Parts-per-million level loading organocatalysed enantioselective silylation of alcohols

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The field of organocatalysis has blossomed over the past few decades, becoming an alternative to transition-metal catalysis or even replacing the realm of transition-metal catalysis. However, a truly powerful organocatalyst with a high turnover number (TON) and turnover frequency (TOF) while retaining high enantioselectivity is yet to be discovered. Similar to metal catalysis, extremely low catalyst loading (p.p.m. or p.p.b. levels) is the ultimate goal of the organocatalysis community. Herein we report a remarkable contribution in this context: 1 p.p.m. loading of a simple 1,1'-bi-2-naphthol-based organocatalyst was enough to achieve highly enantioselective silylation reactions of alcohols. The unprecedented TONs and excellent enantioselectivity are ascribed to the robustness of the catalyst and systematic cooperative hydrogen-bonding organocatalysis in a densely confined chiral space.
Catalysis, in principle, should offer an infinite turnover number (TON) for a desired chemical transformation by regenerating the catalyst without altering its molecular-level structure and physicochemical properties. However, limitations arise from different deactivation mechanisms and catalyst poisoning by chemical impurities and/or side products, lowering the lifetime of catalytically active species.

The current strong interest in asymmetric organocatalysis has pinpointed that small organic molecules are comparable to transition-metal catalysts owing to their noble activation modes and excellent selectivity. However, further application of organocatalysts in industry is often hampered by their relatively low turnover efficiency than those of the corresponding homogeneous or heterogeneous metal-catalysed reactions.

Despite many efforts, the current limit of catalyst loading for asymmetric organocatalysis is usually in the range of 0.1–1 mol% (refs 6,7) for overriding of the non-selective background pathway. Thus, high turnover organocatalysis (for example, TON > 100,000) is considered as a formidable challenge.

Our group has developed a new type of easily accessible organocatalysts, 1,1′-bi-2-naphthol (BINOL)-based polyether catalyst 1 (Fig. 1), that bears phenols and polyether units, for asymmetric cation-binding catalysis. Its unprecedented activation mode and remarkable enantioselectivity are explained by multiple binding and hydrogen-bonding interactions of the polyether and phenols with the metal salt to generate reactive ‘chiral’ anions. Strikingly, the robustness of catalyst 1 enabled the one-pot large-scale production of unnatural α-amino acids even under harsh reaction conditions (refluxing in 6 N HCl) and the subsequent quantitative recovery of the catalyst. The structural simplicity and vast application potential of the catalyst stimulated us to explore other challenging catalytic asymmetric reactions.

The preparation of enantiopure secondary alcohols is of significant interest in the pharmaceutical industry; therefore, diverse methodologies have been developed for preparing these synths with high enantiomeric excess. The kinetic resolution of racemic alcohols is an ideal approach to access both enantiomers by one enantioselective transformation, for example, acylative kinetic resolution reactions. Although silylation of alcohols is one of the most common strategies in protecting alcohol functionalities, the asymmetric silylation reactions of functionally unbiased alcohols is still challenging due to the lack of additional functional groups needed to interact with a chiral catalyst. Until now, the substrate scope of the reported silylation reactions has been mostly limited to the substrates with pendant donors (for example, additional hydroxyl or pyridyl groups), which are necessary to achieve good selectivity by increasing the binding affinity towards catalysts. Snapper and Hoveyda demonstrated remarkable examples in this context by using amino-acid-derived bifunctional organocatalysts.

However, as a high catalyst loading (20–30 mol%) was necessary to obtain the desired products with high enantioselectivity, it may hamper the large-scale application of these organocatalysts. On the other hand, our group showed that catalysts such as 1 (X = Cl, Br or I) catalyse desilylative kinetic resolution of silyl-protected racemic alcohols in the presence of potassium fluoride. Although this approach provided a new synthetic route for chiral alcohols, a practical application was also far from satisfactory due to the high catalyst loading (20 mol%) and very low turnover frequency (TOF; 43–55% conversion after 5 days at 20 °C) (Fig. 1).

Herein we report that the same catalyst 1 can catalyse the enantioselective silylation of simple aryl alkanols, which do not contain any pendant donors, exhibiting unprecedented catalytic TONs (substrate to catalyst = up to 1,000,000) and excellent enantioselectivity. Extremely high TONs and excellent enantioselectivity were obtained by thorough catalyst structure analysis, detailed mechanistic studies and the identification of catalyst regeneration conditions.

Results

Reaction design. We commenced our study by selecting -bi-2-naphthol (BINOL) as the silylating reagent (Supplementary Table 1). HMDS is a stable, commercially available and inexpensive reagent for the trimethylsilylation of alcohols, releasing ammonia as the sole by-product. However, the weak silylating ability of HMDS is the main drawback to its application, particularly in asymmetric catalysis. Because HMDS is usually activated using an acidic catalyst, chiral Brønsted acid catalysts were chosen first for investigation of the enantioselective silylation of alcohols with HMDS; however, these catalysts resulted in very low conversions and selectivities (Supplementary Fig. 1).

Given our previous studies on catalyst 1 (refs 10,11), in spite of the lower acidity of phenolic protons than those of the common Brønsted acid catalysts, we presumed that catalyst 1 would act as a catalyst for the silylative kinetic resolution of racemic alcohols; the interaction between the acidic phenolic protons of the catalyst and the leaving group of the silylating reagent (Y) by hydrogen bonding would enhance the electrophilicity of Si. Moreover, the ether moieties of the catalyst would function as a Brønsted base by the association with an alcohol substrate, enhancing alcohol reactivity (Fig. 2).

Catalyst screening. To prove this assumption, several chiral BINOL-based bis(hydroxy) polyethers 1a–1m (Fig. 3) were screened to shed light on the relationship between the catalyst’s structure and the reaction outcome. Gratifyingly, after the optimization of the reaction conditions (Supplementary Tables 1–3), catalysts 1c, 1d, 1e, 1f and 1g bearing electron-withdrawing groups Cl, Br, I, CF₃ and C₂F₅, respectively, on the 3,3'-positions showed some catalytic activity (Fig. 3). The catalytic performance of these catalysts depends significantly on the steric demand of the substituents. Thus, catalysts 1e and 1f showed the best catalytic performance with s-factors of 42 and 44, respectively (Fig. 3). In contrast, other catalysts without electron-withdrawing substituents at the 3,3'-positions (catalysts 1a and 1b) were inactive under identical reaction conditions. In addition, the less acidic H₃X-BINOL-derived catalyst 1h showed negligible conversion, thus, indicating the importance of the Brønsted acidity of the phenols. To further confirm the importance of an acidic phenol moiety for catalysis, we synthesized the catalysts 1i–1l. A total loss in catalytic activity was observed when one or both phenol.

Figure 1 | Structure of BINOL-based polyether catalyst 1 and our previous work: desilylative kinetic resolution of racemic alcohols.

Selectivity factor (s) = (rate of fast reacting enantiomer)/(rate of slow reacting enantiomer).
groups were replaced by OMe (1i and 1j). Silylated catalysts (1k and 1l) also showed no activity, excluding the possibility of a silyl-transfer reaction from the silylated catalyst to the starting alcohol to afford the desired product. The importance of the polyether chain was confirmed unambiguously by replacing the polyether with the alkyl chain (catalyst 1m), indicating that the polyether backbone is crucial in achieving the observed catalytic activity.

The complexation of an alcohol substrate with the polyether moiety of the catalyst was clearly verified by observing the decreased $^{13}$C spin–lattice relaxation time ($T_1$) on complexation of catalyst 1e with racemic alcohol 2a (Supplementary Table 4). This significant decrease in the $T_1$ value of ether moiety of 1e indicates that the complexation of the alcohol with catalyst 1e significantly reduces the mobility of the ether units. Moreover, the fast-reacting (S)-configured substrate ((S)-2a) exhibited a more decreased $T_1$ value of ether moiety than that of the slow-reacting substrate, (R)-2a, directly indicating a selective association of the catalyst with the fast-reacting (S)-2a (ref. 31). On the other hand, no change in $T_1$ values was observed when alcohol 2a was mixed with the alkyl chain-replaced catalyst 1m, verifying the crucial role of the polyether backbone for the interaction with alcohols (Supplementary Table 5). $^{29}$Si nuclear magnetic resonance (NMR) experiments were also used to establish the interaction.
between the phenolic proton of the catalyst and HMDS (Supplementary Table 6). As expected, the $^{29}$Si NMR data of HMDS in the presence of diverse phenols exhibited $^{29}$Si chemical shifts that are shifted downfield relative to the uncoordinated HMDS, dependent on phenol acidity. This result clearly indicates that the acidic phenolic proton interacts with HMDS, increasing the electrophilic character of the silicon atom. The results from NMR spectroscopy and other experimental results (Fig. 3) strongly support our proposed transition-state model shown in Fig. 2 ($Y = \text{NHSiMe}_3$).

Optimization of the reaction conditions. More importantly, during the optimization studies, we also realized that the major deactivation pathway of the catalyst is the silylation of the phenol moieties under the reaction conditions. In a separated set of experiments, we verified that the steric demand of the 3,3'-substituents of the catalyst is crucial to this deactivation pathway (Supplementary Table 7). As mentioned earlier, the silylated catalysts (1k and 1l) are inactive towards the kinetic resolution reaction (Fig. 3).

Recognizing that the rate of desilylation of trimethylsilyl (TMS)-protected phenols using KF in oligoethylene glycol is much faster than those of TMS-protected secondary alcohols, we speculated that the addition of KF and an appropriate proton source would regenerate the catalyst in situ (Table 1a). As predicted, the desilylation reaction of the silylated catalysts (1k and 1l) and subsequent protonation of the K salt of catalysts clearly improved TON and TOF (Table 1b). As shown in entries 1 and 7 of Table 1b, with catalyst loading of 0.01 mol% (100 p.p.m.), almost no catalytic activity was observed without the additives. However, the addition of KF and a proton source such as water, t-BuOH and Amberlite CG 50 (a weakly acidic cation-exchange resin) was able to restore catalysis (entries 2–5). In particular, a combination of KF and Amberlite CG 50 provided the best result (entry 5). Even with 100 p.p.m. of catalyst loading, 52% conversion was obtained in 12 h with excellent selectivity ($s = 57$). This can be ascribed to the adequate acidity of Amberlite CG 50 for rapid protonation of the K salt of 1e, releasing the insoluble polymeric K salt of Amberlite CG 50 as a by-product without interfering with the catalysis. Moreover, Amberlite CG 50 alone was completely inactive towards catalysis. In addition, we also confirmed that, under the reaction condition where KF and Amberlite CG 50 were used as additives (condition in entry 5), the unwanted desilylation process that takes place with a TMS-protected secondary alcohol such as (R)-3a did not occur (Supplementary Fig. 2) and that the relative catalytic activity of 1a–1f is very similar with that shown in Fig. 3 (Supplementary Table 8).

### Table 1 | Proposed mechanism of catalyst reactivation (a) and effects of KF and proton source additives on turnover numbers (b).

| Entry | Cat 1e (p.p.m.) | KF | H⁺ source | Temp. (°C) | Time | Conv. (%) | s-factor |
|-------|----------------|-----|-----------|-----------|------|----------|----------|
| 1     | 100            | No  | No        | 20        | 12 h | 4        | ND       |
| 2     | 100            | Yes | No        | 20        | 12 h | 17       | 54       |
| 3     | 100            | Yes | t-BuOH    | 20        | 12 h | 15       | 58       |
| 4     | 100            | Yes | H₂O       | 20        | 12 h | 18       | 48       |
| 5     | 100            | Yes | CG 50     | 20        | 12 h | 52       | 57       |
| 6     | 100            | Yes | CG 50/H₂O | 20        | 12 h | 48       | 51       |
| 7     | 100            | No  | No        | –30       | 24 h | 0        | ND       |
| 8     | 100            | Yes | CG 50     | –30       | 24 h | 50       | 132      |
| 9     | 100            | Yes | CG 50/H₂O | –30       | 24 h | 52       | 144      |
| 10#   | 1              | Yes | CG 50     | –30       | 14 d | 33       | 99       |

*The appropriate aliquots were taken from the stock solution of 1e in CH₂Cl₂.

1KF (1 equiv. for entries 2–6, 8 and 9; 0.5 equiv. for entry 10) was added.

2 CG 50 (0.8 equiv. for entries 5, 6, 8 and 9; 0.2 equiv. for entry 10), t-BuOH (0.8 equiv.) or H₂O (0.8 equiv.) was added.

3Selectivity factor ($s$) = (rate of fast reacting enantiomer)/(rate of slow reacting enantiomer).

4Using 5 mmol of racemic alcohol 2a. CG 50 = Amberlite CG 50 (10 mmol H⁺ g⁻¹).
Further improvement of selectivity was achieved by lowering the reaction temperature to \(-30^\circ\text{C}\) (entry 10). More surprisingly, the catalyst is active even at 1 p.p.m. catalyst loading (0.0001 mol%) with excellent s-factor (s = 99) in Table 1, entry 10). The reaction proceeds with p.p.b.-level catalyst loading (100 p.p.b.); however, a significant decrease in selectivity (s = 17) was observed (Supplementary Fig. 3). To the best of our knowledge, this is the lowest catalyst loading for metal-free organocatalysis reported to date, with excellent enantioselectivities and high TOF (TOF \(\sim 1,000\) h\(^{-1}\), entry 11) also being achieved. The high turnover efficiency can be attributed to the stability of the catalyst, its insensitivity to impurities and rapid reactivation under the reaction conditions. Notably, the reactions do not require exclusion of air and moisture, and thus solvent purification is not needed. As shown from the results of entries 6 and 9, the presence of water does not affect catalytic results, which is highly beneficial for further large-scale applications.

**Scope of the reaction.** With the optimized reaction conditions in hand, the substrate scope of our protocol was investigated, and the results are shown in Fig. 4. Various simple acyclic 1-arylalkanols 2a–2r without any secondary binding functionality were successfully resolved with excellent selectivity factors. Both the electron-withdrawing and electron-donating substituents on the aromatic ring were tolerated under the reaction conditions. Sterically demanding ortho-substituted substrates were also...
Figure 5 | Applications of the silylation reaction protocol. (a) Gram-scale kinetic resolution of secondary alcohol 2a using 1 p.p.m. of catalyst: The reactions were performed in the presence of 0.5 equiv of KF and 0.2 equiv of Amberlite CG 50 (CG 50). *Calculated conversion, \( \text{ee}(1e) = \text{ee}(2a) + \text{ee}(3a) \). † Isolated yields. (b) Catalytic enantioselective silylation of meso-diols 4 (0.1 mmol scale): The reactions were performed in the presence of 1 equiv of KF and 0.6 equiv of Amberlite CG 50 (CG 50). ‡ The conversion was determined by \(^1\)H-NMR. § Isolated yields. 

Methods

General procedure for catalytic asymmetric silylation of secondary alcohols.
To a solution of chiral catalyst 1e (0.12 mg, 0.01 mol%) and secondary alcohols 2a–2r (1.0 mmol) in distilled CH\(_2\)Cl\(_2\) (5.0 ml), spray-dried KF (58.1 mg, 100 mol%) and Amberlite CG 50 (80 mg, 0.8 equiv.) were added in one portion. The reaction mixture was stirred at \( -15 ^\circ\text{C} \) by using only 0.012 mg of the catalyst (1 p.p.m. to 2a), with a high TOF (1.309 h\(^{-1}\)) and an excellent s-factor of 77. The reaction was performed in the presence of 1 equiv of KF and 0.6 equiv of Amberlite CG 50 (CG 50). *Calculated conversion, \( \text{ee}(1e) = \text{ee}(2a) + \text{ee}(3a) \). † Isolated yields.
References

1. Crabtree, R. H. Deactivation in homogeneous transition metal catalysis: causes, avoidance, and cure. *Chem. Rev.* 115, 127–150 (2015).
2. List, B. & Yang, J. W. The organic approach to asymmetric catalysis. *Science* 313, 1584–1586 (2006).
3. MacMillan, D. W. C. The advent and development of organocatalysis. *Nature* 455, 304–308 (2008).
4. Lee, J. W. G. W. Lianjotostil catalysis. *Science* 341, 1225–1229 (2013).
5. Cozzi, F. Immobilization of organic catalysts: when, why, and how. *Adv. Synth. Catal.* 348, 1367–1390 (2006).
6. Giacalone, F., Gruttaduria, M., Agrigento, P. & Noto, R. Low-loading asymmetric organocatalysis. *Chem. Soc. Rev.* 41, 2406–2447 (2012).
7. Ingle, G. K., Mormino, M. G., Wojtas, L. & Antilla, J. C. Chiral phosphoric acid catalysis: addition of thiols to N-acyl imines: access to chiral N,S-acetals. *Org. Lett.* 13, 4822–4825 (2011).
8. Ratjen, L., van Gemmeren, M., Pescialioli, F. & List, B. Towards high-performance Lewis acid organocatalysis. *Angew. Chem. Int. Ed.* 53, 8765–8769 (2014).
9. Brak, K. & Jacobsen, E. N. Asymmetric ion-pairing catalysis. *Angew. Chem. Int. Ed.* 52, 534–561 (2013).
10. Yan, H. *et al.* A chiral-anion generator: application to catalytic desilylative kinetic resolution of silyl-protected secondary alcohols. *Angew. Chem. Int. Ed.* 49, 8915–8917 (2010).
11. Yan, H., Oh, J. S., Lee, J. W. & Song, C. E. Scalable organocatalytic asymmetric Strecker reactions catalysed by a chiral cyanide generator. *Nat. Commun.* 3, 1212 (2012).
12. Reeves, J. T., Senanayake, C. H., Song, J. J. & Farina, V. Asymmetric synthesis of active pharmaceutical ingredients. *Chem. Rev.* 106, 2734–2796 (2006).
13. Cobley, C. J. & Holt-Tiffin, K. E. Asymmetric routes to chiral secondary alcohols. *Pharmaceutical Technology* 34, 6–13 (2010).
14. Huism, J. W. G. W., Liang, J. & Krebber, A. Practical chiral alcohol manufacture using ketoreductases. *Curr. Opin. Chem. Biol.* 14, 122–129 (2010).
15. Noyori, R. & Ohkuma, T. Asymmetric catalysis by architectural and functional molecular engineering: practical chemo- and stereoselective hydrogenation of ketones. *Angew. Chem. Int. Ed.* 40, 40–73 (2001).
16. Müller, C. E. & Schreiner, P. R. Organocatalytic enantioselective acyl transfer onto ketones as well as meso alcohols, amines, and thioles. *Angew. Chem. Int. Ed.* 50, 6012–6014 (2011).
17. Isobe, T., Fukuda, K., Araki, Y. & Ishikawa, T. Modified guanidines as chiral superbases: The first example of asymmetric silylation of secondary alcohols. *Chem. Commun.* 3, 243–244 (2001).
18. Sheppard, C. I., Taylor, I. L. & Wiskur, S. L. Silylation-based kinetic resolution of monofunctional secondary alcohols. *Org. Lett.* 13, 3794–3797 (2011).
19. Rendler, S., Auer, G. & Oestreich, M. Kinetic resolution of chiral secondary alcohols by dehydrogenative coupling with recyclable silicon-styrenic silanes. *Angew. Chem. Int. Ed.* 44, 7620–7624 (2005).
20. Klaire, H. F. T. & Oestreich, M. Chiral recognition with silicon-styrenic silanes: remarkable selectivity factors in the kinetic resolution of donor-functionalized alcohols. *Angew. Chem. Int. Ed.* 46, 9335–9338 (2007).
21. Karatas, B., Rendler, S., Frohlich, R. & Oestreich, M. Kinetic resolution of donor-functionalised tertiary alcohols by Cu-H-catalysed stereoselective silylation using a strained silicon-styrenic silane. *Org. Biomol. Chem.* 6, 1435–1440 (2008).
22. Rendler, S. & Oestreich, M. Kinetic resolution and desymmetrization by stereoselective silylation of alcohols. *Angew. Chem. Int. Ed.* 47, 248–250 (2008).
23. Steves, A. & Oestreich, M. Facile preparation of CF₃-substituted carbinals with an azine donor and subsequent kinetic resolution through stereoselective Si-O coupling. *Org. Biomol. Chem.* 7, 4464–4469 (2009).
24. Weckgenannt, A., Mewsald, M. & Oestreich, M. Asymmetric Si-O coupling of alcohols. *Org. Biomol. Chem.* 8, 1497–1504 (2010).

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