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Pseudoephedrine as a Chiral Auxiliary for Asymmetric Michael Reactions: Synthesis of 3-Aryl-δ-lactones

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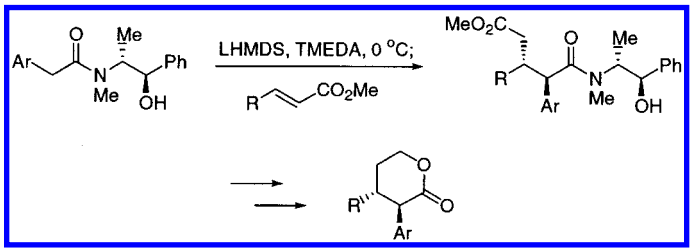
ABSTRACT



The asymmetric Michael reaction of pseudoephedrine amides is reported. The 1,5-dicarbonyl products are converted to 3-aryl-δ-lactones in a two-step reduction/lactonization sequence. This method provides access to enantiomerically enriched *trans*-3,4-disubstituted δ-lactones.

The Michael addition of enolizable substrates to unsaturated carbonyl compounds is a fundamental method for carbon−carbon bond construction.[1,2] The development of asymmetric variants of this important reaction continues to be an ongoing pursuit. Recent progress including the advent of asymmetric catalysis has advanced this form of stereocontrol.[1,3] The use of chiral auxiliaries has also been established as an effective method for control of asymmetry. The most common approach to induce selectivity is the use of a chiral auxiliary on the Michael acceptor.[4] The alternative strategy of using an auxiliary on the Michael donor has been less explored.[5]

We recently required a method for the enantioselective synthesis of aryl-substituted δ-lactones **1** (Scheme 1). A survey of the relevant literature did not provide any substantial precedence for the synthesis of these important chiral molecules. We sought a method that would permit variation of the substituents at the 3- and 4-positions with control of absolute and relative stereochemistry. Retrosynthetic analysis suggested that dicarbonyl derivative **3** was a

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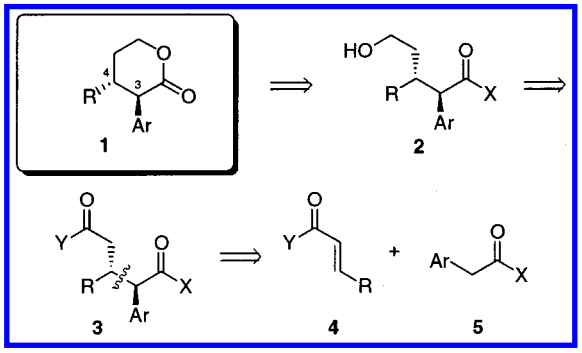
Scheme 1



possible precursor, which we envisioned to arise from a Michael addition reaction. Michael disconnection allows introduction of the ring substituents independent of one another via acceptor **4** and donor **5**. This procedure would access a range of 3,4-disubstituted *trans*-lactones with the appropriate choice of **4** and **5**. In this communication, we describe a new method for the preparation of 3,4-disubstituted lactones that involves an auxiliary-controlled Michael addition of pseudoephedrine amide enolates with unsaturated esters.[6]

Catalytic asymmetric Michael reaction methodology has been extended to both enantio- and diastereoselective systems; however, these systems are not currently applicable to the substitution pattern required for the synthesis of lactone **1**. We consequently focused our attention on chiral-auxiliary-controlled approaches. Auxiliary-controlled Michael reactions can either follow the paradigm of employing a chiral acceptor **4**[4] or a chiral donor **5**.[5] We chose the latter approach by investigating the reaction of chiral amide enolates with α,β-unsaturated esters. This combination was attractive for the following reasons: (1) the selectivity could be optimized by screening a variety of chiral amines, (2) the ester of the resultant adduct **3** could be readily reduced in the presence of the amide, and (3) upon acid-mediated lactonization, the chiral auxiliary could be recovered as an amine salt.

(6) 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.

(7) This method determines selectivity at the 4-position only, as epimerization occurs upon lactonization. Determination of the diastereomeric ratios of the Michael adducts by NMR spectroscopy is hampered by the presence of rotamers.

(8) For a review of the synthetic applications of *cis*-1-amino-2-indanol see: Senanayake, C. H. *Aldrichimica Acta* **1998**, *31*, 3−15.

(9) Myers et al. have demonstrated the power of pseudoephedrine as a chiral auxiliary for enolate alkylations: (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. Myers, A. G.; Yoon, T. *Tetrahedron Lett.* **1995**, *36*, 9429−9432. (d) Myers, A. G.; Gleason, J. L.; Yoon, T. *J. Am. Chem. Soc.* **1995**, *117*, 8488−8489. (e) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361−9362.

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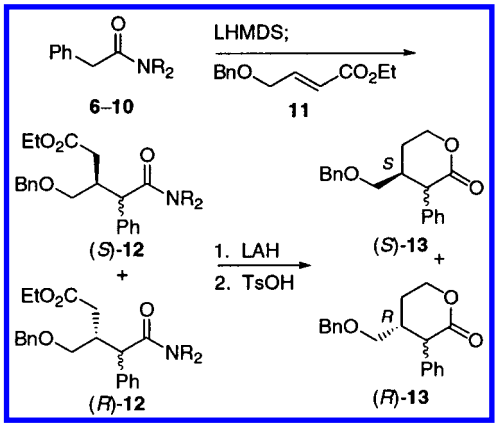
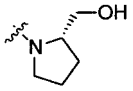
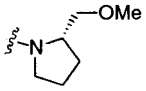
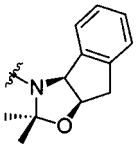
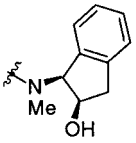
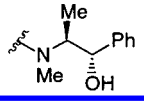
We began our investigation by examining the reaction of several chiral amide enolates **6**−**10** with an unsaturated ester (Scheme 2, Table 1). The resultant adducts (*S*)-**12** and (*R*)-

Scheme 2



12 were submitted to reduction and lactonization to determine facial selectivity on the Michael acceptor.[7] The ratio of the four lactones was determined by chiral SFC analysis.

Table 1. Screen of Chiral Auxiliaries

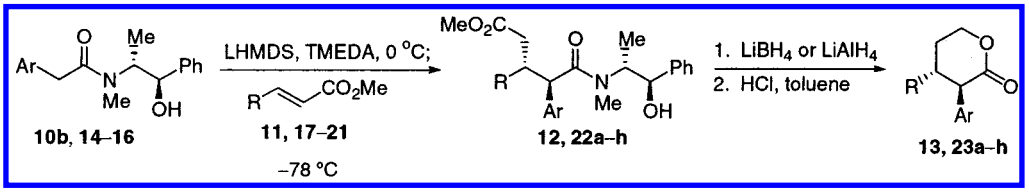
entry	amide	NR_2	(*S*)-**13** : (*R*)-**13**[a]
1	**6**		76 : 24
2	**7**		64 : 36
3	**8**		54 : 46
4	**9**		94 : 6
5	**10a**		95.5 : 4.5

[a] Determined by chiral SFC analysis.

We found that (*S*)-prolinol amide enolates gave low selectivity (Table 1, entry 1), contrary to the report by Yamaguchi for the alkylation of propionate amides.[5d] The protected amino alcohols **7** and **8** did not provide significant selectivity. We were pleased to find, however, that both *cis*-*N*-methylaminoindanol[8] and (*S*,*S*)-pseudoephedrine[9,10] afforded lactone (*S*)-**13** with high selectivity (entries 4 and 5).

Our subsequent work focused on the optimization of the pseudoephedrine amide. We have found that the presence

Scheme 3



of TMEDA and lower temperatures enhanced selectivity. Generation of the dianion at 0 °C in the presence of 2 equiv of TMEDA, followed by cooling to −78 °C and addition of the unsaturated ester, gave optimal selectivity. Under these conditions, the Michael addition is typically complete within 30 min,[11] and with amide **10b** and ester **17**, *anti*-isomer **22a** was isolated in 76% yield (Scheme 3, Table 2 entry 2).[12] The stereochemistry was assigned unambiguously by single-crystal X-ray analysis.

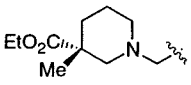
Conversion of the Michael adduct to the lactone was accomplished in a two-step reduction/lactonization sequence (Scheme 3). A variety of reducing agents, including LAH, $LiBH_4$, and $LiAlH(O\text{-}t\text{-}Bu)_3$, were effective for selective reduction of the ester in the presence of the amide.[13] Cyclization was accomplished by treatment with TsOH, MsOH, or anhydrous HCl.[13] Use of HCl permitted recovery of pseudophedrine by filtration of the HCl salt produced upon lactonization.

The scope and limitations of this method were investigated with respect to the donor and acceptor (Table 2). The amides were prepared from (*R*,*R*)-pseudoephedrine and the requisite acid chlorides using Schotten−Bauman conditions.[14] The Michael acceptors were prepared according to literature procedures.[13] Reaction of **10b** with Michael acceptor **11** afforded lactone **13** with the (*R*,*R*)-isomer predominating (entry 1), in contrast to the reaction of enantiomeric **10a**, which gave (*S*)-**13** (Table 1, entry 5). In the case of the acceptor, alkyl, phenyl, and alkyl-ether substituted α,β-unsaturated esters were suitable substrates (entries 1−5). The amine-substituted ester **21** afforded adduct **22e** in high yield and lactone **23e** with moderate selectivity (entry 6). Phenyl, 4-fluorophenyl, and 3,4-difluorophenyl amides **10b**, **14**, and **15**, respectively, afforded the corresponding lactones with good to high selectivity (entries 2, 7, and 8). A decrease in selectivity was exhibited by electron-rich amide **16** (entry 9), where the unpurified Michael adducts afforded lactone **23h** with moderate ee (76%).

The optical purity of the lactone can be increased by purification at either of two points: isolation of the major Michael adduct or, when possible, crystallization of the lactone. The major isomer of Michael adduct **22g** was isolated by crystallization as a 98.8:1.2 ratio of isomers in 60% yield. Conversion to the lactone by the standard protocol afforded **23g** in 78% yield and 99.8% ee. In the case of lactone **23a**, the unpurified mixture of adducts **22** was reduced and then treated with ethereal HCl. The auxiliary was recovered as the HCl salt in 74% yield by filtration. Crystallization afforded lactone **23a** in 62% yield and 98% ee over the three steps (entry 2).

To determine stereoselectivity, the Michael adducts were converted to the lactones[15] without separation of the isomers (Table 2).[7] Assignment of the stereochemistry of the Michael adducts was based on analogy to adducts **22a**, **22e**, and **22g**, 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

Table 2. Michael Reactions of (*R*,*R*) Pseudoephedrine Arylacetamides

entry	donor	Ar	acceptor	R	adduct	yield (%)[a]	lactone	yield (%)[b]	ee (%)[c]
1	**10b**	C_6H_5	**11**	CH_2OBn	**12**	80	**13**	69	91
2	**10b**	C_6H_5	**17**	CH_2OPMP	**22a**	98 (76)[d]	**23a**	71 (62)[e]	92 (98)[e]
3	**10b**	C_6H_5	**18**[f]	CH_3	**22b**	85	**23b**	68	91
4	**10b**	C_6H_5	**19**	$(CH_2)_2Ph$	**22c**	78	**23c**	89	87
5	**10b**	C_6H_5	**20**	C_6H_5	**22d**	89	**23d**	70	83
6	**10b**	C_6H_5	**21**[f]		**22e**	83	**23e**	46	77
7	**14**	4-FC_6H_4	**17**	CH_2OPMP	**22f**	95	**23f**	72	93
8	**15**	3,4-diFC_6H_3	**17**	CH_2OPMP	**22g**	60[g]	**23g**	78	87 (99.8)[h]
9	**16**	4-$MeOC_6H_4$	**17**	CH_2OPMP	**22h**	80	**23h**	62	76

[a] Yields reported for combined isomers isolated after chromatography, unless otherwise noted. [b] Isolated yields over two steps. [c] Determined by chiral SFC analysis; details provided in Supporting Information. [d] Yield reported for major isomer isolated by flash chromatography. [e] Number in parentheses reported for crystallized material. [f] Reaction performed on the ethyl ester. [g] Yield reported for major isomer isolated by crystallization. [h] Number in parentheses reported for crystallized material obtained from a 98.8:1.2 isomeric ratio of **22g**.

of the coupling constants for the protons at the 3- and 4-positions. The predominant enantiomer of lactone **13** was assigned as the (*R*,*R*)-isomer by comparison to an independently synthesized reference compound.

We next shifted our focus to the mechanistic model to account for the observed selectivity of these reactions. Myers first investigated the stereochemical outcome of the alkylation of pseudoephedrine amide enolates with electrophiles.[9] He proposed that the enolate adopts the conformation depicted in Figure 1 and that alkyl halides approach the enolate from

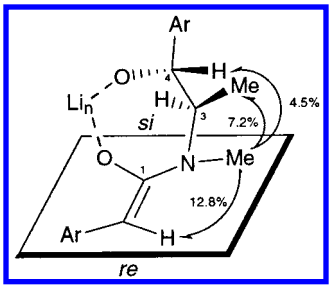


Figure 1.

the less hindered *re* face; however, epoxides are delivered to the *si* face by coordination to the lithium alkoxide of the auxiliary.[9a] We expected that α,*β*-unsaturated esters would follow the epoxide reaction manifold, by coordination of the carbonyl oxygen to the lithium cation. Formation of the observed enantiomer of *anti*-**24**, however, indicates that the Michael acceptor approaches the *re* face of the enolate (Figure 2). NMR spectroscopic analyses of the enolate

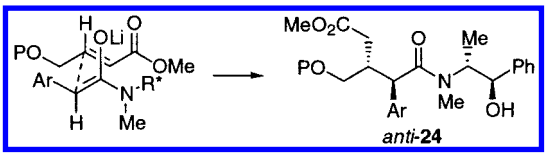


Figure 2.

formed by treatment of amide **15** with 2 equiv of LHMDS supports the structure of the (*Z*)-enolate set forth by Myers (Figure 1). The observed NOE data shown in Figure 1 define the stereochemistry of the enolate. These data, coupled with the absence of an NOE from the *N*-methyl protons to the C_3 proton, place restraints on its conformation and are consistent with a fixed ring system bound at the oxygen atoms by lithium either singularly or as part of a lattice. At this time, we are uncertain as to why esters are apparently not delivered to the *si* face of the enolate. Studies to further elucidate the source of stereochemical control of this and other related stereoselective reactions of chiral amide enolates are in progress and will be reported in due course.

In conclusion, we have developed a diasteroselective Michael reaction of aryl-substituted pseudoephedrine amide enolates. This method provides highly enantiomerically enriched 3-aryl-substituted *δ*-lactones in three steps. The chiral auxiliary is recovered as the HCl salt by filtration. A model to explain the source of facial selectivity based on literature precedence has been investigated and is counterintuitive. Investigations to determine the source of selectivity and to expand the scope of this method are in progress.

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Supporting Information Available: Experimental procedures and characterization data for **6**−**9**, **12**−**16**, **22a**−**h**, **23a**−**h**, and racemic lactones. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The reactions were rapid and did not require the presence of LiCl. For the use of LiCl to accelerate the alkylation reactions of pseudoephedrine amide enolates, see ref 9b.

(12) **General Procedure.** To a cooled (0 °C) solution of amide **10b** (4.25 g, 15 mmol) and TMEDA (4.52 mL, 30 mmol) in THF (15 mL) was added LHMDS (1.0 M solution in THF, 30.0 mL, 30 mmol). After 45 min, the reaction mixture was cooled to −76 °C, and ester **17** (3.33 g, 15 mmol) was added. After the mixture stirred for 1 h, MeOH (1 mL) was added followed by saturated aqueous NH_4Cl. The reaction mixture was allowed to warm to room temperature. The mixture was diluted with water, and the layers were separated. The organic layer was diluted with toluene, washed with 0.1 M HCl, dried (Na_2SO_4), and concentrated in vacuo to afford a yellow oil. Purification by flash chromatography (1:1.5 hexanes/EtOAc) afforded **22a** as a colorless oil (5.79 g, 76%).

(13) Details are provided as Supporting Information.

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

(15) Racemic samples of the lactones were prepared and used for chiral SFC method development. Details are provided as Supporting Information.