

Stereospecific Cross-Coupling of Secondary Alkyl β -TrifluoroboratoamidesDeidre L. Sandrock,^{†,§} Ludivine Jean-Gérard,^{†,§} Cheng-yi Chen,[‡] Spencer D. Dreher,[‡] and Gary A. Molander^{*,†}

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Abstract: The stereospecific cross-coupling of enantioenriched nonbenzylic secondary alkyl boron compounds has been achieved. The high selectivity toward product formation over an undesired β -H elimination pathway is achieved via an intramolecular coordination of an ancillary carbonyl to the metal center in the diorganopalladium intermediate.

The Suzuki–Miyaura cross-coupling reaction has emerged as one of the most versatile transformations available for the generation of C–C bonds.¹ Although there are many strategies that exist for the cross-coupling of sp^2 -hybridized organometallics,² the protocols for the cross-coupling of secondary and potentially enantiomerically enriched sp^3 -hybridized organometallics have limited precedent.³ In a previous communication, we described a development toward this goal by identifying catalytic reaction conditions for the cross-coupling of cyclic, symmetrical secondary alkyltrifluoroborates with aryl electrophiles.⁴ However, when applied to symmetrical acyclic substrates, it became evident that the use of our optimized conditions still led to a β -H elimination/isomerization pathway that resulted in mixtures of the desired cross-coupled products as well as the undesired isomerized primary alkylated products.

More recently, other attempts at secondary cross-coupling using various organoboron derivatives have appeared.⁵ Crudden and co-workers developed a protocol for the preparation of enantioenriched styrene-derived secondary boronate esters and demonstrated their cross-coupling with a variety of aryl iodides.⁵ Although the reactions proceed in good yields with retention of configuration,⁶ this method was limited to the cross-coupling of benzylic boron derivatives.

During the course of this investigation, Suginome reported the cross-coupling of α -(acylamino)benzylboronates with aryl bromides and chlorides, which somewhat surprisingly occurred with overall inversion of configuration.⁷

Herein we report our most recent efforts toward the ultimate goal of cross-coupling nonbenzylic, enantioenriched secondary alkyl organoboron reagents with stereochemical fidelity during the cross-coupling event. Subsequent to our studies on secondary alkyltrifluoroborates, efforts were conducted to extend the study of β -trifluoroborato carbonyls⁹ to the preparation and cross-coupling of acyclic secondary β -trifluoroboratoamides. Using the borylation strategy outlined by Yun and co-workers, a variety of these trifluoroborates were prepared.^{9a,10} With the desired substrates in hand, an initial screen of catalytic conditions led to the combination of 10 mol % of Pd(OAc)₂ and 20 mol % of XPhos, K₂CO₃ in a

Table 1. Cross-Coupling of β -Trifluoroboratoamides with Aryl Halides^a

entry	electrophile	X	product	% isolated yield
1		Cl Br		90 63
2		Cl Br		72 74 ^b
3		Cl		<i>o</i> = 88 <i>p</i> = 91
5		Cl		81
6		Cl Br		76 72 ^b
7		Cl Br		66 ^b 47 ^b
8		Cl		72
9		Br		92
10		Cl		83
11		Cl		80 ^b
12		Cl		92 ^b
13		Cl		71 ^b

^a General conditions: Pd(OAc)₂ (10 mol %), XPhos^{8a} (20 mol %), RBF₃K (1 equiv), K₂CO₃ (3 equiv), and 6.7:1 CPME/H₂O (0.25 M).

^b Reactions perform better with SPhos^{8b} (20 mol %) and Cs₂CO₃ (3 equiv).

cyclopentyl methyl ether (CPME)/H₂O solvent system giving the highest isolated yield of potassium *N*-cyclohexyl-3-(trifluoroborato)butanamide in the coupling reaction with 2-chloroanisole (Table 1, entry 1).

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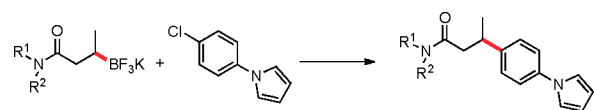
[§] These authors contributed equally.

Encouraged by this initial result, we proceeded with further screening, which revealed that the combination of 10 mol % of XPhos or SPhos with Cs_2CO_3 (3 equiv) also provided good to excellent yields of the cross-coupled products with both aryl chlorides and bromides.

Using 10 mol % of $\text{Pd}(\text{OAc})_2$ and 20 mol % of XPhos, a variety of electrophilic partners (including those containing ketone, aldehyde, ester, nitrile, and nitro groups) cross-coupled with the model trifluoroborate in good yields. In a number of cases, the use of SPhos as the ligand actually provided higher yields of the cross-coupled product (Table 1, entries 6, 7, 11–13). In all of these examples, <2% of products resulting from β -H elimination or isomerization were isolated.

To investigate the scope of this reaction with respect to the nucleophilic partner, all three sets of suitable catalytic conditions were applied to a variety of amide substrates, in each case generating the cross-coupled products in good yields (Table 2, entries 1–7), again observing little or none of the undesired byproducts.

Table 2. Cross-Coupling of Various Trifluoroborates with Aryl Halides^a



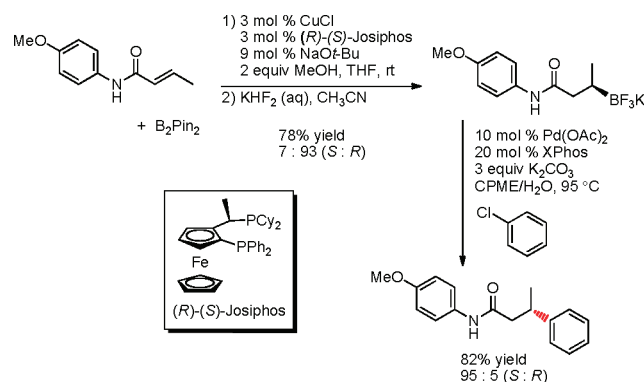
entry	RBF ₃ K	ligand/base	% isolated yield
1		XPhos, K ₂ CO ₃	84
		XPhos, Cs ₂ CO ₃	89
		SPhos, Cs ₂ CO ₃	78
2		XPhos, K ₂ CO ₃	92
		XPhos, Cs ₂ CO ₃	84
		SPhos, Cs ₂ CO ₃	93
3		XPhos, K ₂ CO ₃	87
		XPhos, Cs ₂ CO ₃	99
		SPhos, Cs ₂ CO ₃	98
4		XPhos, K ₂ CO ₃	72
		XPhos, Cs ₂ CO ₃	78
		SPhos, Cs ₂ CO ₃	64
5		XPhos, K ₂ CO ₃	89
		XPhos, Cs ₂ CO ₃	96
		SPhos, Cs ₂ CO ₃	89
6		XPhos, K ₂ CO ₃	79
		XPhos, Cs ₂ CO ₃	91
		SPhos, Cs ₂ CO ₃	86
7		XPhos, K ₂ CO ₃	94
		XPhos, Cs ₂ CO ₃	79
		SPhos, Cs ₂ CO ₃	89

^a General conditions: $\text{Pd}(\text{OAc})_2$ (10 mol %), ligand (20 mol %), RBF₃K (1 equiv), base (3 equiv), and 6.7:1 CPME/H₂O (0.25 M).

With the ultimate goal of developing conditions to generate optically active materials through the use of an appropriate organoboron reagent, we prepared an enantioenriched β -trifluoroboratoamide via an asymmetric β -borylation reaction of the corresponding α,β -unsaturated amide using bis(pinacolato)diboron and (*R*)-(*S*)-Josiphos as the chiral ligand (Scheme 1).¹¹

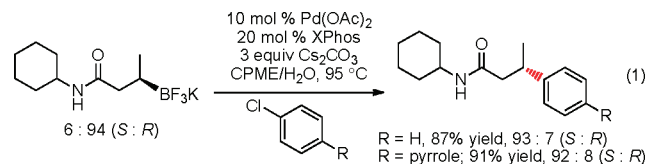
With the enantioenriched secondary organotrifluoroborate in hand, we subjected it to the optimized reaction conditions for the cross-coupling of this family of substrates. Using 10 mol % of $\text{Pd}(\text{OAc})_2$, 20 mol % of XPhos, and 3 equiv of K_2CO_3 in a CPME/H₂O solvent system, the cross-coupled product was obtained in an enantiomeric ratio of 95:5 (*S*:*R*) in 82% yield for the cross-coupling

Scheme 1. Preparation and Cross-Coupling of Enantioenriched β -Trifluoroboratoamide



step. The absolute configurations of the major enantiomers of the borylated starting material and cross-coupled products were determined to be *R* and *S*, respectively, by comparison with the authentic *S* isomers prepared from derivatization of commercially available (*S*)-3-hydroxybutyric acid and (*S*)-3-phenylbutyric acid. This complete inversion in stereochemistry during transmetalation for secondary alkyl boron compounds (in substrates that have the potential for β -hydride elimination) represents an important extension to the previously described methods for the cross-coupling of secondary organometallics.

Subsequent cross-couplings with the enantioenriched cyclohexyl amide derivative with aryl chlorides also revealed the same inversion of configuration with no discernible stereochemical erosion detected (eq 1). Interestingly, neither the analogous β -trifluoroborato ketones nor -esters afford the desired coupled products.

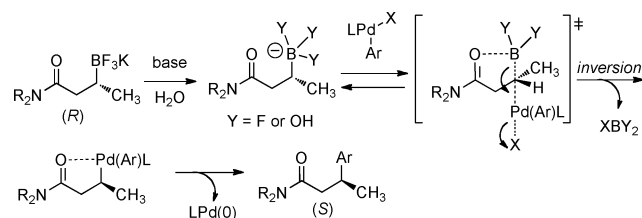


Although other factors could conceivably be involved, the unique reactivity of β -trifluoroboratoamides supports an hypothesis in which the ancillary carbonyl oxygen plays a role in coordinating with the intermediate diorganopalladium complex. Three beneficial features would derive from this interaction: (1) The coordination could facilitate the transmetalation process, as the conditions optimized for this transformation were not optimal for the cross-coupling of unfunctionalized secondary alkyltrifluoroborates described in our previous communication.⁴ (2) The complexation may also restrict the conformation of the diorganopalladium intermediate, inhibiting a syn-coplanar arrangement of the palladium and the acidic hydrogens alpha to the carbonyl required for β -hydride elimination.¹² (3) More importantly, the carbonyl interaction with the coordinatively unsaturated palladium could inhibit the metal from interacting agostically with the β -hydrogens, a feature required for β -H elimination (Scheme 2). These characteristics result in the formulation of a new paradigm for successful secondary alkyl cross-coupling with potentially wide implications.

As in the Sugimoto study, the inversion of configuration observed during the cross-coupling reaction with the β -trifluoroboratoamides is attributed to intramolecular coordination of the carbonyl group to the boron. Chiral benzylstannanes,¹³ silanes,¹⁴ and α -(acylamino)benzylboronic esters⁷ have been shown to undergo transmetalation with inversion of configuration, presumably through an $\text{S}_{\text{E}}2$ mechanism via an open transition state, a process

that is favored in polar solvents. More closely related to the current studies, examples of S_E2 -type reactions that proceed with inversion of configuration in borate substrates have been reported previously as well.¹⁵

Scheme 2. Proposed Mechanism for Complete Stereochemical Inversion



In conclusion, the concept of using pendant ligands to serve as hemilabile ligands¹⁶ to enhance transmetalation and inhibit the β -hydride elimination pathway in the cross-coupling of secondary organometallic species is highlighted. Additionally, the first cross-coupling of a nonbenzylic, enantioenriched secondary alkyl organometallic containing β -hydrogens that proceeds with complete inversion of configuration without any loss of enantioselectivity during the cross-coupling event has been reported.

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Supporting Information Available: Experimental details and spectral data of all compounds synthesized. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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