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Communication

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Copper-Catalyzed Synthesis of Stereodefined Cyclopropyl Bis(Boronates) from Alkenes with CO as the C1 Source

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ABSTRACT: A novel copper-catalyzed stereodefined procedure for the selective synthesis of cyclopropyl bis(boronates) from terminal alkenes has been developed. Various aliphatic alkenes were transformed into the desired bis(boronate ester)-substituted cyclopropanes in moderate to good yields. Synthetic transformations of the resulting cyclopropyl bis(boronates) demonstrate their utility. A possible reaction mechanism is proposed.

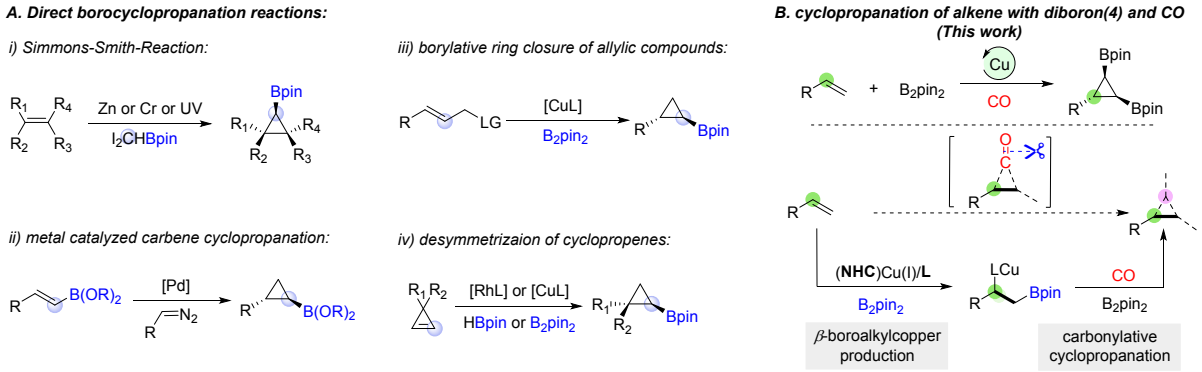

Fig. 1. Synthesis of borocyclopropanes.

Stereodefined cyclopropanes are widely present in biologically active compounds that address multiple barriers during drug discovery, such as enhancing the potency, increasing metabolic stability, improving binding to the target, decreasing plasma clearance, etc.[1] Hence, various cyclopropanes were incorporated into studies of pharmaceutically relevant compounds to modulate new drug's activity and conformational rigidity.[2] In general, 1,2,3-trisubstituted cyclopropane units are frequently found in biologically active natural products.[3,4] Thus, the development of new strategies for preparing 1,2,3-trisubstituted cyclopropanes which contain a reactive synthetic handle that allows for rapid diversification to give more functionalized cyclopropanes is urgently needed. Boronate derivatives are suitable partners for cyclopropane to increase their functionality and complexity *via* Suzuki-Miyaura cross-coupling reactions, amination, oxidation, etc. However, direct access to cyclopropyl boronates with high levels of diastereoselective is a formidable challenge. Typically, the known pathways to access cyclopropyl boronates proceed via Simmons-Smith reaction with boromethylzinc carbenoid,[5-7] metal-catalyzed carbene cyclopropanation of vinyl boronates,[8] borylative ring closure of allylic compounds,[9-12] desymmetrizaion of cyclopropenes[13] and several others (Fig. 1, A).[14] Based on their recognized importance, new procedures for their preparation from readily available substrates are always attractive.

Carbonylation has been considered as one of the most effective and economical pathways by which to increase the carbon chain length of organic compounds by employing CO as a cheap and abundant C1 source.[15] Although carbonylation has experienced impressive progress during the past half century, a strategy for the synthesis of cyclopropane moieties has not been realized. One of the main reasons is that C≡O is the strongest chemical bond in nature, which requires 1076 KJ mol^{-1} energy at 298K to cleave the one σ and two π bonds.[16a] Another conundrum is that cyclopropanation process usually requires highly reactive metals to overcome the ring strain (28 kcal mol^{-1}),[16b] which is the opposite of the inhibitory influence of CO coordination to metals (CO coordinates to a metal and decrease its electron density).

Based on the potential utility of cyclopropyl boronates, a methodology to overcome the difficulties discussed above would be very attractive. In our recent studies on carbonylative transformations of organo boronates,[17] we found that cyclopropyl boronates can be produced effectively from terminal alkenes and bis(pinacolato)diboron (B_2pin_2) in a copper-catalyzed process (Fig. 1, B). One molecule of carbon monoxide was reduced and the carbon incorporated to form a cyclopropane ring. Further synthetic transformations of the resulting cyclopropyl bis(boronates) were also realized.

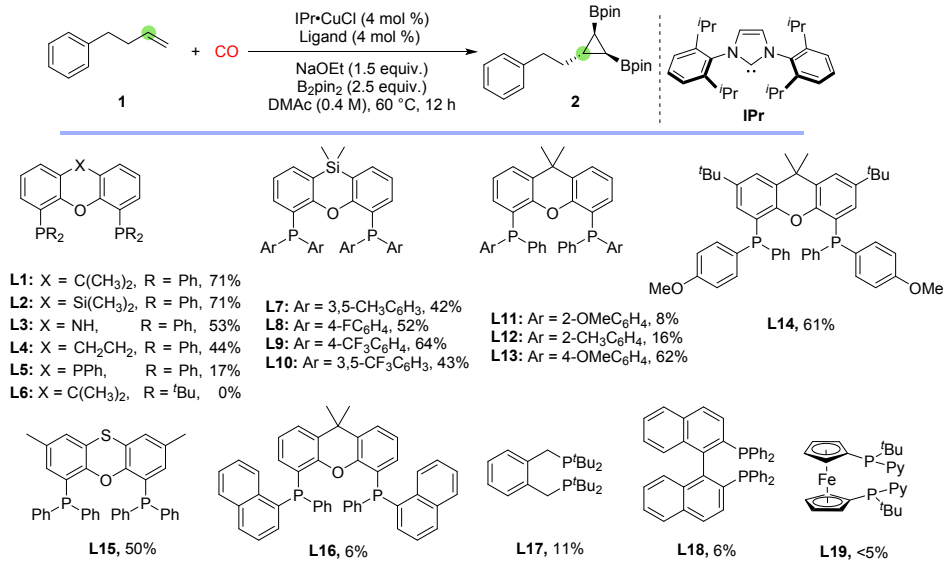

Fig. 2. Impact of ligands on the yield of carbonylative cyclopropanation. Reaction conditions: **1** (0.2 mmol), IPrCuCl (4 mol%), ligand (4 mol%), B_2pin_2 (2.5 equiv.), NaOEt (1.5 equiv.), CO (10 bar), DMAc (0.4 M), 60 °C, 12 h. Yields were determined by GC analysis using hexadecane as internal standard.

In order to study this transformation, but-3-en-1-ylbenzene and bis(pinacolato)diboron (B_2pin_2) were selected as model substrates for detailed studies. Initially, by using IPr·CuCl (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazoline-2-ylidene; see Fig. 2) and Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; Fig. 2, **L1**) as the catalyst system in dimethylacetamide (DMAc) with NaOtBu as the base under CO pressure (10 bar) at 60 °C, product **2** was obtained in 47% yield and identified as 2,2'-((1*R*,2*S*,3*r*)-3-phenethylcyclopropane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). Subsequently, systematic optimization studies were carried out (for details see Supporting Information Tables S1-S9). No desired product was detected when toluene or 1,4-dioxane were used as the solvents. The amount of base and B_2pin_2 were also optimized. In combination with Xantphos, we found that similar yields of **2** were obtained using CuCl or $CuCl_2$ instead of IPr·CuCl as the catalyst precursor. Increasing the load of the phosphine ligand had no significant effect on the reaction outcome. In the testing of bases, the best result was achieved using 1.5 equiv. of NaOEt, which gave a 62% isolated yield. No target product was detected when NaOPh, Na_2CO_3, KOH, K_3PO_4, or Cs_2CO_3 were employed as the base. Interestingly, a decreased yield was observed when the reaction temperature was increased to 70 °C. Surprisingly, we still able to obtain a 52% yield of **2** under 1 bar of CO. Various bidentate phosphine ligands were studied to examine ligand effects (Fig. 2). Xantphos (**L1**) and Sixantphos (**L2**) were found to be the best ligands for this transformation. Other ligands tested, including Xantphos-type and other chelating ligands, were all less effective (Fig. 2. **L3-L19**). It is worth mentioning that the reaction is clean, in general, and the only byproduct detected during the whole optimization process was the mono borylated cyclopropane (4,4,5,5-tetramethyl-2-((1*R*,2*R*)-2-phenethylcyclopropyl)-1,3,2-dioxaborolane).

With optimized reaction conditions in hand, we examined the substrate scope of this process (Fig. 3). In general, moderate to good yields of the desired products were achieved with the aliphatic alkenes tested. Various ethers, esters, silane, thioether, amines, different ring- and heterocycle-substituted terminal alkenes are all suitable starting materials. Substrates containing another double bond are well tolerated and selectively transformed. For example, 4-vinylcyclohex-1-ene was transformed into the corresponding 2,2'-((1*R*,2*S*,3*r*)-3-((*S*)-cyclohex-3-en-1-yl)cyclopropane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) **26** in 55% isolated yield. In addition to internal alkene groups, 1,1-disubstituted alkene groups are also tolerated, and the yields of the final products are even better (**27**, **28**, **29,** **32**). However, the cyclopropanation reaction failed in the case of styrene, and only a trace amount of the desired product **31** was detected together with a significant amount of a hydroboration by-product.[18] More complex alkenes were successfully transformed under our standard conditions giving the target products in moderate yields (**32**, **33**, **34**).

In order to demonstrate further the synthetic value of this procedure, transformations of product **2** were carried out (Fig. 4). Importantly, the cyclopropyl bis(boronate) **2** product was selectively activated at one C-B bond leaving the other one intact. Mono-Bpin-substituted cyclopropanes were produced in good yields in one step, including Suzuki-Miyaura coupling, bromination and protodeboronation (Fig. 4, **36**, **38**, **37**, **35**).[19] Furthermore, the mono-Bpin-substituted cyclopropane was further transformed into high-value products in excellent yields (Fig. 4, **39-43**). Good stereoselectivity was observed in all of these cases.

For better mechanistic understanding, several control experiments were performed (Fig. 5). Our labelling experiments confirmed that no intermolecular hydrogen transfer occurred, and only intramolecular hydrogen transfer was detected (Fig. 5, **A** and **B**). In the reaction without carbon monoxide, alkene borylation occurred and no cyclopropyl product was detected (Fig. 5, **C**). A ß-boryl ketone was prepared and tested under our standard conditions, and no cyclization product was detected, thus excluding the possibility that it functions as an intermediate (Fig. 5, **D**). Finally, a CuBpin complex was prepared *in situ* and used to produce an alkene insertion intermediate, and the target

product **2** was obtained in 28% yield after adding B_2pin_2 and CO gas (Fig. 5, **E**).

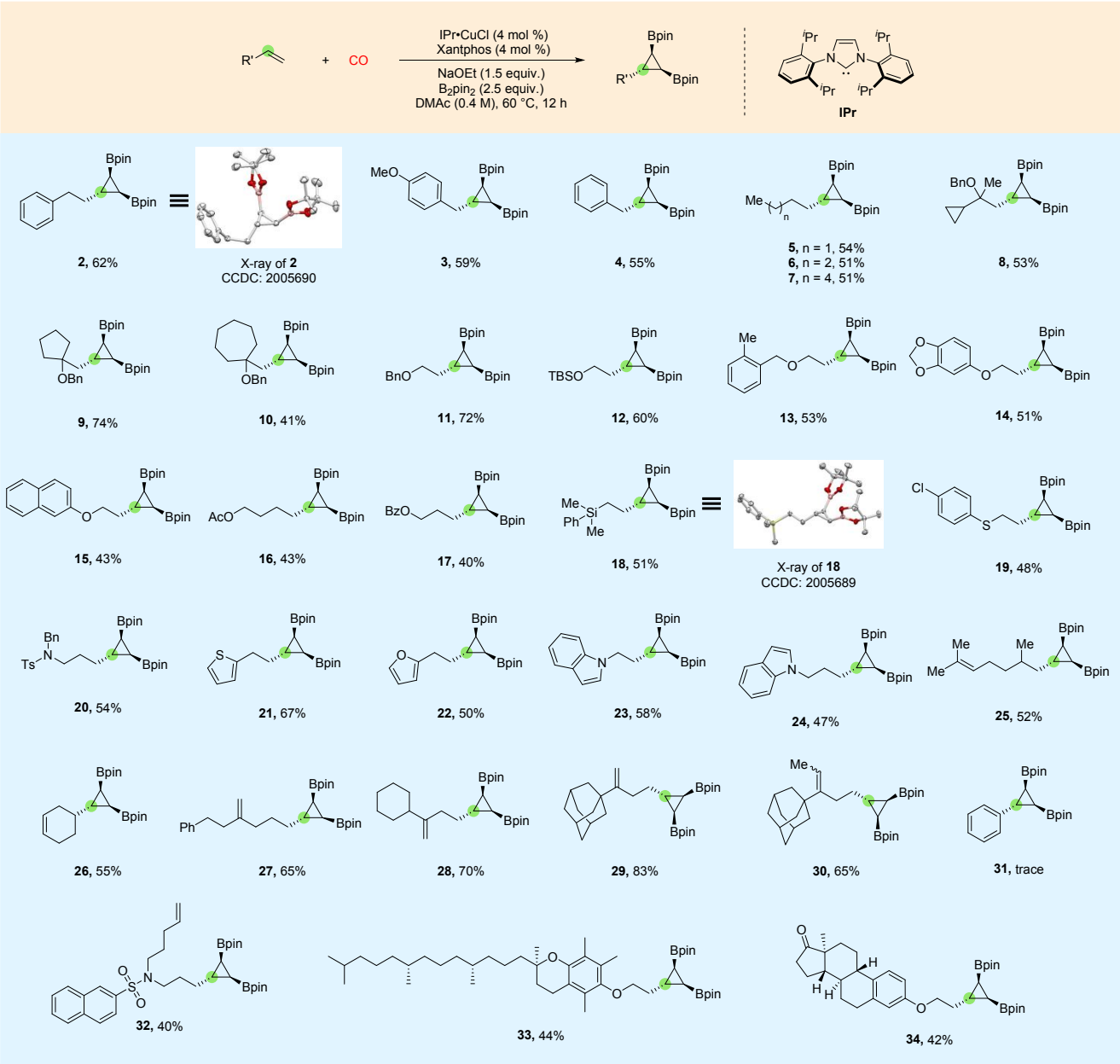

Fig. 3. Scope of the carbonylative cyclopropanation of alkenes. Reaction conditions: **1** (0.2 mmol), IPrCuCl (4 mol%), Xantphos (4 mol%), B_2pin_2 (2.5 equiv.), NaOEt (1.5 equiv.), CO (10 bar), DMAc (0.4 M), 60 °C, 12 h. Yields represent isolated yields of purified products.

Based on the above information and related literature,[20,21,22] a possible reaction pathway is proposed (Fig. 6). Initially, the active LCuBpin complex **IM1** is formed. Then, two catalytic pathways based on this CuBpin complex **IM1** begin. In one cycle, **IM1** coordinates CO, which produces LCu(C=O)Bpin intermediate **IM7** after an insertion step. Then the bis(boryl) ketone intermediate **IM8** is eliminated after reaction with B_2pin_2. In the other cycle, an alkene substate coordinates and inserts into the Cu-Bpin bond of complex **IM1** to give alkyl copper intermediate **IM2**. Afterwards, the *in situ* produced acylboronate intermediate **IM8** reacts with alkyl copper intermediate **IM2** to give intermediate **IM3** which will generate **IM4** intermediate after intramolecular rearrangement. After a 1,3-copper shift,[20] intermediate **IM5** is formed which eliminates cyclopropyl boronate as the final product and generates an LCuOBpin complex **IM6**. Finally, the LCuOBpin complex **IM6** reacts with B_2pin_2 to close the catalytic cycle.

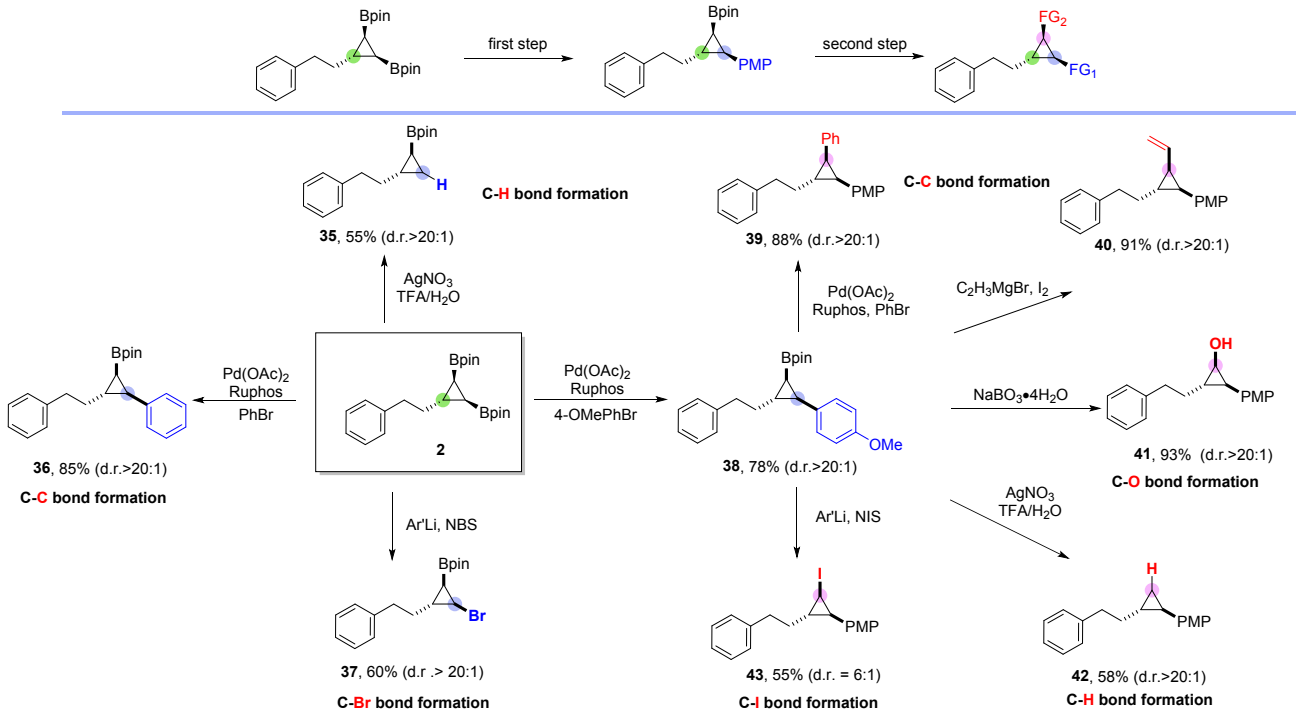

Fig. 4. Derivatization of the B-C bond of cyclopropyl bis(boronate) **2**.

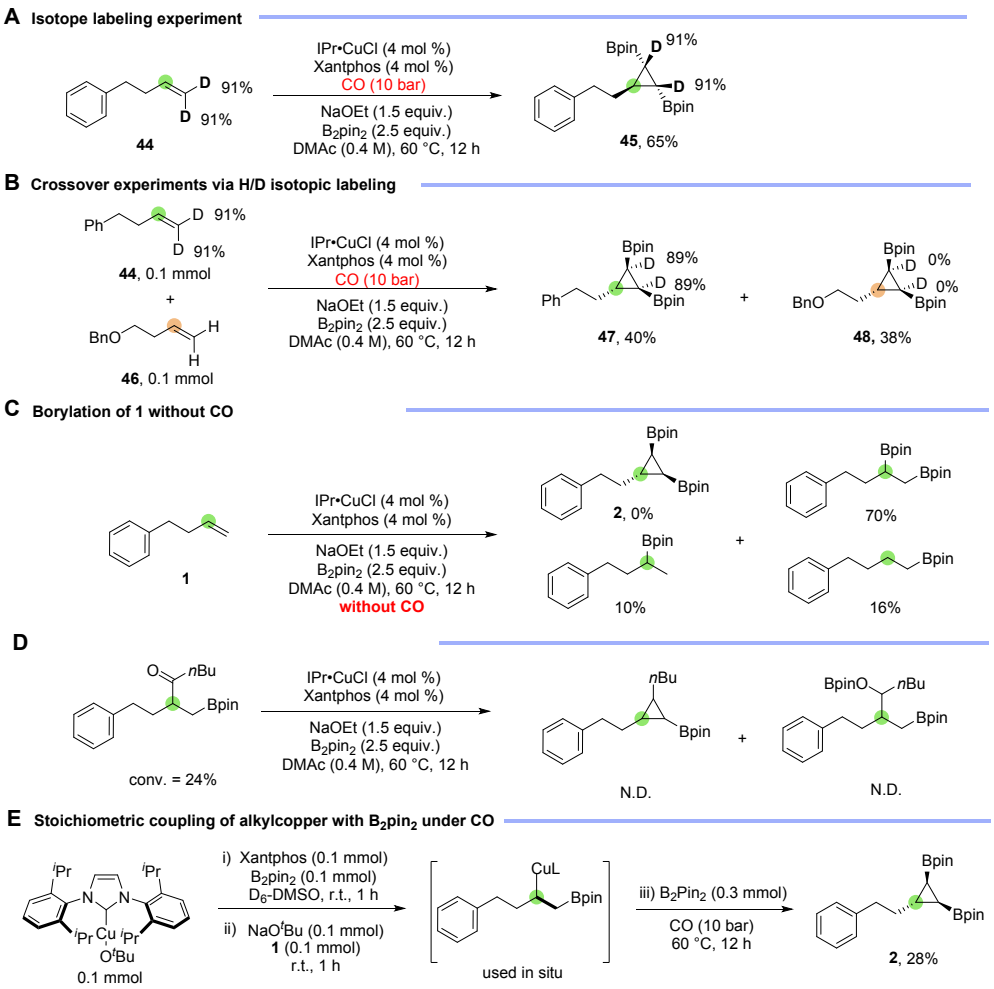

Fig. 5. Control experiments.

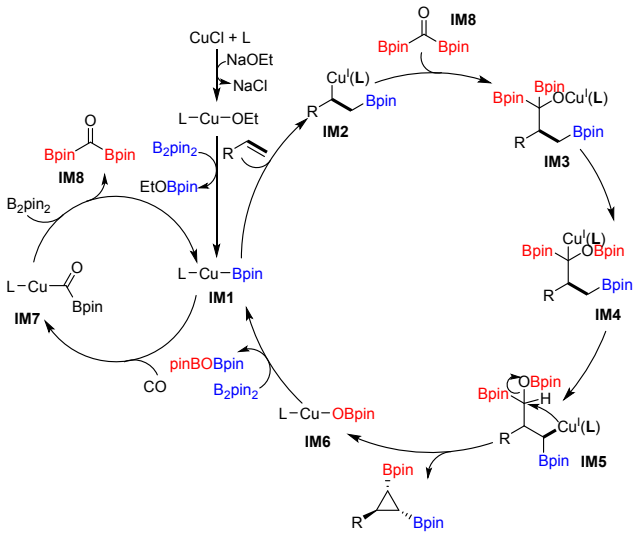

Fig. 6. Plausible reaction mechanism.

In summary, a novel copper-catalyzed stereodefined procedure for the selective synthesis of cyclopropyl bis(boronates) from terminal alkenes has been developed. Various aliphatic alkenes were transformed into the desired bis(boronate ester)-substituted cyclopropanes in moderate to good yields. Synthetic transformations of the cyclopropyl bis(boronate) products clearly demonstrate the utility of this process. Finally, a possible reaction pathway is proposed, and a detailed computational study of the mechanism is in progress.

ASSOCIATED CONTENT

Supporting Information.
Optimization details, general procedures, analytic data, and NMR spectra.
This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

There is no conflict of interests to declare.

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Graphic abstract: