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Stereoinvertive C–C Bond Formation at the Boron-Bound Stereogenic Centers via Copper–Bipyridine-Catalyzed Intramolecular Coupling of α-Aminobenzylboronic Esters

Yukako Yoshinaga, Takeshi Yamamoto,* and Michinori Suginome*

Enantiospecific intramolecular Suzuki-Miyaura-type Abstract: coupling with a-(2-halobenzoylamino)benzylboronic esters giving 3substituted isoindolinones is achieved by using copper catalysts with 2,2'-bipyridine-based achiral ligands. Enantioenriched αaminobenzylboron reactants bearing a hydrogen atom at the boronbound stereogenic carbons undergo stereoinvertive coupling in the presence of 6-phenyl-2,2'-bipyridine ligand with high enantiospecificities. α-Aminobenzylboronates bearing fully substituted boron-bound stereogenic centers also gave the 3,3disubstituted isoindolinones with stereospecific stereochemical inversion in the presence of simple 2,2'-bipyridine as a ligand.

Cross-coupling reactions to form stereogenic sp³-carbon centers¹ are recognized as a highly attractive transformation in asymmetric synthesis. Most typically, enantioenriched or racemic chiral secondary alkyl electrophiles are used in the coupling with achiral organometallic reactants, leading to stereospecific² or enantioconvergent³ cross-coupling. In addition to such coupling using chiral electrophiles, stereospecific crosscouplings using configurationally stable chiral organometallic compounds⁴⁻⁷ have gained increasing attention. Particular attention is paid to Suzuki-Miyaura-type, i.e., boron-based, cross-coupling of enantioenriched alkylboronates (Figure 1a). Such reactions are highly attractive because the starting enantioenriched organoborons are configurationally robust and easily accessible by asymmetric hydroboration and related transformation.8-11 The reaction course of the cross-coupling process can be switched from stereochemically retentive to invertive, allowing the reaction to afford either enantiomer even from single enantiomers of starting organoboron compounds. However, such boron-based stereospecific coupling processes have so far been limited to palladium-catalyzed reactions using organoboron compounds bearing a boron-bound, trisubstituted stereogenic carbon center. To our knowledge, there has been no precedent for stereospecific cross-coupling at fully substituted metal-bound stereogenic carbons to date.

During the course of our study of the stereospecific crosscoupling of α -aminoalkylboronic acid derivatives,^{7b,d,h} a report from the Dumas group caught our attention: α -[(obromobenzoyl)amino]benzylboronates undergo intramolecular cross-coupling reaction to form 3-arylisoindolones in the presence of a 2,2'-bipyridine/copper(II) catalyst.¹² This intramolecular reaction appears highly valuable synthetically,

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because, even though it is a simple cyclization, the substrates can be synthesized through coupling of two easily available components, i.e., a-aminoalkylboronic acids and o-haloaroyl chlorides, through an amidation reaction. Although the report claimed that complete racemization was observed in a reaction enantiopure α -[(o-bromobenzoyl)amino]benzylboronates of under standard reaction conditions, we decided to examine the potentially useful synthetic transformation in more detail. In this paper, we describe stereospecific intramolecular cross-coupling reactions of α -[(o-bromobenzoyl)amino]benzylboronates using bipyridine-copper catalysts. Notably, the reaction proceeds with stereochemical inversion with high enantiospecificity (es).13 Moreover, the reaction has been extended to the coupling at stereogenic carbon fullv substituted centers in αaminobenzylboronates, which proceeds with an even more pronounced stereochemical inversion.



Figure 1. Pioneering works on transition-metal-catalyzed cross-coupling reaction of alkylborons.

(*S*)- α -[(*o*-Bromobenzoyl)amino]benzylboronic acid **1a**, easily synthesized using the protocol described by Ellman in a highly enantioenriched form (>99% ee),^{8h} was subjected to intramolecular coupling in the presence of CuCl₂ (10 mol%) along with 2,2'-bipyridine (**L1**, 11 mol%) under reaction conditions similar to those used by Dumas et al. (Scheme 1). The isoindolinone product was obtained quantitatively, but in an almost racemic form (1% ee), as indicated in the previous report.¹² 4,4'-Disubstituted bipyridine **L2** and **L3** gave the product in good yield, but with low enantiospecificities. By contrast, 6,6'-disubstituted bipyridines bearing *t*-butyl (**L4**) and

phenyl (L5) groups at both the 6- and 6'-positions gave almost no desired product, but gave protodeborylation product in high yields. Upon using 6,6'-dimethyl-2,2'-bipyridine (L6), however, we found that the coupling proceeded with appreciable es (56%) albeit in low chemical yield.^{14,15} These results may suggest that the steric circumstance around the copper center has contradicting effects on the chemical yield and enantiospecificity. We then employed 6-monosubstituted 2,2'-bipyridines (L7-9) to adjust steric demand. Although 6-methyl (L7) and *t*-butyl (L8) derivatives suffered from low stereospecificity or low chemical yield, respectively, use of 6-aryl derivatives resulted in the formation of **2a** in high yields with high es (See Table S1 in Supporting Information (SI) for detail). Among them, 6-phenyl-2,2'-bipyridine (L9) was found to be optimal, giving 89% es with 96% yield.



Scheme 1. Effect of bipyridine ligand for reaction of (*S*)-**1a**. The yield was determined by ¹H NMR using dibenzyl ether as an internal standard. The enantiomeric excess was determined by chiral SFC analysis.

Our further screening of the reaction conditions (Table S2) revealed that (1) Br and I were superior to CI as the leaving group, (2) use of a mixture of toluene and chloroform (2/1) is preferable in terms of both chemical yields and stereospecificity, (3) higher temperature (50 °C) or extended reaction time at low temperature (0 °C) resulted in lower stereospecificities, and (4) higher catalyst loading (20 and 50 mol%) did not alter the reaction outcome significantly.

Reactions of various substrates were conducted under optimized reaction conditions (Scheme 2). Modification of the aryl group at the stereogenic carbon revealed that the electronic effect has a profound influence on the enantiospecificity of the reaction. Electron-donating substituents, such as methoxy (1b) and alkyl groups (1c and 1d), at para-position gave higher enantiospecificities, whereas electron-withdrawing substituents, such as chlorine (1e) and trifluoromethyl (1f) groups, resulted in lower enantiospecificities. Remarkably, 1g bearing a sterically hindered o-tolyl group at the stereogenic carbon atom afforded high enantiospecificity. In addition, substrates 1h-1j with methylenedioxyphenyl, 1-naphthyl, and 2-naphthyl groups gave the corresponding products with high enantiospecificities. It should be noted that electron-withdrawing substituents such as chlorine (1k) and trifluoromethyl group (1m) on the benzoyl group lower the enantiospecificities.

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Scheme 2. Copper-catalyzed stereospecific cross-coupling of (S)-1a-m using L9 as a ligand.

We then turned attention our to α-[(obromobenzoyl)amino]benzylboronic acids in which the stereogenic boron-bound carbon atom is fully substituted, and are hardly reactive in the palladium-catalyzed cross-coupling reactions. This feature was already indicated in the report by Dumas et al. with no examination of the stereochemical course. We initially checked the effect of bipyridine ligands (Scheme 3). Interestingly, 6-phenyl-2,2'-bipyridine (L9), which are the ligands of choice in the reactions shown above, afforded only a trace amount of the coupling product in the reaction of (S)-3a. We found high chemical yields when using less sterically demanding 6-methyl-2,2'-bipyridine (L7) or even unsubstituted 2,2'bipyridine (L1) as ligands. It is noteworthy that the reaction proceeded with high enantiospecificity (98% ee, >99% es)^{16,17} along with high chemical yields. The stereospecificity was found to be insensitive to the reaction temperature, allowing us to conduct the reaction even at 50 °C within a shorter time (1 h).



Scheme 3. Effect of bipyridine ligand for reaction of (S)-3a of which stereogenic carbon center is fully substituted.

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Under the optimized reaction conditions, the scope of substrate was checked (Scheme 4). Although sterically demanding **4c** having 1-naphthyl group at the stereogenic center showed erosion of enantiopurity, 4-chlorophenyl- and 2-naphthyl-substituted boronates gave the corresponding products (**4b** and **4d**) with high enantiospecificity. Some other substrates (**3e**-**3h**), in which the aromatic group on the benzoyl group is functionalized, gave high enantiospecificities with high chemical yields. Importantly, the alkyl group at the stereogenic center could be diversified, as *n*-propyl or 2-phenylethyl group substituted **3i** and **3j** to afford the corresponding product in similarly high yield with high enantiospecificity.



Scheme 4. Copper-catalyzed stereospecific cross-coupling of (*S*)-**3a**-**j** using **L1** as a ligand.

The reaction could be performed in a larger gram scale (Scheme 5). 5.0 mmol of substrate (S)-**3a** (2.15 g) was reacted under the optimized conditions, but using only 1.0 mol% copper catalyst. The reaction gave the 1.05 g of product (94% yield) with similarly high enantiospecificity (99% es). This result shows the high reliability of this reaction. We can conclude that the copper-catalyzed intramolecular cross-coupling at the fully substituted carbon center is more robust in terms of stereospecificity than substrates having hydrogen atoms at the stereogenic center.



Scheme 5. Large scale reaction of (S)-3a.

A possible reaction mechanism is shown in Scheme 6 on the basis of the report by Dumas et al.^{12,18} Our observation of inversion strongly suggested stereochemical that the transmetalation is reasonably explained by the attack of electrophilic copper(I) species from the backside of the boron atom at the stereogenic carbon atom. This backside attack is preferred by the steric congestion at the frontside, because of intramolecular coordination of the amide carbonyl to the boron atom. This intramolecular coordination may also facilitate the transmetalation step, as suggested in the palladium-catalyzed Suzuki-Miyaura cross-coupling reactions reported by our group^{7b,d,h} and others.^{7c,e,f} The observed erosion of enantiopurity could be caused either or both by stereoretentive transmetalation and racemization of the organocopper intermediates.¹⁹ It is assumed that sterically less demanding bipyridine ligand facilitates the racemization of the organocopper intermediates derived from (S)-1 (R = H), leading to low enantiospecificity.



Scheme 6. Possible catalytic cycle.

We finally checked the effect of Brønsted acid additives to support our proposal for the invertive transmetalation and to improve the stereospecificity. Such additives had been found to improve the stereospecificity for the invertive transmetalation in the palladium-catalyzed coupling reaction through protonation of the pinacol oxygen atom, which strengthen the intramolecular coordination of the amide carbonyl group to the boron atom.7d,20 Upon addition of phenol (3 equiv) to the reaction of (S)-1a giving (S)-2a under otherwise identical reaction conditions using L9 as a ligand, enantiospecificity increased to 94% from 89% es in the original reaction conditions (Scheme 7). Note that use of monosubstituted bipyridine L9 was still essential, since use of unsubstituted 2,2'-bipyridine L1 afforded only 15% es. This positive effect of phenol was found to be even pronounced in the reactions of substrates that gave inferior enantiospecificities under the original reaction conditions without using phenol: 1c, n, o, and p gave 84-96% es in the presence of phenol instead of 53-78% es with the original reaction conditions (Scheme 7).

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Scheme 7. Reaction of (S)-2 in the presence of phenol. The yield and enantiospecificity in the absence of phenol are shown in the bracket.

In summary, we have established the reaction conditions for highly enantiospecific copper-catalyzed intramolecular Suzuki-Miyaura-type coupling of α-[(**0**bromobenzoyl)amino]benzylboronates, which affords highly enantioenriched isoindolinone derivatives in high yields. The reaction yield and stereospecificity were contradictorily and sharply affected by the steric effect at the substituents at the 6and 6'-positions of the bipyridyl ligands. Employing 6monosubstituted bipyridine ligands allowed finer tuning of the steric effect than using 6,6'-disubstituted bipyridines. The stereochemical course of the coupling was determined to be invertive, relying on the stereoinvertive transmetalation step, which becomes more preferable by using phenol as a Brønsted acid additive. The reaction protocol was applicable to α aminobenzylboronates of which boron-bound stereogenic carbon center is fully substituted. These results reveal that the stereoinvertive transmetalation with organoboron compounds is not limited to palladium-catalyzed cross-couplings, but has more generality in boron-based transition-metal-catalyzed reactions.

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Enantiospecific intramolecular coupling of enantioenriched α -(2bromobenzamido)benzylboronic esters was achieved by using copper catalysts with 2,2'-bipyridine-based achiral ligands. The reaction proceeded with stereochemical inversion of a boron-bound stereogenic α -carbon center, giving chiral 3-substituted isoindolinones with high enantiospecificities (up to >99% es). Yukako Yoshinaga, Takeshi Yamamoto,* Michinori Suginome*

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