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Pd(II)-Catalyzed Dehydrogenative Olefination of Terminal Arylalkynes with Allylic Ethers: General and Selective Access to Linear (*Z*)-1,3-Enynes

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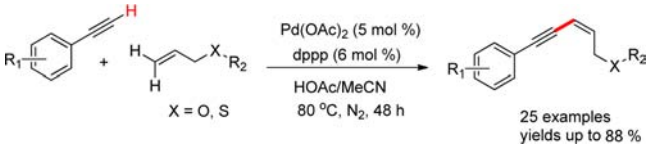
ABSTRACT



This work demonstrates a green and efficient method to prepare 1,3-enynes via Pd(II)-catalyzed direct dehydrogenative olefination of terminal arylalkynes with unactived allylic ethers. Various terminal arylalkynes can participate in the reaction, stereoselectively affording the desired conjugated (*Z*)-1,3-enynes in moderate to good yields.

The conjugated 1,3-enyne moiety is an important unit found in many naturally occurring and pharmaceutically active compounds.[1] For example, terbinafine, bearing the 1,3-enyne moiety, is used in the treatment of superficial fungal infections due to its biological activity.[2] In addition, 1,3-enynes are also efficient precursors to naphthalenes,[3] heterocyclic compounds,[4] and conjugated alkenes.[5] Owing to their great importance, the preparation of 1,3-enynes has been an area of considerable activity in recent years.[6] Among various methods available for 1,3-enynes, the traditional Pd−Cu-catalyzed[7] or Pd-catalyzed[8] Sonogashira coupling reaction of terminal alkynes with vinyl halide is the most convenient and prevalent. At present, most investigations were mainly aimed toward the development of inexpensive catalysts such as copper[9] and iron[10] instead

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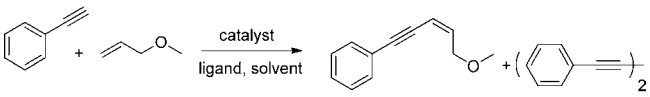
of Pd−Cu (or Pd) as catalyst to improve the Sonogashira coupling reaction. Although remarkable progress has been achieved in terms of catalysts, these reactions are dependent on preactivation of alkene with halide to form the substrate of vinyl halide, which requires several extra synthetic steps and generate waste. The overall process is neither atom-economical nor green. Therefore, more efficient and green protocols to prepare 1,3-enyne would be highly desirable.

Recently, significant progress has been achieved for the synthesis of conjugated dienes via Pd-catalyzed direct dehydrogenative olefination of sp^2 C−H bonds with allylic esters.[11] These excellent works urged us to postulate that 1,3-enyne could be obtained via Pd-catalyzed direct dehydrogenative olefination of terminal alkynes (sp C−H bonds) with unactived alkene (sp^2 C−H bonds, such as allylic ethers, etc.), which exemplifies the ideals of atom and step economy. Fortunately, we successfully accomplished the first example of $Pd(OAc)_2$-catalyzed direct dehydrogenative olefination of terminal arylalkynes with the commercially available allylic ether, stereoselectively affording (*Z*)-1,3-enyne derivatives as the sole products. Herein, we report the results in detail.

We chose phenylacetylene **1a** and allyl methyl ether **2a** as the model substrates to optimize suitable conditions for this reaction. First, the amount of allyl methyl ether **2a** was selected as 2 equiv, while the homocoupled product **3a** dominated in the reaction and only a few of target product **3** can be detected by GC-MS, which may result from the instability of the allyl methyl ether under such a catalytic system. So a large excess of allyl methyl ether (**2a**, 10 equiv) was used to detect the optimal reaction conditions. During the investigation, it was found that the solvents, catalysts, temperature, and ligands critically affected the dehydrogenative cross-coupling reaction efficiency (Table 1). Solvents such as HOAc/DMF, HOAc/DCE, HOAc, MeCN, and DMSO were ineffective (entries 2−6), whereas 15% yield of **3** was obtained by the addition of 25 vol % HOAc as cosolvent into MeCN (entry 1) when using $Pd(OAc)_2$ as catalyst and bpy as ligand at 80 °C. The solvent effect indicates that a specified volume of HOAc plays an important role in this reaction. The low yield of 15% urged us to seek optimal reaction conditions. Then different catalysts such as $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $PdCl_2$, and $Pd(CF_3COO)_2$ were screened to give worse results than $Pd(OAc)_2$ (entries 7−10). After a series of tests, we were pleased to find that the ligands had a dramatic effect on the yield. Among the ligands screened, 1,3-bis(diphenylphosphino)propane (DPPP) turned out to be the best, affording **3** in 43% yield, while 1,10-phenanthroline, tetramethylethylenediamine (TMEDA), and triphenylphosphine (PPh_3) were not that effective (entries 11−14). Remarkably, the yield of cross-coupling product **3** could be dramatically increased to 76% when the reaction was conducted under N_2 atmosphere (entry 15). To our delight, the reaction stereoselectively afforded the conjugated (*Z*)-(5-methoxypent-3-en-1-ynyl)benzene (**3**), whose configuration was confirmed based on the Noesy spectra and *J* value. Unfortunately, decreasing the amount of allyl methyl ether **2a** to 1.5 mmol (5 equiv) resulted in a lower yield of 51% (entry 16). As the amount of allyl methyl ether **2a** was further increased to 4.5 mmol (15 equiv), no obvious increase of the yield was observed (entry 17). The reaction temperature and time were next screened, and it was found that lower or higher reaction temperature led to the low conversion as well as shortening the reaction time to 24 h (entries 18−20). Thus the optimal condition was finally identified as follows: phenylacetylene (1.0 equiv), allyl methyl ether (10 equiv), $Pd(OAc)_2$ (5 mol %), DPPP (6 mol %), HOAc/MeCN (v/v = 1:3), 80 °C, 48 h under N_2. Notably, entries 1−20 are only a sampling of over 50 reactions that have been screened by using different catalysts, ligands, additives, oxidants, bases, and solvents (see Supporting Information).

Table 1. Reaction Condition Optimization[a]



1a 2a 3 3a

entry	catalyst	ligand	solvent[b]	yield (%)[c]
1	$Pd(OAc)_2$	bpy	HOAc/MeCN	15
2	$Pd(OAc)_2$	bpy	HOAc	trace
3	$Pd(OAc)_2$	bpy	MeCN	trace
4	$Pd(OAc)_2$	bpy	DMSO	NR
5	$Pd(OAc)_2$	bpy	HOAc/DMF	trace
6	$Pd(OAc)_2$	bpy	HOAc/DCE	trace
7	$Pd(PPh_3)_4$	bpy	HOAc/MeCN	trace
8	$Pd_2(dba)_3$	bpy	HOAc/MeCN	NR
9	$PdCl_2$	bpy	HOAc/MeCN	11
10	$Pd(CF_3COO)_2$	bpy	HOAc/MeCN	NR
11	$Pd(OAc)_2$	1,10-phenanthroline	HOAc/MeCN	15
12	$Pd(OAc)_2$	TMEDA	HOAc/MeCN	trace
13	$Pd(OAc)_2$	PPh_3	HOAc/MeCN	trace
14	$Pd(OAc)_2$	DPPP	HOAc/MeCN	43
15[d]	**$Pd(OAc)_2$**	**DPPP**	**HOAc/MeCN**	**76**
16[d]	$Pd(OAc)_2$	DPPP	HOAc/MeCN	51[e]
17[d]	$Pd(OAc)_2$	DPPP	HOAc/MeCN	77[f]
18[d]	$Pd(OAc)_2$	DPPP	HOAc/MeCN	66[g]
19[d]	$Pd(OAc)_2$	DPPP	HOAc/MeCN	51[h]
20[d]	$Pd(OAc)_2$	DPPP	HOAc/MeCN	30[i]

[a] Reaction conditions: phenylacetylene **1a** (0.3 mmol), allyl methyl ether **2a** (3.0 mmol), catalyst (5 mol %), ligand (6 mol %), solvent (2 mL), 80 °C, 48 h. [b] v/v = 1:3. [c] Isolated yields. [d] Reaction carried out under N_2. [e] Allyl methyl ether **2a** (1.5 mmol). [f] Allyl methyl ether **2a** (4.5 mmol). [g] Shorten the reaction to 24 h. [h] At 40 °C. [i] 110 °C.

With the optimal catalytic system in hand, the scope of terminal alkynes was next investigated (Table 2). As expected, various arylacetylenes worked well under the reaction conditions. A range of functional groups, such as

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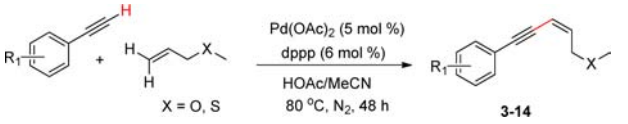
methyl, ethyl, *n*-butyl, methoxyl, chloro, fluoro, bromo, and nitro groups, were tolerated in this dehydrogenative olefination procedure. In generally, the electron-donating substituents on the phenyl ring of arylacetylene were beneficial for the transformation, whereas an electron-withdrawing group decreased the efficiency. For example, the arylacetylenes with methyl, ethyl, *n*-butyl, and methoxyl groups (entries 1−6) gave the dehydrogenative products in more than 65% yields, while their chloro, fluoro, bromo, and nitro equivalents generated the corresponding products in less than 50% yields (entries 7−11). However, steric hindrance affected the efficiency slightly. Substrates with *para*-methyl and *para*-chloro gave similar yields as their *meta*-methyl and *meta*-chloro equivalents (entries 2, 3, 7, and 8). To our delight, treatment of phenylacetylene with allyl methyl sulfide also afforded the 1,3-enyne product **14**, but the yield was decreased to 25% (entry 12). Unfortunately, the aliphatic terminal alkyne such as 1-hexyne was intolerant to the catalytic system (entry 13).

Subsequently, promoted by the successful Pd-catalyzed direct dehydrogenative olefination of arylacetylene with allyl methyl ether, allyl phenyl ether was also examined with respect to various arylacetylenes to synthesize 1,3-eyene compounds (Table 3). Evidently, allyl phenyl ether was found to be more reactive than allyl methyl ether, which may be attributed to the more stable nature of allyl phenyl ether. The targeted 1,3-enyne products were obtained in good yields ranging from 49 to 88%. Similarly, arylacetylenes possessing electron-donating functional groups favored the dehydrogenative cross-coupling reaction (entries 1−6) more than those with electron-withdrawing groups (entries 7−11). When the substrate scope was extended to 4-nitrophenylacetylene, the corresponding 1,3-enyne was obtained in a lower 49% yield (entry 11). Furthermore, the reaction between allyl phenyl ether and 1-hexyne cannot be observed in the optimal condition (entry 12).

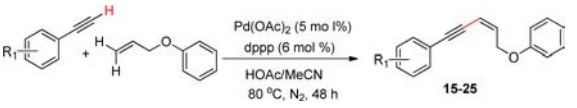
Table 2. Pd-Catalyzed Dehydrogenative Olefination of Terminal Alkynes with Allyl Methyl Ethers (Sulfide)[a,b]



entry	R_1	ether	product	yield (%)
1	H		**3**	76
2	p-Me		**4**	72
3	m-Me		**5**	65
4	p-Et		**6**	69
5	p-n-Bu		**7**	65
6	p-OMe		**8**	70
7	m-Cl		**9**	44
8	p-Cl		**10**	45
9	p-F		**11**	40
10	p-Br		**12**	47
11	p-NO_2		**13**	33
12	H		**14**	25
13	1-hexyne			NR

[a] Reaction conditions: arylacetylene (0.3 mmol), allyl methyl ether (3.0 mmol), $Pd(OAc)_2$ (5 mol %), DPPP (6 mol %), solvent (2 mL, v/v = 1:3), 80 °C, 48 h. [b] Isolated yields.

Table 3. Pd-Catalyzed Dehydrogenative Olefination of Terminal Alkynes with Allyl Phenyl Ethers[a,b]



entry	R_1	ether	product	yield (%)
1	H		**15**	85
2	p-Me		**16**	86
3	m-Me		**17**	83
4	p-Et		**18**	74
5	p-n-Bu		**19**	88
6	p-OMe		**20**	79
7	m-Cl		**21**	70
8	p-Cl		**22**	75
9	p-F		**23**	55
10	p-Br		**24**	75
11	p-NO_2		**25**	49
12	1-hexyne			NR

[a] Reaction conditions: arylacetylene (0.3 mmol), allyl phenyl ether (3.0 mmol), $Pd(OAc)_2$ (5 mol %), DPPP (6 mol %), solvent (2 mL, v/v = 1:3), 80 °C, 48 h. [b] Isolated yields.

In conclusion, we have developed an efficient and green protocol to synthesize 1,3-enyne compounds via $Pd(OAc)_2$-catalyzed direct dehydrogenative olefination of terminal arylalkynes with unactived allylic ethers (10 equiv), which does not require the preactivation of alkene with halide to form the substrate of vinyl halide and exemplifies the ideals of atom and step economy. Various terminal arylalkynes can participate in the reaction, stereoselectively affording the desired conjugated (*Z*)-1,3-enynes in moderate to good yield. Further studies on the mechanism of the reaction are ongoing in our laboratory.

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Supporting Information Available. Description of experimental procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.