Pergamon

Tetrahedron Letters, Vol. 38, No. 40, pp. 7037-7040, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01706-1

Synthesis of Tertiary Alkyl Fluoride Centers by Asymmetric C-C(F) Bond Formation

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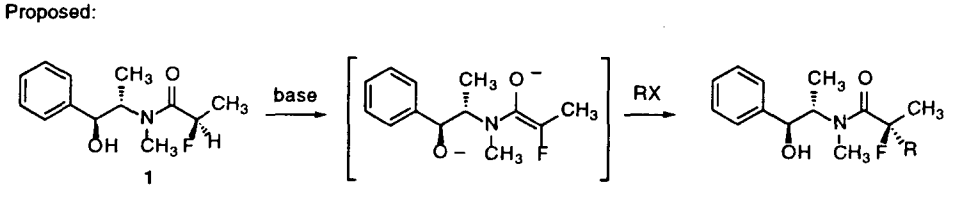
Abstract: Asymmetric alkylation of pseudoephedrine α-fluoropropionamide (1) affords α-alkylated products efficiently and with excellent stereocontrol at the newly formed tertiary alkyl fluoride center. Mild alkaline hydrolysis of the products provides the corresponding carboxylic acids with high enantiomeric excess. © 1997 Elsevier Science Ltd.

In continuing studies of the asymmetric synthesis of chiral organofluorine compounds,[1] we describe herein methodology for the stereocontrolled formation of tertiary alkyl fluoride centers by an asymmetric alkylation procedure. The basis for this study was the conjecture that pseudoephedrine α-fluoropropionamide (1) would undergo sterically-based, selective enolization to form the enolate isomer with the methyl group



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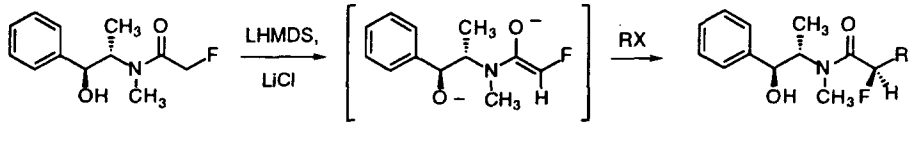
oriented cis to the enolate oxyanion. Subsequent alkylation of this enolate was then expected to proceed with high diastereofacial bias, in accord with much precedence.[2] Potentially mitigating against this proposal was the fact that the less substituted substrate, pseudoephedrine α-fluoroacetamide, was found to undergo highly diastereoselective alkylation in a reaction that was rationalized by invoking a preference for formation of the enolate with fluorine cis to the oxyanion.[3] To the extent that fluorine exhibits such a preference, the geometry



proposed for enolization of **1** would be disfavored. As results below will demonstrate, the alkylation of **1** (and therefore likely the enolization as well) is a highly selective process, with a stereochemical outcome that is

consistent with the proposed enolate structure, albeit conducted under very different reaction conditions than were optimal for diastereoselective alkylation of the parent system, pseudoephedrine α-fluoroacetamide. While these studies were ongoing, an independent report appeared from Staunton et al. describing methodology for the synthesis of tertiary alkyl fluorides by asymmetric alkylation using the Evans' oxazolidinone auxiliaries.[4] We describe below practical methodology for the use of pseudoephedrine as a chiral auxiliary in the asymmetric synthesis of tertiary alkyl fluorides by C-C(F) bond formation.

Alkylation studies were conducted initially by enolate formation from [1*S*(*R*),2*S*]-pseudoephedrine α-fluoropropionamide (**1**)[3] with a base such as lithium hexamethyldisilazide (LHMDS) or lithium diisopropylamide (LDA) followed by the addition of a reactive alkyl halide such as allyl iodide (3-5 equiv). The base used for enolate formation was found to be a critical variable in determining the diastereoselectivity of the subsequent alkylation reaction. Interestingly, the use of lithium hexamethyldisilazide (2.1 equiv), the base of choice for the diastereoselective alkylation of pseudoephedrine α-fluoroacetamide,[3] for deprotonation of **1** (in the presence of 6 equiv of lithium chloride) followed by trapping with allyl iodide (5 equiv) led to a poorly diastereoselective alkylation (de 10-24%, ~70% yield). By contrast, the use of lithium diisopropylamide (2.1 equiv) as base, a nonselective reagent when used for the alkylation of the α-fluoroacetamide derivative,[3] at –78 °C in the presence of 6 equiv of lithium chloride followed by trapping with allyl iodide provided nearly ideal results (crude de 90%, isolated de 94%, isolated yield 80%). As indicated within Table 1 below, these

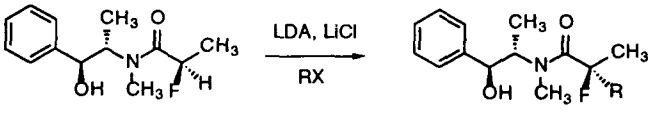


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Table 1. Diastereoselective Alkylation of Pseudoephedrine 2-Fluoropropionamide **1**.

Entry	RX[a]	Temp (°C)	Time (h)	Crude de	Isolated de	Isolated Yield
1	CH_2=$CHCH_2I$	–78	4.5	90	94	80
2	CH_2=$C(CH_3)CH_2Br$	–78	5	97	97	76
3	$C_6H_5CH_2Br$	–78	4.5	≥95	≥99	71
4	$C_2H_5OSO_2CF_3$	–45	5.5	–	87	34

[a]Alkylation reactions employed 3-5 equiv of electrophile.

conditions for enolization and alkylation of **1** led generally to highly selective alkylation reactions with reactive alkyl halides. Less reactive substrates such as ethyl triflate (3 equiv), though selective, proceeded with poor efficiency.

The stereochemistry of the alkylation product from trapping with benzyl bromide (entry 3, Table 1) was established unequivocally by X-ray crystallographic analysis. The other products of Table 1 were assigned by analogy. The benzylation product crystallized forming a network of hydrogen bonds that links the hydroxyl

group of one auxiliary to the amide carbonyl of an adjacent molecule (Figure 1). The stereochemical outcome of the alkylation reaction is consistent with the model for asymmetric alkylation proposed above and depicted in Figure 2, invoking the (*E*)-enolate geometry and electrophilic attack opposite the enolate π-face occupied by the side-chain alkoxide group (as previously proposed for other pseudoephedrine amide enolate alkylations).[2] We speculate that the selectivity-determining step in these reactions forming tertiary alkyl fluorides is the enolization reaction, and that the selective alkylation reaction, utilizing LDA as base, arises as a consequence of kinetic selectivity in that step. Whether the poor selectivity of the reaction with LHMDS as base is attributable to thermodynamic equilibration of enolates or to poor kinetic selectivity in enolization is not

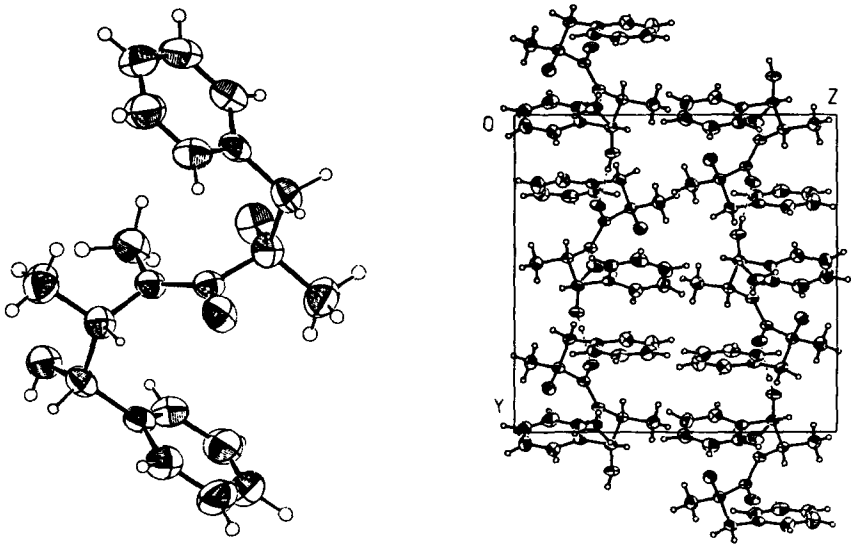

Figure 1. X-ray Crystal Structure of the Benzylated Alkylation Product (Entry 3, Table 1).

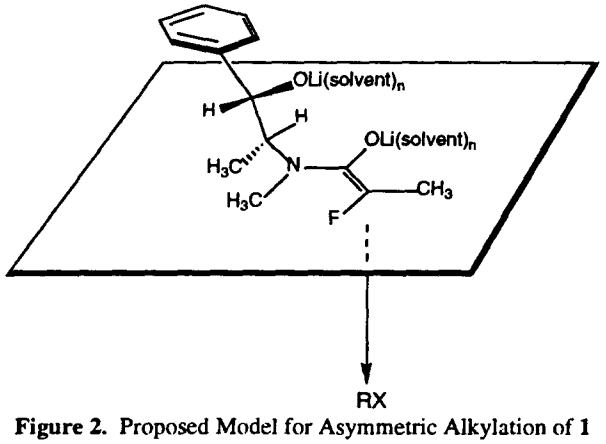

Figure 2. Proposed Model for Asymmetric Alkylation of **1**

known, but both possibilities are favored over the alternative hypothesis invoking poor π-facial selectivity in the alkylation reaction. It is interesting to note that enolizations of both **1** and pseudoephedrine α-fluoroacetamide with LHMDS are believed to favor the formation of greater proportions of the isomer with fluorine cis to the enolate oxyanion than enolizations with LDA.

The alkylation products of Table 1 are readily hydrolyzed under mild alkaline conditions to form the corresponding carboxylic acids in high yield and with high enantiomeric excess. For example, treatment of the allylated product of entry 1 with 2 N aqueous sodium hydroxide solution in a mixed solvent of equal parts *t*-butyl alcohol and methanol at 75 °C for 1 h afforded the acid in 92% ee and 87% yield. Similarly, hydrolysis of the methallylated product of entry 2 afforded the corresponding acid in 95% ee and 86% yield. In both cases the pseudoephedrine auxiliary could be recovered in high yield by a simple extraction procedure.

The methodology described provides an experimentally simple and highly practical route for the preparation of tertiary organofluorine compounds of high enantiomeric excess. Ready access to compounds of this type should facilitate their evaluation as potential structures or component structures for pharmaceutical development.

Acknowledgment This research was generously supported by the National Science Foundation and the National Institutes of Health.

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(*Received in USA* 11 *July* 1997; *revised* 12 *August* 1997; *accepted* 13 *August* 1997)