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# Asymmetric Synthesis of β-Amino Esters by Aza-Michael Reaction of α,β-Unsaturated Amides Using (*S*,*S*)-(+)-Pseudoephedrine as Chiral Auxiliary

Juan Etxebarria, Jose L. Vicario, Dolores Badia,* and Luisa Carrillo

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

*qopbaurm@lg.ehu.es*

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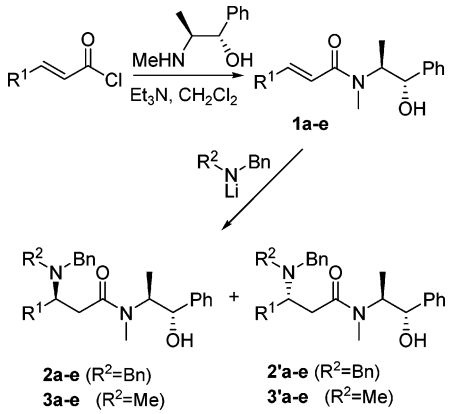
**Abstract:** Chiral nonracemic β-amino esters were prepared in good yields and enantioselectivities using the diastereoselective conjugate addition of nitrogen nucleophiles to α,β-unsaturated amides derived from (*S*,*S*)-(+)-pseudoephedrine as the key step. In this way, several β-amino amide adducts were prepared using different conjugate acceptors and two different lithium benzylamides as nucleophiles. These adducts were easily converted in only one step, into the final, highly enantioenriched β-amino esters

The asymmetric conjugate addition is regarded as one of the most powerful tools for the formation of C−C or C−X bonds that allows the preparation of chiral compounds in a stereocontrolled fashion.[1] A particularly interesting version of this reaction is the conjugate addition of nitrogen nucleophiles to α,β-unsaturated carbonyl compounds, the so-called aza-Michael reaction, which represents one of the most attractive procedures for the asymmetric synthesis of β-amino carbonyl derivatives. On the other hand, the commercially available, cheap reagent pseudoephedrine has provided excellent results as a chiral auxiliary in several C−C and C−X bond-forming reactions in which, in all cases reported, amides derived from this amino alcohol have been employed as nucleophiles via their corresponding enolates.[2] Additional advantages of the use of this auxiliary are related to the unique reactivity of the amide function present in the obtained adducts, which allows the preparation of a wide range of other interesting chiral building blocks.

With all these precedents in mind, we decided to check the ability of (*S*,*S*)-(+)-pseudoephedrine as chiral auxiliary in the conjugate addition reaction of nitrogen nucleophiles to α,β-unsaturated amides derived from this amino alcohol. 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.[3−5] 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, the systems that have been tested with good results in this particular case have resulted in extremely hindered substrates[3] or functionalized moieties that can interact with the conjugate system, either at the carbonyl group[4] or at the C=C double bond (for example by π-stacking interactions),[5] thus reaching a rigid, well-organized intermediate. Therefore, we wish to report herein the first example in which a reagent derived from (*S*,*S*)-(+)-pseudoephedrine has been employed as *chiral electrophile*,[6] showing that this amino alcohol is able to exert a very effective remote stereochemical control in the asymmetric conjugate addition of nitrogen nucleophiles.

**SCHEME 1**




Amides **1a**−**e** (Scheme 1) were easily prepared by *N*-acylation of commercially available (*S*,*S*)-(+)-pseudoephedrine with the corresponding acyl chlorides,[2i] some of which are also commercially available and the others can be prepared without difficulty from the corresponding α,β-unsaturated carboxylic acids. With these amides in hand, we proceeded to perform a preliminary survey of possible nitrogen nucleophiles to be used in the asymmetric conjugate addition, using amide **1a** ($R^1$ = Me) as

* Corresponding author.

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(6) (*S*,*S*)-(+)-Pseudoephedrine has previously been used as auxiliary in Michael reactions, but in these cases, the corresponding amide enolates were employed as chiral *nucleophiles* (see refs 2b and 2f).

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**TABLE 1. Diastereoselective Addition of Lithium Benzylamides to α,β-Unsaturated Amide 1a (R¹ = Me)**

| entry | Nu | equiv[a] | solvent | *T* (°C) | yield (%)b | **2**/**2′** or **3**/**3′**[c] |
|---|---|---|---|---|---|---|
| 1 | $Bn_2NLi$ | 2 | THF | −78 | 67 | 70/30 |
| 2 | $Bn_2NLi$ | 2 | THF | −105 | 81 | 72/28 |
| 3 | $Bn_2NLi$ | 2 | $PhCH_3$ | −78 | 30 | 79/21 |
| 4 | $Bn_2NLi$ | 2 | $PhCH_3$ | −90 | 60 | >99/<1 |
| 5 | $Bn_2NLi$ | 4 | $PhCH_3$ | −90 | 85 | >99/<1 |
| 6 | BnMeNLi | 4 | $PhCH_3$ | −90 | 88 | >99/<1 |

[a] Equivalents of nucleophile. [b] Yield of isolated product. [c] The **2**/**2′** ratio was determined by HPLC (Chiralcel OD column, UV detector, 2-propanol/hexanes 2/98, flow rate 1.00 mL/min).

the starting model compound. We found that the use of simple amines (benzylamine, *N*-methylbenzylamine, and dibenzylamine) as nucleophiles did not afford the desired β-amino amide derivatives in any case, observing that the starting material was recovered unchanged in all cases. When higher temperatures or longer reaction times were employed, the corresponding transamidation derivatives were obtained as a result of competitive 1,2-addition reactions. On the other hand, when we changed to the more reactive lithium *N*,*N*-dibenzylamide as nitrogen nucleophile, we could observe that, in this case, the 1,4-addition products **2a** and **2′a** were cleanly obtained, with no presence of any 1,2-addition byproduct (Scheme 1).

We could also observe that the nature of the solvent had a striking effect in the diastereoselectivity of the reaction (Table 1). In fact, the use of a coordinating solvent like THF led to a consistently lower **2a**/**2′a** ratio (entries 1 and 2), when compared to toluene (entries 3−5), which was therefore chosen as the best solvent for this reaction. The temperature was a parameter that showed a remarkable influence both on the yield and the diastereoselectivity. In fact, the best yields were always obtained at the lowest possible temperature, regardless of the solvent employed (entries 1 and 2 for THF and 3 and 4 for toluene). This also applies to the degree of diastereoselection in toluene, which consistently increased when the temperature was lowered (entries 3 and 4). Finally, we could observe that the yield of the reaction positively increased when working with a large excess of nucleophile, with no loss of diastereoselectivity (entry 5),[7] which led us to adopt these conditions as optimal for this reaction. The optimized experimental conditions could also be applied to the use of lithium *N*-methylbenzylamide as nucleophile, yielding the *N*-benzyl-*N*-methyl-β-amino amide **3a** in excellent yield and diastereoselectivity (entry 6).

Once the preliminary survey was performed, we proceeded to apply these optimized conditions to the other amides **2b**−**e**, which incorporate different substitution patterns at the conjugate system (Table 2). As can be seen, the 1,4-addition products were obtained with good to excellent yields with the exception of the very hindered substrate **2d** ($R^1$ = $^t$Bu) and the amide **2e** ($R^1$ = Ph), which presents extended conjugation by means of the phenyl substituent. Nevertheless, the 1,4-addition products were obtained in good to excellent diastereoselectivities in all cases in which lithium dibenzylamide was employed as nucleophile (entries 1−4), and *N*,*N*-dibenzyl-β-amino amides **2b**−**e** were easily isolated after flash column chromatography purification. We were also able to improve the **2**/**2′** ratio in the cases of amides **2b** and **2c** by adding 2 equiv of the potentially chelating agent TMEDA, together with the lithium dibenzylamide nucleophile (entries 5 and 6 respectively), but the incorporation of this additive did not afford any improvement in the diastereoselectivity of the addition reaction when starting from amides **1d** and **1e** (entries 7 and 8). When we turned to the conjugate addition of lithium *N*-methylbenzylamide, a much smaller nucleophile (entries 9−12), a significant decrease in the diastereoselectivity of the process was observed in all cases except amide **3c** ($R^1$ = $^i$Pr, entry 10).

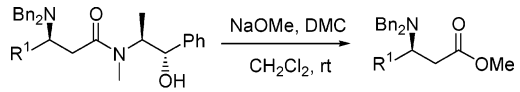
(7) We tried to reduce the amount of nucleophile needed by protecting the OH group of the pseudoephedrine moiety as the corresponding methyl or TBS ether, but this led to a radical decrease of the diastereoselectivity.

**TABLE 2. Diastereoselective Addition of Lithium Benzylamides to Amides 1b−e**

| entry | prod. | $R^1$ | nucleophile | yield (%)[a] | **2**/**2′** or **3**/**3′**[b] |
|---|---|---|---|---|---|
| 1 | 2b | Et | $Bn_2NLi$ | 67 | 82/18 |
| 2 | 2c | $^i$Pr | $Bn_2NLi$ | 78 | 70/30 |
| 3 | 2d | $^t$Bu | $Bn_2NLi$ | 33 | >99/<1 |
| 4 | 2e | Ph | $Bn_2NLi$ | 15 | 98/2 |
| 5 | 2b | Et | $Bn_2NLi$/TMEDA[c] | 85 | 94/6 |
| 6 | 2c | $^i$Pr | $Bn_2NLi$/TMEDA[c] | 62 | 80/20 |
| 7 | 2d | $^t$Bu | $Bn_2NLi$/TMEDA[c] | 24 | 92/8 |
| 8 | 2e | Ph | $Bn_2NLi$/TMEDA[c] | 47 | 65/35 |
| 9 | 3b | Et | BnMeNLi | 62 | 74/26 |
| 10 | 3c | $^i$Pr | BnMeNLi | 53 | 80/20 |
| 11 | 3d | $^t$Bu | BnMeNLi | 52 | 88/12 |
| 12 | 3e | Ph | BnMeNLi | 94 | 72/28 |

[a] Yield of isolated product. [b] The **2**/**2′** ratio was determined by HPLC data (see Supporting Information). [c] 2 equiv of a 1:1 mixture of $Bn_2NLi$ and TMEDA was used as nucleophile.

**SCHEME 2**




**2a-e** **4a-e**

In fact, debenzylation of *N*,*N*-dibenzyl-β-amino ester **4a** furnished directly methyl (−)-3-aminobutanoate (Scheme 3), a known compound,[10] with

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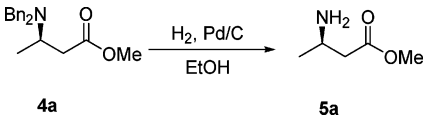
**TABLE 3. Synthesis of the β-Amino Esters 4a−e**

| entry | product | $R^1$ | yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|
| 1 | 4a | Me | 73 | >99 |
| 2 | 4b | Et | 75 | 88 |
| 3 | 4c | $^i$Pr | 52 | 60 |
| 4 | 4d | $^t$Bu | 70 | >99 |
| 5 | 4e | Ph | 63 | 96 |

[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).

**SCHEME 3**




a negative optical rotation value, which indicated the *R*-configuration for its stereogenic center. This configuration was further extended, by analogy, to the other β-amino amides (**2b**−**e** and **3a**−**e**) obtained, assuming the same stereochemical outcome for all the aza-Michael addition reactions performed.

In conclusion, we have shown that the chiral amino alcohol (*S*,*S*)-(+)-pseudoephedrine can be used as an exceptionally useful auxiliary in asymmetric aza-Michael reactions using lithium benzylamides as nucleophiles. This amino alcohol, linked to the conjugate acceptor via an amide linkage, 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, although the experimental conditions have to be changed depending upon the nature of the substituents at the α,β-unsaturated chain. Furthermore, the aza-Michael adducts obtained could be very easily transformed into β-amino esters, which are extremely useful chiral building blocks for the synthesis of many other interesting compounds. Besides, in view of the versatility of the amide moiety to be transformed into other functional groups, the broad application of this method for the stereocontrolled preparation of a wide range of interesting chiral synthetic intermediates may be anticipated.

## Experimental Section[11]

**General Procedure for the Diastereoselective Conjugate Addition of Lithium Benzylamides to α,β-Unsaturated Amides 1a−e. Procedure A (Lithium Amide as Nucleophile).** A solution of *n*-BuLi (4 mmol) was added to a solution of dibenzylamine or *N*-methylbenzylamine (4 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), the combined organic fractions were collected, dried over $Na_2SO_4$, and filtered, and the solvent was removed in vacuo, affording the wanted amides after flash column chromatography purification (hexanes:AcOEt 1:1).

**Procedure B (Lithium Amide/TMEDA as Nucleophile).** A solution of *n*-BuLi (2 mmol) was added to a solution of the benzylamine (2 mmol) and TMEDA (2 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 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), the combined organic fractions were collected, dried over $Na_2SO_4$, and filtered, and the solvent was removed in vacuo, affording the wanted amides after flash column chromatography purification (hexanes:AcOEt 1:1).

**General Procedure for the Conversion of Amides 2a−e into β-Amino Esters 4a−e.** Dimethyl carbonate (7.5 mmol) and MeONa (10 mmol) were added to a solution of the corresponding β-amino amide **2a**−**e** (1 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 sat. $NH_4Cl$. 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, and the solvent was removed in vacuo, affording the wanted β-amino esters after column chromatography purification (hexanes:AcOEt 8:2).

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**Supporting Information Available:** Detailed descriptions of experimental procedures and characterization of compounds **2a**−**e**, **3a**−**e**, and **4a**−**e**. This information is available free of charge via the Internet at http://pubs.acs.org.

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(11) For general experimental procedures, see ref 2d.