Synthetic Methods

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Palladium-Catalyzed Regio- and Stereoselective Cross-Addition of Terminal Alkynes to Ynol Ethers and Synthesis of 1,4-Enyn-3-ones**

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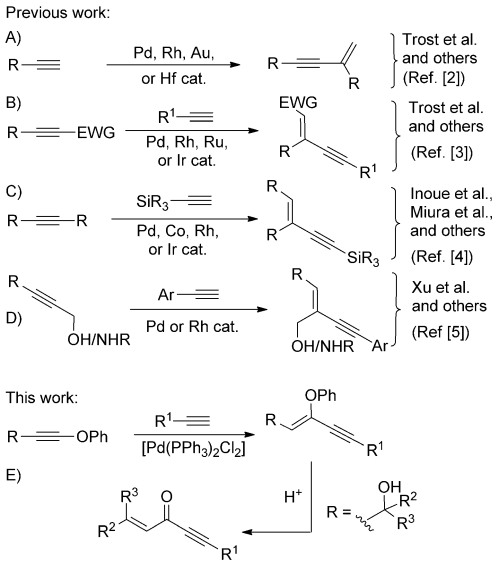
Abstract: *Conjugated enynes, enol ethers, and enynones are versatile building blocks that can be elaborated by a wide variety of synthetic transformations. The selective synthesis of such units is a prerequisite for their effective utilization. The synthesis of conjugated 2-phenoxyenynes through a palladium-catalyzed cross-addition of terminal alkynes to phenylethynyl ethers (hydroalkynylation) is now presented. The reaction is highly regio-, stereo-, and chemoselective, and shows excellent tolerance toward functional groups. The addition further features very mild reaction conditions (room temperature) and an inexpensive catalytic system (without a ligand and with a cheaply available Pd catalyst). The thus synthesized enynyl ethers with allylic hydroxy tethers, which survived the reaction, were shown to be ready precursors for valuable 1-en-4-yn-3-ones.*

Given the importance of conjugated enynes and enol ethers as subunits in bioactive molecules as well as valuable synthetic intermediates,[1] a number of efforts have been made toward their synthesis. Alkyne–alkyne cross-addition was developed as a practical and atom economical means to obtain conjugated enynes,[2–5] with couplings ranging from dimerization to polymerization. After the pioneering studies by Trost et al. on the homodimerization of terminal alkynes (Scheme 1 A)[2] and the selective coupling of terminal alkynes with electron-deficient conjugated alkynes (Scheme 1 B),[3] many groups investigated the selective synthesis of enynes through this pathway. However, most of these studies were limited to the homodimerization of terminal alkynes,[2] which do not have extensive use in organic synthesis.

The cross-addition of two different alkynes is rather limited (Scheme 1 B–D) because of the difficulties associated with regioselectivities and undesired homodimerizations. Although considerable efforts have been made on the heterodimerization of acceptor alkynes (alkynes with electron-withdrawing groups), surprisingly, there are hitherto no precedents on the reactivity of electron-rich alkynes, such as ynol ethers and ynamines.



Scheme 1. Alkyne–alkyne cross-addition.

As part of our ongoing search for reactions of activated alkynes,[6] we investigated (Scheme 1 E) the selective cross-coupling of terminal alkynes with ynol ethers to produce enynes with a phenoxy group tether. Furthermore, we showed the products we obtained to be convenient precursors for synthetically highly valuable enynones.[7]

In an attempt to achieve an alkynylative Meyer–Schuster rearrangement, we treated substrate **1a**[6a] with phenyl acetylene (**2a**) under the Sonogashira reaction conditions (Scheme 2). We hypothesized that the Pd^{II} species would react with the electron-rich β-carbon atom of the ynol ether in an S_N2 fashion before undergoing a metal–ligand exchange with the Cu–acetylide, and the resultant intermediate would undergo 1,3-hydroxy migration and reductive elimination to give **3**. Surprisingly, the reaction produced **4aa**, along with the coupled dimer of **2a** (Glaser–Hay coupling), through a regioselective cross-addition (hydroalkynylation) in a *syn* manner. Apart from the importance of **4aa** as a selectively substituted enyne with an enol ether substructure, it appeared, with its allylic hydroxy group, to be a ready starting material for the synthesis of the useful enynone **5a** through an acid-mediated migration of the allylic hydroxy group. Additionally, these two products, which feature a polarized olefin with a tethered

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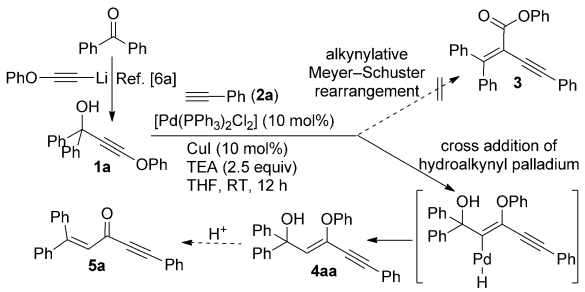


Scheme 2. Cross-addition of phenyl acetylene to **1a**.

alkynyl group, might be attractive substrates for the synthesis of novel building blocks. We thus began our search for ideal conditions for the effective addition of **2a** to **1a**.

In fact, some recent reports showed that the cross-addition of terminal alkynes with propargyl alcohols can be achieved in a regioselective manner (alkyne coupling on the proximal carbon atom to the propargyl hydroxy group, Scheme 1D).[5] However, the present work offers a complete reversal of the regioselectivity (alkyne coupling on the distal carbon atom to the propargyl hydroxy group) by yielding to the inherent polarization of the alkyne rather than to the inductive effect of the propargyl hydroxy group.

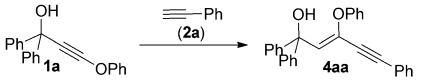
The optimization studies for the conversion of **1a** to **4aa** are presented in Table 1. Initially, we screened various inorganic (entries 1–2) and organic bases (entries 3–5) with the same catalytic system ($[Pd(PPh_3)_2Cl_2]$ and CuI) in THF. None of these reactions led to an improvement in the yield of **4aa**. Surprisingly, the yield increased considerably when CuI was not added (entry 6). Additionally, the undesired homo-coupling (Glaser–Hay coupling) of **2a** was mostly suppressed, suggesting that the cross-addition actually did not require the copper catalyst, which in fact hampered the intended reaction by assisting the unwanted homo-coupling. To our delight, changing the base to TEA resulted in the formation of **4aa** in 85% yield (entry 7). The variation of the solvent (entries 8 and 9), the addition of a phosphorous ligand (entries 10–12), or the change of the catalyst (entries 13–15) led to the formation of **4aa** only in decreased yields. The optimized reaction conditions thus included the use of $[Pd(PPh_3)_2Cl_2]$ as the catalyst and TEA as the base in THF at room temperature. However, the transformation did not occur in the absence of the catalyst or the base (entries 16 and 17).

With the optimized conditions established, we investigated the scope of the reaction of phenoxy propargyl alcohol **1a** with various alkynes (Scheme 3). Similar to **2a**, electron-poor phenyl acetylenes **2b–e** smoothly reacted with **1a** to produce **4ab–ae** in 71–82% yields. Electron-rich alkynes **2f–h** were equally reactive (producing **4af–ah** in 79–81% yields), thus indicating that the electronic nature of the alkyne has no significant effect on the cross-addition. The structure of **4af** was unambiguously confirmed by single-crystal X-ray analysis.[8]

Aliphatic alkynes such as **2i** and **2j**, and enyne **2k** also readily underwent the cross-addition to produce the corresponding products **4ai–ak** in 69–72% yields. The formyl group in alkyne **2l** was tolerated by the reaction to give **4al**. Heteroaryl acetylene **2m** showed similar reactivity and **4am** was produced in 76% yield. Propargyl compounds **2n** and **2o** showed moderate activity (**4an** and **4ao** were obtained in 54 and 61% yield, respectively), partially because of a competitive homo-coupling.

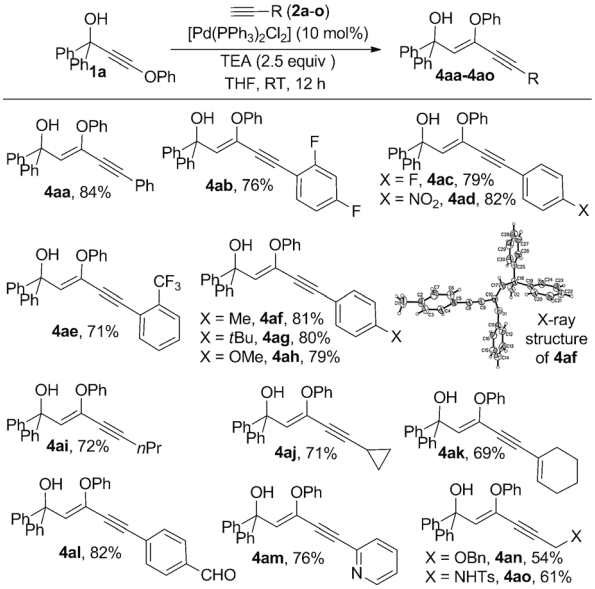
We next focused our attention on the scope of the reaction with regard to different phenoxy propargyl alcohols **1**.[6a] Various tertiary and secondary propargyl alcohols bearing a wide range of substitution patterns (alkyl, aryl, vinyl, and

Table 1: Optimization of the cross-addition.[a]

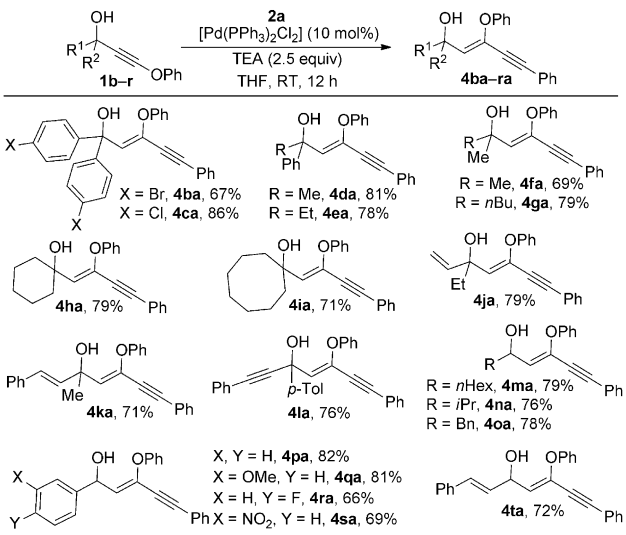


Entry	Catalyst	Co-catalyst	Base	Solvent	Additive	Yield [%][b]
1	$[Pd(PPh_3)_2Cl_2]$	CuI	K_2CO_3	THF	–	50
2	$[Pd(PPh_3)_2Cl_2]$	CuI	Na_2CO_3	THF	–	40
3	$[Pd(PPh_3)_2Cl_2]$	CuI	TEA	THF	–	48
4	$[Pd(PPh_3)_2Cl_2]$	CuI	py	THF	–	–
5	$[Pd(PPh_3)_2Cl_2]$	CuI	DBU	THF	–	35
6	$[Pd(PPh_3)_2Cl_2]$	–	K_2CO_3	THF	–	65
7	**$[Pd(PPh_3)_2Cl_2]$**	**–**	**TEA**	**THF**	**–**	**85**
8	$[Pd(PPh_3)_2Cl_2]$	–	TEA	MeCN	–	80
9	$[Pd(PPh_3)_2Cl_2]$	–	TEA	toluene	–	60
10	$[Pd(PPh_3)_2Cl_2]$	–	TEA	THF	PPh_3	82
11	$[Pd(PPh_3)_2Cl_2]$	–	TEA	THF	dppe	78
12	$[Pd(PPh_3)_2Cl_2]$	–	TEA	THF	dppf	80
13	$Pd(OAc)_2$	–	TEA	THF	–	72
14	$[Pd(PPh_3)_4]$	–	TEA	THF	–	80
15	$Pd(TFA)_2$	–	TEA	THF	–	–
16	–	–	TEA	THF	–	–
17	$[Pd(PPh_3)_2Cl_2]$	–	–	THF	–	–

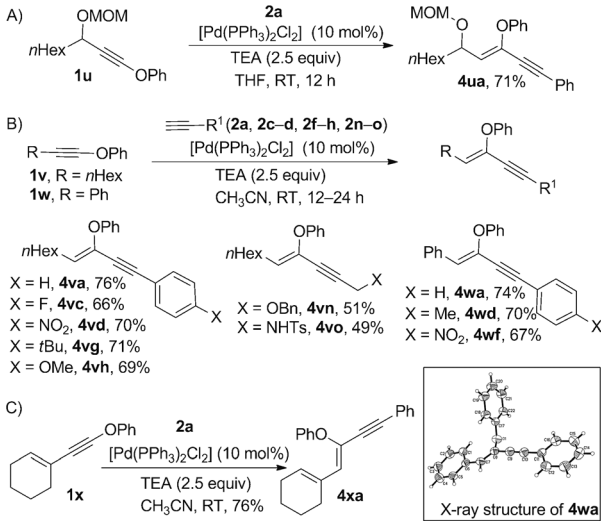
[a] **1a** (1.0 mmol), **2a** (1.2 mmol), base (2.5 mmol), and catalyst (10 mol%) in the indicated solvent (anhydrous) at RT for 12 h. [b] Yields of isolated products. dppf = 1,1'-bis(diphenylphosphanyl)ferrocene, dppe = bis(diphenylphosphanyl)ethane. The entry in bold marks the optimized reaction conditions.



Scheme 3. Cross-addition of acetylenes **2a–o** to **1a**. Reaction conditions: 1.0 mmol of **1a**, 1.2 mmol of **2**, 2.5 equiv of TEA, and 0.1 mmol of $[Pd(PPh_3)_2Cl_2]$ in THF at RT.



Scheme 4. Scope of phenoxy propargyl alcohols in the cross-addition with **2a**.



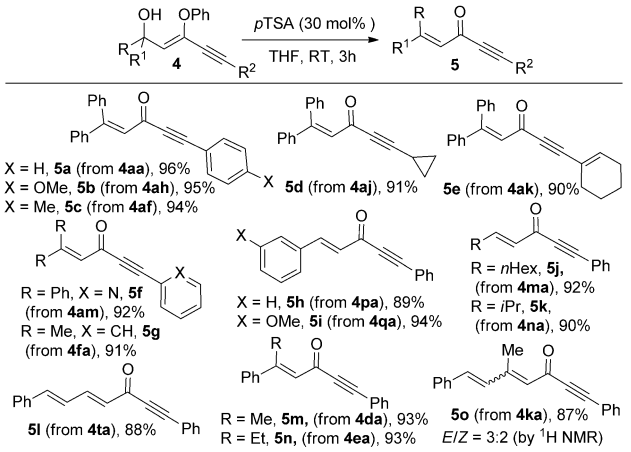
Scheme 5. Scope of phonoxy alkynes other than propargyl alcohols.

alkynyl) were synthesized and subjected to the addition reaction with **2a** to show the generality of the reaction (Scheme 4). Substrates **1b** and **1c**, prepared from the corresponding benzophenones, were cleanly converted (67 and 86% yield, respectively) to the corresponding products **4ba** and **4ca**, respectively, with the halogen functionalities intact (which might have reacted in an equally possible Sonogashira coupling). Phenoxy propargyl alcohols (**1d** and **1e**) derived from aryl alkyl ketones also smoothly underwent the targeted hydroalkynylation (**4da** and **4ea** in 81 and 78% yield, respectively). Similarly, nonbenzylic propargyl alcohols **1f**/**1g** and **1h**/**1i**, prepared from acyclic and cyclic ketones, respectively, reacted equally well in the reaction to give **4fa–ia** in good yields (69–79%). Notably, both terminal and internal alkenyl groups (as in **1j** and **1k**) were tolerated in the synthesis of **4ja** and **4ka**. Very pleasingly, the addition proved to be highly chemoselective by discriminating the phenoxy ethynyl group from the phenyl ethynyl group in **1l** to selectively produce **4la** in 76% yield.

Next, we chose various secondary propargyl alcohols for the selective addition of **2a**. Substrates **1m–o**, obtained from aliphatic aldehydes, were smoothly transformed to the corresponding products **4ma–oa** in 76–79% yields. Similarly, **1p–s** and **1t**, prepared from various benzaldehydes and cinnamaldehyde, respectively, also reacted in the hydroalkynylation to furnish **4pa–ta** in 66–82% yields.

Although the reaction can be predicted (from the previous studies)[2–4] to occur through a concerted syn addition of the hydroalkynyl palladium species to the alkyne using the intrinsic polarization for the regioselectivity, we were interested in finding any possible involvement of the hydroxy functionality in the assembly of the metal–substrate complex. Furthermore, we wanted to expand the scope of the reaction to nonpropargyl substrates to further improve the generality of the approach. Initially, we subjected the MOM-protected propargyl substrate **1u** to the cross-addition with **2a** (Scheme 5A). This reaction cleanly furnished the corresponding product **4ua** in 71% yield, thus demonstrating that the hydroxy functionality does not have any role in the course in the reaction. Next, substrate **1v**, bearing no further functionality,[1m] was subjected to the reaction. Various electron-rich and electron-poor phenyl acetylenes (**2a**, **2c–d**, **2g–h**, **2n–o**, Scheme 5B) successfully reacted with **1v** under the standard reaction conditions, but in the alternative solvent CH_3CN (entry 8, Table 1). The reaction of **1v** with the protected propargyl alcohol **2n** and propargyl amine **2o** afforded the corresponding products in moderate yields of 51% and 49%, respectively. To further broaden the scope of the reaction, conjugated substrate **1w** was successfully coupled with **2a, 2d**, and **2f** to obtain triphenyl-substituted adducts **4wa, 4wd**, and **4wf**, respectively. To our delight, the phenoxy enyne **1x**[6a] could also be coupled with **2a** to furnish dienyne **4xa** in 76% yield (Scheme 5C). Because **1v–x** required a change of the solvent under the reactions conditions, we confirmed one of the structures, **4wa**, by X-ray crystallography.[8]

After we had established the highly general hydroalkynylation of phenoxy acetylenes, we investigated the transformation of the products to useful enynones through an acid-mediated migration of the allylic hydroxy group (Scheme 1E). After some experiments with a few Bronsted acids (HCl, H_2SO_4, trifluoroacetic acid (TFA), and *p*-toluenesulfonic acid (*p*TSA)), we realized the conversion of **4** to **5** in excellent yields at room temperature in THF using 30 mol% *p*TSA (Scheme 6). Thus, various adducts obtained from benzophenone (**4aa**, **4af**, **4ah**, **4aj**, **4ak** and **4am**) were converted to the corresponding 1,1-symmetrically substituted products (**5a–f**) in excellent yields (90–96%), irrespective of the substitution at the alkyne terminus. Similarly, 1,1-dimethyl-substituted enynone **5g** was obtained in 91% yield. We next investigated aldehyde-originating substrates, which may elaborate to two different isomers (*cis* and *trans*). Promisingly, upon exposure to 30% *p*TSA in THF, **4pa** cleanly produced the *trans* isomer **5h**[7a] as the sole product in 89% yield. Similarly, the methoxyphenyl-substituted *trans* enynone **5i** was obtained as the only isomer in 94% yield. Pleasingly, substrates originating from aliphatic aldehydes also gave the single enynone adducts **5j–k** selectively in



Scheme 6. Conversion of enynols **4** to enynones **5**.

similar yields (90–92%). Furthermore, the substrate obtained from cinnamaldehyde was neatly transformed to the di-*trans* dienynone **5l** in 88% yield. To our pleasure, acetophenone- and propiophenone-based substrates **4da** and **4ea**, respectively, also produced the corresponding products **5m–n** as single isomers, thus indicating that the conjugation played a key role in the selectivity. Finally, the cinnamyl ketone based substrate **4ka** gave **5o** in 87% yield as a 3:2 mixture of stereoisomers, probably because of a weaker conjugation, the effect of which could not completely dominate over the steric bulk of the methyl group.

In conclusion, we have demonstrated the cross-addition of terminal alkynes with ynol ethers in a highly stereo- and regioselective manner for the synthesis of conjugated 2-phenoxy-*Z*-enynes with various functional groups. The reaction neither required a copper catalyst or a ligand to assist catalysis by the readily available $[Pd(PPh_3)_2Cl_2]$, nor did it need elevated temperatures. The thus synthesized compounds with tethered allylic hydroxy groups were ready precursors for the stereoselective synthesis of useful enynones. With the high functionalization around the enyne, both substrate classes should find uses in future synthetic endeavors.

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[8] See the Supporting Information for details.

