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A 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 through 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.

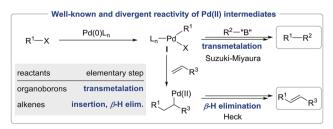
Introduction

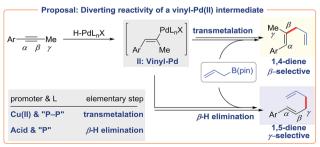
Inventing novel cross-couplings has relied upon our ability to divert readily accessible and common organometallic intermediates. For example, $Pd(\Pi)$ intermediates I (generated from organic halides or their analogues) can transmetallate with organoborons in a Suzuki–Miyaura cross-coupling or undergo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

The hydroallylation of alkynes has attracted attention due to the 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 Breit8 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 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

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 "BuOH (2.0 equiv.), we found that monophosphine ligands such as $PPhCy_2$ and PCy_3 could give 1,5-diene (Chart 1A) as the 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 an active $Pd(\pi)$ -H catalyst. By adding 10 mol% 1-adamantanecarboxylic acid, we obtained **3a** in 83% yield with excellent selectivity (Chart 1B). Bisphosphine ligands gave only trace amounts of





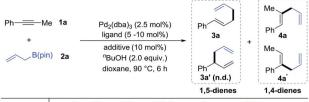
Scheme 1 Divergent reactivity of Pd(II) species.

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Chemical Science

A	Mono P:	PPh ₃	PPhCy ₂	Xphos	PCy ₃	P ^t Bu ₃
	Yield ^b 3a: Yield ^b 4a/4a':	n.d. n.d.	9% trace	n.d. n.d.	18% trace/2%	n.d. n.d.
No Promoter	Bis P-P:	dppm	dppe	dpp-benz	dCype	dppp
	Yield ^b 3a: Yield ^b 4a/4a':	n.d. trace	n.d. n.d.	n.d. n.d.	n.d. n.d.	n.d. n.d.
В	Mono P:	PPh ₃	PPhCy ₂	Xphos	PCy ₃	P ^t Bu ₃
AdCO ₂ H (10 mol%)	Yield ^b 3a: Yield ^b 4a/4a':	34%. 2%/2%	80% trace	21% n.d.	83% trace	12% n.d.
	Bis P-P:	dppm	dppe	dpp-benz	dCype	dppp
	Yield ^b 3a: Yield ^b 4a/4a':	2%. 3%/2%	n.d. n.d.	n.d. n.d.	n.d. n.d.	n.d. n.d.
С	Mono P:	PPh ₃	PPhCy ₂	Xphos	PCy ₃	P ^t Bu ₃
Cu(OAc) ₂ (10 mol%)	Yield ^b 3a: Yield ^b 4a/4a':	3%. trace	9%. trace	10%. n.d.	trace n.d.	9%. n.d.
	Bis P-P:	dppm	dppe	dpp-benz	dCype	dppp
	Yield ^b 3a : Yield ^b 4a/4a' :	n.d. trace	n.d. 53%/5% 79%/7% ^c	12% 34%/4%	n.d. 5%/trace	n.d. 17%/1%

Chart 1 Ligand and promoter effects on hydroallylation. a 1a (0.20 mmol), 2 a (2.0 equiv.), 2 Pd₂(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, and 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, and 24 h.

1,5-diene 3a because these ligands occupy the otherwise vacant sites needed for β -hydride elimination. 1,14

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 cocatalyst that would accelerate transmetalation between the allyl species and the vinyl-Pd intermediate, and 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 monophosphine ligands that promotes the formation of 3a, bisphosphine ligands such as dppe and dpp-benz gave a higher yield of 4a/4a'. When dppe was used as the 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 that 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% yield. Aryl alkynes bearing electron-withdrawing substituents (CF₃, Ph, Ac, and CO₂Me) show slightly higher reactivities, providing 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 with 2naphthalenyl groups, the substrate transforms into a mixture of linear product 30 and branched product 30' in a 1:1.7 ratio. The branched product 30' probably originates from the formed η³-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, the 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 can be transformed into 1,4-dienes using the Pd/Cu catalyst combo. Although substrates bearing electron-donating groups lead to skipped dienes with moderate to good regioselectivities (4b-4d, 4k, and 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, 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 derivatives 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 bisallylations 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

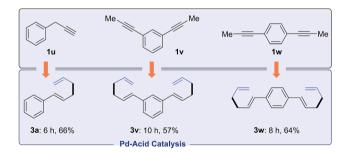
We also tested the scope of allylborons under our Pd-acid conditions (Table 2). Generally, substrates **2b–2d** were less reactive in allyl–allyl couplings. This agrees with previous work reported by Morken's group that substituted allylborons were comparatively reluctant in Pd-catalyzed allyl–allyl coupling reactions. ^{17g} To improve the reactivity, Cu(OAc)₂ was employed as an 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, and 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 literature⁷ and our own observations (Fig. 1A, right). First, the oxidative addition of the carboxylic acid with a Pd(0) precursor generates Pd(π)-hydride species **A**. *Syn*-Migratory insertion of alkyne **1** into Pd(π)-H **A** affords vinyl-Pd intermediate **B**. For the 1,5-diene pathway, a vacant coordination site of complex **B** is spared for β -hydride elimination in the presence of the monophosphine ligand. Allene **5** is subsequently produced and undergoes reinsertion into Pd(π)-H forming the π -allyl-Pd intermediate **C**. Then,

Table 1 Regioselective hydroallylation of alkynes^a

	Ar R	or Ar R	Pd ₂ (dba) ₃ (2.5 mol% PCy ₃ (10 mol%) AdCO ₂ H (10 mol% "BuOH (2.0 equiv.) dioxane, 80-90 °C, 6-1	Ar — R	B(pin) — 2a (2 equiv.)	Pd ₂ (dba) ₃ (2.5 mol%) dppe (5 mol%) Cu(OAc) ₂ (10 mol%) MeOH (3.0 equiv.) dioxane, 70 °C, 24 h	Me Ar 4	Ar 4.
A) 1,5-Dienes Synthesis Promoted By β-H Elimination				B) 1,4-Dienes Synthesis Promoted By Transmetalation —				
		Me	Et	MeO	Me	Me	Me	MeO
	3a : 82%	3b : 78%	3c : 71%	3d : 75% ^b	4a/4a': 71% (11.9:1)	4b/4b': 62% (7.9:1)	4c/4c': 70% (8.7:1)	4d/4d' : 70% (5.6:1) ^b
	F	CI	F ₃ C	Ph	Me	Me	Me F ₃ C	Me
	3e : 74%	3f : 78%	3g : 84%	3h : 84%	4e/4e': 71% (12.0:1)	4f/4f': 75% (18.5:1)	4g/4g': 86%	4h/4h': 88% (17.9:1)
		MeO ₂ C) We	CO ₂ Me		MeO ₂ C	Me Me	Me CO ₂ Me
	3i : 81%	3j : 90%	3k : 72% ^b	3I : 78%	4i : 78%	4j : 99%	4k/4k': 87% (9.6:1)	4I/4I': 93% (20.0:1)
	Me Me	Me		Me	Me Me	Me Me	Me	Et
	3m: 84%	3n : 52% ^b	3o/3o': 78% (1:1.7)	3p: n.d.	4m/4m': 65% (11.8:1)	4n/4n': trace	4o/4o': 80% (18.4:1)	4p/4p': 49% (13.3:1) ^c
	n _{Pr}			H H	"Bu	Me N	Me N	Me H
_	3q: n.d.	3r : 56%	3s/3s': 57% (11.5:1)	Me 3t : 38%	4q/4q': 60% (12.8:1)	4r: 23%	4s : 65% 0	Me 4t/4t': 25% (13.6:1)

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



Scheme 2 Hydroallylation of terminal and bis-alkynes

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 the Pd(0) catalyst (allyl-allyl coupling cycle).

In the presence of a $Cu(\pi)$ co-catalyst, we propose that transmetalation of allylboron 2a to generate allylcopper species 2' is favored. In this protocol, vinyl-Pd species B is also generated by a *syn*-migratory of alkyne 1 into $Pd(\pi)-H$ **A** (Fig. 1A, left). However, when coordinated with a bidentate ligand, vinyl-Pd intermediate B prefers direct transmetalation with

Table 2 The scope of allylborons

Pd₂(dba)₃ (2.5 mol%)

2	Product	w/o Cu(OAc) ₂	Cu(OAc) ₂
Ph B(pin) 2b	Ph 3x	6	34^a
Me B(pin) 2c	Ph 3y	n.d.	<5 ^a
Me B(pin) 2d	Me´ Me	13	38 ^a

^a Cu(OAc)₂ (10 mol%).

allylcopper species 2' to form D' rather than undergoing β -hydride elimination to produce allene 5. Reductive elimination from D' yields the product 1,4-diene 4a (allyl-vinyl coupling cycle).

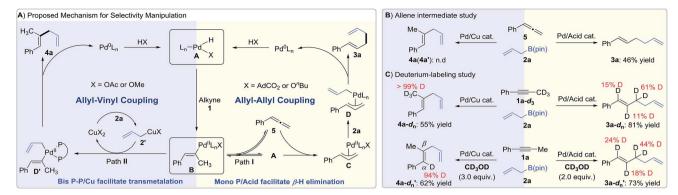


Fig. 1 Divergent reactivity of Pd(II) species.

To probe the feasibility of an allene intermediate, phenylallene 5 was subjected to couple with allyl-B(pin) 2a under two standard conditions (Fig. 1B, see the ESI for details†). The allene was transformed into 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 do not arise from the addition of allylB(pin) 2a to allene 5. Hydroallylation was also performed with deuterated alkyne 1a- d_3 or methanol (Fig. 1C). Under Pd/ acid catalysis, we found that 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 a 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 an α deuterated product was achieved using deuterated methanol (Fig. 1C). This indicates that β -hydride elimination is not involved in 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. The 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 the 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 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.

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