Tetrahedron 70 (2014) 5463–5467

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of α-chiral-β,γ-unsaturated carboxylic acid derivatives using chiral auxiliaries

Kelsey E. Poremba, Victoria A. Lee, Bianca R. Sculimbrene *

College of the Holy Cross, Department of Chemistry, 1 College St., Worcester, MA 01610, USA

ARTICLE INFO

Article history:
Received 6 June 2014
Received in revised form 24 June 2014
Accepted 26 June 2014
Available online 2 July 2014

Keywords:
Chiral auxiliary
Diastereoselective alkylation
Pseudoephedrine
Oxazolidinone

ABSTRACT

We report an efficient and reliable method for the synthesis of α-chiral-β,γ-unsaturated carboxylic acid derivatives using chiral auxiliaries and vinylacetic acid. Two well-established chiral auxiliaries ((*S*,*S*)-pseudoephedrine and (*R*)-benzyl-oxazolidinone) were chosen to test the merits of this method. Six different electrophiles were examined in the diastereoselective alkylation with both auxiliaries. The pseudoephedrine auxiliary provided isolated yields between 61 and 85% and diastereomeric ratios all greater than 96:4. Employing the same reactions as with the pseudoephedrine derivative, the corresponding oxazolidinone auxiliary provided isolated yields between 0 and 80% with diastereomeric ratios from 80:20 to 93:7.

1. Introduction

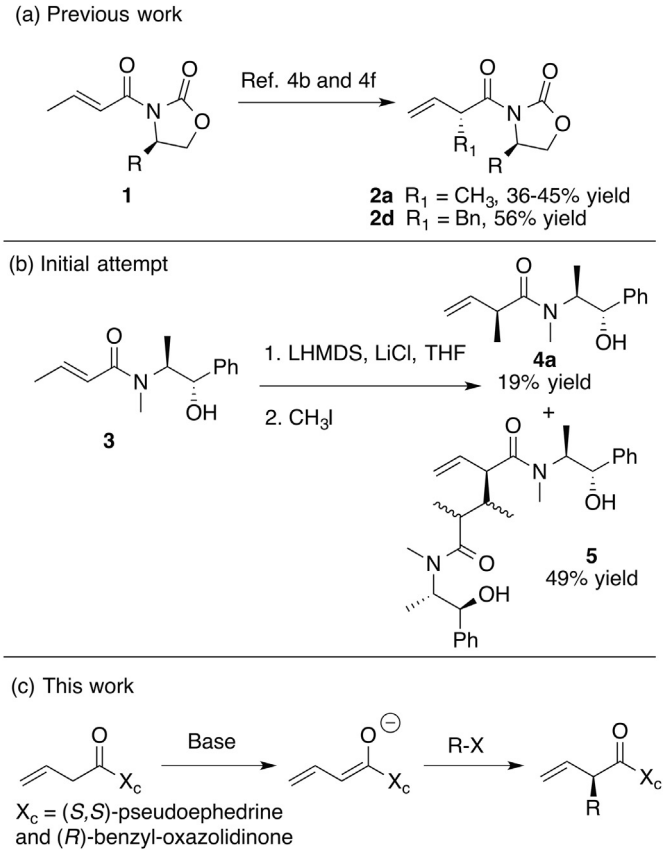
Chiral auxiliaries have long been a preferred method for the α-alkylation of carbonyl compounds.[1] The pioneering work of Evans and co-workers with chiral oxazolidinones[2] and Myers and co-workers with pseudoephedrine[3] has resulted in robust and broadly used methods for the introduction of stereocenters vicinal to carbonyls. The synthesis of optically active molecules via chiral auxiliaries benefits from the use of inexpensive, commercially available reagents that are readily recoverable after cleavage. Additionally, since the new stereogenic center is introduced via a diastereoselective reaction, the minor diastereomer can be detected via NMR and separated using conventional chromatography or recrystallization.

Despite the plethora of alkylation examples using chiral auxiliaries, there are only sporadic reports of the asymmetric synthesis of α-chiral-β,γ-unsaturated carboxylic acid derivatives using chiral oxazolidinones[4] or pseudoephedrine (or pseudoephenamine).[5] While these substrates have been efficiently accessed in high enantiomeric purity through Cu-catalyzed asymmetric allylic alkylations[6] and catalytic Hiyama cross-coupling reactions,[7] we sought to examine the use of chiral auxiliaries to synthesize this synthetically versatile intermediate.

In 1986, Evans and co-workers described aldol addition reactions with crotonate-derived oxazolidinones to give high yields of the desired β,γ-unsaturated addition products.[8] Unfortunately, applying this strategy to alkylation reactions was not as high yielding (Scheme 1a). Literature reports for the γ-deprotonation of *N*-crotonyl oxazolidinone **1**, followed by α-alkylation with methyl iodide or benzyl bromide, provide **2a** and **2b** in 36–45% and 56% yields, respectively.[4b,f] In our hands, this was a difficult and irreproducible reaction that provided yields between 9 and 49%. We initially examined if changing the chiral auxiliary to pseudoephedrine would provide reproducibly higher yields of alkylated product. When *N*-crotonyl pseudoephedrine **3** was deprotonated with LHMDS in the presence of LiCl,[9] followed by treatment with methyl iodide, **4a** was isolated in 19% yield along with 49% of byproduct **5** (Scheme 1b). This byproduct is formed via the conjugate addition of the generated enolate with another molecule of **3**, followed by alkylation. Unsuccessful attempts to optimize this reaction to favor formation of **4a** included varying the concentration, temperature, reaction time, and order of addition. The deprotonation of **3** was attempted with both LHMDS and LDA, but neither base provided high yield of the desired **4a**. Additionally, running the enolization in the presence of excess alkylating agent to avoid the conjugate addition unfortunately led to a complex mixture of products. To circumvent the unwanted conjugate addition, we turned our attention to the synthesis of chiral amides and imides derived from vinylacetic acid (Scheme 1c). α-Deprotonation of the vinylacetic amides or imides provides the identical enolate from Scheme 1a and b while eliminating the conjugate addition acceptor. We sought to demonstrate that this strategy would provide a robust and high yielding synthesis of α-chiral-β,γ-unsaturated carboxylic acid derivatives.

* Corresponding author. Tel.: +1 508 793 3425; fax: +1 508 793 3530; e-mail address: bsculimb@holycross.edu (B.R. Sculimbrene).

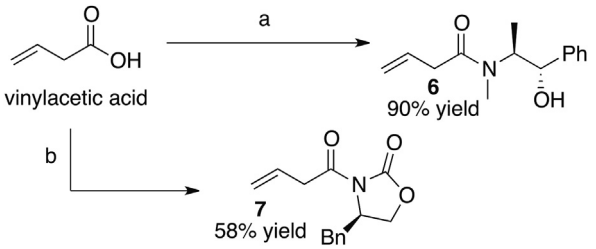
http://dx.doi.org/10.1016/j.tet.2014.06.116
0040-4020/



Scheme 1. Chiral auxiliary strategies for the synthesis of α-substituted-β,γ-unsaturated carboxylic acid derivatives via diastereoselective alkylation reactions.

2. Results and discussion

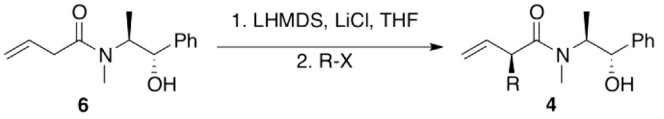
In order to test our hypothesis that chiral β,γ-unsaturated amides and imides would function as good substrates in diastereoselective alkylations, we needed to establish a synthetic procedure for their synthesis that was high yielding and avoided conjugation of the terminal alkene (Scheme 2). We found that in situ conversion of vinylacetic acid to the acid chloride, followed by treatment with pseudoephedrine, delivered the desired product **6** in 90% yield. When amide bond formation was attempted with the carbodiimide reagent EDC, significant amounts of conjugated amide **3** were formed, which was difficult to separate via chromatography. The acid chloride method was applied to the synthesis of **7** in a 58% un-optimized yield. The synthesis of **7** has also previously been reported via formation of the mixed anhydride of the carboxylic acid (in 93% yield).[10]



Scheme 2. Synthesis of β,γ-unsaturated carboxylic derivatives of chiral auxiliaries: (a) oxalyl chloride and DMF then (*S,S*)-pseudoephedrine and NEt_3; (b) oxalyl chloride and DMF then (*R*)-benzyl-oxazolidinone and *n*-BuLi.

With good procedures for the synthesis of **6** and **7**, we began evaluating the diastereoselective alkylation reaction. When **6** was deprotonated with LHMDS in the presence of LiCl at −78 °C for 1 h, 0 °C for 15 min, and rt for 5 min followed by cooling to 0 °C and addition of methyl iodide, the desired product was isolated in 76% isolated yield with a 97:3 diastereomeric ratio (Table 1, entry 1). Consistent with our hypothesis, use of a β,γ-unsaturated enolate precursor provided the desired **4a** in substantially higher yield (14% vs 76%, respectively). We did not detect any undesired conjugation of the double bond and observed the same high levels of diastereoselectivity reported for alkyl amides of pseudoephedrine.[11] The facial selectivity of the alkylation reaction is drawn using the mnemonic developed by Myers where the R-group adds 1,4-*syn* to the methyl group.[11] Other alkyl groups were added with slightly lower yields, but with the same high levels of diastereoselectivity (Table 1, entries 2 and 3). Benzyl and allyl bromide were the best electrophiles examined, providing **4d** and **4e** in 83% and 85% yields, respectively. When an excess of *tert*-butyl bromoacetate was used as the electrophile under the standard reaction conditions the major product was the result of alkylation at both carbon and oxygen (secondary hydroxyl group of pseudoephedrine). Fortunately, conducting the alkylation at −78 °C provided the desired C-alkylation product **4f** in 77% yield. The O-alkylation product was only observed with *tert*-butyl bromoacetate.

Table 1
Diastereoselective alkylation of 3-butenoic pseudoephedrine amide (**6**)[a]



Entry	R–X	R–X (equiv)	Alkylation time (h)	Product	Isolated yield (%)	dr[b]
1	CH_3I	4.0	1	**4a**	76	97:3
2	CH_3CH_2I	4.0	3	**4b**	62	99:1
3	$(CH_3)_2CHCH_2I$	4.0	4	**4c**	61	>99:1
4	$PhCH_2Br$	2.2	2	**4d**	83	96:4
5	$CH_2{=}CHCH_2Br$	4.0	3	**4e**	85	98:2
6	$(CO_2t\text{-}Bu)CH_2Br$	2.0	4.5	**4f**[c]	77	89:11

[a] Enolization of **6** was accomplished at −78 °C for 1 h, 0 °C for 15 min, and rt for 5 min followed by cooling to 0 °C for addition of R–X.
[b] Diastereomeric ratio (dr) was determined by ^1H NMR.
[c] Alkylation was conducted at −78 °C.

Due to the restricted rotation about the N–C(O) bond, tertiary amides typically exhibit rotational isomerism on the NMR timescale. This can make assignment of the NMR spectrum difficult, especially if diastereomers are present. Fortunately, procedures have been developed to aid in the spectroscopic analysis of pseudoephedrine amides.[12] Products **4a**–**4e** existed as a 3:1 rotamer ratio that coalesced in the NMR upon heating to 165 °C.[13] It is interesting to note that only **4f** was observed in a 1:1 rotamer ratio.

We next examined how the oxazolidinone auxiliary would perform in the alkylation reaction of **7**. We speculated that the lower yields of **2** previously reported in the literature and observed by us might also be caused by unwanted conjugate addition of the enolate as it is generated. We are happy to report that when **7** was α-deprotonated at −78 °C for 1 h, 0 °C for 15 min, and rt for 5 min followed by cooling to 0 °C for addition of methyl iodide, **2a** was isolated in 80% yield (Table 2, entry 1). Again, this was a great improvement over the previous method, which generated **2a** in 49% yield at best. The diastereomeric selectivity in the methyl iodide alkylation for the oxazolidinone auxiliary was not as good as pseudoephedrine (80:20 vs 97:3, respectively). However, the diastereomers are separable by chromatography so the lower selectivity is not a major impediment. Larger alkyl groups provided diminished yields of product, but afforded higher levels of diastereoselectivity (Table 2, entry 2). In the case of branched substrates, no product was observed (Table 2, entry 3). Benzyl bromide was also an effective electrophile providing **2d** in 52% yield in