Three-center-four-electron halogen bond enables non-metallic complex catalysis for Mukaiyama-Mannich-type reaction

**Highlights**
- Bis-pyridine halogen(I) complexes with 3c4e X-bond act as anion-binding catalysts
- Bis-pyridine halogen(I) complexes accelerate nucleophilic pyridine de-aromatization
- Bis-pyridine halogen(I) catalysts afford significant yields at ppm-level loading
Three-center-four-electron halogen bond enables non-metallic complex catalysis for Mukaiyama-Mannich-type reaction

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SUMMARY
The three-center-four-electron halogen bond (3c4e X-bond) presents a fundamental design concept for catalysis. By integrating halogen(I) (X+: I+ or Br+), the bis-pyridyl ligand NN, and a non-nucleophilic counteranion Y, we developed non-metallic complex catalysts, [N...X...N]Ys, that exhibited outstanding activity and facilitated the Mukaiyama-Mannich-type reaction of N-heteroaromatics with parts-per-million-level catalyst loading. The high activity of [N...X...N] SbF6 was clearly demonstrated. NMR titration experiments, CSI-MS, computations, and UV-vis spectroscopic studies suggest that the robust catalytic activity of [N...X...N]Y can be attributed to the unique ability of the 3c4e X-bond for binding chloride: i) the covalent nature transforms the [N...X...N]+ complexation to sp2 CH as a hydrogen-bonding donor site, and ii) the noncovalent property allows for the dissociation of [N...X...N]+ for the formation of [Cl...X...Cl]-. This study introduces the application of 3c4e X-bonds in catalysis via halogen(I) complexes.

INTRODUCTION
Recently, the halogen bond (X-bond) in solution has attracted considerable attention (Beale et al., 2013; Carlsson et al., 2015a; Erdélyi, 2012; Jentzsch, 2015; Wilcox et al., 2021) because its electrostatic property is similar to that of the H-bond. X-bond-based organocatalysts have been developed as a representative application of the X-bond in solution, and hence, regarded as a new research area pertaining to organocatalysis (Bamberger et al., 2019; Schindler and Huber, 2015; Sutar, 2021; Sutar and Huber, 2019). In X-bonds-based organocatalysis, the two-center-two-electron (2c2e) bond is commonly a key feature: a small region of positive charge on the terminus of a halogen atom can interact with the negative charge of an electron-rich species. Recent X-bond-based organocatalysts have mainly been halogenated compounds bearing 2c2e X-bond donor sites (Figure 1A), where a halogen atom interacts with a Lewis basic site to generate reactive electrophilic species. Similarly, halogen(I), generally X+ (X = I, Br, Cl), acts as a strong X-bond donor site. In contrast to the 2c2e X-bond, halogen(I) concurrently interacts with two Lewis bases (Erdélyi, 2012; Carlsson et al., 2015b; Rissanen and Haukka, 2015; Turunen and Erdélyi, 2020). This bond has been recognized as the three-center-four-electron (3c4e) X-bond.

Significant efforts have been directed toward spectroscopic and computational studies on the supramolecular structure and nature of the 3c4e X-bond. In the 1950s, Popov et al. reported the formation of bis-pyridine iodine(I) (Py2I+) and iodine dichloride (ICl2) via dissociation from 2 equiv of pyridine iodine monochloride (2PyICl) in absorption spectroscopy (Popov and Pflaum, 1957; Popov and Rygg, 1957). Until the 2000s, 3c4e X-bond-based compounds were conceived and drawn with covalent and/or coordinate bonds. Recently, Erdélyi et al. redefined the 3c4e X-bond as a noncovalent interaction and revealed its unique features using NMR spectroscopy, density functional theory (DFT) calculations, and X-ray crystal analysis (Carlsson et al., 2012a, 2012b; Carlsson et al., 2013; Hakkert and Erdélyi, 2015; Karim et al., 2014; Lindblad et al., 2018; Reiersælmoen et al., 2020).

The 3c4e X-bond enables the formation of a cationic or an anionic 3c4e X-bond, depending on the availability of a neutral Lewis base or an anion as the X-bond acceptor (Figure 1B). For instance, [bis(pyridine)
halogen(I)\textsuperscript{\textdagger} tetrafluoroborate, the so-called Barluenga’s reagent, is a representative 3c4e X-bond complex that facilitates iodination, oxidation, and C–H and C–C bond functionalization (Barluenga, 1999; Chalker et al., 2010; Tsuji et al., 2014). Importantly, successful examples have always entailed the use of a stoichiometric amount of 3c4e complexes. Despite the utility of the 3c4e X-bond in synthetic chemistry, its potential for non-metallic complex catalysis has not been thoroughly investigated thus far.

Based on seminal studies (Beckendorf et al., 2012; Zhang and Schreiner, 2009), we have focused on the 3c4e X-bond to strategically design non-metallic complex catalysts, particularly anion-binding catalysts (Figure 2A). We envisaged that the cationic [\(N\cdot\cdot\cdotX\cdot\cdot\cdotN\)]\textsuperscript{+} bond-assisted sp\textsuperscript{2}-CH-bonding interaction would assemble the chloride at the first stage of catalysis. Subsequently, the electrophilic halogen (X) of the [\(N\cdot\cdot\cdotX\cdot\cdot\cdotY\)] complex would be subjected to a nucleophilic attack by the chloride to transform the anionic [Cl\textsuperscript{−}\cdot\cdot\cdotX\cdot\cdot\cdotCl\textsuperscript{−}] bond through ligand exchange from bis-pyridine to chloride at the second stage, which could serve as a powerful driving force in anion-binding catalysis (Figure 2B). Specifically, we report the development of bis-pyridine halogen(I) complexes \(1\) (\([N\cdot\cdot\cdotX\cdot\cdot\cdotNY]; N \) is the substituted pyridyl ligand, X is I or Br, and Y is a non-nucleophilic counteranion) as non-metallic complex catalysts for anion-binding catalysis.

### RESULTS AND DISCUSSION

#### Determination of the target reaction

To prove our working hypothesis for the 3c4e X-bond complexes as anion-binding catalysts, we determined the primary target based on scatterplots of the yields (%) vs. catalyst loading (mol%) (see Figure S8). For this purpose, the Mukaiyama-Mannich-type reaction of N-heteroaromatics via chloride-binding was selected, because it provides a variety of useful nitrogen-containing intermediates for pharmaceutical applications (Bull et al., 2012; Sowmiah et al., 2018). To generate the scatterplots, datasets were prepared using 396 reactions employing previously reported anion-binding catalysts, particularly the chloride-binding (see Figure S8) ones, in an asymmetric and racemic manner. The scatterplots of yield (%) vs. catalyst loading (mol%) clearly show that 10 mol% of the catalyst was mainly used, and at
Table 1. Evaluation of the catalytic activity of $[N \cdots X \cdots N]Y$ in Mukaiyama-Mannich-type reactions

| Entry | Catalyst (mol%) | Yield (%)<sup>b</sup> |
|-------|----------------|------------------------|
| 1     | 1a (10)        | 98                     |
| 2     | None           | 33                     |
| 3     | 1a (2.5)       | 90                     |
| 4     | 1a (1.0)       | 90                     |
| 5     | 1a (0.10)      | 76                     |
| 6     | 1a (0.050 = 500 ppm) | 61               |
| 7     | Schreiner’s thiourea (0.050 = 500 ppm) | 33               |
| 8     | Bis-triazole (0.050 = 500 ppm) | 49             |
| 9     | Iodimidazolium OTf (0.050 = 500 ppm) | 62              |
| 10    | Dibenzoiodolium OTf (0.050 = 500 ppm) | 61              |
| 11    | [2Me-L1] OTf (0.050 = 500 ppm) | 49             |
| 12    | 1b (0.10)      | 49                     |
| 13    | 1c (0.10)      | 49                     |
| 14    | 1d (0.10)      | 87                     |
| 15    | 1e (0.10)      | 90                     |
| 16    | 1e (0.050 = 500 ppm) | 82             |
| 17    | 1e (0.025 = 250 ppm) | 74             |
| 18    | 1e (0.010 = 100 ppm) | 52             |
| 19    | 1f (0.050 = 500 ppm) | 87             |
| 20    | 1g (0.050 = 500 ppm) | 87             |
| 21    | 1h (0.050 = 500 ppm) | 72             |
| 22    | 1i (0.050 = 500 ppm) | 87             |
| 23    | ICl (0.050 = 500 ppm) | 51             |
| 24    | I<sub>2</sub> (0.050 = 500 ppm) | 60             |
| 25    | 1e + 1 wt % H<sub>2</sub>O (0.050 = 500 ppm) | <1           |
| 26    | 1e + 5 wt % H<sub>2</sub>O (0.050 = 500 ppm) | <1           |

<sup>a</sup>The reactions were performed using pyridine (2a, 0.4 mmol), phenyl chloroformate (3a, 0.42 mmol), and silyl ketene acetal (4a, 0.6 mmol) in the presence of a catalyst for 1 h in tetrahydrofuran (THF, 8 mL).

<sup>b</sup>Isolated yields.
least 5 mol% of the catalyst was required to achieve high yields. This [N···X···N]Ys-driven catalysis might solve the inherent limitation of the catalytic activity in previously reported organocatalysis. Among the representative N-heteroaromatics, i.e., isoquinolines, quinolines, and pyridines, the success of this catalytic process for the reaction of pyridines was significantly limited. Therefore, the Mukaiyama-Mannich-type reaction of pyridine compounds 2, chloroformates 3, and silyl enol ethers 4 was examined for our initial study.

**Reaction optimization**

We initially studied the Mukaiyama-Mannich-type reactions of pyridine (2a), phenyl chloroformate (3a), and silyl ketene acetal (4a) at 0°C for 1 h with and without 1a (Table 1). The primary examinations revealed that 10 mol% of 1a efficiently accelerated the reaction, thus excellently yielding the γ-adduct 5a (entry 1 vs. 2). Despite the lower catalyst loading of 1a, such as 2.5, 1.0, 0.1, and 0.05 mol% (500 ppm), the reaction proceeded smoothly, producing reasonable yields of 5a (entries 3, 4, 5, and 6). For comparison, 1,3-bis[3,5-bistrifluoromethyl]phenyl]thiourea (Schreiner’s thiourea catalyst) (Kotke and Schreiner, 2006) and 1,3-bis(1-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)benzene (Asmus et al., 2014) (mother skeleton of Mancheño’s bis-triazole catalyst (Zurro et al., 2014)) were examined as representative H-bond based anion-binding catalysts. Neither catalyst considerably accelerated the reaction to produce high yields of 5a (entries 7 and 8). Iodimidazolium triflate and dibenzoiodolium triflate were recently recognized as strong 2c2e X-bond donor catalysts (entries 9 and 10), and their activities were comparable to that of 1a. Alternatively, N-methylated pyridyl triflate ([2Me-N1]-2OTf) accelerated the reaction (Berkessel et al., 2014) but yielded 10% less 5a than the corresponding iodine(I)complex 1a (entry 11). Overall, these control experiments indicated the potential of catalyst design using halogen(I) complex 1. Next, to establish the utility of 1 as the 3c4e-X-bond-based catalyst system, various counteranions, halogen(I), and pyridyl ligands were examined. Screening of counteranions (entries 12-17) showed that antimonate complex 1e produced the highest yield (90%) of product 5a, even with 0.1 mol% catalyst loading (entry 15). Notably, a similarly high yield (82%) and a satisfactory yield (74%) were obtained even when the 1e loading was reduced to 0.050 mol% (= 500 ppm) and further to 0.025 mol% (= 250 ppm) (entries 16 and 17, respectively), whereas a 100 ppm catalyst loading only produced a moderate yield (entry 18). Bromine(I) antimonate complex 1f
Figure 4. Scope of 1e-catalyzed Mukaiyama-Mannich-type reaction

a Unless otherwise specified, the reactions were performed using 2 (0.4 mmol), 3 (0.42 mmol), 4 (R^6 = Me_3, 0.6 mmol), and 1e at 0°C for 1 h in THF (8 mL).

b Isolated yields.

c 3 minutes.

d 500 ppm.

1e (500 ppm) or without 1e

THF

0 °C, 1 h

50°C, 15 min

0.5 mol% 1e, 0.4 M solution.

1.0 mol% 1e, 1.0 mol% 1e, 0.4 M solution.

0.5 mol% 1e, 0.1 M solution.

0.5 mol% 1e, 0.1 M solution.

0.1 mol% 1e, 0.1 M – 40°C, 3 h.
and iodine(I) complexes 1g, 1h, and 1i with other pyridyl ligands—L2, L3, and L4—could be used to achieve high yields. Although the handling of these catalysts was complicated owing to the low stability of the complexes, high yields similar to those of 5a were obtained (entries 19-22). Although inorganic compounds, iodine monochloride (ICl), and elemental iodine (I2) accelerated the reaction, the product yields of 5a were lower than that in the case of 1e (entries 16 vs. 23 and 24). To exclude the possibility of hidden acids, resulting from moisture during the manipulations, being the real catalyst species, the reactions were conducted in tetrahydrofuran (THF) with 1 wt % or 5 wt % of H2O; no reactions were observed (entries 25 and 26). Finally, the reaction progress at 0°C in the presence of 1e (500 ppm) was compared with those at 0°C, 20°C, and 30°C in the absence of the catalyst to clearly demonstrate the acceleration by 1e (Figure 3). The reaction profile revealed that the 1e-catalyzed reaction proceeded more than six times faster than those without 1e. These results indicate that \([N\cdots X\cdots N]Ys\), composed of the pyridyl ligand,
halogen(I), and a non-nucleophilic counterion, plays a significant role in efficiently promoting the reaction.

**Scope of 3c4e X-bond-based anion-binding catalysis**

Following the acquisition of the easy-to-handle and optimal complex catalyst 1e, the scope of the Mukaiyama-Mannich-type reaction was examined (Figures 4, see S16 and Table S8). The reactions of 2a with β-disubstituted silyl ketene acetal 4a, 4b, and 4c, were accelerated in the presence of 500 ppm of 1e, and high yields of products 5a, 5b, and 5c, respectively, were obtained with γ-selectivities. In particular, the highly reactive and unstable 4c reacted seamlessly to complete the reaction at −78°C within 15 min.

The reaction of 2a with β-unsubstituted silyl ketene acetal 4d and 4e produced remarkable yields of 5d, along with a mixture of the α and γ products, regardless of the silyl substituents. However, 1e did not show any catalytic activity in the reaction of silyl enol ether 4f. Other chloroformates such as 3b, 3c, and 3d were also adequately tolerated in this reaction. Although higher catalyst loadings of 0.1-1.0 mol% were required for the 2-, 3-, and 4-substituted pyridines 2b-2i owing to the substitution effect for the reactivity of the pyridinium substrates, moderate to high yields were obtained in the presence of 1e. In the cases that involved α/γ selectivity, the product regioselectivities of 5a-5m varied with the electron densities of the nucleophilic carbon in 4; otherwise, 5n-5p depended on the influence of the pyridinium salt. In all cases, 1e affected the reaction acceleration but did not involve α/γ selectivity. The 1e catalyst system also tolerated the reaction of quinoline, isoquinoline, and dihydroxyisoquinoline to yield the corresponding products 5q, 5r, and 5s. To clearly demonstrate the robustness of the [N···X···N]Ys catalyst system, all the experimental data of the primary study and the reaction scope were plotted on 49 previously reported reaction data-points of the yields (%) vs. catalyst loading (mol%) for the Mukaiyama-Mannich-type reaction of N-heteroaromatics via chloride-binding in a racemic manner (Figures 5, see S8). The [N···X···N]Ys catalyst afforded a higher yield with a lower catalyst loading than the previously reported datapoints that were obtained under the best reaction conditions for each system.

Figure 7. The X-ray crystal structures indicating the bond formation of Cl···I···N and [Cl···I···Cl]− and the H-bonding of sp² CH···Cl
X-Ray diffraction analysis of 3c4e X-bonds

As mentioned in previous reports (Turunen and Erdélyi, 2021), N–I–Cl and Cl–I–Cl bonds were found in the crystal structures of halide complexes; therefore, we preliminarily performed X-ray diffraction analysis to demonstrate the transformation of \([\text{N} \cdots \text{I} \cdots \text{N}]^+\) to \([\text{Cl} \cdots \text{X} \cdots \text{Cl}]^-\) via \([\text{NN} \cdots \text{X} \cdots \text{Cl}]^-\). Although co-crystallization was not accomplished with the mixture of any \([\text{N} \cdots \text{X} \cdots \text{N}]Ys\) and chloride sources such as \(n\text{-Bu}_4\text{NCl}\), certain halide complexes were obtained from \(L_1, L_2, \text{and ICl} (\text{Figures 6, see S9, S10, S11, S12})\).

Figure 8. Mechanistic studies with \(n\text{-Bu}_4\text{NCl}\) as the chloride source

(A) \(^1\text{H NMR}\) and (B) CSI-MS titration analyzes of \([\text{N} \cdots \text{I} \cdots \text{N}]\text{SbF}_6 \text{(1e)}\) and \(n\text{-Bu}_4\text{NCl}\). The titration of \([\text{N} \cdots \text{I} \cdots \text{N}]\text{SbF}_6 \text{(1e)}\) against \(n\text{-Bu}_4\text{NCl}\); THF-d8/CD_3CN 9:1 (v/v), 0°C for NMR; THF/CH_3CN 9:1 (v/v), –20°C for CSI-MS.

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and Tables S1, S2, S3, S4). The X-ray crystal packing of the L1 and ICl complexes suggests a L1 ligand to ICl ratio of 1:2, i.e. a [Cl⋯I⋯I][Cl⋯I] complex (Figures 6A, see S13 and Table S5). For the crystals obtained from L2 and ICl, two types of complexes, a 1:1 [F4NN][ClI] complex (Figures 6B, see S14 and Table S6) and 1:2 L2 to ICl complex, i.e. a [Cl⋯I⋯Cl][Cl⋯I] complex (Figures 6C, see, S15 and Table S7), were observed. These structures show the possibility of dissociation from [N⋯I⋯N]Y to [NN⋯I]+Cl−/C0 and further transformation to [Cl⋯I⋯Cl]− in the presence of excess chloride. Furthermore, the X-ray crystal structures of the [F4NN][ClI] complexes reveal that the interatomic distances between sp2 CH(1) and Cl(1) are 2.73 Å and 2.74 Å, respectively (Figures 6B and 6C), which suggest the potential of pyridyl sp2 CH as a weak H-bonding donor site.

Mechanistic studies

The X-ray crystal structures indicate the bond formation of Cl⋯I⋯Cl and [Cl⋯I⋯Cl]− and the further H-bonding of sp2-CH⋯Cl− (Figure 7). Based on the aforementioned results, 1H NMR and CSI-MS measurements were performed using 1e and n-Bu4NCl to gain insight into the chloride-binding modes in the solution. Three phases of peak changes were observed during 1H NMR titration (Figures 8A, see S1, S2, and S3): i) In the cases where 0.1 to 1.0 equiv of n-Bu4NCl was added, aromatic peaks of 1e—green-filled dots—shifted downfield owing to the de-shielding effect on the complex triangular structure of 1e. The trend of these shift changes is similar to that reported by Berkessel et al. (2014). These shift changes demonstrate the H-bonding between the chloride and the protons of 1e. Moreover, new sharp aliphatic peaks—red-filled dots—appeared. These peaks clearly explain that the anion exchange from SbF6− to Cl− occurs at the initial stage. In addition to these peak changes, new sharp aromatic peaks—blue-filled dots—gradually emerged. ii) In cases where 1.0 to 2.0 equiv of n-Bu4NCl was added, sharp aromatic peaks of 1e—green-filled dots—decreased in peak size and disappeared when 2 equiv of n-Bu4NCl were added. By contrast, broad aromatic peaks—blue-filled dots—as well as sharp aliphatic peaks—red-filled dots—gradually increased in peak size. Particularly, the signals of two aromatic protons of the pyridine ring, Hc and Hd (indicated in blue), overlapped and appeared downfield as a single broad peak at 0.1 ppm with respect to those of L1. These peak changes demonstrate the formation of [L1⋯I⋯I]− + n-Bu4N+ ⇌ I−⋯Cl− + n-Bu4N+⋯L1 in equilibrium by the dissociation of the N⋯I⋯N bond. iii) In cases where more than 2 equiv of n-Bu4NCl were added, broad aromatic peaks—purple-filled dots—shifted up-field and were sharpened. Conversely, sharp aliphatic peaks—red-filled dots—shifted downfield and gradually increased in peak size. These observations suggest the formation of [Cl⋯I⋯Cl]− along with the
complexation of n-Bu4N+···L1. CSI-MS spectra show four peaks at m/z = 719.5, 522.4, 407.0, and 242.3 in the positive mode, and two peaks at m/z = 234.9 and 196.9 in the negative mode in the 1:1 mixture of 1e and n-Bu4NCI (Figures 8B, see S4 and S5). These peaks correspond to L1···n-Bu4N+·[ICl2]−, [L1···n-Bu4N+]+, [L1···I]−, [n-Bu4N]+, SbF6−, and [ICl2]−, respectively. The peak intensity of [L1···I]− in the 1:1 mixture was significantly higher than that of L1···n-Bu4N+·[ICl2]− following the addition of 0.5 equiv of n-Bu4NCI to 1e. By contrast, when a solution with 1e and n-Bu4N+ in a 1:2 ratio was used, the peak of [L1···I]− disappeared, whereas the peak of L1···n-Bu4N+·[ICl2]− was maintained. These spectral changes strongly support the following chloride-binding mode using complex catalyst 1: [N···X···N]Y + Cl− → [N···X···N]− + Cl− + Y at the initial stage, [NN···X]− + Cl− → [NN] + X− ···Cl− at the middle stage, and [NN···X]− + Cl− + Cl− → [NN] + X− ···Cl− + Cl− at the final stage.

Considering these experimental studies, we proposed the catalytic cycle shown in Figure 9. In this mechanism, the sp2 CH of the bis-pyridyl ligand in 1 initially interacts with chloride, and the nucleophilic attack of chloride on halogen(I) subsequently causes the formation of N···X− ···Cl−, followed by [Cl− ···X− ···Cl]− bonds. [N···X···N]−, the charge-assisted sp2 CH-bond and the [Cl− ···X− ···Cl]− anionic 3c4e X-bond should be synergistically involved to generate the electrophilic 2···3+ species. The resulting 2···3+ would be subjected to the nucleophilic attack by silyl enol ether 4 to yield the silylated intermediate, yielding product 5 and R3SiCl along with re-generated 1.

To support the proposed mechanism, DFT calculations and UV-vis measurements were performed. The molecular electrostatic potentials (MEPs) of 1e and [NN···X···N]− were mapped on the iso-density surface based on the DFT calculations performed using the SMD18 model (Figures 10A, see S17 and Table S9) (Engelage et al., 2018). The MEP map shows that positive charge is mainly located on the hydrogen atoms of the pyridyl ligand, with some remaining on the iodine atom. An analysis of noncovalent interactions (NCIs) indicated weak attractive interactions: CH···Cl− interactions between the α-protons of the pyridine ring in 1e and chloride, N···I−···N interactions between the pyridyl nitrogen and iodine(I), and C···I− interactions between the ethynyl sp carbon and iodine(I) (Figures 10B, see S18 and Table S10). These results suggest that [N···X···N]Y would promote the reaction via charge-assisted noncovalent interactions, such as hydrogen bonding, in the case of 1e, at the initial stage. Moreover, DFT calculations using the SMD18 model support the formation of the 3c4e X-bond between the pyridyl nitrogen atom and chloride: The transformation of [NN···X···N]Cl to [NN···X···Cl]− resulted in a Gibbs free energy change of −3.2 kcal mol−1, with a transition-state free energy of 12.9 kcal mol−1 (Figure 10C, see Table S11). Although the transition state of the [NN···X···Cl]− conversion could not be found, this conversion is also exothermic, with a Gibbs free energy change of −3.7 kcal mol−1 (Figure 10C, see Table S12). Finally, UV-vis measurements were performed to identify the reformation of [NN···X···N]Ys for the catalytic cycle. The UV-vis spectrum of the crude reaction mixture shows absorption at 307 nm, which was similarly observed in the spectrum of 1e (Figures 10D, see S6), indicating that [Cl− ···X− ···Cl]− is transformed back to [NN···X− ···N]−. This can be explained by the robust catalytic activity of [NN···X···N]Ys owing to the distinct feature of the charged 3c4e X-bond: partially covalent and strongly electrostatic interaction derived from halogen(I).

Limitations of the study
This study is limited to the Mukaiyama-Mannich-type reaction of N-heteroaromatics via chloride-binding in a racemic manner. A method based on the current approach could apply to other catalytic reactions, either through Lewis-acid or Brønsted-acid catalysis.

Figure 10. Mechanistic studies of the complexes
(A) The molecular electrostatic potential map: [N···I···N]+ of 1e. SMD18(THF)/M06-2X-D3/6-311+G(d,p)-SDD-calculated electrostatic potentials on the molecular surface. The surface was computed on a 0.008 a.u. electron-density contour for visualization. The molecular electrostatic potential maps were created using the GaussView 6 software. Surface potential values are indicated in kJ mol−1. The color ranges are as follows: red, less than 240 kJ mol−1; green, greater than 500 kJ mol−1.
(B) The NCI plot between [N···I···N]+ of 1e and Cl−. The isosurface s-value equals 0.3 a.u., green indicates weak attractive interactions.
(C) DFT calculations of [N···I···N]+ → [NN···I···Cl] and [NN···I···Cl] + Cl− → [NN] + [Cl− ···I···Cl]−. The computational studies were conducted at 273 K in THF using the SMD18(THF)/M06-2X-D3/6-311+G(d,p)-SDD-level method.
(D) The UV-vis spectra of the crude reaction mixture, 1e, and L1.
STAR+METHODS
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SUPPLEMENTAL INFORMATION
Supplemental information can be found online at https://doi.org/10.1016/j.isci.2022.105220.

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AUTHOR CONTRIBUTIONS
Conceptualization, N.M.; Methodology, N.M.; Investigation, S.O., T.F., Y.M., T.S., M.K., and N.O.; Writing – Original Draft, N.M., S.O., and T.F.; Writing – Review & Editing, N.M.; Supervision, N.M.; Funding Acquisition, N.M.

DECLARATION OF INTERESTS
The authors declare no competing interests.

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## STAR METHODS

### KEY RESOURCES TABLE

| REAGENT or RESOURCE | SOURCE | IDENTIFIER |
|---------------------|--------|------------|
| **Chemicals, peptides, and recombinant proteins** | | |
| Pyridine, Dehydrated | Wako Pure Chemical Industries Ltd. | Cat#161-18453 |
| Phenyl Chloroformate | TCI | Cat#C0649 |
| N,N'-bis[3,5-bis(trifluoromethyl)phenyl]-Thiourea | TCI | Cat#B3452 |
| Iodine monochloride | Sigma Aldrich | Cat#208221-5G |
| Iodine | Wako Pure Chemical Industries Ltd. | Cat#093-05435 |
| 1-(tert-Butyldimethylsilyloxy)-1-methoxyethene | TCI | Cat#65878 |
| 2,2,2-Trichloroethyl Chloroformate | Sigma Aldrich | Cat#142077-25G |
| 2,2,2-Trichloro-1,1-dimethylethyl chloroformate | Sigma Aldrich | Cat#226505-5G |
| 9-Fluorenylmethyl Chloroformate | TCI | Cat#F0197 |
| 2-Methylpyridine | Kanto Chemical Co., Inc. | Cat#32222-30 |
| 3-Methylpyridine | TCI | Cat#P4016 |
| 3-(Trifluoromethyl)pyridine | TCI | Cat#T2786 |
| Benzylpyridine | TCI | Cat#B0436 |
| Methyl Nicotinate | TCI | Cat#N0086 |
| 4-(Trifluoromethyl)pyridine | Sigma Aldrich | Cat#S29910-1G |
| 4-Cyanopyridine | TCI | Cat#C0457 |
| 4-Phenylpyridine | TCI | Cat#P0162 |
| Quinoline | TCI | Cat#Q0085 |
| Isoquinoline | TCI | Cat#T0182 |
| 3,4-Dihydroisoquinoline | Sigma Aldrich | Cat#779385-1G |
| Tetrabutylammonium Chloride | TCI | Cat#P0366 |
| Tetrabutyl-ammonium, hexafluoro antimonate(v) | Sigma Aldrich | Cat#5337102-1EA |
| 1,2-Diodobenzene | Sigma Aldrich | Cat#238112-10G |
| 1,2-Diodotetrafluorobenzene | Sigma Aldrich | Cat#334707-5G |
| 2-Ethynylpyridine | TCI | Cat#E0340 |
| Silver hexafluoroantimonate(V) | Sigma Aldrich | Cat#227730-5G |
| Silver trifluoromethanesulfonate | Wako Pure Chemical Industries Ltd. | Cat#195-10931 |
| Silver hexafluorophosphate | TCI | Cat#S0981 |
| Silver tetrafluoroborate | TCI | Cat#S0446 |
| Silver nitrate | Sigma Aldrich | Cat#209139-25G |

**Deposited data**

| CCDC | CCDC-2152342 |
| CCDC | CCDC-2152343 |
| CCDC | CCDC-2152345 |
| CCDC | CCDC-2152347 |
| CCDC | CCDC-2152346 |
| CCDC | CCDC-2152341 |
| CCDC | CCDC-2152348 |
| CCDC | CCDC-2152344 |
RESOURCE AVAILABILITY

Lead contact
Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Norie Momiyama (momiyama@ims.ac.jp).

Materials availability
All other data supporting the findings of this study are available within the article and the supplemental information, or can be obtained from the lead contact upon reasonable request.

Data and code availability
- All original crystal structures have been deposited at CCDC and are publicly available as of the date of publication. CCDC numbers are listed in the key resources table.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper can be obtained from the lead contact upon request.

METHOD DETAILS

General reagent information
Unless otherwise specified, all reactions were carried out under an atmosphere of standard-grade nitrogen gas (oxygen <10 ppm) in flame-dried glassware with magnetic stirring. Commercially available reagents and chemicals were purchased and used without further purification. Dichloromethane (CH2Cl2), diethyl ether (Et2O), and tetrahydrofuran (THF) were supplied from a “dehydrated solvent system” by Kanto Chemical Co., Inc. Other solvents were procured in the dehydrated form from Wako Pure Chemical Industries Ltd. Analytical thin-layer chromatography (TLC) was performed on E. Merck precoated (0.25 mm) silica gel 60-F254 plates. Visualization was accomplished using UV light (wavelength (λ) = 254 nm) and a phosphomolybdic acid solution in ethanol with heating. Purification of the reaction products was carried out via flash column chromatography using silica gel 60 N (Merck: 0.040–0.063 mm). The microwave reactions were performed using a Biotage Initiator + model (Biotage Japan Ltd), in which the temperature was monitored via an infrared temperature sensor, and Biotage Microwave Reaction Vials, which were sealed with caps with septa.

General analytical information
1H NMR spectra were recorded on a JEOL ECS-400 (400 MHz) or a JEOL JNM-ECA600 (600 MHz) spectrometer. Chemical shifts in chloroform-d (CDCl3), dimethylsulfoxide-d6 (DMSO-d6), and tetrahydrofuran-d8 (THF-d8) were reported in ppm using tetramethylsilane (TMS) as the internal standard (0.00 ppm). Chemical shifts were reported in ppm using solvent resonance as the internal standard (CD3CN: 1.94, CD2Cl2: 5.32). Data were reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, sext = sextet, sep = septet, oct = octet, dd = doublet of doublets, dt = doublet of triplets, tt = triplet of triplets, ddd = doublet of doublets of doublets, m = multiplet, and brs = broad singlet), and coupling constants (Hz). 13C NMR spectra were recorded on a JEOL ECS-400 (100 MHz) or a JEOL JMN-ECA600 (151 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm using solvent resonance as the internal standard (CDCl3: 77.1, CD2Cl2: 53.84, DMSO-d6: 39.5, CD3CN: 1.30, THF-d8: 25.3). 19F NMR spectra were recorded on a JEOL ECS-400 (376 MHz) spectrometer. Chemical shifts were reported in ppm using CF3C6H5 as the external standard (CD3CN: −63.72, CD2Cl2: −63.72, DMSO-d6: −61.02, THF-d8: −63.4). 31P NMR spectra were recorded on a JEOL ECS-400 (162 MHz) spectrometer. Infrared (IR) spectra were recorded on a Jasco FT/IR-460plus spectrometer. UV-vis spectra were recorded on a Jasco FTIR-460plus spectrometer. UV-vis spectrophotometer using THF (stabilizer free) purchased from Wako Pure Chemical Industries Ltd. HRMS analysis (FAB) was performed at the Instrument Center, Institute for Molecular Science using a JEOL JMS-700 spectrometer and 3-nitrobenzyl alcohol as the matrix. Elemental analysis was performed on a J-Science Lab JM10 CHN Analyzer MICRO CORDER at the Instrument Center, Institute for Molecular Science. X-ray diffraction measurements were performed on a Rigaku XtaLAB Synergy Custom diffractometer using multi-layer-mirror monochromated Mo-Kα radiation. The data were collected and processed using CrysAlisPro (Rigaku Oxford Diffraction; CrysAlisPro: Data Collection and Processing Software, Rigaku Corporation (2015). Tokyo 196–8666, Japan). The structure was solved using a dual-space program (Sheldrick, 2014; SHELXT Version 2014/5: Sheldrick, M. G. (2014). Acta Cryst. A70, C1437) and
expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. Calculations were performed using a CrystalStructure (CrystalStructure 4.3: Crystal Structure Analysis Package, Rigaku Corporation (2000-2018). Tokyo 196–8666, Japan) crystallographic software package, except for refinement, which was performed using SHELXL Version 2014/7 (Sheldrick, 2014; SHELXL Version 2014/7: Sheldrick, M. G. (2008). Acta Cryst. A64, 112–122).

Syntheses of halogen(I) complexes
A variety of halogen(I) complex catalysts were synthesized according to the reported procedure (Bedin et al., 2015; Carlsson et al., 2012a). Among them, 1,2-bis(pyridine-2-ylethynyl)benzene iodine(I) triflate (1a), Erdélyi’s complex, was used as the benchmark complex catalyst because it is relatively stable and easy to handle. Moreover, two types of protonated L1 triflates were prepared as references to prevent H+ from contaminating 1a (Bedin et al., 2015; Suzaki et al., 2014, see Figure S7). We confirmed that the 1H NMR spectra of 1a were significantly different from those of protonated L1, which clearly showed our synthesized 1a iodine complex without the contamination of protonated complexes. All complexes 1 were synthesized and characterized accordingly and used as the halogen(I) complex catalysts.

Synthesis of 1,2-bis(pyridine-2-ylethynyl)benzene (L1)
To a solution of 1,2-diiodobenzene (2.61 mL; 20.0 mmol; 1.0 equiv) in CH3CN (200 mL), 2-ethynylpyridine (4.42 mL; 44.0 mmol; 2.2 equiv), Pd(OAc)2 (449 mg; 2.00 mmol; 10 mol%), PPh3 (1.04 g; 4.00 mmol; 20 mol%), and Et3N (32 mL) were added (Carlsson et al., 2016). The mixture was heated to 80°C and stirred for 16 h. The solvent was concentrated under reduced pressure. CH2Cl2 (150 mL) was added and the suspension was filtered and washed with CH2Cl2 (30 mL). H2O (100 mL) was added to the filtrate, and the two phases were separated. The aqueous phase was extracted using CH2Cl2 (35 mL). The combined organic phases were dried over MgSO4 and concentrated under reduced pressure after filtration. The crude product was purified using silica gel column chromatography (ethyl acetate/hexane = 1:4 to 2:3) to yield the desired product as a white solid (4.15 g; 14.8 mmol; 74%, see Scheme S1).

Synthesis of 1,2,3,4-tetrafluoro-5,6-bis(pyridine-2-ylethynyl)benzene (L2)
To a solution of 1,2,3,4-tetrafluoro-5,6-diiodobenzene (402 mg; 1.00 mmol; 1.0 equiv) in toluene (20 mL), 2-ethynylpyridine (217 mL; 2.10 mmol; 2.1 equiv), Pd(PPh3)4 (35.0 mg; 30.0 mol%; CuI (19.0 mg; 0.100 mmol; 10 mol%), and i-Pr2NH (1.00 mL; 7.00 mmol; 7.0 equiv) were added. The mixture was heated to 100°C and stirred for 15 h. The reaction mixture was quenched with saturated aqueous NH4Cl (20 mL), and the two phases were separated. The aqueous phase was extracted using diethyl ether (30 mL). The combined organic phases were dried over MgSO4 and concentrated under reduced pressure after filtration. The crude product was purified using silica gel column chromatography (ethyl acetate/hexane = 1:1) to yield the desired product as a white solid (211 mg; 0.599 mmol; 60%, see Scheme S2).

Synthesis of 1,2-diethynylbenzene
To a solution of 1,2-diiodobenzene (0.655 mL; 5.00 mmol; 1.0 equiv) in Et3N (13 mL), trimethylsilylacetylene (1.70 mL; 12.0 mmol; 2.4 equiv), Pd(PPh3)2Cl2 (351 mg; 0.500 mmol; 10 mol%), and CuI (95.2 mg; 0.500 mmol; 10 mol%) were added (Bosch and Barnes, 2001). The mixture was heated to 70°C and stirred for 20 h. It was then allowed to cool to room temperature, diluted with hexane, and washed with water. The organic phase was dried over MgSO4 and concentrated under reduced pressure after filtration to yield a crude product. The crude product was immediately deprotected as follows: Na2CO3 (250 mg; 2.40 mmol; 0.60 equiv) was added to a solution of the crude product in MeOH (50 mL). The mixture was stirred at room temperature for 2 h, diluted with water, and extracted using hexane (15 mL × 3). The combined organic phases were dried over MgSO4 and concentrated under reduced pressure after filtration. The crude product was purified using silica gel column chromatography with hexane as the eluant to yield the desired product as a pale yellow oil (405 mg; 3.20 mmol; 76%, see Scheme S3).

Synthesis of 1,2-bis[6-methyl-2-pyridyl]ethynyl]benzene (L3)
To a solution of 1,2-diethynylbenzene (253 mg; 2.00 mmol; 1.0 equiv) in Et3N (15 mL), 6-bromo-2-picoline (0.547 mL; 4.80 mmol; 2.4 equiv), Pd(PPh3)2Cl2 (70.2 mg; 0.100 mmol; 5.0 mol%), and CuI (19.0 mg; 0.100 mmol; 5.0 mol%) were added (Jung et al., 2012). The mixture was stirred at 80°C for 10 min under microwave irradiation. The resulting suspension was filtered through a pad of celite, and the filtrate was concentrated under reduced pressure. The crude product was purified using silica gel column chromatography (ethyl acetate/hexane = 1:1) to yield the desired product as a white solid (232 mg; 0.599 mmol; 60%, see Scheme S4).
chromatography (ethyl acetate/hexane = 1:2) to yield the desired product as a white solid (360 mg; 1.17 mmol; 58%, see Scheme S4).

General procedure for the synthesis of 1,2-bis(pyridine-2-ylethynyl)benzene halogen(I) complexes
Here, the general procedure employing AgOTf and I₂ has been described (Bedin et al., 2015). A mixture of 1,2-bis(pyridine-2-ylethynyl)benzene (280 mg; 1.00 mmol; 1.0 equiv) and AgOTf (270 mg; 1.05 mmol; 1.1 equiv) was dissolved in CH₂Cl₂ (40 mL) and stirred at room temperature for 2 h. I₂ (267 mg, 1.05 mmol, 1.1 equiv) was added to the solution, and immediately a yellow precipitate (AgI) was formed. The reaction mixture was stirred for 2 h and then filtered through a pad of celite. Hexane (20 mL) was added to the filtrate, and the suspension was filtered again. The residue was washed with hexane and dried in vacuo to furnish the halonium complex as a white solid. The syntheses of other 1,2-bis(pyridine-2-ylethynyl) benzene halonium complexes were carried out according to the general procedure using the corresponding reagents, see Scheme S5.

Synthesis of the 1,2,3,4-tetrafluoro-5,6-bis(pyridine-2-ylethynyl)benzene iodonium complex (1g)
AgSbF₆ (108 mg; 0.315 mmol; 1.1 equiv) was added to a solution of 1,2,3,4-tetrafluoro-5,6-bis(pyridine-2-ylethynyl)benzene (106 mg; 0.300 mmol; 1.0 equiv) in CH₂Cl₂ (3 mL), and the mixture was stirred at room temperature for 3 h. Next, CH₃CN (1 mL) was added to the solution, and it was stirred for another 10 min. I₂ (80.0 mg, 0.315 mmol, 1.1 equiv) was then added, and a yellow precipitate (AgI) was immediately formed. The reaction mixture was stirred for 3 h and filtered through a membrane filter (DISMIC-28HP). Hexane (10 mL) was added to the filtrate, and the suspension was filtered. The residue was washed with hexane and dried in vacuo to furnish the iodonium complex as a white solid (99.5 mg; 0.139 mmol; 46%, see Scheme S6).

Synthesis of the 1,2-bis[(6-methyl-2-pyridyl)ethynyl]benzene iodine(I) complex (1h)
A mixture of 1,2-bis[(6-methyl-2-pyridyl)ethynyl]benzene (92.5 mg; 0.300 mmol; 1.0 equiv) and AgSbF₆ (103 mg; 0.300 mmol; 1.0 equiv) was dissolved in CH₂Cl₂ (6 mL) and stirred at room temperature for 2 h. I₂ (76.1 mg; 0.300 mmol; 1.0 equiv) was added to the solution, and a yellow precipitate (AgI) was immediately formed. The reaction mixture was stirred for 2 h and filtered through a pad of Celite. Hexane (10 mL) was added to the filtrate, and the suspension was filtered. The residue was washed with hexane and dried in vacuo to furnish the iodonium complex as a white solid (188 mg; 0.280 mmol; 93%, see Scheme S7).

Synthesis of [2Me-L₁]₂OTf
Methyl triflate (72 μL; 0.660 mmol; 2.2 equiv) was added to a solution of 1,2-bis(2-pyridylethynyl)benzene (84.1 mg; 0.300 mmol; 1.0 equiv) in CH₂Cl₂ (2 mL) at 0°C. The mixture was stirred for 14.5 h at room temperature and the solvent was evaporated under reduced pressure. The remaining solid was obtained via filtration and washed with diethyl ether. The residue was dried under reduced pressure to yield the desired compound as a white solid (169 mg; 0.278 mmol; 93%, see Scheme S9).

Synthesis of [Cl–I–NN–I–Cl]
ICl (32.4 mg; 0.200 mmol; 1.0 equiv) was added to a solution of 1,2-bis(2-pyridylethynyl)benzene (28.0 mg; 0.100 mmol; 1.0 equiv) in CH₂Cl₂ (2 mL) at −78°C. The reaction mixture was stirred for 1.5 h and then warmed to room temperature. Hexane (10 mL) was added to the filtrate, and the suspension was filtered. The residue was washed with hexane and dried in vacuo to furnish the desired compound as a white solid (38.4 mg; 63.4 μmol; 63%, see Scheme S10).
Synthesis of $[^4\text{I}N–I–N][\text{Cl}–I–\text{Cl}]$

Iodine monochloride (105 μL; 2.00 mmol; 2.0 equiv) was added to a solution of 1,2,3,4-tetrafluoro-5,6-bis (pyridine-2-yethynyl)benzene (352 mg; 1.00 mmol; 1.0 equiv) in CH$_2$Cl$_2$ (15 mL). The reaction mixture was stirred at room temperature for 3 h. EtOH (15 mL) was added to the mixture, and CH$_2$Cl$_2$ was concentrated under reduced pressure. The resultant suspension was filtered and washed with EtOH (15 mL). The residue was collected and dried in vacuo to yield the desired compound as a yellow solid (503 mg; 0.743 mmol; 74%, see Scheme S11).

Synthesis of $[^4\text{I}N–I–N][\text{Cl}–I–\text{Cl}]+[\text{Cl}–I–[^4\text{N}N–I–\text{Cl}]$

To a solution of 1,2,3,4-tetrafluoro-5,6-bis (pyridine-2-yethynyl)benzene (352 mg; 1.00 mmol; 1.0 equiv) in CH$_2$Cl$_2$ (15 mL), a solution of iodine monochloride (162 mg; 1.00 mmol; 1.0 equiv) in CH$_2$Cl$_2$ (7 mL) was added. The reaction mixture was stirred at room temperature for 3 h. EtOH (15 mL) was added to the mixture, and CH$_2$Cl$_2$ was concentrated under reduced pressure. The resultant suspension was filtered and washed with EtOH (15 mL). The residue was collected and dried in vacuo to yield the desired compound as a yellow solid (104 mg; 0.154 mmol; 15%, see Scheme S12).

Syntheses of silyl enol ethers

**Synthesis of methyl trimethylsilyl dimethylketene acetal (4a)**

To a solution of i-P$_3$NH (5.26 mL; 38.5 mmol; 1.1 equiv) in THF (50 mL), n-BuLi (1.60 M in n-hexane; 24.1 mL; 38.5 mmol; 1.1 equiv) was added at 0°C. The mixture was stirred for 1 h and cooled to −78°C (Gatzenmeier et al., 2018). Methyl isobutyrate (4.02 mL; 35.0 mmol; 1.0 equiv) was then added to it, and the mixture was stirred for another 1 h. TMSCl (5.31 mL; 42.0 mmol; 1.2 equiv) was added to the reaction mixture, which was stirred for 30 min. It was then slowly warmed to room temperature and stirred for 16 h. The solvent was evaporated under reduced pressure, and n-hexane (50 mL) was added. The mixture was filtered through a pad of celite and membrane filter, and n-hexane was evaporated under reduced pressure. Distillation of the crude product (56°C/19 mmHg) yielded the desired product as a colorless oil (3.84 g; 22.0 mmol; 63%, see Scheme S13).

**Synthesis of 1-methoxy-1-trimethylsilyloxymethylene cyclohexane (4b)**

1-Methoxy-1-trimethylsilyloxymethylene cyclohexane was synthesized according to the reported method (Berkessel et al., 2014). To a solution of diisopropylamine (4.92 mL; 36.0 mmol; 1.2 equiv) in THF (75 mL), n-BuLi (1.60 M in n-hexane; 20.6 mL; 33.0 mmol; 1.1 equiv) was added at 0°C. The mixture was stirred for 1 h and cooled to −78°C. Methyl cyclohexanecarboxylate (4.29 mL; 30.0 mmol; 1.0 equiv) was then added to it, and the mixture was stirred for another 30 min, after which TMSCl (4.17 mL; 33.0 mmol; 1.2 equiv) was added to it. Then the mixture was slowly warmed to room temperature and stirred for 16 h. The solvent was evaporated under reduced pressure and n-hexane (100 mL) was added, which was removed under reduced pressure after filtration. Distillation of the crude product (57°C/6 mmHg) yielded the desired product as a colorless oil (5.59 g; 26.1 mmol; 87%, see Scheme S14).

**Synthesis of α-methyl-γ-butyrolactone trimethylsilyl ketene acetal (4c)**

To a solution of diisopropylamine (4.51 mL; 33.0 mmol; 1.1 equiv) in THF (60 mL), n-BuLi (1.60 M in n-hexane; 21.5 mL; 34.4 mmol; 1.2 equiv) was added at 0°C (Katayev et al., 2015). The mixture was stirred for 20 min and cooled to −78°C. 3-Methyldihydrofuran-2(3H)-one (2.87 mL; 30 mmol; 1.0 equiv) was then added to the mixture, which was stirred for another 30 min, and TMSCl (4.55 mL; 36 mmol; 1.2 equiv) was added to it. The reaction mixture was slowly warmed to room temperature and stirred for 21 h. The resulting suspension was washed with pentane (10 mL) and filtered through a membrane filter. The solvent was evaporated under reduced pressure. Distillation of the crude product (65°C/30 mmHg) yielded the desired product as a colorless oil (2.79 g; 16.2 mmol; 54%, see Scheme S15).

**Synthesis of (1-methoxyvinyl)oxytrimethylsilane (4d)**

To a solution of dicyclohexylamine (12.0 mL; 60.0 mmol; 1.2 equiv) in THF (50 mL), n-BuLi (1.60 M in n-hexane; 37.5 mL; 60.0 mmol; 1.2 equiv) was added at 0°C. The mixture was stirred for 15 min and cooled to −78°C (Lee et al., 2018). A mixture of methyl acetate (3.98 mL; 50.0 mmol; 1.0 equiv) and TMSCl (7.58 mL; 60.0 mmol; 1.2 equiv) was added to it, and it was stirred for another hour. The mixture was then slowly warmed to room temperature and stirred for 16 h. The solvent was evaporated under reduced pressure and n-pentane (20 mL) was added. The mixture was filtered through a pad of celite, and n-pentane.
was evaporated under reduced pressure. Distillation of the crude product (38°C/40 mm Hg) yielded the desired product as a colorless oil (599 mg; 4.09 mmol; 8%, see Scheme S16).

**Synthesis of trimethyl[(1-methylethenyl)oxy]silane (4f)**

A mixture of acetone (2.06 mL; 28.0 mmol; 1.0 equiv) and sodium iodide (4.20 g; 28.0 mmol; 1.0 equiv) was dissolved in CH₃CN (30 mL) and stirred for 5 min at room temperature (Zhang and Lupton, 2017). Et₃N (3.90 mL; 28.0 mmol; 1.0 equiv) and TMSCl (3.54 mL; 28.0 mmol; 1.0 equiv) were added to the solution, and it was stirred at 40°C for 16 h. The reaction mixture was then cooled to room temperature and quenched with cold pentane (50 mL) and ice water (50 mL), when the two phases separated. The aqueous phase was extracted with n-pentane (30 mL x 3) and the combined organic phases were dried over MgSO₄. The solvent was concentrated under reduced pressure after filtration to yield the desired product as a colorless oil (786 mg; 6.03 mmol; 22%, see Scheme S17).

**General procedure for a Mukaiyama-Mannich-type reaction**

Here, the general procedure employing pyridine (1.0 equiv), phenyl chloroformate (1.1 equiv), an iodonium complex catalyst (0.20 mmol; 0.05 mol%), and methyl trimethylsilyl dimethylketene acetal (1.5 equiv) has been described.

Pyridine (32 μL; 0.400 mmol; 1.0 equiv) was dissolved in THF (8 mL) and stirred at 0°C for 10 min. Phenyl chloroformate (55 μL; 0.420 mmol; 1.1 equiv) was added, and the mixture was stirred for another 30 min. The catalyst (0.20 μmol; 0.05 mol%) was added, and the reaction mixture was stirred for 5 min, following which, methyl trimethylsilyl dimethylketene acetal (120 μL; 0.600 mmol; 1.5 equiv) was added. The mixture was then stirred for 1 h and quenched with saturated aqueous NaHCO₃ (20 mL) for phase separation. The aqueous phase was extracted with diethyl ether (10 mL x 3) and the combined organic phases were washed with 2M aq. NaOH (10 mL) and brine (10 mL), dried over Na₂SO₄, and concentrated under reduced pressure after filtration. The crude product was purified using silica gel column chromatography (ethyl acetate/hexane = 1:8) to yield the desired product as a light yellow oil (99.3 mg; 0.330 mmol; 82%, see Scheme S18).

**NMR titration of [N–I–N]SbF₆ with n-Bu₄NCl**

In the NMR tube, [N–I–N]SbF₆ (3.2 mg; 5.0 μmol) was dissolved in THF-d₈ (360 μL) and CD₃CN (40 μL) and mixed thoroughly using a vortexer. The tube was placed in a 600 MHz NMR spectrometer, in which the probe had been pre-cooled to 0°C, and the ¹H NMR spectrum was obtained. A solution of n-Bu₄NCl in THF-d₈/CD₃CN 9:1 (v/v) was added and mixed thoroughly using a vortexer. The NMR tube was then quickly transferred to the NMR spectrometer. The process was repeated to obtain the ¹H NMR spectra in the presence of varying amounts of n-Bu₄NCl (0.10–10.0 equiv, see Figures S1, S2 and S3).

**CSI-MS titration of [N–I–N]SbF₆ with TBACl**

[N–I–N]SbF₆ (3.2 mg, 5.0 μmol) was dissolved in THF (900 μL) and CH₃CN (100 μL). To this solution, a solution of n-Bu₄NCl in THF/CH₃CN 9:1 (v/v) was added and mixed thoroughly. CSI-MS spectra were recorded at ~20°C in the presence of varying amounts of n-Bu₄NCl (0.5, 1.0, and 2.0 equiv; see Figures S4 and S5).

**Spectroscopic details**

1,2-Bis(pyridine-2-ylethynyl)benzene (L1)

¹H NMR (400 MHz, DMSO-d₆): δ 8.67 (ddd, J = 4.8, 2.0, and 1.2 Hz, 2H), 7.90 (dt, J = 7.8 and 1.6 Hz, 2H), 7.84–7.79 (m, 2H), 7.72–7.78 (m, 2H), 7.52–7.58 (m, 2H), and 7.46 (ddd, J = 7.6, 4.8, and 1.2 Hz, 2H) (Carlsson et al., 2016).

¹³C NMR (100 MHz, CDCl₃): δ 150.3, 148.2 (d, J = 247.9 Hz), 142.3, 141.3 (d, J = 262.2 Hz), 136.3, 128.2, 123.8, 111.2, 99.6, and 78.1.

¹⁹F NMR (376 MHz, CDCl₃): δ –134.1 to –133.9 (m, 2F), –153.4 to –153.2 (m, 2F).

IR (ATR): 1580, 1491, 1408, 959, 777, 739, 654, 631, 590, 579, 568, and 553 cm⁻¹.

1,2,3,4-Tetrafluoro-5,6-bis(pyridine-2-ylethynyl)benzene (L2)

¹H NMR (400 MHz, CDCl₃): δ 8.67 (dt, J = 4.9 and 1.3 Hz, 2H), 7.77–7.69 (m, 4H), and 7.33–7.29 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 150.3, 148.2 (d, J = 247.9 Hz), 142.3, 141.3 (d, J = 262.2 Hz), 136.3, 128.2, 123.8, 111.2, 99.6, and 78.1.
Anal. HRMS (FAB): Exact Mass Calculated for C_{20}H_{29}F_{7}N_{2} ([M + H]^+): 353.0702. Found: 353.0696.

**1,2-Diethynylbenzene**

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.52 (dd, \(J = 5.7\) and 3.4 Hz, 2H), 7.32 (dd, \(J = 5.7\) and 3.4 Hz, 2H), and 3.34 (s, 2H) (Bosch and Barnes, 2001).

**1,2-Bis[(6-methyl-2-pyridyl)ethynyl]benzene (L3)**

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.65 (dt, \(J = 9.4\) and 3.5 Hz, 2H), 7.57–7.54 (m, 4H), 7.36 (dt, \(J = 9.4\) and 3.5 Hz, 2H), 7.15–7.10 (m, 2H), and 2.61 (s, 6H) (Jung et al., 2012).

**[N–I–N]OTf (1a)**

The general procedure (Scheme S5) was followed. White solid (343 mg; 0.617 mmol; 62%) (Bedin et al., 2015)

\(^1\)H NMR (400 MHz, CD\(_3CN\)): \(\delta\) 8.67–8.73 (m, 2H), 8.11 (dt, \(J = 8.0\) and 1.6 Hz, 2H), 7.78–7.86 (m, 2H), 7.64–7.71 (m, 2H), 7.47–7.54 (m, 2H), and 7.37–7.44 (m, 2H).

**[N–I–N]BF\(_4\) (1b)**

The general procedure (Scheme S5) was followed. White solid (859 mg; 1.74 mmol; 58%) (Bedin et al., 2015)

\(^1\)H NMR (400 MHz, CD\(_3CN\)): \(\delta\) 8.77–8.83 (m, 2H), 8.19 (dt, \(J = 8.0\) and 1.6 Hz, 2H), 7.90–7.95 (m, 2H), 7.77–7.84 (m, 2H), 7.58–7.65 (m, 2H), and 7.46–7.51 (m, 2H).

**[N–I–N]NO\(_3\) (1c)**

The general procedure (Scheme S5) was followed. White solid (1.27 g; 2.71 mmol; 91%) (Bedin et al., 2015)

\(^1\)H NMR (400 MHz, CD\(_3CN\)): \(\delta\) 8.72–8.77 (m, 2H), 8.13 (dt, \(J = 7.8\) and 1.6 Hz, 2H), 7.83–7.89 (m, 2H), 7.68–7.75 (m, 2H), 7.50–7.57 (m, 2H), and 7.40–7.46 (m, 2H).

**[N–I–N]PF\(_6\) (1d)**

The general procedure (Scheme S5) was followed. White solid (1.23 g; 2.23 mmol; 74%)

\(^1\)H NMR (400 MHz, CD\(_3CN\)): \(\delta\) 8.79–8.83 (m, 2H), 8.20 (dt, \(J = 7.8\) and 1.6 Hz, 2H), 7.92–7.97 (m, 2H), 7.79–7.85 (m, 2H), 7.60–7.65 (m, 2H), and 7.46–7.52 (m, 2H).

**[N–I–N]SbF\(_6\) (1e)**

The general procedure (Scheme S5) was followed. White solid (390 mg; 0.607 mmol; 61%)

\(^1\)H NMR (400 MHz, CD\(_3CN\)): \(\delta\) 8.76–8.78 (m, 2H), 8.17 (dt, \(J = 7.8\) and 1.4 Hz, 2H), 7.89–7.91 (m, 2H), 7.75–7.80 (m, 2H), 7.57–7.61 (m, 2H), and 7.44–7.48 (m, 2H).

\(^{13}\)C NMR (400 MHz, CD\(_3CN\)): \(\delta\) 151.6, 143.2, 142.7, 135.0, 131.7, 131.2, 127.4, 124.8, 98.7, and 91.5.

\(^{19}\)F NMR (376 MHz, CD\(_3CN\)): \(\delta\) –73.5 (d, \(J = 703.1\) Hz, 6F).

\(^{31}\)P NMR (162MHz, CD\(_3CN\)): \(\delta\) –144.6 (sep, \(J = 704.7\) Hz).

IR(ATR): 1749, 1600, 1474, 1363, 1250, 1174, 1089, 1053, 903, 840, 799, 750, 689, 634, and 592 cm\(^{-1}\).

Elemental analysis: Calculated for C\(_{20}\)H\(_{12}\)N\(_2\)IPF\(_6\): C, 43.50; H, 2.19; N, 5.07. Found: C, 43.37; H, 2.34; N, 5.05.

**[N–I–N]SbF\(_6\) (1e)**

The general procedure (Scheme S5) was followed. White solid (390 mg; 0.607 mmol; 61%)

\(^1\)H NMR (400 MHz, CD\(_3CN\)): \(\delta\) 8.76–8.78 (m, 2H), 8.17 (dt, \(J = 7.8\) and 1.4 Hz, 2H), 7.89–7.91 (m, 2H), 7.75–7.80 (m, 2H), 7.57–7.61 (m, 2H), and 7.44–7.48 (m, 2H).

\(^{13}\)C NMR (400 MHz, CD\(_3CN\)): \(\delta\) 151.6, 143.2, 142.7, 135.0, 131.8, 131.2, 127.4, 124.8, 98.7, and 91.5.

\(^{19}\)F NMR (376 MHz, CD\(_3CN\)): \(\delta\) –124.4 (s, \(J\) = 121\(^{19}\)Sb–\(^{19}\)F = 1924.0 Hz, 6F), –124.43 (oct, \(J\) = 1026.5 Hz, 6F).
IR (ATR): 1766, 1474, 1393, 1264, 1169, 1046, 902, 800, 752, 607, and 572 cm$^{-1}$.

Elemental analysis: Calculated for C$_{20}$H$_{12}$N$_2$SbF$_6$: C, 37.36; H, 1.88; N, 4.36. Found: C, 37.08; H, 1.88; N, 4.30.

$[\text{N–Br–N}]$SbF$_6$ (1f)

The general procedure (Scheme S5) was followed. White solid (101 mg; 0.170 mmol; 56%)

$^1$H NMR (400 MHz, CD$_3$CN): δ 8.78–8.76 (m, 2H), 8.24–8.20 (m, 2H), 7.98–7.95 (m, 2H), 7.84–7.80 (m, 2H), and 7.67–7.62 (m, 4H).

$^{13}$C NMR (100 MHz, CD$_3$CN): δ 148.7, 143.2, 140.4, 134.5, 132.1, 131.9, 127.5, 125.1, 97.8, and 89.5.

$^{19}$F NMR (376 MHz, CD$_3$CN): δ 124.37 (sext, $J_{\text{Sb–}19\text{F}} = 1923.6$ Hz, 6F), 124.44 (oct, $J_{\text{Sb–}19\text{F}} = 1063.0$ Hz, 6F).

IR (ATR): 1588, 1562, 1496, 1470, 1282, 1253, 1164, 1104, 1092, 768, and 650 cm$^{-1}$.

Anal. HRMS (FAB): Exact Mass Calculated for C$_{20}$H$_{12}$I$^{81}$BrN$_2$ ([M]⁺): 361.0158. Found: 361.0162.

1,2,3,4-Tetrafluoro-5,6-bis(pyridine-2-ylethynyl)benzene iodonium complex (1g)

$^1$H NMR (400 MHz, CD$_3$CN): δ 8.87–8.89 (m, 2H), 8.26 (dt, $J = 7.8$ and 1.5 Hz, 2H), 7.98–8.02 (m, 2H), and 7.57–7.60 (m, 2H).

$^{13}$C NMR (100 MHz, CD$_3$CN): δ 152.5, 145.0 (d, $J = 248.8$ Hz), 143.8, 143.6 (d, $J = 264.1$ Hz), 141.8, 132.0, 128.8, 110.6, 97.5, and 88.3.

$^{19}$F NMR (376 MHz, CD$_3$CN): δ 133.6 to 133.4 (m, 2F), 151.0 to 150.8 (m, 2F), 123.91 (sext, $J_{\text{Sb–}19\text{F}} = 1915.3$ Hz, 3F), and 123.93 (oct, $J_{\text{Sb–}19\text{F}} = 1019.7$ Hz, 3F).

IR (ATR): 1724, 1592, 1494, 1470, 1282, 1253, 1164, 1104, 1092, 768, and 650 cm$^{-1}$.

Elemental analysis: Calculated for C$_{20}$H$_8$N$_2$F$_{10}$SbF$_6$: C, 33.60; H, 1.13; N, 3.92. Found: C, 33.51; H, 1.23; N, 3.86.

1,2-Bis[(6-methyl-2-pyridyl)ethynyl]benzene iodine(I) complex (1h)

$^1$H NMR (400 MHz, CD$_3$CN): δ 7.92 (t, $J = 7.8$ Hz, 2H), 7.67–7.64 (m, 4H), 7.55–7.50 (m, 2H), 7.41 (d, $J = 7.6$ Hz, 2H), and 2.72 (s, 6H).

$^{13}$C NMR (100 MHz, CD$_3$CN): δ 160.9, 143.2, 142.8, 134.6, 131.9, 129.2, 127.1, 125.2, 98.1, 92.8, and 29.3.

$^{19}$F NMR (376 MHz, CD$_3$CN): δ −124.37 (sext, $J_{\text{Sb–}19\text{F}} = 1926.6$ Hz, 6F), −124.44 (oct, $J_{\text{Sb–}19\text{F}} = 1054.3$ Hz, 6F).

IR (ATR): 1594, 1569, 1488, 1456, 1246, 1184, 1102, 1020, 911, 794, 763, 735, and 651 cm$^{-1}$.

Elemental analysis: Calculated for C$_{22}$H$_{16}$N$_2$F$_{10}$Sb: C, 33.60; H, 1.13; N, 3.92. Found: C, 33.51; H, 1.23; N, 3.86.
IR (ATR): 1465, 1380, 1269, 1166, 1020, 984, 821, 796, 668, and 644 cm\(^{-1}\).

Elemental analysis: Calculated for C\(_{14}\)H\(_{18}\)N\(_2\)F\(_6\)I: C, 29.14; H, 3.14; N, 4.86. Found: C, 28.97; H, 3.19; N, 4.73.

\([2\text{Me-L1]}\cdot 2\text{OTf}\)

\(^{1}\text{H} \text{NMR (400 MHz, CD}_{3}\text{CN):}\ δ 8.87 (d, J = 6.2 Hz, 2H), 8.49 (t, J = 8.0 Hz, 2H), 8.19 (d, J = 8.0 Hz, 2H), 8.01–7.93 (m, 4H), 7.78–7.73 (m, 2H), and 4.39 (s, 6H).

\(^{13}\text{C} \text{NMR (100 MHz, CD}_{3}\text{CN):}\ δ 148.2, 146.3, 138.3, 134.9, 133.1, 132.9, 128.3, 123.3, 122.1 (q, J = 318.4 Hz), 103.7, 84.4, and 48.6.

\(^{19}\text{F} \text{NMR (376 MHz, CD}_{3}\text{CN):}\ δ −79.9 (s, 3F).

IR (ATR): 1734, 1653, 1617, 1576, 1512, 1457, 1254, 1223, 1151, 1028, 776, and 668 cm\(^{-1}\).

Elemental analysis: Calculated for C\(_{24}\)H\(_{18}\)F\(_6\)N\(_2\)O\(_6\)S\(_2\): C, 47.37; H, 2.98; N, 4.60. Found: C, 47.08; H, 3.04; N, 4.64.

\(\text{[Cl–I–NN–I–Cl]}\)

\(^{1}\text{H} \text{NMR (400 MHz, DMSO-d}_{6}\):}\ δ 8.73 (d, J = 4.8 Hz, 2H), 8.01–7.97 (m, 4H), and 7.50–7.44 (m, 2H).

\(^{13}\text{C} \text{NMR (100 MHz, DMSO-d}_{6}\):}\ δ 149.2, 140.6, 138.7, 132.4, 130.1, 128.3, 124.5, 124.0, 91.9, and 88.5.

IR (ATR): 1588, 1558, 1469, 1244, 1158, 1095, 1010, 829, 767, 757, and 732 cm\(^{-1}\).

Elemental analysis: Calculated for C\(_{20}\)H\(_{8}\)N\(_2\)Cl\(_2\)I\(_2\): C, 39.70; H, 2.00; N, 4.63. Found: C, 39.53; H, 2.14; N, 4.52.

\(\text{[Cl–I–NN–I–Cl]} + \text{[Cl–I–F}_{4}\text{NN–I–Cl]}\)

\(^{1}\text{H} \text{NMR (400 MHz, THF-d}_{8}\):}\ δ 3.50 (s, 3H), 1.57 (s, 3H), 1.52 (s, 3H), 0.21 (s, 9H) (Gatzenmeier et al., 2018).

\(^{19}\text{F} \text{NMR (376 MHz, THF-d}_{8}\):}\ δ −13.4 (d, J = 17.3 Hz, 2F) and −153.7 (d, J = 14.4 Hz, 2F).

IR (ATR): 1583, 1492, 1410, 1250, 1153, 1132, 1097, 1012, 962, 772, 642, and 578 cm\(^{-1}\).

Elemental analysis: Calculated for C\(_{20}\)H\(_{8}\)N\(_2\)F\(_4\)Cl\(_2\)I\(_2\): C, 35.48; H, 1.19; N, 4.14. Found: C, 35.31; H, 1.34; N, 4.14.

\(\text{Methyl trimethylsilyl dimethylketene acetal (4a)}\)

\(^{1}\text{H} \text{NMR (400 MHz, CDCl}_{3}\):}\ δ 3.50 (s, 3H), 1.57 (s, 3H), 1.52 (s, 3H), 0.21 (s, 9H) (Gatzenmeier et al., 2018).
1-Methoxy-1-trimethylsilyloxymethylenecyclohexane (4b)

1H NMR (400 MHz, CDCl3): δ 3.50 (s, 3H), 2.08–2.12 (m, 2H), 2.00–2.03 (m, 2H), 1.47 (brs, 6H), and 0.20 (s, 9H) (Berkessel et al., 2014).

α-Methyl-γ-butyrolactone trimethylsilyl ketene acetal (4c)

1H NMR (400 MHz, CDCl3): δ 4.18 (t, J = 8.8 Hz, 2H), 2.53 (t, J = 9.2 Hz, 2H), 1.58 (s, 3H), and 0.22 (s, 9H) (Katayev et al., 2015).

((1-Methoxyvinyl)oxy)trimethylsilane (4d)

1H NMR (400 MHz, CDCl3): δ 3.54 (s, 3H), 3.22 (d, J = 2.8 Hz, 1H), 3.11 (d, J = 2.8 Hz, 1H), and 0.23 (s, 9H) (Lee et al., 2018).

Trimethyl[(1-methylethenyl)oxy]silane (4f)

1H NMR (400 MHz, CDCl3): δ 4.05 (d, J = 4.0 Hz, 2H), 1.78 (s, 3H), and 0.21 (s, 9H) (Zhang and Lupton, 2017).

5a

The general procedure (Scheme S18) was followed. Slight yellow oil (99.3 mg; 0.330 mmol; 82%)

1H NMR (400 MHz, CDCl3): δ 7.36–7.45 (m, 2H), 7.21–7.27 (m, 1H), 7.14–7.16 (m, 2H), 7.01 (dd, J = 21.3 and 8.5 Hz, 2H), 4.80–4.97 (m, 2H), 3.71 (s, 3H), 3.41–3.43 (m, 1H), and 1.19 (s, 6H).

13C NMR (100 MHz, CDCl3): δ 177.4, 150.6, 149.9, 129.5, 126.0, 124.7, 124.4, 121.5, 107.4, 106.9, 52.0, 47.2, 40.5, 21.7, and 21.5.

IR (ATR): 1712, 1391, 1362, 1335, 1306, 1255, 1219, 1119, 953, 813, 735, and 698 cm⁻¹.

Anal. HRMS (FAB): Exact Mass Calculated for C17H18NO4 ([M+H]⁺): 300.1236. Found: 300.1237.

5b

The general procedure (Scheme S18) was followed. White solid (111 mg; 0.325 mmol; 81%)

1H NMR (400 MHz, CDCl3): δ 7.37–7.41 (m, 2H), 7.23–7.26 (m, 1H), 7.13–7.15 (m, 2H), 6.93–7.04 (m, 2H), 4.85–4.96 (m, 2H), 3.72 (s, 3H), 3.19 (t, J = 3.9 Hz, 1H), 2.07–2.09 (m, 2H), 1.63–1.73 (m, 3H), and 1.08–1.34 (m, 5H).

13C NMR (100 MHz, CDCl3): δ 175.7, 150.7, 149.9, 129.5, 126.1, 124.5, 124.3, 121.6, 107.2, 106.7, 53.1, 51.7, 41.6, 30.6, 30.4, 25.9, 23.6, and 23.6.

IR (ATR): 1722, 1640, 1583, 1494, 1329, 1262, 1195, 1134, 978, 913, 734, 689, 616, 590, 576, and 561 cm⁻¹.

Anal. HRMS (FAB): Exact Mass Calculated for C20H23NO4 ([M+H]⁺): 341.1627. Found: 341.1633.

5c

The general procedure (Scheme S18) was followed. White solid (115 mg; 0.383 mmol; 96%)

1H NMR (400 MHz, CDCl3): δ 7.37–7.43 (m, 2H), 7.23–7.28 (m, 1H), 7.03–7.20 (m, 4H), 5.10–5.17 (m, 1H), 4.84–4.93 (m, 2H), 3.93 (t, J = 3.8 Hz, 1H), 2.46–2.60 (m, 1H), 1.86–2.05 (m, 1H), and 1.32 (s, 3H).

13C NMR (100 MHz, CDCl3): δ 180.7, 150.6, 149.8, 129.6, 126.2, 125.8, 125.5, 124.9, 121.5, 106.7, 106.3, 105.9, 105.5, 65.5, 48.0, 47.8, 39.0, 31.5, 31.3, and 20.5.

IR (ATR): 1730, 1597, 1433, 1304, 1259, 1202, 1167, 1120, 1048, 976, 869, 750, 693, 658, 617, 587, 569, and 553 cm⁻¹.

Anal. HRMS (FAB): Exact Mass Calculated for C17H17NO4 ([M+H]⁺): 299.1158. Found: 299.1149.
5d
The general procedure (Scheme S18) was followed. The γ (major) and α (minor) adducts were obtained as a 60:40 mixture. Slight yellow oil (73.3 mg; 0.268 mmol; 67%)

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.36–7.42 (m, γ-2H + α-2H), 7.21–7.28 (m, γ-1H + α-1H), 7.12–7.19 (m, γ-2H + α-2H), 6.81–7.00 (m, γ-2H + α-1H), 6.01–6.07 (m, α-1H), 5.72–5.77 (m, α-2H), 5.27–5.50 (m, α-2H), 4.96–5.06 (m, γ-2H), 3.72 (s, γ-3H), 3.65–3.66 (m, α-3H), 3.45–3.53 (m, γ-1H), 2.57–2.73 (m, α-2H), and 2.47 (d, $J = 7.1$ Hz, γ-2H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 171.9, 170.7, 150.7, 149.9, 129.6, 129.5, 126.1, 125.9, 124.5, 123.4, 123.2, 122.8, 122.3, 121.8, 121.6, 110.0, 109.3, 106.7, 51.8, 49.5, 42.8, 37.8, and 29.6.

IR (ATR): 1721, 1640, 1582, 1368, 1316, 1254, 1190, 1134, 979, 885, 741, 692, 649, 623, 609, 590, and 563 cm$^{-1}$.

Anal. HRMS (FAB): Exact Mass Calculated for C$_{15}$H$_{15}$NO$_4$ ([M]+): 273.1001. Found: 273.0991.

5f
The general procedure (Scheme S18) was followed. White solid (117 mg; 0.328 mmol; 82%) (Hirata and Maeda, 2018)

$^1$H NMR (400 MHz, CDCl$_3$): δ 6.93 (d, $J = 8.4$ Hz, 2H), 4.91–4.96 (m, 1H), 4.81–4.90 (m, 2H), 4.75–4.81 (m, 1H), 3.70 (s, 3H), 3.36–3.39 (m, 1H), and 1.16 (s, 6H).

5g
The general procedure (Scheme S18) was followed. White solid (109 mg; 0.283 mmol; 71%)

$^1$H NMR (400 MHz, CDCl$_3$): δ 6.88 (t, $J = 9.7$ Hz, 2H), 4.73–4.88 (m, 2H), 3.69 (s, 3H), 3.36–3.38 (m, 1H), 1.96 (d, $J = 4.1$ Hz, 6H), and 1.15 (s, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 177.5, 148.7, 124.6, 124.3, 107.0, 106.5, 106.0, 90.0, 52.0, 47.2, 40.5, 21.7, and 21.6.

IR (ATR): 1735, 1351, 1245, 1196, 1153, 1109, 1045, 998, 875, 852, 805, 740, 687, and 605 cm$^{-1}$.

Anal. HRMS (FAB): Exact Mass Calculated for C$_{15}$H$_{19}$Cl$_2$Cl$_2$NO$_4$ ([M–H]+): 384.0350. Found: 384.0345.

5h
The general procedure (Scheme S18) was followed. White solid (110 mg; 0.273 mmol; 68%)

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.78 (d, $J = 7.6$ Hz, 2H), 7.55–7.57 (m, 2H), 7.42 (t, $J = 7.3$ Hz, 2H), 7.33 (dt, $J = 7.5, 1.1$ Hz, 2H), 6.78–6.97 (m, 2H), 4.79–4.86 (m, 2H), 4.49–4.52 (m, 2H), 4.29 (t, $J = 7.1$ Hz, 1H), 3.70 (s, 3H), 3.38 (tt, $J = 4.0, 1.2$ Hz, 1H), and 1.16 (s, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 177.4, 151.3, 143.6, 141.5, 141.0, 128.0, 127.3, 125.1, 124.9, 120.3, 106.6, 68.5, 52.1, 47.4, 47.1, 40.6, 21.7, and 21.5.

IR (ATR): 1709, 1479, 1392, 1187, 1120, 1071, 1003, 821, 751, 616, and 590 cm$^{-1}$.

Anal. HRMS (FAB): Exact Mass Calculated for C$_{25}$H$_{25}$NO$_4$ ([M]+): 403.1784. Found: 403.1783.

5i
The general procedure (Scheme S18) was followed. Colorless oil (105 mg; 0.355 mmol; 84%)
1H NMR (400 MHz, CDCl3): δ 7.36–7.44 (m, 2H), 7.22–7.30 (m, 1H), 7.11–7.14 (m, 3H), 4.97–5.01 (m, 1H), 4.78–4.81 (m, 1H), 3.71 (s, 3H), 3.28 (t, J = 4.6 Hz, 1H), 2.26 (s, 3H), and 1.16 (d, J = 2.7 Hz, 6H).

13C NMR (100 MHz, CDCl3): δ 177.5, 150.6, 150.5, 135.4, 129.5, 127.6, 125.9, 121.7, 109.8, 108.6, 51.9, 47.3, 41.5, 22.2, 21.5, and 21.3.

IR(ATR): 1730, 1593, 1490, 1313, 1193, 1147, 996, 926, 834, 747, 690, and 607 cm⁻¹.

Anal. HRMS (FAB): Exact Mass Calculated for C18H22NO4 ([M + H]+): 316.1549. Found: 316.1534.

5j
The general procedure (Scheme S18) was followed. White solid (97.9 mg; 0.250 mmol; 63%)

1H NMR (400 MHz, CDCl3): δ 7.27–7.44 (m, 4H), 7.18–7.23 (m, 4H), 7.05 (d, J = 8.0 Hz, 1H), 6.85–6.87 (m, 2H), 5.03–5.07 (m, 1H), 5.00 (d, J = 4.6 Hz, 1H), 4.20 (d, J = 15.8 Hz, 1H), 3.88 (d, J = 16.0 Hz, 1H), 3.70 (s, 3H), 3.35 (t, J = 4.9 Hz, 1H), and 1.20 (s, 6H).

13C NMR (100 MHz, CDCl3): δ 177.5, 150.5, 150.2, 138.6, 138.2, 129.7, 129.4, 128.7, 128.4, 126.4, 125.9, 121.6, 121.0, 113.1, 109.2, 52.0, 47.3, 41.8, 40.4, 21.6, and 21.4.

IR(ATR): 1730, 1593, 1473, 1389, 1198, 1148, 1070, 1024, 838, 751, 691, 582, and 569 cm⁻¹.

Anal. HRMS (FAB): Exact Mass Calculated for C24H24NO4 ([M+H]+): 390.1705. Found: 390.1703.

5k
The general procedure (Scheme S18) was followed. g (major) and a (minor) adducts were obtained as an 87:13 mixture.

Colorless oil (111 mg; 0.354 mmol; 88%; a and g mixture)

1H NMR (400 MHz, CDCl3): δ 7.34–7.42 (m, g-2H + a-2H), 7.20–7.29 (m, g-1H + a-1H), 7.12–7.18 (m, g-2H + a-2H), 7.07 (d, d = 17.9 and 8.2 Hz, g-1H), 6.86 (d, d = 22.0 Hz, g-1H), 6.59–6.70 (m, a-1H), 6.00–6.06 (m, a-1H), 5.58–5.68 (m, a-1H), 5.14–5.28 (m, a-1H + g-1H), 5.37–3.64 (m, a-3H), 3.43 (d, J = 4.8 Hz, g-1H), 1.74–1.77 (m, a-3H), 1.63 (d, d = 0.9 Hz, g-3H), and 1.10–1.25 (m, g-6H + a-6H).

13C NMR (100 MHz, CDCl3): δ 178.5, 150.7, 129.5, 126.0, 124.8, 124.4, 121.6, 121.0, 113.1, 109.2, 52.0, 47.3, 41.8, 40.4, 21.6, and 21.4.

IR(ATR): 1724, 1494, 1402, 1323, 1245, 1197, 1126, 1092, 1026, 963, 887, 856, 738, and 688 cm⁻¹.

Anal. HRMS (FAB): Exact Mass Calculated for C18H22NO4 ([M + H]+): 316.1549. Found: 316.1538.

5l
The general procedure (Scheme S18) was followed. γ (major) and α (minor) adducts were obtained as a 60:40 mixture.

Colorless oil (143 mg; 0.388 mmol; 98%; a and g mixture)

1H NMR (400 MHz, CDCl3): δ 7.70 (s, a-1H), 7.54 (s, γ-1H), 7.36–7.43 (m, a-5H), 7.23–7.29 (m, a-1H + γ-1H), 7.05–7.18 (m, γ-2H), 6.26 (d, d = 10.1 Hz, γ-1H), 5.73 (d, d = 10.0, 6.1 Hz, γ-1H), 5.37–5.14 (m, a-1H + γ-1H), 3.84 (d, d = 5.7 Hz, a-1H), 3.69 (s, a-3H), 3.62 (s, γ-3H), 1.42–1.08 (m, a-6H + γ-6H).

13C NMR (100 MHz, CDCl3): δ 176.7, 175.4, 152.5, 150.6, 150.2, 129.6, 129.5, 128.5, 126.5, 126.2, 124.3, 123.9 (q, J = 268.9 Hz), 123.6 (q, J = 267.9 Hz), 121.4, 121.3, 120.1, 119.6, 108.3, 108.0, 57.9, 52.4, 51.9, 49.3, 47.9, 38.4, 22.7, 20.4, and 19.8.
19F NMR (376 MHz, CDCl₃): δ –63.9 (s, α-3F) and –66.7 (s, γ-3F).

IR(ATR): 1735, 1666, 1494, 1351, 1292, 805, 774, 687, and 605 cm⁻¹.

Anal. HRMS (FAB): Exact Mass Calculated for C₁₈H₁₇F₃NO₄ ([M–H]⁺): 368.1110. Found: 368.1121.

5n
The general procedure (Scheme S18) was followed. White solid (116 mg; 0.324 mmol; 81%)

1H NMR (400 MHz, CDCl₃): δ 8.17 (s, 1H), 7.39–7.45 (m, 2H), 7.31–7.26 (m, 1H), 7.18 (d, J = 7.8 Hz, 2H), 7.09 (d, J = 7.1 Hz, 1H), 5.20 (s, 1H), 3.87 (d, J = 5.5 Hz, 1H), 3.76 (s, 3H), 3.68 (s, 3H), 1.16 (s, 3H), and 1.10 (s, 3H).

13C NMR (100 MHz, CDCl₃): δ 176.9, 167.7, 150.3, 149.8, 133.9, 129.7, 126.5, 124.2, 121.3, 110.3, 109.1, 52.0, 51.8, 48.2, 39.6, 21.4, and 20.8.

IR(ATR): 1708, 1381, 1332, 1291, 1239, 1171, 1133, 1109, 1025, 977, 851, 807, 759, 734, 690, 613, 571, and 553 cm⁻¹.

Anal. HRMS (FAB): Exact Mass Calculated for C₁₉H₂₀NO₆ ([M + H]⁺): 358.1291. Found: 358.1288.

5o
The general procedure (Scheme S18) was followed. Colorless oil (134 mg; 0.364 mmol; 91%)

1H NMR (400 MHz, CDCl₃): δ 7.40 (t, J = 7.9 Hz, 2H), 7.24–7.30 (m, 1H), 7.17 (m, 3H), 6.08 (d, J = 5.3 Hz, 1H), 5.50–5.59 (m, 2H), 3.65 (s, 3H), and 1.32–1.24 (m, 6H). Some of the additional signals were observed as rotamers.

13C NMR (100 MHz, CDCl₃): δ 175.4, 152.7, 150.8, 129.6, 129.2, 126.1, 122.5 (q, J = 270.8 Hz), 121.5, 119.7, 102.4, 57.2, 52.6, 49.6, 21.0, and 20.1.

19F NMR (376 MHz, CDCl₃): δ –69.2 (s, 3F).

IR(ATR): 1730, 1597, 1433, 1304, 1259, 1202, 1167, 1120, 1048, 976, 869, 750, 617, 600, and 569 cm⁻¹.

Anal. HRMS (FAB): Exact Mass Calculated for C₁₈H₁₇F₃NO₄ ([M–H]⁺): 368.1110. Found: 368.1109.

5p
The general procedure (Scheme S18) was followed. γ (minor) and α (major) adducts were obtained as a 16:84 mixture.

Colorless oil (116.7 mg; 0.358 mmol; 89%; α and γ mixture)

1H NMR (400 MHz, CDCl₃): δ 7.44–7.35 (m, α-2H + γ-2H), 7.30–7.23 (m, α-1H + γ-3H), 7.17–7.12 (m, α-3H + γ-2H), 6.33 (d, J = 6.4 Hz, α-1H), 5.50–5.40 (m, α-2H), 5.11 (dd, J = 23.7 and 9.0 Hz, γ-2H), 3.77 (s, γ-3H), 3.67 (s, α-3H), 1.36 (s, γ-6H), and 1.32–1.25 (m, α-6H).

13C NMR (100 MHz, CDCl₃): δ 175.0, 174.2, 152.6, 150.7, 131.8, 130.4, 129.7, 129.6, 129.5, 126.5, 126.3, 121.4, 119.6, 116.8, 111.5, 105.5, 104.7, 102.7, 57.7, 52.7, 52.5, 50.5, 49.9, 42.1, 22.1, 21.3, 21.0, and 20.1.

IR(ATR): 1721, 1640, 1582, 1487, 1420, 1367, 1335, 1316, 1254, 1190, 1158, 1135, 1096, 1073, 1029, 979, 921, 884, 775, 741, and 692 cm⁻¹.

Anal. HRMS (FAB): Exact Mass Calculated for C₁₈H₁₉N₂O₄ ([M + H]⁺): 327.1345. Found: 327.1345.
The general procedure (Scheme S18) was followed. Colorless oil (70.9 mg; 0.187 mmol; 47%)

\[ \text{1H NMR (400 MHz, CDCl}_3\text{): } \delta 7.43–7.31 (m, 7H), 7.25–7.21 (m, 1H), 7.18–7.16 (m, 2H), 7.12–7.07 (m, 1H), 5.84–5.75 (m, 2H), 5.47–5.36 (m, 1H), 3.69–3.61 (m, 3H), and 1.36–1.28 (m, 6H). \]

\[ \text{13C NMR (100 MHz, CDCl}_3\text{): } \delta 176.1, 153.0, 151.1, 138.7, 135.9, 129.5, 128.7, 128.4, 128.0, 127.5, 125.9, 121.6, 114.8, 109.8, 108.9, 58.4, 58.2, 52.5, 52.2, 50.0, 22.0, 21.1, and 20.4. \]

\[ \text{IR( ATR): } 1723, 1649, 1585, 1493, 1365, 1331, 1238, 1197, 1162, 1132, 1071, 973, 862, 736, 688, \text{ and } 608 \text{ cm}^{-1}. \]

\[ \text{Anal. HRMS (FAB): Exact Mass Calculated for C}_{23}\text{H}_{22}\text{NO}_4 ([M–H]^-): 376.1549. Found: 376.1553.} \]

The general procedure (Scheme S18) was followed. Colorless oil (132.1 mg; 0.376 mmol; 94%)

C4 (major) and C2 (minor) adducts were obtained as a 78:22 mixture.

C4 adduct:

\[ \text{1H NMR (400 MHz, CDCl}_3\text{): } \delta 8.00 (d, J = 8.5 Hz, 1H), 7.44–7.39 (m, 2H), 7.30–7.25 (m, 3H), 7.20–7.14 (m, 3H), 7.08 (dd, J = 7.6 and 6.4 Hz, 1H), 5.42 (d, J = 6.4 Hz, 1H), 3.84 (d, J = 6.4 Hz, 1H), 3.71 (s, 3H), 1.16 (s, 3H), and 1.14 (s, 3H). \]

\[ \text{13C NMR (100 MHz, CDCl}_3\text{): } \delta 177.3, 150.9, 150.7, 137.4, 129.6, 129.5, 128.4, 128.1, 127.0, 125.9, 125.0, 122.1, 121.6, 111.8, 51.9, 48.9, 45.6, 21.9, \text{ and } 20.7. \]

\[ \text{IR( ATR): } 1720, 1594, 1488, 1331, 1233, 1197, 1161, 1116, 985, 883, 736, \text{ and } 688 \text{ cm}^{-1}. \]

\[ \text{Anal. HRMS (FAB): Exact Mass Calculated for C}_{21}\text{H}_{22}\text{NO}_4 ([M + H]^-): 352.1549. Found: 352.1555.} \]

C2 adduct:

\[ \text{1H NMR (400 MHz, CDCl}_3\text{): } \delta 7.63 (m, 1H), 7.41–7.36 (m, 2H), 7.30–7.20 (m, 2H), 7.16 (d, J = 8.0 Hz, 2H), 7.10–7.07 (m, 2H), 6.67 (d, J = 9.6 Hz, 1H), 6.03 (dd, J = 9.7 and 5.8 Hz, 1H), 5.45 (d, J = 5.7 Hz, 1H), 3.50 \text{ (s, 3H), 1.21 (s, 3H), and 1.08 (s, 3H). Some of the additional signals observed were attributable to the C4 adduct.} \]

\[ \text{13C NMR (100 MHz, CDCl}_3\text{): } \delta 175.7, 153.7, 151.1, 135.7, 129.4, 127.8, 127.6, 127.1, 126.1, 125.6, 125.2, 124.9, 121.5, 58.5, 52.0, 48.5, 22.0, \text{ and } 20.4. \]

\[ \text{IR( ATR): } 1717, 1489, 1397, 1328, 1256, 1198, 1162, 1136, 1118, 981, 879, 735, \text{ and } 688 \text{ cm}^{-1}. \]

\[ \text{Anal. HRMS (FAB): Exact Mass Calculated for C}_{21}\text{H}_{22}\text{NO}_4 ([M + H]^-): 352.1549. Found: 352.1553.} \]

The general procedure (Scheme S18) was followed. Colorless oil (105.7 mg; 0.301 mmol; 75%) (Wieting et al., 2015)

\[ \text{1H NMR (400 MHz, CDCl}_3\text{): The compound exists as a 2.3:1 mixture of carbamate rotamers. Signals corresponding to the major rotamer: } \delta 7.42–7.36 (m, 2H), 7.30–7.18 (m, 4H), 7.15–7.06 (m, 4H), 5.97 (d, J = 7.8 Hz, 1H), 5.76 (s, 1H), 3.63 \text{ (s, 3H), 1.22 (s, 3H), and 1.17 (s, 3H). Signals corresponding to the minor rotamer: } \delta 7.42–7.36 (m, 2H), 7.30–7.18 (m, 4H), 7.15–7.06 (m, 4H), 6.04 (d, J = 7.8 Hz, 1H), 5.88 \text{ (s, 1H), 3.61 (s, 3H), 1.33 (s, 3H), and 1.29 (s, 3H).} \]
The general procedure (Scheme S18) was followed. White solid (117 mg; 0.322 mmol; 81%)

$^1$H NMR (400 MHz, CDCl$_3$): The compound exists as a 1.1:1 mixture of carbamate rotamers. Signals corresponding to the major rotamer: $\delta$ 7.39–7.34 (m, 2H), 7.23–7.04 (m, 7H), 5.65 (s, 1H), 4.22–4.16 (m, 1H), 3.62 (s, 3H), 3.60–3.53 (m, 1H), 3.07–2.87 (m, 2H), 1.24 (s, 3H), and 1.23 (s, 3H).

Signals corresponding to the minor rotamer: $\delta$ 7.39–7.34 (m, 2H), 7.23–7.04 (m, 7H), 5.83 (s, 1H), 4.36–4.30 (m, 1H), 3.86–3.79 (m, 1H), 3.66 (s, 3H), 3.07–2.87 (m, 2H), 1.43 (s, 3H), and 1.36 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 177.0, 176.9, 155.0, 154.3, 151.4, 151.3, 134.2, 134.1, 134.0, 133.9, 129.2, 129.1, 128.6, 127.8, 127.3, 127.0, 125.9, 125.3, 125.2, 121.6, 60.4, 59.8, 52.1, 52.0, 49.6, 49.4, 40.6, 39.3, 27.8, 27.3, 24.9, 24.4, 23.3, and 23.2.

IR(ATR): 1710, 1492, 1396, 1368, 1326, 1257, 1207, 1138, 1063, 940, 876, 758, 733, 706, and 687 cm$^{-1}$.

Anal. HRMS (FAB): Exact Mass Calculated for C$_{21}$H$_{24}$NO$_4$ ([M + H]$^+$): 354.1705. Found: 354.1702.