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Communication

Enantioconvergent Cu-Catalyzed Intramolecular C–C Coupling at Boron-Bound C(sp^3) Atoms of α-Aminoalkylboronates Using a C_1-Symmetrical 2,2′-Bipyridyl Ligand Attached to a Helically Chiral Macromolecular Scaffold

Yukako Yoshinaga, Takeshi Yamamoto,* and Michinori Suginome*

Cite This: https://dx.doi.org/10.1021/jacs.0c09080
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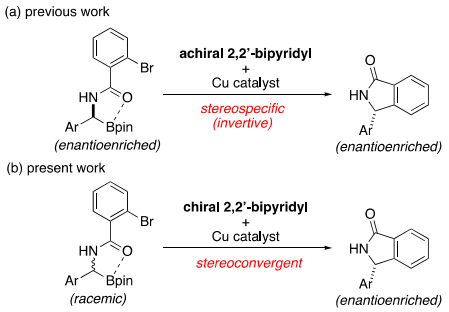
ABSTRACT: Enantioconvergent intramolecular coupling of α-(2-bromobenzoylamino)benzylboronic esters was achieved using a copper catalyst having helically chiral macromolecular bipyridyl ligand, PQXbpy. Racemic α-(2-bromobenzoylamino)benzylboronic esters were converted into (*R*)-configured 3-arylisoindolinones with high enantiopurity using right-handed helical PQXbpy as a chiral ligand in a toluene/$CHCl_3$ mixed solvent. When enantiopure (*R*)- and (*S*)-configured boronates were separately reacted under the same reaction conditions, both afforded (*R*)-configured products through formal stereoinvertive and stereoretentive processes, respectively. From these results, a mechanism involving deracemization of organocopper intermediates in the presence of PQXbpy is assumed. PQXbpy switched its helical sense to left-handed when a toluene/1,1,2-trichloroethane mixed solvent was used, resulting in the formation of the corresponding (*S*)-products from the racemic starting material.

Transition-metal-catalyzed reactions of organoboronic acids have had a great impact on organic synthesis by virtue of their characteristic chemical properties, which differentiate them from other organometallic reagents.[1] Although they are isolable, purifiable, configurationally stable, and chemically stable, they become highly reactive in the presence of basic activators. Of particular note is that a variety of asymmetric C–C bond-forming reactions have been achieved using organoboronic acids as essential reactants.[2] In many of these catalytic reactions, sp^2-hybridized organoboronic acids play major roles because their transmetalation is favored over that of sp^3-hybridized derivatives. Recent progress of boron-based transition metal catalysis has allowed the utilization of unreactive sp^3-hybridized organoboron species, including chiral alkylboronic acids. The use of chiral alkylboronic acids now allows asymmetric cross-coupling reactions, which are classified into either stereospecific or stereoconvergent processes. The former class of asymmetric cross-coupling reactions utilize enantioenriched chiral organoboronic acids with achiral transition-metal catalysts, leading to the formation of highly enantioenriched coupling products either through stereoretentive or stereoinvertive reaction pathways.[3,4] The latter class, i.e., the stereoconvergent process,[5−7] utilizes racemic chiral organoboronic acids as a starting material and is highly attractive because the preparation of enantiomerically pure organoboronic acids can be avoided. However, reports are limited to the Ni-catalyzed coupling of secondary benzyltrifluoroborates with moderate stereoselectivity (up to 65% ee) in the presence of chiral bisoxazoline ligand under photoredox conditions.[6] It is highly desirable to accumulate more knowledge about stereoconvergent coupling reactions, which have some related precedents using chiral alkylmagnesium[8] and alkylzinc[9] reagents as coupling partners.

Scheme 1. Asymmetric Cu-Catalyzed Intramolecular Coupling of α-(*o*-Bromobenzoyl)aminobenzylboronic Esters



Our ongoing research interest has been focused on the stereochemical course of the reactions of chiral α-aminoalkylboronic acids.[10] We reported Pd-catalyzed stereospecific cross-coupling with aryl halides, which proceeds either with stereochemical retention or inversion, depending on the reaction conditions.[4d] Very recently, we reported stereospecific Cu-catalyzed intramolecular coupling of α-aminoalkylboronic acids bearing *o*-bromobenzoyl groups on the amino group

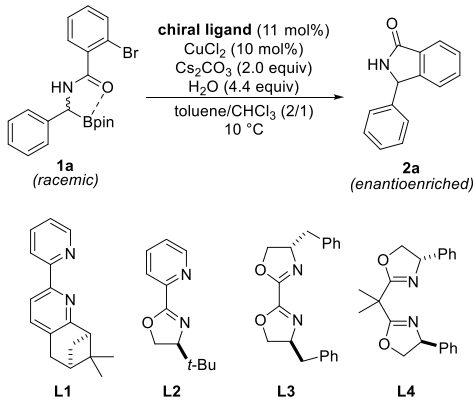
Received: August 24, 2020

https://dx.doi.org/10.1021/jacs.0c09080
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

(Scheme 1a).[11] It was found that a slight modification of the achiral bipyridyl ligand from unsubstituted 2,2′-bipyridyl used in the original protocol of Dumas et al.[12] allowed us to make the reaction highly stereoinvertive. This study revealed that the change of the substituents at 6- and 6′-positions of 2,2′-bipyridyl ligand sharply alters not only the stereochemical course, but also the rate of the reaction. We were particularly interested in the result of the original report, in which a racemic product was obtained from enantiopure α-aminoalkylboronic acid.[11,12] It has been proposed that racemization of the organocopper intermediate is involved in the process. In this paper, we report on the enantioconvergent intramolecular coupling of α-(*o*-bromobenzoyl)aminobenzylboronic acids using PQXbpy,[13] which is a C_1-symmetrical chiral 2,2′-bipyridyl ligand attached at its 6-position to single-handed helical poly(quinoxaline-2,3-diyl)s[14,15] (Scheme 1b). Deracemization of the organocopper intermediates is effectively controlled by the chiral reaction space created by the helical macromolecular ligand PQXbpy.[16−18]

As an initial test, reactions of racemic α-(*o*-bromobenzoyl)-aminobenzylboronic acid pinacol ester (**1a**) was conducted in the presence of a copper catalyst with several chiral dinitrogen ligands including bipyridyl, pyridyloxazoline, and bisoxazoline ligands (Table 1).[19] The C_1-symmetrical bipyridine and

Table 1. Cu-Catalyzed Reactions of Racemic 1a in the Presence of Chiral Ligands[a]



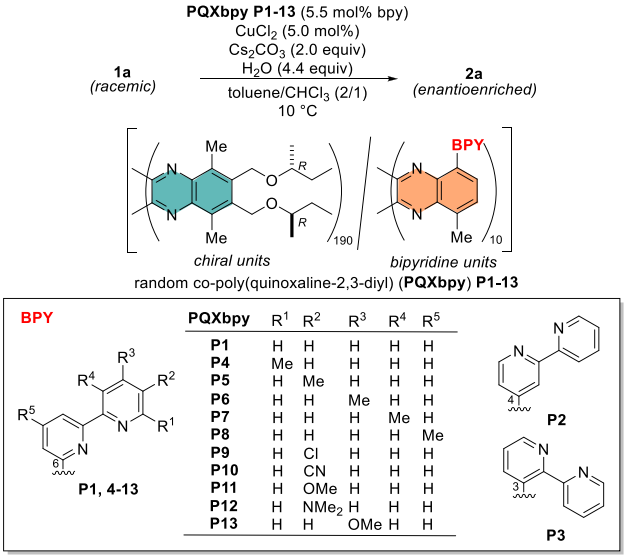
entry	chiral ligand	time/h	yield/%	er (*R*:*S*)
1	**L1**	12	>99	43:57
2	**L2**	24	>99	55:45
3	**L3**	48	7	59:41
4	**L4**	48	12	29:71

[a]The yield was determined by ^{1}H NMR using dibenzyl ether as an internal standard. The enantiomeric excess was determined by chiral SFC analysis.

pyridyloxazoline ligands **L1**[20] and **L2**[21] gave the product **2a** in high yield, albeit with low enantiomeric ratio (er) (entries 1 and 2). The C_2-symmetrical bisoxazoline ligands **L3**[22] and **L4**[23] resulted in low yields; however, a remarkable er value was obtained in the reaction with **L4** (entries 3 and 4). These results suggested that an enantioconvergent or kinetic resolution process is indeed operating and that the pyridyl group is required to achieve reasonable chemical yields.

Derivatives of PQXbpy were then used as chiral ligands under the same reaction conditions, except for the reduction of catalyst loading to 5 mol%. We initially compared PQXbpy **P1**−**P3** having 2,2′-bipyridyl (bpy) groups linked to the polymer backbone at different positions on the bipyridyl groups. PQXbpy **P1**, of which the bpy group is linked at its 6-position, showed a significant enantioinduction of 85:15 in favor of the (*R*)-product **2a** (Table 2, entry 1). Ligands **P2** and

Table 2. Cu-Catalyzed Reactions of Racemic 1a in the Presence of PQXbpy P1−P13[a]



PQXbpy	R^1	R^2	R^3	R^4	R^5
P1	H	H	H	H	H
P4	Me	H	H	H	H
P5	H	Me	H	H	H
P6	H	H	Me	H	H
P7	H	H	H	Me	H
P8	H	H	H	H	Me
P9	H	Cl	H	H	H
P10	H	CN	H	H	H
P11	H	OMe	H	H	H
P12	H	NMe_2	H	H	H
P13	H	H	OMe	H	H

entry	PQXbpy	time/h	yield/%	er (*R*:*S*)
1	**P1**	12	96	85:15
2	**P2**	6	>99	27:73
3	**P3**	18	81	22:78
4	**P4**	72	11	52:48
5	**P5**	24	>99	79:21
6	**P6**	12	>99	80:20
7	**P7**	48	58	66:34
8	**P8**	12	82	83:17
9	**P9**	48	49	58:42
10	**P10**	96	13	56:44
11	**P11**	24	>99	78:22
12	**P12**	6	>99	71:29
13	**P13**	12	>99	77:23

[a]The yield was determined by ^{1}H NMR spectroscopic analysis using dibenzyl ether as an internal standard. The enantiomeric excess was determined by chiral SFC analysis. The progress of the reactions was monitored at 6, 12, 18, 24, 48, 72, and 96 h.

P3, with linkages to the bpy group at the 4- and 3-positions, respectively, gave moderate, but appreciable enantioselectivities, although the chiral macromolecular scaffold is not located at the 6-position of the bpy groups (entries 2 and 3). We then modified **P1** by introducing substituents on the bpy groups (entries 4−13). Although the enantioselectivity never exceeded the result with **P1**, there were notable trends in the relationship between their structure and reactivity/selectivity. First, among the PQXbpy derivatives bearing a methyl group at different positions (entries 4−8), **P4** (R^1 = Me), bearing a methyl group at the 6′-position, showed much lower catalytic activity than others (entry 4). This observation is in good agreement with our previous report on the stereoinvertive system, in which an achiral 6,6′-disubstituted bipyridyl ligand showed low catalytic activity.[11] Second, methyl substitution at the *ortho*-position of the aryl−aryl axis in **P7** (R^4 = Me) gave low enantioselectivity, probably because the methyl group reduces the planarity of the

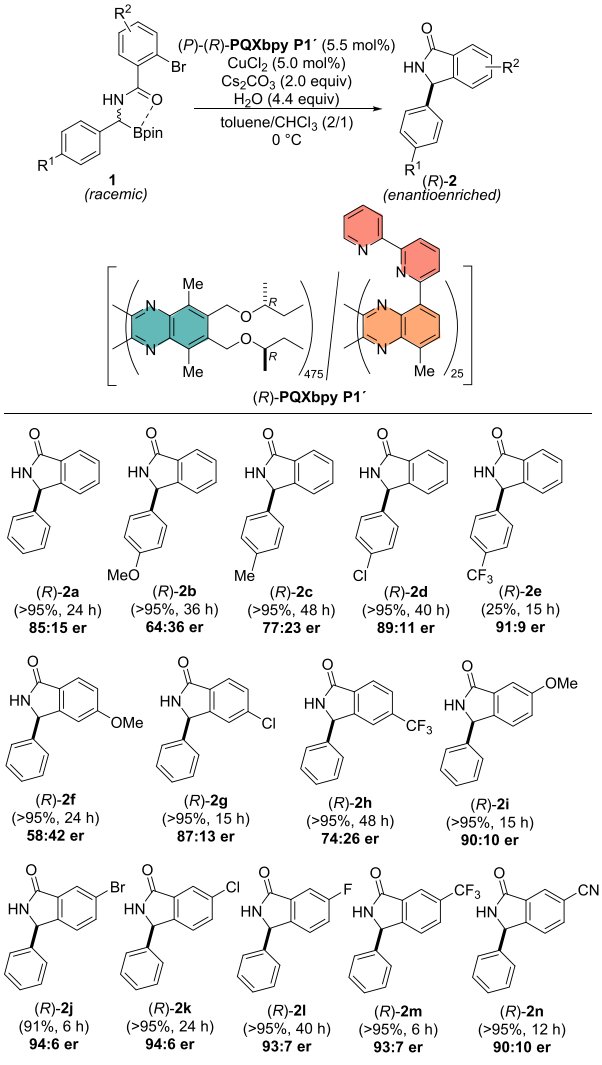
https://dx.doi.org/10.1021/jacs.0c09080
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

bipyridyl group (entry 7). The others carrying methyl groups at the 4- (R^5), 4′- (R^3), and 5′- (R^2) positions showed comparable catalytic activity and enantioselectivities (79:21−83:17) (entries 5, 6, and 8). Third, electronic tuning at the terminal pyridyl groups by introduction of R^2 or R^3 substituents had a remarkable effect on the catalytic activity (entries 9−13). Introduction of electron-withdrawing substituents such as chloro and cyano groups to the terminal pyridyl group significantly lowered both the catalytic activity and enantioselectivity (entries 9 and 10). Based on these results, we selected PQXbpy **P1** for use in further study.

Under the optimized reaction conditions using **P1′** as the chiral catalyst, when the polymerization degree was increased to 500, several substrates were subjected to the intramolecular coupling reaction (Scheme 2). The reactions of **1a−e**, bearing phenyl groups containing different substituents at their *para*-positions in the α-aminobenzylboron moiety, revealed that the stereochemical course is remarkably affected by the electronic nature of the substituents. The enantioselectivity increases with a decrease in the electron density of the phenyl groups, although introduction of a strongly electron-withdrawing group resulted in low chemical yield (**2e**). Among the series of substrates **1f−h** bearing *para*-substituents in the phenyl group of the benzoyl moiety, the presence of either an electron-donating or an electron-withdrawing substituent was found to lead to a deterioration of the enantioselectivity (**1f** and **1h**). In contrast, **1i−n** bearing various functional groups at the *meta*-positions of the benzoyl group generally showed high enantioselectivities up to 94:6 er.

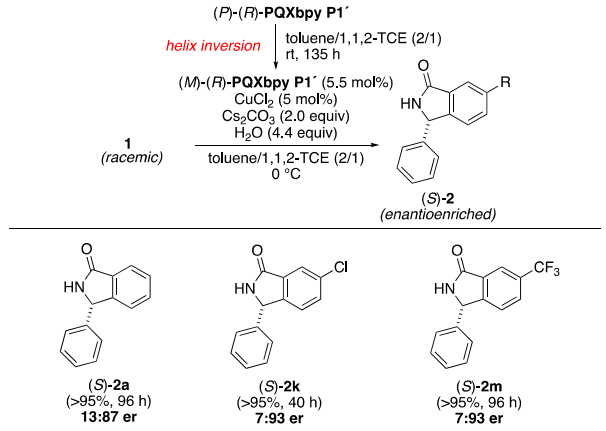
The macromolecular catalyst (*R*)-PQXbpy adopts >99% right-handed helical conformation in most organic solvents, including toluene and $CHCl_3$ used as a reaction solvent. However, the helix sense can be switched in some specific solvents including 1,1,2-trichloroethane (TCE).[13] Indeed, we confirmed that (*R*)-PQXbpy **P1′** adopted >99% left-handed conformation in a mixture of 1,1,2-TCE and toluene (1:2) after equilibration at room temperature for 135 h (Scheme 3).

Scheme 2. Cu-Catalyzed Reactions of Racemic 1 in the Presence of Right-Handed Helical (*R*)-PQXbpy P1′ [a]



[a]The yield was determined by ^{1}H NMR using dibenzyl ether as an internal standard. The enantiomeric excess was determined by chiral SFC analysis.

Scheme 3. Copper-Catalyzed Reactions of Racemic 1 in the Presence of Left-Handed Helical (*R*)-PQXbpy P1′

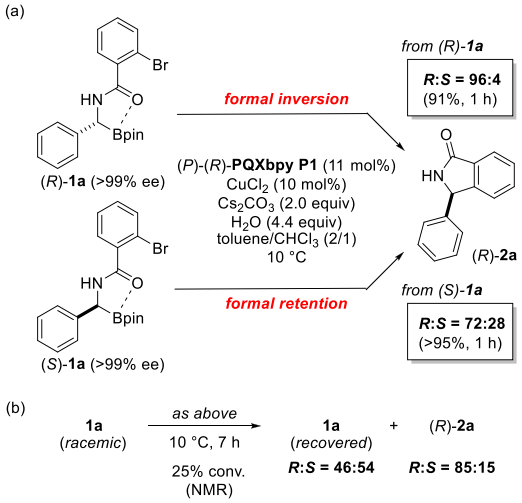


Using the thus generated left-handed (*M*)-(*R*)-**P1′**, (*S*)-configured **2a**, **2k**, and **2m** were obtained in good yields with high enantioselectivities. It should be noted that this result clearly suggests that the enantioselectivity is governed by the helical chirality of the catalyst.[24,25]

It is likely that a mechanism involving epimerization of an organocopper intermediate is involved. Inclusion of the epimerization step in this type of coupling was suggested in reports by Dumas[12] and by our group[11] in the reaction of enantiopure **1** in the presence of achiral 2,2′-bipyridyl as a ligand. In the present system, the epimerization allows deracemization at the stereogenic carbon center, leading to the formation of the product in a stereoconvergent manner. To confirm this assumption, we conducted reactions with enantiopure (*R*)-**1a** and (*S*)-**1a** separately in the presence of right-handed (*P*)-(*R*)-**P1** at 10 °C (Scheme 4a). Both enantiomers in fact afforded product (*R*)-**2a** in good yields, albeit with different er. Whereas (*R*)-**1a** afforded an *R*/*S* ratio of 96:4, (*S*)-**1a** gave an *R*/*S* ratio of 72:28. Under the same reaction conditions (10 °C, 10 mol% catalyst), racemic **1a** provided (*R*)-**2a** with an *R*/*S* ratio of 84:16, which is the average of the two reactions. In addition, it is apparent from the high chemical yield that the high enantiomeric ratio is not due to a major contribution of kinetic resolution. Indeed this was confirmed by inspecting the enantiomer ratios in the remaining starting material (46:54% er) and product (85:15

https://dx.doi.org/10.1021/jacs.0c09080
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

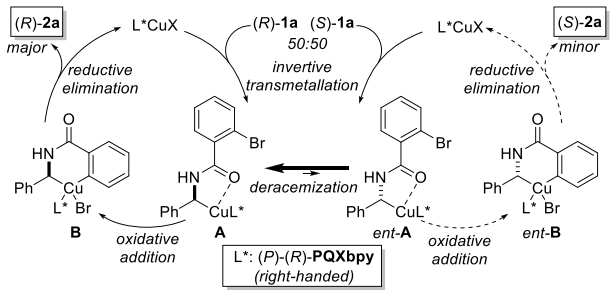
Scheme 4. Reactions of (a) (*R*)- and (*S*)-1a and (b) Racemic 1a in the Presence of Right-Handed PQXbpy P1



er) at 25% conversion, indicating that the two enantiomers are consumed in an almost parallel manner (k_R/k_S < 2) (Scheme 4b). It should be noted that we also conducted a series of reactions of enantiomerically pure (*S*)-**1** (See the SI, Table S5). Notably, (*S*)-**1b** provided (*S*)-**2b** with formal stereochemical retention, while (*S*)-**1d**,**e** afforded (*R*)-**2d**,**e** with formal stereochemical inversion. These results may suggest that the deracemization step is decelerated by electron-donating groups at the benzyl group, leading to ineffective enantioconvergent process.

From these results, we propose a mechanism for this stereoconvergent intramolecular coupling reaction (Scheme 5).[11,12] The B-to-Cu transmetalation affords organocopper

Scheme 5. A Possible Reaction Mechanism Involving Deracemization of Organocopper Intermediate A and *ent*-A Using Right-Handed (*P*)-(*R*)-PQXbpy as a Chiral Ligand



intermediate **A**, which undergoes oxidative addition of an aryl–Br bond to form **B** and subsequent facile reductive elimination to give product **2**. It is assumed that intermediate **A**, which is formed through invertive transmetalation, undergoes epimerization at the copper-bound stereogenic center directed by the chiral ligand on the copper. The er is dependent on the relative reaction rate of deracemization over oxidative addition, which could be the rate-determining and stereodetermining step. The right-handed helical scaffold of PQXbpy may make the formation of **A** more favorable in the equilibrium over diastereomeric *ent*-**A**. In the reaction of (*R*)-**1a**, invertive transmetalation gave **A** directly, which is converted into the product (*R*)-**2a** without significant erosion of the enantiopurity. In contrast, the reaction of enantiomeric (*S*)-**1a** initially gives intermediate *ent*-**A**, which undergoes epimerization to **A**, leading to the formation of (*R*)-**2a**. The greater erosion of enantiopurity in the reaction of (*S*)-**1a** than of (*R*)-**1a** is likely because the oxidative addition, although a slower process, proceeds competitively with the epimerization process, leading to minor, but significant levels of formation of (*S*)-**2a**.

In summary, we have established an enantioconvergent intramolecular boron-based coupling of α-(2-bromobenzoylamino)benzylboronic esters using copper catalysts bearing C_1-symmetrical chiral bipyridyl ligands attached to helical PQX. Although the reaction is classified as a cyclization, amidation-based preparation of the starting material **1** allows easy access to various chiral isoindolinone derivatives. This study also reveals that PQXbpy constitutes a new family of C_1-symmetrical 2,2′-bipyridyl ligands featuring a huge and distinctive chiral reaction space, whereas the choice of the corresponding low-molecular C_1-symmetrical 2,2′-bipyridyl ligands remains quite limited.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c09080.

Detailed experimental procedures and compound characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Takeshi Yamamoto − *Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan*; orcid.org/0000-0002-5184-7493; Email: suginome@sbchem.kyoto-u.ac.jp

Michinori Suginome − *Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan*; orcid.org/0000-0003-3023-2219; Email: yamamoto@sbchem.kyoto-u.ac.jp

Author

Yukako Yoshinaga − *Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c09080

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI on Innovative Areas (Grant Number JP15H05811 in Precisely Designed Catalysts with Customized Scaffolding), KAKENHI (A) (Grant Number 20H00377), and JST CREST (Grant Number JPMJCR14L1 in Establishment of Molecular Technology toward the Creation of New Function).

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