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Author(s)	Ito, Hajime; Yamamoto, Eiji; Kojima, Ryoto et al.
Citation	Synlett, 27(02), 272-276 https://doi.org/10.1055/s-0035-1560721
Issue Date	2016-01
Doc URL	https://hdl.handle.net/2115/63941
Type	journal article
File Information	Ito-S27(2).pdf

Copper(I)-Catalyzed Diastereoselective Borylative *Exo*-Cyclization of Alkenyl Aryl Ketones

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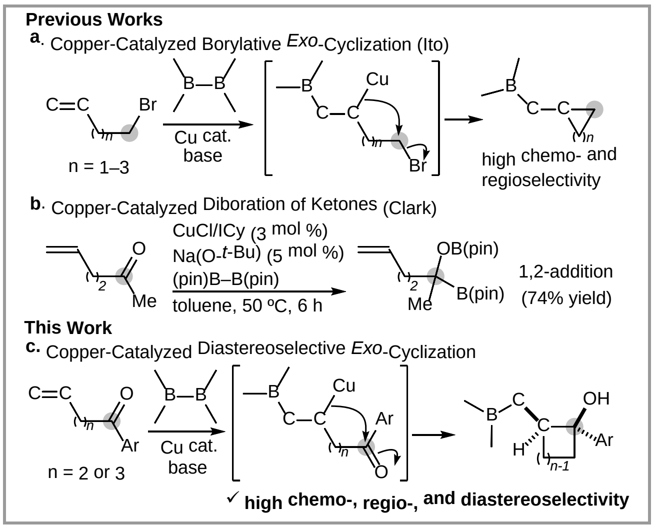
Received: The date will be inserted once the manuscript is accepted.

Abstract: Copper(I)-catalyzed diastereoselective borylative *exo*-cyclization of alkenyl ketones with bis(pinacolato)diboron is reported. The reaction of alkenyl aryl ketones under a CuCl/Xantphos catalyst system provides four- or five-membered-ring *syn*-2-(borylmethyl)cycloalkanol derivatives in good yields with high *syn* selectivities. The utility of this method is demonstrated by further transformations of the cyclic products.

Keywords: boron, cyclization, stereoselective synthesis, copper, catalysis

Borylation of multiple bonds with concomitant C−C bond formation can provide rapid access to complex organoboron compounds,[1-6] which are regarded as useful building blocks in organic synthesis.[7] Recently, copper-catalyzed borylation has emerged as a useful method for synthesizing organoboron compounds.[8,9] Our research group is interested in the efficient synthesis of small-ring carbocyclic organoboron compounds such as cyclopropyl- or cyclobutylboronates, and have reported several copper(I)-catalyzed borylative cyclization reactions of alkenes bearing a good leaving group (Scheme 1a).[10] In this reaction, the *in situ* generated borylcopper species preferably reacts with the alkene moiety to afford the alkylcopper species. Then, subsequent intramolecular substitution leads to *exo*-cyclization products (Scheme 1a).

Looking to extend our borylative cyclization strategy, we envisioned a copper(I)-catalyzed borylative cyclization of γ-alkenyl ketones to provide 2-(borylmethyl)cyclobutanol derivatives containing two adjacent congested stereocenters (Scheme 1c). Cyclobutanols are an important structural motif in organic chemistry because they are often found in natural products,[11] and are used as versatile building blocks through various transformations with concomitant C−C bond activation driven by the relief of the ring strain.[12] However, the routes to access stereodefined cyclobutanols containing multiple stereogenic centers are still relatively limited compared with those for three-, five- and six-membered carbocyclic compounds.[12a,13] The borylative cyclization of γ-alkenyl ketones is a novel and efficient route for the synthesis of 2-(borylmethyl)cyclobutanol derivatives. Clark and co-workers have already reported that carbonyl borylation proceeds exclusively over alkene borylation in the presence of a CuCl/N-heterocyclic carbene (NHC) catalyst when the two groups are present in the same molecule. To achieve the *exo*-borylative cyclization of alkenyl ketones, the chemoselectivity preference of the borylation must be switched from the ketone group to the alkene group using appropriate substrates, catalysts and reagents. (Scheme 1b).[14]

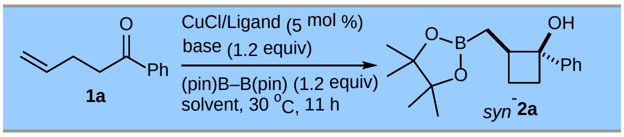


Scheme 1 Copper(I)-catalyzed borylative cyclization.

Herein, we report the diastereoselective *exo*-borylative cyclization of alkenyl aryl ketones catalyzed by a copper(I)/Xantphos catalyst system, which provides *syn*-1-aryl-2-(borylmethyl)cyclobutanol derivatives in high yields and with excellent diastereoselectivity. It is noteworthy that *syn*-selective synthesis of 1,2-substituted tertiary cyclobutanols has been scarcely reported.[15,16] Furthermore, the reaction of δ-alkenyl aryl ketone also affords the corresponding five-membered-ring product.

First, we screened reaction conditions for the borylative cyclization of γ-alkenyl ketone **1a** with copper catalyst systems (Table 1). The boryl cyclization of **1a** with CuCl/Xantphos (5 mol %), bis(pinacolato)diboron (1.2 equiv), and K(O-*t*-Bu) (1.2 equiv) in dimethoxyethane (DME) afforded the corresponding *syn*-2-(borylmethyl)cyclobutanol *syn*-**2a** in high yield (entry 1, 87% yield),[17] and the corresponding diastereomer was not detected by ^{1}H and ^{13}C NMR analyses of the crude reaction mixture. Using catalytic amount of K(O-*t*-Bu) (10 mol %) retarded the yield (66%, entry 2). The reaction of **1a** in the absence of the Xantphos ligand resulted in no reaction (entry 3). Product **2a** is unstable during purification using silica-gel chromatography. Thus, purification was conducted after esterification of the hydroxy group of the crude product **2a** (56% isolated yield, Table 1, entry 1).[18] The relative configuration of the major product was unambiguously determined to be the *syn* configuration by X-ray crystallographic analysis of the boryl cyclization product after esterification (Figure S1). The reaction with monodentate PPh_3 provided no borylative cyclization product (entry 4), and bidentate phosphines afforded lower yields than Xantphos (entries 5–8). Clark et al. reported that selective diboration of the ketone moiety in γ-alkenyl methyl ketone using a borylcopper(I)/ICy complex and Na(O-*t*-Bu) gives the corresponding tertiary α-hydroxy boronate ester.[14] In our case, the reaction with an NHC ligand precursor (ICy·HCl = 1,3-dicyclohexyl-imidazolium chloride) led to a complex mixture (entry 9). When the reaction was performed with Cu(O-*t*-Bu) (1 equiv), instead of the catalytic CuCl and stoichiometric K(O-*t*-Bu) conditions, no desired product was obtained (entry 10). Next, the effect of the base was investigated. Without base, the desired product was not formed (entry 11). The use of Na(O-*t*-Bu), KOMe or KOEt in DME, or the use of THF, Et_2O or toluene solvent with K(O-*t*-Bu) afforded inferior results compared with those using the standard conditions (entries 12–17).

Table 1 Optimization of the reaction conditions for copper(I)-catalyzed boryl cyclization.[a]

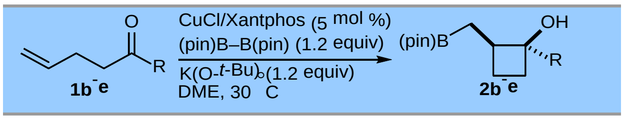


Entry	Ligand	Base	Solvent	Yield (%)[b,c]
1[d]	Xantphos	K(O-*t*-Bu)	DME	87(56)
2[e]	Xantphos	K(O-*t*-Bu)	DME	66
3	None	K(O-*t*-Bu)	DME	0
4	PPh_3	K(O-*t*-Bu)	DME	0
5	dppe	K(O-*t*-Bu)	DME	25
6	dppp	K(O-*t*-Bu)	DME	34
7	dppb	K(O-*t*-Bu)	DME	12
8	dppf	K(O-*t*-Bu)	DME	10
9	ICy·HCl	K(O-*t*-Bu)	DME	0
10[f]	Xantphos		DME	0
11	Xantphos	None	DME	0
12	Xantphos	Na(O-*t*-Bu)	DME	70
13	Xantphos	KOMe	DME	19
14	Xantphos	KOEt	DME	39
15	Xantphos	K(O-*t*-Bu)	THF	85
16	Xantphos	K(O-*t*-Bu)	Et_2O	87
17	Xantphos	K(O-*t*-Bu)	toluene	84

[a] Reaction conditions: **1a** (0.5 mmol), (pin)B–B(pin) (0.6 mmol), CuCl (0.025 mmol), ligand (0.025 mmol), and base (0.6 mmol) in a solvent (1 mL) at 30 °C. [b] Determined by ^{1}H NMR analysis. [c] Isolated yield after esterification of the hydroxy group in the product **2a** are shown in parentheses. For details, see supporting information. [d] The dr of the crude reaction mixture was determined to be *syn*/*anti* = 97:3 based on the ^{1}H NMR analysis. The dr of the crude reaction mixtures with ligands except for Xantphos could not be determined because of overlapping signals. [e] 10 mol % of base was used. [f] Cu(O-*t*-Bu) (1 equiv) was used instead of CuCl/K(O-*t*-Bu).

With the optimized conditions in hand, the substrate scope for this boryl cyclization was investigated (Table 2). Alkenyl aryl ketones with 3,5-xylyl, 2-naphthyl, 4-bromo- or 4-methoxy phenyl groups provided the desired products in moderate to good yields (79%, 75%, 62%, 75%, respectively, Table 2, entries 1–4). Furthermore, the corresponding minor *anti*-isomers were not detected by ^{1}H NMR analysis. However, the isolated yields of derivatized products were generally low due to instability of **2** under the silica-gel purification conditions (32, 23, 21, 20%, respectively). Unfortunately, only aromatic ketone substrates gave the desired products in this reaction. γ-Alkenyl ketones containing an alkyl-, alkenyl- or alkynyl moiety instead of an aromatic group resulted in complex mixtures. These results can be attributed to possible competitive side reactions including 1,2-diboration reaction of ketone, protoboration of carbon-carbon multiple bonds, and aldol reactions.

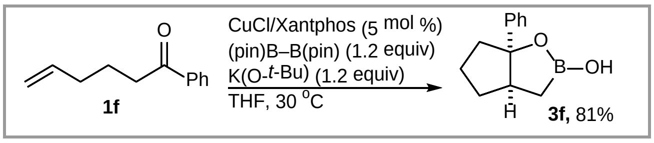
Table 2 Substrate scope for the copper(I)-catalyzed borylative cyclization of alkenyl aryl ketones.[a]



Entry	Substrate (R)	Product	Yield (%)
1	**1b** (3,5-xylyl)	**2b**	79(32)
2	**1c** (2-naphthyl)	**2c**	75(23)
3	**1d** (4-Br-C_6H_4)	**2d**	62(21)
4[b]	**1e** (4-MeO-C_6H_4)	**2e**	75(20)

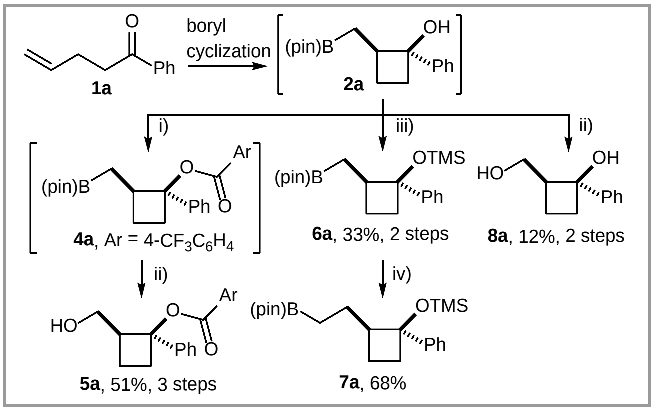
[a] Alkenyl ketone **1** (0.5 mmol), (pin)B–B(pin) (0.6 mmol), CuCl (0.025 mmol), Xantphos (0.025 mmol), and K(O-*t*-Bu) (0.6 mmol) in DME (1 mL) at 30 °C. Yields were determined by ^{1}H NMR analysis of the crude product **2**, and isolated yields of the corresponding esterified products **4** are shown in parentheses. [b] Isolated yield of derivatized product from **2e** is shown in parentheses.

Reaction of δ-alkenyl phenyl ketone **1f** provided product **3f** bearing a bicyclic structure containing a 1,2-oxaborolane in high yield and with good diastereoselectivity (81%, Scheme 2).



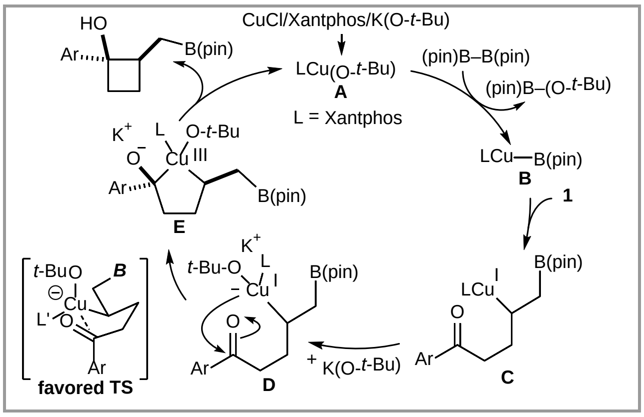
Scheme 2 Reaction of δ-alkenyl phenyl ketone **1f**.

Further derivatization of the products from the crude mixtures was then investigated (Scheme 3). The crude product **4a** was subjected to NaBO$_3$ oxidation to afford the corresponding mono alcohol **5a** in good yield as a single isomer (51%, 3 steps). We also carried out TMS protection of the crude product **2a** to provide a 33% yield of the desired silylated product **6a** over 2 steps, followed by homologation to give **7a** in good yield (68%). Crude product **2a** also afforded the corresponding diol **8a** after NaBO$_3$ oxidation.



Scheme 3 Transformations of product **2a**. *Reagents and conditions*: i) 4-trifluoromethyl benzoyl chloride (1.05 equiv), *i*-Pr$_2$NEt (1.05 equiv), DMAP (10 mol %), DME, 0 °C, 3 h. ii) NaBO$_3$·4H$_2$O (10 equiv), THF/H$_2$O, rt, 2 h. iii) TMSOTf (5.0 equiv), 2,6-lutidine (10 equiv), CH$_2$Cl$_2$, 0 °C, 3 h. iv) ClCH$_2$Br (2.0 equiv), *n*-BuLi (1.5 equiv), THF, −78 °C to rt, 19 h.

A proposed mechanism of the borylative cyclization is shown in Scheme 4. The reaction starts with the generation of Cu(O-*t*-Bu) complex **A** followed by σ-bond metathesis with a diboron species to form borylcopper(I) active species **B**. This then adds to the C−C double bond in **1** to form alkylcopper(I) species **C**. Subsequently, the *t*-butoxide base coordinates with the alkylcopper(I) species **C** to form a more nucleophilic *t*-butoxy(alkyl)cuprate **D**.[19] This step would be facilitated by using strong base, which is compatible to the results shown in Table 1, entries 10–14. In addition, Lewis acidity of the counter cations also might be involved in this step forming cuprate-π complex.[19] Intramolecular nucleophilic attack of the copper(I) center on the carbonyl carbon would then occur, followed by reductive elimination of the resultant dialkylcopper(III) species **E** to lead to the formation of the boryl cyclization product. The high chemoselectivity with the Xantphos ligand may likely be attributed to the formation of a sterically congested borylcopper species.[10d] This catalyst tuning would enable the preferential addition of intermediate **B** to the less sterically hindered alkene moiety over the more bulky aromatic ketone group. The high HOMO level of **B** with the Xantphos ligand is also important for alkene selectivity.[10d] Regarding the origin of the *syn* selectivity, the favored transition state would go through less sterically hindered pathway, which leads to the observed high diastereoselectivity.



Scheme 4 Proposed mechanism of the borylative cyclization.

In conclusion, we have developed a novel method for preparing *syn*-1-aryl-2-(borylmethyl)cycloalkanols through a highly chemo-, regio-, and diastereoselective borylative cyclization of alkenyl ketones catalyzed by a copper(I)/Xantphos complex. This method provides rapid access to four- or five-membered-ring 2-(borylmethyl)cycloalkanols with high *syn* selectivity from simple starting materials. Although the isolation of the cyclized products is difficult, synthetic application should be possible using *in situ* transformations of the crude products. Development of effective transformations and further work toward an enantioselective synthesis are now ongoing in our group.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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Acknowledgments**:** This work was financially supported by the NEXT (Japan) program (Strategic Molecular and Materials Chemistry through Innovative Coupling Reactions) of Hokkaido University. This work was also supported by JSPS KAKENHI Grant Number 15H03804 and 15K13633. This work was supported by JSPS KAKENHI Grant number 26·2447. E. Y. was supported by Grant-in-Aid for JSPS Fellows.

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(17) **Typical Procedure for Borylative Cyclization/Esterification of Aryl Alkenyl Ketones** CuCl (0.025 mmol) and (pin)B−B(pin) (0.60 mmol), Xantphos (0.025 mmol), K(O-*t*-Bu) (0.60 mmol) were placed in an oven-dried vial in a glove box. After the vial was removed from the glove box, DME (1.0 mL) was added to the vial and stirred for 30 min. Then, **1a** (0.50 mmol) was added to the mixture at 30 °C. After the reaction was complete, the reaction mixture was cooled to 0 °C. After that, DMAP [0.05 mmol in THF (1 mL)] and *i*-Pr$_2$NEt (0.52 mmol) were added to the mixture, and 4-trifluoromethyl benzoyl chloride (0.53 mmol) was added dropwise. After the reaction was complete, the reaction mixture was passed through a short florisil column using eluting with Et$_2$O. The crude material was purified by silica gel column chromatography to give *syn*-**4a** (129.7 mg, 0.282 mmol, 56% yield) as a white solid.

^{1}H NMR (392 MHz, CDCl$_3$, δ): 1.25 (s, 6H), 1.26 (s, 6H), 1.36 (dd, J = 10.0, 15.9 Hz, 1H), 1.46 (dd, J = 6.3, 15.7 Hz, 1H), 1.68–1.79 (m, 1H), 2.06–2.16 (m, 1H), 2.62–2.72 (m, 1H), 2.80–2.91 (m, 1H), 2.97–3.07 (m,

1H), 7.21–7.28 (m, 1H), 7.30–7.36 (m, 2H), 7.47–7.51 (m, 2H), 7.68 (d, *J* = 7.8 Hz, 2H), 8.20 (d, *J* = 7.8 Hz, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 12.5 (br, B–*C*H_2), 23.0 (*C*H_2), 24.80 (*C*H_3), 24.86 (*C*H_3), 30.2 (*C*H_2), 44.0 (*C*H), 83.2 (*C*), 85.4 (*C*), 125.0 (q, $J_{\text{C-F}}$ = 273.8 Hz, *C*), 125.1 (*C*H), 125.2–152.4 (m, *C*H), 127.2 (*C*H), 128.3 (*C*H), 130.0 (*C*H), 134.22 (q, $J_{\text{C-F}}$ = 32.7 Hz, *C*), 134.28 (*C*), 143.1 (*C*), 163.8 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{25}H_{28}O_4BF_3Na$, 482.19613; found, 482.19653.

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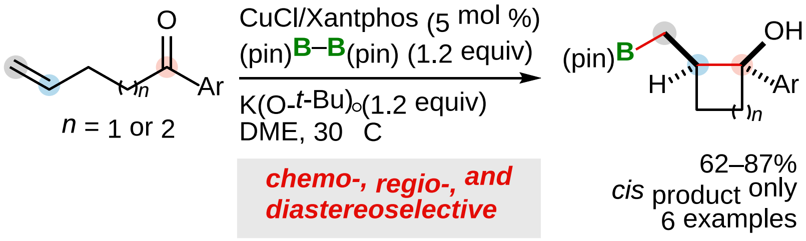

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