Pergamon

Tetrahedron Letters, Vol. 37, No. 31, pp. 5577-5580, 1996
Copyright © 1996 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01129-X

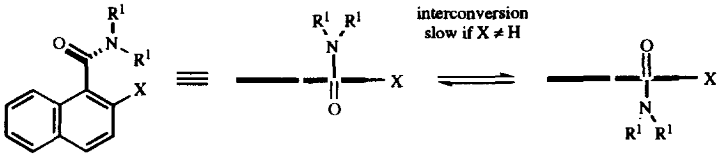
Asymmetric Induction using Atropisomers: Diastereoselective Additions to 2-Acyl-1-Naphthamides

Jonathan Clayden,*[a] Neil Westlund[a] and Francis X. Wilson[b]

[a]Department of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, UK
[b]Roche Products Ltd., 40 Broadwater Rd., Welwyn Garden City, AL7 3AY, UK

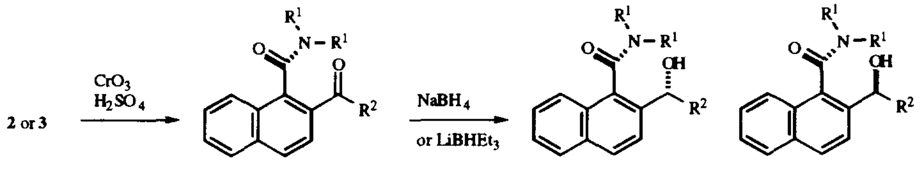
Abstract: The amide group of 2-acyl-*N,N*-dialkyl-1-naphthamides, twisted perpendicular to the naphthyl ring, controls the stereoselectivity of attack of nucleophiles on the 2-substituent. Selectivities of >140:1 may be achieved with bulky nucleophiles, which attack *anti* to the *N,N*-dialkyl group. Copyright © 1996 Elsevier Science Ltd

In *N,N*-dialkyl-1-naphthamides **1**, the amide group and the ring lie nearly perpendicular, and provided the naphthamide bears a 2-substituent X, the two enantiomeric conformations **1a** and **1b** interconvert only slowly and the compound is chiral. **1** (R^1, X = Me), for example, has been resolved by chromatography on chiral stationary phase,[1,2] and recently, Beak and co-workers have made **1** (X = Me) enantioselectively by asymmetric lithiation with sec-BuLi/(–)-sparteine.[3] Furthermore, we have shown that the conformational isomers of **2** and **3** are separable diastereoisomers.[4] Such stereoisomerism due to restricted rotation, or *atropisomerism*,[5] is a phenomenon most widespread and well-known among the biaryls and has been exploited in the form of the binaphthyl class of chiral auxiliaries.[6-8] In this paper we show that the atropisomerism of non-biaryl compounds directs the formation of new chiral centres with stereoselectivity that can exceed 99:1.



1 **1a** **1b**

We started by investigating the directing effect of the conformation of the amide on the stereoselective reduction of ketones **4** and **5**, prepared by CrO_3 oxidation of the mixtures of diastereoisomeric alcohols resulting from addition of lithiated *N,N*-dialkyl-1-naphthamides to aldehydes.[4] We treated each of the ketones with sodium borohydride in ethanol at 0 °C and obtained the alcohols **2** and **3** respectively in quantitative yield.



4 (R^1 = Et) or **5** (R^1 = ^iPr)
(85-95%)

anti-**2** (R^1 = Et)
anti-**3** (R^1 = ^iPr)

syn-**2** (R^1 = Et)
syn-**3** (R^1 = ^iPr)

*Table 1: Stereoselective reductions of 2-acyl-1-naphthamides **4** and **5***

	Reduction with $NaBH_4$^{a}		Reduction with $LiBHEt_3$^{b}	
4 or **5**	Reduction of **4** (R^1 = Et)	Reduction of **5** (R^1 = ^{i}Pr)	Reduction of **4** (R^1 = Et)	Reduction of **5** (R^1 = ^{i}Pr)
R^2 =	*anti*-**2** : *syn*-**2**	*anti*-**3** : *syn*-**3**	*anti*-**2** : *syn*-**2**	*anti*-**3** : *syn*-**3**
Me	79:21	82:18	83:17	93:7
Et	86:14	80:20	88:12	93:7
n-C_5H_{11}	81:19	86:14	87:13	98:2
i-Pr	87:13	89:11	89:11	92:8
Ph	86:14	95:5	97:3	99.3:0.7

Conditions: ^{a}2 eq $NaBH_4$, EtOH, 0 °C, 24 h; ^{b}2 eq $LiBHEt_3$, THF, 0 °C, 2 h

Stereoselectivities were determined by analytical HPLC, and are shown in Table 1. The major atropisomer in every case was the *anti* alcohol, which was also the less polar of the two diastereoisomers.[9]

Using the more bulky reducing agent $LiBHEt_3$ (Super-Hydride®) in THF at 0 °C increased the selectivity of the reaction. Stereoselectivity in the reduction of **5** to **3** was always >92:8, and reached a remarkable 99.3:0.7 for R^2 = Ph. Neither a further increase in the size of the reducing agent nor a reduction in the temperature improved the selectivity of the reaction (Using similar reaction conditions, $LiBH^iBu_3$ [L-selectride®] reduced **5** [R^2 = Me] with 86:14 diastereoselectivity and **5** [R^2 = Et] with 89:11 diastereoselectivity, and at –40 °C $LiBHEt_3$ reduced **5** [R^2 = Me] with 87:13 selectivity).

The stereoselectivities can be explained by a transition state in which the reducing agent attacks the ketone in the conformation shown in figure 2, which is similar to the ground state conformation of the **5** (R^2 = Ph) in its X-ray crystal structure (figure 1). One face of the ketone carbonyl group is crowded by the NR^1_2 group, while the other face lies open to attack. Consistent with this explanation is the greater selectivity displayed in reductions of **3** (with R^1 = ^{i}Pr) in comparison with **2** (with R^1 = Et).

Figure 1

X-ray crystal structure of **5** (R^2 = Ph)

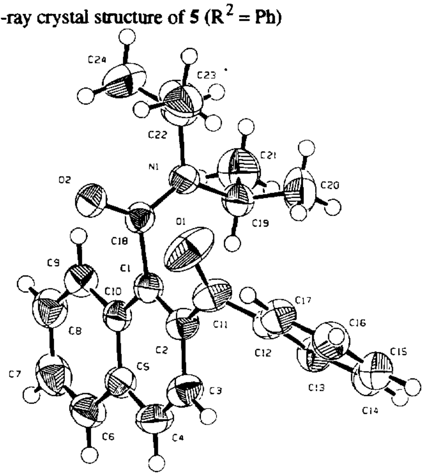
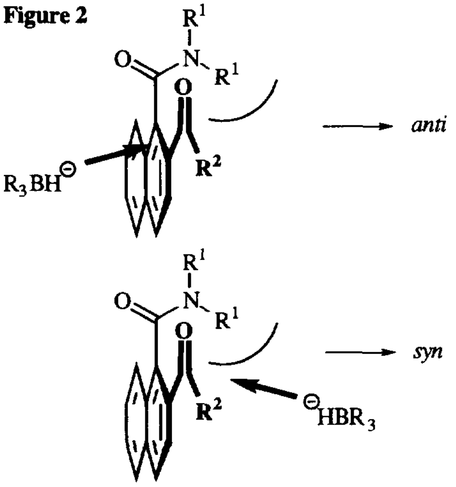
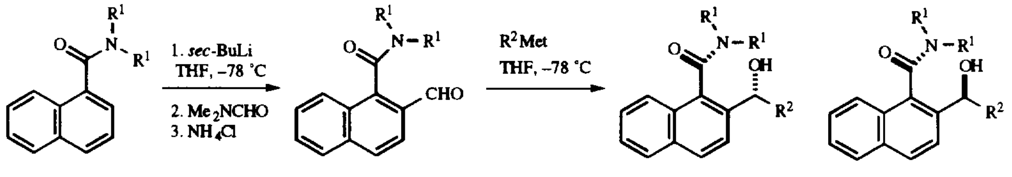


Figure 2



We next turned to the aldehydes **6** and **7**, made from the parent naphthamides **1** (X = H) by ortholithiation followed by electrophilic quench with DMF.[10] That these aldehydes themselves are chiral is evident from their NMR spectra – the diastereotopicity of one CH_AH_BMe group of **6** and of the two $CHMe_AMe_B$ groups of **7** is clear, the latter even at 160 °C in o-$C_6H_4Cl_2$. Aldehyde **7** could also be resolved by chromatography on a chiral stationary phase (Chiralpak-AD).



6 (R^1 = Et) 78%
7 (R^1 = ^{i}Pr) 82%

anti-**2** (R^1 = Et)
anti-**3** (R^1 = ^{i}Pr)

syn-**2** (R^1 = Et)
syn-**3** (R^1 = ^{i}Pr)

The stereoselectivity of nucleophilic addition to these aldehydes was quite dependent on the nature of the nuclephile. Alkyllithium reagents, apart from phenyllithium, gave mainly the *anti* diastereoisomer of the product, *anti*-**2**. Grignard reagents, on the other hand, favoured formation of *syn*-**2**. The selectivities were determined by HPLC and are shown in Table 2.

*Table 2: Stereoselective additions of nucleophiles to aldehydes **6** and 7*[a]

	R^1 = Et		R^1 = ^{i}Pr	
R^2Met =	yield (%)	*anti*-**2** : *syn*-**2**	yield (%)	*anti*-**3** : *syn*-**3**
MeLi	94	70:30	90	80:20
BuLi	56	85:15	83	85:15
PhLi	52	19:81	95	34:66
MeMgBr	91	25:75	66	23:77
AllylMgBr	97	42:58	94	39:61
BuMgCl	72	15:85	57	15:85
PhMgBr	81	14:86	71	3:97

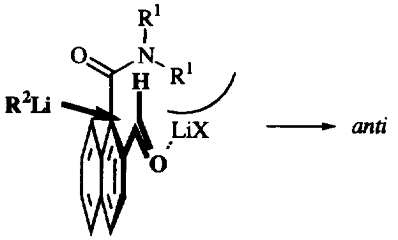
[a] All reactions carried out with 1.1-1.2 eq of reagent in THF at –78 °C

We attribute this intriguing reversal in selectivity to conformational freedom about the C–CHO bond, which allows the aldehyde to present either face to the incoming nucleophile. Assuming attack from the least hindered face in each case, the results can be rationalised in terms of a non-chelated transition state for the alkyllithiums and a chelated transition state for the Grignard reagents.[11-13] The more Lewis-acidic magnesium reagents are able to coordinate simultaneously to both carbonyl groups (amide and aldehyde), twisting the aldehyde group so that it presents its other face for attack by the organometallic reagent.

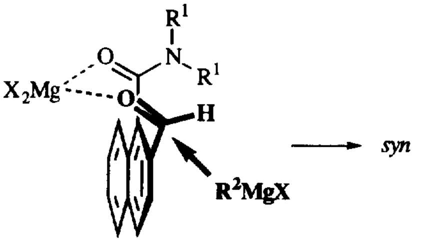
To test this proposal, we added four equivalents of HMPA to the reaction of **7** with BuMgCl. The

Figure 3 (X = R, Hal or OR)

Non-chelation control with organolithiums



Chelation control with Grignard reagents



atropisomers were then formed with reduced 62:38 *syn* selectivity, consistent with an increased preference for the non-chelated transition state in the presence of HMPA. The anomalous selectivity exhibited by PhLi remains unexplained.

Despite the conformational freedom inherent in the aldehydes, it is remarkable that the stereogenic amide group managed to induce a diastereoselectivity of >30:1 in one case (addition of PhMgBr to **7**). This reaction complements nicely the >140:1 selectivity in the opposite sense observed in the reduction of **5** (R^2 = Ph) to the same compounds.

These reactions are among the very first to make use of a non-biaryl atropisomeric chiral element to induce asymmetry at a new chiral centre,[14] and we are currently investigating ways of capitalising on the high levels of asymmetric induction that can be achieved.

Acknowledgments

We thank the EPSRC for a CASE award (to N.W.), the Royal Society for a Research Grant, Zeneca for support through the Strategic Research Fund, and Mr Roy Beddoes for determining the X-ray crystal structure of **5** (R^2 = Ph).

References and Footnotes

1. Cuyegkeng, M. A.; Mannschreck, A. *Chem. Ber.* **1987**, *120*, 803.
2. Pirkle, W. H.; Welch, C. J.; Zych, A. J. *J. Chromatography* **1993**, *648*, 101.
3. Thayumanavan, S.; Beak, P.; Curran, D. P. *Tetrahedron Lett.* **1996**, *37*, 2899.
4. Bowles, P.; Clayden, J.; Tomkinson, M. *Tetrahedron Lett.* **1995**, *36*, 9219.
5. Oki, M. *Top. Stereochem.* **1983**, *14*, 1.
6. Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503.
7. Tomioka, K. *Synthesis* **1990**, 541.
8. Narasaka, K. *Synthesis* **1991**, 1.
9. The relative stereochemistry of *anti*-**3** (R^2 = Ph) was determined by X-ray crystallography (see ref. 4).
10. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
11. Huryn, D. M. in *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I. Eds.; Pergamon: Oxford, 1990; Vol. 1; pp. 49.
12. Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.
13. Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462.
14. For other examples of stereoselective reactions of non-biaryl atropisomers, see Curran, D. P. *J. Chem. Soc., Chem. Commun.* **1993**, 1314; Beagley, B.; Betts, M. J.; Pritchard, R. G.; Schofield, A.; Stoodley, R. J.; Vohra, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1761; Ohno, A.; Kashiwagi, M.; Ishihara, Y.; Ushida, S.; Oka, S. *Tetrahedron* **1986**, *42*, 961; de Kok, P. M. T.; Donkersloot, M. C. A.; van Lier, P. M.; Meulendijks, G. H. W. M.; Bastiaansen, L. A. M.; van Hooff, H. J. G.; Kanters, J. A.; Buck, H. M. *Tetrahedron* **1986**, *42*, 941; Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694; Kawabata, T.; Wirth, T.; Yahiro, K.; Suzuki, H.; Fuji, K. *J. Am. Chem. Soc.* **1994**, *116*, 10809.

(*Received in UK* 3 *May* 1996; *revised* 6 *June* 1996; *accepted* 7 *June* 1996)