Communication

Aminocyclopropenium as a New Class of Hydrogen Bonding Catalyst in Friedel–Crafts Alkylation

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Abstract: H-bonding has achieved massive advancements by utilizing an H-bond donor (HBD) to interact with the electron-rich site of the substrate, and an H-bond acceptor (HBA) to coordinate with the electron-deficient site. Rapid transformation is often correlated with the acidity of HBD, namely the degree of charge deficiency of the hydrogen proton. In addition, the positive cations were employed to enhance the HBD; the electron-withdrawing groups were also a dissimilar approach for increasing the capability of the H-bond donor. We first introduced the H-bonding organic ion pair tris(phenylamino)cyclopropenium (TPAC·Cl) into the Friedel–Crafts alkylation of indoles with nitroalkenes, which was implemented via vicinal positive charges on the cyclopropenium core. The counter ion chloride anion became a potential HBA to activate the electron-deficient part of the substrate. X-ray analyses of a single crystal of TPAC·Cl described the 3D architecture and the delocalized cationic charge in the solid state. The aromatic cyclopropenium endowed the N–H moieties with the ability of the H-bond donor to activate the nitroalkene; meanwhile, the chloride anion acted as the H-bond acceptor to activate the indole. The amino-cyclopropenium-offered HBD and HBA displayed cooperative organocatalysis in the Friedel–Crafts alkylation of indole with nitroalkene. A new class of hydrogen bonding catalysis and a working mechanism were proposed.

Keywords: cyclopropenium; Friedel–Crafts alkylation; hydrogen bond; organocatalysis

1. Introduction

The Friedel–Crafts alkylation is one of the important strategies to facilitate the coupling of the C–C bond [1–3]. Indoles were an important intermediate with pharmaceutical activity, and it was interesting to promote the chemical transformation of indole derivatives. In the traditional F–C alkylation of indole, especially with nitroalkene, most of the catalysts utilized were metal catalysts, such as metal–ligand complexes, metal–organic frameworks (MOFs), and metal salts [4–12]. The Friedel–Crafts alkylation of indole and nitroalkene catalyzed via organocatalysts has only a few examples and remained underdeveloped [13–15].

Hydrogen bonding catalysis has become a thriving and vital domain area in the past two decades [16–24] and is an important form of organocatalysis. Its behavioral mode was the coordination of an H-bond donor (HBD) with the electron-rich site of a substrate and/or the coordination of an H-bond acceptor (HBA) with the electron-deficient site. The control and selection of the reaction was realized via HBD and HBA co-catalysis [17,25–27]. The rate of reaction was often related to the acidity HBD; that is, the degree of the charge deficiency of the H-bond donor proton [28–30]. One category of charged-HBD derived from the protonated strong Brønsted base showing a strong H-bond donor capacity due

to π-delocalization of the positive charge is guanidiniums [31–35] (Scheme 1a). Neutral HBD, such as the urea and thiourea, is enhanced via the substitution of the electron-withdrawing group and has been developed as one mature direction [24,25,27,36–38] (Scheme 1b). Another strategy to increase the ability of HB was electron-withdrawing via σ-bond to the vicinal positively charged atom(s), such as quaternary ammonium [39–42] (Scheme 1c).
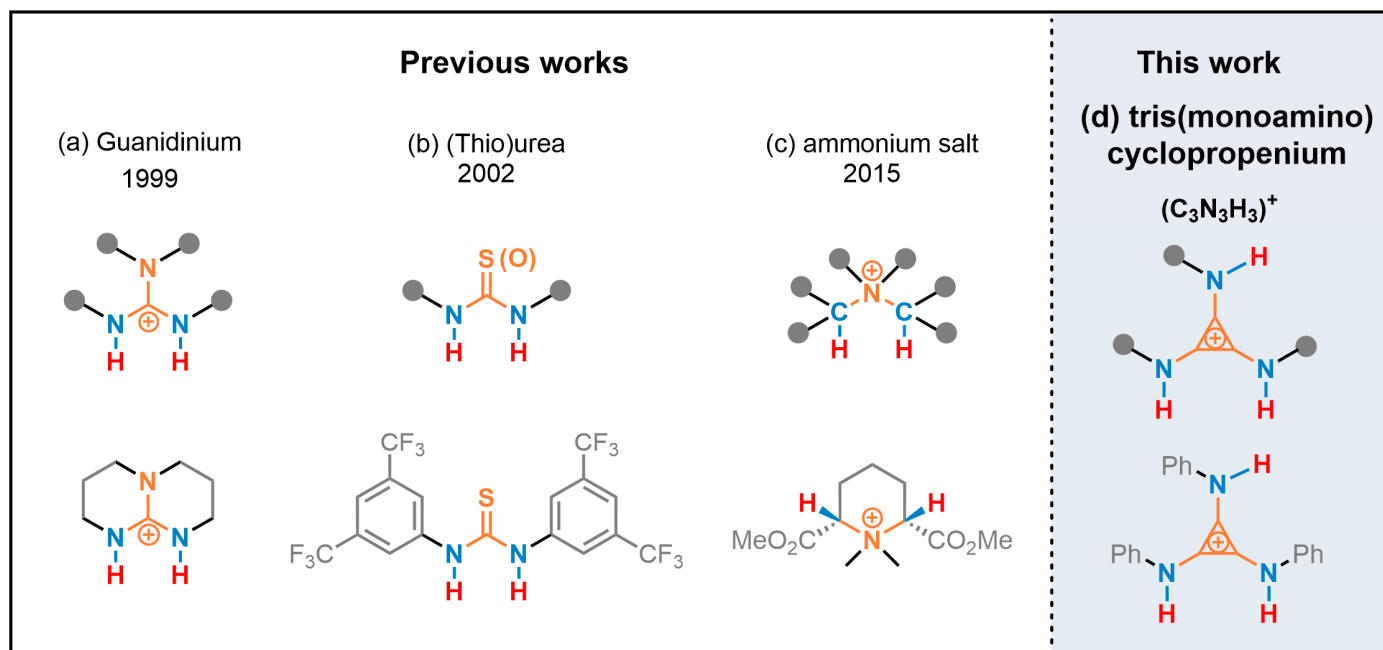
Scheme 1. (**a**) H-bond donor (HBD) was enhanced via π-delocalization of the positive charge; (**b**) HBD was enhanced by electron-withdrawing groups; (**c**) HBD was enhanced by vicinal positively charged atom; and (**d**) HBD was implemented via vicinal positive charges on the cyclopropenium core, such as tris(monoamino)cyclopropenium.
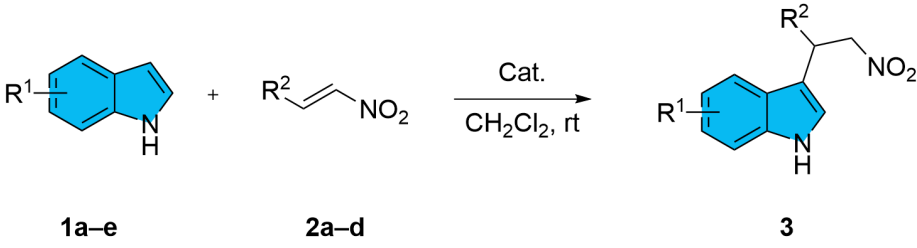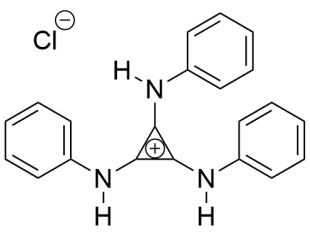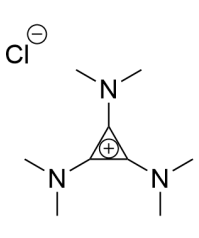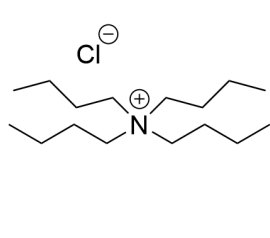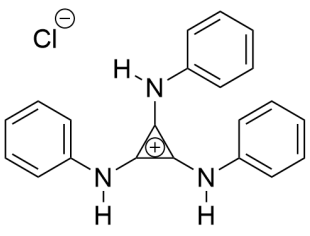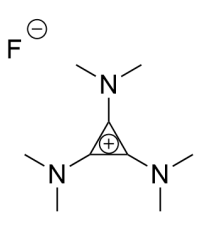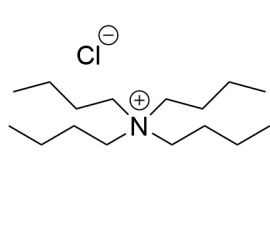
The minimal Hückel aromatic compound cyclopropenium has been utilized as organocatalysts for organic transformation in the past two decades [43–45]. Cyclopropenium ions were mainly used in asymmetric synthesis [46,47], phase transfer catalysis [48,49], and electrophotocatalysis [50], but had not been well studied in hydrogen bonding catalysis. We suggested that the cyclopropenium [51–53] be substituted with amino groups of NHR, and the N–H moieties of tris(monoamino)cyclopropenium would behave as the H-bond donor (Scheme 1d). The capability of the N–H moieties as a new type of H-bond donor was implemented via vicinal positive charges on the cyclopropenium core [54]. The N–H moiety of the unprotected indole was readily activated via hydrogen bonding with the halide anion. Herein, we demonstrated the tris(monoamino)cyclopropenium as a bifunctional H-bonding catalyst to promote the Friedel–Crafts alkylation of indoles with nitroalkenes for the first time.

2. Results and Discussion

In the context of the ordinary H-bond [2,15,55] and the metal-enhanced H-bond catalysis [56], we expanded the exploration of the novel H-bond donor implemented via the π-conjugate system of the cyclopropenium to apply for the F–C alkylation of indole **1** with trans-β-nitroalkene **2**. Tri(phenylamino)cyclopropenium chloride (**TPAC·Cl**) was selected as the typical catalyst (Table 1). The **TPAC·Cl** was able to promote the F–C alkylation of **1a** with **2a** at 25 °C in dichloromethane efficiently (Table 1, entry 2). In contrast, the background reaction without catalysts was negligible (Table 1, entry 1). By switching the chloride to the fluoride anion, The **TPAC·F** performed no activity in the same

reaction (Table 1, entry 3). The poor catalytic performance implied that the chloride anion may be necessary for the F–C alkylation. A possible explanation was that the fluoride anion coordinated with the HBD of the cationic **TPAC** [23,57,58], which indicated that **TPAC·F** formed a tight ion pair [59] and the cationic **TPAC** shown a preference for pairing with the fluoride anion rather than activating the substrate.

Table 1. F–C alkylation of indoles **1a–e** with nitroalkenes **2a–d** [a].

Entry	Catalyst	Indole	R^1	R^2	Nitroalkene	Product	Time/h	Yield [b]/%
1 [c]	-	**1a**	H	Ph	**2a**	**3aa**	24	trace
2	TPAC·Cl	**1a**	H	Ph	**2a**	**3aa**	24	78
3	TPAC·F	**1a**	H	Ph	**2a**	**3aa**	24	trace
4	TDAC·Cl	**1a**	H	Ph	**2a**	**3aa**	24	trace
5	TDAC·F	**1a**	H	Ph	**2a**	**3aa**	24	trace
6	TBA·Cl	**1a**	H	Ph	**2a**	**3aa**	24	trace
7	TBA·F	**1a**	H	Ph	**2a**	**3aa**	24	trace
8	TPAC·Cl	**1b**	2-Me	Ph	**2a**	**3ba**	24	86
9	TPAC·Cl	**1c**	5-OMe	Ph	**2a**	**3ca**	24	88
10	TPAC·Cl	**1d**	5-Cl	Ph	**2a**	**3da**	24 (72) [d]	16 (52)
11	TPAC·Cl	**1e**	7-Me	Ph	**2a**	**3ea**	24	57
12	TPAC·Cl	**1a**	H	4-MeC$_6$H$_4$	**2b**	**3ab**	24	33
13	TPAC·Cl	**1a**	H	4-MeOC$_6$H$_4$	**2c**	**3ac**	24	55
14	TPAC·Cl	**1a**	H	2-thienyl	**2d**	**3ad**	24	71

[a] Indole **1** (1.5 mmol, 1.5 equiv.) along with the nitroalkene **2** (1 mmol, 1 equiv.) catalyzed via 10 mol% of TDAC·Cl in dichloromethane (1 mL) at 25 °C. [b] Yield of isolated product was given. [c] Without catalyst. [d] Reaction time was 72 h.

Tri(alkylamino)cyclopropenium was tested on the F–C alkylation to verify the assumption that the N–H moieties of the TPAC as HBD were essential (Table 1, entries 4 and 5). No products were determined with the tris(dimethylamino)cyclopropenium chloride (TDAC·Cl) as the catalyst (Table 1, entry 4). The lack of the N–H moieties on the cationic core of TDAC may be the possible reason for its diminished capability to function as an H-bond donor. Although fluoride anion was considered an excellent H-bond acceptor and strong nucleophilic, the TDAC·F as the catalyst was not workable on the F–C alkylation (Table 1, entry 5). These experimental results supported the vital role of N–H HBD on **TPAC** in facilitating this transformation.

The tetrabutylammonium chloride (TBA·Cl) along with tetrabutylammonium fluoride (TBA·F), are counterparts to TPAC·Cl and TPAC·F, respectively, and performed inactive in the benchmark F–C alkylations (Table 1, entries 6 and 7). The discrepancy between TPAC·Cl and TBA·Cl suggested the necessity of the structure of cyclopropenium cation. We suggested that the strong N–H H-bond donor enhanced by the vicinal cyclopropenium exhibited a better catalytic performance.

With the optimal catalyst in hand, the substrate scopes of indoles and nitroalkenes in the alkylation reaction were investigated (Table 1, entries 8 to 15). Indoles **1a–e** bearing different substituents on both the benzene ring and the pyrrole ring were conductive in their reactions with nitroalkene **2a**. Whereas the reactions of unsubstituted indole **1a** and the indoles with electron-donating groups (**1b** and **1c**) afforded the corresponding products **3aa**, **3ba**, and **3ca** in good yields (Table 1, entries 8–9), the electron-withdrawing chloride on the 5-position caused **1d** to convert into **3da** in a moderate yield (Table 1, entry 10). Steric hindrance at the 7-position inhibited the reaction (Table 1, entry 11), which could be suffering from the unfavorable interference to the chloride anion. The applicability of the catalyst was further supported by the variation in the nitroalkene. Nitroalkenes with various substitutions on the benzene ring (**2b–d**), both electron-donating and -withdrawing, decreased the yields (Table 1, entries 12–14) as compared with a non-substituted one. Nevertheless, thienyl nitroalkene **2d** reacted stably with indole **1a** to obtain the corresponding products **3ad** in good yield (Table 1, entry 14).

The single crystal of TPAC·Cl was prepared to show the visual view of the construction in the solid, including the interionic distances. A cubic system was confirmed via an X-ray diffraction analysis of the catalyst TPAC·Cl. The chloride anion was closer to the benzene ring than the formally cationic core $(C_3N_3)^+$ (Figure 1a). The chloride anion is coplanar with a cyclopropenium core (Figure 1b), but each phenyl group is slightly skewed out of the plane. Three TPACs coordinate to one Cl (Figure 1c), while each TPAC aligns in one of the three orthogonal planes of x, y, and z (Figure 1d). The structure of TPAC·Cl is C_{3v} symmetry. The distances between the chloride anion and the positive core $(C_3)^+$ of the three carbons showed distinctly larger distances than the normal ones, viz. 4.1086 Å, 4.8124 Å, and 5.3485 Å, respectively [60]. These data described the 3D architecture of TPAC·Cl in the solid state.

NMR titration experiments were performed to verify the H-bonding interaction between the N–Hs of **TPAC·Cl** and the substrate of nitroalkene **2a** (Figure 2). The chemical shifts of the methine of **2a** exhibited downfield shifts from 8.247 to 8.267 ppm by increasing the ratio of [**TPAC·Cl**]/[**2a**]$_0$ from 0 to 2 (Figure 2). The two different methines were due to the geometric isomerism of the **2a** by C=C. These shifts were important evidence that the catalyst cation of **TPAC·Cl** as HBD could activate the nitro compounds of **2a** via H-bonding. To validate the chloride anion as a potential H-bond acceptor (HBA) with N–H of indole **1a**, NMR titration experiments were performed (Figure 3). The chemical shifts of the H-bonding N–H of the indole exhibited downfield shifts from 11.103 to 11.307 ppm by increasing the ratio of [**TPAC·Cl**]/[**1a**]$_0$ from 0 to 2 (Figure 3). These were important evidence that the counter anion of catalyst **TPAC·Cl** as HBA could activate the indole **1a** via H-bonding.
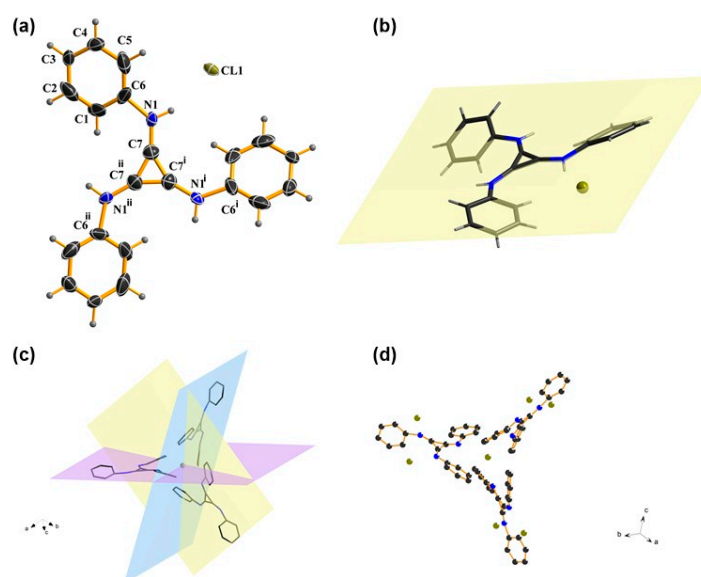
Figure 1. (**a**) Crystal structure of TPAC·Cl. (**b**) Coplanar TPAC·Cl. (**c**) Side-on view of the three orthogonal planes that the cations aligned around one chloride anion. (**d**) Side-on view of the coordination between chloride anion and cation.
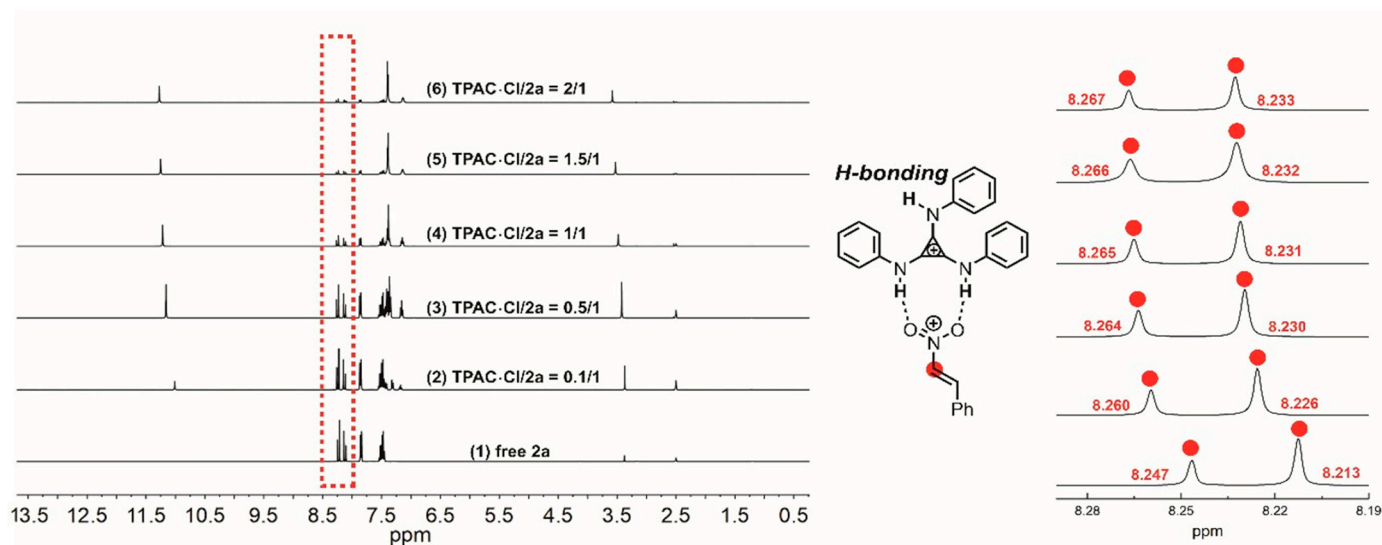

Figure 2. The chemical shifts of the methine of **2a** in the ^{1}H NMR spectrum (DMSO-d_6) observed via titration of **TPAC·Cl** with **2a**: (1) free **2a**, (2) **TPAC·Cl/2a** = 0.1/1, (3) **TPAC·Cl/2a** = 0.5/1, (4) **TPAC·Cl/2a** = 1/1, (5) **TPAC·Cl/2a** = 1.5/1, and (6) **TPAC·Cl/2a** = 2/1.

Two plausible mechanisms were proposed (Scheme 2) based on the experiments and XRD analysis. One possible competitive interaction was the H-bonding attraction between the cationic **TPAC** and the counter anion, which decreased the activation of cationic HBD to the substrate, especially the fluoride anion (Scheme 2A). Thus, the changes of the anion from the fluoride to chloride anion promoting the catalytic performance may be the reason for the weak coordination between the **TPAC** and the chloride anion. The high-lying closed-shell HOMO of the amino-cyclopropenium cation contending against the closed-shell HOMO of chloride anion will counteract the ionic electrostatic attractions [61]. The phenomenon is called "ion pair strain" [62,63]. The cationic **TPAC** and the anionic Cl⁻ will keep away from each other due to the repulsion and reach obviously larger interionic distances under the readjusted dynamic equilibrium. The counter-chloride anion was the potential for HBA to activate the substrate via H-bonding. The **TPAC** acted as an H-bond

donor to coordinate with the two oxygen of the triangle planar nitro group (Scheme 2B). The counter-chloride anion Cl⁻, cooperatively, possibly coordinates to hydrogen of the N–H on the indole ring, played the role of an H-bond acceptor (HBA). Different from the prevailing viewpoint of HBD and the Lewis base as co-catalysis, we preferred to suggest tris(monoamino)cyclopropenium as HBD and the counter-chloride anion as HBA in cooperative catalysis.
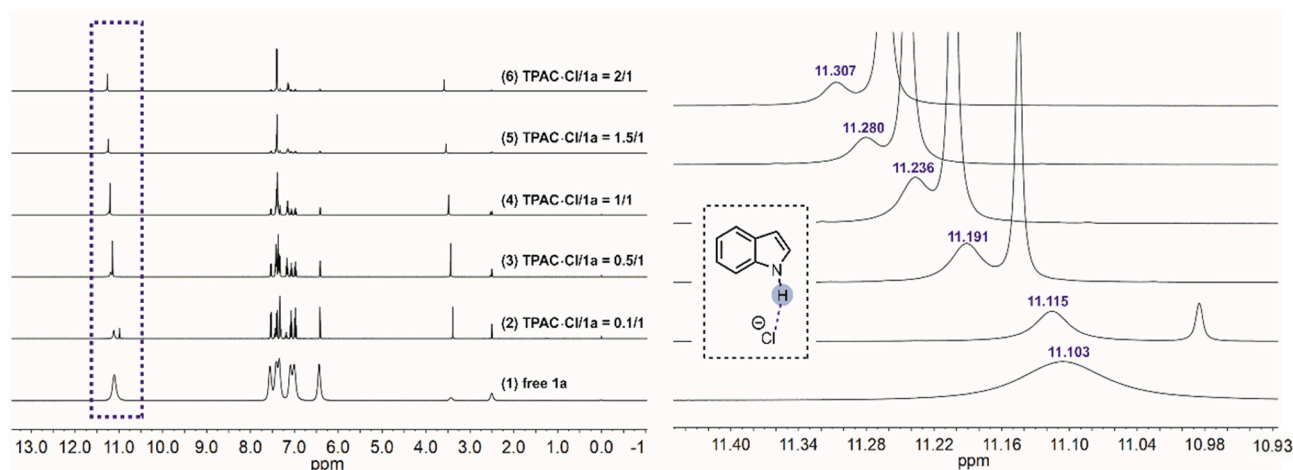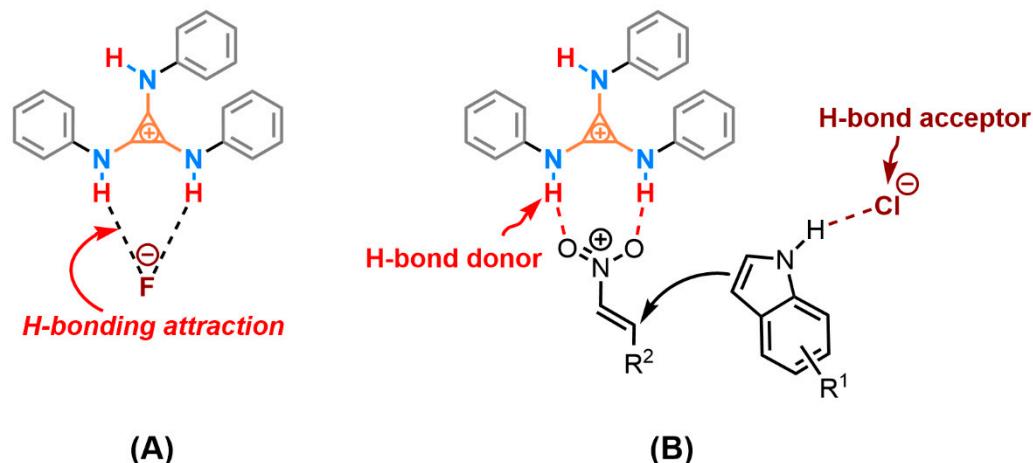

Figure 3. The chemical shifts of the H-bonding N–Hs of **1a** in the ¹H NMR spectrum (DMSO-d_6) observed via titration of **TPAC·Cl** with **1a**: (1) free **1a**, (2) **TPAC·Cl**/**1a** = 0.1/1, (3) **TPAC·Cl**/**1a** = 0.5/1, (4) **TPAC·Cl**/**1a** = 1/1, (5) **TPAC·Cl**/**1a** = 1.5/1, and (6) **TPAC·Cl**/**1a** = 2/1.

Scheme 2. Two possible cooperative activations of the catalyst **TPAC·Cl** in Friedel–Crafts alkylation. (**A**) the cationic TPAC shown a preference for pairing with the fluoride anion. (**B**) the N–H on cation activated the nitroalkene and the chloride anion as HBA activated the indole.

3. Materials and Methods

The NMR spectra were recorded at room temperature on a Bruker AVANCE 400 spectrometer in deuterated solvents as noted. Chemical shifts (δ) are reported in parts per million (ppm) relative to a residual solvent resonance as the internal standard (¹H δ 7.26 for CDCl₃, δ 2.50 for DMSO-d_6; ¹³C δ 77.16 for CDCl₃, δ 39.52 for DMSO-d_6). NMR peak multiplicities are abbreviated as follows: brs = broad signal, s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, and m = multiplet. The substrates of indoles and nitroalkenes were purchased from Sigma Aldrich (Saint Louis, MO, USA) without additional purification. All experiments were executed via standard Schlenk reaction techniques under an argon atmosphere. Dichloromethane was stirred with CaH₂ for 10 h and distilled under an

argon atmosphere. The purified dichloromethane was stored in 3 Å molecular sieve pellets. Toluene, sodium, and diphenyl ketone were heated and stirred until a dark purple color came flooding out. The purified toluene was deposited in 3 Å molecular sieve pellets.

- Preparation of N-trimethylsilylaniline [64,65]

Argon airflow was employed to protect all operations progressing under the standard Schlenk techniques. Freshly distilled aniline (3 mL, 33 mmol, 2.5 equiv.) was mixed with chlorotrimethylsilane (1.7 mL, 13 mmol, 1 equiv.) in 20.0 mL of dry benzene at a reflux for 1 h. Aniline hydrochloride was separated out of this system and removed via filtration. The filtrate was dried using a rotary evaporator to obtain N-trimethylsilylaniline as a yellow oil: 2.46 g, 76% yield. **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.17 (dd, J = 8.5, 7.5 Hz, 2H), 6.73 (t, J = 7.5 Hz, 1H), 6.68 (d, J = 8.5 Hz, 2H), and 3.45 (brs, 1H), 0.30 (s, 9H).

- Preparation of the catalyst TPAC·Cl [66]

Argon airflow was employed to protect all operations progressing under the standard Schlenk techniques. Freshly prepared N-trimethylsilylaniline (2.1 g, 12 mmol, 3 equiv.) was placed in tetrachlorocyclopropene (0.5 mL, 4 mmol, 1 equiv.) in 50.0 mL of dry dichloromethane and stirred for 6 h. The white precipitate was precipitated gradually. The dichloromethane was used to clean up the white solid. Finally, the white solid was recrystallized from methanol: 0.78 g, 52% yield; m.p, 207.3 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 3H), 7.41 (t, J = 7.8 Hz, 6H), 7.36 (d, J = 7.6 Hz, 6H), and 7.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 138.78, 129.68, 123.94, 118.02, 112.83; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for C$_{21}$H$_{18}$N$_3$ 312.1495; found 312.1463.

- Preparation of the catalyst TDAC·Cl [67]

Argon airflow was employed to protect all operations progressing under the standard Schlenk techniques. *N,N*-Dimethyltrimethylsilylamine (0.78 mL, 4.89 mmol, 3 equiv.) was dissolved in 20 mL of dichloromethane and cooled to 0 °C. Tetrachlorocyclopropene (0.2 mL, 1.63 mmol, 1equiv.) was added dropwise, and the solution was allowed to warm to ambient temperature. The solution was removed via rotary evaporation. The residue was dried under vacuum at 60 °C for 12 h and presented the product as a faint yellow solid: 0.31 g, 94% yield; ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.19 (s, 18H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 117.9, 42.8. HRMS (ESI-ToF) *m/z* [M]$^+$ calcd for C$_9$H$_{18}$N$_3$ 168.1495, found 168.1498.

- The general method for Friedel–Crafts Alkylation catalyzed via TPAC·Cl

Argon airflow was employed to protect all operations progressing under the standard Schlenk techniques. Thin-layer chromatography (TLC), combined with UV light, was used to monitor the reaction process. Purification was performed via flash column chromatography with silica gel 60 N (Kanto Chemical Co., Inc., Tokyo, Japan) or Isolera one with a SNAP Ultra Column. In a 10 mL reaction tube, nitroalkenes 2a–d (1 mmol, 1 equiv.) along with the TPAC·Cl (0.0347 g, 0.1 mmol, 10 mol%) were weighted in 1 mL of dichloromethane, where the indoles 1a–e (1.5 mmol, 1.5 equiv.) were placed. The reaction tube was then placed at room temperature for 24 h, and the product **3** was obtained via column chromatography (n-hexane/EtOAc).

4. Conclusions

In summary, we first observed the tris(monoamino)cyclopropenium cation as an H-bond donor (HBD) and the counter anion as a potential H-bond acceptor (HBA) in cooperative organocatalysis. The capability of the N–H moieties as a new type of H-bond donor was implemented via vicinal positive charges on the cyclopropenium core. Tris(phenylamino)cyclopropenium chloride (**TPAC·Cl**) as a representative H-bonding catalyst was used in the Friedel–Crafts alkylation of indoles with nitroalkenes. The X-ray analyses verified the 3D architecture of the **TPAC·Cl** in the solid state. The **TPAC** exhibited an H-bond-donating ability to the nitroalkene enhanced via vicinal cyclopropenium. The counter-chloride anion acted as a potential HBA to activate the indole via H-bonding.

NMR titration, XRD analysis, and the experiment results verified a plausible bifunctional activation mechanism. Taken together, an HBD/HBA as cooperative organocatalysis via **TPAC·Cl** displayed an initial mode in organic transformations. Investigations on a new class of hydrogen bonding catalysis in the wider scope of catalysis and transformations are currently underway.

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