JOC The Journal of Organic Chemistry

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Catalytic Asymmetric α-Alkylation of Ketones and Aldehydes with *N*-Benzylic Sulfonamides through Carbon−Nitrogen Bond Cleavage

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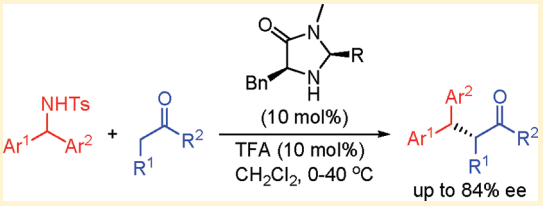
Supporting Information

ABSTRACT: A range of ketones and aldehydes smoothly undergo asymmetric S_N1 α-alkylation with *N*-benzylic sulfonamides in the presence of 10 mol % of a chiral imidazolidinone and trifluoroacetic acid to give the corresponding products in good to excellent yields and with good enantioselectivity. This chemistry has been successfully extended to the asymmetric desymmetrization of 4-substituted cyclohexanones, which exhibits greater than 99:1 diastereoselectivity and good enantioselectivity.



N-Benzylic sulfonamides have recently emerged as useful sp^3 carbon electrophiles to couple with a range of nucleophiles, such as aromatic compounds, active methylene compounds, alkynes, thiols, sulfinic acids, and silanes, through acid-catalyzed carbon−nitrogen bond cleavage in an S_N1 manner.[1,2] Since such reactions yield primary sulfonamides as neutral byproducts, *N*-benzylic sulfonamides have been demonstrated to serve as unique alkylating agents with regard to reducing undesired side reactions, such as overalkylation and elimination, when compared to benzylic halides that are commonly employed but inevitably lead to the formation of hydrogen halides as strongly acidic byproducts.[3] It is noteworthy that in 2010 You and coworkers disclosed a chiral phosphoric acid-catalyzed asymmetric Friedel−Crafts alkylation reaction of indoles with *N*-sulfonyl(3-indolyl)methanamines in moderate enantioselectivity.[1g] To our knowledge, nucleophiles other than aromatic compounds have not been reported previously to be alkylated with *N*-benzylic sulfonamides in a catalytic asymmetric fashion. Herein, we report, for the first time, a chiral amine-catalyzed asymmetric α-alkylation reaction of ketones and aldehydes with *N*-benzylic sulfonamides through carbon−nitrogen bond cleavage.

The asymmetric α-alkylation of ketones and aldehydes has long been recognized as a powerful tool for chemical synthesis and has usually been realized by attacking carbon electrophiles in an S_N2 manner.[4] To extend the scope of carbon electrophiles, catalytic asymmetric S_N1 α-alkylation of aldehydes has recently been realized through enamine activation with a range of chiral amines.[5] 3-(1-Arylsulfonylalkyl)indoles, benzylic alcohols, and benzylic bromides have been employed as effective alkylating agents by Melchiorre,[6] Cozzi,[7] and Jacobsen,[8] respectively. Moreover, Luo and Cheng described an asymmetric S_N1 α-alkylation reaction of ketones with benzylic alcohols in moderate to good enantioselectivity catalyzed by pyrrolidine-derived functionalized chiral ionic liquids.[9,10] Inspired by these findings, we envisaged that chiral amine-activated ketones and aldehydes could undergo asymmetric S_N1 α-alkylation with *N*-benzylic sulfonamides under acidic conditions. Since this reaction would occur through the cleavage of carbon−nitrogen bonds rather than carbon−sulfur, carbon−oxygen, and carbon−bromide bonds, new reactivity and selectivity were expected to extend the scope for the catalytic asymmetric α-alkylation of ketones and aldehydes.

Initially, *N*-(9*H*-thioxanthen-9-yl)-*p*-toluenesulfonamide (**1a**) was selected as the alkylating agent for the catalytic asymmetric α-alkylation of ketones. It was not reported previously for the introduction of a 9*H*-thioxanthen-9-yl group to the α-position of a ketone in a catalytic asymmetric manner. Moreover, the thioxanthene moiety is present in some potent inhibitors of acetyl- and butyrylcholinesterase with potential for treatment of Alzheimer's disease.[11] To our delight, the α-alkylation of cyclohexanone (**2a**, 3.0 equiv) with *N*-benzylic sulfonamide **1a** proceeded smoothly in the presence of L-cysteine (**4a**)/trifluoroacetic acid (1:1, 35 mol %) in dichloromethane at room temperature and gave product **3a** in 74% yield and with 44% ee (Table 1, entry 1). Encouraged by this result, a range of solvents were examined, but no better enantioselectivity was obtained (Table 1, entries 2−5). While a weaker acid, such as acetic acid or benzoic acid, failed to promote the alkylation reaction, a stronger acid, such as *p*-toluenesulfonic acid or trifluoromethanesulfonic acid, failed to induce enantioselectivity (Table 1, entries 6−9). Further studies revealed that the enantioselectivity was significantly affected by the structure of chiral amine catalysts (Table 1, entries 10−16), and gratifyingly, the employment of imidazolidinone **4h** resulted in the formation of product **3a** in 98% yield and with 72% ee (Table 1, entry 16). The enantioselectivity was enhanced to 82% ee by performing the reaction at 10 °C (Table 1, entry 17), but further lowering the temperature did not lead to better enantioselectivity (Table 1, entry 18). Replacement of the *p*-toluenesulfonyl group of substrate

Received: July 8, 2011
Published: August 25, 2011

Scheme 1. Proposed Catalytic Cycle

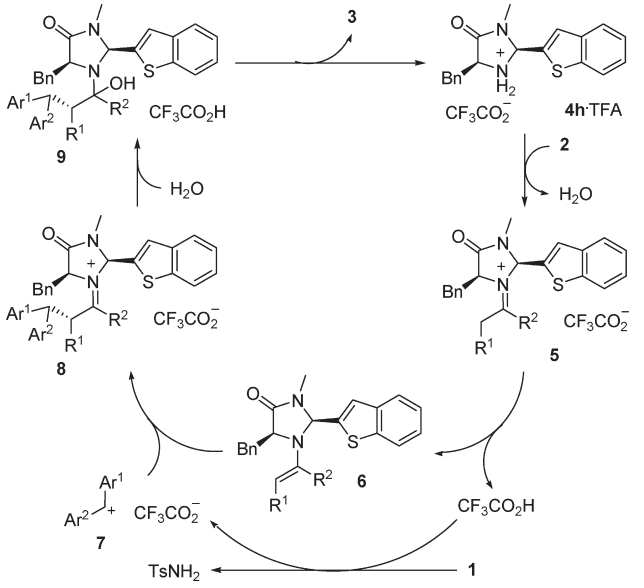
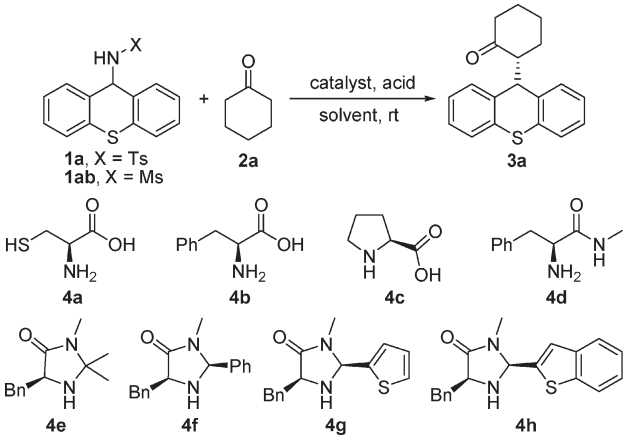


Table 1. Optimization of Reaction Conditions[a]



entry	1a or 1ab	catalyst (mol %)	acid (mol %)	solvent	yield[b] (%)	ee[c] (%)
1[d]	**1a**	**4a** (35)	TFA (35)	CH_2Cl_2	74	44
2	**1a**	**4a** (35)	TFA (35)	$CHCl_3$	68	22
3	**1a**	**4a** (35)	TFA (35)	$(ClCH_2)_2$	93	37
4	**1a**	**4a** (35)	TFA (35)	toluene	75	14
5	**1a**	**4a** (35)	TFA (35)	solvent[e]	trace	
6	**1a**	**4a** (35)	$MeCO_2H$ (35)	CH_2CI_2	0	
7	**1a**	**4a** (35)	$PhCO_2H$ (35)	CH_2Cl_2	0	
8[d]	**1a**	**4a** (35)	PTS (35)	CH_2Cl_2	67	1
9[d]	**1a**	**4a** (35)	TfOH (35)	CH_2Cl_2	53	0
10	**1a**	**4b** (35)	TFA (35)	CH_2Cl_2	79	37
11	**1a**	**4c** (35)	TFA (35)	CH_2Cl_2	86	0
12	**1a**	**4d** (35)	TFA (35)	CH_2Cl_2	90	11
13	**1a**	**4e** (35)	TFA (35)	CH_2Cl_2	39	2
14	**1a**	**4f** (35)	TFA (35)	CH_2Cl_2	93	53
15[d]	**1a**	**4g** (35)	TFA (35)	CH_2Cl_2	94	69
16[d]	**1a**	**4h** (35)	TFA (35)	CH_2Cl_2	98	72
17[f]	**1a**	**4h** (35)	TFA (35)	CH_2Cl_2	97	82
18[g]	**1a**	**4h** (35)	TFA (35)	CH_2C_{12}	60	82
19[f]	**1ab**	**4h** (35)	TFA (35)	CH_2Cl_2	97	80
20[f,h]	**1a**	**4h** (35)	TFA (35)	CH_2Cl_2	95	80
21[h,i]	**1a**	**4 h(10)**	**TFA** (10)	**CH_2Cl_2**	**92**	**81**

[a] Reaction conditions: sulfonamide **1a** or **1ab** (0.20 mmol), ketone **2a** (0.60 mmol), catalyst, acid, solvent (1.0 mL), rt, 2 d. [b] Isolated yield. [c] Determined by chiral stationary-phase HPLC analysis. [d] The reaction was run for 1 d. [e] Et_2O, THF, dioxane, EtOAc, DMF, DMSO, MeCN, or MeOH. [f] The reaction was run at 10 °C. [g] The reaction was run at 0 °C. [h] 0.24 mmol of ketone **2a** was used. [i] The reaction was run in 0.80 mL of CH_2Cl_2 at 10 °C for 3 d.

1a with a methanesulfonyl group slightly decreased the enantioselectivity (Table 1, entry 19). Finally, reducing the amount of ketone **2a** from 3.0 to 1.2 equiv and the catalyst loading from 35 to 10 mol % resulted in the formation of product **3a** in 92% yield and with 81% ee (Table 1, entry 21).

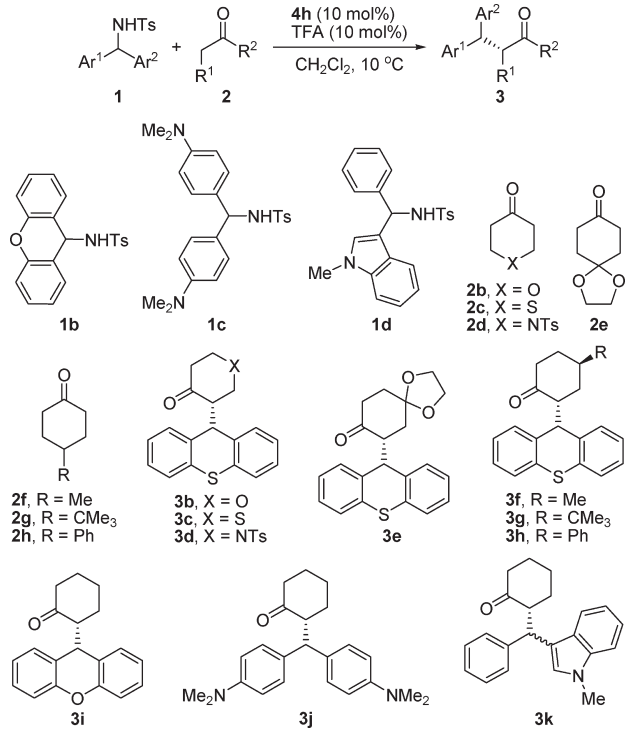
Other than cyclohexanone (**2a**), a range of cyclic ketones were found to serve as suitable substrates. Either 4-oxotetrahydropyran (**2b**) or 4-oxothiane (**2c**) was reacted with sulfonamide **1a** in the presence of 10 mol % of imidazolidinone **4h** and trifluoroacetic acid to give the corresponding alkylation product in an excellent yield and with good enantioselectivity (Table 2, entries 2 and 3). In contrast, lower enantioselectivity was obtained from the reaction with 1-tosyl-4-piperidone (**2d**) or 1,4-cyclohexanedione monoethyleneketal (**2e**) (Table 2, entries 4 and 5). This chemistry was successfully extended to the asymmetric desymmetrization of 4-substituted cyclohexanones such as **2f**, **2g**, and **2h**, which exhibited greater than 99:1 diastereoselectivity and good enantioselectivity (Table 2, entries 6−8). Although cyclopentanone, cyclooctanone, and 1-tetralone were found to react well with sulfonamide **1a** under the same conditions, less than 10% ee was observed. Moreover, acyclic ketones, such as acetone and 5-nonanone, failed to undergo α-alkylation. A few other *N*-benzylic sulfonamides were able to undergo catalytic asymmetric α-alkylation with cyclohexanone (**2a**) to give the corresponding products in moderate to good enantioselectivity (Table 2, entries 9−11). Nevertheless, this reaction was not applicable to less reactive *N*-benzylic sulfonamides such as *N*-benzhydryl-*p*-toluenesulfonamide and *N*-benzyl-*p*-toluenesulfonamide.[12]

According to the previous studies on the acid-catalyzed carbon−nitrogen bond cleavage[1,2] and enamine catalysis,[5] we propose the following catalytic cycle for the chiral amine-catalyzed asymmetric α-alkylation of ketones with *N*-benzylic sulfonamides under acidic conditions (Scheme 1). Enamine **6** is initially generated from imidazolidinone **4h** and ketone **2** via iminium **5** in the presence of trifluoroacetic acid, which also catalyzes the transformation of *N*-benzylic sulfonamide **1** into carbocation **7** through carbon−nitrogen bond cleavage. Diastereoselective attack of enamine **6** to carbocation **7** predominantly results in the formation of iminium **8**, which is subjected to hydrolysis to give product **3** via hemiaminal **9** and meanwhile release the chiral amine catalyst. This catalytic cycle is substantially supported by ESI-MS (positive mode) spectroscopic analysis of the reaction mixture of *N*-benzylic sulfonamide **1a** and ketone **2a** in the presence of 10 mol % of imidazolidinone **4h** and trifluoroacetic acid, from which enamine **6a** and hemiaminal **9a** were identified as critical intermediates (Table 3).

Although imidazolidinone **4h** could catalyze the α-alkylation of aldehyde **2i** with *N*-benzylic sulfonamide **1a** under the same conditions, hardly any enantioselectivity was observed.

dx.doi.org/10.1021/jo2014142 |*J. Org. Chem.* 2011, 76, 8095–8099

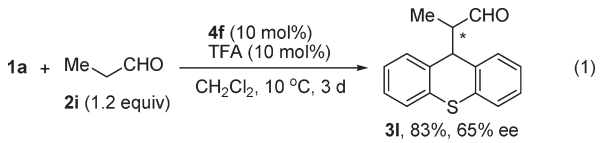
Table 2. Catalytic Asymmetric α-Alkylation of Ketones with *N*-Benzylic Sulfonamides[a]



entry	1	2	product	yield[b] (%)	dr[c]	ee[d] (%)
1	**1a**	**2a**	**3a**	92		81
2	**1a**	**2b**	**3b**	94		80
3	**1a**	**2c**	**3c**	95		84
4	**1a**	**2d**	**3d**	96		60
5[e]	**1a**	**2e**	**3e**	83		62
6	**1a**	**2f**	**3f**	93	99:1	80
7	**1a**	**2g**	**3g**	95	99:1	81
8[f]	**1a**	**2h**	**3h**	96	99:1	80
9[e]	**1b**	**2a**	**3i**	81		60
10[g]	**1c**	**2a**	**3j**	82		50
11	**1d**	**2a**	**3k**	96	59:41	82 (80)[h]

[a] Reaction conditions: sulfonamide **1** (0.20 mmol), ketone **2** (0.24 mmol), imidazolidinone **4h** (10 mol %), TFA (10 mol %), CH_2Cl_2 (0.80 mL), 10 °C, 3 d. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by chiral stationary-phase HPLC analysis. [e] The reaction was run at 0 °C for 4 d. [f] The absolute configuration of product **3h** was determined by single-crystal X-ray analysis and that of the rest of new products was assigned by analogy. [g] The reaction was run at 40 °C. [h] The ee of the minor diastereomer is shown in the parentheses.

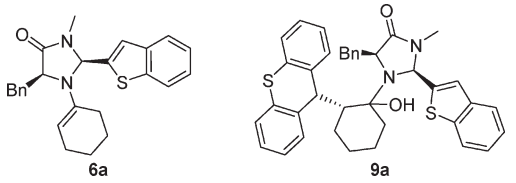
Gratifyingly, alternative use of imidazolidinone **4f** as the catalyst led to the formation of product **3l** in 83% yield and with 65% ee (eq 1).



(1)

In summary, we have developed an unprecedented catalytic asymmetric S_N1 α-alkylation reaction of ketones and aldehydes with *N*-benzylic sulfonamides through carbon−nitrogen bond cleavage. A range of cyclic ketones are reacted with *N*-benzylic sulfonamides in the presence of 10 mol % of a chiral imidazolidinone and trifluoroacetic acid to give the corresponding alkylation products in good to excellent yields and with good enantioselectivity. This chemistry has been successfully extended to the asymmetric desymmetrization of 4-substituted cyclohexanones, which exhibits greater than 99:1 diastereoselectivity and good enantioselectivity. A plausible catalytic cycle is proposed and substantially supported by ESI-MS spectroscopic analysis of the reaction mixture. Moreover, this method is applicable to aliphatic aldehydes by switching the chiral amine catalyst.

Table 3. High-Resolution Mass Data of Intermediates Detected in the Reaction Mixture of Sulfonamide 1a and Ketone 2a

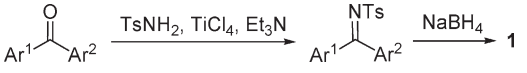


entry	species	mass (calcd)	mass (found)	formula	error (ppm)
1	$[\mathbf{6a} + H]^+$	403.18386	403.18369	$C_{25}H_{27}N_2OS$	0.4
2	$[\mathbf{9a} + H]^+$	617.22910	617.22839	$C_{38}H_{37}N_2O_2S_2$	1.2

EXPERIMENTAL SECTION

General Information. ^{1}H and ^{13}C NMR spectra were recorded using tetramethylsilane as an internal reference. Chemical shifts (δ) and coupling constants (J) are expressed in ppm and Hz, respectively. High-pressure liquid chromatography (HPLC) analyses were performed on an instrument equipped with an isostatic pump, using a chiral stationary-phase column (250 × 4.6 mm), and the UV detection was monitored at 254 nm. Optical rotations were measured on a polarimeter with a sodium lamp at λ = 589 nm and reported as $[\alpha]^{T(°C)}_D$ (c = g/100 mL, solvent). Melting points were uncorrected. Chiral imidazolidinone catalysts were prepared according to known procedures.[13]

Preparation of *N*-Benzylic Sulfonamides.



To a solution of *p*-toluenesulfonamide (2.05 g, 12.0 mmol) and a ketone (10.0 mmol) in 1,2-dichloroethane (40 mL) under nitrogen at room temperature were added dropwise titanium tetrachloride (1.14 g, 0.66 mL, 6.0 mmol) and triethylamine (2.02 g, 2.78 mL, 20.0 mmol). The mixture was heated at reflux for 10 h and cooled to room temperature. The resulting *N*-sulfonylimine was collected by filtration and purified by recrystallization from ethyl acetate and petroleum ether.[14] To a solution of the *N*-sulfonylimine (5.0 mmol) in ethanol (20 mL) at 0 °C was added sodium borohydride (378 mg, 10.0 mmol). The mixture was stirred at room temperature for 8 h, quenched with ice−water (20 mL), and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated. The residue was recrystallized from dichloromethane and petroleum ether to give *N*-benzylic sulfonamide **1**. Sulfonamides **1a**, **1ab**, **1b**, and **1c** were obtained in 63%, 59%, 60%, and 47% yields (two steps), respectively. These sulfonamides are known compounds.

dx.doi.org/10.1021/jo2014142 |J. Org. Chem. 2011, 76, 8095–8099

General Procedure for the Catalytic Asymmetric α-Alkylation of Ketones and Aldehydes with *N*-Benzylic Sulfonamides. To a solution of trifluoroacetic acid (2.3 mg, 10 mol %) in dichloromethane (0.80 mL) under nitrogen at 10 °C was added catalyst **4h** (6.5 mg, 10 mol %). The mixture was stirred for 10 min, and ketone (or aldehyde) **2** (0.24 mmol) and *N*-benzylic sulfonamide **1** (0.20 mmol) were added. The resulting mixture was stirred at 10 °C for 3 d and purified by flash column chromatography on silica gel, eluting with dichloromethane/petroleum ether (1:1 to 8:1), to give product **3**.

*(R)-2-(9H-Thioxanthen-9-yl)cyclohexanone (**3a**):* white solid; mp 142−143 °C; $[\alpha]^{20}_{D}$ +23.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.43−7.35 (m, 2H), 7.25−7.08 (m, 5H), 4.68 (d, *J* = 9.2 Hz, 1H), 3.15−3.05 (m, 1H), 2.35−2.28 (m, 1H), 2.21−2.14 (m, 1H), 1.98−1.92 (m, 1H), 1.75−1.32 (m, 4H), 1.26−1.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0, 138.6, 136.7, 133.8, 132.8, 131.0, 130.3, 127.3, 127.2, 126.7, 126.4, 126.3, 50.5, 47.3, 43.2, 33.9, 28.9, 25.3; IR (film) ν 3020, 2941, 1707, 1523, 1466, 1444 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{18}OS$ (M) 294.1078, found 294.1082. The ee was determined to be 81% by HPLC analysis on a Chiralpak AD column, λ = 254 nm, *n*-hexane/*i*-PrOH (99:1), flow rate = 0.60 mL/min; t_R = 15.70 min (major), 17.38 min (minor).

*(S)-3-(9H-Thioxanthen-9-yl)-4-oxotetrahydropyran (**3b**):* yellow solid; mp 172−173 °C; $[\alpha]^{20}_{D}$ +53.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.39 (m, 3H), 7.34−7.28 (m, 1H), 7.24−7.14 (m, 4H), 4.72 (d, *J* = 9.6 Hz, 1H), 4.02−3.94 (m,1H), 3.90−3.84 (m, 1H), 3.50−3.39 (m, 2H), 3.24−3.16 (m, 1H), 2.63−2.55 (m, 1H), 2.49−2.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 136.8, 134.9, 133.8, 133.0, 130.0, 129.8, 127.6, 127.5, 127.3, 127.0, 126.7, 126.6, 71.6, 69.2, 51.3, 46.1, 43.1; IR (film) ν 2919, 1708, 1465, 1417 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{16}O_2S$ (M) 296.0871, found 296.0859. The ee was determined to be 80% by HPLC analysis on a Chiralpak OD column, λ = 254 nm, *n*-hexane/*i*-PrOH (98:2), flow rate = 0.60 mL/min; t_R = 16.80 min (major), 22.27 min (minor).

*(R)-3-(9H-Thioxanthen-9-yl)-4-oxothiane (**3c**):* white solid; mp 166−167 °C; $[\alpha]^{20}_{D}$ +58.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.38 (m, 3H), 7.35−7.29 (m, 1H), 7.24−7.13 (m, 4H), 4.88 (d, *J* = 10.0 Hz, 1H), 3.48−3.40 (m, 1H), 3.00−2.84 (m, 2H), 2.82−2.74 (m, 1H), 2.63−2.55 (m, 1H), 2.53−2.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 136.8, 135.2, 133.8, 133.1, 130.3, 130.0, 127.7, 127.6, 127.2, 126.9, 126.7, 126.6, 51.6, 47.5, 44.8, 35.4, 31.9; IR (film) ν 3021, 1707, 1524, 1467, 1426 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{16}OS_2$ (M) 312.0643, found 312.0623. The ee was determined to be 84% by HPLC analysis on a Chiralpak OD column, λ = 254 nm, *n*-hexane/*i*-PrOH (98:2), flow rate = 1.0 mL/min; t_R = 9.76 min (major), 16.83 min (minor).

*(S)-3-(9H-Thioxanthen-9-yl)-1-tosyl-4-piperidinone (**3d**):* yellow solid; mp 219−220 °C; $[\alpha]^{20}_{D}$ +34.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.52 (m, 3H), 7.49−7.39 (m, 2H), 7.35−7.23 (m, 5H), 7.21−7.14 (m, 2H), 4.75 (d, *J* = 9.6 Hz, 1H), 3.64−3.56 (m, 1H), 3.24−3.05 (m. 3H), 2.78−2.65 (m, 2H), 2.42−2.33 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 144.3, 135.6, 134.7, 133.5, 133.3, 133.0, 130.8, 130.0, 129.2, 127.7, 127.6, 127.5, 127.2, 126.8, 49.5, 49.0, 47.1, 40.4, 27.1; IR (film) ν 3021, 2402, 1719, 1600, 1524, 1468, 1442 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{23}NO_3S_2$ (M) 449.1119, found 449.1102. The ee was determined to be 60% by HPLC analysis on a Chiralpak AD column, λ = 254 nm, *n*-hexane/*i*-PrOH (80:20), flow rate = 1.0 mL/min; t_R = 13.96 min (minor), 15.59 min (major).

*(R)-3-(9H-Thioxanthen-9-yl)-1,4-cyclohexanedione monoethyleneketal (**3e**):* yellow solid; mp 122−123 °C; $[\alpha]^{20}_{D}$ +33.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.43−7.36 (m, 2H), 7.26−7.10 (m, 5H), 4.75 (d, *J* = 8.8 Hz, 1H), 3.95−3.78 (m, 4H), 3.45−3.36 (m, 1H), 2.57−2.45 (m, 1H), 2.37−2.29 (m, 1H), 2.00−1.84 (m, 2H), 1.59−1.50 (m, 1H), 1.43−1.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.5, 138.4, 136.2, 133.9, 132.9, 130.8, 130.3, 127.3, 127.2, 126.9, 126.5, 107.6, 64.7, 64.5, 47.1, 46.9, 39.8, 38.8, 35.2; IR (film) ν 3021, 2975, 1713, 1523, 1469, 1439 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{20}O_3S$ (M) 352.1133, found 352.1132. The ee was determined to be 62% by HPLC analysis on a Chiralpak OD column, λ = 254 nm, *n*-hexane/*i*-PrOH (90:10), flow rate = 0.50 mL/min; t_R = 11.41 min (major), 13.01 min (minor).

*(2R,4R)-4-Methyl-2-(9H-thioxanthen-9-yl)cyclohexanone (**3f**):* white solid; mp 155−156 °C; $[\alpha]^{20}_{D}$ +63.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.33 (m, 3H), 7.29−7.12 (m, 5H), 4.57 (d, *J* = 10.4 Hz, 1H), 3.21−3.13 (m, 1H), 2.51−2.42 (m, 1H), 2.37−2.30 (m, 1H), 2.21−2.13 (m, 1H), 2.01−1.92 (m, 1H), 1.62−1.44 (m, 2H), 1.21−1.12 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.6, 137.3, 136.0, 133.6, 132.9, 130.0, 129.5, 127.5, 126.9, 126.8, 126.6, 126.3, 48.5, 47.0, 39.4, 38.6, 35.1, 27.0, 19.8; IR (film) ν 3020, 2962, 1706, 1524, 1465, 1441 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{20}OS$ (M) 308.1235, found 308.1239. The ee was determined to be 80% by HPLC analysis on a Chiralpak AD column, λ = 254 nm, *n*-hexane/*i*-PrOH (99:1), flow rate = 0.70 mL/min; t_R = 14.87 min (major), 17.13 min (minor).

*(2R,4R)-4-tert-Butyl-2-(9H-thioxanthen-9-yl)cyclohexanone (**3g**):* white solid; mp 184−185 °C; $[\alpha]^{20}_{D}$ +84.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.40 (m, 2H), 7.38−7.30 (m, 1H), 7.25−7.11 (m, 5H), 4.51 (d, *J* = 10.8 Hz, 1H), 3.13−3.06 (m, 1H), 2.68−2.57 (m, 1H), 2.37−2.29 (m, 1H), 2.13−2.06 (m, 1H), 1.93−1.84 (m, 1H), 1.60−1.45 (m, 2H), 1.35−1.24 (m, 1H), 0.86 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.1, 136.1, 135.2, 133.4, 132.9, 130.3, 128.4, 127.7, 127.2, 127.1, 126.6, 126.1, 49.3, 47.7, 41.3, 39.9, 32.9, 30.0, 27.9, 27.6; IR (film) ν 3020, 2963, 1706, 1526, 1466, 1442 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{26}OS$ (M) 350.1704, found 350.1704. The ee was determined to be 81% by HPLC analysis on a Chiralpak AD column, λ = 254 nm, *n*-hexane/*i*-PrOH (99:1), flow rate = 0.70 mL/min; t_R = 21.30 min (major), 27.56 min (minor).

*(2R,4R)-4-Phenyl-2-(9H-thioxanthen-9-yl)cyclohexanone (**3h**):* yellow solid; mp 179−180 °C; $[\alpha]^{20}_{D}$ +136.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.37 (m, 3H), 7.33−7.14 (m, 10H), 4.67 (d, *J* = 10.8 Hz, 1H), 3.41−3.32 (m, 1H), 3.24−3.17 (m, 1H), 2.76−2.66 (m, 1H), 2.44−2.36 (m, 1H), 2.27−2.21 (m, 1H), 2.17−2.05 (m, 1H), 1.84−1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7, 144.0, 136.4, 135.3, 133.5, 132.9, 130.0, 128.9, 128.8, 127.7, 127.6, 127.2, 127.0, 126.8, 126.7, 126.6, 126.5, 49.0, 48.1, 39.9, 37.5, 36.6, 33.8; IR (film) ν 3021, 1709, 1524, 1466, 1442 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{22}OS$ (M) 370.1391, found 370.1350. The ee was determined to be 80% by HPLC analysis on a Chiralpak OD column, λ = 254 nm, *n*-hexane/*i*-PrOH (95:5), flow rate = 1.0 mL/min; t_R = 22.55 min (minor), 30.31 min (major).

*(R)-2-(9H-Xanthen-9-yl)cyclohexanone (**3i**):*[15] yellow solid; mp 110−111 °C; $[\alpha]^{20}_{D}$ +60.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.27−7.16 (m, 3H), 7.09−6.97 (m, 4H), 4.93 (d, *J* = 3.2 Hz, 1H), 2.55−2.47 (m, 1H), 2.45−2.38 (m, 1H), 2.29−2.18 (m, 1H), 1.96−1.88 (m, 1H), 1.79−1.68 (m, 2H), 1.54−1.36 (m, 2H), 1.16−1.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8, 153.5, 153.2, 130.6, 128.9, 127.9, 127.8, 125.8, 123.6, 123.3, 123.0, 116.4, 116.2, 60.8, 42.2, 36.9, 27.8, 26.8, 24.9. The ee was determined to be 60% by HPLC analysis on a Chiralpak IC column, λ = 254 nm, *n*-hexane/*i*-PrOH (99:1), flow rate =0.60 mL/min; t_R = 14.15 min (major), 18.65 min (minor).

*(R)-2-(Bis(4-(dimethylamino)phenyl)methyl)cyclohexanone (**3j**):*[9a] yellow solid; mp 168−169 °C; $[\alpha]^{20}_{D}$ +65.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15−7.03 (m, 4H), 6.67−6.09 (m, 4H), 4.17 (d, *J* = 10.8 Hz, 1H), 3.27−3.19 (m, 1H), 2.87 (s, 6H), 2.85 (s, 6H), 2.46−2.38 (m, 1H), 2.34−2.25 (m, 1H), 1.94−1.79 (m, 4H), 1.67−1.54 (m, 1H), 1.53−1.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.5, 149.2, 149.0, 132.6, 132.0, 129.0, 128.3, 113.0, 55.7, 49.1, 42.2, 40.9, 33.1, 29.3, 23.9. The ee was determined to be 50% by HPLC analysis on a Chiralpak AD column, λ = 254 nm, *n*-hexane/*i*-PrOH

dx.doi.org/10.1021/jo2014142 |*J. Org. Chem.* 2011, 76, 8095–8099

(85:15), flow rate = 0.80 mL/min; t_R = 11.47 min (major), 12.93 min (minor).

*(2R)-2-((1-Methyl-1H-indol-3-yl)(phenyl)methyl)cyclohexanone (**3k**):* obtained as a 59:41 mixture of diastereomers; yellow solid; mp 126−127 °C; $[\alpha]^{20}_D$ +143.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.41 (m, 1H), 7.37−6.94 (m, 9H), 4.73 (d, *J* = 10.0 Hz, 1H), 3.73 (s, 3H), 3.25−3.17 (m, 1H), 2.51−2.23 (m, 2H), 2.00−1.47 (m, 6H); Partial ^{1}H NMR (400 MHz, $CDCl_3$) for the minor diastereomer: δ 7.61−7.56 (m, 1H), 6.84 (s, 1H), 4.68 (d, *J* = 10.0 Hz, 1H), 3.42−3.34 (m, 1H), 3.70 (s, 3H); IR (film) ν 3021, 2941, 1707, 1523, 1477, 1426 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{23}NO$ (M) 317.1780, found 317.1799. The ee was determined to be 82% (For the minor diastereomer, 80%) by HPLC analysis on a Chiralpak AD column, λ = 254 nm, *n*-hexane/*i*-PrOH (98:2), flow rate = 1.00 mL/min; t_R (major diastereomer) = 19.85 min (major), 36.98 min (minor); ^tR (minor diastereomer) = 21.99 min (minor), 27.62 min (major).

*2-(9H-Thioxanthen-9-yl)propanal (**3l**):*[7] yellow solid; mp 108−109 °C; $[\alpha]^{20}_D$ +12.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, *J* = 2.0 Hz, 1H), 7.48−7.40 (m, 2H), 7.32−7.17 (m, 6H), 4.25 (d, *J* = 9.6 Hz, 1H), 3.23−3.12 (m, 1H), 0.88 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 136.0, 135.5, 133.2, 130.2, 129.9, 127.6, 127.4, 127.2, 126.8, 126.5, 50.6, 45.9, 13.1. The ee was determined to be 65% by HPLC analysis on a Chiralpak AD column, λ = 254 nm, *n*-hexane/*i*-PrOH (100:0), flow rate = 0.80 mL/min; t_R = 11.13 min (minor), 15.86 min (major).

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H NMR, ^{13}C NMR, and HPLC spectra for products, ESI-MS spectra for reaction mixture, and crystal data of compound **3h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

We are grateful for the financial support from the National Natural Science Foundation of China (20972147 and 20732006) and the National Basic Research Program of China (973 Program 2010CB833300).

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