

Achieving conformational control over C–C, C–N and C–O bonds in biaryls, *N,N'*-diarylureas and diaryl ethers: advantages of a relay axis†

Mark S. Betson, Ann Bracegirdle, Jonathan Clayden,* Madeleine Helliwell, Andrew Lund, Mark Pickworth, Timothy J. Snape and Christopher P. Worrall

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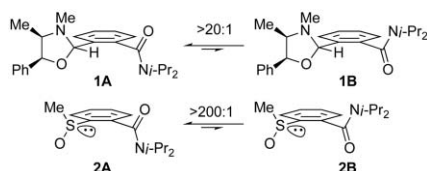
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The orientation of Ar–C, Ar–N and Ar–O bonds in biaryls, *N,N'*-diarylureas and diaryl ethers (whose conformers are distinguishable by NMR) may be controlled with a selectivity up to >95 : 5 by an adjacent stereogenic centre; the selectivity may be greater when a second stereogenic axis is inserted between the controlling centre and the slowly rotating bond.

The orientation of functional groups¹ has consequences for crystal engineering,² for the design of ligands, sensors and other supra-molecular assemblies,³ for stereoselective synthesis⁴ via chiral memory⁵ and relay,^{6,7} and for the asymmetric synthesis of atropisomers.^{8,9} Compared to conformational control in rings, rational conformational control in acyclic systems is in its infancy.¹⁰ Using tertiary aromatic amides (whose conformation can be readily studied by NMR) as a model, we showed recently that certain classes of stereogenic centre may exert a remarkably high degree of conformational control over the orientation of a nearby substituent.¹¹ For example, amides **1** generally adopt the conformation **1A** rather than **1B**, with >20 : 1 selectivity, while in amides related to **2**, the conformational selectivity can reach 200 : 1 **2A** : **2B** (Scheme 1).¹² We have used the conformational bias exhibited by these and other amides as the basis of a strategy for the asymmetric synthesis of atropisomers under thermodynamic control.⁹

It seemed reasonable to propose that control of C–C, along with C–N and C–O bonds, would be achievable in related structures by locating the bonds adjacent to appropriately chosen stereogenic centres. Biaryls **3**, *N,N'*-diaryl ureas **4** and diaryl ethers **5** provide useful model compounds for these studies, and in this communication we report on the success of this strategy. We show that, perhaps surprisingly, greater conformational control is sometimes possible when the centre is located *further away* from the axis, with the stereochemical influence being relayed (and amplified) by an intervening tertiary aromatic amide.

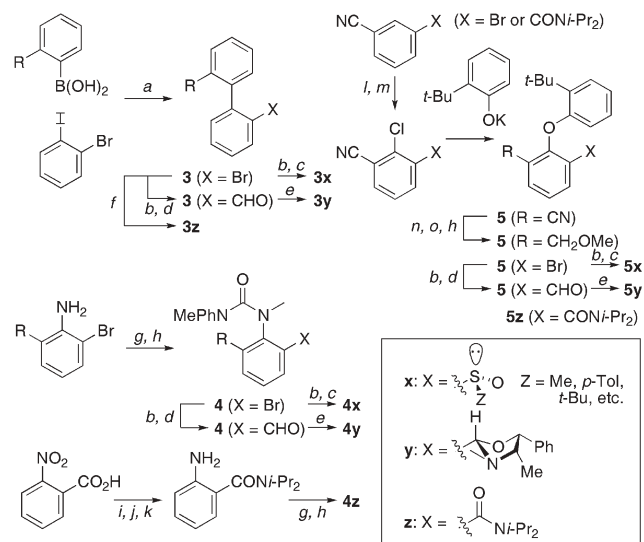


Scheme 1 Conformational control in amides.

School of Chemistry, University of Manchester, Oxford Road, Manchester, UK M13 9PL. E-mail: clayden@man.ac.uk; Fax: +44 (0)161 275 4939

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We used two types of stereogenic centre, X, to control the axial conformation (Scheme 2), both of which had performed well with amides:¹¹ the sulfoxides shown as X = x (with the substituent Z alternatively Me, *p*-Tol, *t*-Bu or other alkyl groups) and the oxazolidine shown as X = y (formed by condensation of (–)-ephedrine¹³ with the corresponding aldehydes X = CHO). We also measured conformational ratios when the bonds under investigation were located *ortho* to a rotationally restricted amide group –CON*i*-Pr₂ (X = z). Biphenyls¹⁴ **3** (X = Br) were made by a Suzuki coupling between 2-iodobromobenzene and a range of arylboronic acids,¹⁵ and converted *via* bromine–lithium exchange to **3x**, **3y** and **3z**. Ureas¹⁶ **4** were made by the condensation of an appropriate aniline with phenyl isocyanate, followed by methylation and conversion to **4x** and **4y** *via* bromine–lithium exchange. Diaryl ethers¹⁷ **5** were formed by the nucleophilic aromatic substitution of chloride from 3-bromo-2-chlorobenzonitrile by 2-*tert*-butylphenoxide, reduction to **5** (R = CH₂OMe, X = Br) and conversion to **5x** and **5y** *via* bromine–lithium exchange. **5z** was made by the same route, with R = CN and X = CON*i*-Pr₂, throughout.



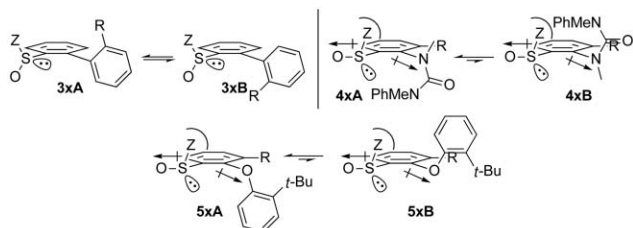
Scheme 2 Synthesis of *ortho*-substituted biaryls, diaryl ureas and diaryl ethers. Reagents and conditions a: Pd(PPh₃)₄, Na₂CO₃, EtOH, H₂O; b: *n*-BuLi, THF; c: [for Z = *p*-Tol] (–)-menthyl *para*-toluenesulfinate or [for Z = *t*-Bu] *t*-BuS(O)*t*-Bu or [for Z = Me] (i) Me₂S₂, (ii) *m*-CPBA or [for Z = *i*-Pr] (i) *i*-Pr₂S₂, (ii) *m*-CPBA or [for Z = *c*-Hex] cyclohexylsulfanyl diacetyl glucose or [for Z = *α*-Me-*c*-Hex] (i) LiTMP, (ii) MeI; d: Me₂NCHO; e: (–)-ephedrine, Tol, Δ; f: ClCON*i*-Pr₂; g: PhNCO, CH₂Cl₂; h: NaH, MeI; i: (COCl)₂, Me₂NCHO, CH₂Cl₂; j: HN*i*-Pr₂, Et₃N, CH₂Cl₂; k: H₂, Pd/C; l: LiTMP, THF, –90 °C; m: C₂Cl₆; n: DIBAL; o: NaBH₄.

Slow C–C, C–N or C–O bond rotation yields two sets of peaks in the NMR spectra of many of these compounds at ambient temperature. We assign these to conformers **A** (major) and **B** (minor), as shown (for **3x–5x**) in Scheme 3 and as indicated in the footnotes of Table 1. In several cases, the interconvertibility of the species giving rise to the paired peaks was confirmed by dynamic NMR analysis or by separation and re-equilibration: the ratios in Table 1 are governed thermodynamically.

Sulfoxides ($X = x$) in general gave good control over bond orientation. Increasing the steric bulk of the sulfoxide substituent **Z** significantly increased conformational selectivity (Table 1, entries 18–22 and 26–38). Low ratios were observed for biaryls **3x**, with biaryl ethers **5x** performing better and *N,N'*-diarylureas **4x** being the most effectively controlled. With $Z = t\text{-Bu}$ or $Z = p\text{-Tol}$, single sets of peaks were observed in the NMR spectra of **4x**. This high level of control led us to suppose that the conformer **4xA**, seen in the X-ray crystal structure (Fig. 1(a)),²¹ is also the unique conformer in solution. Control in **5x** depended heavily on **Z**, with only *t*-Bu and α -methylcyclohexyl sulfoxides giving good conformational selectivity (Table 1, entries 34–38). We again assign the major conformer as structure **5xA** on the basis of the X-ray crystal structure of **5x** ($Z = t\text{-Bu}$, $R = \text{CH}_2\text{OMe}$) (Fig. 1(b)).²¹ Much less effective conformational control was provided by the oxazolidines $X = y$ (Table 1, entries 3–6, 23, 24 and 39), in stark contrast to the control they achieve over amides **1** (Scheme 1).

We propose a common origin for the conformational control in **4x** and **5x**, arising from the sum of the steric and electronic effects illustrated in Scheme 3. Fig. 1(a) and 1(b) show the powerful dipole of the sulfoxide S–O bond more or less opposing the dipole associated with the Ar–N or Ar–O bond, with this electronic interaction fixing the orientation of the sulfoxide group by populating essentially just one Ar–S rotamer. Control over the orientation of the Ar–N or Ar–O bond is then supplied by steric interactions between the sulfoxide substituent **Z** and the rest of the diaryl urea or diaryl ether moiety, explaining the dependence on the size of **Z**. Solvent effects appear to be weak (Table 1, entries 35–38).

Dipoles also appear to govern the selectivities observed in the amido substituted **3z**, **4z** and **5z** structures (Table 1, entries 7–17, 25 and 40). For diaryl ethers **5z** or biaryls **3z** ($R = \text{alkyl}$), levels of control are relatively low, but replacing the $R = \text{alkyl}$ substituent of **3z** with a polar group $R = \text{OR}'$, Cl or COR' raises the control markedly. Single conformers are likewise observed for ureas **4z**, and we propose that **4zA** is also the conformer evident in the X-ray crystal structure of **4z**.²¹ The control in these compounds seems to arise from an electronic interaction between the dipole of the amide's C=O group and, in the case of **3z**, the induced dipole in the second ring, or in the case of **4z**, the urea carbonyl group (Scheme 4). A steric effect may also be at work in **4z**.



Scheme 3 Conformational control with a sulfoxide substituent.

Table 1 Conformational ratios in biaryls, ureas and diaryl ethers

Entry	Compound	R	Z	Ratio A : B	Solvent ^a
1	3x	Me	<i>t</i> -Bu	28 : 72 ^{b,b}	CDCl ₃
2		OMe	<i>t</i> -Bu	59 : 41 ^b	CDCl ₃ ^c
3	3y	Me	—	50 : 50	CDCl ₃
4		Et	—	50 : 50	CDCl ₃
5		Benzo ^d	—	50 : 50	CDCl ₃
6		OMe	—	50 : 50	CDCl ₃
7		3z	Me	—	75 : 25 ^{e,f}
8	Et		—	75 : 25 ^g	CDCl ₃
9	<i>i</i> -Pr		—	75 : 25 ^g	CDCl ₃
10	Benzo ^a		—	80 : 20 ^g	CDCl ₃
11	OMe		—	>94 : 6 ^{e,h}	CDCl ₃
12	OEt		—	>94 : 6 ⁱ	CDCl ₃
13	<i>Oi</i> -Pr		—	>94 : 6 ⁱ	CDCl ₃
14	Cl		—	>94 : 6 ⁱ	CDCl ₃
15	CO ₂ H		—	>94 : 6 ⁱ	CDCl ₃
16	CO ₂ Me		—	>94 : 6 ⁱ	CDCl ₃
17	CHO	—	>94 : 6 ⁱ	CDCl ₃	
18	4x	H (<i>p</i> -Me) ^k	Me	50 : 50	<i>d</i> ₈ -THF ^l
19		Br	Me	50 : 50	<i>d</i> ₈ -Toluene
20		H (<i>p</i> -Me) ^k	<i>p</i> -Tol	>95 : 5 ^m	<i>d</i> ₈ -THF ⁿ
21		H (<i>p</i> -Me) ^k	<i>t</i> -Bu	>95 : 5 ^o	<i>d</i> ₈ -THF ⁿ
22		Br	<i>p</i> -Tol	>95 : 5 ^o	CDCl ₃
23	4y	H (<i>p</i> -Me) ^k	—	50 : 50	<i>d</i> ₈ -THF ^p
24		Br	—	50 : 50	<i>d</i> ₈ -Toluene
25	4z	H	—	>95 : 5 ^q	CDCl ₃
26		5x	CN	Me	50 : 50
27	5y	CN	<i>p</i> -Tol	60 : 40 ^b	CDCl ₃
28		CN	<i>i</i> -Pr	57 : 43 ^r	CDCl ₃
29		CN	<i>c</i> -Hex	60 : 40 ^r	CDCl ₃
30		CH ₂ OMe	Me	57 : 43 ^r	CDCl ₃
31		CH ₂ OMe	<i>p</i> -Tol	60 : 40 ^r	CDCl ₃
32		CH ₂ OMe	<i>i</i> -Pr	66 : 34 ^s	CDCl ₃
33		CH ₂ OMe	<i>c</i> -Hex	57 : 43 ^r	CDCl ₃
34		CH ₂ OMe	α -Me- <i>c</i> -Hex	80 : 20 ^r	CDCl ₃
35		CH ₂ OMe	<i>t</i> -Bu	86 : 14 ^t	CDCl ₃
36		CH ₂ OMe	<i>t</i> -Bu	86 : 14 ^t	C ₆ D ₆
37	CH ₂ OMe	<i>t</i> -Bu	88 : 12 ^u	<i>d</i> ₈ -THF	
38	CH ₂ OMe	<i>t</i> -Bu	88 : 12 ^u	CD ₃ OD	
39	5y	Ac	—	66 : 34 ^b	CDCl ₃
40		5z	CN	—	57 : 43 ^b
41	6x	Me	<i>p</i> -Tol	75 : 25 ^u	CDCl ₃
42		OMe	<i>p</i> -Tol	>94 : 6 ^u	CDCl ₃
43	6y	Me	—	80 : 20 ^v	CDCl ₃
44		OMe	—	93 : 7 ^v	CDCl ₃
45	10y	H (<i>p</i> -Me)	—	>95 : 5 ^v	CDCl ₃

^a Ratio measured at +25 °C unless otherwise stated. ^b Major isomer assigned arbitrarily. ^c NMR recorded at 0 °C. ^d Upper ring is 1-naphthyl. ^e Preferred conformer assigned by molecular modelling (Monte Carlo search, 5000 steps, MM2*, Macromodel). ^f Conformer A favoured by 3.0 kJ mol⁻¹. ^g By analogy with entry 7. ^h Conformer A favoured by 7.8 kJ mol⁻¹. ⁱ By analogy with entry 11. ^j By analogy with the Ar–Ar conformational preference of other 2'-carbonyl substituted 2-phenylbenzamides.^{6,18} ^k These compounds carry, in addition, a methyl group *para* to the urea N. ^l NMR recorded at –90 °C. ^m Assumed preference for the conformation displayed in the crystalline state: see Fig. 1(a). ⁿ NMR spectra recorded at +25 and at –90 °C. ^o By analogy with entry 20. ^p NMR spectrum recorded at –50 °C. ^q Assumed preference for the conformation displayed in the crystalline state: see ref. 21. ^r By analogy with entry 35. ^s 2-D TLC indicates interconversion of the conformers on a timescale of minutes. ^t Assumed preference for the conformation displayed in the crystalline state: see Fig. 1(b). ^u On the basis of the conformational preference of 2-amidosulfoxides^{8,11,12} and of 2-amido biaryls (entries 7 and 11). ^v On the basis of the known conformational preference of 2-amidophenyl oxazolines^{9,11,19,20} and of 2-amido biaryls (entry 7). ^w Assumed preference for the conformation displayed in the crystalline state: see ref. 21.

The coupling of axial conformations, evident in **3z** and **4z**, raises the possibility of using an amide axis to amplify the effect of a stereocontrolling centre by interposing it between that centre and

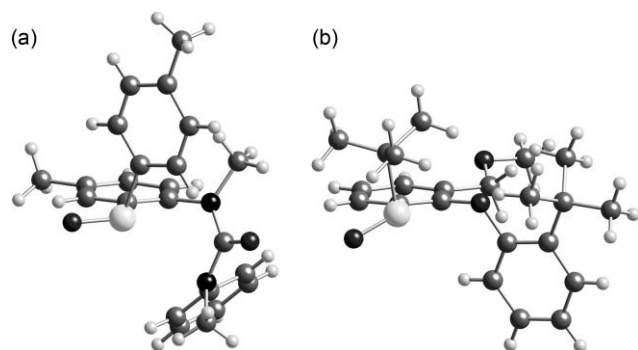
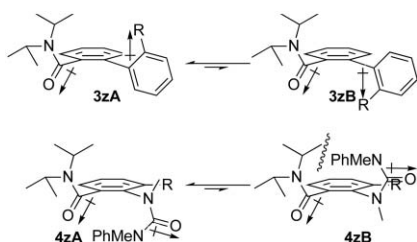
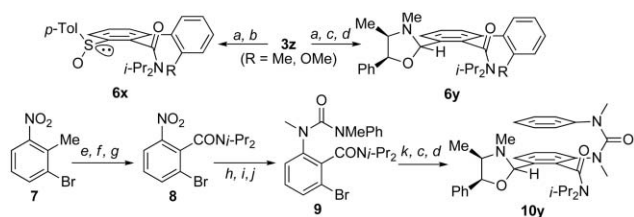


Fig. 1 (a) X-Ray crystal structure of **4x** (R = H, Z = *p*-Tol); (b) X-Ray crystal structure of **5x** (R = CH₂OMe; Z = *t*-Bu).^{21,22}



Scheme 4 Conformational communication with amides.



Scheme 5 Amplification and relay of conformational control. Reagents and conditions: a: *sec*-BuLi, THF, -78 °C; b: (–)-menthyl toluenesulfinate; c: Me₂NCHO; d: (–)-ephedrine, toluene, Δ; e: KMnO₄; f: (COCl)₂, Me₂NCHO, CH₂Cl₂; g: HNi-Pr₂, Et₃N, CH₂Cl₂; h: SnCl₂·2H₂O, HCl; i: PhNCO, CH₂Cl₂; j: NaH, MeI; k: *n*-BuLi, THF, -78 °C.

an otherwise poorly controlled axis. To test this hypothesis, we made biaryls **6x** and **6y** (R = Me and OMe) by the *ortho*-lithiation of **3z** (Scheme 5). We also made diaryl urea **10y** from **7**. Oxidation and amide formation gave **8**, which was shown to be chiral by HPLC on a chiral stationary phase. Reduction and urea formation gave **9**, which, like **4z**, was conformationally uniform. Halogen metal exchange and conversion *via* the aldehyde to the oxazolidine gave **10y** whose X-ray crystal structure is shown in the supplementary information.^{†21}

The NMR spectra of **6x** (R = OMe), **6y** (R = OMe) and **10y** indicated that these compounds exist almost entirely as single conformers about their Ar–Ar or Ar–N bonds (Table 1, entries 42, 44 and 45), despite the fact that their congeners **3x** (R = OMe), **3y** (R = OMe) and **4y**, in which the oxazolidine lies directly adjacent to the axis, exhibit only poor conformational control (Table 1, entries 2, 6, 23 and 24). The amide successfully picks up the stereocontrolling influence of the oxazolidine, amplifies and inverts it (suggesting *projection*¹⁹ as an apt analogy), and hence induces control over an adjacent C–C or C–N bond. Control in **6x** and **6y** (R = Me) is unsurprisingly less good, since the coupling of amide

and biaryl conformations in these compounds is less secure (compare Table 1 pairs of entries 41/42 and 43/44 with the pair of entries 7/11).

These results indicate that rational control over C–C, C–N and C–O bond conformation is possible by judicious exploitation of dipolar interactions. We are currently extending this work to the study of stereochemical relay effects,⁸ and to the stereoselective synthesis of new classes of atropisomers.

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- X-ray crystallographic data and ball-and-stick figures of crystal structures reported in this paper may be found in the Electronic Supporting Information. CCDC 623108 (**4x**, R = H, Z = *p*-Tol), 623109 (**5x**, R = CH₂OMe, Z = *t*-Bu), 623110 (**4z**, R = H) and 623110 (**10y**). For crystallographic data in CIF or other electronic format see DOI: 10.1039/b614618j.
- For clarity and consistency of conformational representation, Fig. 1(b) shows a molecule enantiomeric with that described in the accompanying crystallographic data.