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HFIP Solvent Enables Alcohols To Act as Alkylating Agents in Stereoselective Heterocyclization

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Supporting Information

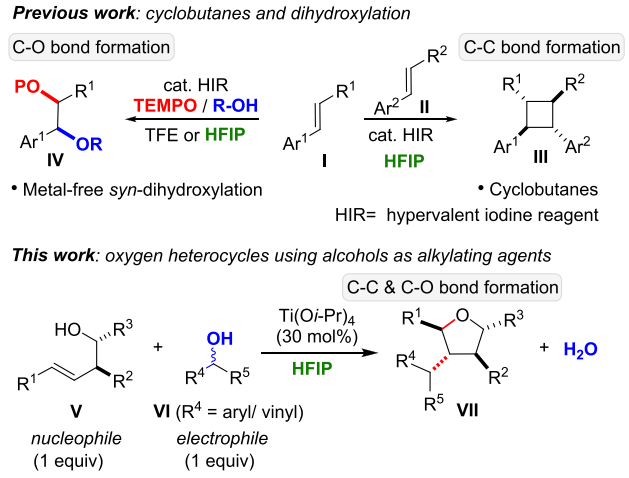
ABSTRACT: A new method for the stereoselective synthesis of highly functionalized oxygen heterocycles using allyl or benzyl alcohols as alkylating agents is presented. The process is efficient and atom economic, generating water as the only stoichiometric byproduct. Substoichiometric amounts of $Ti(OiPr)_4$ in HFIP solvent are key to this reactivity, and the method tolerates a broad substitution pattern on both the alcohol initiator and homoallylic alcohol substrate. Preliminary mechanistic studies reveal *in situ* formation of a titanium complex with HFIP which may initiate the cyclization reaction. Further stereoselective functionalization of the products allows access to a diverse range of interesting heterocyclic structures.

Developing new synthetic methods for the stereocontrolled synthesis of complex and highly functionalized molecules from simple and readily available starting materials is of value for applications in many disciplines such as medicinal chemistry or materials science.

In this regard, we have investigated the unique role that the polar and hydrogen bonding solvent hexafluoroisopropanol (HFIP) can play in facilitating stereoselective functionalization reactions of alkenes. Our work has uncovered the stereoselective synthesis of cyclobutanes **III** from alkenes **I** and **II** in a formal [2+2] cycloaddition, facilitated via a single electron oxidative pathway (Scheme 1).[1,2] Moreover, treating alkenes **I** with a nucleophile (R−OH) and TEMPO in HFIP enabled us to develop a new metal-free *syn*-dihydroxylation reaction (see **IV** in Scheme 1), which proceeds via formation of an oxoammonium cation intermediate.[3]

Herein we report the formation of both a C−C and a C−O bond during heterocyclization to form saturated oxygen containing heterocycles from homoallylic alcohols **V** (Scheme 1). The reaction is notable for its use of an alcohol (**VI**) as an initiator for cyclization and for the high levels of stereoselectivity that ensue. HFIP is essential for this reaction to proceed and this protocol is capable of assembling complex heterocycles in one step. The overall process involves the stereoselective creation of two new bonds in a single step, via a formal 5-*endo*-trig cyclization,[4,5] and produces water as the only stoichiometric byproduct. While related approaches to form tetrahydrofurans by cyclization have been reported,[6−8] the use of carbon-based electrophiles to trigger cyclization is rare and under-exploited.[9,10] In this work, we show that in

Scheme 1. Stereoselective Alkene Functionalization in HFIP



HFIP solvent both allylic and benzylic alcohols can be used as precursors to potent electrophiles[11,12] which initiate cyclization.[13−17]

We performed our initial reaction screen using homoallyl alcohol **1a** as the THF forming component (the alcohol substrate which acts as a nucleophile) and allyl alcohol **2a** as the partner (this alcohol acts as the electrophile). Using HFIP at room temperature gave tetrahydrofuran **3a** in low yield, but as a single *trans* diastereoisomer (Table 1, entry 1). Extensive screening revealed $Ti(Oi\text{-}Pr)_4$ as a promising additive, which improved the yield with 10 mol % loading (Table 1, entry 2). Details of the full screen of alternative solvents and additives are given in the Supporting Information. Increasing the reaction temperature to 40 and 70 °C also had a beneficial impact with an encouraging 31% isolated yield (Table 1, entries 3 and 4). Increasing the $Ti(Oi\text{-}Pr)_4$ loading to 20 and 30 mol % notably improved the results with a respectable 52% yield of **3a** (Table 1, entries 5 and 6). Other Lewis acids, such as $Cu(OTf)_2$, $Sc(OTf)_2$ or $Zn(OAc)_2$ did not perform better (Table 1, entries 7−9). Ionic additives such as $Ph_4P\ BF_4$, designed to increase the cation stabilizing ability of the solvent,[18] were also screened with promising results (Table 1, entry 10) although the starting homoallylic alcohol **1a** was completely consumed under these conditions; this was not the case with the $Ti(Oi\text{-}Pr)_4$ conditions. Notably, the use of other

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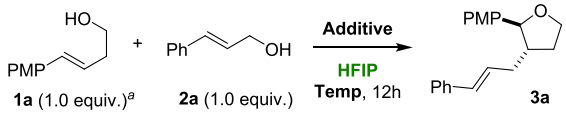
Table 1. Screening of Reaction Conditions



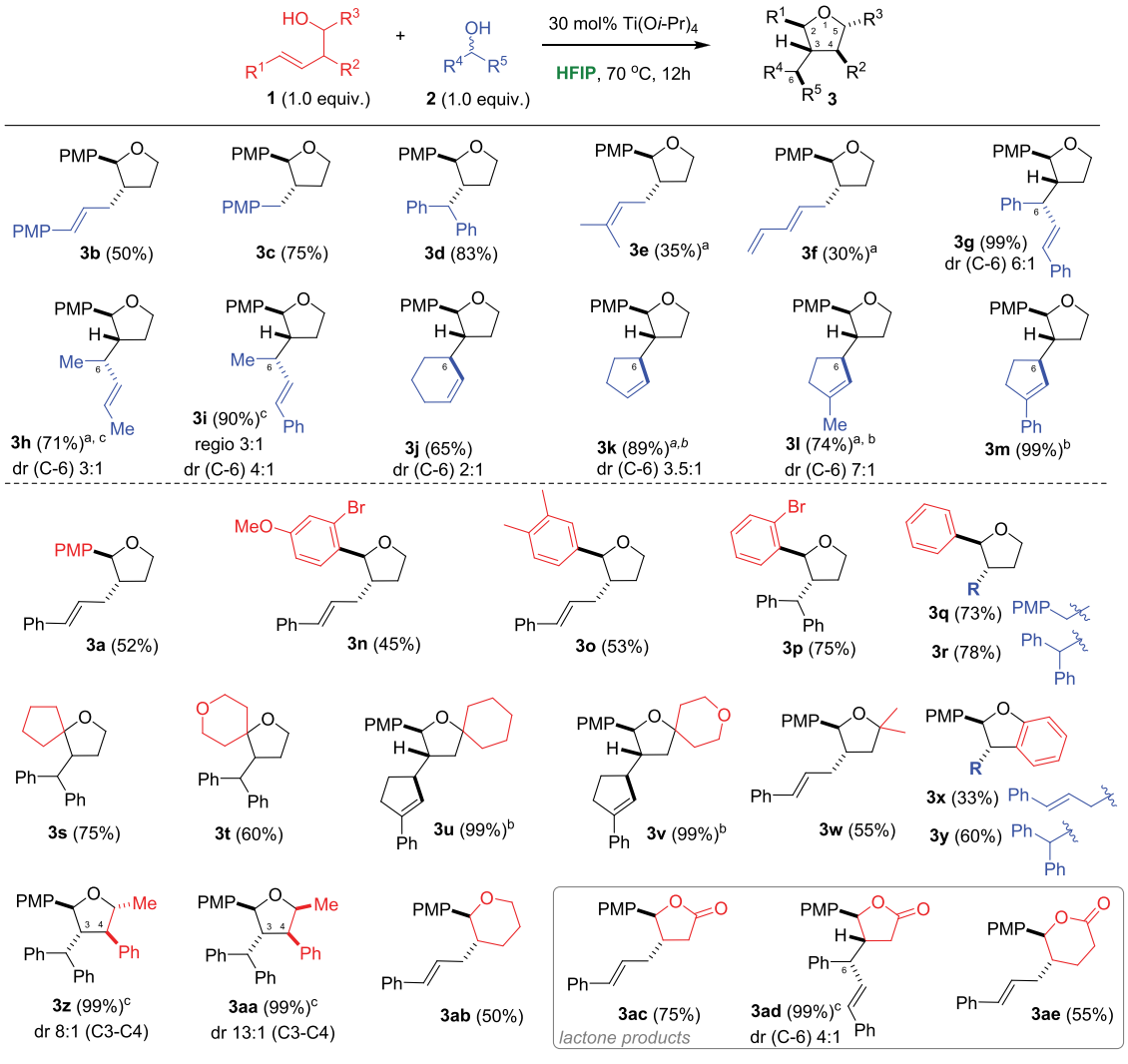
Entry	Additive	Temperature	Yield **3a** (%)
1	–	RT	3
2	10 mol % $Ti(Oi\text{-}Pr)_4$	RT	11
3	10 mol % $Ti(Oi\text{-}Pr)_4$	40 °C	15
4	10 mol % $Ti(Oi\text{-}Pr)_4$	70 °C	31
5	20 mol % $Ti(Oi\text{-}Pr)_4$	70 °C	38
6	30 mol % $Ti(Oi\text{-}Pr)_4$	70 °C	52
7	30 mol % $Cu(Otf)_2$	70 °C	0
8	30 mol % $Sc(Otf)_2$	70 °C	0
9	30 mol % $Zn(OAc)_2$	70 °C	46
10	30 mol % $Ph_4P^{\oplus}BF_4^{\ominus}$	70 °C	47
11 (DCM)	30 mol % $Ti(Oi\text{-}Pr)_4$	70 °C	0

[a]PMP: *para*-methyoxyphenyl.

solvents, for example dichloromethane, shut the reaction down completely (Table 1, entry 11). Further attempts at the optimization using these model substrates were unfruitful, so we opted to evaluate the scope of the method under the optimal conditions. It is important to emphasize that there is no need to use an excess of either component, leading to a very efficient cyclization where every carbon on both components is incorporated into the product in one step.

The scope of this new transformation was first evaluated by varying the nature of alcohol **2** (the electrophilic partner). Using the more electron-rich 4-methoxycinnamyl alcohol allowed the reaction to be carried out at room temperature without harming the reactivity (Table 2, **3b**). Benzylic alcohols, such as 4-methoxybenzyl alcohol (Table 2, **3c**) or bis-benzylic, such as benzhydrol (Table 2, **3d**) were used, with a notable increase in yield. Expanding the scope to less activated acyclic allylic alcohols, such as prenyl alcohol (Table 2, **3e**) or diallyl alcohol (Table 2, **3f**) was also possible, allowing the incorporation of aliphatic (nonaromatic) substitution at C-3 in the tetrahydrofuran product, although with diminished yield. The latter product **3f**, was obtained as a single regioisomeric conjugated diene product, in a net S_N2' fashion. In each case the product was isolated as a single, *trans*, diastereoisomer.

Table 2. Scope of the Cyclization Reaction



[a]Using 2.0 equiv of electrophilic partner **2**. [b]Performed at room temperature (RT). [c]Performed at 0 °C.

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In an effort to increase the product complexity, we next sought to utilize a set of racemic allylic alcohols as the electrophile. We focused on acyclic alcohols with aromatic (Table 2, **3g**) or aliphatic substitution (Table 2, **3h**) to avoid unselective regiocontrol on a presumed allyl cationic intermediate which initiates cyclization. Both alcohols performed well in the reaction, with moderate to good diasterocontrol at the new allylic stereocenter. We then moved to the challenging unsymmetrically substituted allyl alcohol (Table 2, **3i**), where two separable regioisomeric products were obtained in a 3:1 ratio, both of them as a 4:1 mixture of diastereoisomers (at the allylic stereocenter). In spite of this modest regio- and diasterocontrol only the 2,3-*trans* isomer was observed within the THF ring. We then decided to make use of cyclic allyl alcohols, first using cyclohexenyl and cyclopentenyl alcohols as precursors of symmetric intermediates, and were delighted to find diastereocontrol (Table 2, see **3j** and **3k**). When using tertiary cyclopentenyl allyl alcohols, with aliphatic (Table 2, **3l**) or aromatic substitution (Table 2, **3m**) complete regio- and high diastereocontrol over the new allylic stereogenic center was obtained.

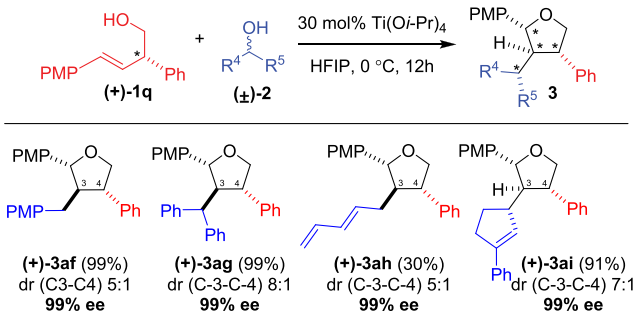
After showing that a broad variety of allyl and benzyl alcohols act as competent electrophilic partners, we moved to explore the versatility of the nucleophilic homoallyl alcohol **1**. Other less electron-rich aromatic rings attached to the alkene were explored with satisfactory results using cinnamyl alcohol as a partner (Table 2 **3n** and **3o**). Electron-deficient (Table 2, **3p**) and neutral aromatic rings (Table 2, **3q,r**) were also compatible substrates. Challenging aliphatic substitution (ie a nonactivated alkene) at the C-2 position was attempted with very satisfying results. While disubstituted alkenes did not react, trisubstituted olefins gave valuable spirocycles (Table 2, **3s,t**). Retaining the PMP unit at C-2, substitution at other positions was then investigated. Aliphatic cyclic substitution at C-5 produced complementary spirocycles in quantitative yields (Table 2, **3u,v**), while an acyclic variant gave valuable tertiary centers (Table 2, **3w**). Interesting benzofuran motifs can also be obtained by using phenol-bearing starting materials (Table 2, **3x,y**). Using substrates containing substituents at both C-4 and C-5 positions allowed us to access fully substituted tetrahydrofurans, with the relative stereochemistry being controlled by the C-4 substituent alone (see Table 2, **3z,aa**).

It is noted that the method is not limited to the formation of 5-membered heterocycles; tetrahydropyrans can also be obtained as a single *trans* isomer (Table 2, **3ab**). In an effort to expand the method to the synthesis of diverse and interesting heterocycles, replacing the alcohols by the corresponding carboxylic acids led to the production of γ-butyrolactone and δ-valerolactone (Table 2, **3ac**–**ae**). These are common structures widely found in natural products and of high relevance for medicinal chemistry.

Note that NOE experiments revealed the stereochemical relationship between the THF ring substituents; the relative stereochemistry of the products bearing an exocyclic stereogenic center (cyclic or acyclic) was assigned by reference to X-ray crystallographic structures obtained using **3v** or **10c**,[19] see Supporting Information for details. Interestingly, these two X-ray structures reveal differing relative stereochemistry at the exocyclic carbon, which likely has its origins in the differing geometries of the acyclic versus cyclic cation precursors.

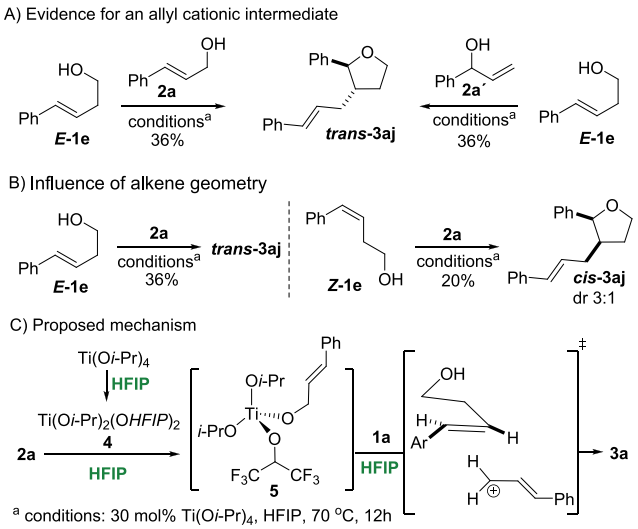
Encouraged by the high stereoselectivity and broad scope shown, we were particularly interested in exploiting the transfer of chirality from a previous established stereogenic center, for example in enantiopure homoallyl alcohol **1q** (Table 3). Pleasingly, employing benzyl (Table 3, **3af,ag**) or allyl (Table 3, **3ah**) alcohols as electrophiles gave the enantiopure products in a stereocontrolled manner. Thus, products with up to three new stereogenic centers can be accessed in a single step by using enantiopure homoallylic alcohols (Table 3, **3ai**).

Table 3. Synthesis of Enantiopure Products



Further experiments were designed to shed light on the mechanism of this new transformation. For those examples that involve allyl alcohols as alkylating agents, using two different regioisomeric allyl alcohols, **2a** and **2a′**, meant that the same product *trans*-**3aj** was obtained in similar yields, under identical conditions (Scheme 2A). These results support the formation of a common allyl cationic intermediate, whose formation is encouraged by the polar HFIP solvent. In addition, the influence of double bond geometry within homoallyl alcohol **1** was investigated. While the *E* isomer gives the *trans* diastereoisomer with high stereoselectivity, the *Z* isomer leads to a major, but not exclusive, *cis* product (Scheme 2B) and reacts via a less stereoselective pathway.

Scheme 2. Experiments To Probe the Mechanism



Finally, our attempts to detect reactive complexes and intermediates *in situ* led to the isolation of a relatively stable titanium complex that has been characterized by NMR (See Supporting Information for further details; monomeric structures are shown for clarity), whereby two isopropoxy ligands of $Ti(Oi\text{-}Pr)_4$ have been replaced by two hexafluoroisopropoxy units (Scheme 2C, **4**). This type of Ti complex

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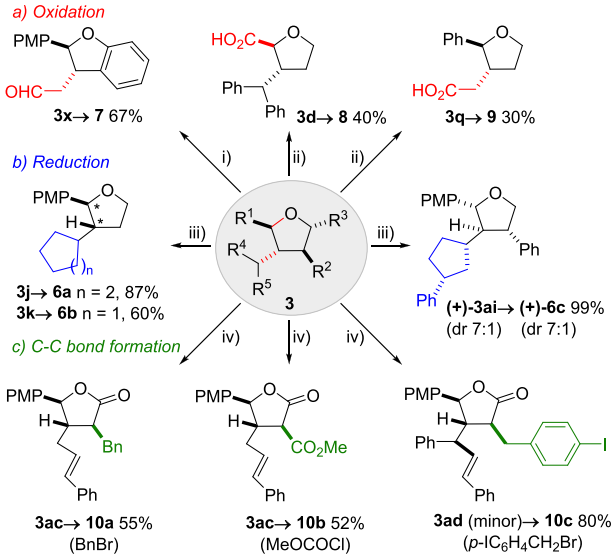
has some precedent in the literature, although its properties and applications remain unexplored;[20] a related ligand exchange using $MoCl_5$ has recently been reported.[21] When we mixed preprepared titanium complex **4** and allyl alcohol **2a** in HFIP, a new species **5**, derived from the substitution of one hexafluoroisopropoxy moiety for an allylalkoxy group, was detected by NMR spectroscopy (Scheme 2C, see Supporting Information for further details). We note that alkoxy ligand exchange at titanium is likely to be easy to accomplish and reversible.[22] Finally, the addition of homoallyl alcohol **1a** to this reaction mixture led to the formation of product **3a**, presumably via an electrophile-triggered cyclization.

Finally, selective functionalization of the heterocyclic products **3** offers an opportunity to install groups that can be used to manipulate these highly functionalized heterocycles. Our reaction toolbox includes oxidation protocols, for example ozonolysis of the remaining alkene afforded an aldehyde (Scheme 3a, **7**). Moreover, the PMP group can be oxidized to a carboxylic acid when attached directly to the heterocycle (Scheme 3a, **8**), or when derived from the cation electrophile (Scheme 3a, **9**). Alternatively, hydrogenation of the double bond in these products gave saturated derivatives (see **6a,b** in Scheme 3b). The diastereoselective transformation of **3ai** to **6c** is noteworthy, creating a new stereogenic center during reduction. Finally, stereoselective alkylation or acylation can be performed on the γ-butyrolactones (Scheme 3c, **10a–c**). These straightforward and stereoselective reactions performed using heterocycles **3** exemplify the rich potential of these compounds for synthetic organic chemistry.

In conclusion, we have developed a new method for the stereoselective preparation of valuable oxygen-containing heterocyclic compounds triggered by the use of alcohols as alkylating agents. HFIP solvent is unique in promoting the heterocyclization and allowing formation of a C–C and C–O bond at the same time. Moroever, enantioenriched products can be obtained from simple chiral starting materials and further functionalization allows us to install useful functional groups.

Scheme 3. Selective THF Product Functionalization[a]



[a](i) O_3, CH_2Cl_2, −78 °C/DMS; (ii) $RuCl_3$ (2.5–5 mol %), $NaIO_4$, Na_2HPO_4, MeCN:CCl_4; (iii) H_2, 10 wt % Pd/C, EtOAc, 0 °C; (iv) 1.1–1.7 equiv. LDA, 1–1.5 equiv. R^2–X, THF, −78 °C.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b02198.

Full experimental details (PDF)
Copies of spectral data (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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