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Stereoselective 1,4-addition of Grignard reagents to α,β-enamides using a combined chiral auxiliary-catalyst approach

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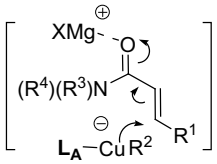
ABSTRACT

A catalyst composed of (*R*,*R*)-MeDuphos and CuBr·SMe_2 catalyzes the addition of RMgBr (R = Et, C_5H_{11}, Ph) to simple enamides (*E*)-$Me_2NCOCH{=}CHR^1$ (R^1 = Me, C_5H_{11}) in acceptable yields (50–78%), but with poor to modest enantioselectivities (0–74% ee). By changing the enamide acceptor to the (*E*)-(Aux)N-COCH=CHMe [Aux = from commercial pseudoephedrine, (*R*,*R*)-NMeCHMeCHPhOH] a stereochemically enhanced regime could be attained. Structurally diverse RMgBr (R = C_5H_{11}, vinyl, allyl, Ph) underwent 1,4-additions in 57–89% de and 88–93% yield. In one case, the resulting enolate could be trapped with allyl bromide.

1. Introduction

We recently described some preliminary studies concerning the catalytic asymmetric 1,4-addition of Grignard reagents to α,β-unsaturated amides via the intermediacy of **A**.[1] Although normally disregarded in favor of more reactive Michael acceptors (e.g., enones and α,β-unsaturated esters and thioesters)[2] it was discovered that the use of Duphos-based ligands $\mathbf{L}_A$ afforded up to 57% ee for the addition of EtMgBr. In order to define the scope of this reaction, further experiments probing the generality of the reaction have been carried out with the aim of attempting to identify reaction conditions that favor highly selective 1,4-addition processes for a range of Grignard reagents.



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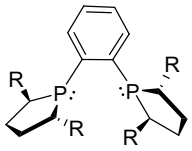
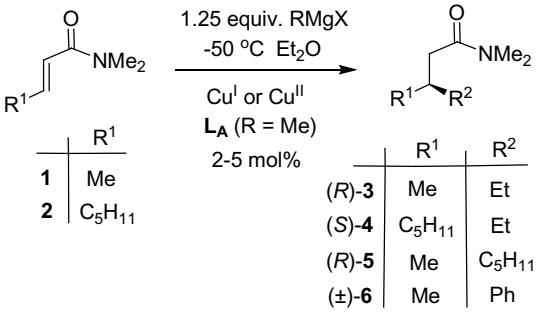


$\mathbf{L}_A$ DialkylDuphos

2. Results and discussion

2.1. Cu^I–DuPhos-catalyzed 1,4 RMgX additions

Further optimization studies on the addition of Grignard reagents were carried out using enamides **1** and **2** (Scheme 1). The latter is simply prepared from the commercially available acid. Screening reactions were typically carried out using EtMgBr at −50 °C in the presence of a 2–5 mol % catalyst attained by in situ mixing of the copper source and $\mathbf{L}_A$. Out of a library of 10 CuX or CuX_2 species and five phosphine ligands, CuBr·SMe_2 and (*R*,*R*)-MeDuphos ($\mathbf{L}_A$, R = Me) proved optimal at ligand loadings of 5 mol %. Selected results using **2** are presented in Table 1. In all cases, conversions were >80%. All enantiomeric excesses were determined by chiral GC and have been assumed to give addition to the *Si* (top) face of **1** and **2** (Scheme 1) by analogy with our previous stereochemical correlation.[1]



Scheme 1. Asymmetric 1,4-additions of RMgX to **1**–**2**.

Polar solvents were of little use in attaining an enantioselective reaction (Table 1, runs 1–2). In diethyl ether, CuBr.SMe_2 consistently provided the highest chemical yield as well as moderate stereoselectivity (>5:1 er, run 4), while CuCN with the identical ligand gave only low yields of racemic material (run 9). Other copper sources offered behavior between these extremes. As we had noted

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Table 1
Optimization studies of EtMgBr to enamides **2**[a]

Run	Solvent	Cu-source	Yield (%)	ee (%) (enantiomer)
1	THF	CuBr·SMe_2	45	30 (*S*)
2	CH_2Cl_2	CuBr·SMe_2	49	36 (*S*)
3	Bu^{t}OMe	CuBr·SMe_2	70	64 (*S*)
4	Et_2O	CuBr·SMe_2	76	68 (*S*)
5	Et_2O	Cu(OTf)$_2$	69	68 (*S*)
6	Et_2O	Cu(TC)	50	50 (*S*)
7	Et_2O	CuBr	30	32 (*S*)
8	Et_2O	CuCl	25	26 (*S*)
9	Et_2O	CuCN	42	<5
10	Et_2O	CuBr·SMe_2	50	38 (*S*)[b]

[a] Ratio of enamide/EtMgBr/CuX/(*R*,*R*)-MeDuphos 1.25:0.05:0.05:1.0, unless otherwise noted. All yields by isolation.
[b] Using (*R*,*R*)-EtDuphos (L_A, R = Et) 5 mol %.

before,[1] the scope for modifying the nature of the Duphos ligand was rather limited, as even (*R*,*R*)-EtDuphos resulted in a very significant loss of stereoselectivity (run 10).

The optimized conditions (−50 °C, Et_2O) were then applied to a range of catalytic additions (Table 2). In all cases, good conversions (88–98%) of the starting enamides **1** and **2** were attained. Unfortunately, both the isolated yields and the induced stereochemistry proved modest (4.6–6.7:1 er; runs 1–3). Furthermore, the system could not be used for asymmetric addition of PhMgBr at all (run 4). While some of our results were encouraging, the system was resistant to further optimization leading us to reconsider our strategy.

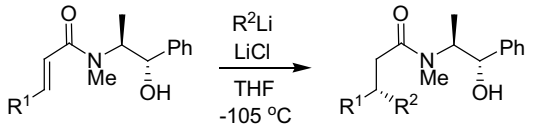
Table 2
Catalytic asymmetric addition of RMgBr to enamides **1**–**2**[a]

Run	Enamide	Grignard	Yield (%)	ee (%) (enantiomer)
1	**1**	EtMgBr	66	64 (*R*)
2	**2**	EtMgBr	78	68 (*S*)
3	**1**	C_5H_{11}MgBr	68	74 (*R*)
4	**1**	PhMgBr	50	<5

[a] Ratio of enamide/RMgBr/CuBr·SMe_2/(*R*,*R*)-MeDuphos 3.0:0.05:0.05:1.0, unless otherwise stated. All yields by isolation; ee by chiral GC.[1]

2.2. Auxiliary-supported 1,4 RMgX additions

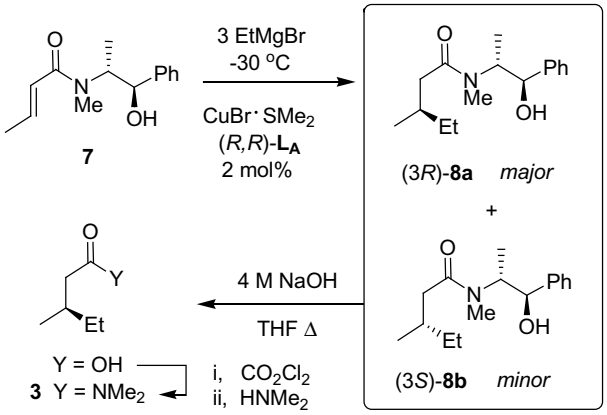
As we had not been able to realize a synthetically useful regime (>80% ee) for (*R*,*R*)-MeDuphos/Cu^I additions to simple α,β-unsaturated enamides, we decided to bolster the stereoselectivity of the 1,4-Grignard addition by the use of an appropriate chiral auxiliary. While conceptually less elegant, such an approach is justifiable if: (i) high levels of stereoinduction are achieved, and (ii) the resultant chiral enolate can be trapped selectively allowing clean generation of two contiguous stereogenic centers. The beautiful work of Badía,[3] who had described highly diastereoselective 1,4-additions of RLi to (*S*,*S*)-(+)-pseudoephedrine-derived species (Scheme 2), seemed to offer a strategy to support the stereoinduction of our chiral catalyst.



Scheme 2. Badía's diastereoselective 1,4-additions of RLi.

In our case (*S*,*S*)-(+)-pseudoephedrine was not available, only its (*R*,*R*)-enantiomer. It was initially unclear to us if the latter would constitute a 'matched' or 'miss-matched' pairing in the presence of the (*R*,*R*)-MeDuphos/Cu^I catalyst. Much more importantly, it was unknown how changing from RLi to Grignard reagents would affect the chemistry of Badía. It is known that the identity of metal alkoxides in such auxiliaries can cause a dramatic change in such delicate transition states. Thus, it could not be assured that the use of Grignard reagents would be appropriate.

The required Michael acceptor **7** could easily be prepared from crotylchloride and (*R*,*R*)-(−)-pseudoephedrine (Scheme 3). The compound exists as a mixture of *s*-cis and *s*-trans rotamers in a 65:45 ratio at ambient temperatures. Coalescence in the ^{1}H NMR spectrum occurred at 70 °C (in C_6D_6), reaching a sharp high-temperature limit at 90 °C. Using standard forms of the Eyring equation,[4] it was estimated that the barrier to rotation was 17.2 kcal mol^{-1}. Compound **7** was found to react with EtMgR in the presence of (*R*,*R*)-MeDuphos and CuBr·SMe_2 to give a mixture of the two diastereoisomers **8a** and **8b** in good combined yield (75%). Due to the poor solubility of **7** in Et_2O, dichloromethane alone was used for this initial study.



Scheme 3. Diastereoselective 1,4-additions of EtMgBr.

Comparative integration of two diastereomeric related ^{1}H NMR signals is normally an effective method for the determination of a reaction's de. Unfortunately both products **8a** and **8b** exist as ~3:1 mixture of rotameric conformers that are appreciably exchange broadened at room temperature. Extracting the relevant 'de' ratio from the resultant morass of broadened signals is problematic. The diastereoselectivity of **8** was easily measured by HPLC on a Daicel-OD column (as suggested by Badía,[3]), giving a ratio of 77:23 for a run carried out in THF. To confirm the HPLC analysis and to verify the proposed facial selectivity, the **8a**–**b** mixture was hydrolyzed and reconverted to **3** with oxalyl chloride and methylamine. Chiral GC analysis revealed the presence of (*R*)-**3** with an ee value equivalent to the original diastereoselectivity toward **8a**. These studies thus revealed that HPLC analysis was effective and unaffected by the rotamer population observed in the ^{1}H and ^{13}C NMR spectra. Therefore, all subsequent de values were determined by chiral HPLC. Additional screening reactions using **7** and EtMgBr revealed a significant solvent dependence (Table 3).

Table 3
Solvent effects on the addition of EtMgBr to enamides **7**[a]

Run	Solvent	Yield (%)	de (%)
1	CH_2Cl_2	55	48
2	THF	55	54
3	4:1 Et_2O/CH_2Cl_2	94	84

[a] Ratio of enamide/EtMgBr/CuBr·SMe_2/(*R*,*R*)-MeDuphos 3.0:0.05:0.05:1.0, unless otherwise stated. All yields by isolation; de by HPLC on a Daicel-OD column; selectivity favors **8a**.

The reaction of EtMgBr with **7**, in 4:1 CH_2Cl_2:Et_2O, in both the presence and absence of a range of catalysts was then studied (Table 4).

Table 4
Catalyst effects on the addition of EtMgBr to enamides **7**[a]

Run	Catalyst	Yield (%)	de (%)
1	None	—[b]	—[b]
2	CuBr·SMe_2	—[b]	—[b]
3	$P(OPh)_3$/CuBr·SMe_2	20	20
4	(*R*,*S*,*S*)-Feringa[c]/CuBr·SMe_2	88	84
5	(*S*,*S*)-MeDuphos/CuBr·SMe_2	78	83
6	(*R*,*R*)-EtDuphos/CuBr·SMe_2	75	82
7	(*R*,*R*)-MeDuphos/CuBr·SMe_2	94	84

[a] Ratio of enamide/EtMgBr/CuBr·SMe_2/(*R*,*R*)-MeDuphos 3.0:0.05:0.05:1.0, unless otherwise stated. All reactions in 4:1 Et_2O/CH_2Cl_2. All yields by isolation; de by HPLC on a Daicel-OD column; selectivity favors **8a**.
[b] No reaction.
[c] Feringa's phosphoramidite [see Ref. 5 for ligand structure].

It was worthwhile determining if the observed facial selectivity arose solely from the auxiliary or from a combination of auxiliary and catalyst effects. From Table 4, it is clear that the (*R*,*R*)-(−)-pseudoephedrine auxiliary dominates the stereocontrol. However, the presence of a copper catalyst is vital if acceptable chemical yields are to be attained. Species of the type Cu^I/'L' are particularly effective in this role if the ligand 'L' shows a strong ligand acceleration effect[6] (runs 4–7). In the absence of such effects, either a poor (run 3) or no yield (runs 1 and 2) was realized. Very little difference was observed in the behavior of (*R*,*R*)- and (*S*,*S*)-MeDuphos (runs 5 and 7). As the former had very slightly superior characteristics, it was used in all further studies. The generality of the reaction was tested with a range of Grignard reagents (Scheme 4, Table 5).

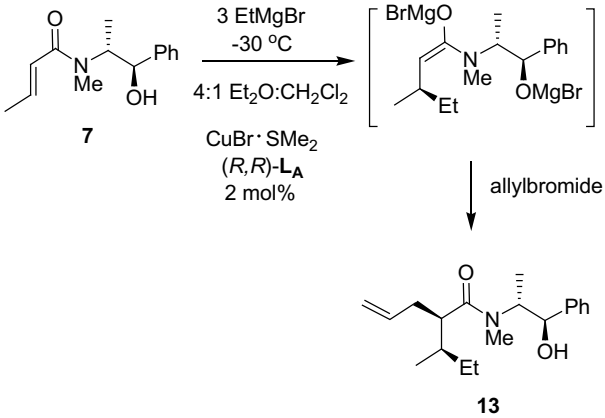
Table 5
Effects on the addition of RMgBr to enamides **7**[a]

Run	RMgX	Yield (%)	de (%)
1	C_5H_{11}	93	74[b]
2	Ph	88	89[c]
3	$CH_2CH{=}CH_2$	92	76[d]
4	$CH{=}CH_2$	88	57[d]

[a] Ratio of enamide/RMgBr/CuBr·SMe_2/(*R*,*R*)-MeDuphos 3.0:0.05:0.05:1.0, unless otherwise stated. All yields by isolation.
[b] De by HPLC analysis on a Daicel OJ-H column.
[c] De by HPLC analysis on a Daicel OD column.
[d] De by HPLC analysis on a Daicel AD-H column.

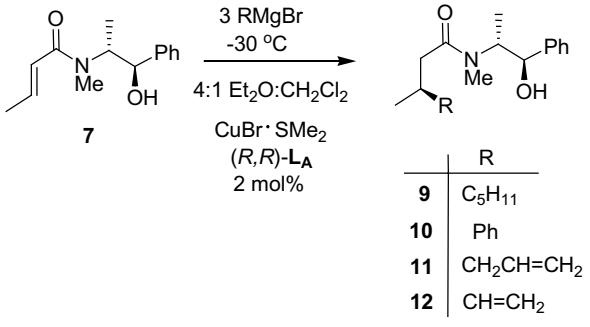
The diastereomers of **9** and **11**–**12** could not be split on a Daicel-OD column, only single peaks were observed. As a control, a sample of **9** was converted to **5** to allow its independent assay by chiral GC. This study revealed (*R*)-**5** in 74% ee indicating that despite the similarity of compounds **9**–**12**, separation of their stereoisomers by chiral HPLC can be nontrivial in some cases. After an extensive screen of conditions and columns, we could identify various assays for direct HPLC measurement of **9**–**12** that correlated with GC measurements on the derived dimethylamides. In some cases, however, the use of such conditions resulted in inversion of the enantiomer elution order. Again, ^1H NMR spectroscopy was not useful as only the rotamers of compounds **9**–**12** were observed in broadened partially overlapping spectra. The dispersion was better in the ^{13}C NMR spectra, but only rotameric signals of the major diastereomer could be detected easily. Assignment of the minor diastereomers was not attempted due to their very low signal intensity. It is worth noting that the ^{13}C NMR signals due to two NR pseudoephedrine substituents in **9**–**12** are especially problematic as they are appreciably broadened at ambient temperature (NMe at ~32 ppm and N-1′CH at ~58 ppm) due to amide rotation. Good signal-to-noise spectra are required for confident assignment. Finally, we note that even under copper catalysis, inadequate reactivity was observed for MeMgBr addition (<5% yield in all substrates trialed). While the stereoselectivities given in Table 4 are in a modest range (57–89% de) an ability to add allyl Grignard-noteworthy. Almost no processes for stereoselective 1,4-additions of allyl organometallics are known. The only publication we are aware of is the allyl additions of Pourcelot who used a related auxillary.[7] However, no detailed experimental details appear in his preliminary note and the auxiliary itself has to be prepared rather than being commercially available.

Although many highly enantioselective catalytic procedures have appeared in recent years,[8] selective alkylation of the resulting metal enolates remains the exception,[9] rather than the norm. Typically, aluminum and zinc enolates are too unreactive to participate in such procedures. Myers has described that lithium enolates containing (*S*,*S*)-(+)-pseudoephedrine can be alkylated highly selectively;[10] an enhanced variant has been described by Tietze very recently.[11] Equivalent reactions using Mg-enolates resulting from conjugate addition have not been described to the best of our knowledge. We probed the reactivity of **8** with allylbromide as a simple representative electrophile (Scheme 5).



Scheme 5. Diastereoselective alkylation studies.

Reaction of this representative Mg-enolate with allylbromide resulted in formation of the expected product in good chemical yield (88% for **13**). The stereochemistry of **13** and **14** has been assigned on the basis of the models of Myers[10] and Badía,[3] where the (*R*,*R*)-(−)-pseudoephedrine auxiliary is expected to engender the formation of the (*R*)-stereochemistry at the C(2) alkylation site (if priority $R_{alkylating} < R_{Michael\ Side\ Chain}$). Our alkylation is quite slow and apparently some kinetic resolution of the stereoisomeric enolates takes place resulting in an enrichment of the final product to



Scheme 4. Diastereoselective 1,4-additions of RMgBr.

92% de. Attempts to further extend the reactivity of the Mg-enolate with PhCHO were not successful. While the desired aldol products were formed in good yield, the diastereoselectivity was very poor.

3. Conclusion

In conclusion we have developed a methodology for a catalyst-assisted 1,4-addition of a wide variety of Grignard reagents to α,β-unsaturated amides. Those Michael acceptors bearing a (*R*,*R*)-(−)-pseudoephedrine-derived auxiliary allow the attainment of higher stereoselectivities than those attained with a chiral catalyst alone. Unusually, allylMgBr can be used in a 1,4-stereoselective addition (76% de). In one case, opportunities to intercept the intermediate enolates with allylbromide exist.

4. Experimental

4.1. General methods

Optical rotations were measured using a JASCO DIP370 digital polarimeter and are quoted as 10^{-1} deg cm^2 g^{-1}. Concentration (*c*) is given in units of g/100 cm^3 solvent. Proton and ^{13}C NMR spectra were recorded on a Bruker AV400 in $CDCl_3$. Chemical shifts are reported as δ values in ppm relative to $CHCl_3$ (7.27 ppm for ^{1}H; 77.0 ppm for ^{13}C) in $CDCl_3$. IR spectra were measured on a Bruker Tensor 27 FT-IR spectrometer. Mass spectra (MS) were recorded at high resolution (HRMS) on a micromass LCT or VG micromass 70E mass spectrometers using electrospray ionization (ESI) or electron impact (EI). Chiral HPLC analysis was performed on a Hewlett Packard 1100LC chromatograph using Daicel Chiracel (250 mm) stationary phase columns. GC analyses were carried out on Varian 3380 instruments using the columns indicated. Preparative chromatography was performed with Fluorochem Davisil silica gel (35–70 μm) using mixtures of ethyl acetate and petrol (40–60 °C) as eluents. Diethyl ether (Et_2O), and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone under argon. Dichloromethane (CH_2Cl_2) was freshly distilled from calcium hydride under argon. Commercially available compounds were used without further purification.

4.2. *N*,*N*-Dimethyl-*trans*-crotonamide 1

The compound was prepared by a literature procedure.[12] A solution of crotonyl chloride (5.00 g, 47.9 mmol) in 30 mL dry Et_2O was cooled to 0 °C in an ice-bath. Anhydrous dimethylamine (48.0 mL of a 2.0 M THF solution, 95.8 mmol) was added for over 5 min and the reaction mixture was allowed to warm to room temperature (12 h). The solvents were evaporated under reduced pressure. Kugerohl distillation of the reaction mixture (110 °C, 9 mmHg) afforded **1** as the colorless liquid (4.90 g, 90%) with literature properties.[13] IR 3001, 1661, 1610, 1493, 1445, 1399, 1278, 1241, 1156, 1100, 995 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 1.86 (dd, *J* = 6.9 and 1.6 Hz, 3H, CH*CH*$_3$), 3.01 (br, s, 2 × NCH_3), 6.26 (dq, *J* = 15.0, 1.7 Hz, 1H, CO*CH*), 6.84 (dq, *J* = 15.0, 6.9 Hz, 1H, *CH*CH_3); ^{13}C NMR (100.6 MHz) δ 15.3, 35.4, 37.3, 121.7, 141.2, 166.9.

4.3. *N*,*N*-Dimethyl-*trans*-oct-2-enmide 2

To a cold (0 °C) solution of octenoic acid (5.5 mL, 36.5 mmol) in dichloromethane (30 mL) were added oxalyl chloride (9.5 mL, 109.5) and dry DMF (100 μL). The solution was then stirred at room temperature (1 h) and concentrated under reduced pressure to remove residual oxalyl chloride. The resulting pale yellow residue was re-dissolved in dichloromethane (20 mL), cooled (0 °C) and *N*,*N*-dimethylamine (21.9 mL of 2.0 M THF solution, 43.8 mmol) in THF was added. Dry triethylamine (6.7 mL, 48.2 mmol) was added and stirring was continued at ambient temperature (6 h). The solvent was removed under reduced pressure and the residue was extracted with dichloromethane (100 mL). The organic phase was washed with dilute hydrochloric acid (2 M, 20 mL × 2), water (25 mL × 2), and brine (30 mL), and dried over sodium sulfate. After removal of the solvent, the resulting crude product was purified by flash chromatography (petrol/ethyl acetate 7:1) to afford **2** as a colorless liquid (5.5 g, 89%). IR 3001, 2959, 2931, 2873, 1659, 1607, 1497, 1467, 1399, 1155 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.3 Hz, CH_3), 1.29–1.36 (m, 4H, CH_2CH_2), 1.42–1.50 (m, 2H, CH_2), 2.20 (dq, *J* = 1.5, 7.2 Hz, 2H, *CH*$_2$CH), 3.00 (s, 3H, NCH_3), 3.07 (s, 3H, NCH_3), 6.24 (dt, *J* = 16.0, 1.5 Hz, 1H, COCH), 6.57 (dt, *J* = 16.0, 7.2 Hz, 1H, *CH*CH_2); ^{13}C NMR (100.6 MHz) δ 14.0, 22.6, 28.1, 31.4, 32.5, 35.6, 37.3, 120.1, 146.4, 167.0; HRMS (M^++Na) requires *m*/*z*, 192.13589; found, 192.13630.

4.4. General procedure for the 1,4-addition to α,β-enamides 1–2

In a typical procedure, solutions of the Cu-salt (2–5 mol %) and chiral ligand (2–5 mol %) in 4 mL of freshly distilled Et_2O were stirred at room temperature (20 min) and then cooled to −50 °C. A solution of Grignard reagent (EtMgBr, pentyl MgBr or phenyl MgBr; 2–3 M in Et_2O, 1.25 equiv) was added dropwise and the resulting solution was stirred for a further 5 min before a solution of enamide (1 mmol) in Et_2O (2 mL) was added dropwise. The reaction mixture was stirred at −50 °C for further 2 h, then quenched with 0.5 mL of 2 M HCl. Undecane (25 μL) was then added as an internal standard, and the organic layer filtered through a plug of silica. Yields and enantiomeric excesses were measured by GC.

4.5. (*R*)-*N*,*N*-Dimethyl-3-methyl-pentanamide 3

The compound was prepared using the procedure described in Section 4.4 with CuBr·SMe_2 (22.6 mg, 0.11 mmol), (*R*,*R*)-MeDuphos (33.7 mg, 0.11 mmol), EtMgBr (0.96 mL, 3.0 M in Et_2O, 2.86 mmol), and a solution of **1** (250 mg, 2.20 mmol) in Et_2O (2 mL). Usual work up afforded a colorless liquid **3** (260 mg, 82%, 64% ee). $[\alpha]_D = -5.6$ (*c* 1.5, $CHCl_3$); IR 3003, 2964, 2932, 2876, 1630, 1498, 1461, 1400 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 0.94 (d, *J* = 6.5 Hz, 3H, $CHCH_3$), 1.18–1.25 (m, 1H, $CH_2\alpha CH_3$), 1.38–1.47 (m, 1H, $CH_{2\beta}CH_3$), 1.90–1.99 (m, 1H. *CH*CH_3), 2.13 (dd, *J* = 14.7 and 8.0 Hz, 1H, CO$CH_2\alpha$), 2.32 (dd, *J* = 14.7 and 6.5 Hz, 1H, CO$CH_{2\beta}$), 2.96 (s, 3H, NCH_3), 3.02 (s, 3H, NCH_3); ^{13}C NMR (100.6 MHz) δ 11.5, 19.5, 29.7, 31.9, 35.4, 37.5, 40.3, 172.8. HRMS (M^++Na) requires *m*/*z*, 166.1208; found, 166.1192. The data were concurrent with literature values.[1] The ee value was determined by chiral GC using an octakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin column, 0.25 μm i.d. (50% in OV1701, w/w) using the programme: 80 °C (isothermal). Retention times: **1** 16.1, *R*-**3** 22.6, *S*-**3** 23.8 min.

4.6. (*S*)-*N*,*N*-Dimethyl-3-ethyl-octanamide 4

The compound was prepared in an identical fashion to that described in Section 4.4 using CuBr·SMe_2 (15.2 mg, 0.074 mmol), (*R*,*R*)-MeDuphos (22.7 mg, 0.074 mmol), EtMgBr (0.65 mL, 3.0 M in Et_2O, 1.95 mmol), and a solution of **2** (250 mg, 1.48 mmol) in Et_2O (2 mL). Usual work up afforded a colorless liquid **4** (252 mg, 85%, 68% ee). $[\alpha]_D = +1.1$ (*c* 1.1, $CHCl_3$); IR 3003, 2961, 2930, 2858, 1630, 1497, 1461, 1399, 1380 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.2 Hz, 3H, CH_2CH_3) overlapped by 0.87 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.27–1.36 (m, 10H, 5 × CH_2), 1.85–1.89 (m, 1H, *CH*CH_2), 2.22 (app. d, *J* = 8 Hz, 2H, CH_2CO), 2.94 (s, 3H, NCH_3), 3.01 (s, 3H, NCH_3); ^{13}C NMR (100.6 MHz) δ 10.8, 14.1,

22.7, 23.9, 26.5, 32.2, 33.4, 35.4, 36.2, 37.5, 37.7, 177.0; HRMS ($M+H^+$) requires *m*/*z*, 200.2014; found, 200.1996. The ee value was determined by chiral GC using an octakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin column, 0.25 μm i.d. (50% in OV1701, w/w) using the programme: 110 °C (isothermal). Retention times: **2** 48.4, *R*-**4** 38.6, *S*-**4** 41.6 min. The structural assignments are by analogy with **3**.

4.7. (*S*)-*N*,*N*-Dimethyl-3-methyl-octanamide 5

The compound was prepared using the procedure described in Section 4.4 with $CuBr{\cdot}SMe_2$ (15.2 mg, 0.074 mmol), (*R*,*R*)-MeDuphos (22.7 mg, 0.074 mmol), MeMgBr (0.65 mL, 3.0 M in Et_2O, 1.95 mmol), and a solution of **2** (250 mg, 1.48 mmol) in Et_2O (2 mL). Usual work up afforded a colorless liquid **5** (240 mg, 87%, 74% ee). $[\alpha]_D = +1.0$ (*c* 1.1, $CHCl_3$); IR 2995, 2951, 2887, 2841, 1628, 1497, 1461, 1399, 1380 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 3H, CH_2CH_3), 0.93 (d, *J* = 6.6 Hz, 3H, $CHCH_3$), 1.16–1.34 (m, 8H, 4 × CH_2), 1.99–2.04 (m, 1H, $CHCH_2$), 2.12 (dd, *J* = 14.6, 7.6 Hz, 1H, $COCH_{2\alpha}$), 2.30 (dd, *J* = 14.6, 5.6 Hz, 1H, $COCH_{2\beta}$), 2.95 (s, 3H, NCH_3), 3.01 (s, 3H, NCH_3); ^{13}C NMR (100.6 MHz) δ 14.1, 19.9, 22.7, 26.7, 30.3, 32.0, 35.4, 37.1, 37.5, 40.7, 172.8; HRMS ($M+H^+$) requires *m*/*z*, 186.1858; found, 186.1846. The ee value was determined by chiral GC using an octakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin column, 0.25 μm i.d. (50% in OV1701, w/w) using the programme: 110 °C (isothermal). Retention times: **1** 10.9, *R*-**5** 31.7, *S*-**5** 34.6 min. The structural assignments are by analogy with **3**.

4.8. (*S*)-*N*,*N*-Dimethyl-3-phenyl-butanamide 6

The compound was prepared using the procedure described in Section 4.4 with $CuBr{\cdot}SMe_2$ (22.6 mg, 0.11 mmol), (*R*,*R*)-MeDuphos (33.7 mg, 0.11 mmol), PhMgBr (0.95 mL, 3.0 M in Et_2O, 2.85 mmol), and a solution of **1** (250 mg, 2.21 mmol) in Et_2O (2 mL). Usual work up afforded a colorless liquid **6** (230 mg, 54%, of near racemic material). IR 3085, 3009, 2935, 1633, 1494, 1453, 1401, 1241 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$) δ 1.36 (d, *J* = 7.1 Hz, 3H, $CHCH_3$), 2.54 (dd, *J* = 7.9, 15.1 Hz, 1H, $CH_{2\alpha}CH$), 2.64 (dd, *J* = 6.0, 15.1 Hz, 1H, $CH_{2\beta}CH$), 2.89 (s, 3H, NCH_3), 2.93 (s, 3H, NCH_3), 3.39 (ddq, *J* = 6.0, 7.9, 7.1 Hz, 1H, $CHCH_3$), 7.25–7.34 (m, 5H, Ph); ^{13}C NMR (100.6 MHz) δ 21.6, 35.4, 36.5, 37.3, 41.9, 126.3, 126.9, 128.5, 146.6, 171.8; HRMS (M^++Na) requires *m*/*z*, 214.1208; found, 214.1195. These data were concurrent with published values.[13] Analysis on an octakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin column, 0.25 μm i.d. (50% in OV1701, w/w) using the programme: 110 °C (isothermal) showed the presence of the racemate: **1** 10.9, *enantiomer1* 45.2, *enantiomer2* 46.0 min.

4.9. (*E*)-(−)-(1′*R*,2′*R*)-*N*-Methyl-*N*-(2′-phenyl-2′-hydroxy-1′-methyethyl)-but-2-enemide 7

Crotonyl chloride (6.10 mL, 58.85 mmol) in THF (25 mL) was slowly added to a solution of (*R*,*R*)-(−)-pseudoephedrine (10.00 g, 58.85 mmol) and Et_3N (9.95 mL, 71.5 mmol) in dry THF (150 mL) at −20 °C. The reaction mixture was stirred at this temperature for 90 min, after which it was quenched with a saturated $NaHCO_3$ solution (100 mL). The mixture was extracted with AcOEt (3 × 100 mL) and the combined organic fractions were dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure affording **7** as a colorless crystalline solid (13.5 g, 92%), mp 100 °C. $[\alpha]_D = -162$ (*c* 1.0 $CHCl_3$); IR 3610, 3008, 1658, 1599, 1481, 1452, 1406, 1302, 1240, 1101, 1046, 965 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$) (3:1 rotamer ratio; ∗ indicates minor rotamer resonances) δ 1.00* (d, *J* = 6.9 Hz, 3H, 1′-$CHCH_3$), 1.16 (d, *J* = 7.0 Hz, 3H, 1′-$CHCH_3$), 1.90 (d, *J* = 6.9 Hz, 3H, 3-$CHCH_3$), 1.98* (d, *J* = 6.9 Hz, 3H, 3-$CHCH_3$), 2.89 (s, 3H, NCH_3), 2.95* (s, 3H, NCH_3), 4.49–4.51* (m, 2H, 1′,2′-CH), 4.51–4.53 (m, 2H, 1′,2′-CH), 6.21 (d, *J* = 15.0 Hz, 1H, 2-CH), 6.37* (d, *J* = 15.0 Hz, 1H, 2-CH), 6.82* (dq, *J* = 15.0, 7.2 Hz, 1H, 3-CH), 6.95 (dq, 1H, *J* = 15.0, 7.2 Hz, 1H, 3-CH), 7.31–7.44 (m, 5H, Ph both rotamers); ^{13}C NMR (100.6 MHz) δ 14.5, 15.5*, 18.3 (both rotamers), 27.2*, 32.7, 58.6*, 58.7, 75.5, 76.5*, 122.4, 122.7*, 126.2*, 226.5, 127.0*, 127.7, 128.4, 128.6, 140.8, 141.2, 142.5*, 142.6, 168.5*, 169.1 (CO both rotamers); HRMS (M^++Na) requires *m*/*z*, 256.1313; found, 256.1261.

4.10. (3*R*)- and (3*S*)-(1′*R*,2′*R*)-*N*-methyl-*N*-(2′-phenyl-2′-hydroxy-1′-methyethyl)-3-methylpentanamide 8a and 8b

Solid $CuBr{\cdot}SMe_2$ (10.2 mg, 0.05 mmol) and (*R*,*R*)-MeDuphos (15.2 mg, 0.05 mmol) were dissolved in 3 mL of freshly distilled Et_2O. The solution was stirred at room temperature for 20 min and then cooled to −30 °C. A solution of EtMgBr (1.0 mL, 3.0 M in Et_2O, 3.0 mmol) was added dropwise, and the resulting solution was stirred for further 5 min before a solution of **7** (233.3 mg, 1.00 mmol) in Et_2O:CH_2Cl_2 (1:1; 2 mL) was added dropwise. The reaction mixture was kept under stirring at that temperature for further 6 h. The reaction mixture was then quenched with 5 mL of 2 M HCl and extracted with ethyl acetate. Usual workup and purification by column chromatography (petrol/ethyl acetate 3:1) gave a 92:8 mixture of diastereomers **8a**–**b** as a colorless oil (250 mg, 95%, 84% de). $[\alpha]_D = -101$ (*c* 1.26, $CHCl_3$) for 84% de material. IR 3609, 3065, 3010, 2965, 2877, 1618, 1488, 1406, 1380, 1242, 1047, 1021 cm^{-1}; both diastereomers exist as a 3.7:1 mixtures of rotamers (∗ indicates minor rotamer resonances), due to its low population full assignment of **8b** could not be attained. For **8a**: ^1H NMR (400.1 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 0.93* (t, *J* = 7.2 Hz, 3H, CH_2CH_3), overlapped by 0.94 (d, *J* = 6.9 Hz, 3H, 1′-$CHCH_3$), 0.95* (d, *J* = 6.9 Hz, 3H, 1′-$CHCH_3$), 1.01* (d, *J* = 6.9 Hz, 3H, 3-$CHCH_3$), 1.15 (d, *J* = 6.9 Hz, 3H, 3-$CHCH_3$), overlapped by 1.01-1.28 (m, 3H, CH_2CH_3 and 3-CH both rotamers), 1.34-1.45 (m, 3H, CH_2CH_3 and 3-CH both rotamers), 1.72 (s, br, 1H, OH both rotamers), 2.13 (dd, *J* = 15.0, 7.7 Hz, 1H, $COCH_{2\alpha}$), 2.28 (dd, *J* = 15.0, 6.5 Hz, 1H, $COCH_{2\beta}$), 2.29* (dd, *J* = 14.9, 6.5 Hz, 1H, $COCH_{2\alpha}$), 2.42 (dd, *J* = 14.9, 5.9 Hz, 1H, $COCH_{2\beta}$), 2.84 (s, 3H, NCH_3), 2.94* (s, 3H, NCH_3), 4.44–4.64 (m, 1H, $CHOH$ both rotomers), 7.26–7.45 (m, 5H, Ph both rotamers); ^{13}C NMR (100.6 MHz) δ 11.4, 11.5*, 14.5, 15.4*, 19.4, 19.6*, 29.5, 29.6*, 31.8, 31.9*, 32.0 (br, NMe), 41.3, 40.7*, 58.5 (br 1′-CH both rotamers), 75.6*, 76.7, 126.3, 126.3*, 126.9*, 127.6, 128.4, 128.8*, 141.2*, 142.6, 173.9*, 175.3. For **8b**: ^1H NMR (400.1 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.0 Hz, 3H, CH_2CH_3), 0.87* (t, *J* = 7.0 Hz, 3H, CH_2CH_3), 2.90 (s, 3H, NCH_3), 4.05-4.08 (m, 1H, 1′-CH), 4.17–4.20* (m, 1H, 2′-CH′), other signal were overlapped by **8a** signals and could not be asigned; HRMS (M^++Na) requires *m*/*z*, 286.1783; found, 286.1725. The diastereoselectivity was determined by HPLC on a Daicel-OD column. 98:2 Hexane/Pr^iOH, 0.8 ml/min; *t*(3*R*,1′*R*,2′*R*) = 62.6 min for **8a**, *t*(3*S*,1′*R*,2′*R*) = 72.9 min for **8b**.

4.11. (−)-(3*R*,1′*R*, 2′*R*)-*N*-Methyl-*N*-(2′-phenyl-2′-hydroxy-1′-methyethyl)-3-methyloctanamide 9

Compound **9** was obtained according to the procedure described in Section 4.10 from **7** (233.3 mg, 1.00 mmol) using $CuBr{\cdot}SMe_2$ (10.2 mg, 0.05 mmol), (*R*,*R*)-MeDuphos (15.2 mg, 0.05 mmol), freshly distilled Et_2O (4 mL) and CH_2Cl_2 (1 mL), and $C_5H_{11}MgBr$ (1.5 mL, 2.0 M in Et_2O, 3.0 mmol) as a colorless oil (283 mg, 93%, 76% de). $[\alpha]_D = -88$ (*c* 1.13, $CHCl_3$). IR 3608, 3006, 2959, 2873, 2858, 1617, 1456, 1406, 1379, 1244, 1140, 1047, 1021 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$) (3.4:1 rotamer ratio; ∗ indicates minor rotamer resonances; minor diastereomer not assigned) δ 0.90 (t, *J* = 7.0 Hz, 3H, CH_2CH_3 both rotamers), 0.94 (d,

J = 6.8 Hz, 3H, 1′-CHCH_3), 0.95* (d, J = 6.7 Hz, 3H, 1′-CHCH_3), 1.00* (d, J = 6.9 Hz, 3H, 3-CHCH_3), 1.14 (d, J = 6.8 Hz, 3H, 3-CHCH_3), 1.23–1.44 (m, 8H, $(CH_2)_4$ both rotamers), 1.92–2.05 (m, 1H, 3-CHCH$_3$ both rotamers), 2.13 (dd, J = 14.6, 7.1 Hz, 1H, COCH$_{2\alpha}$), 2.27 (dd, J = 14.6, 6.1 Hz, 1H, COCH$_{2\beta}$) overlapped by 2.21–2.23* (m, 1H, COCH$_{2\alpha}$), 2.39* (dd, J = 14.9, 6.1, 1H, COCH$_{2\beta}$), 2.85 (s, 3H, NCH$_3$), 2.95* (s, 3H, NCH$_3$), 4.03–4.07* (m, 1H, 1′-CH), 4.44–4.47 (br, m, 1H, 2′-CH) overlapped by 4.44–4.47* (br, m, 1H, 2′-CH), 4.58–4.62 (m, 1H, 2′-CH), 7.31–7.44 (m, 5H, Ph both rotamers); ^{13}C NMR (100.6 MHz) δ 14.1 (both rotamers), 14.5, 15.4*, 19.9, 20.1*, 22.7 (both rotamers), 26.7, 26.8*, 30.2, 30.4*, 32.0 (both rotamers), 33.5 (br, NMe both rotamers), 37.0, 37.1*, 41.1*, 59.0 (br, 1′-CH both rotamers), 75.6*, 76.6, 126.3 (Ph-m major and Ph-p minor rotamers), 126.9*, 127.6, 128.3, 128.7*, 141.2*, 142.6, 173.9*, 175.3; HRMS (M$^+$+Na): m/z, 328.2247; found, 328.2254. The diastereoselectivity was determined by HPLC on a Daicel OJ-H column. 98:2 Hexane/Pr^{i}OH, 1 ml/min; t(3R,1′R,2′R) = 21.8 min for **9a**, t(3S,1′R,2′R) = 24.6 min for **9b**.

4.12. (−)-(1′*R*,2′*R*)-*N*-Methyl-*N*-(2′-phenyl-2′-hydroxy-1′-methyethyl)-3-phenylbutanamide 10

Compound **10** was obtained according to the procedure described in Section 4.10 from **7** using CuBr·SMe$_2$ (10.2 mg, 0.05 mmol), (*R*,*R*)-MeDuphos (15.2 mg, 0.05 mmol), freshly distilled Et$_2$O (4 mL), CH$_2$Cl$_2$ (1 mL), and PhMgBr (1.0 mL, 3.0 M in Et$_2$O, 3 mmol) as a colorless oil (275 mg, 88%, 89% de). [α]$_D$ = −77 (*c* 1.25, CHCl$_3$). IR 3610, 3009, 2936, 2877, 1622, 1493, 1454, 1406, 1378, 1313, 1239, 1134, 1019; ^{1}H NMR (400.1 MHz, CDCl$_3$) (2.77:1 rotamer ratio; ∗ indicates minor rotamer resonances; minor diastereomer not assigned) δ 0.89* (d, J = 6.8 Hz, 3H, 1′-CHCH_3), 1.02 (d, J = 6.8 Hz, 3H, 1′-CHCH_3), 1.34 (d, J = 7.0 Hz, 3H, both rotamers 3-CHCH_3), 2.54 (dd, J = 15.4, 7.6 Hz, 1H, COCH$_{2\alpha}$), 2.62 (dd, J = 15.4, 7.1 Hz, 1H, COCH$_{2\beta}$) overlapped by COCH$_2$ of minor rotamer, 2.74 (s, NCH$_3$), 2.91* (s, NCH$_3$), 3.36 (ddq, J = 7.6, 7.1, 6.8 Hz, 1H, PhCH), 3.49–3.51* (m, 1H, PhCH), 4.35–4.49 (br m, 1H, 1′ and 2′-CH both rotamers), 4.50–4.60 (br m, 1H, 1′ and 2′-CH both rotamers), 7.18–7.46 (m, 10H, Ph both rotamers), OH not detected due to exchange with water at 1.56 ppm; ^{13}C NMR (100.6 MHz) δ 14.5, 15.4*, 21.8, 21.9*, 32.8 br (both rotamers NMe), 36.4*, 36.6, 41.8*, 42.7, 58.4 (br, both rotamers 1′-CH), 75.4*, 76.6, 126.3, 126.4, 126.9, 127.6, 128.5, 128.9, 142.4, 146.3 172.8*, 174.2, complete assignment of the minor aryl rotamer signals could not be made due to overlaps except for the Ph-i signals at 141.1* and 146.8*; HRMS (M$^+$+Na): m/z, 334.17775; found, 334.1783. These data are comparable to those of the enantiomeric compound isolated by Badía.[3] The diastereoselectivity was determined by HPLC on a Daicel-OD column. 98:2 Hexane/Pr^{i}OH, 1 ml/min; t(3R,1′R,2′R) = 62.1 min for **10a**, t(3S,1′R,2′R) = 70.7 min for **10b**.

4.13. (3*R*,1′*R*,2′*R*)-*N*-Methyl-*N*-(2′-phenyl-2′-hydroxy-1′-methyethyl)-3-methylhex-5-enamide 11

Compound **11** was obtained according to the procedure described in Section 4.10 from **7** (233.3 mg, 1.00 mmol) using CuBr·SMe$_2$ (10.2 mg, 0.05 mmol), (*R*,*R*)-MeDuphos (15.2 mg, 0.05 mmol), freshly distilled Et$_2$O (4 mL), CH$_2$Cl$_2$ (1 mL), and allylmagnesiumbromide (3.0 mL, 1.0 M in Et$_2$O, 3 mmol) as a colorless oil (255 mg, 92%, 76% de). [α]$_D$ = −94 (*c* 0.84, CHCl$_3$). IR 3741, 3011, 1618, 1454, 1407, 1264, 1240, 1047, 1021, 918 cm^{-1}; ^{1}H NMR (400.1 MHz, CDCl$_3$) (3.33:1 rotamer ratio; ∗ indicates minor rotamer resonances; minor diastereomer not assigned) δ 0.96 (d, J = 6.6 Hz, 3H, 1′-CHCH_3), 1.00* 96 (d, J = 6.8 Hz, 3H, 1′-CHCH_3), 1.13 (d, J = 7.1 Hz, 3H, 3-CHCH_3) overlapped by 1.14* (d, J = 7.1 Hz, 3H, 3-CHCH_3), 1.94–2.48 (m, 4H, COCH$_2$ and CH$_2$ allyl both rotamers), 2.83 (s, 3H, NCH$_3$), 2.93* (s, 3H, NCH$_3$), 3.99–4.06* (m, 1H, 1′-CH), 4.38–4.52 (m, 1H, 1′-CH and 2′-CH minor rotamer), 4.55–4.58 (m, 1H, 2′-CH), 5.00–5.08 (m, 2H, =CH$_2$ both rotamers), 5.75–5.84 (m, 1H, =CH both rotamers), 7.26–7.42 (m, 5H, Ph both rotamers); ^{13}C NMR (100.6 MHz) δ 14.5, 15.4*, 19.8, 20.0*, 29.9, 30.1*, 33.2 (both rotamers NMe), 40.2*, 40.6, 41.1, 41.3*, 58.4*, 58.8, 75.5*, 76.6, 116.2*, 116.4, 126.4, 126.9, 127.6*, 128.4, 128.4*, 128.7*, 136.7, 137.1*, 141.2*, 142.5, 173.6*, 174.9; HRMS (M$^+$+Na): m/z, 298.17775; found, 298.1497. The diastereoselectivity was determined by HPLC on a Daicel AD-H column. 98:2 Hexane/Pr^{i}OH, 1 ml/min; t(3R,1′R,2′R) = 43.0 min for **11a**, t(3S,1′R,2′R) = 47.1 min for **11b**.

4.14. (3*R*,1′*R*,2′*R*)-*N*-Methyl-*N*-(2′-phenyl-2′-hydroxy-1′-methyethyl)-3-methylpent-4-enamide 12

Compound **12** was obtained according to the procedure described in Section 4.10 from **7** (233.3 mg, 1.00 mmol) using CuBr·SMe$_2$ (10.2 mg, 0.05 mmol), (*R*,*R*)-MeDuphos (15.2 mg, 0.05 mmol), freshly distilled Et$_2$O (4 mL), CH$_2$Cl$_2$ (1 mL), and vinylmagnesiumbromide (3.0 mL, 1.0 M in THF, 3.0 mmol) as a colorless oil (235 mg, 90%, 57% de). [α]$_D$ = −93 (*c* 1.05, CHCl$_3$). IR 3691, 3010, 1621, 1483, 1407, 1375, 1240, 1047, 1020, 920 cm^{-1}; ^{1}H NMR (400.1 MHz, CDCl$_3$) (3.09:1 rotamer ratio; ∗ indicates minor rotamer resonances; minor diastereomer not assigned) δ 1.00* (d, J = 6.9 Hz, 3H, 1′-CHCH_3), 1.07 (d, J = 6.9 Hz, 3H, 1′-CHCH_3) overlapped by 1.08* (d, J = 6.9 Hz, 3H, 3′-CHCH_3) 1.11 (d, J = 6.9 Hz, 3H, 3-CHCH_3), 2.24–2.45 (m, 2H, COCH$_2$ both rotamers), 2.71–2.77 (m, 1H, 3-CHCH$_3$ both rotamers), 2.84 (s, 3H, NCH$_3$), 2.93* (s, 3H, NCH$_3$), 4.00–4.07* (m, 1H, 1′-CH), 4.29 (br, 1H, 1′-CH), 4.45–4.53 (m, 1H, 2′-CH), 4.55–4.64 (m, 1 H, 2′-CH both rotamers), 4.93–5.08 (m, 2H, =CH$_2$ both rotamers), 5.77–5.89 (m, 1H, =CH both rotamers), 7.26–7.41 (m, 5H, Ph); ^{13}C NMR (100.6 MHz) δ 14.6, 15.4*, 19.6*, 19.8, 33.0 br (both rotamers NMe), 34.2, 34.3*, 40.3*, 40.9, 58.3 br (both rotamers 1-CH), 75.5*, 76.5, 112.9*, 113.0, 126.4, 126.9*, 127.7, 128.4 (Ph-o major and Ph-p minor rotamers), 128.7*, 141.2*, 142.4, 143.1, 143.6*, 172.9*, 174.3; HRMS (M$^+$+Na): m/z, 284.16210; found, 284.1336. The diastereoselectivity was determined by HPLC on a Daicel AD-H column. 98:2 Hexane/Pr^{i}OH, 1 ml/min; t(3R,1′R,2′R) = 42.0 min for **12a**, t(3S,1′R,2′R) = 45.1 min for **12b**.

4.15. (−)-(2*R*,3*R*,1′*R*,2′*R*)-*N*-Methyl-*N*-(2′-phenyl-2′-hydroxy-1′-methyethyl)-2-allyl-3-methylpentanamide 13

Compound **13** was obtained using a modification of procedure described in Section 4.10 from **7** (233.3 mg, 1.00 mmol) using CuBr·SMe$_2$ (10.2 mg, 0.05 mmol), (*R*,*R*)-MeDuphos (15.2 mg, 0.05 mmol), freshly distilled Et$_2$O (4 mL), CH$_2$Cl$_2$ (1 mL), and EtMgBr (3.0 mL, 3.0 M in Et$_2$O, 3 mmol). After 3 h at −30 °C neat allyl bromide (0.13 mL, 1.5 mmol) was added at this temperature. After 6 h at −30 °C, the mixture was allowed to come to room temperature overnight. Usual workup followed by column chromatography (petrol/ethyl acetate 5:1) afforded **13** as a colorless oil (268 mg, 88%, 92% de by HPLC). [α]$_D$ = −73 (*c* 1.05, CHCl$_3$). IR 3691, 3008, 2968, 2935, 2877, 1710, 1611, 1482, 1455, 1414, 1363, 1240, 1047 cm^{-1}; ^{1}H NMR (400.1 MHz, CDCl$_3$) (3.09:1 rotamer ratio; ∗ indicates minor rotamer resonances; minor diastereomer not fully assigned) δ 0.86* (t, J = 7.1 Hz, 3H, CH$_2$$CH_3$), 0.90 (t, J = 7.1 Hz, 3H, CH$_2$$CH_3$), overlapped by 0.92 (d, J = 6.9 Hz, 3H, 1′-CHCH_3) and 0.93* (d, J = 6.9 Hz, 3H, 1′-CHCH_3), 0.99* (d, J = 6.9 Hz, 3H, 3-CHCH_3), 1.12 (d, J = 6.9 Hz, 3H, 3-CHCH_3), overlapped by 1.00–1.31 (m, 3H, CH_2CH$_3$ and 3-CH both rotamers), 1.53–1.76 (m, 3H, CH_2CH$_3$ and 3-CH both rotamers) overlapped by 1.71 (s, br, 1H, OH both rotamers), 2.22–2.63 (m, 3H, =CHCH_2 and COCH$_2$ both rotamers), 2.83 (s, 3H, NCH$_3$), 2.92* (s, 3H, NCH$_3$), 4.41–4.71 (m, 1H, CHOH both rotamers), 4.92–5.19 (m,

2H, $=CH_2$ both rotamers), 5.59–5.67* (m, 1H, =CH), 5.82–5.96 (m, 1H, $=CH_2$ minor diastereomer), 5.72–5.82 (m, 1H, $=CH_2$), 7.26–7.45 (m, 5H, Ph both rotamers); ^{13}C NMR (100.6 MHz) δ 11.0, 11.7*, 14.7, 15.4*, 17.0 (both rotamers $CHCH_3$), 25.8, 27.5*, 33.9*, 33.8 (both rotamers NMe), 34.6, 36.9, 37.2*, 47.5, 47.6*, 59.0 (both rotamers 1′-CH), 75.5*, 76.4, 116.3, 116.6*, 126.4, 127.1, 127.5*, 128.3, 128.4*, 128.7*, 136.3, 136.4*, 141.3*, 142.5, 177.7 (both rotamers CO).; HRMS (M^++Na): m/z, 326.20905; found, 326.2114. The diastereoselectivity was determined by HPLC on a Daicel-OJ-H column; 98:2 Hexane/Pr^{i}OH, 0.5 ml/min; t(3*R*,1′*R*,2′*R*) = 18.2 min for **13a**, t(3*S*,1′*R*,2′*R*) = 19.8 min for **13b** (2*R*,3*S* enantiomer of **13a**).

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