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Enantioselective Synthesis of Atropisomeric Benzamides through Peptide-Catalyzed Bromination

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Supporting Information

ABSTRACT: We report the enantioselective synthesis of atropisomeric benzamides employing catalytic electrophilic aromatic substitution reactions involving bromination. The catalyst is a simple tetrapeptide bearing a tertiary amine that may function as a Brønsted base. A series of tri- and dibrominations were accomplished for a range of compounds bearing differential substitution patterns. Tertiary benzamides represent appropriate substrates for the reaction since they exhibit sufficiently high barriers to racemization after ortho functionalization. Mechanism-driven experiments provided some insight into the basis for selectivity. Examination of the observed products at low conversion suggested that the initial catalytic bromination may be regioselective and stereochemistry-determining. A complex between the catalyst and substrate was observed by NMR spectroscopy, revealing a specific association. Finally, the products of these reactions may be subjected to regioselective metal−halogen exchange and trapping with I_2, setting the stage for utility.

Tertiary aromatic amides with appropriate substitution may exhibit axial chirality about the carbonyl carbon−aryl carbon bond axis (Figure 1a).[1] With a sufficiently high barrier to interconversion, **1** and ***ent*-1** thus may be isolated and studied as independent entities. These phenomena have been known from the chemical perspective for many years, and more recently, differential biological activity has been noted for isolated enantiomers of chiral benzamide drugs and drug candidates.[2] In fact, the property of amide atropisomerism is emerging with great frequency in the medicinal chemistry literature.[3] Structures such as **2** (Figure 1b), unless resolved, may exist and function as independent diastereomers.[4] Bioactive compounds like **3**,[5] which cannot be resolved at physiological temperatures because of the low barrier to amide atropisomerization, may function in one conformation but might also exhibit deleterious off-target effects in the other rotameric form. As a result, methods for atropisomer-selective synthesis are a current objective. Approaches involving asymmetric ortho-functionalization reactions are described in the literature,[6] as are applications of chiral auxiliaries.[7] Catalytic asymmetric approaches are less well known but are now emerging, as exemplified by recent studies of [2 + 2 + 2] cycloadditions[8] and dynamic kinetic resolutions.[9] We report herein an addition to the catalytic, enantioselective approaches to the synthesis of this important class of chiral compounds.

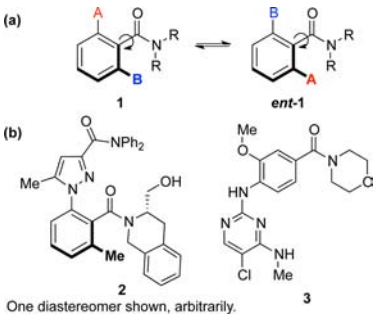
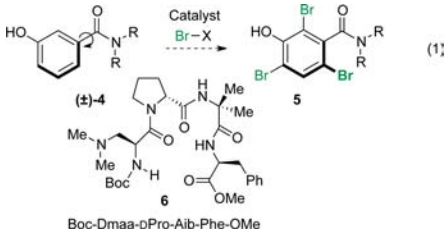


Figure 1. (a) Chiral benzamides, which have barriers to isomerization that are dependent on the nature of A and B. (b) Examples of bioactive compounds that may exist as benzamide atropisomers with either a high (**2**) or low (**3**) barrier to isomerization.

We previously demonstrated that peptide-based catalysts could be effective for the atropisomer-selective bromination of biaryl compounds to establish axial chirality in a series of biphenyls.[10] Given the analogy between the axial chirality implicit in biphenyls and the axis of chirality intrinsic to benzamides, we wondered whether it might be possible to achieve enantioselective reactions of the type shown in eq 1.



Some keys for effective catalysts in our prior studies appear to include functional groups that can form contacts (perhaps through hydrogen bonding[11]) between the catalyst and the substrate.[12] In addition, putative bromine-directing groups (e.g., Lewis base catalysis of bromine transfer involving an amide carbonyl[13]) are likely key for bromine−arene bond formation. Catalyst **6** embodies these elements. Peptide **6** contains the dimethylaminoalanine residue (Dmaa), which we felt might target the acidic *m*-hydroxyl of the benzamide,[14] possibly activating the arene. We elected to embed Dmaa within peptide frameworks we have examined extensively over the years. Among these, the D-Pro-Aib-Phe-OMe fragment (Aib = α-amino-isobutyric acid) has found utility for a wide variety of

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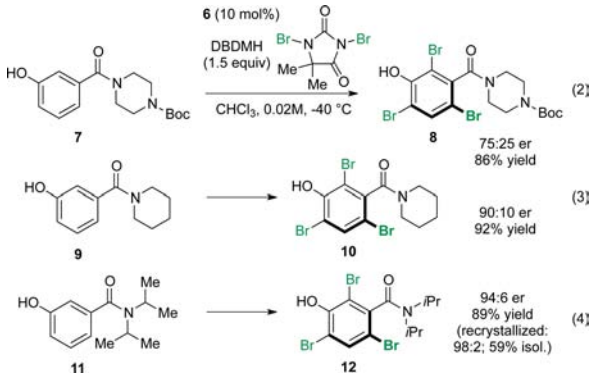
enantioselective processes.[15] Peptide **6** was projected to possess the capacity to exhibit a β-hairpin structure that could provide conformational constraints favoring bifunctional synergy between the Dmaa side chain and a distal Lewis basic functional group.[16]

Notably, as shown in eq 2, evaluation of catalyst **6** for the tribromination of substrate **7** yielded an encouraging initial

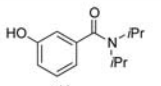
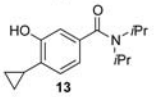
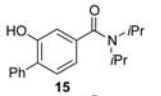
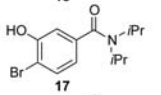
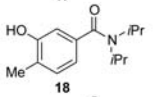
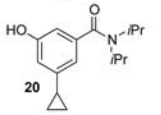
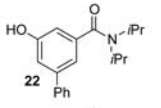
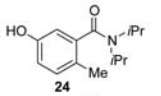
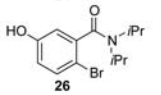
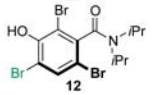
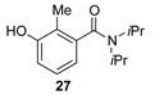
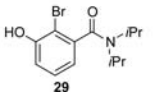


result.[17] When the reaction was conducted with 10 mol % **6** [−40 °C, dibromodimethylhydantoin (DBDMH) as the brominating agent, $CHCl_3$, 20 h], product **8** was isolated in 86% yield, exhibiting a 75:25 enantiomeric ratio (er). Moreover, when the piperizyl moiety of **7** was replaced with a piperidyl group (i.e., **9**; eq 3), the reaction selectivity improved. In this case, tribromide **10** was isolated in 92% yield with a 90:10 er. Importantly, evaluation of the same sample after 40 days revealed no erosion of the er, reflecting a high barrier to racemization. Evaluation of diisopropylbenzamide **11** led to further enhancement of the selectivity, as **12** was now isolated in 89% yield with a 94:6 er (eq 4). In this case, the product could also be recrystallized to give a 98:2 er (59% recovered after a single recrystallization). Our rationale in evaluating compound **11** involved speculation that the amide of substrate **7** or **9** itself might be a Lewis base mediator of autocatalytic (and nonselective) bromination. Compound **11** was selected to probe steric inhibition of such nonselective catalysis, although this hypothesis remains rigorously unproven.[18]

We therefore wished to evaluate the substrate scope for this process. As shown in Table 1, in addition to the parent compound **11** (entry 1), a variety of differentially substituted benzamides were explored under standardized conditions. Substituents ortho to the phenol were well-tolerated, with cyclopropyl-substituted amide **13** undergoing conversion to dibromide **14** with a 96:4 er (79% isolated yield; entry 2). Sterically demanding aryl substitution was also tolerated, as **15** was converted to **16** in 86% yield with a 93:7 er (entry 3). When a pre-existing bromide was present (as in **17**; entry 4), the reaction proceeded similarly, and **12** was produced in 89% yield with a 92:8 er. (The mechanistic ramifications of this observation are discussed in greater detail below). The *o*-methyl-bearing substrate **18** was converted to **19** in 69% yield with a 93:7 er (entry 5). Meta substitution also provided suitable substrates. For example, the cyclopropyl group of **20** was tolerated, allowing **21** to be isolated in 90% yield with a 92:8 er (entry 6). A phenyl group was also accommodated in this position, as **22** was converted to **23** in 89% yield with a 93:7 er (entry 7).

Substitution para to the phenol provided more variation in the results. For example, the *p*-methyl-substituted compound **24** gave **25** with a slightly reduced er of 90:10 (80% yield; entry 8).

Table 1. Substrate Scope for Enantioselective Bromination of Substituted Benzamides Employing Catalyst 6

Entry[a,b]	Substrate	Product	Yield[c]	er[d]
1			89	94:6 (recrystallized: 98:2; 59% isol.)
2			79	96:4
3			86	93:7
4			89	92:8
5			69	93:7
6			90	92:8
7			89	93:7
8			80	90:10[e]
9			90	52:48
10			76	63:37
11			75	51:49

[a]Reactions were conducted at −40 °C for 4−48 h, employing 10 mol % **6** and 0.02 M substrate in $CHCl_3$; 1.0 equiv of DBDMH was used, except for entries 1, 5, and 6 (1.5 equiv). See the Supporting Information for details. [b]All of the experiments were performed in triplicate. [c]Yields of the products after phenol methylation. [d]Determined by chiral HPLC within 1 day of synthesis. [e]After 40 days of storage, this sample exhibited an 81:19 er (see the text).

However, *p*-bromine substitution (as in **26**; entry 9) led to a significant drop in selectivity, as **12** was isolated in 90% yield but in near-racemic form (52:48 er). Moreover, a methyl group ortho to both the phenol and the amide (as in **27**) also led to reduced selectivity, as **28** was isolated with a 63:37 er, albeit in 76% yield (entry 10). Compound **29**, with bromine in the same position, afforded a nearly racemic product (51:49 er; entry 11).

Given the unprecedented nature of this type of catalytic enantioselective approach to atropisomeric amides, we wished to understand the basis for the enantioselectivity. These experiments were in large part stimulated by the fact that the parent compound **11** and the monobromides **17**, **26**, and **29** each gave slightly (entry 1 vs 4) or significantly (entry 1 vs 9 and 11) different results in their respective pathways to **12**. A particularly

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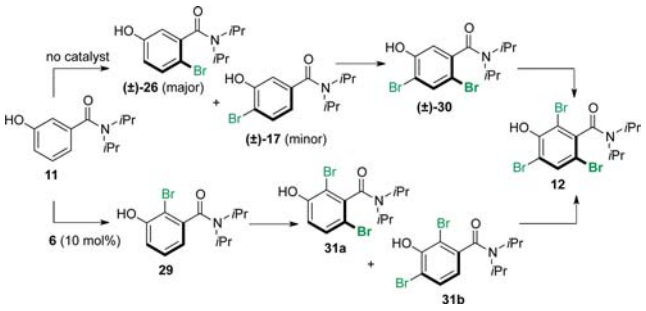
revealing experiment involved subjecting substrate **11** to tribromination conditions in the presence or absence of catalyst **6** (Scheme 1). When these reactions were quenched at low

Scheme 1



conversion,[19] different monobrominated species were apparent in the LCMS and ^{1}H NMR data.[20] In the reaction without catalyst **6**, the dominant species in the reaction mixture, other than the starting material, was monobromide **26**, with bromine installed para to the phenol. In addition, monobromide **17** was also observed. Monobromides **26** and **17** were also the dominant monofunctionalized products when the reaction was conducted in the presence of a simple tertiary amine (e.g., triethylamine) under analogous conditions. On the other hand, in the variant where catalyst **6** was employed, the dominant species was instead monobromide **29**, with bromine installed in the most sterically demanding position, ortho to both the phenol and the amide. These monobromides proceeded to different dibromides: in the uncatalyzed case, **30** was primarily detected; in the catalyzed case, **31a** could be detected prior to completion of the reaction, along with **31b**. Our results suggest that the initial bromination in the **6**-catalyzed reaction, leading to the formation of **29**, may be stereochemistry-determining. This interpretation is consistent with our other observations. As noted, when racemic **26** was used as the starting material under catalytic conditions (Table 1, entry 9), the substrate was not processed enantioselectively. Perhaps monobromide **26** does not undergo racemization at the low temperature at which the reaction was conducted, en route to dibromides and eventually **12**. Interestingly, when the *p*-bromide of **26** was replaced with a methyl group (as in **24**; Table 1, entry 8), significant enantioselectivity was still observed, consistent with the smaller steric demand of the methyl group relative to bromide on most scales of steric effects relevant to atropisomers.[21] Racemization of substrate **24** thus remained possible under these catalytic conditions. Compound **29**, with the 2-bromo substituent, is a particularly poor substrate for the reaction since the putative stereochemistry-determining site is blocked, and the substrate may also exhibit a sluggish rate of isomerization under the reaction conditions. Finally, it is also interesting to note that compound **27** (Table 1, entry 10), in which the site that may be stereochemistry-determining is blocked with a methyl group, was processed with substantially diminished er. It may be that for this case, the site para to the phenol is functionalized in the stereochemistry-determining event, albeit with a less differentiated set of competing transition states. Thus, it is consistent with our observations that a single, initial monobromination ortho to both the phenol and the amide carbonyl is stereochemistry-determining, setting the fate of the atropisomer-selective reaction at that stage.

In pursuit of observable catalyst–substrate interactions, we examined ^{1}H NMR spectra of potentially relevant species (Figure 2). When the spectrum of a 1:1 mixture of **6** and **11** is contrasted with the independent spectra, significant alterations in

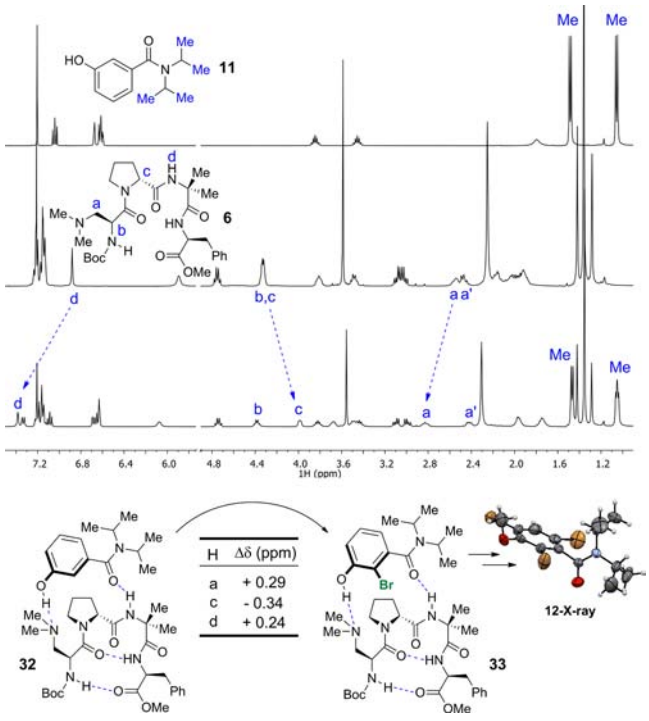


Figure 2. Independent NMR spectra of substrate **11** and catalyst **6** and the spectrum of their 1:1 comixture (0.02 M, $CDCl_3$, 0 °C).

the chemical shifts are evident. In particular, changes consistent with the formation of complex **32** are observed. For example, whereas the Dmaa *β*-proton signals (a, a′) appear nearly coincident for the free catalyst, they become distinct in the complex, with one of the resonances exhibiting a $\Delta\delta$ of 0.29 ppm. Notably, there is also a loss of degeneracy of the methyl groups associated with the isopropyl groups of the substrate. Critically, we also observe a significant change in the chemical shift of the proton associated with the Aib NH (d). In this case, the observed $\Delta\delta$ is 0.24 ppm downfield, consistent with a possible hydrogen bond between the substrate and this locus of the catalyst.[22] Finally, the prolyl Cα proton (c) may be particularly diagnostic. In this case, we observe a $\Delta\delta$ of 0.34 ppm *upfield*.[22] If the catalyst and substrate associate in a manner similar to that drawn for complex **32**, we would expect the ring current of the aromatic ring of the substrate to perturb the prolyl Cα proton in this fashion. It is of further interest to note that if complex **32** is reactive and relevant, one could envision the stereochemistry-determining bromine atom to be introduced as shown in complex **33**. This particular enantiomer would then go on to form the observed major enantiomer of **12**, as demonstrated by heavy-atom X-ray crystallography (**12-X-ray**).[23] At this stage, we are unable to pinpoint which of the catalyst carbonyl groups, if any, might be responsible for delivering the electrophilic bromine. It is nonetheless interesting to note that several seem appropriately disposed. One could also readily imagine, for example, dynamics associated with the system in which amide carbonyls participate in hydrogen bonds at one point along the reaction coordinate but then change roles to deliver bromine at another point.

The intriguing nature of this atropisomer-selective benzamide synthesis has also stimulated our interest in this approach as a

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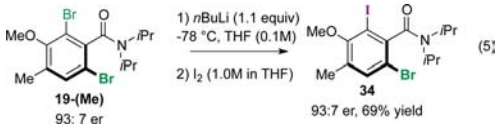
possible entry into druglike compounds. In this vein, selective functionalization of the various aryl bromide positions could heighten utility.[24] To demonstrate the viability of this goal, we subjected **19-(Me)** to metal−halogen exchange conditions at low temperature.[25] In this experiment, we observed efficient, regioselective lithiation[26] followed by trapping with I_2 to give compound **34**. Notably, **34** was isolated without loss of er (eq 5)



(5)

as the illustrated regioisomer.[20] Trapping with alternative electrophiles or selective manipulation of scaffolds like **34** could prove to be a fruitful path for preparing other atropisomerically enriched benzamides.

In summary, we have discovered an enantioselective bromination process that leads to enantioenriched benzamides. The reaction mechanism is complex but appears to follow a pathway that involves a clear mechanistic dichotomy between peptide-catalyzed and uncatalyzed variants. Given the increasing attention to atropisomeric compounds in medicinal chemistry,[3] we are hopeful that this catalytic process will increase access to this family of structures, which along with mechanistic pursuits, will be the continuing focus of this project.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures for all experiments, characterization data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) A variety of peptide-based scaffolds were evaluated. It is notable that **6** proved to be among the best at an early stage in this project. In reactions employing peptides lacking the Dmaa residue, no enantioselectivity was observed. The lead catalyst described in ref 10 delivered **5** in good yield with a 36:64 er under similar conditions, with a preference for the enantiomer opposite to that obtained using **6**.

(18) The results were consistent when reactions were performed on scales ranging from 0.2 through 1.0 mmol of substrate. See the Supporting Information for details.

(19) The reactions were efficiently quenched by the addition of butyl vinyl ether to the reaction mixture at −40 °C.

(20) See the Supporting Information for details.

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(23) The absolute sense of the chirality for the other compounds in Table 1 is not known and has been drawn as shown by analogy to **12**.

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