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S_N2' Regio and Stereoselective Alkylation of Allylic Mesylates Linked to a *N*-Boc Oxazolidine using Organocuprates

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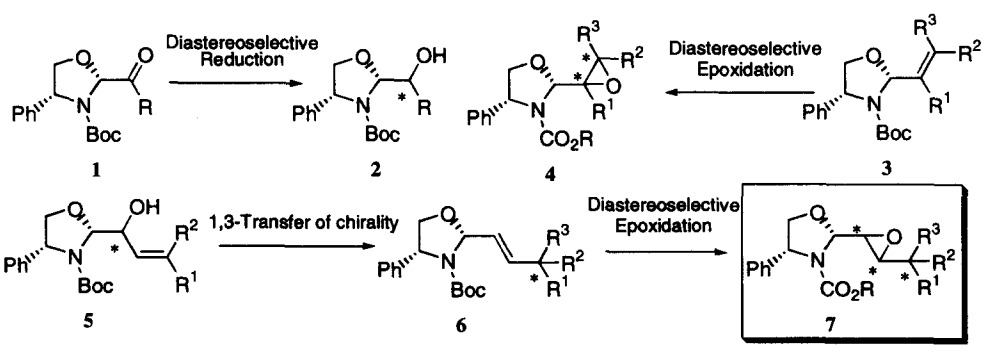
Abstract: *N*-Boc-oxazolidines bearing an allylic alcohol chain were transformed into their mesylate derivatives. A regio and stereoselective 1,3-transfer of chirality was effected on these mesylates during their alkylation by mean of organocuprate additions The resulting *N*-Boc-2-alkenyl oxazolidines undergo an intramolecular bromocarbamoylation with a high level of stereocontrol upon treatment with NBS and afford, after treatment with sodium ethoxide, the corresponding epoxy oxazolidines. The overall methodology allows an efficient control for the formation of three contiguous chiral centers.

Keywords: *Oxazolidines ; Asymmetric synthesis ; Copper and compounds ; Epoxidation.*

The usefulness of *N*-Boc-2-acyl oxazolidines **1** for the asymmetric synthesis of homochiral 1,2-diols,[1] amino acids[2] or piperidinic alkaloids[3] was recently underscored by our group. It was observed, for instance, that diastereoselective reduction of the keto moiety adjacent to the heterocyclic ring occurs very efficiently. On the other hand, *N*-Boc-2-alkenyl oxazolidines **3** undergo a highly efficient epoxidation *via* a two-step sequence involving a treatment with *N*-bromosuccinimide, followed by a sodium alkoxide-mediated cleavage of the resulting cyclic urethane. The produced epoxy oxazolidines **4**, which can be viewed as protected forms of enantiopure epoxy aldehydes turned out to be very valuable synthons.[4] The object of this Letter is to combine the aforementioned methodologies through an effective 1,3-transfer of chirality starting from an allylic alcohol such as **5**. This reaction gives rise to a *N*-Boc-2-alkenyl oxazolidine **6**, which, in turn, could be epoxidized stereoselectively thus allowing the control of three contiguous stereogenic centers on the protected aldehyde **7** (Scheme 1):

Scheme 1



1,3-Transfers of chirality involving allylic alcohols are abundantly described in litterature[5] and are used to introduce most often oxygen, carbon or nitrogen-based functional groups. We first choose to study the scope of this methodology on oxazolidinic substrates with the aim of creating a C-C bond. In this area, the *anti*

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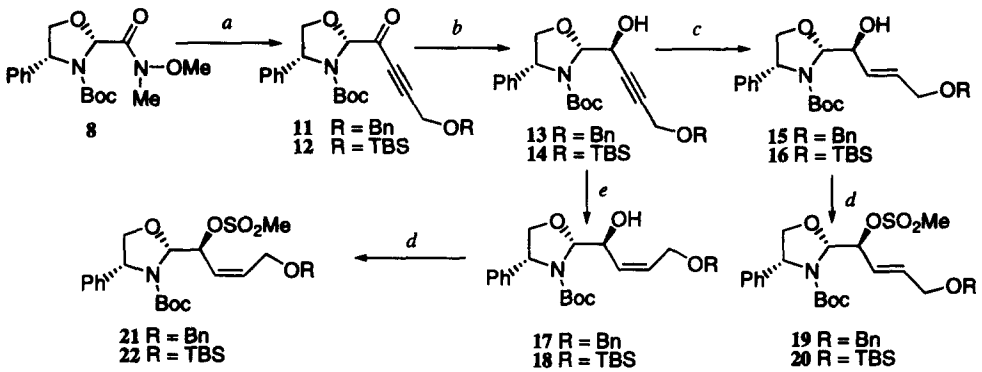
S_N2'reaction of allylic sulfonates with organocopper reagents is a well-known process.[6] Therefore, the *N*-Boc oxazolidines **15-18** bearing a stereodefined allylic alcohol as a C-2 side-chain were synthesized as follows.

Reaction of the previously described Weinreb amide **8**[1] with lithium acetylides **9** or **10** gave the desired 2-acyl oxazolidines **11** and **12** with 77 and 75% respective yields.[7] Stereoselective reduction of these ynones by zinc borohydride in ether at –30°C gave carbinols **13** and **14** (de >95%). The observed selectivities can be rationalized by a chelated model involving coordination of the metal conterion with both oxygen atoms of the C=O moieties.[8] Stereoselective reduction of these carbinols using Red-Al or hydrogenation in the presence of Lindlar catalyst was then effected and afforded respectively stereodefined *E* and *Z* allylic alcohols **15-18** which were converted quantitatively into their methanesulfonyl derivatives **19-22** (Scheme 2):

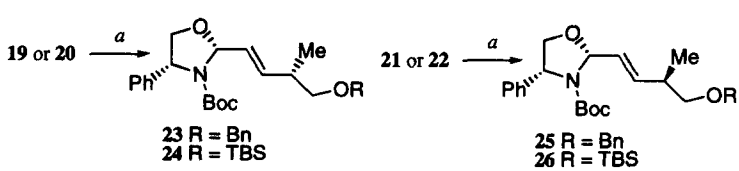
Scheme 2



Reagents and conditions: *a*. Li-≡-CH_2OBn (**9**), or Li-≡-CH_2OTBS (**10**) THF, - 78°C to r .t , 77% (**11**), 75% (**12**). *b*. $Zn(BH_4)_2$, Et_2O, -30°C, 95% (**13**), 96% (**14**). *c*. Red-Al, THF, r.t. ; 80% (**15**), 85 % (**16**). *d*. MsCl, Et_3N, CH_2Cl_2, quant. *e*. H_2, Lindlar catalyst, EtOH, 80% (**17**), 90% (**18**).

Various experimental conditions have been described in order to effect an *anti* S_N2' displacement of allylic mesylates with organocopper reagents. We first choose the Yamamoto's procedure which makes use of higher order zinc cuprate reagent $Me_2Cu(CN)(ZnCl_2)$[6a], but, in our hands, although the stereochemical outcome was efficient, giving only oxazolidine **24** starting from **20**, the yield did not exceed 30%. We eventually found that the simple Gilman reagent Me_2CuLi reacted very efficiently at low temperature to give the corresponding *N*-Boc-2-alkenyl oxazolidines **23-26**, starting from **19-22** (Scheme 3):

Scheme 3

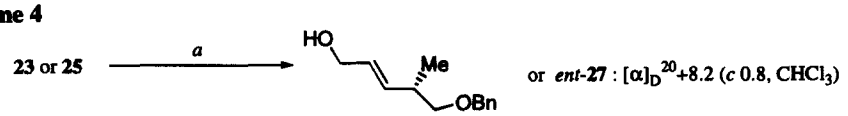


Reagents and conditions: *a*. Me_2CuLi, THF, -78°C, 2h, 78% (**23**), 79% (**24**), 72% (**25**), 70% (**26**).

The *anti* stereochemical outcome of this reaction was secured by a chemical correlation with the known alkenol **27**.[9] With this object, oxazolidines **23** and **26** were treated with trifluoroacetic acid to effect *N*-Boc deprotection. Aqueous hydrolysis released the corresponding aldehyde, which was reduced using sodium

borohydride. Examination of the optical rotation of **27** and *ent*-**27**, obtained respectively from **23** and **25** confirmed the *anti* S_N2' substitution (Scheme 4):

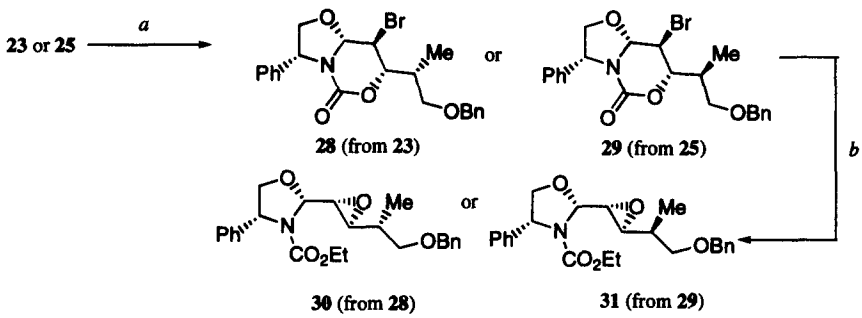
Scheme 4



Reagents and conditions: *a*. (i) CF_3CO_2H, CH_2Cl_2 (ii) THF, H_2O (iii) $NaBH_4$, EtOH, 57% (**27**), 50% (*ent*-**27**).

We next examined the diastereoselective epoxidation of alkenyl oxazolidines **23** and **25** according to our two-step procedure.[4a] Thus, treatment of **23** and **25** with *N*-bromosuccinimide in DME / water mixture induced a regio and stereoselective intramolecular bromocarbamation to give bicyclic urethanes **28** and **29**. It should be noted from a mechanistical point of view that if bromocarbamation of **23** leading to **28** was complete after 10 mn at r.t. the reaction of its diastereoisomer **25** was more sluggish and required 2h to reach completion, suggesting in this case an unfavorable contribution of the stereocenter α to the alkenyl moiety. However, in both cases, the cyclisation proceeded with a total stereoselectivity. Reaction of these bicyclic carbamates with sodium ethoxide in ethanol cleanly opened the urethane to give diastereoisomerically pure epoxy oxazolidines **30** and **31** (Scheme 5):

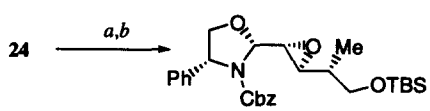
Scheme 5



Reagents and conditions: *a*. NBS, r.t., 1/1 DME/H_2O, 89% (**28**), 70% (**29**). *b*. EtONa/ EtOH, r.t. 83% (**30**), 70% (**31**).

Similarly, in order to examine the compatibility of this process with other protecting groups, it was next carried out starting with **24** and using sodium benzoxide in DMF in the second step in order to introduce a Cbz protecting group on the final oxazolidine ring. It was reported[10] that this protecting group allows a recovery of the protected aldehyde under mild conditions (Scheme 6) :

Scheme 6

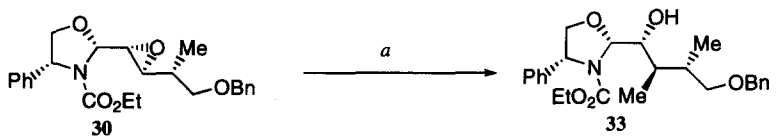


Reagents and conditions: *a*. NBS, r.t., 1/1 DME/H_2O *b*. NaH, $PhCH_2OH$, DMF, r.t. 68 % overall.

Finally, epoxy oxazolidine **30**[11] was reacted with Me_2CuLi in order to determine if the presence of a secondary carbon α to the epoxide moiety did not affect the high regioselectivity usually observed[4a,c] during the nucleophilic opening of these epoxy oxazolidines (i.e. the nucleophile attacks on the epoxide carbon which is

the more distant from the oxazolidine ring). This reaction afforded the expected hydroxy oxazolidine **33** in a 55% yield (66% based on recovered starting product). No trace of the other regioisomer could be detected in the crude reaction mixture (Scheme 7) :

Scheme 7



30 **33**

Reagents and conditions: *a*. Me_2CuLi, THF, r.t. , 12h, 55%.

In conclusion, this efficient 1,3-transfer of chirality considerably enhances the usefulness of *N*-Boc-2-acyl oxazolidines in asymmetric synthesis. Applications of this methodology in synthesis are currently underway in our Laboratory.

References and notes

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7. A reverse quench into a phospate buffer was important to reach good yields. See : Journet, M. ; Cai, D. ; Dimichele, L. ; Larsen, R. D. *Tetrahedron Letters*, **1998**, *39*, 6427-6428.
8. This reduction was previously reported (ref. 2) using sodium borohydride in the presence of $CeCl_3$, 7 H_2O, but the stereoselectivity was lower in this case.
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11. Epoxyde **30** (selected data): ^1H NMR(250 Mhz, $CDCl_3$): 0.94 (d, J = 3, 3H); 1.1 (bs, 3H); 1.74 (hept, J = 6.8, 1H); 2.88 (dd, J = 2.2 and 6.8, 1H); 3.16 (t, J = 2.2, 1H); 3.23-3.42 (m, 2H); 3.90-4.02 (m, 3H); 4.17 (dd, J = 7.1 and 8.6, 1H); 4.32 (d, J = 3, 2H); 4.80 (bt, J = 6.8, 1H); 5.37 (bs, 1H); 7.2-7.4 (m, 10H); $[\alpha]_D^{20}$ – 4.8 (*c* 0.6, $CHCl_3$); Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N 3.40. Found: C, 69.87; H, 7.22; N, 3.35.