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Tandem Asymmetric Conjugate Addition/α-Alkylation Using (*S*,*S*)-(+)-Pseudoephedrine as Chiral Auxiliary

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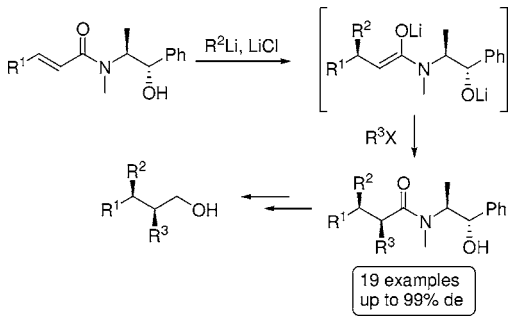
ABSTRACT



α,β-Unsaturated amides derived from the chiral amino alcohol (*S*,*S*)-(+)-pseudoephedrine undergo a very clean and diastereoselective tandem conjugate addition/α-alkylation reaction. Excellent results have been achieved using a wide range of differently substituted conjugate acceptors, organolithium reagents, and alkyl halides. The chiral auxiliary could be easily removed from the obtained adducts by reduction, furnishing chiral nonracemic α,β-branched alcohols in a very easy and efficient way.

Asymmetric tandem C−C bond formation reactions are one of the most attractive strategies in organic synthesis, as they involve multistep processes that turn into a very easy and direct method for increasing molecular complexity from readily available starting materials.[1] In recent years, the asymmetric conjugate addition, which is one of the most versatile methodologies for the stereocontrolled formation of new C−C or C−X bonds,[2] has become a widely used tool for initiating tandem asymmetric transformations, due to the formation of an intermediate chiral enolate nucleophile with potential for α-alkylation, aldol, Mannich, Michael, or similar reactions.[3] In this context, a very reliable possibility for exerting stereochemical control in the formation of the first stereogenic center, which is generated during the conjugate addition step, is the use of the chiral auxiliary methodology, although the use of catalytic asymmetric processes is also well documented. In both cases, special attention has to be paid to the formation of the subsequent stereocenter-

(1) For some reviews, see: Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321. (b) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103. (c) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195.

(2) Reviews: (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221. (c) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 151. (d) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *53*, 8033. (e) Leonard, J.; Díez-Barra, E.; Merino, S. *Eur. J. Org. Chem.* **1998**, 2051. (f) Krause, N, *Angew. Chem., Int. Ed.* **1998**, *37*, 283. (g) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.

(3) For a recent review, see: (a) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354. See also: (b) Taylor, R. J. K. *Synthesis* **1985**, 364. (c) Chapdelaine, M. J.; Hulce, M. *Org. React.* **1990**, *38*, 225.

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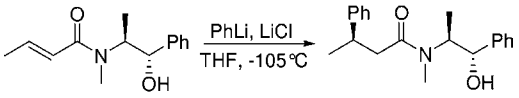
(s), whose formation can be determined by the starting chirality source (the chiral auxiliary or catalyst) or by the stereocenter first created in the conjugate addition step.

As was previously mentioned, literature furnishes many examples for asymmetric tandem transformations initiated by a conjugate addition reaction, typically tandem conjugate addition/aldol reactions. However, the number of examples in which the intermediate enolate is trapped with an alkylating reagent such as an alkyl halide is very scarce.[4] Alkyl halides react very difficultly with the intermediate enolate under the experimental conditions employed in the conjugate addition step and usually require the addition of an additive like HMPA in order to reach to acceptable yields. Moreover, only activated alkylating reagents such as allyl bromide or methyl iodide can usually be employed with good results, which is a clear limitation of the methodologies reported up to date.

In a recent work, we have shown that pseudoephedrine can play the role of a very efficient chiral auxiliary in asymmetric aza-Michael reactions.[5] With this precedent in mind, and taking into account that pseudoephedrine amide enolates are reported to be excellent chiral nucleophiles in asymmetric α-alkylation reactions,[6] we decided to explore the viability of (*S*,*S*)-(+)-pseudoephedrine as chiral auxiliary in stereocontrolled tandem conjugate additions/alkylations.[7] The highly efficient conversion of the obtained adducts into enantioenriched α,*β*-branched alcohols will also be presented, showing the remarkable synthetic potential of this methodology.

Our experiments began with the optimization of reaction conditions for the conjugate addition of the carbon nucleophile to α,*β*-unsaturated amide **1a** (Scheme 1). After trying several organometallic reagents under different reactions

Scheme 1



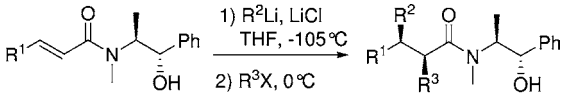
1a **2a** Yield: 86% dr: 97/3

conditions, we found that addition of 2.0 equiv of PhLi to a THF solution of **1a** at −105 °C in the presence of 5 equiv of LiCl furnished cleanly and in a very short time (10 min) the desired conjugate addition product, with an excellent degree of diastereoselection and with no traces of any 1,2-addition byproduct. The absolute configuration of the newly created stereogenic center was determined by chemical correlation via hydrolysis of amide **2a** to (*R*)-3-phenylbutanoic acid.[8]

We determined that LiCl had to be present in the reaction medium for the conjugate addition to proceed with such high diastereoselectivity[9] because it is known that pseudoephedine amide enolates undergo α-alkylation in much faster way when this salt is employed as an additive.[10] Also, the use of organolithium reagents should have a positive effect in the alkylation step due to the higher reactivity exhibited by lithium enolates. In fact, a problem associated with much of the tandem processes reported so far is that organozinc or Grignard reagents had to be used as nucleophiles in the conjugate addition step, therefore generating an intermediate zinc or magnesium enolate, which are known to exhibit significantly lower reactivity in alkylation reactions.

Having established an optimal protocol for the conjugate addition step, we proceeded next to examine the tandem process (Scheme 2). When we treated the mixture of the

Scheme 2



1a (R^1=Me); **1b** (R^1=Et); **1c** (R^1=*n*-Pr); **1d** (R^1=Ph) **3a-s**

conjugate addition reaction with 1.2 equiv of MeI, warmed it to 0 °C, and stirred at this temperature for 4 h, the expected

(4) Relevant examples of asymmetric conjugate addition of organometallic reagents and subsequent α-alkylation: (a) Shintani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 6240. (b) Arai, Y.; Kasai, M.; Ueda, K.; Masaki, Y. *Synthesis* **2003**, 1511. (c) Fleming, F. F.; Wang, Q.; Steward, O. W. *J. Org. Chem.* **2003**, *68*, 4235. (d) Totani, K.; Asano, S.; Takao, K.; Tadano, K. *Synlett* **2001**, 1772. (e) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755. (f) Rawson, D. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2292. (g) Tomioka, K.; Kawasaki, H.; Koga, K. *Tetrahedron Lett.* **1985**, *26*, 3027. (h) Liebeskind, L. S.; Welker, M. E. *Tetrahedron Lett.* **1985**, *26*, 3079. For a tandem 1,4-addition/Pd-catalyzed α-allylation, see: (i) Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem: Soc.* **1999**, *121*, 1104. For a tandem radical conjugate addition/α-alkylation, see: (j) Sibi, M. P.; He, L. *Synlett.* **2006**, 689 and references therein.

(5) Etxebarria, J.; Vicario, J. L.; Badia, D.; Carrillo, L.; Ruiz, N. *J. Org. Chem.* **2005**, *70*, 8790.

(6) (a) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. (b) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9631.

(7) For the use of pseudoephedrine as chiral auxiliary, see the following. Review: (a) 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. See also: (b) Vicario, J. L.; Rodriguez, M.; Badía, D.; Carrillo, L.; Reyes, E. *Org. Lett.* **2004**, *6*, 3171. (c) Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *J. Org. Chem.* **2004**, *69*, 790. (d) Smitrovich, J. H.; Boice, G. N.; Qu, C.; DiMichele, L.; Nelson, T. D.; Huffman, M. A.; Murry, J.; McNamara, J.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1963. (e) Vicario, J. L.; Badía, D.; Carrillo, L. *Tetrahedron: Asymmetry* **2002**, *13*, 745. (f) Vicario, J. L.; Badía; D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 5801. (g) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 9030. (h) Keck, G. E.; Knutson, C. E.; Wiles, S. A. *Org. Lett.* **2001**, *3*, 707. (i) Guillena, G.; Najera, C. *Tetrahedron: Asymmetry* **2001**, *12*, 181. (j) Myers, A. G.; Barbay J. K.; Zhong, B. *J. Am. Chem. Soc.* **2001**, *123*, 7207. (k) Nagula, G.; Huber, V. J.; Lum, C.; Goodman, B. A. *Org. Lett.* **2000**, *2*, 3527. (l) Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428.

(8) The observed optical rotation for the sample prepared from amide **2a**: $[\alpha]^{20}_D = -42.3$ ($c = 0.70$, C_6H_6) was in agreement with the literature data for (*R*)-3-phenylbutanoic acid: $[\alpha]^{20}_D = -45.8$ ($c = 0.77$, C_6H_6). Suzuki, I.; Kin, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1993**, *115*, 10139.

(9) When the conjugate addition reaction was carried out in the absence of LiCl an important decrease in the diastereoselectivity was observed in all cases studied. It is known that LiCl addition significantly impacts stereoselectivity in the Michael reaction of pseudoephedrine amide enolates: Smitrovich, J. H.; DiMichele, L.; Qu, C.; Boice, G. N.; Nelson, T. D.; Huffman, M. A.; Murry, J. *J. Org. Chem.* **2004**, *69*, 1903.

(10) For the influence of LiCl in the reactivity of pseudoephedrine enolates, see refs 6 and 9. See also: (a) Rück, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 433. (b) Henderson, K. W.; Dorigo, A. E.; Liu, Q.-Y.; Williard, P. G.; Schleyer, P. v. R.; Bernstein, P. R. *J. Am. Chem. Soc.* **1996**, *118*, 1339 and references therein.

alkylation product **3a** was obtained in an acceptable yield (50%) and excellent diastereomeric ratio (93:4:3:<1). The yield of the reaction could be further increased by working with excess alkylating reagent with no negative effect on the diastereoselectivity of the reaction (entry 1 in Table 1).

Table 1. Asymmetric Tandem Conjugate Addition/Alkylation with α,β-Unsaturated Amides **1a**−**d**

entry	product	R^1	R^2	R^3	yield[a] (%)	dr[b,c]
1	**3a**	Me	Ph	Me	77	93:4:3:<1
2	**3b**	Me	Ph	Et	96	95:5:<1:<1
3	**3c**	Me	Ph	allyl	70	93:4:2:1
4	**3d**	Me	Ph	Bn	78	94:4:<1:<1
5	**3e**	Me	*n*-Bu	Me	67	91:5:3:<1
6	**3f**	Me	*n*-Bu	Et	73	91:6:2:<1
7	**3g**	Me	*n*-Bu	allyl	71	86:10:4:<1
8	**3h**	Me	*n*-Bu	Bn	63	89:8:3:<1
9	**3i**	Et	Ph	Me	75	95:4:<1:<1
10	**3j**	Et	Ph	Et	80	97:2:<1:<1
11	**3k**	Et	Ph	allyl	77	95:4:1:<1
12	**3l**	Et	Ph	Bn	67	99:<1:<1:<1
13	**3m**	*n*-Pr	Ph	Me	86	99:<1:<1:<1
14	**3n**	*n*-Pr	Ph	Et	82	95:4:1:<1
15	**3o**	*n*-Pr	Ph	allyl	70	96:4:<1:<1
16	**3p**	*n*-Pr	Ph	Bn	73	>99:<1:<1:<1
17	**3q**	*n*-Pr	*n*-Bu	allyl	77	96:3:<1:<1
18	**3r**	*t*-Bu	Ph	Me	70	96:3:2:<1
19	**3s**	*t*-Bu	*n*-Bu	Me	35	97:2:<1:<1

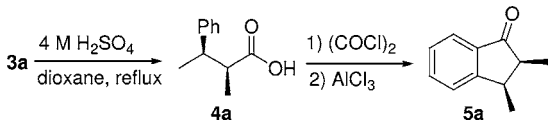
[a] Yield of pure product after column chromatography purification. [b] Ratio of the four possible diastereoisomers that could be formed in the reaction mixture. [c] Calculated by HPLC analysis of the crude reaction mixture (see the Supporting Information for details).

We proceeded next to examine the addition of different organolithium reagents as well as a variety of differently substituted α,β-unsaturated amides and alkyl halides with excellent results concerning both the yield and the stereoselectivity of the reaction (Table 1).

In general, we observed that the reaction proceeded in good yields and stereoselectivities, regardless of the nature of the substituent at the enamide substrate **1a**−**d**, the organolithium reagent, or the alkyl halide employed. Remarkably, it has to be pointed out that not only activated alkyl halides were shown to be useful electrophiles in the alkylation step but also the less reactive ethyl iodide reacted efficiently in all cases studied (entries 2, 6, 10, and 14).

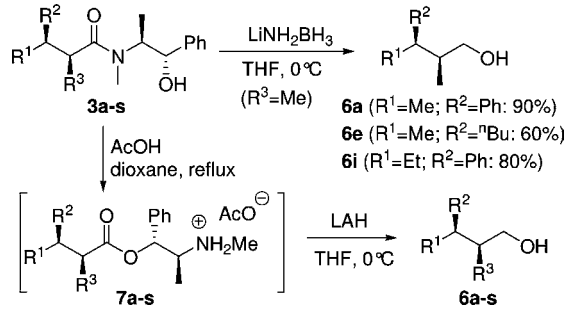
The determination of the absolute configuration of the newly created stereogenic center during the alkylation step was performed as follows: Acid hydrolysis of amide **3a** furnished 2-methyl-3-phenylbutanoic acid **4a** in 98% yield (Scheme 4), and then this was converted into the corresponding acyl chloride and subjected to intramolecular Friedel−Crafts acylation, furnishing indanone **5a** (Scheme 3). NOE experiments on **5a** indicated a cis relationship between both substituents, which was extended to the starting amide **3a** and by analogy to all amides **3b**−**s** prepared.

Scheme 3



The sense of the asymmetric induction observed in the diastereoselective conjugate addition step is in good agreement with the model previously proposed by us for the asymmetric aza-Michael reaction of lithium amides to α,β-unsaturated amides derived from (*S*,*S*)-(+)-pseudoephedrine,[5] and the stereochemical outcome of the alkylation reaction also agrees with what has been proposed in the literature for the alkylation of (*S*,*S*)-(+)-pseudoephedrine amide enolates.[6a,11] This indicates that the stereogenic center generated in the initial conjugate addition step does not hamper the efficient stereochemical control exerted by the chiral auxiliary in the alkylation step.

Scheme 4



We next focused on the removal of the chiral auxiliary from the adducts **3a**−**s** by exploiting the intrinsic reactivity of the pseudoephedrine amide functionality. We therefore focused on the reduction of the amide moiety in order to obtain enantioenriched α,β-branched alcohols which should be compounds of potential interest as chiral building blocks in total synthesis. We first tried the use of lithium amidotrihydroborate (LAB), which is known as a very effective reagent for the conversion of pseudoephedrine amides into the corresponding alcohols,[12] as was our case. The reduction of amides **3a**, **3e**, and **3i** (R^3 = Me) proceeded in a fast and clean way, furnishing the desired alcohols in good yields and as single diastereoisomers. However, other amides such as **3b**−**d**, with bulkier substituents at the α-carbon ($R^3 \neq$ Me), did not react with LAB, even after prolonged reaction times (Scheme 4).

We therefore surveyed a second possibility for performing this transformation (Scheme 4). It is known that pseudoephedrine amides undergo fast N→O acyl transfer when heated in the presence of an acid catalyst,[6a] and therefore, we hypothesized that formed ester should be easily reduced to

(11) Vicario, J. L.; Badia, D.; Dominguez, E.; Carrillo, L. *J. Org. Chem.* **1999**, *64*, 4610.

(12) (a) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623. (b) Myers, A. G.; Yang, B. H.; Chen, H.; Kopecki, D. J. *Synlett* **1997**, 457. See also: (c) Whitlock, G. A.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 2007.

the desired alcohol with an standard reducing agent like LAH. To our delight, when a mixture of amide **3a** and AcOH was refluxed in dioxane and the volatiles were removed under reduced pressure, the quantitative formation of the ammonium ester **7a** was observed by ^{1}H NMR, and when this ester was reduced with LAH in THF at 0 °C, alcohol **6a** was isolated in good yield. These conditions were applied to all amides **3a**−**s** with the results shown in Table 2.

Table 2. Reduction of Amides **3a**−**s**

entry	product	R^1	R^2	R^3	yield[a] (%)
1	**6a**	Me	Ph	Me	82
2	**6b**	Me	Ph	Et	75
3	**6c**	Me	Ph	allyl	73
4	**6d**	Me	Ph	Bn	80
5	**6e**	Me	*n*-Bu	Me	86
6	**6f**	Me	*n*-Bu	Et	98
7	**6g**	Me	*n*-Bu	allyl	80
8	**6h**	Me	*n*-Bu	Bn	98
9	**6i**	Et	Ph	Me	87
10	**6j**	Et	Ph	Et	67
11	**6k**	Et	Ph	allyl	87
12	**6l**	Et	Ph	Bn	80
13	**6m**	*n*-Pr	Ph	Me	98
14	**6n**	*n*-Pr	Ph	Et	70
15	**6o**	*n*-Pr	Ph	allyl	91
16	**6p**	*n*-Pr	Ph	Bn	68
17	**6q**	*n*-Pr	*n*-Bu	allyl	68
18	**6r**	*t*-Bu	Ph	Me	76
19	**6s**	*t*-Bu	*n*-Bu	Me	82

[a] Yield of pure product after column chromatography purification.

In all cases studied, the alcohols **6a**−**s** were isolated in good yields and as single isomers, as ^{1}H NMR analysis of the crude reaction mixture indicated. This means that the reaction conditions employed did not promote any epimerization at the α-stereocenter, which might be expected due to the potential enolizability of the starting materials, specially under the basic conditions in which the reduction step was carried out. It has also to be pointed out that the chiral auxiliary, (*S*,*S*)-(+)-pseudoephedrine, could be recovered from the reaction mixture in ca. 75% yield by means of a simple acid−base workup procedure and with no loss of optical purity, which allowed us to recycle the auxiliary for further use.

In conclusion, we have shown that α,*β*-unsaturated amides derived from the chiral amino alcohol (*S*,*S*)-(+)-pseudoephedrine undergo very clean and diastereoselective 1,4-addition of organolithium reagents, furnishing the corresponding enolate intermediate which is able to undergo a subsequent alkylation process with alkyl halides to furnish the corresponding α,*β*-dialkyl substituted amides **3a**−**s** in excellent yields. The chiral auxiliary is able to exert a very effective asymmetric induction both in the conjugate addition and in the alkylation steps using a wide variety of different acceptors, organolithium reagents, and alkyl halides. Remarkably, the high reactivity shown by the intermediate lithium enolates allows the use of alkyl halides such as ethyl iodide, which are usually unreactive in these kinds of reactions. In addition, the chiral auxiliary can be easily removed from the adducts furnishing chiral nonracemic α,*β*-branched alcohols. An additional advantage of the use of this chiral auxiliary was found in the recyclability of the reagent after cleavage from the adducts.

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Supporting Information Available: Detailed descriptions of experimental procedures, characterization of all new compounds, and ^{1}H and ^{13}C NMR of amides **3a**−**s**. This material is available free of charge via the Internet at http://pubs.acs.org.

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