

Synthesis of Tetrasubstituted Allenes via Palladium-Catalyzed Cross-Coupling of Vinyl Bromides with Diazo Compounds

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Supporting Information Placeholder

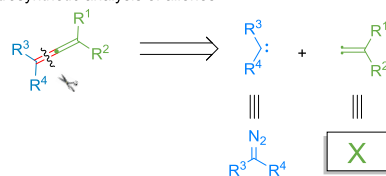
ABSTRACT: A highly efficient palladium-catalyzed cross-coupling of 2,2-diarylvinyl bromides with diazo compounds was developed, providing a convenient approach for the synthesis of tetrasubstituted allenes. Both aryl diazo carbonyl compounds and *N*-tosylhydrazones are competent carbene precursors in this reaction. An unprecedented hydrogen elimination of the π -allyl palladium intermediate is proposed to be the key step.

Allenenes are of great importance due to their wide existence in natural products,¹ pharmaceuticals,² and molecular materials.³ Furthermore, the active nature imparted by its unique orthogonal cumulative π -system makes them highly versatile and useful building blocks in organic synthesis.⁴ Although numerous methods for the preparation of allenes have been developed,^{5,6} they still lag far behind the growing demand in application. At present, the majority of the existing methodologies rely on the utilization of elaborate alkynes. Therefore, it is highly desirable to develop new approaches via novel mechanistic pathways, which may deliver the allenes efficiently from easily accessible starting materials and complement the current methodologies.⁷

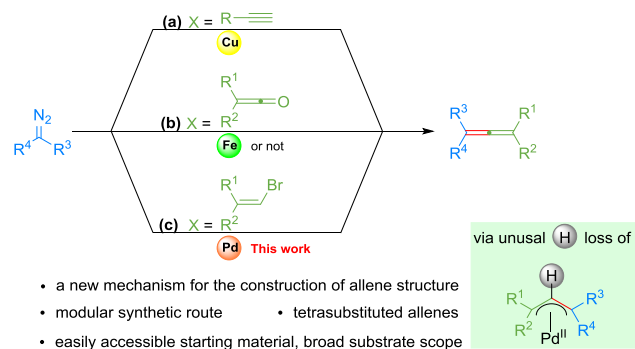
From the standpoint of retrosynthetic analysis, the disconnection of a double bond in allenes represents a convergent synthetic strategy, which means a carbene involved cross-coupling (Scheme 1). Diazo compounds, which may be used directly or in situ generated from *N*-tosylhydrazones, are the widely applied carbene precursors. After the seminal findings by Fu and co-workers,⁸ the systematic research from the group of Wang,⁹ as well as the contribution from Fox¹⁰ and Ley¹¹ matured the copper-catalyzed cross-coupling of diazo compounds with terminal alkynes as a reliable method for the modular synthesis of allenes (Scheme 1a). Recently, the asymmetric version of this reaction was also achieved by the groups of Liu,¹² Wang¹³ and Ley.¹⁴ In the meantime, the iron-catalyzed Wittig reaction between diazo compounds and ketenes was reported by Tang, Zhou and co-workers, offering an alternative approach for the allene synthesis (Scheme 1b).¹⁵ This approach was further modified to a metal-free synthesis using active silyl ketenes.¹⁶

Scheme 1. Synthesis of Allenes with Diazo Compounds

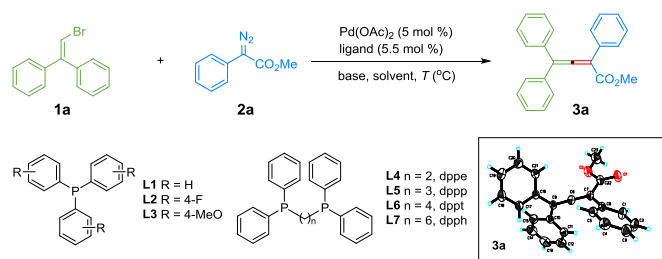
Retrosynthetic analysis of allenes



Different synthetic strategies



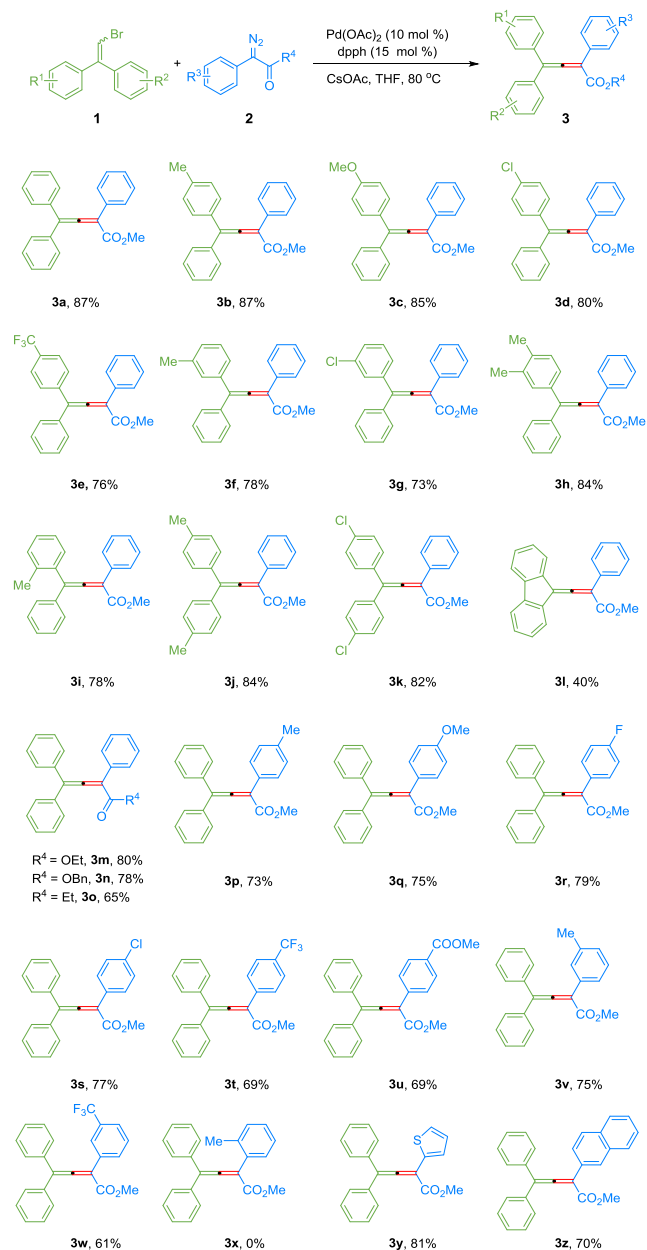
Late transition metals, like palladium and rhodium, are extensively used in the diazo compounds involved transformations.¹⁷ However, in contrast to the success with early transition metals (copper and iron), late transition metals seemed to be incompetent in the allene synthesis and no example has been reported yet. Herein, we investigated a palladium-catalyzed cross-coupling of vinyl bromides with diazo compounds, which afford a new way to fulfill the powerful strategy mentioned above, and proved the feasibility of using late transition metal to promote the desired cross-coupling (Scheme 1c). Interestingly, this transformation is supposed to go through an unusual loss of hydrogen on the central carbon atom of the π -allyl palladium intermediate.

Table 1. Reaction Conditions Optimization^{a,b}

entry	ligand	T (°C)	solvent	base	yield (%)
1	L1	80	THF	CsOAc	80
2	L2	80	THF	CsOAc	60
3	L3	80	THF	CsOAc	66
4	L4	80	THF	CsOAc	77
5	L5	80	THF	CsOAc	82
6	L6	80	THF	CsOAc	63
7	L7	80	THF	CsOAc	87
8	L7	80	THF	CsOPiv	65
9	L7	80	THF	Cs ₂ CO ₃	66
10	L7	80	THF	K ₂ CO ₃	77
11	L7	80	dioxane	CsOAc	82
12	L7	80	TBME	CsOAc	70
13	L7	80	Toluene	CsOAc	10
14	L7	80	DCE	CsOAc	37
15	L7	90	THF	CsOAc	86
16	L7	70	THF	CsOAc	78
17	L7	60	THF	CsOAc	20

^a Reactions conditions: **1a** (0.20 mmol), **2a** (0.30 mmol, 1.5 equiv), Pd(OAc)₂ (0.02 mmol, 0.1 equiv), ligand (0.06 mmol for L1-L3 or 0.03 mmol for L4-L7), CsOAc (0.30 mmol, 1.5 equiv), THF (2 mL). ^b Determined by ¹H NMR spectroscopy using CH₂Br₂ as an internal standard.

Initially, the cross-coupling of 2,2-diarylviny bromide **1a** and diazoacetate **2a** was tested with Pd(OAc)₂/PPh₃ as catalyst (Table 1). Delightfully, the desired allene **3a** was generated in high yield (entry 1), and its structure was unambiguously confirmed by X-ray analysis.¹⁸ Other mono-phosphine ligands, with either electron-withdrawing fluorine (L2) or electron-donating MeO group (L3), gave reduced reaction yields (entries 2 and 3). Bis-phosphine ligands were also competent to promote this reaction, and the ligand bearing a linkage of six carbon atoms further improved the reaction yield to 87% (entries 4-7). Instead of CsOAc, several other bases were also examined, but offered inferior results (entries 8-10). Reaction also went well in other etheral solvents, but was rather sluggish with toluene or DCE as solvent (entries 13 and 14). While a comparable result was obtained in an elevated reaction temperature of 90 °C (entry 15), an obvious loss in reaction yield was observed at lower temperature (entries 16 and 17).

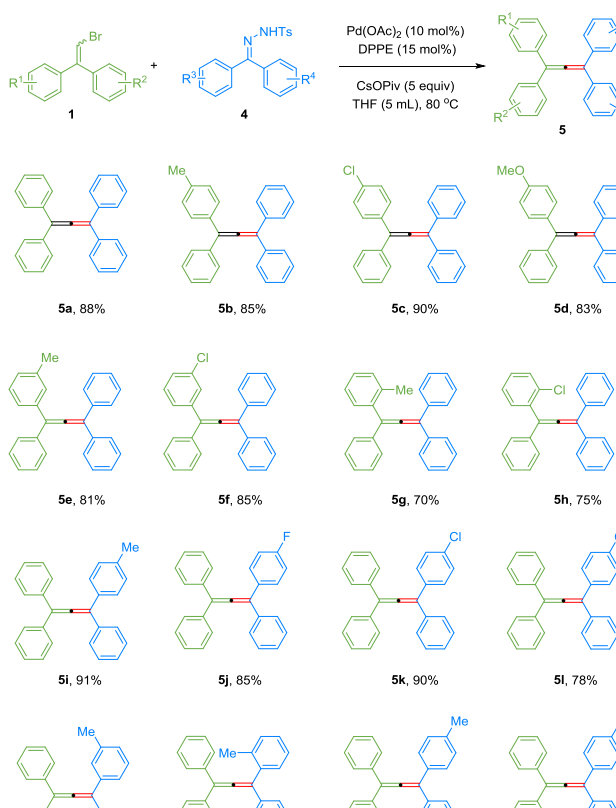
Scheme 2. Cross-Coupling of 2,2-Diarylviny Bromides with Diazo Carbonyl Compounds^{a,b}

^a Reactions conditions: **1** (0.20 mmol), **2** (0.30 mmol, 1.5 equiv), Pd(OAc)₂ (0.02 mmol, 0.1 equiv), dpph (0.03 mmol, 0.15 equiv), CsOAc (0.30 mmol, 1.5 equiv), THF (2 mL). ^b Isolated yields.

With the optimal reaction conditions in hand, we began to explore the generality of this cross-coupling reaction (Scheme 2). First, a variety of 2,2-diarylviny bromides **1** were used in the coupling with phenyl diazoacetate **2a**. All of them afforded high yields, with a deleterious effect on the reaction outcome by introducing electron-withdrawing groups to the phenyl ring, or moving the substituents from *para*- to *meta*- or *ortho*- position (**3d-i**). Vinyl bromide with a flat terminal fluorene substitution, instead of two separate aryl groups, also proceeded well (**3i**). Next, variation of the aryl diazoacetates **2** was also investigated. The methyl ester could be successfully replaced by an ethyl or benzyl ester, as well as an ethyl ketone (**3m-o**). Introduction of different substituents onto the *para*- or *meta*- position of the phenyl ring was well toler-

ated, albeit in slightly reduced reaction yields (**3p-w**). Compared with the vinyl bromide substrates, the diazoacetate part was more sensitive to the steric properties, as the *ortho*-methyl substituted phenyl ring completely blocked the coupling reaction (**3x**). Delightfully, other aromatic rings, like 2-thienyl or naphthyl group, could provide the desired products in good yields (**3y** and **3z**).

Scheme 3. Cross-Coupling of 2,2-Diarylvinyl Bromides with *N*-Tosylhydrazones^{a,b}

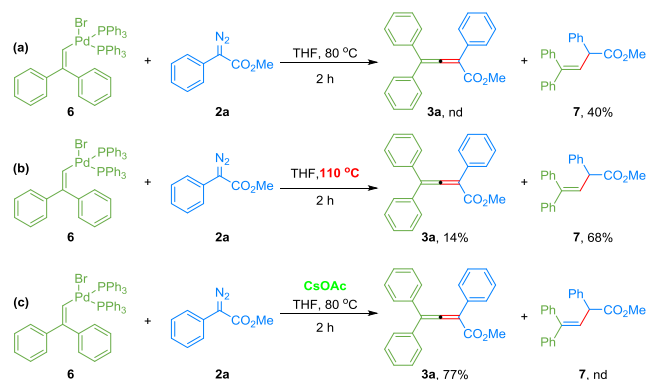


^aAll the reactions were carried out with **1** (0.20 mmol), **4** (0.30 mmol, 1.5 equiv), Pd(OAc)₂ (0.02 mmol, 0.1 equiv), dppe (0.03 mmol, 0.15 equiv), CsOPiv (1.00 mmol, 5 equiv), THF (5 mL). ^b Isolated yields.

Encouraged by the above success, we sought to use diaryldiazomethanes to produce tetra-aryl-substituted allenes, which showed some unique properties in material science,¹⁹ catalysis²⁰ and molecular recognition.²¹ Although a preliminary experiment with diphenyldiazomethane furnished the tetra-phenyl-substituted allene **5a** in moderate reaction yield under the standard reaction conditions, further efforts was hampered by the relatively lower stability of this kind of diazo compounds. Therefore, we switched to the corresponding *N*-tosylhydrazones **4**, a family of stable carbene precursors.²² Gratifyingly, the slight adjustment of the base and ligand to cesium pivalate and dppe could lead to the desired cross-coupling products in good to excellent yields (Scheme 3). While electronic variation on the phenyl ring of the 2,2-diarylvinyl bromides showed marginal effect on the reaction outcome (**5a-h**), the introduction of electron-withdrawing group

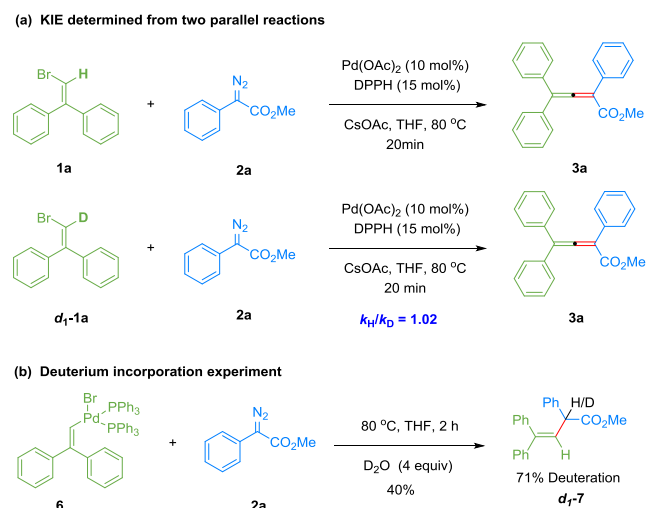
to the diaryl ketones derived *N*-tosylhydrazones gave a slightly reduced yield (**5j-l**). *Ortho*-substituted phenyl ring on either vinyl bromides or *N*-tosylhydrazone part resulted in an obvious loss in reaction yield, consistent with results from diazoacetate species (**5g** and **5n**).

Scheme 4. Control Experiments with Palladium Complex



To probe the mechanism of this catalytic reaction, palladium complex **6** was prepared and subjected to several control experiments (Scheme 4).²³ When the mixture of complex **6** and diazoacetate **2a** in THF was heated at 80 °C for 2 h, the reaction solely afforded olefin **7**, and a small amount of allene **3a** could be observed upon elevation of reaction temperature, with olefin **7** still as the major product. However, the preference of reaction products was completely inverted when cesium acetate was added, and only allene **3a** was produced even at 80 °C. These experiments hint that the reaction generated an allylpalladium intermediate, which could undergo either protodepalladation to afford olefin **7**, or an unusual hydride elimination to give allene **3a**. Such a hydride elimination step was facilitated by the basic carboxylate salts.

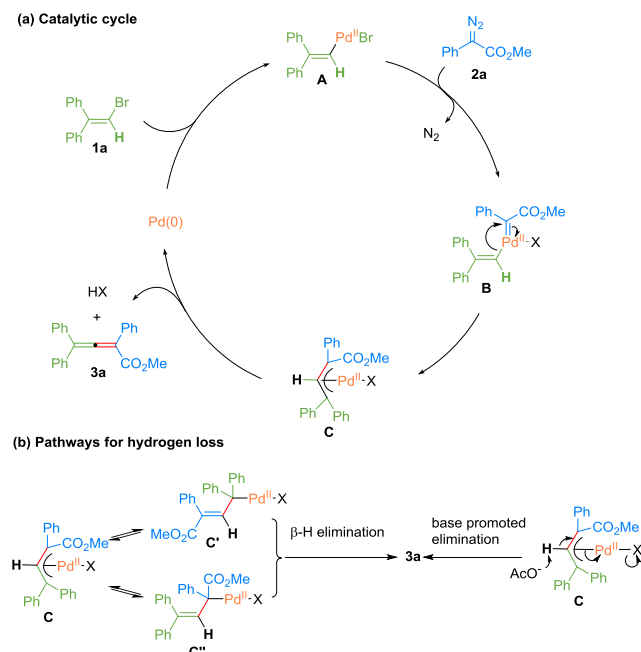
Scheme 5. KIE and Deuterium-Labeling Experiments



To gain more mechanistic insights, two deuterium labeling experiments were carried out (Scheme 5). The kinetic isotope effect (KIE) was measured in two parallel reactions using **1a** and deuterium-labeled **d₁-1a**. A KIE value of 1.02 implicated that the final hydride elimination was not involved in the rate-limiting

step.²⁴ In the presence of 4 equivalents of D₂O, the reaction of complex 6 and diazoacetate 2a afforded deuterated olefin d₁₋₇ with 71% D incorporation, showing the possibility of the protodepalladation by the moisture of the reaction system in the absence of a carboxylate salt.

Figure 1. Plausible reaction mechanism (X = Br or OAc; ligands are omitted for clarity)



Based on the above investigations and literature precedents, a plausible mechanism is outlined in Fig 1. Initially, oxidative addition of vinyl bromide 1a to the Pd⁰ catalyst offers the Pd^{II} species A. Then the Pd^{II} species A reacts with the diazoacetate 2a to form Pd^{II} carbene species B. A subsequent migratory insertion of carbene into the Pd–C bond affords π-allylpalladium species C,²⁵ which is followed by a hydrogen-elimination to provide the desired product 3a. As for the key hydrogen elimination step, two possible pathways are supposed (Figure 1b). The first one involves the isomerization of intermediate C to η¹ intermediate C' or C'' and subsequent β-H elimination (Fig 1b, left). The second one is more like a base promoted dissociation (Fig 1b, right).

In conclusion, a highly efficient palladium-catalyzed cross-coupling of 2,2-diarylviny bromides with diazo compounds was developed, providing a convenient approach to modular synthesis of tetrasubstituted allenes. Both aryl diazoacetates and N-tosylhydrazones proved to be competent coupling partners. The key step in the catalytic cycle is believed to undergo an unprecedented hydrogen elimination on the central carbon atom of the π-allyl palladium intermediate. Investigation of the detailed mechanism and further applications of this methodology are in progress.

ASSOCIATED CONTENT

Supporting Information

Experimental details and compound characterizations. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interests.

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