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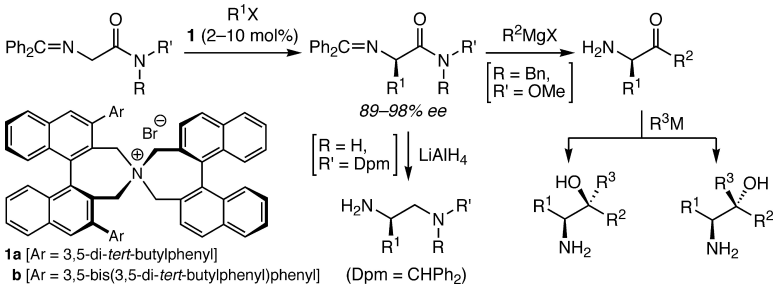

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Highly Enantioselective Phase-Transfer-Catalyzed Alkylation of Protected α-Amino Acid Amides toward Practical Asymmetric Synthesis of Vicinal Diamines, α-Amino Ketones, and α-Amino Alcohols

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Abstract: Highly enantioselective alkylation of protected glycine diphenylmethyl (Dpm) amide **1** and Weinreb amide **10** has been realized under phase-transfer conditions by the successful utilization of designer chiral quaternary ammonium salts of type **4** as catalyst. Particularly, remarkable reactivity of the chiral ammonium enolate derived from **1b** and **4c** allowed the reaction with less reactive simple secondary alkyl halides with high efficiency and enantioselectivity. An additional unique feature of this chiral ammonium enolate is its ability to recognize the chirality of β-branched primary alkyl halides, which provides impressive levels of kinetic resolution and double stereodifferentiation during the alkylation, allowing for two α- and γ-stereocenters to be controlled. Combined with the subsequent reduction using $LiAlH_4$ in cyclopentyl methyl ether (CPME), this system offers a facile access to structurally diverse optically active vicinal diamines. Furthermore, the optically active α-amino acid Weinreb amide **11** can be efficiently converted to the corresponding amino ketone by a simple treatment with Grignard reagents. In addition, reduction and alkylation of the optically active α-amino ketone into both syn and anti α-amino alcohols with almost complete relative and absolute stereochemical control have been achieved. With (*S*,*S*)- and (*R*,*R*)-**4** in hand, the present approach renders both enantiomers of α-amino amides including Weinreb amides readily available with enormous structural variation and also establishes a general and practical route to vicinal diamines, α-amino ketones, and α-amino alcohols with the desired stereochemistry.

Introduction

Research on the development of useful yet practical methods for creating chiral nonracemic organic molecules from prochiral substrates by chiral phase-transfer catalysis is a rapidly growing area in organic chemistry.[1] In particular, extensive studies have been made on the catalytic asymmetric functionalization of protected glycine derivatives mainly due to prime value of the product as optically active α-amino acid derivatives.[2] This process seems to have reached a level of sophistication with the recent emergence of new catalysts and the modification of reaction conditions specifically using glycine esters as a key substrate.[3] In turn, little attention has been given to the advantages of the characteristic property of other glycine derivatives such as glycine amides, and the effectiveness of chiral phase-transfer catalysis in the asymmetric bond construction on prochiral glycine amide derivatives has actually remained unexplored.[4,5] During the course of our effort to expand the scope of the phase-transfer catalysis of designer chiral quaternary

(1) For reviews, see: (a) Shioiri, T. In *Handbook of Phase-Transfer Catalysis*; Sasson, Y., Neumann, R., Eds.; Blackie Academic & Professional: London, 1997; Chapter 14. (b) O'Donnell, M. J. *Phases − The Sachem Phase Transfer Catalysis Review* **1998**, *Issue 4*, 5. (c) O'Donnell, M. J. *Phases − The Sachem Phase Transfer Catalysis Review* **1999**, *Issue 5*, 5. (d) Shioiri, T.; Arai, S. In *Stimulating Concepts in Chemistry*; Vogtle, F., Stoddart, J. F., Shibasaki, M., Eds.; Wiley−VCH: Weinheim, 2000; p 123. (e) O'Donnell, M. J. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley−VCH: New York, 2000; Chapter 10.

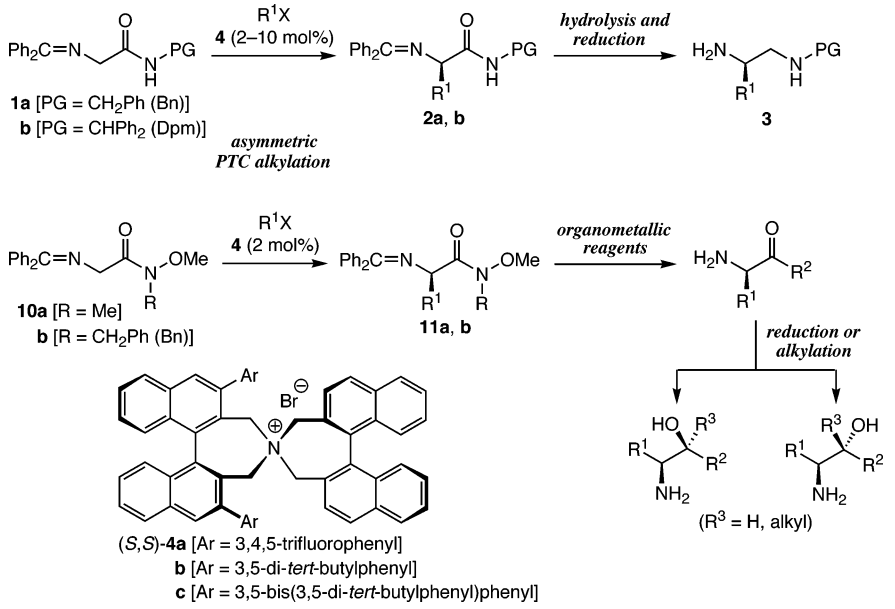
(2) For reviews, see: (a) Abellán, T.; Chinchilla, R.; Galindo, N.; Guillena, G.; Nájera, C.; Sansano, J. M. *Eur. J. Org. Chem.* **2000**, 2689. (b) O'Donnell, M. J. *Aldrichimica Acta* **2001**, *34*, 3. (c) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.

(3) See, for example: (a) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *J. Org. Chem.* **2002**, *67*, 7418. (b) Kita, T.; Georgieva, A.; Hashimoto, Y.; Nakata, T.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2832. (c) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-k.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-s. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036. (d) Arai, S.; Tsuji, R.; Nishida, A. *Tetrahedron Lett.* **2002**, *43*, 9535. (e) Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 9539. (f) Sasai, H. *Jpn. Kokai Tokkyo Koho* **2003**, JP2003335780. (g) Lygo, B.; Allbutt, B. *Synlett* **2004**, 326.

(4) For diastereoselective transformation involving substrates with chiral auxiliaries, see: (a) Oppolzer, W.; Moretti, R.; Zhou, C. *Helv. Chim. Acta* **1994**, *77*, 2363. (b) López, A.; Pleixats, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1967. (c) Abellán, T.; Nájera, C.; Sansano, J. M. *Tetrahedron: Asymmetry* **1998**, *9*, 2211. (d) Guillena, G.; Nájera, C. *Tetrahedron: Asymmetry* **1998**, *9*, 3935. (e) Nájera, C., Abellán, T.; Sansano, J. M. *Eur. J. Org. Chem.* **2000**, 2809. (f) Guillena, G.; Nájera, C. *Tetrahedron: Asymmetry* **2001**, *12*, 181. (g) Kim, H. J.; Lee, S.-k.; Park, Y. S. *Synlett* **2001**, 613. (h) Deng, W.-P.; Wong, K. A.; Kirk, K. L. *Tetrahedron: Asymmetry* **2002**, *13*, 1135. For the sole example of catalytic asymmetric alkylation with moderate enantioselectivity, see: (i) Kumar, S.; Ramachandran, U. *Tetrahedron: Asymmetry* **2003**, *14*, 2539.

(5) For recent representative examples of a non-PTC system, see: (a) Reyes, A.; Juaristi, E. *Tetrahedron: Asymmetry* **2000**, *11*, 1411. (b) Palomo, C.; Aizpurua, J. M.; Galarza, R.; Benito, A.; Khamrai, U. K.; Eikeseth, U.; Linden, A. *Tetrahedron* **2000**, *56*, 5563. (c) Guillena, G.; Nájera, C. *J. Org. Chem.* **2000**, *65*, 7310. (d) Buenadicha, F. L.; Avendaño, C.; Söllhuber, M. *Tetrahedron: Asymmetry* **2001**, *12*, 3019. (e) Caddick, S.; Parr, N. J.; Pritchard, M. C. *Tetrahedron* **2001**, *57*, 6615. (f) Carlier, P. R.; Zhao, H.; DeGuzman, J.; Lam, P. C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 11482.

Scheme 1. Phase-Transfer-Catalyzed Asymmetric Alkylation of Protected Glycine Amides **1** and **10** Using Chiral Quaternary Ammonium Bromides **4**, and Its Synthetic Utility



ammonium bromides of type **4**,[6] we considered it important to address this issue in light of the interest not only in the utility of optically active α-amino amide itself[7] but also in the ample possibility of accessing other versatile chiral building blocks through additional appropriate functionalizations. In this Article, we describe the development of general, highly enantioselective alkylation of protected glycine diphenylmethyl (Dpm) amide **1b** and Weinreb amide **10** by utilizing **4** as an efficient phase-transfer catalyst (Scheme 1), and we emphasize its characteristic features.[8] The fruitful synthetic opportunity offered by this achievement has been clearly visualized by the facile transformation of the resulting alkylation product **2b** into the corresponding optically active vicinal diamines **3**, and of **11b** into the corresponding α-amino ketones, respectively. The optically active α-amino ketones thus obtained can further be derivatized to syn and anti α-amino alcohols with rigorous stereochemical control. Because both enantiomers of the catalyst **4** are available, the present approach allows practical asymmetric synthesis of those valuable chiral compounds with the desired relative and absolute stereochemistries.

Results and Discussion

1. Highly Enantioselective Alkylation of Protected α-Amino Acid Amides: Asymmetric Synthesis of Vicinal Diamines. We started examining the feasibility of stereoselective alkylation of prochiral glycine amide derivatives under typical liquid−liquid phase-transfer conditions with benzophenone Schiff base of glycine benzyl amide **1a** as a representative substrate and *N*-spiro chiral quaternary ammonium bromide (*S*,*S*)-**4a**[6a,b] as catalyst. Treatment of **1a** with 1.2 equiv of benzyl bromide and 2 mol % of (*S*,*S*)-**4a** in toluene-50% KOH aqueous solution (volume ratio = 3:1) at 0 °C for 10 h gave only a trace amount of the corresponding alkylation product **2a** (R^1 = CH_2Ph). In contrast, however, the reaction proceeded smoothly under similar conditions with (*S*,*S*)-**4b**[6c] having 3,5-di-*tert*-butylphenyl substituent as catalyst, furnishing **2a** ($R^1 = CH_2Ph$) almost quantitatively with 36% ee. This observation suggesting the importance of the steric effect of the 3,3′-aromatic substituent of **4** prompted us to conduct the alkylation with sterically more hindered (*S*,*S*)-**4c**[6c] as catalyst, leading to the production of **2a** ($R^1 = CH_2Ph$) with promising enantioselectivity (69% ee). We then investigated the influence of the amide protecting group (PG) on the reactivity and selectivity, where glycine diphenylmethyl (Dpm) amide derivative **1b** was identified as a key substrate and the phase-transfer catalytic benzylation of **1b** in the presence of (*S*,*S*)-**4c** afforded the desired α-amino amide **2ba** in 98% yield with 92% ee (entry 1 in Table 1). This procedure tolerates a variety of primary alkyl halides, and the representative results are listed in Table 1. It should be noted that the use of saturated CsOH is beneficial to constantly attain high chemical yield in the reactions with simple aliphatic alkyl halides (entries 3 and 4).

Quite interestingly, the present system consisting of glycine amide derivative **1b** and the chiral catalyst **4c** exhibited remarkable reactivity, enabling the catalytic asymmetric alkylation of the glycine anion equivalent with less reactive secondary alkyl halides.[4a,9,10] For instance, reaction of **1b** with 2-iodopropane (5 equiv) under otherwise similar conditions gave rise to **2be** in 82% yield with 82% ee (entry 5). Here, use of mesitylene in place of toluene enhanced the enantioselectivity to 90% ee, and increase of the catalyst loading to 5 mol % led

(6) (a) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228. (b) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139. (c) Ooi, T.; Tayama, E.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 579. See also ref 2c.

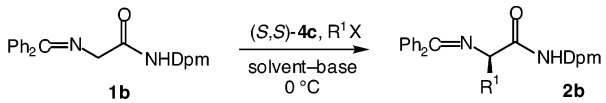
(7) See, for example: (a) Rockwell, A.; Melden, M.; Copeland, R. A.; Hardman, K.; Decicco, C. P.; DeGrado, W. F. *J. Am. Chem. Soc.* **1996**, *118*, 10337. (b) Kaljuste, K.; Tam, J. P. *Tetrahedron Lett.* **1998**, *39*, 9327. (c) Liu, G.; Kozmina, N. S.; Winn, M.; von Geldern, T. W.; Chiou, W. J.; Dixon, D. B.; Nguyen, B.; Marsh, K. C.; Opgenorth, T. J. *J. Med. Chem.* **1999**, *42*, 3679. (d) Fray, M. J.; Burslem, M. F.; Dickinson, R. P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 567.

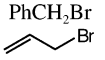
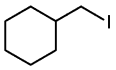
(8) Preliminary communication of this study: Ooi, T.; Sakai, D.; Takeuchi, M.; Tayama, E.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 5868.

(9) For a diastereoselective approach, see: (a) McIntosh, J. M.; Leavitt, R. K.; Mishra, P.; Cassidy, K. C.; Drake, J. E.; Chadha, R. *J. Org. Chem.* **1988**, *53*, 1947. (b) Seebach, D.; Hoffmann, M. *Eur. J. Org. Chem.* **1998**, *1337*.

(10) For O'Donnell's recent contribution using elegant boron alkylation chemistry, see: O'Donnell, M. J.; Drew, M. D.; Cooper, J. T.; Delgado, F.; Zhou, C. *J. Am. Chem. Soc.* **2002**, *124*, 9348. See also: O'Donnell, M. J.; Cooper, J. T.; Mader, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 2370.

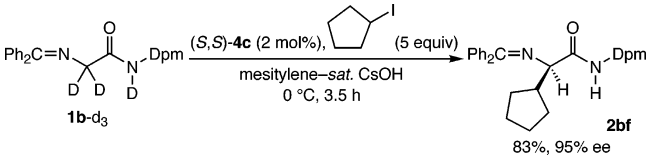
Table 1. Catalytic Enantioselective Phase-Transfer Alkylation of **1b**[a]



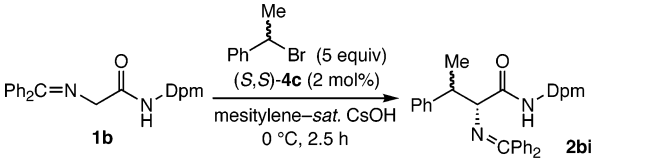
entry	R^1X	mol% of **4c**	solvent	base	react time (h)	% yield [b]	% ee [c] (config) [d]	prod.
1 [e]	$PhCH_2Br$	2	toluene	50% KOH	3	98	92 (*R*)	**2ba**
2 [e]		2			2	99	98 (*R*)	**2bb**
3 [e]	BuI	2		*sat*. CsOH	3	94	97 (*R*)	**2bc**
4 [e]		2			3	82	98 (*R*)	**2bd**
5		2			5	82	82 (*R*)	**2be**
6		2	mesitylene		5	81	90 (*R*)	
7		5			5	90	90 (*R*)	
8		2			3	91	96	**2bf**
9 [f]		10			5	71	95	**2bg**
10		10			3	80	89	**2bh**

[a] Unless otherwise specified, the reaction was carried out with 5 equiv of R^1X in the presence of a catalytic amount of (*S*,*S*)-**4c** under the given reaction conditions. [b] Isolated yield. [c] Enantiopurity was determined by HPLC analysis of the alkylated imine using a chiral column [DAICEL Chiralcel OD (entry 1), Chiralcel OD-H (entry 2), and Chiralpak AD (entries 3−10)] with hexane-2-propanol as solvent. [d] Absolute configuration was determined by comparison of the HPLC retention time with the authentic sample independently synthesized. [e] With 1.2 equiv of R^1X. [f] Use of 10 equiv of iodocyclohexane.

Scheme 2. Complete Protonation of Deuterium Labeled **1b**-d_3 under the Typical Asymmetric Alkylation Conditions



Scheme 3. Attempt for Stereoselective Alkylation of **1b** with Racemic 1-Bromo-1-phenylethane



to improvement of the chemical yield (entries 6 and 7). Various cycloalkyl side chains can also be introduced in satisfactory chemical yields with excellent enantioselectivities using 2−10 mol % of (*S*,*S*)-**4c** as catalyst (entries 8−10), greatly expanding the scope of this method.

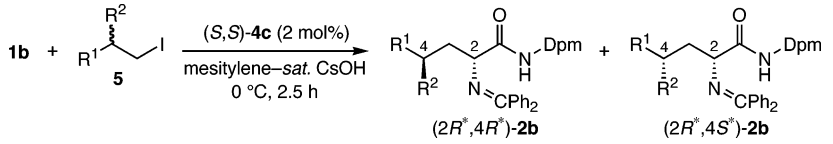
Although the origin of the observed high reactivity is unclear, we conducted the following experiment to gain an insight into it. Deuterium labeled **1b**-d_3 was prepared and exposed to the typical asymmetric alkylation conditions, which furnished the product **2bf** with complete protonation (Scheme 2). This result suggests that the initial generation of the cesium enolate by the deprotonation of **1b** would be in equilibrium with the reverse protonation process and also implies the intervention of the dianion species as a reactive nucleophile.

Given the vast potential of this new asymmetric methodology, we next focused our attention on the investigation of the alkylation with alkyl halides having stereogenic carbon centers, that is, the possibility of diastereo- and enantioselective alkylation through kinetic resolution of racemic alkyl halides.[11] Initially, we attempted the reaction of **1b** with racemic secondary alkyl halide, 1-bromo-1-phenylethane, under the optimized phase-transfer conditions using (*S*,*S*)-**4c** as catalyst; this unfortunately afforded a nearly equimolar mixture of two diastereomers, and the enantiomeric excess of each isomer was determined to be 61% and 33% ee, respectively, as shown in Scheme 3.

To our surprise, however, the alkylation of **1b** with β-branched, racemic primary halide, 1-iodo-2-phenylpropane (**5a**), was found to proceed stereoselectively under similar conditions to give (2*R*,4*R*) isomer predominantly [(2*R*,4*R*)-**2bj**/(2*R*,4*S*)-**2bj** = 91:9] in an essentially enantiopure form (99% ee) (entry 1 in Table 2). This finding indicates that the emergent diastereochemical preference toward (2*R*,4*R*) isomer would directly reflect an additional yet distinct ability of the chiral quaternary ammonium cation of **4c** to recognize the chirality of the rather remote β-carbon of the halide through this alkylation event. Indeed, (*S*,*S*)-**4c**-catalyzed alkylation of **1b** with optically pure (*S*)-**5a** under otherwise identical phase-transfer conditions resulted in

(11) Only a few yet important contributions to the phase-transfer-catalyzed alkylation of glycinate Schiff base with optically active alkyl halides have recently been reported. Unfortunately, however, notable double stereodifferentiation and kinetic resolution have never been demonstrated. See: (a) Lépine, R.; Carbonnelle, A.-C.; Zhu, J. *Synlett* **2003**, 1455. (b) Armstrong, A.; Scutt, J. N. *Org. Lett.* **2003**, *5*, 2331.

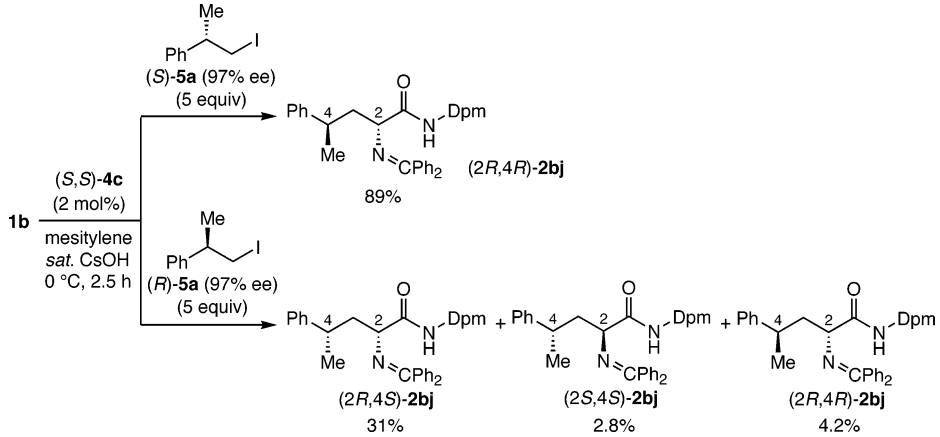
Table 2. Diastereo- and Enantioselective Alkylation of **1b** through Kinetic Resolution of β-Branched Racemic Primary Alkyl Halide **5** under Phase-Transfer-Catalyzed Conditions[a]



entry	R^1	R^2	% yield[b]	(2R*,4R*)/(2R*,4S*)[c]	% ee[d] (config)[e] (2R*,4R*)	% ee[d] (config)[e] (2R*,4S*)	prod.
1	Ph	Me (**5a**)	89	91:9	99 (2*R*,4*R*)	93 (2*R*,4*S*)	**2bj**
2	*p*-Me-C_6H_4	Me (**5b**)	80	92:8	97	89	**2bk**
3	*c*-Hex	Me (**5c**)	93	93:7	97	90	**2bl**
4	Ph	Bu (**5d**)	87	80:20	98	83	**2bm**

[a] The reaction was carried out with 5 equiv each of **5** and saturated CsOH in the presence of 2 mol % of (*S*,*S*)-**4c** in toluene at 0 °C for 2.5 h. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Enantiopurity was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H) with hexane-2-propanol or ethanol as solvent. [e] Relative and absolute configurations were established by the reactions with independently prepared (*R*)- and (*S*)-**5a**.

Scheme 4. Double Stereodifferentiation during the Alkylation of **1b** with Optically Pure 1-Iodo-2-phenylpropane (**5a**)



a very clean formation of (2*R*,4*R*)-**2bj** as a single stereoisomer, while the reaction of **1b** with the (*R*)-**5a** in the presence of (*S*,*S*)-**4c** was sluggish and eventually generated three stereoisomers including (2*S*,4*S*)-**2bj** in 38% combined yield (Scheme 4). The observed considerable double stereodifferentiation confirmed that (*S*)-**5a** is a matched halide for the (*S*,*S*)-**4c**-catalyzed alkylation.[12] It is of interest that the degree of the diastereoselectivity through the kinetic resolution process was subtly affected by the electronic property of the substituent R^1 of **5** and rather sensitive to the steric demand of R^2 as is evident from other representative results listed in Table 2 (entries 2−4).

With this general asymmetric alkylation protocol in hand, we next pursued the transformation of **2b** to the corresponding vicinal diamine through simple reduction.[13,14] This interest certainly originated from the great importance of optically active vicinal diamines as a structural component of various compounds with a broad spectrum of biological activity[15] and also as chiral metal ligands and auxiliaries in asymmetric synthesis.[16] An initial attempt was made by acidic hydrolysis of the imine moiety of **2ba** followed by treatment with $LiAlH_4$ in refluxing THF, giving optically active partially protected vicinal diamine **3a** with complete preservation of the enantiomeric excess, but a considerable amount of intermediary amino amide remained unreacted. Therefore, we tuned the conditions of the reduction process and found that **3a** was obtained in 96% yield by performing the reduction in cyclopentyl methyl ether (CPME) at 100 °C (entry 1 in Table 3). The efficiency of the present transformation was not affected by the structure of the newly introduced α-side chain (Table 3). Starting from protected glycine Dpm amide **1b**, this procedure provides a straightforward yet convenient way to obtain a wide range of optically active monosubstituted vicinal diamines without being afraid of partial racemization.

The robustness of our approach was highlighted by application to the highly enantioselective quaternization of α-amino acid diphenylmethyl amide-derived aldimine Schiff base **6**, enabling catalytic asymmetric synthesis of optically active vicinal diamines possessing quaternary stereogenic centers. Vigorous stirring of the mixture of **6a**, allyl bromide (1.2 equiv),

(12) For double asymmetric induction, see: (a) Horeau, A.; Kagan, H. B.; Vigneron, J. P. *Bull. Chim. Soc. Fr.* **1968**, 3795. (b) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

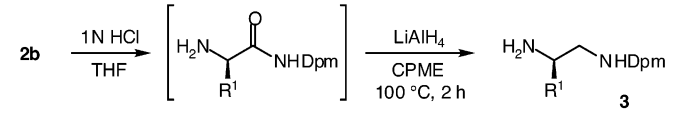
(13) (a) Buono, G.; Triantaphylides, C.; Peiffer, G.; Petit, F. *Synthesis* **1982**, 1030. (b) Brunner, H.; Schmidt, M.; Unger, G.; Schönenberger, H. *Eur. J. Med. Chem. Chim. Ther.* **1985**, *20*, 509. (c) Rossiter, B. E.; Eguchi, M.; Miao, G.; Swingle, N. M.; Hernández, A. E.; Vickers, D.; Fluckiger, E.; Patterson, R. G.; Reddy, K. V. *Tetrahedron* **1993**, *49*, 965. (d) Modin, S. A.; Andersson, P. G. *J. Org. Chem.* **2000**, *65*, 6736.

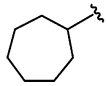
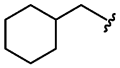
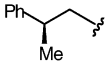
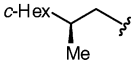
(14) For a recent excellent review on the stereoselective synthesis of vicinal diamines, see: (a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2581 and references therein. For selected leading references, see also: (b) Enders, D.; Schiffers, R. *Synthesis* **1996**, 53. (c) Alexakis, A.; Aujard, I.; Mangeney, P. *Synlett* **1998**, 873. (d) Alvaro, G.; Grilli, S.; Martelli, G.; Savoia, D. *Eur. J. Org. Chem.* **1999**, 1523. (e) Yamada, K.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3504. (f) Demay, S.; Kotschy, A.; Knochel, P. *Synthesis* **2001**, 863. (g) Saravanan, P.; Bisai, A.; Baktharaman, S.; Chandrasekhar, M.; Singh, V. K. *Tetrahedron* **2002**, *58*, 4693. (h) Ashweek, N. J.; Coldham, I.; Haxell, T. F. N.; Howard, S. *Org. Biomol. Chem.* **2003**, *1*, 1532.

(15) Michalson, E. T.; Szmuszkovicz, J. *Prog. Drug. Res.* **1989**, *33*, 135.

(16) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497.

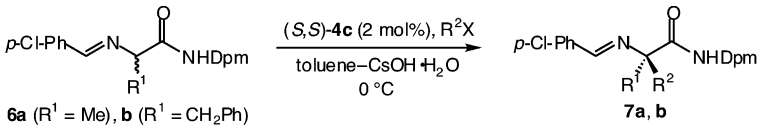
Table 3. Facile Conversion of **2b** to Optically Active Vicinal Diamines **3**[a]

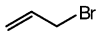
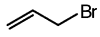


entry	R^1	% yield [b]	prod. [c]	entry	R^1	% yield [b]	prod. [c]
1	$PhCH_2$	96	**3a**	6		97	**3f**
2		88	**3b**	7		90	**3g**
3	Bu	91	**3c**	8		85	**3h**
4		92	**3d**	9		81	**3i**
5	*i*-Pr	>99	**3e**	10		80	**3j**

[a] The hydrolysis was conducted by the simple treatment of **2b** with 1 N HCl in THF, and the subsequent reduction was carried out with 4 equiv of $LiAlH_4$ in CPME at 100 °C. [b] Isolated yield. [c] Enantiopurity was determined by HPLC analysis.

Table 4. Catalytic Enantioselective Quaternization of α-Amino Acid-Derived Dpm Amide Aldimine Schiff Base **6**[a]



entry	substrate	R^2X	react time (h)	% yield [b]	% ee [c] (config) [d]	prod.
1	**6a**		3	93	93	**7aa**
2 [e]		BuI	3	82	93	**7ab**
3 [e,f]			3	81	90 (*R*)	**7ac**
4	**6b**		10	84	82	**7ba**

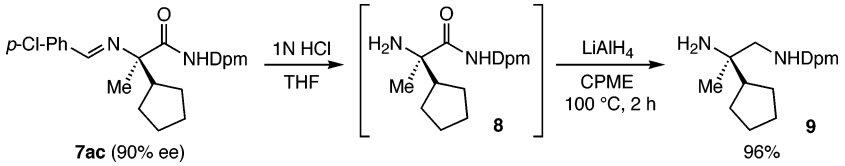
[a] Unless otherwise noted, the reaction was carried out with 1.2 equiv of R^2X and 5 equiv of $CsOH·H_2O$ in the presence of 2 mol % of (*S*,*S*)-**4c** in toluene at 0 °C for the given reaction time. [b] Isolated yield. [c] Enantiopurity was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H) with hexane-2-propanol or hexanes−ethanol as solvent. [d] Absolute configuration was determined by X-ray crystallographic analysis after conversion to the dipeptide with *N*-benzyloxycarbonyl-L-alanine. [e] With 5 equiv of R^1X. [f] Use of mesitylene as solvent.

$CsOH·H_2O$ (5 equiv), and (*S*,*S*)-**4c** (2 mol %) in toluene at 0 °C for 3 h gave rise to the desired α,α-dialkyl-α-amino amide **7aa** in 93% yield with 93% ee (entry 1 in Table 4). As we expected, reactions with simple primary and secondary alkyl halides, iodobutane and iodocyclopentane, also proceeded smoothly to afford the corresponding quaternization products **7ab** and **7ac**, respectively, with excellent asymmetric induction (entries 2 and 3). In addition, alkylation of phenylalanine-derived **6b** appeared feasible under similar conditions (entry 4). The enantiomerically enriched quaternary α-amino amide **7** thus obtained can be cleanly transformed into the corresponding partially protected diamine as demonstrated in the preparation of **9** having a sterically congested quaternary carbon center, which is not readily accessible by ordinary asymmetric methodologies (Scheme 5).

2. Highly Enantioselective Alkylation of Protected Glycine Weinreb Amides: Asymmetric Synthesis of α-Amino Ketones and α-Amino Alcohols. To further explore the possibility and advantage of the phase-transfer-catalyzed alkylation of α-amino acid amide derivatives, we next chose protected glycine-derived Weinreb amide **10** as an intriguing substrate.[17] If direct stereoselective introduction of the requisite α-substituent on **10** becomes feasible, unique reactivity of the Weinreb amide moiety toward organometallic reagents makes it a reliable and practical entry to a broad range of optically active α-amino ketones, particularly those not obtainable from natural α-amino acids.[18,19] The potential utility of this approach is tightly

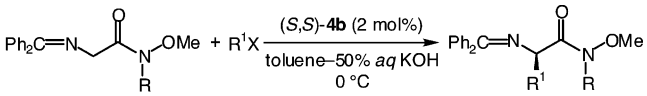
(17) O'Donnell, M. J.; Drew, M. D.; Pottorf, R. S.; Scott, W. L. *J. Comb. Chem.* **2000**, *2*, 172.
(18) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

Scheme 5. Preparation of Vicinal Diamine **9** from **7ac** via Acidic Hydrolysis and Reduction

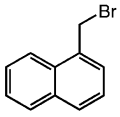
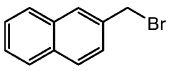


7ac (90% ee)

Table 5. Catalytic Enantioselective Phase-Transfer Alkylation of Protected Glycine Weinreb Amides **10**[a]



10a (R = Me), **b** (R = CH_2Ph) **11a, b**

entry	R	R^1X	react. time (h)	% yield [b]	% ee [c] (config) [d]
1 [e]	Me		3	83	79 (*R*)
2			6	96	96 (*R*)
3	CH_2Ph		6	99	97 (*R*)
4			6	99	97 (*R*)
5			6	92	96 (*R*)
6			6	98	97 (*R*)
7			6	99	91 (*R*)
8 [f]		EtI	8	97	94 (*R*)
9 [f]		BuI	8	77	92 (*R*)

[a] Unless otherwise specified, the reaction was carried out with 1.1 equiv of R^1X in the presence of 2 mol % of (*S*,*S*)-**4b** in toluene−50% KOH aqueous solution (volume ratio = 3:1) at 0 °C. [b] Isolated yield. [c] Enantiopurity of **11** was determined by HPLC analysis using a chiral column [DAICEL Chiralcel OD-H (entries 1−3), Chiralcel OD (entries 4 and 8), and Chiralpak AD (entries 5−7 and 9)]. [d] Absolute configuration was determined by comparison of the HPLC retention time with the authentic sample. [e] With (*S*,*S*)-**4c** as catalyst. [f] Use of saturated CsOH as base.

associated with the synthetic as well as pharmaceutical importance of optically active α-amino ketones serving as key synthetic precursors for optically active α-amino alcohols[20] and also for a number of biologically active molecules.[21,22]

Although we first applied the **4c**-catalyzed phase-transfer alkylation conditions optimized for **2b** to the allylation of **10a**,[23] it turned out to be unsuccessful in terms of both chemical yield and enantioselectivity. This consequence was within our assumption, and reexamination of a suitable catalyst in the allylation revealed that the sterically less demanding **4b** was superior to **4c** in this case. Thus, vigorous stirring of **10a** with allyl bromide (1.1 equiv) in toluene−50% KOH aqueous solution (volume ratio = 3:1) under the influence of (*S*,*S*)-**4b** (2 mol %) at 0 °C for 6 h resulted in the formation of the corresponding alkylation product **11a** ($R^1 = CH_2CH{=}CH_2$) in 96% yield with 96% ee (entry 1 vs 2 in Table 5). Further, we found that the reaction of **10b** possessing a benzyl group on the amide nitrogen under similar conditions afforded **11b** ($R^1 = CH_2CH{=}CH_2$) more cleanly with higher enantioselectivity (99%, 97% ee) (entry 3), and general applicability of this system was investigated with the variety of alkyl halides summarized in Table 5. All reactions proceeded smoothly in the presence of 2 mol % of (*S*,*S*)-**4b** with excellent enantioselectivities (entries 4−7), and use of saturated CsOH as a base was again recommended for the reaction with simple aliphatic alkyl halides (entries 8 and 9).

Having succeeded in developing an asymmetric phase-transfer-catalyzed alkylation of **10** for the first time, the usefulness of the optically active Weinreb amide **11** was demonstrated by its successful conversion to the corresponding α-amino ketones (Scheme 6).[17−19,24] Reaction of **11b** ($R^1 = CH_2CH{=}CH_2$) (97% ee) with PhMgBr (1.6 equiv) in THF at

Scheme 6. Transformation of **11b** into Protected α-Amino Ketone **12**

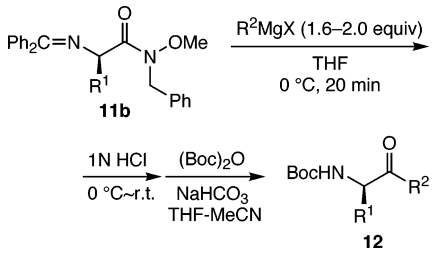
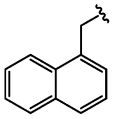


Table 6. Efficient Conversion of Optically Active Weinreb Amide **11b** into the Corresponding α-Amino Ketone **12**[a]

entry	R^1	R^2MgX	% yield [b]
1		PhMgBr	99
2			80 [c]
3		EtMgBr	86 [c]
4		PhMgBr	98
5	Et	PhMgBr	92

[a] Unless otherwise specified, the reaction was carried out with 1.6−2.0 equiv of R^2MgX in THF at 0 °C for 20 min and the amino ketone was isolated as *N*-*tert*-butoxycarbonyl derivative. [b] Isolated yield. [c] Isolated as *N*-benzoate.

(19) For reviews, see: (a) Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15. (b) Mentzel, M.; Hoffmann, H. M. R. *J. Prakt. Chem.* **1997**, *339*, 517.

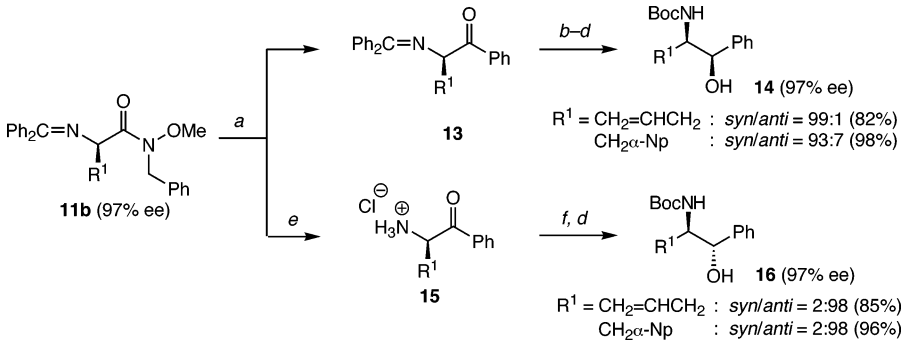
(20) For reviews, see: (a) Ager, D. H.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. See also: (b) Meester, W. J. N.; van Dijk, R.; van Maarseveen, J. H.; Rutjes, F. P. J. T.; Hermkens, P. H. H.; Hiemstra, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2909. (c) Hoffman, R. V.; Maslouh, N.; Cervantes-Lee, F. *J. Org. Chem.* **2002**, *67*, 1045. (d) Zhou, Z. H.; Tang, Y. L.; Li, K. Y.; Liu, B.; Tang, C. C. *Heteroat. Chem.* **2003**, *14*, 603. (e) Makino, K.; Goto, T.; Hiroki, Y.; Hamada, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 882.

(21) For reviews, see: (a) Dondoni, A.; Perrone, D. *Synthesis* **1993**, 1162. (b) Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev.* **1995**, *95*, 1677. (c) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825.

(22) For recent examples, see: (a) Lucet, D.; LeGall, T.; Mioskowski, C.; Ploux, O.; Marquet, A. *Tetrahedron: Asymmetry* **1996**, *7*, 985. (b) MaGee, D. I.; Leach, J. D.; Mallais, T. C. *Tetrahedron Lett.* **1997**, *38*, 1289. (c) Hoffman, R. V.; Tao, J.-H. *J. Org. Chem.* **1998**, *63*, 3979.

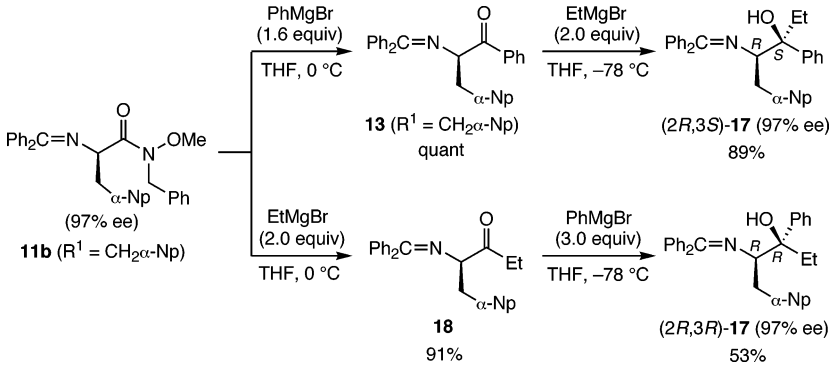
(23) We chose the allylation of **10a** as a model system because of our interest in the preparation of optically active α-amino acid Weinreb amides not obtainable from natural sources.

Scheme 7. Stereoselective Synthesis of α-Amino Alcohols from **11b**[a]



[a] Reactions and conditions: (a) PhMgBr (1.6 equiv), THF, 0°C. (b) L-Selectride (2.0 equiv), THF, −78 °C. (c) 10% citric acid, THF, rt. (d) $(Boc)_2O$ (3.0 equiv), $NaHCO_3$ aq, 0 °C to rt. (e) 1 N HCl, 0 °C to rt then concentration. (f) $NaBH_4$ (2.0 equiv), MeOH, 0 °C to rt.

Scheme 8. Diastereoselective Alkylation of Protected α-Amino Ketones **13** and **18**



0 °C for 20 min and subsequent hydrolysis with 1 N HCl followed by reprotection of the amine moiety produced α-amino ketone **12** ($R^1 = CH_2CH{=}CH_2$, R^2 = Ph) quantitatively without loss of enantiomeric excess (97% ee) (entry 1 in Table 6). As listed in Table 6, not only aryl amino ketones but also alkyl amino ketones can be prepared in a similar manner using an appropriate Grignard reagent (entries 2 and 3), and the structure of the α-substituent subtly influenced the efficiency of this transformation (entries 4 and 5), thereby enabling the facile synthesis of structurally diverse optically active α-amino ketones.

Based on the results, highly stereoselective synthesis of α-amino alcohols has been accomplished.[25] For example, after the reaction of **11b** ($R^1 = CH_2CH{=}CH_2$) with PhMgBr, reduction of the resulting Schiff base protected α-amino ketone **13** ($R^1 = CH_2CH{=}CH_2$) with L-Selectride in THF at −78 °C and subsequent hydrolysis with citric acid and reprotection furnished syn amino alcohol **14** ($R^1 = CH_2CH{=}CH_2$) exclusively in 82% overall yield, while treatment of the α-amino ketone hydrochloride **15** ($R^1 = CH_2CH{=}CH_2$) with $NaBH_4$ in MeOH led to the predominant formation of anti amino alcohol **16** ($R^1 = CH_2CH{=}CH_2$) (85%) (Scheme 7). A similar tendency was observed in the case of protected Weinreb amide **11b** ($R^1 = CH_2$α-Np), and both syn and anti amino alcohols were obtained with excellent diastereoselectivity as also illustrated in Scheme 7. Since the other enantiomer of **11** is readily accessible using (*R*,*R*)-**4b** as catalyst, the present method allows the practical asymmetric synthesis of four possible isomers of the desired α-amino alcohols starting from protected glycine Weinreb amide **10b**.

Finally, synthetic utility of protected unnatural α-amino ketones of type **13** was further demonstrated. Reaction of **13** ($R^1 = CH_2$α-Np) with EtMgBr in THF at −78 °C afforded (2*R*,3*S*)-**17** as a sole isolable product (89%), and, as expected, initial derivatization of **18** from **11b** ($R^1 = CH_2$α-Np) and consecutive alkylation with PhMgBr gave rise to (2*R*,3*R*)-**17** exclusively (53%) (Scheme 8).

Summary and Conclusion

We have developed a phase-transfer alkylation of protected glycine amide derivatives, diphenylmethyl (Dpm) amide **1b** and Weinreb amide **10b**, with high efficiency, enantioselectivity, and broad generality relying on the use of structurally modifiable chiral quaternary ammonium bromide **4** as catalyst. This success opens a door to a new avenue for the preparation of not only optically active α-amino amides but also other versatile, stereochemically homogeneous synthetic intermediates such as vicinal diamines, α-amino ketones, and α-amino alcohols with unprecedented structural diversity. The simplicity of these new asymmetric methodologies for actual implementation should be fully appreciated in their industrial applications.

Experimental Section

General. Infrared (IR) spectra were recorded on a Shimadzu FT-IR 8200A spectrometer. ^{1}H NMR spectra were measured on a JEOL JNM-

(24) Recent syntheses of α-amino ketones via nucleophilic α-amino acylation reactions: (a) Sengupta, S.; Mondal, S.; Das, D. *Tetrahedron Lett.* **1999**, *40*, 4107. (b) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 1519. (c) Di Gioia, M. L.; Legio, A.; Liguori, A.; Napoli, A.; Siciliano, C.; Sindona, G. *J. Org. Chem.* **2001**, *66*, 7002. (d) Garcia, J.; Nicolàs, E.; Albericio, F.; Michelotti, E. L.; Tice, C. M. *Tetrahedron Lett.* **2002**, *43*, 7495. (e) Vázquez, J.; Albericio, F. *Tetrahedron Lett.* **2002**, *43*, 7499. (f) Liu, J.; Ikemoto, N.; Petrillo, D.; Armstrong, J. D., III. *Tetrahedron Lett.* **2002**, *43*, 8223. (g) Sharma, A. K.; Hergenrother, P. J. *Org. Lett.* **2003**, *5*, 2107. See also ref 13.

(25) For the stereoselective synthesis of α-amino alcohols from glycine ester via reduction-alkylation sequence, see: (a) Polt, R.; Peterson, M. A.; DeYoung, L. *J. Org. Chem.* **1992**, *57*, 5469. (b) Palian, M. M.; Polt, R. *J. Org. Chem.* **2001**, *66*, 7178. (c) Harrison, B. A.; Pasternak, G. W.; Verdine, G. L. *J. Med. Chem.* **2003**, *46*, 677.

FX400 (400 MHz) spectrometer and a JMTC-400/54/SS (400 MHz) spectrometer. High-performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments using 4.6 mm × 25 cm Daicel Chiralcel OD, OD-H, Chiralpak AD, and AD-H. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel (E. Merck 9385). High-resolution mass spectra (HRMS) were performed on an Applied Biosystems Mariner API-TOF workstation and JEOL JMS-HX100.

In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were purchased from Kanto Chemical Co. Inc. as "dehydrated". Benzene and toluene were dried over sodium metal. Dichloromethane (CH_2Cl_2) was stored over 4 A molecular sieves. Triethylamine (Et_3N) was stored over potassium hydroxide (KOH) pellets. Cyclopentyl methyl ether (CPME) was kindly supplied by Zeon Corp., Japan. Other simple chemicals were purchased and used as such.

Representative Procedure for Asymmetric Alkylation of Glycine Diphenylmethylamide-Benzophenone Schiff Base 1b under Phase-Transfer Conditions (Table 1). To a solution of Schiff base **1b** (40 mg, 0.10 mmol) and (*S*,*S*)-**4c** (3.2 mg, 0.002 mmol) in mesitylene (1 mL) were added saturated CsOH aqueous solution (30 μL) and 2-iodopropane (50 μL, 0.50 mmol) sequentially at 0 °C under argon atmosphere, and the reaction mixture was stirred for 5 h. The resulting mixture was diluted with water and extracted with ether. The organic phase was washed with brine and dried over Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography on silica gel (hexane/ethyl acetate = 5:1 as eluent) afforded the alkylation product **2be** (R^1 = *i*-Pr, entry 6) (36 mg, 0.081 mmol, 81%, 90% ee (*R*)): $[\alpha]^{25}_D = +51.3°$ (*c* 0.53, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−7.61 (2H, m, ArH), 7.43−7.17 (17H, m, ArH and NH), 7.02−6.99 (2H, m, ArH), 6.35 (1H, d, *J* = 9.2 Hz, Ph_2CH), 3.90 (1H, d, *J* = 4.4 Hz, NCHCO), 2.27−2.19 (1H, m, CH_3CH), 0.98 (3H, d, *J* = 6.8 Hz, CH_3), 0.82 (3H, d, *J* = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 169.9, 141.7, 141.7, 139.3, 135.7, 130.4, 128.6, 128.5, 128.4, 128.1, 127.7, 127.4, 127.3, 127.1, 127.0, 71.4, 56.1, 33.9, 19.7, 18.1; IR (liquid film) 3389, 3061, 3028, 2963, 2928, 1676, 1620, 1495, 1447, 1315, 1281, 1030, 1001, 756, 698 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{31}H_{31}N_2O$ ($[M + H]^+$): 447.2431. Found: 447.2434. The enantiopurity was determined by HPLC analysis using chiral column [DAICEL Chiralpak AD, hexane/*i*-PrOH = 20:1, flow rate = 1.0 mL/min, t_R = 33.1 (*R*) and 36.1 (*S*) min].

Asymmetric Alkylation of 1b with Racemic 1-Bromo-1-phenylethane under Phase-Transfer Conditions (Scheme 3). This alkylation was conducted in a manner similar to that described above to give the alkylation product **2bi** [75.2 mg, 0.148 mmol, 74%, dr = 55 (61% ee):45 (33% ee)]; major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.56 (2H, m, ArH), 7.43−7.31 (6H, m, ArH), 7.27−7.18 (11H, m, ArH), 7.11−7.08 (2H, m, ArH), 6.94 (1H, d, *J* = 8.7 Hz, NH), 6.81−6.76 (4H, m, ArH), 6.17 (1H, d, *J* = 8.7 Hz, Ph_2CH), 4.16 (1H, d, *J* = 5.1 Hz, NCHCO), 3.46−3.39 (1H, m, CH_3CHPh), 1.20 (3H, d, *J* = 7.1 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.2, 142.4, 141.7, 141.2, 139.1, 135.4, 130.4, 128.9, 128.6, 128.5, 128.4, 128.3, 128.1, 127.8, 127.7, 127.2, 127.1, 127.1, 127.0, 126.4, 72.1, 55.9, 44.7, 18.6; IR (liquid film) 3391, 3059, 3028, 2968, 2928, 1676, 1622, 1599, 1493, 1447, 1315, 1290, 1030, 735, 696 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{36}H_{32}N_2O$ ($[M + H]^+$): 509.2587. Found: 509.2587. HPLC condition: DAICEL Chiralpak AD-H, hexane/*i*-PrOH = 9:1, flow rate = 1.0 mL/min, t_R = 21.0 (minor) and 22.7 (major) min. Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (2H, d, *J* = 7.1 Hz, ArH), 7.43−7.04 (22H, m, ArH and NH), 6.35 (1H, d, *J* = 8.7 Hz, Ph_2CH), 6.23 (2H, br d, *J* = 6.7 Hz, ArH), 4.15 (1H, d, *J* = 3.1 Hz, NCHCO), 3.56−3.50 (1H, m, CH_3CHPh), 1.44 (3H, d, *J* = 7.1 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.9, 143.2, 141.6, 139.0, 135.2, 130.4, 128.6, 128.5, 128.4, 128.4, 128.2, 128.1, 128.1, 128.0, 127.5, 127.3, 127.1, 127.0, 127.0, 126.2, 71.3, 56.3, 44.2, 14.4; IR (liquid film) 3391, 3059, 3028, 2932, 1678, 1622, 1599, 1493, 1447, 1315, 1285, 1028, 765, 696 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{36}H_{32}N_2O$ ($[M + H]^+$): 509.2587. Found: 509.2590. HPLC condition: DAICEL Chiralpak AD-H, hexane/*i*-PrOH = 9:1, flow rate = 1.0 mL/min, t_R = 19.9 (minor) and 23.8 (major) min.

Stereoselective Alkylation of 1b with β-Chiral Primary Alkyl Halide 5 (Table 2). The reaction was performed in a manner similar to that of the alkylation with 1-bromo-1-phenylethane, affording the product **2bj** [entry 1, 93.0 mg, 0.178 mmol, 89%, (2*R*,4*R*)-**2bj**/(2*R*,4*S*)-**2bj** = 91:9]; (2*R*,4*R*)-**2bj**: 99% ee, $[\alpha]^{33}_D = +12.09°$ (*c* 2.09, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.56 (2H, m, ArH), 7.48 (1H, d, *J* = 8.5 Hz, NH), 7.44−7.17 (18H, m, ArH), 7.12−7.09 (3H, m, ArH), 6.97−6.95 (2H, m, ArH), 6.28 (1H, d, *J* = 8.5 Hz, Ph_2CH), 4.07 (1H, dd, *J* = 5.9, 7.5 Hz, NCHCO), 2.81−2.73 (1H, m, CH_3CHPh), 2.18−2.04 (2H, m, $NCHCH_2$), 0.99 (3H, d, *J* = 7.1 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 169.4, 146.9, 141.7, 141.6, 139.2, 135.3, 130.4, 128.7, 128.7, 128.6, 128.5, 128.5, 128.2, 128.1, 127.6, 127.3, 127.3, 127.2, 127.1, 126.9, 125.8, 64.8, 56.3, 44.3, 36.2, 21.8; IR (neat) 3389, 3059, 3026, 2959, 2924, 1678, 1622, 1493, 1447, 1315, 1287, 1030, 912, 762, 747, 696 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{37}H_{34}N_2O$ ($[M + H]^+$): 523.2744. Found: 523.2746. HPLC condition: DAICEL Chiralpak AD-H, hexane/*i*-PrOH = 8:1, flow rate = 0.5 mL/min, t_R = 14.0 (2*R*,4*R*) and 18.5 (2*S*,4*S*) min. (2*R*,4*S*)-**2bj**: 93% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.48 (2H, m, ArH), 7.41−7.06 (20H, m, ArH and NH), 7.00−6.97 (2H, m, ArH), 6.80−6.78 (2H, m, ArH), 6.32 (1H, d, *J* = 8.3 Hz, Ph_2CH), 3.99 (1H, dd, *J* = 5.5, 7.5 Hz, NCHCO), 2.90−2.81 (1H, m, CH_3CHPh), 2.24 (1H, ddd, *J* = 5.5, 7.9, 13.9 Hz, $NCHCH_2$), 2.09−2.02 (1H, m, $NCHCH_2$), 1.11 (3H, d, *J* = 7.1 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 169.8, 146.5, 141.7, 139.2, 135.3, 130.4, 128.6, 128.6, 128.5, 128.5, 128.3, 128.2, 128.0, 127.3, 127.3, 127.2, 127.1, 126.9, 125.7, 64.8, 56.2, 43.2, 36.4, 23.3; IR (neat) 3391, 3059, 3026, 2957, 2924, 1678, 1620, 1493, 1447, 1315, 1287, 1028, 912, 760, 745, 696 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{37}H_{34}N_2O$ ($[M + H]^+$): 523.2744. Found: 523.2746. HPLC condition: DAICEL Chiralpak AD-H, hexane/*i*-PrOH = 8:1, flow rate = 0.5 mL/min, t_R = 16.0 (2*R*,4*S*) and 17.4 (2*S*,4*R*) min.

Representative Procedure for Hydrolysis of the Imine Moiety of 2b and Subsequent Reduction of the Amide. Facile Conversion to Optically Active Vicinal Diamine 3 (Table 3). To a solution of **2be** (R^1 = *i*-Pr) (89 mg, 0.20 mmol) (90% ee) in THF (2 mL) was added 1 N HCl (2 mL) at room temperature, and the mixture was stirred for 1 h. The aqueous layer was washed with ether and then basified with 1 M NaOH. Extraction with ethyl acetate and subsequent evaporation afforded *N*-free α-amino acid amide as a white solid quantitatively. Reduction of the amide moiety was then performed with $LiAlH_4$ (30 mg, 0.80 mmol) in cyclopentyl methyl ether (CPME) (3 mL) at 100 °C for 2 h. The reaction was quenched with sequential addition of NaF (0.13 g, 3.2 mmol) and water (43 μL, 2.4 mmol) at 0 °C, and stirring was continued for 1 h. The resulting gray precipitate was filtered off through a pad of Celite, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (short path; ethyl acetate/methanol = 4:1 as eluent) to give **3e** (R^1 = *i*-Pr, entry 5) (54 mg, 0.20 mmol, >99%, 90% ee): $[\alpha]^{30}_D = -27.1°$ (*c* 1.02, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.37 (4H, m, ArH), 7.31−7.25 (4H, m, ArH), 7.21−7.17 (2H, m, ArH), 4.80 (1H, s, Ph_2CH), 2.66 (1H, dd, *J* = 3.6, 11.2 Hz, CH_2), 2.63 (1H, ddd, *J* = 3.6, 5.6, 8.8 Hz, NH_2CH), 2.38 (1H, dd, *J* = 8.8, 11.2 Hz, CH_2), 1.80 (2H, br, NH_2), 1.65−1.57 (1H, m, CH_3CH), 0.86 (3H, d, *J* = 6.8 Hz, CH_3), 0.86 (3H, d, *J* = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 143.9, 128.3, 127.2, 127.1, 126.8, 67.6, 57.0, 52.3, 32.1, 19.5, 17.9; IR (KBr) 2972, 2563, 1558, 1396, 746, 704 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{18}H_{25}N_2$ ($[M + H]^+$): 269.2012. Found: 269.2020. The preservation of the enantiomeric excess through the reduction process was confirmed by HPLC analysis of *N*-benzoate of the resulting Dpm-protected diamine (see below).

BzHNCH(*i*-Pr)CH$_2$NHCHPh$_2$. 90% ee (retained); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, d, J = 7.2 Hz, ArH), 7.50−7.08 (13H, m, ArH), 6.39 (1H, d, J = 9.2 Hz, CONH), 4.81 (1H, s, Ph_2CH), 4.07 (1H, m, CONHC*H*), 2.77 (1H, ddd, J = 6.2, 6.2, 12.8 Hz, CH_2), 2.74 (1H, ddd, J = 4.8, 4.8, 12.8 Hz, CH_2), 1.94 (1H, dq, J = 6.8, 13.6 Hz, CH_3C*H*), 0.94 (6H, d, J = 6.8 Hz, CH_3). HPLC condition: DAICEL Chiralpak AD, hexane/EtOH = 20:1, flow rate = 0.5 mL/min, t_R = 26.4 (major) and 29.5 (minor) min.

Representative Procedure for Catalytic Asymmetric Quaternization of Aldimine Schiff Base 6 under Phase-Transfer Conditions (Table 4). To a solution of aldimine Schiff base **6a** (R^1 = Me) (75 mg, 0.20 mmol), (*S*,*S*)-**4c** (6.2 mg, 0.004 mmol), and iodocyclopentane (0.12 mL, 1.0 mmol) in mesitylene (2 mL) under argon atmosphere was added CsOH·H_2O (176.8 mg, 1.0 mmol) in one portion at 0 °C, and the reaction flask was flushed with argon immediately. After being stirred for 3 h, the reaction mixture was diluted with water and extracted with ether. The organic layer was dried over Na_2SO_4 and concentrated. Purification of the residue by column chromatography on silica gel (hexane/ethyl acetate = 8:1 as eluent) gave the alkylation product **7ac** (R^1 = Me, R^2 = *c*-Pent; entry 3) (72 mg, 0.16 mmol, 81%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (1H, s, ArCH=N), 8.05 (1H, d, J = 8.4 Hz, NH), 7.67 (2H, d, J = 8.4 Hz, ArH), 7.41 (2H, d, J = 8.4 Hz, ArH), 7.38−7.34 (2H, m, ArH), 7.31−7.16 (8H, m, ArH), 6.26 (1H, d, J = 8.0 Hz, Ph_2CH), 2.42 (1H, quint, J = 8.7 Hz, $(CH_2)_4$C*H*), 1.64−1.51 (3H, m, CH(CH_2)$_4$), 1.50 (3H, s, CH_3), 1.46−1.41 (4H, m, CH(CH_2)$_4$), 1.08−0.98 (1H, m, CH(CH_2)$_4$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 156.6, 142.1, 141.8, 137.0, 134.4, 129.1, 129.0, 128.5, 128.4, 127.3, 127.2, 127.1, 126.9, 69.4, 56.7, 49.6, 27.4, 26.4, 25.3, 25.2, 19.3; IR (liquid film) 3377, 3028, 2955, 2868, 1674, 1595, 1493, 1088, 824, 754, 698 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{28}H_{30}ClN_2O$ ([M + H]$^+$): 445.2041. Found: 445.2034. The enantiomeric excess of **7ac** was determined by HPLC analysis after hydrolysis of the imine moiety (see Supporting Information 1).

General Procedure for Asymmetric Alkylation of Glycine Weinreb Amide-Benzophenone Schiff Base 10 under Phase-Transfer Conditions (Table 5). To a mixture of Weinreb amide **10** (0.20 mmol) and (*S*,*S*)-**4b** (4 mg, 0.004 mmol) in toluene (2 mL) were added 50% KOH aqueous solution (0.65 mL) and alkyl halide (0.22 mmol) at 0 °C under argon atmosphere, and the mixture was stirred at the same temperature. After the completion of the reaction was observed via TLC, the mixture was diluted with water and extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. Purification of the crude products by column chromatography on silica gel (hexane/ether as eluent) gave the corresponding alkylation product **11**.

Ph$_2$C=NCH(allyl)CON(OMe)Me (11a, R^1 = CH$_2$CH=CH$_2$; Entry 2). 96% ee (*R*), $[\alpha]^{23}_D$ = +25.8° (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.65 (2H, m, ArH), 7.49−7.42 (3H, m, ArH), 7.38 (1H, m, ArH), 7.33−7.29 (2H, m, ArH), 7.21−7.19 (2H, m, ArH), 5.73 (1H, ddt, J = 7.2, 10.0, 17.2 Hz, CH_2=C*H*), 5.06−4.98 (2H, m, CH=CH_2), 4.41 (1H, t, J = 6.8 Hz, NCHCO), 3.27 (3H, s, OCH_3), 3.15 (3H, s, NCH_3), 2.81 (1H, ddd, J = 6.8, 7.2, 13.9 Hz, CH_2=CHCH_2), 2.64 (1H, ddd, J = 6.8, 7.2, 13.9 Hz, CH_2=CHCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 169.4, 139.4, 136.6, 134.7, 130.0, 128.6, 128.3, 128.2, 127.8, 127.8, 117.1, 62.9, 60.9, 38.0, 32.5; IR (KBr) 3061, 2976, 2937, 1670, 1622, 1597, 1576, 1491, 1447, 1385, 1315, 1286, 1178, 1030, 991, 920, 781, 770, 698 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{20}H_{23}N_2O_2$ ([M + H]$^+$): 323.1754. Found: 323.1750. The enantiopurity was determined by HPLC analysis using chiral column [DAICEL Chiralcel OD-H, hexane/EtOH = 50:1, flow rate = 0.5 mL/min, t_R = 20.1 (*R*) and 22.3 (*S*) min].

General Procedure for Conversion of Schiff Base Protected Weinreb Amide 11 to α-Amino Ketone 12 (Scheme 7, Table 6). To a solution of optically active α-amino acid Weinreb amide-benzophenone Schiff base **11** in THF (0.2 M) was added a 0.9 M ethereal solution of phenylmagnesium bromide (1.6 equiv) at 0 °C under argon atmosphere, and the resulting pale-brown solution was stirred for 20 min at the same temperature. The solution was poured into cooled 1 N HCl quickly, and the mixture was allowed to warm to room temperature. After being stirred for 20 min, the mixture was concentrated under reduced pressure and the residue was dissolved in THF or CH_3CN (0.1 M). Benzoyl chloride (BzCl, 3 equiv) or $(Boc)_2O$ (3 equiv) and solid $NaHCO_3$ (excess amount) were added to this mixture at 0 °C, which was stirred for several hours at room temperature. Water was then added, and the whole mixture was extracted with ether. The combined extracts were washed with 1 N HCl, saturated $NaHCO_3$ and brine sequentially, and dried over Na_2SO_4. Evaporation of solvent and purification of the crude products by column chromatography on silica gel (hexane/ethyl acetate or ether as eluent) gave the corresponding amino ketone **12**.

(2*R*)-*N*-Boc-2-amino-1-phenylpent-4-en-1-one (12, R^1 = CH$_2$CH=CH$_2$, R^2 = Ph; Entry 1). 97% ee, $[\alpha]^{20}_D$ = +4.6° (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (2H, d, J = 7.2 Hz, ArH), 7.60 (1H, t, J = 7.6 Hz, ArH), 7.49 (2H, t, J = 7.6 Hz, ArH), 5.67 (1H, ddt, J = 7.2, 10.0, 17.2 Hz, CH_2=C*H*), 5.47 (1H, br d, J = 7.2 Hz, NH), 5.39−5.34 (1H, m, NCHCO), 5.07 (1H, d, J = 10.0 Hz, CH=CH_2), 5.01 (1H, d, J = 17.2 Hz, CH=CH_2), 2.69 (1H, ddd, J = 7.2, 7.2, 14.0 Hz, CH_2=CHCH_2), 2.38 (1H, ddd, J = 7.2, 7.2, 14.0 Hz, CH_2=CHCH_2), 1.45 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 155.1, 134.6, 133.5, 132.0, 128.7, 128.4, 118.7, 79.7, 54.7, 37.5, 28.4; IR (KBr) 3362, 2980, 2930, 1715, 1686, 1641, 1599, 1582, 1501, 1448, 1393, 1367, 1252, 1227, 1171, 1063, 1020, 1001, 920, 856, 781, 700, 691 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{16}H_{21}NO_3Na$ ([M + Na]$^+$): 298.1414. Found: 298.1408. HPLC condition: DAICEL Chiralpak AD, hexane/EtOH = 50:1, flow rate = 0.5 mL/min, t_R = 16.7 (*R*) and 20.6 (*S*) min.

General Procedure for the Synthesis of Schiff Base Protected α-Amino Ketones (13 or 18) from α-Amino Acid Weinreb Amide 11 (Schemes 8 and 9). To a solution of Weinreb Amide **11** in THF (0.2 M) was added an ethereal solution of Grignard reagent (1.6−2.0 equiv) at 0 °C under argon atmosphere, and the solution was stirred for 20 min at the same temperature. The resulting pale-brown solution was poured into cooled water, and the mixture was extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by column chromatography on silica gel with cooling (powdered dry ice, hexane/ether as eluent) gave the corresponding Schiff base protected α-amino ketone (**13** or **18**).

(2*R*)-2-Diphenylmethyleneamino-1-phenylpent-4-en-1-one (13, R^1 = CH$_2$CH=CH$_2$). 97% ee, $[\alpha]^{21}_D$ = +23.4° (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87−7.84 (2H, m, ArH), 7.67−7.64 (2H, m, ArH), 7.51 (1H, tt, J = 1.2, 7.4 Hz, ArH), 7.45−7.36 (6H, m, ArH), 7.32 (2H, tt, J = 1.2, 7.4 Hz, ArH), 7.12−7.08 (2H, m, ArH), 5.74 (1H, ddt, J = 7.3, 10.0, 17.2 Hz, CH_2=C*H*), 5.05−4.99 (2H, m, CH=CH_2), 4.87 (1H, dd, J = 5.8, 7.3 Hz, NCHCO), 2.83−2.69 (2H, m, CH_2=CHCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 169.7, 139.3, 136.4, 136.1, 134.3, 132.7, 130.2, 128.8, 128.7, 128.6, 128.5, 128.2, 127.9, 127.7, 117.4, 69.4, 39.3; IR (KBr) 3061, 3026, 2961, 2922, 1690, 1616, 1597, 1578, 1491, 1447, 1315, 1290, 1231, 1180, 1074, 1028, 1001, 982, 941, 918, 780, 770, 696 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{24}H_{22}NO$ ([M + H]$^+$): 340.1696. Found: 340.1705. HPLC condition: DAICEL Chiralcel OD, hexane/*i*-PrOH = 200:1, flow rate = 0.5 mL/min, t_R = 20.3 (*S*) and 26.3 (*R*) min.

(2*R*)-2-Diphenylmethyleneamino-3-(1-naphthyl)-1-phenylpropan-1-one (13, R^1 = CH$_2$α-Np). 97% ee, $[\alpha]^{19}_D$ = −211.6° (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (2H, d, J = 8.8 Hz, ArH), 7.78−7.74 (2H, m, ArH), 7.66 (1H, dd, J = 3.0, 6.2 Hz, ArH), 7.55 (2H, dd, J = 1.4, 7.4 Hz, ArH), 7.48 (1H, t, J = 7.4 Hz, ArH), 7.41−7.15 (10H, m, ArH), 7.01 (2H, m, ArH), 6.27 (2H, br d, J = 6.4 Hz, ArH), 5.21 (1H, dd, J = 4.8, 8.8 Hz, NCHCO), 3.76 (1H, dd, J = 4.8, 13.7 Hz, $NpCH_2$), 3.69 (1H, dd, J = 8.8, 13.7 Hz, $NpCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 169.7, 139.0, 136.3, 135.8, 133.7, 133.6,

132.7, 132.0, 130.0, 128.9, 128.6, 128.4, 128.2, 128.1, 128.0, 127.8, 127.7, 127.1, 125.6, 125.2, 125.2, 123.5, 69.9, 38.1; IR (KBr) 3061, 3024, 2970, 2926, 1686, 1616, 1597, 1576, 1510, 1491, 1447, 1394, 1315, 1288, 1260, 1225, 1178, 1074, 1028, 1001, 984, 943, 912, 847, 800, 777, 694 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{32}H_{26}NO$ ($[M + H]^+$): 440.2009. Found: 440.1994. HPLC condition: DAICEL Chiralpak AD, hexane/*i*-PrOH = 20:1, flow rate = 0.5 mL/min, t_R = 15.5 (*R*) and 24.3 (*S*) min.

(2*R*)-2-Diphenylmethyleneamino-1-(1-naphthyl)pentan-3-one (18). 97% ee, $[\alpha]^{25}_D = +361.4°$ (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (1H, d, *J* = 8.4 Hz, ArH), 7.75 (1H, d, *J* = 8.4 Hz, ArH), 7.71 (1H, d, *J* = 8.4 Hz, ArH), 7.55−7.53 (2H, m, ArH), 7.41−7.34 (2H, m, ArH), 7.31−7.24 (5H, m, ArH), 7.21 (1H, d, *J* = 6.8 Hz, ArH), 7.04 (1H, dt, *J* = 1.2, 7.8 Hz, ArH), 6.83 (2H, t, *J* = 6.8 Hz, ArH), 5.98 (1H, br, ArH), 4.29 (1H, dd, *J* = 3.2, 10.0 Hz, NCHCO), 3.82 (1H, dd, *J* = 3.2, 13.5 Hz, $NpCH_2$), 3.35 (1H, dd, *J* = 10.0, 13.5 Hz, $NpCH_2$), 2.84 (1H, dq, *J* = 7.2, 18.8 Hz, CH_3CH_2), 2.53 (1H, dq, *J* = 7.2, 18.8 Hz, CH_3CH_2), 1.08 (3H, t, *J* = 7.2 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 169.5, 139.0, 135.2, 133.9, 133.6, 132.2, 130.0, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 127.1, 126.7, 125.6, 125.3, 125.1, 123.6, 72.7, 37.1, 33.7, 7.5; IR (KBr) 3057, 2976, 2937, 2905, 1713, 1620, 1597, 1578, 1510, 1491, 1447, 1396, 1379, 1346, 1315, 1286, 1155, 1074, 1028, 945, 914, 799, 779, 696 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{28}H_{26}NO$ ($[M + H]^+$): 392.2009. Found: 392.1999. HPLC condition: DAICEL Chiralpak AD, hexane/EtOH = 50:1, flow rate = 0.5 mL/min, t_R = 8.8 (*R*) and 10.5 (*S*) min.

General Procedure for Conversion of Schiff Base Protected α-Amino Ketone 13 to the Corresponding *syn*-Amino Alcohol 14 (Scheme 8). To a solution of **13** in THF (0.2 M) was added a 1.0 M THF solution of L-Selectride (2.0 equiv) at −78 °C. After being stirred for 1 h at the same temperature, the mixture was poured into cooled saturated NH_4Cl. Extractive workup was performed with ether, and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by column chromatography on silica gel (hexane/ether as eluent) gave Schiff base protected α-amino alcohol with a small amount of impurities. A solution of the Schiff base protected α-amino alcohol in THF (0.1 M) was treated with 10% aqueous citric acid (the same amount as THF) and stirred for several hours at room temperature. $(Boc)_2O$ (3.0 equiv) and solid $NaHCO_3$ (excess amount) were then added sequentially at 0 °C. After being stirred for 2 h at room temperature, the resulting mixture was diluted with water and extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/ether or ethyl acetate as eluent) to afford *syn*-amino alcohol **14**.

(1*R*,2*R*)-*N*-Boc-2-amino-1-phenylpent-4-en-1-ol (14, $R^1 = CH_2CH{=}CH_2$). 97% ee, syn/anti = 99:1, $[\alpha]^{20}_D = -15.2°$ (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.25 (5H, m, ArH), 5.79 (1H, ddt, *J* = 7.2, 10.6, 16.2 Hz, $CH_2{=}CH$), 5.10 (1H, d, *J* = 16.0 Hz, $CH{=}CH_2$), 5.09 (1H, d, *J* = 10.6 Hz, $CH{=}CH_2$), 4.75 (1H, br, NH), 4.69 (1H, dd, *J* = 4.4, 4.4 Hz, OCH), 3.79 (1H, br, NCH), 3.25 (1H, br, OH), 2.34 (1H, ddd, *J* = 7.2, 7.2, 14.4 Hz, $CH_2{=}CHCH_2$), 2.15 (1H, ddd, *J* = 7.2, 7.2, 14.0 Hz, $CH_2{=}CHCH_2$), 1.38 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 141.6, 134.3, 128.3, 127.6, 126.3, 117.9, 79.7, 76.0, 56.2, 36.2, 28.4; IR (KBr) 3423, 3078, 3030, 2978, 2930, 1692, 1506, 1454, 1393, 1367, 1252, 1171, 1047, 1024, 916, 856, 770, 702 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{16}H_{23}NO_3Na$ ($[M + Na]^+$): 300.1570. Found: 300.1566. The enantio- and diastereomeric excesses were determined by HPLC analysis of *N*-benzoate derivative (see below).

(1*R*,2*R*)-*N*-Benzoyl-2-amino-1-phenylpent-4-en-1-ol. 85% yield, 97% ee, syn/anti = 99:1, $[\alpha]^{20}_D = -56.4°$ (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.67 (2H, m, ArH), 7.49 (1H, tt, *J* = 1.2, 7.4 Hz, ArH), 7.42−7.24 (7H, m, ArH), 6.42 (1H, br d, *J* = 7.6 Hz, NH), 5.86 (1H, ddt, *J* = 7.4, 10.0, 17.2 Hz, $CH_2{=}CH$), 5.19−5.12 (2H, m, $CH{=}CH_2$), 4.87 (1H, dd, *J* = 4.6, 4.6 Hz, OCH), 4.33 (1H, ddt, *J* = 4.6, 7.4, 7.6 Hz, NCH), 3.55 (1H, br, OH), 2.49 (1H, ddd, *J* = 7.4, 7.4, 14.0 Hz, $CH_2{=}CHCH_2$), 2.35 (1H, ddd, *J* = 7.4, 7.4, 14.0 Hz, $CH_2{=}CHCH_2$); IR (KBr) 3364, 3296, 3071, 1639, 1603, 1580, 1543, 1491, 1456, 1439, 1327, 1298, 1283, 1238, 1157, 1057, 1042, 1028, 968, 914, 864, 766, 704 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{18}H_{19}NO_2Na$ ($[M + Na]^+$): 304.1308. Found: 304.1331. HPLC condition: DAICEL Chiralcel OD, hexane/*i*-PrOH = 10:1, flow rate = 0.5 mL/min, t_R = 24.6 (1*S*,2*R*), 29.5 (1*S*,2*S*), 38.6 (1*R*,2*S*), and 42.2 (1*R*,2*R*) min.

(1*R*,2*R*)-*N*-Boc-2-amino-3-(1-naphthyl)-1-phenylpropan-1-ol (14, $R^1 = CH_2$α-Np). 97% ee, syn/anti = 93:7, $[\alpha]^{21}_D = -42.6°$ (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (1H, d, *J* = 7.6 Hz, ArH), 7.89 (1H, d, *J* = 6.4 Hz, ArH), 7.74 (1H, d, *J* = 6.8 Hz, ArH), 7.53−7.23 (9H, m, ArH), 6.42 (1H, d, *J* = 8.8 Hz, NH), 5.60 (1H, d, *J* = 4.4 Hz, OCH), 4.69 (1H, s, OH), 3.96 (1H, m, NCH), 3.36 (1H, dd, *J* = 4.0, 13.5 Hz, $NpCH_2$), 2.88 (1H, dd, *J* = 9.4, 13.5 Hz, $NpCH_2$), 1.20 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.0, 142.8, 135.1, 133.2, 131.6, 128.3, 127.5, 127.2, 126.6, 126.4, 126.4, 125.6, 125.2, 125.1, 123.5, 77.4, 72.8, 56.6, 33.5, 28.1; IR (KBr) 3422, 3061, 2976, 2930, 1686, 1597, 1510, 1497, 1454, 1393, 1367, 1290, 1250, 1169, 1090, 1063, 1022, 912, 860, 800, 779, 735, 702 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{24}H_{27}NO_3Na$ ($[M + Na]^+$): 400.1883. Found: 400.1870. HPLC condition: DAICEL Chiralcel OD, hexane/EtOH = 30:1, flow rate = 0.5 mL/min, t_R = 23.6 (1*S*,2*R*), 28.0 (1*R*,2*S*), 32.4 (1*S*,2*S*), and 36.2 (1*R*,2*R*) min.

General Procedure for *anti*-α-Amino Alcohol (16) Synthesis from α-Amino Acid Weinreb Amide 11 (Scheme 8). To a solution of Schiff base protected Weinreb amide **11** in THF (0.2 M) was added a 0.9 M ethereal solution of phenylmagnesium bromide (1.6 equiv) at 0 °C under argon atmosphere, and the resulting pale-brown solution was stirred for 20 min at the same temperature. The solution was then poured into cooled 1 N HCl quickly, and the whole mixture was allowed to warm to room temperature and stirred there for 20 min. The volatiles were removed under reduced pressure, and the crude **15** was dissolved in MeOH (0.1 M). $NaBH_4$ (2.0 equiv) was added at 0 °C, and the mixture was stirred for 1−2 h at room temperature. $(Boc)_2O$ (3.0 equiv) and solid $NaHCO_3$ (excess amount) were then added to the resulting mixture at 0 °C. After being stirred for 2 h at room temperature, the mixture was diluted with water and extracted with ether. The combined extracts were washed with 1 N HCl, saturated $NaHCO_3$ and brine, and then dried over Na_2SO_4. Evaporation of solvent and purification of the crude products by column chromatography on silica gel (hexane/ether or ethyl acetate as eluent) afforded *anti*-α-amino alcohol **16**.

(1*S*,2*R*)-*N*-Boc-2-amino-1-phenylpent-4-en-1-ol (16, $R^1 = CH_2CH{=}CH_2$). 97% ee, syn/anti = 2:98, $[\alpha]^{23}_D = -13.3°$ (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.27 (5H, m, ArH), 5.74 (1H, dddd, *J* = 6.6, 7.4, 8.8, 17.6 Hz, $CH_2{=}CH$), 5.05 (1H, d, *J* = 17.6 Hz, $CH{=}CH_2$), 5.04 (1H, d, *J* = 8.8 Hz, $CH{=}CH_2$), 4.91 (1H, br, NH), 4.54 (1H, br, OCH), 3.97 (1H, br, NCH), 3.37 (1H, br, OH), 2.24−2.17 (1H, m, $CH_2{=}CHCH_2$), 2.10−2.02 (1H, m, $CH_2{=}CHCH_2$), 1.45 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 140.6, 134.6, 128.1, 127.4, 126.3, 117.6, 79.8, 76.2, 56.0, 33.8, 28.4; IR (KBr) 3354, 3071, 2984, 2939, 1688, 1639, 1529, 1458, 1441, 1393, 1367, 1312, 1269, 1252, 1175, 1065, 1018, 995, 912, 881, 854, 764, 704, 675 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{16}H_{23}NO_3Na$ ($[M + Na]^+$): 300.1570. Found: 300.1575. The enantio- and diastereomeric excesses were determined by HPLC analysis of *N*-benzoate derivative (see below).

(1*S*,2*R*)-*N*-Benzoyl-2-amino-1-phenylpent-4-en-1-ol. 85% yield, 97% ee, syn/anti = 2:98, $[\alpha]^{22}_D = -39.9°$ (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.70 (2H, m, ArH), 7.51 (1H, tt, *J* = 1.2, 7.4 Hz, ArH), 7.43−7.33 (6H, m, ArH), 7.29 (1H, tt, *J* = 1.8, 6.8 Hz, ArH), 6.20 (1H, d, *J* = 7.8 Hz, NH), 5.77 (1H, dddd, *J* = 6.0, 8.2, 10.5, 16.7 Hz, $CH_2{=}CH$), 5.10−5.02 (3H, m, $CH{=}CH_2$ and OCH), 4.50 (1H, dddd, *J* = 3.2, 4.8, 7.8, 9.7 Hz, NCH), 3.89 (1H, s, OH), 2.37−2.31 (1H, m, $CH_2{=}CHCH_2$), 2.21 (1H, ddd, *J* = 8.2, 9.7, 14.7 Hz, $CH_2{=}CHCH_2$); IR (KBr) 3429, 3314, 3057, 2939, 1634, 1605,

1580, 1528, 1489, 1454, 1414, 1364, 1342, 1315, 1300, 1286, 1246, 1207, 1195, 1153, 1111, 1076, 1061, 1038, 1022, 1003, 912, 881, 766, 729, 702 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{18}H_{20}NO_2$ ($[M + H]^+$): 282.1489. Found: 282.1500. HPLC condition: see the (1*R*,2*R*)-isomer.

(1*S*,2*R*)-*N*-Boc-2-amino-3-(1-naphthyl)-1-phenylpropan-1-ol (16, $R^1 = CH_2$α-Np). 97% ee, syn/anti = 2:98, $[\alpha]^{20}_D = -100.9°$ (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, DMSO-d_6, 82:18 mixture of rotamers) δ 7.84 (1H, d, J = 8.0 Hz, ArH), 7.73−7.69 (1H, m, ArH), 7.54 (1H, d, J = 7.6 Hz, ArH), 7.46−7.25 (9H, m, ArH), 6.76 (0.82H, d, J = 9.6 Hz, NH), 6.24 (0.18H, d, J = 10.0 Hz, NH), 5.67 (0.18H, d, J = 4.4 Hz, OCHPh), 5.62 (0.82H, d, J = 4.4 Hz, OCHPh), 4.71 (0.82H, m, OH), 4.59 (0.18H, m, OH), 3.97−3.90 (0.18H, m, NCH), 3.77−3.73 (0.82H, m, NCH), 3.61 (0.18H, d, J = 13.8 Hz, $NpCH_2$), 3.46 (0.82H, d, J = 13.8 Hz, $NpCH_2$), 2.92 (0.82H, dd, J = 11.0, 13.8 Hz, $NpCH_2$), 2.75 (0.18H, dd, J = 11.0, 13.8 Hz, $NpCH_2$), 1.12 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.6, 143.4, 135.6, 133.2, 131.5, 128.3, 127.5, 126.9, 126.6, 126.4, 126.2, 125.4, 125.1, 125.0, 123.2, 77.1, 75.1, 57.6, 31.7, 28.1; IR (KBr) 3406, 3387, 3061, 3042, 2980, 2934, 2878, 1672, 1531, 1454, 1394, 1367, 1333, 1273, 1252, 1217, 1196, 1171, 1107, 1067, 1040, 1020, 926, 797, 777, 729, 702 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{24}H_{27}NO_3Na$ ($[M + Na]^+$): 400.1883. Found: 400.1885. HPLC condition: see the (1*R*,2*R*)-isomer.

General Procedure for Diastereoselective Alkylation of Schiff Base Protected α-Amino Ketones (Scheme 9). To a solution of Schiff base protected α-amino ketone **13** or **18** (1.0 equiv) in THF (0.2 M) was added an ethereal solution of Grignard reagent (2−3 equiv) at −78 °C under argon atmosphere. The mixture was stirred for 1 h at the same temperature and poured into cooled saturated NH_4Cl. The whole mixture was extracted with ether. The combined extracts were then washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/ether as eluent) to give the corresponding Schiff base protected α-amino *tert*-alcohol **17** as a single diastereomer.

(2*R*,3*S*)-2-Diphenylmethyleneamino-1-(1-naphthyl)-3-phenylpentan-3-ol [(2*R*,3*S*)-17]. 97% ee, $[\alpha]^{24}_D = +189.7°$ (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (1H, d, J = 8.4 Hz, ArH), 7.64 (1H, d, J = 8.4 Hz, ArH), 7.53−7.48 (4H, m, ArH), 7.43 (2H, t, J = 8.0 Hz, ArH), 7.39−7.26 (5H, m, ArH), 7.20 (1H, t, J = 8.0 Hz, ArH), 7.15 (1H, d, J = 8.4 Hz, ArH), 7.09−7.02 (2H, m, ArH), 6.92 (1H, t, J = 7.6 Hz, ArH), 6.68 (2H, br t, J = 7.2 Hz, ArH), 5.74 (2H, br, ArH), 3.85 (1H, d, J = 10.0 Hz, NCH), 3.72 (1H, s, OH), 3.18 (1H, dd, J = 10.0, 13.8 Hz, $NpCH_2$), 2.94 (1H, d, J = 13.8 Hz, $NpCH_2$), 1.79 (1H, dq, J = 7.2, 7.2 Hz, CH_3CH_2), 1.73 (1H, dq, J = 7.2, 7.2 Hz, CH_3CH_2), 0.68 (3H, t, J = 7.2 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 143.1, 139.1, 135.5, 135.4, 133.6, 132.8, 129.9, 128.3, 128.1, 128.0, 127.8, 127.2, 127.0, 126.7, 126.5, 125.8, 125.1, 125.1, 124.9, 123.6, 79.3, 70.4, 34.5, 34.4, 7.8; IR (KBr) 3477, 3057, 3030, 2966, 2932, 2876, 1626, 1597, 1578, 1510, 1491, 1447, 1387, 1313, 1285, 1256, 1178, 1074, 1028, 959, 916, 775, 702 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{34}H_{32}NO$ ($[M + H]^+$): 470.2478. Found: 470.2465. The enantiomeric excess was determined after conversion to its *Z*-derivative (see below).

(2*R*,3*S*)-*N*-*Z*-4-Amino-5-(1-naphthyl)-3-phenylpentan-3-ol. 97% ee, $[\alpha]^{24}_D = +32.5°$ (*c* 1.00, THF); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (1H, d, J = 8.0 Hz, ArH), 7.70 (1H, d, J = 8.0 Hz, ArH), 7.55−7.09 (16H, m, ArH and NH), 4.86 (1H, d, J = 13.2 Hz, $PhCH_2$), 4.85 (1H, s, OH), 4.81 (1H, d, J = 13.2 Hz, $PhCH_2$), 4.00 (1H, dt, J = 3.2, 8.0 Hz, NCH), 2.99−2.77 (2H, m, $NpCH_2$), 1.84 (2H, br q, J = 7.2 Hz, CH_3CH_2), 0.57 (3H, t, J = 7.2 Hz, CH_2CH_3); IR (KBr) 3443, 3335, 3059, 3036, 2970, 2936, 1682, 1553, 1448, 1396, 1340, 1267, 1219, 1194, 1132, 1043, 1028, 1003, 968, 910, 773, 758, 704 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{29}H_{30}NO_3$ ($[M + H]^+$): 440.2220. Found: 440.2209. HPLC condition: DAICEL Chiralpak AD, hexane/EtOH = 4:1, flow rate = 0.5 mL/min, t_R = 12.2 (2*R*,3*S*) and 30.7 (2*S*,3*R*) min.

(2*R*,3*R*)-2-Diphenylmethyleneamino-1-(1-naphthyl)-3-phenylpentan-3-ol [(2*R*,3*R*)-17]. 97% ee, $[\alpha]^{23}_D = +247.3°$ (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (1H, d, J = 8.4 Hz, ArH), 7.69 (1H, d, J = 8.4 Hz, ArH), 7.56 (1H, d, J = 8.4 Hz, ArH), 7.36−7.18 (13H, m, ArH), 7.11 (1H, d, J = 6.8 Hz, ArH), 6.83 (1H, t, J = 7.4 Hz, ArH), 6.51 (2H, t, J = 7.4 Hz, ArH), 5.07 (2H, br, ArH), 4.01 (1H, s, OH), 3.78−3.73 (2H, m, NCH and $NpCH_2$), 3.23 (1H, dd, J = 11.2, 13.6 Hz, $NpCH_2$), 2.32 (1H, dq, J = 7.2, 7.2 Hz, CH_3CH_2), 2.18 (1H, dq, J = 7.2, 7.2 Hz, CH_3CH_2), 0.83 (3H, t, J = 7.2 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 144.6, 139.2, 135.1, 133.7, 132.8, 129.7, 128.3, 128.2, 128.2, 127.7, 127.7, 127.0, 126.9, 126.7, 126.6, 126.5, 126.2, 125.4, 125.2, 125.1, 123.5, 79.5, 70.9, 34.1, 30.0, 8.2; IR (KBr) 3454, 3059, 2968, 2934, 1628, 1597, 1578, 1510, 1491, 1447, 1375, 1313, 1285, 1180, 1074, 1030, 961, 912, 800, 775, 700 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{34}H_{32}NO$ ($[M + H]^+$): 470.2478. Found: 470.2462. HPLC condition: DAICEL Chiralcel OD, hexane/*i*-PrOH = 100:1, flow rate = 0.5 mL/min, t_R = 20.1 (2*S*,3*S*) and 23.1 (2*R*,3*R*) min.

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Supporting Information Available: Preparation of α-amino acid amide-derived Schiff bases **1**, **6**, and **10**, stereochemical assignment of **7ac**, **14**, **16**, and **17**, characterization of new compounds and their ^{1}H and ^{13}C NMR spectra; the crystallographic data for dipeptide **19** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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