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A Metathesis-Based Approach to the Synthesis of Furans

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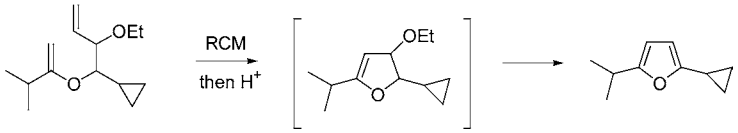
ABSTRACT



The enol ether-olefin ring-closing metathesis reaction has been employed to generate 2,3-dihydrofurans that are equipped with a leaving group. These substrates are at the correct oxidation state to undergo an acid-catalyzed aromatization, and this strategy has been utilized to provide a mild and rapid route (four steps) to a range of novel 2,5-disubstituted furans.

Ruthenium-catalyzed ring-closing metathesis (RCM) has recently emerged as a powerful tool for the synthetic organic chemist.[1] This can largely be attributed to the design of well-defined catalysts that show both increased activity and functional group tolerance.[2] Despite its widespread application in organic synthesis, the use of metathesis to produce aromatic compounds has only recently been highlighted in the literature.[3] One of the most popular approaches has involved the construction of benzo-fused systems, where the existing unsaturated framework results in the formation of a new aromatic ring upon RCM; this protocol has been used to produce benzofurans,[4] indoles,[5] and phenanthrenes.[6]

We have recently reported that the RCM reaction can be employed to form a 2,5-dihydrofuran unit that is equipped with a leaving group at the C-2 position.[7] This intermediate is at the correct oxidation state for aromatization, which proceeds upon treatment with catalytic acid to furnish the corresponding furan. The efficient synthesis of substituted furans continues to be of interest in organic synthesis[8] because of the presence of the furan nucleus in many commercially important pharmaceuticals[9] and flavors and in a variety of naturally occurring biologically active compounds.[10]

We envisaged that the furan core could also be accessed via the synthesis of a 2,3-dihydrofuran unit containing the required leaving group at C-3 (Scheme 1). This alternative

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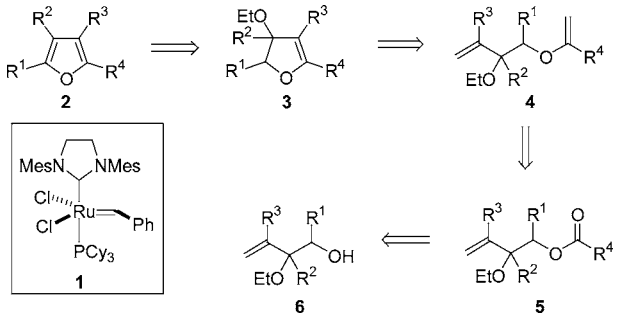
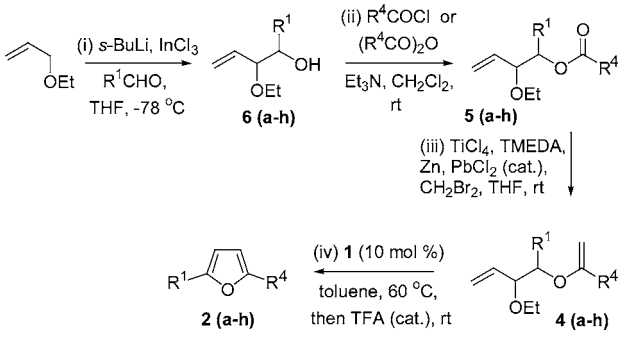
Scheme 1. General Strategy for Formation of Furans



disconnection would involve the formation of the cyclic enol ether **3** via RCM of the acyclic substrate **4**. While the enol ether-olefin RCM reaction using Schrock's molybdenum catalyst has been well documented, this transformation has proven unreliable using Grubbs' first generation ruthenium catalyst.[11] Recently, a number of research groups have reported that the more robust second generation catalyst **1** can successfully generate the corresponding cyclic enol ether.[12] The requisite acylic enol ether precursors could be prepared by olefination of the ester **5**;[13] thus, access to *vic*-diol mono ethers **6** should allow the rapid synthesis of a range of functionalized furans.

Our initial synthetic studies focused on the formation of 2,5-disubstitued furans using the approach as outlined in Scheme 1. It has previously been shown that allyloxy carbanions generally react with carbonyl compounds at the α-position[14] and that complete regiocontrol can be realized by the use of γ-alkoxy allylindium reagents.[15] This procedure was exploited to generate a range of *vic*-diol mono ethers **6a**−**h** in high yields starting from commercially available allyl ethyl ether (Scheme 2). These alcohols were then easily

Scheme 2. Protocol for Synthesis of 2,5-Disubstituted Furans



transformed into a number of ester derivatives **5a**−**h** using the appropriate acid chloride or anhydride. The Takai−Utimoto titanium-based olefination protocol was then employed to convert these precursors into the corresponding enol ethers **4a**−**h** in good yields. Finally, the cyclization was executed using 10 mol % of catalyst **1** to furnish the 2,5-disubstituted furan following acid-catalyzed aromatization.[16−18] It was found that the dihydrofuran substrate (see **3**) partially aromatized under the conditions of the RCM reaction, and therefore the aromatization was carried out in situ. The specific examples studied are given in Table 1. The studies

Table 1. Yields from the Sequence Depicted in Scheme 2

			yield (%)			
entry	R^1	R^4	(i)	(ii)	(iii)	(iv)
1 (a)	4-Br-C_6H_4	Ph	70	93	72	58
2 (b)	2-furyl	Ph	75	82	71	50[a]
3 (c)	cyclopropyl	*i*-Pr	91	99	79	54
4 (d)	Ph	Me	90	95	82	51
5 (e)	Ph	*i*-Pr	90	86	79	52
6 (f)	Ph	CF_3	90	77	62	0
7 (g)	Ph	*t*-Bu	90	70	0	
8 (h)	pentafluorophenyl	*i*-Pr	83	80	63	64[b]

[a] Reference 19. [b] Reference 20.

shown have revealed that the R^1 substituent can be aromatic, aliphatic (Table 1, entry 3), heteroaromatic (Table 1, entry 2), cyclic (Table 1, entry 3), or fluorinated (Table 1, entry 8).

The identity of the R^4 substituent originating from the ester proved to be less versatile. Primary and secondary aliphatic esters were successfully transformed into the desired furans in good yields (Table 1, entries 3−5 and 8), whereas the olefination failed with the tertiary substrate, presumably due to the steric bulk (Table 1, entry 7). The RCM of the trifluoromethyl-enol ether proceeded well to give the cyclic product in 70% yield (Table 1, entry 6); unfortunately, this did not aromatize under the previously developed conditions, and decomposition was eventually observed without formation of the corresponding furan. This failure was attributed to the electron-withdrawing nature of the trifluoromethyl group, which would destabilize the cation formed upon loss of ethanol in an E1 process.

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(16) (a) Takai, K.; Kataoka, Y.; Kahiuchi, T.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668. (b) Takai, K.; Okazoe, T.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 4410.

(17) Rainier has reported that the cyclic product of metathesis can be generated directly upon treatment with the Takai−Utimoto reagent: (a) Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997. (b) Majunder, U.; Rainier, J. D. *Tetrahedron Lett.* **2005**, *46*, 7209. However, this cyclization was not observed in our system, despite the use of modified conditions that used lead(II) chloride and high dilution in dichloromethane.

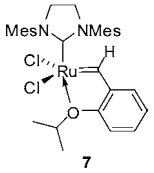
(18) (a) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565. (b) Nicolaou, K. C.; Postema, M. H. D.; Yue, E. W.; Nadin, A. *J. Am. Chem. Soc.* **1996**, *118*, 10335.

It has also been shown that the use of excess Takai–Utimoto reagent can result in the cyclopropanation of aromatic esters.[21] While this unwanted product was observed in some cases, it could be minimized by careful optimization of the conditions, which allowed access to triaryl aromatic compounds in good overall yields (Table 1, entries 1 and 2).

In some cases, it was found that the phosphine ligands from the catalyst coeluted with the furan product during column chromatography. Recently, a number of phosphine-free catalysts have been developed,[2] although these have rarely been utilized in the RCM of enol ethers.[22] We found that this transformation was possible with the Hoveyda–Grubbs second generation ruthenium catalyst **7**; pleasingly, this also resulted in shorter reaction times and increased yield for the metathesis of aliphatic enol ethers (Table 2).

Table 2. Yields of Metathesis/Aromatization (iv) Using Second Generation Hoveyda–Grubbs Catalyst

entry	R^1	R^4	yield (%)
1 (c)	cyclopropyl	*i*-Pr	60
2 (d)	Ph	Me	56
3 (e)	Ph	*i*-Pr	72
4 (h)	pentafluoro-phenyl	*i*-Pr	75[a]



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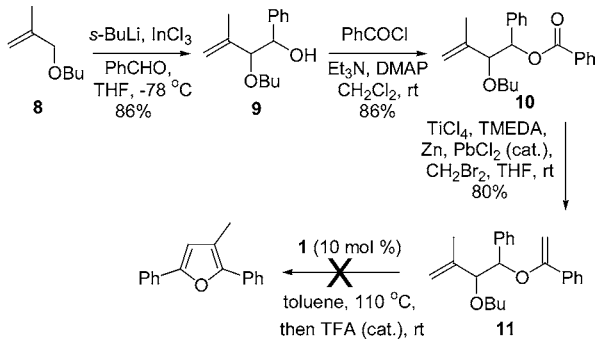
[a] Reference 20.

Unfortunately, this improvement in the process was not observed with the corresponding aromatic enol ethers.

Our attention then turned to the elaboration of substituents R^2 and R^3 (Scheme 1). The R^3 group was altered first, and a R^3 = Me series was synthesized using lithiation of 1-(2-methylallyloxy)butane **8** (Scheme 3).[24] The corresponding

Scheme 3. Elaboration of R^3

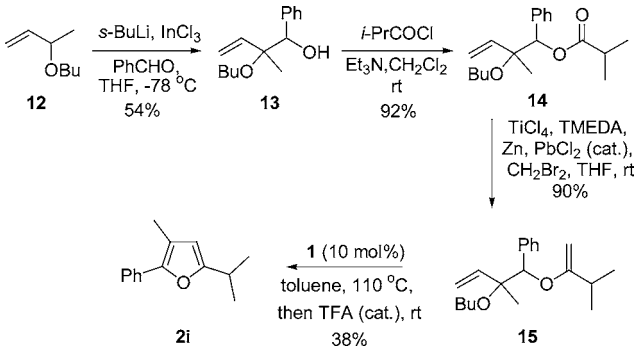


8 **9** **10** **11**

enol ether **11** was then generated using the previously developed protocol. Unfortunately, the RCM of this substrate was unsuccessful under a variety of conditions and returned only starting material. We believe that the catalyst is unable to initiate on the 1,1-disubstituted alkene within **11** as a result of the increased steric bulk around it, which has exceeded the limit tolerated by the catalyst.

Finally, the scope of the R^2 substituent was investigated. The metalation of the γ-alkoxy allylindium reagent **12**, followed by reaction with benzaldehyde, proceeded in good yield to give the alcohol **13** (Scheme 4).[22] This was converted

Scheme 4. Elaboration of R^2

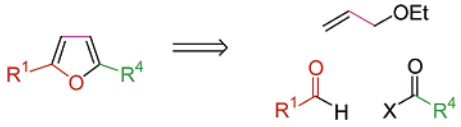


12 **13** **14** **2i** **15**

into enol ether **15**, and the RCM was carried out with catalyst **1** to give the desired trisubstituted furan **2i** in 38% yield. Alcohol **13**, formed by hydrolysis of unreacted enol ether, was also recovered in 56% yield; thus, the yield of furan **2i** is 86% based on recovered starting material. This conversion could not be improved by increasing catalyst loadings or by extending the reaction time. The RCM was also successful with catalyst **7**, but this did not lead to an enhancement in the yield. We believe that by creating a more sterically hindered alkene initation of the RCM process is retarded, resulting in competing initiation on the enol ether.[12a,25] This process may lead to the formation of a Fischer carbene that is not reactive toward metathesis and effectively sequesters the catalyst.

Despite limitations regarding the nature of the $R^{2/3}$ groups, it is noteworthy that by using this new method to prepare furans, the R^1 substituent is derived from an aldehyde, and R^4 is derived from a carboxylic acid equivalent (Scheme 5).

Scheme 5. Origin of the Furan Core



Thus, these substituents can be easily introduced from readily available precursors, providing great flexibility.

To conclude, we have developed a novel and mild synthetic approach to the furan core via an olefination/RCM

(19) 2-(Furan-2-yl)-5-phenylfuran was unstable, and decomposition was observed within hours after purification by column chromatography.

(20) The dihydrofuran product decomposed upon treatment with TFA; therefore, the aromatization was carried out by heating the metathesis reaction mixture at 60 °C with 1 equiv of PPTS until TLC analysis showed complete consumption of starting material.

protocol. This four-step method has been applied to generate an extensive range of 2,5-disubstituted furans where the substituents are readily derived from easily accessible carbonyl compounds.

Not only are we able to prepare differently substituted furans, but we are also able to introduce substituents that are not always easy to install by other methods (e.g., *i*-Pr, cyclopropyl). The flexibility and functional group tolerance of this sequence should provide excellent scope for future studies.

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Supporting Information Available: Copies of ^{1}H NMR spectra and detailed spectroscopic data for all new compounds and representative experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Lee, A.-L.; Malcolmson, S. J.; Puglisi, A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 5153.
(23) Formed in one step from 2-methyl-2-propen-1-ol.
(24) Formed in one step from 3-buten-2-ol.
(25) Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153.