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# Unexpected Catalytic Reactions of Silyl-Protected Enol Diazoacetates with Nitrile Oxides That Form 5-Arylaminofuran-2(3*H*)-one-4-carboxylates

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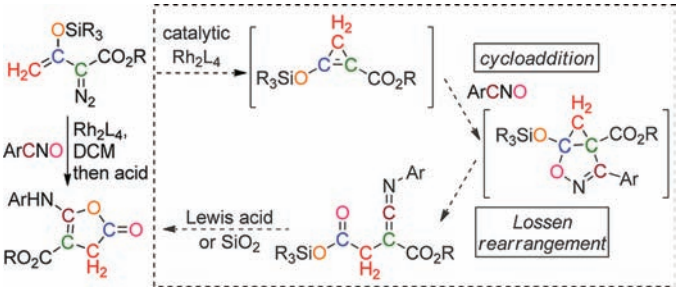
## ABSTRACT




**Silyl-protected enol diazoacetates undergo dirhodium(II)-catalyzed reactions with nitrile oxides to form acid-labile ketenimines via dipolar cycloaddition of nitrile oxides to a donor/acceptor cyclopropene and Lossen rearrangement of the dipolar adduct; acid catalysis converts the ketenimine to the furan product.**

In order to understand carbene-like extensions in reactivity and selectivity, we have been investigating catalytic reactions of 3-(*tert*-butyldimethylsiloxy)-2-diazo-3-butenoate esters (**1**),[1] a subset of vinyldiazoacetates[2] that we will refer to as enoldiazoacetates. These diazo compounds, which are conveniently prepared from methyl diazoacetoacetate and *tert*-butyldimethylsilyl triflate in the presence of base,[3] are stable to intramolecular dipolar cycloaddition[4] and can be stored for long periods of time. Dinitrogen extrusion by selected transition metals changes the polarity of the bound carbon from being susceptible to electrophilic addition in the diazo compound to undergo nucleophilic attack in the metal carbene (Scheme 1). The electrophilic center of the metal carbene formed from enoldiazoacetates **1** is delocalized which makes possible not only the expected carbene addition, insertion, and association reactions but also vinylogous reactions.[5,6]

Based on our previously reported results that enoldiazoacetates undergo formal [3 + 3] cycloaddition reactions with *N*,α-diphenylnitrone catalyzed by Rh(II) catalysts,[6] we envisioned an analogous cycloaddition process with nitrile oxides. Consequently, we were surprised when treatment of methyl TBS-protected enoldiazoacetate (**1a**) with 2,4,6-trimethylbenzonitrile oxide (**2a**) at 0 °C under dirhodium acetate catalysis produced γ-lactone **3a** in 67%

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(2) Basic understandings of vinyl diazoacetates, including enol diazoacetates, in catalytic metal carbene forming reactions have been developed by Davies and co-workers: (a) Qin, C.; Boyarskikh, V.; Hansen, J. H.; Hardcastle, K. I.; Musaev, D. G.; Davies, H. M. L. *J. Am. Chem. Soc.* **2011**, *133*, 19198. (b) Lian, Y.; Davies, H. M. L. *J. Am. Chem. Soc.* **2011**, *133*, 11940. (c) Lian, Y.; Hardcastle, K. I.; Davies, H. M. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 9370.

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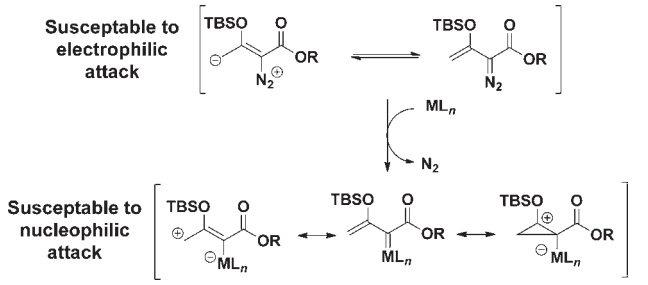
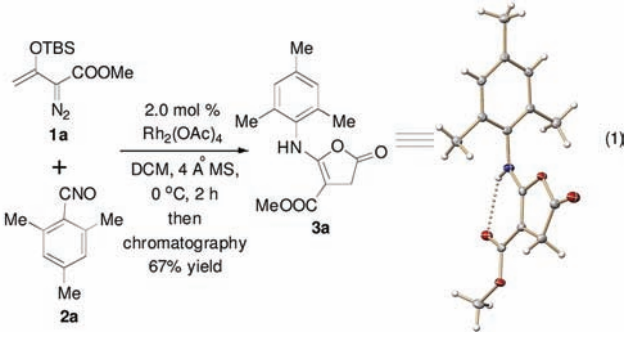
**Scheme 1.** Polarity Reversal from a Vinyldiazo Compound to the Corresponding Metal Vinylcarbene



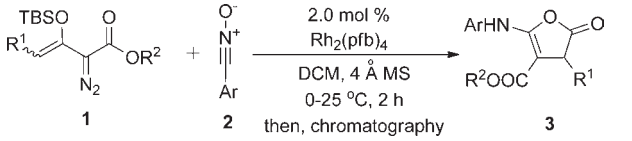

isolated yield after chromatography on silica gel (eq 1). The structure of this lactone product was confirmed by single-crystal X-ray diffraction analysis (see the Supporting Information). Comparing the substrate and product skeletons, structural rearrangement has obviously occurred. We report here the generality of this rearrangement reaction and its cause.

To determine the optimum catalysts for this fascinating rearrangement reaction, a series of Rh(II) compounds was tested under the same reaction conditions. Dirhodium catalysts that included those with octanoate, benzoate, pivalate, and triphenylacetate ligands gave the lactone product in moderate yields (43−59%). Interestingly, $CuPF_6$ catalyzed the reaction as well, providing lactone **3** in modest yield (48%). However, only starting materials and/or hydrolyzed diazo compound were recovered when this reaction was performed in the presence of catalytic amounts of Lewis acids that included $Sc(OTf)_3$, $Zn(OTf)_2$, and $Cu(OTf)_2$, and no reaction occurred in the absence of catalyst, which rules out a direct Lewis acid catalyzed reaction of **1a**. Further screening of the catalysts revealed that rhodium(II) catalysts with electron-withdrawing ligands (heptafluorobutyrate and trifluoroacetate) were significantly more active compared with other dirhodium catalysts, and the highest yield was obtained by controlled addition of the diazo compound via syringe pump at 0 °C to the mixture of nitrile oxide and $Rh_2(pfb)_4$ catalyst (83%) (Supporting Information).




Examination of the scope of the reaction with substituent variations in the diazo compound and nitrile oxides (Table 1) shows that electron-rich nitrile oxides give good to high yields of lactone products **3**. Product yield is not influenced by placement of a methyl substituent at ortho, meta, or para positions of the nitrile oxide (entries 4−6). Steric hindrance from the aryl group of the nitrile oxide appears to have little influence on the reaction outcome, and various esters of the TBS-protected enoldiazoacetate (entries 2, 7, and 8) provide good yields of lactones. However, nitrile oxides having electron-withdrawing substituents react with **1a** to produce mixtures of products whose constitution and source(s) are under investigation. Terminal substitution on the vinyl group of the diazo compound ($R^1$ = Me, Ph: entries 9 and 10) did not interfere with the formation of **3**.

**Table 1.** Substrate Scope of the Rearrangement Reaction[a]

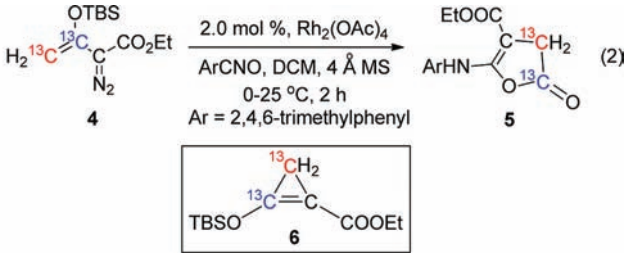



| entry | $R^1/R^2$ (**1**) | Ar (**2**) | product | yield[b] (%) |
|---|---|---|---|---|
| 1 | H/Me (**1a**) | 2,4,6-$Me_3C_6H_2$ (**2a**) | **3a** | 67 |
| 2 | H/Me (**1a**) | 2-$MeOC_6H_4$ (**2b**) | **3b** | 92 |
| 3 | H/Me (**1a**) | 4-$FC_6H_4$ (**2c**) | **3c** | 70[c] |
| 4 | H/Me (**1a**) | 4-$MeC_6H_4$ (**2d**) | **3d** | 76[c] |
| 5 | H/Me (**1a**) | 3-$MeC_6H_4$ (**2e**) | **3e** | 65 |
| 6 | H/Me (**1a**) | 2-$MeC_6H_4$ (**2f**) | **3f** | 76 |
| 7 | H/Bn (**1b**) | 2-$MeOC_6H_4$ (**2b**) | **3g** | 78 |
| 8 | H/$^t$-Bu (**1c**) | 2-$MeOC_6H_4$ (**2b**) | **3h** | 79 |
| 9 | Me/Me (**1d**) | 2-$MeOC_6H_4$ (**2b**) | **3i** | 54 |
| 10 | Ph/Me (**1e**) | 2,4,6-$Me_3C_6H_2$ (**2a**) | **3j** | 86 |

[a] Reaction conditions: diazo compound (1.2 mmol) in DCM (3.0 mL) was added over 1 h via a syringe pump at 0 °C to mixture of 4 Å molecular sieves (100 mg), $Rh_2(pfb)_4$ (2.0 mol %), and nitrile oxide (1.0 mmol) in DCM (5.0 mL) and stirred for another 2 h at room temperature. The reaction mixture was purified by chromatography on silica gel. [b] Isolated yield of **3** based on limiting reagent **2**. [c] Minor unidentified byproduct was detected.

Although lactones **3** hinted that the methylene group of **1a** becomes the methylene group of **3a** and that the TBSO-substituted carbon of **1** becomes the carbon of the lactone carbonyl group, labeling experiments were performed to track carbon atom placement in the newly formed skeleton of 5-arylaminofuran-2(3*H*)-one **3**. Double C-13-labeled **4** was prepared using standard procedures from doubly labeled ethyl acetoacetate[1,3] and then reacted under standard conditions with **2a** (eq 2). The carbon NMR spectrum of the product showed that the terminal vinyl carbon of **4** had been transformed into the $CH_2$ group of **5**, while the vinyl quaternary carbon of **4** became the lactone carbonyl carbon of **5**. This result hinted at rearrangement of the metal carbene formed from TBS-protected enoldiazoacetate **1** to cyclopropene **6** and a subsequent dipolar addition reaction with nitrile oxide. The formation of the analogous cyclopropene methyl ester that possesses both donor and acceptor substituents has been reported by Davies from

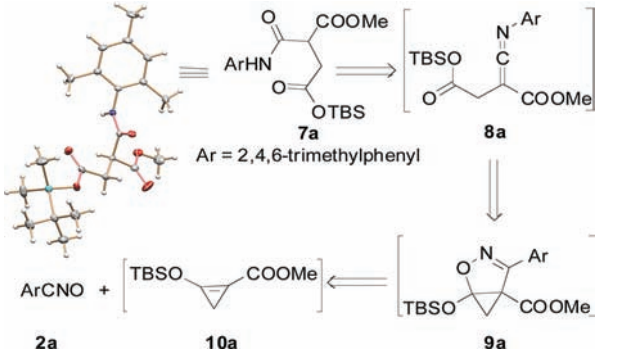
rhodium acetate catalyzed dinitrogen extrusion from **1a**;[7] this cyclopropene was unstable but, as also reported by Davies, could be trapped as a Diels–Alder adduct.[8]



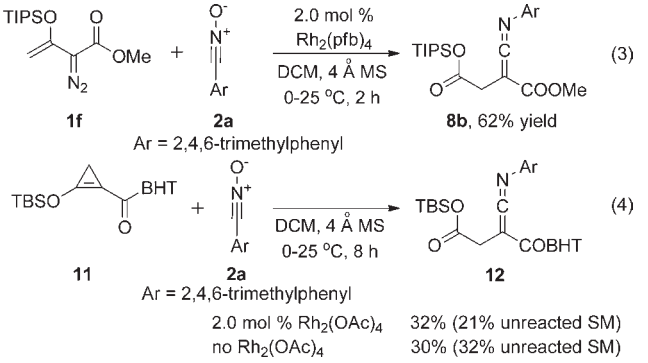

Careful examination of the $^1$H NMR data for the reaction mixture from $Rh_2(pfb)_4$ catalysis of **1a** with **2a** prior to chromatography provided evidence that the chemical shifts of the $CH_2$ group protons of the product are different from those of **3a**, suggesting that an intermediate in the reaction mixture is transformed into **3** during the chromatographic isolation procedure. A product crystallized from this reaction mixture (prior to chromatography, open to the atmosphere) and was identified as **7a**. The connectivity of **7a** suggests the intervention of ketenimine **8a** that could arise from ring-opening of the product (**9**) from dipolar cycloaddition of the nitrile oxide to cyclopropene **10a** (Scheme 2).[9] The conversion of **9a** to **8a** that involves migration of the aryl group from carbon to nitrogen is an example of the rarely reported Lossen rearrangement which is facilitated by aryl group electron-donating substituents.[10]

Ketenimines (RR′C=C=NR″) are versatile reaction intermediates in organic synthesis, and their formation and reactions have been the subjects of intense interest.[11] They are accessible via azide cycloaddition with acetylenes

**Scheme 2.** Possible Intervention of a Ketenimine




("click" chemistry),[12] the isocyanide–Nef–Perkow reaction sequence,[13] from ynamides by Pd(0)-catalyzed N-to-C allyl transfer,[14] and even by pulsed pyrolysis of isoxazole.[15] Their structural diversity is dependent on the methods for their formation, and structure **8** is unique. Is ketenimine **8a** an actual intermediate along the pathway to either **3** or **7**? To answer this question we prepared the triisopropylsilyl (TIPS)-protected enol diazoacetate **1f** and subjected this compound to reaction with **2a** catalyzed by $Rh_2(pfb)_4$. Ketenimine **8b** was the only product formed and was isolated in 62% yield (eq 3). Treatment of **8b** with aqueous trifluoroacetic acid gave the product identical to amide **7** except for the silyl group. These observations confirm that dirhodium(II) catalysis of the reaction between enoldiazoacetates form a highly reactive cyclopropene intermediate that undergoes reaction with nitrile oxides to form ketenimine products. That the ketenimine is formed from a cyclopropene intermediate was established by preparing the stable BHT ester **11**[12] and then adding **2a** with and without the presence of rhodium acetate catalyst. Although reaction was slow in both cases, presumably because of steric inhibition, ketenimine **12** was detected in about 30% yield in the reaction mixture by NMR (eq 4), and its formation confirmed that cyclopropenes with donor and acceptor groups are precursors to ketenimines formed by cycloaddition with nitrile oxide.




The question that now arises is how are ketenimine intermediates converted to **3**? Is acid catalysis involved?

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(8) When this reaction was performed in the presence of **2a** (1.0 equiv) and 1,3-diphenylisobenzofuran (1.0 equiv), **3a** and the Diels–Alder adduct were obtained in a 2:1 ratio.

(9) An analogous rearrangement of a 2-oxa-3-azabicyclo[3.1.0]-hex-3-ene system (one example) involving ketenimine formation has been reported: Nesi, R.; Giomi, D.; Papaleo, S.; Dapporto, P.; Paoli, P. *J. Chem. Soc. Chem. Commun.* **1990**, 1675.

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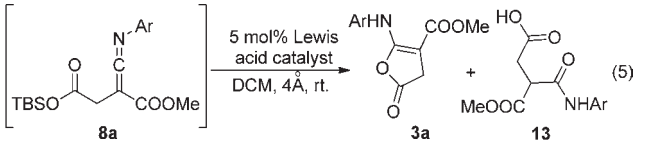
(15) Nunes, C. M.; Reva, I.; Pinho e Melo, T. M. V. D.; Fausto, R.; Šolomek, T.; Bally, T. *J. Am. Chem. Soc.* **2011**, *133*, 18911.

Is the ketenimine intermediate converted to a carboxylic acid that then cyclizes? To answer these questions, various Lewis acids were screened under strictly anhydrous conditions in reactions using preformed **8a** as the substrate (eq 5). Although all of these Lewis acids catalyze the formation of **3a**, reactions occurred at different catalyst-dependent rates, and **3** was prone to hydrolysis at extended reaction times. $CuPF_6$ and $Zn(OTf)_2$ showed lower reaction rates but gave **3a** without hydrolysis over the extended reaction times, and reactions with or without $Rh_2(pfb)_4$ present gave the same result. The use of CsF, which is known to effect removal of TBS,[16] had no effect on **8a** in dichloromethane during a 12 h exposure.




$CuPF_6$, 12 h, 90% isolated yield, **3a**:**13** > 20:1
$Cu(OTf)_2$, 12 h, 100% conversion, **3a**:**13** = 3:1
$In(OTf)_3$, 0.5 h, 100% conversion, **3a**:**13** > 20:1
$Sc(OTf)_3$, 0.5 h, 100% conversion, **3a**:**13** > 20:1
$Sn(OTf)_2$, 0.5 h, 100% conversion, **3a**:**13** > 20:1
CsF, 12 h, <5% conversion

To ascertain the sequence through which conversion of **8** to **3** has occurred (Scheme 3)—either directly from Lewis acid coordinated **8** with silyl group transfer to nitrogen then hydrolysis (path A) or after initial hydrolysis of the trialkylsilyl-ester then cyclization (path B)—the TMS-protected enoldiazoacetate (**1g**) was prepared and subjected to reaction with $Rh_2(pfb)_4$. Ketenimines **8a** and **8b** are stable to lactone formation in the presence of $Rh_2(pfb)_4$. However, lactone product **3a** was formed directly in reactions of TMS-protected enoldiazoacetate, indicating that silyl group transfer (path B) is the barrier in the conversion of ketenimine **8** to lactone **3**.

In summary, the mechanism for formation of **3** from catalytic reactions between **1** and **2** is described in Scheme4. Rhodium-catalyzed dinitrogen extrusion from diazo compound **1** forms cyclopropene **10** that undergoes uncatalyzed dipolar cycloaddition with nitrile oxide to form the unstable 2-oxa-3-azabicyclo[3.1.0]hex-3-ene (**9**). Ring-opening via the Lossen rearrangement (**9**→**8**) forms ketenimine **8** that undergoes catalytic cyclization to form

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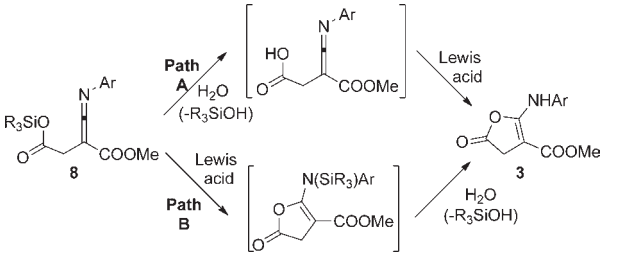
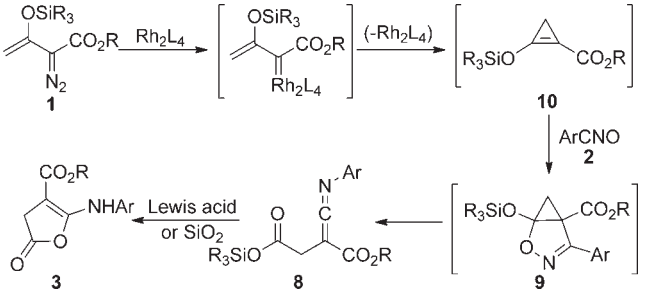
**Scheme 3.** Possible Pathways from Ketenimine **8** to Lactone **3**




**Scheme 4.** Proposed Mechanism for the Catalytic Cascade Reaction of Enoldiazoacetates with Nitrile Oxides




5-arylaminofuran-2(3*H*)-one **3**. Catalysis in the formation of **3** occurs either with Lewis acids or on silica gel during chromatography. Both **8** and **10** have been intercepted along this mechanistic pathway.

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**Supporting Information Available.** General experimental procedures, X-ray structures of **3a** and **7a**, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.