-**1** (17.2 mg, 0.051 mmol) in toluene (5 mL) and then **5** (0.34 mL, 2.0 mmol) were added, and the whole was stirred at −20°C for 30 min. A solution of prenyl bromide (1.17 mL, 10.2 mmol) in toluene (2 mL) was added at −78°C, and the whole was treated as in (a) for the synthesis of (*R*)-**4a** above to give a residue after evaporation of the dried ethereal extracts. The residue was subjected to column chromatography (silica gel 50 g, hexane/ether=60/1) to give (*R*)-**4c** (136.3 mg, 62%, 97% ee by HPLC analysis (Waters Opti-Pak TA, hexane/2-propanol=500/1)) as a colorless oil. $[\alpha]_D^{25}$ −17.9 (c = 1.51, MeOH). IR (neat) cm^{-1}: 1680, 1600. ^{1}H NMR: 1.64 (3H, s, –CH_3), 1.72 (3H, s, –CH_3), 1.75–1.95 (1H, m, –CH_2–C*H*H–CH_2–), 2.15–2.30 (2H, m, –CH_2–CH*H*–CH_2– and –CH*H*–CH=), 2.45–2.55 (1H, m, –CO–C*H*), 2.60–2.75 (1H, m, –C*H*H–CH=), 2.98 (2H, dd, J=7.4, 7.6, Ar-CH_2), 5.18 (1H, dd, J=7.9, 7.6, –CH_2–C*H*=C), 7.23 (1H, d, J=7.6, Ar*H*), 7.30 (1H, t, J=7.3, Ar*H*), 7.46 (1H, t, J=7.3, Ar*H*), 8.04 (1H, d, J=7.6, Ar*H*). ^{13}C NMR: 17.88, 25.86, 27.98, 28.10, 28.64, 48.07, 121.80, 126.54, 127.44, 128.68, 132.61, 133.10, 133.53, 144.13, 200.00. MS *m/z*: 214 (M^+). HRMS *m/z*: Calcd for $C_{15}H_{18}O$: 214.1358. Found: 214.1359.

(*R*)-2-Cinnamyl-1-tetralone ((*R*)-4d). Under argon atmosphere, a solution of MeLi–LiBr in ether (1.16N, 0.81 mL, 0.94 mmol) was added to **2** (204.0 mg, 0.93 mmol), and the whole was stirred at room temperature for 1.5 h. After addition of toluene (7 mL), a solution of (*R*)-**1** (15.8 mg, 0.047 mmol) in toluene (5 mL) and then **5** (0.31 mL, 1.9 mmol) were added, and the whole was stirred at −20°C for 30 min. A solution of cinnamyl bromide (1.84 g, 9.34 mmol) in toluene (2 mL) was added at −78°C, and the whole was treated as in (a) for the synthesis of (*R*)-**4a** above to give a residue after evaporation of the dried ethereal extracts. The residue was subjected to column chromatography (silica gel, hexane/ether=50/1 to 10/1) to give (*R*)-**4d** (179.5 mg, 69%, 91% ee by HPLC analysis (Waters Opti-Pak TA, hexane/2-propanol=100/1)) as a pale yellow oil. $[\alpha]_D^{25}$ +15.0 (c=1.00, EtOH) (reported[1] $[\alpha]_D^{25}$ +16.0 (c=1.02, EtOH) for (*R*)-**4d** of 88% ee). Spectral data (IR, ^{1}H NMR) were identical to those reported.[1]

(*R*)-2-Carbomethoxymethyl-1-tetralone ((*R*)-4e). (a) Under argon atmosphere, a solution of MeLi–LiBr in ether (1.07N, 0.95 mL, 1.02 mmol) was added to **2** (221.4 mg, 1.01 mmol), and the whole was stirred at room temperature for 1.5 h. After addition of toluene (7 mL), a solution of

(*R*)-**1** (17.0 mg, 0.051 mmol) in toluene (5 mL) and then **5** (0.34 mL, 2.0 mmol) were added, and the whole was stirred at −20°C for 30 min. A solution of methyl bromoacetate (0.96 mL, 10.1 mmol) in toluene (2 mL) was added at −78°C, and the whole was treated as in (a) for the synthesis of (*R*)-**4a** above to give a residue after evaporation of the dried ethereal extracts. The residue was subjected to column chromatography (silica gel, hexane/ether=15/2) to give (*R*)-**4e** (185.0 mg, 84%, 81% ee by HPLC analysis (Waters Opti-Pak XC, hexane/2-propanol=100/1)) as a pale yellow oil, which solidified on scratching. $[\alpha]_D^{25}$ −20.0 (*c*=−1.07, MeOH). IR (neat) cm^{-1}: 1730, 1680. ^1H NMR: 1.97 (1H, dddd, *J*=12.9, 12.7, 12.5, 4.6, CH–CH*H*–CH_2), 2.2–2.3 (1H, m, CH–C*H*H–CH_2), 2.44 (1H, dd, *J*=17.7, 7.9, CH–CH*H*–CO), 2.92–3.20 (4H, m, CO–C*H*–C*H*H–CO, Ar–CH_2), 3.37 (3H, s, OCH_3), 7.22–7.33 (2H, m, Ar*H*, 7.47 (1H, t, *J*=7.6, Ar*H*), 8.02 (1H, d, *J*=7.6, Ar*H*). ^{13}C NMR: 29.27, 34.88, 44.80, 51.73, 126.66, 127.46, 128.75, 132.13, 133.42, 144.01, 173.01, 198.31. MS *m/z*: 218 (M^+). Racemic (*R*)-**4e** is reported.[13] A sample ($[\alpha]_D^{25}$ −16.5 (*c*=1.20, MeOH), 67% ee by HPLC analysis (Waters Opti-Pak XC, hexane/2-propanol=100/1)) showed $[\theta]_{365}$=−424 (*c*=1.20, MeOH), indicating *R*-configuration.[4a,9,10]

(b) A stirred suspension of nitrosomethylurea (1 g, 10 mmol) in ether (10 mL) was mixed with 50% aqueous KOH (10 mL) at 0°C. The ethereal phase was separated and dried over KOH. This CH_2N_2 solution (5 mL) was added dropwise to a solution of (*R*)-**10** (19 mg, 0.093 mmol) obtained as described below in ether (10 mL) to give a yellow solution. After quenching the reaction mixture with AcOH (0.5 mL), H_2O (20 mL) was added. The ethereal phase was separated and the aqueous phase was extracted with ether (20 mL) twice. The ethereal extracts were combined, washed with satd. aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$, and evaporated to dryness to give a residue. This residue was subjected to column chromatography (silica gel, hexane/ether=60/1) to give the product (9.7 mg, 48%). Spectral data (IR, ^1H NMR) were identical to those obtained in (a). By HPLC analysis, this sample was found to have *R*-configuration of 82% ee.

(c) (*R*)-**4c** (52.1 mg, 97% ee by HPLC analysis) described above was converted to (*R*)-**4e** (30.8 mg, 58% yield) by the sequence of reactions described below for the conversion of (*R*)-**4b** to (*R*)-**10**, followed by treatment with CH_2N_2 to (*R*)-**4e** described above in (b). Spectral data (IR, ^1H NMR) were identical to those obtained in (a). By HPLC analysis, this sample was found to have *R*-configuration of 72% ee.

(*S*)-2-Methyl-1-tetralone ((*S*)-4f). Under argon atmosphere, a solution of MeLi–LiBr in ether (1.16N, 0.81 mL, 0.94 mmol) was added to **2** (205.0 mg, 0.94 mmol), and the whole was stirred at room temperature for 1.5 h. After addition of toluene (7 mL), a solution of (*R*)-**1** (15.6 mg, 0.047 mmol) in toluene (5 mL) and then **5** (0.31 mL, 1.9 mmol) were added, and the whole was stirred at −20°C for 30 min. A solution of methyl iodide (0.58 mL, 9.4 mmol) in toluene (2 mL) was added at −78°C, and the whole was treated as in (a) for the synthesis of (*R*)-**4a** above to give a residue after evaporation of the dried ethereal extracts. The residue was subjected to column chromatography (silica gel, hexane/ether=60/1) to give (*S*)-**4f** (41.9 mg, 28%, 77% ee by HPLC analysis (Daicel Chiralcel OD-H, hexane/2-propanol=600/1)). Spectral data (IR, ^1H NMR) were identical to those reported.[1]

(*R*)-2-Formylmethyl-1-tetralone ((*R*)-9). Dried ozone-oxygen gas was passed through a colorless solution of (*R*)-**4b** ($[\alpha]_D^{25}$=−29.9 (*c*=1.29, MeOH), 96% ee by HPLC analysis) (39.2 mg) in CH_2Cl_2 (1 mL) at −80°C for 5 min until the resulting solution became blue-white. After addition of CH_2Cl_2 (5 mL), argon gas was passed through at −80°C until the resulting solution became colorless. Dimethyl sulfide (0.2 mL) was added at −80°C, and the resulting solution was stirred at 0°C for 10 min, and at room temperature for 1.5 h. The whole was mixed with CH_2Cl_2 (5 mL) and water (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (20 mL) twice. The organic extracts were combined, washed with brine (10 ml), dried over $MgSO_4$, and evaporated to dryness. The residue was subjected to column chromatography (silica gel, hexane/ether=20/1) to give crude (*R*)-**9** (24.0 mg, 61%) as a colorless oil. This sample was used for the next step without further purification. IR (neat) cm^{-1}: 1720, 1680. ^1H NMR: 1.95 (1H, m, CH_2–CH*H*–CH), 2.15–2.35 (1H, m, CH_2–C*H*H–CH), 2.55 (1H, m, CH–CH*H*–CO), 2.9–3.2 (4H, m, CO–C*H*, Ar-CH_2, CH–C*H*H–CO), 7.20–7.35 (2H, Ar*H*), 7.49 (1H, t, *J*=7.6, Ar*H*), 8.02 (1H, d, *J*=7.6, Ar*H*), 9.92 (1H, s, C*H*O). ^{13}C NMR: 29.29, 29.45, 43.24, 44.26, 126.70, 127.48, 128.77, 131.95, 133.57, 144.01, 198.38, 200.63.

(*R*)-2-Carboxymethyl-1-tetralone ((*R*)-10). A solution of (*R*)-**9** (24.0 mg, 0.13 mmol) obtained above in *t*-BuOH (0.78 mL) was mixed with 5% aqueous NaH_2PO_4 (0.52 mL). Under vigorous stirring, aqueous $KMnO_4$ (1N, 1.3 mL, 0.13 mmol) was slowly added, and the whole was stirred at room temperature for 1.5 h. After addition of satd. aqueous Na_2SO_3 (6 mL), the whole was mixed with 10% aqueous HCl (11 mL) to pH 1, and was extracted with ether (20 mL) four times. The organic extracts were combined, washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, and evaporated to dryness to give crude (*R*)-**10** (19.0 mg, 73%) as a yellow oil. This sample was used for the next step without further purification. IR (neat) cm^{-1}: 1710, 1680. ^1H NMR: 1.85–2.1 (1H, m, CH_2–CH*H*–CH), 2.2–2.35 (1H, m, CH_2–C*H*H–CH), 2.50 (1H, dd, *J*=18.3, 8.3, CH–CH*H*–CO), 2.9–3.2 (4H, m, C*H*–CH_2, Ar-CH_2, CH–C*H*H–CO), 7.2–7.35 (2H, m, Ar*H*), 7.49 (1H, t, *J*=7.6, Ar*H*), 8.03 (1H, d, *J*=7.6, Ar*H*).

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