ORGANIC LETTERS

2001
Vol. 3, No. 26
4133−4136

Conformational Preference and Remote (1,10) Stereocontrol in Biphenyl-2,2′-dicarboxamides

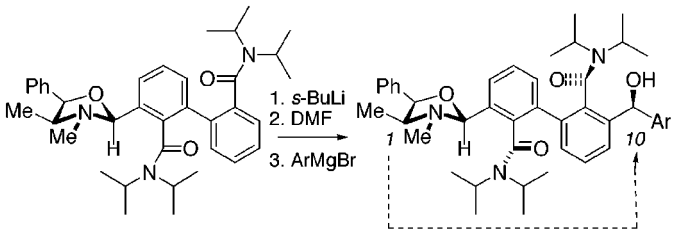
Jonathan Clayden,* Andrew Lund, and Latifa H. Youssef

Department of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, U.K.

j.p.clayden@man.ac.uk

Received September 12, 2001

ABSTRACT



The double ortholithiation and electrophilic quench of *N,N,N′N′*-tetraisopropylbiphenyl-2,2′-dicarboxamide 1 is diastereoselective, giving the chiral, C_2-symmetric atropisomers of the 3,3′-disubstituted products 3. These chiral atropisomers can be converted with moderate to good stereoselectivity to their achiral, centrosymmetric epimers by heating. The stereoselectivity of the double lithiation-quench reaction is determined by the stereochemistry of the intermediate doubly lithiated species 2, either diastereoisomer of which may be formed stereospecfically from the corresponding atropisomeric dibromo compounds.

Tertiary amide groups in substituted benzamides do not lie coplanar with the aromatic ring and adopt a more-or-less perpendicular conformation[1] whose stereochemistry depends on the influence of other stereogenic centers and axes within the molecule.[2] This feature allows tertiary amide groups to relay stereochemistry, and we have used them in the control of remote relationships between new stereogenic centers[3] or axes.[4] In this paper we show that despite conformational freedom about the biaryl axis the tertiary amide substituents of a biphenyl-2,2′-dicarboxamide remain in stereochemical communication and that they direct the atroposelective formation of a range of products from 3,3′-diortholithiation and electrophilic quench.

N,*N*,*N*′,*N*′-Tetraisopropylbiphenyl-2,2′-dicarboxamide **1** was made from 2,2′-biphenic acid by a standard method (3 equiv of $(COCl)_2$, cat. DMF, then 10 equiv of *i*-Pr_2NH). The ^{1}H NMR spectrum of **1** showed a single set of four methyl doublets down to −20 °C, suggesting that **1** exists in solution as a single Ar−CO conformer.[5] Its X-ray crystal structure is shown in Figure 1.

Amide **1** was resistant to double ortholithiation,[6] but treatment with 6−10 equiv of *s*-BuLi in the presence of TMEDA gave the dilithio species **2**, which reacted with electrophiles (MeI, EtI, DMF, or Me_3SiCl) to give the 3,3′-disubstituted products **3a**, **3b**, **3c,** and **3e**, as shown in Scheme 1.

(1) (a) Bowles, P.; Clayden, J.; Helliwell, M.; McCarthy, C.; Tomkinson, M.; Westlund, N. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2607. (b) Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L. W.; McCarthy, C.; Pink, J. H.; Westlund, N.; Yasin, S. A. *Tetrahedron* **1998**, *54*, 13277.

(2) (a) Clayden, J.; Lai, L. W. *Angew. Chem., Int. Ed.* **1999**, *38*, 2556. (b) Clayden, J.; Johnson, P.; Pink, J. H.; Helliwell, M. *J. Org. Chem.* **2000**, *65*, 7033. (c) Clayden, J.; Lai, L. W. *Tetrahedron Lett.* **2001**, *42*, 3163.

(3) (a) Clayden, J.; Pink, J. H.; Yasin, S. A. *Tetrahedron Lett.* **1998**, *39*, 105. (b) Clayden, J.; Kenworthy, M. N.; Youssef, L. H. *Tetrahedron Lett.* **2000**, *41*, 5171. (c) Clayden, J.; Lai, L. W.; Helliwell, M. *Tetrahedron: Asymmetry* **2001**, *12*, 695.

(4) Clayden, J.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1999**, *40*, 3331.

(5) Below −20 °C, decoalescences occur as a result of slow Ar−Ar rotation. Rotation of the conformer shown in Figure 1 about the Ar−Ar axis is an enantiomerization and would interconvert the signals of the two rings.

(6) (a) Mills, R. J.; Horvath, R. F.; Sibi, M. P.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 1145. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

10.1021/ol0167457 CCC: $20.00
Published on Web 11/27/2001

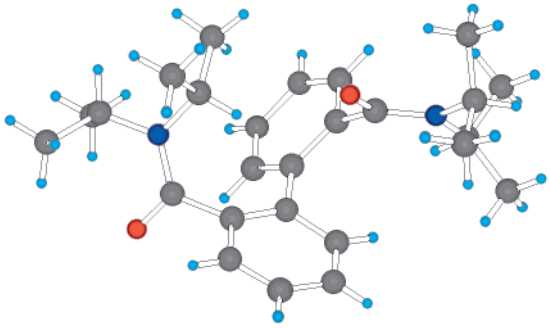
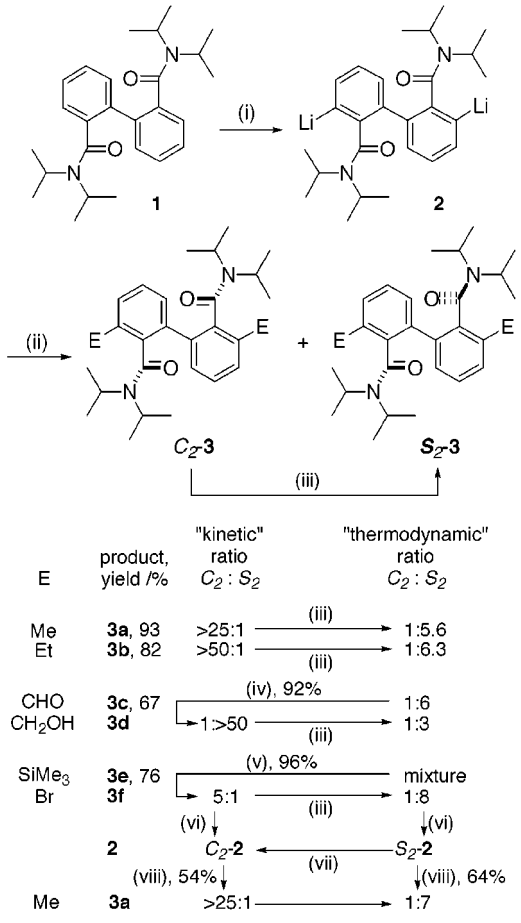


Figure 1. X-ray crystal structure of **1**.

Because the tertiary amide groups of **3** are each flanked by two *ortho* substituents, they possess stereogenic Ar−CO axes,[1] in principle allowing compounds **3** to exist as either of two atropisomers.[7] Since a biphenyl axis usually requires at least three *ortho* substituents for its conformers to become atropisomers,[8] the Ar−Ar axes of **3** are not expected to be stereogenic, though the aryl rings will not lie coplanar. On average, therefore, the atropisomers of **3** will be either chiral and C_2 symmetric (C_2-**3**) or achiral and S_2-symmetric = centrosymmetric (S_2-**3**).

Analytical HPLC on a chiral stationary phase[9] showed that the major products of methylation and ethylation of **1** are chiral and confirmed the assignments of these compounds as C_2-**3a** and C_2-**3b**. However, on heating (toluene, reflux, 1 h) both C_2-**3a** and C_2-**3b** epimerized to give, with moderate to good selectivity, atropisomers that could no longer be resolved by HPLC on a chiral stationary phase and must therefore be S_2-**3a** and S_2-**3b** (Figure 2). The kinetic products of the lithiation-quench of **1** are therefore C_2-**3**, while the more stable atropisomers are S_2-**3**.

Scheme 1. Atropisomers of Biphenyl-2,2′-dicarboxamides[a]



[a] Reagents: (i) 6−10 equiv of *s*-BuLi, TMEDA, THF, −78 °C, 30 min; (ii) MeI or EtI or Me_2NCHO or Me_3SiCl; (iii) toluene, reflux, 1 h; (iv) $NaBH_4$, EtOH, 0 °C, 30 min; (v) 10 equiv of Br_2, CCl_4, reflux, 12 h; (vi) 4 equiv of *t*-BuLi, THF, −78 °C, 5 min; (vii) +10 °C, 1 h; (viii) excess MeI, −78 °C.

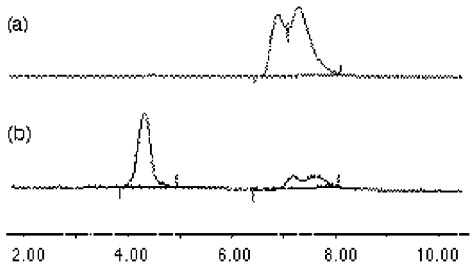


Figure 2. Analytical HPLC traces (chiral stationary phase)[9] of (a) C_2-**3a**; (b) equilibrated mixture of S_2-**3a** and C_2-**3a**.

By contrast, the products of bis-formylation and bis-silylation of **1** (**3c** and **3e**) were isolated as a mixture of atropisomers that displayed no change in stereochemistry on heating. This is presumably because the −CHO and $-SiMe_3$ substituents provide typically poor barriers to bond rotation,[1b] and the isolated products contain an already-equilibrated mixture of atropisomers. The major isomer of **3c** in this mixture was apparently the achiral S_2-**3c** since neither it nor its reduction product, the diol S_2-**3d**, could be resolved by HPLC on a chiral stationary phase.[10] Surprisingly, however, the major isomer of **3e** in the equilibrated mixture appeared to be C_2-**3e**, since double *ipso* bromo-desilylation with Br_2 in CCl_4[11] gave mainly the chiral dibromide C_2-**3f**. Heating this C_2-**3f**-rich mixture in refluxing toluene for 1 h epimerized it to the achiral atropisomer S_2-**3f**.

Since C_2-**3a** and C_2-**3b** are formed selectively under kinetic control, either the intermediate 3,3-dilithio species **2** has C_2 symmetry (maybe C_2-**2** is more stable than S_2-**2** or perhaps

(7) For a related case, see ref 4.

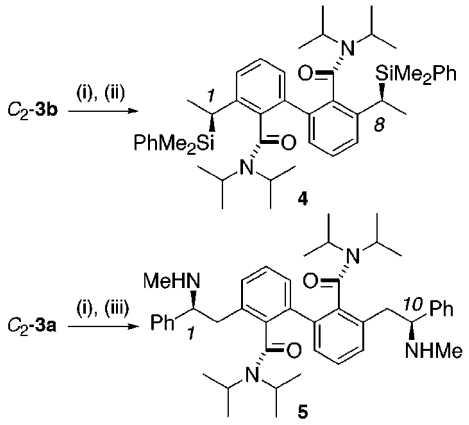
(8) (a) Adams, R.; Yuan, H. C. *Chem. Rev.* **1933**, *12*, 261. (b) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.

(9) Whelk-O1 from Regis.

(10) Consistent differences between the ^{1}H NMR spectra of C_2-**3** and S_2-**3** confirmed this assignment. In the compounds assigned as C_2-**3a**−**f** the highest field methyl doublet lies between δ 0.20 and 0.35; in the compounds assigned as S_2-**3a**−**f** the highest field methyl doublet lies between δ 0.80 and 0.90.

(11) Mills, R. J.; Taylor, N. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4372.

Scheme 2. Remote Stereocontrol with a Biphenyl-2,2′-dicarboxamide[a]



[a] Reagents: (i) 6−10 equiv of *s*-BuLi, TMEDA, THF, −78 °C; (ii) $PhMe_2SiCl$, −78 °C (19%); (iii) PhCH═NMe, −78 °C (12%).

the C_2 conformer of **1** is lithiated faster than the S_2 conformer of **1**) or **2** exists as an interconverting mixture of C_2 and S_2 conformers and C_2-**2** reacts faster. We managed to make both C_2-**2** and S_2-**2** selectively by treating each of the two atropisomeric dibromo compounds C_2-**3f** and S_2-**3f** with *t*-BuLi. On quenching with MeI, a different atropisomer was obtained in each case: C_2-**3a** from C_2-**3f** and S_2-**3a** from S_2-**3f**. The bromine−lithium exchange of **3f** and the alkylation of **2** are therefore stereospecific: the atropisomers of **2** do not interconvert under the conditions of the reaction (THF, −78 °C) and hence stereoselectivity in the conversion **1** → **2** → **3** must arise by selective formation of C_2-**2** under kinetic control. At higher temperatures, though, C_2-**2** and S_2-**2** do interconvert: if the addition of MeI to the organolithium derived from S_2-**3f** is delayed until after the solution of S_2-**2** has been raised to +10 °C for 1 h, only C_2-**3a** is obtained. The relative stabilities of the atropisomers of **2** and of **3** are therefore opposite, with S_2-**2** epimerizing to the more stable C_2-**2** at temperatures between −78 and +10 °C.

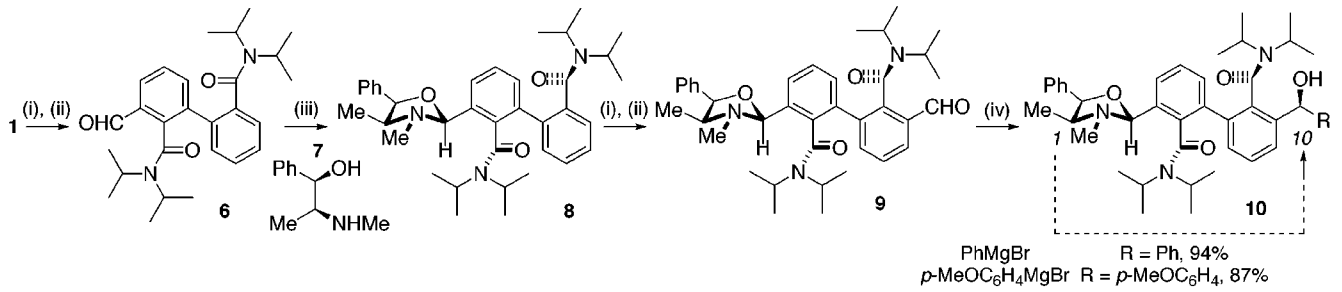
Rotationally restricted amide substituents exert powerful stereochemical control over lateral lithiation reactions[12] and over nucleophilic addition to nearby carbonyl groups.[13] The fact that the two amide groups of **3** are in stereochemical communication therefore offers the prospect of using biphenyl-2,2′-dicarboxamides to mediate the remote control of stereochemistry.[14] C_2-**3b** and C_2-**3a** were doubly laterally lithiated (*s*-BuLi, THF, −78 °C) and treated with phenyldimethylsilyl chloride and *N*-methylbenzaldimine as electrophiles. Yields were poor, but in both cases a single diastereoisomer **4** or **5** was produced. Silane **4** carries 1,8-related and amine **5** 1,10-related stereogenic centers.

It was also possible to use the amide pair to relay (or "project"[3c]) stereochemistry from an auxiliary [(−)-ephedrine **7**] attached to one ring to a new stereogenic center attached to the other. Amide **1** was monolithiated (3 equiv of *n*-BuLi, TMEDA, −78 °C, THF) and formylated to give **6**, which condensed with (−)-ephedrine **7** to form the oxazolidine **8**. A second formylation gave **9**, apparently as a single conformer by NMR, presumably (given the S_2 conformational preference of symmetrical 3,3′-disubstituted compounds **3**) as shown in Scheme 3. The addition of aryl Grignard reagents gave excellent yields of the alcohol **10** as a single diastereoisomer.[15] The stereoselectivity of the reaction demonstrates the ability of the amides to project the stereochemistry at the (−)-ephedrine-derived stereogenic center of **9** to a prochiral center nine bond lengths away.

A brief investigation of the lithiation and alkylation of the biphenyl ether **12** suggests that it behaves similarly to **1**. Ullman coupling of *o*-cresol with 2-chlorobenzoic acid gave the carboxylic acid **11**,[16] which was oxidized ($KMnO_4$)[17] and converted to the amide **12**. Double lithiation of **12** (6−10 equiv of *s*-BuLi, TMEDA, −78 °C, THF) and electrophilic quench with MeI or EtI gave the chiral (by HPLC[8]) atropisomers *dl*-**13a** and *dl*-**13b** with >10:1 atroposelectivity (Scheme 4). On heating **13a**, some of the epimeric *meso*-**13a** was formed, but *dl*-**13a** remained the major component of the equilibrium mixture. As with **3c**, **13c** was formed as a mixture of atropisomers.

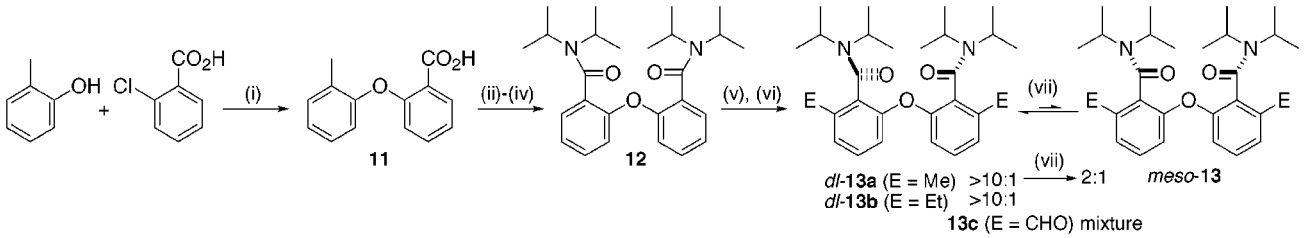
We have demonstrated that molecules such as **3**, **9**, and **13** have a well-defined conformational preference, and it is possible to exploit that preference for the long-range transmission of stereochemical information. The ability of the conformation of a small molecule to transmit information

Scheme 3. Relaying Stereochemistry from an Auxiliary to a Remote Stereogenic Center[a]



[a] Reagents: (i) 3−4 equiv of *n*- or *s*-BuLi, TMEDA, THF, −78 °C; (ii) DMF, −78 → 0 °C (81% **6**; 91% **9**); (iii) 2 equiv of (−)-ephedrine, cat. TsOH, toluene, Δ, 12 h (81%); (iv) ArMgBr, −78 °C, 2 h.

Scheme 4. Atropisomers of a 2,2′-Dicarboxamidobiphenyl Ether[a]



[a] Reagents: (i) Cu, CuI, pyridine, H_2O, 100 °C (ref 16); (ii) $KMnO_4$, K_2CO_3, H_2O, 100 °C, 20 min (ref 17, 90%); (iii) $(COCl)_2$, DMF (cat.); (iv) *i*-Pr_2NH, DMAP (71%); (v) 10 equiv of *s*-BuLi, TMEDA, THF, −78 °C; (vi) MeI (76%) or EtI (31%) or Me_2NCHO (61%); (vii) toluene, reflux, 1 h.

from a "binding site" (for example, the formyl group of **6**, which covalently binds (−)-ephedrine) to an "effector" site (the formyl group of **9**, to which nucleophiles add stereoselectively) is reminiscent of biological allostery, and we are currently working to develop new chemical models of allosteric systems.

Acknowledgment. We are grateful to the EPSRC for support and to Dr. Madeleine Helliwell for determining the X-ray crystal structure of **1**.

Supporting Information Available: ^1H and ^{13}C NMR spectra and physical data for **1**, C_2-**3a**, S_2-**3a**, C_2-**3b**, S_2-**3b**, **3c**, S_2-**3d**, C_2-**3f**, S_2-**3f**, **6**, **8**−**10** (R = Ph, *p*-$MeOC_6H_4$), *dl*-**13a**, *dl*-**13b**, and **13c**; crystallographic data for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0167457

(12) (a) Clayden, J.; Pink, J. H. *Tetrahedron Lett.* **1997**, *38*, 2565. (b) Clayden, J.; Pink, J. H. *Tetrahedron Lett.* **1997**, *38*, 2565. (c) Clayden, J.; Helliwell, M.; Pink, J. H.; Westlund, N. *J. Am. Chem. Soc.* in press. (d) Clayden, J.; Darbyshire, M.; Pink, J. H.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1997**, *38*, 8587.

(13) (a) Clayden, J.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1996**, *37*, 5577. (b) Clayden, J.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1999**, *40*, 7883. (c) Clayden, J.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1999**, *40*, 3329. (d) Clayden, J.; Westlund, N.; Beddoes, R. L.; Helliwell, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1351. (e) Clayden, J.; McCarthy, C.; Westlund, N.; Frampton, C. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1363. (f) Clayden, J.; Westlund, N.; Frampton, C. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1379.

(14) For an example of remote stereochemical control around rigid ring-systems mediated by amides, see ref 3.

(15) Comparison of the ^1H NMR spectrum of the crude product from **9**and PhMgBr with that from the reaction of **9** with PhLi (which gives a 2:1 ratio of diastereoisomers in 94% yield) indicated a stereoselectivity of >20:1. The stereochemistry of **10** is assigned tentatively by analogy additions to 2-formyl naphthamides (see ref 13a,e).

(16) Pellón, R. F.; Carrasco, R.; Milián, V.; Rodés, L. *Synth. Commun.* **1995**, *25*, 1077.

(17) Shapiro, R.; Slobodin, D. *J. Org. Chem.* **1969**, *34*, 1165.