Pergamon

Tetrahedron 54 (1998) 13277–13294

TETRAHEDRON

Barriers to Rotation about the Chiral Axis of Tertiary Aromatic Amides

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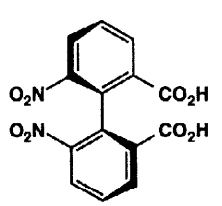
Received 12 June 1998; revised 10 August 1998; accepted 26 August 1998

Abstract: The barrier to rotation about the aryl-carbonyl bond in 40 tertiary aromatic amides was determined by variable temperature NMR spectroscopy (for rapid rotations) or by following the interconversion of atropisomers (for slower rotations). Empirical guidelines to the rate of Ar–CO bond rotation in hindered tertiary aromatic amides, and hence the stability of the atropisomeric stereoisomers of axially chiral amides, are presented. © 1998 Elsevier Science Ltd. All rights reserved.

Introduction

Following the discovery of the first chiral biphenyl **1** by Christie and Kenner in 1922,[1] the factors controlling the rate of racemisation of biaryls **2** were intensively investigated, mainly by Adams,[2] and by 1933 a clear picture had emerged of this class of compounds in which Ar–Ar rotation is hindered by steric encumbrance between the *ortho* substituents W, X, Y and Z. An empirical rule was evident: at least three of W, X, Y and Z must be larger than H for the conformers of **2** to exist as stable enantiomers, and even with this condition satisfied, compounds carrying substituents as small as F or OMe might still not be resolvable.[3] In the 1950's, determination of the rotational barrier in biphenyl offered one of the earliest tests of the power of molecular modelling,[4,5] and more recently, the use of binaphthyls and biphenyls as chiral ligands for metals,[6] along with the discovery of biologically active natural products containing rotationally restricted biaryls,[7-12] has made their enantioselective synthesis an important synthetic goal.[13]



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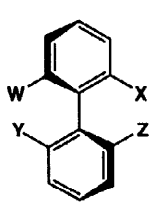

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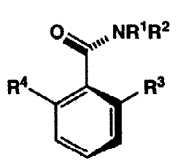

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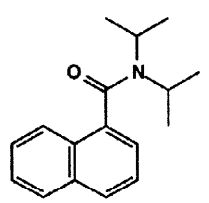

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In this paper, we describe our investigation of the barriers to bond rotation in another class of rotationally restricted compounds: tertiary aromatic amides. The term *atropisomer* ("isomer which can't turn") describes compounds (of which the biaryls are one subclass) whose conformers interconvert sufficiently slowly (with a half life greater than an arbitrarily defined 1000 seconds[14]) that they can exist as stereoisomers, bridging the gap between conformation and configuration.[15] Apart from the biaryls, few atropisomers have been used as synthetic tools,[16] and recently we began a research programme in which we have shown that atropisomeric aromatic amides of the general structure **3**, many of them derived from the naphthamide **4**, are powerful controllers of stereoselectivity.[17-23] Amides **3** and **4** adopt a conformation in which the ring and the amide are perpendicular,[18] and the stereochemical course of their reactions can be strongly influenced by the

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PII: S0040-4020(98)00814-X

steric bulk of the groups on nitrogen, by coordination to the Lewis-basic carbonyl group, or both. We are currently developing methods for the enantioselective synthesis of these amides in order to use them as chiral auxiliaries or as chiral ligands for metals.[16]

Barriers to rotation about the Ar–CO bonds of a limited number of *N,N*-dimethyl amides and thioamides[24] related to **3** (R^1, R^2 = Me) have already been determined by Mannschreck[25-31] and others.[32-36] However, little is known about barriers in amides carrying more hindered nitrogen substituents,[37] despite the fact that (a) these can be easily made using the powerful lithiation chemistry of tertiary amides;[38] (b) the barriers to rotation are expected to be higher, increasing the potential of the amides as synthetic tools; and (c) diastereotopic signals (for example, those of an *N*-isopropyl group) facilitate the use of variable temperature (VT) NMR spectroscopy to determine barriers to racemisation. Our aim in the work described in this paper was to determine the factors necessary to confer sufficient resistance to racemisation to allow the use of the amides as stable axially chiral compounds, and to develop empirical guidelines to the likely conformational stability of axially chiral amides similar to those available for biaryls. We used three analytical methods:

(1) Variable temperature NMR spectroscopy.

(2) Resolution by HPLC on chiral stationary phase, followed by analysis of subsequent racemisation

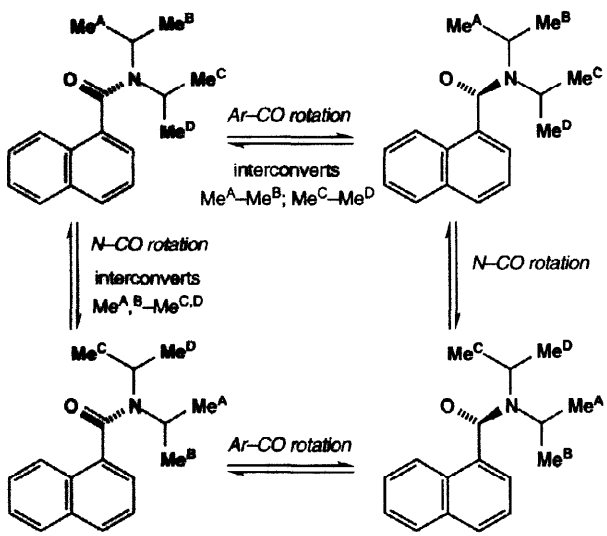
(3) Chromatographic separation on silica, followed by analysis of subsequent epimerisation

VT NMR spectroscopy turned out to be more suited to tertiary amides **3** bearing only one *ortho* substituent (R^3 or R^4 = H), since the barriers to rotation in these compounds are significantly lower (by about 30 kJ mol^{-1}) than barriers in 2,6-disubstituted amides **3** (R^3, $R^4 \neq$ H), for which methods (2) and (3) were more applicable. Similar methods have been used to determine barriers to rotation in hindered aryl sulfoxides,[39] sulfones,[40,41] ketones[42] and imines.[43] We will first present the results obtained by applying these three methods to 40 or so amides. We will then draw general conclusions about the factors which control the barrier to aryl–carbonyl rotation, and deduce mechanisms by which the bond rotation might take place.

Results and Discussion

Variable temperature NMR spectroscopy

The use of NMR spectroscopy to study restricted rotation in amides has a long history,[44] and it was NMR spectroscopic evidence which first indicated that the favoured conformation of 2-substituted benzamides **3** is chiral.[45] Both benzylic CH_2 groups of **3** (R^1, R^2 = Bn; R^3 = H; R^4 = F, NO_2, OMe, Me), for example, appear as diastereotopic AB systems in the ^{1}H NMR spectrum at 0 °C,[46] though the early 1970's saw conflicting interpretations of these and other similar[47] observations.[48-50] Since rotation about the Ar–CO bond in aromatic amides **3** (provided $R^3 \neq R^4$) interconverts not only enantiomeric conformers but also diastereotopic signals in the NMR spectrum (illustrated for amide **4** in Scheme 1), it is possible to use the coalescence of these signals with increasing temperature as a measure of the rate of, and barrier to, this rotation (see Figure 1).[32,51-53] Provided no other process (such as concerted Ar–CO and N–CO rotation – a possibility we discuss below) interconverts the enantiomers, the rate of Ar–CO rotation then gives the rate of enantiomerisation (conversion of one enantiomer into the other) of the amide.



Scheme 1: Bond rotations in tertiary aromatic amide 4

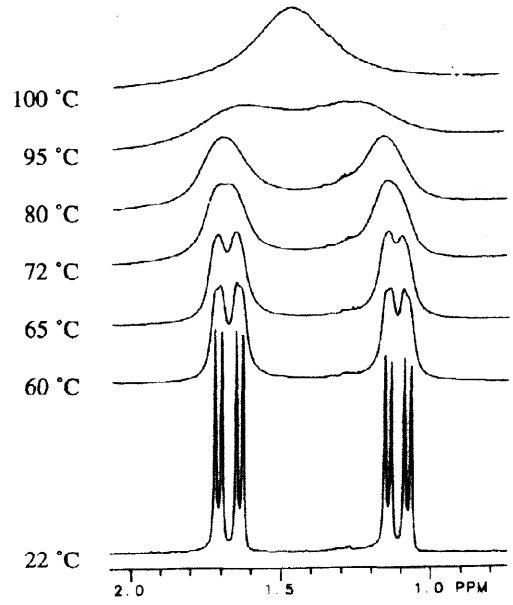


Figure 1: VT NMR experiments on amide 4

We applied this method to the amides shown in Table 1. For each compound, we first obtained a spectrum at low temperature in order to estimate the chemical shift difference $\Delta\nu$ between peaks at the slow-exchange limit, and in the case of compounds containing diastereotopic protons, the J_{AB} coupling constant. We then used variable temperature NMR spectroscopy to find the coalescence temperature of the signals corresponding to the groups indicated. By simulating lineshapes near the boundary between slow and fast exchange we obtained the rate of exchange k at the coalescence temperature T_c.[54] From k, we determined $\Delta G^{\ddagger}_{Ar-CO}$, the barrier to rotation about the Ar–CO bond of the amide at that temperature, using the Eyring relationship. For the bond rotations we are considering, $\Delta S^{\ddagger}$ is expected to be small ($|\Delta S^{\ddagger}| < 40$ J mol^{-1} K^{-1}),[44] and hence $\Delta G^{\ddagger}_{Ar-CO}$ should vary little with temperature, allowing comparison between amides with different coalescence temperatures.

For each amide, Table 1 lists T_c, k and $\Delta G^{\ddagger}_{Ar-CO}$, along with a crude estimate of the half-life for *racemisation*[55] at 20 °C, again based on the approximation that $\Delta G^{\ddagger}_{Ar-CO}$ is invariant with temperature and the assumption that $\Delta G^{\ddagger}_{Ar-CO}$ is identical with the barrier to interconversion of the enantiomers of the amide. We are concerned mainly with orders of magnitude – whether the half life is seconds, hours or days, and this column should be interpreted in that light.

Table 1 demonstrates that 2-substituted benzamides (including 2-*un*substituted 1-naphthamides) cannot be atropisomeric at room temperature: even the slowest racemisations are half complete in a second. More detailed analysis indicates that two primary factors determine the barrier to rotation: the size of the nitrogen substituent lying *trans* to oxygen, and the size of the 2-substituent on the aromatic ring.

The two *N*-isopropyl groups of **4** (entries 1, 2) provide a much better barrier to Ar–CO rotation than the ethyl, propyl or benzyl groups of **5**, **6** and **7** (entries 3-8) but increasing the size of only one of the two *N*-substitutents has very little effect. Replacing one of the benzyl groups of **7** with the *t*-butyl group of **8** (entry 9 vs. entry 7 or 8), for example, if anything lowers the barrier to rotation, though we should be wary of comparing too closely $\Delta G^{\ddagger}$ values determined at different temperatures and in different solvents.

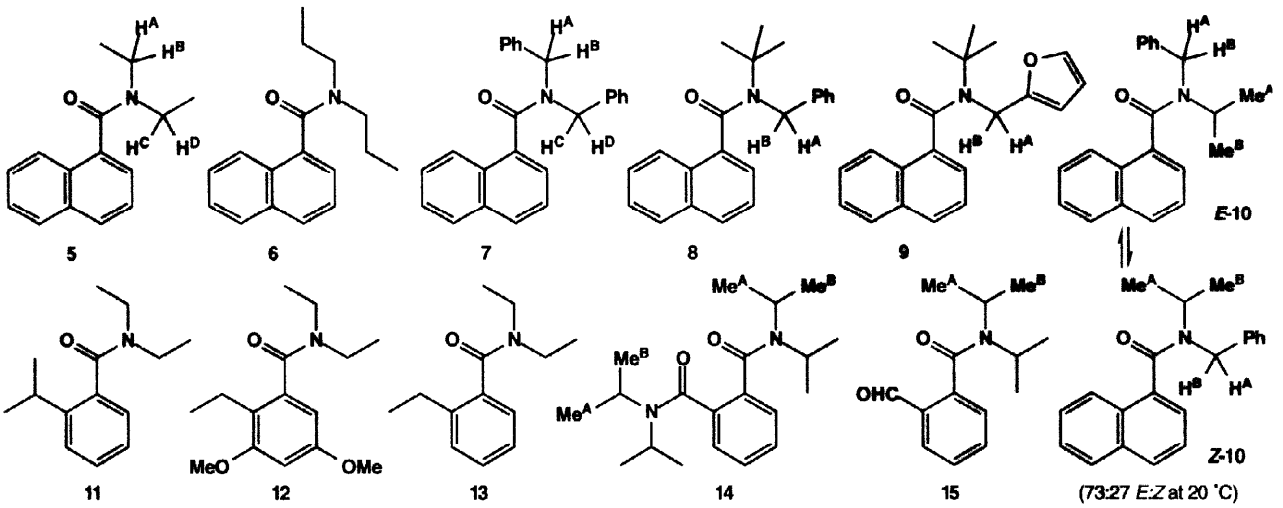


*Table 1: Bond rotation in amides **4-15** measured by VT NMR spectroscopy*

entry	amide	solvent	coalescing signals	Δν /Hz	T_c /°C	k /s^{-1}	$\Delta G^{\ddagger}_{Ar-CO}$[a] /kJ mol^{-1}	half-life[b] /s
1	**4**	d_6-DMSO	Me^A–Me^B	21	72.5	35	74.8	1
2	**4**	d_6-DMSO	Me^C–Me^D	20	71	32	74.7	1
3	**5**	d_6-DMSO	H^A–H^B	74	36	140	63.1[c]	0.01
4	**5**	CD_3OD	H^A–H^B	66	50	130	66.2[c]	0.03
5	**5**	CD_3OD	H^C–H^D	24	40	45	66.8[c]	0.05
6	**6**[d]	e			19		63	0.01
7	**7**	$CDCl_3$	H^A–H^B	225	57	503	64.0[f]	0.015
8	**7**	CD_3OD	H^C–H^D	20	40	64	65.9	0.03
9	**8**	C_6D_6	H^A–H^B	81	32	200	61.3	0.005
10	**9**	$CDCl_3$	H^A–H^B	49	59	143	67.9	0.07
11	***E*-10**	$CDCl_3$	Me^A–Me^B	5	42	8	71.8	0.3
12	***E*-10**	d_6-DMSO	Me^A–Me^B	17	60	26	72.8	0.5
13	***E*-10**	d_6-DMSO	H^A–H^B	40	g	g	72	0.4
14	***Z*-10**	$CDCl_3$	Me^A–Me^B	61	34	130	62.8	0.01
15	***Z*-10**	d_6-DMSO	Me^A–Me^B	34	28	65	63.3	0.01
16	***Z*-10**	d_6-DMSO	H^A–H^B	66	40	169	63.4	0.01
17[h]	**11**	–[i]			–[i]		65.3	0.02
18[h]	**12**	–[i]			–[i]		65.3	0.02
19[j]	**13**	d_6-DMSO			35		59.4	0.002
20	**14**	$CDCl_3$	Me^A–Me^B	39	41	75	65.8	0.03
21	**15**	$CDCl_3$	Me^A–Me^B	21	–10	36	56.3	0.0005

[a]Value at coalescence temperature T_C; error limits ±1 kJ mol^{-1}. [b]Estimated half-life for racemisation[55] at 20 °C. [c]Literature values:[52a] 63 kJ mol^{-1} ($CHCl_3$, 20 °C); 61 kJ mol^{-1} (d_6-acetone–C_6D_6–d_8-toluene, 20 °C). [d]Data taken from ref 52a. [e]CD_2Cl_2–d_6-acetone. [f]Literature value:[52a] 63 kJ mol^{-1} ($CHCl_3$, 31 °C). [g]Lineshape at 50 °C fits k = 15 s^{-1}. At higher temperatures lineshapes are distorted, perhaps due to a correlated rotation about the N–CO bond as discussed below. [h]Data from ref. 52b. [i]Not reported. [j]Data from ref. 32. Literature value:[52b] 60.2 kJ mol^{-1}.

The effect of a polar solvent on the barrier can be judged by comparison of entry 3 with entries 4 and 5, or of entry 7 with 8. Barriers in methanol are slightly, but probably significantly (2-3 kJ mol^{-1}), higher than barriers in less polar solvents – we discuss possible reasons for this later. Barriers in $CDCl_3$ and in DMSO appear not to be significantly different (entries 11-16).

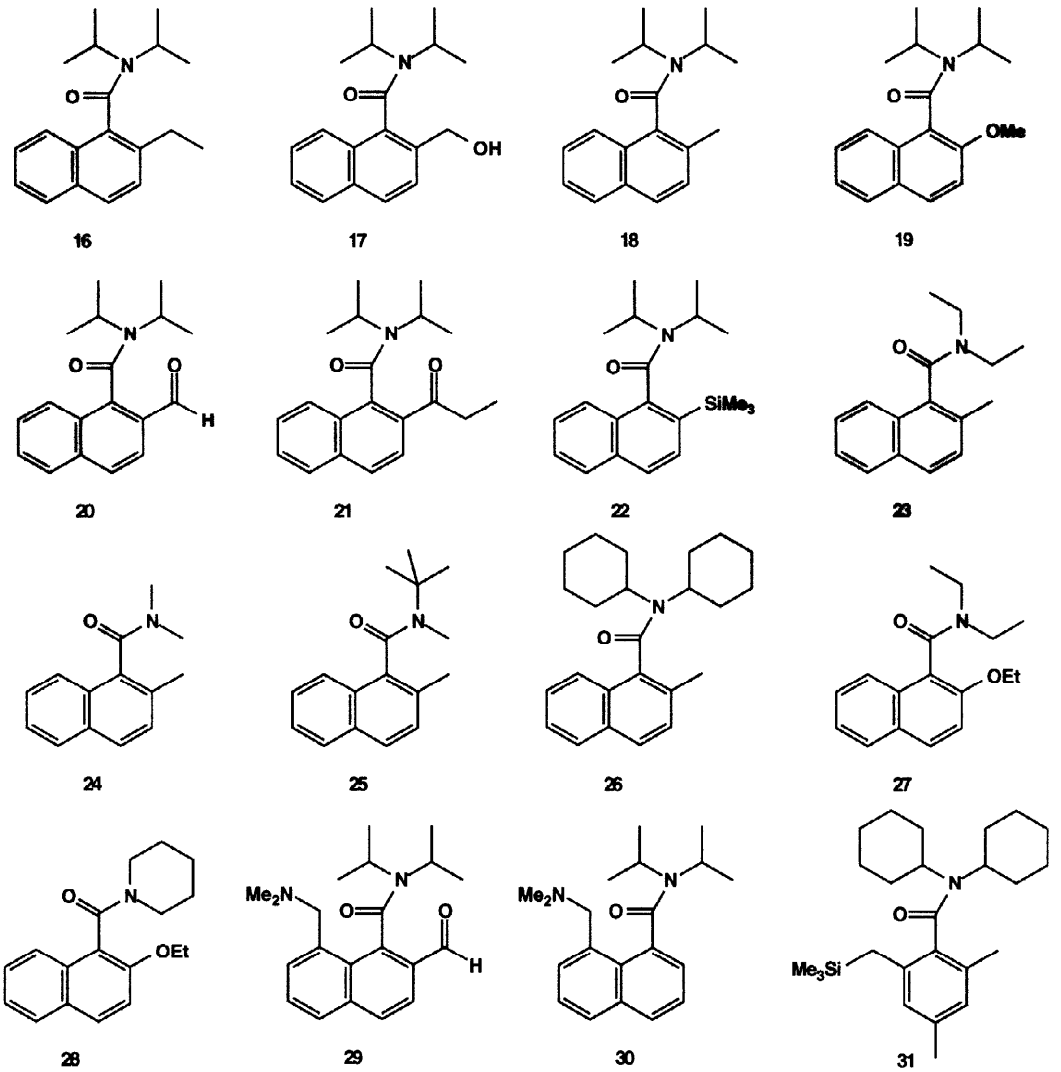
Entries 11-16 reveal the key factor regarding the size of the *N*-substitutents. They detail the barriers to Ar–CO rotation in the two geometrical isomers of amide **10**. In chloroform at ambient temperature, *E* and *Z*-**10** exist in an equilibrium ratio of 73:27, with *E*-**10** predominating. Our assignment of stereochemistry is based on the general rule that ^1H NMR signals of *N*-substituents *cis* to oxygen are shifted downfield relative to *N*-substituents *cis* to the aromatic ring, and this compound's surprising preference for what appears to be the more sterically crowded *E* amide geometry is nonetheless precedented.[56] Importantly, the barriers to rotation (in both $CDCl_3$ and d_6-DMSO) of each isomer of **10** mirror the barriers in other compounds which have the same *N*-substituent *trans* to oxygen: *E*-**10** has a barrier approaching that of **4**, while *Z*-**10** is more similar to that of **7**. It is not surprising that this substituent *trans* to oxygen is the controlling factor, since bond rotation requires it to pass close to the naphthalene ring. This also accounts for the lack of impact of a *t*-butyl substituent (entry 9 vs. entry 7): *N*-*t*-butyl substituents invariably lie *cis* to oxygen.[57]

Changing the fused benzo ring of naphthamides **4**-**10** for substitutents with greater flexibility to bend in the plane of the ring drops the barrier by about 10 kJ mol^{-1}, and comparison of **11** and **12** with **13** indicates that a secondary alkyl substituent, or a buttressed primary one, gives about 5 kJ mol^{-1} greater barrier than a primary one alone. **14** is an interesting case, because enantiomerisation involves rotation about two Ar–CO bonds: only one conformer is evident in the NMR spectrum, which we assume has the amide groups aligned *anti*.[23] The difference between **14** and **15** highlights the inability of a freely-rotating trigonal substituent (–CHO) to block rotation effectively – we return to this point in later discussion.

We also determined, for **4** and **5**, a barrier to N–CO bond rotation using VT NMR spectroscopy.[44] The diisopropyl amide **4** shows four clear methyl doublets in its ^1H NMR spectrum at 20 °C (Figure 1), and we use the general rule that groups *cis* to oxygen are shifted downfield to assign Me^A and Me^B as the downfield pair and Me^C and Me^D as the upfield pair. Coalescences of Me^A–Me^B and Me^C–Me^D occurred, as indicated in Table 1 and shown in Figure 1, at about 72 °C. Heating to 97.5 °C resulted in a further coalescence of the Me^A/Me^B and Me^C/Me^D peaks to a single signal: N–CO bond rotation is now fast, with a rate constant k = 360 s^{-1} at 97.5 °C, and hence $\Delta G^{\ddagger}_{N-CO}$ at this temperature[58] is 73.3 kJ mol^{-1}. We were also able to estimate the barrier to N–CO bond rotation in **5**: lineshape simulation of the broadened signal arising from the two methyl triplets at 90 °C indicated a rate constant k = 100 s^{-1} at this temperature, and hence $\Delta G^{\ddagger}_{N-CO}$ = 75 kJ mol^{-1}.[59] Ar–CO rotation in **5**, unlike **4**, is much faster than N–CO rotation.

Resolution and racemisation

Variable temperature NMR spectroscopy is of value for investigating the rates of processes which occur on a timescale >1 s^{-1}, and 2-substituted tertiary benzamides typically racemise at this rate. Other NMR spectroscopic methods, for example saturation transfer,[60,61] have been used to extend this range, but rates of racemisation in 2,6-*disubstituted* benzamides are too slow for VT NMR spectroscopy to be a useful analytical technique. By and large, slower processes are best observed using chromatographic methods. VT HPLC[31] is currently developing as a complementary partner to VT NMR spectroscopy, but we decided to study the remainder of our amides by separating stereoisomers and analysing their subsequent interconversion over time.



The chiral amides shown in Table 2 were resolved on a 250 x 4.6 mm Chiralpak-AD column.[62] In a few cases, it was necessary to carry out the resolution on a semi-preparative 250 x 10 mm Chiralpak-AD column, and for another subset of amides (**20-22**) the separations had to be carried out at 2 °C because of rapid racemisation (half-lives of the order of minutes) at room temperature. Solutions of the resolved enantiomers were stored in the freezer before being incubated at constant temperature. Aliquots were withdrawn analysed at intervals – in all cases a first order decay to a racemic mixture was observed. A few trial runs allowed us to find optimum temperatures for these experiments – we settled on those which gave half-lives of the order of hours (k in the region of 1 x 10^{-4} s^{-1}) to allow us to follow the decay over a good section of the decay curve: in general the experiments were run for a period of at least 3 half-lives. The first order rate constant obtained by plotting ln(*e.e.*) against time gave the rate of racemisation,[44] from which we determined a half-life, as for the VT NMR experiments. For comparison with the VT NMR experiments, Table 2 presents k (the rate of enantiomerisation, which is half the rate of racemisation), and hence $\Delta G^{\ddagger}_{Ar-CO}$, for each of the amides **16-31**.

Oki defined the term *atropisomers* to mean conformers that interconvert with a half-life greater than 1000 s (0.28 h).[14] By this reckoning, Table 2 indicates that 2,6-disubstituted benzamides (including 2-substituted naphthamides) are in general atropisomeric and can be resolved into enantiomers. Only amides **20**, **22** and **30** fail to meet the criterion, and we discuss them below.

Table 2: Racemisation of amides ***16-31***

entry	amide	solvent: hexane +	T /°C	k /10^{-5} s^{-1}	$\Delta G^{\ddagger}_{Ar-CO}$[a] /kJ mol^{-1}	half-life[b] /h
1	**16**	2.5% EtOH	47	4.38	105.2	86
2	**17**	10% EtOH	40	1.54	105.6	101
3	**18**	20% *i*-PrOH	44	3.49	104.8	75
4	**19**	2% EtOH	48	20.0	101.5	19
5	**20**	5% EtOH	2[c]	4.21	90.2	0.2
6	**21**	7% EtOH	18[c]	12.0	93.0	1
7	**22**	5% EtOH			<90[d]	<0.2
8	**23**	3% EtOH	47	9.90	103.1[e]	36
9[f]	**24**	20% *i*-PrOH	25		102.6[g]	30
10	**25**	10% EtOH	30	2.82	100.6	13
11	**26**	3% EtOH	42	14.6	100.4	12
12[h]	**27**	20% *i*-PrOH	65		99.5	8
13[h]	**28**	20% *i*-PrOH	45		93.5	0.7
14	**29**	10% EtOH	50	4.43	106.2	128
15	**30**	2% EtOH	2[c]	11.9	87.8	0.07
16	**31**	1% EtOH	35	7.15	99.9	10

[a]Value at temperature T; error limits ±0.5 kJ mol^{-1}. [b]Estimated half-life for racemisation at 20 °C. [c]Enantiomers separated at 2 °C. Poor separation at 20 °C due to racemisation on the column. [d]Estimated value: rapid racemisation at 20 °C. [e]Literature value:[36] 103.8 kJ mol^{-1} (hexane–20% *i*-PrOH, 75 °C). [f]Data from reference 35. [g]Alternative literature value:[25] 100.4 kJ mol^{-1} (dioxane, 25.3 °C) [h]Data from reference 36.

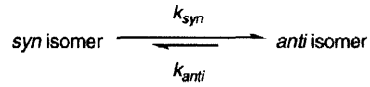
The trends noted in Table 1 are still apparent in Table 2: Ar–CO barriers decrease on moving from *N,N*-diisopropyl to diethyl to dimethyl, (compare amides **18**, **23**, **24** and **26**) but the change is less marked than in amides with only one *ortho* substitutent. Indeed, it is not obvious why dicyclohexyl amide **26** should have a lower barrier even than dimethyl amide **24**, but this may be because steric crowding destabilises its minimum energy conformation. As before, introduction of a *t*-butyl group in **25** has very little effect on the barrier.

The nature of the *ortho* substituents though now becomes rather more important, and it is most revealing to consider the *N,N*-diisopropylnaphthamides **16-22** in order of decreasing barrier to rotation. Hydroxymethyl, ethyl and methyl *ortho* substituents (**16-18** provide almost equal barriers to rotation, followed closely by alkoxy (**19**) (compare also **27** with **23** in the *N,N*-diethyl series). Much less efficient at blocking Ar–CO rotation are the trigonal substituents formyl and propionyl groups (**20** and **21**): we alluded to this earlier (**15** racemises more rapidly than **14** – see Table 1, entries 21 and 20), and a similar lack of steric hindrance from a trigonal substituent has been noted in the biaryl series too.[63] More surprising is the fact that, despite its apparent size, the trimethylsilyl group of **22** provides a very poor barrier to rotation. This may be due to the long, flexible C–Si bond which alows the Me_3Si group to bend out of the way of the rotating amide (Me_3Si has been noted to carry surprisingly little steric influence[64]), though there is additionally a possible stereoelectronic explanation which we discuss below.

Compounds **29-31** illustrate the effect on the barrier of changing the ring itself. An 8-substituent can raise the barrier to rotation of a naphthamide by some 15 kJ mol^{-1} (compare **29** with **20** or **30** with **4**), but a substituent of a given size appears to be much more effective in the 2-position than the 8-position (compare **30** with **17**). The mesitamide **31** has a barrier almost identical to that of its naphthamide analogue **26**.

Separation and epimerisation

We have made a number of compounds bearing chiral 2-substituents using the powerful *ortho* and lateral lithiation chemistry of the tertiary aromatic amides.[65] Since diastereoisomeric separations are usually much easier than resolutions, we decided to use the epimerisation of these atropisomeric diastereoisomers to study in more detail rotation about the Ar–CO bond. We used the same experimental protocol as for the resolutions, carrying out the separation and the analysis using normal achiral silica HPLC columns. We incubated the separated the *syn* and *anti* isomers at constant temperature, and used analytical HPLC to follow their equilibration.



$$K = \frac{[anti]_{eqm}}{[syn]_{eqm}} = \frac{k_{syn}}{k_{anti}}$$

Scheme 2: Equilibration of atropisomeric diastereoisomers

By analysing the results using the methods described by Siddall[44] and applied, for example, by Chupp and Olin,[66] we obtained a combined rate constant $k_{syn} + k_{anti}$ (Scheme 2). The equilibrium contant K was determined by leaving the diastereoisomers to equilibrate for several half lives before the final aliquot was taken. We then used K to partition $k_{syn} + k_{anti}$ into the unidirectional rate constants, and so determine barriers to rotation about the Ar–CO bond, $\Delta G^{\ddagger}_{anti}$ and $\Delta G^{\ddagger}_{syn}$, starting from the *anti* and *syn* diastereoisomers respectively. Table 3 gives these results, and also a half-life for equilibration, which, by analogy with the half life for racemisation we have already discussed, is based on $k_{syn} + k_{anti}$. In some cases we evaluated $k_{syn} + k_{anti}$ by experiments starting from each diastereoisomer.

The first set of compounds we studied were the alcohols **32** and **33** derived from addition of *ortho*lithiated naphthamides to aldehydes,[17,18] reduction of 2-acyl naphthamide, or addition of organometallics to 2-formyl naphthamides.[19] In each case, we separated the isomers by HPLC and allowed them to equilibrate separately at about 60 °C in dioxane, toluene or ethanol as shown in Table 3, entries 1-9.

In every case, the final equilibrium ratio of diastereoisomers showed a modest bias towards the *anti* diastereoisomer, though the ratio was solvent-dependent: the two diastereoisomers reached equilibrium at 1:1 in toluene (entry 4), perhaps due to a change in the degree and nature of intramolecular hydrogen bonding. In general, the same trends with regard to steric hindrance and rates of epimerisation are evident as for the racemising amides in Tables 1 and 2. The 2-substituents of **32** and **33** are all rather similar, and changing R from Me to Et to Bu to Ph decreases the barrier to epimerisation only very slightly. **32** and **33** have secondary tetrahedral substituents, and have barriers to Ar–CO rotation about 4 kJ mol^{-1} higher than comparable amides in Table 2 bearing primary substituents. The other general point is again one we have highlighted before: barriers to rotation in *N,N*-diethylamides are slightly (only about 1 kJ mol^{-1}), but consistently, lower than barriers in *N,N*-diisopropylamides.

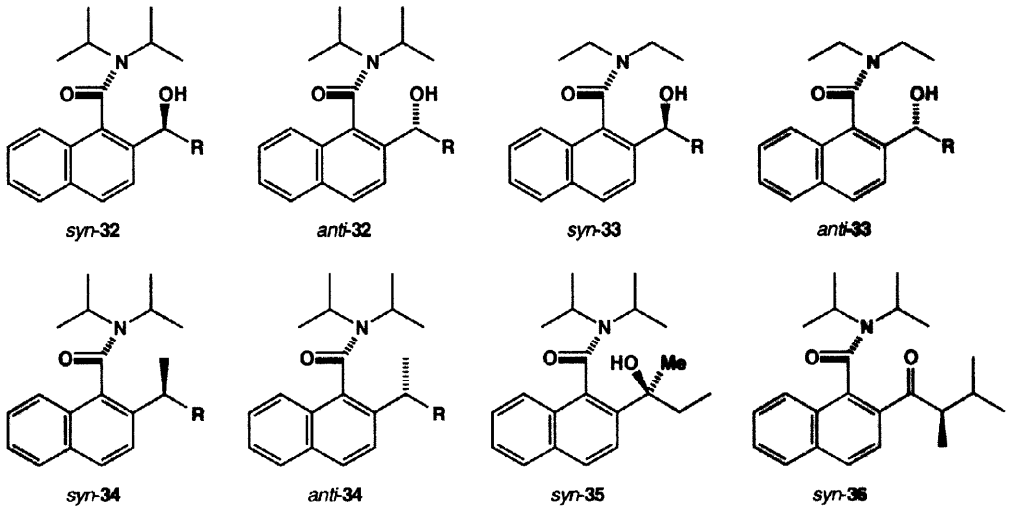


*Table 3: Equilibration of diastereoisomeric amides **32-36***

entry	amide	R	solvent	T /°C	$k_{anti}+k_{syn}$ /10^{-5} s^{-1}	*K*	$\Delta G^{\ddagger}_{anti}$ /kJ mol^{-1}	$\Delta G^{\ddagger}_{syn}$ /kJ mol^{-1}	half life at 20 °C /h
1	**32**	Me	dioxane	62	14.2[a]	1.60	109.7	108.4	380
2	**32**	Et	dioxane	55	5.7[a]	1.40	109.6	108.7	410
3	**32**	Bu	dioxane	61.5	13.0[a] 11.5[b]	1.80	110.0	108.3	400
4	**32**	Bu	PhMe	60	12.3[a] 14.7[b]	1.02	108.7	108.7	340
5	**32**	Bu	EtOH	60	1.98[a] 1.60[b]	1.85	114.7	113	2700
6	**32**	Ph	dioxane	60	10.0[a]	1.78	110.2	108.6	440
7	**33**	Me	dioxane	60	19.6[a] 23.4[b]	1.28	107.8	107.1	200
8	**33**	Bu	dioxane	61.5	17.3[a] 19.6[b]	1.70	109.1	107.6	290
9	**33**	Ph	dioxane	62	18.0[a] 18.0[b]	1.45	108.9	107.8	290
10	**34**	Et	hexane[c]	65	9.5[a]	1.41	112.6	110.1	910
11	**34**	$SiMe_3$	hexane[d]	45	4.5[a]	15.7	111.9	104.7	140
12	**35**	–	dioxane	55	<0.1[a]	–[e]	>120	>120	>40000
13	**36**	–	dioxane	30.3	26.0[f]	1.07	96.9	96.8	3

[a]Starting from *syn* diastereoisomer. [b]Starting from *anti* diastereoisomer. [c]+5% EtOH. [d]+2% EtOH. [e]Not determined. [f]Starting from less polar diastereoisomer (stereochemistry not determined).

Throughout this study we have been forced to use a variety of temperatures to determine $\Delta G^{\ddagger}_{Ar-CO}$ This limits the degree with which comparisons between experiments can be made, but though we do not know the values of $\Delta S^{\ddagger}$ for these bond rotations, we expect it to be small. We have also been forced, because of chemical shifts, HPLC separations, boiling points and freezing points, to use a variety of solvents to perform our kinetic analyses, and in Table 1 we noted that barriers to rotation in two amides were 2-3 kJ mol^{-1} higher in methanol than chloroform or DMSO. Entries 3-5 show the results of epimerising the same amide, **32** (R = Bu) in toluene, dioxane and ethanol, and makes clear that there is an even more marked trend towards increased barriers to rotation in increasing polar solvents. Barriers in toluene and dioxane are similar, but the barrier in ethanol is some 4 kJ mol^{-1} higher than either of these. A similar observation has been made[33] for the racemisation of a nicotinamide, and we discuss this phenomenon below.

Entries 10-13 show the barriers to epimerisation amides with secondary tetrahedral, tertiary tetrahedral, and trigonal substituents. Amides **34**[20] bear secondary 2-substituents, and **34** (R = Et) has a comparable, though slightly higher, barrier to rotation than **32** (R = Et). Amide **34** (R = $SiMe_3$) is remarkable, because unlike **32**, **33** or **34** (R = Me), one diastereoisomeric atropisomer is very much favoured at equilibrium.[23] The barrier to epimerisation of the minor diastereoisomer is therefore rather low, though again the half-life for equilibration is comparable with similar hydroxyl-substituted compounds.

Incubation of the tertiary alcohol *syn*-**35** at 55 °C gave no detectable conversion to its known[22] diastereoisomer after 28 h, allowing us to assign a value for k for this process of $<1 \times 10^{-6}$ s^{-1}. Prolonged heating or higher temperatures decomposed the alcohol. Making the benzylic carbon a quaternary centre provides the largest barrier to rotation we have seen in any 2-substituted naphthamide.

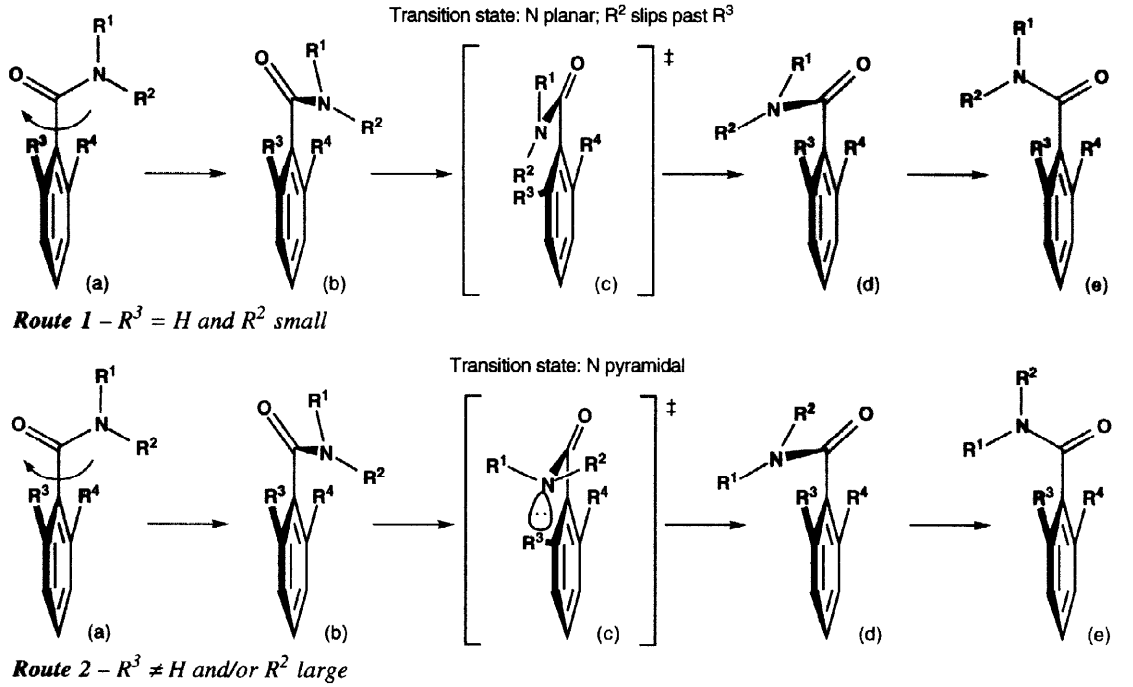
Ketone **36** was available by enolate alkylation,[22] and HPLC at low temperature allowed us to obtain a mixture enriched in the less polar diastereoisomer. Epimerisation was rapid, with the trigonal carbonyl group again demonstrating its inability to block rotation effectively.

Dynamics of the Rotation

Rotation about the Ar–CO bond in amide **3** (Scheme 3) must involve the nitrogen and oxygen atoms passing through the plane of the ring. Since steric hindrance between NR^1R^2 and R^3 or R^4 must be greater than between the carbonyl O atom and R^3 or R^4, the lower energy pathway will be that in which NR^1R^2 passes the smaller of R^3 or R^4, so we assign R^3 as the smaller and R^4 as the larger of these two substituents. This reduces the number of interactions we need to consider in our analysis of the rotation: the key interactions are those between R^2 and R^3 and between the carbonyl oxygen and R^4.

R^4 in most experiments was a benzo ring, but comparison of a few other barriers allows the simple deduction that, as a block to Ar–CO rotation, R^4 = *peri*-alkylbenzo > benzo > alkyl > CHO. Each step in the sequence is relatively small, because the interaction concerned is only with the carbonyl oxygen atom, and when R^3 = H, only a *peri*-substituted benzo ring (**30**) is sufficient to raise the barrier to the point where the conformers are atropisomers.

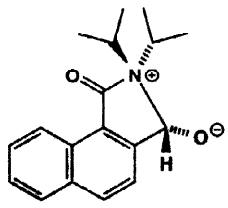
We noted that with R^3 = H, the barrier to rotation was significantly dependent on the size of R^2, and relatively independent of R^1. This makes sense if we consider that, for R^3 = H, the rotation will follow the pathway shown as Route 1 in Scheme 3. At the transition state (c) the C–R^3 bond and N–R^2 bonds bend sufficiently to allow R^2 to slip past R^3: there is close contact between R^2 and R^3, so R^2's size is the key factor in the barrier height.

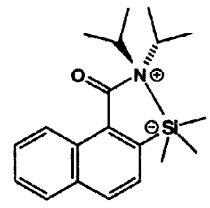


Scheme 3: Dynamics of Bond Rotation

When $R^3 \neq H$, however, we found that the sizes of R^1 and R^2 have little influence on the barrier to rotation: we suggest that in such cases an alternative mechanism comes into action, shown as Route 2 in Scheme 3. No longer is R^3 small enough to allow R^2 to slip past, and instead the only way in which the NR^1R^2 group can pass R^3 is by rotating so it is no longer in the plane of the carbonyl group (c). N–CO conjugation is lost, which is paid for in increased barrier height, though the amide system is partly repaid with greater Ar–CO conjugation at the transition state. The main interaction at the transition state (c) is now between N and R^3, so we expect (and observe) that changing R^2 affects the height of the barrier less than when $R^3 = H$. R^3 is now the key controller of barrier height, and for *N,N*-diisopropyl naphthamides the scale is R^3 = CR^aR^bOH (>120 kJ mol^{-1}) > CR^aR^bH (110) > CH(OH)R (108) > R (105) > OMe (101) > C(=O)R (93) > CHO, $SiMe_3$ (<90 kJ mol^{-1}). We presume the most important factor in this sequence is steric bulk, and particularly the steric bulk of the smallest part of R^3 that can be directed towards the passing N: OH for the barrier over 120 kJ mol^{-1}, H for those between 100 and 110 kJ mol^{-1}, and a π orbital for those less than 95 kJ mol^{-1}. The exception is $SiMe_3$, and the exceptionally low barriers from carbonyl and silyl substituents might also have stereoelectronic origins: interaction of the passing pyramidalised nitrogen's lone pair with π^*(C=O) (**37**) or with an empty d-orbital (**38**) could lower the energy of the transition state.

The proposed loss of N–CO conjugation at the transition state in Route 2 nicely explains the observed dependence of the barrier to epimerisation of **32** (R = Bu) on solvent polarity.[33] A conjugated amide in which there is significant charge transfer from O to N (**39**) should receive stabilisation from polar solvents; a transition state in which this conjugation were lost would not, so polar solvents should increase rotational barriers by stabilising the conjugated ground state of the amide. Barriers to rotation in amides such as **5** and **7**, which we assume follow Route 1, appear to show a lesser solvent dependence, which could be taken to indicate a greater degree of N–CO conjugation maintained at the transition state.


37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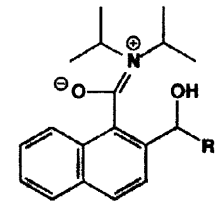

39

There are two further consequences to following Route 2: firstly the barrier to Ar–CO rotation will be at least as large as the barrier to N–CO rotation. In the two instances where N–CO barriers were determined, **5** (with R^1, R^2 = Et) had a N–CO barrier rather higher than the barrier to Ar–CO rotation, so presumably follows Route 1, but **4** (R^1, R^2 = *i*-Pr) has barriers to Ar–CO and N–CO of very similar sizes, and may well follow Route 2, even though R^3 = H. It seems possible that Route 2 is chosen not only by all amides with $R^3 \neq H$ but also by those in which R^2 is large and branched (and therefore presumably has difficulty slipping past even R^3 = H).

The second consequence is that interconversion of the two enantiomers of an amide racemising by Route 2 leads to exchange of R^1 and R^2: Ar–CO and N–CO rotations are concerted (or, to be more accurate, the Ar–CO rotation is "gated"[67] by a N–CO rotation: N–CO rotation could additionally happen independently, and therefore could have a *lower* barrier than Ar–CO rotation).[68] Concerted Ar–CO/N–CO rotation interconverts not the diastereotopic signals in the NMR spectra of R^1 or R^2, but one of the diastereotopic signals of R^1 with one of R^2. This could well be the reason for our inability to model successfully the lineshape of the H_A–H_B coalescence in *E*-**10** (Table 1, entry 13), and estimates of the rate of racemisation derived by VT NMR spectroscopy of amides in which this concerted rotation is a possibility (namely **4** and *E*-**10**) should therefore be treated with even more caution. We are currently examining **4**, **10** and a number of other hindered amides for further evidence of concerted Ar–CO and N–CO bond rotations.[69]

Summary

We propose the following guidelines for estimating the conformational stability of a tertiary aromatic amide:

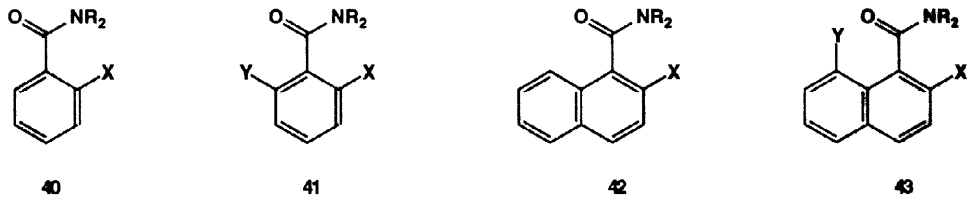
• Tertiary aromatic amides **40** with one *ortho* substituent are chiral on the NMR timescale, but racemise very rapidly with half lives of <2 s at 20 °C.

• Tertiary aromatic amides **41** with two *ortho* substituents can in general be separated into atropisomers, unless either X or Y is a freely rotating trigonal substituent or a silyl group.

• *Peri*-substituted naphthamides **43** are the exception to both of these guidelines, and even with X = H or X = CHO can be separated into atropisomers.

• For 2-substituted tertiary 1-naphthamides **42**, the sequence of stability follows X thus (approximate barriers to rotation in kJ mol^{-1}): CR^aR^bOH (>120) > CR^aR^bH (110) > CH(OH)R (108) > R (105) > OMe (101) > C(=O)R (93) > CHO, $SiMe_3$ (<90)

• For tertiary aromatic amides **41** and **42** with X = H, the size of the *N*-substituent *cis* to oxygen has little influence on the barrier to Ar–CO rotation, and the size of the *N*-substituent *trans* to oxygen is most significant when X ≠ H.



40 41 42 43

Acknowledgements

We are grateful for CASE awards from Merck Sharpe and Dohme (AA), GlaxoWellcome (LWL), Zeneca Pharameuticals (CMcC), Roche Products (NW) and the EPSRC, and to the Leverhulme Trust (JHP), Oxford Asymmetry (RAB) and the Royal Society for funding.

Experimental

Synthesis of the amides

Amides **7-10**, **13**, **21** and **29-36** form part of continuing synthetic projects and their preparation will be described in full elsewhere. Preparations of **4**, **5**, **18**, **22**, **23**, **32** (R = Me, Et, Ph), **33** (R = Me, Ph) [18] and **15**[70] have been published, and amides **8**,[71] **13**,[23] **16**,[20] **20**, **21**, **32**, **33**,[17] **34**,[20] **35** and **36**[22] have appeared in preliminary communications.

Melting points are uncorrected and were carried out on a Gallenkamp melting point apparatus; IR spectra were recorded on an ATi Genesis Series FTIR; ^{1}H NMR spectra were recorded on either Varian Gemini 200 (200 MHz) or Varian XL300 (300MHz), or Bruker XC300 (300 MHz) spectrometers; ^{13}C NMR spectra were recorded on a Bruker XC300 (75 MHz). Coupling constants are given in Hz. Mass spectra were recorded on either Fisons VG Trio 2000 (EI/CI) or a Concept IS (Mass Measurement) Spectrometer.

Flash chromatography[72] was performed using Merck silica gel 60H (230-300 mesh) as the stationary phase. Thin Layer Chromatography (TLC) was performed using Macherey-Nagel 0.25mm silica gel pre-coated plastic sheets with fluorescent indicator UV_{254}.

N,N-Diisopropyl-2-ethyl-1-naphthamide **16**. —*sec*-Butyl lithium (3.31 ml, 1.3M solution in cyclohexane, 4.31 mmol) was added dropwise to a solution of *N,N*-diisopropylnaphthamide[18] (1 g, 3.92 mmol) in THF (100 ml) at –78 °C under an atmosphere of nitrogen. After 1 h at –78 °C ethyl iodide (0.63 ml, 7.83 mmol) was added. The solution was stirred for a further 30 min at –78 °C and allowed to warm to room temperature. Water (40 ml) was added and the THF was removed under reduced pressure The aqueous phase was extracted with dichloromethane (3 x 30 ml) and the combined extracts were washed with water (40 ml), dried over magnesium sulfate, filtered and the solvent was evaporated. The crude product was recrystallised from ethyl acetate to afford the pure *naphthamide* **16** as a white crystalline solid (0.91 g, 82%), m.p. 134–135 °C; ν_{max} (Nujol mull)/cm^{-1} 1619; δ_H ($CDCl_3$) 7.86–7.78 (3H, m, ArH), 7.54–7.40 (3H, m, ArH), 3.72–3.51 (2H, m, 2 x NCH), 2.96–2.67 (2H, m, CH_2), 1.81 (3H, d, *J* 6.7, NCHCH_3), 1.73 (3H, d, *J* 6.9, NCHCH_3), 1.37 (3H, t, *J* 7.6, CH_2CH_3), 1.12 (3H, d, *J* 6.7, NCHCH_3) and 1.02 (3H, d, *J* 6.6, NCHCH_3); δ_C ($CDCl_3$) 169.5 (s, CO), 136.6 (s, Ar), 133.9 (s, Ar), 131.8 (s, Ar), 129.7 (s, Ar), 127.9 (d, Ar), 126.5 (d, Ar), 126.4 (d, Ar), 125.4 (d, Ar), 124.7 (d, Ar), 50.9 (d, NCH), 46.0 (d, NCH), 26.2 (t, CH_2), 21.0 (q, NCHCH_3), 20.9 (q, NCHCH_3), 20.6 (q, NCHCH_3), 20.6 (q, NCHCH_3) and 15.2 (q, CH_2CH_3); *m/z* (EI) 283 (19%, M$^+$), 254 (20), 240 (9), 183 (100) and 155 (19). (Found C, 80.67; H, 8.82; N, 4.83%; M$^+$, 283.1942. $C_{19}H_{25}NO$ requires C, 80.52; H, 8.89; N, 4.94%, *M*, 283.1936).

N,N-Diisopropyl-2-methoxy-1-naphthamide **19**. —Methyl iodide (6.6 ml, 0.106 mol) was added to 2-hydroxy-1-naphthoic acid (5.00 g, 26.6 mmol) and potassium carbonate (8.08 g, 58.5 mmol) in acetone (25 ml) and the mixture was heated to reflux overnight under an atmosphere of nitrogen. Volatile materials were then removed under reduced pressure. Dichloromethane (50 ml) and aqueous sodium hydroxide solution (50 ml) were added and the layers were separated. The aqueous phase was extracted with dichloromethane (2 x 25 ml) and the combined organic layers were washed with water (3 x 40 ml), brine (40 ml), dried over magnesium sulfate and filtered. The solvent was evaporated to give the crude methyl 2-methoxy-1-naphthoate[73] as an orange oil (3.7 g, 52%). δ_H ($CDCl_3$, 200 MHz) 7.90 (1H, d, *J* 9.5), 7.80 (1H, d, *J* 7), 7.75 (1H, d, *J* 7), 7.51 (1H, td, *J* 7 and 1), 7.38 (1H, td, *J* 7 and 1), 7.29 (1H, d, *J* 9.5), 4.05 (3H, s) and 3.96 (3H, s).

The aqueous phase was then acidified and further extracted with dichloromethane (3 x 20 ml). The extracts were washed with water (2 x 15 ml), dried over magnesium sulfate, filtered and the solvent evaporated to afford a mixture of methyl 2-hydroxy-1-naphthoate, 2-hydroxy-1-naphthoic acid and 2-methoxy-1-naphthoic acid.

A solution of methyl 2-methoxy-1-naphthoate (3.7 g, 17.11 mmol) in methanol (20 ml) and aqueous sodium hydroxide (25 ml of a 2M solution) was heated at reflux for 48 h. The methanol was then removed under reduced pressure and water (30 ml) was added. The aqueous phase was washed with dichloromethane (25 ml) and acidified (6M hydrochloric acid). The resulting white precipitate was filtered, washed with water and dried in a desiccator to give 2-methoxy-1-naphthoic acid (3.1 g, 90%),[74] m.p. 168–170 °C (lit.[75] 173-175 °C); ν_{max} (nujol mull)/cm^{-1} 1685; δ_H ($CDCl_3$) 8.06 (1H, d, *J* 8.5, ArH), 7.92 (1H, d, *J* 9, ArH), 7.80 (1H, d, *J* 8, ArH), 7.53 (1H, m, ArH), 7.39 (1H, m, ArH), 7.31 (1H, d, *J* 9, ArH) and 4.01 (3H, s, OCH_3); δ_C ($CDCl_3$) 169.5 (s, CO), 154.5, 132.0, 130.9, 128.6, 128.0, 127.6, 124.1, 112.9 (aromatics) and 56.8 (q, OCH_3); *m/z* (EI) 202 (100%, M^+), 185 (72), 155 (32), 143 (28), 127 (23), 114 (25) and 84 (12). (Found M^+ 202.0632. $C_{12}H_{10}O_3$ requires *M* 202.0630).

The 2-methoxy-1-naphthoic acid (1.29 g, 6.38 mmol) was stirred in thionyl chloride (7 ml) at 60 °C for 3.5 h. Excess thionyl chloride was removed under reduced pressure, and the residual acid chloride was dissolved in dichloromethane (5 ml) and added dropwise over 15 min to an ice-cold solution of diisopropylamine (1.76 ml, 13.40 mmol) in dichloromethane (10 ml). After stirring for 5 min the mixture was allowed to warm to room temperature and stirring continued for 2.5 h. Water (40 ml) was added and the aqueous phase extracted with dichloromethane (3 x 30 ml). The combined organic phases were washed with water (30 ml), saturated aqueous sodium hydrogen carbonate solution (30 ml), water (30 ml), dried over magnesium sulfate, filtered and the solvent was evaporated. The crude yellow solid was recrystallised from ethyl acetate to afford *N,N-diisopropyl-2-methoxy-1-naphthamide* **19** as a white crystalline solid (1.33 g, 74%), m.p. 186–187 °C; ν_{max} (nujol mull)/cm^{-1} 1620; δ_H ($CDCl_3$) 7.83 (2H, t, *J* 9.3, ArH), 7.75 (1H, d, *J* 8.5, ArH), 7.49 (1H, dt, *J* 1.2 and 7.6, ArH), 7.37 (1H, dt, *J* 1.0 and 7.5, ArH), 7.29 (1H, d, *J* 9.2, ArH), 3.97 (3H, s, OCH_3), 3.77–3.53 (2H, m, 2 x NCH), 1.77 (3H, d, *J* 6.9, $NCHCH_3$), 1.72 (3H, d, *J* 6.9, $NCHCH_3$), 1.17 (3H, d, *J* 6.7, $NCHCH_3$) and 1.02 (3H, d, *J* 6.7, $NCHCH_3$); δ_C ($CDCl_3$) 167.8 (s, CO), 152.1 (s, Ar), 131.0 (s, Ar), 129.6 (d, Ar), 128.9 (s, Ar), 128.0 (d, Ar), 127.1 (d, Ar), 123.9 (d, Ar), 123.9 (d, Ar), 122.0 (s, Ar), 113.0 (d, Ar), 56.3 (q, OCH_3), 51.2 (d, NCH), 46.0 (d, NCH), 21.2 (q, $NCHCH_3$), 20.9 (q, $NCHCH_3$), 20.7 (q, $NCHCH_3$), 20.7 (q, $NCHCH_3$); *m/z* (CI) 287 (4%), 286 (21), 273 (15), 272 (100), 185 (2), 130 (2), 102 (6) and 86 (4). (Found C, 75.91; H 7.82; N 5.02%; M^+ 285.1728. $C_{18}H_{23}NO_2$ requires C, 75.76; H, 8.12; N, 4.91%; *M* 285.1729.)

2-Formyl-N,N-diisopropyl-1-naphthamide **20**. —A solution of *N,N*-diisopropyl-1-naphthamide[18] (2.931 g, 11.49 mmol) in THF (40 ml) was added to a stirred solution of *sec*-butyllithium (9.72 ml of a 1.3 M solution in cyclohexane, 11.49 mmol) in THF (80 ml) at –78 °C under an atmosphere of nitrogen. After 1 h at –78 °C DMF (4.29ml, excess) in THF (20ml) was added. The mixture was allowed to warm to ambient temperature and water (50ml) was added. Most of the THF was removed under reduced pressure, and the residue was extracted with dichloromethane (3 x 50ml). The combined organic fractions were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure at room temperature. Flash chromatography (4:1 petroleum ether 40°-60°/ethyl acetate) afforded the aldehyde **20** as a white solid (2.676 g, 82%). m.p. 193–195°C; R_f[40-60 petrol-EtOAc (2:1)] 0.36; υ_{max}(film)/cm^{-1} 1702.1, 1620.0; δ_H(200 MHz; $CDCl_3$) 10.29 (1 H, s, CHO), 8.0–7.5 (6 H, m, ArH), 3.67 (1 H, septet, *J* 6.8, NCH), 3.47 (1 H, septet, *J* 6.7, NCH), 1.79 (3 H, d, *J* 6.9, CH_3), 1.72 (3 H, d, *J* 6.8, CH_3), 1.05 (3 H, d, *J* 6.7, CH_3) and 1.03 (3 H, d, *J* 6.6, CH_3); δ_C(75 MHz; $CDCl_3$) 190.5 (CHO), 167.1 (CON^iPr_2), 142.2, 136.4, 129.5, 129.2, 128.8, 128.7, 128.6, 127.7, 126.2, 122.6 (aromatics), 51.6 (NCH), 46.7 (NCH), 20.8 (CH_3), 20.6 (CH_3), 20.4 (CH_3) and 20.4 (CH_3); *m/z* (CI) 284 (100%, M+H$^+$); EI 283 (3%, M$^+$), 240 (M–^{i}Pr) and 183 [M-N(^{i}Pr)$_2$]. (Found: M+H$^+$, 284.1650. $C_{18}H_{21}NO_2$ requires *M*+H, 284.1650).

2-Hydroxymethyl-N,N-diisopropyl-1-naphthamide **17**. —Sodium borohydride (80 mg) was added to a stirred solution of amide **20** (300 mg) in ethanol (15 ml) at 0°C. After 100 min, water (30ml) was added. The solution was extracted with ether (2 x 20 ml), washed with brine (2 x 20 ml), dried ($MgSO_4$) and evaporated under reduced pressure to yield a white solid (0.302g). Flash column chromatography (1:1 ethyl acetate–petroleum ether 40-60°) gave the *alcohol* **17** (0.2816 g, 93%), R_f 0.25 (1:1 ethyl acetate–petroleum ether 40–60°). δ_H(300 MHz; $CDCl_3$) 7.80-7.70 (3 H, m, ArH), 7.50-7.40 (3 H, m, ArH), 4.77 (1 H, dd, *J* 12 and 3, CH_AH_BOH), 4.52 (1 H, dd, *J* 12 and 10, CH_AH_BOH), 3.56 (1 H, septet, *J* 6.9, NCH), 3.51 (1 H, septet, *J* 6.7, NCH), 3.10 (1 H, dd, *J* 10 and 3, OH), 1.64 (3 H, d, *J* 6.7, CH_3), 1.62 (3 H, d, *J* 6.7, CH_3) and 0.98 (6H, d, *J*6.7, CH_3); δ_C(75 MHz; $CDCl_3$) 170 (CHO), 134.3, 132.7, 129.1, 128.6, 128.2, 126.8, 126.3, 124.6 (Ar), 63.4 (CH_2OH), 51.4 (NCH), 46.3 (NCH), 20.8 (CH_3), 20.5 (CH_3), 20.5 (CH_3) and 20.4 (CH_3); *m/z* (CI) 286 (100%, M+H$^+$). (Found: C, 75.96; H, 8.05; N, 4.91%; M$^+$, 285.1729. $C_{18}H_{23}NO_2$ requires C, 75.96; H, 8.12; N, 4.91%; *M* 285.1729).

N-t-Butyl-2,N-dimethyl-1-naphthamide **25**. —1-Naphthoyl chloride (0.6 ml, 4 mmol) was added dropwise to a vigorously stirred mixture of *N-t*-Butyl methylamine (0.48 ml, 4 mmol), dichloromethane (5 ml) and 2 M aqueous sodium hydroxide (1.6 ml). After 16 h, the layers were separated, the aqueous layer was extracted with ether (3 x 10 ml) and the combined organic fractions were washed with water (10 ml) and brine (2 x 10 ml) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure yielded *N-t-butyl-N-methyl-1-naphthamide* 0.93 g, 96%), m.p. 139.2-140.3 °C. υ_{max}(film)/cm^{-1} 1632; δ_H(300 MHz; $CDCl_3$) 7.94-7.85 (3 H, m, ArH), 7.56-7.40 (3 H, m, ArH), 2.78 (3 H, s, Me) and 1.68 (9 H, s, *t*-Bu); *m/z* (CI) 242 (100%, M+H$^+$). (Found M$^+$, 241.1466. $C_{16}H_{19}NO$ requires *M*, 241.1467).

s-Butyl lithium (1 ml of a 1.3 M solution in cyclohexane, 1.3 mmol) was added to a stirred solution of *N-t*-butyl-*N*-methyl-1-naphthamide (0.2413 g, 1.0 mmol) in THF (20 ml) at –78 °C under an atmosphere of nitrogen. After 1 h, methyl iodide (0.093 ml) was added, and after a further 30 min the mixture was allowed to

warm to 0 °C. Water (10 ml) was added, the layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic fractions were dried ($MgSO_4$) and concentrated to give a crude product (0.1637 g) which was purified by flash chromatography to yield the *amide* **23** (42.3 mg, 17%). υ_{max}(film)/cm^{-1} 1642; δ_H(300 MHz; $CDCl_3$) 7.6-7.4 (6 H, m, ArH), 2.75 (3 H, s), 2.47 (3 H, s, Me x 2) and 1.71 (9 H, s, *t*-Bu); *m/z* (CI) 256 (100%, M+H$^+$). (Found M$^+$, 255.1623. $C_{17}H_{21}NO$ requires *M*, 255.1623).

N,N-Dicyclohexyl-2-methyl-1-naphthamide **26**.[37] —DMF (0.7 ml) was added to a solution of 1-naphthoic acid (3 g, 17.42 mmol) and thionyl chloride (1.4 ml, 19.17 mmol) in dichloromethane (5 ml). The mixture was stirred under a drying tube at room temperature for 2.5 h and excess thionyl chloride was removed under reduced pressure. The residue was dissolved in ether (8 ml) and cooled to 5 °C, and a solution of dicyclohexylamine (7.3 ml, 36.58 mmol) in dry ether (8 ml) was added dropwise. Stirring was continued at room temperature for 16 h. The ether was removed under reduced pressure and dichloromethane (25 ml) and dilute hydrochloric acid (2M, 30 ml) were added. The mixture was filtered, the layers separated and the aqueous phase was extracted with dichloromethane (2 x 20 ml). The combined organic extracts were washed with water (2 x 20 ml) and brine (20 ml), dried over magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography (5% ethyl acetate in light petroleum) to afford *N,N-Dicyclohexyl-1-naphthamide*[37] as a white crystalline solid (2.98 g, 51%), m.p. 120 °C; R_f (10% ethyl acetate in light petroleum) 0.48; ν_{max}(Nujol mull)/cm^{-1} 1737; δ_H($CDCl_3$) 7.94–7.82 (3H, m, ArH), 7.57–7.44 (3H, m, ArH), 7.34 (1H, d, *J* 6.5, ArH), 3.26–3.09 (2H, m, 2 x NCH), 2.99–2.73 (2H, m) and 2.03–0.62 (18H, m, cyclohexyl); δ_C($CDCl_3$) 170.4 (s, CO), 136.8 (s, Ar), 135.5 (s, Ar), 129.6 (s, Ar), 128.2 (d, Ar), 128.2 (d, Ar), 126.6 (d, Ar), 126.3 (d, Ar), 125.2 (d, Ar), 125.0 (d, Ar), 121.9 (d, Ar), 59.9 (d, NCH), 56.2 (d, NCH), 31.3, 31.1, 30.1, 30.1, 26.8, 26.7, 25.6, 25.5, 25.4 and 25.0 (t, CH_2); *m/z* (CI) 338 (16%), 337 (63), 336 (100), 253 (7), 252 (8), 155 (11). (Found: C, 82.45; H, 8.62; N, 4.17%. $C_{23}H_{29}NO$ requires C, 82.34; H, 8.71; N, 4.17%.)

sec-Butyl lithium (0.76 ml, 1.3M solution in cyclohexane, 0.984 mmol) was added dropwise to a solution of the *N,N*-dicyclohexyl-1-naphthamide (0.30 g, 0.894 mmol) in dry THF (30 ml) at –78 °C under an atmosphere of nitrogen. After 1 h methyl iodide (0.11 ml, 1.79 mmol) was added. After 1 h at –78 °C the solution was allowed to warm to room temperature and water (30 ml) was added. The THF was removed under reduced pressure, and the residue was extracted with dichloromethane (3 x 15 ml). The combined extracts were washed with water (25 ml), dried over magnesium sulfate, filtered and the solvent was evaporated. The residual pale yellow oil was purified by column chromatography (5% ethyl acetate in light petroleum) to afford the *2-methyl naphthamide* **26**[37] as a viscous colourless oil which crystallised on standing (0.20 g, 64%), m.p. 112–113 °C; R_f (10% ethyl acetate in light petroleum) 0.52; ν_{max}(Nujol mull)/cm^{-1} 1620; δ_H($CDCl_3$) 7.86–7.77 (2H, m, Ar), 7.75 (1H, d, *J* 8.5, ArH), 7.52–7.40 (2H, m, ArH), 7.33 (1H, d, *J* 8.4, ArH), 3.25–2.82 (4H, m, 2 x NCH and 2 x CH_AH$_B$), 2.50 (3H, s, ArCH_3) and 2.20–1.28 (18H, m, cyclohexyl); δ_C($CDCl_3$) 169.9 (s, CO), 134.6 (s, Ar), 131.7 (s, Ar), 130.3 (s, Ar), 129.7 (s, Ar), 128.3 (d, Ar), 127.8 (d, Ar), 127.5 (d, Ar), 126.3 (d, Ar), 125.2 (d, Ar), 124.5 (d, Ar), 60.1 (d, NCH), 56.2 (d, NCH), 31.5, 31.5, 30.0, 29.9, 26.7, 26.6, 25.6, 25.3, 25.3, 25.0 (t, cyclohexyls) and 19.3 (q, CH_3); *m/z*(CI) 352 (5%), 351 (24), 350 (100), 267 (4), 210 (3) and 169 (10). (Found C, 82.42; H, 8.91; N, 3.98%; *M*$^+$ 349.2401. $C_{24}H_{31}NO$ requires C 82.47, H 8.94, N 4.01%; *M* 349.2406.)

Separation of stereoisomers.

Enantiomers were separated using a Merck-Hitachi HPLC system, the eluent stated in Table 2, and a Chiralpak AD 250 x 4.6 mm or 250 x 10 mm column. Flow rate was 1 ml/min; UV detection at 280 nm.

Diastereoisomeric atropisomers were separated by preparative HPLC on a Dynamax-60A column at 0.15kPa using a Gilson 305 Pump and the eluent given in Table 3. Flow rate was 15.0 ml/min, with UV detection (Gilson 115 detector) at 280nm. Several injections of 50-100 mg were made, collecting pure diastereoisomers and reinjecting mixed fractions. Their epimerisation was analysed by HPLC on a Waters Z Module (10 cm by 8 mm, packed SiO stationary phase) at 200 lb/in^{-2} at room temperature using a Waters 510 HPLC pump, flow rate was 2.0 ml/min; UV detection (Perkin-Elmer LC 480 Auto Scan Diode Array detector) at 280nm.

References and Notes

1. Christie, G. H.; Kenner, J. H. *J. Chem. Soc.* **1922,** *121*, 614.
2. Adams, R.; Yuan, H. C. *Chem. Rev.* **1933,** *12*, 261.
3. Sternhell has quantified these empirical rules in terms of steric interference *I* values: Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618.
4. Westheimer, F. H.; Mayer, J. E. *J. Chem. Phys.* **1946,** *14*, 733.
5. Newman, M. S. *Steric Effects in Organic Chemistry*; Wiley: New York, 1956.
6. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
7. Hoye, T.; Chen, M.; Mi, L.; Priest, O. P. *Tetrahedron Lett.* **1994,** *35*, 8747.
8. Kelly, T. R.; Gracia, A.; Lang, F.; Walsh, J. J.; Bhaskar, K. V.; Boyd, M. R.; Götz, R.; Keller, P. A.; Walter, R.; Bringmann, G. *Tetrahedron Lett.* **1994,** *35*, 7621.
9. Hobbs, P. D.; Upender, V.; Liu, J.; Pollart, D. J.; Thomas, D. W.; Dawson, M. I. *J. Chem. Soc., Chem. Commun.* **1996**, 923.
10. Hobbs, P. D.; Upender, V.; Dawson, M. I. *Synlett* **1997**, 965.
11. Bringmann, G.; Saeb, W.; Koppler, D. *Tetrahedron* **1996,** *52*, 13407.
12. Watanabe, T.; Uemura, M. *J. Chem. Soc., Chem. Commun.* **1998**, 871.
13. Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990,** *29*, 977.
14. Oki, M. *Topics in Stereochem.* **1983,** *14*, 1.
15. Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.
16. Clayden, J. *Angew. Chem., Int. Ed. Engl.* **1997,** *35*, 949.
17. Bowles, P.; Clayden, J.; Tomkinson, M. *Tetrahedron Lett.* **1995,** *36*, 9219.
18. Bowles, P.; Clayden, J.; Helliwell, M.; McCarthy, C.; Tomkinson, M.; Westlund, N. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2607.
19. Clayden, J.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1996,** *37*, 5577.
20. Clayden, J.; Pink, J. H. *Tetrahedron Lett.* **1997,** *38*, 2561.
21. Clayden, J.; Pink, J. H. *Tetrahedron Lett.* **1997,** *38*, 2565.
22. Clayden, J.; Darbyshire, M.; Pink, J. H.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1997,** *38*, 8487.
23. Clayden, J.; Pink, J. H.; Yasin, S. A. *Tetrahedron Lett.* **1998,** *39*, 105.
24. Eiglsperger, A.; Kastner, F.; Mannschreck, A. *J. Mol. Struct.* **1985,** *126*, 421.
25. Cuyegkeng, M. A.; Mannschreck, A. *Chem. Ber.* **1987,** *120*, 803.
26. Kiefl, C.; Zinner, H.; Burgemeister, T.; Mannschreck, A. *Rec. Trav. Chim. Pays-Bas* **1996,** *115*, 125.
27. Holík, M.; Mannschreck, A. *Org. Magn. Reson.* **1979,** *12*, 223.
28. Holík, M.; Turecková, M.; Mannschreck, A.; Stühler, G. *Org. Magn. Reson.* **1982,** *19*, 121.
29. Küspert, R.; Mannschreck, A. *Org. Magn. Reson.* **1982,** *19*, 6.
30. Mannschreck, A.; Mattheus, M.; Rissmann, G. *J. Mol. Struct.* **1967,** *23*, 15.
31. Mannschreck, A.; Zinner, H.; Pustet, N. *Chimia* **1989,** *43*, 165.
32. Beak, P.; Tse, A.; Hawkins, J.; Chen, C. W.; Mills, S. *Tetrahedron* **1983,** *39*, 1983.
33. van Lier, P. M.; Meulendijks, G. H. W. M.; Buck, H. M. *Rec. Trav. Chim. Pays-Bas* **1983,** *102*, 337.
34. Hauer, J.; Treml, E.; Lüdemann, H. D. *J. Chem. Res. (M)* **1982**, 501.
35. Pirkle, W. H.; Welch, C. J.; Zych, A. J. *J. Chromatography* **1993,** *648*, 101.
36. Gasparrini, F.; Misiti, D.; Pierini, M.; Villani, C. *Tetrahedron Asymmetry* **1997,** *8*, 2069.
37. Thayumanavan, S.; Beak, P.; Curran, D. P. *Tetrahedron Lett.* **1996,** *37*, 2899.
38. Snieckus, V. *Chem. Rev.* **1990,** *90*, 879.
39. Casarini, D.; Lunazzi, L.; Gasparrini, F.; Villani, C.; Cirilli, M.; Gavuzzo, E. *J. Org. Chem.* **1995,** *60*, 97.

40. Casarini, D.; Lunazzi, L.; Alcaro, S.; Gasparini, F.; Villani, C. *J. Org. Chem.* **1995,** *60*, 5515.
41. Villani, C.; Pirkle, W. H. *Tetrahedron Asymmetry* **1995,** *6*, 27.
42. Casarini, D.; Lunazzi, L.; Pasquali, F.; Gasparrini, F.; Villani, C. *J. Am. Chem. Soc.* **1992,** *114*, 6521.
43. Guerra, A.; Lunazzi, L. *J. Org. Chem.* **1995,** *60*, 7959.
44. Stewart, W. H.; Siddall, T. H. *Chem. Rev.* **1970,** *70*, 517.
45. Siddall, T. H.; Garner, R. H. *Can. J. Chem.* **1966,** *44*, 2387.
46. Lewin, A. H.; Frucht, M. *Tetrahedron Lett.* **1970**, 1079.
47. Bedford, G. R.; Greatbanks, D.; Rogers, D. B. *J. Chem. Soc., Chem. Commun.* **1966**, 330.
48. Jennings, W. B.; Tolley, M. S. *Tetrahedron Lett.* **1976**, 695.
49. Berg, U.; Sandström, J. *Tetrahedron Lett.* **1976**, 3197.
50. Berg, U.; Sandström, J.; Jennings, W. B.; Randall, D. *J. Chem. Soc., Perkin Trans. 2* **1980**, 949.
51. Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London, 1982.
52. (a) Hauer, J.; Treml, E.; Lüdemann, H.-D. *J. Chem. Res. (M)* **1982**, 516; (b) Court, J. J.; Hlasta, D. J. *Tetrahedron Lett.* **1996**, *37*, 1335.
53. Mannschreck[27] has studied bond rotation in achiral amides by VT NMR in the presence of chiral shift reagents.
54. We used the equations presented by Sandström[51] entered into a spreadsheet, along with the approximations $k = \frac{\pi\Delta\nu}{\sqrt{2}}$ (for uncoupled signals), or $k = \pi\sqrt{\frac{(\Delta\nu)^2 + 6(J_{AB})^2}{2}}$ (for coupled signals) to generate approximate values for k, which we refined with the more sophisticated commercial program gNMR (Cherwell Scientific; demonstration copy available on http://www.cherwell.com). Substitution into the Eyring equation, $\Delta G^{\ddagger}_{Ar-CO} = 0.01914 \times T_c \times \left[10.319 + \log_{10}\left(\frac{T_c}{k}\right)\right]$, gave values of $\Delta G^{\ddagger}_{Ar-CO}$.
55. Calculated k is the rate constant for *enantiomerisation* of the amide. For *racemisation*, $t_{1/2} = \frac{\ln 2}{2k}$
56. Assignment of amide geometry has been a source of contention for many years, but in *aromatic* amides this rule appears to be quite general. The switch in preference for amide isomers from *E* to *Z* (*cf.* **8** and *E*-**10**) remains unexplained, but is well documented,[57] though it has led to some erroneous geometry assignments.[47]
57. Lewin, A. H.; Frucht, M.; Chen, K. V. J.; Benedetti, E.; di Blasio, B. *Tetrahedron* **1975,** *31*, 207.
58. The literature value[34] for this N–CO rotation in $CHCl_3$ is 72 kJ mol^{-1}.
59. The literature value[34] for this N–CO rotation in d_6-acetone–C_6D_6–d_8-toluene is 72 kJ mol^{-1}.
60. Perrin, C. L.; Dwyer, T. J. *Chem. Rev.* **1990,** *90*, 935.
61. Perrin, C. L.; Thouburn, J. D.; Kresge, J. *J. Am. Chem. Soc.* **1992,** *114*, 8800.
62. Amide **24** has been made by an enantioselective ortholithiation reaction and separated into enantiomers on a Regis Whelk-O1 column.[39]
63. Meyers, A. I.; Flisak, J. R.; Aitken, R. A. *J. Am. Chem. Soc.* **1987,** *109*, 5446.
64. Fleming, I, in *Comprehensive Organic Chemistry;* Barton, D. H. R.; Ollis, W. D. Eds.; Pergamon: Oxford, 1979; Vol. 3; p. 547.
65. Clayden, J. *Synlett*, in the press.
66. Chupp, J. P.; Olin, J. F. *J. Org. Chem.* **1967,** *32*, 2297.
67. Kilway, K. V.; Siegel, J. S. *J. Am. Chem. Soc.* **1991,** *1991*, 2332.
68. Concerted Ar–CO and N–CO rotation has been previously proposed[45] and observed in amides[35] and thioamides.[24] See also reference 70.
69. Clayden, J.; Pink, J. H. *Angew. Chem., Int. Ed. Engl.* in the press.
70. Chen, C.-W.; Beak, P. *J. Org. Chem.* **1986,** *51*, 3325.
71. Ahmed, A.; Clayden, J.; Rowley, M. *J. Chem. Soc., Chem. Commun.* **1998**, 297.
72. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978,** *43*, 2923.
73. Klinkmueller, K.-D.; Marschall, H.; Weyerstahl, P. *Chem. Ber.* **1975,** *108*, 191.
74. Gant, T. G.; Meyers, A. I. *J. Am. Chem. Soc.* **1992,** *114*, 1010.
75. Ghosal, M. *J. Org. Chem.* **1960,** *25*, 1856.