Spontaneous transfer of chirality in an atropisomerically enriched two-axis system

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One of the most well-recognized stereogenic elements in a chiral molecule is an sp2-hybridized carbon atom that is connected to four different substituents. Axes of chirality can also exist about bonds with hindered barriers of rotation; molecules containing such axes are known as atropisomers1. Understanding the dynamics of these systems can be useful, for example, in the design of single-atropisomer drugs2 or molecular switches and motors3. For molecules that exhibit a single axis of chirality, rotation about that axis leads to racemization as the system reaches equilibrium. Here we report a two-axis system for which an enantioselective reaction produces four stereoisomers (two enantiomeric pairs): following a catalytic asymmetric transformation, we observe a kinetically controlled product distribution that is perturbed from the system’s equilibrium position. As the system undergoes isomerization, one of the diastereomeric pairs drifts spontaneously to a higher enantiomeric ratio. In a compensatory manner, the enantiomeric ratio of the other diastereomeric pair decreases. These observations are made for a class of unsymmetrical amides that exhibits two asymmetric axes—one axis is defined through a benzamide substructure, and the other axis is associated with differentially N,N-disubstituted amides. The stereodynamics of these substrates provides an opportunity to observe a curious interplay of kinetics and thermodynamics intrinsic to a system of stereoisomers that is constrained to a situation of partial equilibrium.

The generation of enantiopure, chiral molecules remains relevant to many scientific fields, from the study of biological systems to materials science. One critical challenge is that enantiomerically enriched compounds are not fully equilibrated ensembles. Enantiopure compounds represent an ensemble of higher free energy owing to the entropic penalty associated with a one-state, homochiral composition relative to the corresponding two-state racemate4. The thermodynamic benefit of a two-state system can counteract asymmetric synthetic efforts, which are often performed not only for individual enantiomers, but also for individual diastereomers—each of the four possible stereoisomers (5). Whereas peptides such as 1 were envisioned to provide stereochromic control over the atropisomeric axis of 4, it was unclear at the onset of this study whether control of the amide axis disposition (cis amide versus trans amide) could be accomplished with the same catalyst. If interconversion among all possible diastereomers of the two-axis starting material 4 were possible (with low barriers to isomerization within the starting materials12), one could envision four unique catalysts that might accomplish the task. Of course, a critical issue is the overall stability of the individual stereoisomeric products (variants of 5). Low barriers to rotation about either the benzamide axis (Ar–CO, where Ar is aryl; red bond), the amide bond axis (C–N, blue bond)13, or both, in a concerted manner14,15, could conspire to erode kinetic selectivity.

Our studies provided an opportunity to observe a curious result. When rac-4 is exposed to dibromomethylhydantoin (DBDMH) in the absence of a chiral catalyst, under conditions otherwise analogous to those of Fig. 2 (−40 °C), the expected racemic products are formed over the course of about 50 h (70% yield), as a mixture of four stereoisomers (5). After the reaction is quenched, the phenol is converted to the methyl ether for analytical purposes to generate 5-(Me), where Me is methyl. When the isomeric mixture is purified and analysed by chiral high-performance liquid chromatography (HPLC) (about 1 h after quenching, at about 25 °C), the first measurement reveals a ratio of 40:60 trans-5-(Me):cis-5-(Me) isomers, each in racemic form (Fig. 4a). If the sample is allowed to stand at room temperature (dissolved in 10% iPrOH/hexanes, where iPr is iso-propyl) and is reanalysed at a much later time point (50 h), the

![Figure 1](https://example.com/figure1.png)

**Figure 1** | Stereochemical interconversion of chiral organic compounds. a, Racemization of an enantioenriched α-substituted aldehyde. b, Atropisomerization of an axially chiral biaryl compound.

![Figure 2](https://example.com/figure2.png)

**Figure 2** | Catalytic enantioselective bromination of N,N-diisopropyl benzamides. *e.r.*, enantiomeric ratio; i-Pr, iso-propyl; Boc, tert-butoxycarbonyl; rac, racemic; ent, enantiomer; CHCl3, chloroform.
Figure 3 | Proposed catalytic enantioselective bromination of a two-axis, differentially substituted benzamide. The use of the R- and S-stereochemical descriptors are in accord with convention, and are defined interchangeably with the also-used M- and P-stereochemical convention16; R = M; S = P.

trans:cis ratio is observed to increase to 76:24 (Fig. 4b). Notably, although the cis-amide of 4 is the minor component of the starting material over a wide temperature range, including at the reaction temperature of −40 °C, the cis-amide of 5 (assayed as 5-(Me)) appears to be generated in slight excess. Thus, it is apparent that there is some modest kinetic selectivity for the cis-isomer, which equilibrates at room temperature to the thermodynamically more stable trans-amide over time. It is notable that the amide of 5-(Me) exhibits a barrier to C–N bond isomerization that is high relative to typical amides, but still too low to be effectively arrested at room temperature. The experimental and calculated barriers to C–N bond rotation are determined and discussed below.

When the reaction is performed in the same manner with chiral catalyst 1 (94% yield, within 24 h), a more elaborate scenario is observed. When the product mixture is analysed by chiral HPLC at the first time point (about 2 h after quenching, at 25 °C), a trans/cis ratio of 43:57 is observed (Fig. 4c). In this measurement, the trans-amide enantiomeric ratio is 66:34, whereas the cis-amide enantiomeric ratio is recorded as 88:12. As the sample is allowed to stand in solution (10% iPrOH/hexanes)—long after the chiral catalyst has been removed from the system—the following changes occur spontaneously in the product distribution. At 10 h after quenching (Fig. 4d), the trans/cis ratio moves to 54:46, enhancing the population of the trans-isomer as expected. In parallel, the enantiomeric ratios of both amide isomers change as the system moves towards the trans/cis amide equilibrium position, with the cis-amide enantiomeric ratio decreasing to 86:14, while the trans-amide enantiomeric ratio spontaneously increases to 72:28. These changes continue as the system continues to equilibrate. At 24 h (Fig. 4e), the

Figure 4 | Experimental data describing the stereochemical behaviour of the isomeric benzamide products. a-f, Chiral HPLC traces of 5-(Me) analysed at room temperature. a, b, Reactions run at −40 °C in the absence of catalyst. Time zero is defined as the point of reaction quench, followed by purification and HPLC analysis at 25 °C. c–f, Reactions run in the presence of catalyst and subsequently monitored over time after reaction work-up. Peak assignments in order of elution: peak 1: R, trans; peak 2: S, trans, peak 3: S, cis; peak 4: R, cis. g, Graphical representation of changes in isomeric components. h, Crystallographic structure of (S, trans)-derivative used for the absolute stereochemistry assignments16. mAU, milliabsorbance units.
trans-cis ratio is 68:32; the cis-amide enantiomeric ratio erodes to 84:16, and the trans-amide enantiomeric ratio increases to 77:23. After 72 h, the product ratios have stabilized (Fig. 4f), and the apparent equilibrium position of the amide diastereomers has been reached, with a trans-cis ratio of 76:24. At this stage, the cis-amide enantiomeric ratio is 79:21, identical to the trans-amide enantiomeric ratio. These observations are depicted graphically in Fig. 4g. Although data are shown in Fig. 4 for reactions conducted at ~40 °C, the observations are qualitatively reproduced when the experiments are repeated at several different temperatures (see Supplementary Information section VIIa).

Our observations reflect a situation of spontaneous enantioenrichment for one of the product diastereomers (trans), with a compensatory decrease in enantiomeric ratio for the other diastereomer (cis). Interestingly, a 50:50 racemic mixture is not observed, with the system retaining enantioenrichment even after prolonged periods of time at room temperature, a consequence of the two-axis system failing to reach complete equilibrium within the time frame analysed (see below).

Both the trans and the cis isomers of the products could be separated by silica gel chromatography—an unusual circumstance—and each produced the expected diastereomeric trans-cis ratio (76:24) upon standing in solution (10% iPrOH/hexanes). In these cases, the enantiomeric ratio of the samples remains virtually constant (cis, 87:13; trans, 74:26; see Supplementary Information sections VIc and VId and Supplementary Fig. 7 for details).

Through separation of the enantioenriched cis- and trans-amide isomers, enantioenriched trans-material was obtained and provided crystallographic quality material to assign (S, trans)-5 as the major isomeric component after amide equilibration (Fig. 4h; see also Supplementary Information section IV). We note that the stereoisomer obtained for assignment of the S-trans configuration was derived from isolation of the cis product, reflecting the crystallization of the major trans diastereomer, as cis-to-trans equilibration occurs over the course of the crystallization experiment. Parenthetically, the absolute configuration of this S-trans sample, derived from the isolation of enriched cis sample, is the same absolute configuration observed when catalyst 1 operates on substrate 2, to deliver enantioenriched (S-3) with a 94:6 enantiomeric ratio (Fig. 2). Accordingly, these data provide circumstantial support for the equilibration of the S-cis isomer to the S-trans isomer (and also of R-cis to R-trans) without interconversion of the axis of chirality. Further details of this scenario are now considered.

As cis-to-trans amide isomerization occurs and the diastereomeric ratio reaches its equilibrium position, the final enantiomeric ratios for both the trans-amide isomers and the cis-amide isomers emerge as equivalent. As is implicit in Fig. 4g, the sum of the major enantiomers of the amide diastereomers ((S-cis)-5-(Me) + (S-trans)-5-(Me)), divided by the sum of the minor enantiomers of the diastereomeric amides ((R-cis)-5-(Me) + (R-trans)-5-(Me)) is near 79:21 (3.76 ± 0.41) at each time point in Fig. 4 (Supplementary Table 6 and Supplementary Fig. 5 contain expanded data sets detailing this point). The convergence of the enantiomeric ratio for both the trans- and cis-amide diastereomers is consistent with a mechanistic model wherein amide isomerization occurs through independent C–N bond rotation at ambient temperature (Fig. 3), while the enantiomer-defining axis of chirality (Ar–CO) is essentially fixed. The equilibration of the amide isomers, without interconversion of the Ar–CO bond axis, leads to fluctuation of the starting cis-amide enantiomeric ratio downward, and the trans-amide enantiomeric ratio upward, until amide isomerization achieves the equilibrium ratio, and the enantiomeric ratios of the diastereomers are equivalent.

However, when the cis- or trans-amide diastereomers are separated by chromatography, and the isolated amide diastereomers are allowed to re-equilibrate, the enantiomeric ratio remains constant in each series. This situation is once again a manifestation of \( \Sigma(S, cис + S, trans) / \Sigma(R, cис + R, trans) \) remaining constant. In this case, there is no reservoir of the other amide diastereomer, of a different enantiomeric ratio, to distribute its population of either S- or R-configuration differentially to the two amide diastereomers at the C–N bond equilibrium position.

To explore the plausibility of these assertions, we complemented our experiments with a series of density functional theory calculations to ascertain the barriers associated with the critical modes of isomerization. The dynamics described above for amide isomerization correspond to experimentally derived free-energy barriers \( ^{7,18} \text{of 24.8 kcal mol}^{-1} \text{(cis-to-trans)} \) (Fig. 5; see Supplementary Information section VIII). Computations \( ^{20} \text{of 24.4 kcal mol}^{-1} \text{(trans-to-cis)} \) and 24.0 kcal mol\(^{-1} \text{(cis-to-trans)} \) (Supplementary Information section XIII), on a par with both the experimentally determined values and literature values for somewhat related compounds. Additionally, during the entire computed C–N rotation process, the Ar–CO dihedral angle remains close to its value in the ground state, even as the amide axis rotates out of conjugation with the carbonyl and pyramidalizes (TS-5a, Fig. 5b). Thus, independent C–N bond rotation appears to have a much lower barrier than any putative process involving a coupled rotation of the Ar–CO axis. This is consistent with the observation that erosion of the overall enantioenrichment of the system does not occur at room temperature.

Of interest to the present system are previous reports by Clayden, which showed that rotations about the Ar–CO bond axis of sterically hindered tertiary amides follow a mechanistic course involving concerted rotations of the Ar–CO axis and the amide C–N bond axis, in a gearing fashion, when sufficient energy is available to the system. Our calculations for the present system reassert these conclusions. However, the system we present here is distinct in that (1) the action of a chiral catalyst delivers diastereomeric amides of different enantiomeric ratio that allows for the observation of fluctuating enantiomeric ratios, and (2) the system is amenable to simple preparative chromatography, providing proof of principle for a practical asymmetric synthesis.

**Figure 5 | Energetic considerations and analysis of the stereoisomerizations.** a, Energy diagram representing the initial experimental isomeric populations, equilibrium populations (inset 1), and experimentally derived amide rotational barriers (inset 2) of 5-(Me) at 25 °C (10% iPrOH/hexanes). \( \bar{K}_{eq} \) is the equilibrium constant, \( \Delta G \) is the Gibbs free energy and \( \phi \) represents the dihedral angle. b, Computed ground states and transition state (TS) geometries for amide isomerization of (S)-5-(Me). Computed energies were performed with a torsional potential energy scan of the C–N dihedral angle, followed by geometry optimization of all stationary points (transition states and minima) using B3LYP/6-31+ + G(d,p) in the Gaussian 09 software (http://www.gaussian.com). Harmonic vibrational frequencies were calculated at the same level of theory to determine free energies (\( \Delta G \)), and single point energies were computed using M06-2X/6-311 + + G(2d,3p). Cyclic.

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(2) there are distinct steric demands of the substrate that separate the energetic barriers of geared Ar=C=O/C=N isomerization from independent C-N bond rotation substantially. Computations employing a relaxed potential energy scan of the Ar=C=O dihedral angle led to a simultaneous rotation about the amide C-N bond. The optimized transition states along this torsional energy profile were marked by non-coplanar N- and aryl-substituents and imaginary frequencies that showed coupled rotation about both axes. Compared to independent Ar=CO rotation, which suffers from an implausibly high computed barrier, this concerted Ar=CO/C=N rotation represents the lowest-energy pathway to inversion of the atropisomeric axis (TS-5b, Fig. 6a). However, below these energetic thresholds, our results with compound 5 are consistent with independent C-N rotation, as noted above.

Although amide isomerization occurred at ambient temperatures, we could induce racemization only through heating the atropoisomeric benzamides at higher temperatures (toluene, >60 °C). We determined the free-energy barrier to racemization experimentally, and found a value of 27.8 kcal mol⁻¹ (at 70 °C) for the cis-5-(Me) isomer, and a value of 28.6 kcal mol⁻¹ for the lower energy trans-5-(Me) isomer (Fig. 6b; see Supplementary Information section IX). When the barriers were computed, values of 28.2 kcal mol⁻¹ and 28.5 kcal mol⁻¹ for cis-5-(Me) and trans-5-(Me) were found, respectively, in good accord with the experimentally determined values and literature precedent (see Supplementary Information section XIV). Taken together, our results imply that the racemization pathway involves, for a given amide diastereomer (for example, (S, trans)-5-(Me) to (R, trans)-5-(Me), first, a concerted motion of the Ar=C=O/C=N axes to convert (S, trans)-5-(Me) to (R, cis)-5-(Me); and, second, an independent motion of the C=N axis converting (R, cis)-5-(Me) to (R, trans)-5-(Me), as the original amide diastereomer is restored (Fig. 6a). From the experiments and calculations above, it appears that the concerted two-axis rotation operates at increased temperature, and exhibits a high enough barrier that it is prohibitively slow at room temperature.

In summary, we have observed a stereoisomeric system in which spontaneous enantiomeric enrichment occurs in homogeneous solution, with a compensatory erosion of enantiomeric ratio in a coupled diastereomer. The observation is made possible by the formation of a nonequilibrium mixture of amide diastereomers, wherein each enantiomeric pair is produced under the kinetic influence of a chiral catalyst. Amide isomerization occurs with fluctuation of each diastereomer’s enantiomeric ratio as cis→trans amide equilibration occurs, yet the chirality-defining element does not enantiomerize. Instead, the overall enantioenrichment of the system is retained as the populations of each isomer interconvert. Our understanding of the dynamic processes includes an assessment of the intrinsic barriers for the isomerizations, as a function of individual bond rotations, or those that may occur in a concerted manner. The interconversion of stereoisomers in the presence of a fixed element of chirality has been exploited to great advantage in the development of asymmetric reactions.23,26. Yet, the present case of fluctuating enantiomeric ratios, without epimerization of a chiral element within reaction products that have been isolated away from their equilibrium positions, is distinct. These features may be of interest given the current literature on atropoisomerization.23,28. Moreover, these observations may inform endeavours where spontaneous transfer of chirality occurs among the components of a system as a function of the interplay of kinetics and thermodynamics.29.

**METHODS SUMMARY**

Dibromodimethylhydantoin (DBDMH, 85.8 mg, 0.30 mmol) was added to a 0.02 M solution of the aromatic amide (66.9 mg, 0.20 mmol) and catalyst 1 (ref. 10) (11.5 mg, 0.02 mmol) in CHCl₃ (10 ml) at various temperatures (0 °C, −40 °C, or −55 °C). The reaction was allowed to stir overnight (15–22 h). The reaction was then quenched with a 1.5 M solution of butyl vinyl ether in methanol (MeOH, 0.5 ml). The time of quench was recorded for amide equilibration calculations and defined as time zero (see Supplementary Information section VIII). For ease of chiral HPLC development, the phenol was subsequently protected as the methyl ether. The reaction was then allowed to warm to room temperature and additional methanol was added to react with MeOH (1 ml), which was followed by 2.0 M trimethylsilyldiazomethane in hexanes (0.4 ml). The methylation was quenched with silica gel upon completion (15–30 min), filtered and concentrated under reduced pressure. Flash chromatography of the crude residue with hexanes/EtOAc afforded products (as a cis→trans mixture or independently isolated isomers). This material (5-Me) was dissolved in a 10% PrOH/hexanes mixture (0.1 M) and allowed to equilibrate, in solution, at room temperature over a prolonged time course to determine the experimental barriers to amide isomerization. Barriers to racemization of 5-Me were determined experimentally by heating in toluene at 70 °C (0.6 M). Isomeric ratios were determined by chiral HPLC using a Chiralcel OD-H column, with a flow rate of 0.75 ml min⁻¹, in 95:5 hexanes:ethanol and retention times as follows: T⁰ = 14.0 min, T₁ = 15.3 min, and T₂ = 20.6 min. The challenge of atropoisomerism in drug discovery, Angew. Chem. Int. Edn 48, 6398–6401 (2009).

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**Author Information** Crystallographic data are deposited with the Cambridge Crystallographic Data Centre under the accession number CCDC 969575 (for 5-(X-ray)). Reprints and permissions information is available at www.nature.com/ reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to S.J.M. (scott.miller@yale.edu).