ACCOUNTS
of chemical research

Article

pubs.acs.org/accounts

Peptide-Based Catalysts Reach the Outer Sphere through Remote Desymmetrization and Atroposelectivity

Published as part of the Accounts of Chemical Research special issue "Chemical Biology of Peptides".

Anthony J. Metrano[ID] and Scott J. Miller*[ID]

Department of Chemistry, Yale University, P.O. Box 208107, New Haven, Connecticut 06520-8107, United States

Peptide Catalysis as an Enabling Strategy for Reaching the "Outer Sphere"
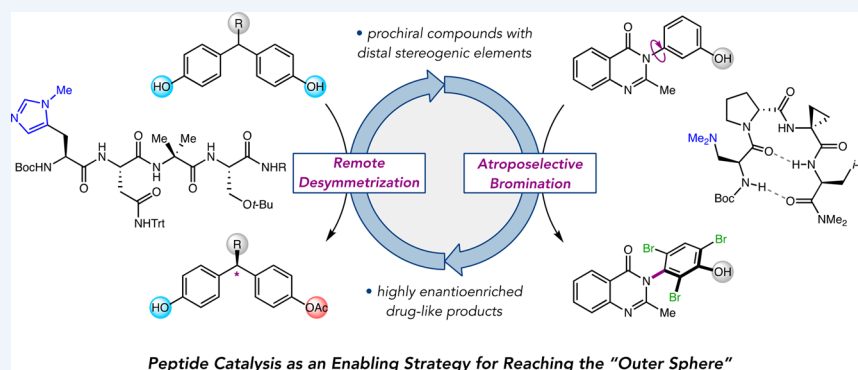
CONSPECTUS: Nature's catalytic machinery has provided endless inspiration for chemists. While the enzymatic ideal has yet to be fully realized, the field has made tremendous strides toward synthetic, small-molecule catalysts for a wide array of transformations, often drawing upon biological concepts in their design. One strategy that has been particularly influenced by enzymology is peptide catalysis, wherein oligopeptides are implemented as chiral catalysts in synthetically relevant reactions. The fundamental goal has been to mimic enzymatic active sites by taking advantage of secondary structures that allow for multifunctional activation of substrates within a framework of significantly reduced molecular complexity.

Our group has now been studying peptide-based catalysis for over two decades. At the outset, there were many reasons to be concerned that general contributions might not be possible. Precedents existed, including the Juliá−Colonna epoxidations mediated by helical oligopeptides, among others. However, we sought to explore whether peptide catalysts could find broad applications in organic synthesis despite what was expected to be their principal liability: conformational flexibility. Over time, we have been able to identify peptidic catalysts for a variety of site- and enantioselective transformations ranging from hydroxyl group and arene functionalizations to redox and C−C bond forming reactions. The peptides often exhibited excellent catalytic activities, in many cases enabling never-before-seen patterns of selectivity. Recent studies even suggest that, in certain situations, the conformational flexibility of these catalysts may be advantageous for asymmetric induction.

In the course of our studies, opportunities to employ peptide-based catalysis to solve long-standing and stereochemically intriguing problems in asymmetric synthesis presented themselves. For example, we have found that peptides provide exceptional enantiotopic group differentiation in catalytic desymmetrization reactions. Early results with symmetrical polyol substrates, such as *myo*-inositols and glycerols, eventually spurred the development of remote desymmetrizations of diarylmethanes, in which the enantiotopic groups are separated from the prochiral center by ~6 Å and from one another by nearly 1 nm. Various hydroxyl group functionalizations and electrophilic brominations, as well as C−C, C−O, and C−N cross-coupling reactions using peptidic ligands on copper(I) have now been developed within this reaction archetype. Additionally, the preponderance of axially chiral, atropisomeric compounds as ligands, organocatalysts, and pharmacophores encouraged us to employ peptides as atroposelective catalysts. We have developed peptide-catalyzed brominations of pharmaceutically relevant biaryl, non-biaryl, and hetero-biaryl atropisomers that take advantage of dynamic kinetic resolution schemes. These projects have vastly expanded the reach of our original hypotheses and raised new questions about peptide-based catalysts and the extent to which they might mimic enzymes.

Herein, we recount the development and optimization of these stereochemically complex reactions, with a particular focus on structural and mechanistic aspects of the peptide-based catalysts that make them well-suited for their respective functions. The ability of these peptides to address important yet fundamentally challenging issues in asymmetric catalysis, combined with their modularity and ease-of-synthesis, make them primed for future use in organic synthesis.
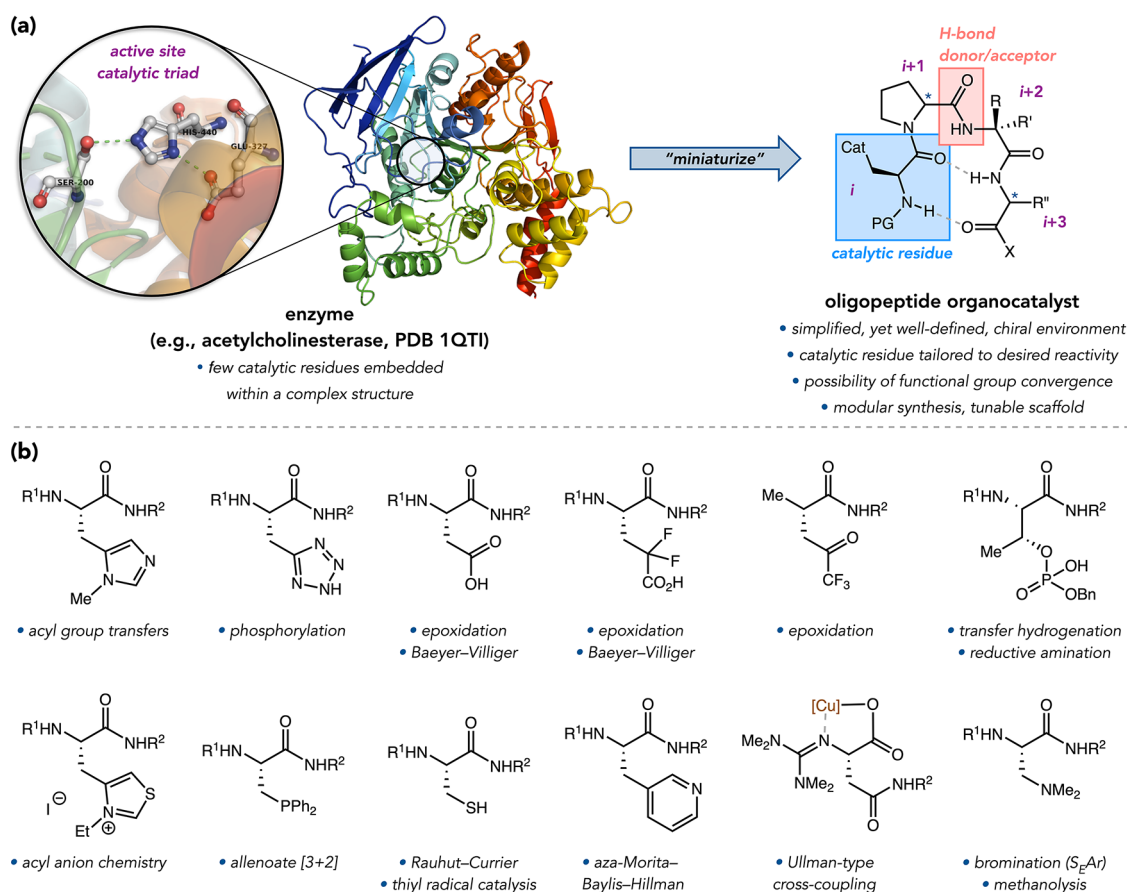
199

Figure 1. (a) Peptide catalysis summarized. (b) Catalytic residues targeting specific transformations.

1. INTRODUCTION

The ability to access enantiopure compounds is a fundamental and critical challenge in modern organic synthesis. The widespread use of single-enantiomer substances in chemical industries, materials science, and chemical biology provides a steady demand for asymmetric methodologies. While resolution continues to be a mainstay of industrial synthesis, asymmetric catalysis is now widely accepted as a reliable way to access enantioenriched compounds. Since its inception, the field of asymmetric catalysis has drawn inspiration from nature's catalysts. Enzymes have evolved to catalyze biochemical reactions with exceptional rate acceleration and selectivity by taking advantage of their well-defined folded structures and their ability to undergo dynamic conformational changes.[1] Within active sites, substrate activation is achieved through the precise orientation of catalytic residues, allowing for significant stabilization of transition states.[2] The kinetic advantages provided by active site organization are typically bolstered by protein dynamics, as conformational changes often occur upon binding to provide additional stabilization of intermediates and transition states along a continuous reaction coordinate.[3,4] Together, these characteristics contribute to the remarkable catalytic activities exhibited by enzymes and provide an ideal for the conception of synthetic catalysts.

Inspired by the possibility of developing small-molecule enzyme mimics with broad synthetic applicability, our group[5,6] and others[7,8] have sought to design short-sequence peptides that capture essential features of enzymatic active sites within greatly simplified molecular frameworks (Figure 1a). Peptides are well suited as asymmetric organocatalysts. They are easily synthe-sized from readily available amino acid residues, and their oligomeric nature renders them modular and tunable. These are helpful assets for deriving structure−selectivity relationships during catalyst development. Moreover, their conformations can be biased toward folded secondary structures by incorporating known sequence elements.[9,10] Peptides are dense with stereo-chemical information: the chirality of the constituent residues often translates into 3D-folded structures, providing a robust platform for asymmetric induction.

The scope of peptide catalysis has expanded dramatically over the past 20 years. Peptides have now been implemented in myriad synthetically relevant transformations, including hydrox-yl and amine group transfers,[5] oxidations,[11] reductions,[12] and C−C bond forming reactions.[13] In addition to asymmetric operations on small molecules, peptides have also proven useful in the site-selective modification of complex, polyfunctional structures.[14] Our own pursuits have been assisted by the design and incorporation of unique catalytic residues, including proteinogenic, non-proteinogenic, and synthetic amino acids, within peptide sequences (Figure 1b). Although these catalytic residues can directly mediate the targeted reaction, the peptide backbone often contributes to rate acceleration and selectivity via stabilizing noncovalent interactions, such as H-bonds.[15] Such multifunctionality is a hallmark of enzymatic catalysis.

In the course of our studies, opportunities arose that allowed us to employ oligopeptides to address unsolved problems in asymmetric catalysis, including the desymmetrization of *meso* and prochiral compounds and DKR reactions of prochiral atropisomers. Regarding the former, the ability to differentiate enantiotopic groups in symmetrical molecules has long been

considered a great challenge, especially in cases where the pro-stereogenic element is remote from the reacting groups.[16] Despite the practical advantages of catalytic remote desymmetrizations, highly selective examples remain uncommon. General methods to catalytically discriminate between rapidly interconverting atropisomers have also been elusive. The prevalence of axially chiral, atropisomeric scaffolds in pharmaceuticals,[17] ligands,[18] and organocatalysts[19] has spurred the need for facile access to atropo-enantioenriched compounds. However, while resolutions and diastereoselective transformations of atropisomers have been known for decades,[20,21] atroposelective catalysis represents a new frontier in asymmetric synthesis.[22,23]

This Account describes our efforts to develop peptide-based catalysts for remote desymmetrizations of diarylmethanes and atroposelective brominations of biaryl, non-biaryl, and heterobiaryl atropisomers (Figure 2). While not obviously related,
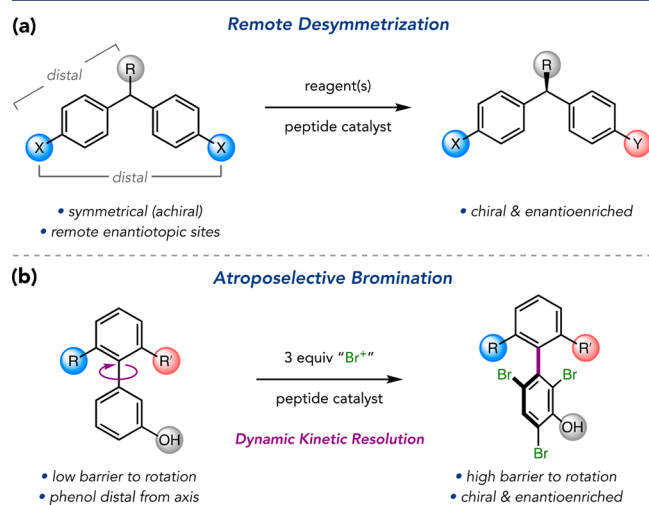
several unique aspects of peptide catalysis contributed to the eventual synergy of these projects. The story highlights the interplay of academic curiosity and industrial collaboration, which, in turn, spawned new questions at the heart of stereoselective catalysis. In each case, peptide catalysis was found to be an enabling strategy, providing highly enantioenriched compounds of demonstrated relevance to medicinal and pharmaceutical chemistry. The structural and mechanistic details leading to the development of selective catalysts are also discussed, as these themes prove central to ongoing work in our group and in the community.

2. EARLY STUDIES ON THE DESYMMETRIZATION OF POLYOLS

Our entry into peptide-catalyzed desymmetrization was inspired by kinases, which are known to phosphorylate polyfunctional substrates with site selectivity *in vivo*. Histidine-dependent kinases mediate phosphorylation events using Lewis base catalysis, wherein an active site His residue transfers phosphate to the substrate through a reactive phosphorylimidazolium intermediate. Encouraged by our early work on peptide-catalyzed acylations,[5] which capitalized on embedded π-methylhistidine (Pmh) residues to deliver acyl groups via an acylimidazolium ion, we sought to extrapolate to the site and enantioselective phosphorylation of *myo*-inositol derivatives (1, Figure 3).[24] A biomimetic transformation of this type would streamline access to phosphorylated *myo*-inositol natural products.

We discovered pentapeptide **3** from a small catalyst library synthesized using a random-number generator. Remarkably, **3** provided D-*myo*-inositol-1-phosphate derivative **2** in 65% yield and >98% ee, presumably via group transfer from the phosphorylated catalyst (Figure 3).[24,25] Expansion of the library led to the identification of peptide **4** that delivered *ent*-**2** in 56% yield and >98% ee under identical conditions.[26] The absolute configuration of the catalytically active Pmh residue is the same in both **3** and **4**, suggesting that the observed enantiodivergence is a function of their different secondary structures. While
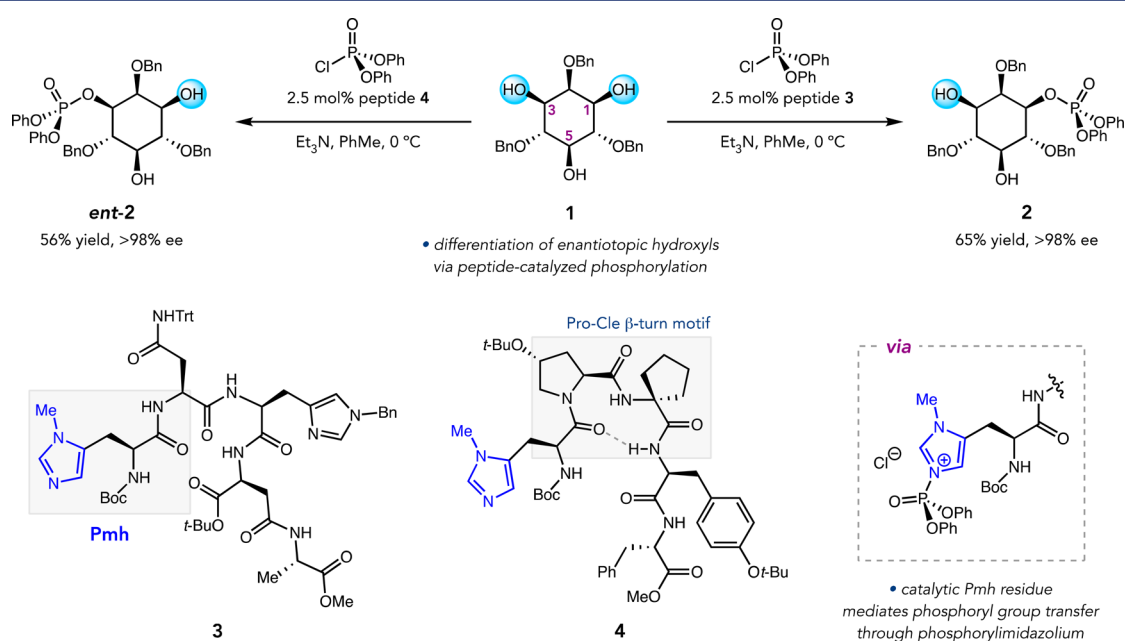

Figure 2. (a) Remote desymmetrization and (b) atroposelective bromination reactions.

Figure 3. Enantiodivergent phosphorylation of a *myo*-inositol derivative.

catalyst **3** possesses no readily identifiable structural motif, **4** is biased toward a β-turn conformation by virtue of its central Pro-Cle sequence and its internal H-bonding network (Cle = cycloleucine).[9,10] Additionally, both peptides accelerated the reaction greatly over simple achiral catalysts, consistent with rate enhancement through H-bonding interactions. The discovery of these enantiodivergent catalysts enabled direct and efficient syntheses of D-*myo*-inositol-1-phosphate and its enantiomer following global deprotection of **2** and *ent*-**2**, respectively, facilitating biological study of these agents.[27]

Building upon this strategy, we later developed a peptide-based catalyst for the desymmetrization of flexible glycerol-type substrates (Figure 4). High throughput screening revealed Pmh-
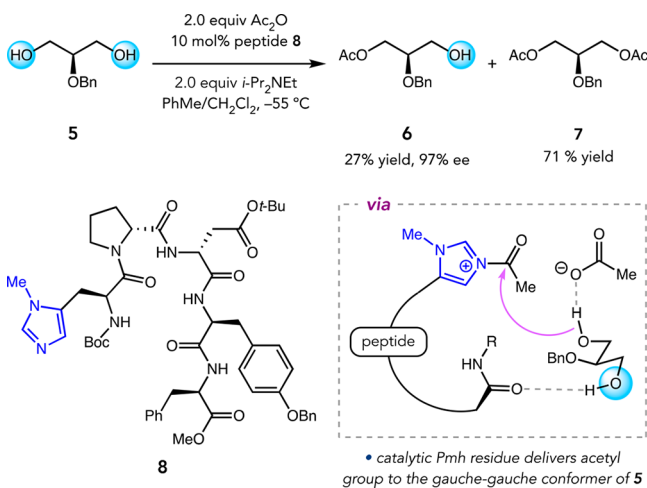

Figure 4. Desymmetrization of glycerols.

containing peptide **8** that catalyzes the conversion of glycerol **5** to mono(acetate) **6** with excellent enantioselectivity, albeit with significant secondary KR in forming bis(acetate) **7**.[28] The catalyst was proposed to selectively transfer an acetyl group from the acylimidazolium intermediate to the *gauche−gauche* conformer of **5** through multipoint association. These results are comparable to state-of-the-art biocatalytic methods for related transformations.[29]

3. REMOTE DESYMMETRIZATION OF DIARYLMETHANE BIS(PHENOL)S

The inositol and glycerol desymmetrizations demonstrated that peptide-based catalysts can differentiate enantiotopic sites in close proximity. Possibly as a result, a collaboration with Merck Research Laboratories surfaced that introduced *remote* desymmetrizations, wherein the reactive functional groups are many bonds removed from one another and from the pro-stereogenic element. A long-standing challenge, remote asymmetric induction is often viewed as the purview of enzymes, given their macromolecular dimensions.[16] However, oligopeptides seemed well suited for this task, given their tunable lengths and structures.

We thus undertook the remote desymmetrization of bis(phenol) **9**, wherein the enantiotopic hydroxyl groups are separated from the prochiral center by 5.7 Å and from one another by ~1 nm (Figure 5a). Researchers at Merck had explored lipases to catalyze the desymmetrizing hydrolysis of bis(acetate) **11**. In a screen of >450 enzymes, synthetically useful enantioselectivities were only achieved with substantial contribution from the secondary KR of mono(acetate) **10**,

resulting in low yields. We therefore set out to develop a Pmh-containing peptide that might do better via acylation of **9**.[30,31]

Our catalyst library was designed around two structural elements. First, we estimated that hexapeptides would be sufficiently long to engage both phenols of **9** if a bifunctional mechanism were operable. Second, we sought to mirror the structural domains of the substrate: the terminal residues would have aromatic side chains, while the central ones would be aliphatic. After five rounds of screening, we arrived at hexapeptide **12**, which delivered **10** in 68% yield and 72% ee (Figure 5a). Sequence truncation studies indicated that the two C-terminal residues were unnecessary for enantioselectivity, so **12** was shortened to a tetramer retaining the critical N-terminal residues. The C-terminal cap also had an effect on selectivity, leading to the (*S,S*)-*N*-tosyl-diamine moiety in the optimal scaffold. Tetrapeptide **13** provided mono(acetate) **10** in 80% isolated yield and 95% ee. Although 20% of bis(acetate) **11** was also formed, secondary KR of **10** only minimally contributed to the observed ee (k_{rel} = 1.4). NMR studies showed that the degeneracy in the aryl resonances of **9** is lost upon catalyst−substrate association, suggesting that **13** breaks the bis(phenol) symmetry via noncovalent interactions.

While investigating the scope of this reaction, we found that yield and enantioselectivity diminished steadily with decreasing steric demand of the prochiral substituent (Figure 5b). In collaboration with the Sigman Group, we identified LFERs correlating the enantioselectivity with various steric parameters, including Sternhell interference energies.[32] Steep negative slopes suggested sensitivity to the size of the substituent. One interpretation is that the steric profile of the substituent influences the propeller-like twisting of **9**, impacting attendant interactions with **13**. The Sigman Group was later able to correlate the enantioselectivity trends with computed arene vibrational frequencies, which are sensitive and directional readouts of both steric and electronic substituent effects.[33]

We surmised that the catalytic Pmh residue of peptide **13** could mediate the desymmetrization of **9** via two limiting mechanisms: (1) Lewis base activation of acetic anhydride or (2) Brønsted base activation of the bis(phenol) (Figure 6). While acylations of aliphatic alcohols (e.g., **1** and **5**) are more likely to proceed through the former mechanism, both possibilities are accessible to **9** due to the increased acidity of phenols. Although the precise activation mode remains undetermined, these mechanistic questions motivated us to consider other reactivity manifolds amenable to peptide-mediated Brønsted base catalysis.

We ultimately arrived at electrophilic aromatic halogenation, which we hypothesized could be accelerated by Brønsted base activation of a phenol, rendering it more phenolate-like. Furthermore, Lewis basic functional groups were known to catalyze halenium ion transfer reactions with substantial rate acceleration.[34] Taken together, we thought peptides might catalyze S$_E$Ar reactions through a mechanism involving Brønsted basic phenol activation and backbone amide-mediated halenium transfer. We initially tested this hypothesis in the bromination of **9** (Figure 7a).[35] Upon exposure to NBS, peptide **13** furnished monobromide **14** in 35% yield and 28% ee; the remainder of the mass balance consisted of polybromides. Because the Pmh residue was also brominated under these conditions, we pursued a new catalytic residue, tertiary amine-containing β-dimethylaminoalanine (Dmaa), which was expected to be more Brønsted basic, yet less prone to irreversible side reactivity. Fortunately, peptide **15** also provided **14** with
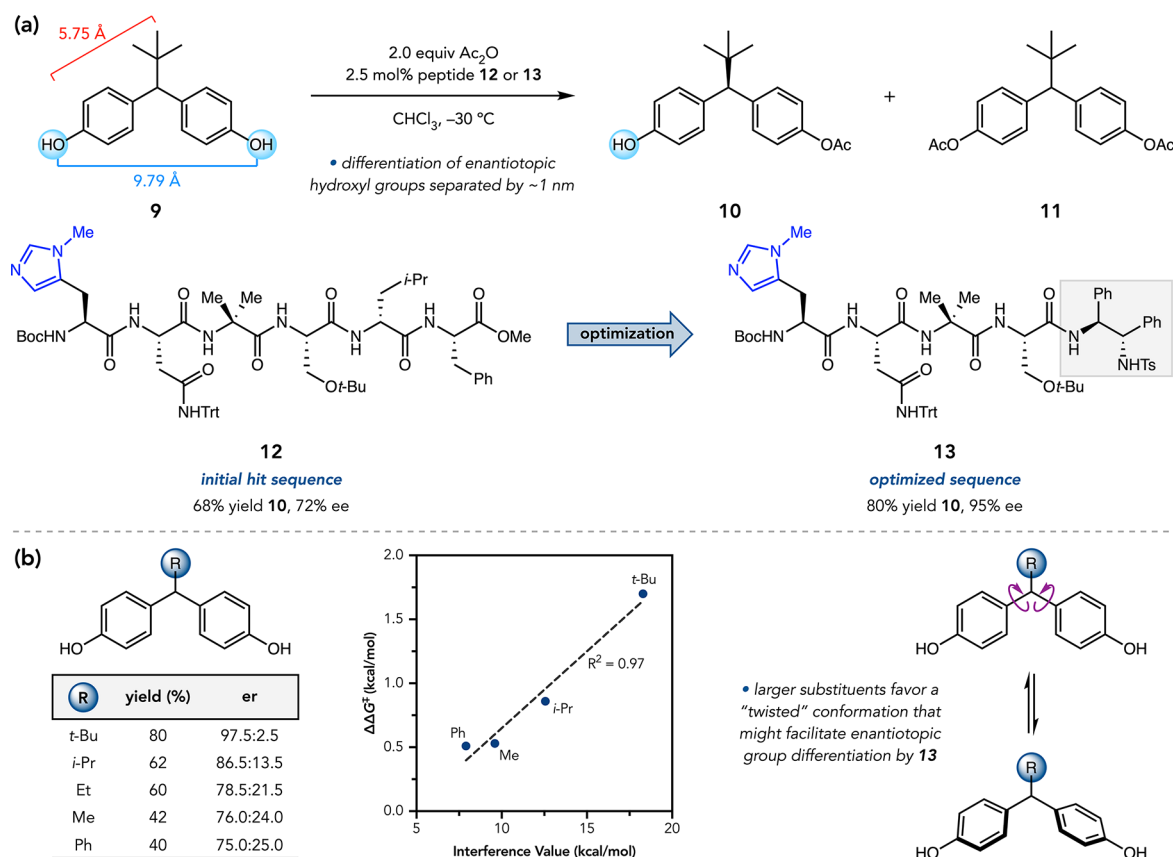
Figure 5. (a) Peptide-catalyzed remote desymmetrization of a bis(phenol). (b) Methine substituent effects.
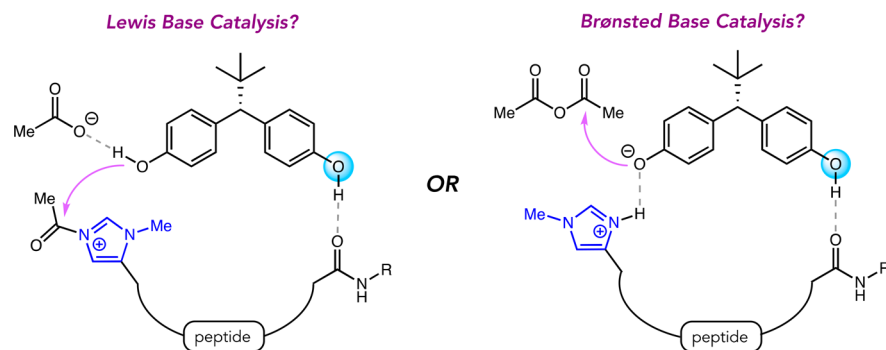

Figure 6. Mechanistic questions in the bis(phenol) desymmetrization.

appreciable selectivity (Figure 7b). Encouraged by these preliminary results, we turned our attention toward new applications of this catalytic activation scheme.

4. ATROPOSELECTIVE BROMINATION REACTIONS

Following our studies of bis(phenol) desymmetrizations, we sought a mode of enantioselective S_EAr that might be of broad synthetic utility. The growing interest in atropisomeric biaryls in pharmaceuticals and natural products,[17,20] as well as in chiral ligands and organocatalysts,[18,19] encouraged us to develop peptide-catalyzed *atroposelective* brominations. We hypothesized that if a biaryl phenol (e.g., **16**) rapidly racemizes *in situ*, preferential bromination of one enantiomer by a peptide-based catalyst could establish a Curtin–Hammett scenario (Figure 8). This type of DKR would require a low substrate enantiomerization barrier, such that racemization is rapid relative to bromination, and that the product is configurationally stable

about the chiral axis. Rotational barriers of mono-*ortho*-substituted biaryls are known to be quite low, ensuring rapid racemization in substrates like **16**. We initially proposed a tribromination of **16** to avoid complicated product mixtures. This strategy also proved fruitful regarding the latter point, as DFT calculations suggested that two *ortho*-bromides would be required to configurationally lock the products. Interestingly, the asymmetry of tribromide **17** stems from a *meta*-hydroxyl group distal from the chiral axis, reminiscent of the central challenge in our Merck collaboration.

At the outset of this study, the field of atroposelective catalysis was quite young, and most reported examples involved asymmetric cross-coupling strategies.[20] However, Bringmann and co-workers pioneered a different DKR-based approach—the atroposelective, nucleophilic ring-opening of strained biaryl lactones (Figure 9).[20] These groundbreaking studies, in addition to a report by Murai involving C–H functionalization,[36]

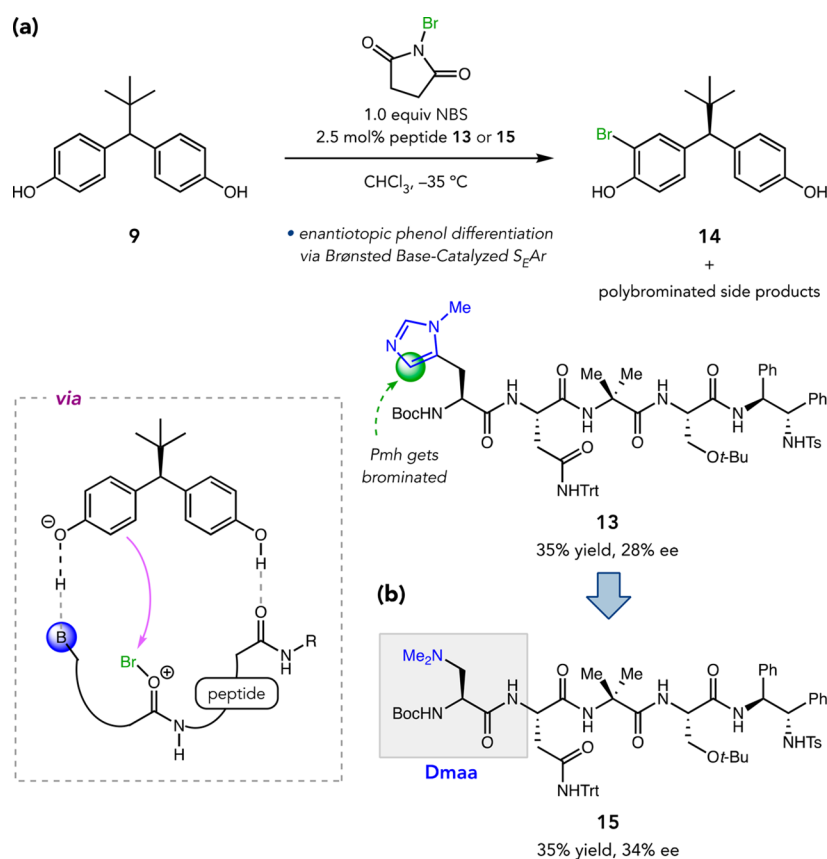**Figure 7.** Desymmetrizing bis(phenol) bromination catalyzed by (a) Pmh-containing and (b) Dmaa-containing peptides.
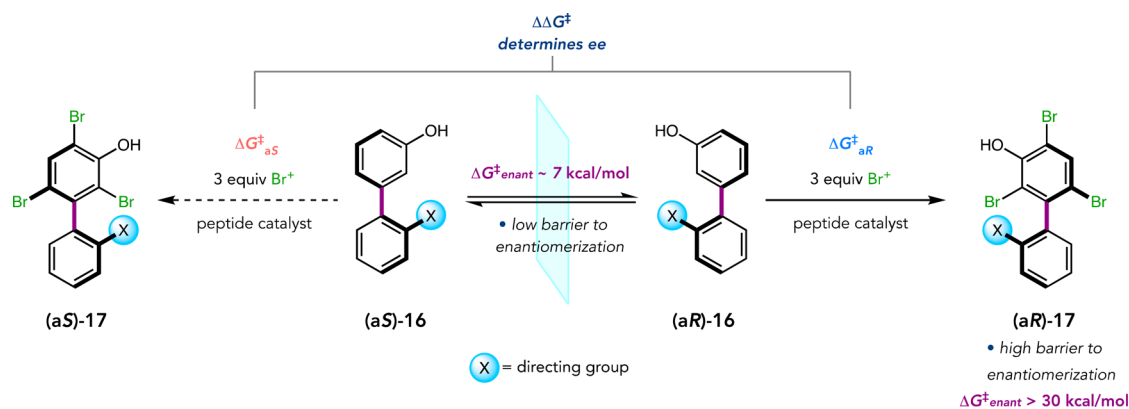

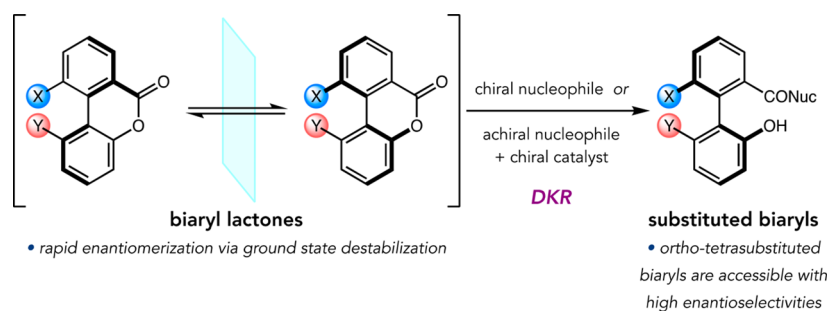**Figure 8.** Biaryl DKR via atroposelective bromination.

Figure 9. DKR of Bringmann lactones.

informed many aspects of our proposed atroposelective bromination.

As our catalyst design centered on Dmaa, we chose to incorporate a carboxylic acid directing group within the biaryl
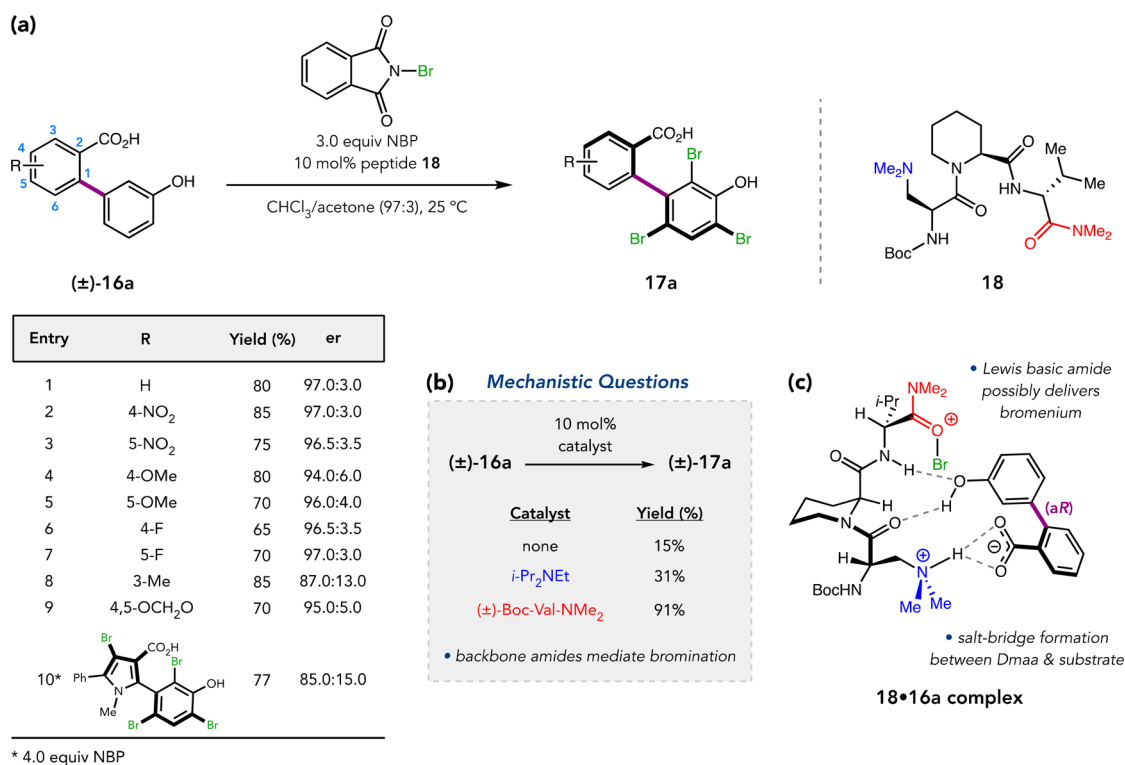
Figure 10. (a) Peptide-catalyzed, atroposelective biaryl bromination. (b) Mechanism-driven experiments. (c) Proposed model for stereoinduction.

substrate to enforce intermolecular association between **16a** and the peptide through salt-bridging. Catalyst optimization led to **18**, which furnished tribromide **17a** in 80% isolated yield and 97:3 er (Figure 10a).[37] Tripeptide **18** was effective over a broad scope that included sterically and electronically diverse biaryls, and even hetero-biaryls. Control experiments showed that the reaction is sluggish and low-yielding both in the absence of catalyst and using substoichiometric Hünig's base to mimic the Dmaa residue. However, catalytic (±)-Boc-Val-NMe$_2$, the isolated C-terminal residue of **18**, boosted the yield to 91%. These mechanistic queries suggest that backbone amides of **18** are essential for catalysis (Figure 10b). In pursuit of further insights, we partnered with the Johnson Group to investigate the noncovalent association of **18** with **16a** using cryogenic gas-phase infrared spectroscopy.[38] The results were consistent with multidentate docking model **18•16a**, wherein the Dmaa side-chain engages the carboxylic acid while upstream backbone amides interact with the phenol, holding **16a** in the (aR)-configuration (Figure 10c). Though difficult to study directly, it is possible that bromenium ion is *delivered* to **16a** by nearby amide, perhaps that of the C-terminal Val residue.

One of the advantages of selective electrophilic aromatic bromination is the possibility for derivatization via cross-coupling. Since products **17** contain three sterically and electronically distinct bromides, we wondered if it might be possible to access highly functionalized scaffolds through regioselective cross-coupling sequences. Following optimization, we developed an "A—B—C coupling" method that enables the synthesis of pentaphenyls and other derivatives **20** via sequential, Pd-catalyzed cross-coupling of methyl esters **19** (Figure 11).[39]

Having established a peptide-catalyzed atroposelective methodology, we sought to expand its scope to include non-biaryl atropisomers.[21] We were particularly attracted to the
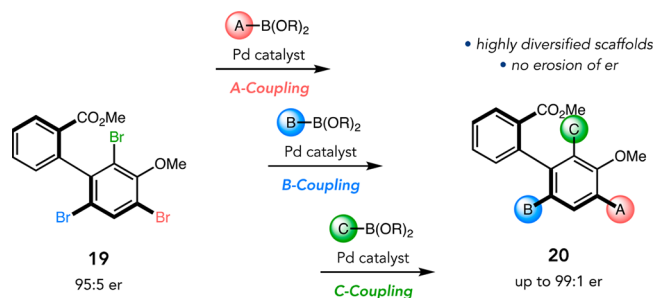

Figure 11. A—B—C cross-coupling of biaryl tribromides.

tertiary benzamide-type scaffolds that had been studied extensively by Clayden and others and which were frequently identified in biologically active compounds.[17] We expected substrates like **21** (Figure 12) to present new challenges for the peptide-catalyzed bromination protocol. Since benzamides might catalyze their own bromination, we opted to employ the bulky N,N-diisopropyl amide motif to both disfavor the autocatalytic reaction and achieve higher enantiomerization barriers. Recognition between **21** and the Dmaa-containing peptide was proposed to be nucleated by H-bonding between the phenol moiety and the Dmaa side-chain, which we hypothesized could also activate **21** toward S$_E$Ar.

We examined a peptide library based on the type II′ β-hairpin architecture that we had previously identified in highly selective catalysts for various transformations.[5,6] Tetrapeptides can be biased toward this secondary structure by strategic incorporation of a central D-Pro-Xaa sequence, where Xaa is either an L-amino acid or an α,α-disubstituted residue.[10,40] Sequence optimization led to **23**, which delivered (aS)-tribromide **22** in 89% yield and 94:6 er (Figure 12a).[41] Catalyst **23** also accommodated substitution at the 4- and 5-positions of **21**, but pre-installation of *ortho*-substituents elicited more interest-
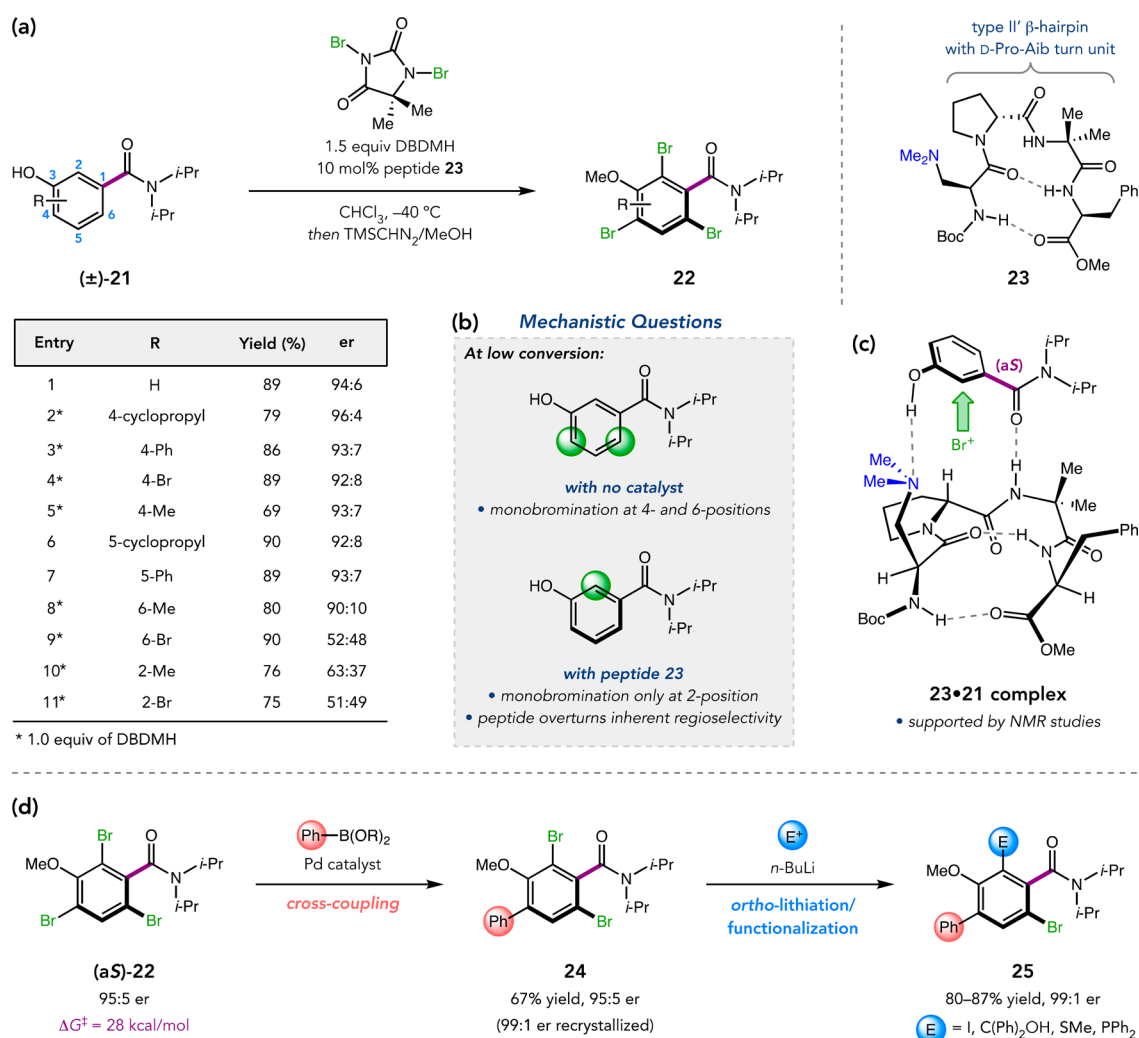
(a)

Entry	R	Yield (%)	er
1	H	89	94:6
2*	4-cyclopropyl	79	96:4
3*	4-Ph	86	93:7
4*	4-Br	89	92:8
5*	4-Me	69	93:7
6	5-cyclopropyl	90	92:8
7	5-Ph	89	93:7
8*	6-Me	80	90:10
9*	6-Br	90	52:48
10*	2-Me	76	63:37
11*	2-Br	75	51:49

* 1.0 equiv of DBDMH

(b) *Mechanistic Questions*

At low conversion:

with no catalyst
• monobromination at 4- and 6-positions

with peptide 23
• monobromination only at 2-position
• peptide overturns inherent regioselectivity

(c)

23•21 complex
• supported by NMR studies

(d)

Figure 12. (a) Peptide-catalyzed, atroposelective benzamide bromination. (b) Low-conversion LC/MS studies provide mechanistic insight. (c) Proposed model for stereoinduction. (d) Regioselective tribromide functionalizations.
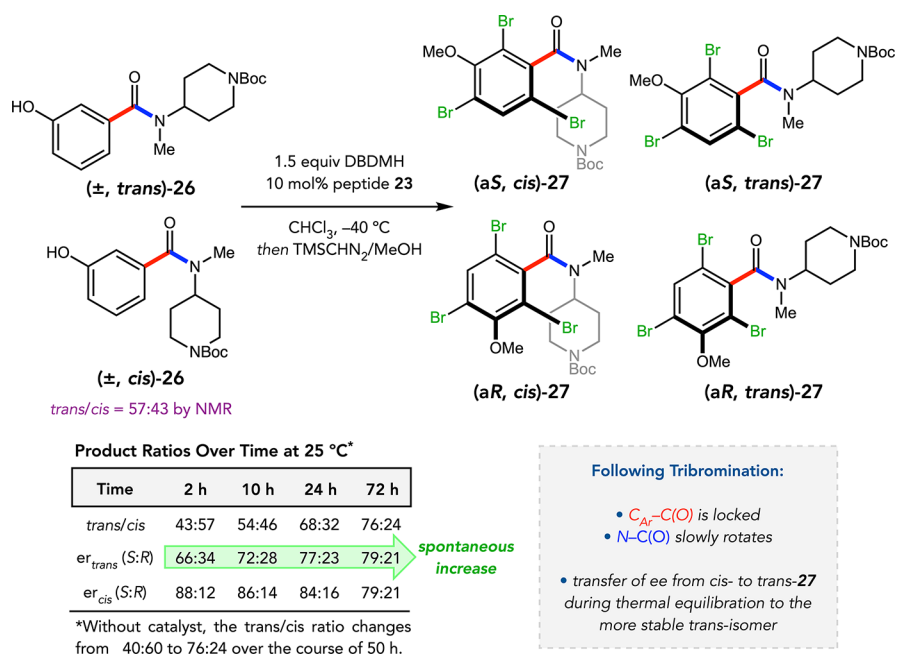

Product Ratios Over Time at 25 °C*

Time	2 h	10 h	24 h	72 h
trans/cis	43:57	54:46	68:32	76:24
er$_{trans}$ (S:R)	66:34	72:28	77:23	79:21
er$_{cis}$ (S:R)	88:12	86:14	84:16	79:21

*Without catalyst, the trans/cis ratio changes from 40:60 to 76:24 over the course of 50 h.

Following Tribromination:

• C_{Ar}–C(O) is locked
• N–C(O) slowly rotates

• transfer of ee from cis- to trans-**27** during thermal equilibration to the more stable trans-isomer

Figure 13. Spontaneous chirality transfer in a two-axis system.
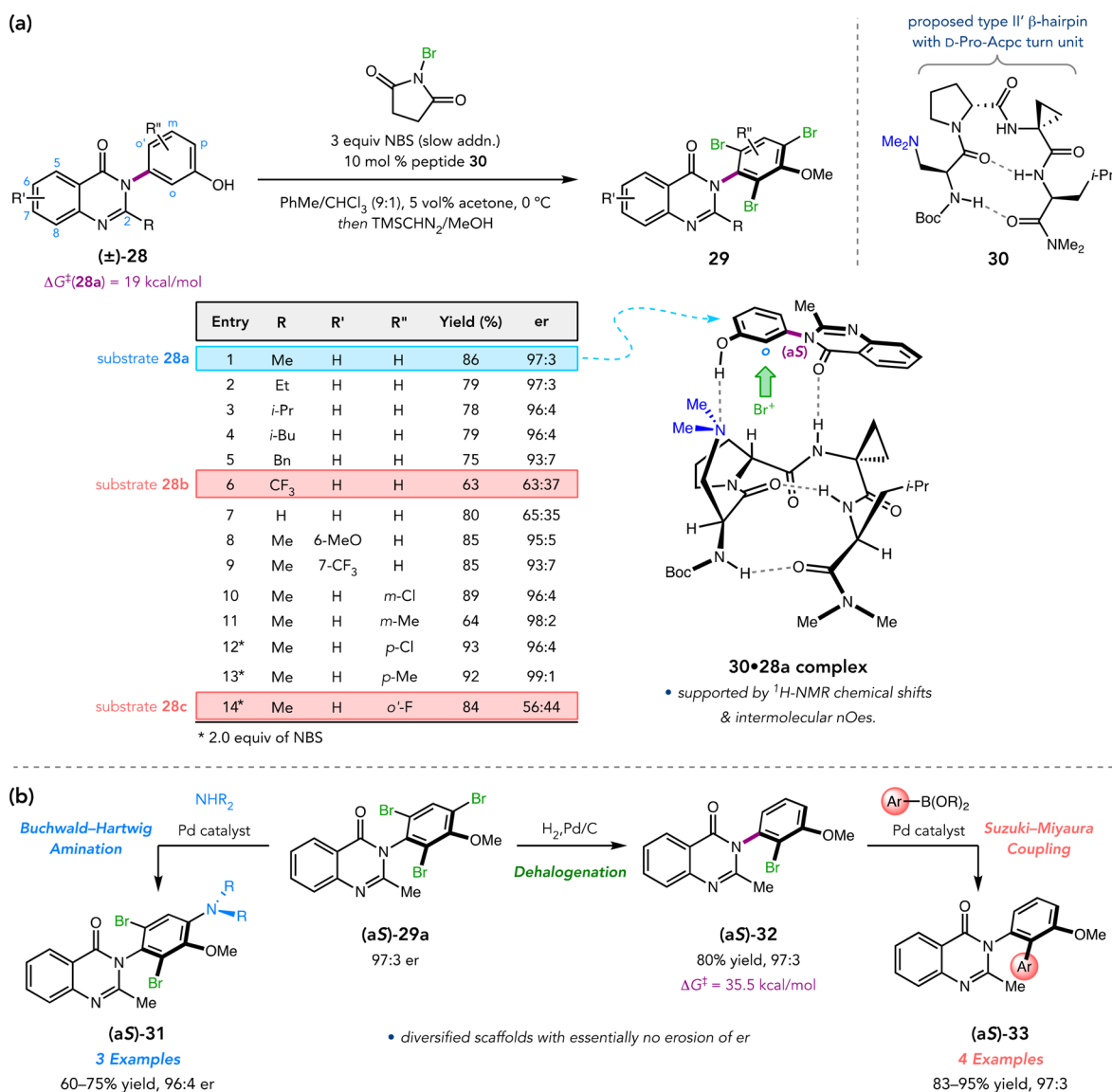
(a)

(b)

Figure 14. (a) Peptide-catalyzed, atroposelective 3-arylquinazolinone bromination. (b) Tribromide functionalization.

ing effects. The 6-methyl substrate was selectively brominated by **23**, while the 6-bromo substrate provided nearly racemic product. These results are consistent with a barrier effect, wherein the more electronically demanding bromide may restrict rotation, preventing effective DKR. At the 2-position, both methyl- and bromide-substitution furnished low er values. Using LC/MS to analyze low-conversion reaction mixtures, we determined that **23** overturns the inherent regioselectivity of the reaction by favoring monobromination at the 2-position (Figure 12b). Therefore, 2-substituted benzamides may be poor substrates because they block the enantiodetermining mono-bromination event. NMR studies of the peptide–substrate complex were consistent with multidentate association between **23** and **21**, likely involving H-bonding (e.g., **23·21**, Figure 12c). Many other transformations catalyzed by this class of peptides have revealed similar evidence of multifunctional catalysis, prompting us to consider whether these well-defined β-turns might be considered "privileged" chiral scaffolds.[42]

The products of benzamide bromination also proved amenable to functionalization with no loss of configurational integrity (Figure 12d).[43] Regioselective Suzuki–Miyaura cross-

coupling of (a*S*)-**22** delivers 4-arylated benzamides **24** in high yields and ers. Other Pd-catalyzed cross-coupling methods, including aminations and carboxymethylations, also selectively target this position. Diversification of **24** via *ortho*-lithiation/electrophile trapping provides an array of derivatives **25** with no erosion of er.

We next targeted benzamides such as **26** that possess two stereogenic axes, one defined by the chiral benzamide axis and the other implicit in differentially *N,N*-disubstituted amides (Figure 13). We initially considered the possibility of optimizing four peptide catalysts that each selectively furnishes one of the four possible product diastereomers **27**. This would be predicated on the assumption that both axes are configurationally locked following bromination, which did not turn out to be the case. Instead, the **23**-catalyzed bromination of **26** led to a kinetically controlled mixture of diastereomers, the ratios of which fluctuated over time due to slow amide isomerization.[44] During equilibration, the kinetically favored *cis*-**27** redistributes its enantiomeric composition to the thermodynamically more stable *trans*-**27**, resulting in a spontaneous increase in the er of the latter, albeit with compensatory enantioerosion of the *cis*-
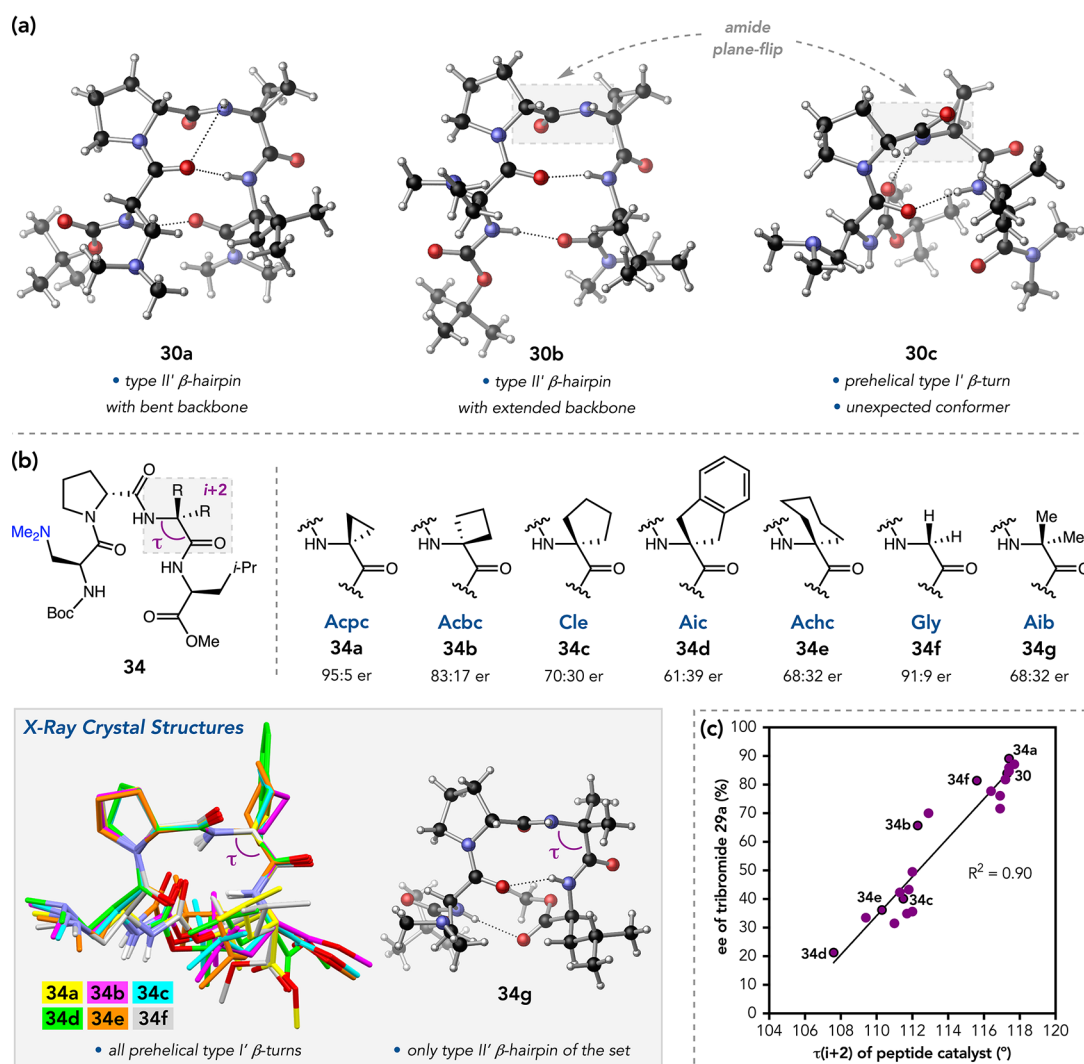
Figure 15. (a) Crystallographic conformers of peptide **30**. (b) Homologous $i + 2$ series of catalysts for the bromination of **28a**. (c) Correlation between crystallographic $\tau(i + 2)$ and enantioselectivity.

isomer. This intriguing phenomenon represents a rare example of spontaneous enantioenrichment in homogeneous solution, and its observation was only possible due to the ability of peptide **23** to differentially process the amide isomers of **26**.

Motivated by the continued identification of hetero-biaryl motifs in pharmaceutically relevant compounds, we became interested in further expanding the atroposelective bromination methodology to include hetero-biaryl substrates.[21] Many such compounds are known to exhibit atropisomerism, though few catalytic methods had been reported for their asymmetric preparation. We were drawn to the 3-arylquinazolin-4(3*H*)-one scaffold (e.g., **28**), which occurs in countless drug compounds spanning a wide range of biochemical functions (Figure 14a).[45] Quinazolinones **28** also presented an interesting challenge, as enantiomerization barriers were expected to be higher than similar biaryls due to the shorter C−N bond defining the chiral axis. Indeed, DFT computations predicted a 19 kcal/mol barrier for **28a**, corresponding to a half-life of 7 s.[46] Thus, racemization could be slow on the rapid bromination time scale, limiting the dynamic aspect of the transformation.

We initially examined a library of 21 Dmaa-containing peptides biased toward type II′ *β*-hairpin secondary structures. Peptide **30**, which possesses a critical 1-aminocyclopropane

carboxamide (Acpc) residue at the $(i + 2)$-position, was found to be a highly selective catalyst, delivering tribromide **29a** in 86% yield and 97:3 er (Figure 14a).[46] Slow addition of NBS was crucial to achieving this level of selectivity, as it possibly allows more complete reracemization of **28a** and thereby enables a more efficient DKR. Under these conditions, **30** addressed a broad scope of quinazolinones. Notable exceptions include 2-CF$_3$-containing **28b** and *ortho′*-fluoride **28c**. While the former was likely unselective due to ineffective catalyst−substrate interactions, the latter had too high of an enantiomerization barrier ($\Delta G^{\ddagger} = 26.7$ kcal/mol) to undergo DKR. Accordingly, **30** delivered tribromide **29c** in 93:7 er at low conversion, demonstrating that **28c** is an effective substrate for classical KR. Analogous to the benzamide bromination, low conversion LC/MS studies showed that **30** overturns the inherent *para*-selectivity by promoting stereodetermining monobromination at the *ortho*-position of **28a**. Additionally, NMR studies of equimolar **28a** and **30** revealed chemical shift changes, intramolecular NOEs in **30**, and even *intermolecular* NOEs consistent with catalyst−substrate complex **30·28a**. This model predicts that the observed (a*S*)-configuration of **29a** derives from a multifunctional binding and activation mechanism, wherein the site of enantiodetermining bromination is oriented

$$\Delta\Delta G^{\ddagger} = 0.77 + 0.34(\nu_{C=O,i+1}) + 0.18(i_{N-H,i+2}) + 0.13(L_{i+3})$$

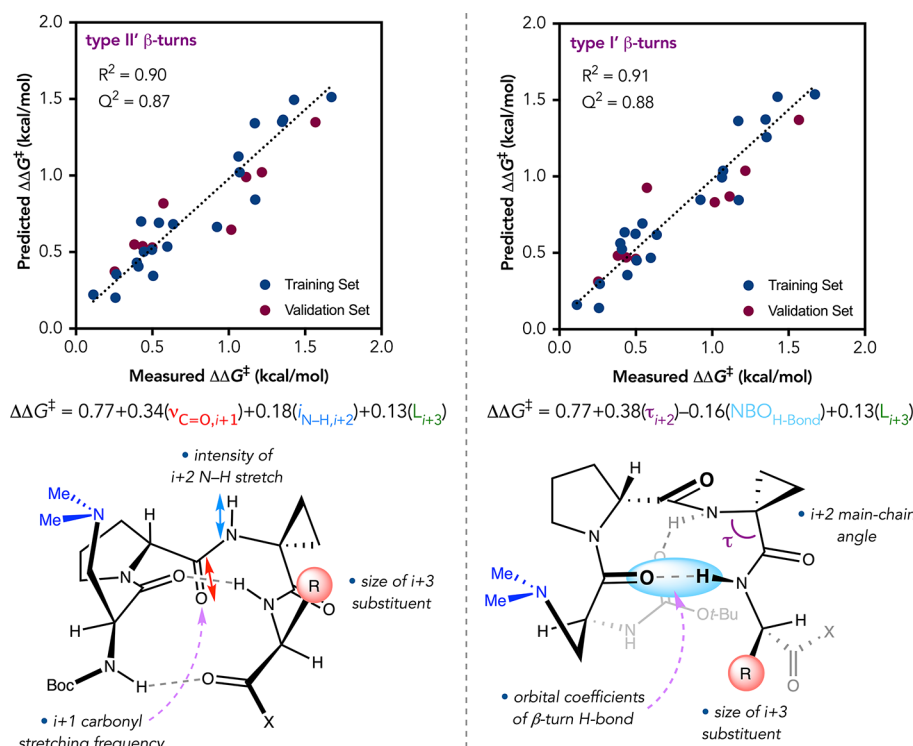$$\Delta\Delta G^{\ddagger} = 0.77 + 0.38(\tau_{i+2}) - 0.16(NBO_{H-Bond}) + 0.13(L_{i+3})$$

Figure 16. Multidimensional parameterization of the limiting catalyst conformations in the bromination of quinazolinone **28a**.

nearby the peptide backbone. It remains a possibility that **30** delivers bromenium ion to **28a** via backbone amides,[34] though evidence of this mechanism remains elusive.

Tribromides **29** were amenable to regioselective derivatization, providing access to a variety of functionalized, drug-like compounds with no erosion of optical purity (Figure 14b).[46] Buchwald–Hartwig amination of (aS)-**29a** selectively targets the *para*-bromide, furnishing amines **31** in good yields. Additionally, regioselective hydrogenolysis of **29a** delivers configurationally stable *ortho*-monobromide **32**, which was subsequently subjected to Suzuki–Miyaura cross-coupling to biarylquinazolinones **33**.

The quinazolinone bromination project also provided a platform from which we launched a thorough structural investigation of β-turn-biased, peptidic catalysts. These studies were initially inspired by a curious finding: three distinct conformations of peptide **30** were observed by X-ray crystallography (Figure 15a).[47] The first two, **30a** and **30b**, were observed within the same asymmetric unit and exhibit the expected type II′ β-hairpin structure based on the ϕ and ψ dihedrals of the loop residues and the intramolecular H-bonding network.[9] A polymorphic crystal structure revealed **30c**, which adopts an overall prehelical conformation defined by a central type I′ β-turn. The realization that these turn-biased tetrapeptides can nucleate such globally different secondary structures raised new questions about this class of catalysts.

In a structural analysis of 35 peptides by X-ray crystallography and solution NMR, we observed more structural heterogeneity than was expected from the catalyst design principles we often employ.[48] In a particularly striking example, we obtained X-ray structures for seven (i + 2)-homologues of peptide **34**. Only Aib-containing **34g** was found to adopt the expected type II′ β-hairpin conformation in the solid state, while **34a–f** exhibited prehelical type I′ turns analogous to **30c** (Figure 15b). In solution, all of the peptides showed NOE signatures satisfying

multiple secondary structures, suggesting that these peptides are conformationally dynamic under catalytically relevant conditions.[49]

We also identified a correlation between the crystallographic main-chain angle (τ) of the i + 2 residue and the enantioselectivity observed in the bromination of quinazolinone **28a** (Figure 15c), with larger values of τ(i + 2) delivering higher ers.[48] Wide τ-angles are often associated with structural flexibility, suggesting that catalyst dynamics could play an important role in the reaction. Indeed, NMR titration studies show that **30** undergoes a conformational change from a prehelical type I′ turn to a type II′ β-hairpin in the presence of **28a**, reminiscent of conformational selection.[50] While the same overall change occurs for poorly selective substrate **28b**, the degree of structural homogeneity in the catalyst–substrate complex is notably less. These data are consistent with a model wherein effective substrates trigger more significant changes toward a catalytically active conformation, as in **30·28a**. MD simulations performed with the Jorgensen Group were consistent with these observations, providing atomic-level resolution on the associated conformational changes.[51] Moreover, in another collaborative study with the Sigman Group, peptides of types II′ and I′ were subjected to multidimensional parametrization.[52] Features of both limiting conformations correlated well with ΔΔG‡ (Figure 16), suggesting that the observed enantioselectivity might emerge from an ensemble of transition states in which the catalyst adopts multiple conformations.

5. REMOTE DESYMMETRIZATION OF DIARYLMETHYLAMIDO-BIS(PHENOL)S

We eventually returned to the original impetus for our study of enantioselective bromination, the desymmetrization of bis-(phenol)s. As diarylmethane scaffolds continued to accumulate in the medicinal chemistry literature,[53] a variety of enantiose-

lective approaches had been reported,[54] including two remarkable examples of desymmetrizing C−H functionalizations reported by Shi/Hartwig and Wang/Yu.[55,56] In a complementary way, we chose to revisit desymmetrizing bromination in the context of diarylmethylamido-bis(phenol)s **35** utilizing a Dmaa-containing peptide to remotely differentiate enantiotopic phenols (Figure 17). We proposed that enantio-
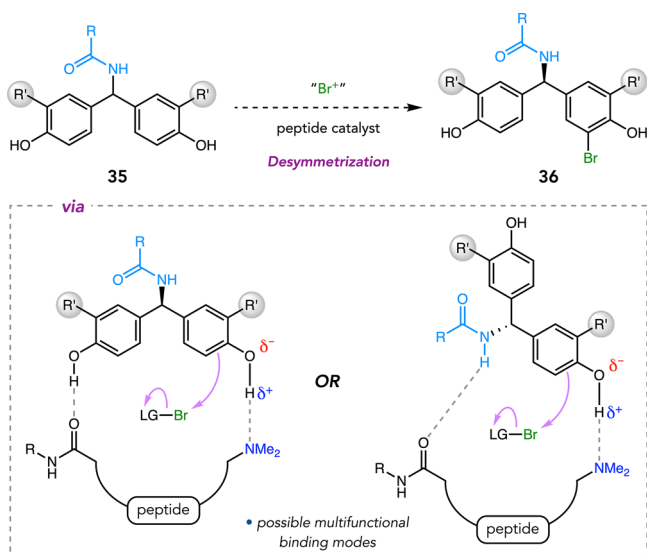
discrimination could either occur analogously to the mechanism proposed for bis(phenol) **9** (Figure 6) or by taking advantage of a different intermolecular H-bond between the catalyst and the prochiral amido group. Polybromination, which could erode yields with complicated product mixtures, was a concern for this system, so we blocked one of the phenol *ortho*-positions with an electronically deactivating carbonyl group, which might also slow bromination to permit more robust enantioinduction.

Following optimization, we identified Acpc-containing peptide **38** that effectively differentiates the enantiotopic arenes of pivalamides **35**, providing monobromides **36** in 55−69% yield and 83:17−97:3 er (Figure 18a).[57] Substrates bearing different *ortho*-functionality were also effectively addressed by **38**. In each case, overbromination to the symmetrical dibromide **37** (31−44% yield) also occurs with minimal contribution from secondary KR (k_{rel} = 3.2), indicating that the primary mode of asymmetric induction is indeed enantiotopic arene differentiation.

During catalyst optimization, we noticed that 2-aminoisobutyramide (Aib)-containing peptide **23** provided similar yields of ***ent*-36**, the opposite enantiomer favored by **38**, with modest enantioselectivity (Figure 18a).[57] The degree of enantiodivergence was found to be substrate-dependent, with ers ranging from 49:51 to 26:74 as a result of a *single point mutation* at *an achiral residue* within an otherwise homologous sequence. Peptides **38** and **23** only differ in mass by an equivalent of H_2, and yet they deliver opposite enantiomers of **36**. This fascinating phenomenon inspired us to consider possible conformational effects on enantioselectivity. We eventually uncovered an $i + 2$ τ-angle correlation even more

Figure 17. Desymmetrizing bromination of diarylmethylamido-bis-(phenol)s.

Entry	R	R′	with peptide 38		with peptide 23		$\Delta(\Delta\Delta G^{\ddagger})$
			35:36:37 (%)	er	35:36:37 (%)	er	(kcal/mol)
1	Me	Ph	0:69:31	95:5	7:46:47	42:58	1.45
2	Me	4-MeOPh	0:56:44	97:3	3:71:26	33:67	1.86
3	Me	4-BrPh	5:59:36	92:8	57:40:3	49:51	1.10
4	*i*-Pr	Ph	1:68:31	94:6	7:57:36	49:51	1.24
5	Me	OMe	7:55:39	83:17	10:50:40	26:74	1.17

- *Catalysts differ only by H_2 in molecular weight.*
- *Single point mutation of an achiral residue leads to enantiodivergent outcomes.*
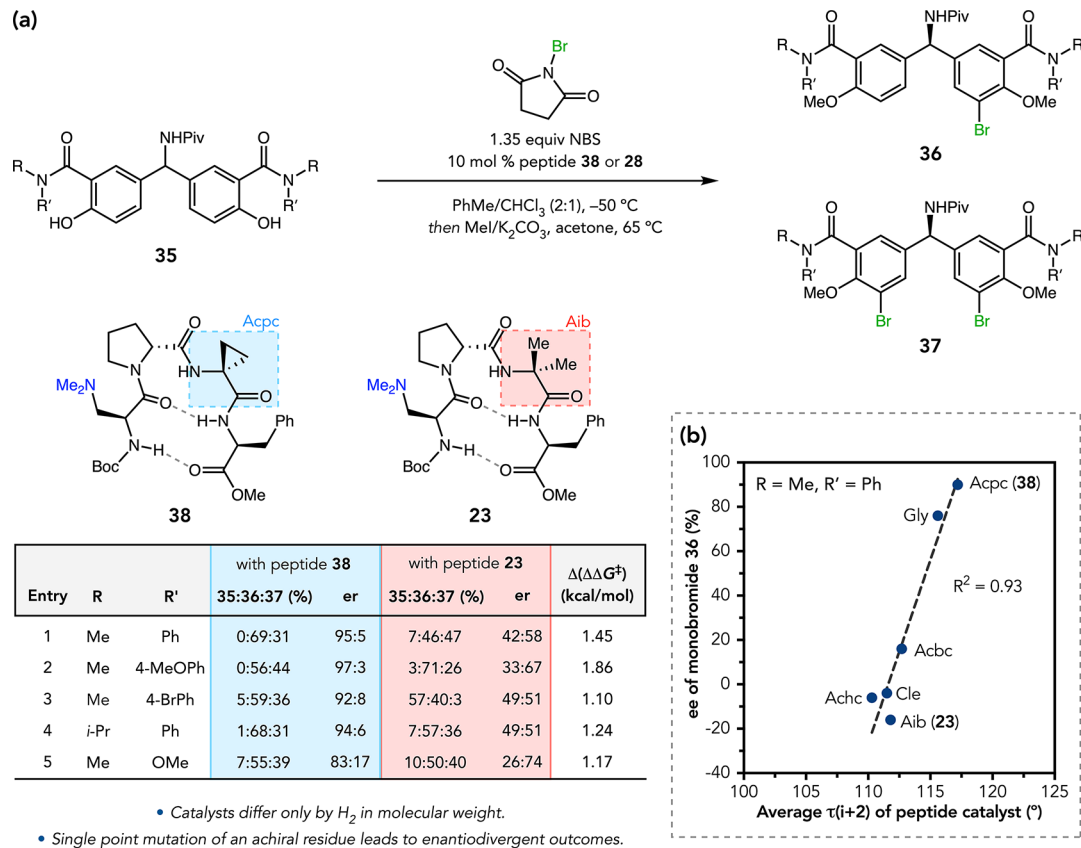
Figure 18. (a) Peptide-catalyzed, desymmetrizing bromination of diarylmethylamido-bis(phenol)s. (b) Correlation between crystallographic $\tau(i + 2)$ and enantioselectivity.

pronounced than that of the quinazolinone example (Figure 18b).[48] Again, higher selectivities were observed for wider $\tau(i+2)$ values. This possibly suggests that peptides **38** and **23** interact with **35** from different conformations, as prehelical type I′ β-turns are significantly more accessible when $\tau(i+2)$ is wide. The observed enantiodivergence might be rationalized by a model wherein **35** preferentially interacts with prehelical **38** and hairpin **23** using either the N–H or C=O of the prochiral pivalamide group, respectively (Figure 19).
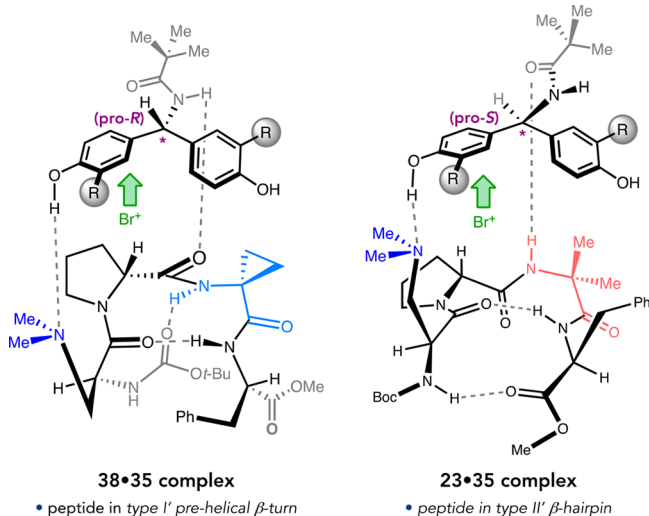

Figure 19. Possible enantiodivergent binding modes in the bromination of **35**.

Thus, our adventures in atroposelective bromination and peptide structure ultimately enabled us to address the unmet challenge that initially inspired those studies, the desymmetrizing bromination of a bis(phenol). Conceptually related, Lewis and co-workers recently reported a biocatalytic system, wherein an engineered halogenase mediates the desymmetrizing chlorination of a bis(aniline) with excellent enantioselectivity.[58] Our studies demonstrate that oligopeptides can be similarly effective for remote desymmetrizations via designed non-covalent interactions.

6. ASYMMETRIC CROSS-COUPLING WITH PEPTIDE-BASED LIGANDS

The catalytic bromination of pharmacologically interesting compounds begged the question of whether selective cross-coupling strategies might be feasible. This challenge first presented to us during our studies on regioselective functionalizations of atropisomeric tribromides.[39,43,46] It was further brought into focus when we developed site-selective halogenations of glycopeptide antibiotics, such as vancomycin and teicoplanin, which provided templates to pursue the effectively unknown area of site-selective cross-coupling.[59] We thus wondered if peptide-ligated transition metals could provide a handle for site-selective cross-couplings. As a prelude to these efforts, we pursued enantioselective cross-coupling as a testing-ground for a new peptide-based ligand architecture.

Given the ongoing interest in diarylmethane-type scaffolds,[53] we devised symmetrical dibromide **39** to investigate enantioselective cross-couplings via distal stereocontrol (Figure 20). The incorporation of trifluoroacetamido groups adjacent to the bromides was inspired by an asymmetric Hurtley reaction reported by Ma,[60] wherein *ortho*-trifluoroacetamides served to direct oxidative addition of a Cu(I)-complex. Moreover, the effectiveness of the simple L-*trans*-Hyp ligand in Ma's system suggested that a peptidic ligand might also work well with Cu(I) to achieve asymmetric cross-couplings. We proposed that a tetraalkylguanidine-containing residue could be a synthetically tractable ligand motif to install within a peptide that both engages in *N,O*-chelation of Cu(I) and is sufficiently electron-rich to promote oxidative addition. By incorporating β-linked, tetramethylguanidinylated aspartic acid (TMG-Asp) as the N-terminal residue, we were able to design peptide-based ligands for asymmetric C–C,[61] C–O,[62] and C–N[63] cross-couplings of **39**, delivering malonates **40**, ethers **41**, and benzimidazoles **42** with excellent enantioselectivities (Figure 21).

The initial desymmetrizing malonate coupling was developed in collaboration with Pfizer and Boehringer–Ingelheim (Figure 21a).[61] Tripeptide **43** was identified as the lead ligand following structure–function optimization. Notably, a C-terminal carboxylate was found to play an important role in asymmetric induction. Under the optimal conditions, ligand **43** provides up to 76% yield and 93:7 er of mono(malonate)s **40**, with *t*-butyl
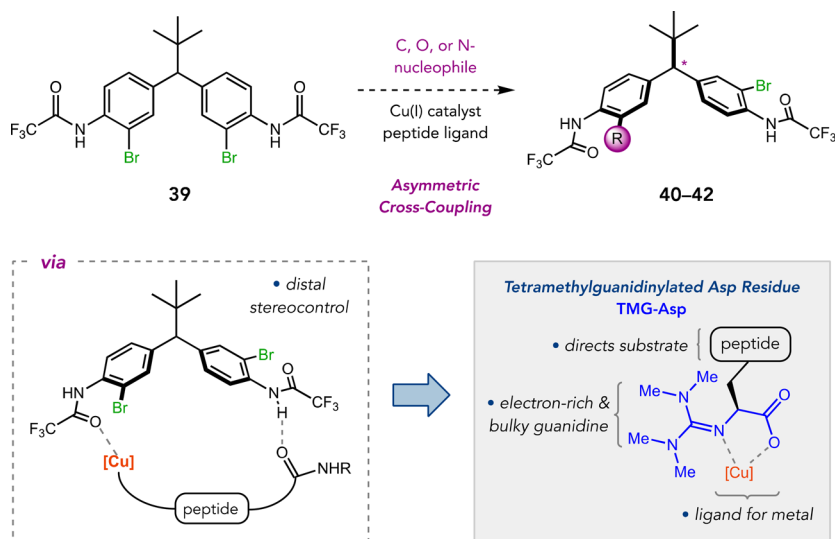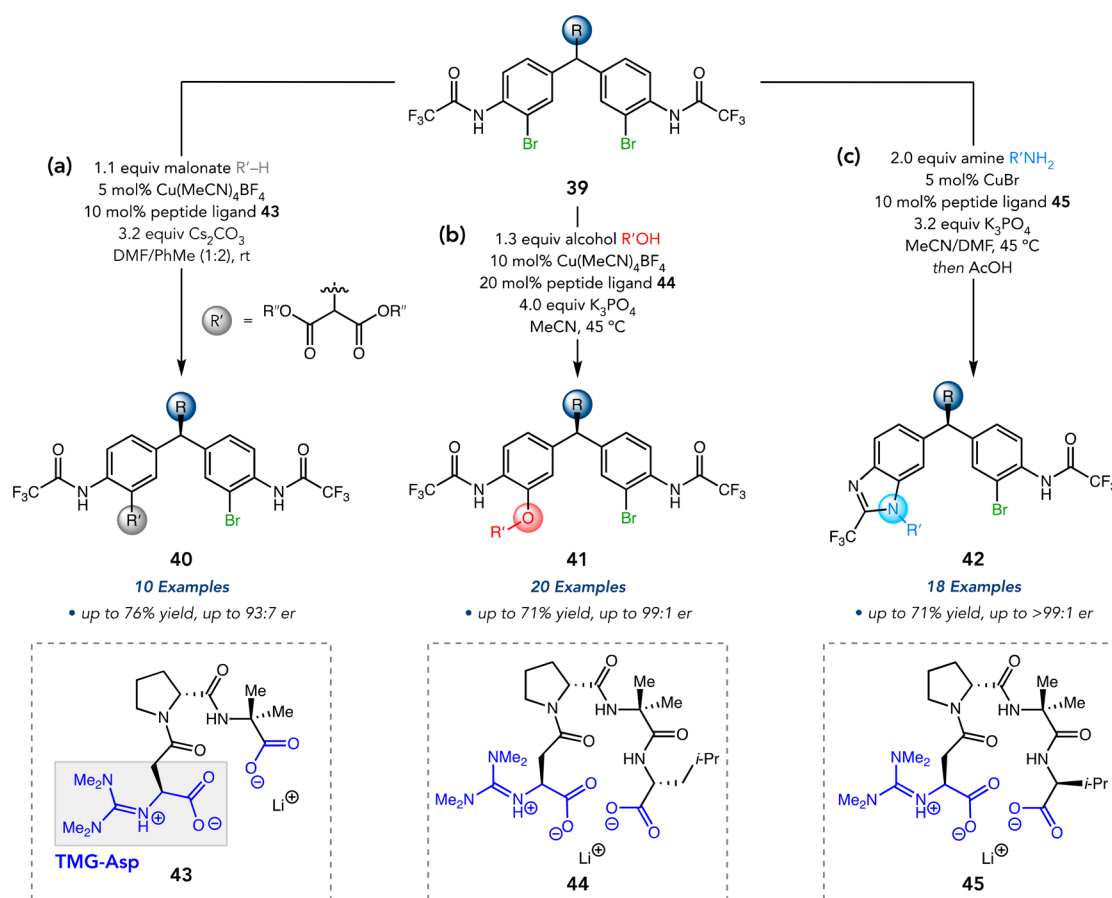

Figure 20. Asymmetric cross-coupling of diarylmethanes.

Figure 21. Desymmetrizing (a) C−C, (b) C−O, and (c) C−N cross-couplings with peptidic ligands.
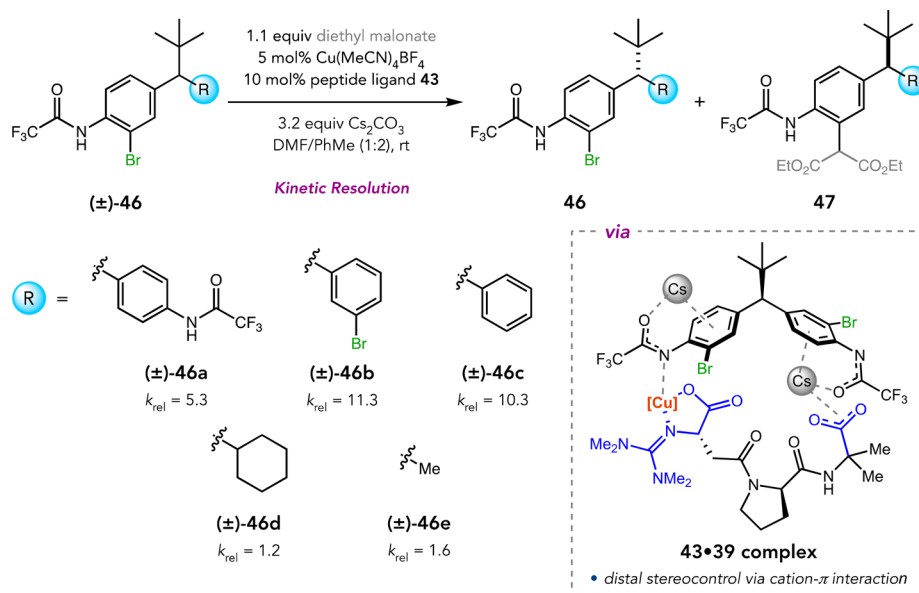

Figure 22. KRs provide mechanistic detail in the malonate cross-coupling.

substitution on the prochiral C atom delivering the best results.[32] Control and mechanistic experiments, including KR studies on racemic analogs of **39**, such as (±)-**46**, led us to propose that remote stereocontrol is achieved via a distal cation−π interaction (i.e., **43·39**, Figure 22).

Tetrapeptide **44** was optimized for the C−O cross-coupling of **39**, furnishing mono(ether)s **41** in up to 71% yield and 99:1 er

(Figure 21b).[62] The reaction worked exceptionally well for a wide scope of alcohol nucleophiles. Good yields and very high selectivities were observed for hindered phenols, which are difficult substrates in standard cross-couplings. Compounds possessing both phenol and amine functionality selectively couple at the phenol with ∼8:1 selectivity and 98:2 er.
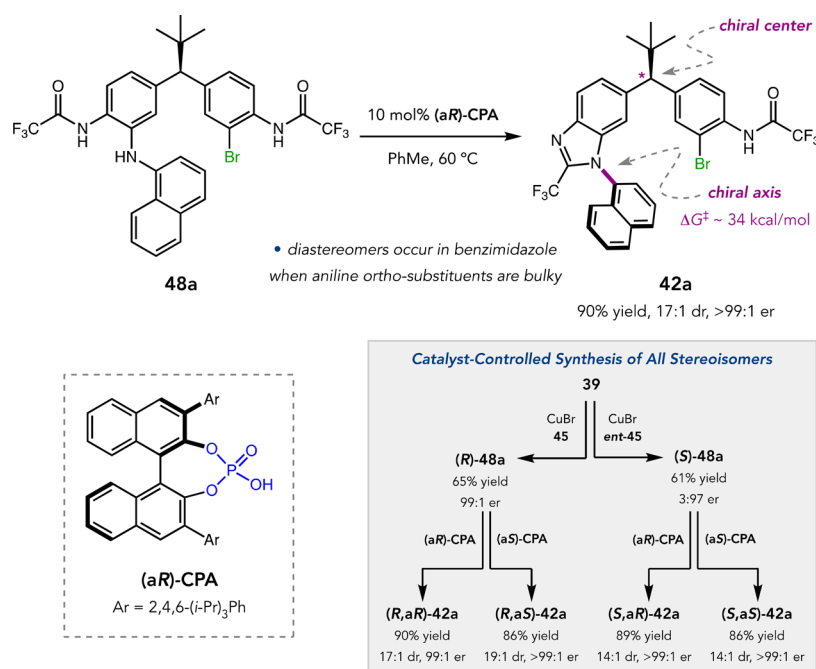
Figure 23. Diastereo- and enantioselective cyclodehydration.

Similarly, ligand **45** enabled the highly enantioselective C−N cross-coupling of **39** with various amine nucleophiles (Figure 21c).[63] *In situ* acid-mediated cyclodehydration converted the amine-coupled products into benzimidazoles **42** to avoid complicated product mixtures in cases where small quantities of benzimidazole formed during cross-coupling. Simple aniline and alkylamine nucleophiles delivered mono(benzimidazole)s **42** in up to 71% yield and 98:2 er. Hindered amines, such as naphthylamines and 2,6-disubstituted anilines, did not cyclodehydrate spontaneously and gave similar yields of mono-(amine)s with up to >99:1 er. Our experience with atropisomerism led us to hypothesize that cyclodehydration of these amines (e.g., **48a**) would give rise to diastereomers upon cyclodehydration due to the formation of a configurationally stable chiral axis within a point-chiral framework (Figure 23). Indeed, treatment of **48a** with a CPA catalyst cleanly delivered benzimidazole **42a** in 90% yield, 17:1 dr, and >99:1 er. We were also able to synthesize all four diastereomers of **42a** with complete catalyst control.

7. CONCLUSIONS

The chemistry detailed herein has expanded the purview of peptide-based catalysts in an intriguing way. Initially stimulated by fundamental questions about enzymes but challenged further by practical problems posed by industrial colleagues, our research program has shifted in focus to what might be called "outer sphere" issues. Our forays into remote asymmetric induction and atroposelective halogenation have unveiled a golden opportunity for oligopeptide catalysis. These processes share a multivalency at their mechanistic core with respect to catalyst−substrate interactions, which appear to operate decisively over great distances from the loci of bond formation. Outer sphere interactions are also central to the selective functionalization of complex systems, including natural products and proteins. Catalyst-controlled site-selectivity seems a field poised to break out of its infancy. Perhaps peptide-based catalysts will have a special role to play in this pursuit. If so, this

might prove to be an additional aspect of their biomimetic capacity, as outer sphere interactions are often central to the selectivity of enzymes.[64] The crafting of the proper outer sphere catalyst environment is currently a major focus of our research.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: scott.miller@yale.edu.

ORCID ⓘ

Anthony J. Metrano: 0000-0002-2599-8917
Scott J. Miller: 0000-0001-7817-1318

Present Address

A.J.M.: Department of Chemistry, Princeton University, Princeton, NJ 08544, United States.

Notes

The authors declare no competing financial interest.

Biographies

Anthony J. Metrano was raised in North Attleborough, MA. He received an A.B. in chemistry from the College of the Holy Cross (2011) and a Ph.D. in organic chemistry from Yale University (2017), where he was an NSF Graduate Research Fellow under Professor Scott J. Miller. He is currently an NIH Postdoctoral Fellow in the Knowles Group at Princeton University.

Scott J. Miller is from Buffalo, NY. He received his B.A. (1989), M.A. (1989), and Ph.D. (1994) from Harvard University, working with Professor David Evans as an NSF Predoctoral Fellow. He was an NSF Postdoctoral Fellow at the California Institute of Technology with Robert Grubbs before joining the faculty at Boston College in 1996. Since 2006, he has been on the faculty at Yale University.

support. We are also grateful to all of our collaborators, including Prof. Matthew Sigman (University of Utah), and to the NIH for support of recent collaborative efforts (GM-121383). We also thank Dr. Karl Hansen (Boston Pharmaceuticals), who initiated our stimulating collaboration with Merck around the desymmetrization of diarylmethane bis(phenol)s.

■ ABBREVIATIONS

Acbc, 1-aminocyclobutane-1-carboxylic acid; Achc, 1-amino-cyclohexane-1-carboxylic acid; Acpc, 1-aminocyclopropane-1-carboxylic acid; Aib, 2-aminoisobutyric acid; Aic, 2-amino-indane-2-carboxylic acid; Cle, cycloleucine; CPA, chiral phosphoric acid; DBDMH, 1,3-dibromo-5,5-dimethylhydan-toin; DFT, density functional theory; DKR, dynamic kinetic resolution; Dmaa, β-dimethylaminoalanine; Gly, glycine; H-bond, hydrogen bond; His, histidine; Hyp, hydroxyproline; KR, kinetic resolution; LFER, linear free energy relationship; MD, molecular dynamics; NBP, *N*-bromopthalimide; NBS, *N*-bromosuccinimide; Pmh, π-methylhistidine; Pro, proline; TMG-Asp, tetramethylguanidinylated aspartic acid; Val, valine

■ REFERENCES

(1) Davidi, D.; Longo, L. M.; Jabłońska, J.; Milo, R.; Tawfik, D. S. A Bird's-Eye View of Enzyme Evolution: Chemical, Physicochemical, and Physiological Considerations. *Chem. Rev.* **2018**, *118*, 8786−8797.

(2) Wolfenden, R.; Snider, M. J. The Depth of Chemical Time and the Power of Enzymes as Catalysts. *Acc. Chem. Res.* **2001**, *34*, 938−945.

(3) Kohen, A. Role of Dynamics in Enzyme Catalysis: Substantial Versus Semantic Controversies. *Acc. Chem. Res.* **2015**, *48*, 466−473.

(4) Klausen, R. S.; Kennedy, C. R.; Hyde, A. M.; Jacobsen, E. N. Chiral Thioureas Promote Enantioselective Pictet-Spengler Cyclization by Stabilizing Every Intermediate and Transition State in the Carboxylic Acid-Catalyzed Reaction. *J. Am. Chem. Soc.* **2017**, *139*, 12299−12309.

(5) Miller, S. J. Search of Peptide-Based Catalysts for Asymmetric Organic Synthesis. *Acc. Chem. Res.* **2004**, *37*, 601−610.

(6) Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. Asymmetric Catalysis Mediated by Synthetic Peptides. *Chem. Rev.* **2007**, *107*, 5759−5812.

(7) Wennemers, H. Asymmetric Catalysis with Peptides. *Chem. Commun.* **2011**, *47*, 12036−12041.

(8) Akagawa, K.; Kudo, K. Development of Selective Peptide Catalysts with Secondary Structural Frameworks. *Acc. Chem. Res.* **2017**, *50*, 2429−2439.

(9) Wilmot, C. M.; Thornton, J. M. Analysis and Prediction of the Different Types of β-Turn in Proteins. *J. Mol. Biol.* **1988**, *203*, 221−232.

(10) Haque, T. S.; Little, J. C.; Gellman, S. H. Stereochemical Requirements for β−Hairpin Formation: Model Studies with Four-Residue Peptides and Depsipeptides. *J. Am. Chem. Soc.* **1996**, *118*, 6975−6985.

(11) Alford, J. S.; Abascal, N. C.; Shugrue, C. R.; Colvin, S. M.; Romney, D. K.; Miller, S. J. Aspartyl Oxidation Catalysts That Dial in Functional Group Selectivity, Along with Regio- and Stereoselectivity. *ACS Cent. Sci.* **2016**, *2*, 733−739.

(12) Shugrue, C. R.; Miller, S. J. Phosphothreonine as a Catalytic Residue in Peptide-Mediated Asymmetric Transfer Hydrogenations of 8-Aminoquinolines. *Angew. Chem.* **2015**, *127*, 11325−11328.

(13) Mbofana, C. T.; Miller, S. J. Diastereo- and Enantioselective Addition of Anilide-Functionalized Allenoates to *N*-Acylimines Catalyzed by a Pyridylalanine-Based Peptide. *J. Am. Chem. Soc.* **2014**, *136*, 3285−3292.

(14) Shugrue, C. R.; Miller, S. J. Applications of Nonenzymatic Catalysts to the Alteration of Natural Products. *Chem. Rev.* **2017**, *117*, 11894−11951.

(15) Doyle, A. G.; Jacobsen, E. N. Small-Molecule H-Bond Donors in Asymmetric Catalysis. *Chem. Rev.* **2007**, *107*, 5713−5743.

(16) García-Urdiales, E.; Alfonso, I.; Gotor, V. Enantioselective Enzymatic Desymmetrizations in Organic Synthesis. *Chem. Rev.* **2005**, *105*, 313−354.

(17) Clayden, J.; Moran, W. J.; Edwards, P. J.; LaPlante, S. R. The Challenge of Atropisomerism in Drug Discovery. *Angew. Chem., Int. Ed.* **2009**, *48*, 6398−6401.

(18) Tang, W.; Zhang, X. New Chiral Phosphorus Ligands for Enantioselective Hydrogenation. *Chem. Rev.* **2003**, *103*, 3029−3070.

(19) Terada, M. Chiral Phosphoric Acids as Versatile Catalysts for Enantioselective Transformations. *Synthesis* **2010**, *2010*, 1929−1982.

(20) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. Atroposelective Synthesis of Axially Chiral Biaryl Compounds. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384−5427.

(21) Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivaguru, J. Nonbiaryl and Heterobiaryl Atropisomers: Molecular Templates with Promise for Atropselective Chemical Transformations. *Chem. Rev.* **2015**, *115*, 11239−11300.

(22) Zilate, B.; Castrogiovanni, A.; Sparr, C. Catalyst-Controlled Stereoselective Synthesis of Atropisomers. *ACS Catal.* **2018**, *8*, 2981−2988.

(23) Wang, Y.-B.; Tan, B. Construction of Axially Chiral Compounds via Asymmetric Organocatalysis. *Acc. Chem. Res.* **2018**, *51*, 534−547.

(24) Sculimbrene, B. R.; Morgan, A. J.; Miller, S. J. Nonenzymatic Peptide-Based Catalytic Asymmetric Phosphorylation of Inositol Derivatives. *Chem. Commun.* **2003**, 1781−1785.

(25) Sculimbrene, B. R.; Miller, S. J. Discovery of a Catalytic Asymmetric Phosphorylation Through Selection of a Minimal Kinase Mimic: A Concise Total Synthesis of D-*myo*-Inositol-1-Phosphate. *J. Am. Chem. Soc.* **2001**, *123*, 10125−10126.

(26) Sculimbrene, B. R.; Morgan, A. J.; Miller, S. J. Enantiodivergence in Small-Molecule Catalysis of Asymmetric Phosphorylation: Concise Total Syntheses of the Enantiomeric D-*myo*-Inositol-1-Phosphate and D-*myo*-Inositol-3-Phosphate. *J. Am. Chem. Soc.* **2002**, *124*, 11653−11656.

(27) Wang, Y. K.; Morgan, A.; Stieglitz, K.; Stec, B.; Thompson, B.; Miller, S. J.; Roberts, M. F. The Temperature Dependence of the Inositol Monophosphatase K_m Correlates with Accumulation of D-*myo*-Inositol 1,1'-Phosphate in Archaeoglobus Fulgidus. *Biochemistry* **2006**, *45*, 3307−3314.

(28) Lewis, C. A.; Sculimbrene, B. R.; Xu, Y.; Miller, S. J. Desymmetrization of Glycerol Derivatives with Peptide-Based Acylation Catalysts. *Org. Lett.* **2005**, *7*, 3021−3023.

(29) Wang, Y. F.; Wong, C. H. Lipase-Catalyzed Irreversible Transesterification for Preparative Synthesis of Chiral Glycerol Derivatives. *J. Org. Chem.* **1988**, *53*, 3127−3129.

(30) Lewis, C. A.; Chiu, A.; Kubryk, M.; Balsells, J.; Pollard, D.; Esser, C. K.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J. Remote Desymmetrization at Near-Nanometer Group Separation Catalyzed by a Miniaturized Enzyme Mimic. *J. Am. Chem. Soc.* **2006**, *128*, 16454−16455.

(31) Lewis, C. A.; Gustafson, J. L.; Chiu, A.; Balsells, J.; Pollard, D.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J. A Case of Remote Asymmetric Induction in the Peptide-Catalyzed Desymmetrization of a Bis(Phenol). *J. Am. Chem. Soc.* **2008**, *130*, 16358−16365.

(32) Gustafson, J. L.; Sigman, M. S.; Miller, S. J. Linear Free-Energy Relationship Analysis of a Catalytic Desymmetrization Reaction of a Diarylmethane-Bis(Phenol). *Org. Lett.* **2010**, *12*, 2794−2797.

(33) Milo, A.; Bess, E. N.; Sigman, M. S. Interrogating Selectivity in Catalysis Using Molecular Vibrations. *Nature* **2014**, *507*, 210−214.

(34) Denmark, S. E.; Burk, M. T. Lewis Base Catalysis of Bromo- and Iodolactonization, and Cycloetherification. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 20655−20660.

(35) Gustafson, J. L. Application of Low Molecular Weight Peptides to Effect Enantioselective and Regioselective Functionalizations of Phenols. Ph.D. Dissertation, Yale University, New Haven, CT, 2011.

(36) Kakiuchi, F.; Le Gendre, P.; Yamada, A.; Ohtaki, H.; Murai, S. Atropselective Alkylation of Biaryl Compounds by Means of Transition Metal-Catalyzed C−H/Olefin Coupling. *Tetrahedron: Asymmetry* **2000**, *11*, 2647−2651.

(37) Gustafson, J. L.; Lim, D.; Miller, S. J. Dynamic Kinetic Resolution of Biaryl Atropisomers via Peptide-Catalyzed Asymmetric Bromination. *Science* **2010**, *328*, 1251−1255.

(38) Garand, E.; Kamrath, M. Z.; Jordan, P. A.; Wolk, A. B.; Leavitt, C. M.; McCoy, A. B.; Miller, S. J.; Johnson, M. A. Determination of Noncovalent Docking by Infrared Spectroscopy of Cold Gas-Phase Complexes. *Science* **2012**, *335*, 694−698.

(39) Gustafson, J. L.; Lim, D.; Barrett, K. T.; Miller, S. J. Synthesis of Atropisomerically Defined, Highly Substituted Biaryl Scaffolds Through Catalytic Enantioselective Bromination and Regioselective Cross-Coupling. *Angew. Chem., Int. Ed.* **2011**, *50*, 5125−5129.

(40) Venkatraman, J.; Shankaramma, S. C.; Balaram, P. Design of Folded Peptides. *Chem. Rev.* **2001**, *101*, 3131−3152.

(41) Barrett, K. T.; Miller, S. J. Enantioselective Synthesis of Atropisomeric Benzamides Through Peptide-Catalyzed Bromination. *J. Am. Chem. Soc.* **2013**, *135*, 2963−2966.

(42) Yoon, T. P.; Jacobsen, E. N. Privileged Chiral Catalysts. *Science* **2003**, *299*, 1691−1693.

(43) Barrett, K. T.; Miller, S. J. Regioselective Derivatizations of a Tribrominated Atropisomeric Benzamide Scaffold. *Org. Lett.* **2015**, *17*, 580−583.

(44) Barrett, K. T.; Metrano, A. J.; Rablen, P. R.; Miller, S. J. Spontaneous Transfer of Chirality in an Atropisomerically Enriched Two-Axis System. *Nature* **2014**, *509*, 71−75.

(45) Khan, I.; Zaib, S.; Batool, S.; Abbas, N.; Ashraf, Z.; Iqbal, J.; Saeed, A. Quinazolines and Quinazolinones as Ubiquitous Structural Fragments in Medicinal Chemistry: An Update on the Development of Synthetic Methods and Pharmacological Diversification. *Bioorg. Med. Chem.* **2016**, *24*, 2361−2381.

(46) Diener, M. E.; Metrano, A. J.; Kusano, S.; Miller, S. J. Enantioselective Synthesis of 3-Arylquinazolin-4(3*H*)-Ones via Peptide-Catalyzed Atroposelective Bromination. *J. Am. Chem. Soc.* **2015**, *137*, 12369−12377.

(47) Metrano, A. J.; Abascal, N. C.; Mercado, B. Q.; Paulson, E. K.; Miller, S. J. Structural Studies of Beta-Turn-Containing Peptide Catalysts for Atroposelective Quinazolinone Bromination. *Chem. Commun.* **2016**, *52*, 4816−4819.

(48) Metrano, A. J.; Abascal, N. C.; Mercado, B. Q.; Paulson, E. K.; Hurtley, A. E.; Miller, S. J. Diversity of Secondary Structure in Catalytic Peptides with *β*-Turn-Biased Sequences. *J. Am. Chem. Soc.* **2017**, *139*, 492−516.

(49) Rigling, C.; Kisunzu, J. K.; Duschmalé, J.; Häussinger, D.; Wiesner, M.; Ebert, M.-O.; Wennemers, H. Conformational Properties of a Peptidic Catalyst: Insights from NMR Spectroscopic Studies. *J. Am. Chem. Soc.* **2018**, *140*, 10829−10838.

(50) Bhabha, G.; Biel, J. T.; Fraser, J. S. Keep on Moving: Discovering and Perturbing the Conformational Dynamics of Enzymes. *Acc. Chem. Res.* **2015**, *48*, 423−430.

(51) Yan, X. C.; Metrano, A. J.; Robertson, M. J.; Abascal, N. C.; Tirado-Rives, J.; Miller, S. J.; Jorgensen, W. L. Molecular Dynamics Simulations of a Conformationally Mobile Peptide-Based Catalyst for Atroposelective Bromination. *ACS Catal.* **2018**, *8*, 9968−9979.

(52) Crawford, J. M.; Stone, E. A.; Metrano, A. J.; Miller, S. J.; Sigman, M. S. Parameterization and Analysis of Peptide-Based Catalysts for the Atroposelective Bromination of 3-Arylquinazolin-4(3*H*)-Ones. *J. Am. Chem. Soc.* **2018**, *140*, 868−871.

(53) Ameen, D.; Snape, T. J. Chiral 1,1-Diaryl Compounds as Important Pharmacophores. *MedChemComm* **2013**, *4*, 893−907.

(54) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. Catalytic Asymmetric Approaches Towards Enantiomerically Enriched Diarylmethanols and Diarylmethylamines. *Chem. Soc. Rev.* **2006**, *35*, 454−470.

(55) Laforteza, B. N.; Chan, K. S. L.; Yu, J.-Q. Enantioselective *ortho*-C−H Cross-Coupling of Diarylmethylamines with Organoborons. *Angew. Chem.* **2015**, *127*, 11295−11298.

(56) Su, B.; Zhou, T.-G.; Li, X.-W.; Shao, X.-R.; Xu, P.-L.; Wu, W.-L.; Hartwig, J. F.; Shi, Z.-J. A Chiral Nitrogen Ligand for Enantioselective, Iridium-Catalyzed Silylation of Aromatic C−H Bonds. *Angew. Chem.* **2017**, *129*, 1112−1116.

(57) Hurtley, A. E.; Stone, E. A.; Metrano, A. J.; Miller, S. J. Desymmetrization of Diarylmethylamido Bis(Phenols) Through Peptide-Catalyzed Bromination: Enantiodivergence as a Consequence of a 2 Amu Alteration at an Achiral Residue Within the Catalyst. *J. Org. Chem.* **2017**, *82*, 11326−11336.

(58) Payne, J. T.; Butkovich, P. H.; Gu, Y.; Kunze, K. N.; Park, H. J.; Wang, D.-S.; Lewis, J. C. Enantioselective Desymmetrization of Methylenedianilines via Enzyme-Catalyzed Remote Halogenation. *J. Am. Chem. Soc.* **2018**, *140*, 546−549.

(59) Pathak, T. P.; Miller, S. J. Chemical Tailoring of Teicoplanin with Site-Selective Reactions. *J. Am. Chem. Soc.* **2013**, *135*, 8415−8422.

(60) Xie, X.; Chen, Y.; Ma, D. Enantioselective Arylation of 2-Methylacetoacetates Catalyzed by CuI/*trans*-4-Hydroxy-l-Proline at Low Reaction Temperatures. *J. Am. Chem. Soc.* **2006**, *128*, 16050−16051.

(61) Kim, B.; Chinn, A. J.; Fandrick, D. R.; Senanayake, C. H.; Singer, R. A.; Miller, S. J. Distal Stereocontrol Using Guanidinylated Peptides as Multifunctional Ligands: Desymmetrization of Diarylmethanes via Ullman Cross-Coupling. *J. Am. Chem. Soc.* **2016**, *138*, 7939−7945.

(62) Chinn, A. J.; Kim, B.; Kwon, Y.; Miller, S. J. Enantioselective Intermolecular C−O Bond Formation in the Desymmetrization of Diarylmethines Employing a Guanidinylated Peptide-Based Catalyst. *J. Am. Chem. Soc.* **2017**, *139*, 18107−18114.

(63) Kwon, Y.; Chinn, A. J.; Kim, B.; Miller, S. J. Divergent Control of Point and Axial Stereogenicity: Catalytic Enantioselective C−N Bond-Forming Cross-Coupling and Catalyst-Controlled Atroposelective Cyclodehydration. *Angew. Chem., Int. Ed.* **2018**, *57*, 6251−6255.

(64) Zeymer, C.; Hilvert, D. Directed Evolution of Protein Catalysts. *Annu. Rev. Biochem.* **2018**, *87*, 131−157.