Article

Enantioselective Intermolecular C–O Bond Formation in the Desymmetrization of Diarylmethines Employing a Guanidinylated Peptide-Based Catalyst

Alex J. Chinn, Byoungmoo Kim, Yongseok Kwon, and Scott J. Miller

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.7b11197 • Publication Date (Web): 08 Nov 2017

Enantioselective Intermolecular C–O Bond Formation in the Desymmetrization of Diarylmethines Employing a Guanidinylated Peptide-Based Catalyst

Alex J. Chinn, Byoungmoo Kim, Yongseok Kwon and Scott J. Miller*

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

Supporting Information Placeholder

ABSTRACT: We report a series of enantioselective C–O bond cross-coupling reactions based on remote symmetry breaking processes in diarylmethine substrates. Key to the chemistry are multifunctional guanidinylated peptide-based ligands that allow highly selective, intermolecular Cu-catalyzed cross-coupling of phenolic nucleophiles. The scope of the process is explored, demonstrating efficiency for substrates with a range of electronic and steric perturbations to the nucleophile. Scope and limitations are also reported for variation of the diarylmethine. While the presence of an intervening *t*Bu-group is found to be optimal for maximum enantioselectivity, several other substituents may also be present such that appreciable selectivity can be achieved, providing an uncommon level of scope for diarylmethine desymmetrizations. In addition, chemoselective reactions are possible when phenolic hydroxyl groups within substrates that contain a second reactive site, setting the stage for applications in diverse complex molecular settings.

Introduction

Enantioselective cross-coupling reactions have become an established method for synthesizing chiral compounds. The most prevalent examples involve the formation of C–C bonds to generate point or axial chirality.[1] The creation of stereogenic C–O bonds by cross-coupling, in comparison, is under developed. In fact, the only presently reported examples are intramolecular.[2] For example, Cai recently reported the elegant desymmetrization of 1,3-diols with this approach.[3] Beaudry also described a fascinating atroposelective Cu-catalyzed macrocyclization (Figure 1a) wherein an axis of chirality was set due to hindered bond rotation about the diarylether.[4] The design of new asymmetric C–O bond-forming reactions must take into consideration the divalency of the *O*-atom involved. That is, on its own the *O*-atom is not necessarily a stereogenic center. However, C–O bond forming cross-coupling reactions may be enantioselective in a broader molecular context. For example, in addition to the symmetry-breaking reactions of Cai, we showed that remote functionalizations such as the reaction of **1** to give **2** (Figure 1b) can also create a stereogenic center.[5] We now report in this study a family of reactions that combine the unusual situation of enantioselective C–O bond forming cross-coupling reactions within the also challenging context of remote asymmetric induction. Herein, we describe symmetry-breaking reactions of diarylmethines such as **3** to give chiral diarylethers like **4** with significant levels of enantiocontrol (Figure 1c). These reactions, to the best of our knowledge, represent the first reports of metal-catalyzed, enantioselective C–O bond cross-coupling that involve intermolecular reactions.

We chose to pursue these reactions for the synthesis of unsymmetrical diarylmethine compounds, in part due to their relevance as pharmacological agents.[6] In addition, they provide scaffolds to explore reactions that break symmetry in mechanistically distinct ways.[7] One type of diarylmethine desymmetrization reaction involves bond formation proximal to the pro-stereogenic methine center, wherein a catalyst interacts explicitly with the pro-chiral center.[8] Oftentimes, these elegant processes possess a requirement for a directing group (eq 1a), or other specific substituent such as a silyl ether at the intervening prostereogenic center (eq 1b).[9] Even in rare cases where the intervening prostereogenic center is varied (eq 1c), proximal functionalization is the norm.[10] When the enantiotopic site is further removed from the pro-chiral center and when it lacks the

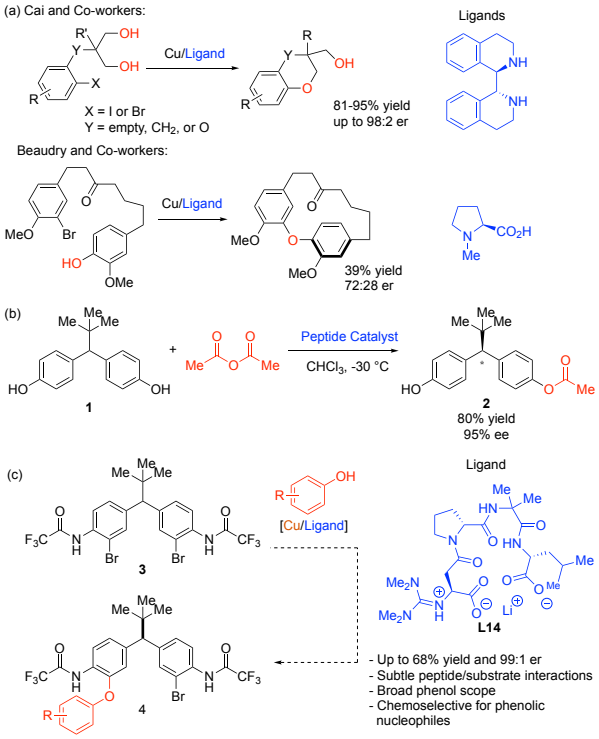
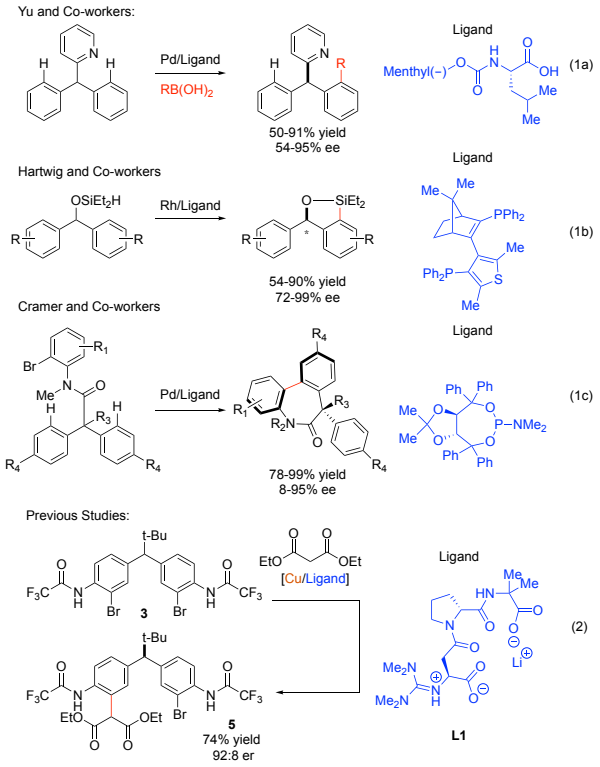


Figure 1. (a) Precedent for enantioselective intramolecular C–O bond forming cross-coupling. (b) Enantioselective acylation of bis(phenol) with remote, enantiotopic sites. (c) Present study: Desymmetrization through remote Cu-catalyzed cross-coupling for intermolecular C–O bond formation.

obvious potential to serve as a catalyst-ligating functional group, it becomes less intuitive how a chiral catalyst might differentiate among the enantiotopic sites. Nonetheless, one strategy that has emerged for the enantioselective synthesis of these molecules is catalytic desymmetrization, wherein peptide-based catalysts are employed to achieve remote site-differentiation. In addition to the organocatalytic acylation of diarylmethinyl bis(phenol) **1** shown in Figure 1b,[5] we recently showed that desymmetrization of **3** was possible through copper-catalyzed cross-coupling of malonyl nucleophiles when guanidinylated peptides such as **L1**are used as ligands (eq 2).[11] As we

show below, exploration of the complementary C–O bond forming desymmetrization reveals a

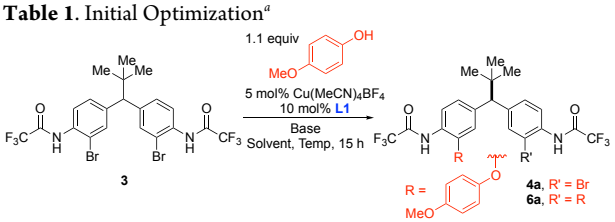


surprising generality of the guanidinylated peptide ligands. Notably, this class of ligand had not been reported for transition metal catalysis prior to our initial study. Several critical facets of this new study are: (a) subtle but significant features within the peptide-based ligand such as the length and stereochemical array of the peptide, (b) generality of the oxygen nucleophile that may be employed, including reasonable tolerance of steric bulk, (c) appreciable scope, but also some documented limitations, for substituents on the intervening pro-stereogenic carbon atom of the diarylmethine, (d) reliable chemoselectivity for phenol-based functionality in substrates that possess more than one *O*-based nucleophilic site, and (e) *O*-selectivity over potentially competitive *N*-reactivity within a bifunctional substrate.

Results and Discussion

Initial optimization. We began our studies with reaction conditions that were previously shown to be successful in the desymmetrization of **3** through C–C bond formation. These proved a useful starting place, as we observed modest conve- rsion to the desired mono-coupled product **4a**, with good enantioselectivity at room temperature (Table 1, entry 1; 26% conv., 89:11 er). We then confirmed through a solvent screen that a DMF/Tol solvent mixture was more effective than other solvents in terms of promoting the enantioselective formation of **4a**. For example, the reaction did not proceed in toluene, DCM or dioxane at room temperature, and lower conversions were observed in DMF, THF and MeCN (Table 1, entries 2–7). Variation of the base revealed that K_3PO_4 led to slightly higher enantioselectivity (Table 1, entry 8; 92:8 er), while K_2CO_3 resulted in no reaction (Table 1, entry 9). We then learned that the reaction could deliver higher levels of conversion to **4a** without significant loss in enantioselectivity through conducting the reaction at elevated temperatures (Table 1, entries 10–12; up to 45% conv., 91:9 er). However, careful analysis of the reaction mixtures revealed side products of the reaction to be **7** and **8** (eq 3); each seemed to originate from small amounts of water in the reaction mixture, which could either serve as the cross-coupling

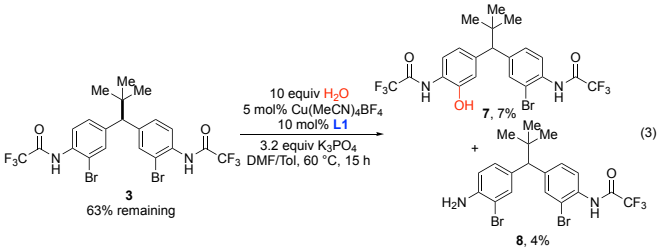
Table 1. Initial Optimization[a]



Entry	Solvent	Temp. (°C)	Base (equiv)	3 % Remaining[b]	4a % Yield[b]	6a % Yield[b]	er[c]
1	DMF/Tol (1:2)	rt	Cs_2CO_3 (3.2)	68	26	0	89:11
2	Tol	rt	Cs_2CO_3 (3.2)	98	0	0	n/a
3	DCM	rt	Cs_2CO_3 (3.2)	100	0	0	n/a
4	Dioxane	rt	Cs_2CO_3 (3.2)	98	0	0	n/a
5	DMF	rt	Cs_2CO_3 (3.2)	77	18	0	85:15
6	THF	rt	Cs_2CO_3 (3.2)	85	9	0	90:10
7	MeCN	rt	Cs_2CO_3 (3.2)	70	22	0	83:17
8	DMF/Tol (1:2)	rt	K_3PO_4 (3.2)	76	22	0	92:8
9	DMF/Tol (1:2)	rt	K_2CO_3 (3.2)	100	0	0	n/a
10	DMF/Tol (1:2)	40	K_3PO_4 (3.2)	72	33	1	91:9
11	DMF/Tol (1:2)	60	K_3PO_4 (3.2)	40	45	3	91:9
12	DMF/Tol (1:2)	80	K_3PO_4 (3.2)	12	40	12	91:9
13	MeCN	40	K_3PO_4 (4.0)	60	30	2	90:10
14	MeCN	45	K_3PO_4 (4.0)	35	56	5	91:9
15	MeCN	50	K_3PO_4 (4.0)	31	55	6	91:9
16	MeCN	60	K_3PO_4 (4.0)	16	59	12	92:8

[a]Reported results are the average of two trials. Reaction conditions: **3** (0.2 mmol), 4-methoxyphenol (1.1 equiv), $Cu(MeCN)_4BF_4$ (5 mol %), peptide (10 mol %), base (see above), and solvent (0.8 mL). [b]Yield was determined using ^1H NMR by comparing to an internal NMR standard (1,4-bis(trimethylsilyl)benzene). [c]Enantiomeric ratios were determined using chiral HPLC analysis. The absolute configuration is currently unknown and enantiomers of **4a** are drawn arbitrarily.

partner (i.e., to give **7**) or as a hydrolytic agent (i.e., to give **8**).[12] Indeed, when reactions were deliberately carried out in the presence of H_2O (10 equiv) notable quantities of phenol **7** and aniline **8** were observed (eq 3). Gratifyingly, conducting the reactions in MeCN with rigorous exclusion of moisture at elevated temperatures resulted in cleaner reactions such that good conversions to **4a** could be obtained, without loss of enantioselectivity (Table 1, entries 13–16). For example, when the reaction was conducted at 60 °C, **4a** could be observed in 59% with 92:8 er (entry 16).



Peptide Optimization Various additional aspects of optimization were carried out, culminating in reactions conducted at 45 °C, in MeCN with 1.1 equiv of nucleophile relative to **3**, and catalyst loading of 10 mol % (1:2, Cu/ligand).[13] Among the most interesting aspects of these studies was the evaluation of different peptide-based ligands (Table 2). These studies were driven by hypotheses that built on earlier observations in the catalysis of C–C bond forming cross-coupling reactions. As shown in Figure 2, our thinking about the attributes of guanidinylated peptides in Cu-catalyzed cross-coupling builds upon models wherein the nature of the *C*-terminus of the peptide proved critical for ensuring communication between the

catalyst and substrate through a distal interaction with the remote arene ring and a cationic species such as Cs^+ or K^+.[11] Given the new reaction media for the enantio-

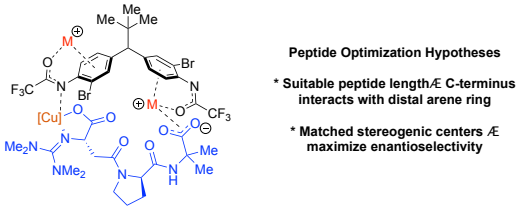


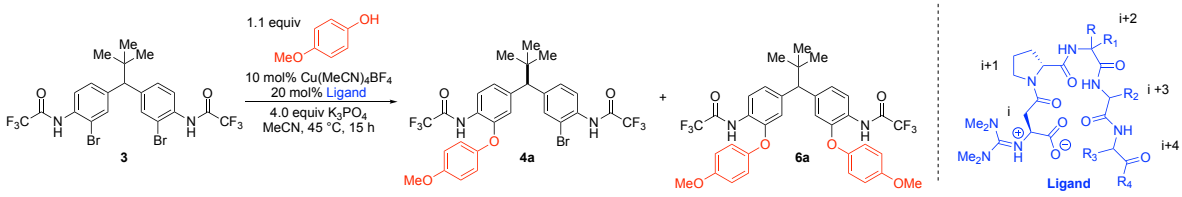
Figure 2. Proposed Catalyst and Substrate Interactions

selective C–O bond formation, we speculated that the peptide ligands could adopt different secondary structures that effect the distal cation-π interaction and, ultimately, enantioselectivity. As such, our ligand screen was designed to assess (a) a suitable peptide length for ensuring optimal interactions, and (b) explore stereochemical arrays within the peptide sequence to achieve maximum levels of enantioselectivity. Of all of the *i*+2 residues examined (Table 2, entries 1–6), aminoisobutyric acid (Aib) was found to be optimal both in 2, entries 1–6), aminoisobutyric acid (Aib) was found to be optimal both in terms of reactivity and enantioselectivity (65% conv., 94:6 er. Table 2, entry 1). This finding is consistent with our observations from previous studies. However, in contrast to those studies, peptides with –OMe and –NHMe *C*-terminal caps showed comparable enantioselectivity values to peptides with a *C*-terminal carboxylate (Table 2, entries 7–8). These catalysts appear to be more active than carboxylate-based catalysts as they lead to a higher total level of conversion, when considering the sum of mono- and di-coupled products, which likely impacts the observed er value. This possibility will be discussed further below (Scheme 1).

While examining the effect of peptide length on catalytic activity, it was found that the truncated dipeptide ligand **L9** (Table 2, entry 9) demonstrated a notable decrease in enantioselectivity, while the elongated pentapeptide ligand **L10** (Table 2, entry 10) showed similar selectivity to **L1** (Table 1, entry 1). However, tetrapeptide ligands (Table 2, entries 12–15) afforded higher levels of enantioselectivity than any other length of peptide that we examined, and we settled upon these for further studies. Intriguingly, these tetrapeptide ligands demonstrated an unusual insensitivity to the identity of the *i*+3 residue. Peptides **L12** and **L13** (Table 2, entries 12–13), which contain opposite enantiomers of the alanine residue at the *i* + 3 residue, perform nearly identically in the reaction (~61% yiled by NMR, 96:4 er). This result is particularly interesting given that heterochirality between a defined secondary structures which in turn can affect catalysis.[14,15] This result is perhaps more striking when compared with **L11**, which demonstrates the importance of the *i* residue's stereo-configuration. Varying this stereocenter reversed enantioselectivity relative to epimeric ligand **L10**, in addition to a reduction in the absolute selectivity with an er value of 34:66 (Table 2, entry 11). Based on this result, it seems that heterochirality between the *i* and the *i*+1 position is important for effective catalysis. Other substitutions at the *i*+3 position also provided **4a** with good yields (Table 2, entries 12-15), and high enantioselectivity. Ultimately, **L14** was selected as the premier ligand for the remaining experiments, given that the level of conversion to the desired mono-coupled product **4a** is higher than other tetrapeptide catalysts. the *i*+1 and the *i*+3 residue often biases peptide sequences towards a defined secondary structures which in turn can affect catalysis.[14,15] This result is perhaps more striking when compared with **L11**, which demonstrates the importance of the *i* residue's stereo-configuration. Varying this stereocenter reversed enantioselectivity relative to epimeric ligand **L10**, in addition to a reduction in the absolute selectivity with an er value of 34:66 (Table 2, entry 11). Based on this result, it seems that heterochirality between the *i* and the *i*+1 position is important for effective catalysis. Other substitutions at the *i*+3 position also provided **4a** with good yields (Table 2, entries 12-15), and high enantioselectivity. Ultimately, **L14** was selected as the premier ligand for the remaining experiments, given that the level of conversion to the desired mono-coupled product **4a** is higher than other tetrapeptide catalysts.

Kinetic Resolution Studies. During these studies, it became apparent that er values were conversion dependent in part due to a

Table 2: Optimization of Peptide Sequence and Length[a]

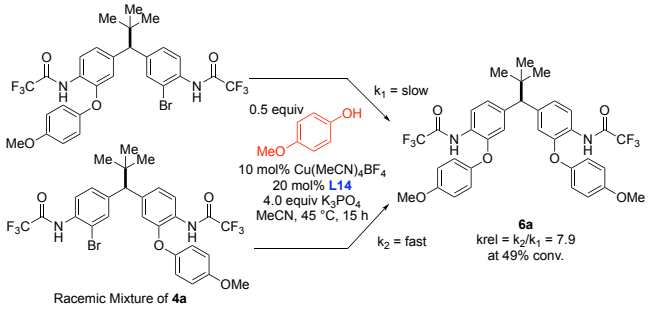


Entry	Ligand	i	i+1	i+2	i+3	i+4	3 % Remaining[b]	4a %Yield[b]	6a % Yield[b]	er[c]
1	**L1**	TMG-Asp	D-Pro	Aib-OLi	-	-	16	65	13	94:6
2	**L2**	TMG-Asp	D-Pro	Cle-OLi	-	-	23	62	8	93:7
3	**L3**	TMG-Asp	D-Pro	D-Ala-OLi	-	-	19	61	11	92:8
4	**L4**	TMG-Asp	D-Pro	Gly-OLi	-	-	22	62	9	92:8
5	**L5**	TMG-Asp	D-Pro	Acpc-OLi	-	-	27	58	6	93:7
6	**L6**	TMG-Asp	D-Pro	Ala-OLi	-	-	21	60	8	93:7
7	**L7**	TMG-Asp	D-Pro	Aib-OMe	-	-	6	52	18	95:5
8	**L8**	TMG-Asp	D-Pro	Aib-NHMe	-	-	9	59	20	95:5
9	**L9**	TMG-Asp	D-Pro-OLi	-	-	-	29	58	6	90:10
10	**L10**	TMG-Asp	D-Pro	Aib	D-Ala	D-Ala-OLi	23	60	9	94:6
11	**L11**	TMG-D-Asp	D-Pro	Aib	D-Ala	D-Ala-OLi	27	57	15	34:66
12	**L12**	TMG-Asp	D-Pro	Aib	D-Ala-OLi	-	15	61	9	96:4
13	**L13**	TMG-Asp	D-Pro	Aib	Ala-OLi	-	13	61	9	96:4
14	**L14**	TMG-Asp	D-Pro	Aib	D-Leu-OLi	-	13	67	8	96:4
15	**L15**	TMG-Asp	D-Pro	Aib	D-Phe-OLi	-	15	65	9	96:4

[a]Reported results are the average of two trials. Reaction conditions: **3** (0.2 mmol), 4-methoxyphenol (1.1 equiv), $Cu(MeCN)_4BF_4$ (10 mol %), peptide (20 mol %), K_3PO_4 (4.0 equiv), and MeCN (0.8 mL), 45 °C [b]Yield was determined using ^1H NMR by comparing to an internal NMR standard (1,4-bis(trimethylsilyl)benzene). [c]Enantiomeric ratios were determined using chiral HPLC analysis. [d]Abbreviations: TMG, tetramethylguanidine; Aib, α-aminoisobutyric acid; Cle, cycloleucine (1-aminocyclpentane-1-carboxylic acid); Acpc, 1-amino-cyclopropane-1-carboxylic acid

catalyst's ability to perform a kinetic resolution on mono-coupled product **4a**,[16] effectively increasing the observed er. In these cases, there is a correlation between enantioselectivity and the degree of over-conversion to the bis-coupled product **6a**. In order to directly assess the possibility a of kinetic resolution, we showed that when racemic **4a** was subjected to the reaction conditions employing the tetrapeptide catalyst derived from **L14**, a significant k_{rel} value of 7.9 was measured (Scheme 1). Indeed, the slow reacting enantiomer in Scheme 1 was found to match the major enantiomer from the previous experiments, verifying the presence of a secondary resolution. This result could explain the higher er values observed for **L7** and **L8** (Table 2, entries 7 and 8) as these reactions gave higher yields of **6a**. With this in mind, several trials were run with increased equivalents of nucleophile in an attempt to increase levels of both overall conversion and er values (see SI). Interestingly, while no notable increase in er was observed, an enhancement in yield of the mono coupled product was obtained.[17] As the medium is constantly changing while these reactions proceed, it is possible that the degree of kinetic resolution in an independent experiment is mostly a qualitative, rather than a quantitative, indicator of an additional factor leading to the observed levels of enantioselectivity.

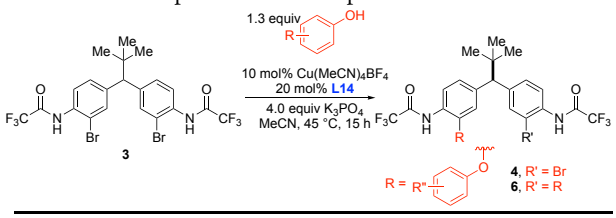
Scheme 1. Kinetic Resolution of a Racemic mixture of **4a**

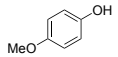
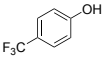
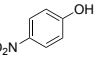
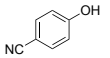
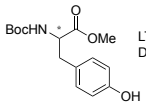


*As the absolute stereochemistry is currently unknown, enantiomers were drawn arbitarily.

***O*-Nucleophile Substrate scope.** With optimized conditions and a ligand associated with both high levels of conversion and enantioselectivity in hand, we began to explore the scope of phenols that could be subjected to effective cross-coupling under these conditions. An electron rich phenol (Table 3, entry 1; 96:4 er), an electron neutral phenol (Table 3, entry 2, 94:6 er), and an electron poor phenol (Table 3, entry 3; 93:7 er) all react smoothly to give products **4a-c** with high enantioselectivity. While 4-nitrophenol (Table 3, entry 4) is unreactive, other substitutions are well tolerated. For example, 4-cyanophenol (Table 3, entry 5) allows **4e** to be observed with a 92:8 er after being produced in 53% yield as well as 3-hydroxypyridine which gives **4f** with excellent enantioselectivity and yield (Table 3, entry 6; 97:3 er, at 63% yield). 4-Bromophenol also proves an interesting substrate, demonstrating high chemoselectivity, as no coupling is observed involving the bromine on the 4-bromophenol (Table 3, entry 7; **4g**, 67% yield, 97:3 er). Both Boc-L-Tyr-OMe and Boc-D-Tyr-OMe give comparably high levels of enantioselectivity and reactivity under the reaction conditions, highlighting a tolerance of different stereochemical arrays on the nucleophile (Table 3, entries 8a and 8b respectively; **4h**, 59% yield, 96:4 er; **4i**, 64% yield, 95:5 er). In an attempt to expand the substrate scope, allyl alcohol was subjected to the reaction conditions (Table 3, entry 9). While only 13% of the desired coupled **4j** is observed, it is nonetheless obtained with essentially total enantioselectivity (>99:1 er). We then turned our attention to more sterically hindered phenols. Notably, palladium-catalyzed reactions have proven effective for cross-coupling of hindered phenols,[18] but these substrates have remained challenging for Cu-catalyzed cross-coupling.[19] 1-Naphthol turned out to be an excellent substrate, such that **4k** is

Table 3. *O*-Nucleophile Substrate Scope[a]



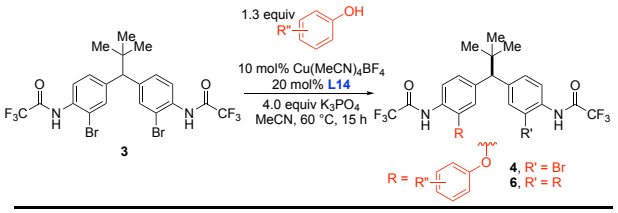
Entry	Nucleophile	3% Remaining[b]	4% Yield[b,c]	6% Yield[b,c]	er[d]
1		10	**4a**, 71 (68)	**6a**, 15 (15)	96:4
2[e]		16	**4b**, 66 (23)	**6b**, 7 (5)	94:6
3		16	**4c**, 61 (41)	**6c**, 13 (5)	93:7
4		90	**4d**, 0	**6d**, 0	n/a
5		18	**4e**, 53 (45)	**6e**, 20 (3)	92:8
6[f]		2	**4f**, 63 (63)	**6f**, 32 (23)	94:6
7		5	**4g**, 67 (66)	**6g**, 21 (17)	97:3
8a 8b		LTyr 9 DTyr 14	**4h**, 59 (49) **4i**, 64 (56)	**6h**, 7 (6) **6i**, 13 (7)	96:4 95:5
9		1	**4j**, 13 (8)	**6j**, 0	>99:1

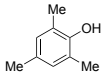
[a]Reported results are the average of two trials. Reaction conditions: **3** (0.2 mmol), nucleophile (1.3 equiv), $Cu(MeCN)_4BF_4$ (10 mol %), peptide (20 mol %), K_3PO_4 (4.0 equiv), and MeCN (0.8 mL), 45 °C (except for entry 8, which was performed at 60 °C). [b]Yield was determined using ^1H NMR by comparing to an internal NMR standard (1,4-bis(trimethylsilyl)benzene). [c]The numbers in parentheses are isolated yields. [d]Enantiomeric ratios were determined using chiral HPLC analysis. [e]Products could not be isolated by the typical procedure. The crude mixture was debrominated following procedure 9 to give **S12** (see SI). NMR yields were determined before debromination. [f]Entry was run at 60 °C

obtained with 97:3 er and in 67% yield (Table 4, entry 1), suggesting that substitution at the *ortho* position of the phenolic hydroxyl group would be well-tolerated. As such, under the presently reported reaction conditions, both 2-phenylphenol and 2-*tert*-butylphenol undergo efficient cross-coupling with high enantioselectivity and only slightly diminished conversion (Table 4, entries 2 and 3 respectively; **4l**, 60% yield, 97:3 er; **4m**, 53% yield, 99:1 er). Even 2,4,6-trimethylphenol which contains *o,o'*-substituents undergoes coupling, although with decreased yields of **4n** (33%), but with substantial enantioselectivity (Table 4, entry 4, 97:3 er). Finally, 2,6-diisopropyl phenol exhibits similar behavior and **4o** is obtained in 18% yield with 96:4 er (Table 4, entry 5). These levels of enantioselectivity, even for such hindered substrates at modest levels of conversion, are auspicious for these demanding couplings.

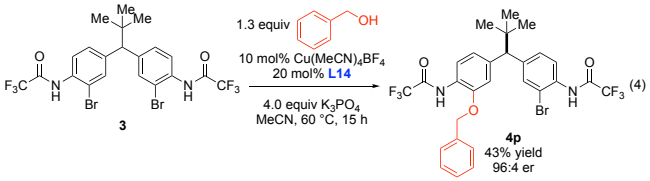
As a prelude to eventual applications in high-complexity molecular environments, we wondered if guanidinylated peptide-based catalysts could display a level of chemoselectivity when multiple nucleophiles were present. For example, if 4-hydroxybenzylalcohol was employed as a substrate, total selectivity could be observed at the phenolic site? As a benchmark, we found that at slightly higher temperatures (60 °C), benzyl alcohol can be employed as a substrate, and **4p** is isolated in 43% yield with 96:4 er (eq 4). Impressively, when 4-hydroxybenzyl alcohol is subjected to the normal reaction conditions of Table 4, the phenolic oxygen is found to couple almost exclusively over the benzyl alcohol, affording the coupled product **4q** in 65% yield, with 96:4 er (eq 5); **4r** is not observed in appreciable quantity. Similarly, when 5-hydroxyindole is employed as the nucleophile, a highly chemoselective C–O bond forming cross-coupling reaction is observed such that **4s** is observed in 38% yield with 98:2 er (eq 6). Notably, only trace amounts of **4t** are detected by LC/MS, and cannot be isolated, despite precedent for C–N bond forming Cu-catalyzed cross-coupling of indoles.[20] These results suggest that guanidinylated peptide ligands could have utility in selective cross-coupling in complex settings when multiple functional groups are present

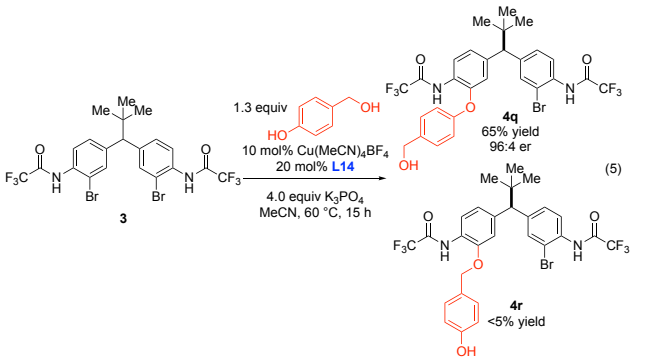
Table 4: Hindered Phenols[a]

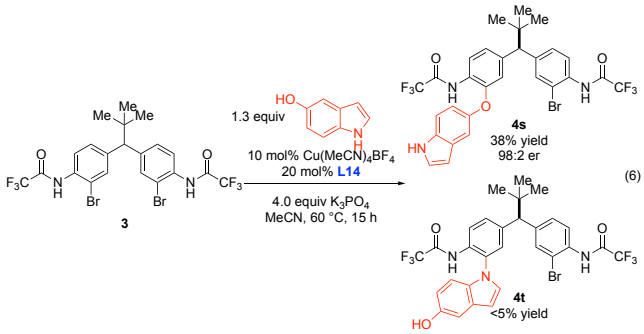


Entry	Phenol	3% Remaining[b]	4% Yield[b,c]	6% Yield[b,c]	er[d]
1		5	**4k**, 67 (50)	**6k**, 14 (9)	97:3
2		7	**4l**, 60 (43)	**6l**, 15 (14)	97:3
3		7	**4m**, 53 (43)	**6m**, 13 (8)	99:1
4		3	**4n**, 33 (33)	**6n**, 14 (6)	97:3
5		4	**4o**, 18 (10)	**6o**, 0	96:4

[a]Reported results are the average of two trials. Reaction conditions: **3** (0.2 mmol), phenol (1.3 equiv), $Cu(MeCN)_4BF_4$ (10 mol %), peptide (20 mol %), K_3PO_4 (4.0 equiv.) and MeCN (0.8 mL), 60 °C. [b]Yield was determined using ^1H NMR by comparing to an internal NMR standard (1,4-bis(trimethylsilyl)benzene). [c]The numbers in parentheses are isolated yields. [d]Enantiomeric ratios were determined using chiral HPLC analysis.





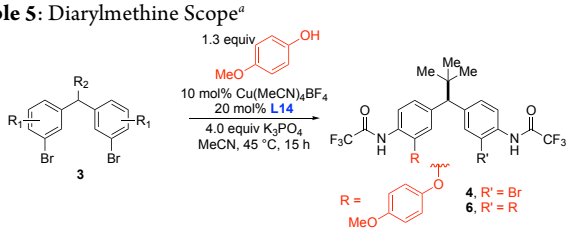


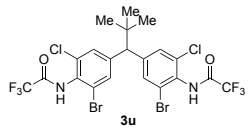
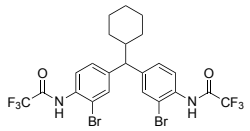
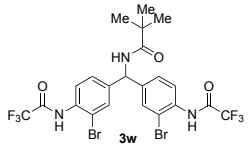
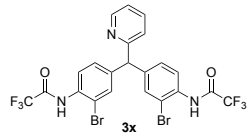
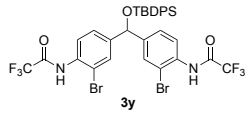
Finally, we explored the scope of the enantioselective C-O bond-forming desymmetrization for a set of alternative diarylmethines (Table 5). As noted in our introduction, venerable diarylmethine desymmetrizations are often reported with limited scope at the pro-stereogenic center,[8-10] and thus it was of considerable interest to explore this question. We thus examined both conservative and more aggressive changes to the high-performing substrate **3**. As shown in Table 5 (entry 1), symmetrical diarylmethane **3u**, bearing additional Cl-substituents, was found to be an excellent substrate, allowing formation of **4u** in 65% yield with a 95:5 er. As a more "conservative" substrate, this reaction does reveal important chemoselectivity for enantioselective C-O bond cross-couplimg at C-Br bonds, rather than C-Cl bonds. In addition, replacement of the *t*Bu group of **3** with a cyclohexyl substituent (i.e. **3v**, Table 5, entry 2) is reasonably well tolerated, as **4v** may be isolated in 57% yield, with a 91:9 er. Examination of an amide-bearing diarymethine (**3w**, Table 5, entry 3) led to a significant decrease in enantioselectivity, with **4w** isolated in modest yield, and 73:27 er. Compounds with an intervening pyridyl ring (**3x**) or a TBDPS-ether (**3y**) did not undergo enantioselective desymmetrization, however, with nearly racemic mono-coupled products observed (Table 5, entries 4 and 5). These findings suggest that the catalyst system developed with ligand **L14** allows excellent scope in terms of the phenol coupling partner, but a more modest – although still significant – scope at the diarylmethine moiety, perhaps at a level comparable or beyond previously reported diarylmethine desymmetrizations.

We conclude our results and discussion with an example that harkens back to our originally stated ambition of remote desymmetrization during diarylmethane desymmetrization. While many of the examples above extend the field beyond *ortho*-functionalization to include many examples of enantioselective *meta*-functionalization, with many er values well into the 90's, what of the more challenging enantioselective

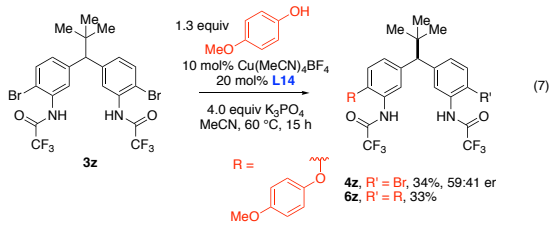
para-functionalization? Such an example was attempted with substrate **3z** (eq 7), with the positions of the Br-atom and the TFA-amide switched. While compound **3z** was prepared, it was found to undergo the cross-coupling with a low level (59:41 er) of enantioselectivity under the optimized conditions developed for the more successful substrates (up to >98:2 er). This observation, while synonymous with a disappointing outcome, harkens back to our current understanding of remote asymmetric induction, which seems to be increasing at an incremental pace.

Table 5: Diarylmethine Scope[a]



Entry	Substrate	3% Remaining[b]	4% Yield[b,c]	6% Yield[b,c]	er[d]
1	 **3u**	17	**4u**, 65 (61)	**6u**, 15 (13)	95:5
2	 **3v**	12	**4v**, 57 (57)	**6v**, 20 (9)	91:9
3[e]	 **3w**	9	**4w**, 54 (36)	**6w**, 38 (31)	73:27
4	 **3x**	5	**4x**, 29 (18)	**6x**, 37 (30)	55:45
5	 **3y**	11	**4y**, 26 (24)	**6y**, 13 (10)	54:46

[a]Reported results are the average of two trials. Reaction conditions: **3** (0.2 mmol), phenol (1.3 equiv), $Cu(MeCN)_4BF_4$ (10 mol %), peptide (20 mol %), K_3PO_4 (4.0 equiv.) and MeCN (0.8 mL), 45 °C. [b]Yield was determined using ^1H NMR by comparing to an internal NMR standard (1,4-bis(trimethylsilyl)benzene.methine). [c]The numbers in parentheses are isolated yields. [d]Enantiomer ratios were determined using chiral HPLC analysis. [e] Reaction conditions: **3** (0.05 mmol), phenol (1.3 equiv), $Cu(MeCN)_4BF_4$ (20 mol %), peptide (40 mol %), K_3PO_4 (4.0 equiv.) and MeCN (0.8 mL), 35 °C



(7)

Conclusion

In summary, we have reported herein a guanidinylated peptide ligand/Cu-based system for the unusual process of enantioselective C–O bond forming cross-coupling reactions. A critical feature of the system is a symmetry-breaking reaction of remote sites within diarylmethine derivatives. At the heart of the selectivity is significant enantiotopic group differentiation, influenced by the length and stereochemical array of the peptide ligand, and a modicum of kinetic resolution that occurs as the product reacts further. A significant scope of phenolic nucleophiles is also reported that reveals tolerance of a range of electronically tuned substituents, as well as considerable steric hindrance. Multifunctional substrates were also demonstrated to participate in the reaction in a manner that supports the predictable functionalization of phenols in the presence of other nucleophilic functional groups, foreshadowing potential applications in complex molecular settings. The scope of the process with respect to the symmetrical diarylmethines, under the auspices of guanidinylated peptide ligand **L14**, was also examined. Aryl chloride substitution is found to be inert in the presence of aryl bromides, and steric demands below that of *t*Bu are well-tolerated at the methine moiety. An intervening amide presents a somewhat intermediate case, while other substituents were not compatible with a highly selective outcome. As an initial status report for this previously unknown, intermolecular enantioselective cross-coupling process, these findings are encouraging. Yet, they beg the questions of further ligand development, and deeper understanding of the general process of remote asymmetric induction, and even of the diarylmethine topological landscape.

ASSOCIATED CONTENT

Supporting Information: The Supporting Information is available free of charge on the ACS Publications website. Experimental methods, characterization of all compounds, and copies of spectra can be found in the Supporting Information.

ACKNOWLEDGMENT

We are grateful to Dr. Daniel R. Fandrick and Dr. Chris H. Senanayake (Boehringer-Ingelheim), Dr. Robert A. Singer (Pfizer) and Dr. Craig A. Parrish and Dr. Shane W. Krska (Merck) for their support and interest in this research. Primary support for this project came from the National Institute of General Medical Science of the National Institutes of Health (GM-068649), for which we are grateful.

AUTHOR INFORMATION

Corresponding Author: scott.miller@yale.edu

REFERENCES

(1) (a) Yang, H.; Yang, X. T.; Tang, W. J. *Tetrahedron* **2016**, *72*, 6143-6174; (b) Choi, J.; Fu, G. C. *Science* **2017**, *356*; (c) Tellis, J. C.; Kelly, C. B.; Primer, D. N.; Jouffroy, M.; Patel, N. R.; Molander, G. A. *Acc. Chem. Res.* **2016**, *49*, 1429-1439; (d) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587-9652.

(2) (a) Zhou, F. T.; Cai, Q. *Beilstein J. Org. Chem.* **2015**, *11*, 2600-2615; (b) Hu, N.; Li, K.; Wang, Z.; Tang, W. *Angew. Chem. Int. Ed.* **2016**, *55*, 5044-5048.
(3) (a) Zhang, Y.; Wang, Q.; Wang, T.; He, H.; Yang, W.; Zhang, X.; Cai, Q. *J. Org. Chem.* **2017**, *82*, 1458-1463; (b) Yang, W.; Liu, Y.; Zhang, S.; Cai, Q. *Angew. Chem. Int. Ed.* **2015**, *54*, 8805-8808.
(4) Salih, M. Q.; Beaudry, C. M. *Org. Lett.* **2013**, *15*, 4540-4543.
(5) (a) Gustafson, J. L.; Sigman, M. S.; Miller, S. J. *Org. Lett.* **2010**, *12*, 2794-2797; (b) Lewis, C. A.; Gustafson, J. L.; Chiu, A.; Balsells, J.; Pollard, D.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 16358-16365; (c) 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. *J. Am. Chem. Soc.* **2006**, *128*, 16454-16455.
(6) (a) Cheltsov, A. V.; Aoyagi, M.; Aleshin, A.; Yu, E. C.-W.; Gilliland, T.; Zhai, D.; Bobkov, A. A.; Reed, J. C.; Liddington, R. C.; Abagyan, R. *J. Med. Chem.* **2010**, *53*, 3899-3906; (b) Huang, Z.; Ducharme, Y.; Macdonald, D.; Robichaud, A. *Curr. Opin. Chem. Biol.* **2001**, *5*, 432-438; (c) Kaplan, S. A.; Roehrborn, C. G.; Rovner, E. S.; Carlsson, M.; Bavendam, T.; Guan, Z. *J. Am. Med. Assoc.* **2006**, *296*, 2319-2328; (d) McRae, A. L.; Brady, K. T. *Exp. Opin. Pharmacother.* **2001**, *2*, 883-892; (e) Messaoudi, S.; Hamze, A.; Provot, O.; Treguier, B.; De Losada, J. R.; Bignon, J.; Liu, J.-M.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.-D.; Alami, M. *ChemMedChem* **2011**, *6*, 488-497.
(7) Harper, K. C.; Bess, E. N.; Sigman, M. S. *Nat. Chem.* **2012**, *4*, 366-374.
(8) (a) Chu, L.; Wang, X.-C.; Moore, C. E.; Rheingold, A. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 16344-16347; (b) Shi, B.-F.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 460-+; (c) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 4882-4886.
(9) Lee, T.; Wilson, T. W.; Berg, R.; Ryberg, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2015**, *137*, 6742-6745.
(10) Saget, T.; Cramer, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 7865-7868.
(11) (a) Kim, B.; Chinn, A. J.; Fandrick, D. R.; Senanayake, C. H.; Singer, R. A.; Miller, S. J. *J. Am. Chem. Soc.* **2016**, *138*, 7939-7945. (b) For pioneering studies of Cu-catalyzed cross-coupling reactions with amino acid-based ligands, see: Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450-1460.
(12) (a) Saphier, M.; Masarwa, A.; Cohen, H.; Meyerstein, D. *Eur. J. Inorg. Chem.* **2002**, 1226-1234; (b) Rusonik, I.; Cohen, H.; Meyerstein, D. *Dalton. Trans.* **2003**, 2024-2028.
(13) See supporting information, Table S1-S6 for full details
(14) Haque, T. S.; Little, J. C.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 6975-6985.
(15) (a) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601-610; (b) Metrano, A. J.; Abascal, N. C.; Mercado, B. Q.; Paulson, E. K.; Hurtley, A. E.; Miller, S. J. *J. Am. Chem. Soc.* **2017**, *139*, 492-516.
(16) (a) Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*; John Wiley & Sons, Inc.: 2007, p 249-330; (b) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5-26; (c) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525-1529.
(17) See supporting information, Table S12 for full details
(18) (a) Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 4321-4326; (b) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369-4378; (c) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224-3225.
(19) (a) Maiti, D.; Buchwald, S. L. *J. Org. Chem.* **2010**, *75*, 1791-1794; (b) Niu, J.; Zhou, H.; Li, Z.; Xu, J.; Hu, S. *J. Org. Chem.* **2008**, *73*, 7814-7817.
(20) (a) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684-11688; (b) Klapars, A.; Antilla, J. C.; Huang, X. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727-7729; (c) Zhu, L.; Cheng, L.; Zhang, Y.; Xie, R.; You, J. *J. Org. Chem.* **2007**, *72*, 2737-2743.

Abstract Figure