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Enantioselective Oxetane Ring Opening with Chloride: Unusual Use of Wet Molecular Sieves for the Controlled Release of HCl

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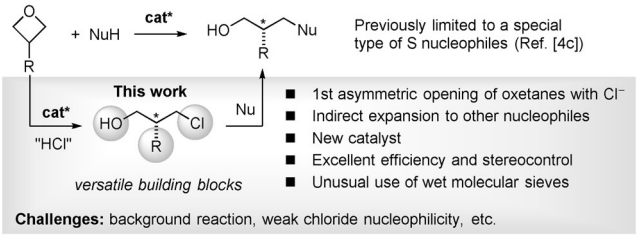
Abstract: *An unprecedented enantioselective oxetane opening with chloride provides access to a range of highly functionalized three-carbon building blocks. The excellent enantiocontrol is enabled not only by a new catalyst, but also by the unusual use of wet molecular sieves for the controlled release of HCl.*

New strategies for the efficient synthesis of chiral building blocks are in great demand in organic synthesis.[1] The enantioselective desymmetrization of prochiral compounds has been shown to be one of the most powerful strategies.[2] Specifically, the enantioselective opening of prochiral oxetanes represents an attractive method for the rapid synthesis of highly functionalized three-carbon chiral building blocks (Scheme 1). However, these reactions remain a challenge, particularly with intermolecular nucleophiles.[3–5]

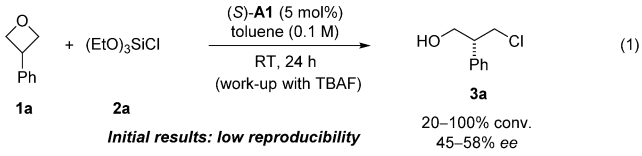


Scheme 1. Catalytic asymmetric intermolecular ring opening of prochiral oxetanes.

The challenges associated with intermolecular oxetane desymmetrization include remote stereocontrol and the low ring-opening propensity of oxetanes. The latter requires a suitable reaction partner that is sufficiently nucleophilic for ring opening but does not deactivate the catalyst. Furthermore, the alcohol product can also be a competing nucleophile. As a result, such reactions are currently limited to particular sulfur nucleophiles and have limited applications.[4c]

Nevertheless, we hypothesized that the desymmetrization of oxetanes with a chloride nucleophile would be highly useful as the chloromethyl moiety in the ring-opening product could serve as a multi-purpose handle for the attachment of various nucleophiles, thereby indirectly achieving oxetane desymmetrization with different nucleophiles (Scheme 1). However, aside from the weak nucleophilicity of the chloride anion and the ability of the alcohol product to act as a competing nucleophile as obvious obstacles, the potential use of HCl or its precursors would result in strong background reactions, particularly with chiral acid catalysis. In this context, we herein describe our successful realization of this process with excellent stereocontrol under mild conditions.

In view of the weak chloride nucleophilicity relative to the resulting alcohol product, we surmised that a latent chloride nucleophile (e.g., a chlorosilane) would not only provide a chloride ion upon activation, but also concomitantly protect the resulting hydroxy group in the same catalytic cycle to inhibit product competition. Indeed, to our delight, a combination of chlorotriethoxysilane (**2a**) and a chiral phosphoric acid could effect the desired transformation [Eq. (1)].[6] In the



presence of the representative STRIP catalyst (**A1**, shown in Table 2), chloride opening of **1a** in toluene as the solvent proceeded smoothly at room temperature. After TBAF work-up, the desired product **3a** was obtained. However, the initial results showed very low reproducibility. Different runs of the same reaction with different batches of material gave quite different conversions and enantioselectivities (20–100% conversion, 45–58% *ee*), which were beyond experimental error. We reasoned that the condition of the chlorosilane and substrate could influence the result through the presence of adventitious moisture and/or HCl, which can promote the background reaction. However, the use of freshly distilled **2a** did not solve the reproducibility issue.

The sensitivity of the results to seemingly random factors prompted us to probe the effect of water (Table 1). In the presence of 5 Å molecular sieves (M.S.), almost no conversion was observed (entry 1). However, the addition of one equivalent of water resulted in full conversion, but low enantioselectivity (entry 2). Alternatively, the addition of both molecular sieves and water gave moderate conversion, but higher enantioselectivity (entry 3). Increasing the amount of water to two equivalents improved the reaction to full conversion and higher enantioselectivity (entry 4). A further

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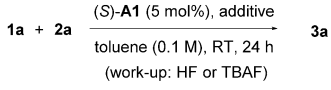
Table 1: Additive screening.



Entry	Additive	Conv. [%][a]	*ee* [%][b]
1	5 Å M.S. (10 mg)	< 10	–
2	H_2O (1.0 equiv)	100	46
3	5 Å M.S. (10 mg) and H_2O (1.0 equiv)	52	58
4	5 Å M.S. (10 mg) and H_2O (2.0 equiv)	100	67
5	5 Å M.S. (10 mg) and H_2O (3.0 equiv)	100	63
6	wet 5 Å M.S. (12 mg)[c]	100	67

[a] Determined by ^{1}H NMR analysis using CH_2Br_2 as the internal standard. [b] Determined by HPLC analysis on a chiral stationary phase. [c] An aliquot of premixed wet M.S. (12 mg) containing approximately 2.0 equiv of water was used.

increase in the amount of water could not improve the enantioselectivity. These results indicate that water is essential to the reaction and more importantly that its amount can dramatically influence the outcome of the reaction. It is worth noting that the simultaneous use of water and molecular sieves has little precedence.[7] However, this combination proved to be beneficial and made the results reproducible. We hypothesized that this combination could help the slow generation of HCl for the reaction. Furthermore, to simplify the experimental method, we premixed 5 Å M.S. and water on large scale (12 g), and an aliquot containing about two equivalents of water was taken for the reaction (entry 6), which resulted in essentially the same results as those achieved with the sequential addition of dry M.S. and water (entry 4).

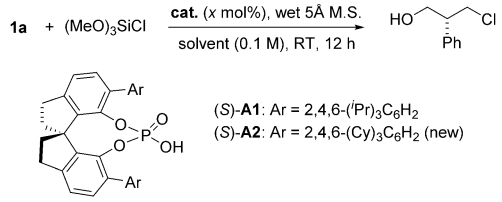
With the above reproducible results as a benchmark, we next examined different chlorosilanes [Eq. (2)]. As shown below, $(MeO)_3SiCl$ gave the best reactivity and enantioselectivity (76% *ee*). Bulkier chlorotrialkoxysilanes and chlorotrialkylsilanes were less reactive (see the Supporting Information for details).

Chlorosilane	$(EtO)_3SiCl$	$(^iPrO)_3SiCl$	$(MeO)_3SiCl$	Et_3SiCl
Results	100% Conv. 67% *ee*	<10% Conv. –	100% Conv. 76% *ee*	<10% Conv. –

(2)

Next, we further evaluated different catalysts and reaction parameters (Table 2). The use of various known chiral phosphoric acids did not improve the enantioselectivity (see the Supporting Information for details). However, after considerable efforts, the new catalyst **A2**, which bears 2,4,6-tricyclohexylphenyl groups at the 3- and 3′-positions of the SPINOL backbone, was shown to be superior, providing both full conversion and excellent enantioselectivity (91% *ee*, entry 2). The solvent has a dramatic influence on the enantioselectivity, with benzene providing the best results among all evaluated solvents. Decreasing the catalyst loading to 1–2 mol% does not affect the outcome of the reaction, albeit at the expense of reaction time. Further investigations

Table 2: Optimization of the reaction conditions.



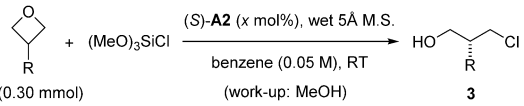
Entry	Catalyst (mol%)	Solvent	Conv. [%][a]	*ee* [%][b]
1	(*S*)-**A1** (5)	toluene	100	74
2	(*S*)-**A2** (5)	toluene	100	91
3	(*S*)-**A2** (5)	DCM	100	82
4	(*S*)-**A2** (5)	Et_2O	76	44
5	(*S*)-**A2** (5)	benzene	100	93
6[c]	(*S*)-**A2** (2)	benzene	100	92
7[c]	(*S*)-**A2** (1)	benzene	100	90
8[c,d]	(*S*)-**A2** (2)	benzene	100	93

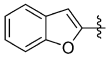
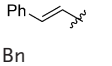
[a] Determined by ^{1}H NMR analysis using CH_2Br_2 as the internal standard. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Run for 24 h. [d] 0.05 M concentration. Cy = cyclohexyl.

with respect to the reaction concentration led the optimal set of parameters (entry 8).

A range of 3-substituted oxetanes smoothly participated in the ring opening with excellent efficiency and good to high enantioselectivity (Table 3). Electron-donating and -withdrawing groups did not affect the reaction. Substrates with 3-alkyl and 3-alkenyl substituents also reacted efficiently. Heteroatom-substituted oxetanes (e.g., with O-, S-, or N-containing substituents) were also excellent substrates and rapidly furnished densely functionalized three-carbon chiral building blocks (Table 4).[8] Under the mild reaction conditions, a wide variety of functional groups, such as ethers, esters, silyl-protected alcohols, tosylates, alkenes, alkynes, and nitriles, are tolerated. Finally, fully substituted stereocenters could also be generated [Eq. (3)]. Notably, in these two cases, $MgSO_4$ was used instead of the molecular sieves (see below).

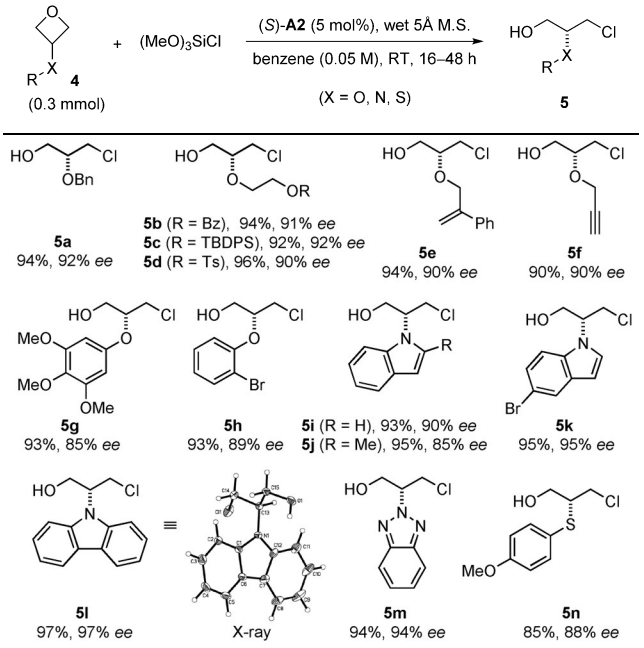
Table 3: Substrate scope with respect to 3-carbon-substituted oxetanes.



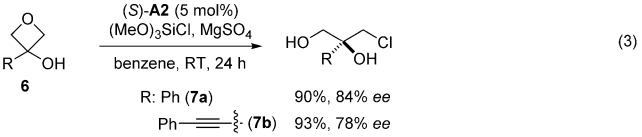
Entry	R	*t* [h]	*x*	**3**	Yield [%][a]	*ee* [%]
1	Ph	24	2	**3a**	91	94
2	4-MeC_6H_4	18	2	**3b**	91	94
3	2-$MeOC_6H_4$	24	5	**3c**	85	90
4	3-BrC_6H_4	24	2	**3d**	90	94
5	3-$CF_3C_6H_4$	24	2	**3e**	90	96
6	4-$CF_3OC_6H_4$	24	2	**3f**	83	95
7	4-CNC_6H_4	24	2	**3g**	92	94
8	2-naphthyl	24	2	**3h**	85	96
9		15	5	**3i**	96	96
10		16	5	**3j**	93	89
11	Bn	24	5	**3k**	81	71

[a] Yield of isolated product.

Table 4: Substrate scope with respect to 3-heteroatom-substituted oxetanes.



Bz = benzoyl, TBDPS = *tert*-butyldiphenylsilyl.



(3)

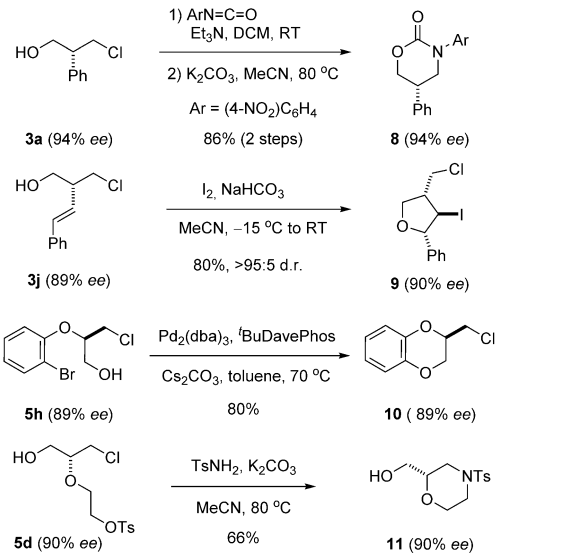
To probe the general superiority of our new catalyst **A2** over the known versatile catalyst **A1** (STRIP), we compared their performance with several substrates. As shown below, under otherwise identical reaction conditions, the enantioselectivities achieved with catalyst **A2** are all higher by about 20%, although their structural differences appear to be trivial [Eq. (4)]. Our new catalyst **A2** should thus find more applications.

Product	3b	3k	5a	5i
ee with **A1**	75% *ee*	57% *ee*	79% *ee*	64% *ee*
ee with **A2**	94% *ee*	71% *ee*	92% *ee*	90% *ee*

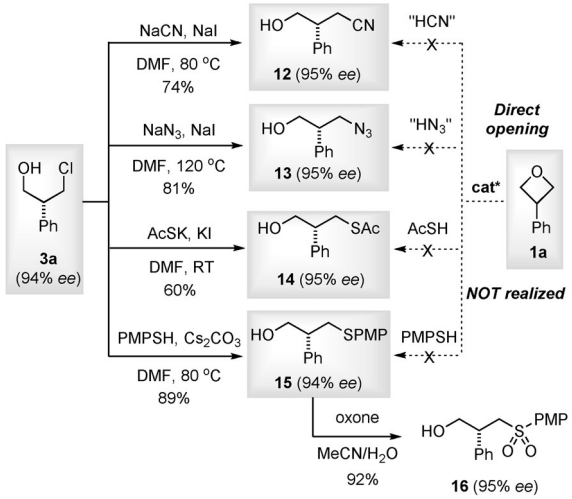
(4)

The desymmetrization products can be transformed into other useful chiral molecules. For example, the heterocycles **8–11** could be efficiently synthesized without erosion of enantiopurity (Scheme 2). Furthermore, this chloride opening could serve as a bridge to achieve indirect oxetane desymmetrization with other nucleophiles owing to the versatility of the alkyl chloride moiety. Simple substitution with different nucleophiles (e.g., NaCN, NaN_3, AcSK, and PMPSH) easily produced the highly enantioenriched derivatives **12–15**, which cannot be synthesized by direct oxetane desymmetrization at this stage (Scheme 3). We also synthesized triazole **17**, an important intermediate towards the antifungal agents ZD0870 and Sch45450.[9] The enantioenriched chloride **7c** could be readily synthesized according to our desymmetrization method. Subsequently, a simple substitution delivered **17**. Its optical purity could be improved to >99% by a single recrystallization (Scheme 4).

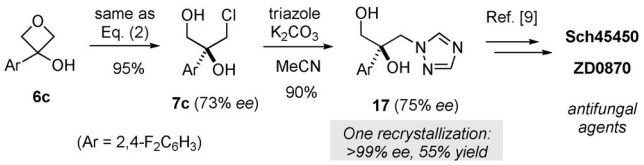
We carried out a series of control experiments to probe the mechanism (Table 5). In the absence of catalyst **A2**, the reaction still proceeded to yield the desired product, which, however, was formed as a racemate, representing a background reaction (entry 1). However, with dry molecular sieves, almost no conversion was observed, either with or without catalyst **A2**. These results further confirm that water is essential to this reaction and suggest that the in situ generated HCl is the nucleophile. The direct use of an HCl



Scheme 2. Further functionalization of the desymmetrization products. dba = dibenzylideneacetone, Ts = *para*-toluenesulfonyl.

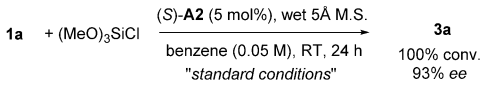


Scheme 3. Indirect desymmetrization reactions with other nucleophiles. PMP = *para*-methoxyphenyl.



Scheme 4. Synthesis of a key intermediate for triazole-containing antifungal agents.

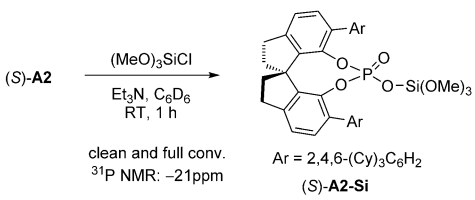
Table 5: Mechanistic control experiments.



Entry	Variation from the "standard conditions"	Conv. [%]	*ee* [%]
1	no (*S*)-**A2**	100	0
2	dry 5 Å M.S. instead of wet 5 Å M.S.	<10	–
3	dry 5 Å M.S. instead of wet 5 Å M.S., no (*S*)-**A2**	<10	–
4	HCl in dioxane (4 M, 2.0 equiv), no $(MeO)_3SiCl$, no 5 Å M.S.	100	57
5	HCl in dioxane (4 M, 1.0 equiv), no $(MeO)_3SiCl$, no 5 Å M.S.	100	78
6	sequential addition of dry $MgSO_4$ and H_2O (2.0 equiv) instead of wet 5 Å M.S.	100	92

solution in dioxane resulted in full conversion, but moderate enantioselectivity (entry 4). Higher enantioselectivity was observed with a smaller amount of HCl (entry 5), suggesting that a higher HCl concentration enhances the background reaction. Furthermore, aside from molecular sieves, $MgSO_4$ worked equally well as an additive in combination with water (entry 6), suggesting that the role of the molecular sieves is to serve as a water carrier for its even dispersion in the reaction mixture for slow HCl generation. The controlled release of HCl is essential to keep the HCl concentration low and thus inhibit the background reaction, thereby contributing to the high enantioselectivity.[10]

To determine the actual catalyst of this transformation (free **A2** or the silyl phosphate **A2-Si**),[11] we monitored the reaction by ^{31}P NMR spectroscopy. Indeed, mixing $(MeO)_3SiCl$ and the chiral phosphoric acid **A2** did result in the partial formation of the corresponding silyl phosphate (**A2-Si**), whose resonance at −21 ppm was confirmed by its separate synthesis [Eq. (5)]. However, in the standard reaction mixture at partial conversion, almost only the free acid **A2** was observed (Figure 1c) as the catalyst resting state, which is thus highly likely to be the actual catalyst. Finally,



(5)

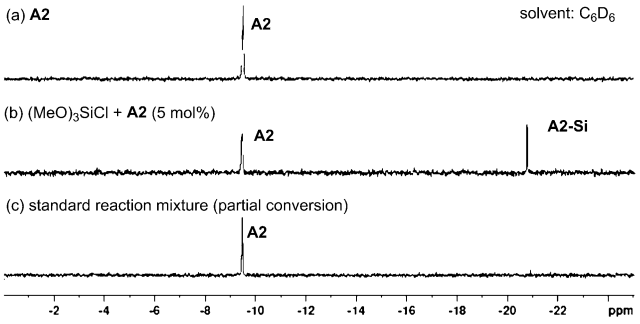
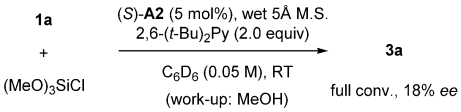


Figure 1. ^{31}P NMR analysis of the possible catalyst states.

2,6-di-*tert*-butylpyridine was added to the standard reaction as it is known to change the outcome of proton-involving pathways. In fact, very low enantioselectivity was observed [Eq. (6)]. These results are consistent with the hypothesis that the free acid **A2** is the actual catalyst under the standard reaction conditions.[12]



(6)

In summary, we have developed the first asymmetric oxetane opening with chloride, providing expedient access to highly functionalized three-carbon chiral building blocks with excellent efficiency and stereocontrol. Several notable challenges, such as the low chloride nucleophilicity, remote stereocontrol, and possible background reactions, were overcome by the employment of a suitable chloride source, a new catalyst, and the unprecedented use of wet molecular sieves for controlled HCl release. Mechanistic studies suggest that the free chiral acid is likely to be the actual catalyst. The unusual reaction conditions should enable the development of further asymmetric reactions that involve the use of HCl.

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Keywords: asymmetric catalysis · desymmetrization · organocatalysis · oxetanes · strained molecules

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[10] Notably, it was found that catalyst **A2** accelerates the background reaction, which explains the observed enantioselectivity (see the Supporting Information for kinetic studies). A similar phenomenon has been previously observed; see: T. Mita, E. N. Jacobsen, *Synlett* **2009**, 1680 – 1684. Free HCl has rarely been used in asymmetric catalysis.

[11] Silyl phosphates or the related sulfonimides have been proposed to be the actual catalysts generated in situ; see: a) E. B. Rowland, G. B. Rowland, E. Rivera-Otero, J. C. Antilla, *J. Am. Chem. Soc.* **2007**, *129*, 12084 – 12085; b) P. García-García, F. Lay, P. García-García, C. Rabalakos, B. List, *Angew. Chem. Int. Ed.* **2009**, *48*, 4363 – 4366; *Angew. Chem.* **2009**, *121*, 4427 – 4430; c) C. H. Cheon, H. Yamamoto, *Org. Lett.* **2010**, *12*, 2476 – 2479; d) Q. Wang, M. Leutzsch, M. van Gemmeren, B. List, *J. Am. Chem. Soc.* **2013**, *135*, 15334 – 15337.

[12] **A2-Si** also catalyzed the reaction, but with diminished enantioselectivity (86 % *ee* for **3a**). However, it is important to note that on the basis of the ^{31}P NMR analysis, **A2-Si** can be hydrolyzed in situ to yield the free acid **A2**.

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