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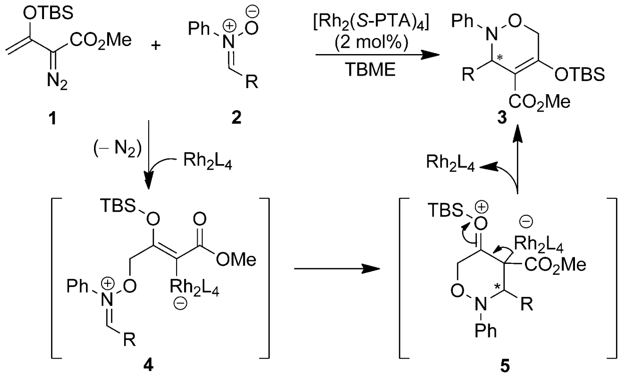
Cascade Reactions

Highly Regio- and Stereoselective Dirhodium Vinylcarbene Induced Nitrone Cycloaddition with Subsequent Cascade Carbenoid Aromatic Cycloaddition/N–O Cleavage and Rearrangement**

*Xiaochen Wang, Quentin M. Abrahams, Peter Y. Zavalij, and Michael P. Doyle**

Vinylcarbene intermediates derived from vinyldiazoacetates exhibit a high level of selectivity in cyclopropanation[1] and carbon–hydrogen insertion reactions.[2] As evidenced by the integration of these transformations with the Cope rearrangement, that at least for the combined C–H insertion/Cope rearrangement appears to be concerted and highly asynchronous,[3] the vinyl group broadens the complexity of applications and enhances the versatility of the process. Their propensity for formal [3+2][4] and [4+3][5] cycloaddition reactions has also been demonstrated. Recently, we reported an efficient and highly enantioselective formal [3+3] cycloaddition reaction between the vinycarbene from TBS-protected enoldiazoacetate **1** catalyzed by chiral dirhodium(II) carboxylates and diverse nitrones (Scheme 1).[6] This reaction occurs stepwise through vinylogous nucleophilic attack by the nitrone (**2**) on the dirhodium vinylcarbene followed by intramolecular iminium ion addition to the catalyst-activated vinyl ether (**4**→**5**) that, with catalyst dissociation, forms the cycloaddition product **3**. In our efforts exploring potential cycloaddition reactions with other vinyldiazoacetates we discovered that the unsubstituted vinyldiazoacetate **6**[7] underwent dirhodium(II)-catalyzed reactions with nitrones by a novel and unexpected pathway to produce tricyclic products by an elaborate cascade pathway.



Scheme 1. Formal [3+3] cycloaddition reactions between **1** and **2** catalyzed by chiral dirhodium(II) carboxylates. TBS = *tert*-butyl dimethylsilyl; PTA = *N*-phthaloylalaninate; TBME = *tert*-butyl methyl ether.

Treatment of methyl 2-diazo-3-butenoate (**6**) with *N*-(4-methoxyphenyl)-α-(4-bromophenyl)nitrone (**7a**) in the presence of rhodium acetate at room temperature gave immediate gas evolution and consumption of nitrone. After a reaction time extending to 20 h two products, accounting for 52% conversion based on **7a**, were isolated. The minor product (7% conversion) was identified as *N*-(4-methoxyphenyl)-α-(4-bromophenyl)imine (**8a**), formed by deoxygenation of the reactant nitrone, presumably by the metal carbene intermediate.[8] The NMR spectrum of the major product (45% conversion) indicated a single compound with the loss of resonances due to the original anisyl group and new olefinic protons suggestive of a methoxy-substituted diene, and structural confirmation of this compound as tricyclic **9a** was obtained by X-ray diffraction of a single crystal[9] (see the Supporting Information). This product reveals that extensive rearrangement has occurred and that the carboxylate group from the vinyldiazoacetate is now bound to a quaternary carbon that connects the tricycle.

Different dirhodium carboxylates were examined in attempts to increase the yield of tricyclic product **9a** (Table 1). Use of rhodium trifluoroacetate [$Rh_2(TFA)_4$], which is a stronger Lewis acid than is rhodium acetate,[10] resulted in a significantly lower conversion into the tricyclic product, but there was increased conversion into imine **8a**. Rhodium triphenylacetate [$Rh_2(TPA)_4$] and rhodium caprolactamate [$Rh_2(cap)_4$] showed low or negligible reactivities toward this transformation under the same conditions. Rhodium octanoate [$Rh_2(Oct)_4$] provided higher conversion, probably due to its higher solubility in 1,2-dichloroethane compared to rhodium acetate.[11] Extending the reaction time or increasing the amount of the vinyldiazoacetate reactant to 10 equiv did not significantly increase conversion into **9a**. Since unreacted nitrone remained, and neither reactant was an inhibitor for the catalyst, we considered that the formation of a coordinating base could cause inhibition of the catalytic reaction with **6** and incomplete conversion; and both **8a** and **9a**, as well as the pyrazoline formed by intramolecular cycloaddition from **6**,[7] are suitable bases. To solve this problem, acidic 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was used as an additive to capture the basic product.[12] When 1 equiv of HFIP was added, and 3 equiv of **6** was used, complete conversion of nitrone was achieved, resulting in 85% conversion into **9a** with 74% yield and the remainder

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[*] X. Wang, Q. M. Abrahams, P. Y. Zavalij, Prof. M. P. Doyle
Department of Chemistry and Biochemistry, University of Maryland
College Park, MD 20742 (USA)
E-mail: mdoyle3@umd.edu

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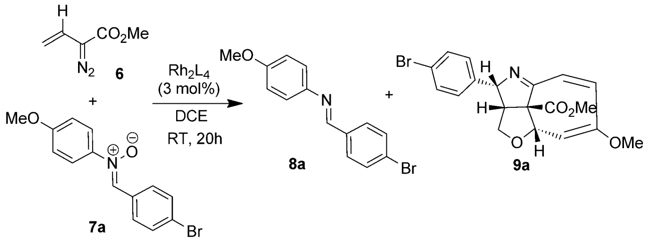
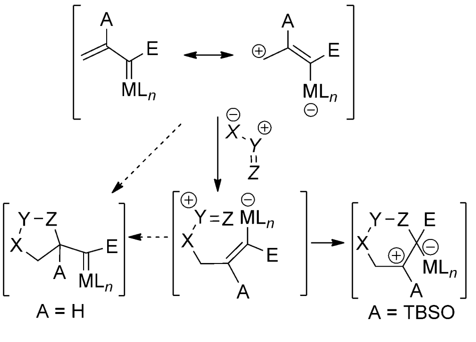
Table 1: Optimization of reaction conditions for the formation of the tricyclic product **9a**.[a]



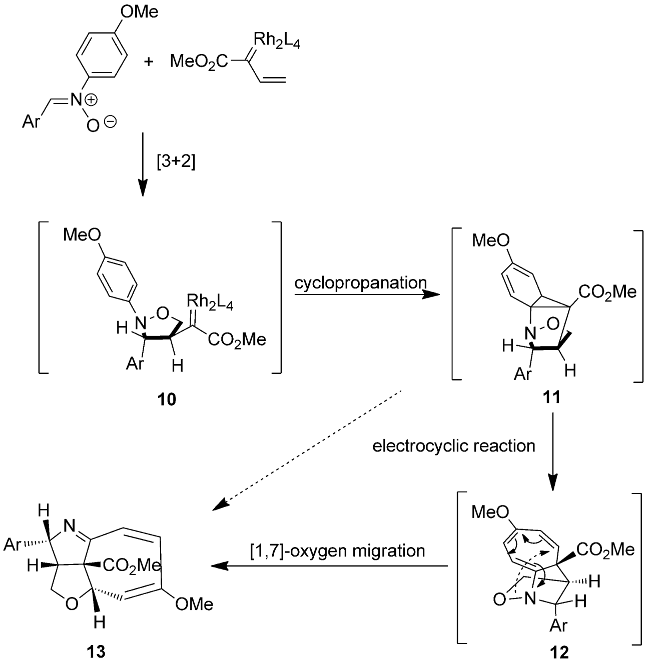
Rh_2L_4[b]	Additive[b]	Conv.[c] [%] **8a**	Conv.[c] [%] **9a**
[$Rh_2(OAc)_4$]	4 Å MS	7	45
[$Rh_2(TFA)_4$]	4 Å MS	24	17
[$Rh_2(TPA)_4$]	4 Å MS	trace	10
[$Rh_2(cap)_4$]	4 Å MS	trace	trace
[$Rh_2(Oct)_4$]	4 Å MS	9	66
[$Rh_2(Oct)_4$] (36 h)	4 Å MS	9	70
[$Rh_2(Oct)_4$][d]	4 Å MS	10	75
[$Rh_2(Oct)_4$]	4 Å MS/HFIP	15	85 (74%)[e]

[a] Reactions were performed by addition of a 1.0 mL solution of the vinyldiazoacetate **6** (0.75 mmol) in dichloroethane (DCE) dropwise over 1 h to the mixture of dirhodium carboxylate catalysts (0.0075 mmol), *N*-(4-methoxyphenyl)-α-(4-bromophenyl)nitrone (0.25 mmol) and 4 Å MS (100 mg) in 1.5 mL of DCE. [b] TFA = trifluoroacetate; TPA = triphenylacetate; cap = caprolactamate; Oct = octanoate; HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. [c] Conversions were determined by ^{1}H NMR spectroscopy of the reaction mixture before workup. [d] 10 equiv of **6** was used. [e] Yield of isolated product after column chromatography.

(15%) due to the imine by-product **8a** after column chromatography. An excess of **6** was required due to its relatively low stability.[7] Nitrone **7a** did not react with vinyldiazoacetate **6** in the absence of the dirhodium catalyst.



Scheme 2. Divergence of reaction pathway dependent on electronic stabilization by A.

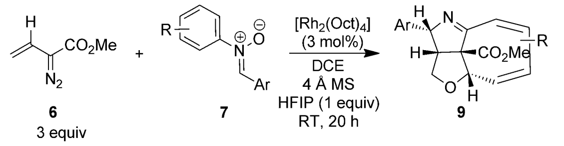


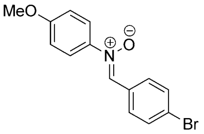
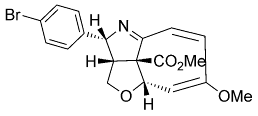
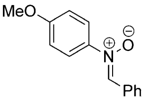
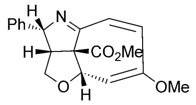
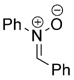
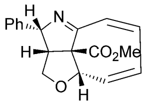
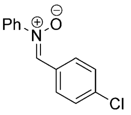
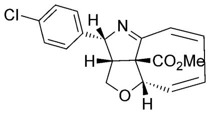
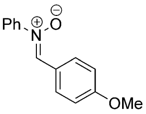
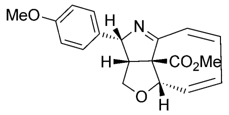
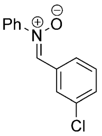
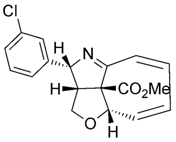
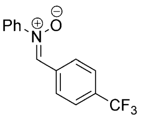
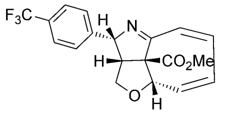
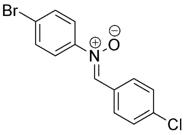
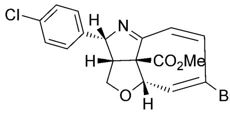
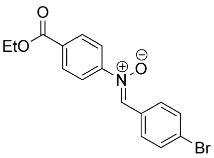
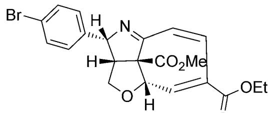
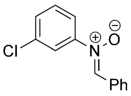
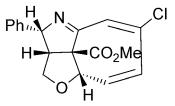
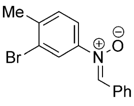
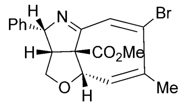
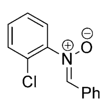
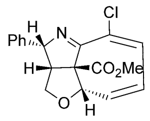
Scheme 3. Proposed reaction pathway.

Since nitrone cycloaddition to **6** does not occur in the absence of catalyst, and dirhodium(II) catalysts are known to undergo rapid dinitrogen extrusion with vinyldiazoacetates, the likely intermediate that allows cycloaddition was the dirhodium vinylcarbene; but instead of the stepwise [3+3] cycloaddition shown in Scheme 1, stepwise or concerted [3+2] cycloaddition occurs (see Scheme 2 for the general representation). We speculate that the overall reaction occurs through a four-step sequential [3+2] cycloaddition/cyclopropanation/rearrangement pathway (Scheme 3) in which the dirhodium carbene intermediate activates the adjacent vinyl group for [3+2] cycloaddition by the nitrone. In [3+2] cycloaddition reactions between diarylnitrones and electron-deficient alkenes, the concerted reaction prefers *endo* addition which explains the exclusive formation of the *trans* isomer **10**.[13] The formation of **13** is consistent with cycloaddition of **7a** with the metal carbene that forms the electronically favored[13,14] 3,4-disubstituted regioisomer **10**; the 3,5-disubstituted regioisomer would have been expected if cycloaddition of **7a** occurred directly with vinyldiazoacetate **6**. Subsequent intramolecular cyclopropanation and electrocyclic opening of the cyclopropane ring (aromatic cycloaddition) by the rhodium carbene on the nitrogen-bound aryl group is proposed to form intermediate **12** that undergoes an unexpected and unique N–O bond cleavage and [1,7]-oxygen migration to **13** to complete the overall process. Aromatic cycloaddition by metal carbenes to form cycloheptatrienes is a well-known process, widely recognized as the Buchner reaction.[15] Cleavage of a N–O bond followed by migration of oxygen to conjugated olefinic carbon atoms has only been observed in acylated *N*-oxides[16] and silyl nitroso acetals,[17] but [1,3]-migration was the only process reported. Strain in the intermediate **12** and the proximity of the reacting atoms could be the driving force of this unusual rearrangement. In this reaction pathway the dual role of the rhodium carbene, which first activates the conjugated double bond for dipolar cycloaddition, and then undergoes aromatic cycloaddition, is unprecedented, as is the [1,7]-oxygen migration. Alternatively, cleavage of the N–O bond in **11** and attack of oxygen at the cyclopropane with imine formation can lead to **13** in a single step.

Using the optimized conditions that include HFIP as an additive we investigated the generality of this process with a broad range of nitrones, and the results of this investigation are reported in Table 2. With diphenylnitrone (**7c**) an 83 % yield of tricyclic product **9c** was produced. Yields for **9** were not obviously dependent on electronic influences from α-aryl ring since yields ranged from 73 % to 85 % (products **9c**–**9g**) with nitrones having electron-donating and electron-withdrawing substituents. Substituents on the N-aryl ring were varied in anticipation of activation from electron-donating substituents and inhibition of addition from electron-withdrawing groups.[18] However, reaction occurred even with the nitrone having a strongly electron-withdrawing ester group on the N-aryl group (nitrone **7i**). Electron-withdrawing groups on aromatic rings are known to deactivate the cyclopropanation by metal carbenes on aromatic rings,[18] but with these substrates (e.g., with **7i**) the electron-donating nitrogen has an overriding activating factor. Also, with *meta-* and *ortho-*substituents on the N-aryl group, cyclopropanation could have occurred on either side of the N-aryl bond which would have led to the formation of two regioisomers; however, only a single regioisomer was formed in good yields (products **9j**–**9l**). A single diastereomer of **9** was obtained in all cases, and formation of the imine by-product, which was observed in the optimization process, was variable depending on the nitrone. Nitrones having the electron-donating methoxy substituent on the N-aryl group (nitrones **7a** and **7b**) appeared to produce the imine by-product with larger conversions, while for the reactions that produce **9c**–**9l**, imine by-products were formed only in trace amounts. Therefore, this multistep cascade process is general and occurs with very high regiocontrol, and the resulting products are predisposed for further elaboration.

Table 2: Scope of nitrones.



Compounds	Nitrones, **7**	Products, **9**	Yield [%][b]
a			74 (15)[c]
b			70 (7)[c]
c			83
d			73
e			85
f			75
g			73
h			80
i			60
j			86
k			82
l[d]			88

[a] Reactions were performed by addition of a 1.0 mL solution of the vinyldiazoacetate **6** (0.75 mmol) in DCE dropwise over 1 h to the mixture of [Rh$_2$(Oct)$_4$] (0.0075 mmol), nitrone (0.25 mmol), 4 Å MS (100 mg), and HFIP (0.25 mmol) in 1.5 mL of DCE. [b] Yield of isolated product after column chromatography. [c] Conversions into imine by-products; for reactions with nitrones **7c**–**7l**, conversions into imine by-products were < 5 %. [d] 6 equiv of **6** was used, and the reaction time was 48 h.

In conclusion, we have developed a general and selective method for preparation of multifunctionalized tricyclic heterocycles through an abnormal cascade process. To undergo this process a metal vinylcarbene activates the vinyl group for nitrone cycloaddition and then undergoes the Buchner reaction that is linked to a [1,7]-oxygen migration which occurs with N–O cleavage. The products of the process, which have both oxygen and nitrogen-fused rings and a quaternary carbon in the middle, are formed with remarkable specificity. Further studies directed to analogous reactions and on an enantioselective methodology for the reported cascade reaction are underway.

Experimental Section

A 10 mL Schlenk flask charged with a magnetic stir bar and 4 Å molecular sieves (100 mg) was placed under high vacuum and heated by Bunsen burner to dryness. After cooling to room temperature, [Rh$_2$(Oct)$_4$] (6.0 mg, 3.0 mol%), diarylnitrone (0.25 mmol), 1,1,1,3,3,3-hexafluoro-2-propanol (27 μL, 0.25 mmol), and 1.5 mL of 1,2-dichloroethane were added under the flow of N$_2$. The resulting green solution was stirred for 5 min, and then the flask was wrapped with aluminum foil to avoid light. Freshly prepared methyl 2-diazobut-3-enoate (95 mg, 0.75 mmol) in 1.0 mL of 1,2-dichloroethane was added into the flask via a syringe pump over 1 h. After complete addition, the mixture was stirred at room temperature for 20 h. The solvent from the reaction solution was evaporated, and the residue was dissolved in a minimal amount of dichloromethane and loaded onto a silica gel column. Column chromatography with hexane/ethyl acetate (3:1) with 5% Et$_3$N provided the final product that was later analyzed by ^{1}H NMR and ^{13}C NMR spectroscopy.

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Keywords: Buchner reaction · cascade reactions · cycloaddition · rhodium · vinylcarbenes

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[8] Although the imine was isolated and fully characterized, attempts to isolate the corresponding methyl 2-oxa-3-butenoate were unsuccessful. However, to establish the validity of this interpretation **7a** was treated with ethyl diazoacetate under identical conditions; the corresponding imine was isolated in 80% yield, and ethyl glyoxalate was the only other reaction product.

[9] CCDC 870594 contains the supplementary crystallographic data 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.

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