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Michael Reactions of Pseudoephedrine Amide Enolates: Effect of LiCl on Syn/Anti Selectivity

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The stereochemical outcome of the asymmetric Michael reaction of pseudoephedrine amide enolates changes dramatically in the presence of LiCl. Reaction of the enolate in the absence of LiCl results in formation of the anti Michael adduct with high selectivity, whereas in the presence of lithium chloride the syn adduct is favored. This method provides access to enantiomerically enriched *trans*-3,4-disubstituted δ-lactones from the anti Michael adducts by a two step reduction/lactonization sequence. Information obtained from NMR studies indicates that, under both enolization conditions, the (*Z*)-enolate is formed. A model to explain the turnover in selectivity based on NMR evidence is presented.

Introduction

The power of pseudoephedrine as a chiral auxiliary for enolate alkylations has been well documented.[1] Several reports have demonstrated that, despite the acyclic framework of this auxiliary, excellent control of stereochemistry is provided. The availability of both antipodes and the facile conversion of the amide moiety to other functional groups make pseudoephedrine an attractive auxiliary. The use of this auxiliary has been extended to aldol,[2] Mannich,[3] and enolate amination[4] reactions. During the development of the alkylation of pseudoephedrine amide enolates, Myers et al. reported that the addition of LiCl (6 equiv) enhanced reactivity and was essential for good conversion. The stereochemistry of alkylation of *N*-acyl pseudoephedrine amide enolates was not affected by the presence of LiCl.[1b,5] Under these conditions, less reactive halides undergo alkylation efficiently and with high selectivity, providing a convenient route to more complicated substrates.[6]

We recently reported that the reaction of pseudoephedrine amide enolates can be extended to Michael additions of α,β-unsaturated esters.[7,8] These Michael acceptors proved highly reactive and did not require LiCl for good conversion. We have subsequently discovered that LiCl has a dramatic influence on the stereochemical outcome of this reaction. In this manuscript, we report both the utility of the Michael addition of pseudoephedrine amide enolates to access anti or syn Michael adducts (Scheme 1) and the NMR spectroscopic evidence that provides insight into the effect of LiCl on selectivity. A model to explain the effect of LiCl on the structure of this acyclic chiral auxiliary is discussed.

Results and Discussion

Michael Addition in the Absence of LiCl. We envisioned that Michael addition of chiral amides with α,β-unsaturated esters to afford adducts **3** would offer an approach to *trans*-3,4-disubstituted δ-lactones **4** following selective ester reduction and lactonization (Scheme 2). A screen of chiral amines as auxiliaries indicated that pseudoephedrine exhibited high diastereoselectivity for

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(1) (a) Myers, A. G.; Schnider, P.; Kwon, S.; Kung, D. W. *J. Org. Chem*. **1999**, *64*, 3322−3327. (b) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511. (c) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656−673. (d) Myers, A. G.; McKinstry, L. *J. Org. Chem*. **1996**, *61*, 2428−2440. (e) Myers, A. G.; Yoon, T. *Tetrahedron Lett*. **1995**, *36*, 9429−9432. (f) Myers, A. G.; Gleason, J. L.; Yoon, T. *J. Am. Chem. Soc.* **1995**, *117*, 8488−8489. (g) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc*. **1994**, *116*, 9361−9362.

(2) (a) Vicario, J. L.; Badía, D.; Carrillo, L. *Tetrahedron: Asymmetry* **2003**, *14*, 489−495. (b) Vicario, J. L.; Badía, D.; Domínguez, E.; Rodríguez, M.; Carrillo, L. *J. Org. Chem*. **2000**, *65*, 3754−3760.

(3) (a) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem*. **2001**, *66*, 9030−9032. (b) Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett*. **2001**, *3*, 773−776.

(4) (a) Anakabe, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; Yoldi, V. *Eur. J. Org. Chem*. **2001**, 4343−4352. (b) Vicario, J. L.; Badía, D.; Domínguez, E.; Crespo, A.; Carrillo, L.; Anakabe, E. *Tetrahedron Lett*. **1999**, *40*, 7123−7126.

(5) Enolates of glycinamides exhibited lower selectivity in the absence of LiCl. See ref 1c.

(6) For examples, see: (a) Duffey, M. O.; Le Tiran, A.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 1458−1459. (b) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420−8421. (c) Roy, R. S.; Imperiali, B. *Tetrahedron Lett*. **1996**, *37*, 2129−2132.

(7) Smitrovich, J. H.; Boice, G. N.; Qu, C.; DiMichele, L.; Nelson, T. D.; Huffman, M. A.; Murry, J.; McNamara, J.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1963−1966.

(8) For the use of other chiral auxiliaries on the Michael donor, see: (a) Enders, D.; Teschner, P.; Gröbner, R.; Raabe, G. *Synthesis* **1999**, 237−242. (b) Kanemasa, S.; Nomura, M.; Yoshinaga, S.; Yamamoto, H. *Tetrahedron* **1995**, *51*, 10463−10476. (c) Evans, D. A.; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem*. **1991**, *56*, 5750−5752. (d) Yamaguchi, M.; Hasebe, K.; Tanaka, S.; Minami, T. *Tetrahedron Lett*. **1986**, *27*, 959−962.

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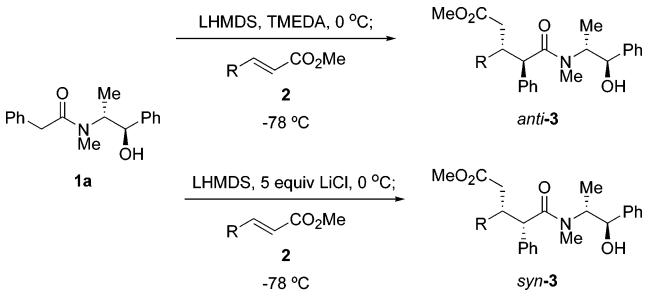
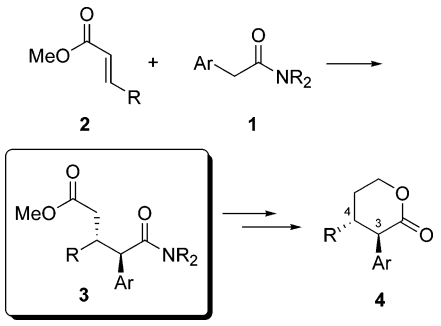
SCHEME 1



SCHEME 2



anti Michael adducts.[7] We have found that Michael addition to α,β-unsaturated esters occurs smoothly and with good selectivity.[9] Initial experiments indicated that the reaction of α,β-unsaturated esters was rapid at −78 °C and occurred in high yield in the absence of LiCl.[10] Generation of the dianion of **1a** at 0 °C in the presence of 2 equiv of TMEDA, followed by cooling to −78 °C, addition of the unsaturated ester **2b**, and aging for 20 min, gave **3b** as an 88:12 ratio of anti/syn isomers and *anti*-**3b** in 76% isolated yield (Scheme 3 and Table 1, entry 2). While TMEDA was not required, its presence did result in slightly enhanced selectivity. In the absence of TMEDA, the reaction of **1a** with acceptor **2b** afforded **3b** with an 84:16 anti/syn ratio. The presence of other additives, including DMPU and 1,2-bis(hexamethyldisilylamino)ethane, led to slightly lower selectivities. While solvent choice was limited due to the solubility of the enolate, DME and MTBE (methyl *tert*-butyl ether) gave similar results to the case of THF, whereas 2:1 THF/toluene led to a substantial decrease in both selectivity and conversion. Conducting the Michael addition at low temperature (< −60 °C) was crucial for high selectivity. For the reaction of amide **1b** with acceptor **2b**, conducting the addition at −40 °C resulted in a 68:32 ratio of products, compared to an 86:14 ratio at −75 °C.

A panel of Michael donors and acceptors was prepared to investigate the scope of the reaction (Scheme 3 and Table 1). The amides were synthesized from (*R*,*R*)-pseudoephedrine and the requisite acid chlorides using Schotten−Bauman conditions.[11] Michael acceptors (*E*)-**2a**[12] and **2d**[13] were prepared following literature procedures. (*Z*)-**2a** was prepared from the corresponding alkyne by hydrogenation with Lindlar's catalyst. Michael acceptors **2b** and **2f** were synthesized using a modification of the literature procedure.[14]

Variability in substitution at the terminus of the Michael acceptor was well tolerated; however, the Michael donor was limited to α-aryl pseudoephedrine amides (Scheme 3 and Table 1). In the case of the acceptor, alkyl-, phenyl-, alkyl-ether-, and alkyl-amine-substituted α,β-unsaturated esters were suitable substrates and exhibited good anti selectivity (entries 1−6). Phenyl, 4-fluorophenyl, and 3,4-difluorophenyl amides **1a**, **1b**, and **1c**, respectively, afforded the corresponding lactones with good selectivity (entries 2, 8, and 9), whereas 4-methoxyphenyl amide **1d** gave lower selectivity (entry 10). All attempts to extend the scope to alkyl-substituted pseudoephedrine amides resulted in poor conversion due to low solubility of the enolates. The stereochemistry about the double bond of the acceptor significantly affected both yield and selectivity. Reaction of the dianion of amide **1a** with (*Z*)-**2** under standard conditions afforded the product in moderate yield with no selectivity (Table 1, entry 7). The reaction was sluggish (25% of amide **1a** was recovered), and conversion was not increased by prolonged reaction times.

The Michael adducts were converted to the lactones without separation of the isomers to determine the facial selectivity on the Michael acceptor (Table 1). Determination of the diastereomeric ratios of the Michael adducts by NMR spectroscopy was hampered by the presence of rotamers. For the reaction of **1a** with **2b**, analysis of the product ratio by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture was possible, and the ratio was determined to be 88:12:8 *anti*-**3b**/*syn*-**3b**/**5** (Scheme 4).[15] Reduction of this mixture followed by cyclization with HCl afforded the lactone as a 92.5:7.5 ratio of enantiomers.

A variety of reducing agents, including LAH, $LiBH_4$, L-Selectride, and $LiAlH(O\text{-}t\text{-}Bu)_3$, were effective for selective reduction of the ester in the presence of the amide. Cyclization was accomplished by treatment with AcOH, MsOH, or anhydrous HCl. The use of HCl permitted recovery of pseudoephedrine by filtration of the HCl salt produced upon lactonization. The optical purity of the lactone can be increased by purification of the anti Michael adduct. The major isomer of Michael adduct **3h** was isolated by crystallization as a 98.8:1.2 ratio of isomers in 60% yield (entry 9). Conversion to the lactone afforded **4h** in 78% yield and 99.7% ee.

Samples of racemic lactones for chiral SFC method development were prepared from the requisite pyrrolidine amides,[16] as illustrated for (±)-**4g** (Scheme 5). Assignment of the stereochemistry of the Michael adducts

SCHEME 3

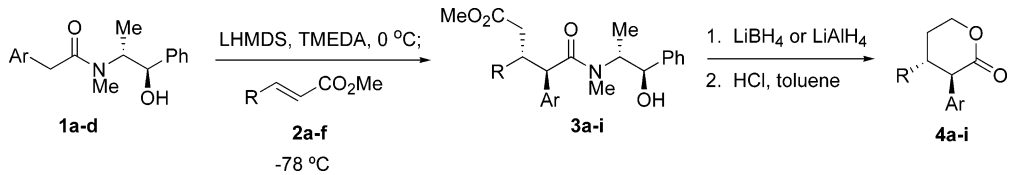
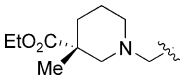
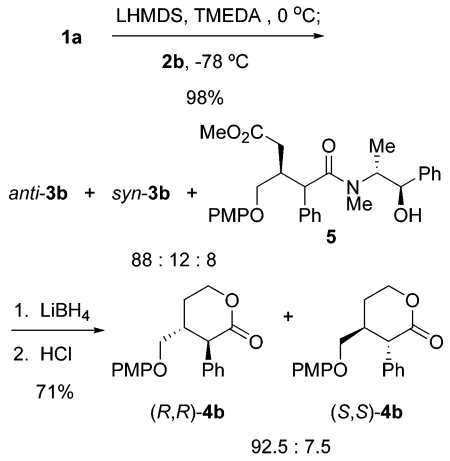


TABLE 1. Michael Reactions of (*R,R*)-Pseudoephedrine Arylacetamide Enolates without LiCl

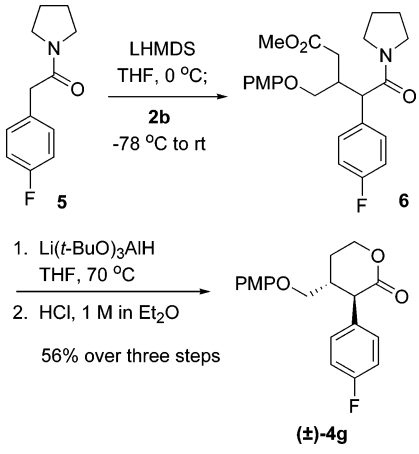
entry	donor	Ar	ester	R	adduct	anti:syn[a]	yield[b] (%)	lactone	yield[c] (%)	ee[d] (%)
1	**1a**	C_6H_5	(*E*)-**2a**	CH_2OBn	**3a**	90:10	80	**4a**	69	91
2			**2b**	CH_2OPMP	**3b**	88:12	98 (76)[e]	**4b**	71	85
3			**2c**[f]	CH_3	**3c**	83:17	85	**4c**	68	91
4			**2d**	$(CH_2)_2Ph$	**3d**	82:18	78	**4d**	89	87
5			**2e**	C_6H_5	**3e**	80:20	89	**4e**	70	83
6			**2f**[f]		**3f**	84:13	83	**4f**	46	77
7			(*Z*)-**2a**	CH_2OBn	**3a**	52:48	49[g]			
8	**1b**	4-FC_6H_4	**2b**	CH_2OPMP	**3g**	89:11	95	**4g**	72	93
9	**1c**	3,4-diFC_6H_3			**3h**	86:14	60[h]	**4h**	78	99.7[i]
10	**1d**	4-$MeOC_6H_4$			**3i**	92:8	80	**4i**	62	76

[a] Determined by ^{1}H NMR spectroscopic analysis. [b] Yields reported for combined isomers isolated after chromatography, unless otherwise noted. [c] Isolated yields over two steps. [d] Determined by chiral SFC analysis (details provided in the Supporting Information). [e] The number in parentheses is reported for the major isomer isolated by flash chromatography. [f] Reaction performed on the ethyl ester. [g] Adduct formed in a 48:43:9 ratio of isomers as determined by chiral HPLC analysis of the unpurified reaction mixture. [h] Yield reported for the major isomer isolated by crystallization. [i] Material synthesized from the crystallized Michael adduct.

SCHEME 4



SCHEME 5



was based on analogy to adducts **3b**, **3e**, and **3h**, where the absolute stereochemistry of the major isomers was determined by single crystal X-ray analysis. For all lactones, the trans relative stereochemistry was assigned by analysis of the coupling constants for the protons at the 3- and 4-positions. The predominant enantiomer of lactone **4a** was assigned as the (*R,R*)-isomer by comparison to an independently synthesized reference compound.

Michael Addition in the Presence of LiCl. Generation of the enolate of amide **1a** in the presence of LiCl (5 equiv) followed by addition of methyl crotonate smoothly afforded adduct **3c** (Scheme 6 and Table 2). Surprisingly, the ^{1}H NMR spectrum of the major isomer was identical to that of the *minor* isomer prepared without LiCl. Single crystal X-ray analysis unambiguously assigned the stereochemistry as *syn*-**3c**. These data indicated that, in the presence of LiCl, the major isomer produced is *syn*-**3c**,

SCHEME 6

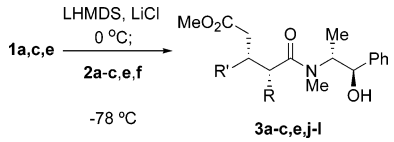


TABLE 2. Michael Reactions of (*R,R*)-Pseudoephedrine Arylacetamide Enolates with LiCl

entry	donor	R	acceptor	adduct	syn:anti[a]	yield[b] (%)
1	**1a**	C_6H_5	**2c**	**3c**	86:14	86
2			**2e**	**3e**	96:4	90
3			**2b**	**3b**	76:24	82
4			(*Z*)-**2a**	**3a**	76:24	28
5	**1c**	3,4-diFC_6H_4	**2e**	**3j**	94:6	80
6[c]			**2f**[d]	**3k**	96:4	95
7	**1e**	$(CH_2)_2Ph$	**2b**	**3l**	85:15	69

[a] Ratios determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixtures. [b] Yields reported for combined isomers isolated after chromatography. [c] Michael addition conducted at −20 °C. [d] Reaction performed on the ethyl ester.

(9) While this work was in progress, Myers et al. reported the conjugate addition of the lithium enolate derived from pseudoephedrine α-fluoroacetamide to a nitroalkene and vinyl sulfoxide with modest selectivities and yields. See: Myers, A. G.; Barbay, J. K.; Zhong, B. *J. Am. Chem. Soc.* **2001**, *123*, 7207−7219.

(10) In contrast, the alkylation requires the presence of 6 equiv of LiCl to increase conversion and the rate of alkylation. See ref 1b.

(11) Kress, M. H.; Yang, C.; Yasuda, N.; Grabowski, E. J. J. *Tetrahedron Lett.* **1997**, *38*, 2633−2636.

(12) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 10819−10820.

(13) Hon, Y.-S.; Lee, C.-F. *Tetrahedron* **2000**, *56*, 7893−7902.

(14) We found that the presence of 5−10 mol % water is crucial for reproducibility. See: Sunitha, K.; Balasubramanian, K. K. *Tetrahedron* **1987**, *43*, 3269−3278.

(15) The stereochemistry at the epimerizable stereocenter of **5** has not been determined.

(16) For the Michael addition of *N,N*-disubstituted amide enolates with α,β-unsaturated ketones, see: Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132−157.

differing from the non-LiCl adduct at the stereocenter α to the amide carbonyl.

Formation of the syn isomer in the presence of LiCl was found to be general for a panel of donors and acceptors (Table 2). Alkyl-, phenyl-, alkyl-ether-, and alkyl-amine-substituted α,*β*-unsaturated esters reacted efficiently and with good to high syn selectivity. As found without LiCl, reaction of (*Z*)-**2** was sluggish, affording the adduct in low yield (28%, entry 4). Under the LiCl conditions, the addition of the Michael acceptor at −20 °C maintained high selectivity (entry 6). Importantly, with LiCl, the enolates of alkyl amides are soluble, allowing the reaction to be extended to alkyl amides. Michael addition of **1e** with acceptor **2b** afforded adduct **3l** in an 85:15 ratio of isomers in 69% isolated yield (entry 7). Assignment of syn stereochemistry was based on analogy to adducts *syn*-**3c** and *syn*-**3e**, where the absolute stereochemistry of the major isomers was determined by single crystal X-ray analysis.

Determination of the facial selectivity on the Michael acceptor by conversion to the lactones was not possible, as the syn Michael adducts were not generally effective precursors to the lactones. For adducts *syn*-**3c** and *syn*-**3e**, selective ester reduction occurred uneventfully; however, attempted lactonization gave low conversion even with prolonged reaction times. A variety of conditions screened to determine if an epimerization/lactonization sequence was possible failed. The anti Michael adducts are more suitable intermediates for the synthesis of lactones. For the reaction of **1a** with **2b**, ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture indicated the adducts were produced as a 76:24:2 ratio of *syn*-**3b**/*anti*-**3b**/**5**.

Stereoselectivity. The turnover in selectivity observed in the presence of LiCl was unexpected, as Myers has reported that the stereochemistry of alkylation of *N*-acyl pseudoephedrine amide enolates is not influenced by the presence of LiCl.[1b] The Michael addition differs from the alkylation reaction in that two stereocenters are produced. Determination of the stereochemistry of the Michael adducts revealed that the center α to the amide carbonyl is the stereocenter affected by the presence or absence of LiCl. This center is analogous to that generated in the alkylation reaction. Myers et al. have reported that alkyl halides and epoxides approach opposite faces of the enolate.[1d,17] In the present report, the additive LiCl, not the nature of the Michael acceptor, is affecting the stereochemical outcome. Possible explanations that can account for the observed turnover in selectivity are (1) interconversion of the Michael adducts under the reaction conditions, (2) generation of different enolate isomers (Figure 1, A vs C or B vs D), or (3) the facial selectivity on the (*Z*)-enolate changing in the presence of LiCl (Figure 1, A vs D).[18]

Isomerization of the Michael adduct under the reaction conditions was ruled out by the following experiments. Treatment of *syn*-**3b** with LHMDS (2 equiv) and TMEDA (2 equiv) in THF at −78 to 0 °C led to a clean recovery of

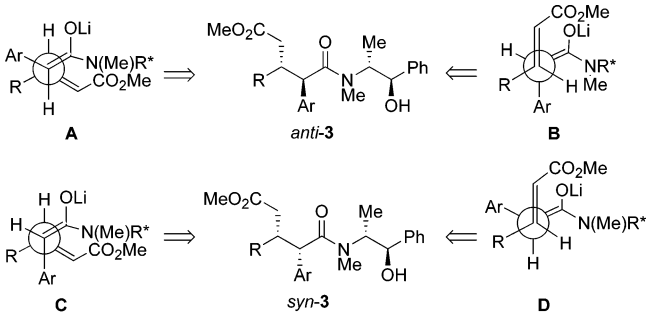


FIGURE 1. Mechanistic possibilities accounting for formation of anti and syn Michael adducts.

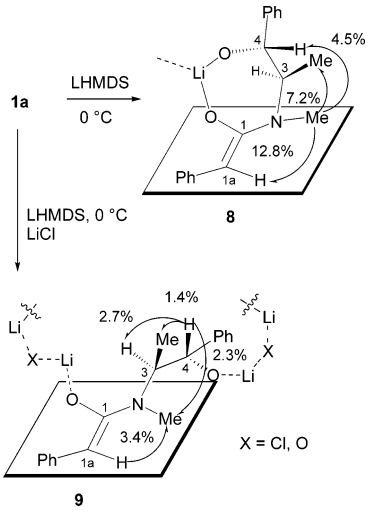


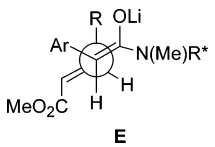
FIGURE 2. NOE data for the enolates.

syn-**3b**, indicating that epimerization of the Michael adduct does not occur under these conditions. Likewise, submission of *anti*-**3b** to the LiCl reaction conditions led to recovery of *anti*-**3b**. To discern between the remaining two explanations, we examined the enolates generated under the two enolization conditions by NMR spectroscopy.

Initial in situ NMR studies were used to examine the reaction of pseudoephedrine phenylacetamide **1a** with LHMDS with and without LiCl.[19] The results are illustrated in Figure 2. The starting amide **1a** in THF-d_8 is comprised of a 50:50 mixture of rotamers generated by restricted rotation about the amide bond. When reacted with 2.1 equiv of LHMDS at −40 °C, the major enolate species[20] **8** exhibited a high field shift of the C_{1a} carbon at 40.2 and 40.6 ppm to a single resonance at 76.6

(17) A reversal in the facial selectivity in the alkylation of prolinol amide enolates with alkyl halides and epoxides was observed by Askin et al., who proposed that the lithium alkoxide of the auxiliary directs the approach of the epoxide to rationalize this observation. See: Askin, D.; Volante, R. P.; Ryan, K. M.; Reamer, R. A.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 4245−4248.

(18) Synclinal orientation of the Michael acceptor is considered on the basis of analogy to the stereochemical rationale proposed by Oare et al. for the addition of lithium enolates of amides and thioamides to α,*β*-unsaturated ketones (ref 16). The formation of *anti*-**3** through an open transition state **E** is also possible.



(19) Although the 3,4-difluoro analogue **1c** was examined as well, and generated similar results, a single representative reaction using **1a** will be our focus.

ppm (J_{CH} = 147.0 Hz) consistent with enolate formation. The structure of the major enolate exhibited a discrete conformation. The observed NOEs shown for **8** defined the (*Z*)-stereochemistry of the enolate. These data, coupled with the absence of an NOE from the *N*-methyl protons to the C_3 proton, placed restraints on the conformation and were consistent with a seven-membered ring system bound at the oxygen atoms by lithium(s) either singularly with coordination to the solvent or as part of a lattice via lithium−oxygen linkages.[21]

Analogous in situ NMR studies in the presence of lithium chloride presented significantly different results. Treatment of the amide with LHMDS and 3 equiv of lithium chloride produced a 3:2 ratio of enolate species for **9**, as observed in the ^{1}H spectrum. These species even at −78 °C are rather broad but still resolved. The stereochemical and structural similarities of the two enolate species suggested that their differences lie in different aggregate forms.[21,22] Oligomers can form via lithium−oxygen or lithium−chloride linkages.[20] The NOE studies revealed two significant observations: (1) both enolate species exhibited (*Z*)-stereochemistry and (2) the observed NOEs for both species dictated free rotation about the C_3−nitrogen bond for **9**, as evidenced by NOE enhancement to both the C_3 (2.7%) and C_{3a} (1.4%) protons from the C_4 proton (Figure 2). The enolate structures presented (**8** and **9**) provide a working hypothesis for the stereoselectivity observed for the Michael adducts. These aggregate structures do not necessarily represent the active species but may be equilibrium precursors to a monomeric intermediate.[21,23]

Information obtained from the NMR studies indicated that, under both enolization conditions, the (*Z*)-enolate is formed. The observed turnover of selectivity in the presence of LiCl is most likely due to a change in the facial selectivity on the (*Z*)-enolate. This change, we propose, is due to the effect of LiCl on the conformation of the pseudoephedrine framework. While the species observed by NMR spectroscopic analysis are not necessarily the active species, the structures derived from the NMR data provide the basis for a model that is consistent with the observed stereochemical outcome of the Michael addition. We propose that, in the absence of LiCl, the pseudoephedrine backbone is fixed in a chelate and the Michael acceptor approaches from the less hindered side of the enolate, as depicted in **A** (Figure 1) and Figure 3, affording *anti*-**3**. In the presence of LiCl, the alkoxide of the auxiliary is not tied in a fixed system and is thus available to coordinate to the Michael acceptor. Under these conditions, the acceptor is delivered to the *si* face of the enolate, as depicted in **D** (Figure 1) and Figure 4 and as reported for the reaction of epoxides,[1d,17] affording *syn*-**3**.

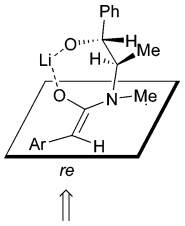


FIGURE 3. Approach of the acceptor to the enolate in the absence of LiCl.

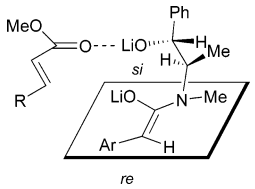


FIGURE 4. Approach of the acceptor to the enolate in the presence of LiCl.

In conclusion, we have developed a diastereoselective Michael reaction of pseudoephedrine amide enolates that can be used to access either anti or syn adducts with good selectivity. This method provides highly enantiomerically enriched 3-aryl-substituted δ-lactones in two steps from the anti adducts. In contrast to the case of the reaction of alkyl halides, the additive LiCl dramatically affects the stereochemical outcome of the Michael reaction. A model to explain the stereochemical results based on NMR spectroscopic studies was developed.

Experimental Section

General Procedure for the Preparation of Anti Michael Adducts: (3*R*,4*R*)-3-Benzyloxymethyl-4-[(1*R*,2*R*)-(2-hydroxy-1-methyl-2-phenylethyl)methylcarbamoyl]-4-phenylbutyric Acid Ethyl Ester (*anti*-3a). A 50 mL three-neck round-bottom flask was charged with amide **1a** (1.00 g, 3.53 mmol), TMEDA (1.07 mL, 7.06 mmol), and THF (2 mL). The mixture was purged with nitrogen for 5 min and then cooled to 0 °C. Lithium bis(trimethylsilyl)amide (1.0 M solution in THF, 7.06 mL, 7.06 mmol) was added dropwise. The reaction mixture was aged for 30 min at 0 °C. The resultant solution was cooled to −78 °C, and (*E*)-**2a** (0.781 g, 3.53 mmol) was added. The reaction mixture was stirred for 40 min at −78 °C. The reaction mixture was quenched with MeOH (1 mL, 25 mmol). When the temperature reached −40 °C, NH_4Cl (30% aq, 10 mL) was added. The mixture was allowed to warm to room temperature. The organic layer was separated and washed with water (10 mL) and brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo to a colorless oil. Purification by flash chromatography (10:90 to 40:60 EtOAc/hexanes) afforded *anti*-**3a** as a colorless oil (1.52 g, 80%): ^{1}H NMR (5:3 rotamer ratio, * denotes minor rotamer peaks, CD_3CN, 400 MHz) δ 7.45−7.21 (m, 15H), 4.59 (m, 2H), 4.28 (m, 3H), 4.07 (q, *J* = 15.2, 7.6 Hz, 2H), 4.00* (m, 1H), 3.97 (br, s, 1H), 3.35 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.29* (dd, *J* = 9.6, 3.6 Hz, 1H), 3.02* (dd, *J* = 9.2, 4.4 Hz, 1H), 2.98 (dd, *J* = 9.2, 4.4 Hz, 1H), 2.90−2.80 (m, 1H), 2.83 (s, 3H), 2.77* (s, 3H), 2.55−2.35 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.20* (t, *J* = 7.2 Hz, 3H), 1.00* (d, *J* = 6.8 Hz, 3H), 0.49 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (CD_3CN, 100 MHz) δ 173.1, 173.0*, 172.5, 172.4*, 142.8, 142.7*, 138.9, 138.6*, 138.4, 137.5*, 128.7, 128.6, 128.5*, 128.44, 128.37, 128.20, 128.16*, 128.0, 127.7*, 127.5, 127.4, 127.3*, 127.2*, 127.1*, 126.9*, 126.8, 126.4*, 74.7, 74.5*, 72.6, 72.5*, 69.4*, 69.3, 59.9, 57.6, 49.5*, 49.4, 40.0*, 39.8, 35.1, 34.8*, 26.9, 14.0, 13.61, 13.57*, 13.2*; IR (thin film) 3420, 3028, 2978, 1731, 1617

(20) The major enolate species **8** accounts for 60−75 mol % of the total reaction mixture on the basis of ^{1}H integration. (Analogous studies using the difluorophenyl analogue **1c** reflected a >95% conversion.) The ^{1}H spectrum revealed that the remaining portion of the reaction is made up of broadened species which may be attributed to partial aggregation.

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cm^{-1}. Anal. Calcd for $C_{31}H_{37}NO_5$: C, 73.93; H, 7.41; N, 2.78. Found: C, 73.73; H, 7.35; N, 2.43.

General Procedure for the Preparation of Syn Michael Adducts: (3*R*,4*S*)-4-[(1*R*,2*R*)-(2-Hydroxy-1-methyl-2-phenylethyl)methylcarbamoyl]-3,4-diphenylbutyric Acid Methyl Ester (*syn*-3e). A 50 mL three-neck round-bottom flask was charged with **1a** (1.50 g, 5.29 mmol), LiCl (1.12 g, 26.5 mmol), and THF (4 mL). The mixture was purged with nitrogen for 5 min and then cooled to 0 °C. Lithium bis(trimethylsilyl)amide (1.0 M solution in THF, 10.6 mL, 10.6 mmol) was added dropwise. The reaction mixture was aged for 30 min at 0 °C. The resultant solution was cooled to −78 °C, and **2e** (0.858 g, 5.29 mmol) was added. The reaction mixture was stirred for 40 min at −78 °C. The reaction mixture was quenched with MeOH (1 mL, 25 mmol). When the temperature reached −40 °C, NH_4Cl (30% aq, 10 mL) was added. The mixture was allowed to warm to room temperature. EtOAc (20 mL) was added. The organic layer was separated and washed with water (10 mL) and brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo to a colorless oil. Purification by flash chromatography (10:90 to 40:60 EtOAc/hexanes) afforded *syn*-**3e** as a white solid (2.12 g, 90%). The selectivity was determined to be 96:4 by chiral SFC analysis (Chiralcel OD (H), 4−40% MeOH at 2%/min, 200 bar, minor t_R = 14.14 min, major t_R = 12.91 min): mp 215−216 °C; ^{1}H NMR (3:2 rotamer ratio, * denotes minor rotamer peaks, CD_3CN, 400 MHz) δ 7.67* (d, J = 8.0 Hz, 2H), 7.52 (d, J = 7.6 Hz, 2H), 7.45−7.29 (m, 7H), 7.29−7.20 (m, 2H), 7.14−7.03 (m, 2H), 6.96 (d, J = 8.0 Hz, 2H), 4.41−4.29 (m, 2H), 4.22 (d, J = 11.2 Hz, 1H), 4.09* (m, 1H), 3.96−3.83 (m, 2H), 3.35 (s, 3H), 3.34* (s, 3H), 2.54 (s, 3H), 2.51* (s, 3H), 2.43−2.34 (m, 1H), 2.32−2.21 (m, 1H), 0.68 (d, J = 7.2 Hz, 3H), 0.48* (d, J = 7.6 Hz, 3H); ^{13}C NMR (CD_3CN, 100 MHz) δ 173.1, 171.99*, 171.95, 142.63, 141.61*, 141.4, 142.3*, 138.6*, 137.2, 129.3, 128.9, 128.6, 128.3*, 128.2, 128.10, 128.05, 128.0*, 127.7, 127.6*, 127.5, 127.2*, 127.0, 126.9*, 126.6*, 126.5*, 126.2, 74.6, 73.9*, 57.9, 53.5, 52.9*, 50.6, 46.6*, 45.9, 38.4, 38.2*, 26.0, 14.4*, 12.5; IR (thin film) 3394, 1734, 1634 cm^{-1}. Anal. Calcd for $C_{28}H_{31}NO_4$: C, 75.48; H, 7.01; N, 3.14. Found: C, 75.17; H, 6.99; N, 3.08.

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Supporting Information Available: Experimental procedures, characterization data for **1b**−**d**, **6**, **2b** and **f**, **3b**−**l**, and **4a**−**i**, and in situ NMR data for **1a** and **c**, **8**, **9**, and the enolate of **1c** formed in the presence or absence of LiCl. This material is available free of charge via the Internet at http://pubs.acs.org.

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