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Enantioselective Construction of All-Carbon Quaternary Centers by Branch-Selective Pd-Catalyzed Allyl−Allyl Cross-Coupling

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Supporting Information

ABSTRACT: The Pd-catalyzed cross-coupling of racemic tertiary allylic carbonates and allylboronates is described. This reaction generates all-carbon quaternary centers in a highly regioselective and enantioselective fashion. The outcome of these reactions is consistent with a process that proceeds by way of 3,3′-reductive elimination of bis-(η^1-allyl)palladium intermediates. Strategies for distinguishing the product alkenes and application to the synthesis of (+)-α-cuparenone are also described.

The catalytic enantioselective construction of all-carbon quaternary centers remains a challenging task in organic synthesis.[1] Relative to reactions that establish tertiary centers, efficient reactions that form quaternary centers are often much more difficult to develop because of barriers imposed as a result of establishing highly congested carbon centers; selectivity is also more challenging as a result of the diminished steric bias between the enantiotopic faces of substrates and intermediates. In terms of catalytic C−C bond-forming constructions of quaternary centers, enantioselective cycloadditions, Heck reactions,[2] enolate α-arylations,[3] and enolate α-allylations[4] have proven to be valuable strategies. Conjugate addition[5] and allylic substitution[6] reactions have also proven to be of significant value. Under the purview of Cu catalysis, S_N2' allylic substitutions can offer high levels of enantiocontrol in the construction of quaternary centers.[7] However, these reactions generally require construction of isomerically pure trisubstituted alkene substrates (i.e., **A** or **B** in Figure 1). While Ru, W, and Ir complexes undergo branch-selective allylic substitution with either internal or terminal allylic electrophiles, $\pi-\sigma-\pi$ isomerization with these complexes is generally slower than nucleophilic addition, and thus, as in the case of copper complexes, the use of isomerically pure substrates is required.[8] In contrast, Pd and Mo allyl complexes undergo rapid $\pi-\sigma-\pi$ isomerization and under appropriate conditions can favor the branched addition product. This feature allows these complexes to process mixtures of stereoisomeric and regioisomeric allylic electrophiles (i.e., **A**−**D** in Figure 1).[9] With these catalysts, remarkable progress in the enantioselective substitution of allylic electrophiles to generate tertiary centers has been made; however, only three examples offering a protocol for the asymmetric construction of all-carbon quaternary centers by branch-selective substitution reactions have appeared. Trost described Pd-catalyzed enantioselective substitutions of isoprene monoepoxide and more recently developed a substrate-specific linalylation reaction.[10] Additionally, Hou described the Pd-catalyzed addition of malonates to tertiary allylic acetates, wherein

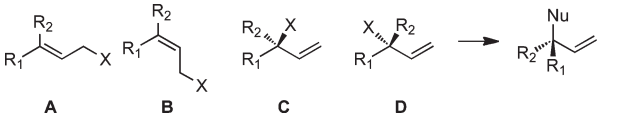
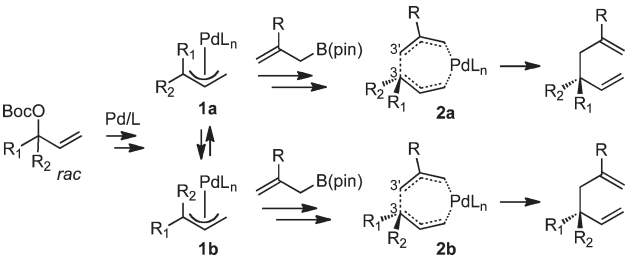


Figure 1. Substrate classes for allylic substitution.

Scheme 1



a key requirement for high selectivity is the use of hindered substrates (e.g., 1-napthyl derivatives).[11] In this manuscript, we detail an effective protocol for Pd-catalyzed enantioselective construction of quaternary centers by allylic substitution. Notably, this reaction employs readily available racemic tertiary allylic carbonates and provides high levels of regio- and enantioselectivity across a range of substrates.

We recently described a Pd-catalyzed regio- and enantioselective allyl−allyl cross-coupling that enables the asymmetric assembly of tertiary stereocenters (Scheme 1; R_1 = aryl, alkyl; R_2 = H).[12] Mechanistic experiments suggested that this transformation likely proceeds by way of π-allyl complexes (**1a** and **1b**) and that a critical feature of the mechanism is the likely intermediacy of bis-(η^1-allyl)palladium intermediates. These compounds undergo inner-sphere 3,3′-reductive elimination[13] (**2a**/**2b** in Scheme 1), thereby delivering the branched allylation products selectively. In light of the discussion above, it was of interest to determine whether this reaction could be extended to the much more demanding case of quaternary center assembly. A primary concern in developing such a process arises from the fact that with tertiary allylic carbonates, mixtures of syn and anti π-allyl complexes (**1a** and **1b**) would likely be generated, and their interconversion, which would be necessary for a stereoconvergent reaction, would require access to hindered tertiary η^1-allylpalladium intermediates.

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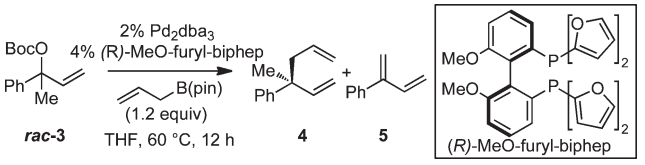
Table 1. Optimization of the Allyl−Allyl Cross-Coupling of 3



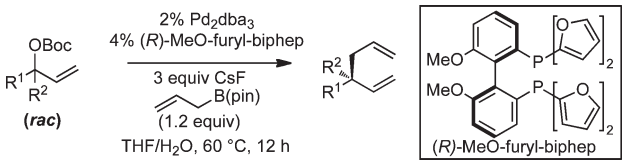
entry	variation of conditions	4:5[a]	yield[b]	er of 4[c]
1	10% catalyst	1:1	38	96:4
2	10% catalyst, Cs_2CO_3 (1.2 equiv)	2:1	90	96:4
3	10% catalyst, CsF (1.2 equiv)	5:1	79	96:4
4	CsF (3 equiv)	9:1	82	95:5
5	CsF (10 equiv)	20:1	77	95:5
6	THF/H_2O (10:1)	14:1	88	96:4
7	CsF (3 equiv), THF/H_2O (10:1)	>20:1	90	96:4

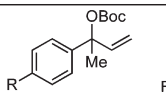
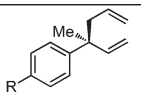
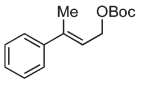
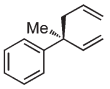
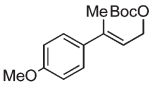
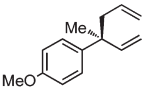
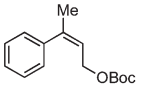
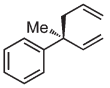
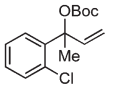
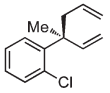
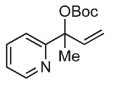
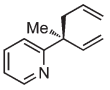
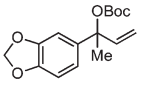
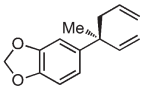
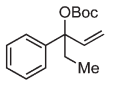
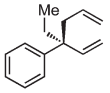
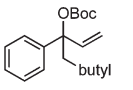
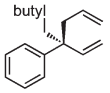
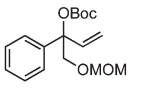
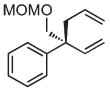
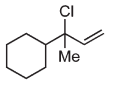
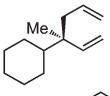
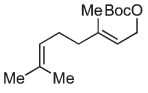
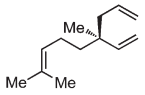
[a] Determined by ^{1}H NMR analysis. [b] Isolated yield of purified product. Compounds **4** and **5** were inseparable by chromatography, and the yield refers to the mixture. [c] Determined by chiral GC chromatography.

To initiate these studies, racemic allyl carbonate **3** was subjected to cross-coupling with allylB(pin), 5 mol % $Pd_2(dba)_3$, and 10 mol % MeO-furyl-biphep.[14] As depicted in entry 1 of Table 1, this reaction indeed delivered the allyl−allyl coupling product **4** with very high levels of enantiomeric purity; however, a significant amount of 1,3-diene **5** was generated, and the reaction proceeded with very low efficiency. While **5** might be produced from an intermediate bis(η^1-allyl)Pd complex by intramolecular H-atom abstraction (to generate propene),[15] it might also be produced prior to transmetalation by elimination from the allyl intermediate (i.e., **1** or related; Scheme 1).[16] That the latter process may operate was verified by treating *rac*-**3** with the catalyst in the absence of allylB(pin); this experiment provided complete conversion to **5** in 12 h. To minimize this side reaction during the coupling process, additives thought to accelerate transmetalation were examined. Both Cs_2CO_3[17] and CsF[18] proved beneficial (entries 2 and 3) and enhanced the **4**:**5** ratio in a concentration-dependent manner. Since addition of water has also been shown to facilitate transmetalation,[19] aqueous solvent systems were examined and also found to minimize production of the 1,3-diene (entry 6). Optimal conditions were found to involve CsF (3 equiv) and employ 10:1 THF/H_2O as the solvent system. In this case, the allyl−allyl coupling product was obtained in excellent yield with high enantioselectivity as a single (>20:1) regioisomer (entry 7).

The scope of the catalytic allyl−allyl coupling was examined using a panel of substrates. As depicted in Table 2, a range of aromatic tertiary allylic carbonates participated in the reaction, and a good level of substitution was tolerated. Notably, oxygen and halogen-substituted substrates were processed in good yield with good chemo- and enantioselectivity. Importantly, ortho substitution in the substrate was also tolerated, as the example in entry 8 indicates. In addition to the methyl ketone-derived electrophiles in entries 1−10, longer alkyl chains and those bearing protected oxygenation were also converted to the corresponding chiral 1,5-dienes with excellent selectivity. Lastly, the results for the aliphatic substrates in entries 14 and 15 suggested that excellent enantiodiscrimination does not require an aromatic substituent. As long as the two enantiotopic groups on the

Table 2. Substrate Scope for the Allyl−Allyl Cross-Coupling



entry	substrate	product	% yield (pdt:elim)[a]	er[b]
1	 R=H		90 (>20:1)	96:4
2	R=Br		90 (20:1)	94:6
3	R=Me		76 (17:1)	96:4
4[c]	R=Cl		70 (>20:1)	95:5
5			86 (>20:1)	96:4
6[d]			83 (12:1)	95:5
7[e]			80 (11:1)	96:4
8[f]			97 (4:1)	92:8
9[g]			81 (>20:1)	95:5
10[c,d]			94 (6:1)	96:4
11[d]			97 (6:1)	94:6
12[d]			78 (6:1)	94:6
13[g]			58 (>20:1)	90:10
14[e,g,h]			45 (8:1)	93:7
15[f]			96 (4:1)	76:24

[a] Isolated yield of purified product. The product:1,3-diene (elimination product) ratio (pdt:elim ratio) was determined by ^{1}H NMR analysis. In general, the product and the 1,3-diene were inseparable by chromatography, and the yield refers to the mixture. [b] Determined by chiral GC, SFC, or HPLC analysis and the average of two or more experiments. [c] Substrate was a mixture of branched and linear allylic carbonates. [d] Reaction at 80 °C. [e] Reaction for 36 h. [f] Reaction employed 10 equiv of CsF and 3 equiv of allylB(pin) in 5:1 THF/H_2O. [g] Reaction in anhydrous THF. [h] Reaction employed a mixture of linear and branched allylic chloride substrates.

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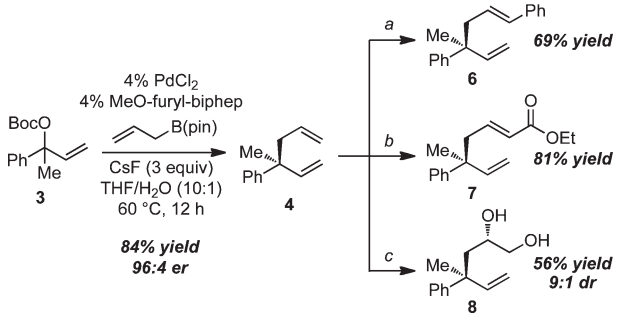
Scheme 2[a]



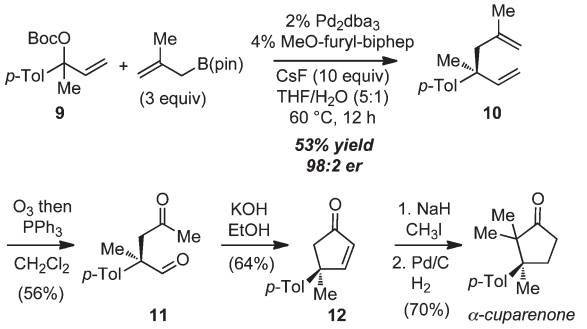
[a] Conditions: (*a*) PhI, 10 mol % $Pd(OAc)_2$, Bu_4NCl, DMF, 80 °C, 16 h. (*b*) 5 mol % HG2 catalyst, ethyl acrylate, CH_2Cl_2, 40 °C, 20 h. (*c*) $B_2(pin)_2$, 3 mol % $Pt(dba)_3$, 3.6 mol % 3,5-Ph_2-taddol-PPh, THF; then NaOH, H_2O_2.

substrate bear a significant difference in size, high levels of selectivity can be observed. For example, cyclohexyl and methyl (entry 14) were well-distinguished, and the product was obtained with 92:8 er, whereas the similar size of the alkyl chain and the methyl group in entry 15 resulted in diminished stereoselection. The example in entry 14 also highlights the fact that allylic halides may serve as coupling partners in this process.

An important feature of the allyl−allyl cross-coupling reaction is that it can employ racemic tertiary allylic alcohol derivatives, which are readily prepared by addition of vinylmagnesium bromide to the corresponding ketone. In some cases, however, the regioisomeric primary allylic electrophile might be more readily available, so it was important to determine whether these substrates could be employed. As depicted in entries 5−7, both the *E* and *Z* terminal allylic carbonates were converted to the same quaternary-center-containing coupling product with similar levels of efficiency and selectivity. One noteworthy difference between the *E* and *Z* substrates is that the *Z* substrate reacted at a substantially lower rate (36 vs 12 h). It is tenable that in the *Z* configuration, the aryl group is oriented orthogonal to the alkene σ-bond framework to avoid an A(1,3) interaction; in this orientation, the aryl group may shield the alkene from attack, thereby slowing the oxidative addition step.

To examine features associated with practicality, the experiments in Scheme 2 were undertaken. First, it was shown that a more economical Pd source, $PdCl_2$, can be employed and that the reaction can be conducted without the aid of a glovebox. Second, it was found that the alkenes in the cross-coupling products could be effectively differentiated, an important prerequisite for target-directed synthesis. As depicted in Scheme 2, this objective may be accomplished in a number of ways. Reaction *a* shows that a regioselective Heck reaction[20] wherein the less-hindered alkene is selectively transformed can be accomplished. Ostensibly, the high regioselection in this reaction results from incipient torsional strain should the other olefin undergo migratory insertion with an arylpalladium complex. Likely for similar reasons, olefin cross-metathesis[21] converts **4** to unsaturated ester **7** in a highly regio- and stereoselective fashion (reaction *b*). Lastly, regio- and diastereoselective dihydroxylation can be accomplished by way of Pt-catalyzed diboration in the presence of a chiral phosphonite catalyst (reaction *c*).[22] In this case, diastereocontrol results from the enantiofacial selectivity that occurs in the diboration step.

Scheme 3



As the preceding data suggest, allylB(pin) can be employed with a broad range of substituted allyl electrophiles. As depicted in Scheme 3, substitution on the allylboronate was also tolerated. Coupling of carbonate **9** and methallylB(pin) occurred with excellent levels of asymmetric induction. Importantly, reaction product **10** is well-suited for construction of cyclopentenones. As depicted, ozonolysis delivered ketoaldehyde **11**, which was converted to cyclopentenone **12** by intramolecular aldol condensation. In analogy to a study by Meyers,[23] **12** was converted to α-cuparenone.[24] This five-step route from **9** represents the shortest catalytic asymmetric synthesis of this target structure.[25]

In conclusion, the 3,3′-reductive elimination reaction that operates in the course of allyl−allyl cross-couplings allows for contrasteric C−C bond constructions between allylic electrophiles and allylboronates. Importantly, these reactions can be used for the asymmetric construction of hindered quaternary carbon centers. Further studies of the utility of these processes are in progress.

■ ASSOCIATED CONTENT

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

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