Effects of Linker Structures in Designing Perfluoroiodobenzene-Based Halogen-Bond Donor Catalysts with Two-Point Activation Modes

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ABSTRACT

Linker structures were systematically investigated for use in designing halogen-bond donor catalysts with two-point activation modes based on perfluoroiodobenzenes. Tetrafluorophenylene, phenylene, and acetylene were examined as potential linkers, and perfluoroiodobenzenes containing these linkers were successfully synthesized. Their activities were evaluated in terms of binding constant $K$ (M$^{-1}$) for Cl$^-$ and reaction yield (%) in the Mukaiyama-Mannich-type reaction of isoquinoline, and the catalyst with the acetylene linker exhibited the highest activity. The significance of the two-point mode was postulated based on the X-ray diffraction analysis of the acetylene-linked halogen-bond donor with two halogen-bond donor sites. Computational studies revealed the effect of the linker on Cl$^-$ binding via halogen bonding. Finally, the utility of the acetylene-linked two-point halogen-bond donor catalyst in the Mukaiyama-Mannich-type reaction was established using various substituted isoquinolines, chloroformates, and ketene silyl acetals.
Introduction

Organocatalysis has recently emerged as an effective strategy for facilitating various chemical reactions.\cite{1} Based on the design concepts reported to date, the activation mode is the most critical element in achieving high reaction efficiency.\cite{2} In noncovalent-interaction-based organocatalysis, multi-point interaction is essential,\cite{3} and a catalyst design based on the two-point hydrogen bond (H-bond) has been established to yield a reactive electrophilic species.\cite{4} In 2002, Schreiner et al.\cite{5} demonstrated, for the first time, that thiourea derivatives exhibit performances similar to those of Lewis acid catalysts via two-point H-bonds. The crystal structure revealed that an intramolecular H-bond between the sp$^2$-CH(2) of 3,5-(CF$_3$)$_2$C$_6$H$_3$ and the S of the thiourea group prevents the free rotation of the HN–C–NH bonds, thereby enabling the two-point activation mode. In 2008, Rawal et al.\cite{6} reported squaramide derivatives that act as alternative scaffolds for two-point H-bond donor catalysts, where the distance between the donor H atoms in the cyclobutene ring is critical to modulating the catalytic activity in two-point H-bond-based organocatalysis. They also investigated the capabilities of CF$_3$-substituted diarylacetylenediols to serve as organocatalysts and observed a 21-fold rate enhancement compared to that of the background reaction.\cite{7} Recent significant advancements in thiourea and (thio)squaramide H-bonding functionalities have resulted in remarkable success in weak H-bond-based asymmetric organocatalysis.\cite{8}

The considerable development of two-point H-bond donor catalysts over the last two decades has expanded the scope of reactions that can be accelerated via weak H-bonding. A novel noncovalent interaction (NCI) may further enhance the utility of and open a novel area in organocatalysis. In this context, we were attracted to the halogen bond (X-bond) of the perfluoroiodoarene (PFIAr) framework,\cite{9} whose interactions were originally utilized in crystal engineering and are currently applied in organocatalysis.\cite{10} In 2008, Bolm\cite{11} revealed the
applicability of the X-bond as a driving force in organocatalysis, with haloperfluoroalkanes catalyzing the reduction of 2-phenylquinoline with Hantzsch ester as the reductant. This field of study remained relatively dormant until Huber et al.\cite{12} reported that catalytic amounts of 2,6-diiodo-3,4,5-trifluorobenzene derivatives promote the bond-forming reaction of 1-chloroisochroman with a ketene silyl acetal. They successfully developed effective two-point X-bond donor catalysts using 2,6-diiodo-3,4,5-trifluorobenzene derivatives\cite{12} and diiodobenzimidazolium salts.\cite{13} Further, they suggested that the design concept of two-point H-bond donor catalysis could be applied in X-bond donor catalysis.\cite{14} Huber’s PFIAr-based X-bond donors were particularly designed to enable two-point activation at more than two sites in a single molecule, regardless of the conformation (Figure 1A). Since the pioneering work of Huber et al., the field of X-bond-based organocatalysis has developed drastically, and various other types of X-bond donors, such as iodoimidazol-,\cite{15} iodontriazol-,\cite{16} iodopyridin-,\cite{17} diaryliodon-,\cite{18} and cycliciodoliums,\cite{19} diiodobisimidazolidines,\cite{20} 1,2,3,4,5-pentafluoro-6-iodo(ethylbenzene),\cite{21} and fluorobis(sulfonyl)methyl iodides\cite{22} have been developed as organocatalysts. We recently contributed to this area of research by developing halogen(I) complex catalysts comprising bis-pyridyl ligands and counteranions.\cite{23} In designing a conformationally flexible two-point X-bond donor catalyst, a linker is the key component for realizing high catalytic activity via the two-point activation mode; however, linker structures have not been sufficiently investigated to date.\cite{12,13,24}

Herein, we describe a systematic study regarding linker structures to reveal the crucial factors in the two-point modes of highly active PFIAr-based X-bond donor $1\text{a}$, $1\text{b}$, and $1\text{c}$ for catalysis (Figure 1B, top). Moreover, the resulting structures were compared with those of X-bond donor without linkers: $\text{C}_6\text{F}_5\text{I}$ and $1\text{d}$ (Figure 1B, bottom).
Results and Discussion

Catalyst Design. To identify an effective linker that enables binding via two-point X-bonds, we hypothesized that the electronic and structural properties of the linker affect the interaction mode when I atoms are used as X-bond donor sites. We prepared three types of X-bond donors with linkers, i.e., tetrafluorophenylene-linked $F_{12}$ diodoterphenyl $1a$, phenylene-linked $F_8$ diodoterphenyl $1b$, and acetylene-linked $F_8$ diodophenylethyne $1c$, to verify this hypothesis. Further, we fabricated two types of X-bond donors without linkers, i.e., $F_5$ iodo benzene $C_6F_5I$ and $F_8$ diodobiphenyl $1d$. The two-point X-bond donors $1a$ and $1b$ were expected to display different electronic properties compared to those of $C_6F_5I$ and $1d$, owing to the presence of the linkers. Conversely, $1c$ would be structurally less sterically hindered than $1a$ and $1b$ in the two-point mode.
Syntheses of the PFIAr Catalysts. In the initial study, catalysts with and without linkers were synthesized based on a previously reported procedure\textsuperscript{[12,25]} which was modified accordingly. Three types of coupling reactions that enable the syntheses of X-bond donor compounds were used in this study. The F\textsubscript{4} phenylene-linked 1a was prepared according to the modified procedure for the syntheses of F\textsubscript{10} tetraiodoterphenyls reported by Huber et al.\textsuperscript{[12]} Suzuki-Miyaura coupling of 2 with (2,3,4,5-tetrafluorophenyl)boronic acid produced 3 (46% yield). The lithiation of 3 with \textit{n}-butyllithium (\textit{n}-BuLi), followed by treatment with I\textsubscript{2}, generated 1a (93% yield, Scheme 1A). Similarly, Suzuki-Miyaura coupling of 4 with (2,3,4,5-tetrafluorophenyl)boronic acid afforded 5 (60% yield). The lithiation of 5, followed by iodination, furnished 1b (90% yield, Scheme 1B). The acetylene-linked F\textsubscript{8} diiodophenylethyne 1c was synthesized via the method reported by Taylor.\textsuperscript{[25]} The Sonogashira coupling of 1,2,3,4-tetrafluoro-5,6-diiodobenzene with 1,2-bis(trimethylsilyl)ethyne (6) produced the desired product 1c and a side product, buta-1,3-diyne 7 (Scheme 1C). We successfully isolated pure 1c using gel permeation chromatography (1c: 3% yield). Finally, the Cu-mediated homocoupling reaction of 8 generated 9 (44% yield).\textsuperscript{[26]} The subsequent magnesiation of 9 with Mg(2,2,6,6-tetramethylpiperidine (TMP))\textsubscript{2}LiBr, followed by iodination,\textsuperscript{[27]} afforded 1d (18% yield, Scheme 1D).
Scheme 1. Syntheses of perfluoroiodoarene-based halogen bond donors 1a, 1b, 1c, and 1d. A) i. (2,3,4,5-tetrafluorophenyl)boronic acid (4.0 equiv.), K$_3$PO$_4$ (6.0 equiv.), Pd(OAc)$_2$ (5 mol%), SPhos (10 mol%), toluene; ii. n-BuLi (2.2 equiv.), I$_2$ (10 equiv.), THF. B) (2,3,4,5-tetrafluorophenyl)boronic acid (3.5 equiv.), K$_3$PO$_4$ (4.0 equiv.), Pd(OAc)$_2$ (3 mol%), SPhos (6 mol%), toluene; ii) n-BuLi (2.2 equiv.), I$_2$ (10 equiv.), THF. C) i. 1,2,3,4-tetrafluoro-5,6-diiodobenzene (2.5 equiv.), Pd(PPh$_3$)$_2$Cl$_2$ (5 mol%), PPh$_3$ (10 mol%), CuI (50 mol%), DMF. D) i. n-BuLi (1.0 equiv.), THF; ii. CuCl$_2$ (2.1 equiv.), THF; iii. Mg(TMPS)$_2$·2LiBr (2.4 equiv.); iv. I$_2$ (4.8 equiv.), THF. SPhos = 2-dicyclohexylphosphino-2’,6’-dimethoxybiphenyl, PPh$_3$ = triphenylphosphine, OAc = acetate.

Activity of the Prepared Catalysts. The activities of 1a, 1b, and 1c were investigated and compared to those of the control compounds, C$_6$F$_5$I and 1d, based on the binding constant $K$ (M$^{-1}$) and reaction yield (%). Titration studies were conducted at 20 °C in acetone, using n-
Bu₄NCl as the Cl⁻ source, to calculate $K (M^{-1})$ according to the $^{19}$F NMR chemical shift (Table 1, center column). Moreover, the Mukaiyama-Mannich-type reaction of an isoquinoline was used as the benchmark reaction of X-bond donor catalysis for Cl⁻ binding, because it is a representative reaction of N-heteroaromatics to generate pharmaceutically useful intermediates (Table 1, right-hand column).[8b, 29]

The $K$ values of 1a and 1d were approximately one-third of that of C₆F₅I, whereas 1b and 1c displayed $K$ values approximately 5-fold higher than that of C₆F₅I. Although two X-bond donor sites were introduced into 1a, 1b, 1c, and 1d, the $K$ values, that is, the binding of 1b and 1c for Cl⁻ were significantly higher than those of 1a and 1d. These results suggest that structural and electronic factors may be required to realize high activity.

Based on the $K$ values for $n$-Bu₄NCl, the catalytic capabilities of the X-bond donors were evaluated in the Mukaiyama-Mannich-type reaction of isoquinoline 10a with ketene silyl acetal 11a, where 2,2,2-trichloroethyl chloroformate (TrocCl) was used as an activator of 10a. When the reaction was conducted at −80 °C for 3 h without a catalyst, the yield of 12a was only 18%. Thus, reaction was conducted under this condition at catalyst loadings of 10, 5, 2.5, and 1.0 mol%, and C₆F₅I was used as a reference. The reactions with C₆F₅I as an X-bond donor were accelerated to afford moderate yields of 12a at catalyst loadings of 10 and 5 mol% (entries 1 and 2). However, the product yields were as high as 28% at catalyst loadings of 2.5 and 1 mol% (entries 3 and 4). Therefore, the contribution of C₆F₅I to the reaction yield is <10% at catalyst loadings of 2.5 and 1 mol%. Despite the incorporation of two X-bond donor sites into 1a, the trend of the reaction yield was similar to that of C₆F₅I (entries 5–8). Compared to that obtained using 1a, the use of 1b (10 mol%) provided a higher yield of 12a (entry 9). The $K$ of 1b was similar to that of 1c, but the yield decreased significantly to 30–40% as the catalyst loading was reduced from 5 to 1 mol% (entries 10–12). Conversely, 1c promoted the Mukaiyama-Mannich-type reaction to afford a high yield at a catalyst loading of 10, 5, or 2.5 mol% (entries
13–15) and a moderate yield at a catalyst loading of 1 mol% (entry 16). These results are expected based on the $K$ of 1c because the less sterically hindered linker enables stronger two-point $\text{I} \cdots \text{Cl} \cdots \text{I}$ interactions. By contrast, although the $K$ of 1d was $< 10\%$ of that of 1b, the reaction yields obtained using 1d were similar to those obtained using 1b (entries 17–20). Overall, two X-bond donor site-bearing 1b, 1c, and 1d were superior to the one X-bond donor site-bearing $\text{C}_6\text{F}_5\text{I}$ in terms of reaction yield, whereas no clear relationship was observed between the $K$ values and reaction yields. Among the four types of synthesized X-bond donors in this study, 1c was optimal, not only in terms of $K$ but also with respect to the catalytic activity.

Table 1. Evaluation of chloride binding ability of 1 by binding constant $K$ and catalytic activity in Mukaiyama Mannich-type reaction[^a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>$K$ [M$^{-1}$][^b]</th>
<th>Catalyst loading [mol%]</th>
<th>Yield [%][^c]</th>
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<td>10</td>
<td>10</td>
<td>61</td>
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<tr>
<td>2</td>
<td>C$_6$F$_5$I</td>
<td>242±16</td>
<td>5</td>
<td>58</td>
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<tr>
<td>3</td>
<td>1a</td>
<td>77.4±5.3</td>
<td>2.5</td>
<td>28</td>
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<td>4</td>
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<td>9</td>
<td>1b</td>
<td>1106±189</td>
<td>10</td>
<td>83</td>
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</table>
[a] The reaction was performed using 10a (0.20 mmol), TrocCl (0.21 mmol), and 11a (0.30 mmol) in the presence of X-bond donor catalyst. [b] Binding constant $K$ with $n$-Bu$_4$NCI at 293 K in acetone determined by curve-fitting of the $^{19}$F NMR titration data to 1:1 binding isotherm. See the supporting information for full details. [c] Isolated yield of 12a.

**Synthesis of Iodophenyl Ethynyl Benzenes 1e, 1f and Control Experiments of 1c.** After demonstrating that the acetylene linker was effective in the Mukaiyama-Mannich-type reaction of 10a via the binding of Cl$^-$, we focused on the syntheses of acetylene-linked one-point X-bond donors as controls. The F$_9$ and F$_4$ iodophenyl ethynyl benzenes 1e and 1f were designed to assess the effects of the structural and electronic factors of two-point X-bond donors (Scheme 2). The Sonogashira coupling of 1-bromo-2,3,4,5,6-F$_5$ benzene 13 with ethynyltrimethylsilane quantitatively yielded the coupling partner 14 for use in synthesizing 1e. The further Sonogashira coupling of 1,2,3,4-tetrafluoro-5,6-diiodobenzene with 14 produced 1e (15% yield, Scheme 2A). Similarly, the Sonogashira coupling of 1,2,3,4-
tetrafluoro-5,6-diodobenzene with ethynylbenzene 15 furnished 1f (36% yield, Scheme 2B).

Based on the same protocol as that followed for the $^{19}$F NMR titration studies, the $K$ values of 1e and 1f, which decrease significantly, were two orders of magnitude smaller than that of 1c (Table 2, center column). Although 1e and 1f contain acetylene as linkers, their one-point X-bond donor sites reduced their catalytic activities, thus producing 12a in yields of 29% and 30%, respectively (Table 2, right-hand column). These control studies indicate that the acetylene linker designed to provide two-point X-bonding is more effective in promoting the Mukaiyama-Mannich-type reaction via the binding of Cl– compared to the mono-PFIArs.

Scheme 2. Syntheses of acetylene-linked one-point X-bond donors. A) F₄ iodophenyl ethynyl benzene 1e. i. Ethynyltrimethylsilane (1.1 equiv.), i-Pr₂NH (2.9 equiv.), Pd(PPh₃)₄ (5 mol%), CuI (5 mol.%), toluene; ii. 1,2,3,4-tetrafluoro-5,6-diodobenzene (1.0 equiv.), i-Pr₂NH (1.4 equiv.), CuCl (1.2 equiv.), Pd(PPh₃)₄ (5 mol%), DMF. B) F₄ iodophenyl ethynyl benzene 1f. i. 1,2,3,4-tetrafluoro-5,6-diodobenzene (1.0 equiv.), i-Pr₂NH (7.0 equiv.), Pd(PPh₃)₄ (3 mol%), CuI (10 mol%), toluene. i-Pr₂NH = diisopropylamine.
**Table 2.** Control experiments for chloride binding ability of 1c by binding constant $K$ and catalytic activity in Mukaiyama Mannich-type reaction$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>$K$ [M$^{-1}$]$^b$</th>
<th>Yield [%]$^c$</th>
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<tr>
<td>1</td>
<td>1c</td>
<td>1224±98</td>
<td>79</td>
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<tr>
<td>2</td>
<td>1e</td>
<td>72.8±8.0</td>
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<tr>
<td>3</td>
<td>1f</td>
<td>48.8±2.0</td>
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$[^a]$ The reaction was performed using 10a (0.20 mmol), TrocCl (0.21 mmol), and 11a (0.30 mmol) under 2.5 mol% of catalyst. $[^b]$ Binding constant $K$ with $n$-Bu$_4$NCl at 293 K in acetone determined by curve-fitting of the $^{19}$F NMR titration data to 1:1 binding isotherm. See the supporting information for full details. $[^c]$ Isolated yield of 12a.

**Crystal Structure of 1c and 1c···Cl$^-$.** To gain insight into the conformational structure of 1c, X-ray diffraction was conducted (Figure 2A). Although both perfluoroiodobenzene (C$_6$F$_4$I) units of 1c lie in the same plane, they lie on opposite sides of the alkyne, with their I atoms facing away from the triple bond. The I atoms form I···F bonds with the closest F atoms in other 1c molecules, with I···F distances of 3.27 Å and C–I···F angles of 163.1°. Furthermore, two types of noncovalent networks were observed: i) the F atoms adjacent to the I atoms participate in C–F···F–C short contacts with a F···F distance of 2.90 Å and C–F···F angle of 129.1° (light-green colored dots) and ii) the C and F atoms of the C–F bonds at the para-positions relative to the I atoms form symmetrical intermolecular C–F···C–F short contacts with a F···C distance.
of 3.09 Å and C–F···C angle of 107.7° (light-blue-colored dots). The combination of these three types of interactions induces molecular packing as 3D sheets.

Subsequently, to understand the factors responsible for the high activity of 1c, we attempted to obtain a co-crystal of 1c and Cl⁻ (Figure 2B). The crystal structure of 1c···Cl⁻ reveals not only a 1:1 association between 1c and n-Bu₄NCl but also the presence of X-bonds with I···Cl distances of 3.17 and 3.25 Å and C–I···Cl angles of 168.3° and 167.2° (pink-colored dots). These results strongly suggest the two-point X-bond mode postulated for catalysis by 1c in the Mukaiyama-Mannich-type reaction of 10a. Two weak C–F···H–C short contacts with F···H distances of 2.44 and 2.58 Å (light-blue-colored dots) were also observed, indicating that the ortho-F atoms of the C–I bonds contribute to the dissociation of the F···F interactions in the 3D sheets of 1c.
Figure 2. X-ray diffraction analysis. A) 1c. Top: Top view of one sheet. The stacked sheet structure is omitted for clarity. Bottom: Side view of the molecular packing as 3D sheets. B) Co-crystal of 1c and n-Bu₄NCl. Top: Top view. Bottom: Side view.

Computational Study. We computationally evaluated the effects of the linker structure on the conformations and X-bond donor abilities of C₆F₄I motifs. The electronic effect of the F₄ phenylene linker of 1a was expected to be the highest among the three types of linkers in 1a, 1b, and 1c. However, 1a exhibited the lowest activity in terms of not only K but also catalytic performance in the Mukaiyama-Mannich reaction. The steric hindrance of the linker decreases in the order of 1a > 1b > 1c, in which least steric linker structure of 1c is consistence with the observation that 1c is preeminent in terms of K (M⁻¹) and product yield (%). To determine which factor significantly affects the X-bonding abilities of C₆F₄I-based X-bond donors in the two-point mode, we employed 1a, 1b, and 1c in calculations using Gaussian 16 (Gaussian, Wallingford, CT, USA). Density functional theory (DFT) calculations were performed at the SMD18(THF)/M06-2X-D3/6-311+G(d,p)-SDD level at 193 K (Table 3 and Supporting Information). The difference in the Gibbs free energies of the cis and trans conformers is <0.2 kcal/mol in all three cases, regardless of the linker structure (Table 3A, left column), suggesting
that the two X-bond donor sites are easily rotated to form the two-point mode. By contrast, once 1a, 1b, and 1c interact with Cl−, the cis conformation is energetically more favorable than the trans conformation. The ΔG values of 1···Cl− support the two-point mode of the X-bond donor catalysts 1a, 1b, and 1c (Table 3B, left-hand column). Unfortunately, the ΔG values do not explain the activities of 1a, 1b, and 1c; the ΔG of 1c-cis···Cl− is smaller than that of 1a-cis···Cl−, and the energetic difference is only 1.1 kcal/mol. Furthermore, while the linker structure affects the maximum positive electrostatic potentials (Vs,max) of the I and C6F4 groups (Table 3A, 2nd column from the left and center column), no correlation between Vs,max and activity is observed. Upon quantifying various structural (Tables 3A and 3B, right-hand columns) and physical properties of the X-bond donors (Supporting Information), we observe that the distortions e of the linkers in 1-cis···Cl− are relevant to the activities of 1 (Table 3B, right column): the order of distortion, i.e., 1c-cis···Cl− < 1b-cis···Cl− < 1a-cis···Cl−, correlates with the order of activity, i.e., 1a < 1b < 1c. The NCI plot of the computationally optimized cis structures indicates that the I···I, C–F···I, and C···I intramolecular interactions in 1a and 1b-cis are drastically altered compared to those in the Cl− complexes. This is due to the attractive X-bonding interaction of I···Cl− (green regions in Figures 3A and 3B). Conversely, no significant differences in the intramolecular interactions of 1c-cis and 1c-cis···Cl− are observed (green regions in Figure 3C). The X-bond donor abilities of 1a and 1b would be lower than those indicated by the electrostatic potentials due to the repulsive forces that distort the linker structures. In contrast, the X-bond donor ability of 1c reflects its electronic property, with no distortion.
Table 3. Computational data of the X-bond donors and their Cl− complexes [a].

A) Molecular properties of 1a, 1b, 1c, and C₆F₅I.

<table>
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<tr>
<th></th>
<th>ΔG [kcal mol⁻¹]</th>
<th>Vₛ,max on I [kJ mol⁻¹][b]</th>
<th>Vₛ,max on C₆F₄ [kJ mol⁻¹][b]</th>
<th>Twisted angle [°][c]</th>
<th>Linker length [Å][d]</th>
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B) Molecular properties of 1a···Cl−, 1b···Cl−, 1c···Cl−, and C₆F₅I···Cl−

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<tr>
<th></th>
<th>ΔG [kcal mol⁻¹]</th>
<th>Twisted angle [°][e]</th>
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a] DFT calculations were performed at the SMD18(THF)/M06-2X-D3/6-311+G(d,p)-SDD level at 193 K. [b] Maximum positive electrostatic potential. [c] Twisted angle between two C₆F₄I rings. [d] Atomic distance between two C atoms at the end of the linker. [e] Twisted angle between two C₆F₄I rings. [f] Atomic distance between two C atoms at the end of the linker. [g] $\epsilon = |\Delta \text{Linker length of } (1\cdots\text{Cl}^-) - 1| / \text{Linker length of } 1$.

[i] Interaction angle of C–I bond to Cl$^-$

**Figure 3.** NCI plot of the computationally optimized cis conformations. A) 1a with and without Cl$^-$. B) 1b with and without Cl$^-$. C) 1c with and without Cl$^-$. The isosurface s-value is 0.4 a.u., and weak attractive interactions are indicated in green.
Scope of the 1c-Promoted Mukaiyama-Mannich-Type Reaction of Isoquinolines\cite{30}

Finally, commercially available isoquinolines, easily accessible silyl enol ethers, and chloroformates were investigated to establish the utility of 1c in the Mukaiyama-Mannich-type reaction (Scheme 3). Catalyst 1c was able to promote the reaction of 10 with an electron-withdrawing group (R': 4-Br, 4-F, 5-Br, 5-NO₂, or 8-Br), regardless of the substitution pattern, to generate the desired products 12b–12f in high yields using 5 mol% of 1c. With methyl substituents, which serve as representative electron-donating groups, 5 or 10 mol% of 1c was sufficient to yield 12g and 12h. Not only 11a but also various substituted ketene silyl acetals were applicable to afford 12i–12k in excellent yields using 5 mol% of 1c. However, in the case of the acetophenone-derived silyl enol ether, 10 mol% of 1c was required to generate a moderate yield of 12l. Moreover, this system with 1c was applicable to other chloroformates, such as methoxy, phenoxy, benzyloxy, and 1,1-dimethyl-2,2,2-trichloroethoxy carbonyl (Tcboc) groups, providing excellent yields of 12m, 12o, and 12p at a catalyst loading of 5 mol% and a moderate yield of 12n at a catalyst loading of 10 mol%.
Scheme 3. Scope of the 1c-promoted Mukaiyama-Mannich-type reaction of isoquinoline 10, silyl enol ether 11, and chloroformate.[a] [b] The reactions were performed using 10 (0.20 mmol), chloroformate (0.21 mmol), and 11 (0.30 mmol) at –80 °C for the indicated reaction time with 5 mol% of 1c. [b] Isolated yields. [c] 10 mol% of 1c was used. [d] A tert-
butyldimethylsilyl group was used instead of a trimethylsilyl group. The reaction was performed at 0 °C.

**Conclusion**

In this study, we elucidated the effect of the linker structure in designing C₆F₄I-based X-bond donor catalysts with two-point activation modes. General, useful synthetic methods were developed for application in preparing C₆F₄I-based X-bond donors with and without linkers. Of the three types of linker structures examined, the acetylene linker was optimal for use in the Mukaiyama-Mannich-type reactions of isoquinolines, resulting in reaction acceleration via the binding of Cl⁻. Control experiments using 1c and one-point catalysts 1e and 1f confirmed the utility of the acetylene linker in realizing high catalytic performance in the two-point activation mode. Moreover, the crystal structure of the Cl⁻ complex of 1c was determined, providing evidence for the presence of the two-point X-bonding interaction between the I of the C₆F₄I unit and Cl⁻. Based on various computationally quantified parameters, the distortion of the linker structure was the dominant factor that affected catalytic activity rather than the electrostatic potential on the I of the X-bond donor. Further investigation of two-point X-bond donor catalysis would open novel avenues in X-bond-mediated asymmetric catalysis, and these efforts are ongoing in our laboratory.

**Experimental Section**

TroCCl (29.0 mL, 0.210 mmol, 1.1 equiv.) was added to a solution of 10a (23.5 mL, 0.200 mmol, 1.0 equiv.) in tetrahydrofuran (THF) (4.0 mL) at –80 °C. After stirring at –80 °C for 30 min, 1c (11.5 mg, 0.020 mmol, 10 mol%) was added to the reaction mixture. After further stirring at –80 °C for 5 min, 1-methoxy-2-methyl-1-(trimethylsilyloxy)-1-propene 11a (61.0 mL, 0.300 mmol, 1.5 equiv.) was added at the same temperature. The mixture was further
stirred at –80 °C for 3 h, and the resultant mixture was quenched with aqueous sat. NaHCO₃ (4 mL) and extracted using diethyl ether (5 mL x 3). The combined organic layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure after filtration. The residual crude product was purified via flash column chromatography on silica gel (hexane/ethyl acetate = 10:1 v/v) to yield the desired product 12a as a colorless oil (70.3 mg, 0.170 mmol, 86% yield) in a 78:22 mixture of rotamers.

R_f = 0.37 (hexane/ethyl acetate = 10:1). ¹H NMR (400 MHz, CDCl₃) δ 7.30–7.18 (m, 2H), 7.12–7.02 (m, 2H), 6.96 (d, J = 7.6 Hz, 1H), 6.05 (d, J = 7.6 Hz, 0.22H), 5.95 (d, J = 7.6 Hz, 0.78H), 5.78 (s, 0.22H), 5.74 (s, 0.78H), 4.97 (d, J = 11.9 Hz, 0.78H), 4.86 (d, J = 2.8 Hz, 0.44H), 4.70 (d, J = 11.9 Hz, 0.78H), 3.64 (s, 2.34H), 3.62 (s, 0.66H), 1.29 (s, 0.66H), 1.20 (s, 2.34H), 1.12 (s, 6H). ¹³C ¹H NMR (101 MHz, CDCl₃) δ 175.7, 152.1, 131.1, 128.2, 127.9, 127.7, 127.0, 126.4, 125.4, 124.8, 124.7, 112.6, 111.7, 95.0, 75.6, 75.4, 61.0, 60.7, 52.0, 51.9, 50.3, 50.1, 23.7, 22.4, 21.3, 20.7. Mass spectrometry (fast atom bombardment) m/z: 408, 406, 304, 130.

The analytical data are consistent with those in the literature.

Supporting Information

The authors have cited additional references within the Supporting Information.[30, 31–45]

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**Keywords:** catalyst design • halogen bond • linker structure • organocatalysis • perfluoroiodobenzenes

**References**


[30] Deposition numbers CCDC-2255029 (for 1c), CCDC-2255030 (for 1c···Cl–), CCDC-2255032 (for 12a), and CCDC-2255030 (for 12c) contain the supplementary crystallographic
data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.


