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Catalytic Arylboration of Spirocyclic Cyclobutenes: Rapid Access to Highly Substituted Spiro[3.n]alkanes

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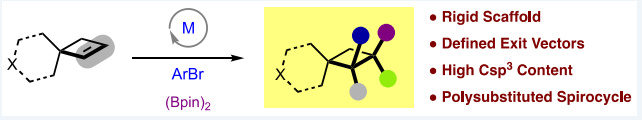
ABSTRACT: A method to achieve the synthesis of highly substituted spirocyclic cyclobutanes is disclosed. The reaction involves the catalytic arylboration of cyclobutenes. Depending on the substitution pattern of the cyclobutene, either a Cu/Pd- or a Ni-catalyzed reaction was utilized. In the case of the Cu/Pd-catalyzed reactions, the identification of a Cu-complex for arylboration was crucial to observe high selectivity. The synthetic utility of the products is demonstrated, and the mechanistic details are discussed.

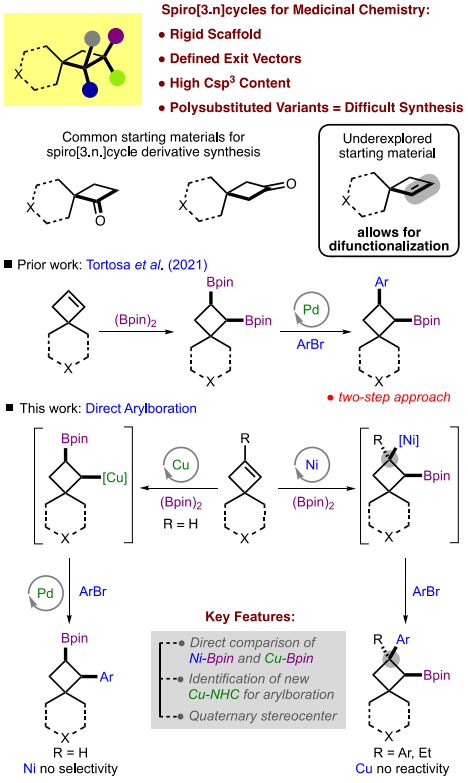


KEYWORDS: *nickel, copper, palladium, boron, arylboration*

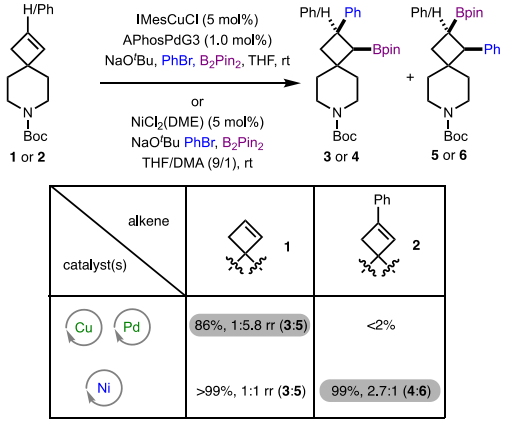
In recent years within the drug development industry, an increased emphasis has been placed on the synthesis and evaluation of molecules with an increased content of Csp^3 centers.[1] In particular, rigid and saturated polycyclic frameworks have been viewed as valuable motifs. Therefore, the development of new methods to make and modify such structures is important to the inclusion of these molecules in compound libraries and ultimately to facilitate drug development.[2]

Among all spirocyclic compounds, cyclobutane variants are particularly valuable because of the high rigidity, which results in defined exit vectors (Scheme 1).[3] While the synthesis of simple monosubstituted cyclobutyl spirocyclic molecules is generally achieved from the often commercially available ketones, protocols for the synthesis of more complex polysubstituted derivatives are more rare.[4] Along these lines, we became interested in derivatization of a spirocyclic cyclobutene by an

Scheme 1. Borylation Approaches to the Synthesis of Spirocyclic Cyclobutenes



Scheme 2. Initial Findings



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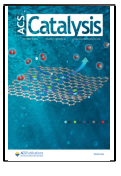

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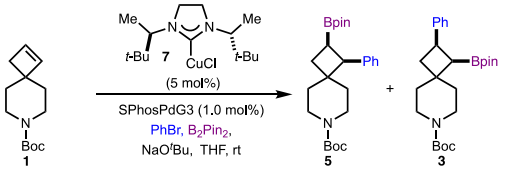
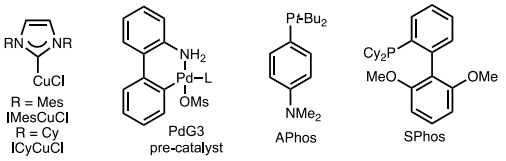
Table 1. Optimization



Entry	Change of Conditions	Yield (%)[a]	5:3
1	no change	93% (78%)[b]	29:1
2	IMesCuCl instead of **7**	88%	12:1
3	ICyCuCl instead of **7**	70%	14:1
4	APhos instead of SPhos	73%	11:1
5	RuPhos instead of SPhos	80%	14:1

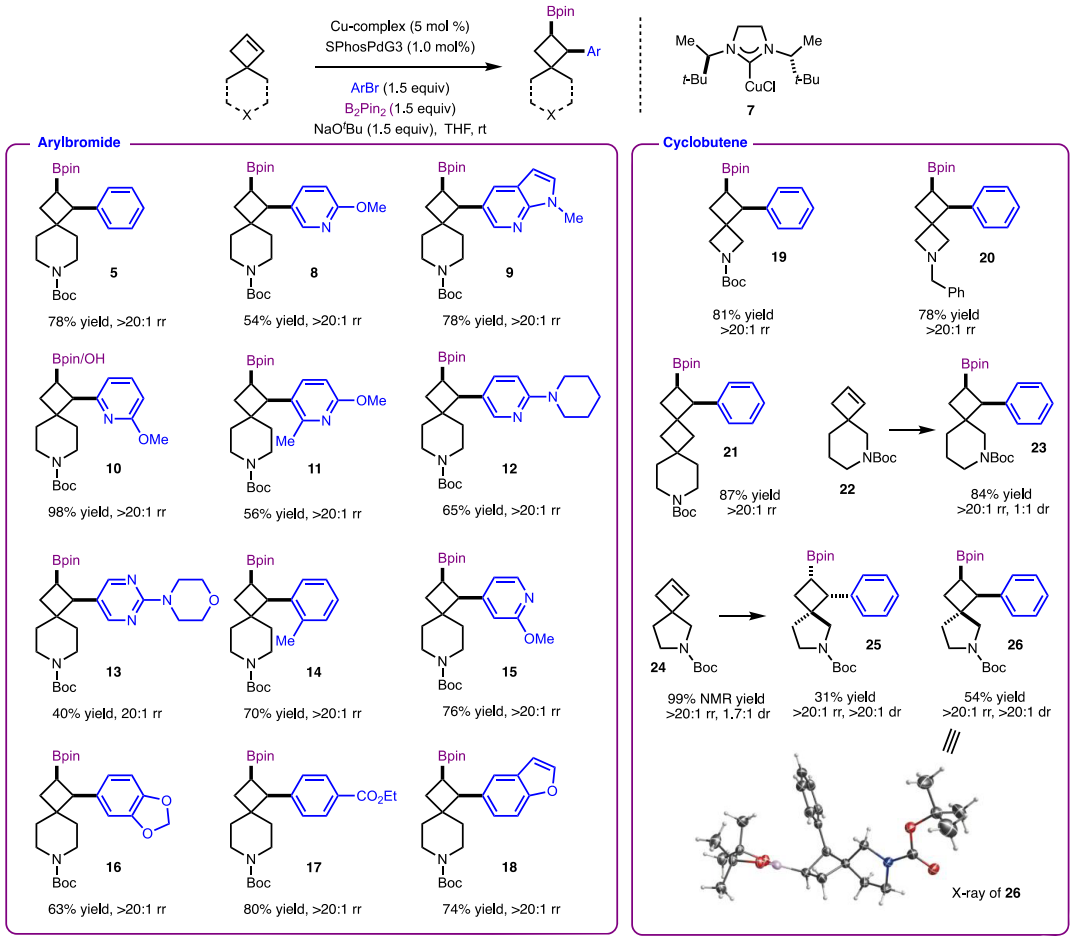


[a]Yield and dr determined by ^{1}H NMR analysis of the crude reaction mixture using an internal standard. [b]Isolated yield.

alkene difunctionalization reaction. Our lab,[5,6] among others,[7−9] has advanced alkene arylboration reactions as a way to rapidly generate molecular complexity from simple alkene components. We envision that application of the principles learned to the challenge of spirocyclic cyclobutene functionalization would provide an enabling tool for the creation of rigid and complex saturated carbo- and heterocycles. During the course of our studies, Tortosa and co-workers reported an elegant approach toward spirocyclic cyclobutene functionalization that involved a diboration followed by regioselective cross coupling of the less sterically encumbered C−B bond.[10,11] This two-step approach enabled the synthesis of many complex molecules. In this manuscript, a one-step process for arylboration of substituted spirocyclic cyclobutenes is presented, wherein two catalytic systems are utilized to achieve broad scope. While the products prepared here are conceptually similar to those described in the Tortosa work, they are distinctly different in the substitution pattern, thus offering an orthogonal approach and allowing access to new chemical space. Importantly, with the methods described herein, congested C−C bonds, including quaternary carbons, are formed which were not previously accessible.[12]

Over the last 7 years, our lab has identified two catalytic systems to achieve arylboration of a wide variety of alkenes. Pd/Cu-catalyzed variants were found to be effective for arylboration of activated alkenes (e.g., alkenylarenes, 1,3-dienes),[5] whereas a Ni-catalyzed reaction was found to be most effective for unactivated alkenes and certain classes of alkenylarenes.[6] In one example, we demonstrated Pd/Cu-catalyzed arylboration of a symmetric cyclobutene.[5c] The extension to nonsymmetrical cyclobutenes adds the additional challenge of regiochemical

Scheme 3. Cu/Pd-Catalyzed Arylboration[a]



[a]Reactions run on 0.2 mmol scale. Yield is of isolated product after silica gel column chromatography.

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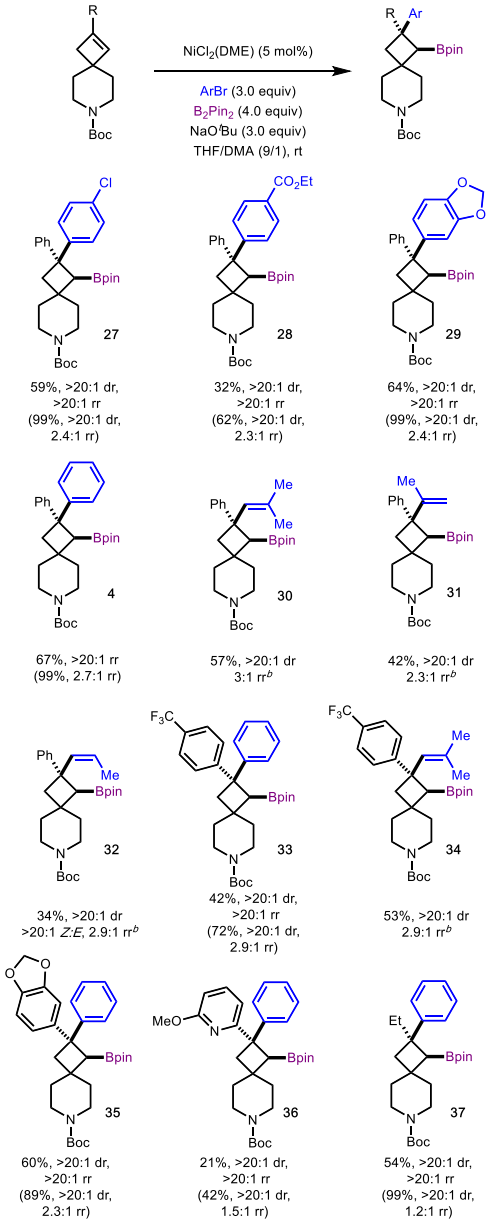
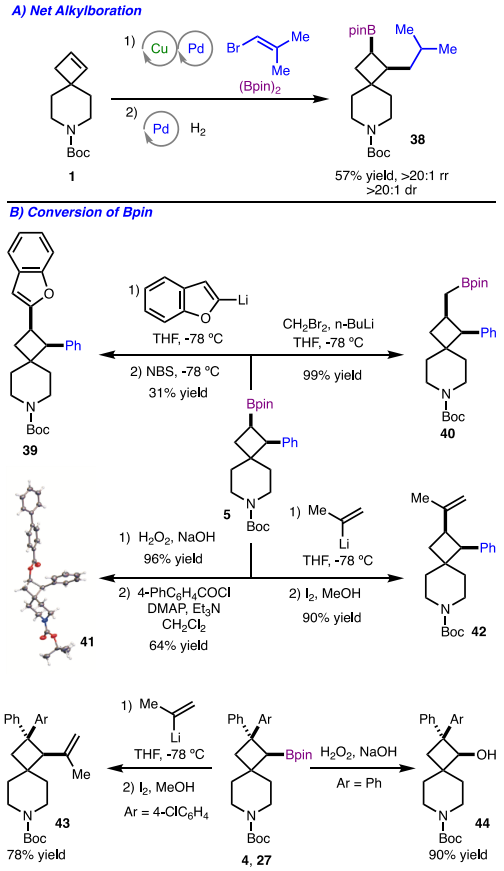
Scheme 4. Ni-Catalyzed Arylboration[a]

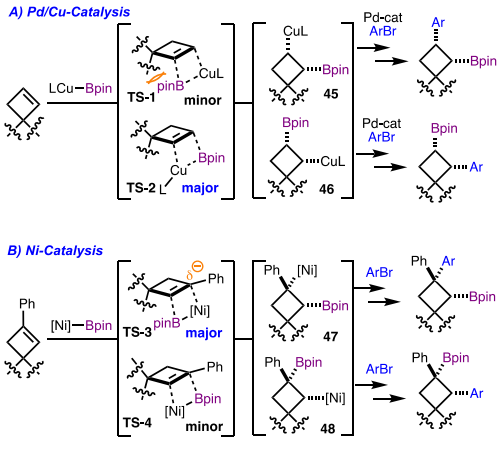


[a]Reactions run on 0.2 mmol scale. Yield is of isolated product after silica gel column chromatography. [b]Reaction run in THF/DMA (4/1) at 30 °C.

Scheme 5. Further Transformations



Scheme 6. Proposed Reaction Pathways



control and overcoming steric issues by forming a bond proximal to the quaternary center of the spirocycle.

Initial efforts probed the reactivity of unsubstituted cyclobutene **1** and the Ph substituted variant (**2**) under both Pd/Cu- and Ni-catalysis (Scheme 2). For reaction of cyclobutene **1**, both the Pd/Cu- and Ni-catalyzed reactions were effective; however, the regioselectivity was good only in the case of the former. Notably, product **5** cannot be generated by the method reported by Tortosa, thus demonstrating complementarity.[10] When the Ph-substituted variant (**2**) was examined under the Pd/Cu-catalyzed reaction conditions, no product was observed, and starting material was recovered. However, in the case of the Ni-catalyzed reactions, the arylboration proceeded in high yield, albeit with moderate regioselectivity to generate **4** as the major isomer.

On the basis of the initial findings illustrated in Scheme 2 for reaction of cyclobutene **1**, the process was optimized to improve the regioselectivity, with Cu-NHC **7** and SPhosPd-G3[13,14] serving as optimal catalysts (Table 1, entry 1). Two aspects of the optimization were crucial for observing high regioselectivity. First, NHC ligands with *N,N*-dialkyl substitution were superior to *N,N*-diaryl NHCs (Table 1, entries 1−3). Second, quite unexpectedly, the regioselectivity was dependent on the Pd-catalyst (Table 1, entries 4−5). On the basis of the accepted catalytic cycles for this reaction, the regioselectivity should only be dependent on the Cu-catalyst.[5] It is possible that the erosion in regioselectivity is the result of β-boryl elimination processes.[8d,15] Finally, it should also be noted that while chiral

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ligand **7** was used, only moderate enantioselectivity was observed.[16] However, it is easily prepared from inexpensive materials.

Under the optimal conditions. the scope of the reaction was evaluated (Scheme 3). With respect to the aryl bromide component, several points are noteworthy: (1) electron-withdrawing (product **17**) and electron-releasing substituents (product **16**) are tolerated. (2) Sterically demanding substitution does not greatly impede the reaction (product **14**). (3) An emphasis was placed on the use of heterocyclic aryl bromides as these are common in biologically relevant molecules. 2-, 3-, and 4-bromo pyridines all functioned well (products **8**, **10**, **11**, **12**, **15**). In addition, pyrimidine (product **13**), benzofuran (product **18**), and azaindoles (product **9**) were also well tolerated.

With respect to the spirocyclic cyclobutene component, other ring sizes could be used with little change in yield or regioselectivity (Scheme 3). Since a focus of these efforts are on reactions of heterocycles, both *N*-Boc (product **19**) and *N*-Bn (product **20**) protected variants were demonstrated to work well. For reactions of nonsymmetric spirocycles, diastereomers were generated. In the case of **22** and **24**, a ∼1:1 mixture of diastereomers was observed. In the case of the latter, the diastereomers (products **25** and **26**) were easily separated by silica gel column chromatography. The relative stereochemistry of the product **26** was determined through single-crystal analysis.

With respect to Ni-catalyzed arylboration of 2-Ph-substituted cyclobutene **2**, other aryl and alkenylbromides were tested, and various azaspiro[3.5]nonanes were formed with quaternary stereogenic centers (Scheme 4). In each case, while a single diastereomer was observed, a mixture of regioisomers was generated (products **27**−**36**). However, separation by silica gel column chromatography was easily accomplished for many cases. Examples **29** and **35** are particularly interesting as starting from different cyclobutenes both diastereomers can be accessed. An alkyl-substituted cyclobutene was also attempted (product **37**). While the reaction proceeded in high yield, a 1.2:1 mixture of regioisomers was observed. In this case, the major isomer was easily separated and isolated in acceptable yield.

On the basis of a recent study from our lab, a net borylalkylation can be achieved via subsequent hydrogenation of the respective borylalkenylation product (product **38**) (Scheme 5).[6b] In addition, because of the presence of the Bpin unit,[17] arylation (product **39**),[18] Matteson homologation (product **40**), Zweifel olefination (product **42**),[19] and oxidation (product **41**) can be carried out from arylboration product **5** to generate more complex derivatives. In addition, further elaboration of products derived from the Ni-catalyzed arylation can be achieved to provide access to **43** and **44**.

With respect to the reaction pathways, on the basis of prior studies, the Pd/Cu-catalyzed reactions likely operate by borylcupration of the alkene, followed by Pd-catalyzed cross coupling of the generated alkyl-Cu intermediates (Scheme 6).[5] In the case of spirocyclic cyclobutenes, the borylcupration event likely proceeds via **TS-2** to generate alkyl-Cu **46**. To rationalize the regiochemical outcome, it is likely that steric pressure between the Bpin unit and the quaternary carbon disfavors **TS-1**.[11] In the case of the Ni-catalyzed reaction, prior mechanistic work supports a process in which a boryl-nickelation occurs to generate alkyl-Ni-complex **47**, which undergoes reaction with the ArBr (Scheme 6).[6] In this case, the regioselectivity is likely controlled by stabilization developing charge at the benzylic site as shown in **TS-3**.[6c]

In summary, a method for the synthesis of complex and sterically congested spiro[3.n]alkanes is presented. The use of two catalytic systems enabled access to a broad range of products that would otherwise be inaccessible with existing methods.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c03491.

Experimental procedures characterization data, X-ray crystal structure and NMR spectra (PDF)

X-ray data (CIF)

X-ray data (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Wei, W.; Cherukupalli, S.; Jing, L.; Liu, X.; Zhan, P. Fsp3: A new parameter for drug-likeness. *Drug Discovery Today* **2020**, *25*, 1839−1845. (b) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752−6756.

(2) (a) Hiesinger, K.; Dar'in, D.; Proschak, E.; Krasavin, M. Spirocyclic Scaffolds in Medicinal Chemistry. *J. Med. Chem.* **2021**, *64*, 150−183. (b) Talele, T. T. Opportunities for Tapping into Three-Dimensional Chemical Space through a Quaternary Carbon. *J. Med. Chem.* **2020**, *63*, 13291−13315. (c) Zheng, Y.-J.; Tice, C. M. The utilization of spirocyclic scaffolds in novel drug discovery. *Expert Opin. Drug Discovery* **2016**, *11*, 831−834. (d) Zheng, Y.; Tice, C. M.; Singh, S. B. The use of spirocyclic scaffolds in drug discovery. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673−3682.

(3) Carreira, E. M.; Fessard, T. C. Four-Membered Ring-Containing Spirocycles: Synthetic Strategies and Opportunities. *Chem. Rev.* **2014**, *114*, 8257−8322.
(4) For examples, see: (a) Murray, P. R. D.; Bussink, W. M. M.; Davies, G. H. M.; van der Mei, F. W.; Antropow, A. H.; Edwards, J. T.; D'Agostino, L. A.; Ellis, J. M.; Hamann, L. G.; Romanov-Michailidis, F.; Knowles, R. R. Intermolecular Crossed [2 + 2] Cycloaddition Promoted by Visible-Light Triplet Photosensitization: Expedient Access to Polysubstituted 2-Oxaspiro[3.3]heptanes. *J. Am. Chem. Soc.* **2021**, *143*, 4055−4063. (b) Zhao, C.-G.; Feng, Z.-T.; Xu, G.-Q.; Gao, A.; Chen, J.-W.; Wang, Z.-Y.; Xu, P.-F. Highly Enantioselective Construction of Strained Spiro[2,3]hexanes through a Michael Addition/Ring Expansion/Cyclization Cascade. *Angew. Chem., Int. Ed.* **2020**, *59*, 3058−3062. (c) Flodén, N. J.; Trowbridge, A.; Willcox, D.; Walton, S. M.; Kim, Y.; Gaunt, M. J. Streamlined Synthesis of C(sp3)-Rich N-Heterospirocycles Enabled by Visible-Light-Mediated Photocatalysis. *J. Am. Chem. Soc.* **2019**, *141*, 8426−8430. (d) Reddy, L. R.; Waman, Y.; Kallure, P.; Nalivela, K. S.; Begum, Z.; Divya, T.; Kotturi, S. Asymmetric synthesis of 1-substituted 2-azaspiro[3.3]-heptanes: important motifs for modern drug discovery. *Chem. Commun.* **2019**, *55*, 5068−5070. (e) Poplata, S.; Bach, T. Enantioselective Intermolecular [2 + 2] Photocycloaddition Reaction of Cyclic Enones and Its Application in a Synthesis of (−)-Grandisol. *J. Am. Chem. Soc.* **2018**, *140*, 3228−3231. (f) Royes, J.; Ni, S.; Farré, A.; La Cascia, E.; Carbó, J. J.; Cuenca, A. B.; Maseras, F.; Fernández, E. Copper-Catalyzed Borylative Ring Closing C−C Coupling toward Spiro- and Dispiroheterocycles. *ACS Catal.* **2018**, *8*, 2833−2838. (g) Chalyk, B. A.; Butko, M. V.; Yanshyna, O. O.; Gavrilenko, K. S.; Druzhenko, T. V.; Mykhailiuk, P. K. Synthesis of Spirocyclic Pyrrolidines: Advanced Building Blocks for Drug Discovery. *Chem. - Eur. J.* **2017**, *23*, 16782−16786. (h) Halskov, K. S.; Kniep, F.; Lauridsen, V. H.; Iversen, E. H.; Donslund, B. S.; Jørgensen, K. A. Organocatalytic Enamine-Activation of Cyclopropanes for Highly Stereoselective Formation of Cyclobutanes. *J. Am. Chem. Soc.* **2015**, *137*, 1685−1691. (i) Qi, L.-W.; Yang, Y.; Gui, Y.-Y.; Zhang, Y.; Chen, F.; Tian, F.; Peng, L.; Wang, L.-X. Asymmetric Synthesis of 3,3′-Spirooxindoles Fused with Cyclobutanes through Organocatalytic Formal [2 + 2] Cycloadditions under H-Bond-Directing Dienamine Activation. *Org. Lett.* **2014**, *16*, 6436−6439. (j) Kubota, K.; Yamamoto, E.; Ito, H. Copper(I)-Catalyzed Borylative exo-Cyclization of Alkenyl Halides Containing Unactivated Double Bond. *J. Am. Chem. Soc.* **2013**, *135* (7), 2635−2640. (k) Burkhard, J. A.; Guérot, C.; Knust, H.; Carreira, E. M. Expanding the Azaspiro[3.3]-heptane Family: Synthesis of Novel Highly Functionalized Building Blocks. *Org. Lett.* **2012**, *14*, 66−69. (l) Burkhard, J. A.; Guérot, C.; Knust, H.; Rogers-Evans, M.; Carreira, E. M. Synthesis and Structural Analysis of a New Class of Azaspiro[3.3]heptanes as Building Blocks for Medicinal Chemistry. *Org. Lett.* **2010**, *12*, 1944−1947. For a review, see: (m) Rios, R. Enantioselective methodologies for the synthesis of spiro compounds. *Chem. Soc. Rev.* **2012**, *41*, 1060−1074.
(5) (a) Smith, K. B.; Logan, K. M.; You, W.; Brown, M. K. Alkene Carboboration Enabled by Synergistic Catalysis. *Chem. - Eur. J.* **2014**, *20*, 12032−12036. (b) Logan, K. M.; Smith, K. B.; Brown, M. K. Copper/Palladium Synergistic Catalysis for the syn- and anti-Selective Carboboration of Alkenes. *Angew. Chem., Int. Ed.* **2015**, *54*, 5228−5231. (c) Logan, K. M.; Brown, M. K. Catalytic Enantioselective Arylboration of Alkenylarenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 851−855. (d) Smith, K. B.; Brown, M. K. Regioselective Arylboration of Isoprene and Its Derivatives by Pd/Cu Cooperative Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 7721−7724. (e) Sardini, S. R.; Brown, M. K. Catalyst Controlled Regiodivergent Arylboration of Dienes. *J. Am. Chem. Soc.* **2017**, *139*, 9823−9826. (f) Bergmann, A. M.; Dorn, S. K.; Smith, K. B.; Logan, K. M.; Brown, M. K. Catalyst-Controlled 1,2- and 1,1-Arylboration of α-Alkyl Alkenyl Arenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 1719−1723. (g) Huang, Y.; Brown, M. K. Synthesis of Bisheteroarylalkanes by Heteroarylboration: Development and Application of a Pyridylidene−Copper Complex. *Angew. Chem., Int. Ed.* **2019**, *58*, 6048−6052. (h) Bergmann, A. M.; Sardini, S. R.; Smith, K. B.; Brown, M. K. Regioselective Arylboration of 1,3-Butadiene. *Isr. J. Chem.* **2020**, *60*, 394−397. (i) Dorn, S. K.; Tharp, A. E.; Brown, M. K. Modular Synthesis of a Versatile Double-Allylation Reagent for Complex Diol Synthesis. *Angew. Chem., Int. Ed.* **2021**, *60*, 16027−16034.
(6) (a) Lambright, A. L.; Liu, Y.; Joyner, I. A.; Logan, K. M.; Brown, M. K. Mechanism-Based Design of an Amide-Directed Ni-Catalyzed Arylboration of Cyclopentene Derivatives. *Org. Lett.* **2021**, *23*, 612−616. (b) Simlandy, A. K.; Sardini, S. R.; Brown, M. K. Construction of Congested Csp3-Csp3 Bonds by a Formal Ni-Catalyzed Alkylboration. *Chem. Sci.* **2021**, *12*, 5517−5521. (c) Sardini, S. R.; Brown, M. K. Nickel-Catalyzed Arylboration of Cyclopentene. *Org. Synth.* **2020**, *97*, 355−367. (d) Chen, L.-A.; Lear, A. R.; Gao, P.; Brown, M. K. Nickel-Catalyzed Arylboration of Alkenylarenes: Synthesis of Boron-Substituted Quaternary Carbons and Regiodivergent Reactions. *Angew. Chem., Int. Ed.* **2019**, *58*, 10956−10960. (e) Sardini, S. R.; Lambright, A. L.; Trammel, G. L.; Omer, H. M.; Liu, P.; Brown, M. K. Ni-Catalyzed Arylboration of Unactivated Alkenes: Scope and Mechanistic Studies. *J. Am. Chem. Soc.* **2019**, *141*, 9391−9400. (f) Logan, K. M.; Sardini, S. R.; White, S. D.; Brown, M. K. Nickel-Catalyzed Stereoselective Arylboration of Unactivated Alkenes. *J. Am. Chem. Soc.* **2018**, *140*, 159−162.
(7) For reviews, see: (a) Semba, K.; Nakao, Y. Cross-coupling reactions by cooperative Pd/Cu or Ni/Cu catalysis based on the catalytic generation of organocopper nucleophiles. *Tetrahedron* **2019**, *75*, 709−719. (b) Xue, W.; Oestreich, M. Beyond Carbon: Enantioselective and Enantiospecific Reactions with Catalytically Generated Boryl- and Silylcopper Intermediates. *ACS Cent. Sci.* **2020**, *6*, 1070−1081. (c) Whyte, A.; Torelli, A.; Mirabi, B.; Zhang, A.; Lautens, M. Copper-Catalyzed Borylative Difunctionalization of π-Systems. *ACS Catal.* **2020**, *10*, 11578−11622.
(8) For selected contribution from other laboratories, see: (a) Semba, K.; Nakao, Y. Arylboration of Alkenes by Cooperative Palladium/Copper Catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 7567−7570. (b) Chen, B.; Cao, P.; Yin, X.; Liao, Y.; Jiang, L.; Ye, J.; Wang, M.; Liao, J. Modular Synthesis of Enantioenriched 1,1,2-Triarylethanes by an Enantioselective Arylboration and Cross-Coupling Sequence. *ACS Catal.* **2017**, *7*, 2425−2429. (c) Liao, Y.; Yin, X.; Wang, X.; Yu, W.; Fang, D.; Hu, L.; Wang, M.; Liao, J. Enantioselective Synthesis of Multisubstituted Allenes by Cooperative Cu/Pd-Catalyzed 1,4-Arylboration of 1,3-Enynes. *Angew. Chem., Int. Ed.* **2020**, *59*, 1176−1180. (d) Semba, K.; Ohtagaki, Y.; Nakao, Y. 1,2-Arylboration of aliphatic alkenes by cooperative palladium/copper catalysis. *Tetrahedron Lett.* **2021**, *72*, 153059.
(9) (a) Li, H.; Long, J.; Li, Y.; Wang, W.; Pang, H.; Yin, G. Nickel-Catalyzed Regioselective Arylboration of Conjugated Dienes. *Eur. J. Org. Chem.* **2021**, *2021*, 1424−1428. (b) Wang, W.; Ding, C.; Pang, H.; Yin, G. Nickel-Catalyzed 1,2-Arylboration of Vinylarenes. *Org. Lett.* **2019**, *21*, 3968−3971.
(10) Nóvoa, L.; Trulli, L.; Parra, A.; Tortosa, M. Stereoselective Diboration of Spirocyclobutenes: A Platform for the Synthesis of Spirocycles with Orthogonal Exit Vectors. *Angew. Chem., Int. Ed.* **2021**, *60*, 11763−11768.
(11) Very recently the Tortosa group reported a Cu-catalyzed protoboration of spirocyclobutenes. Novoa, L.; Trulli, L.; Fernandez, I.; Parra, A.; Tortosa, M. Regioselective Monoborylation of Spirocylobutenes. *Org. Lett.* **2021**, *23*, 7434.
(12) Goetzke, F. W.; Hell, A. M.; van Dijk, L.; Fletcher, S. P. A Catalytic Asymmetric Cross Coupling Approach to the Synthesis of Cyclobutanes. *Nat. Chem.* **2021**, *13*, 880.
(13) Guram, A. S.; King, A. O.; Allen, J. G.; Wang, X.; Schenkel, L. B.; Chan, J.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J.; Reider, P. J. New Air-Stable Catalysts for General and Efficient Suzuki−Miyaura Cross-Coupling Reactions of Heteroaryl Chlorides. *Org. Lett.* **2006**, *8*, 1787−1789.
(14) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. Design and preparation of new palladium precatalysts for C−C and C−N cross-coupling reactions. *Chem. Sci.* **2013**, *4*, 916−920.
(15) Miyaura, N.; Suzuki, A. The Palladium-Catalyzed "Head-to-Tail" Cross Coupling Reaction of 1-Alkenylboranes with Phenyl or 1-Alkenyl Iodides. a Novel Synthesis of 2-Phenyl-1-Alkenes or 2-Alkyl. *J. Organomet. Chem.* **1981**, *213*, C53.

https://doi.org/10.1021/acscatal.1c03491
ACS Catal. 2021, 11, 12815−12820

(16) See the SI for details.
(17) Sandford, C.; Aggarwal, V. K. Stereospecific Functionalizations and Transformations of Secondary and Tertiary Boronic Esters. *Chem. Commun.* **2017**, *53*, 5481−5494.
(18) Odachowski, M.; Bonet, A.; Essafi, S.; Conti-Ramsden, P.; Harvey, J. N.; Leonori, D.; Aggarwal, V. K. Development of Enantiospecific Coupling of Secondary and Tertiary Boronic Esters with Aromatic Compounds. *J. Am. Chem. Soc.* **2016**, *138*, 9521−9532.
(19) Armstrong, R.; Aggarwal, V. 50 Years of Zweifel Olefination: a Transition-Metal-Free Coupling. *Synthesis* **2017**, *49*, 3323−3336.

https://doi.org/10.1021/acscatal.1c03491
ACS Catal. 2021, 11, 12815−12820