Pergamon

Tetrahedron Letters, Vol. 37, No. 17, pp. 3055-3058, 1996
Copyright © 1996 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4039/96 $15.00 + 0.00

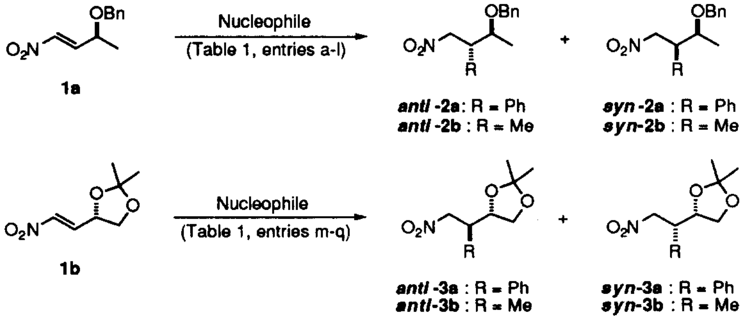
S0040-4039(96)00468-6

Stereoselective Conjugate Addition of Carbon Nucleophiles to Chiral *(E)*-Nitroalkenes Bearing a γ-Stereocenter. Origins of the Observed *anti* Selectivity.

Mirari Ayerbe[a], Iñaki Morao[a], Ana Arrieta[a], Anthony Linden[b]
and Fernando P. Cossío[a,*]
[a]Kimika Fakultatea, Euskal Herriko Unibertsitatea, P.K. 1072, 20080 San Sebastián-Donostia, Spain.
[b]Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057, Zürich, Switzerland.

Abstract. The reaction between different organometallic carbon nucleophiles and chiral (*E*)-nitroalkenes has been studied. *Anti* selectivities have been observed in all cases. SCF-MO calculations suggest that the observed stereocontrol relies on the *anti* disposition of a donor group (methyl or hydrogen) with respect to the C-C bond in formation. Copyright © 1996 Elsevier Science Ltd

Conjugate addition of organometallic carbon nucleophiles to electron deficient olefins has proven to be a very useful method for the synthesis of a wide range of chemically significant structures[1]. In particular, the asymmetric version of this reaction has received great attention[2]. Nitroalkenes are among the most convenient substrates for this reaction[3], since the electron withdrawing nitro group induces a high electrophilic character to the olefinic moiety, and the nitro group is in turn very versatile[4]. However, the number of reports dealing with the interaction of chiral nitroalkenes with achiral nucleophiles is scarce[5]. In this paper we report our experimental and computational results on the 1,2-asymmetric induction observed in the reaction of nitroalkenes[6] **1a,b** with several organometallic nucleophiles (Scheme 1). We have collected in Table 1 the most significant data among the different metals and reaction conditions tested. From these results it can be concluded that nitroalkene **1a** is quite efficient as Michael acceptor both in terms of chemical yield and



Scheme 1

stereoselectivity. For example, reaction of **1a** with phenyl lithium takes place with a diastereomeric excess of 60% (Table 1, entry c). This stereocontrol was slightly improved by using an excess of lithium chloride (entry d). However, the best result for **1a** was obtained using lithium diphenylcuprate as the nucleophile (entry e). The stereoselectivity of methyl nucleophiles was comparatively lower (entries g-l). Nitroalkene **1b** induces in general a lower stereocontrol, and the best result was again obtained using lithium diphenyl cuprate (entry n) and lithium dimethyl cuprate (entry q). Therefore, according to our results, the best reagents for this kind of transformation appear to be lithium organocuprates of type LiR_2Cu. The structure of compound ***anti*-2a** (relative configuration only) was stablished by X-Ray diffraction analysis[7] (Figure 1), and the stereochemistry of the remaining products[8] was elucidated by ^{1}H-NMR analysis of the crude reaction mixtures. The coupling constants between the C$_\beta$-H and C$_\gamma$-H protons were higher for the *anti*-isomers, as was expected from the more populated conformations of these stereoisomers. The chiral integrity of product *anti*-**3a** and therefore that of nitroalkene **1b** was found to be ≥98% on the basis of ^{19}F-NMR experiments with the corresponding Mosher derivatives[9].

Table 1. Reaction of (*E*)-nitroalkene **1a,b** with several nucleophiles.

Entry	Product	Reagent[a]	Time (h)	Yield (%)[b]	*anti:syn*[c]
a	**2a**	PhMgBr (1.2)	1.5	70	77:23
b	**2a**	$PhMgBr/CeCl_3$ (2.0)	4	75	83:17
c	**2a**	PhLi (1.5)	3	90	80:20
d	**2a**	PhLi/LiCl (1.5:5)	3	95	85:15
e	**2a**	PhLi/CuI (3.2:1.6)	2.5	86	91:9
f	**2a**	PhLi/CuCN (5.1:2.6)	6	90	77:23
g	**2b**	MeMgBr (2.0)	3	90	59:41
h	**2b**	$MeMgBr/CeCl_3$ (2.0)	20	71	57:43
i	**2b**	MeLi (1.5)	5	76	76:24
j	**2b**	MeLi/LiBr (1.5)	7	81	70:30
k	**2b**	MeLi/CuI (3.2:1.6)	7	60	65:35
l	**2b**	$MeLi/Me_2.CuBr$ (1.0:1.0)	7	13	55:45
m	**3a**	PhLi (1.5)	2	90	50:50
n	**3a**	PhLi/CuI (3.2:1.6)	2.5	95	91:9
o	**3b**	MeLi (1.5)	6	38[d]	60:40
p	**3b**	MeLi.LiBr (1.5)	7.5	30[d]	50:50
q	**3b**	MeLi/CuI (3.2:1.6)	7.5	90	72:28

[a] Numbers in parentheses are the relative quantities with respect to 1 eq. of substrate. All runs were conducted at -78°C under an argon atmosphere. [b] Yields of products 2 and 3 after isolation by flash chromatography (Silicagel 230-400 mesh, AcOEt/Hx 1:20). [c] Isomeric ratio determined by 300 MHz ^{1}H-NMR on the crude reaction mixture. [d] Formation of addition products over the nitro group was observed.

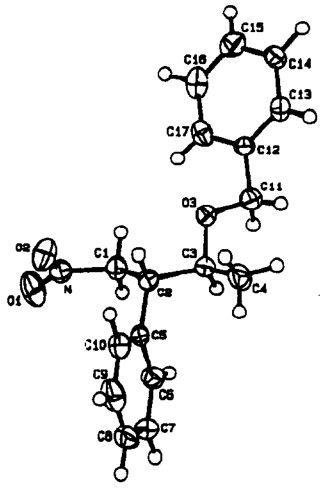


Figure 1. X-Ray structure of compound ***anti*-2a**

The origins of the stereochemical outcome in the reaction between disubstituted (*E*)-Michael acceptors and nucleophiles are not clear at present, and several models have been developed[10,11]. Most of these models rely on qualitative arguments based on the preferred conformations of the acceptors and on sterical models. Dorigo and Morokuma[11], however, have proposed a very interesting model for the conjugate addition of monomeric methyl-copper to (*E*)-2-pentenal. According to their proposal, an electron-donating group in the *anti* position of the corresponding TS (see Figure 2) is favored because it stabilizes the enal fragment.This effect is motivated by the strong interaction between the metal and the carbonyl group.

Table 2. Energies of the transition structures **TS1-12** computed at the RHF/PM3 level[a,b] (see Figure 2)

TS	*anti*	*in*	*out*	L	Product	ΔH_f	ΔG^o
TS1	OH	H	Me	none	*anti*	7.0	-29.6
TS2	OH	Me	H	none	*syn*	6.1	-29.5
TS3	Me	H	OH	none	*syn*	6.3	-30.4
TS4	Me	OH	H	none	*anti*	5.0	-34.0
TS5	H	OH	Me	none	*syn*	4.8	-31.2
TS6	H	Me	OH	none	*anti*	3.8	-31.8
TS7	OH	H	Me	H_2O	*anti*	-124.7	-170.5
TS8	OH	Me	H	H_2O	*syn*	-126.0	-171.5
TS9	Me	H	OH	H_2O	*syn*	-125.9	-171.9
TS10	Me	OH	H	H_2O	*anti*	-127.6	-173.0
TS11	H	OH	Me	H_2O	*syn*	-129.2	-174.8
TS12	H	Me	OH	H_2O	*anti*	-129.4	-175.5

[a] All energies are given in kcal/mol. [b] All the saddle points were fully optimized using the eigenvector-following algorithm and were characterized by harmonic analysis, showing one imaginary frequency corresponding to formation of the $C_{Nu}\cdots C_\beta$ bond.

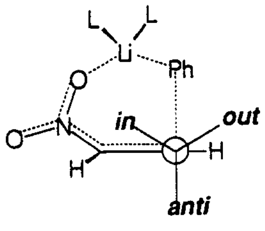


Figure 2

Given that the reaction of phenyl lithium with **1a** takes place with remarkable stereoselectivity and that the preference for the *anti* isomer is the maintained in the experiments reported in Table 1, we have studied the reaction between monomeric phenyl lithium and (S)-(*E*)-3-hydroxy-1-nitro-1-butene using the semiempirical Hamiltonian PM3[11] at RHF level of theory. The twelve possible six-membered ring[12] TSs depicted in Figure 2 have been located and characterized by harmonic analysis. The heats of formation and the standard free energies for **TS1-12** have been collected in Table 2. We have found that the minimum energy TSs are those in which donating groups (hydrogen or methyl) are *anti* with respect to the incoming phenyl group. For non-solvated lithium atoms the most stable TSs are **TS6** (hydrogen *anti*) if we consider the heat of formation, and **TS4** (methyl *anti*) when the standard free energies are considered. Both of these TSs correspond to formation of the *anti* isomers, in agreement with our experimental results. Tetracoordination of lithium (**TS7-12**, see Table 2) results in a lower Lewis acid coordination between the metal and the nitro group and a higher C_{Nu}...C_β bond distance (see Figure 3). In this case, **TS12** (hydrogen *anti*) is the saddle point of lowest energy, particularly in terms of standard free energy (see Table 2). This saddle point also leads to the formation

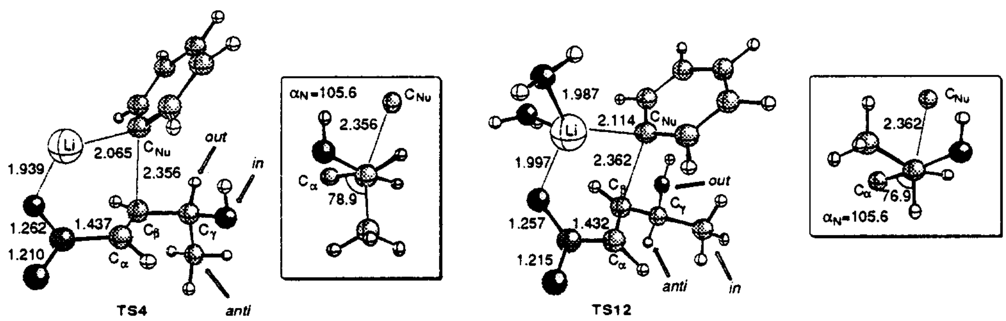


Figure 3. RHF/PM3 fully optimized structures of saddle points **TS4** and **TS12**. Distances and angles are given in Å and deg., respectively. The insets correspond to views above the C_α-C_β bond. α_N is the $C_{Nu}\cdots C_\beta$-C_γ bond angle.

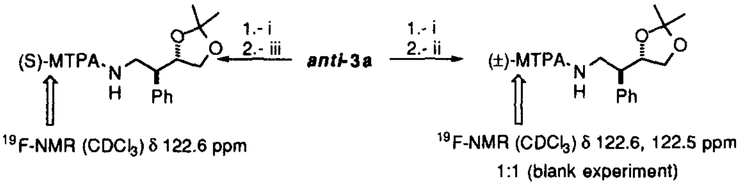
of the *anti* stereoisomer. Therefore, our calculations suggest that the observed preference for the *anti* stereoisomers is not related to allylic strain or Felkin-Ahn geometries, but to transition structures in which donating groups (methyl and, preferably, hydrogen[14]) are *anti* with respect to the carbon-carbon bond being formed (see Figure 3).

Acknowledgement. The present work has been supported by the Universidad del País Vasco-Euskal Herriko Unibertsitatea (Project UPV 170.215-EA156/94) and by the Gobierno Vasco-Eusko Jaurlaritza (Project GV 170.215-0119/94).

References and Notes

1. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992.
2. Rossiter, B.E.; Swingle, N.M. *Chem. Rev.* **1992**, *92*, 771.
3. See for example: (a) Jubert, C.; Knochel, P. *J.Org.Chem.* **1992**, *57*, 5431. (b) Pecunioso, A.; Menicagli, R. *J.Org.Chem.* **1989**, *54*, 2391. (c) Bartoli, G.; Bosco, M.; Sambri, L.; Marcantoni, E. *Tetrahedron Lett.* **1994**, *35*, 8651. (d) Schäfer, H.; Seebach, D. *Tetrahedron* **1995**, *51*, 2305. (e) Lequeux, T.P.; Percy, J.M. *Synlett.* **1995**, 361. (f) Rowley, M.; Leeson, P.D.; Williams, B.J.; Moore, K.W.; Baker, R. *Tetrahedron* **1992**, *48*, 3557.
4. Barrett, A.G.M.; Grabosky, G.G. *Chem.Rev.* **1986**, *86*, 751.
5. For recent examples, see: (a) Barrett, A.G.M.; Lebold, S.A. *J.Org.Chem.* **1990**, *55*, 3853. (b) Barrett, A.G.M.; Rys, D.J. *J.Chem.Soc. Perkin Trans. I* **1995**, 1009. (c) Jackson, R.F.W.; Palmer, N.J.; Wythes, M.J.; Clegg, W.; Elsegood, M.R.J. *J.Org.Chem.* **1995**, *60*, 6431. (d) Jackson, R.F.W.; Palmer, N.J.; Wythes, M.J. *Tetrahedron Lett.* **1994**, *35*, 7433.
6. For the preparation of (*E*)-nitroalkenes **1a,b** see Ayerbe, M.; Cossío, F.P. *Tetrahedron Lett.* **1995**, *36*, 4447.
7. Full details of the crystal structure investigation of ***anti*-2a** have been deposited at the Cambridge Crystallographic Data Centre, Lensfield Road, UK.
8 ***anti*-2a**: m.p.: 98-100°C (from diethyl ether in hexanes); $[\alpha]_{25}^{D}$= +118.1 (c=0.2, CH_2Cl_2); IR (KBr) 1547, 1577 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.41-7.13 (m, 10H); 5.04-4.95 (dd, J=12.8 Hz, J'= 5.3 Hz, 1H); 4.40 (d, J= 11.5 Hz, 1H). 3.81-3.68 (m, 1H), 3.60-3.49 (m, 1H), 1.10 (d, J= 6.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 128.3, 127.9, 127.5, 127.2, 75.9, 75.7, 70.2, 50.4, 16.9.

   ***anti*-3a**: m.p.: 68-70°C (from diethyl ether in hexanes); $[\alpha]_{25}^{D}$= -43.1 (c=0.5, CH_2Cl_2); IR (KBr) 1548, 1378 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.37-7.21 (m, 5H), 4.96 (dd, J= 12.8 Hz, J'= 4.9 Hz, 1H), 4.68 (dd, J= 5.8 Hz, J'= 10.0 Hz, 1H), 4.26 (dt, J= 9.8 Hz, J'= 5.8 Hz, 1H), 3.80 (dd, J= 8.8 Hz, J'= 6.0 Hz, 1H), 3.62 (dd, J= 8.8 Hz, J'= 5.7 Hz, 1H), 3.56 (td, J= 9.8 Hz, J'= 4.9 Hz, 1H), 1.48 (s, 3H), 1.35 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ 136.3, 129.2, 128.4, 127.9, 110.4, 78.3, 77.0, 68.1, 48.9, 26.8, 25.4.
9. These experiments are summarized in the following scheme:



   Reagents and conditions: i: $LiAlH_4$ (4.0 eq), Et_2O, gentle reflux, 5 h. ii: (±)-MTPACl (1.2 eq.), NEt_3 (2.4 eq.), CH_2Cl_2, r.t., 16 h. iii: (S)-MTPACl (1.2 eq.) NEt_3 (2.4 eq.), CH_2Cl_2, r.t., 16 h). (MTPA: α-Methoxy-α-(trifluoromethyl)-phenylacetyl group).
10. (a) Reetz, M.T.; Röhrig, D. *Angew.Chem.Int.Ed.Engl.* **1989**, *28*, 1706. (b) Reetz, M.T.; Röhrig, D.; Harms, K.; Frenking, G. *Tetrahedron Lett.* **1994**, *35*, 8765. (c) Bernardi, A.; Capelli, A.M.; Gennari, C.; Scolastico, C. *Tetrahedron: Asymmetry* **1990**, *1*, 21.
11. Dorigo, A.E.; Morokuma, K. *J.Am.Chem.Soc.* **1989**, *111*, 6524.
12. (a) PM3 method: Stewart, J.J.P. *J.Comput.Chem.* **1989**, *10*, 209. (b) PM3 Parameters for lithium: Anders, E.; Koch, R.; Freunscht, P. *J.Comput.Chem.* **1993**, *14*, 1301.
13. According to our calculations, the alternative four-membered cyclic TSs in which the lithium atom is coordinated to the C_α atom instead of to the nitro group are of higher energy (about 10 kcal/mol). See also: Dorigo, A.E.; Morokuma, K. *J.Am.Chem.Soc.* **1989**, *111*, 4635.
14. It has been suggested that C-H bonds are better donors than C-Me bonds: see Cieplack, A.S.; Tait, B.D.; Johnson, C.R. *J.Am.Chem.Soc.* **1989**, *111*, 8447.

(*Received in UK* 9 *February* 1996; *accepted* 8 *March* 1996)