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Gold-Catalyzed Addition of *N*-Hydroxy Heterocycles to Alkynes and Subsequent 3,3-Sigmatropic Rearrangement

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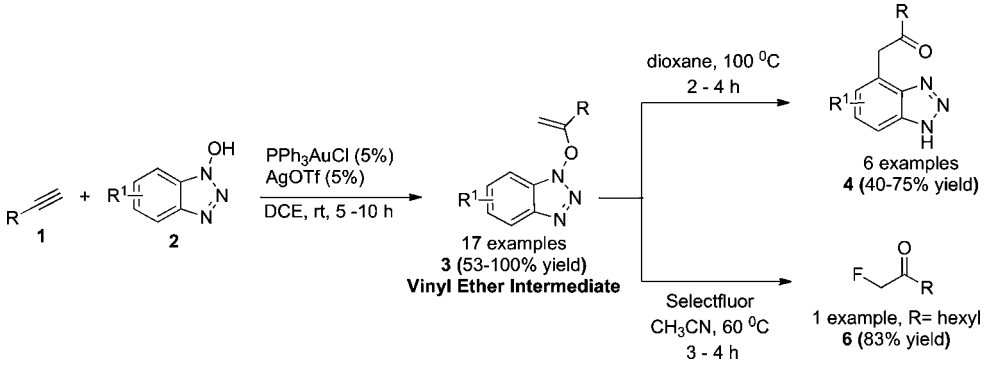
ABSTRACT



Gold-catalyzed intermolecular addition of hydroxybenzotriazole derivatives to alkynes at room temperature, gives vinyl ethers 3 in high yields and with excellent regioselectivity. Unlike many other vinyl ethers, 3 can easily be purified by regular silica-gel chromatography. On heating, 3,3-sigmatropic rearrangement of 3 gives access to highly functionalized benzotriazoles. This two-step sequence represents an efficient oxygen transfer protocol which incorporates a nucleophilic oxygen atom into an alkyne group. Reaction of 3 with an electrophilic fluorinating reagent (Selectfluor) gives a fluorinated ketone regioselectively and in high yield.

Gold catalysis is regarded as one of the landmark additions to the field of organic synthesis.[1] In particular, gold catalyzed addition of *O*-nucleophiles to alkynes will first give synthetically important vinyl ether products,[2] but they are usually not stable enough to be isolated by standard silica gel chromatography.[2] Here we report gold catalyzed addition of *N*-hydroxy heterocycles to alkynes to give an easy isolable vinyl ether product **3**. The subsequent 3,3-sigmatropic rearrangement of **3** (Scheme 1a) gives access to pharmaceutically important functionalized *N*-heterocycles.[3] Furthermore, reaction of **3** with electrophiles, such as the electrophilic fluorinating reagent Selectfluor, gives functionlized α-fluoroketones.

The two-step sequence (nucleophilic addition/sigmatropic rearrangement) represents an efficient protocol for transfer of

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a nucleophilic oxygen atom to an alkyne group (Scheme 1a). Gold-catalyzed oxygen transfers are synthetically useful and attract much attention.[4] In 2009, Asensio and co-workers applied the oxygen transfer concept in their intermolecular gold-catalyzed addition of sulfoxides to alkynes which allowed preparation of diverse sulfur containing arenes (Scheme 1b).[5] A similar approach was employed by Zhang and co-workers in their synthesis of 2-alkylindoles from *N*-arylhydroxylamines and terminal alkynes (Scheme 1c).[6]

We selected the reaction of 4-hydroxyhex-1-yne **1a** with *N*-hydroxybenzotriazole **2a** as our model reaction (Table 1). To our delight, when we treated **1** (1 equiv) with **2a** (1.1 equiv) in the presence of a standard gold catalyst, i.e., Ph_3PAuCl (5%) with AgOTf (5%), we acquired a near-quantitative isolated yield of the vinyl ether **3aa**, using DCE (dichloroethane) as solvent at rt (Table 1, entry 1). Reducing the loading of gold catalyst to 1% did not reduce the yield, although it lengthened the reaction time (Table 1, entry 2). When we reduced the amount of **2a** from 1.5 to 1.1 equiv, either in DCE or acetonitrile, the reaction yields were still excellent, although, the reaction was slower in acetonitrile (Table 1, entries 3–4). With optimized conditions in hand, we studied the reaction scope for synthesis of other vinyl ethers **3** (Table 2).

Scheme 1. Gold-Catalyzed Oxygen Transfer Reactions

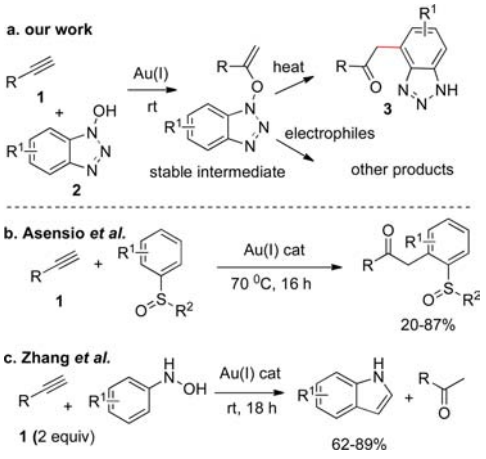
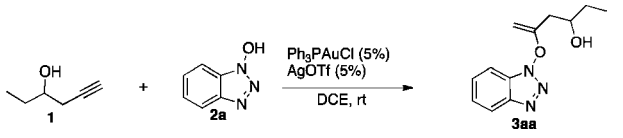


Table 1. Reaction Optimization for Synthesis of Vinyl Ether **3**



entry	equiv of **2**	solvent	time (h)	isolated yield (%)
1	1.5	DCE	6	quantitative
2[a]	1.5	DCE	24	quantitative
3	1.1	DCE	8	99%
4	1.1	CH_3CN	16	quantitative

[a] Ph_3PAuCl (1%), AgOTf (1%).

Terminal alkynes bearing aliphatic substituents (Table 2, entries 1, 3, 5, 7, 9) afforded good to excellent yields of the expected products. Functional groups such as a hydroxyl group (Table 2, entries 1 and 7), methoxy groups (Table 2, entry 5), and alkenes (Table 2, entry 6) were well tolerated. In the case of aromatic alkynes, the reaction also gave high yields (Table 2, entries 2, 4). When we reacted 1,6-heptadiyne with 2.2 equiv of **2a**, an excellent yield of **3ha** was obtained (Table 2, entry 8). When substituted *N*-hydroxybenzotriazoles (Table 2, entries 10–13) were screened, we found that *N*-hydroxybenzotriazoles substituted with electron-donating groups (Table 2, entries 12, 13) or with electron-withdrawing groups (Table 2, entries 10, 11) also gave excellent yields of product **3**. Moreover, when we used *N*-hydroxy-7-azabenzotriazole, we also isolated high yields of the expected 7-azabenzotriazole derivatives (Table 2, entries 14–16). We also investigated use of an allene substrate (Table 2, entry 17). In this case, when

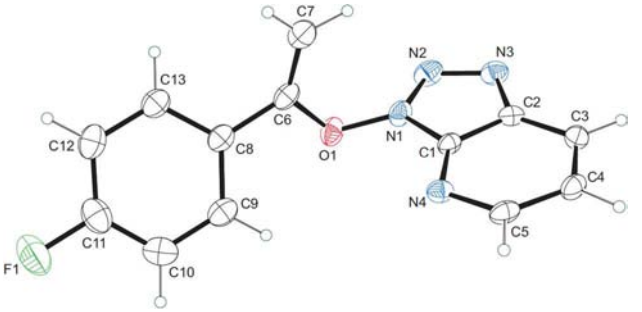


Figure 1. ORTEP-3 diagram of **3od** showing 50% ellipsoids. Selected bond lengths (Å) O1–N1, 1.3697(18); O1–C6, 1.418(2); C6–C7, 1.313(3); N1–N2, 1.345(2); N2–N3, 1.309(2).

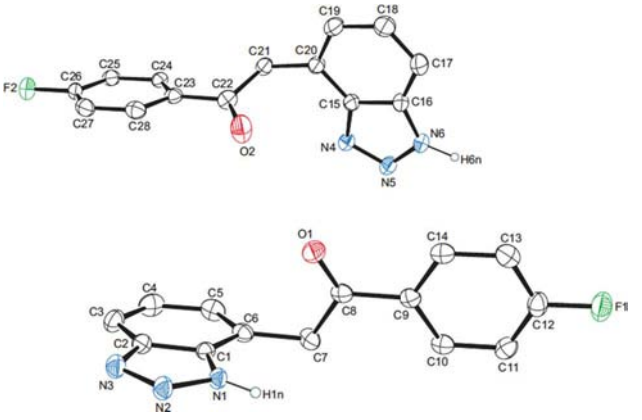
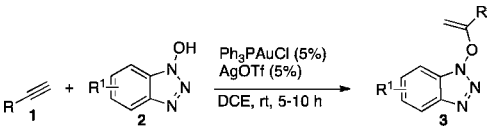


Figure 2. ORTEP-3 diagram of **4e** illustrating two unique conformers present in the asymmetric unit shown at 50% ellipsoids. A third molecule identical to the top conformer in the asymmetric unit has been omitted for clarity. Additionally, only H atoms attached to N atoms are shown. Selected bond lengths (Å): O1–C8, 1.2238(19); C6–C7, 1.504(2); C7–C8, 1.516(2); N1–N2, 1.3497(17); N2–N3, 1.3130(19).

Table 2. Synthesis of Vinyl Ether Intermediates



entry	1	2	3 (isolated yield %)
1.	1a	2a	3aa, 100%
2.	1b	2a	3ba, 80%
3.	1c	2a	3ca, 96%
4.	1d	2a	3da, 83%
5.	1e	2a	3ea, 89%
6.	1f	2a	3fa, 70%
7.	1g	2a	3ga, 53%; 3ga', 12%
8.	1h	2a	3ha, 95%[a]
9.	1i	2a	3ia, 100%
10.	1a	2b	3jb, 81%
11.	1c	2b	3kb, 87%
12.	1c	2c	3lc, 100%
13.	1a	2c	3mc, 92%
14.	1c	2d	3nd, 80%
15.	1d	2d	3od, 80%
16.	1j	2d	3pd, 70%
17.	1k	2a	3qa, 17%
18.	1c	2e	3re, 0%
19.	1c	2f	3sf, 0%
20.	1c	2g	3tg, 0%

[a] 2.2 equiv of **2a** were used.

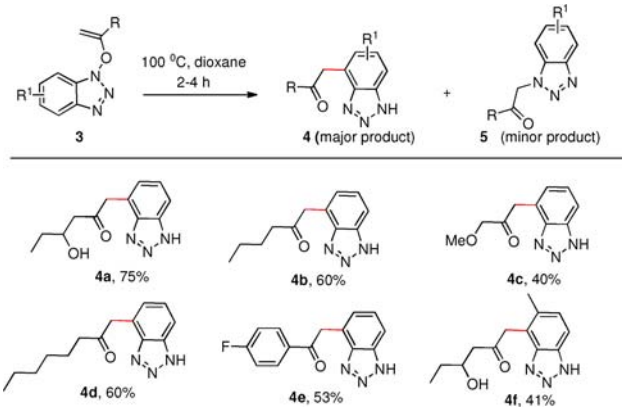
allene **1k** was treated with *N*-hydroxybenzotriazole **2a**, we obtained **3qa** in lower yield (17%); the majority of unreacted allene **1k** was recovered, indicating that an allene is less reactive than the corresponding alkyne under these conditions. Interestingly, 1-hydroxyindazole (**2e**),[7] *N*-hydroxy-4-quinolone (**2f**),[8] and *N*-hydroxyquinazolinediones (**2g**)[9] did not react with alkynes under the same conditions (Table 2, entries 18−20). The reasons for this are not clear to us at this point. Furthermore, we also examined a few *N*-oxides such as benzo[*c*]cinnoline *N*-oxide, and benzofuroxan, but they did not show any reactivity with alkynes under the same conditions. Moreover, we also tested the reaction of internal alkynes such as 2-decyne and 5-decyne with *N*-hydroxybenzotriazole (**2a**), but their reactions were very sluggish.

In nearly all cases the reaction proceeds regioselectively. However, reaction of propargyl alcohol **1g** (Table 2, entry 7) also led to formation of a minor regioisomer **3ga′** (12% yield), possibly due to steric reasons. The structure of **3od** was confirmed by X-ray crystallography (Figure 1).

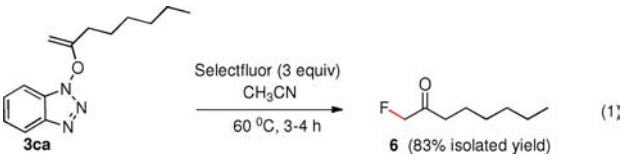
Next, we investigated the use of vinyl ethers **3** as useful synthetic intermediates. We first investigated 3,3-sigmatropic rearrangements of **3**, which would lead to formation of new C−C bonds affording functionalized benzotriazoles. We investigated the effects of Lewis acids, bases, solvents, and temperature and found dioxane/100 °C was optimal for rearrangement. We found that 3,3-sigmatropic rearrangement of vinyl ethers **3** gives the 7-substituted 1-*H*-benzotriazoles **4** as the major product, but we also isolated the *N*-substituted ketones **5** as minor side products. A detailed mechanism explaining the formation of **5** is not clear yet. The structure of **4e** was confirmed unambiguously by X-ray crystallography (Figure 2). Depending on recrystallization conditions, either tautomer of **4e** could be obtained. In order to determine some of the scope of this transformation, we investigated several different vinyl ether substrates (Scheme 2). Conversion into the expected 7-substituted benzotriazoles **4** proceeded with moderate to good yield (40−75%).

Encouraged by the utility of HOBt vinyl ethers in the synthesis of functionalized benzotriazoles, we explored their use in the synthesis of α-fluoroketones. Fluoroketones are known to be important intermediates and targets in medicinal chemistry.[10] However their regioselective synthesis is often nontrivial. We were pleased to discover that the reaction of **3** with Selectfluor gave the functionalized fluoroketone **6** regioselectively and in 83% isolated yield

Scheme 2. Scope for 3,3-Sigmatropic Rearrangements of **3**



(eq 1). By contrast, many similar literature fluorination methods are known to suffer from poor regioselectivity.[11]



In conclusion, we have developed a high yielding gold-catalyzed synthesis of HOBt derived vinyl ethers **3** and briefly explored their synthetic utility. Thus, 3,3-sigmatropic rearrangement of **3** gives access to functionalized *N*-heterocycles, while electrophilic fluorination of **3** gives high yielding regioselective access to a functionalized fluoroketone. We are now exploring other synthetic applications of these useful intermediates **3**.

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Supporting Information Available. CCDC-918814 and 918815 contain the supplementary crystallographic information for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Experimental procedure, compound characterization, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.