Pergamon

Tetrahedron Letters 39 (1998) 2649–2650

TETRAHEDRON
LETTERS

The Aza-[2,3]-Wittig Sigmatropic Rearrangement of Z(C)-Alkenes

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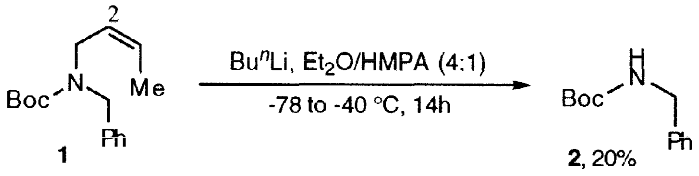
Received 7 January 1998; revised 22 January 1998; accepted 23 January 1998

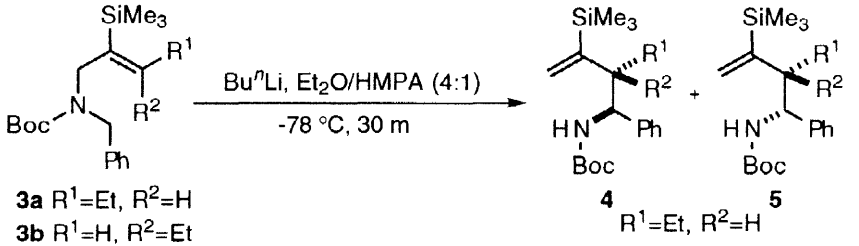
Abstract: The aza-[2,3]-Wittig sigmatropic rearrangement of *Z*(C)-alkenes can be achieved through the use of a trimethylsilyl anion stabilising group. The major diastereoisomer complements previous results and allows access to each diastereoisomer of the homoallylic amine products. A transition state model is described which accounts for the diminished diastereoselection compared to *E*-alkyl substrates.

In our preliminary communication regarding the aza-[2,3]-Wittig sigmatropic rearrangement of crotyl amines we reported that *N*-Boc protected *Z*-crotyl amine **1** did not rearrange under our standard reaction conditions.[1] Only the elimination product **2** (equation 1) was isolated. Prompted by a recent report that the same Z-crotyl benzyl amine, protected as its phosphoramide, does undergo the aza-[2,3]-Wittig rearrangement (90% yield, ds ratio of 1:1)[2] we wish to communicate our studies with these types of substrates.



(1)

The oxy [2,3]-Wittig process is extremely facile at sub-ambient temperatures and inherently diastereoselective. Nitrogen is less electronegative than oxygen so the thermodynamic driving force for the corresponding aza process is diminished. Our solution to this problem was to incorporate a trialkylsilyl group at the central C-2 vinylic carbon atom of our allylic amine precursors. This has the dual effect of lowering the energy of the transition state and controlling the sense of diastereoselection.[3,4] For example substrate **3a** gives major diastereoisomer **4** (equation 2) in high yield. As we are developing this method for the synthesis of unnatural α- and β-amino acids it is essential that we can synthesise the alternate diastereoisomer **5** (R^1=Et, R^2=H). This should be possible by using the other alkene diastereoisomer in our rearrangement precursors such as **3b**.[5] We believe that the elimination of **2** (equation 1) could be attributed to the transition state being too high in energy resulting in the intervention of destructive pathways. Incorporation of a silyl C-2 substituent could electronically facilitate the rearrangement and result in the desired diastereoisomer **5** being formed.



From **3a** 92%, ds ratio of **4**:**5** = 18:1

(2)

The Z(C) relationship in the rearrangement precursor **3b** was established by the addition of a lower order cuprate to trimethylsilylacetylene **6** and quenching with iodine to give the vinyl iodide **7** in 61% yield.[6] A range of other cuprates can be used in this step which furnish alternative precursors. Rearrangement precursor **3b** was

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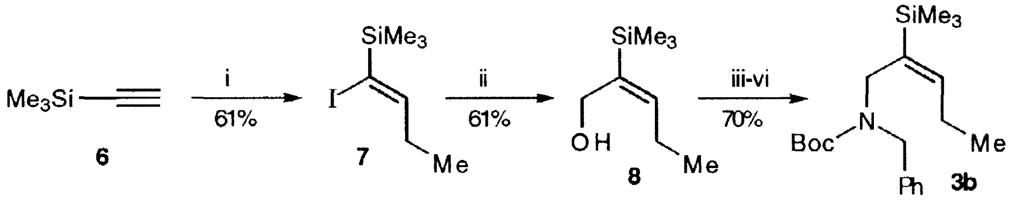
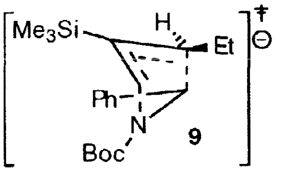
PII: S0040-4039(98)00229-9

prepared in 70% yield by our standard manipulations from the alcohol **8**, itself formed from **7** *via* lithiation and treatment with monomeric formaldehyde[7] in 61% yield (Scheme 1). The *Z*(C) geometry of the alkene was verified by one dimensional nOe studies which amongst other signals showed a 6.6% enhancement of the vinyl proton upon irradiation of the trimethylsilyl protons.



Scheme 1 i) 0.7 equiv. EtMgBr, 0.78 equiv CuBr, 0.78 equiv. $(EtO)_3P$, Et_2O, -20 to 0 °C, 2h then 0.85 equiv. I_2, THF/HMPA (~7:1), -45 °C, 30 m, then rt, 14 h; ii) 2.1 equiv Bu^tLi, Et_2O, -78 °C, 1h then excess H_2CO, THF, -78 °C, 1 h, then rt, 61%; iii) 1.1 equiv. CH_3SO_2Cl, 1.2 equiv. Et_3N, CH_2Cl_2, 0 °C, 1 h; iv) 0.7 equiv. $(Boc)_2NH$, 2.6 equiv. $CsCO_3$, 0.03 equiv. LiI, butanone, 80 °C, 14 h 79%; v) 1.9 equiv. CF_3CO_2H, CH_2Cl_2, rt, 1 h, 95%, vi) 1.2 equiv KH, THF, 0 °C, 2h; 1.2 equiv. $PhCH_2Br$, rt, 14 h, 93%.

For the successful rearrangement of **3b** the use of HMPA as cosolvent (20%) and warming to -40 °C for 14 hours was required. These conditions resulted in a 62% yield (along with 20% recovered starting material) of the rearranged product with a diastereoselection of 3:1 in favour of diastereoisomer **5** (R^1=Et, R^2=H). The yield is testamount to the difficulty we have found in rearranging *Z*(C) substituted alkenes with respect to the *E*(C) systems. The lower diastereoselection in comparison to the *E*(C) series is attributed to competing steric interactions present in each of two possible transition states **9** and **10**. The pseudo 1,3 diaxial interaction between the phenyl ring and trimethylsilyl group in **9** would appear to be more important than the 1,2 interaction between the phenyl ring and ethyl substituent in **10** in controlling the sense of diastereoselection in this rearrangement.



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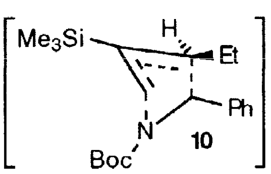

10

We have shown that the silicon assisted aza-[2,3]-Wittig rearrangement can furnish each diastereoisomer of the product homo-allylic amines **4** or **5** in good yield. As the cuprate chemistry used to synthesise **3b** is versatile a range of stereodefined homoallylic amines can now be prepared. Further synthetic studies utilising this rearrangement and enantioselective variants are underway and will be reported in due course.

ACKNOWLEDGEMENTS

We would like to thank the University of Sheffield, the Erasmus exchange programme (PD), the EPSRC for the award of an earmarked studentship (DCS), Zeneca Agrochemicals for the award of a CASE studentship (MES), Zeneca and Pfizer for additional unrestricted financial support.

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