Development of Novel Synthetic Methods Utilizing Mono- or Trivalent Iodine Reagent

（一価あるいは三価のヨウ素反応剤を活用する新規合成反応の開発）

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Preface

The studies presented in this thesis were conducted under the supervision by Professor Dr. Satoshi Minakata, Department of Applied Chemistry, Graduate School of Engineering, Osaka University during 2009-2015.

The objects of this thesis are development of novel synthetic methodologies utilizing mono- or trivalent iodine reagent. The author hopes sincerely that the fundamental work described in this thesis contributes to further development of synthetic methods in iodine chemistry, functional material, and other related fields of chemistry.

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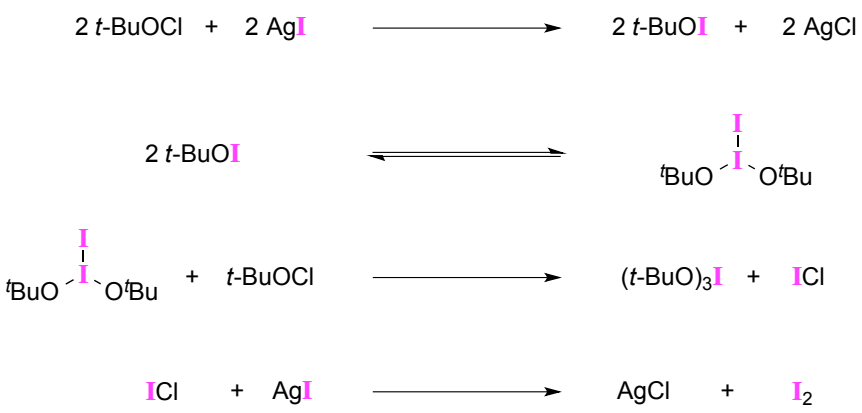
General Introduction

1. Iodine

Iodine is one of the sparse resources which Japan boasts to the world. Although iodine, which is the heaviest non-radioactive element, is most stable with an oxidation state of –1, it can be easily oxidized to oxidation states of +1, +3, +5, +7, because of the largest atomic radius, the least electronegativity and the highest polarizability compared to other halogen atoms such as fluorine, chlorine and bromine. Additionally, the compounds containing iodine atom have high reactivity, due to low bond dissociation energies of Q–I bonds. Therefore, over the past a few decades, organic transformations utilizing unique properties of iodine has experienced a rapid development, owing to the reasons as described above.[1]

2. *tert*-Butyl Hypoiodite: Monovalent Iodine Reagent

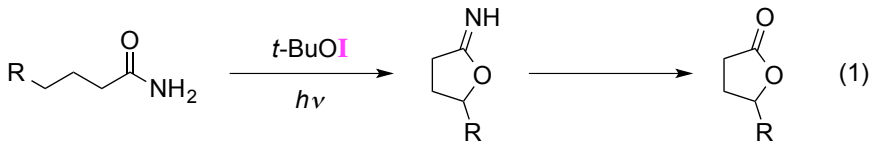
Hypoiodites containing oxygen–iodine bond, have been recently utilized for iodo-functionalizations and oxidative reactions in synthetic organic chemistry.[2] *tert*-Butyl hypoiodite (*t*-BuOI) classified as these monovalent iodine compounds, was firstly employed in the photochemical reaction by Barton in 1964.[3] Since *t*-BuOI has not been isolated in pure form owing to its thermal- and photo-instability, its precise physicochemical property is still uncertain. Although *t*-BuOI can be readily prepared in situ from *tert*-butyl hypochlorite (*t*-BuOCl) with either iodine or metal iodide salts (MI: sodium iodide, potassium iodide, silver iodide and mercury iodide), or potassium *tert*-butoxide with iodine, the reagent generated by the former method (*t*-BuOCl with I_2) is thoroughly different to that prepared from the latter two methods (*t*-BuOCl with MI and *t*-BuOK with I_2) in terms of its properties and reactivities.[4] Among these generation methods of *t*-BuOI, the reaction of *t*-BuOCl with metal iodide was investigated by the spectroscopic measurements of the products as shown in Scheme 1.



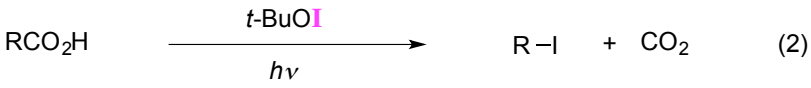
Scheme 1. Generation Method for *t*-BuOI from *t*-BuOCl and AgI

Although *t*-BuOI might have a potential reactivity toward organic molecules, few examples of the reagent being used in organic synthesis have been reported to date. For example, Barton and co-workers reported intramolecular lactonisation by photolysis of *N*-iodoamides generated from amides with *t*-BuOI (Eq. 1)[5] and decarboxylation of carboxylic

acids leading to alkyl iodides (Eq. 2).[6]

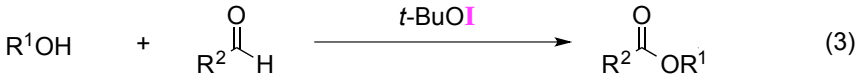


(1)

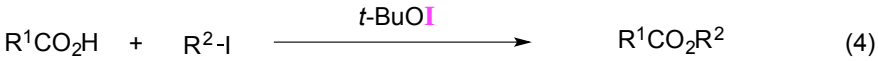


(2)

Synthesis of ester from aldehydes with alcohols (Eq. 3) and from carboxylic acids with alkyl iodides (Eq. 4), respectively, were reperted by Goosen *et al*.[7]

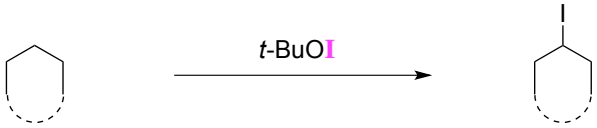


(3)



(4)

The reagent was also found to be used for iodination of hydrocarbons (Eq. 5)[8] and phenol derivatives (Eq. 6).[9]



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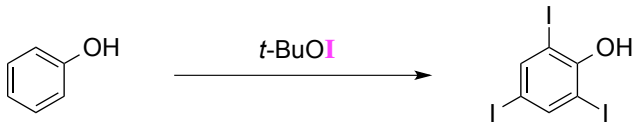
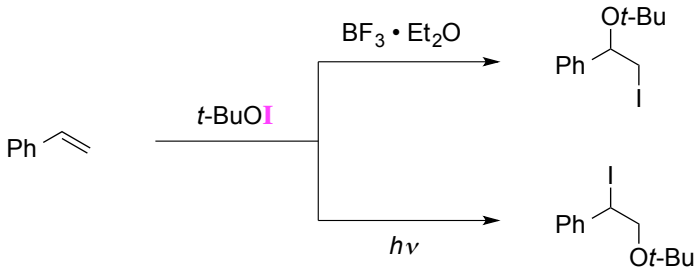


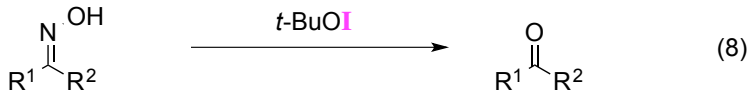
(6)

The group led by Heasley realized regioselective addition of *t*-BuOI to olefins under ionic or radical conditions (Eq. 7).[10]



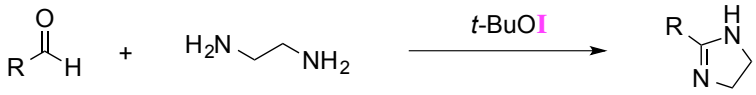
(7)

Telvekar reported oxidative regeneration of carbonyl compounds from their oximes using *t*-BuOI in carbon tetrachloride (Eq. 8).[11]

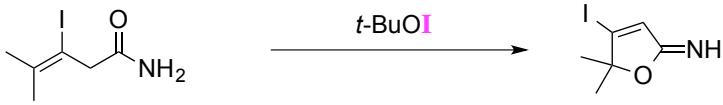


(8)

While preparation of 2-imidazolines from aldehydes and 1,2-diamines was developed by Togo group (Eq. 9),[12] Li utilized this reagent for 5-endo electrophilic cyclization of unsaturated amides (Eq. 10).[13]

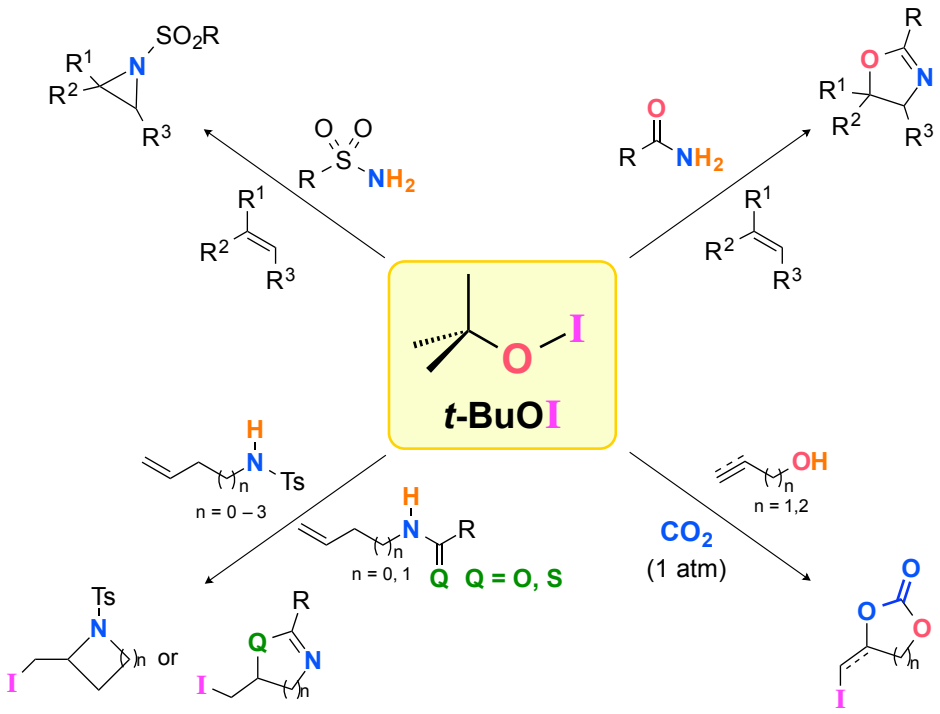


(9)

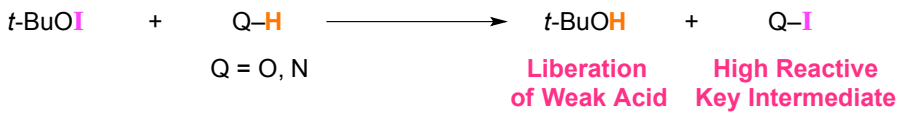


(10)

On the other hand, our group previously developed efficient synthetic methods for heterocyclic compounds from simple amides and alkenes and for CO_2 fixation by unsaturated alcohols utilizing *t*-BuOI (Figure 1).[14] In these reports, our group has demonstrated that *t*-BuOI has a powerful iodinating reactivity for substitution of acidic hydrogen, to generate unique species having Q–I bonds (Q = O, N); such species served as key intermediates in the synthetic reaction. The key to success of exchange of an acidic proton by the iodine atom of *t*-BuOI was liberation of thermodynamically stable compound, *tert*-butyl alcohol (Scheme 2).



Fugure 1. Utilizing *t*-BuOI for Organic Synthesis in Our Group

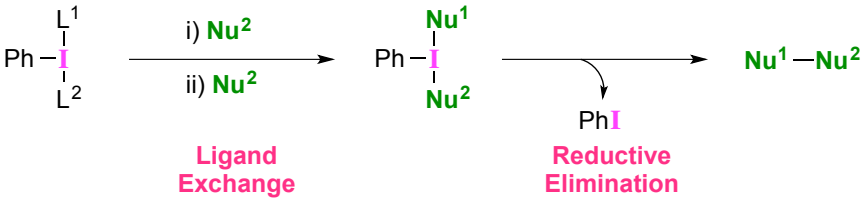


Scheme 2. The Key to Reactivity of *t*-BuOI

3. Hypervalent Iodine(III) Compounds

Hypervalent iodine(III) compounds have caught great attention as efficient, mild, chemselective oxidizing reagents and their environmentally benign property in contrast to heavy-metal oxidants.[1,15] Iodine atom of λ^3-iodane has more electrons (total ten electrons) than an octet in valence shell. The structure of hypervalent iodine(III), $PhIX_2$ (X = heteroatom) is a T-shape with a collinear disposition of the most electronegative ligands X occupying apical positions and with planar disposition of Ph group and two lone pair electrons occupying equatorial position. Because hypervalent bonding (I–X bond) is longer than the sum of the

appropriate covalent radii, ligand exchange on the iodine atom with external nucleophiles (Nu^1 and Nu^2) easily proceed. Subsequent reductive elimination of iodobenzene gives ligand coupling product (Nu^1–Nu^2) (Scheme 3).



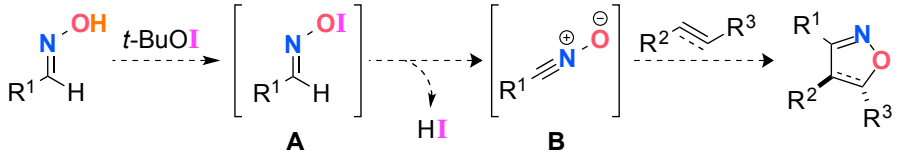
Scheme 3. The Key to Reactivity of Hypervalent Iodine(III) Compounds

Due to these reactivities, hypervalent iodine(III) reagents have been utilized to develop privileged oxidative C–C, C–O and C–N bond forming reactions.[1,15] The appropriate utilizing of hypervalent iodine(III) compounds would provide novel synthetic reactions.

4. Hypothesis and Synopsis of the Thesis

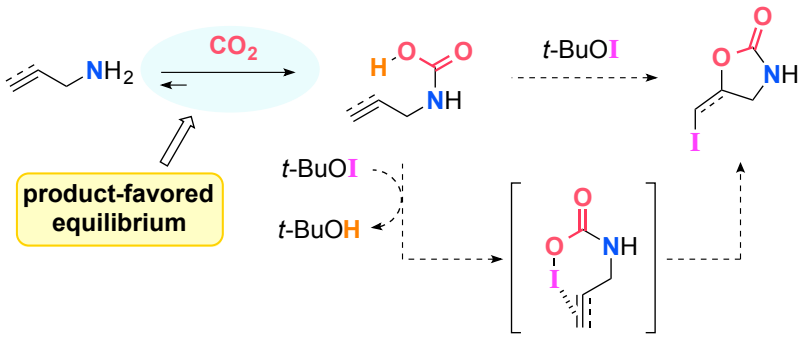
On the basis of these backgrounds, I hypothesized the following novel reactions would be feasible by utilizing *t*-BuOI;

i) If aldoximes, which have a weakly acidic proton attached to the oxygen atom of hydroxyimino group, were treated with *t*-BuOI, *O*-iodinated aldoximes (**A**) would generate and followed by elimination hydrogen iodide to give corresponding nitrile oxides (**B**) (Scheme 4). It is well known that nitrile oxides can readily react with carbon–carbon unsaturated bonds to provide isoxazolines and isoxazoles through 1,3-dipolar cycloaddition.



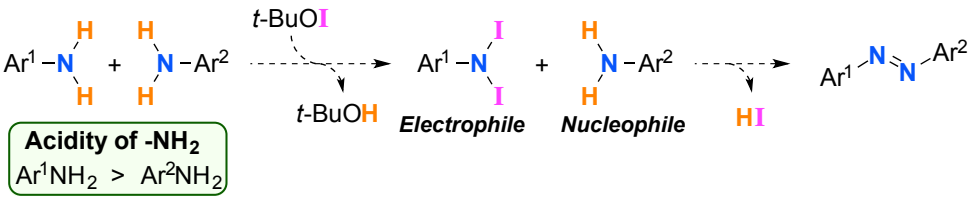
Scheme 4. The Hypothesis of Generation of Nitrile Oxides from Aldoximes

ii) With CO_2 fixation by unsaturated alcohols in mind,[14e] a more efficient cyclizative atmospheric fixation of CO_2 by unsaturated amines utilizing *t*-BuOI under mild conditions would be feasible without the use of external strong bases or metal catalysts (Scheme 5).



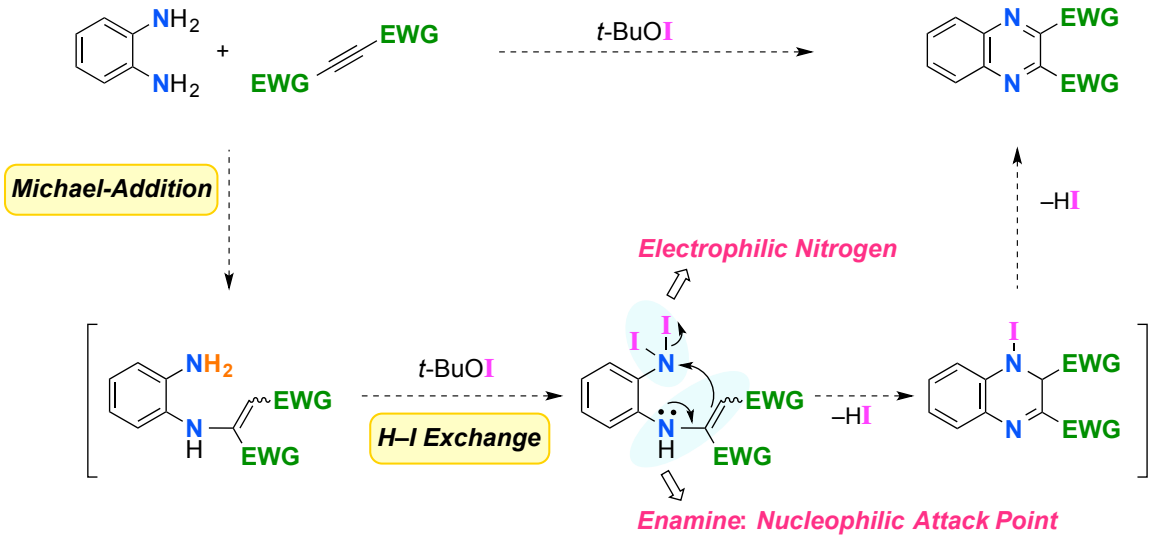
Scheme 5. The Strategy for CO_2 Fixation to Unsaturated Amines

iii) The treatment of aromatic amines, which have two relatively weakly acidic hydrogen atoms, with *t*-BuOI would generate $ArNI_2$ through a hydrogen–iodine exchange process, and the subsequent elimination of 2HI from $ArNI_2$ and unreacted $ArNH_2$ would produce symmetric aromatic azo compounds. Specifically, given that two different aromatic amines are used, the aromatic amine having the more acidic hydrogen atoms (Ar^1NH_2) should undergo iodination prior to the other (Ar^2NH_2). Nucleophilic substitution at the nitrogen atom of Ar^1NI_2 with the remaining Ar^2NH_2 would selectively give the unsymmetric azo product over the homodimer (Scheme 6).



Scheme 6. The Hypothesis of Entry to Unsymmetric Aromatic Azo Compounds

iv) I envisioned that a tandem process consisting of (i) the Michael-addition of *o*-phenylenediamine to an electron-deficient alkyne; (ii) two relatively weakly acidic hydrogen atoms of unreacted amino group would replace the iodine atom of *t*-BuOI; (iii) a subsequent nucleophilic attack on the highly electrophilic N-center (NI_2) by the resulting enamine could form a dihydro-quinoxaline skeleton; (iv) the following elimination of HI would produce electron-deficient quinoxalines (Scheme 7).



Scheme 7. The Hypothesis for the Oxidative [4+2] Annulation

Nevertheless, *t*-BuOI was found to not be appropriate reagent for synthesis of electron-deficient qinoxalines. After extensive screening of iodine-containing reagents, I was delight to find that treatment of phenyliodine diacetate was highly effective for the progression of this annulation.

The purpose of this thesis is the development of novel synthetic methods utilizing mono- or trivalent iodine reagent. This thesis consist of general introduction, four chapters and conclusion.

In Chapter 1, the development of novel generation method for nitrile oxides from aldoximes using *t*-BuOI and synthesis of isoxazolines and isoxazoles by 1,3-dipolar cycloaddition to dipolarophiles under mild conditions is described.

In Chapter 2, cyclizative atmospheric CO_2 fixation by unsaturated amines with *t*-BuOI leading to cyclic carbamates is described.

In Chapter 3, synthesis of symmetric and unsymmetric (hetero)aromatic azo compounds through oxidative dimerization of (hetero)aromatic amines utilizing *t*-BuOI is described.

In Chapter 4, hypervalent iodine(III)-induced oxidative [4+2] annulation of *o*-phenylenediamines and electron-deficient alkynes leading to electron-deficient quinoxlines is described.

5. References and Notes

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Chapter 1

A Novel Generation Method for Nitrile Oxides from Aldoximes Using *t*-BuOI and Synthesis of Isoxazolines and Isoxazoles by 1,3-Dipolar Cycloaddition to Dipolarophiles

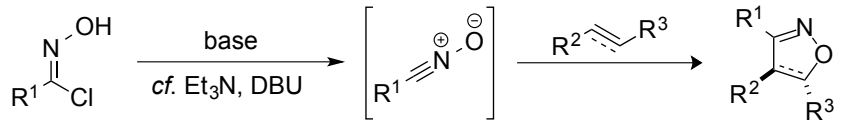
1-1. Introduction

As mentioned in the general introduction, this chapter describes the new generation method for nitrile oxides from aldoximes utilizing *t*-BuOI and the synthesis of isoxazolines and isoxazoles by 1,3-dipolar cycloaddition.

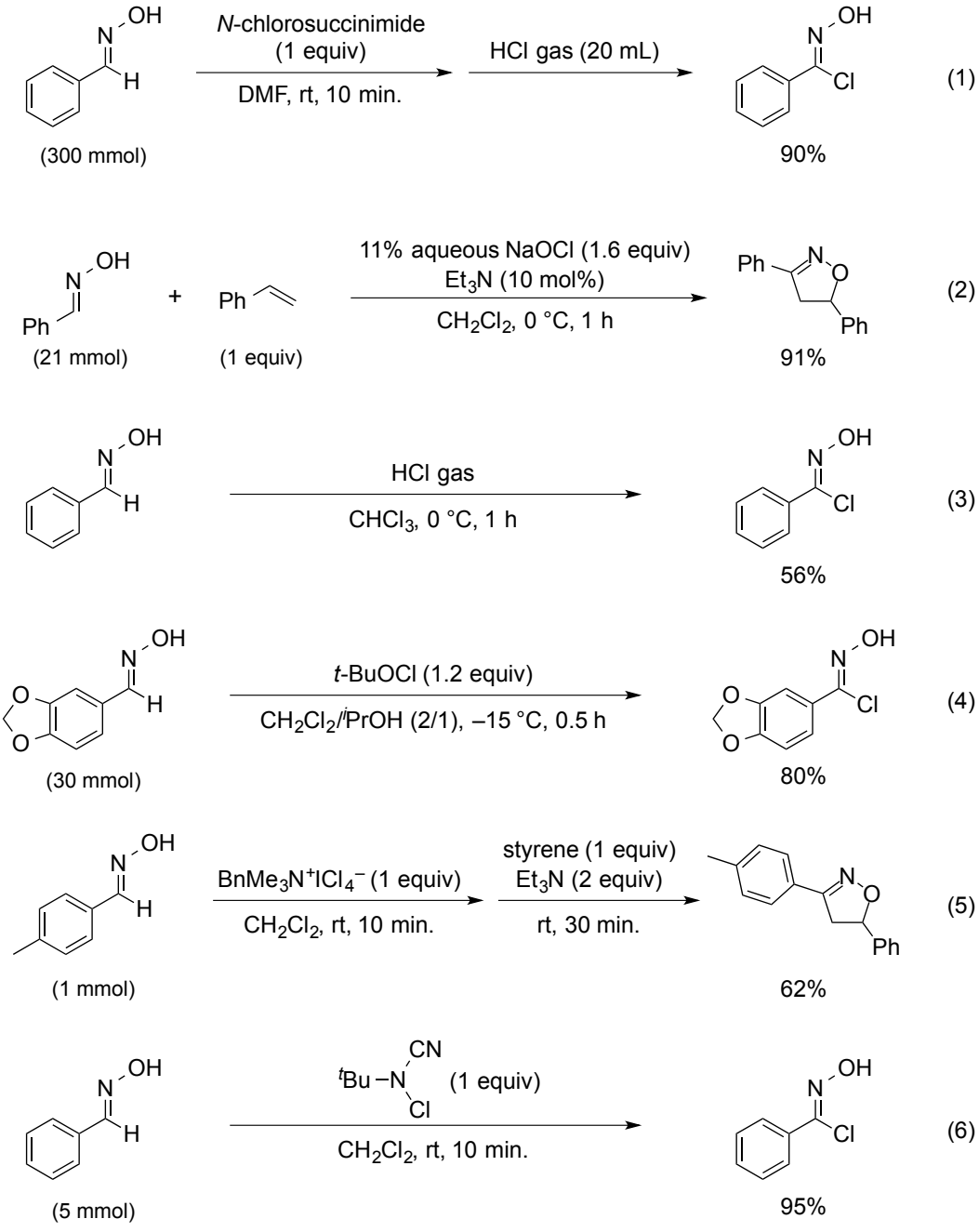
The 1,3-dipolar cycloaddition of nitrile oxides to carbon–carbon unsaturated bonds has proven to be very valuable for the synthesis of isoxazolines and isoxazoles.[1] These frame-works are found in a wide variety of nitrogen-containg heterocycles that are molecular components of a large number of natural products and biologically active compounds.[2] Isoxazoline adducts that are formed in nitrile oxide/alkene cycloaddition reactions can be used as masked β-hydroxy carbonyl aldolate[3] and β-amino alcohol[4] equivalents.

Nitrile oxides are commonly generated by the elimination of HCl from hydroximinoyl chlorides in the presence of a base (Scheme 1).[5] Hydroximinoyl chlorides can be prepared from the corresponding oximes, derived from aldehydes, and electrophilic chlorine-containing

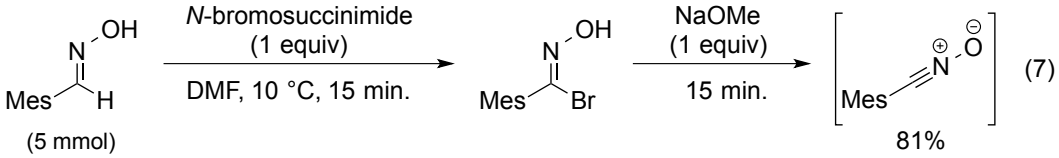
sources, such as *N*-chlorosuccinimide (NCS), NaOCl, Cl_2 (Eqs 1–6).[6]



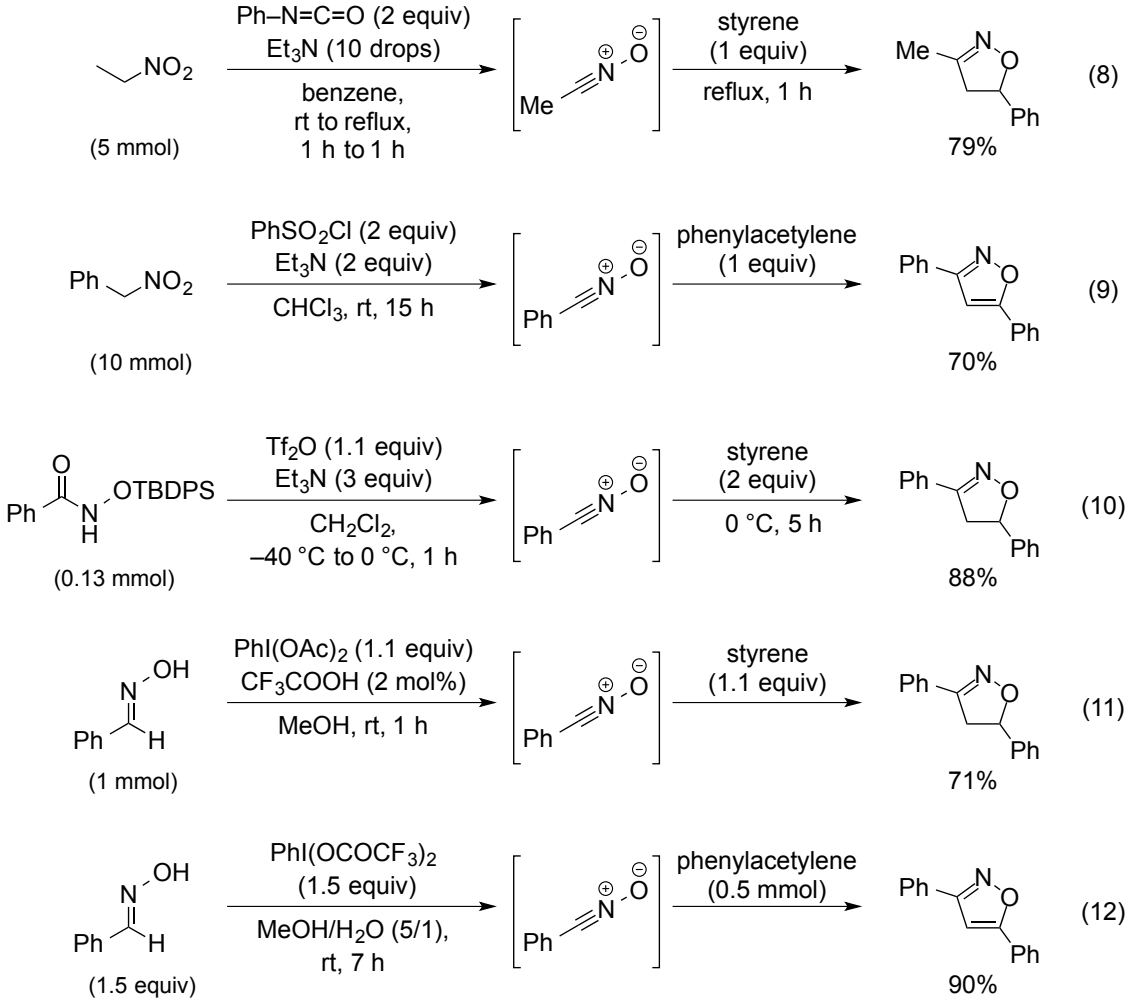
Scheme 1. Conventional Generation Methods for Nitrile Oxides



There are a few reports on the use of an electrophilic bromine reagent, specifically *N*-bromosuccinimide (NBS), for generating nitrile oxides from oximes (Eq 7).[7]



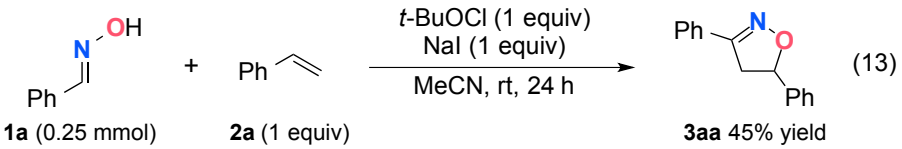
As an alternate approach, dehydrative[8] and oxidative[9] processes were developed (Eqs 8–12), and these methods have been applied to the synthesis of complex molecules. The use of an electrophilic iodine reagent for generation of nitrile oxides from aldoximes has not been reported to date.



Results and Discussion

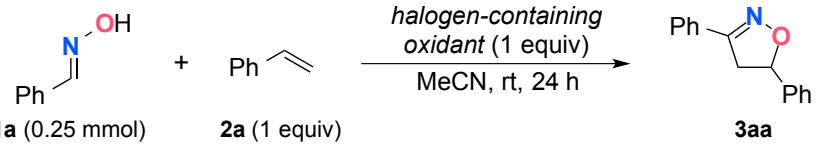
1-2. Reaction of Benzaldoxime and Styrene in the Presence of *t*-BuOI

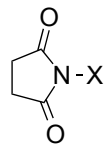
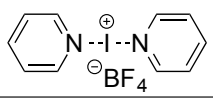
The reagent *t*-BuOI was prepared in situ from commercially available *tert*-butyl hypochlorite (*t*-BuOCl) and sodium iodine (NaI). Initially, I examined a cycloaddition reaction of benzaldoxime (**1a**) and styrene (**2a**) in the presence of an equimolar amount of *t*-BuOI. When 0.25 mmol of **1a** and **2a** were treated with *t*-BuOI (1 equiv) in acetonitrile at room temperature for 24 h, 1,3-dipolar cycloaddition proceeded to give isoxazoline **3aa** in 45% yield (Eq. 13).



To confirm the superiority of the system, I tested the reaction with other halogen-containing oxidants (Table 1). The employment of *t*-BuOCl resulted in rather low yield (entry 1). Widely used halogenating reagents, *N*-chlorosuccinimde (NCS), *N*-bromosuccinimde (NBS) and *N*-iodosuccinimde (NIS) were found to be ineffective for the reaction (entries 2–4). I_2, a combination of I_2/triethylamine and bis(pyridine)iodine tetrafluoroborate (IPy_2BF_4) failed to provide the desired cycloadduct (entries 5–7).

Table 1. Effect of Halogen-Containing Oxidants[a]



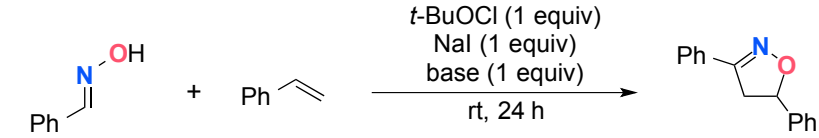
entry	oxidant	yield (%)[b]	entry	oxidant	yield (%)[b]
1	*t*-BuOCl	6	5	I_2	0
2	 X = Cl (NCS)	0	6	I_2 + Et_3N	0
3	Br (NBS)	1	7	 (IPy_2BF_4)	0
4	I (NIS)	11			

[a] Reaction conditions: benzaldoxime (0.25 mmol), styrene (0.25 mmol) and halogen-containing oxidant (0.25 mmol) in MeCN (5 mL) at room temperature for 24 h. [b] ^{1}H NMR yields.

1-3. Optimization Study for 1,3-Dipolar Cycloaddition

To improve the efficiency of the cycloaddition, a variety of solvents were screened (Table 2, entries 1–5). When 1,4-dioxane was used as a solvent, the desired isoxazoline was produced in 54% yield (entry 5). Since HI is liberated during the generation of nitrile oxides, bases were added to the system (entries 6–9). As a result of the screening of bases, 2,6-lutidine was found to be a suitable base for the reaction to afford **3aa** in 88% yield (entry 9).

Table 2. Optimization Study for 1,3-Dipolar Cycloaddition[a]



1a (0.25 mmol) **2a** (1 equiv) **3aa**

entry	solvent	base	yield (%)[b]
1	MeCN	–	45[c]
2	THF	–	15
3	CH_2Cl_2	–	15
4	DMF	–	14
5	1,4-dioxane	–	54
6	1,4-dioxane	K_2CO_3	31
7	1,4-dioxane	Et_3N	20
8	1,4-dioxane	pyridine	64
9	1,4-dioxane	2,6-lutidine	88[c]

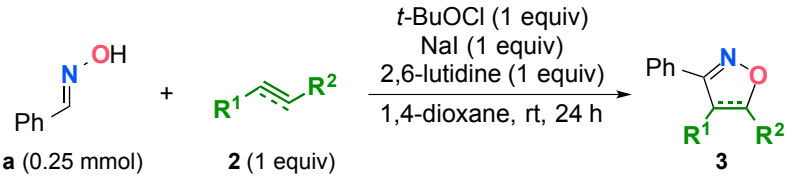
[a] Reaction conditions: benzaldoxime (0.25 mmol), styrene (0.25 mmol), *t*-BuOCl (0.25 mmol), NaI (0.25 mmol) and base (0.25 mmol) in solvent (5 mL) at room temperature for 24 h. [b] ^{1}H NMR yields. [c] Isolated yield.

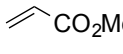
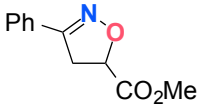
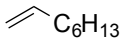
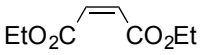
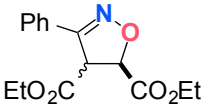
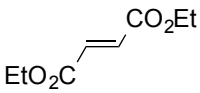
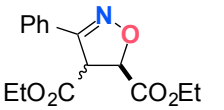
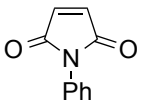
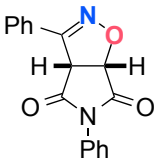
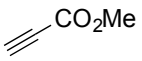
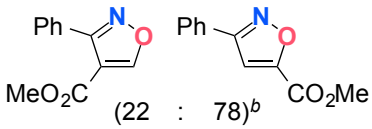
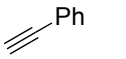
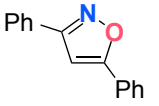
1-4. 1,3-Dipolar Cycloaddition of Benzaldoxime with Various Dipolarophiles

Having optimized the reagents and reaction conditions, the scope of substrates in the 1,3-dipolar cycloaddition was explored using a range of dipolarophiles (Table 3). A terminal electron-deficient olefin **2b** was transformed into the corresponding isoxazoline **3ab** in

excellent yield with complete regioselectivity (entry 1). An aliphatic terminal olefin, 1-octene (**2c**), was applicable to the reaction, with the regioselective formation of the adduct (entry 2). When geometric isomers (ethyl maleate and fumarate) were used, diastereomers **3ad** and **3ad'** were obtained in both cases (entries 3 and 4). The stereochemistry of the major adducts was reflected by the geometry of the dipolarophiles. In order to clarify the origin of the production of the minor adducts, each single stereoisomer **3ad** and **3ad'** was treated separately with 2,6-lutidine, and partial *cis–trans* isomerization of the stereoisomers was observed in both cases (Figure 1). This result indicates that the reaction proceeds in a concerted manner and that the resulting adducts were successively isomerized by the base. *N*-Phenylmaleimide functioned as a dipolarophile to afford the cycloadduct in good yield (entry 5). Although the reaction of aldoxime **1a** with methyl propiolate (**2g**) gave a mixture of regioisomers[10], the reaction with phenylacetylene (**2h**) yielded a sole regioisomer (entries 6 and 7).

Table 3. Substrate Scope: Cycloaddition of Benzaldoxime with Various Dipolarophiles[a]



entry	dipolarophile		product(s)	yield (%)
1		**2b**		98 (**3ab**)
2		**2c**		70 (**3ac**)
3		**2d**	 (*cis* : *trans* = 89 : 11)[b]	72 (**3ad, 3ad'**)
4		**2e**	 (*cis* : *trans* = 8 : 92)[b]	71 (**3ad, 3ad'**)
5		**2f**		92 (**3af**)
6		**2g**	 (22 : 78)[b]	71 (**3ag, 3ag'**)
7		**2h**		75 (**3ah**)

[a] Reaction conditions: aldoxime (0.25 mmol), dipolarophile (0.25 mmol), *t*-BuOCl (0.25 mmol), NaI (0.25 mmol) and 2,6-lutidine (0.25 mmol) in 1,4-dioxane (5 mL) at room temperature for 24 h. [b] Determined by ^{1}H NMR.

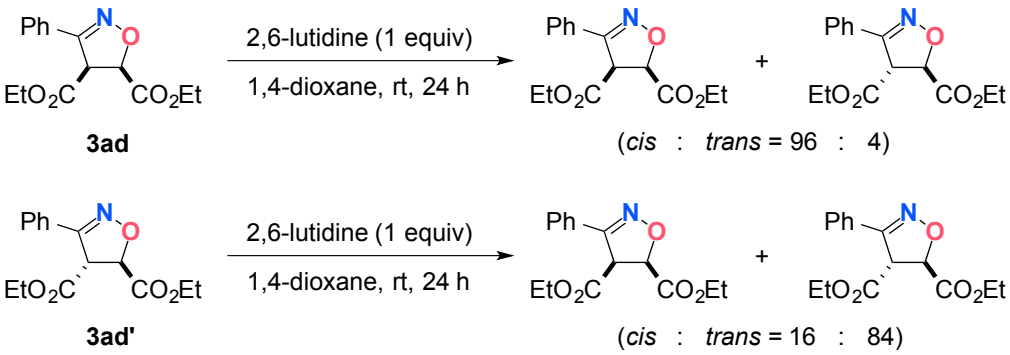
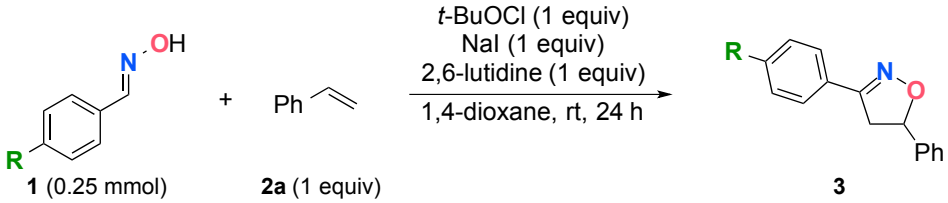


Figure 1. Isomerization of Isoxazolines in the Presence of 2,6-Lutidine

1-5. 1,3-Dipolar Cycloaddition of *p*-Substituted Aldoximes with Styrene

As shown in Table 4, the reaction tolerates a wide diversity of substituents at the para position of benzaldoxime. Benzaldoximes containing both electron-donating and -withdrawing groups reacted readily with styrene, selectively leading to the corresponding isoxazolines in good yields.

Table 4. Substrate Scope: Cycloaddition of *p*-Substituted Benzaldoximes with Styrene[a]



1 (0.25 mmol) **2a** (1 equiv) **3**

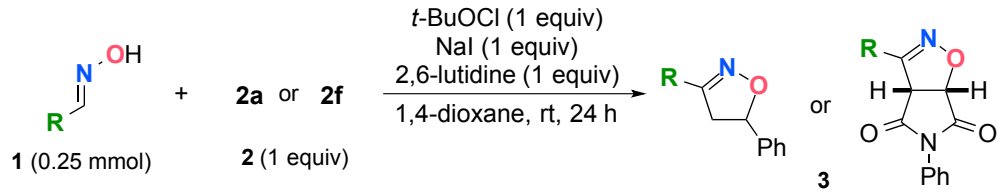
entry	R	yield (%)
1	OMe (**1b**)	71 (**3ba**)
2	Me (**1c**)	76 (**3ca**)
3	NO_2 (**1d**)	83 (**3da**)
4	CF_3 (**1e**)	98 (**3ea**)
5	CN (**1f**)	84 (**3fa**)
6	Br (**1g**)	84 (**3ga**)
7	Cl (**1h**)	86 (**3ha**)

[a] Reaction conditions: aldoxime (0.25 mmol), styrene (0.25 mmol), *t*-BuOCl (0.25 mmol), NaI (0.25 mmol) and 2,6-lutidine (0.25 mmol) in 1,4-dioxane (5 mL) at room temperature for 24 h.

1-6. 1,3-Dipolar Cycloaddition of Alkyl-Substituted Aldoximes

The scope of the reaction was also extended to various aldoximes (Table 5). Aldoximes substituted with alkyl groups derived from acetaldehyde, butanal, and cyclohexyl carbaldehyde were converted into the corresponding nitrile oxides, followed by cycloaddition with styrene (**2a**) or *N*-phenylmaleimide (**2f**), giving a variety of isoxazoline derivatives in moderate to good yields (entries 1–6). The reactions of aldoximes derived from alkanals having a benzyl position with **2f** proceeded with good yields (entries 7 and 8).

Table 5. Substrate Scope: Cycloaddition of Various Aldoximes with **2a** or **2f**[a]

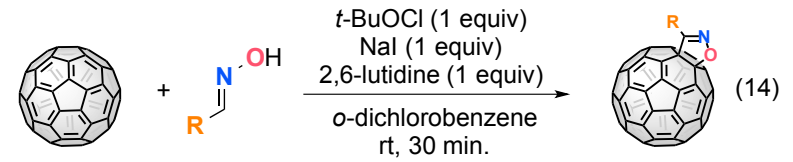


entry	R	dipolarophile	yield (%)
1	Me (**1i**)	styrene (**2a**)	65 (**3ia**)
2	Me (**1i**)	*N*-phenylmaleimide (**2f**)	82 (**3if**)
3	*n*-Pr (**1j**)	styrene (**2a**)	67 (**3ja**)
4	*n*-Pr (**1j**)	*N*-phenylmaleimide (**2f**)	85 (**3jf**)
5	*c*-hex (**1k**)	styrene (**2a**)	81 (**3ka**)
6	*c*-hex (**1k**)	*N*-phenylmaleimide (**2f**)	92 (**3kf**)
7	$PhCH_2$ (**1l**)	*N*-phenylmaleimide (**2f**)	80 (**3lf**)
8	$PhCH_2CH_2$ (**1m**)	*N*-phenylmaleimide (**2f**)	80 (**3mf**)

[a] Reaction conditions: aldoxime (0.25 mmol), dipolarophile (0.25 mmol), *t*-BuOCl (0.25 mmol), NaI (0.25 mmol) and 2,6-lutidine (0.25 mmol) in 1,4-dioxane (5 mL) at room temperature for 24 h.

1-7. 1,3-Dipolar Cycloaddition of Aldoximes with Fullerene

The present cycloaddition was also found to be applicable to C_{60} (Eq 14). When C_{60} was treated with benzaldoxime (**1a**) or acetaldoxime (**1i**) in the presence of *t*-BuOCl, NaI, and 2,6-lutidine in *o*-dichlorobenzene, which is a commonly used solvent for dissolving C_{60}, at room temperature for 30 min, isoxazoline-fused C_{60} derivatives **4a** and **4b** were obtained in good isolation yield along with excellent conversion yield.[11] Taking into account the lower reactivity of fullerene,[12] these results demonstrated the validity of this method.



R = Ph (**4a**) 46%[a] (96%)[b]
R = Me (**4b**) 50%[a] (97%)[b]
[a] Isolated yield. [b] conversion yield.

1-8. Investigation on Reaction Pathway

Although the precise reaction mechanism is unclear at present, the following findings provide support for the reaction pathway depicted in Scheme 2. Since it is known that *t*-BuOCl reacts rapidly with NaI,[13] the reaction of benzaldoxime and *t*-BuOI was monitored by ^{1}H NMR. When an equimolar amount of *t*-BuOI was added to a dioxane-d_8 solution of benzaldoxime, the signals corresponding to hydrogens attached to the imine carbon (δ 8.06 ppm) and the oxygen (δ 9.79 ppm) on benzaldoxime disappeared, and a broad singlet at δ 10.8 ppm was observed, which disappeared when one drop of D_2O was added to the solution (Figure 2).

^{1}H NMR spectrum of benzaldoxime (Chart **A**)

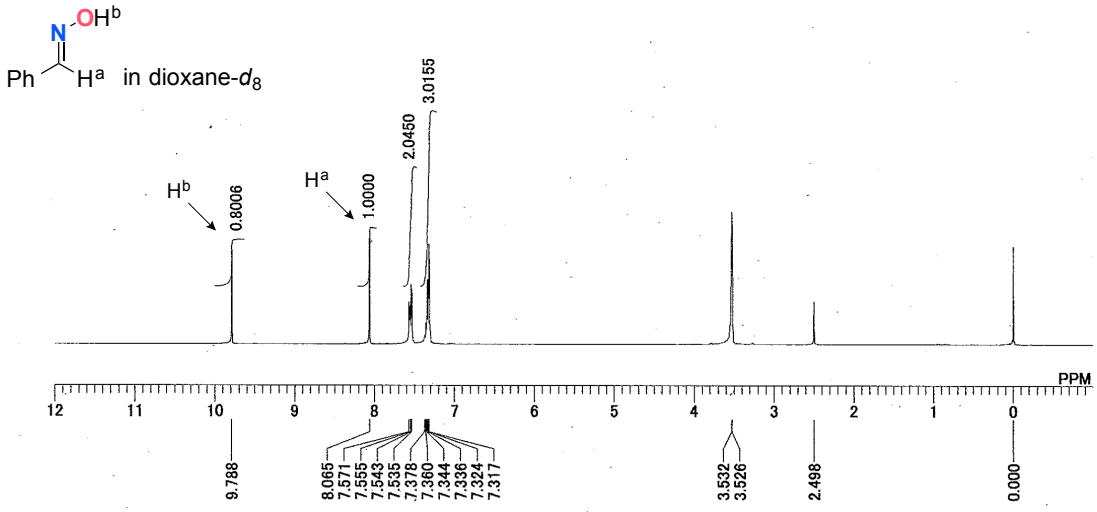


Figure 2-1. ^{1}H NMR spectrum of benzaldoxime (0.025 mmol, 3.0 mg) and NaI (0.025 mmol, 3.8 mg) in d_8-dioxane at room temperature

^{1}H NMR spectrum of benzaldoxime and *t*-BuOI (Chart **B**)

Disappearance of both signals of H^a and H^b in Chart **A** and Appearance of a new signal at δ10.8 ppm

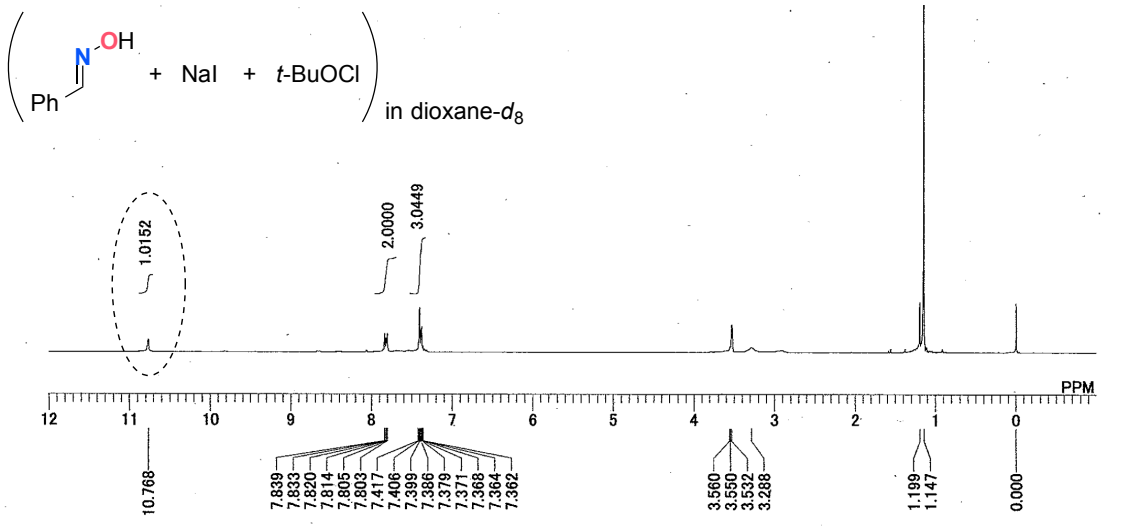


Figure 2-2. ^{1}H NMR spectrum after treating the above mixture with *t*-BuOCl (0.025 mmol, 2.7 mg)

^{1}H NMR spectrum after addition of D_2O to the above solution (Chart **C**)

Disappearance of the signal at δ10.8 ppm

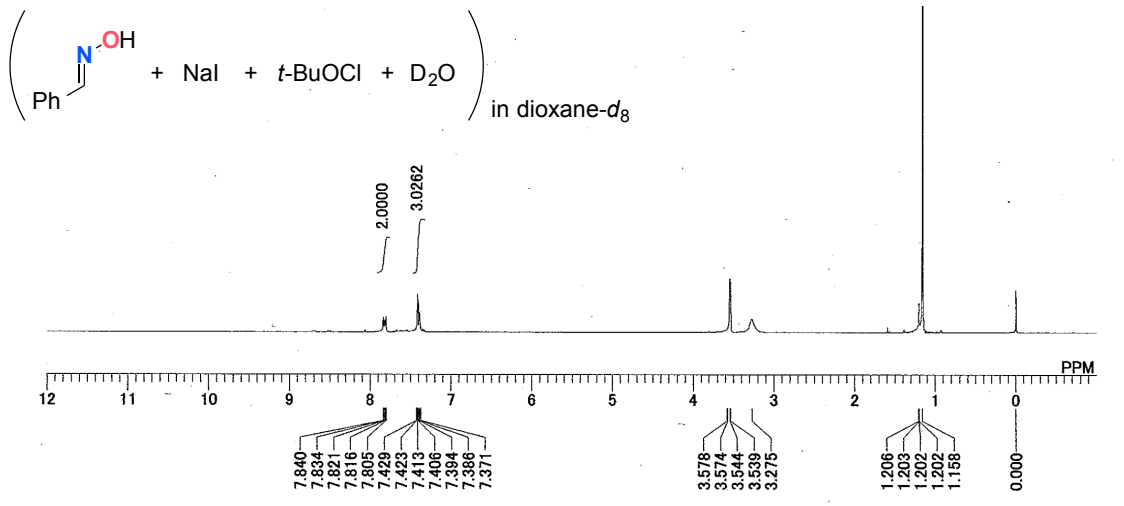
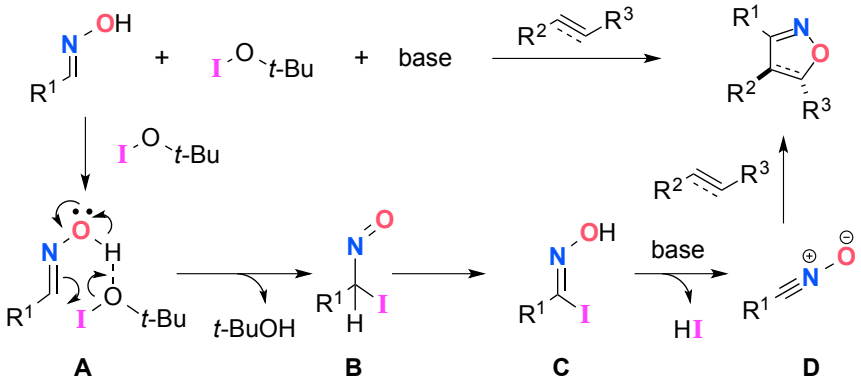


Figure 2-3. ^{1}H NMR spectrum after treating the above mixture with D_2O (one drop)

These results indicate the formation of an imidoyl iodide intermediate **C** by the reaction of benzaldoxime and *t*-BuOI. Thus, the most likely pathway for the cycloaddition is proposed to be as follows: (1) α-iodonitroso intermediate **B** is generated through iodination and deprotonation of aldoxime with *t*-BuOI *via* the 6-membered transition state **A**.; (2) the resulting intermediate **B** smoothly tautomerizes to the oxime derivative **C**, followed by the elimination of HI in the presence of a base to generate the nitrile oxide **D**, which then participates in a cycloaddition to a C–C unsaturated bond, giving an isoxazoline or isoxazole.



Scheme 2. Plausible Reaction Pathway

1-9. Conclusion

The author has developed an efficient, simple and general method for the synthesis of a variety of isoxazolines and isoxazoles by the reaction of aldoximes and alkenes/alkynes in the presence of *t*-BuOI and a base. This is the first report of a method for the generation of nitrile oxides using an electrophilic iodinating reagent.

1-10. Experimental Section

General experimental methods

All reactions were carried out under an atmosphere of nitrogen. Dehydrated 1,4-dioxane was used as received. Melting points were determined on a Yanaco melting point apparatus and are uncorrected. Infrared spectra were obtained on a JASCO FT/IR-410 infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL FT-NMR JNM EX 270 spectrometer (^{1}H NMR, 270 MHz; ^{13}C NMR, 68 MHz) using tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL JMS-DX303HF mass spectrometer. High resolution mass spectra were obtained JEOL JMS-DX303HF mass spectrometer. Products were purified by chromatography on silica gel BW-300 (Fuji Silysia Chemical Co.). Analytical thin-layer chromatography was performed on precoated silica gel glass plates (silica gel 60 F_{254}, 0.25 mm thickness) (Merck Co.). Compounds were visualized by UV light or treatment with an ethanolic solution of phosphomolybdic acid followed by heating.

Typical procedure for the synthesis of aldoximes from aldehydes

To a mixture of an aldehyde (10 mmol) and hydroxylamine hydrochloride (20 mmol) in CH_2Cl_2 (50 mL) was added pyridine (40 mmol). The mixture was stirred under an atmosphere of nitrogen. After stirring for 20 h at room temperature, aqueous HCl (2.0 M, 30 mL) was added to the reaction mixture and the solution was extracted with CH_2Cl_2 (30 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give oxime products.

Oxime derivatives **1a**, **1i** and **1j** were purchased from a commercial supplier and used without further purification.

Typical procedure for the cycloaddition of nitrile oxides and dipolarophiles using *tert*-butyl hypoiodite

To a mixture of an aldoxime (0.25 mmol), a dipolarophile (0.25 mmol), NaI (0.25 mmol, 37.5 mg) and 2,6-lutidine (0.25 mmol, 26.8 mg) in 1,4-dioxane (5 mL) was added *t*-BuOCl (0.25 mmol, 27.1 mg). The mixture was stirred under an atmosphere of nitrogen. After stirring for 24 h at room temperature, aqueous $Na_2S_2O_3$ (1.0 M, 10 mL) was added to the reaction mixture and the solution was extracted with CH_2Cl_2 (20 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude product. Purification by flash column chromatography (silica gel; ethyl acetate in hexane) gave 2-isoxazoline. (for example, compound **3aa**: 49.3 mg, 88%).

Typical procedure for the cycloaddition of nitrile oxides and fullerene using *tert*-butyl hypoiodite

To the mixture of C_{60} (0.05 mmol, 36 mg), an aldoxime (0.05 mmol), NaI (0.05 mmol, 7.5 mg) and 2,6-lutidine (0.05 mmol, 5.4 mg) in *o*-dichlorobenzene (5 mL) was added *t*-BuOCl (0.05 mmol, 5.4 mg). The mixture was stirred under an atmosphere of nitrogen. After stirring for 30 min at room temperature, the solution was passed through a short column of silica gel and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel.

Verification experiment for isomerization of the isoxazolines in the presence of 2,6-lutidine

for **3ad**

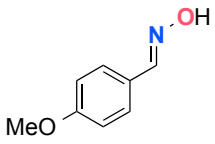
To isoxazoline **3ad** (0.037 mmol, 10.8 mg) in 1,4-dioxane was added 2,6-lutidine (0.037 mmol, 4.0 mg). The mixture was stirred under an atmosphere of nitrogen. After stirring for 24 h at room temperature, H_2O (20 mL) was added to the reaction mixture and the solution was extracted with CH_2Cl_2 (20 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude product (**3ad** : **3ad'** = 96 : 4, Determined by ^1H NMR).

for **3ad'**

To isoxazoline **3ad'** (0.096 mmol, 28.0 mg) in 1,4-dioxane was added 2,6-lutidine (0.096 mmol, 10.3 mg). The mixture was stirred under an atmosphere of nitrogen. After stirring for 24 h at room temperature, H_2O (20 mL) was added to the reaction mixture and the solution was extracted with CH_2Cl_2 (20 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude product (**3ad** : **3ad'** = 16 : 84, Determined by ^1H NMR).

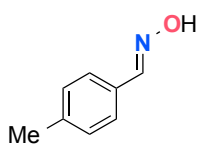
Spectra date of products

p-Methoxybenzaldehyde oxime (1b)[14, 15, 16]



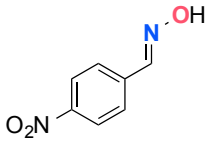
Colorless solid (0.98 g, 66%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.90 (d, 2H, *J* = 8.6 Hz), 7.51 (d, 2H, *J* = 8.6 Hz), 8.09 (s, 1H).

p-Methylbenzaldehyde oxime (1c)[15, 16]



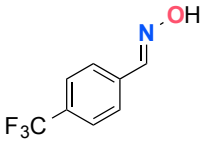
Colorless solid (1.24 g, 92%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.37 (s, 3H), 7.19 (d, 2H, *J* = 8.1 Hz), 7.47 (d, 2H, *J* = 8.1 Hz), 8.16 (s, 1H).

p-Nitrobenzaldehyde oxime (1d)[14]



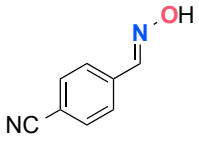
Yellow solid (1.46 g, 88%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.75 (d, 2H, *J* = 8.5 Hz), 8.20 (s, 1H), 8.25 (d, 2H, *J* = 8.5 Hz).

p-Trifluoromethylbenzaldehyde oxime (1e)[14]



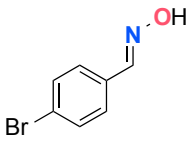
Colorless solid (1.83 g, 97%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.64 (d, 2H, *J* = 8.5 Hz), 7.69 (d, 2H, *J* = 8.5 Hz), 8.19 (s, 1H,).

p-Cyanobenzaldehyde oxime (1f)[16]



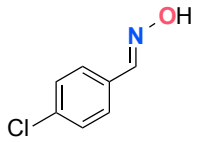
Colorless solid (0.86 g, 59%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.68 (s, 4H), 8.15 (s, 1H).

p-Bromobenzaldehyde oxime (1g)[14]



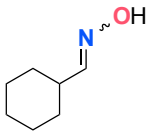
Colorless solid (1.86 g, 93%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.44 (d, 2H, *J* = 8.5 Hz), 7.52 (d, 2H, *J* = 8.5 Hz), 8.10 (s, 1H).

_p_-Chlorobenzaldehyde oxime (1h) [14, 15, 16]



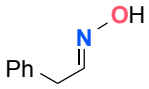
Colorless solid (1.40 g, 90%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.36 (d, 2H, *J* = 8.5 Hz), 7.52 (d, 2H, *J* = 8.5 Hz), 8.10 (s, 1H).

Cyclohexanecarbaldehyde oxime (1k)



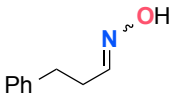
Colorless oil (1.26 g, 97%); IR (KBr, cm^{-1}) 3267, 2927, 1702, 1656, 1449, 1310, 965, 698; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.11–1.81 (m, 10H, *major and minor*), 2.24 (m, 1H, *major*), 2.97 (m, 1H, *minor*), 6.54 (d, 1H, *J* = 7.3 Hz, *minor*), 7.32 (d, 1H, *J* = 5.9 Hz, *major*); ^{13}C NMR (68 MHz, $CDCl_3$) δ 25.1 (*minor*), 25.3 (*major*), 25.7 (*minor*), 25.8 (major), 29.3 (*minor*), 30.1 (*major*), 33.7 (*minor*), 38.4 (*major*), 155.5 (major), 155.9 (*minor*); MS (EI): *m/z* (relative intensity, %) 127 ($[M]^+$, 15); HRMS (EI): *m/z* calcd for $C_{15}H_{13}NO$ (M) 127.0997, found 127.0994.

Phenylacetaldehyde oxime (1l)[17]



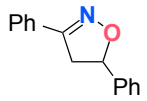
Colorless solid (0.24 g, 33%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.75 (d, 2H, *J* = 5.4 Hz), 6.90 (t, 1H, *J* = 5.4 Hz), 7.22–7.35 (m, 5H), 8.11 (s, 1H).

3-Phenylpropanal oxime (1m)[18]



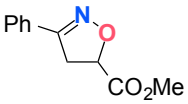
Colorless solid (0.20 g, 60%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.51 (m, 2H, *minor*), 2.71 (m, 2H, *major*), 2.83 (m, 2H, *major and minor*), 6.76 (t, 1H, *J* = 5.4 Hz, *major*), 7.12–7.34 (m, 5H, *major and minor*), 7.47 (t, 1H, *J* = 5.4 Hz, *minor*).

3,5-Diphenyl-2-isoxazoline (3aa)[19, 25]



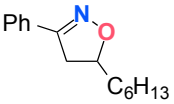
Colorless solid (49.3 mg, 88%); mp. 73–74 °C; IR (KBr, cm^{-1}) 3037, 2924, 2873, 1597, 1448, 1363, 1066, 899, 856, 754, 692; ^1H NMR (270 MHz, $CDCl_3$) δ 3.35 (dd, 1H, *J* = 8.4, 17.3 Hz), 3.79 (dd, 1H, *J* = 10.8, 17.3 Hz), 5.75 (dd, 1H, *J* = 8.4, 10.8 Hz), 7.31–7.42, 7.69–7.72 (m, 10H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 43.2, 82.5, 125.8, 126.6, 128.1, 128.7, 129.3, 130.0, 140.8, 155.9; MS (EI): *m/z* (relative intensity, %) 223 ($[M]^+$, 84), 104 ($PhCHCH_2$, 100); HRMS (EI): *m/z* calcd for $C_{15}H_{13}NO$ (M) 223.0995, found 223.0997.

3-Phenyl-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester (3ab)[20]



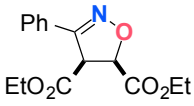
Yellow oil (49.7 mg, 98%); IR (neat, cm^{-1}) 2954, 1742, 1446, 1356, 1215, 890, 762, 692; ^1H NMR (270 MHz, $CDCl_3$) δ 3.66 (dd, 2H, *J* = 7.8, 11.1 Hz), 3.82 (s, 3H), 5.20 (dd, 1H, *J* = 7.8, 11.1 Hz), 7.26–7.43 (m, 3H), 7.66–7.70 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 38.9, 52.9, 77.9, 126.8, 128.3, 128.7, 130.4, 155.9, 170.5; MS (EI): *m/z* (relative intensity, %) 205 ($[M]^+$, 41), 146 ($[M–CO_2Me]^+$, 100); HRMS (EI): *m/z* calcd for $C_{11}H_{11}NO_3$ (M) 205.0739, found 205.0741.

3-Phenyl-5-hexyl-2-isoxazoline (3ac)[21]



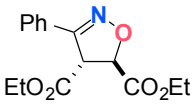
Colorless solid (40.4 mg, 70%); mp. 47–48 °C; IR (KBr, cm^{-1}) 2954, 2921, 2852, 1446, 1360, 754, 690; ^1H NMR (270 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.0 Hz), 1.25–1.80 (m, 10H), 2.96 (dd, 1H, *J* = 7.8, 16.5 Hz), 3.41 (dd, 1H, *J* = 10.5, 16.5 Hz), 4.73 (m, 1H), 7.40 (m, 3H), 7.67 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.2, 22.7, 25.6, 29.2, 31.8, 35.4, 40.0, 81.5, 126.5, 128.5, 129.8, 156.2; MS (EI): *m/z* (relative intensity, %) 231 ($[M]^+$, 14), 146 ($[M–C_6H_{13}]^+$, 100); HRMS (EI): *m/z* calcd for $C_{15}H_{21}NO$ (M) 231.1623, found 231.1622.

(4*S*,5*R*)-3-Phenyl-4,5-dihydro-isoxazole-4,5-dicarboxylic acid diethyl ester (3ad)[22]



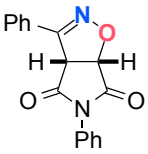
Colorless oil (52.2 mg, 72%); IR (neat, cm^{-1}) 2985, 1738, 1303, 1200, 694; ^1H NMR (270 MHz, $CDCl_3$) δ 1.15 (t, 3H, *J* = 7.3 Hz), 1.33 (t, 3H, *J* = 7.3 Hz), 4.13 (q, 2H, *J* = 7.3 Hz), 4.29 (q, 2H, *J* = 7.3 Hz), 4.61 (d, 1H, *J* = 11.1 Hz), 5.37 (d, 1H, *J* = 11.1 Hz), 7.26–7.47 (m, 3H), 7.72–7.76 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.9, 14.2, 56.6, 62.2, 62.2 81.7, 126.9, 127.5, 128.7, 130.6, 154.5, 166.9, 167.1; MS (EI): *m/z* (relative intensity, %) 291 ($[M]^+$, 27), 218 ($[M–C_3H_5O_2]^+$, 99), 172 ($[C_8H_{12}O_4]^+$, 100); HRMS (EI): *m/z* calcd for $C_{15}H_{17}NO_5$ (M) 291.1107, found 291.1112.

(4*R*,5*R*)-3-Phenyl-4,5-dihydro-isoxazole-4,5-dicarboxylic acid diethyl ester (3ad')[22]



Colorless oil (51.6 mg, 71%); IR (neat, cm^{-1}) 2983, 1738, 1228, 1026, 891, 765, 693; ^1H NMR (270 MHz, $CDCl_3$) δ 1.18 (t, 3H, *J* = 7.3 Hz), 1.33 (t, 3H, *J* = 7.3 Hz), 4.18 (q, 2H, *J* = 7.3 Hz), 4.29 (qd, 2H, *J* = 1.6, 7.3 Hz), 4.62 (d, 1H, *J* = 4.9 Hz), 5.46 (d, 1H, *J* = 4.9 Hz), 7.26–7.44 (m, 3H), 7.74–7.78 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.9, 14.1, 56.7, 62.4, 82.1, 127.3, 127.4, 128.5, 130.5, 153.8, 167.6, 168.6; MS (EI): *m/z* (relative intensity, %) 219 ($[M]^+$, 24), 218 ($[M–C_3H_5O_2]^+$, 100), 172 ($[C_8H_{12}O_4]^+$, 100); HRMS (EI): *m/z* calcd for $C_{15}H_{17}NO_5$ (M) 291.1107, found 291.1102.

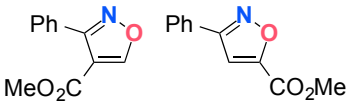
3,5-Diphenyl-3a,6a-dihydro-pyrrolo[3,4-d]isoxazole-4,6-dione (3af)[8b]



Colorless solid (67.5 mg, 92%) ; mp. 177 °C; IR (KBr, cm^{-1}) 3435, 3066, 2926, 1724, 1388, 1198; ^1H NMR (270 MHz, $CDCl_3$) δ 4.96 (d, 1H, *J* = 9.5 Hz), 5.65 (d, 1H, *J* = 9.5 Hz), 7.25, 7.40–7.46, 8.00–8.03 (m, 10H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 54.9, 80.4, 126.0, 126.6, 128.0, 128.7, 129.1, 129.2, 130.7, 131.1, 152.6, 169.6, 170.6; MS (EI): *m/z* (relative intensity, %) 292 ($[M]^+$,100), 119 ($[C_7H_5NO]^+$, 81); HRMS (EI):

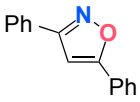
m/z calcd for $C_{17}H_{12}N_2O_3$ (M) 292.0848, found 292.0852.

3-Phenyl-4-methoxycarbonyl-2-isoxazole (3ag)[23] **and 3-Phenyl-5-methoxycarbonyl-2-isoxazole (3ag')**[24]



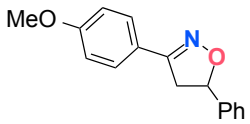
As an inseparable 22:78 in 71% yield.: colorless solid (36.7 mg, 71%); IR (KBr, cm^{-1}) 1731, 1578, 1444 1306, 1229, 1141; ^1H NMR (270 MHz, $CDCl_3$) (**3ag** + **3ag'**) δ 3.84 (s, 1H, **3ag**), 4.01 (s, 1H, **3ag'**), 7.26 (s, 1H, **3ag'**), 7.46–7.48 (m, 6H, 3H of **3ag** and 3H of **3ag'**), 7.75–7.85 (m, 4H, 2H of **3ag** and 2H of **3ag'**), 9.01 (s, 1H, **3ag**); ^{13}C NMR (68 MHz, $CDCl_3$) (**3ag** + **3ag'**) δ 51.9, 52.9, 107.3, 112.4, 126.6, 127.7, 128.0, 128.9, 129.2, 130.0, 130.4, 156.9, 160.3, 161.0, 161.0, 162.7, 163.9; MS (EI): *m/z* (relative intensity, %) 203 ($[M]^+$, 43), 114 (100); HRMS (EI): *m/z* calcd for $C_{11}H_9NO_3$ (M) 203.0582, found 203.0574.

3,5-Diphenyl-isoxazole (3ah)[25]



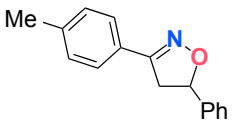
Colorless solid (41.2 mg, 75%); mp. 139–140 °C; IR (KBr, cm^{-1}) 3423, 3113, 3051, 2926, 1606, 1579, 1454, 1396, 1082, 820, 766, 696; ^1H NMR (270 MHz, $CDCl_3$) δ 6.84 (s, 1H), 7.47–7.53 (m, 3H), 7.83–7.89 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 97.4, 125.7, 126.7, 127.4, 128.8, 128.9, 129.0, 129.9, 130.1, 162.8, 170.2; MS (EI): *m/z* (relative intensity, %) 221 ($[M]^+$, 86), 105 ($[M–C_8H_6N]^+$, 100); HRMS (EI): *m/z* calcd for $C_{15}H_{11}NO$ (M) 221.0841, found 221.0841.

3-(*p*-Methylphenyl)-5-phenyl-2-isoxazoline (3ba)[6f]



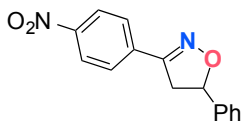
Colorless solid (45.2 mg, 71%); mp. 103–104 °C; IR (KBr, cm^{-1}) 3431, 3045, 2927, 2848, 1605, 1508, 1454, 1358, 1302, 1248, 1178, 1030, 897, 825, 752, 694, 538; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.32 (dd, 1H, *J* = 8.4, 16.5 Hz), 3.79 (dd, 1H, *J* = 11.1, 16.5 Hz), 3.84 (s, 3H), 5.71 (dd, 1H, *J* = 8.4, 10.8 Hz), 6,91–6.94 (m, 2H), 7.26–7.40 (m, 5H), 7.62–7.65 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 43.5, 55.4, 82.3, 114.1, 121.9, 125.8, 128.0, 128.2, 128.6, 141.0, 155.5, 160.9; MS (EI): *m/z* (relative intensity, %) 253 ($[M]^+$, 100); HRMS (EI): *m/z* calcd for $C_{16}H_{15}NO_2$ (M) 253.1103, found 253.1101.

3-(*p*-Methylphenyl)-5-phenyl-2-isoxazoline (3ca)[6f]



Colorless solid (44.9 mg, 76%); mp. 97 °C; IR (KBr, cm^{-1}) 3035, 2917, 2859, 1430, 1349, 1454, 902, 824, 758, 698, 532; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.30 (dd, 1H, *J* = 8.1, 16.5 Hz), 3.74 (dd, 1H, *J* = 10.8, 16.5 Hz), 5.70 (dd, 1H, *J* = 8.1, 10.8 Hz), 7.20 (d, 2H, *J* = 8.1 Hz), 7,22–7.40 (m, 5H), 7.70 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.5, 43.3, 82.3, 125.7, 126.4, 126.5, 128.0, 128.6, 129.3, 140.2, 140.8, 155.9; MS (EI): *m/z* (relative intensity, %) 237 ($[M]^+$, 100) 104 ($PhCHCH_2$, 63); HRMS (EI): *m/z* calcd for $C_{16}H_{15}NO$ (M) 237.1154, found 237.1155.

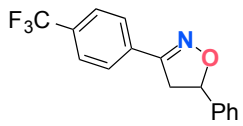
3-(*p*-Nitrophenyl)-5-phenyl-2-isoxazoline (3da)[6f]



Yellow solid (50.8 mg, 83%); mp. 127–129 °C; IR (KBr, cm^{-1}) 3078, 2929, 2852, 1587, 1510, 1443, 1344, 1109, 926, 1134, 926, 850; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.38 (dd, 1H, *J* = 8.4, 16.5 Hz), 3. 82 (dd, 1H, *J* =11.3 16.5 Hz), 5.84 (dd, 1H, *J* = 8.4, 11.3 Hz), 7.37–7.40 (m, 5H), 7.84–7.87 (m, 2H), 8.25–8.29 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 42.5, 83.6, 123.9, 125.8, 127.3, 128.5, 128.8, 135.4, 140.0, 154.5; MS (EI): *m/z*

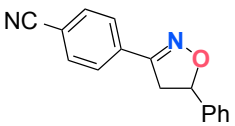
(relative intensity, %) 268 ([M]$^+$, 100), 104 ([PhCHCH$_2$]$^+$, 100); HRMS (EI): *m/z* calcd for $C_{15}H_{12}N_2O_3$ (M) 268.0848, found 268.0846.

3-(*p*-Trifluoromethylphenyl)-5-phenyl-2-isoxazoline (3ea)



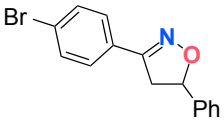
Colorless solid (71.3 mg, 98%); mp. 128–129 °C; IR (KBr, cm^{-1}) 2901, 1410, 1328, 1172, 1125, 1071, 910, 847, 760 700; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.35 (dd, 1H, *J* = 8.4, 16.5 Hz), 3.79 (dd, 1H, *J* = 11.1, 16.5 Hz), 5.79 (dd, 1H, *J* = 8.4, 11.1 Hz), 7.25 (m, 5H), 7,78 (d, 2H, *J* = 1.0 Hz), 7.80 (d, 2H, *J* = 1.0 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 42.8, 83.1, 125.6, 125.6, 125.7, 126.8, 128.3, 128.7, 131.6, 132.8, 140.3, 154.9; MS (EI): *m/z* (relative intensity, %) 291 ([M]$^+$, 76) 104 (PhCHCH$_2$, 100); HRMS (EI): *m/z* calcd for $C_{16}H_{12}F_3NO$ (M) 291.0871, found 291.0868.

3-(*p*-Cyanophenyl)-5-phenyl-2-isoxazoline (3fa)[26]



Colorless solid (52.3 mg, 84%); mp. 127–128 °C; IR (KBr, cm^{-1}) 2222, 1590, 1460, 925, 834, 757; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.34 (dd, 1H, *J* = 8.4, 16.5 Hz), 3.78 (dd, 1H, *J* = 11.1, 16.5 Hz), 5.80 (dd, 1H, *J* = 8.4, 11.1 Hz), 7.32–7.43 (m, 5H), 7,74 (d, 2H, *J* = 6.5 Hz), 7.79 (d, 2H, *J* = 6.5 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 42.5, 83.4, 113,3 118.2, 125.7, 127.0, 128.4, 128.8, 132.4, 133.6, 140.1, 154.7; MS (EI): *m/z* (relative intensity, %) 248 ([M]$^+$, 78) 104 (PhCHCH$_2$, 100); HRMS (EI): *m/z* calcd for $C_{16}H_{12}N_2O$ (M) 248.0950, found 248.0952.

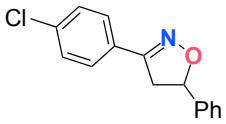
3-(*p*-Bromophenyl)-5-phenyl-2-isoxazoline (3ga)



Colorless solid (63.3 mg, 84%); mp. 141–142 °C; IR (KBr, cm^{-1})1588, 1072, 1008, 905, 832, 757, 698; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.32 (dd,

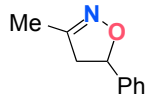
1H, *J* = 8.4, 16.5 Hz), 3.75 (dd, 1H, *J* =11.1 16.5 Hz), 5.75 (dd, 1H, *J* = 8.4, 11.1 Hz), 7.30–7.58 (m, 9H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 43.0, 82.8, 124.3, 125.7, 128.1, 128.2, 128.7, 131.9, 140.5, 155.1; MS (EI): *m/z* (relative intensity, %) 301 ($[M]^+$, 60), 104 ($[PhCHCH_2]^+$, 100); HRMS (EI): *m/z* calcd for $C_{15}H_{12}BrNO$ (M) 301.0102, found 301.0106.

3-(*p*-Chlorophenyl)-5-phenyl-2-isoxazoline (3ha)[27]



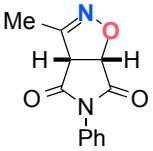
Colorless solid (55.1 mg, 86%); mp. 127–129 °C; IR (KBr, cm^{-1})1590, 1492, 1094, 908, 836, 758, 699; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.32 (dd, 1H, *J* = 8.1, 17.0 Hz), 3.75 (dd, 1H, *J* =11.3 17.0 Hz), 5.75 (dd, 1H, *J* = 8.1, 11.3 Hz), 7.30–7.40 (m, 7H), 7.60–7.65 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 43.0, 82.8, 125.7, 127.8, 128.2, 128.7, 128.9, 136.0, 140.6, 155.0; MS (EI): *m/z* (relative intensity, %) 257 ($[M]^+$, 85), 104 ($[PhCHCH_2]^+$, 100); HRMS (EI): *m/z* calcd for $C_{15}H_{12}ClNO$ (M) 257.0607, found 257.0606.

3-Methyl-5-phenyl-2-isoxazoline (3ia)[28]



Colorless oil (26.1 mg, 65%); IR (neat, cm^{-1}) 2922, 1493, 1454, 1435, 1385, 1324, 871, 758, 700; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.04 (s, 3H), 2.91 (dd, 1H, *J* = 8.4, 17.8 Hz), 3.37 (dd, 1H, *J* = 10.9, 17.8 Hz), 5.56 (dd, 1H, *J* = 8.4, 10.9 Hz), 7.32–7.39 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.3, 46.9, 81.5, 125.6, 127.9, 128.6, 141.1, 154.7; MS (EI): *m/z* (relative intensity, %) 161 ($[M]^+$, 28), 104 ($[PhCHCH_2]^+$, 100); HRMS (EI): *m/z* calcd for $C_{10}H_{11}NO$ (M) 161.0841, found 161.0839.

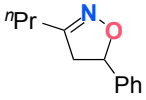
3-Methyl-5-phenyl-3a,6a-dihydro-prrolo[3,4-d]isoaxzole-4,6-dione (3if)



Colorless solid (46.9 mg, 82%); mp. 194 °C; IR (KBr, cm^{-1}) 2978, 1720, 1385, 1188; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.22 (s, 3H), 4.42 (d, 1H, *J* = 9.5 Hz,), 5.48

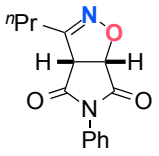
(d, 1H, J = 9.5 Hz), 7.26–7.23 (m, 2H), 7.40–7.53 (m, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 12.0, 57.9, 78.8, 126.0, 129.1, 129.3, 130.6, 151.2, 169.7, 171.2; MS (EI): m/z (relative intensity, %) 230 ($[M]^+$, 51), 119 ($[C_7H_5NO]^+$, 100); HRMS (EI): m/z calcd for $C_{12}H_{10}N_2O_3$ (M) 230.0691, found 230.0693.

5-Phenyl-3-propyl-2-isoxazoline (3ja)[6f]



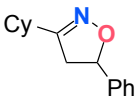
Yellow oil (31.7 mg, 67%); IR (neat, cm^{-1}) 2961, 2932, 1717, 1455, 759, 699; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.97 (t, 3H, 7.3 Hz), 1.61 (m, 2H), 2.36 (t, 2H, J = 7.7 Hz), 2.89 (dd, 1H, J = 8.1, 16.7 Hz), 3.35 (dd, 1H, J = 10.9, 16.7 Hz), 5.54 (dd, 1H, J = 8.1, 10.9 Hz), 7.26–7.36 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.8, 19.9, 29.7, 45.3, 81.1, 125.6, 127.8, 128.5, 141.2, 158.2; MS (EI): m/z (relative intensity, %) 189 ($[M]^+$, 27), 104 ($[PhCHCH_2]^+$, 100); HRMS (EI): m/z calcd for $C_{12}H_{15}NO$ (M) 189.1154, found 189.1151.

5-Phethyl-3-propyl-3a,6a-dihydro-prrolo[3,4-d]isoxazole-4,6-dione (3jf)



Yellow solid (54.8 mg, 85%); mp. 143 °C; IR (KBr, cm^{-1}) 2964, 1720, 1388, 1196; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.02 (t, 3H, J = 7.3 Hz), 1.74 (m, 2H), 2.57 (m, 2H), 4.45 (d, 1H, J = 9.5 Hz), 5.47 (d, 1H, J = 9.5 Hz), 7.27–7.30 (m, 2H), 7.43–7.53 (m, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.8, 19.3, 28.3, 56.9, 78.6, 126.0, 129.1, 129.2, 130.6, 154.5, 169.8, 171.3; MS (EI): m/z (relative intensity, %) 258 ($[M]^+$, 42), 119 ($[C_7H_5NO]^+$, 100); HRMS (EI): m/z calcd for $C_{14}H_{14}N_2O_3$ (M) 258.1004, found 258.1002.

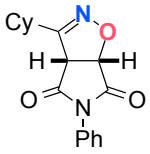
3-Cyclohexyl-5-phenyl-2-isoxazoline (3ka)[29]



Colorless oil (46.2 mg, 81%); IR (neat, cm^{-1}) 2928, 2853, 1449, 874, 758, 699; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.23–1.34 (m, 5H), 1.67–1.87 (m, 5H), 2.44 (m, 1H),

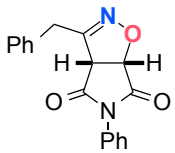
2.89 (ddd, 1H, *J* = 1.0, 8.1, 16.7 Hz), 3.35 (ddd, 1H, *J* = 1.0, 10.8 16.7 Hz), 5.50 (dd, 1H, *J* = 8.1, 10.8 Hz), 7.24–7.37 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 25.7, 25.9, 37.3, 43.6, 80.9, 125.5, 127.8, 128.5, 141.3, 162.0; MS (EI): *m/z* (relative intensity, %) 229 ($[M]^+$, 28), 104 ($[PhCHCH_2]^+$, 100); HRMS (EI): *m/z* calcd for $C_{15}H_{19}NO$ (M) 229.1467, found 229.1462.

3-Cyclohexyl-5-phenyl-3a,6a-dihydro-prrolo[3,4-d]isoxazole-4,6-dione (3kf)



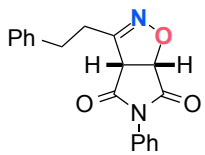
Colorless solid (69.8 mg, 92%); mp. 186–187 °C; IR (KBr, cm^{-1}) 2932, 1721, 1387, 1190; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.26–2.13 (m, 10H), 2.55–2.63 (m, 1H), 2.57 (m, 2H), 4.54 (d, 1H, *J* = 9.5 Hz), 5.45 (d, 1H, *J* = 9.5 Hz), 7.26–7.52 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 25.5, 25.8, 25.9, 29.4, 30.8, 36.3, 55.9, 78.6, 126.0, 129.1, 129.2, 130.7, 158.2, 170.1, 171.4; MS (EI): *m/z* (relative intensity, %) 298 ($[M]^+$, 57), 119 ($[C_7H_5NO]^+$, 100); HRMS (EI): *m/z* calcd for $C_{17}H_{18}N_2O_3$ (M) 298.1317, found 298.1318.

3-Benzyl-5-phenyl-3a,6a-dihydro-prrolo[3,4-d]isoxazole-4,6-dione (3lf)



Colorless solid (61.1 mg, 80%); mp. 190–191 °C; IR (KBr, cm^{-1}) 2967, 1714, 1386, 1187, 870, 699; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.72 (d, 1H, *J* = 14.9 Hz), 4.02 (d, 1H, *J* = 14.9 Hz), 4.28 (d, 1H, *J* = 9.7 Hz), 5.36 (d, 1H, *J* = 9.7 Hz), 7.19-7.50 (m, 10H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 32.3, 55.6, 79.0, 125.9, 127.5, 128.9, 129.1, 129.2, 129.3, 130.6, 133.7, 153.7, 169.7, 171.1; MS (EI): *m/z* (relative intensity, %) 306 ($[M]^+$, 100); HRMS (EI): *m/z* calcd for $C_{18}H_{14}N_2O_3$ (M) 306.1004, found 306.1002.

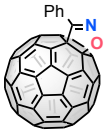
3-Benzyl-5-phenyl-3a,6a-dihydro-prrolo[3,4-d]isoxazole-4,6-dione (3mf)



Colorless solid (63.9 mg, 80%); mp. 159–160 °C; IR (KBr, cm^{-1}) 1719, 1388, 1196, 694; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.72–3.08 (m, 4H), 4.32 (d, 1H, *J*

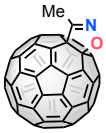
= 9.5 Hz), 5.40 (d, 1H, *J* = 9.5 Hz), 7.22–7.51 (m, 10H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 28.1, 32.0, 57.0, 78.7, 126.0, 126.5, 128.2, 128.5, 129.1, 129.2, 130.6, 139.6, 154.0, 169.8, 171.2; MS (EI): *m/z* (relative intensity, %) 320 ([M]$^+$, 33), 91 (100); HRMS (EI): *m/z* calcd for $C_{19}H_{16}N_2O_3$ (M) 320.1161, found 320.1162.

3-Phenyl-[60]fullereno[1´,2´:4,5]isoxazoline (4a)[30]



Black crystalline solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.56 (m, 3H), 8.17 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 79.28, 104.02, 128.89, 128.92, 129.12, 130.76, 136.79, 137.04, 140.23, 140.38, 141.72, 142.06, 142.30, 142.47, 142.48, 142.85, 142.86, 142.99, 144.11, 144.30, 144.40, 144.64, 144.78, 145.18, 145.25, 145.43, 145.62, 145.81, 145.97, 146.02, 146.27, 146.30, 146.41, 147.30, 147.81, 153.97.

3´-Methylisoxazolo[4´,5´:1,2][60]fullerene (4b)[31]



Black crystalline solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.75 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.49, 80.55, 101.95, 136.72, 137.04, 140.10, 140.78, 141.81, 142.16, 142.19, 142.21, 142.39, 142.80, 142.98, 142.08, 144.12, 144.35, 144.65, 144.71, 144.86, 145.14, 145.22, 145.28, 145.44, 145.67, 145.90, 146.02, 146.24, 146.28, 146.38, 147.25, 147.82, 152.08.

1-11. References and Notes

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Chapter 2

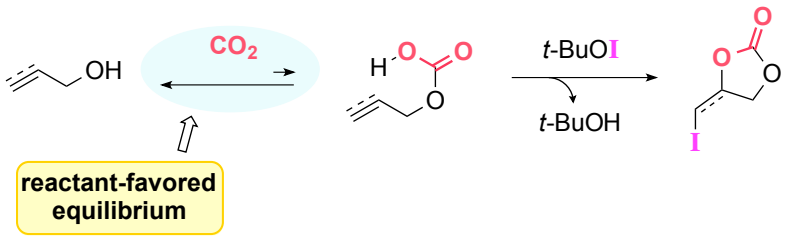
Cyclizative Atmospheric CO_2 Fixation by Unsaturated Amines Utilizing *t*-BuOI Leading to Cyclic Carbamates

2-1. Introduction

In Chapter 2, I reported cyclizative atmospheric CO_2 fixation by unsaturated amines with *t*-BuOI leading to cyclic carbamates.

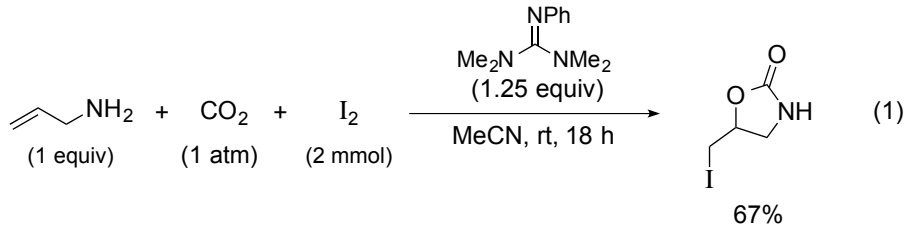
Control of the concentration level of carbon dioxide, a disreputable greenhouse gas, in the atmosphere has been a worldwide issue to be solved urgently.[1] To address the problem, there are two main types of approaches: CO_2 capture and storage/sequestration (CCS); CO_2 capture and its utilization (CCU).[2] The former approach is based on the idea of capturing CO_2 into adsorbents such as solid, liquid, and membranes.[3] On the other hand, the CCU approach would allow for not only consuming CO_2 but also producing value-added chemicals by synthetic methods from abundant and environmentally friendly C1 feedstock. Nevertheless, the biggest obstacle to this approach lies in the thermodynamic stability of CO_2, which is at the highest oxidation state of carbon. To activate CO_2, harsh reaction conditions such as the use of highly reactive metal catalysts and external strong acids/bases, or high pressures, have been

required.[2,4] Therefore, the development of chemical transformation methods of CO_2 without energy-consuming processes is desired. In this regard, our group has previously developed an atmospheric CO_2 fixation method by unsaturated alcohols under mild reaction conditions utilizing *t*-BuOI.[5] The key to success was the use of a powerful iodinating reagent, *t*-BuOI, which readily reacts with carbonic acid monoalkyl esters ((allyl)OC(O)OH)) generated from the equilibrium of CO_2 and allyl alcohols, thereby exchanging the acidic proton with iodine leading to cyclic carbonate products. The only byproduct produced in this reaction is nontoxic *t*-BuOH, which would not interfere with the progression of the reaction. However, due to the existence of a highly reactant-favored equilibrium between two systems of CO_2/allyl alcohols and carbonic acid monoalkyl esters (Scheme 1), two equivalents of *t*-BuOI were required to obtain products in high yields.

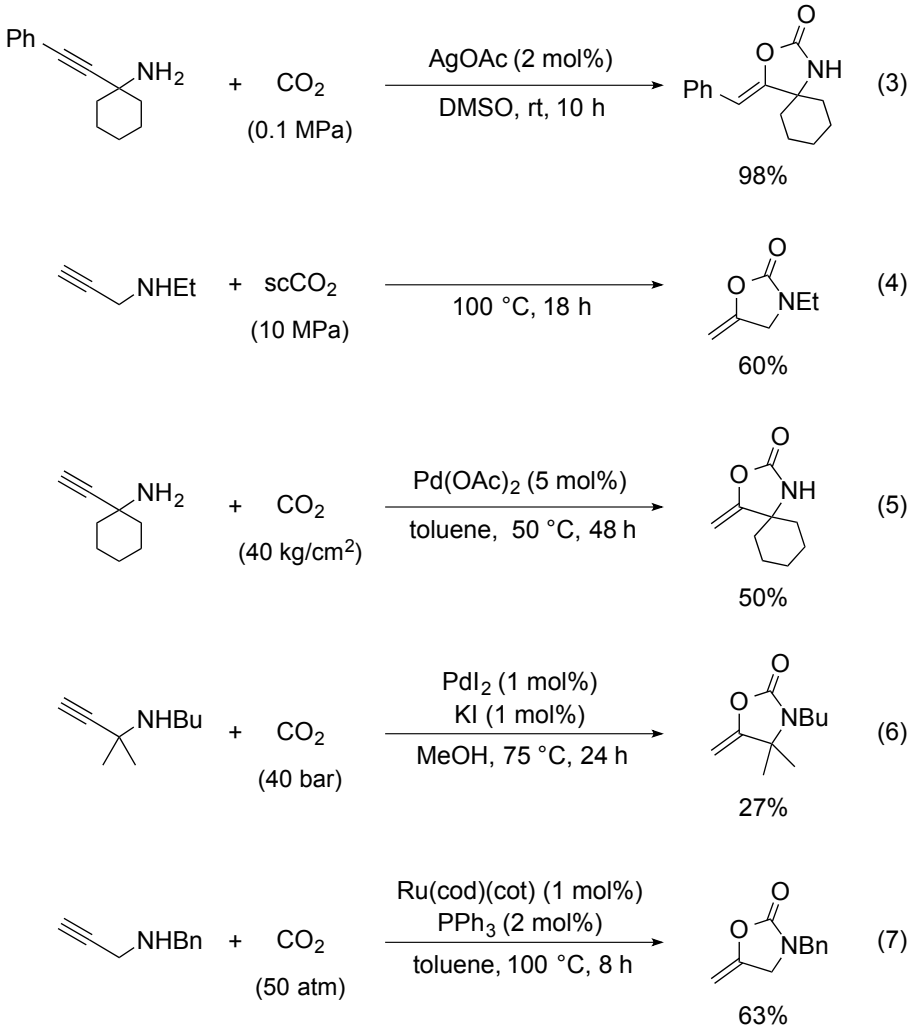


Scheme 1. Cyclizative CO_2 Fixation by Unsaturated Alcohols

Contrary to the system, amines including allyl amines have been known to be good capturing agents for CO_2 to form carbamic acids or ammonium carbamates owing to their higher nucleophilicities than alcohols.[6] Utilization of the thermodynamically favored process in two cyclizative atmospheric CO_2 fixation methods by allyl amines leading to cyclic carbamates, which constitute an important class of heterocyclic compounds serving as synthetic intermediates for complex molecules[7] or as biologically active agents,[8] has been reported (Eqs 1 and 2).[9] Both reactions require the concomitant use of stoichiometric amounts of I_2 and an external strong base (TMG[9a] or Cs_2CO_3[9b]), which would trap the liberated strong acid (HI), to gain high yields of product.



As related reactions, metal-catalyzed cyclizative CO_2 fixations by propargyl amines under pressurized conditions or supercritical CO_2 have also been developed (Eqs 3–7).[10]

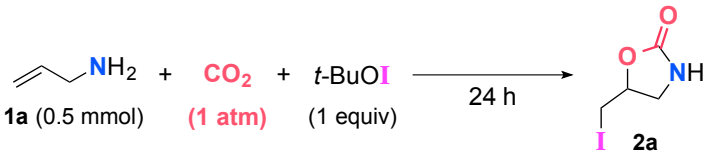


Results and Discussion

2-2. Cyclizative CO_2 Fixation by Allyl Amine in the Presence of *t*-BuOI

At first, when the simplest allyl amine **1a** was treated with an equimolar amount of *t*-BuOI under 1 atm of CO_2 in acetonitrile at room temperature, a five-membered cyclic carbamates containing an iodomethyl group was successful produced in 47% yield (Table 1, entry 1). To improve the efficiency of the CO_2 fixation, reaction parameters such as solvents and temperatures were scrutinized. As a result, the reaction at –20 ˚C in acetonitrile was found to provide the desired carbamate **2a** in the highest yield of 91% (entry 3).

Table 1. Screening Reaction Conditions[a]

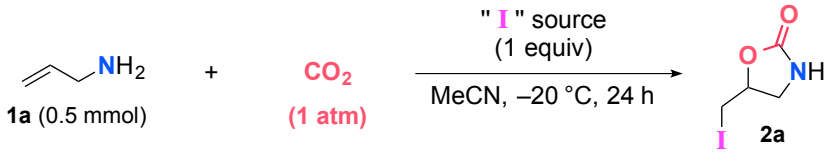


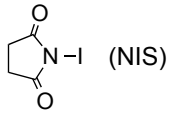
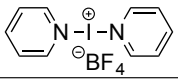
entry	solvent	temp. (°C)	yield (%)[b]
1	MeCN	rt	47
2	MeCN	0	71[c]
3	MeCN	–20	91[c]
4	MeCN	–40	84
5	THF	–20	27
6	DMF	–20	23
7	toluene	–20	48
8	CH_2Cl_2	–20	67

[a] Reaction conditions: allyl amine (0.5 mmol), CO_2 (balloon), *t*-BuOCl (0.5 mmol) and NaI (0.5 mmol) in solvent (3 mL) for 24 h. [b] ^{1}H NMR yields. [c] Isolated yield.

The employment of I_2 alone, or the concomitant use of I_2/Et_3N gave miserable yields. The reactions with other iodinating reagents such as *N*-iodosuccinimide (NIS) and IPy_2BF_4 (BPIT) resulted in rather low yields of **2a** (Table 2). The reason why *t*-BuOI is the most suitable iodinating reagent in this system could be due to the liberation of only a weak acid (*t*-BuOH) instead of HI that should be trapped by an external base in the similar reaction systems.[9]

Table 2. Comparison of Iodinating Reagents[a]



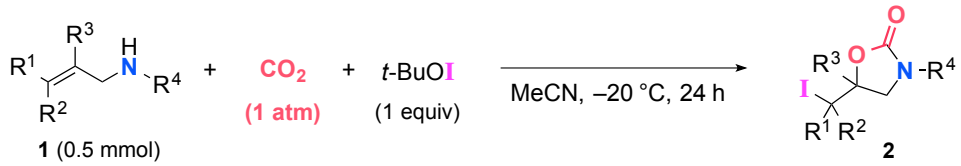
entry	" I " source	yield (%)[b]	entry	" I " source	yield (%)[b]
1	*t*-BuOI	91	4	 (NIS)	4
2	I_2	17			
3	I_2 + Et_3N	0	5	 (IPy_2BF_4)	1

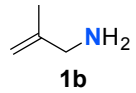
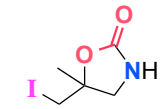
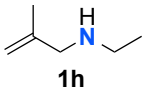
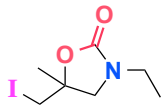
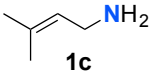
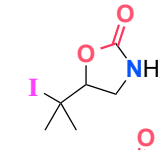
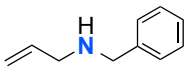
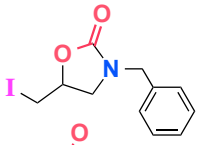
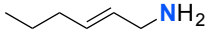
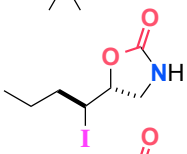
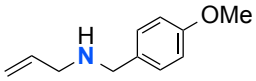
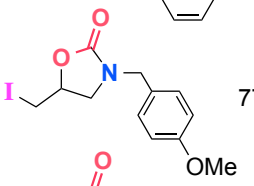
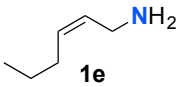
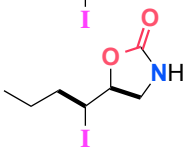
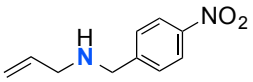
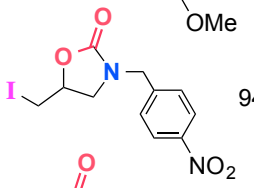
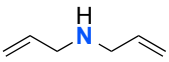
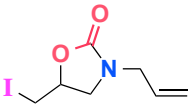
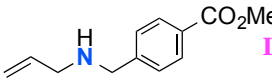
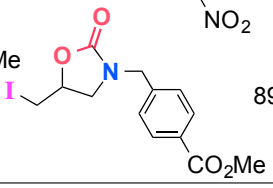
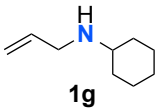
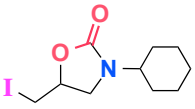
[a] Reaction conditions: allyl amine (0.5 mmol), CO_2 (balloon) and iodinating reagent (0.5 mmol) in MeCN (3 mL) at –20 °C for 24 h. [b] ^1H NMR yields. [c] Isolated yield.

2-3. CO_2 Fixation with Allyl Amines

With the optimal conditions in hand, I next investigated the scope of allyl amine derivatives (Table 3). *β*-Branched allyl amine **1b** was converted into the corresponding carbamate **2b** in moderate yield (entry 1). Allyl amine having a *γ*-disubstituent **1c** was also applicable to this CO_2 fixation (entry 2). When geometric isomers **1d** and **1e** were employed as substrates, the reaction proceeded sterospecifically to give **2d** and **2e** as single stereoisomers in both cases (entries 3 and 4). Moreover, *N*,*N*-diallyl amine (**1f**) was successfully transformed into the corresponding carbamate **2f** with keeping the other allylic moiety intact (entry 5). *N*-substitution with alkyl groups did not retard reaction efficiencies (entries 6–8). Various functionalities, such as methoxy, nitro and ester groups on the benzene ring showed good compatibility with the reaction conditions, leading to the corresponding cyclic carbamates **2j**–**2l** in good to high yields (entries 9–11).

Table 3. Substrate Scope of Allyl Amines[a]



entry	amine	cyclic carbamate	yield (%)	entry	amine	cyclic carbamate	yield (%)
1	 **1b**		58 (**2b**)	7	 **1h**		78 (**2h**)
2	 **1c**		61 (**2c**)	8	 **1i**		87 (**2i**)
3[b]	 **1d**		81 (**2d**)	9	 **1j**		77 (**2j**)
4	 **1e**		81 (**2e**)	10	 **1k**		94 (**2k**)
5[c]	 **1f**		66 (**2f**)	11	 **1l**		89 (**2l**)
6[c]	 **1g**		79 (**2g**)				

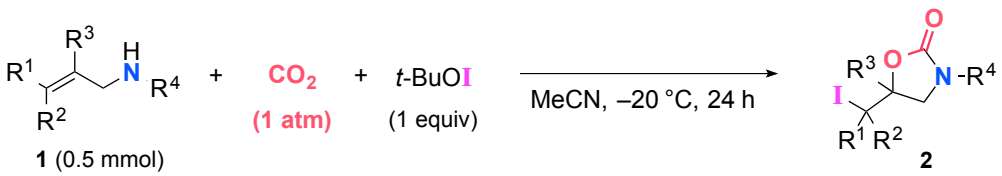
[a] Reaction conditions: allyl amine (0.5 mmol), CO_2 (balloon), *t*-BuOCl (0.5 mmol) and NaI (0.5 mmol) in MeCN (3 mL) at –20 °C for 24 h. [b] Reaction was conducted at 0 °C. [c] CH_2Cl_2 was used as a solvent.

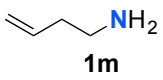
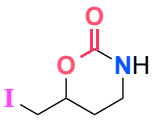
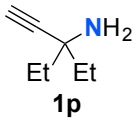
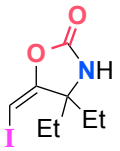
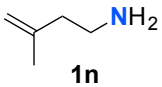
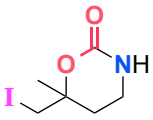
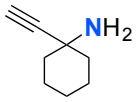
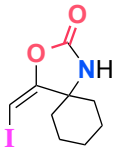
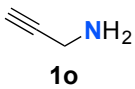
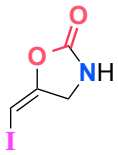
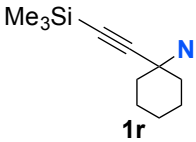
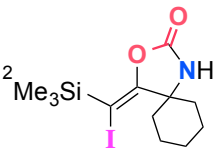
2-4. CO_2 Fixation with Homoallyl and Propargyl Amines

The successful results in the transformation of allyl amines into five-membered cyclic carbamates through the CO_2 fixation prompted me to further investigate the use of homoallyl and propargyl amines as substrates (Table 4). When homoallyl amine **1m** was subjected to the reaction conditions, six-membered carbamate **2m** was obtained in moderate yield (entry 1), while γ-branched homoallyl amine **1n** was also converted to the corresponding carbamate **2n** in moderate yield (entry 2). Unfortunately, the reaction using simplest propargyl amine **1o** failed to provide the desired product **2o** (entry 3). In sharp contrast, amines bearing a *gem*-disubstituent at the propargylic position gave cyclic carbamates **2p** and **2q** in good yields as

sole constitutional isomers with *E*-configuration (entries 4 and 5). This significant discrepancy in these reaction outcomes would be explained in terms of "Thorpe–Ingold effect"[11] through the intramolecular cyclization process from the intermediately generated iodonium intermediates. It is noted that the silyl group on the acetylenic carbon of **1r** survived the reaction conditions in which "I^+" species coexist, leading to **2r** having a tetra-substituted olefinic moiety in moderate yield (entry 6).

Table 4. Substrate Scope of Homoallyl and Propargyl Amines[a]



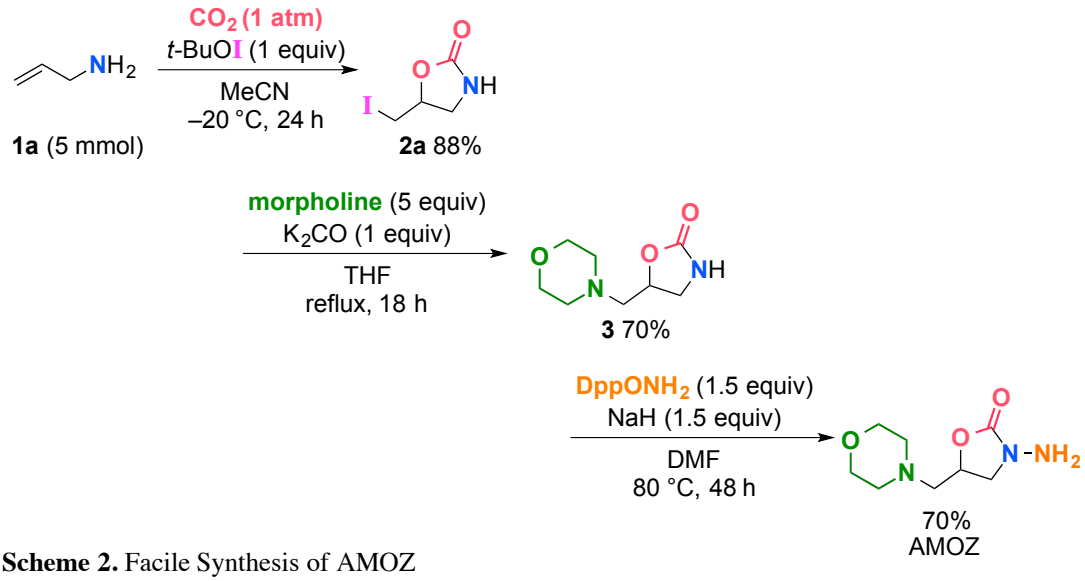
entry	amine	cyclic carbamate	yield (%)	entry	amine	cyclic carbamate	yield (%)
1	 **1m**		62 (**2m**)	4	 **1p**		80 (**2p**)
2	 **1n**		54 (**2n**)	5	 **1q**		68 (**2q**)
3	 **1o**		0 (**2o**)	6	 **1r**		56 (**2r**)

[a] Reaction conditions: unsaturated amine (0.5 mmol), CO_2 (balloon), *t*-BuOCl (0.5 mmol) and NaI (0.5 mmol) in MeCN (3 mL) at –20 °C for 24 h.

2-5. Synthetic Application of Cyclic Carbamate

The cyclic carbamates that were obtained by this method would serve as useful building blocks, because an iodo-functionality attached to sp^3- or sp^2-hybridized carbon atoms can be transformed into other functional groups.[12] To demonstrate a synthetic application of the present reaction, a 3-steps preparation of 3-amino-5-morpholinomethyl-2-oxazolidinone (AMOZ),[13] which is a synthetic intermediate of moxnidazole (anti-parasite drug)[14] and

furaltadone (anti-bacterial drug),[14a,15] was efficiently accomplished starting from allyl amine **1a** (Scheme 2). The CO_2 fixation by **1a** was applicable to a gram scale operation, producing **2a** in 88% yield. The iodo functionality of **2a** was then substituted with a morpholino group, leading to oxazolidinone **3** in good yield. The treatment of **3** with *O*-(diphenylphosphinyl)-hydroxylamine ($DppONH_2$)[16] and NaH in DMF afforded AMOZ in 70% yield. Considering that the conventional synthetic route to AMOZ requires as many as six steps starting from (2,2-dimethyl-1,3-dioxolan-4-yl)methanol as a starting material,[17] this short-step-synthesis demonstrates the utility of my reaction.



Scheme 2. Facile Synthesis of AMOZ

2-6. Investigation on Reaction Pathway

For a deeper understanding of the reaction pathway, several experiments were conducted. In situ monitoring of a CD_3CN solution of a mixture of allyl amine (**1a**) and *t*-BuOI under the N_2 atmosphere using ^1H NMR technique revealed that no change in ^1H NMR spectrum of allyl amine occurred (Figure 1). On the other hand, under a CO_2 atmosphere the similar monitoring (^1H, ^{13}C NMR, and FT-IR) of a CD_3CN solution of **1a** without *t*-BuOI indicated quantative formation of allylammonium allylcarbamate (Figures 2–4).[6] Furthermore, the gradual

formation of cyclic carbamate **2a** in the solution was identified upon successive addition of *t*-BuOI to the solution (Figure 2).[18]

^{1}H NMR monitoring of reaction of allyl amine **1a** with *t*-BuOI under N_2 atmosphere

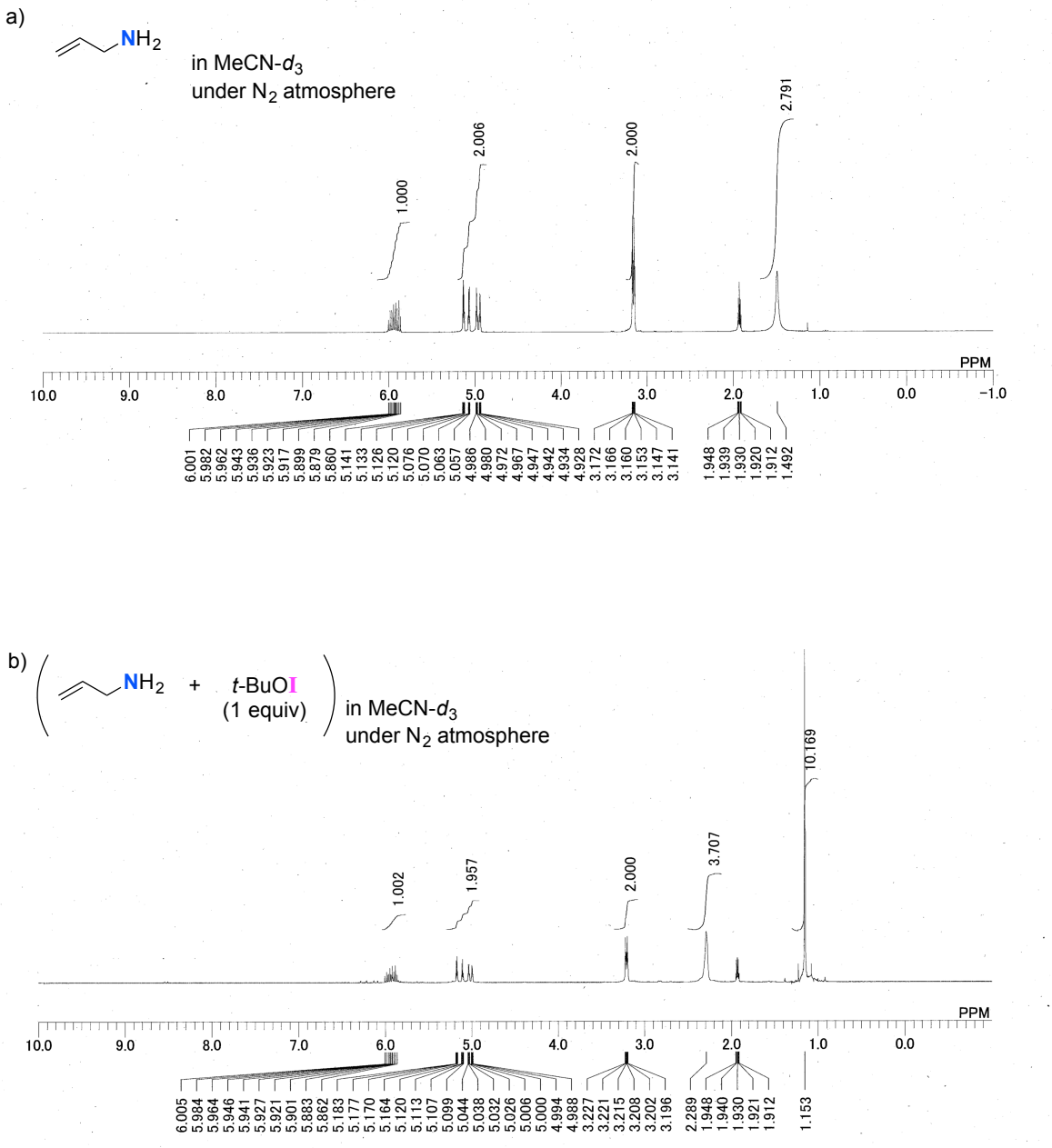


Figure 1. ^{1}H NMR spectra of a) the d_3-MeCN solution of allyl amine (0.1 mmol, 5.7 mg) and NaI (0.1 mmol, 15.0 mg) under N_2 atmosphere; b) the d_3-MeCN solution after the treated with *t*-BuOCl (0.1 mmol, 10.9 mg)

^{1}H NMR monitoring of reaction of allyl amine **1a** with *t*-BuOI under CO_2 atmosphere

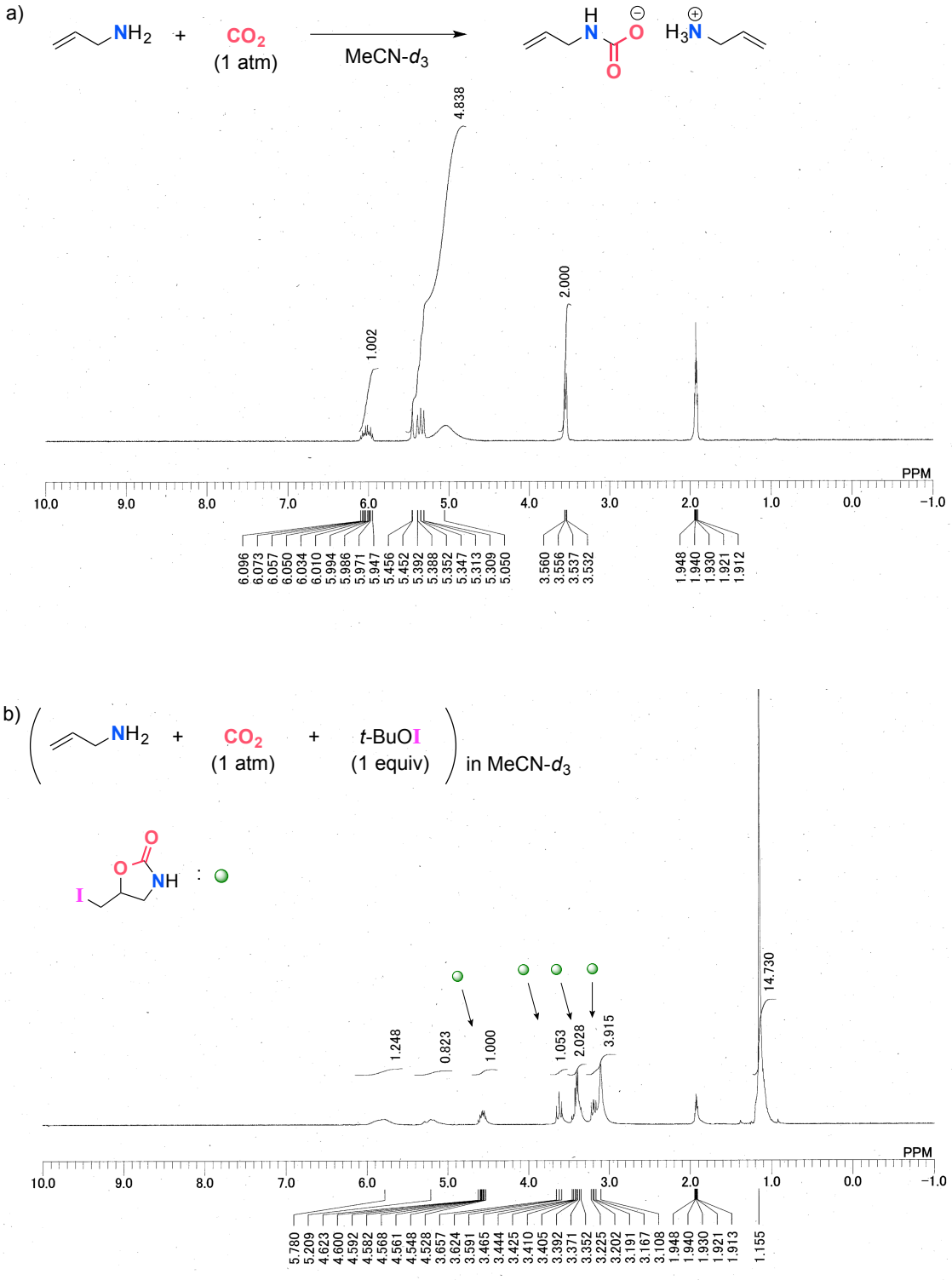


Figure 2. ^{1}H NMR spectra of a) the d_3-MeCN solution of allyl amine (0.1 mmol, 5.7 mg) and NaI (0.1 mmol, 15.0 mg) under CO_2 atmosphere; b) the d_3-MeCN solution after the treated with *t*-BuOCl (0.1 mmol, 10.9 mg)

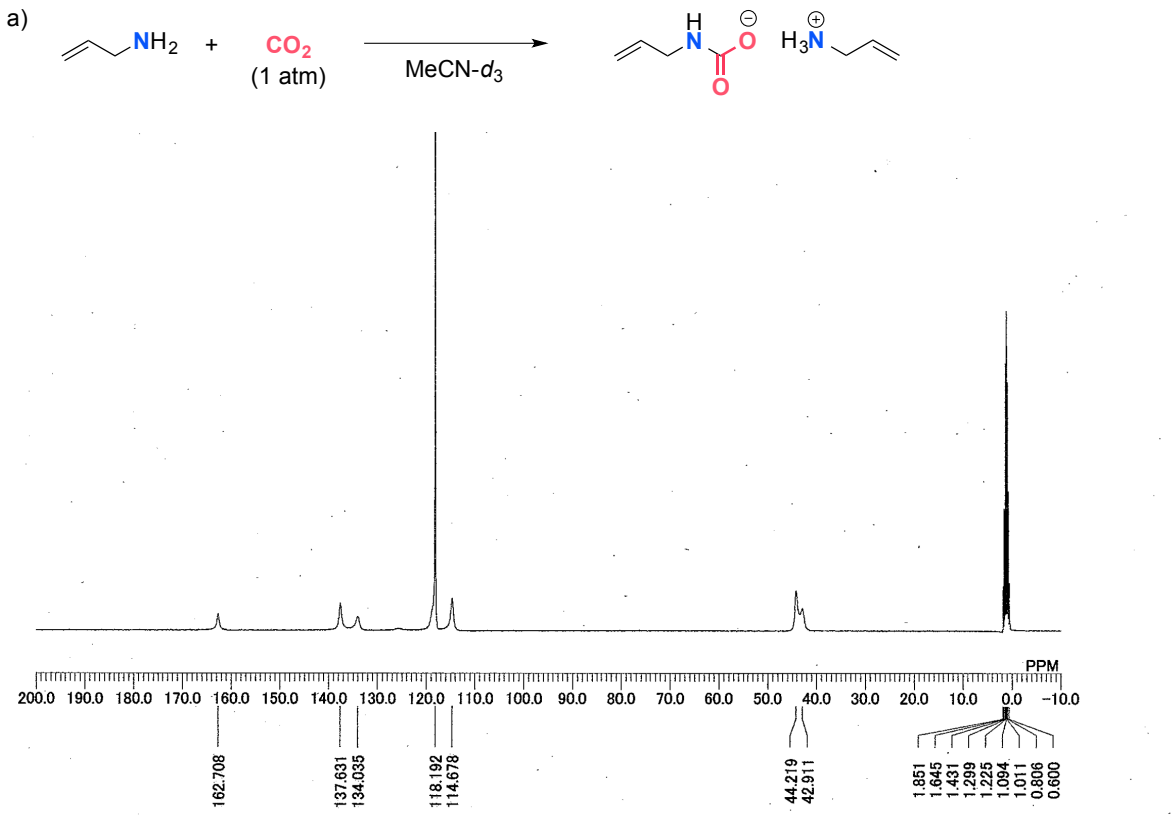
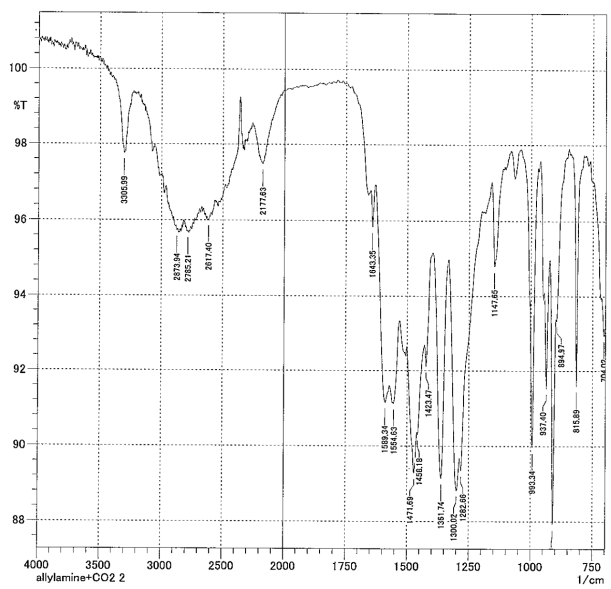


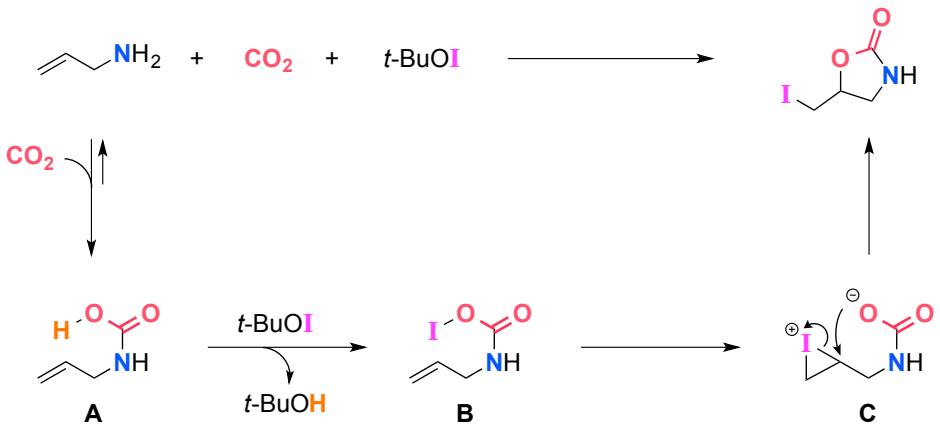
Figure 3. ^{13}C NMR spectra of a d_3-MeCN solution of allyl amine (0.1 mmol, 5.7 mg) and NaI (0.1 mmol, 15.0 mg) under CO_2 atmosphere



No.	ピーク	高さ	補正高さ	ベース (H)	ベース (L)	面積	補正面積
1	704.02	92.942	0.606	713.66	698.23	0.468	0.024
2	815.89	91.593	5.952	831.32	796.6	0.648	0.269
3	894.97	93.331	0.406	898.83	848.68	0.799	0.009
4	910.4	87.917	6.207	923.9	898.83	0.969	0.309
5	937.4	91.525	2.899	945.12	925.83	0.592	0.121
6	993.34	89.969	7.582	1039.63	972.12	1.419	0.718
7	1147.65	94.794	2.323	1159.22	1114.86	0.767	0.221
8	1282.66	89.339	0.58	1286.52	1197.79	2.599	0.019
9	1300.02	88.82	2.244	1332.81	1288.45	1.832	0.262
10	1361.74	89.137	5.898	1396.39	1334.74	2.183	0.779
11	1423.47	92.108	1.073	1429.25	1400.32	0.816	0.05
12	1458.18	90.295	0.227	1460.11	1431.18	1.092	0.008
13	1471.69	89.276	1.613	1502.55	1462.04	1.752	0.176
14	1554.63	91.12	1.231	1571.99	1531.48	1.497	0.128
15	1589.34	91.15	1.925	1629.85	1573.91	1.761	0.295
16	1643.35	95.827	1.01	1649.14	1629.85	0.302	0.036
17	2177.63	97.476	0.104	2202.71	2171.85	0.332	0.011
18	2617.4	96.007	0.022	2621.26	2615.47	0.102	0
19	2785.21	95.69	0.02	2791	2783.28	0.147	0
20	2873.94	95.728	0.086	2881.65	2868.15	0.253	0.003
21	3305.99	97.751	1.399	3354.21	3265.49	0.598	0.276

Figure 4. FT-IR spectra of the precipitates that formed from d_3-MeCN solution of allyl amine and NaI under CO_2 atmosphere (ν 3006, 2874, 2785, 2617, 2178, 1648, 1589, 1555, 1472, 1458, 1362, 1300, 1283, 1148, 993, 937, 910, 816, 704 cm^{-1}).[19]

Based on the experimental results, the most likely reaction pathway is illustrated in Scheme 3:[20] (1) allyl carbamic acid **A** is generated as the result of product-favored equilibrium of allyl amine and CO_2;[6] (2) the resulting carbamic acid **A** reacts with *t*-BuOI to undergo proton–iodine exchange, leading to an *O*-iodinated species **B**; (3) the intermediate **B** would serve as an iodonium source to form cyclic iodonium intermediate **C**; (4) intramolecular cyclization from **C** would give cyclic carbamate product, which process being possibly supported by the stereospefic production of **2d** and **2e**.



Scheme 3. Plausible Reaction Pathway

2-7. Conclusion

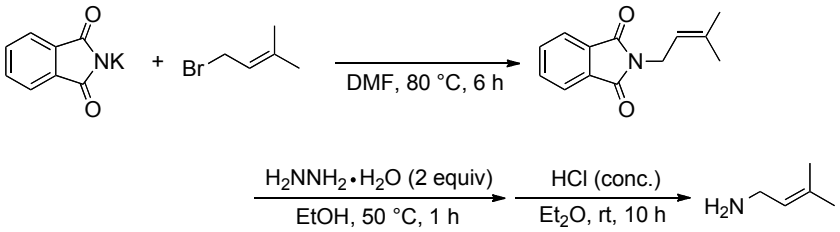
In summary, this chapter describes cyclizative atmospheric CO_2 fixation by unsaturated amines leading to cyclic carbamates utilizing *t*-BuOI. The method was applicable to a wide range of unsaturated amines. The short-step preparation of AMOZ was accomplished starting from cyclic carbmate prepared from 1-amino-2-propene.

2-8. Experimental Section

General experimental methods

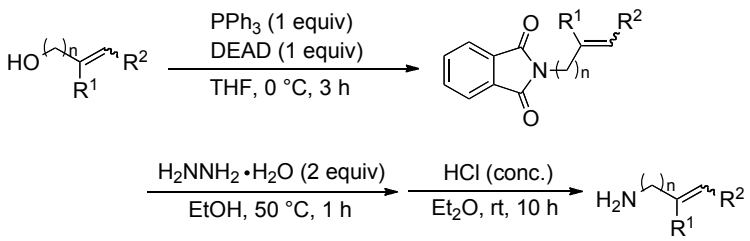
Dehydrated acetonitrile was used as received. Melting points were determined on a Stanford Research Systems MPA100 OptiMelt Automated Melting Point System and are uncorrected. Infrared spectra were recorded on a SHIMADZU IRAffinity-1 FT-IR Spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL FT-NMR JNM EX 270 spectrometer (^{1}H NMR, 270 MHz; ^{13}C NMR, 68 MHz) using tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL JMS-DX303HF mass spectrometer. High-resolution mass spectra were obtained on a JEOL JMS-DX303HF mass spectrometer. Preparative gel permeation liquid chromatography (GPLC) was performed on a JAI (Japan Analytical Industry) LC - 908 instrument with JAIGEL 1H-2H columns and chloroform as an eluent. Products were purified by chromatography on silica gel BW-300 (Fuji Silysia Chemical Ltd.) or NH-silica gel (Fuji Silysia Chemical Ltd.). Analytical thin-layer chromatography (TLC) was performed on precoated silica gel glass plates (Merck silica gel 60 F_{254}, 0.25 mm thickness). Compounds were visualized with UV lamp or treatment with an ethanolic solution of phosphomolybdic acid followed by heating.

Procedure for the preparation of unsaturated amine 1c



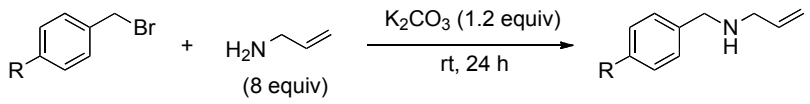
A mixture of potassium phthalimide (30 mmol) and prenyl bromide (30 mmol) in DMF was stirred at 80 °C for 6 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was poured into an ice-water, and the solid was collected on a filter funnel. The crude product was used without further purification. To a mixture of *N*-prenylphthalimide and ethanol (200 mL) was added hydrazine monohydrate (60 mmol) at 50 °C. The mixture was stirred for 1 h and quenched with aq. HCl (6.0 M, 20 mL). The forming solids were removed by filtration. The filtrate was dried over Na_2SO_4 and concentrated under vacuum to give prenylamine hydrochloride. Aqueous NaOH (6.0 M, 10 mL) was added to the amine salt, and the resulting solution was extracted with diethyl ether (50 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give amine **1c** (1.35 g, 53%). The spectroscopic data for this compound were in agreement with the reported data.[21]

Procedure for the preparation of unsaturated amine 1d, 1e and 1n



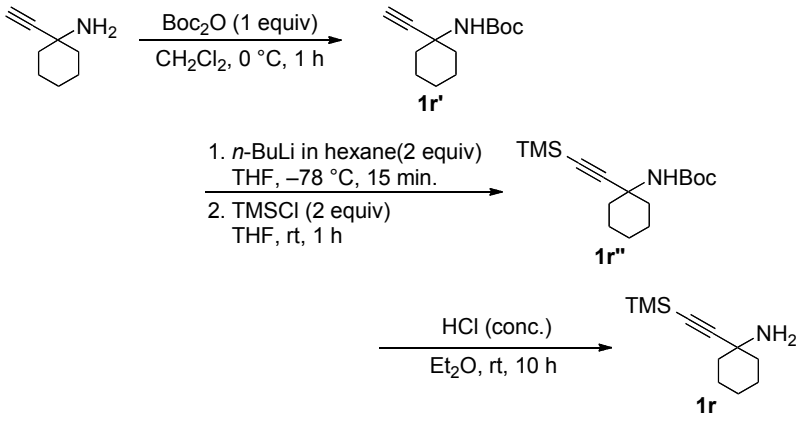
To a mixture of triphenylphosphine (25 mmol) and the corresponding allyl alcohol (25 mmol) in THF (30 mL) was slowly added diethyl azodicarboxylate (DEAD) (25 mmol) at 0 °C under N_2 atmosphere. The mixture was stirred at 0 °C for 3 h. After the reaction completion, *n*-hexane was added to the reaction mixture and filtered. The filtrate was dried over Na_2SO_4 and concentrated under vacuum to give the crude product, which was used without further purification. To a mixture of phthalimide product and ethanol (100 mL) was added hydrazine monohydrate (50 mmol) at 50 °C. The mixture was stirred for 1 h and quenched with aq. HCl (6.0 M, 20 mL) to produce precipitates. The forming solids were removed by filtration, and the filtrate was dried over Na_2SO_4 and concentrated under vacuum to give an unsaturated amine hydrochloride. Aqueous NaOH (6.0 M, 10 mL) was added to the amine salt, and the resulting solution was extracted with diethyl ether (50 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give unsaturated amine (**1d**: 1.58 g, 64%; **1e**: 1.63 g, 66%; **1n**: 0.75 g, 35%). The spectroscopic data for **1d**[22] and **1n**[23] were in agreement with the reported data.

Procedure for the preparation of *N*-benzyl allyl amines 1i–1l[24]



To a mixture of K_2CO_3 (16.1 mmol) and allyl amine (107 mmol) was added the corresponding benzyl bromide (13.4 mmol) over 15 min under N_2 atmosphere. The mixture was stirred at room temperature for 24 h. The extra K_2CO_3 was filtered and washed with CH_2Cl_2. The filtrate was concentrated under vacuum to give the crude product. Purification by flash column chromatography on silica gel (eluent: ethyl acetate/hexane) gave *N*-benzyl allyl amine (**1i**: 1.77 g, 90%; **1j**: 2.21 g, 93%; **1k**: 1.53 g, 60%; **1l**: 2.61 g, 95%). The spectroscopic data for all compounds were in agreement with the reported data (**1i**[24], **1j**[25], **1k**,[26] and **1l**[27]).

Procedure for the preparation of 1-((trimethylsilyl)ethynyl)cyclohexylamine (1r)[28,29]



To a CH_2Cl_2 solution (20 mL) of 1-ethynylcyclohexylamine (10 mmol) was added di-*tert*-butyl dicarbonate (10 mmol) at 0 °C under N_2 atmosphere. The mixture was stirred for 1 h, and the solvent was removed under vacuum to give *N*-Boc protected crude product **1r'**. To a solution of **1r'** in THF (60 mL) was added *n*-BuLi (20 mmol, 1.65 M hexane solution) at –20 °C under N_2 atmosphere. After 15 min stirring, TMSCl (20 mmol) was added dropwise to the mixture over 30 min. The solution was allowed to warm up to room temperature and stirred for 1 h, quenched with aqueous HCl (2 M, 15 mL), and extracted with diethyl ether (50 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude product **1r''**. To a solution of **1r''** in Et_2O (30 mL) was added aqueous HCl (12 M, 3 mL) at 0 °C, and the resulting mixture was allowed to warm up to room temperature. After 10 h stirring, the solution was quenched with aqueous Na_2CO_3 (sat. 20 mL) and extracted with Et_2O (30 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude product **1r**. Purification by flash column chromatography on silica gel (eluent: ethyl acetate/hexane) gave propargyl amine **1r** (1.38 g, 70%).

*Other unsaturated amines **1a**, **1b**, **1f–1h**, **1m** and **1o–1q** were purchased from a commercial supplier.

Typical procedure for CO_2 fixation by unsaturated amines

To a mixture of NaI (0.5 mmol, 75.0 mg) and unsaturated amine (0.5 mmol) in an appropriate solvent (3 mL) was added *t*-BuOCl (0.5 mmol, 54.3 mg) at –20 °C under CO_2 atmosphere. The mixture was stirred for 24 h in dark and quenched with aqueous $Na_2S_2O_3$ (1.0 M, 10 mL), and the resulting mixture was extracted with diethyl ether (20 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude product. Purification by flash column chromatography on silica gel (eluent: ethyl acetate/hexane) gave cyclic carbamate **2** (for example, **2a**: 103.2 mg, 91%).

Procedures for the synthesis of AMOZ

Gram scale preparation of cyclic carbamates 2a

To a mixture of NaI (5.0 mmol, 750 mg) and allyl amine **1a** (5.0 mmol, 286 mg) in acetonitrile (30 mL) was added *t*-BuOCl (5.0 mmol, 543 mg) at –20 °C under CO_2 atmosphere. The mixture was stirred for 24 h in dark and quenched with aqueous $Na_2S_2O_3$ (1.0 M, 30 mL), and the resulting mixture was extracted with diethyl ether (50 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude product. Purification by flash column chromatography on silica gel (eluent: ethyl acetate/hexane) gave **2a** (1.0 g, 88%).

Procedure for the prepartion of 3 through nucleophilic substitution of iodo group[30]

A mixture of **2a** (2 mmol, 454 mg), K_2CO_3 (2 mmol, 276 mg), morpholine (10 mmol, 872 mg), and THF (10 mL) was refluxed for 18 h. After the reaction completion, the extra K_2CO_3 was filtered and washed with THF. The filtrate was concentrated under vacuum to give the crude product. Purification by flash column chromatography on NH-silica gel (eluent: ethyl

acetate) gave **3** (261 mg, 70%).

Procedure for the preparation of AMOZ through *N*-amination of 3[31]

To a solution of **3** (0.5 mmol, 93.2 mg) in DMF (3 mL) was added NaH (0.75 mmol, 18.0 mg) at room temperature under nitrogen atmosphere. The mixture was stirred at 80 °C for 2 h. *O*-(diphenylphoshinyl)hydroxylamine* ($DppONH_2$) (0.75 mmol, 172.6 mg) was added to the mixture, which was stirred at 80 °C for 48 h. Insoluble solids were filtered, and the filtrate was concentrated under vacuum to give the crude product. Purification by flash column chromatography on NH-silica gel (eluent: ethyl acetate) gave AMOZ (70.5 mg, 70%).

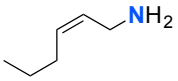
**O*-(diphenylphoshinyl)hydroxylamine (DppONH2) was prepared by reported method.[32]

Comparative study of CO_2 fixation reaction by allyl amine using various iodinating reagents

To a solution of allyl amine **1a** (0.5 mmol) in MeCN (3 mL) was added iodinating reagent (0.5 mmol) at –20 °C under CO_2 atmosphere. The mixture was stirred for 24 h in dark and quenched with aqueous $Na_2S_2O_3$ (1.0 M, 10 mL), and the resulting mixture was extracted with diethyl ether (20 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude product. The product yield was calculated by ^1H NMR integration of the crude product.

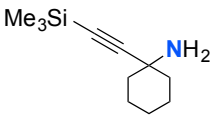
Spectra date of products

***(Z)*-Hex-2-en-1-amine (1e)**



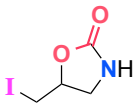
colorless oil; R_f 0.08 (hexane/EtOAc 1:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.90 (m, 3H), 1.30–1.45 (m, 4H), 2.02 (q, 2H, *J* = 6.8 Hz), 3.30 (dd, 2H, *J* = 1.1, 5.7 Hz), 5.38–5.53 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.4, 22.5, 29.0, 38.5, 130.2, 130.8; IR (KBr) *ν* 3290, 3008, 2959, 2872, 1574, 1464, 1377, 1366, 1301 cm^{-1}; MS (CI, isobutane): *m/z* (relative intensity, %) 100 ([M+H]+, 100); HRMS (CI, isobutane): *m/z* calcd for $C_6H_{14}N$ (M+H) 100.1126, found 100.1126.

1-((Trimethylsilyl)ethynyl)cyclohexanamine (1r)



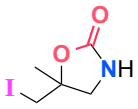
colorless oil; R_f 0.20 (hexane/EtOAc 7:3); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.01 (s, 9H), 0.97–1.75 (m, 12H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 0.09, 23.2, 25.3, 40.2, 49.9, 86.1, 112.6; IR (KBr) *ν* 3360, 3285, 2933, 2900, 2857, 2158, 1447, 1250, 968, 840, 760 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 195 ([M]$^+$, 10), 152 (100); HRMS (EI): *m/z* calcd for $C_{11}H_{21}NSi$ (M) 195.1443, found 195.1448.

5-(Iodomethyl)-oxazolidin-2-one (2a)



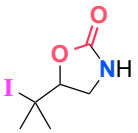
Purified by silica gel column chromatography (hexane/EtOAc 1:1). colorless solid; mp: 117.6–118.5 °C; R_f 0.38 (EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.27–3.44 (m, 3H), 3.77 (dd, 1H, *J* = 8.6, 8.6 Hz), 4.73 (m, 1H), 6.24 (br, s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 5.8, 46.4, 75.1, 159.2; IR (KBr) *ν* 3256, 3151, 1780, 1739, 1242, 1092, 958 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 227 ([M]$^+$, 76), 100 ([M]$^+$–I, 100); HRMS (EI): *m/z* calcd for $C_4H_6INO_2$ (M) 226.9443, found 226.9439.

5-(Iodomethyl)-5-methyloxazolidin-2-one (2b)



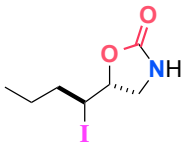
Purified by silica gel column chromatography (hexane/EtOAc 1:1). yellow solid; dec: 84.7–87.2 °C; R_f 0.11 (hexane/EtOAc 6:4); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.69 (s, 3H), 3.35 (d, 1H, *J* = 8.9 Hz), 3.42 (dd, 2H, *J* = 10.5, 17.0 Hz), 3.63 (d, 1H, *J* = 8.9 Hz), 5.96 (br, s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 12.6, 25.2, 51.2, 80.7, 158.9; IR (KBr) *ν* 3232, 3146, 1728, 1481, 1305, 1222, 1095, 987, 764 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 241 ([M]$^+$, 29), 100 ([M]$^+$–I–CH_2, 100); HRMS (EI): *m/z* calcd for $C_5H_8INO_2$ (M) 240.9600, found 240.9603.

5-(2-Iodopropane-2-yl)oxazolidin-2-one (2c)



Purified by silica gel column chromatography (hexane/EtOAc 1:1). yellow solid; dec: 118.7–120.5 °C; R_f 0.24 (EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.57 (s, 3H), 1.58 (s, 3H), 3.71 (m, 2H), 4.19 (dd, 1H, *J* = 5.7, 8.4 Hz), 7.37 (br, s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 24.1, 24.8, 27.7, 47.1, 80.6, 153.8; IR (ATR) *ν* 1692, 1313, 1136, 1111, 1066 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 255 ([M]$^+$, 30), 212 (27), 154 (70), 128 ([M]$^+$–I, 100); HRMS (EI): *m/z* calcd for $C_6H_{10}INO_2$ (M) 254.9756, found 254.9760.

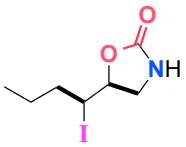
(*R*)-5-((*S*)-1-Iodobutyl)oxazolidin-2-one (2d)



Purified by silica gel column chromatography (hexane/EtOAc 1:1). colorless solid; mp: 97.2–99.8 °C; R_f 0.14 (hexane/EtOAc 6:4); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.96 (t, 3H, *J* = 7.0 Hz), 1.32-1.98 (m, 4H), 3.43 (dd, 1H, *J* = 7.3, 7.3 Hz), 3.79 (dd, 1H, *J* = 7.3, 7.3 Hz), 4.11 (td, 1H, *J* = 3.2, 8.6 Hz), 4.63 (ddd, 1H, *J* = 7.3, 7.3, 8.6 Hz), 6.36 (br, s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.1, 22.2, 37.1, 37.7, 47.3, 79.0, 159.4; IR (ATR) *ν* 1719, 1242, 1092, 1005 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 269 ([M]$^+$,

29), 142 ([M]$^+$–I, 100); HRMS (EI): *m/z* calcd for $C_7H_{12}INO_2$ (M) 268.9913, found 268.9911.

(*S*)-5-((*S*)-1-Iodobutyl)oxazolidin-2-one (2e)



Purified by silica gel column chromatography (EtOAc). colorless solid; mp: 123.2–125.5 °C; R_f 0.33 (EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.96 (t, 3H, *J* = 7.0 Hz), 1.35-1.93 (m, 4H), 3.54 (dd, 1H, *J* = 6.5, 8.9 Hz), 3.76 (dd, 1H, *J* = 8.9, 8.9 Hz), 4.11 (td, 1H, *J* = 3.5, 10.5 Hz), 4.65 (m, 1H), 5.74 (br, s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.0, 22.7, 35.5, 36.6, 44.8, 78.2, 159.7; IR (ATR) *ν* 1751, 1719, 1248, 1087, 953 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 269 ([M]$^+$, 12), 142 ([M]$^+$–I, 100); HRMS (EI): *m/z* calcd for $C_7H_{12}INO_2$ (M) 268.9913, found 268.9912.

*The stereochemistry of compounds **2d** and **2e** were determined by nOe difference spectra. Reaction yielding **2d** and **2e** proceeded stereospecifically as observed in our previous work where CO_2 fixation by unsaturated alcohols.[5]

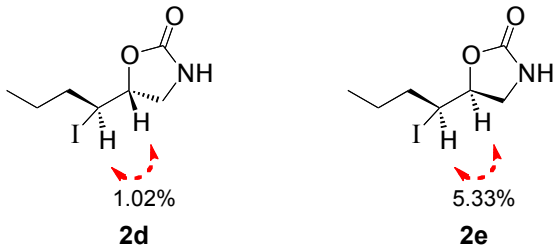
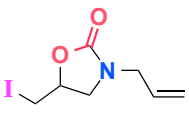


Figure 5. Schematic nOe Difference of **2d** and **2e**

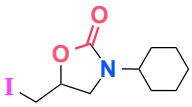
3-Allyl-5-(iodomethyl)oxazolidin-2-one (2f)



Purified by silica gel column chromatography (hexane/EtOAc 7:3). brown oil; R_f 0.26 (hexane/EtOAc 6:4); ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.21-3.43 (m, 3H), 3.68 (t, 1H, *J* = 9.2 Hz), 3.87 (m, 2H), 4.58 (m, 1H), 5.26 (m, 2H), 5.71-5.84 (m, 1H); ^{13}C

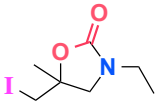
NMR (68 MHz, $CDCl_3$) δ 6.88, 46.7, 49.7, 71.5, 118.9, 131.5, 156.8; IR (ATR) ν 1740, 1440, 1254, 1074, 1009, 912, 727 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 267 ($[M]^+$, 41), 140 ($[M]^+$–I, 62), 96 ($[M]^+$–I–CO_2, 54), 41(C_3H_5, 100); HRMS (EI): *m/z* calcd for $C_7H_{10}INO_2$ (M) 266.9756, found 266.9749.

3-Cyclohexyl-5-(iodomethyl)oxazolidin-2-one (2g)



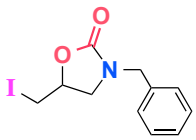
Purified by silica gel column chromatography (hexane/EtOAc 7:3). yellow solid; mp: 75.6–77.9 °C; R_f 0.33 (hexane/EtOAc 6:4); ^1H NMR (270 MHz, $CDCl_3$) δ 1.06–1.82 (m, 10H), 3.26 (m, 2H), 3.39 (dd, 1H, *J* = 3.8, 10.3 Hz), 3.66 (t, 1H, *J* = 8.9 Hz), 3.69 (m, 1H), 4.56 (m, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 6.78, 25.25, 25.30, 30.2, 30.3, 46.5, 52.6, 71.8, 77.2, 156.4; IR (ATR) ν 2924, 2855, 1726, 1433, 1248, 1067 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 309 ($[M]^+$, 80), 266 (62), 228 (100), 187 ($[M]^+$–I, 66); HRMS (EI): *m/z* calcd for $C_{10}H_{16}INO_2$ (M) 309.0226, found 309.0223.

3-Ethyl-5-(iodomethyl)-5-methyloxazolidin-2-one (2h)



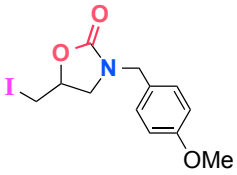
Purified by silica gel column chromatography (hexane/EtOAc 1:1). colorless solid; mp: 39.2–42.9 °C; R_f 0.08 (hexane/EtOAc 8:2); ^1H NMR (270 MHz, $CDCl_3$) δ 1.18 (t, 3H, *J* = 7.8 Hz), 1.66 (s, 3H), 3.29-3.45 (m, 5H), 3.54 (d, 1H, *J* = 8.9 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 12.3, 13.2, 25.1, 38.5, 54.4, 76.5, 156.1; IR (ATR) ν 3493, 2978, 1746, 1450, 1303, 1051, 960, 801, 662 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 269 ($[M]^+$, 100), 128 ($[M]^+$–I–CH_2, 78); HRMS (EI): *m/z* calcd for $C_7H_{12}INO_2$ (M) 268.9913, found 268.9915.

3-Benzyl-5-(iodomethyl)oxazolidin-2-one (2i)



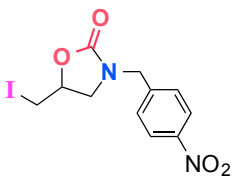
Purified by silica gel column chromatography (hexane/EtOAc 1:1). yellow oil; R_f 0.4 (hexane/EtOAc 1:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.11–3.37 (m, 3H), 3.55 (dd, 1H, *J* = 8.9, 8.9 Hz), 4.36 (d, 1H, *J* = 14.9 Hz), 4.47 (d, 1H, *J* = 14.9 Hz), 4.54 (m, 1H), 7.27–7.40 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 6.6, 48.0, 49.5, 71.5, 127.9, 128.0, 128.7, 135.1, 157.0; IR (ATR) *ν* 1739, 1485, 1429, 1254, 1087, 1064, 1008 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 317 ([M]$^+$, 15), 190 ([M]$^+$–I, 100); HRMS (EI): *m/z* calcd for $C_{11}H_{12}INO_2$ (M) 316.9913, found316.9914.

5-(Iodomethyl)-3-(4-methoxybenzyl)oxazolidin-2-one (2j)



Purified by silica gel column chromatography (hexane/EtOAc 1:1). yellow oil; R_f 0.38 (hexane/EtOAc 5:5); ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.10-3.26 (m, 2H), 3.33 (dd, 1H, *J* = 4.1, 10.5 Hz), 3.53 (dd, 1H, *J* = 8.6, 8.6 Hz), 3.80 (s, 3H), 4.31 (d, 1H, *J* = 14.9 Hz), 4.40 (d, 1H, *J* = 14.9 Hz), 4.52 (m, 1H), 6.88 (d, 2H, *J* = 8.4 Hz), 7.26 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 6.5, 47.5, 49.4, 55.2, 71.6, 114.1, 127.2, 129.5, 157.0, 159.2; IR (ATR) *ν* 2931, 1740, 1610, 1510, 1437, 1242, 1010 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 347 ([M]$^+$, 24), 220 ([M]$^+$–I, 100); HRMS (EI): *m/z* calcd for $C_{12}H_{14}INO_3$ (M) 347.0018, found 347.0018.

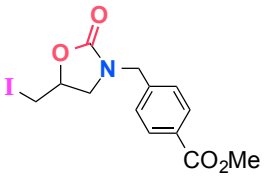
5-(Iodomethyl)-3-(4-nitrobenzyl)oxazolidin-2-one (2k)



Purified by silica gel column chromatography (hexane/EtOAc 1:1). colorless solid; dec: 130.4–131.6 °C; R_f 0.2 (hexane/EtOAc 1:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.20-3.43 (m, 3H), 3.64 (dd, 1H, *J* = 8.6, 8.6 Hz), 4.56 (d, 2H, *J* = 9.5 Hz), 4.62 (m, 1H), 7.50 (d, 2H, *J* = 8.6 Hz), 8.23 (d, 2H, *J* = 8.6 Hz); ^{13}C

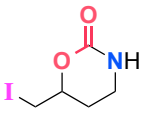
NMR (68 MHz, $CDCl_3$) δ 6.5, 47.6, 50.0, 71.7, 124.1, 128.8, 142.7, 147.7, 157.2; IR (ATR) ν 1748, 1728, 1514, 1444, 1339, 1267, 1076, 1011 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 362 ($[M]^+$, 14), 235 ($[M]^+$–I, 100); HRMS (EI): *m/z* calcd for $C_{11}H_{11}IN_2O_4$ (M) 361.9763, found 361.9765.

Methyl 4-((5-(iodomethyl)-2-oxooxazolidin-3-yl)methyl)benzoate (2l)



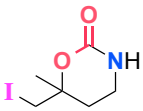
Purified by silica gel column chromatography (hexane/EtOAc 1:1). colorless solid; dec: 97.6–98.8 °C; R_f 0.28 (hexane/EtOAc 1:1); ^1H NMR (270 MHz, $CDCl_3$) δ 3.19 (dd, 1H, *J* = 6.5, 8.9 Hz), 3.67–3.40 (m, 2H), 3.60 (dd, 1H, *J* = 8.9, 8.9 Hz), 3.92 (s, 3H), 4.49 (d, 2H, *J* = 3.2 Hz), 4.57 (m, 1H), 7.38 (d, 2H, *J* = 8.4 Hz), 8.03 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 6.7, 47.7, 49.6, 52.0, 71.5, 127.8, 129.7, 129.9, 140.3, 157.0, 166.3; IR (ATR) ν 1719, 1269, 1107, 1074, 1005 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 375 ($[M]^+$, 18), 248 ($[M]^+$–I, 100); HRMS (EI): *m/z* calcd for $C_{13}H_{14}INO_4$ (M) 374.9968, found 374.9970.

6-(Iodomethyl)-1,3-oxazinan-2-one (2m)



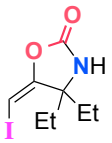
Purified by silica gel column chromatography (EtOAc). colorless solid; dec: 141.4–143.6 °C; R_f 0.11 (EtOAc); ^1H NMR (270 MHz, $CDCl_3$) δ 1.90 (m, 1H), 2.28 (m, 1H), 3.28 (dd, 1H, *J* = 7.6, 10.5 Hz), 3.39–3.44 (m, 3H), 4.32 (m, 1H), 6.15 (br, s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 5.4, 26.2, 38.4, 76.2, 153.9; IR (ATR) ν 1686, 1668, 1479, 1300, 1200, 1130, 1047 cm^{-1}; MS (EI): m/z (relative intensity, %) 241 ($[M]^+$, 100), 114 ($[M]^+$–I, 55), 100 ($[M]^+$–I–CH_2, 56); HRMS (EI): m/z calcd for $C_5H_8INO_2$ (M) 240.9600, found 240.9607.

6-(Iodomethyl)-1,3-oxazinan-2-one (2n)



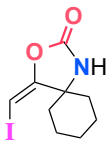
Purified by silica gel column chromatography (EtOAc). colorless solid; dec: 137.6–138.5 °C; R_f 0.11 (EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.57 (s, 3H), 1.94 (m, 1H), 2.18 (m, 1H), 3.35 (m, 4H), 6.93 (br, s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 11.9, 24.9, 29.4, 36.5, 78.6, 153.8; IR (ATR) ν 1702, 1655, 1321, 1111, 1020 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 255 ([M]$^+$, 5), 128 ([M]$^+$–I, 16), 114 ([M]$^+$–I–CH_2, 100); HRMS (EI): *m/z* calcd for $C_6H_{10}INO_2$ (M) 254.9756, found 254.9758.

(*E*)-4,4-Diethyl-5-(iodomethylene)oxazolidin-2-one (2p)



Purified by Preparative gel permeation liquid chromatography. yellow oil; R_f 0.49 (hexane/EtOAc 8:2); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.96 (t, 6H, *J* = 7.3 Hz), 1.66 (dddd, 2H, *J* = 7.3, 7.3, 7.3, 14.6 Hz), 2.28 (dddd, 2H, *J* = 7.3, 7.3, 7.3, 14.6 Hz), 5.80 (s, 1H), 7.01 (br, s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 7.6, 29.6, 47.7, 68.1, 153.5, 155.3; IR (ATR) ν 1772, 1651, 1352, 1080, 968 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 281 ([M]$^+$, 15), 252 ([M]$^+$–C_2H_5, 100); HRMS (EI): *m/z* calcd for $C_8H_{12}INO_2$ (M) 280.9913, found 280.9918.

(*E*)-4-(Iodomethylene)-3-oxa-1-azaspiro[4.5]decan-2-one (2q)



Purified by Preparative gel permeation liquid chromatography. yellow solid; dec: 178.8 °C; R_f 0.33 (hexane/EtOAc 7:3); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.22–1.84 (m, 8H), 2.51 (td, 2H, *J* = 4.1, 13.2 Hz), 5.70 (s, 1H), 7.89 (br, s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.8, 24.5, 33.5, 46.6, 63.4, 155.0, 155.9; IR (ATR) ν 1780, 1744, 1647, 1043 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 293 ([M]$^+$, 100), 166 ([M]$^+$–I, 84); HRMS (EI): *m/z* calcd for $C_8H_{12}INO_2$ (M) 292.9913, found 292.9911.

*The product **2q** was recrystallized from dichloromethane/hexane solution to give the suitable crystal for X-ray analysis.

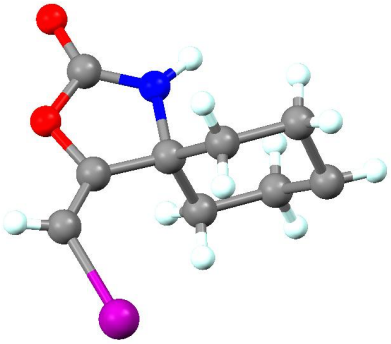
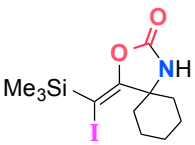


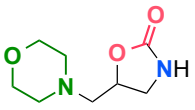
Figure 6. Molecular Structure of **2q**

(*E*)-4-(Iodo(trimethylsilyl)methylene)-3-oxa-1-azaspiro[4.5]decan-2-one (2r)



Purified by Preparative gel permeation liquid chromatography. yellow solid; dec: 213.0–214.5 °C; R_f 0.45 (hexane/EtOAc 7:3); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.28 (s, 9H), 1.26–1.83 (m, 8H), 2.82 (td, 2H, *J* = 13.2, 3.8 Hz), 5.70 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 0.53, 22.1, 22.4, 33.0, 65.2, 72.0, 154.7, 159.4; IR (ATR) *ν* 1769, 1609, 1352, 1327, 1246, 1177, 1036, 1016, 978, 840 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 365 ([M]$^+$, 100), 240 (73); HRMS (EI): *m/z* calcd for $C_{12}H_{20}INO_2Si$ (M) 365.0308, found 365.0306.

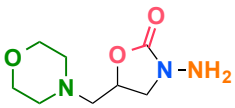
5-(Morpholinomethyl)oxazolidin-2-one (3)



Purified by NH-silica gel column chromatography (EtOAc). yellow solid; dec: 113.7 °C; R_f 0.55 ($CHCl_3$/MeOH 99:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.48–2.75 (m, 6H), 3.36 (dd, 1H, *J* = 8.1, 8.1 Hz), 3.64–3.72 (m, 5H), 4.79 (m, 1H), 6.70 (br, s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 44.3, 54.2, 61.7, 66.8, 75.0, 159.9; IR (ATR) *ν* 1740, 1234, 1112, 1084 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 186 ([M]$^+$, 4), 100 ([M]$^+$–C_4H_8NO, 100);

HRMS (EI): *m/z* calcd for $C_8H_{14}N_2O_3$ (M) 186.1004, found 180.1006.

3-Amino-5-(morpholinomethyl)oxazolidin-2-one (AMOZ)



Purified by NH-silica gel column chromatography (EtOAc). yellow solid; dec: 110.6–112.9 °C; R_f 0.43 ($CHCl_3$/MeOH 99:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.50–2.74 (m, 6H), 3.43 (dd, 1H, *J* = 8.1, 8.1 Hz), 3.70–3.79 (m, 5H), 4.00 (br, s, 2H), 4.65 (m, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 52.0, 54.2, 61.3, 66.7, 71.2, 158.9; IR (ATR) ν 1748, 1128, 1112, 964, 758 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 201 ($[M]^+$, 1), 185 ($[M]^+$–NH_2, 1), 100, ($[M]^+$–C_4H_8NO–NH_2, 100); HRMS (EI): *m/z* calcd for $C_8H_{15}N_3O_2$ (M) 201.1113, found 201.1117.

2-9. References and Notes

1. (a) Olah, G. A.; Goeppert, A.; Prakash, G. K. S. *Beyond Oil and Gas*: *The Methanol Economy*, 2nd ed. Wiley-VCH: Weinheim, Germany, 2009. (b) Bakker, D.; Watson, A. *Nature* **2001**, *410*, 765. (c) Abelson, P. H. *Science* **2000**, *289*, 1293.

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18. Together with **2a**, the formation of an intermediate having unknown structure was also observed, which was too unstable to be isolated.

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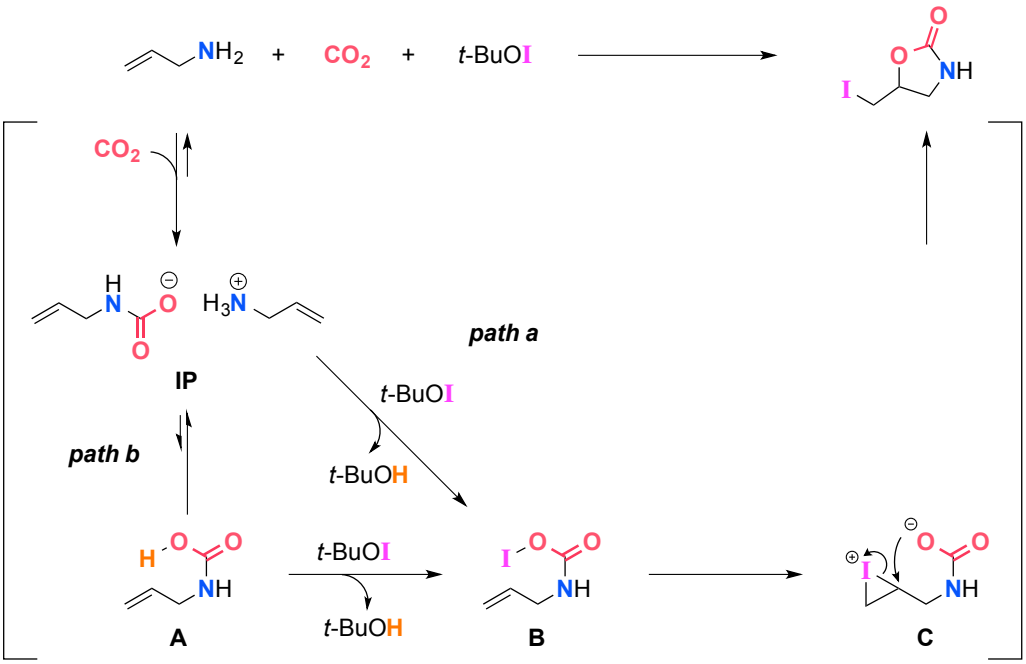
20. The exclusive formation of allylammonium allylcarbamate (**IP**) from allyl amine and CO_2 suggested the existence of possible reaction pathways leading to intermediate **B** other than the one shown in Scheme 4, although the clarification of precise mechanism awaits further study. The first feasible route is that the resulting **IP** directly undergoes *O*-iodination with *t*-BuOI to generate **B** (*path a*) and allyl amine. Since ammonium alkylcarbamates and carbamic acids are reportedly in equilibrium (*Chem. Commun.* **2002**, 1450; *Tetrahedron* **2003**, *59*, 9619), another possible route to **B** is proton-iodine exchange of carbamic acid **A** that is formed as the result of the equilibrium (*path b*).



Scheme 4. Other Plausible Reaction Mechanism

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Chapter 3

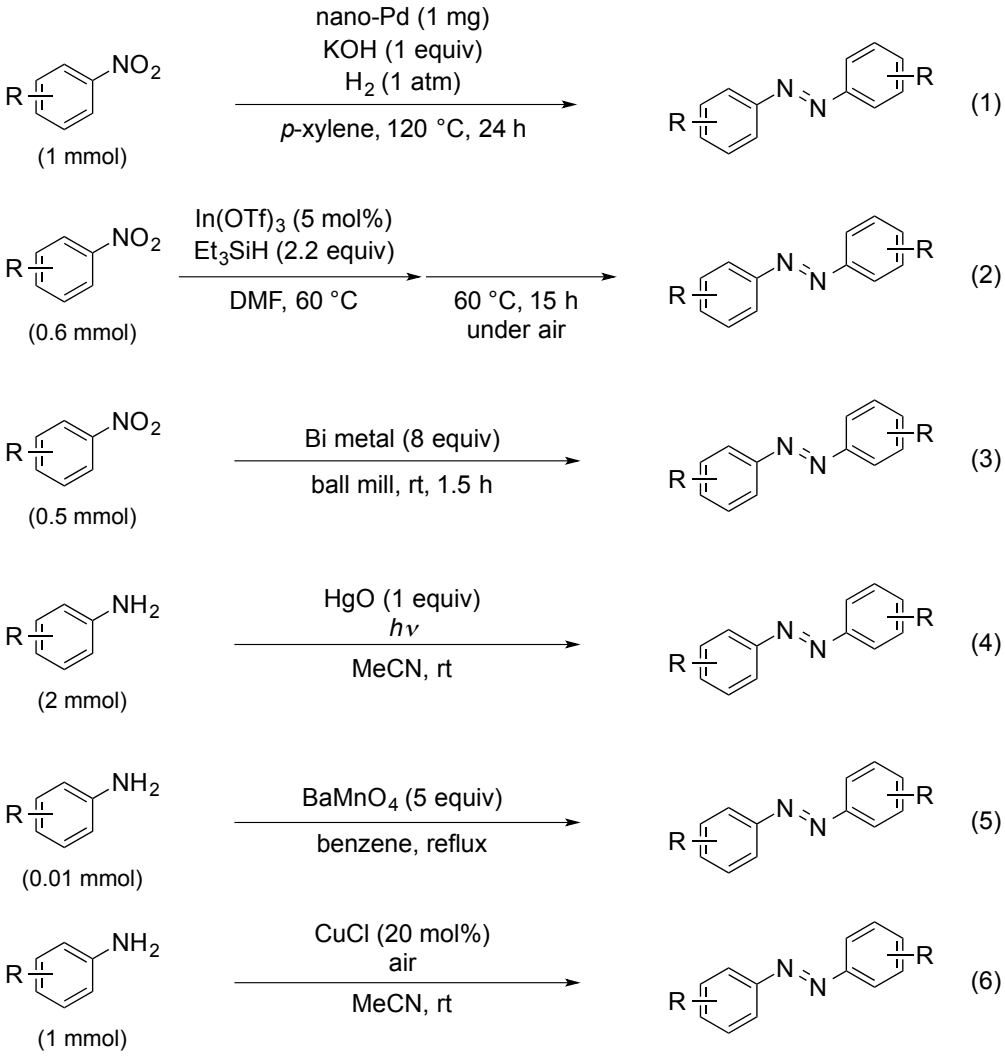
Oxidative Dimerization of (Hetero)aromatic Amines Leading to (Hetaro)aromatic Azo Compounds Utilizing *t*-BuOI

3-1. Introduction

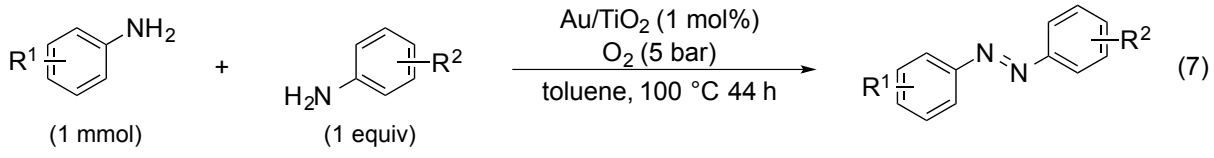
As mentioned in the general introduction, this chapter describes oxidative homo- or cross-dimerization of (hetero)aromatic amines utilizing *t*-BuOI leading to a variety of symmetric and unsymmetric (hetero)aromatic azo compounds.

For over a century, azobenzene derivatives have been utilized as organic dyes, pigments, food additives, indicators, and therapeutic agents in industry.[1] In addition to such traditional use of azo compounds, over the past few decades, there has been a rapid growth in interest in their next-generation applications as photoresponsive soft materials such as smart polymers,[2] liquid crystals,[3] photochromic ligands for optochemical genetics,[4] and photoswitches in biological systems,[5] owing to their ability of photochemical *cis*/*trans*-isomerization.[6] In terms of their preparation, a myriad of synthetic methods are available nowadays.[7] However, an appropriate choice of synthetic method would mostly depend on the structural symmetry of azobenzenes of interest (i.e., symmetric or unsymmetric types). As for the preparation of

symmetric azobenzenes, direct synthetic methods starting from readily available organic compounds involve reductive homodimerization of nitroarenes (Eqs 1–3)[8] and oxidative homodimerization of aromatic amines (Eqs 4 and 5).[9] Nonetheless, the former often confronts the difficulty in controlling product distribution of the azo-/azoxybenzene ratio, and the latter suffers from the stoichiometric use of environmentally unfriendly heavy-metal oxidants such as $BaMnO_4$, $Pb(OAc)_4$, AgO, and HgO. Although Cu-catalyzed homodimerization processes of aromatic amines using air as the co-oxidant have been developed to avoid the use of heavy-metal salts,[10] incompatibility of functional groups and low yields of desired products are still inevitable (Eq 6).



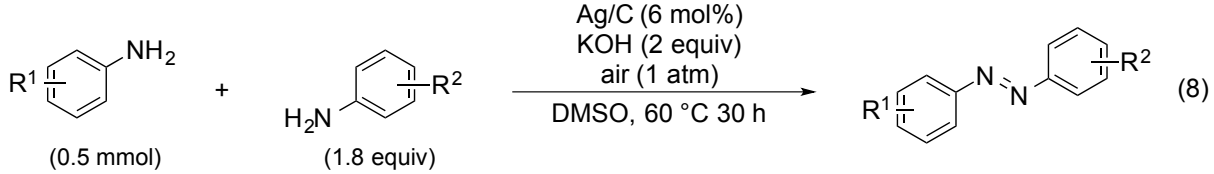
On the other hand, unsymmetric aromatic azo compounds have been exclusively synthesized by diaznium coupling[11] and the Mills reaction.[12] These methods require the preparation of explosive diazonium salts or toxic nitroso compounds as substrates from commercially available organic compounds. More specifically, the main problem of these approaches lies in the substrate scope, which is limited to the combination of electron-rich and -deficient aromatic amines, because of their intrinsic reaction mechanisms. To address these issues, recently, catalytic approaches using oxygen as an oxidant have been developed.[13] While Grirrane, Corma, and García realized the air-oxidation system by employing Au/TiO_2 nanoparticles (Eq 7),[13a,b] He and Li utilized Ag nanoparticles as a heterogeneous catalyst (Eq 8).[13c] The Jiao's group reported Cu/pyridine-catalyzed aerobic oxidative dimerization of aniline derivatives (Eq 9).[13d] Furthermore, an organocatalytic approach using hypervalent iodine(III) has also been developed by Ma and Lei (Eq 10).[14] Although these reports succeeded in synthesizing a series of unsymmetric azobenzenes, there still remains considerable room for improvement in each method: the harsh conditions employing high pressurized O_2 (5 bar) and a high temperature (100 °C) in the Au/TiO_2 system, the stoichiometric use of a strong base (KOH) in the Ag-nanoparticle system, and the use of excess amounts of the electron-deficient aromatic amines in the Cu/pyridine system.



(7)

(1 mmol) (1 equiv)

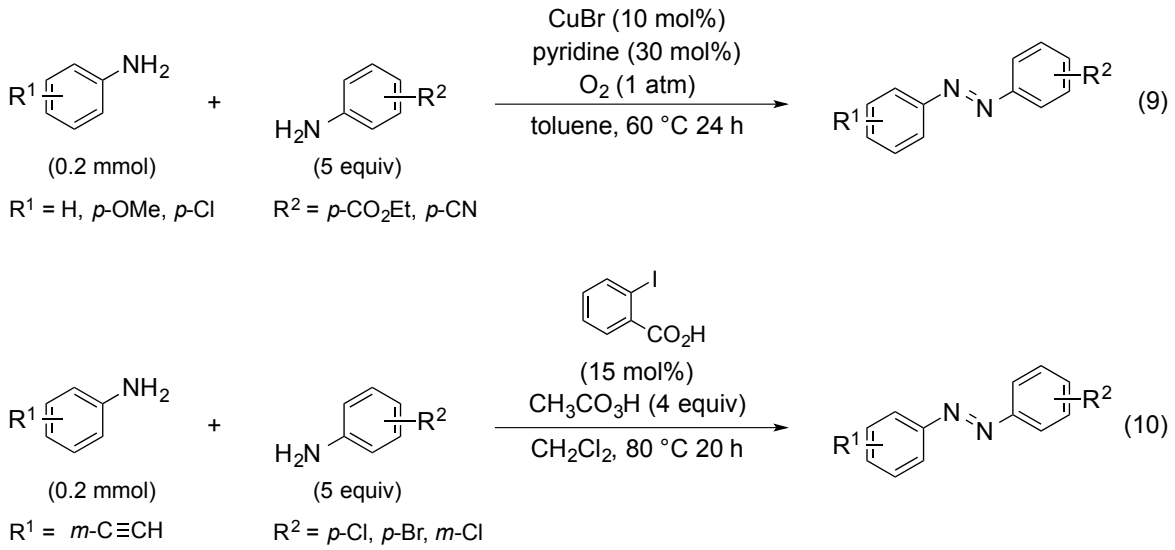
R^1 = *p*-Me, *p*-NMe_2 R^2 = *p*-C(O)Me, *p*-SO_3Na



(8)

(0.5 mmol) (1.8 equiv)

R^1 = H, *p*-OMe, *m*-Me R^2 = *p*-Cl, *p*-Br, *p*-OCF_3

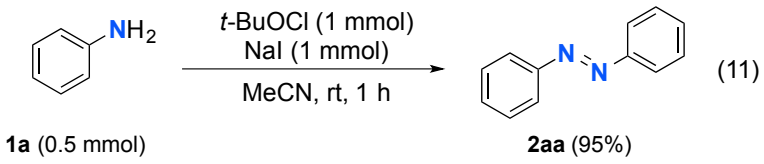


Therefore, the development of robust synthetic methods of azobenzene derivatives with high efficiency, wide diversity, and high functional compatibility is significantly desirable.

Results and Discussion

3-2. Homodimerization of Aniline in the Presence of *t*-BuOI

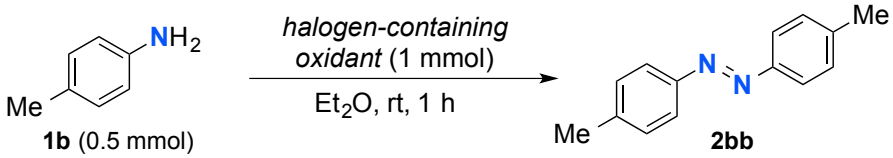
Initially, I examined an oxidative homodimerization of aniline (**1a**) as the model reaction. When **1a** (0.5 mmol) was treated with 2 equiv of *t*-BuOI (1 mmol) in acetonitrile at room temperature for 1 h, oxidative homodimerization to form a N=N double bond was found to smoothly proceed to give *trans*-azobenzene **2aa** in 95% yield (Eq. 11).

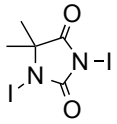
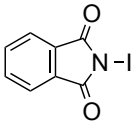
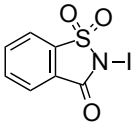
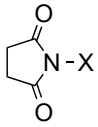


To confirm the superiority of the system, I examined other electrophilic halogen-containing oxidants in the homodimerization of *p*-toluidine (**1b**) as a substrate (Table 1). Whereas the use of *t*-BuOI afforded azo product **2bb** in 97% yield (entry 1), *t*-BuOCl was found to be ineffective for the reaction (entry 2). Iodinating reagents composed of diatomic

interhalogen molecules (I_2, ICl, IBr) and the combination of I_2/Et_3N failed to give the product (entries 3–6). Widely used halogenating reagents, *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS), and *N*-iodosuccimide (NIS) also did not give satisfactory yields of **2bb** in any of the cases (entries 7–9). The employment of *N*-iodopyrrolidin-2-one, 1,3-diiodo-5,5-dimethylhydantoin (DIH), *N*-iodophthalimide (NIPI), and *N*-iodosaccharin (NISac) resulted in rather low yields of **2bb** (entries 10–13). The use of a highly electrophilic iodonium reagent, IPy_2BF_4 (BPIT), failed to provide the desired product (entry 14). The order of the addition of reagents also turned out to be a quite important factor: when *t*-BuOCl was first added prior to NaI, no dimerized product was produced and only monochlorinated amine was detected. This result suggests that in situ generation of *t*-BuOI is much faster than the chlorination of the amine by *t*-BuOCl.

Table 1. Effect of Halogen-Containing Oxidants[a]



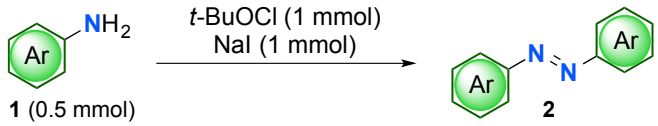
entry	oxidant	yield (%)[b]	entry	oxidant		yield (%)[b]
1	*t*-BuOI	97[c]	10			5
2	*t*-BuOCl	4				
3	I_2	0	11[d]		DIH	15
4	I_2 + Et_3N	0				
5	ICl	0	12		NIPI	8
6	IBr	0				
7	X = Cl	4	13		NISac	trace
8	 Br	0				
9	I	10	14		BPIT	0

[a] Reaction conditions: **1b** (0.5 mmol) and halogen-containing oxidant (1 mmol) in Et_2O (3 mL) at room temperature for 1 h. [b] ^1H NMR yields. [c] Isolated yield. [d] 0.5 mmol of DIH was used.

3-3. Substrate Scope of Homodimerization of (Hetero)aromatic Amines

Having identified a suitable reagent, the substrate scope of the oxidative homodimerization was investigated (Table 2). Anilines bearing an electron-donating substituent such as methyl-, methoxy-, and *N*,*N*-dimethylamino groups at the *para* position were readily transformed into the corresponding aromatic azo compounds **2bb**–**2dd** in moderate to high yields (entries 2–4). Halo-substituted anilines were applicable to the reaction conditions to give the corresponding products in high yields (entries 5–8). Although the homodimerization of electron-deficient aromatic amines required prolonged times compared to the reactions of electron-rich amines, the corresponding azo compounds were produced in excellent yields (entries 9–12). Notably, the employment of amino-azobenzene **1m** under the oxidative conditions gave homodimerized product **2 mm**, which is regarded as an aza-analogue of oligo(*p*-phenylenevinylene)s. *meta*-Substitution on the benzene ring did not significantly

Table 2. Homodimerization of Aromatic Amines[a]



1 (0.5 mmol) **2**

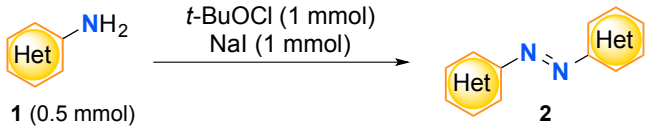
entry	Ar	conditions	yield (%)
1	Ph (**1a**)	MeCN, rt, 1 h	95 (**2aa**)
2	*p*-MeC_6H_4 (**1b**)	Et_2O, rt, 1 h	97 (**2bb**)
3	*p*-$MeOC_6H_4$ (**1c**)	MeCN, rt, 0.25 h	87 (**2cc**)
4	*p*-$Me_2NC_6H_4$ (**1d**)	DMF, 0 °C, 6 h	69 (**2dd**)
5	*p*-FC_6H_4 (**1e**)	acetone rt, 6 h	95 (**2ee**)
6	*p*-ClC_6H_4 (**1f**)	Et_2O, –20 °C, 12 h	96 (**2ff**)
7	*p*-BrC_6H_4 (**1g**)	acetone, rt, 3 h	83 (**2gg**)
8	*p*-IC_6H_4 (**1h**)	Et_2O, –20 °C, 12 h	88 (**2hh**)
9	*p*-$EtO_2CC_6H_4$ (**1i**)	Et_2O, rt, 3 h	95 (**2ii**)
10	*p*-$Me(O)CC_6H_4$ (**1j**)	Et_2O, –20 °C, 12 h	91 (**2jj**)
11	*p*-NCC_6H_4 (**1k**)	THF, rt, 12 h	89 (**2kk**)
12[b]	*p*-$O_2NC_6H_4$ (**1l**)	THF, rt, 6 h	79 (**2ll**)
13	*p*-(Ph-N=N)C_6H_4 (**1m**)	THF, –20 °C, 24 h	67 (**2mm**)
14	*m*-ClC_6H_4 (**1n**)	acetone, rt, 3 h	86 (**2nn**)
15	*m*-$O_2NC_6H_4$ (**1o**)	THF, –20 °C, 12 h	78 (**2oo**)
16	*o*-PhC_6H_4 (**1p**)	Et_2O, –20 °C, 36 h	44 (**2pp**)
17	*o*-NCC_6H_4 (**1q**)	Et_2O, rt, 24 h	73 (**2qq**)
18	3,4-$Me_2C_6H_3$ (**1r**)	Et_2O, rt, 1 h	89 (**2rr**)
19	3,5-$(F_3C)_2C_6H_3$ (**1s**)	THF, rt, 12 h	94 (**2ss**)
20	C_6F_5 (**1t**)	Et_2O, rt, 12 h	67 (**2tt**)

[a] Reaction conditions: aromatic amine (0.5 mmol), *t*-BuOCl (1 mmol) and NaI (1 mmol) in solvent (3 mL).
[b] 2 mmol of *t*-BuOCl and NaI were used.

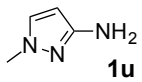
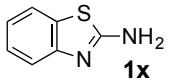
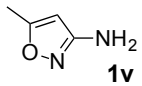
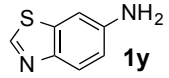
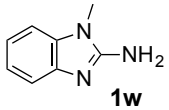
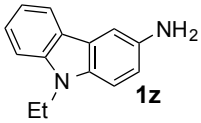
affect the yields of the products (entries 14 and 15). Although anilines having a substituent at the *ortho* position required extended reaction times, presumably because of the steric bulk, the corresponding azobenzenes were successfully obtained in moderate yields (entries 16 and 17). It should be noted that the homodimerization of multiply substituted aromatic amines gave the corresponding azo products in high yields (entries 18–20).

Motivated by the successful results of the homodimerization of aniline derivatives, I then extended substrate scope to heteroaromatic amines (Table 3). The reaction conditions were applicable to five-membered heteroaromatic amines such as pyrazine **1u** and isoxazole **1v**, which are much more electron-rich than aniline and labile toward oxidative conditions, affording the corresponding products **2uu** and **2vv** in good yields (entries 1 and 2). Benzene-fused heteroaromatic amines also successfully dimerized to give homodimers (entries 3–5). Carbazole-containing amine **1z** was also applicable to the reaction (entry 6). Heteroaromatic azo compounds can find new applications such as nonliner optical (NLO) materials,[15] photodissociable ligands (PDLs)[16] and an oxidant in the Mitsunobu reaction.[17] In respect to the limitation of the scope of heteroaromatic amines, electron-poor heteroaromatic amines such as 2-methylquinolin-5-amine and isoquinolin-5-amine did not give the homodimerized products

Table 3. Homodimerization of Heteroaromatic Amines[a]



1 (0.5 mmol) **2**

entry	**1**	conditions	yield (%)	entry	**1**	conditions	yield (%)
1	 **1u**	DME, –40 °C, 12 h then, –20 °C, 12 h	83 (**2uu**)	4	 **1x**	MeCN, rt, 48 h	72 (**2xx**)
2	 **1v**	MeCN, rt, 24 h	76 (**2vv**)	5	 **1y**	acetone, 0 °C, 48 h	62 (**2yy**)
3	 **1w**	DME, –20 °C, 24 h	76 (**2ww**)	6	 **1z**	DME, –20 °C, 3 h	70 (**2zz**)

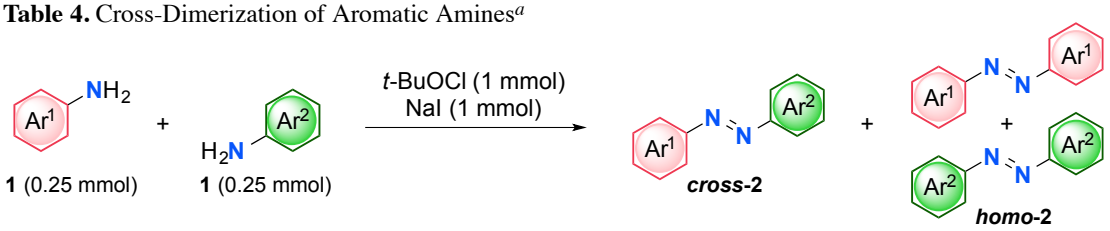
[a] Reaction conditions: heteroaromatic amine (0.5 mmol), *t*-BuOCl (1 mmol) and NaI (1 mmol) in solvent (3 mL).

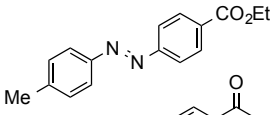
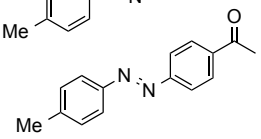
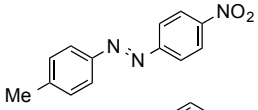
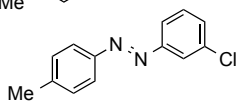
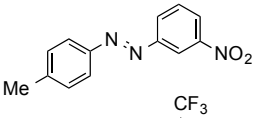
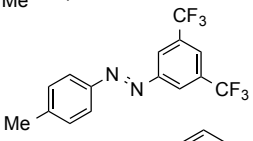
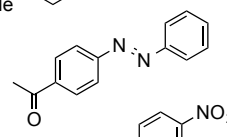
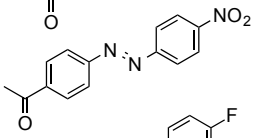
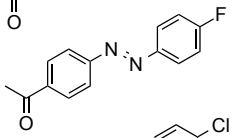
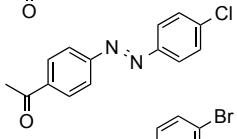
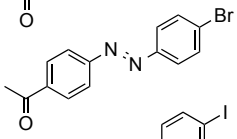
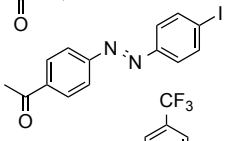
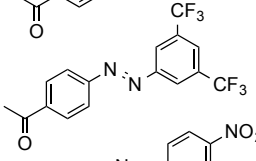
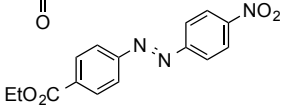
at all or resulted in rather low yields of the products (*e.g.*, in the case of 4-aminopyridine, the corresponding product was formed in less than 50% ^{1}H NMR yield and was difficult to isolate).

3-4. Substrate Scope of Cross-Dimerization of (Hetero)aromatic Amines

The successful homodimerization of aromatic amines into symmetric azo compounds prompted me to apply the reaction conditions to cross-dimerization (Table 4). Initially, I examined the cross-dimerization of *p*-toluidine (**1b**) with an equimolar amount of ethyl 4-aminobenzoate (**1i**). It was revealed that the corresponding unsymmetric azo compound **2bi** was dominantly produced in 62% yield over the homodimers **2bb** and **2ii** (32% and 30% yields, respectively) (entry 1). Considering the difficulty in achieving cross-dimerization of aromatic amines in an oxidative way, this result demonstrates the high superiority of my method.[18] The cross-dimerization of **1b** with **1j** and **1l** also proceeded to give push–pull-type aromatic azo compounds **2bj** and **2bl** in high yields in both cases (entries 2 and 3). When *p*-toluidine (**1b**) was treated with *meta*-substituted anilines **1n**, **1o**, and **1s**, the corresponding aromatic azo compounds **2bn**, **2bo**, and **2bs** were obtained in moderate to good yields (entries 4–6). Cross-dimerization reactions of an electron-deficient aniline, 4-aminoacetophenone (**1j**), with various aromatic amines were also examined (entries 7–13). Aniline (**1a**) selectively reacted with **1j**, leading to the monoacetylated azo compound **2aj** in good yield (entry 7). Anilines containing electron-withdrawing and halogen groups were also applicable to the reaction conditions to afford the corresponding unsymmetric azobenzenes in high yields (entries 8–13). Cross-dimerization of highly electron-deficient anilines **1i** and **1l** also proceeded to give unsymmetric azobenzene **2il** in a selective way, albeit requiring longer time (entry 14). Since it is difficult to synthesize unsymmetric aromatic azo compounds bearing two electron-deficient aromatic rings by conventional methods, this result clearly highlights the advantage of my method.

Table 4. Cross-Dimerization of Aromatic Amines[a]

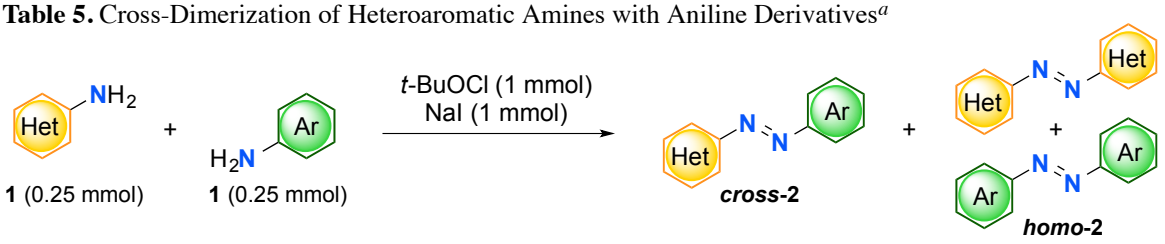


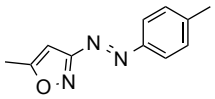
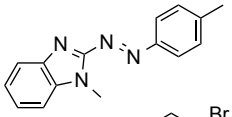
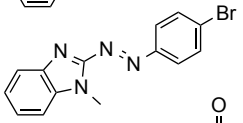
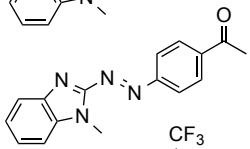
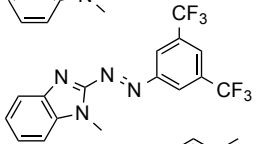
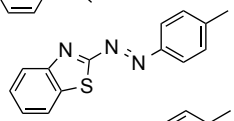
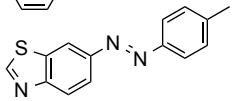
entry	1	conditions	cross-product	yield (%)	yield of **homo-2** (%)
1	**1b** + **1i**	THF, 0 °C, 6 h		62 (**2bi**)	32 (**2bb**) 30 (**2ii**)
2[b]	**1b** + **1j**	THF, –20 °C, 24 h		58 (**2bj**)	60 (**2bb**) 24 (**2jj**)
3	**1b** + **1l**	THF, 0 °C, 3 h then, rt, 1h		64 (**2bl**)	27 (**2bb**) 20 (**2ll**)
4	**1b** + **1n**	acetone, 0 °C, 3 h		52 (**2bn**)	34 (**2bb**) 21 (**2nn**)
5	**1b** + **1o**	THF, –20 °C, 24 h		60 (**2bo**)	32 (**2bb**) 16 (**2oo**)
6	**1b** + **1s**	THF, rt, 12 h		66 (**2bs**)	27 (**2bb**) 20 (**2ss**)
7	**1a** + **1j**	THF, rt, 12 h		54 (**2aj**)	40 (**2aa**) 30 (**2jj**)
8	**1j** + **1l**	MeCN, –20 °C, 24 h		72 (**2jl**)	25 (**2jj**) 22 (**2ll**)
9	**1e** + **1j**	DME, rt, 3 h		61 (**2ej**)	30 (**2ee**) 20 (**2jj**)
10	**1f** + **1j**	MeCN, 0 °C, 18 h		65 (**2fj**)	31 (**2ff**) 26 (**2jj**)
11	**1g** + **1j**	DME, –20 °C, 24 h		58 (**2gj**)	38 (**2gg**) 31 (**2jj**)
12	**1h** + **1j**	THF, rt, 12 h		53 (**2hj**)	35 (**2hh**) 41 (**2jj**)
13	**1j** + **1s**	MeCN, –20 °C, 24 h		63 (**2js**)	29 (**2jj**) 33 (**2ss**)
14[c]	**1i** + **1l**	MeCN, 0 °C, 24 h		66 (**2il**)	25 (**2ii**) 54 (**2ll**)

[a] Reaction conditions: Ar^1NH_2 (0.25 mmol), Ar^2NH_2 (0.25 mmol), *t*-BuOCl (1 mmol) and NaI (1 mmol) in solvent (3 mL). [b] **1b** (0.5 mmol), **1j** (0.25 mmol), *t*-BuOCl (1.5 mmol) and NaI (1.5 mmol). [c] **1i** (0.25 mmol), **1l** (0.5 mmol), *t*-BuOCl (1.5 mmol) and NaI (1.5 mmol).

The scope of the cross-dimerization of heteroaromatic amines with aniline derivatives is shown in Table 5. Five-membered heteroaromatic amine **1v** smoothly reacted with **1b** to give the corresponding product **2bv** in good yield (entry 1). The reaction of 2-amino-1-methyl benzimidazole (**1w**) with various anilines (**1b**, **1g**, **1j**, and **1s**) proceeded to provide unsymmetric azo products in moderate to high yields (entries 2–5). This method was also applicable to the cross-dimerization reactions of **1b** with 2-aminobenzothiazole (**1x**, entry 6) and 6-aminobezothiazole (**1y**, entry 7). In all cases, unsymmetric azobenzenes were dominantly produced over homodimers and easily separated by column chromatography.

Table 5. Cross-Dimerization of Heteroaromatic Amines with Aniline Derivatives[a]

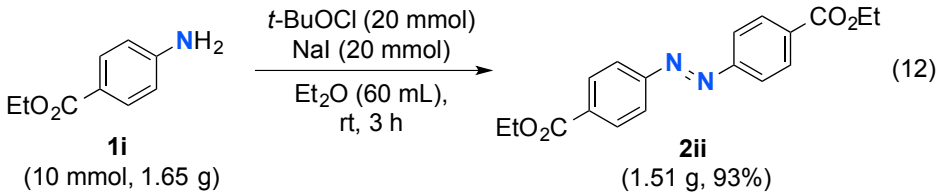


entry	**1**	conditions	cross-product	yield (%)	yield of **homo-2** (%)
1[b]	**1b** + **1v**	THF, rt, 24 h		58 (**2bv**)	50 (**2bb**) 29 (**2vv**)
2	**1b** + **1w**	DME, rt, 12 h		61 (**2bw**)	30 (**2bb**) 31 (**2ww**)
3	**1g** + **1w**	acetone, rt, 6 h		58 (**2gw**)	32 (**2gg**) 28 (**2ww**)
4	**1j** + **1w**	acetone, –20 °C, 24 h		56 (**2jw**)	32 (**2jj**) 27 (**2ww**)
5	**1s** + **1w**	acetone, rt, 12 h		50 (**2sw**)	22 (**2ss**) 31 (**2ww**)
6	**1b** + **1x**	MeCN, rt, 12 h		48 (**2bx**)	38 (**2bb**) 15 (**2xx**)
7	**1b** + **1y**	acetone, rt, 12 h		44 (**2by**)	38 (**2bb**) 30 (**2yy**)

[a] Reaction conditions: Ar^1NH_2 (0.25 mmol), Ar^2NH_2 (0.25 mmol), *t*-BuOCl (1 mmol) and NaI (1 mmol) in solvent (3 mL). [b] **1b** (0.5 mmol), **1v** (0.25 mmol), *t*-BuOCl (1.5 mmol) and NaI (1.5 mmol).

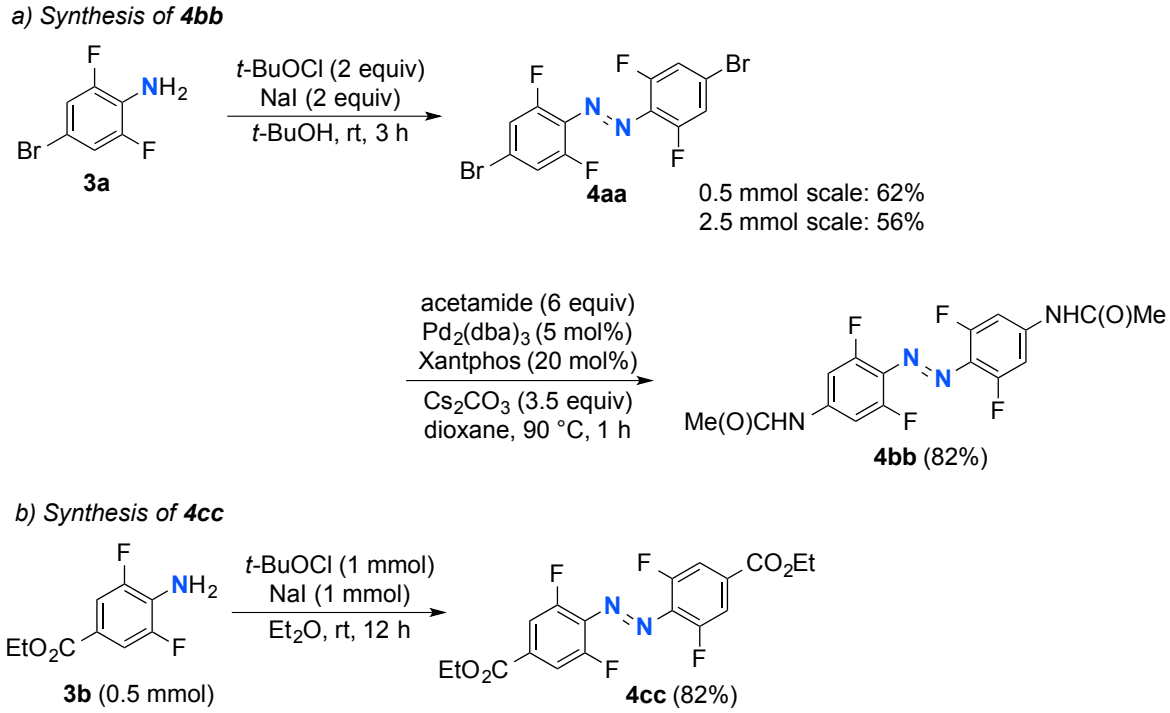
3-5. Synthetic Application of the Oxidative Dimerization

To demonstrate the practicality of the oxidative dimerization method, a gram-scale synthesis of azo product was conducted (Eq. 12). When 10 mmol of ethyl 4-aminobenzoate (**1i**) was treated with a 20 mmol of *t*-BuOI in 60 mL of Et_2O at room temperature for 3 h, the homodimerized product **2ii** was successfully synthesized in 93% yield without any significant loss of reaction efficiency, compared with the small-scale run (0.5 mmol).



(12)

Taking advantage of this straightforward and efficient synthetic method, highly improved syntheses of azobenzene-based photoswitches[19] were demonstrated (Scheme 1). Recently, Bléger, Brouwer, and Hecht have developed a new class of photoswitches **4bb** and **4cc**, which can undergo *E*/*Z* isomerization under visible light irradiation of in a nearly quantitative efficiency.[19b] When 4-bromo-2,6-difluoroaniline (**3a**) was treated with 2 equiv of *t*-BuOI in *t*-BuOH at room temperature for 3 h, tetrafluoroazobenzene **4aa** was obtained in 62% yield (Scheme 1a). Additionally, this reaction was applicable to a 5-fold scale operation, producing **4aa** in 56% yield. Two bromo functionalities of **4aa** were then efficiently substituted with two acetamide groups through Pd-catalyzed amidation,[19b] leading to azobenzene **4bb**. Homodimerization of **3b** also smoothly proceeded to give **4cc** in a high yield (Scheme 1b). According to the literature,[19b] the conventional synthetic method for **4aa** and **4cc** required excess amounts of heavy metal oxidants ($KMnO_4$/$FeSO_4 \cdot 7H_2O$), and **4aa** and **4cc** were produced in rather low yields (22% and 23% yield, respectively). Therefore, our oxidative method allows for much more efficient access to these useful functional molecules.



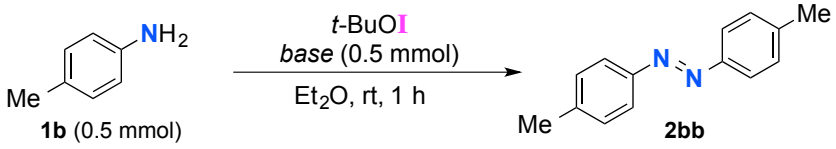
Scheme 1. Efficient Synthesis of Photoswitches **4bb** and **4cc**

3-6. Mechanistic Studies

For deeper understanding of the reaction mechanism, several experiments were conducted. The pH of the aqueous layer extracted from the reaction mixture of homodimerization of *p*-toluidine (**1b**) indicated 4.75, suggesting that hydrogen iodide (HI) was liberated during the reaction. Hydrogen iodide could be trapped by *t*-BuOI to generate *t*-BuOH and I_2. If the generated acid (HI) is efficiently trapped by an adventitious base, the stoichiometry of *t*-BuOI should be reduced by half. To verify the assumption, the addition of bases was examined, with the amount of *t*-BuOI being reduced by half (Table 6). A blank experiment resulted in rather low yield of product **2bb** (entry 2). The addition of 2,6-lutidine did not significantly affect the efficiency of the reaction (entry 3). In contrast, the employment of stronger bases such as *t*-BuOK (entry 4) and hexamethyldisilazane (entry 5) resulted in much higher product yields,

albeit much lower than with the standard conditions (entry 1). These results suggest that *t*-BuOI serves as the most appropriate trapping agent against HI in the actual system.

Table 6. Effect of Base on the Homodimerization[a]



entry	*t*-BuOI (mmol)	base	yield (%)[b]
1	1	–	97[c]
2	0.5	–	16
3	0.5	2.6-lutidine	18
4	0.5	*t*-BuOK	50
5	0.5	$(Me_3Si)_2NH$[d]	53

[a] Reaction conditions: **1b** (0.5 mmol) *t*-BuOCl (0.5–1 mmol), NaI (0.5–1 mmol) and base (0.5 mmol) in Et_2O (3 mL) at room temperature for 1 h. [b] ^1H NMR yields. [c] Isolated yield. [d] 0.25 mmol of hexamethyldisilazane was used.

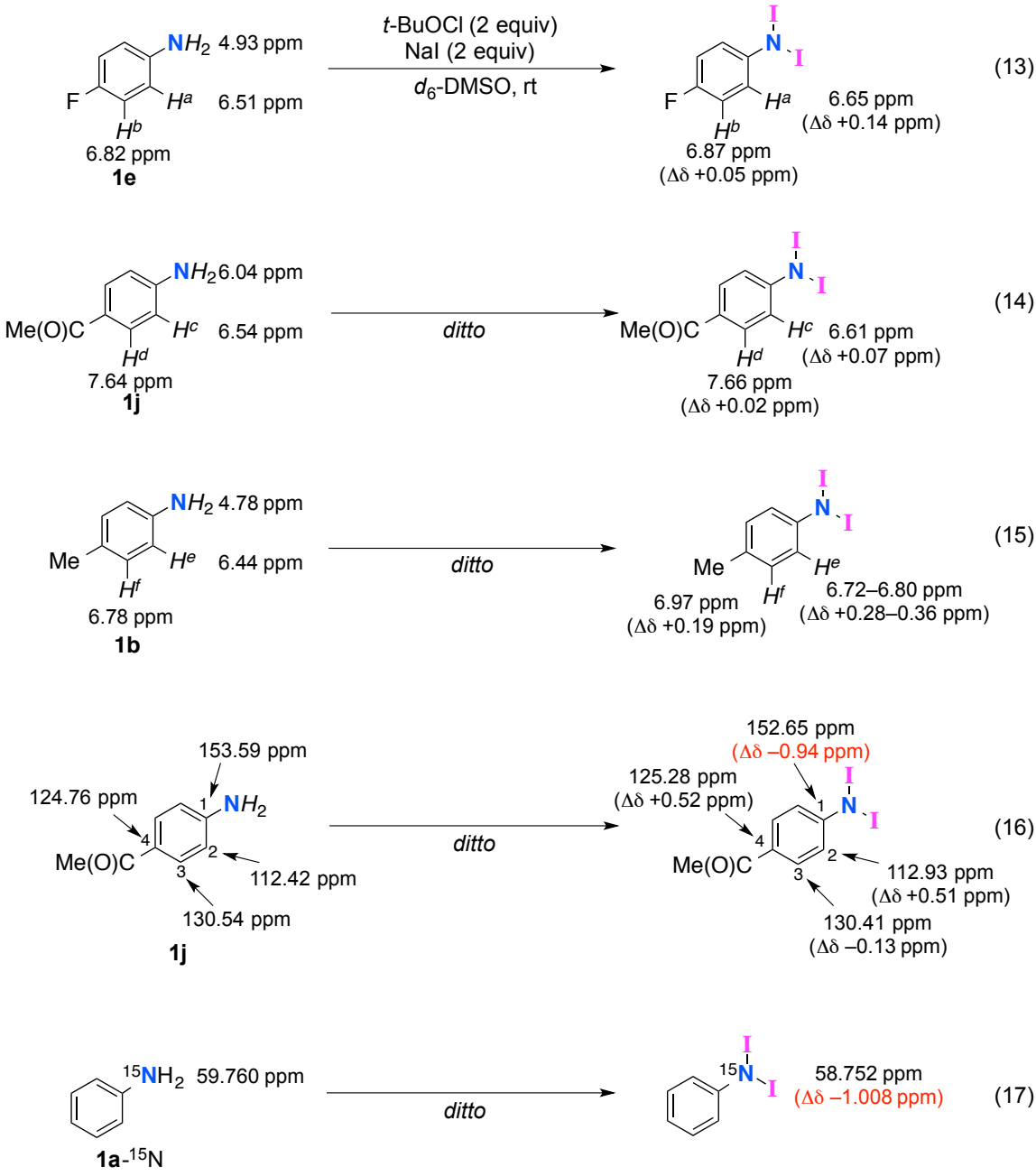
Table 7 shows the results of the homodimerization of **1b** conducted under radical-inhibiting conditions. Clearly, radical scavengers (TEMPO and Garvinoxyl, entries 2 and 3), oxygen (entry 4), and light shielding (entry 5) did not affect the product yields, suggesting that it is not likely to involve the radical species in the dimerization reaction.

Table 7. Homodimerization under Radical-Inhibiting Conditions[a]

entry	additional conditions	yield (%)[b]
1	–	97[c]
2	addition of TEMPO	94[c]
3	addition of Galvinoxyl	88[c]
4	under O_2 atmosohere	89
5	in the dark	92

[a] Reaction conditions: **1b** (0.5 mmol) *t*-BuOCl (1 mmol), NaI (1 mmol) and additive (1 mmol) in Et_2O (3 mL) at room temperature for 1 h. [b] ^1H NMR yields. [c] Isolated yield.

On the basis of our preliminary assumption, we pursued the possibility of the involvement of $ArNI_2$ as the key intermediate. The results of NMR monitoring of aromatic amines under the effect of *t*-BuOI are summarized in Scheme 2, and representative NMR spectra of the experiments are also provided in Figures 1–6. When 2 equiv of *t*-BuOI were added to the d_6-DMSO solution of **1e**, the signal corresponding to the two N–H hydrogens (δ = 4.93 ppm) disappeared, and aromatic hydrogens (δ = 6.51 and 6.82 ppm) shifted to the lower field (δ = 6.65 and 6.87 ppm, respectively) (Eq. 13 in Scheme 2, Figure 1). Similar phenomena were observed in the cases of **1j** and **1b** (Eqs. 14 and 15 in Scheme 2, Figures 2 and 3). These results suggested that the double proton exchange process is very rapid. Furthermore, ^{13}C and ^{15}N NMR analyses of the chemical species generated as the result of the proton exchange were also conducted (Eqs. 16 and 17 in Scheme 2, Figures 4 and 5). Notably, upon treating separately **1j** and **1a** labeled with ^{15}N (**1a**-^{15}N) with *t*-BuOI, the chemical shifts of the C1 of **1j** and the N of **1a**-^{15}N were moved to the upper regime by 0.94 and 1.00 ppm, respectively (Figures 4 and 5), which implies the presence of some sort of "heavy atoms" on the N atom.[20] This was also partly supported by the observation of a singlet peak of **1a**-^{15}N under the nondecoupled conditions (Figure 6).



Scheme 2. Summary of NMR Monitoring of H/I Exchange of Aromatic Amines

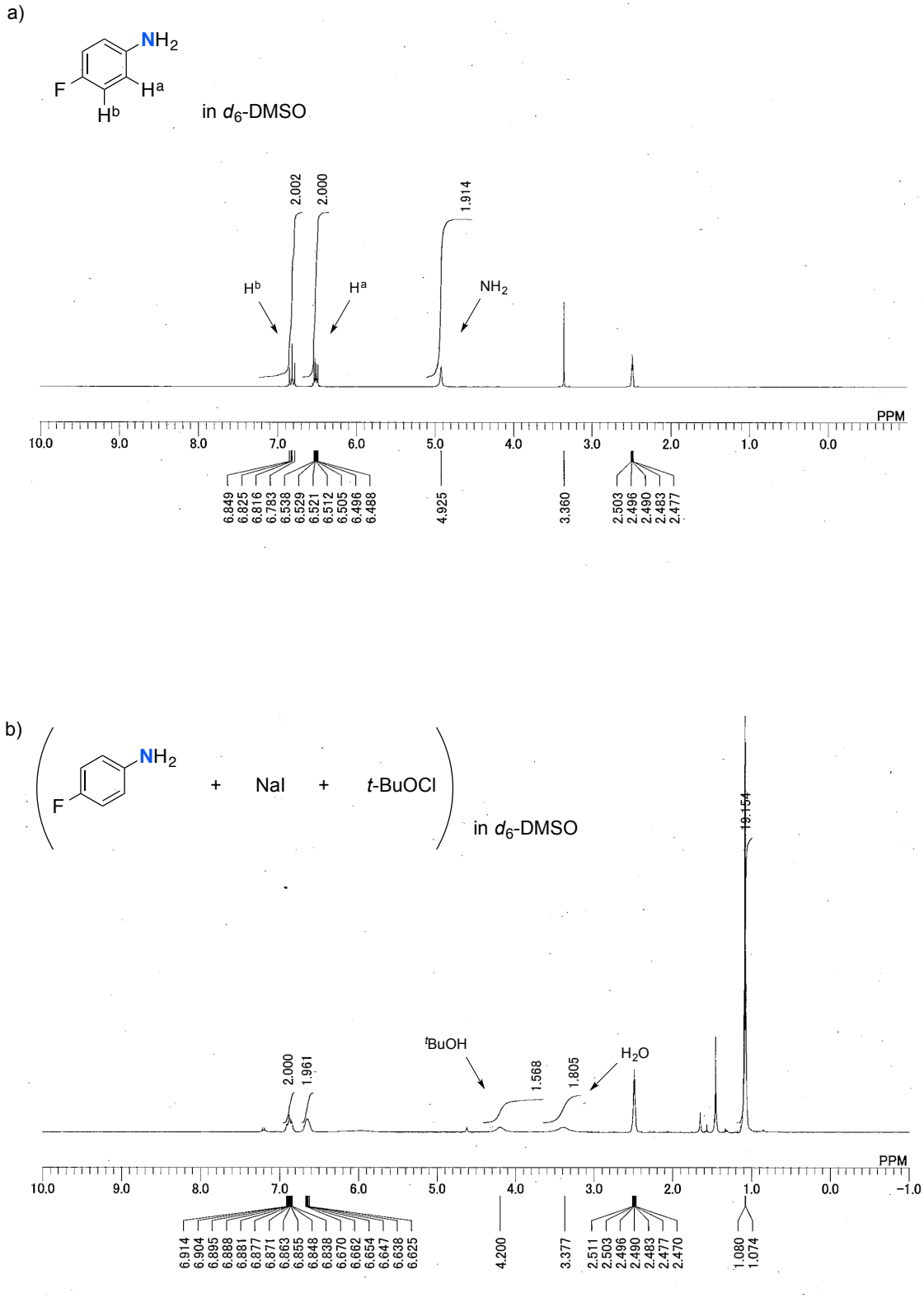


Figure 1. ^{1}H NMR spectra (270 MHz) of a) the mixture of *p*-fluoroaniline (0.05 mmol, 5.5 mg) and NaI (0.1 mmol, 15.0 mg) in d_6-DMSO at room temperature and b) the mixture after treated with *t*-BuOCl (0.1 mmol, 10.9 mg).

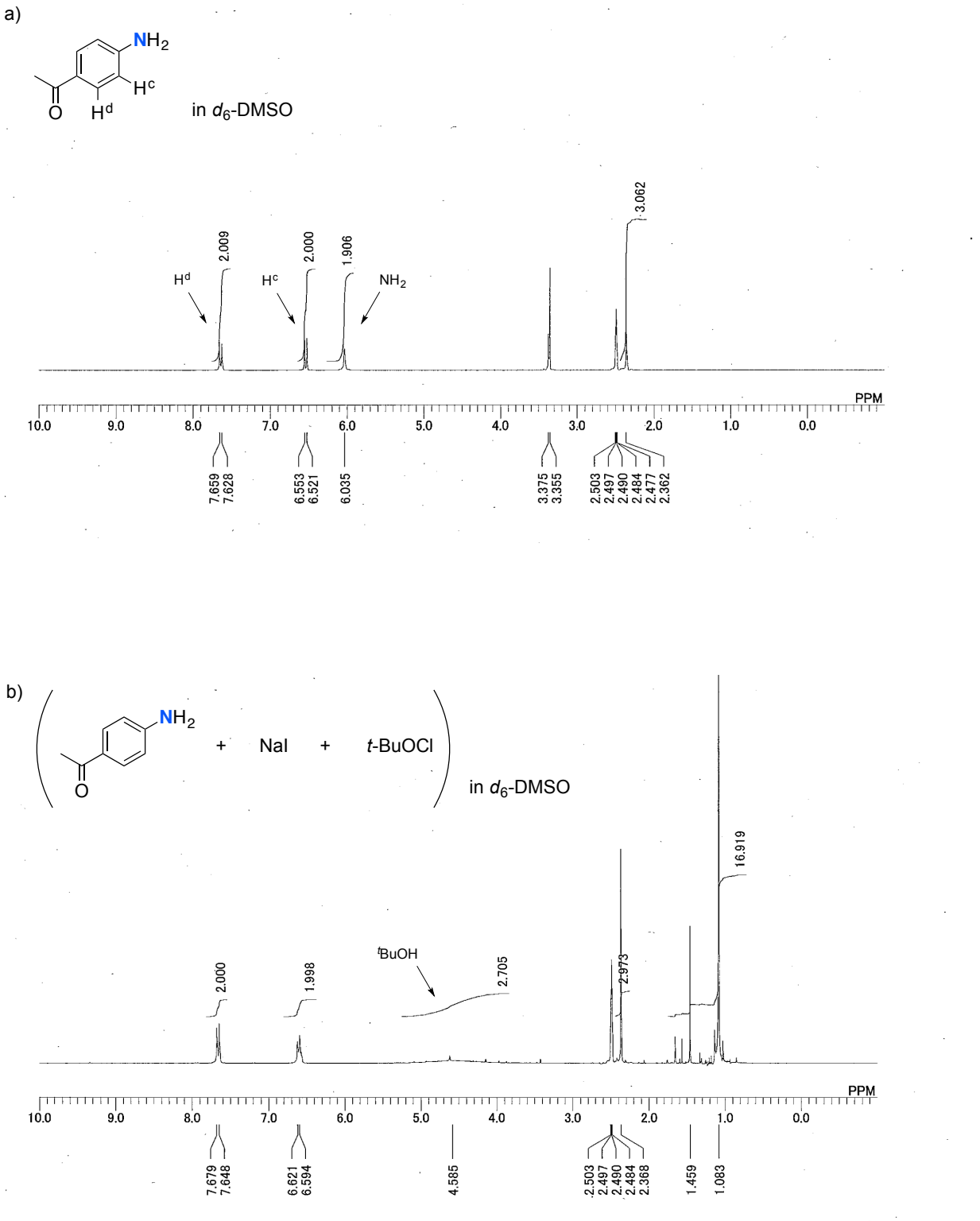


Figure 2. ^{1}H NMR spectra (270 MHz) of a) the mixture of *p*-aminoacetophenone (0.05 mmol, 6.4 mg) and NaI (0.1 mmol, 15.0 mg) in d_6-DMSO at room temperature and b) the mixture after treated with *t*-BuOCl (0.1 mmol, 10.9 mg).

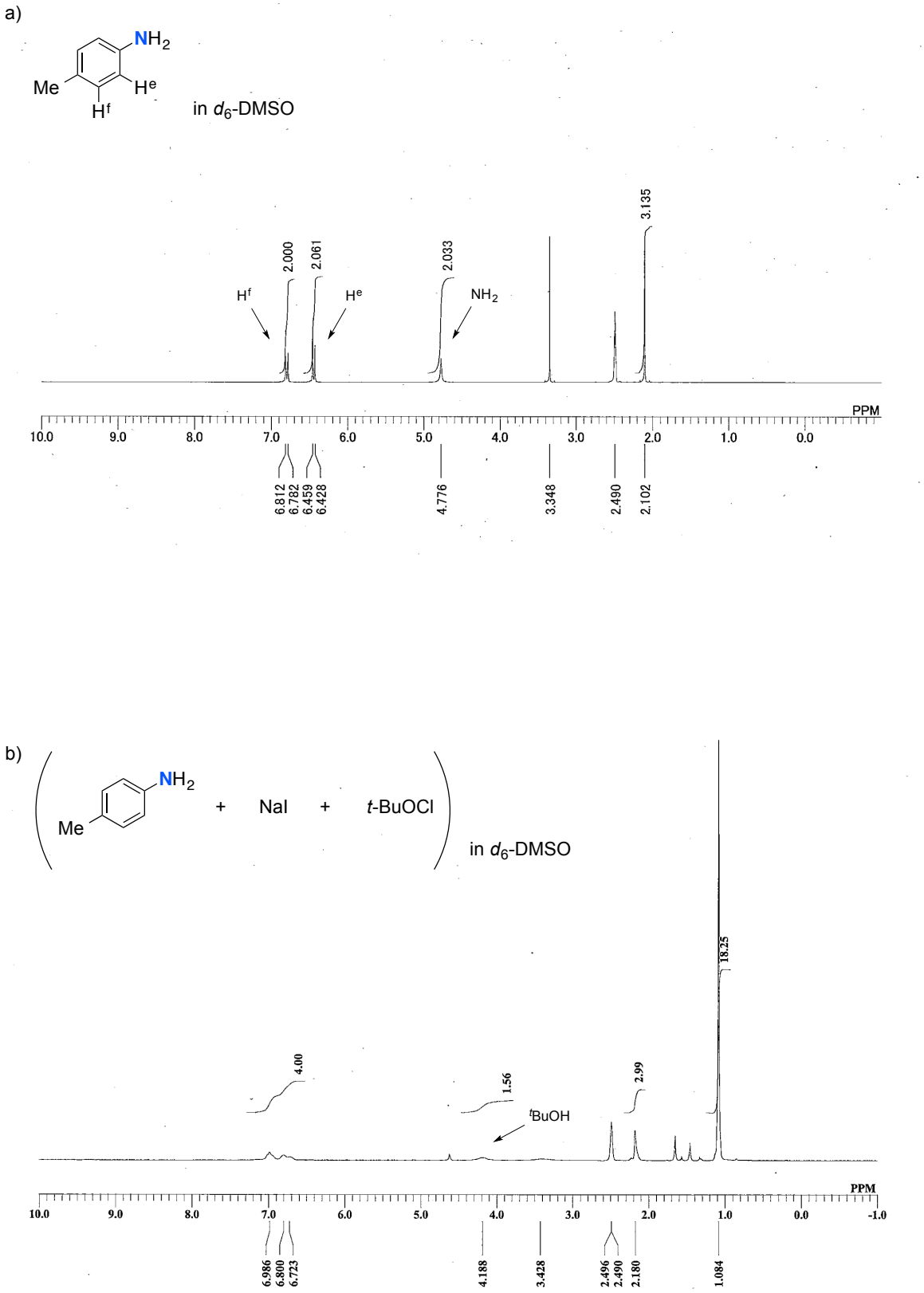


Figure 3. ^{1}H NMR spectra (270 MHz) of a) the mixture of *p*-toluidine (0.05 mmol, 5.4 mg) and NaI (0.1 mmol, 15.0 mg) in d_6-DMSO at room temperature and b) the mixture after treated with *t*-BuOCl (0.1 mmol, 10.9 mg).

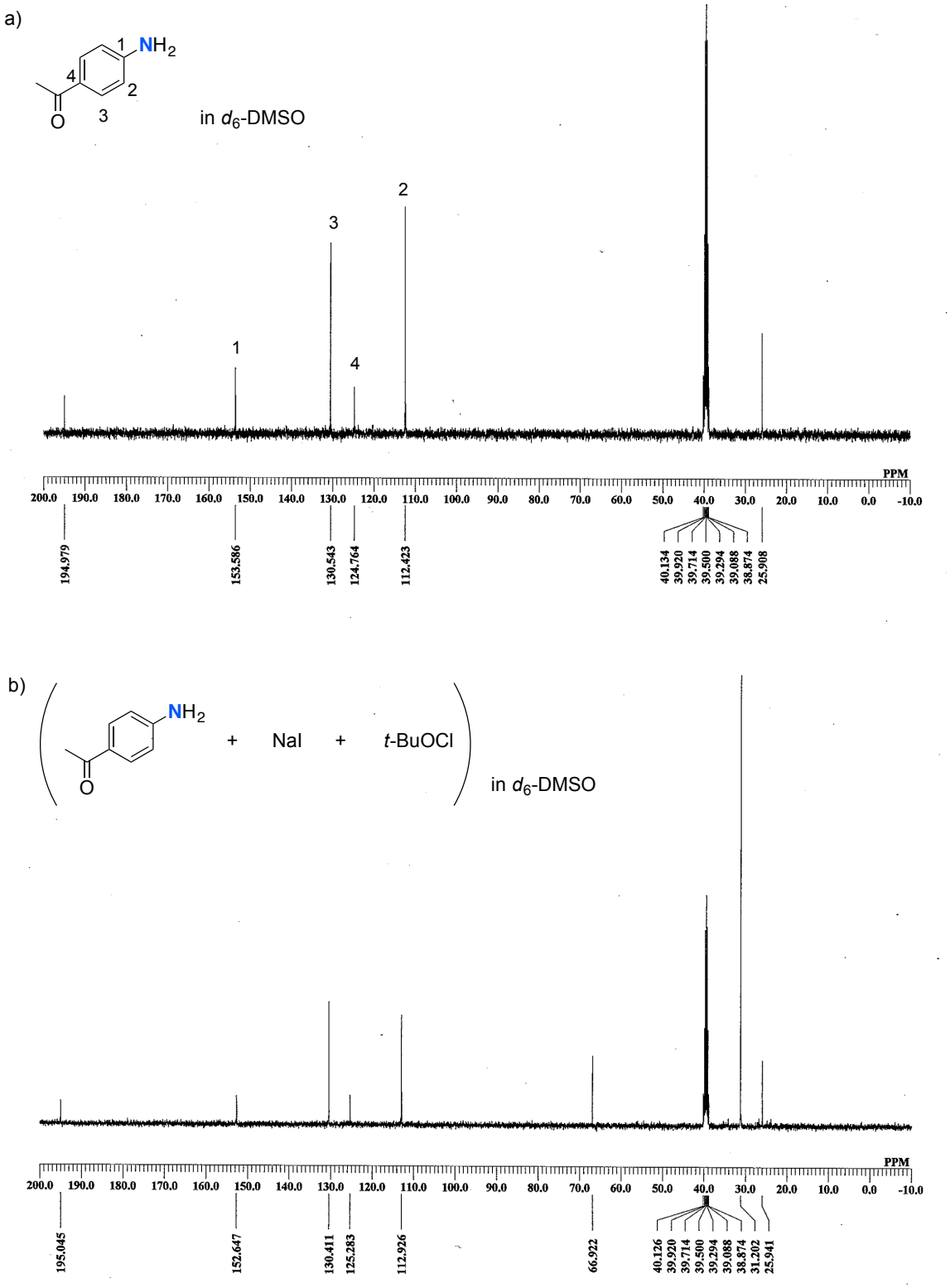


Figure 4. ^{13}C NMR spectra (100 MHz) of a) the mixture of *p*-aminoacetophenone (0.1 mmol, 12.8 mg) and NaI (0.2 mmol, 30.0 mg) in d_6-DMSO at room temperature and b) the mixture after treated with *t*-BuOCl (0.2 mmol, 21.8 mg).

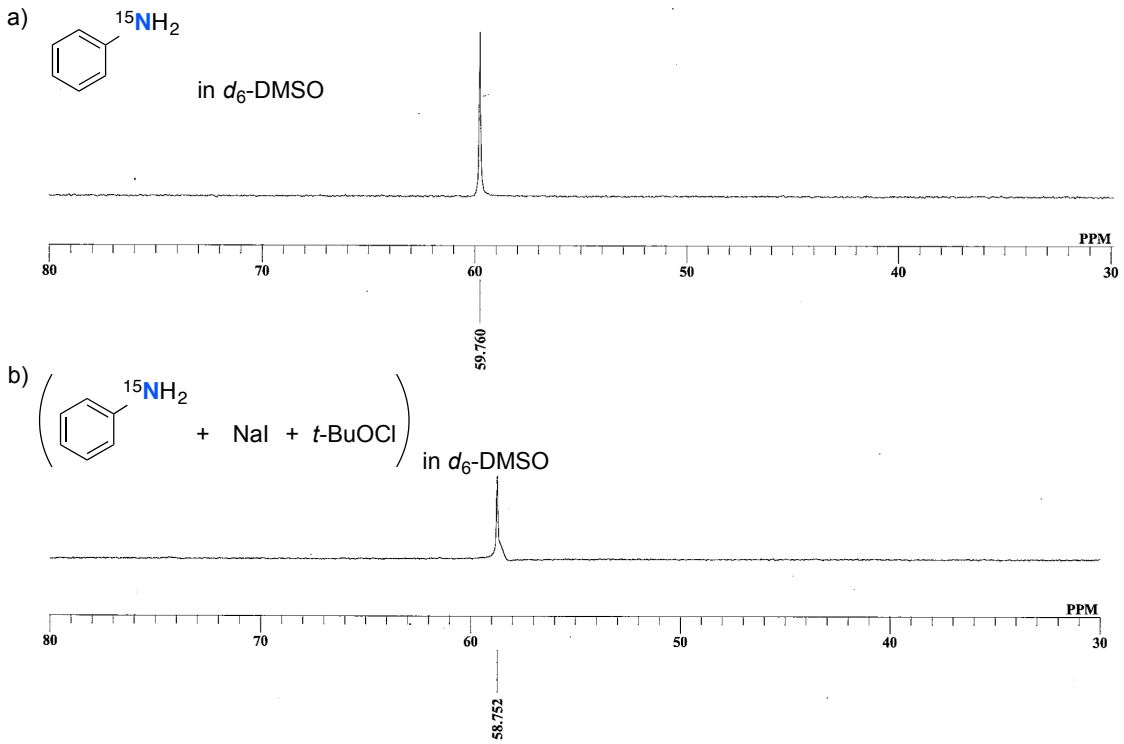


Figure 5. ^{15}N NMR spectra (40 MHz) of a) the mixture of aniline-^{15}N (0.1 mmol, 9.4 mg) and NaI (0.2 mmol, 30.0 mg) in d_6-DMSO at room temperature and b) the mixture after treated with *t*-BuOCl (0.2 mmol, 21.8 mg).

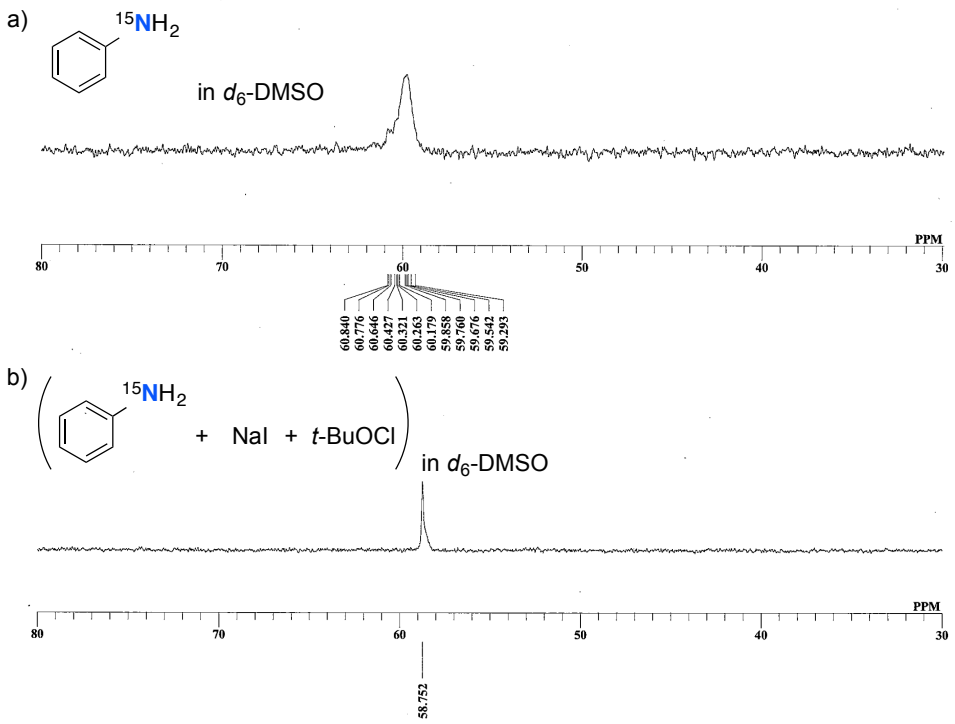


Figure 6. Non-decoupled ^{15}N NMR spectra (40 MHz) of a) the mixture of aniline-^{15}N (0.1 mmol, 9.4 mg) and NaI (0.2 mmol, 30.0 mg) in d_6-DMSO at room temperature and b) the mixture after treated with *t*-BuOCl (0.2 mmol, 21.8 mg).

To further prove the generation of *N*,*N*-diiodoaniline,[21] ESI-MS analysis of the reaction system was conducted using **3a** as a reactant (Figure 7). Although the molecular ion peak of *N*,*N*-diiodoaniline was not detected, the mass fragment of $C_6H_3BrF_2NI$, which corresponds to a radical cation of *N*-monoiodinated **3a**, was detected. This radical cation species could generate through the homolytic cleavage of the N–I bond of the corresponding ammonium form of *N*,*N*-diiodoaniline ($ArNI_2H^+$),[22,23] probably due to the rather small dissociation energy of N–I bond (~130 kJ/mol).[24] Taken together, *N*,*N*-diiodoanilines most likely to generate through an efficient H/I exchange process.

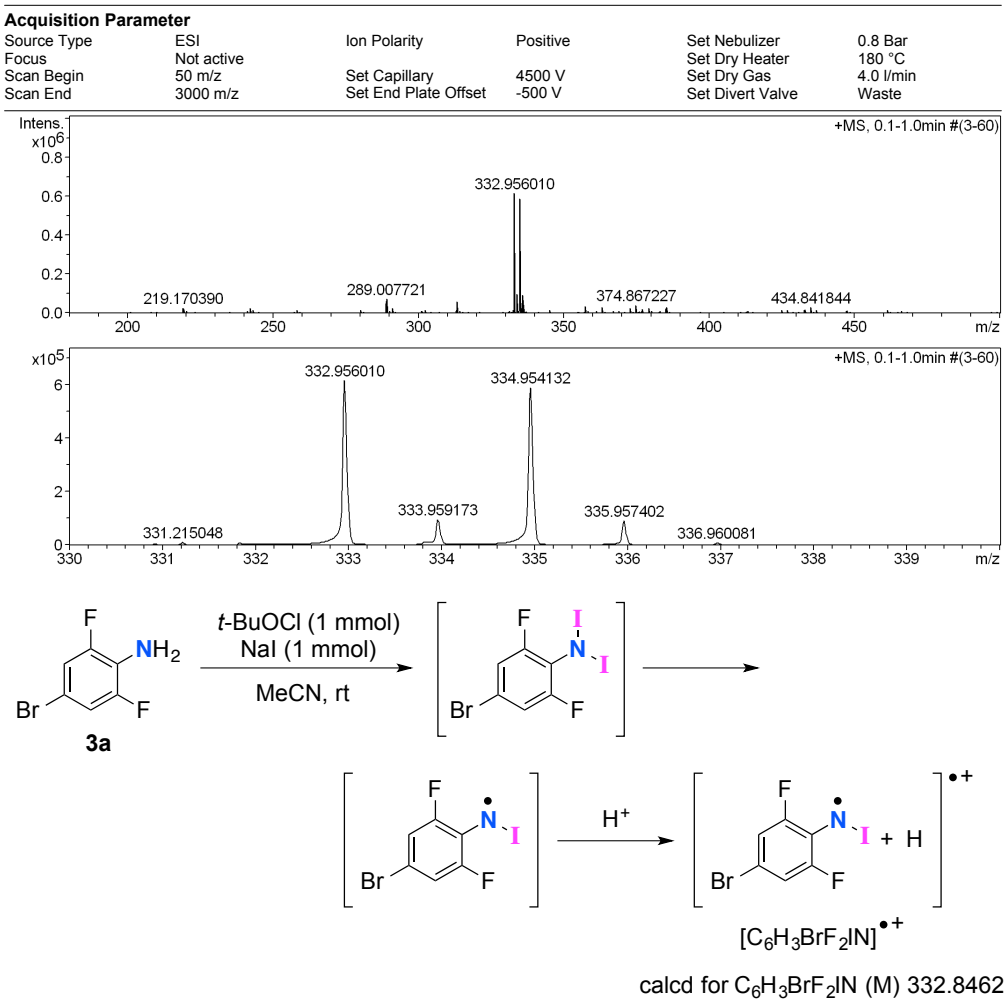
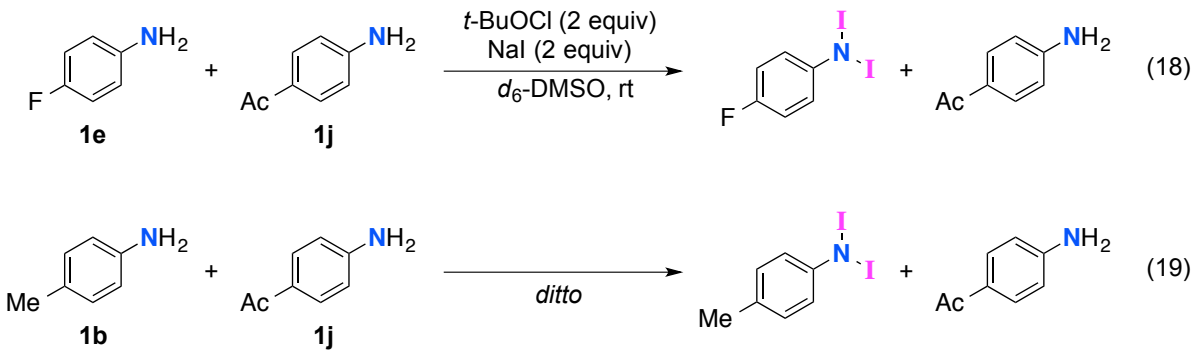


Figure 7. ESI-MS spectra of the reaction of the mixture of **3a** (0.5 mmol, 104.0 mg) and NaI (1.0 mmol, 150.0 mg) in MeCN (3 mL) with *t*-BuOCl (1.0 mmol, 108.6 mg).

To further gain insights into the H/I exchange process, an equimolar mixture of **1e** and **1j** was treated with *t*-BuOI (2 equiv). As the result, ^{1}H NMR spectra indicated the exclusive generation of *p*-fluoro-*N*,*N*-diiodoaniline from **1e** with keeping **1j** intact (Eq. 18 in Scheme 3 and Figure 8). Likewise, the similar experiment using **1b** and **1j** also suggested the exclusive generation of *N*,*N*-diiodoaniline derived from **1b**, while **1j** remained unreacted (Eq. 19 in Scheme 3 and Figure 9). Taking into account the Hammett constants (σ_p) of F, Ac, and Me being 0.06, 0.50, and –0.17,[25] respectively, the H/I exchange proceeded more predominantly with the electron-richer aniline than with the electron-poorer aniline, at least on the NMR time scale.



Scheme 3. Competitive Study of H/I Exchange

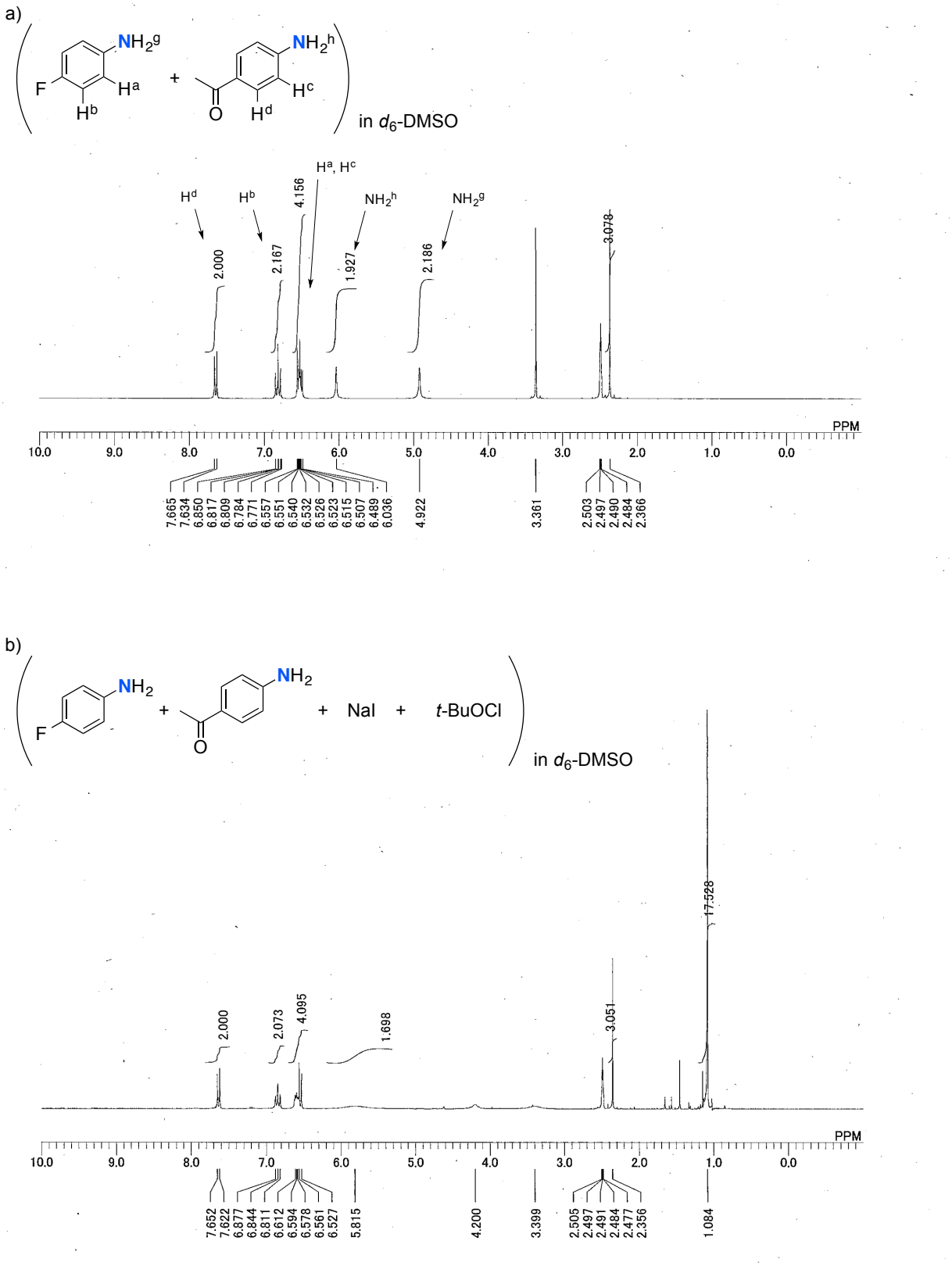


Figure 8. ^{1}H NMR spectra (270 MHz) of a) the mixture of *p*-fluoroaniline (0.05 mmol, 5.5 mg), *p*-aminoacetophenone (0.05 mmol, 6.4 mg) and NaI (0.1 mmol, 15.0 mg) in d_6-DMSO at room temperature and b) the mixture after treated with *t*-BuOCl (0.1 mmol, 10.9 mg).

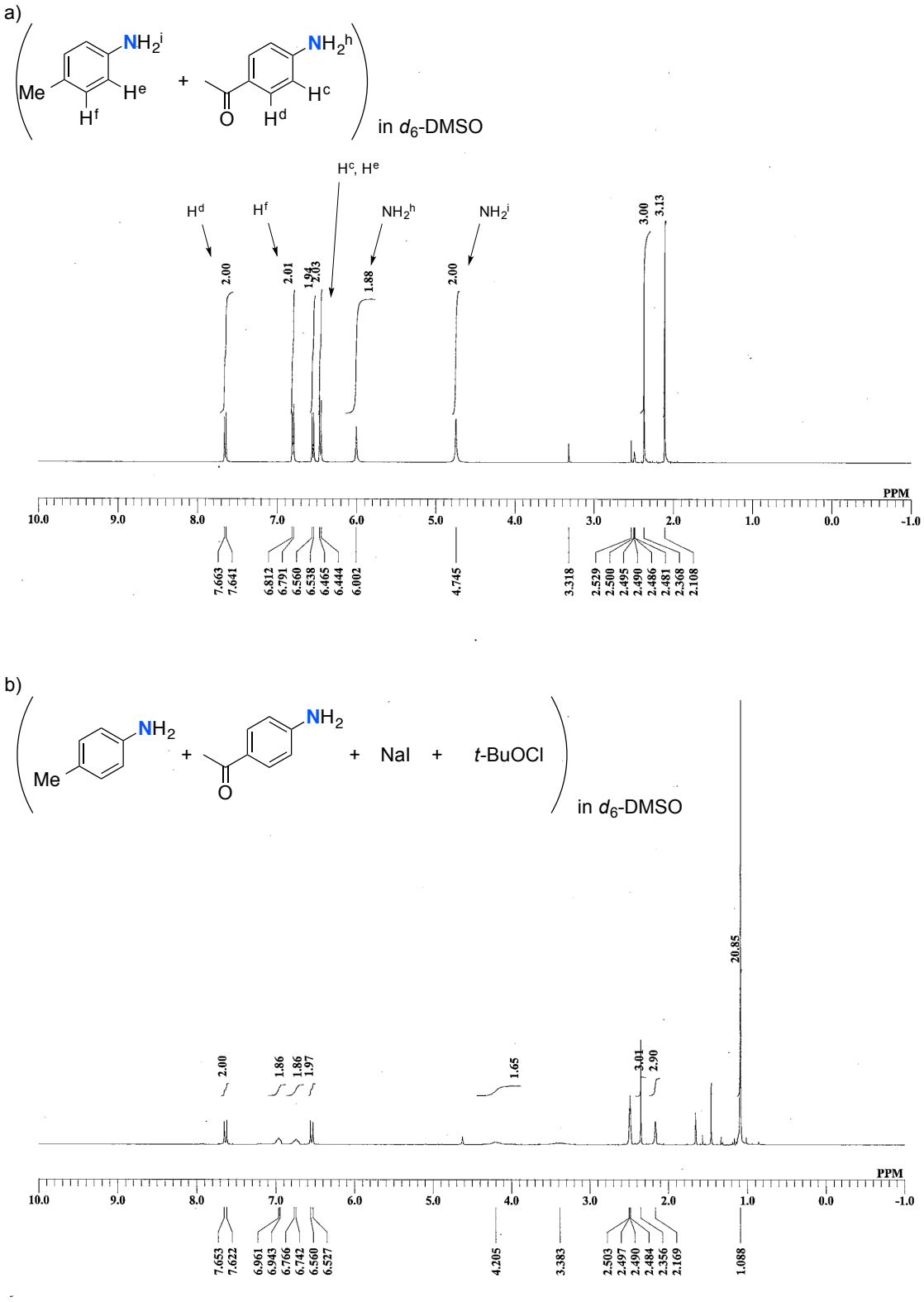
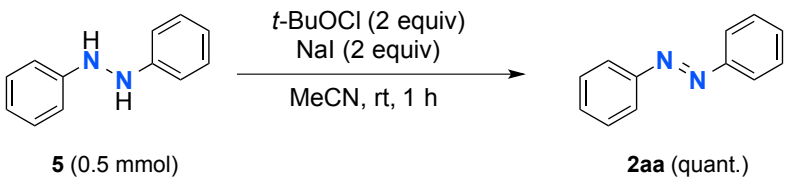
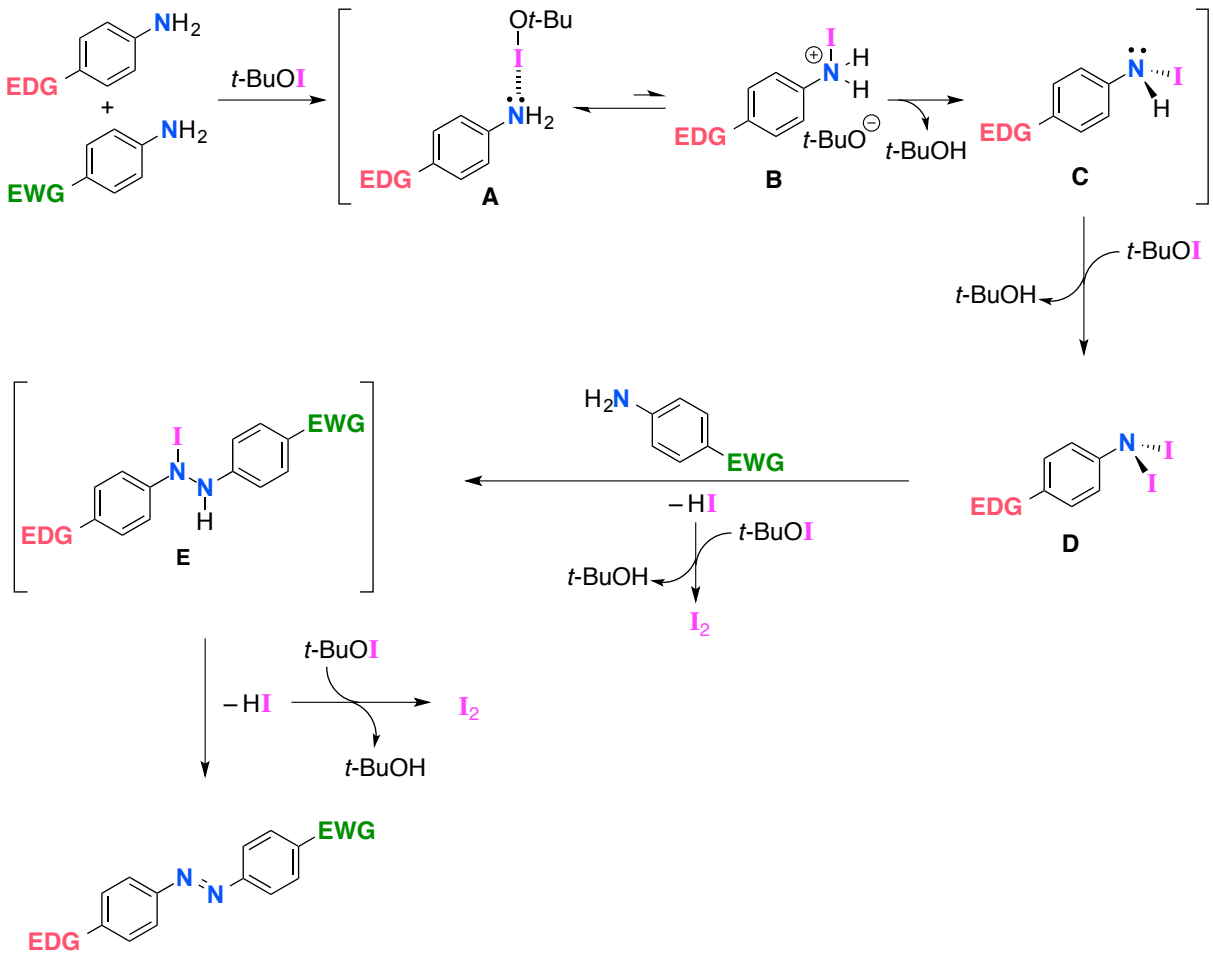


Figure 9. ^{1}H NMR spectra (a: 400 MHz, b: 270 MHz) of a) the mixture of *p*-toluidine (0.05 mmol, 5.4 mg), *p*-aminoacetophenone (0.05 mmol, 6.4 mg) and NaI (0.1 mmol, 15.0 mg) in d_6-DMSO at room temperature and b) the mixture after treated with *t*-BuOCl (0.1 mmol, 10.9 mg).

Based on these experimental results, a plausible reaction pathway is illustrated in Scheme 4. On the basis of the fact that the electron-richer aniline was preferentially diiodinated, I propose H/I exchange mechanism through "halogen bonding"[26] formation between the nitrogen and iodine atoms (**A**) to generate intermediate **B**. Based on this concept, the exchange process of a strong Lewis base (an electron-richer amine) would be more favorable than that with a weak base (an electron-poorer amine), which is in good agreement with the results of NMR experiments. The resulting ammonium salt **B** would be deprotonated by *t*-BuO$^-$ to produce monoiodinated aniline **C**. The following iodination of **C** would afford *N*,*N*- diiodoaniline **D** in a similar manner. It should be noted that the second iodination of **C** proceed more preferentially than the monoiodination of the electron-poorer aniline. This is possibly because the nucleophilicity of monoiodinated intermediate **C** is higher than that of the unreacted electron-deficient aniline as the result of slight pyramidalization of the N-center partly facilitated by steric repulsion.[27] The diiodinated aniline **D** would then serve as an electrophile to form the N–N single bond to afford **E** that accompanies liberation of HI. Generation of nitrene from diiodinated aniline **D** might be possible, although no ring expansion products (*cf*. azepines) was detected in this dimerization reaction. Lastly, elimination of another equivalent of HI would give aromatic azo product, which was supported by the experiment illustrated in Eq 20. Liberated HI would be trapped by 2 equiv of *t*-BuOI, thus resulting in I_2 and *t*-BuOH as discussed in the early part of this section.



(20)



Scheme 4. Plausible Reaction Pathway

3-7. Conclusion

A new synthetic method for both of symmetric and unsymmetric aromatic azo compounds through an oxidative dimerization of aromatic amines under metal-free and mild conditions has been developed. This efficient, low energy-consuming, and straightforward method allowed us easy access to diverse azobenzenes including heteroaromatic azo compounds, which would have high degree of potential for the use as various functional molecules. Furthermore, mechanistic aspects of this new oxidative dimerization have been elucidated.

3-8. Experimental Section

General experimental methods

All reactions were carried out under a nitrogen atmosphere. ^{1}H and ^{13}C NMR spectra were recorded on a NMR spectrometer (^{1}H NMR, 270 or 400 MHz; ^{13}C NMR, 68 or 100 MHz) using tetramethylsilane as an internal standard. ^{15}N NMR spectra were recorded on a NMR spectrometer (^{15}N NMR, 40 MHz) using liquid ammonia as an external standard. ^{19}F NMR spectra were recorded on a NMR spectrometer (^{19}F NMR, 376 MHz) using benzotrifluoride as an internal standard. Products were purified by chromatography on silica gel (200–400 mesh) or aluminum oxide (active stage I, 0.063–0.200 mm). Analytical thin-layer chromatography (TLC) was performed on precoated silica gel glass plates (silica gel, 0.25 mm thickness). Compounds were visualized with UV lamp or treatment with an ethanolic solution of phosphomolybdic acid followed by heating.

Materials

Aromatic Amines except for **1y** and **3b** were purchased from commercial sources and distilled or recrystallized before using. Aromatic amines **1y**[28] and **3b**[19b] were prepared according to the literature. Sodium iodide and *tert*-butyl hypochlorite were purchased from commercial sources and used as received. *N*-iodophthalimide (NIPI)[29] and *N*-iodosaccharin (NIsac)[30] were prepared according to the literature. All other reagents were commercially available and used as received.

Typical procedure for comparative study of halogen-containing oxidants

To a solution of *p*-toluidine (0.5 mmol, 53.6 mg) in diethyl ether (3 mL) was added halogen-containing oxidant (1.0 mmol) under N_2 atmosphere at room temperature. The mixture was stirred for 1 h and quenched with aqueous $Na_2S_2O_3$ (1.0 M, 10 mL), and the solution was extracted with CH_2Cl_2 (20 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give a crude product. The yield of product was calculated by ^1H NMR integration of the crude product using 1,1,2,2-tetrachloroethane as an internal standard.

Typical procedure for the synthesis of symmetric azo compounds using *t*-BuOI

To a mixture of aromatic amine (0.5 mmol) and NaI (1.0 mmol, 150.0 mg) in an appropriate solvent (3 mL) was added *t*-BuOCl (1.0 mmol, 108.6 mg) under N_2 atmosphere at the appropriate temperature. The mixture was stirred for the indicated time and quenched with aqueous $Na_2S_2O_3$ (1.0 M, 10 mL), and the solution was extracted with CH_2Cl_2 (20 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude product. Purification by flash column chromatography on silica gel (eluent: ethyl acetate in hexane) gave homodimerized product.

Typical procedure for the synthesis of asymmetric azo compounds using *t*-BuOI

To a mixture of two aromatic amines (Ar^1NH_2 and Ar^2NH_2, 0.25 mmol for each) and NaI (1.0 mmol, 150.0 mg) in an appropriate solvent (3 mL), was added *t*-BuOCl (1.0 mmol, 108.6 mg) under N_2 atmosphere at the appropriate temperature. The mixture was stirred for the indicated time and quenched with aqueous $Na_2S_2O_3$ (1.0 M, 10 mL), and the solution was extracted with CH_2Cl_2 (20 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude product. Purification by flash column

chromatography on silica gel (eluent: ethyl acetate in hexane) gave cross-dimerized product.

Procedure for the gram-scale synthesis of 2ii

To a mixture of ethyl 4-aminobenzoate (10 mmol, 1.65 g) and NaI (20 mmol, 3.00 g) in Et_2O (60 mL) was added *t*-BuOCl (20 mmol, 2.17 g) under N_2 atmosphere at room temperature. The mixture was stirred for 3 h and quenched with aqueous $Na_2S_2O_3$ (1.0 M, 50 mL), and the solution was extracted with CH_2Cl_2 (100 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane–EtOAc, 9:1) gave **2ii** in 93% yield (1.51 g).

Procedure for the synthesis of 4aa and 4cc

To a mixture of aromatic amine (0.5 mmol) and NaI (1.0 mmol, 150.0 mg) in an appropriate solvent (3 mL) was added *t*-BuOCl (1.0 mmol, 108.6 mg) under N_2 atmosphere at the appropriate temperature. The mixture was stirred for the indicated time and quenched with aqueous $Na_2S_2O_3$ (1.0 M, 10 mL), and the solution was extracted with CH_2Cl_2 (20 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude product. Purification by flash column chromatography on silica gel (eluent: ethyl acetate in hexane) gave homodimerized product.

Procedure for the synthesis of 4bb

To a mixture of **4aa** (0.24 mmol, 98.9 mg), acetamide (1.44 mmol, 85.1 mg), cesium carbonate (0.84 mmol, 272.7 mg), and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) (0.012 mmol, 11.0 mg) in 1,4-dioxane (2 mL) was added $Pd_2(dba)_3$ (0.003 mmol,

2.8 mg) under argon atmosphere at room temperature. The mixture was heated at 90 °C and stirred for 1 h. The mixture was diluted with EtOAc (20 mL) and wash with brine. The organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude product. The crude product was washed with $CHCl_3$ to give **4bb**.

Procedure for pH measurement

To a mixture of *p*-toluidine (0.5 mmol, 53.6 mg) and NaI (1.0 mmol, 150.0 mg) in diethyl ether (3 mL) was added *t*-BuOCl (1.0 mmol, 108.6 mg) under N_2 atmosphere at room temperature. The mixture was stirred for 1 h, and the resulting solution was extracted with water (10 mL). The pH measurement of the water layer indicated 4.75.

Procedure for the base addition experiment

To a mixture of *p*-toluidine (0.5 mmol, 53.6 mg), NaI (0.5 mmol, 75.0 mg), and base (0.5 mmol) in diethyl ether (3 mL) was added *t*-BuOCl (0.5 mmol, 54.3 mg) under N_2 atmosphere at room temperature. The mixture was stirred for 1h and quenched with aqueous $Na_2S_2O_3$ (1.0M, 10mL), and the solution was extracted with CH_2Cl_2 (20 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude product. The yield of product was calculated by ^1H NMR integration of the crude product using 1,1,2,2-tetrachloroethane as an internal standard.

Procedure for the homodimerization reaction under radical-inhibiting conditions

To a mixture of *p*-toluidine (0.5 mmol, 53.6 mg), NaI (1.0 mmol, 150.0 mg), and radical scavenger (1.0 mmol) in diethyl ether (3 mL) was added *t*-BuOCl (1.0 mmol, 108.6 mg) under N_2 atmosphere at room temperature. The mixture was stirred for 1 h and quenched with

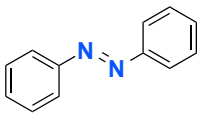
aqueous $Na_2S_2O_3$ (1.0 M, 10 mL), and the solution was extracted with CH_2Cl_2 (20 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude product. Purification by flash column chromatography on silica gel (eluent: ethyl acetate in hexane) gave **2bb**.

Procedure for the reaction of 1.2-diphenylhydrazine with *t*-BuOI

To a mixture of 1.2-diphenylhydrazine (0.5 mmol, 92.1 mg) and NaI (1.0 mmol, 150.0 mg) in MeCN (3 mL) was added *t*-BuOCl (1.0 mmol, 108.6 mg) under N_2 atmosphere at room temperature. The mixture was stirred for 1 h and quenched with aqueous $Na_2S_2O_3$ (1.0 M, 10 mL), and the solution was extracted with CH_2Cl_2 (20 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane/ EtOAc, 99:1) gave **2aa** quantitatively (91.0 mg).

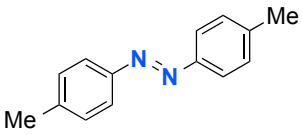
Spectra date of products

(*E*)-1,2-Diphenyldiazene (2aa)



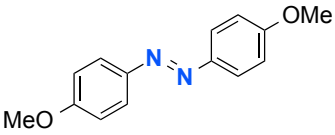
Spectroscopic data were in agreement with those previously reported.[13d] Purified by silica gel column chromatography (hexane/EtOAc 99:1); red solid (43.0 mg, 95%); mp: 67.3–68.2 °C; R_f 0.53 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.41–7.53 (m, 6H), 7.89–7.94 (m, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 122.7, 129.0, 130.9, 152.5; IR (ATR) ν 1580, 1481, 1450, 1298, 1068, 926, 773 cm^{-1}; MS (EI): *m*/*z* (relative intensity, %) 182 ([M]$^+$, 57), 77 ([C_6H_5]$^+$, 100), 105 ([$N_2C_6H_5$]$^+$, 26); HRMS (EI): *m*/*z* calcd for $C_{12}H_{10}N_2$ (M) 182.0844, found 182.0841.

(*E*)-1,2-Di-*p*-tolyldiazene (2bb)



Spectroscopic data were in agreement with those previously reported.[13d] Purified by silica gel column chromatography (hexane/EtOAc 99:1); yellow solid (51.2 mg, 97%); mp: 137.6–140.9 °C; R_f 0.48 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.42 (s, 6H), 7.30 (d, 4H, *J* = 8.4 Hz), 7.81 (d, 4H, *J* = 8.4 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.6, 122.6, 129.6, 141.1, 150.7; IR (ATR) ν 2922, 1597, 1500, 1151, 1109, 823 cm^{-1}; MS (EI): *m*/*z* (relative intensity, %) 210 ([M]$^+$, 37), 91 ([$C_6H_4CH_3$]$^+$, 100), 119 ([$N_2C_6H_4CH_3$]$^+$, 15); HRMS (EI): *m*/*z* calcd for $C_{14}H_{14}N_2$ (M) 210.1157, found 210.1153.

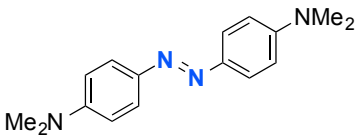
(*E*)-1,2-Bis(4-methoxyphenyl)diazene (2cc)



Spectroscopic data were in agreement with those previously reported.[13d] Purified by silica gel column chromatography (hexane/EtOAc 9:1); yellow solid (52.8 mg, 87%); mp: 154.6–156.3 °C; R_f 0.25

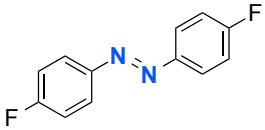
(hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.88 (s, 6H), 6.99 (d, 4H, *J* = 8.9 Hz), 7.87 (d, 4H, *J* = 8.9 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 55.6, 114.1, 124.2, 146.9, 161.4; IR (ATR) *ν* 2920, 1728, 1575, 1240, 1139, 1101, 1022, 813 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 242 ($[M]^+$, 88), 107 ($[C_6H_4OCH_3]^+$, 100), 135 ($[N_2C_6H_4OCH_3]^+$, 41); HRMS (EI): *m/z* calcd for $C_{14}H_{14}N_2O_2$ (M) 242.1055, found 242.1059.

(*E*)-4,4'-(Diazene-1,2-diyl)bis(*N*,*N*-dimethylaniline) (2dd)



Spectroscopic data were in agreement with those previously reported.[8a] Purified by silica gel column chromatography (hexane/EtOAc 9:1); red solid (40.3 mg, 60%); mp: 264.7–265.2 °C (dec.); R_f 0.38 (hexane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.06 (s, 12H), 6.76 (d, 4H, *J* = 9.2 Hz), 7.81 (d, 4H, *J* = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.4, 111.8, 124.0, 144.1, 151.5; IR (ATR) *ν* 2916, 1726, 1591, 1362, 1146, 1130, 894 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 268 ($[M]^+$, 100), 120 ($[C_6H_4N(CH_3)_2]^+$, 79); HRMS (EI): *m/z* calcd for $C_{16}H_{20}N_4$ (M) 268.1688, found 268.1689.

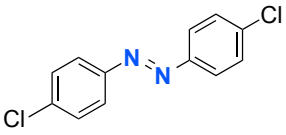
(*E*)-1,2-Bis(4-fluorophenyl)diazene (2ee)



Spectroscopic data were in agreement with those previously reported.[13d] Purified by silica gel column chromatography (hexane/EtOAc 99:1); yellow solid (52.1 mg, 95%); mp: 97.1–99.8 °C; R_f 0.56 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.15–7.21 (m, 4H), 7.88–7.93 (m, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 116.0 (d, *J* = 22.8 Hz), 124.7 (d, *J* = 9.0 Hz), 148.8 (d, *J* = 2.2 Hz), 164.2 (d, *J* = 251.7 Hz); IR (ATR) *ν* 2939, 1729, 1589, 1496, 1228, 1138, 839, 752 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 218

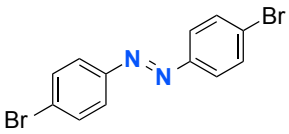
([M]$^+$, 40), 95 ([C_6H_4F]$^+$, 100), 123 ([$N_2C_6H_4F$]$^+$, 25); HRMS (EI): *m/z* calcd for $C_{12}H_8F_2N_2$ (M) 218.0656, found 218.0660.

(*E*)-1,2-Bis(4-chlorophenyl)diazene (2ff)



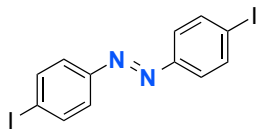
Spectroscopic data were in agreement with those previously reported.[13d] Purified by silica gel column chromatography (hexane/EtOAc 95:5); yellow solid (59.0 mg, 96%); mp: 182.0–184.5 °C; R_f 0.50 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.48 (d, 4H, *J* = 8.9 Hz), 7.87 (d, 4H, *J* = 8.9 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 124.1, 129.3, 137.1, 150.6; IR (ATR) ν 1571, 1475, 1103, 1082, 1002, 842, 825, 715 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 250 ([M]$^+$, 31), 111 ([C_6H_4Cl]$^+$, 100), 139 ([$N_2C_6H_4Cl$]$^+$, 38); HRMS (EI): *m/z* calcd for $C_{12}H_8Cl_2N_2$ (M) 250.0065, found 250.0055.

(*E*)-1,2-Bis(4-bromophenyl)diazene (2gg)



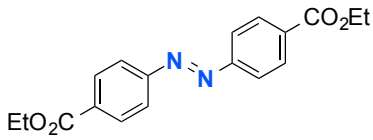
Spectroscopic data were in agreement with those previously reported.[13d] Purified by basic alumina column chromatography (hexane/EtOAc 95:5); red solid (70.7 mg, 83%); mp: 201.3–203.7 °C; R_f 0.50 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.65 (d, 4H, *J* = 8.1 Hz), 7.79 (d, 4H, *J* = 8.1 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 124.3, 125.7, 132.3, 151.0; IR (ATR) ν 1726, 1568, 1469, 1396, 1269, 1062, 1004, 833, 709 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 340 ([M]$^+$, 33), 155 ([C_6H_4Br]$^+$, 100), 183 ([$N_2C_6H_4Br$]$^+$, 61); HRMS (EI): *m/z* calcd for $C_{12}H_8Br_2N_2$ (M) 337.9054, found 337.9053.

(*E*)-1,2-Bis(4-iodophenyl)diazene (2hh)



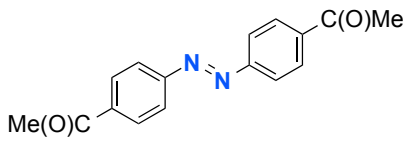
Spectroscopic data were in agreement with those previously reported.[31] Purified by silica gel column chromatography (hexane/EtOAc 95:5); red solid (95.1 mg, 88%); mp: 242.4–244.8 °C; R_f 0.50 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.64 (d, 4H, *J* = 8.6 Hz), 7.86 (d, 4H, *J* = 8.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 98.1, 124.5, 138.4, 151.8; IR (ATR) *ν* 1560, 1467, 1390, 1296, 1278, 1095, 1049, 1001, 810, 713 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 434 ([M]$^+$, 72), 203 ([C_6H_4I]$^+$, 100), 231 ([$N_2C_6H_4I$]$^+$, 53); HRMS (EI): *m/z* calcd for $C_{12}H_8I_2N_2$ (M) 433.8777, found 433.8776.

(*E*)-Diethyl 4,4′-(diazene-1,2-diyl)dibenzoate (2ii)



Spectroscopic data were in agreement with those previously reported.[13d] Purified by silica gel column chromatography (hexane/EtOAc 9:1); red solid (77.9 mg, 95%); mp: 139.7–142.6 °C; R_f 0.26 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.44 (t, 6H, *J* = 7.0 Hz), 4.42 (q, 4H, *J* = 7.0 Hz), 7.98 (d, 4H, *J* = 8.6 Hz), 8.22 (d, 4H, *J* = 8.6 Hz,); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.4, 61.4, 122.8, 130.5, 132.6, 154.7, 165.8; IR (ATR) *ν* 1711, 1265, 1095, 1006, 868, 779, 700 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 326 ([M]$^+$, 33), 149 ([$C_6H_4CO_2Et$]$^+$, 100), 177 ([$N_2C_6H_4$ CO_2Et]$^+$, 13); HRMS (EI): *m/z* calcd for $C_{18}H_{18}N_2O_4$ (M) 326.1267, found 326.1269.

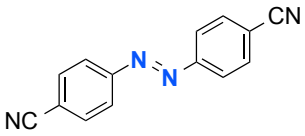
(*E*)-1,2-Bis(4-acetylphenyl)diazene (2jj)



Spectroscopic data were in agreement with those previously reported.[8a] Purified by basic alumina column chromatography (hexane/EtOAc 8:2); red solid (60.7 mg, 91%); mp: 213.0–215.5 °C; R_f 0.16 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.68 (s, 6H), 8.01 (d, 4H, *J* = 8.6 Hz), 8.13 (d, 4H, *J* = 8.6

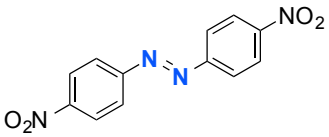
Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 27.0, 123.1, 129.3, 138.7, 154.6, 197.2; IR (ATR) ν 1672, 1404, 1354, 1307, 1258, 1223, 1109, 1006, 961, 856, 837 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 266 ($[M]^+$, 58), 119 ($[C_6H_4COCH_3]^+$, 100), 147 ($[N_2C_6H_4COCH_3]^+$, 14); HRMS (EI): *m/z* calcd for $C_{16}H_{14}N_2O_2$ (M) 266.1055, found 266.1053.

(*E*)-4,4´-(Diazene-1,2-diyl)dibenzonitrile (2kk)



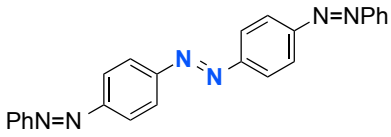
Spectroscopic data were in agreement with those previously reported.[8b] Purified by silica gel column chromatography (hexane/EtOAc 7:3); red solid (51.4 mg, 89%); mp: 277.8–278.2 °C; R_f 0.05 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.86 (d, 4H, *J* = 8.6 Hz), 8.04 (d, 4H, *J* = 8.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 115.1, 118.2, 123.7, 133.4, 153.9; IR (ATR) ν 2924, 2226, 1489, 1408, 1294, 1098, 1011, 851, 839 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 232 ($[M]^+$, 49), 102 ($[C_6H_4CN]^+$, 100), 130 ($[N_2C_6H_4CN]^+$, 22); HRMS (EI): *m/z* calcd for $C_{14}H_8N_4$ (M) 232.0749, found 232.0748.

(*E*)-1,2-Bis(4-nitrophenyl)diazene (2ll)



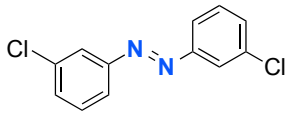
Spectroscopic data were in agreement with those previously reported.[32] Purified by basic alumina column chromatography (hexane/EtOAc 7:3); red solid (54.3 mg, 79%); mp: 223.3–225.4 °C; R_f 0.10 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.11 (d, 4H, *J* = 8.9 Hz), 8.43 (d, 4H, *J* = 8.9 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 123.8, 124.7, 149.2, 154.8; IR (ATR) ν 1608, 1533, 1344, 1319, 1209, 1105, 1002, 862, 806, 758 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 272 ($[M]^+$, 49), 122 ($[C_6H_4NO_2]^+$, 100), 150 ($[N_2C_6H_4NO_2]^+$, 61); HRMS (EI): *m/z* calcd for $C_{12}H_8N_4O_4$ (M) 272.0546, found 272.0547.

(*E*)-4,4´-Bis(phenylazo)azobenzene (2mm)



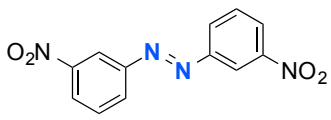
Spectroscopic data were in agreement with those previously reported.[33] Purified by basic alumina column chromatography (hexane/EtOAc 5:5); brown solid (65.1 mg, 67%); mp: 237.0–237.8 °C; R_f 0.45 (hexane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, 4H, *J* = 8.8, Hz), 8.10 (d, 4H, *J* = 8.8, Hz), 7.98 (d, 4H, *J* = 6.8 Hz), 7.54 (m, 6H); IR (ATR) *ν* 3065, 3044, 1942, 1692, 1587, 1306, 1213, 854, 759 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 390 ([M]$^+$, 100), 105 ([$C_6H_5N_2$]$^+$, 41), 181 ([$C_6H_5N_2C_6H_4$]$^+$, 69), 285 ([$C_6H_5N_2C_6H_4N_2C_6H_4$]$^+$, 49); HRMS (EI): *m/z* calcd for $C_{24}H_{18}N_6$ (M) 390.1593, found 390.1595.

(*E*)-1,2-Bis(3-chlorophenyl)diazene (2nn)



Spectroscopic data were in agreement with those previously reported.[31] Purified by silica gel column chromatography (hexane/EtOAc 95:5); yellow solid (53.8 mg, 86%); mp: 100.2–101.6 °C; R_f 0.50 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.43–7.45 (m, 4H), 7.70–7.88 (m, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 121.8, 122.5, 130.1, 131.1, 135.1, 152.9; IR (ATR) *ν* 1584, 1566, 1462, 1198, 1067, 885, 790 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 250 ([M]$^+$, 13), 111 ([C_6H_4Cl]$^+$, 100), 139 ([$N_2C_6H_4Cl$]$^+$, 18); HRMS (EI): *m/z* calcd for $C_{12}H_8Cl_2N_2$ (M) 250.0065, found 250.0061.

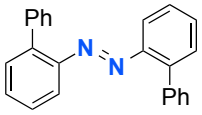
(*E*)-1,2-Bis(3-nitrophenyl)diazene (2oo)



Spectroscopic data were in agreement with those previously reported.[34] Purified by basic alumina column chromatography (hexane/EtOAc 8:2); orange solid (53.3 mg, 78%); mp: 149.8–151.6 °C; R_f 0.14 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.78 (dd, 2H, *J* = 8.1, 8.1 Hz), 8.34 (dd,

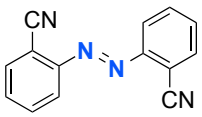
2H, *J* = 1.1, 8.1 Hz), 8.40 (dd, 2H, *J* = 1.1, 8.1 Hz), 8.79 (s, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 117.1, 125.9, 129.6, 130.2, 148.9, 152.2; IR (ATR) ν 1528, 1344, 1312, 1070, 918, 808, 741 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 272 ($[M]^+$, 39), 122 ($[C_6H_4NO_2]^+$, 100), 150 ($[N_2C_6H_4NO_2]^+$, 63); HRMS (EI): *m/z* calcd for $C_{12}H_8N_4O_4$ (M) 272.0546, found 272.0544.

(*E*)-1,2-Bis([1,1´-biphenyl]-2-yl)diazene (2pp)



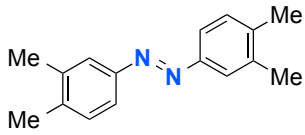
Purified by silica gel column chromatography (hexane/EtOAc 95:5); orange solid (36.5 mg, 44%); mp: 133.5 °C; R_f 0.40 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.26–7.57 (m, 18H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 116.3, 127.2, 127.6, 130.0, 130.6, 130.7, 130.8, 138.8, 141.4, 149.7; IR (ATR) ν 3048, 1586, 1470, 768, 732, 723 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 334 ($[M]^+$, 60), 153 ($[C_6H_4Ph]^+$, 100), 181 ($[N_2C_6H_4Ph]^+$, 25); HRMS (EI): *m/z* calcd for $C_{24}H_{18}N_2$ (M) 334.1470, found 334.1471.

(*E*)-2,2´-(Diazene-1,2-diyl)dibenzonitrile (2qq)



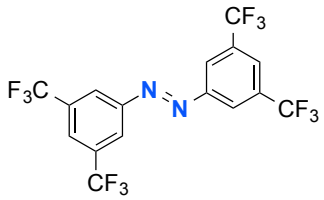
Purified by basic alumina column chromatography (hexane/EtOAc 7:3); red solid (42.1 mg, 73%); mp: 233.1–234.7 °C; R_f 0.05 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.65 (ddd, 2H, *J* = 1.4, 7.6, 7.6 Hz), 7.75 (ddd, 2H, *J* = 1.6, 7.6, 7.6 Hz), 7.89 (dd, 2H, *J* = 1.6, 7.6 Hz), 8.06 (dd, 2H, *J* = 1.4, 7.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 114.8, 116.4, 116.8, 132.3, 133.5, 152.4; IR (ATR) ν 2232, 1589, 1481, 1227, 773, 743 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 232 ($[M]^+$, 23), 102 ($[C_6H_4CN]^+$, 100), 130 ($[N_2C_6H_4CN]^+$, 34); HRMS (EI): *m/z* calcd for $C_{14}H_8N_4$ (M) 232.0759, found 232.0754.

(*E*)-1,2-Bis(3,4-dimethylphenyl)diazene (2rr)



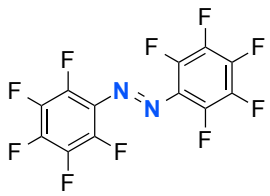
Purified by silica gel column chromatography (hexane/EtOAc 99:1); yellow solid (53.3 mg, 89%); mp: 155.2–157.8 °C; R_f 0.50 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.31 (s, 6H), 2.34 (s, 6H), 7.23 (d, 2H, J = 7.8 Hz), 7.65 (d, 2H, J = 7.8 Hz), 7.68 (s, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.9, 19.9, 120.7, 123.2, 130.2, 137.4, 139.9, 151.2; IR (ATR) ν 1602, 1443, 1242, 1101, 1022, 883, 827, 712 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 238 ([M]$^+$, 45), 105 ([$C_6H_4(CH_3)_2$]$^+$, 81), 133 ([$N_2C_6H_4(CH_3)_2$]$^+$, 16); HRMS (EI): *m/z* calcd for $C_{16}H_{18}N_2$ (M) 238.1470, found 238.1469.

(*E*)-1,2-Bis(3,5-bis(trifluoromethyl)phenyl)diazene (2ss)



Purified by silica gel column chromatography (hexane); yellow solid (109.3 mg, 94%); mp: 115.2–117.2 °C; R_f 0.40 (hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.06 (s, 2H), 8.46 (s, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 122.9 (q, J = 272.9 Hz), 123.4 (q, J = 2.8 Hz), 125.2 (m), 133.2 (q, J = 34.1 Hz), 152.1; IR (ATR) ν 1373, 1277, 1262, 1165, 1105, 1055, 935, 907, 847, 729 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 454 ([M]$^+$, 20), 213 ([$C_6H_4(CF_3)_2$]$^+$, 100), 241 ([$N_2C_6H_4(CF_3)_2$]$^+$, 9); HRMS (EI): *m/z* calcd for $C_{16}H_6F_{12}N_2$ (M) 454.0339, found 454.0340.

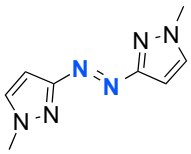
(*E*)-1,2-Bis(pentafluorophenyl)diazene (2tt)



Spectroscopic data were in agreement with those previously reported.[35] Purified by silica gel column chromatography (hexane/EtOAc 99:1); yellow solid (60.7 mg, 67%); mp: 139.6–142.1 °C; R_f 0.55 (hexane/EtOAc 9:1); ^{19}F NMR (376 MHz, $CDCl_3$) δ –150.8 (m, 2F), –151.1 (m, 1F), –163.7 (m, 2F); IR (ATR) ν 1641, 1504, 1408, 1319, 1146, 999, 976 cm^{-1}; MS (EI): *m/z* (relative

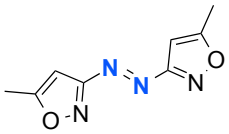
intensity, %) 362 ([M]$^+$, 43), 167 ([C_6F_5]$^+$, 100), 195 ([$N_2C_6F_5$]$^+$, 33); HRMS (EI): *m/z* calcd for $C_{12}F_{10}N_2$ (M) 361.9902, found 361.9904.

(*E*)-1,2-Bis(1-methyl-1*H*-pyrazol-3-yl)diazene (2uu)



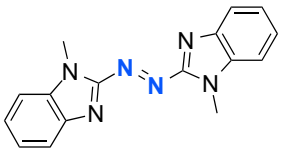
Purified by silica gel column chromatography (EtOAc); yellow solid (39.5 mg, 83%); mp: 200.8–201.6 °C; R_f 0.28 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 (s, 6H), 6.68 (d, 2H, *J* = 2.4 Hz), 7.36 (d, 2H, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.6, 95.3, 131.8, 164.0; IR (ATR) ν 3125, 2924, 1375, 1303, 1209, 869 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 190 ([M]$^+$, 100), 109 ([$N_2C_4H_5N_2$]$^+$, 95); HRMS (EI): *m/z* calcd for $C_8H_{10}N_6$ (M) 190.0967, found 190.0966.

(*E*)-1,2-Bis(5-methylisoxazol-3-yl)diazene (2vv)



Spectroscopic data were in agreement with those previously reported.[17c] Purified by basic alumina column chromatography (hexane/EtOAc 95:5); yellow solid (36.5 mg, 76%); mp: 212.2–212.7 °C; R_f 0.38 (hexane/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (s, 6H), 6.42 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8, 92.0, 172.0, 173.8; IR (ATR) ν 3145, 1599, 1466, 1433, 1413, 1240, 1022, 1001, 929, 819, 740 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 192 ([M]$^+$, 58), 110 ([$N_2C_4H_4NO$]$^+$, 100); HRMS (EI): *m/z* calcd for $C_8H_8N_4O_2$ (M) 192.0647, found 192.0644.

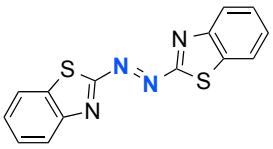
(*E*)-1,2-Bis(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)diazene (2ww)



Purified by basic alumina column chromatography ($CHCl_3$/MeOH 99:1); red solid (55.4 mg, 76%); mp: 282.9–283.3 °C; R_f 0.38 ($CHCl_3$/MeOH 99:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (s, 6H), 7.38-

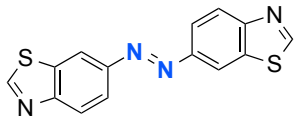
–7.51 (m, 6H), 7.96 (d, 2H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.3, 110.4, 122.4, 124.8, 125.4, 136.6, 142.4, 155.8; IR (ATR) ν 3051, 1573, 1483, 1458, 1325, 1246 cm^{-1}; FAB-MS m/z 291 ([M]$^+$+1); HRMS (FAB): m/z calcd for $C_{16}H_{15}N_6$ (M) 291.1358, found 291.1361.

(*E*)-2,2´-Azobenzothiazole (2xx)



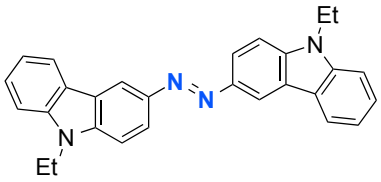
Purified by silica gel column chromatography (hexane/EtOAc 7:3); orange solid (53.4 mg, 72%); mp: 293.7–294.6 °C; R_f 0.10 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.58 (m, 4H), 7.97 (m, 2H), 8.26 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 122.6, 125.8, 127.3, 128.9, 135.4, 153.2, 173.4; IR (ATR) ν 1548, 1474, 1452, 1313, 1244, 1192, 1153, 1115, 893 cm^{-1}; MS (EI): m/z (relative intensity, %) 296 ([M]$^+$, 3), 268 ([M-N_2]$^+$, 100), 130 ([C_7H_4NS]$^+$, 43); HRMS (EI): m/z calcd for $C_{14}H_8N_4S_2$ (M) 296.0190, found 296.0193.

(*E*)-1,2-Bis-benzothiazol-6-yl-diazene (2yy)



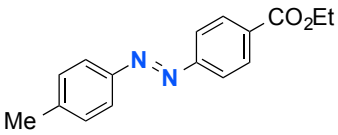
Purified by silica gel column chromatography ($CHCl_3$/MeOH 100:0 to 8.2); yellow solid (46.2 mg, 62%); mp: 250.2–251.1 °C; R_f 0.23 ($CHCl_3$/MeOH 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, 2H, J = 2.0, 8.8 Hz), 8.27 (d, 2H, J = 8.8 Hz), 8.59 (d, 2H, J = 2.0 Hz), 9.13 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 117.7, 121.1, 124.1, 134.7, 150.2, 155.0, 156.4; IR (ATR) ν 3064, 1585, 1466, 1398, 1290, 889, 846 cm^{-1}; MS (EI): m/z (relative intensity, %) 296 ([M]$^+$, 49), 134 ([C_7H_4NS]$^+$, 100), 162 ([$N_2C_7H_4NS$]$^+$, 32); HRMS (EI): m/z calcd for $C_{14}H_8N_4S_2$ (M) 296.0190, found 296.0192.

(*E*)-9,9´-Diethyl-3,3´-azocarbazole (2zz)



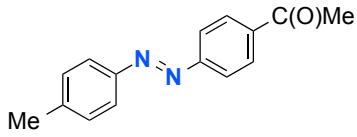
Spectroscopic data were in agreement with those previously reported.[36] Purified by basic alumina column chromatography (hexane/EtOAc 9:1); yellow solid (72.8 mg, 70%); mp: 213.1–2136. °C; R_f 0.28 (hexane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (t, 6H, *J* = 7.2 Hz), 4.44 (q, 4H, *J* = 7.2 Hz), 7.31 (t, 2H, *J* = 6.8 Hz), 7.45–7.53 (m, 6H), 8,21 (m, 4H), 8.75 (d, 2H, *J* = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 37.8, 108.6, 108.9, 116.0, 119.5, 120.7, 120.8, 123.3, 123.6, 126.1, 140.6, 141.2, 146.5; IR (ATR) ν 2972, 1593, 1277, 1323, 1229, 1117, 746 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 416 ($[M]^+$, 57), 194 ($[C_{14}H_{12}N]^+$, 100); HRMS (EI): *m/z* calcd for $C_{28}H_{24}N_4$ (M) 416.2001, found 416.2002.

(*E*)-Ethyl 4-(*p*-tolyldiazenyl)benzoate (2bi)



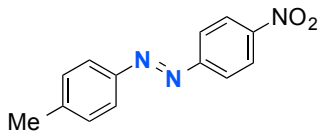
Spectroscopic data were in agreement with those previously reported.[13d] Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); yellow solid (41.3 mg, 62%); mp: 100.6–101.3 °C; R_f 0.43 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.43 (t, 3H, *J* = 7.0 Hz), 2.45 (s, 3H), 4.42 (q, 2H, *J* = 7.0 Hz), 7.32 (d, 2H, *J* = 8.4 Hz), 7.87 (d, 2H, *J* = 8.4 Hz), 7.92 (d, 2H, *J* = 8.6 Hz), 8.19 (d, 2H, *J* = 8.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.4, 21.6, 61.2, 122.4, 123.1, 129.7, 130.4, 131.8, 142.3, 150.6, 155.1, 165.9; IR (ATR) ν 2922, 1715, 1601, 1265, 1103, 1094, 1008, 866, 822, 773, 709 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 268 ($[M]^+$, 53), 91 ($[C_6H_4CH_3]^+$, 100), 119 ($[N_2C_6H_4CH_3]^+$, 33), 149 ($[C_6H_4CO_2Et]^+$, 25); HRMS (EI): *m/z* calcd for $C_{16}H_{16}N_2O_2$ (M) 268.1212, found 268.1214.

(*E*)-1-(4-Acetylphenyl)-2-*p*-tolyldiazene (2bj)



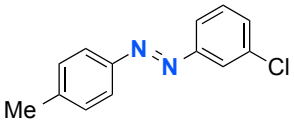
Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); red solid (34.7 mg, 58%); mp: 128.7–130.0 °C; R_f 0.18 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.45 (s, 3H), 2.66 (s, 3H), 7.33 (d, 2H, *J* = 8.4 Hz), 7.86 (d, 2H, *J* = 8.4 Hz), 7.95 (d, 2H, *J* = 8.6 Hz), 8.10 (d, 2H, *J* = 8.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.6, 26.8, 122.7, 123.2, 129.3, 129.8, 138.1, 142.5, 150.7, 155.1, 197.5; IR (ATR) *ν* 1676, 1595, 1354, 1263, 1003, 962, 853, 820, 707 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 238 ([M]$^+$, 38), 91 ([$C_6H_4CH_3$]$^+$, 100), 119 ([$N_2C_6H_4CH_3$]$^+$, 35); HRMS (EI): *m/z* calcd for $C_{15}H_{14}N_2O$ (M) 238.1106, found 238.1109.

(*E*)-1-(4-Nitrophenyl)-2-*p*-tolyldiazene (2bl)



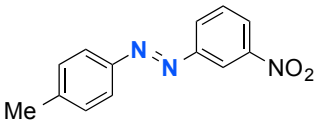
Spectroscopic data were in agreement with those previously reported.[32] Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); orange solid (38.5 mg, 64%); mp: 180.2–181.3 °C; R_f 0.40 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.34 (d, 2H, *J* = 8.1 Hz), 7.87 (d, 2H, *J* = 8.1 Hz), 7.99 (d, 2H, *J* = 8.9 Hz), 8.35 (d, 2H, *J* = 8.9 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.6, 123.1, 123.3, 124.5, 129.7, 143.1, 148.3, 150.4, 155.6; IR (ATR) *ν* 1605, 1589, 1522, 1339, 1306, 1134, 1105, 858, 826, 754 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 241 ([M]$^+$, 34), 91 ([$C_6H_4CH_3$]$^+$, 100), 119 ([$N_2C_6H_4CH_3$]$^+$, 25); HRMS (EI): *m/z* calcd for $C_{13}H_{11}N_3O_2$ (M) 241.0851, found 241.0847.

(*E*)-1-(3-Chlorophenyl)-2-*p*-tolyldiazene (2bn)



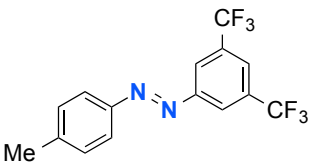
Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); orange solid (29.3 mg, 52%); mp: 104.3–105.2 °C; R_f 0.45 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2,43 (s, 3H), 7.30–7.44 (m, 4H), 7.78–7.88 (m, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.5, 121.7, 122.2, 123.1, 129.8, 139.1, 130.4, 135.1, 142.2, 150.5, 153.5; IR (ATR) ν 2924, 1728, 1599, 1454, 1260, 1070, 823, 791, 710 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 230 ([M]$^+$, 24), 91 ([$C_6H_4CH_3$]$^+$, 100), 111 ([C_6H_4Cl]$^+$, 17), 119 ([$N_2C_6H_4CH_3$]$^+$, 19); HRMS (EI): *m/z* calcd for $C_{13}H_{11}ClN_2$ (M) 230.0611, found 230.0608.

(*E*)-1-(3-Nitrophenyl)-2-*p*-tolyldiazene (2bo)



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); orange solid (38.0 mg, 60%); mp: 113.2–115.9 °C; R_f 0.38 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.33 (d, 2H, *J* = 8.4 Hz), 7.67 (dd, 1H, *J* = 8.1, 8.1 Hz), 7.86 (d, 2H, *J* = 8.4 Hz), 8.21 (d, 1H, *J* = 8.1 Hz), 8.28 (d, 1H, *J* = 8.1 Hz), 8.69 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.6, 116.9, 123.3, 124.5, 129.0, 129.8, 129.9, 143.0, 149.0, 150.3, 153.1; IR (ATR) ν 1601, 1584, 1518, 1346, 1146, 1076, 901, 828, 810, 739, 710 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 241 ([M]$^+$, 27), 91 ([$C_6H_4CH_3$]$^+$, 100), 119 ([$N_2C_6H_4CH_3$]$^+$, 23); HRMS (EI): *m/z* calcd for $C_{13}H_{11}N_3O_2$ (M) 241.0851, found 241.0848.

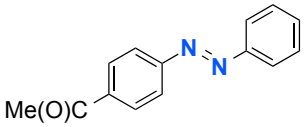
(*E*)-1-(3,5-Bis(trifluoromethyl)phenyl)-2-*p*-tolyldiazene (2bs)



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 9:1); orange solid (54.6 mg, 66%); mp: 82.0–84.4 °C; R_f 0.28 (hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.34 (d, 2H, *J* = 8.1 Hz), 7.87 (d, 2H, *J* = 8.1 Hz), 7.95 (s, 1H), 8.33 (s, 2H); ^{13}C NMR (68 MHz, $CDCl_3$)

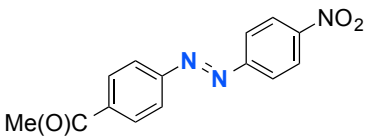
δ 21.6, 122.8 (q, *J* = 3.3 Hz), 123.1 (q, *J* = 272.9 Hz), 123.5, 130.0, 132.6 (q, *J* = 34.1 Hz), 143.4, 150.2, 152.9; IR (ATR) ν 1600, 1504, 1363, 1275, 1261, 1172, 1124, 899, 828 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 332 ($[M]^+$, 31), 91 ($[C_6H_4CH_3]^+$, 100), 119 ($[N_2C_6H_4CH_3]^+$, 19), 213 ($[C_6H_4(CF_3)_2]^+$, 11); HRMS (EI): *m/z* calcd for $C_{15}H_{10}F_6N_2$ (M) 332.0748, found 332.0745.

(*E*)-1-(4-Acetylphenyl)-2-phenyldiazene (2aj)



Spectroscopic data were in agreement with those previously reported.[8a] Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); red solid (30.0 mg, 54%); mp: 102.3–104.7 °C; R_f 0.24 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.66 (s, 3H), 7.50–7.56 (m, 3H), 7.93–7.99 (m, 4H), 8.10 (d, 2H, *J* = 8.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 26.8, 122.8, 123.1, 129.2, 129.3, 131.7, 138.3, 152.5, 155.0, 197.4; IR (ATR) ν 2924, 1674, 1352, 1259, 961, 839, 771 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 224 ($[M]^+$, 100), 77 ($[C_6H_5]^+$, 97), 105 ($[N_2C_6H_5]^+$, 26), 119 ($[C_6H_4COCH_3]^+$, 57); HRMS (EI): *m/z* calcd for $C_{14}H_{12}N_2O$ (M) 224.0950, found 224.0952.

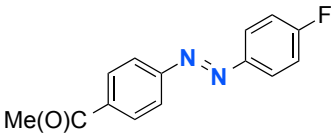
(*E*)-1-(4-Acetylphenyl)-2-(4-nitrophenyl)diazene (2jl)



Spectroscopic data were in agreement with those previously reported.[32] Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); red solid (48.2 mg, 72%); mp: 160.0–161.6 °C; R_f 0.15 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.68 (s, 3H), 8.00-8.15 (m, 6H), 8.38 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 26.8, 123.4, 123.7, 124.7, 129.4, 139.3, 149.1, 154.5, 155.3, 197.1; IR (ATR) ν 1681, 1698, 1534, 1341, 1319, 1261, 1215, 1109 cm^{-1}, 860; MS (EI): *m/z* (relative intensity, %) 269 ($[M]^+$, 68), 119 ($[C_6H_4COCH_3]^+$, 100), 122

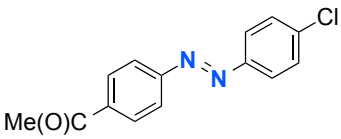
($[C_6H_4NO_2]^+$, 35), 147 ($[N_2C_6H_4\ COCH_3]^+$, 29); HRMS (EI): *m/z* calcd for $C_{14}H_{11}N_3O_3$ (M) 269.0800, found 269.0803.

(*E*)-1-(4-Acetylphenyl)-2-(4-fluorophenyl)diazene (2ej)



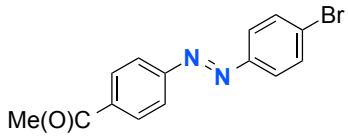
Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); orange solid (36.8 mg, 61%); mp: 111.5–114.1 °C; R_f 0.24 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.66 (s, 3H), 7.18–7.27 (m, 2H), 7.93–8.02 (m, 4H), 8.08–8.13 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 26.8, 116.2 (d, *J* = 22.9 Hz), 122.8, 125.2 (d, *J* = 9.5 Hz), 129.3, 138.4, 149.0 (d, *J* = 2.8 Hz), 154.8, 164.8 (d, *J* = 253.3 Hz), 197.3; IR (ATR) *ν* 1680, 1591, 1489, 1406, 1358, 1233, 1138, 843 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 242 ($[M]^+$, 62), 95 ($[C_6H_4F]^+$, 100), 119 ($[C_6H_4COCH_3]^+$, 41), 123 ($[N_2C_6H_4F]^+$, 36); HRMS (EI): *m/z* calcd for $C_{14}H_{11}FN_2O$ (M) 242.0855, found 242.0855.

(*E*)-1-(4-Acetylphenyl)-2-(4-chlorophenyl)diazene (2fj)



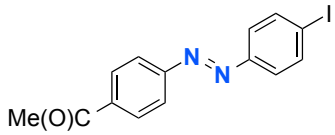
Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); orange solid (42.0 mg, 65%); mp: 149.8–152.3 °C; R_f 0.25 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.65 (s, 3H), 7.49 (d, 2H, *J* = 8.6 Hz), 7.88 (d, 2H, *J* = 8.6 Hz), 7.94 (d, 2H, *J* = 8.6 Hz), 8.09 (d, 2H, *J* = 8.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 26.8, 122.9, 124.4, 129.3, 129.4, 137.7, 138.4, 150.7, 154.7, 197.3; IR (ATR) *ν* 1676, 1478, 1404, 1354, 1261, 1086, 1003, 852, 839 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 258 ($[M]^+$, 86), 111 ($[C_6H_4Cl]^+$, 100), 119 ($[C_6H_4COMe]^+$, 69), 139 ($[N_2C_6H_4Cl]^+$, 43); HRMS (EI): *m/z* calcd for $C_{14}H_{11}ClN_2O$ (M) 258.0560, found 258.0570.

(*E*)-1-(4-Acetylphenyl)-2-(4-bromophenyl)diazene (2gj)



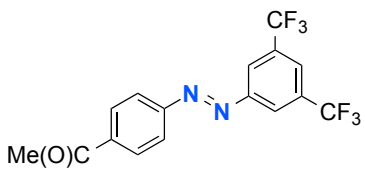
Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); orange solid (44.2 mg, 58%); mp: 168.3–169.4 °C; R_f 0.24 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.67 (s, 3H), 7.67 (d, 2H, *J* = 8.6 Hz), 7.83 (d, 2H, *J* = 8.6 Hz), 7.96 (d, 2H, *J* = 8.6 Hz), 8.10 (d, 2H, *J* = 8.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 26.8, 123.0, 124.6, 126.3, 129.4, 132.4, 138.5, 151.2, 154.7, 197.4; IR (ATR) *ν* 2920, 1668, 1354, 1260, 1067, 1005, 839 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 302 ([M]$^+$, 71), 119 ([C_6H_4COMe]$^+$, 100), 147 ([$N_2C_6H_4COMe$]$^+$, 25), 155 ([C_6H_4Br]$^+$, 95), 147 ([$N_2C_6H_4Br$]$^+$, 41); HRMS (EI): *m/z* calcd for $C_{14}H_{11}BrN_2O$ (M) 302.0055, found 302.0052.

(*E*)-1-(4-Acetylphenyl)-2-(4-iodophenyl)diazene (2hj)



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); red solid (46.3 mg, 53%); mp: 190.0–192.3 °C; R_f 0.33 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.67 (s, 3H), 7.68 (d, 2H, *J* = 8.6 Hz), 7.89 (d, 2H, *J* = 8.6 Hz), 7.96 (d, 2H, *J* = 8.6 Hz), 8.11 (d, 2H, *J* = 8.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 26.9, 98.8, 123.0, 124.7, 129.4, 138.5, 138.6, 151.8 154.7, 197.4; IR (ATR) *ν* 1665, 1354, 1298, 1263, 1003, 828 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 350 ([M]$^+$, 100), 119 ([C_6H_4COMe]$^+$, 69), 147 ([$N_2C_6H_4COMe$]$^+$, 17), 203 ([C_6H_4I]$^+$, 99), 231 ([$N_2C_6H_4I$]$^+$, 43); HRMS (EI): *m/z* calcd for $C_{14}H_{11}IN_2O$ (M) 349.9916, found 349.9914.

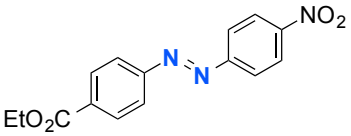
(*E*)-1-(4-Acetylphenyl)-2-(3,5-bis(trifluoromethyl)phenyl)diazene (2js)



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); red solid (56.5 mg, 63%); mp: 82.6–83.4 °C; R_f 0.25 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.70 (s,

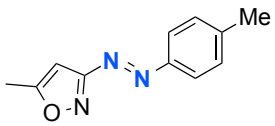
3H), 8.02 (s, 1H), 8.05 (d, 2H, J = 8.6 Hz), 8.15 (d, 2H, J = 8.6 Hz), 8.41 (s, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 26.9, 123.0 (q, J = 273.5 Hz), 123.2 (q, J = 3.4 Hz), 123.4, 124.4 (m), 129.5, 132.8 (q, J = 34.1 Hz), 139.4, 152.6, 154.2, 197.2; IR (ATR) ν 1694, 1369, 1358, 1277, 1258, 1206, 1163, 1126, 1103, 961, 903, 843 cm^{-1}; MS (EI): m/z (relative intensity, %) 360 ([M]$^+$, 52), 119 ([C_6H_4COMe]$^+$, 100), 147 ([$N_2C_6H_4COMe$]$^+$, 16), 213 ([$C_6H_3(CF_3)_2$]$^+$, 42), 241 ([$N_2C_6H_3(CF_3)_2$]$^+$, 2); HRMS (EI): m/z calcd for $C_{16}H_{10}F_6N_2O$ (M) 360.0697, found 360.0698.

(*E*)-Ethyl 4-((4-nitrophenyl)diazenyl)benzoate (2il)



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); red solid (49.3 mg, 66%); mp: 159.7–160.9 °C; R_f 0.23 (hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.44 (t, 3H. J = 7.0 Hz), 4.43 (q, 2H, J = 7.0 Hz), 7.97 (d, 2H, J = 8.9 Hz), 8.05 (d, 2H, J = 8.6 Hz), 8.21 (d, 2H, J = 8.6 Hz), 8.39 (d, 2H, J = 8.9 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.4, 61.4, 123.0, 123.6, 124.6, 130.5, 133.3, 148.9, 154.4, 155.2, 165.5; IR (ATR) ν 1707, 1522, 1343, 1271, 1103, 862, 773 cm^{-1}; MS (EI): m/z (relative intensity, %) 299 ([M]$^+$, 54), 122 ([$C_6H_4NO_2$]$^+$, 33), 149 ([$C_6H_4CO_2Et$]$^+$, 100), 177 ([$N_2C_6H_4CO_2Et$]$^+$, 18); HRMS (EI): m/z calcd for $C_{15}H_{13}N_3O_4$ (M) 299.0906, found 299.0904.

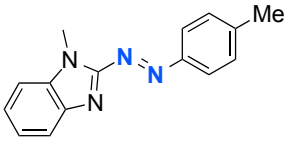
(*E*)-5-Methyl-3-(*p*-tolyldiazenyl)isoxazole (2bv)



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 8:2); yellow solid (29.2 mg, 58%); mp: 97.3–98.0 °C; R_f 0.30 (hexane/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 2.50 (s, 3H), 6.37 (s, 1H), 7.33 (d, 2H, J = 8.0 Hz), 7.89 (d, 2H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8, 21.6, 92.2, 123.6, 129.9, 143.7, 150.5, 171.0, 173.8; IR (ATR) ν 2926, 1726, 1602, 1470, 1153, 927, 823, 799 cm^{-1}; MS (EI): m/z (relative intensity, %) 201 ([M]$^+$, 26), 91

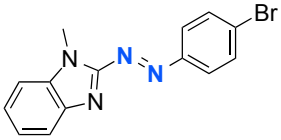
($[C_6H_4CH_3]^+$, 100), 119 ($[N_2C_6H_4CH_3]^+$, 13); HRMS (EI): *m/z* calcd for $C_{11}H_{11}N_3O$ (M) 201.0902, found 201.0900.

(*E*)-2-(4′-Tolylazo)-1-methylbenzimidazole (2bw)



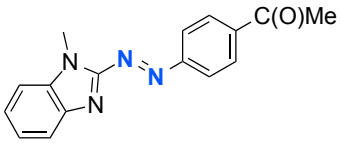
Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); orange solid (38.3 mg, 61%); mp 175.4–176.0 °C; R_f 0.18 (hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 4.21 (s, 3H), 7.35–7.42 (m, 4H), 7.49 (d, 1H, *J* = 7.2 Hz), 7.91 (d, 1H, *J* = 7.2 Hz), 8.04 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 29.6, 109.8, 121.7, 123.7, 123.8, 124.1, 129.8, 135.9, 141.9, 143.7, 151.3, 155.0; IR (ATR) *ν* 1600, 1481, 1331, 1148, 817, 734 cm^{-1}; MS (EI) *m/z* (relative intensity, %) 250 ($[M]^+$, 4), 91 ($[C_6H_4CH_3]^+$, 34), 201 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{14}N_4$ (M) 250.1218, found 250.1217.

(*E*)-2-(4′-Bromophenylazo)-1-methylbenzimidazole (2gw)



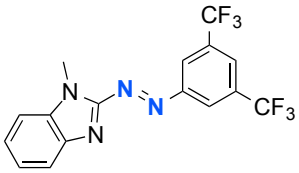
Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); orange solid (45.8 mg, 58%); mp: 205.8–206.2 °C; R_f 0.20 (hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (s, 3H), 7.37–7.53 (m, 3H), 7.71 (d, 2H, *J* = 8.8 Hz), 7.92 (d, 1H, *J* = 7.2 Hz), 8.01 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.8, 110.0, 122.0, 124.2, 124.7, 125.0, 127.5, 132.5, 136.1, 142.1, 151.8, 154.8; IR (ATR) *ν* 1491, 1329, 1146, 1063, 849, 816, 734 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 314 ($[M]^+$, 5), 287 (100); HRMS (EI): *m/z* calcd for $C_{14}H_{11}BrN_4$ (M) 314.0167, found 314.0168.

(*E*)-2-(4´-Acetylphenylazo)-1-methylbenzimidazole (2jw)



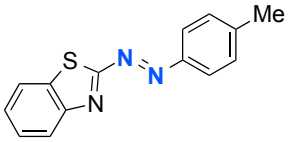
Purified by silica gel column chromatography (CH_2Cl_2/EtOAc 99:1 to 9:1); red solid (39.2 mg, 56%); mp: 228.1–228.8 °C; R_f 0.22 (CH_2Cl_2/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 4.19 (s, 3H), 7.37–7.48 (m, 3H), 7.49 (d, 1H, *J* = 8.0 Hz), 8.11 (d, 1H, *J* = 8.8 Hz), 8.15 (d, 2H, *J* = 8.8 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 29.9, 110.1, 122.2, 123.7, 124.4, 125.0, 129.3, 136.1, 139.3, 142.1, 154.7, 155.2, 197.2; IR (ATR) ν 1678, 1392, 1355, 1329, 1256, 824 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 278 ([M]$^+$, 7), 249 (100); HRMS (EI): *m/z* calcd for $C_{16}H_{14}N_4O$ (M) 278.1168, found 278.1166.

(*E*)-2-(3´,5'-Bis(trifluoromethyl)phenyl)-1-methylbenzimidazole (2jw)



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 8:2); orange solid (46.8 mg, 50%); mp: 194.7–195.2 °C; R_f 0.25 (hexane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (s, 3H), 7.40–7.49 (m, 2H), 7.51 (d, 1H, *J* = 7.6 Hz), 7.94 (d, 1H, *J* = 7.6 Hz), 8.06 (s, 1H), 8.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.1 (s), 110.3 (s), 122.4 (s), 122.8 (q, *J* = 271.7 Hz), 123.4 (q, *J* = 3.3 Hz), 124.8 (s), 125.0 (m), 125.6 (s), 132.9 (q, *J* = 33.7 Hz), 136.3(s), 142.1 (s), 153.1 (s), 154.3 (s); IR (ATR) ν 1369, 1278, 1168, 1120, 901 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 372 ([M]$^+$, 18), 213 ([$C_6H_4(CF_3)_2$]$^+$, 37), 343 (100); HRMS (EI): *m/z* calcd for $C_{16}H_{10}F_6N_4$ (M) 372.0810, found 372.0809.

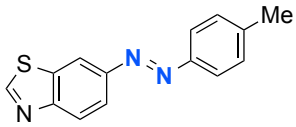
(*E*)-1-(Benzothiazol-2-yl)-2-*p*-tolyldiazene (2bx)



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); orange solid (53.4 mg, 72%); mp: 183.5–184.0 °C; R_f 0.40

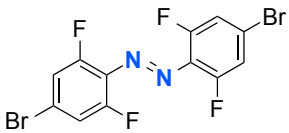
(hexane/EtOAc 9:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.30 (d, 2H, *J* = 8.1 Hz), 7.49 (m, 2H), 7.88 (dd, 1H, *J* = 1.1, 7.3 Hz), 7.98 (d, 2H, *J* = 8.1 Hz), 8.17 (dd, 1H, *J* = 1.4, 7.3 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.8, 122.3, 124.4, 124.8, 126.6, 127.3, 130.1, 134.3, 144.9, 149.8, 152.6, 175.9; IR (ATR) *ν* 1730, 1597, 1494, 1421, 1147, 815, 758, 723 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 253 ($[M]^+$, 14), 91 ($[C_6H_4CH_3]^+$, 100), 119 ($[N_2C_6H_4CH_3]^+$, 10); HRMS (EI): *m/z* calcd for $C_{14}H_{11}N_3S$ (M) 253.0674, found 253.0674.

(*E*)-6-(*p*-Tolyldiazenyl)benzothiazole (2by)



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); orange solid (27.8 mg, 44%); mp: 135.6–136.0 °C; R_f 0.38 (hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.32 (d, 2H, *J* = 8.0 Hz), 7.86 (d, 2H, *J* = 8.0 Hz), 8.12 (dd, 1H, *J* = 2.0, 8.8 Hz), 8.22 (d, 1H, *J* = 8.8 Hz), 8.17 (dd, 1H, *J* = 1.4, 7.3 Hz), 8.50 (d, 1H, *J* = 2.0 Hz), 9.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 117.0, 121.1, 123.0, 123.9, 129.8 (2), 141.9, 150.3, 150.6, 154.6, 156.1; IR (ATR) *ν* 3049, 1599, 1502, 1429, 1408, 1330, 1225, 846, 825 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 253 ($[M]^+$, 78), 91 ($[C_6H_4CH_3]^+$, 100), 134 ($[C_7H_4NS]^+$, 74); HRMS (EI): *m/z* calcd for $C_{14}H_{11}N_3S$ (M) 253.0674, found 253.0676.

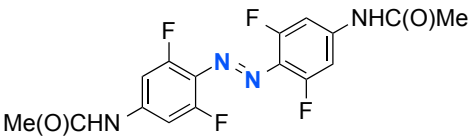
(*E*)-2,2′,6,6′-Tetrafluoro-4,4′-dibromoazobenzene (4aa)



Spectroscopic data were in agreement with those previously reported.[19b] Purified by silica gel column chromatography (hexane/EtOAc 95:5); red solid (63.9 mg, 62%); mp: 169.5–170.4 °C; R_f 0.48 (hexane/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, 4H, *J* = 1.2 Hz); IR (ATR) *ν* 3103, 3084, 1599, 1568, 1420, 1296, 1198, 1051, 874, 862, 839 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 412

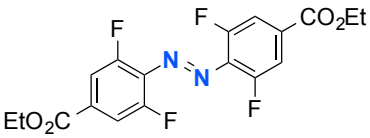
([M]$^+$, 46), 112 (100), 191 ([$C_6H_2BrF_2$]$^+$, 70); HRMS (EI): *m/z* calcd for $C_{12}H_4Br_2F_4N_2$ (M) 409.8677, found 409.8680.

(*E*)-2,2´,6,6´-Tetrafluoro-4,4´-diacetoazobenzene (4bb)



Spectroscopic data were in agreement with those previously reported.[19b] red solid (72.8 mg, 82%); mp: 362.8–364.0 °C; R_f 0.08 (hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, d_6-DMSO) δ 2.11 (s, 6H), 7.48 (d, 4H, *J* = 12.0 Hz), 10.63 (s, br, 2H); IR (ATR) *ν* 3302, 3271, 3121, 1678, 1599, 1539, 1420, 1371, 1348, 1265, 1150, 1053, 993, 841 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 368 ([M]$^+$, 98), 170 ([$C_8H_6F_2NO$]$^+$, 100), 198 ([$N_2C_8H_6F_2NO$]$^+$, 65); HRMS (EI): *m/z* calcd for $C_{16}H_{12}F_4N_4O_2$ (M) 368.0896, found 368.0895.

(*E*)-Diethyl-4,4´-(2,2´,6,6´-tetrafluoro)azobenzene dicarboxylate (4cc)



Spectroscopic data were in agreement with those previously reported.[19b] Purified by silica gel column chromatography (hexane/EtOAc 9:1); red solid (81.7 mg, 82%); mp: 145.8–146.0 °C; R_f 0.25 (hexane/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, 6H, *J* = 6.8 Hz), 4.43 (q, 4H, *J* = 6.8 Hz), 7.75 (dd, 4H, *J* = 1.6, 10.4 Hz); IR (ATR) *ν* 3375, 3098, 2978, 1721, 1574, 1435, 1330, 1236, 1053, 1018, 887, 767 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 398 ([M]$^+$, 47), 213 ([$N_2C_9H_7F_2O_2$]$^+$, 100); HRMS (EI): *m/z* calcd for $C_{18}H_{14}F_4N_2O_4$ (M) 398.0890, found 398.0891.

3-9. References and Notes

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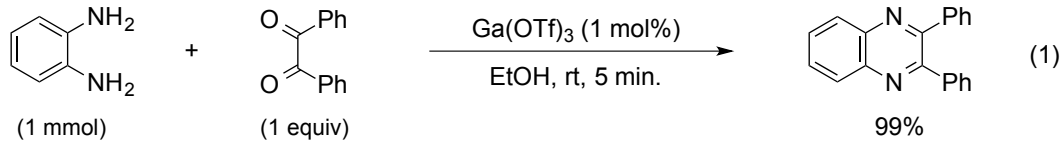
Chapter 4

Hypervalent Iodine(III)-Induced Oxidative [4+2] Annulation of *o*-Phenylenediamines and Eelctron-Deficient Alkynes: Direct Synthesis of Electron-Deficient Quinoxalines from Alkyne Substrates under Metal-Free Conditions

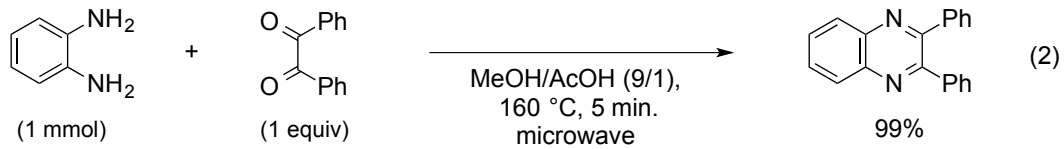
4-1. Introduction

As mentioned in the general introduction, in Chapter 4, hypervalent iodine(III)-induced oxidative annulation of *o*-phenylenediamines and electron-deficient alkynes leading to electron-deficient quinoxalines is described.

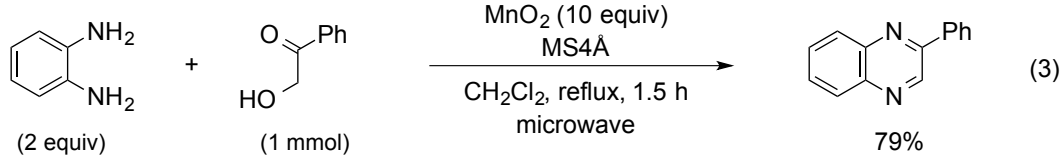
Quinoxalines constitute an important class of biologically active compounds, such as anticancer-, kinase inhibitor-, and anti-inflammatory agents.[1] Additionally, quinoxaline motif finds tremendous applications in materials science such as luminescent materials[2] and low-band-gap polymers.[3] Of the reported synthetic methods (Eqs 1–9),[4–12] the most widely used approach involves condensation of *o*-phenylenediamines with diaryl- or dialkyl α-dicarbonyl compounds (Scheme 1),[5] which are generally prepared by oxidation of upstream alkynes using environmentally-unfriendly heavy metal oxidants (*e.g.*, Mn,[13a] Ru,[13b] and Os[13c] salts) (Eqs 10 and 11). Recently, catalytic oxidation of alkynes have been developed (Eqs 12 and 13).[13d,13e]


NH2
NH2
(1 mmol)
+
O
Ph
O
Ph
(1 equiv)
Ga(OTf)3 (1 mol%)
EtOH, rt, 5 min.
N
Ph
N
Ph
99%

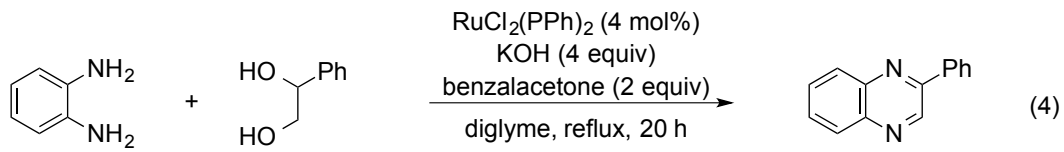
(1)


NH2
NH2
(1 mmol)
+
O
Ph
O
Ph
(1 equiv)
MeOH/AcOH (9/1),
160 °C, 5 min.
microwave
N
Ph
N
Ph
99%

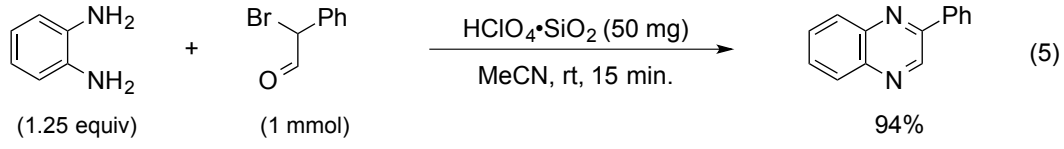
(2)


NH2
NH2
(2 equiv)
+
O
Ph
HO
(1 mmol)
MnO2 (10 equiv)
MS4Å
CH2Cl2, reflux, 1.5 h
microwave
N
Ph
N
79%

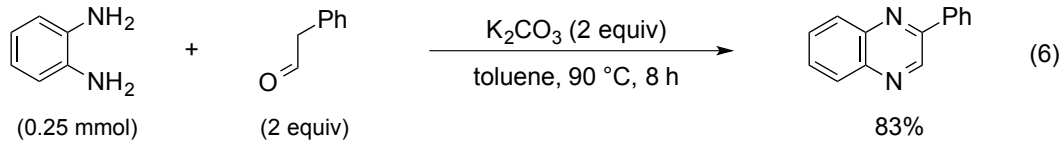
(3)


NH2
NH2
(1 mmol)
+
HO
Ph
HO
(2 equiv)
RuCl2(PPh)2 (4 mol%)
KOH (4 equiv)
benzalacetone (2 equiv)
diglyme, reflux, 20 h
N
Ph
N
82%

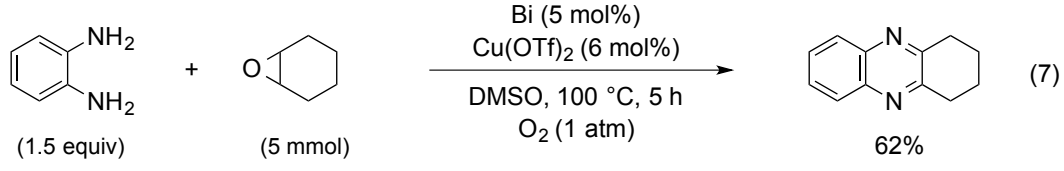
(4)


NH2
NH2
(1.25 equiv)
+
Br
Ph
O
(1 mmol)
HClO4•SiO2 (50 mg)
MeCN, rt, 15 min.
N
Ph
N
94%

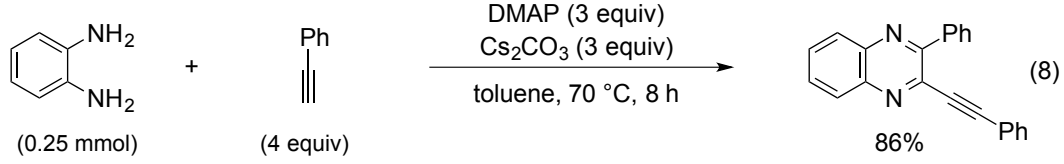
(5)


NH2
NH2
(0.25 mmol)
+
Ph
O
(2 equiv)
K2CO3 (2 equiv)
toluene, 90 °C, 8 h
N
Ph
N
83%

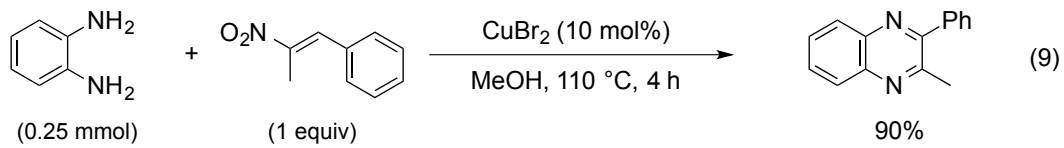
(6)


NH2
NH2
(1.5 equiv)
+
O
(5 mmol)
Bi (5 mol%)
Cu(OTf)2 (6 mol%)
DMSO, 100 °C, 5 h
O2 (1 atm)
N
N
62%

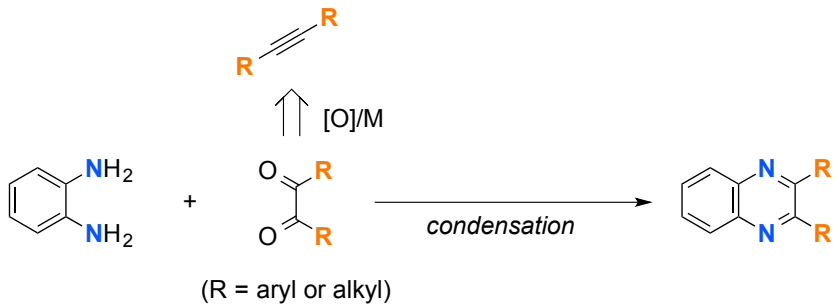
(7)


NH2
NH2
(0.25 mmol)
+
Ph
(4 equiv)
Cu(OAc)2•H2O (10 mol%)
DMAP (3 equiv)
Cs2CO3 (3 equiv)
toluene, 70 °C, 8 h
N
Ph
N
Ph
86%

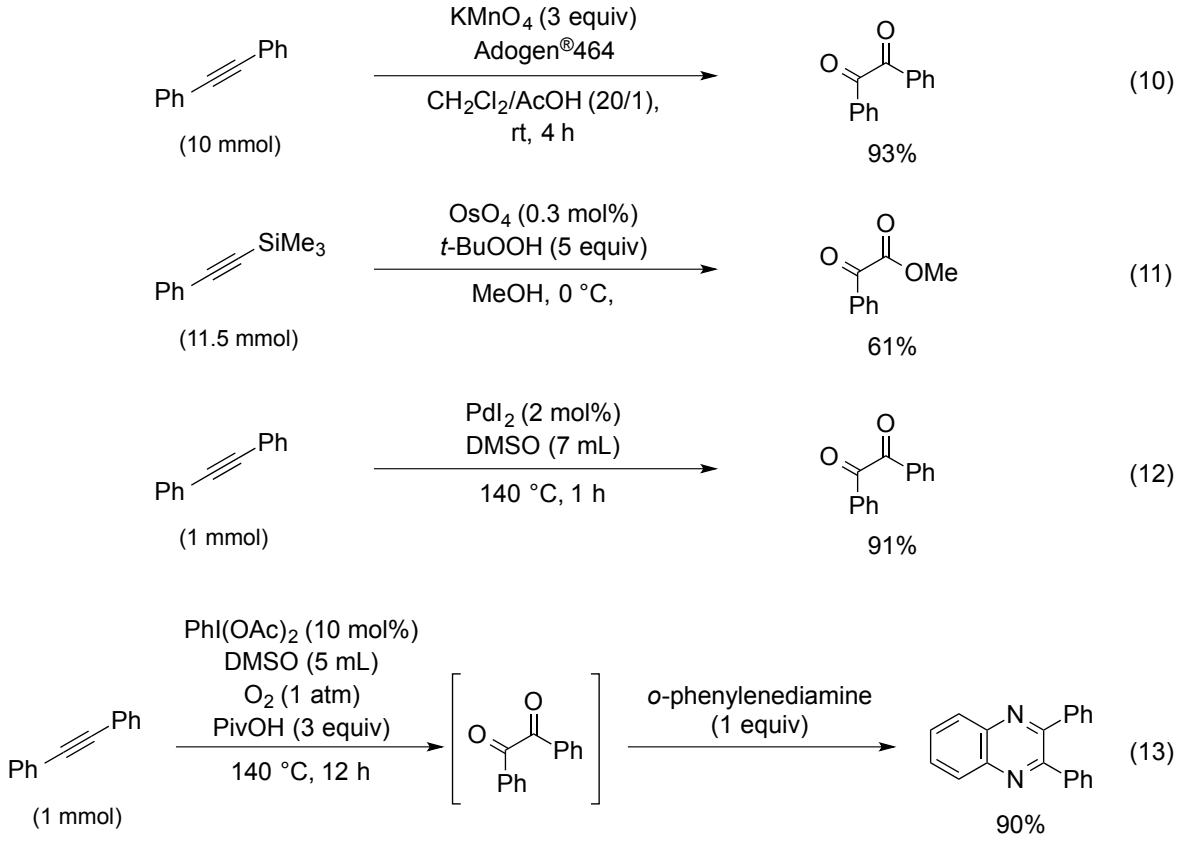
(8)


NH2
NH2
(0.25 mmol)
+
O2N
(1 equiv)
CuBr2 (10 mol%)
MeOH, 110 °C, 4 h
N
Ph
N
90%

(9)

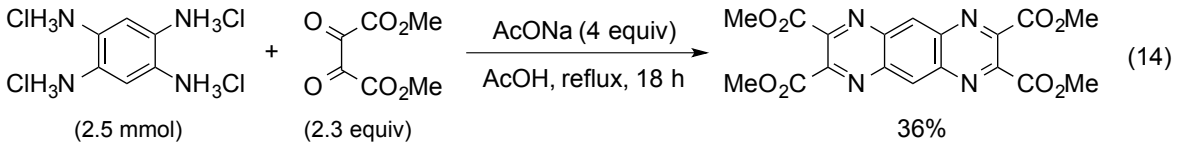


Scheme 1. Classical Approach to Quinoxalines



On the other hand, the synthetic methods of the quinoxalines bearing electron-withdrawing groups (DWGs, *e.g.*, –COR, $–CO_2R$, $–SO_2R$) have been poorly explored (Eqs 14 and 15),[14] although such compounds can serve as promising candidates for (opto)electronic materials[14a,15] and as versatile synthetic intermediates. This scarcity would be closely related to

the difficulty in oxidizing electron-deficient alkynes such as dimethyl acetylenedicarboxylate (DMAD), and in handling the extremely electrophilic diketo substrates. Taken these backgrounds together, the direct synthesis of electron-deficient quinoxalines from the corresponding alkyne substrates and diamines is a big challenge in organic synthesis.



(14)

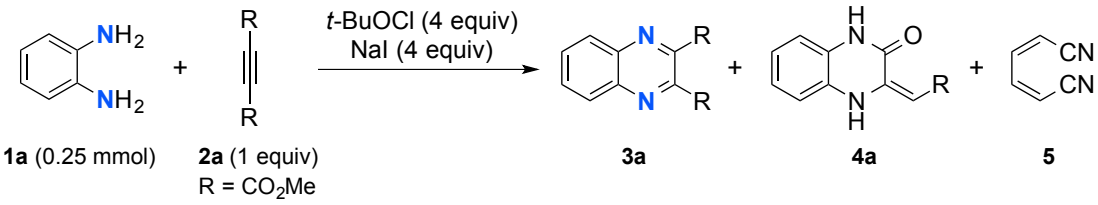
(15)

Results and Discussion

4-2. Screening Reaction Conditions and Iodine-Containing Oxidant

Based on the hypothesis mentioned in the general introduction, I attempted the oxidative annulation of *o*-phenylenediamine (**1a**) and DMAD (**2a**) as a model reaction (Table 1). However, contrary to my preliminary expectation, the results were disappointing. The treatment of an equimolar mixture of **1a** and **2a** with 4 equivalents of *t*-BuOI at –20 ˚C gave *cis*,*cis*-mucononitrile (**5**), which should be formed through oxidative dearomatization and the following C–C bond cleavage of the benzene core,[16] as a major product along with desired product **3a** as a minor. These results clearly suggested that *t*-BuOI is not an appropriate oxidant for the oxidative transformation, probably due to the rapid H–I exchange and dearomatization processes of **1a** prior to the Michael-addition.

Table 1. Screening of Reaction Conditions Using *t*-BuOI[a]



1a (0.25 mmol) **2a** (1 equiv) R = CO_2Me **3a** **4a** **5**

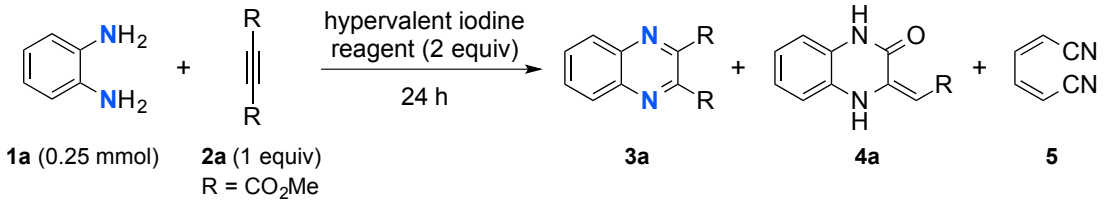
entry	solvent	temp. (°C)	time (h)	yield (%)[b]		
				3a	**4a**	**5**
1	MeCN	rt	3	34	–	27
2	THF	rt	3	5	–	12
3	DME	rt	3	9	–	18
4	THF	0	24	48	–	7
5	DME	0	24	57[c]	–	39[c]
6	MeCN	–20	24	13[c]	0	14[c]
7	THF	–20	24	12	0	64
8	DME	–20	24	2	0	33

[a] Reaction conditions: *o*-phenylenediamine (0.25 mmol), DMAD (0.25 mmol), *t*-BuOCl (1 mmol) and NaI (1 mmol) in solvent (3 mL). [b] ^{1}H NMR yields. [c] Isolated yield.

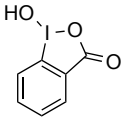
After extensive screening of iodine-containing reagents, I was delighted to find that the employment of phenyliodine diacetate (PIDA) was highly effective for the progression of the desired reaction (Table 2). It should be noted that protecting group-free phenylenediamines, which are usually labile to oxidation reactions, were applicable to the annulation. Specifically, PIDA and its derivatives have been utilized to develop privileged oxidative C–N bond forming reactions.[17] Nonetheless, to best of our knowledge, hypervalent iodine(III)-mediated oxidative annulation reaction that leads to quinoxaline, has not been reported to date.[18] Intriguingly, a significant solvent effect was observed (entries 1–5): as the polarity of solvent increased, the yield of **3a** was enhanced while by-product **4a**[19] decreased. The use of polar solvents also improved the reaction efficiencies. This phenomenon could be ascribed to the drastic change in the modes of hydrogen-bond (*intra- vs intermolecular*) operating in reaction intermediates (*vide infra*). Other representative hypervalent iodine(III) reagents such as phenyliodine bis(trifluoroacetate) (PIFA), iodosylbenzene, *o*-iodosyl benzoic acid, and PhI(OH)OTs

(Koser's reagent) were found ineffective for the annulation (entries 8–11). PIDA is indispensable for the annulation reaction (entry 12).

Table 2. Screening of Reaction Conditions Using Hypervalent Iodine(III) Reagent[a]



1a (0.25 mmol) **2a** (1 equiv) R = CO_2Me **3a** **4a** **5**

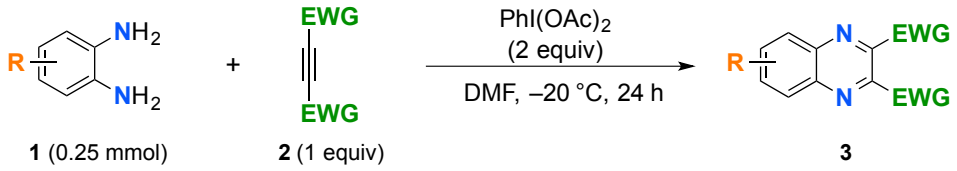
entry	hypervalent iodine reagent	solvent	temp. (°C)	yield (%)[b]		
				3a	**4a**	**5**
1	$PhI(OAc)_2$	THF	–20	63	18	0
2	$PhI(OAc)_2$	CH_2Cl_2	–20	5	40	0
3	$PhI(OAc)_2$	DME	–20	60[c]	4[c]	0
4	$PhI(OAc)_2$	toluene	–20	5	36	0
5	$PhI(OAc)_2$	DMF	–20	92[c]	4[c]	0
6	$PhI(OAc)_2$	DMF	0	72	10	0
7	$PhI(OAc)_2$	DMF	rt	45	28	trace
8	$PhI(OCOCF_3)_2$	DMF	–20	3	–	0
9	PhI=O	DMF	–20	0	–	0
10		DMF	–20	0	–	0
11	PhI(OH)OTs	DMF	–20	0	–	0
12	–	DMF	–20	0	21	0

[a] Reaction conditions: *o*-phenylenediamine (0.25 mmol), DMAD (0.25 mmol) and hypervalent iodine reagent (0.5 mmol) in solvent (3 mL). [b] ^1H NMR yields. [c] Isolated yield.

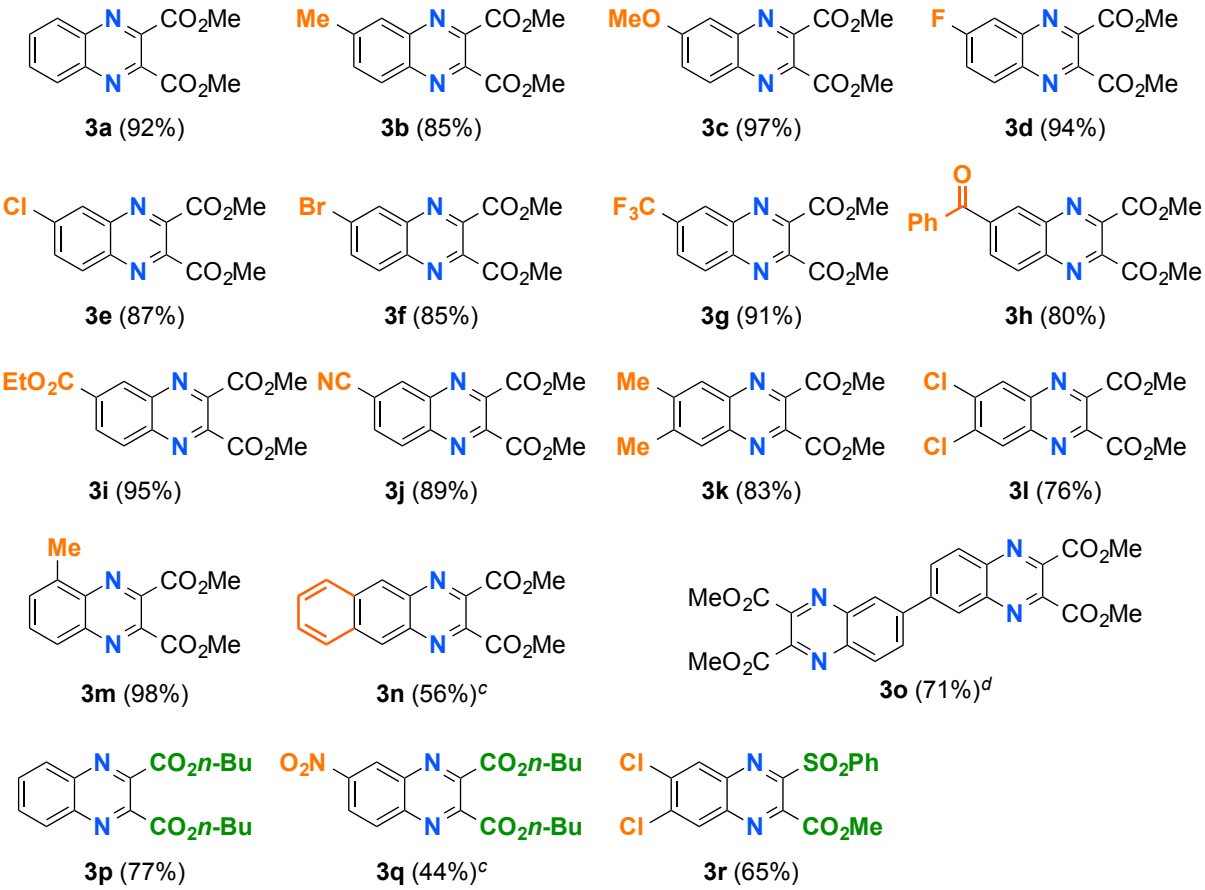
4-3. Scope of the Oxidative [4+2] Annulation

Having optimized the reaction conditions, the scope of the oxidative annulation was investigated (Table 3). Diamines bearing an electron-rich substituent reacted with DMAD to give the corresponding quionxalines **3b** and **3c** in high yields. Halo-substitution on the benzene ring did not significantly affect the product yields (**3d**–**3f**). Diamines having an electron-withdrawing functionality (CF_3, PhCO, CO_2Et, and CN) were also applicable to the reaction conditions, giving **3g**–**3j** in good to high yields. Multiply-substituted diamines afforded products **3k** and **3l**. Furthermore, quinoxaline **3m** was successfully obtained in excellent yield from sterically demanding 3-methyl *o*-phenylenediamine. Although the reaction with naphthalene-2,3-diamine required prolonged time, N-heteroacene **3n**, whose conjugation-extended family has been emerging as promising electron-transporting materials,[20] was obtained in 56% yield. Using the method, biquinoxanline **3o** was prepared in good yield. In respect to the scope of electron-deficient alkynes, dibutyl acetylenedicarboxylate (**2b**) was successfully applied to the reaction conditions to afford **3p** and **3q** in 77% and 44% yield, respectively. In addition, an unsymmetrical alkyne having an ester and a sulfonyl groups also successfully underwent the annulation to produce **3r** in good yield.

Table 3. Screening of Reaction Conditions Using Hypervalent Iodine(III) Reagent[a,b]



1 (0.25 mmol) **2** (1 equiv) **3**

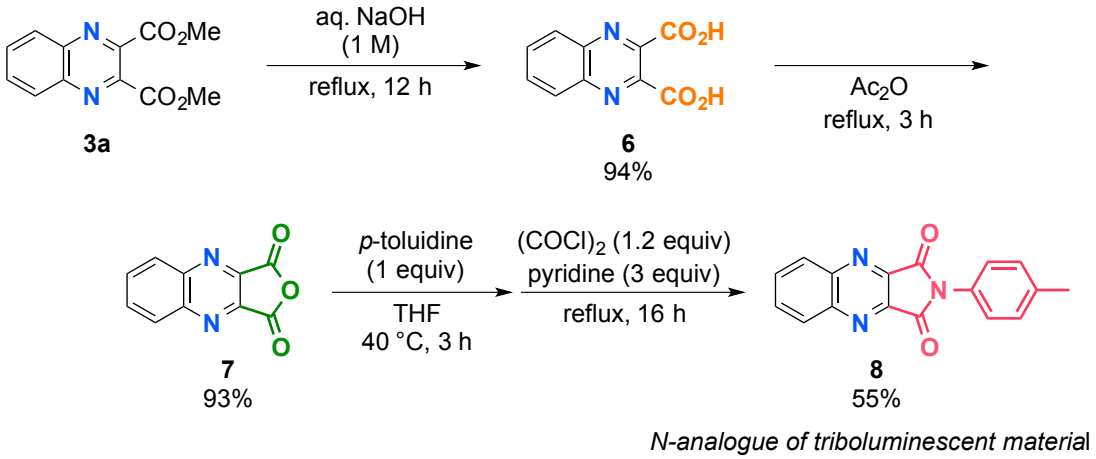


[a] Reaction conditions: **1** (0.25 mmol), **2** (0.25 mmol) and $PhI(OAc)_2$ (0.5 mmol) in DMF (3 mL) at –20 °C for 24 h. [b] The values in parentheses indicate the yields of quinoxaline products. [c] Reaction time: 48 h.[d] [1,1'-biphenyl]-3,3',4,4'-tetraamine (**1o**) (0.25mmol), **2a** (0.50 mmol) and $PhI(OAc)_2$ (1.0 mmol) were employed.

4-4. Synthetic Application of Quinoxaline

Taking advantage of the ester functionality, product **3a** was diversely derivatized into functionalized quinoxalines (Scheme 2). For example, diester groups of **3a** easily underwent hydrolysis to give dicarboxylic acid **6** in high yield, which was further efficiently converted to **7** by dehydration. Moreover, anhydride **7** was successfully transformed into imide-fused quinoxaline **8** by the condensation with *p*-toluidine, which is an N-analogue of

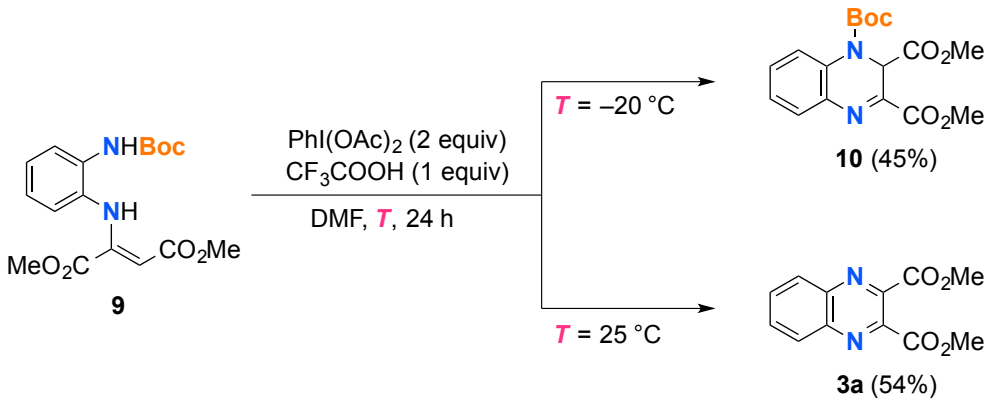
triboluminescent materials.[21] It is noted that such compounds are quite difficult to prepare by traditional condensation method starting from the corresponding diamine and dichloromaleimide substrates.[22]



Scheme 2. Derivatization of Quinoxaline **3a**

4-5. Mechanistic Studies

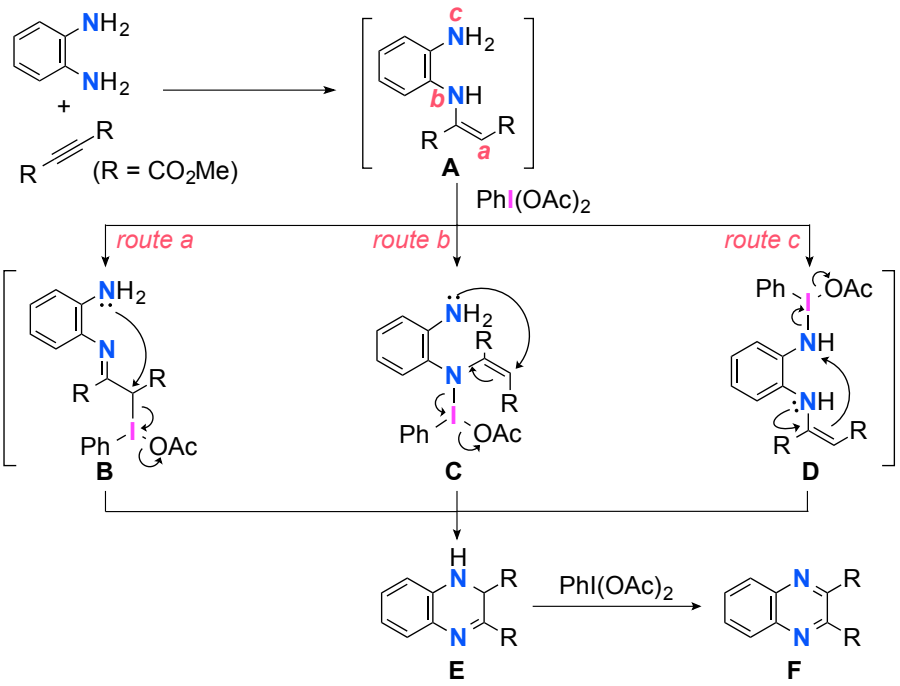
To investigate the reaction pathways of the oxidative [4+2] annulation, several experiments were conducted as follows: enamine **9**, which was readily prepared by the Michael-addition of *N*-Boc-protected *o*-phenylenediamine to DMAD,[19a] was treated with $PhI(OAc)_2$ in the presence of trifluoroacetic acid (Scheme 3). At –20 ˚C, **9** underwent oxidative cyclization to give *N*-Boc dihydro quinoxaline **10** in 45% yield (the upper equation), while enamine **9** was quantitatively recovered in the absence of the hypervalent iodine(III) reagent.[23] In contrast, at room temperature, quinoxaline **3a** was obtained in 54% yield (the lower equation), which was presumably produced through the deprotection of the *N*-Boc of **10** at room temperature and following oxidative aromatization. In conjunction with the fact that DMAD does not react with $PhI(OAc)_2$ in the absence of *o*-phenylenediamine, the most likely intermediate of the [4+2] annulation is the deprotected counterpart of the Michael-adduct **9** as preliminary assumed.



Scheme 3. Oxidative Cyclization of Enamine 9

On the basis of the experimental results and knowledge accumulated from the literature about hypervalent iodine(III)-mediated oxidative C–N bond forming reactions using enamine substrates,[24,25] three conceivable reaction pathways are illustrated in Scheme 4. The reaction would start with Michael addition of *o*-phenylenediamine to DMAD, forming enamine intermediate **A**, which has three possible reactive points when react with $PhI(OAc)_2$, namely, *β*-carbon of enamine (***a***),[24] enamine nitrogen (***b***),[25] and nitrogen on the benzene moiety (***c***).[26] Therefore, three chemical species should be extrapolated as the intermediates prior to cyclization: i) *α*-iodo (III) imine **B** generated through nucleophilic substitution on I (III)-center by the enamine *β*-carbon (*route a*); ii), iii) enamines **C** and **D** formed by the exchange between acidic N–H and an acetate of PIDA (*route b and c, respectively*). Successive cyclizative nucleophilic substitution on the iodine-attached sp^3-carbon (from **B**), on the enamine carbon in a pseudo-S_N2' manner (from **C**), or on the electrophilic N-center (from **D**) would provide common intermediate **E**. Oxidative aromatization of **E** with another equivalent of PIDA should lead to quinoxaline product **F**. Although there is no clear evidence at present, further consideration about the mechanistic aspects based on the literature should be beneficial. Ma and Lei reported an oxidative dimerization of aromatic amines using $PhI(OAc)_2$ to give azobenezenes.[26] However, no azo compounds were detected in this reaction systems,

suggesting that the pathway *via* intermediacy of **D** (*route c*) might be excluded. On one other hand, according to the reactivity of carbonyl-conjugated enamines (*i.e.*, enaminones),[27] electrophilic reagents, including iodine electrophiles such as BTMA•ICl_2,[28a] $I(Py)_2BF_4$,[28b] and $CF_3CH_2I(OH)(OTs)$,[28c] react exclusively at the enamine *β*-carbon. Taken together, although *routes b* and *c* and other possible pathway cannot be excluded completely, I believe that the most likely reaction pathway is *route a*.[29]

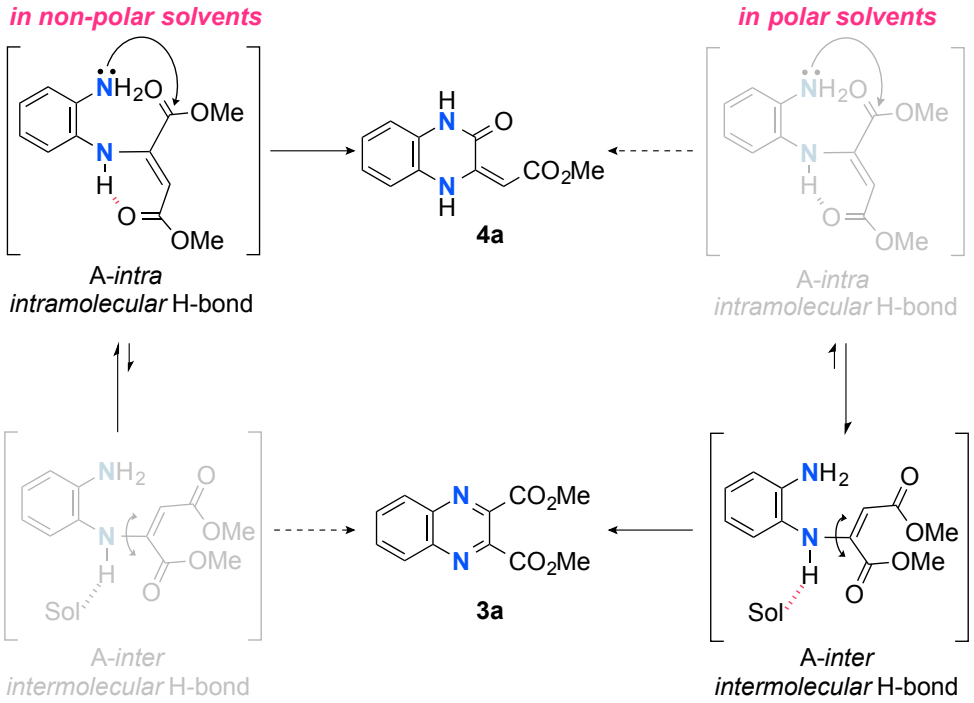


Scheme 4. Conceivable Reaction Pathways

4-6. Solvent Effect

Solvent effect also should be mentioned (Scheme 5). *Intramolecular* hydrogen-bond (H-bond) between enaminone N–H and conjugated carbonyl oxygen[30] would be preferentially operative (**A-*intra***) in non-polar solvents. However, in polar solvents such as DME and DMF, solvent molecules are capable of serving as a Lewis base to form *intermolecular* H-bond with enaminone N–H (**A-*inter***). Such *intermolecular* H-bond would not only allow for free-rotation

around the N–C single bond, but also enhance the anionic (nucleophilic) character of the *β*-carbon.[31] Therefore, the solvent effect can be summarized as follows: non-polar solvents would favor the *intramolecular* H-bond that locks the enamine moiety into the 6-membered plane (**A-*intra***), and thereby nucleophilic cyclization exclusively takes place at the carbonyl carbon to give **4a** as a major product. As the polarity of solvent increases, *intermolecular* H-bond would compete with *intramolecular* H-bond (**A-*inter***), suppressing the production of **4a** and promoting electrophilic attack by PIDA on the nucleophilicity-enhanced *β*-carbon.



Scheme 5. A Plausible Explanation for the Solvent Effect

4-7. Conclusion

In summary, a simple, efficient and metal-free synthesis of electron-deficient quinoxalines through oxidative annulation of *o*-phenylenediamines and alkynes has been developed. The synthetic methods would offer the great opportunities for the creation of new quinoxaline-based functional compounds, which would also serve as versatile building blocks.

4-8. Experimental Section

General experimental methods

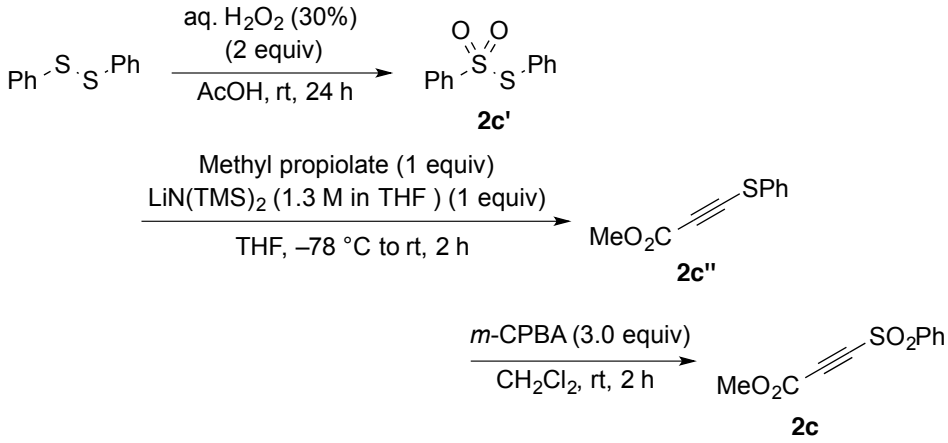
All reactions were carried out under an atmosphere of nitrogen. Dehydrated DMF was used as received. Melting points were determined on a Stanford Research Systems MPA100 OptiMelt Automated Melting Point System and are uncorrected. Infrared spectra were recorded on a SHIMADZU IRAffinity-1 FT-IR Spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JMTC-400/54/SS spectrometer (^{1}H NMR, 400 MHz; ^{13}C NMR, 100 MHz) using tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL JMS-DX303HF mass spectrometer. High-resolution mass spectra were obtained on a JEOL JMS-DX303HF mass spectrometer. Products were purified by chromatography on silica gel BW-300 (Fuji Silysia Chemical Ltd.). Analytical thin-layer chromatography (TLC) was performed on pre-coated silica gel glass plates (Merck silica gel 60 F_{254}, 0.25 mm thickness). Compounds were visualized with UV lamp or treatment with an ethanolic solution of phosphomolybdic acid followed by heating. Dimethyl acetylenedicarboxylate (DMAD) was purchased and distilled before using. *o*-Phenylenediamines and $PhI(OAc)_2$ were purchased and used as received.

Procedure for the preparation of alkyne 2b[32]

2a **2b**

To a *n*-butyl alcohol solution (40 mL) of *p*-toluenesulfonic acid (2.5 mmol), was added dimethyl acetylenedicarboxylate (25 mmol) at room temperature. The mixture was stirred under reflux for 6 h. *n*-Butyl alcohol was removed under vacuum to give the crude product. Purification by flash column chromatography on silica gel (eluent: ethyl acetate in hexane) gave alkyne **2b** (4.38 g, 77%).

Procedure for the preparation of alkyne 2c[33,34]



2c' **2c''** **2c**

To a suspension of diphenyl disulfide (100 mmol) in acetic acid (80 mL) was dropwise added 30% aqueous hydrogen peroxide (200 mmol) over 30 min. After stirring at room temperature for 24 h, the reaction mixture was cooled and filtered. Dilution of the filtrate with water (100 mL) caused phase-separation. The precipitates and oil layer were conbined and dissolved in chloroform (100 mL). The solution was washed with aqueous $NaHCO_3$ (sat. 100mL) and dried over Na_2SO_4 and concentrated under vacuum to give the crude product.

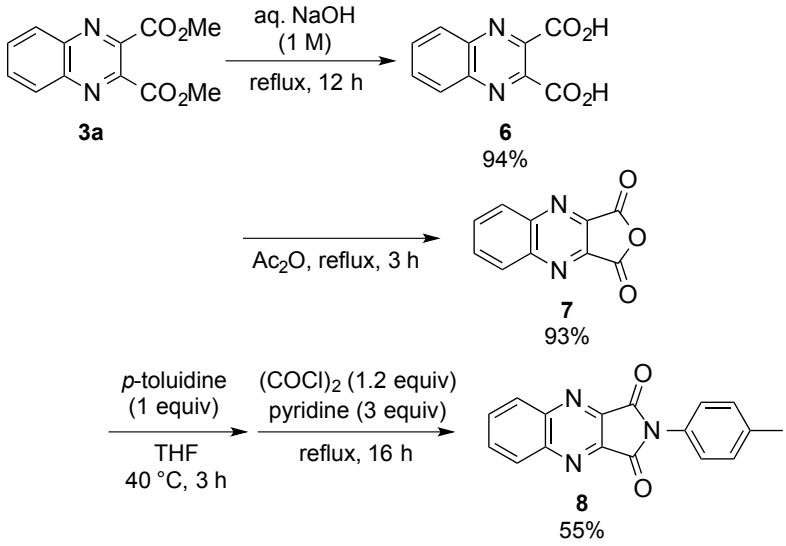
Purification by flash column chromatography on silica gel (hexane/EtOAc 99:1 to 7:3) gave **2c'** (21.4 g, 86%). The spectroscopic data for **2c'** was in agreement with the reported data.[35]

To a THF solution (32 mL) of methyl propiolate (16 mmol) was added slowly a solution of lithium bis(trimethylsilyl)amide (1.3M in THF, 16 mmol) at –78 °C. After 30 min of stirring at –78 °C, a THF solution (24 mL) of **2c'** (16 mmol) was added dropwise at –78 °C, and the resulting mixture was left to react at room temperature for 2 h. After completion of the reaction, the reaction mixture was quenched with aqueous NH_4Cl (sat. 30 mL) and extracted with Et_2O (50 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude product **2c''**, which was used without further purification. To a CH_2Cl_2 solution (45 mL) of 2**c''** was added a CH_2Cl_2 solution (45 mL) of *m*-CPBA (70%, 48 mmol). The reaction mixture was stirred at room temperature for 2 h and quenched with aqueous $Na_2S_2O_3$ (1.0 M, 50 mL) and the resulting solution was extracted with CH_2Cl_2 (50 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give the crude product. Purification by flash column chromatography on silica gel (eluent: ethyl acetate in hexane) gave alkyne **2c** (1.82 g, 50%).

Typical procedure for the oxidative [4+2] annulation

To a mixture of *o*-phenylenediamine (0.25 mmol) and alkyne (0.25 mmol) in DMF (3 mL), was added $PhI(OAc)_2$ (0.5 mmol, 161.0 mg) under N_2 atmosphere at –20 °C. The mixture was stirred in the dark for 24 h and quenched with aqueous $Na_2S_2O_3$ (1.0 M, 5 mL), and the resulting solution was extracted with CH_2Cl_2 (20 mL x 3). The combined organic extracts were washed with aqueous $NaHCO_3$ (sat., 10 mL), dried over Na_2SO_4, and concentrated under vacuum to give the crude product. Purification by flash column chromatography on silica gel (eluent: ethyl acetate in hexane) gave quinoxaline product (for example, compound **3a**: 56.6 mg, 92%).

Procedure for the derivatization of 3a into 6–8

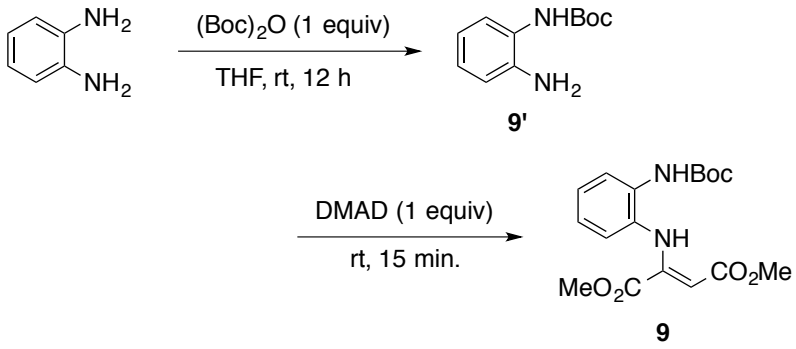


The mixture of quinoxaline **3a** (3 mmol) and aqueous NaOH (1 M, 45 mL) was stirred under reflux for 12 h before quenched with aqueous HCl (2 M, 30 mL). The mixture was extracted with EtOAc/MeOH = 9/1 (v/v), dried over Na_2SO_4, and concentrated under vacuum to give the crude product, which was washed with Et_2O and $CHCl_3$ to give **6** (614 mg, 94%).

Quinoxaline-2,3-dicarcoxylic acid (**6**) (1 mmol) was dissolved in acetic anhydride (1 mL) and the solution was heated at reflux for 3 h. The excess of acetic anhydride was distilled off. The crude was washed with water, Et_2O and $CHCl_3$ to give **7** (186 mg, 93%).

A solution of **7** (0.25 mmol) and *p*-toluidine (0.25 mmol) in THF (3 mL) was heated to 40 °C for 3 h. After cooling to room temperature, oxalyl chloride (0.3 mmol) and pyridine (0.75 mmol) were added, and the reaction mixture was stirred for 16 h under reflux. The solvent was evaporated to give the crude product. Purification by flash column chromatography on silica gel (eluent: CH_2Cl_2) gave imide **8** (39.8 mg, 55%).

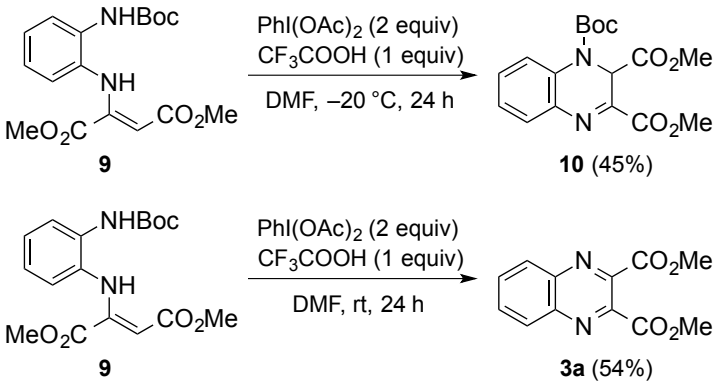
Procedure for the preparation of 9[36,19]



To a THF solution (15 mL) of *o*-phenylenediamine (100 mmol), was dropwise added di-*tert*-butyl dicarbonate (2 M in THF, 50 mL). The mixture was stirred at room temperature for 12 h. After the mixture was concentrated under vacuum, the resulting residue was diluted with hexane/EtOAc = 4/1 (v/v), and the precipitate was removed through filtration. The resulting solution was concentrated to give the crude product. Purification by flash column chromatography on silica gel (eluent: ethyl acetate in hexane) gave *N*-Boc protected phenylenediamine product **9'** (10.8 g, 52%).

The mixture of **9'** (10 mmol) and dimethyl acetylenedicarboxylate (10 mmol) was stirred at room temperature for 15 min. Purification by flash column chromatography on silica gel (eluent: ethyl acetate in hexane) gave product **9** (2.2 g, 62%).

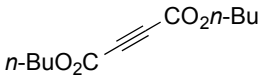
Procedure for the reaction of 9 with PIDA



To a mixture of **9** (0.25 mmol) and trifluoroacetic acid (0.25 mmol) in DMF (3 mL), was added $PhI(OAc)_2$ (0.5 mmol, 161.0 mg) under N_2 atmosphere at the temperature indicated. The mixture was stirred in the dark for 24 h and quenched with aqueous $Na_2S_2O_3$ (1.0 M, 5 mL), and the solution was extracted with CH_2Cl_2 (20 mL x 3). The combined organic extracts were washed with aqueous $NaHCO_3$ (sat., 10 mL), dried over Na_2SO_4, and concentrated under vacuum to give the crude product. Purification by flash column chromatography on silica gel (eluent: ethyl acetate in hexane) gave **10** or **3a**.

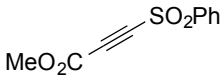
Spectra date of products

Dibutyl acetylenedicarboxylate (2b)[32]



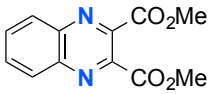
Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 9:1); Colorless oil; R_f 0.45 (hexane/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.2 Hz, 6H), 1.41 (tq, *J* = 7.2, 7.6 Hz, 4H), 1.68 (tt, *J* = 6.8, 7.6 Hz, 4H), 4.25 (t, *J* = 6.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 18.6, 29.9, 66.4, 74.3, 151.5; IR (ATR) *ν* 2963, 1721, 1244, 1059, 1036, 746 cm^{-1}; MS (CI): *m/z* (relative intensity, %) 227 ($[M]^+ + H^+$, 100), 171 (25); HRMS (CI): *m/z* calcd for $C_{12}H_{10}O_4$ (M) 227.1283, found 227.1285.

Methyl 2-(phenylsulfonyl)propiolate (2c)



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); Yellow oil; R_f 0.08 (hexane/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 7.64 (m, 2H), 7.77 (m, 1H), 8.03 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.8, 79.35, 79.42, 128.0, 129.7, 135.3, 139.6, 151.3; IR (ATR) *ν* 3066, 1724, 1448, 1435, 1348, 1242, 1165, 1086, 883, 742 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 224 ($[M]^+$, 48), 193 (14), 125 (100), 77 (99); HRMS (EI): *m/z* calcd for $C_{10}H_8O_4S$ (M) 224.0143, found 224.0141.

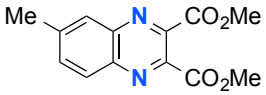
Dimethyl quinoxaline-2,3-dicarboxylate (3a)[14b]



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); Yellow solid (56.6 mg, 92%); mp: 132.6–133.0 °C; R_f 0.20 (hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (s, 6H), 7.96 (dd, *J* = 3.6, 6.8 Hz, 2H), 8.27 (dd, *J* = 3.6, 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.6, 129.8, 132.7, 141.3, 143.7, 165.1; IR (ATR) *ν* 2954, 1718, 1442, 1325, 1290, 1228, 1193, 1166, 1114, 954, 852, 781, 767 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 246 ($[M]^+$, 32), 215 ($[M]^+$ – OMe, 26), 188 ($[M]^+$ – CO_2Me +

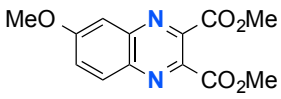
H^+, 31), 130 ([M]$^+$ – 2CO_2Me + 2H^+, 100); HRMS (EI): *m/z* calcd for $C_{12}H_{10}N_2O_4$ (M) 246.0641, found 246.0639.

Dimethyl 6-methylquinoxaline-2,3-dicarboxylate (3b)



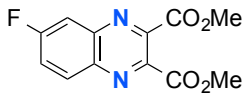
Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); Yellow solid (55.4 mg, 85%); mp: 84.4–85.4 °C; R_f 0.18 (hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65 (s, 3H), 4.09 (s, 6H), 7.77 (dd, *J* = 2.0, 8.8 Hz, 1H), 8.02 (s, 1H), 8.15 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 53.47, 53.53, 128.4, 129.3, 135.0, 135.1, 139.8, 141.5, 142.5, 144.0, 165.1, 165.3; IR (ATR) *ν* 2954, 1738, 1720, 1446, 1342, 1311, 1288, 1224, 1192, 1170, 1148, 1121, 1068, 858, 831, 810 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 260 ([M]$^+$, 43), 229 ([M]$^+$ – OMe, 19), 202 ([M]$^+$ – CO_2Me + H^+, 23), 144 ([M]$^+$ – 2CO_2Me + 2H^+, 100); HRMS (EI): *m/z* calcd for $C_{13}H_{12}N_2O_4$ (M) 260.0797, found 260.0800.

Dimethyl 6-methoxylquinoxaline-2,3-dicarboxylate (3c)



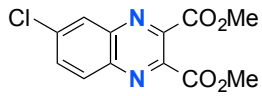
Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); Yellow solid (66.8 mg, 97%); mp: 113.3–113.7 °C; R_f 0.18 (hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 (s, 3H), 4.084 (s, 3H), 4.089 (s, 3H), 7.49 (s, 1H), 7.57 (d, *J* = 9.6 Hz, 1H), 8.13 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.49, 53.52, 56.1, 106.5, 126.6, 130.8, 137.7, 140.3, 143.5, 144.6, 163.1, 165.1, 165.6; IR (ATR) *ν* 296.1, 1739, 1726, 1616, 1491, 1450, 1440, 1413, 1287, 1222, 1198, 1182, 1121, 1067, 1018, 862, 837, 810 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 276 ([M]$^+$, 41), 245 ([M]$^+$ – OMe, 12), 218 ([M]$^+$ – CO_2Me + H^+, 7), 160 ([M]$^+$ – 2CO_2Me + 2H^+, 100); HRMS (EI): *m/z* calcd for $C_{13}H_{12}N_2O_5$ (M) 276.0746, found 276.0744.

Dimethyl 6-fluoroquinoxaline-2,3-dicarboxylate (3d)



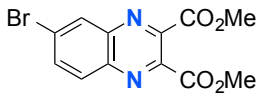
Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 8:2); Yellow solid (62.3 mg, 94%); mp: 88.3–89.0 °C; R_f 0.15 (hexane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.101 (s, 3H), 4.105 (s, 3H), 7.74 (m, 1H), 7.88 (dd, *J* = 2.4, 9.2 Hz, 1H), 8.29 (dd, *J* = 5.6, 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.6 (s), 53.8 (s), 113.3 (d, *J* = 22.2 Hz), 123.4 (d, *J* = 26.3 Hz), 132.3 (d, *J* = 10.7 Hz), 138.6 (s) 142.5 (d, *J* = 14.0 Hz), 142.7 (d, *J* = 2.3 Hz), 145.0 (s), 164.3 (d, J = 257.7 Hz), 164.8 (s), 165.0 (s); IR (ATR) ν 2953, 1715, 1721, 1449, 1298, 1200, 1179, 1115, 1064, 885, 856, 839, 826, 787 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 264 ([M]$^+$, 37), 233 ([M]$^+$ – OMe, 35), 206 ([M]$^+$ – CO_2Me + H$^+$, 32), 148 ([M]$^+$ – 2CO_2Me + 2H$^+$, 100); HRMS (EI): *m/z* calcd for $C_{12}H_9FN_2O_4$ (M) 264.0546, found 264.0545.

Dimethyl 6-chloroquinoxaline-2,3-dicarboxylate (3e)



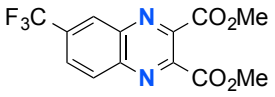
Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); Yellow solid (60.8 mg, 87%); mp: 93.5–94.4 °C; R_f 0.28 (hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (s, 6H), 7.88 (dd, *J* = 2.0, 8.8 Hz, 1H), 8.20 (d, *J* = 8.8 Hz, 1H), 8.25 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.70, 53.77, 128.6, 131.0, 133.8, 139.0, 139.8, 141.6, 143.5, 144.9, 164.7, 164.9; IR (ATR) ν 2956, 1736, 1721, 1443, 1289, 1279, 1234, 1220, 1153, 1124, 876, 856, 835, 816, 804 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 280 ([M]$^+$, 40), 249 ([M]$^+$ – OMe, 31), 222 ([M]$^+$ – CO_2Me + H$^+$, 29), 164 ([M]$^+$ – 2CO_2Me + 2H$^+$, 100); HRMS (EI): *m/z* calcd for $C_{12}H_9ClN_2O_4$ (M) 280.0250, found 280.0251.

Dimethyl 6-bromoquinoxaline-2,3-dicarboxylate (3f)



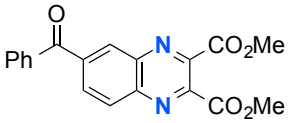
Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); Yellow solid (69.0 mg, 85%); mp: 99.6–100.3 °C; R_f 0.20 (hexane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (s, 6H), 8.02 (d, J = 8.8 Hz, 1H), 8.12 (d, J = 8.8 Hz, 1H), 8.44 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.7, 127.4, 131.0, 132.0, 136.3, 140.1, 141.8, 143.6, 144.8, 164.7, 164.8; IR (ATR) ν 2957, 1738, 1722, 1440, 1298, 1219, 1153, 1124, 1065, 813 cm^{-1}; MS (EI): m/z (relative intensity, %) 324 ([M]$^+$, 66), 293 ([M]$^+$ – OMe, 31), 266 ([M]$^+$ – CO_2Me + H$^+$, 52), 208 ([M]$^+$ – 2CO_2Me + 2H$^+$, 100); HRMS (EI): m/z calcd for $C_{12}H_9BrN_2O_4$ (M) 323.9746, found 323.9749.

Dimethyl 6-(trifluoromethyl)quinoxaline-2,3-dicarboxylate (3g)



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); Orange solid (71.2 mg, 91%); mp: 82.6–83.8 °C; R_f 0.21 (hexane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (s, 6H), 8.12 (d, J = 8.8 Hz, 1H), 8.40 (d, J = 8.8 Hz, 1H), 8.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.7 (s), 123.0 (q, J = 271.7 Hz), 127.7 (q, J = 4.9 Hz), 128.2 (q, J = 2.5 Hz), 131.1 (s), 134.0 (q, J = 32.9 Hz), 140.3 (s), 142.2 (s), 144.8 (s), 145.7 (s), 164.4 (s), 164.5 (s); IR (ATR) ν 2922, 1751, 1732, 1443, 1350, 1175, 1138, 1118, 1070, 1055, 902, 847 cm^{-1}; MS (EI): m/z (relative intensity, %) 314 ([M]$^+$, 34), 283 ([M]$^+$ – OMe, 32), 256 ([M]$^+$ – CO_2Me + H$^+$, 16), 198 ([M]$^+$ – 2CO_2Me + 2H$^+$, 100); HRMS (EI): m/z calcd for $C_{13}H_9F_3N_2O_4$ (M) 314.0514, found 314.0512.

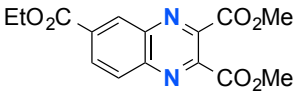
Dimethyl 6-benzoylquinoxaline-2,3-dicarboxylate (3h)



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 6:4); Yellow solid (69.6 mg, 80%); mp: 119.2–120.0 °C; R_f 0.10

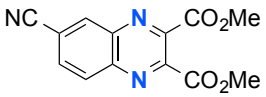
(hexane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (s, 3H), 4.12 (s, 3H), 7.54 (t, *J* = 8.0 Hz, 2H), 7.67 (m, 1H), 7.88 (dd, *J* = 1.2, 6.8 Hz, 2H), 8.38 (d, *J* = 8.8 Hz, 1H), 8.42 (d, *J* = 8.8 Hz, 1H), 8.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.8, 128.7, 130.1, 130.4, 132.4, 132.6, 133.3, 136.3, 140.5, 140.7, 142.9, 144.5, 145.5, 164.7, 164.9, 194.9; IR (ATR) *ν* 2976, 1740, 1726, 1659, 1445, 1296, 1229, 1150, 1117, 1065, 895, 849 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 350 ($[M]^+$, 29), 319 ($[M]^+$ – OMe, 18), 292 ($[M]^+$ – CO_2Me + H^+, 8), 234 ($[M]^+$ – 2CO_2Me + 2H^+, 78), 105 (PhCO, 100); HRMS (EI): *m/z* calcd for $C_{19}H_{14}N_2O_5$ (M) 350.0903, found 350.0905.

6-Ethyl 2,3-dimethyl quinoxaline-2,3,6-tricarboxylate (3i)



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 6:4); Yellow solid (75.6 mg, 95%); mp: 112.8–113.4 °C; R_f 0.10 (hexane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (t, *J* = 7.2 Hz, 3H), 4.11 (s, 6H), 4.49 (q, *J* = 7.2 Hz, 2H), 8.31 (d, *J* = 8.8 Hz, 1H), 8.54 (d, *J* = 8.8 Hz, 1H), 8.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 53.7, 61.9, 129.9, 132.08, 132.10, 134.0, 140.6, 143.0, 144.2, 145.4, 164.56, 164.77, 164.80; IR (ATR) *ν* 3001, 1751, 1719, 1443, 1342, 1294, 1231, 1146, 1120, 1169 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 318 ($[M]^+$, 26), 287 ($[M]^+$ – OMe, 19), 273 ($[M]^+$ – OEt, 28), 260 ($[M]^+$ – CO_2Me + H^+, 16), 245 ($[M]^+$ – CO_2Et, 2), 202 ($[M]^+$ – 2CO_2Me + 2H^+, 100); HRMS (EI): *m/z* calcd for $C_{15}H_{14}N_2O_6$ (M) 318.0852, found 318.0851.

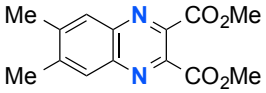
Dimethyl 6-cyanoquinoxaline-2,3-dicarboxylate (3j)



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 5:5); Yellow solid (60.2 mg, 89%); mp: 128.5–129.1 °C; R_f 0.20 (hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (s, 6H), 8.10 (dd, *J* = 2.0, 8.8 Hz, 1H),

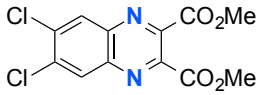
8.37 (d, J = 8.8 Hz, 1H), 8.63 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.8, 116.1, 117.0, 131.4, 133.0, 135.4, 140.3, 142.4, 145.3, 145.9, 164.2, 164.2; IR (ATR) ν 2955, 2230, 1732, 1443, 1307, 1227, 1167, 1125, 1067, 849, 814 cm^{-1}; MS (EI): m/z (relative intensity, %) 271 ([M]$^+$, 47), 240 ([M]$^+$ – OMe, 54), 213 ([M]$^+$ – CO_2Me + H$^+$, 24), 155 ([M]$^+$ – 2CO_2Me + 2H$^+$, 100); HRMS (EI): m/z calcd for $C_{13}H_9N_3O_4$ (M) 271.0593, found 271.0594.

Dimethyl 6,7-dimethylquinoxaline-2,3-dicarboxylate (3k)



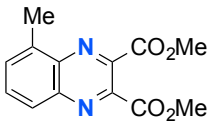
Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); Yellow solid (56.9 mg, 83%); mp: 118.0–119.1 °C; R_f 0.13 (hexane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (s, 6H), 4.08 (s, 6H), 7.99 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 53.5, 128.7, 140.4, 142.9, 144.1, 165.5; IR (ATR) ν 2957, 1732, 1717, 1445, 1348, 1296, 1225, 1203, 1136, 1076, 871 cm^{-1}; MS (EI): m/z (relative intensity, %) 274 ([M]$^+$, 35), 243 ([M]$^+$ – OMe, 14), 216 ([M]$^+$ – CO_2Me + H$^+$, 16), 158 ([M]$^+$ – 2CO_2Me + 2H$^+$, 100); HRMS (EI): m/z calcd for $C_{14}H_{14}N_2O_4$ (M) 274.0954, found 274.0952.

Dimethyl 6,7-dichloroquinoxaline-2,3-dicarboxylate (3l)



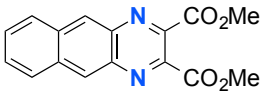
Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); Yellow solid (59.7 mg, 76%); mp: 152.9–153.9 °C; R_f 0.35 (hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (s, 6H), 8.37 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.7, 130.1, 137.8, 139.9, 144.5, 164.5; IR (ATR) ν 1740, 1437, 1221, 1069, 976, 881, 851, 810 cm^{-1}; MS (EI): m/z (relative intensity, %) 314 ([M]$^+$, 58), 283 ([M]$^+$ – OMe, 44), 256 ([M]$^+$ – CO_2Me + H$^+$, 32), 198 ([M]$^+$ – 2CO_2Me + 2H$^+$, 100); HRMS (EI): m/z calcd for $C_{12}H_8Cl_2N_2O_4$ (M) 313.9861, found 313.9858.

Dimethyl 5-methylquinoxaline-2,3-dicarboxylate (3m)



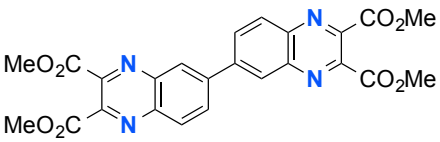
Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); Yellow solid (63.6 mg, 98%); mp: 111.9–112.8 °C; R_f 0.20 (hexane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (s, 3H), 4.087 (s, 3H), 4.095 (s, 3H), 7.76–7.84 (m, 2H), 8.10 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 53.4, 53.6, 127.7, 132.3, 132.6, 138.7, 140.8, 141.5, 142.3, 143.5, 165.1, 165.8; IR (ATR) *ν* 2959, 1744, 1719, 1225, 1167, 1134, 1092, 1032, 831, 797, 779 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 260 ([M]$^+$, 100), 229 ([M]$^+$ – OMe, 43), 202 ([M]$^+$ – CO_2Me + H$^+$, 29), 144 ([M]$^+$ – 2CO_2Me + 2H$^+$, 87); HRMS (EI): *m/z* calcd for $C_{13}H_{12}N_2O_4$ (M) 260.0797, found 260.0796.

Dimethyl benzo[*g*]quinoxaline-2,3-dicarboxylate (3n)



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); Orange solid (41.3 mg, 56%); mp: 169.8–170.9 °C; R_f 0.23 (hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (s, 3H), 7.67 (dd, *J* = 3.2, 6.4 Hz, 2H), 8.15 (dd, *J* = 3.2, 6.4 Hz, 2H), 8.31 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.6, 128.3, 128.8, 129.0, 135.2, 136.8, 143.8, 165.2; IR (ATR) *ν* 3030, 1736, 1719, 1439, 1202, 1142, 1072, 883, 872, 752 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 296 ([M]$^+$, 100), 265 ([M]$^+$ – OMe, 9), 238 ([M]$^+$ – CO_2Me + H$^+$, 5), 180 ([M]$^+$ – 2CO_2Me + 2H$^+$, 83); HRMS (EI): *m/z* calcd for $C_{16}H_{12}N_2O_4$ (M) 296.0797, found 296.0793.

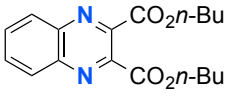
Tetramethyl [6,6'-biquinoxaline]-2,2',3,3'-tetracarboxylate (3o)



Purified by silica gel column chromatography ($CHCl_3$/MeOH 99:1 to 95:5); Brown solid (86.7 mg, 71%); dec: 225.0–225.5 °C; R_f 0.50 ($CHCl_3$/MeOH 95:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13

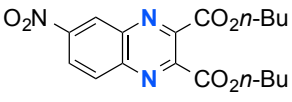
(s, 12H), 8.35 (dd, *J* = 2.0, 8.8 Hz, 2H), 8.44 (d, *J* = 8.8 Hz, 2H), 8.64 (d *J* = 2.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.8, 128.3, 131.0, 132.0, 141.2, 141.6, 142.9, 144.1, 144.8, 165.0; IR (ATR) *ν* 1726, 1437, 1221, 1132, 1068, 812 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 490 ([M]$^+$, 71), 459 ([M]$^+$ – OMe, 13), 432 ([M]$^+$ – CO_2Me + H$^+$, 3), 374 ([M]$^+$ – 2CO_2Me + 2H$^+$, 100); HRMS (EI): *m/z* calcd for $C_{24}H_{18}N_4O_8$ (M) 490.1125, found 490.1123.

Dibutyl quinoxaline-2,3-dicarboxylate (3p)



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); Yellow oil (63.8 mg, 77%); R_f 0.30 (hexane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, *J* = 7.2 Hz, 6H), 1.49 (tq, *J* = 7.2, 7.6 Hz, 4H), 1.83 (tt, *J* = 7.2, 7.6 Hz, 4H), 4.50 (t, *J* = 7.2 Hz, 4H), 7.93 (dd, *J* = 3.6, 6.4 Hz, 2H), 8.26 (dd, *J* = 3.6, 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 18.9, 30.3, 66.6, 129.7, 132.3, 141.2, 144.1, 164.8; IR (ATR) *ν* 2961, 2934, 1749, 1722, 1466, 1331, 1234, 1174, 1132, 1062, 764 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 330 ([M]$^+$, 24), 202 (100), 130 ([M]$^+$ – 2CO_2Bu + 2H$^+$, 77); HRMS (EI): *m/z* calcd for $C_{18}H_{22}N_2O_4$ (M) 330.1580, found 330.1577.

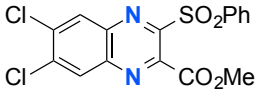
Dibutyl 6-nitroquinoxaline-2,3-dicarboxylate (3q)



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); Red oil (41.2 mg, 44%); R_f 0.35 (hexane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (m, 6H), 1.50 (m, 4H), 1.84 (m, 4H), 4.52 (t, *J* = 6.8 Hz, 4H), 8.43 (d, *J* = 9.2 Hz, 1H), 8.69 (dd, *J* = 2.4, 9.2 Hz, 1H), 9.16 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 19.0, 30.3, 30.4, 67.08, 67.09, 125.6, 125.9, 131.6, 140.3, 143.4, 145.9, 146.9, 149.2, 163.9, 164.0; IR (ATR) *ν* 2960, 2935, 1742, 1728, 1533, 1348, 1219, 1159, 1116, 1064 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 375 ([M]$^+$, 33), 247 (100), 175 ([M]$^+$ – 2CO_2Bu + 2H$^+$,

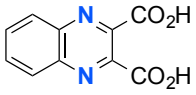
56); HRMS (EI): *m/z* calcd for $C_{18}H_{21}N_3O_6$ (M) 375.1430, found 375.1432.

Butyl 6,7-dichloro-3-(phenylsulfonyl)quinoxaline-2-carboxylate (3r)



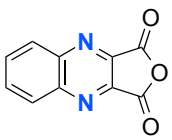
Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); Red solid (64.8 mg, 65%); dec: 133.0–134.8 °C; R_f 0.43 (hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (s, 3H), 7.58–7.71 (m, 3H), 8.15 (d, *J* = 8.0 Hz, 2H), 8.26 (s, 1H), 8.30, (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.0, 129.2, 129.6, 129.8, 130.2, 143.6, 137.5, 138.1, 139.1, 139.4, 139.9, 144.7, 151.8, 164.4; IR (ATR) ν 1754, 1441, 1325, 1159, 1138, 1085, 1043, 882, 849, 733 cm^{-1}; MS (FAB): *m/z* (relative intensity, %) 397 ($[M]^+ + H^+$, 10), 307 (24), 154 (100), 136 (87); HRMS (FAB): *m/z* calcd for $C_{16}H_{12}Cl_2N_2O_4S$ (M) 396.9817, found 396.9818.

Quinoxaline-2,3-dicarcoxylic acid (6)



Purple solid; dec: 188.6–188.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (dd, *J* = 3.2, 6.4 Hz, 2H), 8.22 (dd, *J* = 3.2, 6.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 129.3, 132.7, 140.5, 145.1, 166.1; IR (ATR) ν 3028, 2554, 1682, 1474, 1275, 1240, 1169, 1063, 906, 781, 770, 742 cm^{-1}; MS (FAB): *m/z* (relative intensity, %) 219 ($[M]^+ + H^+$, 33), 154 (100), 136 (77); HRMS (FAB): *m/z* calcd for $C_{10}H_7N_2O_4$ (M) 219.0406, found 219.0410.

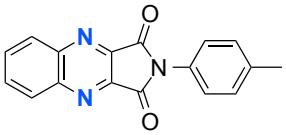
Quinoxaline-2,3-dicarcoxylic acid anhydride (7)



Brown solid; dec: 250.5–251.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (dd, *J* = 3.6, 6.8 Hz, 2H), 8.47 (dd, *J* = 3.6, 6.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 130.8, 134.5, 143.3, 144.9, 159.9; IR (ATR) ν 1876, 1788, 1647, 1585, 1368,

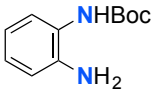
1177, 1103, 927, 887, 775 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 200 ($[M]^+$, 40), 156 (58), 128 (100); HRMS (EI): *m/z* calcd for $C_{10}H_4N_2O_3$ (M) 200.0222, found 200.0220.

2-(*p*-Tolyl)-1*H*-pyrrolo[3,4-*b*]quinoxaline-1,3(2*H*)-dione (8)



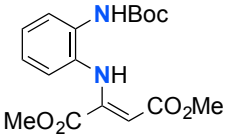
Purified by silica gel column chromatography (CH_2Cl_2); Yellow solid; dec: 374.4–375.5 °C; R_f 0.55 (CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 8.06 (dd, *J* = 3.6, 5.4 Hz, 2H), 8.48 (dd, *J* = 3.6, 5.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.8, 127.0, 128.8, 129.5, 130.6, 133.1, 138.3, 143.0, 146.3, 163.6; IR (ATR) ν 3069, 2918, 1788, 1720, 1510, 1379, 1143, 1117, 1089, 885, 795, 779 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 289 ($[M]^+$, 100), 245 (13), 128 (24); HRMS (EI): *m/z* calcd for $C_{17}H_{11}N_3O_2$ (M) 289.0851, found 289.0850.

***tert*-Butyl (2-aminophenyl)carbamate (9')**[35]



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 5:5); Colorless solid; mp: 112.3–113.8 °C; R_f 0.13 (hexane/EtOAc 8:2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 9H), 3.73 (br, s, 2H), 6.37 (br, s, 1H), 6.72–6.78 (m, 2H), 6.97 (t, *J* = 7.2 Hz, 1H), 7.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 80.4, 117.5, 119.4, 124.7, 126.0 (2C), 139.9, 153.8; IR (ATR) ν 3354, 1678, 1516, 1491, 1456, 1288, 1254, 1153, 1055, 748 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 208 ($[M]^+$, 16), 152 ($[M]^+ - C_4H_9 + H^+$, 57), 108 ($[M]^+$ – Boc + H^+, 100); HRMS (EI): *m/z* calcd for $C_{11}H_{16}N_2O_2$ (M) 208.1212, found 208.1211.

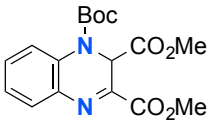
Dimethyl 2-((2-((*tert*-butoxycarbonyl)amino)phenyl)amino)fumarate (9)



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); Yellow solid; mp: 80.2–81.0 °C; R_f 0.40 (hexane/EtOAc 7:3); ^1H NMR

(400 MHz, $CDCl_3$) δ 1.53 (s, 9H), 3.59 (s, 3H), 3.76 (s, 3H), 5.59 (s, 1H), 6.83–6.96 (m, 3H), 7.17 (m, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 9.05 (br, s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 51.0, 52.4, 80.4, 95.2, 120.4, 123.0, 124.2, 126.5, 130.5, 133.2, 149.5, 152.6, 163.9, 169.4; IR (ATR) ν 3377, 2970, 1740, 1721, 1670, 1612, 1595, 1516, 1437, 1363, 1271, 1217, 1143, 1022, 777, 764 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 350 ($[M]^+$, 11), 294 ($[M]^+ - C_4H_9 + H^+$, 12), 250 ($[M]^+$ – Boc + H^+, 24), 191 ($[M]^+$ – Boc – CO_2Me + H^+, 98), 159 (92), 57 (100); HRMS (EI): *m/z* calcd for $C_{17}H_{22}N_2O_6$ (M) 350.1478, found 350.1474.

1-(*tert*-Butyl) 2,3-dimethyl quinoxaline-1,2,3(2*H*)-tricarboxylate (10)



Purified by silica gel column chromatography (hexane/EtOAc 99:1 to 7:3); Colorless solid; mp: 110.6–111.3 °C; R_f 0.19 (hexane/EtOAc 8:2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.57 (s, 9H), 3.64 (s, 3H), 4.03 (s, 3H), 6.47 (br, s, 1H), 7.18 (m, 1H), 7.37 (m, 1H), 7.61 (m, 1H), 7.88 (br, s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 51.3, 53.0, 53.5, 83.5, 122.7, 124.6, 129.0, 129.2, 130.4, 135.4, 150.1, 151.6, 163.3, 167.2; IR (ATR) ν 2959, 1726, 1712, 1476, 1440, 1367, 1338, 1269, 1226, 1157, 1123, 1010, 870, 799, 770, 754 cm^{-1}; MS (EI): *m/z* (relative intensity, %) 348 ($[M]^+$, 3), 289 ($[M]^+$ – CO_2Me, 2), 247 ($[M]^+$ – Boc, 2), 189 ($[M]^+$ – Boc – CO_2Me + H^+, 100), 57 (54); HRMS (EI): *m/z* calcd for $C_{17}H_{20}N_2O_6$ (M) 348.1321, found 348.1325.

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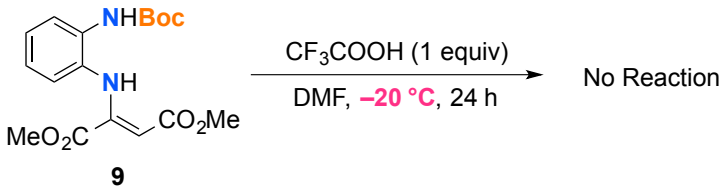

9

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Conclusion

The present thesis deals with the development of novel synthetic methods utilizing mono- or trivalent iodine reagent. The results obtained through the studies described in this thesis are summarized as follows:

Chapter 1 described the development of a novel generation method for nitrile oxides from aldoximes using *t*-BuOI and a synthesis of isoxazolines and isoxazoles by 1,3-dipolar cycloaddition to dipolarophiles. This efficient and simple method was applicable to a wide range of aldoximes and dipolarophiles under mild conditions. This is the first report of a method for the generation of nitrile oxides using an electrophilic iodinating reagent.

In Chapter 2, cyclizative atmospheric CO_2 fixation by unsaturated amines with *t*-BuOI leading to cyclic carbamates was described. This simple and metal/base-free method has a broad scope in terms of both allyl and propargyl amines, thus allowing access to a wide range of five- or six-membered cyclic carbamates. Moreover, taking advantage of iodo substituents

attached to sp^3- and sp^2-hybridized carbon atoms, the short-step preparation of 3-amino-5-morpholinomethyl-2-oxazolidinone (AMOZ) was accomplished starting from cyclic carbmate prepared from 1-amino-2-propene.

Chapter 3 described that *t*-BuOI is found to be a versatile reagent for the synthesis of symmetric and unsymmetric aromatic azo compounds through an oxidative dimerization of aromatic amines having high functional-group tolerance under metal-free and extremely mild conditions. Unlike precedent methods, this efficient, low energy-consuming and straightforward methodology allowed us easy access to diverse azobenzenes including heteroaromatic azo compounds, which would have high degree of potential for the use as various functional molecules. Since it is difficult to synthesize unsymmetric aromatic azo compounds bearing two electron-deficient aromatic rings by conventional methods, the first synthesis of these series of azobenzens clearly highlights the advantage of this method. Furthermore, spectroscopic studies, such as ^1H, ^{13}C, ^{15}N NMR and ESI-MS analyses indicate the involvement of an *N*,*N*-diiodoanilines as the key intermediate in the oxidative reaction.

In Chapter 4, $PhI(OAc)_2$-induced oxidative [4+2] annulation of *o*-phenylenediamines and electron-deficient alkynes leading to electron-deficient quinoxlines was described. Various functional groups are compatible in this annulation. Because there is no report for the synthesis of electron-deficient quinoxalines except this methodology, it would offer the great opportunities for the creation of new quinoxaline-based functional compounds, which would also serve as versatile building blocks.

The study on the unique reactivity of *t*-BuOI, that is powerful iodinating reagent for substrates bearing acidic hydrogen atoms to generate key reactive species having heteroatom-iodine bonds, contributes to the developments of a new generation method for nitrile oxides from aldoximes, an atmospheric CO_2 fixation by unsaturated amines and a synthetic method

for symmetric and unsymmetric aromatic azo compounds through oxidative dimerization of aromatic amines in Chapter 1 to 3. Because these reactions were conducted smoothly by only utilizing *t*-BuOI, this point highlights the superiority of the unique reagent, *tert*-butyl hypoiodite. The development in Chpter 4 provide a new synthetic method for electron-deficient quinoxalines through oxidative [4+2] of *o*-phenylenediamines and electron-deficient alkynes using hypervalent iodine(III) reagent.

The findings obtained through this study as mentioned above should give a significant milestone of synthetic organic chemistry.

List of Publications

The content of this thesis has been published in the following papers.

1) Generation of Nitrile Oxides from Oximes Using *t*-BuOI and Their Cycloaddition
Satoshi Minakata, Sota Okumura, Toshiki Nagamachi, Youhei Takeda
Org. Lett. **2011**, *13*, 2966-2969.

2) Cyclizative Atmospheric CO_2 Fixation by Unsaturated Amines with *t*-BuOI Leading to Cyclic Carbamates
Youhei Takeda, Sota Okumura, Saori Tone, Itsuro Sasaki, Satoshi Minakata
Org. Lett. **2012**, *14*, 4874-4877.

3) Oxidative Dimerization of Aromatic Amines using *t*BuOI: Entry to Unsymmetric Aromatic Azo Compounds
Youhei Takeda, Sota Okumura, Satoshi Minakata
Angew. Chem., Int. Ed. **2012**, *51*, 7804-7808.

4) A Practical Synthesis of Azobenzenes through Oxidative Dimerization of Aromatic Amines Using *tert*-Butyl Hypoiodite
Youhei Takeda, Sota Okumura, Satoshi Minakata
Synthesis **2013**, *45*, 1029-1033.

5) Oxidative Dimerization of (Hetero)aromatic Amines Utilizing *t*-BuOI Leading to (Hetero)aromatic Azo Compounds: Scope and Mechanistic Studies
Sota Okumura, Chun-Hsuan Lin, Youhei Takeda, Satoshi Minakata
J. Org. Chem. **2013**, *78*, 12090-12105.

6) Hypervalent iodine(III)-induced oxidative [4+2] annulation of *o*-phenylenediamines and electron-deficient alkynes: direct synthesis of quinoxalines from alkyne substrates under metal-free conditions
Sota Okumura, Youhei Takeda, Kensuke Kiyokawa, Satoshi Minakata
Chem. Commun. **2013**, *49*, 9266-9268.

List of Supplementary Publication

1) Hypervalent Iodine Mediated Oxidative Amination of Allenes
Nibadita Purkait, Sota Okumura, José A. Souto, Kilian Muñiz
Org. Lett. **2014**, *16*, 4750-4753.

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Publication: Organic Letters

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Title: Oxidative Dimerization of (Hetero)aromatic Amines Utilizing t-BuOI Leading to (Hetero)aromatic Azo Compounds: Scope and Mechanistic Studies

Author: Sota Okumura, Chun-Hsuan Lin, Youhei Takeda, et al

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Sota Okumura