JOC Note

Highly Regio- and Stereoselective Addition of Organolithium Reagents to Extended Conjugate Amides Using (*S*,*S*)-(+)-Pseudoephedrine as Chiral Auxiliary

Marta Ocejo, Luisa Carrillo,* Dolores Badía,*
Jose L. Vicario, Naiara Fernández, and Efraim Reyes

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

marisa.carrillo@ehu.es; dolores.badia@ehu.es

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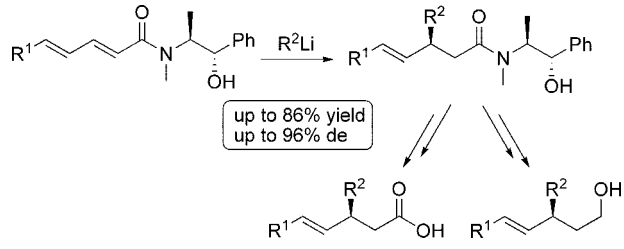

The conjugate addition of organolithium reagents to polyunsaturated conjugate amides containing (*S*,*S*)-(+)-pseudoephedrine as chiral auxiliary has been studied in detail. The reaction proceeded with good 1,4-selectivity and excellent stereoselectivity, affording the corresponding addition products with good yields and as highly diastereoenriched isomers. Removal of the chiral auxiliary by reduction or hydrolysis has allowed the preparation of polyfunctionalized chiral building blocks incorporating an alkene moiety suitable for further transformations.

The asymmetric conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds or related derivatives is considered as one of the most powerful methods for the stereocontrolled formation of C−C bonds.[1] In this context, many enantio- and diastereoselective versions of this transformation have been reported using a wide variety of different organometallic reagents.[2] However, when the conjugate addition reaction is carried out on extended Michael acceptors, besides the typical stereochemical issues to consider, regioselectivity shows up as a challenging element to be controlled.[3] In general, nucleophiles may undergo addition to α,β,γ,δ-unsaturated carbonyl compounds in a 1,2-, 1,4-, or 1,6- fashion, and this might lead to the formation of mixtures of all of the possible regioisomers.[4,5] In this context, literature shows that the 1,4-addition of organometallic reagents to polyunsaturated Michael acceptors leads in most cases to the formation of other regioisomers in variable ammounts.[5]

On the other hand, despite their availability, literature furnishes little information regarding the use of organolithium reagents in asymmetric conjugate additions to extended conjugate carbonyl compounds,[6] mainly because these reagents usually undergo 1,2-addition to the carbonyl moiety rather than giving any conjugate addition product.[7] Related to this topic, we have recently published a very efficient procedure for carrying out asymmetric conjugate additions of organolithium reagents to α,β-unsaturated amides derived from (*S*,*S*)-(+)-pseudoephedrine.[8] In this context, we wish to present herein the use of this aminoalcohol as chiral auxiliary[9] in the stereocontrolled conjugate addition of organolithium reagents to extended conjugate acceptors, also showing that the reaction always proceeds with full 1,4-regioselectivity. In addition, the highly efficient conversion of the obtained adducts into enantioenriched β-branched alcohols containing an additional alkene

(1) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992.

(2) For some reviews, see: (a) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rossle, M. *Synthesis* **2007**, 1279. (b) Lopez, F.; Minnaard, A. J.; Feringa, B. L. *Acc. Chem. Res.* **2007**, *40*, 179. (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (d) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221. (e) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (f) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (g) Leonard, J.; Díez-Barra, E.; Merino, S. *Eur. J. Org. Chem.* **1998**, 2051. (h) Krause, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 283. (i) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.

(3) Review Krause, N.; Thorand, S. *Inorg. Chim. Acta* **1999**, *296*, 1.

(4) For some examples focused on achieving 1,6-addition, see: (a) den Hartog, T.; Harutyunyan, S. R.; Font, D.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 398. (b) Okada, S.; Arayama, K.; Murayama, R.; Ishizuka, T.; Hara, K.; Hirone, N.; Hata, T.; Urabe, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6860. (c) Henon, H.; Mauduit, M.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9122. (d) Nishimura, T.; Yashuhara, Y.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 5164. (e) Fillion, E.; Wilsily, A.; Liao, E.-T. *Tetrahedron: Asymmetry* **2006**, *17*, 2957. (f) Fukuhara, K.; Urabe, H. *Tetrahedron Lett.* **2005**, *46*, 603. (g) de la Herran, G.; Murcia, C.; Csaky, A. *Org. Lett.* **2005**, *7*, 5629. (h) Hayashi, T.; Yamamoto, S.; Tokunaga, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 4224. (i) Canisius, J.; Mobley, T. A.; Berger, S.; Krause, N. *Chem.—Eur. J.* **2001**, *7*, 2671. (j) Uerdingen, M.; Krause, N. *Tetrahedron* **2000**, *56*, 2799. (k) Krause, N. *J. Org. Chem.* **1992**, *57*, 3509. (l) Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588. (m) Barbot, F.; Kadib-Elban, A.; Miginiac, P. *J. Organomet. Chem.* **1983**, *255*, 1. (n) Corey, E. J.; Kim, C. U.; Chen, R. H. K.; Takeda, M. *J. Am. Chem. Soc.* **1972**, *94*, 4395. (o) Näf, F.; Degen, P.; Ohloff, G. *Helv. Chim. Acta* **1972**, *55*, 82. (p) Campbell, J. A.; Babcock, J. C. *J. Am. Chem. Soc.* **1959**, *81*, 4069.

(5) For some examples reporting 1,4-addition, see: (a) Pineschi, M.; del Moro, F.; di Bussolo, V.; Macchia, F. *Adv. Synth. Catal.* **2006**, *348*, 301. (b) Kume, T.; Iwasaki, H.; Yamamoto, Y.; Akiba, K. *Tetrahedron Lett.* **1987**, *28*, 6305. (c) Marshall, J. A.; Audia, J. E.; Shearer, B. G. *J. Org. Chem.* **1986**, *51*, 1730. (d) Oppolzer, W.; Poli, G.; Kingma, A. J.; Starkemann, C.; Bernardinelli, G. *Helv. Chim. Acta* **1987**, *70*, 2201. (e) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119. (f) Barbot, F.; Kadib-Elban, A.; Miginiac, P. *Tetrahedron Lett.* **1983**, *24*, 5089. (g) Marshall, J. A.; Ruden, R. A.; Hirsch, L. K.; Phillippe, M. *Tetrahedron Lett.* **1971**, *12*, 3795.

(6) As far as we know there is only a couple of examples of the (non-stereoselective) conjugate addition of an organolithium reagent (MeLi) to an α,β,γ,δ-unsaturated carbonyl compound: (a) Cooke, M. P.; Goswami, R. *J. Am. Chem. Soc.* **1977**, *99*, 642. (b) Ooi, T.; Kondo, Y.; Kon-I, K.; Maruoka, K. *Chem. Lett.* **1998**, 403. For other examples of organolithium reagents undergoing stereocontrolled 1,4-addition to simple α,β-unsaturated carbonyl compounds, see ref 8a and references therein.

(7) For examples with simple α,β-unsaturated systems, see: (a) Aurell, M. J.; Bañuls, M. J.; Mestres, R.; Muñoz, E. *Tetrahedron* **2001**, *57*, 1067. (b) Sikorski, W. H.; Reich, H. J. *J. Am. Chem. Soc.* **2001**, *123*, 6527.

(8) (a) Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; Uria, U.; Iza, A. *J. Org. Chem.* **2006**, *71*, 7763. (b) Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; Iza, A.; Uria, U. *Org. Lett.* **2006**, *8*, 2535. For some examples regarding the use of lithium amides as nucleophiles, see: (c) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L.; Ruiz, N. *J. Org. Chem.* **2005**, *70*, 8790. (d) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2004**, *69*, 2588.

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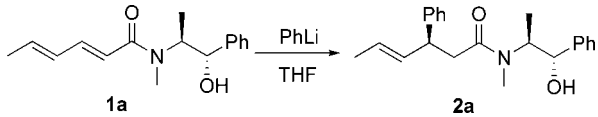
TABLE 1. Stereoselective Addition of PhLi to Amide 1a



1a **2a**

entry	PhLi (equiv)	additive[a]	temp (°C)	yield (%)[b]	dr[c]
1	2	LiCl	−105	30	97:3
2	3	LiCl	−105	58	97:3
3	4	LiCl	−105	80	97:3
4	6	LiCl	−105	70	97:3
5	4	LiCl	−90	65	95:5
6	4	LiCl	−78	60	95:5
7	4	LiCl	0	30	95:5
8	4		−105	68	80:20

[a] Reaction was carried out using 5.0 equiv of LiCl as additive. [b] Yield of pure product after flash column chromatography purification. [c] Determined by HPLC analysis of the corresponding alcohol obtained by reduction (see Supporting Information).

moiety with potential for further manipulations will also be presented, showing the remarkable synthetic potential of this methodology.

Our experiments began with the optimization of the reaction conditions using the addition of PhLi to α,β,γ,δ-unsaturated amide **1a** as model reaction (Table 1). When we applied the conditions previously found in our group for the conjugate addition of organolithium reagents to α,β-unsaturated amides derived from pseudoephedrine (entry 1),[8a] we obtained a low yield of the desired 1,4-adduct **2a** and also could recover an important amount of unreacted starting material (40%). We managed to improve the conversion and the yield of the reaction by increasing the amount of nucleophile added (3 and 4 equiv, entries 2 and 3, respectively), although when changing to 6 equiv of PhLi (entry 4) a slightly lower yield was obtained. In all cases, we could observe that the transformation proceeded with complete 1,4-regioselectivity and very high diastereoselectivity, which indicated that the chiral auxiliary was able to exert a very effective control on the stereochemical outcome of the reaction.

We also carried out additional experiments at higher temperatures, observing that although the diastereoselectivity did not suffer from significant variation, the yield of the reaction decreased on increasing the reaction temperature due mainly to the competitive formation of other 1,6- and 1,2-addition byproducts among other unidentified compounds (entries 5−7). We also verified that the presence of LiCl as an additive was necessary for the reaction to proceed with good yield and diastereoselectivity, as when we proceeded to carry out the reaction without any additive much poorer results were obtained (entry 8).

We therefore took conditions shown in entry 3 of Table 1 as the best ones for this reaction, and we next proceeded to extend them to other organolithium reagents and conjugate acceptors with the results shown in Table 2. As it can be seen in this table, in almost all cases good to excellent 1,4-selectivity was achieved, therefore providing the wanted 1,4-addition products **2a**−**i** in good yields and, remarkably, without the formation of any 1,6-addition byproduct regardless the organolithium employed. The formation of byproducts arising from the competitive 1,2-addition reaction was found to be exclusively dependent upon the nature of the organolithium reagent employed, observing that the reaction proceeded with complete 1,4-regiocontrol when stabilized organolithium reagents were used (the case of PhLi in entries 1 and 2 and the α-silyl-substituted organolithium reagent of entry 7) and also when a very bulky nucleophile (*t*-BuLi, entry 9) was employed. When primary and secondary alkyllithium reagents were employed, 1,2-addition products were obtained in variable ratios (entries 3−6 and entry 8), although in almost all the cases the 1,4-regioisomer was obtained as major reaction product. Remarkably, it has to be pointed out that the reaction took place with excellent degree of diastereoselection in all cases, obtaining the adducts **2a**−**i** as highly diastereoenriched compounds. It has also to be pointed out that the reaction could be easily scaled up and, for example, we could carry out the addition of PhLi to amide **1a** at 3.0 g scale with no significant decrease in the yield or diastereoselectivity (entry 10).

The results relating to the high diastereofacial control observed in this process are in accordance with a previously proposed mechanism,[8] in which the adduct of the conjugate addition reaction should arise from the attack of the organolithium reagent through an intermediate in which the aminoalkoxide chain lies in an open staggered conformation, with the C−H bond α to nitrogen lying in plane with the carbonyl oxygen, in order to minimize allylic strain (Figure 1).[10] In this way, the reaction of the organometallic reagent with amide **1a** should happen via an intermediate in a *syn-s-cis* conformation[11] by means of the stereodirecting ability of the lithium alkoxide moiety,[12] resulting in the formation of the new stereogenic center in the observed absolute configuration. The interaction between both metallic centers can take place either by solvent molecules or by the presence of chlorine anions, which would also account for the higher diastereoselectivity obtained in the presence of excess LiCl. On the other hand, this stereodirecting ability attributed to the lithium alkoxide might also explain the high regioselectivity observed, the 1,6-addition possibly being limited because the γ-carbon of the extended conjugate acceptor remains too far away from this alkoxide moiety. Nevertheless, the interaction of the carbonyl oxygen of the amide moiety with

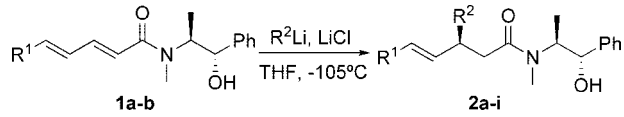
(9) For the first use of pseudoephedrine as chiral auxiliary, see: (a) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361. (b) Myers, A. G.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. For a review, see: (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) Ruiz, N.; Vicario, J. L.; Badía, D.; Carrillo, L.; Alonso, B. *Org. Lett.* **2008**, *10*, 2613. (e) Iza, A.; Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2006**, 4065. (f) Vicario, J. L.; Rodríguez, M.; Badía, D.; Carrillo, L.; Reyes, E. *Org. Lett.* **2004**, *6*, 3171. (g) 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. (h) Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *Org. Lett.* **2002**, *4*, 4583. (i) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 5801. (j) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 9030. (k) Anakabe, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; Yoldi, V. *Eur. J. Org. Chem.* **2001**, 4343. (l) Myers, A. G.; Barbay, J. K.; Zhong, B. *J. Am. Chem. Soc.* **2001**, *123*, 7207. (m) Vicario, J. L.; Badía, D.; Domínguez, E.; Rodríguez, M.; Carrillo, L. *J. Org. Chem.* **2000**, *65*, 3754. (n) Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428.

(10) This open staggered conformation as an intermediate in reactions in which (*S*,*S*)-(+)-pseudoephedrine amides are involved has also been proposed previously (refs 9a and 9b).

(11) For an experimental study regarding the reactive conformation of pseudoephedrine enamides in conjugate additions, see ref 8c.

(12) The stereodirecting power of the lithium alkoxide in other reactions of amides derived from chiral aminoalcohols has also been invoked by other authors in order to account for the observed diastereoselectivity. See, for example: (a) Askin, D.; Volante, R. P.; Ryan, K. M.; Reamer, R. A.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 4245. For the particular case of pseudoephedrine, see: (b) Smitrovich, J. H.; Dimichelle, L.; Qu, C.; Boice, G. N.; Nelson, T. D.; Huffman, M. A.; Murry, J. *J. Org. Chem.* **2004**, *69*, 1903.

TABLE 2. Regio- and Diastereoselective Addition of Organolithium Reagents to α,β,γ,δ-Unsaturated Amides 1a,b



entry	substrate	R^1	R^2	regioselectivity 1,2-:1,4-:1,6-[a]	product	yield (%)[b]	dr[c]
1	**1a**	Me	Ph	<5:>95:<5	**2a**	80	97:3
2	**1b**	H	Ph	<5:>95:<5	**2b**	65	97:3
3	**1a**	Me	Et	20:80:<5	**2c**	61	87:13
4	**1a**	Me	*n*-Bu	40:60:<5	**2d**	60	88:12
5	**1a**	Me	*i*-Bu	33:67:<5	**2e**	56	88:12
6	**1a**	Me	*n*-C_6H_{13}	50:50: <5	**2f**	54	83:17
7	**1a**	Me	$TMSCH_2$	<5:>95:<5	**2g**	54	98:2
8	**1a**	Me	*i*-Pr	20:80: <5	**2h**	65	88:12
9	**1a**	Me	*t*-Bu	<5:>95:<5	**2i**	86	93:7
10[d]	**1a**	Me	Ph	<5:>95:<5	**2a**	75	97:3

[a] Determined by NMR analysis of the crude reaction mixture. [b] Yield of pure products **2a−i** after purification. [c] Determined by HPLC analysis (see Supporting Information). [d] The reaction was carried out at 3.0 g scale.

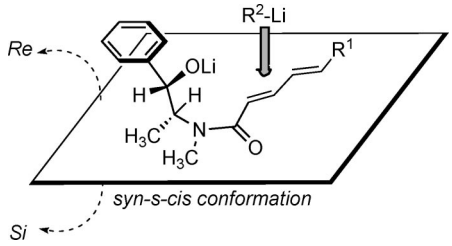


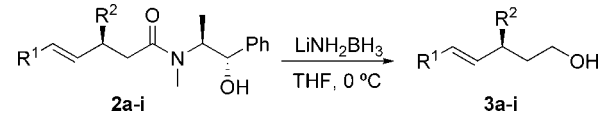
FIGURE 1. Proposed model for the diastereoselective conjugate addition of organometallic reagents to dienamides **1a,b**.

the incoming organolithium reagent should not be discarded as another possible explanation for the high 1,4-selectivity observed.

We next focused on the removal of the chiral auxiliary from the adducts **2a−i** by exploiting the intrinsic reactivity of the pseudoephedrine amide functionality. We started first with the reduction of the amide moiety in order to obtain enantioenriched β-substituted γ,δ-unsaturated alcohols that should be compounds of potential interest as chiral building blocks in total synthesis. We 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.[13] The reduction of amides **2a−i** proceeded in a fast and clean way, furnishing the desired alcohols in good yields and as highly enantioenriched compounds (Table 3).[14]

At this point, we were able to determine the absolute configuration of the stereogenic center created during the conjugate addition step by chemical correlation due to the fact that alcohol **3b** is a known compound. Therefore, comparison of the obtained $[\alpha]^{20}_D$ value for **3b** ($[\alpha]^{20}_D = +32.2$ (*c* 0.17, CH_2Cl_2)) with the reported in the literature for (*S*)-3-phenylpent-4-en-1-ol ($[\alpha]^{20}_D = +32.0$ (*c* 0.17, CH_2Cl_2))[15] allowed us to establish the absolute configuration of **3b** as (3*S*), which should be extended by analogy to the rest of the alcohols **3a−k** and amides **2a−k** obtained in the asymmetric conjugate addition of organolithium reagents to α,β,γ,δ-unsaturated amides derived from (*S*,*S*)-(+)-pseudoephedrine.

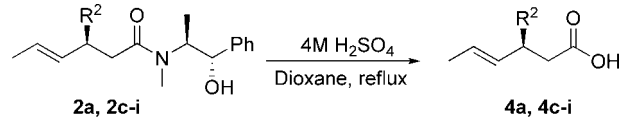
TABLE 3. Reduction of Adducts 2a−i



entry	substrate	R^1	R^2	product	yield (%)[a]
1	**2a**	Me	Ph	**3a**	99
2	**2b**	H	Ph	**3b**	88
3	**2c**	Me	Et	**3c**	93
4	**2d**	Me	*n*-Bu	**3d**	91
5	**2e**	Me	*i*-Bu	**3e**	80
6	**2f**	Me	*n*-C_6H_{13}	**3f**	94
7	**2g**	Me	$TMSCH_2$	**3g**	83
8	**2h**	Me	*i*-Pr	**3h**	94
9	**2i**	Me	*t*-Bu	**3i**	80

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

TABLE 4. Acid Hydrolysis of Adducts 2a and 2c−i



entry	substrate	R^2	product	yield (%)[a]
1	**2a**	Ph	**4a**	94
2	**2c**	Et	**4c**	90
3	**2d**	*n*-Bu	**4d**	96
4	**2e**	*i*-Bu	**4e**	83
5	**2f**	*n*-C_6H_{13}	**4f**	95
6	**2g**	$TMSCH_2$	**4g**	99
7	**2h**	*i*-Pr	**4h**	95
8	**2i**	*t*-Bu	**4i**	85

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

We also faced the removal of the chiral auxiliary by simple hydrolysis, therefore opening the way for the preparation of enantioenriched β-branched carboxylic acids containing an additional olefinic moiety. Consequently, when we treated the adducts **4a−i** under standard acid hydrolysis conditions, the corresponding carboxylic acids were obtained in excellent yields (Table 4). In addition, the chiral auxiliary could also be

(13) (a) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623. (b) Myers, A. G.; Yang, B. H.; Chen, H.; Kopecky, D. J. *Synlett* **1997**, 457. See also: (c) Whitlock, G. A.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 2007, and ref 9.

(14) In some cases, the reduction of adducts obtained as diastereomeric mixtures proceeded to furnish the corresponding alcohol in a significantly higher enantiopurity than that corresponding to the de of the starting material. We have demonstrated in previous reports that this transformation proceeds with no epimerization at the β-stereogenic centre of other closely related compounds (see refs 8a and 8b).

(15) Takekawa, Y.; Shishido, K. *J. Org. Chem.* **2001**, *66*, 8490.

recovered after a simple acid−base workup operation, therefore increasing the utility of this methodology.

In conclusion, we have shown that organolithium reagents add to α,β,γ,δ-unsaturated amides derived from the chiral amino alcohol (*S*,*S*)-(+)-pseudoephedrine in a highly regio- and diastereoselective way, furnishing the corresponding 1,4-addition products in good yields and as highly stereoenriched compounds. Removal of the chiral auxiliary can be carried out using very efficient and simple procedures, therefore allowing the use of this methodology for the preparation of many useful chiral building blocks containing different functionalities.

Experimental Section

Representative Procedure for the Diastereoselective Conjugate Addition of Organolithium Compounds to α,β,γ,δ-Unsaturated Amides. Synthesis of (+)-(1′*S*,2′*S*,3*S*)-*N*-(2′-Hydroxy-1′-methyl-2′-phenylethyl)-*N*-methyl-3-phenylhex-4-enamide (2a). A solution of PhLi (9.60 mL of a 1.6 M solution in dibutylether) was carefully added to a suspension of the dienamide **1a** (1.00 g, 3.86 mmol) and LiCl (0.82 g, 19.30 mmol) in dry THF (40 mL) at −105 °C, and the reaction was stirred at this temperature for 6 h (TLC monitoring). The mixture was allowed to warm to rt and was quenched with a saturated NH_4Cl solution (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic fractions were collected, dried over Na_2SO_4, and filtered. The solvent removed in vacuo, affording amide **2a** (1.04 g, 3.08 mmol) after flash column chromatography purification. Yield: 80%. Mp: 89−90 °C (AcOEt/hexane 1:1). $[\alpha]^{20}_D$ = +97.0 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (δ, ppm): (6:1 rotamer ratio; * indicates minor rotamer resonances) 0.73* (d, 3H, *J* = 6.8 Hz), 0.97 (d, 3H, *J* = 6.8 Hz), 1.67 (d, 3H, *J* = 6.4 Hz), 2.68−2.73 (m, 2H), 2.72 (s, 3H), 2.81−2.85* (m, 2H), 2.81* (s, 3H), 3.87−4.21 (m, 2H), 4.37−4.52 (m, 2H), 5.43- 5.54 (m, 1H), 5.62−5.70 (m, 1H), 7.18−7.27 (m, 10H). ^{13}C NMR (δ, ppm): (6:1 rotamer ratio; * indicates minor rotamer resonances) 14.4, 15.4* (CH_3CHN), 18.0, 26.8*, 32.7, 39.5*, 40.3, 44.9, 58.5, 75.3*, 76.5, 125.3*, 125.5, 126.2, 126.4*, 126.9, 127.5, 127.6, 128.3, 128.4*, 128.7, 133.4, 133.9*, 140.9*, 142.2, 143.8, 144.3*, 172.4*, 173.8. IR ($CHCl_3$): 3382 (OH), 1620 (C=O). MS (EI) *m*/*z* (rel int): 319 (M^+ − 18, 4), 231 (15), 230 (62), 131 (47), 129 (13), 115 (10), 91 (21), 77 (11), 58 (100). HRMS: calcd for $[C_{22}H_{25}NO\ (M - H_2O)]^+$ 319.1931, found 319.1934.

Representative Procedure for the Reduction of Amides 2a−i with LAB. Synthesis of (+)-(*S*)-3-Phenylhex-4-en-1-ol (3a). *n*-BuLi (4.54 mL of a 1.0 M solution in hexanes, 4.54 mmol) was added over a solution of diisopropylamine (0.61 mL, 4.36 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 $BH_3 \cdot NH_3$ (0.14 g, 4.45 mmol) was added at once. The mixture was stirred 15 min at 0 °C and another 15 min at room temperature, after which a solution of the amide **2a** (0.30 g, 0.89 mmol) in THF (10 mL) was added via canula at 0 °C and the reaction was stirred for 2 h. Then the reaction was quenched with 1 M HCl (15 mL) and extracted with AcOEt (3 × 15 mL). The organic fractions were collected, washed with sat. $NaHCO_3$, dried over Na_2SO_4, and filtered, and the solvent removed in vacuo, affording alcohol **3a** (120 mg, 0.71 mmol) as a colorless oil after flash column chromatography purification. Yield: 99%. HPLC analysis of the crude reaction mixture (Chiralcel OD column, hexane/isopropyl alcohol 97:3, flow rate 0.85 mL/min) indicated a 97:3 enantiomeric ratio: t_R for the major (*S*) isomer, 16.12 min; t_R for the minor (*R*) isomer, 19.51 min. $[\alpha]^{20}_D$ = +27.9 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (δ, ppm): 1.68 (d, 3H, *J* = 5.5 Hz), 1.85−1.99 (m, 3H), 3.42 (m, 1H), 3.60 (t, 2H, *J* = 6.5 Hz), 5.46−5.65 (m, 2H), 7.18−7.34 (m, 5H). ^{13}C NMR (δ, ppm): 17.9, 38.5, 45.3, 60.9, 125.1, 126.1, 127.3, 128.4, 134.5, 144.6. IR ($CHCl_3$): 3361 (OH). MS (EI) *m*/*z* (rel int): 143 (M^+-33, 96), 132 (100), 129 (66), 128 (52), 117 (20), 116 (29), 115 (69), 91 (97), 77 (29). HRMS: calcd for $[C_{12}H_{16}O]^+$ 176.1201, found 176.1201.

Representative Procedure for the Acid Hydrolysis of Amides 2a−i. Synthesis of (+)-(*S*)-3-Phenylhex-4-enoic Acid (4a). H_2SO_4 (4 M, 10 mL) was slowly added over a cooled (0 °C) solution of amide **2a** (0.30 g, 0.89 mmol) in 1,4-dioxane (10 mL). The reaction was refluxed for 6 h, after which it was cooled to rt. Water (20 mL) was added, and the mixture was carefully basified to pH = 12 and washed with AcOEt (3 × 20 mL). The aqueous layer was carefully driven to pH = 3 and extracted with CH_2Cl_2 (3 × 20 mL). After drying (Na_2SO_4), filtering, and removal of the solvent from the basic organic extracts, it was possible to recover, after crystallization (hexanes/AcOEt) pure (+)-(*S*,*S*)-pseudoephedrine in 83% yield. The collected organic acidic fractions were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo, yielding **4a** (0.16 g, 0.84 mmol) as a yellowish oil, which was found to be a pure compound as its ^{1}H and ^{13}C NMR spectra indicated. Yield: 94%. $[\alpha]^{20}_D$ = +7.3 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (δ, ppm): 1.71 (d, 3H, *J* = 5.6 Hz), 2.78 (d, 2H, *J* = 7.6 Hz), 3.82−3.89 (m, 1H), 5.52−5.69 (m, 2H), 7.24−7.37 (m, 5H). ^{13}C NMR (δ, ppm): 17.8, 40.6, 44.4, 125.8, 126.5, 127.3, 128.5, 132.8, 143.0, 178.4. IR ($CHCl_3$): 3026 (OH); 1707 (C=O). MS (EI) *m*/*z* (rel int): 190 (M^+, 19), 144 (15), 132 (11), 131 (94), 130 (45), 129 (100), 128 (34), 116 (21), 115 (31), 91 (52), 77 (11). HRMS: calcd for $[C_{12}H_{14}O_2]^+$ 190.0994, found 190.1003.

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

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