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Stereocontrolled Alkylative Construction of Quaternary Carbon Centers

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Abstract

Protocols for the stereodefined formation of α,α -disubstituted enolates of pseudoephedrine amides are presented followed by the implementation of these in diastereoselective alkylation reactions. Direct alkylation of α,α -disubstituted pseudoephedrine amide substrates is demonstrated to be both efficient and diastereoselective across a range of substrates, as exemplified by alkylation of the diastereomeric pseudoephedrine α -methylbutyramides, where both substrates are found to undergo stereospecific replacement of the α -C-H bond with α -C-alkyl, with retention of stereochemistry. This is shown to arise by sequential stereospecific enolization and alkylation reactions, with the alkyl halide attacking a common π -face of the *E*- and *Z*-enolates, proposed to be that opposite the pseudoephedrine alkoxide side-chain. Pseudoephedrine α -phenylbutyramides are found to undergo highly stereoselective but not stereospecific α -alkylation reactions, which evidence suggests is due to facile enolate isomerization. Also, we show that α,α -disubstituted pseudoephedrine amide enolates can be generated in a highly stereocontrolled fashion by conjugate addition of an alkyl lithium reagent to the *s*-cis-conformer of an α -alkyl- α,β -unsaturated pseudoephedrine amide, providing α,α -disubstituted enolate substrates that undergo alkylation in the same sense as those formed by direct deprotonation. Methods are presented to transform the α -quaternary pseudoephedrine amide products into optically active carboxylic acids, ketones, primary alcohols, and aldehydes.

Here we describe practical methods for the stereocontrolled construction of quaternary carbon centers using pseudoephedrine as a chiral auxiliary.^{1–3} Protocols for the stereodefined formation of α,α -disubstituted enolates of pseudoephedrine amides are presented followed by the implementation of these in diastereoselective alkylation reactions.

Equations 1 and 2 illustrate the finding that the diastereomeric α -methylbutyramides **1** and **2** undergo stereospecific enolization with lithium diisopropylamide (LDA) in the presence of lithium chloride at 0 °C to form *Z*- and *E*-enolates, respectively, as inferred from ¹H NMR analysis of the corresponding cyclic siloxane derivatives [formed upon trapping at –40 °C with

dichlorodiisopropylsilane in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU)].⁴ These observations can be rationalized within the framework of prior analyses of pseudoephedrine amide alkylation reactions, extended here to enolate formation.^{1c-f} We propose that in the favored pre-transition state assemblies the alkoxide side-chain and base are positioned on opposite faces of the incipient enolate, with the α -C-H bond aligned for deprotonation (see Figure 1, which illustrates the proposal for the specific case of substrate **1**).

(1)

(2)

Alkylation of enolates derived from amides **1** and **2** at -40 °C, initially examined using an excess of the electrophile benzyl bromide (2 equiv), was also stereospecific; replacement of the α -C-H bond with α -C-benzyl proceeded with net retention of stereochemistry in each case (eq 3–4). Together, the experimental results summarized in equations 1–4 reveal that *Z*- and *E*- α -methyl- α -ethyl disubstituted pseudoephedrine amide enolates are alkylated preferentially from a common diastereoface. The sense of alkylation is the same as that observed in the alkylation of α -monosubstituted pseudoephedrine amides, and is rationalized similarly: the electrophile is proposed to approach the enolate π -face opposite the alkoxide side-chain.^{1c-f, 5} Significantly, benzylation of the *Z*-enolate (derived from **1**) is both more diastereoselective and more rapid than benzylation of the *E*-enolate (derived from **2**). The rate ratio is more than 4, based upon the kinetics of product formation (see Supporting Information). This finding suggests an explanation for the otherwise puzzling observation that the diastereoselectivity of benzylation of **1** is higher at lower conversion (19:1 at 65% conversion versus 9.9:1 at full conversion): the small amount of *E*-enolate that is formed during the deprotonation of amide **1** is alkylated more slowly, and with opposite diastereoselectivity relative to the *Z*-enolate. This consideration further suggested that

(3)

(4)

more highly diastereoselective reactions might be achieved simply by using a slight excess of enolate, with the electrophile as limiting reagent. This proposal was borne out by experiment (Chart 1). Using excess enolate (1.25 equiv), the diastereoselectivity of benzylation of amide **1** increased, to 19:1, with no diminution in yield (93%, now based on the electrophile, first entry, Chart 1). The other entries of Chart 1 reveal that a number of different electrophiles react efficiently and diastereoselectively with various α, α -disubstituted enolates of pseudoephedrine amides, including unactivated alkyl halides such as isobutyl iodide.⁶

An interesting feature of the enolization–alkylation reactions of α, α -disubstituted pseudoephedrine amides emerged when we investigated the α -phenylbutyramides **3** and **4** as substrates, using an excess of benzyl bromide as the electrophile (2 equiv). Both substrates afforded an identical mixture of the two possible alkylation products (19:1 dr), in 91% yield (eq 5–6), which suggests that the *E*- and *Z*- α -phenyl- α -ethyl enolate intermediates

(5–6)

(7)

might interconvert under the reaction conditions. This proposal was supported by enolate trapping experiments with dichlorodiisopropylsilane (eq 7). If the working model described above applies to the alkylation of α -phenylbutyramides **3** and **4**, then the more reactive enolate is the *E*-isomer, with the α -phenyl substituent *cis* to the *N*-methyl group (note that this is also the thermodynamically preferred isomer, see eq 7 and additional data in the Supporting Information).

An alternative method for the stereocontrolled generation of α , α -disubstituted pseudoephedrine amide enolates as alkylation substrates was also developed, following the precedent of Badia et al. for the formation of α -monosubstituted pseudoephedrine amide enolates by conjugate addition.^{1g,h} Equations 8 and 9 depict transformations producing the *Z* and *E* geometric isomers, respectively, of α -*n*-butyl- α -*tert*-butylmethyl pseudoephedrine amide enolates, generated by the conjugate addition of an appropriate organolithium reagent to an α -alkyl- α,β -unsaturated

(8)

(9)

(10)

(11)

pseudoephedrine amide (monodeprotonated, with methyllithium, at $-78\text{ }^\circ\text{C}$ in the presence of lithium chloride) and captured as stable di-*iso*-propylsiloxane derivatives.⁴ ^1H NMR spectroscopic analysis of the latter established that in both cases addition had occurred almost exclusively by conjugate addition to the *s*-cis rotamer of the α,β -unsaturated amide.

As with α,α -disubstituted enolates formed by direct deprotonation, *Z*- and *E*-enolates formed by conjugate addition are alkylated from a common diastereoface, affording major products that are diastereoisomeric (see equations 10 and 11). The alkylation reaction of equation 11 was notably slow (66% yield after 18 h at $0\text{ }^\circ\text{C}$), which is perhaps not surprising, given that the *E*-enolate intermediate (with the *N*-methyl group *cis* to the α -*tert*-butylmethyl group) is sterically hindered (see models of Fig 2). Interestingly, this was also one of the most poorly selective alkylation reactions we have identified, perhaps because the alkoxide side-chain and the *t*-butyl group are oriented on opposite π -faces of the enolate (see Figure 2). That the alkylation occurred at all underscores the point that (pseudoephedrine) amide enolates are remarkably reactive. As the examples presented in Chart 2 make evident, the conjugate addition–alkylation protocol is viable for the construction of a variety of differently substituted quaternary carbon centers, although the yields of conjugate addition–alkylation products are somewhat reduced when primary alkyl lithium reagents are used as nucleophiles in the conjugate addition, as a consequence of competitive 1,2-addition to the amide.⁸

We have explored a number of useful transformations of pseudoephedrine amides bearing α -quaternary carbon centers. Among these, alkaline hydrolysis to form carboxylic acids has proven to be both general and high yielding (eq 12, and Supporting Information).^{1a,e} In preliminary studies, we have also shown that methyl ketones can be formed, using an excess of methyllithium in the presence of HMPA (eq 13), and that primary alcohols can be formed by reduction with lithium amidotrihydroborate (eq 14).⁹ Most recently, we have discovered that the oxazolium triflate derivatives developed for the analysis of diastereomeric ratios¹⁰ also hold promise as reactive intermediates for the synthesis of both methyl ketones (eq 15)

and aldehydes (eq 16).¹¹ Experimental procedures for these new transformations are provided in the Supporting Information.

(12-13)

(14)

(15)

(16)

Supplementary Material

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6. In reactions with limiting electrophile, excess base (LDA) should not be used, for many electrophiles are destroyed with any excess base (benzyl bromide forms a mixture of 1-bromo-1,2-diphenylethane and stilbene, for example).⁷
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Figure 1. Proposed pre-transition state assemblies leading to favored (*Z*) and disfavored (*E*) geometric enolate isomers by sequential deprotonations of pseudoephedrine amide **1**. Lithium is depicted in yellow.

Figure 2. Proposed models of the *E*-enolate derived from α,β -unsaturated pseudoephedrine amide **6**. Lithium is depicted in yellow.

Chart 1. Quaternary Carbon Centers Formed by Enolization–Alkylation of Pseudoephedrine Amides.^a

^a Isolated yields. ^b For activating alkyl groups (allyl, benzyl) alkyl bromides were used and for non-activating groups (ethyl, isobutyl) alkyl iodides were used. ^c Alkylation was conducted at –20 °C.

Chart 2. Quaternary Carbon Centers Formed by Conjugate Addition–Alkylation of α,β -Unsaturated Pseudoephedrine Amides.^a

^a Isolated yields. ^b Methyl iodide was used for introduction of an α -methyl group; otherwise, alkyl bromides were used as electrophiles. ^c Alkylation was conducted at 0 °C. ^d Excess phenyllithium (2.25 equiv) was used in lieu of deprotonation with methyllithium.