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

Madala Hari Babu, Vikas Dwivedi, Ruchir Kant, and Maddi Sridhar Reddy*

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 palladiumcatalyzed 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-3ones.

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

[*] M. Hari Babu, V. Dwivedi, Dr. M. Sridhar Reddy Medicinal & Process Chemistry Division CSIR-Central Drug Research Institute Lucknow, 226031 (India)
E-mail: msreddy@cdri.res.in
R. Kant
Molecular & Structural Biology Division CSIR-Central Drug Research Institute Lucknow, 226031 (India)

[**] This work was supported by CSIR-THUNDER (BSC0102), New Delhi. We are thankful to SAIF, CSIR-CDRI, for providing the analytical facilities and Dr. Tejender S. Thakur, Molecular and Structural Biology Division, CSIR-CDRI, for supervising the collection of X-ray data and the determination of the structure of compound 4af. M.H.B. and V.D. thank CSIR for the fellowships. CSIR-CDRI communication no 8886.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201411261.



Scheme 1. Alkyne-alkyne cross-addition.

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.

As part of our ongoing search for reactions of activated alkynes,^[6] we investigated (Scheme 1 E) the selective crosscoupling 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 envnone 5a through an acid-mediated migration of the allylic hydroxy group. Additionally, these two products, which feature a polarized olefin with a tethered

Angew. Chem. Int. Ed. 2015, 54, 1-5

© 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Wiley Online Library

1

These are not the final page numbers!



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

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 crossaddition 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(PPh₃)₂Cl₂] 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 homocoupling (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**, electronpoor phenyl acetylenes **2b–e** smoothly reacted with **1a** to produce **4ab–ae** in 71–82 % yields. Electron-rich alkynes **2 f–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 **4a**l. Heteroaryl acetylene **2m** showed similar reactivity and **4am**

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

ŅН

	Ph ⁻ / Ph 1a	Ph ⁻ / Ph 1a OPh		Ph Ph 4aa Ph		
Entry	Catalyst	Co-catalyst	Base	Solvent	Additive	Yield [%] ^[b]
1	[Pd(PPh ₃) ₂ Cl ₂]	Cul	K ₂ CO ₃	THF	_	50
2	$[Pd(PPh_3)_2Cl_2]$	Cul	Na ₂ CO ₃	THF	-	40
3	$[Pd(PPh_3)_2Cl_2]$	Cul	TEA	THF	-	48
4	$[Pd(PPh_3)_2Cl_2]$	Cul	ру	THF	_	-
5	$[Pd(PPh_3)_2Cl_2]$	Cul	DBU	THF	_	35
6	$[Pd(PPh_3)_2Cl_2]$	-	K_2CO_3	THF	_	65
7	[Pd(PPh ₃) ₂ Cl 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	PPh₃	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	-	-

-Ph

(2a)

OH OPh

[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.

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

www.angewandte.org

2

© 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



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

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 1 f/1g and 1h/1i, prepared from acyclic and cyclic ketones, respectively, reacted equally well in the reaction to give 4 faia in good yields (69-79%). Notably, both terminal and internal alkenyl groups (as in 1j and 1k) were tolerated in the synthesis of 4 ja and 4 ka. Very pleasingly, the addition proved to be highly chemoselective by discriminating the phenoxy ethynyl group from the phenyl ethynyl group in 11 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 5 A). This reaction cleanly furnished the corresponding product **4ua** in 71 % yield, thus demonstrating that the



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

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 CH₃CN (entry 8, Table 1). The reaction of 1v with the protected propargyl alcohol 2n and propargyl amine 20 afforded the corresponding products in moderate yields of 51% and 49%, respectively. To further broaden the scope of the reaction, conjugated substrate 1 w 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 envnones through an acidmediated migration of the allylic hydroxy group (Scheme 1E). After some experiments with a few Bronsted acids (HCl, H₂SO₄, trifluoroacetic acid (TFA), and *p*-toluenesulfonic acid (pTSA), we realized the conversion of 4 to 5 in excellent yields at room temperature in THF using 30 mol% pTSA (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, 1,1dimethyl-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% pTSA 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 envnone adducts 5i-k selectively in

www.angewandte.org

Angewandte Communications



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 **51** in 88% yield. To our pleasure, acetophenoneand 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 **50** 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)₂Cl₂], 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.

Received: November 20, 2014 Published online:

Keywords: enol ethers · enynes · enynones · hydroalkynylation · stereoselectivity

 For the chemistry of enynes, see: a) P. Nussbaumer, I. Leitner, K. Mraz, A. Stutz, J. Med. Chem. 1995, 38, 1831–1836; b) L. Garlaschelli, E. Magistrali, G. Vidari, O. Zuffardi, Tetrahedron Lett. 1995, 36, 5633–5636; c) N. El-Jaber, A. E. Braun, A. G. Ravelo, O. M. Munoz, A. R. Afonso, J. R. Murguia, J. Nat. Prod. 2003, 66, 722–724; d) T. Akiyama, K. Takada, T. Oikawa, N. Matsuura, Y. Ise, S. Okada, S. Matsunaga, Tetrahedron 2013, 69, 6560–6564; e) M. Rubina, M. Conley, V. Gevorgyan, J. Am. Chem. Soc. 2006, 128, 5818–5827; for the chemistry of enols, see: f) J. F. Briones, H. M. L. Davies, J. Am. Chem. Soc. 2013, 135, 13314–13317; g) J. L. Brice, J. E. Meerdink, S. S. Stahl, Org. Lett. 2004, 6, 1845–1848; h) J. S. Clark, J. G. Kettle, Tetrahedron 1999, 55, 8231–8248; i) K. Hori, J. Ito, T. Ohta, I. Furukawa, Tetrahedron 1998, 54, 12737–12744; j) C. J. Mossman, J. Aube, Tetrahedron 1996, 52, 3403–3408; k) K. C. Majumdar, S. Sarkar, T. Bhattacharrya, Tetrahedron 2003, 59, 4309–4314; l) W. Cui, J. Yin, R. Zheng, C. Cheng, Y. Bai, G. Zhu, J. Org. Chem. 2014, 79, 3487–3493; m) D. C. Harrowven, M. J. Tyte, Tetrahedron Lett. 2002, 43, 5971–5972; n) R. E. Shade, A. M. Hyde, J.-C. Olsen, C. A. Merlic, J. Am. Chem. Soc. 2010, 132, 1202–1203; o) S. G. Levine, J. Am. Chem. Soc. 1958, 80, 6150–6151; p) F. Alonso, I. P. Beletskaya, M. Yus, Chem. Rev. 2004, 104, 3079–3159.

- [2] a) B. M. Trost, C. Chan, G. Ruhter, J. Am. Chem. Soc. 1987, 109, 3486-3487; b) B. M. Trost, I. Hachiya, M. C. McIntosh, Tetrahedron Lett. 1998, 39, 6445-6448; c) C. Xu, W. Du, Y. Zeng, B. Dai, H. Guo, Org. Lett. 2014, 16, 948-951; d) T. Chen, C. Guo, M. Goto, L.-B. Han, Chem. Commun. 2013, 49, 7498-7500; e) S. Sun, J. Kroll, Y. Luo, L. Zhang, Synlett 2012, 54-56; f) H. M. Peng, J. Zhao, X. Li, Adv. Synth. Catal. 2009, 351, 1371-1377; g) M. Yoshida, R. F. Jordan, Organometallics 1997, 16, 4508-4510; h) M. Akita, H. Yasuda, A. Nakamura, Bull. Chem. Soc. Jpn. 1984, 57, 480-487.
- [3] a) B. M. Trost, M. T. Sorum, C. Chan, A. E. Harms, G. Ruhter, J. Am. Chem. Soc. 1997, 119, 698-708; b) Y. Shibata, K. Tanaka, Angew. Chem. Int. Ed. 2011, 50, 10917-10921; Angew. Chem. 2011, 123, 11109-11113; c) L. Chen, C.-J. Li, Tetrahedron Lett. 2004, 45, 2771-2774; d) see Ref. [2b]; e) C. S. Yi, N. Liu, Organometallics 1998, 17, 3158-3160; f) T. Hirabayashi, S. Sakaguchi, Y. Ishii, Adv. Synth. Catal. 2005, 347, 872-876; g) J. Ito, M. Kitase, H. Nishiyama, Organometallics 2007, 26, 6412-6417.
- [4] a) T. Sakurada, Y.-K. Sugiyama, S. Okamoto, J. Org. Chem. 2013, 78, 3583-3591; b) N. Matsuyama, K. Hirano, T. Satoh, M. Miura, J. Org. Chem. 2009, 74, 3576-3578; c) N. Matsuyama, H. Tsurugi, T. Satoh, M. Miura, Adv. Synth. Catal. 2008, 350, 2274-2278; d) N. Tsukada, S. Ninomiya, Y. Aoyama, Y. Inoue, Org. Lett. 2007, 9, 2919-2921; e) T. Nishimura, X.-X. Guo, K. Ohnishi, T. Hayashi, Adv. Synth. Catal. 2007, 349, 2669-2672; f) N. Tsukada, S. Ninomiya, Y. Aoyama, Y. Inoue, Pure Appl. Chem. 2008, 80, 1161-1166.
- [5] a) H.-D. Xu, R.-W. Zhang, X. Li, S. Huang, W. Tang, W.-H. Hu, Org. Lett. 2013, 15, 840–843; b) A. Funayama, T. Satoh, M. Miura, J. Am. Chem. Soc. 2005, 127, 15354–15355; c) B. M. Trost, M. C. McIntosh, Tetrahedron Lett. 1997, 38, 3207–3210; d) A. Horita, H. Tsurugi, A. Funayama, T. Satoh, M. Miura, Org. Lett. 2007, 9, 2231–2233.
- [6] a) S. Puri, N. Thirupathi, M. S. Reddy, Org. Lett. 2014, 16, 5246–5249; b) N. Thirupathi, M. H. Babu, V. Dwivedi, M. S. Reddy, Org. Lett. 2014, 16, 2908–2911; c) Y. Kiran Kumar, G. R. Kumar, M. S. Reddy, J. Org. Chem. 2014, 79, 823–828; d) N. Thirupathi, Y. K. Kumar, R. Kant, M. S. Reddy, Adv. Synth. Catal. 2014, 356, 1823–1834; e) M. S. Reddy, N. Thirupathi, M. H. Babu, S. Puri, J. Org. Chem. 2013, 78, 5878–5888; f) M. S. Reddy, Y. K. Kumar, N. Thirupathi, Org. Lett. 2012, 14, 824–827; g) M. Sridhar Reddy, N. Thirupathi, M. H. Babu, Eur. J. Org. Chem. 2012, 5803–5809.
- [7] For selected examples, see: a) T. Hamura, S. Iwata, K. Suzuki, *Chem. Commun.* 2011, 47, 6891–6893; b) W. Scadeng, F. G. West, *Eur. J. Org. Chem.* 2014, 1860–1865; c) P. A. Jacobi, J. I. Kravitz, W. Zheng, *J. Org. Chem.* 1995, 60, 376–385; d) C. W. am Ende, Z. Zhou, K. A. Parker, *J. Am. Chem. Soc.* 2013, 135, 582–585; e) P. A. Wender, R. T. Stemmler, L. E. Sirois, *J. Am. Chem. Soc.* 2010, 132, 2532–2533; f) V. Druais, C. Meyer, J. Cossy, *Org. Lett.* 2012, 14, 516–519.
- [8] See the Supporting Information for details.

www.angewandte.org

© 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

These are not the final page numbers!



Communications

Stereoselective Cross-Addition of

Synthesis of 1,4-Enyn-3-ones

Terminal Alkynes to Ynol Ethers and



Alkyne plus alkyne: The hydroalkynylation of phenoxy alkynes was achieved with high regio-, chemo-, and stereoselectivities. A catalytic amount of [Pd(PPh₃)₂Cl₂] with 2.5 equiv. of NEt₃ could mediate the reaction without the need for a ligand, or a Cu catalyst for the activation of the terminal alkyne. The products with allylic hydroxy tether are convenient precursors for useful enynones. pTSA = p-toluene-sulfonic acid.