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Expeditious enyne construction from alkynes via oxidative Pd(II)-catalyzed Heck-type coupling

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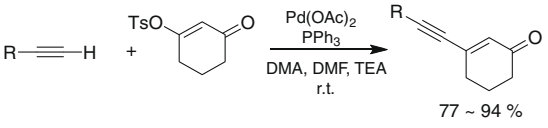
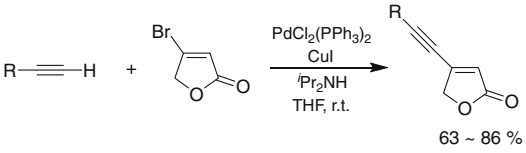
ABSTRACT

The enyne, ubiquitous in natural products, can be a challenge to generate since these moieties require many synthetic transformations to assemble them. We developed a simpler protocol to construct enynes while we found that this oxidative reaction was tolerant in substrate scope. In addition, the utility of this reaction was demonstrated through the attempt in synthesizing antifungal agent Lamisil™.

The enyne moiety can be found in many natural products;[1] therefore, it is crucial to develop a powerful methodology to assemble enynes. Also, the enyne is a useful intermediate, because it can be easily hydroxylated[2] or converted to a diene, triene,[3] or furan;[4] all of which are commonly present in natural products. Although there have been numerous known protocols to construct enynes in the presence of a palladium catalyst,[5] these reactions can be cumbersome since both coupling substrates need to be prepared into reactive alkynes or halide olefins prior to coupling. Especially, the reactions of acetylenes with α,β-unsaturated ketones have been barely reported. Recently, Schumacher[6a] (Eq. 1) and Boukouvalas[6b] (Eq. 2) utilized Pd(II)-catalyzed coupling reaction between terminal alkynes and activated olefins to obtain conjugated enynes.

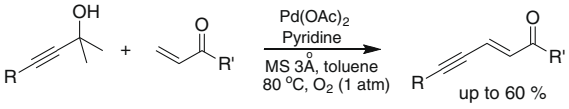


(1)

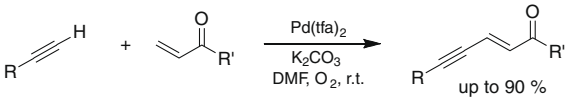


(2)

Utilization of terminal alkynes has been known for many years as Glasier and Sonogashira[7] coupling, however the *sp* variant of the Heck reaction has not been fully investigated yet. In 2003, Uemura, et al. reported palladium-catalyzed oxidative alkynylation of commercially available olefins using *tert*-propargylic alcohols as alkynylation reagents under an oxygen atmosphere[5b] (Eq. 3). However, the reaction required preparation of alkyne substrates, as well as high reaction temperatures and longer reaction times. In order to mitigate these shortcomings, we wish to report a new synthetic protocol to construct enyne compounds and offer an example of a synthetic application such as Lamisil™:



(3)



(4)

While extensively researching for carbon–carbon bond formation using oxidative palladium(II) catalysis, we found that the coupling of commercially available terminal alkynes and olefins produced enyne compounds under mild conditions (Eq. 4). Seeking optimal conditions, we investigated the coupling of 4-ethynyltoluene and *tert*-butyl acrylate using various bases, palladium catalysts, solvents, and atmospheric conditions as shown in Table 1. Although a Glasier-type homocoupling compound (**3**) was formed as a side product through the condensation of two alkynes, this can be circumvented by reacting with an excess of olefin to produce enyne compound (**2**). Generally, bases are well known to be a pivotal component in palladium-catalyzed coupling reactions such as the Miyaura–Suzuki and Sonogashira reactions. The bases in these reactions were believed to facilitate transmetallation of the acetylene compound via formation of acetylide, resulting in the enhancement of the coupling reactions. However, homocoupled compound **3** was concomitantly formed due to the reactive acetylide intermediate. The use of organic bases, such as pyridine, triethyl amine, and diisopropylethyl amine promoted the formation of homocoupled product **3**, which lowers the selectivity **2**/**3** ratio (entries 1–3). Due to a possible chelation with the palladium catalyst, the reactions were incomplete when pyridine was used. It was subsequently determined that inorganic bases led to a better ratio

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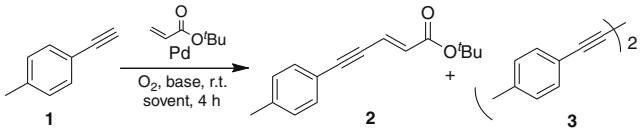
Table 1
Evaluation of various reaction conditions[a]



1 2 3

Entry	Catalyst	Base	Solvent	Conv.[b] (%)	Selectivity[b] (**2**/**3**)
1	$Pd(OAc)_2$	Pyridine	DMF	37	0/100
2	$Pd(OAc)_2$	TEA	DMF	100	32/68
3	$Pd(OAc)_2$	DIPEA	DMF	100	34/66
4	$Pd(OAc)_2$	Na_2CO_3	DMF	100	55/45
5	$Pd(OAc)_2$	K_2CO_3	DMF	100	57/43
6	$Pd(OAc)_2$	None	DMF	12	23/77
7	$Pd(OAc)_2$	K_2CO_3	Toluene	0	—
8	$Pd(OAc)_2$	K_2CO_3	DMA	100	50/50
9	$Pd(OAc)_2$	K_2CO_3	DMSO	100	0/100
10	$Pd(OAc)_2$	K_2CO_3	MeCN	88	26/74
11	$Pd(OAc)_2$	K_2CO_3	THF	66	31/69
12	Pd_2dba_3	K_2CO_3	DMF	100	22/78
13	$PdCl2(PPh3)_2$	K_2CO_3	DMF	100	25/75
14	$Pd(PPh3)_2$	K_2CO_3	DMF	0	—
15	None	K_2CO_3	DMF	0	—
16	$Pd(TFA)_2$	K_2CO_3	DMF	100	**67/33**
17[c]	$Pd(TFA)_2$	K_2CO_3	DMF	62	47/53
18[d]	$Pd(TFA)_2$	K_2CO_3	DMF	51	50/50
19[e]	$Pd(TFA)_2$	K_2CO_3	DMF	39	53/47
20[f]	$Pd(TFA)_2$	K_2CO_3	DMF	100	**70/30**

[a] All reactions were carried out with **1** (0.31 mmol) and *tert*-butyl acrylate (1.24 mmol) in the presence of 2 mol % of Pd and base (0.62 mmol).
[b] Calculated by GC analysis.
[c] Under air condition.
[d] Under N_2 condition.
[e] Under Ar condition.
[f] 10 equiv of *tert*-butyl acylate under O_2 condition.

of cross-coupling product **2** and homocoupled product **3** than organic bases (entries 4 and 5). Among the bases evaluated, K_2CO_3 was the best in the coupling reaction.

In addition, we demonstrated the coupling reactions in various solvent systems. There was no observable cross-coupling reaction when toluene was used (entry 7). In the cases of THF and acetonitrile, the reactions were incomplete; on the other hand, 4-ethynyltoluene was consumed in polar solvents such as DMF, DMA, and DMSO. However, only in the DMF and DMA solvent systems was the desired enyne product **2** obtained in modest yields.

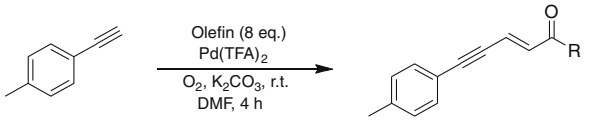
On the basis of these results, we screened other reaction variants, such as atmosphere, sources of palladium, loading of catalyst, and concentration to determine optimal conditions. Varying the palladium source showed that palladium trifluoroacetate has better selectivity to generate the cross-coupled product **2** (entry 16). However, in the presence of Pd_2dba_3 and $PdCl_2(PPh_3)_2$, coupling reactions were converted mostly to homocoupled compound **3** (entries 12 and 13). We found that the reaction did not proceed at all in the presence of $Pd(PPh_3)_4$ (entry 14). Under an air, nitrogen, or argon atmosphere, the conversion was not complete and selectivity was lower (entries 17–19). Many efforts to minimize the formation of the homocoupled product from the reaction of acetylide were investigated, such as slow addition of acetylene via a syringe pump and using large excess of olefins (>10 equiv); however, none of these methods helped suppress formation of the Glasier-type side product, which results in decreasing the overall yield of the cross-coupling product. Overall, although the homocoupling reaction of acetylide cannot be avoided under various reaction conditions due to its high reactivity, we found that the oxidative palladium-catalyzed coupling reactions between acetylide and olefin afforded (*E*)-selective enyne product in our protocol.

With optimized conditions in hand, we carried out the coupling reaction with various olefins and 4-ethynyltoluene. As shown in Table 2, *tert*-butyl and ethyl acrylates were converted efficiently to enyne compounds **2** and **4** in 50% and 41% yields, respectively (entries 1 and 2). However, the reaction with methyl and ethyl vinyl ketone afforded enyne compounds **5** and **6** in poor yields (entries 3 and 4). In addition to these substrates, acrylamide, acrylic acid, styrene, or acrylonitrile as the coupling partner could not give the desired coupled products.

To further investigate the scope and limitation of this methodology, we carried out the cross-coupling of various aryl- and alkylacetylenes with *tert*-butyl acrylate as summarized in Table 3. The coupling reaction involving a straight chain alkyne, a hindered alkyne, and a cyclic alkyne proceeded to afford the corresponding cross-coupling compounds **7**, **8**, and **9** in 72, 71, and 43% yields, respectively (entries 1–3). In addition, the reactions of *tert*-butyl acrylate with an aryl bearing an electron-donating group (methoxy and dimethylamino) afforded compounds **10** and **11** in good yields (entries 4–5). On the contrary, although the cross-coupling still occurs when employing an aryl bearing an electron-deficient group such as *p*-trifluoro methyl and *p*-nitrophenylacetylene, the yields are low at 39% and 33% yields, respectively (entries 9 and 10). We believe that the acidity of the terminal acetylenic proton plays a role in the product composition. The compounds bearing less acidic protons give better selectivity than more acidic substrates. This can be explained by the fact that the increased acidity of certain substrates allows them to quickly react to form reactive palladium-alkynyl intermediates, which then undergo a homo-coupling process more easily. However, the less acidic substrates are not as reactive, thus the formation of the palladium-alkynyl complexes is much slower, and the complexes react more selectively with olefins to generate the desired cross-coupling products. Overall, the kinetic of the palladium intermediate governs the yields of the enyne products.

We believe that this reaction may be the first example of coupling a terminal acetylene with an olefin, where a Heck type mechanism may be involved. Based on a mechanism proposed by Cheng, Martensson, and our previous research results,[8] we postulated that this coupling reaction undergoes process similar to the sp^2 counterparts (Scheme 2). The reaction can be initiated by the formation of an alkynyl palladium complex **II** via base-assisted deprotonation. The second incorporation of an alkenyl group can be carried out by migratory insertion, which would be followed by β-hydride elimination to produce cross-coupling product **IV** and Pd(0) species. Molecular oxygen would then oxidize the resulting Pd(0) to a peroxopalladium complex **VI**,[9] which can react with another alkyne compound to regenerate alkyne–Pd–L complex **II**. This reactive intermediate would react with either the olefin or the alkyne. However, the stronger affinity of alkynes is responsible for the formation of the homocoupled side product.

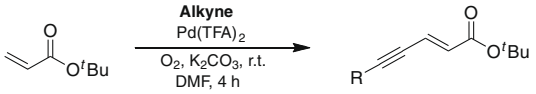
Table 2
The effect of various olefin with 4-ethynyltoluene[a]

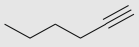
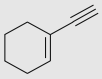
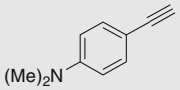
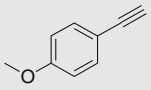
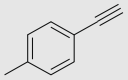
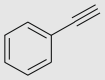
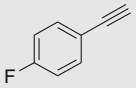
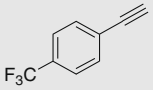
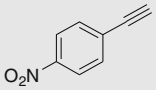
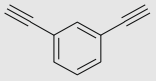


Entry	Olefin		Product (yield)[b]
1		R:O^{t}Bu	**2** (50%)
2		OEt	**4** (41%)
3		Me	**5** (45%)
4		Et	**6** (25%)

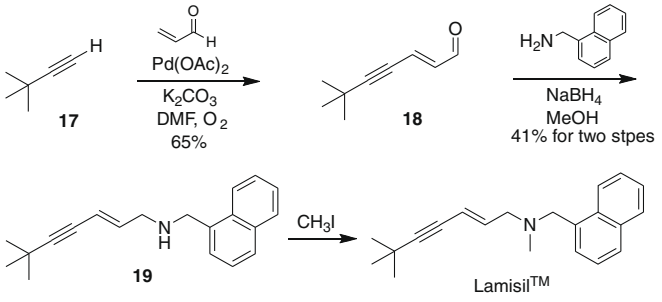
[a] All reactions were carried out with 4-ethynyltoluene (0.31 mmol), olefin (3.1 mmol), $Pd(TFA)_2$ (2 mol %), and K_2CO_3 (0.62 mmol) in DMF (1.5 mL).
[b] Isolated yields.

Table 3
The effect of various alkynes with *tert*-butyl acrylate[a]



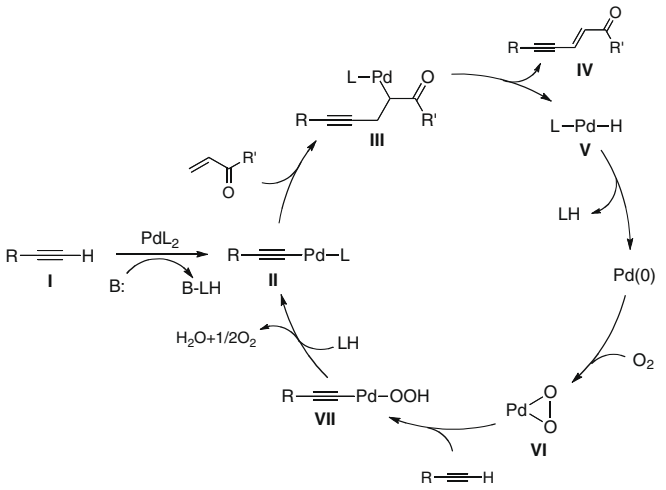
Entry	Alkyne	Product[b] (yield)
1		**7** (72%)
2		**8** (71%)
3		**9** (43%)
4		**10** (92%)
5		**11** (67%)
6		**2** (50%)
7		**12** (48%)
8		**13** (45%)
9		**14** (39%)
10		**15** (33%)
11		**16** (37%)

[a] All reactions were carried out with alkyne (0.31 mmol), *tert*-butyl acrylate (2.5 mmol), $Pd(TFA)_2$ (2 mol %), and K_2CO_3 (0.62 mmol) in DMF (1.5 mL).
[b] Isolated yields.



Scheme 1. Synthesis of Lamisil™.

Finally, we applied this methodology to the synthesis of Terbinafine (Lamisil™) , which is known as a synthetic allylamine antifungal that is highly lipophilic in nature and tends to accumulate in the skin, nails, and fatty tissues (Scheme 1).[10] For the synthesis of Terbinafine, we envisioned **18** as a key structure, which can be obtained from tert-butylacetylene (**17**) and acrolein by an oxidative Pd(II)-catalyzed coupling reaction. The reductive amination of enyne compound **18** with 1-naphthylmethylamine afforded allylic amine compound **19**. Finally, methylation of the secondary amine will produce the target antifungal drug.



Scheme 2. Plausible mechanism pathway.

Therefore, we have demonstrated a simple protocol to synthesize an enyne from commercially available substrates utilizing an oxidative palladium Heck coupling reaction under simple and mild conditions. The substrate limitation was explored; and it was determined that there are no limitations for the alkynyl coupling partner; however, limitations are found for the olefin. Lamisil™ was also synthesized to show the utility of this oxidative Heck reaction.

Typical procedure for the coupling reaction: To a pre-weighed oven-dried vial equipped with magnetic stir bar were placed anhydrous K_2CO_3 (0.62 mmol) and DMF (1.5 mL). Then, alkyne (0.31 mmol) and olefin (3.1 mmol) were added simultaneously, followed by $Pd(TFA)_2$ (2 mol %). Immediately, the vial was capped with a balloon filled with oxygen. Within 1 min, immediate color change of the reaction mixture was observed. After 4 h, the mixture was quenched with addition of water (3 mL) and extracted with hexanes (3 × 5 mL). The organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated to afford a crude mixture, which was purified by silica gel chromatography (2% ethyl acetate in hexanes) to afford the cross-coupled products.

Acknowledgments

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Y.; Uemura, S. *Org. Lett.* **2003**, *5*, 2997–2999; (c) Andrew, R. J.; Mellor, J. M. *Tetrahedron* **2000**, *56*, 7261–7266.; (d) Struve, G.; Seltzer, S. *J. Org. Chem.* **1982**, *47*, 2109–2113; (e) Molander, G. A.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 3106–3108.

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