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Communication

Boronic Ester Enabled [2 + 2]-Cycloadditions by Temporary Coordination: Synthesis of Artochamin J and Piperarborenine B

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Cite This: https://doi.org/10.1021/jacs.2c08777
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ABSTRACT: A strategy for the photosensitized cycloaddition of alkenylboronates and allylic alcohols by a temporary coordination is presented. The process allows for the synthesis of a diverse range of cyclobutylboronates. Key to development of these reactions is the temporary coordination of the allylic alcohol to the Bpin unit. This not only allows for the reaction to proceed in an intramolecular manner but also allows for high levels of stereo and regiocontrol. A key aspect of these studies is the utility of the cycloadducts in the synthesis of complex natural products artochamin J and piperarborenine B.

Cycloaddition reactions are one of the most useful strategies to generate rings.[1] Among these processes, [2 + 2]-cycloaddition of alkenes is regarded as the premier approach for the synthesis of cyclobutanes.[2] The majority of these reactions are photochemical and therefore proceed via high-energy, and short-lived, excited-state intermediates. Consequently, to achieve reasonable reaction rates and minimize secondary photochemical reactions, researchers have extensively developed intramolecular [2 + 2]-cycloadditions. Due to constraints with the ring forming event, stereochemical control can often be achieved (Scheme 1A). However, the substrates must be carefully designed to generate a ring and therefore this necessarily limits the scope of products that can be generated to polycycles. In addition, laborious synthetic sequences can be necessary to prepare the substrate. Intermolecular [2 + 2]-cycloadditions are also known, but to achieve reasonable reaction rates, both substrates typically need activating groups (arenes, dienes, ester, etc.) (Scheme 1A). Since these reactions are bimolecular, a range of cyclobutanes can be synthesized. However, the requirement that both coupling alkenes need activating groups remains a limitation for intermolecular [2 + 2]-cycloadditions. In addition, unlike concerted [4 + 2]-cycloadditions in which the regio- and stereochemistry can be controlled by FMOs (frontier molecular orbitals),[1] in many cases, it is difficult to control the stereo- and regiochemical outcome of intermolecular [2 + 2]-cycloaddition reactions.

In this manuscript, an alternative approach is disclosed in which by virtue of a temporary association between the reactants, a biomolecular reaction can be achieved in an intramolecular fashion (Scheme 1B). In this approach, stereo and regiochemical control can be achieved while retaining the benefits of diversity from an intermolecular [2 + 2]-cycloaddition of readily available components. To implement this approach, we designed a reaction between an allylic alcohol and an alkeneylboronate (Scheme 1C). This process would allow simple unactivated alkenes to participate in [2 + 2]-cycloadditions in the form of allylic alcohols and lead to the formation of diverse borylated cyclobutanes.[3]

Borylated carbocycles and heterocycles are useful intermediates in the construction of complex molecules. This is primarily due to the ease with which the C−B bond can be converted to other functional groups.[4] In recent years, an emphasis has been placed on the synthesis of rigid carbocycles and heterocycles to enable drug development. Consequently, the preparation of cyclobutylboronates is regarded as an important goal. While several strategies are known for cyclobutylboronate synthesis,[5−9] [2 + 2]-cycloadditions retain their own importance because (1) the reactions are convergent, (2) the alkene starting materials are generally widely available, and (3) products can be prepared that would be inaccessible by other approaches.[10,11] With respect to photochemical [2 + 2]-cycloaddition,[12,13] prior work has demonstrated that alkene triplet excited states can be captured with alkenylboronates. More recently, our lab has demonstrated that alkenylboronates can be photosensitized and undergo reaction with a variety of activated alkenes (e.g., styrenes, dienes).[14] In the latter case, the Bpin unit acted as an activating group to allow for the cycloaddition to proceed in good yield. In this study, the Bpin unit is utilized as a coordinating group to direct the cycloaddition to occur with allylic alcohol derivatives (Scheme 1C). Cycloadditions of this type are valuable because (1) allyl alcohol derivatives are widely available yet underutilized in this field and (2) the product contains multiple functional groups for further elaboration to enable the synthesis of complex molecules, such as artochamin J and piperarborenine B.

The initial reaction optimization was conducted with allyl alcohol (**1**) and *E*-styrenylBpin (**2**). The choice to use *E*-styrenylBpin (**2**) stems from the fact that the sytrenyl

Received: August 17, 2022

https://doi.org/10.1021/jacs.2c08777
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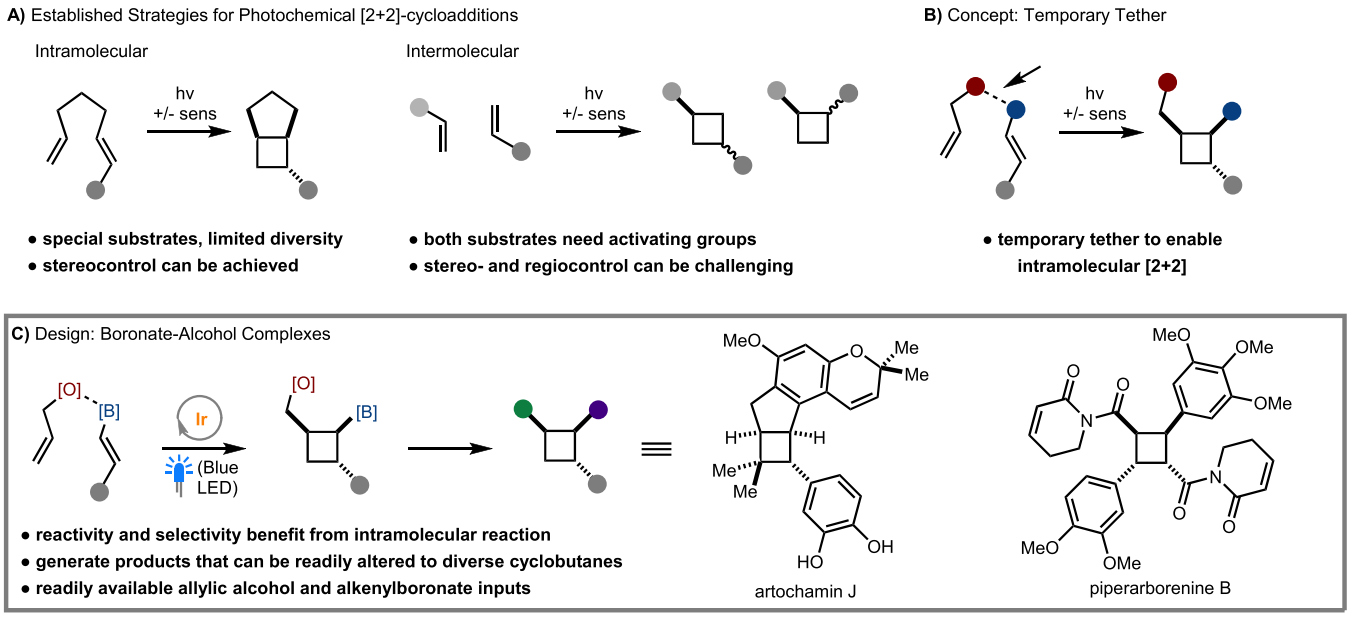
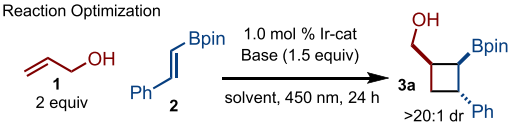
Scheme 1. Approaches Toward [2 + 2]-Cycloadditions



component could be sensitized with common visible-light-activated sensitizers,[14,15] thus avoiding the use of high-energy UV light at this stage of development. Treatment of allyl alcohol (**1**) and *E*-styrenylBpin (**2**) in the presence of *fac*-Ir(ppy)$_3$ did not lead to product formation. It is likely that association of alcohol and the Bpin unit was minimal, and dissociation occurs before cycloaddition (Scheme 2A, entry 1). Therefore, bases were evaluated to shift the position of the equilibrium to the borate complex (Scheme 2A, entries 2−4).

Scheme 2. Reaction Optimization

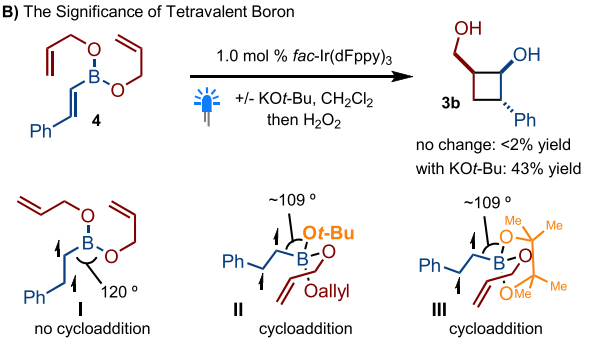
A) Reaction Optimization



entry	Ir-cat	base	solvent (conc.)	yield[a]
1	*fac*-Ir(ppy)$_3$	—	CH_2Cl_2 (0.05M)	<2%
2	*fac*-Ir(ppy)$_3$	Et_3N	CH_2Cl_2 (0.05M)	<2%
3	*fac*-Ir(ppy)$_3$	DBU	CH_2Cl_2 (0.05M)	<2%
4	*fac*-Ir(ppy)$_3$	KO*t*-Bu	CH_2Cl_2 (0.05M)	14%
5	*fac*-Ir(dFppy)$_3$	KO*t*-Bu	CH_2Cl_2 (0.05M)	55%
6[b,c]	*fac*-Ir(dFppy)$_3$	KO*t*-Bu	CH_2Cl_2 (0.05M)	64%
7[b,c]	*fac*-Ir(dFppy)$_3$	KO*t*-Bu	toluene (0.05M)	68%
8[b,d]	*fac*-Ir(dFppy)$_3$	KO*t*-Bu	toluene (0.033M)	89%

[a] Yield was determined by ^{1}H NMR analysis of the unpurified reaction mixture with an internal standard (0.1 mmol scale). [b]3.0 equiv allyl alcohol. [c]2.0 equiv base. [d]1.6 equiv base.

B) The Significance of Tetravalent Boron



It was identified that use of KO*t*-Bu allowed for formation of **3a** (Scheme 2A, entry 4). Continued optimization along this line demonstrated that use of a sensitizer with a higher triplet energy, in conjunction with a more nonpolar solvent, led to formation of [2 + 2] cycloadduct **3a** in 89% yield (Scheme 2A, entry 8). The use of the higher-energy sensitizer is likely necessary to increase the rate of quenching, whereas the use of toluene likely drives the formation of the borate complex. Finally, styrenylBneop and styrenylBdmpd work in the reaction, albeit with reduced yields (see the Supporting Information for details).

Studies were also conducted to probe the importance of the alcohol-Bpin coordination (Scheme 2B). It was found that reaction of bis-allyl boronate **4** was not productive when irradiated in the presence of 450 nm LEDs and an Ir-sensitizer. However, the addition of KO*t*-Bu allowed for the reaction to proceed to generate **3b**. This is likely the result of the formation of tetravalent borate, which constricts the angle (compare **I** to **II**) to be like **III** and thus allows for cycloaddition to occur.

Under the optimized reaction conditions, the scope of the cycloaddition was investigated (Scheme 3). 1,2-Disubstituted alkenes allowed for product formation; however, a mixture of diastereomers was formed (products **6**−**8**). With trisubstituted alkenes, the formation of penta-substituted cyclobutanes could be achieved (products **9**−**15**). Reactions with cyclic trisubstituted alkenes allowed for the formation of bicyclic structures (products **11**−**15**). In a similar vein to reactions of 1,2-disubstituted alkenes, reactions of unsymmetric trisubstituted alkenes gave rise to diastereomers (product **10**). In one example, a tetrasubstituted alkene was tolerated to generate a highly substituted cyclobutane (product **16**). At this stage of development, use of homoallylic alcohols of any substitution patterns did not result in product formation.

In addition to a variety of allylic alcohols, many diverse alkenyl boronates participated in the reaction. The aryl unit could be substituted with various functional groups such as Br (product **22**), unprotected amine (product **24**), and CN (product **21**). In addition, electron-withdrawing (product **20**,

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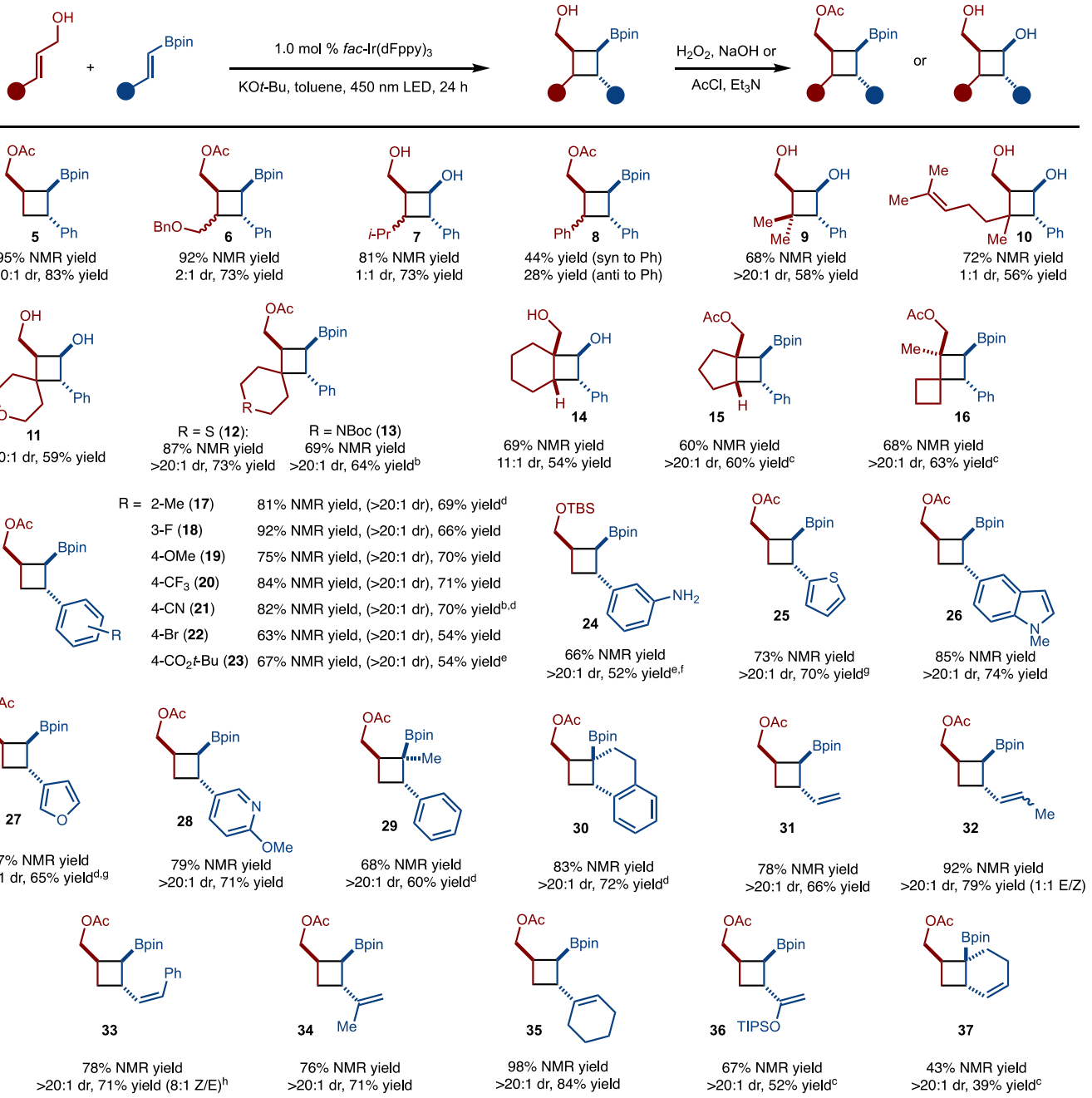
Scheme 3. Substrate Scope



[a]NMR yield refers to yield determined by ^{1}H NMR analysis of the unpurified reaction mixture of the product after functionalization of the Bpin unit. Diastereomeric ratio (dr) determined of the unpurified reaction mixture by ^{1}H NMR analysis. Yield is of isolated, purified product. [b]Chlorobenzene was used as solvent. [c]Penn PhD Photoreactor M2 was used. [d]48 h. [e]DCM was used as solvent. [f]The alcohol was protected using TBSCl and imidazole. [g]2.0 mol % *fac*-Ir(dFppy)$_3$. [h]1.0 mol % *fac*-Ir(ppy)$_3$ was used as catalyst.

21, **23**), electron-donating (product **19**), and sterically demanding (product **17**) substitutions were well-tolerated. Several classes of heteroaromatic compounds could be used such as furan (product **27**), thiophene (product **25**), indole (product **26**), and pyridine (product **28**). The alkenylboronate could also be substituted at the α position to form sterically congested products (**29**-**30**). Finally, dienylboronates of several substitution patterns were also tolerated (products **31**−**37**). When substrates are 1,4-substituted dienes, a secondary photoisomerization was also observed (products **32** and **33**).[16] To achieve better *E*/*Z* selectivity, we envisioned using a lower-energy sensitizer that could still enable the [2 + 2]-cycloaddition to synthesize **33** efficiently (given that the substrate is highly conjugated and likely has a lower triplet energy) yet allow for a more selective photoisomerization. Indeed, *fac*-Ir(ppy)$_3$ catalyzed the reaction to form **33** with 8:1 *Z*/*E* selectivity in good yield. The synthesis of **36** is also notable as the silyl enol ether can be used as a functional handle. Notably, dienylboronates are known to undergo [4 + 2]-cycloadditions with allylic alcohols,[3e] our method demonstrated an alternative reactivity. Finally, under the reaction

https://doi.org/10.1021/jacs.2c08777
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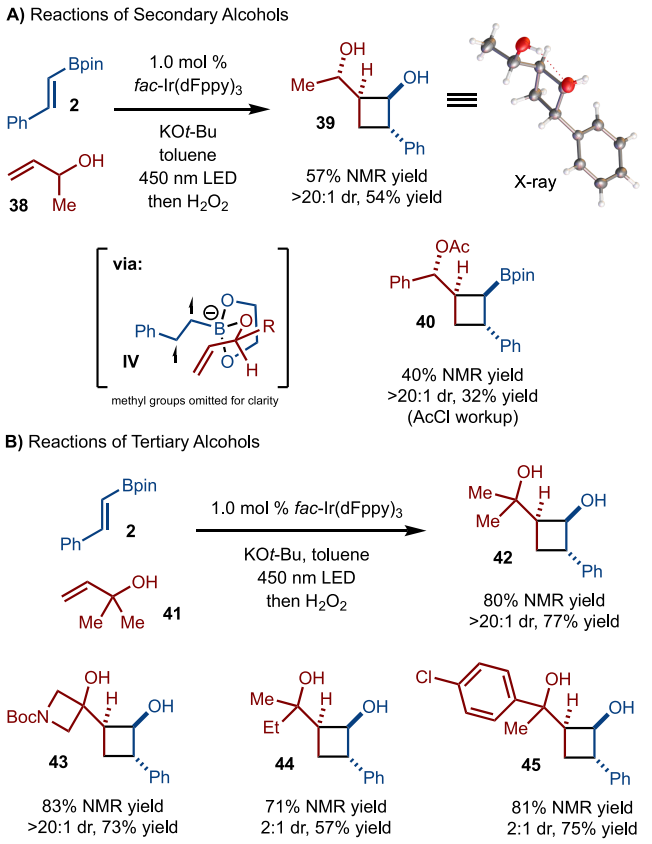
conditions, use of alkyl-substituted alkenyl boronates did not allow for product formation.

With respect to the allylic alcohol unit, both secondary and tertiary examples were tolerated. In the case of secondary alcohols, the reactions led to the formation of single observable diastereomers (products **39** and **40**) (Scheme 4A). It is likely

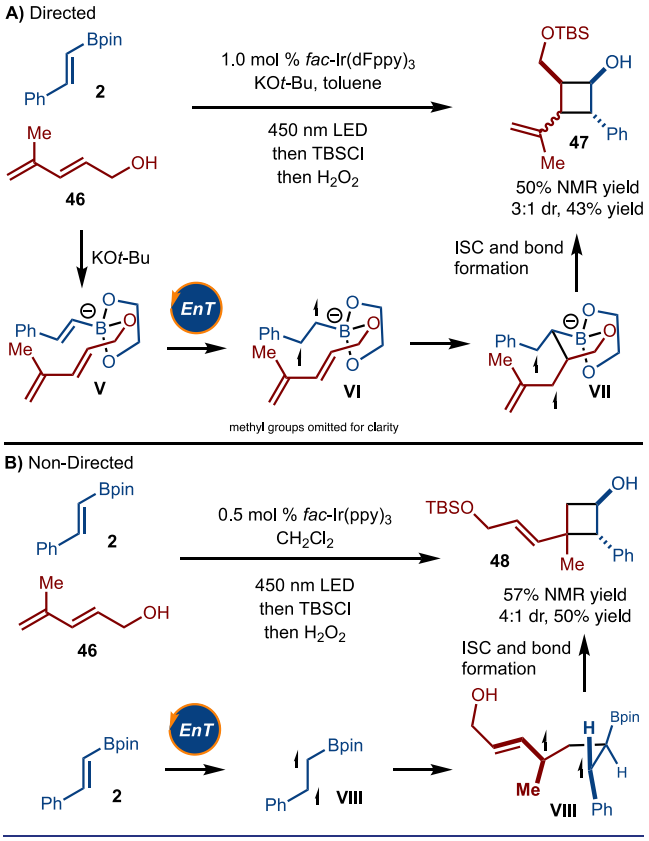
Scheme 4. Additional Examples



that the high levels of stereocontrol were observed because the reaction proceeded via **IV**, in which the R-group was positioned in the pseudoequatorial position. In the case of tertiary alcohols, the reaction occurred smoothly and led to the synthesis of sterically congested products **42**−**45** (Scheme 4B). In the cases of **44** and **45**, low levels of diastereoselectivity were observed due to the relatively small size difference between substituents as compared to **39** and **40**.

The reaction of dieneol **46** is interesting because under different sets of conditions, alternate products could be made (Scheme 5). For example, under the conditions described in this study, the alcohol directs the cycloaddition to occur at the proximal double bond to generate **47** (Scheme 5A). The reaction likely occurred by coordination of the alcohol to the Bpin unit followed by triplet energy transfer to generate **VI**. Radical addition allows for formation of **VII**, which upon intersystem crossing (ISC) and radical recombination, leads to formation of the product. On the other hand, if the conditions are modified such that the Bpin acts as an activating group and not a coordinating group (as previously described),[14] product **48** is generated (Scheme 5B). Here, triplet energy transfer occurs with **2** to form **VIII**. The initial bond formation takes place at the terminal position of the diene. After ISC and radical recombination, product **48** is formed.

Scheme 5. Divergent Reactivity



It is well known that organoboronates can undergo Pd-catalyzed cross coupling with aryl bromides.[17] However, alkylboronates are significantly more reluctant to undergo cross coupling compared to their aryl or alkenyl counterparts.[18] To overcome this issue, the Morken group developed a cross coupling of γ-hydroxyl alkylBpin.[19] In these examples, the hydroxyl group facilitates the cross-coupling reaction.

As illustrated in Scheme 6A, this method can be applied to the cycloadducts to generate diverse cyclobutanes. The reactions proceed with retention of stereochemistry and function for aryl (product **49**), heteroaryl (products **50**−**52**), and alkenyl bromides/triflates (products **53** and **54**).

Moreover, this sequence has been instrumental in the synthesis of the cyclobutane natural products artochamin J[20] and piperaborenine B (Scheme 6B, C).[21] In the case of artochamin J, the synthesis commenced with cycloaddition of allylic alcohol **56** and alkenylBpin **55** (Scheme 6B). The crude material was then subjected to the cross-coupling sequence to generate **58** as a single observable diastereomer on gram scale. At this stage, cyclization of the primary alcohol with the neighboring electron-rich arene was desired. However, even after extensive investigations, the cyclization could not be achieved. Therefore, a sequence was devised that involved oxidation to the acid and Friedel−Crafts cyclization promoted by TFAA to generate **59**. Clemmensen reduction[22] and deprotection with TBAF allowed for the synthesis of artochamin J.

A brief synthesis of piperaborenine B was also enabled by this methodology (Scheme 6C). Starting with alkenylboronic ester **60** and allylic alcohol **61**, [2 + 2]-cycloaddition and cross coupling allowed for the synthesis of **63** in 66% yield and 3.3:1 dr. Oxidative cleavage of the alkene resulted in the formation

https://doi.org/10.1021/jacs.2c08777
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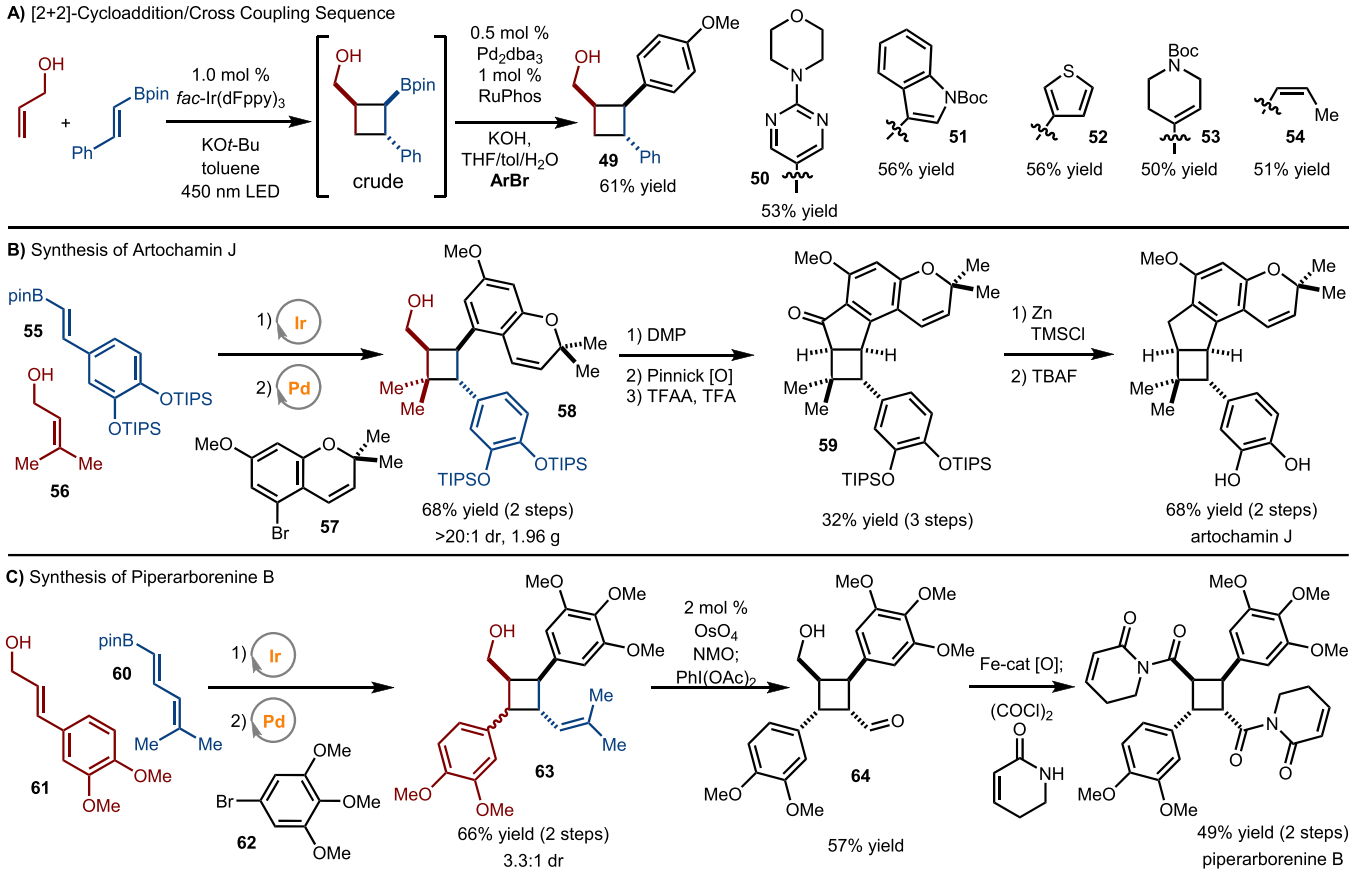
Scheme 6. Synthesis of Complex Molecules



of aldehyde **64**.[23] Exhaustive oxidation under Fe-catalyzed aerobic oxidation[24] led to formation of a dicarboxylic acid, which upon sequential treatment with oxalyl chloride and dihydropyridinone led to formation of piperaborenine B. Our method complements the reported routes, which rely on a directed C−H activation method to install the arene(s).[21] Without additional steps to install and remove the directing group, only six steps were required to prepare piperaborenine B. Finally, it is important to note that the approaches described here are modular and thus amendable to the synthesis of derivatives.

In conclusion, a new strategy to access synthetically versatile cyclobutylboronates is presented. By taking advantage of a temporary tether between an alcohol and boronate, a regio- and stereoselective reaction can be achieved. Due to the functional groups on the cyclobutane, facile diversification can be carried out to allow for the efficient synthesis of complex natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c08777.

Experimental procedures and analytical data for all new compounds (PDF)

Accession Codes

CCDC 2083387 contains 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.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Indiana University and the NIH (R35GM131755) for financial support. This project was partially funded by the Vice Provost for Research through the Research Equipment Fund and the NSF MRI program, CHE-1726633 and CHE-1920026. We thank Dr. Maren Pink and Dr. Veronica Carta of the IU Molecular Structure Center for acquisition of X-ray crystal structure data. Y.L. thanks Dr. Sarah Braley for helpful discussion. Support for the acquisition of the Bruker Venture

D8 diffractometer through the Major Scientific Research Equipment Fund from the President of Indiana University and the Office of the Vice President for Research is gratefully acknowledged.

REFERENCES

(1) (a) Kobayashi, S.; Jørgensen, K. A. *Cycloaddition Reactions in Organic Synthesis*; Wiley, 2002. (b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Elsevier, 2013. (c) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. The Diels−Alder Reaction in Total Synthesis. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698.

(2) (a) Poplata, S.; Tröster, A.; Zou, Y.-Q.; Bach, T. Recent Advances in the Synthesis of Cyclobutanes by Olefin [2 + 2] Photocycloaddition Reactions. *Chem. Rev.* **2016**, *116*, 9748−9815. (b) Brimioulle, R.; Lenhart, D.; Maturi, M. M.; Bach, T. Enantioselective Catalysis of Photochemical Reactions. *Angew. Chem., Int. Ed. Engl.* **2015**, *54*, 3872−3890. (c) Xu, Y.; Conner, M. L.; Brown, M. K. Cyclobutane and Cyclobutene Synthesis: Catalytic Enantioselective [2 + 2] Cycloadditions. *Angew. Chem., Int. Ed.* **2015**, *54*, 11918−11928.

(3) For boron tethered Diels−Alder reactions, see: (a) Kirkham, J. D.; Butlin, R. J.; Harrity, J. P. A. A Mild Benzannulation through Directed Cycloaddition Reactions. *Angew. Chem., Int. Ed.* **2012**, *51*, 6402−6405. (b) Feng, C.; Wang, H.; Xu, L.; Li, P. N−B Dative Bond-Induced [3.3.0] Bicyclic Boronate-Tethered *exo*-Selective Intramolecular Diels−Alder Reaction. *Org. Biomol. Chem.* **2015**, *13*, 7136−7139. (c) Scholl, K.; Dillashaw, J.; Timpy, E.; Lam, Y.-H.; DeRatt, L.; Benton, T. R.; Powell, J. P.; Houk, K. N.; Morgan, J. B. Quinine-Promoted, Enantioselective Boron-Tethered Diels−Alder Reaction by Anomeric Control of Transition-State Conformation. *J. Org. Chem.* **2018**, *83*, 5756−5765. (d) Batey, R. A.; Thadani, A. N.; Lough, A. J. Alkenylboronate Tethered Intramolecular Diels-Alder Reactions. *J. Am. Chem. Soc.* **1999**, *121*, 450−451. (e) Batey, R. A.; Thadani, A. N.; Lough, A. J. Diels−Alder Reactions of Dienylboron Compounds with Unactivated Dienophiles: an Application of Boron Tethering for Substituted Cyclohexenol Synthesis. *Chem. Commun.* **1999**, 475−476.

(4) (a) Armstrong, R. J.; Aggarwal, V. 50 Years of Zweifel Olefination: a Transition-Metal-Free Coupling. *Synthesis* **2017**, *49*, 3323−3336. (b) Sandford, C.; Aggarwal, V. K. Stereospecific Functionalizations and Transformations of Secondary and Tertiary Boronic Esters. *Chem. Commun.* **2017**, *53*, 5481−5494.

(5) For hydroboration/protoboration reactions, see: (a) Clement, H. A.; Boghi, M.; McDonald, R. M.; Bernier, L.; Coe, J. W.; Farrell, W.; Helal, C. J.; Reese, M. R.; Sach, N. W.; Lee, J. C.; Hall, D. G. High-Throughput Ligand Screening Enables the Enantioselective Conjugate Borylation of Cyclobutenones to Access Synthetically Versatile Tertiary Cyclobutylboronates. *Angew. Chem., Int. Ed. Engl.* **2019**, *58*, 18405−18409. (b) Mercer, J. A. M.; Cohen, C. M.; Shuken, S. R.; Wagner, A. M.; Smith, M. W.; Moss, F. R., III; Smith, M. D.; Vahala, R.; Gonzalez-Martinez, A.; Boxer, S. G.; Burns, N. Z. Chemical Synthesis and Self-Assembly of a Ladderane Phospholipid. *J. Am. Chem. Soc.* **2016**, *138*, 15845−15848. (c) Guisán-Ceinos, M.; Parra, A.; Martín-Heras, V.; Tortosa, M. Enantioselective Synthesis of Cyclobutylboronates via a Copper-Catalyzed Desymmetrization Approach. *Angew. Chem., Int. Ed.* **2016**, *55*, 6969. (d) Brener, L.; Brown, H. C. Hydroboration. 47. Unique Stereospecificity of the Hydroboration of 1, 3-Dimethylcycloalkenes with 9-Borabicyclo [3.3.1] Nonane. *J. Org. Chem.* **1977**, *42*, 2702.

(6) For carboboration reactions, see: (a) Hancock, E. N.; Kuker, E. L.; Tantillo, D. J.; Brown, M. K. Lessons in Strain and Stability: Enantioselective Synthesis of (+)-[5]-Ladderanoic Acid. *Angew. Chem., Int. Ed.* **2020**, *59*, 436−441. (b) Logan, K. M.; Brown, M. K. Catalytic Enantioselective Arylboration of Alkenylarenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 851.

(7) For example, see: (a) Silvi, M.; Aggarwal, V. K. Radical Addition to Strained σ-Bonds Enables the Stereocontrolled Synthesis of Cyclobutyl Boronic Esters. *J. Am. Chem. Soc.* **2019**, *141*, 9511−9515. (b) Fawcett, A.; Biberger, T.; Aggarwal, V. K. Carbopalladation of C−C σ-Bonds Enabled by Strained Boronate Complexes. *Nat. Chem.* **2019**, *11*, 117−122. (c) Hari, D. P.; Abell, J. C.; Fasano, V.; Aggarwal, V. K. Ring-Expansion Induced 1,2-Metalate Rearrangements: Highly Diastereoselective Synthesis of Cyclobutyl Boronic Esters. *J. Am. Chem. Soc.* **2020**, *142* (12), 5515−5520.

(8) Giustra, Z. X.; Yang, X.; Chen, M.; Bettinger, H. F.; Liu, S.-Y. Accessing 1,2-Substituted Cyclobutanes Through 1,2-Azaborine Photoisomerization. *Angew. Chem., Int. Ed. Engl.* **2019**, *58*, 18918−18922.

(9) For example, see: He, J.; Shao, Q.; Wu, Q.; Yu, J.-Q. Pd(II)-Catalyzed Enantioselective C(Sp3)-H Borylation. *J. Am. Chem. Soc.* **2017**, *139*, 3344−3347. (b) Murakami, R.; Tsunoda, K.; Iwai, T.; Sawamura, M. Stereoselective C-H Borylations of Cyclopropanes and Cyclobutanes with Silica-Supported Monophosphane-Ir Catalysts. *Chem.—Eur. J.* **2014**, *20*, 13127−13131.

(10) Parsutkar, M. M.; Pagar, V. V.; RajanBabu, T. V. Catalytic Enantioselective Synthesis of Cyclobutenes From Alkynes and Alkenyl Derivatives. *J. Am. Chem. Soc.* **2019**, *141*, 15367−15377.

(11) Conner, M. L.; Brown, M. K. Synthesis of 1,3-Substituted Cyclobutanes by Allenoate-Alkene [2 + 2] Cycloaddition. *J. Org. Chem.* **2016**, *81*, 8050−8060.

(12) For selected 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* (10), 4055. (b) Scholz, S. O.; Kidd, J. B.; Capaldo, L.; Flikweert, N. E.; Littlefield, R. M.; Yoon, T. P. Construction of Complex Cyclobutane Building Blocks by Photosensitized [2 + 2] Cycloaddition of Vinyl Boronate Esters. *Org. Lett.* **2021**, *23*, 3496. (c) Demchuk, O. P.; Hryshchuk, O. V.; Vashchenko, B. V.; Kozytskiy, A. V.; Tymtsunik, A. V.; Komarov, I. V.; Grygorenko, O. O. Photochemical [2 + 2] Cycloaddition of Alkenyl Boronic Derivatives: an Entry Into 3-Azabicyclo[3.2.0]Heptane Scaffold. *J. Org. Chem.* **2020**, *85*, 5927−5940. (d) Coote, S. C.; Bach, T. Enantioselective Intermolecular [2 + 2] Photocycloadditions of Isoquinolone Mediated by a Chiral Hydrogen-Bonding Template. *J. Am. Chem. Soc.* **2013**, *135*, 14948−14951. (e) Kleinnijenhuis, R. A.; Timmer, B. J. J.; Lutteke, G.; Smits, J. M. M.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. Formal Synthesis of Solanoeclepin a: Enantioselective Allene Diboration and Intramolecular [2 + 2] Photocycloaddition for the Construction of the Tricyclic Core. *Chem.—Eur. J.* **2016**, *22*, 1266−1269. (f) Hollis, W. G., Jr; Lappenbusch, W. C.; Everberg, K. A.; Woleben, C. M. The Use of Alkenylboronate Esters in [2 + 2] Enone-Olefin Photocycloadditions. *Tetrahedron Lett.* **1993**, *34*, 7517.

(13) For reviews regarding cycloadditions of alkenylboron, see: (a) Welker, M. E. Recent Advances in Syntheses and Reaction Chemistry of Boron and Silicon Substituted 1,3-Dienes. *Tetrahedron* **2008**, *64* (51), 11529−11539. (b) Eberlin, L.; Tripoteau, F.; Carreaux, F.; Whiting, A.; Carboni, B. Boron-Substituted 1,3-Dienes and Heterodienes as Key Elements in Multicomponent Processes. *Beilstein J. Org. Chem.* **2014**, *10*, 237−250. (c) Pyziak, J.; Walkowiak, J.; Marciniec, B. Recent Advances in Boron-Substituted 1,3-Dienes Chemistry: Synthesis and Application. *Chem. − Eur. J.* **2017**, *23* (15), 3502−3541. (d) Grygorenko, O. O.; Moskvina, V. S.; Hryshchuk, O. V.; Tymtsunik, A. V. Cycloadditions of Alkenylboronic Derivatives. *Synthesis* **2020**, *52* (19), 2761−2780.

(14) Liu, Y.; Ni, D.; Stevenson, B. G.; Tripathy, V.; Braley, S. E.; Raghavachari, K.; Swierk, J. R.; Brown, M. K. Photosensitized [2 + 2]-Cycloadditions of Alkenylboronates and Alkenes. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202200725.

(15) For reviews regarding energy transfer, see: (a) Strieth-Kalthoff, F.; Glorius, F. Triplet Energy Transfer Photocatalysis: Unlocking the Next Level. *Chem.* **2020**, *6*, 1888. (b) Zhou, Q.-Q.; Zou, Y.-Q.; Lu, L.-Q.; Xiao, W.-J. Visible-Light-Induced Organic Photochemical

https://doi.org/10.1021/jacs.2c08777
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Reactions Through Energy-Transfer Pathways. *Angew. Chem., Int. Ed.* **2019**, *58*, 1586−1604. (c) Strieth-Kalthoff, F.; James, M. J.; Teders, M.; Pitzer, L.; Glorius, F. Energy Transfer Catalysis Mediated by Visible Light: Principles, Applications, Directions. *Chem. Soc. Rev.* **2018**, *47*, 7190−7202.

(16) Singh, K.; Staig, S. J.; Weaver, J. D. Facile Synthesis of *Z*-Alkenes via Uphill Catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 5275−5278. Nevesely, T.; Wienhold, M.; Molloy, J. J.; Gilmour, R. Advances in the $E \rightarrow Z$ Isomerization of Alkenes Using Small Molecule Photocatalysts. *Chem. Rev.* **2022**, *122*, 2650−2694.

(17) For selected reviews on Suzuki reaction, see: (a) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Beletskaya, I. P.; Alonso, F.; Tyurin, V. The Suzuki-Miyaura reaction after the Nobel prize. *Coord. Chem. Rev.* **2019**, *385*, 137−173. (c) Biffis, A.; Centomo, P.; Del Zotto, A.; Zecca, M. Pd Metal Catalysts for Cross-Couplings and Related Reactions in the 21st Century: A Critical Review. *Chem. Rev.* **2018**, *118*, 2249−2295. (d) Partyka, D. V. Transmetalation of Unsaturated Carbon Nucleophiles from Boron-Containing Species to the Mid to Late d-Block Metals of Relevance to Catalytic C-X Coupling Reactions (X = C, F, N, O, Pb, S, Se, Te). *Chem. Rev.* **2011**, *111*, 1529−1595.

(18) For selected reviews on Suzuki coupling of alkyl boronates, see: (a) Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkylorganometallics as Reaction Partners. *Chem. Rev.* **2011**, *111*, 1417−1492. (b) Leonori, D.; Aggarwal, V. K. Stereospecific Couplings of Secondary and Tertiary Boronic Esters. *Angew. Chem., Int. Ed.* **2015**, *54*, 1082−1096. (c) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. Enantioselective and Enantiospecific Transition-Metal-Catalyzed Cross-Coupling Reactions of Organometallic Reagents To Construct C−C Bonds. *Chem. Rev.* **2015**, *115*, 9587−9652.

(19) Blaisdell, T. P.; Morken, J. Hydroxyl-Directed Cross-Coupling: A Scalable Synthesis of Debromohamigeran E and Other Targets of Interest. *J. Am. Chem. Soc.* **2015**, *137*, 8712−8715.

(20) (a) Nicolaou, K. C.; Lister, T.; Denton, R. M.; Gelin, C. Cascade Reactions Involving Formal [2 + 2] Thermal Cycloadditions: Total Synthesis of Artochamins F, H, I, and J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7501−7505. (b) Nicolaou, K. C.; Lister, T.; Denton, R. M.; Gelin, C. F. Total Synthesis of Artochamins F, H, I, and J through Cascade Reactions. *Tetrahedron* **2008**, *64*, 4736−4757.

(21) For previous synthesis of piperaborenine B, see: (a) Gutekunst, W. R.; Baran, P. S. Total Synthesis and Structural Revision of the Piperarborenines via Sequential Cyclobutane C−H Arylation. *J. Am. Chem. Soc.* **2011**, *133*, 19076−19079. (b) Gutekunst, W. R.; Baran, P. S. Applications of C−H Functionalization Logic to Cyclobutane Synthesis. *J. Org. Chem.* **2014**, *79*, 2430−2452. (c) Panish, R. A.; Chintala, S. R.; Fox, J. M. A Mixed-Ligand Chiral Rhodium (II) Catalyst Enables the Enantioselective Total Synthesis of Piperarborenine B. *Angew. Chem., Int. Ed.* **2016**, *55*, 4983−4987. (d) Hu, J.-L.; Feng, L.-W.; Wang, L.; Xie, Z.; Tang, Y.; Li, X. Enantioselective Construction of Cyclobutanes: A New and Concise Approach to the Total Synthesis of (+)-Piperarborenine B. *J. Am. Chem. Soc.* **2016**, *138*, 13151−13154.

(22) Xu, S.; Toyama, T.; Nakamura, J.; Arimoto, H. One-pot Reductive Cleavage of *exo*-Olefin to Methylene with a Mild Ozonolysis-Clemmensen Reduction Sequence. *Tetrahedron Lett.* **2010**, *51*, 4534−4537.

(23) Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. An Expedient Procedure for the Oxidative Cleavage of Olefinic Bonds with $PhI(OAc)_2$, NMO, and Catalytic OsO_4. *Org. Lett.* **2010**, *12*, 1552−1555.

(24) Jiang, X.; Zhang, J.; Ma, S. Iron Catalysis for Room-Temperature Aerobic Oxidation of Alcohols to Carboxylic Acids. *J. Am. Chem. Soc.* **2016**, *138*, 8344−8347.

https://doi.org/10.1021/jacs.2c08777
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