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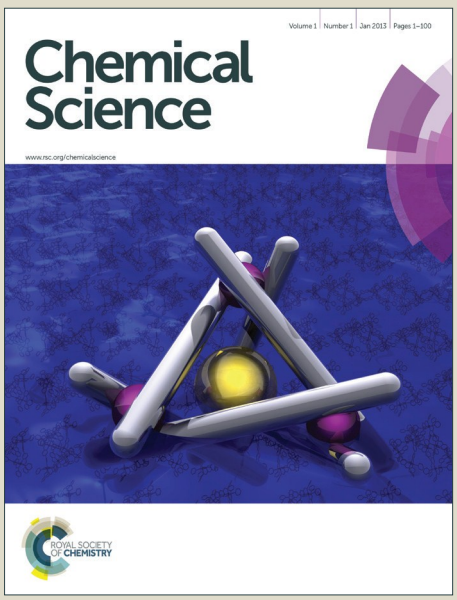

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Chiral Ion-Pair Organocatalyst Promotes Highly Enantioselective 3-*exo* Iodo-cycloetherification of Allyl Alcohols

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By designing a novel chiral ion-pair organocatalyst composed of chiral phosphate and DABCO-derived quaternary ammonium, highly enantioselective 3-*exo* iodo-cycloetherification of allyl alcohols was achieved using NIS as halogen source. Based on this reaction, one-pot asymmetric 3-*exo* iodo-cycloetherification/Wagner-Meerwein rearrangement reaction of allyl alcohols en route to enantioenriched 2-iodomethyl-2-aryl cycloalkanones was subsequently developed. Due to the participation of adjacent iodine, Wagner-Meerwein rearrangement of 2-iodomethyl-2-aryl epoxide proceeds with unusual retention of stereoconfiguration.

Halogenative functionalization of olefin is one of the most important transformations in organic synthesis as this reaction not only provides a versatile handle for further derivatization, but also delivers highly diastereoselective ring closure when nucleophile and alkene are tethered together.[1] Even though applications of halogenation reaction in total synthesis are well documented,[2] catalytic enantioselective halogenation remains a big challenge due to the rapid interexchange of halonium complex between olefins, which leads to rapid racemization of enantiopure halonium intermediate.[3] Therefore limited success has been achieved despite of enormous efforts that are devoted to asymmetric halogenation reactions.[4] Very recently, this field experienced impressive progress after the landmark reports of Bohan,[5a] Tang,[5b] Fujioka,[5c] Jacobsen, [5d] and Yeung[5e] in 2010 by taking advantage of organocatalysts to effect asymmetric halo-lactonizaton.[5] Organocatalyzed enantioselective halocyclization of olefinic amines, alcohols and other substrates subsequently emerged.[6-9] However, asymmetric halocyclization reactions are currently limited to formation of four- to six-membered rings.[5-9] The generation of enantioenriched more strained three-membered rings via catalytic asymmetric halocyclization remains elusive. In this regard, although *3-exo* halo-cycloetherification of allyl alcohol has been long known,[10] reactive halogenating reagents or harsh reaction conditions are needed to effect the energetically disfavored *3-exo* halocyclization, which impede the development of asymmetric version of this reaction.

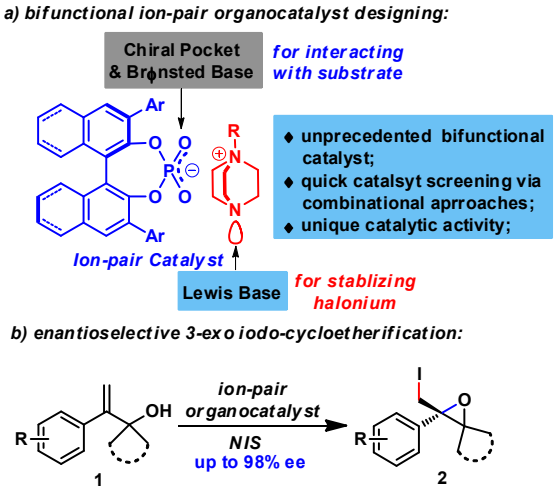

Fig. 1 Ion-pair organocatalyst designing for enantioselective 3-*exo* iodo-cycloetherification of allyl alcohol.

With the advent and booming of organocatalyst,[11a-c] ion-pairing of organocatalysts has emerged as a powerful strategy for designing new efficient organocatalysts.[11d] By cooperatively activating reactive partners, ion-pair catalyst has catalyzed enantioselective reactions that are otherwise difficult to be achieved by other organocatalysts. In addition, ion-pairing strategy also enables catalyst screening via combinational approaches, which greatly accelerates catalyst screening process. Inspiration from recent Toste's work[8b-8f] and our work on enantioselective halogenation reactions using chiral anionic phase transfer catalyst,[12] we postulated that ion-pair catalyst would facilitate enantioselective halogenation

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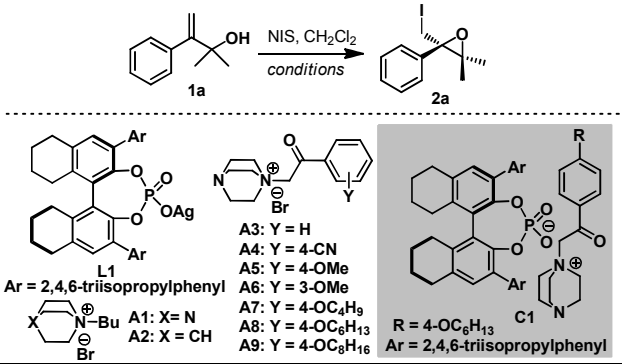
reaction by cooperative and synergistic activation of both reactants (Fig. 1), which is responsible for the success of previous catalysts.[5-9] To this end, chiral phosphate was judiciously chosen as counter anion for its fine-tunable chiral pocket as well as its Brønsted basicity for interacting with substrate.[8] On the other hand, DABCO-derived quaternary ammonium would serve as an excellent candidate for the cation moiety since its tertiary amine moiety could act as Lewis base for stabilizing halonium, which had been utilized for synthesis of the well-known Selectfluor[13] and other halogenating reagents[8d,9c,10b]

Table 1. Reaction condition optimization of enantioselective 3-*exo*-Iodocyclization of allyl alcohol **1a**.[a]



entry	cat. (equiv)	additive (equiv)	T (^{o}C)	t (h)	Yield[b] (%)	ee[c] (%)
1	**L1** (0.1)	**A1** (0.12)	0	40	16	30
2	**L1** (0.1)	**A2** (0.12)	0	40	18	19
3	**L1** (0.1)	**A3** (0.12)	0	40	44	77
4	**L1** (0.1)	**A4** (0.12)	0	40	16	69
5	**L1** (0.1)	**A5** (0.12)	0	40	69	86
6	**L1** (0.1)	**A6** (0.12)	0	40	47	80
7	**L1** (0.1)	**A7** (0.12)	0	40	65	91
8	**L1** (0.1)	**A8** (0.12)	0	40	60	92
9	**L1** (0.1)	**A9** (0.12)	0	40	50	91
10	--	--	0	40	ND	--
11	**L1** (0.1)	--	0	40	ND	--
12	--	**A8** (0.12)	0	40	ND	--
13	**C1** (0.1)	--	0	40	42	83
14	**C1** (0.1)	**A8** (0.1)	0	40	82	92
15	**C1** (0.1)	$S=PPh_3$ (0.1)	0	40	63	90
16[d]	**C1** (0.1)	**A8** (0.1)	0	40	62	69
17[e]	**C1** (0.1)	**A8** (0.1)	0	40	31	67
18	**C1** (0.1)	**A8** (0.1)	20	107	99	94

[a] To a mixture of silver salt **L1** (0.01 mmol), ammonium salt **A** (0.012 mmol) and NIS (0.12 mmol) was added CH_2Cl_2 (1 mL) then the reaction mixture was cooled to 0 ^{o}C. Allyl alcohol **1a** (0.1 mmol) in 0.5 mL CH_2Cl_2 was then added dropwise and the reaction was quenched at indicated time. [b] Isolated yield. [c] Determined by HPLC using Chiralpak AD column. [d] $CHCl_3$ as solvent. [e] EtOAc as solvent. ND = not detected.

Herein, we would like to report the success of implementation of ion-paring strategy, which leads to the discovery of a novel ion-pair organocatalyst. This unprecedented organocatalyst enables the first enantioselective 3-*exo* iodo-cycloetherification of allyl alcohols using commercially available NIS as halogen source. Additionally, this protocol also gives direct access to enantiopure 2-iodomethyl epoxides,[14] which are tediously prepared from allyl alcohols previously via asymmetric Sharpless epoxidation/hydroxyl transformation procedure.[15]

To validate our hypothesis, enantioselective 3-exo-iodocyclization of allyl alcohol **1a** was explored using ion-pair organocatalyst generated *in situ* by combining silver phosphate with DABCO-derived quaternary ammonium salt for convenience of catalyst screening (Table 1). Initially, various ammonium salts were evaluated by using 8*H*-*R*-TRIP-OAg **L1** as chiral counter-anion source. After extensive screening, **A3** was determined to be the privileged scaffold, affording epoxide **2a** in 77% ee with marginal yield (entries 1-3, and Supporting Information). In contrast, ammonium salt **A2** derived from quinuclidine provided lower enantioselectivity, showing that tertiary amine moiety of **A1** played a pivotal role in the reaction (entries 1 and 2). Further structural modification of ammonium salt **A3** revealed that **A8** was the optimal cation fragment for the ion-pair organocatalyst, furnishing epoxide **2a** in 92% ee (entries 3-9). As for the anion fragment, 8*H*-*R*-TRIP-OAg provided better result than any other evaluated chiral silver phosphate (see Supporting Information). Importantly, both cationic and anionic fragments were indispensable for the reaction as indicated by control experiment (entries 10-12). It should be pointed out that other organocatalysts (e.g. chiral phosphoric acid and quinine-derived catalysts) were also surveyed under identical reaction conditions, which gave no desired cyclization product with starting material being fully recovered (Table S2, Supporting Information).

With anionic and cationic moiety of the catalyst being identified, ion-pair organocatalyst **C1** was directly synthesized from 8*H*-*R*-TRIP and ammonium **A8** (see Supporting Information) and examined under the otherwise identical reaction conditions. To our surprise, **2a** was obtained only in moderate enantioselectivity (83% ee, entry 13). As slightly excess amount of **A8** was used in the *in-situ* procedure, we reasoned that **A8** might be an effective promoter for this reaction. Indeed, comparable enantioselectivity (92% ee, entry 14) was obtained by adding catalytic amount of **A8** into the reaction. It's postulated that **A8** might act as Lewis base for stabilizing iodonium intermediate[8d] and facilitates the transfer of iodine from NIS to the DABCO moiety of the ion-pair organocatalyst, which led to accelerating reaction rate and increased enantioselectivity. Employment of $S=PPh_3$[7c,e] as additive also gave comparable result, verifying the positive effect of Lewis base as co-catalyst on this reaction (entry 15). With the suitable catalyst in hand, other reaction variations were subsequently evaluated. Other halogenating reagents such as NCS and NBS gave inferior results, leading to no reaction or sharp drop in enantioselectivities (see Supporting Information). CH_2Cl_2 was determined to be the optimal solvent (entries 16, 17 and Supporting Information) and lowing reaction temperature to -20 ^{o}C was beneficial to the reaction (entry 18).

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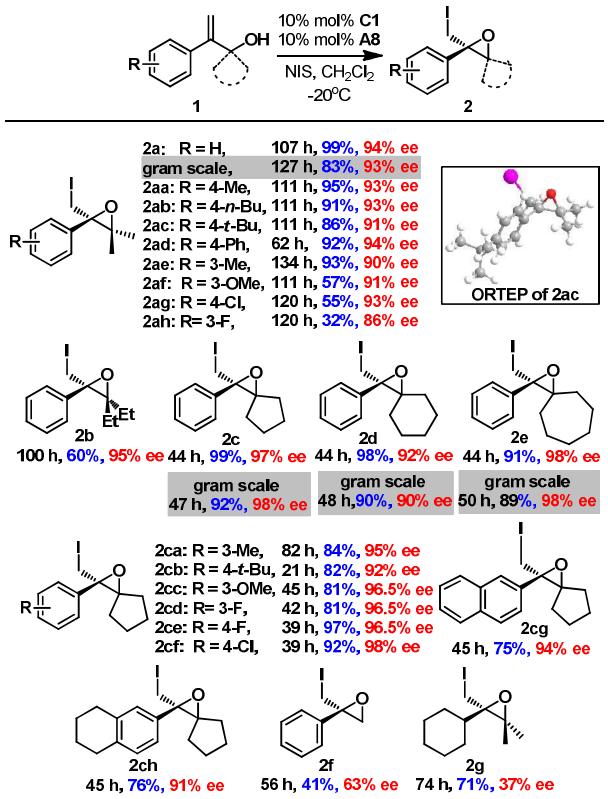
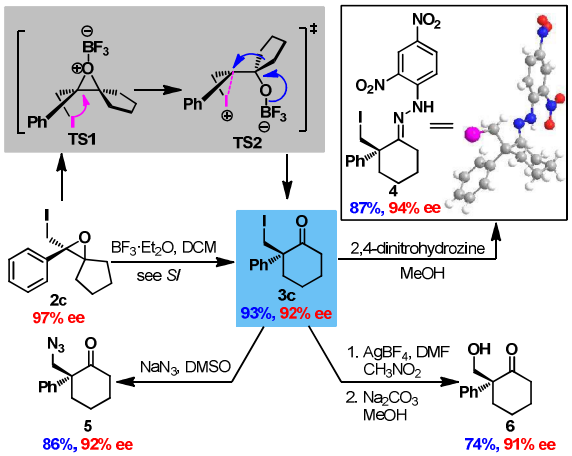


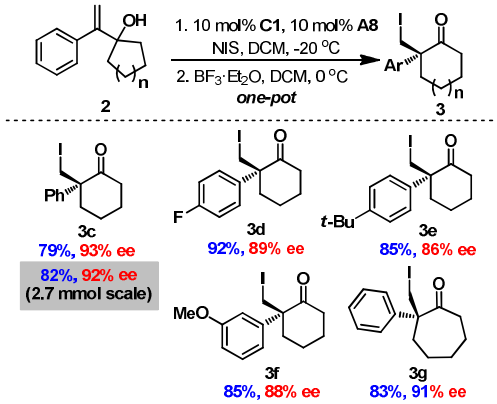
Scheme 1 Substrate variation of enantioselective *3-exo* iodocycloetherification of allyl alcohols.

After establishing the optimal reaction conditions, the substrate scope of this reaction was examined (Scheme 1). Both electron-withdrawing groups (**2aa**-**2af,** and **2ce**-**2cf**) and electron-donating groups (**2ag**-**2ah** and **2ca**-**2ch**) on phenyl moiety were well tolerated, affording corresponding epoxides in good to excellent enantioselectivities (87% ee-99% ee). Gem-substituents were crucial for the reaction as **2f** lacking gem-substituents was obtained only in 41% yield and 63% ee. Epoxides with cyclic gem-substituents were obtained in higher enantioselectivities (**2c**-**2ch** and Supporting Information) than those with acyclic gem-substituents (**2a** and **2b**). 2-Alkyl substituted allyl alcohol was also smoothly converted to epoxide **2g** albeit in low enantioselectivity (37% ee). Furthermore, gram syntheses of epoxide **2a**, **2c**-**2e** were also smoothly realized by using 5 mol% **C1** without affecting enantioselectivities and catalyst loading could even be reduced to 1 mol% to afford comparable results (Scheme 1 and Supporting Information). The absolute configuration of epoxide **2** was determined to be *R* based on X-ray crystallographic analysis of epoxide **2ac**,[16] which was confirmed by vibrational circular dichroism (VCD) studies of epoxide **2c**.[17]

Next, Wagner-Meerwein rearrangement[18] of epoxide **2c** was explored for construction of 2-iodomethyl-2-aryl cyclohexanone with chiral quaternary carbon center (Scheme 1). BF_3•Et_2O was determined to be the most efficient promoter (see Supporting Information), delivering cyclohexanone **3c** in good yields with partial loss of enantioselectivities (93% ee vs 97% ee for epoxide **2c**). Surprisingly, absolute configuration of **3c** was established to be *S* by X-ray crystallographic analysis of hydrozone **4** derived from **3c**,[16] which indicated retention of stereoconfiguration in the Wagner-Meerwein rearrangement. This could be ascribed to the opening of epoxide by the adjacent iodine to generate iodonium **TS2**, which was rearranged to ketone **3c** with double inversion of configuration. Furthermore, derivatizations of **3c** were also performed to display its synthetic utilities. Substitution of iodide with NaN_3 smoothly provided azide ketone **5** and iodide could also be converted to alcohol via formyloxylation/hydrolysis[19] to give hydroxyl ketone **6** in satisfactory yield. It's noteworthy that no erosion of enantiopurity was detected in all these reactions.



Scheme 2 Transformations of spiro-epoxide **2c**.



Scheme 3 One-pot asymmetric *3-exo* iodocycloetherification/Wagner-Meerwein rearrangement reaction.

To simplify the operation, one-pot asymmetric *3-exo* iodocycloetherification/Wagner-Meerwein rearrangement was also implemented (Scheme 2). Fortunately, when iodocycloetherification reaction was completed, addition of BF_3•OEt_2 to the reaction mixture smoothly provided desired cyclohexanone **3c** without reducing enantioselectivity even on 2.7 mmol scale (92% ee). Different substituents on phenyl were found to be compatible with the one-pot process, affording corresponding cyclohexanones **3c**-**3f** in satisfactory enantiopurities. Furthermore, seven-membered cycloketone **3g** could also be obtained via this one-pot cascade

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reaction in 91% ee (comparable with that of corresponding epoxide **2d**), which provided a complementary route to previous protocols on enantioselective halonium-induced semi-Pinacol rearrangement on enantioselective construction of halogenated cycloheptanone.[9a-e]

Conclusions

In conclusion, a novel ion-pair organocatalyst comprised of chiral phosphate and DABCO-derived quaternary ammonium was designed, which enabled the first asymmetric 3-exo iodocycloetherification of allyl alcohols using NIS as halogenating reagent. By employing this novel catalyst, a variety of enantiopure 2-iodomethyl-2-aryl epoxides were successively prepared in good to excellent enantioselectivities even on gram scale. Subsequently, one-pot asymmetric *3-exo* iodocycloetherification/Wagner-Meerwein rearrangement of 2-aryl-2-propen-3-ol was explored, which provided direct access to chiral 2-iodomethyl-2-aryl cycloalkanones in good enantioselectivities. Unusual retention of configuration owing to the assistance of the adjacent iodide was also observed in the Wagner-Meerwein rearrangement.

Acknowledgement

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