

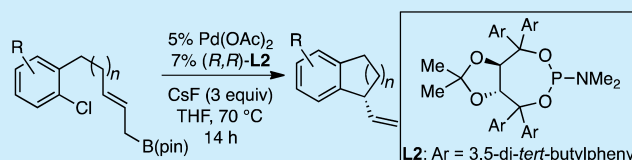
Enantioselective Carbocycle Formation through Intramolecular Pd-Catalyzed Allyl–Aryl Cross-Coupling

Christopher H. Schuster, John R. Coombs, Zachary A. Kasun, and James P. Morken*

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, United States

S Supporting Information

ABSTRACT: Aryl electrophiles containing tethered allylboronate units undergo efficient intramolecular coupling in the presence of a chiral palladium catalyst to give enantioenriched carbocyclic products. The reaction is found to be quite general, affording 5, 6, and 7-membered carbocyclic products as single regioisomers and with moderate enantioselectivities. Examination of differential coupling partners points to rapid allyl–equilibration as a key stereodefining feature.



The development of metal-catalyzed cross-coupling reactions has revolutionized the manner in which molecules are assembled, providing reliable, predictable, and versatile entry to a variety of molecular frameworks.¹ Recently, allylmethyl reagents have garnered significant attention as valuable partners in cross-coupling protocols. Employing nonsymmetric allyl fragments allows bond formation at one of two sites, presenting the opportunity for both regioselective and in some cases enantioselective transformations. In particular, allyl boron compounds^{2–4} have proven to be practical nucleophilic partners, in part due to their ease of handling, high functional group tolerance, and facile preparation.⁵

Recently, several reports engaging allyl boronates as partners in both branch- and linear-selective cross coupling reactions have been disclosed (Scheme 1). In 2006, Szabó achieved a highly branch-selective coupling of allylboronic acids with aryl electro-

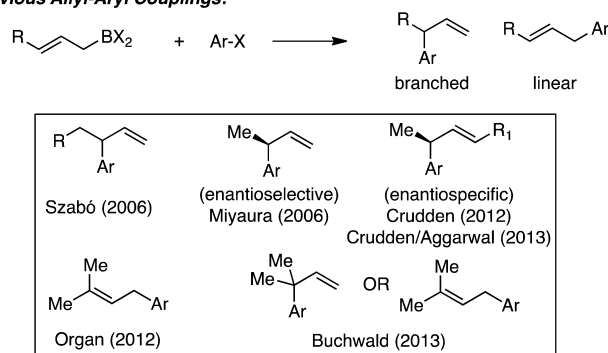
philes.²ⁿ More recently, Crudden reported the regioselective coupling of internal allyl boronates with aryl electrophiles.^{2f} The linear-selective coupling of allyl boronates and aryl electrophiles was accomplished by Organ utilizing a bulky Pd-PEPPSI catalyst.^{2g} Notably, Buchwald was able to achieve both branch- and linear-selective coupling with the proper choice of ligand.^{2h} While Aggarwal and Crudden recently disclosed the enantio-specific cross-coupling of enantiomerically enriched allyl boronates with aryl electrophiles,²ⁱ the only example of enantioselective coupling of allyl boronates and aryl electrophiles with chiral catalysts remains the work of Miyaura.⁶ When an electron-rich Josiphos-based ligand with the use of crotyl potassium trifluoroboronates was employed, a highly branch-selective coupling was achieved with good enantioselectivity.

In stark contrast to the aforementioned intermolecular coupling of allyl boronates, an intramolecular version is unknown.⁷ In related coupling reactions,⁸ allylsilanes,⁹ allylstannanes,¹⁰ and allylindium¹¹ reagents have all been successfully engaged in intramolecular cross coupling to forge the desired carbo- or heterocyclic products. With the notable exception of work by Tietze,^{9d–f} all intramolecular allyl–aryl couplings have thus far been executed in a racemic manner. Herein, we describe the use of allyl boronates as nucleophilic partners in an intramolecular coupling with aryl electrophiles to afford enantiomerically enriched carbocyclic products in a regioselective fashion.

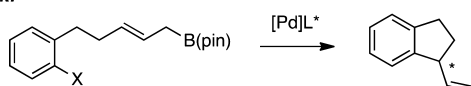
Initial attempts to achieve the desired transformation are outlined in Table 1. The use of a variety of bidentate chiral phosphine ligands generally resulted in efficient conversion to the carbocyclic product in a regioselective fashion, albeit with low levels of enantioselectivity (entries 1–6). In contrast to the good enantioselectivities obtained by Miyaura under similar reaction conditions for intermolecular allyl–aryl coupling, employment of a Josiphos-based catalyst results in a nearly racemic reaction

Scheme 1. Recent Examples of Intermolecular Allyl Boronate Aryl Coupling

Previous Allyl–Aryl Couplings:

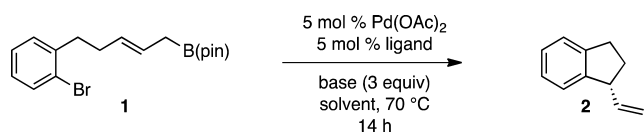


This Work:



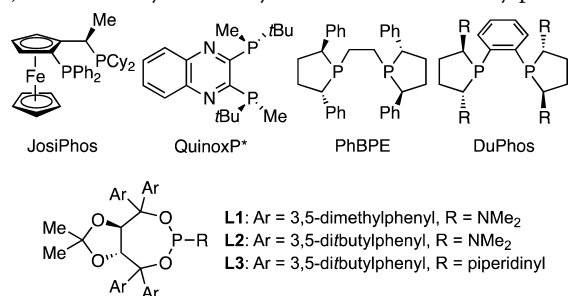
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Table 1. Survey of Chiral Ligands in Intramolecular Allyl–Aryl Coupling^a


entry	base	solvent	ligand	conv (%)	er
1	KOH	THF/H ₂ O	JosiPhos	>98	51:49
2	KOH	THF/H ₂ O	Binap	>98	51:49
3	KOH	THF/H ₂ O	QuinoxP*	>98	56:44
4	KOH	THF/H ₂ O	PhBPE	>98	51:49
5	KOH	THF/H ₂ O	iPr-DuPhos	>98	56:44
6	KOH	THF/H ₂ O	Me-DuPhos	>98	57:43
7	CsF	THF/H ₂ O	Me-DuPhos	63	56:44
8	CsF	THF	Me-DuPhos	>98	59:41
9	CsF	THF	L1	>98	83:17
10	CsF	THF	L2	>98	84:16
11	CsF	THF	L3	>98	71:29

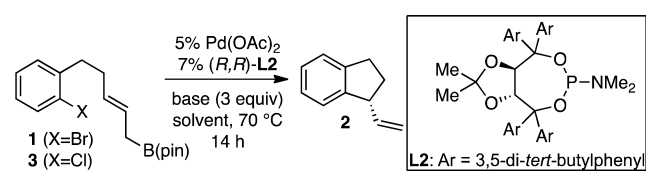
^aPercent conversion determined by ¹H NMR analysis; er (enantiomer ratio) determined by GLC analysis with a chiral stationary phase.



product (entry 1). Utilization of cesium fluoride under anhydrous conditions resulted in a slight improvement in selectivity with Me-DuPhos (entry 8); however, significantly higher enantiomeric selectivity was obtained with the use of monodentate phosphoramidite ligands utilizing a TADDOL based backbone (entries 9–11). While increasing the size of the ligand aryl groups resulted in only marginally elevated selectivities, the nature of the amino group proved more influential, with small groups yielding superior results (cf. L2 vs L3); thus, (*R,R*)-L2 was selected for further study.

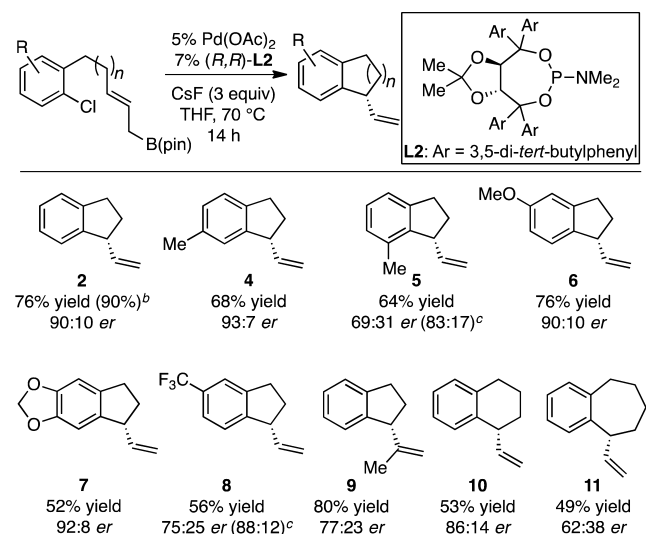
In an effort to improve reaction efficiency further, additional conditions were examined (Table 2). While promoting efficient ring closure in most cases, bases other than CsF gave inferior levels of enantioselectivity (entries 1–5). Similarly, both polar (entries 3, 6–8) and nonpolar (entries 9, 10) solvents proved to be suitable reaction media, with THF affording the best selectivity. Because of its ability to promote π – σ – π isomerization, the use of NBu₄Cl was examined. In line with observations by Trost¹² and Togni,¹³ this led to a significant increase in the levels of enantioselectivity obtained. Employing aryl chlorides (entry 12) in place of aryl bromides also resulted in greater selectivity, which can be further augmented with the use of NBu₄Cl (entry 13); however, reactivity generally suffers under these conditions. Taken together, the use of aryl chlorides without additive in THF, and with CsF as the base, was found to yield the best results, achieving full conversion with good levels of enantioselectivity.

With the optimal conditions in hand, the scope of the intramolecular allyl–aryl coupling was examined (Scheme 2). Compared to unsubstituted substrate 3, meta-substituted

Table 2. Survey of Reaction Conditions in Intramolecular Allyl–Aryl Coupling^a


entry	X	base	solvent	additive	conv (%)	er
1	Br	Cs ₂ CO ₃	THF		>98	68:32
2	Br	K ₃ PO ₄	THF		>98	56:44
3	Br	CsF	THF		>98	84:16
4	Br	KF	THF		24	76:24
5	Br	TBAF	THF		>98	46:54
6	Br	CsF	MeCN		>98	61:39
7	Br	CsF	EtOAc		74	83:17
8	Br	CsF	dioxane		>98	82:18
9	Br	CsF	toluene		>98	74:26
10	Br	CsF	hexane		>98	74:26
11	Br	CsF	THF	Bu ₄ NCl	70	90:10
12	Cl	CsF	THF		>98	90:10
13	Cl	CsF	THF	Bu ₄ NCl	45	93:7

^aPercent conversion determined by ¹H NMR analysis; er (enantiomer ratio) determined by GLC analysis with a chiral stationary phase.

Scheme 2. Survey of Reaction Conditions in Intramolecular Allyl–Aryl Coupling^a

^aYield refers to isolated yield of purified material and is an average of two experiments. er was determined chromatographically by either GC or SFC analysis using a chiral stationary phase. ^bYield in parentheses determined by ¹H NMR versus internal standard. ^cSelectivity obtained with NBu₄Cl (1.5 equiv), < 30% conversion in both cases.

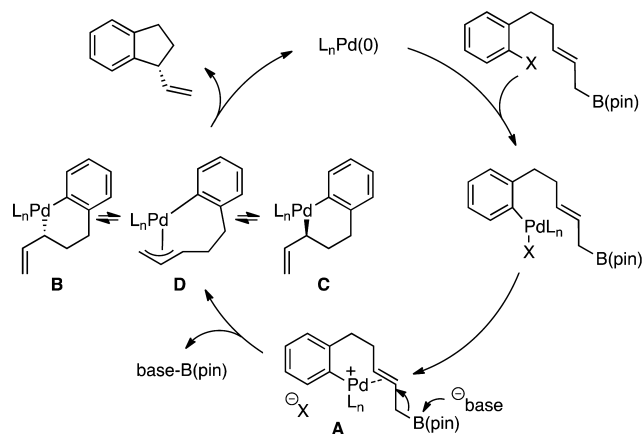
substrates exhibited enhanced selectivity (products 4, 7) with substitution in the ortho position affording lower selectivities (5). Importantly, the use of NBu₄Cl can restore selectivity to achieve moderate levels of asymmetric induction for this more challenging substitution pattern, albeit with diminished yield.

Both electron-rich (6) and electron-poor (8) substrates engage smoothly in intramolecular coupling, with the selectivity for electron-poor substrates benefiting from the use of NBu₄Cl. Notably, substitution on the allyl boronate moiety is well tolerated, and 9 is produced in good yield with moderate

enantioselectivity. Changing the tether length between the aryl electrophile and the allyl boronate allows efficient formation of six- and seven-membered rings (**10** and **11**) in moderate yield with moderate levels of enantioselectivity.

Seeking a more complete understanding of the origins of stereoinduction in the reaction, it was reasoned that selectivity could be imparted during olefin binding (formation of **A**), transmetalation (**A** → **D**, Scheme 3), or reductive elimination (**B**,

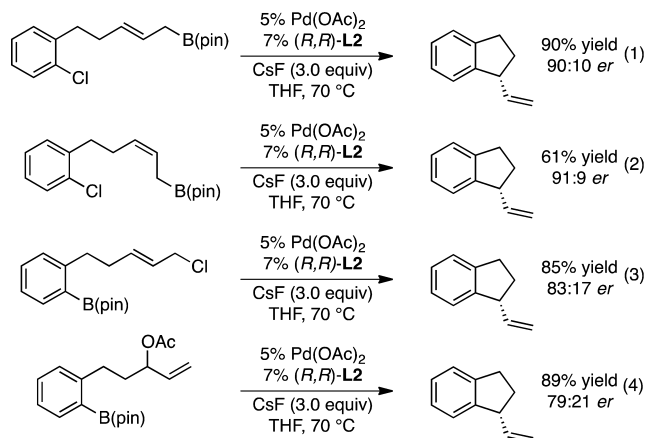
Scheme 3. Proposed Catalytic Cycle



C, D → product). Miyaura and co-workers found that during the related enantioselective intermolecular allyl–aryl coupling, transmetalation was the stereochemistry determining step.^{6b} Thus, after oxidative addition with an aryl halide, the Josiphos-based catalyst effectively selected one of the prochiral faces of the crotyl boronate during S_E2' transmetalation, thereby establishing a palladium–carbon bond in an enantioselective fashion. For the Miyaura system, in order to suppress competing allyl isomerization, a subsequent rapid reductive elimination of the product was found to be essential to achieve high regio- and enantioselectivity.

To test whether the intramolecular reaction occurs with a similar mode of selectivity to the intermolecular variant, a series of substrates were prepared in which the nucleophile and electrophile components were altered (Scheme 4). If the stereochemistry-determining step of the intramolecular coupling

Scheme 4. Examination of Alternate Substrate Configurations^a



^aYields determined by ¹H NMR versus internal standard.

followed the intermolecular precedent established by Miyaura,⁶ it was reasoned that changing the geometry of the allyl boronate moiety would have a significant impact on the stereochemical outcome of the coupling reaction. However, employing the *Z*-allyl boronate under the standard reaction conditions produces the same enantiomer of product that is observed when the *E*-allyl boronate is used and with nearly identical levels of selectivity (Scheme 4, eq 1 vs 2). Moreover, the use of substrates with inverse polarity coupling partners also resulted in formation of the same enantiomer of product (eqs 3 and 4). Since the likelihood of achieving similar levels of selectivity during transmetalation of vastly different species is low, it seems plausible that allyl equilibration¹⁴ of the transmetalation adducts results in stereochemical convergence to a common palladacycle intermediate, followed by stereochemistry-determining reductive elimination to give the observed carbocycle.

This mechanistic proposal in Scheme 3 accounts for many of the observations noted earlier. In order to have the opportunity to correct for a nonselective transmetalation that gives both **B** and **C**, the rate of this isomerization must be rapid relative to reductive elimination. Consequently, any features of the reaction system which either expedite reductive elimination or slow isomerization, may ultimately result in decreased enantioselectivity. For instance, in line with experiments by Trost,¹² the beneficial influence of NBu₄Cl can be attributed to stabilization of 14 electron η^1 allyl intermediates, which are required for stereoinvertive isomerization. Similarly, the detrimental effects of bidentate ligands could arise from accelerated reductive elimination and the suppression of isomerization by disfavoring η -bound Pd(II) intermediates required for isomerization.¹³ While these high energy 18-electron intermediates appear to be accessible in intermolecular systems^{3b,c,e,f} and with the use of nickel,¹⁶ in the current Pd-catalyzed intramolecular case this could be problematic.¹⁷

In conclusion, we have described a catalytic strategy for the stereoselective construction of carbocycles by intramolecular allyl aryl cross-couplings. Further exploration of the scope and applications of this process is in progress and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: morken@bc.edu.

Notes

The authors declare no competing financial interest.

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(17) Employing Ni(cod)₂ in place of Pd(OAc)₂ with (R,R)-Me-DuPhos under the standard reaction conditions results in significantly higher levels of enantioselectivity (80:20 er and 59:41 er, respectively). While it is possible the mode of selectivity may change between the two metals, the greater ease with which Ni can form 18 electron allyl species may be a factor (ref 16).