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Silyl triflate-accelerated additions of catalytically generated zinc acetylides to N-phenyl nitrones

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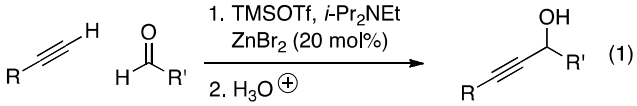
ABSTRACT

Terminal alkynes readily form zinc acetylides in the presence of *i*Pr$_2$NEt and 20 mol% ZnBr$_2$, then attack *N*-phenyl nitrones activated by trimethylsilyl trifluoromethanesulfonate. Deprotection with aqueous acid yields the *N*-hydroxyl propargylamine. Yields are generally high for nitrones derived from aromatic aldehydes. Control experiments suggest that the silyl triflate has a significant accelerating effect upon the reaction.

Keywords: *nitrones, zinc acetylides, silyl triflates, propargylamines*

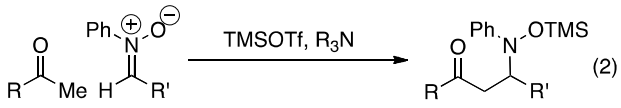
The catalytic generation of metal acetylides from terminal alkynes and their subsequent addition to nitrones has garnered significant interest in recent years. Copper catalysts typically yield β-lactams via the Kinugasa reaction, a process that is now well developed in both racemic and asymmetric forms.[1] In contrast, catalytically generated zinc acetylides undergo simple addition to nitrones to produce *N*-hydroxylated propargylamines. Such a zinc-catalyzed process was reported by Carreira[2] and later rendered asymmetric via a chiral *N*-protecting group on the nitrone.[3] Alternatively, the zinc acetylides have been produced via treatment of terminal alkynes with stoichiometric dialkylzinc reagents, a reaction that proceeds asymmetrically in the presence of a tartrate-derived ligand.[4] The utility of the propargylamine products derives from their facile conversion to isoxazolines.[5] More recently, Studer reported similar zinc-catalyzed dehydrogenative coupling of alkynes with nitrones when the reaction was performed in the presence of oxidants.[6] We now report that trimethylsilyl trifluoromethanesulfonate (TMSOTf) accelerates zinc(II)-catalyzed additions of terminal alkynes to nitrones.

Our interest in catalytically generated zinc acetylides stems from the observation that zinc-catalyzed additions of terminal alkynes to aldehydes show a substantial rate acceleration when performed in the presence of stoichiometric TMSOTf (eq 1).[7] More recent results from our laboratory show that TMSOTf activates *N*-phenylnitrones toward attack by in situ-generated enol silanes (eq 2).[8] Accordingly, we began a study to determine the ability of TMSOTf to accelerate the zinc-catalyzed alkynylation of *N*-phenylnitrones, and challenging class of electrophiles that appears to be significantly less reactive than *N*-benzylnitrones.[2]



R = aryl, alkyl, silyl
R' = aryl, alkenyl, branched alkyl

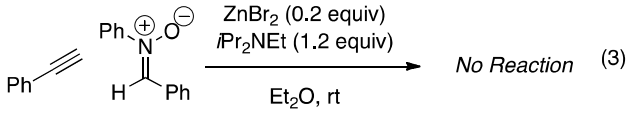
59-97% yield



R = aryl, t-*Bu, NR$_2$, SR*
R' = aryl, alkenyl, branched alkyl

63-99% yield

Test experiments began with the addition of phenylacetylene to *N*,α-diphenylnitrone in the presence of 20 mol% ZnBr$_2$, and focused upon minimizing terminal silylation of the alkyne, a transformation reported by Shaw and Rahaim.[9] A brief survey of solvents (CH_2Cl_2, THF, PhMe, Et_2O) and amine bases (*i*Pr$_2$NEt, Et_3N, Cy_2NMe) revealed that the optimal reaction conditions included treatment of the alkyne with 1.2 equiv *i*Pr$_2$NEt, 1.3 equiv TMSOTf, 20 mol% ZnBr$_2$, and 1.2 equiv nitrone in Et_2O. In the absence of TMSOTf, no reaction was observed under these conditions (eq 3).



In the presence of TMSOTf, however, the reaction proceeded to completion in as little as one hour in Et_2O. After establishment of the optimal reaction conditions, the reaction scope of the alkyne was determined (Table 1). The reaction appears to be quite robust with respect to the alkyne reaction partner. Aromatic substitution is well tolerated (entries 1-4), with uniformly excellent yields observed regardless of the electronic properties of the aryl ring. The use of an aliphatic alkyne resulted in slightly lower yield (entry 5), but silyl substitution well tolerated (entry 6). Even the electron-poor ethyl propiolate was an effective substrate, providing the product in 80% yield. The initial *N*-silyloxylated propargylamine products could be easily purified and isolated, but removal of the TMS protecting group was slightly sensitive to the reaction conditions. Deprotection with trifluoroacetic acid in methanol resulted in significant product decomposition, but *p*-toluenesulfonic acid proved to be a reliable alternative for the series of products

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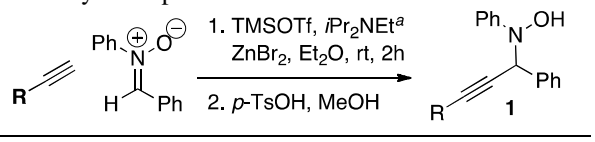
illustrated in Table 1. In some cases, slightly higher yields were observed when the alkynylation mixtures were stirred overnight as opposed to the standard 2 h reaction time (97% vs. 90% for entry 1, 85% vs. 62% for entry 6, 80% vs. 69% for entry 7).

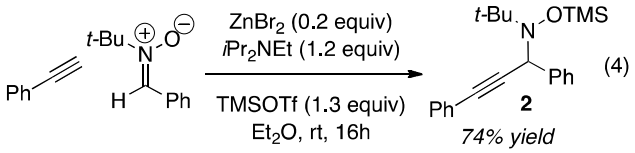
Table 1. Alkyne scope



entry	R	product	yield (%)[b]
1	**X** = H	**1a**	97[c]
2	**X** = 4-MeO	**1b**	85
3	**X** = 2-NO_2	**1c**	95
4	**X** = 4-pentyl	**1d**	90
5	*n*-butyl	**1e**	71
6	triethylsilyl	**1f**	85[c]
7	CO_2Et	**1g**	80[c]

[a]Reaction conditions: 1.0 mmol alkyne, 1.2 mmol nitrone, 0.2 mmol $ZnBr_2$, 1.2 mmol iPr$_2$NEt, 1.3 mmol TMSOTf, 6 mL Et_2O. [b]Isolated yield after chromatography. [c]Reaction stirred 16 h.

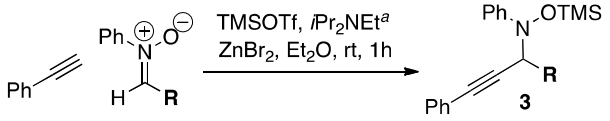
Once the alkyne scope was determined, other challenging *N*-substitution patterns were briefly examined. Although neither outperformed *N*-phenyl nitrones, reactivity was observed for both *N*-methyl and *N*-*tert*-butyl variants. The *N*-methylated products proved prone to decomposition and could not be isolated in >25% yield, either before or after deprotection. The TMS-protected products of the *N*-*tert*-butyl nitrones, however, were conveniently purified in 74% yield (eq 4). An attempt to deprotect the *N*-*tert*-butyl adduct under our standard conditions (*p*-TsOH, MeOH) resulted largely in decomposition, affording only a 32% yield, and remaining experiments were conducted with *N*-phenyl nitrones.



(4)

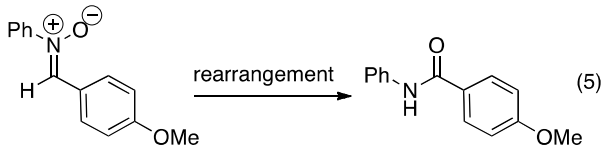
We turned our attention to the nitrone scope (Table 2). In general, the addition of phenylacetylene to nitrones derived from aromatic aldehydes performed reliably. Unfortunately, removal of the TMS group following the reaction frequently resulted in some decomposition of the product, and yields generally suffered by 20-40% compared to the original silylated product. For example, additions to nitrones derived from 4-fluorobenzaldehyde and 4-bromobenzaldehyde provided relatively poor yields after deprotection (64% and 55%, respectively), despite performing well under the initial silylative reaction conditions (88% and 91% yield, respectively, entries 3 and 4). Accordingly, we focused our efforts on the isolation of the trimethylsilylated products **3**. Even without a deprotection sequence, however, efforts to achieve a synthetically useful yield with the *p*-anisylnitrone remained unsuccessful (entry 2). Close examination of the ^{1}H NMR spectrum of the unpurified reaction mixture suggested that the electron-rich *p*-anisylnitrone rearranges under the reaction conditions to produce the corresponding amide (eq 5).[10] Analogous *N*-arylamides have been employed in our laboratory to generate silyl imidates in the presence of TMSOTf and a trialkylamine, conditions very similar to those employed here.[11] This rearrangement and subsequent silyl imidate formation accounts for the removal of TMSOTf, iPr$_2$NEt, and nitrone from the desired reaction pathway and provides a rationale for the drastically reduced yield for the *p*-anisyl substrate.

Table 2. Nitrone scope



entry	R	product	yield (%)[b]
1	**X** = H	**3a**	90
2	**X** = 4-MeO	**3b**	30
3	**X** = 4-F	**3c**	88
4	**X** = 4-Br	**3d**	91
5	2-furyl	**3e**	83
6	2-thiophenyl	**3f**	77
7	cinnamyl	**3g**	63[c]
8	cyclohexyl	**3h**	43[c,d]

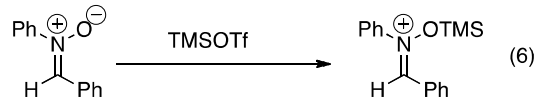
[a]Reaction conditions: 1.0 mmol alkyne, 1.2 mmol nitrone, 0.2 mmol $ZnBr_2$, 1.2 mmol iPr$_2$NEt, 1.3 mmol TMSOTf, 6 mL Et_2O. [b]Isolated yield after chromatography. [c]Product yield includes ~5–10% inseparable impurities. [d]Yield of free hydroxyl amine after deprotection with *p*-TsOH and MeOH.



(5)

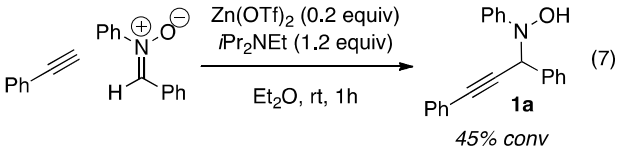
Nitrones derived from other electron-rich aryl aldehydes, however, did provide good yields under our conditions. Furan- and thiophene-containing products were generated in good yield (entries 5 and 6). Alkenyl and aliphatic substrates performed less well, and some unidentified byproducts were discernible even after chromatography (entries 7 and 8). Interestingly, cyclohexyl product **3h** was produced as a mixture of silylated and desilylated (*N*-hydroxyl)propargylamines. The deprotection was completed through treatment with *p*-TsOH and MeOH to afford a modest yield of the free hydroxylamine.

With the scope of the reaction fully established, some further effort was made to determine the role of TMSOTf in the acceleration of the reaction. As mentioned above, no reaction was observed in the absence of TMSOTf when $ZnBr_2$ was employed as the catalyst (eq 3). Furthermore, replacement of TMSOTf with triethylsilyl trifluoromethanesulfonate (TESOTf) or (*tert*-butyl)dimethylsilyl trifluoromethanesulfonate (TBSOTf) greatly reduced the rate of the reaction, generally providing <25% conversion after 16 h. The presence of a strong Si-O bond in the initial product may provide some driving force for the desired reaction, but the data above suggest that *O*-silylation of the nitrone to generate a cationic electrophile is a more important factor in rate acceleration. Silylation of the nitrone is easily observed by ^{1}H NMR spectroscopy, producing a cationic electrophile that would presumably be highly reactive even with mild nucleophiles (eq 6).



(6)

In addition, the trifluoromethanesulfonate anion liberated by nitrone silylation may exchange with the bromides on the metal center to generate a catalytic amount of $Zn(OTf)_2$, the reagent employed by Carreira and Studer in very similar reactions.[2,3a,6] To test this hypothesis, a reaction was performed in the absence of TMSOTf, using $Zn(OTf)_2$ in the place of $ZnBr_2$ (eq 7). Unlike $ZnBr_2$, which displays no reactivity in the absence of TMSOTf, $Zn(OTf)_2$ does indeed provide a significant amount of product, supplying a 45% conversion under these conditions. In comparison, however, the combination of $ZnBr_2$ and TMSOTf affords >90% conversion under otherwise identical conditions. Although these experiments do not rule out the importance of adventitious $Zn(OTf)_2$ in our reactions, they do suggest that TMSOTf plays some additional role in the rate acceleration.



(7)

45% conv

This report documents the ability of TMSOTf to accelerate the addition of catalytically generated zinc acetylides to nitrones. The reaction displays broad substrate scope with respect to the alkyne, and generally performs well with nitrones derived from aromatic aldehydes. Ongoing studies target the addition of zinc acetylides to other electrophiles in the presence of silyl trifluoromethanesulfonates.

Acknowledgments

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