An Asymmetric Aromatic Finkelstein Reaction: A Platform for Remote Diarylmethane Desymmetrization

Tobias Morack[a], Tyler E. Myers[a], Lucas J. Karas[b], Melissa A. Hardy[b], Brandon Q. Mercado[a], Matthew S. Sigman[b]*, Scott J. Miller[a]*

[a]Department of Chemistry, Yale University, New Haven, Connecticut 06520-8107, United States

[b]Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, Utah 84112, United States

ABSTRACT: A first-of-its-kind enantioselective aromatic Finkelstein reaction is disclosed for the remote desymmetrization of diarylmethanes. The reaction operates through a copper-catalyzed C–I bond forming event and high levels of enantioselectivity are achieved through the deployment of a tailored guanidinylated peptide ligand. Strategic use of transition-metal mediated reactions enabled the chemoselective modification of the aryl iodide, thus, the synthesis of a diverse set of otherwise difficult-to-access diarylmethanes in excellent levels of selectivity is realized from a common intermediate. A mixed experimental/computational analysis of steric parameters and substrate conformations identifies the importance of remote conformational effects as a key to achieving high enantioselectivity in this desymmetrization reaction.

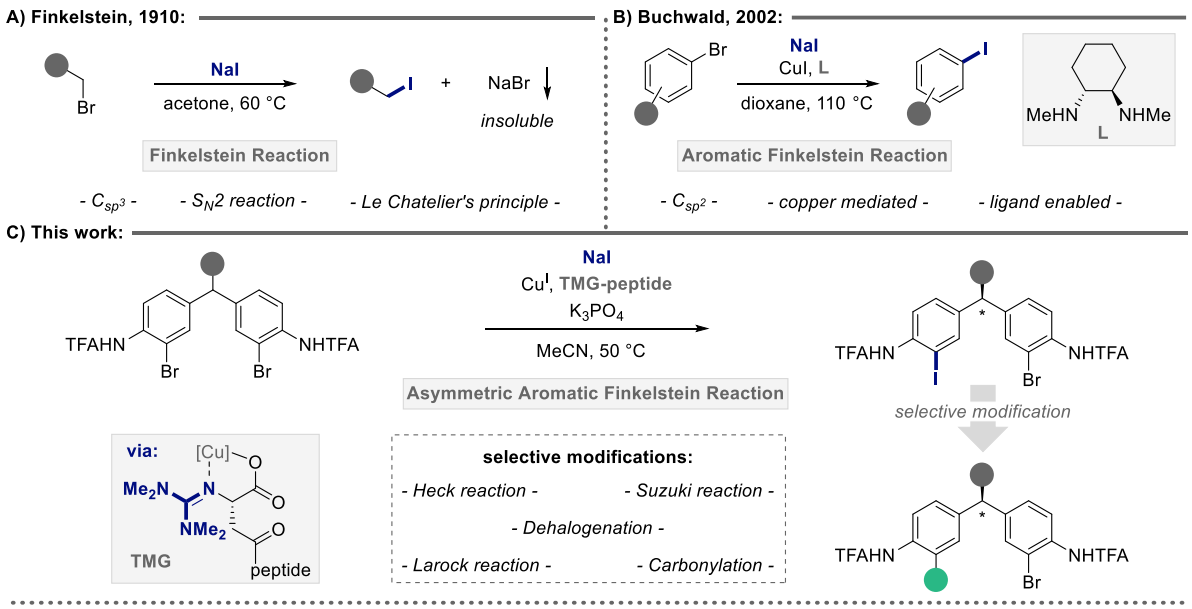
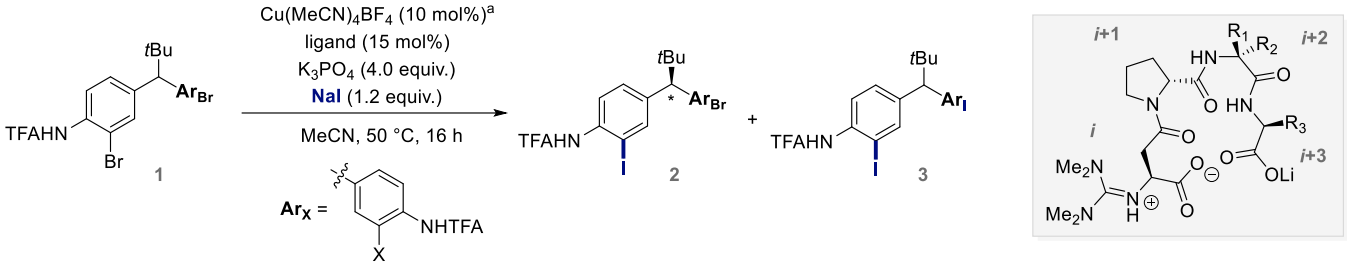


Figure 1. Development of an asymmetric aromatic Finkelstein reaction.

Since its discovery in 1910, the Finkelstein reaction has been synonymous with halide exchange for the preparation of primary alkyl iodides.[1-3] The substitution of alkyl bromides and chlorides under a well-defined S_N2 regime[4-5] and the elegant exploitation of Le Chatelier's principle to drive the reaction by precipitation of NaBr or NaCl have rendered the Finkelstein reaction a classic in introductory organic chemistry textbooks and a reliable tool for organic synthesis (Figure 1A).[6-8] While halide exchange in aryl halides is also precedented,[9-10] it took nearly a century following Finkelstein's discovery, until Buchwald's report on the copper-catalyzed aromatic Finkelstein reaction appeared, realizing a synthetically useful protocol for C–Br to C–I exchange at C_{sp^2} centers with a broad substrate scope (Figure 1B).[11] Despite a renewed interest in the development of milder methods to achieve aromatic Finkelstein chemistry due to the synthetic importance of aryl iodides in cross-coupling chemistry,[12-16] Buchwald's method remains state-of-the-art. Indeed, the traditional copper mediated approach that operates via an efficient oxidative addition / halide exchange / reductive elimination sequence has shown utility in various synthetic campaigns.[17-19]

Table 1. Ligand optimization.



entry	ligand	*i*	*i*+1	*i*+2	*i*+3	1 [%]	2 [%]	3 [%]	*er* (2)
1	L1	TMG-Asp	D-Pro	Aib-OLi		15	62	20	6 : 94
2	L2	TMG-Gly-OLi				14	37	29	50 : 50
3	L3	TMG-1NaI-OH				13	38	30	58 : 42
4	L4	TMG-Neo-OH				25	44	18	66 : 34
5	L5	TMG-D-Asp	Pro-OLi			23	47	7	90 : 10
6	L6	TMG-D-Asp	αMe-Pro-OLi			24	52	10	91 : 9
7	L7	TMG-Asp	D-Pro	Acpc-OLi		51	40	4	10 : 90
8	L8	TMG-Asp	D-Pro	Acpc	2NaI-NHMe	42	48	9	19 : 81
9	L9	TMG-Asp	D-Pro	Acpc	Leu-OLi	13	62	19	5 : 95
10	**L10**	**TMG-Asp**	**D-Pro**	**Acpc**	***t*Leu-OLi**	**8**	**62**	**22**	**4 : 96**
11	L11	TMG-Asp	D-Pro	Acpc	Chg-OLi	14	64	14	4 : 96
12	L12	TMG-Asp	D-Pro	Acpc	Phe-OLi	8	55	16	4 : 96
13	L13	TMG-Asp	D-Pro	Aic	Phe-OLi	8	54	17	5 : 95
14	L14	TMG-Asp	D-Pro	Aib	Val-OLi	6	56	20	4 : 96
15	L15	TMG-Asp	D-Pro	Aib	D-Leu-OLi	31	52	8	8 : 92
16	L16	TMG-D-Asp	D-Pro	Acpc	Phe-OLi	45	30	4	72 : 28

[a]Reaction conditions: **1** (0.10 mmol), $Cu(MeCN)_4BF_4$ (10 mol%), ligand (15 mol%), K_3PO_4 (0.40 equiv.), NaI (0.12 mmol), MeCN (0.2 mL), 50 °C, 16 h. Yield determined by ^1H NMR using dibromomethane as internal standard. Enantiomeric ratio (*er*) determined by chiral HPLC. Abbreviations: TMG, tetramethylguanidine; 1NaI, 1-naphtylalanine; Neo, neopentylglycine; αMe-Pro, α-methyl proline; Aib, 2-aminoisobutyric acid; Acpc, 1-Aminocyclopropane-1-carboxylic acid; Aic, 2-Aminoindane-2-carboxylic acid; Chg, cyclohexylglycine.

Notably, implementation of the enantioselective aromatic Finkelstein reaction has not yet been reported in the literature, despite the plethora of chiral ligands that are in principle available to realize such a transformation.

Motivated by recent observations applying guanidinylated peptide-based ligands in asymmetric copper-based cross-coupling catalysis, we sought to establish a synthetic platform that would allow for the development of an enantioselective aromatic Finkelstein reaction for remote desymmetrization of diarylmethanes.[20-23] The generation of stereocenters removed from the center of reaction remains a major challenge in contemporary asymmetric catalysis.[24-26] In this field, peptide-based catalysts have found particular utility, stimulating the present study of their capacity to mediate remote aryl bromide to aryl iodide substitution. We further hypothesized that leveraging the enhanced reactivity of the C–I bond towards venerable cross-coupling reactions would allow for translation of the installed stereoinformation into chemoselective transition metal-catalyzed transformations (Figure 1C).[27] Consequently, the asymmetric aromatic Finkelstein reaction would, from a strategic perspective facilitate the streamlined synthesis of a structurally diverse library of enantio-enriched diarylmethanes.

The selection of **1** as a model substrate for the development of the asymmetric aromatic Finkelstein reaction was motivated by the privileged role of diarylmethanes in drug discovery.[28-33] We commenced our studies by subjecting **1** to a CuI / TMG-Asp-D-Pro-OLi catalyst system using sodium iodide as iodide source and we were gratified to observe the formation of **2** in 49% NMR-yield with 90:10 *er*, alongside achiral bis-substituted product **3** (10% yield) (see supporting information for initial results and reaction conditions screen). Encouraged by this result, ligand optimization was initiated (Table 1). While utilization of monomeric, dimeric, and trimeric tetramethylguanidine *N*-capped peptides furnished **2** in promising levels of enantioselectivity (up to 91:9 *er*, **L3**-**L7**), tetrameric β-turn peptides with a L_i-D_{i+1}-L_{i+3} sequence proved superior, generating the desired product in good yields (up to 64%) and excellent selectivities (up to 96:4 *er*) (**L8**-**L16**). In general, the nature of the *i*+3 position had only a minor influence on the reaction outcome (**L9**-**L12**), yet the presence of a *C*-terminal carboxylate proved essential (**L8**).

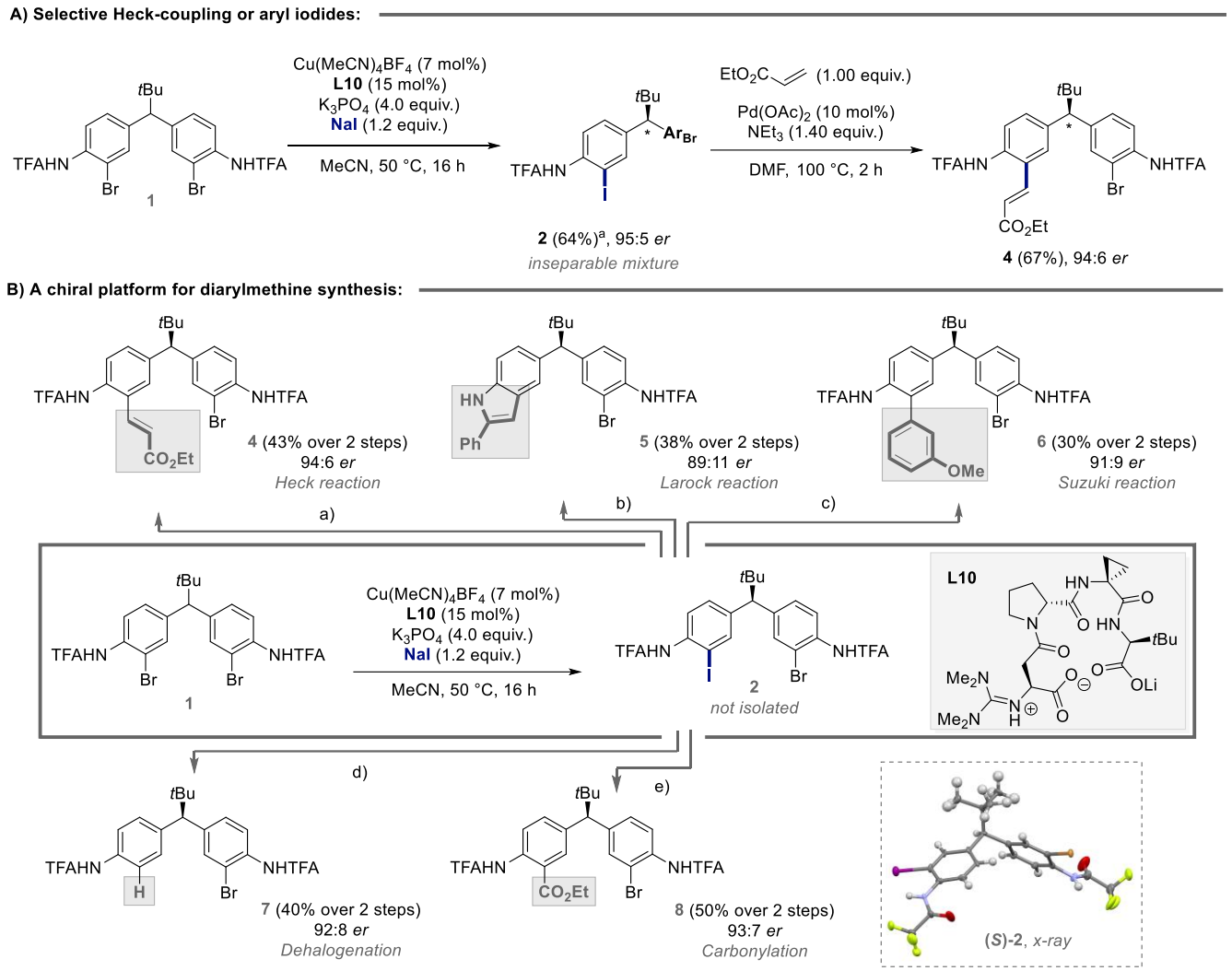


Figure 2. A) Identification of an asymmetric aromatic Finkelstein / Heck reaction sequence. [a]Yield determined by ^{1}H NMR using dibromomethane as internal standard. B) Asymmetric aromatic Finkelstein reaction as platform for the synthesis of enantioenriched diarylmethane. Reaction conditions (0.2 mmol scale): a) $Pd(OAc)_2$ (10 mol%), NEt_3 (1.4 equiv.), ethyl acrylate (0.95 equiv.), DMF (0.2 M); b) acetylene; c) $Pd(OAc)_2$ (10 mol%), NEt_3 (1.4 equiv.), 3-methoxyphenylboronic acid (1.4 equiv.), toluene (0.2 M); d) $Pd(OAc)_2$ (10 mol%), $NaBH_4$ (0.95 equiv.), TMEDA (1.3 equiv.), DMF (0.2 M); e) $Pd(OAc)_2$ (10 mol%), NEt_3 (10 equiv.), EtOH/DMF (1:4, 0.09 M), CO (1 atm.). X-ray structure of **2** is shown with atomic thermal parameters calculated at 50% probability levels.

Similarly, alteration of the catalyst τ-angle through incorporation of disubstituted amino acids (Acpc, Aic, Aib) at the *i*+2 position did not impact the reaction outcome and **2** was isolated in good yield and excellent *er* (**L12**-**L14**).[34] Finally, we aimed to investigate the effect of stereochemical alteration of the amino acid sequence. Employing **L15**, which contains an optically inverted *i*+3 position had a negligible effect on the reaction outcome. In contrast, substitution of Asp for D-Asp (*i*-position) resulted in an inversion of the sense of enantioinduction with **2** obtained in 72:28 *er*. While **L9**-**L13** furnished the product in similar yield and selectivity, **L10** provided marginally better results when reactions were performed on a larger scale and was therefore selected for the remainder of this study.

While separation of **2** from remaining starting material **1** and side-product **3** was not possible, a crystal structure of **2** could be obtained, allowing for assignment of the absolute configuration as (*S*) (Figure 2B, see Supporting Information for details). Since our overall strategic vision included the use of the aromatic Finkelstein reaction to set up subsequent reactions based on the canonical selective transformation of the C–I over the C–Br bond, separation of reaction sequence products was envisioned to be more straightforward, and we therefore turned our attention to product derivatization.

Initial attempts targeted chemoselective Heck-reactions. While the use of phosphine ligands resulted in complex product mixtures, a $Pd(OAc)_2$/NEt_3-catalyst system enabled the desired conversion of **2** (purified mixture containing **1** and **3**) to Heck-product **4** in 67% yield with retention of enantioselectivity (Figure 2A). Stimulated by this result, we aimed to advance the asymmetric aromatic Finkelstein / cross-coupling strategy to a more general derivatization platform, that would enable the synthesis of a small library of diarylmethanes over two steps with a single chromatographic purification.

Pleasingly, the same strategy was compatible with various transition-metal catalyzed transformations, and we were able to synthesize a set of structurally diverse diarylmethanes in good yields and enantioselectivities (Figure 2B).

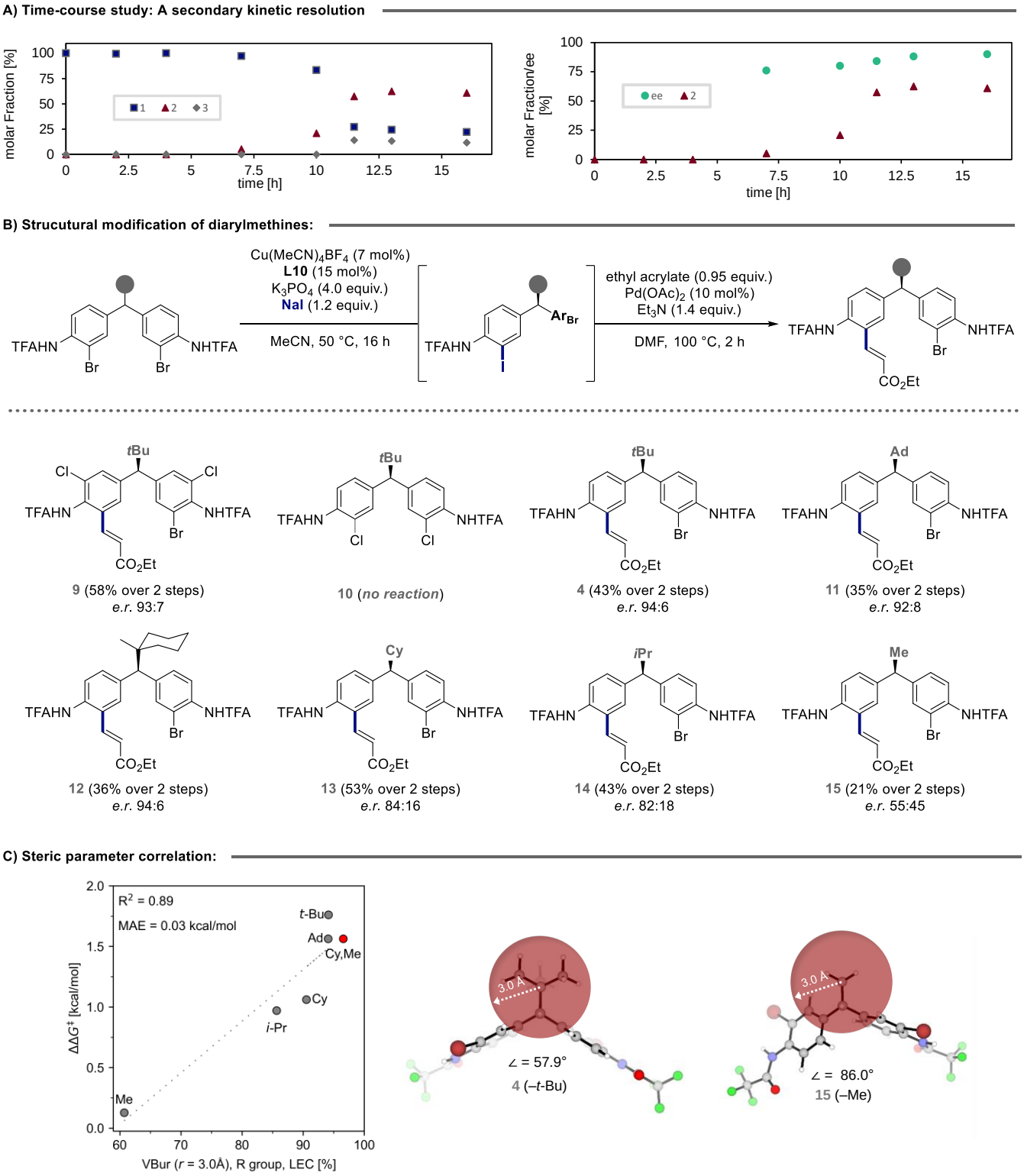


Figure 3. Diarylmethane scope and correlation of steric demand with enantioselectivity.

Heck-product **4** could thus be isolated in 43% over 2 steps with excellent enantioselectivity (94:6 *er*). Our strategy was furthermore compatible with a Cu(I)-catalyzed Larock-type indole formation, which enabled the synthesis of **5** in 38% over 2 steps, despite an observable drop in selectivity (89:11 *er*), which in this case, can be attributed to background reaction of the remaining starting material under the reaction conditions. Implementation of a Suzuki-reaction using 3-methoxyphenyl-boronic acid proved fruitful and enabled isolation of **6** in 30% over 2 steps and 91:9 *er*. Enantioenriched mono-brominated diarylmethane **7** could be synthesized via a palladium-catalyzed dehalogenation using $NaBH_4$ as reductant (40% over 2 steps, 92:8 *er*). Finally, we attempted the selective insertion of carbon monoxide into the newly installed C–I bond in the presence of a palladium catalyst resulting in the formation of **8** in 50% over 2 steps with 93:7 *er*. It is notable, from a strategic standpoint, that each of these transformations is enabled by the desymmetrization of a simple, and common starting material, such that campaigns

for new chiral ligands and catalysts for each of the other metal-catalyzed reactions is not required.

Having established the synthetic potential of the asymmetric aromatic Finkelstein reaction as a platform for chiral diarylmethane synthesis, we aimed to explore mechanistic and structural requirements to achieve high selectivity. Diarylmethanes have been successfully utilized in several methodology and drug discovery campaigns.[25-33] In particular, a series of reports from our lab established a high degree of compatibility with small-peptide catalysis over a broad range of mechanistically distinct transformations.[20-23, 34-35] A series of experiments was therefore undertaken to identify key parameters that govern mechanism and structure to elucidate the privileged role of diarylmethanes in peptide catalysis.

The role of a secondary kinetic resolution in the enhancement of selectivity has also been noted in previous studies. While the formation of bis-iodinated compound **3** is in agreement with this hypothesis, the involvement of a secondary kinetic resolution would be characterized by an increase of enantioselectivity over time. We thus monitored the reaction progress and indeed observed a continuous increase in *er* from 88:12 to 95:5 *er* (Figure 3A). Furthermore, the reaction features an induction period of around 6 h, which likely results from the required deprotonation of the -NHTFA moiety to reveal the active substrate for catalysis.

Next, we investigated the influence of diarylmethane structure on reaction outcome (Figure 3B). Evaluation of the impact of structural modification was possible by isolation of the corresponding Heck-reaction products. Initially, the role and nature of the halide substituent was investigated. Addition of chloro-substituents to the aryl-core was well-tolerated and indeed enantioselective replacement of bromide for iodide was possible, as well as the highly selective Heck-coupling of aryl iodides. Diarylmethane **9** could thus be isolated in 58% yield over two steps in 94:6 *er*. In contrast, no conversion to product was observed upon subjecting **10** to the reaction conditions, highlighting the relatively poor reactivity of aryl chlorides compared to aryl bromides.

Perhaps most interesting in the context of structural variation of the diarylmethane is the impact of the remote substituents, bridging the two aromatic rings of the substrate. Considering the excellent enantioselectivity obtained for *t*Bu-substituted substrate **4** (94:6 *er*), the very good levels of selectivity upon installation of an adamantyl (**11**, 92:8 *er*) and a methylcyclohexyl group (**12**, 94:6 *er*) are unsurprising. The presence of a tertiary carbon-center in the α-position to the stereogenic center, however, resulted in a notable drop in selectivity (cyclohexyl, **13**, 84:16 *er*; isopropoyl, **14**, 82:18 *er*). Further decrease of the steric profile upon installation of a methyl group (**15**), yielded a near racemic product (55:45 *er*).

In previous studies, we have noted linear free energy relationships between empirical steric parameters and the observed enantioselectivity in the catalytic desymmetrization reaction of diarylmethane-bis(phenol) substrates.[35-36] Here we show that a computed steric descriptor, buried volume (VBur) computed at 3.0 Å sphere centered at the substituent group carbon, correlates well with the measured enantioselectivities (R^2 = 0.89, Figure 3C).[37-38] Computed steric descriptors provide advantages over empirically derived parameters, particularly because they can be readily computed for uncommon substituents (e.g., methylcyclohexyl group in **12**). To showcase this advantage, we used **12** as a test case to evaluate the accuracy of the correlation and found that it accurately predicted the enantioselectivity within 0.03 kcal/mol of the measured value. Given the nature of this remote functionalization, we sought to bridge the effect of this with a mechanistic understanding of the origins of enantioselectivity. Visualization of the lowest energy conformer of each diarylmethane revealed that the size of the substituent group can influence the adopted conformation of the substrate; specifically, the plane angle (∠) between the two aryl groups varies ca. 30° depending on the size and identity of the R group (57.9° for **4** and 86.0° for **15**, Figure 3C). This suggests that the structural pre-organization influenced by the size of the substituent group is determining enantioselectivity. In consideration of the remote nature of desymmetrization, this observation is in line with intuition that a degree of rigidity is necessary to translate the stereochemical information from the center of reaction to the element of stereochemical information.

In summary, we herein disclose the first report of a highly enantioselective, copper-catalyzed aromatic Finkelstein reaction. Guanidinylated peptide ligands serve as enabling tool for the desymmetrization of diarylmethanes via stereoselective bromide for iodide substitution at C_{sp2}-centers. Subsequent stereoretentive transition metal-catalyzed transformations render this system a platform for the generation of chiral diarylmethane libraries. To elucidate the privileged nature of diarylmethanes in desymmetrization reactions, this study further identified key parameters that govern selectivity, establishing underlying design principles for future studies. As such, a secondary kinetic resolution was identified as a crucial contributor to the excellent levels of enantioselectivity and a computed steric parameter led to insight into the preorganization required for selective catalysis. The overall features of the diarylmethane scaffold remain of great interest in not only asymmetric catalysis, but also in the study of ligand receptor interactions in medicinal chemistry. It seems plausible that the determinants of selectivity in one field may be related to selectivity in the other, and perhaps reports like these may stimulate further exploration of this analogy in the future.

ASSOCIATED CONTENT

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org."

Detailed experimental procedures and analytical data; X-ray crystallographic data for **2** (CCDC 2286887); computational data.

AUTHOR INFORMATION

Corresponding Author

*E-mail: scott.miller@yale.edu
*E-mail: sigman@chem.utah.edu

Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

Funding:
R35 GM 132092 to S.J.M. (NIH)
R35 GM 136271 to M.S.S. (NIH)
MO 4495/1-1 to T.M. (DFG)
DGE-2139841 to T.E.M. (NSF)
PF-21-089-01-ET to M.A.H. (American Cancer Society)

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We are grateful to Juan Serviano for help with collecting IR spectroscopic data. This work is supported by the National Institute of General Medical Sciences of the United States National Institutes of Health (R35 GM 132092 to S.J.M. and R35 GM 136271 to M.S.S.). T.M. is also grateful to the Deutsche Forschungsgemeinschaft (DFG) for a Walter Benjamin Fellowship (MO 4495/1-1). A National Science Foundation Graduate Research Fellowship (DGE-2139841) for T.E.M, as well as a Roaring Fork Valley Research Circle Postdoctoral Fellowship for M.A.H. (American Cancer Society, PF-21-089-01-ET) are kindly acknowledged. L.J.K, M.A.H, and M.S.S are furthermore thankful to the Center for High Performance Computing (CHPC) at the University of Utah for the support and resources provided.

REFERENCES

(1) Finkelstein, H. Darstellung organischer Jodide aus den entsprechenden Bromiden und Chloriden. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1528−1532.

(2) Sharts, C. M.; Sheppard, W. A. Modern methods to prepare monofluoroaliphatic compounds. *Org. React.* **1974**, *21*, 125−406.

(3) Miller, J. A.; Nunn, M. J. Synthesis of alkyl iodides. *J. Chem. Soc., Perkin Trans. 1* **1976**, 416−420.

(4) Hayami, J.; Hihara, N.; Kaji, A. S_N2 reactions in dipolar aprotic solvents. IX. An estimation of nucleophilicities and nucleofugicities of anionic nucleophiles studied in the reversible Finkelstein reactions of benzyl derivatives in acetonitrile - dissociative character of the reaction as studied by the nucleofugicity approach. *Chem. Lett.* **1979**, 413−414.

(5) Chalk, C. D.; McKenna, J.; Williams, I. H. NPE effects in bimolecular nucleophilic substitution. *J. Am. Chem. Soc.* **1981**, *103*, 272−281.

(6) Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*. Elsevier, Amsterdam **2005**.

(7) Smith, M. B.; March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (6th Ed.), Wiley-Interscience, New York **2007**.

(8) Olah, G. A.; Narang, S. C.; Field, L. D. *Synthetic methods and reactions. 103. Preparation of alkyl iodides from alkyl fluorides and chlorides with iodotrimethylsilane or its in situ analogs. J. Org. Chem.* **1981**, *46*, 3727−3728.

(9) Takagi, K.; Hayama, N.; Okamoto, T. Synthesis of aryl iodides from aryl halides and potassium iodide by means of Nickel catalyst. *Chem. Lett.* **1978**, *7*, 191−192.

(10) Lindley, J. Copper assisted nucleophilic substitution of aryl halogen. *Tetrahedron* **1984**, *40*, 1433−1456.

(11) Klapars, A.; Buchwald, S. L. Copper-Catalyzed Halogen Exchange in Aryl Halides: An Aromatic Finkelstein Reaction. *J. Am. Chem. Soc.* **2002**, *124*, 14844−14845.

(12) Li, L.; Liu, W.; Zeng, H.; Mu, X.; Cosa, G.; Mi, Z.; Li, C.-J. Photo-induced Metal-Catalyst-Free Aromatic Finkelstein Reaction. *J. Am. Chem. Soc.* **2015**, *137*, 8328−8331.

(13) Evano, G.; Nitelet, A.; Thilmany, P.; Dewez, D. F. Metal-Mediated Halogen Exchange in Aryl and Vinyl Halides: A Review. *Front. Chem.* **2018**, *6*, 114.

(14) Meyer-Eppler, G.; Küchler, L.; Tenten, C.; Benkhäuser, C.; Brück, S.; Lützen, A. Cheap and Easy Synthesis of Highly Functionalized (Het)aryl Iodides via the Aromatic Finkelstein Reaction. *Synthesis* **2014**, *46*, 1085–1090.

(15) Jin, X.; Davies, R. P. Copper-catalysed aromatic-Finkelstein reactions with amine-based ligand systems. *Cat. Sci. Technol.* **2017**, *7*, 2110–2117.

(16) Andrews, M. J.; Carpentier, A.; Slawin, A. M. Z.; Cordes, D. B.; Macgregor, S. A.; Watson, A. J. B. Mechanism of Cu-Catalyzed Iododeboronation: A Description of Ligand-Enabled Transmetalation, Disproportionation, and Turnover in Cu-Mediated Oxidative Coupling Reactions *ACS Catal.* **2023**, *13*, 11117–11126.

(17) Fürstner, A.; Kennedy, J.W. Total syntheses of the tylophora alkaloids cryptopleurine, (–)-antofine, (–)-tylophorine, and (–)-ficuseptine, C. *Chem. Eur. J.* **2006**, *12*, 7398–7410.

(18) Kim, C. H.; An, H. J.; Shin, W. K.; Yu, W.; Woo, S. K.; Jung, S. K.; Lee, E. Total Synthesis of (–)-Amphidinolide E. *Angew. Chem. Int. Ed.* **2006**, *45*, 8019–8021.

(19) Jones, C. P.; Anderson, K. W.; Buchwald, S. L. Sequential Cu-catalyzed amidation-base-mediated camps cyclization: a two-step synthesis of 2-aryl-4-quinolones fromo-halophenones. *J. Org. Chem.* **2007**, *72*, 7968–7973.

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

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

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

(23) Yoon, H.; Galls, A.; Rozema, S. D.; Miller, S. J. Atroposelective Desymmetrization of Resorcinol-Bearing Quinazolines via Cu-Catalyzed C–O Bond Formation. *Org. Lett.* **2022**, *24*, 762–766.

(24) Chu, L.; Wang, X-C.; Moore, C. E.; Rheingold, A. L.; Yu, J.-Q. Pd-Catalyzed Enantioselective C–H Iodination: Asymmetric Synthesis of Chiral Diarylmethylamines. *J. Am. Chem. Soc.* **2013**, *135*, 16344–16347.

(25) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. Catalytic asymmetric approaches towards enantiomerically enriched diarylmethanols and diarylmethylamines. *Chem. Soc. Rev.* **2006**, *35*, 454–470.

(26) Wei, J.; Gandon, V.; Zhu, Y. Amino Acid-Derived Ionic Chiral Catalysts Enable Desymmetrizing Cross-

Coupling to Remote Acyclic Quaternary Stereocenters. *J. Am. Chem. Soc.* **2023**, *145*, 16796–16811.

(27) Toto, P.; Gesquière, J.-C.; Cousaert, N.; Deprez, B.; Willand, N. UFU ("Ullmann–Finkelstein–Ullmann"): a new multicomponent reaction. *Tetrahedron Lett.* **2006**, *47*, 4973–4978.

(28) Chu, W.-D.; Zhang, L.-F.; Bao, X.; Zhao, X.-H.; Zeng, C.; Du, J.-Y.; Zhang, G.-B.; Wang, F.-X.; Ma, X.-Y.; Fan, C.-A. Asymmetric Catalytic 1,6-Conjugate Addition/Aromatization of *para*-Quinone Methides: Enantioselective Introduction of Functionalized Diarylmethine Stereogenic Centers. *Angew. Chem. Int. Ed.* **2013**, *52*, 9229−9233.

(29) Cheng, X.-F.; Li, Y.; Su, Y.-M.; Yin, F.; Wang, J.-Y.; Sheng, J.; Vora, H. U.; Wang, X.-S.; Yu, J.-Q. Pd(II)-Catalyzed Enantioselective C–H Activation/C–O Bond Formation: Synthesis of Chiral Benzofuranones. *J. Am. Chem. Soc.* **2013**, *135*, 1236−1239.

(30) Lee, T.; Wilson, T. W.; Berg, R.; Ryberg, P.; Hartwig, J. F. Rhodium-Catalyzed Enantioselective Silylation of Arene C–H Bonds: Desymmetrization of Diarylmethanols. *J. Am. Chem. Soc.* **2015**, *137*, 6742−6745.

(31) Guduguntla, S.; Hornillos, V.; Tessier, R.; Fananas-Mastral, M.; Feringa, B. L. Chiral Diarylmethanes via Copper-Catalyzed Asymmetric Allylic Arylation with Organolithium Compounds. *Org. Lett.* **2016**, *18*, 252−255.

(32) Bishop, M. J.; McNutt, R. W. An efficient synthesis of the benzhydrylpiperazine delta opioid agonist (+)-BW373U86. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1311−1314.

(33) Wada, S.; Hitomi, T.; Tokuda, H.; Tanaka, R. Anti-Tumor-Initiating Effects of Spiro-biflavonoids from *Abies sachalinensis*. *Chem. Biodivers.* **2010**, *7*, 2303−2308.

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

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

(36) Sigman, M. S.; Harper, K. C.; Bess, E. N.; Milo, A. The Development of Multidimensional Analysis Tools for Asymmetric Catalysis and Beyond. *Acc. Chem. Res.* **2016**, *49*, 1292–1301.

(37) Poater, A.; Cosenza, B.; Correa, A.; Giudice, S.; Ragone, F.; Scarano, V.; Cavallo, L. SambVca: A web application for the calculation of the buried volume of N-heterocyclic carbene ligands. *Eur. J. Inorg. Chem.* **2009**, *13*, 1759–1766.

(38) Clavier, H.; Nolan, S. P. Percent buried volume for phosphine and *N*-heterocyclic carbeneligands: steric properties in organometallic chemistry. *Chem. Commun.* **2010**, *46*, 841–861.

Insert Table of Contents artwork here