C–C Coupling

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Palladium-Catalyzed Oxidative Cross-Coupling of *N*-Tosylhydrazones or Diazoesters with Terminal Alkynes: A Route to Conjugated Enynes**

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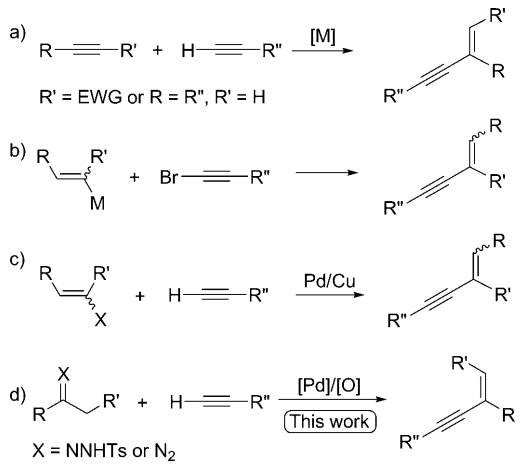
Conjugated enynes have attracted considerable attention owing to their biological importance, their occurrence in various natural products,[1] and their versatility as building blocks for the synthesis of organic conducting polymers.[2] As a result, enormous effort has been devoted to the regio- and stereoselective synthesis of conjugated enynes. Among the various methods developed in the past decades for the synthesis of enynes, the metal-catalyzed dimerization of terminal alkynes is a straightforward and atom-efficient approach (Scheme 1a, R = R″, R′ = H).[3] However, the complicated regio- and stereoselectivity of the dimerization process hampers the wide application of this method. Moreover, only in limited cases is the selective cross-coupling of two different alkynes possible.[3a,b] A solution to overcome this setback is the coupling of alkynes with structurally defined organometallic alkenes (Scheme 1b).[4] However, organometallic substrates are usually difficult to handle and are toxic in general.



Scheme 1. Synthesis of conjugated enynes. EWG = electron-withdrawing group, Ts = *p*-toluenesulfonyl.

The coupling of terminal alkynes with vinyl halides under the catalysis of palladium complexes and copper(I) iodide, namely, the Sonogashira reaction, is another option for the synthesis of conjugated enynes (Scheme 1c).[5] This elegant process does not require a stoichiometric amount of an organometallic reagent and can produce enynes in a stereoselective manner. The major limitation of this method is that multiple steps are generally required for the preparation of the vinyl halide. In view of the limitations and shortcomings of these established methods, we conceived that it would be desirable to further develop a new type of coupling reaction that may circumvent these drawbacks.[6]

Palladium-catalyzed cross-coupling reactions involving diazo compounds as coupling partners have emerged as a new type of C=C bond-forming reaction.[7,9–15] In pioneering studies, Van Vranken and co-workers demonstrated palladium-catalyzed coupling reactions with trimethylsilyldiazomethane.[7,8] Barluenga et al. first discovered a palladium-catalyzed coupling reaction of *N*-tosylhydrazones with aryl bromides.[9] We have also reported a series of palladium-catalyzed cross-coupling reactions with α-diazocarbonyl compounds or *N*-tosylhydrazones as coupling partners.[10a,e,f,11c,13,14] Migratory insertion involving a palladium carbene is proposed to account for these cross-coupling reactions.[15] Aryl,[9,10] benzyl,[11] vinyl,[12] allyl,[13] and acyl groups[14] have so far been used as the migratory group. As a continuation of our interest in palladium-catalyzed migratory-insertion reactions, we report the palladium-catalyzed cross-coupling of terminal alkynes with *N*-tosylhydrazones or diazoesters. The reaction involves an unprecedented alkynyl migratory insertion of a palladium carbene[16] to afford conjugated enynes in a highly stereoselective manner (Scheme 1d).

Initially, we chose phenylbromoethyne (**2a**) as the cross-coupling partner and examined its reaction with the *N*-tosylhydrazone **1a** in the presence of various palladium catalytic systems. However, none of the desired product was obtained. We then decided to explore an oxidative coupling process with a terminal alkyne. Li and co-workers reported a palladium-catalyzed 1,4-addition of terminal alkynes to C=C bonds in which the reactivity of the alkynyl C–Pd bond could be increased by an electron-rich ligand.[17] Enlightened by this report, we attempted the coupling of phenylacetylene (**2b**)

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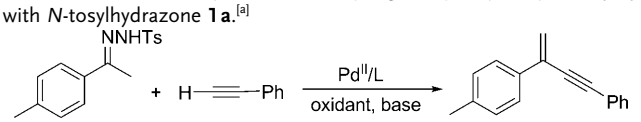
Table 1: Palladium-catalyzed cross-coupling of phenylacetylene (**2b**) with *N*-tosylhydrazone **1a**.[a]



1a **2b** **3a**

Entry	Catalyst (mol%)	Oxidant (equiv)	Base	Yield [%][b]
1	[Pd(allyl)(IPr)Cl] (3)	BQ (2)	*t*BuOLi	15
2	$Pd(OAc)_2$ (5)/PMe_3 (10)	BQ (2)	*t*BuOLi	20
3	$Pd(OAc)_2$(5)/Xphos (10)	BQ (2)	*t*BuOLi	5
4	$Pd(OAc)_2$ (5)/PCy_3 (10)	BQ (2)	*t*BuOLi	29
5	$Pd(OAc)_2$ (5)/PPh_3 (10)	BQ (2)	*t*BuOLi	13
6	$Pd(OAc)_2$ (5)/P(2-furyl)$_3$ (10)	BQ (2)	*t*BuOLi	67
7	**$Pd(OAc)_2$ (5)/P(2-furyl)$_3$ (20)**	**BQ (2)**	***t*BuOLi**	**85**
8	$Pd(OAc)_2$ (5)/P(2-furyl)$_3$ (20)	BQ (2)	K_2CO_3	0
9	$Pd(OAc)_2$(5)/P(2-furyl)$_3$(20)	BQ (2)	Cs_2CO_3	21
10	$Pd(OAc)_2$(5)/P(2-furyl)$_3$(20)	BQ (2)	NaOEt	3
11	$Pd(OAc)_2$ (5)/P(2-furyl)$_3$ (20)	DDQ (2)	*t*BuOLi	10
12	$Pd(OAc)_2$ (5)/P(2-furyl)$_3$ (20)	AQ (2)	*t*BuOLi	0
13	$Pd(OAc)_2$ (5)/P(2-furyl)$_3$ (20)	BQ (1)	*t*BuOLi	42
14	$Pd(OAc)_2$ (5)/P(2-furyl)$_3$ (20)	BQ (3)	*t*BuOLi	60
15	–	BQ (2)	*t*BuOLi	0

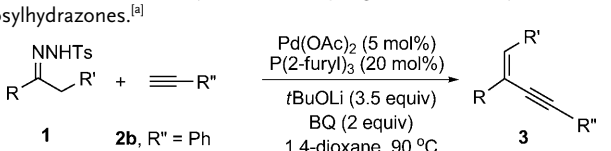
[a] Reaction conditions: **1a** (0.25 mmol), **2b** (1.5 equiv), base (3.5 equiv), 1,4-dioxane (2 mL), BQ (1.5 equiv), catalyst, 90°C, 4 h. [b] The yield was determined by GC with dodecane as an internal standard. AQ = anthraquinone, BQ = benzoquinone, Cy = cyclohexyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazole, Xphos = 2-dicyclohexylphosphanyl-2′,4′,6′-triisopropylbiphenyl.

with **1a** in the presence of [Pd(allyl)(IPr)Cl] and benzoquinone (BQ) at 90°C. To our delight, we obtained the desired enyne **3a**, albeit in low yield (Table 1, entry 1). We tested different ligands and found that the weak electron-rich ligand tri(2-furyl)phosphane provided the optimal result and afforded the desired product **3a** in 67% yield (Table 1, entries 2–6). When the ratio of P(2-furyl)$_3$ to $Pd(OAc)_2$ was increased from 2:1 to 4:1, the reaction improved further (Table 1, entry 7).

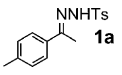
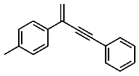
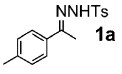
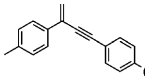
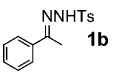
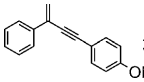
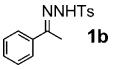
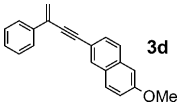
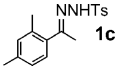
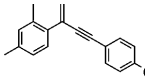
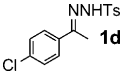
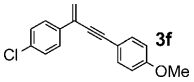
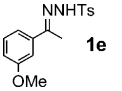
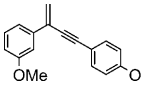
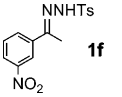
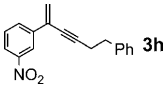
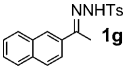
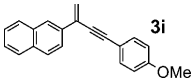
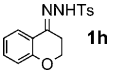
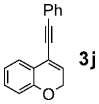
Next, we investigated the effect of the base. A number of bases, including K_2CO_3, Cs_2CO_3, and NaOEt, were examined; however, they were all less efficient than *t*BuOLi (Table 1, entries 7–10). We also studied the effect of the oxidant and found that oxidants other than BQ, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or anthraquinone (AQ), were not as effective (Table 1, entries 11 and 12). The reaction resulted in diminished yields when the loading of BQ was less or more than 2 equivalents (Table 1, entries 13 and 14).

Having established the optimal reaction conditions (Table 1, entry 7), we next explored the scope of the reaction with a variety of terminal alkynes and *N*-tosylhydrazones (Tables 2 and 3). The palladium-catalyzed oxidative cross-coupling of *N*-tosylhydrazones with terminal alkynes led to the formation of the corresponding enynes (Table 2). The reaction occurred smoothly with *ortho*-, *para*-, and *meta*-substituted aromatic *N*-tosylhydrazones to afford the desired enynes in moderate to good yields (Table 2, entries 2 and 5–8). Both electron-donating and electron-withdrawing groups were tolerated on the aromatic ring (Table 2, entries 6–8).

Table 2: Palladium-catalyzed cross-coupling of terminal alkynes with *N*-tosylhydrazones.[a]



1 **2b**, R" = Ph; **2c**, R" = *p*-anisyl; **2d**, R" = 6-methoxy-2-naphthyl; **2e**, R" = CH_2CH_2Ph **3**

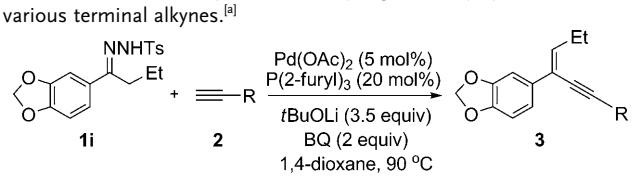
Entry	1	2	3	Yield [%][b]
1	 **1a**	**2b**	 **3a**	65
2	 **1a**	**2c**	 **3b**	77
3	 **1b**	**2c**	 **3c**	74
4[c]	 **1b**	**2d**	 **3d**	42
5	 **1c**	**2c**	 **3e**	73
6	 **1d**	**2c**	 **3f**	71
7	 **1e**	**2c**	 **3g**	53
8	 **1f**	**2e**	 **3h**	68
9	 **1g**	**2c**	 **3i**	69
10	 **1h**	**2b**	 **3j**	65

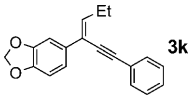
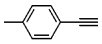
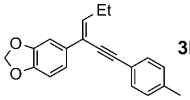
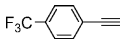
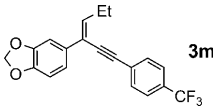
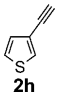
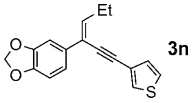
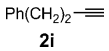
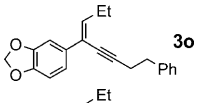
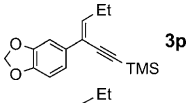
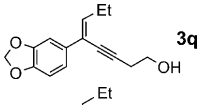
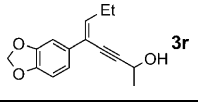
[a] Reaction conditions: **1** (0.25 mmol), **2** (1.5 equiv), *t*BuOLi (3.5 equiv), BQ (2 equiv), $Pd(OAc)_2$ (5 mol%), P(2-furyl)$_3$ (20 mol%), 1,4-dioxane (2 mL), 90°C, 4 h. [b] Yield of the isolated product. [c] 45% of alkyne **2d** was recovered.

The naphthyl *N*-tosylhydrazone **1g** was also a suitable substrate for this reaction (Table 2, entry 9). Notably, cyclic *N*-tosylhydrazone **1h**, which was readily derived from naturally occurring 4-chromanone, also underwent a smooth reaction to afford the corresponding enyne **3j** in 65% yield (Table 2, entry 10).

Next, we used *N*-tosylhydrazone **1i** to examine the cross-coupling reaction with a series of terminal alkynes (Table 3). The reaction was found to tolerate a variety of functional groups in the alkyne substrate, including phenyl, alkyl, and hydroxy groups. Alkyne substrates containing an aromatic ring with a functional group at the *para* position or a heterocyclic or phenylethyl substituent were all converted into the corresponding enynes in good yields (Table 3, entries 1–5). The reaction of an alkyne bearing a $SiMe_3$

Table 3: Palladium-catalyzed cross-coupling of *N*-tosylhydrazone **1i** with various terminal alkynes.[a]



Entry	Alkyne **2**	Enyne **3**	Yield [%][b]	*Z*/*E*[c]
1	 **2b**	 **3k**	76	>20:1
2	 **2f**	 **3l**	81	>20:1
3	 **2g**	 **3m**	70	>20:1
4	 **2h**	 **3n**	72	>20:1
5	 **2i**	 **3o**	75	>20:1
6	 **2j**	 **3p**	83	>20:1
7	 **2k**	 **3q**	66	>20:1
8	 **2l**	 **3r**	61	>20:1

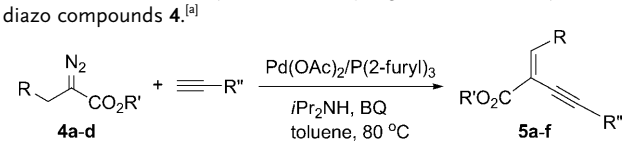
[a] Reactions were carried out under the conditions described in Table 2. TMS = trimethylsilyl. [b] Yield of the isolated product. [c] The *Z*/*E* selectivity was determined by ^{1}H NMR spectroscopy. For product **3p**, the configuration was further confirmed by NOESY and COSY spectra.

group resulted in the enyne product **3p** in 83% yield; desilylation did not occur under the reaction conditions (Table 3, entry 6). We were also pleased to find that alkynes containing a primary or secondary hydroxy group reacted smoothly with *N*-tosylhydrazones to afford the corresponding enynes in good yields without the need for functional-group protection (Table 3, entries 7 and 8). In all reactions in Table 3, the *Z* isomer was obtained as the sole product.

To further expand the scope of the reaction, we used α-diazocarbonyl compounds **4a–d** as substrates under slightly modified conditions (Table 4). The treatment of terminal alkynes with this series of α-diazocarbonyl compounds in the presence of $Pd(OAc)_2$ and $P(2\text{-furyl})_3$ at 80 °C furnished the corresponding products **5a–f** in moderate to good yields with complete stereoselectivity.

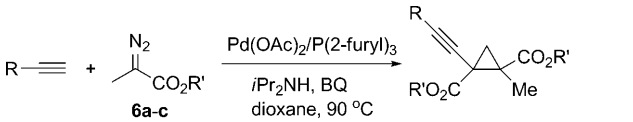
Interestingly, when α-diazocarbonyl compounds **6a–c** were treated with terminal alkynes under similar conditions, cyclopropanes **7a–c** were obtained as the only diastereoisomers according to NMR spectra (Scheme 2). This result is consistent with our previous observation that the palladium-

Table 4: Palladium-catalyzed cross-coupling of terminal alkynes with diazo compounds **4**.[a]



Entry	R	R′	R″	Product	Yield [%][b]
1	$PhCH_2CH_2$	Me	Ph	**5a**	64
2	CH_2CH_3	Me	Ph	**5b**	71
3	n-C_4H_9	Bn	Ph	**5c**	58
4	CO_2Et	Et	Ph	**5d**	27
5	CH_2CH_3	Me	TMS	**5e**	75
6	CH_2CH_3	Me	3-thienyl	**5f**	52

[a] Reaction conditions: **4** (0.25 mmol), the alkyne (1.5 equiv), iPr_2NH (4 equiv), toluene (2 mL), BQ (1.5 equiv), $Pd(OAc)_2$ (5 mol%), $P(2\text{-furyl})_3$ (20 mol%), 80 °C, 4 h. [b] Yield of the isolated product. In all cases only one isomer was formed. The configuration of the product was determined by ^{1}H NMR spectroscopy.



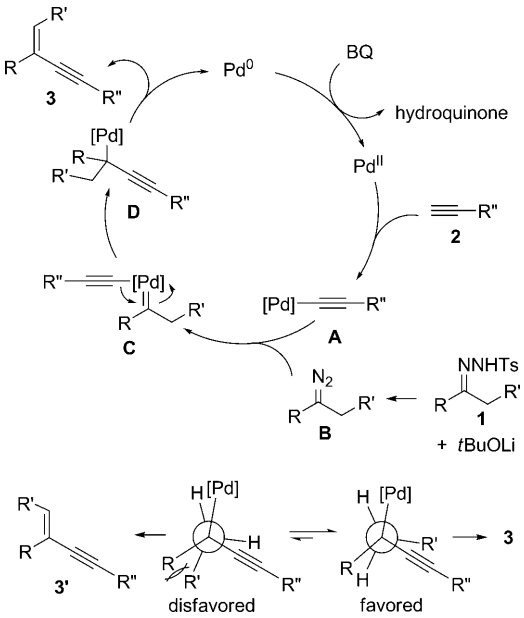
7a, R = Ph, R' = Me, 51%
7b, R = Ph, R' = Bn, 41%
7c, R = 3-thienyl, R' = Me, 55%

Scheme 2. Palladium-catalyzed tandem cross-coupling/cyclopropanation reaction. Bn = benzyl.

catalyzed cyclopropanation of olefins occurs readily when the C=C bond bears an electron-withdrawing substituent.[18] Thus, the initially formed enyne products react further with a second equivalent of the α-diazoester under conditions of palladium catalysis to afford the cyclopropane derivatives as the final products.

A plausible mechanism for the cross-coupling reaction is proposed in Scheme 3. The electron-rich ligand promotes the formation of the alkynyl palladium intermediate **A**,[3b,17,19] which reacts with diazoesters or the diazo substrate **B** generated in situ to afford a palladium carbene complex **C**. Migratory insertion of the alkynyl group into the palladium carbene at the carbenic carbon atom leads to the intermediate **D**, β-H elimination from which gives enynes **3**. Finally, Pd^0 is oxidized by benzoquinone to regenerate the Pd^{II} species. The high stereoselectivity for the formation of enynes **3** can be explained on the basis of the transition state of the *syn* β-H elimination from intermediate **D**: the alkyl group R′ prefers to eclipse with the less bulky linear alkyne moiety, and this arrangement leads to enynes **3** as the main products.[9,11b]

In conclusion, we have developed a novel method for the synthesis of conjugated enynes through the cross-coupling of *N*-tosylhydrazones with terminal alkynes. This reaction, which involves an unprecedented alkynyl migratory insertion of a palladium carbene, was used to obtain a variety of conjugated enynes in a stereoselective manner. Unlike established methods for enyne synthesis, the current methodology requires no additional organometallic reagent or halide. Moreover, the *N*-tosylhydrazones used are readily available



Scheme 3. Proposed mechanism.

from the corresponding ketones and are easy to handle. All of these features make this method a useful extension of palladium-catalyzed coupling reactions for enyne synthesis. Further studies on the reaction mechanism, its scope, and synthetic applications are in progress.

Experimental Section

Representative procedure: $Pd(OAc)_2$ (5 mol%), tri(2-furyl)phosphane (20 mol%), *t*BuOLi (3.5 equiv), benzoquinone (2 equiv), and *N*-tosylhydrazone **1a** (75 mg, 0.25 mmol) were suspended in 1,4-dioxane (2 mL) in a 5 mL Schlenk tube under nitrogen. Phenylacetylene (**2b**; 1.5 equiv) was then added, and the resulting solution was stirred at 90°C for 4 h. The mixture was then cooled to room temperature and filtered through a short path of silica gel with hexane and CH_2Cl_2 as eluents. The volatile compounds were removed in vacuo, and the crude residue was purified by column chromatography (silica gel, hexane) to give **3a** (35 mg, 65%) as a light-yellow oil.

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