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Pd-Catalyzed Enantioselective Allyl−Allyl Cross-Coupling

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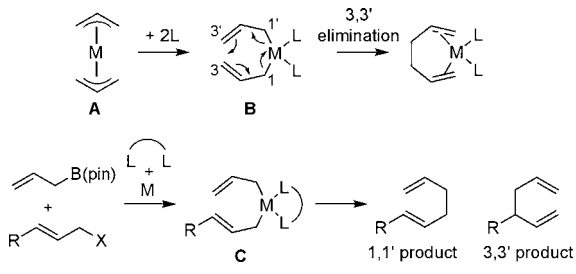
Abstract: The Pd-catalyzed cross-coupling of allylic carbonates and allylB(pin) is described. The regioselectivity of this reaction is sensitive to the bite angle of the ligand, with small-bite-angle ligands favoring the branched substitution product. This mode of regioselection is consistent with a reaction that operates by a 3,3′ reductive elimination reaction. In the presence of appropriate chiral ligands, this reaction is rendered enantioselective and applies to both aromatic and aliphatic allylic carbonates.

The Pd-catalyzed cross-coupling of organic electrophiles with organometallic reagents, especially organoboron derivatives, is broadly developed and has made a significant impact on the way complex molecules are prepared.[1] One exception to this generalization is the cross-coupling of substituted allylmetal reagents. This reaction has received less attention but holds significant promise for asymmetric synthesis;[2] recently reported Pd-catalyzed enantioselective couplings of crotyl boronates and aryl electrophiles are illustrative.[3] Similarly, cross-coupling of allylmetal reagents with allyl electrophiles is attractive because it has the capacity to establish two new stereocenters with concomitant formation of an sp^3-sp^3 carbon−carbon bond.[4] This catalytic reaction is not well developed either, perhaps because of the propensity for π-allyl intermediates to undergo β-hydride elimination[5] (delivering 1,3-dienes) and perhaps because these reactions often lack regioselectivity or favor achiral products. Indeed, unlike the isoelectronic decarboxylative allylation of allyl enol carbonates[6] and the Tsuji−Trost reaction with preformed enolates,[7] allyl−allyl coupling does not benefit from an inherent regiocontrol bias. In this report, we present a paradigm for regiocontrol in allyl−allyl coupling reactions and use it to establish highly regio- and enantioselective catalytic variants.

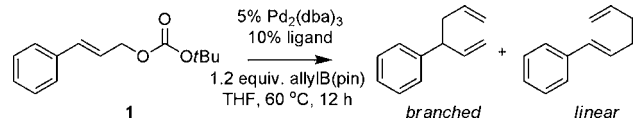
Recent studies in our laboratory have focused on the transition-metal-catalyzed enantioselective addition of allylboronates to unsaturated carbonyls.[8] These reactions proceed by way of oxygenated bis(allyl)metal species, with a 3,3′ reductive elimination being responsible for construction of the C−C bond. The 3,3′ reductive elimination mechanism, as put forward by Echavarren,[4j,9] operates when coordination of a ligand to a bis(allyl)metal species causes both allyl groups to adopt the η^1 bonding mode (as in **B** in Scheme 1) instead of the more common η^3 mode (as in **A**). We surmised that in the case of simple allyl−allyl cross-coupling, bidentate ligands would be most effective in prompting the bis(η^1-allyl) bonding mode and that, if the allyl groups are able to rapidly isomerize at some point on the reaction pathway, the least hindered bis(η^1-allyl) (**C**) might predominate when substitution is present. In such a situation, the selectivity for formation of the chiral, branched 3,3′ elimination product relative to the linear 1,1′ elimination product should be sensitive to the bite angle of the ligand, and this feature provides a potential control element for the reaction.[10]

Scheme 1



Inspired by the observations of Miyaura[11a] and others,[11b,c] our initial experiments probed the reactivity of allylB(pin) and allylic carbonates. Efficient reactivity was observed with carbonate **1**. As shown in Table 1, in the presence of Pd(0) and bidentate ligands, the allyl−allyl cross-coupling reaction occurs, and with small-bite-angle ligands, complete conversion and high selectivity is observed. From the data in Table 1, it is clear that smaller-bite-angle ligands favor the branched product, whereas larger-bite-angle ligands are nonselective. This is consistent with the reaction proceeding through an intermediate such as **C** (Scheme 1); the increased C1−C1′ separation that accompanies small-bite-angle ligands[12] may disfavor the 1,1′ elimination pathway relative to the 3,3′ path.[13]

Table 1. Pd-Catalyzed Branch-Selective Cross-Coupling



entry	ligand	bite angle[a]	% yield[b]	branched/linear[c]
1	PPh_3	−	96	1:>20
2	dpp-benzene	83	70	97:3
3	dppe	85	77	98:2
4	dppp	91	80	97:3
5	dppf	96	43	94:6
6	dppb	98	77	38:62
7	DPEphos	102	58	72:28

[a] Ligand-preferred bite angle (see ref 10b). [b] Yield of purified material. [c] Determined by GC.

With an effective means of controlling the regioselectivity in allyl−allyl cross-coupling reactions in hand, a survey was undertaken to gauge the ability of small-bite-angle chiral bidentate ligands to control the enantioselectivity in the process. 2,2′-Bis(difurylphosphino)-6,6′-dimethoxybiphenyl[14] (**A** in Table 2) was found to deliver the allyl−allyl cross-coupling product with high regio- and enantioselectivity. As depicted in Table 2, the reaction is effective with a number of allyl carbonates, generally delivering the branched substitution product with excellent regio- and enantioselectivity. As shown in entries 1 and 2, *tert*-butyl and methyl carbonates can be used interchangeably in the reaction. It is also noteworthy that the corresponding internal racemic carbonate (entry 3) reacts with levels of selectivity that are comparable to those of primary-alcohol-derived substrates (entries 1 and 2). This observation has mechanistic implications (see below) and is also of practical importance: substrates such as that depicted in entry 3 can be more

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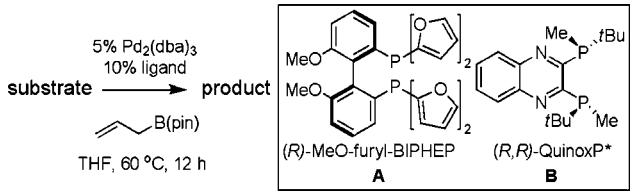
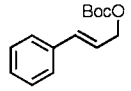
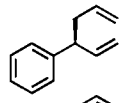
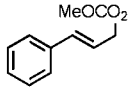
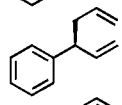
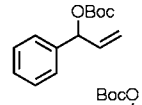
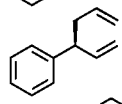
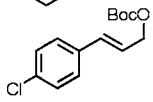
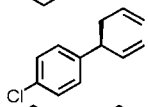
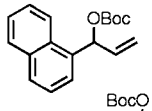
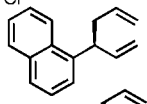
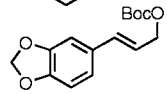
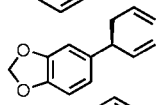
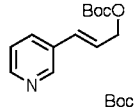
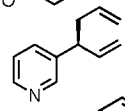
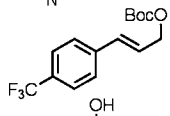
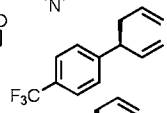
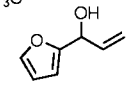
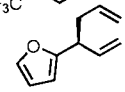
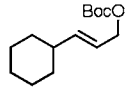
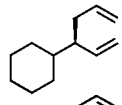
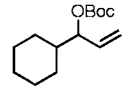
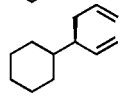
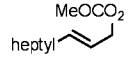
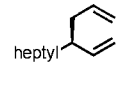
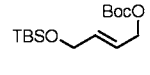
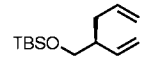
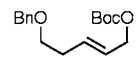
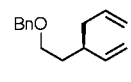
Table 2. Catalytic Enantioselective Allyl−Allyl Cross-Coupling[a]



entry	substrate	product	ligand	yield	regio.	ee
1			A	72	>20:1	91
2			A	69	>20:1	91
3			A	75	>20:1	91
4			A	59	>20:1	90
5[b]			A	87	>20:1	90
6			A	83	>20:1	91
7			A	52	>20:1	90
8			A	60	>20:1	74
9[c]			A	64	>20:1	87
10			A B	35 9	>20:1 3:1	83 94
11			B	63	10:1	91
12			B	80	11:1	84
13[d]			B	91	>20:1	90
14			B	75	>20:1	85

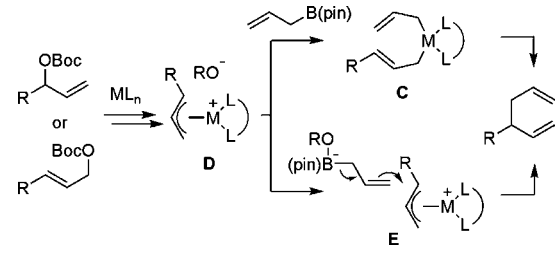
[a] Unless otherwise noted, reactions employed 1.2 equiv. of allylB(pin). [b] Reaction with 1.5 equiv of allylB(pin). [c] Reaction with 2.0 equiv allylB(pin) for 36 h. [d] With the addition of 1.2 equiv of Cs_2CO_3.

accessible than substrates such as in entries 1 and 2. Entries 4−7 and 9 show that sterically encumbered substrates and those possessing halogens or heteroatoms are also suitable partners for the reaction. Remarkably, as the example in entry 9 indicates, unactivated alcohols are reactive leaving groups in the coupling reaction, although this feature currently appears to be most effective with electron-rich substrates (additional data not shown). Currently, one limitation of the reaction is that an electron-deficient allyl electrophile was observed to react with diminished levels of selectivity (entry 8).

A notable observation with respect to synthetic utility is that aliphatic substrates also participate in the allyl−allyl coupling reaction: while the example in entry 10 occurred with moderate selectivity using (*R*)-MeO-furyl-BIPHEP, the selectivity could be improved substantially by employing (*R,R*)-QuinoxP*[15] as the ligand. The problematic low yield in entry 10 was easily ameliorated by employing the regioisomeric internal carbonate depicted in entry 11. It merits mention that linear alkyl substrates as well as those bearing allylic and homoallylic oxygen functionality are readily processed in the reaction (entries 12−14) and deliver the branched product efficiently and with good regio- and enantioselectivity.

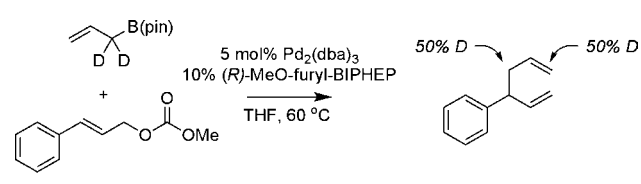
The observation that isomeric allylic carbonates (i.e., entries 1−3, 10, and 11) react with similar levels of enantioselectivity suggests that oxidative addition of the allyl carbonate to Pd(0) provides a common intermediate (such as **D** in Scheme 2). Subsequent reaction with allylB(pin) might occur by transmetalation from boron to Pd followed by inner-sphere 3,3′ reductive elimination, as mentioned above (see **C** in Scheme 2). Alternatively, the reaction might occur by backside outer-sphere attack of the allylboronate on a η^3-allyl−Pd complex (**E** in Scheme 2).[16]

Scheme 2



To distinguish between the above-described mechanisms, isotopically labeled allylB(pin) was employed as the substrate in the allyl−allyl coupling reaction (Scheme 3). When this experiment was conducted in the presence of the chiral catalyst, the deuterium label was found at both allyl termini in the reaction product (recovered allylBpin was unscrambled). Since nucleophilic addition involving allylmetal reagents often occurs by an S_E2' reaction mechanism,[17] it might be expected that the outer-sphere pathway would proceed without isotope scrambling. Alternatively, S_E2' transmetalation[8b,18] followed by equilibration of the bis(allyl)Pd complex may account for the reaction outcome. Along these lines, it should be noted that while four-coordinate bis(allyl)Pd complexes most often adopt the bis(η^1) bonding mode (such as in **C** in Scheme 2), (η^1-methallyl)(η^3-methallyl)Pd(dcpe) is a known compound whose existence supports the accessibility of intermediates required for isotope scrambling.[19]

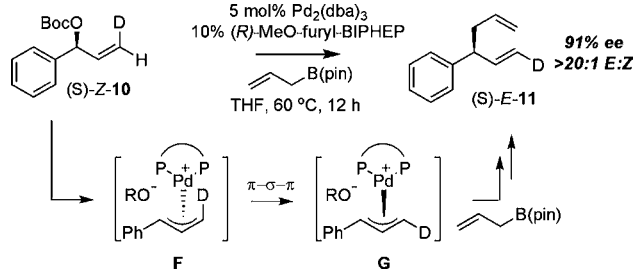
Scheme 3



To further validate the proposed inner-sphere reductive elimination pathway, enantiomerically enriched (*S*)-*Z*-**10** (Scheme 4) was prepared and subjected to the asymmetric cross-coupling with (*R*)-MeO-furyl-BIPHEP as the ligand. This reaction provided (*S*)-*E*-**11** as the sole product in 91% ee. With the assumption that conversion of (*S*)-*Z*-**10**

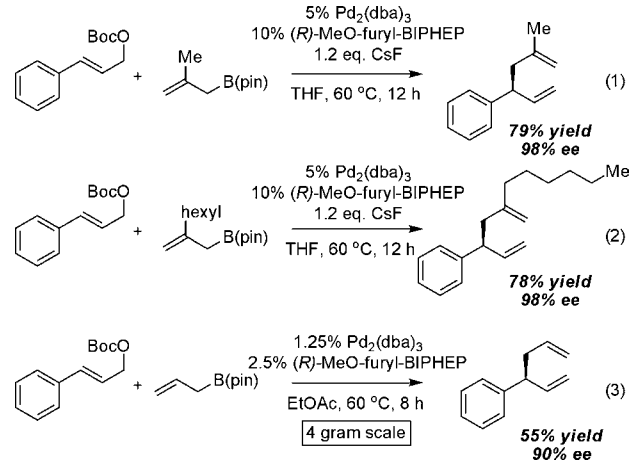
to the derived π-allyl complex occurs by an anti displacement of the leaving group (to give **F**), as is known to occur for related systems,[20] it can be concluded that (*S*)-*E*-**11** can only be produced by C−C bond formation syn to palladium after the metal has migrated to the opposite face of the cinnamyl-derived allyl fragment (**G** or related); this outcome is consistent only with an inner-sphere reductive elimination.

Scheme 4



Substituted allyl boronates are readily prepared by Miyaura borylation of the corresponding allyl acetates.[21] With this strategy, both 2-methyl- and 2-hexyl-substituted allyl boronates were prepared and employed in the allyl−allyl cross-coupling reaction. With (*R*)-MeO-furyl-BIPHEP as the ligand, both compounds underwent smooth cross-coupling with the cinnamyl alcohol-derived carbonate and provided products with excellent levels of selectivity (eqs 1 and 2 in Scheme 5). To further probe the practical utility of the allyl−allyl cross-coupling reaction, the experiment described by eq 3 in Scheme 5 was carried out. It was found that the catalyst loading could be lowered to 2.5 mol % palladium and that the THF solvent typically employed in the cross-coupling could be replaced with ethyl acetate. Under these conditions, the allyl−allyl coupling could be executed on larger scale and still furnished the product in good enantioselectivity, albeit with some erosion of efficiency.

Scheme 5



In conclusion, a highly regio- and enantioselective allyl−allyl coupling reaction has been described. The regiochemical outcome of the reaction and the described isotope-labeling experiments are consistent with a pathway involving 3,3′ reductive elimination of bis(allyl)Pd complexes. An important feature of the reaction is that it provides enantiomerically enriched vicinal $\pi-\pi$ systems that are not accessible by the Cope rearrangement, and this may find use in organic synthesis.

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

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