# Remote Site Specific Radical Alkynylation of Unactivated C-H Bonds

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| Journal: | *Organic Letters* |
| Manuscript ID | ol-2018-025147.R1 |
| Manuscript Type: | Communication |
| Date Submitted by the Author: | 27-Aug-2018 |
| Complete List of Authors: | Wang, Lin; University of Münster, Chemistry<br>Xia, Yong; University of Münster, Chemistry<br>Bergander, Klaus; University of Münster, Chemistry<br>Studer, Armido; University of Münster, Chemistry |
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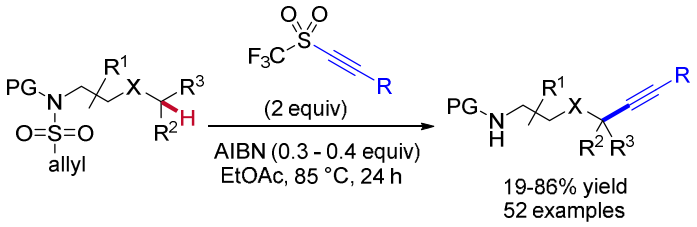
# Remote Site Specific Radical Alkynylation of Unactivated C–H Bonds

Lin Wang, Yong Xia, Klaus Bergander and Armido Studer*

Institute of Organic Chemistry, University of Münster, Corrensstrasse 40, 48149 Münster, Germany

*Supporting Information Placeholder*

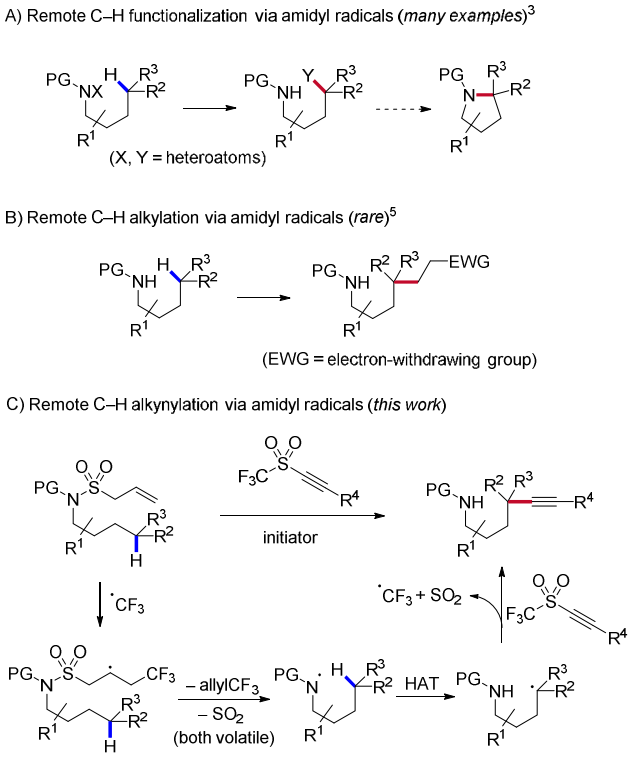



**ABSTRACT:** A method for remote radical C–H alkynylation at unactivated sites is reported. C–H functionalization proceeds via 1,5-hydrogen atom transfer (HAT) to amidyl radicals that are generated via an addition/fragmentation reaction. The readily installed N-allylsulfonyl moiety is used as a precursor of the N-centered radical. Unactivated secondary and tertiary as well as selected primary C–H bonds can be functionalized by this method.

Functionalization of inert C–H bonds has received great attention over the past years, as it allows for late stage modification of complex compounds opening up novel retrosynthetic routes.[1] Along with transition-metal-mediated processes, radical chemistry has turned out to be highly valuable for alkane C–H functionalization.[2] Radical C–H modification generally relies on the H-abstraction (hydrogen atom transfer, HAT) from a C–H bond by a reactive (mostly) heteroatom centered radical.[3] By using an intermolecular HAT, the regioselectivity problem has to be addressed. Along these lines, site-selectivity is more readily achieved upon switching to intramolecular variants. In particular, the 1,5-HAT to reactive N-centered radicals has a long history with the Hoffmann-Löffler-Freytag (HLF) reaction to be named as the basis for many recent developments.[1b,3c,4,5c] In HLF-type reactions, the N-atom of the substrate amine/amide is first charged with a radical leaving group X allowing for N-radical generation (Scheme 1, A).[3c,5] Remote 1,5-HAT and subsequent C-radical functionalization afford the remotely functionalized amine/amide in a chain reaction by X-atom or X-group transfer. Hence, the installed functionality Y is often equal to X and at the same time is also a good ionic leaving group. Ionic cyclization eventually leads to pyrrolidines. In contrast, remote C–H functionalization via amidyl radicals comprising intermolecular C–C bond formation (formal C–H alkylation) is rare and has been developed only very recently (Scheme 1, B).[6,7] Herein, we introduce a method for remote site-selective C–H alkynylation.[8-10] To our knowledge, remote C–H alkynylation at unactivated C–H bonds proceeding via intramolecular HAT has been explored only very recently.[11]

In 2004, Zard showed that N-allylsulfonamides can be used as precursors for N-radical generation to construct lactams via radical cyclization reactions.[12] The readily installed allylsulfonyl

**Scheme 1. Remote radical C–H functionalization via HAT to amidyl radicals**



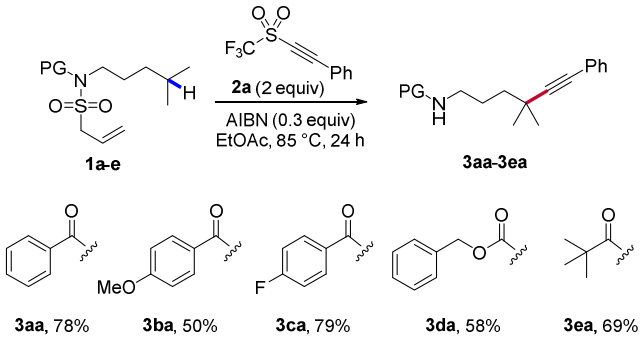
moiety serving as a stable amidyl radical precursor has surprisingly not found any application along these lines since.

Our reaction design is depicted in Scheme 1, C. As radical alkynylation reagents we chose acetylenic triflones, which were first introduced by Fuchs for this purpose.[8a] In our approach, they serve both as trifluoromethyl and alkynyl sources. By alkynylation of the initiating radical, a $CF_3$ radical will be generated.[13] For electronic and steric reasons, this electrophilic radical should chemoselectively react at the terminal double bond of the allyl sulfone. The thus formed secondary adduct radical will fragment allyl$CF_3$ and $SO_2$ to give the corresponding amidyl radical (Scheme 1). Importantly, both side products are highly volatile and allyl$CF_3$ as undesirable radical acceptor should be removed from the reaction mixture. 1,5-HAT to the amidyl radical will lead to the translocated C-radical which in turn gets alkynylated by the triflone reagent to provide via addition/elimination the targeted product along with $SO_2$ and the chain carrying $CF_3$ radical.

The starting allylic sulfones **1a-c** were prepared from the corresponding amines by converting them first to allylsulfonamides (allyl$SO_2$Cl) followed by N-protection (see the Supporting Information (SI)). Careful reaction optimization on sulfonamide **1a** revealed that remote alkynylation with reagent **2a** (2 equiv) is best conducted in EtOAc as a solvent and α,α'-azobisisobutyronitrile (AIBN, 0.3 equiv) as an initiator in a sealed tube at 85 °C to provide benzamide **3aa** in 78% isolated yield (Scheme 2, see SI for reaction optimization). Note than in acetonitrile a similar result was obtained. Lowering the amount of reagent **2a** led to a decreased yield and increasing reagent stoichiometry to 3 equiv did not further improve reaction outcome. Dibenzoyl peroxide can also be used as an initiator to obtain a similar yield (see SI). With sulfonamide **1b**, leading to a less electrophilic amidyl radical, reaction was lower yielding under otherwise identical conditions (**3ba**, 50%). The fluorobenzoylated amide **1c** reacted with similar efficiency than **1a** (**3ca**, 79%) and benzyloxycarbonyl-protected **1d** gave target **3da** in 58% yield. A good result was achieved with pivaloylated amide **1e** (**3ea**, 69%).

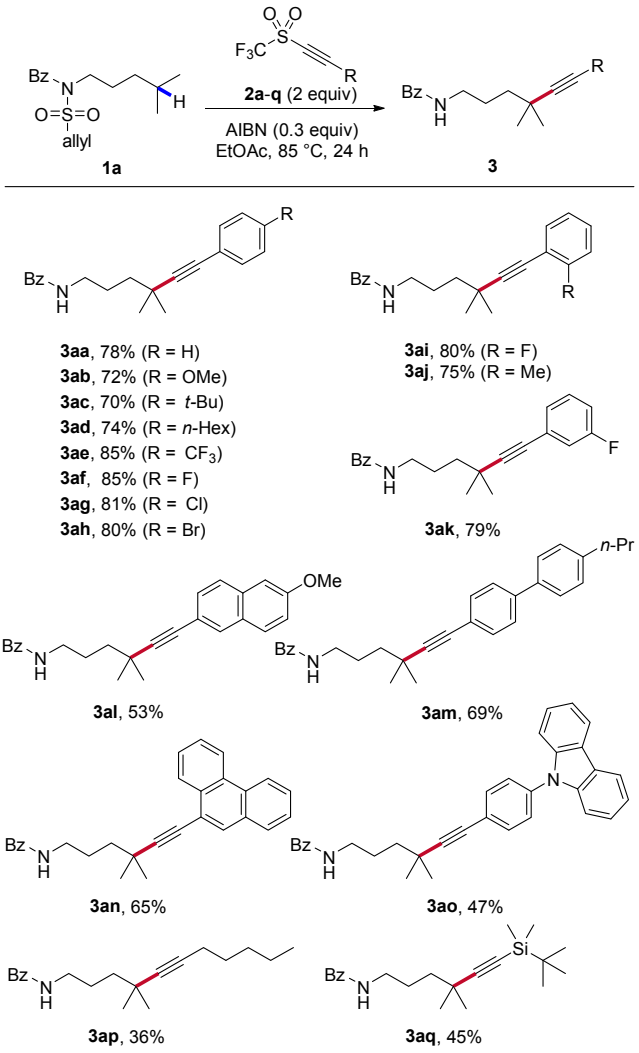
Based on these screenings, all further experiments were conducted with the N-benzoylated derivatives since the para-fluorobenzoyl congeners are more expensive. In agreement with our reaction design, remote alkynylation of **1a** with $PhCCSO_2Ph$ was not a clean reaction and a significantly lower yield of **3aa** (27%) was obtained.

**Scheme 2. Variation of the N-protecting group (PG)**




Under the optimized conditions substrate scope was evaluated with respect to reagent **2** keeping sulfonamide **1a** as the substrate (Scheme 3). In the first series of experiments the R substituent in **2** was systematically varied. For aryl-substituted alkynes, electronic effects exerted by the aryl moiety are weak and various electronically distinct *para*-substituted phenylalkynyl triflones **2b-h** reacted to the corresponding C–H alkynylation products **3ab-3ah** in 70-85% yields. Since the aryl moiety in these alkynes is distal from the site of radical addition, steric effects do not play an important role and similar yields were obtained for reagents bearing *ortho* and *meta*-substituted aryl groups (**3ai-3ak**). Slightly worse results were achieved for the naphthyl, biphenyl, phenanthryl and phenyl carbazole systems (see **3al-3ao**). As expected, the activating aryl moiety in the alkynylation reagent is beneficial for the transformation and with the alkylalkynyl sulfone **2p**, the targeted product **3ap** was isolated in moderate 36% yield. An improved yield was noted for the silylalkynylation (**3aq**, 45%).

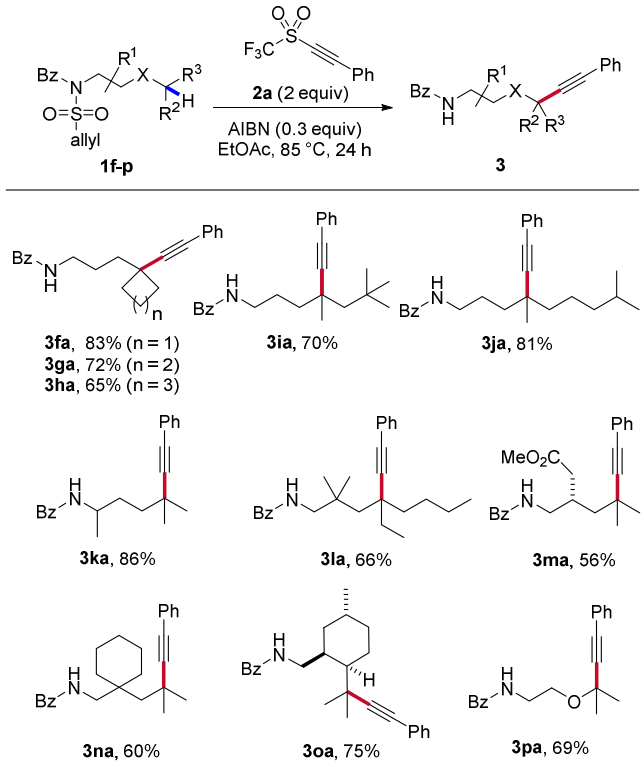
**Scheme 3. Remote alkynylation of allylsulfonamide 1a – variation of reagent 2**




The substrate scope with respect to the sulfonamide component **1** was evaluated next, first focusing on the alkynylation of tertiary C–H bonds (Scheme 4). The reaction worked well on 4-, 5- and 6-membered cyclic systems (**3fa**, **3ga**, **3ha**). The backbone of the amide can also be substituted, as documented by the successful preparation of **3ka-3oa** (60-86% yields). Importantly, regioselectivity was excellent also for these more complex derivatives. Of particular note are products **3ja**, **3ma** and **3oa** which carry additional activated C–H bonds that were not functionalized but would be tackled in an intermolecular HAT-approach. These examples convincingly document the benefit of the regioselective

intramolecular 1,5-HAT-step. As expected, remote alkynylation next to an O-atom can also be achieved (see **3pa**, 69%).

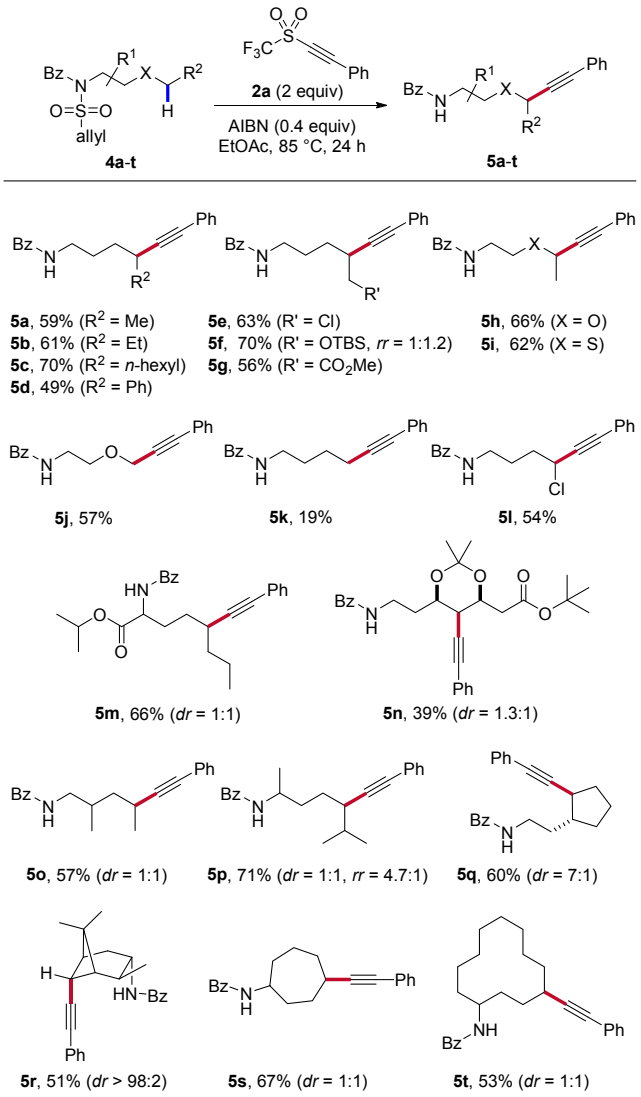
**Scheme 4. Variation of substrate 1 – alkynylation of tertiary C–H bonds**




The more challenging C–H-functionalization at secondary C–H bonds was studied next. Pleasingly, radical alkynylation of N-protected pentyl-, hexyl- and decylamine occurred with complete regiocontrol in good yields (**5a-5c**, 59-70%). Compound **5b** was successfully also prepared at larger scale (2 mmol, 53%). Functionalization of the secondary benzylic position was achieved with slightly lower yield (**5d**) and methylene-alkynylation also worked with complete 1,5-regioselectivity next to a chloromethyl group (**5e**, 63%). However, for the congener bearing a silyloxymethyl substituent, the 1,5-alkynylation product **5f** was formed as minor regioisomer along with the corresponding 1,6-product (70% combined yield, regioselectivity = 1:1.2). Although the ester functionality also activates the α-$CH_2$ group, complete 1,5-regioselectivity was noted for the formation of product **5g**. This can be understood considering polar effects, since the amidyl radical is an electrophilic radical and 1,6-H abstraction would lead to an electrophilic α-ester radical.

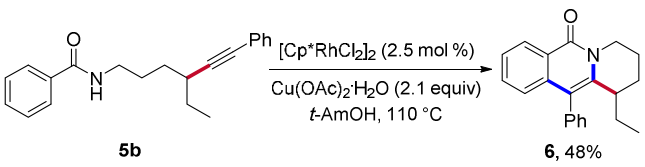
C–H alkynylation next to O and S-atoms in ethers and thioethers worked well (**5h**, **5i**) and an activating O-atom even allows for remote alkynylation of a primary C–H bond (**5j**). However, for non-activated primary C–H bonds, the yields significantly decreased (**5k**). Methylene groups next to a chloride could be functionalized (**5l**) and reaction worked well for remote functionalization of an α-amino acid ester (see **5m**) and other complex amino esters (**5n**). No stereoselectivity was observed (1,3- and 1,4-stereoinduction) for the intermolecular radical C–H alkynylation in open chain systems (**5m**, **5o**, **5p**). The same is true for 7- and 12-membered ring-systems that show conformational flexibility (see **5s**, 67%; **5t**, 53%). However, for a rigid cyclic system, the 1,2-stereoinduction was good (**5q**, 60%, *trans*:*cis* = 7:1) and even complete stereocontrol was achieved for alkynylation of a rigid bicyclic compound (see **5r**). In case of **5p**, regioselectivity was not perfect and alkynylation at the tertiary C–H bond occurred to a small extent. Note that only for **5p** and **5f** (see above), regioselectivity was not complete and in all other cases studied other regioisomers could not be identified.

**Scheme 5. Variation of substrate – alkynylation of secondary and primary C–H bonds**




Finally, we can show that the product δ-alkynylated benzamides can be readily transformed to isoquinolinones using known Rh-catalysis,[14] as documented by the successful transformation of **5b** to the heterocycle **6** (Scheme 6).

**Scheme 6. Further transformation to an isoquinolinone**



In summary, a method for remote radical C–H-alkynylation of unactivated C–H bonds was introduced. The process uses readily prepared allylsulfonamides as N-radical precursors and excellent regioselectivity is achieved via reliable intramolecular 1,5-H atom transfer. The allylsulfonyl moiety, which is clearly underdeveloped in our eyes, shows great potential as a stable readily accessed N-radical precursor moiety.[15] Using this approach, functionalization of secondary and tertiary unactivated C–H bonds can be achieved. In the case of methyl group activation, reasonable yields are obtained for activated systems, where the methyl group sits next to a heteroatom. Thanks to the great functional group tolerance of radical chemistry, substrate scope is broad for these transformations.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental procedures and analytical data for all compounds. (PDF)

AUTHOR INFORMATION

### Corresponding Author

studer@uni-muenster.de

### Notes

The authors declare no competing financial interests.

## ACKNOWLEDGMENT

This work was financially supported by the China Scholarship Council (stipend to L.W.) and the Deutsche Forschungsgemeinschaft (DFG).

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