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Diastereocontrol in Asymmetric Allyl−Allyl Cross-Coupling: Stereocontrolled Reaction of Prochiral Allylboronates with Prochiral Allyl Chlorides

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Supporting Information

ABSTRACT: Palladium-catalyzed allyl−allyl cross-coupling was investigated with substituted prochiral allylic boronates. These reactions deliver products bearing adjacent stereocenters, and the issue of diastereocontrol is therefore paramount. Under appropriately modified conditions, this allyl−allyl coupling strategy was found to apply to a range of substrates, generally occurring with high enantioselectivity (92:8 to >99:1 er) and good diastereoselection (4:1 to 14:1 dr).

Vicinal alkenes are common motifs in natural products and in synthetic intermediates. Retrosynthetically, these substructures indicate the Cope rearrangement,[1] a reaction that occurs with predictable relative stereochemical outcomes, but which has not been developed from the standpoint of asymmetric catalysis.[2] A significant hurdle preventing the development of such a process is that the conversion of achiral linear substrates to chiral, internally substituted vicinal alkenes (eq 1, Scheme 1) is not only reversible but also thermodynamically disfavored. As an alternative catalytic enantioselective route to chiral vicinal alkenes, we have recently described the catalytic asymmetric allyl−allyl cross-coupling between prochiral allylic electrophiles and unsubstituted allylboronates (Scheme 1, R_2 = H).[3−5] This reaction delivers vicinal $\pi-\pi$ systems by a reaction that appears to proceed by an inner-sphere 3,3′ reductive elimination[6] from a bis(allyl)Pd intermediate.[7] In this report, we describe a protocol whereby prochiral γ-substituted allylboronates can participate in cross-coupling reactions with allyl electrophiles. These processes deliver products bearing adjacent tertiary stereocenters, and they are not only diastereoselective but also occur with excellent levels of enantioselection.[8]

Critical concerns that face development of the above-described allyl−allyl coupling reaction are (1) whether 3,3′ reductive elimination can facilitate coupling of two hindered tertiary carbon centers or whether coupling of the less hindered 1 and 1′ carbons will predominate; (2) whether coupling of the two prochiral carbon atoms will occur with diastereocontrol; and (3) whether the reaction will maintain useful levels of enantiocontrol. Initial experiments focused on the Pd(0)-catalyzed reaction between Boc-protected phenyl vinyl carbinol (**A**, X = OBoc) and *cis*-crotylB(pin). As depicted in Table 1 (entry 1), in the presence of (*R*)-methoxy(furyl)biphep,[9] this reaction occurred with low efficiency but with a level of enantiocontrol (99:1 er) that far surpasses other allyl−allyl coupling reactions. Notably, this reaction also occurred with excellent regioselectivity (>20:1) and with good levels of diastereocontrol (4:1 *anti*:*syn*). It was noted that, in addition to the allyl−allyl coupling product, this reaction generated significant amounts of ethereal products, presumably

Scheme 1

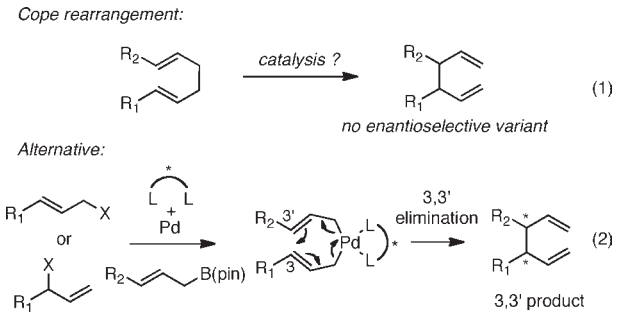
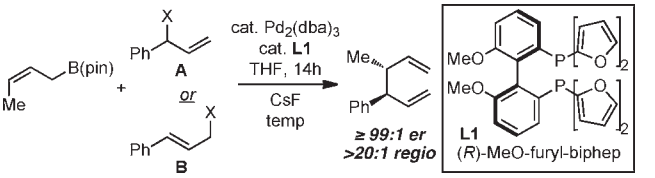


Table 1. Optimization of Allyl−Allyl Cross-Coupling with CrotylB(pin)[a]



entry	E^+ (X)	CsF (equiv)	temp (°C)	Pd (%)	dr	yield (%)
1	**A** (OBoc)	none	60	10	4:1	25
2	**A** (OBoc)	3	60	10	4:1	61
3	**A** (OBoc)	3	rt	10	6:1	50
4	**A** (OAc)	3	rt	10	5:1	26
5	**A** (OTFA)	3	rt	10	6:1	61
6	**B** (Cl)	3	rt	2.5	6:1	72
7	**B** (Cl)	10	rt	2.5	6:1	90

[a] Reactions were conducted for 14 h at 22 °C with 1:1 **L1**:Pd(0) and employed 1.2 equiv of the allylboronate relative to the allylic chloride. Yield refers to isolated yield of the diastereomer mixture. Diastereoselectivity was determined by ^{1}H NMR analysis, and enantioselection was determined by GC analysis on a chiral stationary phase.

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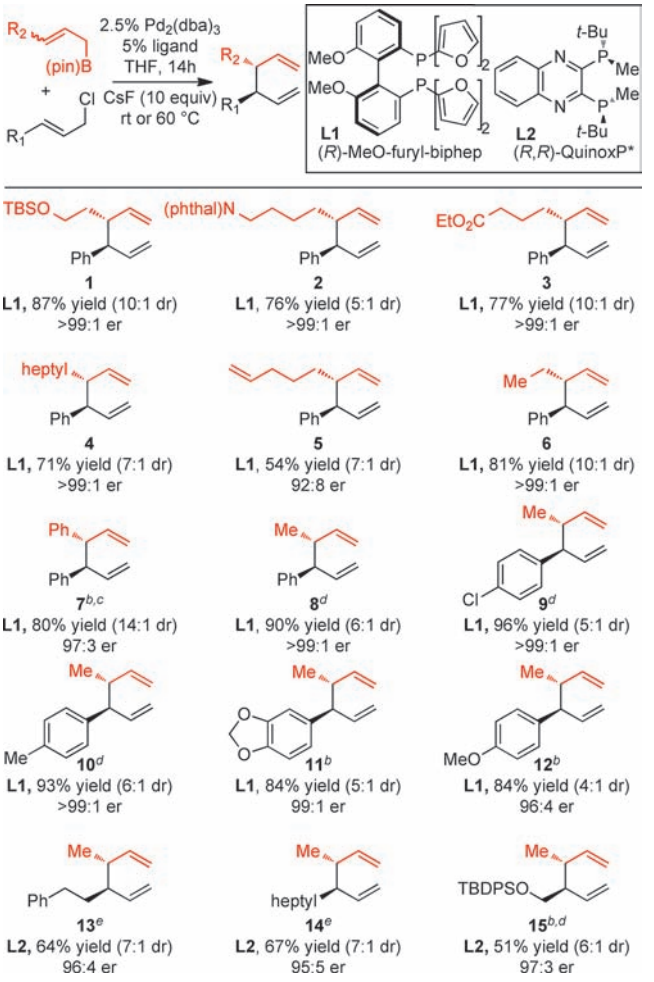
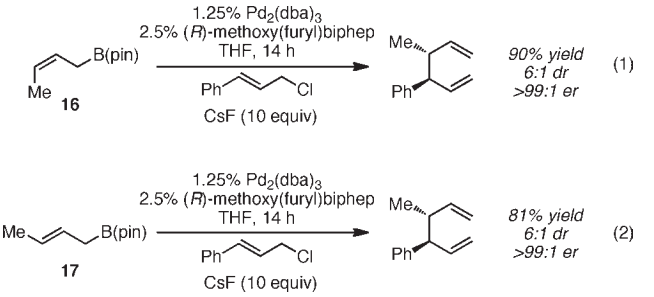
Table 2. Catalytic Diastereo- and Enantioselective Allyl–Allyl Cross-Coupling[a]



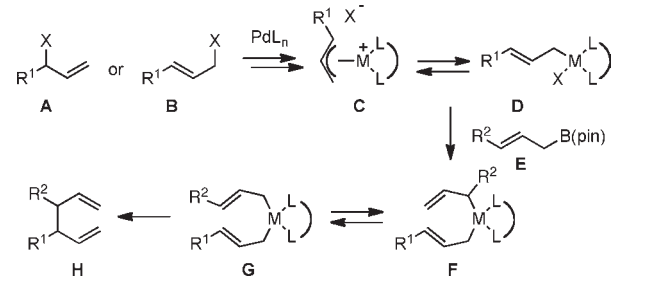
[a] *E*-Allylic boronate was employed for entries 5 and 7, *Z* isomer for others. Unless otherwise noted, reactions were conducted for 14 h at 22 °C and employed 1.2 equiv of the allyl boronate relative to the allylic chloride. Yield refers to isolated yield of the diastereomer mixture and is an average of two experiments. Diastereoselectivity was determined by GC or ^{1}H NMR analysis; enantioseletion was determined by GC, SFC, or HPLC analysis on a chiral stationary phase. Unless otherwise noted, regioselection >20:1. [b] Reaction at 60 °C. [c] Isolated material contains 40% of regioisomeric products. [d] Reaction employed 2.5% Pd_2dba_3 and 5% **L1**. [e] Reaction at 60 °C in 5:1 THF/H_2O.

derived from addition of eliminated butoxide to an intermediate (allyl)Pd complex. Considering that transmetalation with allylmetal reagents often occurs by an S_E2' pathway,[10] it was thought that the added substitution of the crotyl reagent, relative to the allyl reagent, hinders the transmetalation step. To improve reactivity, CsF was examined as an additive that would facilitate transmetalation,[11] and, as shown in entries 2 and 3, this led to improved yields at both 60 and 22 °C. Notably, diastereoselectivity was enhanced when the reaction was conducted at room temperature (entry 3) while still maintaining high enantio- and regioselection. To improve the reaction efficiency further, electrophiles bearing more labile leaving groups were examined. Of acetate, trifluoroacetate, and chloride, the chloride leaving group was optimal, and, in the presence of 10 equiv of CsF and only 2.5 mol % palladium loading, the substrate was converted to

Scheme 2



Scheme 3



the product in 90% yield and in excellent enantioselectivity (>99:1 er, entry 7). A significant practical feature of the allylic chloride substrates is that they may be generated directly from either internal or terminal allylic alcohols by treatment with $SOCl_2$, and they can be employed directly, without purification.

With an effective protocol in place for enantio- and diastereoselective allyl–allyl coupling reactions, the substrate range of the reaction was examined. As depicted in Table 2, diastereocontrol is generally >5:1, and enantioselection is excellent for most substrates. While cis boronates, readily available from diene hydroboration[12] (compounds **1**–**6**), were employed effectively, it was also found that the trans boronates react selectively (product 7) and in good yield. Critically, a number of functional groups are tolerated in the allyl boronate reagent, with silyl ethers, esters, imides, and pendant alkenes all remaining intact over the course of the reaction. As demonstrated by reactions that deliver compounds **9**–**12**, substitution on the cinammyl chloride electrophile is similarly tolerated. A last point to mention is that the coupling involving nonaromatic electrophiles (compounds **13**–**15**) did not furnish the product when (*R*)-methoxy(furyl)biphep was employed; however, with QuinoxP*[13] as the ligand, these reactions were effective and furnished the product in outstanding enantiomeric purity.

As mentioned above, both cis and trans boronates participate in selective allyl–allyl coupling reactions. To assess whether they provide the same experimental outcome, the direct comparison in Scheme 2 was undertaken. Thus, *E*-cinnamyl chloride was treated with both *Z* and *E* crotylboronates (**16** and **17**). Under standard reaction conditions, the allyl–allyl coupling products were obtained in nearly identical yields and levels of selectivity. A mechanism consistent with these observations is depicted in Scheme 3. We propose that, subsequent to transmetalation between the substituted allylboronate (**E**) and an intermediate allyl palladium chloride complex (either **C** or **D**[14]), the boronate-derived

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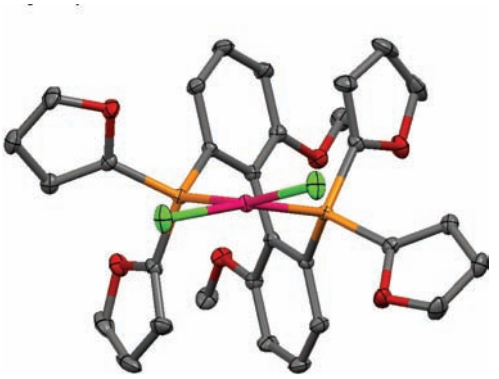

Figure 1. X-ray structure of (*R*)-methoxy(furyl)biphep·$PdCl_2$. Elipsoids are shown at 50% probability level.

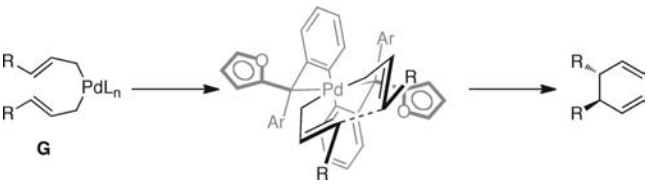

Figure 2. Model for stereochemical outcome in allyl−allyl couplings.

allyl fragment is able to undergo isomerization (minimizing steric effects to give **G**) prior to stereochemistry-determining reductive elimination to give **H**.

To gain a sense for the stereocontrol mechanisms that underlie this and other allyl−allyl coupling reactions, the crystal structure of (*R*)-methoxy(furyl)biphep complexed to $PdCl_2$ was determined. As depicted in Figure 1, the *R* configuration of the biaryl ligand causes the cyclic chelate involving Pd to adopt the λ skew conformation, with the furyl rings adopting pseudoaxial and pseudoequatorial postions about the seven-membered ring. The pseudoequatorial furyl rings impinge on the Pd square plane in a manner that causes the chlorine atoms to cant above and below the plane, and this is an important feature with respect to stereoinduction in allyl−allyl couplings (*vide infra*).

In accord with the experiments described above, we proposed that reductive elimination from bis(*trans*-η^1-allyl)Pd complex **G** (Scheme 3) is the stereochemistry-determining step and that this elimination occurs in a 3,3′ mode. Computational studies by Echavarren[6b] concluded that such reactions occur through chair-like transition structures. Collectively, these data suggest that a favored reaction path is that depicted in Figure 2. In this model, the η^1-allyl ligands are each canted in a manner that minimizes interaction with the pseudoequatorial furyl rings of the ligand. This causes one chair conformer to be favored (shown) over the other and leads to high asymmetric induction.

In conclusion, we have described a simple but highly effective method for establishing vicinal stereocenters in a catalytic asymmetric fashion. Analysis of ligand−metal structures allows for straightforward predictions of the stereochemical outcome of these reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Characterization and procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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