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DOI: 10.1039/D0CC05509C

COMMUNICATION

Desymmetrization of *gem*-diols via water-assisted organocatalytic enantio- and diastereoselective cycloetherification

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

The first desymmetrization of *gem*-diols forming chiral hemiketal carbons was accomplished via organocatalytic enantio- and diastereoselective cycloetherification, which afforded optically active tetrahydropyrans containing a chiral hemiketal carbon and tetrasubstituted stereocenters bearing synthetically versatile fluorinated groups. The desymmetrization of silanediols was also demonstrated as an asymmetric route to chiral silicon centers.

Desymmetrization of achiral substrates is an efficient strategy for constructing tetrasubstituted chiral carbons, which are fundamental motifs that increase molecular complexity and diversity, but are among the most challenging targets in synthetic organic chemistry.[1] In particular, the desymmetrization of achiral diols has been extensively studied as it provides chiral molecules bearing oxygen-containing functional groups,[1d–1f] which play important roles within organisms.[2] However, to the best of our knowledge, *gem*-diols, which are the shortest achiral diols, have not been employed in this synthetic approach, even though desymmetrization of *gem*-diols allows for asymmetric construction of chiral hemiketal carbons, which are ubiquitous functional groups found in a variety of bioactive compounds and pharmaceuticals (Figure 1a).[3] In addition, while catalytic asymmetric ketalization and acetalization have been reported over the last decade,[4] there have been no examples of a catalytic enantioselective construction of hemiketals.

We recently developed methods for asymmetric construction of tetrasubstituted chiral carbons via enantio- and diastereoselective cycloetherification of cyanohydrins with bifunctional organocatalysts.[5] In these studies, a cyano group, which is a small and electronegative functional group, preferentially occupies the axial positions on anomeric carbons in saturated six-membered oxacycles; various cyanohydrins are enantioselectively transformed to densely functionalized tetrasubstituted chiral carbon units while forming tetrahydropyran (THP) rings. A hydroxy group is also a potent small and electronegative functional group, and indeed it is partially located in the axial position on anomeric carbons of saccharides in nature (Figure 1b). These concepts inspired us to investigate the desymmetrization of *gem*-diols via organocatalytic enantio- and diastereoselective cycloetherification (Scheme 1); this transformation affords optically active THP derivatives containing a chiral hemiketal carbon. The desymmetrization of silanediols was also investigated for the asymmetric construction of chiral silicon centers.

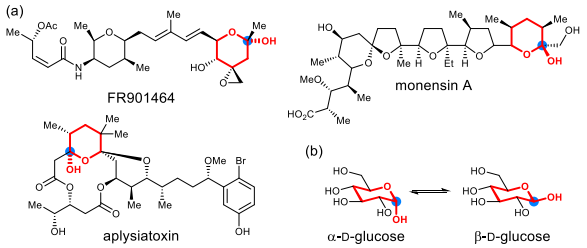
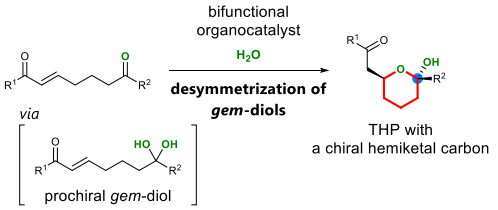


Fig. 1 Bioactive 2-hydroxy-THPs: (a) chiral hemiketals and (b) equilibrium of D-glucose.



Scheme 1 Desymmetrization of *gem*-diols via organocatalytic enantio- and diastereoselective cycloetherification.

We began our investigations using (*E*)-8,8,8-trifluoro-1-phenyloct-2-ene-1,7-dione (**1a**) and 3 equiv of water with 10 mol % of a bifunctional organocatalyst (**3a**–**3e**, Figure 2)[6] in

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† Electronic Supplementary Information (ESI) available: Experimental procedures, analytical and spectroscopic data for synthetic compounds, and copies of NMR. CCDC 2022129; 2022132.
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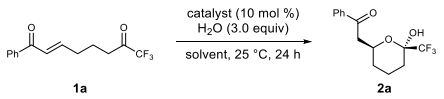
Table 1 Optimization of conditions[a]



1a 2a

Entry	Catalyst	Solvent	Yield (%)[b]	dr[c]	*ee* (%)
1	**3a**	CH_2Cl_2	93	>20:1	97
2	**3b**	CH_2Cl_2	89	>20:1	95
3	**3c**	CH_2Cl_2	81	>20:1	–96
4	**3d**	CH_2Cl_2	84	>20:1	–95
5	**3e**	CH_2Cl_2	87	>20:1	–97
6	**3f**	CH_2Cl_2	<5	—	—
7	**3g**	CH_2Cl_2	37	>20:1	–4
8	**3a**	H_2O	89	>20:1	63
9	**3a**	neat	36	>20:1	90

[a]Reactions were run using the substrate (0.15 mmol), H_2O (0.45 mmol), and the catalyst (0.015 mmol) in the solvent (0.30 mL). The mixture of **1a** and its hydrated diol **4a** (4.6:1–2.6:1) was used as the substrate. [b]Isolated yields.

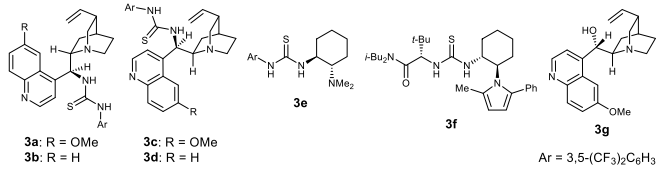
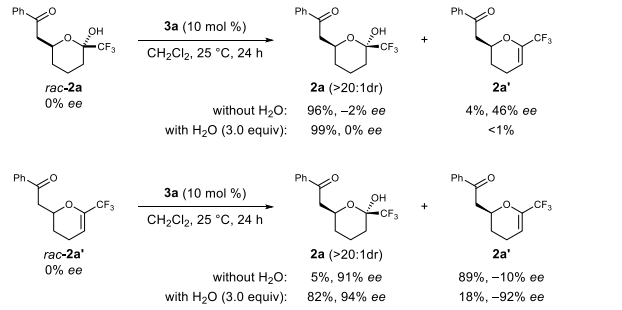


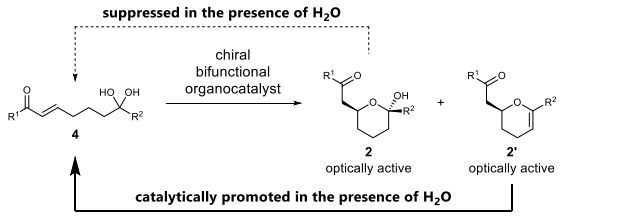
Fig. 2 Organocatalysts.

CH_2Cl_2 at 25 °C (Table 1, entries 1–5). All the bifunctional organocatalysts we investigated gave high yields and excellent enantio- and diastereoselectivities (Table 1, entries 1–5):[7] quinine- and cinchonidine-derived catalysts **3a** and **3b** afforded **2a** with high enantiomeric purity, and quinidine- and cinchonine-derived catalysts **3c** and **3d** afforded the opposite enantiomer of **2a** with high enantioselectivities (Table 1, entries 1–4). Moreover, catalyst **3e**, having a cyclohexanediamine framework, also afforded the product in good yield with high enantioselectivity (Table 1, entry 5). In contrast, catalyst **3f**, which has a significantly less basic nitrogen atom, provided only a trace amount of **2a** (Table 1, entry 6), and quinidine (**3g**) resulted in a significantly lower yield and enantioselectivity than those exhibited by catalysts **3a**–**3e** (Table 1, entry 7). These results demonstrate the significance of the bifunctionality of the catalyst containing amino and thiourea functional groups for not only the chemical yield but also the enantioselectivity. Various solvents were next investigated using **3a** as the catalyst; this reaction was hardly affected by solvent effects, and most organic solvents gave good to excellent yields and stereoselectivities.[8] Using water as the solvent also gave promising results, albeit with lower enantioselectivity (Table 1, entry 8), and even neat conditions provided **2a** with good stereoselectivity, although with lower yield (Table 1, entry 9).

During the optimization studies shown in Table 1, in order to construct the chiral hemiketal carbon of **2a** it proved to be necessary to suppress the formation of dihydropyran by-product **2a'** (Scheme S1 in the SI). By-product **2a'** may be also formed via intramolecular oxy-Michael addition of an enol form of **1a**;[9] further investigations revealed water plays an important role not only for generating *gem*-diol substrates, but also for controlling the reaction reversibility.[10] Using isolated *gem*-diol **4a**, the product selectivity of **2a** over **2a'** during the reaction was monitored in the presence and absence of 3.0 equiv of water (Scheme S1 in the SI). Although the ratio of **2a** to **2a'** gradually increased in both cases, the use of water proved to be of significance for obtaining high product selectivity. In addition, the absolute configurations of **2a** and its enantio- and diastereomeric purity did not change throughout reaction time (96–97% *ee*, >20:1 dr),[11] while those of **2a'** gradually changed (without water: from 77% to 16% *ee*; with water: from 79% to –16% *ee*).



Scheme 2 Effects of H_2O.

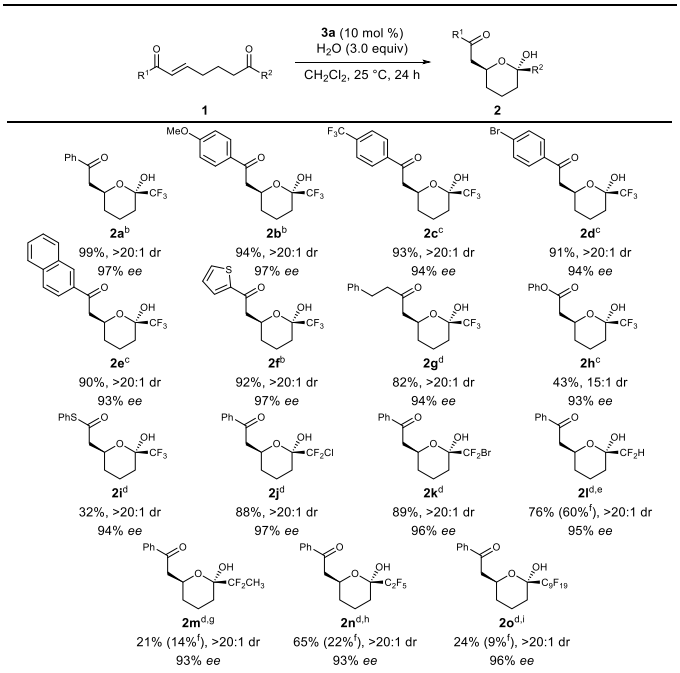


Scheme 3 Plausible reaction pathway.

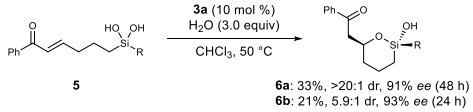
We also investigated the effect of water on the reaction reversibility (Scheme 2). Isolated products **2a** and **2a'** were prepared as racemic forms, then each exposed to the reaction conditions with or without water. In the absence of water, both *rac*-**2a** and *rac*-**2a'** slowly converted to each other.[12] Meanwhile, in the presence of water, *rac*-**2a** was not converted to **2a'**; instead all of **2a** was recovered as a racemate, implying the conversion of *rac*-**2a** was inhibited. In contrast, *rac*-**2a'** was rapidly converted to **2a** in the presence of water, and the resulting **2a** had excellent enantiomeric and diastereomeric purity. Thus, it is suggested that water accelerates the retro-Michael reaction of **2'** followed by enantio- and diastereoselective formation of **2**, while water inhibits the degradation of **2**, which is favorable for attaining efficient stereoselective construction of chiral hemiketal carbons (Scheme 3).[13] In addition, all the products resulting from the interconversion were optically active (Scheme 2). In the absence of **3a**, no interconversion took place, even in the presence of water (Scheme S2 in the SI). These results indicate that **3a** selectively catalyzes the conversion of **2'** in the presence of water.

With the optimized conditions using 3.0 equiv of water, we then explored the substrate scope (Table 2).[14] Both electron-rich

Table 2 Substrate scope[a]



[a]Reactions were run using the substrate (0.15 mmol), H_2O (0.45 mmol), and **3a** (0.015 mmol) in CH_2Cl_2 (0.30 mL). Yields represent material isolated after silica gel column chromatography. [b]Isolated diols **4** were used as the substrate. [c]The mixtures of **1** and its hydrated diol **4** (2.0:1–1:3.3) were used as the substrate. [d]Isolated ketones **1** were used as the substrate. [e]Reaction was run for 397 h. [f]Yields of the reactions for 24 h. [g]Reaction was run for 489 h. [h]Reaction was run for 579 h. [i]Reaction was run for 168 h.



Scheme 4 Desymmetrization of silanediols.

and electron-poor enones were tolerated, affording the corresponding products in good yields, high enantioselectivities, and excellent diastereoselectivities (Table 2, **2b** and **2c**). Enones bearing 4-bromophenyl, 2-naphthyl, and heterocyclic groups gave comparable results (Table 2, **2d**–**2f**). In addition, an alkyl group-bearing enone provided the product in comparable yield with good stereoselectivity (Table 2, **2g**). Furthermore, an α,β-unsaturated ester and thioester, which are useful for further transformations because of their higher oxidation state,[15,16] afforded the products with high stereoselectivities in moderate yields (Table 2, **2h** and **2i**). We also investigated the substituents (R^2) on the ketone; although electron-withdrawing groups were necessary to promote the formation of *gem*-diols,[17] various fluorinated substrates were useful. We observed that chlorodifluoromethyl and bromodifluoromethyl ketones provided the desired products in high yields with good stereoselectivities (Table 2, **2j** and **2k**). Halodifluoromethyl groups afford access to a wide variety of difluoroalkylated compounds,[18] which offer unique pharmacological properties associated with the fluorinated functional groups; however, the lack of enantioselective approaches to such units on sterically congested chiral carbons has limited their synthetic application to the construction of tetrasubstituted difluoromethylene-containing stereocenters.[19] In addition, because substrates bearing difluoromethyl, difluoroethyl, pentafluoroethyl, or longer perfluoroalkyl groups gave higher amounts of the dihydropyran by-product **2'** after 24 h, longer reaction times were used, which improved the yield of the desired products **2** via the interconversion of **2'** to **2** while maintaining high stereoselectivities (Table 2, **2l**, **2m**, **2n**, and **2o**).[20] Moreover, this method also enabled the desymmetrization of silanediols **5** to yield silicon-containing oxacyclic products **6** with high enantio- and diastereoselectivities, albeit in moderate yields. Thus, chiral silicon centers were constructed with high stereoselectivities; such species are also challenging synthetic targets in asymmetric catalysis (Scheme 4).[21,22] The absolute configurations of **2d** and the corresponding dihydropyran by-product **2d'** were determined by X-ray crystallography (see the SI), and the configurations of all other **2**, **6**, and **2'** products were assigned analogously.

Conclusions

In conclusion, desymmetrization of *gem*-diols to form chiral hemiketal carbons was accomplished for the first time via organocatalytic enantio- and diastereoselective cycloetherification and afforded optically active THP derivatives, which are otherwise difficult to achieve. The use of water is important not only for generating the *gem*-diols, but also for controlling the interconversion between the desired hemiketal products and the by-products that do not contain a hemiketal carbon. The desymmetrization of silanediols was also demonstrated as a catalytic asymmetric route to construct silicon-stereogenic silanes. This synthetic method facilitates the construction of densely functionalized heterocyclic architectures bearing chiral hemiketals and silicon centers. This method is also useful as an approach to construct tetrasubstituted chiral carbons bearing synthetically versatile fluorinated groups. Further studies to expand the scope of this methodology and its application in the asymmetric synthesis of bioactive compounds are currently underway in our laboratory and will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported financially by the Japanese Ministry of Education, Culture, Sports, Science and Technology (JP15H05845, JP17K19120, JP18K14214, JP18H04258, and JP20K05491). K.A. also acknowledges the Institute for Synthetic Organic Chemistry, Toyo Gosei Memorial Foundation, the Sumitomo Foundation, Fukuoka Naohiko Memorial Foundation, Inoue Foundation for Science, and Mizuho Foundation for the Promotion of Sciences. A.M. also acknowledges the Japan Society for the Promotion of Science for Young Scientists for the fellowship support.

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8 Results of further solvent screening are described in the SI (Table S2).

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11 Even after 5 min, the reaction of **4a** yielded **2a** with >20:1 dr (Scheme S1 in the SI). Thus, we believe the diastereoselectivity as well as enantioselectivity were kinetically controlled through the involvement of the highly stereoselective desymmetrization of the *gem*-diol.

12 In the conversion of *rac*-**2a'** to **2a**, dissolved water was probably incorporated into **2a**.

13 The reaction of *rac*-**2a'** also yielded **1a** in the absence of water (Scheme S2 in the SI). In addition, when a cyclic enol ether, which is analogous to **2'**, was exposed to the reaction conditions in the presence of water, hydration did not take place (Scheme S3 in the SI). Moreover, in the presence of an achiral bifunctional catalyst, optically active **2a** and **2a'** were converted to racemic **2a'** and **2a**, respectively (Scheme S3 in the SI). Thus, we believe the interconversion between **2** and **2'** involved a retro-Michael addition.

14 See Schemes S4–S6 in the SI for more details.

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22 In CH_2Cl_2 at 25 °C for 24 h, **6a** was obtained in 7% yield with >20:1 dr and 95% *ee*; in $CHCl_3$ at 50 °C for 48 h without H_2O, **6a** was obtained in 35% yield with >20:1 dr and 90% *ee*. See Scheme S8 in the SI for more details.

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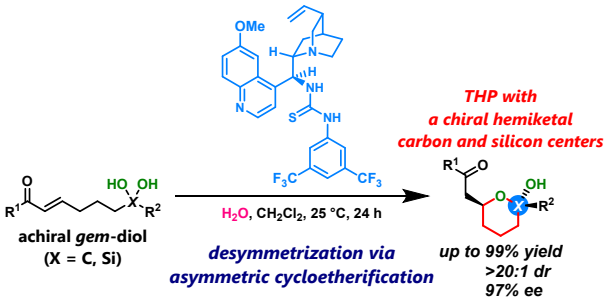
DOI: 10.1039/D0CC05509C



The first desymmetrization of *gem*-diols forming chiral hemiketal carbon and silicon centers was accomplished via organocatalytic enantio- and diastereoselective cycloetherification.