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N-Chlorinative Ring Contraction of 1,4-Dimethoxyphthalazines via a Bicyclization/Ring-Opening Mechanism

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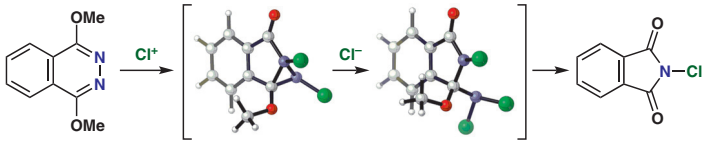

- Chlorenium-promoted ring contraction
- Bicyclization/ring-opening mechanism
- Elimination of a nitrogen fragment

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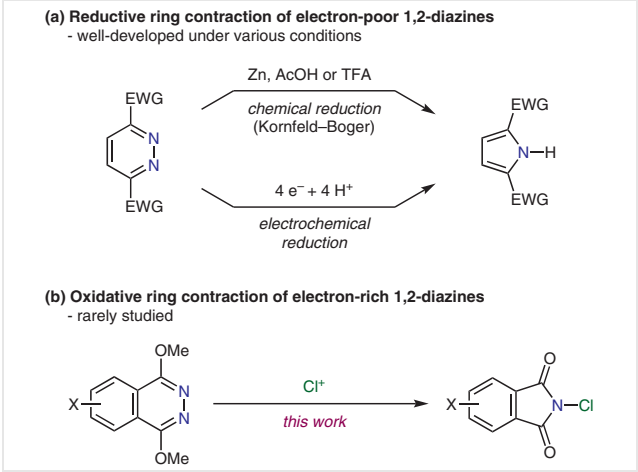
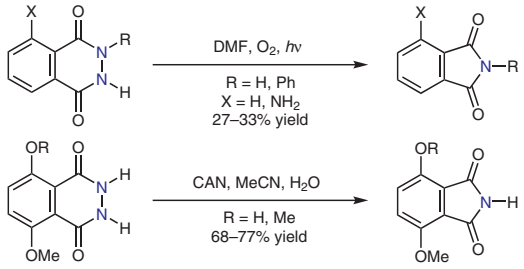
Abstract An unprecedented *N*-chlorinative ring contraction of 1,2-diazines was discovered and investigated with an electrophilic chlorinating reagent, trichloroisocyanuric acid (TCICA). Through optimization and mechanistic analysis, the assisting role of *n*-Bu_4NCl as an exogenous nucleophile was identified, and the optimized reaction conditions were applied to a range of 1,4-dimethoxyphthalazine derivatives. Also, an improvement of overall efficiency was demonstrated by the use of a labile *O*-silyl group. A bicyclization/ring-opening mechanism, inspired by the Favorskii rearrangement, was proposed and supported by the DFT calculations. Furthermore, the efforts on scope expansion as well as the evaluation of other electrophilic promoters revealed that the newly developed ring contraction reactivity is a unique characteristic of 1,4-dimethoxyphthalazine scaffold and TCICA.

Key words halogenation, heterocycles, trichloroisocyanuric acid, ring contraction, phthalazine, phthalimide

Ring contraction of polyaza-heterocycles can serve as a useful method for the construction of smaller aza-heterocycles.[1] 1,2-Diazines are particularly suitable substrates for such purpose because of the presence of a weak, easily cleavable N–N bond. The loss of a nitrogen fragment typically takes place in the form of ammonia or ammonium ion. Reductive ring contraction of electron-poor 1,2-diazine has been the main focus of this field and investigated by many research groups under a variety of reaction conditions (Scheme 1a).[2–4] For example, pyridazine 3,6-diester can be contracted to pyrrole in the presence of chemical reductant such as Zn/AcOH via reductive cleavage of the N–N bond with high efficiency. This process has been effectively adopted by the groups of Kornfeld and Boger in a sequential tetrazine Diels–Alder cycloaddition/reductive ring contraction strategy.[2c,2g–i] Similar transformations could also be conducted under electrochemical conditions,[3] in which electricity serves as the source of electrons. Thermal and photochemical activation effect the contraction of electron-poor 1,2-diazine derivatives as well.[4,5] On the other hand, the complementary, oxidative ring contraction of electron-rich 1,2-diazines has been investigated sporadically and thus not found its synthetic utility, yet (Scheme 1b).[6] Only a few related examples with 2,3-dihydrophthalazine-1,4-dione derivatives have been reported a while ago (Scheme 2).[7] In the presence of either oxygen gas or ceric ammonium nitrate (CAN), ring contraction took place to give phthalimides in moderate yields. However, such reactivity has not been systematically examined, and the contraction mechanism is still unknown. Recently, our group has reported a preliminary communication on a rare type of oxidative ring contraction of electron-rich 1,4-dimethoxyphthalazines that is initiated by *N*-chlorination (Scheme 1b).[8] The newly observed oxidative reaction is complementary to the well-known reductive ring contraction and applicable to a range of alkyl- and halogen-substituted phthalazine derivatives although the reaction efficiency was moderate. Herein, we report a detailed full account on the investigation of this unusual mode of ring contraction.



Scheme 1 Ring contraction of 1,2-diazine under (a) reductive and (b) oxidative conditions

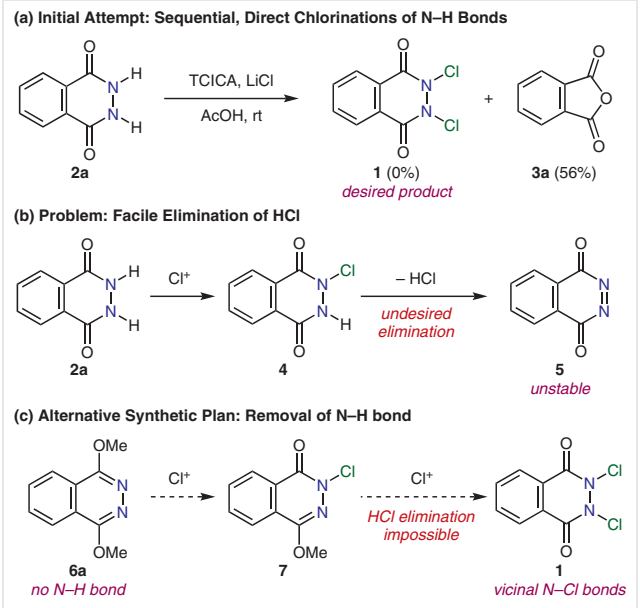


Scheme 2 Oxidative ring contraction of 2,3-dihydrophthalazine-1,4-diones

Common electrophilic chlorinating reagents such as *N*-chlorosuccinimide and *N*-chlorophthalimide have a polarized N–Cl bond. The electron affinity of nitrogen is enhanced by the presence of one or more electron-withdrawing groups on it, and the attached chlorine atom is thereby rendered electron-deficient. We were curious about the unknown, potentially interesting chlorinating reactivity of the consecutively arranged N–Cl bonds. The desired structural motif can be represented as *N*,*N*′-dichlorophthalazinedione (**1**) (Scheme 3). Initially, direct, sequential *N*-chlorinations of 2,3-dihydrophthalazine-1,4-dione (**2a**) was attempted with a variety of electrophilic chlorinating reagents including trichloroisocyanuric acid (TCICA) in AcOH.[9] However, phthalic anhydride (**3a**) was obtained as a major product along with insoluble polymeric materials,[10] and no sign of *N*-chlorination was detected (Scheme 3a). It is probable that, after the first *N*-chlorination, the facile elimination of HCl must have taken place prior to the second *N*-chlorination, thus preventing the formation of **1** (Scheme 3b). Then, the resulting oxidized form, phthalazine-1,4-dione (**5**) could have either polymerized by itself or reacted with solvent (AcOH) to give **3a**.[11] To avoid the undesired HCl elimination of the putative intermediate **4**, the N–H bonds need to be removed. We hypothesized that an imidate moiety may serve as a reactive nitrogen nucleophile that is absent of N–H bonds (Scheme 3c). Therefore, 1,4-dimethoxyphthalazine (**6a**) was selected as a potential precursor to the vicinal *N*,*N*′-dichloride.

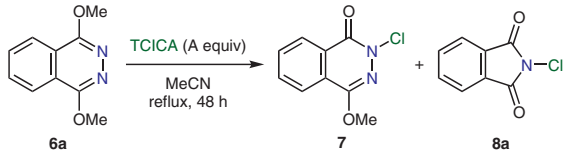
N-Chlorination of **6a** was examined with TCICA (Table 1). At room temperature, the reaction was sluggish (Table 1, entry 1). Only a small amount of monochloride **7** was produced, and no trace of dichloride was detected. The formation of **5** was prevented as proposed, but the reaction stalled after the first *N*-chlorination. The transformation was driven forward at higher temperature in refluxing MeCN (entry 2). Unexpectedly, instead of the intended second *N*-chlorination, an unprecedented type of electrophilic halogenation-induced ring contraction took place to give *N*-chlorophthalimide (**8a**) via elimination of one nitrogen atom. The ability of TCICA in promoting ring contraction of **6a** seems unique as other common electrophilic halogenating reagents are ineffective.[12] Subsequently, the amount of TCICA was increased up to eight equivalents, and the conversion was gradually improved up to 89% (entries 3–5). At this stage, it was found that the addition of exogenous chloride facilitates the ring contraction (see the mechanistic discussion below). In the presence of *n*-Bu_4NCl, a sizable enhancement of the conversion was observed (entry 3 vs 6).[13] However, loss of the product during repeated chromatographic purification on silica gel led to erroneous isolated yields. Interestingly, simple change of the reaction solvent from MeCN to chlorinated hydrocarbon such as 1,2-DCE attenuated the ring contraction even at reflux and resulted in the formation **7** as the major product (entry 7). The low nucleophilicity of **7** and the relative instability of the cationic, chlorinated intermediate in nonpolar solvent are likely to be responsible for the attenuation of the second *N*-chlorination as well as the subsequent ring contraction.

Even though the chlorinative ring contraction product **8a** was generated in high conversion, its instability on silica gel prevented quantitative recovery of pure material. This problem could be alleviated by the reduction of the reactive N–Cl bond with reducing agent prior to the purification (Table 2). It was found that $NaBH_4$ reduces **8a** quantitatively.[14] With this reductive workup process, phthalimide (**9a**) could be obtained in a reliable fashion (Table 2, entry 1). Again, the ring contraction was assisted by the addition of *n*-Bu_4NCl (entry 2). As the amount of *n*-Bu_4NCl was increased, the isolated yield of **9a** was improved a bit (entries 3 and 4).[15] A large excess of TCICA was also beneficial (entries 5 and 6). However, the isolation procedure became cumbersome. When the ring contraction was attempted at higher



Scheme 3 Synthetic approach toward the formation of vicinal N–Cl bonds: (a) unsuccessful direct N–H chlorination, (b) decomposition of intermediate via HCl elimination, (c) alternative reactant without N–H bond.

Table 1 Initial Survey of Reaction Variables[a]



Entry	A (equiv)	**6a**[b]	**7**[b]	**8a**[b]	Yield (%) of **8a**
1[c]	1	88	12	0	0
2	1	14	50	36	10
3	2	0	49	51	34
4	4	0	25	75	49
5	8	0	11	89	44[d]
6[e]	2	0	18	82	37[d]
7[f]	4	0	80	20	ND

[a] Reaction conditions: 1.0 mmol of **6a** at 0.17 M concentration.
[b] Approximate integration ratio by ^{1}H NMR analysis of the crude mixture.
[c] At room temperature.
[d] Chromatographed twice on silica gel.
[e] With 1 equiv of *n*-Bu_4NCl.
[f] In 1,2-DCE.

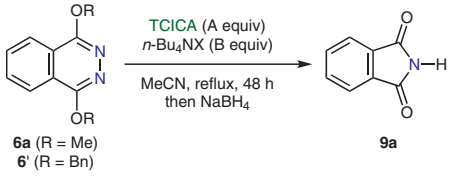
temperature in refluxing EtCN, TCICA was consumed through the chlorination of solvent, leading to a noticeably decreased product formation (entry 7). Bromide turned out to be an incompetent nucleophile, and its oxidation by TCICA probably complicated the reaction progress (entry 8). Additionally, the ease of dealkylation appeared critical as the benzyl derivative **6′** was less reactive (entry 9). With the reaction conditions in entry 4, we set out to survey substrates.

A variety of 1,4-dimethoxyphthalazine derivatives **6** were prepared from readily available phthalic anhydride (**3**) via a three-step sequence in a straightforward manner (Scheme 4). First, condensation of **3** with hydrazine hydrate afforded 2,3-dihydrophthalazine-1,4-diones **2**, which were subsequently transformed to 1,4-dichlorophthalazines **10** upon treatment with $POCl_3$.[16] Then, the following displacement of the chlorides with sodium methoxide provided **6** in variable overall yields.[17] This procedure generally tolerates substituents at the 6-position. Weakly electron-donating alkyl groups (**b**, **c**) as well as electron-withdrawing bromine and chlorine substituents (**d**, **e**) could be installed at the 6-position. The introduction of substituents at the sterically hindered 5-position was accomplished in slightly lower overall yields (**f**–**h**). In addition, a disubstituted substrate (**i**) was also prepared with moderate efficiency.

Unfortunately, it was difficult to access higher substitution patterns. From tetrachloro- and tetrabromophthalic anhydrides **3l** and **3m**, the corresponding *N*-aminophthalimides **11l** and **11m** were produced as the major constitutional isomers probably because sterically crowded environment favors the formation of smaller five-membered cyclic structures (Scheme 5a). In addition, the installation of a fluorine substituent was hampered by nucleophilic displacement in the last step (Scheme 5b). From the reactions of **10j**[8] and **10h** with NaOMe under the standard conditions, the corresponding trimethoxyphthalazines **6j** and **6k** were obtained. The relative reactivity of halogen substituents could be estimated by stopping these reactions prematurely and analyzing the remaining halogens. It turned out that the 6-fluorine substituent of **10j** is more labile than the 1- and 4-chlorine substituents. In contrast, the 5-fluorine substituent of **10h** was found to be slightly less reactive than the chlorine, and thus it was possible to produce **6h** by reducing the amount of NaOMe to two equivalents albeit the low isolated yield (Scheme 4). A similar problem was also present when the introduction of a NO_2 group was attempted.

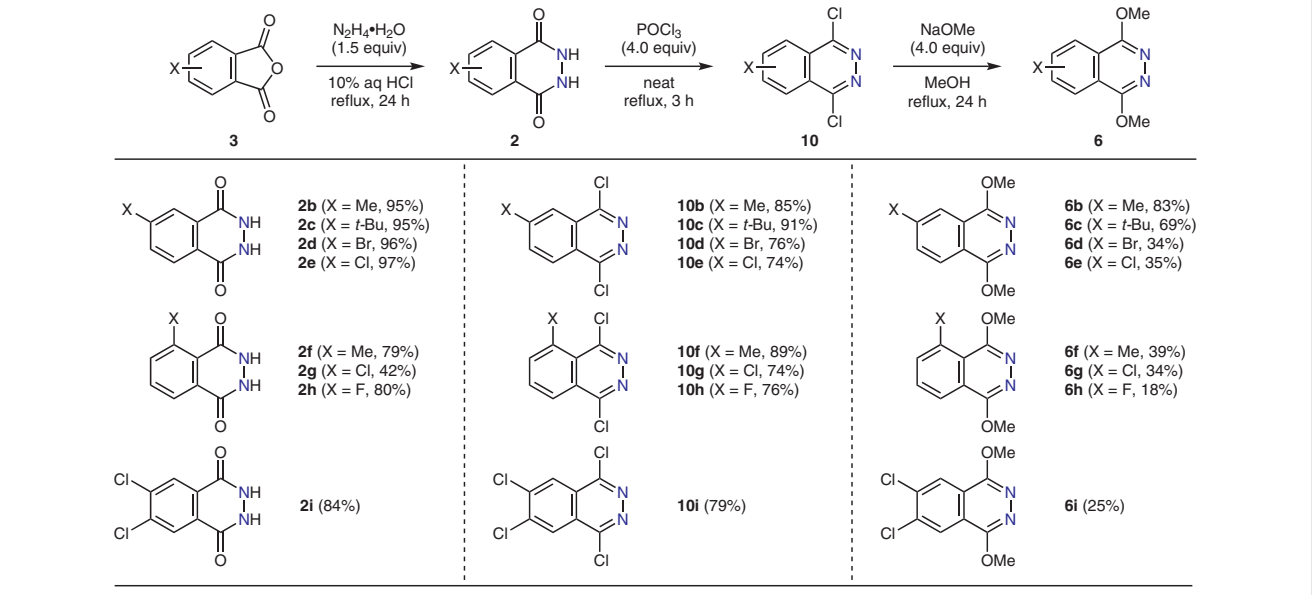
The scope of *N*-chlorinative ring contraction was examined with these 1,4-dimethoxyphthalazines **6** under the optimized reaction conditions (Scheme 6). As observed with **6a**, the addition of *n*-Bu_4NCl usually resulted in an improved yield. On the other hand, the reductive $NaBH_4$ workup was not always helpful as it often led to a diminished mass recovery. Thus, the substrate survey was conducted both with and without $NaBH_4$ workup in some cases. The derivatives with an alkyl group at the 6-position contract to the corresponding *N*-chlorophthalimides **8b**,**c** and phthalimide **9c** in moderate yields. The reaction conditions also tolerate electron-withdrawing halogen substituents (**8e**, **9d**,**e**). Fortunately, steric hindrance at the 5-position does not have noticeable influence on ring contraction. An alkyl group as well as halogen substituents can be em-

Table 2 Reaction Condition Optimization with Reductive Workup[a]



Entry	R	X	A (equiv)	B (equiv)	Yield (%)[b]
1	Me	Cl	4	0	35
2	Me	Cl	4	1	49
3	Me	Cl	4	2	52
4	Me	Cl	4	4	54
5	Me	Cl	8	1	44
6	Me	Cl	8	2	54
7[c]	Me	Cl	4	1	32
8	Me	Br	4	4	11
9	Bn	Cl	4	1	28

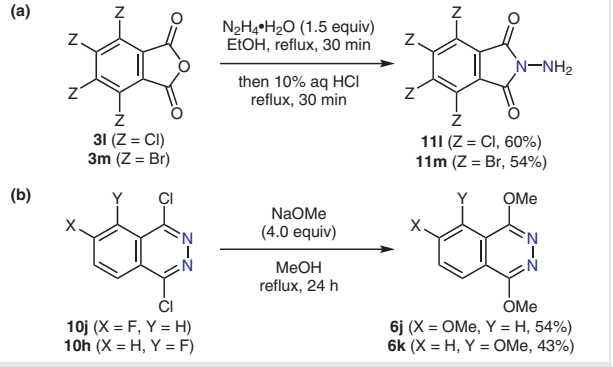
[a] Reaction conditions: 1.0 mmol of **6a** or **6′** at 0.17 M concentration.
[b] Isolated yield after column chromatography.
[c] In refluxing EtCN.



Scheme 4 Preparation of 1,4-dimethoxyphthalazine substrates. Yield of the crude material is given for **2** and **10**. Isolated yield after column chromatography is given for **6**. For **6h**: The reaction was conducted with 2.0 equiv of NaOMe.

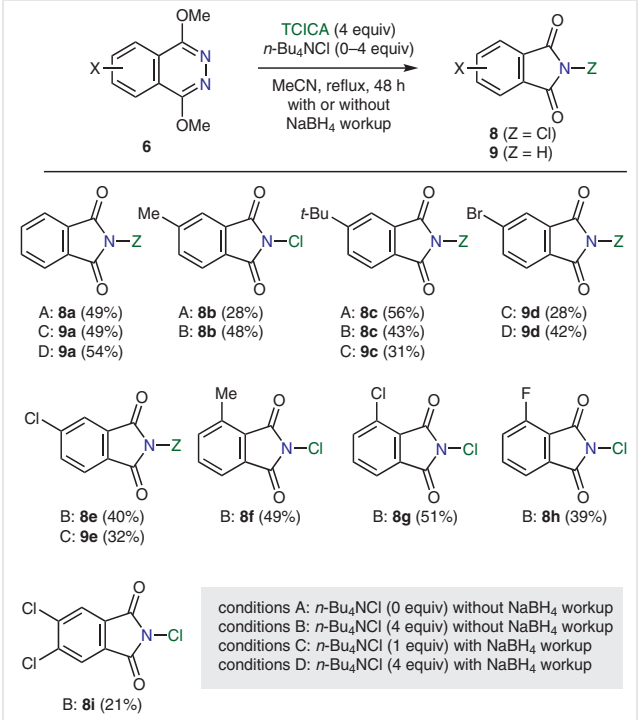
ployed with comparable efficiencies (**8f–h**). Strangely, 6,7-dichlorinated substrate **6i** is reluctant to the ring contraction. Upon the standard operation, the unreacted reactant and the monochlorinated intermediate were produced as the major components. Only a small amount of the ring contraction product **8i** could be obtained even after 5 days of reaction time. Unfortunately, the current oxidative process is not applicable to highly electron-rich substrates such as **6j** and **6k**, which decompose under the reaction conditions.

To probe the possibility of scope expansion, a monocyclic analogue, 3,6-dimethoxypyridazine (**12**) was examined (Equation 1). *N*-Chlorination may take place, but it is generally more difficult to break the aromaticity of monocyclic π-system than that of polycyclic one. Consequently, instead of the ring contraction, an electrophilic chlorination of the aromatic ring was observed.

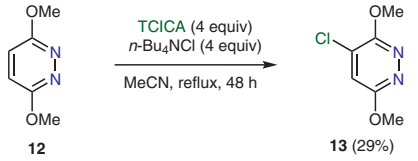


Scheme 5 Problems encountered during substrate preparation

Additionally, several control experiments were carried out (Scheme 7). A few readily available and structurally related heterocyclic compounds such as 2,3-dihydrophthala-

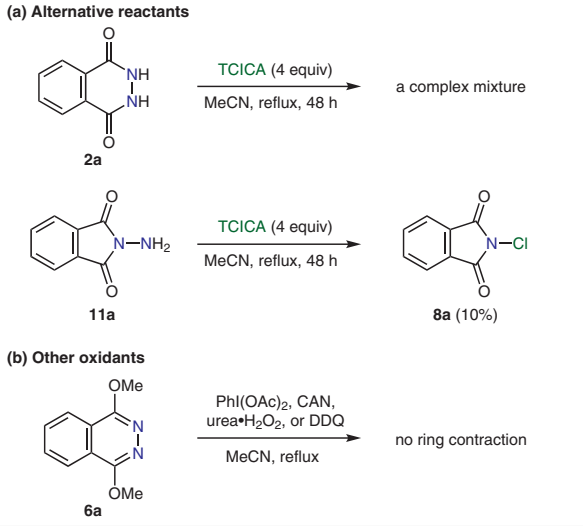


Scheme 6 *N*-Chlorinative ring contraction of 1,4-dimethoxyphthalazines. The reactions were conducted with 1.0 mmol of **6** at 0.17 M concentration. Isolated yields after column chromatography are shown in the parenthesis. For **8i**: Reaction time: 5 days.



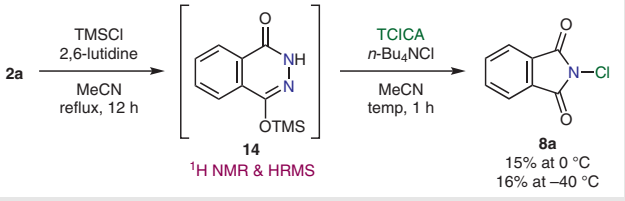
Equation 1 Attempt at scope expansion to monocyclic analogue

zine-1,4-dione (**2a**) and *N*-aminophthalimide (**11a**) were used as potential alternative starting materials (Scheme 7a). However, a complex mixture was obtained from **2a** without any sign of **8a**, and only a small amount of **8a** was produced from **11a**. Thus, it appears that the *N*-chlorinative ring contraction reactivity is a characteristic property of the electron-rich phthalazine scaffold. On the other hand, other common oxidants including $PhI(OAc)_2$, ceric ammonium nitrate (CAN), urea·H_2O_2 (UHP), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) are unable to promote analogous oxidative ring contraction of **6a** (Scheme 7b).



Scheme 7 Control experiments: (a) related heterocycles as reactants and (b) examination of common oxidants.

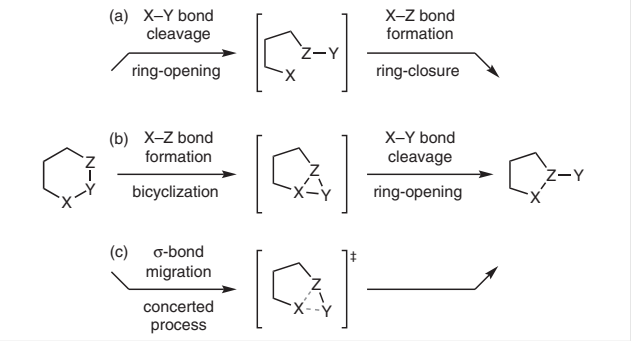
Though an unprecedented reactivity has been discovered, the ring contraction efficiency is only moderate. One of the most difficult bond-forming/breaking events in the transformation of **6** was thought to be the removal of two *O*-methyl groups, which may, at least partly, be responsible for the slow reaction rate. Thus, it was hypothesized that the replacement of these robust methyl groups with more labile protecting groups such as silyl groups may facilitate the overall process. Moreover, the direct *O*-silylation of **2** will significantly decrease the number of steps, and thus the step-economy could be improved as well. However, whereas the first silylation took place readily, the installation of the second silyl group was sluggish, providing a mixture of mono- and disilylated products. The purification of these compounds was also challenging because these O–Si bonds are hydrolytically unstable as expected. To avoid the exposure of the silylated intermediates to moisture, a one-pot operation was pursued (Scheme 8). Accordingly, the treatment of **2a** with TMSCl in the presence of 2,6-lutidine afforded the monosilylated species **14**, which was characterized by ^{1}H NMR and HRMS. Even when excess amounts of TMSCl and base were employed, **14** was formed as a major product. Therefore, the subsequent one-pot ring contraction was investigated with **14**, hoping that the *N*-chlorination would produce an intermediate analogous to **7**. Interestingly, the reaction of **14** with TCICA proceeds vigorously even at room temperature, and immediate gas evolution was observed upon mixing. To control the high reactivity, the chlorinative contraction step was performed in a cooling bath. The reaction was still facile at 0 °C, and **14** was completely consumed within one hour. Unfortunately, the crude mixture was complex, and the product **8a** was isolated in low yield. Further lowering the reaction temperature to –40 °C did not lead to meaningful improvement. Although the chemical yield of this process is not yet high enough to be practical, the overall efficiency has been noticeably enhanced through the modification of the *O*-protecting group. By utilizing the easily attachable and readily cleavable TMS group, the previous lengthy reaction sequence became dramatically shortened, and much milder reaction conditions were accomplished in terms of both reaction time and temperature.



Scheme 8 Shorter sequence and milder conditions via the use of a labile *O*-silyl protecting group

Ring contraction mechanism can be categorized into three types (Scheme 9). The transformation can be initiated by cleavage of a bond within the ring, and then the subsequent cyclization onto a closer site leads to ring contraction (Scheme 9a). Most of the reductive ring contractions of 1,2-diazine were proposed to proceed via this type of ring-opening/ring-closure mechanism.[2,3] Alternatively, bond formation can take place first to generate a bicyclic intermediate (Scheme 9b). Then, the following opening of the strained small ring completes the bicyclization/ring-opening mechanism. A representative example of this category is the well-known Favorskii rearrangement.[18] Similar mechanisms have also been proposed for oxidative as well as reductive ring contraction of polyaza-heterocycles.[19] The third pathway involves simultaneous migration of a σ-bond

in a concerted fashion (Scheme 9c). After these ring contractions, the resulting exocyclic part Y is often eliminated as a small fragment.



Scheme 9 Three types of ring contraction mechanism: (a) ring-opening/ring-closure mechanism, (b) bicyclization/ring-opening mechanism, and (c) concerted σ-bond migration mechanism.

The ring-opening/ring-closure mechanism would require a high activation energy because this process is initiated by the cleavage of a strong bond.[20] Thus, a pathway involving a bond formation at an early stage is more probable, and we propose a bicyclization/ring-opening mechanism for the newly developed *N*-chlorinative ring contraction (Figure 1a).[8] Starting from the identified intermediate **7**, chlorination of the nucleophilic imidate nitrogen (N^b) with TCICA affords a delocalized cation ***i*** containing a highly electrophilic low-lying π-system, which can then be attacked by the adjacent nitrogen (N^a) to form a [3,1,0] bicyclic species ***ii***. The opening of strained diaziridinium ring would be assisted by exogenous nucleophile, and this proposal is consistent with the observed beneficial effect of *n*-Bu_4NCl (Tables 1 and 2). Finally, the extrusion of a small nitrogen fragment from ***iii*** and the subsequent demethylation of ***iv*** completes the *N*-chlorinative ring contraction to **8a**. This proposed mechanism is supported by density functional theory (DFT) calculation (Figure 1b). The transition states for the critical bicyclization/ring-opening sequence were successfully located at the M06-2X-D3/6-311+G(d,p) level of theory[21,22] with the implicit Solvation Model based on Density (SMD)[23] by the GAMESS(US) software package.[24–26] The precise single point energies were calculated with a larger 6-311++G(2d,2p) basis set. The high activation barrier of the bicyclization step is probably responsible for the moderate efficiency of overall ring contraction (from ***i*** to ***ii***, $\Delta G^{\ddagger}$ = 29.3 kcal/mol). The unassisted opening of diaziridinium is energetically uphill (from ***ii*** to ***v***, ΔG° = 27.6 kcal/mol), and the resulting chloronitrenium (R–N=Cl^+)[27] species ***v*** resides on a saddle point. On the other hand, the incorporation of a chloride nucleophile renders this process highly favorable (from ***ii*** to ***iii***, ΔG° = –40.9 kcal/mol), and only a small amount of activation energy is required ($\Delta G^{\ddagger}$ = 2.0 kcal/mol), thus supporting the beneficial role of *n*-Bu_4NCl.

On the basis of the calculation results, a few modifications of the reaction conditions that may accelerate the ring contraction process were suggested and evaluated computationally in a similar manner as described above (Figure 2). The introduction of a more electronegative element such as fluorine in place of the chlorine (Cl^b) in ***i*** will enhance the electrophilicity of the cationic π-system and potentially facilitate the diaziridinium formation. This argument is supported by the DFT calculation as a decreased activation energy ($\Delta G^{\ddagger}$ = 25.6 kcal/mol) is found for the ring contraction

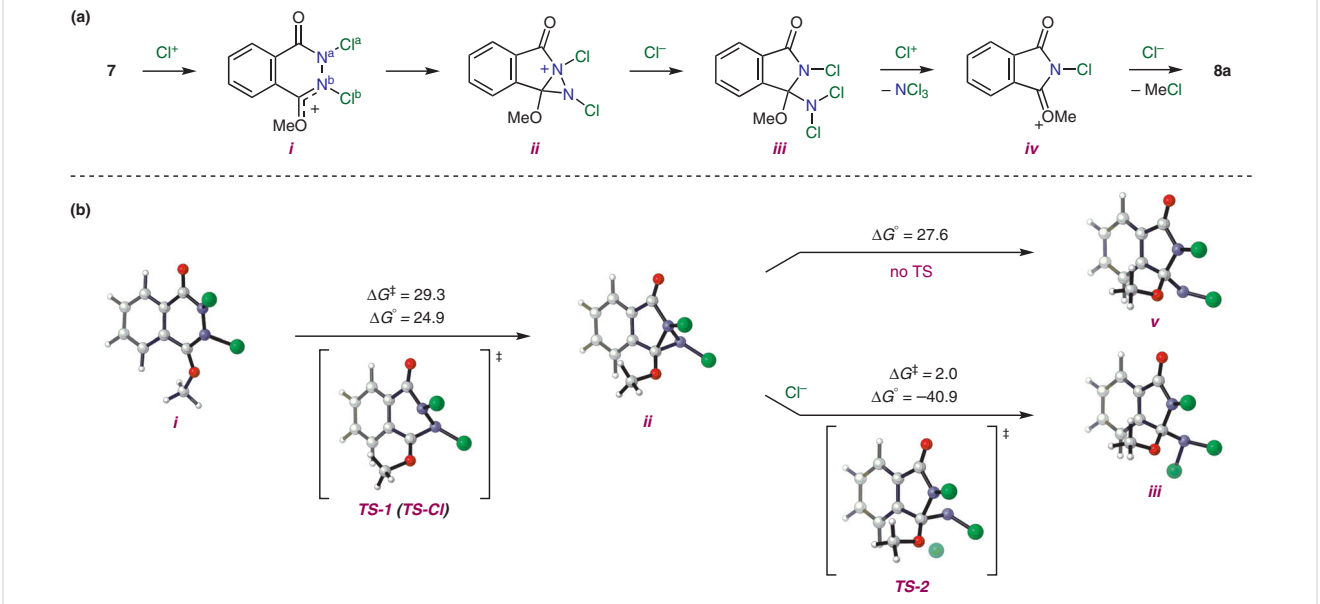


Figure 1 (a) Proposed bicyclization/ring-opening mechanism and (b) DFT calculation (M06-2X-D3/6-311++G(2d,2p)//6-311+G(d,p), SMD-MeCN). The free energies are shown in kcal/mol.

of the fluorinated analogue (X = F). On the other hand, the presence of a more Lewis basic element such as oxygen is expected to accelerate the N–N bond cleavage. Interestingly, the internal nucleophilic assistance of the oxygen lone pair of the *N*-oxide analogue (X = O⁻) led to a dramatic change of the reaction mechanism. In this case, the N–N bond cleavage takes place simultaneously during the C–N bond formation via a concerted σ-bond migration (see Scheme 9c), directly leading to an uncharged nitroso species without the intermediacy of a bicyclic diaziridinium species. In consequence, the transformation becomes thermodynamically favorable (ΔG° = –12.5 kcal/mol). However, the activation energy increases significantly ($\Delta G^\ddagger$ = 34.0 kcal/mol). The 3D structures of these transition states from the DFT calculation are depicted in Figure 2b. To verify these computational predictions, additional experiments were carried out under the modified reaction conditions.

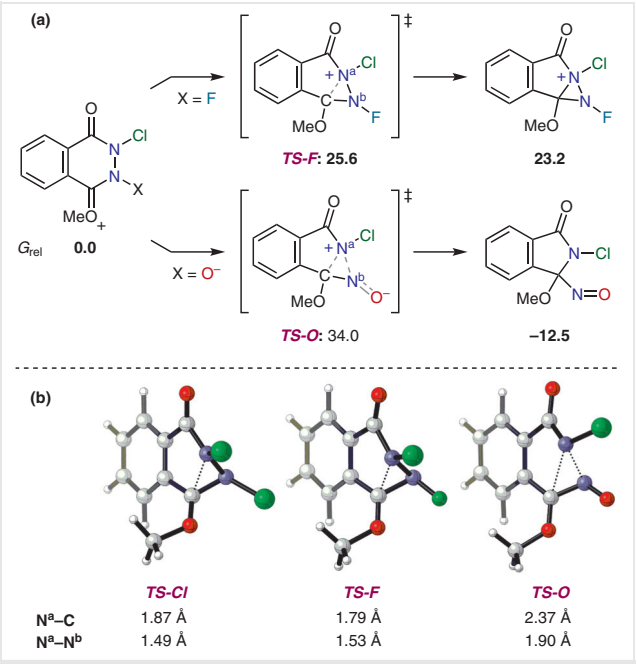
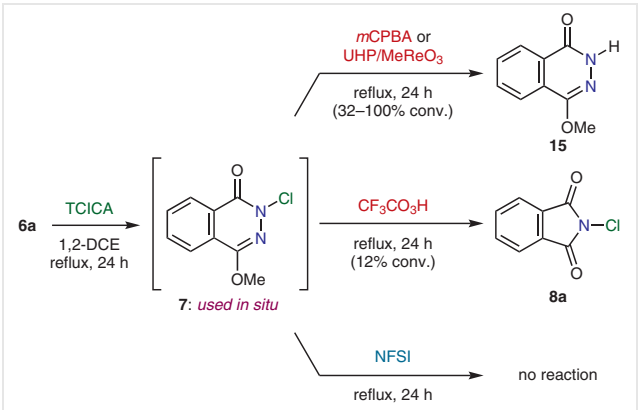


Figure 2 The computational analysis on the effects of other *N*-substituents on ring contraction process (M06-2X-D3/6-311++G(2d,2p)//6-311+G(d,p), SMD-MeCN). (a) thermochemical data (the relative free energies in kcal/mol), (b) transition states comparison.

The reasonably selective formation of the monochlorinated intermediate **7** in 1,2-DCE (Table 1, entry 7) allowed the survey of other electrophilic promotors for the ring contraction step. Unfortunately, a majority of these experiments could not be conducted in refluxing MeCN because most peroxides and fluorenium reagents react with the solvent. Therefore, one-pot operation in 1,2-DCE was attempted instead (Scheme 10), even though 1,2-DCE is a poor solvent for the ring contraction with TCICA. However, the imidate nitrogen of **7** is insusceptible to oxidation under these reaction conditions. Upon treatment with *m*CPBA or UHP/$MeReO_3$, a loss of the *N*-chlorine substituent to **15** was observed without any detectable sign of ring contraction. With CF_3CO_3H, **7** remained mostly unreacted, and only a small amount of **8a** was produced. Moreover, the reaction with *N*-fluorobenzenesulfonimide (NFSI) did not proceed at all. Other fluorenium reagents such as Selectfluor could not be examined properly because of their low solubility in 1,2-DCE. The lack of oxidative ring contraction reactivity in 1,2-DCE suggests that it is necessary to find oxidants that are compatible with MeCN.

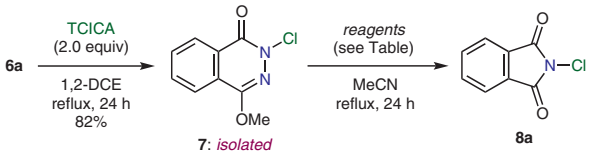


Scheme 10 Examination of other potential electrophilic promotors via one-pot operation in 1,2-DCE

After a brief screening, it was found that $K_2S_2O_8$, an inorganic oxidant, does not oxidize MeCN. Thus, the promoting ability of $K_2S_2O_8$ was evaluated in MeCN (Table 3). For this study, **7** was isolated so that the unreacted TCICA would not hamper the precise analysis of the next reaction. Disappointingly, $K_2S_2O_8$ was unable to trigger the ring contraction (Table 3, entry 1). Although $K_2S_2O_8$ is a poor promoter by itself, it may have an assisting effect as was observed with *n*-Bu_4NCl. To test this hypothesis, $K_2S_2O_8$ was employed in combination with TCICA, and a small amount of **8a** was produced (entry 2). However, the isolated yield is much lower than those of the reactions with TCICA/*n*-Bu_4NCl (entry 3) and even TCICA alone (entry 4). Therefore, it appears that $K_2S_2O_8$ actually interferes with the ring contraction. Although the inferior promoting ability of oxygenating reagents has been predicted by the DFT calculation (Figure 2), the inhibiting effect is unexpected, and the reasons are currently unknown.

In summary, a rarely observed oxidative ring contraction of 1,2-diazines was accomplished by *N*-chlorination. TCICA promoted this unusual reactivity whereas other oxidants were ineffective. On the basis of the mechanistic proposal, the presence of a soluble chloride was found to facilitate the ring contraction, and the exogenous nucleophile was expected to assist the opening of the putative diaziridinium intermediate. The newly developed reactivity was applied to a variety of 1,4-dimethoxyphthalazine derivatives with the exception of highly electron-rich substrates.

Table 3 Evaluation of $K_2S_2O_8$ as an Electrophilic Promoter in MeCN[a]



Entry	$K_2S_2O_8$ (equiv)	TCICA (equiv)	*n*-Bu_4NCl (equiv)	Yield (%)[b]
1	2.0	–	–	0
2	2.0	2.0	–	14
3	–	2.0	2.0	45
4	–	2.0	–	26

[a] Reaction conditions: 0.5 mmol of **7** at 0.17 M concentration.
[b] Isolated yield after column chromatography.

Also, although further exploration is still needed, the overall sequence as well as the reaction conditions could be improved by utilizing a more labile *O*-TMS group. For this unprecedented transformation, a bicyclization/ring-opening mechanism was proposed from the isolated monochlorinated intermediate and supported by DFT calculation. Additional theoretical analysis suggested potential rate acceleration and even a change of the reaction pathway through alteration of the electronic property of the second *N*-substituent. However, the examination of several other electrophilic reagents only revealed the unique ring contraction-promoting ability of TCICA. Nonetheless, whereas reductive ring contractions of polyaza-heterocycles are well-documented, the complementary transformations under oxidative conditions are far less developed. We believe that our new finding will provide a valuable addition to the modern synthetic toolbox in heterocyclic chemistry

All reactions were performed in oven-dried (140 °C) or flame-dried glassware under an atmosphere of dry argon unless otherwise noted. Purification of solvents and reagents are described in the Supporting Information. Column chromatography was performed with Merck Millipore silica gel (SiO_2) 60 (0.040–0.063 mm). Analytical TLC was performed on Merck Millipore TLC silica gel 60 F_{254}. Visualization of TLC was accomplished with UV (254 nm) and a $KMnO_4$ staining solution. ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a JEOL ECS400 spectrometer (400 MHz, ^1H; 100 MHz, ^{13}C). Chemical shifts are referenced to residual $CHCl_3$ (7.26 ppm for ^1H; 77.23 ppm for ^{13}C) and DMSO; (2.50 ppm for ^1H; 39.52 ppm for ^{13}C). Chemical shifts are reported in ppm. Multiplicities are indicated by standard abbreviations. Coupling constants, *J*, are reported in hertz (Hz). Kugelrohr distillation was performed by a Büchi B585 glass oven with a Büchi bulb-to-bulb distillation apparatus, and the temperatures reported are air bath temperatures (ABT). ESI-HRMS was performed on an Agilent 6520 quadrupole time-of-flight (Q-TOF) mass spectrometer at Environmental OMICS Laboratory, GIST, and EI-HRMS was performed on a JEOL JMS-700 MStation mass spectrometer with magnetic sector-electric sector double focusing mass analyzer at Korea Basic Science Institute (KBSI), Daegu Center. The preparations of **2b–i**, **6b–k**, **8b–i**, **10b–h**, and **9d** have been described previously.[8]

1,4-Dibenzyloxyphthalazine (6′)

To a stirred slurry of NaH (622 mg, 15.6 mmol, 4.0 equiv) in THF (22 mL) was added benzyl alcohol (1.62 mL, 15.6 mmol, 4.0 equiv) dropwise over 5 min at 0 °C in an ice bath. The mixture was stirred at rt for 15 min. Then, a solution of 1,4-dichlorophthalazine (774 mg, 3.89 mmol, 1.0 equiv) in THF (18 mL) was added dropwise over 5 min at 0 °C, and the reaction mixture was refluxed in an oil bath for 24 h. After cooling the mixture to rt, H_2O was added, and the aqueous layer was extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried (anhyd $MgSO_4$), filtered through a glass frit, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, R_f = 0.39 in EtOAc/hexanes 1:10) and bulb-to-bulb distillation (100 mTorr, ABT 280–300 °C) to give **6′** as a white solid; yield: 998 mg (75%); mp 104.1–108.1 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.21–8.16 (m, 2 H), 7.83–7.79 (m, 2 H), 7.59–7.56 (m, 4 H), 7.45–7.41 (m, 4 H), 7.39–7.35 (m, 2 H), 5.66 (s, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 137.2, 132.1, 128.7, 128.4, 128.2, 123.3, 122.6, 68.9.

HRMS (ESI/Q-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{18}N_2O_2Na$: 365.1260; found: 365.1263.

N-Chlorinative Ring Contraction of 1,4-Dimethoxyphthalazines 6 to Phthalimides 9; General Procedure I (GP I) (Scheme 6)

A stirred solution of 1,4-dimethoxyphthalazine **6** (1.0 equiv), *n*-Bu_4NCl (1.0 equiv), and TCICA (4.0 equiv) in MeCN was refluxed in an oil bath for 48 h. Then, the reaction mixture was cooled to 0 °C in an ice bath prior to the addition of $NaBH_4$ (5.0 equiv) and EtOH.[28] After 15 min, sat. aq NH_4Cl was added, and the aqueous layer was extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried (anhyd $MgSO_4$), filtered through a glass frit, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2) to give phthalimide **9**.

4-*tert*-Butylphthalimide (9c)

Following GP I, **6c** (246 mg, 1.00 mmol), *n*-Bu_4NCl (278 mg, 1.00 mmol), and TCICA (930 mg, 4.00 mmol) were reacted in MeCN (6 mL) to give **9c** as a white solid after column chromatography (SiO_2, R_f = 0.27 in EtOAc/hexanes 1:5); yield: 46 mg (31%); mp 137.4–140.6 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.23 (br s, 1 H), 7.84 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.78 (d, *J* = 0.6 Hz, 1 H), 7.73 (d, *J* = 7.6 Hz, 1 H), 1.33 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.4, 169.1, 157.9, 132.9, 131.2, 130.1, 122.8, 119.6, 35.4, 30.8.

4-Chlorophthalimide (9e)

Following GP I, **6e** (225 mg, 1.00 mmol), *n*-Bu_4NCl (278 mg, 1.00 mmol), and TCICA (930 mg, 4.00 mmol) were reacted in MeCN (6 mL) to give **9e** as a white solid after column chromatography (SiO_2, R_f = 0.35 in EtOAc/hexanes 1:5); yield: 58 mg (32%); mp 206.4–213.9 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.49 (s, 1 H), 7.86–7.80 (m, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.3, 167.9, 139.1, 134.7, 134.1, 131.2, 124.7, 123.1.

Attempted Preparation of 2,3-Dihydrophthalazine-1,4-diones 2 Resulting in the Formation of *N*-Aminophthalimides 11; General Procedure II (GP II)[29] (Scheme 5)

A stirred solution of phthalic anhydride **3** (1.0 equiv) and $N_2H_4{\cdot}H_2O$ (1.5 equiv) in EtOH was refluxed in an oil bath for 30 min. Then, aq HCl (10 wt%) was added, and the reaction mixture was refluxed for an additional 30 min. The mixture was cooled to rt and filtered through filter paper. The filter cake was washed with EtOH and dried under reduced pressure to give *N*-aminophthalimide **11**. The crude material was characterized without further purification.

N-Aminotetrachlorophthalimide (11l)

Following GP II, **3l** (2.86 g, 10.0 mmol), aq HCl (10 wt%, 10 mL), and $N_2H_4{\cdot}H_2O$ (728 μL, 15.0 mmol) were reacted in EtOH (20 mL) to give **11l**; yield: 1.79 g (60%); ivory solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.10 (br s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.6, 138.0, 127.9, 127.0.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_8H_2{}^{35}Cl_4N_2O_2$, $C_8H_2{}^{35}Cl_3{}^{37}ClN_2O_2$, $C_8H_2{}^{35}Cl_2{}^{37}Cl_2N_2O_2$: 297.8870 (77.6%), 299.8841 (100.0%), 301.8811 (48.5%); found: 297.8870 (75.1%), 299.8850 (100.0%), 301.8818 (50.5%).

N-Aminotetrabromophthalimide (11m)

Following GP II, **3m** (4.64 g, 10.0 mmol), aq HCl (10 wt%, 10 mL), and $N_2H_4{\cdot}H_2O$ (728 μL, 15.0 mmol) were reacted in EtOH (20 mL) to give **11m**; yield: 2.59 g (54%); ivory solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.05 (br s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.0, 136.2, 129.7, 120.3.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_8H_2{}^{79}Br_3{}^{81}BrN_2O_2$, $C_8H_2{}^{79}Br_2{}^{81}Br_2N_2O_2$, $C_8H_2{}^{79}Br_2{}^{81}Br_2N_2O_2$: 475.6829 (68.3%), 477.6809 (100.0%), 479.6788 (65.3%); found: 475.6826 (65.5%), 477.6810 (100.0%), 479.6786 (65.3%).

3,6-Dimethoxypyridazine (12)[30]

A stirred solution of 3,6-dichloropyridazine (500 mg, 3.36 mmol, 1.0 equiv) and NaOMe (725 mg, 13.4 mmol, 4.0 equiv) in MeOH (17 mL) was refluxed in an oil bath for 24 h. Then, the reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 and washed with H_2O (3 ×). The combined aqueous layers were extracted with CH_2Cl_2 (2 ×). The combined organic layers were dried (anhyd $MgSO_4$), filtered through a glass frit, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, R_f = 0.28 in CH_2Cl_2/EtOAc 30:1) to give **12** as a white solid; yield: 271 mg (58%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.19 (s, 2 H), 3.93 (s, 6 H).

4-Chloro-3,6-dimethoxypyridazine (13) (Equation 1)

A stirred solution of **12** (140 mg, 1.00 mmol, 1.0 equiv), *n*-Bu_4NCl (1.11 g, 4.00 mmol, 4.0 equiv), and TCICA (930 mg, 4.00 mmol, 4.0 equiv) in MeCN (6 mL) was refluxed in an oil bath for 48 h. Then, the reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, R_f = 0.38 in CH_2Cl_2) to give **13** as a white solid; yield: 50 mg (29%); mp 79.5–83.9 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (s, 1 H), 4.13 (s, 3 H), 4.05 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1, 158.3, 130.0, 120.4, 55.7, 55.2.

HRMS (ESI/Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_6H_8{}^{35}ClN_2O_2$, $C_6H_8{}^{37}ClN_2O_2$: 175.0274 (100.0%), 177.0245 (32.0%); found: 175.0264 (100.0%), 177.0237 (28.1%).

One-Pot Ring Contraction of 2,3-Dihydrophthalazine-1,4-dione (2a) via a Silylated Intermediate (Scheme 8)

A stirred solution of 2,3-dihydrophthalazine-1,4-dione (**2a**; 162 mg, 1.00 mmol, 1.0 equiv), TMSCl (253 μL, 2.00 mmol, 2.0 equiv), and 2,6-lutidine (232 μL, 2.00 mmol, 2.0 equiv) in MeCN (1.5 mL) was refluxed in an oil bath under argon for 12 h to form **14**. Then, the reaction mixture was cooled to 0 °C or –40 °C prior to the addition of a solution of *n*-Bu_4NCl (1.11 g, 4.00 mmol, 4.0 equiv) in MeCN (1.5 mL). Then, a solution of TCICA (930 mg, 4.00 mmol, 4.0 equiv) in MeCN (3.0 mL) was added dropwise over 10 min. After 50 min, the mixture was warmed to rt and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, R_f = 0.19 in CH_2Cl_2/hexanes 1:1) to give *N*-chlorophthalimide **8a** as a white solid; yield: 27 mg (15%) at 0 °C and 29 mg (16%) at –40 °C.

4-[(Trimethylsilyl)oxy]phthalazin-1(2*H*)-one (14)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70–9.67 (br s, 1 H), 8.30 (d, *J* = 7.6 Hz, 1 H), 7.91 (d, *J* = 7.3 Hz, 1 H), 7.80–7.71 (m, 2 H), 0.34 (s, 9 H).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{14}N_2O_2Si$: 234.0825; found: 234.0825.

Electrophilic Promotor Survey via One-Pot Operation; General Procedure III (GP III) (Scheme 10)

A stirred solution of 1,4-dimethoxyphthalazine (**6a**; 0.2 mmol, 1.0 equiv) and TCICA (0.8 mmol, 4.0 equiv) in 1,2-DCE (1.2 mL) was refluxed in an oil bath for 24 h to form the monochlorinated intermediate **7**. Then, a solution of either oxygenating or fluorinating reagent in 1,2-DCE was added at rt, and the reaction mixture was refluxed for an additional 24 h. After the mixture was cooled to down rt and concentrated under reduced pressure, the crude mixture was analyzed by ^{1}H NMR spectroscopy.

*m*CPBA

Following GP III, **6a** (38 mg, 0.20 mmol) and TCICA (190 mg, 0.80 mmol) in 1,2-DCE (1.2 mL) and then *m*CPBA (49 mg, 0.20 mmol, 1.0 equiv) in 1,2-DCE (0.9 mL) were reacted together. A partial loss of the *N*-chlorine substituent in **7** was observed (**7**:**15** = 68:32).

UHP/$MeReO_3$

Following GP III, **6a** (38 mg, 0.20 mmol) and TCICA (190 mg, 0.80 mmol) in 1,2-DCE (1.2 mL) and then UHP (56 mg, 0.60 mmol, 3.0 equiv) and $MeReO_3$ (5 mg, 0.02 mmol, 0.1 equiv) were reacted together. A complete loss of the *N*-chlorine substituent in **7** was observed (**7**:**15** = 0:100).

CF_3CO_3H

A stock solution of CF_3CO_3H was prepared by UHP (94 mg, 1.0 mmol, 5.0 equiv) and TFAA (153 μL, 1.10 mmol, 5.5 equiv) in 1,2-DCE (1.0 mL).[31] Following GP III, **6a** (38 mg, 0.20 mmol) and TCICA (190 mg, 0.80 mmol) in 1,2-DCE (1.2 mL) and then a portion of the CF_3CO_3H solution (0.5 mL, 0.5 mmol, 2.5 equiv) and Na_2CO_3 (150 mg, 1.4 mmol, 7.0 equiv) were reacted together. Approximately 12% conversion to **8a** was observed.

NFSI

Following GP III, **6a** (38 mg, 0.20 mmol) and TCICA (190 mg, 0.80 mmol) in 1,2-DCE (1.2 mL) and then NFSI (63 mg, 0.20 mmol, 1.0 equiv) in 1,2-DCE (0.9 mL) were reacted together. No reaction was observed.

4-Methoxyphthalazin-1(2*H*)-one (15)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.21 (s, 1 H), 8.41–8.38 (m, 1 H), 8.01–7.99 (m, 1 H), 7.85–7.78 (m, 2 H), 3.99 (s, 3 H).

HRMS (ESI/Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_9H_9N_2O_2$: 177.0664; found: 177.0659.

2-Chloro-4-methoxyphthalazin-1-one (7)[8] (Table 3)

A stirred solution of 1,4-dimethoxyphthalazine (**6a**; 151 mg, 0.79 mmol, 1.0 equiv) and TCICA (369 mg, 1.59 mmol, 2.0 equiv) in 1,2-DCE (4.8 mL) was refluxed in an oil bath for 24 h. Then, the reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, R_f = 0.16 in CH_2Cl_2/hexanes 1:1) to give **7** as a white solid; yield: 136 mg (82%); mp 156.9–162.2 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42–8.38 (m, 1 H), 8.00–7.96 (m, 1 H), 7.86–7.79 (m, 2 H), 4.02 (s, 3 H).

Electrophilic Promotor Survey with Isolated 7; General Procedure IV (GP IV) (Table 3)

A stirred solution of 2-chloro-4-methoxyphthalazin-1-one (**7**; 0.5 mmol, 1.0 equiv) and required reagents (1.0 mmol, 2.0 equiv each) in MeCN (3.0 mL) was refluxed in an oil bath under argon for 24 h. The reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, R_f = 0.27 in CH_2Cl_2/hexanes 1:1) to give *N*-chlorophthalimide (**8a**) as a white solid.

$K_2S_2O_8$

Following GP IV, **7** (105 mg, 0.50 mmol) and $K_2S_2O_8$ (270 mg, 1.00 mmol) were reacted. Ring contraction product **8a** was not detected.

TCICA and $K_2S_2O_8$

Following GP IV, **7** (105 mg, 0.50 mmol), TCICA (232 mg, 1.00 mmol), and $K_2S_2O_8$ (270 mg, 1.00 mmol) were reacted to give **8a**; yield: 13 mg (14%).

TCICA and *n*-Bu_4NCl

Following GP IV, **7** (105 mg, 0.50 mmol), TCICA (232 mg, 1.00 mmol), and *n*-Bu_4NCl (278 mg, 1.00 mmol) were reacted to give **8a**; yield: 41 mg (45%).

TCICA

Following GP IV, **7** (105 mg, 0.50 mmol) and TCICA (232 mg, 1.00 mmol) were reacted to give **8a** ; yield: 24 mg (26%).

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706639.

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(12) Ineffective reagents include *N*-chlorosuccinimide (NCS), 1,3-dichloro-5,5-dimethylhydantion (DCDMH), Palau'Chlor, 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dien-1-one (HCCO), *N*-bromosuccinimide (NBS), *N*-fluorobenzenesulfonimide (NFSI), and Selectfluor™.

(13) Other soluble chloride such as Me_4NCl exhibited comparable promoting reactivity. In contrast, insoluble chloride such as LiCl was completely ineffective.

(14) Other common reductive workup procedures with aq $Na_2S_2O_3$ or aq $NaHSO_3$ resulted in less quantitative mass recovery.

(15) An approximate ^{1}H NMR yield of **8a** was measured with 1,1,2,2-tetrachloroethane as an internal standard. From the reaction of **6a** with TCICA (4 equiv) and *n*-Bu_4NCl (4 equiv), ca. 42% yield of

8a was observed in the crude mixture, and a small amount of **7** was detected as the only major side product. This result indicates the moderate ring contraction efficiency as well as the intractable decomposition of **6a** during the reaction. See the SI for details.

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