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Rapid and Stereoselective Synthesis of Spirocyclic Ethers via the Intramolecular Piancatelli Rearrangement

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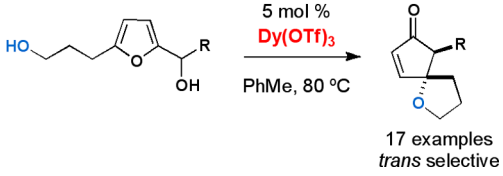
ABSTRACT

First example of a Piancatelli rearrangement with alcohols



The first example of a Piancatelli rearrangement of alcohols is demonstrated utilizing dysprosium(III) triflate as a catalyst to access oxaspirocycles in a highly diastereoselective manner. The cascade reaction constructs the spirocyclic ether ring system and the tertiary stereocenter in a single operation and is experimentally easy to perform.

Oxabicycles represent an important class of compounds in organic synthesis, and they have served as key intermediates in the total synthesis of numerous biologically active molecules (Figure 1), such as grindelic acid (**1**),[1] heliespirones B (**2**) and C (**3**),[2] ophiobolin A (**4**),[3] and sieboldine A (**5**).[4] Within the oxabicycle family, spirocyclic ethers (**6**) represent one of the most challenging structural motifs to access. To overcome synthetic challenges associated with their synthesis a number of strategies have been developed.[5] Generally, the routes rely on a two-step process where the tertiary carbon center and the spirocycle are formed in separate, discrete steps. An especially direct way to construct this motif would be to combine the construction of the ether and the formation of the spirocyclic ring system in a single operation using a cascade reaction. Despite the potential, this strategy remains largely unexplored.

Recently, we developed an intramolecular cascade rearrangement of 2-furylcarbinols to provide direct access to azaspirocycles, based on the aza-Piancatelli reaction (eq 1).[6] We recognized that the ability to employ alcohols in the intramolecular rearrangement of 2-furylcarbinols would provide an attractive alternative to stepwise spirocyclic ether synthesis. In addition, it would provide a platform to further expand the synthetic utility of the Piancatelli rearrangement, since there are no examples with alcohol

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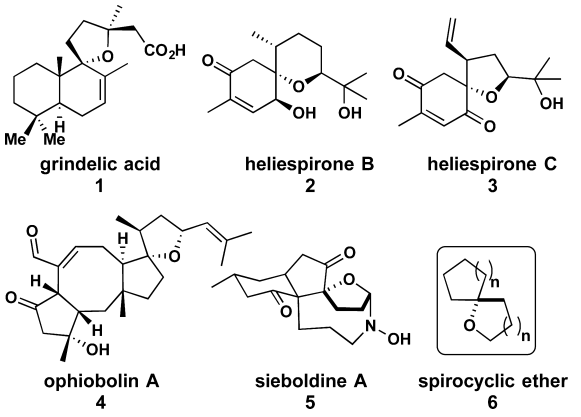
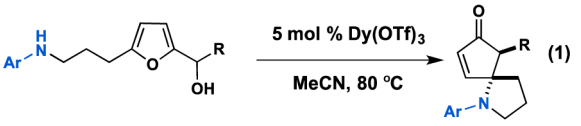


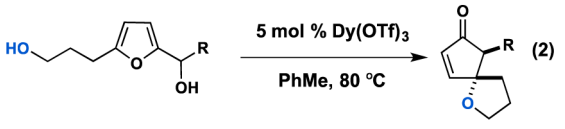
Figure 1. Natural products that contain spirocyclic ether motifs.

nucleophiles.[7] Herein, we report our studies leading to the development of a general protocol for the synthesis of spirocyclic ethers (eq 2). This reaction is highly diastereoselective, constructs the spirocyclic ether ring system and the tertiary stereocenter in a single operation, and is the first example of a Piancatelli rearrangement with alcohols.

Previous work: **Intramolecular aza-Piancatelli rearrangement:**



This work: **Intramolecular oxa-Piancatelli rearrangement:**



As shown in Figure 2, we envisioned a mechanistic scenario that would proceed analogous to the intramolecular aza-Piancatelli rearrangement.[6] We hypothesized that the critical step for the proposed rearrangement was the fate of spiroketal enol ether **8**. We envisioned using a Lewis acid to mediate the ring opening of **8** into oxocarbenium ion **A** by coordination to O-1. Once **A** is formed the desired process would rely on the same principles as the aza-Piancatelli reaction to govern the generation of spirocyclic cyclopentenone **9** through a Nazarov-type electrocyclization.[8]

Wu et al. have extensively studied the chemistry of spiroketal enol ether derivatives (**8**), but to our knowledge conditions that facilitate the formation of oxocarbenium ion **A** have never been reported.[9,10] Spiroketal enol ether

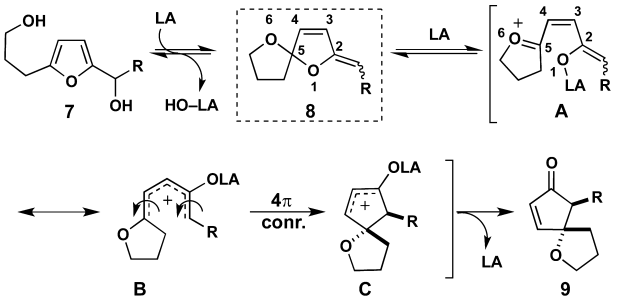
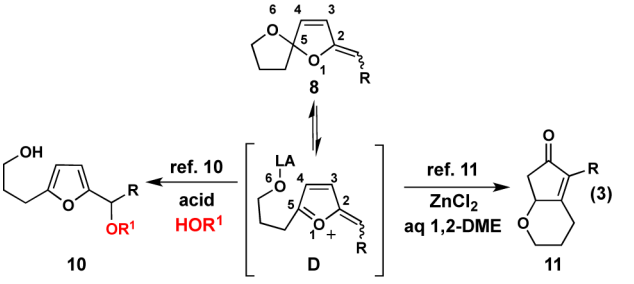


Figure 2. Proposed mechanism of the intramolecular Piancatelli rearrangement. LA = Lewis acid, conr. = conrotatory.

derivatives are known to ring open in the opposite direction in the presence of an acid catalyst, forming oxocarbenium ion **D** (eq 3). For example, in the presence of catalytic amounts of acid (*p*-TsOH or $ZnCl_2$), alcohols react with **8** via **D** to give furan derivative **10**.[11] Similar conditions, $ZnCl_2$ in aqueous 1,2-dimethoxyethane, are reported to convert **8** into oxabicyclic cyclopentenones (**11**).[12] Water was found to be critical for this transformation, and it is believed that oxocarbenium ion **D** is intercepted by water. Presumably from this proposed intermediate the reaction proceeds analogously to the Piancatelli rearrangement followed by formation of the more stable cyclopentenone product. We sought to develop a new strategy that would selectively proceed through oxocarbenium ion **A**.



Initially, a series of Lewis acid salts were tested for their ability to promote spirocyclic ether formation in acetonitrile (Table 1, entries 1−3). Unfortunately, we observed decomposition using $Dy(OTf)_3$ and $ZnCl_2$. Copper sulfate pentahydrate led exclusively to the formation of spiroketal enol ether **13**. A 16% yield of oxabicyclic cyclopentenone **15** was obtained when water was added to the reaction mixture catalyzed by $ZnCl_2$ (entry 4). Attempts to use other Brønsted or rare earth Lewis acids (CSA, HCl, TFA, AcOH, H_2SO_4, PMMA, PTSA, $Sc(OTf)_3$, $DyCl_3$) were also unsuccessful at catalyzing the transformation of **12** into **14**. However, spiroketal enol ether **13** could be formed under a variety of conditions, including heating in toluene in the absence of catalyst (entry 5). Upon closer analysis of

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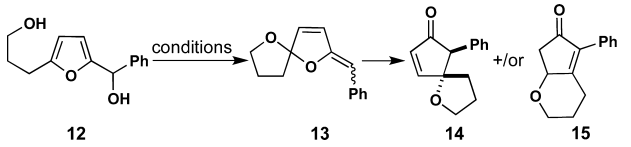
the reaction, we found that ketal **13** forms and decomposition was occurring from this species.

Table 1. Optimization Studies for Spirocyclic Ether Synthesis



12 13 14 15

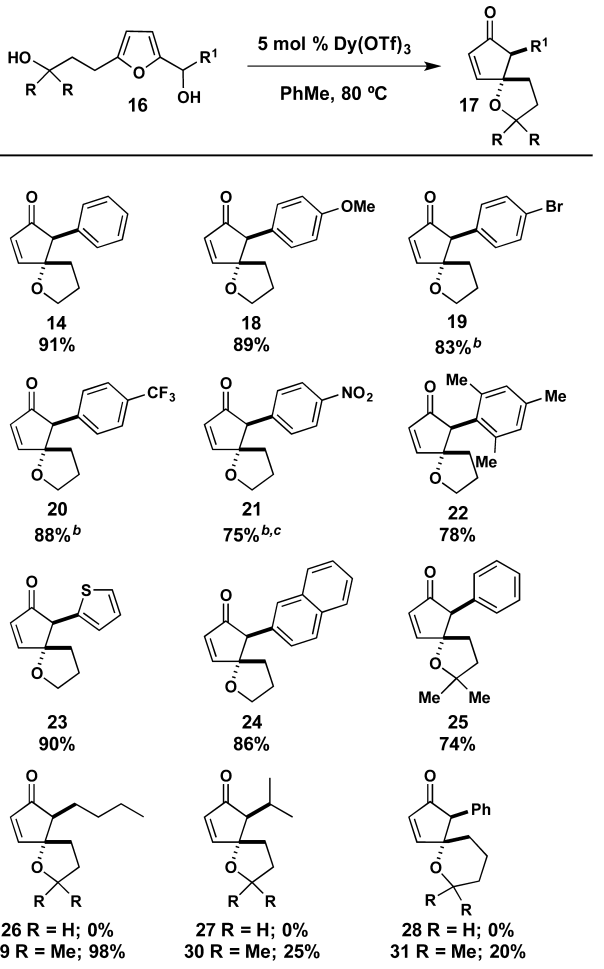
entry	catalyst	solvent	temp (°C)	yield (%)[a] **13:14:15**
1	$Dy(OTf)_3$	MeCN	80	decomp
2	$ZnCl_2$	MeCN	80	decomp
3	$CuSO_4 \cdot 5H_2O$	MeCN	60	33:0:0
4	$ZnCl_2$	$MeCN/H_2O$	80	0:0:16
5	–	PhMe	60	28:0:0[b]
6	$Dy(OTf)_3$	$MeCN,K_2CO_3$	60	71:0:0
7	$Dy(OTf)_3$	PhMe	60	0:89:0[c]
8	**$Dy(OTf)_3$**	**PhMe**	**80**	**0:91:0**[d]
9	$Dy(OTf)_3$	PhMe	100	0:73:0[e]
10	$Dy(OTf)_3$	$PhMe/H_2O$	80	0:82:0

[a] Yield of isolated product. [b] Reaction quenched after 6 d. Base-washed glassware was used. [c] Reaction was complete in 20 h. **13** could be isolated in 82% yield when the reaction was quenched after 2.5 h. [d] Reaction was complete in 6 h. [e] Reaction was complete in 2 h.

Knowing that the formation of **13** was facile, we shifted our focus to the reactivity of the spiroketal enol ether (**13**). It has been reported that the choice of solvent can affect oxocarbenium ion reactivity.[13] We were pleased to find that the desired transformation to **14** could be realized using $Dy(OTf)_3$ as the catalyst and toluene as the solvent. It is critical that the reactions be run in base-washed glassware, but an inert atmosphere and distilled solvents are unnecessary.[14] Pleasingly, it was found that increasing the reaction temperature resulted in an enhanced rate of conversion (20 to 2 h, entries 7–9) with little effect on the isolated yield. We settled on 80 °C as the optimal temperature; however for sluggish reactions increasing the temperature can be beneficial. In contrast to the reaction mediated by $ZnCl_2$ (entry 4), bicyclic cyclopentenone **15** was not observed when water was added to the reaction mixture catalyzed by $Dy(OTf)_3$ (entry 10).

With an optimized protocol in hand, we next investigated the scope of this cascade rearrangement process. Scheme 1 summarizes these studies. The reaction proceeded in moderate to excellent yields, and in all cases only a single diastereomer of the product was generated.[15] Electron-rich (**18**) and bulkier aromatic substituents (**22** and **24**) proceeded cleanly and efficiently, with a slight drop in yield for the most challenging mesityl substrate, a

Scheme 1. Substrate Studies for Intramolecular Piancatelli[a]



[a] Yield of isolated product. [b] Reaction performed at 100 °C. [c] An inseparable 9:1 ratio of diastereomers was isolated in this case.

trend seen in the corresponding aza-Piancatelli rearrangement.[6] When the aryl group at the 2-position of the furylcarbinol possessed a strong electron-withdrawing group we noticed the reactions took up to 7 d for completion. To our gratification, it was found that a good yield could be achieved in a reasonable time (16 h) with an increase in the reaction temperature from 80 to 100 °C (**19**–**21**). A thiophene heterocycle can also be incorporated at the 2-position without a decrease in efficiency (**23**).

In contrast to the analogous aza-Piancatelli reaction nonaryl substituents at the 2-position of the furylcarbinol proved more challenging. Initial attempts to rearrange substrates containing an alkyl group at this position were unsuccessful (**26** and **27**). In both cases we observed decomposition, accompanied by substitution (formation of **10** via nucleophilic attack of the pendant alcohol) for the isopropyl substrate (**27**). It was noticed that the reaction to construct **25** proceeded more rapidly than the analogous transformation to form **14** (2 vs 6 h, respectively). In this case, there was no evidence of formation of the transient ketal (**8**), which is easily identified (by isolation or TLC analysis) in reactions of all the successful primary alcohol

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(14) See Supporting Information.

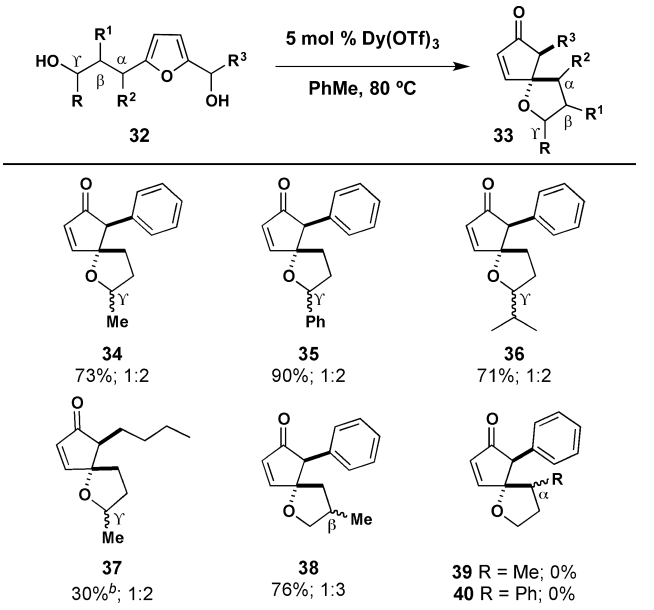
(15) The diastereomeric ratio was >99:1 for all cases examined, with the exception of **21** (see Supporting Information).

substrates (**14**, **18**–**24**) before proceeding to the desired products (**17**). This observation led us to discover that the installation of a substituent α to the oxygen on the alkyl chain, such as a gem dimethyl (**29** and **30**), provided a solution to the use of 2-alkyl substituted furylcarbinols in the rearrangement. It is unclear exactly why the gem dimethyl has such a beneficial effect, but it may block coordination to O-6 which helps drive the reaction toward oxocarbenium ion **A** (Figure 2). Extending the chain length of the appended alcohol to yield 5,6-spirocycles (**28** and **31**) proved more taxing. Formation of ketal (**8**) occurred relatively well; however only the substrate employing a pendant tertiary alcohol formed the desired product (**31**), where other substrates led to decomposition.

Encouraged by these results, we performed an exploratory study to determine whether substituents on the furan could control the torquoselectivity of the 4π electrocyclization event.[16] The two possible conrotation modes, clockwise or counterclockwise, lead to two different diastereomers.[17] Substituents were placed at three separate positions (α, β, and γ position relative to the furan ring) along the backbone of the appended alcohol (Scheme 2). Surprisingly, initial experiments showed that these groups do not greatly influence the torquoselectivity; in all cases a moderate diastereoselectivity of 1:2 to 1:3 was observed (**34**–**38**). However, these studies provide insight into the steric tolerance of the overall transformation. Substituents at the β- and γ-position are well tolerated. Substituents at the α-position failed to afford cyclopentenones. In these cases the spiroketal enol ether (**8**) was observed prior to decomposition.

Single-crystal X-ray analysis of the spirocyclic cyclopentenone **14**[18] as well as 2D NMR evidence confirmed that the rearrangement had taken place with the expected *trans* selectivity, consistent with our aza-Piancatelli reaction[19] and a 4π electrocyclization of pentadienyl cation **B** (Figure 2).[8] Further investigations are ongoing to understand why the ether moiety in pentadienyl cation **B** appears to prefer an *E* configuration.

Scheme 2. Substrate Studies for Intramolecular Piancatelli[a]



[a] Yield of isolated product. [b] Yield determined by ^{1}H NMR spectroscopy using dimethyl terephthalate as the internal standard.

In conclusion, a novel Piancatelli rearrangement with alcohol nucleophiles has been developed. The rearrangement is catalyzed by dysprosium(III) triflate under operationally simple reaction conditions.[20] The spirocyclic ethers are formed exclusively as the *trans* diastereomer and the fully substituted carbon center bearing an oxygen heteroatom, and a spirocyclic ring system is constructed in a single operation. Current efforts are focused on extending the methodology to include an asymmetric variant and employing it to access biologically important scaffolds.

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Supporting Information Available. Full experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(20) For a review on dysprosium chemistry, see: Veits, G. K.; Read de Alaniz, J. *Tetrahedron* **2012**, *68*, 2015.