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APPLICATION OF STABLE NITRENIUM IONS TO PREPARATIVE ORGANIC CHEMISTRY

Yasuo Kikugawa

Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-0295, Japan
E-mail: kikugawa@josai.ac.jp

Abstract – Nitrenium ions and their related species are involved in many important chemical and biological processes. The present review will survey the recent progress of their utility in preparative organic chemistry.

CONTENTS

1 INTRODUCTION

Nitrenium ions (**1**) are divalent, electron-deficient nitrogen species which show umpolung of reactivity relative to the usual trivalent nitrogen species and can exist in either the singlet or triplet state as the lowest energy configuration (Figure 1).

The increased interest in nitrenium ions is mainly due to the important role of these species in carcinogenetic processes and also is related to their applications in the development of novel methods in synthetic organic chemistry. A critical survey of carcinogenetic processes that might involve these intermediates is beyond the intended scope of this review. Instead, nitrenium ions having important

synthetic applications form the subject of this report. Useful reviews dealing with the general chemistry of nitrenium ions have been published.[1]

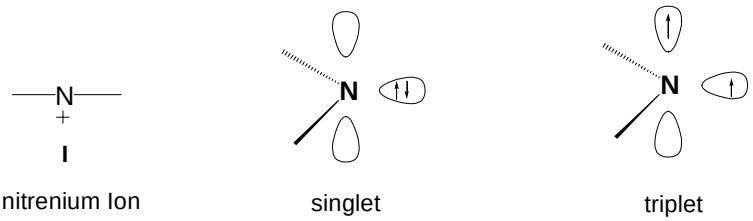


Figure 1

Subclasses of nitrenium ions include alkyl, aryl, and acyl nitrenium ions having, respectively, alkyl, aryl, and acyl groups attached to the nitrogen. The majority of these ions are reactive short-lived species that are generally difficult to identify and investigate experimentally. However, arylnitrenium ions are more stable than alkylnitrenium ions owing to delocalization of the positive charge onto the aryl ring. Furthermore, the presence of at least one powerful donor substituent on the nitrogen atom increases the stability of nitrenium ion with the singlet state being stabilized to a great extent than the triplet state. These stable long-lived nitrenium ions open up exceptional opportunities for the development of synthetically useful new reactions. Quite recently, many reports have appeared concerning practical applications of nitrenium ions in organic synthesis. The present review includes a survey of the recent advances of the chemistry of nitrenium ions and their derivatives, particularly of new chemical reactions having synthetic utility in organic synthesis.

2 USES OF NITRENIUM IONS IN ORGANIC SYNTHESIS

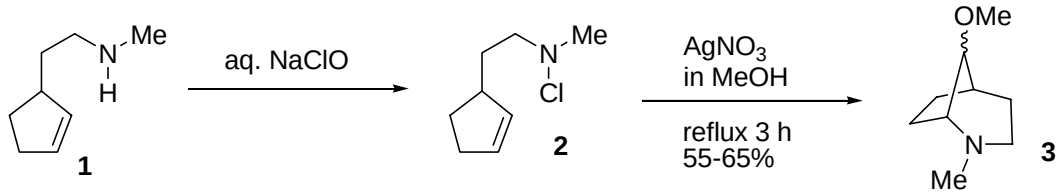
2-1 *N*-ALKYLNITRENIUM IONS

Although many *N*-alkylnitrenium ions are known, this section will be relatively short, since few new synthetically useful reactions of these ions have been reported. This is probably because they are short-lived and are not suitable for generation of synthetically useful intermediates. An extensive series of studies by Gassman marked the beginning of the development of the chemistry of these reactive nitrogen-containing intermediates.[2]

Many compounds that contain an N-Hal bond have proven to be very convenient substrates for the preparation of nitrenium ions. Scheme 1 illustrates the formation of nitrenium ions by solvolysis of 2-(cyclopent-2-enyl)-*N*- methylethanamine (**1**) in a methanol solution of silver nitrate.[3]

Generally arylnitrenium ions have higher stabilization energy than the aliphatic ions.[2] Therefore, it can be concluded that *N*-alkylnitrenium ions are less applicable to synthetic organic chemistry than *N*-arylnitrenium ions. Alkylhydroxylamines bearing a benzene ring in a molecule were subjected to

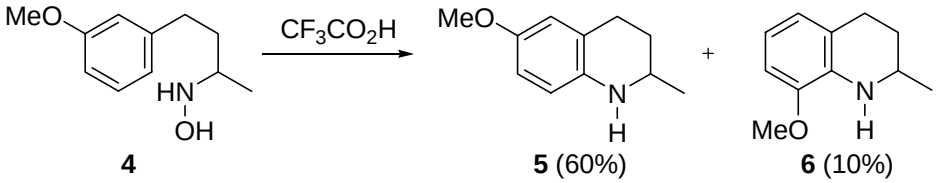
intramolecular cyclization in trifluoroacetic acid (TFA) or in the presence of Lewis acids, and benzene-fused six-menbered nitrogen heterocycles (**5** and **6**) were obtained in moderate yields (Scheme 2).[4] However, it is not clear that the cyclization reaction proceeds *via* a nitrenium ion intermediate.



1 **2** **3**

Scheme 1

Nonetheless, it is evident that an electrophilic electron-deficient nitrogen must play an important role in this reaction because an electron-donating substituent on the benzene ring facilitates the cyclization reaction.

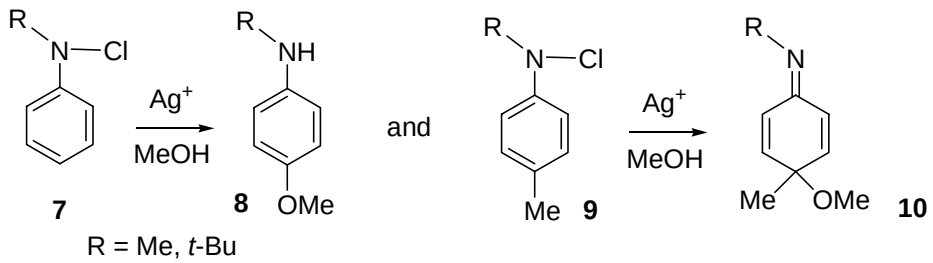


4 **5** (60%) **6** (10%)

Scheme 2

2-2 *N*-ARYLNITRENIUM IONS

N-Arylnitrenium ions are expected to be more stable than alkyl substituted ions owing to the possible delocalization of the positive charge onto the aryl ring. Nucleophilic attack on these intermediates results in the introduction of various substituents on the aryl ring. Gassman, *et al*. first reported a synthetic method for preparation of anisoles (**8**) and derivatives (**10**) of 2,5-cyclohexadienone by solvolysis of *N*-chloroanilines (**7** and **9**) through a nitrenium ion intermediate in a methanol solution of silver trifluoroacetate (Scheme 3).[5]

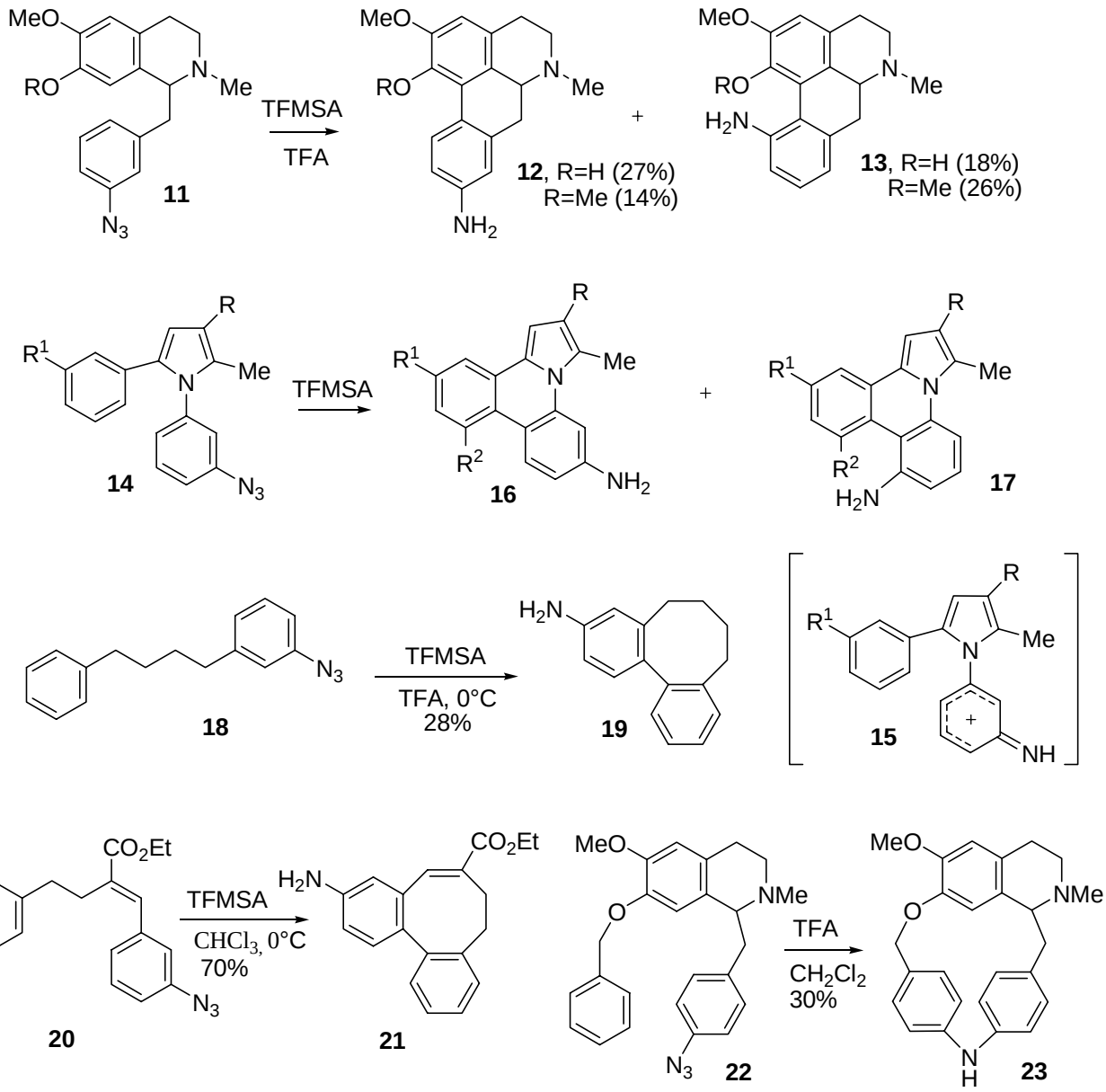


7 **8** **9** **10**

R = Me, *t*-Bu

Scheme 3

Many compounds that contain an azide group are very convenient substrates for the preparation of arylnitrenium ions. Olah, *et al*. reported that phenyl azide/trifluoromethanesulfonic acid (TFMSA) is a highly efficient reagent for the electrophilic phenylamination of aromatics.[6] Phenylnitrenium ions generated from phenyl azides in the presence of TFMSA/TFA undergo nucleophilic substitution reactions, that is, aromatic N-substitutions and/or C-substitutions, depending on the initial azide structure.[7]

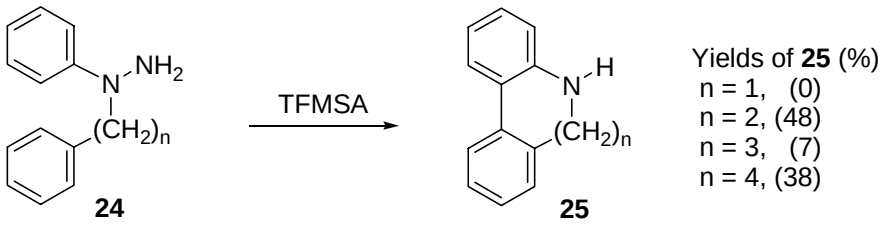


Scheme 4

1-(*m*-Azidobenzyl)-1,2,3,4-tetrahydroisoquinolines (**11**) with TFMSA/TFA afforded the corresponding 9- and 11-aminoaporphines (**12** and **13**).[8] Similarly, TFMSA catalyzed decomposition of 1-(3-azidophenyl)pyrroles (**14**) produced the 6- and 8-aminopyrrolo[1,2-*f*]phenanthridines (**16** and **17**) through cyclization of the intermediate arylnitrenium ions (**15**) in good overall yields.[9] Medium-sized

rings were formed by a similar methodology and 3-aminodibenzo[a,c]octadiene (**19**) (28%) and **21** (70%) were synthesized by the intramolecular cyclization of arylnitrenium ions generated from azides (**18** and **20**) with TFMSA.[10] Generally 6-menbered ring formation is favorable. However, in a special case, the 16-menbered ring (**23**) was formed by a nitrenium ion upon an aromatic nucleus (Scheme 4).[8]

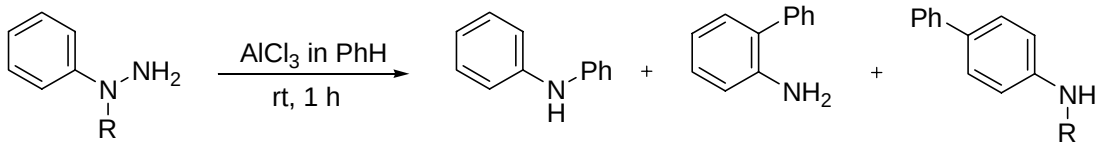
Phenylnitrenium ions generated from phenylhydrazines in the presence of TFMSA undergo intramolecular aromatic C-substitutions to afford cyclized products. Treatment of *N*-phenyl-*N*-(4-phenylbutyl)hydrazine (**24**, n = 4) in TFMSA at 80 °C for 30 min produced dibenz[b,d]azonine (**25**, n = 4) in 38% yield (Scheme 5).[11]



24 **25**

Scheme 5

Similarly, phenylnitrenium ions generated from phenylhydrazines (**26**) in the presence of $AlCl_3$ were trapped with solvent arenes to give both N-substitution and C-substitution products (**27** and **28**), while an *N*-methyl-*N*-phenylnitrenium ion generated from *N*-methyl-*N*-phenylhydrazine (**26b**) reacted with arenes to give exclusively aromatic C-substitution products **29b** (Scheme 6).[12] Reaction of *N*-arylaminophthalimide derivatives with $AlCl_3$ in benzene results in heterolytic N-N bond cleavage to give an arylnitrenium ion and canonical forms involving the arene. These species are trapped by benzene to give aminobiaryls and *N*-arylanilines.[13]



26a: R = H
26b: R = Me

27a (44%)
27b -

28a (8%)
28b -

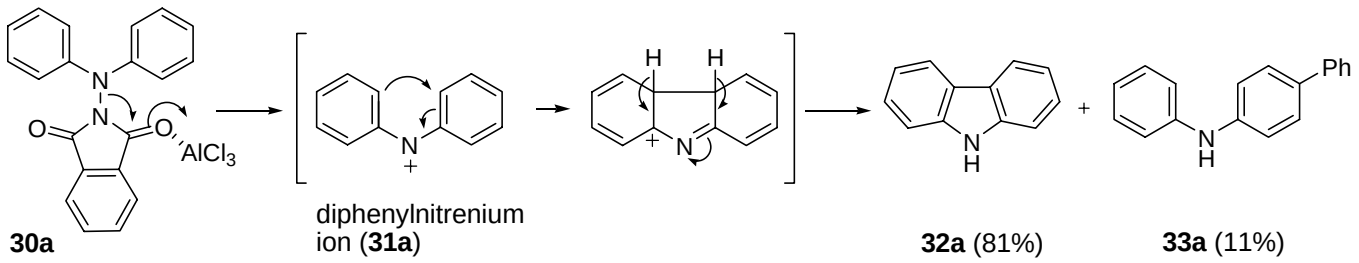
29a (44%)
29b (92%)

Scheme 6

In an extension of this work the reaction of *N*-(*N*,*N*-diarylamino)phthalimides (**30**) with $AlCl_3$ in benzene was investigated, with the expectation that $AlCl_3$-mediated cleavage of the N-N bond would give a diarylnitrenium ion (**31a**).[14]

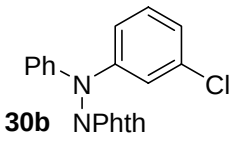
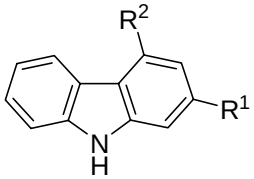
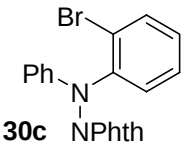
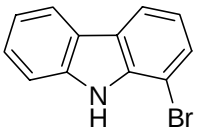
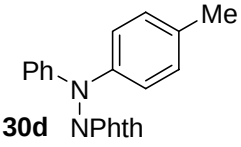
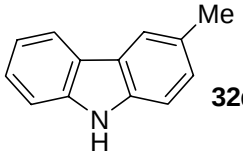
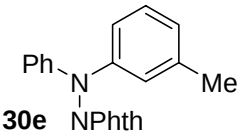
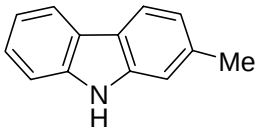
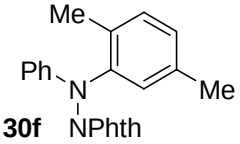
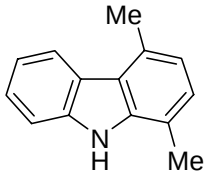
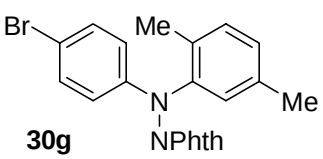
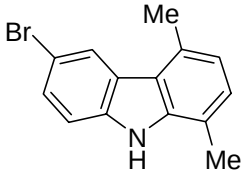
Treatment of *N*-(*N*,*N*-diphenylamino)phthalimide (**30a**) with $AlCl_3$ in benzene for 4 h at rt gave carbazole

(**32a**) along with *N*-*p*-biphenyl-*N*-phenylamine (**33a**). The formation of these products indicates that $AlCl_3$-mediated heterolytic cleavage of the N-N bond in fact produces a



Scheme 7

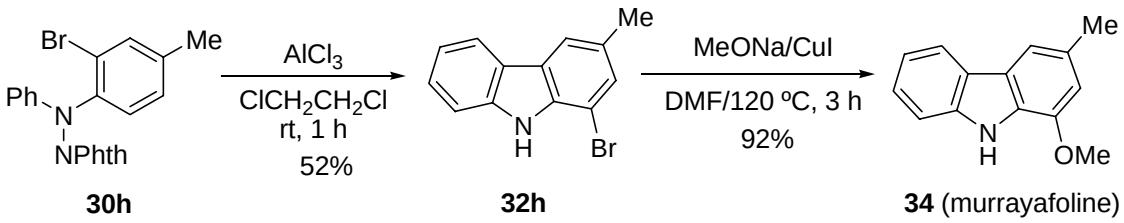
Table 1. Reaction of *N*-(*N*,*N*-diarylamino)phthalimides (**30**) with $AlCl_3$

entry	starting material	time (h)	product (%)
1	 **30b**	4	 **32b** (64): (R^1 = Cl, R^2 = H) **34b** (15): (R^1 = H, R^2 = Cl)
2	 **30c**	17	 **32c** (73)
3	 **30d**	0.5	 **32d** (81)
4	 **30e**	4	 **32d** (81)
5	 **30f**	1	 **32f** (89)
6	 **30g**	4	 **32g** (39) **32f** (14)

diphenylnitrenium ion. Arylation of the phenylnitrenium intermediate could occur at three sites (nitrogen, the *para* ring carbon and the *ortho* ring carbon). In the present case, the *ortho* ring carbon is attacked

intramolecularly by the adjacent *ortho* ring carbon to form a new C-C bond (Scheme 7). The results are presented in Table 1.

In the case of methoxy-substituted substrates **30**, the reaction did not proceed smoothly. Therefore, for the synthesis of methoxycarbazoles, the corresponding bromocarbazoles are synthesized by the above method. Subsequent replacement of the bromine atom with a methoxy group by the published procedure produces the methoxycarbzoles.[15] This methodology was applied to the synthesis of a carbazole alkaloid, 1-methoxy-3-methyl-9*H*-carbazole (murrayafoline) (**34**).[14]



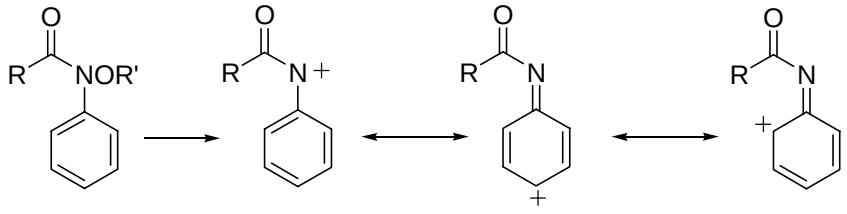
30h **32h** **34** (murrayafoline)

Scheme 8

Falvey *et al*. reported that photolysis of protonated 1,1-diarylhydrazines and *N*,*N*-(diarylamino)-2,4,6-trimethylpyridinium ions generates the corresponding nitrenium ions. These were trapped by added Cl^- to give chlorinated *N*-phenylanilines. There was negligible cyclization to form carbazoles.[16]

2-3 *N*-ACYL-*N*-ARYLNITRENIUM IONS

Although the rearrangement of *N*-alkoxy- and *N*-hydroxy-*N*-arylamides **35** has not been investigated in detail in comparison with those of arylazides and of *N*-arylhydroxylamines, it is generally assumed that these amides decompose under acidic conditions *via* N-O bond heterolysis to yield *N*-acyl-*N*-arylnitrenium ions **36**. These have a positive charge on the nitrogen that is delocalized among the canonical forms involving the aryl group. Nucleophilic attack results in the introduction of various substituents on the aryl ring (Scheme 9).

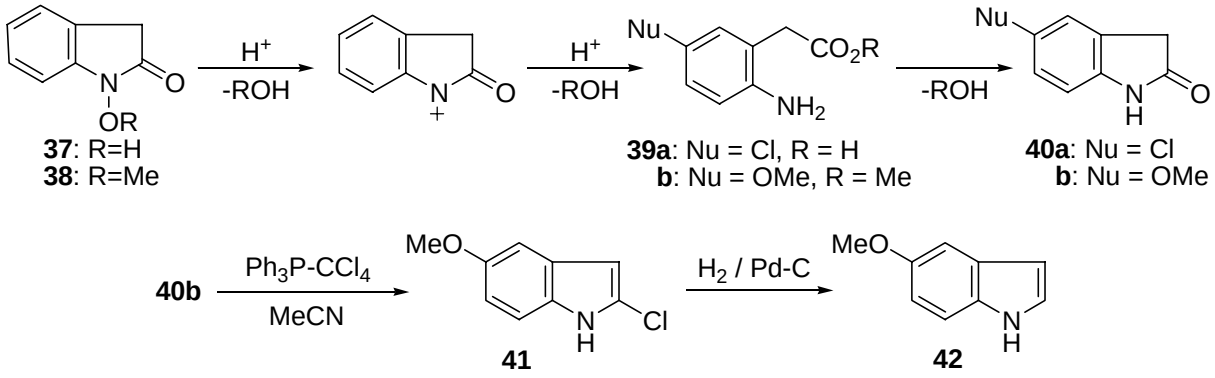


35 **36a** **36b** **36c**

Scheme 9

1-Hydroxy-2-oxindole (**37**) was converted to the unstable *p*-toluenesulfonate at -78 °C. Warming the

p-toluenesulfonate to rt with addition of methanol brought about the formation of 5-methoxy- and 7-(*p*-toluenesulfonyloxy)-2-oxindole in 42 % and 34 % yields, respectively.[17] The same compound **40b** was synthesized from 1-hydroxy- and 1-methoxy-2-oxindoles (**37** and **38**) under the conditions of refluxing methanol containing few drops of concentrated sulfuric acid.[18] The initial product was a ring-opened methyl 2-amino-5-methoxyphenyl acetate (**39**). Subsequent cyclization gave 5-methoxy-2-oxindole (**40b**) in 72 % yield. Conversion of **40b** to 5-methoxyindole (**42**) was accomplished in 66 % yield by chlorination of **40b** with triphenylphosphine-carbon tetrachloride in acetonitrile, followed by the catalytic hydrogenolysis of the chlorine atom from **41** (Scheme10).



Scheme 10

No ring opening was observed in the case of a six-membered ring. Thus, under similar acidic reaction conditions, 6-substituted-3,4-dihydrocarbostyrils (**44**) were obtained from 3,4-dihydro-1-methoxy- or 1-hydroxy-carbostyril (**43**) in moderate to good yields (Figure 2).[19] *N*-Methoxy- or *N*-hydroxy-*N*-phenylbenzamide underwent rearrangement in 20 % hydrochloric acid, or in benzene with

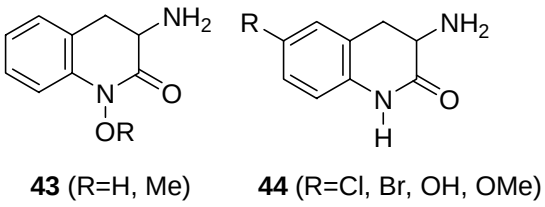
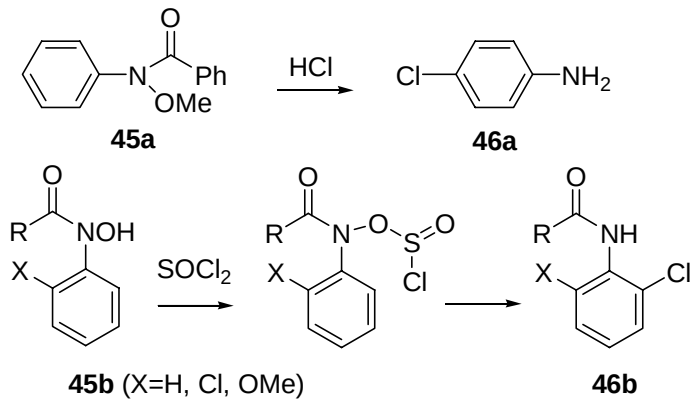


Figure 2

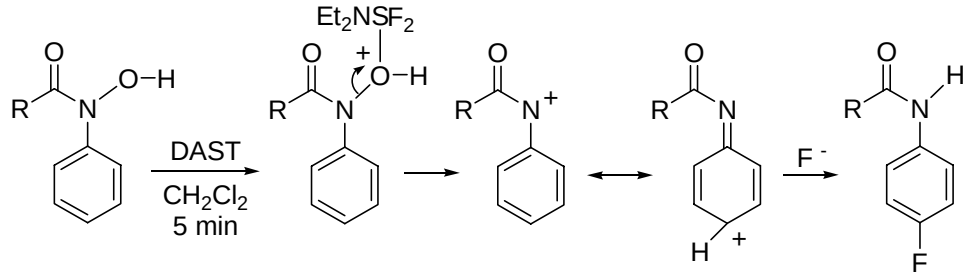


Scheme 11

thionyl chloride, to give 4-chloroaniline (**46a**) or *N*-(2-chlorophenyl)benzamide (**46b**) in 25 % or in 84 %

yield, respectively (Scheme 11).[20, 21]

In a manner similar to that described above, introduction of a fluorine atom into the aryl group was attempted using concentrated hydrogen fluoride. Howerver, this was unsuccessful because of the weak nucleophilicity of the fluoride ion in these protic reaction conditions. However, treatment of *N*-aryl-*N*-hydroxyamides with diethylaminosulfur trifluoride (DAST) [22] in dichloromethane for 5 min with cooling, resulted in the removal of the hydroxy function and the introduction of a fluorine atom at the *para* position of the aromatic ring in high yield (Scheme 12).[23] DAST is a commercially available reagent and often used for replacement of the hydroxyl group with fluorine. The merits of this method include regioselective introduction of a fluorine atom to an aromatic ring (the *para* position only), use of a commercially available reagent, high yields, short reaction times and technical simplicity.



47a, **48a** **47b**, **48b**

Scheme 12

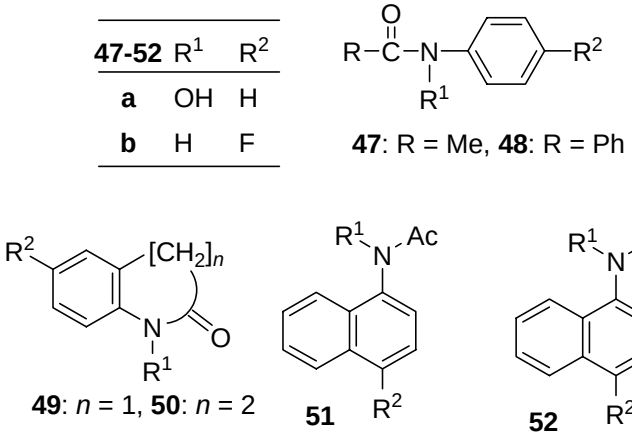


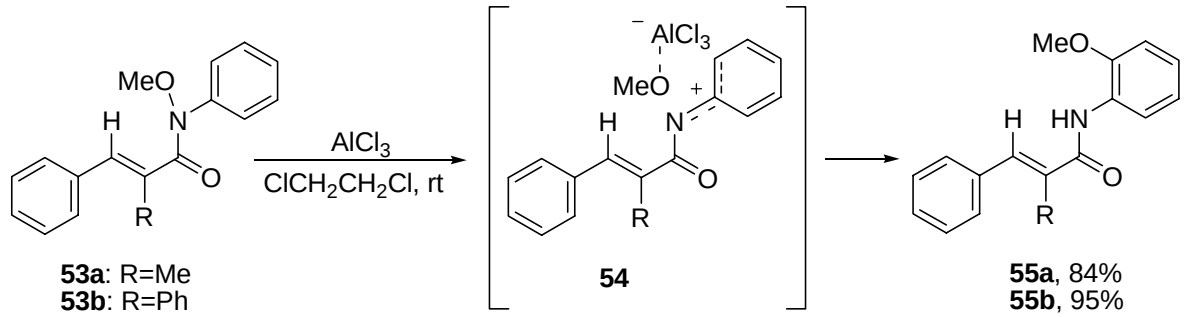
Figure 3

Table 2. Aromatic fluorination of *N*-aryl-*N*-hydroxyamides with DAST

entry	substrate	product	yield (%)
1	**47a**	**47b**	71
2	**48a**	**48b**	83
3	**49a**	**49b**	81
4	**50a**	**50b**	75
5	**51a**	**51b**	79
6	**52a**	**52b**	70

$AlCl_3$-mediated decomposition of *N*-methoxy-*N*-phenylamides **53** in 1,2-dichloroethane has been reported to provide a new source of *N*-acyl-*N*-arylnitrenium ions **54** that undergo nucleophilic intramolecular migration of the methoxy group from the nitrogen to the *ortho* position of the phenyl ring to give *N*-(2-methoxyphenyl)amides **55**.[24] *N*-Methoxycinnamamides bearing *a*-substituent groups rearrange rapidly in high yields (Scheme 13), while 1-methoxycarbostyrils do not, even with prolonged reaction

time. The most interesting aspect of this reaction is that the rearrangement of **54** gave exclusively *ortho* methoxy compounds **55**. The complete absence of the corresponding *para*-substituted product can be accounted for by assuming a mechanism involving a tight ion pair intermediate **54**.



53a: R=Me
53b: R=Ph

54

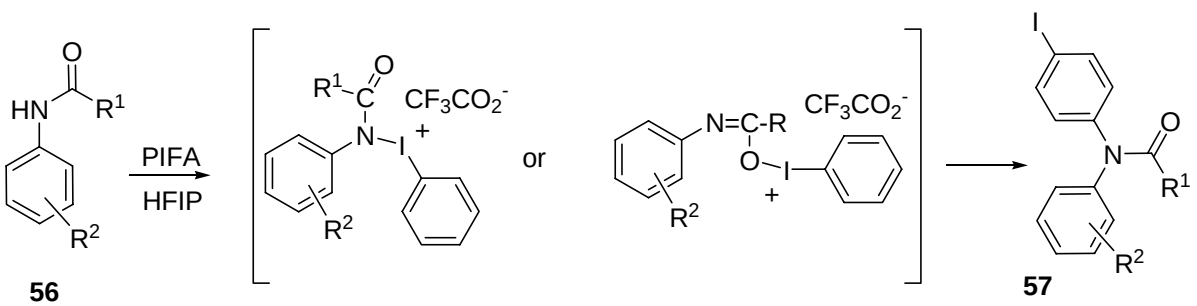
55a, 84%
55b, 95%

Scheme 13

A similar transhydroxylation of *N*-phenylamides by the system $(n\text{-Bu})_3P$-CCl_4-CH_3CN was reported.[25] The hydroxy group of *N*-hydroxy-*N*-phenylamide (**45b**, R = Ph, X = H) rearranged mainly to the *ortho* position of the *N*-phenyl group and to the *para* position to a much lesser extent. It is interesting to note that use of less than the stoichiometric amount of $(n\text{-Bu})_3P$ (0.55 molar eq.) is effective for the reaction, although a somewhat longer reaction time is required for completion.

As described above, the N-O bond heterolyses in acidic conditions generate nitrenium ions. Recently, it was reported that some oxidants such as phenyliodine(III) bis(trifluoroacetate) (PIFA) react with an N-H group of *N*-arylamides in TFA to yield *N*-acylnitrenium ions. Hypervalent iodine reagents such as PIFA have received a great deal of attention due to their ready availability, low toxicity, easy handling, and similar reactivity to that of heavy metal reagents (*vide post*, **2**-**4**).

The reaction of anilides with PIFA in TFA, TFA-$CHCl_3$ or hexafluoroisopropyl alcohol (HFIP) was reported.[26] When the acyl group of the anilide is highly electronegative such as trifluoroacetyl or the



56

57

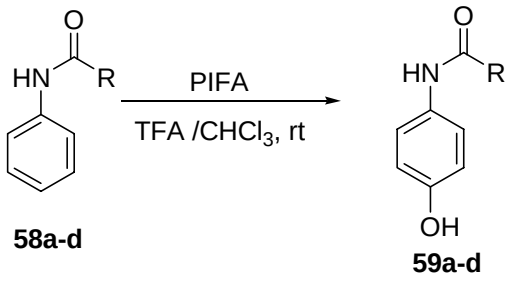
Scheme 14

phenyl group is substituted with an electron-withdrawing group such as chloro or ethoxycarbonyl group,

the 4-iodophenyl group is transferred from PIFA to the amide nitrogen of **56** to afford acetyldiarylamines (**57**). The N-iodophenylation reaction rate was remarkably increased using HFIP as solvent. Several acetyldiarylamines having an iodo group on the *para* position were prepared in high yield even in the case of sterically crowded 2,6-dichloroacetanilide. The proposed reaction mechanism is illustrated in Scheme 14.[26]

On the other hand, when the acyl group contains an electron-donating function such as 4-methoxyphenyl or the phenyl group is substituted with an electron-donating group, a trifluoroacetoxy group is transferred to the *para* position of the anilide aromatic ring. This group is hydrolyzed during work-up to produce the corresponding phenol. Both reactions occur in synthetically useful yields (Tables 3 and 4).[26]

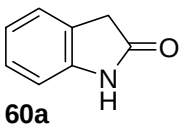
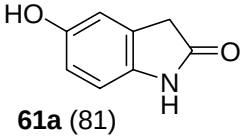
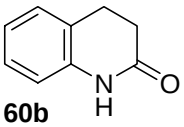
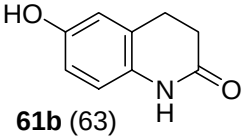
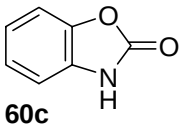
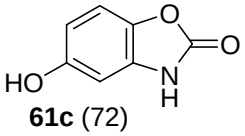
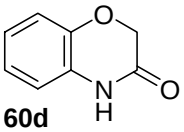
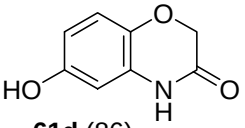
Table 3. *para*-Hydroxylation of anilides using PIFA



58a-d **59a-d**

starting material	R	time (min)	product yield (%)
58a	Me	90	**59** (64)
58b	C_6H_5	30	**59** (82)
58c	CMe_3	15	**59** (70)
58d	C_6H_4-4-OMe	20	**59** (91)

Table 4. Hydroxylation of benzannulated lactams with PIFA

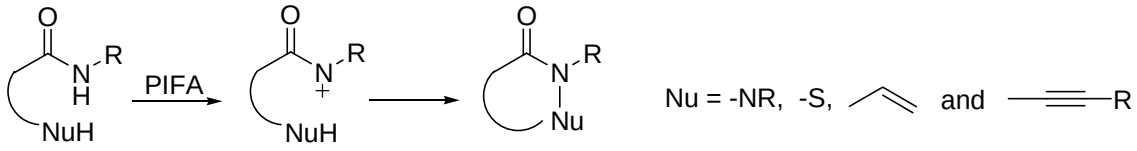
starting material	time (h)	product yield (%)
 **60a**	25	 **61a** (81)
 **60b**	33	 **61b** (63)
 **60c**	3[a]	 **61c** (72)
 **60d**	2[a]	 **61d** (86)

[a] Min.

A novel approach to the synthesis of a wide variety of heterocycles using PIFA was undertaken based on this strategy (Scheme 15).

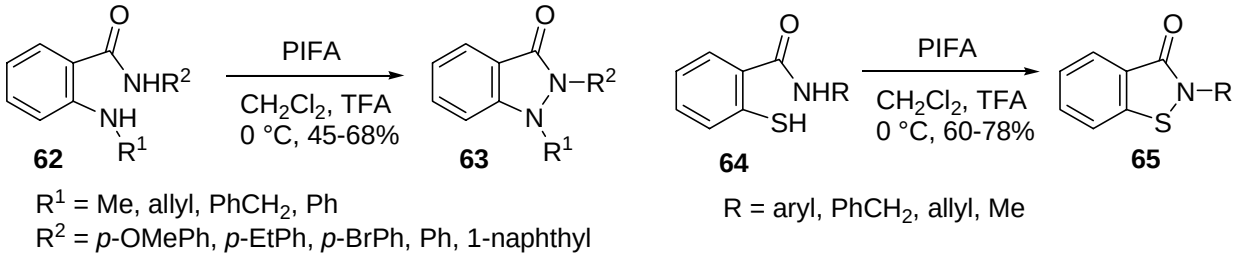
The oxidation of conveniently substituted *N*-arylamides (**62** and **64**) by PIFA affords the corresponding *N*-acylnitrenium ions. These can be intramolecularly trapped with amine functionalities and with thiol functionalities leading to the formation of new N-N and N-S bonds producing indazol-3-ones **63** and benzothiazol-3-ones **65**, respectively. In the synthesis of **63**, success is restricted to *N*-arylamides.

N-Alkyl- or *N*-alkoxy-amides failed to afford **63**, which indicates that an aromatic ring seems to be



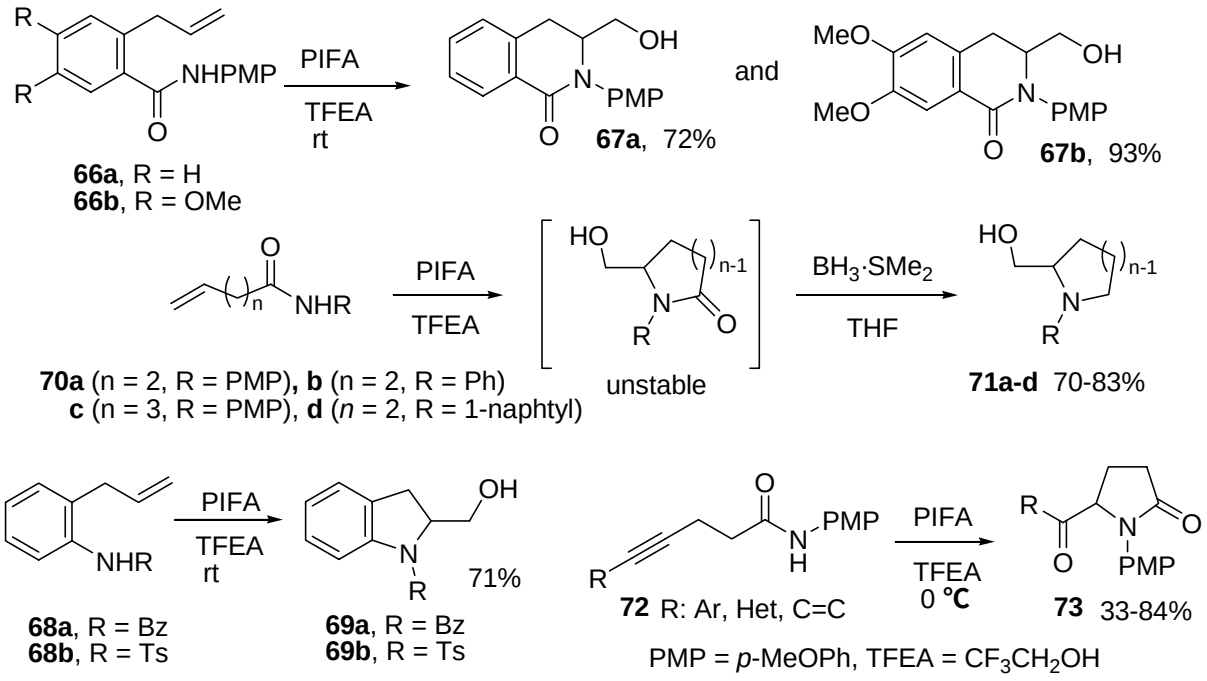
Scheme 15

important to stabilize the corresponding *N*-acylnitrenium intermediate (Scheme 16).[27]



Scheme 16

On the other hand, both *N*-arylamides and *N*-alkylamides successfully generate the corresponding nitrenium ions with PIFA to produce the benzothiazolones (**65**).[28]



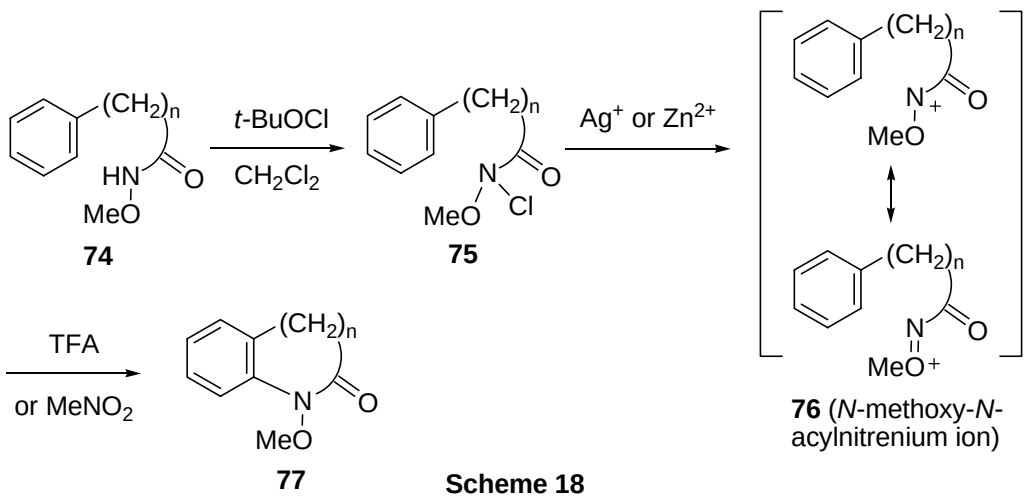
Scheme 17

Other approaches to the synthesis of nitrogen heterocycles using PIFA have been investigated. PIFA promotes the intramolecular electrophilic olefin amidation to afford five- and six-menbered nitrogen heterocycles.[29, 30] From 2-allyl-*N*-(phenyl or 4,5-dimethoxyphenyl)benzamide derivatives (**66a** and **b**) the isoquinolin-1-one derivatives (**67a** and **b**) were obtained by PIFA-promoted olefin amidohydroxylation reactions in 2,2,2-trifluoroethanol (TFEA).[29] Similarly, when the amides **68a** and **b** were treated with PIFA in TFEA at rt, indolines (**69a** and **b**) were obtained in moderate yields. These were transformed into the corresponding acetyl derivatives due to their labile nature.[30a] In other solvent such as CH_2Cl_2 and CH_3CN no indolines were obtained.

Pyrrolidine and piperidine derivatives (**71**) were also prepared through 5-exo-trig and 6-exo-trig cyclization modes by PIFA-promoted olefin amidohydroxylation of compounds **70**.[30b] Analogously, the oxidation of alkynylamides **72** by PIFA leads to the generation of *N*-acylnitrenium ions. These are trapped by intramolcular reaction with a triple bond producing the pyrrolidinones **73**. In this case also the solvent is limited to TFEA (Scheme 17).[31]

2-4 *N*- METHOXY- AND *N*-ALLYLOXY-*N*-ACYLNITRENIUM IONS

Nitreniuon ions in general are quite short-lived electrophilic reactive intermediates. In order to increase their utility in organic synthesis, it would be advantageous to prolong their lifetimes. It is reasonable to suspect that this could be accomplished by the presence of at least one powerful electron donor substituent on the nitrogen atom that would stabilize the positively charged nitrenium ion. Therefore, the selection of the appropriate N-substituent is of key importance. Among the most easily formed and useful members of this class are *N*-methoxy-*N*-acylnitrenium ions. *N*-Methoxy-*N*-acylnitrenium ions, which were first reported independently by Glover[32] and Kikugawa[33] in 1984, proved to be the most easily formed and useful electrophiles, and readily undergo inter- and intra-molecular substitution reactions with a range of aromatic ring systems.

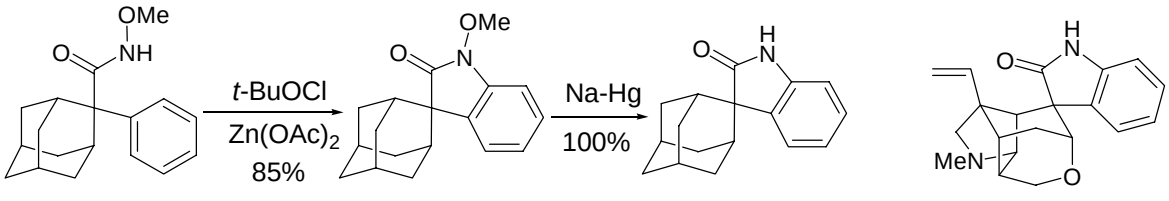


Scheme 18

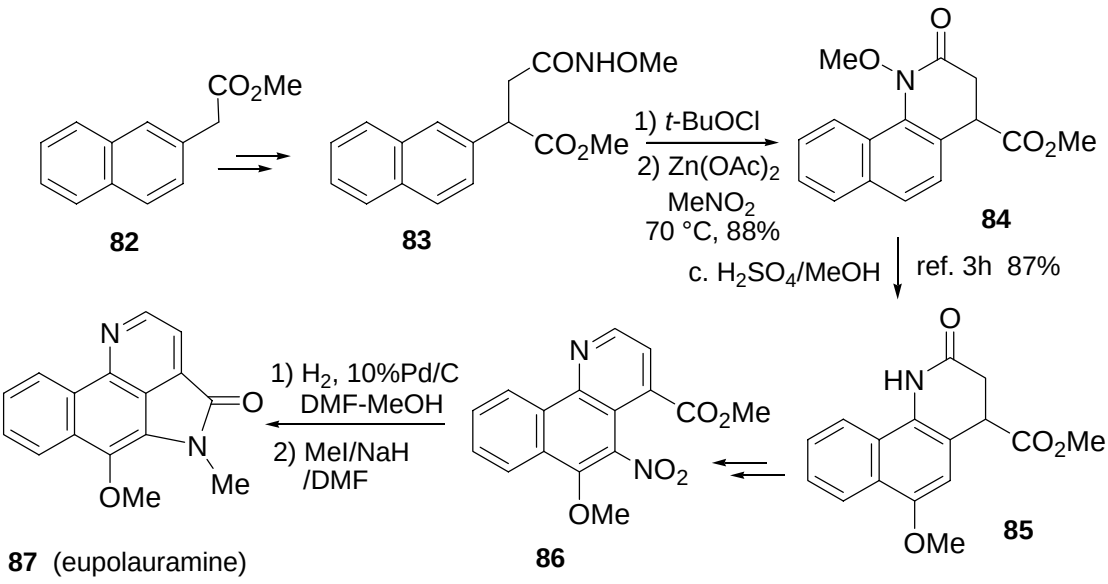
They can be generated by the treatment of the corresponding *N*-methoxy-*N*-chloroamides with a variety of Lewis acids, typically silver[32, 33a, b] or zinc ions.[33c] A number of nitrogen heterocyclic compounds bearing an *N*-methoxy group have been synthesized using these methods (Scheme 18). The synthetic success of this substitution is mainly due to the fact that ions **76** are stabilized by the electron-donating effect of the adjacent methoxy group and exist long enough to react with an aromatic ring.

In addition to the *N*-methoxy group, other *N*-alkoxy groups may be used in these reactions. Benzyl and methoxyethoxymethyl groups are not suitable. A nitrogen heterocyclic compound bearing an *N*-allyloxy group can be synthesized by the procedure described above and this is readily converted to the corresponding *N*-hydroxy compound by palladium-catalyzed removal of the allyl group.[34]

Since nitrogen heterocyclic compounds such as **38** and **43** bearing a methoxyamido group have been successfully modified by the introduction of a methoxy group *para* to the nitrogen (*vide ante*, **2-3**), this methodology will offer a new route for the synthesis of not only nitrogen heterocyclic rings, but also natural products bearing nitrogen heterocyclic rings and oxygen functions.



Scheme 19



Scheme 20

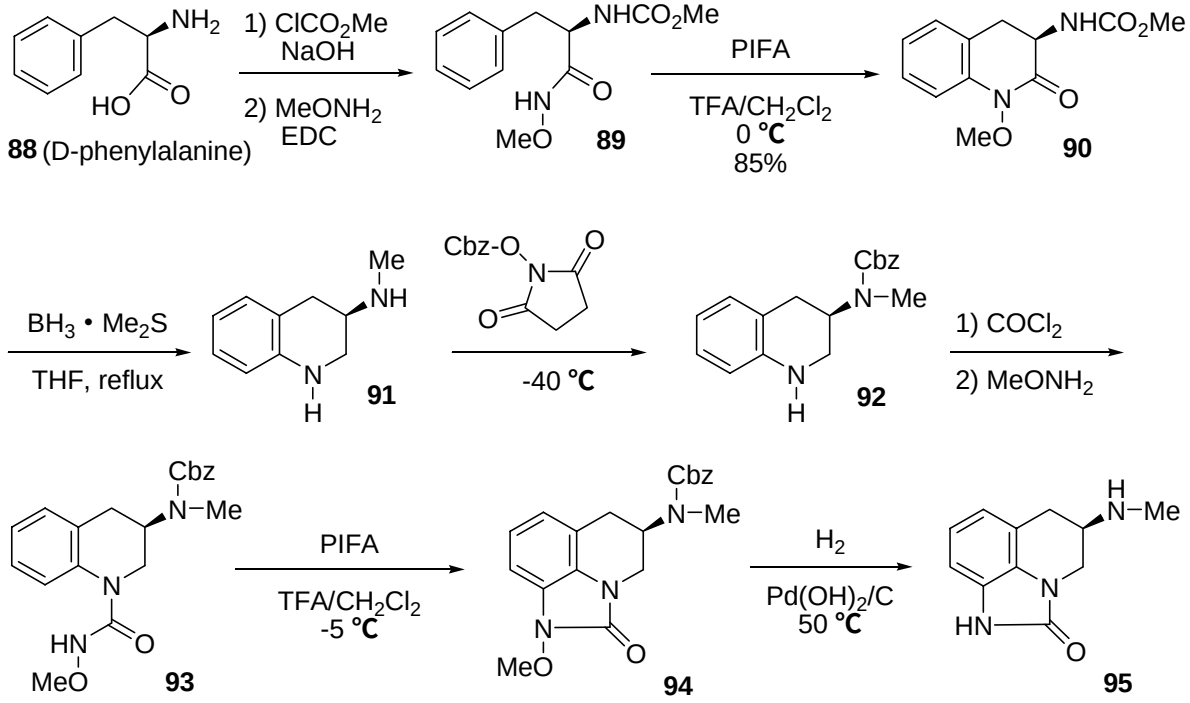
Thus, a convenient synthesis of the oxindole moiety of gelsemine (**81**)[35] and a total synthesis of

6-methoxy-5-methylbenzo[*h*]pyrrolo[4,3,2-*de*]quinolin-4(5*H*)-one (eupolauramine) (**87**)[36] have been achieved (Schemes 19 and 20).

N-Chloro-*N*-methoxyamides are synthesized by chlorination of the corresponding *N*-methoxyamides with *tert*-butyl hypochlorite in CH_2Cl_2 in quantitative yields and can be used without further purification. However, because *tert*-butyl hypochlorite is not commercially available in most countries and is not recommended for use in bulk quantities from the standpoint of green chemistry, this method is unsuitable for large scale synthesis.[37] Subsequently, limitations associated with these protocols were overcome by direct methoxyamidation of arenes using PIFA.

In the last decades hypervalent iodine compounds such as PIFA have found wide application in synthetic organic chemistry because of their low toxicity, ready availability, ease of handling, and environmentally friendly nature. PIFA was used for the generation of *N*-methoxy-*N*-acylnitrenium ions first by Kikugawa[38] and successively by Romero[39] who reported elegant application of this methodology for the preparation of the dopamine D_2 receptor agonist PNU-95666E (**95**) (Scheme 21).

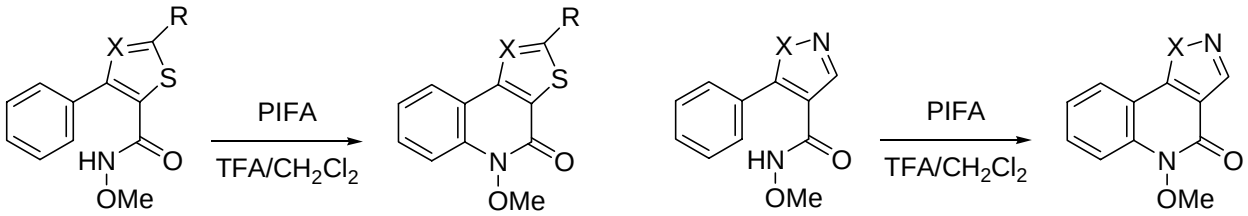
Notably, Wardrop has tentatively expanded the applicability of PIFA to the synthesis of nitrogen-containing biologically active natural products.[40] Subsequently, PIFA has been widely used for the generation of nitrenium ions not only from *N*-methoxy-*N*-acylamides, but also from *N*-aryl-*N*-acylamides (*vide ante*, **2-3**).



Scheme 21

Recently Tellitu and Domínguez reported the PIFA-promoted intramolecular aromatic amidation reaction,

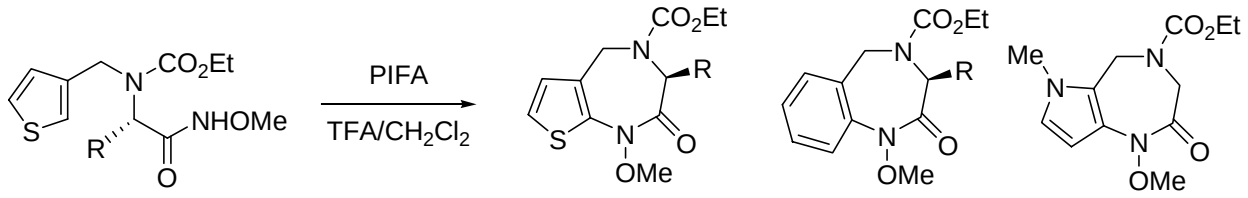
which turned out to be a general and efficient route for the synthesis of series of naturally occurring and biologically active benzene- and heterocycle-fused compounds. Thus, the PIFA-promoted intramolecular aromatic N-methoxyamidation reaction *via N*-methoxy-*N*-acylnitrenium ion intermediates was applied for the construction of a series of N, O, and S-containing heterocycle-fused quinolinones in a general and efficient way (Scheme 22).[41]



96a: X=CH, R=Me; **b**: X=N, R=Me; **c**: X=N, R=Ph — **97a~c** — **98a**: X=O; **b**: X=NPh — **99a**, **b**

Scheme 22

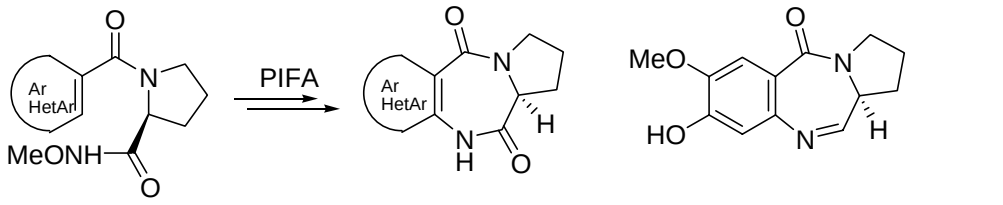
Analogously, the preparation of novel benzene- and heterocycle-fused 1,4-diazepin-2-ones (**101~103**) from glycine or L-alanine was carried out without loss of enantiometric purity throughout the process (Scheme 23).[42]



100a: R=H; **b**: R=Me — **101a**, **b** — **102a**: R=H; **b**: R=Me — **103**

Scheme 23

Next, the PIFA-promoted intramolecular aromatic N-methoxyamidation reaction *via*

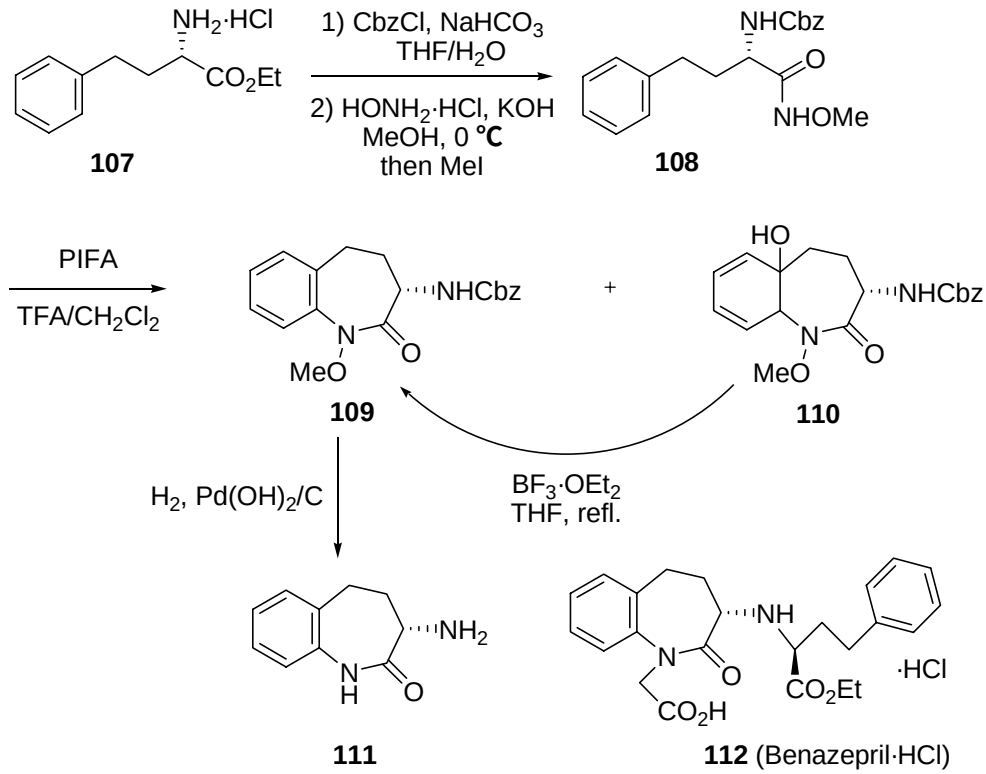


104 — **105** — **106** (antitumor antibiotic DC-81)

Scheme 24

N-methoxy-*N*-acylnitrenium ion intermediates has been utilized for the synthesis of optically pure benzo-, naphtho-, and heterocycle-fused pyrroro[2,1-c][1,4]-diazepin-5,11-dione derivatives starting from L-proline methyl ester. Following this methodology an alternative synthesis of the antibiotic DC-81 (**106**) has been accomplished (Scheme 24).[43]

Chang and Yang reported the synthesis of optically active (-)-α-aminobenzolactam (**111**), a key synthetic intermediate of an angiotensin converting enzyme inhibitor Benazepril (**112**), from commercially available L-homophenylalanine ethyl ester hydrochloride (**107**) using the similar PIFA-promoted intramolecular aromatic amidation reaction as a key step. The successful synthesis of **111** suggests that this strategy could be used for the synthesis of other structurally related biologically active benzolactam derivatives, such as an antithrombotic agent (CVS-1778) and a growth hormone secretagogue (L-692428) (Scheme 25).[44]

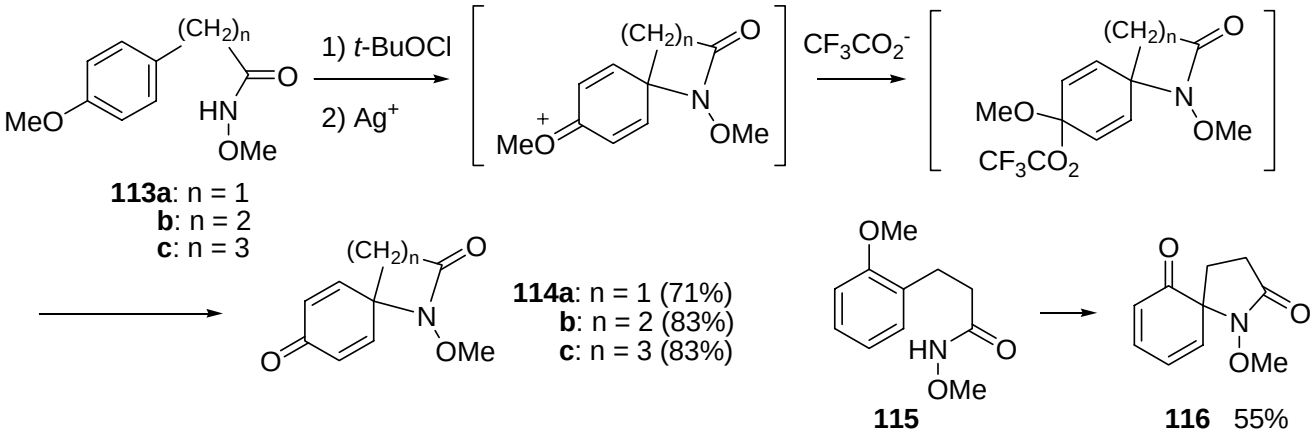


Scheme 25

As described above, the intramolecular aromatic substitution reaction with *N*-methoxy-*N*-acylnitrenium ions proved to be a useful tool for the synthesis of heterocycle-fused compounds. At the same time, when the aromatic ring bears a methoxy group *ortho* or *para* to the alkyl side chain, the nitrenium ion attacks the ipso position of the aromatic ring to afford the spirodienones (**114** and **116**) as the major or exclusive products (Scheme 26).[33b, c, 45]

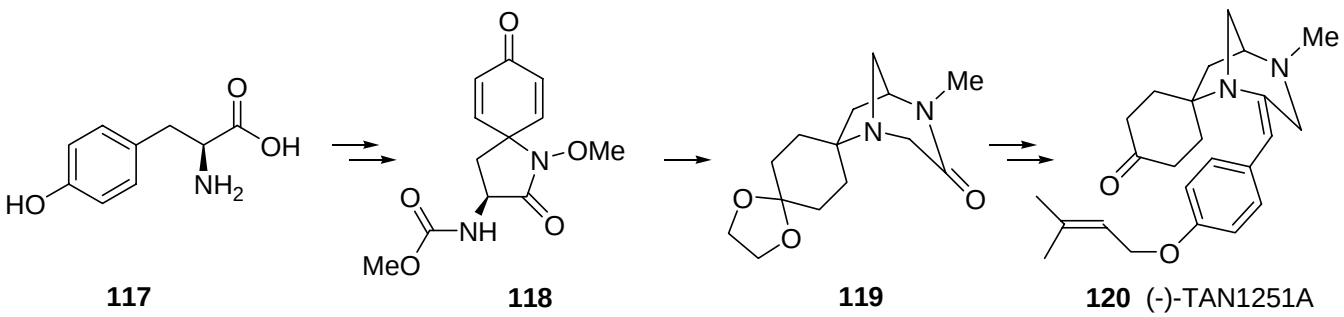
The dearomatization of benzene is very energetically unfavorable, and the Birch reduction[46] has long

been the most important dearomatising reaction of substituted benzene rings. Therefore, this unexpected reaction is a very useful transformation since this process could lead to unusual compounds which would otherwise not be readily accessible and provides valuable intermediates for an efficient synthesis of biologically important compounds. In particular this methodology opens up opportunities for expedient preparations of biologically active natural products which have the 1-azaspiro[4.5]decane and 1-azaspiro[5.5]undecane ring systems.



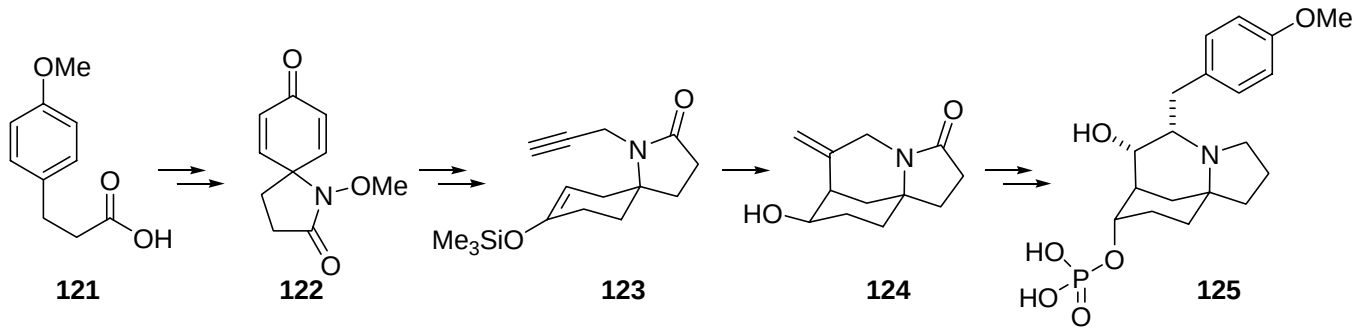
Scheme 26

The utility of this methodology was demonstrated by Wordrop's elegant syntheses of several biologically active natural products. 1-Azaspiranes prepared using this strategy served as key intermediates.[40,48-50,52-54] First, Wordrop undertook the formal synthesis of the muscarinic M_1 receptor antagonist (-)-TAN1251A (**120**) from L-tyrosine (**117**). The key intermediate **118** was synthesized by azaspirocyclization of the *N*-methoxy-*N*-acylnitrenium ion derived from **117** using Kikugawa's method.[33,34] No racemization occurred during reaction and **119** was converted to **120** following Kawahara's procedure[47] (Scheme 27).[40]

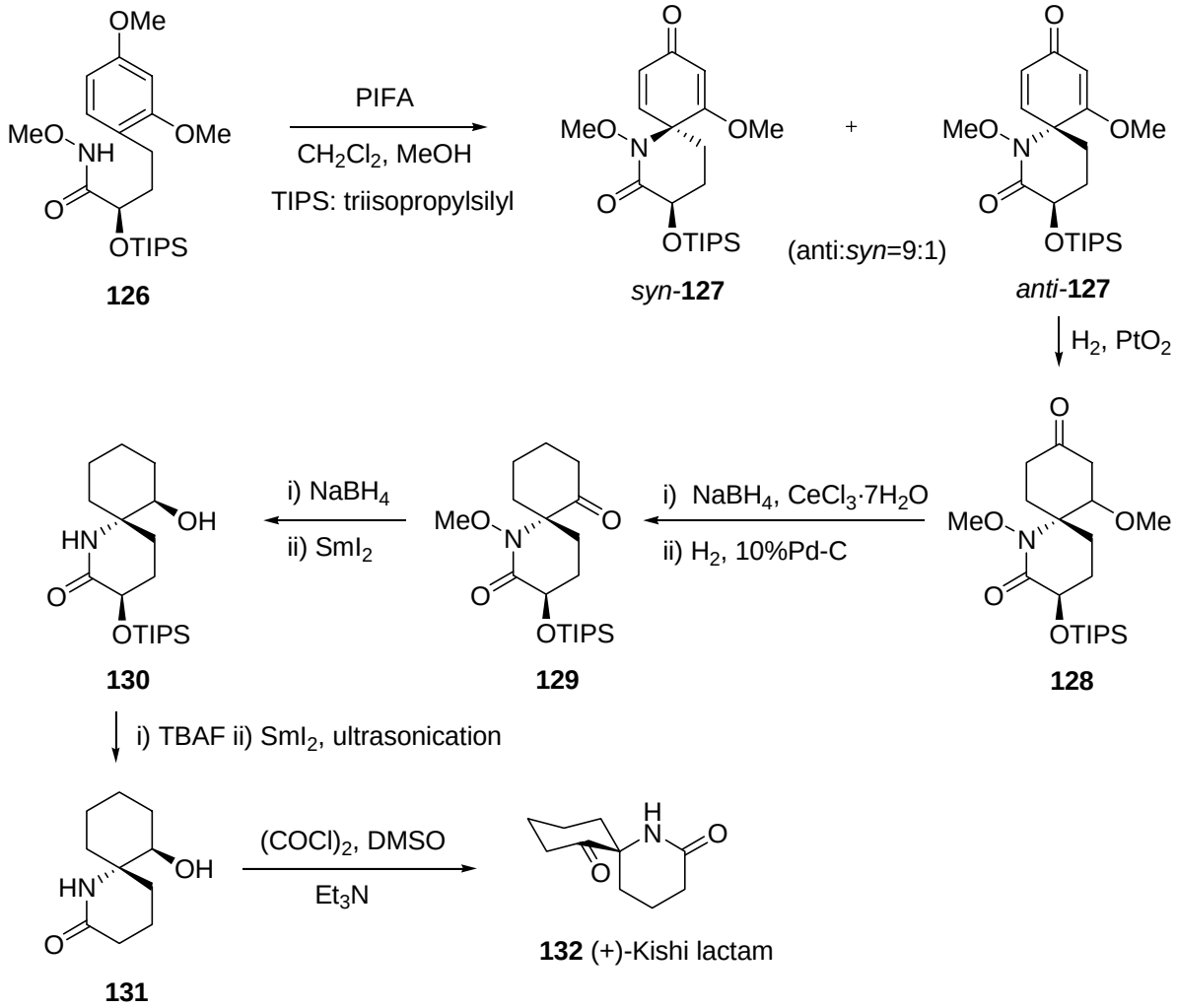


Scheme 27

Similarly, the formal synthesis of (±)-desmethylamino FR901483 (**125**), a potent immunosuppressant, isolated by a group at Fujisawa, was carried out from commercially available 3-(4-methoxyphenyl)propanoic acid (**121**) *via* spirocyclization of the corresponding *N*-methoxy-*N*-acylnitrenium ion. This alkaloid has the same 1-azaspiro[4.5]decane ring system as that of (-)-TAN1251A (**120**) and the same synthetic strategy is applicable for the synthesis of the key intermediate (**122**) (Scheme 28).[48]



Scheme 28

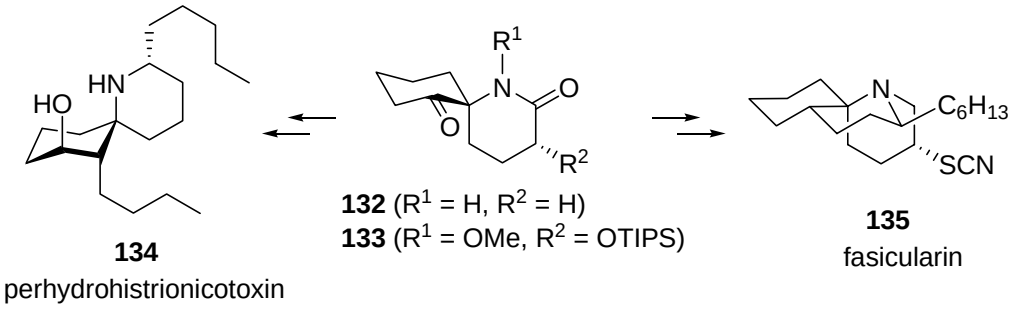


Scheme 29

This methodology can also be used to access the 1-azaspiro[5.5]undecane ring system using 4-(4-methoxyphenyl)butanoic acid derivatives as starting compounds.

The asymmetric synthesis of the (+)-Kishi lactam (**132**) and a useful intermediate (**133**) for the synthesis of the marine natural product fasicularin (**135**) was performed.[49] The key intermediate, *anti*-**127**, was synthesized with *anti* selectivity utilizing a novel strategy reported recently for the stereocontrolled preparation of 1-azaspiranes (Scheme 29).[50]

Since the transformation of **132** into (±)-perhydrohistrionicotoxin (**134**) was reported previously,[51] the synthesis of (+)-**132** constitutes a formal synthesis of (-)-perhydrohistrionicotoxin. In addition, **133** is a usefully functionalized intermediate for the preparation of fasicularin (**135**) (Scheme 30).



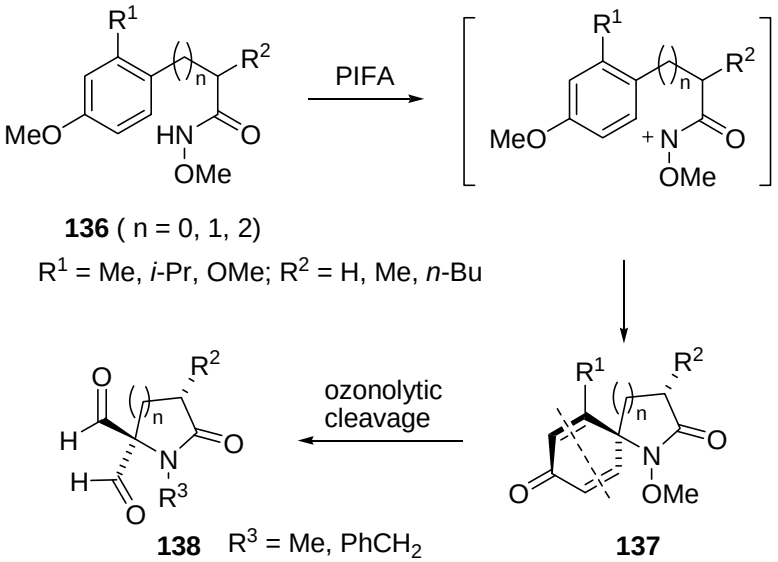
134
perhydrohistrionicotoxin

132 (R^1 = H, R^2 = H)
133 (R^1 = OMe, R^2 = OTIPS)

135
fasicularin

Scheme 30

As shown in Scheme 29, oxidative spirocyclization of an *N*-acylnitrenium ion would proceed selectively to generate *anti* dienone. Therefore, ozonolytic cleavage of the carbon-carbon double bonds of the



136 (n = 0, 1, 2)
R^1 = Me, *i*-Pr, OMe; R^2 = H, Me, *n*-Bu

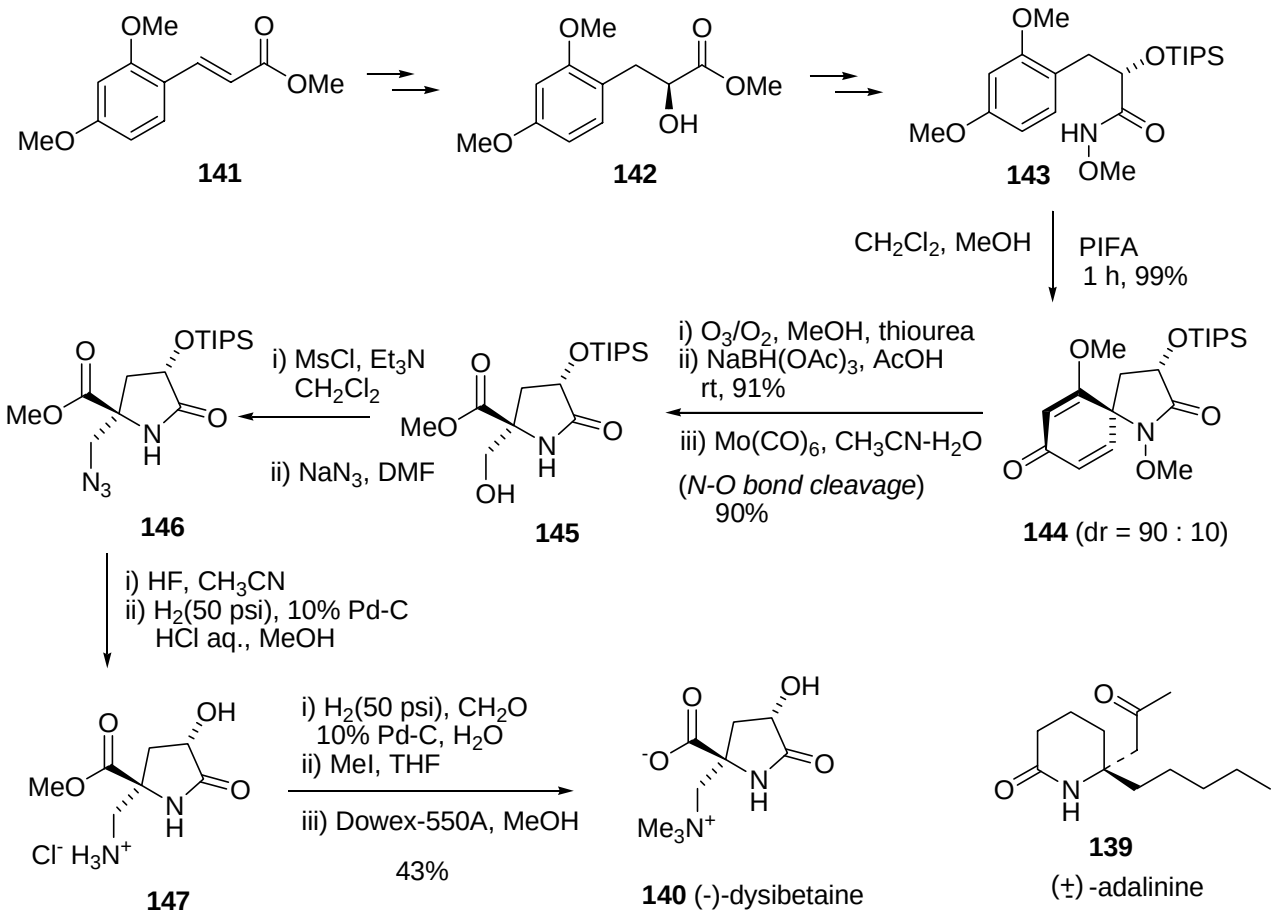
138 R^3 = Me, $PhCH_2$

137

Scheme 31

dienone ring would afford a convenient route to trisubstituted azetidinone, pyrrolidinone and piperidinone derivatives (**138**) with useful levels of diastereoselectivity (Scheme 31).

Utilizing this expanded strategy (the nitrenium ion spirocyclization-dienone cleavage strategy), the total synthesis of (±)-adalinine (**139**), α,α-disubstituted piperidinone alkaloid, and the diastereoselective total synthesis of the marine natural product (-)-dysibetaine (**140**) were performed (Scheme 32).[52, 53]

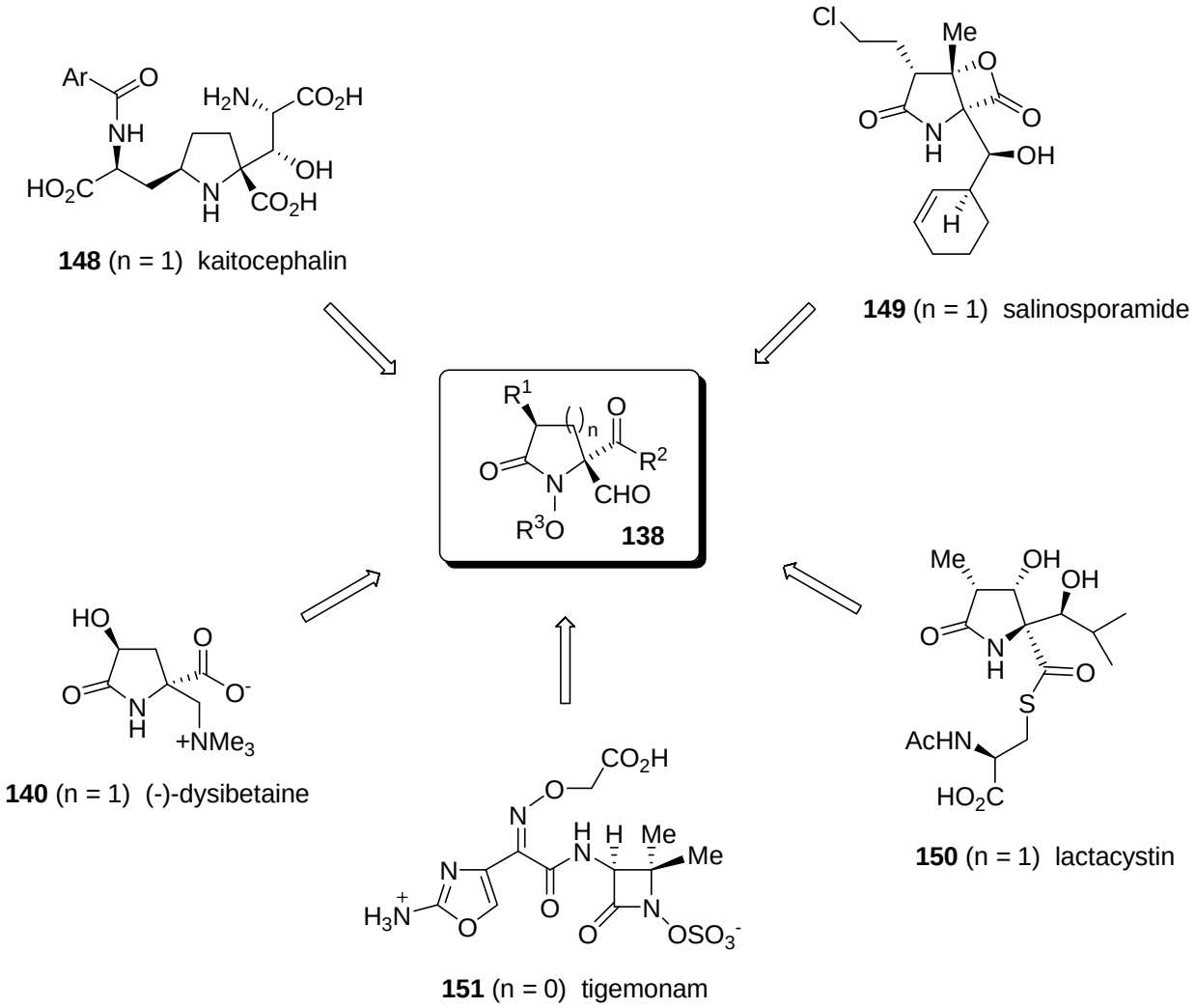


Scheme 32

Furthermore, not only (-)-dysibetaine (**140**), but also other biologically active compounds such as **148~151** are potentially accessible through application of this nitrenium ion spirocyclization-dienone cleavage strategy (Scheme 33).[54]

As described above, using the above conditions, the presence of an *ortho* or *para* methoxy substituent is essential for the spirocyclization. In order to make the process even more versatile, more readily accessible starting compounds were explored. Since 4-halogenophenyl compounds are more readily available than the corresponding methoxy compounds, the spirocyclization reaction was examined using *N*-methoxy-(4-halogenophenyl)amides (**152**) with hypervalent iodine compounds.[55] The results are

presented in Table 5. Generally fluorine substituted starting compounds give good results.

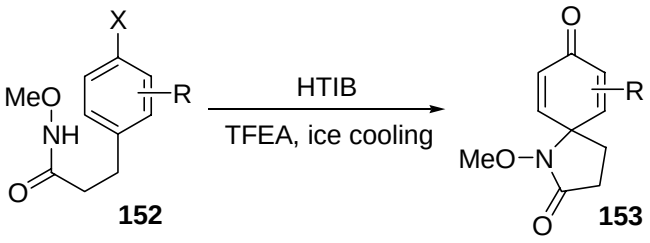


Scheme 33

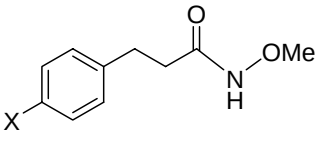
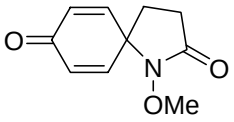
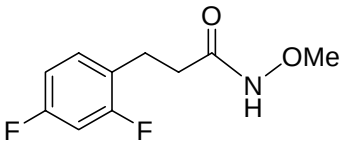
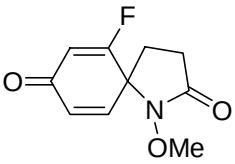
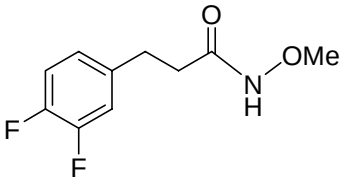
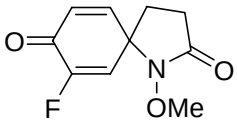
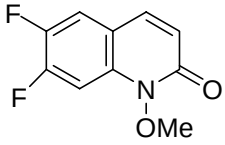
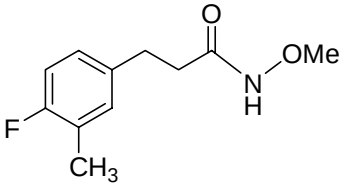
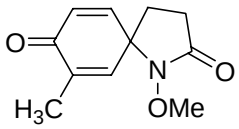
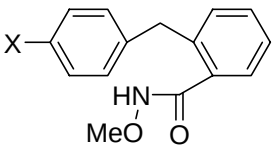
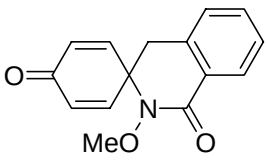
Use of [hydroxy(tosyloxy)iodo]benzene (HTIB) gives better yield than use of PIFA. As for solvents, TFEA proved to be the solvent of choice.

Furthermore, in TFEA unexpected results are obtained.[56] Thus, treatment of unactivated **154a** with PIFA in TFEA for 1 min under ice cooling afforded the benzannulated compound **155a** (55%) in addition to the spirodiene compound **156a** (34%). From *o*-tolyl derivative **154c** the spirodiene compound **156c** (84%) was exclusively obtained. This result was quite surprising since most reactions of unactivated monobenzenoid aromatics lead to substitution rather than addition. Ipso-Cyclization in the absence of other activating groups on the phenyl group to form the spirodiene derivatives is a very unusual result,

Table 5. Synthesis of spirodienones **153** from *N*-methoxy-(4-halogenophenyl)amides **152** with HTIB in TFEA

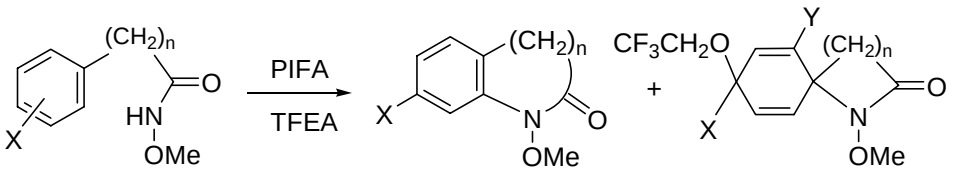


152 **153**

entry	starting material		time (min)	product yield (%)	
1		**152a**: X = F	5		**153a** (82)
2		**152b**: X = Cl	60		**153b** (72)
3		**152c**: X = Br	60		**153c** (62)
4		**152d**	5		**153d** (65)
5		**152e**	5	 **153e** (37)	 **153e'** (14)
6		**152f**	5		**153f** (66)
7		**152g**: X = F	5		**153g** (88)
8		**152h**: X = Cl	60		**153h** (80)

since this requires the loss of aromaticity. Several unactivated benzenoid compounds reacted similarly and the results are presented in Table 6.

Table 6. Cyclization of *N*-methoxyphenylamides with PIFA in TFEA



154a: n = 2, X = H
b: n = 3, X = H
c: n = 2, X = 2-Me
d: n = 2, X = 4-Me

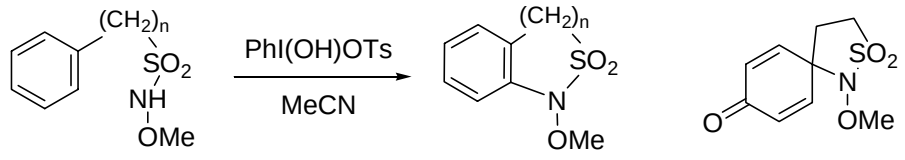
155a: n = 2, X = H
b: n = 3, X = H
d: n = 2, X = Me

156a: n = 2, X = H, Y = H
b: n = 3, X = H, Y = H
c: n = 2, X = H, Y = Me
d: n = 2, X = Me, Y = H

entry	starting material	time (min)	product yield (%)
1	**154a**	1	**155a** (55), **156a** (34)
2	**154b**	15	**155b** (50), **156b** (48)
3	**154c**	5	**156c** (84)
4	**154d**	1	**155d** (20), **156d** (62)

The 1-azaspiro[4.5]decane ring system (compound **114b**) is also synthesized from *N*-methoxy-3-(4-methoxyphenyl)propanamide (**113b**) by an anodic oxidation under usual constant current electrolysis conditions through a nitrenium ion intermediate.[57]

Not only *N*-methoxyamides but also *N*-methoxysulfonamides react with HTIB to afford the benzannulated compounds. Moreover, 2-aryl-*N*-methoxyethanesulfonamide bearing a 4-methoxy group at the aromatic ring generates the spiro compound **159** resulting from attack of the nitrogen to the ipso position of the molecule (Scheme 34).[58] Recently it was reported that 1-methoxy-3,4-dihydro-1*H*-2,1-benzothiazine 2,2-dioxide (**158**, n = 2) was obtained from **157** (n = 2) in CH_3CN in high yield with HTIB, formed *in situ* by a combination of iodobenzene, *p*-toluenesulfonic acid monohydrate, and *m*-chloroperoxybenzoic acid.[59]



157 (n = 1, 2, 3)

158 (n = 1, 52%; n = 2, 86%; n = 3, 37%)

159

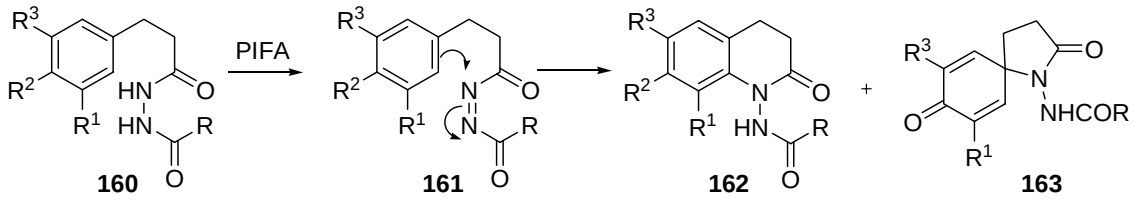
Scheme 34

2-5 *N*-PHTHALIMIDO-*N*-ACYLNITRENIUM IONS AND NITRENIUM IONS FROM AZODICARBOXYLATES

The previous section reviewed reactions of *N*-methoxy-*N*-acylnitrenium ions which are stabilized by the oxygen lone pair of a methoxy group attached to the nitrogen and are able to undergo inter- and intra-molecular substitution reactions with a range of aromatic compounds. The stabilization of nitrenium ions by other heteroatoms, such as nitrogen and sulfur, would also be expected.[60] It is reasonable to predict that replacing an oxygen atom by nitrogen in the precursor would also have an additional stabilizing influence on a generated nitrenium ion. The present section describes the chemistry of nitrenium ions derived from unsymmetrical azodicarbonyl compounds and from *N*-acylaminophthalimides.

Intermolecular electrophilic amination of activated aromatics and other electron-rich olefins with diethyl azodicarboxylate either acid-catalysed or otherwise has already been reviewed[1f] and is excluded here. Therefore the intramolecular version of such a reaction is described herein, although it is uncertain that the real reaction intermediate is actually a nitrenium ion.

Table 7. Synthesis of quinoline derivatives



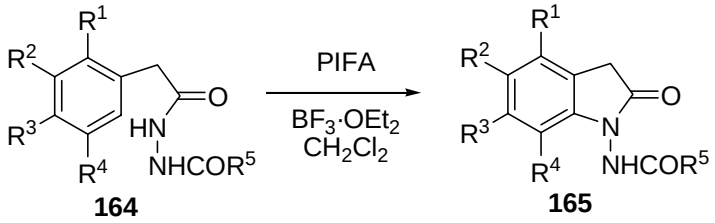
#	starting compd **160**				oxidant[a)]	product **162**				product **163**			Yield	
	R^1	R^2	R^3	R		R^1	R^2	R^3	R	R^1	R^3	R	**162**	**163**
1	H	H	OMe	OMe	A	H	H	OMe	OMe	—			71	—
2	H	OMe	H	OMe	B	—				H	H	OMe	—	25
					C	H	H	OMe	OMe	H	H	OMe	17	50
3	OMe	H	OMe	OMe	A					—			40	—
					C	OMe	H	OMe	OMe	—			73	—
4	OMe	H	OMe	OPh	A	OMe	H	OMe	OPh	—			64	—
5	H	OMe	OMe	OMe	A	H	OMe	OMe	OMe	H	OMe	OMe	12	50
					C	H	OMe	OMe	OMe	H	OMe	OMe	54	14
6	OMe	OMe	OMe	OMe	A	—				OMe	OMe	OMe	—	12
					D	OMe	OMe	OMe	OMe	—			30	47
7	OMe	OMe	OMe	OCH_2Ph	A	—				OMe	OMe	OCH_2Ph	—	76
8	OMe	H	OMe	OPh	A	—				OMe	OMe	OPh	—	75

[a)] A: PIFA; B: PIFA-BF_3·OEt_2 (1.0 eq); C: Ag_2CO_3- BF_3·OEt_2 (0.2 eq); D: Ag_2CO_3- BF_3·OEt_2 (1 eq).

It is well known that azodicarboxylates are effective sources of electrophilic nitrogen.[1f] Treatment of the unsymmetrical hydrazides (**160**) with PIFA in CH_2Cl_2 using BF_3·Et_2O allowed the formation of quinolones (**162**), presumably *via* the unsymmetrical azodicarbonyl compounds (**161**).[61]

However, the reaction is limited to highly electron-rich arenes bearing such substitutents as a methoxy or dimethoxy function. This limitation is consistent with the reported behavior of an intermolecular version of a similar reaction, in which highly electron-rich arenes alone can react with azodicarboxylates.[62] When arenes bear a methoxy group *para* to the alkyl side chain, the electron-deficient nitrogen attacks the ipso position to afford the spirodienones (**163**). The results are presented in Table 7.

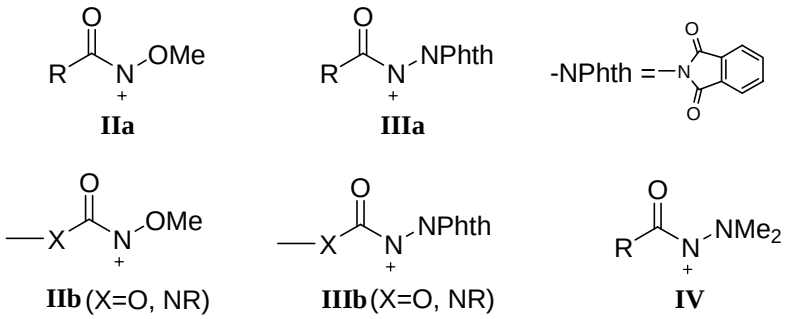
Table 8. Synthesis of oxindoles with oxidative cyclization of azodicarbonyl compounds



164 **165**

starting materials **164**	product **165**	yield (%)
a. $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = OMe$		
b. $R^1 = R^3 = R^4 = H$, $R^2 = R^5 = OMe$	**b.** $R^1 = R^3 = R^4 = H$, $R^2 = R^5 = OMe$	51
c. $R^1 = R^3 = R^4 = H$, $R^2 = OMe$, $R^5 = OPh$	**c.** $R^1 = R^3 = R^4 = H$, $R^2 = OMe$, $R^5 = OPh$	60
d. $R^1 = H$, $R^2 = R^3 = R^4 = R^5 = OMe$	**d.** $R^1 = H$, $R^2 = R^3 = R^4 = R^5 = OMe$	40
e. $R^1 = R^4 = H$, $R^2 = R^3 = R^5 = OMe$	**e.** $R^1 = R^4 = H$, $R^2 = R^3 = R^5 = OMe$	41
f. $R^2 = R^3 = H$, $R^1 = R^4 = R^5 = OMe$	**e.** $R^1 = R^4 = H$, $R^2 = R^3 = R^5 = OMe$ **f.** $R^1 = R^4 = H$, $R^2 = OH$, $R^3 = R^5 = OMe$	5 5
g. $R^1 = R^3 = R^4 = H$, $R^2 = Me$, $R^5 = OMe$	**g.** $R^1 = R^3 = R^4 = H$, $R^2 = Me$, $R^5 = OMe$	28

Not only quinolones but also other important heterocyclic systems such as oxindoles, benzazepinones, benzazocinones, benzimidazolones, benzoxazinones and pyrazolones are prepared by this method.[63] The results using **164** as a starting compound are presented in Table 8.



IIa **IIIa**

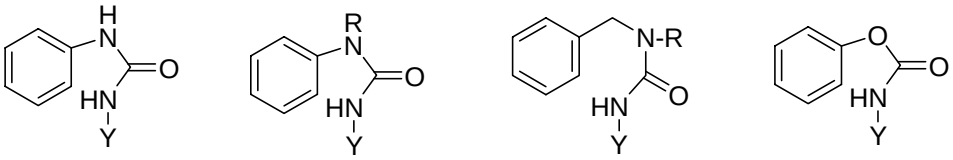
IIb (X=O, NR) **IIIb** (X=O, NR) **IV**

Figure 4

It is expected that replacing a methoxy group by nitrogen in *N*-methoxyamides would also have a stabilizing influence on a generated nitrenium ion. Recently, *N*-phthalimido-*N*-acylnitrenium ions (**IIIa**) were generated from *N*-acylaminophthalimides, a new class of precursors, by treatment with hypervalent iodine compounds (PIFA and HTIB), and their chemistry was investigated (Figure 4).[64]

It is evident that *N*-methoxy-*N*-acylnitrenium ions (**IIa**) are useful electrophiles, as described in section **2-4**. However, the nitrenium ions (**IIb**) generated from **166a**, **168a** and **169a** failed to cyclize, giving unidentifiable product mixtures.[39]

On the other hand, *N*-phthalimido-*N*-acylnitrenium ions (**IIIb**) generated from **167b**, **168b** and **169b** readily undergo PIFA-promoted intramolecular aromatic amidation to afford benzene-fused nitrogen and oxygen heterocycles.[64, 65] The PIFA-promoted cyclization reaction using **IV** gave ambiguous results along with recovery of the starting compound.



166a: Y=OMe
b: Y=Phth

167a, **b**

168a, **b**

169a, **b**

Figure 5

These facts confirm that the phthalimido group plays an important role for the stabilization of **IIIa** and **b** and for promotion of further reaction.[64]

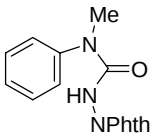
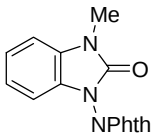
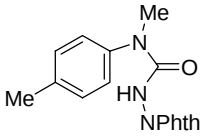
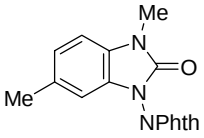
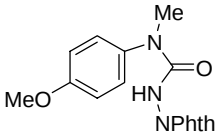
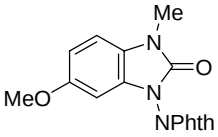
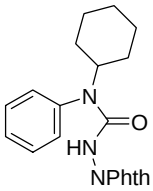
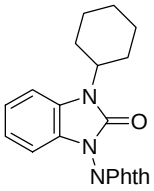
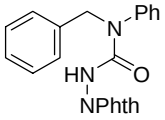
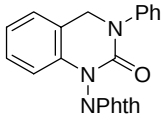
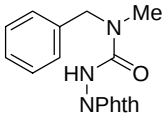
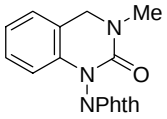
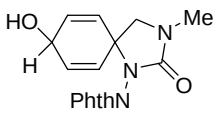
A novel approach to the PIFA-promoted synthesis of a wide variety of nitrogen and oxygen heterocycles, and also spirodiene derivatives from **IIIa** and **b** has been carried out.[64, 65]

Treatment of **170a** with PIFA (1.3 mol eq.) for 1 h in refluxing $CHCl_3$ gave **171a** in 91% yield. Several urea derivatives (**170a-d**, **172a**, **b**) reacted in this way, and the results are presented in Table 9. 1,3-Dihydrobenzoimidazol-2-ones (**171a-d**) and 3,4-dihydro-1*H*-quinazolin-2-ones (**173a**, **b**) were obtained in synthetically useful yields.[65]

Similarly, carbamate derivatives (**175a-d**) were submitted to the same cyclization reaction. Treatment of **175a** with PIFA (1.1 mol eq.) in TFEA for 3 h at rt gave **176a** and the *para*-iodophenylated compound (**177**) in 30% and in 20% yields, respectively. It is evident that the oxygen function directly attached to the phenyl group unfavorably affected the cyclization reaction and the *para*-iodophenyl group of PIFA migrated to the amide nitrogen to afford **177**.[26] Use of 4-chlorophenyliodine(III) bis(trifluoroacetate) (*p*-ClPIFA) instead of PIFA in TFA improved the yield of **176a** to 74%.

Several aryl carbamates (**175a**-**d**) and **175e** reacted in this way, and the results are presented in Table 10. *N*-Phthalimido-3*H*-benzoxazol-2-ones (**176a**-**d**) and 4*H*-benzo[1,4]oxazin-3-one (**176e**) were obtained in synthetically useful yields.[64]

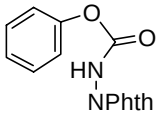
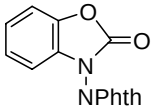
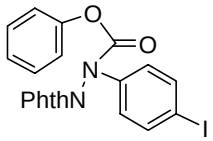
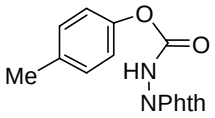
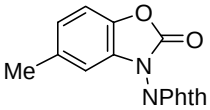
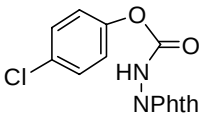
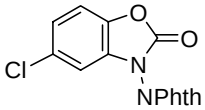
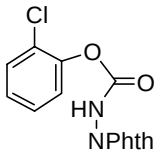
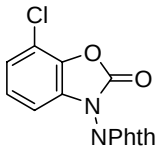
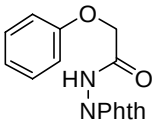
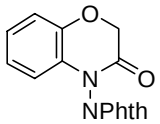
Table 9. Synthesis of 2-benzimidazolinones and 1*H*-quinazolin-2-ones

entry	starting material	PIFA (eq.)	condition reflux (h)	product yield (%)
1	 **170a**	1.3	1	 **171a** (91)
2	 **170b**	1.3	0.5	 **171b** (85)
3	 **170c**	1.3	6	 **171c** (46)
4	 **170d**	1.3	1	 **171d** (99)
5	 **172a**	1.5	1	 **173a** (79)
6	 **172b**	1.5	1 min	 **173b** (27)  **174** (34)

This reaction is influenced greatly by the choice of solvent. In the reaction of **178a** with PIFA, the use of TFEA as solvent resulted in unexpected attack of the nitrenium ion on the ipso position to give a spirodiene derivative (**179a**) in 76% yield along with the 3,4-dihydrocarbostyril derivative (**180a**) (17%). From *o*-tolyl derivative (**178c**) the spirodiene compound (**179c**) was exclusively obtained (88%, Table 11, entry 3). Several unactivated benzenoid compounds reacted similarly and the results are presented in Table 11.

The formation of **179d** can be explained as follows. The trifluoroethoxy group of the transient spirodiene intermediate can be eliminated to afford the exo methylene compound and subsequent addition of TFEA

Table 10. Synthesis of benzannulated compounds from *N*-acylaminophthalimides having phenoxy function

entry	starting material	reagent[a]	solvent	time[b] (h)	product yield (%)
1	 **175a**	A[c]	TFEA	3	 **176a** (30)  **177** (20)
2	**175a**	B[d]	TFEA	6	**176a** (61)
3	**175a**	B[d]	TFA	0.5[f]	**176a** (74)
4	 **175b**	B[e]	TFA	0.5[f]	 **176b** (62)
5	 **175c**	B[e]	TFA	0.5[f]	 **176c** (66)
6	 **175d**	B[e]	TFA	0.5[f]	 **176d** (30)
7	 **175e**	B[e]	CH_2Cl_2	17	 **176e** (63)
8	**175e**	B[e]	$ClCH_2CH_2Cl$	5.5	**176e** (72)

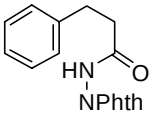
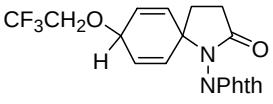
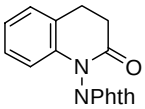
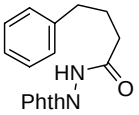
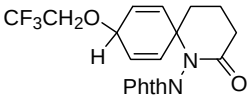
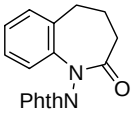
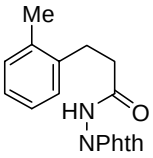
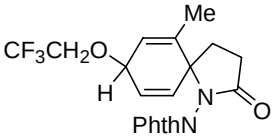
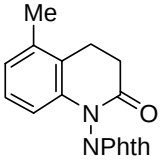
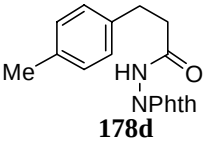
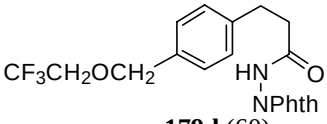
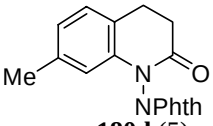
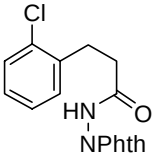
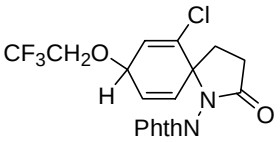
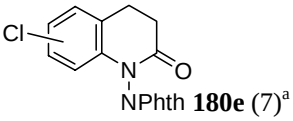
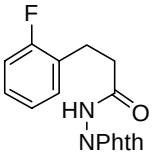
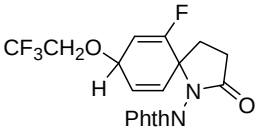
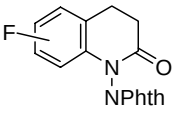
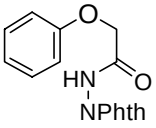
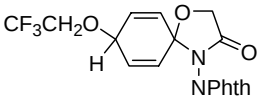
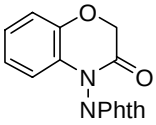
[a] A: PIFA; B: *p*-ClPIFA. [b] At rt. [c] 1.1 eq. [d] 1.3 eq. [e] 2.0 eq. [f] At reflux.

to the methylene group would give **179d** (Scheme 35, path a). It is interesting to note that the methyl group of the corresponding *N*-methoxyamide **154d** remains intact in the similar spirodiene formation reaction (Table 6, entry 4). Compound **180d** could be formed through direct *ortho* attack or through ipso attack followed by C-N bond migration (Scheme 35, path b).[61, 63, 66]

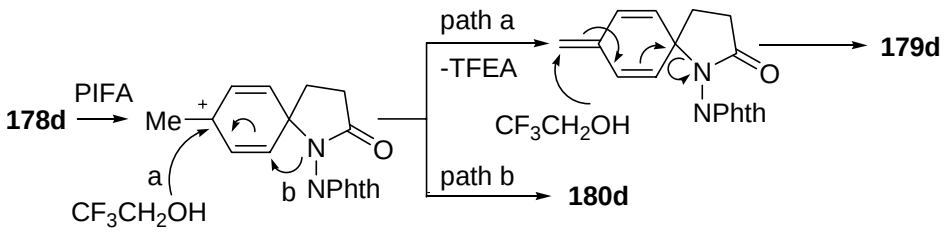
Transformation of benzenoid compounds to nonbenzenoid compounds can provide valuable intermediates for the synthesis of a variety of functionalized six-membered ring compounds.[54, 67] Conversion of *N*-methoxy- and *N*-phthalimido-*N*-acylnitrenium ions (**IIa** and **IIIa**) to spirodienones and spirodienes bearing the nitrogen atom bound to the spiro carbon should offer valuable intermediates for the synthesis of a variety of organic compounds.

To expand the synthetic applications of **IIIa**, the reactions of **IIIa** with other functional groups have been investigated. It was assumed that olefinic moieties might play a similar role as the nucleophilic partner of

Table 11. Cyclization of *N*-acylaminophthalimides with PIFA (1.0 eq.) in TFEA at rt

entry	starting material	time (h)	product yield (%)	
1	 **178a**	3	 **179a** (76)	 **180a** (17)
2	 **178b**	17	 **179b** (44)	 **180b** (46)
3	 **178c**	4	 **179c** (88)	 **180c** (5)
4	 **178d**	17	 **179d** (60)	 **180d** (5)
5	 **178e**	1	 **179e** (77)	 **180e** (7)[a]
6	 **178f**	0.5	 **179f** (88)	 **180f** (6)[a]
7	 **178g**	17	 **179g** (31)	 **180g** (26)

[a] Small amounts of a mixture of benzannulated regioisomers were obtained.



Scheme 35

the reaction. Indeed, *N*-phthalimido-*N*-acylnitrenium ions (**IIIa**) readily undergo inter- and intra-molecular substitution reactions with carbon-carbon double bonds.[68, 69]

Initially, the reaction of *N*-methoxycyclohex-3-enecarboxamide with PIFA in $CHCl_3$ was examined. However, the resulting reaction mixture contained a mixture of unidentified products (TLC). In contrast, when the N-substituent of the starting compound was changed from an *N*-methoxy to an *N*-phthalimido group, the ring closure reaction underwent smoothly and the reaction mixture contained a single product (TLC), the structure of which was determined to be the cyclized compound **182a**. Cyclization reactions of other starting compounds (**181b-g**) were carried out similarly. The results are presented in Table 12.[68]

Intermolecular substitution reactions of **IIIa** with carbon-carbon double bond also were studied. Regioselective hydrazidohydroxylation of styrenes (**184**) with *N*-acetylaminophthalimide (**185**) using PIFA were performed to afford 2-(*N*-acetyl-*N*-phthalimido)aminoethyl trifluoroacetates (**186**) in high yield.[69]

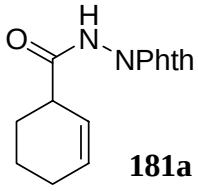
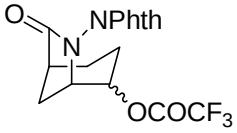
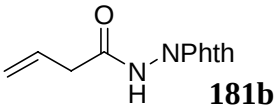
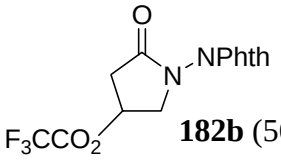
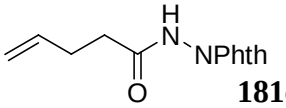
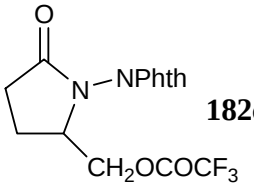
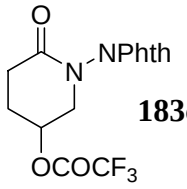
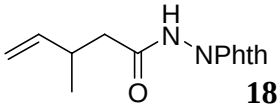
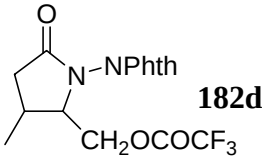
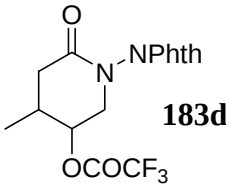
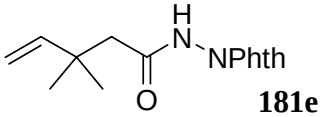
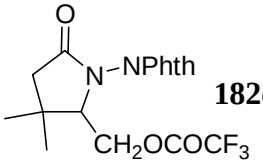
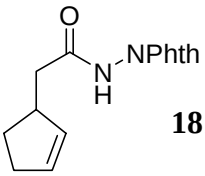
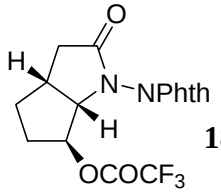
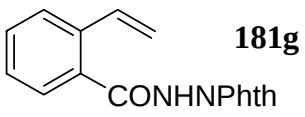
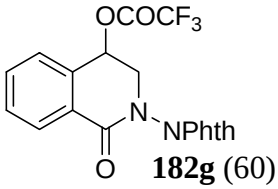
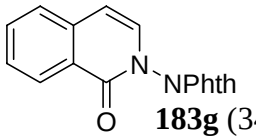
Normally, the nitrenium ion (**IIIa**) could attack both α- and β-carbons of styrenes to afford two regioisomers. In practice, however, HPLC analysis of the reaction mixture revealed that the reaction is extremely regioselective and a single regioisomer is obtained in high yield in the case of unsubstituted and α-methyl substituted styrenes (Table 13, entries 1-9).[69] With β-methyl substituted styrene (**184j**) two regioisomers (**186j** and **j'**) were obtained (Table 13, entry 10). As for the reaction mechanism, the hydrazidohydroxylation reaction is initiated by an electrophilic attack of **IIIa** on the double bond. Subsequently, without formation of aziridinium ions,[70] the carbocationic species created can be captured by a trifluoroacetate anion or quenched by the elimination of an adjacent hydrogen (Table 13, entry 9) to afford the products.

It is often observed that changing the solvent can change the site attacked by a nitrenium ion. Intramolecular cyclization of *N*-(5-phenylpentanamido)phthalimide (**187a**) with PIFA in various solvents was examined with anticipation of formation of an eight-membered ring formation. However, the nitrenium ion generated by PIFA attacked the benzylic position to afford 5-phenyl-*N*-phthalimido-δ-lactam (**188a**) in 46% yield in 2,2,3,3-tetrafluoro-1-propanol and in 36% yield in TFEA.[71] As it is generally accepted that a nitrenium ion attacks electron-rich site, this is the first case wherein a nitrenium ion attack at an aliphatic carbon is preferred over aromatic substitution.

Several *N*-(phenylpentanamido)phthalimides (**187b-g**) reacted in a similar way and the results are presented in Table 14.

These results show that benzylic cyclization occurs in good yields with compounds having a 4-halogenophenyl group (Table 14, entries 1-5). Compound **187g**, which has an electron-withdrawing cyano group in the *para*-position, did not give rise to either the benzannulated or spirobenzannulated products. Instead, the 4-iodophenyl group was transferred from PIFA to the amide nitrogen to afford the acyldiarylamine **191** in 70% yield.[26]

Table 12. Intramolecular cyclization of alkenyl *N*-acylaminophthalimides using PIFA (1.3 eq.) in refluxing $CHCl_3$

entry	starting material	time (h)	product, yield (%)
1	 **181a**	0.5	 **182a** (97)
2	 **181b**	1	 **182b** (56)
3	 **181c**	0.5	 **182c**  **183c**	**182c**+**183c** (92) (**182c**:**183c** = 3:1)
4	 **181d**	0.5	 **182d**  **183d**	**182d**+**183d** (93) (**182d**:**183d**= 9:1)
5	 **181e**	0.5	 **182e** (98)
6	 **181f**	0.5	 **182f** (79)
7	 **181g**	0.5	 **182g** (60)  **183g** (34)

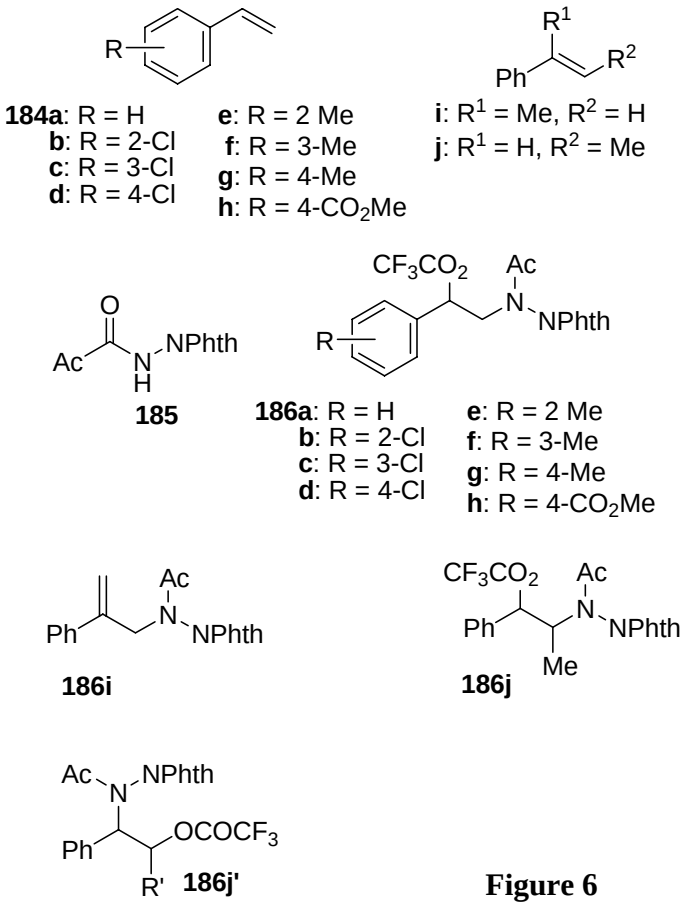


Figure 6

Table 13. Hydrazidohydroxylation of **184** with **185** (1.1 eq.) in $CHCl_3$ for 0.5-1 h at reflux using PIFA (1.2 eq.)

entry	starting material	product yield (%)
1	**184a**	**186a** (90)
2	**184b**	**186b** (92)
3	**184c**	**186c** (74)
4	**184d**	**186d** (85)
5	**184e**	**186e** (82)
6	**184f**	**186f** (74)
7	**184g**	**186g** (80)
8	**184h**	**186h**(68+10[a])
9	**184i**	**186i** (90)
10	**184j**	**186j** (32) **186j'** (44)

[a] A hydrolysis product of **186h** was detected in this case.

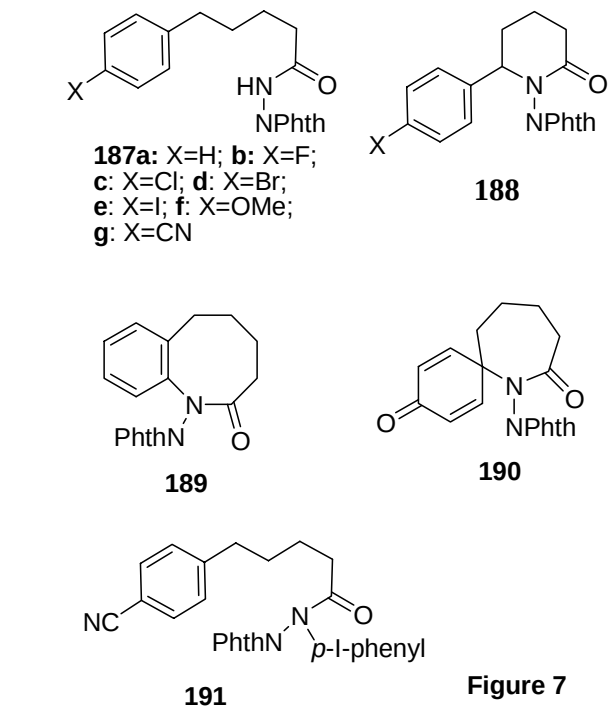


Figure 7

Table 14. Benzylic cyclization of *N*-(5-phenylpentanamido)phthalimides (**187**) with PIFA

187 —PIFA (1.5 eq.), $CHF_2CF_2CH_2OH$, Ar, rt→ **188-190**

entry	starting material	reaction time (h)	product yield (%)
1	**187a**	18	**188a** (46) **189** (10)
2	**187b**	5	**188b** (73)
3	**187c**	18	**188c** (56)
4	**187d**	18	**188d** (71)
5	**187e**	18	**188e** (72)
6	**187f**	4	**190** (54)
7	**187g**	18	**191** (70)

Regarding the reaction mechanism, it is assumed from the by-products that PIFA initially attacks the amide moiety of **187** to afford an electron deficient nitrogen that behaves as a nitrenium ion. However, the precise reaction mechanism, especially the reason for the benzylic carbon-nitrogen bond formation, remains unclear.

3 ADDENDUM

A nitrenium ion is a nitrogen atom which bears a formal positive charge and two covalent bonds. It is not easy to clarify whether all the electrophilic nitrogens in the present review should be truly regarded as nitrenium ions from the strict definition. Therefore it should be emphasized that the proposed mechanisms concerning nitrenium ion intermediates are often speculative.

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Yasuo Kikugawa was born in 1939 in Tokyo. He graduated from the University of Tokyo, Faculty of Pharmaceutical Sciences, in 1964 and received Ph. D. in 1969 from the same university under the direction of Professor S. Yamada. He became Assistant Professor (1969 ~ 1974), and spent three years (1970 ~ 1973) at NIH (National Institutes of Health) as a postdoctoral fellow with Dr. L. A. Cohen. Then, he moved to Josai University as Associate Professor (1974 ~1984), and was promoted to Professor (1984 ~). He received Miyata Award (1994) from the Pharmaceutical Society of Japan. His research interests are chemistry of amine-boranes and synthetic organic chemistry using electron deficient nitrogens (nitrenium ions).