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Highly Substituted 2-Amido-furans From Rh(II)-Catalyzed Cyclopropenations of Ynamides

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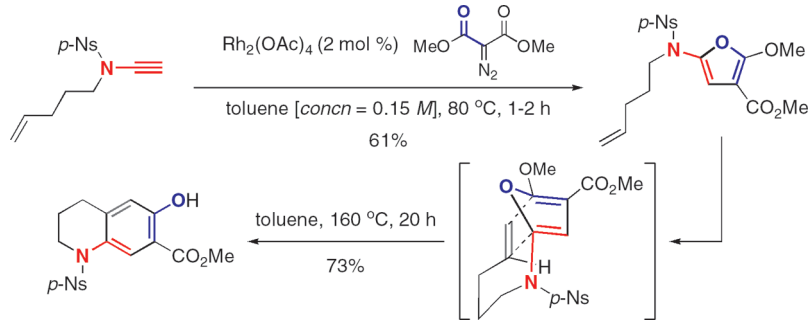
ABSTRACT



Rh(II)-catalyzed cyclopropenations of ynamides are described. Although an actual amido−cyclopropene intermediate may not be involved, these reactions provide a facile entry to highly substituted 2-amido-furans, thereby formerly constituting a [3 + 2] cycloaddition. An application of these de novo 2-amido-furans in N-tethered intramolecular [4 + 2] cycloadditions is also illustrated, leading to dihydroindoles and tetrahydroquinolines.

Our involvement with the chemistry of ynamides[1,2] and recent interest in cyclopropanation reactions[3,4] of various enamides[5−7] converged and provoked us to investigate a possible ynamide−cyclopropenation manifold[8] that could be useful in synthesis. As shown in Scheme 1, cyclopropenations of ynamides **1** could take place via metal decomposition of α-diazoacetates[4,9,10] to provide cyclopropenes **2** [pathway a] or metal-bound zwitterionic intermediates or 1,3-dipoles **3a** and **3b** [pathway b]. The former can ring-open to give zwitterion **4** [or leading to **3b** with the metal assistance],

(1) For reviews on ynamides, see: (a) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575. (b) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379. (c) Katritzky, A. R.; Jiang, R.; Singh, S. K. *Heterocycles* **2004**, *63*, 1455.

(2) For chemistry of ynamides just in the past 8 months from the literature, see: (a) Cockburn, N.; Karimi, E.; Tam, W. *J. Org. Chem.* **2009**, *74*, 5762. (b) Yao, B.; Liang, Z.; Niu, T.; Zhang, Y. *J. Org. Chem.* **2009**, *74*, 4630. (c) Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 4381. (d) Gourdet, B.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 3802. (e) Couty, S.; Liegault, B.; Meyer, C.; Cossy, J. *Tetrahedron* **2009**, *65*, 3882. (f) Deweerdt, K.; Birkedal, H.; Ruhland, T.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 221. (g) Alayrac, C.; Schollmeyer, D.; Witulski, B. *Chem. Commun.* **2009**, 1464. (h) Garcia, P.; Moulin, S.; Miclo, Y.; Leboeuf, D.; Gandon, V.; Aubert, C.; Malacria, M. *Chem.—Eur. J.* **2009**, *15*, 2129. (i) Sato, A.; Yorimitsu, H.; Oshima, K. *Synlett* **2009**, 28. (j) Oppenheimer, J.; Johnson, W. L.; Figueroa, R.; Hayashi, R.; Hsung, R. P. *Tetrahedron* **2009**, *64*, 5001. (k) Zhang, Y.; DeKorver, K. A.; Lohse, A. G.; Zhang, Y.-S.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 899.

(3) For a leading review on cyclopropanations, see: Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.

(4) For other recent reviews on cyclopropanations, see: (a) Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4493. (b) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041. (c) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603. (d) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213. (e) de Meijere, A.; Kozhushkov, S. I. *Chem. Rev.* **2000**, *100*, 93.

(5) Song, Z.; Lu, T.; Hsung, R. P.; Al-Rashid, Z. F.; Ko, C.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4069.

(6) Lu, T.; Song, Z.; Hsung, R. P. *Org. Lett.* **2008**, *10*, 541.

(7) Lu, T.; Hayashi, R.; Hsung, R. P.; DeKorver, K. A.; Lohse, A. G.; Song, Z.; Tang, Y. *Org. Biomol. Chem.* **2009**, *9*, 3331.

(8) For reviews on cyclopropenations of alkynes: (a) Padwa, A. *Molecules* **2000**, *6*, 1. (b) Padwa, A. *J. Organomet. Chem.* **2001**, *617−618*, 3. (c) Doyle, M. P.; Hu, W. *Synlett* **2001**, 1364.

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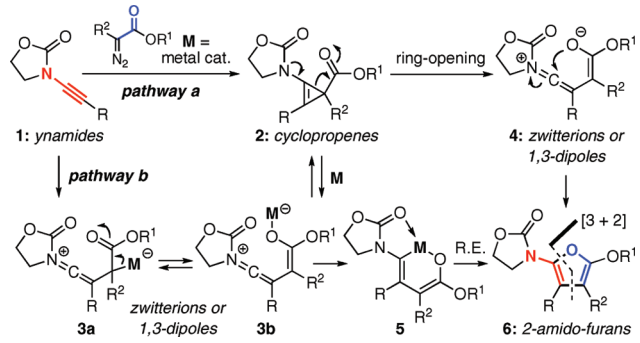
Scheme 1. Possible Cyclopropenations of Ynamides



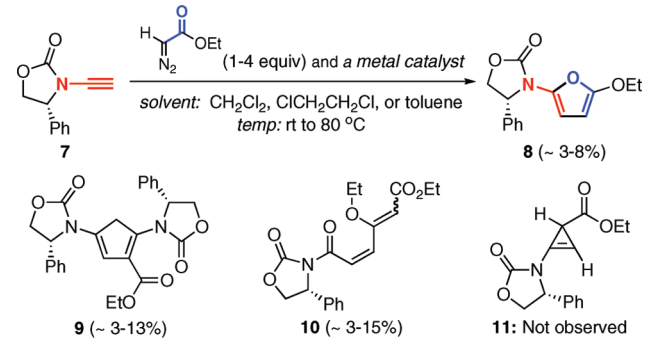
while the latter can in fact serve as intermediates en route to cyclopropenes **2** or provide metallo-oxocyclohexadiene **5** without actually proceeding through a cyclopropenation process.

While it is difficult to precisely distinguish the two pathways, we were interested in the possibility of observing the actual cyclopropenes **2**, which can be synthetically useful as demonstrated by an array of elegant work that has appeared in the recent literature.[8,11−13] Although cyclopropenations of alkynes have already been beautifully demonstrated as a practical entry to cyclopropenes,[8,11−13] accessing **2** could be challenging because with the amide substitution the ring-opening pathway leading to 1,3-dipoles **4** would be expedited even without the metal assistance.

On the other hand, we were equally intrigued by either metal bound zwitterionic intermediates **3a** and **3b** or nonmetal bound **4**, as both could afford synthetically useful 2-amido-furans **6**, respectively, via 5-*dig*-cyclization and reductive elimination [via **5**],[14,15] thereby formerly constituting a [3 + 2] cycloaddition. Given that there have been no studies on cyclopropenations of ynamides,[1,16] we explored this process and report here our success in the synthesis of highly substituted 2-amido-furans via a Rh(II)-catalyzed cyclopropenation of ynamides.

Initial cyclopropenation attempts were carried out employing ethyl α-diazoacetate with either well-known metal catalysts[8−13] such as $Rh_2(OAc)_4$ and $Cu(OTf)_2$ or newer Rh(II) catalysts such as $Rh_2(capy)_4$[17] and Dubois' catalyst[18] (Scheme 2). These attempts led to a range of low-yielding

Scheme 2. Initial Attempts with Ethyl α-Diazoacetate



Rh(II) catalysts (5-10 mol %): $Rh_2(OAc)_4$; $Rh_2(TFA)_4$; $Rh_2(capy)_4$; Dubois' cat.
other metal catalysts (5-10 mol %): $Cu(OTf)_2$; CuOTf; $Pd(OAc)_2$; $Ru_3(CO)_{12}$

products, which included 2-amido-furan **8**, cyclopentadiene **9**, and diene **10**.[19] However, amido-cyclopropene **11** was not one of them.[20] The formation of cyclopentadiene **9** could be readily rationalized through a [3 + 2] cycloaddition of zwitterion **12** along with an ensuing 1,5-H-shift to rearrange the conjugation (Scheme 3).[21] On the other hand, diene **10** could be derived from 2-amido-furan **8** through a second

(9) For reviews on cyclopropanations via metal-catalyzed decompositions of diazo-esters, see: (a) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. (b) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385. (c) Calter, M. A. *Curr. Org. Chem.* **1997**, *1*, 37. (d) Doyle, M. P.; Forbe, D. C. *Chem. Rev.* **1998**, *98*, 911. (e) Davies, H. M. L.; Autoulinakis, E. *Org. React.* **2003**, *57*, 1. (f) Maas, G. *Chem. Soc. Rev.* **2004**, *33*, 183. (g) Doyle, M. P. *J. Org. Chem.* **2006**, *71*, 9253.

(10) Also see: Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis With Diazo Compounds*; John Wiley and Sons, Inc., 1998; Chapter 4 and references therein.

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(12) For earlier reviews, see: (a) Deem, M. L. *Synthesis* **1972**, 675. (b) Billups, W. E.; Haley, M. M.; Lee, G.-A. *Chem. Rev.* **1989**, *89*, 1147. (c) Padwa, A.; Fryxell, G. E. *Adv. Strain Org. Chem.* **1991**, *1*, 117.

(13) For leading examples on cyclopropenations of alkynes and recent chemistry of cyclopropenes, see: (a) Panne, P.; Fox, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 22. (b) Chuprakov, S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 4463. (c) Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew Chem., Int. Ed.* **2007**, *46*, 4757. Yang, Z.; Xie, X.; Fox, J. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3960. (d) Rubin, M.; Gevorgyan, V. *Synthesis* **2004**, 796. (e) Davis, H. M.; Lee, G. H. *Org. Lett.* **2004**, *6*, 1233. (f) Doyle, M. P.; Hu, W. *Tetrahedron Lett.* **2000**, *41*, 6265. (g) Doyle, M. P.; Ene, D. G.; Forbes, D. C.; Pillow, T. H. *Chem. Commun.* **1999**, 1691. (h) Müller, P.; Imogai, H. *Tetrahedron: Asymmetry* **1998**, *9*, 4419. (i) Padwa, A.; Kassir, J. M.; Xu, S. L. *J. Org. Chem.* **1997**, *62*, 1642.

(14) For earlier documentations of furan formation from cyclopropenation processes, see: (a) Cho, S. K.; Liebeskind, L. S. *J. Org. Chem.* **1987**, *52*, 2631. (b) Davies, H. M. L.; Romines, K. R. *Tetrahedron* **1988**, *44*, 3343. (c) Müller, P.; Pautx, N.; Doyle, M. P.; Baheri, V. *Helv. Chim. Acta* **1990**, *73*, 1233. (d) Hoye, T. R.; Dinsmore, C. J.; Johnson, D. S.; Korkowski, P. F. *J. Org. Chem.* **1990**, *55*, 4518. (e) Padwa, A.; Kassir, J. M.; Xu, S. L. *J. Org. Chem.* **1991**, *56*, 6971. (f) Fairfax, D. J.; Austin, D. J.; Xu, S. L.; Padwa, A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2837.

(15) For recent examples of synthesizing furans from cyclopropenations, see: (a) Zhao, L.-B.; Guan, Z.-H.; Han, Y.; Xie, Y.-X.; He, S.; Liang, Y.-M. *J. Org. Chem.* **2007**, *72*, 10276. (b) Ma, S.; Lu, L.; Lu, P. *J. Org. Chem.* **2005**, *70*, 1063. (c) Rubin, M.; Gevorgyan, V. *Synthesis* **2004**, 796. (d) Padwa, A.; Straub, C. S. *J. Org. Chem.* **2003**, *68*, 227. (e) For an example of using iodonium ylide C see: Lee, Y. R.; Yoon, S. H. *Synth. Commun.* **2006**, *36*, 1941.

(16) For alone example of pyrrole-substituted ynamine-cyclopropenation, see: Pirrung, M. C.; Zhang, J.; Morehead, A. T., Jr. *Tetrahedron Lett.* **1994**, *35*, 6229.

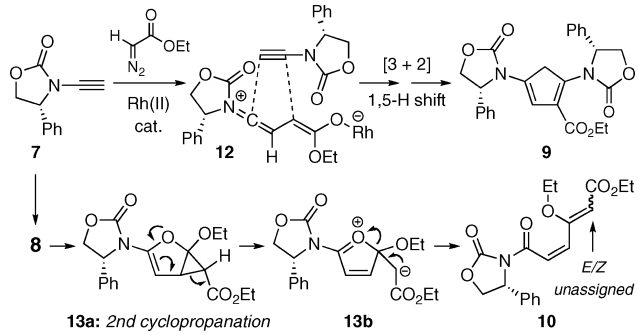
(17) $Rh_2(capy)_4$: dirhodium(II) tetrakis(caprolactam). For leading references, see: (a) Doyle, M. P.; Peterson, C. S.; Protopopova, M. N.; Marnett, A. B.; Parker, D. L., Jr.; Ene, D. G.; Lynch, V. *J. Am. Chem. Soc.* **1997**, *119*, 8826. (b) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N. *J. Am. Chem. Soc.* **1992**, *114*, 1874.

(18) Dubois' catalyst: Bis[rhodium(αα, α′,α′-tetramethyl-1,3-benzenedipropionic acid)]. For a leading reference, see: Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378.

(19) See Supporting Information.

(20) As suggested by a referee, we are currently attempting to detect possible formation of cyclopropenes at low temp using NMR.

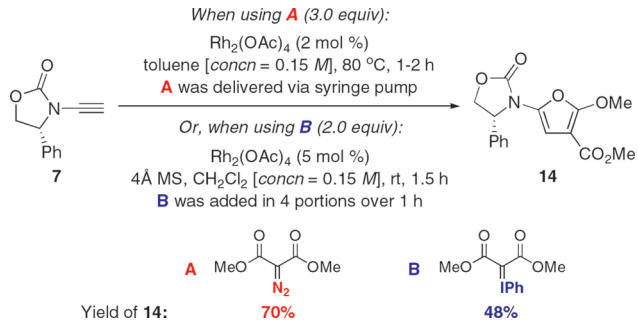
Scheme 3. Pathways to Cyclopentadiene **10** and Diene **11**



cyclopropanation process followed by cyclopropyl ring-opening [see **13a**[22]]. The stereochemistry of the vinylogous carbonate double bond in **10** was unassigned.

While cyclopentadiene **9** and diene **10** can be useful synthetically, 2-amido-furan **8** represents the most attractive building block in addition to being an emerging pharmacophore with a range of important biological activities.[23] Consequently, we focused on identifying an effective catalytic protocol for the furan formation, which constitutes a [3 + 2] cycloaddition. As shown in Scheme 4, we elected

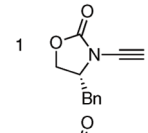
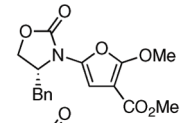
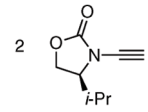
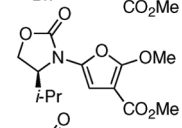
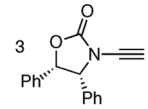
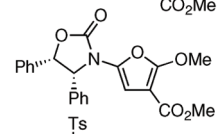
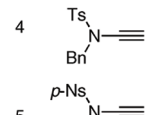
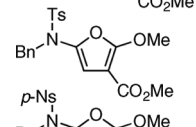
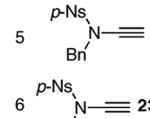
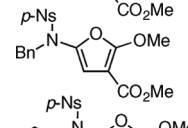
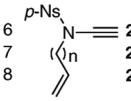
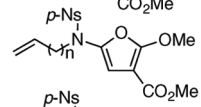
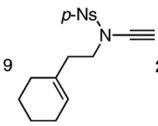
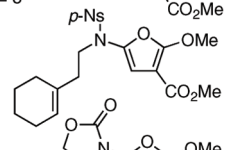
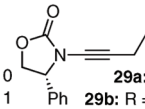
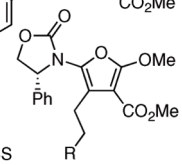
Scheme 4. Success with Diazo Malonate **A** and Ylide **B**



to use diazo dimethyl malonate **A** as well as phenyl iodonium ylide **B**[15e,24] as the cyclopropenating agent. While the corresponding cyclopropene product remained elusive, after optimizations, we were able to isolate the desired 2-amido-furan **14** in 70% and 48% yield, respectively, from employing **A** and **B**. It is noteworthy that the optimized conditions involved delivering diazo malonate **A** as a toluene solution via syringe pump over 1−2 h and addition of ylide **B** as solids in four separate portions over 1 h.

These protocols turned out to be general for constructing a diverse array of de novo 2-amido-furans as summarized in Table 1 and Table 2. In Table 1, a clear trend is that diazo malonate **A** is a better cyclopropenating agent than phenyl iodonium ylide **B**, consistently providing higher yields in all entries. In addition, sulfonyl-substituted ynamides **21**−**24** were quite feasible [entries 4−9] and so were terminally substituted ynamides **29a** and **29b** to give tetra-substituted furans **30a** and **30b**, albeit reactions

Table 1. General Synthesis of 2-Amido-furans

entry	ynamides		2-amido-furans	yield [%]:[a] using A[b]	B[c]
1		**15**		**18** 82	44
2		**16**		**19** 65	48
3		**17**		**20** 77	48
4		**21**		**25** 50	24
5		**22**		**26** 47	29
6 7 8		**23a:** n = 1 **23b:** n = 2 **23c:** n = 3		**27a** 49 **27b** 58 **27c** 61	32 35 47
9		**24**		**28** 52	39
10 11		**29a:** R = Ph **29b:** R = CH_2OTBS		**30a** 45[d] **30b** 24[d]	37[e] 22[e]

[a] Isolated yields. [b] When using **A**, all reactions were run in toluene at 80 °C with 2 mol % $Rh_2(OAc)_4$, and ynamide concn = 0.15 M. Reagent **A** [3.0 equiv] was delivered over 1−2 h as a solution in toluene [concn = 0.30 M] via a syringe pump. [c] When using **B**, all reactions were run in CH_2Cl_2 at rt for 1.5 h with 5 mol % $Rh_2(OAc)_4$ and 4 Å MS, and ynamide concn = 0.15 M. Reagent **B** [2.0 equiv] was delivered as solid in 0.5 equiv portions over 1 h. [d] 4.0 equiv of **A** and 5 mol % $Rh_2(OAc)_4$ were used, and the temp was 110 °C. [e] Reactions were carried out in $ClCH_2CH_2Cl$ [concn = 0.15 M] at 50 °C, and a total of 4.0 equiv of reagent **B** was used.

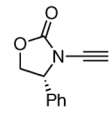
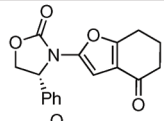
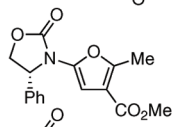
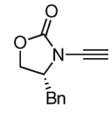
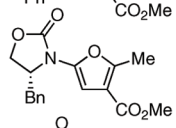
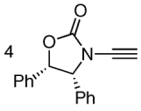
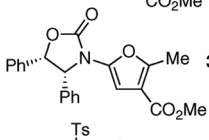
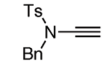
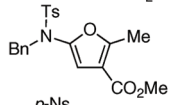
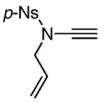
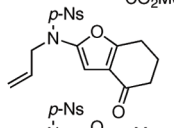
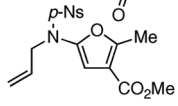
(21) For a beautiful precedent, see: Hoye, T. R.; Dinsmore, C. J. *Tetrahedron Lett.* **1991**, *32*, 3755.

(22) For reports on isolable products related to intermediate **13a**, see: (a) Böhm, C.; Schinnerl, M.; Bubert, C.; Zabel, M.; Labahn, T.; Parisini, E.; Reiser, O. *Eur. J. Org. Chem.* **2000**, 2955. (b) Schinnerl, M.; Böhm, C.; Seitz, M.; Reiser, O. *Tetrahedron: Asymmetry* **2003**, *14*, 765.

(23) For recent references on biological activities of amino-furans, see: (a) Patch, R. J.; Brandt, B. M.; Asgari, D.; Baindur, N.; Chadha, N. K.; Georgiadis, T.; Cheung, W. S.; Petrounia, I. P.; Donatelli, R. R.; Chaikin, M. A.; Player, M. R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6070. (b) Hall, A.; Billinton, A.; Brown, S. H.; Chowdhury, A.; Giblin, G. M. P.; Goldsmith, P.; Hurst, D. N.; Naylor, A.; Patel, S.; Scoccitti, T.; Theobald, P. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2684. (c) Isabel, L. C.; Garcia-Mera, X.; Stefanachi, A.; Nicolotti, O.; Isabel Loza, M.; Brea, J.; Esteve, C.; Segarra, V.; Vidal, B.; Carotti, A. *Bioorg. Med. Chem.* **2009**, *17*, 3618.

(24) For some examples of using iodonium ylides, see: (a) Batsila, C.; Kostakis, G.; Hadjiarapoglou, L. P. *Tetrahedron Lett.* **2002**, *43*, 5997. (b) Muller, P.; Allenbach, Y. F.; Bernardinelli, G. *Helv. Chim. Acta* **2003**, *86*, 3164. (c) Huang, X.-C.; Liu, Y.-L.; Liang, Y.; Pi, S.-F.; Wang, F.; Li, J.-H. *Org. Lett.* **2008**, *10*, 1525. (d) Also see ref 15e.

Table 2. Other Diazo Compounds and Iodonium Ylides

entry	ynamides		2-amido-furans		yield [%]:[a] C	D	E	F
1		7		31	69	56[b]		
2		7		32			57	55
3		15		33			61	48
4		17		34			63	47
5		21		35			31	39
6		23a		36	29			
7		23a		37			41	38

[a] Isolated yields. For reaction conditions, see footnotes b and c in Table 1. [b] 4 Å MS was not used, and 3.0 equiv of the ylide was added over 8 h with the reaction mixture being stirred at rt for 20 h after addition.

were slower and yields are lower as a consequence [entries 10 and 11].

In Table 2, we were able to examine other diazo compounds as well as iodonium ylides. While yields are again better with diazo compounds in comparison to the respective ylides, when using either diazo compound **E** or ylide **F**, the furan formation was highly regioselective [entries 2−5 and 7]. The regiochemistry was unambiguously assigned via X-ray single-crystal structure of 2-amido-furan **34** (Figure 1).

Lastly, we engaged in an immediate application of these 2-amido-furans given their power in serving as a platform for intramolecular Diels−Alder cycloadditions.[25] As shown in Scheme 5, after heating 2-amido-furans **27b** and **27c** at 160 °C in toluene in a sealed tube for 20 h, respective products dihydroindole **38** and tetrahydroquinoline **39** were

(25) For leading examples of intramolecular Diels−Alder reactions of 1-amido-furans, see: (a) Boonsombat, J.; Zhang, H.; Chughtai, M. J.; Hartung, J.; Padwa, A. *J. Org. Chem.* **2008**, *73*, 3539. (b) Zhang, H.; Padwa, A. *Org. Lett.* **2006**, *8*, 247. (c) Padwa, A.; Brodney, M. A.; Dimitroff, M. *J. Org. Chem.* **1998**, *63*, 5304.

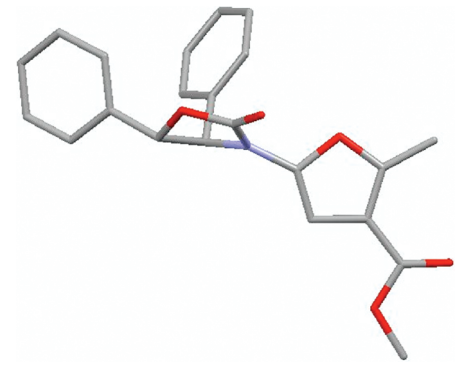
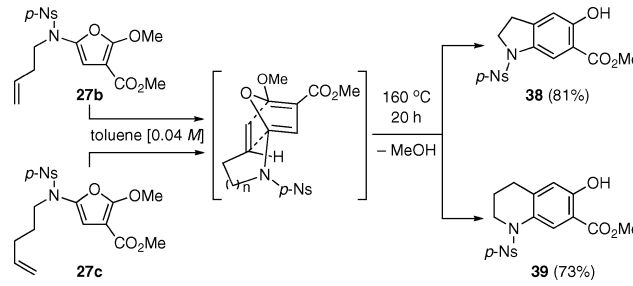


Figure 1. X-ray structure of 2-amido-furan **34**.

isolated in high yields. These final products are a result of loss of MeOH from the initial cycloadducts. It is noteworthy that the ability to carry out these N-tethered intramolecular Diels−Alder cycloadditions demonstrates a distinct advantage of furan synthesis from ynamides through the cyclopropenation process.

Scheme 5. Application of 2-Amido-furans in Diels−Alder



We have described here a process of $Rh_2(OAc)_4$-catalyzed cyclopropenations of ynamides. Although an actual amido−cyclopropene intermediate may not be involved, these reactions provide a facile entry to highly substituted de novo 2-amido-furans, which formerly constitute a [3 + 2] cycloaddition. Development of useful applications of this furan formation is underway.

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Supporting Information Available: Experimental procedures as well as characterizations, X-ray structural data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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