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Copper-Catalyzed, Stereoconvergent, *cis*-Diastereoselective Borylative Cyclization of *ω*-Mesylate-*α,β*-Unsaturated Esters and Ketones

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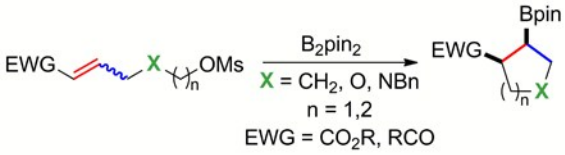
The Cu(I)-catalyzed stereoconvergent borylative cyclization of *ω*-mesylate-*α,β*-unsaturated compounds is facilitated by a simple Cu-bisphosphine catalyst. This reaction provides a novel route to *cis*-*β*-boron-substituted five- and six-membered carbocycle and heterocycle esters. Mechanistic studies indicate that stereoconvergence and *cis*-substitution likely stem from the rapid enolation of the borylcopper adduct with the substrate double bond and the formation of a five-membered intermediate, respectively.

Five- and six-membered carbocycles are common motifs in both natural and synthetic compounds that exhibit important biological and pharmaceutical activities. Cycloalkylboron compounds are important building blocks for the stereoselective preparation of a wide range of carbocycles due to their versatility for derivatization. In general, cycloalkylboron compounds are prepared via the hydroboration of cycloalkene derivatives,[1] or the hydrogenation of cycloalkenylboronates.[2] However, in recent years, the metal-catalyzed intramolecular borylative cyclization reaction has appeared as a novel method for the preparation of boron-containing cyclic compounds. For example, Cárdenas and Bäckval reported the Pd-catalyzed borylative cyclization of 1,6-enynes[3] and enallenes,[4] respectively. However, Cu-catalyzed borylative cyclization reactions have attracted more attention, with Lam et al. reporting an enantioselective copper-catalyzed domino conjugate boration/aldol cyclization of enone diones to produce a range of highly functionalized bicyclic compounds.[5] In addition, Liu et al. achieved a tandem regioselective *β*-borylation of an alkyne/conjugate addition reaction of cyclohexadienone-containing 1,6-enynes, which also yielded highly functionalized bicyclic compounds.[6] Furthermore, Ito et al. reported the Cu-catalyzed borylative exo-cyclization of alkenyl halides to produce monocyclic and spirocyclic compounds.[7] Ito's works show that Cu-catalyzed diastereoselective borylative cyclization of terminal-functionalized *α,β*-unsaturated aromatic and silyl compounds can be employed to synthesize cyclopropyl and cyclobutylboronates.[8] Although the hydroboration of *α,β*-unsaturated esters, ketones, amides, aldehydes, thioesters, and nitriles is wildly used to prepare organoboron compounds,[9] the borylative cyclization of such substrates bearing a terminal leaving group has not yet been reported. In this context, 2-alkoxycarbonylcycloalkyl boronate is a potential synthetic intermediate for the preparation of cyclic *β*-amino acids, which have attracted the attention of synthetic and medicinal chemists over the past two decades[10] due to their interesting bioactivities.[11] As part of our studies into borylative C–C bond formation,[8b, 12] we herein report the first copper-catalyzed stereoconvergent borylative cyclization of *ω*-mesylate-functionalized *α,β*-unsaturated esters and ketones to afford five- and six-membered cycloalkylboronates bearing either a 2-alkoxycarbonyl or 2-acyl substituent, with high levels of *cis*-selectivity (Scheme 1).[13]



Scheme 1. Copper-Catalyzed Stereoconvergent Borylative Cyclization

The borylative cyclization of model compound (*Z*)-ethyl 6-[(methylsulfonyl)oxy]-2-hexenoate [(*Z*)-1a] was carried out using bis(pinacolato)diboron (2) in the presence of CuCl/PCy_3/KO*t*Bu in THF at 25 °C (Table 1) to yield 3a in 84% yield. Analysis by ^{1}H NMR spectroscopy and GC-MS confirmed that 3a is a mixture of *cis*- and *trans*-3a (9:1).[10] Thus, to improve the stereoselectivity, several bisphosphine ligands were screened (Table 1, entries 2–7). As indicated in Table 1, 1,1'-bis(diphenylphosphino)ferrocene (dppf, entry 2), (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (binap, entry 3), and 1,4-bis(diphenylphosphino)butane (dppb, entry 4) did not yield any improvement in stereoselectivity, and 1,1-bis(diphenylphosphino)methane (dppm) gave a poor yield (entry 5, 26%). In addition, 1,3-bis(diphenylphosphino)propane (dppp) afforded *cis*-**3a** in >99% selectivity but only 56% yield (entry 6), while 1,2-bis(diphenylphosphino)ethane (dppe) gave an improved yield of 67% with >99% *cis*-selectivity (entry 7). Furthermore, the *N*-heterocyclic carbine (NHC) ligand IPr gave a poorer yield and a lower selectivity (entry 8, 52% yield, 85% *cis*-selectivity).

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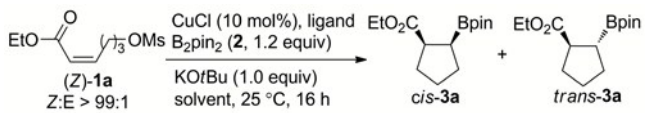
Table 1. Condition optimization for the copper-catalyzed borylative cyclization[a]



Entry	Ligand/Equiv.	Solvent	Yield (%)[b]	cis-**3a**/trans-**3a**[c]
1	PCy_3[d]/0.2	THF	84	90:10
2	dppf/0.1	THF	76	90:10
3	(±)-binap/0.1	THF	65	85:15
4	dppb/0.1	THF	51	90:10
5	dppm/0.1	THF	26	–
6	dppp/0.1	THF	56	>99:<1
7	dppe/0.1	THF	67	>99:<1
8	IPr·HCl/0.1	THF	52	85:15
9	dppe/0.1	toluene	80	97:3
10	dppe/0.1	1,4-dioxane	89	99:1
11	dppe/0.1	DMF	95(86)	99:1
12[e]	dppe/0.1	DMF	82	99:1

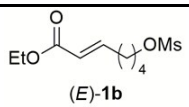
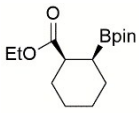
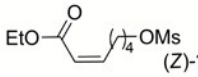
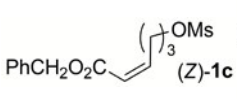
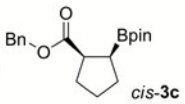
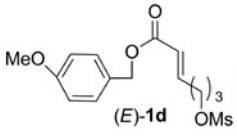
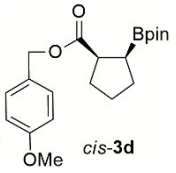
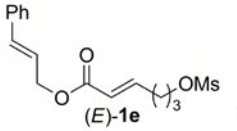
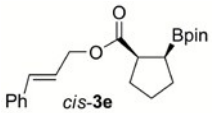
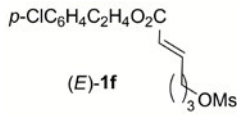
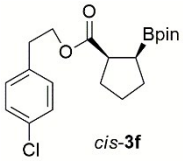
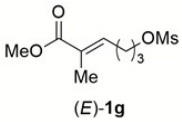
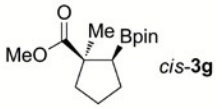
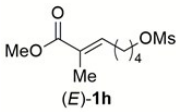
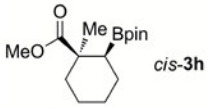
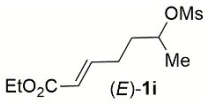
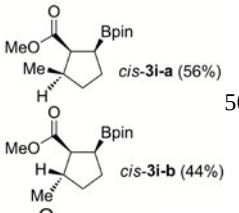
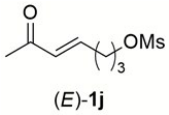
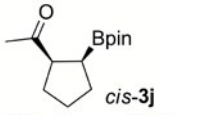
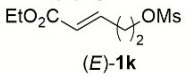
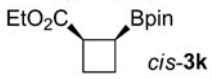
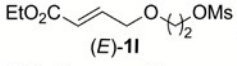
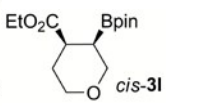
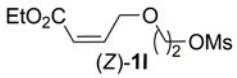
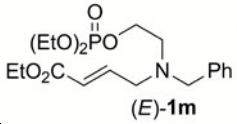
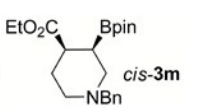
[a]Conditions: **1a** (0.5 mmol), **2** (0.6 mmol), CuCl (0.05 mmol), KO*t*Bu (0.5 mmol), solvent (1.0 mL), 25 °C, 16 h. [b]GC yields. Isolated yields are shown in parenthesis. [c]Determined by ^{1}H NMR spectroscopy. [d]Cy = cyclohexyl. [e](*E*)-**1a** was used.

To further improve the yield, the reaction employing dppe was attempted in a range of solvents (entries 9–11). Reaction in toluene afforded **3a** in 80% yield, but with a slight decrease in selectivity (entry 9, 97%), while reaction in 1,4-dioxane gave an improved yield of 89% with 99% *cis*-selectivity (entry 10). An almost quantitative yield (and excellent *cis*-selectivity) was obtained when the reaction was carried out in DMF (entry 11, 95%).

To investigate the stereochemical relationship between substrate and product, the reaction was carried out using (*E*)-**1a** instead of (*Z*)-**1a** under previously optimized conditions (Table 1, entry 11). *Cis*-**3a** was produced in a comparable isolated yield and selectivity to the reaction using (*Z*)-**1a** (entries 11 and 12). These results indicate that stereoconvergent transformation is crucial for obtaining products exhibiting excellent *cis*-selectivity, as it is both difficult and tedious to obtain pure *E* or *Z* alkenes.

A series of cycloalkyl boronates containing an electron withdrawing group and a boron atom on the same side of the ring were then synthesized using a CuCl/dppe catalyst in DMF (Table 2). In this case, the six-membered ring product *cis*-**3b** was produced from both (*E*)-**1b** and (*Z*)-**1b** in half the isolated yield of that obtained for the five-membered ring product (entries 1 and 2). This low yield may be due to decomposition during the isolation process. We then investigated the effect of employing ester groups containing different alkyl substituents, such as benzyl, *para*-methoxybenzyl, cinnamyl, and *para*-chlorophenylethyl (Table 2, entries 3–6), and the corresponding five-membered ring boronates were obtained in moderate to good yields (*cis*-**3c**, 70%; *cis*-**3d**, 40%; *cis*-**3e**, 56%, and *cis*-**3f**, 82%). Substrates (*E*)-**1g** and (*E*)-**1h**, which bear a methyl group at the α-position of the acrylate, were also used to give the corresponding five- and six-membered ring

Table 2. Scope and limitations[a]

Entry	Reactant	Product	Yield (%)[b]
1	 (*E*)-**1b**	 *cis*-**3b**	40
2	 (*Z*)-**1b**		44
3	 (*Z*)-**1c**	 *cis*-**3c**	70
4	 (*E*)-**1d**	 *cis*-**3d**	40
5	 (*E*)-**1e**	 *cis*-**3e**	56
6	 (*E*)-**1f**	 *cis*-**3f**	82
7	 (*E*)-**1g**	 *cis*-**3g**	71
8	 (*E*)-**1h**	 *cis*-**3h**	76
9	 (*E*)-**1i**	 *cis*-**3i-a** (56%) *cis*-**3i-b** (44%)	50
10	 (*E*)-**1j**	 *cis*-**3j**	52
11	 (*E*)-**1k**	 *cis*-**3k**	complex mixture
12	 (*E*)-**1l**	 *cis*-**3l**	65[c]
13	 (*Z*)-**1l**		65[c]
14	 (*E*)-**1m**	 *cis*-**3m**	62[c]

[a]Conditions: **1** (0.5 mmol), **2** (0.6 mmol), CuCl (0.05 mmol), dppe (0.05 mmol), KO*t*Bu (0.5 mmol), DMF (1.0 mL), 25 °C, 16 h. [b]Isolated yield. [c]NMR yields.

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products *cis*-**3g** and *cis*-**3h** in moderate yields (entry 7, *cis*-**3g**, 71%; entry 8, *cis*-**3h**, 76%). In this case, the higher yield of *cis*-**3h** is attributed to the improved stability of its quaternary carbon center. Furthermore, the introduction of a methyl group at the terminal of the chain [(*E*)-**3i**] produced a mixture of *cis*-**3i** and *trans*-**3i** (entry 9, *cis*-**3i**/*trans*-**3i** = 56/44). In addition to acrylates, *α,β*-unsaturated ketone (*E*)-**1i** reacted smoothly to produce *cis*-**3i** in moderate yield (entry 10, 52%). Unfortunately, these reaction conditions are not applicable to the synthesis of four-membered ring products (entry 11).

In addition to carbocycles, we found that oxygen- and nitrogen-containing substrates (*E*)-**1l**, (*Z*)-**1l** and (*E*)-**1m** were also borylative cyclized and heterocycle compounds *cis*-**3l** and *cis*-**3m** were obtained in moderate yields (entries 12 – 14)[14].

Two possible reaction mechanisms were then proposed to account for the stereoconvergent features of the transformation (Scheme 2). Pathway **1**, i.e., the *Z*-*E* isomerization mechanism, involves the isomerization of (*Z*)-**1a** to (*E*)-**1a** prior to the addition of borylcopper (LCu-Bpin) to its double bond. (*E*)-**1a** then undergoes a *syn*-addition with borylcopper to produce intermediate **A**, with a subsequent intramolecular oxidative addition (to form **B**) and reductive elimination yielding product *cis*-**3a**. Pathway **2**, i.e., the enolate mechanism, initially involves the adducts formed from the addition of (*Z*)-**1a**/(*E*)-**1a** with borylcopper undergoing a fast enolation process to form species **C**. Upon coordination of the enolate oxygen atom and the boron atom of species **C**, a five-membered ring is formed. However, for catalysts bearing bulky ligands (e.g., dppf, binap, PCy_3, or IPr), interactions between the ligand and the boron group likely prevent the formation of such a five-membered ring. Subsequently, species **C** undergoes an intramolecular nucleophilic substitution reaction via transition state **D**, in which the ester group and the boron atom are on the same side of the forming ring. This results in the formation of *cis*-**3a**.

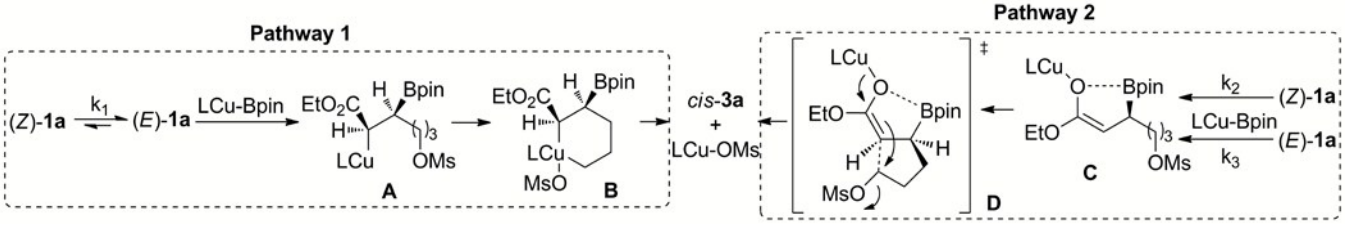
We also found that the *Z*-*E* isomerization process takes place in *α,β*-unsaturated esters. For example, (*Z*)-ethyl crotonate and (*Z*)-ethyl cinnamate isomerized to give their corresponding (*E*)-isomers at 23 °C under the reaction conditions (e.g. (*Z*)-ethyl cinnamate is transformed into a mixture of *Z*/*E* = 5/1 over 8 min at 23 °C under the reaction conditions outlined in Table 1, entry 10).

To differentiate between the two reaction mechanisms, we carried out Cu-catalyzed hydroboration reactions using (*E*)-**4** and (*Z*)-**4** (Table 3, see Supporting Information for details). Hydroboration reactions of (*E*)-**4** and (*Z*)-**4** were conducted in the presence of CD_3OD under identical conditions. Indeed, 5:1 mixtures of *syn*-**5** and *anti*-**5** were obtained following the hydroboration reactions of both (*E*)-**4** and (*Z*)-**4**.[15] This result indicates that a mechanistic study into the hydroboration of (*E*)-**4** and (*Z*)-**4** should provide key information to aid in the understanding of the stereoconvergent characteristics of these borylative cyclization reactions.

In addition, the variation in substrate conversion with time was then measured for the hydroboration of (*E*)-**4** and (*Z*)-**4**, and the results are shown in Table 3. To eliminate any influences arising from small differences in reaction conditions, a competitive reaction using a mixture of (*Z*)-**4** and (*E*)-**4** (1:1) was conducted. (*Z*)-**4** was consumed considerably faster than (*E*)-**4**. When the reactions were conducted separately using (*Z*)-**4** and (*E*)-**4** under the same reaction conditions, similar reaction kinetics were observed, and no (*E*)-**4** was detected by GC analysis in the reaction using (*Z*)-**4** (see Supporting Information for details).

The results obtained from these experiments indicate that addition of the borylcopper catalytic species to the C–C double bond of *α,β*-unsaturated esters is the rate-determining step. Moreover, the addition of borylcopper to the (*Z*)-isomers is faster than its addition to the (*E*)-isomers and also than the *Z*-*E* isomerization process. These kinetic studies therefore indicate that Pathway 2 is a more plausible mechanism, as it accounts for the stereoconvergent characteristics and excellent *syn*-selectivity of the reaction. As such, *trans*-**3a** is likely produced through a transition state, in which no O–B interaction exists, due to interactions between the bulky ligand and the Bpin group.

In summary, we successfully developed a Cu-catalyzed stereoconvergent borylative cyclization of *ω*-methylate-functionalized *α,β*-unsaturated esters and ketones to yield five- and six-membered boron-substituted carbocycles and heterocycles with excellent *cis*-selectivity (*cis*:*trans* >99:1). The enolation of adducts formed from borylcopper and *α,β*-unsaturated esters, in addition to coordination between the enolate oxygen and the boron atom, account for such stereoconvergence and excellent *cis*-selectivity. This result is of particular importance, as few synthetic examples of *cis*-substituted cyclic boronates have been reported previously. In addition, we expect that our catalytic system will be widely accessible, as it employs commercially available materials, and the reaction is conducted under mild conditions. Further studies into additional transformations and the asymmetric synthesis of the *cis*-products are currently underway.



Scheme 2. Two plausible mechanistic pathways for the transformation.

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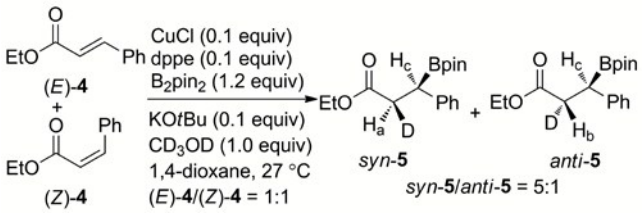
Table 3. Variation of the (*E*)-4 and (*Z*)-4 conversions with time in the copper-catalyzed competitive deuteroboration of a 1:1 mixture of (*E*)-4 and (*Z*)-4.



Time(min)		2	5	10	20	30
Conv.(%)	(*Z*)-**4**	85	99	100	100	100
	(*E*)-**4**	35	59	76	96	100

Conflicts of interest

There are no conflicts of interest to declare.

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13. The direct hydroboration of cycloalkkenyl carboxylate ester leads to a mixture of cis/trans diastereomers, see ref. 2.
14. cis-3l and cis-3m decompoesed to compecated mixtures upon silica gel chromatography seperation. However, 1H NMR spectra of crude products and HRMS clearly show the formation of them.
15. See Supporting Information for details.

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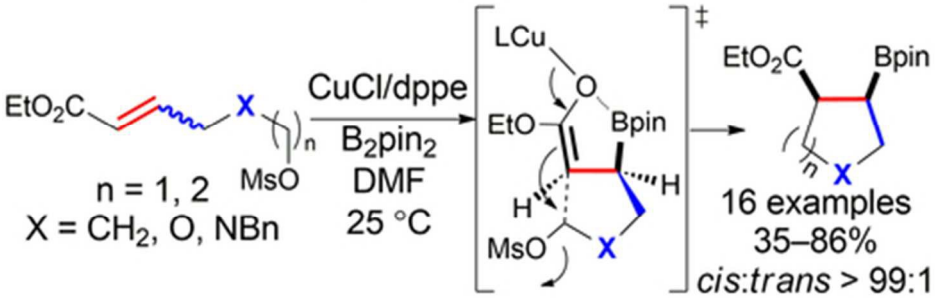
The *cis*-β-boron-substituted carbocyclic and heterocyclic esters or ketones were obtained from *E*- and *Z*-substrates with >99% *cis*-selectivity.



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