Quantification of Catalytic Activity for Electrostatically Enhanced Thioureas via Reaction Kinetics and a UV−Vis Spectroscopic Measurement

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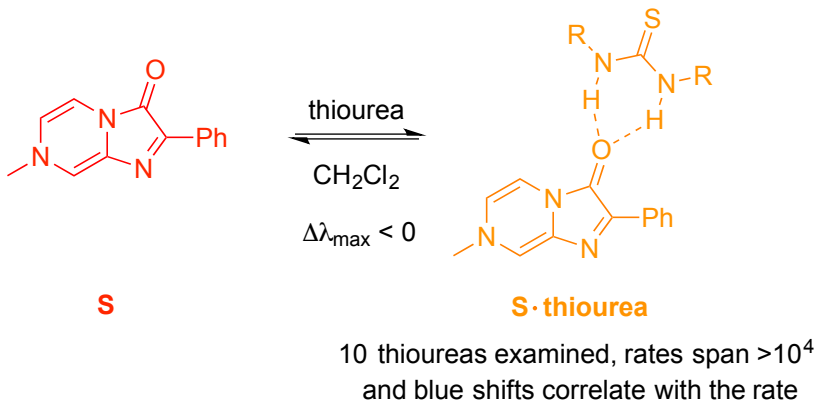


ABSTRACT

Charged thiourea derivatives containing one and two methylated or octylated pyridinium ion centers and a tetraarylborate or triflate counteranion are reported. These novel catalysts are much more active in the Friedel–Crafts reactions of *trans*-β-nitroalkenes with *N*-methylindoles than the privileged *N*,*N*'-bis(3,5-bis(trifluoromethyl)phenyl)thiourea (i.e., Schreiner's thiourea) by up to 2-3 orders of magnitude. A previously reported UV-Vis spectroscopic method by Kozlowski et al. was exploited to rationalize their reactivity order along with non-charged analogs. These results offer a new design strategy for organocatalysts by introducing positively charged centers without adding additional N–H, O–H, or S–H hydrogen bond donor sites.

INTRODUCTION

Nature exploits noncovalent interactions such as hydrogen bonds to reduce the activation energy barriers of enzyme-catalyzed chemical transformations.[1] A wealth of small-molecule organocatalysts that mimic this behavior have been developed over the past two decades and this field has emerged as a fast-growing research area.[2] Metal-free catalysts that use hydrogen bonds most commonly activate electrophiles towards nucleophilic attack by lowering their LUMO energies to enhance the overall reaction rates, but other pathways have been proposed and are operational.[3]

Thioureas are a widely used class of hydrogen bond donors that can simultaneously provide two N−H activating sites.[4] Of these compounds, incorporation of four electron withdrawing trifluoromethyl groups into *N*,*N*'-diphenylthiourea (**1**) to afford *N*,*N*'-bis(3,5-bis(trifluoro-methyl)phenyl)thiourea (**2**, Schreiner's thiourea)[5] is regarded as a seminal contribution. This is due to the enhanced acidity of the latter compound, the generally assumed stabilization of its active Z,Z-conformer via internal C−H···S hydrogen bonds, an increase in solubility in nonpolar media and the significantly greater reactivity observed when **2** is used.[6] As a result, the 3,5-bis(trifluoromethyl)phenyl ring has been incorporated into most thiourea catalysts and occupies a privileged position in the field of organocatalysis.[7]

Inspired by the use of Schreiner's thiourea and the wealth of chiral variants, we recently reported on the synthesis and reactivity of several electrostatically enhanced thioureas that possess one or two activating *N*-methylpyridinium ion centers along with an appropriate noncoordinating counteranion (**3** and **4**, Figure 1).[8] These compounds were found to outperform Schreiner's thiourea in several organic transformations by leading to rate enhancements of 1–3

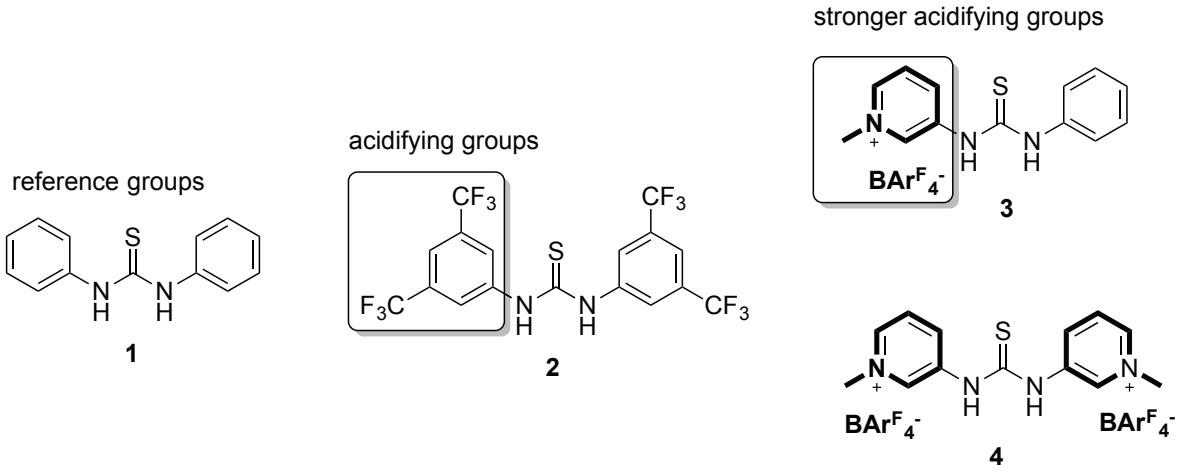


Figure 1. *N*,*N*'-Diphenylthiourea (**1**), Schreiner's thiourea (**2**), and charged thiourea salts **3** and **4**, where $BAr^F_4^-$ = $(3,5\text{-}(CF_3)_2C_6H_3)_4B^-$.

orders of magnitude without changing the hydrogen bonding arrangement of the catalyst. As they also can be readily prepared, and a chiral variant was found to give good enantioselectivities while still maintaining the enhanced activity,[9] a quick and direct manner for quantitatively assessing their catalytic abilities in nonpolar media was sought.

A variety of different types of hydrogen bond donating catalysts have been developed and their measured pK_a values in DMSO commonly are used as a guide to their activity.[10] That is, for related compounds, more acidic derivatives typically are found to be more reactive catalysts. Substituent effects in a polar aprotic medium, however, need not be the same as in nonpolar solvents, and it is the latter conditions that are usually employed with hydrogen bond catalysts. Other physical measures for structure-reactivity relationships therefore might be more valuable. Building upon the work of Reed et al.,[11] we reported an IR method for determining the acidities of phenols in carbon tetrachloride by comparing the free O–H stretch with the lower frequency band resulting from the formation of a O–H···$NCCD_3$ hydrogen bond upon addition of a small amount of acetonitrile-d_3.[12] The resulting frequency shifts of twenty *meta*- and *para*-substituted phenols were found to better correlate with their gas-phase acidities (ΔG°_{acid}) than their DMSO

pK_a values. This approach is more challenging when the Brønsted acid is a double hydrogen bond donor, however, especially if there is conformationally flexibility as is the case for thioureas.

To our delight, Kozlowski et al. recently reported a colorimetric sensor molecule, 7-methyl-2-phenylimidazo[1,2a]pyrazine-3(7H)-one (**S**, Figure 2) for quantitatively determining the electrophilic activating ability of a large number (i.e., 33 compounds) of single and double hydrogen bond donors with different structural motifs.[13] In this approach, **S** is titrated with a hydrogen bond donor HY in dichloromethane and UV-Vis spectra are recorded over the course of this process. The absorption maxima (λ_{max}) of the resulting hydrogen bonded complexes **S**···HY empirically were found to be blue shifted to lower wavelengths, and the inverse of the change relative to the unbound sensor ($\Delta\lambda_{max}^{-1}$) correlate with the logarithm of the equilibrium association constant (K) and catalyzed reaction rate constants (k).

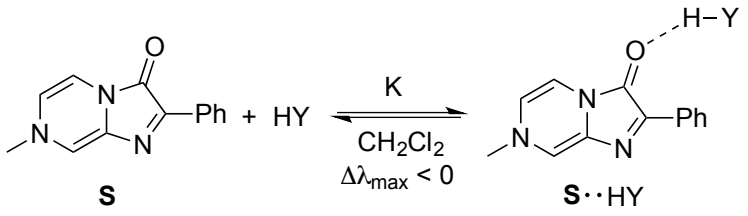


Figure 2. UV-Vis sensor **S** which is responsive to hydrogen bond interactions with Brønsted acids HY.

In this contribution we report kinetic data for Friedel−Crafts alkylations of *N*-methylindole with *trans*-β-nitrostyrene catalyzed by a variety of charged thiourea salts. Solvent effects, catalyst loading and substrate scope were also investigated with our most active thiourea derivative. In addition, the UV-Vis method reported by Kozlowski et al. was successfully applied to a series of 10 thioureas and a good correlation between their catalytic activity and hydrogen bond donating ability was observed.

RESULTS AND DISCUSSION

Based upon recent communications dealing with electrostatically enhanced thioureas and phosphoric acids,[8,14] a series of thiourea derivatives with one and two *N*-alkylpyridinium ion centers (**3-10**, Figure 3) were synthesized from commercially available arylamines. These compounds differ in their structural symmetry, alkyl chain length and the identity of the counteranion, and were prepared by reacting *N*-alkylated isothiocyanates (which were readily obtained from their corresponding amines) with an *N*-alkylated aminopyridine or aniline (Scheme 1).[8] The final step in this process was the exchange of an iodide or triflate anion to a

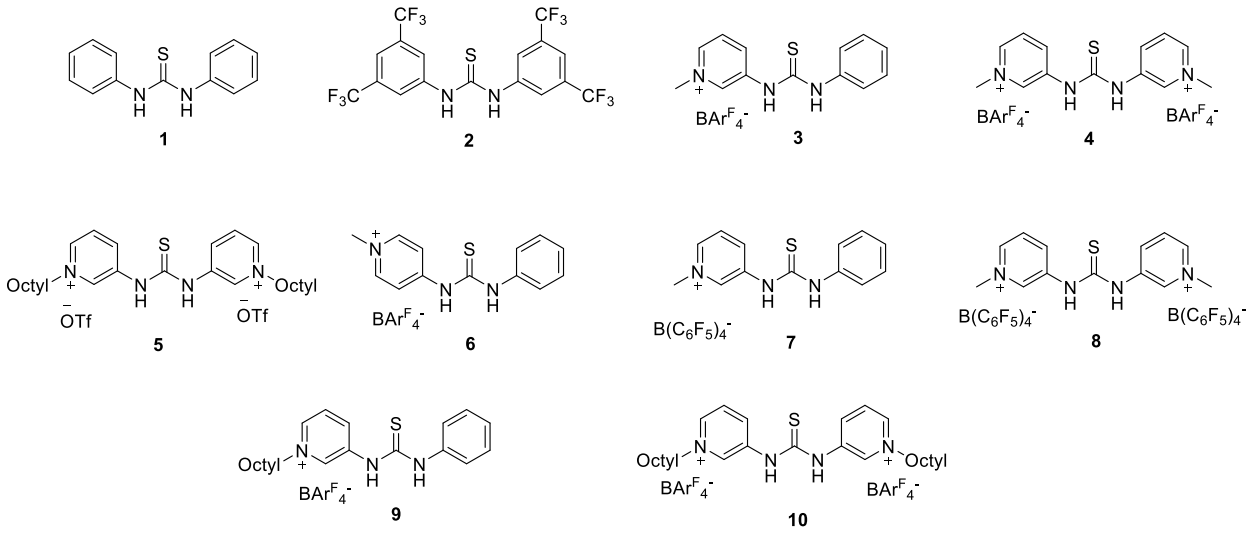
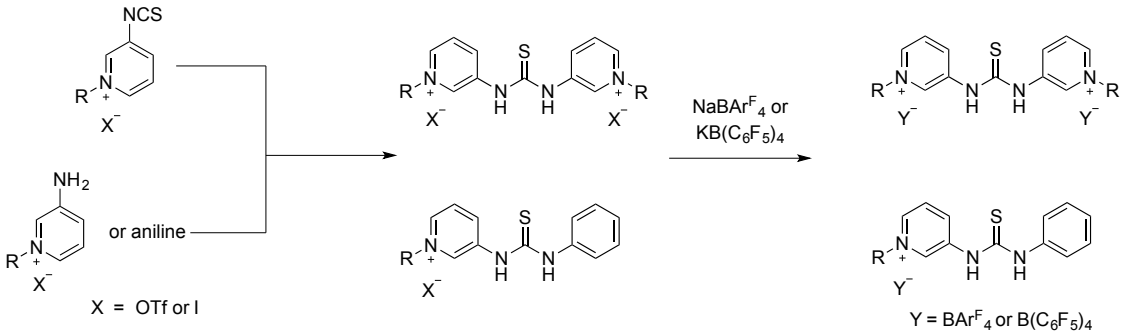


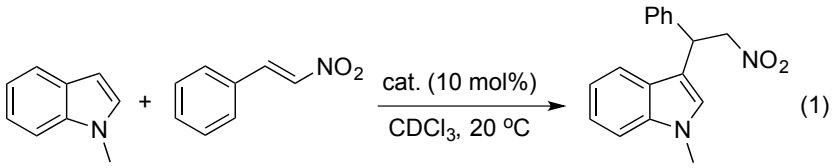
Figure 3. Thiourea catalysts screened in this work.



Scheme 1. General synthetic route for the preparation of thioureas **3-10**.

tetrakis(3,5-bis(trifluoromethyl)phenyl)borate ($BAr^{F}_{4}^{-}$) or tetrakis(pentafluorophenyl)borate ($B(C_6F_5)_4^-$) counterion. This transformation was readily accomplished by stirring the thiourea precatalyst in dichloromethane with the sodium or potassium salt of the tetraarylborate anion and subsequently filtering away the insoluble NaX (X = I or OTf) salt. This anion interchange is critical as the iodide salts typically are poorly soluble in nonpolar solvents such as CH_2Cl_2 and both the iodides and triflates are much less active catalysts, presumably due to the formation of $NH\cdots I^-$ and $NH\cdots OSO_2CF_3^-$ hydrogen bonds.

To evaluate the catalytic activity of *N*-alkylpyridinium ion containing thiourea salts **3-10** along with noncharged reference compounds **1** and **2**, the Friedel−Crafts alkylation of *N*-methylindole with *trans*-β-nitrostyrene (eq. 1) was examined. This transformation was selected



(1)

because it has been well-studied and reaction rates with Brønsted acid and hydrogen bond catalysts have been found to correlate with their acidities.[15] Rate data were originally fit to a second-order kinetic model and good linear behavior was observed. Rate constants were obtained, but given the rate law at a given catalyst concentration (eq. 2), this approach is only appropriate if K • [*trans*-β-nitrostyrene] << 1, where K is the equilibrium binding constant for the employed catalyst and *trans*-β-nitrostyrene. This was assumed to be the case in our initial communication[8] because the nitro group is known to be an especially poor hydrogen bond acceptor.[16] To test this assumption, the association of **8** with *trans*-β-nitrostyrene was examined.

$$\text{Rate} = \frac{k_{obs}[\textit{trans}\text{-}\beta\text{-nitrostyrene}][\textit{N}\text{-methylindole}]}{1 + K[\textit{trans}\text{-}\beta\text{-nitrostyrene}]} \quad (2)$$

A ^{1}H NMR monitored titration of a fixed 8.3 mM concentration of **8** with 1-28 equivalents of *trans*-β-nitrostyrene was carried out (Figure 4). Both the N–H and the singlet aromatic C–H hydrogen adjacent to the formally charged nitrogen were found to shift downfield upon addition

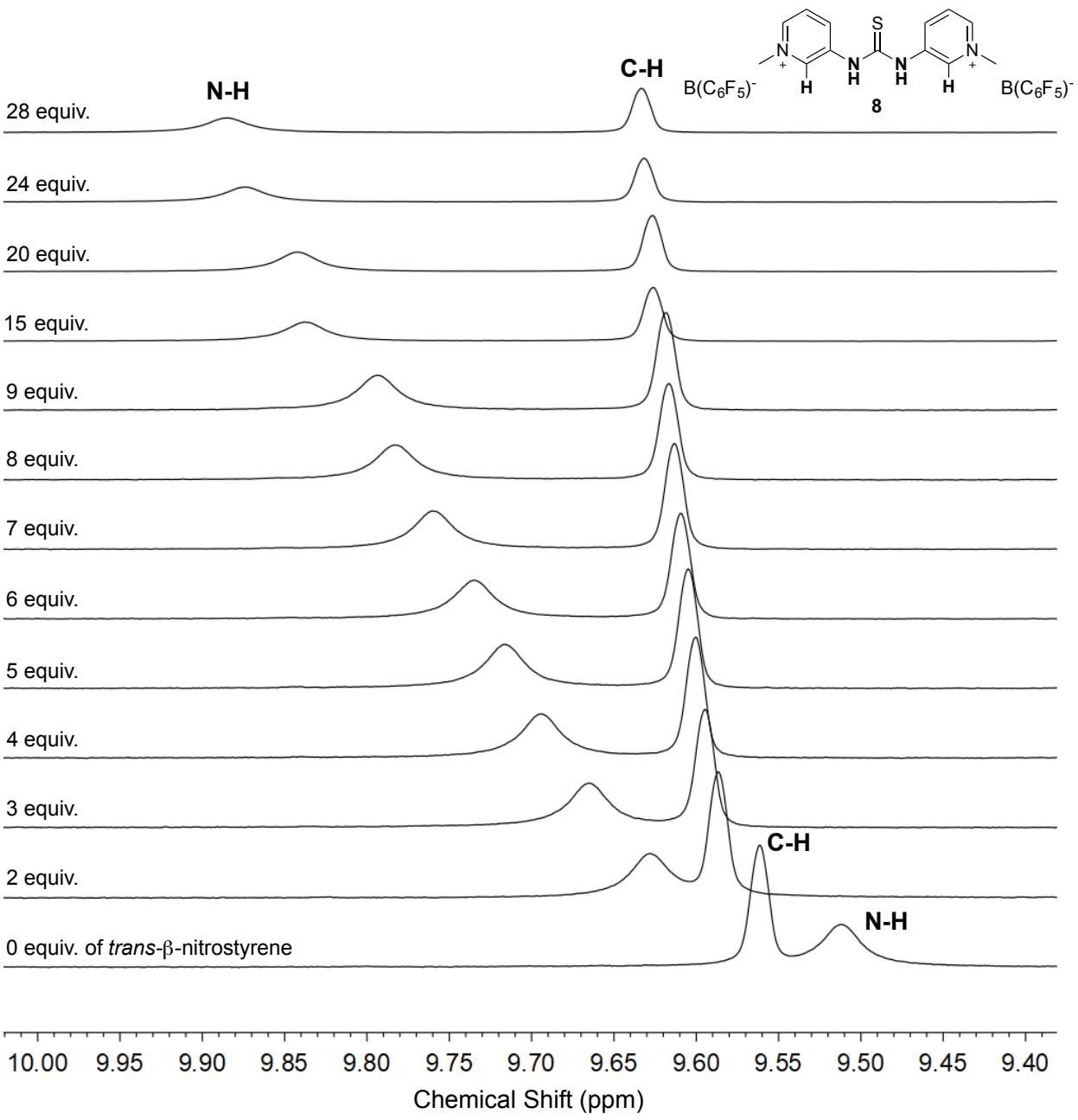


Figure 4. Proton NMR titration data of the illustrated NH and CH hydrogens in thiourea **8** in the presence of increasing amounts of *trans*-β-nitrostyrene.

of *trans*-β-nitrostyrene. These data were fit with a 1:1 binding model using BindFit[17] (Figure 5) to afford K = 27 M^{-1}. This small equilibrium constant is large enough, however, to lead to intermediate kinetic behavior between first- and second-order processes. Consequently, simple integer order kinetics is not a given for the various catalysts employed and rate profile data (Table S1 and Figure S1) were used to obtain reaction half-lifes and relative rates (Table 1).[18]

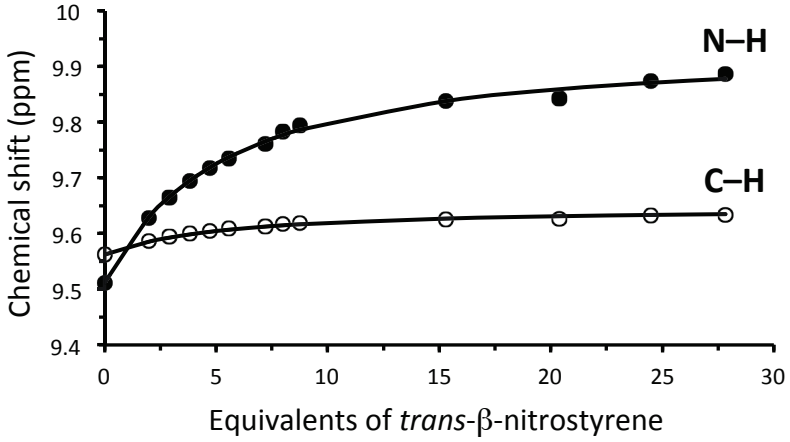


Figure 5. Non-linear binding curves (solid lines) for the ^{1}H NMR titration data of **8** with *trans*-β-nitrostyrene; filled and open circles are for the N–H and C–H hydrogens, respectively.

The uncatalyzed reaction is extremely slow and takes about 7 weeks for half of the *trans*-β-nitrostyrene to be consumed (entry 1). Diphenylthiourea (**1**) is an ineffective catalyst in that the reaction rate is on the same order of magnitude as the background process and more than a month is needed to convert half of the limiting reagent (i.e., *trans*-β-nitrostyrene) to the product (entry 2). Schreiner's thiourea (**2**), which was reported as a good catalyst for this transformation,[19] is much better than **1** (entry 3), but still requires more than a day to convert half of the *trans*-β-nitrostyrene to product under the employed reaction conditions. The *N*-alkylpyridinium containing thioureas were found to be much more active than **2**. One charged

Table 1. Reactivity Data for the Friedel–Crafts Alkylation of *N*-Methylindole with *trans*-β-Nitrostyrene Catalyzed by Thiourea Catalysts 1-10.[a]

entry	catalyst	$t_{1/2}$ (h)	rel. rate
1		940	
2	**1**	710	0.013[b]
3	**2**	26	1.0
4	**3**	4.0	6.6
5	**4**	0.11 (6.4 min)	250
6	**5**	530	0.020[b]
7	**6**	2.8	9.5
8	**7**	6.8	3.9
9	**8**	0.37 (22 min)	71
10	**9**	1.5	18
11	**10**	0.12 (7.4 min)	230

[a] These reactions were carried out in NMR tubes with *N*-methylindole and *trans*-β-nitrostyrene concentrations of 250 and 83 mM, respectively. [b] This value is corrected for the uncatalyzed reaction rate.

site makes **3** a more active catalyst than Schreiner's thiourea by a factor of 7 (entry 4). Incorporation of a second charged site in **4** leads to the most effective catalyst of the examined series corresponding to a 250-fold rate acceleration relative to **2**, and a reaction half-life of just 6 min (entry 5). Catalyst **6** with the positively charged center at the *para* position outpaces its *meta* analogue **3** (entry 7) presumably because conjugation makes this derivative more acidic. When the $BAr^F{}_4^-$ counteranion is switched to $B(C_6F_5)_4^-$, this leads to a decrease in catalytic activity as reflected by the performances of **7** and **8** (entries 8 and 9) compared to those of **3** and **4**, respectively. A much greater decrease is observed when $CF_3SO_3^-$ is used as the counterion (entry 6) as **5** is found to be less active than Schreiner's thiourea and only marginally better than diphenyl thiourea. This deactivation of the catalyst can be attributed to one or two $NH\cdots OSO_2CF_3^-$ hydrogen bonds and emphasizes the importance of a weakly coordinating anion

as the counterion. Finally, when *N*-octyl substituents are used instead of methyl groups, this leads to a rate enhancement of a factor of ~3 for the mono charged species (i.e., **9** vs **3** (entries 10 and 4)) but a slight reduction for the doubly charged thioureas (**10** vs **4** (entries 11 and 5)). This reversal is indicative of more than one effect being involved and suggests that sterics are an issue when both aromatic rings are alkylated.

Solvent effects and catalyst loadings were also explored with **4**, the most active thiourea catalyst examined (Table 2). When the Friedel-Crafts reaction between *N*-methylindole and *trans*-β-nitrostyrene is carried out in toluene-d_8 instead of $CDCl_3$ there is a small twofold difference in the observed rates (entry 1 vs 6). An ~10-fold increase is observed when CD_2Cl_2 is used as the solvent (entry 2 vs 6) presumably because it has a larger dielectric constant than toluene and chloroform but does not have a good hydrogen bond accepting site. For the two other nonpolar solvents examined, benzene-d_6 is a much less effective medium and no reaction was observed after 24 h in tetrahydrofuran-d_8. These latter two results can be attributed to the limited solubility of **4** in C_6D_6 and the hydrogen bond accepting oxygen atom in THF-d_8.

Table 2. Solvent and Catalyst Loading Effects.

entry	**4** mol%	solvent	$t_{1/2}$ (h)	rel. rate
1	5	$C_6D_5CD_3$	0.12 (7.4 min)	
2	5	CD_2Cl_2	0.016 (1.0 min)	
3[a]	10	C_6D_6	2.4	
4[b]	10	THF-d_8		
5	10	$CDCl_3$	0.11 (6.4 min)	31
6	5	$CDCl_3$	0.29 (17 min)	12
7	2.5	$CDCl_3$	3.3	1
8	1	$CDCl_3$	200	0.017

[a] Catalyst **4** is only partially soluble in C_6D_6. [b]No reaction was observed after 24 h.

Catalyst loading was also explored (entries 5-8), and a linear correlation between the relative rate and the square of the catalyst concentration was found (Figure S2). This is suggestive of a second-order dependence on the thiourea and the catalytically active species being the dimer.[8,20] Presumably, the enhanced electrophilic activation brought about by the dimer is sufficient to offset the resulting entropic cost of bringing together *N*-methylindole, *trans*-β-nitrostyrene and the dimer of **4** in the reaction transition structure. At low catalyst concentrations, of course, this dependence will break down.

To examine the scope of the Friedel−Crafts alkylation, a series of substituted aromatic *trans*-β-nitroalkenes were explored (eq. 3, Table 3). All of these reactions afforded the corresponding

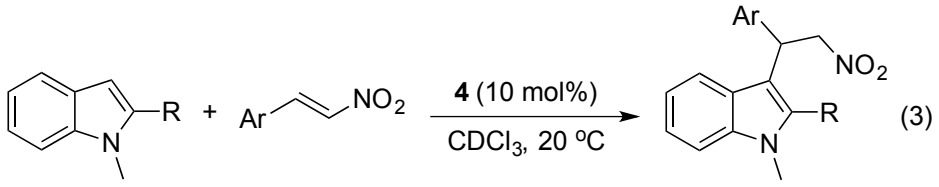


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Table 3. Substrate Scope for the Catalytic Friedel−Crafts Alkylation of *N*-Methylindoles with Aromatic Nitroalkenes.[a]

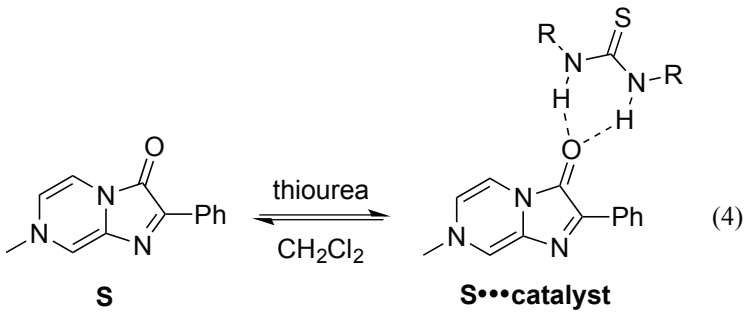
entry	Ar	R	conversion (%)[b]
1	Ph	H	91
2	4-ClC_6H_4	H	96
3	4-BrC_6H_4	H	98
4	4-FC_6H_4	H	88
5	4-MeC_6H_4	H	92
6	4-$OMeC_6H_4$	H	83
7	4-$CF_3C_6H_4$	H	91
8	2-furyl	H	88
9	Ph	Me	86

[a] Standard reaction conditions at room temperature of 0.25 M *N*-methylindole, 0.083 M *trans-β*-nitrostyrene and 10 mol% of **4** were used. [b] Reaction conversions were obtained directly by ^1H NMR without isolation of the product.

addition products efficiently and with excellent conversions in a 20 min time period regardless of the electron donating or withdrawing ability of the substituent. Incorporation of a methyl group at C2 in *N*-methylindole (i.e., R = CH_3 in eq. 3) also only had a small effect. These perfectly atom economical transformations are clean processes and the products are robust compounds that can be readily purified by column chromatography. All of this suggests that this reaction can be successfully scaled up, and this was accomplished by increasing the reaction scale by a factor of 10. That is, after allowing *N*-methylindole and *trans*-β-nitrostyrene to react in the presence of 10 mol% of **10** for 0.5 hr, 146 mg of the product was isolated after chromatography in an essentially quantitative yield.

All of the *N*-alkylpyridinium ion containing thiourea salts examined in this work are substantially more active catalysts for the Friedel−Crafts alkylation of *N*-methylindole with *trans*-β-nitrostyrene than *N*,*N*′-diphenyl- and Schreiner's thioureas with the exception of **5**. This latter charged salt has two deactivating hydrogen bond accepting trifluoromethylsulfonate counteranions, and is the only *N*-alkylpyridinium substituted thiourea that was used without a non-coordinating tetraarylborate anion. To rationalize the entire reactivity order, we turned to Kozlowski's UV−Vis spectroscopy approach.[13] This method is carried out in CH_2Cl_2, a nonpolar solvent in which our catalysts operate, and a common medium for hydrogen bond catalysis studies. In contrast, pK_a's of organic compounds are usually measured in DMSO, which is an unsuitable solvent for most catalytic investigations due to its strong hydrogen bond accepting ability.

A series of titrations of a colorimetric sensor **S** (red) with thioureas **1-10** were carried out. Two hydrogen bonds to the carbonyl group can be formed in the bound sensor···thiourea complex (eq. 4), and blue shifts in the UV-Vis spectra and visible color changes to the naked eye



(4)

were observed (Figure S3). That is, upon adding increasing concentrations of **1-10**, the observed values for λ_{max} decreased from the value for **S** (498.6 nm) to lower wavelengths. This hypsochromic shift continued until an endpoint was reached where the sensor fully exists as the bound complex, **S**···thiourea. This is illustrated for the data with **4** (Figures 6 and S4), and from the resulting titration curve the equilibrium association constant can be determined.[13] The measured values along with λ_{max} for the bound complexes, and the relative rates for the Friedel-Crafts reaction of *N*-methylindole with *trans*-β-nitrostyrene catalyzed by **1-10**, are given in Table 4.[17,21] A Job plot was also carried out for **6** to verify the proposed (entropically favored and expected) 1:1 binding stoichiometry (Figure S5).

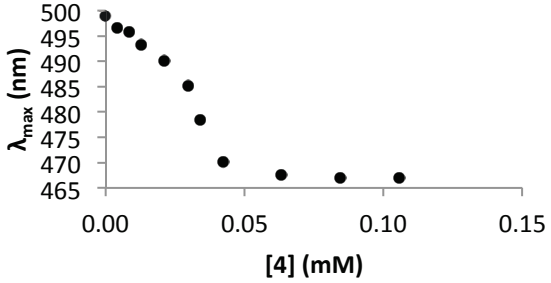


Figure 6. Changes in the observed UV−Vis absorption maxima values upon titrating a 2.22 x 10^{-5} M solution of **S** in CH_2Cl_2 with thiourea **4**.

Table 4. Wavelength Shifts, Equilibrium Association Constants and Catalyzed Relative Rates for the Friedel–Crafts Alkylation of *N*-Methylindole with *trans*-β-Nitrostyrene.[a]

catalyst	λ_{max} (nm)	K (M^{-1})	relative rate
1	495.0	20.0	0.013[a]
2	479.5	1,210	1.0
3	475.5	4,120	6.6
4	467.0	2.08×10^5	250
5	495.6	972	0.020[a]
6	473.5	1.01×10^4	9.5
7	480.8	2,650	3.9
8	470.7	6.41×10^4	7.1
9	472.0	4,260	18
10	468.8	1.02×10^5	230

[a]Background corrected relative rate.

Bound complexes of the sensor with thioureas **1–10** were found to have λ_{max} absorptions of 495.0 to 467.0 nm, and these values correspond to shifts of 3.6 to 31.6 nm relative to **S**. The equilibrium association constants track these changes and span a 10,000-fold range. A plot of the natural logarithm of K versus the change in the reciprocal values of λ_{max} upon complexation of **S** with a thiourea (i.e., $\lambda_{max}(\mathbf{S}\cdots\text{thiourea})^{-1} - \lambda_{max}(\mathbf{S})^{-1}$) is linear (Figure 7). This indicates that the absorption maximum of 7-methyl-2-phenylimidazo[1,2a]pyrazine-3(7H)-one complexed to a thiourea is a good surrogate for the corresponding equilibrium association constant. The only exception is for **5**, which has two triflate counterions that can serve as hydrogen bond acceptors even though this anion is the conjugate base of a strong acid. Interactions of this sort between the thiourea and one or both of the triflate ions would lead one to expect that K should be diminished, and that **5** would display a negative deviation from the line in Figure 7. This is not the case, and

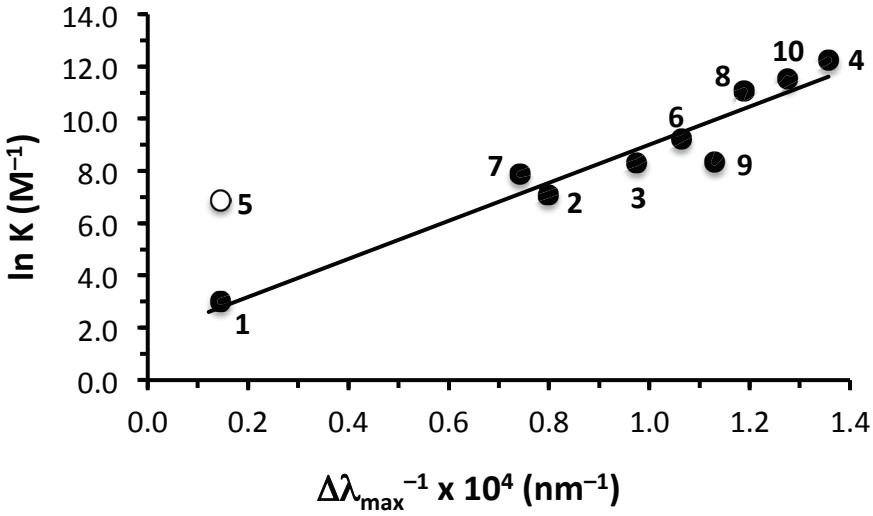


Figure 7. Changes in the reciprocals of the absorption wavelength maxima of **S** and **S**···thiourea compared to the logarithms of the corresponding equilibrium association constants. The equation for the linear least-squares fit of the data is ln K (M^{-1}) = 7.29 x $\Delta\lambda_{max}^{-1}$ (nm^{-1}) + 1.72, r^2 = 0.92, where the value for **5** was omitted from the analysis.

suggests that one or both of the triflate ions are able to energetically interact with **S** in a favorable manner. To assess this possibility, both B3LYP and M06-2X geometry optimizations were carried out with the cc-pVDZ basis set on a single bound conformer structure. The resulting geometries are similar, and as illustrated for the latter case in Figure 8, the two triflate anions

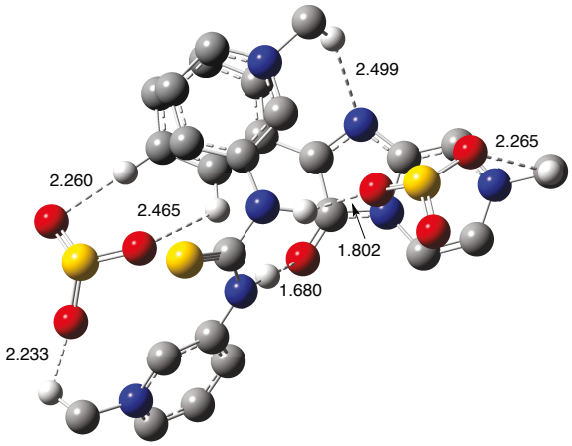


Figure 8. An M06-2X/cc-pVDZ optimized structure of **S**···**5**. Select interactions are illustrated with dashed lines and the given distances are in Angstroms. Both trifluoromethyl groups and the majority of the hydrogen atoms have been omitted for clarity sake.

coordinate with both the thiourea and the sensor via a number of hydrogen bonds.

A plot of the natural logarithm of the relative rates for the thiourea-catalyzed Friedel–Crafts reactions of *N*-methylindole with *trans*-β-nitrostyrene versus $\Delta\lambda_{max}^{-1}$ is also linear (Figure 9). In this case the data for all ten catalysts (**1-10**) fit on the correlation including the result for **5**, the doubly charged salt with two triflate counterions. These relative rates span a sizable range of 10^4 – 10^5, but are well correlated with the UV-Vis spectroscopic changes induced by hydrogen bond formation. Non-charged thioureas, mono- and bis-charged derivatives with two different noncoordinating tetraarylborate counteranions, and a deactivated species with two hydrogen bond accepting triflate anions are all well behaved with respect to Kozlowski's spectroscopic approach. Since this methodology is relatively insensitive to water, the requisite sensor can be readily obtained, and micromolar solutions can be used, it is well suited for rapidly screening charged thiourea catalysts.

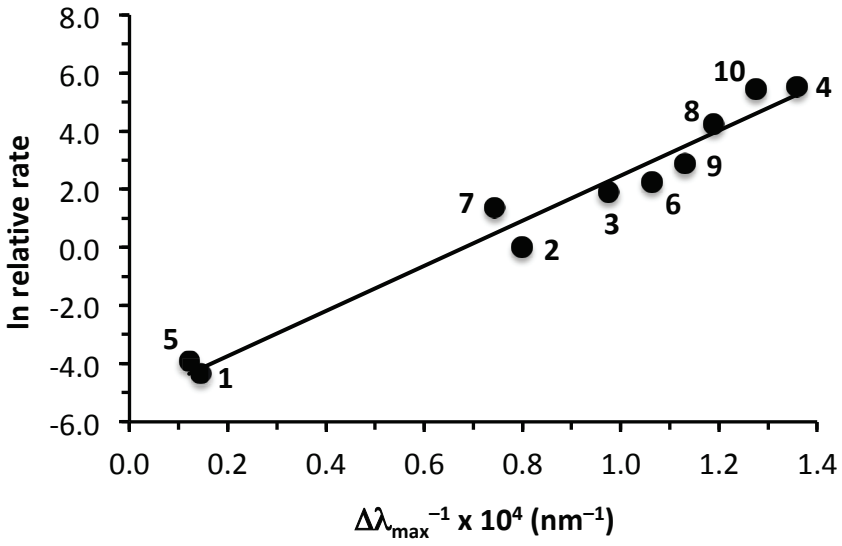


Figure 9. A linear correlation between the logarithm of the relative rate for the transformation given in eq. 1 and $\Delta\lambda_{max}^{-1}$, where the equation of the line obtained by a least-squares fit of the data is ln relative rate = 7.76 x $\Delta\lambda_{max}^{-1}$ (nm^{-1}) – 5.29, $r^2 = 0.97$.

CONCLUSION

A series of electrostatically enhanced thiourea catalysts were prepared and their performance in the Friedel−Crafts alkylation of *N*-methylindoles with *trans*-β-nitroalkenes was evaluated. Reactivity enhancements of 2–3 orders of magnitude were observed relative to Schreiner's thiourea, which for the past 15 years has been widely regarded as the benchmark in this area of organocatalysis. The concept of introducing a non-coordinating positively charged center and a non-interacting counteranion suggests a new strategy for catalyst development. A UV-Vis spectroscopic method developed by Kozlowski et al. can be used to rationalize the catalytic abilities of **1-10**, and should be of value in rapidly screening subsequent derivatives.

Experimental

General. All chemicals were obtained and used as received from Sigma Aldrich, Alfa Aesar and Matrix Scientific except for deuterated solvents which came from Cambridge Isotope Laboratories. Glassware (i.e., flasks, vials, syringes and NMR tubes) was oven-dried before use and reactions were carried out under an argon atmosphere. Uncorrected melting points were obtained with a Uni-Melt apparatus in unsealed tubes. Proton and ^{13}C NMR spectra were acquired with a 400 or 500 MHz instrument and the respective chemical shifts were referenced in ppm as follows: δ 7.26 and 77.2 ($CDCl_3$), 5.32 and 53.8 (CD_2Cl_2), 2.50 and 39.5 (DMSO-d_6), 2.08 (toluene-d_8), and 2.05 and 29.8 (acetone-d_6). IR spectra were recorded with a FT-IR equipped with an ATR source, and high resolution mass spectrometry data were obtained by ESI with a TOF analyzer using methanol solutions and polyethylene glycol as an internal standard. UV−Vis spectra were obtained with a Lambda XLS spectrometer and a 10 mm septum-covered

quartz cell. Catalysts **3**-**4** and their requisite precursors along with related kinetic data were previously reported in a recent communication.[8]

3-Amino-1-(1-octyl)pyridinium triflate. In a 6 dram vial, 50 mg (0.53 mmol) of 3-aminopyridine was dissolved in 1 mL of CH_2Cl_2 and 0.28 g (1.07 mmol) of 1-octyl triflate[22] was added at room temperature. The reaction mixture was allowed to stir overnight before being concentrated under reduced pressure. The resulting residue was washed with 2 mL of pentane and dried under vacuum to afford the product as a yellow oil (0.19 g, 100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.75 (d, J = 5.4 Hz, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.48 (dd, J = 5.9, 8.8 Hz, 1H), 5.81 (s, 2H), 4.28 (t, J = 7.8 Hz, 2H), 1.88 (m, 2H), 1.37 – 1.02 (m, 10H), 0.81 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.0, 130.5, 128.9, 128.1, 127.9, 120.6 (q, $J_{C\text{-}F}$ = 320 Hz), 62.2, 31.7, 31.3, 29.0, 28.9, 26.1, 22.6, 14.1. IR (ATR source): 3349, 3232 cm^{-1}. HRMS-ESI: calcd for $C_{13}H_{23}N_2^+$ $(M - CF_3SO_2^-)^+$ 207.1856, found 207.1856.

1,3-bis-3-(1-Octylpyridylium)thiourea triflate (**5**). In a 6 dram vial under argon, 3-isothiocyanato-1-octylpyridinium triflate (50 mg, 0.13 mmol) was dissolved in 1 mL of CH_2Cl_2 and 3-amino-1-octylpyridinium triflate (45 mg, 0.13 mmol) was added at room temperature. The reaction mixture was allowed to stir overnight and then concentrated under reduced pressure. The resulting residue was washed with 2 mL of pentane and dried under vacuum to afford the product as a pale yellow oil (93 mg, 98%). ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 10.62 (s, 2H), 9.66 (s, 2H), 8.99 (d, J = 5.9 Hz, 2H), 8.74 (d, J = 8.4 Hz, 2H), 8.25 (dd, J = 5.9, 8.4 Hz, 2H), 4.85 (t, J = 7.3 Hz, 4H), 2.14 (m, 4H), 1.45 – 1.24 (m, 20H), 0.85 (t, J = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, $(CD_3)_2CO$) δ 181.5, 141.3, 140.5, 140.4, 128.8, 121.7 (q, $J_{C\text{-}F}$ = 322 Hz), 63.1, 32.3, 31.8, 29.6, 29.5, 26.5, 23.1, 14.2. IR (ATR source): 3446 cm^{-1}. HRMS-ESI: calcd for $C_{27}H_{43}N_4S^+$ $(M - 2CF_3SO_2^- - H^+)^+$ 455.3203, found 455.3203.

1-Methyl-4-(3-phenylthioureido)pyridinium iodide (**6I**). In a 6-dram vial, 60 mg (0.22 mmol) of 4-isothiocyanato-1-methylpyridinium iodide[9] was dissolved in 3 mL of CH_3CN under argon. Aniline (20 μL, 0.22 mmol) was added dropwise and the reaction mixture was allowed to stir overnight at room temperature. A minimal amount of a 1 : 1 mixture of ethyl acetate and pentane was subsequently added (~ 2 mL) and the resulting precipitate was filtered, washed with 5 mL of ethyl acetate and dried under vacuum to afford 40 mg (49%) of **6I** as a yellow solid (mp 186 – 187 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.18 (s, 1H), 11.01 (s, 1H), 8.64 (d, J = 7.4 Hz, 2H), 8.10 (d, J = 6.9 Hz, 2H), 7.53 (d, J = 7.8 Hz, 2H), 7.41 (t, J = 7.8 Hz, 2H), 7.24 (t, J = 7.8 Hz, 1H), 4.14 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 178.4, 152.8, 145.0, 138.1, 128.9, 126.0, 123.9, 115.0, 46.1. IR (ATR source): 3339, 3242 cm^{-1}. HRMS-ESI: calc for $C_{13}H_{14}N_3S^+$ (M – I^-)$^+$ 244.0903, found 244.0900.

1-Octyl-3-(3-phenylthioureido)pyridin-1-ium triflate (**9OTf**). In a 6 dram vial, 3-isothio-cyanato-1-octylpyridinium triflate[8] (50 mg, 0.13 mmol) was dissolved in 1 mL of CH_2Cl_2 and 12 mg (0.13 mmol) of aniline was added at room temperature. The reaction mixture was allowed to stir overnight before being concentrated under reduced pressure. The resulting residue was washed with 2 mL of pentane and dried under vacuum to afford 61 mg (99%) of the product as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.21 (br s, 1H), 9.85 (s, 1H), 9.57 (br s, 1H), 8.60 (d, J = 8.8 Hz, 1H), 8.26 (d, J = 5.4 Hz, 1H), 7.75 (dd, J = 5.9, 8.8 Hz, 1H), 7.56 (d, J = 8.3 Hz, 2H), 7.36 (t, J = 7.8 Hz, 2H), 7.23 (t, J = 7.4 Hz, 1H), 4.40 (t, J = 7.4 Hz, 2H), 1.96 (t, J = 6.4 Hz, 2H), 1.37 – 1.15 (m, 10H), 0.86 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.3, 141.7, 138.0, 137.0, 136.7, 136.4, 128.9, 127.6, 126.6, 124.9, 120.4 (q, $J_{C\text{-}F}$ = 320 Hz), 62.9, 31.7, 31.2, 29.0, 28.9, 26.1, 22.6, 14.2. IR (ATR source): 3273, 3086, 2927, 1497, 1223, 1162, 1026 cm^{-1}. HRMS-ESI: calcd for $C_{20}H_{28}N_3S^+$ (M – $CF_3SO_2^-$)$^+$ 342.1998, found 342.1993.

General Procedure for Preparing Thiourea Catalysts 6–10. Thiourea catalysts **6-10** were prepared from their iodide or triflate salts using our previous reported general procedure.[8,9]

1-Methyl-4-(3-phenylthioureido)pyridinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (**6**). This compound was prepared following the general procedure starting with 0.081 mmol of **6I** and was obtained in a 94% yield (85 mg) as a white solid (mp 60 – 62 °C). ^{1}H NMR (500 MHz, acetone-d_6) δ 10.36 (br s, 1H), 8.77 (d, J = 6.4 Hz, 2H), 8.47 (d, J = 6.9 Hz, 2H), 7.80 (s, 8H), 7.69 (s, 4H), 7.57 (d, J = 6.9 Hz, 2H), 7.44 (t, J = 7.4 Hz, 2H), 7.30 (t, J = 7.4 Hz, 1H), 4.42 (s, 3H), 3.02 (br s, 1H). ^{13}C NMR (126 MHz, acetone-d_6) δ 179.6, 162.5 (q, $^{1}J_{B\text{-}C}$ = 50.5 Hz), 154.6, 146.0, 138.7, 135.5, 130.0 (qq, $^{3}J_{B\text{-}C}$ = 3.0 Hz and $^{2}J_{F\text{-}C}$ = 32.3 Hz), 129.9, 127.5, 125.3, 125.2 (q, $^{1}J_{F\text{-}C}$ = 272 Hz), 118.4, 116.7, 47.2. IR (ATR source): 3405, 3351cm^{-1}. HRMS-ESI: calc for $C_{13}H_{14}N_3S^+$ (M – $C_{32}H_{12}BF_{24}^-$)$^+$ 244.0903, found 244.0909 and calc for $C_{32}H_{12}BF_{24}^-$ (M – $C_{27}H_{44}N_4S^+$)$^-$ 863.0654, found 863.0667.

1-Methyl-3-(3-phenylthioureido)pyridinium tetrakis(pentafluorophenyl)borate (**7**). This compound was prepared following the general procedure starting with 0.067 mmol of 1-methyl-3-(3-phenylthioureido)pyridinium iodide[8] (**3I**) and was obtained in a 96% yield (60 mg) as a white solid (mp 94 – 96 °C). ^{1}H NMR (500 MHz, acetone-d_6) δ 9.89 (s, 2H), 9.61 (s, 1H), 8.83 (d, J = 5.9 Hz, 1H), 8.70 (d, J = 8.3 Hz, 1H), 8.16 (dd, J = 6.4, 8.3 Hz, 1H), 7.52 (d, J = 7.9 Hz, 2H), 7.43 (t, J = 7.4 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 4.64 (s, 3H). ^{13}C NMR (126 MHz, acetone-d_6) δ 181.4, 149.0 (d, J = 250 Hz), 141.6, 141.3, 140.4 (d, J = 194 Hz), 140.0, 138.6, 138.0, 137.0 (d, J = 243 Hz), 130.1, 129.8, 128.1, 127.4, 125.7 (*ipso*-C), 49.4. IR (ATR source): 3356 cm^{-1}. HRMS-ESI: calc for $C_{13}H_{14}N_3S^+$ (M – $C_{24}BF_{20}^-$)$^+$ 244.0903, found 244.0929 and calc for $C_{24}BF_{20}^-$ (M – $C_{13}H_{14}N_3S^+$)$^-$ 679.0426, found 679.0420.

1,3-bis-3-(1-Methylpyridylium)thiourea tetrakis(pentafluorophenyl)borate (**8**). This compound was prepared following the general procedure starting with 0.065 mmol of 1,3-bis-3-(1-methylpyridylium)thiourea iodide[8] (**4I**) and was obtained in a 88% yield (92 mg) as a white solid (mp 115 – 117 °C). ^{1}H NMR (500 MHz, acetone-d_6) δ 10.72 (s, 2H), 9.61 (s, 2H), 8.96 (d, J = 5.9 Hz, 2H), 8.82 (d, J = 8.3 Hz, 2H), 8.28 (dd, J = 6.4, 8.3 Hz, 2H), 4.68 (s, 6H). ^{13}C NMR (126 MHz, acetone-d_6) δ 182.2, 149.0 (d, J = 243 Hz), 141.9 (d, J = 194 Hz), 140.7, 140.2, 140.1, 140.0, 139.9, 137.0 (d, J = 247 Hz), 128.7 (*ipso*-C), 49.6. IR (ATR source): 3305 cm^{-1}. HRMS-ESI: calc for $C_{13}H_{15}N_4S^+$ $(M - H - 2C_{24}BF_{20}^-)^+$ 259.1007, found 259.1015 and calc for $C_{24}BF_{20}^-$ $(M - C_{13}H_{15}N_4S^+)^-$ 679.0426, found 679.0431.

1-Octyl-3-(3-phenylthioureido)pyridin-1-ium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (**9**). This compound was prepared following the general procedure starting with 0.17 mmol of 1-octyl-3-(3-phenylthioureido)pyridin-1-ium triflate[9] (**9-OTf**) and was obtained in a 100% yield (0.21 g) as a yellow oil. ^{1}H NMR (500 MHz, acetone-d_6) δ 9.94 (s, 1H), 9.85 (s, 1H), 9.75 (s, 1H), 8.91 (d, J = 5.9 Hz, 1H), 8.65 (d, J = 8.8 Hz, 1H), 8.20 (dd, J = 6.4, 8.3 Hz, 1H), 7.83 (s, 8H), 7.70 (s, 4H), 7.54 (d, J = 8.3 Hz, 2H), 7.44 (t, J = 7.8 Hz, 2H), 7.30 (t, J = 7.4 Hz, 1H), 4.87 (t, J = 7.4 Hz, 2H), 2.17 (m, 2H), 1.50-1.27 (m, 10H), 0.84 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, acetone-d_6) δ 181.6, 162.6 (q, $^{1}J_{B\text{-}C}$ = 50.5 Hz), 141.8, 141.2, 140.1, 139.7, 138.6, 135.5, 130.1, 130.0 (qq, $^{3}J_{B\text{-}C}$ = 3.0 Hz and $^{2}J_{F\text{-}C}$ = 32.3 Hz), 128.5, 127.4, 125.8, 125.4 (q, $^{1}J_{F\text{-}C}$ = 272 Hz), 118.4, 83.1, 32.4, 32.0, 29.7, 29.6, 26.6, 23.2, 14.2. IR (ATR source): 3415 cm^{-1}. HRMS-ESI: calc for $C_{20}H_{28}N_3S^+$ $(M - C_{32}H_{12}BF_{24}^-)^+$ 342.1998, found 342.2006 and calc for $C_{32}H_{12}BF_{24}^-$ $(M - C_{20}H_{28}N_3S^+)^-$ 863.0654, found 863.0679.

1,3-bis-3-(1-Octylpyridylium)thiourea tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (**10**). This compound was prepared following the general procedure starting with 0.080 mmol of 1,3-bis-3-

(1-octylpyridylium)thiourea triflate[9] (**5**) and was obtained in a 100% yield (0.17 g) as a yellow oil. ^{1}H NMR (500 MHz, acetone-d_6) δ 10.65 (s, 2H), 9.74 (s, 2H), 9.04 (d, J = 5.4 Hz, 2H), 8.74 (d, J = 8.8 Hz, 2H), 8.29 (dd, J = 5.4, 8.8 Hz, 2H), 7.80 (s, 16H), 7.66 (s, 8H), 4.89 (t, J = 6.8 Hz, 4H), 2.14 (m, 4H), 1.46-1.22 (m, 20H), 0.79 (t, J = 6.4 Hz, 6H). ^{13}C NMR (126 MHz, acetone-d_6) δ 182.8, 162.6 (q, $^{1}J_{B\text{-}C}$ = 49.4 Hz), 141.8, 141.3, 140.7, 140.7, 135.6, 130.0 (qq, $^{3}J_{B\text{-}C}$ = 3.0 Hz and $^{2}J_{F\text{-}C}$ = 31.3 Hz), 129.2, 125.4 (q, $^{1}J_{F\text{-}C}$ = 273 Hz), 118.4, 63.4, 32.4, 32.1, 30.5, 29.7, 26.7, 23.2, 14.2. IR (ATR source): 3285 cm^{-1}. HRMS-ESI: calc for $C_{27}H_{43}N_4S^+$ ($M - H^+ - 2C_{32}H_{12}BF_{24}^-$)$^+$ 455.3203, found 455.3194 and calc for $C_{32}H_{12}BF_{24}^-$ ($M - C_{27}H_{44}N_4S^+$)$^-$ 863.0654, found 863.0660.

Binding Determination. Two stock solutions were prepared in 1 mL volumetric flasks with CD_2Cl_2 as the solvent. The first (*A*) contained 13.4 mg of thiourea **8** and had a concentration of 8.3 mM while the second (*B*) was made up with 75.8 mg of *trans*-β-nitrostyrene (508 mM) and the same amount of **8** as in *A*. A NMR tube was filled with 0.6 mL of *A* and an initial proton spectrum was recorded. A series of additions of *B* were then carried out, the NMR tube was inverted twice each time to ensure good mixing, and spectra were acquired to monitor the titration. The chemical shifts of the two most downfield signals were used to obtain the equilibrium binding constant via a non-linear fit of the data using the freely available BindFit v0.5 software package (http://app.supramolecular.org/bindfit).[17] *trans*-β-Nitrostyrene concentrations, the observed chemical shifts and those obtained from the resulting non-linear fit are provided in Table S2.

General Procedure for Friedel–Crafts reactions. In oven-dried NMR tubes, 7.5 mg (0.050 mmol) of *trans*-ß-nitrostyrene, 19 μL (0.15 mmol) of *N*-methylindole and the desired amount of catalyst were mixed in 0.6 mL of $CDCl_3$ (or an alternative solvent) at room temperature under an

inert atmosphere. Proton NMR spectra were recorded to monitor reaction progress using signals for *trans*-ß-nitrostyrene (8.04 ppm) and the alkylation product (5.23 ppm). Reaction rate data are given in Table S1 and Figure S1.

Computations. Calcuations were carried out with Gaussian 16[23] on computers at the Minnesota Supercomputer Institute for Advanced Computational Research. Full geometry optimizations with the B3LYP[24] and M06-2X[25] functionals and the cc-pVDZ[26] basis set were performed on a single conformer of the **S**···**5** complex.

Supporting Information Available: Kinetic, titration and UV-Vis data along with NMR spectra, computed xyz Cartesian coordinates, and the complete citation to ref. 23. This material is available free of charge via the internet at http://pubs.acs.org.

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