Published in final edited form as:

Angew Chem Int Ed Engl. 2018 May 22; 57(21): 6251–6255. doi:10.1002/anie.201802963.

Divergent Control of Point and Axial Stereogenicity: Catalytic Enantioselective C–N Bond-Forming Cross-Coupling and Catalyst-Controlled Atroposelective Cyclodehydration

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Abstract

Catalyst control over reactions that produce multiple stereoisomers is a challenge in synthesis. Control over reactions that involve stereogenic elements remote from one another is particularly uncommon. Additionally, catalytic reactions that address both stereogenic carbon and an element of axial chirality are also rare. Reported herein is a catalytic approach to each stereoisomer of a scaffold containing a stereogenic center remote from an axis of chirality. Newly developed peptidyl Cu-complexes catalyze an unprecedented remote desymmetrization, involving enantioselective C–N bond-forming cross-coupling. Then, chiral phosphoric acid catalysts set an axis of chirality, through an unprecedented atroposelective cyclodehydration to form a heterocycle with high diastereoselectivity. The application of chiral Cu-complexes and phosphoric acids provides access to each stereoisomer of a framework with two different elements of stereogenicity.

Point the way to the Axis

A fully catalyst-controlled, stereodivergent approach to all possible stereoisomers of a point-and-axial chiral heterocyclic scaffold is reported. Asymmetric desymmetrization is achieved by intermolecular C–N cross coupling with a peptidyl metal complex. Both C_2 -symmetric chiral phosphoric acids and a new class of phosphothreonine-derived peptidyl organocatalysts enable highly selective atroposelective cyclodehydration.

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Keywords

asymmetric catalysis; atropisomerism; cross-coupling; cyclodehydration; peptides

Stereochemically complex molecules hold a special place in the development of bioactive substances. Often, their distinct chirality and topology allow for selective interactions with the intricate binding sites associated with their biological targets.^[1] Scaffolds that possess two or more chiral centers pose particular challenges for design and synthesis.^[2] Furthermore, in the formation of the additional stereogenic centers, matched/mismatched effects are introduced, as the intrinsic selectivity of a chiral substrate may influence the facile formation of all possible stereoisomers.^[2,3] The field of asymmetric synthesis deals with these situations, often masterfully, through the application of chiral catalysts,^[3] which can take the form of transition metal complexes,^[4] small organic molecules,^[5] enzymes,^[6] or combinations of a metal-based catalyst and an organocatalyst.^[7] A particularly intriguing situation emerges when the scaffold of interest bears two different types of stereogenic elements.^[8] For example, when a molecule possesses both a stereogenic center (Figure 1a), and an axis of chirality (Figure 1b), four possible diastereomers exist (Figure 1c) in a manner rendering asymmetric synthesis of all possible stereoisomers quite complex. Therefore, developing new approaches to address all of these issues not only contributes to fundamental questions in the area of asymmetric catalysis, but also creates avenues for the consideration of novel chemotypes in medicinal chemistry.^[9]

We chose to explore this stereochemically complex situation through examination of catalytic reactions that would combine a number of challenging features, several of which, on their own, constituted unprecedented aspects of asymmetric synthesis. First, we endeavored to develop a new enantioselective C–N bond-forming cross-coupling reaction,^[10] testing the generality of recently developed Cu-complexes employing guanidinylated peptidyl ligands.^[11] We targeted a desymmetrization process that would create a remote stereogenic center on the nominally privileged diarylmethine scaffold (Figure 1d).^[12,13] At the outset of this work, to our knowledge, only a few enantioselective C–N bond-forming cross-couplings had been reported for intermolecular couplings.^[14] Second, we discovered during these studies that enantioselective C–N bond-forming cross-coupling could also be accompanied by the formation of an axis of chirality^[15] about the newly formed C–N bond,

provided that the right substitution environment be induced subsequent to the cross-coupling event. For example, if enantioselective cross-coupling could be followed by atroposelective benzimidazole formation (Figure 1e), unprecedented access to atropisomerically defined variants of this medically relevant heterocycle could be at hand.^[13,16] Combining these concepts into a singular chemotype culminated in the hypothesis that compounds such as the symmetrical diarylmethine shown in Figure 1f could be subjected to tandem desymmetrization/cyclodehydration to deliver complex chiral compounds merging both point and axial chirality elements. Full control of the stereochemical possibilities in this situation is, to our knowledge, rare. In order to meet this challenge, we now report the application of a recently described guanidinylated Cu-based catalyst for a previously unknown asymmetric C–N bond-forming cross-coupling event. Then, we show that venerable, *C*₂-symmetric chiral phosphoric acids^[17] enable a previously unknown atropisomer-selective cyclodehydration to form a benzimidazole ring. We also discovered that peptide-based phosphoric acids^[18] provide a complementary capacity to effect atroposelective cyclodehydrations. The result is a fully catalyst-controlled solution to the stereoisomeric landscape presented by these scaffolds. Control experiments for the atroposelective cyclodehydrations reveal a high potential for both *C*₂-symmetric chiral phosphoric acids and phosphothreonine (*p*Thr)-derived phosphoric acids to achieve high enantioselectivity in related reactions.

To assess our hypothesis, we began by evaluating the effects of multifunctional peptides on the enantioselective C–N cross-coupling of **1a**. Based on our previous findings on Cu-catalyzed desymmetrization of **1** via C–C and C–O cross-coupling,^[11] a range of peptides were tested (Table 1). In our preliminary study, the reaction with tripeptide **L2** gives the desired cross-coupled product **2a** and the undesired di-coupled product **3a**, which can be easily transformed to benzimidazole **4a** and **5a** upon *in situ* treatment with acetic acid (60% conversion for **4a**, 96:4 e.r.). While our previous studies have demonstrated that tetramethylguanidinylated L-aspartic acid, D-proline, and aminoisobutyric acid are essential to achieve high enantioselectivity at the *i*, *i*+1, and *i*+2 positions (Table 1), respectively, these ligands also show variable selectivity depending on the C-terminal extension of the peptide sequence. Indeed, the reaction employing a shorter dipeptide ligand (**L1**) shows considerably lower conversion and enantioselectivity. Longer peptides (**L3–5**) result in variable efficiencies on the desymmetrization of **1**. Among them, tetrapeptide **L3** was found to be an optimal peptide with a suitable length and stereoconfigurations. Epimeric peptide **L4** leads to diminished conversion and enantioselectivity. This result is especially intriguing, considering insensitivity to the substitutions at the *i*+3 position (**L4** vs **L6–10**). Eventually, we declared **L6** as the optimal ligand for the catalytic desymmetrization of **1a** via C–N cross-coupling, in terms of conversion and enantioselectivity. We then evaluated additional reaction parameters, including the Cu source, base, solvent, and temperature,^[19] culminating in the conditions depicted and applied in Scheme 1.

With optimal reaction conditions in hand, the scope of nitrogen nucleophiles was explored (Scheme 1). A range of *para*-substituents on anilines, from electron-donating (–Me, –OMe), to electron-withdrawing groups (–CF₃, –NO₂), are tolerated, providing **4a–e** with up to an e.r. value of 98:2. However, cross-coupled products bearing electron-withdrawing groups (**2d**

and **2e**) require prior purification and higher temperature (120 °C) in the eventual cyclization due to their low nucleophilicity. Primary and secondary aliphatic amines are compatible with our catalytic system, affording **4f–h** and **2i** in moderate yield. A variety of *ortho*-substituents are also tolerated in the cross-coupling to afford products **2j–p**, even though conversions vary depending on the size of substituent and nucleophilicity of the aniline. Upon cyclization to the corresponding benzimidazoles, products **2j–p** create the possibility of diastereomeric atropisomers, a point we discuss below (*vide infra*). We also examined the substrate scope with respect to the symmetrical diarylmethine (Scheme 1, **2q** and **2r**). Moving beyond the *tert*-butyl substituent, we observed that a cyclohexyl substituent is well tolerated providing **2q** with 96:4 e.r. A substrate bearing a pivalamide at the pro-stereogenic center led to the cross-coupled product **2r**, albeit in moderate yield and selectivity. This result is of interest given the distinct pharmacological properties of unsymmetrical benzhydrylamine derivatives.^[13,20]

Intriguingly, we found that the acid-catalyzed cyclization of racemic **2j** produced a statistical mixture of four stereoisomers, which we quickly realized were stable atropisomers about the newly created C–N bond axis. For example, when the racemic mixture of **2j** was subjected to AcOH at 80 °C, all four diastereomers of **4j** could be observed by chiral HPLC analysis (Scheme 2a). Therefore, we turned to investigating control of atropisomerism around the C–N bond of the *N*-arylbenzimidazoles. We hypothesized that *N*-aryl benzimidazoles bearing sterically hindered substituents at the *ortho*-position could be synthesized stereoselectively employing chiral Brønsted acid catalysts.^[21] Indeed, BINOL-derived phosphoric acid catalyst (*R*)-CPA^[22] induces the cyclodehydration of racemic **2j**, giving two different sets of peaks with a 1:1 ratio in chiral HPLC analysis,^[19] which suggests that each enantiomer of **2j** is stereospecifically cyclized at a similar rate by parallel kinetic resolution.^[23] The cyclodehydration of enantiopure **2j** with (*R*)-CPA results in **4j** in 90% yield with 17:1 d.r. and >99:1 e.r. of major diastereomer (Scheme 2b).

With a highly selective catalyst in hand, we explored the substrate scope of diastereoselective cyclodehydration (Scheme 2b). High diastereoselectivities (28:1) are observed for substrates bearing aliphatic groups at the aniline *ortho*-position, affording benzimidazoles **4k** and **4l**. Even though the cyclodehydration of *ortho*-disubstituted substrate **2m** shows lower diastereoselectivity (2:1 d.r.), it provides enantiopure **4m** in reasonable yield. More forcing conditions are required for the cyclodehydration of the bromo- and phenyl-substituted substrates to afford **4n** (9:1 d.r.) and **4o** (7:1 d.r.) with good diastereoselectivities, respectively. However, substrate **2p** bearing a *tert*-butyl group at the *ortho*-position failed to cyclize, even under extreme reaction conditions. The replacement of the *tert*-butyl group at the pro-stereogenic center with a cyclohexyl group is well tolerated to afford **4q** in high diastereoselectivity (12:1 d.r.). While the observed ~2:1 d.r. of **4r** is reflected from the initially modest enantiopurity of **2r** (70:30 e.r.), highly atroposelective cyclodehydration led to enantiopure **4r**, providing enantioenrichment of these compounds through the second, atroposelective cyclodehydration.

These observations stimulated assessment of the intrinsic enantioselectivity of these atropisomer-selective reactions as a control experiment. Thus, having achieved the highly diastereoselective cyclodehydration of **2**, we envisioned an enantioselective

cyclodehydration of a simpler substrate. Thus, compound **6** was exposed to chiral phosphoric acids (Table 2). The reaction of **6** with (*R*)-CPA smoothly afforded benzimidazole **7** with 96:4 e.r. in a nearly quantitative yield. As a prelude to more demanding, diastereoselective cyclodehydrations, we also examined phosphothreonine-containing peptides for their capacity to induce enantioselective cyclodehydration. We recently reported the *p*Thr class of chiral phosphoric acids as catalysts for asymmetric transfer hydrogenations.^[18] In this new context, we observed that *p*Thr-embedded tetrapeptide **pThr1** efficiently catalyzed the cyclodehydration of **6** affording **7** with 94:6 e.r. in 99% yield (Table 2). Strikingly, the epimeric *allo-p*Thr-containing peptide (**pThr2a**) shows a reversal in enantioselectivity (17:83 e.r.). Other diastereomers of the *p*Thr-containing peptides also modulate the enantioselectivity (e.g., Table 2, entry 4; 71:29 e.r.). These results suggested that substantial diversity among the *p*Thr-containing catalysts exists such that tuning of selectivity is possible.

In order to test this point aggressively, we then examined the possibility of the stereodivergent construction of all four stereoisomers of **4j**. Two different types of catalysts, (*R*)-CPA and **pThr1** showed comparable efficiency in terms of both of selectivity and yield to afford **4j** from **2j**. For example, (*R*)-CPA delivers (*R,aR*)-**4j** from (*R*)-**2j** with 17:1 d.r. and 90% yield; **pThr1** delivered (*R,aR*)-**4j** from (*R*)-**2j** 17:1 d.r. with (*R,aR*)-**4j** isolated in 92% yield (Scheme 3). Also of note, these compounds are each formed with >99:1 e.r., as a result of the highly enantioselective cross-coupling. Notably, X-ray analysis allowed the structural assignment of both the absolute and relative configuration of the products, which also allowed structural assignment throughout the series.^[24] The reaction of (*R*)-**2j** with (*S*)-CPA provides access to predominantly the other axial epimer, (*R,aS*)-**4j** with 19:1 d.r. and 86% yield. The *allo-p*Thr-containing peptide (**pThr2a**) also gives the alternative diastereomer (*R,aS*)-**4j** in this case, although with somewhat lower diastereoselectivity (4:1 d.r.) and yield (69%). To complete the series, we followed through with the analogous experiments with (*S*)-**2j**. Accordingly, we found that (*R*)-CPA could induce formation of (*S,aR*)-**4j** with 14:1 d.r. and 99:1 e.r., when a sample of (*S*)-**2j** of 97:3 e.r. was employed as the starting material. (*S*)-CPA provides (*S,aS*)-**4j** in an analogous manner.

The achievement of a fully catalyst controlled synthesis of each diastereomer of these complex scaffolds required several key concepts in asymmetric catalysis. A unique class of peptidyl Cu-complexes was found to be highly effective for desymmetrization through enantioselective C–N bond-forming cross-coupling. The molecular outputs were then found to undergo cyclodehydration reactions wherein an axis of chirality was introduced, and with it, the creation of atropisomers. In order to control this second stereogenic element, two families of chiral phosphoric acid were applied, and each was found to control the issue of atroposelectivity with high levels of diastereoselectivity. Control experiments verified that both *C*₂-symmetric CPA catalysts and the biologically inspired *p*Thr-containing peptidyl catalysts can control enantioselective cyclodehydration to create highly enantioenriched benzimidazoles about a stereogenic C–N bond axis. Given the evermore stereochemically complex compounds emanating from drug discovery campaigns,^[25] and the increasing primacy of issues involving atropisomers,^[26] we project the findings presented herein may be of broad interest.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work is supported by the National Institute of General Medical Sciences of the United States National Institutes of Health (GM-068649). We would like to thank Dr. B. Q. Mercado for solving our X-ray crystal structures. We would also like to thank A. L. Featherston, C. R. Shugrue, and Dr. A. J. Metrano for advice and materials.

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Figure 1.

(a) sp^3 -Hybridized carbon atoms with four different substituents. (b) Atropisomerism of axially chiral biaryl compounds. (c) Stereodivergent synthesis of four possible stereoisomers containing both point and axial chirality. (d) Enantioselective desymmetrization of diarylmethines (e) Atroposelective cyclodehydration for the formation of benzimidazoles. (f) Our strategy for constructing all four stereoisomers of benzimidazole.

Scheme 1.
Cu-Catalyzed Desymmetrization of Diarylmethines with Nitrogen Nucleophiles.

Scheme 2.

(a) Observation of Four Stereoisomers in the Cyclodehydration of (±)-2j. (b) C_2 -Symmetric Chiral Phosphoric Acid-Catalyzed Atroposelective Cyclodehydration for Benzimidazoles.

Scheme 3.
Catalytic controlled stereodivergent synthesis of all four stereoisomers of benzimidzoles.

Table 1

Evaluation of Peptide Ligands.^[a]

Ligand	<i>i</i>	<i>i</i> +1	<i>i</i> +2	<i>i</i> +3	<i>i</i> +4	Conv. ^[b] (%)		e.r. of 4a/c
						4a	5a	
L1	TMG-Asp	D-Pro-OLi	-	-	-	40	5	90:10
L2	TMG-Asp	D-Pro	Aib-OLi	-	-	60	15	96:4
L3	TMG-Asp	D-Pro	Aib	Ala-OLi	-	66	17	98:2
L4	TMG-Asp	D-Pro	Aib	D-Ala-OLi	-	52	9	92:8
L5	TMG-Asp	D-Pro	Aib	Ala	Ala-OLi	51	15	96:4
L6	TMG-Asp	D-Pro	Aib	Val-OLi	-	70	20	98:2
L7	TMG-Asp	D-Pro	Aib	Leu-OLi	-	66	22	98:2
L8	TMG-Asp	D-Pro	Aib	Tle-OLi	-	63	27	99:1
L9	TMG-Asp	D-Pro	Aib	Phe-OLi	-	69	21	98:2
L10	TMG-Asp	D-Pro	Aib	Met-OLi	-	68	24	99:1

^[a]Reaction conditions: **1a** (0.2 mmol), CuBr (5 mol %), ligand (**L**, 10 mol %), *p*-toluidine (2.0 equiv), K₃PO₄ (3.2 equiv), PhMe/DMF (2/1, 0.8 mL), 60 °C, 14 h.

^[b]Conversions (as a percentage) were determined by ¹H NMR analysis of the unpurified reaction mixture, using 1,4-bis(trimethylsilyl)benzene as the internal standard.

^[c]Enantiomeric ratios were determined by chiral HPLC analysis.

Table 2

Enantioselective Synthesis of Chiral Benzimidazoles.

Entry	Chiral Phosphoric Acid Catalysts	Conv. ^[b] (%)	e.r. ^[c]
1	(<i>R</i>)-CPA	99	96:4
2	Fmoc- <i>p</i> Thr- ^D Pro-Acp- <i>Chg</i> -NMe ₂ (pThr1)	99	94:6
3	Fmoc- <i>allo-p</i> Thr- ^D Pro-Aib-Phe-NMe ₂ (pThr2a)	73	17:83
4	Fmoc- <i>p</i> Thr- ^D Pro-Aib-Phe-NMe ₂ (pThr2b)	74	71:29

^[a] Reaction conditions: **6** (0.02 mmol), (*R*)-CPA, **pThr1**, or **pThr2** (10 mol %), PhMe (0.2 mL), 60 °C, 24 h.

^[b] Conversions (as a percentage) were determined by ¹H NMR integrations of the aromatic peaks for the substrate and product.

^[c] Enantiomeric ratios were determined by chiral HPLC analysis.