Cycloadditions

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A Rhodium(II)-Catalyzed Formal [4+1]-Cycloaddition toward Spirooxindole Pyrrolone Construction Employing Vinyl Isocyanates as 1,4-Dipoles

*Jennifer L. Meloche and Brandon L. Ashfeld**

Abstract: *A Rh^{II}-catalyzed, formal [4+1]-cycloaddition between diazooxindoles as electrophilic C_1 synthons and 1,3-heterodienes for the construction of spirooxindole pyrrolones is described. Employing vinyl isocyanates as 1,4-dipoles, the cycloannulation occurs under relatively mild conditions and provides the corresponding pyrrolones in good to excellent yields.*

The strain-driven ring expansion of cyclopropanes has emerged as a powerful design strategy for the assembly of small and medium-sized carbocyclic frameworks.[1] Perhaps two of the most common synthetic applications of this approach include the [3,3]-rearrangement of divinyl cyclopropanes to yield 1,4-cycloheptadienes[2] and the assembly of cyclopentenes from vinyl cyclopropanes in a formal [1,3]-carbon migration.[3] However, despite accessibility of the requisite starting materials, extensions of these rearrangements to heterocyclic motifs are rare.[4] A notable exception is the analogous rearrangement of *N*-cyclopropylimines to the corresponding pyrrolines requiring high thermal or photochemical conditions to generate a presumptive diradical intermediate resulting from homolytic cyclopropyl C–C bond cleavage (Figure 1 a).[5] Alternatively, Rigby demonstrated in 2003 that the addition of thermally generated nucleophilic carbenes to vinyl isocyanates initiates a 4π-electrocyclization to yield the corresponding γ-lactams (Figure 1 b).[6] While elegant in their own rights, the forcing conditions and indiscriminate nature of synthetic intermediates can limit their general utility. These complementary approaches inspired us to develop a relatively mild, formal [4+1]-cycloaddition[7] assembly of *N*-heterocycles that exploits the chemoselectivity of *electrophilic* metallocarbenes with the 1,4-dipole behavior of vinyl isocyanates.[1b,7d,8]

Given the prevalence of biologically active spirooxindole alkaloids (i.e., mitraphylline,[9] voachalotine oxindole[10]) and readily available oxindole derivatives, we chose to target congeners of the core spirooxindole dihydropyrrole framework (Figure 1 c).[11] Employing diazooxindole **1** as a C_1 synthon, we discovered that the Rh^{II}-catalyzed cyclopropanation of vinyl isocyanate **2** generates a cyclopropyl isocyanate **3** that then rapidly undergoes ring expansion in situ to provide the target spirooxindole pyrrolone **4** (Figure 1 d).[12] This design exploits the electron deficient central carbon of the isocyanate bearing an orthogonal π-bond and weakened migrating C–C cyclopropyl bond by virtue of the donating potential of the isocyanate and withdrawing nature of the oxindole amide to alleviate the high kinetic barrier to a formal [1,3]-migration of the C3-oxindole quaternary carbon.[12,13] Herein, we describe the successful implementation of this approach under milder conditions with improved substrate scope and demonstrated synthetic utility.

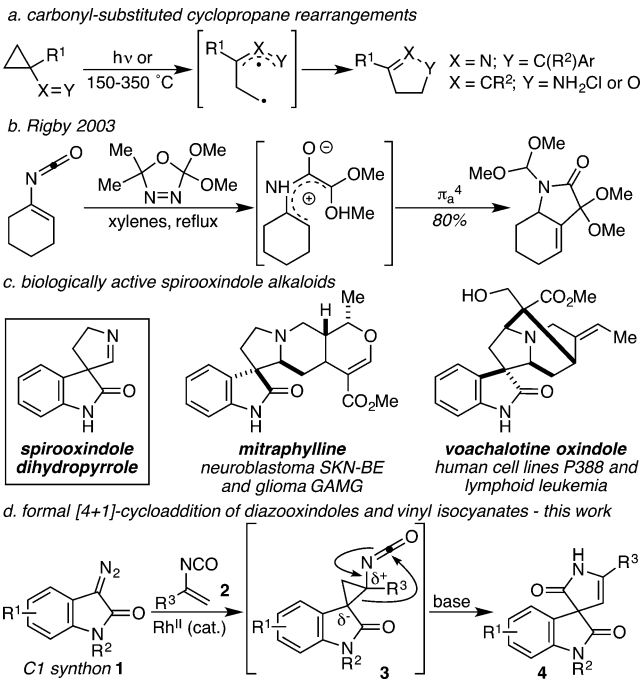

Figure 1. a) Ring expansion of iminocyclopropanes and cyclopropyl carboxaldehydes; b) formal [4+1]-cycloaddition involving vinyl isocyanates; c) targeting spirooxindole natural products; d) this work.

Recently, Davies demonstrated that the treatment of α,β-unsaturated ketones and aldehydes with Rh^{II}-stabilized carbenoids led to epoxides resulting from addition of the carbonyl to the electrophilic carbene carbon.[14] Based on these findings, we were cognizant that the Lewis basic heteroatoms of the isocyanate may hinder cyclopropanation of the pendant olefin. Additionally, based on our previous work and those of others, spirooxindole cyclopropanes are surprisingly stable, and often require Lewis or Bronsted acid activation to initiate ring expansion.[15] Despite these challenges, we began by examining the addition of diazooxindole

[*] J. L. Meloche, Dr. B. L. Ashfeld
Department of Chemistry and Biochemistry
University of Notre Dame
Notre Dame, IN 46556 (USA)
E-mail: bashfeld@nd.edu

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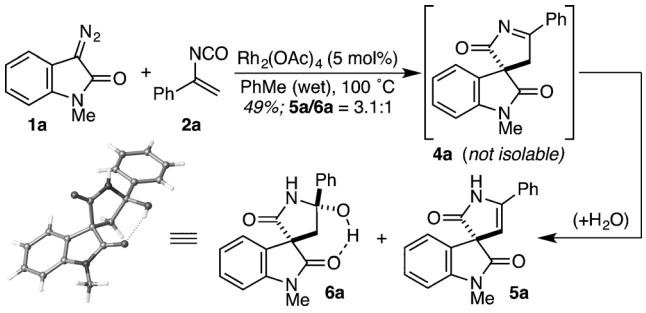
1a to vinyl isocyanate **2a** in the presence of $Rh_2(OAc)_4$ (Scheme 1). While a syringe pump addition of **1a** in dry PhMe at 0.01 M minimized diazo dimerization, an intractable mixture of products was observed. Speculating that this result

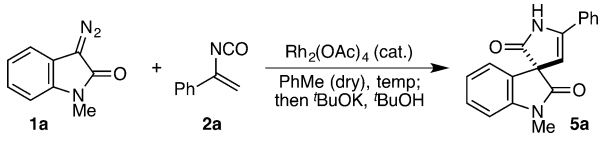


Scheme 1. Proof of concept.

was due to the instability of pyrrolone **4a** under the reaction conditions, we sought to trap this intermediate with adventitious water as the hemiaminal by using wet PhMe. Gratifyingly, this seemingly minor modification led to a fortuitous mixture of acyl enamine **5a** and hemiaminal **6a** in a 3.1:1 ratio and combined yield of 44%. Cycloadduct **6a** was obtained as a single diastereomer and confirmed by X-ray crystallography. Interestingly, the addition of water (1.0 equiv) led to conversion of **1a** to *N*-methyl isatin illustrating a delicate balance in the concentration of trapping agent employed. Owing to its synthetic potential and stability, we chose to develop conditions that would optimize the formation of acyl enamine **5a**.

To drive the isomerization of **4a** to spirooxindole **5a**, we discovered that by following the formal [4+1]-cycloaddition of diazooxindole **1a** and vinyl isocyanate **2a** in dry PhMe with the introduction of ^{t}BuOK/^{t}BuOH, provided spirooxindole pyrrolone **5a** in 83% yield (Table 1, entry 1). Illustrating the comparatively mild conditions required for the spirocyclopropylisocyanate rearrangement, we could lower the reaction

Table 1: Optimization of **5a** formation.[a]



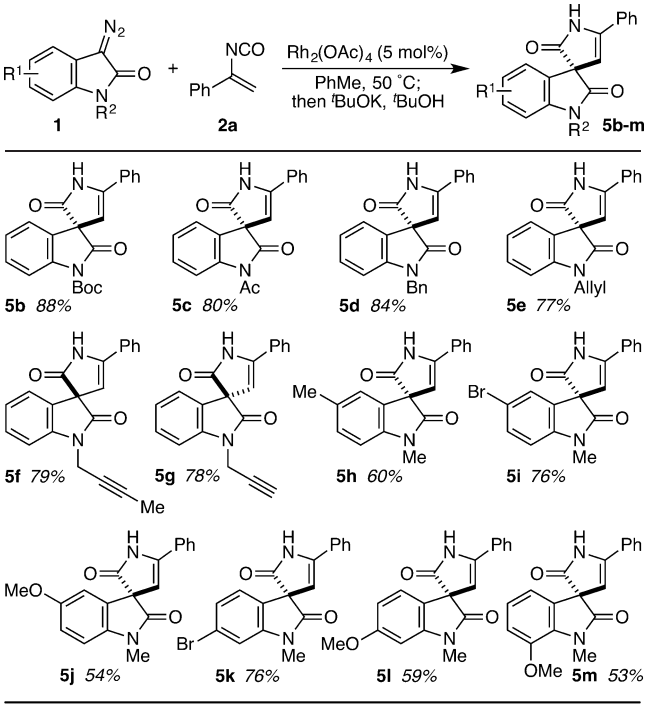
Entry	**2a** (equiv)	$Rh_2(OAc)_4$ (mol%)	*T* [°C]	Yield [%]
1	2.0	5.0	100	83
2	2.0	5.0	50	83 (95)[b]
3	***3.0***	***5.0***	***50***	***87***
4	2.0	1.0	50	50
5	2.0	1.0	65	66
6	3.0	1.0	75	72

[a] Conditions: slow addition of **1a** (0.09 mmol) over 10 h to **2a** and $Rh_2(OAc)_4$ (5 mol%) in PhMe (0.01 M) at 50°C, followed by the introduction of ^{t}BuOK/^{t}BuOH (50 mol%). See the Supporting Information for detailed experimental procedures. [b] Yield based on recovered **1a** dimer.

temperature to 50°C without seeing an adverse effect on the yield of **5a** (entry 2). However, dimerization of diazooxindole **1a** accounted for a 95% mass recover. Decreasing the reaction concentration or extending the addition time of **1a** failed to mitigate this undesired side reaction. Increasing the concentration of **2a** enabled complete conversion of diazooxindole **1a** and improved the yield to 87% (entry 3). Reducing the catalyst loading at temperatures ranging from 50–75°C led to inferior yields of **5a** (entries 4–6). Using the optimized conditions in entry 3, we sought to evaluate this formal [4+1]-cycloaddition approach toward the spirooxindole lactam framework.

Our assessment of functional group compatibility began by examining the effects of diazooxindole substitution on the formal [4+1]-cycloaddition with vinyl isocyanate **2a** (Table 2). In general, good to excellent yields of cycloadducts

Table 2: Structural variability in the diazooxindole **1**.[a]



[a] Conditions: slow addition of **1** (0.08 mmol) over 10 h to **2a** (0.24 mmol) and $Rh_2(OAc)_4$ (5 mol%) in PhMe (0.01 M) at 50°C, followed by the introduction of ^{t}BuOK/^{t}BuOH (50 mol%). See the Supporting Information for detailed experimental procedures.

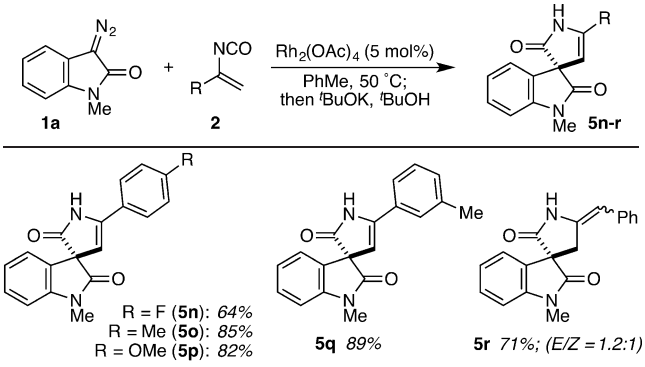
5 were obtained from oxindoles with various *N*- and arene-substitution patterns. Common *N*-acyl and *N*-alkyl diazooxindole substitution were well tolerated, as demonstrated by the formation of **5b–f** in 77–88% yields. Notably, the presence of *N*-allyl and *N*-propargyl groups underwent cycloaddition in good yields without competitive alkene/alkyne cyclopropanation observed, and the presence of an acetylenic C–H did not adversely affect the yield of adduct **5g**. As a result of its poor solubility in PhMe, the formal cycloaddition of diazooxindole ($R^1 = R^2 = H$) proceeded in significantly lower yield ($\approx$35% by ^{1}H NMR).

While the formal [4+1]-cycloaddition tolerated a variety of diazooxindole arene substitution, the presence of an

electron withdrawing bromide generally led to higher yields of the cycloadducts than alkyl or electron donating methoxy groups.[16] For example, methyl and bromide substitution at the C5 provided adducts **5h** and **5i** in 60% and 76% yield, respectively, while 5-methoxy diazooxindole gave **5j** in 54%. Similarly, C6-Br substitution led to formation of **5k** in 76%, whereas the 6- and 7-methoxy spirooxindoles **5l** and **5m** were obtained in 59% and 53% yield, respectively. These results are consistent with an electrophilic metallocarbene cyclopropanation of **2a**.

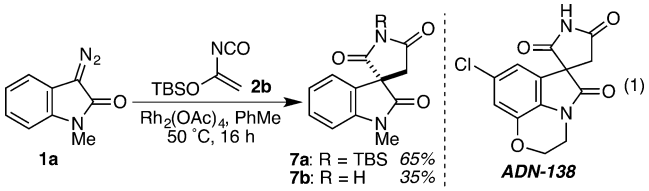
Varying olefin substitution on isocyanate **2** exhibited a similar, albeit inverse trend of electronic influence on the yield of formal [4+1]-cycloadducts **5** with diazooxindole **1a** (Table 3). While the vinyl isocyanate bearing a *p*-F-C_6H_4 substituent at the α-position gave adduct **5n** in 64% yield, *p*-tolyl or *p*-anisol substitution yielded **5o** and **5p** in 85% and 82% yield, respectively. Employing *m*-tolyl-substituted vinyl isocyanate led to formation of cycloadduct **5q** in comparable yield (89%). Despite the potential for endo/exocyclic olefin formation, employing an α-benzyl vinyl isocyanate provided exclusively the exocyclic acyl enamine **5r**, favoring aryl conjugation, as a mixture of *E*/*Z* isomers. Tri- and tetrasubstituted vinyl isocyanates failed to provide the corresponding cycloadduct **5** in greater than trace quantities, leading to primarily dimerization of **1a**, even at elevated temperatures (≥100 °C). These results are consistent with an initial cyclopropanation of the vinyl isocyanate prior to pyrrolone formation.

Table 3: Assessment of vinyl isocyanate **2** substitution.[a]

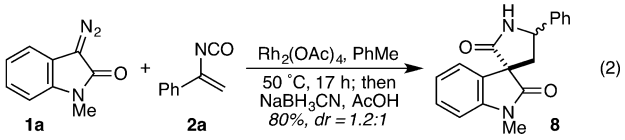


[a] Conditions: slow addition of **1a** (0.08 mmol) over 10 h to **2** (0.24 mmol) and $Rh_2(OAc)_4$ (5 mol%) in PhMe (0.01 M) at 50 °C, followed by the introduction of ^{t}BuOK/^{t}BuOH (50 mol%). See the Supporting Information for detailed experimental procedures.

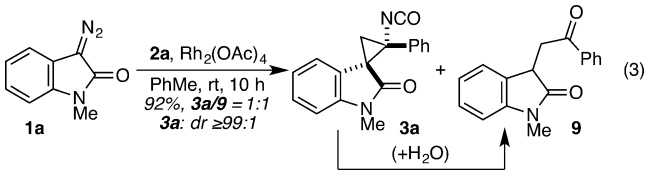
We next sought to expand the synthetic potential of the formal [4+1]-cycloadducts by examining α-siloxy vinyl isocyanates as a means of incorporating an additional functional handle into the newly formed heterocycle. Treatment of vinyl isocyanate **2b** bearing a TBS ether at the α-position led to formation of silylated and protiodesilylated spirosuccinimides **7a** and **7b** in a combined quantitative yield [Eq. (1)]. It bears noting that *N*-silyl succinimide **7a** is readily converted to **7b** under mildly acidic conditions and that exogenous base was not required to facilitate *O*-to-*N* silyl migration. The spirooxindole succinimide framework is a relevant pharmacophore present in a number of biologically active compounds applicable to the alleviation of diabetic complications.[17] For example, spirooxindole succinimide ADN-138 is a potent aldose reductase inhibitor that improves cataract and neuropathy in diabetic mice.[18]



Furthermore, we examined alternative methods of manipulating the olefin present in pyrrolone intermediate **4**. Access to the saturated lactam was readily achieved by an in situ reduction of the acyl enamine functionality. Treatment of diazooxindole **1a** with vinyl isocyanate **2a** in the presence of $Rh_2(OAc)_4$ (5 mol%) at 50 °C for 17 h followed by the addition of $NaBH_3CN$ and AcOH in THF (0.02 M) for 2 h, in place of ^{t}BuOK/^{t}BuOH, led to formation of spirooxindole lactam **8** in 80% yield as a 1.2:1 mixture of diastereomers [Eq. (2)]. Likewise, catalytic hydrogenation of **4** afforded lactam **8** by transferring the reaction mixture to a flask containing Pd/C under 1 atm of H_2 in EtOAc (0.01 M), following consumption of vinyl isocyanate **2a**, in comparable yield and diastereoselectivity.



To gain mechanistic insight into this formal [4+1]-cycloaddition, we explored the intermediacy of presumptive spirooxindole cyclopropyl isocyanate **3**. Performing the Rh^{II}-catalyzed cyclopropanation of diazooxindole **1a** and vinyl isocyanate **2a** at room temperature sufficiently slowed the ring expansion event [Eq. (3)]. This enabled isolation of cyclopropane **3a** as a single diasteromer in a 1:1 mixture consisting of ketone **9** in 92% combined yield. However, ^{1}H NMR of the mixture prior to chromatographic purification revealed an 81% yield of **3a**. Thus, ketone **9** likely arises from exposure of cyclopropane **3a** to adventitious water, which when combined with the mildly acidic conditions of chromatographic purification, results in a reaction cascade involving carbamic acid generation, decarboxylation, and hydrolysis of the resulting imine. Heating a solution of **3a** in PhMe at 50 °C led to smooth conversion to cycloadduct **5a**, supporting our hypothesis that the cyclopropyl isocyanate is a viable intermediate en route to the formal [4+1]-cycloaddition products.



In summary, we have demonstrated the use of diazooxindoles as C_1 synthons in a Rh^{II}-catalyzed, formal [4+1]-cycloaddition toward the construction of spirooxindole pyrrolones effectively employing vinyl isocyanates as 1,3-heterodiene surrogates. The method exhibits good tolerance to a diverse array of functional groups and substitution patterns across each component, and the unsaturated spiro-γ-lactams are amenable to further synthetic manipulations pertinent to target directed synthesis. The intermediacy of a cyclopropyl isocyanate enables ring expansion to the corresponding 5-membered *N*-heterocycle to occur under comparably milder conditions than previously established photochemical and thermal rearrangements of cyclopropylimines. Studies toward elucidating a detailed mechanism of the ring expansion event and the development of an enantioselective protocol are currently under investigation, and will be reported in due course.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: [4+1]-cycloadditions · cyclopropane rearrangements · diazooxindoles · spirooxindole alkaloids · vinyl isocyanates

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[16] Treatment of *N*-methyl-5-nitro diazooxindole ($R^1 = 5\text{-}NO_2$, $R^2 =$ Me) resulted in low yield ($\approx 20\%$) of the corresponding cycloadduct as an inseparable 3:1 mixture of an unidentified side product.

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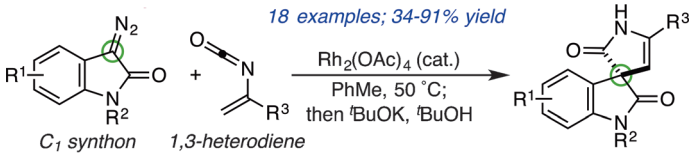
Communications

Cycloadditions

J. L. Meloche,
B. L. Ashfeld* ——— ■■■■–■■■■

A Rhodium(II)-Catalyzed Formal [4+1]-Cycloaddition toward Spirooxindole Pyrrolone Construction Employing Vinyl Isocyanates as 1,4-Dipoles



Put a ring on it: The title reaction between diazooxindoles as electrophilic C_1 synthons and 1,3-heterodienes enables the construction of spirooxindole pyrrolones. Employing vinyl isocyanates as 1,4-dipoles, the cycloannulation occurs under relatively mild conditions and provides the corresponding pyrrolones in good to excellent yields.

