Letter

Stereoselective Palladium-Catalyzed 1,3-Arylboration of Unconjugated Dienes for Expedient Synthesis of 1,3-Disubstituted Cyclohexanes

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Stereoselective Palladium-Catalyzed 1,3-Arylboration of Unconjugated Dienes for Expedient Synthesis of 1,3-Disubstituted Cyclohexanes

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ABSTRACT: As a significant pharmacophore, 1,3-disubstituted cyclohexanes are widespread in natural products and synthetic bioactive molecules. A palladium-catalyzed arylboration of 1,4-cyclohexadienes is reported, which allows expeditious access to an array of functionalized 1,3-disubstituted cyclohexanes from the readily available starting materials. Palladium catalysis enables the arylboration to proceed in a reversed regioselectivity compared with earlier nickel catalysis. The most striking feature of this protocol lies in the 1,3-regioselectivity and exclusive *cis*-diastereoselectivity. Intriguingly, the success of this three-component reaction does not rely on the application of dative ligands, but a cheap ammonium chloride salt instead. The synthetic utility of this method is highlighted by a series of downstream stereospecific transformations and a drug molecule synthesis.

KEYWORDS: *Alkenes, 1,3-Arylboration, Palladium, Metal migration, Stereoselectivity*

Over the past few decades, fragment-based drug discovery (FBDD) has developed into an important strategy to identify the lead pharmaceutical compounds.[1] However, compared with the sp^2-rich, planar compounds, three-dimensional (3D) fragments are highly limited in candidate libraries.[1a] In this context, the 1,3-disubstituted cyclohexane fragment is widely investigated as a privileged scaffold in many significant, pharmaceutically relevant molecules, such as *anti*-diabetic agent, cannabinoid receptors, MAO-B inhibitor and so on, as depicted in Figure 1A.[2] However, general synthetic approach towards this class of compounds is quite scarce.[2a, 2d, 3] Therefore, the development of a general, efficient and stereoselective method for direct synthesis of 1,3-disubstituted cyclohexanes from readily available starting materials is a highly desirable yet challenging task. On the other hand, the chemical dearomatization of nonactivated arenes provides a powerful platform for rapid assembly of value-added, complex molecules from inexpensive fundamental aromatic compounds, which has attracted extensive interest in the synthetic community in the past few years.[4] For example, a great advance in the transformation of simple arenes into cyclohexane derivatives has been achieved recently by the Sarlah group through a sequence of photochemical arene-arenophile cycloaddition and metal catalysis (Figure 1B, left).[5] With this method, a set of 1,2- and 1,4-disubstituted cyclohexanes were selectively prepared.[5b,d-f] Herein, we present a protocol which can convert benzene into a diverse range of functionalized 1,3-disubstituted cyclohexanes by combination of the well-known Birch reduction[6] and an unprecedented arylboration[7] (Figure 1B, right). Remarkably, the palladium catalysis allows the arylboration to proceed in an extraordinarily 1,3-regioselective and *cis*-diastereoselective manner.[8-9] Furthermore, the incorporation of a boron group into the products enables further stereospecific transformations to afford a variety of highly functionalized 3D molecules.[10]

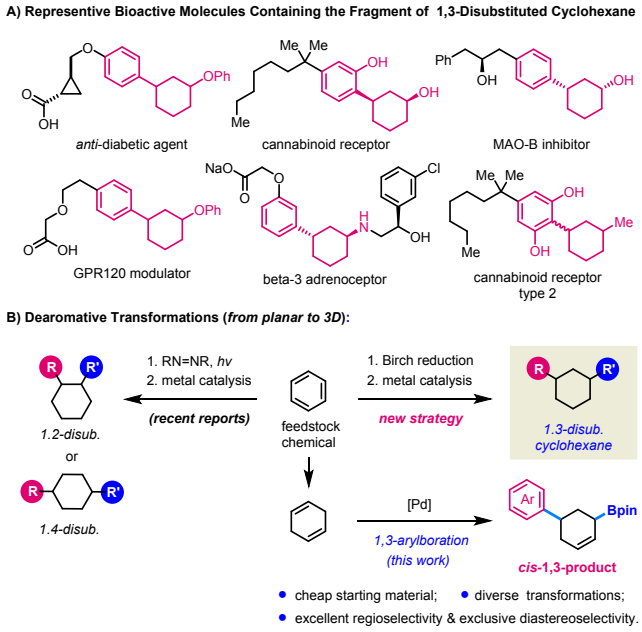
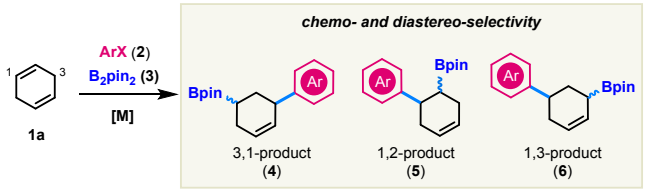


Figure 1. Background Introduction and Reaction Design

As an extension of our interest in the application of nickel migration,[11-12] we commenced this study by exploring a nickel-catalyzed arylboration of 1,4-cyclohexadienes, with 1,4-cyclohexadiene (**1a**), bromobenzene (**2a**) and bis(pinacolato)diboron (B_2pin_2, **3**) as model substrates. As depicted in Table 1, the regio- and diastereo-selectivity would be the main challenge of this arylboration reaction. For example, it was found that with a nickel(II) salt and a 1,10-phenanthroline derivative **L1** as the catalyst, only the 3,1-arylboration product **4a** was isolated, albeit in lower yield with a poor diastereoisomeric ratio (1:1) (entry 1). Without the ligand, the 1,2-arylboration product *cis*-**5a** was isolated as a

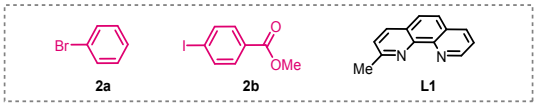
single isomer in this three-component reaction (Table 1, entry 2), which is consistent with Brown's ligand-free system.[9i] These results reveal that the epimerization should derive from nickel migration. After extensively screening reaction conditions, the diastereoselectivity could not be improved, therefore we turned our attentions to other transition metal catalysts.

Table 1. Reaction Optimization

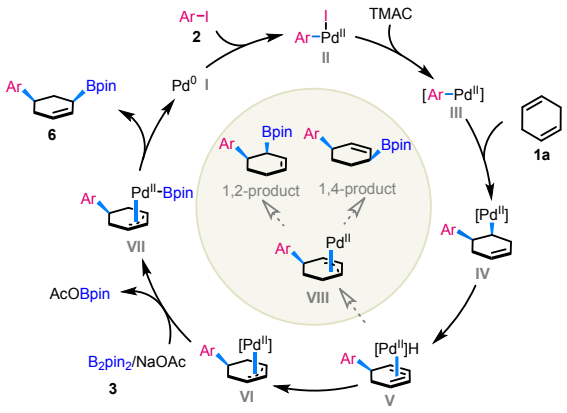


Entry	Derivation from conditions **A**	Results
1	no change	30%(1:1)[a] **4a**
2	no ligand	33% *cis*-**5a**
	Derivation from conditions **B**	*cis*-**6a**, [%]
3	no change	82(78)[b]
4	$Pd(OAc)_2$ instead of $Pd(acac)_2$	57
5	$NiBr_2$·DME instead of $Pd(acac)_2$	0
6	TBAC instead of TMAC	23
7	TMAB instead of TMAC	20
8	TMAI instead of TMAC	6
9	$NaHCO_3$ instead of NaOAc	39
10	Na_2CO_3 instead of NaOAc	56
11	DCE instead of $CHCl_3$	45
12	Dioxane instead of $CHCl_3$	52
13	no TMAC	5
14	no NaOAc	2

Conditions **A**: $NiBr_2$·DME (5 mol %), **L1** (5 mol %), **1a** (1.0 mmol), **2a** (0.5 mmol), B_2pin_2 (**3**, 0.75 mmol), LiOMe (1.0 mmol), in DMF, 30 °C, 24 h. Isolated yield. [a] The ratio in parenthese is *cis*-/*trans*-**4a**. Conditions **B**: $Pd(acac)_2$ (5 mol %), **1a** (0.4 mmol), **2b** (0.2 mmol), B_2pin_2 (**3**, 0.2 mmol), TMAC (0.2 mmol), NaOAc (0.4 mmol), in anhydrous $CHCl_3$, 60 °C, 24 h; GC yields against naphthalene. [b] **1a** (0.6 mmol), isolated yield.



After carefully surveying a series of commonly used metal catalysts, $Pd(acac)_2$ proved to be most efficient in this three-component transformation. As illustrated in Table 1, entry 3, when aryl iodide **2b** was used, the 1,3-arylboration product *cis*-**6a** was isolated in 78% yield. Notably, only a single *cis*-isomer was detected in this reaction. In addition, no 1,2-arylboration products were observed in the Pd-catalyzed conditions. Further catalyst evaluation indicated that $Pd(acac)_2$ gave the best yield (Table 1, entries 3 and 4). Replacing the palladium catalyst with nickel salt resulted in no desired product formation (Table 1, entry 5). The importance of tetramethylammonium chloride (TMAC) additive was highlighted by replacing it with tetrabuthylammonium chloride (TBAC), tetramethylammonium bromide (TMAB) and tetramethylammonium iodide (TMAI) leading to dramatically decreased yields (Table 1, entries 6-8). These results indicate that both the cation and anion of the amounium salt are crucial to this three-component reaction. The additive likely plays a role to generate an active anionic palladium complex and/or stablize the Pd(0) catalyst from precipitation.[13] Moreover, the examination of bases and solvents indicated that NaOAc and $CHCl_3$ were the best choices (Table 1, entries 9-12). Control experiments revealed that both the additive and the base played an essential role for the success of this aryboration reaction (Table 1, entries 13 and 14).

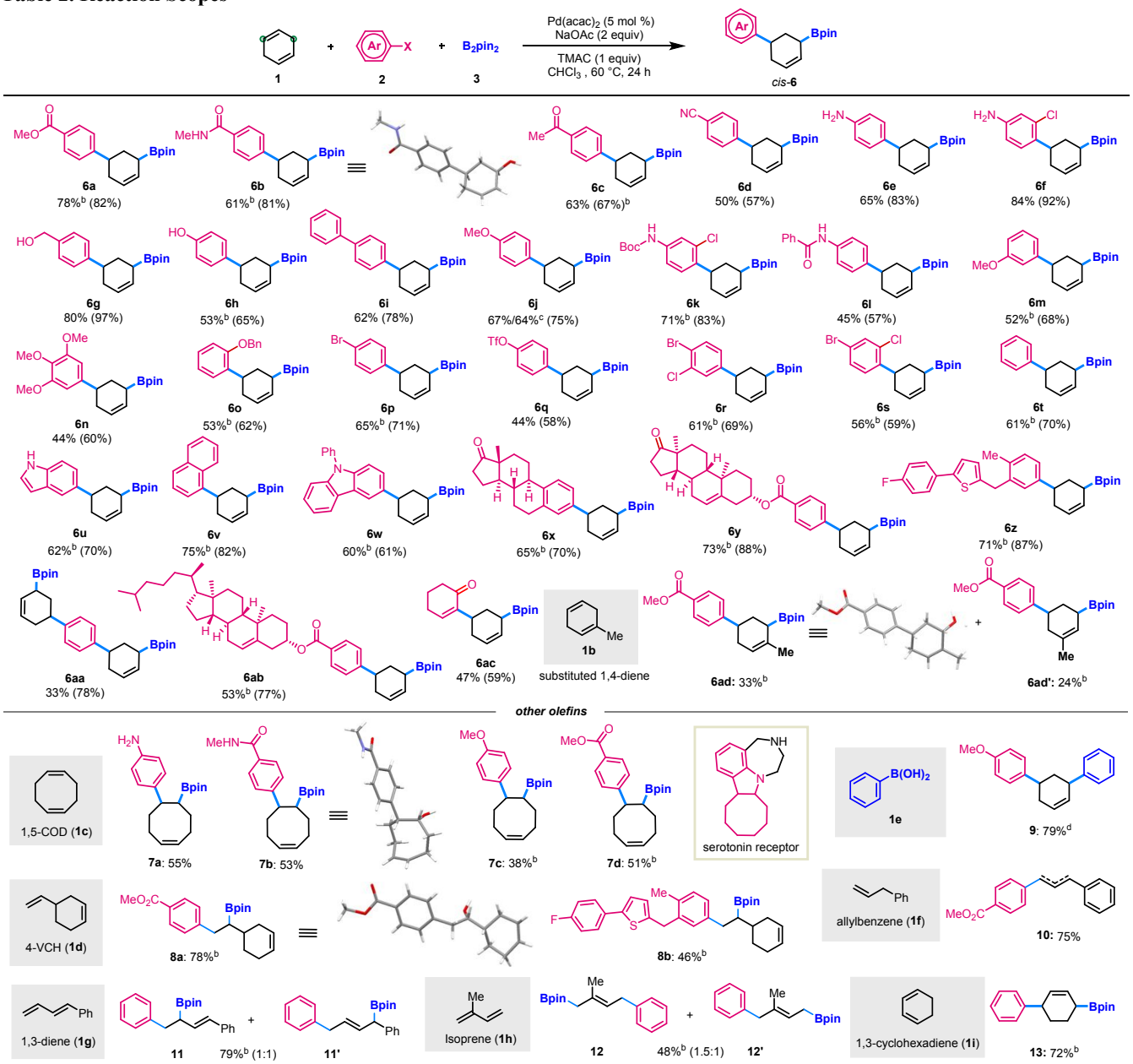


Scheme 1. Proposed Mechanism

Subsequently, a catalytic cycle involving *cis*-2,3-palladium migration was proposed to rationalize this stereoselective transformation. As shown in Scheme 1, the reaction is initiated by oxidative addition of ArI with a Pd(0) species (**I**). In the presence of the ammonium salt (TMAC), a new Pd(II) complex **III** is probably generated from the Pd(II) complex **II**, which reacts with the unconjuagated diene **1a** to deliver intermediate **IV**. Then the intermediate **IV** rapidly undergoes *β*-H elimination and migratory insertion. The excellent stereoselectivity observed in products suggest that the Pd-H does not diassociate from the substrate in this process, which is in accordance with Larock's observations in the Pd-catalyzed carboarylation reactions.[14,15] Therefore, the migratory insertion preceeds in a coplanar manner affording a stable π-allylPd(II) complex **VI**. Subsequent transmetalation with B_2pin_2 forms intermediate **VII**, which delivers the arylboration product **6** and the Pd(0) catalyst by reductive elimination. Interestingly, the migratory insertion of Pd-H also proceeds in a highly regioselective manner, as no 1,2- and 1,4-products are observed.

With the optimal reaction conditions in hand, we next turned our attention to the investigation of the generality of this palladium-catalyzed arylboration reaction. As outlined in Table 2, both electron-rich and electron-deficient aryl iodides successfully yielded the *cis*-1,3-arylboration products in moderate to good yields. Accordingly, a number of 1,3-disubstituted cyclohexene derivatives were prepared. Significantly, in all cases, the *cis*-1,3-arylboration products were isolated as a single constitutional isomer. Remarkably, this reaction exhibited extraordinary functional group compatibility. A broad set of functional groups, such as ethers (OR), chlorides (Cl), bromides (Br), esters (COOR), ketones (C=O), amides (CONHR), cyano (CN), trifluoromethylsulfonates (OTf), olefins (C=C), as well as arylamines ($ArNH_2$), phenols (ArOH), alcohols (ROH) and indoles are all well tolerated in this reaction. *Ortho*-substituted (Cl and OBn) aryl iodides can also furnish the desired products in good yields (**6f**, **6k** and **6o**). It is worthy highlighting that this palladium-catalyzed arylboration shows good chemoselectivity towards polyhalogenated arenes (**6p-6s**), which provides further opportunities for iterative cross-couplings.[16] Moreover, this method could be used to directly modify the complex bioactive molecules and their derivatives (**6x-6z** and **6ab**).

Table 2. Reaction Scopes [a]

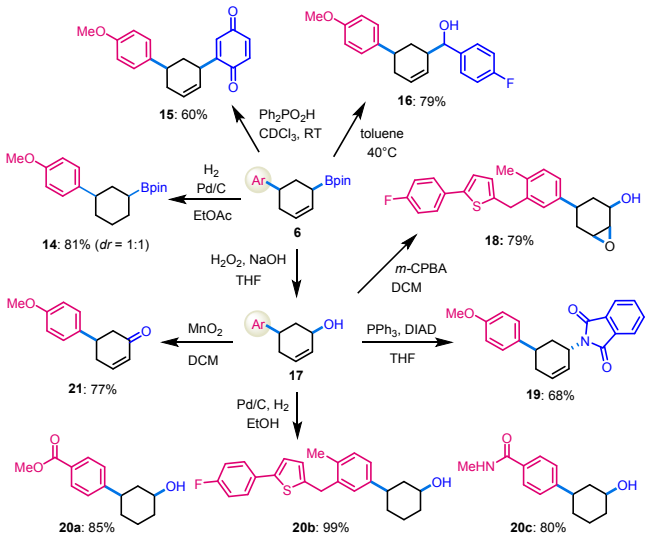


[a] Isolated yields on 0.5 mmol scale; the number in parentheses is NMR yield. [b] Yield of the corresponding alcohol after oxidation. [c] Isolated yields on 6.0 mmol scale; [d] CsF instead of NaOAc, DCE instead of $CHCl_3$.

Additionally, the carboboration product **6ac** can be obtained in a moderate yield as well, when 2-iodocyclohexenone was used as the substrate. Finally, substituted 1,4-cyclohexadiene **1b** was also able to provide 1,3-arylboration products in a good yield, albeit with a poor regioisomeric ratio (**6ad** and **6ad'**). Fortunately, the two isomers could be separated by flash column chromatography.

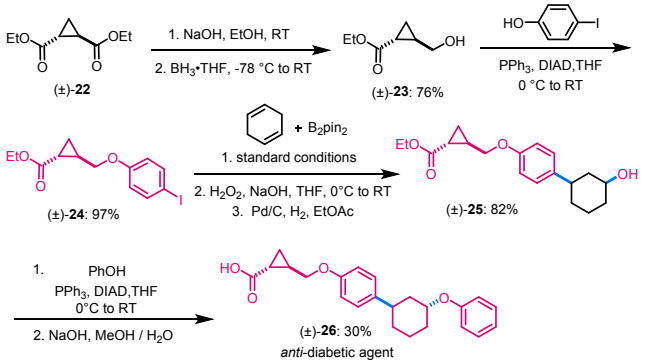
To further demonstrate the synthetic value of this palladium-catalyzed arylboration reaction, the scope of other dienes was explored. As shown in Table 2, when 1,5-cyclooctadiene (1,5-COD) was used as the reactant, surprisingly, a series of *cis*-1,2-arylboration products were selectively obtained (**7a-7d**), probably owing to the second double bond plays a role of ligand to facilitate the reductive elimination at the *original* position.[17] Moreover, the products of regioselective 1,2-arylboration only occurred at the terminal double bond, when 4-vinylcyclohexene (4-VCH) was used (**8a** and **8b**). It is noteworthy that this is the first example to achieve a selective 1,2-arylboration with unactivated terminal olefins.[9] Furthermore, replacing B_2pin_2 with arylboronic acid (**1e**) led to the formation of *cis*-1,3-diarylation product (**9**) in a good yield by slightly optimizing the reaction conditions. Heck product, rather than arylboration product, were isolated from the reaction with allybenzene as the substrate (**10**). This result indicated that the C-B bond could only be constructed from π-allyl-palladium species, rather than from the π-benzyl-palladium intermediates in this catalytic system.[8c] Additionally, the arylboration products could also be anticipated with acyclic conjugated dienes (**1g** and **1h**), albeit with poor selectivity between 1,2- and 1,4-regioisomers under the current reaction conditions, which offers a different

regioselectivity from the previous dual metal catalysis methods.[9f-9g] While the 1,3-cyclohexadiene **1i** afforded the single *cis*-1,4-arylboation product **13** with a good yield.



Scheme 2. Stereospecific Transformations

To illustrate the potential of this 1,3-arylboration to create diverse structures, we conducted subsequent transformations of several products. As illustrated in Scheme 2, saturated product **14** was obtained first after hydrogenation of the olefin. Then the C-B bonds were reacted with a benzoquinone and an aryl aldehyde, providing **15**[18] and **16**[19] respectively. The C-B bonds were converted to hydroxyl groups by oxidation with H_2O_2, resulting in a series of cyclic allylalcohols (**17**). The alcohols were further transformed to **18** by selective oxidation of the double bond, **19** by a Mitsunobo reaction with phthalimide,[20] and a plethora of saturated alcohols **20a**-**20c** via hydrogenation. In addition, a 5-arylsubstituted cyclohexenone **21** was provided by a selective oxidation of the alcohol. Notably, except the direct hydrogenation reaction (**14**), all other transformations are stereospecific processes.



Scheme 3. Synthesis of Bioactive Molecule

Finally, the synthetic utility of this palladium-catalyzed arylboration reaction is further demonstrated in an efficient synthesis of *anti*-diabetic agent **26**,[2f, 21] using commercially available **22** as the starting material (Scheme 3).

In summary, we have developed a novel strategy to access 1,3-disustituted cyclohexanes from benzene. This strategy integrates the classical Birch reduction with a newly developed palladium-catalyzed arylboration. 1,2-Arylboration of 1,5-COD and 4-VCH, the downstream specific transformation and the rapid synthesis of pharmaceutically relevant molecule address the synthetic potentials of this protocol, and provide valuable additions to the FBDD libraries. Therefore, we believe this chemistry will greatly advance complex molecules synthesis and medicinal chemistry candidates.

ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org." Condition investigation, experimental procedures and compound characterization (PDF), and Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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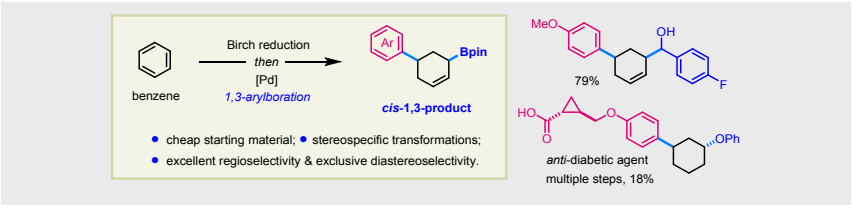
REFERENCES

(1) (a) Velvadapu, V.; Farmer, B. T.; Reitz, A. B. The Practice of Medicinal Chemistry (Fourth Edition), **2015**, Pages 161-180; (b) Erlanson, D. A.; Fesik, S. W.; Hubbard, R. E.; Jahnke, W.; Jhoti, H. Twenty Years on: the Impact of Fragments on Drug Discovery. *Nat. Rev. Drug Discov.* **2016**, *15*, 605-619.

(2) (a) Melvin, L. S.; Johnson, M. R.; Harbert, C. A.; Milne, G. M.; Weissman, A. A Cannabinoid Derived Prototypical Analgesic. *J. Med. Chem.* **1984**, *27*, 67-71; (b) Tsuchiya, S.; Yasuda, N.; Matsumoto, T.; Hiratsuka, K.; Iizuka, H.; Hukuzaki, A.; Matsunaga, K. Phenylethanolamine Compounds Useful as β 3 Agonists, Process for Producing the Same, and Intermediates in the production of the same. WO Patent WO 97/15549 A1, May 01, **1997**; (c) Wiley, J. L.; Beletskaya, I. D.; Ng, E. W.; Dai, Z. M.; Crocker, P. J.; Mahadevan, A.; Razdan, R. K.; Martin, B. R. Resorcinol derivatives: A Novel Template for the Development of Cannabinoid CB1/CB2 and CB2-Selective Agonists. *J. Pharmacol. Exp. Ther.* **2002**, *301*, 679-689; (d) Huffman, J. W.; Thompson, A. L.; Wiley, J. L.; Martin, B. R. Synthesis and Pharmacology of 1-Deoxy Analogs of CP-47,497 and CP-55,940. *Bioorg. Med. Chem.* **2008**, *16*, 322-335; (e) Kare, P.; Bhat, J.; Sobhia, M. E. Structure-based Design and Analysis of MAO-B Inhibitors for Parkinson's Disease: Using In Silico Approaches. *Mol. Divers.* **2013**, *17*, 111-122; (f) Cheng, P. T. W.; Yoon, D. S. Phenyl-(aza)cycloalkyl Carboxylic Acid GPR 120 Modulators. WO Patent WO 2016/040225 A1, Mar 17, **2016**.

(3) (a) Tajuddin, H.; Shukla, L.; Maxwell, A. C.; Marder, T. B.; Steel, P. G. "One-pot" Tandem C-H Borylation/1,4-Conjugate Addition/Reduction Sequence. *Org. Lett.* **2010**, *12*, 5700-5703; (b) Llona-Minguez, S.; Mackay, S. P. Stereoselective Synthesis of Carbocyclic Analogues of the Nucleoside Q Precursor (PreQ0). *Beilstein J. Org. Chem.* **2014**, *10*, 1333-1338; (c) Martinez-Prieto, L. M.; Ferry, A.; Rakers, L.; Richter, C.; Lecante, P.; Philippot, K.; Chaudret, B.; Glorius, F. Long-chain NHC-stabilized RuNPs as

Versatile Catalysts for One-pot Oxidation/Hydrogenation Reactions. *Chem. Commun.* **2016**, *52*, 4768-4771.
(4) Wertjes, W. C.; Southgate, E. H.; Sarlah, D. Recent Advances in Chemical Dearomatization of Nonactivated Arenes. *Chem. Soc. Rev.* **2018**, *47*, 7996-8017.
(5) (a) Southgate, E. H.; Pospech, J.; Fu, J.; Holycross, D. R.; Sarlah, D. Dearomative Dihydroxylation with Arenophiles. *Nature Chem.* **2016**, *8*, 922-928; (b) Okumura, M.; Nakamata Huynh, S. M.; Pospech, J.; Sarlah, D. Arenophile-Mediated Dearomative Reduction. *Angew. Chem., Int. Ed.* **2016**, *55*, 15910-15914; (c) Southgate, E. H.; Holycross, D. R.; Sarlah, D. Total Synthesis of Lycoricidine and Narciclasine by Chemical Dearomatization of Bromobenzene. *Angew. Chem., Int. Ed.* **2017**, *56*, 15049-15052; (d) Okumura, M.; Shved, A. S.; Sarlah, D. Palladium-Catalyzed Dearomative *syn*-1,4-Carboamination. *J. Am. Chem. Soc.* **2017**, *139*, 17787-17790; (e) Hernandez, L. W.; Klockner, U.; Pospech, J.; Hauss, L.; Sarlah, D. Nickel-Catalyzed Dearomative trans-1,2-Carboamination. *J. Am. Chem. Soc.* **2018**, *140*, 4503-4507; (f) Wertjes, W. C.; Okumura, M.; Sarlah, D. Palladium-Catalyzed Dearomative syn-1,4-Diamination. *J. Am. Chem. Soc.* **2019**, *141*, 163-167.
(6) Birch, A. J.; Smith, H. Reduction by Metal–Amine Solutions: Applications in Synthesis and Determination of Structure. *Quart. Rev.* **1958**, *12*, 17-33.
(7) (a) Neeve, E. C.; Geier, S. J.; Mkhalid, I. A.; Westcott, S. A.; Marder, T. B., Diboron (4) Compounds: From Structural Curiosity to Synthetic Workhorse. *Chem. Rev.* **2016**, *116*, 9091-9161; (b) Hemming, D.; Fritzemeier, R.; Westcott, S. A.; Santos, W. L.; Steel, P. G., Copper-boryl mediated organic synthesis. *Chem. Soc. Rev.* **2018**, *47*, 7477-7494.
(8) (a) Nelson, H. M.; Williams, B. D.; Miro, J.; Toste, F. D. Enantioselective 1,1-Arylborylation of Alkenes: Merging Chiral Anion Phase Transfer with Pd Catalysis. *J. Am. Chem. Soc.* **2015**, *137*, 3213-3216; (b) Yang, K.; Song, Q. Palladium-Catalyzed Arylboration of Bicyclic Alkenes. *J. Org. Chem.* **2016**, *81*, 1000-1005; (c) Yang, K.; Song, Q. Pd-Catalyzed Regioselective Arylboration of Vinylarenes. *Org. Lett.* **2016**, *18*, 5460-5463.
(9) (a) Semba, K.; Nakao, Y. Arylboration of Alkenes by Cooperative Palladium/Copper Catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 7567-7570; (b) Smith, K. B.; Logan, K. M.; You, W.; Brown, M. K. Alkene Carboboration Enabled by Synergistic Catalysis. *Chem. Eur. J.* **2014**, *20*, 12032-12036; (c) 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; (d) Semba, K.; Ohtagaki, Y.; Nakao, Y. Arylboration of 1-Arylalkenes by Cooperative Nickel/Copper Catalysis. *Org. Lett.* **2016**, *18*, 3956-3959; (e) Chen, B.; Cao, P.; Yin, X. M.; Liao, Y.; Jiang, L. Y.; Ye, J. L.; 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; (f) 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; (g) Sardini, S. R.; Brown, M. K. Catalyst Controlled Regiodivergent Arylboration of Dienes. *J. Am. Chem. Soc.* **2017**, *139*, 9823-9826; (h) Logan, K. M.; Brown, M. K. Catalytic Enantioselective Arylboration of Alkenylarenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 851-855; (i) 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; (j) Bergmann, A. M.; Dorn, S. K.; Smith, K. B.; Logan, K. M.; Brown, M. K. Catalyst-Controlled 1,2- and 1,1-Arylboration of alpha-Alkyl Alkenyl Arenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 1719-1723; (k) Liu, Z.; Li, X. H.; Zeng, T.; Engle, K. M. Directed, Palladium(II)-Catalyzed Enantioselective anti-Carboboration of Alkenyl Carbonyl Compounds. *Acs Catal.* **2019**, *9*, 3260-3265.
(10) (a) Han, F. S. Transition-Metal-Catalyzed Suzuki-Miyaura Cross-Coupling Reactions: a Remarkable Advance from Palladium to Nickel Catalysts. *Chem. Soc. Rev.* **2013**, *42*, 5270-5298; (b) Leonori, D.; Aggarwal, V. K. Stereospecific Couplings of Secondary and Tertiary Boronic esters. *Angew. Chem., Int. Ed.* **2015**, *54*, 1082-1096.
(11) Reviews on metal migration: (a) Vasseur, A.; Bruffaerts, J.; Marek, I. Remote Functionalization through Alkene Isomerization. *Nature Chem.* **2016**, *8*, 209-219; (b) Sommer, H.; Julia-Hernandez, F.; Martin, R.; Marek, I. Walking Metals for Remote Functionalization. *ACS Cent. Sci.* **2018**, *4*, 153-165.
(12) (a) Wang, W.; Ding, C.; Li, Y.; Li, Z.; Li, Y.; Peng, L.; Yin, G. Migratory Arylboration of Unactivated Alkenes Enabled by Nickel Catalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 4612-4616; (b) Li, Y.; Pang, H.; Wu, D.; Li, Z.; Wang, W.; Wei, H.; Fu, Y.; Yin, G. Nickel-Catalyzed 1,1-Alkylboration of Electronically Unbiased Terminal Alkenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 8872-8876.
(13) (a) Jeffery, T. Palladium-Catalysed Vinylation of Organic Halides under Solid–liquid Phase Transfer Conditions. *J. Chem. Soc., Chem. Commun.* **1984**, 1287-1289; (b) Amatore, C.; Jutand, A. Anionic Pd(0) and Pd(II) Intermediates in Palladium-Catalyzed Heck and Cross-Coupling Reactions. *Acc. Chem. Res.* **2000**, *33*, 314-321; (c) Carrow, B. P.; Hartwig, J. F. Ligandless, Anionic, Arylpalladium Halide Intermediates in the Heck Reaction. *J. Am. Chem. Soc.* **2010**, *132*, 79-81; (d) Robinson, E. E.; Thomson, R. J. A Strategy for the Convergent and Stereoselective Assembly of Polycyclic Molecules. *J. Am. Chem. Soc.* **2018**, *140*, 1956-1965; (e) Schroeter, F.; Strassner, T. Understanding Anionic "Ligandless" Palladium Species in the Mizoroki-Heck Reaction. *Inorg. Chem.* **2018**, *57*, 5159-5173.
(14) (a) Larock, R. C.; Lu, Y. D.; Bain, A. C.; Russell, C. E. Palladium-Catalyzed Coupling of Aryl Iodides, Nonconjugated Dienes, and Carbon Nucleophiles by Palladium Migration. *J. Org. Chem.* **1991**, *56*, 4589-4590; (b) Larock, R. C.; Berriospena, N. G.; Fried, C. A.; Yum, E. K.; Tu, C.; Leong, W. Palladium-Catalyzed Annulation of 1,4-Dienes Using Ortho-Functionally-Substituted Aryl Halides. *J. Org. Chem.* **1993**, *58*, 4509-4510.
(15) Examples on stereoselective Pd migration: (a) Stokes, B. J.; Opra, S. M.; Sigman, M. S. Palladium-Catalyzed Allylic Cross-Coupling Reactions of Primary and Secondary Homoallylic Electrophiles. *J. Am. Chem. Soc.* **2012**, *134*, 11408-11411; (b) Mei, T. S.; Patel, H. H.; Sigman, M. S. Enantioselective Construction of Remote Quaternary Stereocentres. *Nature* **2014**, *508*, 340-344; (c) Singh, S.; Bruffaerts, J.; Vasseur, A.; Marek, I. A Unique Pd-Catalysed Heck Arylation as a Remote Trigger for Cyclopropane Selective Ring-Opening. *Nat. Commun.* **2017**, *8*, 14200; (d) Thornbury, R. T.; Saini, V.; Fernandes, T. A.; Santiago, C. B.; Talbot, E. P. A.; Sigman, M. S.; McKenna, J. M.; Toste, F. D. The Development and Mechanistic Investigation of a Palladium-Catalyzed 1,3-Arylfluorination of Chromenes. *Chem. Sci.* **2017**, 8, 2890-2897. Example on non-stereoselective Pd migration: (e) Larionov, E.; Lin, L.; Guenee, L.; Mazet, C. Scope and Mechanism in Palladium-Catalyzed Isomerizations of Highly Substituted Allylic, Homoallylic, and Alkenyl Alcohols. *J. Am. Chem. Soc.* **2014**, 136, 16882-16894.
(16) For recent examples: (a) Sperger, T.; Guven, S.; Schoenebeck, F. Chemoselective Pd-Catalyzed C-TeCF_3 Coupling of Aryl Iodides. *Angew. Chem., Int. Ed.* **2018**, *57*, 16903-16906; (b) Diehl, C. J.; Scattolin, T.; Englert, U.; Schoenebeck, F. C-I-Selective Cross-Coupling Enabled by a Cationic Palladium Trimer. *Angew. Chem., Int. Ed.* **2019**, *58*, 211-215.
(17) Devasagayaraj, A.; Stüdemann, T.; Knochel, P. A New Nickel-Catalyzed Cross-Coupling Reaction between sp3 Carbon Centers. *Angew. Chem., Int. Ed.* **1995**, *34*, 2723-2725.
(18) Deng, H. P.; Wang, D.; Szabo, K. J. Direct Allylation of Quinones with Allylboronates. *J. Org. Chem.* **2015**, *80*, 3343-3348.
(19) Mao, L.; Bertermann, R.; Rachor, S. G.; Szabo, K. J.; Marder, T. B. Palladium-Catalyzed Oxidative Borylation of Allylic C-H Bonds in Alkenes. *Org. Lett.* **2017**, *19*, 6590-6593.
(20) (a) Swamy, K. C.; Kumar, N. N.; Balaraman, E.; Kumar, K. V. Mitsunobu and Related Reactions: Advances and Applications. *Chem. Rev.* **2009**, *109*, 2551-2651; (b) Wang, X. L.; Yang, F.; Xue, Z. Y.; Wang, X. Q. Progress of Mitsunobu Reaction in Construction of Chemical Bonds. *Chin. J. Org. Chem.* **2015**, *35*, 29-38.
(21) Amori, L.; Katkevica, S.; Bruno, A.; Campanini, B.; Felici, P.; Mozzarelli, A.; Costantino, G. Design and Synthesis of trans-2-Substituted-Cyclopropane-1-Carboxylic Acids as the first Non-natural Small Molecule Inhibitors of O-Acetylserine Sulfhydrylase. *Med. Chem. Comm.* **2012,** *3*, 1111-1116.


benzene
Birch reduction
then
[Pd]
1,3-arylboration
Ar
Bpin
cis-1,3-product
cheap starting material; stereospecific transformations;
excellent regioselectivity & exclusive diastereoselectivity.
MeO
OH
F
79%
HO
O
O
OPh
anti-diabetic agent
multiple steps, 18%