Synthesis of Enantioenriched Axially Chiral Anilides from Atropisomerically Enriched Tartarate Ortho-Anilides

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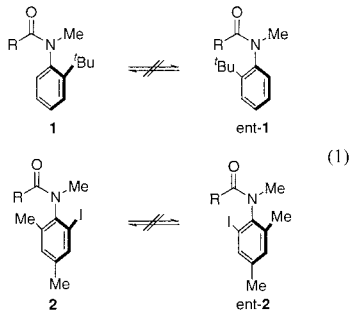
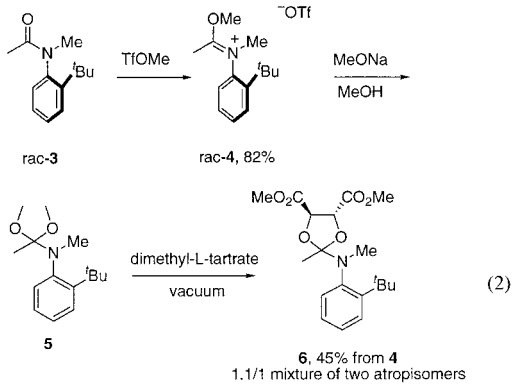
Anilides such as **1** and **2** bearing appropriate ortho-substituents exist as stable atropisomers at room temperature and above,[1] and these axially chiral anilides undergo an assortment of diastereoselective reactions.[1,2] Barriers to racemization of **1**, **2**, and related analogues are in the range of 28−30 kcal/mol.[1b,3]



(1)

Limiting the usefulness of these and related transformations is the lack of general methods that provide single enantiomers of anilide atropisomers.[4] Most current methods involve nonselective synthesis of isomers followed by physical or chromatographic separation.[1,2,5,6] We report herein a new approach to enantiomerically enriched anilide atropisomers through the selective cleavage of ortho-anilide diastereomers. These ortho-anilides belong to a rare class of atropisomers originating from restricted rotation about an sp^2-sp^3 C−N bond.[7] The configuration of the ortho-anilide precursor determines the configuration of the resulting anilide in an unusual cleavage reaction that changes one type of axial chirality (sp^2-sp^3) into another (sp^2-sp^2). In turn, the configuration of the ortho-anilide is controlled either by a crystallization-induced asymmetric transformation or by a thermodynamic equilibrium.

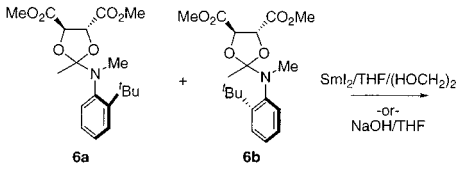
Ortho-anilide **6** was synthesized from *rac*-**3** as shown in eq 2. *O*-Methylation of *rac*-**3** with methyl trifluoromethanesulfonate

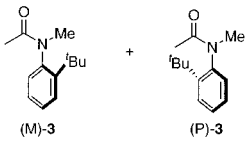


(2)

provided an intermediate alkoxy imminium salt *rac*-**4** that was quenched with sodium methoxide to provide ortho-anilide **5**. Trans-ketalization of **5** with (+)-dimethyl L-tartrate then provided ortho-anilide **6**. At the onset, we hypothesized that the conversion of the sp^2 amide carbonyl carbon to an sp^3 anilide ketal carbon would significantly lower the C−N rotation barrier and allow an asymmetric hydrolysis of **6** to occur under conditions of dynamic kinetic resolution. However, the ^1H and ^{13}C NMR spectra of **6** showed pairs of resonances (ratio 1.1/1) for most peaks, suggesting that C−N bond rotation was not especially rapid. In addition, all attempts to conduct asymmetric acidic hydrolysis of **6**,[8] both with and without chiral additives, consistently occurred in poor yields to give product **3** of about 15−20% ee. The rough correspondence of the low ee of **3** to the diastereomer ratio of **6** and the inability to influence the ee with additives led us to speculate that the hydrolysis was faster than interconversion of the rotamers of **6**. If this is true, then hydrolysis of one isomer of **6** might give one enantiomer of **3**.

In an important breakthrough, we discovered that isomer **6a** (eq 3) selectively crystallizes (20/1 ratio, mp 84−86 °C) in 95%





(3)

yield from hexane under conditions where the two atropisomers **6a**,**b** are in equilibrium. This process shows all the hallmarks of a crystallization-induced asymmetric transformation.[7a,9] If crystallization occurs too rapidly, then the diastereoisomer ratio is greatly reduced. Crystals of the enriched 20/1 mixture retain the ratio for weeks, but equilibration to the starting 1.1/1 mixture occurs in a matter of hours at ambient temperature in solution. Attempts

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(2) (a) Hughes, A. D.; Price, D. A.; Shishkin, O.; Simpkins, N. S. *Tetrahedron Lett.* **1996**, *37*, 7607. (b) Hughes, A. D.; Price, D. A.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1295.

(3) Curran, D. P.; Liu, W. D.; Chen, C. H.-T. *J. Am. Chem. Soc.* **1999**, *121*, 11012.

(4) Benzamides with a chiral C−C axis have been resolved by a number of dynamic methods: (a) Clayden, J.; Lai, L. W. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2556. (b) Clayden, J.; McCarthy, C.; Cumming, J. G. *Tetrahedron Lett.* **2000**, *41*, 3279.

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(6) Uemura has recently reported a highly enantioselective synthesis of 2-methyl-6-alkyl-substituted anilides by selective deprotonation of prochiral chromium carbene complexes with chiral bases, but this method is not applicable to either of the classes of compounds shown in eq 1. Hata, T.; Koide, H.; Taniguchi, N.; Uemura, M. *Org. Lett.* **2000**, *2*, 1907.

(7) (a) Eliel, E. L.; Wilen, S. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; pp 1150−1153. (b) Oki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*; VCH: Deefield Beach, 1986; pp 195−206.

(8) Under acidic conditions, hydroylsis with C−N bond cleavage competes. Hydrolyses under both acidic and basic conditions probably go through imidate salts. See: Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983; pp 101−162.

(9) (a) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; Wiley: New York, 1981; pp 369−377. (b) Vedejs, E.; Donde, Y. *J. Org. Chem.* **2000**, *65*, 2337.

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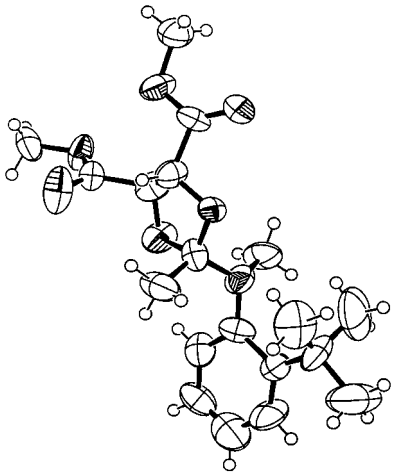


Figure 1. Crystal Structure of Anilide Ketal **8a**.

Table 1. Cleavage of an Anilide Ketal Mixture **8a**/**b** To Give Enantiomerically Enriched **5**

entry	ratio **8a/8b**	conditions[a]	temp, °C	% yield **M/P-5**	obsd ee,[b] %	calcd ee,[c] %
1	1.1/1	SmI_2	25	99[d]	18	7
2	1.1/1	SmI_2	0	99[d]	18	7
3	7.5/1	SmI_2	25	84[e]	88	77
4	20/1	SmI_2	25	68[e]	92	91
5	20/1	SmI_2	0	86[e]	93	91
6	1.1/1	NaOH	25	99[e]	13	7
7	20/1	NaOH	25	99[e]	87	91

[a] SmI_2 = 4.5 equiv of SmI_2, THF, 20 equiv of ethylene glycol, 30 min; NaOH = 0.05 M NaOH/THF, 5 h. [b] **M-5** is the major enantiomer in all cases. [c] This is the diastereomeric excess (de) % **8a** − % **8b**. [d] Crude yield. [e] Isolated yield.

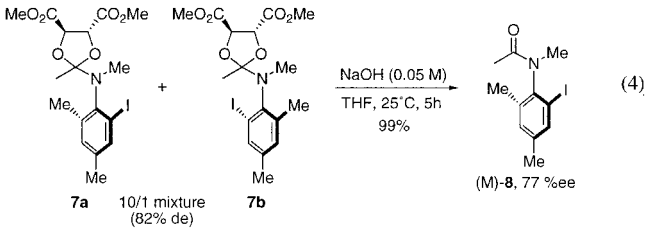
to increase the isomer ratio by recrystallizing the 20/1 mixture failed, presumably because return to the equilibrium ratio is faster than crystallization.

The barrier to interconversion of the atropisomers **6a**,**b** was measured to be about 23 kcal/mol by a standard NMR experiment (see Supporting Information). The structure of **6a** as determined by X-ray crystallography is shown in Figure 1. As expected, the nitrogen atom of the ortho-anilide is now pyramidal, and the *o*-*tert*-butyl group adopts an orientation that is roughly syn to the vicinal nitrogen lone pair. We suggest that the sp^2-sp^3 C−N bond is the source of the restricted rotation in **6a** and that its isomer **6b** (eq 3) has the C−N bond rotated roughly 180° with the nitrogen inverted to again be pyramidalized away from the *tert*-butyl group. Accordingly, formation of **6a** may be the first example of a crystallization-induced asymmetric transformation that involves atroposelectivity about an sp^2-sp^3 bond.

Given the poor yields of acidic hydrolysis, we initially cleaved **6** with samarium iodide[10] to provide **3** in good yield. As shown in Table 1, the ee of **3** (in favor of the M-isomer) depends directly on the diastereomeric ratio of **6a/b**. The 1.1/1 equilibrium mixture again gave **5** with about 18% ee (entry 1), while the 20/1 mixture gave **3** in 92% ee (entry 4). The ratios were not dependent on temperature (compare entries 1/2 and 4/5). An intermediate 7.5/1 mixture (obtained by partial isomerization of the 20/1 prior to quenching with SmI_2) gave product of intermediate ee (88%, entry 3). We subsequently discovered that hydrolysis under basic conditions occurred in high yield.[8] Once again, the ee of the product **3** depended directly on the diastereomer ratio of the precursor **6** (entries 6 and 7). These results suggest that the reactions (reduction or hydrolysis) are fast relative to C−N bond rotation, and that the ee of the product **5** is determined predominately by the de of the precursor **6**.

(10) Molander, G. A. *Org. React.* **1994**, *46*, 211.

We next prepared ortho-anilide **7** (eq 4) by a similar sequence to the one in eq 2 (not shown). To our surprise, this ortho-amide existed as a 10/1 mixture of atropisomers according to ^1H NMR analysis. The oily mixture could not be crystallized and was a



single peak on HPLC, so we have not yet been able to obtain a sample with a different isomer ratio. Prolonged heating of **7** at 50 °C did not change the 10/1 ratio and we assume that this is the thermodynamic ratio. Cleavage of **7** with samarium iodide is not applicable because of the presence of the iodide, but hydrolysis under basic conditions provided (M)-**8** in 99% yield and 77% ee (eq 4). Once again, the ee of the product **8** roughly corresponds to the de of the precursor **7**. The configuration of (M)-**8** has been assigned by X-ray crystallography (see Supporting Information), and that of **7a** is assigned accordingly.

These results show that ortho-anilides bearing either one large and one small ortho substituent **6** or two medium ortho substituents **7** comprise a new class of atropisomers with restricted rotation imparted by the sp^2-sp^3 C−N bond. The rate of many reactions occurring at room temperature or below will typically exceed the rate of rotation. When reactions convert the ketal to an amide, the rotation barrier increases significantly (~6 kcal/mol) so the ratio of the precursor ortho-anilide can be locked in. The needed high diastereomer ratio of the ortho-anilides may occur naturally due to the thermodynamic stability of the isomers, or it may be secured kinetically through a crystallization-induced asymmetric transformation. Neither of these approaches is necessarily predictable or general, so the acetate derivatives **3** and **8** made in this paper are especially important since they can readily be converted into more complex amides by alkylation or related reactions.[1−3,5]

Even though a stoichiometric quantity of tartrate has been used, this work has two important implications for future efforts directed at the catalytic asymmetric synthesis of axially chiral amides. First, the development of an asymmetric hydrolysis of an ortho-anilide or related intermediate (for example, treatment of **5** with a chiral Lewis acid) may be difficult since the rate of hydrolysis must exceed the rate of rotation of the ortho-anilide but be slower than the rate of rotation of the anilide product. Second, a projected asymmetric acylation reaction to make an axially chiral anilide (for example, reaction of an acid chloride and an aniline with a chiral catalyst) will likely require selective formation of a tetrahedral intermediate since atropisomers of that intermediate (which resemble amide ketals) would not interconvert under the reaction conditions and would collapse to give enantiomeric products. Thus, design of chiral acylation catalysts should focus on the first (addition) not the second (elimination) step.

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Supporting Information Available: Complete experimental and characterization details for all new compounds and details for the crystal structures of **6a** and **7a** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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