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# Calcium catalyzed hydroalkoxylation

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ABSTRACT

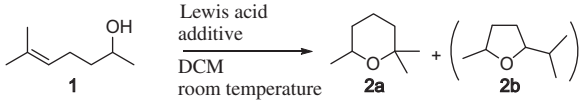
A calcium catalyzed intramolecular hydroalkoxylation reaction is presented, as a transition metal free, inexpensive, and very mild process for the highly atom economic formation of cyclic ethers from γ,δ-unsaturated alcohols. In contrast to most of the previously reported procedures, room temperature conditions are fully sufficient in most cases for a high yielding cycloisomerization in the presence of a combination of 5 mol-% $Ca(NTf_2)_2$ and 5 mol-% $Bu_4NPF_6$. Full regioselectivity is observed in all transformations.



Cyclic ethers, such as tetrahydropyrans or tetrahydrofurans are very common motifs in many natural products, such as polyether antibiotics, marine macrocycles, and flavor compounds.[1] Due to their interesting and diverse biological properties, considerable effort has been devoted to the development of synthetic methodologies for an efficient formation of these building blocks.[2,3] Among the most elegant reactions for the formation of cyclic ethers is the direct addition of the alkoxy moiety across an olefinic double bond in an intramolecular fashion, thus allowing for a completely atom economic transformation.[3,4] Efficient conversions are generally hampered by the large O–H enthalpies and the poor reactivity of unactivated, electron rich double bonds. Therefore most hydroalkoxylation reactions require harsh reaction conditions such as elevated temperatures, strongly acidic or basic reaction media, or the action of transition metal catalysts.[5–7] In only three cases Lewis acidic catalysts were found to be effective for the cyclization of unsaturated alcohols, owing to the fact that the electrophilic activation of the olefinic double bond toward the subsequent attack of a nucleophile requires a Lewis acidic catalyst of particularly high potency.[5,8] Hence, we set out to test the suitability of our calcium based catalyst system, that was found highly active in previous transformations,[9] for the hydroalkoxylation reaction, in order to develop a transition metal free, inexpensive, and mild protocol. This adds a valuable and sustainable process to the portfolio of synthetic methodology for the formation of cyclic unsaturated ethers.

In an initial study we optimized the reaction conditions for 6-methylhept-5-en-2-ol **1**, that was found to yield regioselectively the 6-membered ring **2a**. Comparison of the cyclization efficiency of our calcium based catalyst (Table 1, entry 2) with catalytic amounts of other early main group metal triflimides, in the presence of $Bu_4NPF_6$ as an additive (Table 1, entries 1–3), clearly evidences the superiority of the calcium catalyst in terms of yield and reaction rate.

**Table 1**
Optimization of the reaction conditions




| Entry [a] | Lewis acid | Additive | *t* | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $Mg(NTf_2)_2$ | $Bu_4NPF_6$ | 5 d | – |
| **2** | **$Ca(NTf_2)_2$** | **$Bu_4NPF_6$** | **1 h** | **98** |
| 3 | $Ba(NTf_2)_2$ | $Bu_4NPF_6$ | 5 d | 84 |
| 4 | $Ca(OTf)_2$ | $Bu_4NPF_6$ | 5 d | 96 |
| 5 | $Ca(NTf_2)_2$ | – | 5 d | 16 |
| 6 | $Ca(NTf_2)_2$ | $Bu_4NPF_6$ | 0.5 h | 25 |
| 7 | $Ca(NTf_2)_2$ | $Bu_4NSbF_6$ | 0.5 h | 12 |
| 8 | $Ca(NTf_2)_2$ | $Bu_4NBF_4$ | 0.5 h | 2 |
| 9[c] | $Ca(NTf_2)_2$ | $Bu_4NPF_6$ | 2 d | 9 |
| 10[d] | $Ca(NTf_2)_2$ | $Bu_4NPF_6$ | 24 h | 85 |
| 11[e] | $Ca(NTf_2)_2$ | $Bu_4NPF_6$ | 4 h | 96 |

[a] Additive (5 mol-%) and Lewis acid (5 mol-%) were added at rt to alcohol **1** (0.25 mmol) in $CH_2Cl_2$ (2 mL) and stirred for the time indicated.
[b] Isolated yield of **2a**. **2b** is not formed.
[c] Reaction in 2 mL toluene.
[d] Reaction in 2 mL $Et_2O$.
[e] Reaction in 2 mL $CHCl_3$.

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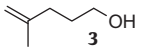
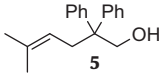
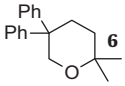
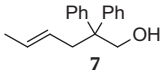
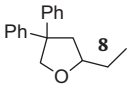
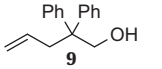
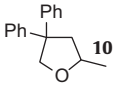
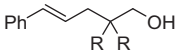
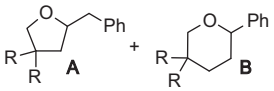
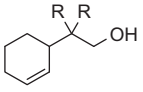
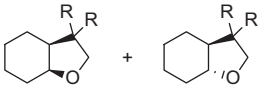
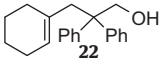
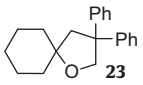
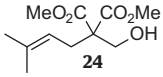
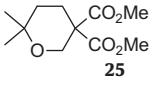
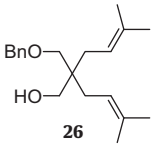
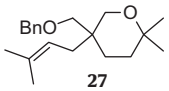
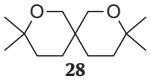
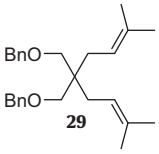
Calcium triflate, as an alternative calcium source, also catalyzed the cyclization, albeit at much lower reaction rate. In analogy to our previous findings, the catalytic activity of the calcium salt proves to be inadequate in the absence of an additive (Table 1, entry 5). In a previous publication, a detailed investigation revealed that the active catalytic species is formed by an anion exchange reaction between $Ca(NTf_2)_2$ and the respective additive. [9a] This anion exchange is crucial for enhancing the solubility of the calcium catalyst in organic reaction media. To evaluate the performance of different additives the reaction was stopped at partial conversion after 30 min (Table 1, entries 6–8), as near quantitative yield was obtained with all three additives after 1 h reaction time. The cyclization of **1** was most advanced in the presence of hexafluorophosphate (Table 1, entry 6), therefore this additive was chosen for further investigations. Suitable solvents were polar, aprotic, and non-coordinating such as dichloromethane or dichloroethane, both giving similar results. No reaction was observed in ethyl acetate, tetrahydrofuran, acetonitrile, or hexane. In toluene the conversion terminates at as little as 9%. A significant drop of the reaction rate in diethyl ether and chloroform forecloses their utilization, even though a satisfying yield was obtained in both solvents.

In order to evaluate the scope of the calcium catalyzed hydroalkoxylation, the cyclization of differently substituted unsaturated alcohols was performed (Table 2). In analogy to the results obtained during the optimization process, cyclization generally occurred with Markovnikov selectivity, leading exclusively to the product resulting from the attack of the alcohol at the higher substituted carbon atom of the double bond. The same trend in selectivity was observed in previous investigations of this reaction type, in which transition metal, Lewis as well as Brønsted acid catalysts were used. Hence, the cyclization of 2,2-disubstituted γ,δ-unsaturated alcohol **3** yielded tetrahydrofuran **4** (Table 2, entry 1), whereas trisubstituted γ,δ-unsaturated alcohol **5** reacted to the corresponding tetrahydropyran **6** (Table 2, entry 2). In both cases, none of the associated regioisomeric ether was detected. For the cyclization of alcohols with 1,2-disubstituted double bonds the selectivity was case sensitive. In the presence of two phenyl substituents in the α-position the five-membered ring was formed exclusively (Table 2, entry 3/5/11). Owing to the inferior angle compression induced by other substitution patterns than the *gem*-diphenyl moiety, the reaction led solely to the 6-membered ether when the α-position was *gem*-dimethyl substituted or unsubstituted (Table 2, entry 6/7). Interestingly, the selectivity appeared to be independent of the substituents at the olefin in these cases (cf. Table 2, entry 3/5/11). The reactivity of the unsaturated alcohol was found to be closely related to the double bond substitution, with trisubstituted double bonds being the most reactive, directly followed by 1,1-disubstituted olefins. The reaction rate for 1,2-disubstituted double bonds and finally monosubstituted olefins was significantly lower. This reactivity order is nicely reflected in the reaction rates observed for the cyclization of alcohols **5**–**9** (Table 2, entries 2–4). In addition to its impact on the selectivity, the angle compression ability of the chain substituents had a significant influence on the reaction rate. This is the most conclusive for the transformation of alcohols **17** to **21**, as the moderate reactivity of their 1,2-disubstituted double bond does not predefine the reaction rate. The α-*gem*-diphenyl substituted alcohol **17** displays a significantly higher reactivity than the *gem*-dimethyl substituted alcohol **19**, and the unsubstituted alcohol **21** was unreactive, even upon heating to 100 °C under microwave conditions. Furthermore, the diastereoselectivity of the addition of the hydroxyl moiety to the double bond was apparently governed by the conformational restriction imposed by the angle compression rate in these substrates. Thus, the α-*gem*-diphenyl substituted alcohol **17** and the *gem*-dimethyl substituted alcohol **19** both cyclized selectively to the *cis*-products **18** and **20**. Tetrahydropyran **27** and bis-tetrahydropyran **28** could be selectively obtained from the mono-benzylated double-unsaturated diol **26** (Table 2, entry 13/14). The unprotected alcohol attacks first, leading to the formation of tetrahydropyran **27**. Unexpectedly, calcium catalyzed deprotection of the benzylether group occurs after prolonged reaction time, allowing a second reaction to take place between the alcohol and the second olefin to afford the spirobicyclic ether **28**. Products **27** and **28** could also be obtained selectively from the bis-benzylated diol **29** (Table 2, entry 15/16).

**Table 2**
Cyclization of different alcohols

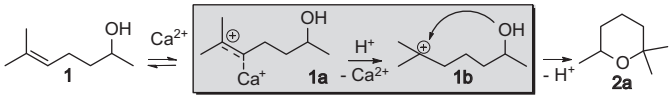
| Entry[a] | Alcohol | Product | *t* | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  **3** |  **4** | 2 h | 96 |
| 2 |  **5** |  **6** | 1 h | 85 |
| 3[c] |  **7** |  **8** | 24 h | 82 |
| 4 |  **9** |  **10** | 24 h | 81 |
| |  |  **A** + **B** | | |
| 5[c] | R = Ph (**11**) | A (**12**) | 20 h | 96 |
| 6[c] | R = Me (**13**) | B (**14**) | 20 h | 97 |
| 7 | R = H (**15**) | B (**16**) | 20 h | 81 |
| |  |  | | |
| 8 | R = Ph (**17**) | *cis*:*trans* 98:2 (**18**) | 2 h | 80 |
| 9[c] | R = Me (**19**) | *cis*:*trans* 98:2 (**20**) | 20 h | 9 |
| 10 | R = H (**21**) | — | 24 h | — |
| 11 |  **22** |  **23** | 1.5 h | 82 |
| 12 |  **24** |  **25** | 1.5 h | 72 |
| 13[d] |  **26** |  **27** | 5 h | 70[e] |
| 14[d] | |  **28** | 24 h | 65 |
| 15[f] |  **29** | **27** | 2 h | 57[g] |
| 16[f] | | **28** | 3 h | 46 |

[a] 5 mol-% $Bu_4NPF_6/Ca(NTf_2)_2$, 0.25 mmol of alcohol, in $CH_2Cl_2$ (2 mL) stirred at rt for the time indicated.
[b] Isolated yield.
[c] At 35 °C.
[d] 10 mol-% $Bu_4NPF_6/Ca(NTf_2)_2$, at 50 °C.
[e] 15% of **28**.
[f] 10 mol-% Bu4NPF6/Ca(NTf2)2, at 80 °C.
[g] 26% of **28**.

**Table 3**
Cyclization of **1** by Lewis *vs.* Brønsted acid

| Entry[a] | (Lewis) acid (mol-%) | Additive 1 (mol-%) | Additive 2 (mol-%) | *t* | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $Ca(NTf_2)_2$ (5) | $Bu_4NPF_6$ (5) | — | 1 h | 98 |
| 2 | $Ca(NTf_2)_2$ (5) | $Bu_4NPF_6$ (5) | 2,6-*t*-Butyl pyridine (5) | 20 h | 53 |
| 3 | $HNTf_2$ (5) | — | — | 1 h | 81 |
| 4 | $HNTf_2$ (5) | — | — | 1.5 h | 93 |
| 5 | $HNTf_2$ (5) | $Bu_4NPF_6$ (5) | — | 5.5 h | 97 |
| 6 | $HNTf_2$ (5) | — | 2,6-*t*-Butyl pyridine (5) | 5 d | — |
| 7 | $HNTf_2$ (5) | $Bu_4NPF_6$ (5) | 2,6-*t*-Butyl pyridine (5) | 5 d | — |

[a] Additives and (Lewis) acid were added at room temperature to alcohol **1** (0.25 mmol) in $CH_2Cl_2$ (2 mL) and stirred for the time indicated.
[b] Isolated yield.




**Scheme 1.** Mechanistic proposals for the cyclization of **1**.

It is known that the cationic intramolecular hydroalkoxylation of highly reactive substrates, such as alcohol **1**, is promoted by catalytic amounts of super Brønsted acids and proceeds in strongly acidic media.[3,4,10,11] However, apart from the apparent incompatibility of these protocols with many functional groups, the superacid catalyzed cycloisomerizations were reported to be difficult to handle, since highly accurate control of acid concentration is oftentimes crucial for obtaining synthetically useful product yields.[7,10] For a better understanding of the role of the calcium catalyst in the presented hydroalkoxylation protocol a comparative study of the cyclization of **1** with different additives was carried out in the presence of catalytic amounts of the $Ca(NTf_2)_2$ catalyst or $HNTf_2$. The latter could be formed in situ by the protonation of minor amounts of $Ca(NTf_2)_2$ with alcohol.

In the presence of 5 mol-% $HNTf_2$ alcohol **1** cyclizes to tetrahydropyran **2a** in almost quantitative yield in a slightly longer reaction time compared to the reaction in the presence of our calcium based catalyst system (1.5 h vs 1 h, Table 3, entries 1/3/4). Despite this very similar result for the conversion of the highly reactive alcohol **1** in the presence of the acid $HNTf_2$ and the calcium catalyst, it shall be emphasized at this point that alcohols **7**, **11** and **22**, which are less reactive than **1**, were found unreactive under acid catalysis. Upon addition of 5 mol-% of $Bu_4NPF_6$ to the acid catalyzed cyclization the reaction rate slowed down significantly and 5.5 h was required to achieve complete conversion (Table 3, entry 5). In the presence of an equimolar amount of 2,6-*t*-butyl pyridine, as a sterically hindered base, the acid catalyzed reaction ceased (Table 3, entries 6/7), whereas the calcium catalyzed reaction yielded 53% of the desired product after 20 h reaction time (Table 3, entry 2). This notable drop of the reaction rate indicates for a cooperative effect of the calcium based catalyst system and minor amounts of in situ formed acid, which is presumably no longer operative in the presence of base. These investigations clearly indicate that the acid catalyst shows a different behavior than the calcium based catalyst system. Even though it cannot be fully excluded at this point that in situ formed superacid represents the only active catalytic species, as it is known to have different properties than an acid catalyst that is directly added to the reaction mixture, the reaction proceeds presumably through the above mentioned cooperative catalyst system. A proposed mechanistic pathway (Scheme 1) is initiated by the coordination of the calcium catalyst to the double bond leading to the intermediate Lewis acid bound carbocation **1a**, that is subjected to immediate protodemetallation, leading to the carbocationic intermediate **1b**, cyclization of which leads to product **2a**. This hypothesis is sustained by the fact that the reaction slows down significantly in the presence of 2,6-*t*-butyl pyridine, as under these conditions the protodemetallation event is no longer enhanced by the presence of minor amounts of acid.

A coordination of the calcium catalyst to the hydroxyl moiety, which thereby enhances the acidity of the hydroxyl hydrogen atom by several orders of magnitude followed by intramolecular protonation of the double bond was confirmed as the olefin activation mechanism for the aluminum triflate catalyzed hydroalkoxylation.[8] However, in our case, experiments carried out with 6-methylhept-5-en-2-ol-*d2* show no incorporation of deuterium in the cyclized product.[12]

In summary, we have demonstrated the suitability of our calcium based catalyst system for the intramolecular hydroalkoxylation reaction, and thus developed a transition metal and acid free, inexpensive, and very mild process for the highly atom economic formation of cyclic ethers from γ,δ-unsaturated alcohols. In contrast to most of the previously reported procedures, room temperature conditions were fully sufficient in most cases for a high yielding cycloisomerization in the presence of a combination of 5 mol-% $Ca(NTf_2)_2$ and 5 mol-% $Bu_4NPF_6$. Full selectivity to the Markovnikov products was observed for mono-, 1,1-di-, and trisubstituted double bonds. The regioselectivity of the attack of the hydroxyl moiety to 1,2-disubstituted olefins was governed by angle compression effects induced by the substituents in the α-position of the alcohol functionality. Both, the double bond substitution pattern and the degree of angle compression exerted by the chain substituents affect the reactivity of the unsaturated alcohol.

## Supplementary data

Supplementary data (general procedure and spectral data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.129.

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12. The reaction was performed under strict exclusion of air and moisture in dry $CDCl_3$ (2 mL) with 6-methylhept-5-en-2-ol-*d2* (0.25 mmol) and 5 mol-% $Ca(NTf_2)_2/Bu_4NPF_6$.