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Stereoselective and Regioselective Intramolecular Friedel–Crafts Reaction of Aziridinium Ions for Synthesis of 4-Substituted Tetrahydroisoquinolines

Hyun-Soon Chong* and Yunwei Chen

Department of Biological and Chemical Sciences, Illinois Institute of Technology, Chicago, Illinois 60616, United States

Chong@iit.edu

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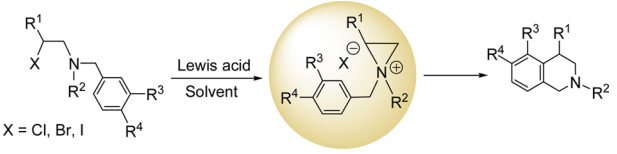
ABSTRACT



Optically active 4-substituted tetrahydroisoquinolines were synthesized via intramolecular Friedel–Crafts (FC) reactions of aziridinium ions in a highly regio- and stereoselective manner. Control experiments suggest the formation and ring-opening of aziridinium ions as the key intermediates in the Lewis acid catalyzed FC reactions.

Aziridinium ions have been utilized as highly reactive intermediates in the asymmetric synthesis of diverse small molecules and complex natural products.[1−3] Strained aziridinium ions have been limitedly isolated and characterized.[4−8] Nucleophilic ring opening of substituted aziridinium ions has been recognized as an efficient synthetic route to chiral precursor molecules including amines, amino nitriles, amino ethers, and aminoesters.[9−12] Despite synthetic versatility, ring-opening reaction of aziridinium ions remains an underexplored area, while other three-membered congeners such as aziridines and epoxides have numerous applications in organic synthesis. Limited investigations on ring opening of the aziridinium ions in part stems from difficulty in isolation and characterization of the labile entities and the lack of general and efficient methods for the synthesis of aziridinium ions or their precursors with functionalities. Nucleophilic opening reactions of the aziridinium ions are expected to occur at the two electrophilic carbons (C_2 and C_3) under mild conditions. *N*-Substituents, *C*-substituents, or counteranions in the aziridinium ions are potential nucleophiles that can attack the electrophilic carbons in intramolecular nucleophilic reactions. With this potential diverse reactivity, we were interested in the exploration of azirindium ions for intramolecular Friedel–Crafts (FC) reaction. FC reaction is a useful synthetic method for C−C bond formation in organic synthesis.[13,14] We hypothesized that aziridinuim ions containing an aromatic *N*-substituent will undergo intramolecular FC reactions to provide 4-substituted tetrahydroisoquinolines (THIQ) in high regio- and stereoselectivity. THIQ derivatives were reported to possess biological

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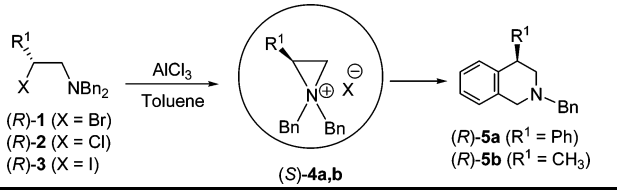
functions including anticancer, antibiotic, and dopamine inhibitory or stimulating activities.[15−17] In particular, 4-substituted THIQs such as nomifensine and dichlofensine are known to display dopamine inhibitory or antidepressant action.[16,17] However, straightforward and general synthetic methods for optically active 4-substituted THIQs are rarely reported.[18,19] Herein we report a new synthetic method for enantiomerically enriched 4-substituted THIQs based on the intramolecular FC reaction of aziridinium ions. Enantiomerically enriched β-haloamines **1**−**3** (Table 1) were prepared from β-amino alcohols with various functionalities and substituents and used as precursor molecules to generate aziridinium ions in situ for intramolecular FC reactions.

β-bromoamines (*R*)-**1a** (R^1 = Ph) and (*R*)-**1b** (R^1 = Me) were used for our initial feasibility study on intramolecular FC reactions (Table 1). In the presence of $AlCl_3$, FC reaction of (*R*)-**1a** in toluene under mild conditions (0 °C, 1 min) instantly provided (*R*)-**5a** (81% isolated yield, 71% ee) (Table 1, entry 1). The retained stereochemistry at the benzylic chiral center in (*R*)-**5a** suggests that the FC reaction involved formation of aziridinium ion (*S*)-**4a** as the key intermediate. Opening of aziridinium ion (*S*)-**4a** occurred at the stabilized benzylic position to furnish (*R*)-**5a** as the regiospecific isomer. The same reaction of (*R*)-**1a** at lower temperature (−20 or −70 °C) provided (*R*)-**5a** in similar stereoselectivity but lower isolated yield (Table 1, entries 2 and 3). (*R*)-**1b** (R^1 = Me) required a longer reaction time and heating (0 °C to reflux, 4 h) due to the inherent lower reactivity of a secondary alkyl substrate relative to a benzylic substrate toward substitution reactions. It is noteworthy that the reaction gave (*R*)-**5b** in excellent yield and stereoselectivity (90%, 97% ee) (Table 1, entry 7). Retained stereochemistry at the chiral center in (*R*)-**5b** also suggests formation and ring opening of aziridinium ion (*S*)-**4b**. Change of the leaving group (Cl or I) led to formation of (*R*)-**5a** in lower isolated yield and ee (Table 1, entries 4 and 5). This result suggests that a leaving group plays a role in the formation of aziridinium ions and THIQs.

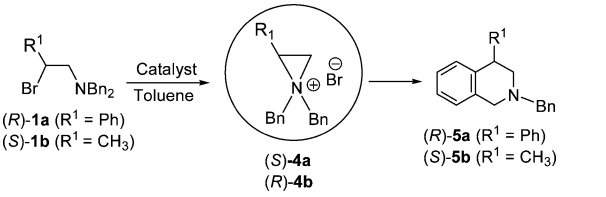
Lewis acid catalysts were screened for the formation of THIQs (*R*)-**5a** and (*S*)-**5b** (Table 2). Other catalysts weaker than $AlCl_3$ were surveyed for the reaction of (*R*)-**1a** in toluene. $FeBr_3$ was the most effective catalyst producing (*R*)-**5a** in the highest stereoselectivity (83% ee) (Table 2, entry 2). The FC reaction using $InCl_3$ and $TiCl_4$ (Table 2, entries 3 and 4) was significantly slower compared to the reaction using $FeBr_3$ and provided (*R*)-**5a** in a slightly higher isolated yield and stereoselectivity (72−78%, 77−81% ee). $SnCl_4$ was significantly less efficient (29%) than other catalysts, although the reaction provided (*R*)-**5a** in high enantioselectivity (81% ee). (*S*)-**1b** required a stronger Lewis acid and provided (*S*)-**5b** from the reaction

Table 1. Synthesis of THIQ Analogues (*R*)-**5a** and (*R*)-**5b**



entry	substrate	R^1	X	time	temp	yield (%)	ee (%)
1	(*R*)-**1a**	Ph	Br	1 min	0 °C	81	71
2	(*R*)-**1a**	Ph	Br	45 min	− 70 to −20 °C	50	79
3	(*R*)-**1a**	Ph	Br	15 min	−20 °C	55	70
4	(*R*)-**2a**	Ph	Cl	1 min	0 °C	75	63
5	(*R*)-**3a**	Ph	I	1 min	0 °C	72	61
6	(*R*)-**1b**	CH_3	Br	4 h	0 °C	NR	–
7	(*R*)-**1b**	CH_3	Br	4 h	reflux	90	97

Table 2. Effect of Catalyst on the Formation of THIQ Analogues (*R*)-**5a** and (*S*)-**5b**



entry	substrate	catalyst	temp	time	yield (%)	ee (%)
1	(*R*)-**1a**	$AlCl_3$	0 °C	1 min	81	71
2	(*R*)-**1a**	$FeBr_3$	0 °C	1 min	59	83
3	(*R*)-**1a**	$InCl_3$	rt	20 h	78	77
4	(*R*)-**1a**	$TiCl_4$	rt	15 h	72	81
5	(*R*)-**1a**	$SnCl_4$	rt	2.5 h	29	81
6	(*S*)-**1b**	$AlCl_3$	reflux	4 h	93	97
7	(*S*)-**1b**	$FeBr_3$	reflux	14 h	25	85
8	(*S*)-**1b**	$InCl_3$	reflux	96 h	22	97

using $FeBr_3$ and $InCl_3$ in poor isolated yield (< 25%) but good enantioselectivity. No FC product was obtained from the reaction of (*S*)-**1b** with $TiCl_4$ and $SnCl_4$ under reflux. The reaction of (*R*)-**1a** or (*S*)-**1b** was carried out in different solvents (Table 3). Among the solvents screened for the reaction of (*R*)-**1a**, dichloroethane (DCE) gave the best result (95%, 78% ee) (Table 3, entry 4). A lower isolated yield observed with aromatic solvents (toluene, benzene, xylene, < 81%) compared to halogenated solvents (DCE, $CHCl_3$, and CH_2Cl_2, > 91%) is ascribed to the formation of intermolecular FC products from reaction of (*R*)-**1a** with the aromatic solvents. No product was formed from the reaction of (*R*)-**1a** in THF and hydrocarbon solvents, cyclohexane (Chx) and hexane (Table 3, entries 7−9). Less reactive (*S*)-**1b** was more selective in solvent. The FC reaction of (*S*)-**1b** proceeded only in the aromatic solvents producing (*S*)-**5b** in excellent yield, and

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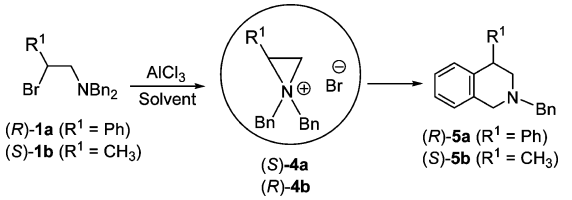
Table 3. Effect of Solvents on the Formation of THIQ Analogues (*R*)-**5a** and (*S*)-**5b**

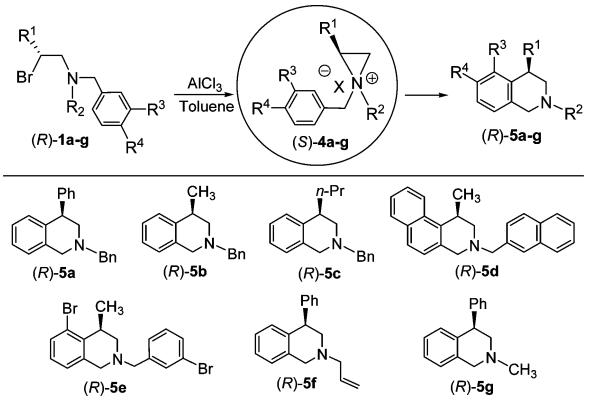


entry	substrate	solvent	time	temp	yield (%)	ee (%)
1	(*R*)-**1a**	toluene	1 min	0 °C	81	71
2	(*R*)-**1a**	benzene	1 min	0 °C	81	59
3	(*R*)-**1a**	xylene	1 min	0 °C	70	69
4	(*R*)-**1a**	$(CH_2Cl)_2$	1 min	0 °C	95	78
5	(*R*)-**1a**	CH_2Cl_2	1 min	0 °C	91	75
6	(*R*)-**1a**	$CHCl_3$	1 min	0 °C	94	62
7	(*R*)-**1a**	Chx	48 h	0 °C	NR	–
8	(*R*)-**1a**	hexane	48 h	0 °C	NR	–
9	(*R*)-**1a**	THF	48 h	0 °C	NR	–
10	(*S*)-**1b**	toluene	4 h	reflux	93	97
11	(*S*)-**1b**	benzene	4 h	reflux	87	>99
12	(*S*)-**1b**	xylene	3 h	reflux	73	98
13	(*S*)-**1b**	$(CH_2Cl)_2$	48 h	reflux	NR	–

no FC product was obtained from the reaction of (*S*)-**1b** in halogenated solvents (DCE, CH_2Cl_2, $CHCl_3$).

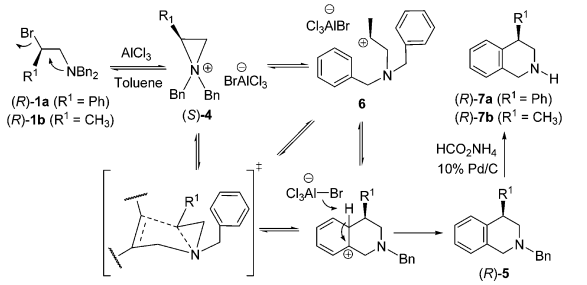
We also investigated the substrate scope for intramolecular FC reactions using β-bromoamines **1a**–**g** (Table 4). FC reactions of β-bromoamines **1a**–**g** were screened for reactions using $AlCl_3$. The reaction of (*R*)-**1a** and (*R*)-**1b** provided (*R*)-**5a** and (*R*)-**5b** (71% ee and 97% ee), respectively (Table 4, entries 1 and 2). Replacement of the *C*-substituent from methyl to *n*-propyl (**1c**) led to formation of (*R*)-**5c** in lower isolated yield but as a nearly exclusive enantiomer (79%, >99% ee) (Table 4, entry 3). The effect of *N*-substitution on the formation of THIQ analogues was studied. The intramolecular FC reaction was found to be quite sensitive to *N*-substitution. The reactions of β-bromoamine (*R*)-**1d** containing *N*-naphthyl groups (**1d**) provided (*R*)-**5d** in lower isolated yield (49%) but in excellent stereoselectivity (Table 4, entry 4). A significant drop in both isolated yield and ee of (*R*)-**5e** was observed from the reaction of (*R*)-**1e** having *m*-bromobenzyl group (54%, 78% ee) (Table 4, entry 5). In both of the substrates **1d** and **1e**, FC reactions occurred at the aromatic carbon ortho to the *N*-methylene group with exclusive regioselectivity. Change in the *N*-substituent from a benzyl (**1a**) to an allyl group (**1f**) led to the formation of (*R*)-**5f** in poor isolated yield and stereoselectivity (41% yield and 19% ee) (Table 4, entry 6). FC Reaction of (*S*)-enantiomers of **1a**–**f** provided (*S*)-**5a**–**f** in comparable yield and ee to the enantiomeric counterparts (Supporting Information).When *N*-Bn (**1a**) was replaced with *N*-CH_3 (**1g**), the chiral center in **5g** was almost completely racemized (Table 4, entry 7). This result appears to imply that π–π stacking between the nucleophilic aromatic ring and the nonreactive *N*-aromatic ring or interaction between the aromatic π system and nitrogen

Table 4. Substrate Scope for the Synthesis of Various THIQ Analogues **5**



entry	substrate	temp	solvent	product	yield (%)	ee (%)
1	(*R*)-**1a**	0 °C	toluene	(*R*)-**5a**	81	71
2	(*R*)-**1b**	reflux	toluene	(*R*)-**5b**	90	97
3	(*R*)-**1c**	reflux	toluene	(*R*)-**5c**	79	>99
4	(*R*)-**1d**	reflux	toluene	(*R*)-**5d**	49	>99
5	(*R*)-**1e**	reflux	toluene	(*R*)-**5e**	54	78
6	(*R*)-**1f**	−20 °C	DCE	(*R*)-**5f**	41	19
7	(*R*)-**1g**	−20 °C	DCE	(*R*)-**5g**	68	2

Scheme 1. Proposed Mechanism of the Intramolecular Friedel–Crafts Reaction and Confirmation of the Stereochemistry in the THIQ Analogues (**5**)



cation in the aziridinium intermediate is essential for the formation of the FC products in high stereoselectivity.[12,20]

The stereochemistry in (*R*)-**5a** and (*R*)-**5b** was confirmed by preparing the known THIQ analogues (*R*)-**7a**[21] and (*R*)-**7b**[22] by *N*-debenzylation of (*R*)-**5a** and (*R*)-**5b** (Scheme 1). The formation and ring opening of aziridinium ions **4** was proposed as the basis for good to absolute control of stereochemistry in the synthesis of THIQs **5** as shown in Scheme 1. The retained stereochemistry at the chiral center in **5** can be explained by a mechansim wherein an aziridinium ion **4** was first formed via an intramolecular S_N2 reaction followed by subsequent cleavage of the loose N_1–C_2 bond in

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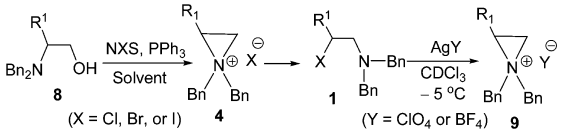
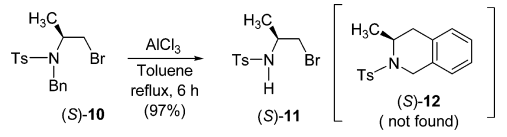
Scheme 2. Synthesis and Characterization of Optically Active β-Haloamines **1** and Aziridinium Ions **9**



Scheme 3. Lewis Acid Promoted Debenzylation of β-Bromoamine **10**



aziridinium ion **4** by the attack of the *N*-aromatic ring from the front side in an S_Ni pathway. This unusual nucleophilic reaction proceeding with retention at the chiral center appears to occur due to the nature of the strained aziridinium ring and the presence of the nonreacting *N*-aromatic group which can stabilize the postive charge in C_2 of the aziridinium ion **4** via cation–π interaction or interact with the attacking aromatic ring via π–π stacking. A similar mechanism was proposed for an acid-promoted intramolecular ring opening of aziridine proceeding with retained stereochemistry at the chrial center.[23−26]

The observed high stereoselectivity in the reaction of (*R*)-**5a**–**e** rules out a classical S_N1 pathway of the FC reaction of (*R*)-**1a**–**e**. A direct S_N2 inversion at the chiral center from the intramolecular FC reaction of (*R*)-**1** by displacement of bromide by the aromatic ring was excluded, as the obvious *N*-substitution effect by displacement of bromide by the aromatic ring was observed. As stated above, a change of the *N*-substituent from benzyl to allyl (**1f**) and methyl (**1g**) led to a significant or almost complete loss of stereoselectivity in the respective formation of (*R*)-**5f** and (*R*)-**5g**. The FC reaction of β-bromoamines **1f** and **1g** are reasonably speculated to proceed via an S_N1 pathway involving a more dissociated carbocation that can be formed from the aziridinium ion (Scheme 1).

To further prove the hypothesis based on the formation of an aziridinium ion as the key reactive intermediate, control experiments were conducted. First, optically active aziridinium ions **9** were prepared (Scheme 2) and characterized by ^1H and ^{13}C NMR and optical rotation. Bromination of β-amino alcohols **8** using NXS (X = Br, Cl, I) and PPh_3 provided β-haloamines **1** from the ring opening of aziridinium ions **4** by the halide counteranion. The intramolecular

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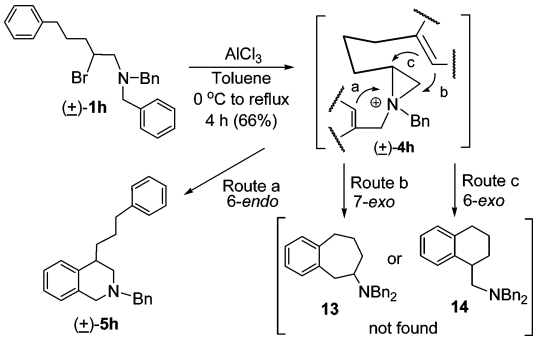
Scheme 4. Friedel–Crafts Reaction of *C*-Substituted Aziridinium Ion **5h**



substitution reaction of β-bromoamines **1** proceeded in an S_N2 pathway to provide aziridinium ions **9** with inverted stereochemistry. The formation of aziridinium ion **9** was promoted by sequestration of the halide in **1** using $AgClO_4$ or $AgBF_4$. We then prepared β-bromoamine (*S*)-**10** containing a tosyl (Ts) group to understand anchimeric participation of the neighboring nitrogen to form aziridinium ion (Scheme 3). No neighboring group participation and resultant formation of aziridinium ion was expected for (*S*)-**10** substituted with the tosyl group. Reaction of (*S*)-**10** provided only debenzylation product **11** in 97% yield, and no FC product **12** was formed. Finally, we investigated whether involvement of the *N*-aromatic ring in the FC reaction was more favorable than that of the aromatic ring in a *C*-substituent (Scheme 4). The FC reaction of (±)-**1h** containing a phenylpropyl group gave only *endo*-THIQ **5h**. No exocyclization products **13** and **14** were formed, and involvement of the phenyl ring linked to the propyl spacer in the FC reaction was found to be a disfavorable process. It should be noted that formation of **14** from a direct S_N2 displacement of bromide by the phenyl group linked via the propyl chain was not observed. The experimental results described above suggest that intramolecular FC reaction of β-haloamines **1** for stereoselective synthesis of THIQs **5** involves formation and opening of aziridinium ions **4**, and direct conversion of β-haloamines **1** to THIIQs **5** in a S_N2 pathway is unlikely.

In conclusion, we have shown that the reactive aziridinium ions can be utilized for the synthesis of 4-substituted THIQs in high yield and enantioselectivity. We have also carried out the control experiments and demonstrated that the intramolecular FC reactions proceed via stereoselective and regiospecific ring opening of the aziridinium ions to produce THIQs.

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Supporting Information Available. Experimental procedures and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.