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Enantioselective Synthesis of *trans*-Aryl- and -Heteroaryl-Substituted Cyclopropylboronates by Copper(I)-Catalyzed Reactions of Allylic Phosphates with a Diboron Derivative

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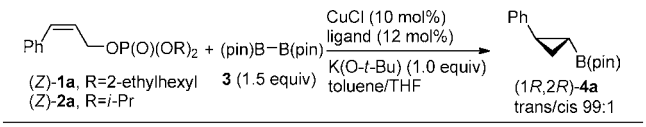
Abstract: A new asymmetric route for the synthesis of *trans*-2-aryl- and -heteroaryl-substituted cyclopropylboronates has been developed. (*Z*)-3-arylallylic phosphates were converted to the optically active products with high yield and diastereo- and enantioselectivity through a copper(I)-catalyzed reaction with a diboron derivative. Under mild reaction conditions, the reaction affords the arylcyclopropane products with a functional group and a heteroaromatic group in a highly enantioselective manner. When (*E*)-allylic phosphates were used as substrates, a ligand-controlled product switch between the trans and cis configurations was observed.

Optically active cyclopropane structural moieties are found in a wide range of naturally occurring compounds and pharmaceuticals. In recent years, substantial effort has been put into the enantioselective synthesis of cyclopropanes.[1] Chirally substituted cyclopropylboronates are attractive building blocks for the synthesis of cyclopropane-containing compounds.[2] A number of methods have been developed for the synthesis of cyclopropylboronic derivatives.[3] Many examples that employ stoichiometric optically active groups on the boron atom as the chiral auxiliary have also been reported for the preparation of optically active cyclopropylboronates.[4] However, only two reported examples that have taken advantage of metal-catalyzed asymmetric methods have been reported, one by us and one by other group.[5] The asymmetric synthesis of optically active cyclopropylboronates with high enantiomeric purity remains a difficult synthetic challenge. We recently reported the synthesis of optically active allylboronates using copper(I)-catalyzed S_N2' substitution of allylic carbonates with a diboron compound.[6] When the allylic carbonates have a silyl group at the γ-position of the leaving group, optically active *trans*-silyl-substituted cyclopropylboronates were obtained with high enantio- and diastereoselectivity (up to 98% ee, trans/cis = 99:1).[5b] More recently, silyl- or aryl-substituted homoallylic methanesulfonates were found to be converted to racemic cyclobutane analogues in the presence of an achiral copper(I) catalyst.[7] We propose that the anomalous product switch from allylboronates to cyclic boronates can be attributed to the reverse regioselectivity of the Cu−B addition to the C=C double bond induced by the electronic directing effect of the silyl or aryl substituent. These results prompted us to develop a direct methodology for the synthesis of substituted cyclopropylboronates. We report herein that *trans*-aryl- and -heteroaryl-substituted cyclopropylboronates can be synthesized with high enantio- and diastereoselectivity through a copper(I)-catalyzed reaction. Furthermore, ligand-dependent stereoselectivity switching between the cis and trans isomers is also reported.

The reaction conditions were optimized, and the best result was obtained using a bulky phosphate leaving group, as shown in Table 1.[8] With the catalyst system of 10 mol % CuCl, 12 mol % (*R*,*R*)-*i*-Pr-DuPhos, and 1.0 equiv of K(O-*t*-Bu), (*Z*)-**1a**, the phosphate with 2-ethylhexyl groups, reacted with bis(pinacolato)diboron (**3**) to produce (1*R*,2*R*)-2-phenylcyclopropylboronate [(1*R*,2*R*)-**4a**] in 71% yield with 94% ee and excellent diastereoselectivity (trans/cis = 99:1; entry 1). Decreasing the catalyst loading resulted in an improved yield (89%; entry 2). We found that (*R*,*R*)-*i*-Pr-DuPhos was superior to other chiral ligands in yield and enantioselectivity (entries 4−8). Using the isopropyl phosphate (*Z*)-**2a** rather than the 2-ethylhexyl phosphate resulted in a low yield (entry 9).[8] No desired product (**4a**) was obtained in the absence of the ligand (entry 10). The stereochemical outcome indicates that this reaction of a *Z*-configured substrate proceeds in a manner similar to those for the silyl-substituted compounds that we previously reported.[9]

Table 1. Optimization of Reaction Conditions for the Synthesis of Optically Active *trans*-**4a**[a]



entry	substrate	ligand	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	(*Z*)-**1a**	(*R*,*R*)-*i*-Pr-DuPhos	0	36	71	94
2[d]	(*Z*)-**1a**	(*R*,*R*)-*i*-Pr-DuPhos	0	45	89	94
3	(*Z*)-**1a**	(*R*,*R*)-*i*-Pr-DuPhos	rt	17	76	91
4	(*Z*)-**1a**	(*R*,*R*)-Me-DuPhos	rt	17	35	80 (1*S*,2*S*)
5	(*Z*)-**1a**	(*R*,*R*)-QuinoxP*	rt	17	55	91 (1*S*,2*S*)
6	(*Z*)-**1a**	(*R*)-Segphos	rt	18	32	81 (1*S*,2*S*)
7[e]	(*Z*)-**1a**	(*S*,*S*)-DIOP	rt	17	34	35
8	(*Z*)-**1a**	(*R*,*R*)-BDPP	rt	17	23	27
9	(*Z*)-**2a**	(*R*,*R*)-QuinoxP*	rt	17	49	92 (1*S*,2*S*)
10	(*Z*)-**1a**	none	rt	25	0	−

[a] Conditions: (*Z*)-**1a** or **2a** (0.2 mmol), **3** (0.3 mmol), CuCl (0.02 mmol), ligand (0.024 mmol), K(O-*t*-Bu) (1.2 M in THF, 0.2 mmol), toluene (0.6 mL). [b] The yield and cis/trans ratio were determined by GC. [c] Determined by HPLC. [d] CuCl (5 mol %, 0.01 mmol), (*R*,*R*)-*i*-Pr-DuPhos (6 mol %, 0.012 mmol), **3** (1.2 equiv, 0.24 mmol). [e] The trans/cis ratio was >30:1.

Under the optimized conditions, allylic phosphates with diverse aryl and heteroaryl groups were subjected to the copper(I)-catalyzed enantioselective synthesis of cyclopropylboronates (Table 2). Substrates with a range of substituents on the benzene ring afforded the corresponding products with high trans selectivity (entries 1−9). Generally, substrates with electron-donating substituents on the benzene ring resulted in higher enantioselectivity (94% ee; entries 1, 5, and 7) than those with electron-withdrawing groups (64−86% ee; entries 2−4 and 6). A substrate with a 1-naphthyl group was converted to the product with a high ee value and the highest

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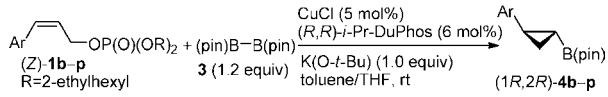
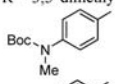
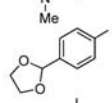
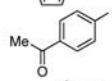
isolated yield (90% yield, 92% ee; entry 10). We further found that cyclopropylboronates with an aromatic heterocyclic group can also be furnished with high enantioselectivity (92% ee; entries 11 and 12). Various functional groups such as chloro, ether, ester, $BocNR_2$, and acetal were tolerated in this reaction (entries 1, 2, 4, 8, 9, and 11), whereas the presence of ketone and bromo groups led to diminished yields (entries 13 and 14). The substrate with an alkenyl substituent did not undergo the cyclopropanation reaction (entry 15).

Table 2. Substrate Scope and Limitation for the Synthesis of Optically Active Cyclopropylboronates[a]



entry	Ar		time (h)	product	yield[b] (%)	trans/cis[c]	ee[d] (%)
							
1	R = 4-MeO	**1b**	72	**4b**	46	>20:1	94
2	R = 4-Cl	**1c**	47	**4c**	76	>20:1	84
3	R = 4-CF_3	**1d**	36	**4d**	59	20:1	82
4	R = 4-MeOCO	**1e**	36	**4e**	56	>20:1	64
5	R = 2-Me	**1f**	96	**4f**	51	>20:1	94
6	R = 4-Ph	**1g**	50	**4g**	60	16:1	86
7	R = 3,5-dimethyl	**1h**	93	**4h**	65	>20:1	94
8		**1i**	53	**4i**	50	20:1	89
9		**1j**	24	**4j**	65	20:1	86
10		**1k**	44	**4k**	90	36:1	92
11		**1l**	72	**4l**	54	>20:1	92
12		**1m**	72	**4m**	70	48:1	92
13[e]		**1n**	26	**4n**	11	15:1	85
14		**1o**	26	**4o**	8	>20:1	-
15		**1p**	48	**4p**	0	-	-

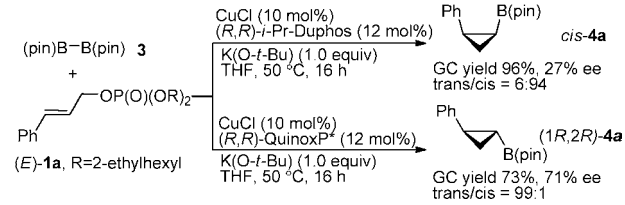
[a] Conditions: **1** (0.4 mmol), **3** (0.48 mmol), CuCl (0.02 mmol), ligand (0.024 mmol), K(O-*t*-Bu) (1.2 M in THF, 0.4 mmol), toluene (1.2 mL). [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC. [e] Reaction was carried out at −10 °C.

In the process of ligand screening using (*E*)-allylic phosphates, we were surprised to find that the diastereoselectivity of the product could be drastically switched by using different ligands (Scheme 1). In contrast to the observation that the cis product (*cis*-**4a**) was produced with excellent yield (96% GC yield) when the (*R*,*R*)-*i*-Pr-DuPhos ligand was used, the trans product [(1*R*,2*R*)-**4a**] was obtained in the presence of (*R*,*R*)-QuinoxP*.[10]

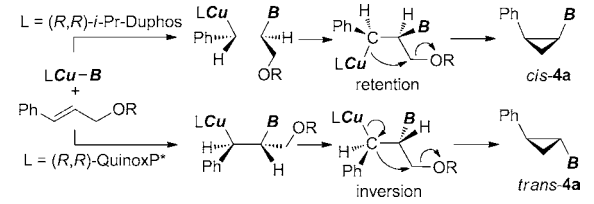
A possible explanation for the product switching is shown in Scheme 2. In the case of the reaction with the (*R*,*R*)-*i*-Pr-DuPhos ligand, the addition product[5b,11] generated from the reaction between the borylcopper(I) intermediate and the (*E*)-allylic substrate undergoes intramolecular substitution with retention of the stereochemistry at the α-carbon atom on the copper(I) center to form *cis*-**4a**. Contrary to this, the substitution reaction in the presence of (*R*,*R*)-QuinoxP* would proceed with inversion of the stereochemistry, affording *trans*-**4a**.

In other words, the reaction with (*R*,*R*)-*i*-Pr-DuPhos proceeded in a stereospecific manner, whereas the reaction with (*R*,*R*)-QuinoxP* showed a stereoselective feature (see the Supporting Information). This catalyst-dependent stereospecificity/selectivity switching is unique among the analogous copper(I)/diboron catalyst systems; the cyclopropanation from silyl-substituted allylic carbonates is a stereoselective reaction (trans product only), and the cyclobutane synthesis reaction from homoallylic sulfonates showed stereospecific features (from *E* substrate to cis product and vice versa).[5b,7] The detailed rationale for these differences requires further mechanistic studies.

Scheme 1. Ligand-Controlled Product Switch with (*E*)-**1a**



Scheme 2. Explanation for the Formation of *trans*- and *cis*-**4a**



In conclusion, we have described a highly enantioselective copper(I)-catalyzed synthesis of *trans*-aryl- and -heteroaryl-substituted cyclopropylboronates from (*Z*)-allylic phosphates and a diboron derivative. The reaction shows excellent diastereoselectivity and good functional group compatibility. When (*E*)-allylic phosphates were used as the substrate, the products switched from the trans configuration in the presence of (*R*,*R*)-QuinoxP* to the cis configuration in the presence of (*R*,*R*)-*i*-Pr-DuPhos. These reactions offer a new, efficient route to chirally substituted cyclopropylboronates.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The substrates with a carbonate leaving group, which is operative in the γ-silyl substrates (see ref 5b), generally gave low yields (<50%; see Table S4). The impacts of solvents, copper salts, base additives, and diverse ligands were also further investigated (see the Supporting Information for details).

(9) See the Supporting Information for the detailed explanation.

(10) The absolute configuration of *cis*-**4a** could not be determined.

(11) For related studies on borylcopper(I) addition to aromatic alkenes, see: (a) Laitar, D.; Tsui, E.; Sadighi, J. *Organometallics* **2006**, *25*, 2405. (b) Dang, L.; Zhao, H.; Lin, Z.; Marder, T. *Organometallics* **2007**, *26*, 2824. (c) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160.

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