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Catalytic Dynamic Kinetic Resolutions in Tandem to Construct Two-Axis Terphenyl Atropisomers

Omar M. Beleh, Edward Miller, F. Dean Toste,* and Scott J. Miller*

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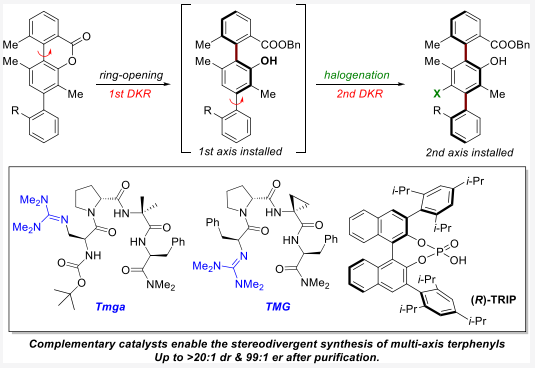
ABSTRACT: The defined structure of molecules bearing multiple stereogenic axes is of increasing relevance to materials science, pharmaceuticals, and catalysis. However, catalytic enantioselective approaches to control multiple stereogenic axes remain synthetically challenging. We report the catalytic synthesis of two-axis terphenyl atropisomers, with complementary strategies to both chlorinated and brominated variants, formed with high diastereo- and enantioselectivity. The chemistry proceeds through a sequence of two distinct dynamic kinetic resolutions: first, an atroposelective ring opening of Bringmann-type lactones produces a product with one established axis of chirality, and second, a stereoselective arene halogenation delivers the product with the second axis of chirality established. In order to achieve these results, a class of Brønsted basic guanidinylated peptides, which catalyze an efficient atroposelective chlorination, is reported for the first time. In addition, a complementary bromination is reported, which also establishes the second stereogenic axis. These bromo-terphenyls are accessible following the discovery that chiral anion phase transfer catalysis by C_2-symmetric phosphoric acids allows catalyst control in the second stereochemistry-determining event. Accordingly, we established the fully catalyst-controlled stereodivergent synthesis of all possible chlorinated stereoisomers while also demonstrating diastereodivergence in the brominated variants, with significant levels of enantioselectivity in all cases.



INTRODUCTION

Arising from hindered bond rotation, atropisomerism has become recognized as an important structural element within numerous chiral ligands, organocatalysts, and biologically active molecules. Tremendous strides have been made toward efficient and modular catalytic syntheses of single-axis atropisomers, especially in recent years.[1] Common strategies include stereoselective cross-coupling of two aryl units,[2] kinetic resolution of a pre-existing stereochemically undefined axis,[3,4] and atroposelective *de novo* construction of an arene ring.[5] However, application of these methods to multiaxis systems has only been recently explored.[6−19] These reports have often featured some of the established methods, including atroposelective cross-coupling,[7,13] [2+2+2]-cycloaddition,[8,10,11] or central-to-axial chirality transfer[15,16,18] to install two stereogenic axes at different sites of a substrate in a single step. This approach, which has many advantages, may also limit the modularity and scope of accessible multiaxis structures, especially in cases where different classes of reactions are required to allow differential functionalization in the vicinity of each stereogenic axis; moreover, a singular chemical reaction to set two axes with a common reaction may not be amenable to the development of diastereodivergent outcomes.

On the other hand, decoupling the individual steps and controlling the configuration of each chiral axis independently can offer a path to stereodivergency,[15,18] potentially through different chemical events at each axis. Achieving catalyst control over all possible stereoisomers is challenging, however, and can require extensive assessment of reaction conditions and multiple synthetic steps. Additionally, substrate-controlled stereoselectivity preferences must be addressed and overcome in molecules containing one or more stereochemical elements. Pioneering work in this area has come from the Sparr laboratory, which triumphantly demonstrated atroposelective aldol condensations to obtain products with high levels of atroposelectivity in systems possessing up to four fully controlled chiral axes in the oligonaphthalene template.[5a,15]

The approach we detail below describes a strategy to two-axis terphenyls based on catalytic dynamic kinetic resolution (DKR)[20] of starting materials that contain two configurationally labile axes. Rapid interconversion between two atropisomers at each axis through bond rotation defines the challenge as a four-stereoisomer problem and requires that

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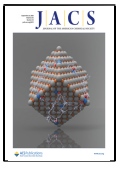

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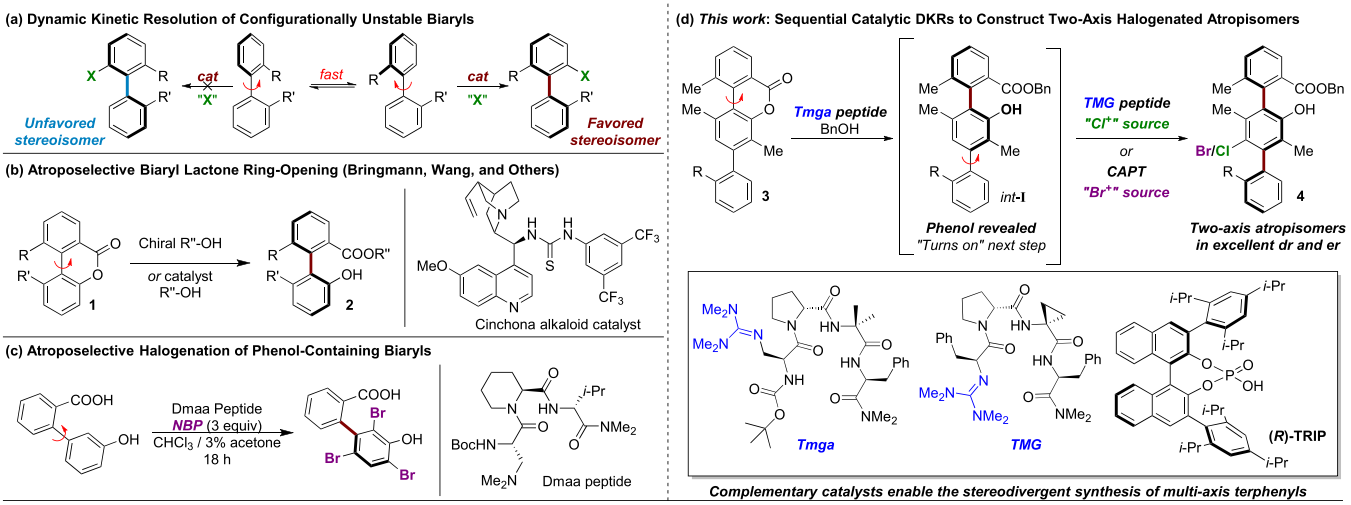


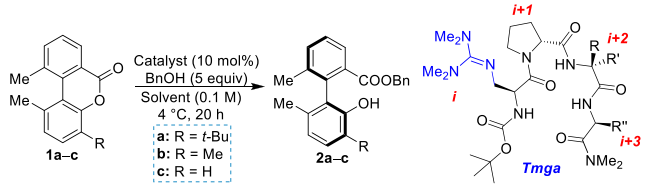
Figure 1. (a) General scheme for the catalytic dynamic kinetic resolution of configurationally unstable biaryls. (b) Previous approaches to the DKR of biaryl lactones. (c) Peptide-catalyzed atroposelective bromination of phenol-containing biaryls. (d) Our catalytic strategy to two-axis terphenyls **4** by a two-step dynamic kinetic resolution sequence.

each atroposelective reaction yields a configurationally stable axis (Figure 1a). The exploitation of this dynamic behavior was pioneered by Bringmann with biaryl lactones like **1**;[3] selective ring opening of the lactone yields configurationally stable enantioenriched biaryls like **2**, as was elegantly demonstrated with a cinchona alkaloid-based catalyst by Wang (Figure 1b).[21−23] Our group[24] and others[3,4] have also previously utilized the concepts of catalytic atroposelective DKR, most relevantly in the bromination of phenol-containing biaryls promoted by a Brønsted basic dimethylaminoalanine (Dmaa) peptide (Figure 1c).[24a] Building on these precedents, we envisioned a two-event sequence by combining the two strategies that could access products with multiple configurationally stable axes. The key to this strategy is that atroposelective biaryl lactone ring-opening unveils a phenol, which is required for the next reaction, atroposelective electrophilic aromatic substitution. In order to test this hypothesis, we designed terphenyl lactone **3** (Figure 1d). In this proposed scenario, selective base-catalyzed alcoholysis of **3** yields enantioenriched *int*-**I**, which is then "turned on" for further functionalization, as the now revealed phenol enhances the reactivity of the *para*-position of the middle arene ring. An additional catalytic DKR through electrophilic halogenation of *int*-**I** installs the second stereogenic axis, yielding multiaxis atropisomers **4**. In addition to the fundamental interests presented by the terphenyl scaffold, these types of structures have proven to be of great interest to a number of applications, including as α-helix mimetics in medicinal chemistry[25] and as subunits in studies of oligoarene-based materials.[26]

RESULTS AND DISCUSSION

To establish a relevant catalytic atroposelective biaryl lactone ring opening, we developed a new class of Brønsted basic guanidinylated peptides as catalysts for ring-opening of Bringmann-type lactones (Table 1). Notably, we were also mindful that Lewis basic catalysts of this type may catalyze an asymmetric arene halogenation,[24,27] therefore possibly establishing the second chiral axis. Initially, we had hoped that Dmaa-based peptides, effective for enantioselective ring-openings of oxazolones through DKR[28] and for arene halogenation,[24] would be effective in the selective conversion of **3** to **4**. However, these experiments were unsuccessful in attempted conversions of **1a** to **2a** (with **P1**; Table 1, entry 1), and in fact Et_3N was also ineffective as a catalyst (Table 1, entry 2). Anticipating that a stronger base was required, we discovered that *N*,*N*,*N*′,*N*′-tetramethylguanidine (**TMG**) was a competent catalyst for the ring-opening (70% conv.; Table 1, entry 3), thus grounding our interest in TMG-based peptides as Brønsted basic catalysts.[29−31] Accordingly, we prepared a small set of tetramethylguanidinylalanine (Tmga)-containing peptides for evaluation in the enantioselective ring-opening of lactone **1a**. For this new family of guanidinylated peptide

Table 1. Optimization of Atroposelective Ring-Opening



entry	"-R"	catalyst	solvent	Conv. (%)[a]	er[b]
1	**1a**	Boc-**Dmaa**-D-Pro-Acpc-Leu-NMe_2 (**P1**)	CH_2Cl_2	0	N/A
2	**1a**	Triethylamine	CH_2Cl_2	<5	N/A
3	**1a**	*N*,*N*,*N*′,*N*′- tetramethylguanidine (**TMG**)	CH_2Cl_2	70	50:50
4	**1a**	Boc-**Tmga**-D-Pro-Aib-Leu-NMe_2 (**P2**)	CH_2Cl_2	48	74:26
5	**1a**	Boc-Tmga-D-Pro-Aib-Leu-NMe_2 (**P2**)	**PhMe**	62	65:35
6	**1a**	Boc-Tmga-D-Pro-Aib-Leu-NMe_2 (**P2**)	**MeCN**	98	83:17
7	**1a**	Boc-Tmga-D-Pro-Aib-Leu-NMe_2 (**P2**)	**THF**	85	87:13
8	**1a**	Boc-Tmga-D-Pro-Aib-**Phe**-NMe_2 (**P3**)	THF	82	91:9
9	**1a**	Boc-Tmga-D-Pro-Aib-**2Nal**-NMe_2 (**P4**)	THF	95	90:10
10[c]	**1a**	Boc-Tmga-D-Pro-Aib-Phe-NMe_2 (**P3**)	THF (0.25 M)	91	93:7
11[c]	**1b**	Boc-Tmga-D-Pro-Aib-Phe-NMe_2 (**P3**)	THF (0.25 M)	70	88:12
12[c]	**1c**	Boc-Tmga-D-Pro-Aib-Phe-NMe_2 (**P3**)	THF (0.25 M)	85	62:38

[a]Conversion determined by ^{1}H NMR integration ratios of product to substrate. [b]Enantiomeric ratios determined by HPLC equipped with a chiral stationary phase. [c]Reaction performed at −10 °C, 2 equiv of BnOH (abbreviations: Dmaa = dimethylaminoalanine; Tmga = tetramethylguanidinylalanine; Aib = 2-aminoisobutyric acid; 2Nal = 3-(2-naphthyl)-alanine).

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catalysts, we were motivated to focus on β-turn-biased sequences,[32] as this type of secondary structure had proven successful in the past for mechanistically similar chemistry.[24,28]

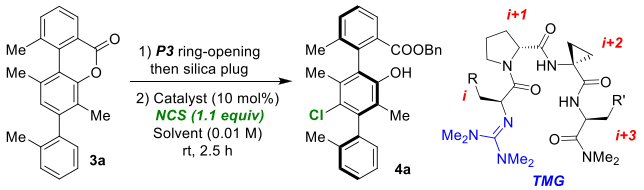
Thus, through examination of such Brønsted basic guanidinylated sequences, we were pleased to find that the Tmga peptides could induce atroposelectivity via ring-opening with appreciable enantioselectivity, albeit at moderate conversion (**P2**, 74:26 er, 48% conv.; Table 1, entry 4). An evaluation of solvent effects included observations of enhanced conversion and selectivity in polar, aprotic solvents (with **P2**, up to 87:13 er and up to 98% conv.; Table 1, entries 5−7, see Supporting Information for full details of the solvent effect studies). We attribute these enhancements to the modulation of the guanidinium pK_a, as reflected in the acid−base equilibria between the peptide catalyst and the liberated phenol of **2** following ring-opening in the different solvents.[33] For example, in THF and MeCN, the phenolate is more basic, resulting in the major species at equilibrium to be the protonated phenol and guanidine free base; this is the desired state of affairs to facilitate catalytic turnover. Further variation of the peptide sequence provided minor changes to er (see Supporting Information for details); however, improvements could be observed with an aryl group at the i + 3 position (**P3**, 91:9 er, **P4**, 90:10 er; Table 1, entries 8 and 9). Thus, we selected the sequence Boc-Tmga-D-Pro-Aib-Phe-NMe_2 (**P3**) for further optimization of reaction parameters. Increasing the reaction concentration, while lowering the temperature and equivalents of nucleophile improved enantioselectivity (93:7 er; Table 1, entry 10).

Also of note, we investigated the effect of substituents on the "lower" ring of biaryl lactone **1a**. In analogy to the observations of Wang,[22b] the highest enantioselectivity is observed when the position *ortho*- to the phenolic oxygen is substituted. In the present system, with catalyst **P3**, this appears to primarily be a steric effect; for example, permuting the *tert*-butyl group to a methyl substituent results in a small decrease of enantioselectivity (**1b**, 88:12 er; Table 1, entry 11). Removal of this group altogether (R = H) significantly lowers er (**1c**, 62:38 er, Table 1, entry 12). We believe that lactone ring-opening can be reversible under the basic conditions, leading to thermodynamic equilibration and racemization, which we observe when we resubmit **2c** to basic reaction conditions. Lactone **1a** is also vulnerable to these erosions, but more forcing conditions are required for complete racemization of **2a** (see Supporting Information for details).

With desirable ring-opening conditions in hand, we turned our attention to developing the targeted atroposelective halogenation to set the second axis. For this event, we were initially motivated to develop a novel atroposelective chlorination, despite the fact that atroposelective brominations were better precedented,[24] because the new Tmga catalysts provide enhanced Lewis basicity than the previously studied Dmaa-based catalysts. Atroposelective arene chlorinations have been historically slower to emerge, perhaps due to the lower reactivity of many conventional electrophilic chlorination reagents relative to the brominated counterparts [e.g., *N*-chlorosuccinimide (NCS) vs *N*-bromosuccinimide (NBS)],[34,35] although enantioselective alkene chlorinations are well-known.[36] Introduction of aryl chlorides is also highly desirable due to their oft-noted pharmacological properties.[37] These issues, taken together, stimulated our pursuit of an atroposelective chlorination to establish the second axis, given our newfound access to the more active guanidinylated peptides.

We thus prepared terphenyl **3a**, and following lactone ring-opening, we investigated the catalytic viability of arene chlorination. Treatment of the resulting phenol with NCS in the absence of a catalyst resulted in only recovered starting material, establishing a minimal background rate (Table 2, entry 1). However, in the presence of Tmga peptide **P3**, the desired product **4a** was observed with full conversion and with a 4.6:1 dr (Table 2, entry 2), confirming suitable catalytic activity. Parenthetically, a Dmaa-containing sequence that was previously optimized for bromination[24c] failed to catalyze the arene chlorination reaction (**P1**; Table 2, entry 3). That said, guanidinylated catalyst **P3** provided only a minor enhancement of the intrinsic, substrate-controlled diastereoselectivity since a similar result was obtained with an achiral guanidine base, triazabicyclodecene (**TBD**) (3.9:1 dr; Table 2, entry 4). A survey of a small set of Tmga-containing catalysts did not significantly perturb the diastereoselectivity beyond that observed with catalyst **P3** (see Supporting Information for details). However, we were pleased to observe that a related set of guanidinylated peptides, possessing the TMG moiety at the *N*-terminus of the peptide sequence, was not only an excellent catalyst for chlorination but was also able to significantly influence the dr. Accordingly, after minimal optimization, we found that catalyst **P5** (TMG-Phe-D-Pro-Acpc-Phe-NMe_2) furnished **4a** cleanly in 13:1 dr and with 92:8 er for the major diastereomer (Table 2, entry 5). A brief investigation of the peptide structure showed that the TMG-L-Phe-D-Pro stereochemistry was important for stereoselectivity (lower dr observed with **P6** and **P7**; Table 2, entries 6−7). The cyclopropyl ring of Acpc also at the i + 2 position also conferred advantages, as its replacement with Aib led to a less

Table 2. Optimization of Atroposelective Chlorination



entry[a]	catalyst	solvent	dr[b]	er (maj-**4a**)[b]
1	No catalyst	CH_2Cl_2	N.R.	N.R.
2	Boc-Tmga-D-Pro-Aib-Phe-NMe_2 (**P3**)	CH_2Cl_2	4.6:1	88:12
3	Boc-Dmaa-D-Pro-Acpc-Leu-NMe_2 (**P1**)	CH_2Cl_2	N.R.	N.R.
4	Triazabicyclodecene (**TBD**)	CH_2Cl_2	3.9:1	88:12
5	TMG-Phe-D-Pro-Acpc-Phe-NMe_2 (**P5**)	CH_2Cl_2	13:1	92:8
6	TMG-D-Phe-D-Pro-Acpc-Phe-NMe_2 (**P6**)	CH_2Cl_2	7:1	88:12
7	TMG-Phe-Pro-Acpc-Phe-NMe_2 (**P7**)	CH_2Cl_2	5.7:1	83:17
8	TMG-Phe-D-Pro-Aib-Phe-NMe_2 (**P8**)	CH_2Cl_2	9:1	88:12
9[c]	TMG-Phe-D-Pro-Acpc-Phe-NMe_2 (**P5**)	CH_2Cl_2	9:1	94:6
10[c]	TMG-Phe-D-Pro-Acpc-Phe-NMe_2 (**P5**)	CH_2Cl_2/PhMe	14:1	97:3

[a]All reactions run to complete conversion of **3a**. [b]Diastereomeric and enantiomeric ratios determined by HPLC equipped with a chiral stationary phase. [c]5 mol % catalyst loading (abbreviations: Tmga = tetramethylguanidinylalanine; TMG = *N*,*N*,*N*′,*N*′-tetramethylguanidine; Aib = 2-aminoisobutyric acid; Acpc = 1-aminocyclopropane carboxylic acid; Dmaa = dimethylaminoalanine).

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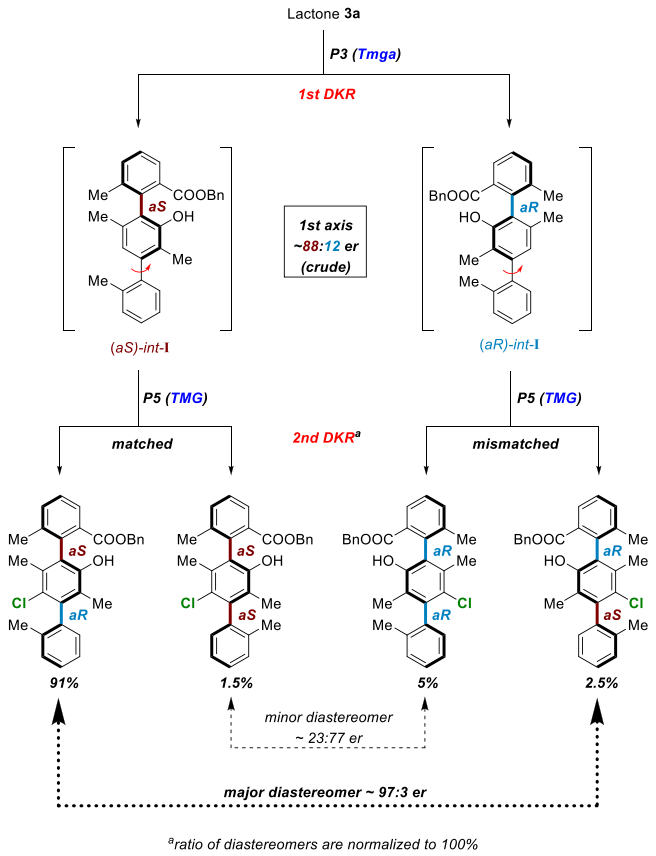
selective catalyst (**P8**, Table 2, entry 8). Finally, lowering the catalyst loading of **P5** to 5 mol % (Table 2, entry 9) and addition of PhMe as a cosolvent provided improvements to 14:1 dr and 97:3 er for the major diastereomer (Table 2, entry 10).

Intriguingly, the er of **4a** was significantly enhanced relative to the simple ring-opened **2b** (97:3 er versus 88:12 er, respectively; compare Table 2 entry 10 to Table 1 entry 11). We ascribe this to a kinetic resolution of the intermediate chiral phenol (*int*-**I**, Figure 1d). For the chlorination step, **P5** is well-matched with the major phenol (*aS*)-enantiomer, and the reaction proceeds with excellent diastereoselectivity, favoring (*aS*,*aR*)-**4a** in over 50:1 dr (Scheme 1). Furthermore, the

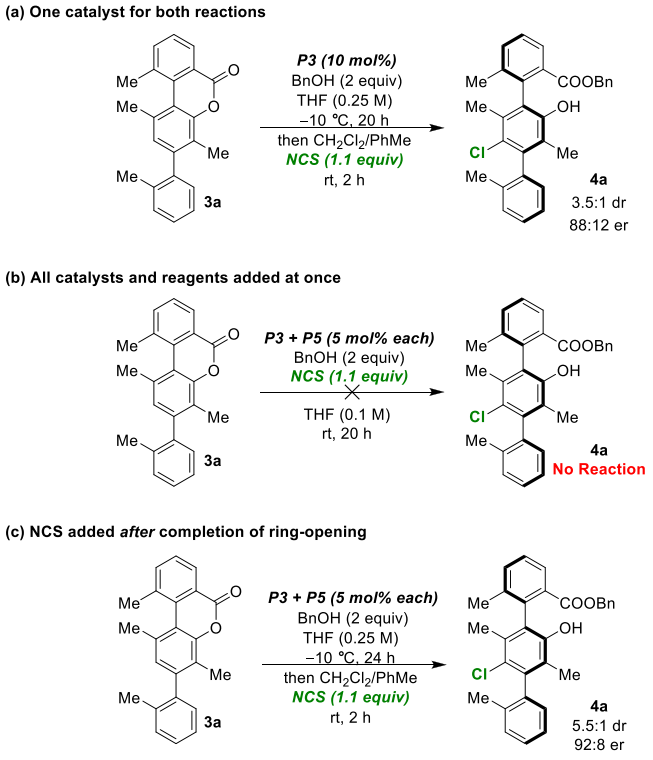
Scheme 1. Reaction Process and Effects of Kinetic Resolution on Stereoselectivity



halogenation reaction of the minor phenol (*aR*) enantiomer with **P5** slightly favors the opposite diastereomer, (*aR*,*aR*)-**4a**, in 2:1 dr. This differential reactivity and distribution of products account for the overall enrichment of er—i.e., the increased ratio of (*aS*,*aR*)-**4a** to (*aR*,*aS*)-**4a** from the initial 88:12 er of **2b** attained after ring-opening.

We do wish to note it was not lost on us that since each DKR is promoted by a basic guanidine catalyst a one-catalyst, one-pot procedure might be possible, wherein *a singular guanidine-based catalyst might affect both atroposelective reactions, notably by a different reaction and distinct mechanism in each step*. Accordingly, we subjected lactone **3a** to the optimized ring-opening and chlorination sequence in a single pot with **P3**, which cleanly furnished **4a**, albeit with modest diastereoselectivity (3.5:1 dr, 88:12 er; Scheme 2a). This was not surprising, as **P3** alone was not particularly efficient in the

Scheme 2. Initial Results Towards a One-Pot Protocol to 4b[a]



[a]One-pot conditions: **3a** (0.1 mmol, 1.0 equiv), **P3** (5 mol %), **P5** (5 mol %), BnOH (2.0 equiv), THF (0.4 mL), −10 °C, 20 h, then CH_2Cl_2/PhMe (1:1, 9.6 mL) and NCS (1.1 equiv), rt, 2 h. Reactions are run to complete conversion of **3a**. HPLC equipped with a chiral stationary phase was used to determine dr and er.

chlorination event (as in Table 2, entry 1). We thus expected that an improved result could be obtained when the two guanidine-based catalysts **P3** and **P5** are present in one pot, as each peptide is optimized for each mechanistically distinct reaction. However, the situation is nuanced. When adding all catalysts and reagents immediately, we were surprised to see that reactivity was completely shut down (Scheme 2b). This may point to a guanidinium NCS complex rapidly forming in solution, which would diminish the basicity of the catalyst and thereby inhibit the ring-opening. Nonetheless, we found that addition of NCS only after formation of the ring-opened intermediate yielded **4a** in desirable levels of stereoselectivity (5.5:1 dr and 92:8 er for the major diastereomer; Scheme 2c). It is thus notable that good stereoselectivity in chlorination is retained, even with two catalyst sequences competing at differing efficiencies (compare Table 2, entry 1 vs entry 10).

Returning to the optimized, sequential reaction conditions for establishing the synthesis of two-axis terphenyl products, we were interested in exploring the reaction scope. Therefore, we examined substituent effects on the efficiency and selectivity of the two-step sequence. Since an efficient DKR requires rapid isomerization of the second axis,[20] we tested the steric and electronic nature of the substituents on the bottom arene ring, which would directly influence the rate of bond rotation (Figure 2). Lactone **3b** bearing an *ortho*-methoxy substituent yielded the two-axis terphenyl **4b** in 72% yield, in 12:1 dr, and in 97:3 er for the major diastereomer. Notably, no appreciable overchlorination was detected in the electron-rich

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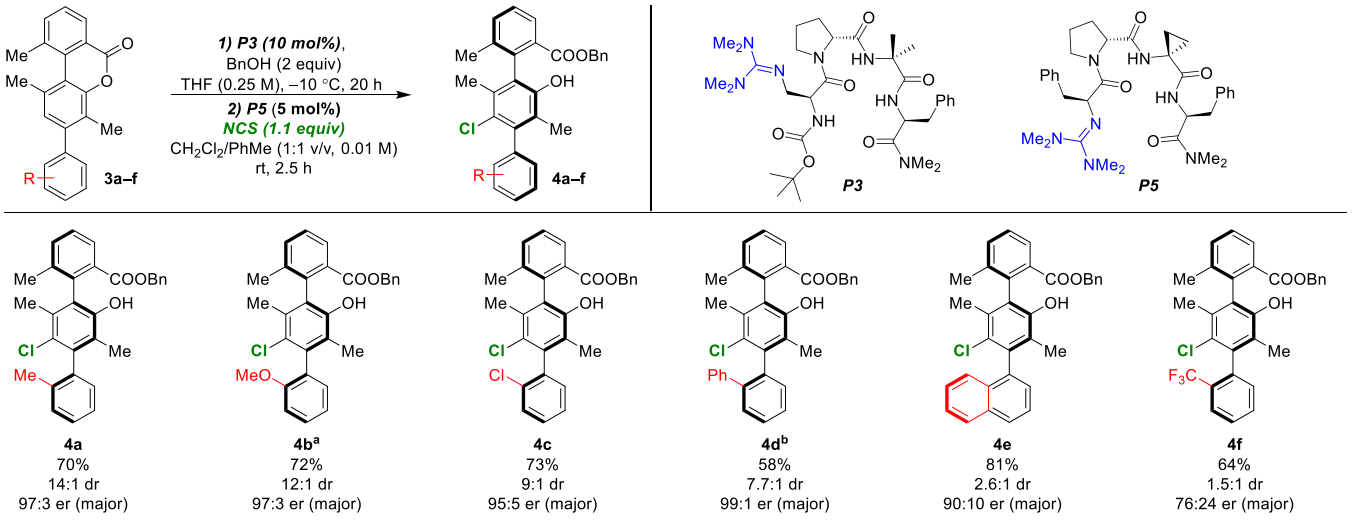


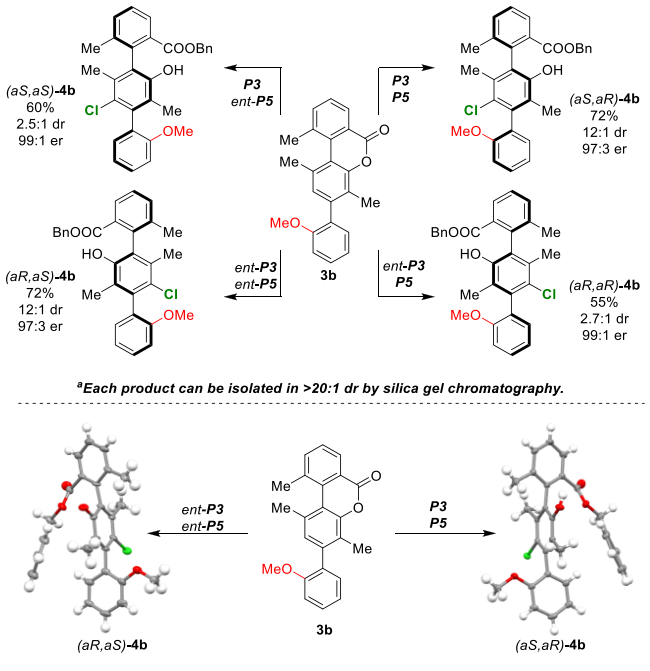
Figure 2. Effect of bottom aryl ring substitution. Reactions are run at 0.1 mmol of lactone **3**. A short silica plug is required to remove **P3** prior to chlorination. Isolated yields, dr, and er are based off the average of two trials. Yields are reported as a mixture of diastereomers. HPLC equipped with a chiral stationary phase was used to determine dr and er. [a]Scale-up conditions were performed on 0.75 mmol (258 mg) of **3b** with the modification of portion-wise addition of NCS in the second step (see Supporting Information for experimental details). **4b** was isolated in 53% overall yield (194 mg), with 14:1 dr and 97:3 er (average of two trials). [b]2:1 THF/CH_2Cl_2 solvent for ring-opening due to the poor solubility of **3d**.

bottom arene ring. Chloro- (**3c**) and phenyl (**3d**) substituents are also well tolerated at the *ortho*-position, providing **4c** (9:1 dr, 95:5 er) and **4d** (7.7:1 dr, 99:1 er), respectively. However, sterically bulkier[38] substituents that may slow down aryl−aryl bond rotation eroded dr, as demonstrated by naphthyl-substituted **4e** (2.6:1 dr) and trifluoromethylated **4f** (1.5:1 dr). The er for both of these substrates was also lower (**4e**, 90:10 er; **4f**, 76:24 er). While we do not have a solid explanation for the lower overall er for substrate **4f**, it is possible that inductive effects make this compound more acidic at the phenol, rendering racemization through reversible lactone and/or tetrahedral intermediate formation a vulnerability. Finally, the optimized conditions can be scaled successfully, albeit with slightly diminished yield. Performing the two-reaction sequence on 0.75 mmol (258 mg) of lactone **3b** furnished terphenyl **4b** in 53% overall yield (194 mg) in 14:1 dr and 97:3 er for the major diastereomer. We note that portion-wise addition of NCS was key to minimize the formation of overchlorinated byproducts (see Supporting Information for experimental details).

We now turn to the goal of fully stereodivergent conditions to achieve selective syntheses of all possible chlorinated terphenyl diastereomers. When developing a reaction system with multiple stereogenic elements, a catalyst might generally be optimized for one relative configuration of products (i.e., only one diastereomeric pair). Extensive reaction optimization and synthetic workarounds can be necessary to access the other diastereomers.[39] In the present case of setting two consecutive axes of chirality, when each axis is set by a different reaction (and thus differing reaction mechanisms), there exists a requirement for catalyst control, and any substrate-controlled selectivity biases must be identified and overcome.

Throughout our studies of the terphenyl system **3**, we observed that **P5** reacts primarily with the (*aS*)-enantiomer of the ring-opened intermediate *int*-**I** in high efficiency (as in Scheme 1), and as such we expected *ent*-**P5** to be matched with the (*aR*)-enantiomer. Thus, we envisioned utilizing the enantiomers of **P3** and **P5** in each possible combination, as these matched/mismatched effects of substrate and catalyst might overturn the intrinsic diastereoselectivity and achieve stereodivergency. We selected methoxy-substituted **3b** to assess this hypothesis. As a benchmark for the intrinsic diastereoselectivity, we determined that **3b** is converted to **4b**

Scheme 3. Stereodivergent Synthesis of All Diastereomers of 4b[a]



[a]Standard conditions: Ring-opening. **3b** (0.1 mmol, 1.0 equiv), **P3** (10 mol %), BnOH (2.0 equiv), THF (0.4 mL), −10 °C, 20 h; Chlorination. **P5** (5 mol %), NCS (1.1 equiv), CH_2Cl_2/PhMe (1:1 v/v, 10 mL). A short silica plug is required to remove **P3** prior to chlorination. Isolated yields, dr, and er are based off the average of two trials. Yields are reported as a mixture of diastereomers, which are separable by silica gel column chromatography. HPLC equipped with a chiral stationary phase was used to determine dr and er.

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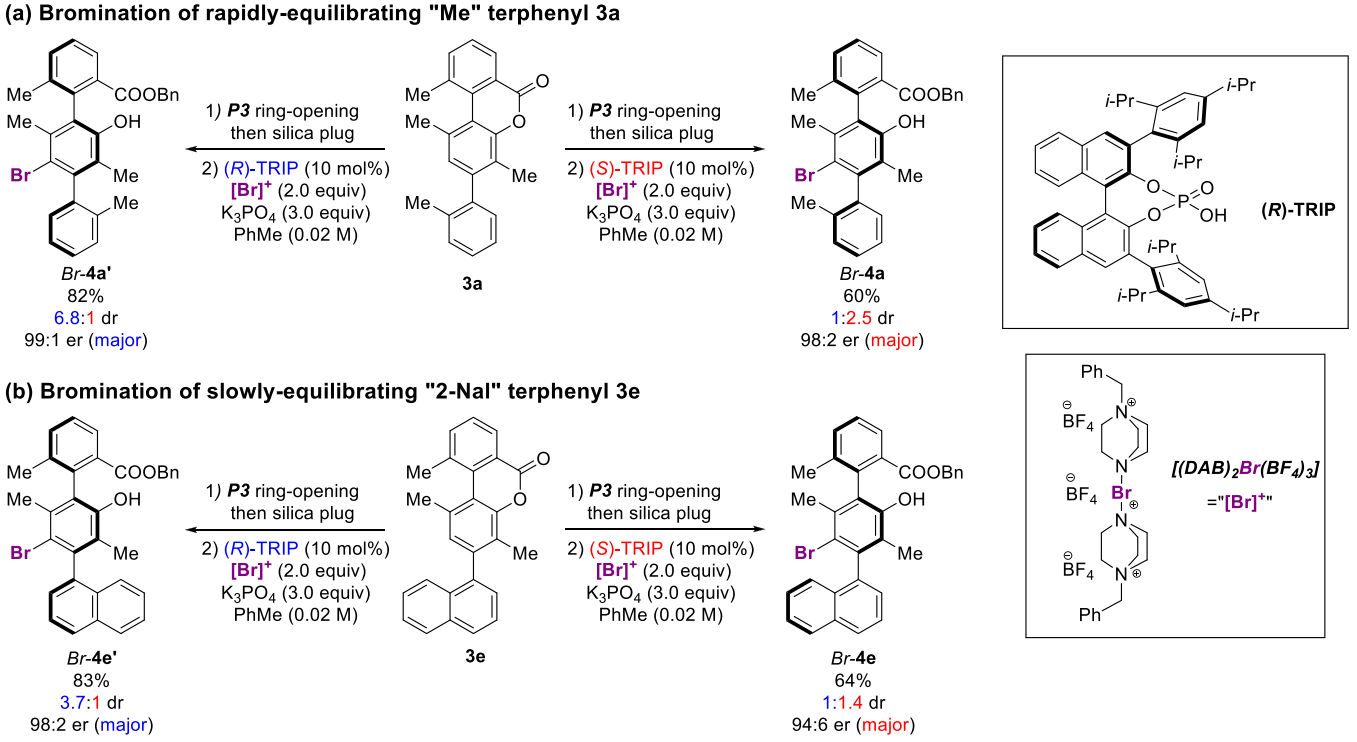
Scheme 4. Diastereodivergent Chiral Anion Phase Transfer Catalysis to Brominated Two-Axis Terphenyls[a]



[a]Standard conditions: ring-opening. **3** (0.1 mmol, 1.0 equiv), **P3** (10 mol %), BnOH (2.0 equiv), THF (0.4 mL), −10 °C, 20 h. Bromination. TRIP (10 mol %), [$(DAB)_2Br(BF_4)_3$] (2.0 equiv), K_3PO_4 (3.0 equiv), PhMe (5 mL), rt, 48 h. A short silica plug is required to remove **P3** prior to bromination. Isolated yields are reported as a mixture of diastereomers. HPLC equipped with a chiral stationary phase was used to determine dr and er. We note that the stereochemical assignments for *Br*-**4a**, *Br*-**4a**′, *Br*-**4e**, and *Br*-**4e**′ are drawn in analogy to the X-ray-based assignments of the chlorinated products but have not been directly determined themselves (see Supporting Information for details).

in the **TBD**-catalyzed chlorination with a 6:1 dr (favoring (*aS*,*aR*)-**4b** from (*aS*)-ring-opened product of type *int*-**I**; see Supporting Information for details). In the substrate−catalyst matched scenarios, treatment of **3b** with catalysts **P3** and **P5** yielded (*aS*,*aR*)-**4b** (72% yield, 12:1 dr, 97:3 er; Scheme 3, top right). By analogy, treatment of **3b** with *ent*-**P3** and *ent*-**P5** delivered (*aR*,*aS*)-**4b** (Scheme 3, bottom left), in 72% yield, 12:1 dr, and 97:3 er, reflecting a high level of reproducibility. These results represent an overall enhancement of the intrinsic substrate-controlled diastereoselectivity. Furthermore, the substrate−catalyst mismatched cases successfully overturn the substrate-controlled diastereoselectivity observed with achiral base **TBD**. With catalysts **P3** and *ent*-**P5**, the intrinsically disfavored product (*aS*,*aS*)-**4b** is now the major diastereomer formed, and it is observed with very high enantioselectivity (2.5:1 dr, 99:1 er, in 60% yield; Scheme 3, top left). Finally, with catalysts *ent*-**P3** and **P5**, product (*aR*,*aR*)-**4b** is isolated in 55% yield, with a 2.7:1 dr, and with 99:1 er (Scheme 3, bottom right; we ascribe the small difference in dr for the two cases to variable levels of conversion). The absolute and relative configurations for the series were unambiguously determined by X-ray crystallography. To further highlight the utility of this approach, each of the four diastereomers could be purified chromatographically to stereochemical homogeneity.

In parallel to the above studies on atroposelective chlorination to set the second stereogenic axis, we also wished to develop a complementary bromination, in line with previous studies of atroposelective arene brominations.[24] Initial evaluation of a few guanidine-based catalysts that are the focus of the present study with common electrophilic brominating reagents (namely *N*-bromosuccinimide and *N*-bromophthalimide) did not deliver dramatic nor improved dr and er values for brominated terphenyls of type *Br*-**4** (generally under 5:1 dr and no higher than 88:12 er). In contrast, an entirely different approach for the bromination step led to significantly better results. Predicated on chiral anion phase-transfer (CAPT) and C_2-symmetric chiral phosphoric acid-derived counterions, this strategy had been successfully applied to a variety of asymmetric halogenation reactions.[40] We posited this strategy could be well-suited for the bromination step to deliver *Br*-**4a** with stereodivergency. The approach also brings the advantage of low background reactivity in analogy to conventional chlorination chemistry—the brominating reagent is an insoluble solid, effectively isolating it from the substrate in solution. Thus, the brominating reagent only comes into solution upon salt metathesis with the phosphate anion catalyst, resulting in a soluble chiral ion pair and initiating reactivity. Moreover, we were stimulated by the success of Akiyama in applying C_2-symmetric chiral phosphoric acid catalysts to atroposelective biaryl desymmetrizations with conventional electrophilic halogenating reagents.[41]

The CAPT strategy thus examined the efficacy of DABCOnium salts as brominating reagents in terphenyl system **3**. Building on the utility of these reagents in the enantioselective bromocyclization of difluoroalkenes,[42] we surmised that analogous conditions could be directly applied to atroposelective electrophilic bromination of phenols. Notably, these DABCOnium-based reagents provided an additional parameter to optimize the stereoselectivity of the bromination event. A screen of several distinct salts revealed

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that $[(DAB)_2Br(BF_4)_3]$ (Scheme 4, abbreviated as $[Br]^+$) was a judicious choice for catalyst-controlled modulation of diastereoselectivity (see Supporting Information for details). Thus, following the **P3**-catalyzed ring-opening of **3a**, we treated the unpurified intermediate with (*S*)-TRIP (10 mol %) as the phase transfer catalyst and DABCOnium salt $[(DAB)_2Br(BF_4)_3]$, which delivered the two-axis terphenyl product *Br*-**4a** in 60% yield, 2.5:1 dr, and with excellent enantioenrichment (98:2 er; Scheme 4a, to the right). We again attribute this overall enhancement in er to the differential functionalization rates of the enantiomers of the ring-opened phenol, in analogy to the kinetic resolution process described in Scheme 1. Strikingly, and in line with our goals, the diastereoselectivity can be overturned by swapping the chirality of the phase transfer catalyst. Employing (*R*)-TRIP in the bromination step affords *Br*-**4a′** in 82% yield, 6.8:1 dr, and excellent enantiopurity (99:1 er; Scheme 4a, to the left). We also assessed the CAPT strategy on substrates that performed less efficiently in chlorination. Importantly, subjecting 2-naphthyl-substituted lactone **3e** to the same ring-opening and bromination sequence with (*S*)-TRIP as the phase transfer catalyst yielded *Br*-**4e** in 64% yield with 1.4:1 dr and improved enantioselectivity relative to the chlorinated variant (94:6 er; Scheme 4b, to the right). As with *Br*-**4a**, diastereodivergence could be achieved by swapping the stereochemistry of the catalyst to (*R*)-TRIP, furnishing the opposite diastereomer *Br*-**4e′** in 83% yield, albeit with a modest 3.7:1 dr but with excellent enantioenrichment (98:2 er; Scheme 4b, to the left). Despite the clear mechanistic differences between the chlorination and bromination reactions, they are complementary in allowing stereodivergent access to either chlorinated or brominated products, offering access to all stereoisomers of linear terphenyls of type **4** and with excellent enantiopurity throughout the series.

CONCLUSIONS

In summary, we report conditions to synthesize two-axis atropisomers with access to all possible diastereomers with catalyst control. We demonstrated complementary approaches to chlorinated and brominated terphenyls in excellent enantiopurity. In our studies, we developed a new class of strongly Brønsted basic guanidine peptide catalysts, which can be useful in targeting challenging transformations, such as the ring-opening and chlorination described in this work. As these two distinct reactions are both catalyzed by the guanidine moiety, we also established the possibility that a unique catalyst can afford appreciable levels of control for these two mechanistically distinct reactions in this sequence. Alongside these studies on chlorination, we established conditions for an atroposelective phosphoric-acid-catalyzed diastereodivergent bromination through the CAPT strategy. In both the peptidyl-guanidine-catalyzed reactions and in the C_2-symmetric phosphoric-acid-catalyzed reactions, not only were high levels of enantioselectivity achieved but also both catalytic approaches were found to be capable of overcoming and reversing the intrinsic, substrate-controlled diastereoselectivity. Taken together, this combination of approaches accomplishes comprehensive and controlled stereodivergent access to all possible diastereomers of the targeted terphenyl scaffolds. The catalyst-controlled, stereodivergent synthesis of multiaxis atropisomers remains a challenging endeavor but seems likely to increase in importance as capabilities grow and as appreciation of their properties expands in interdisciplinary contexts.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c08057.

Experimental details, characterization, and X-ray crystallographic data (PDF)
NMR files (ZIP)
X-ray data for (*aS*,*aR*)-**4b** (CIF)
X-ray data for (*aR*,*aS*)-**4b** (CIF)

AUTHOR INFORMATION

Corresponding Authors

Scott J. Miller − *Department of Chemistry, Yale University, New Haven, Connecticut 06520, United States;* orcid.org/0000-0001-7817-1318; Email: scott.miller@yale.edu

F. Dean Toste − *Department of Chemistry, University of California, Berkeley, California 94720, United States;* orcid.org/0000-0001-8018-2198; Email: fdtoste@berkeley.edu

Authors

Omar M. Beleh − *Department of Chemistry, Yale University, New Haven, Connecticut 06520, United States;* orcid.org/0000-0001-8927-5382

Edward Miller − *Department of Chemistry, University of California, Berkeley, California 94720, United States;* orcid.org/0000-0002-2842-9330

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c08057

Notes

The authors declare no competing financial interest.

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