Pergamon

Tetrahedron Letters 41 (2000) 8301–8305

TETRAHEDRON LETTERS

Claisen rearrangement of allylic alcohols prepared through *N*-Boc-2-acyloxazolidine methodology. Application to the synthesis of trisubstituted cyclopropanes

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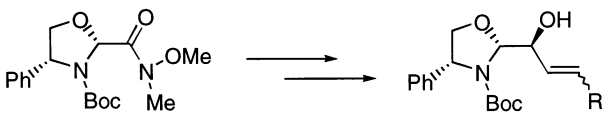
Received 18 July 2000; accepted 1 September 2000

Abstract

Stereodefined allylic alcohols prepared from a (*R*)-phenylglycinol-derived Weinreb amide undergo a Claisen rearrangement with a high level of stereocontrol. The produced *N*-Boc-2-alcenyloxazolidines can be either hydrolyzed to afford enantiomerically enriched enals or further epoxidized using a two-step sequence. The resulting epoxyoxazolidines can then be transformed into trisubstituted cyclopropanes.

Keywords: oxazolidines; asymmetric synthesis; Claisen rearrangement; epoxidation.

(*R*)- or (*S*)-Phenylglycinol-derived allylic alcohols such as **2**, bearing a *Z* or *E* stereodefined alkenyl moiety are easily prepared through a well established methodology, starting from Weinreb amide **1**[1] (Scheme 1). These allylic alcohols were previously shown to be useful chiral substrates for the synthesis of piperidinic amino acids.[2]



1 **2**

Scheme 1.

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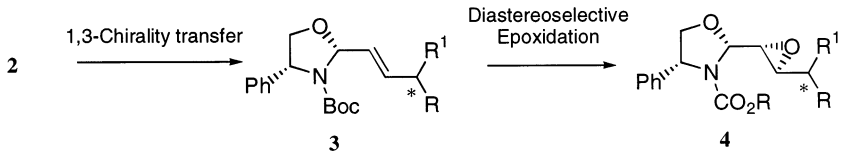
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01465-9

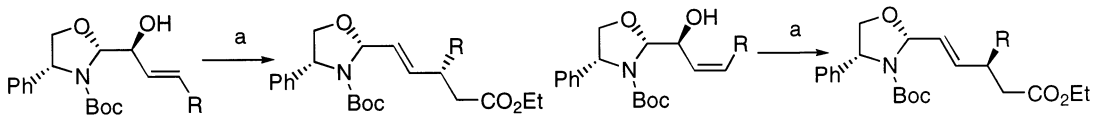
In order to extend the use of *N*-Boc-2-acyl oxazolidines in asymmetric synthesis,[3] we began to study 1,3-chirality transfers performed on these allylic alcohols **2** and producing alkenyl oxazolidines **3**.[4] The double bond of these compounds can indeed be epoxidized in a highly stereoselective way prior to other chemical transformations[5] (Scheme 2), thus allowing the preparation of valuable homochiral synthons such as trisubstituted cyclopropanes.



Scheme 2.

The aim of this letter is to present our preliminary results with regard to the Claisen rearrangement performed on alkenols **2**, and the epoxidation of the resulting alkenyl oxazolidines. This methodology ultimately allows the preparation of densely functionalized cyclopropanes.

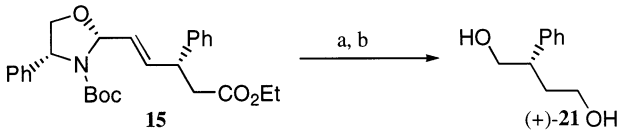
(*Z*)- and (*E*)-Alkenyl substrates **5**–**12** were prepared from Weinreb amide **1** following a previously reported three-step procedure[4] including: (i) addition of a lithium acetylide; (ii) $Zn(BH_4)_2$-mediated reduction of the produced ynone and (iii) stereoselective reduction (using Red-Al or an hydrogenation with Lindlar catalyst) of the alkyne moiety. Through this sequence, unreported compounds **8**, **11** and **12** were, respectively, obtained in 38, 80 and 48% overall yields. Claisen rearrangement was performed on these compounds giving alkenyl oxazolidines **13**–**20** in good yields and with a high level of stereocontrol since no minor stereoisomer could be detected in the crude reaction product (Scheme 3):



R = CH_2OTBS	**5**	**13** (93%)	**9**	**17** (73%)
R = CH_2OBn	**6**	**14** (98%)	**10**	**18** (83%)
R = Ph	**7**	**15** (55%)	**11**	**19** (39%)
R = TMS	**8**	**16** (93%)	**12**	**20** (79%)

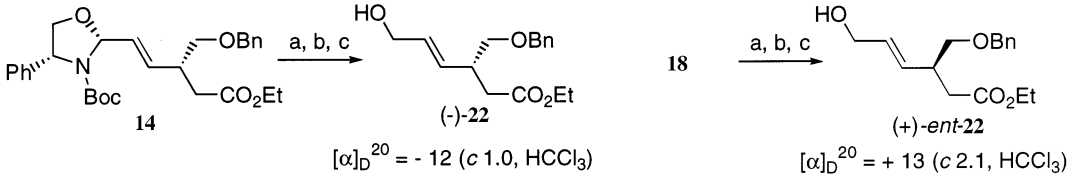
Scheme 3. *Reagents and conditions*: (a) $CH_3C(OEt)_3$, propionic acid (cat.), reflux, 3 h[6d]

This efficient 1,3-chirality transfer is controlled by the classical Zimmerman–Traxler transition state[6] and the configuration of the double bond of the starting alkenol determines the configuration of the newly formed stereocenter. Yet this was verified through the sequence depicted in Scheme 4. Oxidative cleavage of the alkenyl moiety in compound **15**, followed by reduction of the resulting aldehyde ester, gave diol **21**. Determination of the configuration of this known diol[7] by examination of its optical rotation then confirmed the course of the chirality transfer.



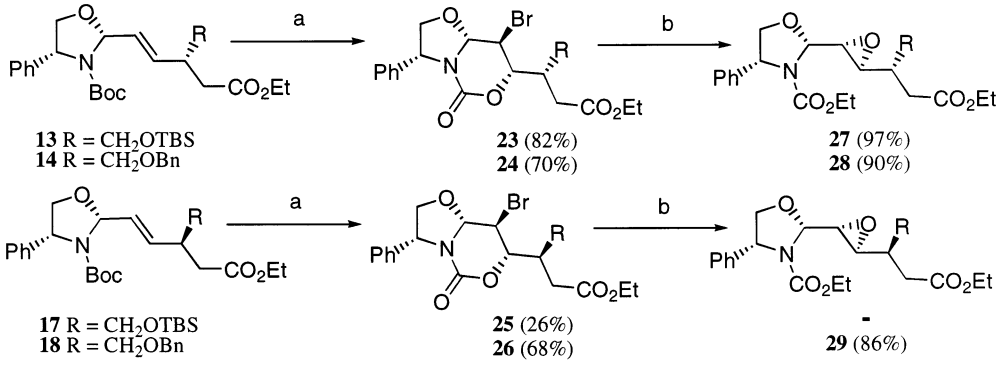
Scheme 4. *Reagents and conditions*: (a) OsO_4 (cat.), $NaIO_4$, THF/H_2O. (b) $NaBH_4$, EtOH, 53% overall yield

The aldehydic moiety masked as an oxazolidine ring could be recovered starting from alkenyl oxazolidines **14** and **18**. To this end, *N*-Boc deprotection and mild hydrolysis gave the corresponding enals that were reduced into allylic alcohols (−)-**22** and (+)-*ent*-**22** (Scheme 5). Enantiomeric excesses of these alcohols were determined by chiral GC analysis (Chirasil-DEX-CB, 160°C, tr of 9.6 and 10.7 mn, respectively, for (−)-**22** and (+)-**22**) and found to be 98 and 93%, respectively. This demonstrates that little or no racemization occurs during these steps.



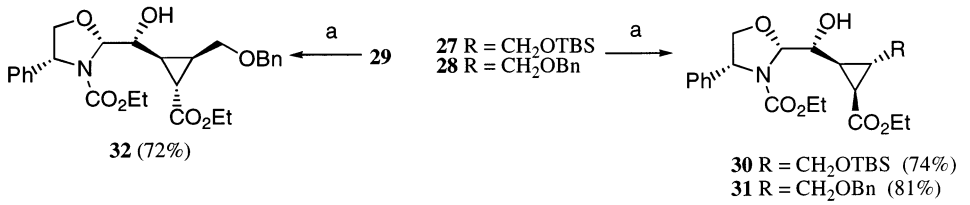
Scheme 5. *Reagents and conditions*: (a) CF_3COOH, DCE. (b) THF, H_2O. (c) $NaBH_4$, $CeCl_3$, $7H_2O$, EtOH, 0°C. **22**: 72%; *ent*-**22**: 52%

We next examined the epoxidation of alkenyl oxazolidines **13**, **14**, **17** and **18** following our previously described procedure[5] that consists of bromocarbamation of the alkene, followed by treatment of the resulting cyclic urethane with sodium ethoxide, as depicted in Scheme 6. As previously reported with similar substrates,[4] the configuration of the stereocenter set by the Claisen rearrangement does not influence the stereochemical course of the bromocarbamation process: urethanes **23**–**26** were in all cases obtained as unique stereoisomers. Relative configurations of these urethanes were deduced from their ^1H NMR data and were in accordance with previous results.[5,8] Epoxides **27**–**29** were then prepared in high yields from the corresponding urethanes.

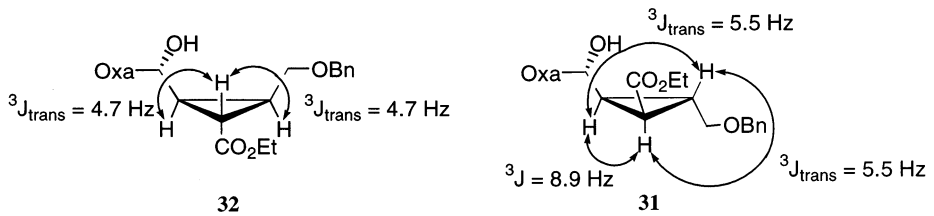


Scheme 6. *Reagents and conditions*: (a) NBS, DME/H_2O. (b) EtONa/EtOH

A further chemical transformation was then studied on these highly functionalized epoxides. The epoxy esters **27**–**29** were transformed into their respective enolates by treatment with LiHMDS; subsequent cyclization of these intermediates gave cyclopropanes **30**–**32** in good yields and in a totally stereoselective way (Scheme 7). The stererochemistry of diastereoisomeric cyclopropanes **30** and **32** was assigned on the basis of the values of the vicinal coupling constants, as depicted in Scheme 8.[9] Clearly, the configuration of the stereocenter created during the Claisen rearrangement governs the stereochemical outcome of this intramolecular cyclopropanation: indeed, the carboethoxy moiety and the R group always show a *trans* relationship in the product, and this is in accordance with previous results.[10]

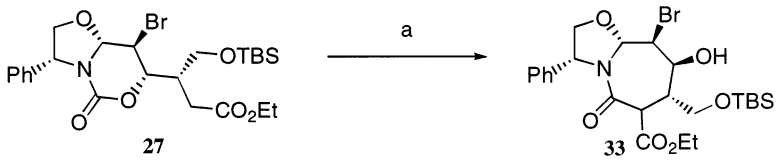


Scheme 7. *Reagents and conditions*: (a) LiHMDS, THF, −50°C



Scheme 8.

Finally, treatment of the bicyclic urethane **23** with LiHMDS was examined: it led to oxazoloazepinone **33** through an intramolecular opening of the urethane ring by the enolate, instead of the expected intramolecular displacement of the bromine atom by the enolate (Scheme 9). In compound **33**, the *cis* relationship between the released alkoxide and the halogen atom prohibits its nucleophilic displacement to give the corresponding epoxide.



Scheme 9. *Reagents and conditions*: (a) LiHMDS, THF, −50°C, 61%

It should be noted that **33** is produced as a single diastereomer in which the configuration of the newly created stereogenic center was not determined.

In conclusion, we have shown that Claisen rearrangements of allylic alcohols linked to a *N*-Boc-oxazolidine ring provide a new access to enantiopure original chirons. Combined with a diastereoselective epoxidation, this methodology allows the synthesis of trisubstituted cyclo-

propanes. This work extends the scope of the use of *N*-Boc-acyloxazolidines in asymmetric synthesis, and further applications of this methodology are under study in our group.

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9. All new compounds gave satisfactory analytical data. Selected data for **30**: R_f: 0.45 (ether/petroleum ether: 60/40); $[\alpha]_D^{20}$ +32 (*c* 1.3, $CHCl_3$); IR (NaCl, film): 3420, 2955, 1680; ^{1}H NMR: 0.00 (s, 6H), 0.83 (s, 9H), 1.07 (t, $J=6.9$, 3H), 1.12 (t, $J=6.9$, 3H), 1.47 (td, $J=9$ and 6, 1H), 1.75 (dd, $J=9$ and 5.2, 1H), 1.86 (broad quint, $J=5.2$, 1H), 3.53 (dd, $J=10.7$ and 5.2, 1H), 3.80 (dd, $J=10.7$ and 4.9, 1H), 3.85–4.09 (m, 6H), 4.21 (dd, $J=8.7$ and 7.2, 1H), 4.93 (t, $J=6.6$, 1H), 5.23 (d, $J=7.2$, 1H), 7.18–7.33 (m, 5H); ^{13}C NMR: −5.2, 14.3, 14.4, 18.4, 22.4, 26.0, 27.0, 28.1, 60.5, 61.0, 62.4, 62.7, 70.7, 73.7, 93.1, 126.6, 127.7, 128.7, 139.7, 156.7, 173; anal. calcd for $C_{26}H_{41}NO_7Si$, C, 61.51; H, 8.14; N, 2.76. Found. C, 61.79; H, 8.57; N, 2.56.
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