Organocatalytic Asymmetric 1,6-Additions of β -Ketoesters and Glycine Imine

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Table S1. Preliminary experiments for the reactions between 1-indanone derived β -ketoester **1a** and dienes **3a** and **3d**.^a

entry	diene	solvent	base	T (°C)	t (h)	conversion (%) ^b	ee (%) ^c
1	3a	<i>o</i> -xylene/CHCl ₃ 7:1	Cs ₂ CO ₃ 40%	+4	4	>95	86
2	3a	<i>o</i> -xylene/CHCl ₃ 7:1	K ₂ CO ₃ 33%	-20	16	>95	94
3	3a	<i>o</i> -xylene/CHCl ₃ 7:1	K ₂ HPO ₄ 50%	-20	17	>95	96
4	3d	toluene	Cs ₂ CO ₃ 40%	+4	15	nd	92
5	3d	toluene/CHCl ₃ 3:1	Cs ₂ CO ₃ 40%	+4	15	nd	94
6	3d	toluene/CHCl ₃ 7:1	Cs ₂ CO ₃ 40%	+4	15	nd	94
7	3d	<i>o</i> -xylene/CHCl ₃ 7:1	Cs ₂ CO ₃ 40%	+4	40	>95	96
8	3d	<i>o</i> -xylene/CHCl ₃ 7:1	Cs ₂ CO ₃ 66%	+4	15	>95	60
9	3d	<i>o</i> -xylene/CHCl ₃ 7:1	Cs ₂ CO ₃ (s, 5 equiv.)	+4	20	50	nd

^a Reactions carried out using 0.05 mmol of β -ketoester **1a** (0.15 M), 0.10 mmol of diene **3**, 3 mol% of catalyst **6**, 0.15 mL of base. ^b Determined by ¹H NMR spectroscopy and/or TLC analysis. ^c Determined by chiral stationary phase HPLC. nd = not determined.

Table S2. Preliminary experiments for the reactions between cyclopentanone derived β -ketoester **1e** and dienes **3a** and **3e**.^a

entry	diene	solvent	base	T (°C)	t (h)	conversion (%) ^b	ee (%) ^c
1	3a	<i>o</i> -xylene/ CHCl_3 7:1	K_2CO_3 33%	-20	40	>95	72
2	3a	<i>o</i> -xylene/ CHCl_3 7:1	K_2HPO_4 50%	-20	40	>95	74
3	3a	<i>o</i> -xylene/ CHCl_3 7:1	K_3PO_4 50%	-20	18	>95	75
4	3a	<i>o</i> -xylene/ CHCl_3 7:1	K_3PO_4 50%	-30	18	>95	79
5	3e	<i>o</i> -xylene/ CHCl_3 7:1	Cs_2CO_3 66%	-20	18	40	78
6	3e	<i>o</i> -xylene/ CHCl_3 7:1	Cs_2CO_3 66%	+4	18	>95	74
7	3e	toluene/ CHCl_3 7:1	Cs_2CO_3 66%	+4	18	>90	67
8	3e	<i>o</i> -xylene/ CHCl_3 7:1	NaOH 33%	-20	20	<10	nd
9	3e	<i>o</i> -xylene/ CHCl_3 7:1	Cs_2CO_3 66%	-20	92	76	nd
10	3e	<i>o</i> -xylene/ CHCl_3 7:1	K_3PO_4 50%	-20	60	>95	80

^a Reactions carried out using 0.05 mmol of β -ketoester **1e** (0.15 M), 0.10 mmol of diene **3**, 3 mol% of catalyst **6**, 0.15 mL of base. ^b Determined by ^1H NMR spectroscopy and/or TLC analysis. ^c Determined by chiral stationary phase HPLC. nd = not determined.

Table S3. Preliminary experiments for the reaction between cyclohexanone derived β -ketoester **1f** and diene **3e**.^a

entry	base	T (°C)	t (h)	conversion (%) ^b	ee (%) ^c
1	Cs_2CO_3 66%	+4	18	15	97
2	K_3PO_4 50%	+4	40	22	nd
3	NaOH 33%	+4	20	<5	nd
4	CsOH 66%	+4	20	35	57
5	Cs_2CO_3 (4 equiv.)	+4	18	>95	40
6	K_2CO_3 (4 equiv.)	+4	20	20	94
7	Cs_2CO_3 66%	+4	18	>90	67
8 ^{d,e}	K_3PO_4 (2 equiv.)	+4	40	60	90
9^d	Cs_2CO_3 (1 equiv.)	-20	60	80	95
10 ^{d,e}	Cs_2CO_3 (1 equiv.)	-20	60	83	nd

^a Reactions carried out using 0.05 mmol of β -ketoester **1f** (0.15 M in *o*-xylene/ CHCl_3 7:1), 0.10 mmol of diene **3**, 3 mol% of catalyst **6**, 0.15 mL or stated amount of base. ^b Determined by ^1H NMR spectroscopy and/or TLC analysis. ^c Determined by chiral stationary phase HPLC. ^d 6 mol% catalyst was used. ^e BF_4 salt of the catalyst was used. nd = not determined.

Table S4. Preliminary experiments for the reaction between the glycine derived Schiff base **2** and dienes **3a** and **3e**.^a

<p> $\text{Ph}_2\text{C}=\text{N}-\text{CH}_2-\text{CO}_2t\text{-Bu}$ (2) + $\text{CH}_2=\text{CH}-\text{CH}=\text{CH}-\text{C}(=\text{O})\text{R}$ (3a: R = Me, 3e: R = OEt) $\xrightarrow[\text{base}]{\text{Solvent, } \mathbf{8'} (10 \text{ mol}\%)}$ $\text{Ph}_2\text{C}=\text{N}-\text{CH}(\text{CO}_2t\text{-Bu})-\text{CH}=\text{CH}-\text{C}(=\text{O})\text{R}$ (5a: R = Me, 5d: R = OEt) </p>							
entry	diene	solvent	base	T (°C)	t (h)	yield (%) ^b	ee (%) ^c
1	3a	<i>o</i> -xylene/CHCl ₃ 7:1	K ₃ PO ₄ 50%	+4	18	67 ^d	98
2	3a	toluene	K ₃ PO ₄ 50%	+4	18	33 ^d	80
3	3a	CH ₂ Cl ₂	K ₃ PO ₄ 50%	+4	18	72 ^d	93
4	3a	toluene/CHCl ₃ 3:1	K ₃ PO ₄ 50%	+4	18	84 ^d	97
5	3a	toluene/CHCl ₃ 3:1	K ₃ PO ₄ 50%	+4	40	83 ^d	nd
6	3a	toluene/CHCl ₃ 3:1	K ₃ PO ₄ 50%	+4	20	51	nd
7	3a	toluene/CHCl ₃ 3:1	K ₃ PO ₄ 50%	-20	42	51	96
8	3a	toluene/CH₂Cl₂ 3:1	Cs₂CO₃ 66%	-20	60	73	96
9	3a	CH ₂ Cl ₂	CsOH·H ₂ O	-78	10	<20	nd
10	3a	toluene/CHCl ₃ 3:1	NaOH 10%	+4	18	52 ^d	97
11	3a	toluene/CH ₂ Cl ₂ 3:1	KOH 50%	-20	2	<20	nd
12	3a	toluene/CH₂Cl₂ 3:1	KOH 50%	-40	1	63	98
13	3e	toluene/CHCl ₃ 3:1	NaOH 10%	+4	42	65	79
14	3e	toluene/CH₂Cl₂ 3:1	KOH 50%	-40	1	98	92

^a Reactions carried out using 0.15 mmol of glycine imine **2** (0.15 M), 0.30 mmol of diene **3**, 10 mol% of catalyst **8'**, 0.15 mL of base. ^b Isolated yield. ^c Determined by chiral stationary phase HPLC. ^d Conversion, as determined by ¹H NMR spectroscopy. nd = not determined.

General Methods. NMR spectra were acquired using CDCl₃ as the solvent (unless otherwise noted) on a Varian AS 400 spectrometer, running at 400 and 100 MHz for ¹H and ¹³C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals (CHCl₃, 7.26 ppm for ¹H NMR, CDCl₃, 77.0 ppm for ¹³C NMR). ¹³C NMR spectra were acquired on a broad band decoupled mode. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES⁺) ionization techniques. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or KMnO₄ dip. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AS/AD or Daicel Chiralcel OJ columns).

Materials. Analytical grade solvents and commercially available reagents were used as received, unless otherwise stated. For flash chromatography (FC) silica gel was purchased from Fluka (Silica gel 60, 230-400 mesh). *tert*-Butyl β-ketoesters **1a-c** were prepared from the corresponding methyl esters¹ by Bu₂SnO catalyzed transesterification with *tert*-BuOH in refluxing toluene.² *tert*-Butyl β-ketoester **1d** was prepared by acylation of 1-tetralone with *tert*-butyl cyanofomate, as previously reported by us.³ *tert*-Butyl β-ketoesters **1e** and **1f** were prepared by a Dieckmann condensation from the corresponding diesters.⁴ 3-Vinylcyclohex-2-enone **3c** was synthesized by the substitution reaction of 3-ethoxycyclohex-2-enone with vinyl magnesium bromide.⁵ Diastereomerically pure (*E*)-methyl penta-2,4-dienoate **3d** was obtained by chromatographic purification of commercially available material. The corresponding ethyl ester **3e** was synthesised by a Wittig-Horner-Emmons reaction.⁶ (*E*)-(Buta-1,3-dienylsulfonyl)benzene **3f** was prepared from methylsulfonylbenzene following a two steps procedure reported in the literature.⁷ *O*-1-Adamantoyl-*N*-9-anthracenylmethyl dihydrocinchoninium chloride **6** and *O*-1-adamantoyl-*N*-9-anthracenylmethyl

¹ 1-Indanone and 5-chloro-1-indanone derivatives a) House, H. O.; Hudson, C. B. *J. Org. Chem.* **1970**, 35, 674; 5,6-dimethoxy-1-indanone derivative: b) Fukushi, H.; Mabuchi, H.; Itoh, K.; Terashita, Z.-i.; Nishikawa, K.; Sugihara, H. *Chem. Pharm. Bull.* **1994**, 42, 541.

² a) Otera, J.; Yano, T.; Kawabata, A.; Nozaki, H. *Tetrahedron Lett.* **1986**, 27, 2383; b) Nakajima, M.; Yamamoto, S.; Yamaguchi, Y.; Nakamura, S.; Hashimoto, S. *Tetrahedron*, **2003**, 59, 7307.

³ Poulsen, T. B.; Bernardi, L.; Aléman, J.; Overgaard, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, 129, 441.

⁴ Bunnage, M. E.; Davies, S. G.; Parkin, R. M.; Roberts, P. M.; Smith, A. D.; Withey, J. M. *Org. Biomol. Chem.* **2004**, 2, 3337.

⁵ Barriault, L.; Thomas, J. D. O.; Clément, R. *J. Org. Chem.* **2003**, 68, 2371.

⁶ Ishii, Y.; Gao, C.; Xu, W.-X.; Iwasaki, M.; Hidai, M. *J. Org. Chem.* **1993**, 58, 6818.

⁷ Hwang, S. H.; Kurth, M. J. *Tetrahedron Lett.* **2002**, 43, 53.

dihydrocinchonidinium chloride **6'** were prepared as previously described.⁸ Racemic samples were prepared using TBAI as the catalyst.

Preparation of (*E*)-hexa-3,5-dien-2-one (**3a**):⁹

Acetone (2.94 mL, 40 mmol) in dry THF (5 mL) was added to a cooled (-78 °C), stirred solution of LDA (freshly prepared from diisopropylamine (6.7 mL, 48 mmol) and *n*-BuLi (1.6 M in hexanes, 48 mmol)) in dry THF (50 mL). After 1 h stirring at the same temperature, acrolein (2.93 mL, 44 mmol) in THF (5 mL) was added dropwise. After 5 min stirring at -78 °C, the reaction was quenched by addition of sat. NH₄Cl. The mixture was then poured onto ether, washed with sat. NaCl, the organic phase separated, dried over MgSO₄, filtered and evaporated, furnishing the corresponding aldol product in quantitative yield, which was used in the next reaction with no further purification. The crude product obtained (40 mmol) was treated with Ac₂O (10.2 mL, 80 mmol) and NaOAc (2.0 g). The mixture was stirred overnight at room temperature then heated at 100 °C for 1 h. After cooling, the reaction was treated with sat NaHCO₃, extracted with Et₂O, the organic phase dried over MgSO₄, filtered and carefully evaporated (p >300 mbar, T <30 °C). Chromatographic purification of the product (pentane /Et₂O, removed at p >300 mbar, T <30 °C) furnished **3a** as a pale yellow liquid (1.50 g, 39% yield). ¹H NMR δ 7.10 (br ddd, *J* = 15.7, 10.8, 0.7 Hz, 1H), 6.47 (br dt, *J*_d = 16.9 Hz, *J*_t = 10.0 Hz, 1H), 6.15 (d, *J* = 15.7 Hz, 1H), 5.67 (br d, *J* = 16.3 Hz, 1H), 5.54 (br d, *J* = 10.6 Hz, 1H), 2.29 (s, 3H).

Preparation of (*E*)-1-phenyl-penta-2,4-dien-1-one (**3b**):

The aldol reaction was carried out like described for compound **3a** starting from acrolein (0.63 g, 11.2 mmol) and acetophenone (1.22 g, 10.2 mmol) using LDA prepared from diisopropylamine (1.24 g, 11.2 mmol) and *n*-BuLi (7.0 mL, 11.2 mmol). The crude aldol product was subsequently treated with *p*-TsOH (1.0 g) in refluxing CH₂Cl₂ (10 mL) for 3 h. The reaction mixture was then diluted with CH₂Cl₂ and H₂O and the aqueous phase was extracted with CH₂Cl₂. The organic layers were dried over MgSO₄ and the solvent was evaporated. The crude product was purified by column chromatography (pentane/Et₂O) to give a pale yellow liquid (422 mg, 26% yield). ¹H NMR δ 7.88 (dd, *J* = 8.4 Hz, 2H), 7.56-7.45 (m, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.38-7.28 (m, 1H), 6.93 (d, *J* = 15.1 Hz, 1H), 6.64-6.41 (m, 1H), 5.66 (d, *J* = 16.9 Hz, 1H), 5.53 (d, *J* = 10.0 Hz, 1H).

⁸ Poulsen, T. B.; Bernardi, L.; Bell, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6551.

⁹ Aldol reaction: Smith, A. B. III; Levenberg, P. A. *Synthesis* **1981**, 567. Dehydration: Das, N. B.; Torssell, K. B. G. *Tetrahedron* **1983**, *39*, 2247.

General procedure for the catalytic asymmetric 1,6-addition of β -keto esters **1** to dienes **3**.

To a vial, equipped with a magnetic stirring bar, were sequentially added the β -ketoester **1** (0.15 mmol), *o*-xylene/ CHCl_3 7:1 (1.0 mL) and the catalyst **6** (3.0 mg, 3 mol%). The vial was placed at the temperature stated, then the diene **3** (0.30 mmol) was added, followed by the inorganic base (0.45 mL). No precautions were taken to exclude moisture or air. After vigorous stirring of the resulting biphasic mixture for the stated reaction time, the organic phase was charged on a silica column, the aqueous phase extracted twice with a small amount of toluene, and the extracts charged on the column as well. After washing the column with pentane, the product **4** was obtained eluting with pentane/ Et_2O mixtures.

(*R,E*)-*tert*-Butyl 1-oxo-2-(5-oxohex-2-enyl)-2,3-dihydro-1*H*-indene-2-carboxylate (**4a**):

The title compound was obtained according to the general procedure, after 17 h reaction at -20 °C using K_2HPO_4 50% as the base and diene **3a** as the electrophile, as a colorless oil (99% yield). ^1H NMR δ 7.72 (d, J = 7.5 Hz, 1H), 7.58 (t, J = 7.3 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.36 (t, J = 7.3 Hz, 1H), 5.62 (dt, J_d = 15.2 Hz, J_t = 6.8 Hz, 1H), 5.38 (dt, J_d = 15.2 Hz, J_t = 7.2 Hz 1H), 3.54 (d, J = 17.3 Hz, 1H), 3.08 (d, J = 17.3 Hz, 1H), 3.02 (br d, J = 6.8 Hz, 2H), 2.79 (dd, J = 14.0, 7.3 Hz, 1H), 2.54 (dd, J = 13.9, 7.1 Hz, 1H), 2.02 (s, 3H), 1.36 (s, 9H). ^{13}C NMR δ 206.8, 202.5, 169.7, 153.1, 135.2, 135.1, 129.1, 127.5, 126.6, 126.3, 124.5, 81.9, 60.7, 47.3, 37.5, 36.1, 27.7, 20.0. HRMS calc.: $\text{C}_{20}\text{H}_{24}\text{NaO}_4$ 351.1567; found: 351.1578. The ee was determined by HPLC using a Chiralpak AS column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 10.0 min, τ_{minor} = 11.3 min (96% ee). $[\alpha]_{\text{D}}^{25} +72$ (c 1.0, CH_2Cl_2).

(*R,E*)-*tert*-Butyl 1-oxo-2-(5-oxo-5-phenylpent-2-enyl)-2,3-dihydro-1*H*-indene-2-carboxylate (**4b**):

The title compound was obtained according to the general procedure, after 18 h reaction at -20 °C using K_2HPO_4 50% as the base and diene **3b** as the electrophile, as a colorless oil (79% yield). ^1H NMR δ 7.87 (d, J = 7.2 Hz, 2H), 7.72 (d, J = 7.7 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.53 (t, J = 7.4 Hz, 1H), 7.44-7.38 (m, 3H), 7.35 (t, J = 7.3 Hz, 1H), 5.80 (dt, J_d = 15.3 Hz, J_t = 6.8 Hz, 1H), 5.48 (dt, J_d = 15.4 Hz, J_t = 7.2 Hz 1H), 3.62 (br d, J = 6.9 Hz, 2H), 3.52 (d, J = 17.3 Hz, 1H), 3.09 (d, J = 17.3 Hz, 1H), 2.85 (dd, J = 14.0, 6.9 Hz, 1H), 2.55 (dd, J = 14.0, 7.2 Hz, 1H), 1.37 (s, 9H). ^{13}C NMR δ 202.6, 197.9, 169.7, 153.2, 136.3, 135.2, 135.1, 133.1, 128.9, 128.6, 128.1, 127.5, 127.1, 126.3, 124.5, 81.8, 60.8, 42.2, 37.6, 36.0, 27.7. HRMS calc.: $\text{C}_{25}\text{H}_{26}\text{NaO}_4$ 413.1723; found: 413.1737. The

ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 18.1$ min, $\tau_{\text{minor}} = 16.6$ min (99% ee). $[\alpha]_{\text{D}}^{25} +60$ (c 0.80, CH₂Cl₂).

White crystals of **4b** suitable for X-ray crystallographic analysis were obtained leaving a solution of **4b** in CH₂Cl₂/hexane at -20 °C for several weeks. X-ray analysis of the crystals, using a copper source, allowed to determine the absolute configuration of **4b** to be (*R*).

X-ray figure of 4b:

(*R*)-*tert*-Butyl 1-oxo-2-(2-(3-oxocyclohex-1-enyl)ethyl)-2,3-dihydro-1*H*-indene-2-carboxylate (4c):

The title compound was obtained according to the general procedure, after 40 h reaction at -20 °C using K₂HPO₄ 50% as the base and diene **3c** as the electrophile as a colorless oil (66% yield). The corresponding β,γ -unsaturated compound **4c'** was isolated in 17% yield. Data for **4c**: ¹H NMR δ 7.75 (d, *J* = 7.7 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 5.80 (s, 1H), 3.66 (d, *J* = 17.3 Hz, 1H), 3.04 (d, *J* = 17.3 Hz, 1H), 2.34-2.26 (m, 5H), 2.21-2.11 (m, 2H), 2.05-1.92 (m, 3H), 1.38 (s, 9H). ¹³C NMR δ 202.7, 200.0, 170.0, 165.4, 153.0, 135.6, 135.5, 128.1, 126.6, 126.1, 124.9, 82.4, 60.9, 37.5, 37.2, 33.5, 32.2, 29.8, 28.0, 22.9. HRMS calc.: C₂₂H₂₆NaO₄ 377.1723; found: 377.1740. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 22.5$ min, $\tau_{\text{minor}} = 19.8$ min (90% ee). $[\alpha]_{\text{D}}^{25} +35$ (c 1.0, CH₂Cl₂).

(*R,E*)-*tert*-Butyl 2-(5-methoxy-5-oxopent-2-enyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (4d):

The title compound was obtained according to the general procedure, after 40 h reaction at +4 °C using Cs₂CO₃ 40% as the base and diene **3d** as the electrophile, as a colorless oil (96% yield). ¹H NMR δ 7.72 (d, *J* = 7.7 Hz, 1H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 1H), 5.63 (dt, *J*_d = 15.4 Hz, *J*_t = 6.9 Hz, 1H), 5.41 (dt, *J*_d = 15.4 Hz, *J*_t = 7.3 Hz, 1H), 3.61 (s, 3H), 3.55 (d, *J* = 17.3 Hz, 1H), 3.07 (d, *J* = 17.3 Hz, 1H), 2.95 (br d, *J* = 6.9 Hz, 2H), 2.82 (dd, *J* = 14.1, 7.3 Hz, 1H), 2.49 (dd, *J* = 14.1, 7.2 Hz, 1H), 1.36 (s, 9H). ¹³C NMR δ 202.4, 171.9, 169.6, 153.1, 135.1 (2 C), 128.8, 127.5, 126.3, 126.2, 124.5, 81.8, 60.8, 51.7, 37.5, 37.4, 35.9, 27.7. HRMS calc.: C₂₀H₂₄NaO₅ 367.1516; found: 367.1501. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 9.6 min, τ_{minor} = 9.2 min (97% ee). [α]_D^{rt} +70 (c 1.0, CH₂Cl₂).

(*S,E*)-*tert*-Butyl 2-(5-methoxy-5-oxopent-2-enyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (*ent*-4d):

The title compound was obtained according to the general procedure, after 40 h reaction at +4 °C using Cs₂CO₃ 40% as the base, diene **3d** as the electrophile and catalyst **6'** derived from dihydrocinchonine, as a colorless oil (81% yield). Spectral data were identical to compound **4d**. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 9.2 min, τ_{minor} = 9.6 min (80% ee). [α]_D^{rt} -62 (c 1.0, CH₂Cl₂).

(*R,E*)-*tert*-Butyl 2-(5-ethoxy-5-oxopent-2-enyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (4e):

The title compound was obtained according to the general procedure, after 43 h reaction at +4 °C using Cs₂CO₃ 40% as the base and diene **3e** as the electrophile, as a colorless oil (80% yield). ¹H NMR δ 7.73 (d, *J* = 7.7 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 1H), 5.64 (dt, *J*_d = 15.3 Hz, *J*_t = 6.9 Hz, 1H), 5.41 (dt, *J*_d = 15.3 Hz, *J*_t = 7.2 Hz, 1H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.55 (d, *J* = 17.3 Hz, 1H), 3.08 (d, *J* = 17.3 Hz, 1H), 2.94 (br d, *J* = 6.9 Hz, 2H), 2.83 (dd, *J* = 14.0, 7.3 Hz, 1H), 2.49 (dd, *J* = 14.0, 7.1 Hz, 1H), 1.37 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H). ¹³C NMR δ 202.5, 171.5, 169.6, 153.2, 135.1, 135.2, 128.7, 127.5, 126.4, 126.3, 124.5, 81.8, 60.8, 60.5, 37.9, 37.5, 35.9, 27.7, 14.1. HRMS calc.: C₂₁H₂₆NaO₅ 381.1672; found: 381.1665. The ee was

determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (99:1)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 15.2$ min, $\tau_{\text{minor}} = 16.1$ min (97% ee). $[\alpha]_{\text{D}}^{25} +72$ (c 1.0, CH₂Cl₂).

(*R,E*)-*tert*-Butyl 1-oxo-2-(4-(phenylsulfonyl)but-2-enyl)-2,3-dihydro-1*H*-indene-2-carboxylate (4f):

The title compound was obtained according to the general procedure, after 17 h reaction at -20 °C using K₂HPO₄ 50% as the base and diene **3f** as the electrophile, as a colorless oil (94% yield). ¹H NMR δ 7.79 (d, *J* = 7.3 Hz, 2H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.63-7.56 (m, 2H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 1H), 5.54-5.39 (m, 2H), 3.68 (br d, *J* = 6.5 Hz, 2H), 3.42 (d, *J* = 17.3 Hz, 1H), 2.89 (d, *J* = 17.3 Hz, 1H), 2.78 (dd, *J* = 14.3, 6.4 Hz, 1H), 2.43 (dd, *J* = 14.3, 6.8 Hz, 1H), 1.31 (s, 9H). ¹³C NMR δ 202.0, 169.3, 152.9, 138.2, 135.8, 135.2, 134.8, 133.6, 129.0, 128.2, 127.6, 126.3, 124.6, 120.3, 82.0, 60.3, 59.7, 37.1, 35.9, 27.6. HRMS calc.: C₂₄H₂₆NaO₅S 449.1393; found: 449.1387. The ee was determined by HPLC using a Chiralcel OJ column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 31.2$ min, $\tau_{\text{minor}} = 41.4$ min (95% ee). $[\alpha]_{\text{D}}^{25} +43$ (c 1.0, CH₂Cl₂).

(*R,E*)-*tert*-Butyl 5,6-dimethoxy-1-oxo-2-(5-oxohex-2-enyl)-2,3-dihydro-1*H*-indene-2-carboxylate (4g):

The title compound was obtained according to the general procedure, after 20 h reaction at -20 °C using K₂HPO₄ 50% as the base and diene **3a** as the electrophile, as a colorless oil (98% yield). ¹H NMR δ 7.13 (br s, 1H), 6.85 (br s, 1H), 5.61 (br dt, *J*_d = 15.3 Hz, *J*_t = 7.0 Hz, 1H), 5.36 (br dt, *J*_d = 15.3 Hz, *J*_t = 7.2 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.42 (d, *J* = 17.2 Hz, 1H), 3.10-2.95 (m, 2H), 2.97 (d, *J* = 17.3 Hz, 1H), 2.77 (dd, *J* = 14.0, 7.4 Hz, 1H), 2.53 (ddd, *J* = 14.0, 7.0, 0.8 Hz, 1H), 2.03 (s, 3H), 1.37 (s, 9H). ¹³C NMR δ 206.8, 201.0, 170.0, 155.8, 149.4, 148.7, 129.3, 127.8, 126.4, 107.1, 104.7, 81.7, 61.0, 56.2, 56.0, 47.3, 37.5, 35.7, 29.3, 27.7. HRMS calc.: C₂₂H₂₈NaO₆ 411.1778; found: 411.1764. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 22.4$ min, $\tau_{\text{minor}} = 23.6$ min (92% ee). $[\alpha]_{\text{D}}^{25} +106$ (c 0.95, CH₂Cl₂).

(*S,E*)-*tert*-Butyl 5,6-dimethoxy-1-oxo-2-(5-oxohex-2-enyl)-2,3-dihydro-1*H*-indene-2-carboxylate (*ent*-4g):

The title compound was obtained according to the general procedure, after 18 h reaction at -20 °C using K₂HPO₄ 50% as the base, diene **3a**

as the electrophile and catalyst **6'** derived from dihydrocinchonidine, as a colorless oil (98% yield). Spectral data were identical to compound **4g**. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 23.6$ min, $\tau_{\text{minor}} = 22.4$ min (89% ee). $[\alpha]_{\text{D}}^{25} -80$ (c 0.92, CH₂Cl₂).

(*R,E*)-*tert*-Butyl 5-chloro-1-oxo-2-(5-oxohex-2-enyl)-2,3-dihydro-1*H*-indene-2-carboxylate (4h**):**

The title compound was obtained according to the general procedure, after 18 h reaction at -20 °C using K₂HPO₄ 50% as the base and diene **3a** as the electrophile, as a colorless oil (89% yield). ¹H NMR δ 7.66 (br d, $J = 8.2$ Hz, 1H), 7.45 (br s, 1H), 7.34 (dd, $J = 8.2, 1.1$ Hz, 1H), 5.63 (br dt, $J_{\text{d}} = 15.3$ Hz, $J_{\text{t}} = 6.6$ Hz, 1H), 5.35 (br dt, $J_{\text{d}} = 15.4$ Hz, $J_{\text{t}} = 7.4$ Hz, 1H), 3.51 (d, $J = 17.5$ Hz, 1H), 3.12-2.88 (m, 3H), 2.78 (dd, $J = 14.0, 7.4$ Hz, 1H), 2.54 (dd, $J = 14.0, 7.2$ Hz, 1H), 2.05 (s, 3H), 1.37 (s, 9H). ¹³C NMR δ 206.6, 201.1, 169.4, 154.6, 141.7, 133.7, 128.7, 128.4, 126.9, 126.6, 125.6, 82.2, 61.0, 47.2, 37.5, 35.7, 29.4, 27.7. HRMS calc.: C₂₀H₂₃ClNaO₄ 385.1183; found: 385.1178. The ee was determined by HPLC using a Chiralcel OJ column [hexane/*i*PrOH (98:2)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 24.6$ min, $\tau_{\text{minor}} = 22.2$ min (93% ee). $[\alpha]_{\text{D}}^{25} +84$ (c 0.90, CH₂Cl₂).

(*S,E*)-*tert*-Butyl 1-oxo-2-(5-oxohex-2-enyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (4i**):**

The title compound was obtained according to the general procedure, after 36 h reaction at -25 °C using CsCO₃ 66% as the base and diene **3a** as the electrophile, as a colorless oil (78% yield). ¹H NMR δ 8.01 (d, $J = 7.8$ Hz, 1H), 7.45 (t, $J = 7.4$ Hz, 1H), 7.29 (t, $J = 7.6$ Hz, 1H), 7.20 (d, $J = 7.8$ Hz, 1H), 5.63 (q, $J = 6.0$ Hz, 2H), 3.11 (d, $J = 5.4$ Hz, 2H), 3.09-2.99 (m, 1H), 2.90 (dt, $J_{\text{t}} = 17.1$, $J_{\text{d}} = 4.2$ Hz, 1H), 2.79-2.51 (m, 2H), 2.43 (dt, $J_{\text{t}} = 13.6$, $J_{\text{d}} = 4.4$ Hz, 1H), 2.12 (s, 3H), 2.10-2.01 (m, 1H), 1.32 (s, 9H). ¹³C NMR δ 207.0, 195.5, 170.7, 142.8, 133.2, 132.4, 129.8, 128.6, 127.6, 126.6, 126.1, 82.1, 57.7, 47.5, 37.4, 31.0, 27.7, 25.9. HRMS calc.: C₂₁H₂₆NaO₄ 365.1729; found: 365.1733. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (99:1)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 22.1$ min, $\tau_{\text{minor}} = 26.7$ min (94% ee). $[\alpha]_{\text{D}}^{25} -40$ (c = 1.21, CHCl₃).

(*R,E*)-*tert*-Butyl 1-oxo-2-(5-oxohex-2-enyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (*ent*-4i**):**

The title compound was obtained according to the general procedure, after 48 h reaction at 4 °C using CsCO₃ 66% as the base and diene **3a** as the

electrophile in presence **6'** as catalyst, as a colorless oil (65% yield). The spectroscopical data was identical to the corresponding data for compound **4i**. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (99:1)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 26.8$ min, $\tau_{\text{minor}} = 22.3$ min (79% ee). $[\alpha]_{\text{D}}^{25} +37$ (c = 1.55, CHCl₃).

(*S,E*)-tert-Butyl 2-oxo-1-(5-oxohex-2-enyl)cyclopentanecarboxylate (4j**):**

The title compound was obtained according to the general procedure, after 18 h reaction at -30 °C using K₃PO₄ 50% as the base and diene **3a** as the electrophile, as a colorless oil (95% yield). ¹H NMR δ 5.60 (dtt, $J_{\text{d}} = 15.3$ Hz, $J_{\text{t}} = 6.9$, 1.1 Hz, 1H), 5.45 (dtt, $J_{\text{d}} = 15.3$ Hz, $J_{\text{t}} = 7.2$, 1.2 Hz, 1H), 3.20-3.00 (m, 2H), 2.56 (ddd, $J = 14.0$, 7.1, 1.0 Hz, 1H), 2.44-2.28 (m, 3H), 2.24-2.12 (m, 1H), 2.12 (s, 3H), 2.05-1.85 (m, 3H), 1.41 (s, 9H). ¹³C NMR δ 215.0, 206.8, 170.2, 129.4, 126.3, 81.8, 60.4, 47.4, 38.0, 36.3, 32.4, 29.4, 27.8, 19.5. HRMS calc.: C₁₆H₂₄NaO₄ 303.1567; found: 303.1551. The ee was determined by HPLC using a Chiralcel OJ column [hexane/*i*PrOH (99:1)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 28.3$ min, $\tau_{\text{minor}} = 25.1$ min (79% ee). $[\alpha]_{\text{D}}^{25} +24$ (c 0.87, CH₂Cl₂).

(*S,E*)-tert-Butyl 2-oxo-1-(5-oxohex-2-enyl)cyclohexanecarboxylate (4k**):**

The title compound was obtained according to the general procedure, after 24 h reaction at -20 °C using K₃PO₄ 50% as the base and diene **3a** as the electrophile, as a colorless oil (84% yield). ¹H NMR δ 5.60-5.40 (m, 2H), 3.20-2.95 (m, 2H), 2.53 (dd, $J = 14.7$, 4.2 Hz, 1H), 2.48-2.35 (m, 3H), 2.29 (dd, $J = 15.4$, 6.9 Hz, 1H), 2.11 (s, 3H), 2.03-1.96 (m, 1H), 1.78-1.50 (m, 3H), 1.42 (s, 9H), 1.39-1.35 (m, 1H). ¹³C NMR δ 207.9, 207.0, 170.5, 129.6, 125.5, 82.0, 61.2, 47.5, 41.1, 38.1, 35.9, 29.4, 27.9, 27.5, 22.5. HRMS calc.: C₁₇H₂₆NaO₄ 317.1723; found: 317.1721. The ee was determined by HPLC using a Chiralcel OJ column [hexane/*i*PrOH (97:3)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 11.9$ min, $\tau_{\text{minor}} = 10.6$ min (91% ee). $[\alpha]_{\text{D}}^{25} -64$ (c 0.88, CH₂Cl₂).

(*S,E*)-tert-Butyl 1-(5-ethoxy-5-oxopent-2-enyl)-2-oxocyclopentanecarboxylate (4l**):**

The title compound was obtained according to the general procedure, after 60 h reaction at -20 °C using K₃PO₄ 50% as the base and diene **3e** as the electrophile, as a colorless oil (92% yield). ¹H NMR δ 5.60 (dtt, $J_{\text{d}} = 15.3$ Hz, $J_{\text{t}} = 6.9$, 1.1 Hz, 1H), 5.44 (dtt, $J_{\text{d}} = 15.3$ Hz, $J_{\text{t}} = 7.2$, 1.2 Hz, 1H), 4.21 (q, $J = 7.1$ Hz, 2H), 3.05-2.95 (m, 2H), 2.59 (ddd, $J = 14.0$, 7.2, 0.9 Hz, 1H), 2.44-2.28 (m, 3H), 2.24-2.12 (m, 1H), 2.04-1.58 (m, 3H), 1.41 (s, 9H), 1.23 (t, $J = 7.1$ Hz, 3H). ¹³C NMR δ 215.1, 171.7, 170.1, 128.9,

126.2, 81.8, 60.6, 60.4, 38.0, 37.9, 36.2, 32.2, 27.8, 19.5, 14.1. HRMS calc.: C₁₇H₂₆NaO₅ 333.1672; found: 333.1761. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 6.4 min, τ_{minor} = 7.4 min (80% ee). $[\alpha]_{\text{D}}^{25}$ +24 (c 1.0, CH₂Cl₂).

(*S,E*)-*tert*-Butyl 1-(5-ethoxy-5-oxopent-2-enyl)-2-oxocyclohexanecarboxylate (4m):

The title compound was obtained according to the general procedure, after 60 h reaction at -20 °C using Cs₂CO₃ (0.15 mmol, 1 equiv.) as the base, diene **3e** as the electrophile and 6 mol% of catalyst **6**, as a colorless oil (66% yield). ¹H NMR δ 5.62-5.46 (m, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.08-2.94 (m, 2H), 2.52 (dd, *J* = 14.0, 6.3 Hz, 1H), 2.48-2.36 (m, 3H), 2.28 (dd, *J* = 14.1, 6.9 Hz, 1H), 2.14-1.96 (m, 1H), 1.75-1.52 (m, 3H), 1.43 (s, 9H), 1.40-1.32 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H). ¹³C NMR δ 207.9, 171.7, 170.5, 129.1, 125.4, 81.9, 61.2, 60.5, 41.1, 38.0, 35.9, 27.9, 27.8, 27.6, 22.5, 14.2. HRMS calc.: C₁₈H₂₈NaO₅ 347.1834; found: 347.1830. The ee was determined by HPLC using two Chiralcel OJ columns connected in series [hexane/*i*PrOH (95:5)]; flow rate 0.75 mL/min; τ_{major} = 18.6 min, τ_{minor} = 17.6 min (95% ee). $[\alpha]_{\text{D}}^{25}$ -85 (c 1.0, CH₂Cl₂).

General procedure for the catalytic, asymmetric 1,6-addition of Schiff base **2 to dienes **3**.**

To a vial, equipped with a magnetic stirring bar, were sequentially added benzophenone imine **2** (44 mg, 0.15 mmol) and the catalyst **8'** (9.1 mg, 10 mol%). The solids were suspended in the solvent mixture (toluene/CH₂Cl₂ 3:1, 1.0 mL), then the diene **3** (0.30 mmol) was added. The vial was placed at the temperature stated, then the aqueous base, pre-cooled to the appropriate temperature, was added (0.45 mL). No precautions were taken to exclude moisture or air. After vigorous stirring of the resulting biphasic mixture for the stated reaction time, the organic phase was charged on a silica column, the aqueous phase extracted twice with a small amount of toluene, and the extracts charged on the column as well. After washing the column with pentane, the product **5** was obtained eluting with pentane/Et₂O mixtures.

(*S,E*)-*tert*-Butyl 2-(diphenylmethyleneamino)-7-oxooct-4-enoate (5a):

The title compound was obtained according to the general procedure, after 1 h reaction at -40 °C using KOH 50% as the base, and diene **3a** as the electrophile, as a colorless oil (63% yield, 98% ee). The same compound could be obtained after 60 h reaction at -20 °C, using Cs₂CO₃ 66% as the base, and diene **3a** as the electrophile (73% yield, 96% ee). ¹H NMR δ 7.65-7.62 (m, 2H), 7.43-7.28 (m, 6H), 7.18-7.10 (m, 2H), 5.60 (br dt, *J*_d = 15.3 Hz, *J*_t = 6.6 Hz, 1H), 5.52 (br dt, *J*_d = 15.4 Hz, *J*_t = 6.7

Hz, 1H), 3.98 (dd, $J = 7.0, 5.7$ Hz, 1H), 3.18-2.98 (m, 2H), 2.58-2.52 (m, 2H), 2.09 (s, 3H), 1.43 (s, 9H). ^{13}C NMR δ 207.4, 171.0, 170.5, 139.8, 136.8, 131.2, 130.5, 129.0, 128.8, 128.7, 128.2, 128.0, 124.9, 81.3, 66.1, 47.9, 37.2, 29.6, 28.3. HRMS calc.: $\text{C}_{25}\text{H}_{29}\text{NNaO}_3$ 414.2040; found: 414.2032. The ee was determined by HPLC using two Chiralpak AD columns connected in series [hexane/*i*PrOH (95:5)]; flow rate 0.75 mL/min; $\tau_{\text{major}} = 17.6$ min, $\tau_{\text{minor}} = 16.5$ min (98% ee). $[\alpha]_{\text{D}}^{\text{rt}} -63$ (c 0.73, CH_2Cl_2).

(*S*)-*tert*-Butyl 2-(diphenylmethyleneamino)-4-(3-oxocyclohex-1-enyl)butanoate (5b):

The title compound was obtained according to the general procedure, after 1.5 h reaction at -40 °C using KOH 50% as the base, and diene **3c** as the electrophile, as a colorless oil (49% yield). ^1H NMR δ 7.62 (br d, $J = 7.6$ Hz, 2H), 7.48-7.30 (m, 6H), 7.15 (br dd, $J = 7.3, 3.6$ Hz, 2H), 5.82 (br s, 1H), 3.92 (t, $J = 6.2$ Hz, 1H), 2.29 (t, $J = 6.4$ Hz, 2H), 2.26-2.16 (m, 4H), 2.12-2.04 (m, 2H), 1.92 (br quint, $J = 6.3$ Hz, 2H), 1.44 (s, 9H). ^{13}C NMR δ 199.8, 170.9, 170.6, 165.7, 139.3, 136.4, 130.4, 128.7, 128.6, 128.4, 128.0, 127.7, 125.8, 81.3, 65.1, 37.2, 34.4, 30.9, 29.6, 28.0, 22.6. HRMS calc.: $\text{C}_{27}\text{H}_{31}\text{NNaO}_3$ 440.2196; found: 440.2194. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 13.1$ min, $\tau_{\text{minor}} = 10.3$ min (60% ee). $[\alpha]_{\text{D}}^{\text{rt}} -51$ (c 1.0, CH_2Cl_2).

(*S,E*)-7-*tert*-Butyl 1-methyl 6-(diphenylmethyleneamino)hept-3-enedioate (5c):

The title compound was obtained according to the general procedure, after 1 h reaction at -40 °C using KOH 50% as the base, and diene **3d** as the electrophile, as a colorless oil (84% yield). ^1H NMR δ 7.65-7.62 (m, 2H), 7.48-7.28 (m, 6H), 7.18-7.13 (m, 2H), 5.59 (br dt, $J_{\text{d}} = 15.4$ Hz, $J_{\text{t}} = 6.7$ Hz, 1H), 5.49 (br dt, $J_{\text{d}} = 15.4$ Hz, $J_{\text{t}} = 7.0$ Hz, 1H), 3.98 (t, $J = 7.0$ Hz, 1H), 3.58 (s, 3H), 3.08-2.92 (m, 2H), 2.67-2.55 (m, 2H), 1.44 (s, 9H). ^{13}C NMR δ 172.1, 170.8, 170.2, 139.6, 136.6, 130.4, 130.2, 128.8, 128.5, 128.4, 128.0, 127.8, 124.4, 81.0, 65.8, 51.7, 38.1, 36.8, 28.0. HRMS calc.: $\text{C}_{25}\text{H}_{29}\text{NNaO}_4$ 430.1994; found: 430.1979. The ee was determined by HPLC using two Chiralpak AD columns connected in series [hexane/*i*PrOH (95:5)]; flow rate 0.75 mL/min; $\tau_{\text{major}} = 16.6$ min, $\tau_{\text{minor}} = 15.6$ min (95% ee). $[\alpha]_{\text{D}}^{\text{rt}} -82$ (c 0.95, CH_2Cl_2).

(*R,E*)-7-*tert*-Butyl 1-methyl 6-(diphenylmethyleneamino)hept-3-enedioate (*ent*-5c):

The title compound was obtained according to the general procedure, after 1 h reaction at -40 °C using KOH 50% as the base, diene **3d** as the electrophile, and catalyst **8**, as a colorless oil (90% yield). Spectral data were identical to compound **5c**. The ee was determined by HPLC using two Chiralpak AD columns connected in series [hexane/*i*PrOH (95:5)]; flow rate 0.75 mL/min; $\tau_{\text{major}} = 15.6$ min, $\tau_{\text{minor}} = 16.6$ min (96% ee). $[\alpha]_{\text{D}}^{25} +80$ (c 1.0, CH₂Cl₂).

(*S,E*)-7-*tert*-Butyl 1-ethyl 6-(diphenylmethyleneamino)hept-3-enedioate (5d**):**

The title compound was obtained according to the general procedure, after 1 h reaction at -40 °C using KOH 50% as the base, and diene **3e** as the electrophile, as a colorless oil (98% yield). ¹H NMR δ 7.62 (br d, $J = 7.4$ Hz, 2H), 7.48-7.28 (m, 6H), 7.18-7.12 (m, 2H), 5.59 (br dt, $J_{\text{d}} = 15.4$ Hz, $J_{\text{t}} = 6.8$ Hz, 1H), 5.49 (br dt, $J_{\text{d}} = 15.4$ Hz, $J_{\text{t}} = 6.9$ Hz, 1H), 4.05 (q, $J = 7.1$ Hz, 2H), 3.98 (br t, $J = 6.8$ Hz, 1H), 3.08-2.92 (m, 2H), 2.67-2.55 (m, 2H), 1.43 (s, 9H), 1.19 (t, $J = 7.0$ Hz, 3H). ¹³C NMR δ 171.7, 170.8, 170.1, 139.6, 136.6, 130.2, 130.1, 128.8, 128.5, 128.4, 128.0, 127.9, 127.8, 124.6, 81.0, 65.8, 60.5, 38.3, 36.8, 28.0, 14.1. HRMS calc.: C₂₆H₃₁NNaO₄ 444.2151; found: 444.2137. The ee was determined by HPLC using two Chiralpak AD columns connected in series [hexane/*i*PrOH (95:5)]; flow rate 0.75 mL/min; $\tau_{\text{major}} = 14.2$ min, $\tau_{\text{minor}} = 13.4$ min (92% ee). $[\alpha]_{\text{D}}^{25} -80$ (c 0.97, CH₂Cl₂).

(*S,E*)-*tert*-Butyl 2-(diphenylmethyleneamino)-6-(phenylsulfonyl)hex-4-enoate (5e**):**

The title compound was obtained according to the general procedure, after 18 h reaction at -40 °C using KOH 50% as the base, and diene **3f** as the electrophile (1.5 equiv.), as a colorless oil (89% yield). ¹H NMR δ 7.67 (br d, $J = 8.3$ Hz, 2H), 7.53 (br d, $J = 7.3$ Hz, 2H), 7.48 (br t, $J = 7.5$ Hz, 1H), 7.40-7.22 (m, 8H), 7.08-7.05 (m, 2H), 5.43 (br dt, $J_{\text{d}} = 15.4$ Hz, $J_{\text{t}} = 7.1$ Hz, 1H), 5.36 (br dt, $J_{\text{d}} = 15.5$ Hz, $J_{\text{t}} = 6.8$ Hz, 1H), 3.86 (dd, $J = 7.2, 5.3$ Hz, 1H), 3.70-3.55 (m, 2H), 2.60-2.45 (m, 2H), 1.32 (s, 9H). ¹³C NMR δ 170.5, 170.2, 139.3, 138.2, 137.3, 136.3, 133.5, 130.2, 128.9, 128.8, 128.7, 128.5, 128.4, 128.2, 127.9, 127.6, 118.5, 81.1, 65.2, 59.9, 36.7, 27.9. HRMS calc.: C₂₉H₃₁NNaO₄S 512.1871; found: 512.1872. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 17.1$ min, $\tau_{\text{minor}} = 14.6$ min (93% ee). $[\alpha]_{\text{D}}^{25} -32$ (c 1.0, CH₂Cl₂).

(1*R*,4*R*, 5*S*)-*tert*-Butyl 4-(2-ethoxy-2-oxoethyl)-8-oxobicyclo[3.2.1]octane-1-carboxylate (7).

To a screw-cap vial containing a solution of **4I** (31 mg, 0.10 mmol) in THF (1 mL), DBU (45 μ L, 0.30 mmol) was added. The vial was closed tightly, heated at 120 °C for 14 h, then cooled to room temperature. The solution was filtered through a short pad of silica to remove DBU, the pad washed several times with Et₂O and the solvents evaporated. The title compound was then obtained as a colorless oil (18 mg, 60% yield) after FC (2 purifications, pentane/Et₂O 8:2, then CHCl₃/EtOAc 98:2). ¹H NMR δ 4.11 (q, J = 7.1 Hz, 2H), 2.58-2.46 (m, 2H), 2.32-2.24 (m, 3H), 2.17 (dt, J_t = 13.3 Hz, J_d = 5.1 Hz, 1H), 1.96 (dd, J = 13.5, 5.5 Hz, 1H), 1.92-1.82 (m, 2H), 1.79-1.75 (m, 2H), 1.46-1.42 (m, 1H), 1.45 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H). ¹³C NMR δ 213.9, 171.4, 170.5, 81.3, 60.6, m57.4, 49.8, 42.1, 38.5, 36.3, 28.0, 27.0, 24.3, 17.3, 14.2. HRMS calc.: C₁₇H₂₆NaO₅.333.1672; found: 333.1684. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 9.2 min, τ_{minor} = 8.8 min (80% ee), and was found to be consistent with the ee of the starting material **4I**. $[\alpha]_D^{25}$ -18 (c 0.90, CH₂Cl₂).

The absolute configuration at C₄ was tentatively assigned as (*R*) on the basis of the coupling constant between H₄ and H_{3A}, obtained from its ¹H NMR spectrum recorded in benzene-*d*₆. ¹H NMR (benzene-*d*₆, 400 MHz) δ 3.88 (q, J = 7.1 Hz, 2H, CH₂CH₃), 2.46 (dt, J_t = 12.4 Hz, J_d = 3.6 Hz, 1H, H₆), 2.42-2.33 (m, 1H, H₄), 2.18 (dt, J_t = 13.2 Hz, J_d = 3.7 Hz, 1H, H_{2A}), 2.20-2.30 (m, 1H, H₅), 1.79 (dd, J = 15.4, 7.3 Hz, 1H, H₉), 1.75 (dd, J = 14.6, 6.6 Hz, 1H, H₉), 1.70 (dt, J_t = 14.8 Hz, J_d = 4.2 Hz, 1H, H_{2B}), 1.45 (s, 9H, C(CH₃)₃), 1.39-1.30 (m, 1H, H₆), 1.29-1.18 (m, 2H, H₇ + H_{3B}), 1.04 (ddd, J = 14.4, 10.9, 4.4 Hz, 1H, H₇), 0.91 (t, J = 7.1 Hz, CH₂CH₃), 0.81 (dq, J_q = 13.1 Hz, J_d = 5.8 Hz, 1H, H_{3A}). ¹³C NMR (benzene-*d*₆ 100 MHz) δ 212.6 (C₈), 170.8 and 170.4 (CO₂Et and CO₂*t*-Bu), 80.6 (C(CH₃)₃), 60.1 (CH₂CH₃), 57.5 (C₁), 49.8 (C₅), 41.9 (C₄), 38.1 (C₉), 36.4 (C₂), 28.0 (C(CH₃)₃), 27.1 (C₆), 24.2 (C₃), 17.0 (C₇), 14.1 (CH₂CH₃). The NMR signals were assigned on the basis of DEPT, HETCOR and H-H decoupling experiments. The coupling constant between H₄ and H_{3A} was determined by means of H-H decoupling experiments: H_{3A} gives a double quartet at 0.81 ppm which upon irradiation of the signal relative to H_{2B} (1.68 ppm) becomes a quartet (J = 13.0 Hz), which is accounted for by a geminal coupling with H_{3B}, an axial-axial coupling with H_{2A}, and the coupling with H₄. Considering the value of this latter coupling constant, (J = 13.0 Hz), and the most stable conformation for the title compound as shown,¹⁰ we assumed an axial-axial relationship between H₄ and H_{3A} thus giving a (*R*) configuration at C₄.

¹⁰ Filippini, M.-H.; Rodriguez, J. *Chem. Rev.* **1999**, 99, 27.

(2*S*,5*S*)-5-Methoxycarbonylmethyl-pyrrolidine-2-carboxylic acid *tert*-butyl ester *trans*-(9) and (2*S*,5*R*)-5-methoxycarbonylmethyl-pyrrolidine-2-carboxylic acid *tert*-butyl ester *cis*-(9):

To a solution of **5c** (295 mg, 0.73 mmol) in THF (7 mL) was added a citric acid solution (10% in H₂O, 5 mL). The mixture was stirred at room temperature for 4 h. After the reaction was finished, a sat. NaHCO₃ solution (5 mL) was added and the aqueous phase was extracted with EtOAc. The organic layers were dried over MgSO₄ and the solvent was evaporated. The crude product was used directly for the next step without any purification. The residue was dissolved in THF (7 mL) and DBU (333 mg, 2.19 mmol) was added. The resulting mixture was warmed to 60 °C for 18 h. Afterwards the solvent was evaporated and the residue was purified by flash chromatography (CH₂Cl₂/MeOH) yielding the title compounds as a mixture of *cis*- and *trans*-isomers in a ratio of 1:1.6 (155 mg, 87%). It was possible to obtain analytical samples of the single isomers in pure form by submitting the mixture to flash chromatography on a very long column. The relative configuration of the single isomers was determined by comparison of their NMR spectra with the corresponding spectra reported in the literature¹¹ and upon chemical correlation of compounds **10** and **11** with literature data (see below).

trans-**9**: ¹H NMR δ 3.73-3.63 (m, 2H), 3.65 (s, 3H), 2.45 (m, 2H), 2.23-2.15 (m, 1H), 1.99-1.92 (m, 1H), 1.85-1.79 (m, 1H), 1.45-1.39 (m, 1H), 1.43 (s, 9H). ¹³C NMR δ 174.7, 172.7, 81.1, 60.0, 54.4, 51.6, 41.3, 31.1, 29.7, 28.0. HRMS calc.: C₁₂H₂₁NNaO₄.266.1368; found: 266.1362. [α]_D²⁵ -18 (c 0.60, CHCl₃). The enantiomeric excess of *cis*-**9** was determined after Cbz-protection and was found to be consistent with the ee of the starting compound **5c** (97% ee).

cis-**9**: ¹H NMR δ 3.67-3.64 (m, 1H), 3.66 (s, 3H), 3.52-3.33 (m, 1H), 2.52 (dq, *J* = 15.70 Hz, 2H), 2.39-2.19 (m, 1H), 2.13-1.99 (m, 1H), 1.99-1.79

¹¹(a) Bulychiev, A., Massova, I., Miyashita, K., Mobashery, S. *J. Am. Chem. Soc.* **1997**, *119*, 7619-7625. (b) Collado, I., Ezquerro, J., Vaquero, J. J., Pedregal, C. *Tetrahedron Lett.* **1994**, *35*, 8037-8040.

(m, 2H), 1.43 (s, 9H), 1.40-1.29 (m, 1H). ^{13}C NMR δ 174.2, 172.5, 80.9, 60.4, 55.7, 51.6, 40.2, 30.7, 29.8, 28.0. $[\alpha]_{\text{D}}^{25}$ -30 (c 1.30, CHCl_3). The enantiomeric excess of *cis*-**9** was determined after Cbz-protection and was found to be consistent with the ee of the starting compound **5c** (96% ee).

Determination of the enantiomeric excess and of the absolute configuration of compounds **9** by chemical correlation

(2*S*,5*S*)-1-(Benzyloxycarbonyl)-5-[(methoxycarbonyl)methyl]proline *tert*-butyl ester *trans*-(**10**):

Pyrrolidine *trans*-**9** (20 mg, 82 μmol) was dissolved in EtOAc (0.5 mL) and H_2O (0.25 mL) and subsequently K_2CO_3 (17 mg, 123 μmol) and CbzCl (35 μmol , 247 μmol) were added. After 1 h at room temperature the mixture was poured into H_2O and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with HCl (1 M), dried over MgSO_4 and the solvent was evaporated. The residue was purified by flash chromatography (PE/ Et_2O) to yield a colorless oil (29 mg, 94%). The NMR spectra show a doubling of signals, due to the slow interconversion between the different rotamers: see spectra section for more details. HRMS calc.: $\text{C}_{20}\text{H}_{27}\text{NNaO}_6$, 400.1736; found: 400.1732. The enantiomeric excess was determined on the HPLC using a Chiralpak AD column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 14.2 min, τ_{minor} = 12.5 min (97% ee) and was found to be consistent with the ee of the starting benzophenone imine **5c**. *trans*-isomer: $[\alpha]_{\text{D}}^{25}$ -48.9 (c 1.45, CHCl_3).

(2*S*,5*R*)-1-(Benzyloxycarbonyl)-5-[(methoxycarbonyl)methyl]proline *tert*-butyl ester *cis*-10):

Following the procedure used for *trans*-**10**, the title compound was obtained starting from *cis*-**9** in 85% yield as a colorless oil. The NMR spectra show a doubling of signals, due to the slow interconversion between the different rotamers: see spectra section for more details. The enantiomeric excess was determined on the HPLC using a Chiralpak AD column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 9.6$ min, $\tau_{\text{minor}} = 8.3$ min (96% ee) and was found to be consistent with the ee of the starting benzophenone imine **5c**. $[\alpha]_{\text{D}}^{25} -20.3$ (c 0.86, CHCl₃).

(2*S*)-*trans*-1-(*tert*-Butyloxycarbonyl)-5-(hydroxyethyl]proline *tert*-butyl ester (11**)**

Pyrrolidine *trans*-**9** (18 mg, 74 μmol) was dissolved in MeOH (0.5 mL) and treated with Boc₂O (32 mg, 148 μmol). After 20 h at room temperature the reaction mixture was filtered through a short plug of silica, the solvent was evaporated and the residue was purified by flash chromatography (PE/Et₂O). The obtained product was next dissolved in Et₂O (0.5 mL) and an excess LiBH₄ (15 mg) was added. After 1 h at room temperature the mixture was diluted with Et₂O and poured into saturated NaHCO₃ solution. The aqueous phase was extracted with Et₂O. The organic layers were dried over MgSO₄ and after evaporation of the solvent the crude product was purified by flash chromatography (PE/Et₂O). The product was obtained as a colorless oil (15 mg, 64% yield over two steps). ¹H NMR δ 4.32-4.27 (m, 1H), 4.10 (d, $J = 8.4$ Hz, 1H), 3.65-3.52 (m, 2H), 2.82-2.09 (m, 2H), 1.93-1.88 (m, 1H), 1.73-1.65 (m, 1H), 1.56-1.50 (m, 1H), 1.46-1.43 (m, 19H). ¹³C NMR δ 171.9, 156.0, 81.2, 80.6, 60.8, 59.1, 54.2, 39.2, 29.2, 28.9, 28.3, 28.1. HRMS calc.: C₁₆H₂₉NNaO₅.338.1943; found: 338.1937. $[\alpha]_{\text{D}}^{25} -24.2$ (c 0.77, CHCl₃).

The absolute configuration of the compounds *cis*-**10** and **11** was determined to be 2*S* by comparison of their specific optical rotation with literature values.

Literature value for compound **10**:¹² $[\alpha]_{\text{D}}^{20} -20.5$ (c 1.1, CHCl₃).

Literature value for compound **11**:¹³ $[\alpha]_{\text{D}}^{20} -31.2$ (c 1.12, CHCl₃).

¹² Cambell, J. A., Rapoport, H. *J. Org. Chem.* **1996**, *61*, 6313-6325.

¹³ Mulzer, J., Schülzchen, F., Bats, J.-W. *Tetrahedron* **2000**, *56*, 4289-4298.