Aminocyclopropenium as a new class of hydrogen bonding catalyst in Friedel–Crafts alkylation

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Article

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

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Abstract: H-bonding, including H-bond donor (HBD) with electron-rich part of a substrate and H-bond acceptor (HBA) with electron-deficient part of a substrate, has achieved massive success. Faster transformation often correlates with more donicity of HBD. Besides the positive charge are employed to enhance the donicity of HBD, the electron withdrawing groups become a dissimilar approach for increasing the donicity of HBD. We describe newly designed H-bond donor catalysts, tris(monoalkylamino)cyclopropenium, implemented by vicinal positive charged on the cyclopropenium core. The counter anion became potential HBA to activate the electron-deficient part of a substrate. The tris(phenylamino)cyclopropenium chloride (TPAC·Cl) as a representative catalyst was applied in Friedel–Crafts alkylation of indoles with nitroalkenes. X-ray analyses of a single crystal of TPAC·Cl described the 3D architecture and the delocalized cationic charge in the solid state. Unit formal positive charge turned N–H moieties into H-bond donor (HBD) and the counter chloride anion exhibited potential H-bond acceptor (HBA). The HBD and HBA displayed cooperative organocatalysis in Friedel–Crafts alkylation of indoles with nitroalkenes. A new class of hydrogen bonding catalysis and working mechanism were proposed.

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

1. Introduction

Hydrogen bonding catalysis has become a thriving and vital domain area in the past two decades [1–9]. Its behavioral mode is coordination of an H-bond donor (HBD) with electron-rich part of a substrate and/or coordination of an H-bond acceptor (HBA) with electron-deficient part of a substrate. Elaboration on control and selectivity is realized by HBD and HBA cocatalysis [2,10–12]. Fast reaction rate often correlates with high donicity of HBD [13–15]. One category of charged HBD, deriving from protonated super strong Brønsted base, shows high donicity due to pi-delocalization of the positive charge, such as in guanidiniums [16–20] (Scheme 1, a). Neutral HBD enhanced by the deliberate installation of electron withdrawing groups, such as in ureas and thioureas, has been developed as one mature direction [9,10,12,21–24] (Scheme 1, b). Another strategy for increasing the donicity of HBD is electron-withdrawing via sigma-bond to vicinal positive charged atom(s), such as in quaternary ammonium [25–28] (Scheme 1, c).

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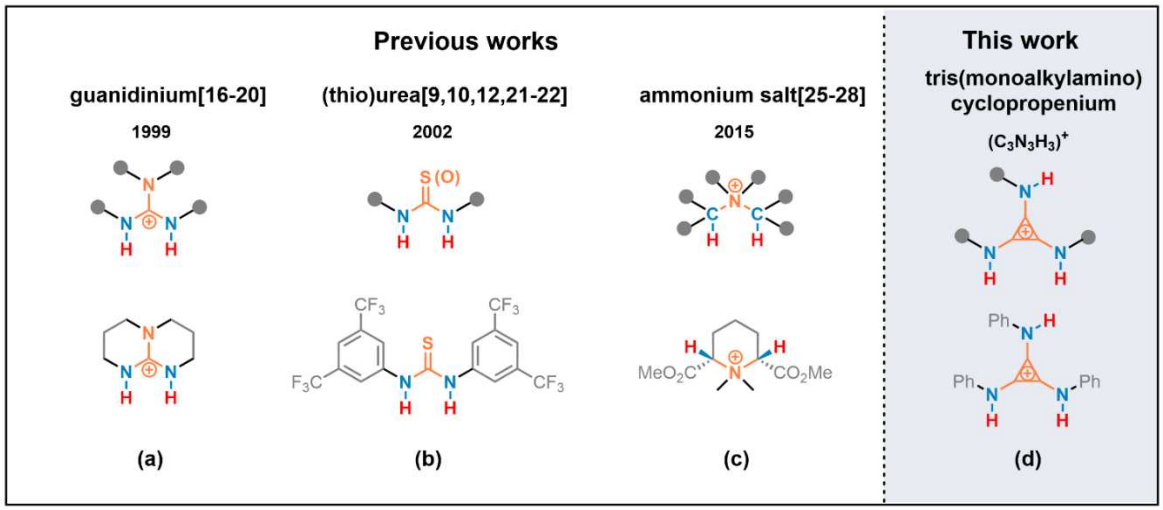

Scheme 1. (a) H-bond donor is enhanced by pi-delocalization of the positive charge; (b) H-bond donor is enhanced by electron withdrawing groups; (c) H-bond donor is enhanced by vicinal positive charged atom; (d) H-bond donor was implemented by vicinal positive charged on the cyclopropenium core, such as tris(monoalkylamino)cyclopropenium.

We suggested that the minimal Hückel aromatic ring cyclopropenium [29,30] in a pattern of tri-substitution with amino groups of NHR, i.e. tris(monoalkylamino)cyclopropenium, would behave as an H-bond donor on the N–H moieties (Scheme 1, d). The donicity of the N–H moieties in this new type of H-bond donor was implemented by vicinal positive charges on the cyclopropenium core. Herein, we demonstrated, for the first time, the tris(monoalkylamino)cyclopropenium as H-bonding catalyst to promote Friedel–Crafts alkylation of indoles with nitroalkenes.

2. Results and Discussion

Friedel–Crafts alkylation (F–C alkylation) of indoles is an important reaction for the formation of new carbon-carbon bonds and construction of versatile indole-containing scaffolds [35,36]. Organocatalysis in this area has received tremendous success under nearly all the major catalytic activation modes. Particular interest was focused on H-bonding catalytic F–C alkylation due to the mildness of reaction conditions and the broad tolerance of functional groups [1,36–38]. A valuable unprotected indole N–H moiety made the F–C adducts readily accessible to bioactive compounds [37]. Importantly, a free N–H readily accepts H-bond donor from a nucleophilic catalyst.

In the context of the ordinary H-bond [36,37,39] and the metal-enhanced H-bond catalysis,[40] we expanded exploration of the novel H-bond donor implemented by the vicinal positive on the cyclopropenium in F–C alkylation of indole **1** with trans-β-nitroalkene **2**. Tri(phenylamino)cyclopropenium chloride (TPAC·Cl) was selected as a quintessential HBD 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 noncatalyzed background reaction was negligible (entry 1). The TPAC·F ion pair, replacing the TPAC·Cl, performed no activity in the same reaction by changing the chloride to fluoride anion (entry 3). Poor catalytic performance implied that the chloride anion may be necessary for F–C alkylation. A possible reason was that the fluoride anion was easily coordinated with the HBD of the cationic TPAC, similar to the normal fluoride anion receptors with HBD structures [9,41,42]. Poor catalytic performance suggested that TPAC·F formed a tight ion pair [43] and the cationic TPAC preferably paired with the fluoride anion rather than to activate a substrate.

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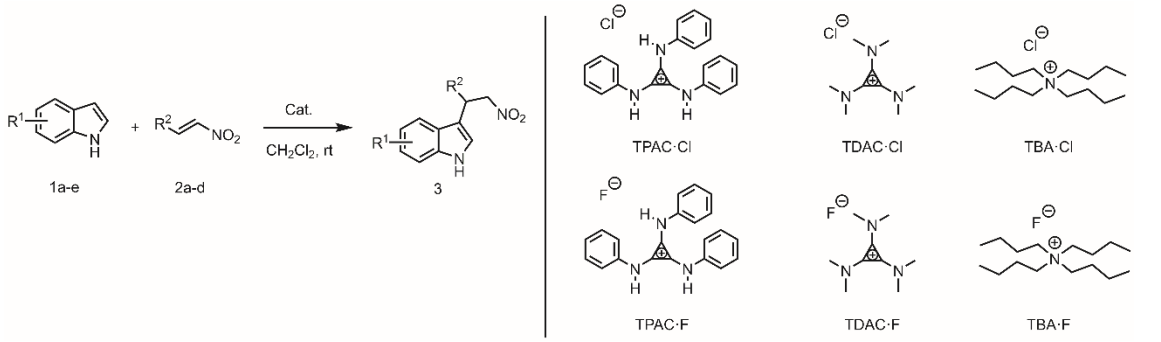
Table 1. F–C alkylation of indoles **1a–e** with nitroalkenes **2a–d**[a].



Entry	Ion pair catalyst	Indole	R^1	R^2	Nitroalkene	product	Time / h	Yield / %[b]
1	-	**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_6H_4	**2b**	**3ab**	24	33
13	TPAC·Cl	**1a**	H	4-MeOC_6H_4	**2c**	**3ac**	24	55
14	TPAC·Cl	**1a**	H	2-thienyl	**2d**	**3ad**	24	71

[a] 1.5 mmol indole **1** along with the 1 mmol nitroalkene **2** were added to 1 mL dichloromethane at 25 °C. [b] Yield of isolated product. [c] Without catalyst. [d] Reaction time was 72 h.

Dialkylamino-substituted cyclopropenium was tested on the F–C alkylation to verify the assumption that N–H moieties of the TPAC as an HBD were essential in the H-bonding catalysis (entries 4 and 5). The tris(dimethylamino)cyclopropenium chloride (TDAC·Cl) displayed no catalytic performance on the F–C alkylation (entry 4). The possible reason was the lack of N–H moiety on the cationic core TDAC and loss of the ability to work as an H-bond donor. Although fluoride anion, possessing strong nucleophilic, was supposed an excellent H-bond acceptor, the TDAC·F as catalysts was not workable on F–C alkylation (entry 5). These experimental results supported that the N–H moieties of TPAC as an HBD were essential.

The tetrabutylammonium chloride (TBA·Cl) along with tetrabutylammonium fluoride (TBA·F), counterparts to TPAC·Cl and TPAC·F, respectively, performed inactive in the benchmark F–C alkylations (entries 6 and 7). The discrepancy between TPAC·Cl and TBA·Cl suggested the necessity of the cationic structure of tris(monoalkylamino)cyclopropenium. We suggested that the H-bond donor realized by the vicinal cyclopropenium show excellent catalytic performance.

With primary success, we expanded substrates by using various indoles along with nitroalkenes (entries 8 to 15). Indoles **1a–e** bearing different substituents on both the benzene ring and the pyrrole ring were conductive in reactions with nitroalkene **2a**. Whereas the reactions of bare indole **1a** and indoles with electron-donating groups (**1b** and **1c**) afforded the corresponding products **3aa**, **3ba**, and **3ca** in good yields (Table 1, entries 8–9), an electron-withdrawing chlorine on the 5-position caused **1d** proceeded in a moderate yield of **3da** (Table 1, entry 10). Steric hindrance at 7-position retarded

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the reaction (Table 1, entry 11), which could be accounted for by the unfavorable interference to chloride anion. The applicability of the catalyst was further supported by the variation of the nitroalkene partners. Nitroalkenes with 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, thienly 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 by an X-ray diffraction analysis of the catalyst of TPAC·Cl. The chloride anion was closer to the benzene ring than the formally cationic $(C_3N_3)^+$ core (Figure 1, a). The chloride anion is coplanar with cyclopropenium core (Figure 1, b), but each phenyl group is slightly skewed out of the plane. Three TPAC coordinate to one Cl (Figure 1, c), while each TPAC aligns in one of the three orthogonal planes of x, y, and z (Figure 1, d). 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 [44]. These data described the 3D architecture of TPAC·Cl in the solid state.

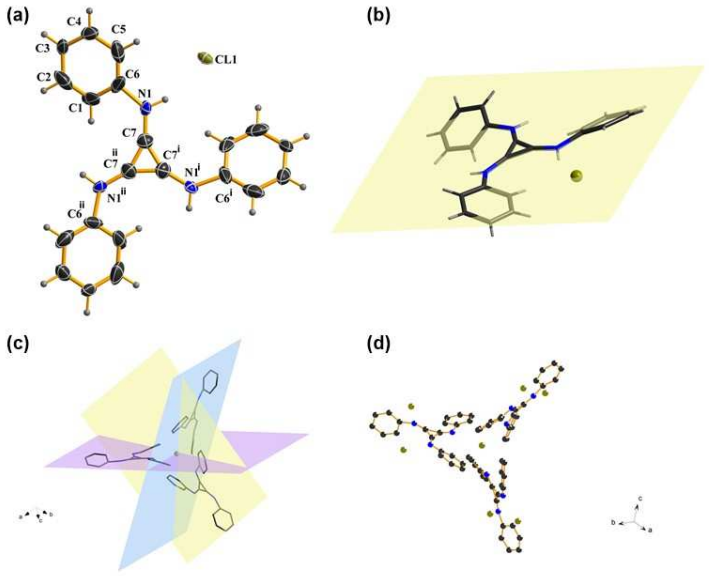

Figure 1. (a) Crystal structure of TPAC·Cl. (b) Coplanar TPAC·Cl. (c) Side-on view of the three orthogonal planes that the cations aligned around one chloride anion. (d) Side-on view of the coordination between chloride anion and cation.

Two plausible mechanisms were proposed (Scheme 2) based on the HBD implemented by cyclopropenium. 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 2, A). Thus, the changes of the anion from fluoride to chloride anion promoting the catalytic performance may be the reason for the weak attraction between the TPAC and the chloride anion. The high-lying closed-shell HOMO of aminocyclopropenium cation contending against the closed-shell HOMO of chloride anion will counteract the ionic electrostatic attractions [45]. The phenomenon is called "ion pair strain" [46,47]. The cationic TPAC and the anionic Cl^-, in this case, will keep away from each other due to the resistance, and reach obviously larger interionic distances under the readjusted dynamic equilibrium. The counter chloride anion is potential HBA to activate the substrate nucleophilically. The TPAC as an H-bond donor, implemented by vicinal positive charged on the cyclopropenium core, coordinated to the two oxygen of the triangle planar nitro group (Scheme 2 B). The counter chloride anion Cl^-, cooperatively, possibly coordinating to hydrogen of the N–H on the indole ring, played the role of an H-bond

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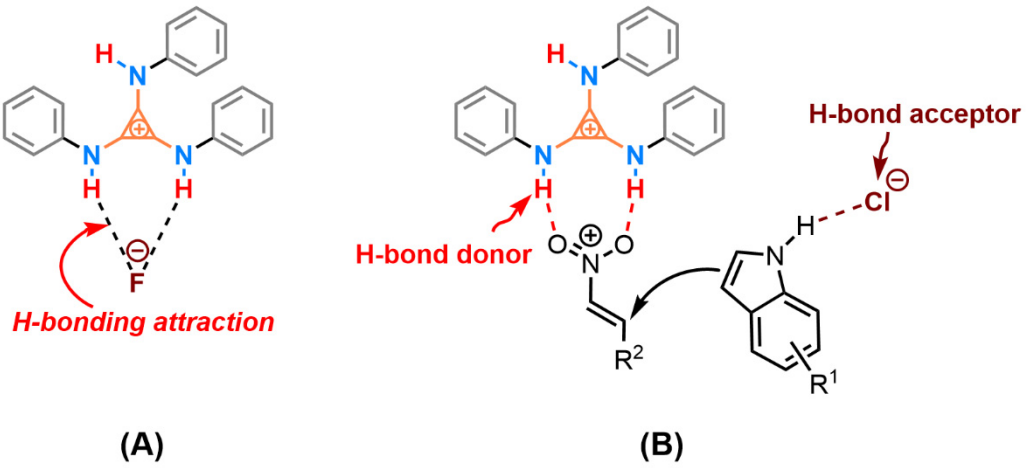
acceptor (HBA). Different from the prevailing viewpoint of HBD and Lewis base as co-catalysis, we preferred to suggest tris(monoalkylamino)cyclopropenium as HBD and counter chloride anion as potential HBA in cooperative catalysis.



Scheme 2. Two possible cooperative activations of the catalyst TPAC·Cl in Friedel–Crafts alkylation.

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** by 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 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** by H-bonding.

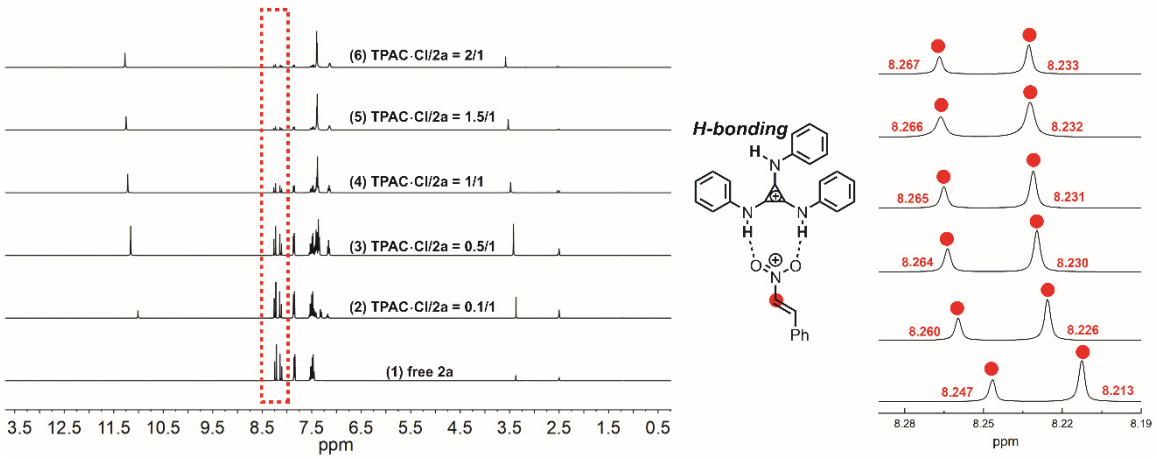


Figure 2. The chemical shifts of the methine of **2a** in the ^{1}H NMR spectrum (DMSO-d_6) observed by titration of TPAC·Cl with **2a**: (1) free **2a**, (2) TPAC·Cl/**2a** = 0.1/1, (3) TPAC·Cl/**2a** = 0.5/1, (4) TPAC·Cl/**2a** = 1/1, (5) TPAC·Cl/**2a** = 1.5/1, (6) TPAC·Cl/**2a** = 2/1.

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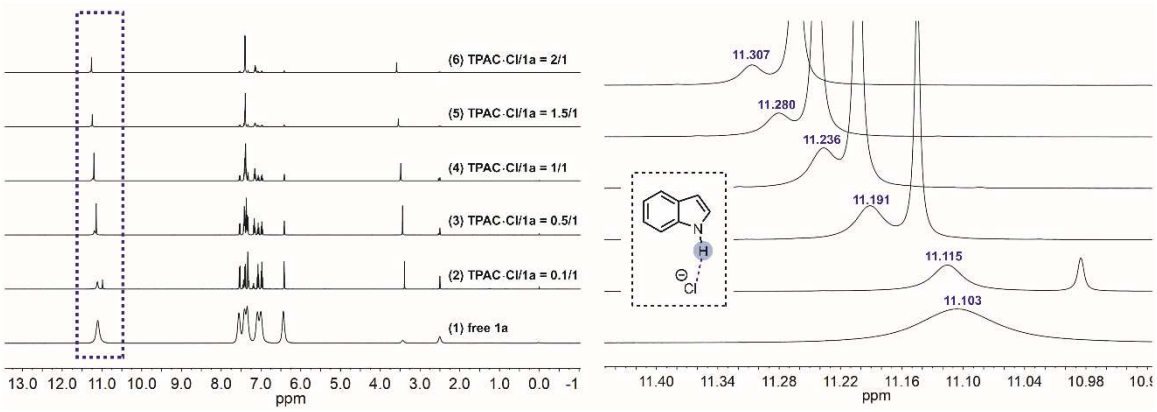

Figure 3. The chemical shifts of the H-bonding N–Hs of **1a** in the ^{1}H NMR spectrum (DMSO-d_6) observed by titration of TPAC·Cl with **1a**: (1) free **1a**, (2) TPAC·Cl/**1a** = 0.1/1, (3) TPAC·Cl/**1a** = 0.5/1, (4) TPAC·Cl/**1a** = 1/1, (5) TPAC·Cl/**1a** = 1.5/1, (6) TPAC·Cl/**1a** = 2/1.

3. Materials and Methods

The organic solution was concentrated using Buchi rotary evaporator or IKA rotary evaporator. The machine of nuclear magnetic resonance was a type of Bruker-AV-400 (400 MHz). The detecting temperature was 25 °C and the protic solvent was $CHCl_3$ or DMSO. The substrates of indoles and nitroalkenes were purchased from Sigma Aldrich without additional purification. All experiments were executed by standard Schlenk reaction techniques under an argon atmosphere. Dichloromethane was stirred with CaH_2 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 dark purple color came flooding out. The purified toluene was deposited in 3 Å molecular sieve pellets.

Preparation of N-trimethylsilylaniline [31–33]

Argon airflow was employed to protect all operations progress under standard Schlenk techniques. Freshly distilled 3.0 mL aniline mixed with 1.7 mL chlorotrimethylsilane in 20.0 mL dry benzene at reflux for 1 h. Aniline hydrochloride was separated out in this system and removed by filtration. The filtrate was dried by rotary evaporator to obtain N-trimethylsilylaniline as a yellow oil: 2.46 g, 76 % yield. ^{1}H NMR (400 MHz, CDCl3) 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), 3.45 (brs, 1H), 0.30 (s, 9H).

Preparation of the catalyst TPAC·Cl [34]

Argon airflow was employed to protect all operations progress under standard Schlenk techniques. Freshly prepared 2.10 g N-trimethylsilylaniline was placed to 0.5 mL tetrachlorocyclopropene in 50.0 mL 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); 1H NMR (400 MHz, DMSO-d6) δ 11.11 (s,3H), 7.41 (t, J = 7.8 Hz, 6H), 7.36 (d, J = 7.6 Hz, 6H), 7.16 (t, J = 7.2 Hz, 3H); 13C NMR (100 MHz, DMSO) δ 138.78, 129.68, 123.94, 118.02, 112.83; HRMS (ESI-TOF) m/z: [M + H]+ calcd for C21H18N3 312.1495; Found 312.1463.

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

Argon airflow was employed to protect all operations progress under standard Schlenk techniques. Thin-layer chromatography (TLC), combined with UV light, was used to monitor the reaction process. Purification was performed by flash column chromatography with silica gel 60 N (Kanto Chemical Co., Inc) or Isolera one with SNAP Ultra Column. In 10 mL reaction tube, 1.0 mmol nitroalkenes **2a–d** along with the 0.0347 g TPAC·Cl were weighted in 10.0 mL dichloromethane, the 1.5 mmol indoles **1a–e** were placed. The reaction tube was then placed at room temperature for 24 h, the product 3 was obtained by column chromatography (n-hexane/EtOAc mixtures).

4. Conclusions

In summary, we first observed the tris(monoalkylamino)cyclopropenium cation as an H-bond donor (HBD) and the counter anion as potential H-bond acceptor (HBA) by cooperative organocatalysis. The donicity of the N–H moieties in this new type of H-bond donor was implemented by vicinal positive charges on the cyclopropenium core. Tris(phenylamino)cyclopropenium chloride (TPAC·Cl) as a representative H-bonding catalyst was used in Friedel–Crafts alkylation of indoles with nitroalkenes. The X-ray analyses verify the 3D architecture of the TPAC·Cl in the solid state. The TPAC exhibited an H-bond donating ability to the nitroalkene by vicinal cyclopropenium. The counter chloride anion as a potential HBA activated the indole. The proposed mechanisms were certified by using NMR measurements and supported the cooperative activation mechanism. Taken together, an HBD/HBA as cooperative organocatalysis by TPAC·Cl displayed 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.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

Author Contributions: Conceptualization, **Zhenjiang Li**; Funding acquisition, **Zhenjiang Li**; Investigation, **Xuesuo Ma**, **Jiaxi Xu**, **Jingjing Liu**, **Jun He**, **Qingbiao Yang**, **Ning Li** and **Dong Qian**; Methodology, **Xuesuo Ma**, **Jiaxi Xu** and **Jingjing Liu**; Project administration, **Zhenjiang Li**; Resources, **Zhenjiang Li**; Validation, **Jun He**; Writing – original draft, **Xuesuo Ma**, **Jiaxi Xu** and **Tong Chang**; Writing – review & editing, **Xuesuo Ma**, **Tong Chang** and **Zhenjiang Li**.

Data Availability Statement: We encourage all authors of articles published in MDPI journals to share their research data. In this section, please provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study. Where no new data were created, or where data is unavailable due to privacy or ethical restrictions, a statement is still required. Suggested Data Availability Statements are available in section "MDPI Research Data Policies" at https://www.mdpi.com/ethics.

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Conflicts of Interest: The authors declare no conflict of interest.

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