ACCOUNTS
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Utilization of N−X Bonds in The Synthesis of N-Heterocycles

SATOSHI MINAKATA*

Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Yamadaoka 2-1, Suita, Osaka 565-0871, Japan

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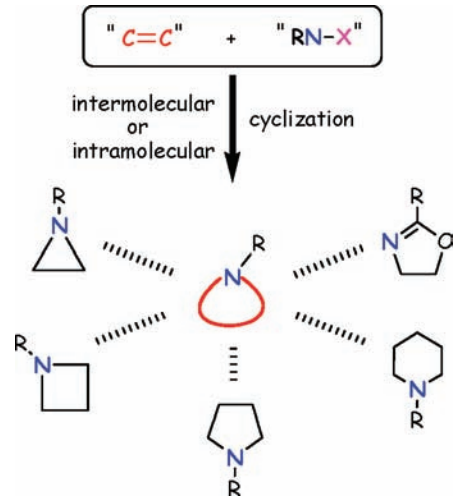
CONSPECTUS

Nitrogen-containing heterocycles—such as aziridines, pyrrolidines, piperidines, and oxazolines—frequently show up as substructures in natural products. In addition, some of these species show potent biological activities. Therefore, researchers would like to develop practical and convenient methods for constructing these heterocycles. Among the available methods, the transfer of N_1 units to organic molecules, especially olefins, is a versatile method for the synthesis of N-heterocycles. This Account reviews some of our recent work on the synthesis of N-heterocycles using the N−X bond. A nitrogen−halogen bond bearing an electron-withdrawing group on the nitrogen can be converted to a halonium ion. In the presence of C−C double bonds, these species produce three-membered cyclic halonium intermediates, which can be strong electrophiles and can produce stereocontrolled products. *N*-Halosuccinimides are representative sources of halonium ions, and the nitrogen of succinimide is rarely used in organic synthesis. If the nitrogen could act as a nucleophile, after releasing halonium ions to C−C double bonds, we expect great advances would be possible in the stereoselective functionalization of olefins. We chose *N*-chloro-*N*-sodio-*p*-toluenesulfonamide (chloramine-T, CT), an inexpensive and commercially available reagent, as our desired reactant. In the presence of a catalytic amount of CuCl or I_2 and $AgNO_3$, we achieved the direct aziridination of olefins with CT. The reaction catalyzed by I_2 could be carried out in water or silica−water as a green process. The reaction of iodoolefins with CT gave pyrrolidine derivatives under extremely mild conditions with complete stereoselectivity. We also extended the utility of the *N*-chloro-*N*-metallo reagent, which is often unstable and difficult to work with. Although CT does not react with electron-deficient olefins without a metal catalyst or an additive, we found that *N*-chloro-*N*-sodiocarbamates react with electron-deficient olefins in the presence of a phase transfer catalyst to give the corresponding aziridines. We also used this method to synthesize asymmetric aziridines using quaternary cinchona alkaloid catalysts. We also developed a facile synthetic method for preparing N-heterocycles that involves the in situ generation of an N−X bond using *tert*-butyl hypochlorite or *tert*-butyl hypoiodite (*tert*-BuOI). Treatment of alkenylamides containing an active hydrogen on the nitrogen with *tert*-BuOI led to the production of various N-heterocycles via intramolecular cyclization. Iodination of readily available sulfonamides or carboxamides with *tert*-BuOI generated reactive *N*-iodinated amides, which smoothly reacted with olefins to give aziridines or oxazolines. The reaction of fullerene, C_{60}, with CT also led to aziridination: the resulting aziridinofullerene underwent a unique rearrangement to an azafulleroid. Chlorination of readily available amide derivatives with *tert*-BuOCl, followed by a reaction with C_{60} in the presence of an organic base, afforded aziridinofullerenes with various substituents on the nitrogen. The results in this Account contribute to the development of convenient methods for constructing simple and useful heterocycles.



Introduction

Nitrogen-containing heterocycles, such as aziridines, pyrrolidines, piperidines and oxazolines, are frequently present as substructures in a number of natural products and some show potent biological activities.[1] The development of practical and convenient methods for constructing these heterocycles is highly desirable.[2] Among the variety of available methods, the transfer of N_1 units to organic molecules, especially olefins, is a versa-

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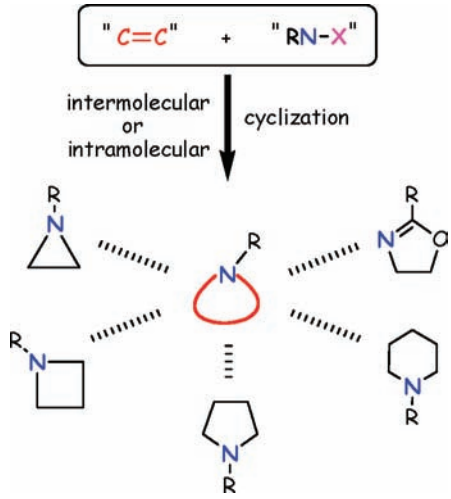
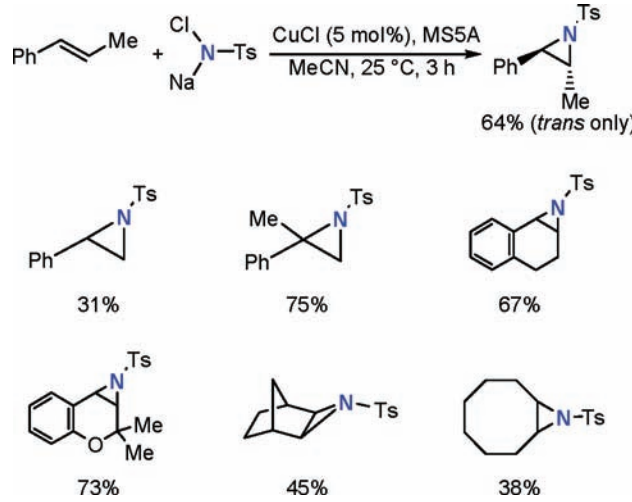
SCHEME 1. Utilization of the N−X Bond for Construction of N-Heterocycles



tile method for the synthesis of N-heterocycles. Great progress has been made in this area, using various combinations of nitrogen sources and catalysts or activators in the generation of active nitrogen species that are required for the synthesis of N-heterocycles. [*N*-(*p*-Toluenesulfonyl)imino]phenyliodinane (PhI=NTs) has been extensively used as a primary nitrene source for transition metal-catalyzed aziridination reactions[3] including asymmetric reactions.[4] The formation of azepines or aziridines by the addition of nitrenes, which can be thermally, photochemically, or catalytically generated from azides, to benzene or olefins is a well-known reaction in this area.[5] Quite recently, a fascinating account concerning N_1 transfer was reported by Yudin's group.[6] In addition, *N*,*N*-dichlorinated sulfonamides were elegantly used for the aminohalogenation of electron-deficient olefins by Li et al.[7]

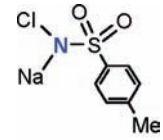
Alternative sources of N_1 units, such as haloamines and simple amides, were recently developed for use in new methods for the synthesis of N-heterocycles. Because haloamines and amides are readily available and inexpensive, the direct production of N-heterocycles from such N_1 units would enhance the scope and synthetic value of the reaction. The Hofmann−Löffler−Freytag reaction is well-known as the most famous transformation from *N*-haloamines.[8] The method is quite useful for formation of pyrrolidines and piperidines because C−N bond formation takes place at the sp^3 carbon via intramolecular cyclization involving a radical and ionic mechanism. As alternative and complementary approaches, the present study reports on investigations of some novel methods of synthesizing N-heterocycles utilizing N−X bonds through intermolecular and intramolecular cyclization involving cyclic halonium intermediates (Scheme 1).

SCHEME 2. CuCl-Catalyzed Aziridination of Olefins with CT



Synthesis of Aziridines from Olefins Using Haloamine-T

Chloramine-T (CT) is a well-known commercially available oxidizing agent, which can be used as a source of chloronium cations, nitrogen anions, or both.[9] As a result, CT has enjoyed widespread use in syntheses because of its reactivity toward a wide variety of functional groups.[10] The most impressive synthetic methodology to date, in which CT is used as a nitrogen source, was reported by Sharpless and co-workers. Their procedure involves the catalytic aminohydroxylation of olefins with CT, and the method has been elegantly extended to an asymmetric version of the reaction.[11] Based on these previous studies, new methods for the synthesis of N-heterocycles, using CT as the N_1 unit are now available.

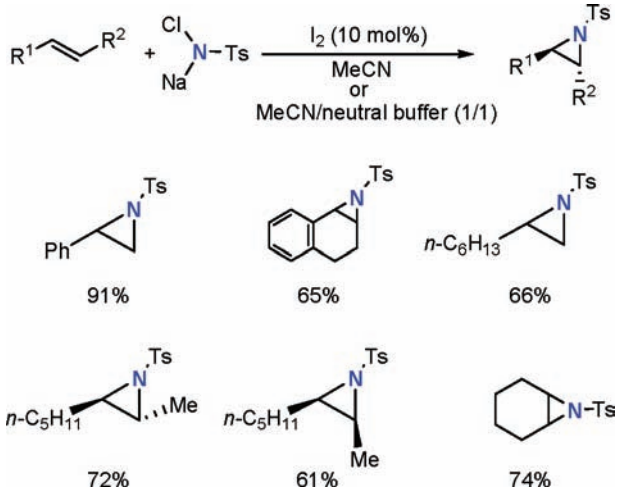


Chloramine-T

CT was found to be an efficient nitrogen source for the aziridination of olefins. Among the transition metals, copper(I) chloride was found to be the most suitable catalyst for the aziridination. For example, (*E*)-*β*-methylstyrene was successfully aziridinated with CT at 25 °C in acetonitrile in the presence of a catalytic amount of CuCl (5 mol %). Other olefins can also be aziridinated using this method to yield the following products (Scheme 2).[12] This was the first example of the direct aziridination of olefins utilizing CT as the N_1 unit. Our discovery that olefins can be aziridinated with CT prompted us to examine the use of bromamine-T (BT), which contains a N−Br bond.[13]

More efficient and convenient methods for one-step aziridinations using CT were reported by our research group

SCHEME 3. I_2-Catalyzed Aziridination of Olefins with CT



(I_2 catalyst; Scheme 3)[14] and by Sharpless et al. (phenyltrimethylammonium tribromide, PTAB, catalyst).[15]

These two methods are applicable to a wide range of olefins, and the reactions appear to proceed via the same pathway (Scheme 4). In particular, complete stereospecificity was observed in the aziridination of (*E*)- and (*Z*)-2-octene, indicating that the reactions are consistent with a pathway involving a cyclic iodonium intermediate. Sharpless and co-workers also proposed the same mechanism involving cyclic halonium intermediates.

The iodine-catalyzed formation of aziridines from olefins using CT can be successfully used in aqueous systems if a phase-transfer catalyst (PTC) is employed, because of the ionic character of CT.[16] The process has some advantages over reactions using organic solvents as follows: it involves an organic-solvent-free system, provides higher yields, and requires a shorter reaction time.

Based on these results, a more advanced green process was developed as follows. Because the PTC, which permits the reaction to proceed in aqueous media, must be removed after completion of the reaction, an alternative aqueous process was devised that involves taking advantage of the adsorptive nature of silica gel. Silica is as effective as an organic reaction medium in water because the organic substrate adsorbs to the silica due to hydrophobic interactions between the surface of the silica and the organic molecule (Scheme 5).

The use of MCM-41[17] gave interesting results, in that the large specific surface area of the silica reduced the amount of media required and the pore size of MCM-41 influenced the efficiency of the reaction (Table 1). These results strongly suggest that the reaction occurs on the silica surface.[18]

In order to show the generality of these products in organic synthesis,[19] the ring opening of *N*-tosylaziridines with KCN, NaN_3, and ZnI_2 was examined (Table 2).[20] The reaction of the

SCHEME 4. Plausible Pathway for I_2-Catalyzed Aziridination

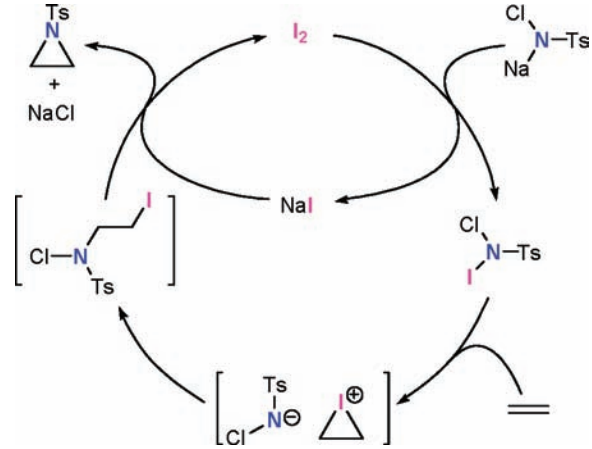
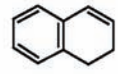
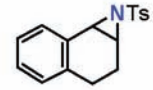
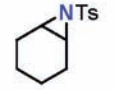
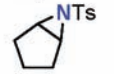
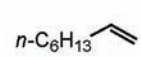
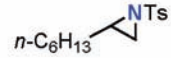
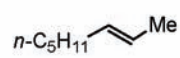
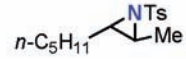
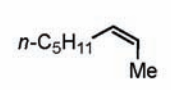
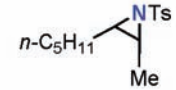
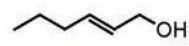
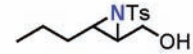
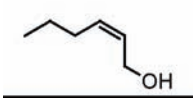
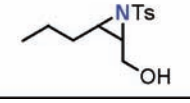


TABLE 1. Silica−Water-Mediated Formation of Aziridines from Various Olefins[a]

olefin	aziridine	yield (%) MCM-41	yield (%) Silica gel 60
		75	68
		75	68
		65	53
		7	26[b] 49
		4[c]	42[c]
		27[d]	70[d]
		56[c]	58[c]
		72[d]	61[b,d] 59[d]

[a] Reaction conditions: olefin (1 mmol), CT (2 mmol), I_2 (20 mol %), K_2CO_3 (2 mmol), silica (MCM-41, 0.25 g, or silica gel 60, 1 g), H_2O (1.5 mL), rt, 3 h. [b] Silica gel 60 (0.5 g). [c] *Trans* only. [d] *Cis* only.

aziridines with these water-soluble nucleophiles in water in the absence of silica resulted in no detectable reaction products. When silica gel 60 was added, however, the reaction proceeded to afford the regioselective ring-opening products. This

SCHEME 5. Schematic of an Organic Reaction Using a Silica−Water System

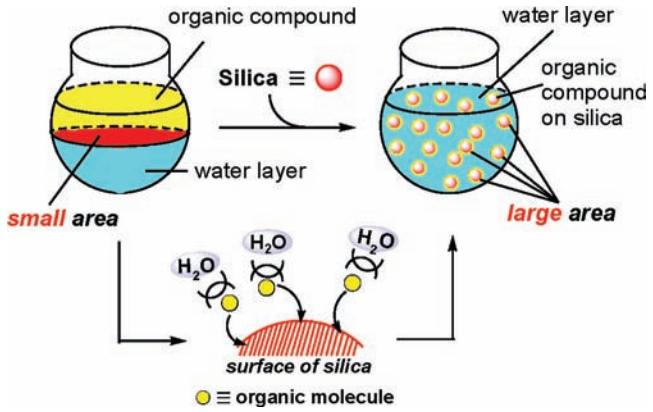
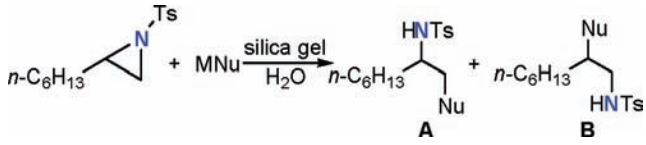


TABLE 2. Ring Opening of Aziridines in a Silica−Water Reaction Medium



			yield (%)	
MNu (equiv)	temp (°C)	time (h)	**A**	**B**
NaN_3 (2)	80	24	89	0
KCN (2)	80	24	69	0
ZnI_2 (2.5)	rt	48	90	6

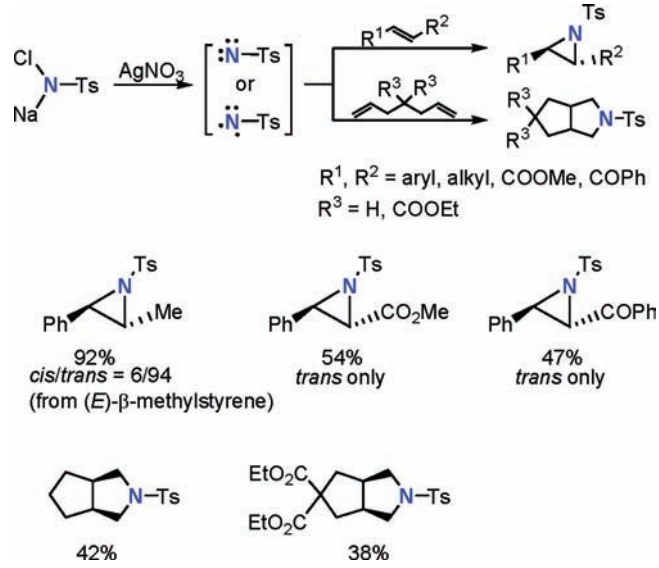
novel silica−water reaction medium, in which hydrophobic interactions are utilized, was applied to inclusion chemistry in periodic mesoporous hosts. Taking advantage of the fact that C_{60} is not readily soluble in organic solvents, solvophobic interactions between the internal surface of MCM-41 and C_{60} were induced, resulting in an organic−inorganic nanocomposite of highly concentrated C_{60} in MCM-41.[21]

To further extend the use of CT, $AgNO_3$, a potent reagent for capturing chloride ions, was employed in the synthesis of nitrogen-containing heterocycles.[22] The combination of CT and $AgNO_3$ resulted in the generation of a nitrene species, which successfully reacted not only with unfunctionalized olefins but also with electron-deficient olefins and 1,6-dienes to give aziridines and bicyclic pyrrolidines (Scheme 6).

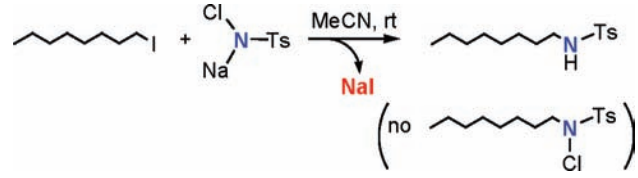
Synthesis of Pyrrolidines by the Reaction of Iodoolefins with Chloramine-T

With the intention of expanding the utility of CT as an N_1 unit, this potent reagent was used in the synthesis of five-membered nitrogen heterocycles. The genesis for this process was the result of the following experiment. The iodo group of 1-iodooctane was smoothly substituted by CT in acetonitrile at room temperature to give *N*-tosyloctylamine (Scheme 7). To

SCHEME 6. Generation of a Nitrene Species from CT and Its Application to the Synthesis of Aziridines and Bicyclic Pyrrolidines



SCHEME 7. The Reaction of an Iodoalkane with CT

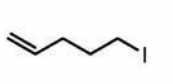
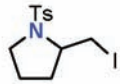
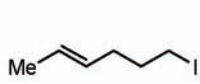
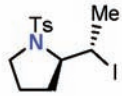
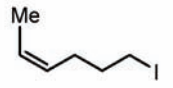
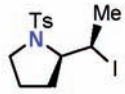
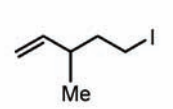
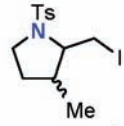
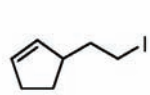
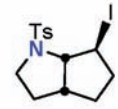
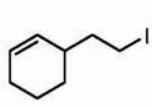
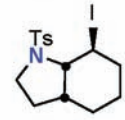
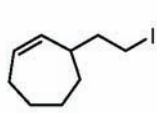
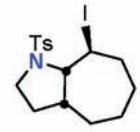


produce the final product from the initial substitution product (TsNClR), treatment with a reducing agent, such as Na_2SO_3, is required.

Considering the mechanism of the iodine-catalyzed aziridination of olefins with CT, NaI generated by the substitution should reduce the N−Cl bond. If an ε-iodoolefin is substituted for the iodoalkane in the reaction with CT, iodine atom transfer cyclization should take place via a cyclic iodonium intermediate thus leading to the production of pyrrolidine derivatives. Based on this working hypothesis, the treatment of 5-iodo-1-pentene with CT in MeCN at room temperature for 48 h resulted in the production of the predicted iodomethylated pyrrolidine in high yield. This method effectively gave the corresponding pyrrolidines from a variety of ε-iodoolefins. It is noteworthy that complete stereospecificity was observed in the reactions involving geometric isomers of 6-iodo-2-hexenes. Bicyclic pyrrolidines also were stereoselectively produced from cyclic olefins (Table 3).

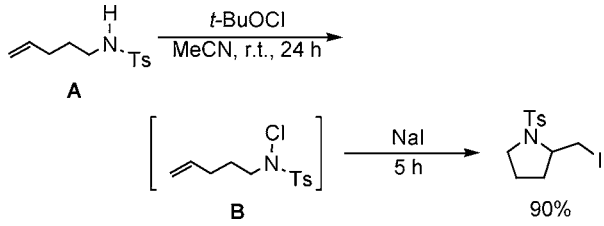
To determine the most likely reaction pathway, the following experiment was carried out. The putative intermediate **B** was prepared in situ by the chlorination of an authentic sample **A** with *t*-BuOCl. The subsequent addition of NaI to the mixture gave the pyrrolidine in 90% yield from **A** (Scheme 8).

TABLE 3. Synthesis of Various Pyrrolidines from ε-Iodoolefins and CT[a]

ε-iodoolefin	product	yield (%)
		91
		75
		81
		77[b]
		50[c]
		83[c]
		64[c]

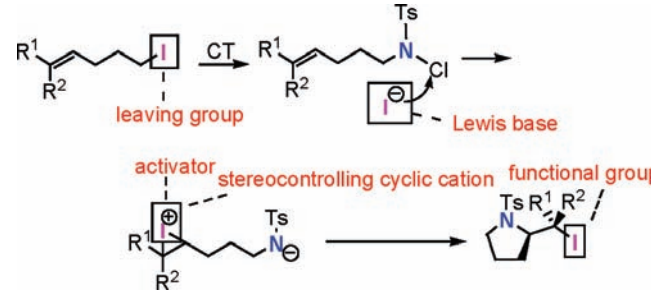
[a] Reaction conditions: alkenyliodide (0.5 mmol), CT (1 mmol), MeCN (3 mL), rt, 48 h. [b] *Cis/trans* = 69:31. [c] Anhydrous CT and 12 mL of MeCN were used.

SCHEME 8. Experiment Designed To Clarify the *N*-Chloro Derivative **B** as an Intermediate in the Production of the Pyrrolidine



This result supports the view that the formation of pyrrolidines proceeds via the following pathway (Scheme 9). The iodo group of an iodoolefin is substituted by CT to give an N-chlorinated alkenylsulfonamide. The liberated iodine (I^-) reacts with the Cl group of the substituted intermediate, permitting the interconversion of iodide (I^-) to iodonium ion (I^+), thus generating cyclic iodonium ions. The intramolecular cyclization of the iodonium ion proceeds smoothly to afford pyrrolidines. The iodo group of the substrate has multiple

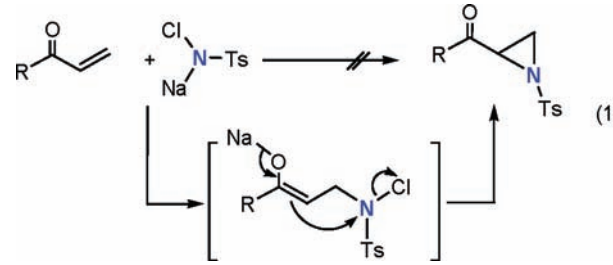
SCHEME 9. Multiple Functions of the Iodo Group



roles as follows: (1) a leaving group for substitution with CT; (2) a Lewis base for abstraction of the Cl atom; (3) an activator of the olefin moiety; (4) a stereocontrolling cyclic cation; (5) a functional group on the product.[23]

Catalytic Aziridination of Electron-Deficient Olefins with *N*-Chloro-*N*-sodiocarbamate and Applications to Asymmetric Synthesis

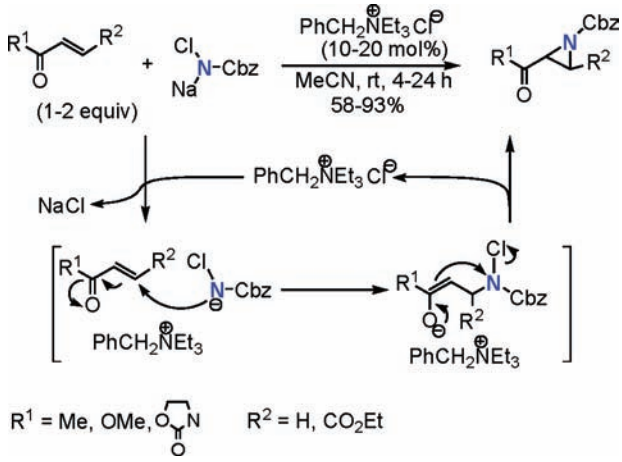
Since the nitrogen of CT has the ability to function as a nucleophile and the chlorine atom could serve as an eliminating group, electron-deficient olefins such as α,β-unsaturated carbonyl compounds would be expected to be converted to aziridines via conjugate addition followed by a cyclization process as shown in eq 1.



However, the anticipated reaction did not proceed at all, even though phase transfer catalysts were added to the reaction to solubilize the CT. Thus, an alternative *N*-chloro salt, benzyl *N*-sodio-*N*-chlorocarbamate[24] (chloramine-Cbz) was chosen for the desired aziridination. Since the pK_a value (15.3) of chloramine-Cbz is greater than that (13.5) of CT, chloramine-Cbz would be predicted to attack the β-carbon of an electron-deficient olefin. Because chloramine-Cbz is only sparingly soluble in organic solvents, benzyltriethylammonium chloride was employed as a solid−liquid phase-transfer catalyst. As illustrated in Scheme 10, treatment of electron-deficient olefins with chloramine-Cbz in the presence of a catalytic amount of benzyltriethylammonium chloride in acetonitrile at room temperature provided the desired aziridines in good yield.

The asymmetric aziridination of this type of olefin was investigated using chiral ammonium catalysts derived from

SCHEME 10. Catalytic Aziridination of Electron-Deficient Olefins with Chloramine-Cbz

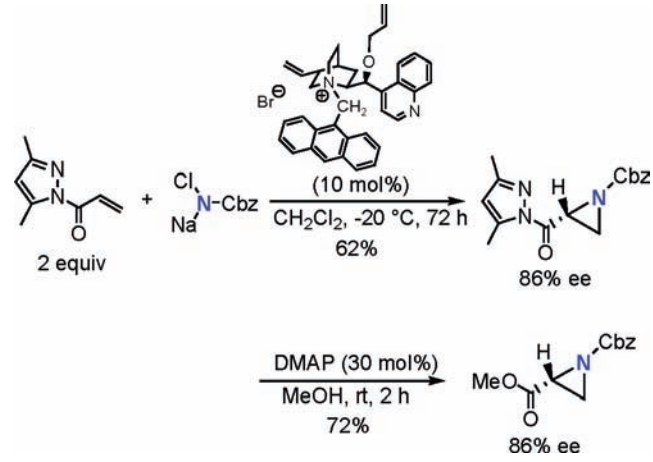


cinchona alkaloids. As a result of optimizing the reaction conditions, when the olefin containing a dimethylpyrazole substituent and the cinchonine-derived anthracenylmethylated ammonium salt as a chiral catalyst was employed in the reaction under the conditions shown in Scheme 11, the aziridination proceeded with good enantioselectivity. Removal of pyrazole moiety was performed using a DMAP catalyst, yielding the methyl ester-substituted aziridine with no change in optical purity (Scheme 11).[25]

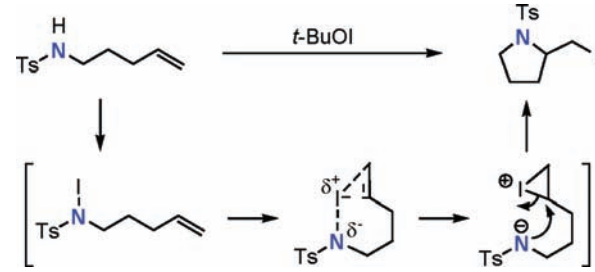
Simple Amides as N_1 Units for Synthesis of Aziridines and Oxazolines

Although CT was found to be a good nitrogen source for the synthesis of various nitrogen heterocycles, the substituent on the nitrogen is restricted to a tosyl group. Some *N*-metallo-*N*-chloro derivatives have been synthesized, but they are often unstable and are not easily handled. If more readily available amides, including sulfonamides, are to be used as N_1 units in the synthesis of heterocycles, more general and practical processes need to be established. Although it is well-known that *t*-BuOI can function as an iodination reagent and that it can be readily prepared from *t*-BuOCl and metal iodides,[26] few examples of the reagent being used in organic reactions have been reported to date.[27] In the present Account, *tert*-butyl hypoiodite (*t*-BuOI) was found to play an important role in the efficient and convenient cyclization of *N*-alkenylsulfonamides. This reaction involves iodination of the sulfonamide nitrogen followed by an intramolecular iodonium ion transfer to the olefin moiety and cyclization (Scheme 12). The method was applicable to the synthesis of, not only three- to six-membered N-heterocycles from *N*-alkenylsulfonamides, but also other heterocycles from alkenylbenzamides or alkenylbenzthioamides (Scheme 13).[28]

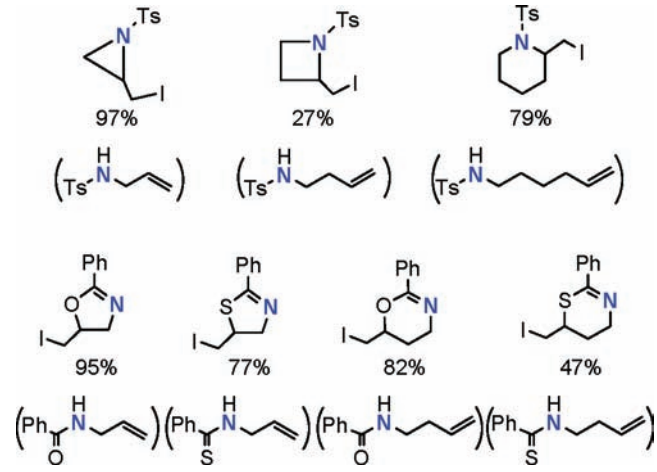
SCHEME 11. Catalytic Asymmetric Aziridination of Electron-Deficient Olefin with Chloramine-Cbz



SCHEME 12. Intramolecular Cyclization of *N*-Alkenylsulfonamides via an Iodonium Ion Using *t*-BuOI

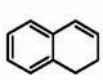
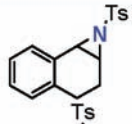
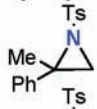
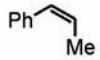
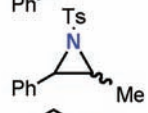
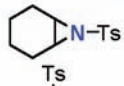
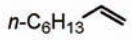
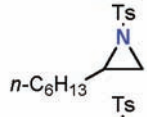
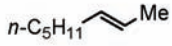
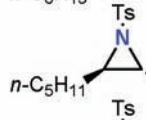
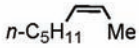
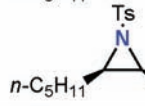


SCHEME 13. Cyclization Products from *N*-Alkenylamides Using *t*-BuOI



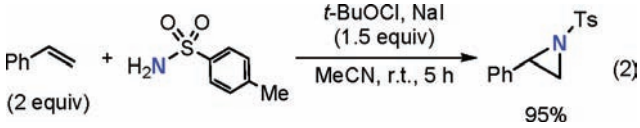
Intramolecular cyclization was applied to an intermolecular version of the reaction, that is, the reaction of amides and olefins, utilizing *t*-BuOI as a powerful oxidant. If the reaction were to proceed successfully, metal-free ring formation would be expected. An electrochemical process and a method using hypervalent iodine for aziridination represent alternative metal-free procedures.[29] Che and co-workers also developed a related aziridination using aminophthalimide as the nitrogen source.[30]

TABLE 4. Olefin Aziridination from a Sulfonamide Using *t*-BuOI[a]

olefin	aziridine	yield (%)[b]
		76[c]
		81[d,e]
		66[f,g]
		58[h]
		77
		63
		82

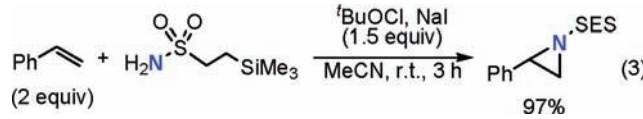
[a] Reaction conditions: *p*-toluenesulfonamide (0.5 mmol), olefin (1.0 mmol), *t*-BuOCl (1.5 mmol), NaI (1.5 mmol), MeCN (3 mL), rt, 96 h. [b] Isolated yields based on *p*-toluenesulfonamide. [c] Reaction time: 0.5 h. [d] Reaction time: 2 h. [e] ^{1}H NMR yield. [f] Reaction time: 5 h. [g] *Cis*/*trans* = 41:59. [h] *t*-BuOCl and NaI: 1 mmol.

In an initial experiment, the model aziridination of styrene with *p*-toluenesulfonamide was investigated. As shown in eq 2, treatment of *p*-toluenesulfonamide and styrene (2 equiv) with *t*-BuOI (1.5 equiv), prepared in situ by the reaction of *t*-BuOCl and NaI, at room temperature in acetonitrile led to the desired aziridine in 95% yield (eq 2).



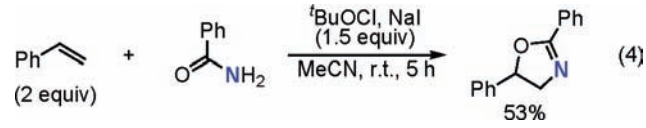
The range of functional substrates for aziridination by *t*-BuOI with *p*-toluenesulfonamide was explored using various olefins under optimized conditions (Table 4). It is noteworthy that the reaction of (*E*)-2-octene proceeded with complete stereoselectivity, giving a *trans*-substituted aziridine as the sole product. In contrast to (*Z*)-β-methylstyrene, the aziridination of (*Z*)-2-octene was stereoselective and stereospecific and gave the corresponding *cis*-aziridine exclusively in good yield. The complete stereoselective and stereospecific aziridinations are fully consistent with a reaction pathway involving a cyclic iodonium intermediate.

Some other sulfonamides (*o*-nitrobenzenesulfonamide and alkylsulfonamides) can also function as competent nitrogen sources in aziridination. Among them, alkylsulfonamides are good nitrogen sources, giving the corresponding aziridines in high yields. For example, the treatment of styrene with 2-(trimethylsilyl)ethanesulfonamide ($SESNH_2$) in the presence of *t*-BuOI led to the production of *N*-SES-aziridine in 97% yield (eq 3). As mentioned above, the SES group can be readily deprotected to afford N-unsubstituted aziridine.



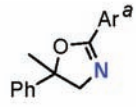
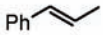
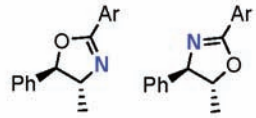
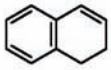
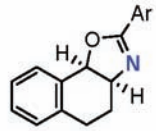
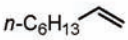
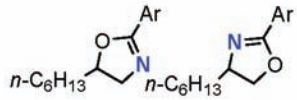
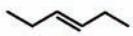
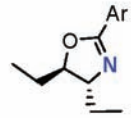
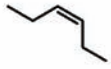
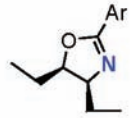
An efficient and convenient method for the synthesis of aziridines from olefins and sulfonamides using *t*-BuOI was also developed. These preliminary findings provide the first example of the metal-free aziridination of olefins using readily available sulfonamides as the nitrogen source.[31]

To demonstrate the utility of this unique system, the reaction of benzamide instead of sulfonamides was examined. When benzamide and styrene were treated with *t*-BuOI in acetonitrile at room temperature, an oxazoline was obtained in 53% yield without the formation of an *N*-benzoylaziridine (eq 4). Although an example of the multistep preparation of oxazolines from benzamide and olefins has been reported,[32] this is the first report of the direct synthesis of an oxazoline from readily available starting materials.



Some other amides were examined for their potential use in the synthesis of oxazoline from styrene (Table 5). The reaction of styrene with *p*-methoxybenzamide using *t*-BuOI under the above conditions afforded the oxazoline in 37% yield. An electron-deficient amide, *p*-nitrobenzamide, was found to be reactive, giving the desired oxazoline in 67% yield along with the regioisomer in 11% yield; the two compounds could be easily separated by silica gel chromatography. Although the efficiency of the reactions needs to be improved, an aliphatic amide also functioned as a component of an oxazoline. Since *p*-nitrobenzamide was found to act as a good component for the synthesis of oxazolines, some unfunctionalized olefins were subjected to the reaction using the amides and *t*-BuOI. α-Methylstyrene was smoothly converted into one regioisomer of oxazoline by a reaction with *p*-nitrobenzamide. When (*E*)-β-methylstyrene was employed, two regioisomers were produced in 72% yield; the reaction gave *trans*-oxazolines exclusively, and the stereochemistry of the starting olefin was preserved. The reaction of 1,2-dihydronaphthalene with *p*-ni-

TABLE 5. Synthesis of Oxazolines from Olefins with *p*-Nitrobenzamide

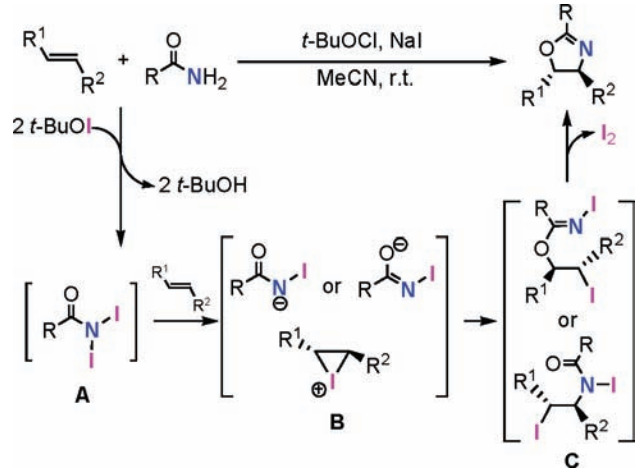
olefin	time (h)	yield (%)	product (ratio)
	5	79	
	12	72	 (90 : 10)
	12	55	
	24	50	 (70 : 30)
	96	71	
	96	68	

[a] Ar = *p*-$NO_2C_6H_4$.

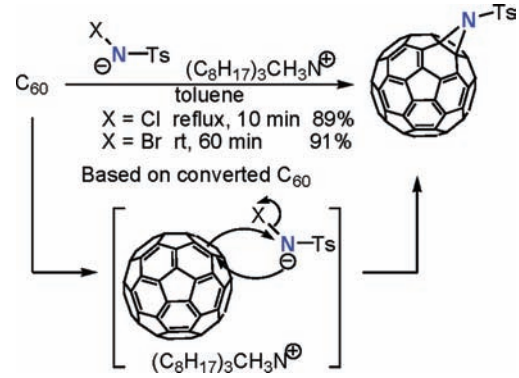
trobenzamide proceeded to afford the corresponding oxazoline as the sole product. Mono- and disubstituted aliphatic olefins were also used in the reaction, and in the reactions of (*E*)- and (*Z*)-3-hexene, complete stereoselectivity was observed, indicating that a cyclic iodonium intermediate might be involved in the reaction path. From another synthetic viewpoint, the present method can be regarded as an aminohydroxylation of olefins, since oxazolines are easily converted into the corresponding β-amino alcohols.

The proposed pathway for the synthesis of oxazoline is shown in Scheme 14. Two equivalents of *t*-BuOI, generated in situ, initially react with an amide, but not with olefins, to give a diiodinated amide **A**. This occurs because a Lewis acid or UV

SCHEME 14. Plausible Reaction Pathway Leading to Oxazolines



SCHEME 15. Addition−Cyclization of Haloamine-T to C_{60}



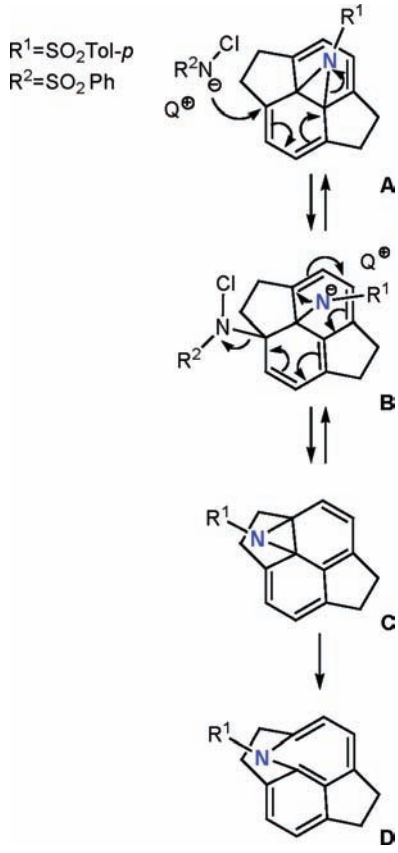
light is required[27c] for olefins to react with *t*-BuOI. The active species **A** functions as an iodonium source, which reacts with olefins to generate the cyclic iodonium intermediate **B**, followed by the addition of the amide counteranion (O^- or N^-), yielding adduct **C**. It is assumed that the route to aziridines from olefins and sulfonamides involves the same pathway.

A simple synthetic method for the direct formation of oxazolines from unfunctionalized olefins and readily available amides is reported. The method can be viewed as the aminohydroxylation of olefins. Because of this, the findings reported herein promise to have significant influence in the area of synthetic organic chemistry.[33]

Introduction of an N_1 Unit to C_{60} Utilizing Haloamine Salts

In contrast to normal electron-deficient olefins depicted in eq 1, fullerene (C_{60}) can function as a strong electron acceptor. Thus, the reaction of C_{60} with CT was examined, and the desired aziridination was found to proceed. CT was first converted into its ammonium salt because of its low solubility in toluene. The reaction of C_{60} with an equimolar amount of ion-exchanged CT in toluene under reflux for 10 min gave the

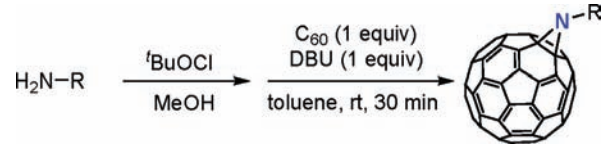
SCHEME 16. Plausible Pathway for the Rearrangement



closed [6,6]-bridged aziridinofullerene in 89% yield (Scheme 15). Since bromide is a better leaving group than chloride, when bromamine-T was used, the reaction proceeded even at room temperature to afford the desired aziridine with a high degree of selectivity (91%). Since it is known that a nitrene is generated from the reaction of CT with $AgNO_3$ (Scheme 6),[22] this reaction system was employed in the reaction with C_{60}, but no adduct was formed. Moreover, the treatment of C_{60} with ion-exchanged CT under an atmosphere of oxygen gave the same result as that shown in Scheme 15, indicating that the reaction did not involve radical species such as a triplet nitrene. Therefore, the active species in the present reaction appears to be the anionic nitrogen of CT, and the aziridination can be regarded as an aza-version of the Bingel reaction.[34]

Interestingly, the addition of MS4A to the reaction system not only improved the efficiency of the reaction but also produced opened [5,6]-bridged azafulleroid as a main product (eq 5). Since the aziridinofullerene underwent rearrangement at 180 °C in *o*-dichlorobenzene for 5 h to give the azafulleroid in 58% yield, the effect of MS4A on the formation of the azafulleroid was readily apparent. This finding indicates that the azafulleroid was formed under thermodynamic control and the aziridinofullerene

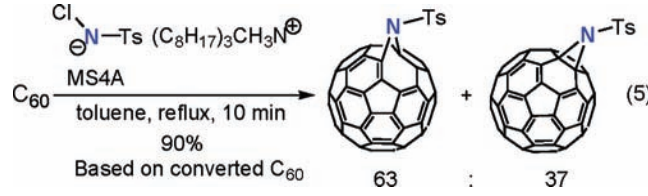
TABLE 6. Aziridination of C_{60} with Various Amides



amide (equiv)		time (min)	yield (%)[a,b]
H_2N O^tBu	(1.5)	15	80 (26)
H_2N $O^nC_{16}H_{33}$	(1.0)	300	60 (15)
H_2N O	(1.0)	300	57 (17)
H_2N NMe_2	(1.5)	30	77 (35)
H_2N $N(^nC_{12}H_{25})_2$	(1.0)	10	66 (35)
H_2N Ph	(1.0)	60	99 (7)
H_2N N	(1.5)	120	61 (11)
H_2N P(O)(OEt)(OEt)	(1.5)	30	60 (28)
H_2N P(O)(Ph)(Ph)	(1.5)	30	100 (50)

[a] Based on converted C_{60}. [b] The numbers in parentheses are isolated yields.

was selectively formed under kinetic control under the relatively mild conditions used for this reaction.

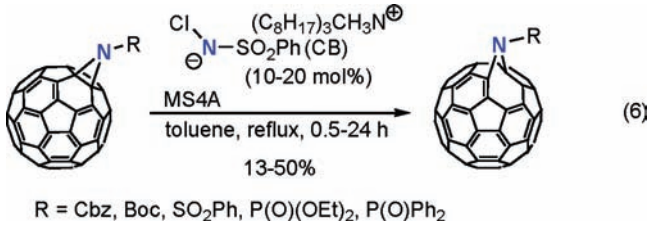


To clarify the reaction pathway, isolated *N*-tosylaziridinofullerene and MS4A were heated in toluene under reflux, but the reaction did not proceed at all. In contrast, when the aziridinofullerene was treated with ion-exchanged CT under reflux in the presence of MS4A, the *N*-tosylazafulleroid was obtained, indicating that the azafulleroid is formed from the aziridinofullerene. A catalytic amount of chloramines (*N*-chloro-*N*-sodiobenzenesulfonamide, chloramine-B) could permit the rearrangement to proceed. Based on these results, a proposed mechanism for the rearrangement of aziridinofullerene is

shown in Scheme 16 (illustrated by a part of fullerene). The most highly strained carbon on aziridinofullerene **A** is first attacked by a chloramine to give the diaminated intermediate, **B**. The reaction illustrated by the curved arrows in intermediate **B** leads to thermodynamically stable azafulleroid **D** through the closed [5,6]-bridged intermediate, **C**. Although the function of MS4A is unclear at present, the ability to eliminate nitrogen anions generated in situ may be enhanced by the sodium cation in MS4A.[35]

Although the aziridination is unique and unprecedented, the method essentially requires the use of chloramine salts, some of which are not stable. Thus, a practical aziridination of C_{60} with a variety of simple amides, many of which are commercially available, was subsequently developed.[36] In order to expand the generality of the aziridination of C_{60}, a facile method for the chlorination of amides and their deprotonation in situ needed to be developed. *tert*-Butyl hypochlorite (*t*-BuOCl), in methanol, was employed in the chlorination of various amides, and the solvent was exchanged with toluene followed by addition of C_{60} and a base. As shown in Table 6, various amides were applicable to the aziridination of C_{60}.

The aziridinofullerenes obtained by our original method underwent rearrangement to the corresponding azafulleroids (eq 6), in which reaction was catalyzed by chloramine-B (CB) in the presence of MS4A as shown in Scheme 16.



Conclusion

The present study investigated the N−X bond for its potential use in the synthesis of N-heterocycles. The efficient and convenient synthesis of N-heterocycles, such as aziridines and pyrrolidines, was achieved using CT as an N_1 unit. It is noteworthy that iodine-catalyzed aziridination not only proceeded with stereospecificity but could also be used in reactions in aqueous media using a novel silica−water system. Noncatalytic reactions of CT and ε-iodoolefins presented unique ionic iodine atom transfer cyclization with the iodo group on the substrates serving multiple functions. The results of the CT studies allow simplification of the N_1 units. We also found that *N*-chloro-*N*-sodiocarbamates react with electron-deficient olefins in the presence of a phase transfer catalyst to give the corresponding aziridines. The method was applied to the catalytic asymmetric synthesis of aziridines using quaternary cincona alkaloid catalysts. The use of *t*-BuOI supported the reactions of simple amides, including sulfonamides and olefins, which are readily available reagents, leading to the production of aziridines and oxazolines. Fullerene, C_{60}, was also aziridinated by CT and readily available amides, and the resulting aziridinofullerene underwent a unique rearrangement to an azafulleroid. The heterocycles produced in the present study are useful building blocks for organic syntheses. In addition, the evolution of the N−X bond for the synthesis of these heterocycles based on this research promises to lead to a variety of highly general synthetic procedures that will be useful in synthetic organic chemistry.

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BIOGRAPHICAL INFORMATION

Satoshi Minakata was born in Wakayama, Japan, in 1964. He received his Ph.D. in 1993 from Osaka University under the direction of Prof. Y. Ohshiro. After spending two years at the Central Research Laboratories of Dainippon Ink & Chemicals, Inc., he was appointed to the position of Assistant Professor in the Department of Applied Chemistry in Prof. Komatsu's group at Osaka University. In 2002, he was promoted to Associate Professor. From 1997 to 1998, he worked with Prof. Erick M. Carreira at the California Institute of Technology as a Visiting Associate Professor. His current research interest is the development of new methodologies using the N_1 unit transfer reaction for the synthesis of achiral and chiral nitrogen-containing heterocyclic compounds.

FOOTNOTES

*E-mail: minakata@chem.eng.osaka-u.ac.jp.

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