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(*S*,*S*)-(+)-Pseudoephedrine α-Iminoglyoxylamide as a Chiral Glycine Cation Equivalent: A Modular and Flexible Approach to Enantioenriched α-Amino Ketones

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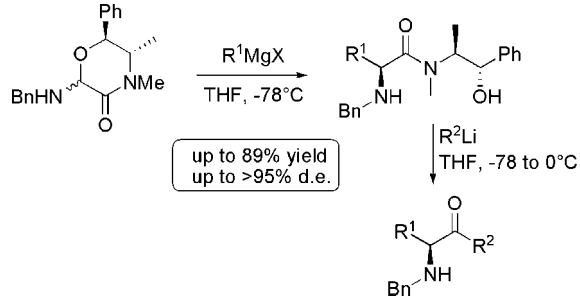
ABSTRACT



We have studied the ability of an α-imino glyoxylamide derived from (*S*,*S*)-(+)-pseudoephedrine as a valuable chiral electrophile for the preparation of α-amino carbonyl compounds. In this context, the addition of Grignard reagents to the azomethine moiety of this chiral electrophile afforded the expected α-amino amide adducts in good yields and diastereoselectivities. Moreover, these adducts have been transformed into enantioenriched α-amino ketones by exploiting the ability of pseudoephedrine amides to undergo selective monoaddition to the carbamoyl group with organolithium reagents.

The stereoselective addition of carbon nucleophiles to the C=N double bond of α-imino carbonyl compounds is an important reaction in organic synthesis.[1] This transformation enables the preparation of optically active α-amino carbonyl compounds such as α-amino acids among others, which are valuable synthetic intermediates and chiral building blocks in organic synthesis.[2] In this context, several catalytic[1b,3] and chiral auxiliary-mediated[4] methods have been reported in the literature for the asymmetric addition reaction of organometallic reagents to α-imino esters or related derivatives. However, despite the presence of a highly electrophilic azomethine functionality, the conjugation of the C=N double bond to a carbonyl group leads to a lack of regiochemical

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(2) For some reviews on the asymmetric synthesis of α-amino acids, see: (a) Najera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584. (b) Groger, H. *Chem. Rev.* **2003**, *103*, 2795.

(3) For some recent examples, see: (a) Aydin, J.; Kumar, K. S.; Sayah, M. J.; Wallner, O. A.; Szabo, K. J. *J. Org. Chem.* **2007**, *72*, 4689. (b) Colombo, F.; Annunziata, R.; Benaglia, M. *Tetrahedron Lett.* **2007**, *48*, 2687. (c) Fuchibe, K.; Hatemata, R.; Akiyama, R. *Tetrahedron* **2006**, *62*, 11304. (d) Kiyohara, H.; Nakamura, Y.; Matsubara, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1615. (e) Basra, S.; Fennie, M. W.; Kozlowski, M. C. *Org. Lett.* **2006**, *8*, 2659. (f) Kong, J.-R.; Cho, C.-W.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 11269. (g) Ji, J.-X.; Au-Yeung, T. T.-L.; Wu, J.; Yip, C. W.; Chan, A. S. C. *Adv. Synth. Catal.* **2004**, *346*, 42. (h) Hamada, T.; Manabe, K.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3927. (i) Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844. (j) Hanessian, S.; Yang, R.-Y. *Tetrahedron Lett.* **1996**, *37*, 8997.

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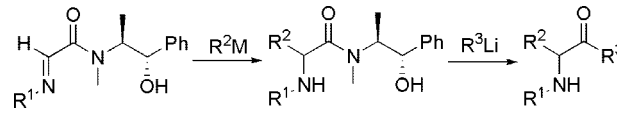
control in the addition reaction, as competitive conjugate addition leads to *N*-alkylated products.[5]

The commercially available, inexpensive reagent (*S*,*S*)-(+)-pseudoephedrine has provided excellent results as chiral auxiliary in several C−C and C−X bond-forming reactions in which, in most cases reported, amides derived from this amino alcohol have been employed as nucleophiles via their corresponding enolates.[6] We have recently shown that pseudoephedrine can also play the role of an efficient chiral auxiliary linked to the electrophile reagent in conjugate addition reactions.[7] Additional advantages of the use of this auxiliary are related to the unique reactivity pattern displayed by amide function present at the obtained adducts, which allows the preparation of a wide range of other interesting chiral building blocks. In particular, we became interested in the formation of ketones by 1,2-addition of organolithium reagents to the carbamoyl functional group in which the pseudoephedrine amino alcohol moiety has shown to play a crucial role by stabilizing the tetrahedral intermediate formed after the 1,2-addition step and therefore avoids the competitive overaddition reaction. In this context, pseudoephedrine amides have shown to operate with similar efficiency as morpholine or Weinreb amides.[8]

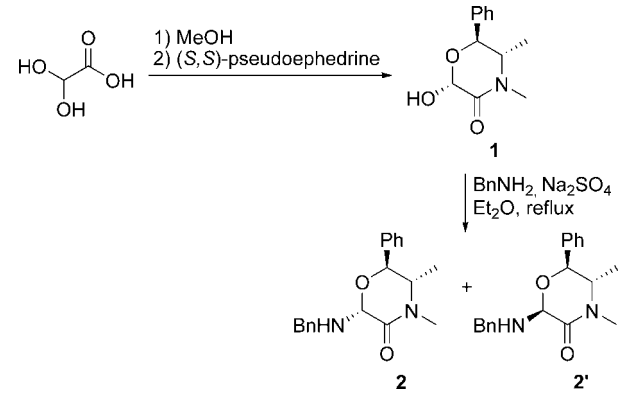
With these precedents in mind, we decided to explore the possibility of carrying out stereocontrolled additions to the azomethine function of an α-imino amide derived from (*S*,*S*)-(+)-pseudoephedrine glyoxylamide in which the amino alcohol plays the role of an efficient chiral auxiliary linked to the electrophile (Scheme 1). In addition, we also anticipated that the obtained adducts could be suitable substrates for the preparation of enantioenriched α-amino ketones by means of a subsequent selective addition of organolithium reagents to the pseudoephedrine amide moiety.[9]

Scheme 1



We started our work with the synthesis of the starting *N*-benzyl-α-imino amide derived from pseudoephedrine (Scheme 2), which was carried out by esterification of commercially available glyoxylic acid monohydrate with MeOH followed by treatment with (*S*,*S*)-(+)-pseudoephedrine, yielding the corresponding glyoxylamide in its cyclic form (**1**). Next, **1** was reacted with benzylamine in the presence of anhydrous Na_2SO_4, furnishing 2-benzylamino-4,5-dimethyl-6-phenyl-morpholin-3-one (**2**), which is also the cyclic form of the required α-imino glyoxylamide derived from (*S*,*S*)-pseudoephedrine. This compound was obtained pure by ^{1}H NMR and as a 3:1 mixture of diastereoisomers **2** and **2′**, which could not be separated and therefore had to be employed in the next step without further purification.

Scheme 2



We next proceeded to carry out the reaction of organometallic reagents to the mixture of **2** and **2′** (Table 1). When we performed the reaction using 2.2 equiv of MeMgCl in THF at −78 °C (entry 1) we observed the clean formation

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(5) Fiaud, J.-C.; Kagan, H. B. *Tetrahedron Lett.* **1971**, *12*, 1019.

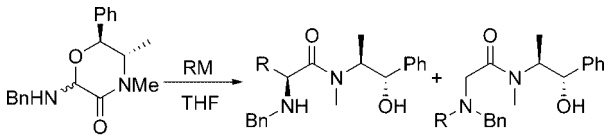
(6) For the first use of pseudoephedrine as chiral auxiliary, see: (a) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361. (b) Myers, A. G.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. For a review, see: (c) Myers, A. G.; Charest, M. G. *Handbook of Reagents for Organic Synthesis: Chiral Reagents for Asymmetric Synthesis*; Paquette, L. A., Ed.; Wiley Interscience: New York, 2003; p 485. For other examples, see: (d) Iza, A.; Vicario, J. L.; Badia, D.; Carrillo, L. *Synthesis* **2006**, 4065. (e) Vicario, J. L.; Rodriguez, M.; Badia, D.; Carrillo, L.; Reyes, E. *Org. Lett.* **2004**, *6*, 3171. (f) 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*, 1. (g) Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *Org. Lett.* **2002**, *4*, 4583. (h) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 5801. (i) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 9030. (j) Anakabe, E.; Vicario, J. L; Badía, D.; Carrillo, L.; Yoldi, V. *Eur. J. Org. Chem.* **2001**, 4343. (k) Myers, A. G.; Barbay, J. K.; Zhong, B. *J. Am. Chem. Soc.* **2001**, *123*, 7207. (l) Vicario, J. L.; Badía, D.; Domínguez, E.; Rodríguez, M.; Carrillo, L. *J. Org. Chem.* **2000**, *65*, 3754. (m) Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428.

(7) (a) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badia, D.; Uria, U.; Iza, A. *J. Org. Chem.* **2006**, *71*, 7763. (b) Etxebarria, J.; Vicario, J. L.; Badia, D.; Carrillo, L.; Ruiz, N. *J. Org. Chem.* **2005**, *70*, 8790.

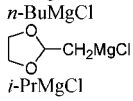
(8) For a detailed study see ref 6a. For other related examples, see: (a) Zhou, X.-T.; Lu, L.; Furkert, D. P.; Wells, C. E.; Carter, R. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7622. (b) Robertson, J.; Dallimore, J. W. P.; Meo, P. *Org. Lett.* **2004**, *6*, 3857. (c) White, J. D.; Xu, Q.; Lee, C.-S.; Valeriote, F. A. *Org. Biomol. Chem.* **2004**, *2*, 2092. (d) Vicario, J. L.; Badía, D.; Carrillo, L. *Tetrahedron: Asymmetry* **2003**, *14*, 489. (e) Vicario, J. L.; Badía, D.; Carrillo, L. *Tetrahedron: Asymmetry* **2002**, *13*, 745. (f) Smith, A. B., III; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925. See also refs 6d and 6k.

(9) Myers has reported the 1,2-addition of Grignard reagents to *N*-Boc α-amino amides derived from pseudoephedrine. Myers, A. G.; Yoon, T. *Tetrahedron Lett.* **1995**, *36*, 9429.

Table 1. Diastereoselective Addition of Organometallic Reagents to the Mixture of Morpholin-3-ones **2** and **2′**



2 + 2' **3a-f** **4a-f**

entry	compd	RM	temp (°C)	3/4	yield (%)[a]	dr[b]
1	**3a**	MeMgCl	-78	>98/<2	70	93:7
2	**3a**	MeMgCl	-90	>98/<2	46	85:15
3	**3a**	MeMgCl	-105	>98/<2	36	90:10
4	**3a**	MeLi	-78	>98/<2	55	70:30
5	**3a**	MeLi	-105	>98/<2	38	60:40
6	**3a**	MeMgCl	-78[c]	>98/<2	89	93:7
7	**3b**	CH_2=$CHCH_2$MgCl	-78[c]	>98/<2	79	92:8
8	**3c**	CH_2=CH_2MgCl	-78[c]	>98/<2	62	93:7
9	**3d**	PhMgCl	-78[c]	>98/<2	19	>95:<5
10	**3e+4e**	*n*-BuMgCl	-78[c]	65/35	79[d]	-
11	**3f+4f**		-78[c]	10/90	58[d]	-
12	**3g+4g**	*i*-PrMgCl	-78[c]	5/95	46[d]	-

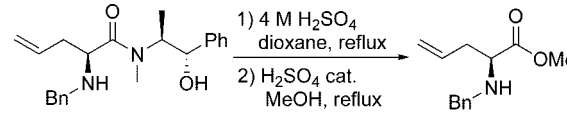
[a] Yield of pure product after flash column chromatography purification. [b] Determined by ^{1}H NMR analysis of crude reaction mixture. [c] Reaction was carried out using 4.4. equiv of Grignard reagent. [d] Global yield for both regioisomers (eluted together during flash column chromatography purification).

of the expected addition product to the azomethine moiety in good yield and diastereoselectivity. Surprisingly, lowering the temperature had a remarkable negative effect on both yield and diastereoselectivity (entries 2 and 3). We tried to increase the yield of the reaction by using the more reactive MeLi as nucleophile (entries 4 and 5) but with no success, observing a sluggish reaction with poorer yield and dr. We could significantly improve the yield by using excess MeMgCl without affecting the diastereoselectivity of the reaction (entry 6). In all of these experiments we did not observe the formation of any regioisomeric *N*-alkylation byproduct. However, when we proceeded to extend these optimized conditions to other different Grignard reagents (entries 7−11), we found that the nature of the organometallic reagent had a striking influence in the regioselectivity of the reaction, observing that, while methyl, allyl, aryl, and vinyl Grignard reagents reacted cleanly to furnish exclusively the desired product **3** derived from the addition to the C=N double bond (entries 6−9), the use of primary and secondary alkyl magnesium halides resulted in mixtures of regioisomers **3**/**4** in a variable ratio (entries 10−12).

The determination of the absolute configuration of the newly created stereogenic center during the addition step was carried out by chemical correlation. Acid hydrolysis of amide **3b** followed by esterification with MeOH furnished known[10] methyl (*S*)-2-benzylamino-pent-4-enoate **5** (Scheme 3). The obtained $[\alpha]^{20}_D$ value matched with that reported in the literature for the same (*S*)-enantiomer, which allowed us to

(10) Del Valle, J. R.; Goodman, M. *J. Org. Chem.* **2004**, *69*, 8946.

Scheme 3

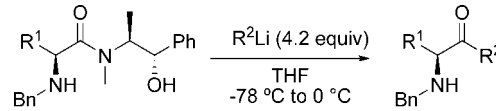


3b **5**

propose an *S* configuration for the newly created stereogenic center for amide **3b** and, by analogy, to all amides **3a**−**d** prepared.

Finally, we proceeded with the synthesis of enantioenriched α-amino ketones by monoaddition of organolithium reagents to the amide moiety of adducts **3a**−**f** (Table 2).[11]

Table 2. Synthesis of Enantioenriched α-Amino Ketones



3a-e **6a-h**

entry	substrate	R^1	R^2	product	yield (%)[a]	ee (%)[b]
1	**3a**	Me	*n*-Bu	**6a**	83	84
2	**3a**	Me	*i*-Pr	**6b**	55	84
3	**3a**	Me	*t*-Bu	**6c**	29	>99
4	**3a**	Me	Ph	**6d**	54	82
5	**3b**	CH_2=$CHCH_2$	Et	**6e**	42	78
6	**3c**	CH_2=CH_2	Me	**7**[c]	24	
7	**3d**	Ph	Ph	**6f**	27	94
8	**3e** + **4e**	*n*-Bu	Me	**6g**	54[d]	80
9	**3e** + **4e**	*n*-Bu	Ph	**6h**	80[d]	90

[a] Yield of pure product after flash column chromatography purification. [b] Determined by chiral HPLC analysis of crude reaction mixture (see Supporting Information for details). [c] The addition reaction took place as expected but together with a rearrangement process, furnishing a dehydro-α-amino ketone product (**7**) in which no stereogenic centers were present (see Supporting Information). [d] Calculated yield by considering that a 65/35 mixture of **3e** and **4e** was employed as starting material.

As can be observed in Table 2, the addition took place as anticipated, affording α-amino ketones **5a**−**i** in moderate yields and allowing the use of different organolithium reagents. An excess of nucleophile had to be employed in order to quantitatively deprotonate the two acidic NH and OH groups before the 1,2-addition step occurs. It is noteworthy that the adducts **6a**−**h** were obtained with optical purities comparable to those of the corresponding precursors **3a**−**e**, which indicates that the addition reaction to the pseudoephedrine amide moiety took place with none or very little epimerization at the highly acidic α-protons of the substrates **3a**−**e**, which might have been expected under these basic conditions.

(11) We also tested the addition of Grignard reagents to *N*-benzylglycinamide **3a** as reported by Myers for *N*-Boc-glycinamides (see ref 9), but the reaction proceeded sluggisly and we could not observe the formation of any α-amino ketone product.

In conclusion, we have explored the ability of (*S*,*S*)-(+)-pseudoephedrine α-iminoglyoxylamide as a useful chiral glycine cation equivalent for the preparation of α-amino carbonyl compounds. This substrate can be easily prepared from cheap and readily available starting materials and reacts eficiently with Grignard reagents, affording the corresponding α-amino amide adducts in good yields and diastereoselectivities, although the regioselectivity strongly depends upon the nature of the Grignard reagent. In addition, the intrinsic reactivity of the pseudoephedrine amide moiety allows the preparation of enantioenriched α-amino ketones by carrying out a selective monoaddition reaction across the amide functional group, leading to the target compounds without signifficant epimerization in the previously created stereogenic center. This results in a very practical and modular synthetic protocol for the construction of a range of α-amino ketones in which the two substituents can be assembled provided that the adequate Grignard and organolithium reagent are chosen.

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Supporting Information Available: Characterization of all new compounds and copies of their ^{1}H and ^{13}C NMR spectra. This information is available free of charge via the Internet at http://pubs.acs.org.

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