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Regioselectivity Switch in Pd-Catalyzed Hydroallylation of Alkynes

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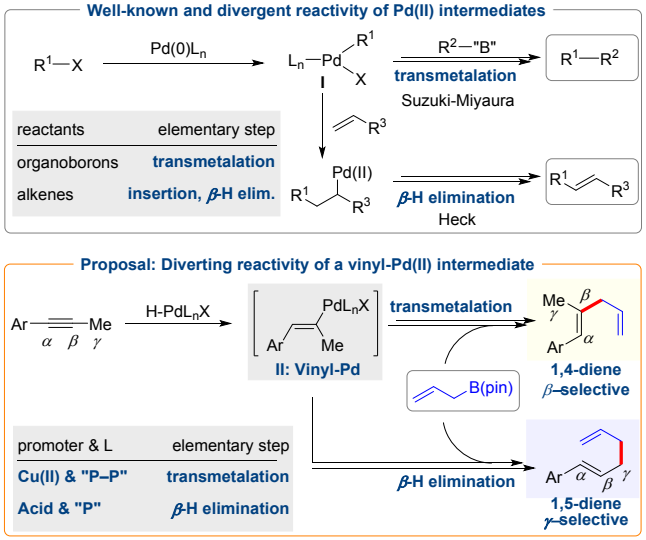
By exploiting the reactivity of a vinyl-Pd species, we control the regioselectivity in hydroallylation of alkynes under Pd-hydride catalysis. A monophosphine ligand and carboxylic acid combination promotes 1,5-dienes by a pathway involving isomerization of alkynes to allenes. In contrast, a bisphosphine ligand and copper cocatalyst favor 1,4-dienes *via* a mechanism that involves transmetalation. Our study highlights how to access different isomers by diverting a common organometallic intermediate.

Introduction

Inventing novel cross-couplings has relied upon our ability to divert readily accessible and common organometallic intermediates.[1] For example, Pd(II) intermediates **I** (generated from organic halides or their analogues) can transmetallate with organoborons in a Suzuki-Miyaura cross-coupling[2] or undergo insertion to olefins and subsequent β-hydride elimination in the Heck reaction (Scheme 1, top).[3] Inspired by the power of this concept, we set out to divert the reactivity of a vinyl-Pd(II) intermediate **II** (generated from alkynes, Scheme 1, bottom) to achieve useful skipped dienes.

The hydroallylation of alkynes has attracted attentions due to occurrence of skipped dienes in bioactive compounds and natural products.[4] While various catalysts have been developed to generate the 1,4-diene motif,[5] access to the 1,5-diene isomer *via* hydroallylation of alkynes has been elusive. In considering this challenge, we were inspired by the work of Trost,[6] Yamamoto,[7] and Breit[8] who have used alkynes as redox-neutral allyl precursors.[9-12] Early studies established that Pd–H can add to a alkyne to generate the vinyl-Pd species **II**. With this in mind, we set out to manipulate the reactivity of this Pd(II) species **II** towards transmetalation or β-H elimination to enable selective access to the 1,4 or 1,5-dienes, respectively (Scheme 1, bottom). Herein, we report the use of ligands and promoters to enable a regiodivergent synthesis of skipped dienes. Our study contributes to the art of diverging catalytic intermediates to access different constitutional isomers.[13]



Scheme 1. Divergent reactivity of Pd(II) species

Results and discussion

We began our study with 1-phenyl-1-propyne **1a** and allyl-B(pin) **2a** as the model substrates. After examining various combinations of ligands and additives, we obtained compelling results (Chart 1). In the presence of $Pd_2(dba)_3$ (2.5 mol%) and a proton source ^{n}BuOH (2.0 equiv.), we found that monophosphine ligands such as $PPhCy_2$ and PCy_3 could give 1,5-diene (Chart 1A) as major product. With the aid of PCy_3, 1,5-diene **3a** could be obtained in 18% yield accompanied by trace amounts of 1,4-dienes **4a** and **4a'** mixture. To improve the yield of 1,5-diene **3a**, we chose Brønsted acid to facilitate the formation of active Pd(II)–H catalyst.[7] By adding 10 mol% 1-adamantanecarboxylic acid, we observed **3a** in 83% yield with excellent selectivity (Chart 1B). Bisphosphine ligands gave only trace amount of 1,5-diene **3a** because these ligands occupy the otherwise vacant sites needed for β-hydride elimination.[1,14]

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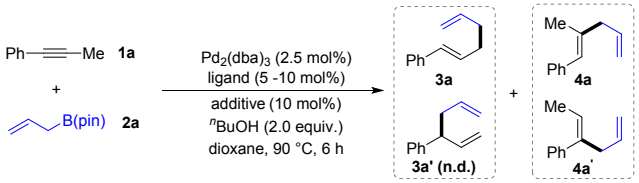
Chart 1. Ligand and promoter effects on hydroallylation[a]



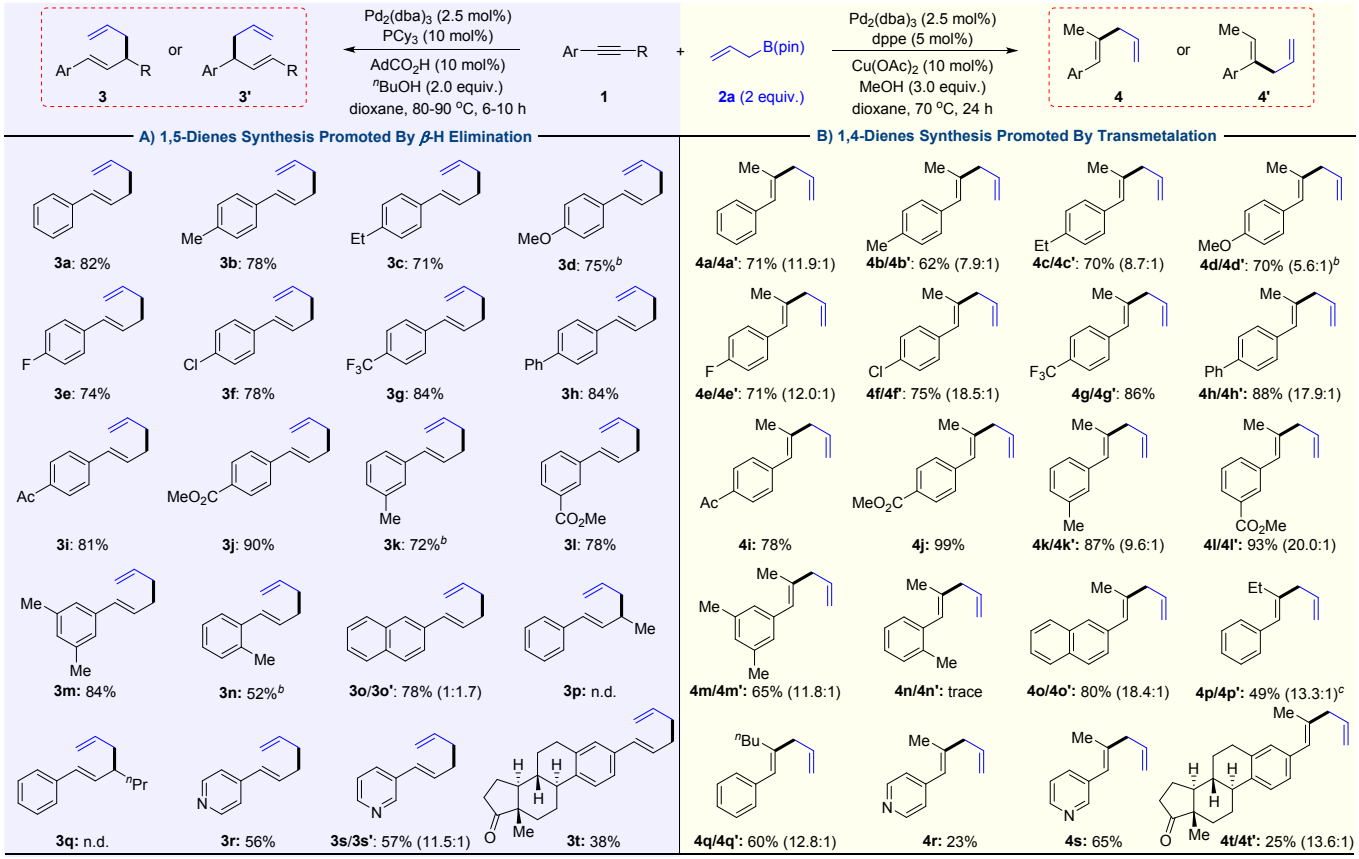
A	**Mono P:**	PPh_3	$PPhCy_2$	Xphos	**PCy_3**	P^tBu_3
No Promoter	Yield[b] **3a**:	n.d.	9%	n.d.	**18%**	n.d.
	Yield[b] **4a/4a'**:	n.d.	trace	n.d.	**trace/2%**	n.d.
	Bis P-P:	dppm	dppe	dpp-benz	dCype	dppp
	Yield[b] **3a**:	n.d.	n.d.	n.d.	n.d.	n.d.
	Yield[b] **4a/4a'**:	trace	n.d.	n.d.	n.d.	n.d.
B	**Mono P:**	PPh_3	$PPhCy_2$	Xphos	**PCy_3**	P^tBu_3
$AdCO_2H$ (10 mol%)	Yield[b] **3a**:	34%.	80%	21%	**83%**	12%
	Yield[b] **4a/4a'**:	2%/2%	trace	n.d.	**trace**	n.d.
	Bis P-P:	dppm	dppe	dpp-benz	dCype	dppp
	Yield[b] **3a**:	2%.	n.d.	n.d.	n.d.	n.d.
	Yield[b] **4a/4a'**:	3%/2%	n.d.	n.d.	n.d.	n.d.
C	**Mono P:**	PPh_3	$PPhCy_2$	Xphos	PCy_3	P^tBu_3
$Cu(OAc)_2$ (10 mol%)	Yield[b] **3a**:	3%.	9%.	10%.	trace	9%.
	Yield[b] **4a/4a'**:	trace	trace	n.d.	n.d.	n.d.
	Bis P-P:	dppm	**dppe**	dpp-benz	dCype	dppp
	Yield[b] **3a**:	n.d.	**n.d.**	12%	n.d.	n.d.
	Yield[b] **4a/4a'**:	trace	**53%/5%**	34%/4%	5%/trace	17%/1%
			79%/7%[c]			

[a] **1a** (0.20 mmol), **2a** (2.0 equiv), $Pd_2(dba)_3$ (2.5 mol%), monophosphine (10 mol%) or bis-phosphine (5 mol%), promoter (10 mol%), ^{n}BuOH (2.0 equiv), dioxane (1.0 mL), 90 °C, 6 h. [b] Determined by ^{1}H NMR or GC-FID with 1,3,5-trimethoxybenzene as the internal standard. [c] MeOH (3.0 equiv) instead of ^{n}BuOH, dioxane (0.5 mL), 70 °C, 24 h.

Next, we aimed to selectively prepare the 1,4-diene **4a**, which is the minor isomer that results from direct coupling of alkyne **1a** and allylboron **2a**. To alter regioselectivity, we pursued a co-catalyst that would accelerate transmetalation between the allyl species and the vinyl-Pd intermediate, therefore enable the synthesis of 1,4-dienes. An evaluation of co-catalysts revealed that $Cu(OAc)_2$ promoted the formation of **4a/4a'** (Chart 1C). Moreover, in contrast to the monphophine ligands that promotes the formation of **3a**, bisphosphine ligands such as dppe and dpp-benz gave higher yield of **4a/4a'**. When dppe was used as ligand, **4a/4a'** was delivered in 58% combined yield as a 10:1 mixture of regioisomers. Using methanol instead of butanol as the proton source improved the yield of **4a** to 79%. In the absence of palladium, no products were detected, which indicates this transformation is not catalyzed by copper alone.

As shown in Table 1A, we obtained various 1,5-dienes in moderate to good yields and high selectivities (>20:1, **3** *vs* **4**). Substrates with electron-donating groups proceed smoothly to deliver 1,5-dienes **3b-3d**. Fluoro and chloro groups are also well tolerated, yielding products **3e** and **3f** in 74% and 78%. Aryl alkynes bearing electron-withdrawing substituents (CF_3, Ph, Ac, and CO_2Me) show slightly higher reactivities, providing the linear products (**3g-3j**) in high yields (81-90%). High selectivities are still obtained for *meta*-substituted 1-arylalkyne **1k-1m**. The steric hindrance of alkyne influences the reactivity and offers **3n** with 52% yield. On replacing the phenyl group

Table 1. Regioselective hydroallylation of alkynes[a]



[a]Isolated Yield of the all isomers. Unless otherwise noted, selectivity > 20:1; [b]Accompanied by small amount of inseparable alkyne **1**, the yield of product has been adjusted accordingly. [c]Isolated product together with 1-phenyl-1,3-butadiene in a 4.0:1 ratio, the yield of product has been adjusted accordingly.

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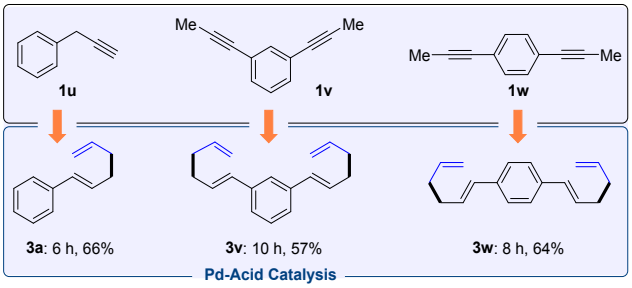
with 2-naphthalenyl groups, the substrate transforms into a mixture of linear product **3o** and branched product **3o'** in a 1:1.7 ratio. The branched product **3o'** probably originates from the formation η^3-π-benzyl-palladium intermediate.[15] No desired 1,5-diene product is obtained when alkyl-substituted alkyne **1p** or **1q** is subjected to standard conditions. Instead, isomerization product 1-phenyl-1,3-butadiene is observed for the conversion of **1p**. Notably, substrates bearing pyridine rings, which were incompatible in previously reported palladium catalysis,[16] also lead to **3r** and **3s** in moderate yields. Finally, the late-stage modification of the estrone derivative **1t** affords **3t** in 38% yield. This 1,5-diene synthesis complements known allyl-allyl couplings that require pre-functionalized allyl precursors such as allyl chlorides or carbonates.[16-17]

Then, we examined the substrate scope for the synthesis of 1,4-dienes (Table 1B). Various alkynes transform to 1,4-dienes using the Pd/Cu catalyst combo. Although substrates bearing electron-donating groups lead to skipped dienes in moderate to good regioselectivities (**4b**-**4d**, **4k**, **4m**), electron-withdrawing substrates perform well in terms of yields and selectivities (**4e**-**4j**, **4l**). Ortho-Substituted alkyne **1n** exhibits no reactivity due to steric hindrance. It is noteworthy that **4p** and **4p'** are successfully acquired in 49% yield, while accompanied by a small amount of isomerization side product (1-phenyl-1,3-butadiene). Comparatively, the cross-coupling between 1-phenyl-1-hexyne **1q** and **2a** provides 1,4-diene products **4q**/**4q'** without any 1,3-diene side product. Heterocyclic substituted alkynes (**1r** and **1s**) and estrone derivative all successfully deliver the 1,4-diene products.

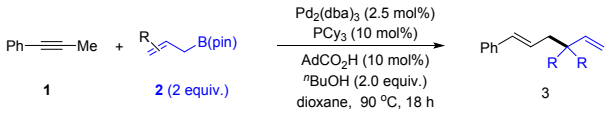
Besides internal alkynes, terminal alkyne **1u** couples with allylB(pin) **2a** to yield 1,5-diene **3a** (Scheme 2). The bis-allylations of di(prop-1-yn-1-yl)benzene **1v** and **1w** proceed smoothly with high selectivities and moderate yields. These olefin products are potential monomers for polymerization.[18]

We also tested the scope of allylborons under our Pd-acid condition (Table 2). Generally, substrates **2b**-**2d** were less reactive in allyl-allyl couplings. This agrees with previous work



Scheme 2. Hydroallylation of terminal and bis-alkynes

Table 2. The scope of allylborons



1 2 (2 equiv.) 3

2		product		yield (%) w/o $Cu(OAc)_2$	yield (%) $Cu(OAc)_2$
Ph, B(pin)	**2b**	Ph, Ph	**3x**	6	34[a]
Me, Me, B(pin)	**2c**	Ph, Me, Me	**3y**	n.d.	< 5[a]
B(pin), Me, Me	**2d**			13	38[a]

[a] $Cu(OAc)_2$ (10 mol%)

reported by Morken's group that substituted allylborons were comparatively reluctant in Pd-catalyzed allyl-allyl coupling reactions.[17g] To improve the reactivity, $Cu(OAc)_2$ was employed as additional promoter to facilitate transmetalation. The yields of **3x** and **3y** were successfully increased to 34% and 38%, respectively. It should be noted that these reactions all give interesting linear-branched coupling products, this selectivity is rare in Suzuki-type allyl-allyl coupling reactions.[17]

While further studies are warranted, we propose the following mechanisms on the basis of literature[7] and our own observations (Figure 1A, right). First, the oxidative addition of the carboxylic acid with a Pd(0) precursor generates Pd(II)-hydride species **A**. S*yn*-migratory insertion of alkyne **1** into the Pd(II)–H **A** affords vinyl-Pd intermediate **B**. For 1,5-dienes pathway, a vacant coordination site of complex **B** is spared for β-hydride elimination in the presence of monophosphine ligand. Allene **5** is subsequently produced and undergoes reinsertion to Pd(II)–H forming the π-allyl-Pd intermediate **C**. Then, electrophilic intermediate **C** reacts with allylB(pin) **2** to deliver bis(allyl)Pd species **D**.[19] Reductive elimination yields the allyl-allyl coupling product **3a** and turns over Pd(0) catalyst (allyl-allyl coupling cycle).

In the presence of a Cu(II) co-catalyst, we propose that transmetalation of allylboron **2a** to generate allylcopper species **2'** is favored.[5i,17k] Under this protocol, vinyl-Pd species **B** is also generated by a syn-migratory of alkyne **1** into the Pd(II)–H **A** (Figure 1A, left). However, when coordinated with a bidentate ligand, vinyl-Pd intermediate **B** prefers direct transmetalation with allylcopper species **2'** to form **D'** rather than undergoing β-hydride elimination to produce allene **5**. Reductive elimination from **D'** yields product 1,4-diene **4a** (allyl-vinyl coupling cycle).

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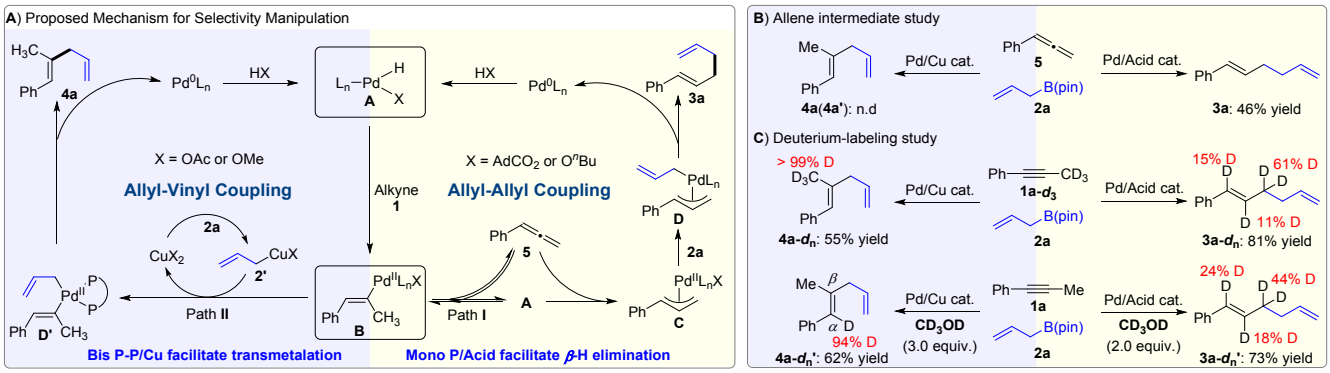

Figure 1. Divergent reactivity of Pd(II) species

To probe the feasibility of an allene intermediate, phenylallene **5** was subjected to couple with allyl-B(pin) **2a** under two standard conditions (Figure 1B, see the SI for details). The allene was transformed into the 1,5-diene **3a** in 46% yield. No formation of **4a** or **4a'** under the Pd-Cu conditions supports that the 1,4-diene products does not arise from the addition of allylB(pin) **2a** to allene **5**. The hydroallylation was also performed with deuterated alkyne **1a**-d_3 or methanol (Figure 1C). Under Pd/acid catalysis, we found the deuterium label was scrambled into the α-, β-, and γ-positions of 1,5-diene **3a**-d_n using **1a**-d_3. Similar deuterium scrambling was observed when conducting reaction with deuterated methanol as proton source. This observation supports a reversible hydrometallation of the internal π-system of the allene in the synthesis of 1,5-dienes. When experiments were carried out under Pd-Cu catalysis, the deuterium label remained intact in 1,4-diene **4a**-d_n with deuterated alkyne **1a**-d_3. Only α-deuterated product was achieved using deuterated methanol (Figure 1C). This indicates β-hydride elimination is not involved under Pd/Cu catalysis.

Conclusions

Our work complements other alkyne hydroallylation methods for the synthesis of 1,4-dienes including those developed by Hilt, Hartwig, Lalic and Zhang.[5] Key to the success of this method is the switchable reactivity of vinyl-Pd intermediates. Acid additive promotes the β-hydride elimination pathway for allyl-allyl coupling with the aid of a monophosphine ligand. Whereas Cu co-catalyst facilitates the direct transmetalation for vinyl-allyl coupling in the presence of a bisphosphine ligand. Transmetalation and β-hydride elimination are two elementary steps featured in many well-known organometallic mechanisms, including the Suzuki-Miyaura and Heck cross-coupling. Insights from this study will guide the future development of related regiodivergent methods in catalysis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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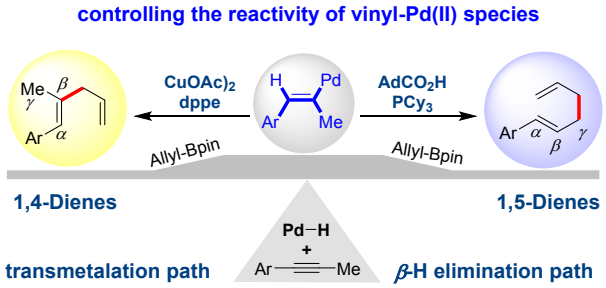

Through rational evaluation of ligands and promoters, the reactivity of a key Pd(II) species towards transmetalation or β-H elimination is manipulated.