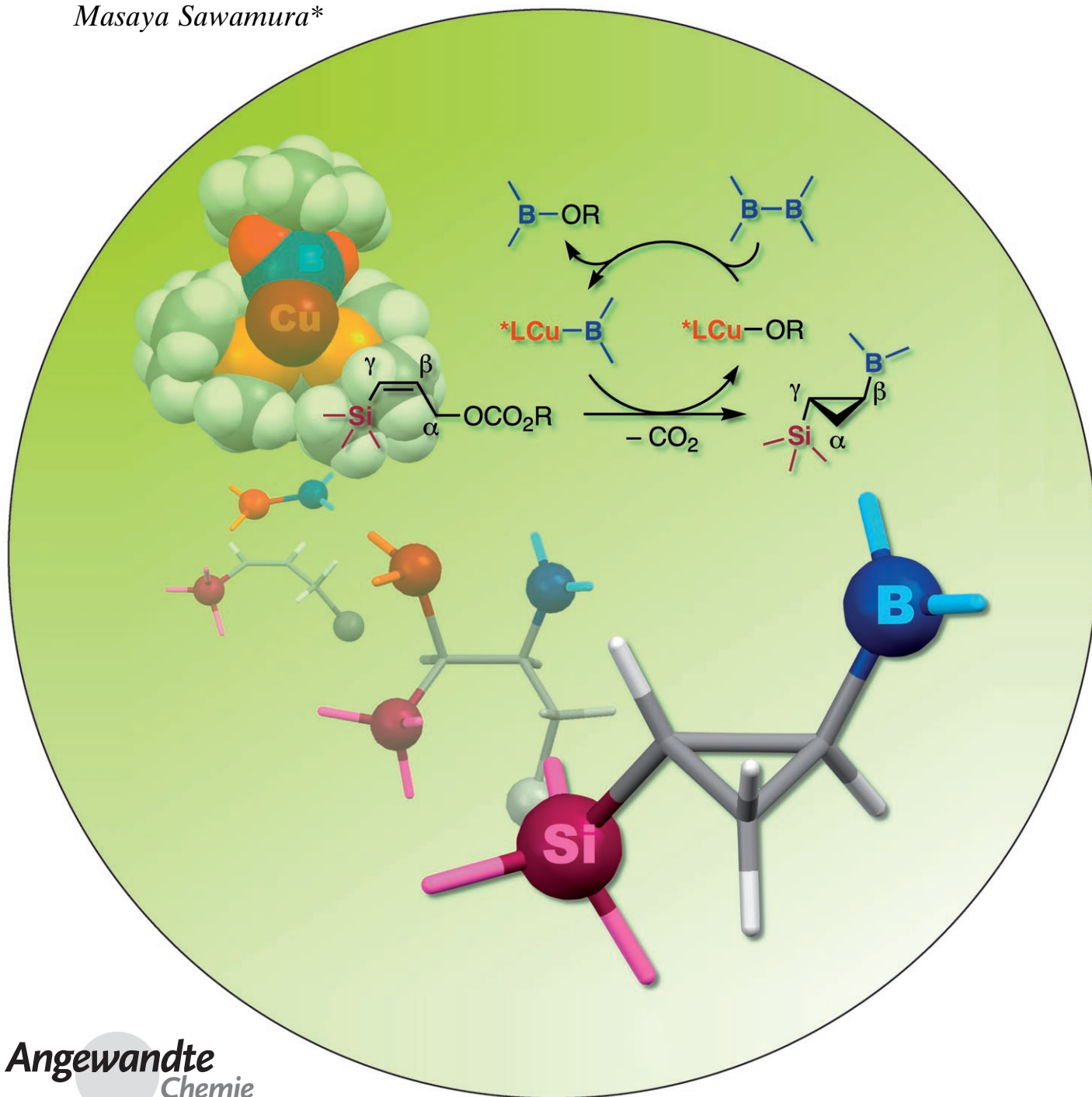
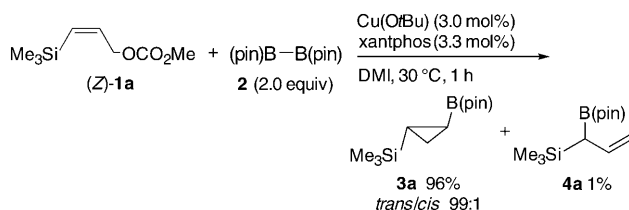


Synthesis of Optically Active Boron–Silicon Bifunctional Cyclopropane Derivatives through Enantioselective Copper(I)-Catalyzed Reaction of Allylic Carbonates with a Diboron Derivative**

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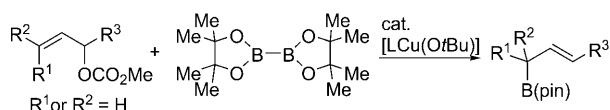


Chirally substituted cyclopropane frameworks are widely found in naturally occurring organic compounds and pharmaceuticals. Their stereoselective and efficient synthesis is hence an important issue in organic synthesis.^[1] Herein we report a highly diastereo- and enantioselective copper(I)-catalyzed reaction that converts γ -silylated allylic carbonates (**1**) and a diboron species (**2**) into previously unreported, optically active *B*,*Si* bifunctional cyclopropane derivatives (*B* = (pin)B; *Si* = Me₃Si **3a**, PhMe₂Si **3b**, BnMe₂Si **3c**, Scheme 1).^[2,3] *B*,*Si* bifunctional cyclopropane (1*S*,2*S*)-**3c** was derivatized into (1*S*,2*R*)-2-phenyl-1-cyclopropanol by Suzuki–Miyaura coupling and Tamao oxidation.



Scheme 1. Cyclopropane formation with (Z)-**1a** in the presence of copper(I) xantphos catalyst and diboron derivative **2**. pin = pinacolato, xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, DMI = 1,3-dimethyl-2-imidazolidinone.

During the course of our studies on the synthesis of optically active allylboronates using copper(I)-catalyzed reactions,^[4] which involve the nucleophilic γ -substitution of allylic carbonates with a borylcopper(I) intermediate (Scheme 2),^[5] we encountered a drastic product switch from allylboronates to cyclopropylboronates when allylic carbonates with a γ -silicon substituent were employed instead of alkyl-substituted ones. Thus, the reaction of silylated carbonate (Z)-**1a** with bis(pinacolato)diboron (**2**)^[6] in the presence of an achiral copper(I) xantphos catalyst (3 mol % Cu) gave 1-(trimethylsilyl)cyclopropan-2-ylboronate **3a**^[7] with high *trans* selectivity (*trans/cis* 99:1) in 96 % yield after 1 h (Scheme 1).



Scheme 2. Synthesis of allylboronates through copper(I)-catalyzed substitution of allylic carbonates with a diboron derivative.^[4]

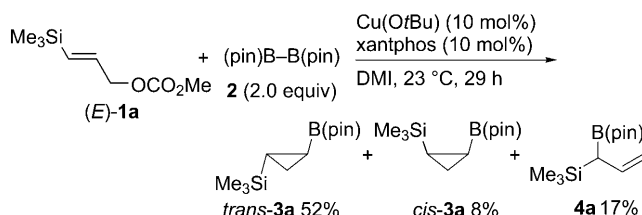
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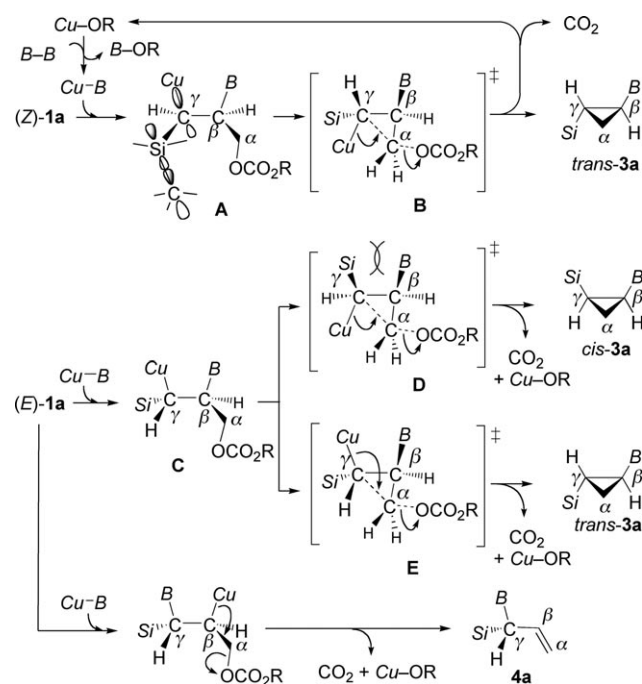
Only a trace amount of the corresponding allylboronate (**4a**) was detected. Notably, the cyclopropane formation from silyl-substituted substrate (Z)-**1a** is significantly faster than the allylboron formation from alkyl-substituted ones,^[4] implying an activating effect of the silyl group.

The *E* or *Z* configuration of the substrates greatly influenced the reaction rate, chemoselectivity (**3a/4a**), and *trans/cis* selectivity. Reactions of (E)-**1a** in 1,3-dimethyl-2-imidazolidinone (DMI) required a higher catalyst loading (10 mol %) and a longer reaction time (29 h) than those of (Z)-**1a**, producing considerable amounts of *cis*-**3a** (8 %) and allylboronate **4a** (17 %) along with *trans*-**3a** (52 %, *trans/cis* 87:13, Scheme 3).



Scheme 3. Cyclopropane and allylboron formation with (E)-**1a** in the presence of copper(I) xantphos catalyst and diboron derivative **2**.

The cyclopropane formation can be explained by assuming a reversal of the regioselectivity in the addition of a borylcopper(I) intermediate, which is formed through the reaction between an alkoxycopper(I) complex and a diboron derivative, across the C–C double bond of the γ -silylated allylic carbonate.^[8] This selectivity is driven by an interaction between the σ [C(γ)–Cu] and the σ^* [Si–C(Si)] orbitals in the addition product (**A**, Scheme 4).^[9] Subsequent intramolecular

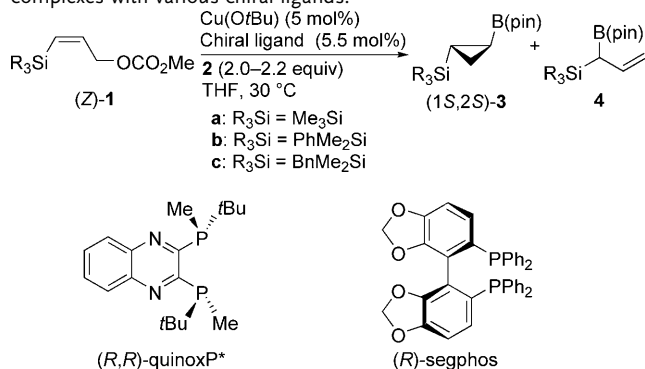


Scheme 4. Possible pathways for cyclopropane and allylboron formation with (Z)- and (E)-**1a**. Si = Me₃Si, B = B(pin), Cu = (xantphos)Cu

nucleophilic substitution (**B**) between the C(γ)–Cu and C(α)–O bonds would afford *trans*-**3a** with retention of the configuration at the γ carbon atom.^[10] In the case of (*E*)-**1a**, the lower reactivity, chemoselectivity, and *trans/cis* selectivity can be explained as follows: The corresponding nucleophilic substitution that forms the addition product (**C**) with retention of the C(γ) configuration that leads to *cis*-**3a** would suffer from steric repulsion between the boryl and silyl groups (**D**) and hence become a minor pathway. Instead, the intramolecular nucleophilic substitution with inversion of the C(γ) configuration (**E**), which demands a pseudo-linear Cu–C(γ)–C(α)–O arrangement, would proceed as a major pathway, affording *trans*-**3a**. Since the cyclopropane formation from (*E*)-**1a** should be slower than that from (*Z*)-**1a**, it would be reasonable that the route to give the allylboron compound (**4a**) also competes with cyclopropane formation.^[11]

Next, we examined enantioselective reactions. Various copper(I) phosphine catalysts prepared in situ by mixing Cu(O*t*Bu) (5 mol %) and chiral ligands (5.5 mol %) were examined for catalytic activity and enantioselectivity in the reaction of (*Z*)-**1a** and **2** in THF at 30 °C (Table 1, entries 1–

Table 1: Enantioselective reaction of **1a–c** with **2** catalyzed by copper(I) complexes with various chiral ligands.^[a]

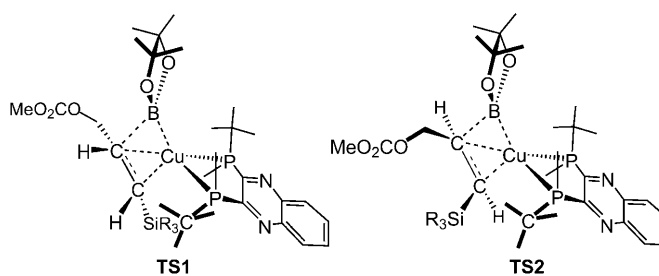


Entry	R ₃ Si	Carbonate	Ligand	<i>t</i> [h]	Yield [%] ^[b] 3	4	<i>ee</i> [%] ^[c]
1	Me ₃ Si	(<i>Z</i>)- 1a	(<i>R,R</i>)-quinoxP*	8	99	< 1	98
2	Me ₃ Si	(<i>Z</i>)- 1a	(<i>R</i>)-segphos	8	94	2	94
3	Me ₃ Si	(<i>Z</i>)- 1a	(<i>R</i>)-tol-binap	8	75	< 1	90
4	Me ₃ Si	(<i>Z</i>)- 1a	(<i>R,R</i>)-Me-duphos	1	97	< 1	82
5	Me ₃ Si	(<i>Z</i>)- 1a	(<i>S,S</i>)-diop	1	98	< 1	13 ^[d]
6	Me ₃ Si	(<i>Z</i>)- 1a	(<i>R</i>)-(<i>S</i>)-josiphos	2	93	3	0
7	PhMe ₂ Si	(<i>Z</i>)- 1b	(<i>R,R</i>)-quinoxP*	8	91	4	91 ^[e]
8 ^[f]	PhMe ₂ Si	(<i>Z</i>)- 1b	(<i>R</i>)-segphos	7	86 ^[g]	< 1	97 ^[e]
9	BnMe ₂ Si	(<i>Z</i>)- 1c	(<i>R,R</i>)-quinoxP*	8	88	9	92 ^[e]
10 ^[f]	BnMe ₂ Si	(<i>Z</i>)- 1c	(<i>R</i>)-segphos	8	83 ^[g]	2	94 ^[e]
11 ^[h]	Me ₃ Si	(<i>Z</i>)- 1a	(<i>R</i>)-segphos	24	86 ^[g]	2	96

[a] Conditions: Cu(O*t*Bu) (5 mol %, 0.0125 mmol), ligand (5.5 mol %, 0.014 mmol), **1** (0.25 mmol), **2** (0.5 mmol, 2.0 equiv) in THF (0.125 mL). [b] Yield was determined by GC unless otherwise noted. In all reactions, yields of *cis*-**3** were less than 1 %. [c] The *ee* value of **3a** was determined by chiral GC analysis. [d] (1*R*,2*R*)-**3a** was the major isomer. [e] The *ee* values of **3b** and **3c** were determined by chiral HPLC analysis. [f] Reaction with 1.0 mmol **1b** or **1c** and 2.2 mmol **2**. [g] Yield of isolated product. [h] Reaction with 5.0 mmol **1a** with 10.5 mmol **2**. Bn = benzyl, tol-binap = 2,2'-bis[(*d*-*p*-tolylphosphino)-1,1'-binaphthyl], Me-duphos = 1,2-bis[(2*R*,5*R*)-2,5-dimethylphospholano]benzene, diop = 1,4-bis(diphenylphosphino)-1,4-dideoxy-2,3-O-isopropylidene-L-threitol, josiphos = 2-[(diphenylphosphino)ferrocenyl]ethylidicyclohexylphosphine.

6). The reaction with the (*R,R*)-quinoxP* ligand^[12] was completed in 8 h and gave optically active *trans*-cyclopropane (1*S*,2*S*)-**3a** with 98 % *ee* in 99 % yield (Table 1, entry 1). The axially chiral ligand (*R*)-segphos^[13] was also effective for this reaction, showing slightly lower enantioselectivity (94 % *ee*, Table 1, entry 2). The catalyst that was prepared from (*R*)-tol-binap showed a significantly decreased enantioselectivity (Table 1, entry 3). The reactions with Me-duphos, diop, and josiphos were faster than those with (*R,R*)-quinoxP* and (*R*)-segphos, but they were less enantioselective (Table 1, entries 4–6). Optically active cyclopropylboronates with dimethylphenylsilyl [(*S*)-**3b**] or benzyldimethylsilyl [(*S*)-**3c**] groups, which can be converted more easily into other functional groups than the trimethylsilyl group, were obtainable in good yields through the reaction with the copper(I) (*R,R*)-quinoxP* or the copper(I) (*R*)-segphos catalysts (Table 1, entries 7–10). For these substrates, (*R*)-segphos (Table 1, entries 8 and 10) was superior to (*R,R*)-quinoxP* (Table 1, entries 7 and 9) in terms of enantioselectivity and **3/4** ratio. The reaction of (*Z*)-**1a** was also successful on a gram scale (Table 1, entry 11).^[14]

The stereochemical outcome of the copper(I)-catalyzed reactions of (*Z*)-**1** can be explained by comparing the transition states during the addition of the Cu–B bond across the C–C double bond (Scheme 5). Favored transition

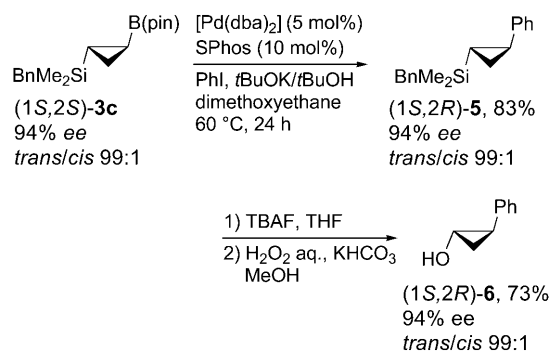


Scheme 5. Proposed stereodiscriminating transition-state models.

state **TS1** is free from steric repulsion between the substituents of (*Z*)-**1** and the *t*Bu groups of the quinoxP* ligand, thus delivering (1*S*,2*S*)-**3** as a major enantiomer. In contrast, less favored **TS2** is severely destabilized by steric repulsion between the substituents of (*Z*)-**1** and one of the ligand *t*Bu groups. The rigidity of the four-center diastereomeric transition states should be responsible for the highly efficient enantiofacial discrimination.

Stepwise, stereoselective transformation of the boron and silicon functionalities allows for making use of the bifunctional cyclopropane derivatives as building blocks for the synthesis of cyclopropane-containing chiral compounds. Preliminary results of studies toward this end are illustrated in Scheme 6. Suzuki–Miyaura coupling of (1*S*,2*S*)-**3c** with iodo-benzene afforded *trans*-2-phenyl-1-silylcyclopropane [(1*S*,2*R*)-**5**] in 83 % yield with high stereoselectivity.^[15] Subsequent Tamao oxidation^[16] of (1*S*,2*R*)-**5** gave the corresponding alcohol (1*S*,2*R*)-**6**^[17] in 73 % yield without decrease in the enantiomeric and diastereomeric purity of the product.

The regioselectivity of copper(I)-catalyzed allylic substitutions is generally determined by α - versus γ -selectivity.^[18]



Scheme 6. Stereoselective Suzuki–Miyaura coupling and Tamao oxidation. dba = dibenzylideneacetone, SPhos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, TBAF = tetrabutylammonium fluoride.

The present reaction represents exceptional regioselectivity: Formal nucleophilic attack occurs at the β -position of the leaving group in the allylic electrophile. Further studies on the application of the bifunctional cyclopropane derivatives are currently underway.

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