

Synthetic Studies on Nitro Compounds and Aziridines

Mikio Sasaki

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Preface

The studies presented in this thesis have been carried out under the direction of Professor Andrei K. Yudin at the Department of Chemistry, University of Toronto during 2001-2003 and Professor Masamitsu Tamura at the Faculty of Engineering, The University of Tokyo during 1989-1992. The studies are concerned with synthetic studies on nitro compounds and aziridines.

The author wishes to express his sincerest gratitude to Professor Andrei K. Yudin for his kind guidance and valuable suggestions throughout the work regarding aziridines. The author also wishes to express his sincerest gratitude to Professor Masamitsu Tamura for his kind guidance and valuable suggestions throughout the work regarding aromatic nitration. The author wishes to express his sincere gratitude to Professor Jun-ichi Yoshida at Kyoto University for his kind guidance to complete this thesis. The author is deeply grateful to Professor Yoshiaki Akutsu for his constant advice and valuable discussions during the course of the work regarding aromatic nitration. The author is also indebted to Professor Tadao Yoshida and Professor Mitsuru Arai for their helpful suggestions.

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Finally, the author expresses his deepest appreciation to his wife, Ms. Chie Sasaki and his parents, Mr. Sadao Sasaki and Ms. Etsuko Sasaki for their constant assistance and continuous encouragement.

Mikio Sasaki

Technology Research and Development Center
Dainippon Sumitomo Pharma Co., Ltd.

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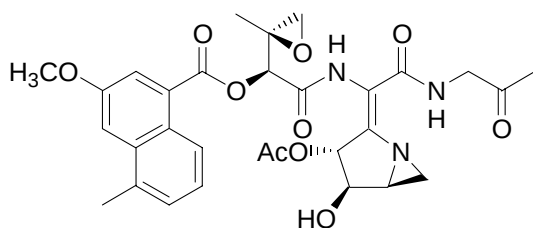
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General Introduction

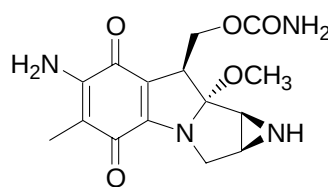
Nitrogen-containing organic compounds are among some of the most abundant class of compound in the biological world. Their biological importance has been well appreciated although other aspects of their chemistry are also important for organic chemists. A number of methods for the construction of nitrogen-containing organic compounds have been developed so far, but exploring new methods is still needed to expand the scope of the chemistry. This thesis deals with two approaches to the chemistry of nitrogen-containing organic compounds; the synthesis and reactions of aziridines and nitration of aromatic compounds.

A) Development and Applications of Novel Reactions with Aziridines

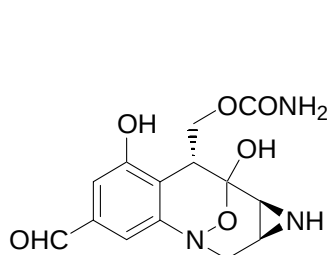
The chemistry of aziridines, the nitrogeneous analogues of epoxides, continues to attract the attention of the synthetic community.¹ In part, this interest is driven by useful properties of aziridines centered around their ring-opening transformations.² The reactivity of aziridines as carbon electrophiles makes them versatile nitrogen-containing building blocks for the synthesis of biologically important compounds.³ As well, biological properties of aziridine-containing molecules such as azinomycins,⁴ mitomycins,⁵ FR-900482,⁶ and miraziridine⁷ are of considerable interest.



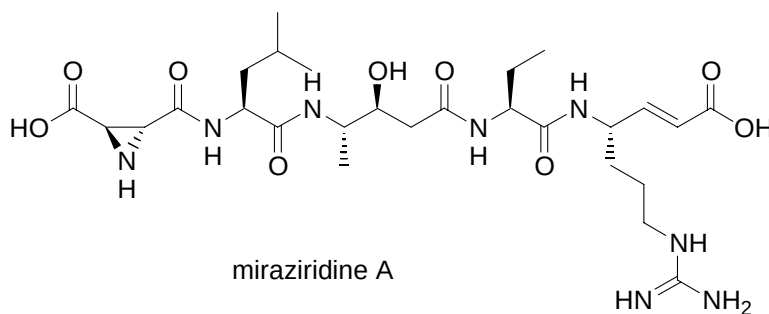
azinomycin A



mitomycin C



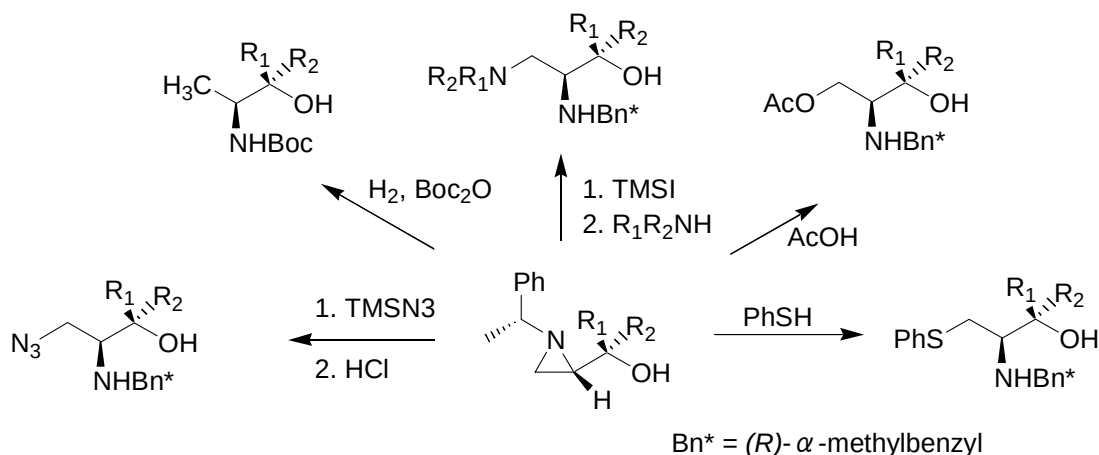
FR-900482



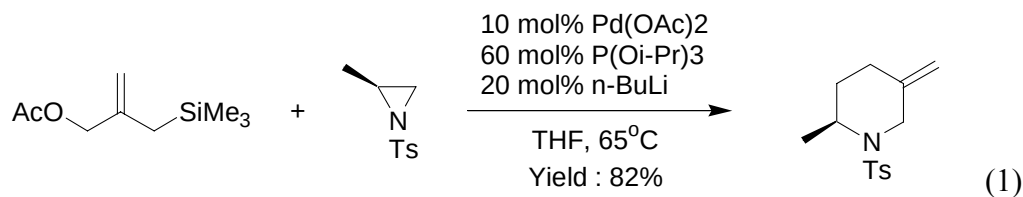
miraziridine A

The aziridine unit is widely recognized as a valuable building block for elaboration of such molecules. For example, aziridinecarboxylates have been used as intermediates in the synthesis of amino acids and alcohols (Scheme 1).⁸

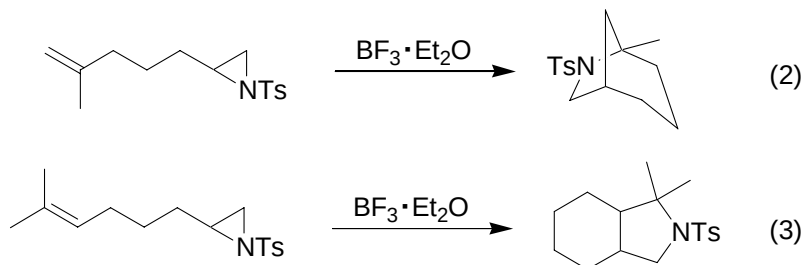
Scheme 1. Conversion of Aziridine-2-methanols into More Functionalized Amino Alcohols.



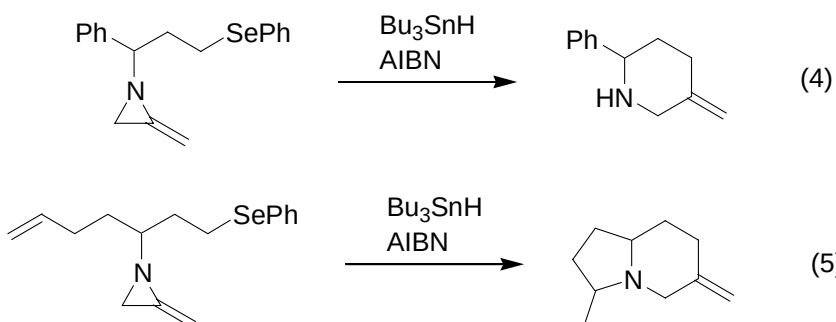
Cycloadditions of *N*-protected aziridines with Pd-trimethylenemethane complexes afford protected piperidines (eq 1).⁹



Under Lewis-acid activation, toluenesulfonyl-containing aziridines undergo cyclization with π -nucleophiles to form six-membered carbocycles or heterocycles (eq 2, 3).¹⁰

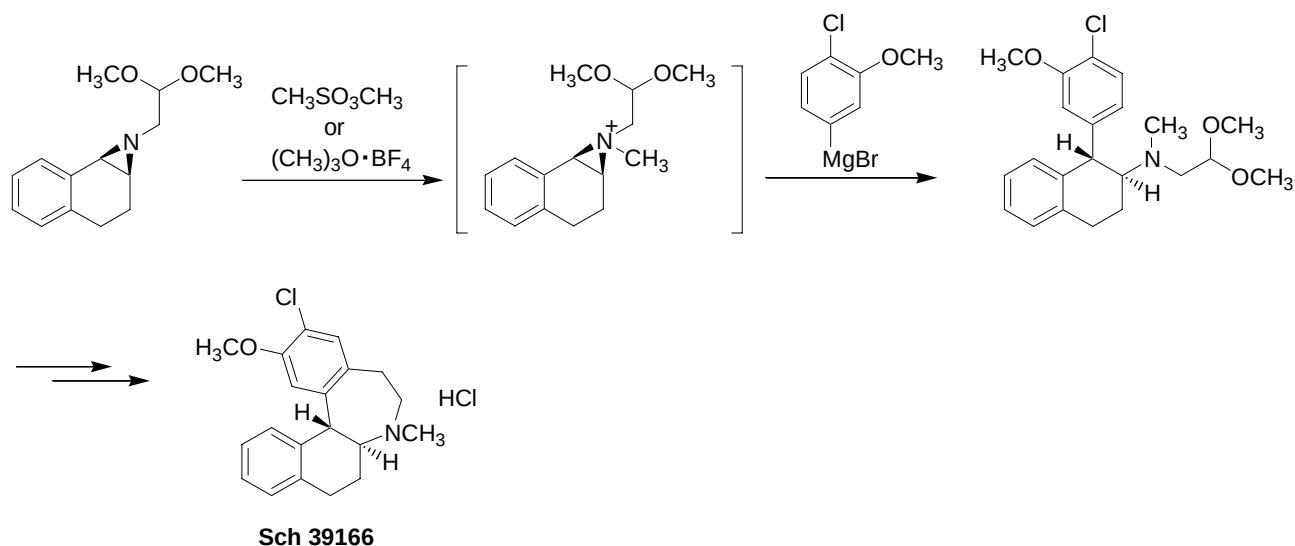


2-Methyleneaziridine phenylselenide derivatives undergo tandem radical cyclizations to produce functionalized piperidines or bicyclic octahydroindolizines (eq 4, 5).¹¹



In the synthesis of Sch 39166, a dopamine D_1 antagonist, methylated aziridinium salt was used as a crucial intermediate, which was later opened by Grignard reagents (Scheme 2).¹²

Scheme 2. Synthetic route on Sch 39166.



Despite these important advances, aziridines are still rarely used in complex molecule synthesis.¹³ If functionalization of an aziridine-containing building block is required during synthesis, nitrogen protection/deprotection sequences are unlikely to be successful due to aziridines' susceptibility to acidic reagents and harsh reaction conditions.

The strategy of the present study to explore the use of aziridines includes a) transition metal catalyzed reactions of aziridines, b) oxidative nitrogen transfer of aziridines, c) making new aziridine-containing building blocks, and d) applications to the synthesis of saturated nitrogen-containing heterocycles such as pyrrolidines and piperidines. The pyrrolidine and piperidine rings are incorporated into the structures of a wide range of natural products and pharmaceuticals which makes them an important class of targets for stereoselective synthesis.¹⁴

Chapter 1 describes the utility of metal-bound aziridine species in nitrogen transfer processes. A range of *N*-arylaziridines were prepared by the palladium or copper catalyzed amination reaction between *N*-H aziridines and arylbromides or arylboronic acids (eq 6). These results showcase the utility of aziridinyll N-metal complexes in amination reactions (Figure 1).

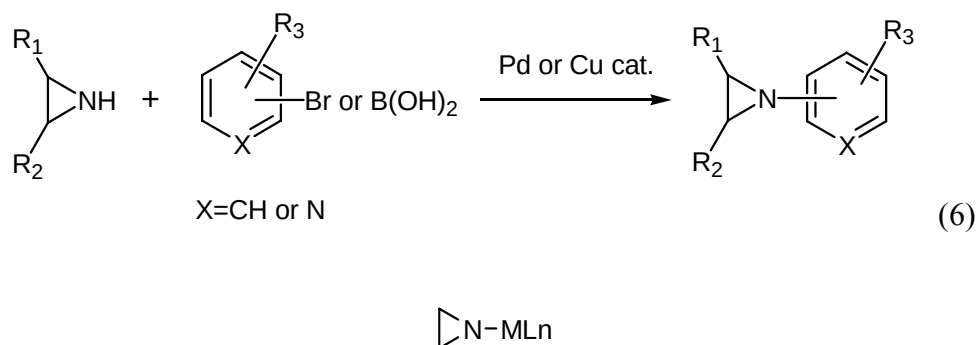
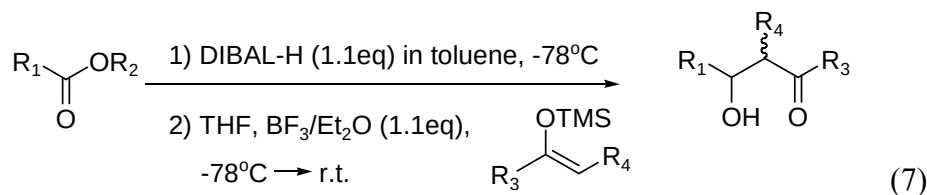
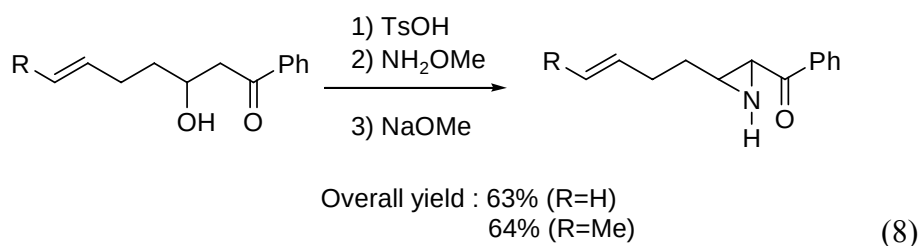


Figure 1. Metal-bound aziridine species.

Chapter 2 describes one-pot reduction-aldol reaction of esters and the synthesis of aziridine building blocks from the aldols. A new protocol was developed for making aldol adducts in a one-pot reaction between esters and silyl enol ethers in the presence of DIBAL-H without isolating the intermediate aldehydes (eq 7). Lewis acid activation of the initially formed aluminated hemiacetals produces highly reactive electrophilic aldehyde equivalents *in situ*. Using this protocol, various aldol adducts can be readily obtained in up to 90% yield on a large scale. Particularly exciting is the possibility of applying the highly reactive aluminated intermediates in other types of nucleophilic addition processes.



The obtained aldols can be converted to the corresponding β -ketoaziridines (eq 8). The double bond functionalization of this aziridine ($\text{R}=\text{H}$) can be achieved by the Heck reaction or by the cross-metathesis. These aziridines are used as the starting materials of the oxidative cycloamination described in chapter 3.



Chapter 3 describes *N*-bromosuccinimide mediated oxidative cycloamination of olefins with aziridines. It was reasoned that despite its basic character, aziridine nitrogen should be quite resistant to oxidative degradation so that transformations of aziridine-containing building blocks can be realized. At the outset of the previous investigations, a significant (0.8V) difference had been observed in the oxidation potential of cyclohexene imine compared to the value recorded for a typical secondary amine such as piperidine, known for its low stability towards oxidation. This finding can be explained on the basis of thermodynamically uphill formation of the iminium species in the case of aziridine oxidation which opens a range of opportunities to explore the NH-containing aziridines in oxidative nitrogen transfer under non-acidic conditions. Of particular value are intramolecular versions of such amination protocols (eq 9) as they should allow for straightforward synthesis of a wide range of larger ring heterocycles.

Highly reactive [5,3]- and [6,3]- bicyclic aziridines can be readily prepared from the corresponding NH-aziridines and *N*-bromosuccinimide by intramolecular oxidative cycloamination of olefins (eq 10). Dehydrobromination of the resulting bicycles gave exo-methylene bicyclic aziridines, which are

surprisingly highly stable enamines with the orthogonal orientation of the nitrogen electron pair in relation to the double bond (Figure 2).

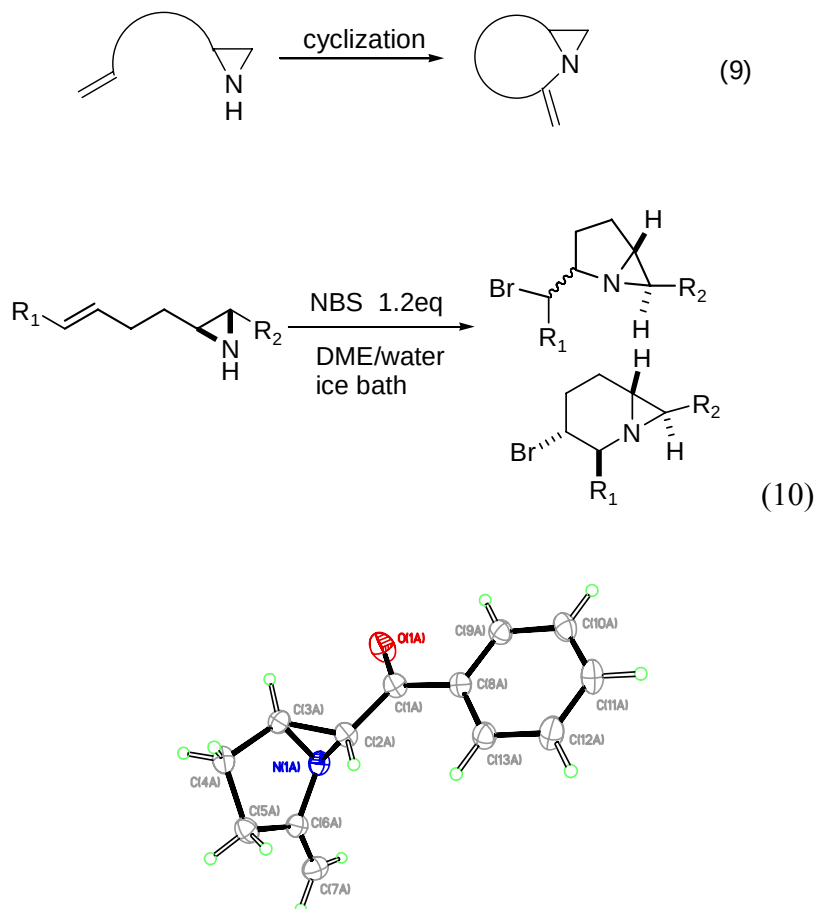
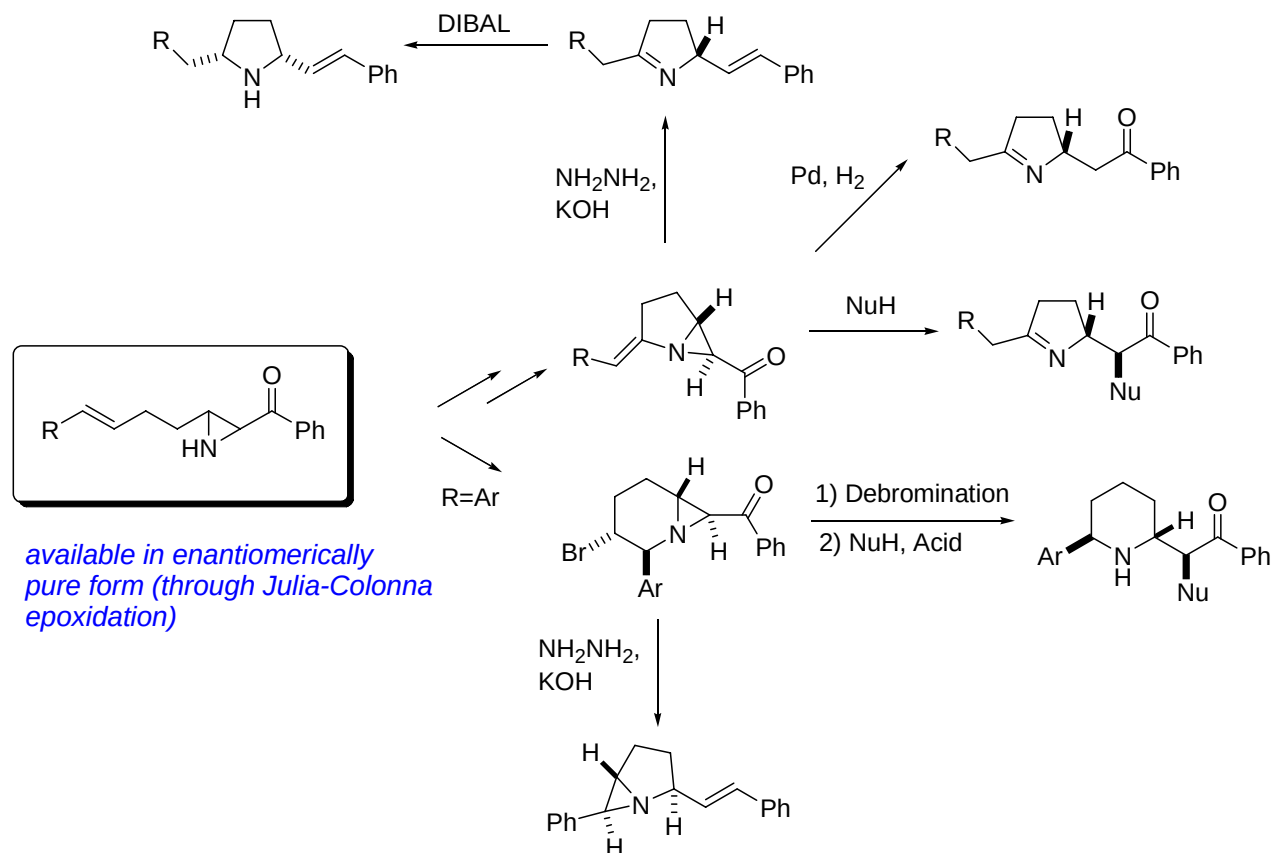


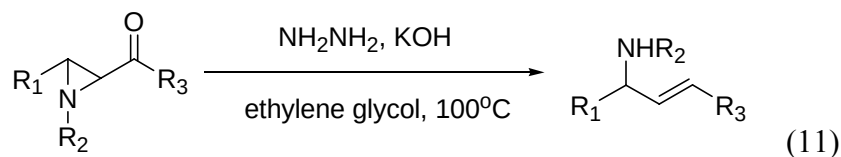
Figure 2. The X-ray structure of bicyclic aziridine.

Chapter 4 describes the applications of bicyclic aziridines described in chapter 3. The nucleophilic ring opening reactions, reductive ring opening reactions, and hydrazine mediated reductive ring opening reactions provided wide range of nitrogen-containing heterocycles with high diastereoselectivities (Scheme 3). This strategy serves as a valuable alternative to existing methods for the construction of substituted pyrrolidines and piperidines, especially since stereocontrol still poses significant challenges with known methods.

Scheme 3. Nitrogen-containing heterocycles from aziridine building blocks.



Reference Chapter describes facile preparation of allylamines by hydrazinolysis of 2-ketoaziridines. A new method for making unprotected allyl amines by simple hydrazinolysis of 2-ketoaziridines has been developed. A variety of aziridines, including N-unprotected, N-substituted, as well as bicyclic enamine and amination type, can be transformed into diversely substituted allyl amines (eq 11). Notably, the 2-ketoaziridine starting materials can be prepared in enantiomerically pure form by using the Julia-Colonna epoxidation reaction, thus, enantiomerically pure allyl amines can be obtained by this method. Allylamines are often seen in the structures of natural products and pharmaceuticals, which makes them another important class of targets for stereoselective synthesis.

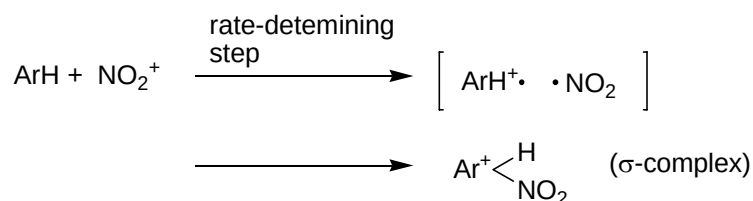


B) Mechanistic Studies on Aromatic Nitration with NO₂

It was reported that aromatic nitro compounds, identified as cancer-causing or mutagenic, is formed by the reaction between aromatic compounds and NO₂ discharged from diesel vehicles and so on in the atmosphere.¹⁵⁻¹⁷ These compounds exist in particulate matter contained in gas emission from diesel vehicles and might give harmful effects to living bodies by inhalation of such compounds.² Therefore, it is important to clarify the formation process for aromatic nitro compounds in order to depress their formation.

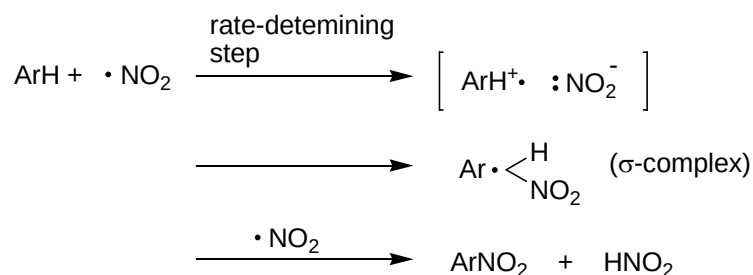
In 1977 Perrin proposed one electron transfer mechanism for aromatic nitration with NO₂⁺, in which radical cation plays an important role as an intermediate (Scheme 4).¹⁸

Scheme 4. Proposed mechanism for aromatic nitration with NO₂⁺



Based on this proposal a mechanism involving radical cation formed via rate-determining electron transfer process was proposed for aromatic nitration with NO₂ (Scheme 5).^{19,20}

Scheme 5. Proposed Mechanism for aromatic nitration with NO₂



However, the detail of aromatic nitration mechanism with NO₂ radical has not been clarified yet.

Chapter 5 describes the solvent effects on the nitration of mono-substituted benzenes with NO_2 in various solvent. From the comparison of the isomer distributions and the yields of the nitro products among various solvents and from Hammett's ρ values, it was suggested that in solvents with lower polarity aromatic nitration should occur by one electron-transfer process [indicating Hammett's ρ value is -1.7], and that in solvents with higher polarity like acetonitrile aromatic nitration should occur by the mechanism involving NO^+ produced from the heterolitic decomposition of N_2O_4 [indicating Hammett's ρ value is -3.2].

Chapter 6 describes the unusual dinitro-isomer distribution in the nitration of benzene and toluene with NO_2 and calculation studies on heats of formation and atomic electron densities of the nitration intermediates. A mechanism involving the addition of NO_2 to the initial adduct (the σ -complex intermediate) followed by the elimination of nitrous acid has been suggested for the formation of mononitrobenzene. A mechanism involving further addition of two mole of NO_2 to form a tetranitro-intermedaite followed by the elimination of two moles of nitrous acid has also been suggested for the formation of dinitrobenzene.

References:

- (1) (a) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, 31, 247. (b) Tanner, D. *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 599. (c) Padwa, A.; Murphree, S. S.; In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilchrist, T. L., Eds.; Pergamon Elsevier Science: Oxford, UK, 2000; Vol. 12, Chapter 4.1 p 57. (d) Padwa, A.; Pearson, W. H.; Lian, B. N.; Bergmeyer, S. C. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F., Eds.; Pergamon: Oxford, UK, 1994; Vol. 1A, p1. (e) Padwa, A.; Woolhouse, A. D. In *Comprehensive Heterocyclic Chemistry*; Lwowski, W., Ed.; Pergamon: Oxford, UK, 1994; Vol. 7.
- (2) Stamm, H. *J. Prakt. Chem., Chem. Ztg.* **1999**, 341, 319.
- (3) (a) Reetz, M. T.; Jaeger, R.; Drewlies, R.; Hubel, M. *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 103 and references therein. (b) Hudlicky, T.; Luna, H.; Price, J. D.; Rulin, F. *J. Org. Chem.* **1990**, 55, 4683. (c) Lautens, M.; Fagmou, K.; Zunic, V. *Org. Lett.* **2002**, 4, 3465. (d) Gust, R.; Keilitz, R.; Schmidt, K. *J. Med. Chem.* **2002**, 45, 2325. (e) Tanner, D.; He, H. M. *Tetrahedron* **1992**, 48, 6079. (f) Dureault, A.; Tranchepain, I.; Depezay, J. C. *J. Org. Chem.* **1989**, 54, 5324.
- (4) (a) Nagaoka, K.; Matsumoto, M.; Ono, J.; Yokoi, K.; Ishizeki, S.; Nakashima, T. *J. of Antibiotics* **1986**, 39, 1527. (b) Coleman, R. S.; Perez, R. J.; Burk, C. H.; Navarro, A. *J. Am. Chem. Soc.* **2002**, 124, 13008. (c) Coleman, R. S.; Li, J.; Navarro, A. *Angew. Chem. Int. Ed.* **2001**, 40, 1736. (d) Coleman, R. S. *Synlett* **1998**, 1031.
- (5) (a) Coleman, R. S.; Chen, W. *Org. Lett.* **2001**, 3, 1141. (b) Kasai, M.; Kono, M. *Synlett* **1992**, 778.
- (6) Ducray, R.; Ciufolini, M. A. *Angew. Chem. Int. Ed.* **2002**, 41, 4688. (b) Suzuki, M.; Kambe, M.; Tokuyama, H.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2002**, 41, 4686. (c) Judd, T. C.; Williams, R. M. *Angew. Chem. Int. Ed.* **2002**, 41, 4683.
- (7) Nakao, Y.; Fujita, M.; Warabi, K.; Matsunaga, S.; Fusetani, N. *J. Am. Chem. Soc.* **2000**, 122, 10462.
- (8) For review, see: Lee, W. K.; Ha, H. *Aldrichimica Acta*. **2003**, 36 (2), 57-63.
- (9) Hedley, S. J.; Morgan, W. J.; Prenzel, A. H.G. P.; Price, D. A.; Harrity, J. P. A. *Synlett*. **2001**, 1596-1598.
- (10) Bergmeier, S. C.; Katz, S. J.; Huang, J.; McPherson, H.; Donoghue, P. J.; Reed, D. D. *Tetrahedron Lett.* **2004**, 45, 5011-5014.

- (11) (a) Prevost, N; Shipman, M. *Org. Lett.* **2001**, 3, 2386-2385. (b) Prevost, N.; Shipman, M. *Tetrahedron* **2002**, 58, 7165-7175.
- (12) Draper, R. W.; Hou, D.; Iyer, R.; Lee, G. M.; Liang, J. T.; Mas, J. L.; Tormos, W.; Vater, E. J. *Org. Proc. Res. Dev.* **1998**, 2, 175-185.
- (13) For use of aziridines in complex molecule synthesis, see ref. 2b.
- (14) For example, see: (a) Dewick, P. M. In *Medicinal Natural Products*; J. Wiley & Sons: Chichester, 1997; Chapter 6. (b) Hagan, D. O. *Nat. Prod. Rep.* **2000**, 17, 435.
- (15) Bayona, J. M.; Markides, K. E.; Lee, M. L. *Environ. Sci. Technol.* **1988**, 22, 1440.
- (16) Kaji, H. *Anzen kogaku* **1988**, 27, 373.
- (17) Chuma, I.; Kondo, S.; Kakebe, K.; *Kankyo to Jintai II*; Todaishuppankai, 1983
- (18) Perrin, C. L. *J. Am. Chem. Soc.* **1977**, 99, 5516
- (19) Pryor, W. A.; Gleicher, G. J.; Cosgrove, J. P.; Church, D. F. *J. Org. Chem.* **1984**, 49, 5189.
- (20) Akutsu, Y.; Sasaki, M.; Saito, T.; Tamura; Yoshida, T. *Kogyo Kayaku* **1990**, 51, 61.

Chapter 1

N-Arylation of Aziridines**Abstract**

A range of *N*-arylaziridines were prepared by the palladium or copper catalyzed amination reaction between *N*-H aziridines and arylbromides or arylboronic acids. These results showcase the synthetic utility of metal-bound aziridine species in nitrogen transfer processes.

Introduction

Palladium-catalyzed carbon-nitrogen bond forming reactions have received considerable attention in recent years.^{1,2} A wide range of amines, amides, indoles, and imines participate in this useful process. Great interest in the synthetic applications of functionalized aziridines,^{3,4} and more recently in metal-bound aziridine species (Figure 1), led to investigate the possibility of reductive elimination of the arylated aziridines from a variety of transition metal complexes.

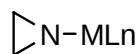


Figure 1. Metal-bound aziridine species.

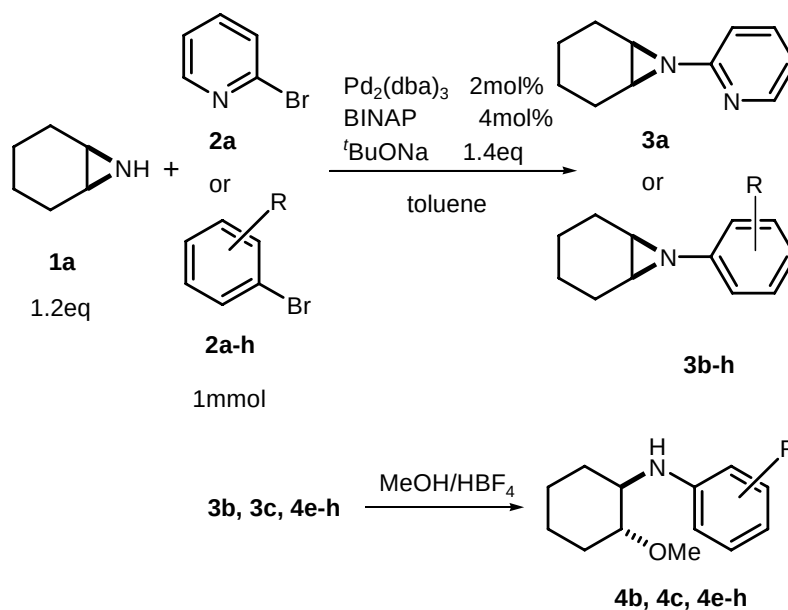
Traditional routes to *N*-arylated aziridines are based on (a) ring closure of *N*-aryl- β -amino alcohols,⁵⁻⁸ and (b) addition of carbenoid species to imines.⁹⁻¹² Amination of aryl halides is well-known but, to the best of my knowledge, has not been applied in the amination with aziridines. This is partly due to the difficulties associated with the preparation of *N*-H aziridines. Hartwig reported an example of the reaction between Ar-Pd-Br complexes and parent ethyleneimine lithium amide to produce *N*-arylated aziridine but, to the best of my knowledge, no investigation into the scope and potential applications of this process has been documented.¹³

Results and Discussion

The aziridine starting materials was prepared by using one of the following two methods: (a) ring closure of 1-azido-2-hydroxycyclohexane with triphenylphosphine,¹⁴ and (b) 1,4-addition of methoxylamine to α,β -unsaturated ketone followed by ring closure.¹⁵ It was subsequently found that $\text{Pd}_2(\text{dba})_3/\text{BINAP}$ served as an effective catalyst for amination of N-H aziridines. Using this methodology, several types of *N*-arylated products have been synthesized. BINAP and DPPP were tried as ligands for the reaction between *o*-bromopyridine (**2a**) and cyclohexeneimine (**1a**), which revealed that BINAP was effective ligand in this process, whereas DPPP did not give the desired product. This contrasts with success of DPPP in the amination of **2a** with various arylamines or cyclic amines.¹⁶

In the case of pyridine substrates, direct nucleophilic displacement of halide has been ruled out: heating the mixture of **1a** and **2a** did not give the desired product. To the delight, the insertion of palladium into the nitrogen-carbon bond was not observed in any of these cases, although oxidative addition of Ni to *N*-tosylaziridines has been reported¹⁷ and oxidative addition of transition metals to aziridines has been invoked in catalytic carbonylation of aziridines to give β -lactams.^{18,19}

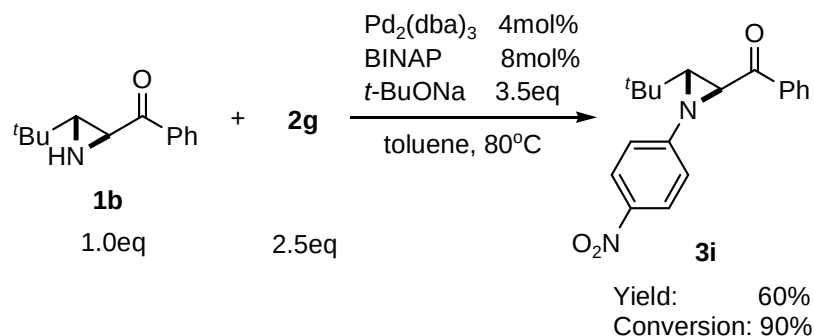
The scope of *N*-arylation of **1a** using Pd/BINAP was investigated. The results are shown in Table 1. Both electron-withdrawing and electron-donating groups on the aryl halide moiety can be tolerated. Electron-withdrawing groups tend to increase reactivity (Table 1, entry 7), while electron-rich substrates, such as *o*-bromoanisole (**2f**), needed more forceful conditions to complete the reaction (Table 1, entry 6). Aryl chlorides did not react under the reaction conditions (Table 1, entry 9). Thus, *o*-bromochlorobenzene (**2d**) led to *N*-(2-chlorophenyl)aziridine (**3d**) with high chemoselectivity (Table 1, entry 4). Benzoyl-N-H aziridines also gave *N*-aryl aziridines under these conditions with moderate selectivity. The reaction between 2-benzoyl-3-*tert*-butylaziridine (**1b**) and 1-bromo-4-nitrobenzene (**2g**) gave 1-(4-nitrophenyl)-2-benzoyl-3-*tert*-butylaziridine (**3i**) in moderate yield (Scheme 1).

Table 1. The Scope of Aziridine *N*-Arylation.

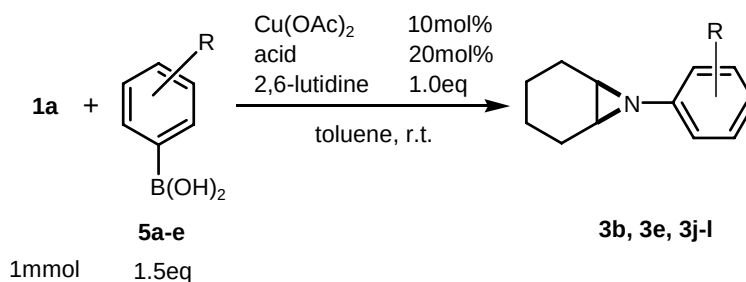
Entry	Substrate	Product	Reaction temperature (°C)	Reaction time (hrs)	Yield (%)
1	2a	3a	50	12	70 ^b
2	R=H (2b)	3b	70	14	53 ^a
3	R=o-F (2c)	3c	80	7	58 ^a
4	R=o-Cl (2d)	3d	80	19	95 ^b
5	R=o-Me (2e)	3e	70	24	64 ^a
6	R=o-OMe (2f)	3f	80	22	78 ^a
7	R=p-NO ₂ (2g)	3g	70	3	96 ^a
8	R=p-CN (2h)	3h	50	15	79 ^a
			→ 60	→ 2	
9	p-cyanochlorobenzene	3h	80	24	trace

^a Yield was determined after ring opening reaction with MeOH/ HBF_4 (i.e. as **4b**, **4c**, and **4e-h**).

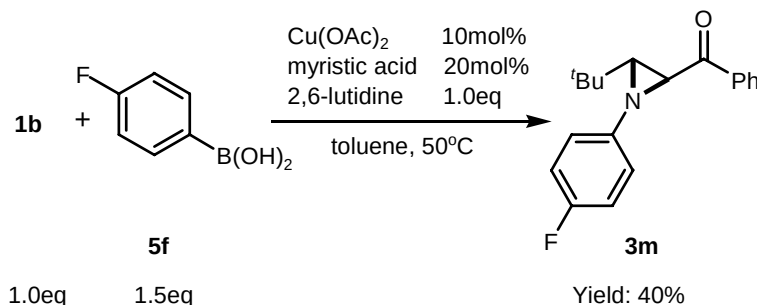
^b Yield was determined after purification on alumina (for **3a**) or silica (for **3d**) column.

Scheme 1. *N*-arylation of 2-benzoyl-3-tert-butylaziridine

Copper catalyzed amination system developed by Buchwald for the arylation of anilines, acyclic amines, and piperidines²⁰ was also effective for the synthesis of *N*-arylated aziridines. Coupling between **1a** or **1b** and arylboronic acids (**5a-f**) catalyzed by copper acetate/myristic acid gave *N*-arylated aziridines (**3b**, **3e**, and **3j-m**) in good to moderate yields (Table 2, Scheme 2).

Table 2. The Scope of Aziridine *N*-Arylation Using Arylboronic Acids

Entry	Substrate	Product	Acid	Yield (%)
1	R=H (5a)	3b	myristic acid	87
2	5a	3b	camphanic acid	40
3	5a	3b	2-phenylbutyric acid	no reaction
4	R=o-Me (5b)	3e	myristic acid	78
5	R=m-Br (5c)	3j	myristic acid	68
6	R=m-NO ₂ (5d)	3k	myristic acid	60
7	R=p-OMe (5e)	3l	myristic acid	65

Scheme 2. *N*-arylation of 2-benzoyl-3-*tert*-butylaziridine using arylboronic acid

Conclusion

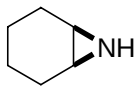
It has been shown that a range of *N*-arylaziridines were prepared by the palladium or copper catalyzed amination reaction between *N*-H aziridines and arylbromides or arylboronic acids. These results showcase the utility of aziridinyl *N*-metal complexes in amination reactions.²¹

Experimental Section

General: Unless otherwise stated, all reactions were performed under nitrogen or argon atmosphere using flame-dried glassware and standard syringe-pump techniques.

Nuclear magnetic resonance spectra: ^1H , ^{19}F , and ^{13}C NMR spectra were recorded on either Mercury 300, Varian Gemini 300, or VRX-S (Unity) 400 spectrometer. ^1H NMR spectra were referenced to residual CDCl_3 (δ 7.27 ppm), ^{19}F NMR were referenced to CFCl_3 (δ 0 ppm), and ^{13}C NMR spectra were referenced to CDCl_3 (δ 77.23 ppm). Peak multiplicities are designated by the following abbreviations: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets; br, broad; and *J*, coupling constant in Hz.

Chromatography: Analytical thin layer chromatography (TLC) was performed on Macherey Nagel pre-coated glass-backed TLC plates (SIL G/UV₂₅₄, 0.25mm) and visualized by UV lamp (254 nm), iodine, ninhydrin, and potassium permanganate stains. Solvent ratios for *R_f* values are reported as v/v. Column chromatography was carried out using Silicycle 230-400 mesh silica gel.

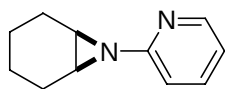
7-azabicyclo[4.1.0]heptane (1a)²²

A mixture of cyclohexene oxide (30.1 g, 306 mmol) and NaN_3 (50.4 g, 775 mmol) in H_2O /acetone (1:1) was heated to reflux for 17 hrs. Acetone was removed by rotavapor vacuum, and the residue was extracted with *tert*-butyl methyl ether (3×160 mL) and dichloromethane (3×160 mL). The combined organic phases were washed with water and dried over MgSO_4 . The solvent was removed in vacuo and the azido alcohol was obtained as a yellow oil (40 g, 283 mmol, 93%), which was reacted without further purification. PPh_3 (57.7 g, 220 mmol) was added to a solution of azido-cyclohexanol (31.1 g, 220 mmol) in *tert*-butyl methyl ether (250 mL). N_2 evolved from the mixture, and after heating to reflux for 16 hrs., the solvent was removed through distillation at 760 mmHg. Continued distillation under reduced pressure yielded compound 7-azabicyclo[4.1.0]heptane (**1a**, 16.8 g, 173 mmol, 79%) as a colorless liquid, which solidified at 0°C .

^1H NMR (CDCl_3 , 400 MHz): δ 3.21 ppm (d, 1H, $J=2$ Hz), 2.17 ppm (s, 2H), 1.80 ppm (s, 4H), 1.34-1.16 ppm (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 29.5 ppm, 24.8 ppm, 20.4 ppm

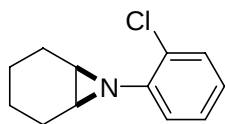
1. **Procedure for palladium-catalyzed arylation reaction** (Table 1, entry 1): To $\text{Pd}_2(\text{dba})_3$ (73 mg, 2 mol%) in 30 mL toluene (dried according to Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, 15, 1518) was added *rac*-BINAP (100 mg, 4 mol%), 2-bromopyridine (**2a**, 640 mg, 4 mmol), NaO^tBu (540 mg, 5.6 mmol), and 7-azabicyclo[4.1.0]heptane (**1a**, 470 mg, 4.8 mmol) at room temperature. The reaction mixture was stirred at 50°C for 12 hrs. After completion, the mixture was washed with water (3×30 mL) and dried over sodium sulfate. The solvent was subsequently removed under reduced pressure. Hexane was added to the crude product and the precipitated solid was removed by filtration, and the filtrate was evaporated. Pentane and neutral alumina were added to the residue and stirred for a few minutes at room temperature and then filtered. The filtrate was concentrated under reduced pressure, to give 490 mg of 7-(2-pyridinyl)-7-azabicyclo[4.1.0]heptane (**3a**, yield: 70%).

7-(2-pyridinyl)-7-azabicyclo[4.1.0]heptane (3a):



^1H NMR (CDCl_3 , 400MHz): δ 8.27 ppm (dd, J = 5.2 Hz, 2.0 Hz, 1H), 7.54 ppm (dt, J = 8.0 Hz, 1.6 Hz, 1H), 6.92 ppm (d, J = 8.0 Hz, 1H), 6.88 ppm (dd, J = 7.6 Hz, 5.2 Hz), 2.61-2.65 ppm (m, 2H), 2.08-2.15 ppm (m, 2H), 1.92-1.99 ppm (m, 2H), 1.51-1.60 ppm (m, 2H), 1.30-1.39 ppm (m, 2H); ^{13}C NMR (CDCl_3 , 75MHz): δ 166.4 ppm (s), 148.3 ppm (s), 137.5 ppm (s), 117.8 ppm (s), 115.8 ppm (s), 38.9 ppm (s), 25.0 ppm (s), 20.8 ppm (s); HR-MS (EI) m/z : calcd. for $\text{C}_{11}\text{H}_{14}\text{N}_2$ 174.1157, found 174.1157

7-(2-chlorophenyl)-7-azabicyclo[4.1.0]heptane (3d):

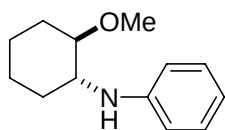


^1H NMR (CDCl_3 , 300MHz): δ 7.28 ppm (dd, J = 10.8 Hz, 1.5 Hz, 1H), 7.11 ppm (dt, J = 7.8 Hz, 1.5 Hz, 1H), 6.83-6.94 ppm (m, 2H), 2.35-2.40 ppm (m, 2H), 2.13-2.22 ppm (m, 2H), 1.88-1.98 ppm (m, 2H), 1.47-1.58 ppm (m, 2H), 1.26-1.38 ppm (m, 2H); ^{13}C NMR (CDCl_3 , 100MHz): δ 151.4 ppm (s), 129.8 ppm (s), 127.1 ppm (s), 122.6 ppm (s), 121.4 ppm (s), 117.5 ppm (s), 39.9 ppm (s), 24.2 ppm (s), 20.4 ppm (s); HR-MS (EI) m/z : calcd. for $\text{C}_{12}\text{H}_{14}\text{ClN}$ 207.0810, found 207.0812

Procedure for palladium-catalyzed arylation reaction (Table 1, entry 8): To $\text{Pd}_2(\text{dba})_3$ (18 mg, 2 mol%) in 10 mL toluene was added *rac*-BINAP (25 mg, 4 mol%), *p*-nitrobromobenzene (**2h**, 202 mg, 1 mmol), NaO^tBu (135 mg, 1.4 mmol), and 7-azabicyclo[4.1.0]heptane (**1a**, 110 mg, 1.2 mmol) at room temperature. The reaction mixture was stirred at 70°C for 3 hrs and then at 50°C overnight. After completion, the mixture was washed with water (3×10 mL) followed by drying over sodium sulfate. The solvent was subsequently removed under reduced pressure, and 20 mL methanol together with 48% aqueous tetrafluoroboric acid (200mg) were added to the crude product. After stirring at room temperature, the solvent was removed under reduced pressure. To the residue, dichloromethane (10 mL) and dilute aqueous potassium carbonate (10 mL) were added. The layers were separated, washed

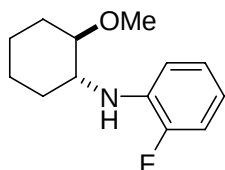
with water, dried over sodium sulfate, and the solvent was evaporated. The residue was purified on a silica gel column (hexane/ethyl acetate = 6/4), to give 239 mg of *trans*-1-methoxy-2-*p*-nitrophenylaminocyclohexane (**4h**, yield: 96%).

***trans*-1-methoxy-2-phenylaminocyclohexane (**4b**)²³:**

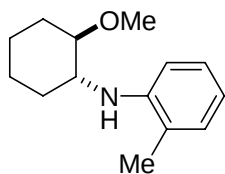


¹H NMR (CDCl₃, 400MHz): δ 7.20 ppm (t, *J* = 8.0 Hz, 2H), 6.71-6.75 ppm (m, 3H), 3.42 (s, 3H), 3.27 ppm (dt, *J* = 8.8 Hz, 4.0 Hz, 1H), 3.17 ppm (dt, *J* = 8.4 Hz, 3.6 Hz, 1H), 2.22-2.26 ppm (m, 1H), 2.11-2.16 ppm (m, 1H), 1.79-1.83 ppm (m, 1H), 1.68-1.71 ppm (m, 1H), 1.20-1.46 ppm (m, 4H); ¹³C NMR (CDCl₃, 100MHz): δ 148.0 ppm (s), 129.2 ppm (s), 117.5 ppm (s), 113.9 ppm (s), 82.1 ppm (s), 56.6 ppm (s), 56.2 ppm (s), 31.2 ppm (s), 29.1 ppm (s), 23.8 ppm (s), 23.7 ppm (s)

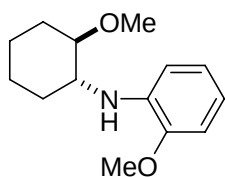
***trans*-1-methoxy-2-*o*-fluorophenylaminocyclohexane (**4c**):**



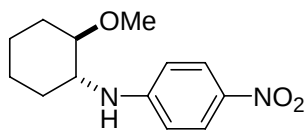
¹H NMR (CDCl₃, 400MHz): δ 6.96-7.02 ppm (m, 2H), 6.85 ppm (dt, *J* = 8.4 Hz, 1.6 Hz, 1H), 6.61-6.66 ppm (m, 1H), 4.1 ppm (br, 1H), 3.42 ppm (s, 3H), 3.27 ppm (dt, *J* = 8.8 Hz, 4.0 Hz, 1H), 3.17 ppm (dt, *J* = 8.4 Hz, 3.6 Hz, 1H), 2.13-2.22 ppm (m, 2H), 1.80-1.83 ppm (m, 1H), 1.70-1.75 ppm (m, 1H), 1.27-1.45 ppm (m, 4H); ¹³C NMR (CDCl₃, 100MHz): δ 153.1 ppm (s), 124.4 ppm (d, *J* = 3.0 Hz), 116.6 ppm (d, *J* = 6.8 Hz), 114.3 ppm (d, *J* = 19.0 Hz), 113.2 ppm (s), 82.5 ppm (s), 56.62 ppm (s), 56.57 ppm (s), 31.4 ppm (s), 29.3 ppm (s), 23.9 ppm (s), 23.7 ppm (s); HR-MS (EI) *m/z*: calcd. for C₁₃H₁₈FNO 223.1372, found 223.1375

***trans*-1-methoxy-2-*o*-methylphenylaminocyclohexane (4e):**

^1H NMR (CDCl_3 , 300MHz): δ 7.03-7.13 ppm (m, 2H), 6.62-6.72 ppm (m, 2H), 3.77 ppm (br, 1H), 3.39 ppm (s, 3H), 3.30 ppm (dt, J = 8.7 Hz, 3.9 Hz, 1H), 3.22 ppm (dt, J = 8.1 Hz, 3.6 Hz, 1H), 2.20-2.29 ppm (m, 1H), 2.18 ppm (m, 3H), 2.08-2.13 ppm (m, 1H), 1.75-1.84 ppm (m, 1H), 1.60-1.72 ppm (m, 1H), 1.29-1.48 ppm (m, 4H); ^{13}C NMR (CDCl_3 , 100MHz): δ 146.1 ppm (s), 130.1 ppm (s), 127.0 ppm (s), 122.5 ppm (s), 116.9 ppm (s), 110.8 ppm (s), 82.0 ppm (s), 56.4 ppm (s), 56.2 ppm (s), 31.3 ppm (s), 29.0 ppm (s), 23.8 ppm (s), 23.7 ppm (s), 17.6 ppm (s); HR-MS (EI) m/z : calcd. for $\text{C}_{14}\text{H}_{21}\text{NO}$ 219.1623, found 219.1622

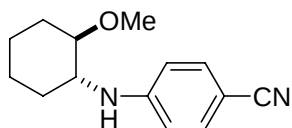
***trans*-1-methoxy-2-*o*-methoxyphenylaminocyclohexane (4f):**

^1H NMR (CDCl_3 , 400MHz): δ 6.88 ppm (dt, J = 7.6 Hz, 1.2 Hz, 1H), 6.76-6.81 ppm (m, 2H), 6.69 (t, J = 7.6 Hz, 1H), 4.4 ppm (br, 1H), 3.89 ppm (s, 3H), 3.42 (s, 3H), 3.29 ppm (dt, J = 8.4 Hz, 3.6 Hz, 1H), 3.23 ppm (dt, J = 8.4 Hz, 4.0 Hz, 1H), 2.10-2.22 ppm (m, 2H), 1.68-1.82 ppm (m, 2H), 1.30-1.48 ppm (m, 4H); ^{13}C NMR (CDCl_3 , 100MHz): δ 121.2 ppm (s), 116.3 ppm (s), 110.7 ppm (s), 109.5 ppm (s), 82.1 ppm (s), 56.4 ppm (s), 56.1 ppm (s), 55.5 ppm (s), 31.0 ppm (s), 29.1 ppm (s), 23.7 ppm (s), 23.5 ppm (s); HR-MS (EI) m/z : calcd. for $\text{C}_{14}\text{H}_{21}\text{NO}_3$ 235.1572, found 235.1573

***trans*-1-methoxy-2-*p*-nitrophenylaminocyclohexane (4h):**

^1H NMR (CDCl_3 , 300MHz): δ 8.05 ppm (d, J = 9.3 Hz, 2H), 6.57 ppm (d, J = 9.0 Hz, 2H), 4.54 ppm (br, 1H), 3.29-3.39 ppm (m, 4H), 3.08 ppm (dt, J = 9.0 Hz, 4.2 Hz, 1H), 2.11-2.20 ppm (m, 2H), 1.68-1.85 ppm (m, 2H), 1.17-1.46 ppm (m, 4H); ^{13}C NMR (CDCl_3 , 100MHz): δ 153.4 ppm (s), 137.7 ppm (s), 126.3 ppm (s), 111.7 ppm (s), 82.8 ppm (s), 56.5 ppm (s), 56.4 ppm (s), 31.4 ppm (s), 29.5 ppm (s), 24.1 ppm (s), 23.7 ppm (s); HR-MS (EI) m/z : calcd. for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_3$ 250.1317, found 250.1318

***trans*-1-methoxy-2-*p*-cyanophenylaminocyclohexane (4i):**



^1H NMR (CDCl_3 , 300MHz): δ 7.38 ppm (d, J = 8.7 Hz, 2H), 6.60 ppm (d, J = 9.0 Hz, 2H), 4.26 ppm (br, 1H), 3.34 ppm (s, 3H), 3.22-3.32 ppm (m, 1H), 3.07 ppm (dt, J = 8.7 Hz, 3.9 Hz, 1H), 2.10-2.19 ppm (m, 2H), 1.76-1.85 ppm (m, 1H), 1.66-1.74 ppm (m, 1H), 1.23-1.43 ppm (m, 4H); ^{13}C NMR (CDCl_3 , 100MHz): δ 151.3 ppm (s), 133.6 ppm (s), 120.6 ppm (s), 112.8 ppm (s), 98.4 ppm (s), 82.7 ppm (s), 56.3 ppm (s), 56.2 ppm (s), 31.3 ppm (s), 29.4 ppm (s), 24.0 ppm (s), 23.7 ppm (s); HR-MS (EI) m/z : calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}$ 230.1419, found 230.1416

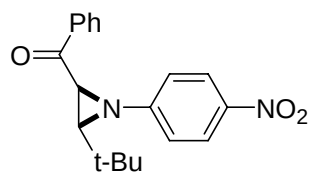
(*E*)-4,4-Dimethyl-1-phenyl-2-penten-1-one²⁴: A mixture of pivalaldehyde (2.58 g, 30 mmol), acetophenone (3.60 g, 30 mmol), NaOH (1.20 g, 30 mmol) and water (6 mL) in methanol (60 mL) was heated under reflux for 6 hrs. After removal of methanol, CH_2Cl_2 and aq. NH_4Cl were added to the reaction mixture. The product was extracted with CH_2Cl_2 . The combined organic extracts were dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was purified on a silica gel column (hexane/ethyl acetate = 95/5), to give 2.60 g of (*E*)-4,4-dimethyl-1-phenyl-2-penten-1-one (yield 46%).

3-Methoxyamino-4,4-dimethyl-1-phenyl-1-pentanone²⁴: A mixture of (*E*)-4,4-dimethyl-1-phenyl-2-penten-1-one (1.88 g, 10 mmol) and NH_2OMe (719 mg, 15.3 mmol) in ethanol (10 mL) was heated under reflux for 5 hrs. The solvent was evaporated and the residue was purified on a silica gel column

(hexane/ethyl acetate = 9/1), to give 1.30 g of 3-methoxyamino-4,4-dimethyl-1-phenyl-1-pentanone (yield: 55%).

***trans*-2-Benzoyl-3-*tert*-butylaziridine (**1b**)**²⁴: To a stirred solution of NaO^tBu (657 mg, 12.2 mmol) in DMF (20 mL), a solution of 3-methoxyamino-4,4-dimethyl-1-phenyl-1-pentanone (1.30 g, 5.5 mmol) in DMF (10 mL) was added dropwise at room temperature. After the solution was stirred for 20 min at the same temperature, water (60 mL) was added and the product was extracted with CH₂Cl₂ (2 × 30 mL). The combined organic extracts were washed with water (20 mL) and the solvent was evaporated. The residue was purified on silica gel column (hexane/ethyl acetate = 9/1), to give 975 mg of *trans*-2-benzoyl-3-*tert*-butylaziridine (**1b**, yield: 87%). ¹H NMR (CDCl₃, 300 MHz) δ 8.00-8.05 ppm (m, 2H), 7.60-7.66 ppm (m, 1H), 7.39-7.54 ppm (m, 2H), 3.35-3.38 ppm (m, 1H), 2.00-2.10 ppm (m, 2H), 1.00 ppm (s, 9H)

***trans*-1-*p*-Nitrophenyl-2-benzoyl-3-*tert*-butylaziridine (**3j**, Scheme 1)**:



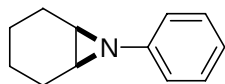
To Pd₂(dba)₃ (6.5 mg, 2 mol%) in 4mL toluene was added *rac*-BINAP (8.6 mg, 4 mol%), *p*-nitrobromobenzene (**2h**, 182.5 mg, 0.75 mmol), NaO^tBu (122.5 mg, 1.05 mmol), and *trans*-2-benzoyl-3-*tert*-butylaziridine (**1b**, 73 mg, 0.3 mmol) at room temperature. The reaction mixture was stirred at 80°C for 20 hrs. After completion, toluene (10 mL) was added. The mixture was washed with water (3 × 10 mL) and was dried over sodium sulfate. The solvent was subsequently removed under reduced pressure, and the residue was purified on a silica gel column (hexane/ethyl acetate = 9/1), to give 70 mg of *trans*-1-*p*-nitrophenyl-2-benzoyl-3-*tert*-butylaziridine (**3j**, yield: 60%).

¹H NMR (CDCl₃, 400MHz): δ 8.13 ppm (d, *J* = 8.4 Hz, 2H), 8.05 ppm (d, *J* = 7.6 Hz, 2H), 7.70 ppm (t, *J* = 7.6 Hz, 1H), 7.59 ppm (t, *J* = 8.0 Hz, 2H), 6.83 ppm (d, *J* = 8.4 Hz, 2H), 4.20 ppm (d, *J* = 2.8 Hz, 1H), 2.82 ppm (d, *J* = 2.8 Hz, 1H), 1.16 ppm (s, 9H); ¹³C NMR (CDCl₃, 100MHz): δ 193.2 ppm (s), 156.2 ppm (s), 137.5 ppm (s), 134.0 ppm (s), 129.1 ppm (s), 128.2 ppm (s), 125.0 ppm (s), 120.0 ppm

(s), 57.8 ppm (s), 42.8 ppm (s), 40.8 ppm (s), 26.9 ppm (s); HR-MS (EI) m/z : calcd. for $C_{19}H_{20}N_2O_3$ 324.1474, found 324.1476

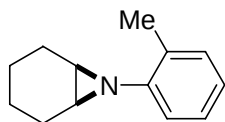
General procedure for copper-catalyzed arylation reaction (Table 2, entry 1): To the mixture of phenylboronic acid (**5a**, 183 mg, 1.5 mmol), $Cu(OAc)_2$ (18 mg, 0.1 mmol), and myristic acid (46 mg, 0.2 mmol) were successively added toluene (2 mL), 2,6-lutidine (107 mg, 1 mmol), and cyclohexeneimine (**1a**, 97 mg, 1 mmol). The reaction mixture was stirred at room temperature for 24 hrs, diluted with ethyl acetate (10 mL), filtered through a plug of silica gel, and then purified on a silica gel column (hexanes/ethyl acetate = 9/1), to give 150 mg of 7-phenyl-7-azabicyclo[4.1.0]heptane (**3b**, yield: 87%).

7-phenyl-7-azabicyclo[4.1.0]heptane (3b**)²⁵.**



1H NMR ($CDCl_3$, 400 MHz): δ 7.12 ppm (t, J = 8 Hz, 1H), 6.89 ppm (d, J = 8 Hz, 2H), 6.83 ppm (t, J = 7.4 Hz, 2H), 2.23 ppm (d, J = 4 Hz, 2H), 1.98-1.93 ppm (m, 2H), 1.85-1.80 ppm (m, 2H), 1.43-1.39 ppm (m, 2H), 1.24-1.18 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.9 ppm (s), 129.0 ppm (s), 122.0 ppm (s), 120.6 ppm (s), 38.9 ppm (s), 24.9 ppm (s), 20.6 ppm (s)

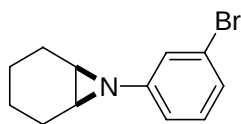
7-(2-methylphenyl)-7-azabicyclo[4.1.0]heptane (3e**)²⁶.**



1H NMR ($CDCl_3$, 400 MHz): δ 6.99 ppm (d, J = 7.6 Hz, 2H), 6.76 ppm (dd, J = 7.6 Hz, 2H), 2.23 ppm (s, 3H), 2.18 ppm (d, J = 4 Hz, 2H), 2.03-1.96 ppm (m, 2H), 1.86-1.83 ppm (m, 2H), 1.47-1.42 ppm (m, 2H), 1.28-1.19 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 131.2 ppm (s), 130.6 ppm (s), 127.0 ppm (s), 126.4

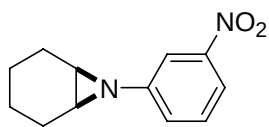
ppm (s), 126.1 ppm (s), 122.0 ppm (d, $J = 9.6$ Hz), 119.3 ppm (s), 38.8 ppm (s), 34.6 ppm (s), 24.7 ppm (s), 20.7 ppm (s)

7-(3-bromophenyl)-7-azabicyclo[4.1.0]heptane (3k)²⁶.



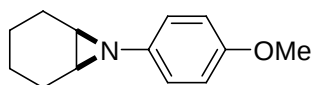
¹H NMR (CDCl₃, 400 MHz): δ 7.10 ppm (s, 1H), 7.04 ppm (t, $J = 2$ Hz, 2H), 6.89-6.87 ppm (m, 1H), 2.31 ppm (d, $J = 1.8$ Hz, 2H), 2.05-1.98 ppm (m, 2H), 1.9-1.87 ppm (m, 2H), 1.50-1.44 ppm (m, 2H), 1.33-1.26 ppm (m, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 157.4 ppm (s), 130.3 ppm (s), 125.0 ppm (s), 123.7 ppm (s), 122.5 ppm (s), 119.4 ppm (s), 39.2 ppm (s), 24.7 ppm (s), 20.5 ppm (s)

7-(3-nitrophenyl)-7-azabicyclo[4.1.0]heptane (3l).

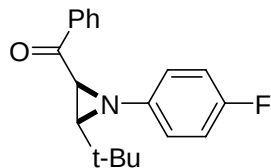


¹H NMR (CDCl₃, 400 MHz): δ 7.77 ppm (d, $J = 3$ Hz, 1H), 7.34 ppm (t, $J = 8.6$ Hz, 2H), 7.28-7.26 ppm (m, 1H), 2.40 ppm (d, $J = 1.2$ Hz, 2H), 2.10-2.04 ppm (m, 2H), 1.96-1.93 ppm (m, 2H), 1.51-1.46 ppm (m, 2H), 1.36-1.26 ppm (m, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 134.8 ppm (s), 129.6 ppm (s), 127.1 ppm (s), 123.7 ppm (s), 116.9 ppm (s), 115.4 ppm (s), 39.7 ppm (s), 24.6 ppm (s), 20.4 ppm (s); HR-MS (EI) m/z : calcd. for C₁₂H₁₄N₂O₂ 218.1055, found 218.1049

7-(4-methoxyphenyl)-7-azabicyclo[4.1.0]heptane (3g)²⁶.



¹H NMR (CDCl₃, 400 MHz): δ 6.89 ppm (d, $J = 8.8$ Hz, 2H), 6.75 ppm (d, $J = 8.8$ Hz, 2H), 3.74 ppm (s, 3H), 2.23 ppm (d, $J = 3.6$ Hz, 2H), 2.04-2.19 ppm (m, 2H), 1.91-1.88 ppm (m, 2H), 1.48-1.45 ppm (m, 2H), 1.30-1.26 ppm (m, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 154.9 ppm (s), 149.3 ppm (s), 121.3 ppm (s), 114.3 ppm (s), 55.7 ppm (s), 39.1 ppm (s), 24.9 ppm (s), 20.6 ppm (s)

***trans*-1-*p*-fluorophenyl-2-benzoyl-3-*tert*-butylaziridine (3m).**

^1H NMR (CDCl_3 , 400 MHz): δ 8.01 ppm (d, $J = 7.2$ Hz, 2H), 7.62 ppm (t, $J = 7.2$ Hz, 1H), 7.52 ppm (t, $J = 7.8$ Hz, 2H), 6.86 ppm (t, $J = 8.2$ Hz, 2H), 6.70 ppm (dd, $J = 8.8$ Hz, 2H), 4.00 ppm (d, $J = 2.8$ Hz, 1H), 2.82 ppm (d, $J = 2.8$ Hz, 1H), 1.08 ppm (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 194.1 ppm (s), 145.6 ppm (s), 138.5 ppm (s), 133.7 ppm (s), 129.1 ppm (s), 128.4 ppm (s), 121.38 ppm (d, $J = 8.3$ Hz), 115.75 ppm (s), 115.5 ppm (s), 57.3 ppm (s), 41.3 ppm (s), 31.5 ppm (s), 27.2 ppm (s); ^{19}F NMR (CDCl_3 , 400 MHz): δ -122.17 ppm; HR-MS (EI) m/z : calcd. for $\text{C}_{19}\text{H}_{20}\text{FNO}$ 297.1529, found 297.1523

REFERENCES:

- (1) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L., *Acc. Chem. Res.* **1998**, *31*, 805.
- (2) Hartwig, J. F. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2046.
- (3) Siu, T.; Yudin, A. K. *J. Am. Chem. Soc.* **2002**, *124*, 530.
- (4) Caiazzo, A.; Dalili, S.; Yudin, A. K. *Org. Lett.* **2002**, *4*, 2597.
- (5) Padwa, A.; Woolhouse, A. D.; *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 7, p 47.
- (6) Tanner, D. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599.
- (7) Kelly, J. W.; Eskew, N. L.; Evans, S. A. *J. Org. Chem.* **1986**, *51*, 95.
- (8) Kuhnau, D.; Thomasen, I.; Jorgensen, K. A. *J. Chem. Soc. Perkin Trans. 1* **1996**, 1167.
- (9) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 676.
- (10) Rasmussen, K. G.; Jorgensen, K. A. *J. Chem. Soc. Chem. Com.* **1995**, 1401.
- (11) Casarrubios, L.; Perez, J. A.; Brookhart, M.; Templeton, J. L. *J. Org. Chem.* **1996**, *61*, 8358.
- (12) Aggarwal, V. K.; Stenson, R. A.; Jones, R. V. H.; Fieldhouse, R.; Blacker, J. *Tetrahedron Lett.* **2001**, *42*, 1587.
- (13) Louie, J.; Paul, F.; Hartwig, J. F.; *Organometallics* **1996**, *15*, 2794.
- (14) Christoffers, J.; Schulze, Y.; Pickardt, J. *Tetrahedron* **2001**, *57*, 1765.
- (15) Seko, S.; Tani, N. *Tetrahedron Lett.* **1998**, *39*, 8117.
- (16) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240.
- (17) Lin, B. L.; Clough, C. R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 2890.
- (18) Alper, H.; Perera, C. P.; Ahmed, F. R. *J. Am. Chem. Soc.* **1981**, *103*, 1289.

- (19) Calet, S.; Urso, F.; Alper, H. *J. Am. Chem. Soc.* **1989**, *111*, 931.
- (20) Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077.
- (21) For other known metal-aziridine species, see: Yamamoto, Y.; Asao, N.; Meguro, M.; Tsukada, N.; Nemoto, H.; Sadayori, N.; Wilson, J. G.; Nakamura, H. *J. Chem. Soc. Chem. Com.* **1993**, 1201.
- (22) Christoffers, J.; Schulze, Y.; Pickardt, J. *Tetrahedron* **2001**, *57*, 1765
- (23) Barluenga, J.; Alonso-Cires, L.; Asensio, G. *Synthesis* **1981**, 376
- (24) Seko, S.; Tani, N. *Tetrahedron Lett.* **1998**, *39*, 8117
- (25) Kuhnau, D.; Thomasen, I.; Jorgensen, K. A. *J. Chem. Soc. Perkin Trans. 1* **1996**, 1167
- (26) Sekar, G.; Singh, V. K. *J. Org. Chem.* **1999**, *64*, 2537

Chapter 2

One-pot Reduction-Aldol Reaction of Esters and Synthesis of Aziridine Building Blocks

Abstract

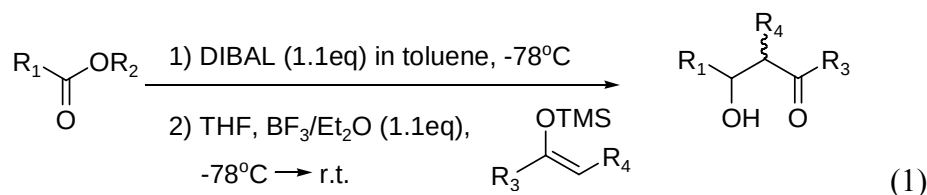
A new protocol was developed for making aldol adducts in a one-pot reaction between esters and silyl enol ethers in the presence of DIBAL-H without isolating the intermediate aldehydes. Lewis acid activation of the initially formed aluminated hemiacetals produces highly reactive electrophilic aldehyde equivalents *in situ*. Using this protocol, various aldol adducts can be readily obtained in up to 90% yield on a large scale. The obtained aldols can be converted to the corresponding β -ketoaziridines. The double bond functionalization of this aziridine (R=H) can be achieved by the Heck reaction or by the cross-metathesis. These aziridine building blocks are used as the starting materials of the oxidative cycloamination described in chapter 3.

Introduction

Aldol reaction is one of the most important carbon-carbon bond forming processes in contemporary organic chemistry.¹ In addition, the aldol fragments or its derivatives are often present in the structures of natural products and pharmaceuticals.² The typical aldol reaction is accomplished by reacting an aldehyde and an enolate in the presence of a Lewis acid.^{3,4} The aldehydes are prepared by either oxidation of alcohols or by reduction of esters. The traditional method of generating aldol products from the ester-containing starting materials is based on reducing the ester to the corresponding aldehyde using DIBAL-H followed by treating the isolated aldehyde with a silyl enol ether in the presence of a suitable Lewis acid.⁵ However, aldehyde isolation can be troublesome, especially on a large scale, because of the sensitivity of aldehydes and/ difficulty commonly encountered during their purification. In this regard, one-pot processes that avoid isolation of aldehyde building blocks are highly desirable, especially in the case of low boiling point aldehydes. Reissig reported an example of one-pot reaction of lactones to aldol derivatives, however, in that case the worse result was obtained than the corresponding stepwise reaction and, to the best of my knowledge, one-pot reactions of esters to aldols have not been documented.⁶

Results and Discussion

At the outset of the investigation, the hope was that the silyl enol ether would attack the aluminated hemiacetal which is formed upon initial reduction of the aldehyde with DIBAL.⁷ Using this protocol, ethyl 4-pentenoate was converted to the corresponding aldol in excellent yield by the DIBAL reduction followed by the *in situ* aldol reaction with 1-phenyl-1-(trimethylsilyloxy)ethylene in the presence of boron trifluoride without isolating the corresponding aldehyde (eq 1). Remarkably, α,β -unsaturated ketone was not observed in this reaction at all. The presence of boron trifluoride was found to be mandatory as no reaction took place in its absence. It is noteworthy that this reaction condition is not sensitive as opposed to other aldol reactions such as titanium chloride promoted reaction.

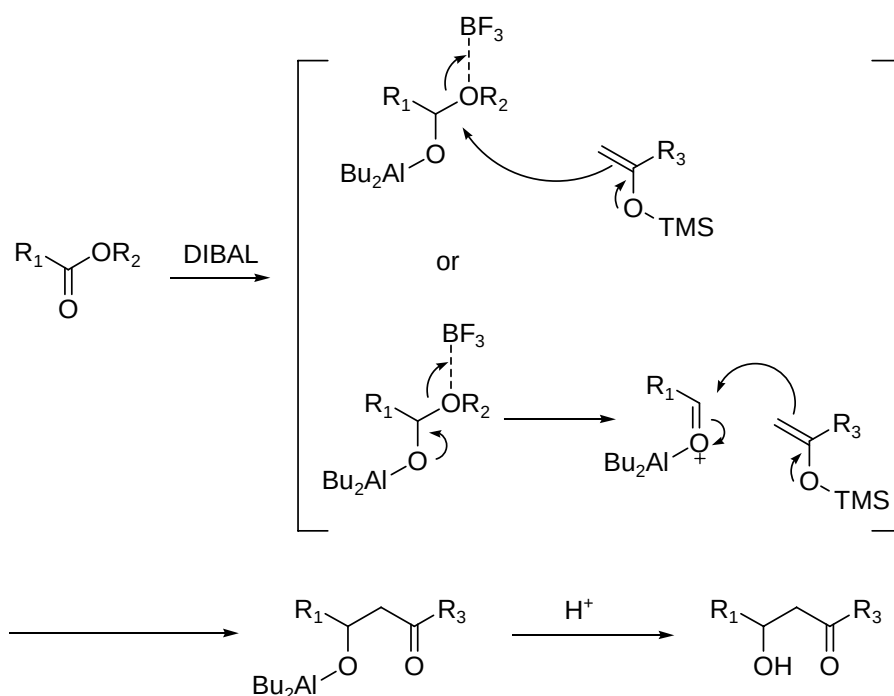


The scope of this reduction-aldol reaction was investigated and the results are shown in Table 1. Primary esters gave good to excellent yields (Table 1, entry 1, 2, 3 and 6), while secondary esters gave lower yields (Table 1, entry 4). The α,β -unsaturated esters gave reduced alcohols instead of the aldol (Table 1, entry 5). Both aromatic and aliphatic groups R_3 gave comparable yields (Table 1, entry 3 and 6). The 1,1,2-trisubstituted enolates gave lower yields with low diastereoselectivities, while typical Mukaiyama aldol reaction gives high diastereoselectivity (Table 1, entry 7).

The proposed mechanism is shown in Scheme 1. The ester is first reduced by DIBAL-H to give the aluminated hemiacetal, which coordinates to boron trifluoride, producing a highly electrophilic aluminated intermediate. There are two possible routes from this complex: in the first possibility, the silyl enol ether attacks the complex to give the aluminated aldol, which is hydrolyzed to the corresponding aldol. In the other route, the initially produced complex is decomposed to give aluminated aldehyde, which is subsequently attacked by the silyl enol ether to give the aluminated aldol adduct, which is subsequently hydrolyzed to the corresponding aldol. As a result, the aldol adduct is produced in a one-pot reaction from the corresponding ester without isolating the intermediate aldehyde.

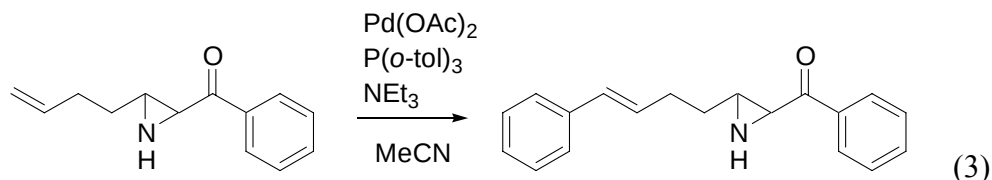
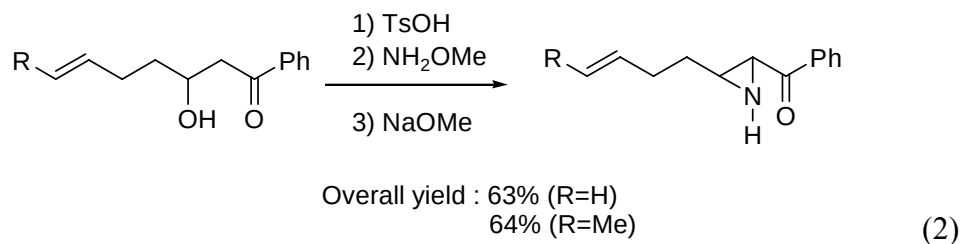
Table 1. The Scope of the Reduction-Aldol Reaction.

Entry	R ₁	R ₂	R ₃	R ₄	Yield
1 ^b	CH ₂ =CH(CH ₂) ₂ -	Et	Ph	H	90
2 ^b	CH ₃ CH ₂ =CH(CH ₂) ₂ -	Et	Ph	H	89
3	PhCH ₂ -	Me	Ph	H	75
4	cyclopropyl	Me	Ph	H	25
5	PhCH=CH-	Me	Ph	H	0
6	PhCH ₂ -	Me	Me	H	63
7	CH ₂ =CH(CH ₂) ₂ -	Et	Ph	Me	38 ^a
^a diastereo ratio=1.4:1					
^b 1.1eq of TMS ether was used. For the others 1.5eq of TMS ether was used.					

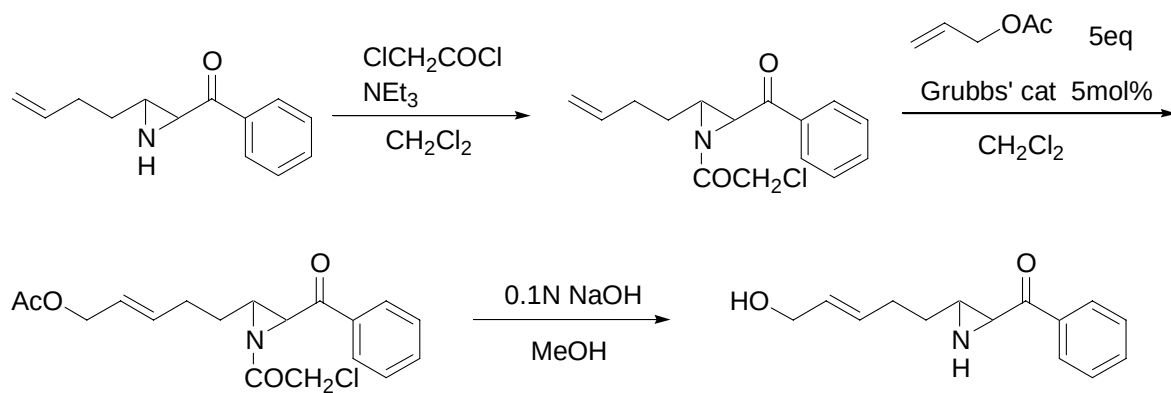
Scheme 1. Proposed mechanism of the reduction-aldol reaction.

The obtained aldols can be converted to the corresponding β -ketoaziridines (eq 2). The double bond functionalization of this aziridine ($R=H$) can be achieved by the Heck reaction or by the cross-metathesis. In the case of metathesis, protection of the NH aziridine was found to be mandatory,

whereas the Heck reaction took place on the parent NH system using $\text{Pd}(\text{OAc})_2/\text{P}(\text{o-tolyl})_3$ catalyst (eq 3, Scheme 2). These aziridines are used as the starting materials of the oxidative cycloamination described in chapter 3.



Scheme 2. Double bond functionalization of aziridines by the cross-metathesis.



Conclusion

A new method was developed to synthesize aldol adducts from esters in a one-pot reaction without isolating the corresponding aldehydes. The obtained aldols can be converted to the corresponding β -ketoaziridines, which are used as the starting materials of the oxidative cycloamination described in chapter 3. This study also shows the particularly exciting possibility of applying the highly reactive aluminated intermediates in other types of nucleophilic addition processes.

Experimental Section

3-Hydroxy-1-phenylhept-6-en-1-one (Table 1, entry 1): To a mixture of ethyl 4-pentenoate (10 g, 78 mmol) and toluene (100 mL), 1.5M DIBAL-H in toluene (57 mL, 86 mmol) was slowly added at -78 °C, and the mixture was stirred for 1 hour at -78 °C. To this reaction mixture, THF (240 mL), boron trifluoride diethyl ether (11 mL, 86 mmol), and 1-phenyl-1-trimethylsilyloxyethylene (16.5 g, 86 mmol) were successively added at -78 °C, and the reaction mixture was allowed to warm up to around 0 °C with stirring. After completion (judged by TLC), 1N HCl (240 g), cooled in an ice bath, was added to the reaction mixture and the organic layer and the aqueous layer were separated and the aqueous layer was extracted with toluene (50 mL). The combined organic layers were washed with water (150 mL) and dried over sodium sulfate. The solvent was removed in vacuo and 3-hydroxy-1-phenylhept-6-en-1-one was obtained as crude yellow oil (16.2 g). The purity was 88 % and containing 12 % of acetophenone (yield: 90%). ¹H NMR (CDCl₃, 300MHz): δ 7.97-8.00 ppm (m, 2H), 7.59-7.64 ppm (m, 1H), 7.48-7.53 ppm (m, 2H), 5.83-5.96 ppm (m, 1H), 5.00-5.14 ppm (m, 2H), 4.24-4.32 ppm (m, 1H), 3.05-3.24 ppm (m, 2H), 2.20-2.34 ppm (m, 2H), 1.58-1.82 ppm (m, 2H); ¹³C NMR (CDCl₃, 75MHz): δ 200.8 ppm, 138.3 ppm, 136.8 ppm, 133.6 ppm, 128.7 ppm, 128.1 ppm, 115.0 ppm, 67.2 ppm, 45.0 ppm, 35.6 ppm, 29.8 ppm

3-Hydroxy-1-phenyloct-6-en-1-one (Table 1, entry 2): ¹H NMR (CDCl₃, 300MHz): δ 7.97-8.01 ppm (m, 2H), 7.58-7.65 ppm (m, 1H), 7.51-7.53 ppm (m, 2H), 5.43-5.57 ppm (m, 2H), 4.22-4.31 ppm (m, 1H), 3.04-3.26 ppm (m, 3H), 2.11-2.28 ppm (m, 2H), 1.58-1.78 ppm (m, 5H); ¹³C NMR (CDCl₃, 100MHz): δ 200.9 ppm, 136.8 ppm, 133.5 ppm, 130.7 ppm, 128.7 ppm, 128.1 ppm, 125.6 ppm, 67.3 ppm, 45.0 ppm, 36.3 ppm, 28.7 ppm, 17.9 ppm

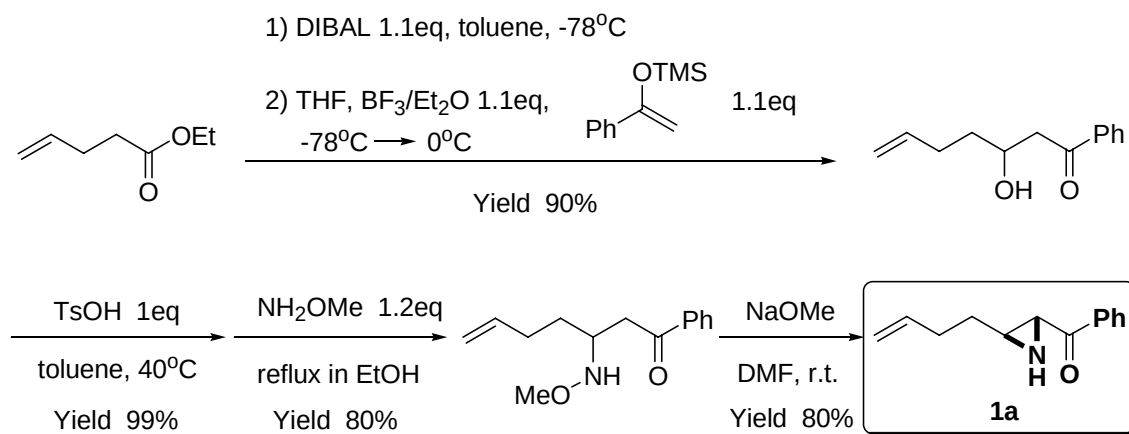
Phenyl (2-hydroxy-3-phenyl)propyl ketone (Table 1, entry 3): ¹H NMR (CDCl₃, 300MHz): δ 7.93-7.97 ppm (m, 2H), 7.58-7.64 ppm (m, 1H), 7.47-7.52 ppm (m, 2H), 7.25-7.39 ppm (m, 5H), 4.48-4.58 ppm (m, 1H), 2.84-3.24 ppm (m, 5H); ¹³C NMR (CDCl₃, 75MHz): δ 200.6 ppm, 138.1 ppm, 136.8 ppm, 133.6 ppm, 129.5 ppm, 128.7 ppm, 128.6 ppm, 128.1 ppm, 126.6 ppm, 69.0 ppm, 44.1 ppm, 43.0 ppm

Phenyl (3-cyclopropyl-2-hydroxy)propyl ketone (Table 1, entry 4): ^1H NMR (CDCl_3 , 400MHz): δ 8.03-8.06 ppm (m, 2H), 7.63-7.68 ppm (m, 1H), 7.51-7.57 ppm (m, 2H), 3.53-3.59 ppm (m, 1H), 3.24-3.43 ppm (m, 3H), 1.06-1.14 ppm (m, 1H), 0.48-0.71 ppm (m, 3H), 0.26-0.33 ppm (m, 1H); ^{13}C NMR (CDCl_3 , 75MHz): δ 200.7 ppm, 136.9 ppm, 133.5 ppm, 128.7 ppm, 128.2 ppm, 72.6 ppm, 45.1 ppm, 16.9 ppm, 3.4 ppm, 2.2 ppm

Methyl (2-hydroxy-3-phenyl)propyl ketone (Table 1, entry 6): ^1H NMR (CDCl_3 , 300MHz): δ 7.23-7.38 ppm (m, 5H), 4.31-4.36 ppm (m, 1H), 2.97 ppm (d, $J=3.6$ Hz, 1H), 2.73-2.93 ppm (m, 2H), 2.60-2.63 ppm (m, 2H), 2.19 ppm (s, 3H); ^{13}C NMR (CDCl_3 , 75MHz): δ 209.5 ppm, 137.9 ppm, 129.4 ppm, 128.6 ppm, 126.6 ppm, 68.6 ppm, 49.1 ppm, 42.9 ppm, 30.8 ppm

3-Hydroxy-2-methyl-1-phenylhept-6-en-1-one (E/Z mixture; Table 1, entry 7): ^1H NMR (CDCl_3 , 300MHz): δ 7.96-8.00 ppm (m, 2H), 7.58-7.64 ppm (m, 1H), 7.48-7.54 ppm (m, 2H), 5.79-5.94 ppm (m, 1H), 4.97-5.12 ppm (m, 2H), 4.07-4.10 ppm (m, 1.4/2.4H), 3.90-3.94 ppm (m, 1/2.4H), 3.54-3.64 ppm (m, 1/2.4H), 3.46-3.53 ppm (m, 1.4/2.4H), 3.19 ppm (br, 1.4/2.4H), 3.03 ppm (br, 1/2.4H), 2.15-2.38 ppm (m, 2H), 1.49-1.86 ppm (m, 2H), 1.29 ppm (d, $J=4.5$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75MHz): δ 205.8 ppm, 205.7 ppm, 138.4 ppm, 138.3 ppm, 136.6 ppm, 135.9 ppm, 133.5 ppm, 133.4 ppm, 128.8 ppm, 128.8 ppm, 128.5 ppm, 128.4 ppm, 115.0 ppm, 114.9 ppm, 73.5 ppm, 70.8 ppm, 45.8 ppm, 44.7 ppm, 34.1 ppm, 33.6 ppm, 30.3 ppm, 30.1 ppm, 15.5 ppm, 11.3 ppm

(3-But-3-enyl-*trans*-aziridin-2-yl)-phenylmethanone⁸

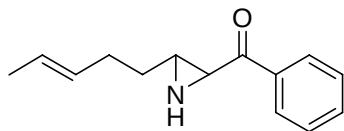


A mixture of the aldol (18.0 g) obtained by the method described above, *p*-toluenesulfonic acid hydrate (16.7 g, 88 mmol), and toluene (200 mL) was heated to 40 °C for 4 hours. After completion judged by TLC, sodium sulfate was added to the reaction mixture and filtered, and the solid residue was washed by toluene (40 mL). The solvent was removed from the filtrate in vacuo and α,β -unsaturated ketone was obtained as crude yellow oil (15.5 g).

A mixture of the α,β -unsaturated ketone (15.5 g), 12% NH_2OMe in ethanol (33 g, 84 mmol), and ethanol (100 mL) was heated to gentle reflux for 4 hours. After completion judged by TLC, the solvent was removed in vacuo. The residue was added to DMF (100 mL), and this solution was added to the mixture of sodium methoxide (9.3g, 172 mmol) and DMF (250 mL) at room temperature and the reaction mixture was stirred for 1 hour. Dichloromethane (1000 mL) and water (670 mL) was added to the reaction mixture. The organic layer and the aqueous layer were separated, and the aqueous layer was extracted with dichloromethane (670 mL). The combined organic layers were washed with water (330 mL) and dried over sodium sulfate. The solvent was removed in vacuo and the residue was purified on a silica gel column (hexane/ethyl acetate = 7/3), to give 9.2 g of (3-but-3-enyl-*trans*-aziridin-2-yl)-phenylmethanone (**1a**, total yield: 53% vs. ethyl 4-pentenoate).

^1H NMR (CDCl_3 , 300MHz): δ 8.00-8.03 ppm (m, 2H), 7.58-7.64 ppm (m, 1H), 7.48-7.53 ppm (m, 2H), 5.76-5.90 ppm (m, 1H), 4.95-5.06 ppm (m, 2H), 3.27 ppm (br, 1H), 2.11-2.29 ppm (m, 4H), 1.65-1.72 ppm (m, 2H); ^{13}C NMR (CDCl_3 , 75MHz): δ 197.3 ppm, 137.7 ppm, 136.3 ppm, 133.9 ppm, 129.0 ppm, 128.4 ppm, 115.6 ppm, 42.9 ppm, 40.0 ppm, 32.8 ppm, 31.5 ppm

(*trans*-3-Pent-3-enyl-*trans*-aziridin-2-yl)-phenylmethanone



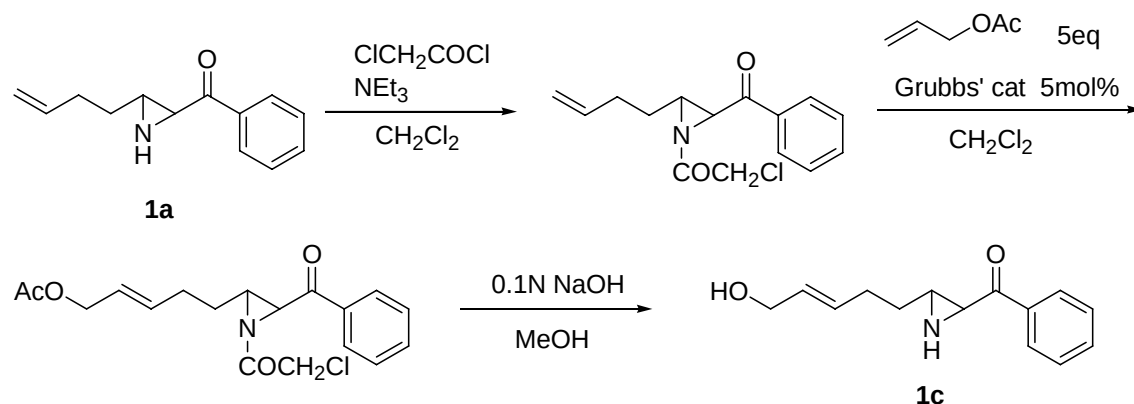
Starting from *trans*-ethyl 4-hexenoate in the same way above (total yield: 57%).

trans-Ethyl 4-hexenoate was synthesized as follows: a mixture of 3-buten-2-ol (720 mg, 10 mmol) and triethyl orthoacetate (4.86 g, 30 mmol) was heated to 135 °C and stirred overnight. Pentane (20 mL) and water (20 mL) were added to the reaction mixture and the mixture was stirred at room

temperature for 3 days. After separation, the water layer was extracted with pentane (10 mL). The combined organic layers were washed with water (10 mL) and dried over sodium sulfate. The solvent was removed in vacuo and the residue was purified by distillation, to give 700 mg of *trans*-ethyl 4-hexenoate (yield: 49%).

^1H NMR (CDCl_3 , 300MHz): δ 8.03-8.06 ppm (m, 2H), 7.54-7.67 ppm (m, 1H), 7.52-7.56 ppm (m, 2H), 5.43-5.52 ppm (m, 2H), 3.30 ppm (br, 1H), 2.13-2.26 ppm (m, 4H), 1.59-1.75 ppm (m, 5H); ^{13}C NMR (CDCl_3 , 75MHz): δ 197.3 ppm, 136.2 ppm, 133.6 ppm, 130.0 ppm, 128.8 ppm, 128.2 ppm, 126.0 ppm, 42.9 ppm, 39.9 ppm, 33.3 ppm, 30.2 ppm, 17.9 ppm

[3-(*trans*-5-Hydroxy-pent-3-enyl)-*trans*-aziridin-2-yl]-phenylmethanone



To a mixture of (3-but-3-enyl-*trans*-aziridin-2-yl)-phenylmethanone (**1a**, 500mg, 2.5 mmol), dichloromethane (10 mL), and triethylamine (377 mg, 3.7 mmol) was added chloroacetyl chloride (421 mg, 3.7 mmol) at the temperature of ice bath. The reaction mixture was stirred for 2 hours in ice bath. After completion judged by TLC, the reaction mixture was washed with water (5 mL), and was dried over sodium sulfate. The solvent was removed in vacuo and the residue was purified on a silica gel column (hexane/ethyl acetate = 7/3), to give 670 mg of *N*-protected aziridine (yield: 97%).

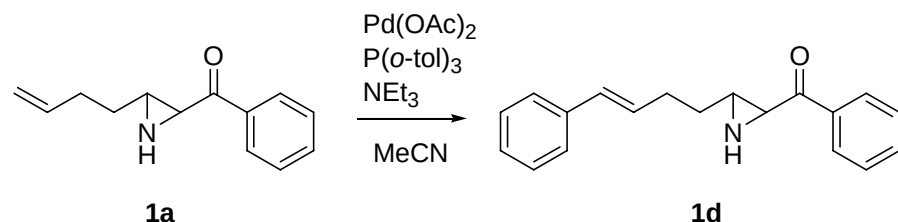
A mixture of this *N*-protected aziridine (139 mg, 0.5 mmol), allyl acetate (270 mg, 2.7 mmol), 2nd generation Grubbs' catalyst⁹ (23 mg, 0.027 mmol) and dichloromethane (7 mL) was heated to 40 °C for 1.5 hours. After the reaction, the solvent was removed in vacuo and the residue was purified on a silica

gel column (hexane/ethyl acetate = 7/3), to give 82 mg of the cross-metathesis product and 50 mg of the starting material (yield: 47%, conversion: 64%, selectivity: 73%).

A mixture of this product (201 mg, 0.57 mmol), methanol (20 mL), and 0.1N aq. NaOH (20 mL) was stirred at room temperature. Methanol was removed in vacuo and dichloromethane (20 mL) and water (10 mL) was added to the residue. The water layer was extracted with dichloromethane (10 mL) and the combined organic layers were washed with water (10 mL), and were dried over sodium sulfate. The solvent was removed in vacuo, to give 128 mg of [3-(*trans*-5-hydroxy-pent-3-enyl)- *trans*-aziridin-2-yl]-phenylmethanone (**1c**, yield: 96%, containing 16% of *cis*-olefin product).

^1H NMR (CDCl_3 , 300MHz): δ 8.05-8.10 ppm (m, 2H), 7.67-7.71 ppm (m, 1H), 7.55-7.60 ppm (m, 2H), 5.62-5.82 ppm (m, 2H), 4.10 ppm (br, 2H), 3.32 ppm (br, 1H), 2.15-2.38 ppm (m, 4H), 2.03 ppm (br, 1H), 1.70-1.77 ppm (m, 2H); ^{13}C NMR (CDCl_3 , 75MHz): δ 197.0 ppm, 136.1 ppm, 133.8 ppm, 131.2 ppm, 130.2 ppm, 128.9 ppm, 128.2 ppm, 63.4 ppm, 42.7 ppm, 39.7 ppm, 32.8 ppm, 29.9 ppm

[3-(*trans*-4-Phenyl-but-3-enyl)-*trans*-aziridin-2-yl]-phenylmethanone



A mixture of acetonitrile (25 mL), triethylamine (500 mg, 5 mmol), tri-*o*-tolylphosphine (17 mg, 0.056 mmol), palladium (II) acetate (6 mg, 0.027 mmol), (3-but-3-enyl-*trans*-aziridin-2-yl)-phenylmethanone (**1a**, 500 mg, 2.5 mmol), and iodobenzene (1 g, 5 mmol) was heated to 50 °C for overnight. After the reaction, the solvent was removed in vacuo and the residue was purified on a silica gel column (hexane/ethyl acetate = 7/3), to give 402 mg of [3-(*trans*-4-phenyl-but-3-enyl)-*trans*-aziridin-2-yl]-phenylmethanone (**1d**). (yield: 58%)

^1H NMR (CDCl_3 , 400MHz): δ 8.04-8.02 ppm (m, 2H), 7.60-7.64 ppm (m, 1H), 7.45-7.48 ppm (m, 2H), 7.30-7.35 ppm (m, 4H), 7.22-7.27 ppm (m, 1H), 6.45 ppm (d, J = 16 Hz, 1H), 6.28 ppm (dt, J =16

Hz, 6.8 Hz, 1H), 3.35 ppm (br, 1H), 2.41-2.53 ppm (m, 2H), 2.23-2.30 ppm (m, 1H), 2.15-2.21 ppm (m, 1H), 1.74-1.92 ppm (m, 2H); ^{13}C NMR (CDCl_3 , 100MHz): δ 197.1 ppm, 137.5 ppm, 136.1 ppm, 133.7 ppm, 130.9 ppm, 129.3 ppm, 128.8 ppm, 128.5 ppm, 128.2 ppm, 127.1 ppm, 126.0 ppm, 42.7 ppm, 39.9 ppm, 33.1 ppm, 30.6 ppm

REFERENCES:

- (1) For reviews, see: (a) Heathcock, C. H. *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon, Oxford, 1991; Vol. 4, 133-275; (b) Braun, M. *Houben-Weyl: Methods of Organic Chemistry*; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; George Thieme Verlag, Stuttgart, 1995; Vol. E21, 1603
- (2) For example, see: (a) Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531; (b) Heathcock, C. H.; McLaughlin, M.; Hubbs, J. L.; Wallace, G. A.; Scott, R.; Claffey, M. M.; Hayes, C. J.; Ott, G. R. *J. Am. Chem. Soc.* **2003**, *125*, 12844; (c) Kiyooka, S.; Shahid, K. A.; Goto, F.; Okazaki, M.; Shuto, Y. *J. Org. Chem.* **2003**, *68*, 7967; (d) Gaul, C.; Njardarson, J. T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 6042; (e) Kalesse, M.; Chary, K. P.; Quitschalle, M.; Burzlaff, A.; Kasper, C.; Scheper, T. *Chem. A Euro. J.* **2003**, *9*, 1129
- (3) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503
- (4) For recent development of the aldol reaction, for example, see: (a) Yanagisawa, A.; Sekkiguchi, T. *Tetrahedron Lett.* **2003**, *44*, 7163; (b) Nagasawa, T.; Fujiwara, H.; Mukaiyama, T. *Chem. Lett.* **2003**, *44*, 6187; (c) Calter, M. A.; Orr, R. K. *Tetrahedron Lett.* **2003**, *44*, 5699
- (5) For example, see: (a) Evans, D. A.; Hu, E.; Burch, J. D.; Jaeschke, G. *J. Am. Chem. Soc.* **2002**, *124*, 5654; (b) Wong, Y.-S. *Chem. Commun.* **2002**, 686; (c) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033
- (6) Schmitt, A.; Reissig, H.-U. *Euro. J. Org. Chem.* **2001**, 1169
- (7) For one-pot reduction-Wittig reaction of esters, see: Takacs, J. M.; Helle, M. A.; Seely, F. L. *Tetrahedron Lett.* **1986**, *27*, 1257
- (8) Seko, S.; Tani, N. *Tetrahedron Lett.* **1998**, *39*, 8117.
- (9) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.

Chapter 3

Oxidative Cycloamination of Olefins with Aziridines

Abstract

Highly reactive [5,3]- and [6,3]- bicyclic aziridines can be readily prepared from the corresponding NH-aziridines and *N*-bromosuccinimide by intramolecular oxidative cycloamination of olefins. These compounds, including surprisingly stable exo-methylene bicyclic aziridines, provide versatile synthetic entries into a wide range of pyrrolidine- and piperidine-containing heterocycles.

Introduction

Selective transfer of nitrogen-containing fragments to readily available olefins is one of the fundamental ways of incorporating nitrogen atoms into the frameworks of organic molecules.¹ The interest in synthetic applications of functionalized aziridines² has led to the investigation of their utility in the synthesis of larger nitrogen-containing heterocycles. Known for the difficulties in controlling their reactivity, aziridines are rarely used in complex molecule synthesis.³ If functionalization of an aziridine-containing building block is required during synthesis, nitrogen protection/deprotection sequences are unlikely to be successful due to aziridines' susceptibility to acidic reagents and harsh reaction conditions.

It was reasoned that despite its basic character, aziridine nitrogen should be quite resistant to oxidative degradation so that transformations of aziridine-containing building blocks can be realized. At the outset of the previous investigations, a significant (0.8V) difference had been observed in the oxidation potential of cyclohexene imine compared to the value recorded for a typical secondary amine such as piperidine, known for its low stability towards oxidation.⁴ This finding can be explained on the basis of thermodynamically uphill formation of the iminium species in the case of aziridine oxidation which opens a range of opportunities to explore the NH-containing aziridines in oxidative nitrogen transfer under non-acidic conditions.⁵ Of particular value are intramolecular versions of such amination protocols (eq 1) as they should allow for straightforward synthesis of a wide range of larger ring heterocycles. The resulting enamine-containing compounds have not received attention in synthesis.

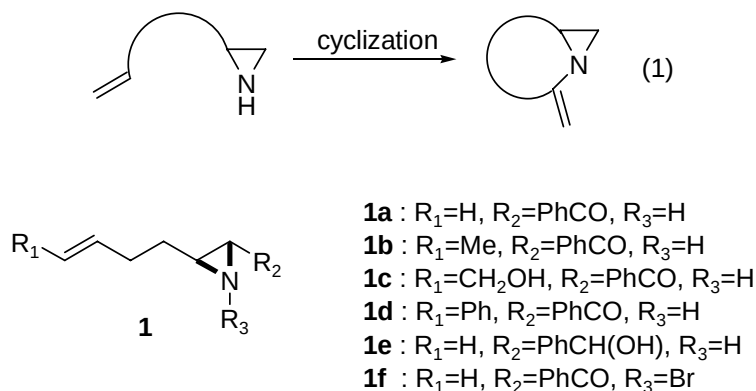
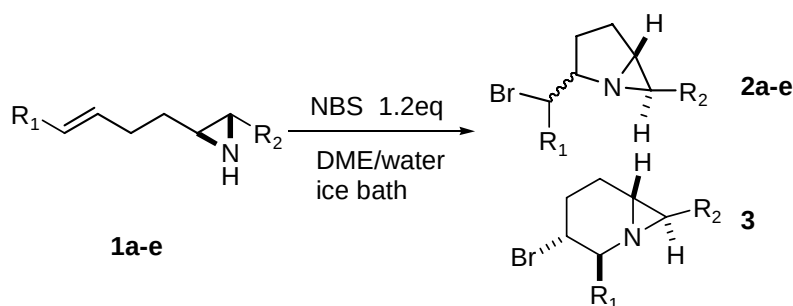


Figure 1. Aziridine-containing building blocks.

Toward this goal, aziridine-containing building blocks (**1a-e**, Figure 1) were synthesized from commercially available starting materials as described in Chapter 2. The NH portion of **1a** is separated from the olefin by the $(CH_2)_2$ linker, positioned towards cyclization to give pyrrolidine- and piperidine-containing heterocycles. The pyrrolidine and piperidine rings are incorporated into the structures of a wide range of natural products and pharmaceuticals which makes them an important class of targets for stereoselective synthesis.⁶ If relative stereochemistry of the products can be controlled during cyclization and subsequent ring-opening steps, the oxidative aziridine cycloamination methodology should be a valuable addition to the established methods.⁷

Results and Discussion

It was revealed that aziridines **1a** are converted into 1-azabicyclo[3.1.0]hexane derivatives **2a** in good yields upon treatment with *N*-bromosuccinimide (NBS) in DME/water.⁸ The TLC analysis indicated complete conversion of the NH aziridine to the corresponding N-Br species within the first 2 minutes of the reaction.⁹ The bromoamine **1f** (Figure 1) thus formed attacked the double bond of the molecule to give the cycloamination product. Table 1 shows the scope of the reaction. The products are [5,3] bicyclic rings in the case of the terminal double bond-containing substrates, whereas aryl-substituted double bonds preferentially give six-membered ring products.

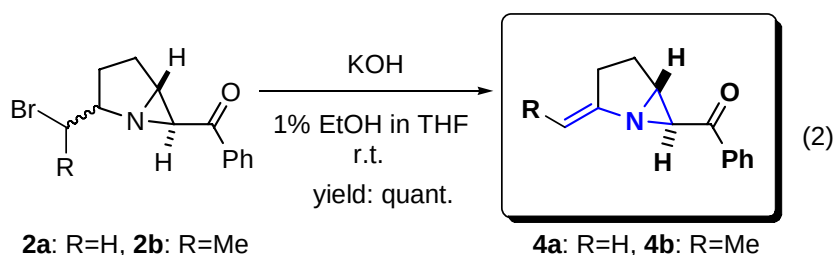
Table 1. Intramolecular cycloamination of olefins.

Entry	R ₁	R ₂	Product ^b	Yield ^a
1	H	PhCO	2a	76
2	Me	PhCO	2b	51
3	CH ₂ OH	PhCO	2c	54
4	Ph	PhCO	3 ^c	67
5	H	PhCH(OH)	2e	55

^a The diastereomeric ratios were as follows: for **2a**, 41:59; for **2b**, 33:67; for **2c**, 33:67; for **3**, 19:81;

^b Structures were determined by NMR analysis (NOE, HMBC and COSY); ^c23% of **2d** was also isolated.

The resulting bicycles **2a-b** were converted into exo-methylene bicyclic aziridines **4** in quantitative yields by dehydrobromination (eq 2). Surprisingly high stability of the resulting enamines is attributed to the orthogonal orientation of the nitrogen electron pair in relation to the double bond, evident from the single crystal X-ray analysis (Figure 2). The X-ray data shows that the bond length between C(6A) and C(7A) is 1.32Å, which is typical of an olefin system. Worthy of note, this interesting and uncommon structural motif is present in azinomycin family of antibiotics.¹⁰



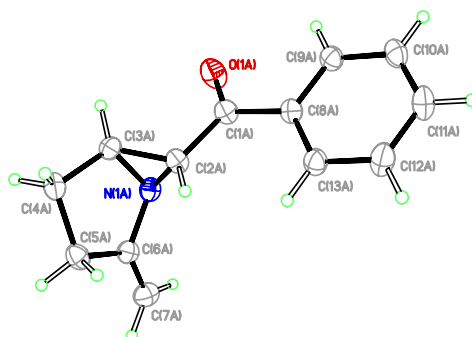
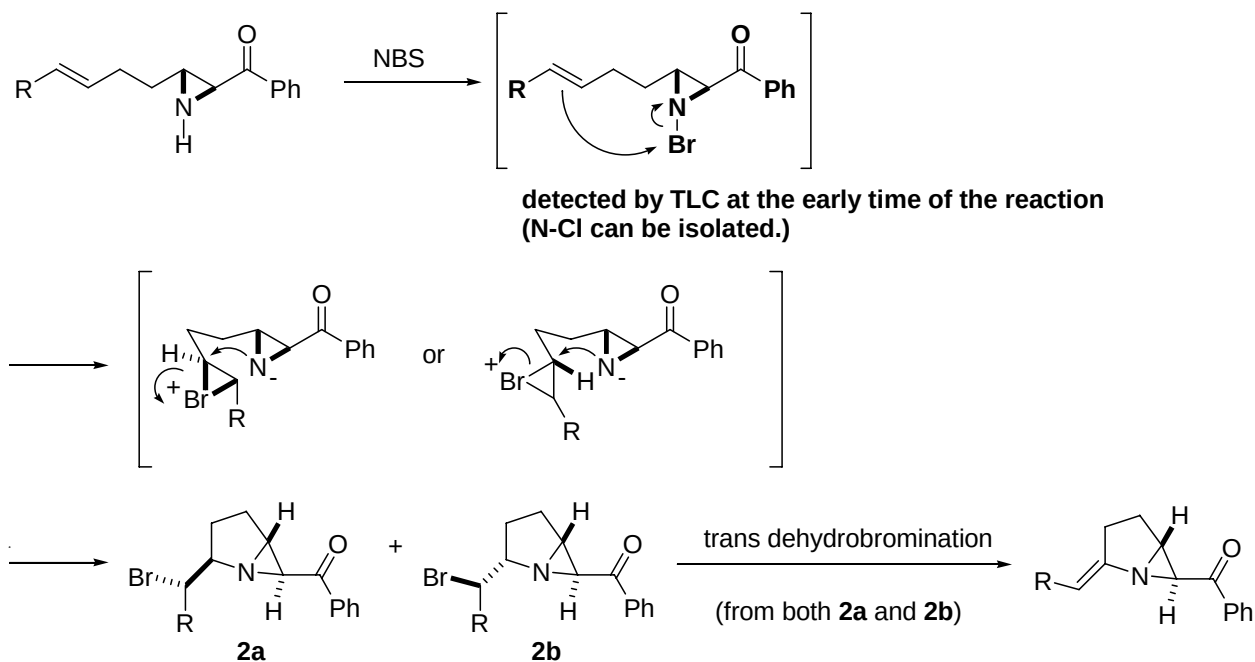


Figure 2. The X-ray structure of bicyclic aziridine **4a**.

The proposed mechanism is shown in Scheme 1. The bromoamine formed at first is attacked by double bond to form three-membered ring containing bromo cation. This intermediate has two conformations and each conformation gives corresponding diastereomer after the attack of nitrogen on aziridine ring. Both diastereomers give same product after trans-dehydrobromination. In case of $R=Ar$, the nitrogen on aziridine ring preferably attacks more electrophilic benzylic position, to give six-membered ring.

Scheme 1. Plausible mechanism of haloamidation–dehydrobromination.



Conclusion

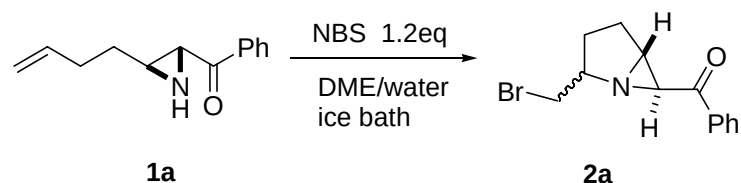
It has been shown that highly reactive [5,3]- and [6,3]- bicyclic aziridines can be readily prepared from the corresponding NH-aziridines and *N*-bromosuccinimide by intramolecular oxidative cycloamination of olefins. The resulting bicyclic aziridines were converted into surprisingly stable exo-methylene bicyclic aziridines by dehydrobromination. The usabilities of these reactive bicyclic aziridines will be described in Chapter 4.

Experimental Section

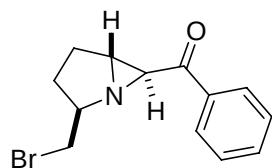
General: The chemicals were purchased from Aldrich Chemical Co., Strem Chemical Co., Fischer Scientific Ltd., and Lancaster and were used without further purification. In experiments requiring anhydrous solvents: ether, toluene, hexanes, acetonitrile, and dichloromethane were purified using the method described by Grubbs (Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518). Tetrahydrofuran (THF) was distilled over sodium-benzophenone ketyl under argon. Unless otherwise stated, all reactions were performed under nitrogen or argon atmosphere using flame-dried glassware.

Nuclear magnetic resonance spectra: ^1H and ^{13}C NMR spectra were recorded on either Mercury 300, Varian Gemini 300, or VRX-S (Unity) 400 spectrometer. ^1H NMR spectra were referenced to residual CDCl_3 (δ 7.27 ppm) and ^{13}C NMR spectra were referenced to CDCl_3 (δ 77.23 ppm). Peak multiplicities are designated by the following abbreviations: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets; br, broad; and *J*, coupling constant in Hz.

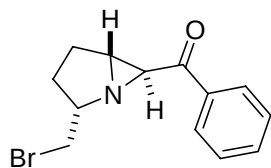
Chromatography: Analytical thin layer chromatography (TLC) was performed on Macherey Nagel pre-coated glass-backed TLC plates (SIL G/UV₂₅₄, 0.25mm) purchased from Rose Scientific Limited and visualized by UV lamp (254 nm) or iodine. Solvent ratios for R_f values are reported as v/v. Column chromatography was carried out using Silicycle 230-400 mesh silica gel.

Procedure for intramolecular cycloamination (Table 1, Entry 1):

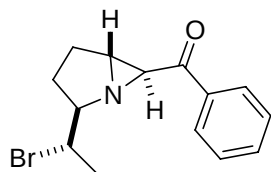
To a mixture of (3-but-3-enyl-*trans*-aziridin-2-yl)-phenylmethanone (**1a**, 2.5 g, 12.4 mmol), dimethoxyethane (100 mL), and water (25 mL) was added *N*-bromosuccinimide (2.65 g, 1.49 mmol) at the temperature of ice bath and the mixture was stirred for 2 hours in ice bath. After completion judged by TLC, 10% aq. Na₂SO₃ (50mL) and diethyl ether (100 mL) were added. The organic layer and the aqueous layer were separated, and the aqueous layer was extracted with diethyl ether (50 mL). The combined organic layers were dried over sodium sulfate and the solvent was removed in vacuo at lower than room temperature. The residue was purified on a silica gel column (hexane/ethyl acetate = 6/4), to give 1.08g of (2*R*^{*},5*R*^{*},6*S*^{*})-(2-bromomethyl-1-aza-bicyclo[3.1.0]hex-6-yl)-phenylmethanone and 1.56g of (2*S*^{*},5*R*^{*},6*S*^{*})-(2-bromomethyl-1-aza-bicyclo[3.1.0]hex-6-yl)-phenylmethanone, respectively (**2a**, combined yield: 76%, the ratio between two diastereomers: 41:59).

(2*R*^{*},5*R*^{*},6*S*^{*})-(2-Bromomethyl-1-azabicyclo[3.1.0]hex-6-yl)-phenylmethanone (2a)

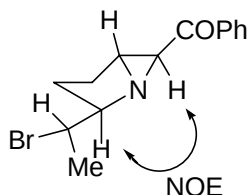
¹H NMR (CDCl₃, 500MHz): δ 8.00-8.02 ppm (m, 2H), 7.61-7.64 ppm (m, 1H), 7.50-7.53 ppm (m, 2H), 3.68-3.73 ppm (m, 2H), 3.25-3.30 ppm (m, 1H), 3.03 ppm (d, *J* = 2.5 Hz, 1H), 2.97 ppm (dd, *J* = 4.5 Hz, 2.5 Hz, 1H), 2.19-2.35 ppm (m, 2H), 2.01-2.06 ppm (m, 1H), 1.78-1.85 ppm (m, 1H); ¹³C NMR (CDCl₃, 100MHz): δ 195.9 ppm, 136.9 ppm, 133.3 ppm, 128.7 ppm, 128.2 ppm, 66.3 ppm, 49.9 ppm, 41.5 ppm, 35.7 ppm, 25.2 ppm, 24.4 ppm

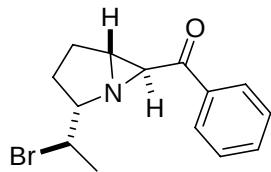
(2*S*^{*},5*R*^{*},6*S*^{*})-(2-Bromomethyl-1-azabicyclo[3.1.0]hex-6-yl)-phenylmethanone (2a)

¹H NMR (CDCl₃, 500MHz): δ 7.99-8.02 ppm (m, 2H), 7.57-7.61 ppm (m, 1H), 7.46-7.50 ppm (m, 2H), 3.68-3.75 ppm (m, 2H), 3.48-3.52 ppm (m, 1H), 3.27 ppm (d, *J* = 2.5 Hz, 1H), 2.93 ppm (dd, *J* = 4.5 Hz, 2.5 Hz, 1H), 2.35 ppm (dd, *J* = 14.0, 8.0, 1H), 2.12-2.19 ppm (m, 1H), 1.95-2.01 ppm (m, 1H), 1.37-1.44 ppm (m, 1H); ¹³C NMR (CDCl₃, 100MHz): δ 195.0 ppm, 137.0 ppm, 133.3 ppm, 128.7 ppm, 128.2 ppm, 65.0 ppm, 49.1 ppm, 35.9 ppm, 33.1 ppm, 27.0 ppm, 25.1 ppm

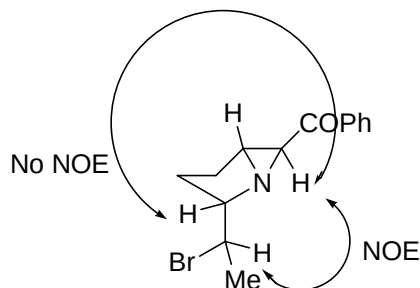
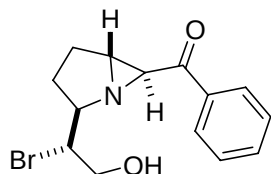
(1'*S*^{*},2*R*^{*},5*R*^{*},6*S*^{*})-[2-(1'-Bromoethyl)-1-azabicyclo[3.1.0]hex-6-yl]- phenylmethanone (2b)

¹H NMR (CDCl₃, 500MHz): δ 8.01-8.03 ppm (m, 2H), 7.58-7.62 ppm (m, 1H), 7.48-7.51 ppm (m, 2H), 4.28-4.33 ppm (m, 1H), 3.43-3.46 ppm (m, 1H), 2.99 ppm (t, *J* = 3.0 Hz, 1H), 2.92 ppm (d, *J* = 3.0 Hz, 1H), 2.24-2.35 ppm (m, 2H), 2.08-2.12 ppm (m, 1H), 1.76-1.85 ppm (m, 1H), 1.82 ppm (d, *J* = 6.5, 3H); ¹³C NMR (CDCl₃, 100MHz): δ 196.0 ppm, 137.0 ppm, 133.2 ppm, 128.6 ppm, 128.3 ppm, 72.2 ppm, 54.2 ppm, 50.5 ppm, 42.5 ppm, 26.6 ppm, 24.5 ppm, 24.0 ppm



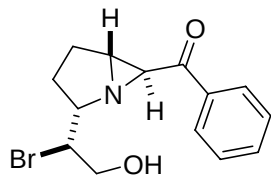
(1'R*,2S*,5R*,6S*)-[2-(1'-Bromoethyl)-1-azabicyclo[3.1.0]hex-6-yl]- phenylmethanone (2b)

^1H NMR (CDCl_3 , 500MHz): δ 8.03-8.05 ppm (m, 2H), 7.62-7.65 ppm (m, 1H), 7.51-7.55 ppm (m, 2H), 4.14-4.20 ppm (m, 1H), 3.56-3.61 ppm (m, 1H), 3.33 ppm (d, J = 2.5 Hz, 1H), 3.01 ppm (dd, J = 4.5 Hz, 2.5 Hz, 1H), 2.36 ppm (dd, J = 13.5, 8.0, 1H), 2.08-2.21 ppm (m, 2H), 1.92 ppm (d, J =7.0, 3H), 1.43-1.52 ppm (m, 1H); ^{13}C NMR (CDCl_3 , 100MHz): δ 195.7 ppm, 137.0 ppm, 133.3 ppm, 128.7 ppm, 128.2 ppm, 71.1 ppm, 51.2 ppm, 49.8 ppm, 35.6 ppm, 26.7 ppm, 25.6 ppm (2C)

**(1'R*,2R*,5R*,6S*)-[2-(1'-Bromo-2'-hydroxyethyl)-1-azabicyclo[3.1.0]hex-6-yl]-phenylmethanone (2c)**

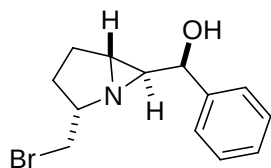
^1H NMR (CDCl_3 , 300MHz): δ 7.96-8.00 ppm (m, 2H), 7.61-7.67 ppm (m, 1H), 7.50-7.55 ppm (m, 2H), 5.04 ppm (d, J = 7.8, 1H), 4.01-4.18 ppm (m, 2H), 3.87 ppm (dt, J = 9.3 Hz, 3.9 Hz, 1H), 3.70-3.76 ppm (m, 1H), 3.11 ppm (d, J = 2.7 Hz, 1H), 3.01 ppm (t, J =3.6 Hz, 1H), 2.12-2.37 ppm (m, 3H), 1.73-1.96 ppm (m, 1H); ^{13}C NMR (CDCl_3 , 75MHz): δ 194.5 ppm, 136.6 ppm, 133.5 ppm, 128.8 ppm, 128.2 ppm, 72.0 ppm, 68.1 ppm, 54.4 ppm, 49.1 ppm, 41.5 ppm, 26.0 ppm, 24.9 ppm

(1'S*,2S*,5R*,6S*)- [2-(1'-Bromo-2'-hydroxyethyl)-1-azabicyclo[3.1.0]hex-6-yl]-phenylmethanone (2c)



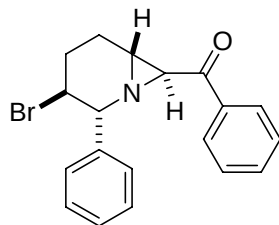
^1H NMR (CDCl_3 , 300MHz): δ 7.96-8.00 ppm (m, 2H), 7.59-7.64 ppm (m, 1H), 7.47-7.53 ppm (m, 2H), 4.00-4.10 ppm (m, 2H), 3.91-3.98 ppm (m, 2H), 3.67-3.74 ppm (m, 1H), 3.29 ppm (d, $J = 2.1$ Hz, 1H), 3.03 ppm (dd, $J = 4.5$ Hz, 2.4 Hz, 1H), 2.31-2.38 ppm (m, 1H), 2.06-2.23 ppm (m, 2H), 1.44-1.55 ppm (m, 1H); ^{13}C NMR (CDCl_3 , 75MHz): δ 195.1 ppm, 136.4 ppm, 133.6 ppm, 128.8 ppm, 128.2 ppm, 68.6 ppm, 67.4 ppm, 54.5 ppm, 50.6 ppm, 36.7 ppm, 26.6 ppm, 25.8 ppm

(S*)-[(2S*,5R*,6S*)-(2-Bromomethyl-1-aza-bicyclo[3.1.0]hex-6-yl)]-phenylmethanol (2e)¹¹

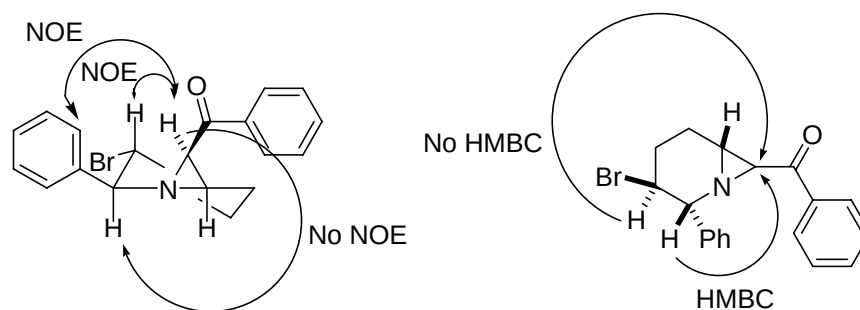


^1H NMR (CDCl_3 , 400MHz): δ 7.31-7.44 ppm (m, 5H), 4.73 ppm (d, $J = 4.4$ Hz, 1H), 3.53-3.61 ppm (m, 1H), 3.42 ppm (dd, $J = 10.0$ Hz, 6.8 Hz, 1H), 3.30 ppm (dd, $J = 10.0$ Hz, 6.8 Hz, 1H), 3.15 ppm (br s, 1H), 2.70 ppm (dd, $J = 5.2$ Hz, 3.2 Hz, 1H), 2.11-2.17 ppm (m, 1H), 1.98-2.08 ppm (m, 2H), 1.82-1.89 ppm (m, 1H), 1.11-1.22 ppm (m, 1H); ^{13}C NMR (CDCl_3 , 100MHz): δ 141.9 ppm, 128.5 ppm, 127.8 ppm, 126.2 ppm, 71.6 ppm, 64.0 ppm, 42.9 ppm, 39.1 ppm, 33.1 ppm, 26.4 ppm, 26.1 ppm; HR-MS (EI) m/z : calcd. for $\text{C}_{14}\text{H}_{16}\text{BrNO}_2$ 281.0415, found 281.0419

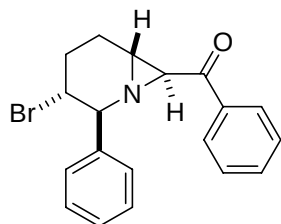
(2R*,3S*,6R*,7S*)-(3-Bromo-2-phenyl-1-azabicyclo[4.1.0]hept-7-yl)- phenylmethanone (3d)



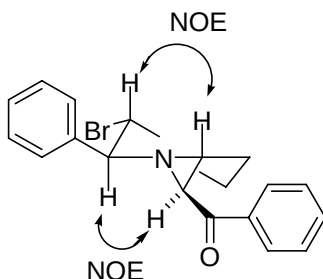
^1H NMR (CDCl_3 , 500MHz): δ 7.53-7.55 ppm (m, 2H), 7.46-7.50 ppm (m, 3H), 7.25-7.35 ppm (m, 5H), 4.66 ppm (d, $J = 10.5$ Hz, 1H), 4.27-4.32 ppm (m, 1H), 3.10 ppm (d, $J = 2.5$ Hz, 1H), 2.99 ppm (dt, $J = 7.5$ Hz, 3.0 Hz, 1H), 2.35-2.43 ppm (m, 2H), 2.14-2.20 ppm (m, 2H); ^{13}C NMR (CDCl_3 , 125MHz): δ 196.6 ppm, 139.6 ppm, 137.1 ppm, 133.1 ppm, 128.8 ppm, 128.6 ppm, 128.3 ppm, 128.2 ppm, 128.0 ppm, 66.4 ppm, 46.7 ppm, 42.6 ppm, 42.2 ppm, 31.7 ppm, 23.8 ppm; HR-MS (EI) m/z : calcd. for $\text{C}_{19}\text{H}_{18}\text{BrNO}$ 355.0572, found 355.0582



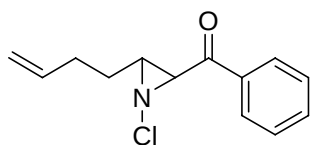
(2*S,3*R**,6*R**,7*S**)-(3-Bromo-2-phenyl-1-azabicyclo[4.1.0]hept-7-yl)- phenylmethanone (3d)**



^1H NMR (CDCl_3 , 500MHz): δ 8.01-8.03 ppm (m, 2H), 7.58-7.61 ppm (m, 1H), 7.46-7.51 ppm (m, 4H), 7.36-7.40 ppm (m, 2H), 7.30-7.33 ppm (m, 1H), 4.10-4.15 ppm (m, 2H), 3.62 ppm (d, $J = 3.0$ Hz, 1H), 2.99 ppm (dt, $J = 5.5$ Hz, 2.5 Hz, 1H), 2.33-2.47 ppm (m, 3H), 2.08-2.15 ppm (m, 1H); ^{13}C NMR (CDCl_3 , 125MHz): δ 196.2 ppm, 142.5 ppm, 136.8 ppm, 133.3 ppm, 128.7 ppm, 128.5 ppm, 128.4 ppm, 128.0 ppm, 127.7 ppm, 70.7 ppm, 52.8 ppm, 47.1 ppm, 41.6 ppm, 29.3 ppm, 22.6 ppm; HR-MS (EI) m/z : calcd. for $\text{C}_{19}\text{H}_{18}\text{BrNO}$ 355.0572, found 355.0568



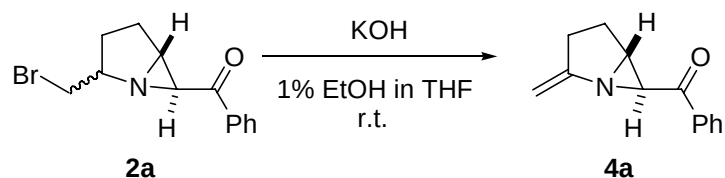
(3-But-3-enyl-1-chloroaziridin-2-yl)-phenylmethanone



To a mixture of (3-but-3-enyl-*trans*-aziridin-2-yl)-phenylmethanone (40 mg, 0.2 mmol), dimethoxyethane (2 mL) and water (0.5 mL) was added *N*-chlorosuccinimide (29 mg, 0.22 mmol) at room temperature and the mixture was stirred for 2 hours. The solvent was removed in vacuo, to give crude (3-but-3-enyl-1-chloroaziridin-2-yl)-phenylmethanone.

^1H NMR (CDCl_3 , 300MHz): δ 8.02-8.06 ppm (m, 2H), 7.63-7.69 ppm (m, 1H), 7.52-7.57 ppm (m, 2H), 5.82-5.96 ppm (m, 1H), 5.01-5.16 ppm (m, 2H), 3.51 ppm (d, $J=5.4$ Hz, 1H), 2.83 ppm (q, $J=6.0$ Hz, 1H), 2.04-2.50 ppm (m, 4H)

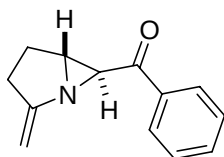
Procedure for the dehydrobromination (eq 2, R=H):



To a mixture of (2*S*^{*},5*R*^{*},6*S*^{*})-(2-bromomethyl-1-aza-bicyclo[3.1.0]hex-6-yl)-phenylmethanone (**2a**, 1.0 g, 3.6 mmol), (2*R*^{*},5*R*^{*},6*S*^{*})-(2-bromomethyl-1-aza-bicyclo[3.1.0]hex-6-yl)-phenylmethanone (**2a**, 1.4 g, 5.0 mmol), THF (200 mL) and ethanol (2 mL) was added crushed potassium hydroxide (1.4 g, 25

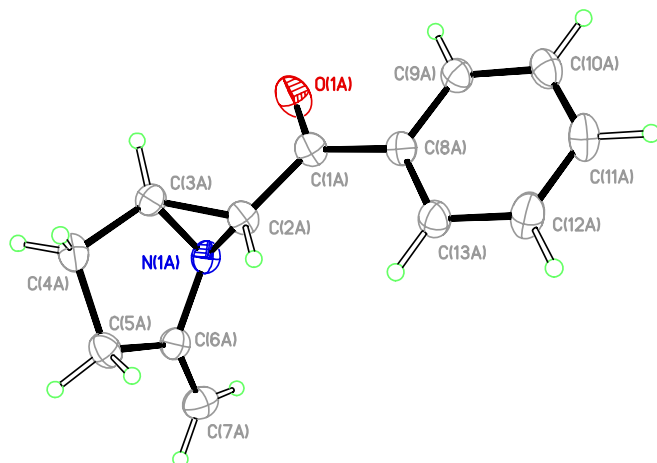
mmol) at room temperature and the resulting mixture was stirred for 4 hours. After completion judged by TLC, dichloromethane (500 mL) and water (300 mL) were added. The organic layer and aqueous layer were separated, and the aqueous layer was extracted with dichloromethane (150 mL). The combined organic layers were washed with water (200 mL) followed by drying over sodium sulfate and the solvent was removed in vacuo, to give 1.70 g of (5*R**,6*S**)-(2-methylene-1-azabicyclo[3.1.0]hex-6-yl)-phenylmethanone (**4a**, yield: quant.). Further purification was achieved on a silica gel column (hexane/ethyl acetate = 6/4).

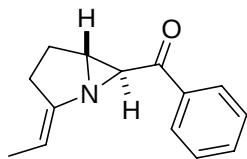
(5*R,6*S**)-(2-Methylene-1-azabicyclo[3.1.0]hex-6-yl)-phenylmethanone (4a)**



^1H NMR (CDCl_3 , 400MHz): δ 8.02-8.05 ppm (m, 2H), 7.61-7.65 ppm (m, 1H), 7.50-7.54 ppm (m, 2H), 5.31 ppm (d, $J = 1.6$ Hz, 1H), 4.74 ppm (d, $J = 1.6$ Hz, 1H), 3.22-3.25 ppm (m, 2H), 2.24-2.60 ppm (m, 4H); ^{13}C NMR (CDCl_3 , 100MHz): δ 196.2 ppm, 158.6 ppm, 136.8 ppm, 133.3 ppm, 128.7 ppm, 128.4 ppm, 101.9 ppm, 50.6 ppm, 45.4 ppm, 26.2 ppm, 25.3 ppm; HR-MS (EI) m/z : calcd. for $\text{C}_{13}\text{H}_{13}\text{NO}$ 199.0997, found 199.0998

X-ray structure:



(5*R*^{*},6*S*^{*})-(E-2-Ethylidene-1-azabicyclo[3.1.0]hex-6-yl)-phenylmethanone (4b)

¹H NMR (CDCl₃, 300MHz): δ 7.99-8.03 ppm (m, 2H), 7.57-7.63 ppm (m, 1H), 7.46-7.52 ppm (m, 2H), 5.74-5.80 ppm (m, 1H), 3.17 ppm (dd, *J* = 4.5 Hz, 3.0 Hz, 1H), 3.10 ppm (d, *J* = 3.0 Hz, 1H), 2.14-2.64 ppm (m, 4H), 1.61-1.64 ppm (m, 3H); ¹³C NMR (CDCl₃, 75MHz): δ 195.1 ppm, 151.0 ppm, 137.0 ppm, 133.2 ppm, 128.6 ppm, 128.3 ppm, 111.9 ppm, 49.8 ppm, 45.3 ppm, 25.2 ppm, 22.6 ppm, 14.0 ppm

REFERENCES:

- (1) Ricci, A., Ed. *Modern Amination Methods*; Wiley-VCH: Weinheim, 2000.
- (2) (a) Siu, T.; Yudin, A. K. *J. Am. Chem. Soc.* **2002**, *124*, 530. (b) Caiazzo, A.; Dalili, S.; Yudin, A. K. *Org. Lett.* **2002**, *4*, 2597. (c) Sasaki, M.; Dalili, S.; Yudin, A. K. *J. Org. Chem.* **2003**, *68*, 2045. (d) Watson, I. D. G.; Yudin, A. K. *Curr. Opin. Drug Disc. Dev.* **2002**, *5*, 906.
- (3) The use of aziridines in complex molecule synthesis, see: Tanner, D. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599.
- (4) For a one-electron process, the 0.8V anodic shift corresponds to the 18 kcal/mol increase in oxidative stability.
- (5) Iminium ions are known to form during secondary amine oxidation processes: Gilchrist, T. L. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, 735.
- (6) For example, see: (a) Dewick, P. M. In *Medicinal Natural Products*; J. Wiley & Sons: Chichester, 1997; Chapter 6. (b) Hagan, D. O. *Nat. Prod. Rep.* **2000**, *17*, 435.
- (7) For reviews, see: (a) Mitchinson, A.; Nadin, A. *J. Chem. Soc. Perkin Trans. 1* **2000**, 2862 and references therein. (b) Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927 and references therein. (c) Higasio, Y.; Shoji, T. *Applied Catalysis A: General* **2001**, *221*, 197. For the synthesis of [5,3] bicyclic aziridines, see: (d) Coleman, R. S.; Kong, J.-S.; Richardson, T. E. *J. Am. Chem. Soc.* **1999**, *121*, 9088. (e) Mulzer, J.; Becker, R.; Brunner, E. *J. Am. Chem. Soc.* **1989**, *111*, 7500. (f) Guillemin, J. C.; Denis, J. M. *Angew. Chem.* **1982**, *94*, 715. (g) Chaabouni, R.; Laurent, A.; Marquet, B. *Tetrahedron* **1980**, *36*, 877.
- (8) Tamaru, Y.; Kawamura, S.; Bando, T.; Tanaka, K.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5491.
- (9) We were able to isolate and characterize the N-Cl containing intermediate.

- (10) Nagaoka, K.; Matsumoto, M.; Ono, J.; Yokoi, K.; Ishizeki, S.; Nakashima, T. *J. of Antibiotics* **1986**, 39, 1527.
- (11) The other three diastereomers were obtained as a mixture.

Chapter 4

Applications with Bicyclic Aziridines: as a Versatile Route to Saturated Nitrogen-Containing Heterocycles

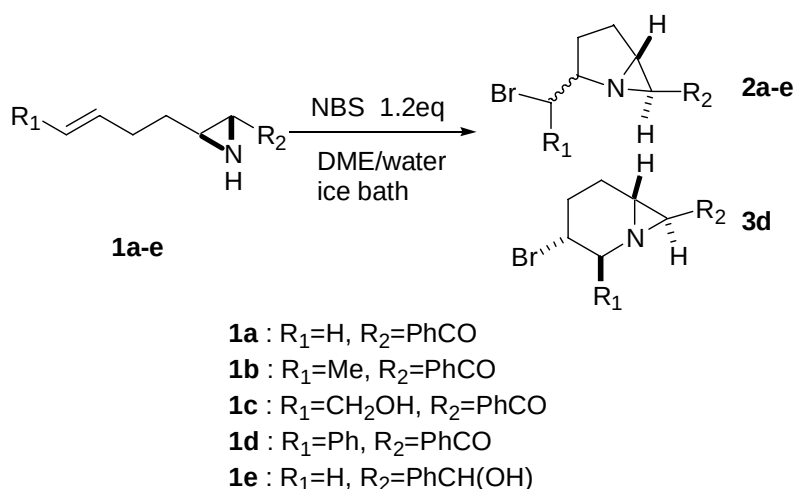
Abstract

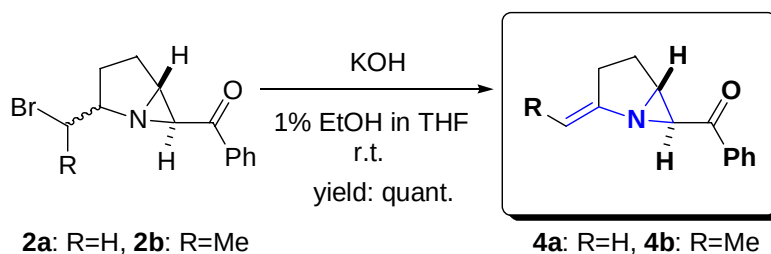
Highly reactive [5,3]- and [6,3]- bicyclic aziridines described in Chapter 3, including surprisingly stable exo-methylene bicyclic aziridines, provide versatile synthetic entries into a wide range of pyrrolidine- and piperidine-containing heterocycles. This strategy serves as a valuable alternative to existing methods for the construction of substituted pyrrolidines and piperidines.

Introduction

The pyrrolidine and piperidine rings are incorporated into the structures of a wide range of natural products and pharmaceuticals which makes them an important class of targets for stereoselective synthesis.¹ As described in Chapter 3, it has been found that the stereoselective synthesis of bicyclic aziridines is achieved by intramolecular oxidative cycloamination of NH-aziridines (Scheme 1).

Scheme 1. Synthesis of bicyclic aziridines.





If relative stereochemistry of the products can be controlled during ring-opening steps of these bicyclic aziridines, the oxidative aziridine cycloamination methodology should be a valuable alternative to the established methods.³ In this chapter, the application of these bicyclic aziridines is described.

Results and Discussion

The bicyclic aziridine **4** possesses considerable synthetic potential because of the enamine-like aziridine ring that can be transformed into an imine/enamine upon ring-opening. The ring-opening reactions proceed with high yields and excellent diastereoselectivities. The reactions are regioselective and afford the corresponding pyrrolidine derivatives. The resulting enamines are *in situ* tautomerized into cyclic imines. The reductive ring opening of aziridine **4a** by hydrogen on Pd/C gives 5-membered cyclic imine in excellent yield (Table 1, entry 5).

Table 1. Ring opening reactions of bicyclic aziridines **4**.

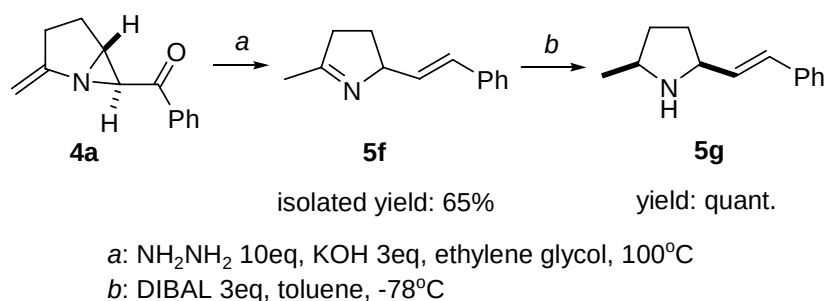
4a, 4b $\longrightarrow$ **5a-e**

Entry	R ₁	Condition	R ₂	Yield
1	H	TMSN ₃ 2eq, H ₂ O 10eq, in DCM, r.t.	N ₃	99
2	Me	TMSN ₃ 2eq, H ₂ O 10eq, in DCM, r.t.	N ₃	95
3	H	HBFe ₄ 1.5eq, in MeOH, r.t.	OMe	65
4	H	AcOH 5eq, in DCM, r.t.	OAc	73

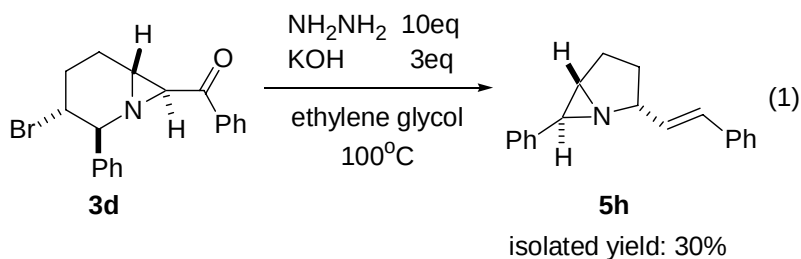
5	H	10%Pd/C 0.1wt, H ₂ , in MeOH, r.t.	H	99
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Aziridine ring opening was also triggered under the reductive conditions. Upon treatment with hydrazine, valuable 2-allylamine derivatives were obtained in good yields (Scheme 2). The resulting cyclic imines can be readily reduced to pyrrolidines using DIBAL. For example, **5f** was reduced to cis-2,5-disubstituted pyrrolidine **5g** with excellent yield and diastereoselectivity (Scheme 2). The 2,5-disubstituted fragments similar to **5g** are often seen in natural products, for example, in pinidine.³

Scheme 2. Hydrazine reduction of bicyclic aziridine **4a**.



The reactions of [6,3] bicyclic aziridine **3** were also investigated under hydrazinolysis conditions. The presence of endocyclic bromine substituent in compound **3** suggested further relay of the aziridine functionality within the bicyclic ring system. Under the hydrazinolysis conditions, compound **3d** can be converted into bicyclic aziridine **5h**, another valuable precursor to functionalized pyrrolidines, via ring-opening reaction followed by a ring-closing step (eq 1).

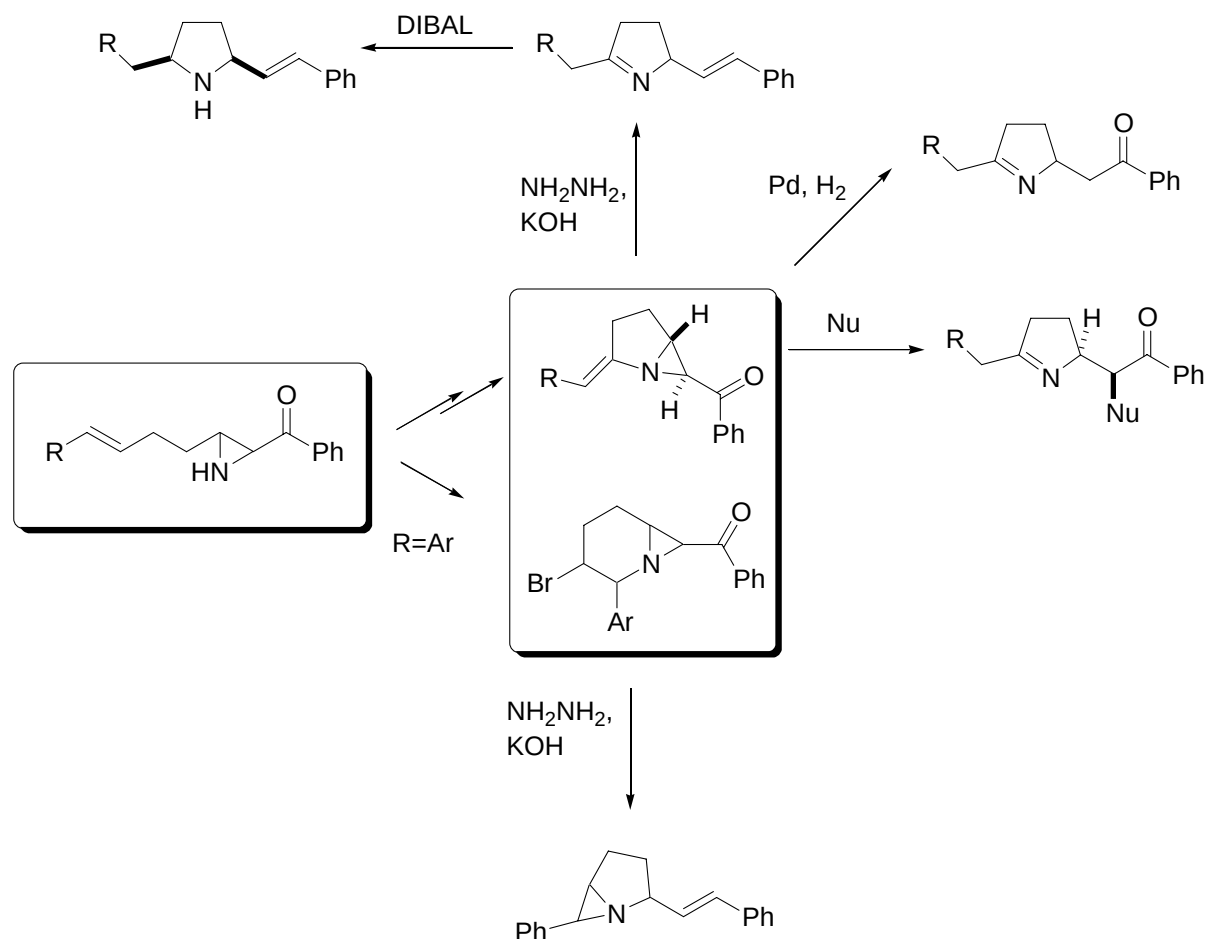


Conclusion

It has been shown that versatile chemistry of functionalized bicyclic aziridines enables rapid construction of a variety of heterocyclic products with high levels of stereocontrol (Scheme 3). Notably,

the starting materials can be prepared in enantiomerically pure form using the Julia-Colonna epoxidation reaction followed by epoxide conversion into aziridine.⁴ This strategy serves as a valuable alternative to existing methods for the construction of substituted pyrrolidines and piperidines, especially since stereocontrol still poses significant challenges with known methods.

Scheme 3. Versatile chemistry of functionalized bicyclic aziridines.



Experimental Section

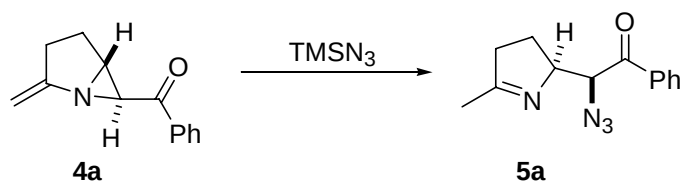
General: The chemicals were purchased from Aldrich Chemical Co., Strem Chemical Co., Fischer Scientific Ltd., and Lancaster and were used without further purification. In experiments requiring anhydrous solvents: ether, toluene, hexanes, acetonitrile, and dichloromethane were purified using the method described by Grubbs (Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518). Tetrahydrofuran (THF) was distilled over sodium-

benzophenone ketyl under argon. Unless otherwise stated, all reactions were performed under nitrogen or argon atmosphere using flame-dried glassware.

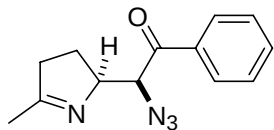
Nuclear magnetic resonance spectra: ^1H and ^{13}C NMR spectra were recorded on either Mercury 300, Varian Gemini 300, or VRX-S (Unity) 400 spectrometer. ^1H NMR spectra were referenced to residual CDCl_3 (δ 7.27 ppm) and ^{13}C NMR spectra were referenced to CDCl_3 (δ 77.23 ppm). Peak multiplicities are designated by the following abbreviations: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets; br, broad; and J , coupling constant in Hz.

Chromatography: Analytical thin layer chromatography (TLC) was performed on Macherey Nagel pre-coated glass-backed TLC plates (SIL G/UV₂₅₄, 0.25mm) purchased from Rose Scientific Limited and visualized by UV lamp (254 nm) or iodine. Solvent ratios for R_f values are reported as v/v. Column chromatography was carried out using Silicycle 230-400 mesh silica gel.

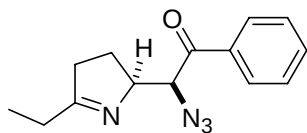
Procedure for the ring opening with TMSN_3 (Table 1, Entry 1):



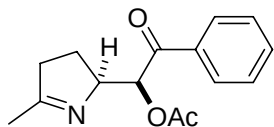
To a mixture of $(5R^*,6S^*)$ -(2-methylene-1-azabicyclo[3.1.0]hex-6-yl)- phenylmethanone (**4a**, 380 mg, 1.9 mmol), dichloromethane (10 mL) and water (343 mg, 19 mmol) was added azido trimethylsilane (440 mg, 3.8 mmol) at room temperature and stirred overnight. After completion judged by TLC, the solvent and other volatile derivatives were removed in vacuo, to give 460 mg of $(2S^*,2'S^*)$ -2-azido-2-(5'-methyl-3',4'-dihydro-2H-pyrrol-2'-yl)-1-phenylethanone (**5a**, yield: quant.).

(2S*,2'S*)-2-Azido-2-(5'-methyl-3',4'-dihydro-2H-pyrrol-2'-yl)-1-phenylethanone (5a)

^1H NMR (CDCl_3 , 300MHz): δ 8.04-8.07 ppm (m, 2H), 7.65-7.71 ppm (m, 1H), 7.53-7.59 ppm (m, 2H), 5.44 ppm (d, $J=3.6$ Hz, 1H), 4.63-4.68 ppm (m, 1H), 2.67-2.79 ppm (m, 1H), 2.49-2.61 ppm (m, 1H), 2.13 ppm (d, $J=1.5$ Hz, 3H), 1.81-2.02 ppm (m, 2H); ^{13}C NMR (CDCl_3 , 100MHz): δ 194.8 ppm, 178.1 ppm, 134.9 ppm, 134.0 ppm, 129.0 ppm, 128.8 ppm, 73.8 ppm, 67.5 ppm, 39.6 ppm, 23.2 ppm, 19.7 ppm

(2S*,2'S*)-2-Azido-2-(5'-ethyl-3',4'-dihydro-2H-pyrrol-2'-yl)-1-phenylethanone (5b)

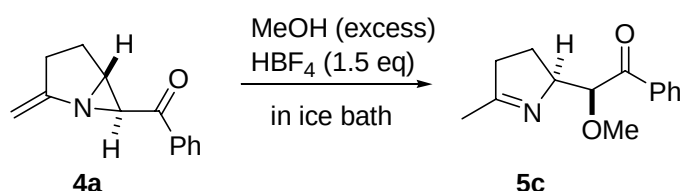
^1H NMR (CDCl_3 , 400MHz): δ 8.03-8.05 ppm (m, 2H), 7.62-7.67 ppm (m, 1H), 7.51-7.55 ppm (m, 2H), 5.50 ppm (d, $J = 4.0$ Hz, 1H), 4.64-4.68 ppm (m, 1H), 2.66-2.74 ppm (m, 1H), 2.48-2.57 ppm (m, 1H), 2.43 ppm (q, $J = 7.6$ Hz, 2H), 1.80-1.95 ppm (m, 2H), 1.20 ppm (t, $J=7.6$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100MHz): δ 194.8 ppm, 182.8 ppm, 134.9 ppm, 133.9 ppm, 128.9 ppm, 128.7 ppm, 73.7 ppm, 67.7 ppm, 38.0 ppm, 26.9 ppm, 22.7 ppm, 10.6 ppm

(2S*,2'S*)-2-Acetoxy-2-(5'-methyl-3',4'-dihydro-2H-pyrrol-2'-yl)-1-phenylethanone (5d)

Glacial acetic acid (5 eq) was used instead of azido trimethylsilane and water was not added. After removing the solvent, the residue was purified on a silica gel column (ethyl acetate).

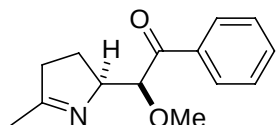
^1H NMR (CDCl_3 , 300MHz): δ 8.05-8.09 ppm (m, 2H), 7.60-7.66 ppm (m, 1H), 7.49-7.54 ppm (m, 2H), 6.33 ppm (d, $J = 2.7$ Hz, 1H), 4.50-4.60 ppm (m, 1H), 2.61-2.73 ppm (m, 1H), 2.44-2.55 ppm (m, 1H), 2.15 ppm (s, 3H), 1.97-2.09 ppm (m, 1H), 2.09 ppm (d, $J = 1.5$ Hz, 3H), 1.73-1.85 ppm (m, 1H); ^{13}C NMR (CDCl_3 , 75MHz): δ 195.1 ppm, 177.5 ppm, 170.3 ppm, 134.8 ppm, 133.7 ppm, 128.8 ppm, 128.6 ppm, 76.9 ppm, 72.2 ppm, 39.7 ppm, 22.6 ppm, 20.7 ppm, 19.7 ppm

Procedure for the ring opening with methanol (Table 1, Entry 3):



To $(5R^*,6S^*)$ -(2-methylene-1-azabicyclo[3.1.0]hex-6-yl)-phenylmethanone (**4a**, 50 mg, 0.25 mmol) in methanol (5 mL) was added 54% tetrafluoroboric acid in diethyl ether (60 mg, 0.37 mmol) at the temperature of ice bath and the mixture was stirred for 1 hour. After completion judged by TLC, sodium bicarbonate (100 mg) and water (4 mL) were added and methanol was evaporated. Dichloromethane (8 mL) and water (3 mL) were added to the residue, and the aqueous layer was extracted with dichloromethane (3 mL). The combined organic layers were washed with water (5 mL) and were dried over sodium sulfate and the solvent was removed in vacuo. The residue was purified on a silica gel column (hexane/ethyl acetate = from 5/5 to 0/10), to give 38 mg of $(2S^*,2'S^*)$ -2-methoxy-2-(5'-methyl-3',4'-dihydro-2H-pyrrol-2'-yl)-1-phenylethanone (**5c**, yield: 65 %).

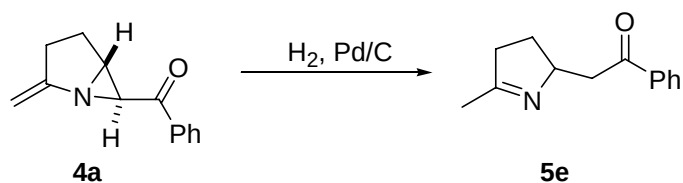
$(2S^*,2'S^*)$ -2-Methoxy-2-(5'-methyl-3',4'-dihydro-2H-pyrrol-2'-yl)-1-phenylethanone (5c**)**



^1H NMR (CDCl_3 , 300MHz): δ 8.07-8.10 ppm (m, 2H), 7.57-7.61 ppm (m, 1H), 7.47-7.51 ppm (m, 2H), 5.12 ppm (d, $J = 3.0$ Hz, 1H), 4.46-4.50 ppm (m, 1H), 3.40 ppm (s, 3H), 2.60-2.70 ppm (m, 1H),

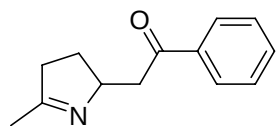
2.40-2.47 ppm (m, 1H), 2.09 ppm (d, $J=1.5$ Hz, 3H), 1.98-2.06 ppm (m, 1H), 1.68-1.76 ppm (m, 1H); ^{13}C NMR (CDCl_3 , 100MHz): δ 198.7 ppm, 177.0 ppm, 135.5 ppm, 133.5 ppm, 128.8 ppm, 128.5 ppm, 85.4 ppm, 74.2 ppm, 58.5 ppm, 39.7 ppm, 22.6 ppm, 19.7 ppm; HR-MS (EI) m/z : calcd. for $\text{C}_{14}\text{H}_{17}\text{NO}_2$ 231.1260, found 232.1328 (as proton adduct)

Procedure for the reductive ring opening with hydrogen (Table 1, Entry 5):

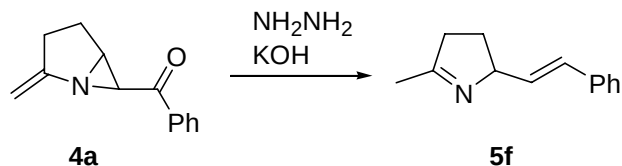


A mixture of (5*R**,6*S**)-(2-methylene-1-azabicyclo[3.1.0]hex-6-yl)- phenylmethanone (**4a**, 20 mg, 0.1 mmol), 10% palladium on carbon (2 mg) and methanol (1 mL) was stirred under hydrogen (1 atmosphere) at room temperature for 1 hour. The solid was removed by filtration and the solvent was removed from the filtrate in vacuo, to give 20 mg of 2-(5'-methyl-3',4'-dihydro-2H-pyrrol-2'-yl)-1-phenylethanone (**5e**, yield: quant.).

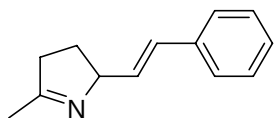
2-(5'-Methyl-3',4'-dihydro-2H-pyrrol-2'-yl)-1-phenylethanone (**5e**)



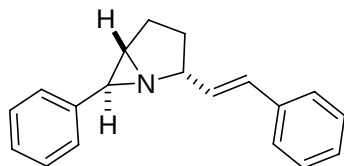
^1H NMR (CDCl_3 , 300MHz): δ 7.99-8.02 ppm (m, 2H), 7.56-7.61 ppm (m, 1H), 7.46-7.51 ppm (m, 2H), 4.53-4.58 ppm (m, 1H), 3.64 ppm (dd, $J = 16.8$ Hz, 4.5 Hz, 1H), 2.98 ppm (dd, $J = 16.8$ Hz, 9.0 Hz, 1H), 2.53-2.61 ppm (m, 2H), 2.26-2.37 ppm (m, 1H), 2.07 ppm (d, $J = 1.5$ Hz, 3H), 1.47-1.60 ppm (m, 1H); ^{13}C NMR (CDCl_3 , 100MHz): δ 198.6 ppm, 175.1 ppm, 137.1 ppm, 133.1 ppm, 128.6 ppm, 128.2 ppm, 68.8 ppm, 45.5 ppm, 39.1 ppm, 29.6 ppm, 19.8 ppm

Procedure for hydrazine reduction (Scheme 2):

A mixture of (5*R*^{*},6*S*^{*})-(methylene-1-azabicyclo[3.1.0]hex-6-yl)-phenylmethanone (**4a**, 50 mg, 0.25 mmol), hydrazine monohydrate (125 mg, 2.5 mmol), potassium hydroxide (42 mg, 0.75 mmol) and ethylene glycol (1 mL) was stirred at 100 °C for 1 hour. After completion judged by TLC, dichloromethane (5 mL) and water (5 mL) were added. The organic layer and the aqueous phase were separated, and the aqueous layer was extracted with dichloromethane (3 mL). The combined organic layers were washed with water (5 mL) and were dried over sodium sulfate and the solvent was removed in vacuo. The residue was purified on a silica gel column (hexane/ethyl acetate = 6/4), to give 30 mg of 5-methyl-2-styryl-3,4-dihydro-2H-pyrrole (**5f**, yield: 65%).

5-Methyl-2-styryl-3,4-dihydro-2H-pyrrole (5f)

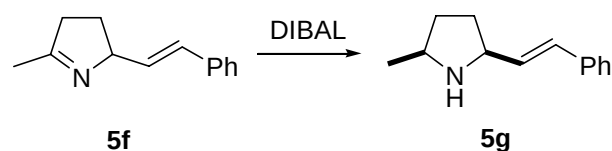
¹H NMR (CDCl₃, 300MHz): δ 7.34-7.45 ppm (m, 4H), 7.24-7.30 ppm (m, 1H), 6.59 ppm (d, *J* = 11.4 Hz, 1H), 5.59 ppm (dd, *J* = 11.4Hz, 9.6 Hz, 1H), 4.92-5.01 ppm (m, 1H), 2.46-2.70 ppm (m, 2H), 2.17-2.28 ppm (m, 1H), 2.11 ppm (d, *J* = 1.8 Hz, 3H), 1.62-1.75 ppm (m, 1H); ¹³C NMR (CDCl₃, 100MHz): δ 175.5 ppm, 137.1 ppm, 134.4 ppm, 129.9 ppm, 129.0 ppm, 128.1 ppm, 126.9 ppm, 69.9 ppm, 39.4 ppm, 30.9 ppm, 19.9 ppm; HR-MS (EI) *m/z*: calcd. for C₁₃H₁₅N 185.1205, found 185.1202

(2*R*^{*},5*S*^{*},6*S*^{*})-6-Phenyl-2-styryl-1-azabicyclo[3.1.0]hexane (5h)

The reaction temperature and time for **5h** were as follows: the reaction mixture was stirred at 60 °C for 30 minutes, then heated up to 100 °C and stirred for 10 minutes.

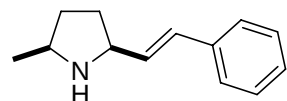
¹H NMR (CDCl₃, 400MHz): δ 7.44-7.45 ppm (m, 2H), 7.36-7.40 ppm (m, 2H), 7.22-7.33 ppm (m, 6H), 6.62 ppm (d, *J* = 11.6 Hz, 1H), 5.75 ppm (dd, *J* = 11.6Hz, 9.2 Hz, 1H), 4.32-4.39 ppm (m, 1H), 2.73 ppm (d, *J* = 2.8 Hz, 1H), 2.52 ppm (dd, *J* = 4.4 Hz, 2.8 ppm, 1H), 2.37 ppm (dd, 9.6 Hz, 8.4 Hz, 1H), 2.07-2.16 ppm (m, 1H), 1.89-1.96 ppm (m, 1H), 1.43-1.54 ppm (m, 1H); ¹³C NMR (CDCl₃, 100MHz): δ 131.7 ppm, 131.6 ppm, 128.8 ppm, 128.2 ppm, 128.2 ppm, 127.0 ppm, 126.7 ppm, 126.4 ppm, 61.1 ppm, 50.4 ppm, 36.0 ppm, 28.0 ppm, 27.7 ppm; HR-MS (EI) *m/z*: calcd. for C₁₉H₁₉N 261.1518, found 261.1512

Procedure for the reduction of cyclic imines (Scheme 2):



To 5-methyl-2-styryl-3,4-dihydro-2H-pyrrole (**5f**, 32 mg, 0.17 mmol) in toluene (1 mL) was added 1.5M DIBAL in toluene (0.33 mL, 0.5 mmol) at -78 °C and stirred for 1 hour. After the reaction, sat. aq. NH₄Cl (0.5 mL) was added and the mixture was warmed up to room temperature. Dichloromethane (20 mL) and sodium sulfate were added and the solid residue was removed by filtration. The solvent was removed in vacuo, to give 35 mg of *cis*-2-methyl-5-styrylpyrrolidine (**5g**, yield: quant.).

***cis*-2-Methyl-5-styryl-pyrrolidine (5g)**



¹H NMR (CDCl₃, 400MHz): δ 7.25-7.39 ppm (m, 5H), 6.52 ppm (d, *J* = 11.6 Hz, 1H), 5.73 ppm (dd, *J* = 11.6 Hz, 9.2 Hz, 1H), 4.04-4.10 ppm (m, 1H), 3.18-3.24 ppm (m, 1H), 2.81 ppm (br, 1H), 1.91-2.08 ppm (m, 2H), 1.63-1.72 ppm (m, 1H), 1.39-1.49 ppm (m, 1H), 1.25 ppm (d, *J* = 6.0 ppm, 3H); ¹³C

NMR (CDCl₃, 100MHz): δ 137.1 ppm, 135.2 ppm, 130.0 ppm, 128.7 ppm, 128.2 ppm, 126.9 ppm, 56.3 ppm, 54.8 ppm, 33.4 ppm, 32.9 ppm, 21.4 ppm; HR-MS (EI) *m/z*: calcd. for C₁₃H₁₇N 187.1361, found 187.1356

REFERENCES:

- (1) For example, see: (a) Dewick, P. M. In *Medicinal Natural Products*; J. Wiley & Sons: Chichester, 1997; Chapter 6. (b) Hagan, D. O. *Nat. Prod. Rep.* **2000**, 17, 435.
- (2) For reviews, see: (a) Mitchinson, A.; Nadin, A. *J. Chem. Soc. Perkin Trans. 1* **2000**, 2862 and references therein. (b) Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, 7, 927 and references therein. (c) Higasio, Y.; Shoji, T. *Applied Catalysis A: General* **2001**, 221, 197. For the synthesis of [5,3] bicyclic aziridines, see: (d) Coleman, R. S.; Kong, J.-S.; Richardson, T. E. *J. Am. Chem. Soc.* **1999**, 121, 9088. (e) Mulzer, J.; Becker, R.; Brunner, E. *J. Am. Chem. Soc.* **1989**, 111, 7500. (f) Guillemin, J. C.; Denis, J. M. *Angew. Chem.* **1982**, 94, 715. (g) Chaabouni, R.; Laurent, A.; Marquet, B. *Tetrahedron* **1980**, 36, 877.
- (3) Tallent, W. H.; Horning, E. C. *J. Am. Chem. Soc.* **1956**, 78, 4467.
- (4) For highly enantioselective Julia-Colonna epoxidation followed by conversion into aziridine, see: (a) Nemoto, T.; Ohshima, T.; Shibasaki, M. *Yuki Gosei Kagaku Kyokaishi* **2002**, 60, 94 and references therein. For ring opening by azide and reductive ring closing to aziridine, see: (b) Jin, X. L.; Sugihara, H.; Daikai, K.; Tateishi, H.; Jin, Y. Z.; Furuno, H.; Inanaga, J. *Tetrahedron* **2002**, 58, 8321-8329. (c) Legters, J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1989**, 30, 4881-4.

Chapter 5

Solvent Effects on Aromatic Nitration with NO₂

Abstract

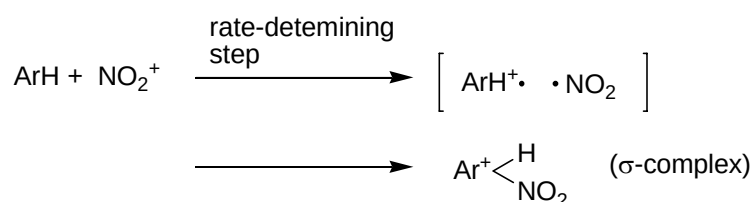
In order to get an insight into the mechanism of nitration of aromatic compounds with NO₂, the nitration of mono-substituted benzenes in various solvents was investigated. On the basis of the solvent effect on the yield of the products and the isomer distributions, it was suggested that in solvents with lower polarity aromatic nitration proceeds by one electron-transfer mechanism [Hammett's ρ value is -1.7], and that in solvents with higher polarity like acetonitrile aromatic nitration proceeds by the mechanism involving NO⁺, which is produced by the heterolytic decomposition of N₂O₄ [Hammett's ρ value is -3.2].

Introduction

Aromatic nitro compounds are important intermediates in organic synthesis and nitration of aromatic compounds serves as a straightforward access to aromatic nitro compounds. Because aromatic nitro compounds are identified as cancer-causing or mutagenic and might give harmful effects to living bodies by inhalation, their formation by the reaction of aromatic compounds with NO₂ discharged from diesel vehicles and so on in the atmosphere has also received significant research interests.¹⁻³ Therefore, it is important to get a deep insight into the mechanism of nitration of aromatic compounds.

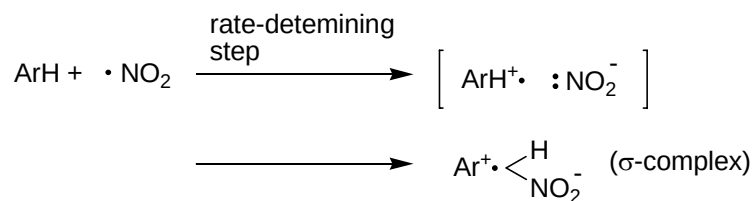
In 1977 Perrin proposed an one electron-transfer mechanism for aromatic nitration with NO₂⁺, in which radical cation plays an important role as an intermediate (Scheme 1).⁴

Scheme 1. Proposed mechanism for aromatic nitration with NO₂⁺



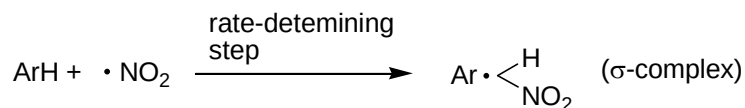
Based on this proposal Pryor investigated the nitration with NO_2 in dichloromethane at 25°C , and proposed a mechanism involving radical cation, which is formed via rate-determining electron transfer process for aromatic nitration with NO_2 (Scheme 2).⁵

Scheme 2. Proposed mechanism for aromatic nitration with NO_2



They also suggested a possibility of a mechanism involving rate-determining σ -complex formation process via the reaction with NO_2 radical (Scheme 3).

Scheme 3. Another proposed mechanism for aromatic nitration with NO_2



The previous work suggested that the nitration with NO_2 proceeds by one electron-transfer process via radical cation, because the nitration of mono-substituted benzenes with NO_2 in carbon tetrachloride at 15°C showed lower Hammett's ρ value [indicating -1.7] than that with NO_2^+ [indicating Hammett's ρ value is -6], which indicates that NO_2 would be a weaker electrophile.⁶

However, the detail of the mechanism of aromatic nitration with NO_2 radical has not been clarified yet. In this chapter the mechanism of aromatic nitration with NO_2 was investigated on the basis of the solvent effects on the nitration of mono-substituted benzenes with NO_2 .

Results and Discussion

The rate constants of the nitration of mono-substituted benzenes with NO₂ in acetonitrile were determined according to eq 1 (*a*: initial concentration of substrate, *x*: yield of product, *t*: reaction time, *k*: reaction rate constant) based on the assumption that the reaction would be pseudo-first-order reaction. With this data, relative rates of the reactions with several substrates were determined. The results are shown in Table 1, which also includes the relative rate observed in carbon tetrachloride solvent.⁶

$$\ln \frac{a}{a-x} = kt \quad (1)$$

Table 1. Relative rates in the nitration of mono-substituted benzenes with NO₂

substrate	relative rate	
	in CH ₃ CN	in CCl ₄
C ₆ H ₅ OCH ₃	4.8 x 10 ²	3.4
C ₆ H ₅ CH ₃	2.8	1.7
C ₆ H ₆	1	1
C ₆ H ₅ Br	0.38	0.49
C ₆ H ₅ Cl	0.38	0.35

Isomer distributions observed for the nitration of several mono-substituted benzenes with NO₂ in dichloromethane, dibromomethane and acetonitrile are shown in Table 2, with the isomer distributions observed for the nitration with NO₂ in carbon tetrachloride and that observed for the nitration with a mixture of sulfuric acid and nitric acid.⁷ In carbon tetrachloride, dibromomethane and dichloromethane aromatic nitration with NO₂ exhibited similar isomer distribution. The distribution is also similar to the mixed acid case in which the active species is known to be NO₂⁺. However, in acetonitrile solvent, the

nitration with NO_2 exhibited different product distribution. The content of m-product was much higher than those for other cases.

Table 2. Isomer distribution in the nitration of mono-substituted benzenes with NO_2

substrate	isomer distribution														
	in CH_3CN			in CH_2Cl_2			in CH_2Br_2			in CCl_4			ref 7		
	(mol%)			(mol%)			(mol%)			(mol%)			(mol%)		
	o-	m-	p-	o-	m-	p-	o-	m-	p-	o-	m-	p-	o-	m-	p-
$\text{C}_6\text{H}_5\text{OCH}_3$	41	0	59	30	0	70	23	0	77	23	0	77	40	0	60
$\text{C}_6\text{H}_5\text{CH}_3$	64	10	26	56	6	39	55	3	42	54	6	41	57	3	40
$\text{C}_6\text{H}_5\text{Br}$	30	10	41	41	2	57	39	2	59	31	0	69	43	1	56
$\text{C}_6\text{H}_5\text{Cl}$	27	10	63	37	3	60	34	3	63	32	3	65	35	1	64

Partial rate factors were calculated from the isomer distribution and relative rates for the nitration with NO_2 in acetonitrile and plotted against the Hammett value (Fig. 1). As shown in Fig. 1, good relationship was found when σ^+ was used and Hammett's ρ value was -3.2. Therefore, this reaction should be electrophilic and the electrophilicity is greater than that in the nitration with NO_2 in carbon tetrachloride solvent ($\rho = -1.7$) and smaller than that in the nitration with NO_2^+ ($\rho = -6$).

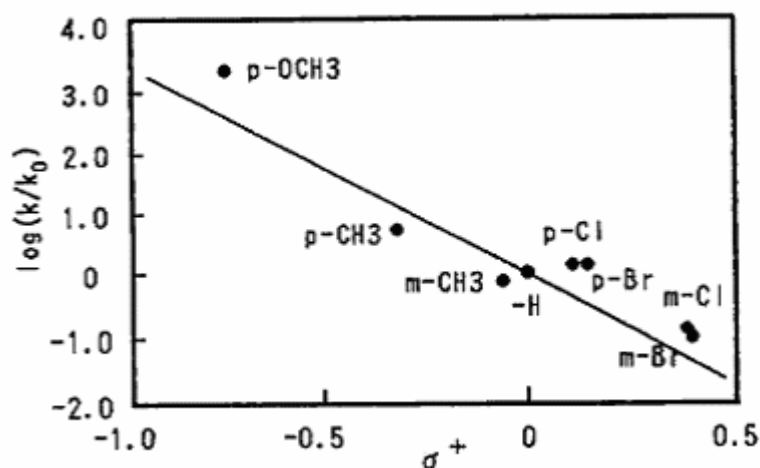


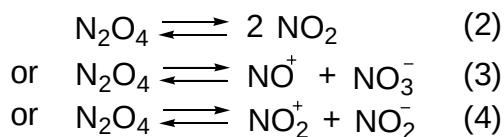
Fig. 1. Hammett plot for the nitration of mono-substituted benzenes with NO_2 in acetonitrile.

The yields of the mononitro compounds obtained in the nitration with NO_2 in several solvents (6 hours) are shown in Table 3. The yield increased with the increase in the polarity of solvent in a series of carbon tetrachloride, dibromomethane, and dichloromethane. However, the yield obtained in acetonitrile was lower than that in dichloromethane, although the polarity of acetonitrile is greater than that of dichloromethane. This fact suggests that the mechanism in acetonitrile is different from that for other solvents.

Table 3. Yield of the mononitro products in the nitration of benzene and toluene with NO_2

		yield of the mononitro products			
		in CCl_4	in CH_2Br_2	in CH_2Cl_2	in CH_3CN
dipole moment (D)		0	1.43	1.62	3.91
substrate	C_6H_6	8.3×10^{-5}	-	6.6×10^{-4}	3.0×10^{-4}
	$\text{C}_6\text{H}_5\text{CH}_3$	4.9×10^{-4}	9.0×10^{-4}	9.6×10^{-4}	7.7×10^{-4}

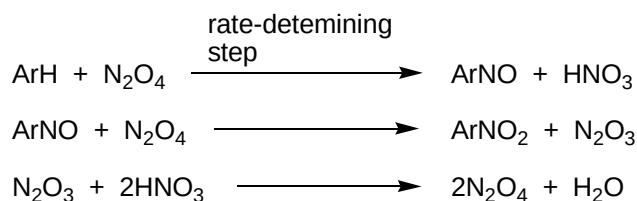
The difference in the nitration mechanism seems to be attributed to the difference of the decomposition mechanism of N_2O_4 . It is known that N_2O_4 undergoes decomposition in two different decomposition modes: homolytic cleavage (eq 2) and heterolytic cleavage (eqs 3 and 4), and heterolytic decomposition is preferentially occurred in polar solvents.⁸



NO_2 radical produced by homolytic decomposition of N_2O_4 might be the active species in lower polarity solvents such as dichloromethane. In such solvents, aromatic nitration seems to proceed by one electron-transfer from an aromatic substrate to NO_2 radical to give a radical cation intermediate, which reacts with NO_2 anion (Scheme 2).

On the other hand, in acetonitrile the active species should not be NO_2^+ nor NO_2 radical because Hammett's ρ value was -3.2. NO^+ produced by the heterolytic decomposition of N_2O_4 seems to be the active species in acetonitrile. (Scheme 4).

Scheme 4. Proposed scheme for aromatic nitration with NO_2 in polar solvent



Conclusion

In order to get an insight into the mechanism of the production of nitro-polyaromatic compounds in the atmosphere and to obtain fundamental information on the aromatic nitration mechanism with NO_2 , the solvent effects on the nitration of mono-substituted benzenes with NO_2 was investigated. In solvents of lower polarity the aromatic nitration with NO_2 is suggested to proceed via radical cation intermediate, which is formed by one electron-transfer from an aromatic substrate to NO_2 radical. On the other hand, in solvents of higher polarity such as acetonitrile the aromatic nitration seems to proceed via the reaction with NO^+ , which is produced by the heterolytic decomposition of N_2O_4 .

Experimental Section

Anisole, toluene, benzene, chlorobenzene and bromobenzene were used as mono-substituted benzene substrates. Carbon tetrachloride, dibromomethane, dichloromethane and acetonitrile were used as solvents. These substrates and solvents were obtained as extra pure reagents from Wako Junyaku Kogyo. Dinitrogen tetroxide, which is in equilibrium with NO_2 radical, was manufactured as 100% pure in cylinder by Takachiho Chemical.

A mixture of substrate 2mL, dinitrogen tetroxide 10mL (or 1 or 2 mL in case of anisole as a substrate) and solvent 15mL was stirred in 100 mL flask for 6 hrs at 15°C. Analysis of products was carried out by Gas chromatograph. The analytical condition is as follows:

Detector: FID

Carrier gas: nitrogen, 40mL/min

Column: stainless column, 3 mm ϕ x 2.5 m

Filling agent: Silicon OV 101 5wt%

Support: Uniport HP 60/80 mesh

Detector temperature: 210 °C

Column temperature: 140-170 °C

In the analysis for the reaction of chlorobenzene and bromobenzene the following column was used.

Column: glass column, 3 mm ϕ x 1 m

Filling agent: Unisole 10T 2wt%

Support: Uniport HP 60/80 mesh

REFERENCES:

- (1) Bayona, J. M.; Markides, K. E.; Lee, M. L. *Environ. Sci. Technol.* **1988**, 22, 1440.
- (2) Kaji, H. *Anzen kogaku* **1988**, 27, 373.
- (3) Chuma, I.; Kondo, S.; Kakebe, K.; *Kankyo to Jintai II*; Todaishuppankai, 1983.
- (4) Perrin, C. L. *J. Am. Chem. Soc.* **1977**, 99, 5516.
- (5) Pryor, W. A.; Gleicher, G. J.; Cosgrove, J. P.; Church, D. F. *J. Org. Chem.* **1984**, 49, 5189.
- (6) Akutsu, Y.; Sasaki, M.; Saito, T.; Tamura; Yoshida, T. *Kogyo Kayaku* **1990**, 51, 61.
- (7) Hoggett, J. G.; Moodie, R. B.; Penton, J. R.; Schofield, K.; *Nitration and Aromatic Reactivity*; Cambridge University Press, 1971.
- (8) Schofield, K.; *Aromatic Nitration*; Cambridge University Press, 1980.

Chapter 6

Mechanism of Aromatic Nitration with NO₂

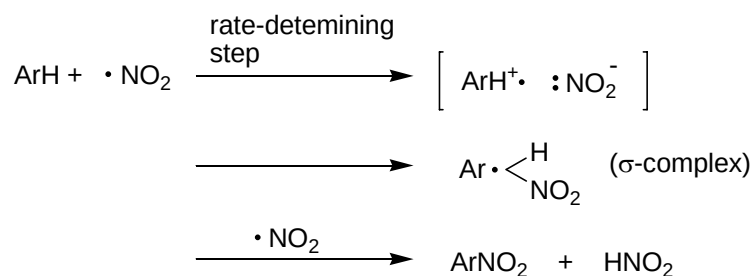
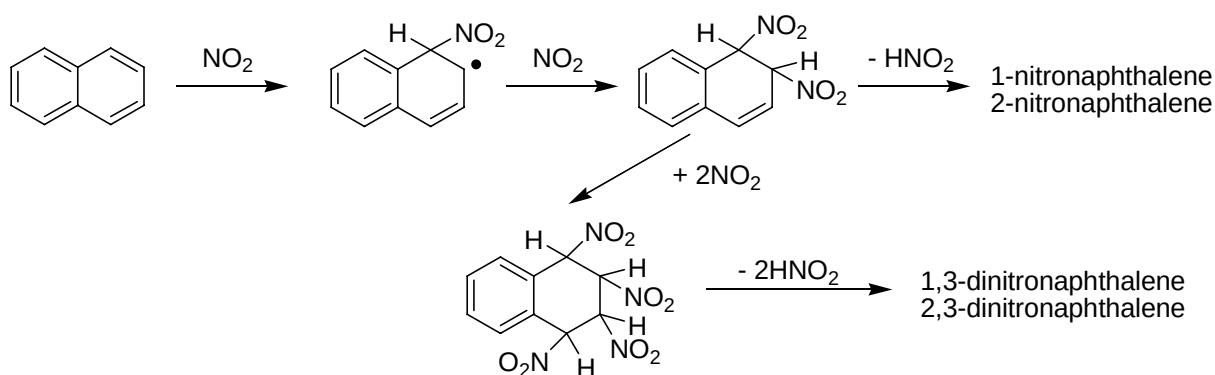
Abstract

In order to get an insight into the formation process for aromatic nitro compounds in the atmosphere and the aromatic nitration mechanism with NO₂, the isomer distribution of dinitro compounds formed in the nitration of benzene and toluene with NO₂ was studied based on heats of formation and atomic electron densities of the intermediates obtained with PM3 calculations. A mechanism involving the addition of NO₂ to the initial adduct (the σ -complex intermediate) followed by the elimination of nitrous acid has been suggested for the formation of mononitrobenzene. A mechanism involving further addition of two mole of NO₂ to form a tetranitro-intermedaite followed by the elimination of two moles of nitrous acid has been suggested for the formation of dinitrobenzene.

Introduction

Mechanisms of aromatic nitration with NO₂ have received research interest from both synthetic and environmental view points.¹⁻³ The previous work⁴ suggested that aromatic nitration with NO₂ in solution phase depends on the polarity of solvent. In solvents with lower polarity such as carbon tetrachloride or dichloromethane aromatic nitration seems to proceed by an one-electron-transfer process (Scheme 1).

It is important to note that the nitration of benzene with NO₂ gave dinitrobenzenes as well as mononitrobenzene whereas the nitration of nitrobenzene never gave dinitrobenzenes.⁵ As for the mechanism of the formation of dinitrobenzenes, the addition of the second NO₂ to the initial adduct (σ -complex intermediate) seems to be likely. Pryor proposed a mechanism including multi-step addition of NO₂ in the nitration of naphthalene with NO₂ in carbon tetrachloride (Scheme 2).⁶

Scheme 1. Proposed mechanism for aromatic nitration with NO_2 **Scheme 2.** Proposed mechanism for nitration of naphthalene with NO_2 ⁶

In this chapter, the isomer distribution of dinitro compounds in the nitration of benzene and toluene with NO_2 in dichloromethane was studied, and the mechanism of aromatic nitration with NO_2 was discussed based on the experimental results and heats of formation and atomic electron densities of the nitration intermediates obtained with PM3 calculations.

Results and Discussion

Isomer distribution in the nitration of benzene with NO_2 was determined and the result is shown in Table 1. o-Dinitrobenzene was a major isomer and p-dinitrobenzene was not formed. On the other hand the nitration of toluene with NO_2 gave a trace amount of dinitro compounds. The isomer distribution in the nitration of nitrobenzene with mixed acid of sulfuric and nitric acid reported in the literature⁷ is also shown in Table 1. It is interesting to note that the product distribution observed for NO_2 nitration

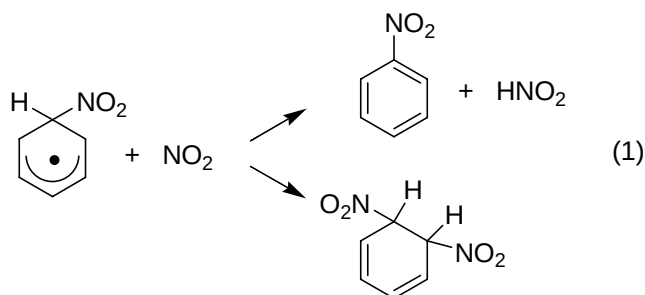
was very different from that obtained with mixed acid. A possible mechanism for dinitration with NO_2 seems to involve the attack of the second NO_2 to the initial adduct (σ -complex intermediate).

Table 1. Isomer distribution in the dinitration of benzene with NO_2 in dichloromethane

isomer distribution	this work (mol%)	ref 7 (mol%)
o-dinitrobenzene	75	7
m-dinitrobenzene	25	88
p-dinitrobenzene	0	5

In order to get an insight into this unusual dinitration of benzene and toluene with NO_2 , heats of formation and atomic electron densities of possible σ -complex intermediate of the nitration of benzene and toluene were calculated with semiempirical molecular orbital method PM3 of MOPAC ver. 5.⁸ using a HITAC M-682H in University of Tokyo. The structures were optimized by the program.

PM3 calculation was carried out for NO_2 -added σ -complex intermediate (1), (2) and (3). The results are shown in Table 2. In the case of benzene's σ -complex (1) C2 and C6 carbons have high electron densities. Therefore, it was considered that NO_2 should attack H1 hydrogen (abstraction) or carbon in o-position (radical addition). The abstraction of H1 hydrogen gives nitrobenzene, and the addition to the carbon in o-position gives intermediates (4) (trans) and (5) (cis) (eq 1).



In the case of toluene the calculation was carried out for o- and p-substituted intermediates as the initial NO_2 adducts. C3 carbon in the o-substituted adduct or C3/C5 carbons in the p-substituted adduct show high electron densities. Therefore, these intermediates are considered to give o- or p-nitrobenzene

by hydrogen abstraction, intermediate (6) by NO_2 addition to C3 carbon of o-substituted adduct, and intermediate (7) by NO_2 addition to C3 or C5 carbon of p-substituted adduct (eqs 2, 3).

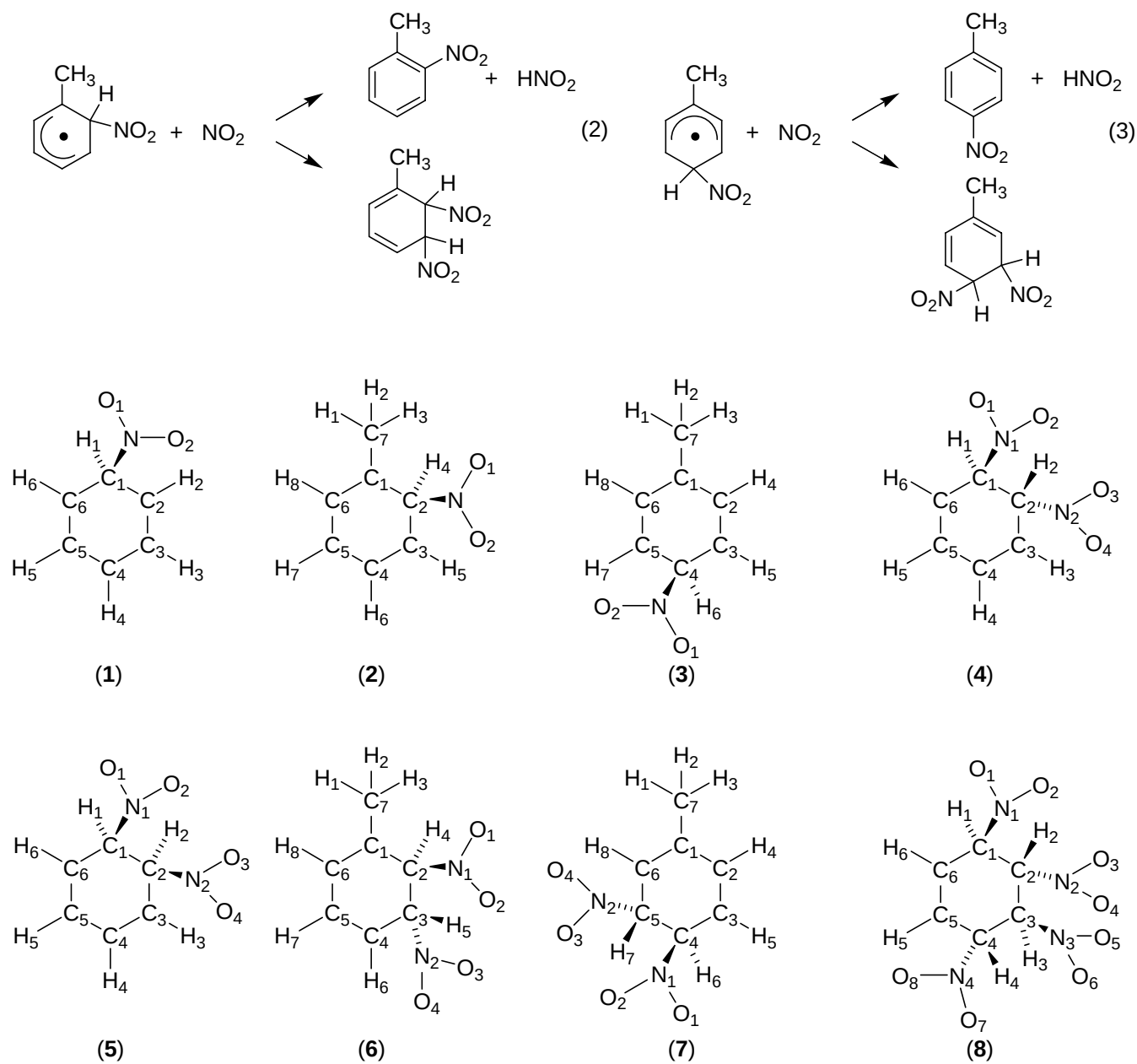


Figure 1. Structures of σ -complexes

Table 2. Heats of formation and net atomic charges of the compounds (1), (2) and (3)

	Compounds					
	(1)		(2)		(3)	
Heats of formation / kcal mol ⁻¹		40.32		31.05		29.63
Net atomic charge	C1	-0.210	C1	-0.128	C1	-0.081
	C2	-0.172	C2	-0.197	C2	-0.058
	C3	-0.062	C3	-0.177	C3	-0.156
	C4	-0.100	C4	-0.058	C4	-0.203
	C5	-0.063	C5	-0.098	C5	-0.176
	C6	-0.149	C6	-0.066	C6	-0.058
	N	+1.211	C7	-0.075	C7	-0.062
	O1	-0.585	H1	+0.061	H1	+0.057
	O2	-0.564	H2	+0.055	H2	+0.049
	H1	+0.125	H3	+0.053	H3	+0.052
	H2	+0.122	N	+1.205	H4	+0.110
	H3	+0.109	O1	-0.586	H5	+0.116
	H4	+0.111	O2	-0.563	N	+1.206
	H5	+0.109	H4	+0.125	O1	-0.586
	H6	+0.117	H5	+0.119	O2	-0.564
			H6	+0.108	H6	+0.123
			H7	+0.111	H7	+0.119
			H8	+0.111	H8	+0.110

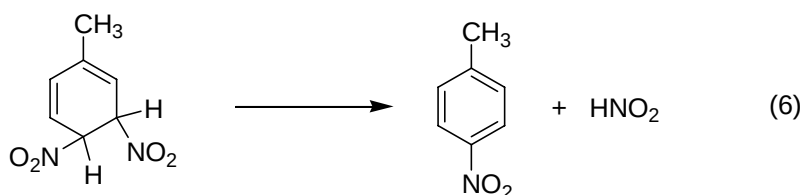
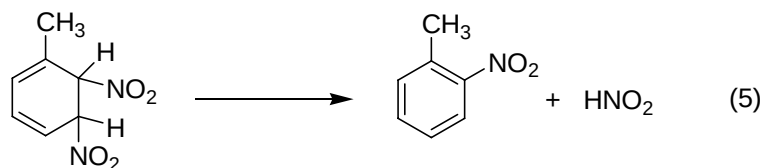
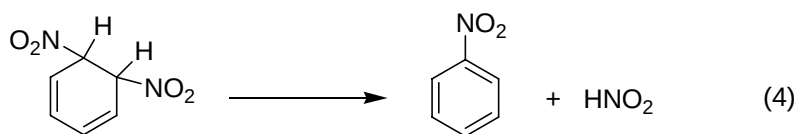
In any case the next question to be answered is which is preferentially occurred hydrogen abstraction or addition to ring carbon as the act of NO₂ to σ -complex. Thus, the possibility of NO₂-addition to the ring carbon of σ -complex intermediate was evaluated by calculating heats of formation and atom electron densities of the intermediates (4)-(7).

PM3 calculation was carried out for intermediates (4), (5), (6) and (7), which are considered to be formed by the addition of NO₂ to the σ -complexes (1), (2) and (3). The results are shown in Table 3. It was suggested that trans-addition intermediate (4) is more preferably formed than cis-addition one (5) by comparing their heats of formation. Therefore, hereafter the calculations were done only for trans-addition intermediates.

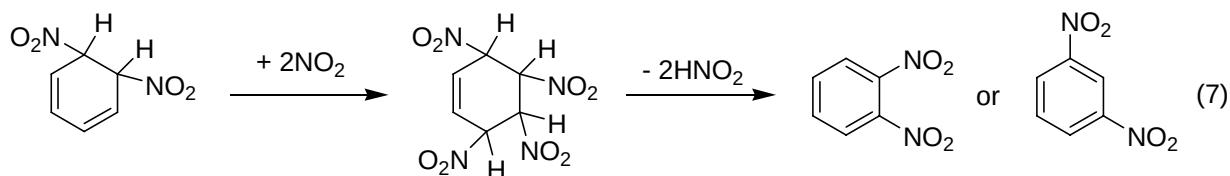
Table 3. Heats of formation and net atomic charges of the compounds (1), (2), (3) and (4)

	Compounds							
	(4)		(5)		(6)		(7)	
Heats of formation / kcal mol ⁻¹		21.20		21.82		11.90		11.79
	C1	-0.304	C1	-0.261	C1	-0.106	C1	-0.033
	C2	-0.249	C2	-0.245	C2	-0.250	C2	-0.076
	C3	-0.171	C3	-0.179	C3	-0.245	C3	-0.130
	C4	-0.060	C4	-0.053	C4	-0.192	C4	-0.303
	C5	-0.085	C5	-0.097	C5	-0.034	C5	-0.246
	C6	-0.126	C6	-0.121	C6	-0.078	C6	-0.184
	N1	+1.231	N1	+1.242	C7	-0.075	C7	-0.075
	O1	-0.588	O1	-0.588	H1	+0.057	H1	+0.057
	O2	-0.560	O2	-0.558	H2	+0.058	H2	+0.052
Net	H1	+0.172	H1	+0.120	H3	+0.058	H3	+0.057
atomic	N2	+1.221	N2	+1.237	N1	+1.212	H4	+0.119
charge	O3	-0.548	O3	-0.561	O1	-0.558	H5	+0.138
	O4	-0.582	O4	-0.580	O2	-0.553	N1	+1.229
	H2	+0.143	H2	+0.128	H4	+0.142	O1	-0.588
	H3	+0.135	H3	+0.132	N2	+1.224	O2	-0.560
	H4	+0.115	H4	+0.118	O3	-0.566	H6	+0.171
	H5	+0.120	H5	+0.121	O4	-0.570	N2	+1.219
	H6	+0.135	H6	+0.144	H5	+0.123	O3	-0.550
					H6	+0.134	O4	-0.585
					H7	+0.117	H7	+0.146
					H8	+0.121	H8	+0.138

As for the fate of intermediate (4), the major reaction course seems to be the elimination of nitrous acid to give mononitrobenzene (eq 4). In a similar way, the elimination of nitrous acid in intermediates (6) and (7) gives mononitrotoluenes. Since hydrogen of lower electron density was considered to be more easily eliminated, o-nitrotoluene should be preferentially formed from intermediate (6) by elimination of H4 hydrogen, which has lower electron density than H5 hydrogen, and NO₂ on C3 carbon. p-Nitrobenzene should be preferentially formed from intermediate (7) as well, and this speculation does not explain the experimental result of nitration of toluene by NO₂ in dichloromethane at 15°C, in which isomer distribution⁵ was o- : m- : p- = 54 : 6 : 41 (eq 5, 6).



The formation of dinitrobenzenes can be explained as follows: The elimination of two hydrogen atoms in intermediate **(4)** (oxidation by NO_2) should give o-dinitrobenzene. However, the formation of m-dinitrobenzene as a byproduct (o- : m- : p- = 75 : 25 : 0) cannot be explained by this process. Therefore, a mechanism involving further addition of NO_2 to C3 and C6 carbon on intermediate **(4)** gives tetranitro-intermediate **(8)** seems to be work considering.



The heat of formation and atom electron densities of intermediate **(8)** are shown in Table 4. Similar to intermediate **(4)**, the elimination of two molecules of nitrous acid seems to take place in intermediate **(8)**. Generally, hydrogen which has higher electron density seems to be less easily eliminated. H1 and H4 hydrogen has slightly higher electron density than H2 and H3, and therefore they would be more difficult to be eliminated. The major product seems to be o-dinitrobenzene, which is produced by elimination of H2- NO_2 and H3- NO_2 . m-Dinitrobenzene could also be formed by elimination of H1- NO_2 and H3- NO_2 in small amount (eq 7). These considerations are in accord with the experimental results.

Table 4. Heats of formation and net atomic charges of the compounds (8)

Heats of formation / kcal mol ⁻¹		11.95				
Net atomic charge	C1	-0.321	O2	-0.557	O6	-0.555
	C2	-0.335	H1	+0.184	H3	+0.194
	C3	-0.349	N2	+1.231	N4	+1.222
	C4	-0.253	O3	-0.537	O7	-0.531
	C5	-0.156	O4	-0.565	O8	-0.571
	C6	-0.078	H2	+0.194	H4	+0.142
	N1	+1.237	N3	+1.229	H5	+0.146
	O1	-0.566	O5	-0.546	H6	+0.141

In the case of toluene, the formation of tetranitro-intermediate by further addition of NO₂ seems to be less likely because of steric effect of methyl group. As a matter of fact, nitration of toluene gave much lower amount of dinitro products than that of benzene, which is consistent with the mechanism involving tetranitro-intermediate.

Conclusion

In order to get an insight into the formation process for aromatic nitro compounds in the atmosphere and the aromatic nitration mechanism with NO₂, the dinitro-isomer distribution in the nitration of benzene and toluene with NO₂ was studied and a mechanism was proposed on the basis of the experimental results and the heats of formation and atomic electron densities of the intermediates obtained with PM3 calculations. A mechanism involving the addition of NO₂ to the initial adduct (the σ -complex intermediate) followed by the elimination of nitrous acid has been suggested for the formation of mononitrobenzene. A mechanism involving further addition of two mole of NO₂ to form a tetranitro-intermediate followed by the elimination of two moles of nitrous acid has also been suggested for the formation of dinitrobenzene. It is hoped that further mechanistic studies will open a deeper insight into the formation of harmful aromatic nitro compounds, and will contribute to the development of an effective method for suppression of their formation.

Experimental Section

A mixture of substrate 2mL, dinitrogen tetraoxide 10mL and dichloromethane 15mL was stirred in 100 mL flask for 6 hrs at 15°C. Analysis of products was carried out by Gas chromatograph. The analytical condition is as follows:

Detector: FID

Carrier gas: nitrogen, 40mL/min

Column: stainless column, 3 mm ϕ x 2.5 m

Filling agent: Silicon OV 101 5 wt%

Support: Uniport HP 60/80 mesh

Detector temperature: 210 °C

Column temperature: 140-170 °C

REFERENCES:

- (1) Bayona, J. M.; Markides, K. E.; Lee, M. L. *Environ. Sci. Technol.* **1988**, 22, 1440.
- (2) Kaji, H. *Anzen kogaku* **1988**, 27, 373.
- (3) Chuma, I.; Kondo, S.; Kakebe, K.; *Kankyo to Jintai II*; Todaishuppankai, 1983
- (4) Sasaki, M.; Akutsu, Y.; Arai, M.; Tamura, M. *Kogyo Kayaku* **1992**, 53, 121.
- (5) Akutsu, Y.; Sasaki, M.; Saito, T.; Tamura; Yoshida, T. *Kogyo Kayaku* **1990**, 51, 61.
- (6) Squadrito, G. L.; Fronczek, F. R.; Church, D. F.; Pryor, W. A. *J. Org. Chem.* **1989**, 54, 548.
- (7) Hoggett, J. G.; Moodie, R. B.; Penton, J. R.; Schofield, K.; *Nitration and Aromatic Reactivity*; Cambridge University Press, 1971.
- (8) Stewart, J. J. *J. Comp. Chem.* **1989**, 10, 209.

Reference Chapter

Facile Preparation of Allylamines by Hydrazinolysis of 2-Ketoaziridines

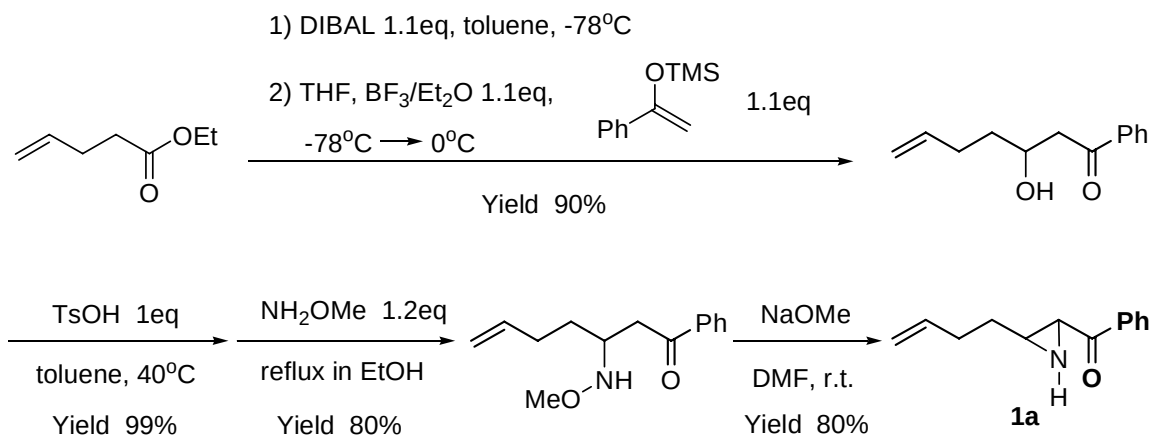
Abstract

A new method for making unprotected allyl amines by simple hydrazinolysis of 2-ketoaziridines has been developed. A variety of aziridines, including N-unprotected, N-substituted, as well as bicyclic enamine and amination type, can be transformed into diversely substituted allyl amines.

Introduction

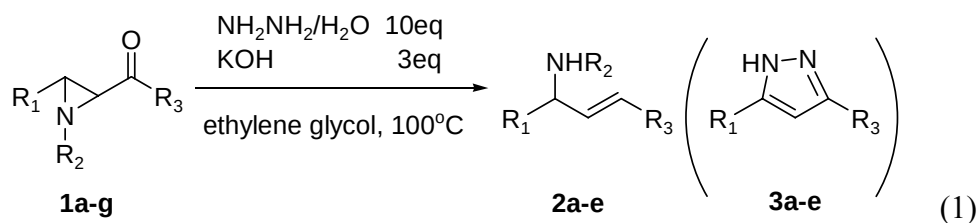
Allyl amines are often found in the structures of natural products and pharmaceuticals. Specific examples of the allyl amine-containing drugs are flunarizine,¹ naftifine,² and terbinafine,³ to name a few. In addition, allylamines are useful synthetic intermediates for the preparation of other value-added molecules. One of the well known examples of allyl amine involvement in synthesis is the catalytic asymmetric hydrogen migration during the synthesis of (-)-menthol, α -tocopherol and methoprene.⁴ Traditional synthetic routes to allyl amines have been based on (a) Gabriel synthesis, (b) allylation of amines, (c) reaction of lithium amide and substituted alkyne in the presence of the zirconocene complex, (d) allylic amination catalyzed by the transition metal complexes, (e) azidation of allylhalide followed by azide reduction, (f) reduction of α,β -unsaturated imines or oximes, and (g) reaction between nitrobenzenes and allylmagnesium halides followed by reduction.⁵

The interest in functionalized aziridines⁶ has led to investigate their use in the synthesis of other nitrogen-containing molecules such as allyl amines. At the outset, it has been decided to investigate the Wolff-Kishner type reduction of carbonyl group in 2-ketoaziridines.⁷ The 2-ketoaziridine starting materials were prepared using 1,4-addition of methoxyamine to α,β -unsaturated ketones following by base-promoted ring closure (Scheme 1)⁸ or by electrochemical olefin aziridination.⁶

Scheme 1. Synthetic route on the starting 2-ketoaziridines.

Results and Discussion

It was subsequently found that under alkaline conditions the hydrazine reduction of 2-ketoaziridines preferentially affords allyl amine derivatives instead of 2-alkylaziridines or pyrazoles (eq 1)⁹.



The scope of base-mediated hydrazine reduction of 2-ketoaziridines was investigated (Table 1). The reactions are clean and give two readily separable spots on TLC, one of which corresponds to the allylamine and the other - to the pyrazole by-product. The selectivity between allyl amine and pyrazole is moderate to high. The separation of pyrazoles from allyl amines can be easily preformed on silica gel.¹⁰

The unprotected aziridines are within the scope of the process (Table 1). The aziridines which contain sterically demanding R_1 substituents show improved selectivity for allyl amine formation. Chalcone-derived aziridines afford low selectivity for allyl amine formation if the aryl group distal to the carbonyl functionality contains an electron-donating substituent or if the proximal aryl ring contains an electron-withdrawing substituent. In the cases of activated aziridines that contain amide nitrogen, the yields of pyrazoles are increased. The N-aminophthalimide containing aziridines do not

result in any allyl amine formation. The strained bicyclic enamines give clean formation of allyl amines, whereas the bromine-containing bicycle **1g** leads to the concomitant transposition of the aziridine ring within the molecule. Finally, the aldehyde derived aziridine **1h** led to cyclic imine **2h** underhydrazinolysis conditions. The compounds of this type can be readily and stereoselectively reduced to the corresponding pyrrolidine derivatives using DIBAL-H.¹¹

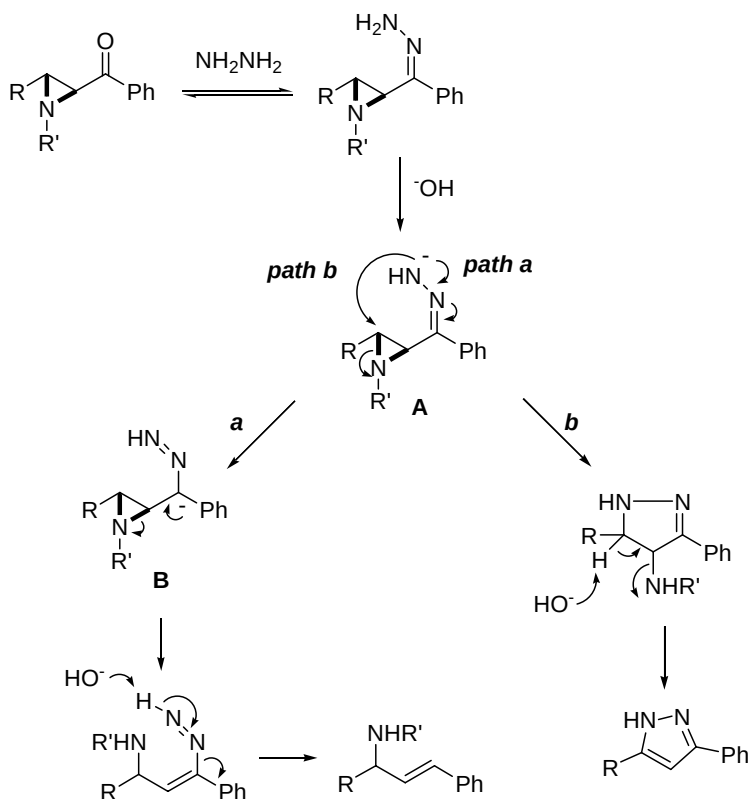
Table 1. Hydrazine Reduction of 2-Ketoaziridines under Alkaline Conditions.

Entry	Starting material	Product	Yield ^c
1	(1a)	(2a)	60%
2	(1b)	(2b)	67% ^b
3	(1c)	(2c)	2c-1: R₁, R₂, R₃ = H 46% 2c-2: R₁, R₃ = H; R₂ = Cl 60% 2c-3: R₂, R₃ = H; R₁ = Cl 65% 2c-4: R₁, R₂ = H; R₃ = Cl 33% 2c-5: R₁, R₃ = H; R₂ = OMe 11%
4	(1d)	(2a)	50%
5	(1e)	(3e)	45%
6	(1f)	(2f)	65% ^a
7	(1g)	(2g)	30%
8	(1h)	(2h)	40% ^a

^a The initial enamine product was tautomerized to cyclic imine. ^b based on 95% conversion. ^c Isolated yield.

In a typical Wolff - Kishner reduction, the anionic portion of intermediate **B** is protonated followed by further deprotonation of the N=N-H fragment and subsequent elimination of nitrogen to give the methylene group. In the case of 2-ketoaziridines, the intermediate **B** reacts with the adjacent aziridine ring at the alpha position and opens it up to give the allyl amine product (Scheme 2, path a). Alternatively, the anionic nitrogen center in the intermediate **A** can attack the aziridine ring at the beta position to form the pyrazole ring (Scheme 2, path b).

Scheme 2. Proposed mechanism for the hydrazine reduction of 2-ketoaziridines



Conclusion

In conclusion, it has been developed a mild method for making allyl amines by simple hydrazinolysis of 2-ketoaziridine derivatives in good yields and moderate selectivity. Notably, the 2-ketoaziridine starting materials can be prepared in enantiomerically pure form using the Julia-Colonna epoxidation reaction.¹² Thereby, enantiomerically enriched allyl amines should be readily available using this method.

Experimental Section

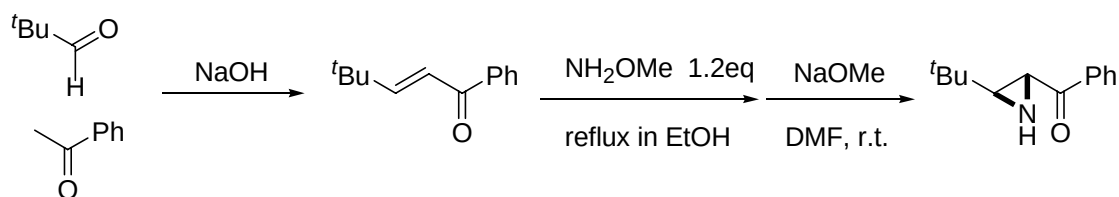
General: Anhydrous solvents such as ether, toluene, acetonitrile, and dichloromethane were prepared using the method described by Grubbs (Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518). Tetrahydrofuran (THF) was distilled over sodium-benzophenone ketyl under argon. Unless otherwise stated, all reactions were performed under nitrogen or argon atmosphere using flame-dried glassware.

Nuclear magnetic resonance spectra: ^1H and ^{13}C NMR spectra were recorded on either Mercury 300, Varian Gemini 300, or VRX-S (Unity) 400 spectrometer. ^1H NMR spectra were referenced to residual CDCl_3 (δ 7.27) and ^{13}C NMR spectra were referenced to CDCl_3 (δ 77.23). Peak multiplicities are designated by the following abbreviations: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets; br, broad; and J , coupling constant in Hz.

Chromatography: Analytical thin layer chromatography (TLC) was performed on Macherey Nagel pre-coated glass-backed TLC plates (SIL G/UV₂₅₄, 0.25mm) purchased from Rose Scientific Limited and visualized by UV lamp (254 nm) or iodine. Solvent ratios for R_f values are reported as v/v. Column chromatography was carried out using Silicycle 230-400 mesh silica gel.

Compounds **1a**, **1f**, **1g**, and **1e** were prepared according to the previous work.^{6a,11}

trans-2-Benzoyl-3-*tert*-butylaziridine (**1b**).



A mixture of pivalaldehyde (2.58 g, 30 mmol), acetophenone (3.60 g, 30 mmol), NaOH (1.20 g, 30 mmol) and water (6 mL) in methanol (60 mL) was heated under reflux for 6 hrs. After removal of methanol, CH_2Cl_2 and aq. NH_4Cl were added to the reaction mixture. The product was extracted with CH_2Cl_2 . The combined organic extracts were dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified on a silica gel column (hexane/ethyl acetate = 95/5), to give 2.60 g of (*E*)-4,4-dimethyl-1-phenyl-2-penten-1-one (yield 46%).

A mixture of (*E*)-4,4-dimethyl-1-phenyl-2-penten-1-one (1.88 g, 10 mmol) and NH_2OMe (719 mg, 15.3 mmol) in ethanol (10 ml) was heated under reflux for 5 hrs. The solvent was evaporated and the residue was purified on a silica gel column (hexane/ethyl acetate = 9/1), to give 1.30 g of 3-methoxyamino-4,4-dimethyl-1-phenyl-1-pentanone (yield: 55%).

To a stirred solution of NaO^tBu (657 mg, 12.2 mmol) in DMF (20 mL), a solution of 3-methoxyamino-4,4-dimethyl-1-phenyl-1-pentanone (1.30 g, 5.5 mmol) in DMF (10 mL) was added dropwise at room temperature. After the solution was stirred for 20 min at the same temperature, water (60 mL) was added and the product was extracted with CH_2Cl_2 (2×30 mL). The combined organic extracts were washed with water (20 mL) and the solvent was evaporated. The residue was purified on silica gel column (hexane/ethyl acetate = 9/1), to give 975 mg of *trans*-2-benzoyl-3-*tert*-butylaziridine (**1b**, yield: 87%).

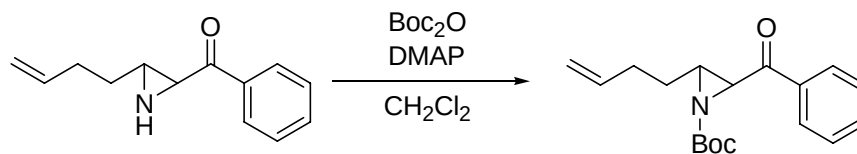
^1H NMR (CDCl_3 , 300 MHz): δ 8.00-8.05 (m, 2H), 7.60-7.66 (m, 1H), 7.39-7.54 (m, 2H), 3.35-3.38 (m, 1H), 2.00-2.10 (m, 2H), 1.00 (s, 9H).

***trans*-2-Benzoyl-3-phenylaziridine (**1c**).**

trans-2-Benzoyl-3-phenylaziridine (**1c**) was prepared in the same way as *trans*-2-benzoyl-3-*tert*-butylaziridine starting from *trans*-chalcone.

^1H NMR (CDCl_3 , 300MHz): δ 8.01-8.05 (m, 2H), 7.63-7.68 (m, 1H), 7.50-7.55 (m, 2H), 7.35-7.41 (m, 5H), 3.55 (br, 1H), 3.22 (br, 1H), 2.71 (br, 1H).

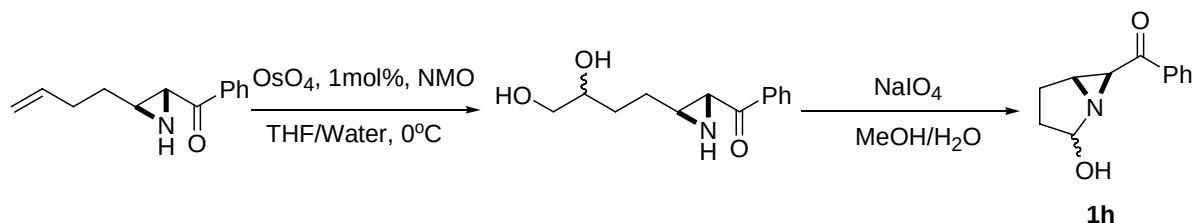
2-Benzoyl-3-but-3-enylaziridine-1-carboxylic acid *tert*-butyl ester (1d**).**



To a mixture of (3-but-3-enyl-*trans*-aziridin-2-yl)-phenylmethanone (**1d**, 500mg, 2.5 mmol), dichloromethane (10 mL), and DMAP (610 mg, 5.0 mmol) was added di-*tert*-butyl dicarbonate (818 mg, 3.7 mmol) at room temperature and stirred for 3 hours. After completion judged by TLC, the reaction

mixture was washed with water (5 mL), and was dried over sodium sulfate. The solvent was removed in vacuo and the residue was purified on a silica gel column (hexane/ethyl acetate = 7/3), to give 677 mg of 2-benzoyl-3-but-3-enylaziridine-1-carboxylic acid *tert*-butyl ester (**1d**, yield: 90%).

(2-Hydroxy-1-aza-bicyclo[3.1.0]hex-6-yl)-phenyl-methanone (1h).



To a mixture of (3-but-3-enyl-*trans*-aziridin-2-yl)-phenylmethanone (**1a**, 0.9 g, 4.5 mmol), *N*-methylmorpholine oxide (0.53 g, 4.5 mmol), THF (40 mL), and water (4 mL) was added OsO₄ (4% aqueous solution, 286 μ L, 0.045 mmol) at the ice bath temperature and the mixture was stirred overnight in ice bath. After completion judged by TLC, the reaction mixture was concentrated. The volatiles were removed under vacuum to afford the crude product as brown oil (1.05 g, yield: >99%, NMR indicates purity over 90%). The crude product was used in next step without additional purification.

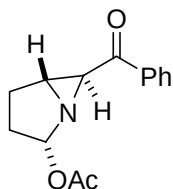
To a mixture of [3-(3, 4-dihydroxy-butyl)-aziridin-2-yl]-phenyl-methanone (1.0 g, 4.3 mmol), MeOH (40 mL) and water (0.5 mL) was added sodium periodate (0.92 g, 4.3 mmol) at room temperature and the mixture was stirred for 2 hours. After completion judged by TLC, the reaction mixture was concentrated. To the residue, water (50 mL) was added. Product was precipitated as yellow solid. The suspension was treated in an ultrasonic bath for 20 min, and then filtered. After drying over P₂O₅ over 48 hours, the product (2-hydroxy-1-aza-bicyclo[3.1.0]hex-6-yl)-phenyl-methanone (**1h**) was collected as yellow solid (0.86 g, yield: 99 %).

NMR of product **1h** is complicated with board peaks due to the equilibria between its open (aldehyde) form and closed (hemiaminal) forms. HR-MS (EI) *m/z*: calcd. for C₁₂H₁₃NO₂ 204.1025, found 204.1026. The characterization was achieved by forming the acetylated derivative (see below).

To a mixture of (2-hydroxy-1-aza-bicyclo[3.1.0]hex-6-yl)-phenyl-methanone (**1h**), (120 mg, 0.59 mmol), 4-dimethylaminopyridine (144 mg, 1.18 mmol) and dichloromethane (2 mL), was added acetic anhydride (111 μ L, 1.18 mmol). The mixture was stirred at room temperature for 1 hour. The reaction

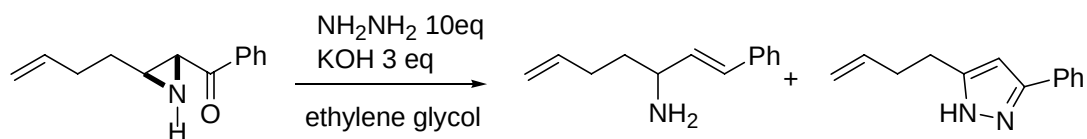
mixture was concentrated and purified on a silica gel column chromatography (EtOAc) to afford one diastereomeric acetate ($2R^*$, $5R^*$, $6S^*$)-6-benzoyl-1-aza-bicyclo[3.1.0]hex-2-yl ester (102 mg, yield 71%) as major product. A trace amount of the other diastereomer (less than 10 mg) was obtained as a minor product.

Acetic acid ($2R^*$, $5R^*$, $6S^*$)-6-benzoyl-1-aza-bicyclo[3.1.0]hex-2-yl ester



^1H NMR (CDCl_3 , 400MHz): δ 8.06 (d, J = 8.0 Hz, 2H), 7.61 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.2 Hz, 2H), 6.03 (t, J = 7.2 Hz, 1H), 3.44 (d, J = 2.8 Hz, 1H), 3.05 (d, J = 2.0 Hz, 2H), 2.39-2.11 (m, 7H, includes 2.11, s, 3H); 1.55-1.44 (m, 1H); ^{13}C NMR (CDCl_3 , 100MHz): δ 195.3, 169.6, 136.9, 133.4, 128.7, 128.4, 90.7, 47.6, 37.7, 25.6, 25.0, 21.0; HR-MS (EI) m/z : calcd. for $\text{C}_{14}\text{H}_{15}\text{NO}_3$ 245.1130, found 245.1132.

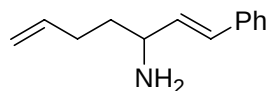
Typical procedure for hydrazine reduction (Table 1, entry 1):



A mixture of (3-but-3-enyl-*trans*-aziridin-2-yl)-phenylmethanone (**1a**, 100 mg, 0.5 mmol), hydrazine monohydrate (250 mg, 5.0 mmol), potassium hydroxide (84 mg, 1.5 mmol) and ethylene glycol (2 mL) was stirred at 100 °C for 1 hour. After completion judged by TLC, dichloromethane (10 mL) and water (10 mL) were added, and the water layer was extracted with dichloromethane (5 mL). The combined organic layers were washed with water (10 mL), and were dried over sodium sulfate and the solvent was removed in vacuo. The residue was purified on a silica gel column (hexane/ethyl acetate = 6/4), to

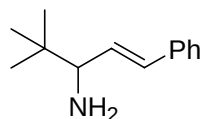
give 1-styrylpent-4-enylamine (**2a**, yield: 60%) and 5-but-3-enyl-3-phenyl-1H-pyrazole (**3a**, yield: 30%).

1-Styrylpent-4-enylamine (2a).



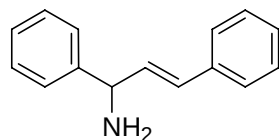
^1H NMR (CDCl_3 , 400MHz): δ 7.25-7.37 (m, 5H), 6.50 (d, $J=11.6$ Hz, 1H), 5.79-5.86 (m, 1H), 5.57 (dd, $J=11.6$ Hz, 6.0 Hz, 1H), 4.94-5.04 (m, 1H), 3.89-3.91 (m, 1H), 2.11-2.17 (m, 2H), 1.58-1.66 (m, 2H); ^{13}C NMR (CDCl_3 , 100MHz): δ 138.3, 137.3, 129.1, 128.6, 128.3, 128.2, 126.9, 114.7, 48.2, 37.3, 30.4; HR-MS (EI) m/z : calcd. for $\text{C}_{13}\text{H}_{16}\text{N}$ 186.1283, found 186.1278.

1-tert-Butyl-3-phenylallylamine (2b).

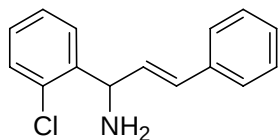


^1H NMR (CDCl_3 , 400MHz): δ 7.33-7.40 (m, 4H), 7.25-7.30 (m, 1H), 6.55 (d, $J=11.6$ Hz, 1H), 5.71 (d, $J=11.6$ Hz, 10.4 Hz, 1H), 3.59 (d, $J=10.4$ Hz, 1H), 1.26 (bs, 2H), 0.93 (s, 9H); ^{13}C NMR (CDCl_3 , 100MHz): δ 137.5, 134.0, 130.1, 128.7, 128.2, 126.7, 56.8, 26.1.

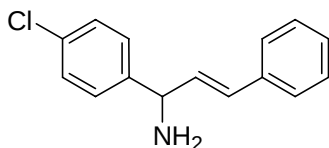
1,3-diphenylallylamine (2c-1).



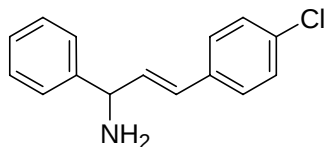
^1H NMR (CDCl_3 , 300MHz): δ 7.29-7.49 (m, 5H), 6.62 (d, $J=11.6$ Hz, 1H), 5.91 (dd, $J=11.6$ Hz, 9.6 Hz, 1H), 5.05 (d, $J=9.6$ Hz, 1H), 1.71 (br, 2H); ^{13}C NMR (CDCl_3 , 75MHz): δ 136.9, 136.0, 129.1, 128.7, 128.7, 128.3, 127.2, 126.6, 52.7.

1-(2-Chloro-phenyl)-3-phenyl-allylamine (2c-2).

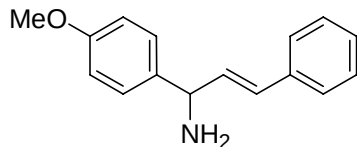
^1H NMR: (300 MHz, CDCl_3) δ 7.44 (dd, $J = 6.6$ Hz, 1.8 Hz, 1H), 7.39-7.17 (m, 8H), 6.59 (d, $J = 11.4$ Hz, 1H), 5.92 (dd, $J = 11.5$ Hz, 9.3 Hz, 1H), 5.34 (d, $J = 9.3$ Hz, 1H), 1.96-1.82 (b, 2H); ^{13}C NMR: (75 MHz, CDCl_3) δ 142.6, 136.8, 133.8, 133.3, 130.5, 130.1, 128.8, 128.5, 128.4, 128.1, 127.5, 127.4, 50.4; HR-MS (EI) m/z : calcd. for $\text{C}_{15}\text{H}_{14}\text{ClN}$ 243.0737, found 243.0738.

1-(4-Chloro-phenyl)-3-phenyl-allylamine (2c-3).

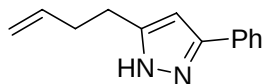
^1H NMR: (300 MHz, CDCl_3) δ 7.38-7.29 (m, 9H), 6.62 (d, $J = 11.4$ Hz, 1H), 5.83 (t, $J = 11.4$ Hz, 1H), 5.02 (d, $J = 9.6$ Hz, 1H), 1.79-1.57 (b, 2H); ^{13}C NMR: (75 MHz, CDCl_3) δ 143.2, 136.7, 135.5, 132.8, 129.5, 128.8, 128.7, 128.4, 128.1, 127.3, 52.2; HR-MS (EI) m/z : calcd. for $\text{C}_{15}\text{H}_{14}\text{ClN}$ 243.0737, found 243.0739.

3-(4-Chloro-phenyl)-1-phenyl-allylamine (2c-4).

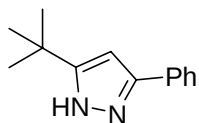
^1H NMR: (300 MHz, CDCl_3) δ 7.41-7.20 (m, 9H), 6.50 (d, $J = 11.7$ Hz, 1H), 5.88 (dd, $J = 11.7$ Hz, 9.6 Hz, 1H), 4.99-4.87 (b, 1H), 1.90-1.56 (b, 2H); ^{13}C NMR: (75 MHz, CDCl_3) δ 135.4, 133.1, 130.2, 129.0, 128.7, 128.1, 127.8, 127.5, 126.7, 125.9, 52.9; HR-MS (EI) m/z : calcd. for $\text{C}_{15}\text{H}_{14}\text{ClN}$ 243.0737, found 243.0737.

1-(4-Methoxy-phenyl)-3-phenyl-allylamine (2c-5).

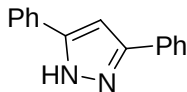
^1H NMR: (500 MHz, CDCl_3) δ 7.36-7.24 (m, 7H), 6.89 (d, J = 7.2 Hz, 2H), 6.54 (d, J = 11.8 Hz, 1H), 5.84 (dd, J = 11.5 Hz, 9.5 Hz, 1H) 4.96 (d, J = 9.0 Hz, 1H), 3.80 (s, 3H), 1.80-1.62 (b, 2H); ^{13}C NMR: (125 MHz, CDCl_3) δ 158.9, 137.1, 136.3, 128.9, 128.9, 128.5, 127.9, 127.3, 114.2, 55.5, 52.3; HR-MS (EI) m/z : calcd. for $\text{C}_{16}\text{H}_{17}\text{NO}$ 239.1310, found 239.1311.

5-But-3-enyl-3-phenyl-1H-pyrazole (3a).

^1H NMR (CDCl_3 , 400MHz): δ 7.75-7.77 (m, 2H), 7.40-7.44 (m, 1H), 7.30-7.36 (m, 2H), 6.42 (s, 1H), 5.84-5.94 (m, 1H), 5.04-5.14 (m, 2H), 2.79 (t, J =7.6 Hz, 2H), 2.43-2.49 (m, 2H); ^{13}C NMR (CDCl_3 , 100MHz): δ 137.4, 128.7, 127.9, 125.7, 115.7, 101.2, 33.2, 25.9; HR-MS (EI) m/z : calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_2$ 198.1157, found 198.1154.

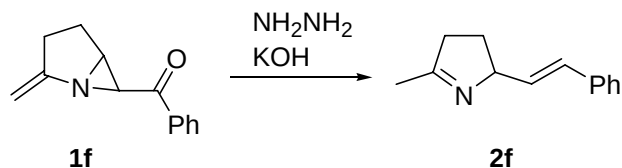
5-tert-Butyl-3-phenyl-1H-pyrazole (3c).

^1H NMR (CDCl_3 , 400MHz): δ 7.78-7.80 (m, 2H), 7.42-7.45 (m, 2H), 7.33-7.37 (m, 1H), 6.44 (s, 1H), 1.43 (s, 9H); ^{13}C NMR (CDCl_3 , 100MHz): δ 128.7, 127.8, 125.6, 98.8, 30.4.

3,5-diphenyl-1H-pyrazole (3e).

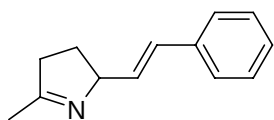
^1H NMR (CDCl_3 , 300MHz): δ 7.77-7.80 (m, 4H), 7.37-7.51 (m, 6H), 6.90 (s, 1H); ^{13}C NMR (CDCl_3 , 75MHz): δ 128.9, 128.4, 125.6, 100.2.

Typical procedure for hydrazine reduction of bicyclic aziridines (Table 1, entry 2):



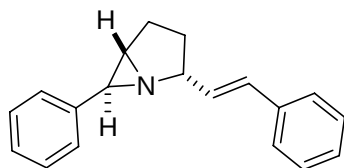
A mixture of (5*R**,6*S**)-(methylene-1-azabicyclo[3.1.0]hex-6-yl)-phenylmethanone (**1f**, 50 mg, 0.25 mmol), hydrazine monohydrate (125 mg, 2.5 mmol), potassium hydroxide (42 mg, 0.75 mmol) and ethylene glycol (1 mL) was stirred at 100 °C for 1 hour. After completion judged by TLC, dichloromethane (5 mL) and water (5 mL) were added, and the water layer was extracted with dichloromethane (3 mL). The combined organic layers were washed with water (5 mL), and were dried over sodium sulfate and the solvent was removed in vacuo. The residue was purified on a silica gel column (hexane/ethyl acetate = 6/4), to give 30 mg of 5-methyl-2-styryl-3,4-dihydro-2H-pyrrole (**2b**, yield: 65%).

5-Methyl-2-styryl-3,4-dihydro-2H-pyrrole (2f).



^1H NMR (CDCl_3 , 300MHz): δ 7.34-7.45 (m, 4H), 7.24-7.30 (m, 1H), 6.59 (d, $J=11.4$ Hz, 1H), 5.59 (dd, $J=11.4$ Hz, 9.6 Hz, 1H), 4.92-5.01 (m, 1H), 2.46-2.70 (m, 2H), 2.17-2.28 (m, 1H), 2.11 (d, $J=1.8$ Hz, 3H), 1.62-1.75 (m, 1H); ^{13}C NMR (CDCl_3 , 100MHz): δ 175.5, 137.1, 134.4, 129.9, 129.0, 128.1, 126.9, 69.9, 39.4, 30.9, 19.9; HR-MS (EI) m/z : calcd. for $\text{C}_{13}\text{H}_{15}\text{N}$ 185.1205, found 185.1202.

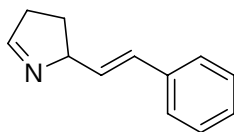
(2*R,5*S**,6*S**)-6-Phenyl-2-styryl-1-azabicyclo[3.1.0]hexane (2g).**



The reaction temperature and time for **2e**: the reaction mixture was stirred at 60 °C for 30 minutes, then heated up to 100 °C and stirred for 10 minutes.

^1H NMR (CDCl_3 , 400MHz): δ 7.44-7.45 (m, 2H), 7.36-7.40 (m, 2H), 7.22-7.33 (m, 6H), 6.62 (d, $J=11.6$ Hz, 1H), 5.75 (dd, $J=11.6$ Hz, 9.2 Hz, 1H), 4.32-4.39 (m, 1H), 2.73 (d, $J=2.8$ Hz, 1H), 2.52 (dd, $J=4.4$ Hz, 2.8 , 1H), 2.37 (dd, 9.6 Hz, 8.4 Hz, 1H), 2.07-2.16 (m, 1H), 1.89-1.96 (m, 1H), 1.43-1.54 (m, 1H); ^{13}C NMR (CDCl_3 , 100MHz): δ 131.7 , 131.6 , 128.8 , 128.2 , 128.2 , 127.0 , 126.7 , 126.4 , 61.1 , 50.4 , 36.0 , 28.0 , 27.7 ; HR-MS (EI) m/z : calcd. for $\text{C}_{19}\text{H}_{19}\text{N}$ 261.1518, found 261.1512.

2-Styryl-3,4-dihydro-2H-pyrrole (2h).



^1H NMR: (300 MHz, CDCl_3) δ 7.69 (s, 1H), 7.44-7.23 (m, 5H), 6.59 (d, $J = 11.7$ Hz, 1H), 5.54 (dd, $J=11.4$ Hz, 9.6 Hz, 1H), 4.97 (d, $J = 7.2$ Hz, 1H), 2.79-2.49 (m, 2H), 2.20-2.09 (m, 1H), 1.62-1.55 (m, 1H); ^{13}C NMR: (125 MHz, CDCl_3) δ 167.3, 137.2, 134.0, 130.5, 129.1, 128.3, 127.2, 70.4, 37.5, 28.8; HR-MS (EI) m/z : calcd. for $\text{C}_{12}\text{H}_{13}\text{N}$ 171.1048, found 171.1043.

REFERENCES:

- (1) Holmes, B.; Brogden, R. N.; Heel, R. C.; Speight, T. M.; Avery, G. S. *Drugs* **1984**, 29, 6.
- (2) Monk, J. P.; Brogden, R. N. *Drugs* **1991**, 42, 659.
- (3) Balfour, J. A.; Faulds, D. *Drugs* **1992**, 43, 259.
- (4) For review, see: Otsuka, S.; Tani, K. *Synthesis* **1991**, 665
- (5) Marson, C. M.; Hobson, A. D.; *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon: Oxford, 1995; Vol. 2, p 297.
- (6) (a) Siu, T.; Yudin, A. K. *J. Am. Chem. Soc.* **2002**, 124, 530. (b) Caiazzo, A.; Dalili, S.; Yudin, A. K. *Org. Lett.* **2002**, 4, 2597. (c) Sasaki, M.; Dalili, S.; Yudin, A. K. *J. Org. Chem.* **2003**, 68, 2045.
- (7) For conversion of 2-ketoepoxides to allyl alcohols with hydrazine, see: Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, 26, 3615.
- (8) Seko, S.; Tani, N. *Tetrahedron Lett.* **1998**, 39, 8117.
- (9) Interestingly, the reactions between 2-ketoaziridines and hydrazine in the presence of acids proceed to give pyrazoles: Cromwell, N. H.; Barker, N. G.; Wankel, R. A.; Vanderhorst, P. J.; Olson, F. W.; Anglin, Jr., J. L. *J. Am. Chem. Soc.* **1951**, 73, 1044.
- (10) For conversion of 2-ketoepoxides into allyl alcohols with hydrazine, see: Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, 26, 3615.
- (11) Sasaki, M.; Yudin, A. K. *J. Am. Chem. Soc.*, **2003**, 125, 14242
- (12) For highly enantioselective Julia-Colonna epoxidation followed by conversion into aziridine, see: (a) Nemoto, T.; Ohshima, T.; Shibasaki, M. *Yuki Gosei Kagaku Kyokaishi* **2002**, 60, 94 and references therein. For ring opening by azide and reductive ring closing to aziridine, see: (b) Jin, X. L.; Sugihara, H.; Daikai, K.; Tateishi, H.; Jin, Y. Z.; Furuno, H.; Inanaga, J. *Tetrahedron* **2002**, 58, 8321-8329. (c) Legters, J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1989**, 30, 4881-4.

List of Publications

- (1) *N*-Arylation of Aziridines

Sasaki, M.; Dalili, S.; Yudin, A. K. *J. Org. Chem.* **2003**, 68, 2045-2047

- (2) Oxidative Cycloamination of Olefins with Aziridines as a Versatile Route to Saturated Nitrogen-Containing Heterocycles

Sasaki, M.; Yudin, A. K. *J. Am. Chem. Soc.* **2003**, 125, 14242-14243

- (3) One-Pot Reduction-Aldol Reaction of Esters

Sasaki, M.; Yudin, A. K. *Synlett* **2004**, 2443-2444

- (4) New Methods for the Synthesis of Heterocyclic Compounds

Caiazza, A.; Dalili, S.; Picard, C.; Sasaki, M.; Siu, T.; Yudin, A. K. *Pure Appl.Chem.* **2004**, 76, 603-613

- (5) Mechanism for aromatic nitration with nitrogen dioxide

Sasaki, M.; Akutsu, Y.; Arai, M.; Tamura, M. *Kogyo Kagaku* **1992**, 53, 115-120

- (6) Solvent effects on aromatic nitration with nitrogen dioxide

Sasaki, M.; Akutsu, Y.; Arai, M.; Tamura, M. *Kogyo Kagaku* **1992**, 53, 121-124

Other Publications

- (1) Facile Preparation of Allyl Amines and Pyrazoles by Hydrazinolysis of 2-Ketoaziridines
Chen, G.; Sasaki, M.; Yudin, A. K. *Tetrahedron Lett.*, **2006**, 47, 255-259
- (2) Strained Enamines as Versatile Intermediates for Stereocontrolled Construction of Nitrogen Heterocycles
Chen, G.; Sasaki, M.; Li, X.; Yudin, A. K. *J. Org. Chem.*, **2006**, 71, 6067-6073
- (3) A study on the reactivity of aromatic compounds with nitrogen dioxide
Akutsu, Y.; Sasaki, M.; Saito, T.; Tamura; Yoshida, T. *Kogyo Kayaku* **1990**, 51, 61-64