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Asymmetric Synthesis *via* Heteroconjugate Addition: Valinol Template as Oxazolidine Heteroolefin *vs* Acetylenic Nucleophiles

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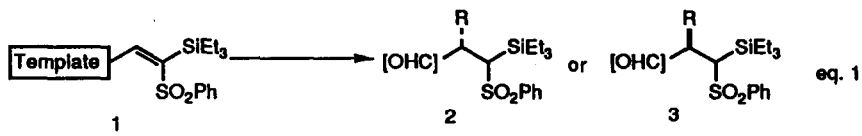
Abstract The diastereoselective C-C bond forming reaction via heteroconjugate addition strategy was expanded for asymmetric synthesis. A valinol derivative was employed as chiral template to induce chelation control in the heteroconjugate addition of alkyls and alkynyls.

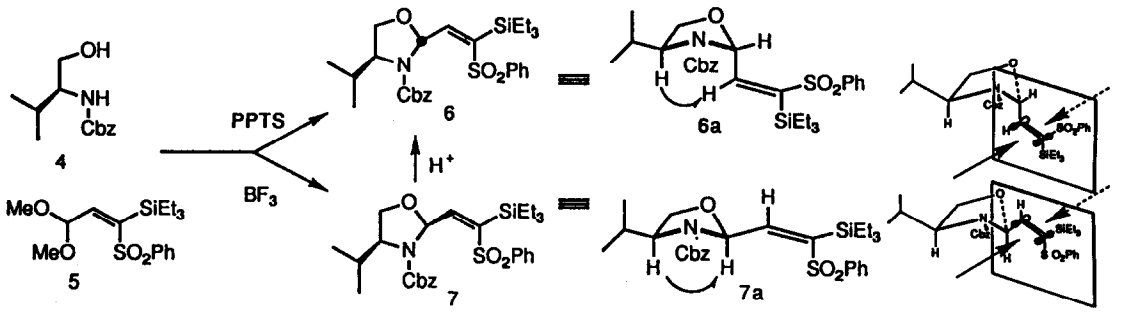
Asymmetric synthesis *via* heteroconjugate addition is an important methodology for constructing molecules with stereochemical complexity. In our previous papers, some sugars or a terpenoid were employed as chiral template,[1] and several examples had been demonstrated in the total syntheses of a polyether, okadaic acid[2] and an ansa-macrolide, maytansine.[3] Recently, we have reported a system exemplified by equation 1; where a camphor derivative was employed as a template in the electrophile **1**.[4] Addition of R-Li or RMgX to **1** should afford the adduct equivalent to **2** or **3** with almost complete stereoselectivity. In this paper, the stereoselective C-C bond forming process giving products of type **2** (α) or type **3** (β) is described with a new chiral template prepared from an amino acid derivative, L-valinol.



Coupling between Cbz-(L)-valinol (**4**) and the heteroolefin dimethyl acetal (**5**) in the presence of acid as catalyst gave the heteroolefins **1** having this specific template in the form of **6** and **7**. The acetal **5** was prepared from the corresponding aldehyde originally derived from propargyl alcohol through sulfinilation, hydrosililation and oxidation.[4] Stereochemistry of the major products in this coupling varied depending upon the kind of acid catalyst; eg. camphorsulfonic acid (CSA) or pyridinium p-toluenesulfonate (PPTS) afforded the *trans* substituted oxazolidine product **6**[5] as the major product (the ratio of **6** and **7** being 10:1), while BF_3-OEt_2 gave the *cis* oxazolidine product **7**[6] (the ratio being 1:3-8)(see Scheme 1). The assignment of *trans* or *cis* configuration was based on the NOE study between the two stereoisomers of oxazolidines. Namely, **6** exhibited NOE between the olefinic proton and H-C-N(*i*Pr) as shown in **6a**. The other isomer **7** showed the effect between the allylic proton and H-C-N(*i*Pr). The conformation in solution is likely to be as those shown in **6a** and **7a** judging from the coupling constant (*ca.* 7.8 Hz in both cases) between the olefinic and allylic protons.[7]

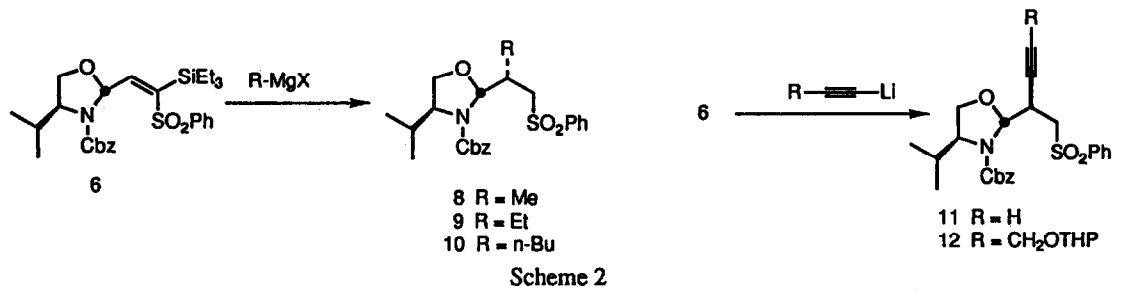
Addition of alkyl Grignard reagents such as MeMgBr, EtMgBr and n-BuMgBr to the *trans* oxazolidine **6** in THF at 0° C and following treatment with n-BuN_4F in CH_3CN afforded only the α products **8**, **9** and **10** in 72%, 74% and 75% yields, respectively (see Scheme 2). Attempted addition of alkynyl Grignard reagents did not occur under the similar condition but occurred only at 0°C to give a 1:1 mixture of diastereoisomers. The

corresponding alkynyllithiums added, on the other hand, to **6** and gave the desilylated products **11** and **12** in 70% and 50% yields, respectively. The β stereochemistry of the acetylenic adducts, **11** and **12**, was unusually opposite to the alkyl α adducts. These results were proven through chemical conversion of the products to common compounds *(vide infra)*.

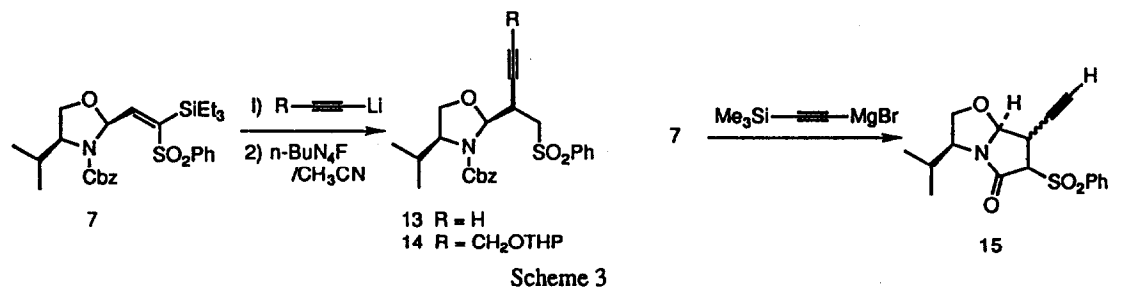


Scheme 1 Fig 1

Addition of carbon nucleophiles in the case of *cis* oxazolidine **7** was a little bit different as shown in Scheme 3 from the case of *trans* isomer **6** (Scheme 2). Employment of alkyl metals (MeLi, EtMgBr etc.) did not give any adduct, but two alkynyl lithiums reacted to produce β isomers such as **13** and **14** in 46% and 61%, respectively (after removing the silyl group). When $Me_3Si\text{-}C{\equiv}C\text{-}MgBr$ was added to **7**, a new γ-lactam **15** (1730 cm^{-1}) was isolated (after n-Bu_4NF treatment) as only the isolable product in 59% yield. The asymmetric carbons in **15** were homogeneous, although the assignment is open. Reactivity of the cis oxazolidine was less than the trans one. The asymmetric carbon induced in the acetylenic adducts from both *cis* and *trans* oxazolidine was identical and the β stereochemistry was proven as shown in Scheme 5.

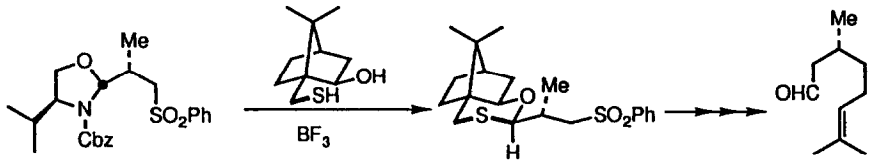


Scheme 2



Scheme 3

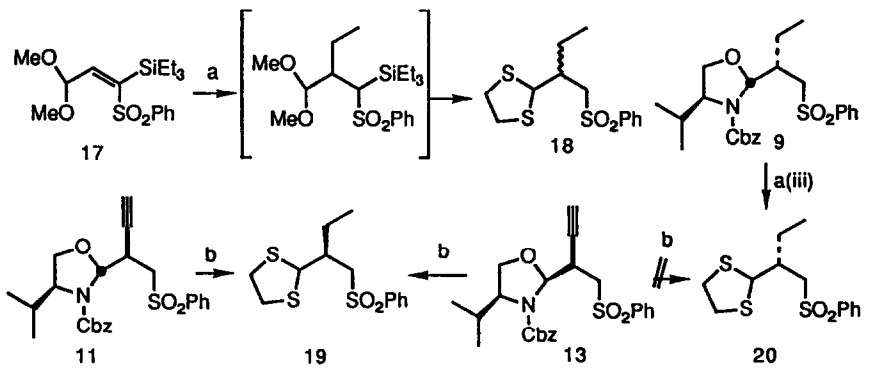
The stereochemistry of the newly formed asymmetric center in the adducts was proven through the following relative transformations. First of all, the methyl adduct **8** was converted into **16**, a camphor hemithioacetal derivative, with the camphorsulfide in the presence of BF_3-OEt_2. The hemithioacetal was identical with the authentic sample (identified *via* ^1H and ^{13}C nmr), which was reported to have been synthesized through heteroconjugate addition to camphor-heteroolefin and further transformed into (-)-citroneral (Scheme 4).[4] Thus, the stereochemical course in the heteroconjugate addition of methyl (most likely other alkyls) to **6** was occurred through the chelation control effected on the Cbz-N face (solid arrow) rather than O face (dotted arrow) in Fig. 1 to have the stereochemistry as shown for **8**, **9**, and **10**.



8 16

Scheme 4

The relative stereochemistry of the acetylenic adducts was compared. Assumption that the mode of alkyl addition of the methyl group in **8** would be identical in the case of ethyl (**9**) in Scheme 2. For comparison, a racemic mixture of the ethyl-adduct dithiane **18** was prepared from **17**. Authentic sample of the α isomer **20** was prepared from **9**. Compounds **20** and **18** (=**19** + **20**) was analyzed with HPLC on a chiral column (Chiralcel OB from JASCO Co. Ltd.) as shown in Fig. 2. Thus, absolute stereochemistry of the ethynyl derivative **11** was proven to be β by reducing the triple bond through catalytic hydrogenation and following conversion of the chiral template into the thioacetal **19**.[8] The ethynyl adduct **13** obtained from the *cis* oxazolidine derivative was assigned to be β by converting into **19** but not **20**. These results led us to conclude that stereochemistry of the acetylenic adducts was β.[9]



Scheme 5

(a) i EtMgBr; ii n-Bu_4NF, iii $(CH_2SH)_2/BF_3$-OEt_2.
(b) i H_2/Pd-C, ii $(CH_2SH)_2/BF_3$-OEt_2.

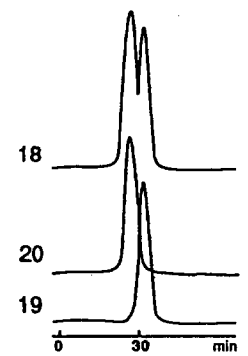
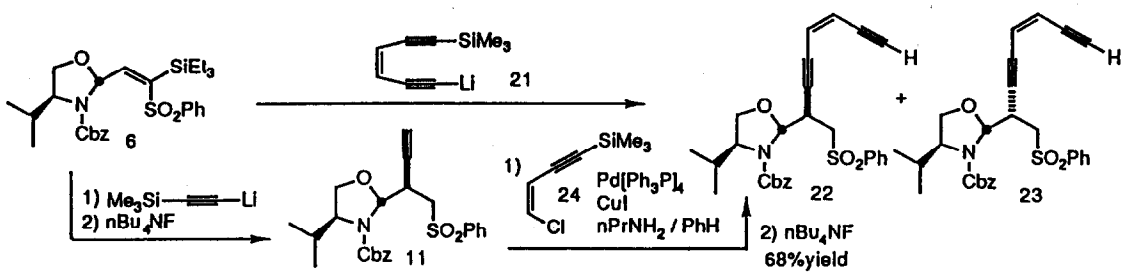


Fig. 2

HPLC on Chiralcel OB (0.5 ml/min)
20% iPrOH-Hexane

The acetylenic nucleophile such as 21[10] was employed as the partial source of enediyne antitumor antibiotic compounds, for example. The product was a mixture of 22 and 23 in a ratio of 3:1. The major component was proven to be β through the following experiments; thus, the lithium trimethylsilyl acetylide adduct (11) was coupled with the vinyl chloride 24 with palladium (0)[11] giving the major product 22 (68% yield).



Most of the addition of nucleophiles to the heteroolefins with above chiral oxazolidines underwent through chelation with N-Cbz as ligand (see Fig. 1). Addition of the acetylide to trans oxazolidine derivative was only the exceptional case. The enediyne group was attached to a chiral center under this method. Further application of this method is expected.

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References and Notes

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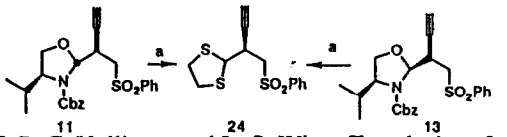
4. M. Isobe, J. Obeyama, Y. Funabashi and T. Goto; *Tetrahedron Lett.*, 29, 4774 (1988).
5. 6 *trans*: (CDCl3 200MHz), δ 0.52-0.72(6H, m), 0.73-0.92(9H, m), 0.97(3H, d, J= 7 Hz), 1.01(3H, d, J= 7), 2.00(1H, CH-iPr), 3.83(2H, ABC, OC*H*2-CH-N), 4.01(1H, m, CH-N), 5.14(2H, AB, JAB= 12, benzylic), 6.32(1H, d, J= 7.8, allylic), 6.68(1H, d, J= 7.8, vinylic), 7.28-7.62(8H, m), 7.86-8.06(2H, m). NOE were measured in C6D6 (200 MHz), δ 0.51-0.72(21 H, m), 1.88(1H, m), 3.31(1H, O-CH2-C*H*-N), 3.63(2H, ABC, OC*H*2-CH-N), 5.16(2H, AB, JAB= 12, benzylic), 6.44(1H, d, J= 7.8, allylic), 6.92-7.42(6H, m), 7.28-7.46(3H, m), 8.04-8.22(2H, m). Similar oxazolidine template was reported by C. Scolastico et al., *J. Org. Chem.*, 53, 1600 (1988) and see the references cited therein.
6. 7 *cis*: (CDCl3 200MHz), δ 0.52-0.84(15H, m), 0.86(3H, d, J= 7), 0.91(3H, d, J= 7), 2.36(1H, br), 4.00(3H, s, OC*H*2-CH-N), 5.14(2H, AB, JAB= 12), 7.32-7.61(8H, m), 7.94-8.04(2H, br).
7. Me-adduct (8): δ 1.07(3H, d, J= 6.4 Hz), 2.99(1H, dd, J= 14.4, 8.9), 3.33(1H, dd, J= 14.4, 4.5). Et-adduct (9): δ 0.77(3H, t, J= 7.2), 3.10(1H, dd, J= 15, 6), 3.36(1H, dd, J= 15, 6.5). Acetylene adduct (11), δ 1.96(1H, d, J= 2.5 Hz), 3.36(2H, d, J= 6); (13), δ 1.98(d, J= 2.6).
8. The ethanedithiol (19): δ 0.93(3H, d, J= 7.2Hz), 3.54(1H, dd, J= 14.4, 3.6), 4.90(1H, d, J= 4.3).
9. The results were also confirmed by converting both of 11 and 13 into the identical acetylenic dithiane derivative as shown below.



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