

Rh(III)-Catalyzed Addition of Alkenyl C—H Bond to Isocyanates and Intramolecular Cyclization: Direct Synthesis 5-Ylidenepyrrol-2(5*H*)-ones

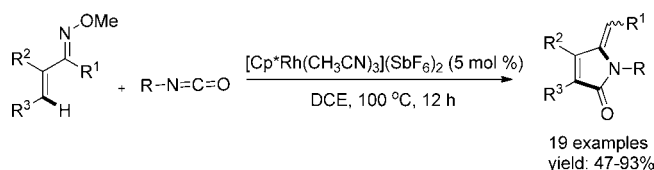
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ABSTRACT



The rhodium-catalyzed addition of an alkenyl C—H bond to isocyanates via sp^2 C—H bond activation followed by an intramolecular cyclization is described. This atom-economic and catalytic reaction affords a simple and straightforward access to biologically relevant 5-ylidene pyrrol-2(5*H*)-ones and can be carried out under mild and neutral conditions in the absence of any additives and environmentally hazardous waste production.

5-Ylidenepyrrol-2(5*H*)-ones are found in a number of bioactive natural products¹ as well as designed pharmaceutical molecules (Figure 1).² Despite its importance, only a few examples are reported for the preparation of 5-ylidenepyrrol-2(5*H*)-ones. The classical methods are based on using maleimides as starting materials, which undergo a Wittig reaction to give the target molecules.³ However, this procedure suffers from poor regioselectivity in the cases of unsymmetrical substrates. Several synthetic protocols have been developed in the past few years.⁴ Among them, Abarbri's electrophilic cyclization strategy generates

stoichiometric amounts of halide waste.^{4a,b} The transition-metal-mediated domino reaction requires the harsh reaction conditions and stoichiometric amounts of transition metal.^{4c} Yoshimatsu's method^{4d} is limited to selenium-stabilized alkynyl amide substrates, and Murakami's strategy suffers from harsh acidic reaction conditions.^{4e}

Therefore, the development of simple, effective, and catalytic methods for synthesis of valuable 5-ylidenepyrrol-2(5*H*)-ones under mild and neutral reaction conditions remains a great goal.

On the other hand, synthetic transformation via transition-metal-catalyzed C—H bond functionalization, one of the hot topics in current organic chemistry, has considerably improved the field of cross-coupling chemistry in terms of atom- and step-economical points of view.⁵ Recently, several investigations revealed that Rh^{III} complexes are promising catalysts for direct addition of C(sp^2)—H to polarized C=O⁶ and C—N⁷ multiple bonds

(1) Selected examples: (a) Celmer, W. D.; Solomons, I. A. *J. Am. Chem. Soc.* **1955**, *77*, 2861. (b) Simmons, C. J.; Marner, F.-J.; Cardellina, J. H., II; Moore, R. E.; Seff, K. *Tetrahedron Lett.* **1979**, *20*, 2003. (c) Cardellina, J. H., II; Moore, R. E. *Tetrahedron Lett.* **1979**, *20*, 2007. (d) Falk, H.; Grubmayr, K.; Herzig, U.; Hofer, O. *Tetrahedron Lett.* **1975**, *16*, 559. (e) Lightner, D. A.; Park, Y.-T. *J. Heterocycl. Chem.* **1977**, *14*, 415.

(2) Selected examples: (a) Falk, H. *The Chemistry of Linear Oligopyrrole Compounds*; Springer Verlag: New York, 1989. (b) Birru, W.; Fernley, R. T.; Graham, L. D.; Grusovin, J.; Hill, R. J.; Hofmann, A.; Howell, L.; James, P. J.; Jarvis, K. E.; Johnson, W. M.; Jones, D. A.; Leitner, C.; Liepa, A. J.; Lovrecz, G. O.; Lu, L.; Nearn, R. H.; O'Driscoll, B. J.; Phan, T.; Pollard, M.; Turner, K. A.; Winkler, D. A. *Bioorg. Med. Chem.* **2010**, *18*, 5647. (c) Kumar, N.; Iskander, G. WO2007085042. (d) Li, B.; Lyle, M. P. A.; Chen, G.; Li, J.; Hu, K.; Tang, L.; Alaoui-Jamali, M. A.; Webster, J. *Bioorg. Med. Chem.* **2007**, *15*, 4601.

(3) Gill, G. B.; James, G. D.; Oates, K. V.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, *23*, 2567.

(4) (a) Cherry, K.; Duchene, A.; Thibonnet, J.; Parrain, J.-L.; Anselmi, E.; Abarbri, M. *Synthesis* **2009**, 257. (b) Cherry, K.; Thibonnet, J.; Duchene, A.; Parrain, J.-L.; Abarbri, M. *Tetrahedron Lett.* **2004**, *45*, 2063. (c) Wuckelt, J.; Doring, M.; Langer, P.; Beckert, R.; Gorls, H. *J. Org. Chem.* **1999**, *64*, 365. (d) Yoshimatsu, M.; Machida, K.; Fuseya, T.; Shimizu, H.; Kataoka, T. *J. Chem. Soc., Perkins Trans. 1* **1996**, 1839. (e) Murakami, M.; Hayashi, M.; Ito, Y. *J. Org. Chem.* **1994**, *59*, 7910.

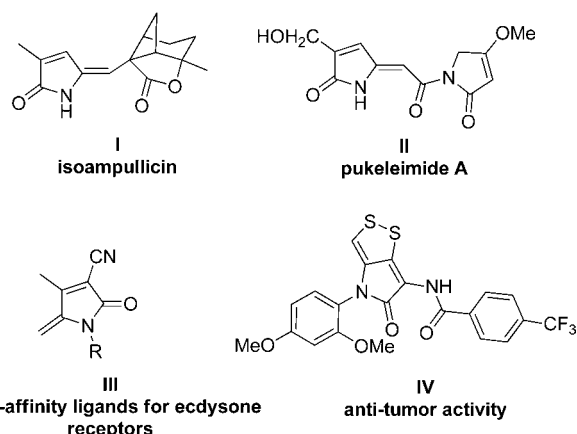
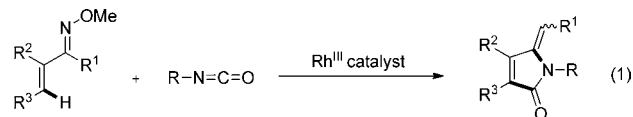


Figure 1. Structures of some biologically important 5-ylidene-pyrrol-2(5H)-ones.

via a chelation-assisted electrophilic metalation of the *ortho* C(sp²)–H bond. However, applying these directed arene C–H functionalization methods to alkenes is still challenging due to the increased reactivity and lability of olefins. Until now, only a few examples have been reported.⁸ Recently, Bergman and Ellman reported the addition of alkenyl C–H bonds of enamides to isocyanates.^{8a} Very recently, Shi^{8b} and Ellman^{8c} reported alkenyl C–H bond

addition to *N*-tosylimines and aldehydes using a pyridine and oxime as directing groups, respectively. Herein we report the direct Rh^{III}-catalyzed alkenyl C–H bond addition to isocyanates, wherein the directing group for C–H bond functionalization serves an auxiliary role of capturing the resulting amide group to afford synthetically and pharmaceutically important 5-ylidene-pyrrol-2(5H)-ones (eq 1). More importantly, in contrast to previous methods,^{3,4} this Rh^{III}-catalyzed annulation reaction⁹ proceeded in the absence of any additives and environmentally hazardous waste production under mild and neutral reaction conditions.



As indicated in Table 1, we initiated our studies by conducting the Rh^{III}-catalyzed addition of α,β -unsaturated oxime (**1a**) to *p*-tolyl isocyanate (**2a**). Although the use of 5 mol % of (Cp*RhCl₂)₂ proved unsuccessful in catalyzing this reaction (entry 1), (Cp*RhCl₂)₂ (5 mol %) in the presence of AgSbF₆ (20 mol %) in THF at 100 °C provided the desired product **3a** in 60% yield (entry 2). The prepared Rh^{III} precursor [Cp*Rh(CH₃CN)₃](SbF₆)₂ showed superior reactivity compared to that observed with (Cp*RhCl₂)₂ and AgSbF₆ (entry 3). A screen of solvents revealed DCE to be superior to THF (entries 3–6). A longer reaction time and a higher temperature (120 °C) did not result in any reduction in yield (entry 7) and lowering the temperature led to a slightly low conversion (entry 8). A lower catalyst

(5) For selected recent reviews on C–H bond functionalization, see: (a) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (b) Patureau, F. W.; Wencel-Delord, J.; Glorius, F. *Aldrichimica Acta* **2012**, *45*, 31. (c) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (d) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (e) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (f) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (g) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (h) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (i) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (j) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (k) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (l) Mkhali, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (m) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212. (n) Shi, R. B. F.; Engle, K. M.; Mangel, N.; Yu, J. Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (o) Park, Y. J.; Park, J. W.; Hun, C. H. *Acc. Chem. Res.* **2008**, *41*, 222. (p) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (q) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. For selected recent examples, see: (r) Yang, L.; Qian, B.; Huang, H. *Chem.—Eur. J.* **2012**, *18*, 9511. (s) Qian, B.; Shi, D.; Yang, L.; Huang, H. *Adv. Synth. Catal.* **2012**, *354*, 2146. (t) Zhao, P.; Niu, R.; Wang, F.; Han, K.; Li, X. *Org. Lett.* **2012**, *14*, 4166. (u) Zhao, P.; Wang, F.; Han, K.; Li, X. *Org. Lett.* **2012**, *14*, 5506. (v) Li, H.; Li, Y.; Zhang, X.-S.; Chen, K.; Wang, X.; Shi, Z.-J. *J. Am. Chem. Soc.* **2011**, *133*, 15244. (w) Zeng, R.; Fu, C.; Ma, S. *J. Am. Chem. Soc.* **2012**, *134*, 9597. (x) Xie, P.; Xie, Y.; Qian, B.; Zhou, H.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2012**, *134*, 9902. (y) Jia, X.; Zhang, S.; Wang, W.; Luo, F.; Cheng, J. *Org. Lett.* **2009**, *11*, 3120. (z) Chan, C.-W.; Zhou, Z.; Yu, W.-Y. *Adv. Synth. Catal.* **2011**, *353*, 2999. (aa) Xiao, F.; Shuai, Q.; Zhao, F.; Basle, O.; Deng, G.; Li, C.-J. *Org. Lett.* **2011**, *13*, 1614.

(6) For the rhodium(III)-catalyzed direct addition of arene C–H bonds to aldehydes, see: (a) Yang, L.; Correia, C. A.; Li, C.-J. *Adv. Synth. Catal.* **2011**, *353*, 1269. (b) Li, Y.; Zhang, X.-S.; Chen, K.; He, K.-H.; Pan, F.; Li, B.-J.; Shi, Z.-J. *Org. Lett.* **2012**, *14*, 636. (c) Park, J.; Park, E.; Kim, A.; Lee, Y.; Chi, K. W.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Org. Lett.* **2011**, *13*, 4390. (d) Yang, Y.; Zhou, B.; Li, Y. *Adv. Synth. Catal.* **2012**, *354*, 2916. (e) Sharma, S.; Park, E.; Park, J.; Kim, I. S. *Org. Lett.* **2012**, *14*, 906. (f) Zhou, B.; Yang, Y.; Li, Y. *Chem. Commun.* **2012**, *48*, 5163. (g) Lian, Y.; Bergman, R. G.; Ellman, J. A. *Chem. Sci* **2012**, *3*, 3088.

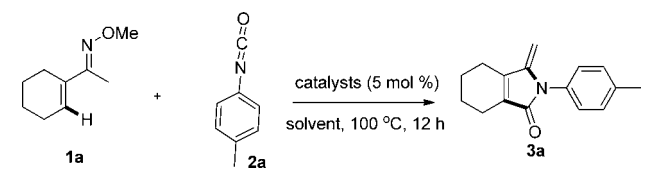
(7) For the rhodium(III)-catalyzed direct addition of arene C–H bonds to imines, isocyanates, isocyanide, and azides, see: (a) Tsai, A. S.; Taichert, M. E.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 1248. (b) Li, Y.; Li, B.-J.; Wang, W.-H.; Huang, W.-P.; Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 2115. (c) Taichert, M. E.; Incarvito, C. D.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 1482. (d) Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2012**, *14*, 2304. (e) Li, Y.; Zhang, X.-S.; Li, H.; Wang, W.-H.; Chen, K.; Li, B.-J.; Shi, Z.-J. *Chem. Sci.* **2012**, *3*, 1634. (f) Zhou, B.; Yang, Y.; Lin, S.; Li, Y. *Adv. Synth. Catal.* **2013**, *355*, 360. (g) Zhu, C.; Xie, W.; Falck, J. R. *Chem.—Eur. J.* **2011**, *17*, 12591. (h) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110. (i) Shi, J.; Zhou, B.; Yang, Y.; Li, Y. *Org. Biomol. Chem.* **2012**, *10*, 8953. (j) Ryu, J.; Shin, K.; Park, S. H.; Kim, J. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 9904. (k) Zhou, B.; Hou, W.; Yang, Y.; Li, Y. *Chem.—Eur. J.* **2013**, *19*, 4701.

(8) (a) Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 11430. (b) Li, Y.; Zhang, X.-S.; Zhu, Q.-L.; Shi, Z.-J. *Org. Lett.* **2012**, *14*, 4498. (c) Lian, Y.; Huber, T.; Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 629.

(9) Selected rhodium(III)-catalyzed annulation reaction using non-polar alkynes and alkenes as substrates: (a) Li, B.-J.; Wang, H.-Y.; Zhu, Q.-L.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 3948. (b) Wang, D.; Wang, F.; Song, G.; Li, X. *Angew. Chem., Int. Ed.* **2012**, *124*, 12514. (c) Pham, M. V.; Ye, B.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 10610. (d) Patureau, F. W.; Besset, T.; Kuhl, N.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2154. (e) Wei, X.; Zhao, M.; Du, Z.; Li, X. *Org. Lett.* **2011**, *13*, 4636. (f) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449. (g) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1338. (h) Patureau, F. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1977. (i) Su, Y.; Zhao, M.; Han, K.; Song, G.; Li, X. *Org. Lett.* **2010**, *12*, 5462. (j) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565. (k) Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2010**, *12*, 5688. (l) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350. (m) Wang, H.; Grohmann, C.; Nimphius, C.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 19592. (n) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (o) Besset, T.; Kuhl, N.; Patureau, F. W.; Glorius, F. *Chem.—Eur. J.* **2011**, *17*, 7167. (p) Patureau, F. W.; Nimphius, C.; Glorius, F. *Org. Lett.* **2011**, *13*, 6346. (q) Zhang, J.; Loh, T.-P. *Chem. Commun.* **2012**, *48*, 11232.

loading proved to be effective. At a 2.5 mol % catalyst loading, complete conversion into product was maintained by simply lengthening the reaction time to 24 h (entry 9). Finally, we were pleased to observe that this reaction was scaled-up without difficulty (entry 10).

Table 1. Reaction Optimization^a



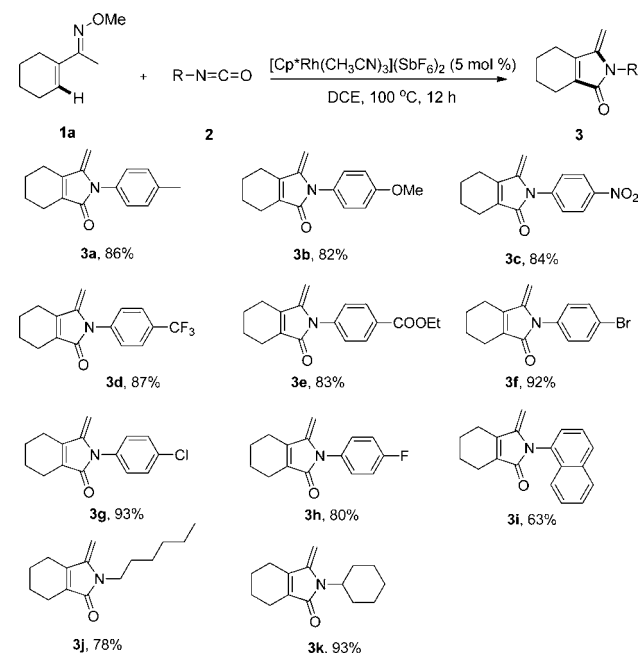
entries	catalysts (5 mol %)	solvent	yield ^b (%)
1	(Cp*RhCl ₂) ₂	THF	0
2	(Cp*RhCl ₂) ₂ , AgSbF ₆	THF	60
3	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	THF	73
4	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	PhMe	35
5	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	DCM	44
6	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	DCE	86
7 ^c	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	DCE	86
8 ^d	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	DCE	77 (87)
9 ^e	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	DCE	84
10 ^f	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	DCE	80

^a Reaction conditions: 0.2 mmol of **1a**, 0.3 mmol of **2a**, 0.01 mmol of Rh catalyst, 1 mL of solvent, 100 °C, 12 h. ^b Yield of isolated product. Yield in parentheses is based on recovered starting material. ^c The reaction was carried out at 120 °C for 20 h. ^d The reaction was carried out at 90 °C. ^e 2.5 mol % of catalyst was used. Reaction time is 24 h. ^f The reaction was scaled up to a 2 mmol substrate level.

With the optimal conditions established, we next investigated the substrate scope of various isocyanates in this transformation (Scheme 1). The isocyanates **2** allowed incorporation of a wide range of functionalization in the products; aromatic groups bearing electron-donating (**3a** and **3b**) or -withdrawing groups (**3c–h**) were tolerated and excellent yields were observed, irrespective of the electronic nature of the substituents on the phenyl ring. Notably, the tolerance of the ester (**3e**), bromo (**3f**), and chloro group (**3g**) offers the opportunity for further functionalization. In addition, 1-naphthyl isocyanate was also readily converted to the corresponding product (**3i**) in good yields. In addition to phenyl isocyanate, primary and secondary alkyl isocyanate substrates showed good reactivity, providing the corresponding products **3j** and **3k** in excellent yields.

To evaluate the scope of the present catalytic reaction, we next investigated the substrate scope with a range of α,β -unsaturated oximes (**1**) having different substitution patterns (Scheme 2). In addition to (*E*)-1-(cyclohex-1-en-1-yl)ethanone *O*-methyl oxime (**3a**), acyclic oximes were readily converted to the corresponding fully substituted 5-ylidene-pyrrol-2(5*H*)-ones (**3l–r**) in good yields. The variation of R³ in the oximes **1** to alkyl group (**3l**), phenyl group with electron-donating and electron-withdrawing substitution (**3m–p**) as well as to 2-naphthyl group (**3q**) led to moderate to good yields. We also explored variation at R¹ and established that ethyl group also work well in this

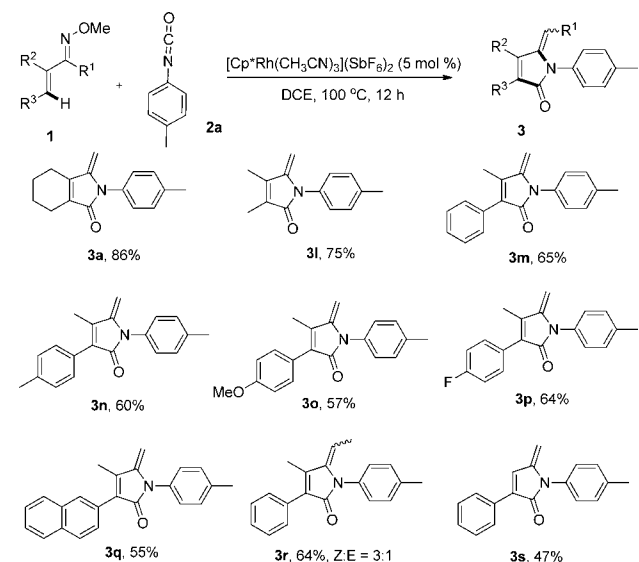
Scheme 1. Substrate Scope for Isocyanates^a



^a Reaction conditions: 0.2 mmol of **1a**, 0.3 mmol of **2**, 0.01 mmol of catalyst, 1 mL of DCE, 100 °C, 12 h. Yield of isolated product.

transformation (**3r**), providing easily separable *Z*- and *E*-isomers in a ratio of 3:1. The R² substituent is not essential for the success of the reaction, thereby enabling the preparation of 3-substituted 5-ylidene-pyrrol-2(5*H*)-ones (**3s**).

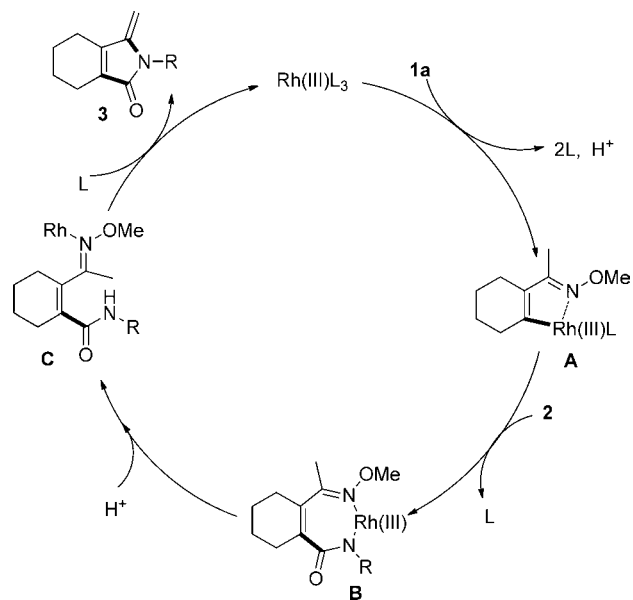
Scheme 2. Oxime Substrate Scope^a



^a Reaction conditions: 0.2 mmol of **1**, 0.3 mmol of **2a**, 0.01 mmol of catalyst, 1 mL of DCE, 100 °C, 12 h. Yield of isolated product.

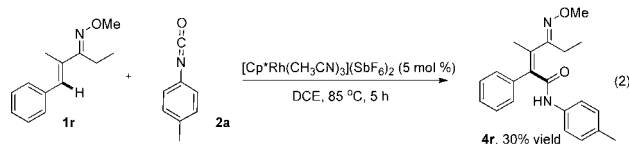
Based on the known chemistry of metal-catalyzed C–H bond activation and addition reactions,^{6,7} we tentatively

Scheme 3. Proposed Mechanism ($L = \text{CH}_3\text{CN}$)



propose the following reaction pathway (Scheme 3). The catalytic annulation reaction is initiated by the oxime-directed *ortho* C–H bond activation to form a relatively stable five-membered rhodacycle **A** and is accompanied by a release of one equivalent of proton (H^+). Selective insertion of isocyanate into the Rh–C bond of intermediate **A** gives the seven membered rhodacycle **B**, which is protonated to produce the intermediated **C**. The existence

of intermediate **C** was observed by carrying out the reaction at 85°C for 5 h (eq 2). Finally, intramolecular nucleophilic addition followed by elimination of one molecule of methoxyamine, provided compound **3a** and regenerated the catalyst.



In summary, we described herein a novel method for synthesis of substituted 5-ylidene pyrrol-2(5*H*)-ones via Rh^{III} -catalyzed addition of an alkenyl C–H bond to isocyanates with subsequent cyclization. This operationally simple approach exhibits high regioselectivity and functional group tolerance and is amenable to a number of different substituents on the isocyanates and α,β -unsaturated oximes. Most importantly, this reaction gives a simple and straightforward access to biologically relevant 5-ylidene pyrrol-2(5*H*)-ones and can be carried out under mild and neutral conditions in the absence of any additives and environmentally hazardous waste production. Because of the potential utility of the resulting 5-ylidene pyrrol-2(5*H*)-ones, we expect this catalytic method to be widely applied in the pharmaceutical fields.

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

The authors declare no competing financial interest.