Stereocontrolled Mannich Reaction with Enolizable Imines Using (*S*,*S*)-(+)-Pseudoephedrine as Chiral Auxiliary. Asymmetric Synthesis of α,*β*-Disubstituted *β*-Aminoesters and *β*-Lactams

Jose L. Vicario, Dolores Badía,* and Luisa Carrillo

Departamento de Química Orgánica II, Facultad de Ciencias, Universidad del País Vasco/Euskal Herriko Unibertsitatea, P.O. Box 644, E-48080 Bilbao, Spain

qopbaurm@lg.ehu.es

Received July 10, 2001

Introduction

The Mannich reaction involving enolizable azomethine compounds in most cases fails to give good results due to the preference of the azomethine substrate to undergo enolization rather than the desired nucleophilic addition.[1] There are only a few procedures that overcome these limitations, and in this context, modified derivatives of either the enolate[2] or the azomethyne reagent[3] have been employed.

On the other hand, the strategies employed to exert stereocontrol in the newly created chiral centers involve the introduction of the chiral information by incorporating chiral ligands present in the reaction medium in either a stoichiometric or a catalytic way or by using chiral imines or enolates.[4] In regard to this last topic, there are only a few known methods for diastereoselective Mannich reactions employing chiral auxiliaries attached to the enolate. This is in contrast with the parent aldol reactions that have been extensively developed. We have recently[4a] reported a very effective procedure for performing stereocontrolled Mannich reactions using a chiral enolate derived from (*S*,*S*)-(+)-pseudoephedrine propionamide, in which several nonenolizable imines were tested. Now, we report herein the extension of this methodology to the use of enolizable imines only by manipulating the enolate counterion and therefore without the need to convert either the initial carbonyl substrate or the azomethine reagent into a more reactive derivative. This procedure represents a very straightforward and general access to chiral nonracemic α,*β*-disubstituted *β*-aminoester derivatives with any kind of substitution pattern at the alkyl chain.

Results and Discussion

When the lithium enolate of propionamide **1** was reacted with the *p*-anisidine-based (*E*)-imine **2a**[5] in the presence of 4 equiv of LiCl (Scheme 1), as previously reported,[4a] no addition product was obtained and the starting propionamide was recovered unchanged together with a complex mixture of products probably derived from polymerization of the imine reagent (entry 1, Table 1). The same results were obtained when the reaction was performed with prior activation of the imine with a Lewis acid like $BF_3{\cdot}OEt_2$ (entries 2−4, Table 1). Only in the case of imine **2c**, which is slightly less prone to racemization, was obtained a small amount of the desired addition product. However, when we submitted the lithium enolate derived from propionamide **1** to a transmetalation step with 2 equiv of $ZnCl_2$ prior to the addition of the imine, the desired *β*-aminoamide adducts were obtained in good yields after flash column chromatography purification (entries 5−8, Table 1).[6] The yield of the addition reaction was significantly improved when an excess of azomethine reagent was used, in the conditions previously reported for nonenolizable imines.[4a] It should be pointed out that the use of nonenolizable imine **2d** (R = Ph) yielded the desired adduct in comparable yield and in the same absolute configuration in both newly created chiral centers to that found when the lithium enolate of **1** was employed (entries 8 and 9, Table 1).[4a]

In all cases, the reaction proceeded with extremely high simple (anti/syn ratio **3**/**3′** > 99:1) and facial (**3**/**4** ratio > 99:1) diastereoselection, and amides **3a**−**d** were obtained as one diastereoisomer out of the four possible ones,

(1) Risch, N.; Arend, M. *Stereoselective Synthesis (Houben-Weyl), Vol. E21/3*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; p 1833.

(2) (a) Schneider, C.; Reese, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 2948. (b) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (c) Glasson, S. R.; Canet, J.-L.; Troin, Y. *Tetrahedron Lett.* **2000**, *41*, 9797. (d) Cozzi, P. G.; di Simone, B.; Umani-Ronchi, A. *Tetrahedron Lett.* **1996**, *37*, 1691. (e) Ojima, I.; Habus, I.; Zhao, M.; Georg, G. I.; Jayasinghe, L. R. *J. Org. Chem.* **1991**, *56*, 1681. (f) Liebeskind, L. S.; Welker, M. E.; Goedken, V. *J. Am. Chem. Soc.* **1984**, *106*, 441. (g) Dubois, J.-E.; Axiotis, G. *Tetrahedron Lett.* **1984**, *25*, 2143.

(3) (a) Cooke, J. W. B.; Berry, M. B.; Caine, D. M.; Cardwell, K. S.; Cook, J. S.; Hodgson, A. *J. Org. Chem.* **2001**, *66*, 334. (b) Palomo, C.; Oiarbide, M.; González-Rego, C.; Sharma, A. K.; García, J. M.; González, A.; Landa, C.; Linden, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1063. (c) Saito, S.; Hatanaka, K.; Yamamoto, H. *Org. Lett.* **2000**, *2*, 1891. (d) D'Oca, M. G. M.; Pilli, R. A.; Vencato, I. *Tetrahedron Lett.* **2000**, *41*, 9709. (e) Kise, N.; Ueda, N. *J. Org. Chem.* **1999**, *64*, 7511. (f) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278. (g) Kawakami, T.; Ohtake, H.; Arakawa, H.; Okachi, T.; Imada, Y.; Murahashi, S.-I. *Org. Lett.* **1999**, *1*, 107. (h) Higashiyama, K.; Kyo, H.; Takahashi, H. *Synlett* **1998**, 489. (i) Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *Tetrahedron* **1996**, *52*, 1685. (j) Davis, F. A.; Reddy, R. T.; Teddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387. (k) Andrés, C.; González, A.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron Lett.* **1992**, *33*, 2895. (l) Brown, M. J.; Overman, L. E. *J. Org. Chem.* **1991**, *56*, 1933. (m) Uyehara, T.; Suzuki, I.; Yamamoto, Y. *Tetrahedron Lett.* **1989**, *30*, 4275. (n) Nagao, Y.; Dai, W.-M.; Ochiai, M. *Tetrahedron Lett.* **1988**, *29*, 6133.

(4) (a) Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2001**, *3*, 773 and references therein. See also: (b) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 199. (c) Saito, S.; Hatanaka, K.; Yamamoto, H. *Tetrahedron* **2001**, *57*, 875. (d) McLaren, A. B.; Sweeney, J. B. *Synlett* **2000**, 1625. (e) Ahn, J.-B.; Yun, C.-S.; Kim, K. H.; Ha, D.-C. *J. Org. Chem.* **2000**, *65*, 9249. (f) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180. (g) Enders, D.; Oberbörsch, J.; Adam, J. *Synlett* **2000**, 644. (h) Allef, P.; Kunz, H. *Tetrahedron: Asymmetry* **2000**, *11*, 375. (i) Palomo, C.; Aizpurua, J. M.; Gracenea, J. J. *J. Org. Chem.* **1999**, *64*, 1693. (j) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450. (k) Viso, A.; De la Pradilla, R.; García, A.; Alonso, M.; Guerrero-Strachan, L.; Fonseca, I. *Synlett* **1999**, 1543.

(5) The preference for the *E* configuration in imines in which the C=N bond is conjugated with one or more aromatic rings has already been described; see: Hine, J.; Yeh, C. Y. *J. Am. Chem. Soc.* **1967**, *89*, 2669.

(6) For some examples of Mannich-type reactions using zinc(II) enolates, see: (a) Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. J.; Concolino, T. E.; Rheingold, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 2651. (b) van Maanen, H. L.; Kleijn, H.; Jastrzebski, J. T. B. H.; Verweij, J.; Kieboom, A. P. G.; van Koten, G. *J. Org. Chem.* **1995**, *60*, 4331. (c) van Maanen, H. L.; Kleijn, H.; Jastrzebski, J. T. B. H.; van Koten, G. *Bull. Soc. Chim. Fr.* **1995**, *132*, 86. (d) van der Steen, H. H.; Kleijn, H.; Britovsek, G. J. P.; Jastrzebski, J. T. B. H.; van Koten, G. *J. Org. Chem.* **1992**, *57*, 3906.

10.1021/jo010697m CCC: $20.00
Published on Web 11/29/2001

Scheme 1

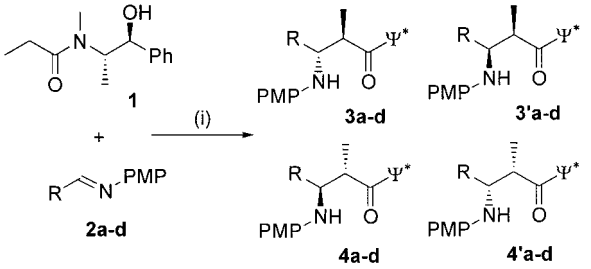

Table 1. Stereocontrolled Reaction of Enolates of Amide 1 with Several Imines 2a−d

entry	product	R	procedure[a]	yield[b] (%)	**3**/**4**[c]	**3**/**3′**[c]
1	**3a**	Me	A	0		
2	**3a**	Me	A[d]	0		
3	**3b**	Et	A[d]	0		
4	**3c**	*i*-Pr	A[d]	15	>99:1	>99:1
5	**3a**	Me	B	79	>99:1	>99:1
6	**3b**	Et	B	81	>99:1	>99:1
7	**3c**	*i*-Pr	B	85	>99:1	>99:1
8	**3d**	Ph	B	83	>99:1	>99:1
9	**3d**	Ph	A	86	>99:1	>99:1
10	**3a**	Me	A[e]	0		

[a] Procedure A: Reaction using the lithium enolate of **1** (see ref 4a). Procedure B: Reaction using the Zn (II) enolate of **1**. [b] Yield of product after flash column chromatography purification. [c] Calculated by HPLC (Chiralcel OD column, UV detector, *n*-hexane/2-propanol 70:30, 1.00 mL/min). [d] Reaction using the imine previously activated with $BF_3{\cdot}OEt_2$. [e] Reaction using the imine previously activated with $ZnCl_2$.

attending to the configuration of the two newly created chiral centers. This fact was checked by HPLC analysis of the crude reaction mixtures under conditions previously optimized for a mixture of the four possible isomers.[7]

To ensure that a zinc(II) enolate-like species was formed during the reaction and that $ZnCl_2$ was not acting simply as a Lewis acid that activates the azomethine bond toward the nucleophilic addition (like in the case of the lithium enolate of **1** and imine **2c** activated with $BF_3{\cdot}OEt_2$, entry 4, Table 1), we subjected the lithium enolate of **1** to reaction with a solution containing 4 equiv of the imine **2a** and 4 equiv of $ZnCl_2$. Under these conditions, no addition product was obtained (entry 10, Table 1), a result that confirms our hypothesis that the formation of an intermediate zinc(II) enolate was responsible for the good results obtained in the reaction with enolizable imines. Relying on the fact that the configuration of the newly chiral centers (entries 8 and 9, Table 1) is independent of the metallic enolate counterion, the high stereocontrol observed is in accordance with a previously proposed mechanism for Mannich reaction with nonenolizable imines employing enolates derived from pseudoephedrine amide derivatives.[4a] This mechanism consistent with an absolute configuration (2*R*,3*R*) for the newly chiral centers created at the adducts **3a**−**c**.

The so-obtained amides **3a**−**d** were subjected to a hydrolysis/esterification procedure, affording the corresponding α-methyl-*β*-amino acid derivatives as their corresponding methyl esters **5a**−**d**. These derivatives were recovered in good yields after flash chromatography

(7) A sample containing the four possible diastereoisomers, to used as a standard mixture for chiral HPLC, was obtained as previously reported (ref 4a)

Scheme 2

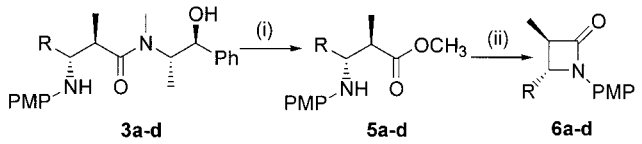

Table 2. Hydrolysis/Esterification of Amides 3a−e and Subsequent Base-Promoted Cyclization

R	product	yield[a] (%)	product	yield[b] (%)
Me	**5a**	88	**6a**	93
Et	**5b**	89	**6b**	88
i-Pr	**5c**	88	**6c**	90
Ph	**5d**	83	**6d**	91

[a] Yield of product after flash column chromatography purification with ee >99% calculated by HPLC (Chiralcel OD column, UV detector, *n*-hexane/2-propanol 90:10, 1.00 mL/min). [b] Yield of product after flash column chromatography purification with ee >99% calculated by HPLC (Chiralcel OD column, UV detector, *n*-hexane/2-propanol 98:2, 0.80 mL/min).

and found to be almost enantiomerically pure as proven by HPLC analysis in a chiral stationary phase, under conditions previously optimized for a racemic mixture (Scheme 2, Table 2). Finally, *β*-aminoesters **5a**−**d** were subjected to a already reported base-promoted cyclization[8] affording, after flash column chromatography purification, the target *β*-lactams **6a**−**d** in good yields and as only one detectable stereoisomer (Scheme 2, Table 2). Thus, the observed value for $J_{3,4}$ coupling constants in the ^{1}H NMR spectrum in comparison with those reported in the literature allowed us to confirm an anti configuration for the *β*-lactams **6**.[9] Besides, a comparison of the obtained $[\alpha]^{20}_D$ value for **6d** with that reported in the literature[9a] allowed us to establish the absolute configuration of the newly created chiral centers in the Mannich reaction. This is also indicating that all conversions performed on the amides **3a**−**d** (hydrolysis, esterification, and base-promoted cyclization) proceeded without racemization in any of the chiral centers.

In summary, a very easy and efficient procedure for performing stereocontrolled Mannich reactions that allows the use of either nonenolizable and enolizable imines as azomethine electrophilic reagents has been developed using (*S*,*S*)-(+)-pseudoephedrine as chiral auxiliary. The methodology involves the addition of a pseudoephedrine propionamide Zn(II) enolate to the imine C=N double bond. The obtained *β*-aminoamide adducts have shown to be adequate synthons for the synthesis of α-methyl-*β*-alkyl-*β*-aminoesters and 3-methyl-4-alkyl-*β*-lactams in an enantiopure form. In view of the large number of amides and imines susceptible to be employed, the broad application of this method should be anticipated, thus opening the access to a full range of chiral nonracemic *β*-amino acid derivatives with different substitution patterns at the alkyl chain. The fact that pseudoephedrine is cheap and commercially available in both enantiomeric forms makes the reported procedure even more interesting from a synthetic and economic point of view.

(8) (a) Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1987**, *28*, 4331. (b) Gennari, C.; Venturini, I.; Gislon, G.; Schimperna, G. *Tetrahedron Lett.* **1987**, *28*, 227.

(9) (a) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060. (b) Barbaro, G.; Battaglia, A.; Giorgianni, P. *J. Org. Chem.* **1994**, *59*, 906. (c) Palomo, C.; Aizpurua, J. M.; Galarza, R.; Iturburu, M.; Legido, M. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2461.

Experimental Section[10]

General Procedure for Stereocontrolled Mannich Reactions with Enolizable Imines. Synthesis of (2*R*,3*R*,1′*S*,2′*S*)-(+)-3-(4-Methoxyphenylamino)-*N*,2-dimethyl-*N*-(2′-phenyl-2′-hydroxy-1′-methylethyl)butanamide (3a). A solution of propionamide **1** (1 mmol) in THF (10 mL) was slowly added to a solution of LDA (2 mmol) in THF (20 mL) at −78 °C. After being stirred for 1 h at this temperature, the mixture was allowed to reach to room temperature and stirred for another 15 min. The reaction was then cooled to −78 °C, and a solution of $ZnCl_2$ (2 mmol) in THF (10 mL) was added. The reaction was stirred for 1 h at −78 °C and then allowed to warm to 0 °C, at which time a solution of the imine **2a** (4 mmol) was slowly added. The mixture was stirred until TLC analysis indicated full conversion, and water (2 mmol) was then added. The resulting ZnO precipitate was filtered off and washed with CH_2Cl_2, and a saturated solution of Na_2CO_3 (40 mL) was added to the filtrate. The crude reaction mixture was extracted with CH_2Cl_2, the combined organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent rwas removed in vacuo affording **3a** after flash column chromatography purification (hexanes/AcOEt 2:8). Yield: 79%. Mp: 86−89 °C (Et_2O). $[\alpha]^{20}_D$: +58.6 (*c* = 0.2, CH_2Cl_2). ^{1}H NMR (*δ*, ppm) (2:1 rotamer ratio; *indicates minor rotamer resonances): 0.96−1.38 (m, 9H); 2.27 (m, 1H); 2.78 (s, 3H); 2.88* (s, 3H); 3.21* (m, 1H); 3.53 (m, 1H); 3.70 (s, 3H); 3.72* (s, 3H); 3.98 (m, 1H); 4.51 (m, 1H); 6.58 (m, 2H); 6.78 (m, 2H); 7.26−7.33 (m, 5H). ^{13}C NMR (*δ*, ppm) (2:1 rotamer ratio; *indicates minor rotamer resonances): 9.1; 9.5*; 14.2*; 14.3; 17.9*; 18.0; 32.3; 32.9*; 41.2*; 41.4; 52.8; 53.6*; 55.6; 57.7*; 58.2; 75.8; 76.3*; 114.6, 114.7*, 114.9, 115.1*, 126.4*, 126.8, 127.6, 127.8*, 128.3, 128.6*; 141.2, 141.7*, 142.0, 142.3*; 151.8*, 152.1; 176.6*, 177.6. IR (KBr): 3338 (NH); 1619 (C=O). MS (EI) *m*/*z* (rel int): 370 (M^+, 1), 204 (100). Anal. Calcd for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.39; H, 8.11; N, 7.57.

General Procedure for the Hydrolysis/Esterification of Amides 2a−d. Synthesis of (2*R*,3*R*)-(−)-Methyl 3-(4-Methoxyphenylamino)-2-methylbutanoate (5a). A solution of the starting amide **3a** (1 mmol) in dioxane (10 mL) was added to a 4 M H_2SO_4 solution (10 mL) and heated at reflux for 6 h. The reaction was carefully quenched with a 4 M NaOH solution until pH = 12 and extracted with CH_2Cl_2 (3 × 10 mL). (*S*,*S*)-(+)-Pseudoephedrine was recovered from the organic extracts in ca. 83% yield. The aqueous phase was then acidified with concentrated HCl, and the volatile residues were removed under vacuum. MeOH (15 mL) and concentrated H_2SO_4 (1 mL) were then added to the resulting sluggish solid, following by heating at reflux the mixture for 6 h. Water (10 mL) was added, the mixture was carefully basified with NaOH and extracted with CH_2Cl_2, the collected organic fractions were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo affording **5a** after flash column chromatography purification (hexanes/AcOEt 1:1). Yield: 88%. $[\alpha]^{20}_D$: −15.6 (*c* = 0.1, CH_2Cl_2). ^{1}H NMR (*δ*, ppm): 1.12 (d, 3H, *J* = 6.4 Hz); 1.15 (d, 3H, *J* = 6.7 Hz); 2.73 (m, 1H); 3.68 (s, 3H); 3.73 (s, 3H); 3.78 (m, 1H); 6.58 (d, 2H, *J* = 7.9 Hz); 6.77 (d, 2H, *J* = 7.9 Hz). ^{13}C NMR (*δ*, ppm): 11.9; 17.4; 43.5; 51.6; 52.6; 55.7; 114.8, 115.4; 141.0; 152.0; 175.8. IR ($CHCl_3$): 3375 (NH); 1728 (C=O). MS (EI) *m*/*z* (rel int): 237 (M^+, 18), 150 (100). Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.75; H, 8.02; N, 5.81.

General Procedure for the Base-Promoted Cyclization of Aminoesters 5a−d. Synthesis of (3*R*,4*R*)-(−)-1-(4-Methoxyphenyl)-3,4-dimethylazetidin-2-one (6a). A solution of LHMDS (1 mmol) in THF was slowly added over a cooled (−20 °C) solution of the starting *β*-aminoester **5a** (1 mmol) in dry THF (15 mL). The mixture was stirred for 5 min at this temperature and quenched with a 4 M HCl solution (15 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), the collected organic fractions were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo yielding pyrrolidin-2-one **6a** after flash column chromatography purification (hexanes/EtOAc 8:2). Yield: 93%. Mp: 77−79 °C (EtOH). $[\alpha]^{20}_D$: −17.6 (*c* = 0.2, CH_2Cl_2). IR (KBr): 1760 (C=O). ^{1}H NMR (*δ*, ppm): 1.34 (d, 3H, *J* = 7.5 Hz); 1.47 (d, 3H, *J* = 6.0 Hz); 2.84 (dq, 1H, *J* = 2.2, 7.5 Hz); 3.71 (dq, 1H, *J* = 2.2, 6.0 Hz); 3.76 (s, 3H); 6.86 (d, 2H, *J* = 7.8 Hz); 7.30 (d, 2H, *J* = 7.8 Hz). ^{13}C NMR (*δ*, ppm): 12.9; 17.8; 46.5; 51.3; 55.5; 114.4, 118.3; 131.1; 155.8; 167.4. MS (EI) *m*/*z* (rel int): 205 (M^+, 40), 149 (100). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.20; H, 7.32; N, 6.88.

Acknowledgment. Financial support from the Basque Government (a fellowship to J.L.V. and Project No. GV00170.30-7307/19) is gratefully acknowledged.

Supporting Information Available: Experimental details for compounds **3b−d**, **5b−d**, and **6b−d** are provided. Chiral HPLC chromatograms for compounds **3a**, **5a**, and **6a** and retention times for all isomers of compounds compounds **3b−d**, **5b−d**, and **6b−d** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

JO010697M

(10) For general experimental procedures, see: Vicario, J. L.; Badía, D.; Domínguez, E.; Carrillo, L. *J. Org. Chem.* **1999**, *64*, 4610.