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

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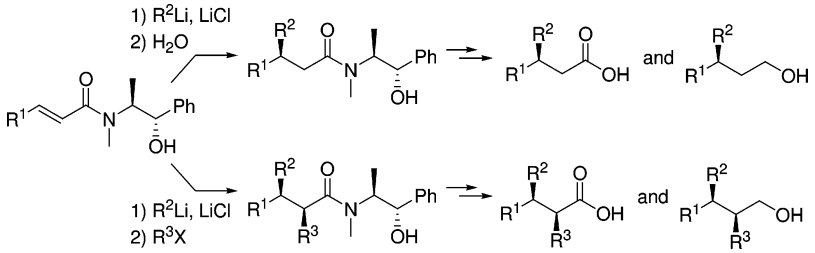

Organolithium reagents undergo highly regio- and diastereoselective 1,4-addition to (*S*,*S*)-(+)-pseudoephedrine enamides furnishing the corresponding *β*-alkyl-substituted adducts in excellent yields and diastereoselectivities. In addition, the intermediate lithium enolates generated after the conjugate addition step undergo a highly diastereoselective alkylation reaction, furnishing α,*β*-dialkyl-substituted amides in high yields. The obtained adducts have been converted into chiral nonracemic *β*-alkyl- and α,*β*-dialkyl-substituted carboxylic acids and *γ*-alkyl- and *β*,*γ*-dialkyl-substituted alcohols using very simple and high-yielding procedures.

Introduction

The conjugate addition of organometallic reagents to α,*β*-unsaturated carbonyl compounds or related derivatives is regarded as one of the most powerful methods for the formation of C−C bonds.[1] In addition, when the starting material contains prochiral centers at the α- and/or *β*-position, the generation of one or more stereogenic centers occurs concomitant with the conjugate addition process, which means that highly branched enantiomerically pure compounds can be easily obtained once the stereochemical outcome of the reaction becomes suitably controlled.[2] In this context, enantio- and diastereoselective conjugate addition reactions of organocopper[3] and Grignard[4] reagents or different metal-catalyzed versions of this transformation with dialkylzinc,[5] Grignard,[6] organoboron,[7] aluminum,[8] bismuth,[9] zirconium,[10] titanium,[11] tin,[12] organosilicon,[13] and copper acetylide[14] reagents, among others, have been exhaustively studied. However, despite their availability, the literature furnishes little information regarding the use of organolithium reagents in asymmetric conjugate additions to α,*β*-unsaturated carbonyl compounds,[15] mainly due to the fact that these reagents add to the carbonyl group in a 1,2-fashion rather than giving the desired 1,4-adduct.[16]

Concerning the methodologies applied in order to achieve the desired stereochemical control during the conjugate addition reaction, although the enantioselective approaches involving asymmetric catalysis have enjoyed a surge in popularity,

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especially in recent years, the use of chiral auxiliaries linked covalently to the acceptor still remains as one of the most powerful methodologies employed so far in the stereocontrolled 1,4-addition of organometallic reagents. The problems associated to the chiral auxiliary methodology can be overcome if efficient and simple procedures are devised to recover and recycle the chiral auxiliary after its removal of the conjugate addition product, and this methodology can turn into a very powerful synthetic tool if the chiral auxiliary provides special reactivity features to the adduct, which allows much more powerful synthetic versatility when transforming it into other useful chiral compounds. Related to this topic, the commercially available and cheap reagent (*S*,*S*)-(+)-pseudoephedrine has provided excellent results as a chiral auxiliary in many asymmetric transformations such as alkylations,[17] aldol[18] and Mannich reactions,[19] aminations,[20] aziridine[21] and epoxide[22] ring-opening reactions, and Michael additions.[23] Additional advantages of the use of this auxiliary are related to the unique reactivity of the amide function present in the obtained adducts, which has allowed the preparation of a wide range of many interesting chiral building blocks. In all of the cases previously mentioned,

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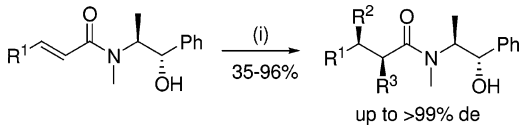
amides derived from this amino alcohol have been employed as nucleophiles via their corresponding enolates, but in recent reports, we have shown that pseudoephedrine can also play the role of a very efficient chiral auxiliary linked to the electrophilic counterpart in asymmetric aza-Michael reactions.[24]

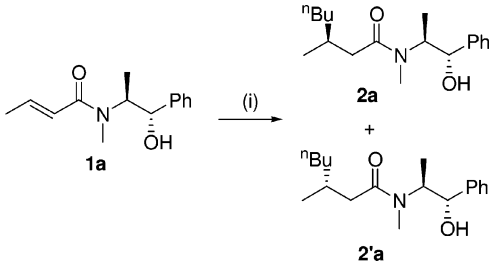
On the other hand, a very attractive application which can be found in the conjugate addition reaction is the formation of an intermediate enolate species with potential for subsequent α-alkylation, aldol, Mannich, Michael, or similar reactions in a typical tandem sequence.[25] These asymmetric tandem processes initiated by conjugate additions turn into a very easy and direct method for increasing molecular complexity from readily available starting materials, and therefore, target structures can be built up in a modular way by stepwise introduction of the desired substituents at the different reagents employed in the process. As previously mentioned, the literature furnishes many examples for asymmetric tandem transformations initiated by the conjugate addition of an organometallic reagent, like tandem conjugate addition followed by aldol,[26] Mannich,[27] Michael,[28] halogenation,[29] or Dieckmann reactions.[30] However, the number of examples in which the intermediate enolate is trapped with an alkylating reagent such an alkyl halide is very scarce.[11,31] Alkyl halides are known to 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 halides or methyl iodide can usually be employed with good results, which is a clear limitation of the methodologies reported up to date.

SCHEME 1[a]



[a] Reagents and conditions: (i) (1) R^2Li, LiCl, THF, −105 °C, (2) R^3X, 0 °C.

SCHEME 2[a]



[a] Reagents and conditions: see Table 1.

In this context we have reported very recently that asymmetric tandem conjugate addition/α-alkylation can be performed in a very simple and efficient way using (*S,S*)-(+)-pseudoephedrine as chiral auxiliary (Scheme 1).[32] In these preliminary studies excellent results have been achieved using a wide range of differently substituted α,*β*-unsaturated amides derived from this chiral amino alcohol and several organolithium reagents and alkyl halides.

With all of these precedents in mind, and in connection with our studies directed toward the development of new methodologies in asymmetric synthesis using amino alcohols as chiral auxiliaries, in this paper we report in detail our findings when working in the optimization of the reaction conditions for the first stereocontrolled 1,4-addition step, which has allowed us to develop a very efficient procedure for performing asymmetric conjugate addition of organometallic reagents. The highly efficient conversion of the adducts obtained in the 1,4-addition/protonation and the tandem conjugate addition/α-alkylation sequences into enantioenriched branched carboxylic acids and alcohols will also be presented, showing the remarkable synthetic potential of this methodology.

Results and Discusion

Our experiments began with the optimization of the reaction conditions for the conjugate addition of organometallic reagents to α,*β*-unsaturated amide **1a** (Scheme 2). As shown in Table 1, when we carried out the reaction using a Grignard reagent (*n*-BuMgCl) as nucleophile at −78 °C, it proceeded with very low yield, and a large excess of organometallic reagent together with a prolonged reaction time were needed in order to achieve some conversion (entry 1). The reaction with *n*-Bu_2CuLi was found to be equally slow, although in this case we only had to employ 2 equiv of the nucleophile in order to obtain complete conversion (entry 2). However, when we performed the addition of 2.0

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TABLE 1. Asymmetric Conjugate Addition of Organometallic Reagents to Enamide 1a

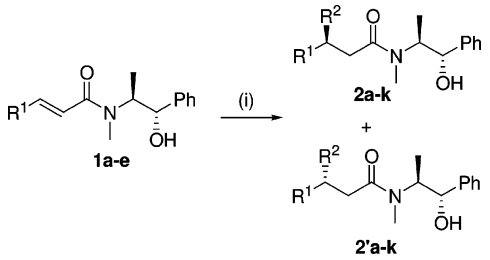
entry	nucleophile	equiv[a]	solvent	T (°C)	time	additive	yield (%)	**2a**/**2′a**[b]
1	*n*-BuMgCl	6	THF	−78	24 h		16	80/20
2	*n*-Bu_2CuLi	2	THF	−78	12 h		50	76/24
3	*n*-BuLi	2	THF	−78	10 min		72	73/27
4	*n*-BuLi	2	Et_2O	−78	10 min		50	64/36
5	*n*-BuLi	2	toluene	−78	10 min		40	77/23
6	*n*-BuLi	2	THF	−78	15 min	LiCl	77	85/15
7	*n*-BuLi	2	THF	−105	15 min	LiCl	84	92/8
8	*n*-BuLi	2	THF	−105	15 min	LiBr	76	86/14
9	*n*-BuLi	2	THF	−105	15 min	LiI	12	79/21
10	*n*-BuLi	2	THF	−105	15 min	LiF	90	80/20
11	*n*-BuLi	2	THF	−105	1 h	HMPA	63	77/23
12	*n*-BuLi	1	THF	−105	15 min		90	77/23
13	*n*-BuLi	1	THF	−105	15 min	LiCl	74	92/8

[a] Equivalents of nucleophile. [b] Calculated by HPLC (Chiracel OD column, UV detector, hexanes/2-propanol 98:2, flow rate 0.85 mL/min.).

equiv of *n*-BuLi to a THF solution of **1a** at −78 °C, a very fast and clean reaction occurred and the conjugate addition product was cleanly isolated in a very short time (10 min.), although with rather poor diastereoselectivity (entry 3). Changing the solvent (entries 4 and 5) did not significantly improve the **2a**/**2′a** ratio. Remarkably, it has to be pointed out that in all these cases the reaction was shown to be completely regioselective, with no presence of any 1,2-addition byproduct.[33]

With the aim of improving the diastereoselectivity of the reaction, we surveyed next the influence that different additives could have in the stereochemical outcome. It has been previously reported that the use of LiCl as an additive entails a dramatic influence in the stereochemical outcome of many transformations[34] and particularly in the Michael reaction of pseudoephedrine amide enolates.[23a] This effect was also operating in our case, and performing the reaction in the presence of excess LiCl led to a significant improvement in the yield and the diastereoselectivity of the reaction (entry 6). The temperature of the reaction was another key parameter to be controlled due to its influence in the diastereoselectivity, and when the reaction was carried out at −105 °C, the almost exclusive formation of the diastereoisomer **2a** was observed in excellent yield and in a very short time (entry 7). The use of other lithium salts as additives did not afford better results (entries 8−10), and a similar result was obtained when HMPA was introduced as cosolvent in the reaction (entry 11). Finally, it has to be pointed out that a very interesting result was obtained when using only 1 equiv of organolithium reagent both in the absence and in the of presence LiCl as additive (entries 12 and 13). In these cases, we unexpectedly observed that the 1,4-addition reaction proceeded also very fast affording the corresponding adduct **2a** in only slightly lower yields and the same diastereoselectivities as those obtained in the parent reactions in which 2 equiv of *n*-BuLi were employed. This means that the conjugate addition of the organolithium reagent is an extremely fast process which occurs even faster than the expected deprotonation of the free OH present at the pseudoephedrine moiety. This is a particularly interesting feature of the developed methodology, especially in the cases in which the organometallic reagent to be employed is very expensive or has to be previously prepared by means of a multistep synthesis.

SCHEME 3 [a]



[a] Reagents and conditions: (i) (1) R^2Li, LiCl, THF, −105 °C, (2) NH_4Cl_{aq}.

TABLE 2. Asymmetric Conjugate Addition of Organolithium Reagents to α,β-Unsaturated Amides 1a−e

entry	enamide	product	R^1	R^2	yield[a] (%)	**2**/**2′**[b]
1	**1a**	**2a**	Me	*n*-Bu	84	92/8
2	**1a**	**2b**	Me	*i*-Pr	80	89/11
3	**1a**	**2c**	Me	*t*-Bu	52	90/10
4	**1a**	**2d**	Me	Ph	86	94/6
5	**1b**	**2e**	Et	*n*-Bu	73	98/2
6	**1b**	**2f**	Et	Ph	82	91/9
7	**1c**	**2g**	*n*-Pr	*n*-Bu	73	98/2
8	**1c**	**2h**	*n*-Pr	*t*-Bu	94	90/10
9	**1c**	**2i**	*n*-Pr	Ph	82	93/7
10	**1d**	**2j**	*t*-Bu	Ph	84	97/3
11	**1e**	**2k**	Ph	*t*-Bu	61	91/9
12	**1a**		Me	Me	−(40)[c]	
13	**1e**		Ph	Me	−(46)[c]	

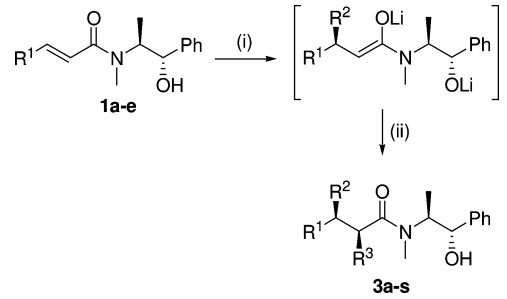
[a] Yield of pure product after column chromatography purification. [b] Calculated by HPLC (see the Supporting Information for details). [c] The 1,2-addition product was obtained. Yield is shown in parentheses.

Finally, we proceeded to examine the addition of different organolithium reagents as well as a variety of differently substituted α,β-unsaturated amides (Scheme 3). As shown in Table 2, the application of the previously optimized conditions resulted in high yields and diastereoselectivities regardless of the R^1 substituent present at the enamide acceptors **1a**−**d** and the nature of the organolithium reagent employed. Besides, in all these cases the reaction was found to be completely regioselective, in the sense that the formation of 1,2-addition byproducts was not observed. The only exception was found in the use of MeLi as nucleophile, for which the only product observed in the reaction crude was the corresponding ketone arising from a 1,2-addition process (entries 12 and 13 in Table 2).

(33) The occurrence of this side reaction was only observed at temperatures over −40 °C.

(34) For the influence of LiCl in the reactivity of pseudoephedrine enolates see refs 17b and 23a. 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.

SCHEME 4 [a]



[a] Reagents and conditions: (i) R^2Li, LiCl, THF, −105 °C; (ii) (1) R^3X, THF, 0 °C, (2) NH_4Cl_{aq}.

Having established an optimal protocol for the conjugate addition step, we focused next on the tandem conjugate addition/α-alkylation process (Scheme 3). In this context, the fact that LiCl had to be present in the reaction medium for the conjugate addition to proceed with such high diastereoselectivity should have a positive effect on the alkylation step because it is known that the α-alkylation reaction of pseudoephedine amide enolates proceeds much faster and the formation of side products due to the *O*-alkylation at the free OH group of the pseudoephedrine moiety is not observed when this salt is employed as an additive.[34] The use of organolithium reagents as nucleophiles should also have a positive effect on the alkylation step due to the higher reactivity exhibited by lithium enolates. Actually, 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. In addition, special attention has to be paid to the generation of the second stereocenter, whose configuration can be determined by the starting chirality source (the chiral auxiliary) or by the stereocenter first created in the conjugate addition step.

Therefore, we carried out the reaction of amide **1a** with PhLi under the previously optimized conditions, and once complete conversion was achieved, a solution of MeI (5 equiv) in THF was added and the mixture was stirred at −78 °C for 72 h, obtaining the expected alkylation product **3a** in good yield (72%) and excellent diastereomeric ratio (93:4:3:<1). When we performed the alkylation step at 0 °C, we found that the reaction proceeded much faster (4 h for complete conversion) and with the same yield and diastereoselectivity. Unfortunately, we were not able to reduce the amount of electrophile needed for the reaction to proceed in an acceptable interval of time.[35] Interestingly, when we changed to EtI as the electrophile only traces of the tandem product **3b** was obtained when the alkylation step was performed at −78 °C, while an excellent yield (96%) and diastereoselectivity (dr: 95:5:<1:<1) were obtained when the mixture of the intermediate enolate and ethyl iodide were stirred at 0 °C for 4 h. After all these experiments, we concluded that the best conditions for the tandem process both concerning the yield and diastereoselectivity consisted on the addition of an excess of the alkylating agent to the solution of the intermediate enolate generated after the conjugate addition step followed by stirring at 0 °C for 4 h (Scheme 4). We next proceeded to perform the tandem reaction sequence under the optimized conditions using a variety of differently substituted α,β-unsaturated amides, organolithium reagents and alkyl halides with excellent results concerning both the yield and the stereoselectivity of the reaction (Scheme 4, Table 3).

(35) Performing the reaction with 1.2 equiv of MeI furnished the tandem product **3a** in 50% yield and 93:4:3:<1 diastereomeric ratio.

TABLE 3. Asymmetric Tandem Conjugate Addition/α-Alkylation with α,β-Unsaturated Amides 1a−d

entry	enamide	product	R^1	R^2	R^3	yield[a] (%)	dr[b,c]
1	**1a**	**3a**	Me	Ph	Me	77	93:4:3:<1
2	**1a**	**3b**	Me	Ph	Et	96	95:5:<1:<1
3	**1a**	**3c**	Me	Ph	allyl	70	93:4:2:1
4	**1a**	**3d**	Me	Ph	Bn	78	94:4:<1:<1
5	**1a**	**3e**	Me	*n*-Bu	Me	67	91:5:3:<1
6	**1a**	**3f**	Me	*n*-Bu	Et	73	91:6:2:<1
7	**1a**	**3g**	Me	*n*-Bu	allyl	71	86:10:4:<1
8	**1a**	**3h**	Me	*n*-Bu	Bn	63	89:8:3:<1
9	**1b**	**3i**	Et	Ph	Me	75	95:4:<1:<1
10	**1b**	**3j**	Et	Ph	Et	80	97:2:<1:<1
11	**1b**	**3k**	Et	Ph	allyl	77	95:4:1:<1
12	**1b**	**3l**	Et	Ph	Bn	67	99:<1:<1:<1
13	**1c**	**3m**	*n*-Pr	Ph	Me	86	99:<1:<1:<1
14	**1c**	**3n**	*n*-Pr	Ph	Et	82	95:4:1:<1
15	**1c**	**3o**	*n*-Pr	Ph	allyl	70	96:4:<1:<1
16	**1c**	**3p**	*n*-Pr	Ph	Bn	73	>99:<1:<1:<1
17	**1c**	**3q**	*n*-Pr	*n*-Bu	allyl	77	96:3:<1:<1
18	**1d**	**3r**	*t*-Bu	Ph	Me	70	96:3:2:<1
19	**1d**	**3s**	*t*-Bu	*n*-Bu	Me	35	97:2:<1:<1
20	**1a**		Me	Ph	*i*-Pr	<5[d]	-

[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). [d] Only traces of the tandem product were observed, isolating the 1,4-addition product **2d** in 88% yield after 24 h at rt.

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). Disappointingly, other more bulky, ramified alkyl halides such as *i*-PrI did not afford the expected tandem product in any of the cases tested, even using higher temperatures during prolonged reaction times (entry 20).

Mechanistic Aspects. The results relating to the high diastereofacial control observed in the conjugate addition process are in accordance with a previously proposed mechanism,[24a] in which the adduct of the conjugate addition reaction should arise from the attack of the organolithium reagent through an intermediate in which it is proposed that the aminoalkoxide chain of the auxiliary should lie in an open staggered conformation, with the C−H bond α to nitrogen lying in plane with the carbonyl oxygen, to minimize allylic strain (Figure 1). In this way, the reaction of the organometallic reagent with amides **1a**−**e** should happen via an intermediate in a syn-s-cis conformation by means of the stereodirecting ability of the lithium alkoxide moiety present at the pseudoephedrine chain,[36] resulting in the formation of the new stereogenic center in the observed absolute configuration. The existence of such a reactive

(36) The stereodirecting power of the lithium alkoxide in other reactions of amides derived from chiral amino alcohols 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 and for the particular case of pseudoephedrine see refs 21, 22, and 23a.

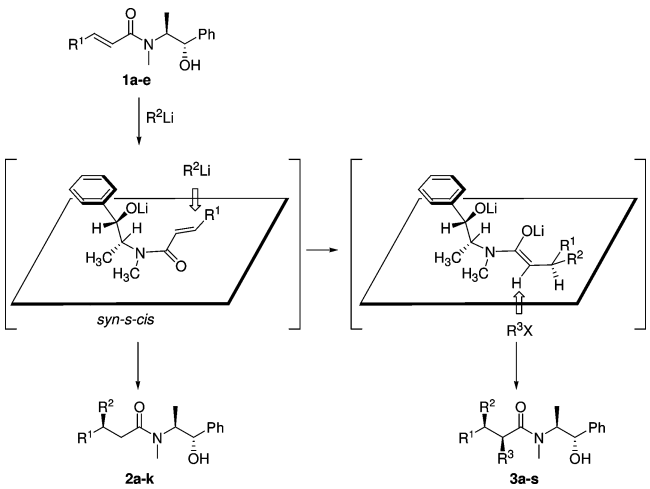


FIGURE 1. Proposed model for the diastereoselective conjugate addition and conjugate addition/α-alkylation of (*S,S*)-(+)-pseudoephedrine enamides **1a**−**e**.

conformer and the stereodirecting effect exerted by this lithium alkoxide moiety was previously demonstrated by us in the aza-Michael reaction of lithium benzylamides to α,β-unsaturated amides derived from (*S,S*)-(+)-pseudoephedrine.

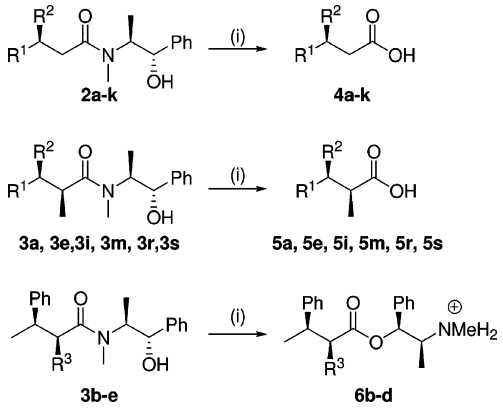
With respect to the tandem conjugate addition/α-alkylation reaction, the stereochemistry of the adducts **3a**−**s** is also in agreement with a previously proposed mechanism in which the alkylation product should arise from the attack of the alkyl halide to an intermediate *Z* enolate from the less hyndered *si* face of an intermediate in which again, the pseudoephedrine moiety adopts the same staggered conformation but in which the lithium alkoxide moiety now provides a sterical blockade for the incoming of the electrophile (Figure 1).[17b,h] The formation of this intermediate enolate in a *Z* configuration is also compatible with the reactive s-cis conformation proposed for the preceding 1,4-addition step. In addition, the fact that the tandem adducts **3a**−**s** were obtained with a very high degree of stereocontrol regardless of the configuration of the stereogenic center generated in the previous conjugate addition step also indicates that the stereochemical outcome of the alkylation step is completely dominated by the presence of the chiral auxiliary under the conditions employed.

Transformation of the Addition Products into Other Valuable Synthons. The highly enantioenriched adducts obtained from the asymmetric conjugate addition and conjugate addition/α-alkylation reactions were subjected to several derivatization processes in order to survey their possibilities in synthetic organic chemistry. In this way, enantiopure β- and α,β-branched carboxylic acids and γ- and β,γ-disubstituted alcohols were obtained from amides **2a**−**k** and **3a**−**s**.

(a) Synthesis of Carboxylic Acids. We first proceeded to perform the hydrolytic removal of the chiral auxiliary by treating amides **2a**−**k** and **3a**−**s** with 4 M H_2SO_4 in refluxing dioxane (Scheme 5), which are typical conditions employed for the hydrolysis of pseudoephedrine amides.[17b] Under these conditions, it is known that a fast *N*→*O* acyl-transfer process is operating followed by the rate-determining hydrolysis of the intermediate ester. In our case, refluxing a solution of amides **2a**−**k** in dioxane/4 M H_2SO_4 for 12 h yielded cleanly β-branched chiral carboxylic acids **4a**−**k** in excellent yields and as pure compounds after simple acid−base standard workup (Table 4). However, when we performed this reaction with α,β-disubstituted amides **3a**−**s**, we found that the hydrolysis reaction was strongly dependent upon the bulkiness of the α-alkyl substituent. While amides **3a**, **3e**, **3i**, **3m**, **3r**, and **3s** (R^3 = Me) furnished the corresponding carboxylic acids **5a**, **5e**, **5i**, **5m**, **5r**, and **5s**, when we tested the same reaction conditions with amides **3b**−**d** (R^3 = Et, allyl, Bn) we could only observe the formation of ammonium esters **6b**−**d**. This indicates that while the fast *N*→*O* acyl transfer process took place in an efficient way, the hydrolysis of the esters resulted hampered by the sterical hindrance exerted by the α-substituent. We also observed that, after isolation of the derivatives **6b**−**d**, these provided spontaneously the starting materials **3b**−**d** upon standing for 24 h, which also indicates that the acyl transfer process is reversible, being the amide form the thermodynamically favored one. We also tested basic hydrolysis conditions and refluxing a solution of amide **2b** in a 4 M KOH/THF solution afforded cleanly the expected carboxylic acid but as a 3:1 mixture of syn/anti diastereoisomers, which showed us that the α-hydrogen atom either at the starting amide or at the target carboxylic acid was undergoing a deprotonation process under these reaction conditions.

It has to be pointed out that, in all cases, the target carboxylic acids were isolated after a simple standard acid−base workup procedure and that the chiral auxiliary, (*S,S*)-(+)-pseudoephedrine, could be recovered from the extracts of the basic aqueous layer after workup followed by evaporation of the solvent and

SCHEME 5 [a]



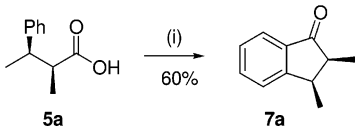
[a] Reagents and conditions: (i) 4M H_2SO_4, dioxane, reflux.

TABLE 4. Synthesis of Chiral Carboxylic Acids by Acid Hydrolysis

entry	product	R^1	R^2	R^3	yield[a] (%)
1	**4a**	Me	*n*-Bu	H	88
2	**4b**	Me	*i*-Pr	H	89
3	**4c**	Me	*t*-Bu	H	99
4	**4d**	Me	Ph	H	91
5	**4e**	Et	*n*-Bu	H	75
6	**4f**	Et	Ph	H	99
7	**4g**	*n*-Pr	*n*-Bu	H	79
8	**4h**	*n*-Pr	*t*-Bu	H	87
9	**4i**	*n*-Pr	Ph	H	97
10	**4j**	*t*-Bu	Ph	H	64
11	**4k**	Ph	*t*-Bu	H	99
12	**5a**	Me	Ph	Me	98
13	**5e**	Me	*n*-Bu	Me	93
14	**5i**	Et	Ph	Me	80
15	**5m**	*n*-Pr	Ph	Me	99
16	**5r**	*t*-Bu	Ph	Me	99
17	**5s**	*t*-Bu	*n*-Bu	Me	78

[a] Yield of pure product after standard acid/base workup purification.

SCHEME 6 [a]



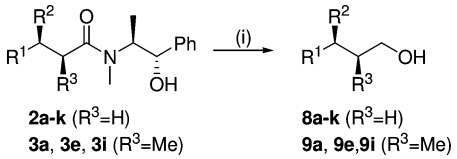
[a] Reagents and conditions: (i) (1) $(COCl)_2$, CH_2Cl_2, rt, (2) $AlCl_3$, CH_2Cl_2, −20 °C.

crystallization in hexane/EtOAc 1:1 in ca. 80% yield and with no loss of optical purity as its $[\alpha]^{20}_D$ value indicated, which allowed us to recycle the auxiliary for further uses. In addition, it has to be mentioned that, 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 some of the obtained acids were known compounds. For example, comparison of the obtained $[\alpha]^{20}_D$ value for acid **4d** with the reported in the literature[37] allowed us to establish the absolute configuration of **2a** as (3*S*) which should be extended by analogy to the rest of the amides **2a**−**k** obtained in the asymmetric conjugate addition of organolithium reagents to (*S*,*S*)-(+)-pseudoephedrine enamides **1a**−**e**.[38]

At this point, we also proceeded to determine the absolute configuration of the two stereogenic centers simultaneously formed in the tandem conjugate addition/α-alkylation (Scheme 6). Carboxylic acid **5a** was converted into the corresponding acid chloride and subsequently subjected to intramolecular Friedel−Crafts acylation, furnishing indanone **7a** in 60% yield. NOE experiments on **7a** indicated a cis relationship between both substituents, and given the (3*R*) configuration previously established for the stereogenic center formed in the conjugate addition step, we could assign a (2*S*,3*R*) absolute configuration for indanone **7a**, which was extended to the starting acid **5a** and amide **3a** and, by analogy, to all amides **3b**−**s** prepared.

(b) Synthesis of Alcohols. We next turned our attention to the reduction of the amide moiety in order to obtain enantioenriched *β*-alkyl- and *β*,*γ*-dialkyl-substituted primary alcohols which should be compounds of potential interest as chiral building blocks in total synthesis. In our case, such a functionality should be easily reached from the highly enantioenriched adducts obtained in the conjugate addition and tandem conjugate addition/α-alkylation reactions, provided that a procedure is found that readily reduces the amide functionality to the corresponding alcohol overriding the parallel formation of any amine-type byproducts. 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[39] (Scheme 7), and indeed, we found that the reduction of α-unsubstituted amides **2a**−**k** with this reducing agent under the reported conditions proceeded in a fast and clean way, furnishing the desired alcohols **8a**−**k** in good yields (Table 5). However, in the same way as we have experienced in the hydrolysis reactions, the reduction of amides **3a**−**s** was found to be strongly dependent upon the nature of the α-alkyl substituent. The reduction of amides **3a**, **3e**, and **3i** (R^3 = Me) proceeded in a fast and clean way, furnishing the desired alcohols **9a**, **9e**, and **9i** in good yields and as single diastereoisomers, while other amides such as **3b**−**d**, with bulkier substituents at the α-carbon, did not react with LAB, even after prolonged reaction times. It has also to be pointed out that in this case we were also able to recover and recycle the chiral auxiliary after its removal from the starting compounds during the reduction step.

SCHEME 7 [a]



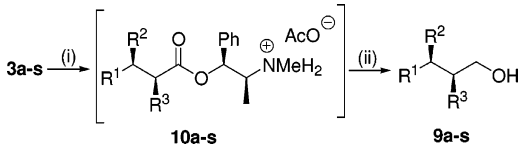
[a] Reagents and conditions: (i) $LiNH_2BH_3$, THF, rt.

TABLE 5. Synthesis of Chiral Primary Alcohols by LAB-Mediated Reduction

entry	product	R^1	R^2	R^3	yield[a] (%)
1	**8a**	Me	*n*-Bu	H	79
2	**8b**	Me	*i*-Pr	H	63
3	**8c**	Me	*t*-Bu	H	75
4	**8d**	Me	Ph	H	72
5	**8e**	Et	*n*-Bu	H	65
6	**8f**	Et	Ph	H	78
7	**8g**	*n*-Pr	*n*-Bu	H	66
8	**8h**	*n*-Pr	*t*-Bu	H	84
9	**8i**	*n*-Pr	Ph	H	74
10	**8j**	*t*-Bu	Ph	H	80
11	**8k**	Ph	*t*-Bu	H	71
12	**9a**	Me	Ph	Me	90
13	**9e**	Me	*n*-Bu	Me	60
14	**9i**	Et	Ph	Me	80

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

SCHEME 8 [a]



[a] Reagents and conditions: (i) AcOH, dioxane, reflux; (ii) LAH, THF, 0 °C

We therefore surveyed a second possibility for performing this transformation (Scheme 8). As we had previously observed in the course of our studies directed toward the acid hydrolysis of the amide adducts (vide supra) that these pseudoephedrine amides underwent fast *N*→*O* acyl transfer when heating in the presence of an acid, we hypothesized that formed ester should be easily reduced to the desired alcohol with a standard reducing agent like LAH. When a mixture of amide **3a** and AcOH was refluxed for 24 h and, after removal of the volatiles under reduced pressure, we could observe the quantitative formation of the ammonium ester **10a** by ^{1}H NMR, and when this ester was reduced with LAH in THF at 0 °C, alcohol **9a** was isolated in good yield and as a single diastereoisomer. These conditions were applied to all amides **3a**−**s** yielding the wanted *β*,*γ*-dialkyl-substituted alcohols in good yields in all cases studied (Table 6). In addition, alcohols **9a**−**s** were isolated as single diastereoisomers, as ^{1}H NMR analysis of the crude reaction mixture

(37) Observed optical rotation for the sample prepared from amide **2a**: $[\alpha]^{20}_D = -2.28$, $c = 0.10$, $CHCl_3$. Literature data for (*R*)-3-methylheptanoic acid: $[\alpha]^{20}_D = -2.34$, $c = 0.10$, $CHCl_3$. Norsikian, S.; Marek, I.; Klein, S.; Poisson, J. F.; Normant, J. F. *Chem. Eur. J.* **1999**, 2055.

(38) Due to CIP priority rules, configuration at C3 changes to (3*R*) in amides **2b**−**d**,**f**,**h**,**i** ,**k**.

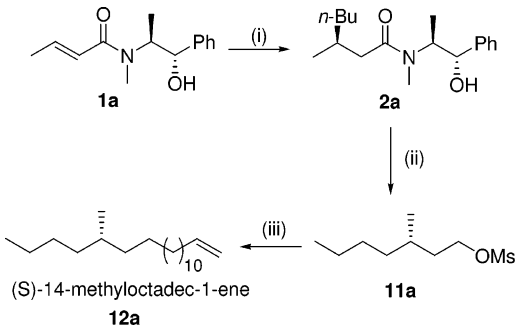
(39) (a) Myers, A. G.; Yang, B. H.; Kopecky, D. *Tetrahedron Lett.* **1996**, *37*, 3623. (b) Myers, A. G.; Yang, B. H.; Chen, H.; Kopecki, D. J. *Synlett* **1997**, 457. See also (c) Whitlock, G. A.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 2007.

TABLE 6. Synthesis of Chiral β,γ-Dialkyl-Substituted Alcohols by Acid-Promoted *N*→*O* Acyl Transfer/Reduction

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

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

SCHEME 9 [a]



[a] Reagents and conditions: (i) *n*-BuLi, LiCl, THF, 105 °C; (ii) (1) LAB, THF, rt, (2) MsCl, Et_3N, CH_2Cl_2, 0 °C; (iii) $Li(CH_2)_{10}CH{=}CH_2$, THF, −78 °C to rt.

indicated. This also 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, especially under the basic conditions in which the reduction step was carried out. Again, in this case we could recover the chiral auxiliary, (*S*,*S*)-(+)-pseudoephedrine, from the reaction mixture in ca. 75% yield by means of a simple acid−base workup procedure and with no loss of optical purity.

(c) Application of the Methodology. Asymmetric Synthesis of (*S*)-14-Methyloctadec-1-ene. As an example to demonstrate the potential of the methodology described herein, we decided to synthesize (*S*)-14-methyloctadec-1-ene (Scheme 9), the female sex pheromone of the peach leafminer moth (*Lyonetia clerkella*). Infestation by this insect causes almost complete defoliation of the trees and reduces cropping and fruit production potential for the future, which typically affects to fruit trees such as apple, pear, cherry, plum, quince, and peach.[40] The synthesis of this compound was easily accomplished starting from amide **2a**, which was prepared previously by us by asymmetric conjugate addition of *n*-BuLi to (*S*,*S*)-(+)-pseudoephedrine crotonamide **1a**. We therefore performed the LAB-mediated reduction of amide **2a** under the conditions previously described and we proceeded to carry out a subsequent mesylation procedure using crude unpurified alcohol **8a** to obtain the corresponding mesylate **11a** in a single step and in excellent yield (89%). Coupling of **11a** with 1-lithioundec-10-ene, prepared in situ by metalation of 11-chloroundec-1-ene with *t*-BuLi, furnished cleanly the wanted compound in 48% yield. All the data recorded for our synthetic sample of (*S*)-14-methyloctadec-1-ene matched those reported in the literature.[41]

Conclusions

We have shown that α,β-unsaturated amides derived from the chiral amino alcohol (*S*,*S*)-(+)-pseudoephedrine undergo very regio- and diastereoselective 1,4-addition of organolithium reagents, furnishing the corresponding β-alkyl substituted amides **2a**−**k** in short reaction times and with excellent yields. In addition, we have also shown that the intermediate enolate generated after the conjugate addition step is able to undergo a subsequent alkylation process with alkyl halides under the conditions employed, furnishing the corresponding α,β-dialkyl substituted amides **3a**−**s**. The chiral auxiliary is able to exert a very effective asymmetric induction both in the conjugate addition and in the α-alkylation steps using a wide variety of different acceptors, organolithium reagents and alkyl halides. Furthermore, the adducts obtained can be very easily transformed into chiral nonracemic β-alkyl and α,β-dialkyl substituted carboxylic acids and γ-alkyl- and β,γ-dialkyl-substituted alcohols, which are very useful chiral building blocks for the synthesis of many other interesting compounds. An additional advantage of the use of this chiral auxiliary was found in the recyclability of the reagent after cleavage from the adducts in all cases studied.

Experimental Section

General Procedure for the Diastereoselective Conjugate Addition of Organolithium Compounds to α,b-Unsaturated Amides 1a−e. A solution of organolithium reagent (4.10 mmol) was carefully added to a suspension of the corresponding enamide **1a**−**e** (2.00 mmol) and LiCl (10.0 mmol) in dry THF (60 mL) at −105 °C, and the reaction was stirred at this temperature for 10−30 min (TLC monitoring). The mixture was allowed to warm to rt, and it was quenched with a saturated NH_4Cl solution (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 30 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.

(+)-(1′*S*,2′*S*,3*S*)-*N*-(2′-Hydroxy-1′-methylethyl-2′-phenyl)-*N*,3-dimethylheptanamide (2a). Amide **2a** (0.49 g, 1.70 mmol) was prepared according to the general procedure starting from enamide **1a** (0.46 g, 2.00 mmol), LiCl (0.42 g, 10.00 mmol), and *n*-BuLi (3.4 mL of a 1.3,M solution in hexanes). HPLC analysis of the crude reaction mixture (Chiracel OD column, hexanes/2-propanol 98:2, flow rate 0.85 mL/min) indicated a 92:8 diastereomeric ratio: t_R for the major isomer, 25.31 min; t_R for the minor isomer, 36.28 min. Amide **2a** was isolated as a yellowish oil after flash column chromatography purification (hexanes/AcOEt 1:1). Yield: 84%. $[\alpha]^{20}_D = +89.0$ ($c = 1.0$, CH_2Cl_2). ^1H NMR (δ, ppm) (3:1

(40) (a) Park, J. H.; Han, K. S.; Mori, K.; Boo, K. S. *J. Chem. Ecol.* **2002**, *28*, 8515. (b) Gries, R.; Gries, G.; King, G. G. S.; Maier, C. T. *J. Chem. Ecol.* **1997**, *23*, 1119. (c) Sato, R.; Abe, N.; Sugie, H.; Kato, M., Mori, K.; Tamaki, Y. *Appl. Entomol. Zool.* **1986**, *21*, 478.

(41) Kharisov, R. Y.; Latypova, E. R.; Talipov, R. F.; Muslukhov, R. R.; Ishmuratov, G. Y.; Tolstikov, G. A. *Russ. Chem. Bull. Int. Ed.* **2003**, *52*, 2267.

(42) Chiacchio, U.; Corsaro, A.; Gambera, G., Rescifina, A.; Piperno, A.; Romeo, R.; Romeo, G. *Tetrahedron: Asymmetry* **2002**, *13*, 1915.

rotamer ratio; *indicates minor rotamer resonances): 0.87 (m, 6H); 0.97* (d, 3H, $J = 6.9$ Hz); 1.07 (d, 3H, $J = 6.7$ Hz); 1.27 (m, 6H); 1.95 (m, 1H); 2.04 (m, 1H); 2.17 (m, 1H); 2.78 (s, 3H); 2.87* (s, 3H); 4.04 (m, 1H), 4.43* (m, 1H); 4.55 (m 1H); 4.62 (bs, 1H); 7.32 (m, 5H). ^{13}C NMR (δ, ppm) (3:1 rotamer ratio; *indicates minor rotamer resonances): 14.0; 14.4; 15.3*; 19.7; 19.9*; 22.7; 29.0; 29.3*; 30.0; 30.2*; 33.1; 36.5; 36.6*; 40.9*; 41.4; 58.3; 75.2*; 76.3; 126.2; 126.8*; 127.4; 128.0*; 128.2; 128.5*; 141.5*; 142.4; 173.8*; 175.0. IR ($CHCl_3$): 3382 (OH); 1619 (C═O). MS (EI) *m*/*z* (rel int): 273 ($M^+ - 18$, 16), 216 (93), 184 (11), 148 (100), 118 (23); 91 (14), 69 (27), 58 (69), 56 (28). Anal. Calcd for $C_{18}H_{29}NO_2$: C, 74.18; H, 10.03; N, 4.81. Found: C, 74.23; H, 9.93; N, 4.69.

General Procedure for the Diastereoselective Tandem Conjugate Addition/α-Alkylation. A solution of organolithium reagent (2.05 mmol) was carefully added to a suspension of the corresponding enamide **1a**−**d** (1.00 mmol) and LiCl (5.00 mmol) in dry THF (30 mL) at −105 °C, and the reaction was stirred at this temperature until TLC analysis of the aliquots indicated complete consumption of the starting material (typically 30 min). The corresponding alkyl halide (4.00 mmol) was added at once, and the mixture was allowed to warm to 0 °C at which temperature it was stirred for further 5 h. The reaction was quenched with a saturated NH_4Cl solution (20 mL) and extracted with CH_2Cl_2 (3 × 10 mL), the combined organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo affording the tandem pure products after flash column chromatography.

(+)-(1′*S*,2′*S*,2*S*,3*R*)-*N*-(2′-Hydroxy-1′-methyl-2′-phenylethyl)-2,*N*-dimethyl-3-phenylbutanamide (3a). Amide **3a** (0.50 g, 1.54 mmol) was prepared according to the general procedure starting from enamide **1a** (0.46 g, 2.00 mmol), LiCl (0.42 g, 10.00 mmol), PhLi (4.43 mL of a 1.0 M solution in dibutyl ether), and MeI (0.50 mL, 8.00 mmol). HPLC analysis of the crude reaction mixture (Chiracel OD column, hexanes/2-propanol 95:5, flow rate 1.00 mL/min) indicated a 93:4:3:<1 diastereomeric ratio: t_R for the major isomer, 37.75min. (93%). The other isomers eluted at 17.55 min (<1%), 24.71 min (4%), and 28.07 min (3%). Amide **3a** was isolated in pure form as a yellowish oil after flash column chromatography (hexanes/AcOEt 1:1). Yield: 77%. $[\alpha]^{20}_D$ = +116.1 ($c = 1.0$, CH_2Cl_2). ^{1}H NMR (δ, ppm) (4:1 rotamer ratio; *indicates minor rotamer resonances): 0.75 (d, 3H, $J = 6.7$ Hz); 0.89* (d, 3H, $J = 5.0$ Hz); 1.00* (d, 3H, $J = 6.7$ Hz); 1.15 (d, 3H, $J = 6.7$ Hz); 1.22 (d, 3H, $J = 7.0$ Hz); 2.73 (m, 1H); 2.82 (s, 3H); 2.94* (s, 3H); 2.98 (m, 1H), 4.19* (m, 1H); 4.34 (m, 1H); 4.57* (m, 1H); 4.65 (m, 1H); 5.07 (bs, 1H); 7.15−7.33 (m, 10H). ^{13}C NMR (δ, ppm) (4:1 rotamer ratio; *indicates minor rotamer resonances): 14.3; 15.4*; 16.6; 16.9*; 20.3*; 20.5; 27.1*; 34.3; 42.4*; 43.6; 43.9; 44.2*; 58.4; 60.0*; 75.1*; 76.1; 126.0; 126.1*; 126.2; 126.7*; 127.5; 127.6; 128.0*; 128.1; 128.2*; 128.3; 128.5*; 141.6*; 142.4; 144.8; 145.1*; 177.1*; 178.2. IR ($CHCl_3$): 3380 (OH); 1716 (C═O). MS (EI) *m*/*z* (rel int): 307 ($M^+ - 18$, 1), 218 (10), 204 (10), 202 (15), 147 (16), 145 (15), 117 (11), 115 (10); 105 (27), 91 (37), 58 (100). Anal. Calcd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.76; H, 8.51; N, 4.50.

General Procedure for the Acid Hydrolysis. Synthesis of Carboxylic Acids 4a−k and 5a,e,i,m,r,s. H_2SO_4 (4 M, 10 mL) was slowly added over a cooled (0 °C) solution of the corresponding amide **2a**−**k** or **3a**,**e**,**i**,**m**,**r**,**s** (1 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 EtOAc (3 × 20 mL). The aqueous layer was carefully driven to pH = 3 by careful addition of a 4 M HCl solution and extracted with CH_2Cl_2 (3 × 20 mL). After drying (Na_2SO_4), filtering, and removing the solvent from the basic organic extracts it was possible to recover, after crystallization (hexanes/EtOAc), pure (+)-(*S*,*S*)-pseudoephedrine in ca. 83% yield. The collected organic acidic fractions were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo yielding the wanted acids **4a**−**k** and **5a**,**e**,**i**,**m**,**r**,**s** as pure compounds as their ^{1}H and ^{13}C NMR spectra indicated.

(−)-(*S*)-3-Methylheptanoic Acid (4a). Carboxylic acid **4a** (0.11 g, 0.74 mmol) was obtained as a yellowish oil starting from amide **2a** (0.24 g, 0.84 mmol) according to the general procedure. Yield: 88%. $[\alpha]^{20}_D = -2.28$ ($c = 0.10$, $CHCl_3$) (lit.[37] $[\alpha]^{20}_D = -2.34$, $c = 0.10$, $CHCl_3$). ^{1}H NMR (δ, ppm): 0.88 (t, 3H, $J = 6.5$ Hz); 0.96 (d, 3H, $J = 6.5$ Hz); 1.28 (m, 6H); 1.92 (m, 1H); 2.11 (dd, 1H, $J = 14.9$, 8.1 Hz); 2.33 (dd, 1H, $J = 14.9$, 5.9 Hz); 10.5−11.0 (bs, 1H). ^{13}C NMR (δ, ppm): 14.0; 19.6; 22.7; 29.0; 30.1; 36.3; 41.6; 180.2. IR ($CHCl_3$): 3025 (OH); 1715 (C═O). MS (EI) *m*/*z* (rel int): 144 (M^+, 5), 124 (14), 118 (14), 105 (19), 95 (66), 79 (66), 68 (72), 65 (99), 51 (100).

General Procedure for the Reduction of Amides with LAB. Synthesis of Alcohols 8a−k. *n*-BuLi (4.0 mmol) was added over a solution of diisopropylamine (4.0 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 $NH_3{\cdot}BH_3$ (4.0 mmol) was added at once. The mixture was stirred for 15 min at 0 °C and another 15 min at room temperature, after which a solution of the amide **2a**−**k** (1.0 mmol) in THF (10 mL) was added via cannula 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 satd $NaHCO_3$, dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo affording the wanted alcohols **8a**−**k** after flash column chromatography purification.

(−)-(*S*)-3-Methylheptan-1-ol (8a). Alcohol **8a** (142 mg, 1.08 mmol) was prepared according to the general procedure starting from amide **2a** (0.40 g, 1.37 mmol), *n*-BuLi (7.6 mL of a 0.7M solution in hexanes, 5.36 mmol), *i*-Pr_2NH (0.81 mL, 5.77 mmol), and $BH_3{\cdot}NH_3$ (0.19 g 5.48 mmol) and isolated as a yellowish oil after flash column chromatography purification (hexanes/AcOEt 8:2). Yield: 79%. $[\alpha]^{20}_D = -1.7$ ($c = 0.1$, $CHCl_3$) (lit.[42] $[\alpha]^{20}_D = -1.82$, $c = 0.06$, $CHCl_3$). ^{1}H NMR (δ, ppm): 0.88 (m, 6H); 1.27 (m, 6H); 1.57 (m, 3H); 3.65 (m, 2H). ^{13}C NMR (δ, ppm): 14.0; 19.5; 22.9; 29.1; 29.3; 36.7; 39.8; 60.9. IR ($CHCl_3$): 3215 (OH). MS (EI) *m*/*z* (rel int): 130 (M^+, 35), 115 (33), 99 (100), 85 (27), 65 (36), 59 (12), 52 (26).

General Procedure for the Reduction of Amides by Acid-Promoted *N*→*O* Acyl Transfer/Reduction. Synthesis of Alcohols 9a−s. A solution of the starting amide **3a**−**s** (1.0 mmol) in AcOH (10.0 mL) was refluxed for 12 h after which the solvent was removed under reduced pressure yielding the crude esters **10a**−**s** which were used in the next step without further purification. Next, LAH (3.0 mmol) was added at once over a cooled (0 °C) solution of the ester **10a**−**s** (1.0 mmol) in dry THF (15 mL). The mixture was refluxed for 3 h, quenched with 1 M HCl (15 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo affording the wanted alcohols **9a**−**s** after flash column chromatography purification. The chiral auxiliary could be recovered from the aqueous layer after basifying (pH = 10) with a 4 M NaOH solution and extracting with CH_2Cl_2 (3 × 15 mL), filtering, and removing the solvent. (*S*,*S*)-(+)-Pseudoephedrine was isolated in ca. 75% yield after crystallization (hexanes/AcOEt) and with no loss of optical purity as the measurement of its $[\alpha]^{20}_D$ value indicated.

(−)-(2*S*,3*R*)-2-Methyl-3-phenylbutan-1-ol (9a). Alcohol **9a** (203 mg, 1.21 mmol) was prepared according to the general procedure starting from amide **3a** (487 mg, 1.48 mmol), AcOH (30 mL), and LAH (168 mg 4.44 mmol) and isolated as a colorless oil after flash column chromatography purification (hexanes/AcOEt 9:1). Yield: 82%. $[\alpha]^{20}_D = -19.5$ ($c = 0.4$, $CHCl_3$). ^{1}H NMR (δ, ppm): 0.64 (d, 3H, $J = 6.8$ Hz); 1.23 (d, 3H, $J = 6.7$ Hz); 1.74 (m, 1H); 2.68 (m, 1H); 3.46 (m, 1H); 3.53 (m, 1H); 7.24 (m, 5H). ^{13}C NMR (δ, ppm): 14.4; 19.1;37.6; 41.6; 65.9; 125.9; 126.0; 128.3;

146.4. IR ($CHCl_3$): 3369 (OH). MS (EI) *m*/*z* (rel int): 164 (M^+, 1), 146 (8), 105 (15), 91 (19), 77 (4), 58 (100). Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.32; H, 9.73.

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Supporting Information Available: General methods and characterization of amides **2b**−**k**, carboxylic acids **4b**−**k**, **5a**,**e**,**i**,**m**,**r**,**s**, alcohols **8b**−**k**, mesylate **11a**, and pheromone **12a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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