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Ligand-Controlled Palladium-Catalyzed Regiodivergent Suzuki–Miyaura Cross-Coupling of Allylboronates and Aryl Halides

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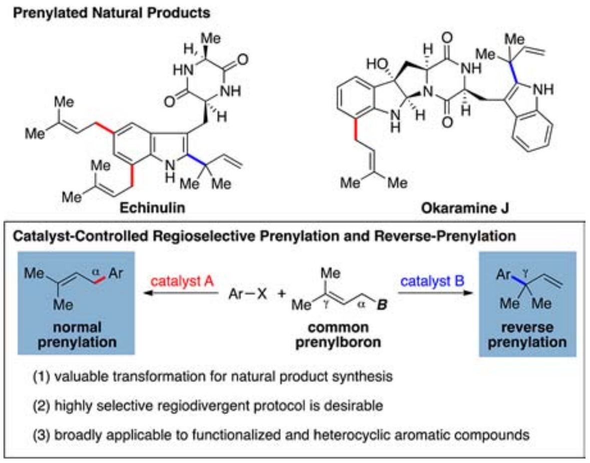
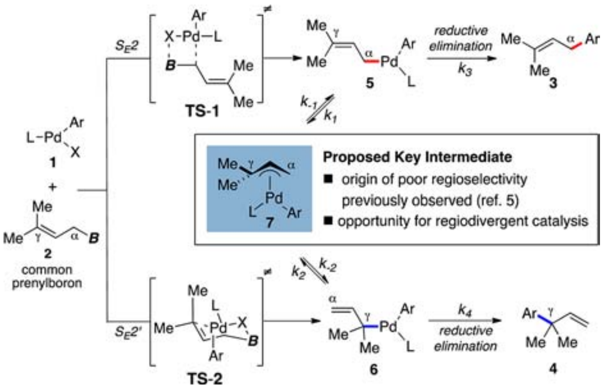
Supporting Information

ABSTRACT: An orthogonal set of catalyst systems has been developed for the Suzuki–Miyaura coupling of 3,3-disubstituted and 3-monosubstituted allylboronates with (hetero)aryl halides. These methods allow for the highly selective preparation of either the α- or the γ-isomeric coupling product.

Scheme 1. Prenylated Natural Products and Proposed Regioselective Allylation of Aryl Halides



Scheme 2. Proposed Mechanism



The broad spectrum of intriguing molecular architectures and biological activities of prenylated and reverse-prenylated natural products[1] has spurred extensive efforts toward the development of efficient methods to prepare these compounds. In this context, the selective syntheses of both of these isomers based on a regiodivergent coupling methodology using a common prenyl-metal species and an aryl halide are very appealing (Scheme 1).[2] Among various types of organometallic reagents, organoboron compounds are most frequently used due to their air and moisture stability, functional group compatibility, ready availability, and low toxicity.[3] However, the successful development of a coupling process involving 3-substituted allylboronates has been hampered by regioselectivity issues (Scheme 2). In principle, a linear σ-allylpalladium complex (**5**) could isomerize to the corresponding branched σ-allylpalladium species (**6**) through a π-allyl intermediate (**7**),[4] thus producing mixtures of isomers (**3** and **4**) following reductive elimination. Moreover, transmetalation of a prenylboron reagent (**2**) with oxidative addition complex **1** could proceed through either an S_E2 or S_E2' pathway, which may also contribute to the poor selectivity often observed.[5] Previously, Szabó[6] and Miyaura[7] have reported good regioselectivity for the formation of the branched product with 3-monosubstituted allylboron reagents. However, a general and practical γ-selective coupling of 3,3-disubstituted allylboronates to prepare branched products that bear a sterically demanding quaternary center (**4**), and in particular, a method for *tert*-prenylation, remains to be developed.[8] To date, Organ's well-tailored NHC-based catalyst remains the only α-selective system to access the linear product (**3**).[9] However, this protocol necessitated the use of strong aqueous base at high temperature (5 M aq KOH in refluxing THF for 24 h), thereby limiting the functional group tolerance. More importantly, a unifying regiodivergent method providing rapid access to both the α- and the γ-regioisomers employing a set of catalysts that are structurally similar but furnish orthogonal selectivities continues to be a daunting challenge. In addition, despite the fact that heterocycles are ubiquitous structural motifs in biologically active compounds, the regioselective allylation of heteroaryl halides has rarely been studied.[10]

To overcome these challenges, we reasoned that the choice of ligand would influence the transmetalation mechanism, the rate of σ–π–σ interconversion, and the rate of reductive elimination and thus represent the key to achieving high regioselectivity. Over the past decade, our research group has been engaged in the design, development, and utilization of bulky biarylphosphine ligands that have proven effective for a broad range of palladium-catalyzed cross-coupling reac-

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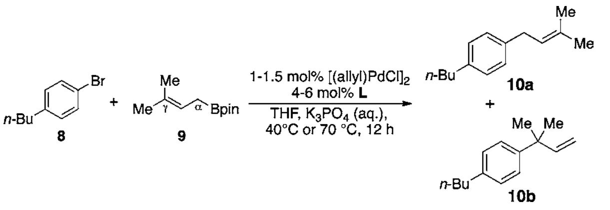
tions.[11,12] In general, the synthesis of these ligands is simple and flexible and allows rational tuning of their steric and electronic properties.[13] Taken together, these features could greatly facilitate the development of highly α- and γ-selective allylation catalysts that are broadly applicable to a diverse array of functionalized aryl halides.

We commenced our study by examining palladium catalysts derived from dialkylbiarylphosphine ligands (Table 1).

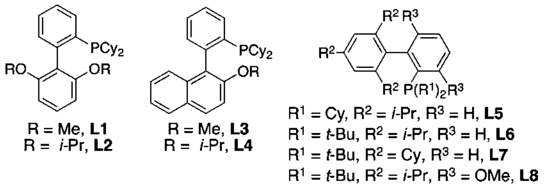
Table 1. Ligand Evaluation[a]



entry	L	α/γ	yield of **10a**	yield of **10b**
1	**L1**	<1:99	<1%	55%
2	**L2**	1:99	<1%	42%
3	**L3**	<1:99	<1%	99%
4	**L4**	17:83	16%	80%
5	**L5**	90:10	63%	7%
6	**L6**	98:2	68% (84%)[b]	<1%
7	**L7**	88:12	53%	7%
8	**L8**	46:64	6%	7%

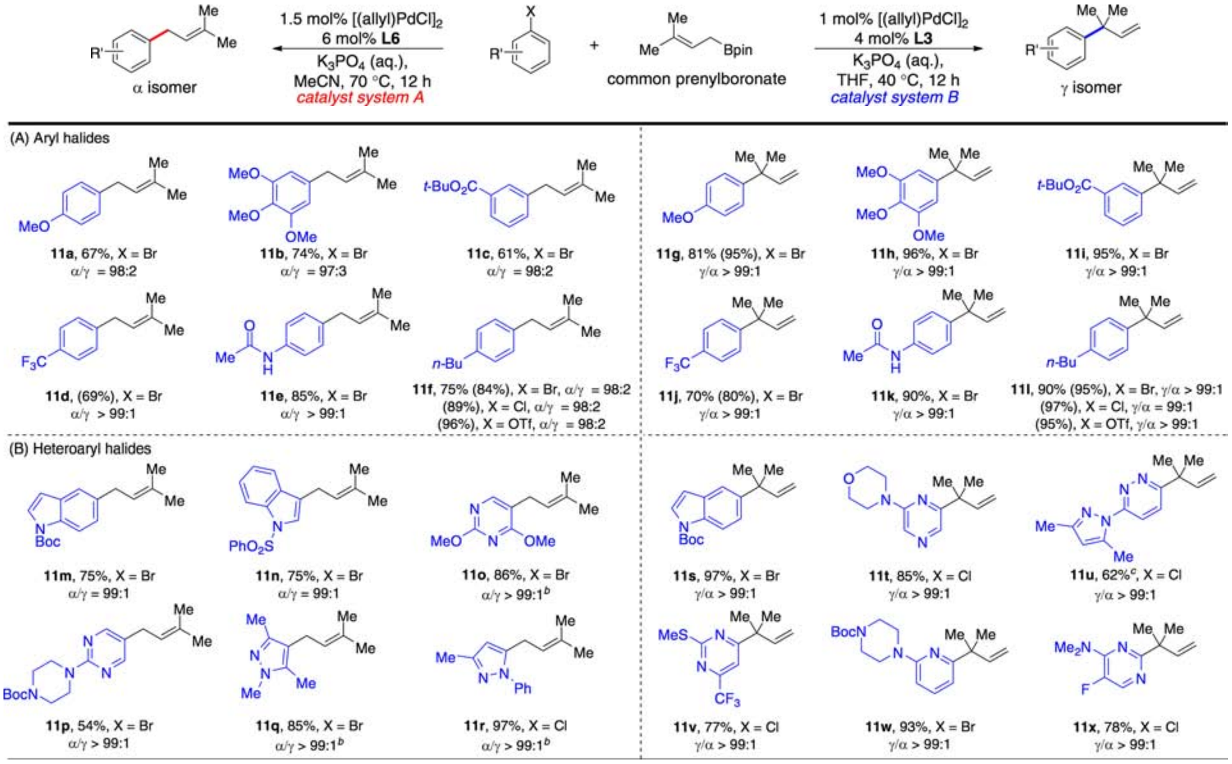
[a]Reactions with **L1**−**L4** were carried out with 1 mol % [(allyl)PdCl]$_2$ and 4 mol % **L** at 40 °C; reactions with **L5**−**L8** were carried out with 1.5 mol % [(allyl)PdCl]$_2$ and 6 mol % **L** at 70 °C. Yields were determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b]Reaction was performed in MeCN.

Although catalysts generated from SPhos (**L1**) and RuPhos (**L2**) provided good regioselectivity for the branched product (**10b**), only moderate conversion of the aryl bromide was observed using 2 mol % Pd. However, the yield of **10b** could be increased dramatically using a catalyst derived from **L3**. Interestingly, replacing the methoxy group on the bottom naphthyl ring of **L3** with an isoproxy group resulted in inferior selectivity (**L4**). At this stage, we hypothesized that the use of more sterically demanding ligands would destabilize and/or inhibit the formation of the branched σ-allylpalladium species **6**, thus favoring the formation of the linear product (**10a**). Indeed, the regioselectivity could be reversed when bulkier di-*tert*-butylbiarylphosphine ligands were employed. In particular, the catalyst generated from *t*-BuXPhos (**L6**) was found to be highly selective for the production of α-isomer, but further increasing the size of the *t*-BuXPhos biaryl backbone (**L7** and **L8**) led to less selective catalysts. After extensive optimization, biphasic MeCN/aq K$_3$PO$_4$ was identified as the optimal reaction media for the α-selective coupling. Thus, under the optimized conditions, the *t*-BuXPhos-based catalyst afforded the linear product in 83% yield with excellent selectivity.



Utilizing both protocols, we examined the substrate scope with respect to the aryl halide component (Table 2). A wide variety of aryl bromides, bearing electron-donating or -withdrawing substituents (**11a**−**11l**), could be effectively converted

Table 2. Substrate Scope of Aryl and Heteroaryl Halides[a]



11a, 67%, X = Br
α/γ = 98:2

11b, 74%, X = Br
α/γ = 97:3

11c, 61%, X = Br
α/γ = 98:2

11d, (69%), X = Br
α/γ > 99:1

11e, 85%, X = Br
α/γ > 99:1

11f, 75% (84%), X = Br, α/γ = 98:2
(89%), X = Cl, α/γ = 98:2
(96%), X = OTf, α/γ = 98:2

11g, 81% (95%), X = Br
γ/α > 99:1

11h, 96%, X = Br
γ/α > 99:1

11i, 95%, X = Br
γ/α > 99:1

11j, 70% (80%), X = Br
γ/α > 99:1

11k, 90%, X = Br
γ/α > 99:1

11l, 90% (95%), X = Br, γ/α > 99:1
(97%), X = Cl, γ/α = 99:1
(95%), X = OTf, γ/α > 99:1

11m, 75%, X = Br
α/γ = 99:1

11n, 75%, X = Br
α/γ = 99:1

11o, 86%, X = Br
α/γ > 99:1[b]

11p, 54%, X = Br
α/γ > 99:1

11q, 85%, X = Br
α/γ > 99:1[b]

11r, 97%, X = Cl
α/γ > 99:1[b]

11s, 97%, X = Br
γ/α > 99:1

11t, 85%, X = Cl
γ/α > 99:1

11u, 62%[c], X = Cl
γ/α > 99:1

11v, 77%, X = Cl
γ/α > 99:1

11w, 93%, X = Br
γ/α > 99:1

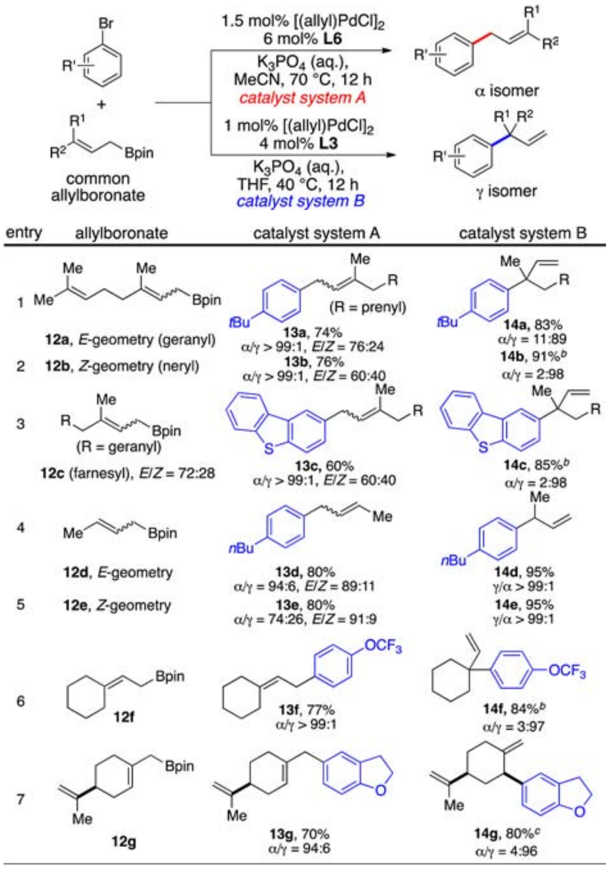
11x, 78%, X = Cl
γ/α > 99:1

[a]Yields are of isolated product, see Supporting Information for details; α/γ ratio and yields in parentheses were determined by ^{1}H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [b]**L5** was used instead of **L6**. [c]60 °C.

to the linear or the branched product with high level of regioselectivity. In addition to aryl bromides, aryl chlorides and triflates were also compatible substrates for this transformation (**11f** and **11l**). While various heteroaryl halides could be transformed (Table 2B), we were unable, in most cases, to develop a set of regiodivergent conditions for these substrates.[14] Still the examples shown represent the most general ones for transforming a variety of difficult heterocyclic substrates.

Next, we sought to extend the scope of allylboronate substrates that could be employed in the Suzuki−Miyaura coupling (Table 3). In general, unsymmetrical 3,3-disubstituted allylboronates (**12a**-**12c**) could be coupled with excellent regioselectivity. Starting from an E/Z mixture of farnesylboronate[15] (**12c**), either the α- or the γ-isomer could also be accessed under these conditions. Similarly, 3-monosubstituted allylboronates (**12d** and **12e**) represented suitable coupling partners with both conditions. It is noteworthy that an α-selective coupling protocol for 3-monosubstituted allylboronates has not been previously described. Tethering the terminal methyl group together with a $(CH_2)_3$ spacer (**12f**) imposed no detrimental effects on regioselectivity. In addition, a cyclic allylboronate (**12g**) could be successfully applied in this reaction, maintaining both good yields and selectivities. Finally, **12g** reacted smoothly to provide **14g** with high diastereocontrol using the γ-selective system.

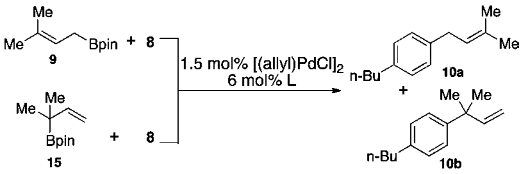
Table 3. Substrate Scope of Allylboronates[a]



[a] Yields are of isolated product, see Supporting Information for details; α/γ ratio was determined by ^1H NMR spectroscopy of the crude reaction mixture; E/Z ratio was determined by GC analysis. [b] 60 °C. [c] Stereochemistry was confirmed by NOESY NMR spectroscopy.

Although these coupling processes are highly regioselective, we observed scrambling of the olefin configuration when unsymmetrical 3,3-disubstitued allylboronates were subjected to system A (Table 3, entry 1−2). For example, geranylboronate (**12a**) and nerylboronate[16] (**12b**) furnished the linear product with different degrees of isomerization of olefin geometry (**13a** and **13b**). Interestingly, with catalyst system B, **12b** delivered higher selectivity for the branched isomer than **12a** (**14a** and **14b**). Taken together, these results suggest the intermediacy of a post-transmetalation π-allylpalladium species (**7**);[17] presumably, the two different (allyl)Pd(Ar)(**L**) species generated from the transmetalation of (Ar)Pd(X)(**L**) with **12a** and **12b** do not fully equilibrate via $\sigma-\pi-\sigma$ interconversion prior to reductive elimination. To gain further insight into the origin of regioselectivity, tertiary allylboronate **15**[18] was subjected to the coupling conditions. With the catalyst derived from **L3**, reaction of boronates **15** or **9** with **8** afforded drastically different results with regard to regioisomer distribution (Table 4, entry 1−2). Again, these results imply that σ-allyl palladium complexes **5** and **6** do not reach equilibrium via a π-allylpalladium intermediate before reductive elimination occurs.[19] In contrast, using **L6**-based catalyst, both **15** and **9** provided excellent selectivity for the linear product (entry 3−4). Therefore, if transmetalation of (Ar)Pd(X)(**L6**) with **9** and **15** furnishes two different σ-allylpalladium complexes (**5** or **6**), the rate of $\sigma-\pi-\sigma$ interconversion is faster relative to reductive elimination to form **10b**. Alternatively, the transmetalation of ArPd(X)(**L6**) with **9** and **15** proceeds via two different pathways, S_E2 and S_E2', respectively, to furnish the same σ-allylpalladium complex (**5**), which does not undergo $\sigma-\pi-\sigma$ isomerization at a rate that is competitive with reductive elimination to form **10a**.

Table 4. Mechanistic Insights



entry	L	boronate	α/γ	yield of **10a**	yield of **10b**
1[a]	**L3**	**9**	<1:99	<1%	99%
2[a]	**L3**	**15**	25:75	20%	52%
3[b]	**L6**	**9**	98:2	84%	<1%
4[b]	**L6**	**15**	>99:1	92%	<1%

[a] Reaction was carried out in THF/aq K_3PO_4 at 40 °C for 12 h. [b] Reaction was carried out in MeCN/aq K_3PO_4 at 70 °C for 12 h; yield and α/γ ratio were determined by ^1H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

In summary, we have developed a complementary set of palladium-catalyzed regiodivergent protocols for the Suzuki−Miyaura coupling of 3-substituted allylboronates with aryl halides that allow for the rapid construction of allylated arene architectures. This method features excellent regioselectivity, enhanced operational simplicity, and a broad scope of aryl halides. Notably, a number of allylated heteroaromatic compounds prepared by the current method would be difficult or tedious to synthesize by other means. Further mechanistic investigations aimed at determining the origin of this regiochemical dichotomy and broadening the application of this method in the context of natural product synthesis are ongoing topics in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): MIT has patents on some of the ligands used in this study from which S.L.B. receives royalty payments.

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