

## Ruthenium-catalyzed [2 + 2 + 1] Cocyclization of Isocyanates, Alkynes, and CO Enables the Rapid Synthesis of Polysubstituted Maleimides

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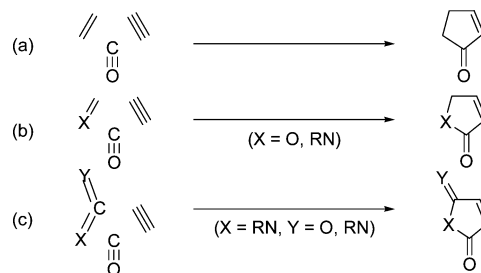
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The formal [2 + 2 + 1] cocyclization of alkenes, alkynes, and CO by transition metal complexes, represented by cobalt complexes, (known as the Pauson–Khand reaction) has been accepted as one of the most powerful, convergent, and atom-economical methods for the construction of cyclopentenones (path a in Scheme 1).<sup>1</sup> Many advances related to this method have recently been reported, including the development of catalytic versions of this reaction.<sup>2</sup> Allenes have also been used as an alkene partner in this cocyclization reaction to give 4- and/or 5-alkylidenecyclopentenones.<sup>3</sup> A carbonyl or imino moiety can also be used in place of a carbon–carbon double bond to give  $\gamma$ -lactones<sup>4</sup> or  $\gamma$ -lactams,<sup>5</sup> respectively (path b, Scheme 1). If heterocumulenic compounds such as carbodiimides and/or isocyanates can be used in the catalytic [2 + 2 + 1] cocyclization with alkynes and CO, it could lead to a new approach for the construction of novel heterocyclic compounds, as a heteroatomic variant of the Pauson–Khand reaction (path c, Scheme 1).

However, such processes are strictly limited to very recent examples of the Mo(CO)<sub>6</sub>-mediated<sup>6</sup> and Co<sub>2</sub>(CO)<sub>8</sub>-catalyzed<sup>7</sup> intramolecular cocyclization of alkynecarbodiimides with CO. Two other examples of the intermolecular [2 + 2 + 1] cocyclization of isocyanates, alkynes, and CO have required stoichiometric amounts of metal complexes such as Fe(CO)<sub>5</sub><sup>8</sup> and Ni(cod)<sub>2</sub> (cod = 1,5-cyclooctadiene).<sup>9</sup> At the outset of our study on ruthenium-catalyzed cocyclization reactions,<sup>10</sup> we found a novel and rapid synthesis of polysubstituted maleimides by the ruthenium-catalyzed intermolecular [2 + 2 + 1] cocyclization of isocyanates, alkynes, and CO. A traditional industrial process for manufacturing maleimides is the reaction of amines with maleic anhydride obtained by the oxidation of benzene or C<sub>4</sub>-hydrocarbons, which gives only unsubstituted and/or symmetrically substituted maleimides.<sup>11</sup> The present reaction offers a highly efficient method for preparing novel unsymmetrically polysubstituted maleimides in excellent yields with high selectivity, which are important building blocks in materials science<sup>12</sup> and biological chemistry.<sup>13</sup>

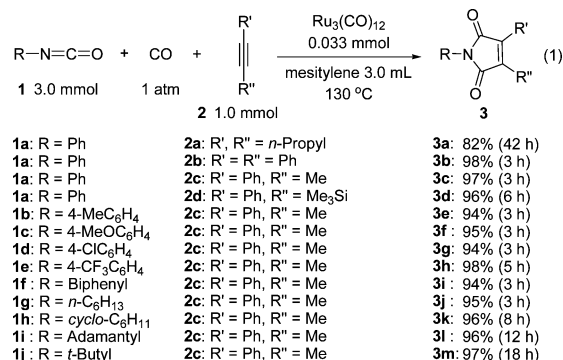
First, the effects of catalysts and the reaction conditions were examined in the synthesis of maleimide **3a** from the reaction of phenyl isocyanate **1a** with 4-octyne **2a** under 1 atm of CO. Among the transition metal complexes, Ru<sub>3</sub>(CO)<sub>12</sub> showed the highest catalytic activity. Ru(CO)<sub>3</sub>(PPh<sub>3</sub>)<sub>2</sub>, RuH<sub>2</sub>(CO)(PPh<sub>3</sub>)<sub>3</sub>, and RuHCl(CO)(PPh<sub>3</sub>)<sub>3</sub> also showed some catalytic activity (**3a**, up to 28%), while [RuCl<sub>2</sub>(CO)<sub>3</sub>]<sub>2</sub>, Cp\*RuCl(cod) [Cp\* = pentamethylcyclopentadienyl], and CpRuCl(cod) [Cp = cyclopentadienyl] were totally ineffective. No **3a** was obtained with rhodium complexes, such as RhCl(CO)(PPh<sub>3</sub>)<sub>2</sub>, Rh<sub>4</sub>(CO)<sub>12</sub>, Rh<sub>6</sub>(CO)<sub>16</sub>, and [Cp\*Rh(CO)<sub>2</sub>]<sub>2</sub>. Mesitylene is the best solvent. The reactions in toluene or decane also gave **3a** in moderate yield (40% and 38%, respectively); however, no reaction occurred in diglyme, 1,4-dioxane, *N,N*-dimethylacetamide, and propionitrile. The use of an excess (3 equiv) amount of **1a** relative to **2a** completely suppressed the cyclotri-

**Scheme 1.** Synthesis of Five-membered Carbonyl Compounds via the [2 + 2 + 1] Cocyclization Reactions



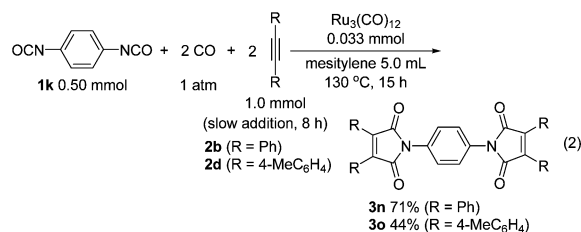
merization of **2a** to hexa-*n*-propylbenzene, and the only product detected by GLC was **3a**. A higher CO pressure (over 5 atm) drastically suppressed the reaction to result in a low yield of **3a**.

Consequently, when the reaction of phenyl isocyanate (**1a**, 3.0 mmol) with 4-octyne (**2a**, 1.0 mmol) was carried out in the presence of a catalytic amount of Ru<sub>3</sub>(CO)<sub>12</sub> (0.033 mmol) in mesitylene (3.0 mL) at 130 °C for 42 h under 1 atm of CO, the corresponding maleimide, 1-phenyl-3,4-dipropylazoline-2,5-dione (**3a**), was obtained in an isolated yield of 82%. Various substrates were subjected to the present [2 + 2 + 1] cocyclization reaction under the optimum reaction conditions, and the results are summarized in eq 1.



Aryl-substituted alkynes such as diphenylacetylene (**2b**) and 1-phenyl-1-propyne (**2c**) are more reactive than 4-octyne (**2a**), and the reactions with phenyl isocyanate (**1a**) were almost complete within 3 h to give **3b** and **3c** in isolated yields of 98% and 97%, respectively (vide infra). With terminal alkynes such as 1-octyne and phenylacetylene, however, a trace amount of the desired maleimides was obtained (<10%). We next examined the cocyclization of a variety of aryl and alkyl isocyanates with 1-phenyl-1-propyne (**2c**) and CO. No significant effect was observed for electron-donating (4-Me (**1b**) and 4-MeO (**1c**)) and electron-withdrawing (4-Cl (**1d**), 4-CF<sub>3</sub> (**1e**), and 4-Ph (**1f**)) substituents on a phenyl ring in aryl isocyanate, while bulky alkyl isocyanates (**1i** and **1j**) required a longer reaction time for the complete conversion of **2c**.

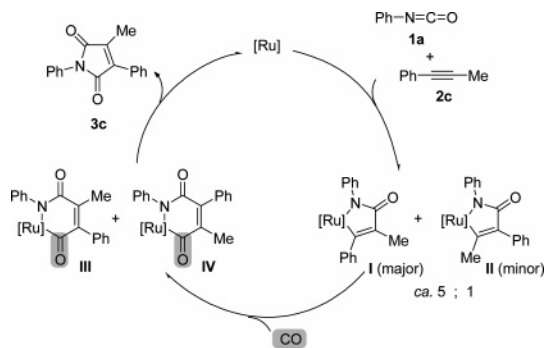
1,4-Phenylene diisocyanate (**1k**) can be used for the present reaction, and the corresponding dimaleimides (**3n** and **3o**) were obtained in isolated yields of 71% and 44%, respectively (eq 2). A slow addition of alkynes (**2b** and **2d**) to diisocyanate (**1k**) is essential. No reaction occurred by simple mixing of alkynes with diisocyanates, which suggests that the higher coordination ability of alkynes causes deactivation of the catalyst.



The carbonyl carbon observed at a lower field as a quartet (170.6 ppm,  $^3J = 4.67$  Hz) is adjacent to a methyl-substituted  $sp^2$  carbon, while another carbonyl group attached to a phenyl-substituted  $sp^2$  carbon appeared at a higher field as a singlet (169.6 ppm), as clearly shown in a detailed NMR study ( $^{13}\text{C}$  gated decoupling and Inadequate (Incredible Natural Abundance Double Quantum Transfer Experiment) measurements) with maleimide (**3c**). In addition, the reaction of **1a** with **2c** was carried out in the presence of  $\text{Ru}_3(\text{CO})_{12}$  catalyst under 1 atm of  $^{13}\text{CO}$  to give the corresponding  $^{13}\text{C}$ -labeled maleimides, **3c**- $^{13}\text{C}$ .  $^{13}\text{C}$  NNE measurement of the carbonyl regions of **3c**- $^{13}\text{C}$  clearly showed that the carbonyl carbon at a higher field (169.6 ppm) was mainly derived from external  $^{13}\text{CO}$  (see, Supporting Information).

Considering the results obtained above, we postulated a mechanism for this newly developed intermolecular [2 + 2 + 1] cycloaddition of **1a**, **2c**, and CO, as shown in Scheme 2. The reaction starts with the formation of azaruthenacyclopentenones **I** (major) and **II** (minor) by the oxidative cyclization of **1a** and **2c** on an active ruthenium center.<sup>9,14</sup> For aryl-substituted alkynes, this oxidative cyclization process is thought to proceed significantly faster than with alkyl-substituted alkynes to preferably generate an  $\alpha$ -aryl-substituted azaruthenacyclopentenone of type **I** (vide supra). A  $^{13}\text{CO}$ -labeling experiment also suggests the formation of azaruthenacyclopentenones, **I** and **II**, and  $\alpha$ -phenyl-substituted **I** is more favorable than  $\alpha$ -methyl-substituted **II** (the ratio of **I** and **II** is estimated to be approximately 5 to 1 based on the  $^{13}\text{C}$  NNE spectrum of **3c**- $^{13}\text{C}$ ; see Supporting Information). Next, the insertion of CO into a Ru–C( $sp^2$ ) bond rather than a Ru–N bond<sup>15</sup> predominantly occurred to give azaruthenacyclohexenediones, **III** and **IV**, followed by reductive elimination to give maleimides **3c** in an excellent yield with high selectivity and with the regeneration of an active low-valent ruthenium species.

**Scheme 2.** A Possible Mechanism of Ru-Catalyzed [2 + 2 + 1] Cycloaddition of **1a**, **2c**, and CO to **3c**



In conclusion, we have developed the first catalytic intermolecular [2 + 2 + 1] cycloaddition of alkynes, isocyanates, and CO. This process provides a rapid and atom-economical method for the synthesis of a variety of unsymmetrically polysubstituted maleimides in one step. Isolation of azaruthenacyclopentenones and a DFT calculation for the process of CO insertion are currently under investigation.

**Acknowledgment.** This work was supported in part by Grant-in-Aid for Scientific Research (B), and the 21st century COE program (COE for a United Approach to New Materials Science) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. T.K. acknowledges financial support from the Japan Science and Technology Agency (Research for Promoting Technological Seeds, JST). This research was partly conducted at the Advanced Research Institute of Environmental Material Control Engineering, Katsura-Int'tech Center, Graduate School of Engineering, Kyoto University. We gratefully acknowledge Dr. Markus Waelchli (Bruker BioSpin Corporation) for performing  $^{13}\text{C}$  NMR gated decoupling and Inadequate measurements of **3c**.

**Supporting Information Available:** Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA066305G