

Dynamic Kinetic Resolution of Atropisomeric Amides

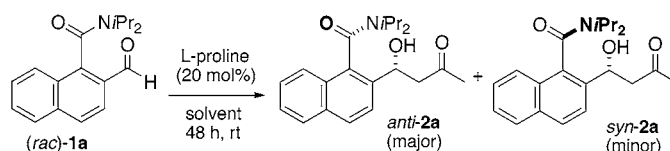
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ABSTRACT



Using L-proline as catalyst in the asymmetric aldol reaction and a series of benzamides and naphthamides, we have accomplished a dynamic kinetic resolution that simultaneously establishes the stereochemistry of the atropisomeric amide's chiral axis and a stereogenic center. The enantioselectivities ranged from 82% to 95% and the diastereoselectivities from 2.1:1 to 7.0:1.

Advances in asymmetric catalysis have enabled chemists to generate many classes of chiral organic molecules with high levels of enantioselectivity.¹ Even chiral quaternary centers, once challenging targets for asymmetric catalysts,^{2–4} can now be installed with greater ease. Progress toward the synthesis of compounds with chiral axes has also been notable. The oxidative coupling of naphthols to afford atropisomeric biaryls with high enantioselectivities can be accomplished, providing access to important classes of chiral ligands.^{5,6} Along similar lines, Bringmann⁷ has developed a novel method to prepare atropisomeric biaryls employing a dynamic kinetic resolution,⁸ wherein a rapidly racemizing lactone can be opened to afford biaryls with high levels of enantioselectivity.

In contrast to these methods, efforts to perform catalytic asymmetric syntheses of nonbiaryl atropisomers have met

with little success, despite the ability of these compounds to control stereochemistry.⁹ For example, Curran has demonstrated that atropisomeric anilides and imides are excellent chiral auxiliaries in diastereoselective reactions.^{10–12} Likewise, Clayden,^{10–15} Simpkins,^{16,17} and Taguchi^{18–20} have successfully employed nonbiaryl atropisomers in asymmetric synthesis with high diastereoselectivity.²¹ From these results it is apparent that the perpendicular architecture of atropi-

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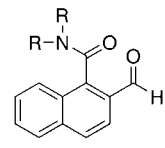
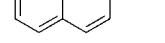
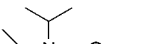
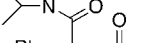
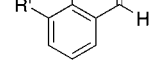


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Table 1. Dynamic Kinetic Resolution of Atropisomeric Amides in 4:1 DMSO/Acetone

entry	substrate	combined ^[a] yield [%]	dr ^[b] (<i>anti</i> : <i>syn</i>)	ee (major) [%]	
1		1a , R = <i>i</i> Pr	81	2.2:1	86
2		1b , R = Cy	78	3.7:1	86
3		1c , R' = NMe ₂	82	2.5:1	93
4		1d , R' = CF ₃	82	2.5:1	77
5		1e , R' = Ph	77	1.6:1	81
6		1f , R' = OMe	80	2.2:1	95
7		1g , R' = SiMe ₃	71	8.0:1	88

^a Combined yield after purification. ^b The dr was determined by ¹H NMR spectroscopic analysis of the crude reaction mixture.

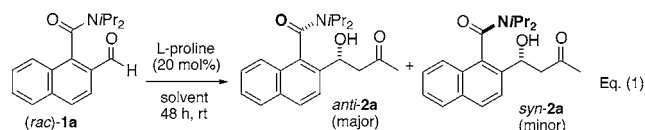
someric anilides, benzamides, and naphthamides effectively exerts control over the formation of new stereogenic centers. The high degree of diastereoselectivity in reactions with nonbiaryl atropisomers as chiral auxiliaries suggests that such compounds hold considerable promise in organic synthesis. Routes to atropisomeric benzamides and naphthamides entail enantio-^{14,16,22} or diastereoselective^{13,15} reactions with stoichiometric chiral reagents or auxiliaries. Catalytic enantioselective methods have only recently been employed to synthesize atropisomeric anilides, with enantioselectivities reaching 50% ee.^{23,24}

One of the aims of our research is to develop methods to prepare atropisomeric amides in a catalytic asymmetric fashion. Along these lines, we recently reported the first successful catalytic kinetic resolution of atropisomeric amides.²⁵ We now disclose a dynamic kinetic resolution that simultaneously establishes the stereochemistry of the atropisomeric amide chiral axis and a stereogenic center. To our knowledge, this is the first highly enantioselective method to prepare such compounds and the first demonstration of the use of atropisomeric amides in a dynamic kinetic resolution.

The aldehydes **1a–g** (Table 1) are chiral as a result of the orthogonal orientation of the aryl and amide moieties. We chose these as substrates for our dynamic kinetic resolution because they readily undergo racemization at room temperature through rotation about the aryl–amide bond.²⁶

For example, the half-life to racemization of **1a** is estimated to be 12 min at 20 °C.²⁷ In contrast, reduction or alkylation of **1a** to afford the primary or secondary alcohol increases the half-life to racemization and epimerization to 101 and >380 h, respectively.²⁶ Our initial attempts at a dynamic kinetic resolution, employing Lewis acid catalysts, were thwarted by the basicity of the amide carbonyl group, resulting in formation of racemic products.²⁸ A new strategy was clearly needed.

We were attracted to the use of organocatalysts such as proline,^{29,30} because they have a minimal affinity for the amide carbonyl group.³¹ Furthermore, the List³² and MacMillan³³ groups had shown that proline is an efficient catalyst for the asymmetric aldol reaction.³² We therefore employed L-proline with aldehydes **1a–g** under the reported conditions³² as illustrated for **1a** in eq 1. Using a DMSO/acetone



ratio of 4:1, **1a** underwent aldol condensation over 48 h. The diastereomeric ratio (dr) of the product was 2.2:1, as determined by analysis of the ¹H NMR spectrum. The combined yield of both diastereomers was 81%, and the ee of the major diastereomer was determined to be 86% by chiral phase HPLC. An X-ray crystallographic study of **2a**³⁴ showed the stereochemistry of the major diastereomer to be the *anti*-product, in which the hydroxyl and amide oxygens are on opposite sides of the extended C–C backbone, as shown in eq 1.

As shown in Table 1, similar results were obtained with aldehydes **1b–f**, with diastereoselectivities ranging from 1.6 to 3.7:1 and enantioselectivities of the major diastereomer between 77% and 95%. In these examples, it is noted that the group meta to the aldehyde impacts both the enantioselectivity and diastereoselectivity of the reaction. An exception was found with the trimethylsilyl derivative **2g**, which was determined to have a dr of 8.0:1 favoring the *anti*-diastereomer (based on comparison of the NMR spectra of **2g** with those of **2a–f**). The *o*-trimethylsilyl group has been shown to facilitate atropisomerization,^{25,26,28} and thus we believe that the thermodynamic product is obtained as a result of the reduced barrier to atropisomerization.

To determine the stereochemical relationship of the major and minor diastereomers, the diastereomers **2b** were separated and each was oxidized to the diketone with PCC. The

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Table 2. Dynamic Kinetic Resolution of Atropisomeric Amides in Acetone

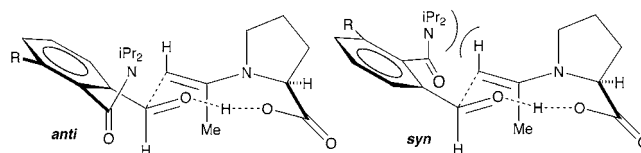
entry	substrate	combined ^[a] yield [%]	dr ^[b] (<i>anti</i> : <i>syn</i>)	ee (major) [%]	
1		1a , R = <i>i</i> Pr	87	5.5:1	91
2		1b , R = Cy	89	4.8:1	92
3		1c , R' = NMe ₂	92	3.6:1	94
4		1d , R' = CF ₃	86	7.0:1	82
5		1e , R' = Ph	100	3.0:1	90
6		1f , R' = OMe	80	2.1:1	95
7		1g , R' = SiMe ₃	79	8.0:1	89

^a Combined yield after purification. ^b The dr was determined by ¹H NMR spectroscopic analysis of the crude reaction mixture.

diketone products racemize readily under our reaction and purification conditions. Nonetheless, the predominant enantiomers were opposite in configuration, indicating that the stereogenic centers of **2b** have the same configuration in the diastereomeric products and the axial chirality is opposite.

From the data in Table 1, L-proline exerts very good enantiocontrol over formation of the stereogenic center in the aldol condensation. Not surprisingly, the stereochemistry at the chiral axis is more challenging to influence. Given that racemization of the aldehydes is reported to be fast at room temperature, it is likely that the rates of reaction of the intermediate enamine with the enantiomeric atropisomers are similar. We therefore set out to examine different solvent systems, because it is known that solvent effects can impact relative rates of reaction. In this study, we discovered that use of neat acetone generally resulted in higher enantio- and diastereoselectivities. The results of this study are outlined in Table 2.

The naphthamides **1a** and **1b** gave diastereoselectivities of 5.5:1 and 4.8:1 with enantioselectivities of 91% and 92%. The dimethylamino, trifluoromethyl, and phenyl derivatives also exhibited improved diastereoselectivities of 3.6:1, 7.0:1, and 3.0:1 (entries 3–5) with enantioselectivities of the major diastereomers of 94%, 82%, and 90%, respectively. Complex **1f**, bearing a methoxy group, exhibited the same enantio- and diastereoselectivity on switching solvents. As expected, the trimethylsilyl derivative **2f** again gave an 8.0:1 ratio of diastereomers.

**Figure 1.** Proposed *anti* and *syn* transition states.

Possible transition states to explain the observed enantio- and diastereoselectivity, based on the results of Houk and List, are illustrated in Figure 1.^{35,36} We propose the *syn*-transition state to be less favorable as a result of interaction of the amide with the axial hydrogen in the Zimmerman–Traxler³⁷ six-membered chairlike transition state model.

In summary, asymmetric transformations with substrates containing stereochemically labile groups represent an elegant method to establish simultaneously two or more stereogenic centers or stereochemical elements in a single chemical operation.^{38,39} Such reactions are particularly challenging when the stereochemical elements are separated by intervening atoms, as in our system. In this report, we demonstrate that molecules that are chiral by virtue of hindered rotation can be employed in a dynamic kinetic resolution to establish the configuration of a chiral axis. Furthermore, this work represents a rare use of organocatalysts in a dynamic kinetic resolution.⁴⁰

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Supporting Information Available: Procedure and full characterization of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(34) CCDC 230166 contains the supplementary crystallographic data for **2a**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, U.K.; fax (+44)1223-336-033 or email deposit@ccdc.cam.ac.uk).

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