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Palladium-Catalyzed Carbo-oxygenation of Propargylic Amines using In Situ Tether Formation

Phillip D. G. Greenwood, Erwann Grenet and Jerome Waser*[a]

Dedication ((optional))

Abstract: 1,2-Amino alcohols and α-aminocarbonyls are frequently found in natural products, drugs, chiral auxiliaries and catalysts. Herein, we report a new method for the palladium-catalyzed oxyalkynylation and oxyarylation of propargylic amines. The reaction is perfectly regioselective based on the *in situ* introduction of a hemiacetal tether derived from trifluoroacetaldehyde. *Cis*-selective carbo-oxygenation was achieved for terminal alkynes, whereas internal alkynes gave *trans*-carbo-oxygenation products. The obtained enol ethers could be easily transformed into 1,2-amino alcohols or α-amino ketones using hydrogenation or hydrolysis respectively.

Compounds containing vicinal oxygen- and nitrogen-functionalities are highly represented among bioactive molecules. Examples of α-amino ketones include the protease inhibitor Rupintrivir (**1**)[1] and the antidepressant Bupropion (**2**).[2] Bioactive amino alcohols are even more widespread, with a broad range of bioactivities, as shown by the well-known stimulant pseudoephedrine (**3**), the gastroprotective AI-77-B (**4**)[3] or the antidepressant **5**.[4] Chiral amino alcohols have also found applications as ligands or organocatalysts in asymmetric synthesis, as exemplified by the Jorgensen-Hayashi catalyst **6**.[5]

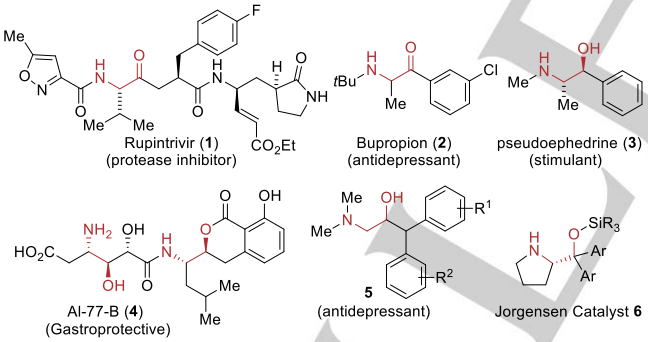
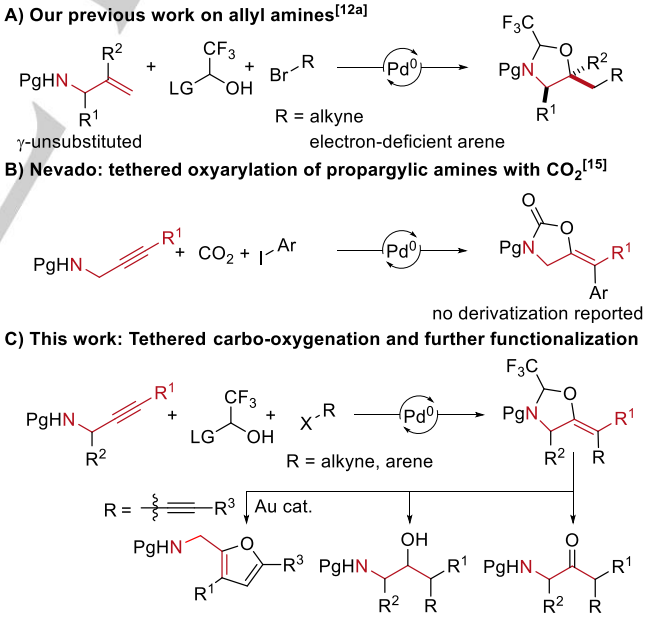


Figure 1. Important organic compounds containing amino ketones and amino alcohols.

The synthesis of amino alcohols from broadly available unsaturated hydrocarbons such as alkenes and alkynes is particularly attractive, but leads to formidable challenges in reactivity, regio- and stereo-selectivity.[6] The use of tethering groups installed onto existing functional groups such as alcohols or amines allows the functionalization of π bonds under mild conditions with high regioselectivity, but several steps are usually required to install and remove the tether.[7] Inspired by pioneering works of Beauchemin,[8] Hiemstra,[9] Stahl[10] and Menche,[11] our group has developed new tethers based on acetaldehydes for the palladium-catalyzed functionalization of allylic alcohols and amines.[12] In particular, a one-pot tether introduction/olefin carbo-oxygenation of allyl amines was developed for the synthesis of aminoalcohols (Scheme 1A).[12a] Nevertheless, important limitations remain for this transformation due to the challenging carbon-carbon formation on a sp^3 center: only alkyne and electron-deficient arene halogenides could be used as electrophiles and only primary positions could be functionalized. Therefore, products bearing a stereocenter in γ position to the amine could not be accessed.



Scheme 1. Allyl and propargyl amines as precursors for the tethered carbooxygenation of olefins.

To overcome these limitations, we considered propargylic amines as widely available starting materials.[13] After oxypalladation, the formed palladium-Csp^2 intermediate should undergo reductive elimination more efficiently, leading to a broader scope. Furthermore, both amino ketones and amino alcohols could be accessed from the products via hydrolysis and hydrogenation respectively. Such a transformation will also give access to highly

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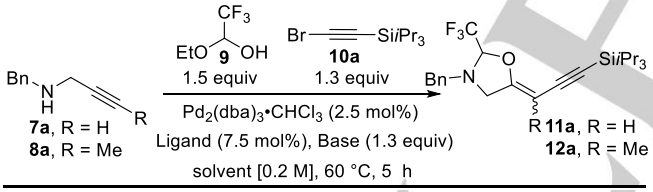
substituted enol ethers, which are challenging to synthesize stereoselectivity, in particularly starting from non-heteroatom substituted alkynes.[14] When considering the synthetic versatility of enol derivatives, new synthetic methods are urgently needed. In comparison to olefins, the tethered multi-functionalization of alkynes has been less investigated. Most success has been met using CO_2 as tether precursor from propargylic amines for the synthesis of oxazolidinones.[15] However, only one new C-O bond is formed in these processes. Using palladium catalysis, an important breakthrough was reported by Nevado and co-workers in 2016, with the oxyarylation of propargylic amines using CO_2 as tether precursor (Scheme 1B).[16] Multi-functionalized oxazolidinones were obtained as products, but no transformation into other valuable building blocks was reported.

Herein, we report the first successful use of acetaldehyde-derived tethers for both the oxy-alkynylation and -arylation of propargylic amines (Scheme 1C). In contrast to our previous work with allyl amines, substituted alkynes could also be used, resulting in the highly stereoselective synthesis of tetrasubstituted alkenes. The tether could be easily removed, enabling the synthesis of amino ketones, amino alcohols and furan heterocycles.

We started our investigations with the oxyalkynylation of simple benzylated propargylic amine **7a** (Table 1). Using silylated bromoalkyne **10a** and the conditions developed previously for allylic amines (Pd(0) catalyst,[17] hemiacetal **9**, DPEPhos as ligand, cesium carbonate as a base, in toluene), the desired product could be obtained in 82% yield and 4:1 *Z:E* ratio (entry 1).[18] In contrast, P(2-furyl)$_3$, which was one of the best ligands in the case of allylic amines, led to inferior results (entry 2). An improvement in *Z*:*E* selectivity could be achieved using dichloroethane (DCE) as solvent (entry 3).

Table 1. Optimization of the oxyalkynylation of amine **7a** and **8a**



Entry	R	Ligand	Base/solvent	Yield[a]/ Z:E ratio
1	H	DPEPhos	Cs_2CO_3/toluene	82%/4:1
2	H	P(2-furyl)$_3$	Cs_2CO_3/toluene	23%/3:1
3	H	DPEPhos	Cs_2CO_3/DCE	83%/9:1
4	Me	DPEPhos	Cs_2CO_3/DCE	40%/1:7
5	Me	DPEPhos	Cs_2CO_3/toluene	20%/1:5
6	Me	P(2-furyl)$_3$	Cs_2CO_3/DCE	-
7	Me	DPEPhos	CsOAc/DCE	19%/ND
8	Me	DPEPhos	K_3PO_4/DCE	67%/1:6
9	Me	XantPhos	K_3PO_4/DCE	73%/1:10

[a]NMR yields using *p*-difluorobenzene as internal standard.[19]

These reactions conditions were then applied to the more challenging internal alkyne **8a**. We were pleased to see that the desired product **12a** could be obtained in 40% yield (entry 4), whereas β-substituted allyl amines could not be used in our previous work.[12a] Interestingly, formation of the *E* product was now favored. Attempts to increase the yield by changing the solvent or ligand were not successful (entries 5 and 6). In contrast, a strong effect of the base was observed: the use of cesium acetate led to low yield (entry 7), but 67% of **12a** could be obtained using potassium phosphate (entry 8). Finally, using XantPhos as ligand allowed increasing both yield and selectivity (entry 9).

With optimized conditions in hand, we investigated first the functional group tolerance on the amine substituent with terminal propargylic alkynes and bromide **10a** as electrophile (Scheme 2A). Methoxy- and chloro- substituted benzyl amines **11b-d** were obtained in more than 80% yield with good *Z* selectivity. In addition, a furyl, a methyl and a phenyl group were also tolerated (products **11e-g**). When a bis-propargylic amine was used as starting material, enyne **11h** was obtained as the Z isomer only. The moderate yield was due to the formation of diyne **13** as side product through sp-sp coupling. The formation of **13** could be increased to 41% by doubling the number of equivalents of bromide **10a**. The carbo-oxygenation was also successful in case of an aliphatic alkynyl bromide as partner to give product **11i** (Scheme 2B).

We then turned to the more challenging internal alkynes (Scheme 2C), which are a particular interesting class of substrates, as the corresponding olefins did not react in our previous work. Gratifyingly, primary, secondary, tertiary and cyclic alkyl groups were all well tolerated on the alkyne (products **12a-f**). With bulky alkyl groups, only the *E* isomer was obtained. Aryl-substituted enynes **12g-j** were also obtained with perfect *E* selectivity. When substituents were introduced at the propargylic position of the amine, the reaction was too slow with bidentate phosphine ligands. Fortunately, useful yields could be still obtained using tris(2-furyl)phosphine as ligand (Scheme 2D). Enynes **14a-b** were obtained as mixtures of two diastereoisomers.

Next, aryl iodides were examined as electrophiles (Scheme 2E). Only low yields were obtained with DPEPhos or XantPhos as ligands, but better results were obtained with RuPhos.[19] The reaction of propargylamine **8a** with phenyl iodide gave enol ether **15a** in 78% yield and complete *E* selectivity.[20] This result is noteworthy, as only electron-poor aryl electrophiles could be used in our previous work on allyl amines. Aryl electrophiles bearing electron-rich or –poor substituents could be used to give the desired products **15b-f** in good yields. Only in the case of an *ortho*-methyl substituent the yield decreased to 45% (product **15c**). A cyclopropyl substituent on the alkyne was also well tolerated to give alkene **15g**. Finally, difficult to access tetrasubstituted olefins **15h-j** bearing two aryl groups were also obtained with perfect *E* selectivity. Such compounds are important pharmacophores: for example, the drug tamoxifen (**16**), which is used to treat breast cancer, bears an olefin with the same two aryl substituents as compound **15j**.

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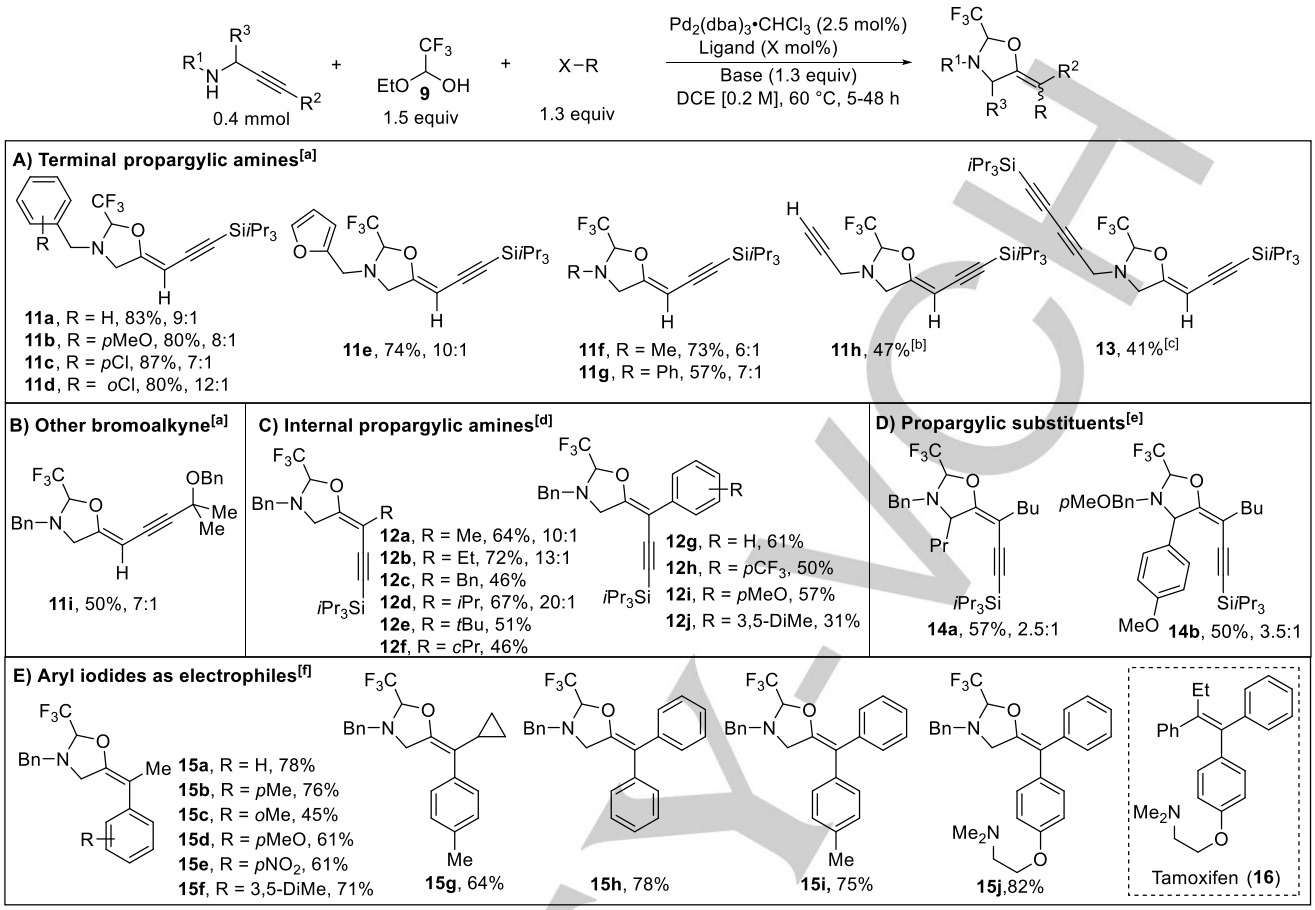
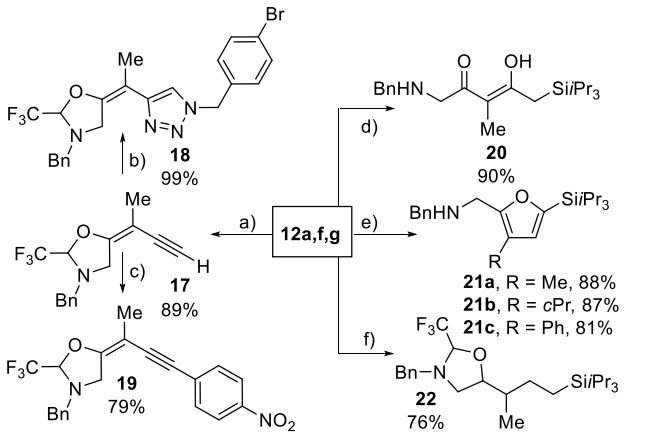
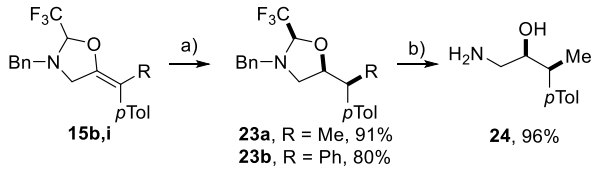


Scheme 2. Scope of the carbooxygenation reaction with alkynyl bromides and aryl iodides. The olefins are obtained with >20:1 stereoselectivity, unless noted otherwise. The major isomer obtained is drawn. [a]DPEPhos as (7.5 mol%) ligand, Cs_2CO_3 as base. [b]**13** also isolated in 13% yield. [c]2.6 equiv. bromoalkyne used. [d]XantPhos (7.5 mol%) as ligand, K_3PO_4 as base. [e]P(2-furyl)$_3$ (15 mol%) as ligand, K_3PO_4 as base. [f]RuPhos (7.5 mol%) as ligand, K_3PO_4 as base.

With a broad range of enynes and styrene derivatives in hand, we turned to the functionalization of the obtained products. Deprotection of product **12a** with TBAF gave surprisingly stable electron-rich terminal enyne **17** in 89% yield (Scheme 3). Enyne **17** could be easily further modified to give products **18** and **19** via [3+2] addition and Sonogashira coupling respectively. The main objective of this work was to access both amino ketone and amino alcohol building blocks. Therefore, the removal of the acetal functionality was investigated next. Hydrolysis in presence of trifluoroacetic acid (TFA) was successful, but hydration of the alkyne occurred upon isolation to give diketone **20** in 90% yield. When a gold catalyst was added directly after acetal removal, furan **21a** was obtained in 88% yield. This transformation was also successful with a cyclopropyl or phenyl substituent on the alkyne (products **21b-c**). Finally, hydrogenation of enyne **12a** gave protected amino alcohol **22** in 76% yield. In the case of styrene derivatives **15**, hydrogenation was completely stereoselective with both alkyl and aryl substituents to give **23a** and **23b** in 91% and 80% yield respectively (Scheme 4). The latter is especially interesting, due to the importance of diarylmethane derivatives as bioactive compounds, such as antidepressant **5**. Compound **23a** was easily deprotected to give amino alcohol **24** in 96% yield.



Scheme 3. Transformations of enyne products **12**. Reaction conditions: a) TBAF, THF, 0 °C; b) *p*Br-BnN$_3$, $CuSO_4$; Na-ascorbate, THF:H_2O, rt; c) *p*NO_2-Ph-I, $Pd(OAc)_2$, DABCO, MeCN; d) TFA, H_2O, $CHCl_3$, rt; e) TFA, H_2O, $CHCl_3$, rt *then* $Au(PPh_3)_2Cl_2$, $Ag(SbF_6)$, rt; f) H_2, Pd/$BaSO_4$, EtOH, 55 °C.



Scheme 4. Hydrogenation and deprotection of styrene derivatives **15**. Reaction conditions: a) H_2, $Pd(OH)_2$/C, MeOH, rt; b) TsOH, THF/H_2O, rt.

In summary, we have described a new tethered carbo-oxygenation of propargylic amines using palladium catalysis. The reaction was successful with trifluoroacetaldehyde derived tethers with both alkynyl bromides and aryl iodides as nucleophiles and could be used for the stereoselective synthesis of tri- and tetra-substituted olefins with high stereoselectivity. The switch of Z- to *E*- selectivity observed when going from terminal to internal alkynes as starting material may indicate a switch from *syn*- to *anti*- palladation in the C-O bond forming step, but further mechanism studies will be required to fully understand the observed selectivity and the subtle ligand effects observed.[21] The obtained products could be easily transformed into useful building blocks, such as amino ketones, amino alcohols or furans. Further studies are currently ongoing for applying the tether strategy to other classes of substrates and chemical transformations.

Acknowledgements

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Keywords: alkynes • tethers • amino alcohols • stereoselective synthesis • palladium catalysis

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[17] In our previous work (ref. 12a), Pd(Cp)cinnamyl had been used as palladium source, but as no difference was observed with the more convenient $Pd_2(dba)_3$•$CHCl_3$ with propargylic amines, the latter was used.

[18] The structure of **11e**, **12j**, **15b**, **15i** and **19** was confirmed by X-ray analysis. The data is available at the Cambridge Crystallographic Data Center (ccdc numbers: 1873997 (**11e**), 1874007 (**12j**), 1874005 (**15b**), 1874008 (**15i**), 1874014 (**19**)).

[19] See Supporting Information for a more detailed list of tested ligands and reaction conditions.

[20] A complex mixture of products was obtained using terminal alkynes as starting materials. As access to tetrasubstituted enol derivatives is generally more difficult and therefore synthetically more useful, no attempt was made to optimize the reaction for terminal alkynes.

[21] See Scheme S1 in Supporting Information for a speculative reaction mechanism. For a discussion of *syn*- vs- *anti* oxy-palladation on alkene substrates, see: J. S. Nakhla, J. W. Kampf, J. P. Wolfe, *J. Am. Chem. Soc.* **2006**, *128*, 2893.

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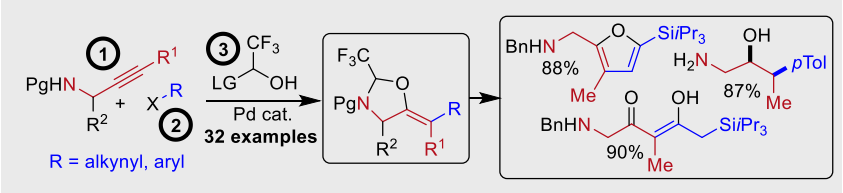

Tether control: *In-situ* tether formation allows the selective palladium-catalyzed oxyalkynylation and oxyarylation of propargyl amines in high yield and selectivity. The obtained products are easily transformed into useful building blocks, such as amino ketones, amino alcohols and furans.

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Page No. – Page No.

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