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Diastereoisomeric atropisomers of *peri*-substituted naphthamides: synthesis, stereoselectivity and stability

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 Discovery (Welwyn), 40 Broadwater Rd, Welwyn Garden City, Herts AL7 3AY, UK*

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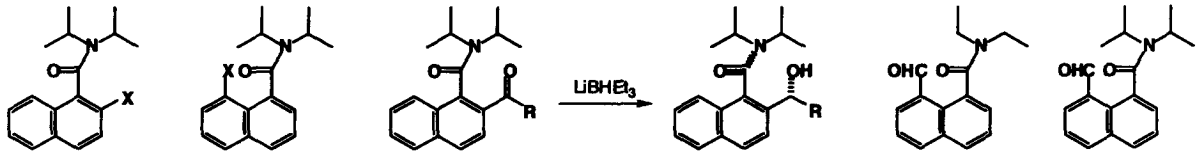
Abstract

8-Formyl-1-naphthamides can be made by perilithiation of 1-(dimethylaminomethyl)-naphthalene, quenching the organolithium with a carbamoyl chloride and subjecting the product amine to a Polonovski reaction. The naphthamides react stereoselectively with nucleophiles to give predominantly the *syn* atropisomers of the product alcohols. Oxidation gives ketones which also give mainly the *syn* atropisomer on reduction. The rate of thermal epimerisation of the products is high relative to 2-substituted 1-naphthamides: the barrier to Ar–CO rotation is ca. 90 kJ mol^{-1}.

Our interest in hindered naphthalene systems began with the discovery that the 2-substituted tertiary naphthamides **1**, which are axially chiral by virtue of restricted rotation about the Ar–CO axis, undergo highly stereoselective reactions.[1] Reagent approach is governed by the amide, whose perpendicular conformation differentiates the two faces of the naphthalene ring and its substituents. Reduction of the ketones **3** with $LiBHEt_3$, for example, gives the *anti*-diastereoisomer **4** with high stereoselectivity.[2] The 2-substituent of **4** has a dual stereochemical role: without it, Ar–CO rotation would be too fast for the aryl–amide axis to be stereogenic (2-unsubstituted naphthamides are not atropisomeric),[3] and by being chiral the 2-substituent makes the atropisomers into diastereoisomers.



1 **2** **3** **4** up to >99:1 **5** **6**

In this Letter, we show that 8-substituted naphthamides **2** behave similarly: prochiral 8-substituents can react stereoselectively, governed by the conformation of the amide, and an 8-substituted naphthamide need have no 2-substituent to have a stereogenic Ar–CO axis.

* Corresponding author.

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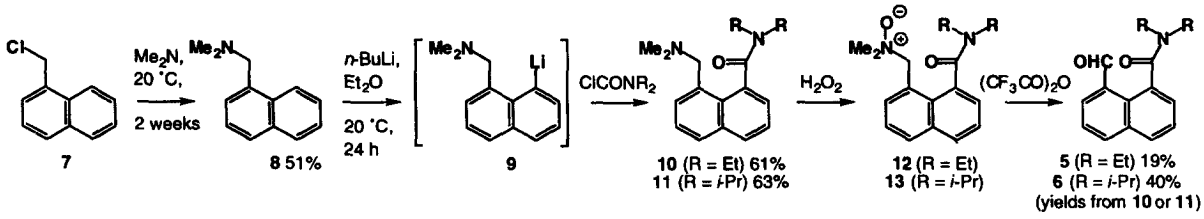
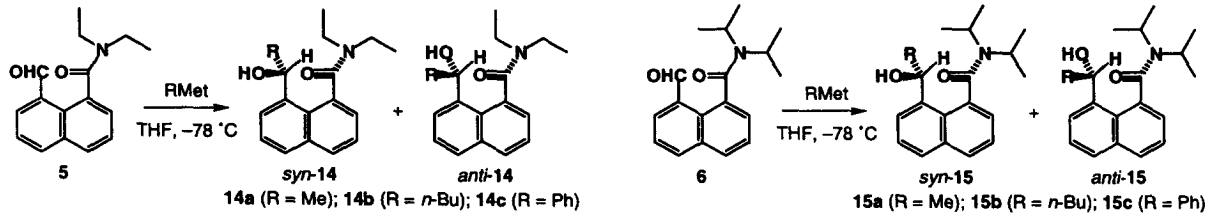
Additions to 2-formyl naphthamides **1** (X=CHO) are in general only moderately stereoselective because of the rotational freedom about the Ar–CHO bond.[2] We expected this rotational freedom to be lessened in the 8-substituted naphthamides **2**,[4] so we started by investigating the stereoselectivity of the reactions of **5** and **6**. The route we chose to make these aldehydes (Scheme 1) started with chloromethylnaphthalene **7**. Stirring with dimethylamine gave the tertiary amine **8**, one of a very few substituted naphthalenes which undergo high-yielding perilithiation.[5] Treatment of **8** with *n*-BuLi in ether for 24 h at 20°C gave an organolithium **9** which reacted with *N,N*-diethyl or *N,N*-diisopropylcarbamoyl chloride to give **10** or **11**. Oxidation (H_2O_2) to the *N*-oxides **12** and **13** and rearrangement with trifluoroacetic anhydride[6] gave the aldehydes **5** and **6** in poor but reproducible (on a 3 g scale) yield.



Scheme 1. Synthesis of 8-formyl-1-naphthamides

We treated the aldehydes **5** and **6** with a selection of organometallic reagents at –78°C in THF (Scheme 2), quenched the reactions at –78°C, and ensured the product mixtures were kept close to 0°C throughout the work-up. Stereoselectivities were determined immediately by analytical HPLC and are shown in Table 1.



Scheme 2. Additions of organometallics to 8-formyl-1-naphthamides

Table 1
Additions to 8-formyl-1-naphthamides

		Reaction with **5**			Reaction with **6**		
entry	RMet =	product	ratio *syn*:*anti*-**14**	yield /% [a]	product	ratio *syn*:*anti*-**15**	yield /% [a]
1	MeLi	**14a**	82:18	76	**15a**	56:44	99
2	*n*-BuLi	**14b**	89:11	68	**15b**	90:10	79
3	PhLi	**14c**	>99:1	69	**15c**	>99:1	55
4	MeMgBr	**14a**	83:17	83	**15a**	83:17	81
5	*n*-BuMgCl	**14b**	83:17	64	**15b**	75:25	61
6	PhMgBr	**14c**	>99:1	77	**15c**	>99:1	78

[a] Isolated yields. Also obtained were traces of the lactones **18**, particularly from **5**.

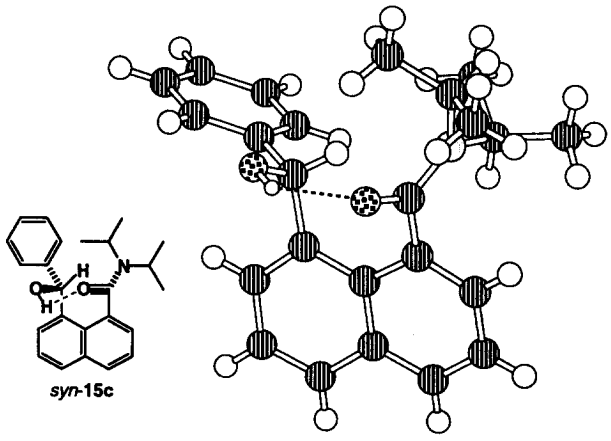
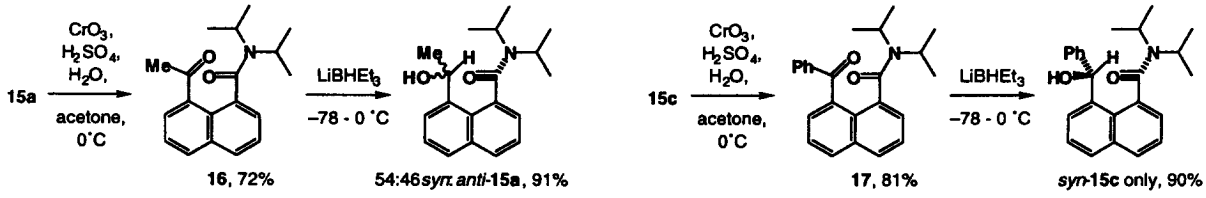


Figure 1. X-Ray crystal structure of *syn*-**15c**

Stereoselectivity was generally high: it was possible to obtain any of the six products **14a–c** and **15a–c** in >80:20 *syn*-selectivity: in contrast to the reactions of 2-formyl-1-naphthamides,[2] the sense of stereoselectivity was not dependent on the metal counter-ion. We deduced the stereochemistry of *syn*-**15c** from its X-ray crystal structure, shown in Fig. 1. The hydroxyl proton is hydrogen-bonded to the amide carbonyl group, and appears as a sharp signal in the ^{1}H NMR at δ 5.2. This feature was common to all the major product diastereoisomers and it allowed us to be confident that **5** and **6** give products of predominantly *syn*-stereochemistry in every case.

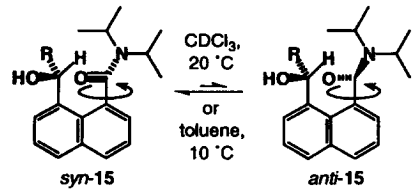
In order to test the amide's ability to control stereochemistry in other reactions, we made the ketones **16** and **17** by oxidising the mixtures of diastereoisomers **15a** and **15c** with Jones' reagent at 0°C. The ketones were reduced with $LiBHEt_3$ to return **15a** and **15c** (Scheme 3).[7] The reduction of **17** was very highly selective, and gave only *syn*-**15c**. The reduction of **16** was, on the other hand, almost completely non-selective.



Scheme 3. Reductions of 8-acyl-1-naphthamides

It was not clear whether the product ratios from all of these reactions represented the kinetic outcome of the reaction, or whether they had arisen simply by thermal epimerisation about the Ar–CO bond to an equilibrium mixture. We already knew that, although the 8-substituted naphthamide **11** is chiral, it has a half life for racemisation of only 5 min at 20°C,[3] and we expected **14** and **15** to have barriers to epimerisation significantly lower than their 2-substituted counterparts. To determine the ratios of atropisomers at equilibrium, we allowed mixtures of the isomers of **15a**, **15b** and **15c** to stand in chloroform at 20°C for several days (Scheme 4).[8] The values obtained were 89:11, 85:15, and >99:1 *syn*:*anti* for **15a**, **15b**, and **15c**, respectively. These are close to some of the ratios found in the product mixtures, but our ability to isolate more or less 50:50 mixtures of *syn*- and *anti*-**15a** indicates that this ratio at least must contain a significant kinetic component.

The rate of rotation about the Ar–CO bond of **15a** was determined by following (by HPLC) the equilibration at 10°C in toluene of a 72:18 mixture of *syn*- and *anti*-**15a**. Over a period of a few days,



Scheme 4. Equilibration of atropisomers

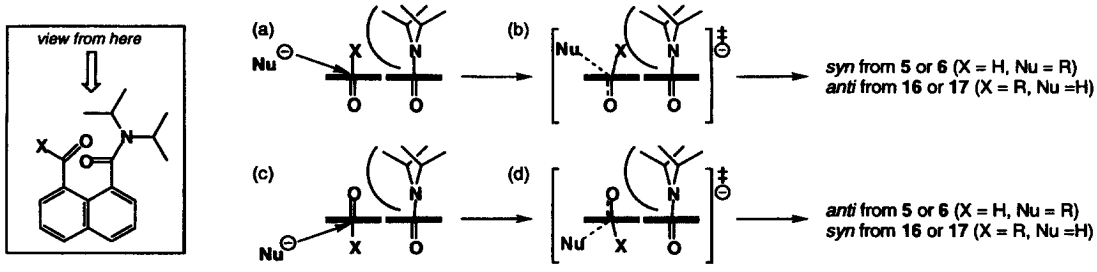


Figure 2. Stereoselectivity in additions to 8-acyl-1-naphthamides

this mixture approached thermodynamic equilibrium. Using the method described previously,[3,9,10] we determined barriers to rotation about Ar–CO from each epimer to be $\Delta G^{\ddagger}_{syn}$=92 kJ mol^{-1} and $\Delta G^{\ddagger}_{anti}$=89 kJ mol^{-1}, or a half-life for epimerisation of 13 h at 10°C. Assuming $\Delta G^{\ddagger}$ remains approximately constant with temperature, we estimate that at ambient temperature the half-life for epimerisation is about 3 h. Barriers to epimerisation of this magnitude (which is about 15–20 kJ lower than the barrier to epimerisation of the isomeric 2-substituted alcohols) mean that the observed ratios probably represent kinetic product mixtures that have been eroded to some extent by equilibration.[11]

It is nonetheless clear that the *sense* of the stereoselectivity — favouring the *syn* isomer — is the same in every case, irrespective of nucleophile or starting material. We assume that steric hindrance in the starting materials **5**, **6**, **16** and **17** twists the carbonyl group out of the plane of the naphthalene ring. There are two possible conformers of this type, shown in Fig. 2(a) and (c), which we assume to be rapidly interconverting (certainly for X=H) at –78°C. X will determine the relative populations of these two conformers. For **5** and **6**, X=H, and the least hindered conformation approximates to (a). The transition state (b) arising from attack on this conformation may, furthermore, be stabilised by chelation of the metal ion by the two oxygen atoms. For **16**, X=Me, and (a) and (c) are of approximately equal energies, while for **17**, X=Ph, and (c) is favoured. Similar interactions determine the relative energies of the transition states (b) and (d), so while **16** gives mixtures of *syn* and *anti*, **17** gives the *syn*-product only.

Acknowledgements

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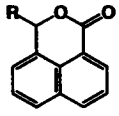
References

1. For an overview, see: Clayden, J. *Synlett* **1998**, 810.
2. Clayden, J.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1996**, *37*, 5577.

3. Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L. W.; McCarthy, C.; Pink, J. H.; Westlund, N.; Yasin, S. A. *Tetrahedron* **1998**, *54*, 13277.
4. The closeness in space of the 1- and 8-substituents of a naphthalene means each substituent has a profound effect on the reactivity of the other. For a discussion, see: Kirby, A. J.; Percy, J. M. *Tetrahedron* **1988**, *44*, 6903 and 6911.
5. Gay, R. L.; Hauser, C. R. *J. Am. Chem. Soc.* **1967**, *89*, 2297.
6. Grierson, D. *Org. Reac.* **1990**, *39*, 85.
7. $LiBHEt_3$ (Superhydride®) gives high selectivities in the reduction of 2-acyl-1-naphthamides. See Ref. 2.
8. We were unable to do this with the amides **14a–c** because in solution at room temperature (and even over a period of months as solids at −18°C) they cyclised to the lactones **18**.



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9. Stewart, W. H.; Siddall, T. H. *Chem. Rev.* **1970**, *70*, 517.
10. Chupp, J. P.; Olin, J. F. *J. Org. Chem.* **1967**, *32*, 2297.
11. It is quite possible that the ratios for **14** are essentially under thermodynamic control: it is noticeable that **14a**, **14b**, and **14c** are each formed with similar stereoselectivities from two different reagents. Our assessment of the role of thermodynamic control in determining the product ratios is tentative because we have no information about the rate of epimerisation of either **14** or **15** under the conditions of the reaction — a second pathway for epimerisation could include the metal-catalysed reversible formation of **18**, for example.