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Lewis Acid-Promoted Ring-Contraction of 2,4,6,8-Tetrasubstituted 1,5-Diazacyclooctatetraenes to 2,4,6-Trisubstituted Pyridines

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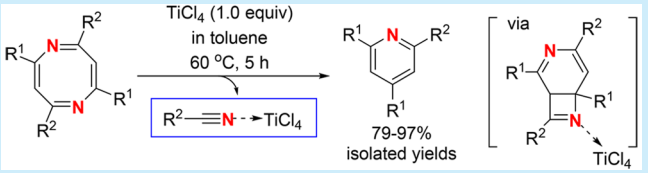
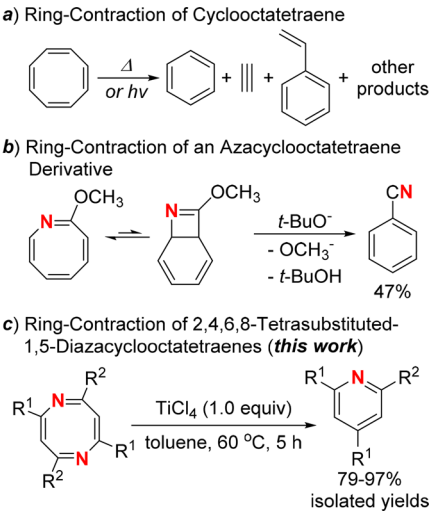
Supporting Information

ABSTRACT: Ring-contraction of 2,4,6,8-tetrasubstituted 1,5-diazacyclooctatetraenes was highly efficiently promoted by Lewis acid such as $TiCl_4$, affording 2,4,6-trisubstituted pyridines in excellent yields, along with release of a nitrile. A reaction mechanism involving a 6π electrocyclic ring-closing followed by a retro [2 + 2] cyclization of an 1-azetine moiety was supported by both experimental observations and density functional theory calculation.



Ring-contraction reactions are synthetically useful methods in organic synthesis for making smaller rings from larger rings.[1] While a number of anion,[2a] cation,[2b] and carbenoid[2c] ring-contractions have been well documented and applied, ring-contractions via intramolecular pericyclic protocol are less explored and often not useful for synthesis.[3] For example, cyclooctatetraene (COT) could undergo ring-contraction to benzene under photoirradiation condition[3a] or thermal condition,[3d] but isomerization of COT to styrene took place at the same time and resulted in mixed products (Scheme 1a). The ring-contraction of 2-methoxy-azacyclooctatetraene in the presence of base generated benzonitrile in a moderate yield (Scheme 1b).[3b] Herein, we report a useful ring-contraction of 2,4,6,8-tetrasubstituted 1,5-diazacyclooctatetraenes (NCOTs) to 2,4,6-trisubstituted pyridines with excellent yields under mild condition by treatment with $TiCl_4$ (Scheme 1c). In this process, an intramolecular 6π electrocyclic ring-closing of NCOT was followed by Lewis acid mediated retro [2 + 2] cyclization.

Scheme 1. Ring-Contractions of Cyclooctatetraene and Azacyclooctatetraene Derivatives



NCOT is interesting analogues of COT, but its reactivity remains almost entirely unknown except the reduction with alkali metals.[4] We have developed a one-pot synthetic route to NCOTs from 1,4-dilithio-1,3-dienes and nitriles.[5] It is supposed that the introduction of *N* atoms into the conjugated system may bring about new reactivity as Schiff base, so we carried out reactions of NCOTs with Lewis acids.

As shown in Scheme 2, $TiCl_4$ (1 M in toluene) was added to the solution of the NCOT **1a** at −78 °C, and insoluble oil appeared as the mixture was allowed to warm up to room temperature. Then, the reaction mixture was heated at 60 °C and monitored by GC−MS. The NCOT **1a** was completely converted into the product (m/z = 287) after 5 h. The product was isolated in 95% yield and characterized as 2,4,6-trisubstituted pyridine **2a**. This transformation could also be mediated by some other Lewis acids (Scheme 2). Pyridine derivatives **2b,c** could be obtained in excellent isolated yields from the reaction of their corresponding NCOTs with $TiCl_4$. NCOT **1d** with two different alkyl groups could also undergo this transformation to generate **2d** in 79% yield, along with **2e** as a minor product, which was observed by GC−MS and NMR. It should be noted that, the lack of more examples is mainly due to the limitation in the preparation of starting materials NCOTs. Aryl nitriles such as benzonitrile tend to trimerize to form triazine derivatives in the presence of dilithio reagents. Nitriles with other tertiary alkyl groups such as $-C$*n*$-Pr_3$ and $-CMe(Et)_2$ afforded a mixture of products. It is worthy to note

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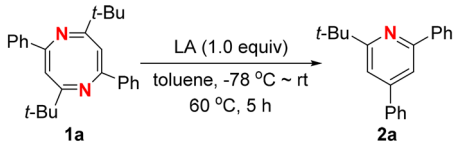
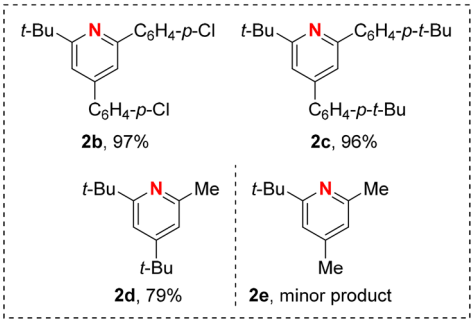
Scheme 2. Reactions of NCOTs with Lewis Acids



LA	yield (%)[a]
$TiCl_4$	98 (95[b])
$Ti(Oi\text{-}Pr)_4$	0
$ZrCl_4$	89
$HfCl_4$	77
$AlCl_3$	95
$FeBr_2$	46
$ScCl_3$	0

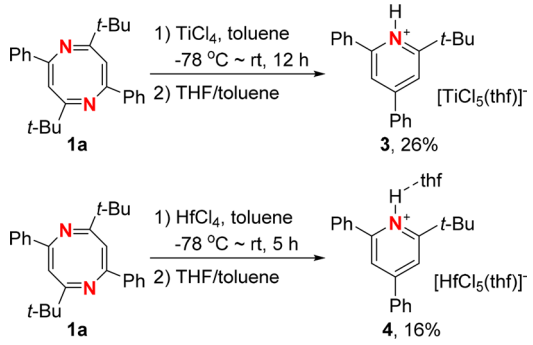
[a]GC yield. [b]Isolated yield.



that pyridine derivatives with bulky substituents (e.g., *t*-Bu group) adjacent to the N atom could be used as the base component of an FLP,[6] but efficient synthetic methods are limited.[7]

It was assumed that the coordination of the *N* atom of NCOTs to $TiCl_4$ might be a key step in this transformation, so we tried to isolate the intermediate (Scheme 3). After adding

Scheme 3. Formation of the Pyridinium Salts



the solution of $TiCl_4$ at −78 °C, the mixture was kept at room temperature for 12 h. Then the reaction mixture was dissolved in a mixed solvent of THF/toluene from which single crystals of **3** were obtained (Figure 1). We also tried less reactive $HfCl_4$, and similar crystals of **4** were obtained (Figure 2). Both **3** and **4** contained a trisubstituted pyridinium cation.

In order to figure out whether the proton of the pyridinium cation came from the *t*-Bu group of NCOT, *in situ* NMR experiments were carried out (Scheme 4). Pure liquid of $TiCl_4$ was added to a solution of **1a** in C_6D_6. Yellow solid precipitated immediately, and after 5 h at room temperature, the NMR spectra indicated that **1a** was completely converted into four products: two pyridines (**2a** and **5**) and two nitrile−$TiCl_4$

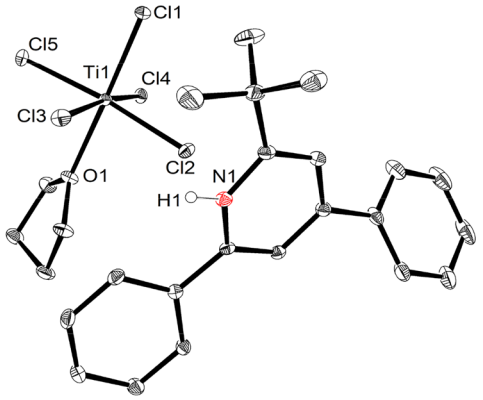


Figure 1. ORTEP drawing of **3** with 30% thermal ellipsoids. Hydrogen atoms, except for H(1), are omitted for clarity.

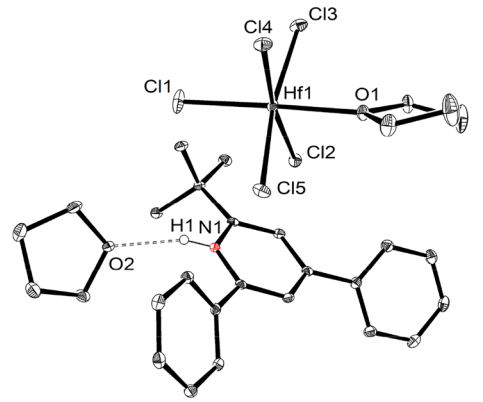
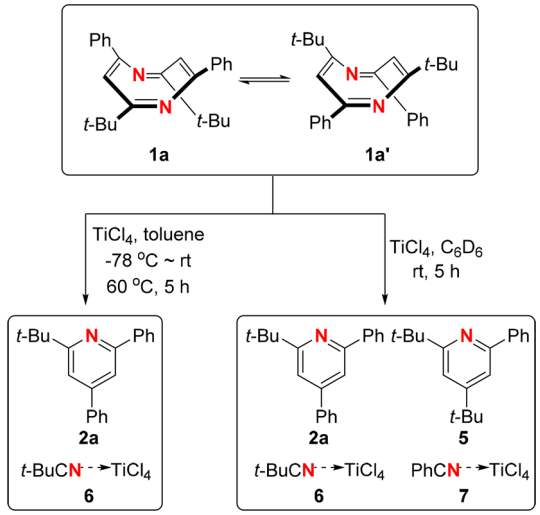


Figure 2. ORTEP drawing of **4** with 30% thermal ellipsoids. Hydrogen atoms, except for H(1), are omitted for clarity.

Scheme 4. In Situ NMR Experiments



complexes (**6** and **7**) (Scheme 4). The doublet at 7.58 (J = 1.4 Hz) and 7.48 ppm (J = 1.5 Hz) in ^{1}H NMR could be assigned to two different 2,4,6-trisubstituted pyridines **2a** and **5**, which were also detected by GC−MS. When the isolated **2a** was treated with $TiCl_4$ in C_6D_6, no change of **2a** was observed as monitored by NMR. The nitrile−$TiCl_4$ complexes **6** and **7** were confirmed by independent preparation from the corresponding nitriles and $TiCl_4$ in C_6D_6 (see Supporting Information (SI)). The reaction carried out in toluene-d_8 produced a similar result,

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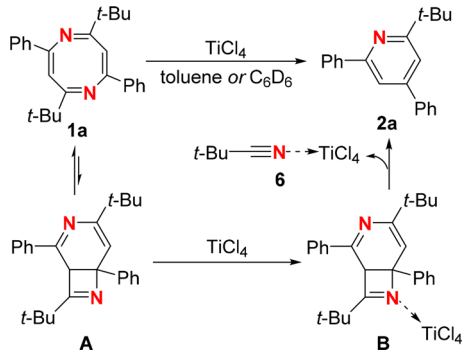
but the reaction in CD_2Cl_2 was messy. In the solution there might be an equilibrium between **1a** and its valence isomers **1a′**.[4,5] The products **5** and **7** should be generated from the reaction between **1a′** and $TiCl_4$. When a solution of $TiCl_4$ was added at −78 °C, only the ring-contraction of **1a** occurred, so **2a** could be isolated in nearly quantitative yield. This could also be realized by using a weaker Lewis acid $ZrCl_4$ as indicated by the *in situ* NMR, but the reaction was much slower. However, when pure $TiCl_4$ was added at room temperature, both **1a** and **1a′** could undergo this transformation to generate four products. No other products were found in both ^1H NMR and ^{13}C NMR spectra, indicating that the proton of the pyridinium cation was not from **1a** or **1a′**. Thus, we supposed that the protonation of pyridine might be a result of partial hydrolysis of $TiCl_4$ and $HfCl_4$ due to their extreme moisture sensitivity. The hydrolysis of Lewis acid could occur in the presence of a small amount of moisture to result in the protonation of a pyridyl ligand.[8]

Based on these results, we proposed a mechanism for this transformation (Scheme 5). As the equilibration between COTs and their bicyclo[4.2.0]octatriene isomers has been well studied,[9] a similar bicyclic isomer **A** might be formed through the 6π electrocyclic ring-closing of **1a** as well. Subsequent coordination of $TiCl_4$ to the N atom generated the activated intermediate **B**, which could undergo a [2 + 2] cycloreversion to give the final products **2a** and **6**. Similar mechanism has been described for the ring-contraction of COT to benzene under thermal condition,[3a] photoirradiation condition,[3d] and on solid surfaces.[3g] Compared to these processes, the present Lewis acid mediated ring-contraction of NCOTs proceeds with higher selectivity and higher yield under mild condition.

Computation results for this transformation are shown in Figure 3. The Gaussian09 program package was used,[10] and the optimization structure of all the minima and transition states were fully calculated at the B3LYP level[11] using the LANL2DZ[12] basis set (for Ti) and the 6-31+G(d)[13] basis set (for other elements) in toluene evaluated by SCRF using the PCM model.[14] According to the results shown in Figure 3, the 6π electrocyclic ring-closing of **1a** is the rate-determining step with an activation free energy of 25.1 kcal/mol, which could be realized under the reaction condition. Another possible pathway initiated by direct coordination of $TiCl_4$ to **1a** requires 36.0 kcal/mol energy and should be disfavored (see SI). The energy barrier for the [2 + 2] cycloreversion would be much higher (42.7 kcal/mol) without $TiCl_4$, which indicates that the coordination of $TiCl_4$ is necessary for this step. Compounds **1a** and **1a′** can be interconverted to each other with a computed activation free energy of 17.6 kcal/mol, and the 6π electrocyclic ring-closing of **1a′** requires a higher activation free energy (27.6 kcal/mol) than **1a**. Based on the three competing pathways (**1a** to **1a′**, **1a** to **2a**, and **1a′** to **5**), we can understand that at low temperature the pathway from **1a′** to **5** cannot take place and that **1a′** will be converted to **1a** and then to **2a**, so **2a** could be obtained in nearly quantitative yield. However, at room

Scheme 5. Proposed Mechanism



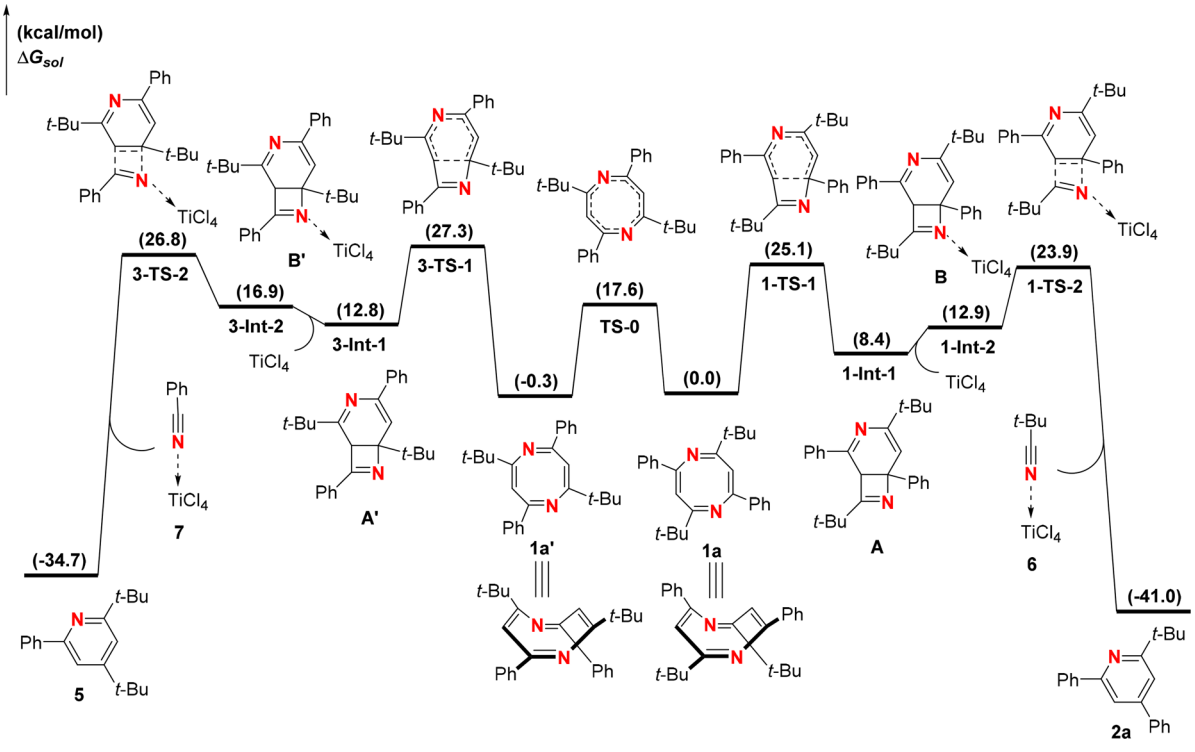


Figure 3. DFT-calculated potential energy surfaces of the transformation.

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temperature there is enough energy to make both transformations (**1a** to **2a** and **1a′** to **5**) occur, so a mixture of **2a** and **5** was observed.

In summary, a ring-contraction of 2,4,6,8-tetrasubstituted 1,5-diazacyclooctatetraenes (NCOTs) mediated by $TiCl_4$ afforded 2,4,6-trisubstituted pyridines in nearly quantitative yields under mild condition. This transformation might proceed via 6π electrocyclic ring-closing and Lewis acid-mediated retro [2 + 2] cyclization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03917.

Experiment details, X-ray data for **3** and **4**, and scanned NMR spectra of all new products (PDF)

Accession Codes

CCDC 1570799−1570800 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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