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# Gold-Catalyzed Synthesis of 3-Pyrrolidinones and Nitrones from *N*-Sulfonyl Hydroxylamines via Oxygen-Transfer Redox and 1,3-Sulfonyl Migration

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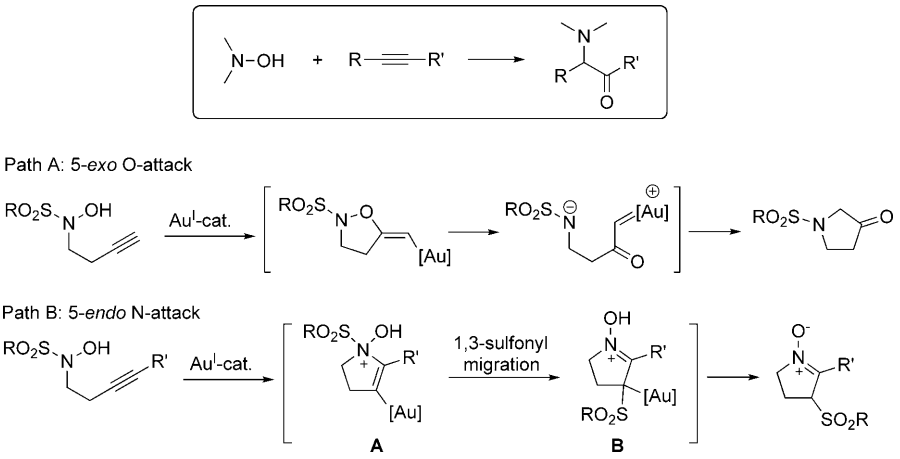
*Dedicated to Professor Barry M. Trost on the occasion of his 70th birthday*

In order to increase the molecular complexity of simple organic substrates, atom-transfer protocols have received intense attention from a viewpoint of atom- and redox-economy.[1] For example, various hydrogen-exchange protocols enable a synthetic design that bypasses redox adjustment steps required to generate reactive functional groups for the desired C–C bond formation.[2,3] Redox reactions with the cleavage of weak N–O bonds can also lead to an oxygen-atom transfer to π bonds, leading to diverse atom- and redox-economical transformations.[4,5] Recently, we and others have reported various electrophilic metal-catalyzed oxygen-transfer redox reactions of nitrones,[6a–c] amine-*N*-oxides,[6d–f] oximes,[5b,6g] and hydroxamates.[5d] Hydroxylamine derivatives are particularly appealing for this redox application, because of its ready availability, safety of handling, and versatile reactivity.




Scheme 1. 3-Pyrrolidinones and nitrones from *N*-sulfonylhydroxylamines.

We projected that a formal addition of hydroxylamine derivatives across alkynes would directly lead to α-amino carbonyl compounds that constitute an important organic building block. Along this line, we envisioned *N*-sulfonylhydroxylamines as precursors of 3-pyrrolidinones through Au$^I$-catalyzed *5-exo*-dig addition (path A, Scheme 1)[7] based on the hypothesis that the N–O bond cleavage step will be rate-limiting and that an electron-withdrawing sulfonyl group on the nitrogen atom will facilitate the overall process.[8] During this study, we also uncovered a new method of forming nitrones based on the alternative *5-endo*-dig nitrogen attack, following an 1,3-sulfonyl migration (path B).[9] We report herein a successful realization of these two concepts and the details of our discovery.

With *N*-benzenesulfonyl homopropargylhydroxylamine (**2a**), we tested various conditions for the desired oxygen-transfer redox cyclization (Table 1). First, treatment of **2a** with $[Au(PPh_3)][NTf_2]$ catalysts at 60 °C gave extensive hydration by-product **4a** (20–30 %). While lowering the temperature or changing solvent gave no improvement, addition of 5 Å molecular sieves effectively suppressed the hydration. Variation of ligands were then tested with the $NTf_2$ counterion (entries 1–5): *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene carbene (IPr) gave the best result and was chosen as an optimal ligand (entry 5). Compared to the rather small ligand effect, the counterion of a cationic Au complex had pronounced impact on the efficiency (entries 6–9). Gratify-

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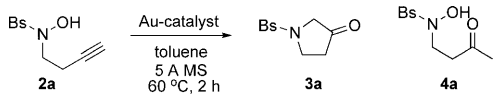
Table 1. Optimization of conditions.



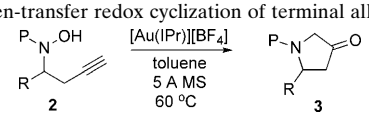

| Entry[a] | Catalyst (5 mol %)[b] | **3** [%][c] | **4** [%][c] |
|---|---|---|---|
| 1 | $[Au(PPh_3)][NTf_2]$ | 39 | 10 |
| 2 | $[Au\{tBu_2P(o\text{-biphen})\}][NTf_2]$ | 44 | – |
| 3 | $[Au\{P(C_6F_5)_3\}][NTf_2]$ | 12 | 9 |
| 4 | $AuCl_3$ | trace (71)[d] | – |
| 5 | [Au(IPr)][$NTf_2$] | 52 | 8 |
| 6 | [Au(IPr)][OTf] | trace | – |
| 7 | [Au(IPr)][$ClO_4$] | 40 | 2 |
| 8 | [Au(IPr)][$SbF_6$] | 66 | 6 |
| 9 | [Au(IPr)][$BF_4$] | 72 | – |
| 10 | HOTf | no reaction | – |

[a] 5 Å molecular sieve was added. [b] $Au^I$ catalysts were generated in situ by mixing of [Au(L)]Cl with AgX (1:1). [c] Crude yield based on $^1H$ NMR spectroscopy (1,3,5-trimethoxybenzene as internal reference). [d] Recovered starting **2a** (in parenthesis).

ingly, treating **2a** with [Au(IPr)]Cl (5 mol %) and $AgBF_4$ (5 mol %) in toluene gave desired **3a** in 72 % yield after 2 h at 60 °C with complete suppression of hydration. Purification of the crude mixture on a silica gel gave analytically pure **3a** as a white solid (70 % yield).

To investigate the scope and limitation of this novel N–O redox cyclization, various *N*-sulfonylhydroxylamines were subject to the optimized conditions (Table 2). Changing the *N*-sulfonyl groups did not have much effect on the yield of pyrrolidinones (entries 1–4). Various aryl and alkyl substituents at the homopropargylic position were well-tolerated, giving reasonable yields of the corresponding pyrrolidinones (entries 5–9).

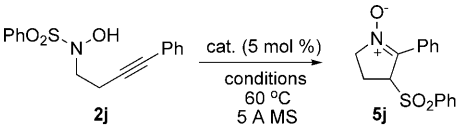
Table 2. Oxygen-transfer redox cyclization of terminal alkynes.




| Entry[a] | Substrate | P | R | *t* [h] | **3** [%][c] |
|---|---|---|---|---|---|
| 1 | **2a** | Bs | H | 1.5 | 70 |
| 2 | **2b** | Ms | H | 1 | 65 |
| 3 | **2c** | Ts | H | 1 | 67 |
| 4 | **2d** | Ns[d] | H | 1 | 74 |
| 5 | **2e** | Bs | Ph | 3 | 57 |
| 6 | **2f** | Bs | 2-naphthyl | 4 | 64 |
| 7 | **2g** | Bs | 4-$CH_3$-$C_6H_4$ | 1 | 58 |
| 8 | **2h** | Bs | 4-Cl-$C_6H_4$ | 1 | 49 |
| 9 | **2i** | Bs | Me | 2 | 58 |

[a] Au catalyst was generated in situ from [Au(IPr)]Cl (5 mol %) and $AgBF_4$ (5 mol %). [b] Isolated yield after chromatography. [c] *p*-Nitrobenzenesulfonyl.

We next investigated the reaction of internal alkyne substrate **2j** and surprisingly, the reaction took a completely different path [Eq. (1)]. Treatment of **2j** under a similar condition ([Au(IPr)][$NTf_2$] (5 mol %) in toluene with 5 Å MS) gave none of the desired pyrrolidinone **3j**, but instead gave product **5j** (38 %), which was assigned as a nitrone based on the spectroscopic data [Eq. (1)]. A brief optimization identified [Au{$tBu_2P$(*o*-biphenyl)}][$NTf_2$] in MeOH at 60 °C as the optimal condition for the nitrone formation. The possible mechanism for its formation is given in Scheme 1 (Path B). In the case of internal alkynes such as **2j**, the nucleophilic attack on the alkyne occurs primarily from nitrogen atom rather than the oxygen atom giving **A**, and the following 1,3-*N*-sulfonyl migration leads to **B**.[9] The turnover of gold catalyst generates the corresponding vinyl hydroxylamine, which tautomerize into the more stable nitrone **5j**.[10] Our assignment of the nitrone structure was confirmed by reacting **5j** with different dipolarophiles for [3+2] cycloaddition (vide infra, Table 3).

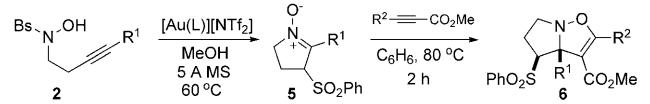



(1)

[Au(IPr)][$NTf_2$] / toluene (1 h) 38 %
[Au{$tBu_2P$(*o*-biphenyl)}][$NTf_2$] / toluene (1 h) 61 %
[Au{$tBu_2P$(*o*-biphenyl)}][$NTf_2$] / MeOH (24 h) 84 %

We next investigated the scope of this novel nitrone formation. As shown in Table 3, various aryl substituted alkynes underwent smooth reactions (entries 1–6), except the strongly electron-withdrawing substrate **2l**, which gave a poor yield of the desired nitrone (entry 5). The current protocol could be extended to the alkyl-substituted alkynes as well (entries 7 and 8). In these cases, much faster conversion was observed, giving good yields of the corresponding nitrones. Treating the thus obtained **5j** with five equivalents of dimethyl acetylenedicarboxylate (DMAD), ethyl propiolate, or methyl 2-butynoate in benzene at 80 °C gave the respective dihydroisoxazoles **6ja**–**jc** smoothly in excellent regio- and diastereofacial selectivity. The sulfonyl group effectively

Table 3. Nitrone formation from internal alkynes.




| Entry[a] | Substrate | $R^1$ | $R^2$ | *t* [h][b] | **5** [%][c] | **6** [%][c,d] |
|---|---|---|---|---|---|---|
| 1 | **2j** | Ph | $CO_2Me$ | 24 | 81 | 89 (**6ja**) |
| 2 | **2j** | Ph | H | | – | 83 (**6jb**) |
| 3 | **2j** | Ph | Me | | – | 60 (**6jc**) |
| 4 | **2k** | 4-Cl-$C_6H_4$ | $CO_2Me$ | 18 | 76 | 86 (**6ka**) |
| 5 | **2l** | 4-$NO_2$-$C_6H_4$ | $CO_2Me$ | 15[e] | 39 | 83 (**6la**) |
| 6 | **2m** | 1-naphthyl | $CO_2Me$ | 15[e] | 87 | 67(**6ma**) |
| 7 | **2n** | Me | $CO_2Me$ | 1 | 88 | 25 (**6na**) |
| 8 | **2o** | *n*Bu | $CO_2Me$ | 1 | 79 | 50 (**6oa**) |

[a] Au catalyst was generated in situ from [Au{$tBu_2P$(*o*-biphen)}]Cl (5 mol %) and $AgNTf_2$ (5 mol %). [b] The reaction time for the nitrone formation. [c] Isolated yield after chromatography. [d] Five equivalents of dipolarophiles; single respective diastereomers were observed. [e] At 80 °C.

directs the approach of dipolarophiles from the opposite face of nitrones. 2-Aryl-substituted nitrones **5k**–**m** also underwent smooth [3+2] cycloadditions to give good yields of the corresponding dihydroisoxazoles **6k**–**m**, except that the sterically hindered **5m** gave a slightly diminished yield. On the other hand, 2-alkyl substituted nitrones **5n** and **5o** gave distinctly reduced yields.

In conclusion, we report herein a novel synthetic route to 3-pyrrolidinone derivatives by means of an intramolecular, oxygen-atom-transfer, redox reaction of *N*-sulfonyl hydroxylamines. Remarkably, the current procedure for the 3-pyrrolidinone synthesis opens new efficient entry into pharmaceutically useful derivatives: For example, 3-pyrrolidinones are the precursors of 3-aminopyrrolidine,[11] 2-oxo-1,2-dihydrobenzo[*d*][1,3]oxazine,[12] and cucurbitine analogues.[13] The current report not only demonstrates the viability of N–O bond redox chemistry of hydroxylamine, but also provides an efficient entry into the useful 3-pyrrolidinone derivatives. In addition, we disclosed a new method of forming nitrones through 1,3-sulfonyl migration from *N*-sulfonyl alkynylhydroxylamines, providing cyclic nitrones equipped with sulfone functionality.

## Experimental Section

**Representative procedure for synthesis of 3-pyrroldinone**: A solution of [Au(IPr)][$BF_4$] (0.0111 mmol, 5 mol%) and 5 Å MS (75 mg) in toluene (2.2 mL) to a vial containing homopropargyl hydroxylamine **2a** (50 mg, 0.222 mmol) and the mixture was stirred 2 h at 60°C. The mixture was quenched with three drops of triethylamine and was concentrated to dryness. The residue was purified by silica gel chromatography (*n*-hexane/EtOAc=4:1) to give 35.0 mg (70%) of product **3a** as white solid. A similar procedure was followed for the nitrone formation except the following ([Au{$t$Bu$_2$P(*o*-biphen)}][$NTf_2$] as catalyst precursor and MeOH as solvent).

**Representative procedure for a dipolar cycloaddtion between the nitrone and the dipolarophiles**: The product **5j** (40 mg, 0.131 mmol) was mixed with dimethyl acetylendicarboxylate (93 mg, 0.655 mmol) in benzene and was heated for 24 h at 60°C. After removal of solvent, the residue was purified by silica gel chromatography (*n*-hexane/EtOAc=3:1) to give 52.4 mg (89%) of product **6ja** as colorless oil.

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**Keywords:** gold · homogeneous catalysis · hydroxylamines · nitrones · pyrrolidinones · redox chemistry

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