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Enantioselective Rhodium-Catalyzed [4+2+2] Cycloaddition of Dienyl Isocyanates for the Synthesis of Bicyclic Azocine Rings

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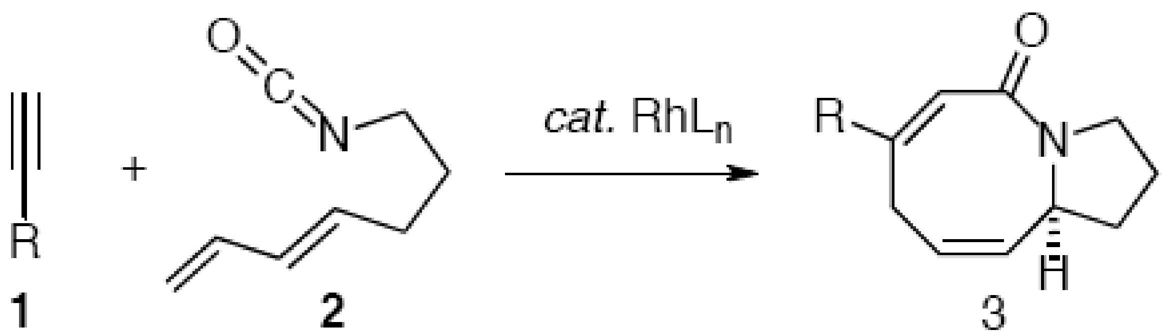
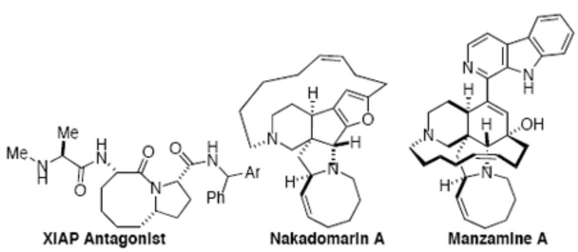
Transition metal-catalyzed cycloadditions have proven among the most attractive methods to construct medium-sized ring systems.[1] Although [4+4],[2] [6+2],[3] [5+2+1],[4] and [4+2+2][5] cycloadditions have been elegantly demonstrated to assemble various eight-membered carbocycles, formation of eight-membered nitrogen-containing rings (azocines) has not been explored. In addition, there are no reported examples of successful enantioselective cycloadditions to construct eight-membered rings.[6] We have recently demonstrated that Rh(I) catalysts are capable of effecting enantioselective [2+2+2] cycloadditions with the use of alkenyl heterocumulenes.[7] Herein we describe a highly asymmetric rhodium-catalyzed [4+2+2] cycloaddition of terminal alkynes and dienyl isocyanates to afford bicyclo[6.3.0] azocine derivatives (eq 1).



(1)



Bicyclo[6.3.0] azocine ring systems are unique architectures found in several biologically active compounds. Wang and coworkers have recently designed a potent XIAP antagonist, a small molecule consisting of the bicyclic azocine as the basic template.[8] A number of

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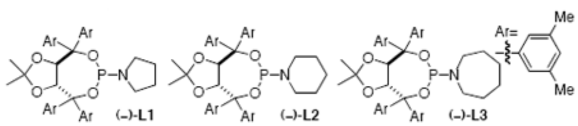
Supporting Information Available: Experimental procedures, characterization, ^{1}H and ^{13}C NMR spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

manzamine alkaloids such as nakadomarin A and manzamine A, which exhibit potent antimalarial and antituberculosis activity, are equipped with such ring systems.[9] Previous approaches to bicyclo[6.3.0] heterocycles have been stepwise including a ring-closing metathesis to afford the eight-membered ring.[10]

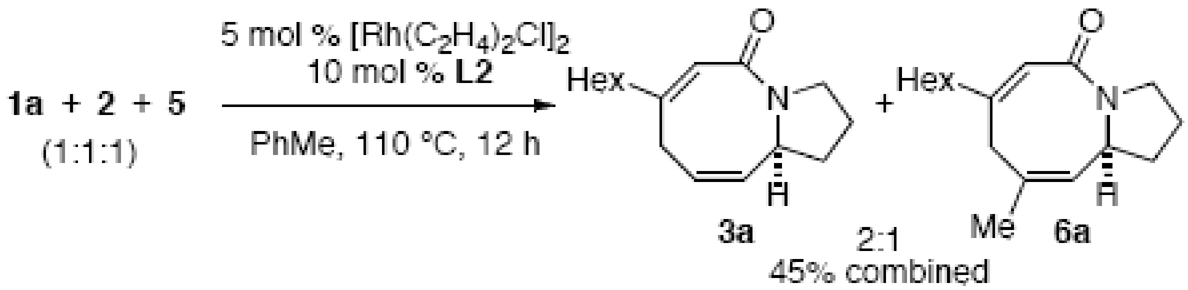
Our initial efforts to effect the [4+2+2] cycloaddition focused on 1-octyne **1a** and the dienyl isocyanate **2** as a mixture of *E/Z* isomers (Table 1, entry 1). Treatment of the substrates with $[Rh(C_2H_4)_2Cl]_2$ modified with phosphoramidite **L1** furnishes both the [4+2+2] cycloadduct **3a** and the [2+2+2] cycloadduct **4a** in 40% yield as an inseparable 4:1 mixture.[11] Further investigation led to the isomerically pure diene **(*E*)-2** as the optimal substrate to provide **3a** selectively (entry 2).[12] Despite a significant amount of unreacted isocyanate **2**, the desired bicyclic azocine **3a** is obtained with an exceptional enantioselectivity (99% ee). Replacing the pyrrolidinyl group on the phosphoramidite ligand with either the piperidine (**L2**) or azepine **(L3**) dramatically increases reactivity toward azocine ring formation while maintaining the high level of enantioselectivity (entries 3 – 4).[13]



With optimal conditions in hand, a variety of substituted bicyclic azocines can be synthesized in good yields and superb enantioselectivities (Chart 1). Alkyl alkynes bearing a chloride, a methyl ester, or an unprotected terminal alkyne (**1b** – **1d**) all participate smoothly to provide the corresponding cycloadducts (**3b** – **3d**). Alkynes possessing functionalities such as silyl ether, phthalimide, phenyl, and Boc-protected indole at the propargylic positions (**1e** – **1h**) are well tolerated to furnish the [4+2+2] cycloadducts (**3e – 3h**) in good yields and identical enantioselectivities.[14]

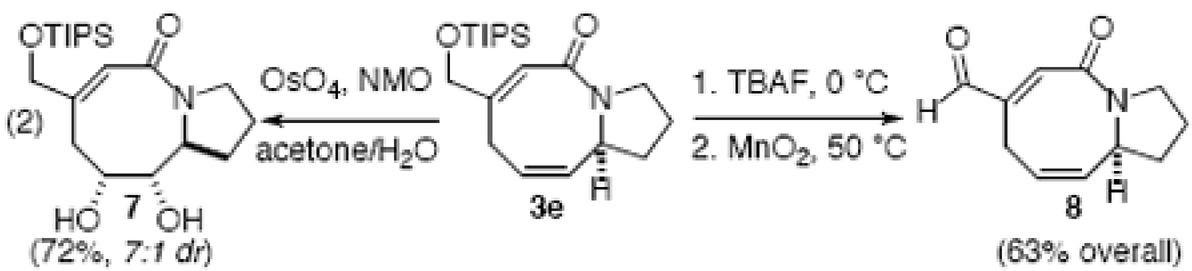
Cycloaddition of isocyanates with substitution at the diene portion is also feasible. For example, when 2-methyl dienyl isocyanate **5** is reacted under the standard conditions, [4+2+2] cycloadditions with various alkynes all proceed uneventfully (**6a, 6e, 6j**).[15] Reactions with aryl alkynes, however, proceed only in moderate yield. With 1-bromo-4-ethynylbenzene (**1i**), cycloadduct **3i** can only be obtained in 35% isolated yield with the same high enantioselectivity.

Several aspects of these findings suggest that there may be a mechanistic divergence from our previously developed reaction. Prime among these is the invariant enantioselectivity with regard to alkyne structure as well as the failure to observe any vinylogous amide adducts in this chemistry. In order to gain insight into the reaction mechanism, we conducted a competition experiment between dienyl isocyanates **2** and **5**. If oxidative cycloaddition occurs between the alkyne and isocyanate first (path a in Scheme 1), the ratio of products **3** and **6** should be 1:1.[7h] In the event, **3** is formed with 2:1 selectivity over **6**.[16] We suggest that this is most consistent with initial oxidative cyclization between the diene and isocyanate following path b to form **V**. Coordination and insertion of alkyne then provides the [4+2+2] adduct. With more reactive nucleophilic alkynes, path a becomes competitive forming rhodacycle **II**. Diene coordination and insertion is slow, presumably for steric reasons, allowing competitive alkyne insertion to form pyridone. The diene found in ***Z-2*** is a poor ligand for Rh and thus prefers path a, leading to increased amounts of both **4** and pyridone.[17]



(2)

The Rh-catalyzed cycloaddition protocol allows access to synthetically useful bicyclic azocines. Dihydroxylation affords diol **7** in 72% yield for the major diastereomer (7:1 dr, eq 2). Alternately, an α,β-unsaturated aldehyde functionality can be readily unmasked in two simple steps from **3e**, eq 3.



(3)

In conclusion, we have developed the first enantioselective rhodium-catalyzed [4+2+2] cycloaddition of terminal alkynes and dienyl isocyanates. The process provides access to highly functionalized bicyclo[6.3.0] azocine ring systems with exceptional enantioselectivities. Further studies on the full scope of this new process are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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6. In their full paper, Gilbertson and coworkers reported a single example of 41% ee as the highest selectivity observed. See: ref [5h].

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11. This reaction also forms ~4% pyridone. Conducting this reaction at 0.06 M in **2** leads to 25% combined yield of **3** and **4** in a 3:1 ratio along with ~10% pyridone.

12. Further studies on [2+2+2] cycloadditions with various 1,2-disubstituted alkenyl isocyanates are ongoing.

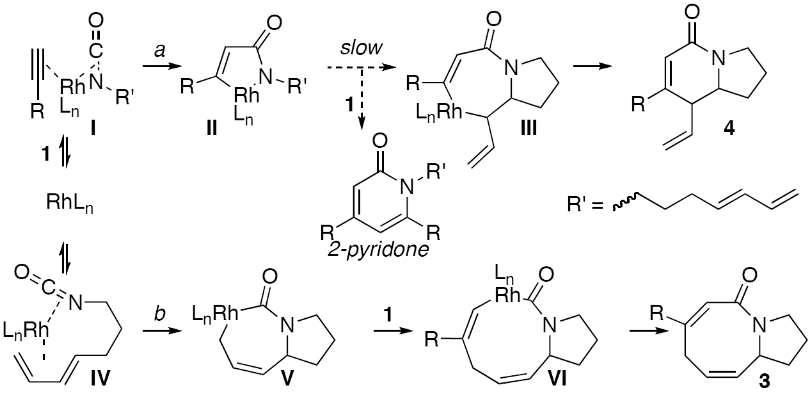
13. We observe symmetrical ureas derived from the isocyanate as the only significant byproduct. No regioisomers have been observed.

14. Larger scale reactions may be conducted with lower catalyst loading and slightly higher concentration; with 3 mol % $[Rh(C_2H_4)_2Cl]_2$ and 6 mol% **L3** at 0.073M using 1.5 mmol of **2, 3e** is formed in 68% yield and 99% ee.

15. Substitution at the terminus of the diene leads to only [2+2+2] adduct under these conditions (E,E-octa-4,6-dienyl isocyanate and **1a** afford **4a**' in 46% yield, 46% ee). Bicyclo [6.4.0] systems are not accessible under these conditions.

16. At higher catalyst loading (25 mol% $[Rh(C_2H_4)_2Cl]_2$), **3** and **6** are formed quantitatively in a 4:1 ratio.

17. At 0.02 M, no pyridone is observed with *E*-**2**. At 0.1 M, we see <5% pyridone (75% yield of **3a**). Also see entry 1, Table 1 and footnote 11.



Scheme 1.
Proposed Mechanism

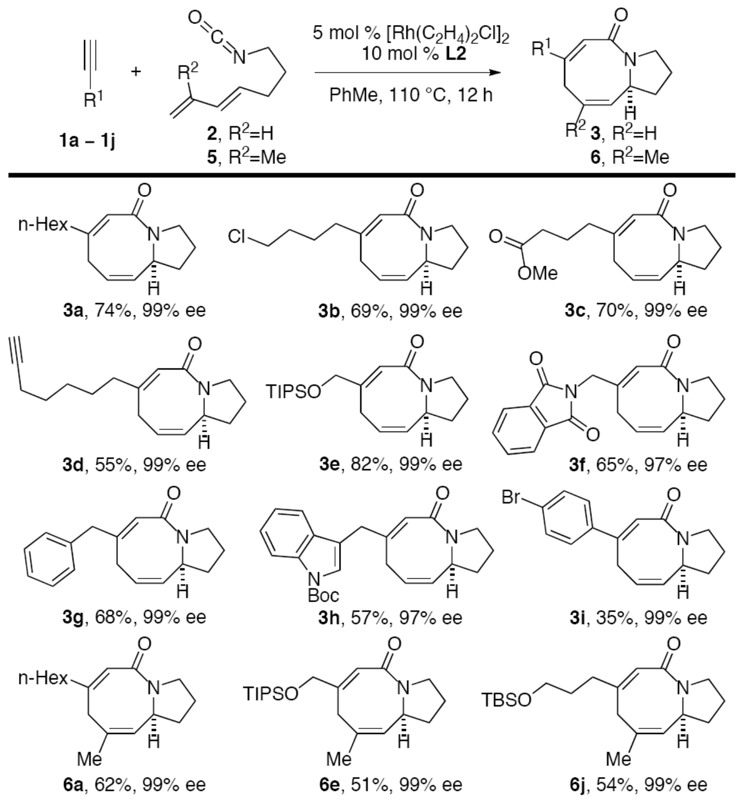


Chart 1.
Enantioselective Synthesis of [6.3.0] Bicyclic Azocines

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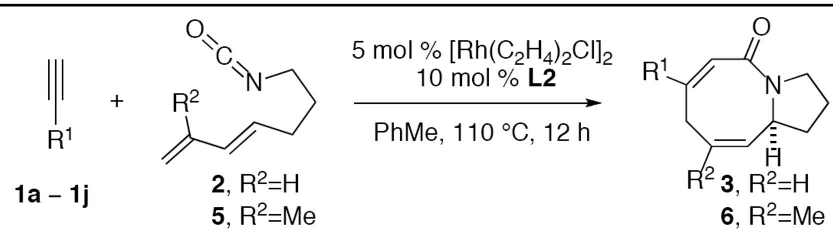
Table 1

Development of the Rh-catalyzed [4+2+2] Cycloaddition



entry[a]	E/Z ratio of 2	L*	3 : 4[b] 2 : 3[b]	yield (%) of 3[c]	*ee* (%) of 3[d]
1	1.4 : 1	**L1**	4 : 11 : 2.5	40[e]	n.d.
2	≥19 : 1	**L1**	≥19 : 11 : 2.5	47	99
3	***≥19 : 1***	***L2***	***≥19 : 11 : 10***	***74***	***99***
4	≥19 : 1	**L3**	≥19 : 11 : 10	67	99

[a] Conditions: **1** (1.5 equiv), **2** (0.18 mmol), Rh catalyst, **L** in PhMe (0.02 M) at 110 °C.

[b] Ratio determined by ^{1}H NMR of the unpurified reaction mixture.

[c] Isolated yield.

[d] Determined by HPLC using a chiral stationary phase.

[e] Combined yield of **3** and **4**.