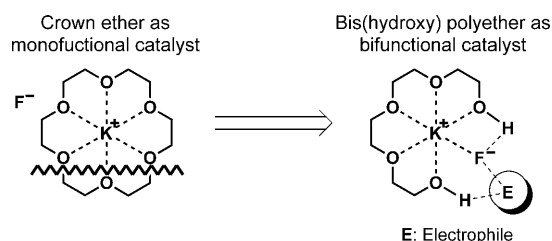**Chiral Anions**

A Chiral-Anion Generator: Application to Catalytic Desilylative Kinetic Resolution of Silyl-Protected Secondary Alcohols**

*Hailong Yan, Hyeong Bin Jang, Ji-Woong Lee, Hong Ki Kim, Soon Won Lee, Jung Woon Yang, and Choong Eui Song*

Various important classes of organic reactions can be conducted with fluoride anions as a catalyst or nucleophilic reagent.[1] Although alkali-metal fluorides are a readily available source of the fluoride ion, their applications are limited, owing to their low solubilities in organic solvents. To increase the solubility of alkali-metal salts, crown ethers are frequently employed to generate a "naked" fluoride ion.[2] Although this simple but innovative concept of crown ethers has had a profound impact on science,[3] their application to chemical reactions is limited, as they can only activate fluorides (or, more generally, anions) as monofunctional promoters.

Recently, much effort has been made to develop efficient multifunctional organocatalysts which enable cooperative catalysis in an enzymelike manner.[4] In this context, we wondered if bis(hydroxy) polyethers generated by breaking an ether unit of crown ethers could serve as a new type of multifunctional organic promoter in which 1) the ether groups would act as a Lewis base toward K⁺, thus freeing the counteranion and enhancing the solubility of the alkali-metal salts, and 2) the terminal OH groups generated by breaking the ether unit would be able to simultaneously activate the electrophile by hydrogen bonding, thereby stabilizing the transition state (Scheme 1).

On the basis of our hypothesis, we developed a remarkably powerful protocol for nucleophilic fluorination using bis(hydroxy) polyethers such as tetraethylene glycol as a new type of promoter.[5] We could also show that this type of promoter can easily be modified to yield chiral variants (Scheme 2); thus, the enantioselective desilylative kinetic resolution of silyl ethers of racemic secondary alcohols with KF using the chiral bis(hydroxy) polyether as an organo-

Scheme 1. New multifunctional promoters, bis(hydroxy) polyethers, generated by breaking an ether unit of crown ethers.

Chiral bis(hydroxy) polyether:
Chiral-anion generator
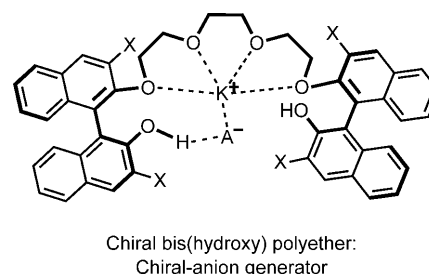
Scheme 2. Chiral variants of bis(hydroxy) polyethers: very broadly applicable chiral-anion generators.

catalyst is in principle possible. We have now completed an extensive screening of catalysts and report herein the highly efficient desilylative kinetic resolution of various silyl-protected racemic alcohols, which constitutes a conceptually new approach to the production of optically active silyl-protected secondary alcohols.[6,7] The single-crystal X-ray structure of the complex consisting of the catalyst and KF provides detailed and interesting insight into the origin of the catalytic activity and stereoselectivity.

To gain insight into the structure–activity relationship, we synthesized a variety of chiral 1,1′-bi-2-naphthol (BINOL)-based bis(hydroxy) polyethers and examined their catalytic efficiency for the desilylative kinetic resolution of the trimethylsilyl (TMS)-protected alcohol *rac*-**1** as a model substrate with KF (0.7 equiv) in the presence of the catalyst (20 mol%) in 1,4-dioxane[8] at 20°C. The results are summarized in Table 1.

Quite surprisingly, as shown from the results in Table 1, only those catalysts having halogen substituents at the 3,3′-position on the BINOL group exhibited catalytic activity. When catalysts having no halogen substituent at the 3,3′-position, such as **3** and **4**, were employed, no or only trace conversion was observed (Table 1, entries 1 and 2). More interestingly, a dramatic enhancement in both the activity and enantioselectivity was observed when going from chlorine to

[*] H. Yan, H. B. Jang, J.-W. Lee,[+] H. K. Kim, Prof. Dr. S. W. Lee, Prof. Dr. C. E. Song
Department of Chemistry, Sungkyunkwan University
Suwon 440-746 (Korea)
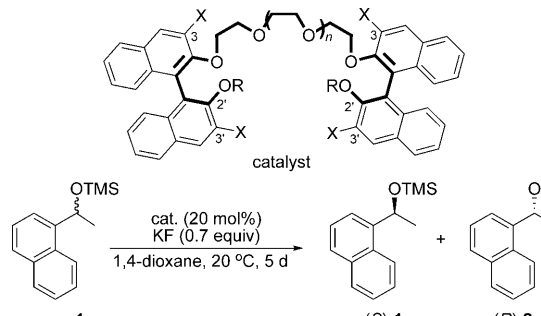Fax: (+82) 31-290-7075
E-mail: s1673@skku.edu

Prof. Dr. J. W. Yang, Prof. Dr. C. E. Song
Department of Energy Science, Sungkyunkwan University
Suwon 440-746 (Korea)

[+] Present address: Max-Planck-Institut für Kohlenforschung
45470 Mülheim an der Ruhr (Germany)

Table 1: Catalyst screening for desilylative kinetic resolution of *rac*-1 with KF.

Entry	Catalyst	Conv. [%]	*ee* of (S)-1[a]	s[b]
1	(S)-3 (X=H, n=1, R=H)	8	n.d.	n.d.
2	(S)-4 (X=Ph, n=1, R=H)	n.r.	–	–
3	(S)-5 (X=Cl, n=1, R=H)	43.5	11	1.5
4	(R)-6 (X=Br, n=1, R=H)	56	93[c]	21
5	(R)-7 (X=Br, n=0, R=H)	30	6[c]	1.3
6	(R)-8 (X=Br, n=2, R=H)	n.r.	–	–
7	(R)-9 (X=Br, n=1, R=Me)	n.r.	–	–
8	(S)-10 (X=I, n=1, R=H)	55.5	97	29

[a] After deprotection of the TMS group, the enantiomeric excess of the resulting alcohol was determined by HPLC analysis. [b] The selectivity factors (s) are the averages of two runs. [c] The product has the R configuration. n.r. = no reaction, n.d. = not determined.

iodine (Table 1, entries 3, 4, and 8). Thus, the best selectivity factor (s=29) was obtained when the 3,3′-iodo-substituted chiral BINOL catalyst **10** was employed (Table 1, entry 8). As expected, it was also observed that the terminal free hydroxy group at the 2′,2′-position of the BINOL backbone plays an essential role in maintaining the superior catalytic performance of the multifunctional catalyst.[9] When the reaction was carried out using a catalyst in which the 2′,2′-hydroxy groups are methylated, no reaction was observed (Table 1, entry 7). Finally, the ether chain length was also shown to play a crucial role in the performance of the catalyst, which, as would be expected, is responsible for the formation of a suitable chiral coordination cage with KF. The catalyst having three ether units (-(OCH$_2$CH$_2$)$_3$-); n=1) was shown to be a more effective catalyst in terms of the s factor than the other catalysts bearing longer (n=2) or shorter (n=0) ether units (compare the results in Table 1, entries 4, 5, and 6).

Fortunately, we were able to obtain the single-crystal X-ray structure of the dimeric form of the complex of KF and **6**, which provides detailed insight into the origin of the catalytic activity and stereoselectivity (Figure 1).[10] According to the X-ray structure, the Lewis basic halogen substituents (bromine in this case) at the 3,3′-positions of the BINOL unit interact strongly with the potassium ion as a counterpart of the Lewis base, thereby reducing the Coulombic interaction between K$^+$ and F$^-$ ions. Thus, we attributed the higher activity and stereoselectivity of **10** (X=I) than of **5** (X=Cl) and **6** (X=Br) to the greater polarizability of the iodine atom, which allows it to more strongly coordinate to the potassium cation. In addition to this strong coordination of the iodine atom to the potassium cation, the steric size of the former might also influence the chiral environment of the transition
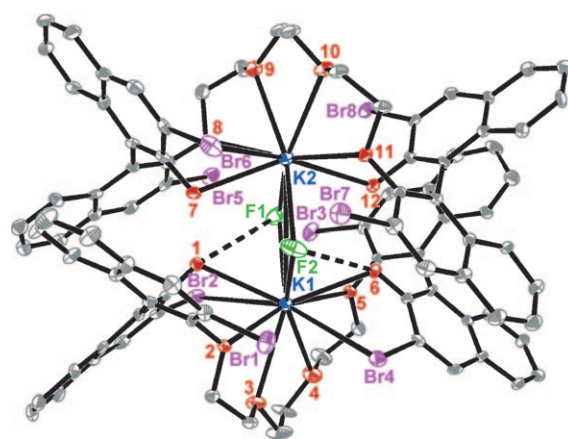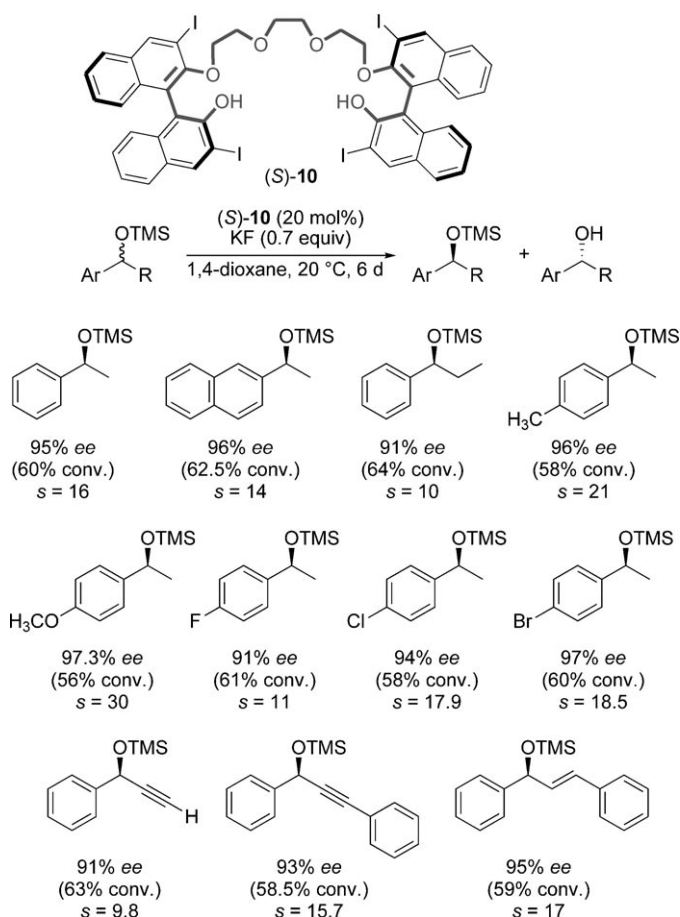

Figure 1. ORTEP structure of a dimeric form of the complex of KF-(R)-6.[10]

state, thus resulting in the observed enhanced enantioselectivity.[11]

Having established that the iodine-substituted catalyst **10** is the optimum catalyst, we explored the scope of the substrate using (S)-**10** as the catalyst. As shown in Scheme 3, an array of O-TMS-protected secondary aryl

Scheme 3. Scope of the reaction. After deprotection of the TMS group of the remaining substrates, the enantiomeric excess of the resulting alcohols was determined by HPLC analysis. The selectivity factors (s) are the averages of two runs; see the Supporting Information for details.

alkyl carbinols can be kinetically resolved with good selectivity factors, affording the enantioenriched *O*-TMS-protected secondary aryl alkyl carbinols with excellent *ee* values. The TMS-protected aryl propargyl and aryl alkenyl carbinols can also be easily accessed in excellent enantioselectivities by desilylative kinetic resolution. To our knowledge, this is the first successful catalytic example of the desilylative kinetic resolution of the silyl ethers of racemic secondary alcohols, which, as mentioned above, provides a conceptually new approach to the production of optically active silyl-protected secondary alcohols.[6,7]

The in situ generation of chiral fluorides, which can serve as catalysts for a variety of asymmetric reactions, is one of the most challenging problems in modern organic chemistry. We developed a new structural motif for use as a chiral-anion generator, composed of a bis(hydroxy) polyether bearing a 3,3′-halogen-substituted chiral BINOL unit, showing excellent enantioselectivity (*s* up to 30, or greater than 97 % *ee* for the remaining substrate at 56 % conversion) for the enantioselective desilylative kinetic resolution of a variety of silyl-protected racemic alcohols with KF. The single-crystal X-ray structure of the complex of the catalyst and KF provides detailed insight into the origin of the catalytic activity and enantioselectivity. This study can open up a new avenue of research for chiral-fluoride-catalyzed asymmetric reactions,[1b,c] which have vast synthetic potential but remain a relatively undeveloped field. More generally, our results offer a new concept for the molecular design of chiral-anion generators as well as opportunities for the development of related applications.

[1] For a general review, see: a) J. H. Clark, *Chem. Rev.* **1980**, *80*, 429–452; for reviews on chiral fluoride-catalyzed asymmetric reactions, see: b) S. Shirakawa, T. Ooi, K. Maruoka in *Asymmetric Phase Transfer Catalysis* (Ed.: K. Maruoka), Wiley-VCH, Weinheim, **2008**, chap. 9, pp. 189–206; c) T. Ooi, K. Maruoka, *Acc. Chem. Res.* **2004**, *37*, 526–533; for a recent example of a chiral fluoride nucleophile, see: d) J. A. Kalow, A. G. Doyle, *J. Am. Chem. Soc.* **2010**, *132*, 3268–3269.

[2] C. L. Liotta, H. P. Harris, *J. Am. Chem. Soc.* **1974**, *96*, 2250–2252.

[3] C. J. Pedersen, Nobel Lecture, http://nobelprize.org/nobel_prizes/chemistry/laureates/1987/pedersen-lecture.html.

[4] Cooperative catalysis using bifunctional organocatalysts: a) J.-A. Ma, D. Cahard, *Angew. Chem.* **2004**, *116*, 4666–4683; *Angew. Chem. Int. Ed.* **2004**, *43*, 4566–4583; b) C. Allemann, R. Gordillo, F. R. Clemente, P. H.-Y. Cheong, K. N. Houk, *Acc. Chem. Res.* **2004**, *37*, 558–569.

[5] In the presence of tetraethyleneglycol, the fluorination reactions proceeded unprecedentedly fast and were completed within 1.5 h, affording the fluorinated product in quantitative yields. Moreover, under microwave conditions, the reaction was completed within a minute. In contrast to these results, in organic solvents and even in the presence of crown ethers, the fluorination reaction gave only 4 % yield after the same reaction time. J. W. Lee, H. Yan, H. B. Jang, H. K. Kim, S.-W. Park, S. Lee, D. Y. Chi, C. E. Song, *Angew. Chem.* **2009**, *121*, 7819–7822; *Angew. Chem. Int. Ed.* **2009**, *48*, 7683–7686.

[6] Reviews: a) S. Rendler, M. Oestreich, *Angew. Chem.* **2008**, *120*, 254–257; *Angew. Chem. Int. Ed.* **2008**, *47*, 248–250; b) A. Weickgenannt, M. Mewald, M. Oestreich, *Org. Biomol. Chem.* **2010**, *8*, 1497–1504.

[7] Examples for organocatalytic enantioselective silylation of alcohols: a) T. Isobe, K. Fukuda, Y. Araki, T. Ishikawa, *Chem. Commun.* **2001**, 243–244; b) Y. Zhao, J. Rodrigo, A. H. Hoveyda, M. L. Snapper, *Nature* **2006**, *443*, 67–70; c) Y. Zhao, A. W. Mitra, A. H. Hoveyda, M. L. Snapper, *Angew. Chem.* **2007**, *119*, 8623–8626; *Angew. Chem. Int. Ed.* **2007**, *46*, 8471–8474; d) Y. Zhao, A. H. Hoveyda, M. L. Snapper, *Angew. Chem.* **2009**, *121*, 555–558; *Angew. Chem. Int. Ed.* **2009**, *48*, 547–550.

[8] Other solvents were also screened for this reaction using the catalyst **6**, but its enantioselectivity with them was found to be much inferior to that with dioxane: toluene ($s = 3.9$), Et$_2$O ($s = 2.5$), THF ($s = 6$), CH$_3$CN ($s = 1.0$), ClCH$_2$CH$_2$Cl ($s = 4.7$), and CH$_2$Cl$_2$ ($s = 10$). For more experimental results, see Table S-2 in the Supporting Information.

[9] This result is in agreement with our recent study on nucleophilic fluorination reactions using bis(hydroxy) polyethers and KF.

[10] CCDC 777372 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] To understand the effect of halogen substituents on the catalytic activity and enantioselectivity in more detail and to explain the observed sense of stereoselectivity, computational studies are currently underway in our laboratory.