DOI: 10.1002/asia.200700302

Amidophosphane–Copper(I)-Catalyzed Asymmetric Conjugate Addition of Dialkylzinc Reagents to Racemic 6-Substituted Cyclohexenones to Form 2,5-Di- and 2,2,5-Trisubstituted Cyclohexanones

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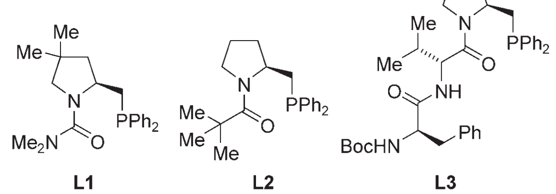
Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday

Abstract: The asymmetric conjugate addition of dialkylzinc reagents to racemic 6-substituted cyclohexenones under the catalysis of chiral amidophosphane–copper(I) complexes gave a mixture of nearly equal amounts of the corresponding *trans*- and *cis*-disubstituted cyclohexanones with extremely high catalyst-controlled enantioselectivity. Epimerization with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) led to the conversion of these mixtures into the thermodynamically more stable *trans*-2,5-disubstituted cyclohexanone as the major product with up to 96% *ee* in up to 96% yield. The regio- and stereoselective alkylation of the disubstituted cyclohexanone products via the thermodynamically favored enolate gave 2,2,5-trisubstituted cyclohexanones with a quaternary asymmetric carbon atom in good yield.

Keywords: asymmetric catalysis · copper · Michael addition · phosphane ligands · zinc

Introduction

The catalytic asymmetric conjugate addition of organometallic reagents to activated alkenes has been the focus of much energetic research.[1] We have applied chiral amidophosphanes, such as **L1**–**3** (Boc = *tert*-butoxycarbonyl), as ligands for copper or rhodium catalysts in such reactions. The **L2**–rhodium-catalyzed asymmetric conjugate arylation of cyclohex-2-enone (**1**) with arylboronic acids gave **2** with high enantioselectivity (Scheme 1).[2] We also used an **L1**–copper catalyst with Grignard reagents[3] and an **L3**–copper catalyst with diorganozinc reagents[4] for the catalytic asymmetric conjugate alkylation of **1** to give **3**.



L1 **L2** **L3**

When we extended these reactions to the use of a racemic mixture of substituted cyclohexenones as the substrate, we obtained enantiomerically enriched substituted cyclohexanone derivatives.[5–7] The asymmetric conjugate arylation of racemic 5-(trimethylsilyl)cyclohexenone ((±)-**4**) provided highly enantiomerically enriched 5-arylcyclohexenones **6** through oxidative detrimethylsilylation of **5**,[6] whereas the asymmetric conjugate alkylation of (±)-**4** provided enantiomerically enriched **4** through kinetic resolution.[7] Racemic cyclohexenones (±)-**8** with a substituent at the 6-position are also good substrates for the asymmetric conjugate arylation: We observed the formation of *trans*-2-substituted 5-arylcyclohexanones *trans*-**9** with extremely high enantioselectivity through the thermodynamically controlled epimerization of a mixture of *trans*- and *cis*-**9**.[8] Enantiofacial differentiation by the chiral rhodium catalyst overcomes the substrate-controlled *trans* arylation of (±)-**4** and (±)-**8** to give a mixture of nearly equal amounts of the *trans* and *cis* isomers of **5** and **9**, respectively.[9] Alkylation variants of the reaction with copper catalysis provide complementary methodology to the rhodium-catalyzed arylation (Scheme 1). Herein, we describe the asymmetric conjugate alkylation of (±)-**8** to

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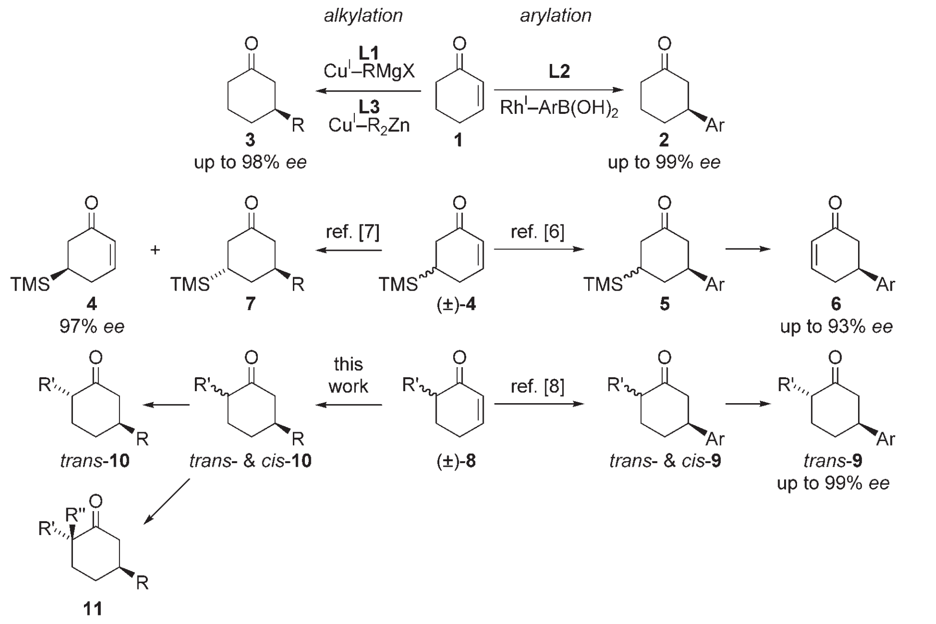


Scheme 1. Asymmetric conjugate addition to cyclohexenones under the catalysis of chiral amidophosphane–copper or amidophosphane–rhodium complexes to give chiral substituted cyclohexanones. TMS = trimethylsilyl.

give *trans*-2-substituted 5-alkylcyclohexanones *trans*-**10** through the epimerization of a mixture of *trans*- and *cis*-**10**, as well as the synthesis of 2,2,5-trisubstituted cyclohexanones **11** with an asymmetric quaternary carbon atom through the regio- and stereoselective alkylation of *trans*- and *cis*-**10**.

Results and Discussion

Asymmetric Conjugate Addition of Dialkylzinc Reagents to Racemic 6-Substituted Cyclohexenones

We examined the conjugate addition of dialkylzinc reagents[4] to racemic 6-substituted cyclohexenones under the catalysis of a copper complex with the dipeptide amidophosphane **L3** (Table 1). Racemic 6-methylcyclohexenone ((±)-**8a**) was added to a solution at room temperature of the catalyst prepared from **L3** (7.5 mol%) and copper(I) tetrafluoroborate acetonitrile complex (5 mol%) in toluene. Diethylzinc (2 equiv) was then added as a 1.0 M solution in hexane at 0 °C, and the resulting mixture was stirred at 0 °C for 24 h.

Abstract in Japanese:

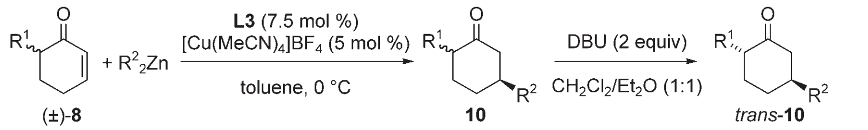
キラルアミドホスファン配位子–銅(I)錯体を触媒として用いるジアルキル亜鉛の不斉共役付加反応をラセミ体の 6-置換シクロヘキセノンに適用した。反応はいずれのエナンチオマーに対しても高選択的に進行し、*trans*-および *cis*-体の 2,5-二置換シクロヘキサノンが高い光学純度で、ほぼ等量ずつ得られた。得られた付加体は *trans*-2,5-二置換シクロヘキサノン、もしくは 4 級不斉炭素を有する 2,2,5-三置換シクロヘキサノンへと容易に変換可能である。

Workup with 10% hydrochloric acid gave a 43:57 mixture[10] of *trans*- and *cis*-**10a** with 99 and 90% *ee*, respectively, in 66% yield, together with recovered (*S*)-**8a** with 55% *ee* in 14% yield (Table 1, entry 1). The *S* absolute configuration of recovered **8a** was deduced from the 2*R*,5*S* configuration of the major enantiomer of **10a** produced by the addition reaction. Epimerization of the mixture with sodium methoxide in methanol at room temperature for 2.5 days gave an 83:17 mixture of *trans*- and *cis*-**10a** with 96 and 91% *ee*, respectively, in 72% yield. For the products in Table 1, the absolute configurations of all new stereogenic centers were assigned by analogy with the corresponding addition to cyclohex-2-enone (**1**),[4] and the relative configuration of **10** was determined on the basis of the thermodynamic preference for *trans*-2,5-disubstituted cyclohexanones.[5c]

Similarly, racemic 6-allylcyclohexenone ((±)-**8b**) gave a 38:62 mixture of *trans*- and *cis*-**10b**, each with 84% *ee*, in a combined yield of 80%, together with recovered (*R*)-**8b** with 36% *ee* in 17% yield (Table 1, entry 2). The absolute configuration of recovered **8b** was deduced from the *S*,*S* configuration of the major enantiomer of **10b** produced by the addition reaction. Epimerization with DBU gave a 79:21 *trans*/*cis* mixture of **10b** in 92% yield, with 84% *ee* observed for both diastereomers. The reaction of 6-benzylcyclohexenone ((±)-**8c**) gave a 41:59 diastereomeric mixture of *trans*- and *cis*-**10c** with 89 and 91% *ee*, respectively, in 78% yield (Table 1, entry 3). The substrate **8c** was recovered in 22% yield as predominantly the *R* enantiomer with 73% *ee*. The *R* configuration of recovered **8c** was confirmed by catalytic hydrogenation to (*R*)-(+)-2-benzylcyclohexanone.[11] Following epimerization with DBU, the diastereomers of **10c** were separated by column chromatography on silica gel to give *trans*- and *cis*-**10c** with 89 and 92% *ee* in 82 and 18% yield, respectively.

In contrast to the slight preference for the formation of the *cis* product in the addition reaction of **8a–c** (Table 1, entries 1–3), the copper-catalyzed addition of diethylzinc to racemic 6-phenylcyclohexenone ((±)-**8d**) gave a 58:42 mixture of **10d** in favor of the *trans* product. The *trans* and *cis* diastereomers were formed with high *ee* values of 92 and 99%, respectively, in a combined yield of 80%, and (*S*)-**8d** was recovered with 94% *ee* in 9% yield (Table 1, entry 4). The *S* configuration of recovered **8d** was confirmed by catalytic hydrogenation to (*S*)-(−)-2-phenylcyclohexanone.[12] Epimerization with DBU gave a *trans*-enriched 81:19 mix-

Table 1. Cu-catalyzed enantioselective 1,4-addition of dialkylzinc reagents to racemic 6-substituted cyclohexenones (±)-**8** and subsequent epimerization to give *trans*-**10** as the major product.[a]



Entry	8	R^1	R^2	*t* [h]	10[b]	Catalytic asymmetric addition Yield [%]	*trans*/*cis*	*ee* [%] *trans*	*ee* [%] *cis*	Recovered 8 Yield [%]	*ee* [%]	Epimerization Yield [%]	*trans*/*cis*	*ee* [%] *trans*	*ee* [%] *cis*
1	**8a**	Me	Et	24	**10a**	66	43:57	99	90	14	55 (*S*)	72[c]	83:17	96	91
2	**8b**	allyl	Et	39	**10b**	80	38:62	84	84	17	36 (*R*)	92	79:21	84	84
3	**8c**	Bn	Et	37	**10c**	78	41:59	89	91	22	73 (*R*)	99	83:17	89	92
4	**8d**	Ph	Et	43	**10d**	80	58:42	92	99	9	94 (*S*)	89	81:19	94	99
5	**8d**	Ph	Me	55	**10e**	20	70:30	89	86	80	5 (*S*)	88	80:20	86	85
6	**8d**	Ph	*i*Pr	41	**10f**	85	60:40	86	97	4	64 (*S*)	99	86:14	92	94
7	**8c**	Bn	*i*Pr	44	**10g**	98	48:52	93	92	–	–	98	88:12	92	92

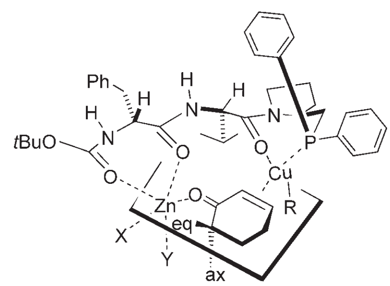
[a] Diastereomer ratios were determined by ^{1}H NMR spectroscopy of the crude product. The *ee* values were determined by HPLC or GC on a chiral phase; see Experimental Section. [b] The absolute configuration of **10** was assigned tentatively by analogy with the products of the equivalent reaction with cyclohex-2-enone (**1**); see reference [4]. [c] The product mixture was epimerized with NaOMe in MeOH. Bn = benzyl, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene.

ture of isomers of **10d** with 94 (*trans*) and 99% *ee* (*cis*) in 89% yield.

Unfortunately, 6-*tert*-butylcyclohexenone was not a good substrate for the conjugate addition of diethylzinc, and the racemic starting material was recovered quantitatively after 44 h. Although the reaction proceeded in the presence of the additive TMSCl[13] (2 equiv), the product was obtained as a racemic *trans*/*cis* (64:36) mixture in 51% yield after 28 h.

Diorganozinc reagents other than diethylzinc were also used successfully in this reaction. With diisopropylzinc as the alkylating agent, the reaction with (±)-**8d** afforded a 60:40 mixture of the *trans* and *cis* isomers of **10f** with 86 and 97% *ee*, respectively, in 85% yield. The mixture was epimerized subsequently with DBU to provide *trans*- and *cis*-**10f** with 92 and 94% *ee* in 86 and 14% yield, respectively (Table 1, entry 6). The reaction with (±)-**8c** proceeded to completion to afford a 48:52 mixture of the *trans* and *cis* isomers of **10g** with 93 and 92% *ee*, respectively, in 98% yield. After epimerization with DBU, *trans*- and *cis*-**10g** were both isolated with 92% *ee*, in 87 and 12% yield, respectively (Table 1, entry 7). The *trans* and *cis* isomers of **10f** and **10g** were separated readily by column chromatography on silica gel. The reaction of (±)-**8d** with dimethylzinc was slower than that with diethylzinc. Although **10e** was obtained as an 80:20 mixture of *trans* and *cis* isomers in just 18% yield after epimerization with DBU, the *ee* values of the two isomers were as high as 86 and 85%, respectively (Table 1, entry 5).

In the addition reactions of the racemic 6-alkylcyclohexenones (±)-**8a–c**, the recovered starting material **8** had the same stereochemistry in each case, and in the *cis*/*trans* mixtures of **10** obtained, the *cis* isomer predominated. In contrast, in the reaction of 6-phenylcyclohexenone, the starting enone **8d** with the opposite stereochemistry was recovered, and the *trans* isomers of **10d–f** were formed as the major isomers. On the basis of these observations and the well-established preference of nucleophiles for axial attack,[5a,c,14] we propose a plausible transition-state model for the addition reaction in Scheme 2. As a result of steric repulsion be-



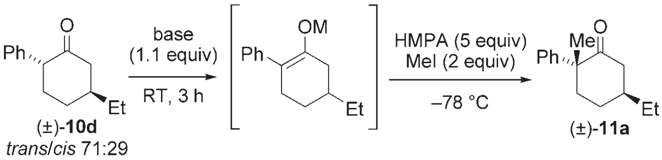
Scheme 2. Rationale for the stereochemical outcome of the addition reaction.

tween the substituent at the 6-position and the zinc fragment coordinated to the carbonyl oxygen atom of the enone,[15] the substituent shows a greater preference for a pseudoaxial orientation the bulkier it is. Therefore, smaller substituents at the 6-position, such as methyl, allyl, and benzyl groups (*A* values:[16] 1.53–1.68), favor a pseudoequatorial orientation in the transition state to give the *cis* isomer of **10** as the major isomer, whereas the relatively larger phenyl group (*A* value: 2.8) favors a pseudoaxial orientation to give the *trans* isomer of **10** as the major isomer. A similar switching of facial selectivity has been reported for Lewis acid promoted conjugate addition reactions of 6-substituted cyclohexenones.[17]

Regio- and Stereoselective Alkylation of 2,5-Disubstituted Cyclohexanones

We envisaged that the regio- and stereoselective alkylation of 2,5-disubstituted cyclohexanones **10** would provide 2,2,5-

trisubstituted cyclohexanones **11** with an asymmetric quaternary carbon center and sought to identify a suitable base for the regioselective formation of the thermodynamically favored enolate from cyclohexanones **10** and subsequent alkylation. Thus, after the deprotonation of (±)-**10d** by treatment with lithium diisopropylamide (LDA; 1.1 equiv) at room temperature for 3 h, HMPA (5 equiv) and iodomethane (2 equiv) were added at −78 °C (Scheme 3). The mixture was stirred for 16 h at the same temperature to give



Scheme 3. Formation of the thermodynamically favored enolate from (±)-**10d** and subsequent methylation with MeI to give (±)-**11a**. HMPA = hexamethyl phosphoramide.

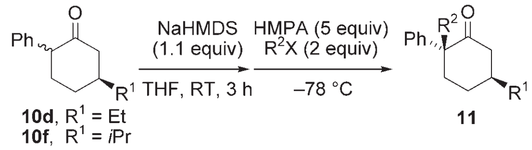
(±)-**11a** with d.r. 90:10 in 78 % yield. Without HMPA, the methylation was much slower and provided (±)-**11a** with a decreased diastereomer ratio of 77:23 in 67 % yield after 19 h at room temperature. The relative configuration of (±)-**11a** was determined by comparison of the ^{13}C NMR chemical shifts of the methyl groups at the 2-position of the two diastereomers.[18] Substantial preference for axial attack was shown in the methylation of the enolate derived from (±)-**10d**. Thus, (±)-**11a** with the *R*,*S* and *S*,*R* configuration was formed as the major product.[19]

Although the reaction in which lithium hexamethyldisilazide (LiHMDS) was used as the base also gave (±)-**11a** with d.r. 90:10 in 78 % yield, NaHMDS was found to improve the rate of methylation to give (±)-**11a** with the same diastereoselectivity in 84 % yield after 6 h. A much greater acceleration of the methylation reaction was observed with KHMDS; however, the enolate was formed with lower regioselectivity: The desired product (±)-**11a** was obtained after 1 h with d.r. 88:12 in 73 % yield along with a diastereomeric mixture of 2,3,6-trisubstituted cyclohexanones (12 %) derived from methylation of the kinetic enolate.

The optimized conditions were applied to the alkylation of the enantiomerically enriched 2,5-disubstituted cyclohexanones **10d** and **10f** (Table 2). Thus, in the presence of the base NaHMDS, the methylation of a 68:32 mixture of *trans*- and *cis*-**10d** with 91 and 99 % *ee*, respectively, gave **11a** in 91 % yield as a 90:10 diastereomeric mixture with 93 % *ee* for the major 2*R*,5*S* isomer (Table 2, entry 1). In the same way, benzylation and allylation with benzyl bromide and allyl bromide afforded diastereomeric mixtures of the corresponding products **11b** and **11c** in 81 % yield (d.r. 90:10) with 92 % *ee* (major isomer) and in 84 % yield (d.r. 85:15) with 93 % *ee* (major isomer), respectively (Table 2, entries 2 and 3).

The enolate formed by the deprotonation of **10f** underwent methylation with iodomethane to afford a 90:10 mixture of **11d** in 83 % yield with 92 % *ee* for the major isomer (Table 2, entry 4). Similarly, **11e** was formed with the alkylating agent benzyl bromide as an 88:12 mixture of diastereomers in 89 % yield, with 93 % *ee* for the major diastereomer (Table 2, entry 5).

Table 2. Regio- and diastereoselective alkylation of **10d** and **10f** with alkyl halides.



Entry	**10**, *trans*/*cis* (*ee* [%]/[%])	R^2X	*t* [h]	**11**[a]	Yield [%]	*ee*[b] [%]	d.r.[c]
1	**10d**, 68:32 (91/99)	MeI	5	**11a**	91	93	90:10
2	**10d**, 68:32 (91/99)	BnBr	3	**11b**	81	92	90:10
3	**10d**, 68:32 (91/99)	allyl bromide	1.5	**11c**	84	93	85:15
4	**10f**, 60:40 (86/97)	MeI	4	**11d**	83	92	90:10
5	**10f**, 60:40 (86/97)	BnBr	2	**11e**	89	93	88:12

[a] The relative configuration of **11** was determined by comparison of the ^{13}C NMR chemical shifts of the methyl or methylene carbon atom of the R^2 group of the two diastereomers.[18] [b] The *ee* value of the major diastereomer was determined by HPLC on a chiral phase. [c] The diastereomer ratio was determined by ^{1}H NMR spectroscopy of the crude product or HPLC analysis of the isolated product; see Experimental Section.

Conclusions

A Cu^I complex with the chiral dipeptide amidophosphane ligand **L3** was used as a catalyst for the asymmetric conjugate addition of dialkylzinc reagents to racemic 6-substituted cyclohexenones. The epimerization of the product completes a general two-step asymmetric synthesis of *trans*-2,5-disubstituted cyclohexanones. Regio- and stereoselective alkylation of the resulting 2,5-disubstituted cyclohexanones gave enantiomerically enriched 2,2,5-trisubstituted cyclohexanones with a quaternary carbon center.

Experimental Section

General

All melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 and 125 MHz, respectively. Chemical-shift values are expressed in parts per million relative to internal tetramethylsilane. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The multiplicity of the signals in the ^{13}C NMR spectra was determined on the basis of DEPT (distortionless enhancement by polarization transfer) or HMQC (heteronuclear multiple quantum coherence) experiments. Column chromatography was carried out with silica gel. All methods for the determination of *ee* and d.r. values were established with racemic samples. Diethylzinc in hexane, diisopropylzinc in toluene, NaHMDS in THF, and KHMDS in toluene were purchased from Aldrich; dimethylzinc in hexane was purchased from Kanto Chemical Co. The racemic 6-substituted cyclohexenones **8a–d** were prepared by procedures analogous to those reported.[20]

Syntheses

General procedure for the synthesis of (±)-**10**: A solution of P*n*Bu_3 (25.3 mg, 0.125 mmol) in toluene (3 mL) was added to dry $Cu(OTf)_2$ (22.6 mg, 0.062 mmol) under argon atmosphere at room temperature. The resulting solution was stirred for 0.5 h at the same temperature, then cooled to −20 °C. A solution of the dialkylzinc reagent (1.0 M, 2.5 mL, 2.5 mmol) was added, followed by (±)-**8** (1.25 mmol), and the mixture was allowed to warm to room temperature. When the reaction had reached completion (as shown by TLC), it was quenched by the addition of 5 % HCl. The aqueous layer was extracted with Et_2O three times, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, and then dried over Na_2SO_4. Concentration and purification by column chromatography (hexane/Et_2O = 10:1) afforded (±)-**10** in moderate to high yield.

Typical procedure for the asymmetric conjugate addition of dialkylzinc reagents to **8** (TP1) and subsequent epimerization (TP2): A solution of **L3** (79 mg, 0.128 mmol) in toluene (13.6 mL) was added to a suspension of $[Cu(MeCN)_4]BF_4$ (26 mg, 0.085 mmol) in toluene (48 mL) under argon atmosphere at room temperature, and the resulting solution was stirred for 1 h at room temperature. A solution of (±)-**8b** (1.7 mmol) in toluene (44 mL) was then added, and the mixture was stirred at room temperature for 20 min, then cooled to 0 °C and stirred at 0 °C for 30 min. Et_2Zn (1.0 M in hexane; 3.4 mL, 3.4 mmol) was then added over 3 min, and the resulting mixture was stirred at 0 °C for 39 h. The reaction was quenched by the addition of 10 % HCl, and the mixture was stirred at room temperature for 0.5 h. The organic layer was then separated, and the aqueous layer was extracted with Et_2O three times. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, and then dried over Na_2SO_4. Column chromatography (pentane/Et_2O = 1:0–20:1) gave a 38:62 mixture of (2*R*,5*S*)- and (2*S*,5*S*)-2-allyl-5-ethylcyclohexan-1-one (*trans*- and *cis*-**10b**; 226 mg, 80 %) as a colorless oil. $[\alpha]_D^{25} = -39.8$ (c = 1.32, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 1713 cm^{-1}; ^{1}H NMR (*trans*): δ = 0.90 (t, *J* = 7.3 Hz, 3H), 1.24–1.44 (m, 4H), 1.63 (m, 1H), 1.91–2.02 (m, 3H), 2.14 (m, 1H), 2.23 (m, 1H), 2.44 (m, 1H), 2.53 (m, 1H), 4.99 (d, *J* = 10.1 Hz, 1H), 5.02 (d, *J* = 17.1 Hz, 1H), 5.78 ppm (m, 1H); ^{1}H NMR (*cis*): δ = 0.89 (t, *J* = 7.3 Hz, 3H), 1.31 (dq, *J* = 7.3, 7.3 Hz, 2H), 1.58–1.70 (m, 2H), 1.79 (m, 1H), 1.89–1.92 (m, 2H), 2.09 (ddd, *J* = 7.6, 7.6, 13.8 Hz, 1H), 2.19 (dd, *J* = 7.6, 13.7 Hz, 1H), 2.35–2.49 (m, 3H), 5.01 (d, *J* = 8.9 Hz, 1H), 5.04 (d, *J* = 16.5 Hz, 1H), 5.74 ppm (m, 1H); ^{13}C NMR (*trans*): δ = 11.1 (CH_3), 29.7 (CH_2), 31.5 (CH_2), 32.3 (CH_2), 33.4 (CH_2), 42.1 (CH), 48.2 (CH_2), 49.8 (CH), 116.1 (CH_2), 136.7 (CH), 212.2 ppm (C); ^{13}C NMR (*cis*): δ = 11.4 (CH_3), 27.1 (CH_2), 27.4 (CH_2), 28.6 (CH_2), 34.4 (CH_2), 39.8 (CH), 45.9 (CH_2), 49.7 (CH), 116.5 (CH_2), 136.0 (CH), 213.4 ppm (C); MS (EI): *m*/*z* = 166 $[M]^+$; elemental analysis: calcd (%) for $C_{11}H_{18}O$: C 79.46, H 10.91; found: C 79.55, H 10.15. The diastereomer ratio was determined by integration of the ^{1}H NMR signals at δ = 2.53 ppm for *trans*-**10b** and at δ = 1.79 ppm for *cis*-**10b**. Enantiomerically enriched (*R*)-**8b** was recovered as a pale-yellow oil (39 mg, 17 %) with 36 % *ee*, as determined by GC (Supelco beta DEX 225, 90 °C; t_R(*R* isomer) = 19.6 min, t_R(*S* isomer) = 18.4 min). The absolute configuration of recovered **8b** was deduced from the 2*S*,5*S* configuration of the major isomer of **10b** produced by the addition reaction.

DBU (123 mg, 0.81 mmol) was added to a solution of the mixture of *trans*- and *cis*-**10b** (67 mg, 0.41 mmol) in CH_2Cl_2/Et_2O (1:1; 4 mL) under argon atmosphere at room temperature, and the resulting mixture was stirred at room temperature for 5 days. The mixture was then diluted with Et_2O (5 mL), washed with 5 % HCl (4 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), and dried over Na_2SO_4. Concentration and column chromatography (heptane/Et_2O = 20:1) gave a 79:21 mixture of *trans*- and *cis*-**10b** (62 mg, 92 %).

The absolute configuration of the new stereogenic center and the relative configuration of **10** were assigned by analogy with the corresponding addition to cyclohex-2-enone (**1**)[4] and on the basis of the thermodynamic preference for the formation of *trans*-2,5-disubstituted cyclohexanones,[5c] respectively.

Typical procedure for catalytic hydrogenation (for the determination of *ee* values; TP3): Pd/C (10 %, 17 mg, 0.014 mmol) was added to a stirred solution of a 38:62 mixture of *trans*- and *cis*-**10b** (23 mg, 0.14 mmol) in EtOAc (1 mL) at room temperature, and the reaction mixture was stirred under hydrogen atmosphere at room temperature for 13 h. The catalyst was removed by passing the mixture through a short pad of silica gel, which was then washed with EtOAc. Concentration and purification by column chromatography (heptane→heptane/Et_2O = 20:1) gave a 42:58 mixture of (2*R*,5*S*)- and (2*S*,5*S*)-5-ethyl-2-propylcyclohexan-1-one (22 mg, 97 %, each 84 % *ee*) as a colorless oil. The diastereomer ratio and the *ee* value were determined by GC (Supelco gamma DEX 225, 90 °C: t_R(major *trans* isomer) = 35.6 min, t_R(minor *trans* isomer) = 42.5 min, t_R(major *cis* isomer) = 38.9 min, t_R(minor *cis* isomer) = 37.8 min). IR (neat): $\tilde{\nu}$ = 1713 cm^{-1}; ^{1}H NMR (*trans*): δ = 0.89 (t, *J* = 7.5 Hz, 3H×2), 1.14 (m, 1H), 1.23–1.39 (m, 5H), 1.62–1.79 (m, 3H), 1.92 (m, 1H), 1.99 (dd, *J* = 12.8, 12.8 Hz, 1H), 2.11 (m, 1H), 2.22 (m, 1H), 2.41 ppm (ddd, *J* = 2.0, 3.8, 12.8 Hz, 1H); ^{1}H NMR (*cis*): δ = 0.90 (t, *J* = 7.3 Hz, 3H×2), 1.26–1.44 (m, 6H), 1.57 (m, 1H), 1.63–1.88 (m, 4H), 2.18 (dd, *J* = 8.9, 13.8 Hz, 1H), 2.32 (m, 1H), 2.36 ppm (ddd, *J* = 1.2, 4.6, 13.8 Hz, 1H); ^{13}C NMR (*trans*): δ = 11.1 (CH_3), 14.2 (CH_3), 20.2 (CH_2), 27.8 (CH_2), 29.7 (CH_2), 31.1 (CH_2), 32.8 (CH_2), 42.2 (CH), 48.3 (CH_2), 49.9 (CH), 213.1 ppm (C); ^{13}C NMR (*cis*): δ = 11.3 (CH_3), 13.9 (CH_3), 20.3 (CH_2), 27.2 (CH_2), 29.5 (CH_2), 31.6 (CH_2), 32.5 (CH_2), 40.3 (CH), 45.5 (CH_2), 49.9 (CH), 214.7 ppm (C); MS (EI): *m*/*z* = 168 $[M]^+$; HRMS (EI): *m*/*z* calcd for $C_{11}H_{20}O$: 168.1514 $[M]^+$; found: 168.1518.

10a: A 43:57 mixture of (2*S*,5*S*)- and (2*R*,5*S*)-5-ethyl-2-methylcyclohexan-1-one (*trans*- and *cis*-**10a**; 156 mg, 66 %) was obtained as a colorless oil by the procedure TP1 and column chromatography (hexane/Et_2O = 1:0–20:1). $[\alpha]_D^{21} = -29$ (c = 0.42, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 1713 cm^{-1}; ^{1}H NMR (*trans*): δ = 0.91 (t, *J* = 7.3 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 1.32–1.44 (m, 3H), 1.56–1.66 (m, 2H), 1.91 (m, 1H), 1.98 (ddd, *J* = 1.2, 13.0, 13.0 Hz, 1H), 2.08 (ddd, *J* = 2.8, 5.8, 12.4 Hz, 1H), 2.34 (m, 1H), 2.44 ppm (ddd, *J* = 2.2, 3.9, 13.0 Hz, 1H); ^{1}H NMR (*cis*): δ = 0.89 (t, *J* = 7.5 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.24–1.34 (m, 3H), 1.57–1.67 (m, 2H), 1.82 (m, 1H), 1.87–1.94 (m, 2H), 2.24 (ddd, *J* = 1.2, 6.5, 13.7 Hz, 1H), 2.41 ppm (dd, *J* = 5.2, 13.7 Hz, 1H); ^{13}C NMR (*trans*): δ = 11.1 (CH_3), 14.3 (CH_3), 27.5 (CH_2), 29.7 (CH_2), 31.6 (CH_2), 42.1 (CH), 44.8 (CH), 48.0 (CH_2), 213.4 ppm (C); ^{13}C NMR (*cis*): δ = 11.5 (CH_3), 15.3 (CH_3), 26.7 (CH_2), 31.2 (CH_2), 35.0 (CH_2), 39.6 (CH), 44.7 (CH), 45.5 (CH_2), 214.6 ppm (C); MS (EI): *m*/*z* = 140 $[M]^+$; HRMS (EI): *m*/*z* calcd for $C_9H_{16}O$: 140.1201 $[M]^+$; found: 140.1199. The diastereomer ratio was determined by integration of the ^{1}H NMR signals at δ = 1.02 ppm for *trans*-**10a** and at δ = 1.06 ppm for *cis*-**10a**. The *ee* values of *trans*- and *cis*-**10a** were determined to be 99 and 90 %, respectively, by GC (Supelco gamma DEX 225, 70 °C; t_R(major *trans* isomer) = 49.2 min, t_R(minor *trans* isomer) = 51.2 min, t_R(major *cis* isomer) = 56.5 min, t_R(minor *cis* isomer) = 54.4 min). Enantiomerically enriched (*S*)-**8a** (26 mg, 14 %) was recovered as a colorless oil with 50 % *ee*, as determined by GC (Supelco gamma DEX 225, 70 °C; t_R(*S* isomer) = 26.4 min, t_R(*R* isomer) = 28.5 min). The absolute configuration of recovered **8a** was deduced from the 2*R*,5*S* configuration of the major enantiomer of **10a** produced by the addition reaction.

A solution of NaOMe in MeOH (0.5 M, 0.12 mL, 0.060 mmol) was added to the mixture of *trans*- and *cis*-**10a** (81 mg, 0.58 mmol) in MeOH (2 mL) under argon atmosphere at room temperature. The resulting mixture was stirred at room temperature for 2.5 days, then diluted with Et_2O (10 mL) and washed with 5 % HCl (1 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O three times. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/Et_2O = 5:1) gave an 83:17 mixture of *trans*- and *cis*-**10a** (58 mg, 72 % yield) with 96 and 91 % *ee*, respectively, as a colorless oil.

10c: A 41:59 mixture of (2*R*,5*S*)- and (2*S*,5*S*)-2-benzyl-5-ethylcyclohexan-1-one (*trans*- and *cis*-**10c**; 287 mg, 78 %) was obtained as a colorless oil by the procedure TP1 and column chromatography (hexane/Et_2O = 10:1):

$[\alpha]_D^{25}=-28.7$ ($c=1.18$, $CHCl_3$). The diastereomeric ratio was determined by integration of the ^1H NMR signals at $\delta=3.24$ ppm for *trans*-**10c** and at $\delta=3.12$ ppm for *cis*-**10c**. The *ee* values of *trans*- and *cis*-**10c** were determined to be 89 and 91%, respectively, by HPLC (Daicel chiralpak IA, hexane/CH_2Cl_2=200:15, 0.5 mL min^{-1}, 254 nm; t_R(major *trans* isomer)=36.3 min, t_R(minor *trans* isomer)=32.5 min, t_R(major *cis* isomer)=47.8 min, t_R(minor *cis* isomer)=45.3 min). Enantiomerically enriched (*R*)-**8c** (70 mg, 22%) was recovered as a colorless oil with 73% *ee*, as determined by HPLC (Daicel chiralpak AD-H, hexane/*i*PrOH=100:1, 1 mL min^{-1}, 254 nm; t_R(*R* isomer)=14.2 min, t_R(*S* isomer)=13.7 min): $[\alpha]_D^{25}=-16.5$ ($c=1.20$, $CHCl_3$). For the determination of the absolute configuration, **8c** was subjected to catalytic hydrogenation according to the procedure TP3. (*R*)-2-Ethylcyclohexanone[11] was obtained as a colorless oil: $[\alpha]_D^{22}=+30$ ($c=0.46$, MeOH).

Following epimerization of the mixture of *trans*- and *cis*-**10c** with DBU according to the procedure TP2, the diastereomers were separated by column chromatography (hexane/Et_2O=20:1) to give *trans*-**10c** (238 mg, 81%, 89% *ee*) as a colorless oil and *cis*-**10c** (52 mg, 18%, 92% *ee*) as a colorless oil.

trans-**10c**: $[\alpha]_D^{25}=+25$ ($c=0.93$, $CHCl_3$; for 89% *ee*); IR (neat): $\tilde{\nu}$=1713 cm^{-1}; ^1H NMR: δ=0.89 (t, *J*=7.0 Hz, 3H), 1.22–1.43 (m, 4H), 1.66 (m, 1H), 1.87 (m, 1H), 1.99–2.05 (m, 2H), 2.38 (dd, *J*=8.6, 14.0 Hz, 1H), 2.47 (ddd, *J*=2.2, 3.9, 12.8 Hz, 1H), 2.50 (m, 1H), 3.24 (dd, *J*=4.6, 14.0 Hz, 1H), 7.16 (d, *J*=7.1 Hz, 2H), 7.17–7.29 ppm (m, 3H); ^{13}C NMR: δ=11.1 (CH_3), 29.7 (CH_2), 31.5 (CH_2), 32.4 (CH_2), 35.2 (CH_2), 42.2 (CH), 48.3 (CH_2), 52.0 (CH), 125.9 (CH), 128.3 (CH), 129.2 (CH), 140.6 (C), 212.2 ppm (C); MS (EI): *m/z*=216 $[M]^+$; elemental analysis: calcd (%) for $C_{15}H_{20}O$: C 83.28, H 9.32; found: C 83.36, H 9.19.

cis-**10c**: $[\alpha]_D^{25}=-59$ ($c=0.27$, $CHCl_3$; for 92% *ee*); IR (neat): $\tilde{\nu}$=1705 cm^{-1}; ^1H NMR: δ=0.90 (t, *J*=7.3 Hz, 3H), 1.28–1.37 (m, 2H), 1.57–1.68 (m, 2H), 1.72–1.83 (m, 2H), 1.93 (m, 1H), 2.28 (ddd, *J*=0.9, 6.7, 13.8 Hz, 1H), 2.46 (dd, *J*=5.2, 13.8 Hz, 1H), 2.53 (dd, *J*=9.2, 13.1 Hz, 1H), 2.58 (m, 1H), 3.12 (dd, *J*=4.6, 13.1 Hz, 1H), 7.15 (d, *J*=6.8 Hz, 2H), 7.18–7.29 ppm (m, 3H); ^{13}C NMR: δ=11.5 (CH_3), 26.8 (CH_2), 27.5 (CH_2), 28.3 (CH_2), 35.9 (CH_2), 39.7 (CH), 46.0 (CH_2), 51.9 (CH), 126.2 (CH), 128.4 (CH), 129.1 (CH), 139.9 (C), 213.3 ppm (C); MS (EI): *m/z*=216 $[M]^+$; elemental analysis: calcd (%) for $C_{15}H_{20}O$: C 83.28, H 9.32; found: C 83.50, H 9.02.

10d: A 58:42 mixture of (2*R*,5*S*)- and (2*S*,5*S*)-5-ethyl-2-phenylcyclohexan-1-one (*trans*- and *cis*-**10d**; 80 mg, 80%) was obtained as a colorless oil by the procedure TP1 and column chromatography (hexane/Et_2O=10:1). The diastereomer ratio was determined by integration of the ^1H NMR signals at $\delta=3.56$ ppm for *trans*-**10d** and at $\delta=3.66$ ppm for *cis*-**10d**. The *ee* values of *trans*- and *cis*-**10d** were determined to be 92 and 99%, respectively, by HPLC (Daicel chiralpak AD-H, hexane/*i*PrOH=150:1, 0.5 mL min^{-1}, 254 nm; t_R(major *trans* isomer)=45.9 min, t_R(minor *trans* isomer)=34.6 min, t_R(major *cis* isomer)=24.3 min, t_R(minor *cis* isomer)=25.2 min). Enantiomerically enriched (*S*)-**8d** (8 mg, 9%) was recovered as a white solid with 94% *ee*, as determined by HPLC (Daicel chiralcel OD-H, hexane/*i*PrOH=100:1, 0.5 mL min^{-1}, 254 nm; t_R(*S* isomer)=49.2 min, t_R(*R* isomer)=46.5 min): $[\alpha]_D^{25}=+22$ ($c=0.23$, $CHCl_3$). For the determination of the absolute configuration, **8d** was subjected to catalytic hydrogenation according to the procedure TP3. (*S*)-2-Phenylcyclohexanone[12] was obtained as a white solid: m.p.: 53–56 °C; $[\alpha]_D^{29}=-97$ ($c=0.45$, $CHCl_3$).

Following epimerization of the mixture of *trans*- and *cis*-**10d** with DBU according to the procedure TP2, column chromatography (hexane/EtOAc=10:1) gave an 81:19 mixture of *trans*- and *cis*-**10d** (65 mg, 89%) with 94 (*trans*) and 99% *ee* (*cis*) as a colorless oil. $[\alpha]_D^{25}=+13$ ($c=1.1$, $CHCl_3$); IR (neat): $\tilde{\nu}$=1713 cm^{-1}; ^1H NMR (*trans*): δ=0.95 (t, *J*=9.3 Hz, 3H), 1.35–1.54 (m, 3H), 1.82 (m, 1H), 1.97 (dddd, *J*=4.4, 16.3, 16.3, 16.3 Hz, 1H), 2.06 (m, 1H), 2.17 (dd, *J*=16.3, 16,3 Hz, 1H), 2.28 (m, 1H), 2.59 (ddd, *J*=2.6, 4.9, 16.3 Hz, 1H), 3.56 (dd, *J*=6.9, 16.3 Hz, 1H), 7.13 (dd, *J*=1.2, 9.8 Hz, 2H), 7.23–7.36 ppm (m, 3H); ^1H NMR (*cis*): δ=0.91 (t, *J*=7.3 Hz, 3H), 1.37 (dq, *J*=7.3, 7,3 Hz, 2H), 1.73 (m, 1H), 1.90–2.02 (m, 2H), 2.09 (m, 1H), 2.26 (dd, *J*=7.2, 13.6 Hz, 1H), 2.34 (m, 1H), 2.51 (dd, *J*=4.7, 13.6 Hz, 1H), 3.66 (dd, *J*=6.9, 6.9 Hz, 1H), 7.19 (d, *J*=7.3 Hz, 2H), 7.24–7.36 ppm (m, 3H); ^{13}C NMR (*trans*): δ=11.1 (CH_3), 29.7 (CH_2), 31.8 (CH_2), 34.2 (CH_2), 41.9 (CH), 48.3 (CH_2), 57.2 (C), 127.0 (CH), 128.4 (CH), 128.7 (CH), 138.8 (C), 209.8 (C); ^{13}C NMR (*cis*): 11.5 (CH_3), 27.2, (CH_2) 28.0 (CH_2), 29.6 (CH_2), 40.0 (CH), 46.2 (CH_2), 55.5 (C), 126.8 (CH), 127.8 (CH), 128.5 (CH), 138.4 (C), 210.8 ppm (C); MS (EI): *m/z*=202 $[M]^+$; HRMS (EI): *m/z* calcd for $C_{14}H_{18}O$: 202.1358 $[M]^+$; found: 202.1360.

Diastereomerically pure *trans*-**10d** (16.7 mg, 23%) was isolated by column chromatography (benzene) of the *trans*-enriched mixture as a colorless oil: $[\alpha]_D^{25}=+45$ ($c=0.28$, $CHCl_3$; for 94% *ee*).

10e: A 70:30 mixture of (2*R*,5*S*)- and (2*S*,5*S*)-5-methyl-2-phenylcyclohexan-1-one (*trans*- and *cis*-**10e**; 19 mg, 20%) was obtained as a light-yellow oil by the procedure TP1 and column chromatography (hexane/Et_2O=10:1). $[\alpha]_D^{25}=-2.1$ ($c=0.35$, $CHCl_3$); IR (neat): $\tilde{\nu}$=1713 cm^{-1}; ^1H NMR (*trans*): δ=1.09 (d, *J*=6.5 Hz, 3H), 1.55 (m, 1H), 2.01 (m, 3H), 2.19 (dd, *J*=13.1, 13.1 Hz, 1H), 2.27 (m, 1H), 2.53 (ddd, *J*=1.9, 3.3, 13.1 Hz, 1H), 3.53 (dd, *J*=5.7, 13.6 Hz, 1H), 7.12 (d, *J*=7.0 Hz, 2H), 7.24–7.35 ppm (m, 3H); ^1H NMR (*cis*): δ=1.03 (d, *J*=6.7 Hz, 3H), 1.67 (m, 1H), 1.94 (m, 1H), 2.12 (m, 1H), 2.21 (dd, *J*=7.5, 13.3 Hz, 1H), 2.28 (m, 1H), 2.38 (m, 1H), 2.50 (dd, *J*=4.4, 13.3 Hz, 1H), 3.65 (t, *J*=6.9 Hz, 1H), 7.20 (d, *J*=7.1 Hz, 2H), 7.24–7.36 ppm (m, 3H); ^{13}C NMR (*trans*): δ=22.4 (CH_3), 34.2 ($CH_2\times2$), 35.4 (CH), 50.5 (CH_2), 56.7 (C), 126.9 (CH), 128.3 (CH), 128.7 (CH), 138.8 (C), 209.7 ppm (C); ^{13}C NMR (*cis*): δ=20.3 (CH_3), 29.5 (CH_2), 30.4 (CH_2), 33.2 (CH), 48.1 (CH_2), 55.4 (C), 126.9 (CH), 127.9 (CH), 128.6 (CH), 138.4 (C), 211.1 ppm (C); MS (EI): *m/z*=188 $[M]^+$. These spectroscopic data are identical to those reported previously.[21] The diastereomer ratio was determined by integration of the ^1H NMR signals at $\delta=3.53$ ppm for *trans*-**10e** and $\delta=3.65$ ppm for *cis*-**10e**. The *ee* values of *trans*- and *cis*-**10e** were determined to be 89 and 86%, respectively, by HPLC (Daicel chiralcel OD-H, hexane/*i*PrOH=150:1, 0.5 mL min^{-1}, 254 nm; t_R(major *trans* isomer)=43.9 min, t_R(minor *trans* isomer)=38.4 min, t_R(major *cis* isomer)=21.9 min, t_R(minor *cis* isomer)=24.2 min). (*S*)-**8d** (69 mg, 80%, 5% *ee*) was recovered as a white solid: $[\alpha]_D^{21}=+0.80$ ($c=0.33$, $CHCl_3$).

Following epimerization of the mixture of *trans*- and *cis*-**10e** (13 mg, 0.069 mmol) with DBU according to the procedure TP2, column chromatography (hexane/Et_2O=10:1) gave an 80:20 mixture of *trans*- and *cis*-**10e** (11.5 mg, 88%) with 86 and 85% *ee*, respectively, as a light-yellow oil.

10f: A 60:40 mixture of (2*R*,5*S*)- and (2*S*,5*S*)-5-isopropyl-2-phenylcyclohexan-1-one (*trans*- and *cis*-**10f**; 92 mg, 85%) was obtained as a colorless oil by the procedure TP1 and column chromatography (hexane/Et_2O=10:1): $[\alpha]_D^{25}=-49$ ($c=0.55$, $CHCl_3$). The diastereomer ratio was determined by integration of the ^1H NMR signals at $\delta=3.54$ ppm for *trans*-**10f** and $\delta=3.68$ ppm for *cis*-**10f**. The *ee* values of *trans*- and *cis*-**10f** were determined to be 86 and 97%, respectively, by HPLC (Daicel chiralpak AD-H, hexane/*i*PrOH=100:1, 1 mL min^{-1}, 254 nm; t_R(major *trans* isomer)=20.9 min, t_R(minor *trans* isomer)=15.2 min, t_R(major *cis* isomer)=10.5 min, t_R(minor *cis* isomer)=8.7 min). Enantiomerically enriched (*S*)-**8b** (3.4 mg, 4%, 64% *ee*) was recovered as a white solid.

Following epimerization with DBU according to the procedure TP2, the diastereomers were separated by column chromatography (hexane/Et_2O=80:3) to give *trans*-**10f** (75.7 mg, 86%, 92% *ee*) as a white solid and *cis*-**10f** (12.3 mg, 14%, 94% *ee*) as a colorless oil.

trans-**10f**: M.p.: 67–69 °C; $[\alpha]_D^{25}=+44$ ($c=0.39$, $CHCl_3$; for 92% *ee*); IR (KBr): $\tilde{\nu}$=1705 cm^{-1}; ^1H NMR: δ=0.94 (d, *J*=6.7 Hz, 3H), 0.95 (d, *J*=6.7 Hz, 3H), 1.57–1.66 (m, 2H), 1.75 (m, 1H), 1.93 (dddd, *J*=3.5, 13.1, 13.1, 13.1 Hz, 1H), 2.02 (m, 1H), 2.24 (dd, *J*=13.1, 13.1 Hz, 1H), 2.30 (m, 1H), 2.55 (ddd, *J*=2.3, 3.8, 13.1 Hz, 1H), 3.54 (dd, *J*=5.6, 13.3 Hz, 1H), 7.12 (d, *J*=7.0 Hz, 2H), 7.22–7.35 ppm (m, 3H); ^{13}C NMR: δ=19.3 (CH_3), 19.6 (CH_3), 29.1 (CH_2), 32.7 (CH), 34.3 (CH_2), 45.7 (CH_2), 46.4 (CH), 57.2 (CH), 126.9 (CH), 128.3 (CH), 128.7 (CH), 138.8 (C), 210.4 ppm (C); MS (EI): *m/z*=216 $[M]^+$; elemental analysis: calcd (%) for $C_{15}H_{20}O$: C 83.28, H 9.32; found: C 83.20, H 9.50; HPLC: Daicel chiralcel OD-H, hexane/*i*PrOH=50:1, 1 mL min^{-1}, 254 nm; t_R(major enantiomer)=14.1 min, t_R(minor enantiomer)=11.6 min.

cis-**10f**: $[\alpha]_D^{25}=-140$ ($c=0.31$, $CHCl_3$; for 94% *ee*); IR (neat): $\tilde{\nu}$=1712 cm^{-1}; ^1H NMR: δ=0.89 (d, *J*=6.7 Hz, 3H), 0.90 (d, *J*=6.7 Hz, 3H), 1.53 (m, 1H), 1.70–1.79 (m, 2H), 1.84 (m, 1H), 2.07 (m, 1H), 2.30 (dd,

J = 10.4, 13.8 Hz, 1 H), 2.38–2.45 (m, 2 H), 3.68 (t, J = 6.0 Hz, 1 H), 7.21–7.25 (m, 3 H), 7.33–7.36 ppm (m, 2 H); ^{13}C NMR: δ = 19.8 ($CH_3 \times 2$), 25.5 (CH_2), 29.3 (CH_2), 31.2 (CH), 43.8 (CH_2), 45.1 (CH), 54.7 (CH), 126.8 (CH), 127.6 (CH), 128.7 (CH), 138.2 (C), 212.1 ppm (C); MS (EI): m/z = 216 $[M]^+$; HRMS (EI): m/z calcd for $C_{15}H_{20}O$: 216.1514 $[M]^+$; found: 216.1511; HPLC: Daicel chiralcel OD-H × 2, hexane/*i*PrOH = 150:1, 0.5 mL min^{-1}, 254 nm; t_R(major enantiomer) = 39.9 min, t_R(minor enantiomer) = 41.5 min.

10g: A 48:52 mixture of (2*R*,5*S*)- and (2*S*,5*S*)-2-benzyl-5-isopropylcyclohexan-1-one (*trans*- and *cis*-**10g**; 384 mg, 98%) was obtained as a colorless oil by the procedure TP1 and column chromatography (hexane/Et_2O = 10:1): $[\alpha]_D^{24}$ = −29 (c = 0.81, $CHCl_3$). The diastereomer ratio was determined by integration of the ^{1}H NMR signals at δ = 3.24 ppm for *trans*-**10g** and δ = 3.07 ppm for *cis*-**10g**. The *ee* values of *trans*- and *cis*-**10g** were determined to be 93 and 92%, respectively, by HPLC (Daicel chiralcel OJ-H, hexane/*i*PrOH = 100:1, 0.5 mL min^{-1}, 254 nm; t_R(major *trans* isomer) = 16.0 min, t_R(minor *trans* isomer) = 17.7 min, t_R(major *cis* isomer) = 33.4 min, t_R(minor *cis* isomer) = 22.8 min).

Following epimerization with DBU according to the procedure TP2, the diastereomers were separated by column chromatography (hexane/Et_2O = 80:3) to give *trans*-**10g** (199 mg, 87%, 92% *ee*) as a colorless oil and *cis*-**10g** (27 mg, 12%, 92% *ee*) as a colorless oil.

trans-**10g**: $[\alpha]_D^{24}$ = +25 (c = 0.83, $CHCl_3$; for 92% *ee*); IR (neat): $\tilde{\nu}$ = 1705 cm^{-1}; ^{1}H NMR: δ = 0.88 (d, J = 6.4 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 3 H), 1.23–1.38 (m, 2 H), 1.51–1.62 (m, 2 H), 1.82 (m, 1 H), 2.04 (m, 1 H), 2.09 (ddd, J = 1.2, 12.8, 12.8 Hz, 1 H), 2.38 (dd, J = 8.6, 14.0 Hz, 1 H), 2.43 (ddd, J = 2.5, 3.7, 12.8 Hz, 1 H), 2.49 (m, 1 H), 3.24 (dd, J = 4.6, 14.0 Hz, 1 H), 7.15 (d, J = 7.1 Hz, 2 H), 7.17–7.28 ppm (m, 3 H); ^{13}C NMR: δ = 19.2 (CH_3), 19.5 (CH_3), 28.7 (CH_2), 32.4 (CH_2), 32.7 (CH), 35.2 (CH_2), 45.6 (CH_2), 46.7 (CH), 52.0 (CH), 125.9 (CH), 128.3 (CH), 129.2 (CH), 140.6 (C), 212.7 ppm (C); MS (EI): m/z = 230 $[M]^+$; elemental analysis: calcd (%) for $C_{16}H_{22}O$: C 83.43, H 9.63; found: C 83.39, H 9.63.

cis-**10g**: $[\alpha]_D^{24}$ = −73 (c = 0.37, $CHCl_3$; for 92% *ee*); IR (neat): $\tilde{\nu}$ = 1713 cm^{-1}; ^{1}H NMR: δ = 0.91 (d, J = 6.7 Hz, 3 H), 0.93 (d, J = 6.7 Hz, 3 H), 1.53 (m, 1 H), 1.63–1.78 (m, 5 H), 2.38 (d, J = 6.4 Hz, 2 H), 2.58–2.63 (m, 2 H), 3.07 (m, 1 H), 7.16 (d, J = 7.0 Hz, 2 H), 7.19–7.30 ppm (m, 3 H); ^{13}C NMR: δ = 19.9 (CH_3), 19.9 (CH_3), 24.9 (CH_2), 28.2 (CH_2), 30.8 (CH), 36.2 (CH_2), 43.5 (CH_2), 44.8 (CH), 51.5 (CH), 126.3 (CH), 128.5 (CH), 129.0 (CH), 139.6 (C), 214.1 ppm (C); MS (EI): m/z = 230 $[M]^+$; elemental analysis: calcd (%) for $C_{16}H_{22}O$: C 83.43, H 9.63; found: C 83.22, H 9.89.

Typical procedure for the alkylation of **10** (TP4): A solution of NaHMDS in THF (1.0 M; 0.20 mL, 0.20 mmol) was added to a 68:32 mixture of *trans*- and *cis*-**10d** (36 mg, 0.18 mmol; 91 and 99% *ee*, respectively) in THF (0.8 mL) at −78 °C under argon atmosphere. The resulting mixture was stirred for 10 min at −78 °C, then allowed to warm to room temperature and stirred at room temperature for an additional 3 h. The pale-yellow solution was then cooled to −78 °C, and a solution of HMPA (0.16 mL, 0.89 mmol) in THF (0.8 mL) was added. The resulting mixture was stirred for 10 min at −78 °C, then iodomethane (0.02 mL, 0.36 mmol) was added, and the mixture was stirred at −78 °C for 5 h. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (4 mL), and the mixture was diluted with Et_2O (5 mL) at −78 °C and allowed to warm to room temperature. The organic layer was separated, and the aqueous layer was extracted with Et_2O three times. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (hexane/Et_2O = 10:1) to give (2*R*,5*S*)- and (2*S*,5*S*)-5-ethyl-2-methyl-2-phenylcyclohexan-1-one (**11a**; 35 mg, 91%, d.r. 90:10) as a colorless oil. $[\alpha]_D^{25}$ = +87.3 (c = 0.695, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 1705 cm^{-1}; ^{1}H NMR: δ = 0.82 (t, J = 7.5 Hz, 0.3 H), 0.90 (t, J = 7.4 Hz, 2.7 H), 1.12–1.30 (m, 0.2 H), 1.25 (s, 0.3 H), 1.30–1.45 (m, 1.9 H), 1.33 (s, 2.7 H), 1.61 (m, 0.9 H), 1.67–1.78 (m, 0.3 H), 1.87–1.98 (m, 2.7 H), 2.03 (dd, J = 12.9, 12.9 Hz, 0.1 H), 2.23 (ddd, J = 1.5, 5.2, 13.7 Hz, 0.9 H), 2.34 (ddd, J = 2.2, 3.7, 12.9 Hz, 0.1 H), 2.44 (m, 0.9 H), 2.53 (dd, J = 5.5, 13.7 Hz, 0.9 H), 2.69 (ddd, J = 3.1, 3.1, 14.4 Hz, 0.1 H), 7.17–7.27 (m, 3.1 H), 7.33–7.36 ppm (m, 1.9 H); ^{13}C NMR (major isomer): δ = 11.7 (CH_3), 25.7 (CH_2), 26.2 (CH_2), 27.2 (CH_3), 34.3 (CH_2), 39.5 (CH), 44.3 (CH_2), 53.8 (C), 126.3 (CH), 126.6 (CH), 128.7 (CH), 143.5 (C), 241.0 ppm (C); ^{13}C NMR (minor isomer): δ = 11.1 (CH_3), 28.1 (CH_2), 28.3 (CH_3), 29.5 (CH_2), 36.7 (CH_2), 42.8 (CH), 45.9 (CH_2), 53.6 (C), 126.0 (CH), 129.0 (CH), 143.2 (C), 213.7 ppm (C); MS (EI): m/z = 216 $[M]^+$; elemental analysis: calcd (%) for $C_{15}H_{20}O$: C 83.28, H 9.32; found: C 83.53, H 9.56. The diastereomer ratio was determined by integration of the ^{1}H NMR signals at δ = 2.53 ppm for the major diastereomer and δ = 2.69 ppm for minor diastereomer. The *ee* value of the major diastereomer was determined to be 93% by HPLC (Daicel chiralcel OJ-H × 2, hexane/*i*PrOH = 100:1, 0.5 mL min^{-1}, 254 nm; t_R(major diastereomer) = 27.5 min, t_R(minor diastereomer) = 40.0 min). The relative configuration of the products was determined from the ^{13}C NMR chemical-shift values of the methyl carbon atom of the methyl group at the 2-position of (2*R*,5*S*)-**11a** (at δ = 27.2 ppm) and (2*S*,5*S*)-**11a** (at 28.3 ppm).[18]

11b: A 90:10 mixture of (2*S*,5*S*)- and (2*R*,5*S*)-2-benzyl-5-ethyl-2-phenylcyclohexan-1-one (**11b**; 56 mg, 81%) was obtained as a colorless oil by the procedure TP4 and column chromatography (hexane/Et_2O = 1:0–20:1). $[\alpha]_D^{24}$ = +152 (c = 0.305, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 1705 cm^{-1}; ^{1}H NMR: δ = 0.81 (t, J = 7.3 Hz, 0.3 H), 0.89 (t, J = 7.3 Hz, 2.7 H), 1.15–1.92 (m, 6 H), 2.03 (dd, J = 12.8, 12.8 Hz, 0.1 H), 2.20–2.27 (m, 1.8 H), 2.36 (ddd, J = 2.1, 3.4, 12.8 Hz, 0.1 H), 2.45 (ddd, J = 3.1, 3.1, 14.4 Hz, 0.1 H), 2.53 (dd, J = 5.5, 13.4 Hz, 0.9 H), 2.96 (d, J = 13.6 Hz, 0.1 H), 3.11 (d, J = 13.4 Hz, 0.9 H), 3.12 (d, J = 13.6 Hz, 0.1 H), 6.46 (d, J = 8.0 Hz, 0.2 H), 6.56 (d, J = 6.7 Hz, 1.8 H), 6.94 (d, J = 8.0 Hz, 0.2 H), 6.99 (d, J = 7.3 Hz, 1.8 H), 7.04–7.30 ppm (m, 6 H); ^{13}C NMR (major isomer): δ = 11.7 (CH_3), 24.8 (CH_2), 25.4 (CH_2), 29.2 (CH_2), 38.9 (CH), 44.5 (CH_2), 46.0 (CH_2), 57.6 (C), 125.9 (CH), 126.8 (CH), 127.3 (CH), 128.5 (CH), 130.7 (C), 137.3 (C), 139.9 (C), 213.1 ppm (C); ^{13}C NMR (minor isomer): δ = 11.1 (CH_3), 27.8 (CH_2), 29.6 (CH_2), 33.5 (CH_2), 42.7 (CH), 46.2 (CH_2), 46.2 (CH_2), 57.3 (C), 125.9 (CH), 126.8 (CH), 127.3 (CH), 128.6 (CH), 130.7 (C), 137.3 (C), 139.9 (C), 212.9 ppm (C); MS (EI): m/z = 292 $[M]^+$; elemental analysis: calcd (%) for $C_{21}H_{24}O$: C 86.26, H 8.27; found: C 86.23, H 8.28. The diastereomer ratio was determined by HPLC. The *ee* value of the major diastereomer was determined to be 92% by HPLC (Daicel chiralpak AD-H × 2, hexane/*i*PrOH = 100:1, 0.5 mL min^{-1}, 254 nm; t_R(major diastereomer) = 29.7 min, t_R(minor diastereomer) = 25.2 min). The relative configuration of the products was determined from the ^{13}C NMR chemical-shift values of the benzylic methylene carbon atoms of (2*S*,5*S*)-**11b** (at δ = 46.0 ppm) and (2*R*,5*S*)-**11b** (at δ = 46.2 ppm).[18]

11c: An 85:15 mixture of (2*S*,5*S*)- and (2*R*,5*S*)-2-allyl-5-ethyl-2-phenylcyclohexan-1-one (**11c**; 48 mg, 84%) was obtained as a colorless oil by the procedure TP4 and column chromatography (hexane/Et_2O = 20:1–10:1). $[\alpha]_D^{24}$ = +137 (c = 0.53, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 1705 cm^{-1}; ^{1}H NMR: δ = 0.82 (t, J = 7.5 Hz, 0.45 H), 0.89 (t, J = 7.3 Hz, 2.55 H), 1.15–1.25 (m, 0.3 H), 1.25–1.38 (m, 1.7 H), 1.43 (m, 0.15 H), 1.64 (m, 0.85 H), 1.69 (m, 0.15 H), 1.78 (m, 0.15 H), 1.84–1.99 (m, 2.85 H), 2.19 (ddd, J = 2.1, 4.0, 13.7 Hz, 0.85 H), 2.32 (ddd, J = 2.1, 3.7, 13.2 Hz, 0.15 H), 2.38–2.53 (m, 3.7 H), 2.66 (ddd, J = 3.1, 3.1, 14.7 Hz, 0.15 H), 4.85–4.94 (m, 2 H), 5.40–5.48 (m, 1 H), 7.15 (dd, J = 1.2, 8.3 Hz, 0.3 H), 7.19 (dd, J = 1.2, 8.3 Hz, 1.7 H), 7.24 (tt, J = 1.2, 7.4 Hz, 1 H), 7.35 ppm (dd, J = 7.4, 8.3 Hz, 2 H); ^{13}C NMR (major isomer): δ = 11.7 (CH_3), 25.0 (CH_2), 25.6 (CH_2), 29.6 (CH_2), 39.0 (CH), 44.4 (CH_2), 44.5 (CH_2), 56.5 (C), 117.7 (CH_2), 126.7 (CH), 126.9 (CH), 128.7 (CH), 134.2 (CH), 140.7 (C), 213.0 ppm (C); ^{13}C NMR (minor isomer): δ = 11.1 (CH_3), 27.8 (CH_2), 29.6 (CH_2), 33.5 (CH_2), 42.6 (CH), 44.9 (CH_2), 46.1 (CH_2), 56.1 (C), 117.6 (CH_2), 126.8 (CH), 128.8 (CH), 134.4 (CH), 140.6 (C), 212.9 ppm (C); MS (EI): m/z = 242 $[M]^+$; elemental analysis: calcd (%) for $C_{17}H_{22}O$: C 84.25, H 9.15; found: C 84.18, H 9.18. The diastereomer ratio was determined by integration of the ^{1}H NMR signals at δ = 2.19 ppm for the major diastereomer and δ = 2.66 ppm for the minor diastereomer. The *ee* value of the major diastereomer was determined to be 93% by HPLC (Daicel chiralcel OD-H × 2, hexane/*i*PrOH = 100:1, 0.5 mL min^{-1}, 254 nm; t_R(major diastereomer) = 19.0 min, t_R(minor diastereomer) = 20.8 min). The relative configuration of the products was determined from the ^{13}C NMR chemical-shift values of the allylic methylene carbon atoms of (2*S*,5*S*)-**11c** (at δ = 44.4 ppm) and (2*R*,5*S*)-**11c** (at δ = 44.9 ppm).[18]

11d: A 90:10 mixture of (2*R*,5*S*)- and (2*S*,5*S*)-5-isopropyl-2-methyl-2-phenylcyclohexan-1-one (**11d**; 34 mg, 85%) was obtained as a colorless oil by the procedure TP4 and column chromatography (hexane/Et_2O =

10:1). $[\alpha]_D^{26}=+40$ ($c=0.74$, $CHCl_3$); IR (neat): $\tilde{\nu}=1705\,cm^{-1}$; ^1H NMR: $\delta=0.77$ (d, $J=6.8$ Hz, 0.3 H), 0.80 (d, $J=6.8$ Hz, 0.3 H), 0.91 (d, $J=6.5$ Hz, 2.7 H), 0.93 (d, $J=6.5$ Hz, 2.7 H), 1.25 (s, 0.3 H), 1.39 (s, 2.7 H), 1.47 (dd, $J=3.2$, 12.3 Hz, 0.1 H), 1.51–1.76 (m, 3 H), 1.82–1.94 (m, 1.8 H), 2.08 (dd, $J=12.8$, 12.8 Hz, 0.1 H), 2.32 (ddd, $J=2.2$, 3.7, 12.8 Hz, 0.1 H), 2.36–2.47 (m, 2.8 H), 2.71 (ddd, $J=3.1$, 6.8, 14.5 Hz, 0.1 H), 7.17–7.36 ppm (m, 5 H); ^{13}C NMR (major isomer): $\delta=20.0$ (CH_3), 20.2 (CH_3), 24.2 (CH_2), 26.2 (CH_3), 30.0 (CH), 35.7 (CH_2), 42.5 (CH_2), 44.5 (CH), 53.5 (C), 126.5 (CH), 126.6 (CH), 128.6 (CH), 143.8 (C), 214.2 ppm (C); ^{13}C NMR (minor isomer): $\delta=19.4$ (CH_2), 19.6 (CH_2), 25.5 (CH_2), 28.3 (CH_3), 32.8 (CH), 36.8 (CH_2), 43.5 (CH_2), 47.4 (CH), 53.6 (C), 126.0 (CH), 129.0 (CH), 143.2 (C), 214.3 ppm (C); MS (EI): $m/z=230$ $[M]^+$; elemental analysis: calcd (%) for $C_{16}H_{22}O$: C 83.43, H 9.63; found: C 83.31, H 9.60. The diastereomer ratio was determined by integration of the ^1H NMR signals at $\delta=1.88$ ppm for the major diastereomer and $\delta=2.71$ ppm for the minor diastereomer. The *ee* value of the major diastereomer was determined to be 90% by HPLC (Daicel chiralcel OJ-H×2, hexane/*i*PrOH=150:1, 0.5 mL min^{-1}, 254 nm; t_R(major diastereomer)=35.0 min, t_R(minor diastereomer)=52.3 min). The relative configuration of the products was determined from the ^{13}C NMR chemical-shift values of the methyl carbon atom of the methyl group at the 2-position of (2*R*,5*S*)-**11d** (at $\delta=26.2$ ppm) and (2*S*,5*S*)-**11d** (at $\delta=28.3$ ppm).[18]

11e: An 88:12 mixture of (2*S*,5*S*)- and (2*R*,5*S*)-2-benzyl-5-isopropyl-2-phenylcyclohexan-1-one (**11e**; 51.6 mg, 89%) was obtained as a white solid by the procedure TP4 and column chromatography (hexane/Et_2O=20:1). M.p.: 65–68 °C; $[\alpha]_D^{26}=+146$ ($c=0.650$, $CHCl_3$); IR (neat): $\tilde{\nu}=1705\,cm^{-1}$; ^1H NMR: $\delta=0.76$ (d, $J=6.7$ Hz, 0.36 H), 0.78 (d, $J=6.7$ Hz, 0.36 H), 0.88 (d, $J=6.1$ Hz, 2.64 H), 0.93 (d, $J=6.1$ Hz, 2.64 H), 1.36–1.58 (m, 1.88 H), 1.63–1.88 (m, 3.12 H), 2.07 (dd, $J=12.9$, 12.9 Hz, 0.12 H), 2.24 (m, 0.88 H), 2.33–2.48 (m, 2 H), 2.96 (d, $J=13.7$ Hz, 0.12 H), 2.99 (d, $J=13.5$ Hz, 0.88 H), 3.11 (d, $J=13.7$ Hz, 0.12 H), 3.12 (d, $J=13.5$ Hz, 0.88 H), 6.54–6.58 (m, 0.24 H), 6.57 (d, $J=7.0$ Hz, 1.76 H), 6.94 (d, $J=7.1$ Hz, 0.24 H), 7.02–7.10 (m, 4.52 H), 7.24–7.30 ppm (m, 3.24 H); ^{13}C NMR (major isomer): $\delta=20.3$ (CH_3), 20.7 (CH_3), 23.5 (CH_2), 28.6 (CH), 29.4 (CH_2), 42.9 (CH_2), 43.7 (CH), 45.8 (CH_2), 57.4 (C), 126.0 (CH), 126.8 (CH), 127.2 (CH), 127.4 (CH), 128.5 (CH), 130.6 (CH), 137.3 (C), 140.0 (C), 213.3 ppm (C); ^{13}C NMR (minor isomer): $\delta=19.4$ (CH_3), 19.6 (CH_3), 25.0 (CH_2), 32.7 (CH), 33.5 (CH_2), 43.8 (CH_2), 46.2 (CH_2), 47.2 (CH), 57.2 (C), 125.9 (CH), 127.3 (CH), 127.3 (CH), 128.6 (CH), 130.7 (CH), 137.4 (C), 139.9 (C), 213.5 ppm (C); MS (EI): $m/z=306$ $[M]^+$; elemental analysis: calcd (%) for $C_{22}H_{26}O$: C 86.23, H 8.55; found: C 86.13, H 8.79. The diastereomer ratio was determined by integration of the ^1H NMR signals at $\delta=2.24$ ppm for the major diastereomer and at $\delta=2.07$ ppm for the minor diastereomer. The *ee* value of the major diastereomer was determined to be 93% by HPLC (Daicel chiralpak AD-H×2, hexane/*i*PrOH=200:1, 0.5 mL min^{-1}, 254 nm; t_R(major diastereomer)=37.2 min, t_R(minor diastereomer)=34.7 min). The relative configuration of the products was determined from the ^{13}C NMR chemical-shift values of the benzylic methylene carbon atoms of (2*S*,5*S*)-**11f** (at $\delta=45.8$ ppm) and (2*R*,5*S*)-**11f** (at $\delta=46.2$ ppm).[18] Recrystallization from heptane gave a pure sample of the major diastereomer as colorless prisms (m.p.: 89–90 °C).

Acknowledgements

This research was partially supported by the 21st Century COE (Center of Excellence) Program “Knowledge Information Infrastructure for Genome Science”, a Grant-in-Aid for Scientific Research in Priority Areas “Advanced Molecular Transformations of Carbon Resources”, and the Targeted Proteins Research Program of the Ministry of Education, Culture, Sports, Science, and Technology, Japan. K.S. thanks the Egyptian Government for a predoctoral fellowship.

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Received: September 15, 2007
Published online: December 11, 2007

