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Enantioselective Synthesis of *anti-syn*-Trihalides and *anti-syn-anti*-Tetrahalides *via* Asymmetric *β*-Elimination

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ABSTRACT: Structural motifs containing contiguous halide-bearing stereocenters are common in natural products as well as bioactive molecules. A few successful examples have been reported in the area of asymmetric vicinal dihalogenation of alkenes for accessing dihalogenated products; in this report, an alternative generation method of contiguous halide-bearing stereocenters *α,β,γ,δ* relative to carbonyl group in excellent enantioselectivity is proposed by utilizing a Song's oligoEG catalyst-catalyzed asymmetric *β*-elimination. According to this methodology, a wide range of *anti-syn*-trihalides and *anti-syn-anti*-tetrahalides with high levels of enantioselectivity were synthesized. The synthetic utility of the contiguous halide-bearing stereocenters was demonstrated by several transformations. The results of high-resolution mass spectrometry indicated that the favorable interaction between catalyst and one of the enantiomers of racemic contiguously multi-halogenated ketone contributed to the original enantioselectivity of dehydrohalogenation. Deuterium kinetic isotope effect experiment revealed that this *β*-elimination reaction proceeds by the *E2* mechanism. This strategy opens a new pathway for the asymmetric synthesis of contiguous halide-bearing stereocenters of great complexity.

INTRODUCTION

Structural motifs containing contiguous halide-bearing stereocenters are found in numerous natural products and important bioactive compounds and their absolute and relative configurations are often crucial for their biological activities.[1] In addition, the stereogenic halides can also undergo various selective transformations with high fidelity to afford a range of stereodefined compounds in chemistry and medicine.[2] Accordingly, much effort has been devoted to developing new and efficient methods for their preparation, and great progress has been made in recent years.[3] Among several methods, metal- and/or organo-catalyzed asymmetric vicinal dihalogenation of alkenes has been proven as the most powerful tool for accessing the vicinal dihalogenated molecules. In 2009, the Snyder group reported the first asymmetric dichlorination of an isolated alkene and successfully realized the total synthesis of (–)-napyradiomycin A1 with this method.[4] In 2011, the Nicolaou group demonstrated a catalytic asymmetric dichlorination of allylic alcohols by employing dimeric cinchona alkaloid derivatives as the catalyst.[5] Recently, the Burns group made a landmark achievement not only in the asymmetric dibromination and bromochlorination of allylic alcohols but also in the dichlorination of non-conjugated alkenes with TADDOL and tridentate Schiff base as ligands, respectively.[6] Most recently, Borhan[7] and his co-workers reported an enantioselective vicinal dihalogenation of allyl amides catalyzed by $(DHQD)_2PHAL$. Moreover, the research groups of Denmark,[8] Vanderwal,[9] Carreira,[10] and Tanaka[11] et al. also contributed to the development of dihalogenating agents, methods and total synthesis of halogenated natural products. However, those methodologies mainly focused on the synthesis of either *anti*-dihalides from easily accessible *E*-alkenes or *syn*-dihalides from *Z*-alkenes. The asymmetric synthesis of *syn*-dihalides from *E*-alkenes has not been reported, although *syn*-dihalides are an important privileged structure in halogenated natural products (Figure 1).[1b] In particular, to date, the asymmetric method regarding the direct enantioselective preparation of contiguous 1,2,3-trihalides and/or 1,2,3,4-tetrahalides containing *syn*-dihalides has not been reported due to two challenges. Firstly, sequential chiral centers increase the difficulty in steric control. Secondly, multiple diastereoisomers are obtained in these reactions. Therefore, it is necessary to develop asymmetric variants for the direct preparation of contiguous halogen-dense compounds, especially the compounds containing *syn*-dihalides.

In this study, we attempted to develop an alternative approach to prepare those motifs containing contiguous halide-bearing stereocenters with readily available catalysts and reagents. Since racemic contiguous halide-bearing stereocenters are easily accessible,[12] kinetic resolution[13] is an alternative and complementary strategy for the preparation of motifs containing contiguous halide-bearing stereocenters. A possible drawback of this hypothetical approach is that except dynamic kinetic

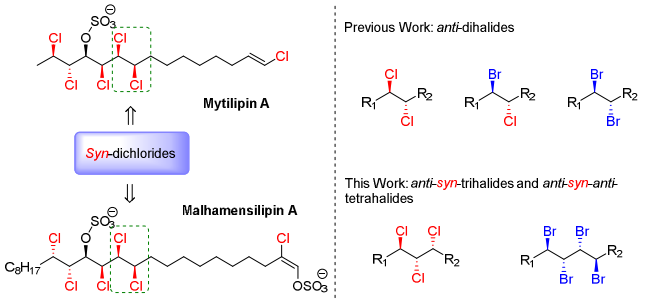


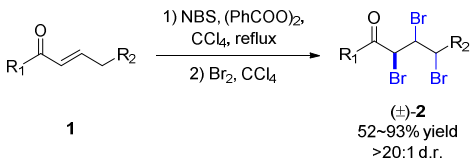
Figure 1. Representative bioactive natural compounds and related work

resolution, a mixture of the product and unreacted starting material is often obtained. If these compounds are potentially important halogenated materials produced in high enantiomeric excess, a kinetic resolution would become a more attractive strategy because it would allow the simultaneous synthesis of two chiral halogenated targets by single transformation. We recently developed a kinetic resolution of *β*-sulfonyl ketones via *β*-elimination[14] catalyzed by Song's oligoEG catalyst[15] and envisioned that such a strategy might enable an enantioselective dehydrohalogenation of *β*-halogenated ketones. Herein, we report our successful development of a kinetic resolution of contiguously multi-halogenated ketones to deliver highly enantioenriched contiguous halide-bearing stereocenters via asymmetric *β*-elimination.

RESULTS AND DISCUSSION

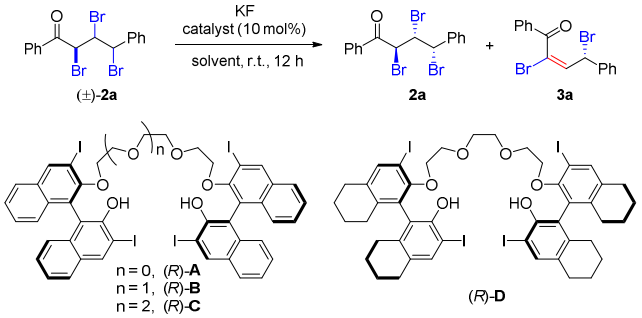
To validate our hypothesis, we initiated our studies with racemic *anti-syn-α,β,γ*-tribromo ketone (±)-**2a** as a model substrate and confined Song's oligoEG catalyst which has previously identified as an excellent catalyst for asymmetric catalysis, as the catalyst. The required racemic *anti-syn-α,β,γ*-tribromo ketones can be easily obtained via Wohl-Ziegler bromination (the introduction of a bromine substituent at the allylic position of olefins) and subsequent dibromination of olefins with moderate yield and excellent d.r. values (Scheme 1). To our delight, via the kinetic resolution process, one of the enantiomers of the racemic *anti-syn-α,β,γ*-tribromo ketone was converted into trisubstituted allyl bromide **3a** with a *γ* stereogenic center by the elimination of *β*-bromine and its efficiency was markedly dependent on the catalyst structure (entry 1-4) (Table 1). The subsequent studies on chiral Song's oligoEG catalyst revealed that the catalyst bearing three ether units ((*R*)-**B**; S = 25; entry 2) was proved to be a much more effective catalyst compared with the other catalysts bearing longer (4-ether units; (*R*)-**C**; S = 3; entry 3) or shorter (2-ether units; (*R*)-**A**; S = 4; entry 1) ether

Scheme 1. Synthesis of Racemic Substrates



units. The 3,3'-diiodo-substituted catalyst (*R*)-**B** showed the highest activity and enantioselectivity. Among the tested solvents (entry 2, 5-10), toluene exhibited the best selectivity. After further optimization of reaction conditions, the equivalent of KF markedly improved the S value. Henceforth, the reaction of *anti-syn-α,β,γ*-tribromo ketone (±)-**2a** with excess KF (1.5 equiv.) in the presence of 10 mol% catalyst (*R*)-**B** in toluene at room temperature resulted in the highest S value (S = 33; entry 12). After 12 h, the remaining **2a** exhibited a high enantiomeric excess (97%) at 55% conversion.

Table 1. Optimization of the Reaction Conditions[a]



Entry	Cat.	Solvent (0.05 M)	KF (equiv.)	ee (%)/**2a**[b]	Conv. (%)[c]	S[d]
1	(*R*)-**A**	toluene	1.0	14	20	4
2	(*R*)-**B**	toluene	1.0	86	52	25
3	(*R*)-**C**	toluene	1.0	6	11	3
4	(*R*)-**D**	toluene	1.0	29	27	10
5	(*R*)-**B**	CH_2Cl_2	1.0	61	45	12
6	(*R*)-**B**	*m*-xylene	1.0	97	60	20
7	(*R*)-**B**	*o*-xylene	1.0	78	51	16
8	(*R*)-**B**	1,4-dioxane	1.0	6	43	1
9	(*R*)-**B**	mesitylene	1.0	64	45	15
10	(*R*)-**B**	THF	1.0	11	32	2
11	(*R*)-**B**	toluene	0.8	41	34	13
12	(*R*)-**B**	toluene	1.5	97	55	33
13	(*R*)-**B**	toluene	2.0	99	64	18

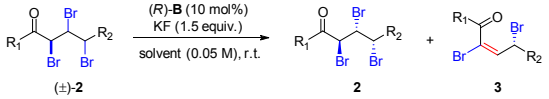
[a]Reaction conditions: (±)-**2a** (0.05 mmol), catalyst (0.005 mmol) and KF in solvent (1.0 mL) at r.t. for 12 h, unless otherwise specified. [b]Enantiomeric excesses were determined by HPLC analysis. [c]Conversion ratio was calculated by the methods of Fiaud: Conv. = ee/(ee+ee'). [d]Selectivity values were calculated by the methods of Fiaud: S = ln[(1-Conv.)(1-ee)]/ln[(1-Conv.)(1+ee)].

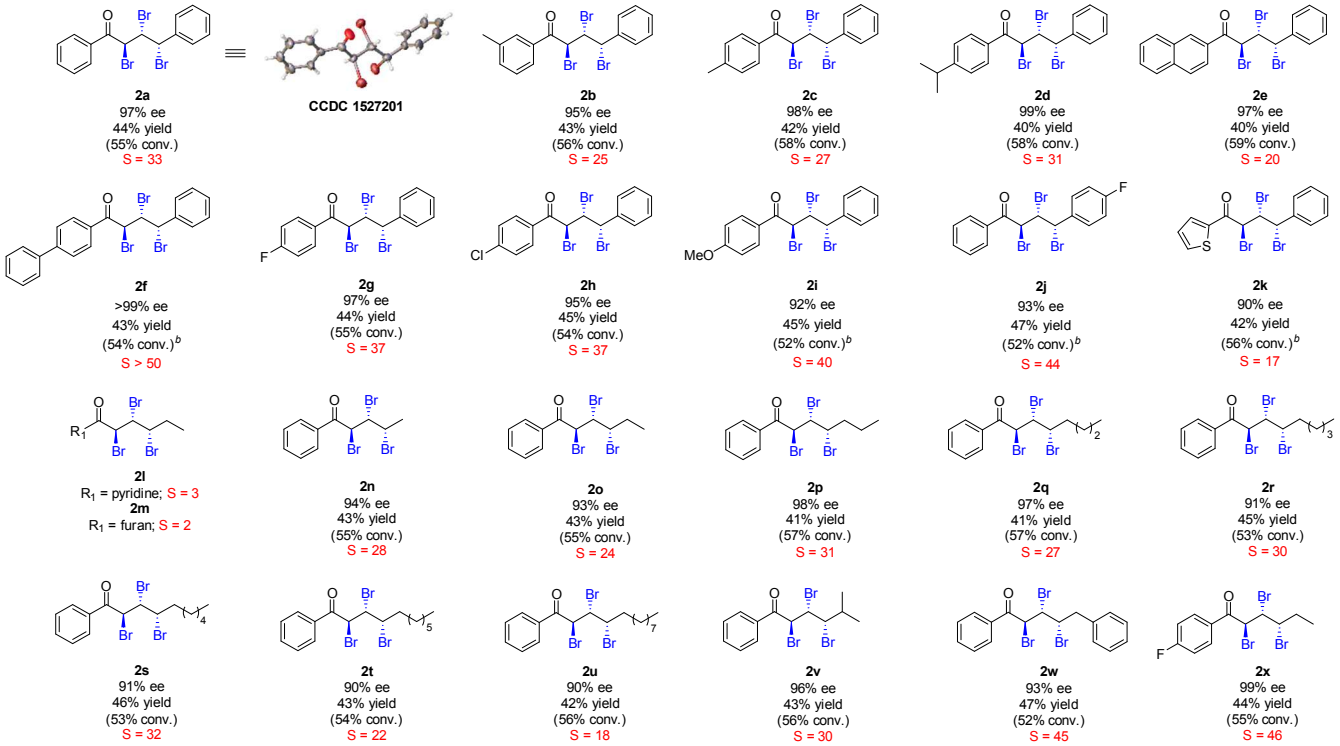
After establishing the optimal reaction conditions, a wide range of *anti-syn-α,β,γ*-tribromo ketones (±)-**2a**-(±)-**2j** with different aromatic substituents were then tested under the optimized reaction conditions (1.5 equiv. of KF, and 10 mol% of catalyst in toluene at room temperature) to verify the generality of the reaction, and the results are summarized in Table 2. The reaction of *α,β,γ*-tribromo ketones (±)**2a**-(±)**2j** bearing different aryl substituents of either electron-donating or electron-withdrawing groups proceeded smoothly to afford the trisubstituted allyl bromide **3a**-**3j** with excellent *E*/*Z* selectivity (*E*:*Z* > 20:1) and good enantioselectivity (see Supporting Information for details), meanwhile the unreacted *α,β,γ*-tribromo ketones **2a**-**2j** were recovered in 40-47% yield with 90-99% ee. For the heteroaromatic *α,β,γ*-tribromo ketones, only (±)-**2k** in which the thiophene is known isostere of phenyl

can underwent the kinetic resolution process with useful S factor (S = 17). Other heteroaromatic *α,β,γ*-tribromo ketones (pyridine and furan) led to dramatically reduced S factor (Table 2, **2l**, **2m**). The relative and absolute configurations were determined to be '*anti-syn*' and (*S,R,S*) by single crystal X-ray crystallographic analysis of the compound **2a**.[16] By analogy, the same configuration was assigned to all **2** compounds.

We then investigated the applicability of this catalytic system to the other classes of substrates. Gratifyingly, when R_2 group of (±)-**2n**-(±)-**2x** was an aliphatic substituent, the reaction also showed excellent enantioselectivity.

Table 2. Substrate Scope[a]





[a]Unless otherwise indicated, the reactions were carried out with (±)-**2** (0.1 mmol), KF (1.5 equiv.) and catalyst (*R*)-**B** (10 mol%) in toluene (**2a–2k**, 2.0 mL) or CH_2Cl_2 (**2l–2x**, 2.0 mL) at r.t.; enantiomeric excesses were determined by HPLC analysis; yield was determined after chromatographic purification; conversion ratio was calculated by the methods of Fiaud: Conv. = ee/(ee+ee'); selectivity values were calculated by the methods of Fiaud: S = ln[(1-Conv.)(1-ee)]/ln[(1-Conv.)(1+ee)]. [b]Determined by ^{1}H NMR.

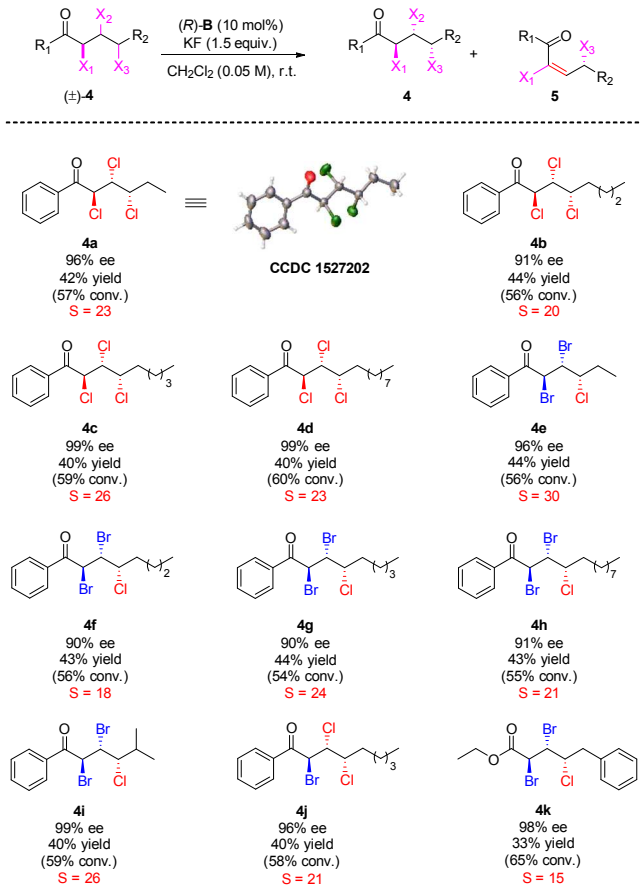
The chain length of R_2 group slightly affected the S value. The trisubstituted allyl bromides **3n**-**3x** with good enantioselectivity and excellent *E:Z* selectivity (*E:Z* > 20:1) were obtained, meanwhile unreacted *anti-syn*-**2n**-**2x** were recovered in 90-99% ee and 41-47% yield (Table 2).

Furthermore, we envisioned that this methodology might also be used in the resolution of some more challenging substrates, such as the substrate containing different halogen atoms. The resolution of *α,β,γ*-trichloro ketones, *α,β*-dibromo-*γ*-chloro ketones and *α*-bromo-*β,γ*-dichloro ketone proceeded as efficiently as that of *anti-syn-α,β,γ*-tribromo ketones (Table 3, **4a–4j**). Gratifyingly, extension to ester substituent at R1 position such as **4k** also worked out well with a useful S factor (S = 15) (Table 3, **4k**). The substrate bearing alkyl substituent at R1 position, however, led to poor selectivity (see Supporting Information for details). The relative and absolute configuration of **4a** was unambiguously established by X-ray crystallographic analysis.[16] The wide substrate scope showed the power of this approach for the asymmetric induction.

To demonstrate the practicality of this process, we carried out a preparative scale synthesis of **4a** under the optimal reaction conditions. As displayed in Scheme 2, the chemical yield and enantioselectivity almost showed no change. Next, a few transformations were selected and performed on **4a** to further demonstrate the synthetic potential of the chiral *anti-syn*-trihalogenated ketone. The carbonyl group of **4a** could be reduced stereoselectivitively without affecting enantiopurity to provide the resulting alcohol **6** containing four contiguous stereogen-

ic centers. The relative configuration of the compound **7** derived from **6** was established by single crystal X-ray crystallographic analysis.[16] Motivated by many bioactive natural products containing a sulfate functional moiety attached to the chiral halides,[17] sulfation of the secondary alcohol on **6** was conducted according to Carreira's condition[10] to provide sulfated product **8** in almost quantitative yield. Epoxide formation by treatment of **6** with NaH provided enantiomerically enriched epoxide **9**. For the elimination product **30**, the γ-bromide could be substituted by NaN_3 to provide azide product **10** in excellent yield.

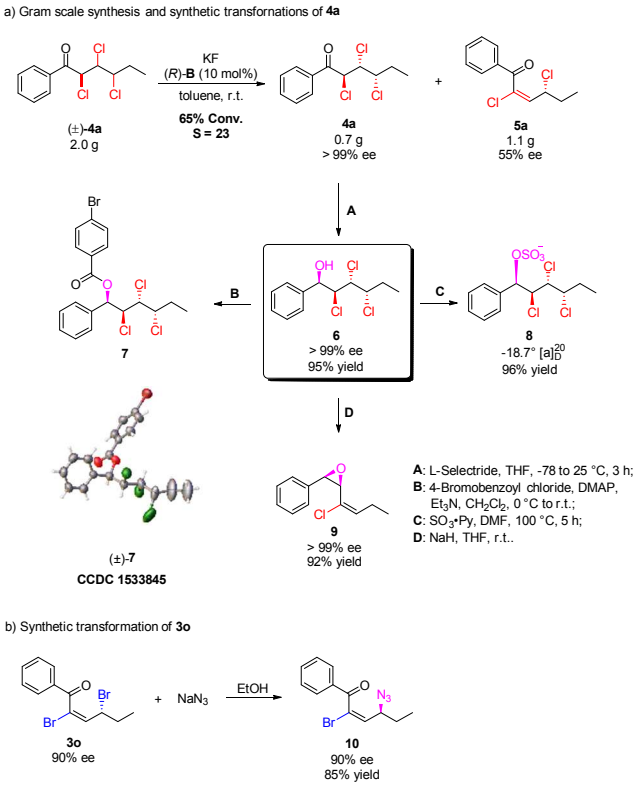
Table 3. Substrate Scope[a]



[a]Unless otherwise indicated, the reactions were carried out with (±)-**4** (0.1 mmol), KF (1.5 equiv.) and catalyst (*R*)-**B** (10 mol%) in CH_2Cl_2 (2.0 mL) at r.t.; enantiomeric excesses were determined by HPLC analysis; yield was determined after chromatographic purification; conversion ratio was calculated by the methods of Fiaud: Conv. = ee/(ee+ee'); selectivity values were calculated by the methods of Fiaud: S = ln[(1-Conv.)(1-ee)]/ln[(1-Conv.)(1+ee)].

We were further interested in expanding this methodology to the kinetic resolution of α,β,γ,δ-tetrahalogenated ketones. In theory, the kinetic resolution of α,β,γ,δ-tetrahalogenated ketones is challenging because the double elimination may occur and produce the dienone product. After screening the reaction conditions, we find that the addition of the Amberlite CG 50 can improve the performance of catalyst (*R*)-**B**, meanwhile the dienone product was not detected. This can be ascribed to the adequate acidity of Amberlite CG 50 for rapid protonation of the potassium salt of (*R*)-**B**, releasing the insoluble polymeric potassium salt of Amberlite CG 50 as a by-product without interfering with the catalysis. Thus a combination of excessive KF and Amberlite CG 50 provided the best result. The preliminary results of this transformation were shown in Table 4. Irrespective of the electronic and steric nature of the substituents, the *anti-syn-anti* **11a-11d** were recovered with excellent enantioselectivity. The absolute configuration of **11a** was determined to be (*S,S,S,S*) by X-ray crystallography.[16]

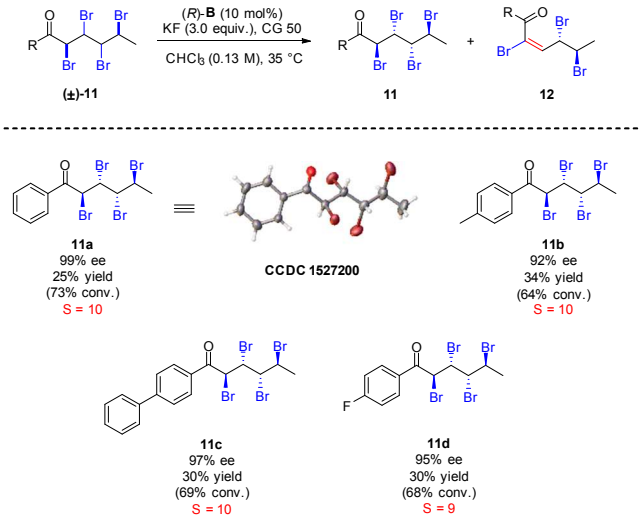
Scheme 2. Gram-scale Preparation and Synthetic Applications



To gain insight into the reaction mechanism, a series of experiments and spectroscopic studies were carried out (Scheme 3). An intermolecular competition between (±)-**2a** and (±)-**D-2a** demonstrated a kinetic isotope effect (k_H/k_D = 4.43), which suggested that the deprotonation of α-proton was probably involved in the rate-determining step. Based on the kinetic isotope effect studies and additional experimental results (see Supporting Information for details), we speculated that the C-H and C-halogen bonds broke simultaneously.[18] Furthermore, we also conducted an in situ electrospray ionization mass spectroscopy (ESI-MS) analysis with the reaction mixture containing (*R*)-**B**, KF, **4a** and **4c'** (1:1:1:1 mixture). Gratifyingly, the proposed intermediate **I** could be observed in the measurements of ESI-MS (positive ion mode). This result suggested that the complexation between the (2*R*,3*S*,4*R*)-**4c'**

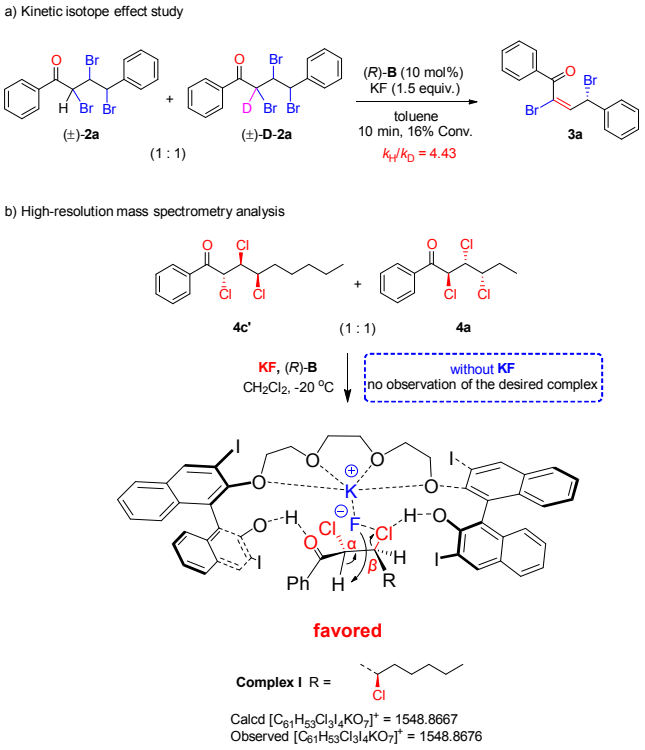
enantiomer and catalyst (*R*)-**B** (found, m/z 1548.8676) was better than that between the (2*S*,3*R*,4*S*)-**4a** enantiomer and the catalyst (*R*)-**B**. This finding revealed that the interaction between the chiral catalyst and its favored enantiomers of racemic substrates contributed to the original enantioselectivity of dehydrohalogenation. In contrast, in the absence of KF, the desired complex was not observed

Table 4. Substrate Scope[a]



[a]Unless otherwise indicated, the reactions were carried out with (±)-**11** (0.1 mmol), KF (3.0 equiv.), CG 50 (8.0 mg) and catalyst (*R*)-**B** (10 mol%) in $CHCl_3$ (0.75 mL) at 35 °C; enantiomeric excesses were determined by HPLC analysis; yield was determined after chromatographic purification; conversion ratio was calculated by the methods of Fiaud: Conv. = ee/(ee+ee'); selectivity values were calculated by the methods of Fiaud: S = ln[(1-Conv.)(1-ee)]/ln[(1-Conv.)(1+ee)].

Scheme 3. Preliminary Mechanistic Studies



in HRMS. The difference can be explained by the essential role of K^+ (potassium fluoride) in promoting the formation of the complex. Taking the results described above and our previous report into consideration, we proposed the mode of stereoinduction, as shown in Scheme 3b. The carbonyl group of substrate is presumably hydrogen bonded to one of OH groups of (*R*)-**B**, thus placing the *α*-halide stereocenter in its close vicinity. The formation of hydrogen bond between the *β*-halide and another OH group of (*R*)-**B** is the enantio-discriminating step in our reaction.

CONCLUSIONS

In summary, we have successfully developed an efficient catalytic asymmetric reaction for the synthesis of the derivatives of *anti-syn*-trihalides and *anti-syn-anti*-tetrahalides by *β*-elimination. According to this method, a wide range of motifs containing contiguous halide-bearing stereocenters with excellent enantioselectivity are synthesized, delivering a practical and straightforward approach to this fundamental and important privileged structure. The method can be readily scaled up to a preparative scale (2.0 gram). The HRMS studies suggest that the formation of complex between the chiral polyether, potassium fluoride and *α,β,γ*-trihalogenated ketone is responsible for the high stereoselectivity. Kinetic isotope effect experiment revealed that this *β*-elimination reaction proceeds by the *E2* mechanism. Further efforts regarding the synthetic utility of this approach to other important organic transformations are ongoing.

ASSOCIATED CONTENT

Supporting Information.

Experimental procedure and characterization data for all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) CCDC 1527201 (**2a**), 1527202 (**4a**), 1533845 (**7**), and 1527200 (**11a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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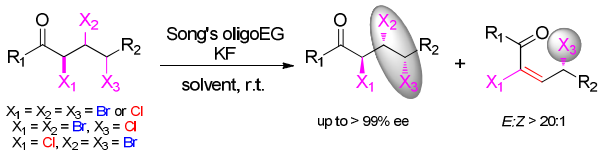

- **Contiguous halide-bearing stereocenters**
- ***Containing syn-dihalides***
- ***S factor up to >50***
- ***Mild reaction conditions***
- ***Preparative scale***