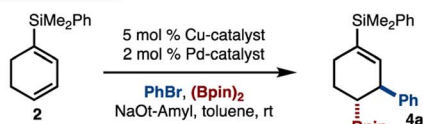
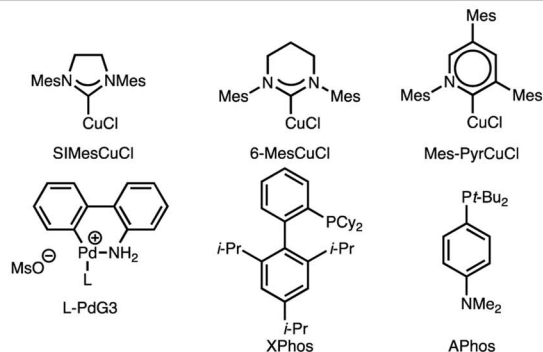


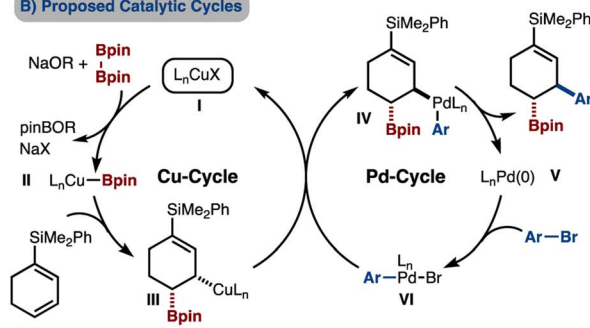
A) Reaction Optimization



entry	Cu-catalyst	Pd-catalyst	yield (%)	dr
1	SIMesCuCl	XPhosPdG3	92	3:1
2	SIMesCuCl	APhosPdG3	80	12:1
3	Mes-PyrCuCl	APhosPdG3	95	>20:1
4	6-MesCuCl	APhosPdG3	74	>20:1



B) Proposed Catalytic Cycles

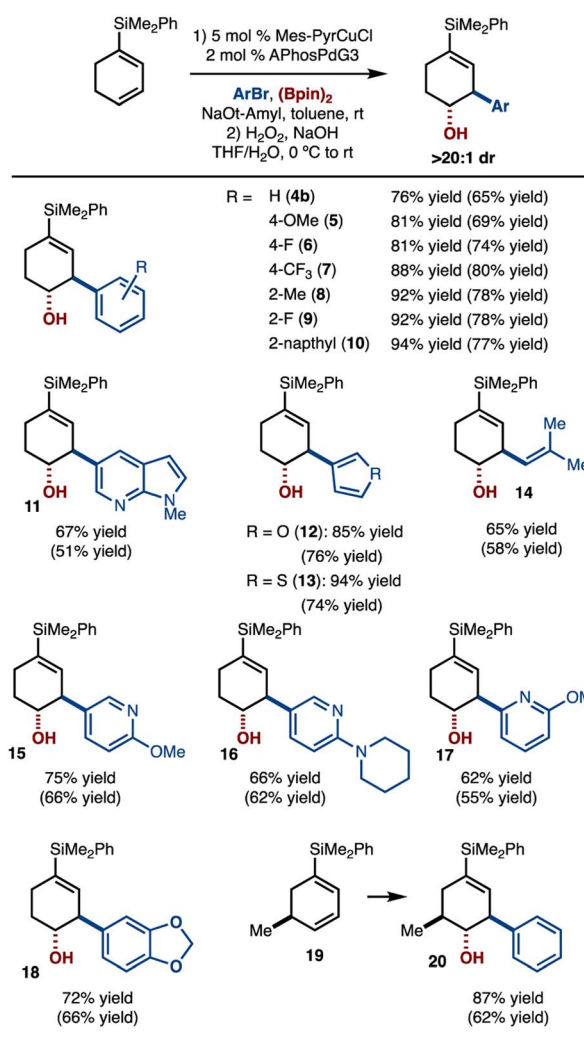


Scheme 3 Initial results. Yield and diastereoselectivity determined by ^1H NMR analysis with an internal standard of the unpurified reaction mixture.

various conditions a complex mixture of products was observed with the desired product being generated in <10% yield. The failure of these reactions may be due, in part, to the γ -carbon being nucleophilic by virtue of electron donation from the oxygen atom and therefore, addition of the nucleophilic Cu–Bpin is disfavored. To overcome the polarity mismatch, we designed a new substrate, 1-silyl-1,3-cyclohexadiene **2**. The electropositive Si-atom removes electron density from the π -system and renders C2 and C4 electron-poor and thus allows for borylcupration to occur in a polarity matched scenario.

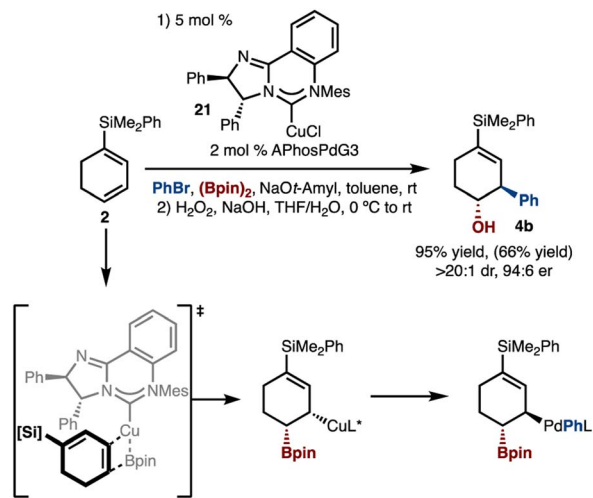
The requisite silyl diene **2** can easily be prepared on gram scale from **1** through a robust two-step procedure that involves (1) addition of LiSiMe_2Ph to cyclohexenone (**1**),¹⁰ and (2) [2,3]-sigmatropic rearrangement and *syn*-elimination with 2,4-(NO_2)₂- $\text{C}_6\text{H}_3\text{SCL}$.¹¹ Under a standard set of conditions with SiMe_2CuCl and XPhosPdG3 ¹² that has been used for arylboration of other alkenes,⁷ product **4a** was generated in good yield but moderate diastereomeric ratio (dr), thus supporting the polarity-matched hypothesis.

Based on the initial findings, evaluation of Pd-catalysts led to the finding that APhospdG3 (ref. 13) delivered the product with improved dr (Scheme 3A, compare entries 1–2). Further reaction optimization through examination of various Cu-catalysts revealed that reaction promoted by $\text{Mes-PyridylideneCuCl}$ afforded the product in high yield and diastereoselectivity (Scheme 3A, entry 3).¹⁴ This class of catalyst was recently reported by our lab, and has been shown to, at times, offer superior reactivity compared to SiMe_2CuCl .^{7g} We hypothesized that the increased diastereoselectivity may be due to the more sterically demanding Mes-Pyridylidene as compared to SiMe_2CuCl (due to the positioning of the Mes groups closer to the Cu-atom as a result of the six- vs. five-membered ring). This hypothesis was tested by use of the related 6-MesCuCl catalyst, which also led to high diastereoselectivity, albeit with reduced yield (Scheme 3A, entry 4). Finally, based on our prior studies, these reactions likely operate by the catalytic cycles illustrated in Scheme 3B. Key aspects of the catalytic cycles are: (1) *syn*-borylcupration of an alkene with L_nCu –



Scheme 4 Substrate scope. See the ESI† for details. Yield and diastereoselectivity determined by ^1H NMR analysis with an internal standard of the unpurified reaction mixture after oxidation. Yield in parentheses is of isolated purified product after oxidation.





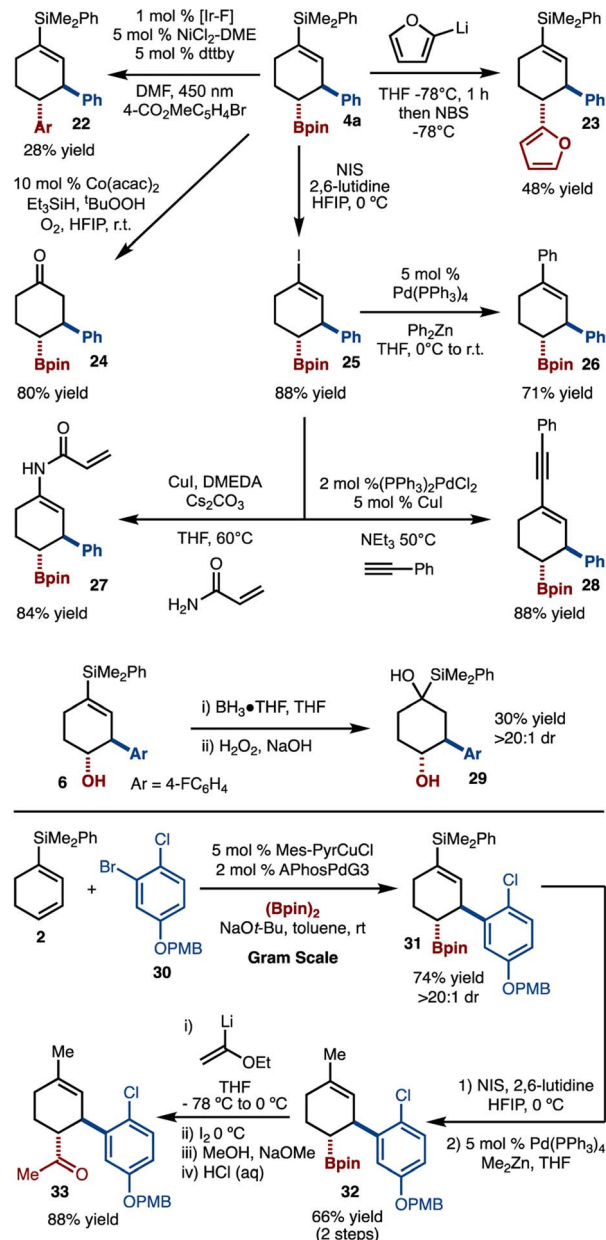
Scheme 5 Enantioselective arylation. Yield and diastereoselectivity determined by ¹H NMR analysis with an internal standard of the unpurified reaction mixture after oxidation. Yield in parentheses is of isolated purified product after oxidation. Enantiomeric ratio (er) determined by HPLC analysis with a chiral column.

Bpin (**II–III**), (2) transmetalation with an L_nPdArBr complex that can either proceed with inversion (shown) or retention (not shown) of configuration (**III–IV**), (3) reductive elimination of an alkyl–Pd-complex (**IV–V**).

Under the conditions outlined in Scheme 3A, entry 3, the scope of the reaction was evaluated (Scheme 4). It was found that aryl-bromides that bear electron-donating (products **5**, **11**, **18**) and electron-withdrawing substituents (products **6–7**, **9**) functioned well. In addition, use of sterically demanding 2-MeC₆H₄Br did not impede the reaction (product **8**). Various heterocycles (products **11–13**, **15–17**) as well as an alkenyl bromide were also tolerated (product **14**). In addition, alkene **19** could be used and allowed for control of stereochemistry with respect to the existing stereogenic center. It should be noted that the products were oxidized prior to isolation to facilitate purification.

Enantioselective variants of the reaction were also investigated (Scheme 5). It was found that use of McQuadeCuCl (**21**)¹⁵ allowed for formation of **4b** in high yield, enantioselectivity, and diastereoselectivity.^{8a} It is suggested that the borylcupration occurs *via* the model illustrated in Scheme 5, such that the bulk of the diene is positioned distal to the N-Mes group and opposite the proximal Ph-group.

A key motivation behind this study was to selectively harness the reactivity of the C–B bond and vinyl-silanes to allow for a variety of products to be generated (Scheme 6). For example, metallophotoredox¹⁶ and transition-metal-free cross coupling¹⁷ could be achieved to prepare **22** and **23**, respectively. Oxidation of the alkenylsilane could be achieved by Co-catalyzed oxidation to generate **24**, thus realizing the β,γ-functionalization of cyclohexenone.¹⁸ Hiyama coupling of the vinylsilane was attempted; however, cross coupling was not observed. To address this issue a two-step protocol was devised that involved conversion to vinyl iodide **25** with NIS and HFIP.¹⁹ The iodide could then be subjected to Negishi,²⁰ amidation,²¹ and



Scheme 6 Larger scale and further functionalizations.

Sonogashira²² reactions to provide access to **26**, **27**, and **28**, respectively. Hydroboration of the alkenylsilane was also attempted and gave rise to **29** in 30% yield and >20:1 dr.²³ In addition, we have carried out an alternative series of functionalizations. Starting with gram scale synthesis of **31**, conversion by iodination and Negishi cross coupling led to **32**. Finally, Zweifel reaction with lithiated ethylvinyl ether and hydrolysis led to formation of ketone **33**.

Conclusions

In summary, through the introduction of Cu/Pd-catalyzed arylation of 1-silyl-1,3-cyclohexadiene, a new strategy to prepare diverse cyclohexanes is presented. To observe high levels of



diastereoselectivity and yield, it was crucial to use a pyridylidene Cu-complex (Mes-PyrCuCl). The demonstrated synthetic transformations of the products serves to highlight the utility of these processes.

Data availability

The ESI[†] contains method description, product characterization data, and NMR spectra.

Author contributions

M. K. B. and A. R. L. conceived and initiated the project. P. F. C., A. R. L. and S. D. collected the data. All authors composed the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- R. J. K. Taylor, *Synthesis*, 1985, **4**, 364.
- K. F. Podraza, *Org. Prep. Proced. Int.*, 1991, **23**, 217.
- (a) W. Fudickar, K. Vomdran and T. Linker, *Tetrahedron*, 2006, **62**, 10639; (b) S. Saito, M. Shiozawa, M. Ito and H. Yamamoto, *J. Am. Chem. Soc.*, 1998, **120**, 813; (c) C. C. Zou, C. K. Zeng, Z. Liu, M. Lu, X. H. Sun and J. X. Ye, *Angew. Chem., Int. Ed.*, 2016, **55**, 14255; (d) G. Saini, A. Mondal and M. Kapur, *Org. Lett.*, 2019, **21**, 9071.
- (a) X. G. Liu, X. H. Chen and J. T. Mohr, *Org. Lett.*, 2015, **17**, 3572; (b) X. H. Chen, X. G. Liu and J. T. Mohr, *Org. Lett.*, 2016, **18**, 716; (c) X. H. Chen, X. G. Liu and J. T. Mohr, *J. Am. Chem. Soc.*, 2016, **138**, 6364; (d) X. G. Liu, X. H. Chen and J. T. Mohr, *Org. Lett.*, 2016, **18**, 3182; (e) X. Zhao, F. Yang, S. Y. Zou, Q. Q. Zhou, Z. S. Chen and K. G. Ji, *ACS Catal.*, 2022, **12**, 1732.
- (a) Z. Liu, Y. Gao, T. Zeng and K. M. Engle, *Isr. J. Chem.*, 2020, **60**, 219; (b) D. R. Pye and N. P. Mankad, *Chem. Sci.*, 2017, **8**, 1705; (c) G. J. P. Perry, T. Jia and D. J. Procter, *ACS Catal.*, 2020, **10**, 1485.
- (a) K. Semba and Y. Nakao, *Tetrahedron*, 2019, **75**, 709; (b) S. K. Dorn and M. K. Brown, *ACS Catal.*, 2022, **12**, 2058.
- (a) K. Semba and Y. Nakao, *J. Am. Chem. Soc.*, 2014, **136**, 7567; (b) K. B. Smith, K. M. Logan, W. You and M. K. Brown, *Chem. –Eur. J.*, 2014, **20**, 12032; (c) K. M. Logan, K. B. Smith and M. K. Brown, *Angew. Chem., Int. Ed.*, 2015, **54**, 5228; (d) K. M. Logan and M. K. Brown, *Angew. Chem., Int. Ed.*, 2017, **56**, 851; (e) K. B. Smith and M. K. Brown, *J. Am. Chem. Soc.*, 2017, **139**, 7721; (f) B. Chen, P. Cao, X. Yin, Y. Liao, L. Jiang, J. Ye, M. Wang and J. Liao, *ACS Catal.*, 2017, **7**, 2425; (g) S. R. Sardini and M. K. Brown, *J. Am. Chem. Soc.*, 2017, **139**, 9823; (h) A. M. Bergmann, S. K. Dorn, K. B. Smith, K. M. Logan and M. K. Brown, *Angew. Chem., Int. Ed.*, 2019, **58**, 1719; (i) Y. Huang and M. K. Brown, *Angew. Chem., Int. Ed.*, 2019, **58**, 6048; (j) A. M. Bergmann, S. R. Sardini, K. B. Smith and M. K. Brown, *Isr. J. Chem.*, 2020, **60**, 394; (k) H. Lee, S. Lee and J. Yun, *ACS Catal.*, 2020, **10**, 2069; (l) S. K. Dorn, A. E. Tharp and M. K. Brown, *Angew. Chem., Int. Ed.*, 2021, **60**, 16027; (m) A. K. Simlandy, M.-Y. Lyu and M. K. Brown, *ACS Catal.*, 2021, **11**, 12815; (n) G. L. Trammel, P. B. Kannangara, D. Vasko, O. Datsenko, P. Mykhailiuk and M. K. Brown, *Angew. Chem., Int. Ed.*, 2022, e202212117.
- (a) S. R. Sardini and M. K. Brown, *J. Am. Chem. Soc.*, 2017, **139**, 9823; (b) K. B. Smith and M. K. Brown, *J. Am. Chem. Soc.*, 2017, **139**, 7721; (c) Y. Liao, X. Yin, X. Wang, W. Yu, D. Fang, L. Hu, M. Wang and J. Liao, *Angew. Chem., Int. Ed.*, 2020, **59**, 1176.
- C. Sandford and V. K. Aggarwal, *Chem. Commun.*, 2017, **53**, 5481.
- M. Koreeda and S. Koo, *Tetrahedron Lett.*, 1990, **31**, 831.
- H. J. Reich and S. Wollowitz, *J. Am. Chem. Soc.*, 1982, **104**, 7051.
- N. C. Bruno, M. T. Tudge and S. L. Buchwald, *Chem. Sci.*, 2013, **4**, 916.
- A. S. Guram, A. O. King, J. G. Allen, X. Wang, L. B. Schenkel, J. Chan, E. E. Bunel, M. M. Faul, R. D. Larsen, M. J. Martinelli and P. J. Reider, *Org. Lett.*, 2006, **8**, 1787.
- K. Hata, Y. Segawa and K. Itami, *Chem. Commun.*, 2012, **48**, 6642.
- (a) J. K. Park, H. H. Lackey, M. D. Rexford, K. Kovnir, M. Shatruk and D. T. McQuade, *Org. Lett.*, 2010, **12**, 5008; (b) J. K. Park and D. T. McQuade, *Angew. Chem., Int. Ed.*, 2012, **51**, 2717; (c) J. Park and D. T. McQuade, *Synthesis*, 2012, **44**, 1485; (d) L. Delvos, A. Hensel and M. Oestreich, *Synthesis*, 2014, **46**, 2957.
- E. K. Edelstein, A. C. Grote, M. P. Palkowitz and J. P. Morken, *Synlett*, 2018, **29**, 1749.
- M. Odachowski, A. Bonet, S. Essafi, P. Conti-Ramsden, J. N. Harvey, D. Leonori and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2016, **138**, 9521.
- (a) X. S. Ma and S. B. Herzon, *J. Org. Chem.*, 2016, **81**, 8673; (b) M. Pantin, M. A. Brimble and D. P. Furkert, *J. Org. Chem.*, 2018, **83**, 7049.
- E. A. Ilardi, C. E. Stivala and A. Zakarian, *Org. Lett.*, 2008, **10**, 1727.
- A. Zakarian, A. Batch and R. A. Holton, *J. Am. Chem. Soc.*, 2003, **125**, 7822.
- W. W. Zhang, S. L. Zhang and B. J. Li, *Angew. Chem., Int. Ed.*, 2020, **59**, 6874.
- X. Du, H. Chen and Y. Liu, *Chem. –Eur. J.*, 2008, **14**, 9495.
- J. A. Soderquist and H. C. Brown, *J. Org. Chem.*, 1980, **45**, 3571.

