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(*S*,*S*)-(+)-Pseudoephedrine as Chiral Auxiliary in Asymmetric Aza-Michael Reactions. Unexpected Selectivity Change when Manipulating the Structure of the Auxiliary

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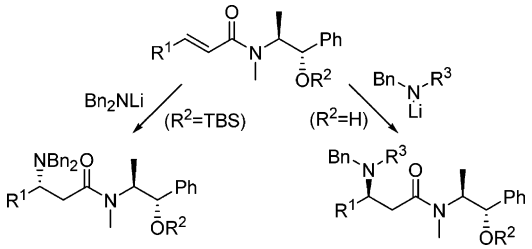

The asymmetric aza-Michael reaction of metal benzylamides to α,β-unsaturated amides derived from the chiral amino alcohol (*S*,*S*)-(+)-pseudoephedrine has been studied in detail. A deep study of the most important experimental parameters (solvent, temperature, nucleophile structure, influence of additives) has been carried out, showing that the reaction usually proceeds with good yields and diastereoselectivities, although the experimental conditions have to be modified depending on the substitution pattern of the conjugate acceptor. Additionally, a very interesting facial selectivity inversion has been observed when manipulating the structure of the chiral auxiliary, which has allowed a diastereodivergent procedure to be set up for performing asymmetric aza-Michael reactions using the same chirality source. Finally, the adducts obtained in the asymmetric aza-Michael reaction have proven to be very versatile synthetic intermediates in the preparation of other interesting compounds such as β-amino esters, γ-amino alcohols, and β-amino ketones in highly enantioenriched form.

Introduction

The development of new procedures for the stereocontrolled synthesis of β-amino acid derivatives continues to attract an enormous interest from organic chemists.[1] These β-amino acid derivatives are extremely important compounds not only because of their ubiquitous occurrence as constituents of a plethora of biologically important natural and synthetic products but also because they have shown to be very versatile intermediates in the synthesis of other nitrogen-containing compounds. Furthermore, the substitution of α-amino acids for β-amino acids in biologically active peptides has been used in recent years as a promising tactic to prepare peptide analogues with increased potency and/or enzymatic stability.[2]

Among the different methodologies found in the literature for the asymmetric synthesis of β-amino acid derivatives, one of the most widely used is the asymmetric Mannich-type reaction of enolates or analogous reagents to the C=N double bond of an azomethine compound.[3,4] Alternatively, the stereocontrolled conjugate addition of nitrogen nucleophiles to α,β-unsaturated esters, amides, imides, or related derivatives, the so-called aza-Michael reaction, has also been exploited by several research groups worldwide (Scheme 1).[5]

(1) For some reviews, see: (a) Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290. (b) Sewald, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5794. (c) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (d) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1. (e) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, 117. (f) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. See also: (g) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997.

(2) See, for example: (a) Hodgson, D. R. W.; Sanderson, J. M. *Chem. Soc. Rev.* **2004**, *33*, 422. (b) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219. (c) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (d) Seebach, D.; Abele, S.; Schreiber, J. V.; Martinoni, B.; Nussbaum, A. K.; Schild, H.; Schulz, H.; Hennecke, H.; Woessner, R.; Bitsch, F. *Chimia* **1998**, *52*, 734. (e) Seebach, D.; Mathews, J. L. *Chem. Commun.* **1997**, 2015. (f) Hintermann, T.; Seebach, D. *Chimia* **1997**, *50*, 244.

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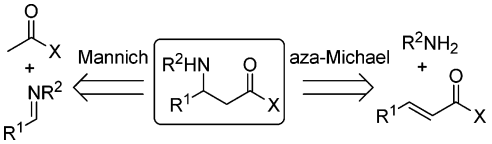
SCHEME 1. Two Most Employed Synthetic Approaches to β-Amino Acid Derivatives



Related to this topic, the strategies usually employed to exert stereocontrol in the newly created stereogenic centers involve the introduction of the chiral information either at the conjugate acceptor,[6] at the nitrogen nucleophile, as has been brilliantly demonstrated by the groups of Davies and Enders among others,[7] or by incorporating chiral ligands in the reaction medium in either a stoichiometric[8] or catalytic way.[9] In the first case, it is particularly important to remark that only a limited number of examples can be found in the literature in which chiral auxiliaries have been used directly attached to the carbonyl moiety of the acceptor in asymmetric aza-Michael reactions.[6] The main reason for this is that the chiral information remains located too far away from the position in which the new stereocenter is going to be formed. In fact, conformationally fixed cyclic or metal-chelated rigid auxiliaries have been the systems commonly tested, with good results in conjugate additions in general and aza-Michael reactions in particular. On the other hand, only a few reports can be found in the literature in which acyclic compounds have been used as chiral auxiliaries in this reaction.[6e,j,o] However, despite their conformational unpredictability, the use of acyclic templates can constitute a very powerful alternative to other auxiliaries because of their flexibility and potential for adopting an induced fit type conformation, which can be controlled at will, provided that the appropriate experimental conditions are chosen.

In this context, we and others have proven that the commercially available and cheap chiral amino alcohol pseudoephedrine constitutes an extremely useful and efficient chiral auxiliary in many asymmetric transformations such as alkylations,[10] aldol[11] and Mannich reactions,[4] aminations,[12] aziridine[13] and epoxide[14] ring-opening reactions, and Michael additions.[15] In all cases

(3) (a) Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem.* **2000**, 563. (b) Denmark, S.; Nicaise, J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 2, p 954. (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (d) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (e) Risch, N.; Arend, M. In *Stereoselective Synthesis, Houben-Weyl,* Helmchen, G., Hoffmann, R., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. E21/b, p 1833. (f) Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 4.1.

(4) We have previously reported a highly efficient procedure for the asymmetric synthesis of β-amino esters via asymmetric Mannich reaction using (*S*,*S*)-(+)-pseudoephedrine as chiral auxiliary. (a) Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2001**, *3*, 773. (b) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 9030.

(5) For a recent review on asymmetric catalytic aza-Michael reactions, see: (a) Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, 633. For general reviews on asymmetric conjugate additions in which aza-Michael reactions are extensively covered, see: (b) Christoffers, J. *Chem.*−*Eur. J.* **2003**, *9*, 4862. (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (d) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (e) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (f) Leonard, J.; Díez-Barra, E.; Merino, S. *Eur. J. Org. Chem.* **1998**, 2051. (g) Krause, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 283. (h) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. (i) d'Angelo, J.; Desmaele, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459.

(6) (a) Williams, D. R.; Nold, A. L.; Mullins, R. J. *J. Org. Chem.* **2004**, *69*, 5374. (b) Davies, S. G.; Dupont, J.; Easton, R. J. C.; Ichihara, O.; McKenna, J. M.; Smith, A. D.; de Sousa, J. A. A. *J. Organomet. Chem.* **2004**, *689*, 4184. (c) Sani, M.; Bruche, L.; Chiva, G.; Fustero, S.; Piera, J.; Volonterio, A.; Zanda, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2060. (d) Cardillo, G.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Org. Lett.* **2001**, *3*, 1165. (e) Volonterio, A.; Bravo, P.; Zanda, M. *Org. Lett.* **2000**, *2*, 1827. (f) Dumas, F.; Mezrhab, B.; d'Angelo, J. *J. Org. Chem.* **1996**, *61*, 2293. (g) Andres, C. J.; Lee, P. H.; Nguyen, T. H.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 3189. (h) Shimano, M.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7445. (i) Ishikawa, T.; Nagai, K.; Kudoh, T.; Saito, S. *Synlett* **1995**, 1171. (j) Shida, N.; Kabuto, C.; Niwa, T.; Ebata, T.; Yamamoto, Y. *J. Org. Chem.* **1994**, *59*, 4068. (k) Suzuki, I.; Kin, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1993**, *115*, 10139. (l) Amoroso, R.; Cardillo, G.; Sabatino, P.; Tomasini, C.; Trere, A. *J. Org. Chem.* **1993**, *58*, 5615. (m) Pyne, S. G.; Bloem, P.; Griffith, R. *Tetrahedron* **1989**, *45*, 7013. (n) Lange, B.; Bolhuis, F. V.; Feringa, B. L. *Tetrahedron* **1989**, *45*, 6799. (o) d'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112. (p) Davies, S. G.; Dordor-Hedgecock, I. M.; Sutton, K. H.; Walker, J. C. *Tetrahedron* **1986**, *42*, 5123.

(7) (a) Prieto, A.; Fernandez, R.; Lassaletta, J. M.; Vazquez, J.; Alvarez, E. *Tetrahedron* **2005**, *61*, 4609. (b) Davies, S. G.; Diez, D.; Dominguez, S. H.; Garrido, N. M.; Kruchinin, D.; Price, P. D.; Smith, A. D. *Org. Biomol. Chem.* **2005**, *3*, 1284. (c) Lee, H.-S.; Park, J.-S.; Kim, B. M.; Gellman, S. H. *J. Org. Chem.* **2003**, *68*, 1575. (d) Lagnenhan, J. M.; Gellman, S. H. *J. Org. Chem.* **2003**, *68*, 6440. (e) Podlech, J. *Synth. Commun.* **2000**, *30*, 1779. (f) Lucet, D.; Sabelle, S.; Kostelitz, O.; Le Gall, T.; Mioskowski, C. *Eur. J. Org. Chem.* **1999**, 2583. (g) Enders, D.; Müller, S. F.; Raabe, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 195. (h) Davies, S. G.; Garrido, N. M.; McGee, P. A.; Shilvock, J. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3105. (i) Sewald, N.; Hiller, K. D.; Körner, M.; Findeisen, M. *J. Org. Chem.* **1998**, *63*, 7263. (j) Ishikawa, T.; Nagai, K.; Kudoh, T.; Saito, S. *Synlett* **1998**, 1291. (k) Enders, D.; Wiedemann, J. *Synthesis* **1996**, 1443. (l) Enders, D.; Wahl, H.; Bettray, W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 455. (m) Tsukada, N.; Shimada, T.; Gyoung, Y. S.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **1995**, *60*, 143. (n) Rico, J. G.; Lindmark, R. J.; Rogers, T. E.; Bovy, P. R. *J. Org. Chem.* **1993**, *58*, 7948. (o) Hawkins, J. M.; Lewis, T. A. *J. Org. Chem.* **1992**, *57*, 2114. (p) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183. (q) Baldwin, S. W.; Aube, J. *Tetrahedron Lett.* **1987**, *28*, 179. For a selected example of asymmetric aza-Michael reaction using α,β-unsaturated amides as acceptors, see: (r) Davies, S. G.; Edwards, A. J.; Walters, I. A. S. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 175.

(8) (a) Sakai, T.; Doi, H.; Kawamoto, Y.; Yamada, K.; Tomioka, K. *Tetrahedron Lett.* **2004**, *45*, 9261. (b) Bi, Y.; Bailly, L.; Marsais, F.; Levacher, V.; Papamicael, C.; Dupas, G. *Tetrahedron: Asymmetry* **2004**, *15*, 3703. (c) Doi, H.; Sakai, T.; Iguchi, M.; Yamada, K.; Tomioka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2886.

(9) (a) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313. (b) Gandelman, M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 2393. (c) Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 9188. (d) Hamashima, Y.; Somei, H.; Shimura, Y.; Tamura, T.; Sodeoka, M. *Org. Lett.* **2004**, *6*, 1861. (e) Li, K.; Cheng, X.; Hii, K. K. *Eur. J. Org. Chem.* **2004**, 959. (f) Sibi, M. P.; Prabagaran, N.; Ghorpade, S. G.; Jasperse, C. P. *J. Am. Chem. Soc.* **2003**, *125*, 11796. (g) Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 16178. (h) Fadini, L.; Togni, A. *Chem. Commun.* **2003**, 30. (i) Nakama, K.; Seki, S.; Kanemasa, S. *Tetrahedron Lett.* **2002**, *43*, 829. (j) Jin, X. L.; Sugihara, H.; Daikai, K.; Takeishi, H.; Jin, Y. Z.; Furuno, H.; Inanaga, J. *Tetrahedron* **2002**, *58*, 8321. (k) Cardillo, G.; Gentilucci, L.; Gianotti, M.; Kim, H.; Perciaccante, R.; Tolomelli, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2395. (l) Kawatsura, M.; Hartwig, J. F. *Organometallics* **2001**, *20*, 1960. (m) Sundararajan, G.; Prabagaran, N. *Org. Lett.* **2001**, *3*, 389. (n) Sibi, M. P.; Liu, M. *Org. Lett.* **2001**, *3*, 4181. (o) Zhuang, W.; Hazell, R. G.; Jorgensen, K. A. *Chem. Commun.* **2001**, 1240. (p) Horstman, T. E.; Guerin, E. J.; Miller, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3635. (q) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959. (r) Zhou, F.; Detty, M. R.; Lachicotte, R. J. *Tetrahedron Lett.* **1999**, *40*, 585. (s) Falborg, L.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2823.

(10) (a) Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *J. Org. Chem.* **2004**, *69*, 790. (b) Keck, G. E.; Knutson, C. E.; Wiles, S. A. *Org. Lett.* **2001**, *3*, 707. (c) Guillena, G.; Najera, C. *Tetrahedron: Asymmetry* **2001**, *12*, 181. (d) Nagula, G.; Huber, V. J.; Lum, C.; Goodman, B. A. *Org. Lett.* **2000**, *2*, 3527. (e) Myers, A. G.; Schnider, P.; Kwon, S.; Kung, D. W. *J. Org. Chem.* **1999**, *64*, 3322. (f) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. (g) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656. (h) Myers, A. G.; McKinstry, L.; Gleason, J. L. *Tetrahedron Lett.* **1997**, *38*, 7037.

reported, amides derived from this amino alcohol have been employed as nucleophiles via their corresponding enolates. In fact, we have reported very recently in a preliminary form the first case in which a pseudoephedrine-containing chiral substrate has acted as the electrophilic counterpart in an asymmetric aza-Michael reaction.[16] In this article, we report in detail our findings when working in the expansion of the scope of our original procedure, together with an unexpected selectivity change observed when we decided to modify the structure of the chiral auxiliary, trying to further optimize its behavior as stereodirecting element.

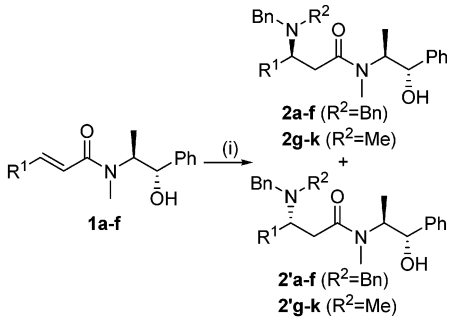
Results and Discusion

As mentioned before, we have published recently a first approach to the asymmetric aza-Michael reaction of lithium dibenzylamide or lithium benzyl methylamide to α,β-unsaturated amides derived from the chiral amino alcohol (*S*,*S*)-(+)-pseudoephedrine.[16] In this preliminary work, we optimized some experimental variables such as the solvent, the temperature, and the equivalents of nucleophile to be employed, showing that the reaction proceeded cleanly and in good yields in most cases when it was performed in toluene, at −90 °C, and using 4 equiv of the lithium benzylamide reagent (method A, Scheme 2). However, we also found that the diastereoselectivity of the reaction was rather dependent upon the nature of the substituents at the α,β-unsaturated chain, and therefore, modified experimental conditions (method B) had to be used to reach high levels of stereocontrol in some particular cases. We have also extended this experimental protocol to another previously unpublished substrate ($R^1 = {}^n$Pr, **1f**), and the best results concerning the diastereoselectivity of the aza-Michael reaction with Bn_2NLi were obtained using the Bn_2NLi/TMEDA combination of reagents (method B, Scheme 2). Moreover, in this case the diastereomeric mixture was easily resolved by flash column chromatography rendering both diastereoisomers with high de.

Taking into consideration that the scope of our experimental protocol was somewhat limited, in the sense that α,β-unsaturated enamides **1c**, **1e**, and **1f** furnished the conjugate addition products in relatively lower diastereomeric ratio compared to the others, and also considering the moderate yields obtained in some cases, we decided to survey other modified reaction conditions, starting with the inclusion of additives in the reaction medium that would have a positive influence in both the yield and the diastereoselectivity of this transformation (Scheme 3, Table 1). First, because it has been previously reported that the use of LiCl as an additive entails a dramatic influence in the stereochemical outcome of the process in many transformations, and in the Michael reaction of pseudoephedrine amide enolates in particular,[17] we proceeded to perform the conjugate addition reaction of lithium dibenzylamide with enamide **1b** in the presence of 5 equiv of LiCl, but in our case the only effect that we experienced was a dramatic decrease in the yield of the reaction (entry 1). We also considered the use of HMPA in the same context (entry 2), observing that the reaction proceeded with poorer yield (70 versus 85%) and slightly lower diastereoselection (**2b/2′b** ratio 85/15 versus 94/6) than the reaction performed in the presence of TMEDA (method B, Scheme 2).

Because we had also previously explored the use of the potentially chelating diamine TMEDA as additive in this reaction, with good results in some cases (see Scheme 2, method B), we also tested other possible diamine additives such as pentamethyldiethylenetriamine (PMDETA) and (−)-sparteine. As can be seen in Table 1, conducting

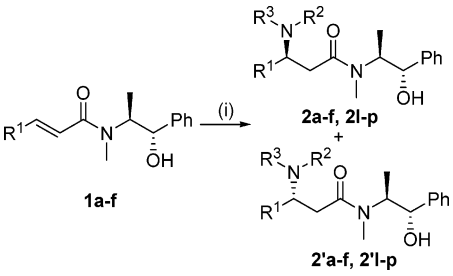
SCHEME 2[a]



2a (R^1=Me): 85% Yield, **2a/2'a**: >99/<1 (Method A)	
2b (R^1=Et): 85% Yield, **2b/2'b**: 94/6 (Method B)	
2c (R^1=^{i}Pr): 62% Yield, **2c/2'c**: 80/20 (Method B)	
2d (R^1=^{t}Bu): 33% Yield, **2d/2'd**: >99/<1 (Method A)	
2e (R^1=Ph): 15% Yield, **2e/2'e**: 98/2 (Method A)	
2f (R^1=^{n}Pr): 68% Yield, **2f/2'f**: 73/27 (Method B)	
2g (R^1=Me): 88% Yield, **2g/2'g**: >99/<1 (Method A)	
2h (R^1=Et): 62% Yield, **2h/2'h**: 74/26 (Method A)	
2i (R^1=^{i}Pr): 53% Yield, **2i/2'i**: 80/20 (Method A)	
2j (R^1=^{t}Bu): 52% Yield, **2j/2'j**: 88/12 (Method A)	
2k (R^1=Ph): 94% Yield, **2k/2'k**: 72/28 (Method A)	

[a] Reagents and conditions: Method A: Bn_2NLi or BnMeNLi, toluene, −90 °C. Method B: Bn_2NLi, TMEDA, toluene, −90 °C.

SCHEME 3[a]



[a] For reagents and conditions, see Table 1.

(11) (a) Vicario, J. L.; Rodriguez, M.; Badía, D.; Carrillo, L.; Reyes, E. *Org. Lett.* **2004**, *6*, 3171. (b) Vicario, J. L.; Badía, D.; Rodríguez, M.; Carrillo, L. *Tetrahedron: Asymmetry.* **2003**, *14*, 489. (c) Vicario, J. L.; Badía, D.; Domínguez, E.; Rodríguez, M.; Carrillo, L. *J. Org. Chem.* **2000**, *65*, 3754.

(12) (a) Vicario, J. L.; Badía, D.; Carrillo, L. *Tetrahedron: Asymmetry* **2002**, *13*, 745. (b) Anakabe, E.; Vicario, J. L.; Badía; D.; Carrillo, L.; Yoldi, V. *Eur. J. Org. Chem.* **2001**, 4343.

(13) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 5801.

(14) Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428.

(15) (a) Smitrovich, J. H.; DiMichele, L.; Qu, C.; Boice, G. N.; Nelson, T. D.; Huffman, M. A.; Murry, J. *J. Org. Chem.* **2004**, *69*, 1903. (b) Smitrovich, J. H.; Boice, G. N.; Qu, C.; Dimichelle, L.; Nelson, T. D.; Huffman, M. A.; Murry, J.; McNamara, J.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1963. (c) Myers, A. G.; Barbay, J. K.; Zhong, B. *J. Am. Chem. Soc.* **2001**, *123*, 7207.

(16) Etxebarria, J.; Vicario, J. L.; Badia, D.; Carrillo, L. *J. Org. Chem.* **2004**, *69*, 2588.

(17) See, for example: Rück, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 433. See also ref 15

TABLE 1. Survey of Different Additives and Nucleophiles in the Diastereoselective Conjugate Addition to (*S,S*)-(+)-Pseudoephedrine Enamides 1a−f

entry	R^1	R^2	R^3	product	Nu	solvent	*T* (°C)	yield (%)[a]	**2/2′**[b]
1	Me	Bn	Bn	**2a**	Bn_2NLi/LiCl	THF	−105	20	n.d.[c]
2	Me	Bn	Bn	**2a**	Bn_2NLi/HMPA	THF	−105	70	85/15
3	Et	Bn	Bn	**2b**	Bn_2NLi/PMDETA	toluene	−90	85	79/21
4	Et	Bn	Bn	**2b**	Bn_2NLi/(−)-sparteine	toluene	−90	traces	n.d.[c]
5	Et	PMB	PMB	**2l**	$(PMB)_2NLi$	THF	−105	50	80/20
6	Et	Cbz	H	**2n**	CbzNHLi	toluene	−90	traces	n.d.[c]
7	Et	OBn	H	**2p**	OBnNHLi	toluene	−90	traces	n.d.[c]
8	^{n}Pr	Bn	H	**2m**	BnTMSNLi	toluene	−90	38	65/35
9	Me	Bn	Bn	**2a**	$(Bn_2N)_2Cu{\cdot}Li$/TMEDA	THF	−105	57	92/8
10	Et	Bn	Bn	**2b**	$(Bn_2N)_2Cu{\cdot}Li$/TMEDA	THF	−105	63	93/7
11	^{i}Pr	Bn	Bn	**2c**	$(Bn_2N)_2Cu{\cdot}Li$/TMEDA	THF	−105	33	58/42
12	^{t}Bu	Bn	Bn	**2d**	$(Bn_2N)_2Cu{\cdot}Li$/TMEDA	THF	−105	60	>99/<1
13	Ph	Bn	Bn	**2e**	$(Bn_2N)_2Cu{\cdot}Li$/TMEDA	THF	−105	46	38/62
14	^{n}Pr	Bn	Bn	**2f**	$(Bn_2N)_2Cu{\cdot}Li$/TMEDA	THF	−105	78	68/32

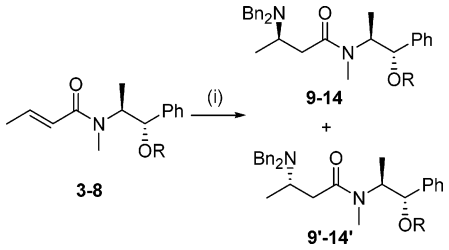
[a] Global yield for the mixture of both diastereoisomers isolated after flash column chromatography purification. [b] Determined by HPLC (Chiracel OD column, UV detector, *n*-hexane/^{i}PrOH 95:5, flow rate 1.00 mL/min). [c] n.d. = not determined.

the reaction in the presence of such chelating amines did not afford results (entries 3 and 4) better than those previously obtained with the use of TMEDA and enamide **1b**. Furthermore, we also surveyed other possible modified amide reagents as nucleophiles. In a first approach, lithium bis(*para*-methoxybenzylamide ($(PMB)_2NLi$) was reacted with enamide **1b** under method A reaction conditions, but the addition product was obtained as a 4:1 mixture of diastereoisomers (entry 5). The use of other structurally different metal amides such as lithium benzyloxycarbonylamide or lithium *O*-benzylhydroxylamide was also ineffective (entries 6 and 7). We also tested lithium trimethylsilylbenzylamide as nucleophile, which has been successfully employed before in a variety of aza-Michael additions,[18] but in this case we isolated the corresponding β-amino amide adduct **2m** with low yield and diastereoselectivity (entry 8).

An interesting result was achieved when using a dibenzylamine-derived lithium amidocuprate as nucleophile and performing the reaction in THF as solvent (entries 9−14). The reagent was prepared in situ by mixing lithium dibenzylamide, CuI, and TMEDA in 2:1:2 ratio,[19] and a THF solution of the conjugate acceptor was added over the resulting solution. In all cases, the diastereoselectivities were similar to the best ones obtained previously with lithium dibenzylamide or the Bn_2NLi/TMEDA combination (see Table 1), with the only exception of amide **1e**, in which, in addition, a reversal of the diastereofacial selectivity of the reaction was observed (entry 13). However, we observed a remarkable improvement in the yield of the reaction with enamides **1d** and **1f**, and therefore, we decided to adopt these conditions as the best ones for the preparation of *N*,*N*-dibenzyl-β-amino amides **2d** and **2f**.

Modification of the Chiral Auxiliary. Unexpected Facial Selectivity Inversion. Next, we proceeded to modify the structure of the chiral auxiliary to further increase the scope of the reaction. In this context, we focused on the modification of the free hydroxyl group present in the pseudoephedrine moiety. This group suffers a quick proton lithium exchange at the first stage

SCHEME 4[a]



[a] For reagents and conditions, see Table 2.

of the reaction, as can be observed during the first stages of the addition of the deep violet colored Bn_2NLi nucleophile over the solution containing the starting pseudoephedrine enamide. The formation of this alkoxide is believed to play a very important role in the development of the stereoselective process. For that reason, we hypothesized that by protecting this hydroxy functionality with groups of different nature we should be able to modify the conformational arrangement of the auxiliary, and therefore a fine-tuning of the steric environment around the place in which the aza-Michael reaction has to occur could be achieved.

Consequently, we prepared a wide range of differently protected derivatives of compound **1a** by introducing various alkyl and silyl substituents using standard procedures. In this way, several modified pseudoephedrine enamides were obtained in which a small substituent such as methyl, medium-size groups such as benzyl and trimethylsilyl, and bulky ones such as TBS, TBDPS, and TIPS were incorporated at the hydroxyl function of the pseudoephedrine moiety. We next proceeded to perform the conjugate addition reaction of Bn_2NLi under the optimized conditions (Scheme 4), obtaining in all cases the corresponding β-amino amide adducts in good to excellent yields (Table 2). However, the most outstanding effect observed in this sequence was the fact that the stereochemical outcome of the reaction had been inverted and the major product in all cases showed the opposite configuration at the newly created stereogenic center, compared to the reaction using the unmodified auxiliary.[20]

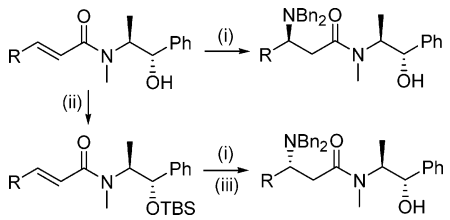
(18) (a) Asao, N.; Uyehara, T.; Yamamoto, Y. *Tetrahedron* **1988**, *44*, 4173.
(19) Yamamoto, Y.; Asao, N.; Uyehara, T. *J. Am. Chem. Soc.* **1992**, *114*, 5427.

TABLE 2. Diastereoselective Conjugate Addition of Lithium Dibenzylamide to O-Protected (*S*,*S*)-(+)-Pseudoephedrine Enamides 3−8

entry	R	enamide	solvent	nucleophile	product	*T* (°C)	yield (%)[a]	dr[b]
1	Me	**3**	toluene	Bn_2NLi	**9**	−90	60	38/62
2	Bn	**4**	toluene	Bn_2NLi	**10**	−90	76	40/60
3	TMS	**5**	toluene	Bn_2NLi	**11**	−90	51	47/53
4	TBDPS	**6**	toluene	Bn_2NLi	**12**	−90	65	9/91
5	TIPS	**7**	toluene	Bn_2NLi	**13**	−90	67	37/63
6	TBS	**8**	toluene	Bn_2NLi	**14**	−90	80	9/91
7	TBS	**8**	toluene	Bn_2NLi/TMEDA	**14**	−90	87	43/57
8	TBS	**8**	THF	Bn_2NLi	**14**	−105	63	41/59
9	TBS	**8**	THF	Bn_2NLi/TMEDA	**14**	−105	66	37/63

[a] Global yield for the mixture of both diastereoisomers isolated after flash column chromatography purification. [b] dr indicates the **9**−**14**/**9′**−**14′** ratio determined by HPLC (Chiracel OD column, UV detector, *n*-hexane/^{i}PrOH 95:5, flow rate 1.00 mL/min) of the β-amino amides **2a**−**f** obtained after deprotecting the hydroxylic group.

SCHEME 5[a]



[a] Reagents and conditions: (i) Bn_2NLi, toluene, −90 °C. (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, room temperature (rt). (iii) TBAF, THF, rt.

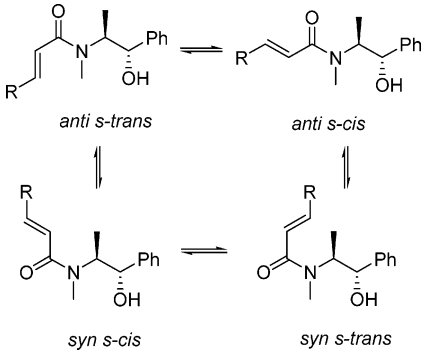


FIGURE 1. Four possible conformers that can be present in the reaction medium during the aza-Michael reaction of lithium dibenzylamide to (*S*,*S*)-(+)-pseudoephedrine enamides **1a**−**f**.

As can be seen in Table 2, the best results concerning the diastereoselectivity of the reaction were obtained when the bulky TBS and TBDPS substituted derivatives were used (entries 4 and 6), while the protection with small- and medium-size groups afforded in all cases an almost 4:6 mixture of diastereoisomers (entries 1−3). We also tried the very bulky TIPS group, but the use of enamide **7** led to a very poor degree of diastereoselection (entry 5). We also tried other modified conditions with the *O*-TBS-protected substrate **8** but no improvement in the diastereoselectivity was obtained either by using the Bn_2NLi/TMEDA combination of reagents (entries 7 and 9) or by changing the nature of the solvent (entries 8 and 9). It has to be mentioned that other lithium amides such as BnMeNLi or BnTMSNLi were tested but with similar low degrees of stereochemical control in the conjugate addition reaction with these O-protected α,β-unsaturated amides.

Therefore, we can consider this reaction as a very powerful alternative protocol in the field of the chiral auxiliary methodology (Scheme 5). By means of this procedure, chiral nonracemic β-amino carbonyl compounds can be prepared with any desired configuration at the newly created stereogenic center via a diastereodivergent asymmetric aza-Michael reaction with no need to change between the two enantiomers of the chiral auxiliary to obtain the final adduct in the right configuration.

Mechanistic Aspects. The conjugate addition of benzyl amides to (*E*)-enamides **1a**−**f** may occur via any of the four possible conformers present in the reaction medium as a result of the presence of the tertiary amide functionality and the α,β-unsaturated carbonyl moiety (Figure 1). Nevertheless, the preference for lithium amides to react with *E*-α,β-unsaturated acceptors exclusively in the *s*-cis conformation is known,[21] which rules out the contribution of the two *s*-trans conformers. In addition, the ^{1}H NMR spectrum of the lithium alkoxide derived from enamide **1a** recorded in toluene at −80 °C showed the presence of an approximately 1.8:1 syn/anti rotamer ratio, which indicates that the reaction proceeds via one reactive conformer, the other one unreactive under the reaction conditions employed.[22]

In other reactions in which (*S*,*S*)-pseudoephedrine amides have been involved, it has been previously proposed that the reaction proceeds through an intermediate in which the aminoalkoxide chain adopts an open staggered conformation, with the C−H bond α to nitrogen lying in plane with the carbonyl oxygen to minimize allylic strain (Figure 2).[10f,14] This hypothesis has also been supported by the X-ray crystal structures of some pseudoephedrine amides. On the basis of this model, we propose that the different facial selectivity induced by the auxiliary when used in its −OH or −*O*-TBS form should be attributed to the ability of the lithium alkoxide (generated after the first deprotonation

(20) An example of facial selectivity inversion after protection of a prolinol-derived auxiliary in asymmetric alkylation reactions has been reported recently. (a) Andersson, F.; Hendenström, E. *Tetrahedron: Asymmetry* **2004**, *15*, 2539. For other examples, see: (b) Gebert, A.; Heimgartner, H. *Helv. Chim. Acta* **2002**, *85*, 2073. (c) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233. (d) Sonnet, P. A.; Heath, R. R. *J. Org. Chem.* **1980**, *45*, 3137.

(21) (a) Davies, S. G.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1129. (b) Asao, N.; Uyehara, T.; Yamamoto, Y. *Tetrahedron* **1990**, *46*, 4563.

(22) The terms syn and anti refer to the relative position of the *N*-Me group with respect to the carbonyl oxygen group in the amide moiety.

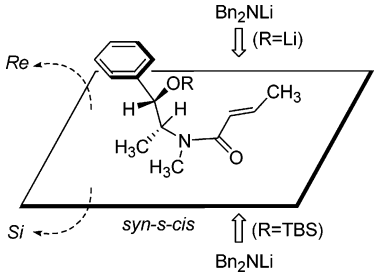


FIGURE 2. Proposed model that accounts for the observed facial selectivity in the conjugate addition of Bn_2NLi to (*S*,*S*)-pseudoephedrine enamides.

of the hydroxy group in amides **1a**−**f**) to direct the attack of the lithium amide by coordination,[23] while in the O-protected version of the auxiliary, the bulky TBS group provides a sterical blockade, forcing the income of the nucleophile through the opposite face. Under this assumption, and in sight of the absolute configuration of the newly created stereogenic center in the reaction, a *syn-s-cis* arrangement should be postulated as the reactive conformation for the acceptor.

In a recent report, Davies et al. brilliantly demonstrated that the 1,4-addition of lithium benzylamides to chiral (*E*)-enoyloxazolidinones proceeds via one reactive conformer, which could be identified by means of double asymmetric induction as a mechanistic probe using chiral lithium *N*-benzyl-*N*-α-methylbenzylamides together with the chiral acceptor.[24] For that reason, we decided to perform the same experiments to support the proposed *syn-s-cis* reactive conformation for the conjugate addition reaction of pseudoephedrine enamides with lithium amides (Figure 3). The reaction of α,*β*-unsaturated amide **1a** with lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **(*S*)-15** in toluene at −78 °C afforded the corresponding *β*-amino amide adduct as a 40:60 mixture of the two possible **(3*S*,1′*S*,2′*S*,α*S*)-16/(3*R*,1′*S*,2′*S*,α*S*)-16′** epimers,[25] while the same reaction with lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **(*R*)-15** furnished the final compound **(3*S*,1′*S*,2′*S*,α*R*)-17** with high diastereoselectivity (90:10 dr). The absolute configuration of the newly created stereogenic center was determined by chemical correlation, obtaining known methyl-3-aminobutanoate by removal of the pseudoephedrine moiety and conversion into the corresponding methyl ester followed by hydrogenolytic debenzylation using procedures described later in this article. The experiments performed indicate that the reaction proceeds under stereochemical control of the chiral amide nucleophile, **(*R*)-15/1a** being the matched combination of reagents and **(*S*)-15/1a** being the mismatched one.

Given the known preference of chiral lithium amide **(*R*)-15** to react with *N*,*N*-dimethylcrotonamide via its *s*-cis conformation, yielding the corresponding (*R*)-*β*-amino amide adduct,[7r] the obtained matched/mismatched relationship between amide **1a** and chiral lithium amides **15** is consistent with a mechanistic scenario such as that depicted in Figure 3 and is consistent with our proposal. In this way, the reaction of the chiral nitrogen nucleophile **(*R*)-15** with amide **1a** should happen via an intermediate in a *syn-s-cis* conformation by means of the stereodirecting ability of the lithium alkoxide moiety, resulting in the formation of the new stereogenic center in an *R* configuration (matched case), while the reaction of **1a** with **(*S*)-15**, which occurred with stereochemical control of the chiral amide reagent, should happen after the attack to the acceptor through the opposite face resulting in the low degree of diastereoselection observed (mismatched case).

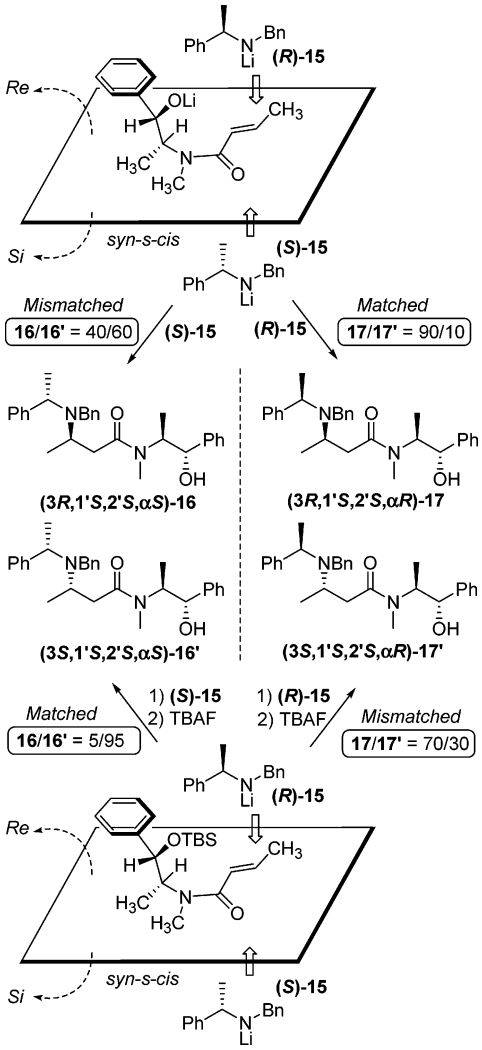


FIGURE 3. Double asymmetric induction as a mechanistic probe using chiral lithium *N*-benzyl-*N*-α-methylbenzylamides and (*S*,*S*)-(+)-pseudoephedrine enamides **1a** and **8**.

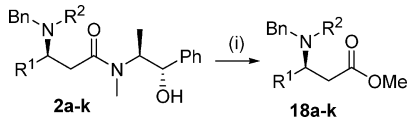
We also performed the same double asymmetric induction experiments on the *O*-TBS enamide **8** (Figure 3). In this case, the reaction of **8** with chiral lithium amide **(*R*)-15** followed by desilylation furnished a 70:30 mixture of diastereoisomers (**17** and **17′**), while the use of **(*S*)-15** resulted in a highly diastereoselective transformation (**16/16′** ratio = 5:95). As expected, a change in the double asymmetric induction pattern was observed, and in this

(23) The stereodirecting power of the lithium alkoxide in other reactions of amides derived from chiral amino alcohols has also been invoked by other authors to account for the observed diastereoselectivity. See, for example: Askin, D.; Volante, R. P.; Ryan, K. M.; Reamer, R. A.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 4245. See also refs 13 and 14.

(24) Davies, S. G.; Hermann, G. J.; Sweet, M. J.; Smith, A. D. *Chem. Commun*. **2004**, 1128.

(25) The reaction of enamide **1a** with Bn_2NLi in toluene at −78 °C furnished the corresponding *β*-amino amide adduct in 30% yield and in 79:21 dr (see ref 16).

SCHEME 6[a]



[a] Reagents and conditions: (i) NaOMe, Me_2CO_3, CH_2Cl_2, rt.

case, the chiral amide **(*S*)-15** and the substrate **8** resulted as the matched combination of reagents. These results are also consistent with a change in the facial selectivity induced by the auxiliary as a result of the silylation of the pseudoephedrine chain, which now directs the attack of the nucleophile through the less hindered *Si* face.

Transformation of the Addition Products into Other Valuable Synthons. The highly enantioenriched β-amino amides obtained from the asymmetric aza-Michael reaction were subjected to several derivatization processes to survey their possibilities in synthetic organic chemistry. In this way, β-amino esters, γ-amino alcohols, and β-amino ketones were obtained in nearly optically pure form.

(a) Synthesis of β-Amino Esters. Acid hydrolysis of β-amino amides **2a**−**e** with 4 M H_2SO_4 and subsequent esterification under conditions successfully employed by us with other highly functionalized pseudoephedrine amides[4,11−13] yielded the corresponding β-amino esters **18a**−**e** with no loss of enantiomeric excess but in rather low yields (15−35%). The presence of β-elimination side products in the reaction mixture revealed that this process was an important side reaction and thus provided an explanation for these low yields. Hydrolysis under basic conditions (4 M NaOH) allowed us to isolate the wanted esters in better yields but with significantly lower enantiomeric excesses.[26]

Because these results indicated that the starting β-amino amides were not tolerant of the conditions required for an acid- or base-promoted hydrolysis, we decided to move to a procedure that should allow us to obtain the desired β-amino esters and avoid this previous hydrolysis step. In this context, the use of the sodium methoxide/dimethyl carbonate combination of reagents (Scheme 6) led, in a single step, to the isolation of the desired β-amino esters **18a**−**k** in good to excellent yields and with complete conservation of the stereochemical integrity (Table 3).

This transformation has to be understood in terms of a first base-promoted *N*−*O* acyl transfer of the β-amino carbonyl moiety into the β-amino alcohol structure of the pseudoephedrine chain, followed by a trans-esterification process. The chiral auxiliary was recovered as an oxazolidinone derivative after the flash column chromatography purification step, the formation of this stable cyclic carbamate being what precludes the reversion of the trans-esterification equilibrium and therefore providing the driving force for the reaction to occur in such a high yield.

It has to be mentioned that, at this point, we were able to determine the absolute configuration of the newly created stereogenic center during the conjugate addition step by chemical correlation. In fact, debenzylation of

TABLE 3. Synthesis of the β-Amino Esters 18a−k

entry	product	R^1	R^2	yield (%)[a]	ee (%)[b]
1	**18a**	Me	Bn	73	>99
2	**18b**	Et	Bn	75	88
3	**18c**	^{i}Pr	Bn	52	60
4	**18d**	^{t}Bu	Bn	70	>99
5	**18e**	Ph	Bn	63	96
6	**18g**	Me	Me	51	>99
7	**18h**	Et	Me	26	48
8	**18i**	^{i}Pr	Me	24	60
9	**18j**	^{t}Bu	Me	32	76
10	**18k**	Ph	Me	41	44

[a] Yield of isolated product. [b] Determined by chiral HPLC (Chiralcel OJ column, UV detector, 2-propanol/hexanes, 5:95, flow rate: 0.85 mL/min).

N,*N*-dibenzyl-β-amino ester **18a** (H_2, Pd/C) directly furnished methyl (−)-3-aminobutanoate, a known compound[27] with a negative optical rotation value, which indicated the *R* configuration for its stereogenic center. In the same way, the esterification/debenzylation sequence performed on β-amino amide **2′a**, which was obtained via aza-Michael reaction on the *O*-TBS-protected α,β-unsaturated amide **8**, afforded the corresponding (*S*)-β-amino ester, as could be checked by its positive $[\alpha]^{20}_D$ value. This configuration assignment was further extended, by analogy, to the other β-amino amides (**2a**−**p** and **2′a**−**p**) obtained, assuming the same stereochemical outcome for all the aza-Michael addition reactions performed.

(b) Synthesis of γ-Amino Alcohols. Chiral γ-amino alcohols are extremely interesting building blocks in organic synthesis, not only because of their ubiquitous occurrence by themselves or as constituents of many valuable natural and synthetic products but also because they are very versatile precursors of other important compounds as well as their application as chiral auxiliaries or ligands in asymmetric synthesis.[28,29] In our case, such a functionality should be easily reached from the highly enantioenriched adducts obtained in the previous aza-Michael reaction, provided that a procedure is found that readily reduces the amide functionality to the corresponding alcohol overriding the parallel formation of any amine-type byproducts.

Using β-amino amide **2a** as model compound, we surveyed first some reducing reagents such as LAH, DIBAL, $LiHBEt_3$, and AlH_3 at different temperatures but in all cases we could only recover the starting material unchanged or isolate the corresponding (*S*,*S*)-(+)-pseudoephedrine-containing diamine. In contrast, when we treated the β-amino amide **2a** with lithium amidotrihydroborate[30] (prepared in situ by treatment of borane−ammonia complex with LDA) at 50 °C, the corresponding γ-*N*,*N*-dibenzylamino alcohol **19a** was obtained with good yield and no formation of any diamine byproduct was observed (Scheme 7). However, the reaction proceeded with significant epimerization (ee = 74%, starting from

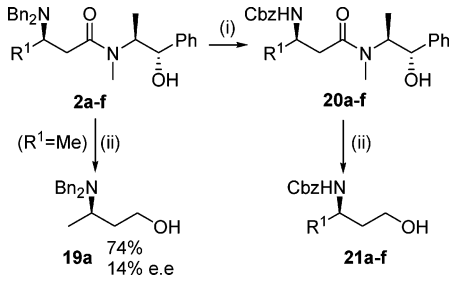
(26) Davies et al. have also reported difficulties in the hydrolysis of *N*′-benzyl-*N*′-(α-methylbenzyl)-*N*,*N*-dimethylcarboxamides. See ref 7r.

(27) Murer, P.; Rheiner, B.; Juaristi, E.; Seebach, D. *Heterocycles* **1994**, *39*, 319.

(28) See, for example: (a) Bartoli, G.; Cimarelli, C.; Mercantoni, E.; Palmieri, G.; Petrini, M. *J. Org. Chem.* **1994**, *59*, 5328 and references therein. See also (b) Hashiguchi, S.; Kawada, A.; Natsugari, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2435. (c) Wang, Y.-F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465.

(29) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley & Sons: New York, 1995.

SCHEME 7[a]



[a] Reagents and conditions: (i) 1. H_2, Pd/C, EtOH, rt; 2. Cbz_2O, NaOH, rt. (ii) LDA, $BH_3{\cdot}NH_3$, THF, 0 °C.

TABLE 4. Synthesis of the γ-Amino Alcohols 21a−f

entry	R^1	product	yield (%)[a]	product	yield (%)[a]	ee (%)[b]
1	Me	**20a**	68	**21a**	88	99
2	Et	**20b**	75	**21b**	76	90
3	^{t}Bu	**20d**	64	**21d**	72	98
4	Ph	**20e**	43	**21e**	90[c]	96
5	^{n}Pr	**20f**	72	**21f**	61	98

[a] Yield of isolated product. [b] Determined by chiral HPLC (Chiralcel OJ column, UV detector, 2-propanol/hexanes, 5:95, flow rate: 0.85 mL/min). [c] Based on recovered **2e**.

diastereomerically pure amide **2a**) in the stereogenic center created in the aza-Michael reaction. We believe that, in the same way that it happened in the hydrolysis of the same amide, the basic medium at such high temperatures should be responsible for this unwanted process. All attempts to perform this reaction at lower temperatures failed, recovering in all cases the starting material unchanged.

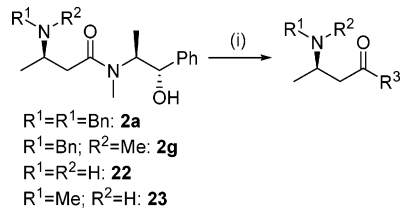
Suspecting that the presence of the dibenzylamino group should have an important role in this epimerization side reaction, due to its facility to suffer a β-elimination process,[31] we proceeded to change the groups attached to the amino group. Hydrogenation of amide **2a** and protection of the corresponding debenzylated compound with a benzyloxycarbonyl group led to the corresponding *N*-Cbz amide **20a**, which when reduced with LAB proceeded smoothly even at low temperatures, furnishing *N*-Cbz-γ-amino alcohol **21a** in good yield and with no epimerization (Scheme 7). These conditions were applied to the other amides **2b**−**e**, providing the corresponding N-protected γ-amino alcohols in good to excellent yields and with complete conservation of the stereochemical integrity (Table 4).

The resulting reduction was very clean, with no byproducts in the crude reaction mixture and, therefore, affording almost pure compounds after a simple acid−base standard workup procedure. Remarkably, it was possible to recover the chiral auxiliary from the basic organic extracts in ca. 80% yield, which allowed us to recycle it for further uses and, therefore, increasing the synthetic efficiency of this procedure.

(30) Myers, A. G.; Yang, B. H.; Chen, H.; Kopecky, D. J. *Synlett* **1997**, 457. See also ref 10f.

(31) We believe that the epimerization of the C-3 stereocenter occurs via base-promoted elimination of the dibenzylamino group (retro-aza-Michael reaction) followed by re-addition of the dibenzylamide anion and the α,β-unsaturated amide both generated in the retro-aza-Michael reaction. However, the possibility of epimerization via a retro-Mannich reaction should also be taken into account.

SCHEME 8[a]



[a] Reagents and conditions: (i) 1. R^3Li, THF, 0 °C; 2. NH_4Cl.

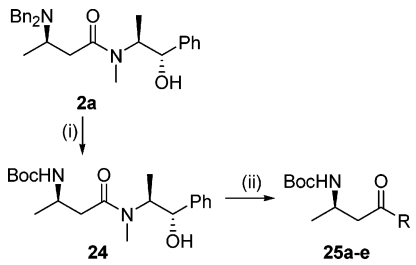
(c) Synthesis of Chiral β-Amino Ketones. The β-amino ketone functionality is another interesting structure present in a great variety of compounds found in nature which present interesting biological activities, and it is also a common intermediate in the preparation of many interesting compounds in the areas of pharmaceutical and medicinal chemistry.[32] In our case, ready access to enantioenriched β-amino ketones can be accomplished from β-amino amides **2** via 1,2-addition of organolithium reagents to the pseudoephedrine amide moiety, which has previously proven to be a very appropriate group for such a transformation, giving in many cases comparable or even better results than the well-known Weinreb amides.[33] In most of the examples reported, the addition of organolithium reagents to the carbonyl group of pseudoephedrine amides is known to be extremely fast and clean, with no presence of overaddition byproducts, and very tolerant of other functionalities present in the substrate.[10f,11a,c,12a]

With these precedents in mind, we treated β-amino amide **2a** with 2.5 equiv of methyllithium (Scheme 8), but unfortunately we were not able to isolate the desired β-amino ketone target compound and only a mixture of unidentifiable products was obtained. The same disappointing result was observed when we tried the same reaction with other organolithium reagents such as *n*-BuLi or PhLi and also when we used *N*-benzyl-*N*-methyl-β-amino amide **2g** with the same organolithium reagents. We attributed this behavior to the presence of the tertiary β-amino group in the starting amides **2a** and **2g**, in the same manner as we hypothesized before in the synthesis of γ-amino alcohol derivatives. Consequently, we turned our attention to study the influence exerted by the nature of the *N*-substituents in the 1,2-addition reaction of organolithium reagents to the pseudoephedrine amide moiety present in substrate **2a**. In this context, the reaction of the primary amino derivative **22** was also unsuccessful, and when we used the *N*-methyl-

(32) (a) *Medicinal Natural Products. A Biosynthetic Approach*; Dewick, P. M., Ed.; Wiley & Sons: Sussex, 1997; p 286. (b) *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1996; Vol. 10, p 85. (c) *The Alkaloids: Chemistry and Physiology*; Manske, R. H. F., Ed.; Academic Press: New York, 1968; Vol. 5, p 299. For some selected examples, see: (d) Ogata, M.; Matsumoto, H.; Kida, S.; Shimizu, S.; Tawara, K.; Kawamura, Y. *J. Med. Chem.* **1987**, *30*, 1497. (e) Corey, E. J.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5207. (f) Gao, Y.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 4081.

(33) Davies et al. have already reported one example of the addition of PhMgBr and MeMgBr to a chiral nonracemic *N*′-benzyl-*N*′-(α-methylbenzyl)-substituted β-amino Weinreb amide. (a) Burke, A. J.; Davies, S. G.; Garner, A. C.; McCarthy, T. D.; Roberts, P. M.; Smith, A. D.; Rodríguez-Solla, H.; Vickers, R. J. *Org. Biomol. Chem.* **2004**, *2*, 1387. (b) Davies, S. G.; McCarthy, T. D. *Synlett* **1995**, 700. In our case, Grignard reagents failed to react with *N*,*N*-dibenzyl-β-amino amide **2a**.

SCHEME 9[a]



[a] Reagents and conditions: (i) 1. H_2, Pd/C, EtOH, rt; 2. Boc_2O, Et_3N, THF, rt. (ii) 1. RLi, THF, 0 °C; 2. NH_4Cl.

TABLE 5. Synthesis of the *N*-Boc-*β*-Amino Ketones 25a−e

entry	R	product	yield (%)[a,b]
1	Me	**25a**	72
2	^{i}Pr	**25b**	70
3	Et	**25c**	71
4	^{n}Bu	**25d**	57
5	Ph	**25e**	98

[a] Yield of isolated product based on recovered starting material. [b] Products **25a−e** were >99% ee determined by chiral HPLC (Chiralcel OD column, UV detector, 2-propanol/hexanes, 10:90, flow rate: 0.90 mL/min).

β-amino amide **23** only a small amount of the corresponding ketone could be isolated, even though complete consumption of starting material was observed.

On the contrary, the *N*-Boc-protected substrate **24**, prepared by debenzylation/protection of the starting amide **2a**, reacted cleanly with several organolithium reagents (Scheme 9), providing the desired chiral β-amino ketones **25a−e** with no epimerization at the stereogenic center previously generated in the asymmetric aza-Michael reaction (Table 5). It has also to be mentioned that, even though the reaction was very clean, complete conversion could not be achieved in all cases, but the starting material **21** could be easily recovered after flash column chromatography purification and with complete conservation of the stereochemical integrity so it could be used in further transformations.

Conclusions

We have set up the conditions for performing a highly stereoselective asymmetric aza-Michael reaction with lithium benzylamides as nucleophiles employing the amino alcohol (*S*,*S*)-(+)-pseudoephedrine as chiral auxiliary directly attached to the conjugate acceptor via an amide bond linkage. This amino alcohol is able to exert a very effective, 1,5-asymmetric induction, thus affording the corresponding β-amino amides in good to excellent yields and diastereoselectivities, provided that the appropriate experimental conditions are chosen. Interestingly, we have also observed that a reversible and simple modification on the structure of the chiral auxiliary, like the protection of its free OH group as a bulky silyl ether, led to a complete change of the sense of the asymmetric induction exerted by the auxiliary process, obtaining this way the opposite configuration on the newly created stereogenic center. Therefore, a very efficient and promising diastereodivergent methodology has been developed in which β-amino carbonyl compounds can be prepared with any desired absolute configuration, with no need to change the configuration of the starting chiral auxiliary. In addition, a mechanistic rationale that accounts for the observed diastereoselectivity has been provided supported by double asymmetric induction experiments using chiral lithium amides as nucleophiles. Finally, the differently substituted enantiomerically enriched β-amino amides prepared could be transformed afterward into several interesting compounds, such as β-amino esters, γ-amino alcohols, and β-amino ketones, which were also obtained in highly optically pure form. During these transformations, we found that carefully optimized conditions have to be employed, which mainly consist in protective group tuning.

Experimental Section

General Procedures for the Diastereoselective aza-Michael Addition of Lithium Benzylamides to α,β-Unsaturated Amides 1a−e. Method A (Lithium Amide as Nucleophile). Synthesis of Amides 2a, 2e, and 2g−k. A solution of *n*-BuLi (4.00 mmol) was added to a solution of the corresponding benzylamine (4.00 mmol) in dry toluene (40 mL) at −78 °C, and the reaction was stirred at this temperature for 30 min. This mixture was slowly added within 2 h over a cooled (−90 °C) solution of the corresponding amide **1a−e** (1 mmol) in dry toluene (20 mL). The reaction was stirred for 20 h at this temperature, after which it was quenched with a saturated NH_4Cl solution (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic fractions were collected, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, affording the wanted amides after flash column chromatography purification (hexanes/AcOEt, 1:1).

(+)-(1′*S*,2′*S*,3*R*)-3-Dibenzylamino-*N*-methyl-*N*-(2′-phenyl-2′-hydroxy-1′-methylethyl)butanamide (2a). Amide **2a** was prepared in >99% de (Chiralcel OD column, UV detector, 2-propanol/hexanes, 2:98, flow rate: 1.00 mL/min), according to procedure A starting from amide **1a** (0.40 g, 1.70 mmol) and using Bn_2NH (1.40 mL, 7.00 mmol) and *n*-BuLi 1.4 M (4.90 mL, 6.90 mmol). Yield: 85% (0.63 g, 1.50 mmol). mp 117−119 °C (hexanes/*iso*-PrOH). $[\alpha]^{23}_D$ +67.1 (*c* 0.31, CH_2C1_2). ^{1}H NMR (250 MHz, $CDCl_3$) (δ, ppm) (3:1 rotamer ratio; *indicates minor rotamer resonances): 0.65* (d, 3H, *J* = 6.7 Hz), 0.75 (d, 3H, *J* = 6.7 Hz), 1.11 (t, 3H, *J* = 6.l Hz), 2.31 (dd, 2H, *J* = 14.2, 8.3 Hz), 2.57 (s, 3H), 2.65 (dd, 2H, *J* = 13.4, 8.3 Hz), 2.86* (s, 3H), 3.18 (m, 1H), 3,53 (d, 2H, *J* = 13.8 Hz), 3.64 (d, 2H, *J* = 13.8 Hz), 4.46 (m, 1H), 4.55 (d, 1H), 7.29 (m, 15H); ^{13}C NMR (62.8 MHz, $CDCl_3$) (δ, ppm) (* indicates minor rotamer resonances): 14.2, 14.3*, 26.8, 33.1, 37.8*, 39.2, 50.54, 51.3*, 53.5, 58.4, 75.4*, 76.4, 126.1, 126.8, 127.4, 128.0, 128.2, 139.4, 140.4*, 141.2*; 142.3, 172.8*, 174.0; IR (KBr): 1610 (C=O), 3358 (OH). MS (EI) *m/z* (relative intensity): 339 (40), 321 (10), 224 (30), 196 (20), 148 (20), 132 (20), 107 (10), 91 (100), 79 (10), 65 (10). Anal. Calcd for $C_{27}H_{34}N_2O_2$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.16; H, 8.08; N, 6.42.

Method B (Lithium Amide/TMEDA as Nucleophile). Synthesis of Amides 2b and 2c. A solution of *n*-BuLi (2.00 mmol) was added to a solution of the benzylamine (2.00 mmol) and TMEDA (2.00 mmol) in dry toluene (40 mL) at −78 °C, and the reaction was stirred at this temperature for 30 min. The mixture was cooled to −90 °C, and a solution of the corresponding amide **1a−e** (1.00 mmol) in dry toluene (20 mL) was added within 30 min. The reaction was stirred for 7 h at this temperature, after which it was quenched with a saturated NH_4Cl solution (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic fractions were collected, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, affording the wanted amides after flash column chromatography purification (hexanes/AcOEt, 1:1).

(+)-(1′*S*,2′*S*,3*R*)-3-Dibenzylamino-*N*-methyl-*N*-(2′-phenyl-2′-hydroxy-1′-methylethyl)pentanamide (2b). Amide **2b** was prepared in 88% de (Chiralcel OD column, UV detector, 2-propanol/hexanes, 2:98, flow rate: 1.00 mL/min.), according to procedure B starting from amide **1b** (0.40 g, 1.60 mmol) and using Bn_2NH (0.65 mL, 3.30 mmol), TMEDA (0.48 mL, 3.00 mmol), and *n*-BuLi 1.4 M (2.30 mL, 3.20 mmol). Yield: 85% (0.60 g, 1.40 mmol). ^{1}H NMR (250 MHz, $CDCl_3$) (δ, ppm) (3:1 rotamer ratio; *indicates minor rotamer resonances): 0.65* (d, 3H, 6.73 Hz), 0.96 (t, 3H, J = 7.3 Hz), 1.07 (d, 3H, J = 6.3 Hz), 1.36 (m, 1H), 1.60 (m. IH), 2.27 (dd, 1H, J = 14.5, J = 8.9 Hz), 2.62 (dd, IH, J = 14.5, J = 8.9 Hz), 2.72 (s, 3H), 2.84* (s, 3H), 3.0 (m, 1H), 3.46 (d, 2H, J = 13.4 Hz), 4.49 (m, 1H), 4.57 (d, 1H, J = 7.3 Hz), 7.29 (m, 15H); ^{13}C NMR (62.8 MHz, $CDCl_3$) (δ, ppm) (*indicates minor rotamer resonances): 11.6, 14.4, 14.8*, 24.2, 32.9*, 34.3, 53.1, 56.8, 57.5*, 58.4, 75.4*, 76.4, 126.2, 126.6, 126.8, 126.9, 127.2, 127.2, 127.9, 128.2, 128.3, 128.57, 128.7, 128.9, 139.8, 140.3*, 141.3*, 142.3, 173.5*, 174.5; IR (film): 1610 (C=O), 3358 (OH); MS (El) *m/z* (relative intensity): 415 (M^+ − 18, 1), 353 (24), 335 (3), 250 (2), 238 (19), 196 (16), 188 (3), 146 (17), 132 (4), 91 (100), 79 (13), 58 (15). Anal. Calcd for $C_{29}H_{36}N_2O_2$: C, 78.34; H, 8.16; N, 6.30. Found: C, 78.41; H, 8.07; N, 6.24.

Method C ($(Bn_2N)_2CuLi\cdot LiI$ as Nucleophile). Synthesis of Amides 2d and 2f. A solution of *n*-BuLi (2.00 mmol) was added to a solution of the benzylamine (2 mmol), TMEDA (2.00 mmol), and CuI (1.00 mmol) in dry THF (40 mL) at −78 °C, and the reaction was stirred at this temperature for 30 min. This mixture was cooled to −105 °C, and a solution of the corresponding amide **1a**−**e** (1.00 mmol) in dry THF (20 mL) was added within 30 min. The reaction was stirred for an additional 4−7 h at this temperature, after which it was quenched with a saturated NH_4C1 solution (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic fractions were collected, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, affording the wanted amides after flash column chromatography purification (hexanes/AcOEt, 1:1).

(+)-(1′*S*,2′*S*,3*S*)-3-Dibenzylamino-*N*,4,4-trimethyl-*N*-(2′-phenyl-2′-hydroxy-1′-methylethyl)pentanamide (2d). Amide **2d** was prepared in >99% de (Chiralcel OD column, UV detector, 2-propanol/hexanes, 4:96, flow rate: 0.80 mL/min), according to procedure C starting from amide **1d** (0.40 g, 1.50 mmol) and using Bn_2NH (0.6 mL, 3.10 mmol), *n*-BuLi 1.4 M (2.10 mL, 3.00 mmol), CuI (0.28 g, 1.50 mmol), and TMEDA (0.48 mL, 3.00 mmol). Yield: 50% (0.35 g, 0.75 mmol). $[\alpha]^{20}_D$ +52.9 (*c* 0.58, CH_2C1_2). ^{1}H NMR (250 MHz, $CDCl_3$) (δ, ppm) (3:1 rotamer ratio; *indicates minor rotamer resonances): 0.87 (m, 9H), 1.14 (d, 3H, J = 7.1 Hz), 2.31 (m, 1H), 2.52 (m, 1H), 2.80 (s, 3H), 2.87* (s, 3H), 3.12 (m, 1H), 3.38 (d, 2H, J = 13.8 Hz), 3.75 (d, 2H, J = 13.8 Hz), 4.48 (m, 1H), 4.61 (m, 1H), 7.29 (m, 15H); ^{13}C NMR (62.8 MHz, $CDCl_3$) (δ, ppm) (*indicates minor rotamer resonances): 14.4, 19.8*, 20.8, 31.4, 31,8, 33.1, 54.0*, 54.5, 60.7, 60.9*, 75.8*, 76.3, 126.2, 126.5, 127.4, 127.7, 128.3, 140.0, 140.3*, 141.8*, 142.4, 174.0*, 174.6; IR (film): 1610 (C=O), 3358 (OH); MS (EI) *m/z* (relative intensity): 415 (4), 367 (4), 347 (2), 290 (83), 252 (11), 220 (3), 196 (15), 160 (10), 148 (15), 107 (12), 91 (100), 58 (17); Anal. Calcd for $C_{31}H_{40}N_2O_2$: C, 78.77; H, 8.53; N, 5.93. Found: C, 78.83; H, 8.74; N, 6.71.

Diastereodivergent Procedure: Synthesis of Amide (+)-(1′*S*,2′*S*,3*S*)-3-Dibenzylamino-*N*-methyl-*N*-(2′-phenyl-2′-hydroxy-1′-methylethyl)butanamide (2′a). Amide **14′** was prepared according to procedure A from *O*-TBS enamide **8** (0.57 g, 1.70 mmol) and using Bn_2NH (1.40 mL, 6.90 mmol) and *n*-BuLi (4.86 mL of a 1.4 M solution in hexane, 6.80 mmol). Yield: 91% (0.77 g, 1.55 mmol). $[\alpha]^{23}_D$ +96.9 (*c* 0.52, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$) (δ, ppm) (3:1 rotamer ratio: * indicates minor rotamer resonances) (δ, ppm): −0.28 (s, 3H), −0.26* (s, 3H), 0.01 (s, 3H), 0.03* (s, 3H), 0.55* (d, 3H, J = 6.3 Hz), 0.82 (s, 9H), 0.91* (s, 9H), 1.12 (d, 3H, J = 6.3 Hz), 2.25 (m, 1H), 2.60 (m, 1H), 2.68* (s, 3H), 2.74 (s, 3H), 2.97 (m, 1H), 3.57 (m, 4H), 4.41 (d, 1H, J = 7.5 Hz), 4.68 (m, 1H), 7.23 (m, 15H), ^{13}C NMR (62.8 MHz, $CDCl_3$) (δ, ppm) (* indicates minor rotamer resonances) (δ, ppm): −5.3, −4.8*, 13.4, 14.0*, 14.2*, 15.1, 17.7, 17.9*, 25.5, 25.7*, 27.2, 38.9*, 39.8, 50.2, 53.3, 53.7*, 58.5, 76.7, 126.3, 126.6, 126.9, 127.0, 127.1, 127.3, 127.7, 127.8, 127.2, 128.2, 128.4, 128.6, 140.1, 140.2*, 141.9*, 142.1, 171.6*, 172.7; IR (film): 1620 (C=O); MS (EI) *m/z* (relative intensity): 453 (41), 416 (1), 348 (1), 323 (11), 280 (6), 224 (78), 196 (23), 174 (19), 132 (30), 105 (8), 91 (100), 58 (8).

Next, amide **14′** (0.60 g, 1.20 mmol) was dissolved in THF and treated with TBAF (2.40 mL of a 1 M solution in THF, 2.40 mmol) at room temperature, and the mixture was stirred for 20 h. Amide **2′a** was obtained after aqueous workup and flash column chromatography purification (hexanes/AcOEt, 1:1). Yield: 99% (0.50 g, 1.20 mmol). $[\alpha]^{23}_D$ +41.6 (*c* 0.35, CH_2C1_2). ^{1}H NMR (250 MHz, $CDCl_3$) (δ, ppm) (3:1 rotamer ratio; *indicates minor rotamer resonances): 0.52* (d, 3H, J = 6.7 Hz), 1.08 (m, 6H), 2.31(m, 2H), 2.61 (s, 3H), 2.70 (m, 2H), 2.84* (s, 3H), 3.24 (m, 1H), 3.55 (m, 4H), 4.43 (m, 1H), 4.54 (d, 1H, J = 7.5 Hz), 7.26 (m, 15H); ^{13}C NMR (62.8 MHz, $CDCl_3$) (δ, ppm) (* indicates minor rotamer resonances): 13.9*, 14.4, 26.8, 29.6, 32.8*, 38.9, 39.4*, 50.3*, 50.6, 53.4*, 53.6, 58.7, 75.3, 126.3, 126.7, 126.8, 127.0, 127.6, 128.2, 128.3, 128.4, 128.6, 140.1, 141.3*, 142.0, 173.4*, 174.2; IR (KBr): 1616 (C=O), 3377 (OH). MS (EI) *m/z* (relative intensity): 340 (13), 321 (2), 225 (32), 196 (40), 132 (18), 106 (19), 91 (100), 79 (8), 65 (13). Anal. Calcd for $C_{27}H_{34}N_2O_2$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.06; H, 7.91; N, 6.57.

Typical Procedure for the Conversion of Amides 2a−k into β-Amino Esters 18a−k. Synthesis of (−)-(3*R*)-Methyl 3-dibenzylaminobutanoate (18a). Dimethyl carbonate (0.40 g, 4.49 mmol) and MeONa (0.32 g, 6.00 mmol) were added to a solution of β-amino amide **2a** (0.25 g, 0.60 mmol) in CH_2Cl_2 (20 mL) at room temperature. The mixture was stirred at this temperature for 24 h, after which it was quenched with saturated NH_4Cl. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic fractions were collected, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, affording the wanted β-amino ester **18a** (0.13 g, 0.44 mmol) after column chromatography purification (hexanes/AcOEt, 8:2). Yield: 73%, >99% ee (determined by chiral HPLC: Chiralcel OJ column, UV detector, 2-propanol/hexanes, 5:95, flow rate: 0.85 mL/min). $[\alpha]^{20}_D$ −9.7 (*c* 0.21, CH_2CI_2). ^{1}H NMR (250 MHz, $CDCl_3$) (δ, ppm): 1.10 (d, 3H, J = 6.7 Hz), 2.29 (dd, 1H, J = 13.8, 6.7 Hz), 2.65 (dd, 1H, J = 13.8, 6.7 Hz), 3.31 (m, 1H), 3.45 (d, 2H, J = 13.8 Hz), 3.65 (d, 2H, J = 13.8 Hz), 3.60 (s, 3H), 7.27 (m, 10H); ^{13}C NMR (62.8 MHz, $CDCl_3$) (δ, ppm): 14.1, 39.3, 50.2, 51.1, 53.5, 127.1, 128.3, 128.5, 140.2, 173.6; IR (film): 1605 (C=O); MS (EI) *m/z* (relative intensity): 297 (2), 282 (7), 224 (100), 206 (7), 181 (11), 132 (5), 91 (97), 65 (3), 56 (12); Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.60; H, 8.06; N, 4.72.

Typical Procedure for the Conversion of *N*-Cbz-β-Amino Amides 20a−f into γ-Amino Alcohols 21a−f. Synthesis of (−)-(3*R*)-3-Benzyloxycarbonylaminobutanol (21a). *n*-BuLi (3.00 mL of a 1.4 M solution in hexane, 4.16 mmol) was added over a solution of diisopropylamine (0.60 mL, 4.16 mmol) in dry THF (10 mL) at −78 °C, and the mixture was stirred for 15 min. The reaction was warmed to 0 °C, and $NH_3\cdot BH_3$ (0.13 g, 4.16 mmol) was added all at once. The mixture was stirred for 15 min at 0 °C and another 15 min at room temperature, after which a solution of **20a** (0.40 g, 1.04 mmol) in THF (10 mL) was added via cannula at 0 °C, and the reaction was stirred for 2 h. Then the reaction was quenched with HCl 1 N (15 mL) and extracted with AcOEt (3 × 15 mL). The organic fractions were collected, washed with saturated $NaHCO_3$, dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo, affording the wanted γ-amino alcohol **21a** after flash column chromatography purification (hexanes/AcOEt, 1:1). Yield: 88% (0.20 g, 0.91 mmol), 99% ee (determined by chiral HPLC: Chiralcel OJ column, UV

detector, 2-propanol/hexanes, 5:95, flow rate: 0.85 mL/min). $[\alpha]^{20}_D$ −14.7 (*c* 0.36, CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$) (δ, ppm): 1.19 (d, 3H, *J* = Hz), 1.39 (m, 1H), 1.77 (m, 1H), 3.23 (s, 1H), 3.62 (m, 2H), 3.92 (m, 1H), 4.87 (m, 1H), 5.09 (s, 2H), 7.34 (m, 5H); ^{13}C NMR (62.8 MHz, $CDCl_3$) (δ, ppm): 21.2, 40.1, 43.9, 58.8, 66.8, 127.9, 128.5, 136.3, 156.9; IR (film): 3352 (OH, NH); MS(EI) *m/z* (relative intensity): 224 (M^+, 5), 205 (12), 149 (11), 91 (100), 56 (45); Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.53; H, 7.71; N, 6.40.

Typical Procedure for the Conversion of *N*-Boc-*β*-Amino Amide 21 into *β*-Amino Ketones 25a−e. Synthesis of (+)-(4*R*)-4-(*terc*-Butoxycarbonylamino)pentan-2-one (25a). MeLi (1.64 mL of a 1.0 M solution in Et_2O, 1.57 mmol) was added over a solution of amide **24** (0.25 g, 0.71 mmol) in dry THF (40 mL) at −78 °C. The reaction mixture was stirred for 15 min at this temperature, and then it was warmed to 0 °C and stirred for an additional 45 min, after which a saturated NH_4Cl solution (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo, affording the wanted *β*-amino ketone **25a** after flash column chromatography purification (AcOEt/hexanes, 1:4). Yield: 72% (67 mg, 0.33 mmol; 86 mg of **24** were recovered, 0.24 mmol), >99% ee (determined by chiral HPLC: Chiralcel OD column, UV detector, 2-propanol/hexanes, 10:90, flow rate: 0.90 mL/min). $[\alpha]^{23}_D$ +7.65 (*c* 0.98, CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$) (δ, ppm): 1.07 (d, 3H, *J* = 5.1 Hz), 1.39 (s, 9H), 2.19 (s, 3H), 2.63 (dd, 1H, *J* = 16.2, 5.1 Hz), 2.97 (dd, 1H, *J* = 16.2, 5.1 Hz), 3.97 (m, 1H); ^{13}C NMR (62.8 MHz, $CDCl_3$) (δ, ppm): 20.5, 28.3, 30.4, 43.2, 49.5, 79.2, 155.1, 207.6; IR (film): 1522 (C═O), 1709 (C═O), 3352 (NH); MS(EI) *m/z* (relative intensity): 147 (1), 128 (13), 100 (22), 85 (9), 73 (1), 59 (19), 58 (26), 57 (100), 56 (6); Calcd. for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.59; H, 9.57; N, 7.03.

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Supporting Information Available: Detailed descriptions of experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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