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Catalytic Stereospecific Allyl–Allyl Cross-Coupling of Internal Allyl Electrophiles with AllylB(pin)

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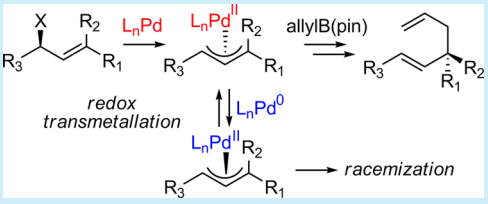
Supporting Information

ABSTRACT: Application of internal electrophiles in catalytic stereospecific allyl–allyl cross-coupling enable the rapid construction of multisubstituted 1,5-dienes, including those with all carbon quaternary centers. Compounds with minimal steric differentiation can be synthesized with high enantiomeric excess.



Compounds bearing vicinal 1,5-diene frameworks are versatile building blocks in chemical synthesis. While one strategy for their direct synthesis is the metal catalyzed cross-coupling of allyl electrophiles and allyl nucleophiles,[1] an inherent challenge is the difficulty in controlling regioselectivity of the reaction. Linear-selective allyl–allyl cross-couplings have been well developed.[2] Recently, our laboratory has developed several palladium-catalyzed methods to synthesize 1,5-dienes in a branch-selective and highly enantioselective fashion.[3] The excellent selectivity observed in these reactions is reliant on $\pi-\sigma-\pi$ isomerization[4] and 3,3′-reductive elimination processes, both of which are influenced by the choice of chiral bidentate phosphine ligands on the catalyst.[5,6] As depicted in Figure 1, our previous studies employed terminal allyl electrophiles and capitalized on the ability of Pd to migrate from one prochiral allyl face to the other (**A** ↔ **B**). To broaden the scope of selective allyl–allyl cross-coupling reactions further, we have explored the use of internal allyl electrophiles.

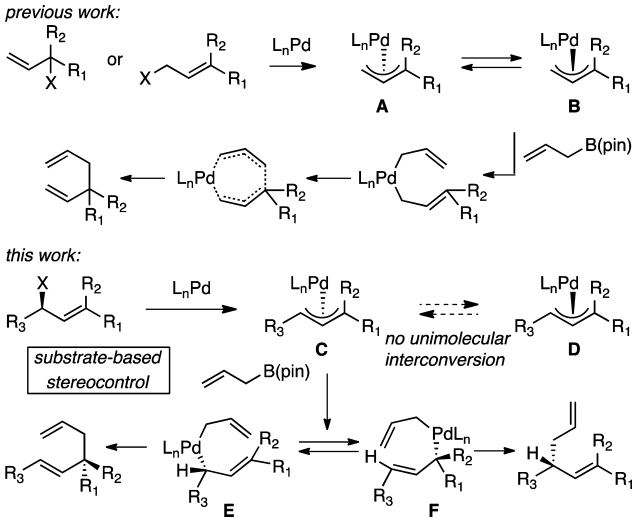


Figure 1. Allyl–allyl coupling with non-interconvertable allyl groups.

Effective use of this class of electrophiles is desirable as it would not only facilitate rapid construction of 1,5-dienes with high levels of complexity but also provide products with differentiated olefins. A distinctive feature of reactions involving internal allylic electrophiles is that Pd is generally not able to migrate from one π-face to the other (**C** → **D** is not possible; Figure 1). This feature eliminates the need for chiral ligands: the enantiopurity of the product 1,5-dienes should only be dependent on that of the starting electrophiles.[7] In this paper, we describe regiocontrol elements in such allyl–allyl coupling reactions and also document a racemization mechanism that operates in isolated cases.

Several difficulties may arise when utilizing internal allyl electrophiles in allyl–allyl cross-coupling. These include (a) competing formation of byproduct 1,3-dienes, ostensibly arising from β-hydride elimination;[8] (b) regioselectivity of product formation; and (c) the degree of chirality transfer from the starting electrophiles. We surmised that if 3,3′ reductive elimination is operative, the regioselectivity of the reaction may be controlled by the relative size difference between the substituents at the two termini of the allyl electrophile (**E** versus **F**, Figure 1). To initiate this study, reaction conditions were examined using allyl acetate **1a** as a probe substrate (Table 1). After some initial optimizations, **1a** was found to couple effectively with allylB(pin) to afford a mixture of 1,5-diene products **2a** and **3a** in a 3:1 ratio and 88% combined yield (Table 1, entry 1). The remainder of the mass was accounted for by formation of 1,3-dienes as byproducts. To understand the regioselectivity with this class of electrophiles further, we investigated substrates with alternate substitution. The electronic properties of the substrate had a measurable effect on the regioselectivity of the reaction: electron rich substrate **1b** yielded 1:1 mixture of regioisomers (entry 2), while electron-poor substrates favored formation of **2** (for example, *p*-CF_3 substrate **1d** affording 10:1 selectivity for **2**, entry 4). To

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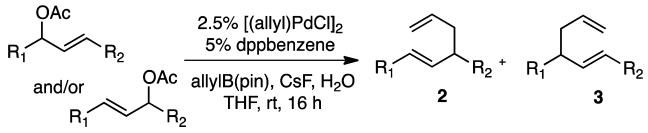
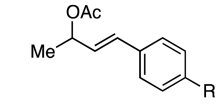
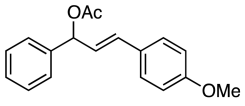
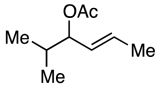
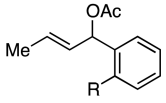
Table 1. Allyl−Allyl Cross-Coupling of Secondary Allyl Acetates[a]



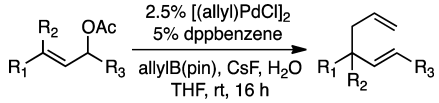
entry	substrate		2:3[b]	yield (%)[c]
1		**1a** (R = H)	3:1	88
2		**1b** (R = OMe)	1:1	69
3		**1c** (R = Cl)	4:1	92
4		**1d** (R = CF_3)	10:1	50
5		**1e**	1:2	77
6		**1f**	1:2	80[d]
7		**1g** (R = Me)	7:1	96
8[e]		**1h** (R = OMe)	7:1	80
9		**1i** (R = *i*Pr)	10:1	78

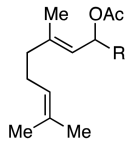
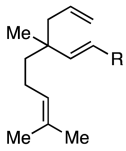
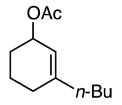
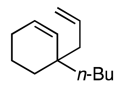
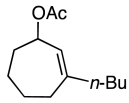
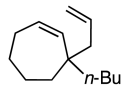
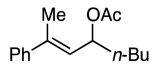
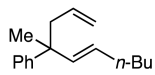
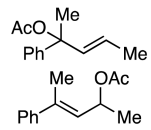
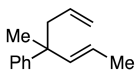
[a]Conditions: 3 equiv of allylB(pin), 10 equiv of CsF, 15 equiv of H_2O, 0.2 M THF. [b]Ratios were determined by ^{1}H NMR of crudes. [c]Yields are average of two or more experiments, and the mass balance is >95% in all cases. Yields are corrected to account unseparable 1,3-diene elimination products. [d]Yield determined by ^{1}H NMR using trimethoxybenzene as internal standard. [e]Starting material is a mixture of regioisomers.

understand further the significance of electronic and steric factors in isolation in this reaction, substrates **1e** and **1f**, with substituents differentiated only by electronic or steric properties (entry 5 and 6), were examined. Surprisingly, the coupling of both substrates proceeded with poor regioselectivity, indicating only subtle dependence on both effects. However, when substrates with significant steric bias were employed, such as those containing an *ortho*-substituted aromatic ring, high levels of regioselectivity were achieved. *o*-Me-substituted substrate **1g** and *o*-OMe-substituted substrate **1h** both yielded 1,5 dienes with 7:1 regioselectivity favoring isomer **2**. Lastly, when **1i**, a substrate bearing an encumbered *o*-isopropyl group was employed, the selectivity was improved to 10:1.

The observations in Table 1 suggest that the 3,3′-elimination reaction depicted in Figure 1 is influenced by the size and the nature of the allyl substituents with large substituents and electron-withdrawing groups being disfavored at the R^3 site in structure **E**. To employ this information to construct quaternary centers, we investigated trisubstituted allyl electrophiles (Table 2). In accordance with the previous observations, significant steric differences dictated regioselectivity across all tested substrates, and only 1,5-diene products bearing all carbon quaternary centers were observed. Acyclic, aliphatic substrates were tolerated well, affording good to excellent yields of the product, including those with sterically demanding substitution patterns (entries 1−5). Cyclic substrates with 6 and 7 membered ring also worked effectively in the cross-coupling (entry 7 and 8). Lastly, trisubstituted substrates with

Table 2. Allyl−Allyl Cross-Coupling of Trisubstituted Allyl Acetates[a]



entry	substrate	product		yield (%)[b]
1			**4** (R = Me)	80
2			**5** (R = Me[c])	90
3			**6** (R = *n*Bu)	75
4			**7** (R = *i*Pr)	65
5			**8** (R = Cy)	74
6			**9** (R = Ph)	55
7			**10**	58
8			**11**	78
9			**12**	86
10	 (1.3:1 mixture)		**13**	78

[a]Conditions: 3 equiv of allylB(pin), 10 equiv of CsF, 15 equiv of H_2O, 0.2 M THF. [b]Yields are average of two or more experiments and are corrected to account for inseparable elimination product 1,3-diene. [c]Z-allylic acetate was employed.

an aromatic substituent are also suitable for the reaction regardless of the substituent's relative position (entries 6, 9, and 10).

To study the efficiency of chirality transfer, we investigated the use of enantiomerically enriched secondary allylic acetate (*S*)-**14** (Table 3), prepared by Sharpless epoxidation-based kinetic resolution of the precursor alcohol.[9] Applying previously optimized conditions, a >20:1 mixture of 1,5-diene isomers was formed, favoring product (*R*)-**13**, with 79% yield (entry 1). The er of (*R*)-**13** was determined to be 79:21, which corresponded to only 65% conservation of enantiomeric excess (cee) from starting material (*S*)-**14**. When the amount of allylB(pin) and CsF was increased to 10 and 30 equiv, respectively, the reaction afforded a 3:1 mixture of 1,5-dienes in 60% yield with 80% cee for (*R*)-**13** (entry 2). Further investigation revealed a correlation between the cee value and catalyst concentration; as the catalyst concentration increased, the chirality transfer decreased. At 1 mol % catalyst loading, almost complete chirality transfer was observed, though at the cost of diminishing yield and regioselectivity (entry 3). At 2.5 mol % catalyst, product (*R*)-**13** was obtained with 70% yield and 92:8 er, corresponding to 90% cee (entry 4). Increasing catalyst concentration to 10 and 15 mol % provided reduced cee at 47% and 26% cee, respectively (entries 5 and 6).

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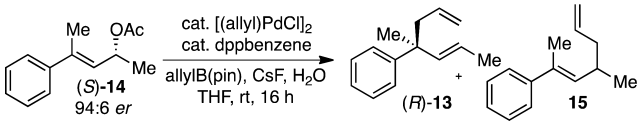
Table 3. Optimizations for Stereospecific Allyl−Allyl Cross-Coupling[a]



entry	% cat.	13:15[b]	yield[c] (%)	er[d]	cee[e] (%)
1	5	>20:1	79	79:21	65
2[f]	5	3:1	60	85:15	80
3	1	1:1	50	94:6	98
4	2.5	7:1	70	92:8	90
5	10	>20:1	72	71:29	47
6	15	>20:1	73	61:39	26

[a]Conditions: 3 equiv of allylB(pin), 10 equiv of CsF, 15 equiv of H_2O, 0.2 M THF. [b]Ratios were determined by ^{1}H NMR of crudes. [c]Yields are average of two or more experiments and are combined yields of **13** and **15** corrected to account for inseparable elimination product 1,3-diene. [d]er ratios were determined using chiral GC or HPLC. Absolute configuration assigned in analogy to known compounds. See the Supporting Information. [e]cee is calculated as follow: cee = (product ee/starting material ee) × 100. [f]10 equiv of allylB(pin) and 30 equiv of CsF were employed.

In accord with findings by Bäckvall,[10d] Amatore,[10f] and others, we surmised that the incomplete chirality transfer observed at higher catalyst loading may be a result of a redox-transmetalation process (Figure 2).[10] Upon formation of

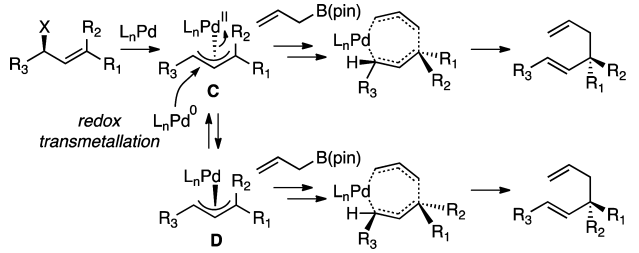
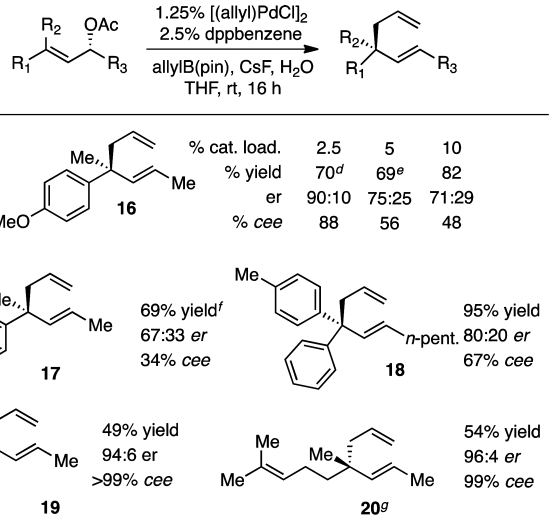


Figure 2. Racemization during allyl−allyl cross-coupling may occur by redox transmetalation (**C** → **D**).

Pd−π-allyl intermediate **C**, available Pd^0 complexes in the reaction media may displace the Pd^{II} from **C** in an anti fashion, leading to enantiomer **D**.[3a,11] This could then undergo transmetalation and 3,3′ reductive elimination to afford enantiomeric 1,5-diene product, thereby diminishing the er of the reaction product. This mechanism for racemization should be second order in [Pd], whereas the cross-coupling process itself should exhibit first-order dependence on [Pd]. Thus, improved cee is anticipated at lower catalyst concentrations. The observation that increased concentrations of allylB(pin) and CsF improve cee (entry 2) suggest that the redox transmetalation operates on intermediates **C** and **D** and does not operate on subsequent bis(allyl)Pd complexes.

The scope of chirality transfer was studied with a range of substrates, including those with aromatic and aliphatic substitution (Scheme 1). *p*-Methoxy-substituted **16** exhibited a correlation between cee and catalyst loading level similar to **13**.[12] At 2.5 mol % catalyst loading, 88% cee was obtained, while at 5% and 10% catalyst loadings, the cee dropped to 56% and 48%, respectively. When *p*-CF_3-substituted product **17** was examined, significant erosion of enantiomeric purity was observed and the products were acquired with only 34% cee

Scheme 1. Chirality Transfer in Allyl−Allyl Cross-Coupling[a]



[a]Conditions: 3 equiv of allylB(pin), 10 equiv of CsF, 15 equiv of H_2O, 0.2 M THF. [b]Yields are average of two or more experiments. [c]er ratios were determined using chiral GC or HPLC analysis. [d]2:1 mixture of regioisomers. [e]10:1 mixture of regioisomers. [f]5:1 mixture of regioisomers. [g]Starting material with (*S*) configuration was employed.

using 2.5 mol % of catalyst. Diphenylmethane derivative **18** was synthesized with excellent yield and regioselectivity and moderate cee of 67%. In contrast with aromatic-substituted substrates, aliphatic substrates demonstrated excellent chirality transfer properties. Allyl−allyl coupling product **19** was obtained in 49% yield and 94:6 er, corresponding to >99% cee. Geraniol-derived 1,5-diene **20** was also produced with 96:4 er, corresponding to 99% cee.

In conclusion, we have extended the Pd-catalyzed allyl−allyl cross-coupling reaction to include internal allyl electrophiles. This strategy enables rapid construction of multisubstituted 1,5-dienes with predictable regio- and enantioselectivity while omitting the requirement for chiral phosphine ligand.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and characterization data (^{1}H and ^{13}C NMR, IR, and mass spectrometry). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) From the reaction to synthesize **16**, the absolute configuration of the minor regioisomer was determined to have (*R*) configuration and 99% cee; the mixture with major regioisomer **16** had 88% cee. See the Supporting Information for details.