Asymmetric Cyclopropanation

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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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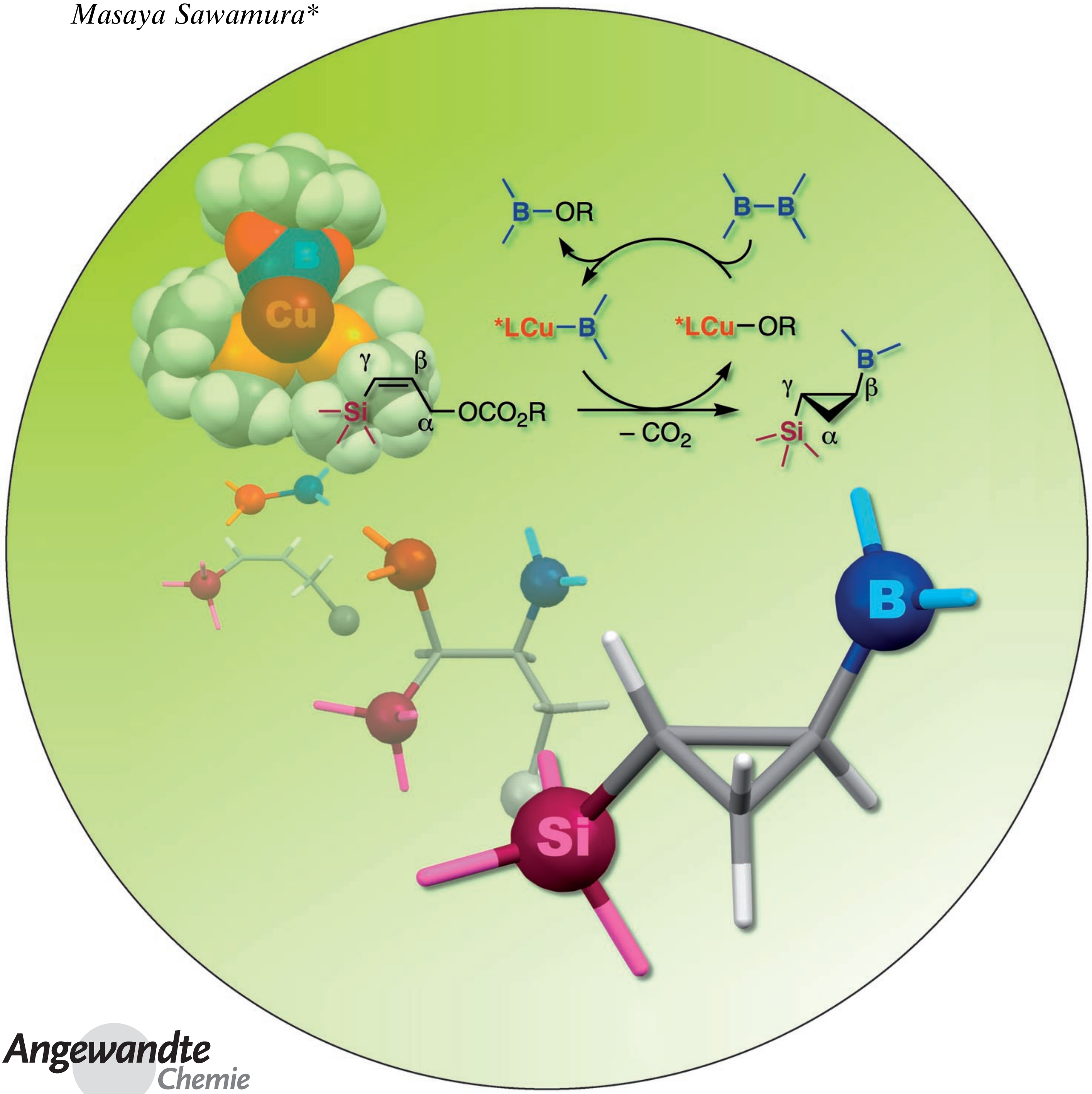
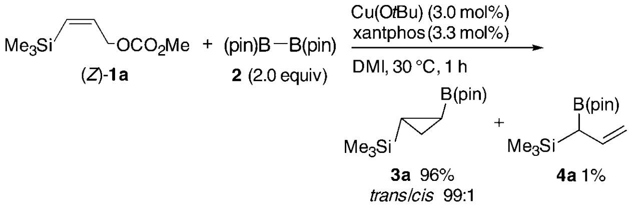
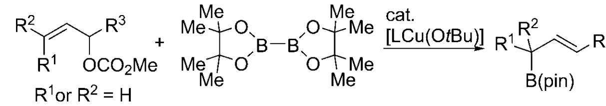


Chirally substituted cyclopropane frameworks are widely found in naturally occurring organic compounds and pharmaceuticals. Their stereoselective and efficient synthesis is hence an important issue in organic synthesis.[1] Herein we report a highly diastereo- and enantioselective copper(I)-catalyzed 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* = Me_3Si **3a**, $PhMe_2Si$ **3b**, $BnMe_2Si$ **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.



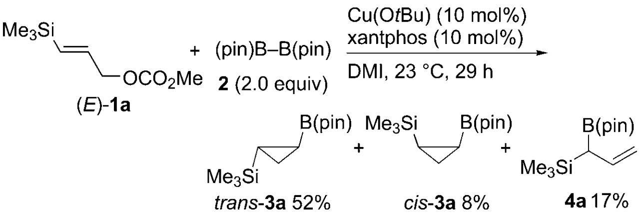
Scheme 1. Cyclopropane formation with (*Z*)-**1a** in the presence of copper(I) xantphos catalyst and diboron derivative **2**. pin = pinacolato, xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, DMI = 1,3-dimethyl-2-imidazolidinone.

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). 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.



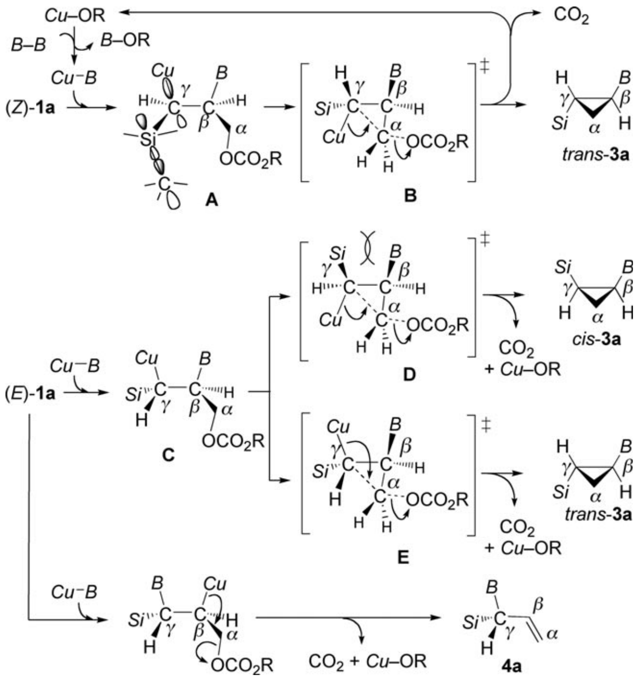
Scheme 2. Synthesis of allylboronates through copper(I)-catalyzed substitution of allylic carbonates with a diboron derivative.[4]

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* = Me_3Si, *B* = B(pin), *Cu* = (xantphos)Cu

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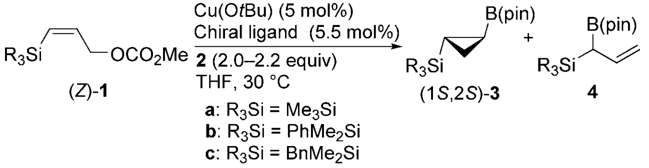
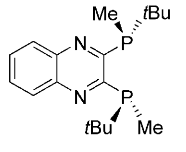
nucleophilic substitution (**B**) between the C(γ)–Cu and C(α)–O bonds would afford *trans*-**3a** with retention of the configuration at the γ carbon atom.[10] In the case of (*E*)-**1a**, the lower reactivity, chemoselectivity, and *trans*/*cis* selectivity can be explained as follows: The corresponding 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]

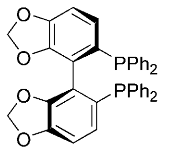
Next, we examined enantioselective reactions. Various copper(I) phosphine catalysts prepared in situ by mixing Cu(O*t*Bu) (5 mol%) and chiral ligands (5.5 mol%) were examined for catalytic activity and enantioselectivity in the reaction of (*Z*)-**1a** and **2** in THF at 30 °C (Table 1, entries 1–6). 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]

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





(*R*,*R*)-quinoxP*

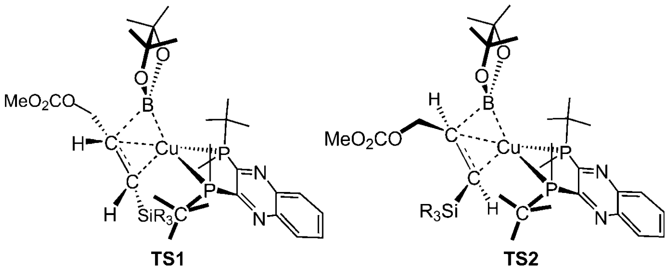


(*R*)-segphos

Entry	R_3Si	Carbonate	Ligand	*t* [h]	Yield [%][b] **3**	Yield [%][b] **4**	*ee* [%][c]
1	Me_3Si	(*Z*)-**1a**	(*R*,*R*)-quinoxP*	8	99	<1	98
2	Me_3Si	(*Z*)-**1a**	(*R*)-segphos	8	94	2	94
3	Me_3Si	(*Z*)-**1a**	(*R*)-tol-binap	8	75	<1	90
4	Me_3Si	(*Z*)-**1a**	(*R*,*R*)-Me-duphos	1	97	<1	82
5	Me_3Si	(*Z*)-**1a**	(*S*,*S*)-diop	1	98	<1	13[d]
6	Me_3Si	(*Z*)-**1a**	(*R*)-(*S*)-josiphos	2	93	3	0
7	$PhMe_2Si$	(*Z*)-**1b**	(*R*,*R*)-quinoxP*	8	91	4	91[e]
8[f]	$PhMe_2Si$	(*Z*)-**1b**	(*R*)-segphos	7	86[g]	<1	97[e]
9	$BnMe_2Si$	(*Z*)-**1c**	(*R*,*R*)-quinoxP*	8	88	9	92[e]
10[f]	$BnMe_2Si$	(*Z*)-**1c**	(*R*)-segphos	8	83[g]	2	94[e]
11[h]	Me_3Si	(*Z*)-**1a**	(*R*)-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(di-*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]ethyldicyclohexylphosphine.

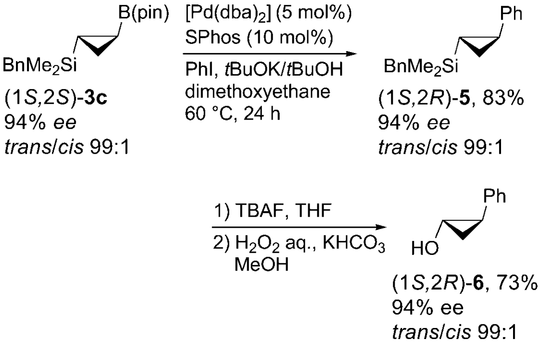
The stereochemical outcome of the copper(I)-catalyzed reactions of (*Z*)-**1** can be explained by comparing the transition states during the addition of the Cu–B bond across the C–C double bond (Scheme 5). Favored transition state **TS1** is free from steric repulsion between the substituents of (*Z*)-**1** 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.



Scheme 5. Proposed stereodiscriminating transition-state models.

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 iodobenzene 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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