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Construction of 1,5-Enynes by Stereospecific Pd-Catalyzed Allyl–Propargyl Cross-Couplings

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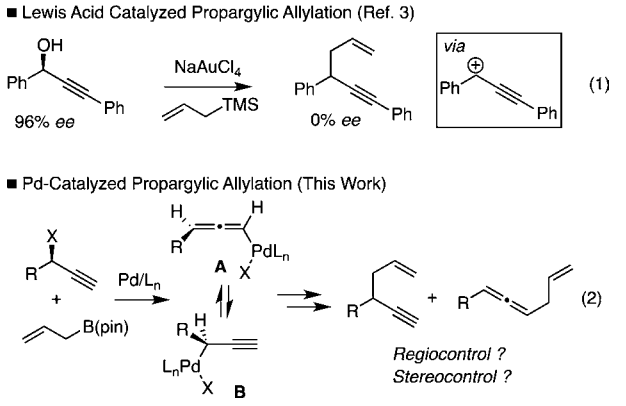
Supporting Information

ABSTRACT: The palladium-catalyzed cross-coupling of chiral propargyl acetates and allyl boronates delivers chiral 1,5-enynes with excellent levels of chirality transfer and can be applied across a broad range of substrates.

1,5-Enynes are important and versatile synthetic intermediates. In addition to offering differentiated π-systems for selective functionalization, 1,5-enynes can be transformed into a diverse array of cyclic structures.[1] A current challenge to reaction methodology surrounding 1,5-enynes lies in the preparation of these structures in an enantiomerically enriched fashion. Synthesis of 1,5-enynes is commonly accomplished by allylation of propargylic electrophiles, employing either stoichiometric or catalytic Lewis acid activation.[2] While high levels of regiocontrol have been observed in these processes, they appear to proceed through an achiral carbocation intermediate and this feature precludes the transfer of chirality from enantiomerically enriched starting materials to 1,5-enyne products (Scheme 1, eq 1).[3,4] Transition metal catalysis could

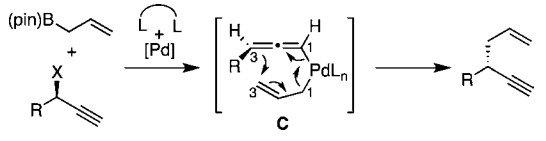
Scheme 1



provide a solution to this limitation: palladium undergoes stereospecific anti S_N2' oxidative addition with propargylic electrophiles.[5] This reaction delivers an η^1-(allenyl)palladium complex (**A**, Scheme 1) whose configuration reflects that of the starting material. While (allenyl)palladium complexes can undergo isomerization to η^1-(propargyl)palladium species (**A**→**B**), this transformation is also stereospecific.[5,6] With appropriately substituted substrates, both the propargyl (**B**) and the allenyl (**A**) palladium complexes are chiral and the fact that they are configurationally stable enables stereospecific cross-couplings.[7] However, the Pd-catalyzed cross-coupling of organometallic reagents and branched propargylic electrophiles generally favors the allene as opposed to the 1,5-enyne product.[7,8] This regioselectivity likely arises from steric effects; complex **A** is less hindered than complex **B**, and this leads to allene products on reductive elimination. This reaction manifold renders traditional palladium catalysis ineffective for the construction of chiral alkyne-containing compounds from chiral propargylic electrophiles.

In contrast to the cross-coupling of alkyl, aryl, and vinyl metal reagents, cross-couplings of allyl metal reagents may occur with allyl migration. To exploit this feature, our lab has studied cross-couplings of allyl metal reagents and allylic electrophiles and has found that these reactions appear to occur by an inner sphere 3,3′-reductive elimination.[9−11] In the presence of appropriately selected ligands (bidentate, small bite-angle diphosphines), allyl−allyl cross-couplings occur with excellent levels of regio- and stereocontrol. Along these lines, we considered that allyl−propargyl cross-couplings might also occur by 3,3′-elimination and, if the elimination occurred from an allenyl(allyl)Pd complex (**C**, Scheme 2), this might provide a method for the stereocontrolled construction of nonracemic 1,5-enynes from readily available enantiomerically enriched propargylic alcohols.[12]

Scheme 2



To initiate these studies, cross-couplings of allylB(pin) and propargylic chlorides were examined in the presence of $Pd_2(dba)_3$ and CsF. With dppf as the ligand, the reaction furnished the 1,5-enyne product regioselectively for both aromatic (entry 1) and aliphatic (entry 2) substrates. More conveniently prepared propargylic acetates were also found to participate in the coupling, and while the regioselectivity was moderate with dppf (entries 3 and 4), a marked improvement was observed when *rac*-binap was employed. These reactions occurred with high levels of selectivity for the 1,5-enyne product and in exceptional yields (entries 5 and 6). In light of prior studies on the impact of ligand structure on regioselectivity,[9a] it was not surprising that a monodentate

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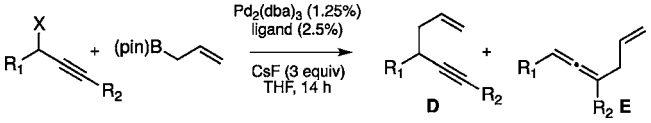
ligand such as triphenyl phosphine (entries 7 and 8) favored allene products. Lastly, internal alkynes appear to react with diminished levels of selectivity (entry 9), perhaps because the added substituent at C1 of the allenyl palladium intermediate (**C**, Scheme 2) suffers an interaction with the ligand framework. Fortunately, this synthetic limitation is easily addressed: C-alkylation of the terminal alkyne-derived products (**D**, R_2 = H, Table 1) provides ready access to the corresponding internal alkyne allylation products.

Table 1. Selectivity in Allyl–Propargyl Coupling[a]



entry	R_1	R_2	X	ligand	temp (°C)	D:E	yield (%)
1	Ph	H	Cl	dppf	rt	83:17	85
2	pentyl	H	Cl	dppf	rt	95:5	75
3	Ph	H	OAc	dppf	60	68:32	79
4	pentyl	H	OAc	dppf	60	84:16	74
5	Ph	H	OAc	*rac*-binap	60	93:7	91
6	pentyl	H	OAc	*rac*-binap	60	98:2	96
7	Ph	H	OAc	PPh_3	60	<1:99	-
8	pentyl	H	OAc	PPh_3	60	<1:99	-
9	pentyl	Bu	OAc	*rac*-binap	60	27:73	68

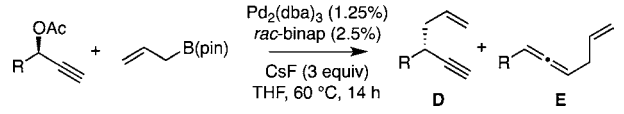
[a]Reactions employed 1.2 equiv of allylB(pin). Regioselectivity was determined by ^{1}H NMR analysis; yield refers to isolated yield of the regioisomer mixture.

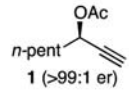
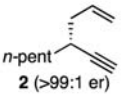
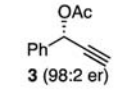
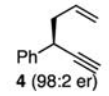
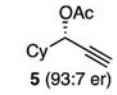
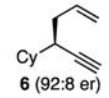
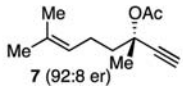
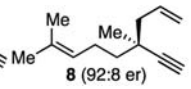
With an effective protocol for enyne-selective coupling, the capacity for chirality transfer from enantiomerically enriched propargylic acetate substrates was explored. As depicted in Table 2, the reaction showed excellent conservation of enantiomeric enrichment (>99% *cee*) with aliphatic substrates (entries 1, 3, and 4). While the aromatic substrate in entry 2 suffered some loss of optical purity with *rac*-binap (77% *cee*),[13] high levels of chirality transfer (>99% *cee*) were obtained when (*R*)-methoxy(furyl)biphep[14] was employed as the ligand (entry 2). Of special interest was the ability to utilize tertiary acetates to access enantiomerically enriched 1,5-enynes bearing all-carbon quaternary centers (entry 4). Despite slightly diminished regioselection, the ability to establish quaternary centers with high *cee* (>99%) and yield could prove especially useful in the construction of complex products.

In addition to the substrates in Table 2, a broad array of other propargylic acetates were found to participate in the regioselective allyl–propargyl coupling and generally delivered 1,5-enyne products in good to excellent yields. As depicted in Table 3, substrates can possess silyl and benzyl ethers, remote alkenes, indoles, and aryl chloride groups. Of particular note is reaction product **13**, which results from regioselective reductive elimination from a conjugated (enallenyl)palladium intermediate.

Aspects of the allyl–propargyl coupling reactions described above merit mention. First the high level of chirality transfer observed with *rac*-binap suggests that the catalyst configuration may have little impact on the product stereochemistry. To examine this feature in more detail, both enantiomers of ligand were employed with enantiomerically enriched substrate **1**. As shown in Scheme 3 (eq 3), there is a slight level of double diastereodifferentiation but both reactions deliver the product with net inversion of configuration at carbon as the predominant outcome. These experiments indicate that the product configuration is dictated almost exclusively by the starting material structure. To learn more about the innate basis for the product regioselectivity, the experiment in eq 4 was

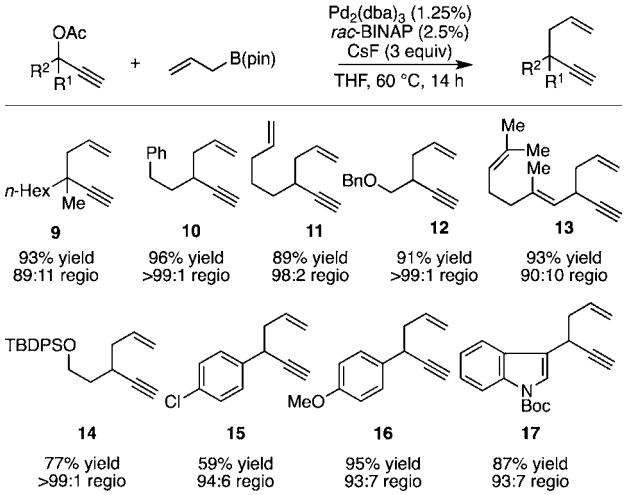
Table 2. Conservation of Enantiomeric Enrichment in Allyl–Propargyl Couplings[a]



entry	substrate	product	*cee* (%)	D:E	yield (%)
1	 **1** (>99:1 er)	 **2** (>99:1 er)	>99	98:2	93
2[b]	 **3** (98:2 er)	 **4** (98:2 er)	>99	98:2	90
3	 **5** (93:7 er)	 **6** (92:8 er)	96	98:2	87
4	 **7** (92:8 er)	 **8** (92:8 er)	>99	89:11	96

[a]Reactions employed 1.2 equiv of the allylboronate. Yield refers to isolated yield of the regioisomer mixture. Ratio of **D:E** was determined by ^{1}H NMR analysis; enantiomer ratios were determined by GC analysis on a chiral stationary phase. [b]For entry 2, (*R*)-methoxy-(furyl)biphep (2.5%) used as the ligand; *rac*-binap gave a product er of 87:13, 77% *cee*, 93:7 **D:E**, and 80% yield.

Table 3. Substrate Scope of Propargyl–Allyl Cross-Coupling[a]



[a]Reactions were conducted for 14 h at 60 °C with 1:1 ligand/Pd(0) and employed 1.2 equiv of the allylboronate relative to the propargyl acetate. Yield refers to isolated yield of the regioisomeric mixture. Regioselectivity was determined by ^{1}H NMR analysis.

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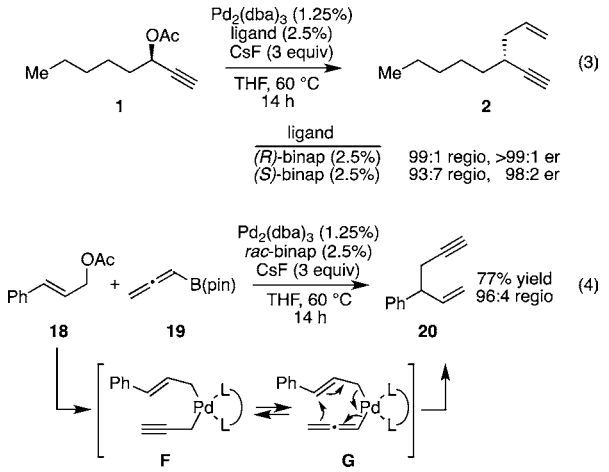
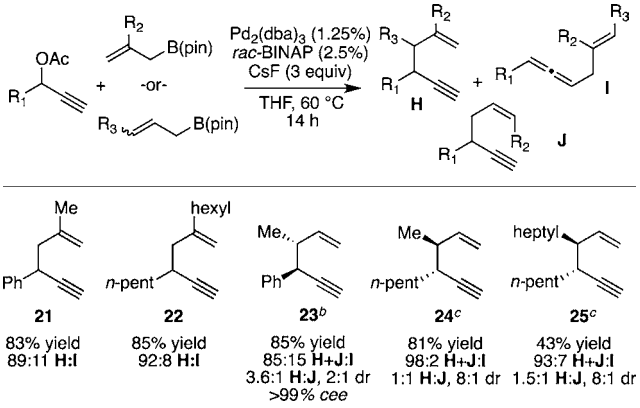
Scheme 3



conducted. In this experiment, the reaction of allenyl B(pin) and cinnamyl acetate was found to deliver 1,5-enyne **20** as the predominant reaction product. In this experiment, the presumed reactive intermediate bears an interconverting allyl/propargyl ligand without a steric bias between the two isomers (**F** and **G**). This reaction delivers the 1,5-enyne selectively, an outcome that is most consistent with 3,3′-reductive elimination from allenyl complex **G**. Thus, even in the absence of a steric bias, the innate preference appears to be for reductive elimination through the allenyl palladium intermediate.

Allylboronates substituted at the β and γ positions are readily available by catalytic hydroboration of dienes and by catalytic borylation of allylic electrophiles.[15] To learn about the broader generality of the allyl−propargyl cross-coupling, the utility of these substituted nucleophiles was examined. As depicted in Table 4, β-substituted allyl boronates maintain high levels of regioselectivity in coupling with propargyl acetates (products **21** and **22**). γ-Substituted allyl boronates can also exhibit high levels of reactivity and selectivity; however, they require modifications to the reaction. To produce compound **23** in good yield required use of enantiomerically enriched substrate (*R*)-**3** and (*R*)-methoxy(furyl)biphep. With these conditions, the reaction was efficient, and while both crotyl- (**H**) and *cis*-2-butenyl derivatives (**J**) were generated, the reaction exhibited a strong preference for the alkyne product. Similarly, efficient production of **24** and **25** could be accomplished with the use of the (*R*)-propargylic acetate and (*S,S*)-QuinoxP*. In these reactions, when the opposite ligand enantiomer was employed diminished levels of selectivity were observed. A rationale for the observed matched and mismatched interactions is presented in Figure 1 and is based on a stereochemical

Table 4. Propargyl−Allyl Cross-Coupling with Substituted Allylboronates[a]



[a]Reactions were conducted for 14 h at 60 °C with 1:1 ligand/Pd(0) and employed 1.2 equiv of the allylboronate relative to the propargyl acetate. Yield refers to isolated yield of the regioisomeric mixture. Regioselectivity was determined by ^{1}H NMR analysis. [b](*R*)-Methoxyfurylbiphep employed as the ligand, and 10 equiv of CsF were employed. [c](*S,S*)-QuinoxP* employed as the ligand, and 10 equiv of CsF were employed.

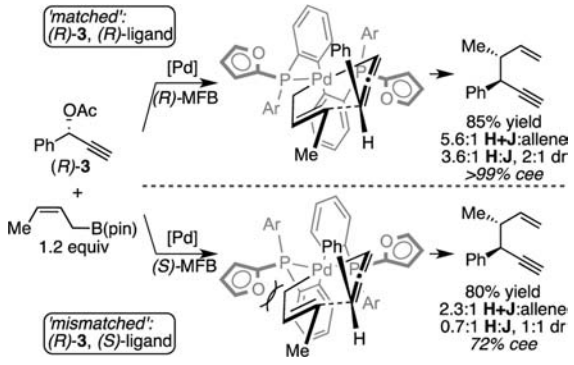
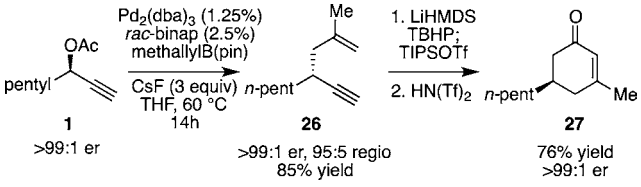


Figure 1. Matched and mismatched catalyst substrate interactions in propargyl−allyl couplings.

model for related allyl−allyl couplings. As depicted, the matched pairing appears to minimize nonbonded interactions between the pseudoequatorial furyl ring and the allyl/allenyl ligands as the latter couple to form a staggered C−C bond.

Synthetically, the allyl−propargyl coupling serves as a strategically useful link between methodologies for the synthesis of enantiomerically enriched propargyl alcohols and methods for the transformation of enyne substrates. For example, Kozmin and co-workers have described a straightforward protocol for the synthesis of substituted cyclohexenones through cyclization of siloxy alkynes derived from 1,5-enynes.[16] Using the allyl−propargyl coupling described above, the requisite substrates can be prepared in an enantiomerically enriched fashion thereby facilitating the use of the Kozmin transformation in asymmetric synthesis; as depicted in Scheme 4, coupling of methallylB(pin) converts **1** to **26** with excellent

Scheme 4



stereocontrol. From **26**, disubstituted cyclohexenone **27** can be easily produced in high yield and without racemization. With a general procedure to access a broad range of highly enantiomerically enriched enynes bearing aliphatic, aromatic, and all carbon quaternary substitution, the allyl−propargyl coupling should serve as a useful new route to a myriad of other optically enriched synthetic intermediates.

In conclusion, the development of a new Pd(0)-catalyzed allyl−propargyl coupling has opened a general method for the

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construction of enantiomerically enriched 1,5-enynes. These motifs are often used in a racemic fashion, and this strategy now provides a simple method for their construction in enantiomerically enriched form.

■ ASSOCIATED CONTENT

Supporting Information

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 no competing financial interest.

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