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Rhodium-Catalyzed [2 + 2 + 2] Cycloaddition of Alkenyl Isocyanates and Alkynes

Robert T. Yu and Tomislav Rovis*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

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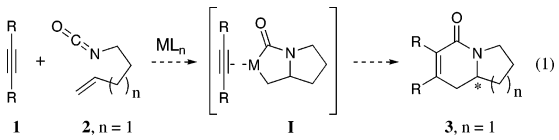
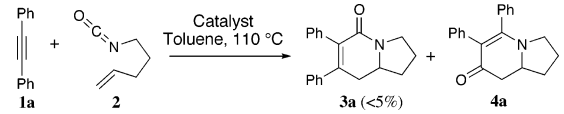
Transition-metal-catalyzed multicomponent cycloaddition reactions represent powerful tools for the rapid construction of polycyclic carbocycles and heterocycles.[1] Because many such polycyclic molecules possess motifs resembling a variety of biologically active compounds, developing new strategies, such as [*m* + *n* + *o*]-type three-component cycloadditions, has become increasingly important.[2] Isocyanates are particularly attractive building blocks for the construction of nitrogen-containing heterocycles, owing to their facile reactivity and embedded functionalities.[3] To date, several groups have investigated [2 + 2 + 2] cycloadditions between isocyanates and diynes utilizing Co, Ru, Ni, and most recently cationic Rh-based catalyst systems to provide bicyclic 2-pyridones.[4−7] The resulting bicyclic molecules lack sp^3-stereocenters[7] and flexibility for further chemical transformations, and thus their applications toward complex molecule synthesis are inherently limited. Herein, we report the development of a rhodium-catalyzed [2 + 2 + 2] cycloaddition involving alkenyl isocyanates and alkynes (eq 1). The resulting products contain sp^3-stereogenic centers and functionalities, which should allow further manipulation to many important indo- and quinolizidine alkaloids.[8]



At the outset of our investigation, we hypothesized that alkenes were reluctant to participate in these [2 + 2 + 2] cycloadditions due to the propensity of competitive insertion of alkyne. Should the alkene be tethered to the isocyanate, the reaction may proceed via metalacycles,[9] such as **I** (eq 1), and should compete more effectively with the exogenous alkyne to form indolizinone-type products **3**. Our study began by examining the cycloaddition of alkenyl isocyanate **2**, derived from the corresponding acid, and diphenylacetylene **1a** as the representative alkyne. Remarkably, in the presence of a neutral rhodium-based catalyst with an electron-rich monodentate phosphine ligand, **1a** and **2** underwent a unique [2 + 2 + 2] cycloaddition to furnish the bicyclic vinylogous amide product **4a**, rather than the expected **3a**, in good yields (Table 1). Employing bidentate or bulky phosphine ligands resulted in either no reactivity or low yields (entries 2 and 3). The structural assignment of **4a** was based on spectroscopic data and was unambiguously established by X-ray structure analysis (see Supporting Information). The combination of $[Rh(ethylene)_2Cl]_2$ and 1 equiv tris(4-methoxyphenyl)phosphine per metal provided **4a** in 74% yield (entry 6, Table 1). This unusual Rh-catalyzed cycloaddition reaction consists of two C−C and two C−N bond-forming events and results in a rare fragmentation of the isocyanate unit.

With this result in hand, we examined the substrate scope with a range of symmetrical bisaryl alkynes (tolanes **1b**−**1i**). The newly developed [2 + 2 + 2] cycloaddition tailored well with a wide range of substituted tolanes, providing the desired bicyclic products

Table 1. Catalyst Screening for the [2 + 2 + 2] Cycloaddition[a]



entry	catalyst	yield (%) of **4a**[b]
1	10 mol % $RhCl(PPh_3)_3$	54[c]
2	5 mol % $[Rh(COD)Cl]_2$, 10 mol % Binap or Dppb	0, 13[c]
3	5 mol % $[Rh(COD)Cl]_2$, 20 mol % P(2-OMe-$C_6H_4)_3$ or P(tBu)$_3$	trace
4	5 mol % $[Rh(COD)Cl]_2$, 20 mol % P(4-OMe-$C_6H_4)_3$	42
5	5 mol % $[Rh(COD)Cl]_2$, 10 mol % P(4-OMe-$C_6H_4)_3$	61
6	**5 mol % $[Rh(ethylene)_2Cl]_2$, 10 mol % P(4-OMe-$C_6H_4)_3$**	**74**

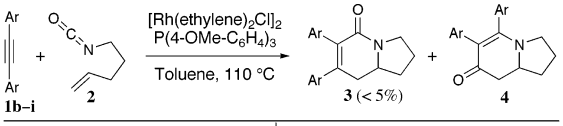
[a] Reaction conditions: **1a** (2 equiv), **2**, indicated amount of Rh/L in toluene at 110 °C. [b] Isolated yields. [c] Determined by ^1H NMR of the unpurified reaction mixture using an internal standard.

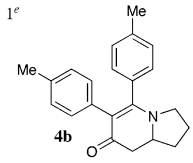
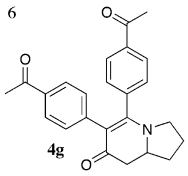
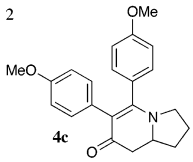
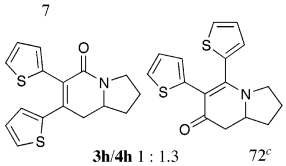
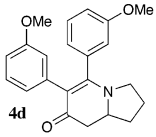
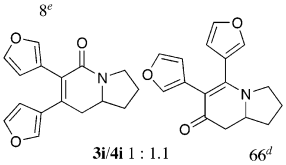
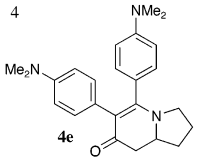
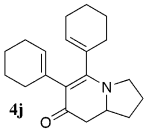
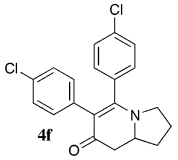
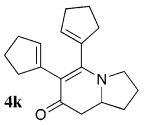
in satisfactory chemical yields (**4b**−**4g**, Table 2). Neutral and electron-rich substituents at either the *para*- or *meta*-positions readily participated in the cycloaddition (entries 1−3). Tolanes bearing amino and halogen functional groups (Me_2N, Cl) were also well tolerated (entries 4 and 5). Electron-withdrawing substituted tolanes appear to be less reactive,[10] with acetyl-substituted tolane affording the desired product in a modest yield (entry 6). Each of these tolanes furnishes the vinylogous amide-type products **4** selectively, resulting from an apparent CO migration, while compounds **3** were only observed in trace amounts (<5%). The cycloadditions with the heteroaryl tolanes (Ar = thiophene, furan) were also successful (entries 7 and 8). Interestingly, both the thiophene and furan tolanes generate both types of compounds in an approximately 1:1 ratio with good combined yields. The substrate scope was further expanded to the more sterically demanding cyclic dienynes. Cycloaddition between **1j** and **2** proceeds smoothly to afford exclusively indolizinone **4j** in 75% isolated yield (entry 9). Similarly, the bis(cyclopentene) substituted indolizinone **4k** was obtained in a useful yield from enyne **1k** (entry 10), although lowering the temperature to 80 °C was necessary to prevent product decomposition.[11]

The steric environment of the substrates seems to dictate the reaction outcome. Bulky alkynes, such as dienyne **1j**, afford compounds **4** exclusively, while heteroaryl alkynes, such as **1h** and **1i**, possibly due to their lesser steric demand, might trigger an alternative mechanism and thus afford a mixture of both types. With this hypothesis in hand, the cycloaddition of primary dialkyl alkynes was examined with an anticipation of possibly changing the reaction course (Table 3). The cycloadditions proceed with almost complete inversion of selectivity, affording the direct cycloaddition products **3** with good isolated yields (entries 1−3). TBS-protected homopropargyl alcohol also participates in the reaction efficiently, providing **3n** in 56% yield (entry 3). The current protocol can also be employed for constructing the bicyclic quinolizinone framework. Thus, by reacting an alkyl alkyne with the alkenyl isocyanate **5**, the resulting bicyclic compounds **6** may be obtained in good yields and selectivity (entries 4 and 5).

10.1021/ja057803c CCC: $33.50

Table 2. Scope of the Rh-Catalyzed [2 + 2 + 2] Cycloaddition[a]



entry	product	yield (%)[b]	entry	product	yield (%)[b]
1[e]	 **4b**	63	6	 **4g**	34
2	 **4c**	72	7	 **3h**/**4h** 1 : 1.3	72[c]
3	 **4d**	70	8[e]	 **3i**/**4i** 1 : 1.1	66[d]
4	 **4e**	61	9	 **4j**	75
5	 **4f**	60	10[f]	 **4k**	50

[a] Reaction conditions: **1** (2 equiv), **2**, Rh cat. (5 mol %), L (10 mol %) in toluene at 110 °C. [b] Isolated yield. [c] Inseparable, combined yield. [d] Separable, combined yield. [e] With 1.1 equiv of alkyne employed. [f] At 80 °C.

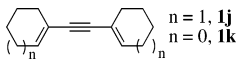
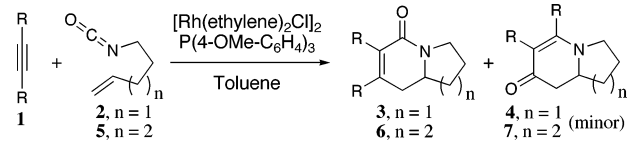


Table 3.

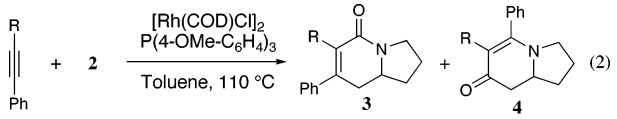


entry	R	isocyanate	yield (%) **3** or **6**[b]	yield (%) **4** or **7**[b]
1[c]	**1l**, R = *n*-Pr	**2**	60	trace
2[c]	**1m**, R = *n*-Bu	**2**	70	12
3[d]	**1n**, **R** = $(CH_2)_2OTBS$	**2**	56	trace
4[d]	**1m**	**5**	62	18
5[d]	**1n**	**5**	56	trace

[a] For reaction conditions, see Table 2. [b] Isolated yields. [c] At 80 °C. [d] At 110 °C.

The reaction of unsymmetrical alkyne **1o** generates both **3** and **4** with a slight preference for **3** (eq 2). The use of the homologous alkyne **1f** inverts this selectivity in favor of **4**, providing further support for the steric argument. It is noteworthy that in each case the bicyclic products were obtained in high regioselectivity (~10: 1; see Supporting Information).

A plausible mechanism is illustrated in Scheme 1. Although still speculative, formation of **3** is thought to proceed through metalacycle **IV** of the initial intermolecular cycloaddition between **1** and the isocyanate moiety of **2**, followed by olefin insertion and reductive elimination (pathway A). For the more sterically hindered alkynes, the intramolecular cyclization of isocyanate and the tethered

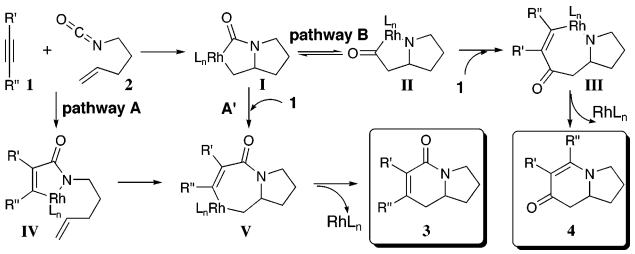


1o: R = Me
1p: R = Et

3o : **4o** (1.3 : 1), 60%
3p : **4p** (1 : 2.0), 63%

olefin is thought to proceed significantly faster to generate intermediate **I**. A CO migration[12] followed by alkyne insertion and reductive elimination would afford **4** (pathway B). Alternative routes, such as **A′**, cannot be ruled out at this stage.

Scheme 1. Proposed Mechanism



In summary, we have discovered and developed a rhodium-catalyzed [2 + 2 + 2] cycloaddition involving alkynes and alkenyl isocyanates. Efforts focused on mechanistic investigations and expanding the substrate scope[13] are currently underway.

Acknowledgment. We thank Mark Kerr and Susie Miller for X-ray analysis of **4a**. We thank Merck, GlaxoSmithKline, Eli Lilly, Amgen, and Boehringer Ingelheim for unrestricted support, and Johnson and Johnson for a Focused Giving grant. T.R. thanks the Monfort Family Foundation for a Monfort Professorship. T.R. is a fellow of the Alfred P. Sloan Foundation.

Supporting Information Available: Detailed experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Under these conditions, terminal alkynes undergo competitive dimerization, while internal alkenes provide <10% yield of cycloadduct.

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