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# Transition-Metal-Catalyzed Ring Expansion of Diazocarbonylated Cyclic *N*-Hydroxylamines: A New Approach to Cyclic Ketonitrones

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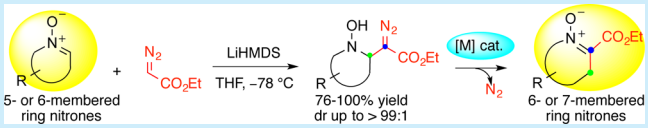
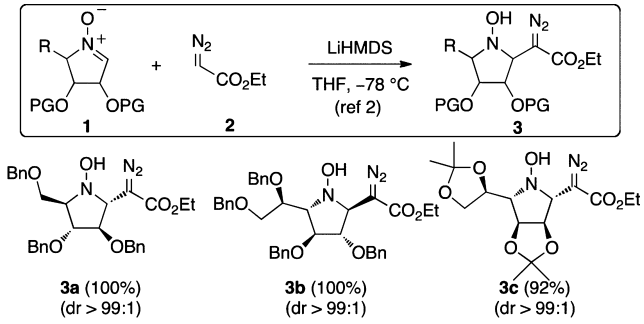
Supporting Information

**ABSTRACT:** Novel *C*-ethoxycarbonyl cyclic ketonitrones are synthesized from the Ag- or Cu-catalyzed ring expansion of *β*-diazo cyclic hydroxylamines. The latter are themselves easily obtained by the addition of lithiated ethyl diazoacetate onto cyclic nitrones. The regioselective metal-catalyzed rearrangement of *β*-diazo cyclic hydroxylamines proved highly efficient and resulted in a synthetically useful ring expansion to produce 6- or 7-membered ring functionalized nitrones. The outcome of the two steps, i.e. nucleophilic addition of *α*-diazoesters to nitrones and ring expansion, is a formal nitrone homologation.




Diazo compounds are highly versatile intermediates in organic synthesis. In particular, they are precursors of metal carbenoids that can undergo powerful synthetic transformations.[1] We recently reported the synthesis of *β*-diazo *N*-hydroxylamines by addition of lithiated *α*-diazoesters on a variety of nitrones.[2] From carbohydrate-derived cyclic nitrones **1**, the expected *N*-hydroxypyrrolidines **3a**–**c** were obtained in high yields and excellent diastereoselectivities (Scheme 1).

**Scheme 1. Previous work[2]**




Intrigued by the reactivity of these novel highly functionalized diazoester derivatives, we decided to investigate their transformation in the presence of metal catalysts. We report herein an extension of the scope of preparation of cyclic *β*-diazo *N*-hydroxylamines from nitrones and the first study on their transformation in the presence of metal catalysts, granting access to novel, homologated cyclic nitrones conjugated to an ester function.

Variously substituted cyclic nitrones[3] were treated with ethyl lithiodiazoacetate (1.5 equiv) in THF at −78 °C (Table 1), according to our reported protocol. From nitrone **1d**[4] or **1e**,[5] the corresponding *β*-diazo *N*-hydroxypyrrolidines **3d** and **3e** were readily obtained in good yields, as single *trans* diastereomers (Table 1, entries 1 and 2).[6] In contrast, a mixture of diastereoisomeric hydroxylamines **3f** and **3g** (*trans*/*cis* = 60:40) was obtained from nitrone **1f**,[7] albeit in excellent overall yield (93%) (Table 1, entry 3). The noncarbohydrate nitrone **4**[8] (MiPNO, Table 1, entry 4) was readily converted into **8** in good yield and with excellent diastereoselectivity (76%, dr >99:1), in line with the total diastereocontrol previously observed in the addition of Grignard reagents to this nitrone.[9]

The addition of ethyl lithiodiazoacetate was next extended to six-membered-ring nitrones. From 3,4-dihydroisoquinoline *N*-oxide **5**[10] the expected *β*-diazo *N*-hydroxylamine **9** was obtained in 78% yield.[11] In the case of the arabinopyranose-derived nitrone **6**[12] the nucleophilic addition was also found to proceed efficiently (97% yield), although in a 64:36 ratio of diastereomers (Table 1, entry 6). The *cis* *N*-hydroxypiperidine **10a** was the major diastereomer, in contrast with previous reports on organometallic additions on this nitrone, yielding preferentially *trans* hydroxylamines.[3d,e,13] Interestingly, the cyclic ketonitrone **7**[14] was smoothly transformed into the corresponding *α*-quaternary *β*-diazo *N*-hydroxypiperidine **11**, in good yield (79%) and excellent diastereoselectivity.[6] This represents a unique example of organometallic addition on a 6-membered ring ketonitrone.[15]

The reactivity of *β*-diazo hydroxylamines has not been reported to date. As they could represent excellent precursors of oxazetidines[16] by intramolecular O–H-insertion of a transient carbenoid, we studied their reactivity in the presence of metal catalysts. A variety of metal complexes are known to induce decomposition of the diazo functionality, with extrusion of gaseous dinitrogen and formation of highly reactive metal carbenoids. The latter can evolve through different processes including X–H insertion,[17] 1,2-hydride shift, and 1,2-C → C or 1,2-X → C bond migration (e.g., X = O, N, S, Si). Although

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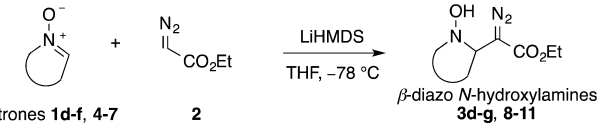
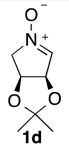
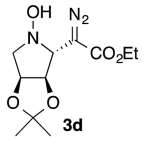
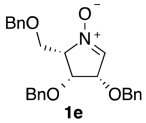
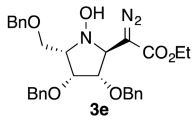
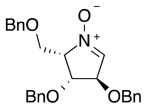
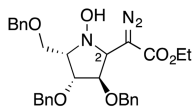
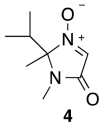
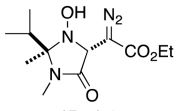
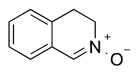
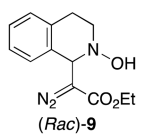
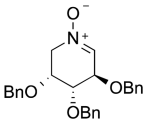
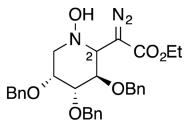
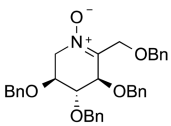
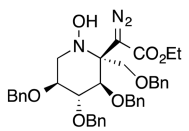
**Table 1. Scope of Nucleophilic Addition of Ethyl Diazoacetate on Cyclic Nitrones**



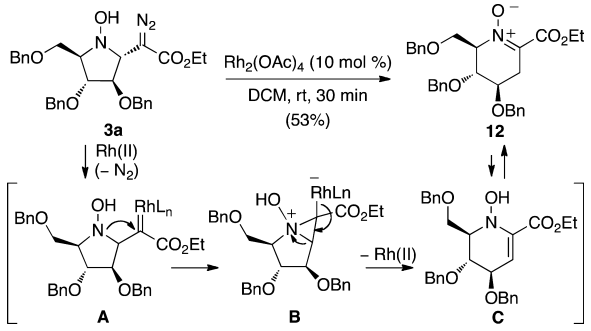

| entry | cyclic nitrone | β-diazo N-hydroxylamine | time (h) | yield (%)[a] | dr[b] |
|---|---|---|---|---|---|
| 1 |  1d |  3d | 1.5 | 93 | > 99:1 |
| 2 |  1e |  3e | 3 | 78 | > 99:1 |
| 3 |  1f |  3f (2*R*), 3g (2*S*) | 1.5 | 93 | 60:40 |
| 4 |  4 |  (*Rac*)-8 | 1.5 | 76 | > 99:1 |
| 5 |  5 |  (*Rac*)-9 | 3 | 78 | - |
| 6 |  6 |  10a (2*S*), 10b (2*R*) | 1.5 | 97 | 64:36 |
| 7 |  7 |  11 | 3.5 | 79 | > 99:1 |

[a]Isolated yield after column chromatography. [b]Determined by integration of representative signals in $^1$H NMR.

examples of chemo- and regioselective rearrangements of carbenoids generated from diazo compounds have been reported,[18] most often several processes compete, leading to mixtures of products.[1]

Dirhodium tetraacetate, the most popular catalyst for carbenoid formation,[1a,19] was tested first on *N*-hydroxypyrrolidine **3a**. The six-membered ring nitrone **12** was the only isolated product, with no trace of oxazetidine. The formation of the nitrone **12** can be explained by generation of the Rh(II) carbenoid **A**, from which 1,2-migration of nitrogen would take place to afford an ammonium ylide intermediate **B** (Scheme 2). Then, ring enlargement would occur producing a six membered-enehydroxylamine **C** that tautomerizes to **12**.[20] A concerted mechanism for the conversion of metallocarbenoid **A** to intermediate **C** is also plausible.

**Scheme 2. Preliminary Result and Proposed Pathway**




In order to optimize this unprecedented ring expansion, other catalysts were screened (see Supporting Information for complete screening). Copper and silver complexes[21] have been described to promote NH-insertion and, in some cases, ring expansion.[22] In the present process, they were found to be the most efficient to generate nitrone **12** from **3a** in high yields (Table 2). In particular, the tetrakis(acetonitrile)copper(I)

**Table 2. Selected Results on Catalyst Screening**

| entry | catalyst[a] | solvent | temp | time | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $Rh_2(OAc)_4$ | $CH_2Cl_2$ | rt | 30 min | 53 |
| 2[c] | $Cu(OTf)_2$ | $CH_2Cl_2$ | rt | 45 min | 77 |
| 3 | $Cu(CH_3CN)_4BF_4$ | $CH_2Cl_2$ | rt | <5 min | 86 |
| 4[d] | $Cu(CH_3CN)_4PF_6$ | $CH_2Cl_2$ | rt | <5 min | 96 |
| 6 | $AgBF_4$ | $CH_2Cl_2$ | rt | 50 min | 82 |
| 7 | AgOBz | $CH_2Cl_2$ | rt | 1.25 h | 83 |
| 8 | AgOTf | $CH_2Cl_2$ | rt | 20 min | 97 |
| 9 | no catalyst | $CH_2Cl_2$ | 40 °C | 120 h | 0[e] |
| 10 | no catalyst | $PhCF_3$ | 80 °C | 50 min | 57 |

[a]The reactions were performed in the presence of 10 mol % catalyst unless otherwise stated. [b]Isolated yield after column chromatography. [c]15 mol % catalyst. [d]With 0.5 mol % catalyst, nitrone **12** was isolated in 86% yield (40 min). [e]Starting material was totally recovered.

hexafluorophosphate $[Cu(CH_3CN)_4PF_6]$ was an excellent catalyst, producing rapidly the desired nitrone **12** in 96% yield (<5 min) with a 10 mol % catalyst loading, and in 86% yield (40 min) with 0.5 mol % catalyst. Catalysis with AgOTf (10 mol %) delivered **12** in 97% yield in 20 min. Thermal decomposition of **3a** was also examined: while no trace of nitrone **12** was detected in refluxing $CH_2Cl_2$ after several days (Table 2, entry 9), the ring-expanded nitrone was isolated in 57% yield by heating **3a** at 80 °C during 50 min in trifluorotoluene (Table 2, entry 10).[23]

With these results in hand, $Cu(CH_3CN)_4PF_6$ and AgOTf were selected as catalysts to evaluate the substrate scope (Table 3). As in the case of *N*-hydroxypyrrolidine **3a**, all other five-membered ring β-diazo-hydroxylamines **3** underwent Ag- and Cu-mediated ring expansion to 6-membered ring cyclic nitrones in excellent yields (68−100%) (Table 3, entries 1−13). Nitrones **13**−**17** were isolated as single products and exhibited good stability. The diastereoisomeric *N*-hydroxypyrrolidines **3f** and **3g** were both transformed into the same nitrone **17** in good yields, upon Ag- or Cu-catalysis. In general, reactions mediated by $Cu(CH_3CN)_4PF_6$ catalysis were faster than those mediated by AgOTf. In addition, with 2 mol % copper catalyst the reaction efficiency was maintained (Table 3, entry 9).


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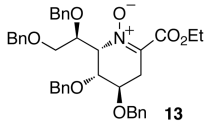
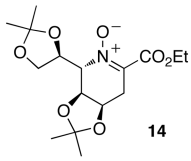
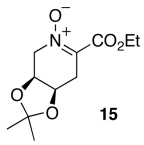
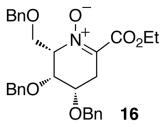
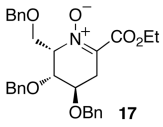
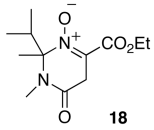
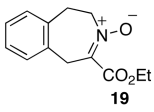
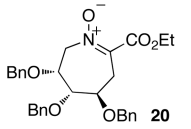
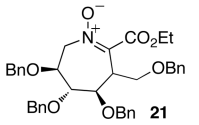
**Table 3. Formation of Ketonitrones 13−20 Mediated by Ag(I) and Cu(I) Catalysts**[a]

| entry | β-diazo-*N*-hydroxylamine [cat.][b] | reaction time | ketonitrone | yield (%)[c] |
|---|---|---|---|---|
| 1 | **3b** [Ag] | 30 min |  **13** | 100 |
| 2 | **3b** [Cu] | < 5 min | | 100 |
| 3 | **3c** [Ag] | 20 min |  **14** | 99 |
| 4 | **3c** [Cu] | < 5 min | | 88 |
| 5 | **3d** [Ag] | 130 min |  **15** | 83 |
| 6 | **3d** [Cu] | 20 min | | 88 |
| 7 | **3e** [Ag] | 45 min |  **16** | 95 |
| 8 | **3e** [Cu] | < 5 min | | 89 |
| 9 | **3e** [Cu][d] | < 5 min | | 93 |
| 10 | **3f/3g** [Ag] | 30 min |  **17** | 97 |
| 11 | **3f/3g** [Cu] | 30 min | | 68 |
| 12 | **8** [Ag] | < 5 min |  **18** | 96 |
| 13 | **8** [Cu] | < 5 min | | 90 |
| 14 | **9** [Ag] | 100 h |  **19** | 36[f] |
| 15 | **9** [Ag][e] | 160 min | | 78 |
| 16 | **9** [Cu] | 35 min | | 60 |
| 17 | **10a** [Ag] | 70 min |  **20** | 96 |
| 18 | **10a** [Cu] | < 5 min | | 46[g] |
| 19 | **10b** [Ag] | 23 h | | 64 |
| 20 | **10b** [Cu] | 20 min | | 7[g] |
| 21 | **11** [Ag][e] | 40 min |  **21** | 0[g] |
| 22 | **11** [Cu][e] | 40 min | | 0[g] |

[a]All reactions were performed in dichloromethane, at room temperature, with 10 mol % catalyst, unless otherwise stated. [b][Ag]: AgOTf; [Cu]: $Cu(CH_3CN)_4PF_6$. [c]Isolated yield after chromatography. [d]2 mol % cat. [e]100 mol % cat. [f]24% imine resulting from dehydration of **9** was isolated as a side product. [g]CH-insertion competes favorably with ring expansion (see Supporting Information).

We next turned our attention to the more challenging conversion of *N*-hydroxypiperidines **9**−**11** into 7-membered-ring ketonitrones. When the β-diazo hydroxylamine **9** was treated with 10 mol % AgOTf (Table 3, entry 14) the expected nitrone **19** was isolated in only 36% yield, accompanied by ethyl 2-diazo-2-(3,4-dihydroisoquinolin-1-yl)acetate (24%) arising from dehydration of **9**. However, the 7-membered-ring nitrone **19** could be obtained in 78% yield, by increasing the amount of silver triflate to 1 equiv (Table 3, entry 15). Using $Cu(CH_3CN)_4PF_6$ (10 mol %) as the catalyst, nitrone **19** formed in only 35 min (60%, Table 3, entry 16). This result confirms the superiority of the copper catalyst over silver triflate, a trend already observed for the 5 → 6-membered ring expansions. Again, when diastereomeric *N*-hydroxypiperidines **10a** and **10b** were treated with the Ag- or Cu-catalysts, the starting materials were consumed much faster with the latter (minutes instead of hours). However, from these β-diazo hydroxylamines, nitrone **20** was isolated in higher yield with the silver catalyst (96% from **10a**, 64% from **10b**). The lower yields in the Cu-catalyzed ring expansion of these *N*-hydroxypiperidines is due to competing insertion of the transient carbenoid in a benzylic C−H bond of the C-3 benzyloxy-substituent in hydroxylamines **10a** or **10b** (see Supporting Information).[1c,f] Unfortunately, nitrone **21** that was expected to arise from ring expansion of hydroxylamine **11** was not isolated from treatment of **11** with AgOTf or $Cu(CH_3CN)_4PF_6$, neither with a 10 mol % (not shown) nor with a 100 mol % (Table 3, entries 21, 22) loading. The only products that could be identified from the reaction mixture resulted from CH-insertion (see Supporting Information). This side reaction, which was never observed from β-diazo *N*-hydroxy pyrrolidines, occurs competitively from *O*-benzyl-protected β-diazo *N*-hydroxy-piperidines (Table 3, entries 18 and 20−22), as the formation of 7-membered rings is energetically demanding.

In summary, the efficient addition of α-diazo esters to cyclic nitrones, followed by metal-catalyzed ring expansion, results in homologation to new *C*-ethoxycarbonyl cyclic ketonitrones. In contrast to the well-documented preparation of aldonitrones,[3] methods for the preparation of cyclic ketonitrones are scarce and suffer from low yields.[14,24,25] This novel approach for their synthesis opens new opportunities for development of the rich chemistry of nitrones. Further applications of these novel structures to access cyclic amino acids and bioactive alkaloids are currently ongoing in our laboratory. We are also investigating the factors that influence the selectivity of these reactions depending on the nature of the catalysts.

## ■ ASSOCIATED CONTENT

### Supporting Information

Characterization data, full experimental procedures, and copies of $^1H$ and $^{13}C$ NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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