

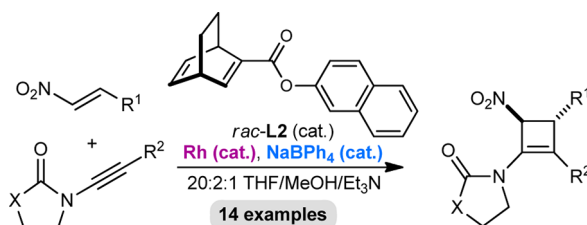
Rhodium-Catalyzed [2 + 2] Cycloaddition
of Ynamides with NitroalkenesDonna L. Smith,[†] Suresh Reddy Chidipudi,[†] William R. Goundry,[‡] and Hon Wai Lam^{*,†}

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ABSTRACT



In the presence of a diene-ligated rhodium complex, ynamides and nitroalkenes undergo catalytic [2 + 2] cycloadditions to provide cyclobutenamides. The presence of sodium tetraphenylborate was found to be crucial for the reactions to proceed efficiently.

The Ficini reaction is the stepwise [2 + 2] cycloaddition of ynamines¹ with cyclic electron-deficient alkenes to form cyclobutenamines.^{2–4} Key to the success of these reactions is the high reactivity of ynamines. However, this reactivity

means that ynamines are often difficult to prepare, handle, and store due to their sensitivity toward hydrolysis. In contrast, ynamides^{1b–d,5,6} possess increased stability due to delocalization of the nitrogen lone pair into the carbonyl/sulfonyl group, thus diminishing electron donation into the alkyne. Despite their greater stability, ynamides retain sufficient levels of reactivity to participate in a range

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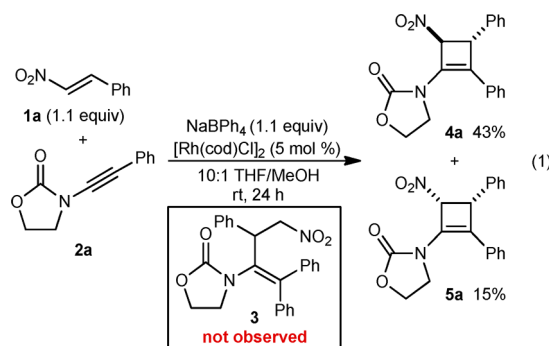
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of [2 + 2] cycloaddition reactions with strained bicyclic alkenes,⁷ ketenes,⁸ carbonyl compounds,⁹ and imines.¹⁰ However, it was not until recently that Ficini [2 + 2] cycloadditions of ynamides with cyclic enones were reported.¹¹ Hsung and co-workers described a racemic Cu-catalyzed variant that also proceeds with certain acyclic enones,^{11a} while the Mezzetti group reported an enantioselective Ru-catalyzed variant with cyclic unsaturated β -ketoesters.^{11b–d} Although this progress is highly encouraging, expansion of the substrate scope of ynamide [2 + 2] cycloadditions to encompass other types of alkene reaction partners would be highly valuable. Here, we describe the discovery and development of Rh-catalyzed [2 + 2] cycloadditions of ynamides with nitroalkenes.

These investigations were initiated by a serendipitous discovery; in an attempt to induce a domino reaction sequence consisting of Rh-catalyzed ynamide arylation¹² followed by conjugate addition of the resulting alkenylrhodium species to an electron-deficient alkene, nitroalkene **1a** and ynamide **2a** were treated with NaBPh₄ (1.1 equiv) and catalytic [Rh(cod)Cl]₂ in 10:1 THF/MeOH at room temperature. Instead of obtaining the hoped-for product **3**, cyclobutenes **4a** and **5a** were obtained in 43% and 15% yield, respectively (eq 1).



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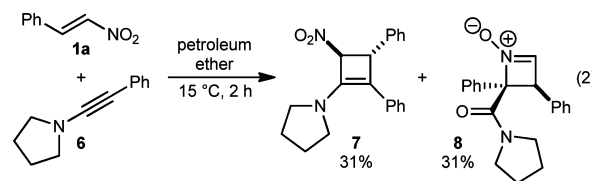
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The closest precedent to this process is the work of the Reinhoudt group describing the uncatalyzed reactions of ynamines with nitroalkenes which, in addition to cyclobutenamines, gave, in most cases, four-membered cyclic nitrones (representative example in eq 2).¹³



The [2 + 2] cycloaddition of **1a** with **2a** to give **4a** does not appear to be a simple Lewis-acid-catalyzed process¹¹ as evidenced by the complete failure of CuCl₂/AgSbF₆,^{11a} InBr₃, and Sn(OTf)₂ to promote the reaction. Furthermore, control experiments conducted in the absence of either [Rh(cod)Cl]₂ or NaBPh₄ established that both components are crucial for the reaction to proceed.

Table 1. Optimization of Reaction Conditions^a

entry	[Rh] (5 mol %)	ligand	additive	conv (%) ^b	4a/5a ^b
1	[Rh(cod)Cl] ₂	—	—	66	67:33
2	[Rh(cod)Cl] ₂	—	Et ₃ N ^c	66	82:18
3	[Rh(C ₂ H ₄) ₂ Cl] ₂	L1	Et ₃ N ^c	60	84:16
4	[Rh(C ₂ H ₄) ₂ Cl] ₂	<i>rac</i> - L2	Et ₃ N ^c	>90	87:13

^a Reactions were conducted using 0.30 mmol of **2a**. ^b Determined by ¹H NMR analysis of the unpurified reaction mixtures. ^c Reaction conducted in a 20:2:1 THF/MeOH/Et₃N mixture.

Additional experiments were then performed in an attempt to increase the efficiency of the reaction presented in eq 1 (Table 1). First, we found that appreciable quantities of the products **4a** and **5a** (66% conversion) were still obtained when the loading of NaBPh₄ was decreased to 10 mol % (entry 1). Second, conducting the reaction in a 20:2:1 THF/MeOH/Et₃N mixture improved the ratio of **4a**/**5a** by base-promoted equilibration toward the

(14) Stirring the pure *cis*-isomer **5a** in 20:2:1 THF/MeOH/Et₃N for 2 h provided an 81:19 mixture of **4a**/**5a**.

thermodynamic mixture (entry 2).¹⁴ While an attempt to render the reaction enantioselective by use of α -phellandrene-derived chiral diene **L1**¹⁵ in combination with $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ as the precatalyst afforded only racemic products (entry 3), the related racemic chiral diene **L2** gave increased conversion (entry 4). Ligand **L2** was therefore selected for further exploration of the scope of this process. It should be noted that the use of rhodium–diene complexes was optimal; when various rhodium–bisphosphine complexes were employed, the conversion decreased dramatically.

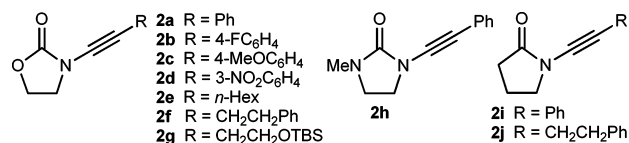


Figure 1. Ynamides employed in this study.

With effective conditions in hand, a range of ynamides **2a–2j** (Figure 1) were evaluated in the reaction with nitroalkene **1a** (Figure 2).¹⁶ Oxazolidinone-based ynamides **2a–2g** containing various aryl or aliphatic groups on the alkyne were found to be effective substrates, resulting in cyclobutenamides **4a–4g** along with their corresponding diastereomers **5a–5g**. With ynamide **2g**, a reaction temperature of 40 °C was required to ensure reasonable conversion. With aryl-substituted ynamides, the two diastereomers of the corresponding products could in many cases be separated by column chromatography. With aliphatic-substituted ynamides, however, the products were isolated as inseparable diastereomeric mixtures. The overall yields of these reactions were mostly good, except when ynamide **2d** containing a 3-nitrophenyl group was employed (products **4d** and **5d** isolated in 48% combined yield). Imidazolidinone- and pyrrolidinone-based ynamides **2h–2j** were also competent reaction partners when the reaction was conducted at 40 °C, though ynamide **2j** provided a mixture of **4j** and **5j** in only 41% yield.

The relative stereochemistry of the products was established by X-ray crystallographic analysis of **4b**, which confirmed the *trans*-relationship of the nitro and phenyl groups in the major isomers (Figure 3).

Figure 4 presents a brief investigation of the scope of the nitroalkene in reactions with ynamide **2a**. A range of aryl substituents on the nitroalkene were tolerated in these reactions, including 1-naphthyl (products **9a/10a**), 4-fluorophenyl (products **9b/10b**), 4-bromophenyl (products **9c/10c**), and

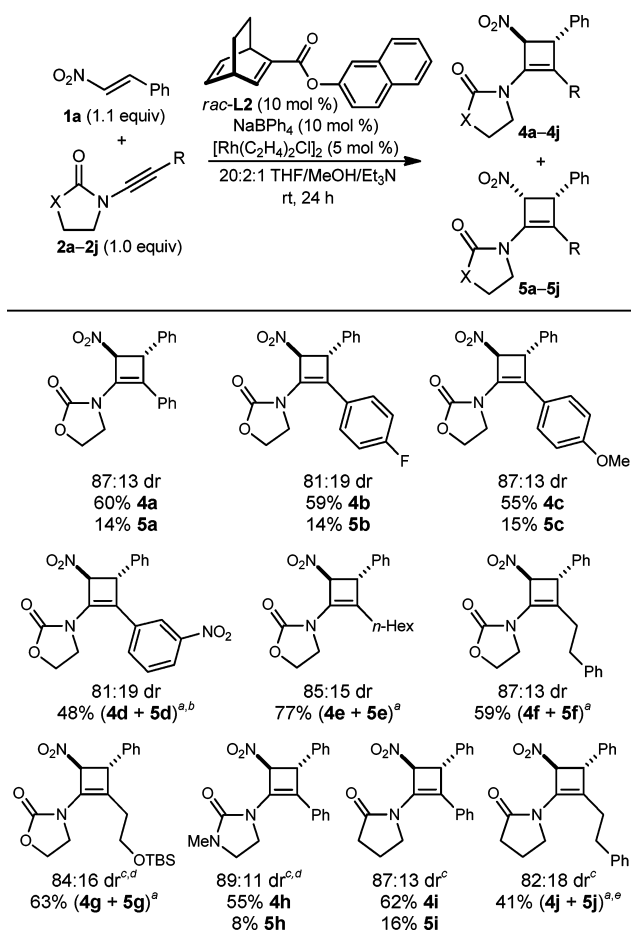


Figure 2. Rh-catalyzed [2 + 2] cycloaddition of ynamides with nitroalkene **1a**. Reactions were conducted using 0.30 mmol of **2**. Yields are of isolated material. Diastereomeric ratios were determined by ¹H NMR spectroscopy of the unpurified reaction mixtures. ^a Inseparable mixture of diastereomers. ^b Ratio of **4d/5d** in isolated product was 83:17. ^c Reaction conducted at 40 °C. ^d Reaction time of 6 h. ^e Ratio of **4j/5j** in isolated product was 90:10.

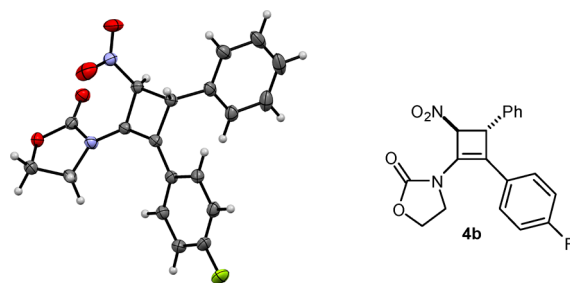


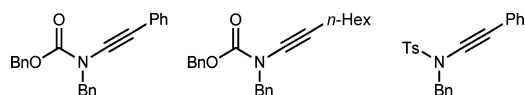
Figure 3. X-ray structure of product **4b**.

4-nitrophenyl (products **9d/10d**). Aliphatic nitroalkenes were unreactive in these cycloadditions.

A tentative catalytic cycle for these reactions, using nitroalkene **1a** for illustrative purposes, is depicted in Scheme 1. We assume that an as-yet-unidentified Rh(I)

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(16) The following ynamides, in which the nitrogen atom is not part of a cyclic system, were poor substrates in these reactions, generally providing very low conversions.



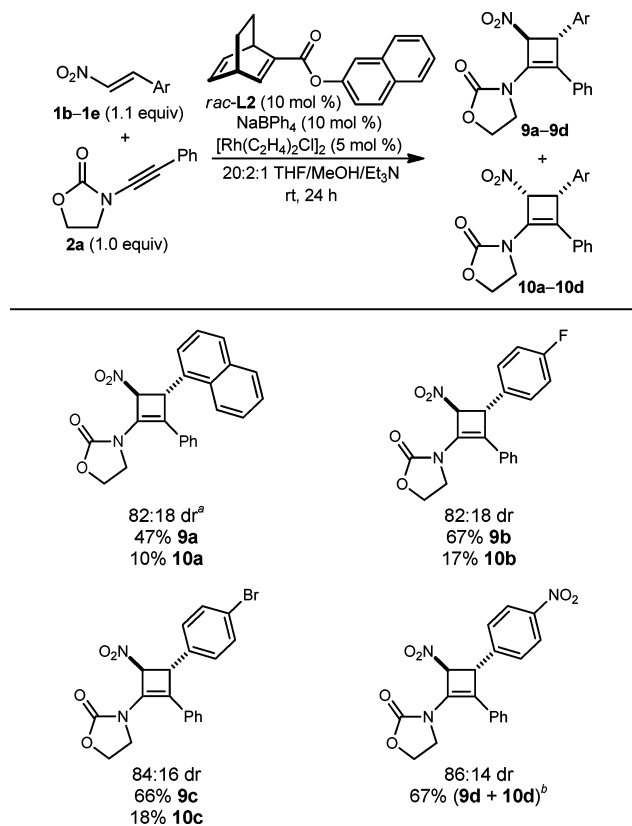


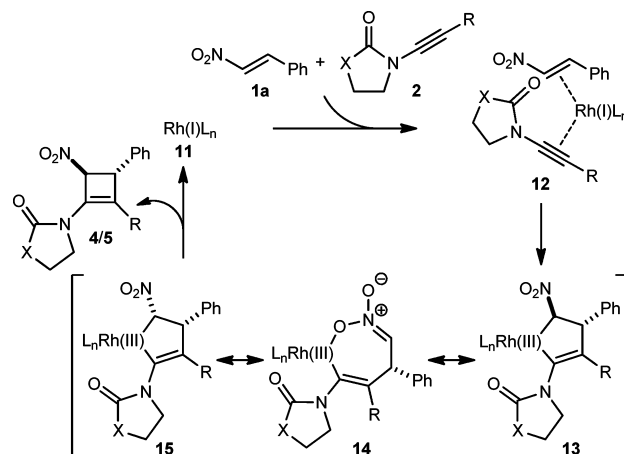
Figure 4. Rh-catalyzed [2 + 2] cycloaddition of ynamide **2a** with nitroalkenes **1b–1e**. Reactions were conducted using 0.30 mmol of **2**. Yields are of isolated material. Diastereomeric ratios were determined by ^1H NMR spectroscopy of the unpurified reaction mixtures. ^a Reaction was conducted at 40 °C for 6 h. ^b Ratio of **9d/10d** in isolated product was 81:19.

complex **11** formed in the reaction mixture can coordinate to the ynamide **2** and nitroalkene **1a** to form **12**, which then undergoes oxidative cyclization to form a rhodacycle. This rhodacycle can interconvert between the *trans* isomer **13** and the *cis* isomer **15** via **14**.¹⁷ Reductive elimination of this rhodacycle then releases the product **4/5** while regenerating **11**. However, the nature of the active catalytic species **11** and the important role of NaBPh_4 in these reactions are not clear at the current time. On the basis of literature precedent,¹⁸ it appears likely that $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$, *rac*-**L2**, and NaBPh_4 would react initially to form $\text{Rh}(\text{L2})(\eta^6\text{-C}_6\text{H}_5)\text{BPh}_3$ (**16**)

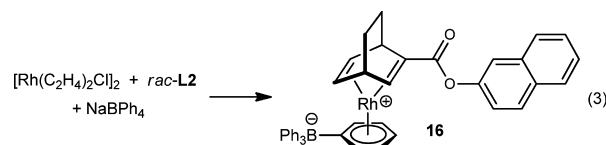
(17) For an example of a similar oxidative cyclization involving an alkyne, an alkene, and $\text{Ni}(0)$, see: Hratchian, H. P.; Chowdhury, S. K.; Gutierrez-Garcia, V. M.; Amarasinghe, K. K. D.; Heeg, M. J.; Schlegel, H. B.; Montgomery, J. *Organometallics* **2004**, *23*, 4636–4646.

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Scheme 1. Tentative Catalytic Cycle for These Reactions



(eq 3), but whether this is the active catalytic species itself, or whether it is converted into the active catalyst by some other means in the reaction, is unclear at present.¹⁹



In conclusion, we have reported the first metal-catalyzed [2 + 2] cycloadditions of ynamides with nitroalkenes. The reactions are promoted by substoichiometric quantities of a racemic chiral diene–rhodium complex in conjunction with NaBPh_4 , resulting in a range of cyclobutenamide products. Further work is aimed at elucidation of the mechanism of these reactions, which may guide the development of related rhodium-catalyzed cycloadditions.

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Supporting Information Available. Experimental procedures, full spectroscopic data for all new compounds, and crystallographic data in cif format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(19) A repeat of the reaction in Table 1, entry 4 on a 0.10 mmol scale using BPh_3 (10 mol %) in place of NaBPh_4 , provided **4a/5a** in 36% conversion.

The authors declare no competing financial interest.