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Chiral ion-pair organocatalyst promotes highly enantioselective 3-exo iodo-cycloetherification of allyl alcohols†

Zhigao Shen,^{‡ab} Xixian Pan,^{‡c} Yisheng Lai,^{‡b} Jiadong Hu,^b Xiaolong Wan,^d Xiaoge Li,^d Hui Zhang^e and Weiqing Xie^{*a}

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 a halogen source. Based on this reaction, one-pot asymmetric 3-exo iodo-cycloetherification/Wagner–Meerwein rearrangement of allyl alcohols en route to enantioenriched 2-iodomethyl-2-aryl cycloalkanones was subsequently developed. Due to the participation of adjacent iodine, the Wagner–Meerwein rearrangement of 2-iodomethyl-2-aryl epoxide proceeds with unusual retention of stereoconfiguration.

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Halogenative functionalization of olefins is one of the most important transformations in organic synthesis, as it not only provides a versatile handle for further derivatization, but also delivers highly diastereoselective ring closure when the nucleophile and alkene are tethered together.¹ Even though applications of halogenation reactions in total synthesis are well documented,² catalytic enantioselective halogenation remains a significant challenge due to the rapid interexchange of the halonium complex between olefins, which leads to rapid racemization of the enantiopure halonium intermediate.³ Therefore, limited success has been achieved, despite enormous efforts being devoted to asymmetric halogenation reactions.⁴ Very recently, there has been impressive progress in this field after the landmark reports of Borhan,^{5a} Tang,^{5b} Fujioka,^{5c} Jacobsen,^{5d} and Yeung^{5e} in 2010, taking advantage of organocatalysts to effect asymmetric halo-lactonization.⁵ Organocatalyzed enantioselective halocyclization of olefinic amines,

alcohols and other substrates subsequently emerged.^{6–9} However, asymmetric halocyclization reactions are currently limited to the 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 alcohols has long been known,¹⁰ reactive halogenating agents or harsh reaction conditions are needed to effect the energetically disfavored 3-exo halocyclization, which impedes the development of an asymmetric version of this reaction.

With the advent and booming of organocatalysis,^{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 catalysts have catalyzed enantioselective reactions that are otherwise difficult to achieve using other organocatalysts. In addition, the ion-pairing strategy also enables catalyst screening *via* combinational approaches, which greatly accelerates the catalyst screening process. Inspired by Toste's recent work^{8b–f} and our work on enantioselective halogenation reactions using chiral anionic phase transfer catalysts,¹² we postulated that an ion-pair catalyst could facilitate the enantioselective halogenation reaction by cooperative and synergistic activation of both reactants (Fig. 1), which has been 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 to allow interaction with the substrate.⁸ Furthermore, DABCO-derived quaternary ammonium could serve as an excellent candidate for the cation moiety, since its tertiary amine moiety could act as a Lewis base to stabilize the halonium complex, an approach which has been utilized for the

^aShaanxi Key Laboratory of Natural Products & Chemical Biology, College of Science, Northwest A&F University, 22 Xinong Road, Yangling 712100, China. E-mail: xiewqsic@aliyun.com

^bState Key Laboratory of Natural Medicines, Jiangsu Key Laboratory of Drug Discovery for Metabolic Diseases, Center of Drug Discovery, China Pharmaceutical University, 24 Tongjiexiang, Nanjing 210009, China

^cHubei Collaborative Innovation Center for Rare Metal Chemistry, Hubei Normal University, China

^dShanghai Institute of Organic Chemistry, Chinese Academy of Sciences, China

^eSchool of Science & Laboratory for Microstructures, Instrumental Analysis and Research Center, Shanghai University, China

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‡ These authors contributed equally to this work.



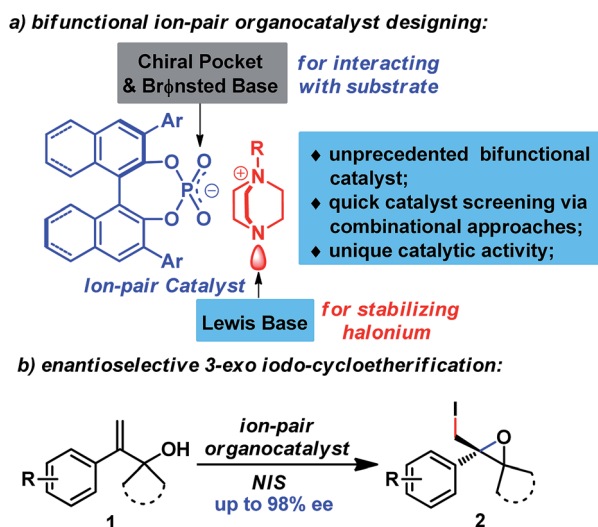


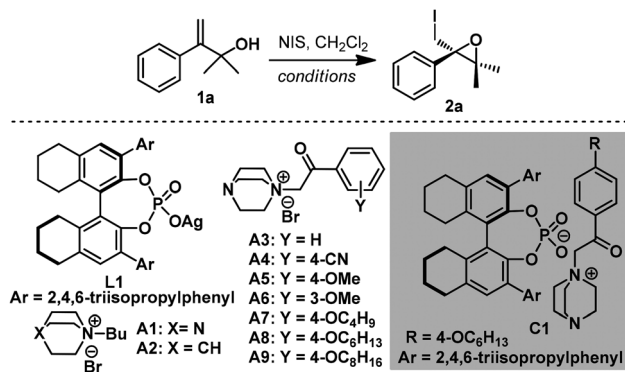
Fig. 1 Ion-pair organocatalyst design for enantioselective 3-*exo* iodo-cycloetherification of allyl alcohols.

synthesis of well-known Selectfluor¹³ and other halogenating reagents.^{8d,9c,10b}

Herein, we would like to report the success of implementation of the ion-pairing strategy, leading 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 a halogen source. Additionally, this protocol provides direct access to enantiopure 2-iodomethyl epoxides,¹⁴ which have previously been tedious to prepare from allyl alcohols, requiring an asymmetric Sharpless epoxidation/hydroxyl transformation procedure.¹⁵

To validate our hypothesis, enantioselective 3-*exo*-iodocyclization of allyl alcohol **1a** was explored using an 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 using 8*H*-*R*-TRIP-OAG **L1** as a chiral counter-anion source. After extensive screening, **A3** was determined to be a privileged scaffold, affording epoxide **2a** with 77% ee in

Table 1 Optimization of reaction conditions for enantioselective 3-*exo*-iodocyclization of allyl alcohol **1a**^a

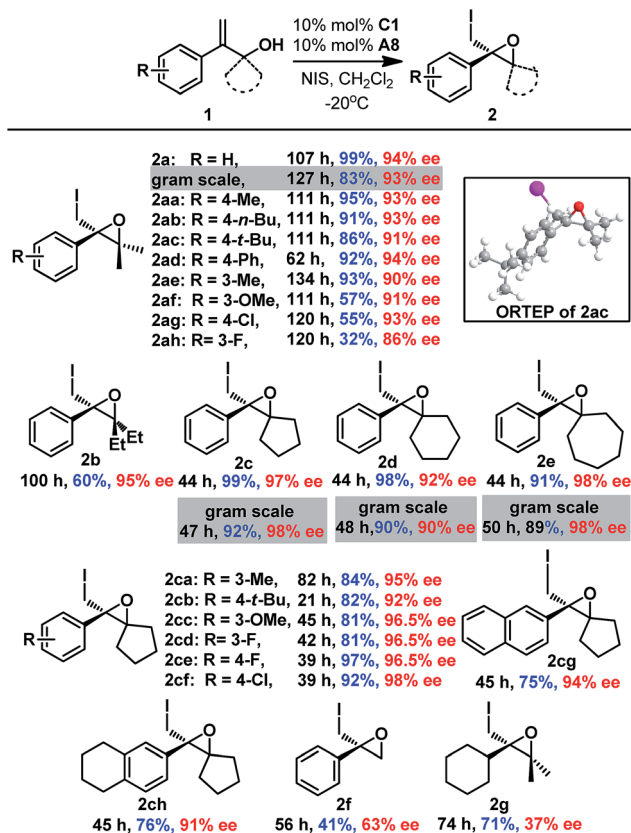


Entry	Cat. (equiv.)	Additive (equiv.)	T (°C)	t (h)	Yield ^b (%)	ee ^c (%)
1	L1 (0.1)	A1 (0.12)	0	40	16	30
2	L1 (0.1)	A2 (0.12)	0	40	18	19
3	L1 (0.1)	A3 (0.12)	0	40	44	77
4	L1 (0.1)	A4 (0.12)	0	40	16	69
5	L1 (0.1)	A5 (0.12)	0	40	69	86
6	L1 (0.1)	A6 (0.12)	0	40	47	80
7	L1 (0.1)	A7 (0.12)	0	40	65	91
8	L1 (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

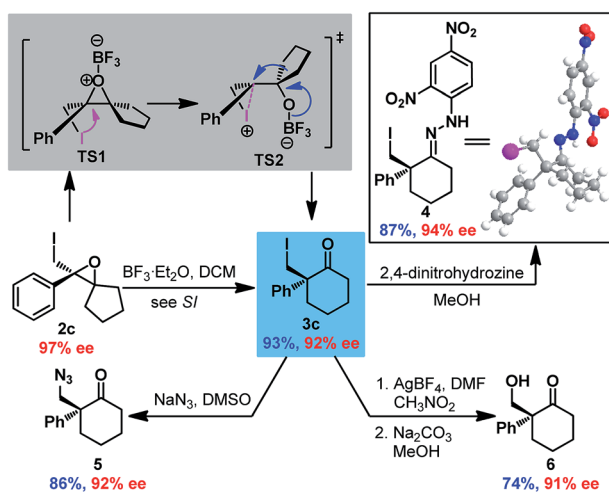
^a CH₂Cl₂ (1 mL) was added to a mixture of silver salt **L1** (0.01 mmol), ammonium salt **A** (0.012 mmol) and NIS (0.12 mmol), and the reaction mixture was cooled to 0 °C. Allyl alcohol **1a** (0.1 mmol) in 0.5 mL CH₂Cl₂ was then added dropwise, and the reaction was quenched at the indicated time.

^b Isolated yield. ^c Determined by HPLC using a Chiralpak AD column. ^d CHCl₃ as solvent. ^e EtOAc as solvent. ND = not detected.





Scheme 1 Substrate variation in the enantioselective 3-exo iodo-cycloetherification of allyl alcohols.



Scheme 2 Transformations of spiro-epoxide 2c.

moderate yield (entries 1–3 and ESI[†]). In contrast, ammonium salt A2 derived from quinuclidine provided lower enantioselectivity, showing that the 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 with 92% ee (entries 3–9). As for the

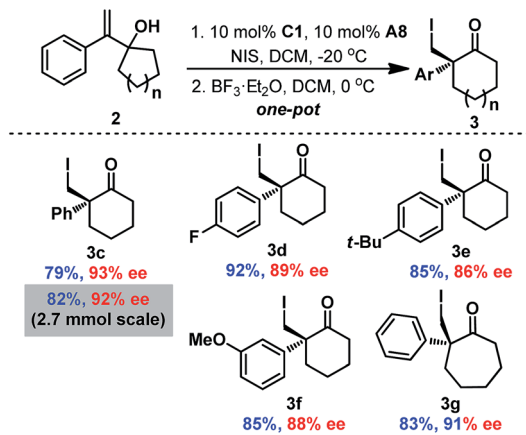
anion fragment, 8*H*-*R*-TRIP-OAg provided a better result than any other chiral silver phosphate evaluated (see ESI[†]). Importantly, both cationic and anionic fragments were indispensable for the reaction, as indicated by control experiments (entries 10–12). It should be pointed out that other organocatalysts (*e.g.* chiral phosphoric acid and quinine-derived catalysts) were also surveyed under identical reaction conditions but gave no desired cyclization product, with the starting material being fully recovered (Table S2, ESI[†]).

With the optimal anionic and cationic moiety of the catalyst identified, ion-pair organocatalyst C1 was synthesized directly from 8*H*-*R*-TRIP and ammonium A8 (see ESI[†]) and examined under otherwise identical reaction conditions. To our surprise, 2a was obtained with only moderate enantioselectivity (83% ee, entry 13). As a slight excess 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 a catalytic amount of A8 to the reaction. It is postulated that A8 might act as a Lewis base to stabilize the iodonium intermediate^{8d} and facilitate the transfer of iodine from NIS to the DABCO moiety of the ion-pair organocatalyst, leading to an acceleration of the reaction rate and increased enantioselectivity. Employing S=PPh₃ (ref. 7c and e) as an additive also gave a comparable result, verifying the positive effect of a Lewis base as co-catalyst in this reaction (entry 15). With a 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 a sharp drop in enantioselectivity (see ESI[†]). CH₂Cl₂ was determined to be the optimal solvent (entries 16, 17 and ESI[†]), and lowering the reaction temperature to -20 °C was beneficial for the reaction (entry 18).

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 the phenyl moiety were tolerated, affording the corresponding epoxides with good to excellent enantioselectivities (87% to 99% ee). Gem-substituents were crucial for the reaction, as 2f lacking gem-substituents was obtained in only 41% yield and 63% ee. Epoxides with cyclic gem-substituents were obtained with higher enantioselectivities (2c–2ch and ESI[†]) than those with acyclic gem-substituents (2a and 2b). A 2-alkyl substituted allyl alcohol was also smoothly converted to epoxide 2g, albeit with low enantioselectivity (37% ee). Furthermore, gram syntheses of epoxides 2a and 2c–2e were also smoothly realized by using 5 mol% C1 without affecting enantioselectivities, and the catalyst loading could even be reduced to 1 mol% affording comparable results (Scheme 1 and ESI[†]). 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 rearrangement¹⁸ of epoxide 2c was explored for the construction of 2-iodomethyl-2-aryl cyclohexanones with a chiral quaternary carbon center (Scheme 2). BF₃·Et₂O was determined to be the most efficient promoter (see ESI[†]), delivering cyclohexanone 3c in good yield with partial





Scheme 3 One-pot asymmetric 3-*exo* iodo-cycloetherification/Wagner–Meerwein rearrangement reaction.

loss of enantioselectivity (93% ee vs. 97% ee for epoxide **2c**). Surprisingly, the absolute configuration of **3c** was established to be *S* by X-ray crystallographic analysis of hydrazone **4** derived from **3c**,¹⁶ which indicated retention of stereoconfiguration in the Wagner–Meerwein rearrangement. This could be ascribed to the opening of the epoxide by the adjacent iodine to generate iodonium **TS2**, which then rearranged to ketone **3c** with double inversion of configuration. Furthermore, derivatizations of **3c** were also performed to demonstrate its synthetic utility. Substitution of the iodide with NaN₃ provided azide ketone **5** smoothly, and the iodide could also be converted to an alcohol *via* formyloxylolation/hydrolysis¹⁹ to give hydroxyl ketone **6** in satisfactory yield. It is noteworthy that no erosion of enantiopurity was detected in all these reactions.

To simplify the operation, one-pot asymmetric 3-*exo* iodo-cycloetherification/Wagner–Meerwein rearrangement was also developed (Scheme 3). Fortunately, when the iodo-cycloetherification reaction was completed, addition of BF₃·OEt₂ to the reaction mixture smoothly provided the desired cyclohexanone **3c** without reducing enantioselectivity, even on a 2.7 mmol scale (92% ee). Different substituents on the phenyl group were found to be compatible with the one-pot process, affording the corresponding cyclohexanones **3c–3f** in satisfactory enantiopurities. Furthermore, seven-membered cycloketone **3g** could also be obtained *via* this one-pot cascade reaction with 91% ee (comparable with that of the corresponding epoxide **2d**), providing a complementary route to previous protocols involving enantioselective halonium-induced semi-Pinacol rearrangement for the enantioselective construction of halogenated cycloheptanones.^{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* iodo-cycloetherification of allyl alcohols using NIS as a halogenating reagent. By employing this novel catalyst, a variety of enantiopure 2-iodomethyl-2-aryl epoxides were successively prepared

with good to excellent enantioselectivities, even on a gram scale. Subsequently, one-pot asymmetric 3-*exo* iodo-cycloetherification/Wagner–Meerwein rearrangement of 2-aryl-2-propen-3-ol was explored, which provided direct access to chiral 2-iodomethyl-2-aryl cycloalkanones with good enantioselectivities. Unusual retention of configuration owing to the assistance of the adjacent iodide was also observed in the Wagner–Meerwein rearrangement.

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