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SYNTHESIS OF 8-OXA-2-AZABICYCLO[3.2.1]OCTANE USING A 1,3-DIPOLAR CYCLOADDITION REACTION

Kazuhiro Higuchi,* Yoshiki Matsubayashi, Takuma Sakurai, Motoki Ito, and Shigeo Sugiyama

Meiji Pharmaceutical University, 2-522-1 Noshio, Kiyose, Tokyo 204-8588, E-mail: khiguchi@my-pharm.ac.jp

Abstract – Herein, we report the application of 1,3-dipolar cycloaddition reaction toward the synthesis of a variety of 8-oxa-2-azabicyclo[3.2.1]octane compounds, the core structure of atkamine. The target compounds were obtained using a combination of a vinyl ether and carbonylylide, which was generated from a diazo compound and rhodium catalyst, in the presence of a Lewis acid.

INTRODUCTION

A large number of unique molecules with novel skeletons and important biological activities have been discovered from marine organisms, and have great potential as novel lead compounds for drug discovery. Since the late 1980s, a number of pyrroloiminoquinone alkaloids have been isolated and characterized (Figure 1), which show inhibitory activity against DNA topoisomerase II.[1] For example, discorhabdin A (**1**) exhibits cytotoxicity against L5178Y and P388 mouse leukemia cells, and makaluvamine F (**2**) and tsitsikammamine A (**3a**) and B (**3b**) display cytotoxicity against human colon tumor cell line HCT116. Aleutianamine (**4**), the most recently isolated compound, has cytotoxic activity toward pancreatic cancer (PANC-1).[2] In 2013, a new pyrroloiminoquinone alkaloid, atkamine (**5**), was isolated from *Latrunculia* sp., an Alaska sponge, and its structure was elucidated.[3] Since this compound has a pyrroloiminoquinone structure, its biological activity has attracted substantial interest, however, no data have been reported to date. Additionally, atkamine (**5**) has an 8-oxa-2-azabicyclo[3.2.1]octane skeleton (**6**) possessing four continuous asymmetric centers at the central structure, which is not found in common pyrroloiminoquinone alkaloids, and a linear 20-carbon side chain bearing *cis* alkene positioned at the junction of the benzothiophene ring. Therefore, atkamine (**5**) is a biologically and synthetically attractive molecule.

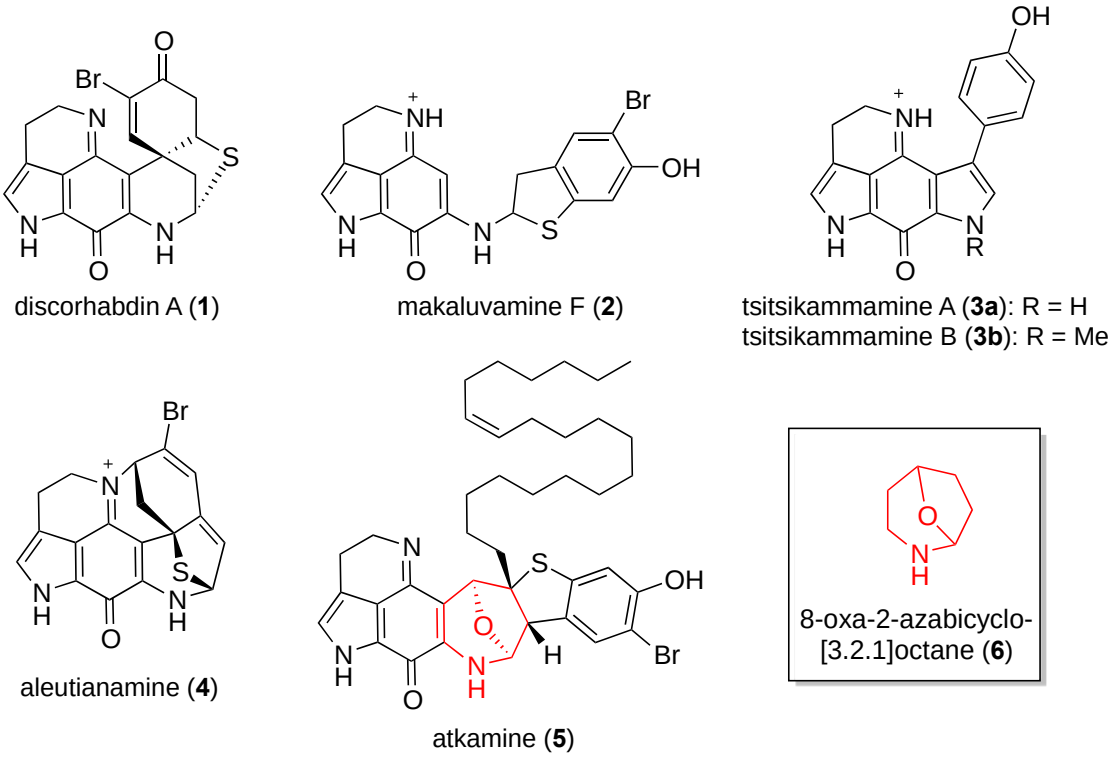
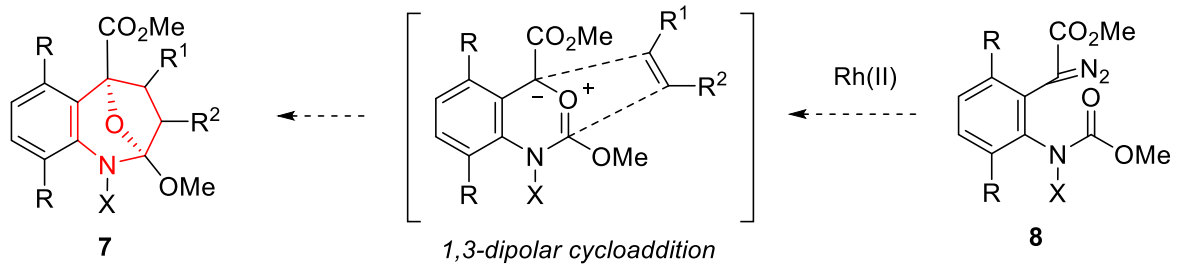


Figure 1. Examples of pyrroloiminoquinone alkaloids

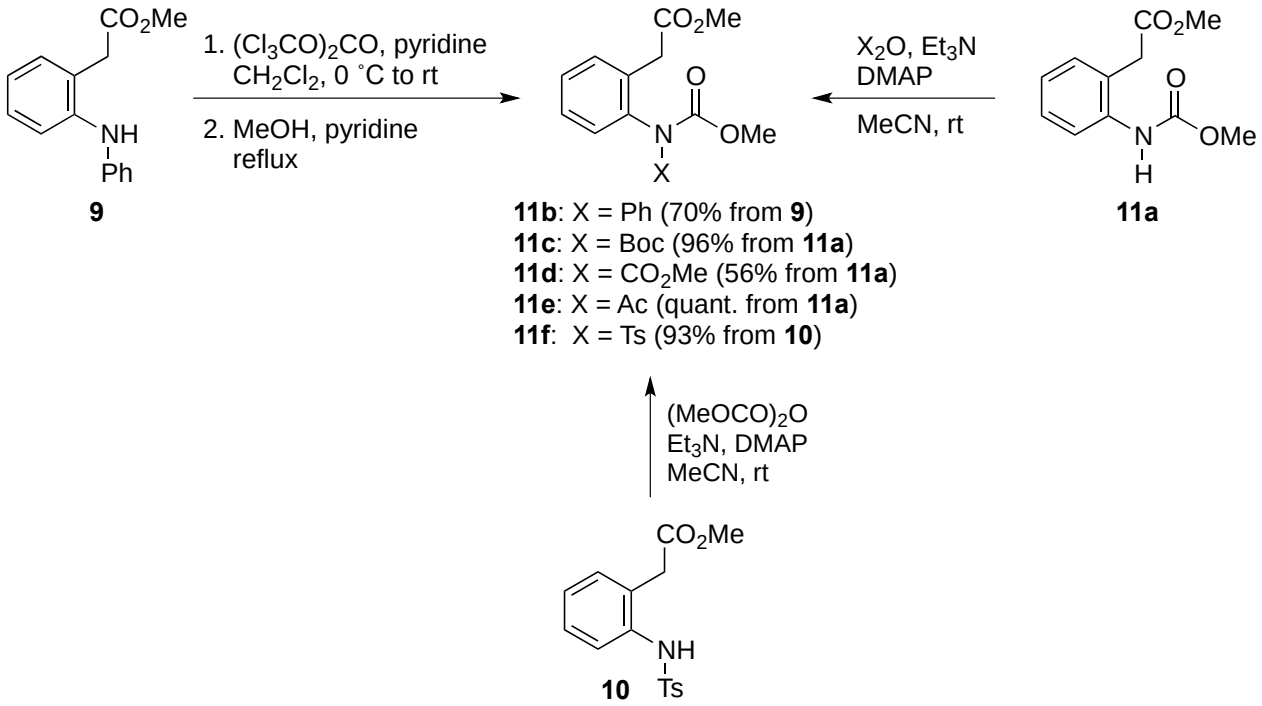
The formation of 8-oxa-2-azabicyclo[3.2.1]octane (**6**) has been reported using a Heck reaction and subsequent cyclization,[4] and via an intramolecular carbonyl-ene reaction.[5] However, these methods are difficult to apply to the synthesis of **5** due to a substituent tolerance and a steric control. On the other hand, 1,3-dipolar cycloaddition reaction is one of the most valuable synthetic methods used for the construction of a variety of heterocyclic compounds corresponding to the combination of a wide range of dipoles and dipolarophiles.[6] Among them, the cycloaddition of a cyclic carbonyl ylide generated from an α-diazocarbonyl compound in the presence of a rhodium(II) catalyst can give oxabicyclic compounds. This type of reaction was first reported by Takebayashi and Ibata in 1972 and has led to its subsequent use toward the preparation of several polysubstituted oxabicyclic skeletons utilizing various dipolarophiles.[7] Further investigations have been reported by Suga,[8] Hashimoto[9] and Padwa,[10] including the asymmetric variant of the reaction and its application in natural product synthesis.[11] Thus, 1,3-dipolar cycloaddition would be an efficient synthetic method for the highly stereoselective construction of polysubstituted 8-oxa-2-azabicyclo[3.2.1]octane ring systems **7**. Here we report a 1,3-dipolar cycloaddition using α-diazocarbonyl compounds **8** as a carbonyl ylide precursor to prepare 8-oxa-2-azabicyclo[3.2.1]octane skeleton of the core structure of atkamine (**5**).



Scheme 1. Synthetic strategy for the construction of 8-oxa-2-azabicyclo[3.2.1]octane **7**

RESULTS AND DISCUSSION

N-Arylcarbamate derivatives **11** bearing different substituents on the nitrogen atom were synthesized (Scheme 2). A methoxycarbonyl group was introduced into compounds **9** and **10** to give their corresponding *N*-phenyl and *N*-tosyl derivatives, **11b** and **11f**, respectively. Compound **11a** was treated with a variety of acid anhydrides to give carbamates **11c-e**.

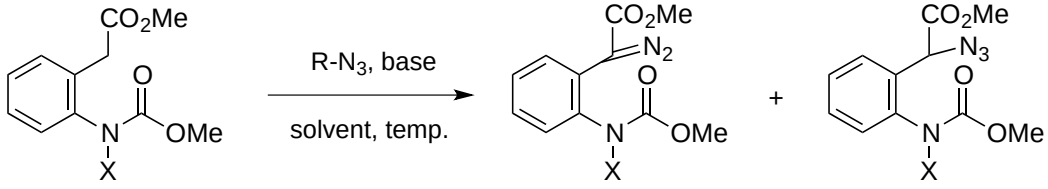


Scheme 2. Synthesis of *N*-arylcarbamate derivatives **11a-f**

Thereafter, the diazotizations of carbamate **11** were studied (Table 1).[12] The diazo (azido) transfer reactions[13] were examined for azidation reagents and bases referring to the guidelines of Evans.[14] The reaction of **11a** was carried out using tosyl azide and DBU to obtain diazo compound **12a** in 67% yield (entry 1).[11f] However, the reaction of **11b** with the same reagents afforded diazo compound **12b** and azide **13b** as an inseparable mixture (entry 2). In the case of *p*-acetylaminobenzenesulfonyl azide, the ratio of

12b and **13b** was reversed (entry 3). On the other hand, by the use of nonafluorobutanesulfonyl azide, which is known as a bench-stable electron-deficient diazo transfer reagent, a mixture of **12b** and **13b** was obtained with high selectivity in a moderate yield (entry 4).[15] Furthermore, using diphenylphosphoryl azide and LDA at –78 ºC,[16] high selectivity toward the diazo form was observed, but the yield was low (entry 5). The diazotization of *N*-arylcarbamate derivatives **11c-f** was investigated using the condition of entry 4. Reaction of Boc **11c** and tosyl **11f** derivatives gave the diazo compounds as the major products (entries 6 and 9). In the case of methoxycarbonyl compound **11d**, diazo form **12d** was obtained with excellent selectivity (entry 7). When an electron withdrawing group substituted on the nitrogen atom in the substrate **11**, the ratio of azide **13** tended to be increased (entry 1 vs 2, 7 vs 8).

Table 1. Diazotization of *N*-arylcarbamate **11a-f**

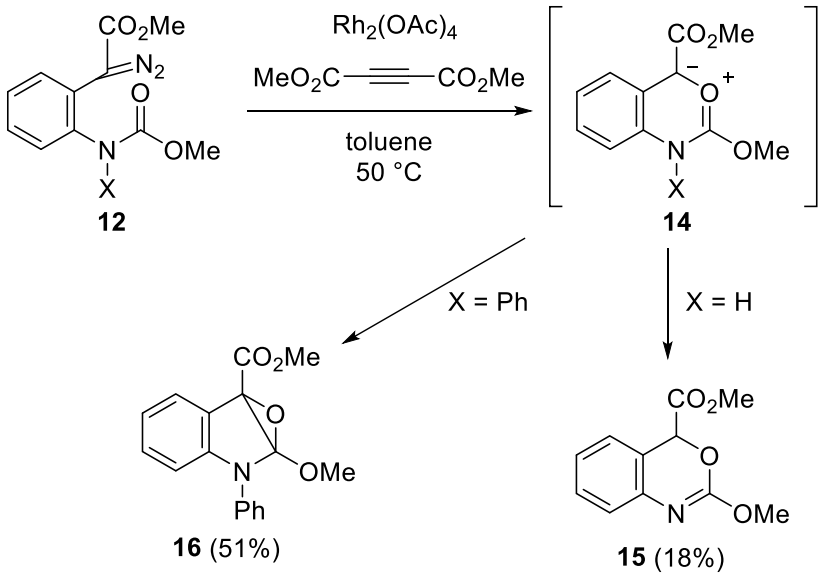


11 **12** **13**

entry	**11** (X =)	R-N_3 (equiv.)	base (equiv.)	solvent	temp.	time (h)	yield (%) and ratio of **12** : **13** [a,b]
1	**11a** (H)	*p*-Me-C_6H_4-SO_2N_3 (2.0)	DBU (3.0)	MeCN	rt	3.5	67 (**12a** only)
2	**11b** (Ph)	*p*-Me-C_6H_4-SO_2N_3 (1.5)	DBU (2.0)	MeCN	rt	5	66 (2 : 1)
3	**11b** (Ph)	*p*-AcNH-C_6H_4-SO_2N_3 (1.5)	DBU (1.5)	MeCN	rt	6	81 (1 : 2)
4	**11b** (Ph)	$F_9C_4SO_2N_3$ (1.5)	DBU (1.5)	MeCN	rt	3	43 (15 : 1)
5	**11b** (Ph)	$(PhO)_2P(O)N_3$ (1.2)	LDA (1.2)	THF	–78 °C	1.5	33 (15 : 1)
6	**11c** (Boc)	$F_9C_4SO_2N_3$ (1.5)	DBU (1.5)	MeCN	rt	3	49 (6 : 1)
7	**11d** (CO_2Me)	$F_9C_4SO_2N_3$ (1.5)	DBU (1.5)	MeCN	rt	16	22 (22 : 1)
8	**11e** (Ac)	$F_9C_4SO_2N_3$ (1.5)	DBU (1.5)	MeCN	rt	1.5	50 (2.5 : 1)
9	**11f** (Ts)	$F_9C_4SO_2N_3$ (1.5)	DBU (1.5)	MeCN	rt	23	41 (6 : 1)

a) combined yields for the inseparable mixtures of **12** and **13**
b) Ratio of **12** and **13** was determined by ^{1}H NMR.

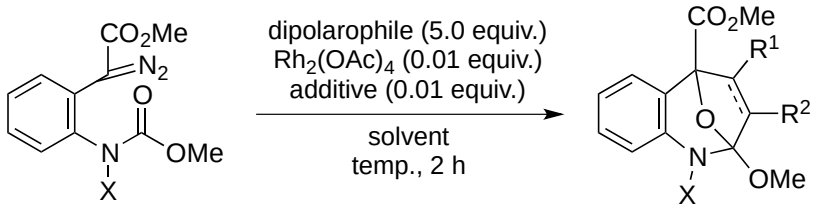
The 1,3-dipolar cycloaddition reactions between diazo esters **12** and dimethyl acetylenedicarboxylate (DMAD) were studied in the presence of rhodium(II) acetate dimer (Scheme 3). When compound **12a** (X = H) was used in the reaction, 6*H*-1,3-oxazine **15** was obtained as the sole product. In the case of *N*-phenyl compound **12b** (X = Ph), oxirane **16** was obtained. Considering these results, we assumed that the carbonyl ylide intermediate **14** should be formed under the reaction condition. Although a mixture of compound **16** and DMAD in toluene was stirred at 50 ºC, the reaction did not proceed at all.



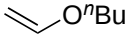
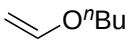
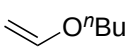
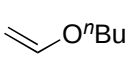
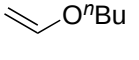
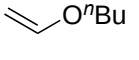
Scheme 3. Reaction of carbonyl ylide **14** with DMAD

Subsequentry, the addition of lanthanum(III) triflate as a Lewis acid to the reaction was investigated (Table 2).[8a] A solution of **12b** and DMAD in dichloromethane was added slowly to a solution of lanthanum(III) triflate in dichloromethane under the reflux condition, however, the desired product was not obtained (entries 1 and 2). The reaction of butyl vinyl ether and **12b** without the addition of a Lewis acid, a trace amount of the desired product 8-oxa-2-azabicyclo[3.2.1]octane **17b** was generated (entry 3). When a catalytic amount of lanthanum(III) triflate was added and the resulting mixture was stirred at room temperature, **17b** was obtained in 6% yield (entry 4). The reaction was carried out at refluxing temperature of dichloromethane, the yield of **17b** was improved to 35% yield (entry 5), however, at 80 ºC in 1,2-dichroromethane, the yield of **17b** decreased to 18% (entry 6). In the reaction using Boc derivative **12c**, the product **17c** was not be detected (entry 7). The desired compounds were obtained in 5% yield for methoxycarbonyl compound **17d** (entry 8), trace amounts for acetyl compound **17e** (entry 9), and 10% yield for tosyl derivative **17f** (entry 10). The reaction using other dipolarophiles such us vinyl acetate, 1-hexene, and 4-methoxystyrene did not form the corresponding cycloadducts.

Table 2. The 1,3-dipolar cycloaddition with butyl vinyl ether

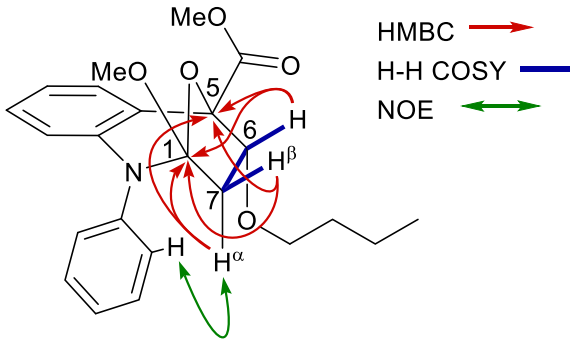


12 **17**

entry	**12** (X =)	dipolarophile	additive	solvent	temp.	R^1	R^2	yield of **17** (%) [a]
1	**12b** (Ph)	DMAD	-	CH_2Cl_2	reflux	$-CO_2Me$	$-CO_2Me$	N.D.[b]
2	**12b** (Ph)	DMAD	$La(OTf)_3$, 4Å MS	CH_2Cl_2	reflux	$-CO_2Me$	$-CO_2Me$	N.D.[b]
3	**12b** (Ph)		-	CH_2Cl_2	reflux	$-O^nBu$	H	**17b** (trace)
4	**12b** (Ph)		$La(OTf)_3$, 4Å MS	CH_2Cl_2	rt	$-O^nBu$	H	**17b** (6)
5	**12b** (Ph)		$La(OTf)_3$, 4Å MS	CH_2Cl_2	reflux	$-O^nBu$	H	**17b** (35)
6	**12b** (Ph)		$La(OTf)_3$, 4Å MS	$(CH_2Cl)_2$	80 °C	$-O^nBu$	H	**17b** (18)
7	**12c** (Boc)		$La(OTf)_3$, 4Å MS	CH_2Cl_2	reflux	$-O^nBu$	H	**17c** N.D.[b]
8	**12d** (CO_2Me)		$La(OTf)_3$, 4Å MS	CH_2Cl_2	reflux	$-O^nBu$	H	**17d** (5)
9	**12e** (Ac)		$La(OTf)_3$, 4Å MS	CH_2Cl_2	reflux	$-O^nBu$	H	**17e** (trace)
10	**12f** (Ts)		$La(OTf)_3$, 4Å MS	CH_2Cl_2	reflux	$-O^nBu$	H	**17f** (10)

a) Yields were calculated using the ratio of diazo compound including in starting material; b) N.D.: Not Detected.

The stereochemistry of compound **17b** was determined as follows (Figure 2). HMBC correlations were observed between each hydrogen atom at C6 and C7 and both carbon atoms at C1 and C5. Moreover, the NOE of hydrogens between the phenyl group and C7 were observed. In addition, the coupling constant of ^{1}H NMR spectrum between two hydrogens at C6 and C7 suggest the dihedral angle of H7β-C7-C6-H6. From the above results, it was determined that compound **17b** includes 8-oxa-2-azabicyclo[3.2.1]octane as an *endo* adduct.

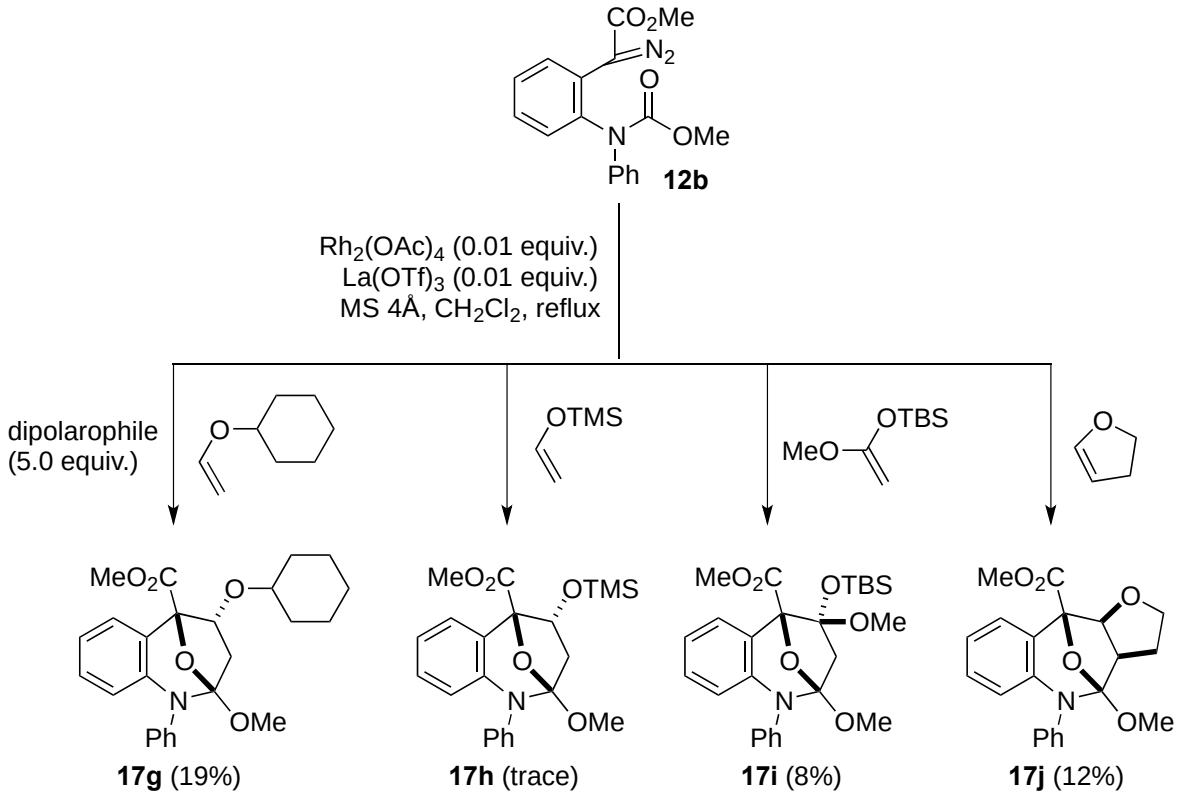


	^{13}C-NMR (ppm) [a]	^{1}H-NMR (ppm) [b]
1	107.7 (C)	—
5	92.7 (C)	—
6	104.8 (CH)	5.28 (d, *J* = 5.2 Hz)
7	40.3 (CH_2)	α = 2.42 (d, *J* = 13.7 Hz) β = 2.51 (dd, *J* = 13.7, 5.2 Hz)

a) 100 MHz in $CDCl_3$; b) 400 MHz in $CDCl_3$.

Figure 2. Structural elucidation of compound **17b**

Finally, we examined the scope of the dipolarophiles in the reaction (Scheme 4). The reaction of **12b** with cyclohexyl vinyl ether gave cycloadduct **17g** in 19% yield. In the case of a silyl ether-type dipolarophiles such as trimethylsilyl vinyl ether and silylketene acetal, the desired products **17h** and **17i** were obtained in low yields, respectively. The cyclization reaction also proceeded using 2,3-dihydrofuran as a cyclic vinyl ether to obtain the desired product **17j** in 12% yield.



Scheme 4. The 1,3-dipolar cycloaddition with various vinyl ethers

CONCLUSION

We have examined the construction of the 8-oxa-2-azabicyclo[3.2.1]octane skeleton contained in atkamine (**5**) using the 1,3-dipolar cycloaddition of a variety of carbonyl ylides and vinyl ethers in the presence of rhodium acetate dimer and lanthanum(III) triflate as catalysts. This method provides a new synthetic approach to the 8-oxa-2-azabicyclo[3.2.1]octane framework.

EXPERIMENTAL

General. All melting points were measured on a Yanagimoto micro melting point apparatus. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer and absorbance bands are reported in wavenumber (cm^{-1}). ^1H NMR spectra were recorded on JEOL JNM-AL 300 (300 MHz) spectrometer or JEOL JNM-ECA 400 (400 MHz) spectrometer. Chemical shifts are reported relative to internal standard (tetramethylsilane at δ_H 0.00, $CDCl_3$ at δ_H 7.26, DMSO-d_6 at δ_H 2.50). Data are presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant and integration. ^{13}C NMR spectra were recorded on JEOL JNM-ECA 400 (100 MHz) spectrometer. Chemical shifts are reported relative to internal standard ($CDCl_3$ at δ 77.00, DMSO-d_6 at δ 40.45). Mass spectra were recorded on a JEOL JMS 700 instrument with a direct inlet system. Column chromatography was carried out on Kanto silica gel 60 N (40–50 mesh). Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates with visualization by ultraviolet, anisaldehyde stain solution or phosphomolybdic acid stain solution. All non-aqueous reactions were carried out in flame-dried glassware under Ar atmosphere unless otherwise noted. Reagents and solvents were used without purification. 4Å MS from nacalai tesque was used after drying. Nonafluorobutanesulfonyl azide was prepared according to the literature.[17]

1. Procedure for the preparation of methyl {2-[(methoxycarbonyl)(phenyl)amino]phenyl}acetate (11b).

To a solution of triphosgene (197 mg, 0.66 mmol) in CH_2Cl_2 (3.0 mL) was added pyridine (321 μL, 5.30 mmol) at 0 °C. After stirring at the same temperature for 5 min, a solution of **9**[2] (480 mg, 1.99 mmol) in CH_2Cl_2 (7.0 mL) was added via cannula. After stirring at the room temperature for 3 h, the reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$. Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (silica gel, 4:1 *n*-hexane/EtOAc) to give acid chloride (483 mg, 80%) as a colorless oil.

To a solution of obtained acid chloride (483 mg, 1.59 mmol) in MeOH (20 mL) was added pyridine (176 μL, 2.19 mmol), and the mixture was refluxed for 8 h. After the completion of the reaction, the whole

mixture was concentrated in vacuo to furnish the crude product, which was purified by column chromatography (silica gel, 3:1 *n*-hexane/EtOAc) to give **11b** (419 mg, 88%) as a brown oil. The spectroscopic data of the product were fully consistent with those reported in the literature.[12]

2. Typical procedure for the acylation of methyl (2-methoxycarbonylaminophenyl)acetate (11a).

To a solution of **11a**,[18] Et_3N, and acid anhydride (X_2O) in MeCN was added DMAP. After the completion of the reaction, the whole mixture was concentrated in vacuo to furnish the crude product, which was purified by column chromatography.

Methyl {2-[(*tert*-butoxycarbonyl)(methoxycarbonyl)amino]phenyl}acetate (11c)

Carbamate **11a** (500 mg, 2.24 mmol), Et_3N (468 μL, 3.36 mmol), Boc_2O (772 μL, 3.36 mmol), DMAP (821 mg, 6.72 mmol), and MeCN (22 mL) were used (reaction time: 10 h). The crude product was purified by column chromatography (silica gel, 3:1 *n*-hexane/EtOAc) to give **11c** (625 mg, 96%) as an orange oil: IR ($CHCl_3$) *v* 3025, 2984, 2955, 1788, 1743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.39 (9H, s), 3.55 (2H, s), 3.66 (3H, s), 3.70 (3H, s), 7.13 (1H, dd, *J* = 7.4, 1.6 Hz), 7.25-7.44 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.4, 36.3, 51.7, 53.4, 82.9, 127.8, 128.2, 128.4, 130.6, 131.8, 137.2, 150.6, 152.8, 170.5; MS (FAB) *m*/*z* (%) 324 ($[M+H]^+$, 44), 268 (98), 224 (47), 192 (94), 185 (78), 164 (20), 132 (28), 93 (100), 75 (24), 57 (29); HRMS (FAB) calcd for $C_{16}H_{22}NO_6$ $[M+H]^+$ 324.1447, found 324.1441.

Methyl {2-[bis(methoxycarbonyl)amino]phenyl}acetate (11d)

Carbamate **11a** (500 mg, 2.24 mmol), Et_3N (468 μL, 3.36 mmol), $(MeOCO)_2O$ (288 μL, 2.69 mmol), DMAP (82 mg, 0.67 mmol), and MeCN (22 mL) were used (reaction time: 21 h). The crude product was purified by column chromatography (silica gel, 1:1 *n*-hexane/EtOAc) to give **11d** (350 mg, 56%) as a light yellow solid: mp 125–127 °C (EtOAc); IR ($CHCl_3$) *v* 3031, 2956, 1793, 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.54 (2H, s), 3.64 (3H, s), 3.71 (6H, s), 7.16 (1H, d, *J* = 7.3 Hz), 7.26-7.48 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.6, 51.8, 53.7 (CH_3×2), 128.0, 128.7 (CH×2), 131.0, 131.9, 136.7, 152.6 (C×2), 170.4; MS (EI) *m*/*z* (%) 281 ($[M]^+$, 36), 250 (10), 249 (28), 206 (35), 205 (100), 190 (41), 178 (11), 162 (54), 147 (19), 146 (41), 132 (57), 118 (14), 91 (10), 77 (12), 59 (10); HRMS (EI) calcd for $C_{13}H_{15}NO_6$ $[M]^+$ 281.0899, found 281.0898.

Methyl {2-[(acetyl)(methoxycarbonyl)amino]phenyl}acetate (11e)

Carbamate **11a** (500 mg, 2.24 mmol), Et_3N (937 μL, 6.72 mmol), Ac_2O (635 μL, 6.72 mmol), DMAP (821 mg, 6.72 mmol), and MeCN (22 mL) were used (reaction time: 1.5 h). The crude product was purified by column chromatography (silica gel, 1:1 *n*-hexane/EtOAc) to give **11e** (590 mg, quant.) as a light yellow solid: mp 62–65 °C (EtOAc); IR ($CHCl_3$) *v* 3027, 2956, 1745, 1711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.65 (3H, s), 3.46 (2H, d, *J* = 1.2 Hz), 3.64 (3H, s), 3.68 (3H, s), 7.08 (1H, dd, *J* = 7.1, 1.6 Hz), 7.31-7.43 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1, 37.5, 52.0, 53.8, 128.4, 128.9, 129.2,

131.4, 132.3, 137.3, 154.5, 170.7, 172.5; MS (EI) *m*/*z* (%) 265 ([M]$^+$, 7), 223 (70), 192 (25), 191 (53), 163 (38), 159 (14), 133 (11), 132 (100), 118 (10); HRMS (EI) calcd for $C_{13}H_{15}NO_5$ [M]$^+$ 265.0950, found 265.0947.

3. Procedure for the preparation of methyl {2-[(methoxycarbonyl)(tosyl)amino]phenyl}acetate (11f).

To a solution of **10**[19] (500 mg, 1.57 mmol), Et_3N (327 μL, 2.35 mmol), and $(MeOCO)_2O$ (336 μL, 3.13 mmol) in MeCN (16 mL) was added DMAP (57 mg, 0.47 mmol). After stirring at room temperature for 11 h, the whole mixture was concentrated in vacuo to furnish the crude product, which was purified by column chromatography (silica gel, 1:1 *n*-hexane/ EtOAc) to give **11f** (550 mg, 93%) as a colorless solid: mp 135–138 °C (EtOAc); IR ($CHCl_3$) *v* 3036, 2956, 1739, 1598 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C): δ 2.45 (3H, s), 3.55 (3H, s), 3.59 (3H, s), 3.64 (2H, d, *J* = 5.9 Hz), 7.15 (1H, dd, *J* = 7.8, 1.0 Hz), 7.37 (1H, dt, *J* = 7.8, 2.0 Hz), 7.44 (1H, dt, *J* = 7.3, 1.0 Hz), 7.48 (3H, d, *J* = 7.8 Hz), 7.87 (2H, d, *J* = 8.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6, 80 °C): δ 20.7, 35.8, 51.2, 53.5, 127.9, 128.3, 128.5, 129.2, 129.4, 131.1, 134.0, 134.4, 135.5, 144.8, 151.4, 169.6; MS (EI) *m*/*z* (%) 377 ([M]$^+$, 2), 314 (19), 313 (100), 222 (28), 207 (11), 206 (91), 191 (73), 190 (15), 162 (56), 155 (23), 132 (51), 91 (39); HRMS (EI) calcd for $C_{18}H_{19}NO_6S$ [M]$^+$ 377.0933, found 377.0931.

4. Procedure for the diazotization of methyl (2-methoxycarbonylaminophenyl)acetate (11a).

To a solution of **11a** (300 mg, 1.34 mmol) and TsN_3 (11-15% in toluene, 2.75 mL, ca. 2.69 mmol) in MeCN (7.0 mL), DBU (603 μL, 4.03 mmol) was slowly added at 0 °C. After stirring at room temperature for 3 h, the reaction was quenched with 10% aqueous citric acid, and the mixture was extracted with EtOAc. The combined organic extracts were successively washed with brine, and dried over anhydrous $MgSO_4$. Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (silica gel, 4:1 *n*-hexane/EtOAc) to give **12a** (225 mg, 67%) as a yellow oil: IR ($CHCl_3$) *v* 3029, 2956, 2100, 1732, 1681 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77 (3H, s), 3.88 (3H, s), 7.16 (1H, dt, *J* = 7.3, 1.0 Hz), 7.23 (1H, dd, *J* = 7.8, 1.5 Hz), 7.36 (1H, dt, *J* = 8.0, 2.0 Hz), 7.60 (1H, brs), 7.86 (1H, brd, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.4, 52.6, 60.0, 116.8, 124.0, 124.7, 128.8, 129.6, 136.8, 154.6, 167.1; MS (FAB) *m*/*z* (%) 249 ([M]$^+$, 14), 223 (13), 222 (100), 221 (58), 190 (33), 162 (26), 155 (23), 154 (90), 146 (23), 138 (26), 137 (49), 136 (58), 107 (16), 89 (13), 77 (12); HRMS (FAB) calcd for $C_{11}H_{11}N_3O_4$ [M]$^+$ 249.0750, found 249.0751.

5. Typical procedure for the diazotization of methyl (2-methoxycarbonylaminophenyl)acetates 11b-f.

To a solution of arylacetate **11** (1.0 equiv) and $C_4F_9SO_2N_3$ (1.2-1.5 equiv) in MeCN (0.1 M), DBU (1.4-1.5 equiv) was slowly added at 0 °C and the mixture was stirred at room temperature. After completion of the reaction was confirmed by TLC analysis, the reaction was quenched with saturated

aqueous NH_4Cl, and the mixture was extracted with EtOAc. The combined organic extracts were successively washed with brine, and dried over anhydrous $MgSO_4$. Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography to give inseparable mixture of diazo compound **12** and azide **13**.

Methyl {2-[(methoxycarbonyl)(phenyl)amino]phenyl}diazoacetate (12b) and methyl azido-{2-[(methoxycarbonyl)(phenyl)amino]phenyl}acetate (13b)

Arylacetate **11b** (500 mg, 1.67 mmol), $C_4F_9SO_2N_3$ (814 μL, 2.51 mmol), DBU (375 μL, 2.51 mmol), and MeCN (17 mL) were used (reaction time: 3 h). The crude product was purified by column chromatography (silica gel, 4:1 *n*-hexane/EtOAc) to give a 15:1 mixture of **12b** and **13b** (233 mg, 43%) as a yellow oil: IR ($CHCl_3$) *v* 3026, 3014, 2955, 2099, 1703, 1595 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.67 (3H, s), 3.74 (3H, s), 5.28 (1/15H, s), 7.09-7.16 (1H, m), 7.17-7.31 (4H, m), 7.33-7.44 (3H, m), 7.52-7.60 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.0, 53.3, 59.6, 124.0, 124.4, 125.4, 128.1, 128.7, 129.3, 130.3, 132.0, 140.2, 141.3, 154.9, 165.7; MS (ESI) *m*/*z* (%) 348 ($[M+Na]^+$, 12), 320 (33), 299 (21), 298 (100), 266 (14), 239 (12), 238 (74), 194 (12); HRMS (ESI) calcd for $C_{17}H_{15}N_3NaO_4$ $[M+Na]^+$ 348.0960, found 348.0956.

Methyl {2-[(*tert*-butoxycarbonyl)(methoxycarbonyl)amino]phenyl}diazoacetate (12c) and methyl azido-{2-[(*tert*-butoxycarbonyl)(methoxycarbonyl)amino]phenyl}acetate (13c)

Arylacetate **11c** (500 mg, 1.55 mmol), $C_4F_9SO_2N_3$ (603 μL, 1.86 mmol), DBU (324 μL, 2.17 mmol), and MeCN (15 mL) were used (reaction time: 3 h). The crude product was purified by column chromatography (silica gel, 5:1 *n*-hexane/EtOAc) to give a 6:1 mixture of **12c** and **13c** (262 mg, 49%) as a yellow oil: IR ($CHCl_3$) *v* 3030, 2099, 1789, 1750, 1703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.37 (9H, s), 3.73 (3H, s), 3.81 (3H, s), 5.29 (1/6H, s), 7.17-7.22 (1H, m), 7.33-7.47 (2H, m), 7.52-7.58 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.6 (CH_3×3), 52.2, 53.9, 83.7, 124.2, 128.7, 129.16, 129.19, 131.3, 137.2, 150.6, 153.0, 165.7 (C×2); MS (FAB) *m*/*z* (%) 350 ($[M+H]^+$, 13), 307 (18), 294 (15), 189 (11), 266 (56), 265 (30), 248 (11), 222 (48), 221 (14), 220 (12), 206 (13), 190 (45), 162 (20), 155 (26), 154 (100), 146 (17), 139 (12), 138 (30), 137 (55), 136 (65), 120 (13), 107 (21), 91 (14), 89 (17), 57 (63); HRMS (FAB) calcd for $C_{16}H_{20}N_3O_6$ $[M+H]^+$ 350.1352, found 350.1356.

Methyl {2-[bis(methoxycarbonyl)amino]phenyl}diazoacetate (12d) and methyl azido-{2-[bis(methoxycarbonyl)amino]phenyl}acetate (13d)

Arylacetate **11d** (300 mg, 1.07 mmol), $C_4F_9SO_2N_3$ (416 μL, 1.28 mmol), DBU (223 μL, 1.49 mmol), and MeCN (11 mL) were used (reaction time: 16 h). The crude product was purified by column chromatography (silica gel, 5:1 *n*-hexane/EtOAc) to give a 22:1 mixture of **12d** and **13d** (71 mg, 22%) as a yellow oil: IR ($CHCl_3$) *v* 3034, 3020, 2957, 2099, 1794, 1758, 1703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):

δ 3.74 (6H, s), 3.78 (3H, s), 5.28 (1/22H, s), 7.19-7.31 (1H, m), 7.34-7.66 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.2, 54.0, 72.7, 124.2, 129.1, 129.4, 129.5, 131.4, 136.8, 152.5, 165.4; MS (ESI) *m*/*z* (%) 330 ($[M+Na]^+$, 43), 303 (18), 302 (100), 280 (25), 274 (18), 162 (11); HRMS (ESI) calcd for $C_{13}H_{13}N_3NaO_6$ $[M+Na]^+$ 330.0702, found 330.0701.

Methyl {2-[(acetyl)(methoxycarbonyl)amino]phenyl}diazoacetate (12e) and methyl azido-{2-[(acetyl)(methoxycarbonyl)amino]phenyl}acetate (13e)

Arylacetate **11e** (300 mg, 1.13 mmol), $C_4F_9SO_2N_3$ (441 μL, 1.36 mmol), DBU (237 μL, 1.58 mmol), and MeCN (11 mL) were used (reaction temperature: 0 °C, reaction time: 1.5 h). The crude product was purified by column chromatography (silica gel, 5:1 *n*-hexane/EtOAc) to give a 2.5:1 mixture of **12e** and **13e** (262 mg, 50%) as a yellow oil: IR ($CHCl_3$) *ν* 3030, 2098, 1748, 1708, 1439 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.62 (3H, s), 3.70 (3H, s), 3.80 (3H, s), 5.26 (2/5H, s), 7.10-7.20 (1H, m), 7.35-7.52 (2H, m), 7.53-7.58 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3, 26.0, 52.0, 53.7, 72.0, 124.0, 128.8, 129.5, 131.1, 136.6, 153.9, 165.3, 172.3; MS (EI) *m*/*z* (%) 291 ($[M]^+$, 0.3), 263 (41), 221 (17), 220 (12), 205 (14), 204 (100), 146 (47), 144 (29); HRMS (EI) calcd for $C_{13}H_{13}N_3O_5$ $[M]^+$ 291.0855, found 291.0853.

Methyl {2-[(methoxycarbonyl)(tosyl)amino]phenyl}diazoacetate (12f) and methyl azido-{2-[(methoxycarbonyl)(tosyl)amino]phenyl}acetate (13f)

Arylacetate **11f** (500 mg, 1.33 mmol), $C_4F_9SO_2N_3$ (517 μL, 1.59 mmol), DBU (277 μL, 1.86 mmol), and MeCN (13 mL) were used (reaction time: 23 h). The crude product was purified by column chromatography (silica gel, 5:1 *n*-hexane/EtOAc) to give a 6:1 mixture of **12f** and **13f** (216 mg, 41%) as a yellow oil: IR ($CHCl_3$) *ν* 3040, 3023, 2956, 2100, 1741, 1700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (3H, s), 3.66 (3H, s), 3.81 (3H, s), 5.01 (1/6H, s), 7.14 (1H, dd, *J* = 1.2, 7.8 Hz), 7.35 (2H, d, *J* = 8.4 Hz), 7.38 (1H, dt, *J* = 1.5, 7.8 Hz), 7.49 (1H, dt, *J* = 1.2, 7.5 Hz), 7.64 (1H, dd, *J* = 1.5, 7.8 Hz), 7.92 (2H, d, *J* = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 52.3, 54.2, 60.4, 126.8, 129.1, 129.2, 129.5, 130.1, 130.3, 131.4, 134.5, 135.7, 145.2, 152.4, 165.5; MS (FAB) *m*/*z* (%) 404 ($[M+H]^+$, 1), 403 ($[M]^+$, 0.4), 376 (22), 307 (25), 187 (31), 155 (58), 154 (100), 138 (30), 137 (68), 136 (69), 107 (21), 91 (28), 89 (17); HRMS (FAB) calcd for $C_{18}H_{18}N_3O_6S$ $[M+H]^+$ 404.0916, found 404.0913.

6. Procedure for the $Rh_2(OAc)_4$-catalyzed reaction of methyl [2-(methoxycarbonylamino)phenyl]-diazoacetate (12a).

To a solution of **12a** (50 mg, 0.201 mmol) and DMAD (49 μL, 0.401 mmol) in toluene (2.0 mL) was added $Rh_2(OAc)_4$ (0.8 mg, 0.002 mmol). After stirring for 20 min at 50 °C, the whole mixture was concentrated in vacuo to furnish the crude product, which was purified by column chromatography (silica gel, 3:1 *n*-hexane/EtOAc) to give **15** (8.2 mg, 18%) as a yellow oil: IR ($CHCl_3$) *ν* 2956, 1755, 1645, 1601 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (3H, s), 4.00 (3H, s), 5.82 (1H, s), 7.00-7.15 (2H, m),

7.20-7.25 (1H, m), 7.28-7.32 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.0, 55.9, 77.2, 118.4, 123.7, 124.7, 125.3, 130.1, 140.1, 155.7, 168.9; MS (EI) *m*/*z* (%) 221 ([M]$^+$, 21), 162 (100), 130 (24); HRMS (EI) calcd for $C_{11}H_{11}NO_4$ [M]$^+$ 221.0688, found 221.0687.

7. Procedure for the $Rh_2(OAc)_4$-catalyzed reaction of methyl {2-[(methoxycarbonyl)(phenyl)-amino]phenyl}diazoacetate (12b).

To a solution of DMAD (68 μL, 0.550 mmol) and $Rh_2(OAc)_4$ (0.8 mg, 0.002 mmol), and MS 4Å (100 mg) in refluxing CH_2Cl_2 (0.50 mL), a solution of **12b** (39.4 mg, 0.121 mmol) in CH_2Cl_2 (1.5 mL) was added over 1 h using syringe pump, and the mixture was further stirred for 1 h at the same temperature. After the completion of the reaction, the whole mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo to furnish the crude product, which was purified by column chromatography (silica gel, 5:1 *n*-hexane/EtOAc) to give **16** (18.4 mg, 51%) as a yellow oil: IR ($CHCl_3$) *v* 3027, 1764, 1721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.46 (3H, s), 3.55 (3H, s), 6.96 (1H, t, *J* = 6.8 Hz), 7.10 (1H, d, *J* = 8.3 Hz), 7.24-7.33 (1H, m), 7.36-7.46 (4H, m), 7.52 (1H, dt, *J* = 7.3, 1.4 Hz), 7.68 (1H, d, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.5, 52.9, 94.4, 111.7, 119.8, 120.5, 124.2, 125.2, 126.7, 129.6, 138.2, 138.3, 159.7, 165.1, 194.6; MS (EI) *m*/*z* (%) 297 ([M]$^+$, 9), 239 (16), 238 (100), 195 (35), 167 (15), 166 (10); HRMS (EI) calcd for $C_{17}H_{15}NO_4$ [M]$^+$ 297.1001, found 297.1002.

8. Typical procedure for the cycloaddition of methyl [2-(methoxycarbonyl-amino)phenyl]diazoacetates (12) and *n*-butyl vinyl ether.

To a solution of $La(OTf)_3$ (0.01 equiv), $Rh_2(OAc)_4$ (0.01 equiv), and MS 4Å (100 mg) in refluxing CH_2Cl_2 (0.50 mL), a solution of **12** (1 equiv) and *n*-butyl vinyl ether (5 equiv) in CH_2Cl_2 (1.5 mL) was added over 1 h using syringe pump, and the mixture was further stirred for 1 h at the same temperature. After the completion of the reaction, the whole mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo to furnish the crude product, which was purified by column chromatography.

Methyl 4-butoxy-2-methoxy-1-phenyl-1,2,3,4-tetrahydro-5*H*-2,5-epoxybenzo[*b*]azepine-5-carboxylate (17b)

A mixture of **12b** and **13b** (15:1, 50 mg) was used. The crude product was purified by column chromatography (silica gel, 5:1 *n*-hexane/EtOAc and CH_2Cl_2 only) to give **17b** (20 mg, 35%) as a yellow solid: mp 79–82 °C (EtOAc); IR ($CHCl_3$) *v* 2955, 2932, 1741, 1596 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.69 (3H, t, *J* = 7.3 Hz), 0.93-1.05 (2H, m), 1.07-1.22 (2H, m), 2.42 (1H, d, *J* = 13.7 Hz), 2.51 (1H, dd, *J* = 13.7, 5.2 Hz), 3.07-3.15 (1H, m), 3.23 (3H, s), 3.29-3.37 (1H, m), 3.88 (3H, s), 5.28 (1H, d, *J* = 5.2 Hz), 6.86 (1H, dt, *J* = 8.3, 1.0 Hz), 7.05 (1H, d, *J* = 8.7 Hz), 7.13 (1H, tt, *J* = 6.8, 1.9 Hz), 7.23 (1H, dt, *J* = 7.3, 1.0 Hz), 7.29-7.48 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 18.8 (CH_2), 31.3 (CH_2), 40.3 (CH_2), 51.6 (CH_3), 52.9 (CH_3), 66.9 (CH_2), 92.7 (C), 104.8 (CH), 107.7 (C), 109.4 (CH), 119.4 (CH),

122.0 (CH×2), 124.0 (CH), 126.3 (CH), 128.0 (C), 129.1 (CH×2), 130.0 (CH), 140.5 (C), 148.5 (C), 169.9 (C); MS (EI) *m*/*z* (%) 397 ([M]$^+$, 100), 324 (13), 321 (20), 310 (10), 266 (10), 264 (21), 238 (24), 236 (13), 204 (14), 195 (12), 193 (11), 192 (42), 133 (14); HRMS (EI) calcd for $C_{23}H_{27}NO_5$ [M]$^+$ 397.1889, found 397.1888.

Dimethyl 4-butoxy-2-methoxy-3,4-dihydro-1*H*-2,5-epoxybenzo[*b*]azepine-1,5(2*H*)-dicarboxylate (17d)

A mixture of **12d** and **13d** (22:1, 140 mg) was used. The crude product was purified by column chromatography (silica gel, 5:1 *n*-hexane/EtOAc and CH_2Cl_2 only) to give **17d** (7.8 mg, 5%) as a colorless oil: IR ($CHCl_3$) *v* 3025, 2956, 1733, 1718, 1704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (3H, t, *J* = 7.3 Hz), 1.07-1.30 (2H, m), 1.30-1.52 (2H, m), 2.71 (1H, dd, *J* = 13.9, 4.6 Hz), 2.98 (1H, dd, *J* = 13.9, 4.7 Hz), 3.35-3.60 (2H, m), 3.17 (3H, s), 3.78 (3H, s), 3.79 (3H, s), 5.86 (1H, t, *J* = 4.6 Hz), 7.15 (1H, dt, *J* = 7.9, 1.3 Hz), 7.27-7.42 (2H, m), 7.54 (1H, d, *J* = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 19.0, 31.4, 37.1, 52.9, 53.17, 53.24, 56.1, 67.3, 80.6, 124.5, 125.3, 127.0, 128.0, 128.2, 134.6, 154.8, 170.2, 170.8; MS (EI) *m*/*z* (%) 380 ([M+H]$^+$, 13), 379 ([M]$^+$, 64), 306 (55), 246 (100), 232 (33), 202 (15), 189 (22), 144 (12); HRMS (EI) calcd for $C_{19}H_{25}NO_7$ [M]$^+$ 379.1631, found 379.1632.

Methyl 1-acetyl-4-butoxy-2-methoxy-1,2,3,4-tetrahydro-5*H*-2,5-epoxybenzo[*b*]azepine-5-carboxylate (17e)

A mixture of **12e** and **13e** (2.5:1, 20 mg) was used. The crude product was purified by column chromatography (silica gel, 5:1 *n*-hexane/EtOAc and CH_2Cl_2 only) to give **17e** (trace) as a colorless oil: IR ($CHCl_3$) *v* 2957, 2930, 1872, 1770, 1744, 1701, 1604 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): δ 0.62 (3H, s), 0.65-1.02 (4H, m), 1.57 (3H, brs), 2.19 (1H, dd, *J* = 14.1, 4.9 Hz), 3.12 (2H, dt, *J* = 6.6, 2.2 Hz), 2.80-3.30 (1H, m), 3.80 (3H, s), 3.89 (3H, s), 5.37 (1H, d, *J* = 5.1 Hz), 7.03 (1H, t, *J* = 7.5 Hz), 7.25-7.40 (2H, m), 7.54-8.02 (1H, brd); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): δ 13.6, 14.0, 18.9, 29.7, 31.2, 52.4, 52.6, 66.9, 104.9, 115.8, 122.8, 125.2, 130.1, 152.9, 170.6; MS (EI) *m*/*z* (%) 364 ([M+H]$^+$, 10), 363 ([M]$^+$, 48), 304 (17), 290 (11), 205 (14), 204 (100), 160 (10); HRMS (EI) calcd for $C_{10}H_{11}N_3O_3$ [M]$^+$ 221.0800, found 221.0801. $C_{19}H_{25}NO_6$ [M]$^+$ 363.1682, found 363.1683.

Methyl 4-butoxy-2-methoxy-1-tosyl-1,2,3,4-tetrahydro-5*H*-2,5-epoxybenzo[*b*]azepine-5carboxylate (17f)

A mixture of **12f** and **13f** (6:1, 90 mg) was used. The crude product was purified by column chromatography (silica gel, 5:1 *n*-hexane/EtOAc and CH_2Cl_2 only) to give **17f** (9.4 mg, 10%) as a colorless oil: IR ($CHCl_3$) *v* 3791, 2955, 1767, 1734, 1601 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.78 (3H, t, *J* = 7.1 Hz), 1.02-1.21 (2H, m), 1.28-1.45 (2H, m), 2.16 (1H, dd, *J* = 14.1, 2.6 Hz), 2.38 (3H, s), 2.83 (1H, dd, *J* = 14.1, 3.3 Hz), 3.35-3.54 (1H, m), 3.58 (3H, s), 3.66 (3H, s), 3.60-3.80 (1H, m), 5.67 (1H, t, *J* = 3.1 Hz), 7.13 (1H, dt, *J* = 7.9, 1.3 Hz), 7.22 (2H, d, *J* = 7.9 Hz), 7.28-7.40 (2H, m), 7.52 (2H, d, *J* = 8.4

Hz), 7.93 (1H, dd, *J* = 8.3, 0.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 18.9, 21.5, 31.1, 32.7, 52.8, 53.1, 54.7, 67.4, 82.3, 123.6, 124.1, 124.5, 127.3, 128.7, 129.7, 130.3, 133.3, 135.9, 143.9, 170.2, 170.9; MS (EI) *m*/*z* (%) 476 ($[M+H]^+$, 17), 475 ($[M]^+$, 62), 402 (25), 342 (29), 320 (23), 202 (100), 188 (62), 156 (10), 155 (17), 144 (13), 91 (23); HRMS (EI) calcd for $C_{24}H_{29}NO_7S$ $[M]^+$ 475.1665, found 475.1663.

9. Procedure for the cycloaddition of methyl {[2-(methoxycarbonyl)(phenyl)-amino]phenyl}diazoacetates (12b) and cyclohexyl vinyl ether.

To a solution of $La(OTf)_3$ (1.8 mg, 3.07×10^{-3} mmol), $Rh_2(OAc)_4$ (1.4 mg, 3.07×10^{-3} mmol), and MS 4Å (100 mg) in refluxing CH_2Cl_2 (0.75 mL), a solution of **12b** (100 mg, **12b**:**13b** = 15:1) and cyclohexyl vinyl ether (218 μL, 1.54 mmol) in CH_2Cl_2 (2.25 mL) was added over 1 h using syringe pump, and the mixture was further stirred for 1 h at the same temperature. After the completion of the reaction, the whole mixture was filtered through a pad of Celite, and the combined filtrate was concentrated in vacuo to furnish the crude product, which was purified by column chromatography (silica gel, 5:1 *n*-hexane/EtOAc and CH_2Cl_2 only) to give **17g** (24 mg, 19%) as a colorless oil: IR ($CHCl_3$) *v* 2935, 2858, 1741, 1595 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): δ 0.75-1.68 (10H, m), 2.37 (1H, d, *J* = 13.5 Hz), 2.49 (1H, dd, *J* = 13.5, 5.2 Hz), 3.23 (3H, s), 3.25-3.37 (1H, m), 3.86 (3H, s), 5.44 (1H, d, *J* = 5.2 Hz), 6.83 (1H, dt, *J* = 7.6, 0.9 Hz), 7.00 (1H, d, *J* = 8.0 Hz), 7.08-7.17 (1H, m), 7.20 (1H, dt, *J* = 8.2, 1.1 Hz), 7.30-7.43 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): δ 23.75 (CH_2), 23.84 (CH_2), 25.7 (CH_2), 31.3 (CH_2), 32.9 (CH_2), 40.8 (CH_2), 51.6 (CH_3), 52.7 (CH_3), 74.2 (CH_2), 92.8 (C), 102.7 (CH), 108.0 (C), 109.3 (CH), 119.3 (CH), 122.7 (CH×2), 124.1 (CH), 126.4 (CH), 128.3 (C), 129.1 (CH×2), 129.9 (CH), 140.7 (C), 148.9 (C), 170.0 (C); MS (EI) *m*/*z* (%) 424 ($[M+H]^+$, 27), 423 ($[M]^+$, 100), 340 (39), 324 (16), 264 (12), 250 (12); HRMS (EI) calcd for $C_{25}H_{29}NO_5$ $[M]^+$ 423.2046, found 423.2042.

10. Procedure for the cycloaddition of methyl {[2-(methoxycarbonyl)(phenyl)-amino]phenyl}diazoacetates (12b) and trimethylsilyl vinyl ether.

To a solution of $La(OTf)_3$ (1.8 mg, 3.07×10^{-3} mmol), $Rh_2(OAc)_4$ (1.4 mg, 3.07×10^{-3} mmol), and MS 4Å (100 mg) in refluxing CH_2Cl_2 (0.75 mL), a solution of **12b** (100 mg, **12b**:**13b** = 15:1) and trimethylsilyl vinyl ether (229 μL, 1.54 mmol) in CH_2Cl_2 (2.25 mL) was added over 1 h using syringe pump, and the mixture was further stirred for 1 h at the same temperature. After the completion of the reaction, the whole mixture was filtered through a pad of Celite, and the combined filtrate was concentrated in vacuo to furnish the crude product, which was purified by column chromatography (silica gel, 5:1 *n*-hexane/EtOAc and CH_2Cl_2 only) to give **17h** (1.2 mg, trace) as a colorless oil: IR ($CHCl_3$) *v* 2954, 1741, 1595, 1499 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.00 (9H, s), 2.59 (1H, d, *J* = 13.3 Hz), 2.73 (1H, dd, *J* = 13.3, 5.0 Hz), 3.42 (3H, s), 4.08 (3H, s), 5.86 (1H, d, *J* = 5.0 Hz), 7.06 (1H, t, *J* = 7.3 Hz), 7.18-7.90 (8H, m); MS (EI) *m*/*z* (%) 414 ($[M+H]^+$, 28), 413 ($[M]^+$, 100), 266 (14), 265 (25), 264 (68), 238 (22), 236

(14), 221 (37), 204 (14), 195 (13), 133 (14); HRMS (EI) calcd for $C_{22}H_{27}NO_5Si$ $[M]^+$ 413.1658, found 413.1655.

11. Procedure for the cycloaddition of methyl {[2-(methoxycarbonyl)(phenyl)-amino]phenyl}diazoacetates (12b) and 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene.

To a solution of $La(OTf)_3$ (1.5 mg, 2.58×10^{-3} mmol), $Rh_2(OAc)_4$ (1.1 mg, 2.58×10^{-3} mmol), and MS 4Å (100 mg) in refluxing CH_2Cl_2 (0.65 mL), a solution of **12b** (84 mg, **12b**:**13b** = 15:1) and 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (282 μL, 1.29 mmol) in CH_2Cl_2 (1.95 mL) was added over 1 h using syringe pump, and the mixture was further stirred for 1 h at the same temperature. After the completion of the reaction, the whole mixture was filtered through a pad of Celite, and the combined filtrate was concentrated in vacuo to furnish the crude product, which was purified by column chromatography (silica gel, 5:1 *n*-hexane/EtOAc and CH_2Cl_2 only) to give **17i** (9 mg, 8%) as a colorless solid: mp 131–132 °C (EtOAc); IR ($CHCl_3$) *v* 2952, 2930, 2857, 1741, 1596, 1500 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ –0.46 (3H, s), –0.02 (3H, s), 0.63 (9H, s), 2.44 (1H, d, *J* = 13.6 Hz), 2.69 (1H, d, *J* = 13.2 Hz), 3.20 (3H, s), 3.49 (3H, s), 3.87 (3H, s), 6.87 (1H, td, *J* = 7.3, 1.0 Hz), 7.06-7.18 (2H, m), 7.23 (1H, td, *J* = 7.3, 1.4 Hz), 7.32-7.47 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ –4.3 (CH_3), –3.6 (CH_3), 17.7 (C), 25.7 ($CH_3\times3$), 40.7 (CH_2), 51.4 (CH_3), 51.7 (CH_3), 52.7 (CH_3), 91.6 (C), 105.8 (C), 109.2 (CH), 119.7 (CH), 121.3 (C), 121.4 (CH×2), 123.7 (CH), 126.7 (CH), 127.4 (C), 129.1 (CH×2), 130.1 (CH), 139.8 (C), 148.6 (C), 169.7 (C); MS (EI) *m*/*z* (%) 485 ($[M]^+$, 22), 470 (11), 428 (27), 339 (11), 338 (24), 298 (18), 297 (100), 294 (12), 280 (10), 238 (14), 236 (11), 205 (10); HRMS (EI) calcd for $C_{26}H_{35}NO_6Si$ $[M]^+$ 485.2234, found 485.2236.

12. Procedure for the cycloaddition of methyl {[2-(methoxycarbonyl)(phenyl)-amino]phenyl}diazoacetates (12b) and 2,3-dihydrofuran.

To a solution of $La(OTf)_3$ (1.7 mg, 2.83×10^{-3} mmol), $Rh_2(OAc)_4$ (1.3 mg, 2.83×10^{-3} mmol), and MS 4Å (100 mg) in refluxing CH_2Cl_2 (0.70 mL), a solution of **12b** (92 mg, **12b**:**13b** = 15:1) and 2,3-dihydrofuran (107 μL, 1.41 mmol) in CH_2Cl_2 (2.1 mL) was added over 1 h using syringe pump, and the mixture was further stirred for 1 h at the same temperature. After the completion of the reaction, the whole mixture was filtered through a pad of Celite, and the combined filtrate was concentrated in vacuo to furnish the crude product, which was purified by column chromatography (silica gel, 5:1 *n*-hexane/EtOAc and CH_2Cl_2 only) to give **17j** (12 mg, 12%) as a colorless solid: mp 130–133 °C (EtOAc); IR ($CHCl_3$) *v* 3017, 2954, 1733, 1596, 1495 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.56-1.75 (1H, m), 2.05-2.23 (1H, m), 3.60 (3H, s), 3.65-3.78 (2H, m), 3.89 (3H, s), 3.80-4.04 (1H, m), 5.51 (1H, d, *J* = 8.1 Hz), 6.89-7.10 (3H, m), 7.10-7.40 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1 (CH_2), 49.0 (CH), 53.0 (CH_3), 53.2 (CH_3), 60.2 (C), 66.7 (CH_2), 89.8 (CH), 120.7 (CH×2), 120.8 (CH), 122.0 (CH), 122.9 (CH), 127.4 (CH), 127.8 (C),

128.8 (CH), 129.1 (CH×2), 142.2 (C), 145.9 (C), 169.5 (C), 171.2 (C); MS (EI) *m*/*z* (%) 368 ($[M+H]^+$, 23), 367 ($[M]^+$, 100), 308 (37), 278 (22), 276 (18), 248 (19), 220 (10); HRMS (EI) calcd for $C_{21}H_{21}NO_5$ $[M]^+$ 367.1420, found 367.1414.

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