Tetrahedron: Asymmetry Vol. 4, No. 4, pp. 613-616, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00

Regioselective SN' Allylic Substitution versus 1,4-Addition : Asymmetric Induction with Oppolzer's Chiral Sultam.

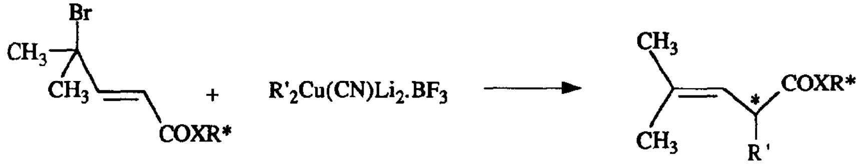
Christian Girard, Gérard Mandville and Robert Bloch*

Laboratoire des Carbocycles (Associé au CNRS), Institut de Chimie Moléculaire d'Orsay,
Bât. 420, Université de Paris-Sud, 91405 ORSAY (France)

(*Received in UK* 22 *January* 1993)

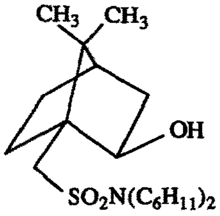
***Abstract** : The reaction of organocuprate reagents $R'_2Cu(CN)Li_2.BF_3$ with γ-bromo conjugated N-acyl sultams derived from camphor gave, with high regio- and stereoselectivity, compounds arising from a SN' allylic substitution. Reductive removal of the chiral auxiliary furnished α-substituted β,γ-unsaturated alcohols of excellent enantiomeric purity.*

The introduction of a new asymmetric centre at the α-position of a carbonyl group is a useful reaction in organic synthesis which has been intensively investigated these last few years. Most of the reported efficient methods consist of the alkylation of chiral metal enolates (1,2). However highly diastereoselective α-alkylations, via 1,3-chirality transfer, of optically active γ-mesyloxy-α,β-enoates (3,4) or of cyclic sulfites and carbonates of γ,δ-dihydroxy-α,β-unsaturated esters (5), have been recently developed, using cuprate reagents. We have recently shown that highly regioselective SN' substitutions can be realized by reaction of organocopper reagents $R'_2Cu(CN)Li_2.BF_3$ with γ-bromo-α,β-unsaturated esters, leading to the introduction of a nucleophilic substituent at the α-position of the ester group (6). We report here the first examples of the enantioselective version of such SN' reactions in which the asymmetric induction is due to a chiral auxiliary(7).

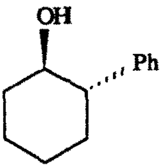


X = O, N

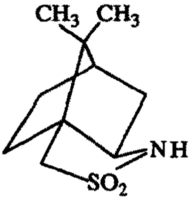
First we explored the enantioselective allylic substitution of γ-bromo-α,β-unsaturated esters derived from the chiral alcohols **1** or **2**. However, although the regioselectivity was excellent (no compound arising from 1,4-addition or SN allylic substitution could be detected), the diastereofacial selectivities observed during the approach of the cuprate reagents were only poor to fair (de = 30 to 75%). In order to achieve higher enantioselectivities we next tried as the chiral auxiliary, Oppolzer's chiral sultam **3**, derived from D-camphorsulfonic acid (8,9).



1

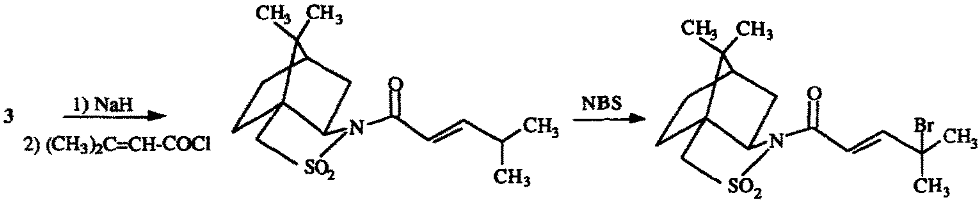


2



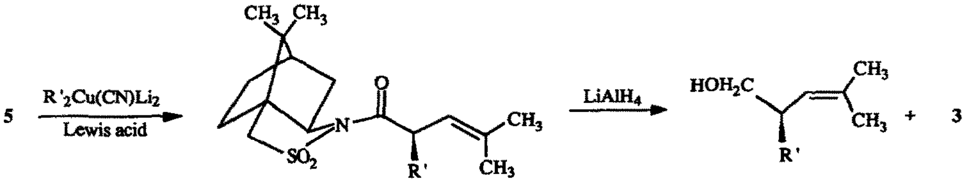
3

Deprotonation of D-camphor sultam **3** with NaH and subsequent acylation with 2-methyl-3-pentenoic acid chloride gave the conjugated N-acyl sultam **4** (80%, mp 161°C) which was brominated by N-bromosuccinimide to afford the allylic bromo compound **5** (80% after recrystallization, mp 146°C).



4 **5**

The products obtained by reaction of the γ-bromo conjugated acyl sultam **5** with the cuprate $R'_2Cu(CN)Li_2$ in the presence of a Lewis acid are gathered in Table 1. In all cases highly regioselective and diastereoselective substitutions α to the carbonyl group were observed since no other regioisomer or diastereomer could be detected by ^1H NMR spectroscopy. Reduction of the substituted products **6** by lithium aluminum hydride gave rise to the optically active β,γ-unsaturated alcohols **7** with regeneration of the chiral sultam 3. The excellent diastereofacial selectivities (de > 95%) of the SN' allylic substitutions have been confirmed by the excellent enantiomeric purities found for the alcohols **7**.



6(a-d) **7(a-d)**

Table 1. Synthesis of optically active 2-substituted-4-methyl-3-pentenols **7**

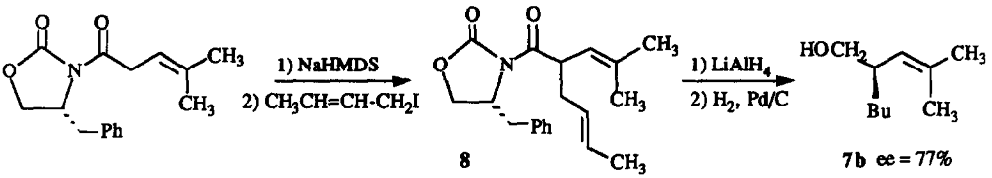
Diastereoselective SN' allylic substitution			Reduction			
Reagent	Product	Yield % [a]	Product	Yield % [a]	ee % [b]	absolute configuration
$Me_2Cu(CN)Li_2.BF_3$ [c]	**6a** ($R = CH_3$)	88	**7a**	80	98	R
$Bu_2Cu(CN)Li_2.BF_3$	**6b** (R = nBu)	96	**7b**	85	98	R
$Bu_2Cu(CN)Li_2$, $EtAlCl_2$	**6b**	82	**7b**	85	98	R
$(CH_2{=}CH)_2Cu(CN)Li_2.BF_3$	**6c** (R = vinyl)	72	**7c**	73	96	R
$Ph_2Cu(CN)Li_2.BF_3$	**6d** (R = Ph)	90	**7d**	83	95	S

[a] Yields are given for pure compounds isolated by column chromatography on silica gel.

[b] Enantiomeric excesses have been determined by gas chromatography using a capillary chiral cyclodextrin B column.

[c] A similar π-face differenciation was observed using two equivalents of $BF_3.Et_2O$.

The (R) absolute configuration of **7a** and **7b** have been assigned by comparison (retention times on chromatography and signs of optical rotation) with the same alcohols obtained by the methodology of Evans (10) starting from R-(+)-4-benzyl-2-oxazolidinone (11). However although this methology gave **7a** with a good yield and excellent enantiomeric purity (ee = 98%), it was impossible to obtain **7b** directly since we were unable to alkylate **8** with the unreactive butyl iodide. The (R)-alcohol **7b** has been obtained by the following sequence of reactions :

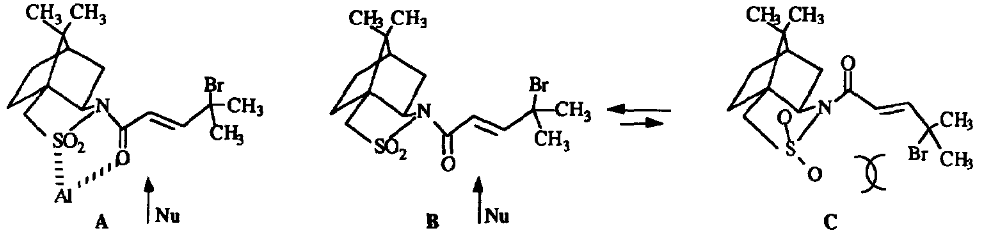


8

7b ee = 77%

The absolute configurations of **7c** and **7d** have been attributed by analogy considering both the sign of the optical rotations and the mode of formation.

In order to rationalize the observed asymmetric induction, we assumed two preferred transition states, depending on the Lewis acid used, **A** ($EtAlCl_2$) or **B** (BF_3), both involving a "syn" conformation for $SO_2/C{=}O$. The transition state **A** is stabilized by chelation with the Lewis acid (12) and the transition state **B** is preferred to **C** in order to avoid a steric repulsion betweeen the SO_2 group and substituents of the quaternary γ-C atom (13). Addition of the organocopper reagent takes place from the less hindered face of the double bond (bottom side attack).



A **B** **C**

In conclusion, we have shown that highly diastereoselective SN' allylic substitutions of γ-bromo-α,β-unsaturated carbonyl compounds can be induced by Oppolzer's chiral auxiliaries. The generalisation and applications of this reaction are currently underway in our laboratory.

References and Notes

(1) For a review see Evans, D.A. in Asymmetric Synthesis, Morrison, J.D. Ed. Academic Press, New York **1984**, vol. 3, p. 1.

(2) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30* , 5603 and references there in.

(3) Ibuka, T.; Yamamoto, Y. *Synlett* **1992**, 769.

(4) Yamamoto, Y.; Chounan, Y.; Tanaka, M.; Ibuka, T. *J. Org. Chem.* **1992**, *57*, 1024.

(5) Kang, S.K.; Park, Y.W.; Lee, D.H.; Sim, H.S.; Jeon, J.H. *Tetrahedron : Asymmetry* **1992**, *3*, 705.

(6) Girard, C.; Romain, I.; Ahmar, M.; Bloch, R. *Tetrahedron Lett.* **1989**, *30*, 7399.

(7) One example of a similar enantioselective SN' substitution by Li-t-Butylphenylacetate has been very recently reported : Sevin, A.F.; Seyden-Penne, J.; Boubekeur, K. *Tetrahedron* **1992**, *48*, 6253.

(8) For reviews on camphor derivatives in asymmetric synthesis see : a) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969. b) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241.

(9) For recent uses of the sultam **3** as chiral auxiliary, see a) Wu, M.J.; Wu, C.C.; Lee, P.C. *Tetrahedron Lett.* **1992**, *33*, 2547. b) Zoretic, P.A.; Weng, X.; Biggers, C.K.; Biggers, M.S.; Caspar, M.L. *Tetrahedron Lett.* **1992**, *33*, 2637. c) Yokomasou, T.; Iwasawa, H.; Shibuya, S. *J. Chem. Soc. Chem. Commun.* **1992**, 728. d) Kim, B.H; Curran, D.P. *Tetrahedron* **1993**, *49*, 293.

(10) Evans, D.A.; Ennis, M.D.; Mathre, D.J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(11) Evans, D.A.; DiMare, M. *J. Am. Chem. Soc.* **1986**, *108*, 2476.

(12) Oppolzer, W.; Mills, R.J.; Pachinger, W.; Stevenson, T. *Helv. Chim. Acta* **1986**, *69*, 1541.

(13) Oppolzer, W.; Schneider, P. *Helv. Chim. Acta* **1986**, *69*, 1817.