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Phase-transfer-catalyzed Asymmetric Alkylation with Epoxy Triflates as Alkylating Agents: Highly Stereoselective Synthesis of γ,δ-Epoxy-α-amino Acids

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Although alkyl sulfonates are commonly used for alkylating agents, there are very few reports on phase-transfer-catalyzed asymmetric alkylation with alkyl sulfonates. Herein, we report that the asymmetric reaction using glycine Schiff base **1** and optically pure epoxy triflates *op*-**2** proceeded smoothly in the presence of phase-transfer catalyst (*S*,*S*)-**4a** to furnish γ,δ-epoxy-α-amino acids **3** in good yield with high enantioselectivity.

Alkylation has been utilized as the one of the most fundamental, yet versatile reactions for carbon–carbon bond formation in synthetic organic chemistry, and asymmetric alkylation has been developed with several types of phase-transfer catalysts.[1] However, asymmetric alkylation under phase-transfer conditions is strictly limited to only alkyl halides (i.e., R–X; X = Br and I), and this fact is always inherently problematic when the required alkyl halides are not easily available. For a particular example, the preparation of epoxy halides is relatively cumbersome, and especially the synthesis of chiral epihalohydrin requires multiple steps, thereby often resulting in low yields (eq 1, Figure 1).[2]

On the other hand, although alkyl sulfonates are utilized as useful alkylating agents and easily prepared by one step from the corresponding alcohols,[3] there are sparse examples of phase-transfer-catalyzed asymmetric alkylation with alkyl sulfonates, which give unsatisfactory results.[4] If alkyl sulfonates can be applied as alkylating agents under phase-transfer conditions, it will certainly expand the synthetic value of phase-transfer catalysis. In order to realize our strategy, we focus our attention on the use of epoxy sulfonates as alkylating agents, which can be prepared from the corresponding alcohols concisely by the Sharpless asymmetric epoxidation in two steps as shown in eq 2 (Figure 1). Here, we wish to report a first practical phase-transfer-catalyzed asymmetric alkylation of glycine Schiff base **1** with epoxy triflates **2** for the stereoselective synthesis of γ,δ-epoxy-α-amino acid derivatives, which are frequently encountered as important scaffolds in several total syntheses.[5]

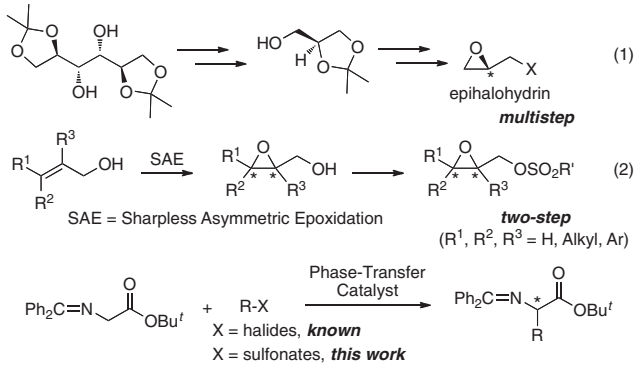
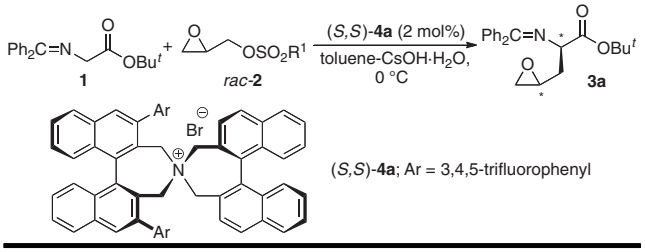


Figure 1. Preparation of optically active epihalohydrin and epoxy sulfonates for asymmetric alkylation of glycine derivatives under phase-transfer conditions.

First, the effect of the sulfonate moiety of *rac*-**2** was examined (Table 1). Attempted treatment of **1** and *rac*-**2a** (2 equiv) using catalyst (*S*,*S*)-**4a** in toluene with CsOH·H_2O[6] at 0 °C for 2 h gave γ,δ-epoxy-α-amino acid derivative **3a** in only 36% yield with poor diastereo- and enantioselectivity (Entry 1). Other substituted aryl sulfonate groups with an electron-withdrawing or -donating group did not give any improvements (Entries 2–5). In contrast, reaction with epoxy triflate with *rac*-**2f** gave **3a** in moderate yield with low diastereoselectivity but better enantioselectivity. Furthermore, by lowering the reaction temperature to −20 °C, sufficient enantioselectivities for each diastereomers (dr = 57:43) were observed (Entry 7).

Next, we investigated the effect on structures of catalysts to attain higher reactivity and selectivity. The aryl groups at the 3,3′-position of binaphthyl subunits turned out to influence crucially the enantioselective outcome (Table 2). Thus, the

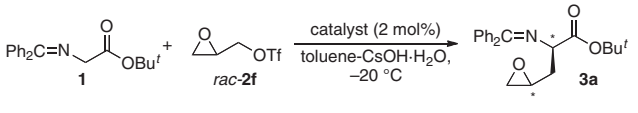
Table 1. Effects of sulfonate moieties of epoxy sulfonates *rac*-**2**[a]

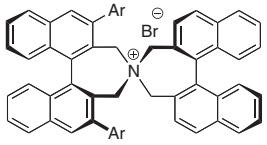


Entry	R^1	Time /h	Yield[b] /%	dr[c]	ee[d,e] /%
1	*p*-ClC_6H_4 (**2a**)	2	36	55:45	3 (11)
2	*p*-BrC_6H_4 (**2b**)	2.5	no rxn.	—	—
3	*p*-$NO_2C_6H_4$ (**2c**)	2	trace	—	—
4	*m*-$NO_2C_6H_4$ (**2d**)	5	41	55:45	5 (11)
5	*p*-MeC_6H_4 (**2e**)	3	trace	—	—
6	CF_3 (**2f**)	2	52	57:43	47 (43)
7[f]	CF_3 (**2f**)	23	52	57:43	80 (77)

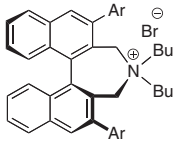
[a]Unless otherwise noted, the reaction was conducted with 2 equiv of *rac*-**2**, 2 mol % of (*S*,*S*)-**4a**, and 5 equiv of CsOH·H_2O in toluene at 0 °C for given reaction time. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Enantiopurity of **3a** was determined by HPLC analysis using a chiral column with hexane–isopropanol as a solvent after derivatization to *N*-benzoate (See Supporting Information; SI[6]). [e]The value in parentheses is enantiopurity of the minor diastereomer. [f]Performed at −20 °C.

Table 2. Screening of catalyst structures[a]





(*S*,*S*)-**4a**; Ar = 3,4,5-trifluorophenyl
(*S*,*S*)-**4b**; Ar = 4-(trifluoromethyl)phenyl
(*S*,*S*)-**4c**; Ar = 3,5-di-*tert*-butylphenyl
(*S*,*S*)-**4d**; Ar = 3,5-bis(3,5-di-*tert*-butylphenyl)phenyl



(*S*)-**4e**; Ar = 3,4,5-trifluorophenyl

Entry	Catalyst **4**	Time /h	Yield[b] /%	dr[c]	ee[d,e] /%
1	(*S*,*S*)-**4a**	23	52	57:43	80 (77)
2	(*S*,*S*)-**4b**	24	64	54:46	43 (43)
3	(*S*,*S*)-**4c**	23	67	52:48	63 (47)
4	(*S*,*S*)-**4d**	4	58	51:49	23 (6)
5	(*S*)-**4e**	29	70	48:52	76 (75)

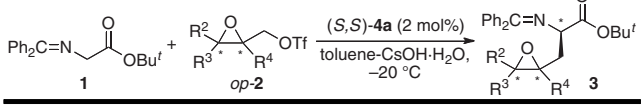
[a]Unless otherwise noted, the reaction was conducted with 2 equiv of *rac*-**2f**, 2 mol % of catalysts, and 5 equiv of CsOH·H_2O in toluene at −20 °C for given reaction time. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Enantiopurity of **3a** was determined by HPLC analysis using chiral column with hexane–2-propanol as solvent after derivatization to the corresponding *N*-benzoate (See SI[6]). [e]The value in parentheses is the enantiopurity of the minor diastereomer.

catalyst (*S*,*S*)-**4b** possessing 4-(trifluoromethyl)phenyl group led to deterioration of the enantioselectivity (Entry 2, Table 2), and other catalysts possessing bulkier substituents such as (*S*,*S*)-**4c** and (*S*,*S*)-**4d**, lowered the enantioselectivity (Entries 3 and 4). Additionally, structurally simpler catalyst (*S*)-**4e** showed similar catalytic efficiency as (*S*,*S*)-**4a**, which was found to be the most efficient catalyst among all.

Although the enantioselectivity was further increased by judiciously tuning catalysts and reaction conditions, the diastereoselectivity still remained at unsatisfactory levels. From comparison of the reaction with glycine Schiff base **1** and racemic secondary alkyl halides, where the catalyst invoked kinetic resolution of racemic secondary alkyl halides to provide excellent diastereoselectivity,[7] it is assured that catalysts **4** are unable to differentiate the stereochemistry of epoxides *rac*-**2**, and therefore we turned to utilize optically pure epoxides *op*-**2**.[8] As we expected, with the optimal conditions in hand, it showed marked enhancements of diastereoselectivity with excellent enantioselectivity, and also the smoother reaction led to increasing product yields in shortened reaction times (Table 3). Other optically pure epoxides having different stereochemistry and substituents were all tolerant to furnish the corresponding products[9] in good yield with good diastereoselectivity and excellent enantioselectivity.[10]

In conclusion, we have successfully demonstrated the first practical example of asymmetric alkylation using alkyl sulfonates, especially epoxy triflates as notable examples in this letter, under phase-transfer catalysis conditions. This research provides a new entry to phase-transfer-catalyzed asymmetric reaction.

Table 3. The reaction of glycine Shiff base **1** and optically pure epoxides *op*-**2**[a]



Entry	*op*-**2** R^2, R^3, R^4	Time /h	Yield[b] /%	dr[c]	ee[d] /%
1	H, H, H (*R*)	10	80	13:87	99
2	H, H, H (*S*)	10	84	92:8	99
3	Me, H, H (2*R*, 3*S*)	8	71	90:10	98
4	H, Me, H (2*R*, 3*R*)	8	74	89:11	97
5	H, H, Me (*S*)	8	82	87:13	95

[a]Unless otherwise noted, the reaction was conducted with 2 equiv of *op*-**2**, 2 mol % of (*S*,*S*)-**4a**, and 5 equiv of CsOH·H_2O in toluene at −20 °C for given reaction time. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Enantiopurity of the major isomer was determined by HPLC analysis using chiral column with hexane–isopropanol as solvent after derivatization to the corresponding *N*-benzoate (See SI[6]).

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