Published in final edited form as:

J Am Chem Soc. 2013 February 27; 135(8): 2963–2966. doi:10.1021/ja400082x.

Enantioselective Synthesis of Atropisomeric Benzamides through Peptide-Catalyzed Bromination

Kimberly T. Barrett and Scott J. Miller*

Department of Chemistry, 225 Prospect Street, Yale University, New Haven, CT 06520-8107

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 are 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 provide some insight into the basis for selectivity. Examination of the observed products at low conversion suggests that the initial catalytic bromination may be regioselective and stereochemistry-determining. A complex between catalyst and substrate is observed by NMR, revealing a specific association. Finally, products of these reactions may be subjected to regioselective metal-halogen exchange and trapping with I₂, 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 (Figure 1).³ Structures such as **2** (Figure 1b), unless resolved, may exist and function as independent diastereomers.⁴ Bioactive compounds like **3**,⁵ while they cannot be resolved at physiological temperatures given the low barrier to amide atropisomerization, may also 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]-cycloadditions⁸ and dynamic kinetic resolutions.⁹ We report below an addition to the catalytic, enantioselective approaches to the synthesis of this important class of chiral compounds.

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

Corresponding Author: scott.miller@yale.edu.

Supporting Information.

Experimental procedures for all experiments, characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

axis of chirality intrinsic to benzamides, we wondered if it might be possible to achieve enantioselective reactions of the type shown in Equation 1.

(1)

Some keys for effective catalysts in our prior studies appear to include functional groups that could form contacts, perhaps through hydrogen bonding,¹¹ between catalysts and substrates.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 dimethylamino-alanine residue (Dmaa), which we felt might target the acidic *meta*-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 DPro-Aib-Phe-OMe fragment has found utility for a wide variety of 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 equation 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** could be isolated in 86% yield, exhibiting a 75:25 enantiomer ratio (er). Moreover, when the piperizyl moiety of **7** is replaced with a piperidyl group (i.e., **9**; eq 3), the reaction selectivity improves. In this case, tribromide **10** is 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 di-isopropylbenzamide **11** led to further enhancement of selectivity, as **12** is now isolated in 89% yield as a 94:6 enantiomer mixture (eq 4). In this case, the product may also be recrystallized such that it exhibits a 98:2 er (59% recovered after a single recrystallization). Our rationale in evaluating compound **11** involved speculation that the amide itself of substrate **7** or **9** might be responsible as a Lewis base mediator of autocatalytic (and nonselective) bromination. Compound **11** was selected to probe steric inhibition of nonselective catalysis, although this hypothesis remains rigorously unproven.¹⁸

(2)

(3)

(4)

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 are well-tolerated, with cyclopropyl-substituted amide **13** undergoing conversion to dibromide **14** with a 96:4 er (entry 2, 79% isolated yield). Sterically demanding aryl substitution is also tolerated, as **15** is converted to **16** in 86% yield, with a 93:7 er (entry 3). When a pre-existing bromide is present (as in **17**; entry 4), the reaction proceeds similarly and **12** is produced in 89% yield with a 92:8 er. (The mechanistic ramifications of this observation are discussed in greater detail below). The *ortho*-methyl-bearing substrate **18** is converted to **19** in 69% yield, as a 93:7 mixture of enantiomers (entry 5). *meta*-Substitution also provides suitable substrates. For example, as shown in entry 6, the cyclopropyl group of **20** is tolerated such that **21** is isolated in 90% yield with a 92:8 er. A phenyl group is also accommodated in this position, and **22** is converted to **23** in 89% yield, with a 93:7 er (entry 7).

Substitution *para* to the phenol provides more variation in the results. For example, the *para*-methyl substituted compound **24** undergoes reaction to give **25** with a slightly reduced er of 90:10 (80% yield, entry 8). However, *para*-bromine substitution (as in **26**, entry 9) leads to a significant drop in selectivity, with **12** isolated in 90% yield, but in near-racemic form (52:48 er). Moreover, as shown in entry 10, a methyl group *ortho* to both the phenol and the amide (as in **27**) also leads to reduced selectivity, as **28** is isolated as a 63:37 enantiomeric mixture, albeit in 76% yield. Compound **29**, with Br in the same position, affords a near 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 enantioselectivity. These experiments were in large part stimulated by the fact that parent compound **11**, and the mono-bromides **17**, **26** and **29** each give slightly (entry 1 versus 4), or significantly different (entry 1 versus 9) results in their respective pathways to **12**. A particularly revealing experiment involved subjecting substrate **11** to tribromination conditions in the presence or absence of catalyst **6** (Scheme 1). When these reactions are quenched at low conversion,¹⁹ different mono-brominated species are apparent in the LCMS and ¹H NMR data.²⁰ In the reaction without catalyst **6**, the dominant species in the reaction mixture, other than the starting material, is mono-bromide **26**, with bromine installed *para* to the phenol. In addition, mono-bromide **17** is also observed. Mono-bromides **26** and **17** are also the dominant mono-functionalized products when the reaction is conducted in the presence of a simple tertiary

amine, such as triethyl amine, under analogous conditions. On the other hand, in the variant where catalyst **6** is employed, the dominant species is instead mono-bromide **29**, with bromine installed in the most sterically demanding position, *ortho* to both the phenol and the amide. These mono-bromides appear to proceed to the corresponding different di-bromides, primarily **30** in the uncatalyzed case; in the catalyzed case, di-bromide **31a** may be detected prior to completion of the reaction, along with di-bromide **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** is the starting material under catalytic conditions (entry 9/Table 1), the substrate is not processed enantioselectively. Perhaps, mono-bromide **26** does not undergo racemization at the low temperature at which the reaction is conducted, en route to di-bromides and eventually **12**. Interestingly, when the *para*-bromide of **26** is replaced with a methyl group (as in **24**, entry 8/Table 1), significant enantioselectivity is still observed, consistent with the smaller steric demand of the methyl group relative to bromide in most scales of steric effects relevant to atropisomers.²¹ Racemization of substrate **24** thus remains 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** (entry 10/Table 1), which blocks what may be the stereochemistry-determining site with a methyl group, is 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 mono-bromination, *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 ¹H 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, it is evident that significant alterations in chemical shift result. In particular, changes are observed that are consistent with the formation of complex **32**. For example, whereas the Dmaa β-protons (a, a') appear nearly coincident in the free catalyst, they become distinct and one of the resonances reflects Δδ of 0.29 ppm in the complex. Notably, there is also a loss of degeneracy for the methyl groups associated with the *iso*-propyl groups of the substrate. Critically, we also observe a significant change in the chemical shift for the proton associated with the aminoisobutyric acid NH (d). In this case, the observed Δδ is 0.24 ppm downfield, consistent with a possible hydrogen bond between the substrate and this locus of the catalyst.²² Finally, the prolyl C_α-proton (c) may be particularly diagnostic. In this case, we observe a Δδ 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 C_α-proton in this fashion. It is of further interest to note that if complex **32** is reactive and relevant, one could envision introduction of the stereochemistry-determining bromine atom to appear 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 on 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 possible entry into drug-like 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 I₂ to give compound **34**. Notably, **34** is isolated without loss of er (Eq 5) and as the illustrated regioisomer.²⁷ Trapping with alternative electrophiles, or the selective manipulation of scaffolds like **34** could prove a fruitful path to prepare other atropisomerically enriched benzamides.

(5)

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to the National Institutes of General Medical Sciences of the NIH (GM-068649) for support. We are grateful to Timothy Schmeier for X-ray crystallography.

References

1. (a) Cuykeng MA, Mannschreck A. *Chem Ber.* 1987; 120:803. (b) Ahmed A, Bragg RA, Clayden J, Lai LW, McCarthy C, Pink JH, Westlund N, Yasin SA. *Tetrahedron.* 1998; 54:13277.
2. (a) Ikeura Y, Ishichi Y, Tanaka T, Fujishima A, Murabayashi M, Kawada M, Ishimaru T, Komo I, Doi T, Natsugari H. *J Med Chem.* 1998; 41:4232. [PubMed: 9784098] (b) Albert JS, Ohnmacht C, Bernstein PR, Rumsey WL, Aharony D, Alelyunas Y, Russell DJ, Potts W, Sherwood SA, Shen L, Dedinas RF, Palmer WE, Russell K. *J Med Chem.* 2004; 47:519. [PubMed: 14736234] (c) Takahashi H, Wakamatsu S, Tabata H, Oshitari T, Harada A, Inoue K, Natsugari H. *Org Lett.* 2011; 13:760. [PubMed: 21250752]
3. (a) Clayden J, Moran WA, Edwards PJ, LaPlante SR. *Angew Chem, Int Ed.* 2009; 48:6398. (b) LaPlante SR, Fader LD, Fandrick HR, Fandrick DR, Hucke O, Kemper R, Miller SPF, Edwards PJ. *J Med Chem.* 2011; 54:7005. [PubMed: 21848318] (c) LaPlante SR, Edwards PJ, Fader LD, Jakalian A, Hucke O. *ChemMedChem.* 2011; 6:505. [PubMed: 21360821]
4. Porter J, Payne A, Whitcombe I, de Candole B, Ford D, Garlish R, Hold A, Hutchinson B, Trevitt G, Turner J, Edwards C, Watkins C, Davis J, Stubberfield C. *Bioorg Med Chem Lett.* 2009; 19:1767. [PubMed: 19217289]

5. (a) Deng X, Dzamko N, Prescott A, Davies P, Liu Q, Yang Q, Lee JD, Patricelli MP, Nomanbhoy TK, Alessi DR, Gray NS. *Nature Chem Bio.* 2011; 7:203. [PubMed: 21378983] (b) Choi HG, Zhang J, Deng X, Hatcher JM, Patricelli MP, Zhao Z, Alessi D, Gray NS. *ACS Med Chem Lett.* 2012; 3:658. [PubMed: 23066449]
6. (a) Thayumanavan S, Beak P, Curran DP. *Tetrahedron Lett.* 1996; 37:2899.(b) Clayden J, Johnson P, Pink JH. *J Chem Soc, Perkin Trans I.* 2001:371.(c) Clayden J. *Chem Comm.* 2004:127. [PubMed: 14737515] (d) Clayden J, Lai LW, Helliwell M. *Tetrahedron.* 2004; 60:4399.
7. Koide H, Hata T, Yoshihara K, Kamikawa K, Uemura M. *Tetrahedron.* 2004; 60:4527.
8. Suda T, Noguchi K, Hirano M, Tanaka K. *Chem Eur J.* 2008; 14:6593. [PubMed: 18567026]
9. (a) Rios R, Jimeno C, Carroll PJ, Walsh PJ. *J Am Chem Soc.* 2002; 124:10272. [PubMed: 12197717] (b) Dai WM, Zhang Y, Zhang Y. *Tetrahedron: Asymmetry.* 2003; 15:525.(c) Chan V, Kim JG, Jimeno C, Carroll PJ, Walsh PJ. *Org Lett.* 2004; 6:2051. [PubMed: 15176816]
10. Gustafson JL, Lim D, Miller SJ. *Science.* 2010:328. [PubMed: 20075252]
11. Taylor MS, Jacobsen EN. *Angew Chem, Int Ed.* 2006; 45:1520.
12. Garand E, Kamrath MZ, Jordan PA, Wolk AB, McCoy AB, Miller SJ, Johnson MA. *Science.* 2012; 335:694. [PubMed: 22267579]
13. (a) Mitchell RH, Lai YH, Williams RV. *J Org Chem.* 1979; 44:4733.(b) Ahmad S, Braddock DC, Hermitage G. *Tetrahedron Lett.* 2007; 48:915.(c) Denmark SE, Burk MT. *Proc Natl Acad Sci USA.* 2010; 107:20655. [PubMed: 20705900]
14. (a) Gilli P, Pretto L, Bertolasi V, Gilli G. *Acc Chem Res.* 2009; 42:33. [PubMed: 18921985] (b) Etxebarria J, Degenbeck H, Felten AS, Serres S, Nieto N, Vidal-Ferran A. *J Org Chem.* 2009; 74:8794. [PubMed: 19835401]
15. (a) Copeland GT, Jarvo ER, Miller SJ. *J Org Chem.* 1998; 63:6784. [PubMed: 11672295] (b) Jarvo ER, Copeland GT, Papaioannou N, Bonitatebus PJ Jr, Miller SJ. *J Am Chem Soc.* 1999; 121:11638.(c) Cowen BJ, Saunders LB, Miller SJ. *J Am Chem Soc.* 2009; 131:6105. [PubMed: 19354290] (d) Fowler BS, Mikochik PJ, Miller SJ. *J Am Chem Soc.* 2010; 132:2870. [PubMed: 20158213]
16. Haque TS, Little JC, Gellman SH. *J Am Chem Soc.* 1996; 118:6975.
17. A variety of peptide-based scaffolds were evaluated. It is notable that **6** proved 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 reference 10 delivered product **5** in good yield and 36:64 er under similar conditions, with a preference for the opposite enantiomer afforded in the presence of **6**.
18. Results were consistent when reactions were performed on scales ranging from 0.2 mmol through 1.0 mmol of substrate. See Supporting Information for details.
19. Reactions are efficiently quenched by the addition of butyl vinyl ether to the reaction mixture at -40°C .
20. See Supporting Information for details.
21. Bott G, Field LD, Sternhall S. *J Am Chem Soc.* 1980; 102:5618.
22. (a) Williams, DH.; Fleming, I. *Spectroscopic Methods in Organic Chemistry.* 3. McGraw Hill; Maidenhead, UK: 1980. (b) Gomes JANF. *Chem Rev.* 2001; 101:1349. [PubMed: 11710225]
23. The absolute sense of chirality for the other compounds in Table 1 is not known, and is drawn as shown only by analogy to **12**.
24. Gustafson JL, Lim D, Barrett KT, Miller SJ. *Angew Chem, Int Ed.* 2011; 50:5125.
25. (a) Beak P, Allen DJ. *J Am Chem Soc.* 1992; 114:3420.(b) Nájera C, Sansano JM, Yus M. *Tetrahedron.* 2003; 59:9255.
26. Gilman H, Langham W, Moore FW. *J Am Chem Soc.* 1940; 62:2327.
27. See Supporting Information for details.

Figure 1.

(a) Chiral benzamides, with 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 high barriers to isomerization (**2**) or low barriers (**3**).

Figure 2. Independent NMR spectra of substrate **11**, catalyst **6** and the spectrum for their 1:1 co-mixture (0.02 M, CDCl₃, 0 °C).

Scheme 1.

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
10

Entry ^{a,b}	Substrate	Product	Yield ^c	er ^d
11			75	51:49

^aReactions were conducted at $-40\text{ }^{\circ}\text{C}$ for 4–48 h, employing 10 mol% **6**, 0.02 M in substrate/ CHCl_3 . DBDMH was employed at 1.0 equiv, except for entries 1, 5, and 6 (1.5 equiv). See Supporting Information for details.

^bAll experiments in Table 1 were performed in triplicate.

^cData is reported for the products of the reaction after phenol methylation.

^dDetermined by chiral HPLC within one day of synthesis.

^eAfter 40 days of storage, this sample exhibits 81:19 er (*vide infra*).