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Synthesis of α-Stereogenic Amides and Ketones by Enantioselective Conjugate Addition of 1,4-Dicarbonyl But-2-enes

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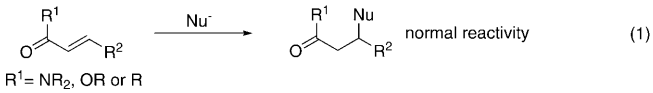
Abstract: In the conjugate addition reaction of a α,β-unsaturated compound, the new stereogenic center is created in the β-position. In contrast, conjugate addition to 1,4-dicarbonyl but-2-enes will generate an α-stereogenic center with respect to one of the carbonyl groups, which informally, can be considered as an inversion of normal reactivity patterns or Umpolung. In this paper, we demonstrate that chiral bicyclic guanidine can catalyze the addition of 1,3-dicarbonyl compounds to 1,4-dicarbonyl but-2-enes [(*E*)-4-oxo-4-arylbutenamides and (*E*)-4-oxo-4-arylbutenones] with high regioselectivity and enantioselectivity (*ee* values up to 97%).

Keywords: asymmetric catalysis · dicarbonyl compounds · enantioselectivity · organocatalysis

Introduction

Both amides and ketones with α-stereogenic centers are useful building blocks for the synthesis of biologically active compounds. While conjugate addition to α,β-unsaturated substrates result in stereogenic centers in the β-position [Eq. (1)], addition to 1,4-dicarbonyl but-2-enes will generate an α-stereogenic center with respect to one of the carbonyl groups. As this α-stereogenic center is obtained through the action of a nucleophile, this can be informally considered as an inversion of normal reactivity patterns or Umpolung reactivity.[1] The Michael reactions of arylboronic acids to 1,4-dicarbonyl but-2-enes, such as dialkyl fumarate and (*E*)-4-oxo-4-arylbutenamides, catalyzed by rhodium complexes were reported to proceed with high enantioselectivities.[2] The aza-Michael reactions of (*E*)-4-oxo-4-arylbutanotes[3] and (*E*)-4-oxo-4-arylbutenamides[4] were also reported to show high regioselectivitives; the only product observed was derived from the β-attack by the *N*-nucleophiles to the enone moeity. (*E*)-4-Oxo-4-arylbutenones, on the other hand, have not been investigated as acceptors in asymmetric Michael reaction and there was only one previous report describing a non-asymmetric reaction.[5]

There is a recent interest to develop guanidines as enantioselective catalysts, particularly the axially chiral guanidines[6] and the C_2-symmetric bicyclic guanidines.[7] We have reported that bicyclic guanidines catalyzed protonation reaction,[7b] phospha-Michael[7c] and Diels–Alder with high enantioselectivities.[7d] This class of catalyst also worked well for conjugate additions of 1,3-alkylthiomalonates,[8] giving high levels of enantioselectivities with cyclic substrates such as 5(2*H*)-furanone, 2-cyclohexen-1-one, 2-cyclopenten-1-one and *N*-substituted maleimides. The scope of this reaction also include linear substrates such as (*E*)-4-oxo-4-arylbutenoates which proceeded in a regioselective fashion [Eq. (2)].[8b] Herein, we expanded the scope of this approach with examples that will generate α-amides and α-keto stereogenic centers [Eq. (3) and (4)]. Using thiomalonates as donors, highly enantioselective and regioselective addition of 1,4-dicarbonyl but-2-enes [(*E*)-4-oxo-4-arylbutenamides and *E*-4-oxo-4-arylbutenones] were observed.



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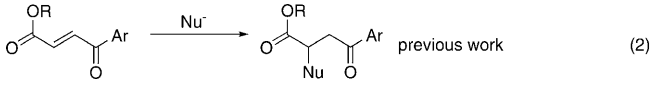

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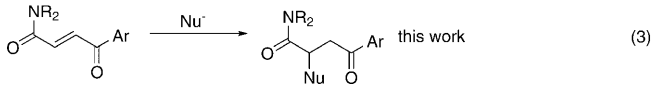

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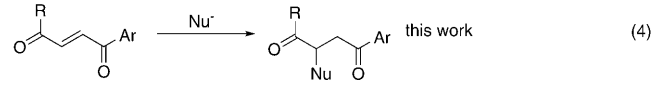

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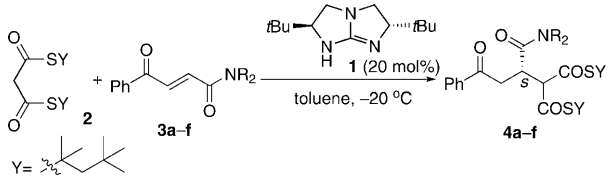
Results and Discussion

Our initial investigation revealed that guanidine-catalyzed conjugate addition of *S*,*S*′-dialkyl dithiomalonate **2** to various (*E*)-*N*,*N*-dialkyl-4-oxobutenamides **3a–d** (Table 1, entries 1–4) occurred at slow rates. Low yields were obtained and only moderate enantioselectivities were observed. When 2-oxopyrrolidine **4e** (entry 5) was introduced, the reaction proceeded at a much faster rate and *ee* was improved to 82%. With 2-oxazolidinone **3f** (entry 6), both reaction rate and enantioselectivity reached satisfactory levels. Enantioselectivity was further improved when the reaction temperature was lowered to −50°C and a lower catalyst loading became possible (Table 2, entry 1).

Various (*E*)-4-oxo-4-arylbutenamides with 2-oxazolidinone as amide substituents (NR_2) were prepared[9] and used as Michael acceptors (Table 2). Excellent *ee* values (96–97%) were obtained when the experiments were conducted at −50°C. This includes various *para*-substituted 4-arylbutenamides **3g–j** (entries 2–5). The solubility of amides **3k–n** (entries 6–9) was poor at −50°C; thus reactions had to be carried out at −20°C. Electron-withdrawing or donating *meta*-substituted substrates **3n–o** (entries 9 and 10) gave excellent levels of enantioselectivities.

Table 1. Chiral bicyclic guanidine **1** catalyzed conjugate additions of different *N*, *N*-dialkyl-4-oxobutenamides with *S*,*S*′-dialkyl dithiomalonates **2**.

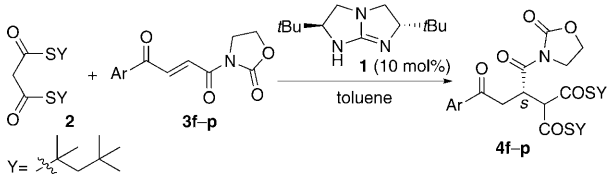


Entry	**3**	NR_2	Product	*t* [h]	Yield [%][a]	*ee* [%][b]
1	**3a**	NEt_2	**4a**	48	24	74
2	**3b**		**4b**	48	25	59
3	**3c**		**4c**	48	57	79
4	**3d**		**4d**	48	40	70
5	**3e**		**4e**	48	91	82
6	**3f**		**4f**	24	82	91

[a] Isolated yield. [b] Chiral HPLC.

2-Oxazolidinones are widely used as chiral auxiliaries for asymmetric synthesis.[10] The conversion of 2-oxazolidinones to alcohols,[11] acids[12] and Weinreb amide[13] are facile processes and have been fully exploited. For the conversion to esters, reagents such as magnesium methoxide and lithium phenoxide were utilized and conditions reported were typically strongly basic.[14] In order to determine the absolute configuration of the addition adducts **4f–p**, we were keen to remove the 2-oxazolidinone from **4i** (Table 2, entry 4) to the free acid. Simple E-esterification of the free acid will lead to known compounds.[8b] However, strong basic conditions would cleave the thioester groups and also lead to racemization. We searched for milder conditions and found that ethyl ester can be obtained from 2-oxazolidinone using 1.0 equiv K_2CO_3 and ethanol as solvent.[15]

Table 2. Chiral bicyclic guanidine **1** catalyzed conjugate additions of various (*E*)-4-oxo-4-arylbutenamides with *S*,*S*′-dialkyl dithiomalonates **2**.



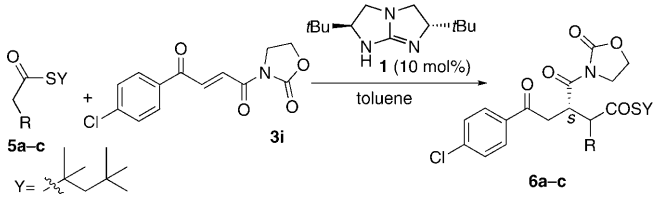
Entry	Substrate [Ar]	*T* [°C]	*t* [h]	Product	Yield [%][a]	*ee* [%][b]
1	**3f** [Ph][c]	−50	48	**4f**	80	93
2	**3g** [4-CNC_6H_4]	−60	24	**4g**	95	96
3	**3h** [4-FC_6H_4]	−50	48	**4h**	80	97
4	**3i** [4-ClC_6H_4][d]	−50	40	**4i**	85	97
5	**3j** [4-BrC_6H_4][e]	−50	8	**4j**	89	96
6	**3k** [4-PhC_6H_4]	−20	24	**4k**	87	92
7	**3l** [2-furanyl][c]	−20	18	**4l**	90	93
8	**3m** [2-naphthyl]	−20	24	**4m**	99	90
9	**3n** [3-CNC_6H_4]	−20	24	**4n**	81	95
10	**3o** [3-$MeOC_6H_4$][c]	−60	36	**4o**	90	90
11	**3p** [2-$NO_2C_6H_4$]	−50	48	**4p**	75	70

[a] Isolated yield. [b] Chiral HPLC. [c] 20 mol% catalyst utilized. [d] −20°C, 4 h, Yield 83%, *ee* 92%. [e] −20°C, 1 h, Yield 99%, *ee* 89%.

The reaction was further explored by using several β-keto thioesters **5a–b** (Table 3, entries 1 and 2) as Michael donors. Adducts **6a–b** were obtained in excellent yields and *ee* values. 2-Cyanoethanethioate **5c**, which is a useful two carbon synthon donor that we have developed, also gave high *ee* (entry 3). The regiochemistry of the adducts were confirmed by NOE analysis.[9]

Following amides, (*E*)-4-oxo-4-arylbutenones [(*E*)-1,4-unsaturated diketones] were attempted. Unsymmetrical (*E*)-4-oxobutenones with both aromatic and aliphatic enone moieties were investigated initially [Eq. (5)]. Chiral α-aliphatic ketone adducts were obtained with high enantioselectivities; however, a significant amount of side product was observed. The side product was found to be the conjugate addition product of (*E*)-4-oxobutenones and the 1,1,3,3-tetramethylbutane-1-thiol. Although impurity from the synthesis of **2** was meticulously excluded, the side-reaction still persisted.

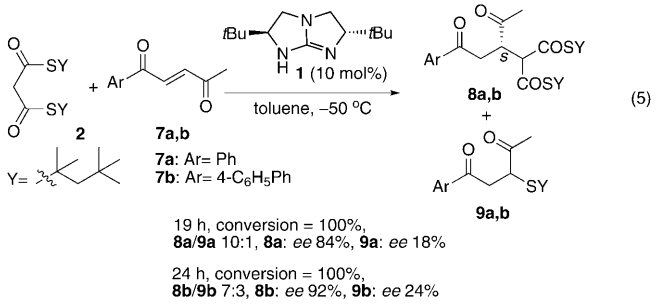
Table 3. Chiral bicyclic guanidine **1** catalyzed conjugate additions of (*E*)-4-oxo-4-arylbutenamides **3i** with β-ketothioesters **5a–c**.



Entry	Substrate [R]	*T* [°C]	*t* [h]	Product	Yield [%][a]	*ee* [%][b]
1	**5a** [PhCO][c]	−50	48	**6a**	99	93, 97
2	**5b** [4-MeOC$_6$H$_4$CO]	−20	24	**6b**	87	90, 92
3	**5c** [CN]	−60	24	**6c**	80	90, 90

[a] Isolated yield. [b] Chiral HPLC, d.r. 1:1 determined by ^{1}H NMR spectroscopy. [c] −20 °C, 18 h, Yield 99 %, *ee* 90, 93 %.

This side-product was not present when the other 1,4-dicarbonyl but-2-enes were used. While the mechanism for formation of the side product is not clear, we believe that the thiol group was cleaved from *S*,*S*′-dialkyl dithiomalonate **2** under the reaction conditions.



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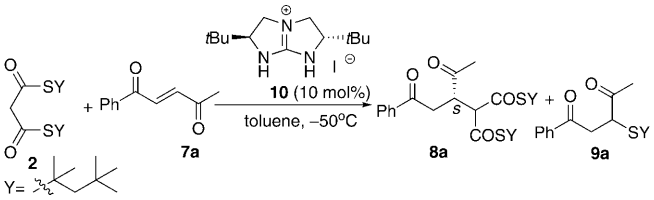
Guanidinium salts were known to function as phase transfer catalysts[15] as well as Brønsted acid catalyst.[16] Guanidinium iodide salt **10** under phase transfer-like condition resulted in higher selectivity for the desired adduct **8a** and a significantly reduced amount of thiol-Michael adduct **9a** (Table 4, entries 1–3). In situ basification of guanidinium iodide **10** with 1 equiv K_2CO_3, resulted in a high **8a**/**9a** ratio of >99:1 (entry 1). A slight increase in enantioselectivity was observed when 10 equiv of water was added (entry 2). Inorganic or organic bases used in place of K_2CO_3 gave unsatisfactory *ee* values (entries 3–5).

Using the optimized conditions, (*E*)-1-arylpent-2-ene-1,4-diones **7b–h** (Table 5) were subjected to conjugate additions with *S*,*S*′-dialkyl dithiomalonate **2**. Most reactions were completed within 24 h and adducts were obtained with high regioselectivity. The adducts **8b–h** were also obtained in high yields and good *ee* values. In some reactions, side products were found but their levels were insignificant (within 10 %). NOE analysis was used to confirm the regioselectivity of the reaction.[9]

High yields and *ee* values were obtained with ketones **7i–k**, bearing a thiophenyl enone moiety and aliphatic alkyl

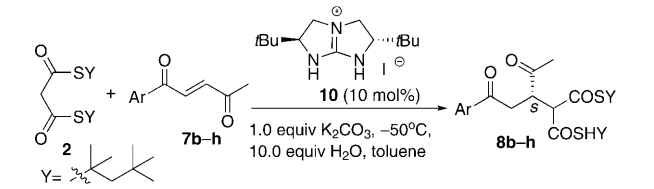
Table 4. Conjugate addition of (*E*)-1-phenylpent-2-ene-1,4-dione **7a** with *S*,*S*′-dialkyl dithiomalonates **2** catalyzed by chiral bicyclic guanidinium iodide **10**.[a]



Entry	Base	*t* [h]	Yield [%][b]	**8a**/**9a**[c]	*ee* [%][d]
1	K_2CO_3	24	99	>99:1	85
2	K_2CO_3[e]	24	99	61:1	88
3	Cs_2CO_3	48	88	22:1	69
4	NaOH	24	87	15:1	54
5	Et_3N	48	85	9:1	85

[a] 0.02 mmol scale, 100 μL toluene, 1.0 equiv inorganic base. [b] Isolated yield, **8a** and **9a**. [c] Determined by crude ^{1}H NMR. [d] Chiral HPLC. [e] 10 equivalents water was added.

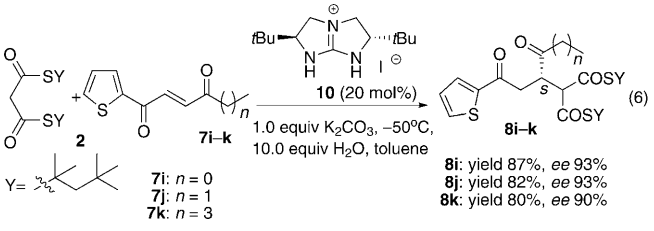
Table 5. Conjugate additions of (*E*)-1-arylpent-2-ene-1,4-diones **7b–h** with *S*,*S*′-dialkyl dithiomalonates **2** catalyzed by chiral bicyclic guanidinium iodide **10**.



Entry	Substrate [Ar]	*t* [h]	Product	Yield [%][a]	*ee* [%][b]
1	**7b** [4-PhC$_6$H$_4$]	24	**8b**	99	90
2	**7c** [4-ClC$_6$H$_4$]	24	**8c**	80	88
3	**7d** [4-BrC$_6$H$_4$]	24	**8d**	99	90
4	**7e** [2-naphthyl]	24	**8e**	88	84
5	**7f** [3,5-diMeC$_6$H$_3$]	48	**8f**	95	90
6	**7g** [2-furanyl]	24	**8g**	80	89
7	**7h** [3-CNC$_6$H$_4$]	24	**8h**	90	83

[a] Isolated yield of pure **8**. [b] Chiral HPLC.

enone moieties with different chain lengths [Eq. (6)]. The extension of the alkyl chains did not affect the enantioselectivities of the resulting adducts **8i–k**, thus highlighting the potential to modify and prepare the side chain of natural products. Another interesting class of substrates, the symmetrical (*E*)-1,4-unsaturated diketones are also useful substrates to prepare α-keto chiral centers [Eq. (7)]. Two different diketones **7l–m** were investigated and high yields and *ee* values were obtained for both.



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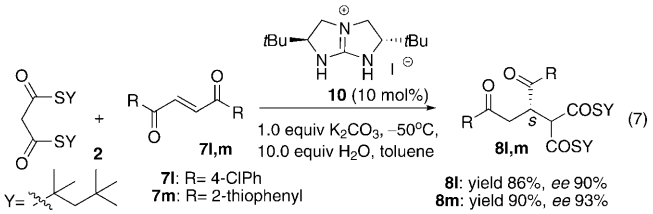

Conclusion

In summary, we have shown that 1,3-dicarbonyl compounds react with (*E*)-4-oxo-4-arylbutenamides and (*E*)-4-oxo-4-arylbutenones in a regioselective fashion to provide adducts with α-amide and α-ketone stereogenic centers, respectively. Informally, this Umpolung approach allows the use of nucleophiles to generate stereogenic centers in the α-position to the carbonyl group. With chiral bicyclic guanidine **1** as catalyst, highly enantiopure amides, aliphatic ketones and aromatic ketones with α-stereogenic centers could be obtained. The pre-catalyst, guanidinium iodide **10**, could also be used directly under phase-transfer-like conditions with K_2CO_3 as the base.

Experimental Section

General procedure for the conjugate addition of 1,3-dicarbonyl compounds 2 and 5a–c to 3a–o catalyzed by chiral bicyclic guanidine 1: (*E*)-4-Oxo-4-arylbutenamides **3a–p** (0.1 mmol, 1.0 equiv) and 1,3-dicarbonyl compounds **2**, **5a–c** (0.3 mmol, 3 equiv) were dissolved in toluene (795 μL). Stirring at the required temperature (−60 to −20 °C) for 30 min, the pre-cooled catalyst **1** (0.01 mmol, 0.1 equiv, 2.235 mg in 5 μL toluene) was added. The reaction mixtures were stirred at same temperature and monitored by TLC. Upon the complete consumption of the (*E*)-4-oxo-4-arylbutenamides **3a–p**, the reaction mixtures were loaded onto a short silica gel column, followed by flash chromatography using gradient elution with hexane/EA mixtures (10:1→2:1). After removing the solvent, products **4a–p**, **6a–c** were obtained.

General procedure for the conjugate addition of *S,S'*-dialkyl dithiomalonates 2 to (*E*)-4-oxo-4-arylbutenones 7a–m using pre-catalyst guanidinium iodide salt 10: Dithiomalonate **2** (54 mg, 0.15 mmol, 3 equiv), potassium carbonate (6.9 mg, 0.05 mmol, 1.0 equiv) and **10** (1.756 mg, 0.005 mmol, 0.1 equiv) were dissolved in toluene (395 μL) and H_2O (9 μL, 0.5 mmol, 10 equiv) was added and stirred at −50 °C for 30 min before (*E*)-4-oxo-4-arylbutenones **7a–m** (0.05 mmol, 1.0 equiv) were added. The reaction mixtures were stirred at −50 °C and monitored by TLC. Upon complete consumption of **7a–m**, the reaction mixtures were loaded onto a short silica gel column, followed by flash chromatography using gradient elution with hexane/EA mixtures (100:1→10:1). After removing the solvent, products **8a–m** were obtained.

The reactions were conveniently performed in capped round bottom flasks without special precautions. Catalysts can be recovered from the column using MeOH/CH_2Cl_2 1:4 and reused without loss of *ee*.

Compound 4a: Pale yellow oil; 74% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, J = 7.3 Hz, 2H), 7.52 (t, J = 7.3 Hz, 1H), 7.41 (t, J = 7.5 Hz, 2H), 4.32–4.07 (m, 2H), 3.65–3.15 (m, 5H), 3.35 (dd, J = 7.2, 3.0 Hz, 1H), 1.91–1.67 (m, 4H), 1.51 (s, 6H), 1.49 (s, 6H), 1.28 (t, J = 7.1 Hz, 3H), 1.02–0.98 ppm (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.3, 192.3, 192.1, 170.9, 136.5, 133.1, 128.5, 128.1, 71.5, 54.5, 54.2, 53.1, 42.7, 40.2, 40.0, 37.2, 32.5, 31.6, 29.4 (two peaks), 29.1, 29.0, 13.6, 12.7 ppm; IR (film): $\tilde{\nu}$ = 3019, 1636, 1217 cm^{-1}; LRMS (ESI): m/z: 614.2 [M+Na$^+$]; HRMS (ESI): m/z: calcd for $C_{33}H_{53}O_4NNaS_2$: 614.3308; found: 614.3323 [M+Na$^+$].

The *ee* was determined by HPLC analyses. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol 90:10; flow rate 1.0 mL min^{-1}; 25 °C; 254 nm; retention time: 6.98 min (major) and 14.81 min (minor).

Compound 4e: Pale yellow oil; 82% *ee*; $[\alpha]_D^{28}$ = +31.4 (c = 0.79, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, J = 7.0 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 4.91–4.86 (m, 1H), 4.18 (d, 7.3, 1H), 3.86–3.78 (m, 2H), 3.56–3.54 (m, 2H), 2.64 (t, J = 8.2 Hz, 2H), 2.08–1.99 (m, 2H), 1.88–1.72 (m, 4H), 1.59–1.52 (m, 12H), 0.99 ppm (S, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.8, 192.4, 192.2, 174.9, 172.8, 136.6, 133.1, 128.5, 128.1, 68.1, 54.7, 54.2, 53.4, 53.3, 46.0, 41.0, 37.9, 33.7, 32.6, 31.6, 29.5, 29.0, 17.1 ppm; IR (film): $\tilde{\nu}$ = 3019, 1686, 1522, 1213 cm^{-1}; LRMS (ESI): m/z: 626.1 [M+Na$^+$]; HRMS (ESI): m/z: calcd for $C_{33}H_{49}O_5NNaS_2$: 626.2944; found: 626.2965 [M+Na$^+$].

The *ee* was determined by HPLC analyses of the Michael adduct. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol 90:10; flow rate 1.0 mL min^{-1}; 25 °C; 254 nm; retention time: 11.8 min (minor) and 20.6 min (major).

Compound 4f: Pale yellow oil; 93% *ee*; $[\alpha]_D^{28}$ = +31.6 (c = 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, J = 7.7 Hz, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 4.92–4.85 (m, 1H), 4.42 (t, J = 8.4 Hz, 1H), 4.16 (d, ^{1}H, J = 8.0 Hz), 4.11–3.96 (m, 2H), 3.62–3.46 (m, 2H), 1.89–1.73 (m, 4H), 1.56–1.52 (m, 12H), 1.00 ppm (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.6, 192.2, 192.0, 172.5, 153.0, 136.4, 133.3, 128.5, 128.1, 68.5, 62.0, 54.8, 54.3, 53.4, 53.3, 42.9, 39.5, 38.3, 32.6, 31.6, 29.5, 29.4, 29.0 ppm; IR (film): $\tilde{\nu}$ = 3019, 1780, 1686, 1521, 1213 cm^{-1}; LRMS (ESI): m/z: 604.2 [M−H$^+$]; HRMS(ESI): m/z: calcd for $C_{32}H_{47}O_6NNaS_2$: 628.2737; found: 628.2747 [M+Na$^+$].

The *ee* was determined by HPLC analyses of the Michael adduct. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol 90:10; flow rate 1.0 mL min^{-1}; 25 °C; 254 nm; retention time: 17.8 min (minor), 21.1 min (major).

Compound 4l: Pale yellow oil. 93% *ee*, $[\alpha]_D^{29}$ = +20.0 (c = 1.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55 (d, J = 1.5 Hz, 1H), 7.16 (d, J = 3.3 Hz, 1H), 6.51 (dd, J = 3.3, 1.5 Hz, 1H), 4.90–4.85 (m, 1H), 4.44–4.37 (m, 2H), 4.14 (d, J = 8.2 Hz, 1H), 4.08–3.96 (m, 1H), 3.42 (dd, J = 17.5, 3.8 Hz, 1H), 3.28 (dd, J = 17.5, 9.8 Hz, 1H), 1.89–1.75 (m, 4H), 1.58–1.51 (m, 12H), 1.01 (s, 9H), 0.99 ppm (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.1, 192.0, 186.4, 172.4, 152.9, 152.1, 146.5, 117.5, 112.3, 68.8, 62.0, 54.8, 54.3, 53.3 (two peaks), 42.9, 39.1, 38.0, 32.6, 32.5, 31.6, 29.5, 29.4 (two peaks), 29.1 ppm; IR (film): $\tilde{\nu}$ = 3019, 1782, 1686, 1522, 1476, 1423, 1213 cm^{-1}; LRMS (ESI): m/z: 618.1 [M+Na$^+$]; HRMS (ESI): m/z: calcd for $C_{30}H_{45}O_7NNaS_2$: 618.2530; found: 618.2532 [M+Na$^+$].

The *ee* was determined by HPLC analyses. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol 90:10; flow rate 1.0 mL min^{-1}; 25 °C; 254 nm; retention time: 16.1 min (minor) and 19.5 min (major).

Compound 6a: Pale yellow oil; mixture of diastereomers, 93% and 97% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03–7.77 (m, 4H), 7.60–7.35 (m, 5H), 5.14–4.97 (m, 2H), 4.46–4.40 (m, 2H), 4.04–3.98 (m, 2H), 3.71–3.44 (m, 2H), 1.73–1.58 (m, 4H), 1.47–1.42 (m, 6H), 0.91 (s) and 0.88 ppm (s) (together 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.5, 193.6, 192.9, 172.9, 153.2, 139.8, 136.1, 134.9, 133.8, 133.6, 129.6, 128.9, 128.6, 114.4, 63.6, 62.7, 62.2, 62.0, 55.2, 53.4, 42.9, 40.0, 39.6, 38.7, 37.9, 32.4, 31.5, 29.3, 29.0 pm; IR (film): $\tilde{\nu}$ = 3019, 1780, 1688, 1524, 1423, 1211 cm^{-1}; LRMS (ESI): m/z: 569.9 [M−H$^+$]; HRMS (ESI): m/z: calcd for $C_{30}H_{34}O_6NClNaS$: 594.1688; found: 594.1701 [M+Na$^+$].

The *ee* was determined by HPLC analyses of the Michael adduct. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol 85:15; flow rate 1.0 mL/min^{-1}; 25 °C; 254 nm; retention time: 22.8 min (minor), 27.3 min (major); 42.0 min (major), 72.7 min (minor).

Compound 6b: Pale yellow oil; mixture of diastereomers, 90% and 92% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02–7.76 (m, 4H), 7.50–7.34 (m, 2H), 6.95–6.91 (m, 2H), 5.12–4.93 (m, 2H), 4.52–4.39, 4.16–3.98 (m, 2H), 3.87 (s) and 3.86 (s) (together 3H), 3.70–3.40 (m, 2H), 1.77–1.60 (m, 2H), 1.47 (s) and 1.46 (s) (together 6H), 0.91 (s) and 0.89 ppm (s) (together 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.7, 196.6, 193.8, 191.1,

173.0, 164.0, 153.2, 139.8, 136.8, 134.9, 131.5, 131.3, 130.3, 130.0, 129.6, 129.2, 129.1, 128.9, 128.8, 114.0, 113.8, 63.3, 62.6, 62.4, 62.1, 62.0, 55.5, 55.0, 54.7, 53.4, 53.3, 42.9, 42.6, 40.0, 39.6, 38.8, 38.0, 32.5, 31.5, 30.8, 29.7, 29.3, 29.0 ppm; IR (film): $\tilde{\nu}$ = 3019, 1778, 1686, 1601, 1522, 1423, 1215 cm^{-1}; LRMS (ESI): *m/z*: 624.0 [*M*+Na^+]; HRMS(ESI): *m/z*: calcd for $C_{31}H_{36}O_7NClNaS$: 624.1793; found: 624.1777 [*M*+Na^+].

The *ee* was determined by a HPLC analyses of the Michael adduct. CHIRALPAK IA (4.6 mm i.d.×250 mm); hexane/2-propanol 80:20; flow rate 1.0 mL min^{-1}; 25 °C; 254 nm; retention time: 25.5 min (major), 31.8 min (minor); 48.0 min (major), 68.2 min (minor).

Compound 6c: Pale yellow oil; mixture of diastereomers, 90% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90–7.86 (m, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 4.90–4.79 (m, 1H), 4.52–4.74 (m, 2H), 4.23 (t, *J* = 5.9 Hz, 1H), 4.07 (t, *J* = 8.3 Hz, 2H), 3.86–3.64 (m, 1H), 3.43–3.34 (m,1H), 1.89–1.76 (m, 2H), 1.59 (s, 6H), 1.02 (s) and 1.01 ppm (s) (together 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.5, 194.9, 189.8, 189.3, 170.7, 170.5, 153.4, 153.2, 140.4, 140.3, 134.2, 134.1, 129.6, 129.5, 129.1, 115.0, 114.5, 62.5, 62.4, 56.0, 53.5, 53.4, 46.0, 45.8, 42.8, 42.7, 38.9, 38.8, 37.9, 37.7, 32.6, 31.6 (two peaks), 29.7, 29.4, 29.3 (two peaks), 29.1 ppm; IR (film): $\tilde{\nu}$ = 3019, 1778, 1522, 1423, 1215 cm^{-1}; LRMS (ESI): *m/z*: 515.0 [*M*+Na^+]; HRMS (ESI): *m/z*: calcd for $C_{24}H_{29}O_5N_2ClNaS$: 515.1378; found: 515.1386 [*M*+Na^+].

The *ee* was determined by HPLC analyses of the Michael adduct. CHIRALPAK IB (4.6 mm i.d.×250 mm); hexane/2-propanol 80:20; flow rate 1.0 mL min^{-1}; 25 °C; 254 nm; retention time: 10.4 min (minor), 14.4 min (major); 25.1 min (minor), 35.1 min (major).

Compound 8a: Colorless oil; 88% *ee*; $[\alpha]_D^{29}$ = +11.2 (*c* = 2.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 7.3 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 2H), 4.02–3.90 (m, 2H), 3.45–3.36 (m, 1H), 3.27–3.21 (m, 1H), 2.36 (s, 3H), 1.89–1.72 (m, 4H), 1.55–1.51 (m, 12H), 1.00 (s, 9H), 0.98 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.2, 197.2, 192.4, 192.3, 136.0, 133.4, 128.6, 128.0, 69.8, 54.7, 54.5, 53.2, 46.7, 39.4, 32.5, 31.6, 31.2, 29.5, 29.4, 29.2, 29.1 ppm; IR (film): $\tilde{\nu}$ = 2957, 1686, 1367, 1205 cm^{-1}; LRMS (ESI): *m/z*: 533.3 [*M*−H^-] HRMS (ESI): *m/z*: calcd for $C_{30}H_{46}O_4NaS_2$: 557.2730; found: 557.2750 [*M*+Na^+].

The *ee* was determined by HPLC analyses of the Michael adduct. CHIRALPAK IA (4.6 mm i.d.×250 mm); hexane/2-propanol 92:8; flow rate 0.8 mL min^{-1}; 25 °C; 254 nm; retention time: 12.4 min (major), 13.5 min (minor).

Compound 8b: Pale yellow oil; 90% *ee*, $[\alpha]_D^{29}$ = +12.4 (*c* = 0.26, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 7.3 Hz, 2H), 7.49–7.37 (m, 3H), 4.04–3.96 (m, 2H), 3.48–3.39 (m, 1H), 3.31–3.24 (m, 1H), 2.37 (s, 1H), 1.90–1.73 (m, 4H), 1.56–1.53 (m, 3H), 1.01 (s, 9H), 0.99 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.1, 196.8, 192.4, 192.3, 146.1, 139.7, 134.8, 128.9, 128.6, 128.3, 127.2, 69.8, 54.8, 54.5, 53.3, 46.8, 39.5, 32.5, 31.6, 31.1, 29.5, 29.4, 29.3, 29.2 ppm; IR (film): $\tilde{\nu}$ = 3018, 1682, 1219 cm^{-1}; LRMS (ESI): *m/z*: 633.2 [*M*+Na^+]; HRMS (ESI): *m/z*: calcd for $C_{36}H_{50}O_4NaS_2$: 633.3043; found: 633.3037 [*M*+Na^+].

The *ee* was determined by HPLC analyses of the Michael adduct. CHIRALPAK IA (4.6 mm i.d.×250 mm); hexane/2-propanol 90:10; flow rate 1.0 mL min^{-1}; 25 °C; 254 nm; retention time: 11.7 min (major), 13.7 min (minor).

Compound 8g: Colorless oil; 89% *ee*; $[\alpha]_D^{26}$ = +24.2 (*c* = 0.47, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (s, 1H), 7.16 (d, *J* = 3.5 Hz, 1H), 6.52 (dd, *J* = 3.5, 1.8 Hz, 1H), 3.94 (d, *J* = 3.1 Hz, 2H), 3.30–3.06 (m, 2H), 2.33 (s, 9H), 1.88–1.72 (m, 4H), 1.58–1.47 (m, 12H), 1.00 (s, 9H), 0.99 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.0, 192.3, 186.2, 152.0, 146.5, 117.3, 112.4, 69.8, 54.7, 54.5, 53.2, 46.3, 38.9, 32.5, 31.6, 31.2, 29.6, 29.5, 29.4, 29.3, 29.2 ppm; IR (film): $\tilde{\nu}$ = 2957, 1716, 1685, 1570, 1469, 1260 cm^{-1}; LRMS (ESI): *m/z*: 547.1 [*M*+Na^+]; HRMS (ESI): *m/z*: calcd for $C_{28}H_{44}O_5NaS_2$: 547.2522; found: 547.2532 [*M*+Na^+].

The *ee* was determined by HPLC analyses of the Michael adduct. CHIRALPAK IA (4.6 mm i.d.×250 mm); hexane/2-propanol 95:5; flow rate 1.0 mL min^{-1}; 25 °C; 254 nm; retention time: 10.0 min (major), 11.2 min (minor).

Compound 8i: Pale yellow oil; 93% *ee*; $[\alpha]_D^{28}$ = +34.2 (*c* = 0.62, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.62 (m, 2H), 7.12–7.09 (m, 1H), 3.96–3.94 (m, 2H), 3.38–3.14 (m, 2H), 2.33 (s, 3H), 1.88–1.71 (m, 4H), 1.54–1.51 (m, 12H), 0.99 ppm (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.9, 192.3 (two peaks), 190.0, 143.1, 134.0, 132.2, 128.1, 69.8, 54.8, 54.5, 53.3 (two peaks), 46.7, 39.8, 32.5, 31.6, 31.2, 29.5, 29.4, 29.3, 29.2 ppm; IR (film): $\tilde{\nu}$ = 3019, 1520, 1213 cm^{-1}; LRMS (ESI): *m/z*: 539.2 [*M*−H^+]; HRMS (ESI): *m/z*: calcd for $C_{28}H_{44}O_4NaS_3$: 563.2294; found: 563.2308 [*M*+Na^+].

The *ee* was determined by HPLC analyses of the Michael adduct. CHIRALCEL OF (4.6 mm i.d.×250 mm); hexane/2-propanol 92:8; flow rate 1.0 mL min^{-1}; 25 °C; 254 nm; retention time: 10.2 min (major), 18.0 min (minor).

Compound 8j: Colorless oil; 93% *ee*; $[\alpha]_D^{28}$ = −4.5 (*c* = 0.44, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 4.3, 1H), 7.62 (d, *J* = 4.3, 1H), 7.10 (t, *J* = 4.3, 1H), 3.98–3.89 (m, 2H), 3.36–3.23 (m, 1H), 3.17–3.10 (m, 1H), 2.87–2.73 (m, 1H), 2.68–2.54 (m, 1H), 1.88–1.65 (m, 4H), 1.55–1.50 (m, 12H), 1.02–0.97 ppm (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.4, 192.3, 190.1, 143.2, 133.9, 132.2, 128.1, 70.1, 54.8, 54.5, 53.3, 53.2, 46.2, 39.9, 37.2, 32.6, 32.5, 31.6, 29.4 (two peaks), 29.2, 7.45 ppm; IR (film): $\tilde{\nu}$ = 3019, 1683, 1518, 1418, 1215 cm^{-1}; LRMS (ESI): *m/z*: 553.1 (M-H^+); HRMS (ESI): *m/z*: calcd for $C_{29}H_{46}O_4NaS_3$: 577.2450; found: 577.2455 [*M*+Na^+].

The *ee* was determined by HPLC analyses of the Michael adduct. CHIRALCEL ADH (4.6 mm i.d.×250 mm); hexane/2-propanol 97:3; flow rate 0.3 mL min^{-1}; 25 °C; 254 nm; retention time: 105.4 min (minor), 117.6 min (major).

Compound 8k: Colorless oil; 90% *ee*; $[\alpha]_D^{26}$ = −7.4 (*c* = 0.54, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 4.3, 1H), 7.63 (d, *J* = 4.3, 1H), 7.10 (t, *J* = 4.3, 1H), 3.98–3.89 (m, 2H), 3.36–3.22 (m, 1H), 3.17–3.11 (m, 1H), 2.81–2.70 (m, 1H), 2.64–2.53 (m, 1H), 1.89–1.70 (m, 4H), 1.59–1.42 (m, 14H), 1.33–1.20 (m, 2H), 1.00 (s, 18H), 0.87 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.8, 192.3 (two peaks), 190.0, 143.2, 133.9, 132.2, 128.1, 70.0, 54.7, 54.5, 53.3 (two peaks), 46.4, 43.5, 39.7, 32.6, 29.4, 29.2, 25.3, 22.1, 13.9 ppm; IR (film): $\tilde{\nu}$ = 2957, 1719, 1685, 1415, 1367 cm^{-1}; LRMS (ESI): *m/z*: 605.1 [*M*+Na^+]; HRMS (ESI): *m/z*: calcd for $C_{31}H_{50}O_4NaS_3$: 605.2763; found: 605.2760 [*M*+Na^+].

The *ee* was determined by HPLC analyses of the Michael adduct. CHIRALPAK IA (4.6 mm i.d.×250 mm); hexane/2-propanol 90:10; flow rate 1.0 mL min^{-1}; 25 °C; 254 nm; retention time: 10.8 min (minor), 12.6 min (minor).

Compound 8l: Colorless oil; 90% *ee*; $[\alpha]_D^{26}$ = −30.6 (*c* = 1.19, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.4, 2H), 7.79 (d, *J* = 8.4, 2H), 7.41 (t, *J* = 9.1, 4H), 4.83 (dt, *J* = 14.4, 3.5, 1H), 3.98 (d, *J* = 10.1, 1H), 3.55 (dd, *J* = 9.4, 7.8, 1H), 3.31 (dd, *J* = 7.8, 3.1, 1H), 1.89–1.71 (m, 2H), 1.58–1.53 (m, 8H), 1.28 (s, 6H), 1.00 (s, 9H), 0.90 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.7, 195.8, 191.9, 191.6, 140.0, 139.8, 134.9, 134.2, 130.7, 129.5, 128.9, 128.7, 70.2, 54.9, 54.6, 53.2, 53.0, 41.4, 40.0, 32.6, 32.4, 31.6, 31.5, 29.5, 29.3, 29.1, 28.6 ppm; IR (film): $\tilde{\nu}$ = 2957, 1681, 1590, 1400, 1367 cm^{-1}; LRMS (ESI): *m/z*: 663.3 [*M*−H^+]; HRMS (ESI): *m/z*: calcd for $C_{35}H_{46}O_4Cl_2NaS_2$: 687.2107; found: 687.2125 [*M*+Na^+].

The *ee* was determined by HPLC analyses of the Michael adduct. CHIRALPAK IA (4.6 mm i.d.×250 mm); hexane/2-propanol 95:5; flow rate 0.5 mL min^{-1}; 25 °C; 254 nm; retention time: 31.7 min (minor), 43.7 min (major).

Compound 8m: Colorless oil; 93% *ee*; $[\alpha]_D^{26}$ = −145.8 (*c* = 0.12, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 3.0, 1H), 7.67 (d, *J* = 3.0, 1H), 7.61 (t, *J* = 5.2, 2H), 7.13–7.08 (m, 2H), 4.73 (dt, *J* = 10.1, 3.5, 1H), 4.04 (d, *J* = 10.4, 1H), 3.50 (dd, *J* = 17.1, 9.8, 1H), 3.23 (dd, *J* = 17.1, 3.3, 1H), 1.90–1.53 (m, 10H), 1.31–1.29 (m, 6H), 1.01 (s, 9H), 0.92 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.7, 191.7, 191.6, 189.5, 143.7, 143.2, 134.7, 134.6, 133.9, 132.2, 128.3, 128.1, 70.3, 54.9, 54.4, 53.2, 53.0, 43.4, 40.1, 32.6, 32.4, 31.6 (two peaks), 29.5, 29.3, 29.0, 28.6 ppm; IR (film): $\tilde{\nu}$ = 2956, 1725, 1685, 1669, 1415 cm^{-1}; LRMS (ESI): *m/z*: 607.3 (M-H^+); HRMS (ESI): *m/z*: calcd for $C_{31}H_{44}O_4NaS_4$: 631.2015; found. 631.2013 [*M*+Na^+].

The *ee* was determined by HPLC analyses of the Michael adduct. CHIRALPAK IA (4.6 mm i.d.×250 mm); hexane/2-propanol 90:10; flow rate

1.0 mL min^{-1}; 25 °C; 254 nm; retention time: 9.1 min (major), 9.8 min (minor).

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[1] D. Seebach, *Angew. Chem.* **1979**, *91*, 259–278; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239–258.
[2] a) J. L. Zigterman, J. C. S. Woo, S. D. Walker, J. S. Tedrow, C. J. Borths, E. E. Bunel, M. M. Faul, *J. Org. Chem.* **2007**, *72*, 8870–8876; b) R. Shintani, K. Ueyama, I. Yamada, T. Hayashi, *Org. Lett.* **2004**, *6*, 3425–3427.
[3] a) X. Han, *Tetrahedron Lett.* **2007**, *48*, 2845–2849; b) L.-T. Yu, J.-L. Huang, C.-Y Chang, T.-K. Yang, *Molecules* **2006**, *11*, 641–648.
[4] P. Jakubec, D. Berkeš, F. Povašanec, *Tetrahedron Lett.* **2004**, *45*, 4755–4758.
[5] R. Ballini, L. Barboni, D. Fiorini, G. Giarlo, A. Palmieri, *Chem. Commun.* **2005**, 2633–2634.
[6] a) M. Terada, T. Ikehara, H. Ube, *J. Am. Chem. Soc.* **2007**, *129*, 14112–14113; b) M. Terada, M. Nakano, H. Ube, *J. Am. Chem. Soc.* **2006**, *128*, 16044–16045; c) M. Terada, H. Ube, Y. Yaguchi, *J. Am. Chem. Soc.* **2006**, *128*, 1454–1455.
[7] a) E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157–160; b) D. S. Leow, S. S. Lin, S. K. Chittimalla, X. Fu, C.-H. Tan, *Angew. Chem.* **2008**, *120*, 5723–5727; *Angew. Chem. Int. Ed.* **2008**, *47*, 5641–5645; c) X. Fu, Z. Y. Jiang, C.-H. Tan, *Chem. Commun.* **2007**, 5058–5060; d) J. Shen, T. T. Nguyen, Y.-P. Goh, W. P. Ye, X. Fu, J. Y. Xu, C.-H. Tan, *J. Am. Chem. Soc.* **2006**, *128*, 13692–13693.
[8] a) Z. Y. Jiang, W. P. Ye, Y. Y. Yang, C. H. Tan, *Adv. Synth. Catal.* **2008**, *350*, 2345–2351; b) W. P. Ye, Z. Y. Jiang, Y. J. Zhao, L. M. Serena, Y.-P. Goh, D. S. Leow, Y.-T. Soh, C.-H. Tan, *Adv. Synth. Catal.* **2007**, *349*, 2454–2458; c) W. P. Ye, D. S. Leow, L. M. Serena, Y.-P. Goh, C.-T Tan, C.-H. Chian, C.-H. Tan, *Tetrahedron Lett.* **2006**, *47*, 1007–1010.
[9] D. S. Lawrence, J. T. Zilfou, C. D. Smith, *J. Med. Chem.* **1999**, *42*, 4932–4941.
[10] D. A. Evans, *Aldrichimica Acta* **1982**, *15*, 23–32.
[11] a) M. Prashad, D. Har, H.-Y. Kim, O. Repic, *Tetrahedron Lett.* **1998**, *39*, 7067–7070; b) D. A. Evans, A. E. Weber, *J. Am. Chem. Soc.* **1986**, *108*, 6757–6761.
[12] D. A. Evans, J. A. Ellman, R. L. Dorow, *Tetrahedron Lett.* **1987**, *28*, 1123–1126.
[13] D. A. Evans, S. L. Bender, *Tetrahedron Lett.* **1986**, *27*, 799–802.
[14] a) D. A. Evans, M. M. Morrissey, R. L. Dorow, *J. Am. Chem. Soc.* **1985**, *107*, 4346–4348; b) D. A. Evans, M. D. Ennis, D. J. Mathre, *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739.
[15] See supporting information.
[16] a) T. Kita, A. Georgieva, Y. Hashimoto, T. Nakata, K. Nagasawa, *Angew. Chem.* **2002**, *114*, 2956–2958; *Angew. Chem. Int. Ed.* **2002**, *41*, 2832–2834; b) M. T. Allingham, A. Howard-Jones, P. J. Murphy, D. A. Thomas, P. W. R. Caulkett, *Tetrahedron Lett.* **2003**, *44*, 8677–8680; c) Y. Sohtome, Y. Hashimoto, K. Nagasawa, *Adv. Synth. Catal.* **2005**, *347*, 1643–1648.
[17] C. Uyeda, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 9228–9229.

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