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Kinetic Resolution of Atropisomeric Amides

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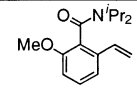
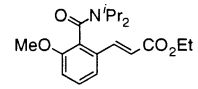
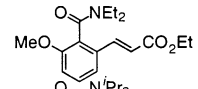
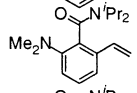
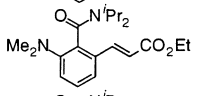
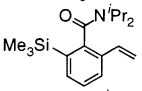
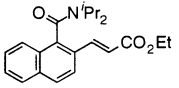
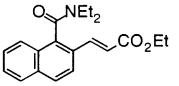
As the field of asymmetric catalysis has matured, several types of ligands have emerged that consistently form highly enantioselective catalysts.[1,2] The biaryl atropisomers BINOL[3−5] and BINAP[3,6,7] are prominent members of this elite class. It is, therefore, surprising that nonbiaryl atropisomers have only recently been examined in asymmetric synthesis.[8,9] The pioneering work of Curran using atropisomeric anilides and imides showed that atropisomeric compounds could exhibit excellent diastereoselectivity.[10−12] Impressive diastereoselectivity with nonbiaryl atropisomers has also been realized by Simpkins,[13,14] Clayden,[15−17] and Taguchi.[18−20] The perpendicular architecture of atropisomeric anilides and benzamides exerts powerful control over the generation of new stereogenic centers.

The successful application of nonbiaryl atropisomers as chiral auxiliaries alludes to the great potential of these, and related compounds, as axially chiral ligands and catalysts.[17,21] An impediment to the examination of this potential is the generation of enantiopure atropisomers. Routes to benzamides and naphthamides of high enantiopurity are currently based on enantio-[13,17,22] or diastereoselective[15,16] reactions requiring stoichiometric chiral reagents.[10−12] With the goal of developing simple and direct methods for the resolution of these compounds, we focused on their *catalytic* kinetic resolution.[23,24] To our knowledge there are no such previous reports. This efficient kinetic resolution has allowed us to isolate atropisomeric amides in high enantiopurity and to determine their barriers to racemization.

Kinetic resolution of the olefins **1**−**8** was performed with the Sharpless asymmetric dihydroxylation reaction (AD)[25] employing the commercially avaliable AD-mix-α and AD-mix-*β* [with $(DHQ)_2$-PHAL and $(DHQD)_2$-PHAL ligands, respectively]. The AD has been used with varying degrees of success in kinetic resolutions.[26−31] We hoped that the preexisting chiral axis in the olefin substrates would affect the relative rates of dihydroxylation of the enantiomers. The reactions were performed at 0 °C or room temperature in *t*-BuOH−H_2O (1:1) at a concentration of 0.1 M substrate.[25] Reactions were followed by removal of samples, workup, and analysis. The extent of conversion was measured by ^{1}H NMR, and the ee's of the olefins were determined by HPLC (Chiralcel OD-H **1**, **4**, **5**, and **8**; Pirkle **7**) and shift reagent (**2**, **3**, **6**). Low-to-excellent levels of kinetic enantioselection with k_{rel} up to 32 were realized under these conditions (Table 1).

The k_{rel} values in Table 1 are particularly important because they are the relative rates of oxidation of the fast- versus slow-reacting enantiomers. The relative rate constants (k_{rel}) enable one to calculate the degree of conversion necessary to obtain the desired enantiopurity.[24] Our most impressive results were obtained for α,*β*-unsaturated ester **2**, affording a k_{rel} of 32 (AD-mix α). Thus, at 57% conversion, **2** would have 98% ee. By reacting **5** with AD-mix-α, we isolated **5** of 94% ee in 36% yield.

Table 1. Kinetic Resolution of Atropisomeric Amides with the Sharpless Asymmetric Dihydroxylation

	Amide[a]	Cat AD-mix	Cat (mol%)	T(°C)	k_{rel}
1		α	1	25	6.2
		β	1	25	5.6
		α	1	0	16
		β	1	0	6.4
2		α	1	25	32
		β	1	25	27
3		α	1	25	6.3
		β	1	25	5.9
4		α	2	25	26
		β	2	25	20
5		α	2	25	19
		β	2	25	15
6		α	3	25	1
		β	3	25	1
7		α	2	25	4.4
		β	2	25	6.6
8		α	2	25	7.4
		β	2	25	14

[a] Syntheses of **1**−**8** are outlined in the Supporting Information.

Several trends are apparent from the data in Table 1. Kinetic resolutions with $(DHQ)_2$-PHAL are more effective with benzamides while the diastereomer $(DHQD)_2$-PHAL is more efficient with naphthamides. In general, benzamide derivatives are superior substrates for the kinetic resolution with the Sharpless AD than are analogous naphthamides. Decreasing the size of the *N*,*N*-dialkyl groups from isopropyl to ethyl resulted in lower k_{rel} values for the benzamide **3** (vs **2**) and higher values for the naphthamide **8** (vs **7**). The presence of the *o*-trimethylsilyl group in **6** significantly lowers the barrier to atropisomerization, and no kinetic resolution of **6** was detected. It is possible that the silicon facilitates racemization by coordinating the carbonyl oxygen in the transition state.[32]

An intriguing result was realized in the kinetic resolution of terminal olefin **1**. Examination of the diol products after consumption of the olefin was complete indicated that the initial diastereoselectivity was 4.8:1. It decreased slightly after 24 h at 23 °C to 4.1:1 due to slow epimerization about the chiral axis. Heating the

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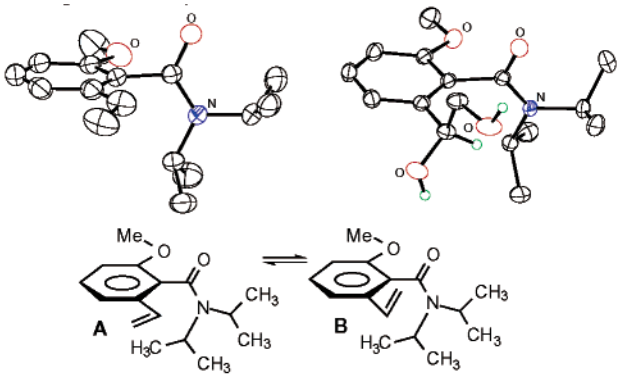

Figure 1. The X-ray structures of **1** and the major diastereomer formed on its dihydroxylation are shown (top). The proposed reactive conformation of **1**, **B**, is illustrated (bottom).

Table 2. Barriers to Racemization of Atropisomeric Amides

entry	amide	temp (°C)	half-life (h)	k (10^{-6} s^{-1})	$\Delta G^{\ddagger}_{temp}$ (kcal/mol)
1	**1**	25	16		24.1
2	**1**	4	181	1.1	23.8
3	**1**	−16	1970	0.10	23.6
4	**4**	25	135	1.4	27.3
5	**7**	25	12	16	24.0
6	**7**	4	118	1.6	23.5
7	**7**	−16	680	0.28	23.0
8	**8**	25	7	27	23.7
9	**8**	4	57	3.4	23.1
10	**8**	−16	379	0.52	22.7

4.8:1 mixture of diaostereomers to 80 °C (C_6D_6, 9 h) resulted in equilibration of the diasteromers to a 1:1 mixture that did not change on further heating. The de of the diol product using pyridine as ligand under the same reaction conditions was also 4.8:1. Therefore, the kinetic diastereoselectivity in the AD of **1** was dictated by the substrate and not the catalyst. To explore the stereochemistry of the diol product formed from **1**, crystal structures of the starting olefin and racemic diol product were obtained. The structure of the olefin is illustrated in Figure 1 and shows the double bond in the plane of the aromatic ring. Also evident from the structure is the orthogonality of the amide and aryl groups. Surprisingly, the structure of the diol product indicates that the oxygens have been delivered to the face of the olefin proximal to the bulky *N*,*N*-diisopropyl groups. The NMR spectrum of the dissolved crystals is consistent with the major diastereomer. To account for this unexpected result, we propose that the active conformation of the olefin is **B** in Figure 1, in which the *re* face is preferentially attacked.

In contrast to the reactivity of terminal olefin **1**, dihydroxylation of **2** resulted in initial generation of a single diastereomer. As the conversion approaches 50%, a second diastereomer is formed, leading to a 1:1 ratio of the diastereomers on completion of the reaction. Thus, with the α,β-unsaturated ester **2**, the diastereoselectivity is controlled by the catalyst and not the substrate.

Application of the Sharpless AD to the kinetic resolution of atropisomeric olefins enabled us to isolate these materials with high enantiopurity. We then determined their racemization rates at different temperatures employing HPLC. The results are listed in Table 2. Racemizations were first-order with half-lives at 23 °C ranging from 7 h for **8** to 135 h for **4**. Larger *N*-alkyl groups lead to higher barriers to racemization and bulkier substituents ortho to the amide decrease racemization rates.

In summary, we have demonstrated the feasibility of the kinetic resolution of atropisomeric amides using the commercially avaliable AD-mix. To our knowledge, this methodology represents the first catalytic kinetic resolution of such compounds. The resolution of the amides examined here would be difficult to otherwise achieve. Their half-lives to racemization range from 7 to 135 h at 23 °C. Such data is essential in the construction of ligands for asymmetric catalysis from these precursors.

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Supporting Information Available: Substrate preparation, AD procedure, and ee analyses (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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