Distal Ionic Substrate—Catalyst Interactions Enable Long-Range Stereocontrol: Access to Remote Quaternary Stereocenters through a Desymmetrizing Suzuki—Miyaura Reaction

Yazhou Lou,† Junqiang Wei,† Mingfeng Li, and Ye Zhu* 

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ABSTRACT: Spatial distancing of a substrate’s reactive group and nonreactive catalyst-binding group from its pro-stereogenic element presents substantial hurdles in asymmetric catalysis. In this context, we report a desymmetrizing Suzuki—Miyaura reaction that establishes chirality at a remote quaternary carbon. The anionic, chiral catalyst exerts stereocontrol through electrostatic steering of substrates, even as the substrate’s reactive group and charged catalyst-binding group become increasingly distanced. This study demonstrates that precise long-range stereocontrol is achievable by engaging ionic substrate—ligand interactions at a distal position.

The remarkable ability of enzymes to utilize attractive noncovalent interactions with distant, nonreactive groups of substrates to accelerate reactions and modulate selectivity has been regarded as a fundamental distinction from small-molecule catalysts. In recent years, substantial advances, particularly by Phipps and co-workers, have been achieved in harnessing distal ionic substrate—ligand interactions to control regio- and site-selectivity of transition-metal-catalyzed transformations (Scheme 1a, top). By contrast, integrating distal ionic interactions represents a compelling, yet undeveloped enantiocontrol strategy in transition-metal catalysis (Scheme 1a, bottom). In a prominent work, Miller and co-workers accomplished remote desymmetrization through asymmetric Ullmann coupling (Scheme 1b). Mechanistic investigation revealed an exquisite preorganization through proximal trifluoroacetamide anion—Cu binding and a distal Cs+ bridge between the substrate’s nonreacting enantiotopic arene and the peptide ligand’s terminal carboxylate. Notwithstanding, chiral ligand scaffolds bearing nonligating charged groups (mostly tethered chirotopic ionic groups to date) are uncommon, and the general effects of ion—ion interaction’s low directionality on long-range enantioinduction have not been studied. The broad potential of asymmetric transition-metal catalysis directed by distal ionic interactions has remained underexploited.

In pursuit of such an enantiocontrol strategy, we targeted an untapped class of stereocenters through a transformation that allows us to rigorously test its viability. To date, remote desymmetrization to trisubstituted stereocenters has been made possible by only a handful of ingenious catalysts, and creation of remote quaternary carbon stereocenters has remained elusive. Quaternary stereocenters embedded in fluorenes and xanthenes possess distinctive ability to project chirality to distant loci of three-dimensional dispositions, an appealing feature for functional materials and pharmaceuticals (Scheme 1c). However, these enanti-enriched molecules are accessible only through chiral chromatography. We envisaged that Pd-catalyzed desymmetrizing Suzuki—Miyaura reaction of bis(chloroaryl)methane derivatives could furnish this class of core quaternary stereocenters (Scheme 1d).

Establishing quaternary stereocenters bearing sterically similar geminal substituents poses a major obstacle in catalytic desymmetrization, and distant reactive groups may conceivably exacerbate the challenge. We were drawn to the design principle by Phipps and co-workers using cation bridges between anionic substrates and sulfonated dialkylbiliary phosphines in site-selective cross-coupling of dichloroaromatics. We surmised that a novel anionic dialkylbiliary phosphate—Pd catalyst could interact with the charged substituent (Z M+) of the substrate preferentially (Scheme 1d). Furthermore, we reasoned that integrating the catalyst’s axial chirality spatial arrangement of Pd and phosphonate—into stereocontrol relay from ionic group Z to C—Cl bonds could be a viable approach to long-range asymmetric induction. As such, the effects of spatial distancing of ionic group Z and C—Cl bonds could be elucidated through judicious variation of the substrates. Here, we report that catalyst-controlled electrostatic steering of substrates led to realization of an enantioselective desymmetrizing Suzuki—Miyaura reaction that establishes chirality at remote quaternary stereocenters.

We commenced our study by synthesizing 3′-phosphonate dialkylbiphenyl phosphines (Scheme 2). Racemic L1, readily prepared from RuPhos, was converted to L2 as separable atropo-diastereomers in three steps. Upon desulfonylation, the axial chirality of L2 was preserved in the resulting individual...
enantiomers of L1 by a methyl “atropo-tag”. Subsequent phosphorylation and hydrolysis afforded enantioenriched L4. Besides, L5 (depicted in Table 1) was prepared following an analogous synthetic route starting from SPhos.22

The nature of substrate’s catalyst-binding group is anticipated to influence the stereochemical outcome of desymmetrization if distal substrate–ligand interactions are operating. Therefore, we evaluated a range of Brønsted acidic groups3 (Table 1). Each group is separated from fluorene C9 by four rotatable bonds. This way, differences between their steric effects imposed on the pro-stereogenic center are minimized. Using (S)-L4 as ligand, the substrate bearing a distal triamide underwent the desymmetrizing Suzuki–Miyaura reaction, affording the product in an encouraging 44% yield with 73:27 er (1). Replacing the triamide with sulfo (2) and carboxyl group (3) led to markedly improved results. By contrast, pendent hydrogen bond donors (4–6) resulted in comparably low enantioselectivity.

Subsequently, we focused our efforts on reaction optimization (Tables S1–S5 in the Supporting Information (SI)). The model reaction gave merely 56:44 er using SPhos-derived (S)-L5 (Table 1, 3). Investigating solvent effects using (S)-L4, we found that the enantioselectivity diminished in DMF (66:34 er). This observation is consistent with a participating cation bridge, which is disrupted by strong solvation of cations in polar aprotic solvents.7c To probe the effects of cations, we surveyed alkali-metal hydroxides and carbonates as exogenous base. Similar results were observed using Na, K, and Cs bases irrespective of the counteranions (96:4–97:3 er), while Li bases were inferior. The reaction remained enantioselective using Bu4NOH as base (91:9 er), suggesting that stereocontrol is attainable in the organic phase. Finally, a 2-MeTHF–aqueous K3PO4 system was identified as the optimal reaction media.

We next studied the effects of distancing the ionic pendent group (Table 2a, 3 and 7–12). Initially, we anticipated a steep drop in enantioselectivity once the distance between C–Cl bond and the distal carboxylate exceeds the span of catalyst. The entropic penalty incurred could obliterate the energetic differentiation of desymmetrization. Surprisingly, the catalyst system adapted well to changes in length of (CH2)n (n = 1–7) linking the carboxyl group (32–67% yield, 82.5:17.5–96:4 er). Notably, desymmetrization was achieved even when the carboxylate was placed eight C–C bonds away from the quaternary carbon (12, 86.5:13.5 er). The results also substantiate the attractive nature of substrate–ligand interactions involving the distal carboxylate. Repulsive forces unlikely play the dominant role, because they can be easily avoided by shifting the carboxylate away without affecting the catalysis at the Pd center. Furthermore, increasing the conformational rigidity by incorporating a double bond into the linker only led to
The absolute configurations of products were assigned by analogy to 37.  
Standard reaction conditions: substrate (0.25 mmol), Pd(II)Cl₂ (1.0 mol%), L₄ (2.2 mol%), K₂PO₄ (10 equiv), 2-MeTHF (20 mL/mmol), H₂O (1.6 mL/mmol), 60 °C, 18 h. Isolated yields reported. 1 Isolated as ethyl ester. dba = dibenzylideneacetone.

The transformation is compatible with a broad spectrum of arylboronic acids (Table 2c). Substituents at the para- (20–22), meta- (23 and 24), and ortho- (25–27) positions, irrespective of electronic properties, had an insignificant influence on the enantioselectivity (57–73% yield, 93:7–97:5:2.5 er). Additionally, a wide range of polycyclic aromatics commonly employed in π-conjugated materials can be installed in 61–70% yield, 92.5:7.5–98.2 er (28–33).

The remote desymmetrization strategy is also applicable to accessing enantioenriched xanthenes (Table 2d). Specifically, dichloroxanthenes participated in the transformation with various electron-rich aryl (34–36), electron-deficient aryl (37–39), heteroaryl (40–42), and polycyclic aryl (43–46) boronic acids, affording the products in 42–70% yield, 93:7–97:5:2.5 er.

Intrigued by the catalyst’s ability in exerting long-range stereocontrol, we further evaluated its adaptability to distancing the reactive group and to altering the catalyst-binding substituent. First, we placed the C–Cl bonds farther apart (Scheme 3a). Despite the substantial structural change in the substrates, the catalyst remained capable of imparting asymmetric induction (47 and 48, up to 89:5:10.5 er). Next, we studied the stereochemical outcome of incorporating an oxygen atom adjacent to the pro-stereogenic carbon, which possibly provides additional interaction with the K⁺ bridge (Scheme 3b). Indeed, the remote desymmetrization reactions proceeded in up to 99:1 er (49 and 50).

Based on the results of control experiments, we concluded that K⁺, phosphonate of (S)-L₄, and carboxylate of substrate contribute collectively to the ionic substrate–ligand interactions (Scheme 3c). Encapsulation of K⁺ by 18-crown-6 led to diminished enantioselectivity (61:39 er), and reduction in er paralleled the quantity of added 18-crown-6 (S₁). The critical role of ligand’s phosphonate was evidenced by the negligible enantioinduction by truncated ligand (R)-L₁ (56:44 er). In comparison, the reaction using (S)-L₃ gave 83:17 er. The ion–dipole interaction between K⁺ and P=O of (S)-L₃ is inferior to the ion–ion interaction between K⁺ and P=O⁻ of (S)-L₄ in asymmetric induction. In contrast to the preformed carboxylate salt (52), racemic product was obtained from corresponding ethyl ester (53), which lacks the key ion–ion interactions with K⁺.

The oxidative addition step is plausibly selectivity-determining, while other steps in the catalytic cycle could contribute to the enantioselectivity. 25 On the basis of the
absolute configurations of (S)-L4 and 37, we hypothesized a model to illustrate the putative distal ionic interactions (Scheme 3d). Unlike enzymes’ large and deep binding clefts that confer substrate specificity, Pd–(S)-L4, which carries a diffuse negative charge at an unshielded phosphonate, preserves distal ionic interactions when it adapts to substrates’ structural diversity in pendant groups and linkers, non-ionic substituents (R), and distanced C−Cl bonds.

Nature utilizes long-range electrostatic attractions to significantly accelerate biochemical processes that require precise orientations of biomolecules. We postulated that the Pd-catalyzed remote desymmetrization follows the same principle of electrostatic steering of charged substrates. To elucidate this phenomenon, we carried out competition experiments between carboxylate acid 51 and ethyl ester 53 (Scheme 3e). Under the standard conditions, 51 reacted predominantly regardless of the electronic property of aryl boronic acids (entries 1 and 2). Such selectivity is catalyst-controlled, as competition experiments using RuPhos slightly favored 53 (entries 3 and 4). The observations, coupled with the noticeable difference between their enantioselectivities (Scheme 3c), indicate that compared with 53, the ionic interactions arising from distal carboxylate of 51 lead to a preferential increase in the rate of selectivity-determining step at one of the enantiotopic reaction sites.

The desymmetrization strategy offers efficient access to core quaternary stereocenters that project substituents to widely spaced positions (Scheme 4). As an illustration, 3 underwent Pd-catalyzed C–B, C–C, and C–N bond formation reactions (Scheme 4a), furnishing combinations of functionalities at two distant sites (54–56). Moreover, the sequential desymmetrizing cross-coupling is enantiodivergent (Scheme 4b).

As a practical feature, the remote desymmetrization can be readily adopted to construct chiral building blocks of fluorene-based materials without rerouting existing syntheses. For example, desymmetrization of 51 with 4-B(dan) phenylboronic pinacol ester (dan = naphthalene-1,8-diaminato) proceeded smoothly on a 1 mmol scale using 1 mol% Pd–(S)-L4, affording AB-type monomer 63 in 97:3 er upon deprotection of coupling product 62. Notably, we also succeeded in synthesizing enantioenriched (99:1 er) AA-type monomer 64 in one step using 1,4-phenylenediboronic pinacol ester as bis-coupling partner (Scheme 4c). Additionally, the pendant carboxyl group can be readily converted to other
functionalties, such as ethylene glycol chain of a chiral precursor for polyimine dynamers \(^{12c}\) (Scheme 4d, 65).

In summary, we have realized a desymmetrizing Suzuki–Miyaura reaction that establishes chirality at a remote quaternary carbon. The anionic catalyst’s ability to transmit asymmetry across large distances enables facile access toenantioenriched molecules that project chirality to widely spaced loci. We have demonstrated that by engaging distal ionic substrate–catalyst interactions, it is possible to surmount the hurdle in asymmetric catalysis arising from spatial distancing of substrate’s reactive group and catalyst-binding group. We anticipate that pursuing this strategy could stimulate rational design of catalysts capable of long-range asymmetric induction to create chirality that would be difficult to construct using conventional methods.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c12345.

Experimental details and characterization data (PDF)

### Accession Codes

CCDC 2054848 and 2054849 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

## AUTHOR INFORMATION

### Corresponding Author

Ye Zhu − Department of Chemistry, Faculty of Science, National University of Singapore, Singapore 117543; orcid.org/0000-0002-8566-576X; Email: chmzhu@nus.edu.sg

Authors

Yazhou Lou − Department of Chemistry, Faculty of Science, National University of Singapore, Singapore 117543
Junqiang Wei − Department of Chemistry, Faculty of Science, National University of Singapore, Singapore 117543
Mingfeng Li − Department of Chemistry, Faculty of Science, National University of Singapore, Singapore 117543

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.1c12345

### Author Contributions

\(^{3}\)Y.L. and J.W. contributed equally.

Notes

The authors declare no competing financial interest.

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## REFERENCES

1. (a) Barelier, S.; Cummings, J. A.; Rauwerdink, A. M.; Hitchcock, D. S.; Farelli, J. D.; Almo, S. C.; Raushel, F. M.; Allen, K. N.; Shoichet, B. K. Substrate Deconstruction and the Nonadditivity of Enzyme Recognition. J. Am. Chem. Soc. 2014, 136, 7374−7382. (b) Schwans, J.; Kraut, D. A.; Herschlag, D. Determining the catalytic role of remote substrate binding interactions in ketosteroid isomerase. Proc. Natl. Acad. Sci. U.S.A. 2009, 106, 14271−14275.
2. (a) Lee, B.; Mihai, M. T.; Stojalnikova, V.; Phipps, R. J. Ion-Pair-Directed Borylation of Aromatic Phosphonium Salts. J. Org. Chem. 2019, 84, 13124−13134. (b) Mihai, M. T.; Davis, H. J.; Genov, G. R.; Phipps, R. J. Ion Pair-Directed C-H Activation on Flexible Ammonium Salts: Meta-Selective Borylation of Quaternized Phenylthylamines and Phenylpropylamines. ACS Catal. 2018, 8, 3764−3769. (c) Davis, H. J.; Mihai, M. T.; Phipps, R. J. Ion Pair-Directed Regiocontrol in Transition Metal Catalysis: A Meta-Selective C-H Borylation of Aromatic Quaternary Ammonium Salts. J. Am. Chem. Soc. 2016, 138, 12759−12762.
3. (a) Golding, W. A.; Schnitt, H. L.; Phipps, R. J. Systematic Variation of Ligand and Cation Parameters Enables Site-Selective C-C and C-N Cross-Coupling of Multiply Chlorinated Arenes through Substrate-Ligand Electrostatic Interactions. J. Am. Chem. Soc. 2020, 142, 21891−21898. (b) Golding, W. A.; Phipps, R. J. Electrostatically-directed Pd-catalysis in combination with C-H activation: site-selective coupling of remote chlorides with fluorooarenes and fluoroheteroarenes. Chem. Sci. 2020, 11, 3022−3027. (c) Golding, W. A.; Pearce-Higgins, R.; Phipps, R. J. Site-Selective Cross-Coupling of Remote Chlorides Enabled by Electrostatically-Directed Palladium Catalysis. J. Am. Chem. Soc. 2018, 140, 13570−13574.
4. (a) Trouvé, J.; Gramage-Doria, R. Beyond hydrogen bonding: recent trends of outer sphere interactions in transition metal catalysis. Chem. Soc. Rev. 2021, 50, 3565−3584. (b) Toste, F. D.; Sigman, M. S.; Miller, S. J. Pursuit of Noncovalent Interactions for Strategic Site-Selective Catalysis. Acc. Chem. Res. 2017, 50, 609−615. (c) Davis, H. J.; Phipps, R. J. Harnessing non-covalent interactions to exert control over regioselectivity and site-selectivity in catalytic reactions. Chem. Sci. 2017, 8, 864−877. (d) Dydio, P.; Reek, J. N. H. Supramolecular control of selectivity in transition-metal catalysis through substrate preorganization. Chem. Sci. 2014, 5, 2135−2145. (e) Raynal, M.; Ballester, P.; Vidal-Ferran, A.; van Leeuwen, P. W. N. M. Supramolecular catalysis. Part 1: non-covalent interactions as a tool for building and modifying homogeneous catalysts. Chem. Soc. Rev. 2014, 43, 1660−1733.
5. (a) Ye, X.; Tan, C.-H. Enantioselective transition metal catalysis directed by chiral cations. Chem. Soc. Rev. 2021, 12, 533−539. (b) Zhao, Q.; Dong, X.; Wen, J.; Zhang, X. Noncovalent Interaction-Assisted Ferroceny Phosphine Liganes in Asymmetric Catalysis. Acc. Chem. Res. 2020, 53, 1905−1921. (c) Fanourakis, A.; Docherty, P. J.; Chentragool, P.; Phipps, R. J. Recent Developments in Enantioselective Transition Metal Catalysis Featuring Attractive Noncovalent Interactions between Ligand and Substrate. ACS Catal. 2020, 10, 10672−10714. (d) Brak, K.; Jacobsen, E. N. Asymmetric Ion-Pairing Catalysis. Angew. Chem., Int. Ed. 2013, 52, 534−561.
6. (a) Metrano, A. J.; Chinn, A. J.; Shugue, C. R.; Stone, E. A.; Kim, B.; Miller, S. J. Asymmetric Catalysis Mediated by Synthetic Peptides, Version 2.0: Expansion of Scope and Mechanisms. Chem. Rev. 2020, 120, 11479−11615. (b) Metrano, A. J.; Miller, S. J. Peptide-Based Catalysts Reach the Outer Sphere through Remote Desymmetrization and Atroposelectivity. Acc. Chem. Res. 2019, 52, 199−215. (c) Lewis, C. A.; Chiu, A.; Kubryk, M.; Balsells, J.; Pollard, D.; Eser, C. K.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J. Remote Desymmetrisation at Near-Nanometer Group Separation Catalyzed by a Miniaturized Enzyme Mimic. J. Am. Chem. Soc. 2006, 128, 16454−16455.
7. (a) Kwon, Y.; Chinn, A. J.; Kim, B.; Miller, S. J. Divergent Control of Point and Axial Stereogenicity: Catalytic Enantioselective C-N Bond-Forming Cross-Coupling and Catalyst-Controlled Atroposelective Cyclohydrogen. Angew. Chem., Int. Ed. 2018, 57, 6251−6255. (b) Chinn, A. J.; Kim, B.; Kwon, Y.; Miller, S. J.
Enantioselective Intermolecular C-O Bond Formation in the Desymmetrization of Diarylmethanes Employing a Guanidylated Peptide-Based Catalyst. J. Am. Chem. Soc. 2017, 139, 18107–18114. (c) Kim, B.; Chinn, A. J.; Fondrick, D. R.; Senanyake, C. H.; Singer, R. A.; Miller, S. J. Distal Stereocenter Using Guanidylated Peptides as Multifunctional Ligands: Desymmetrization of Diarylmethanes via Ullman Cross-Coupling. J. Am. Chem. Soc. 2016, 138, 7939–7945. 

(8) (a) Zhang, Z.; Smal, V.; Retailleau, P.; Voituriez, A.; Frison, G.; Marinetti, A.; Guinhard, X. Tethered Counterion-Directed Catalysis: Merging the Chiral Ion-Pairing and Bifunctional Ligand Strategies in Enantioselective Gold(I) Catalysis. J. Am. Chem. Soc. 2020, 142, 3797–3805. (b) Willig, F.; Lang, J.; Hans, A. C.; Ringenberg, M. R.; Pfeffer, D.; Frey, W.; Peters, R. Polynuclear Imidazolyl Aroyloxy Betaine/Lewis Acid Catalysts as Tools for the Asymmetric Synthesis of Disfavored Diastereomers. J. Am. Chem. Soc. 2019, 141, 12029–12043. (c) Mehlcr, M.; Peters, R. Diastereodivergent Asymmetric 1,4-Addition of Oxindoles to Nitroolefins by Using Polynuclear Nickel-Hydrogen-Bond-Azolium Catalysts. Angew. Chem., Int. Ed. 2015, 54, 10303–10307. (d) Ohmatsu, K.; Kawai, S.; Imagawa, N.; Ooi, T. Palladium-Catalyzed Asymmetric [3 + 2] Cycloaddition of 5-Z.-Q.; Liao, L.-S. Circularly Polarized Thermally Activated Delayed Lewis, J. C. Enantioselective Desymmetrization of Methylenedianion, M.; Häussinger, D.; Wenzel, W.; Kappes, M. M.; Mayor, M. Enantiomeric Separation of Semiconducting Single-Walled Carbon Nanotubes by Acid Cleavable Chiral Polyfluorene. ACS Nano 2020, 15, 6469–6479. (b) Yang, S.-Y.; Wang, Y.-H.; Gu, W.; Tang, W.-T.; Li, H.-C.; Zheng, Y.-X.; Jiang, Z.-Q.; Liao, L.-S. Circularly Polarized Thermally Activated Delayed Fluorescence Emitters in Through-Space Charge Transfer on Asymmetric Spiro Skeletons. J. Am. Chem. Soc. 2020, 142, 17756–17765. (c) Sakai, N.; Matile, S. Conjugated Polymine Dynamers as Phase-Sensitive Membrane Probes. J. Am. Chem. Soc. 2018, 140, 11438–11443. (d) Kudla, C. J.; Koenen, N.; Psula, W.; Scherf, U. First Synthesis of Isotactic Poly(9-alkyl-9-alkylfluorene) via Directed Aryl-Aryl Coupling of Chiral AB-Type Monomers. Macromolecules 2009, 42, 3483–3488. 

(13) (a) Epstein, O.; Bryan, M. C.; Cheng, A. C.; Derakhchan, K.; Dineen, T. A.; Hickman, D.; Hua, Z.; Human, J. B.; Kreiman, C.; Marx, I. E.; Weiss, M. M.; Wahl, R. C.; Wen, P. H.; Whittington, D. A.; Wood, S.; Zheng, X. M.; Fremeau, R. T., Jr; White, R. D.; Patel, V. F. Lead Optimization and Modulation of hERG Activity in a Series of Aminoalcohol Xanthene β-Site Amyloid Precursor Protein Cleaving Enzyme (BACE1) Inhibitors. J. Med. Chem. 2014, 57, 9796–9810. (b) Huang, H.; La, D. S.; Cheng, A. C.; Whittington, D. A.; Patel, V. F.; Chen, K.; Dineen, T. A.; Epstein, O.; Graceff, R.; Hickman, D.; Yang, Y.-H.; Louie, S.; Luo, Y.; Wahl, R. C.; Wen, P. H.; Wood, S.; Fremeau, R. T., Jr Structure- and Property-Based Design of Aminoalcohol Xanthenes as Selective, Orally Efficacious, and CNS Penetrable BACE Inhibitors for the Treatment of Alzheimer’s Disease. J. Med. Chem. 2012, 55, 9156–9169. (14) (a) Talete, T. T. Opportunities for Tapping into Three- Dimensional Chemical Space through a Quaternary Carbon. J. Med. Chem. 2020, 63, 13291–13315. (b) Carreira, E. M.; Fessard, T. C. Four-Membered Ring-Containing Spirocycles: Synthetic Strategies and Opportunities. Chem. Rev. 2014, 114, 8257–8322. (15) For a report on asymmetric synthesis of polycyclic aromatic hydrocarbons, see: Savary, D.; Baudoin, O. Enantioselective Pd Catalyst-Catalyzed C(sp³)-H Arylation for the Synthesis of Chiral Warped Peptides. Angew. Chem., Int. Ed. 2021, 60, 5136–5140. (16) (a) Sun, C.; Potter, B.; Morken, J. P. A Catalytic Enantiotopic-Group-Selective Suzuki Reaction for the Construction of Chiral Organoboronates. J. Am. Chem. Soc. 2014, 136, 6534–6537. (b) Willis, M. C.; Powell, L. H. W.; Claverie, C. K.; Watson, S. J. Enantioselective Suzuki Reactions: Catalytic Asymmetric Synthesis of Compounds Containing Quaternary Carbon Centers. Angew. Chem., Int. Ed. 2004, 43, 1249–1251. (c) Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. Catalytic asymmetric synthesis of axially chiral biaryls by palladium-catalyzed enantiotopic-selective cross-coupling. J. Am. Chem. Soc. 1995, 117, 9101–9102. (17) Xu, P.; Huang, Z. Catalytic reductive desymmetrization of malonic esters. Nat. Chem. 2021, 13, 634–642. (18) (a) Rodriguez, J.; Dhanjee, H. H.; Buchwald, S. L. Amphiphilic Biaryl Monophosphine Ligands by Regioselective Sulfonation. Org. Lett. 2021, 23, 777–780. (b) Anderson, K. W.; Buchwald, S. L. General Catalysts for the Suzuki-Miyaura and Sonogashira Coupling Reactions of Aryl Chlorides and for the Coupling of Challenging Substrate Combinations in Water. Angew. Chem., Int. Ed. 2005, 44, 6173–6177. (19) For axially chiral dialkylbiphenyl monophosphines bearing sterically dissimilar 2'- and 6'-substituents see: (a) Far, J. M.; Cinquabre, J.; Bortoluzzi, J.; Ches, M.; Leroux, G. R.; Panossian, A. When Chirality Meets “Buchwald-Type” Phosphines: Synthesis and Evaluation in Frustrated Lewis Pair-Lewis Base- and Palladium-Promoted Asymmetric Catalysis. Eur. J. Org. Chem. 2016, 2016, 4545–4553. (b) Hirai, S. The Synthesis and Applications of a Biaryl-Based Asymmetric Phosphine Ligand. M.S. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 2005. https://dspace.mit. edu/handle/1721.1/32490 (accessed 2021-12-27). 

(20) For examples of dialkylbiphenyl monophosphines possessing point chirality, see: (a) Yang, H.; Sun, J.; Gu, W.; Tang, W. Enantioselective Cross-Coupling for Axially Chiral Tetra-ortho-Substituted Biaryls and Asymmetric Synthesis of Gossypol. J. Am. Chem. Soc. 2020, 142, 8036–8043. (b) Zuccarello, G.; Mazans, J. G.; Escofet, I.; Scharnagel, D.; Kirkillo, M. S.; Pérez-Jimeno, A. H.; Calleja, P.; Booth, J. R.; Echavarren, A. M. Enantioselective Folding of Enynes by Gold(I) Catalysts with a Remote Chiral Element. J. Am. Chem. Soc. 2019, 141, 11858–11863. (c) Cheng, X.; Wang, Z.; Quintanilla, C. D.; Zhang, L. Chiral Biphenyl Phosphine Ligand Enabling Gold-Catalyzed Asymmetric Isomerization of Alkylene to Allene and Asymmetric Synthesis of 2,5-Dihydrofuranc. J. Am. Chem. Soc. 2019, 141, 3787–3791.
(21) Milne, J. E.; Buchwald, S. L. An Extremely Active Catalyst for the Negishi Cross-Coupling Reaction. *J. Am. Chem. Soc.* 2004, 126, 13028−13032.

(22) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. A Rationally Designed Universal Catalyst for Suzuki-Miyaura Coupling Processes. *Angew. Chem., Int. Ed.* 2004, 43, 1871−1876.

(23) (a) Tang, C. G.; Syafiqah, M. N.; Koh, Q.-M.; Zhao, C.; Zaini, J.; Seah, Q.-J.; Cass, M. J.; Humphries, M. J.; Grizzi, I.; Burroughes, J. H.; Png, R.-Q.; Chua, L.-L.; Ho, P. K. H. Multivalent anions as universal latent electron donors. *Nature* 2019, 573, 519−525. 
(b) Tang, C. G.; Ang, M. C. Y.; Choo, K.-K.; Keerthi, V.; Tan, J.-K.; Syafiqah, M. N.; Kugler, T.; Burroughes, J. H.; Png, R.-Q.; Chua, L.-L.; Ho, P. K. H. Doped polymer semiconductors with ultrahigh and ultralow work functions for ohmic contacts. *Nature* 2016, 539, 536−540.

(24) (a) Dhanjee, H. H.; Buslov, I.; Windsor, I. W.; Raines, R. T.; Pentelute, B. L.; Buchwald, S. L. Palladium-Protein Oxidative Addition Complexes by Amine-Selective Acylation. *J. Am. Chem. Soc.* 2020, 142, 21237−21242. 
(b) Uehling, M. R.; King, R. P.; Krskak, T.; Buchwald, S. L. Pharmaceutical diversification via palladium oxidative addition complexes. *Science* 2019, 363, 405−408.

(c) Vinogradova, E. V.; Zhang, C.; Spokoyny, A. M.; Pentelute, B. L.; Buchwald, S. L. Organometallic palladium reagents for cysteine bioconjugation. *Nature* 2015, 526, 687−691.

(25) (a) Jones, D. J.; Lautens, M.; McGlacken, G. P. The emergence of Pd-mediated reversible oxidative addition in cross coupling, carbohalogenation and carbonylation reactions. *Nat. Catal.* 2019, 2, 843−851. 
(b) Lennox, A. J. J.; Lloyd-Jones, G. C. Transmetalation in the Suzuki-Miyaura Coupling: The Fork in the Trail. *Angew. Chem., Int. Ed.* 2013, 52, 7362−7370.

(26) For a computational study on conformational multiplicity of catalysts during the oxidative addition step, see: Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. Structural Insights into Active Catalyst Structures and Oxidative Addition to (Biaryl)phosphine-Palladium Complexes via Density Functional Theory and Experimental Studies. *Organometallics* 2007, 26, 2183−2192.

(27) Schreiber, G.; Fersht, A. R. Rapid, electrostatically assisted association of proteins. *Nat. Struct. Biol.* 1996, 3, 427−431.

(28) In addition, it is possible that the electric field resulting from the ionic substrate−ligand interactions could influence the reactivity of the Pd center: (a) Shaik, S.; Danovich, D.; Joy, J.; Wang, Z.; Stuyver, T. Electric-Field Mediated Chemistry: Uncovering and Exploiting the Potential of (Oriented) Electric Fields to Exert Chemical Catalysis and Reaction Control. *J. Am. Chem. Soc.* 2020, 142, 12551−12562. 
(b) Joy, J.; Stuyver, T.; Shaik, S. Oriented External Electric Fields and Ionic Additives Elicit Catalysis and Mechanistic Cross-over in Oxidative Addition Reactions. *J. Am. Chem. Soc.* 2020, 142, 3836−3850.