Atroposelective Thermal Reactions of Axially Twisted Amides and Imides

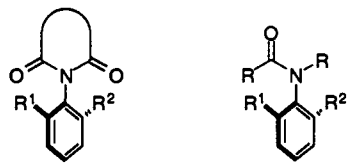
Dennis P. Curran,* Hongyan Qi, Steven J. Geib, and Nicholas C. DeMello

Department of Chemistry, University of Pittsburgh Pittsburgh, Pennsylvania 15260

Received December 15, 1993

The 2,2′-disubstituted binaphthyl subunit is among the most common and important motifs used in asymmetric organic synthesis today.[1] From a structural standpoint, binaphthyls and related biaryls are a small subclass of a large group of (potentially) axially chiral molecules that feature two sp^2-hybridized atoms linked by a single bond: $X_{sp^2}Y_{sp^2}$. There are many known molecules in this class that have both axial chirality and a high barrier to X–Y bond rotation,[2] yet outside of biaryls the use of such molecules in asymmetric synthesis has rarely been explored.[3]

N-Phenyl imides **1a**[4] and amides **2a** are not planar in the ground state, but instead twist to relieve unfavorable steric interactions between the *o*-hydrogens on the phenyl ring and the imide or amide substituents (eq 1).[5] Replacing each *o*-hydrogen with a



(1)

1 **2**

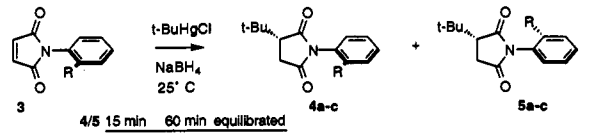
1a, 2a (R^1, R^2 = H), small N–Ar twist angle (~30°), low barrier to rotation

1b, 2b (R^1, R^2 = n-alkyl, OR, NR_2), large N–Ar twist angle (~90°), high barrier to rotation

1c, 2c (R^1 = H, R^2 = 3°-alkyl), large N–Ar twist angle (~90°), high barrier to rotation

different "medium-sized" group like halogen, *n*-alkyl, alkoxy, or dialkylamino increases both the N–Ar torsion angle and the barrier to rotation through planarity (see **1b, 2b**).[2] Though molecules like **1b** and **2b** have axial chirality and will resist racemization, they will probably be of restricted use in asymmetric synthesis because the sizes and shapes of the two medium-sized groups are too similar.[6] We hypothesized that molecules like **1c** and **2c** bearing one large (tertiary alkyl) and one small (H) ortho substituent might still retain sufficient rotational barriers to be stable to racemization at room temperature while at the same time possessing shapes that are much more conducive to applications in asymmetric synthesis. Herein we report preliminary results in support of this hypothesis.

The interplay between stereoselectivity and rotation barrier as a function of ortho substituent was first studied qualitatively with readily available maleimides **3a–c** (eq 2). We added the



(2)

	4/5 15 min	60 min	equilibrated	
a, R = Et	55 : 45	52 : 48	52 : 48	all ratios at 25°C
b, R = i-Pr	90 : 10	52 : 48	52 : 48	except * at 120°C
c, R = t-Bu	94 : 06	94 : 06	65 : 35*	

tert-butyl radical to these imides by a standard Giese reaction with *tert*-butyl mercuric chloride. In these radical additions, achiral reactants give chiral, racemic atropisomers **4a–c**/**5a–c**. Addition of *tert*-butyl radical to **3a** provided a very low initial ratio of **4a**/**5a** (55/45) that decreased slightly (52/48) on standing for 24 h (final ratio).[7] Addition to **3b** provided a good selectivity in favor of **4b** over **5b** (90/10), but this selectivity vanished on standing (52/48). In contrast, addition to **3c** was highly selective (94/6), and the adduct **4c** was indefinitely stable at room temperature. At 120 °C, an equilibrium mixture of **4c** and **5c** was finally obtained (65/35) after several days.

In each of the above three experiments, the initial product ratio represents the minimum kinetic atroposelectivity for the reaction. Imide **3a** gives poor selectivity in the radical addition, while imides **3b** and **3c** give good levels of selectivity. With adducts **4a,b**/**5a,b**, the final ratios (after 24 h at room temperature) are thermodynamic and result from relatively rapid equilibration by N–Ar bond rotation. That the initial and final ratios of **4c** are unchanged shows that these atropisomers are stable and do not equilibrate at room temperature.

To probe the reactions of the *o-tert*-butyl system further, we selected the known, readily available imide **6**,[8] which can be prepared on a gram scale simply by melting together maleic anhydride and 2,5-di-*tert*-butylaniline. With substrate **6**, the stereochemistry should be dictated by the *o*- rather than the *m-tert*-butyl group. Reactions of **6** with several dienes, nitrile oxides, and radicals are summarized in Scheme 1. In each case, only the structure of the major atropisomer is shown. Minor atropisomers were formed to some extent in most reactions, and the ratios of the major/minor isomers are shown for each reaction. In some cases, isomers could be separated by chromatography and thermally equilibrated at temperatures above 120 °C. With the exception of **7** (which never isomerizes up to 150 °C), all of the adducts provided major/minor atropisomer ratios of about 65/35 to 55/45 when equilibrium was finally reached. The equilibration experiments show (1) that all of the ratios reported in Scheme 1 are kinetic and (2) that product stability is not an important feature influencing kinetic atroposelectivity.

Diels–Alder cycloaddition of **6** with cyclopentadiene and 2,3-dimethylbutadiene produced a single isomer (**7** or **8**) at room temperature, though the reaction with dimethylbutadiene was slow (only 20% conversion after 24 h). With dimethylbutadiene, the minor atropisomer could be detected along with **8** when the cycloaddition was conducted at 80 °C (93/7). Cycloadditions of **6** with *p*-nitrobenzonitrile oxide and neopentanenitrile oxide produced adducts **9a** and **9b** accompanied by their atropisomers.

(1) Reviews: (a) Noyori, R.; Kitamura, M. In *Modern Synthetic Methods 1989*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1989; Vol. 5. (b) Narasaka, K. *Synthesis* **1991**, 1. (c) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503. (d) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.

(2) Review of axially chiral hetereoaromatics: (a) Gallo, R.; Roussel, C.; Berg, U. *Adv. Heterocycl. Chem.* **1988**, *46*, 173. Recent examples: (b) Roussel, C.; Adjimi, M.; Chemlal, C.; Djafri, A. *J. Org. Chem.* **1988**, *53*, 5076. (c) Mintas, M.; Mihaljevic, N.; Koller, H.; Schuster, D.; Mannschreck, A. *J. Chem. Soc., Perkin Trans. 2* **1990**, 619. (d) Hirose, Y.; Kariya, K.; Sasaki, I.; Kurono, Y.; Ebiike, H.; Achiwa, K. *Tetrahedron Lett.* **1992**, *33*, 7157. (e) Saito, K.; Yamamoto, M.; Yamada, K. *Tetrahedron* **1993**, *49*, 4549. (f) Dogan, I.; Pustet, N.; Mannschreck, A. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1557.

(3) For relevant examples of diastereoselective reactions of axially chiral flavins, see: (a) Kawamoto, T.; Tomishima, M.; Yoneda, F.; Hayami, J. *Tetrahedron Lett.* **1992**, *33*, 3169, 3173. (b) Kawamoto, T.; Tomishima, M.; Kunitomo, J.; Yoneda, F.; Hayani, J. *Tetrahedron Lett.* **1993**, *34*, 7173.

(4) Twisted imides are a key design feature in many of Rebek's molecular clefts: Rebek, J., Jr. *Chemtracts: Org. Chem.* **1989**, *2*, 337.

(5) Leading references: (a) Oki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*; VCH: Deerfield Beach, FL, 1985. (b) Jones, K.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1992**, 1766. (c) Curran, D. P.; DeMello, N. C. *J. Chem. Soc., Chem. Commun.* **1993**, 1314.

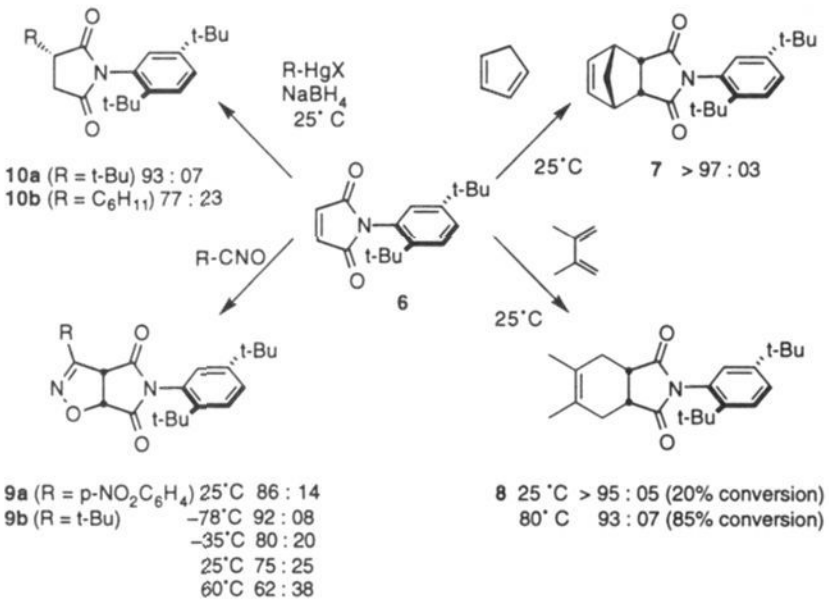
(6) For example, see the unselective nitrile oxide cycloadditions to axially chiral *N*-aryl maleimides in the following paper: Konopikova, M.; Fisera, L.; Goljer, I; Varkonda, S.; Hyblova, O.; Sturdik, E.; Ujhelyova, R. *Chem. Pap.* **1991**, *45*, 789; *Chem. Abstr.* **1992**, *116*, 151622u.

(7) Chemical shifts of the ortho aromatic hydrogens are diagnostic for rotamer assignments. See: Verma, S. M.; Singh, N. B. *Aust. J. Chem.* **1976**, *29*, 295. Examples of determination of rotamer ratios by ^{1}H NMR are reproduced in the supplementary material.

(8) Several examples of cycloadditions of *o*-quinodimethanes to **6** have been reported. The prime focus of this study was aromatization of the adducts, so stereochemical ramifications in the Diels–Alder reaction were left unclarified. See: Rak, S. F.; Jozefiak, T. H.; Miller, L. L. *J. Org. Chem.* **1990**, *55*, 4794.

0002-7863/94/1516-3131$04.50/0

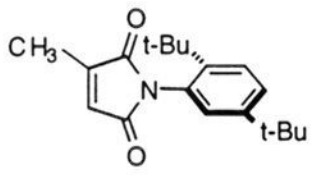
Scheme 1



For neopentanenitrile oxide, the temperature dependence was studied, and the ratio of **9b** to its atropisomer varied from 92/8 at –78 °C to 62/38 at 60 °C. Radical additions to **6** at room temperature gave product ratios that depended on the radical: addition of the cyclohexyl radical gave **10b** and its isomer in a 77/23 ratio while addition of *tert*-butyl radical gave **10a** and its isomer in an improved 93/7 ratio. This 93/7 ratio is close to that in the addition of the *tert*-butyl radical to **3c** (**4c**/**5c**, 94/6). Apparently, the *m-tert*-butyl group in **6** does not adversely affect selectivity.

The structure of major cycloadduct **8** in the reaction of **6** and 2,3-dimethylbutadiene was solved by X-ray crystallography, as was the structure of the starting maleimide **6**. These structures (Figure 1) highlight the features that control the shape and stereoselectivity of these molecules. In the precursor **6**, the planes of the imide and aryl rings are twisted by about 90°, and the ortho-*tert*-butyl group significantly shields the approach of a reagent to one face. The face bearing the *m-tert*-butyl group is reasonably open to attack. Diels–Alder reactions exhibit especially high selectivities because the endo approach of the dienophile to **6** magnifies steric interactions in the unfavorable transition state by placing the diene very close to the *o-tert*-butyl group.

Chiral analogs of **6** are generated simply by breaking the plane of symmetry that passes through the aromatic ring. We have prepared one of the simplest chiral analogs, **11**, and conducted the full battery of reactions shown in Scheme 1. Analogous products (not shown) are formed in similar yields and with similar atroposelectivities. To date, we have not attempted to resolve **11**, but we are certain that the enantiomers of **11** will be stable to racemization at room temperature.



11

The preliminary experiments shown in eq 3 demonstrate that atroposelectivity is not limited to cyclic substrates. Cycloaddition of benzonitrile oxide to (racemic) **12**[9] provided atropisomers **13** and **14** in a ratio of >97/3 while radical allylation of **15** provided **16** and **17** in a ratio of 93/7.[10] These isomers do not interconvert at room temperature, but they are somewhat more labile than the

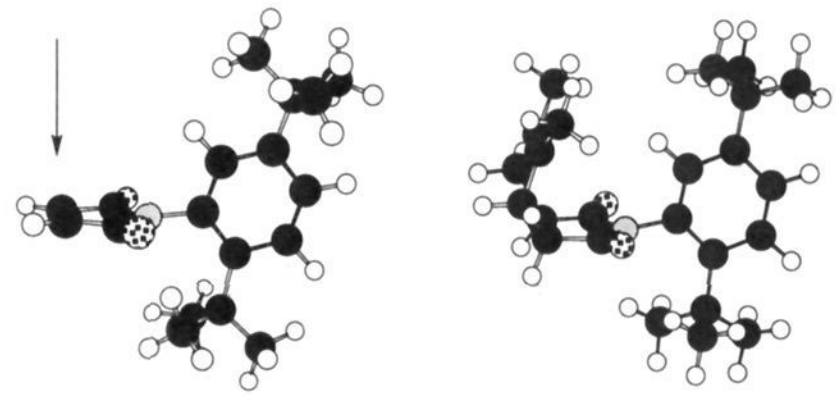
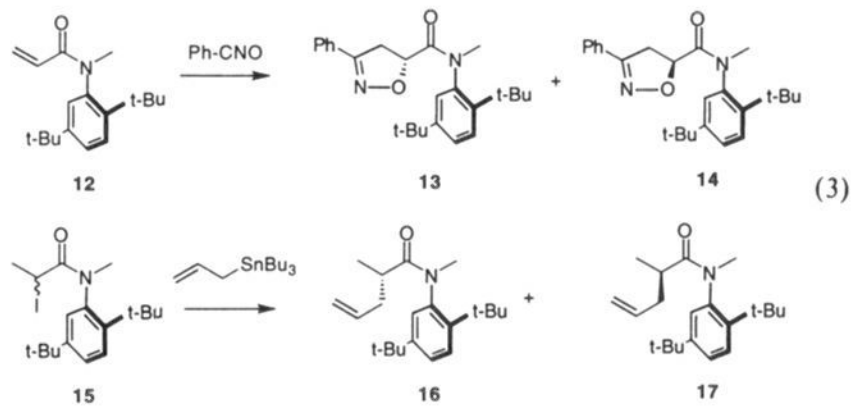


Figure 1. Crystal structures of **6** (left) and **8** (right).



(3)

rotamers in the imide series and equilibration begins to set in at about 80 °C. The shapes of cyclic imide **6** and acyclic amide **12** bear little similarity: **6** is forced to exist with the alkene and the carbonyl groups s-trans and the carbonyl groups and the *N*-aryl group *Z* while **12** prefers its carbonyl and alkene groups to be s-cis and its carbonyl and *N*-aryl groups to be *E*.[4] Despite this, both classes of molecules exhibit good levels of asymmetric induction.

These preliminary results are the first steps toward developing a new class of chiral auxiliaries based on axially chiral amides and imides. We can now design axially chiral amides that will be stable to N–Ar bond rotation at or above room temperature and that will give good to excellent levels of asymmetric induction in many types of important reactions. We are currently directing our experiments toward producing chiral auxiliaries that can be prepared in optically active form prior to the asymmetric transformation and that can be removed after it. We also suggest that related structures might make interesting ligands for use in asymmetric catalysis.

Acknowledgment. We thank the National Institutes of Health for funding this work.

Supplementary Material Available: Full details of the crystal structures of **6** and **8** and copies of ^{1}H NMR spectra illustrating representative examples of determination of rotamer ratio (**3c**, **10a**) (20 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(9) Anilide **12** is readily formed by acylation of *N*-methyl-2,5-di-*tert*-butylaniline with acryloyl chloride. The initial selection of this substrate was inspired in part by Seebach's work on "sterically protected" *o,o*-di-*tert*-butylphenyl esters. See: Suzuki, K.; Seebach, D. *Liebigs Ann. Chem.* **1992**, 51.

(10) In these two examples, product structures are not rigorously proven, and we assign them by assuming that reagents attack the radical or the alkene opposite the *o-tert*-butyl group.