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

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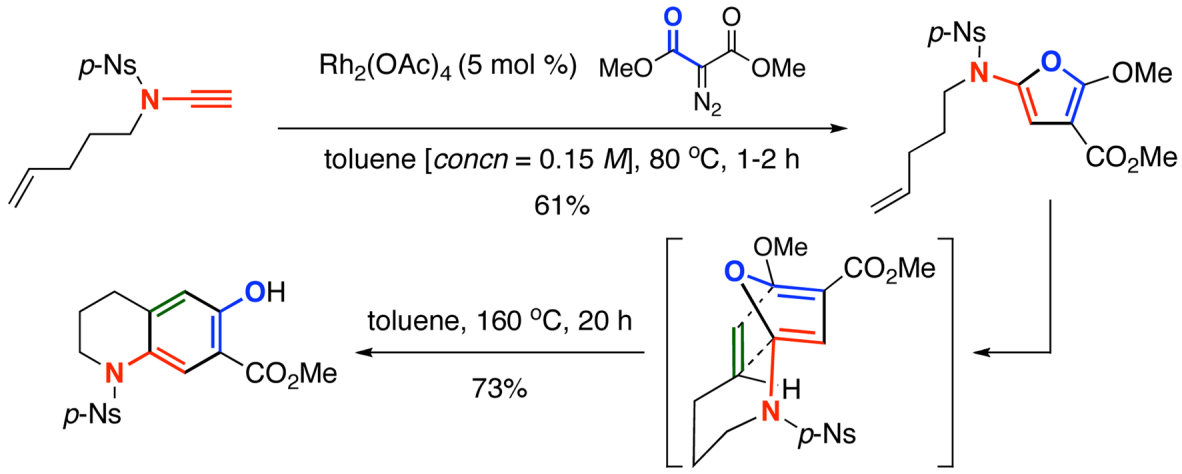
Abstract



Rh(II)-catalyzed cyclopropenations of ynamides are described. Although an actual amido-cylopropene intermediate may not be involved, these reactions provide a facile entry to highly substituted 2-amido-fuans, 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], while the latter can in fact serve as intermediates en route to cyclopropenes **2**, or providing metallo-oxocyclohexadiene **5** without actually proceeding through a cyclopropenation process.

While it is difficult to precisely distinguish the two pathways, we were interested with 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]

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

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' catalyst18 [Scheme 2]. These attempts led to a range of low yielding 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 cyclopropanation process followed by cyclopropyl ring-opening [see **13a**22]. The stereochemistry of the vinylogous carbonate double bond in **10** was unassigned.

While cyclopentadi ene **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 to use diazo dimethyl malonate **A** as well as phenyl iodonium ylide **B**[15e,24] as the cyclopropanating 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 cyclopropanating 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 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 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.

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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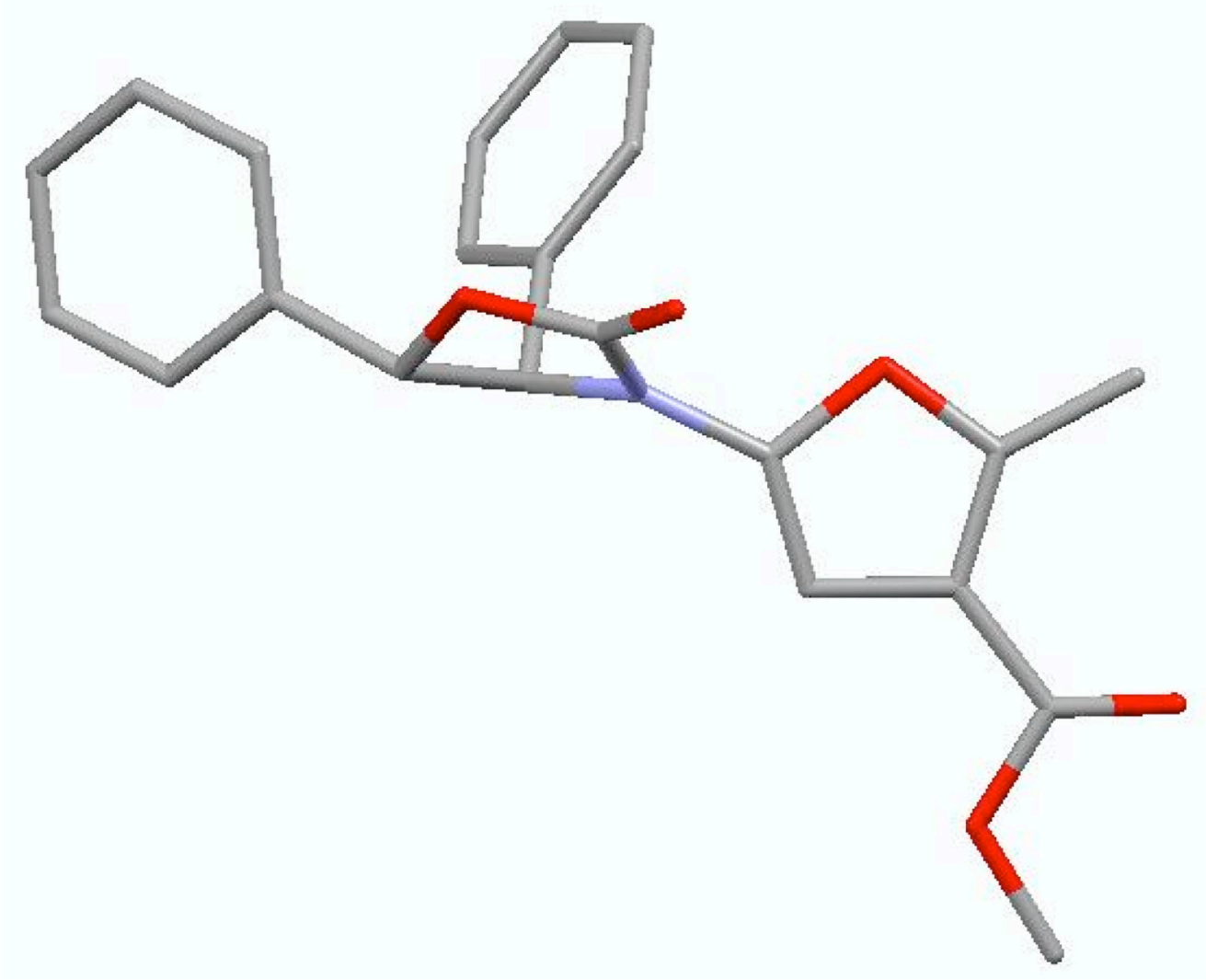
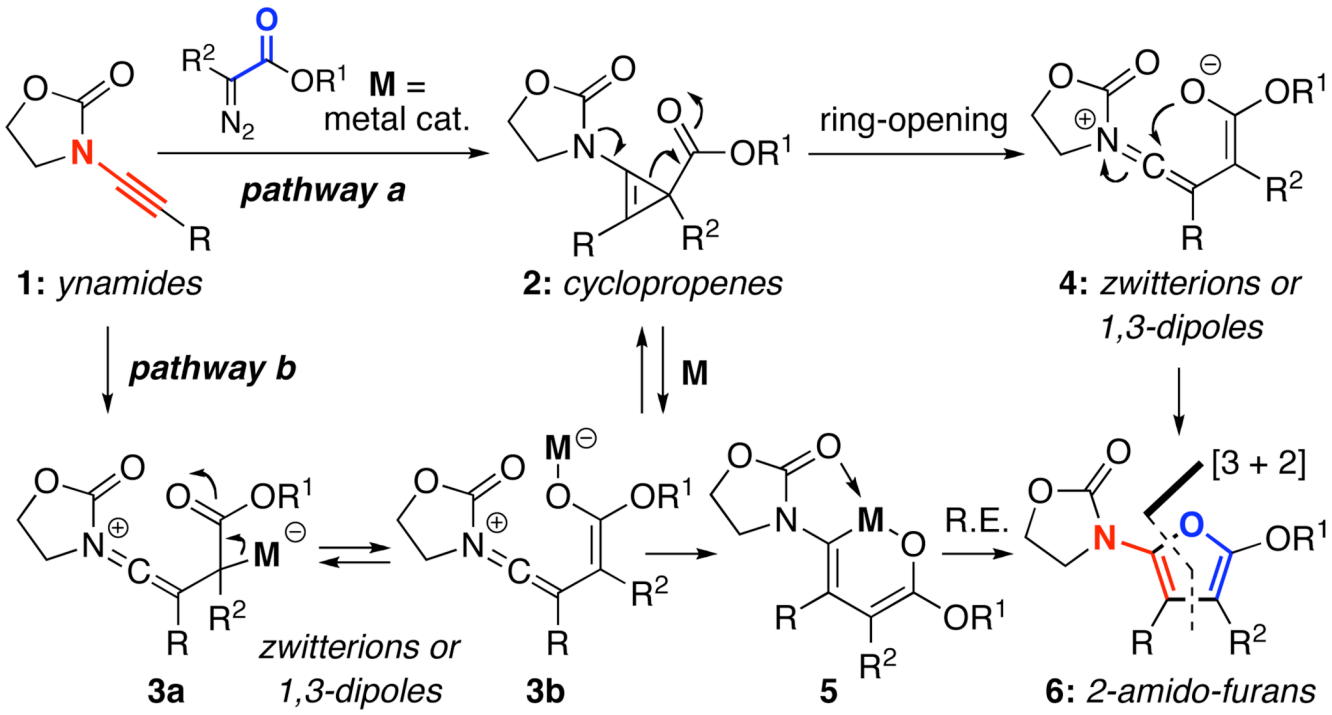
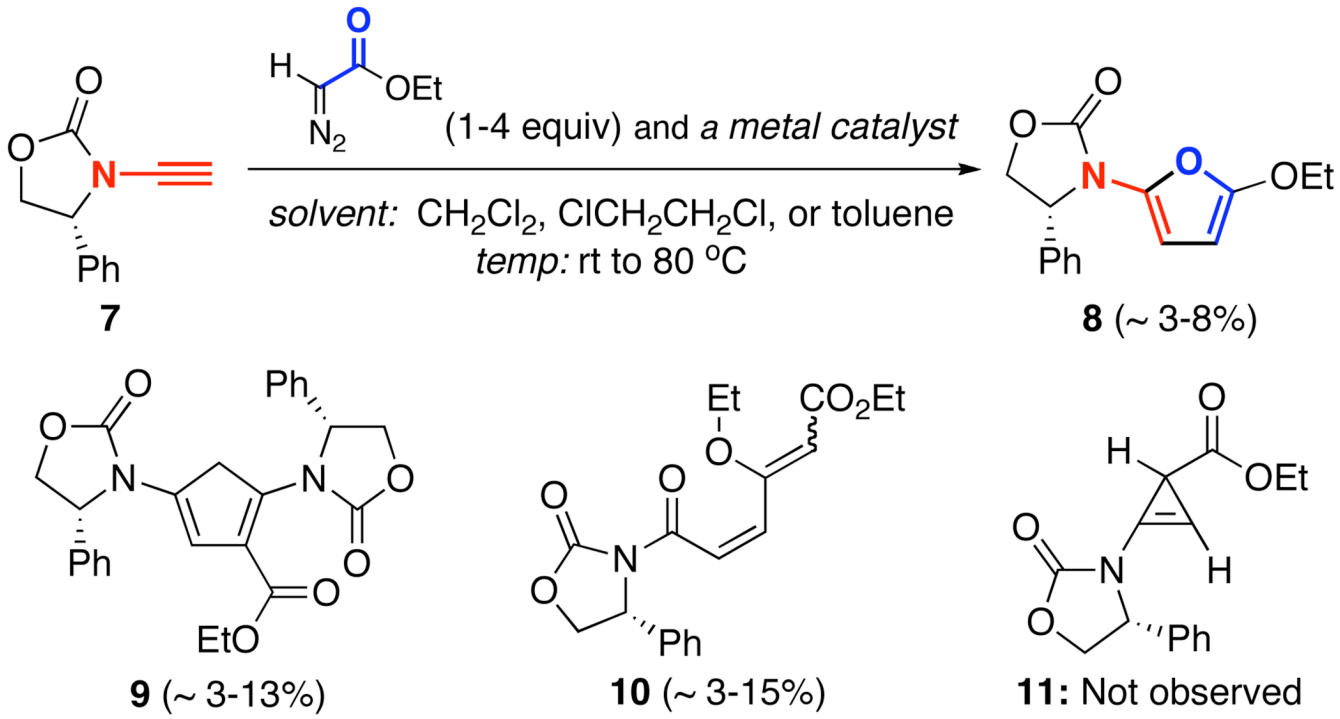


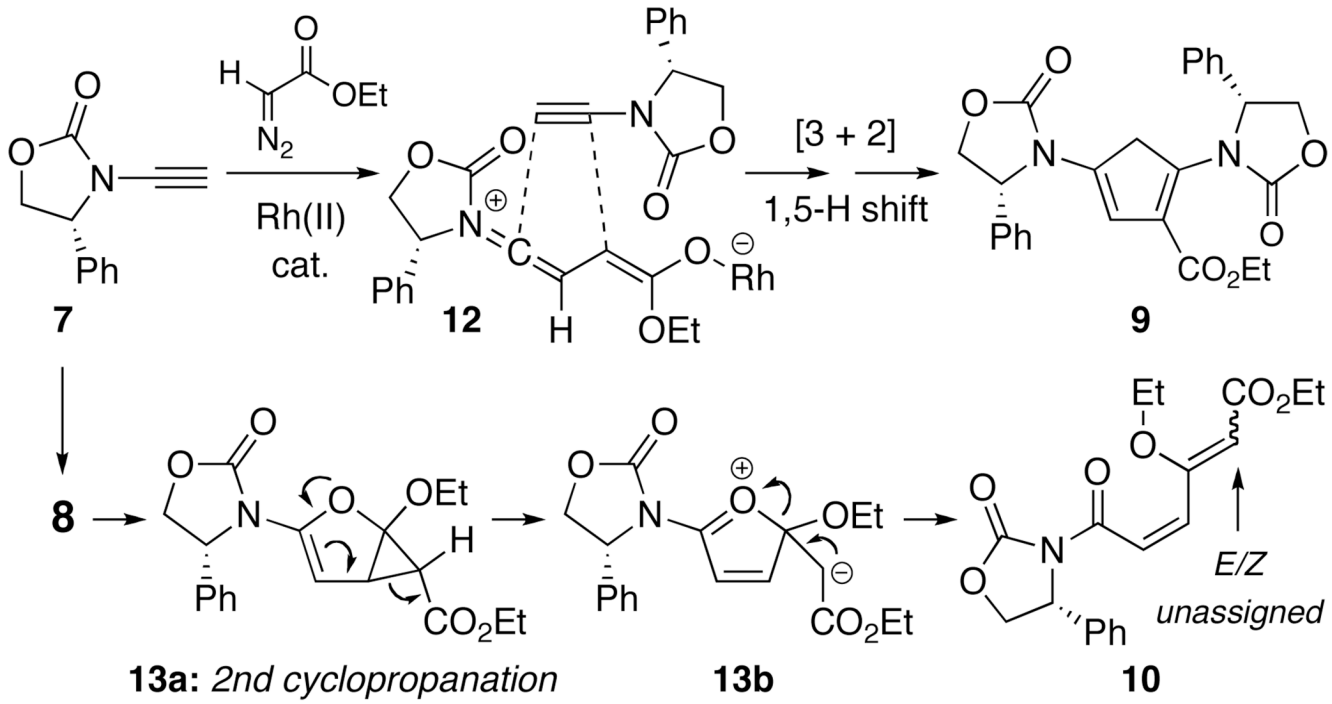
Figure 1.
X-Ray Structure of 2-Amido-Furan **34**.



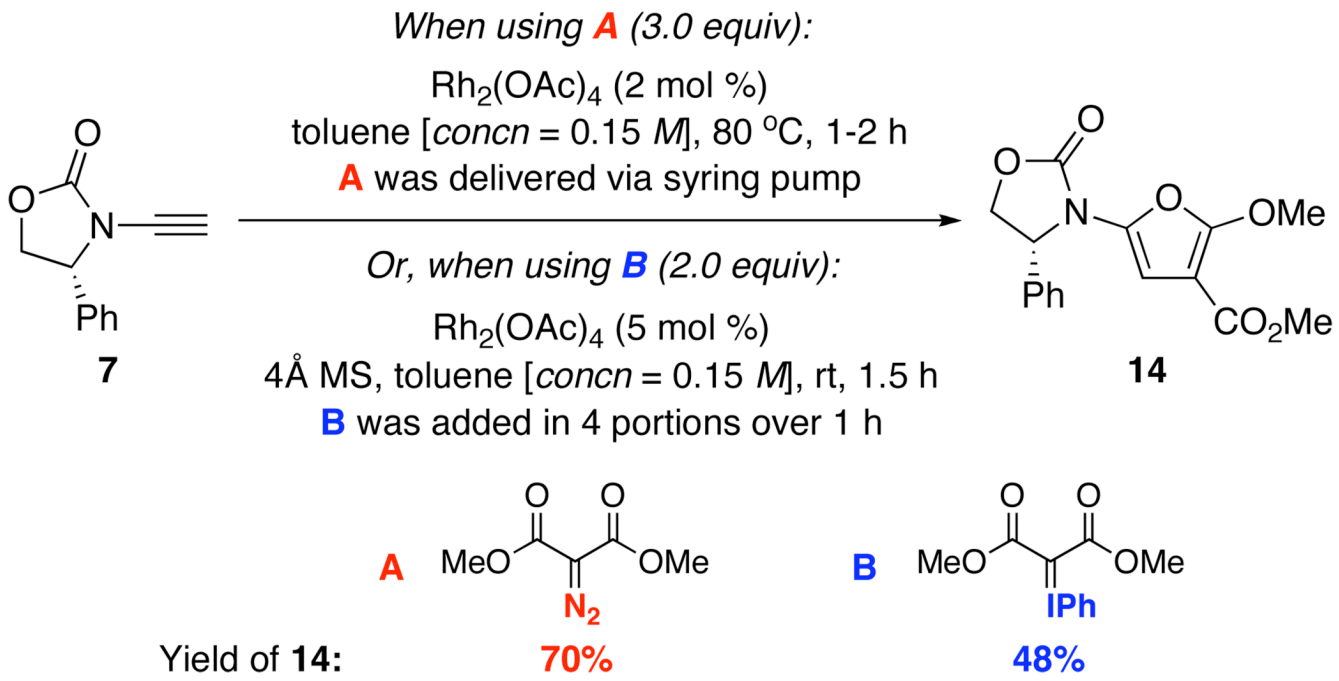
Scheme 1.
Possible Cyclopropenations of Ynamides.



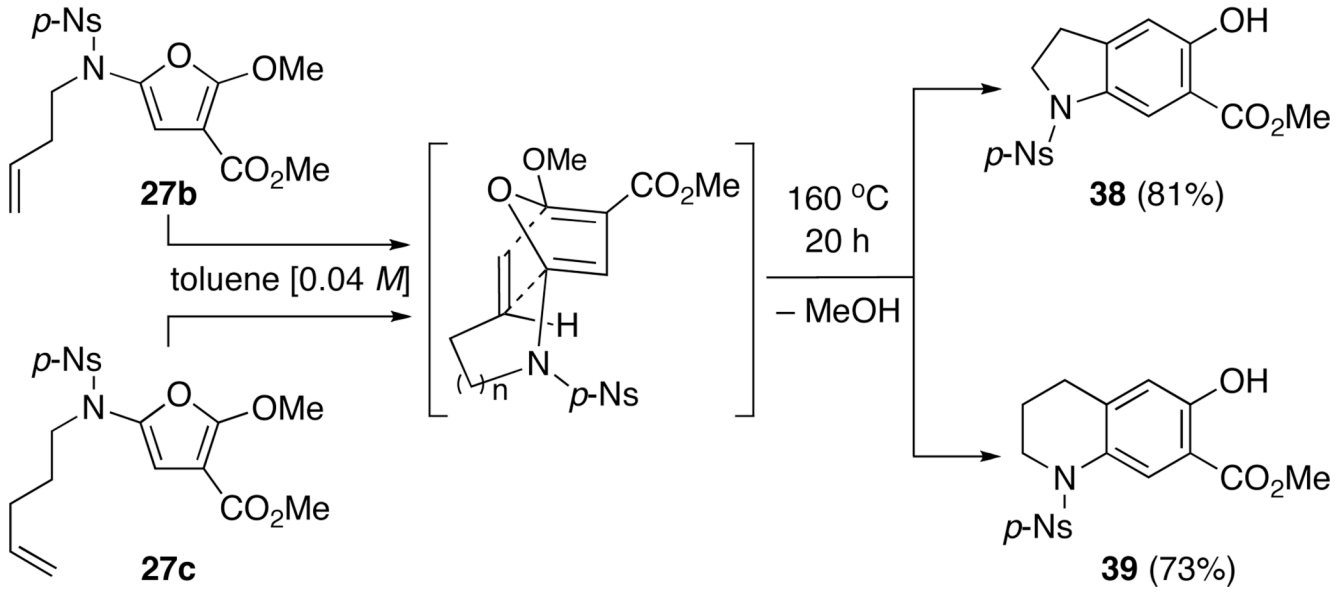
Scheme 2.
Initial Attempts with Ethyl α-Diazoacetate.



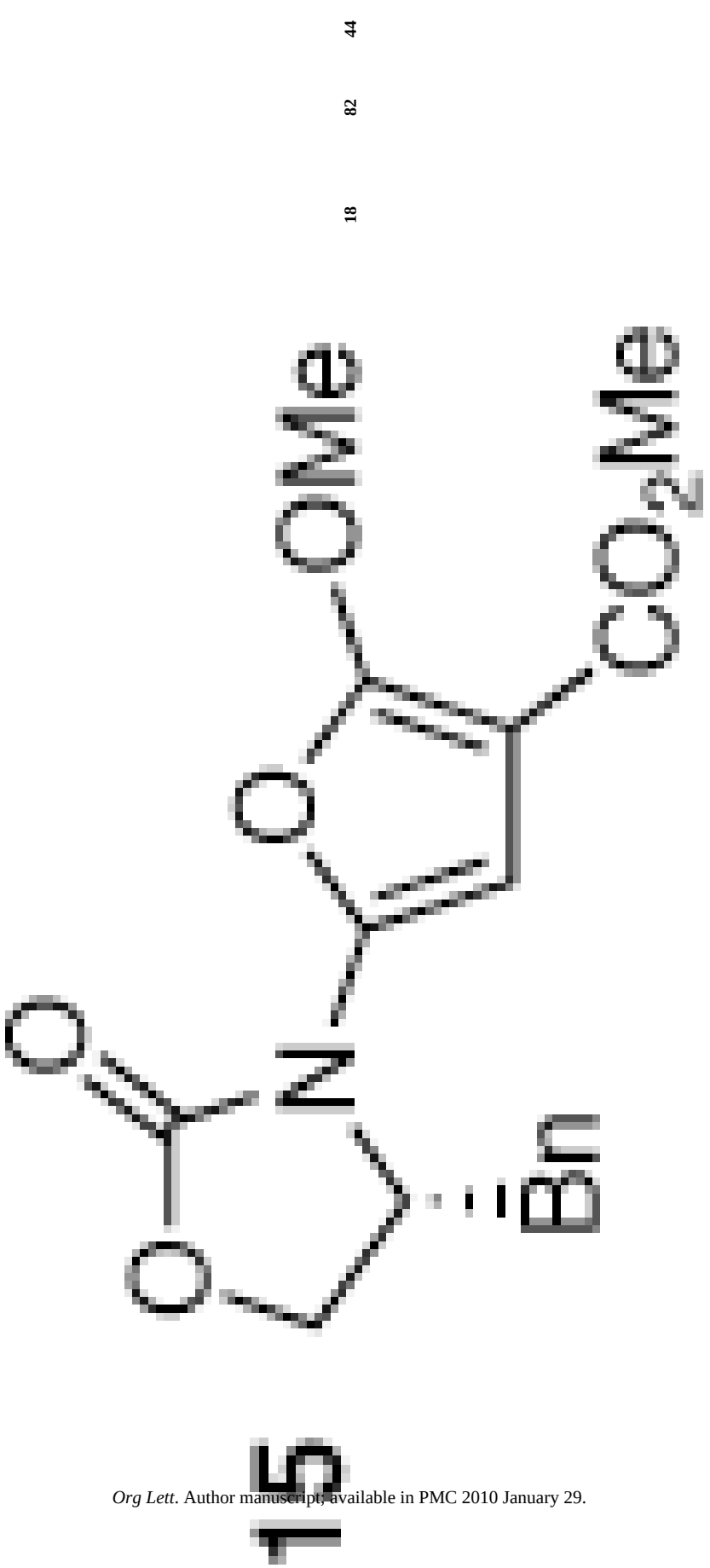
Scheme 3.
Pathways to Cyclopentadiene **10** and Diene **11**.



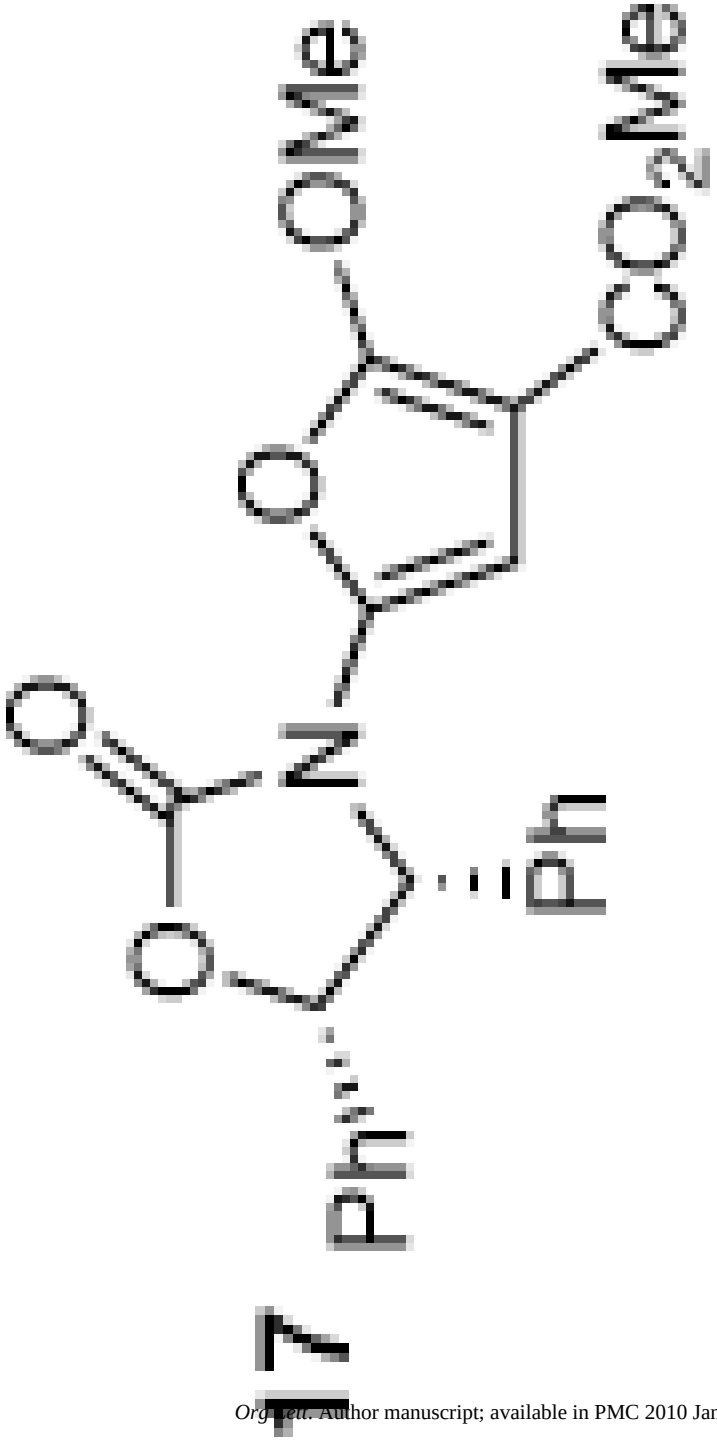
Scheme 4.
Success with Diazo Malonate **A** and Ylide **B**.



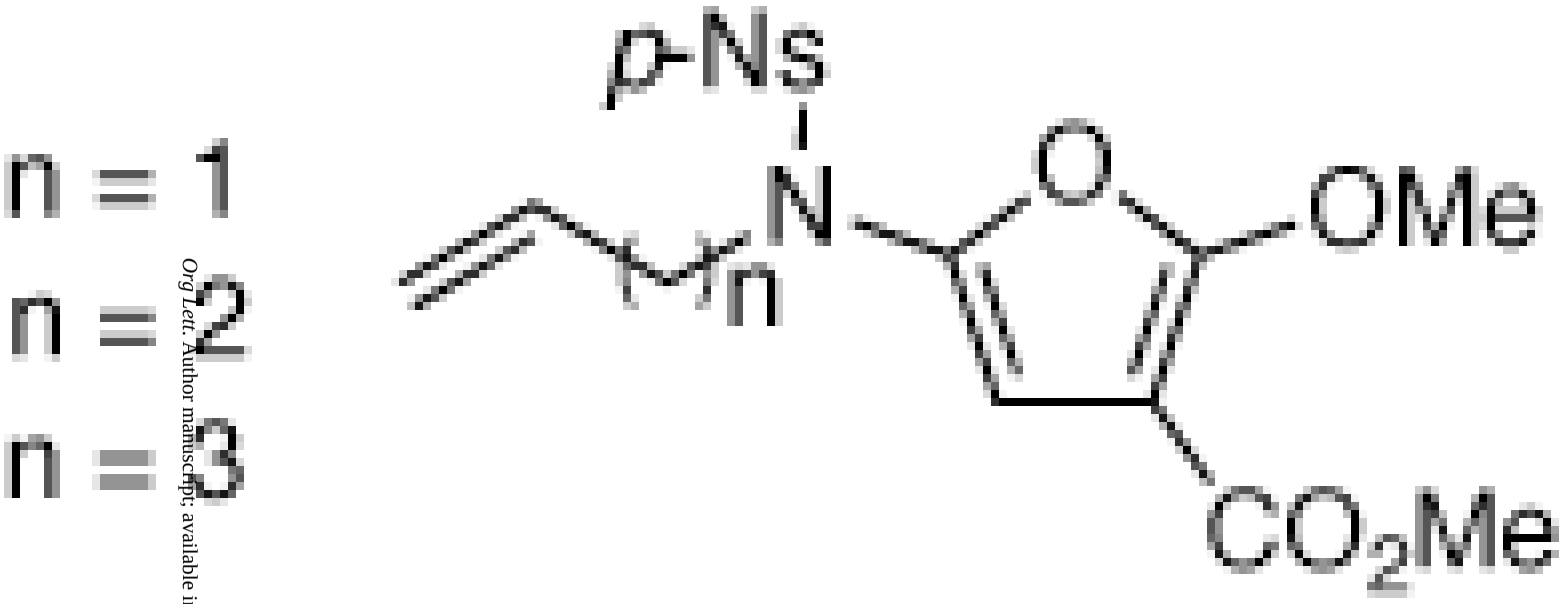
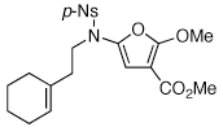
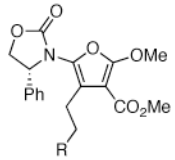
Scheme 5.
An Application of 2-Amido-Furans in Diels-Alder.

	2-amido-furans	yield [%]:[a]	using A[b]	B[c]
15		18	82	44

2-amido-furans	yield [%]:[a]	using A[b]	B[c]
16	19	65	48

2-amido-furans	yield [%]:[a]	using A[b]	B[c]
	20	77	48

2-amido-furans	yield [%]:[a]	using A[b]	B[c]
	25	50	24
	26	47	29

2-amido-furans	yield [%]:[a]	using A[b]	B[c]
	**27a**	**49**	**32**
	27b	**58**	**35**
	27c	**61**	**47**
	**28**	**52**	**39**
	**30a**	**45**[d]	**37**[e]
	30b	**24**[d]	**22**[e]

[3.0 equiv] was delivered over 1–2 h as a solution in toluene [*concn* = 0.30 *M*]

15 *M*. Reagent **B** [2.0 equiv] was delivered as solid in 0.5 equiv portions over 1

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[d] 4.0 equiv of **A** and 5 mol % $Rh_2(OAc)_4$ were used, and temp was 110 °C.

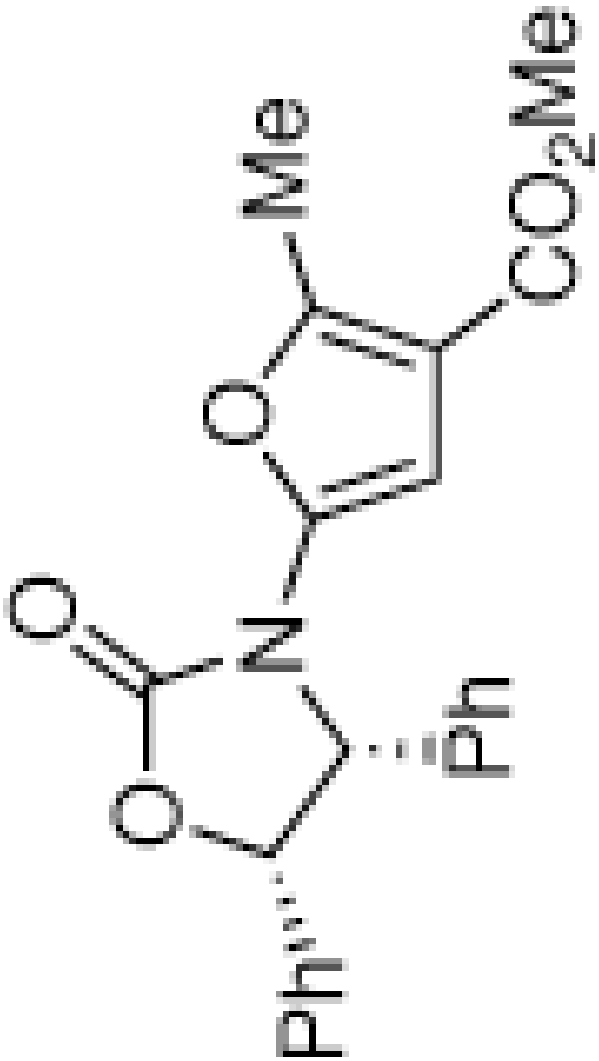
[e] Reactions were carried out in $ClCH_2CH_2Cl$ [*concn* = 0.15 *M*] at 50 °C, and a total of 4.0 equiv of reagent **B** was used.

2-amido-furans	yield [%]:[a] C	D	E	F
	31	69	56[b]	

	C	D	E	F
yield [%]:[a]	32	33	57	55
2-amido-furans			61	48

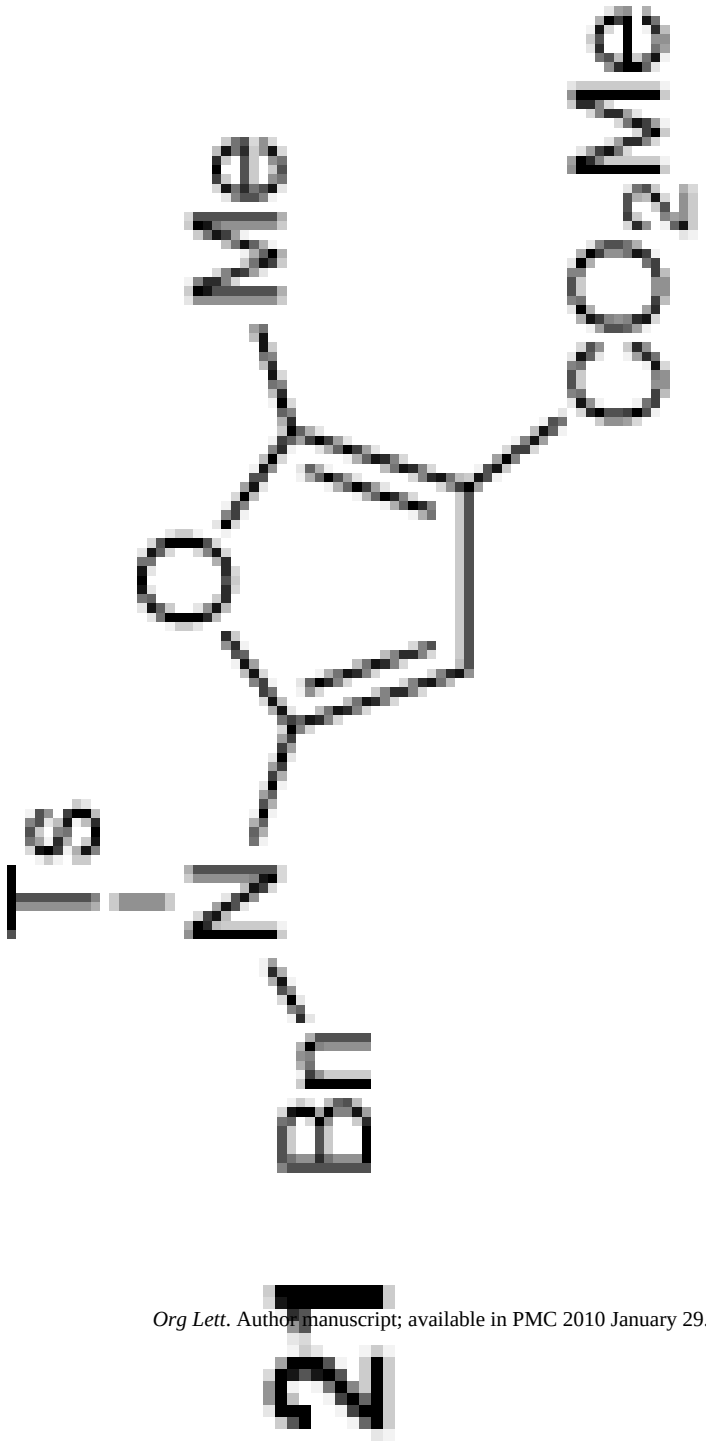
	C	D	E	F
yield [%]:[a]	34		63	47

2-amido-furans



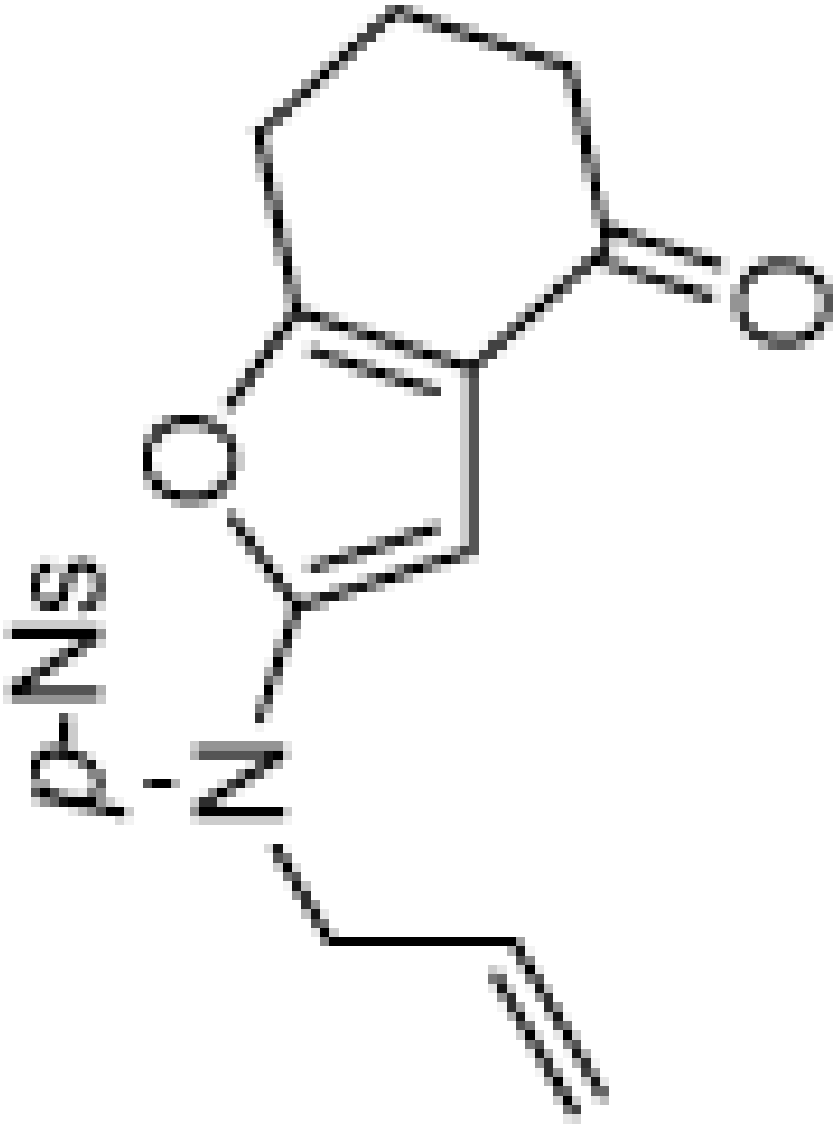
2-amido-furans

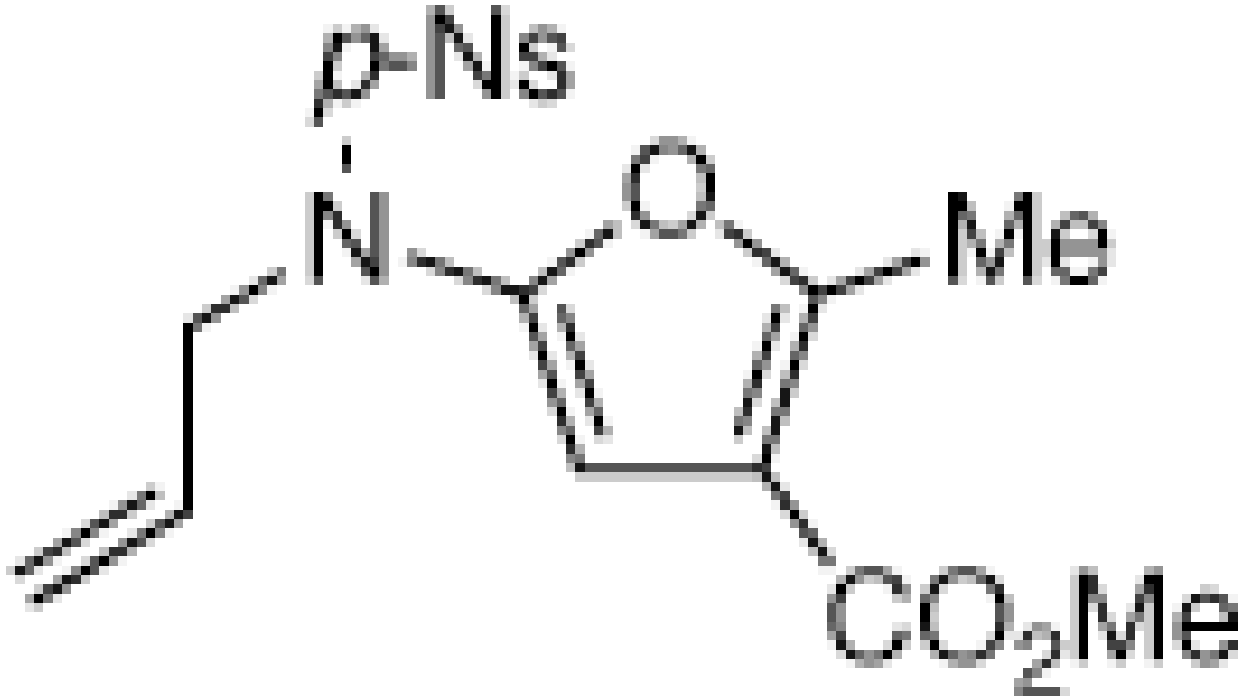
	yield [%]:[a]
C	35
D	
E	31
F	39

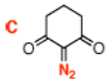
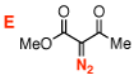
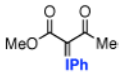


	C	D	E	F
yield [%]:[a]	29	36		

2-amido-furans



2-amido-furans	yield [%]:[a] C	D	E	F
	37		41	38

C  D  E  F 

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h after addition.