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Cu-Catalyzed Hydroboration of Benzylidenecyclopropanes: Reaction Optimization, (Hetero)Aryl Scope, and Origins of Pathway Selectivity

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Abstract

The copper-catalyzed hydroboration of benzylidenecyclopropanes, conveniently accessed in one step from readily available benzaldehydes, is reported. Under otherwise identical reaction conditions, two distinct phosphine ligands grant access to different products by either suppressing or promoting cyclopropane opening via β-carbon elimination. Computational studies provide insight into how the rigidity and steric environment of these different bis-phosphine ligands influence the relative activation energies of β-carbon elimination versus protodecupration from the key benzylcopper intermediate. The method tolerates a wide variety of heterocycles prevalent in clinical and pre-clinical drug development, giving access to valuable synthetic intermediates. The versatility of the tertiary cyclopropylboronic ester products is demonstrated through several derivatization reactions.

Graphical Abstract

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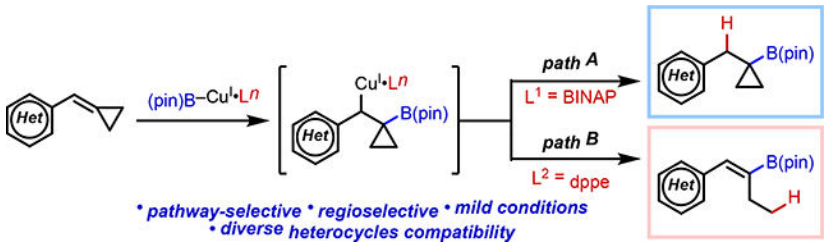
ASSOCIATED CONTENT

Supporting Information

Detailed experimental and computational procedures, compound characterization, Cartesian coordinates of the calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.



Keywords

Copper catalysis; hydroborations; benzylidenecyclopropanes; cyclopropylboronic esters; β-carbon elimination; heterocycles

Conformationally constrained small carbocyclic ring systems are among the most important motifs in modern organic chemistry and drug discovery.[1] Cyclopropane substructures are of special importance as they can imbue a molecule with unique properties, including increased potency, metabolic stability, and brain permeability as well as attenuated pK_a and lipophilicity.[2] Indeed, cyclopropyl groups are found in a wide range of secondary metabolites, insecticides, pharmaceutical products, for example a TRPV1 agonist,[3] GSK1360707F,[4] and foretinib[5] (Figure 1A). Accessing cyclopropane motifs with diverse substitution patterns is often a challenging aspect of the synthesis of such compounds.[6]

Tertiary cyclopropylboronic esters have emerged as a versatile family of building blocks that can be further elaborated to prepare multi-substituted cyclopropane motifs. As a consequence, chemists have developed many important synthetic methods for their preparation (Figure 1B). For example, traditional cyclopropanation of vinyl boronates has been used to afford desired tertiary cyclopropylboronic esters.[7] More recently, the Baran and Aggarwal groups independently demonstrated that decarboxylative borylation of cyclopropyl carboxylic acids produces the corresponding cyclopropylboronic esters.[8] In addition, Morken and coworkers published a method for deborylative alkylation of *gem*-bis(boryl)cyclopropanes which gives tertiary cyclopropylboronic esters as products.[9] Recently, Harris and Pfizer coworkers demonstrated selective Suzuki–Miyaura coupling using these *gem*-bis(boryl)cyclopropane precursors to afford aryl cyclopropylboronic esters.[10] This impressive progress notwithstanding, existing methods also have some limitations in terms of restricted scope, harsh reaction conditions, cost of reagents, and requirement of pre-functionalized precursors.

For ongoing programs in drug discovery at Pfizer, we sought a convenient and reliable method to access tertiary cyclopropylboronates bearing diverse -CH_2Ar/Het substitution at the α-position. In this context, we were attracted to copper–boryl chemistry, which has emerged as a powerful reactivity paradigm for hydroboration and borylative difunctionalization of alkenes.[11, 12] Indeed, the synthesis of secondary cyclopropylboronic esters from cyclopropenes[13] or allylic electrophiles[14] using copper–boryl catalysis has been previously documented. Generally speaking, this class of reactions often proceeds under mild conditions and exhibits broad functional group tolerance, making it well suited for our purposes. In particular, we envisioned highly strained benzylidenecyclopropanes

(BCPs) **1** would be ideal tertiary cyclopropylboronic esters precursors upon Cu-catalyzed hydroboration. The utility of the alkylidene/benzylidenecyclopropane substrate class stems largely from the relief of strain energy, which provides a thermodynamic driving force for engaging a wide array of reaction partners in complexity-generating transformations.[15]

In considering the integration of BCP substrates into copper–boryl catalysis, we envisioned two potential competitive reaction pathways (Figure 1C) from the common intermediate **2** which is generated by migratory insertion of copper–boryl complex to BCP **1**.[15] Direct protodecupration of **2** would generate cyclopropylboronic esters **3** (path A). On the other hand, alkenylboronates **4** could also be generated if β-carbon elimination of **2** is preferred over protodecupration (path B). We envisioned that by tuning the ligand sphere around the metal we could control the pathway selectivity of this process and enable straightforward access to these coveted building blocks. At the outset, we took inspiration from the work of Shi, who described a method for 1,2-aminoboration of BCPs using BINAP as ligand.[12f]

We began our study by preparing several representative BCPs (**1a**–**1c**, Table 1). All BCP substrates were derived from the corresponding aldehydes through Wittig reactions with commercially available and inexpensive starting materials (see SI for details).[16] The heterocycles were chosen based on their prevalence in bioactive compounds and their different electronic properties, which we thought might play a role in stabilizing intermediate **2** thereby impacting the innate tendency to undergo ring opening (Figure 1C).[17,18] We explored various mono- and bis-phosphine ligands with different electronic and steric properties under conditions similar to those developed for the copper-catalyzed hydroboration of styrenes.[19] For ease of visualization, the results in Table 1 are color-coded to highlight outcomes where the ^{1}H NMR yield for one of the two isomers was higher than 70% (**3** in blue and **4** in red). Entries 1–5 show results obtained with mono-phosphine ligands arranged from most electron-donating (entry 1) to most electron-withdrawing (entry 5). Although results varied from substrate to substrate, we observed a clear correlation between the electron-donating character of the ligand and the propensity for β-carbon elimination, which leads to formation of alkenylboronates **4**. Notably, use of tris(pentafluorophenyl)phosphine (entry 5), a ligand not commonly used in copper–boryl catalysis, provided cyclopropylboronic esters **3** exclusively, albeit in variable yields, showing that β-carbon elimination could be fully suppressed with ligands that deplete electron density at the metal center.

We then turned our attention to bis-phosphine ligands containing two –PPh_2 arms with varied natural bite angles (β_n) (entries 6–10).[20] Using dppm (entry 6, β_n = 72°), all three substrates preferentially formed cyclopropylboronic esters **3**. With dppbz as the ligand (entry 7, β_n = 83°), most substrates gave **4** preferentially. In similar fashion, dppe (entry 8), which is known to bind copper with a larger bite-angle than dppm and dppbz (β_n = 85°), favored formation of alkenylboronates **4**. Larger bite angle ligands (entries 9 and 10) such as *rac*-BINAP (β_n = 92°) and xantphos (β_n = 111°) switched the selectivity to favor product **3**. The lack of a clear trend between bite angle and selectivity points to a complex interplay of steric and conformational factors (vide infra). With the insights gained from this study, we opted to use *rac*-BINAP and dppe as the ligands for selective formation of products **3** and **4**, respectively.

We turned our attention to exploring the scope with respect to arene substituents (Scheme 1). The protocol to prepare cyclopropylboronic esters **3** was first examined and found to tolerate a number of electron-withdrawing groups relevant to medicinal chemistry. For example, BCPs containing fluoride at the *ortho* and *para* positions gave boronic esters **3d** and **3e** in good yields. A substrate with a bromide at the *para* position gave the desired cyclopropylboronic ester **3f** in 36%. As demonstrated by the synthesis of **3g** and **3h**, substrates containing trifluoromethyl groups can also be utilized in the reaction. Additionally, the cyano group was well-tolerated, as shown by the synthesis of product **3i**. BCPs bearing electron-donating groups also worked well under the optimized reaction conditions. With certain electron-poor substrates **1d**, **1e**, and **1g**, we found that tris(pentafluorophenyl)phosphine offered moderately higher yields (yield with this ligand in parentheses). Substrates with dimethylamine and methoxy substituents at the *para* position gave products **3j** and **3k**, respectively. A particularly electron-rich BCP bearing three methoxy groups gave the desired product **3l** in 88%. Moreover, cyclopropylboronic ester **3m**, containing the difluoro benzodioxole moiety, could be formed in excellent yield.

We then shifted our focus to more challenging BCPs containing heterocycles prevalent in biologically active molecules (Scheme 2). Many heterocyclic motifs are known to present problems in catalysis, as they can bind strongly to the metal center and inhibit progress. The transformation proved to be tolerant of diverse 5-membered heterocycles, including thiophene, Ts-protected pyrroles, oxazole, and thiazole to give the corresponding products **3n**–**3s** in good to excellent yields. 6-membered heterocycles, including various substituted pyridines, performed well in the reaction, as exemplified by formation of boronic esters **3t**–**3z**. It is worth mentioning that pyridine is the most common aromatic nitrogen-containing heterocycle in drug molecules. Synthetic methods that allow access to building blocks resembling **3t**–**3z** are highly sought-after. We also explored other heterocycles of interest, namely pyrimidine, quinoxaline, quinoline, pyrazolo pyrimidine, benzimidazole, and benzofuran, which gave products **3za**–**3zf** in synthetically useful to good yields.[21]

Next, we explored the feasibility of β-carbon elimination on a number of substrates containing various substituents and heterocyclic motifs (Scheme 3). The system developed utilizing dppe as the ligand served to give alkenylboronates in good to excellent yields.

Having established access to various tertiary cyclopropylboronic esters, we set out to demonstrate their synthetic utility through derivatization reactions (Scheme 4). We chose to focus our efforts on derivatizations of the tertiary cyclopropylboronic esters, as vinyl-boronates are widely known to be versatile building blocks. Compound **3a** was chosen as the model substrate for select C–X and C–C bond forming transformations. Exposure of **3a** to sodium perborate gave tertiary alcohol **5** in 99%.[22] A modified amination protocol developed by Morken furnished primary amine **6** in modest yield.[23] A Matteson–Aggarwal homologation delivered boronic ester **7**;[24] and lastly, the gram-scale conversion of **3a** to tertiary trifluoroborate **8** occurred in 81%.[25]

Furthermore, as illustrated in Scheme 5, facile access to trifluoroborate **8** enabled several Suzuki–Miyaura couplings. Under conditions developed by Harris and coworkers, use of alkenyl triflate electrophiles gave alkenyl cyclopropanes **9**–**11** in good yields.[26] Likewise,

use of heteroaryl bromides efficiently delivered products **12**–**14** containing nitrogen-based heterocycles and substituents (e.g. fluorine, trifluoromethyl, and methyl) critical in drug development.[27]

Given the wide discrepancy between outcomes obtained with seemingly related bis-phosphine ligands under otherwise identical reaction conditions, we pursued further understanding of the ligand effects with computational studies. We performed DFT calculations at the M06/6–311+G(d,p)–SDD/SMD(THF)//M06L/6–31G(d)–LANL2DZ level of theory to investigate the reaction energy profiles leading to the alkenylboronate and cyclopropylboronic ester products with dppe and BINAP ligands (see Figure S1). The calculations suggest that the pathway selectivity is determined by the activation energy difference between β-carbon elimination (**TS1**) and protodecupration (**TS2**) from the benzylic copper intermediate **2** formed via the irreversible migratory insertion of the BCP **1a** (Scheme 6).[28] Consistent with the experimental observations, with the dppe ligand the β-carbon elimination is favored over protodecupration by 3.2 kcal/mol, leading to the formation of the alkenylboronate product **4a**. The use of BINAP ligand completely reverses the pathway selectivity. β-Carbon elimination from the benzylic copper complex with BINAP as ligand requires a much higher barrier ($\Delta G^{\ddagger}$ = 22.4 kcal/mol) than that with dppe as ligand ($\Delta G^{\ddagger}$ = 13.9 kcal/mol). On the other hand, ligand effects have a much smaller impact on the barrier of protodecupration (**TS2**). Therefore, the reaction using BINAP as ligand forms the cyclopropylboronic ester **3a** via favorable protodecupration.

The origin of ligand effects on the β-carbon elimination barrier can be visualized in the quadrant diagrams in Figure 2A. The β-carbon elimination TS with the Cu(I) center prefers a tetrahedral geometry that places the benzylic (C_α) and γ-carbons (C_γ) within the vertical region perpendicular to the P–Cu–P plane. With dppe, this vertical region is not occupied by the $–PPh_2$ arms. Thus, no unfavorable steric repulsions are observed in **TS1a**. On the other hand, the more rigid BINAP is confined to a C_2-symmetric conformation, in which the vertical region is blocked by the pseudo-axial phenyl groups (Ph_{ax}) of the $–PPh_2$ arms. The benzylic and γ-carbons in **TS1b** are significantly distorted to be placed in the less occupied diagonal regions in quadrants **II** and **IV** to avoid repulsions with the BINAP ligand. Consequently, the distorted tetrahedral **TS1b** is energetically disfavored. An isomer of **TS1b** that places C_α and C_γ in the more occupied **I** and **III** quadrants was also located and requires an even higher activation energy (26.7 kcal/mol). By contrast, the ligand steric effects have a smaller impact on the geometry and energy of the protodecupration transition states, which are less sterically congested (**TS2**, Figure 2B). With either dppe or BINAP as ligand, the protodecupration transition state has an undistorted tetrahedral geometry with comparable activation energies.

In summary, we have developed conditions for the hydroboration of benzylidenecyclopropanes that lead to formation of two distinct products, namely cyclopropylboronic esters and alkenylboronates. Both products represent highly versatile building blocks that enable access to diverse derivatives based on downstream manipulation of boronic ester functionality. This work should be of particular interest to the pharmaceutical industry and represents an example of an emerging concept in catalysis, whereby pathway selectivity can be tuned through ligand space.[29] Computational analysis

reveals the origins of ligand effects affecting a key β-carbon elimination step, providing a conceptual framework for strategically employing this family of strained alkenes in a broader range of catalytic transformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(17). Qualitatively, the degree of aromaticity of the aryl-substituent appears to impact the inherent reactivity for ring-opening. More aromatic substituents, like phenyl in BCP 1a, appear to make the substrate more prone to rearrangement via β-carbon elimination leading to alkenylboronates 4a. The origin of this effect may be the decreased Brønsted basicity of the C–Cu bond in these types of substrates, compared to those with less aromatic substituents. A thiazole-containing substrate was found to be resistant to ring opening with all of the ligands in Table 1 (see SI).

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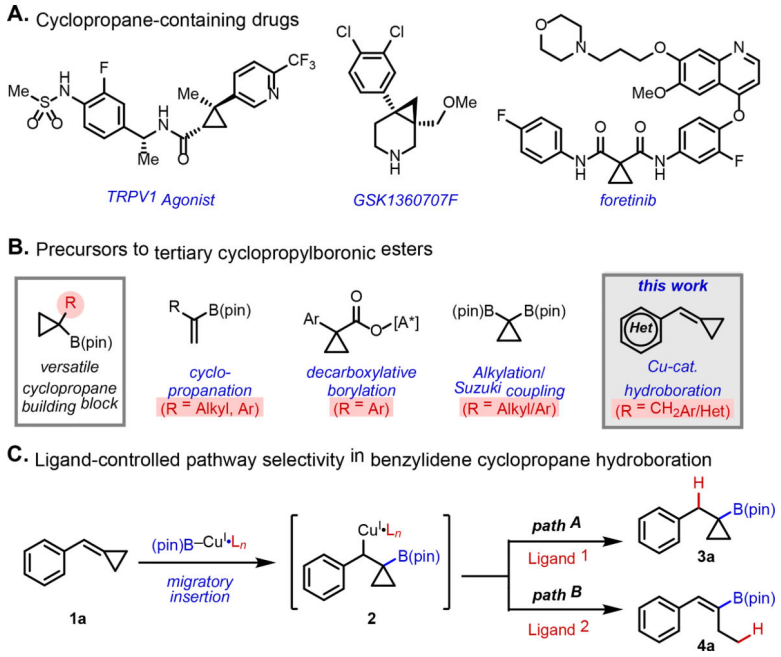


Figure 1.
Overview of Proposed Approach to Preparation of Cyclopropylboronic Esters.

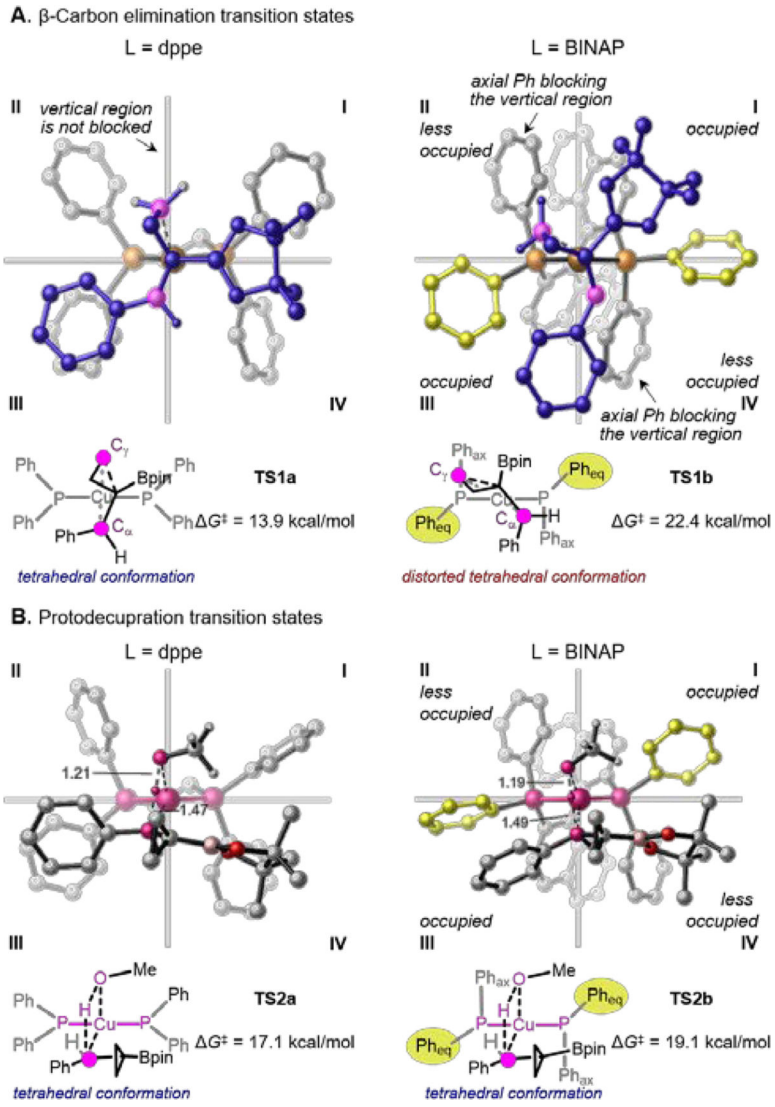
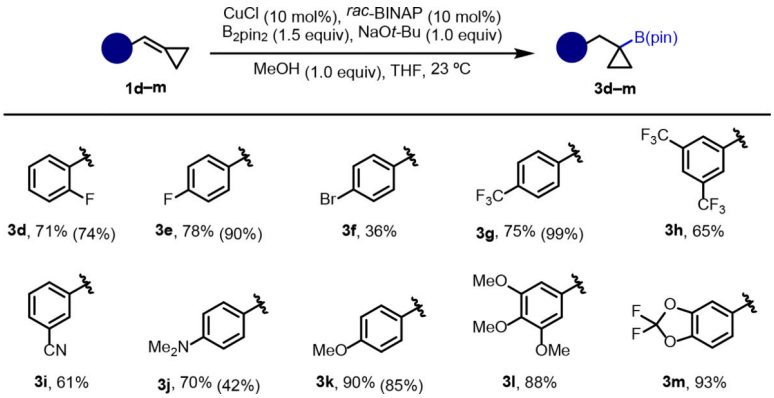


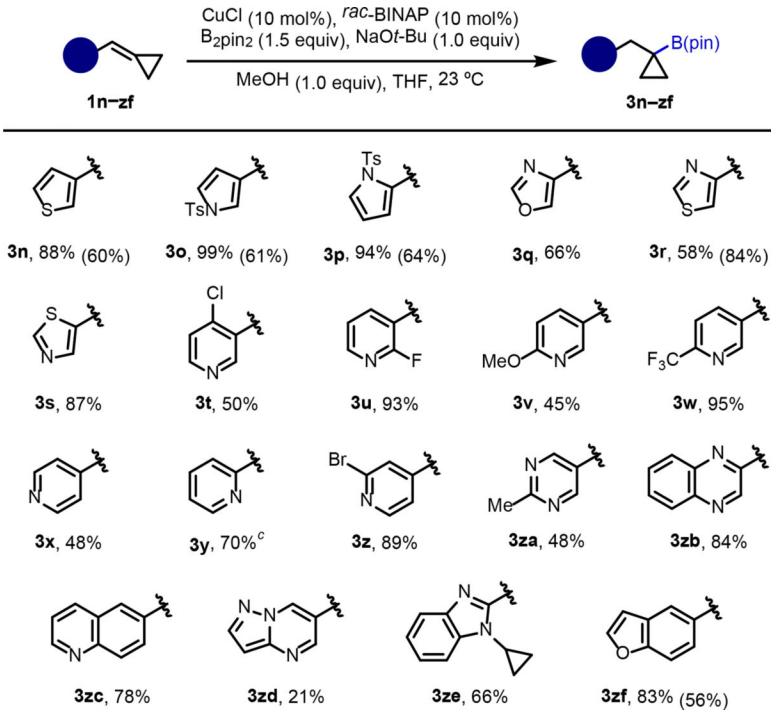
Figure 2.

Origin of ligand effects on β-carbon elimination and protodecupration barriers.



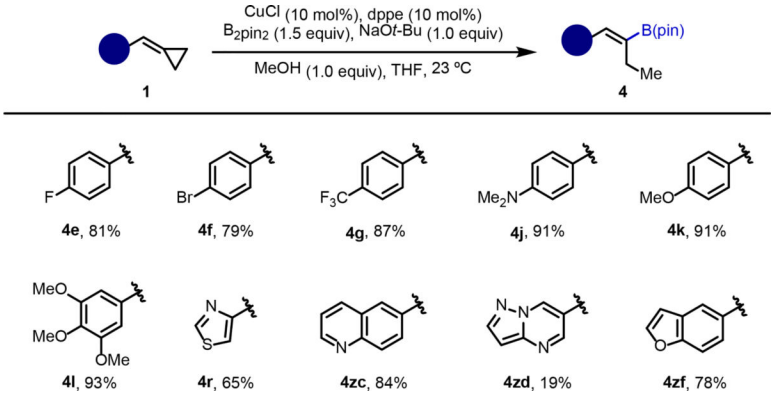
Scheme 1. Hydroboration of BCPs with substituted arenes

[a]Reaction conditions: 1 (0.2 mmol), CuCl (10 mol%), *rac*-BINAP (10 mol%), B_2pin_2 (0.3 mmol), NaO*t*-Bu (0.2 mmol), MeOH (0.2 mmol) in THF (0.5 mL) at room temperature. Percentages refer to the isolated yields. [b]The values in parentheses correspond to NMR yields with $(C_6F_5)_3P$ as ligand in place of *rac*-BINAP



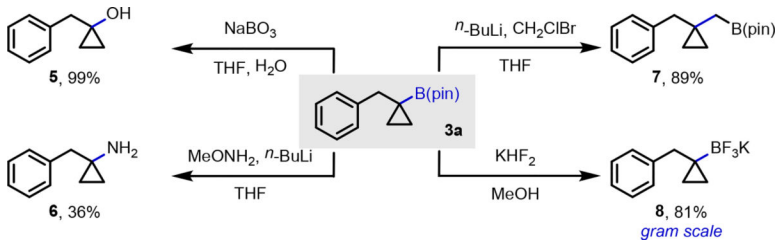
Scheme 2. Hydroboration of BCPs with heterocycles

[a]Reaction conditions: 1 (0.2 mmol), CuCl (10 mol%), *rac*-BINAP (10 mol%), B_2pin_2 (0.3 mmol), NaO*t*-Bu (0.2 mmol), MeOH (0.2 mmol) in THF (0.5 mL) at room temperature. Percentages refer to the isolated yields. [b] The values in parentheses correspond to NMR yields with $(C_6F_5)_3P$ as ligand in place of *rac*-BINAP. [c]Yield determined by ^1H NMR. The product was isolated as the corresponding BF_3K salt in 51% yield over two steps.



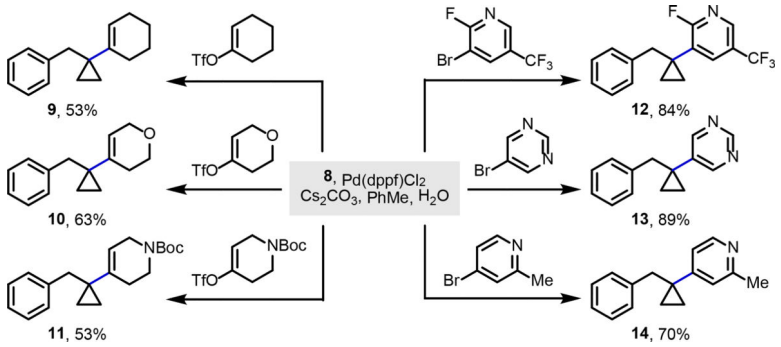
Scheme 3. Synthesis of alkenyl boronates via β-C elimination

[a]Reaction conditions: 1 (0.2 mmol), CuCl (10 mol%), dppe (10 mol%), B_2pin_2 (0.3 mmol), NaO*t*-Bu (0.2 mmol), MeOH (0.2 mmol) in THF (0.5 mL) at room temperature. Percentages refer to the isolated yields.



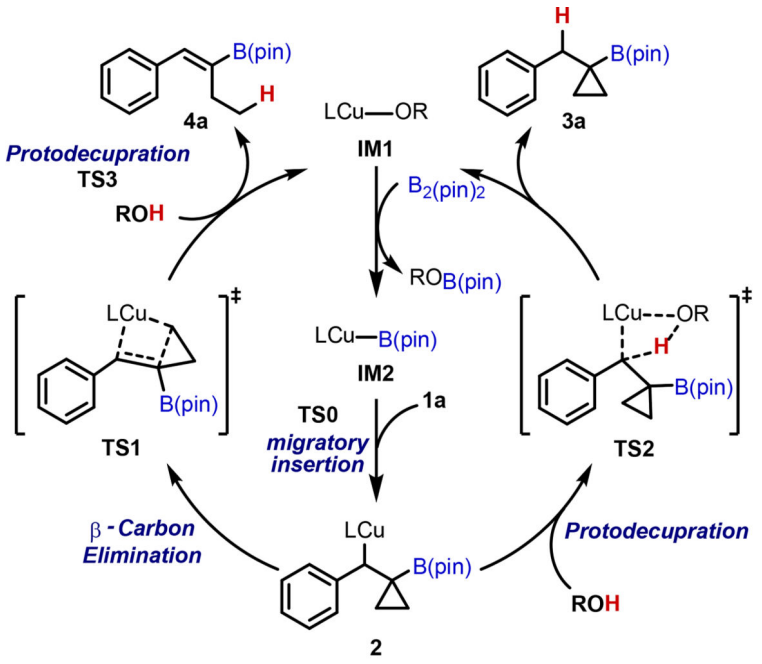
Scheme 4.

Select derivatization reactions with tertiary boronic ester 3a



Scheme 5.

Enabling Suzuki–Miyaura couplings with tertiary trifluoroborate 8

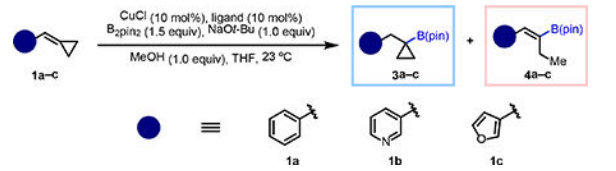


	$\Delta G^{\ddagger}_{TS1}$ (kcal/mol) β - carbon elimination	$\Delta G^{\ddagger}_{TS2}$ (kcal/mol) protodecupration
L = dppe	13.9 (favored)	17.1
L = BINAP	22.4	19.1 (favored)

Scheme 6.
Activation energies of the selectivity-determining steps.

Table 1.

Ligand optimization with representative substrates



entry[a]	ligand	β_n[b]	product ratio (3 : 4) in % yield[c]		
1	$P(t\text{-Bu})_3 \cdot HBF_4$	---	8 : 82	22 : 62	62 : 20
2	PCy_3	---	7 : 78	41 : 30	55 : 18
3	PPh_3	---	53 : 27	65 : 6	68 : 0
4	$(p\text{-}CF_3\text{-}C_6H_4)_3P$	---	42 : 23	67 : 10	41 : 0
5	$(C_6F_5)_3P$	---	57 : 0	84 : 0	18 : 0
6	dppm	72°	70 : 21	93 : 6	55 : 0
7	dppbz	83°	0 : 88	2 : 72	21 : 66
8	**dppe**	**85°**	**0 : 93**	**6 : 76**	**16 : 70**
9	***rac*-BINAP**	**92°**	**79 : 0**	**83 : 6**	**91 : 0**
10	xantphos	111°	71 : 0	34 : 0	41 : 0

[a]Reaction conditions: **1** (0.2 mmol), CuCl (10 mol%), ligand (10 mol%), B_2pin_2 (0.3 mmol), NaO*t*-Bu (0.2 mmol), MeOH (0.2 mmol) in THF (0.5 mL) at room temperature.

[b]Natural bite angle (β_n)

[c]Yield determined by ^1H NMR.