Published in final edited form as:
Science. 2010 June 4; 328(5983): 1251–1255. doi:10.1126/science.1188403.

Dynamic Kinetic Resolution of Biaryl Atropisomers via Peptide-Catalyzed Asymmetric Bromination

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Abstract

Despite the widespread use of axially chiral, or atropisomeric, biaryl ligands in modern synthesis, and the occurrence of numerous natural products exhibiting axial chirality, general catalytic methods for the direct asymmetric preparation of this compound class have proven elusive. Here we present a tripeptide-derived small molecule catalyst for the dynamic kinetic resolution of racemic biaryl substrates. The reaction proceeds via an atropisomer-selective electrophilic aromatic substitution reaction employing simple bromination reagents. The result is an enantioselective synthesis that delivers chiral non-racemic biaryl compounds with excellent optical purity and good isolated chemical yields (in most cases >95:5 enantiomer ratio and isolated yields 65 to 87%). A mechanistic model is advanced that explains the basis of selectivity observed.

The stereochemical implications of hindered rotation in non-planar molecules, termed atropisomerism, have intrigued chemists for at least 89 years (1,2). Atropisomeric compounds exhibit an axis of chirality (Fig. 1a), rather than a stereogenic atom, such as an sp^3-hybridized carbon with four distinct substituents (Fig. 1b). The capacity of the single bond between two aromatic rings to freely rotate is the basis of racemization for many atropisomeric compounds (3). Yet, in naturally occurring compounds, atropisomeric molecules are often found in single isomeric form due to substituents on aryl rings that raise the barriers to racemization. Also, the localization of aryl rings within multicyclic ring systems can constrain single bond rotations, preventing isomerization, and the observation of mixtures (4,5). These properties, no doubt, contribute to the remarkable structures and functions of numerous biologically active compounds that contain single atropisomers as part of their structure. Perhaps the glycopeptide antibiotic vancomycin is the signature bioactive natural product of this type (Fig. 1c). The chiral ligand BINAP (Fig. 1d), a venerable ligand for enantioselective catalysis, may be the best-known designed example (6).

Despite the prevalence and importance of atropisomerism in organic structures, the field of asymmetric catalysis has not yet recorded extensive success in the development of catalysts that control this stereochemical feature. Steps have been taken in the control of atropisomer-selective biaryl bond forming reactions (7,8,9,10,11). Yet, only a few reports deal with the selective reaction of a single enantiomer of a dynamic mixture of atropisomeric biaryl compounds, as freely rotating, rapidly racemizing species, including pioneering work by Bringmann (12) and Clayden (13). Catalytic reactions of this nature are presently rare, and only modest atropisomer selectivity has been observed (14). Here we report a simple chiral catalyst that mediates highly enantioselective electrophilic aromatic substitution reactions,

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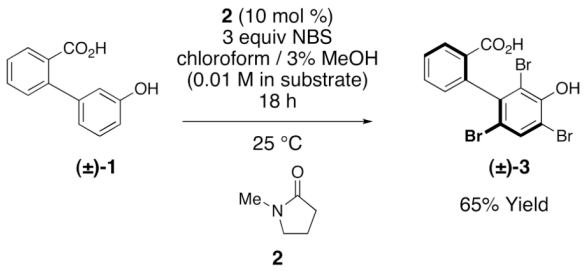
thereby promoting atropisomer-selective functionalization of rapidly racemizing biaryl compounds.

We began our project by identifying a substrate class that would exhibit axial chirality with atropisomers that might rapidly interconvert. Compound **1** fulfills this criterion, with a barrier to atropisomer interconversion that may be estimated to be ~7 kcal/mol (15). Upon reaction with *N*-bromosuccinimide (NBS) in the presence of catalytic *N*-methylpyrrolidine (10 mol% **2**), compound **1** was triply brominated to yield **3** (eq. 1), which exhibits much more restricted rotation about the bond connecting the aromatic rings. In fact, the barrier to racemization for compound **3** may be estimated to be ~30 kcal/mol (16). This barrier is sufficiently high so that in principle, if an enantioselective catalyst could be found for the conversion of **1** to **3**, isolation of optically enriched, non-racemizing products could be obtained at room temperature. Notably, singly or doubly brominated intermediates were not observed under the reaction conditions we employed.



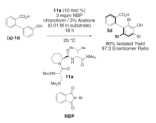
(1)

We then turned our attention to the issue of enantioselectivity. Our choice of catalyst for these studies followed an empirical path, given the paucity of precedents for this type of asymmetric catalytic reaction. Nonetheless, we were guided by the principle that Lewis base catalysis of electrophilic bromination reactions is possible (17,18,19,20,21,22). Furthermore, we were driven by the recognition that simple peptide-based catalysts have substantial capacity to mediate a wide variety of mechanistically diverse enantioselective transformations (23,24). Moreover, we had recently shown that peptide-based catalysts exhibit remarkable enantioselectivity in the derivatization of unusual aromatic compounds (25).

We chose peptide **4** as a starting place for catalyst screening (Table 1), with the rationale that the chiral environment of the peptide β-turn (26) could lead to atropisomer selection during the electrophilic aromatic substitution reaction. β−*N*,*N*-Dimethylamino alanine (Dmaa) was introduced as the *N*-terminal residue with hope that it might function as an additional basic site, favoring catalyst-substrate contacts. This first-generation catalyst provided encouraging results, with methyl ester **1a** giving the product in non-racemic form (entry 1). Swapping **1a** for benzyl amide **1b** improved enantioselectivity to nearly 2:1 (entry 2). Nitro group substitution led to lower selectivity (entry 3). However, carboxylic acid **1d** proved a very promising substrate for the reaction, affording **3d** with 75:25 e.r. (entry 4). We were particularly encouraged by the mathematical implications of this result for dynamic kinetic resolution (27). A 75:25 ratio of enantiomers at high levels of conversion requires that substrate racemization occur (28), at least to some extent during the course of the overall reaction. Moreover, we observed no erosion of e.r.'s upon extended storage or heating (100 °C, 15 hours), consistent with the expected high barriers to biaryl bond rotation/racemization required for our fundamental premise to operate.

We then turned our attention to the optimization of the catalyst structure. Tripeptide catalysts were initially examined with the Dmaa residue at the *N*-terminus and chiral α-methylbenzylamides (αMba) at the *C*-terminus (Table 2). Simple replacement of L-Pro in **4** for L-pipecolinic acid (Pip) led to a significant improvement in selectivity (catalyst **5**, entry 2). Substitution of a range of amino acids in the *i*+2 position reduced enantioselectivity slightly (entries 3 to 5), whereas altering the stereogenic sense at this position (entry 6) or the adjacent C-terminal position (entry 7) led to an even greater loss in selectivity. Even so, catalyst **11a**, with a simplified *N*,*N*-dimethyl amide at the *C*-terminus, delivered **3d** in the highest observed enantioselectivity under the initial reaction conditions (entry 8). Ester substitution in place of the *N*,*N*-dimethyl amide lowered selectivity substantially (entry 9). We therefore declared peptide **11a** our lead catalyst for further study.

We then evaluated additional reaction parameters, including solvents, concentration, temperature and brominating agent. Among these factors, the bromine source proved particularly influential. *N*-Bromophthalimide (NBP) consistently gave the best results. In combination with optimized solvent and concentration conditions (29), catalyst **11a** (10 mol %) was found to promote conversion of racemic (±)-**1d** to an 80% yield of **3d**, with an enantiomer ratio of 97:3 (eq. 2). These results were obtained at room temperature, on a 0.5 mmol scale, and we observed no variation over a range of reaction scales up to 9 mmol (~2 grams).



(2)

With an effective catalyst and mild reaction conditions in hand, we then examined substrate scope. The substrates shown in Table 3 were readily prepared employing established aryl-aryl bond forming cross-coupling reactions (30). A range of substitutents on the aryl rings of the substrate proved compatible with the excellent results obtained for substrate **1d**. For example, electron withdrawing NO_2-group substitution *para* to the phenolic arene, as in compound **12**, led to the isolation of **13** with a 97:3 e.r. (entry 2). Compound **14**, with *meta*-NO_2 substitution gave a similar result (entry 3), as did electron rich anisoles **16** (entry 4) and **18** (entry 5). Given the importance of fluorinated aromatic compounds, we assessed *meta*-substituted fluorobenzene **20** and *para*-substituted fluorinated substrate **22** (31), and found they also were excellent substrates for the reaction (entry 6 and 7). Alkyl substitution *ortho* to the carboxylic acid leads to somewhat lower enantioselectivity (entry 8).

It appears that this catalytic methodology could be quite useful for asymmetric synthesis of a range of heteroarene compounds containing functionalities of relevance to bioactive natural product substructures (32). For example, pyrrole analog **26** was converted to **27** with a moderate, but encouraging 85:15 e.r. (entry 9). Catechol **28**, a potential substructure in the stegane natural products (33) was converted to **29** with an e.r. of 95:5 (entry 10), and can be enriched to exhibit enantiomer ratios of >98:2 by a single recrystallization. The results shown in Table 3, taken together, reveal that catalyst **11a**, and perhaps more importantly, its analogs could be quite useful conceptually for synthesis of a broad range of optically enriched biaryl-type compounds.

We have also gained some insight in to the mechanism of these intriguing reactions. Several experiments with stripped down, potentially catalytic moieties confirm the possibility of amide catalysis, (19) perhaps via a type of [O-Br]-cationic species. For example, when the

reaction is conducted in the absence of a catalyst, bromination is sluggish, and **1** is converted to **3d** in only 15% yield after 18 h (Fig. 2). Tertiary amines, such as *N*,*N*-diisopropylethylamine also provide only slight rate acceleration, and the yield of **3d** is 30% under analogous conditions. However, the use of the *N*,*N*-dimethylamide **30** leads to 91% isolated yield of **3d**. These results point to a functional role for one of the several amides resident in catalyst **11a**, including the terminal *N*,*N*-dimethylamide. Neither mono- nor dibrominated products were observed in substantial quantities under these conditions.

These observations, in combination with our knowledge of stereochemical aspects of the reaction, have allowed us to posit a possible explanation for the stereochemical outcome. Single crystal, heavy atom X-ray analysis allowed assignment of the absolute configuration of the major product of enantioenriched **3d** as the (*R*)-atropisomer (Fig. 3). The conformation of catalyst **11a** is likely as shown in Figure 3, with axial disposition of the pipecolinic acid substituent, due to the well-known preference of *N*-acyl piperidines to adopt conformations with axial 2-substituents to avoid allylic strain (34). Docking of the substrate **1d** through salt bridge formation between the Dmaa tertiary amine and the substrate carboxylic acid disposes a putative *O*-bromonium ion toward formation of the observed stereoisomer of **3d**. Notably, free rotation of the partially brominated (e.g., mono- and dibromonated) species may be possible until the *ortho*-*ortho*' substituents are each installed, leading to a barrier to rotation high enough to preclude product racemization. On the other hand, a hydrogen bond between the phenolic proton and the Dmaa amide *O*-atom may prevent such bond rotation at intermediate stages of the reaction.

Synthesis of optically enriched biaryl compounds utilizing enantioselective catalysts and dynamic kinetic resolution should enable improved access to stereodefined atropisomeric materials. More broadly, the approach described herein may also stimulate related research involving selective reactions of other interconverting, axially chiral compounds, promoted by simple peptide-based catalysts (35).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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35. We are grateful to the National Institute of General Medical Sciences of the NIH for support (GM068649).

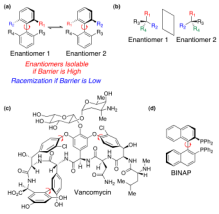


Figure 1.

(a) Biaryl atropisomers are isolable if the barrier to rotation about the single bond linking the rings is high. The enantiomers interconvert via racemization if the barrier is low. *(b)* sp^3-Hybridized carbon atoms with four different substituents form generally stable enantiomers. *(c)* Vancomycin is a natural product that exists as a single atropisomer. *(d)* BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) is a widely used chiral ligand.

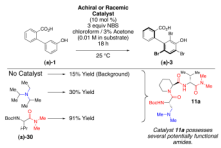


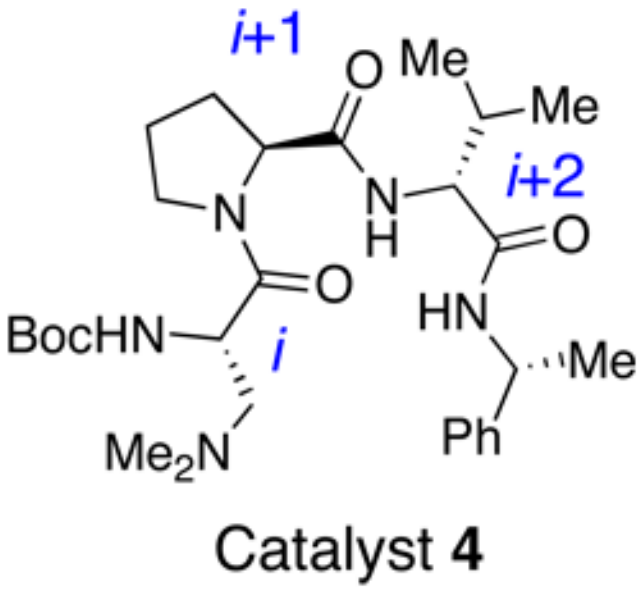
Figure 2.
Assessment of the catalytic efficiency of simple functional groups.

Figure 3.
X-ray structure of the major enantiomer of **3d**, and a possible docking model explaining selectivity. Structure shown is an ORTEP diagram (ellipsoids shown at the 30% probability level).

Table 1

Initial screen of catalysis for asymmetric bromination of **1**. Isolated yields correspond to the anisole methyl ester after treatment with 4 equiv TMS-diazomethane (2M in Et_2O) for 15 minutes in 0.2 M toluene:MeOH (3:1). This work-up assists in purification and e.r. determination by chiral HPLC. See Supporting Online Material for details. Enantiomer ratios were determined by chiral HPLC.

Entry	R	Yield (%)	Enantiomer Ratio (e.r.)*
1	CO_2Me (**1a**)	80	57.5:42.5
2	CONHBn (**1b**)	80	65.0: 35.0
3	NO_2(**1c**)	80	52.0: 48.0
4	CO2H (**1d**)	90	75.0: 25.0

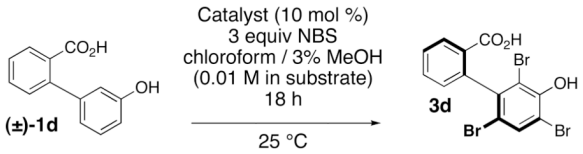


Catalyst **4**

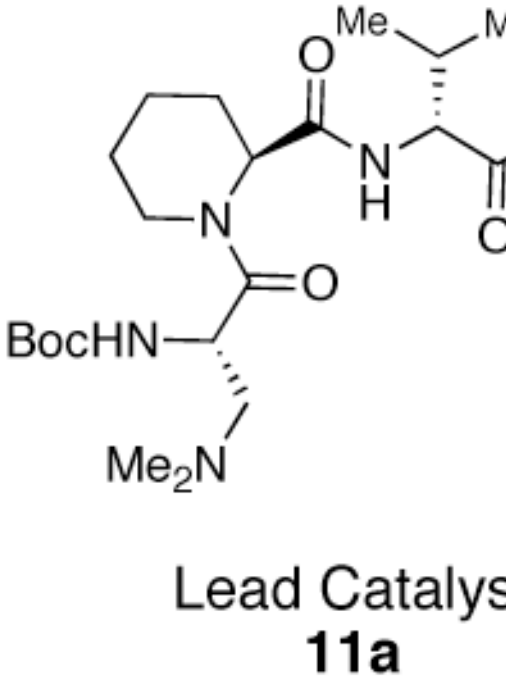
*The major atropisomer of **3d** was assigned to the *R*-configuration by X-ray analysis.

Table 2

Optimization of the catalyst structure. Data determined as in Table 1.



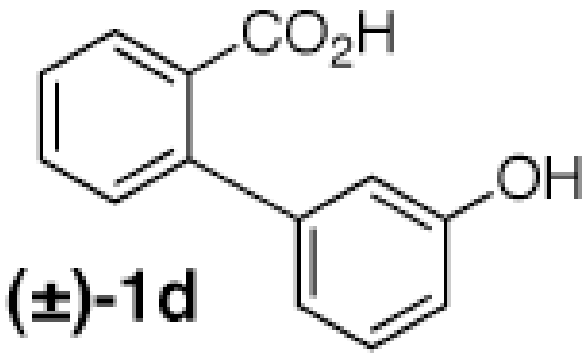
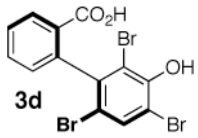
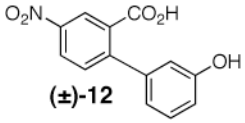
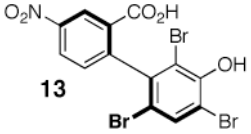
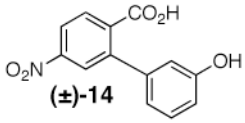
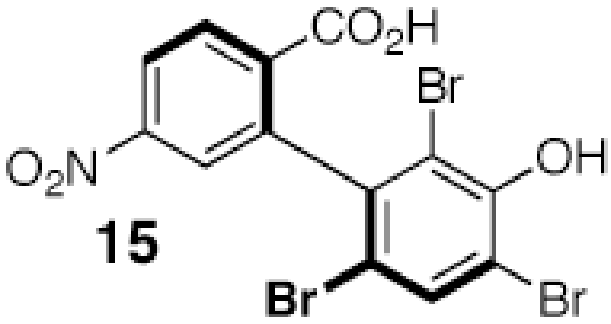
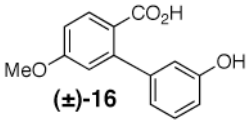
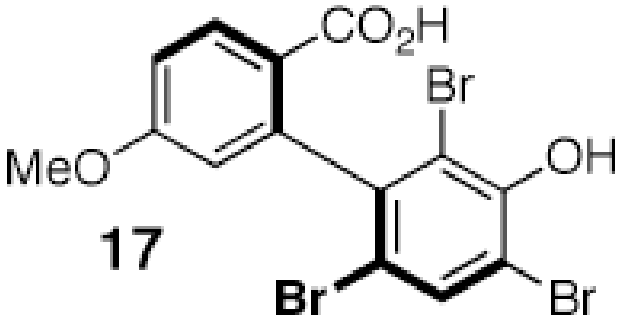
Entry	Catalyst	Yield (%)	E.r.
1	Boc-β-Dmaa-Pro-(D)Val-(*R*)-βMba (**4**)	90	75.0:25.0
2	Boc-β-Dmaa-Pip-(D)Val-(*R*)-αMba (**5**)	87	90.0:10.0
3	Boc-β-Dmaa-Pip-(D)Phe-(*R*)-αMba (**6**)	73	86.5:13.5
4	Boc–β-Dmaa-Pip-(D)Tle-(*R*)-αMba (**7**)	85	89.0:11.0
5	Boc-β-Dmaa-Pip-(D)Ile-(*R*)-αMba (**8**)	65	82.5:17.5
6	Boc-β-Dmaa-Pip-(L)Val-(*R*)-αMba (**9**)	95	75.0:25.0
7	Boc-β-Dmaa-Pip-(D)Val-(*S*)-αMba (**10**)	80	75.0:25.0
8	Boc-β-Dmaa-Pip-(D)Val-NMe_2 (**11a**)	90	**92.0:8.0**
9	Boc-β-Dmaa-Pip-(D)Val-OMe (**11b**)	90	65.0:35.0

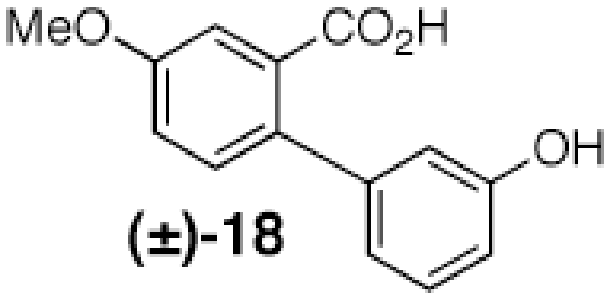
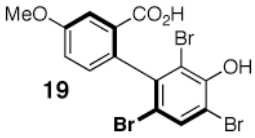
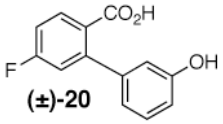
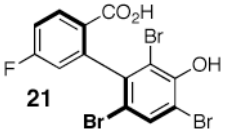
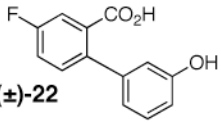
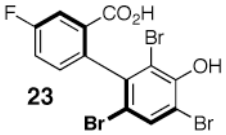
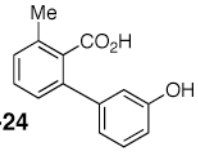
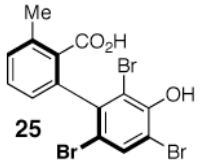
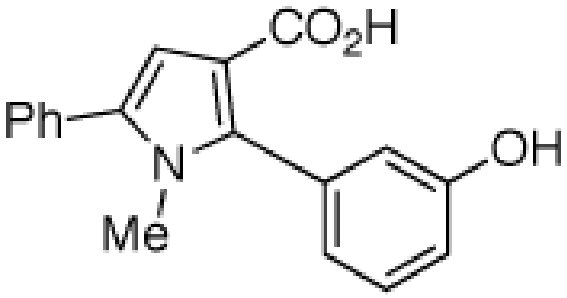
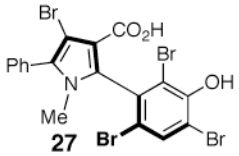
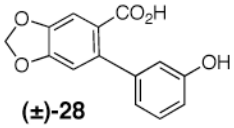
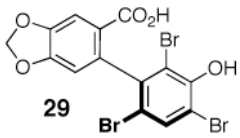


Lead Catalys
11a

Table 3

Substrate scope for enantioselective bromination. Data determined as in Table 1. Results represent the average of 2–3 runs per substrate.

Entry	Racemic Starting Material	Product	Yield
1	 (±)-1d	 3d	80
2	 (±)-12	 13	85
3	 (±)-14	 15	75
4	 (±)-16	 17	70

Entry	Racemic Starting Material	Product	Yield
5	 (±)-18	 19	80
6	 (±)-20	 21	70
7	 (±)-22	 23	65
8	 (±)-24	 25	85
9	 (±)-26	 27	77*
10	 (±)-28	 29	70

* 4 equiv of NBP.