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Enantioselective Friedel-Crafts Alkylation between Nitroalkenes and Indoles Catalyzed by Charge Activated Thiourea Organocatalysts

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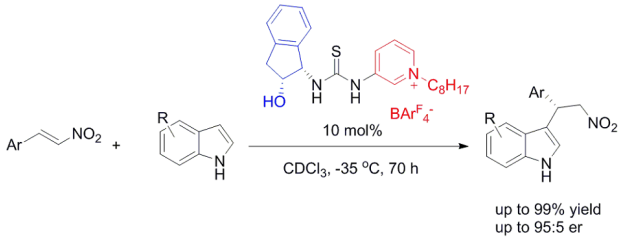
Table of Content Graphic



ABSTRACT

A series of methylated and octylated pyridinium and quinolinium containing thiourea salts with a chiral 2-indanol substituent are reported. These organocatalysts are positively charged analogs of privileged bis(3,5-trifluoromethyl)phenyl substituted thioureas, and are found to be much more active catalysts despite the absence of an additional hydrogen bond donor or acceptor site (i.e., the presence of a heteroatom-hydrogen or heteroatom). Friedel-Crafts reactions of *trans*-β-nitorostyrenes with indoles are examined and good yields and enantioselectivities are obtained. Mechanistic studies indicate that this is a second-order transformation under the employed conditions, and are consistent with the dimer of the thiourea being the active catalyst. Charged organocatalysts, consequently, represent an attractive design strategy for catalyst development.

INTRODUCTION

Small molecule metal-free organocatalysts are commonly exploited in carrying out a wide variety of chemical transformations.[1] Over the past two decades asymmetric control of these reactions has emerged as one of the most vibrant and challenging research areas in organic synthesis.[2] Hydrogen bond interactions are commonly used in this regard and play a key role in lowering activation barriers and organizing three-dimensional transition state geometries.[3] Thioureas with their two N–H hydrogen bond donating sites have proven to be a particularly successful functional group motif and continue to be extensively investigated.[4]

Reaction rates often correlate with organocatalyst acidities. That is, faster transformations typically occur with more acidic species of a given structural type.[5] Electron withdrawing groups are routinely employed because of this, and no substituent has been exploited more than a 3,5-bis(trifluoromethyl)phenyl ring. Doubly activated *N*,*N*′-bis(3,5-bis(trifluoromethyl)phenyl)-thiourea [$(3,5\text{-}(CF_3)_2C_6H_3NH)_2CS$, **1**] is commonly referred to as Schreiner's thiourea and represents a milestone in the development of hydrogen bond donating organocatalysts.[6] Its greater catalytic ability leads to faster transformations and has been attributed to an enhanced acidity due to the presence of four electron withdrawing trifluoromethyl groups and two weak intramolecular C–H···S hydrogen bonds. The incorporation of the CF_3 groups also stabilize the reactive *Z*,*Z*-conformer, increase the structural rigidity and enhance the solubility of the thiourea in non-polar solvents.[7] Replacement of one of the 3,5-bis(trifluoromethyl)phenyl rings with a chiral moiety leads to a versatile platform for catalyst design and extensive efforts have been reported in this regard.[8]

Inspired by the many remarkable studies carried out with thiourea catalysts, we recently communicated the synthesis and reactivity of charge-containing derivatives with one or two cationic *N*-methylpyridinium ion centers and an appropriate noncoordinating anionic counterion (**2** and **3**, Figure 1).[9] These achiral compounds were found to lead to rate enhancements of one to

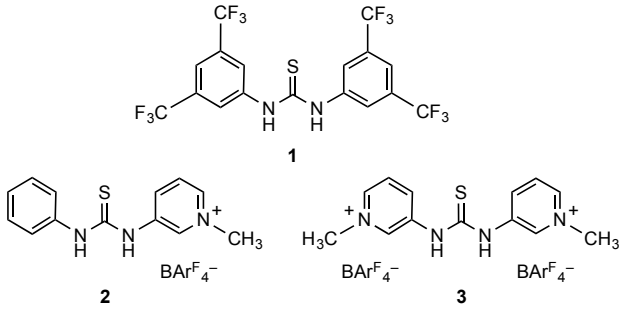
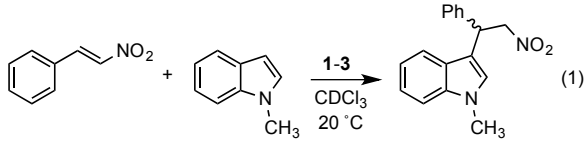
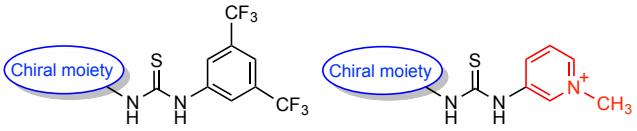


Figure 1. Schreiner's thiourea (**1**) and previously studied pyridinium ion containing analogs (**2** and **3**), where $BAr^{F}_{4}^{-} = (3,5\text{-}(CF_3)_2C_6H_3)_4B^-$.

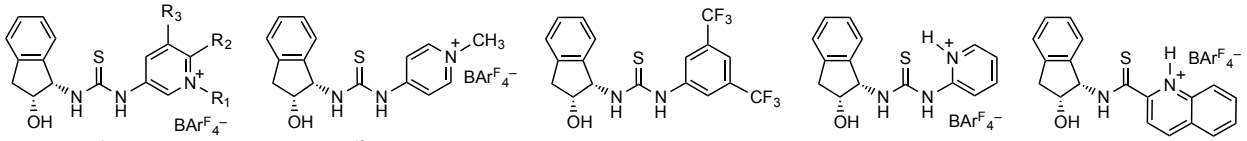
three orders of magnitude relative to Schreiner's thiourea in several organic transformations without altering the binding motif or introducing an additional N–H or O–H hydrogen bond donating site.[10,11] For example, the reaction of *trans*-β-nitrostyrene with *N*-methylindole (eq. 1) was found to have a half-life of 29 hours when 10 mol% of **1** was used as the catalyst whereas this was reduced to 4.5 hours and 4.3 minutes with **2** and **3**, respectively. Given that the incorporation of a single charged center outperformed the presence of four trifluoromethyl groups, it seemed worthwhile to explore chiral variants of **2** (Scheme 1).





Scheme 1. New chiral design strategy for introducing a charged substituent to enhance the acidity and reactivity of a thiourea catalyst in nonpolar media.

A wealth of chiral thioureas with a 3,5-bis(trifluoromethyl)phenyl substituent have been developed but relatively few have an acidic group on the chiral moiety.[12] As these bifunctional species are expected to be compatible with the strategy illustrated in Scheme 1 (i.e., more acidic thioureas), we focused our attention on (1*S*, 2*R*)-1-amino-2-indanol derivatives (**4**, Scheme 2). The enantioselective Friedel-Crafts alkylation of indoles with *trans*-β-nitroalkenes was chosen as the test platform because it is a fundamental transformation that leads to increased molecular complexity via the formation of a new carbon-carbon bond. This reaction is also a perfectly atom economical process that affords valuable pharmaceutical and biology-based intermediates.[13,14] Moreover, this transformation has been frequently used to test new Brønsted acids and hydrogen bond catalysts, and was employed by both Herrera et al.[8a,15] and Ganesh and Seidel[11f] to investigate **5–7**.

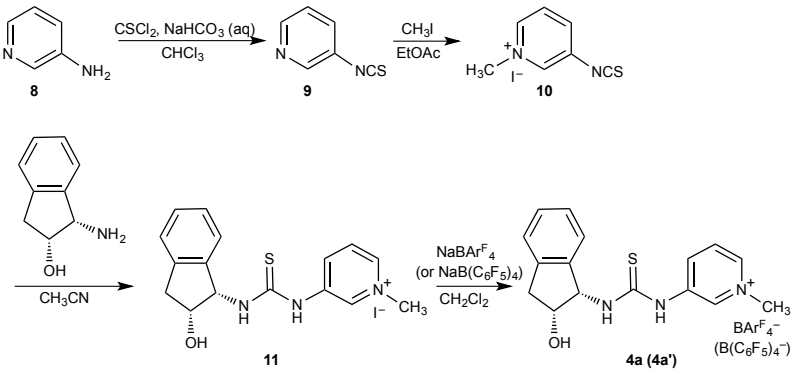


a: R_1 = CH_3, R_2, R_3 = H
b: R_1 = 1-C_8H_{17}, R_2, R_3 = H
c: R_1 = CH_3, R_2, R_3 = CH=CHCH=CH
d: R_1 = 1-C_8H_{17}, R_2, R_3 = CH=CHCH=CH
e: R_1 = CH_3, R_2 = H, R_3 = Ph
f: R_1 = 1-C_8H_{17}, R_2 = H, R_3 = Ph
g: R_1 = CH_3, R_2 = H, R_3 = 4-*t*-BuPh

Scheme 2. Chiral thioureas examined in this work (**4-5**) and previously reported (**6-7**).

RESULTS AND DISCUSSION

A series of chiral thiourea hydrogen bond catalysts **4a–4h** bearing an *N*-alkylpyridinium ion center and a 2-indanol substituent were synthesized starting from commercially available 3- or 4-aminopyridines. These compounds were formed in a similar fashion as illustrated for **4a** in Scheme 3 by first converting the aminopyridine to its corresponding isothiocyanate. Alkylation with methyl iodide or octyl triflate was then followed by reaction with (1*S*, 2*R*)-1-amino-2-indanol to afford the thiourea precatalyst (i.e., the iodide or triflate salt). Substitution of the counterion to the weakly coordinating tetrakis(3,5-bis(trifluoromethyl)phenyl)borate anion ($BAr^F_4{}^-$) was carried out to give the desired thiourea catalysts except in one instance when a tetrakis(pentafluorophenyl)borate ($B(C_6F_5)_4{}^-$) salt **4a'** was formed; this compound differs from **4a** only in the tetrakis(aryl)borate counterion.



Scheme 3. Synthetic route for the formation of charge-containing thiourea catalysts **4a** and **4a'**.

To assess the catalytic performance of these charged thiourea salts, the Friedel-Crafts alkylation of indole with *trans*-β-nitrostyrene and 10 mol% of **4a** was initially examined under various conditions (Table 1). At room temperature in chloroform-*d* this transformation went to completion over the course of two days with a modest enantiomeric ratio (*er*) of 75 : 25 (entry 1).[16]

Table 1. Evaluation of 4a Under Various Conditions.[a]

entry	cat. loading (mol%)	solvent	temp. (°C)	t (h)	Conversion (%)[b]	*er*[c]
1	10	$CDCl_3$	20	49	100	75 : 25
2	10	CD_2Cl_2	20	44	81	74 : 26
3	10	$C_6D_5CD_3$	20	45	66	70 : 30
4	10	$CDCl_3$	0	43	93	86 : 14
5	10	$CDCl_3$	-20	48	91	89 : 11
6	10	$CDCl_3$	-35	48	76	91 : 9
7	10	$CDCl_3$	-45	48	37	92 : 8
8	10	CD_3CN	-35	48	4	-
9[d]	10	$CDCl_3$	-35	425	38	85 : 15
10[e]	10	$CDCl_3$	-35	48	52	88 : 12
11[f]	10	$CDCl_3$	-35	48	49	90 : 10
12[g]	10	$CDCl_3$	-35	48	trace	-
13[h]	10	$CDCl_3$	-35	48	59	91 : 9
14[i]	10	$CDCl_3$	-35	48	52 (54)	87 : 13 (77 : 23)
15	20	$CDCl_3$	-35	29	91	90 : 10
16	5	$CDCl_3$	-35	51	42	89 : 11
17	1	$CDCl_3$	-35	72	23	90 : 10

[a]Unless otherwise indicated, these reactions were carried out with 0.05 mmol of *trans*-β-nitrostyrene and 3 equivalents of indole with the specified amount of catalyst in 0.6 mL of solvent. [b]Conversions were determined by ^{1}H NMR analysis of crude reaction mixtures. [c]Enantiomeric ratios were determined by chiral HPLC. [d]This reaction was carried out with 0.017 mmol of *trans*-β-nitrostyrene (i.e., ~3 x more dilute than in entries 1-8). [e]1.5 equivalents of indole were used. [f]$Bu_4NBAr^F_4$ (5 mol%) was added. [g]*p*-Toluenesulfonic acid (10 mol%) was added. [h]$Et_3NHBAr^F_4$ (10 mol%) was added. [i]1.5 mg of 3 or 4 Å molecular sieves were utilized; the latter values are given in parentheses.

Dichloromethane-d_2 and toluene-d_8 were also used (entries 2 and 3) but this led to lower product conversions and small decreases in the observed selectivities. Improved *er*s up to 92 : 8 were obtained by lowering the temperature to -45 °C (entries 4-7), but since nearly the same

selectivity was observed at -35 ˚C (i.e., 91 : 9) and the reaction is noticeably faster (i.e., 37% vs 76% at t = 48 h), the higher temperature was adopted for our standard conditions. A change in the solvent to acetonitrile-d_3 led to a conversion of < 5% (entry 8), and this can be attributed to the polar nature of CD_3CN and its ability to serve as a hydrogen bond acceptor with the thiourea catalyst. Concentrations and the *trans*-β-nitrostyrene/indole ratio were also varied (entries 9 and 10) but this slowed down the transformation without improving the stereoselectivity.

Several additives influence on the reaction were examined as well (entries 11-14). Added salt in the form of $Bu_4NBAr^F_4$ (5 mol%) reduced the amount of product formed over a 48 h reaction time period but had little, if any, effect on the *er*. External acids can activate thioureas as reported by Herrera et al.,[15] but in this case the addition of 10 mol% *p*-toluenesulfonic acid had the opposite effect and only a trace of product was observed. We attribute this catalyst deactivation to protonation of the thiourea or indole and coordination of the resulting tosylate anion with **4a** (i.e., hydrogen bonding to OTs^- is detrimental). The use of 3 and 4 Å molecular sieves to remove adventitious water are also disadvantageous with regard to yield and stereoselectivity.[17] Here too, hydrogen bonding between the oxygen atoms of the molecular sieves (i.e., an aluminosilicate) and the thiourea catalyst is apt to be the cause. Finally, triethylammonium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate has no effect on the *er* but does lower the yield from 76% to 59%.

Catalytic loadings from 1–20 mol% were examined (entries 6 and 15-17) but have no noticeable impact on the enantioselectivity of the Friedel-Crafts reaction. Kinetic studies revealed second-order behavior, first-order in both indole and *trans*-β-nitrostyrene as one might expect.[18] Rate constants and the first half-life's of the limiting reagent (*trans*-β-nitrostyrene) are given in Table 2. The latter values decrease with the amount of catalyst added and span from 140 to 7.0

Table 2. Reaction Rate Constants and Half-life's as a Function of Catalyst Loading.[a]

entry	cat. loading (mol%)	k ($M^{-1}h^{-1}$)	$t_{1/2}$ (h)
1	1	0.022	140
2	5	0.059	52
3	10	0.15	21
4	20	0.44	7.0

[a]Standard reaction conditions of ~0.083 M *trans*-β-nitrostyrene, 0.25 M indole and the indicated amount of catalyst (**4a)** in $CDCl_3$ at -35 ˚C were employed. The first half-life ($t_{1/2}$) of the limiting reagent (i.e., the styrene) is given since this value changes as the reaction proceeds.

hours at -35 ˚C in going from 1 to 20 mol% of **4a**. A plot of the second-order rate constants versus the square of the catalyst mol% is linear (Figure 2), consistent with previous findings and suggests that the active catalytic species of the thiourea is dimeric.[9,19] To assess this further, the ^{1}H NMR spectra of **4a** were recorded from 5.0 to 20.0 mM and both NH signals were found to move downfield linearly with increasing concentration (Table 3). This is consistent with a rapidly occurring monomer/dimer equilibrium and suggests that the association constant is small and the resting state for the catalyst is largely monomeric. It also led us to propose the catalytic cycle illustrated in Scheme 4.[20]

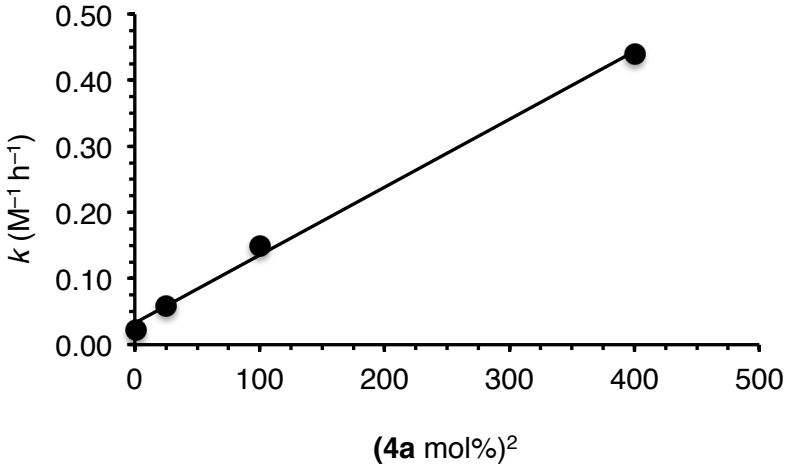
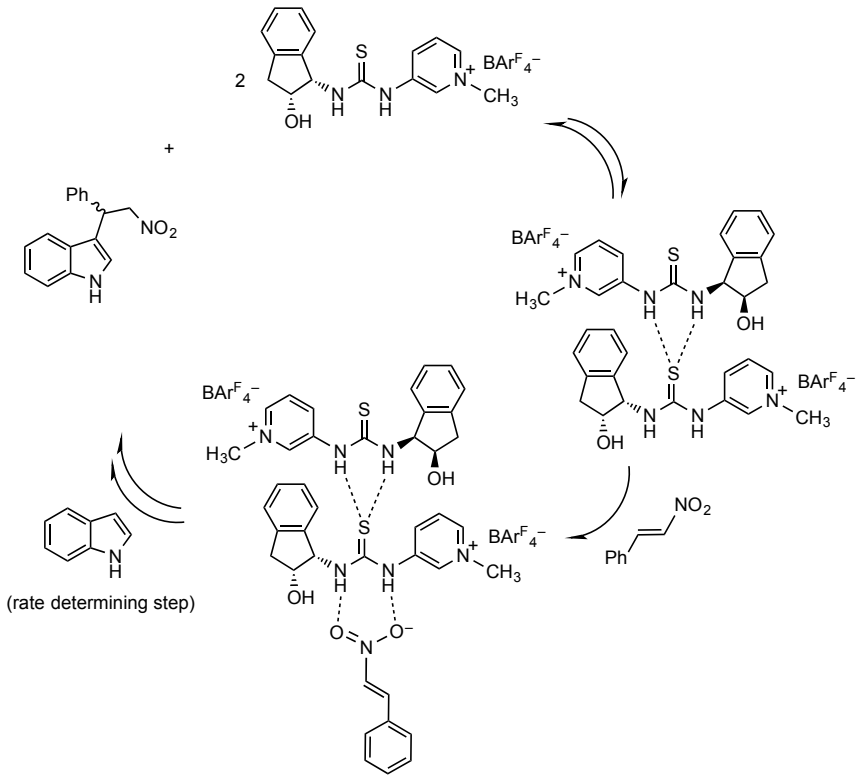


Figure 2. A plot of second-order Friedel-Crafts alkylation rate constants versus the square of the catalyst mol%; a least squares fit of the data affords: k (M^{-1} h^{-1}) = 0.00103 x (**4a** mol%)^2 + 0.33, r^2 = 0.997.

Table 3. Dilution ^{1}H NMR Data for 4a at Room Temperature in $CDCl_3$.[a]

[**4a**] mM	δNH_1 (ppm)	δNH_2 (ppm)	$\Delta\delta NH_2$(ppm)
5.0	10.15	9.01	0.29
6.7	10.15	9.07	0.23
10	10.17	9.14	0.16
20	10.18	9.30	0.00

[a]Presumably NH_1 and NH_2 in **4a** are attached to the pyridinium and indanol rings, respectively. A plot of $\Delta\delta NH_2$ vs [**4a**] is linear; $\Delta\delta NH_2$ (ppm) = -0.0185 [**4a**] + 0.363, r^2 = 0.982.



Scheme 4. Proposed catalytic cycle for the Friedel-Crafts alkylation of indole with *trans*-β-nitrostyrene.

To try and gain a better understanding of the structure-reactivity and selectivity correlation in this enantioseletive Friedel-Crafts alkylation,[21] a series of modified catalyst structures **4a**–**4h** and **4a'** were examined.[22] Variations in the achiral positively charged ring structure, the alkyl group attached to the aromatic nitrogen atom, and the weakly coordinating counterion were explored. Screening results for these thiourea catalysts at –35 ˚C with a 10 mol% catalyst loading in $CDCl_3$ are summarized in Table 4. The reaction conversions were found to vary widely (i.e., 23% (71 h) to 91% (50 h)) whereas the stereoselectivies spanned a narrow range with *er*s of 88 : 12 to 93 : 7. For the pyridinium ions, substitution of a methyl group with a larger and more flexible 1-octyl chain at the formally charged nitrogen center led to a small increase in the *er*s from 91 : 9 to 93 : 7 (entries 1 vs 2 and 5 vs 6) but larger decreases in the reaction rates. Methylated quinolinium ion **4c** (entry 3) with an expanded π-system and a larger ring system behaved similarly to the

Table 4. Screening Results for the Friedel-Crafts Alkylation of *trans*-β-Nitrostyrene with Indole Using Catalysts 4a-h, 4a', and 5.[a]

entry	catalyst	*t* (h)	conversion (%)[b]	*er*[c]
1	**4a**	48	76	91 : 9
2	**4b**	48	41	93 : 7
3	**4c**	49	48	93 : 7
4	**4d**	71	23	88 : 12
5	**4e**	48	83	91 : 9
6	**4f**	46	70	93 : 7
7	**4g**	46	41	91 : 9
8	**4h**	50	91	89 : 11
9	**4a'**	45	61	89 : 11
10	**5**	48	trace	–

[a]Standard reaction conditions of ~0.083 M *trans*-β-nitrostyrene and 0.25 M indole were employed. [b]Conversions were determined by ^{1}H NMR on crude reaction mixtures. [c]Enantiomeric ratios were determined by chiral HPLC.

octylated pyridinium ion **4b**, but a combination of these two design features (i.e., the larger quinoline ring and an octyl substituent) in **4d** led to the smallest reaction conversion and stereoselectivity (entry 4). Incorporation of a phenyl substituent at the 5-position of the pyridinium ion ring in **4a** and **4b** to afford **4e** and **4f**, interestingly, improved the reaction rate without affecting the stereoselectivity (entries 5 and 6). If the para hydrogen on the phenyl ring of **4e** is replaced by a *tert*-butyl group to afford **4g**, then the reaction conversion is reduced significantly but the *er* is unaffected (entry 7). The catalyst **4h** with a *para*-pyridinium ion center proved to be the most efficient catalyst tested but among the least selective (*er* = 89 : 11, entry 8). Conjugation of the formally charged center with one of the thiourea NH groups presumably makes this derivative the most acidic one studied and accounts for its enhanced reactivity. Finally, replacing the weakly coordinating $BAr^{F}_{4}{}^{-}$ counterion in **4a** with $(C_6F_5)_4B^-$ to afford **4a'** led to a lower product conversion and *er* value (entry 9).

All of the *N*-alkylated positively charged catalysts noted above can be compared to the performance of **5**, an analogous non-charged thiourea with a privileged 3,5-bis(trifluoromethyl)-phenyl substituent. This latter catalyst is at least one to two orders of magnitude less effective than **4a–4h** and **4a'** under the employed reaction conditions as only a trace (< 5%) of the product was observed. Excellent results with catalyst **5** previously have been reported[8a&d] but these reactions were carried out at a higher temperature (–25 vs –35 ˚C) with a larger catalyst loading (20 vs 10 mol%) and at significantly higher reaction concentrations (0.08 vs 0.0083 M catalyst, 0.40 vs 0.083 M *trans*-β-nitrostyrene and 0.60 vs 0.25 M indole). It is not surprising, consequently, that little product conversion with **5** was observed under our reaction conditions. Similar results to ours were obtained by Ganesh and Seidel with **6** (a protonated 2-pyridine containing thiourea) and somewhat greater stereoselectivities were observed with **7**, a related

quinolinium thioamide catalyst.[11f] All of these findings reveal the advantage of charged catalysts, and are in accord with our earlier reports on achiral thioureas and phosphoric acids.[9,10]

To try and further improve the reaction efficiency, several increased reactant concentrations and altered relative ratios were examined with **4b**, **4c**, and **4f**, the three most selective catalysts previously identified (Table 5). This was done in part because we worried that by varying the

Table 5. Results for Catalyzed Friedel-Crafts Alkylations at -35 ˚C Using 4b, 4c or 4f and Varying Substrate Concentrations After 48 h.[a]

entry	Concentration (M^{-1})		catalyst (10 mol%)		
	[βNS][b]	[indole]	**4b**	**4c**	**4f**
1	0.083	0.25	41 (93 : 7)[c]	48 (93 : 7)	70 (93 : 7)[d]
2	0.17	0.25	56 (90 : 10)	45 (92 : 8)	73 (92 : 8)
3	0.25	0.375	60 (95 : 5)	58 (92 : 8)	81 (92 : 8)
4	0.25	0.75	99 (92 : 8)[e]	88 (91 : 9)	91 (92 : 8)

[a]Reactant conversions were determined by ^{1}H NMR of the crude reaction mixtures and the enantiomeric ratios were measured by chiral HPLC. [b]βNS = *trans*-β-nitrostyrene. [c]*t*= 49 h. [d]*t*= 46 h. [e]*t*= 72 h.

substrate concentrations the overall polarity of the medium would be perturbed since $CDCl_3$ is a low-polarity solvent, and the stereoselectivity might be negatively impacted. This concern was not born out in that all three catalysts gave good enantiomeric ratios and there is little variation with substrate concentration over the range that was examined. Since **4b** led to the highest *er* (95 : 5), this catalyst and the reactant concentrations that led to this result were adopted for examining the scope of this transformation.

Friedel-Crafts alkylations of a series of substituted *trans*-β-nitroalkenes and indoles (eq 2) were found to afford high yields and good enantioselectivities (Table 6). Substituents on the aromatic ring of the nitrostyrene had relatively little impact upon the reaction rate or the *er*

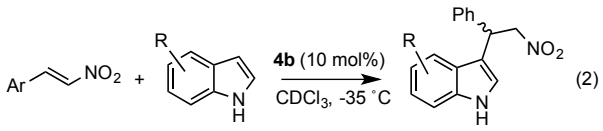


Table 6. Reaction Scope for Friedel-Crafts Alkylations Catalyzed by 4b at -35 ˚C Using Substituted *trans*-β-Nitroalkenes and Indoles as Illustrated in Eq. 2.[a]

entry	Ar	R	*t* (h)	Yield[b]	*er*[c]
1	Ph	H	71	76	93 : 7
2	Ph	5-OMe	70	99	91 : 9
3	Ph	6-OMe	70 (5 d)	99 (99)	95 : 5 (92 : 8)[d]
4	Ph	5-Cl	72	35	92 : 8
5	Ph	6-Cl	72	32	89 : 11
6	4-MeC_6H_4	H	70	83	92 : 8
7	2-ClC_6H_4	H	72	91	89 : 11
8	3-BrC_6H_4	H	72	85	92 : 8

[a]Standard conditions of 10 mol% catalyst, 0.083 M *trans*-β-nitrostyrene and 0.25 M indole were used. [b]Determined by ^{1}H NMR of the crude reaction mixtures. [c]Measurements were carried out using chiral HPLC. [d]Parenthetical values are for a larger scale reaction with 1.5 mmol of *trans*-β-nitrostyrene (220 mg), 2.25 mmol of 6-methoxyindole (330 mg), 10 mol% **4b** and 0.075 mmol (12 mg) of hexamethylbenzene as an internal standard in 6.0 mL of $CHCl_3$ at –35 ˚C. Recycled catalyst on ~1/3 of this larger reaction scale gave an 85% yield after 47 h with a 91 : 9 *er*.

whereas incorporation of an electron donating methoxy group or an electron withdrawing chlorine atom on to the indole enhanced and retarded the reactivity, respectively. The stereoselectivity, however, was only slightly perturbed and gave good results in each case. A 30 times larger scale reaction under similar conditions was also carried out and gave similar results (parenthetical values in entry 3). The catalyst can also be recovered and reused with little or no falloff in activity and selectivity.

CONCLUSION

Asymmetric Friedel-Crafts alkylations of *trans*-β-nitrostyrenes with indoles are promoted by non-protonated positively charged thiourea catalysts (i.e., **4**). These atom economical transformations add molecular complexity via carbon-carbon bond formation in good yields and enantioselectivities. Mechanistic studies reveal a first-order dependence on both reactants and second-order behavior of the catalyst under the employed reaction conditions. These results are consistent with the dimer of the thiourea being the active catalyst and lead to some sensitivity to sterics in **4** on the yield, whereas the enantiomeric ratios are relatively constant. Incorporation of a charged center and the use of salts with non-interactive counteranions as a means of activating catalysts without introducing new N–H or O–H hydrogen bond donating sites offers a promising avenue for catalyst development. It also suggests a method for improving existing catalytic platforms by replacing the privileged 3,5-bis(trifluoromethyl)phenyl substituent with a charged group.

Experimental

General. Commercially obtained chemicals were used as received from Sigma Aldrich and Alfa Aesar except for tetrakis(3,5-bis(trifluoromethyl)phenyl)borate ($NaBAr^F_4$) and deuterated solvents. These latter materials came from Matrix Scientific and Cambridge Isotope Laboratories, respectively. Oven-dried glassware (i.e., flasks, vials and NMR tubes) was employed for all transformations under an inert atmosphere of argon unless specified otherwise. Thin-layer chromatography was carried out using precoated 250 mm silica gel 60 Å plates and the separated compounds were visualized with a hand held UV lamp. A medium pressure liquid chromatography system with silica gel columns (60 Å, 40-75 μm) was used for purification purposes. Melting points were obtained with a Uni-Melt apparatus in unsealed tubes and are uncorrected. NMR spectra were obtained with a 500 MHz instrument and the respective ^{1}H and ^{13}C chemical shifts were referenced in ppm as follows: δ 8.03 and 34.9 (DMF-d_7); 7.26 and 77.2 ($CDCl_3$); 5.32 and 53.8 (CD_2Cl_2); 3.31 and 49.0 (CD_3OD); 2.50 and 39.5 (DMSO-d_6); 2.05 and 29.8 (acetone-d_6); 1.94 and 1.3 (CD_3CN); 2.08 (toluene-d_8). A FT-IR with an ATR source was used to obtain IR spectra. High resolution mass spectrometry data were obtained with an ESI TOF instrument using aqueous methanolic and acetonitrile solutions containing polyethylene glycol as an internal standard. Enantiomeric ratios (*er*) were measured with a HPLC and a 25 cm x 4.6 mm (5 μm) RegisCell™ chiral column. Thiourea **5** was prepared as previously described.[8a]

5-(4-tert-Butyl)phenylpyridin-3-amine (**8g**). A mixture of 5-bromopyridin-3-amine (248 mg, 1.43 mmol), $Pd(PPh_3)_4$ (50.4 mg, 43.6 μmol), toluene (3 mL), aqueous sodium carbonate (2 M, 3 mL, 6 mmol), and 4-*tert*-butylphenylboronic acid (285 mg, 1.60 mmol) dissolved in ethanol (3 mL) was heated at 90 °C overnight. The reaction mixture was then allowed to cool to ambient temperature and extracted with EtOAc (20 mL × 2). The combined organic material was washed

with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. Purification of the residue by column chromatography (10% EtOAc/hexanes to 10% methanol/EtOAc) afforded 255 mg (79%) of **8g** as a white solid (R_f = 0.10 in 33% EtOAc/hexanes, mp 145 – 146 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.06 (s, 1H), 7.50 (d, *J* = 8.3 Hz, 4H), 7.14 (s, 1H), 3.84 (br s, 2H), 1.36 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.2, 142.6, 138.8, 136.9, 136.2, 135.2, 126.9, 126.0, 119.8, 34.7, 31.4. IR (ATR source): 3427, 3314 cm^{-1}. HRMS-ESI: calcd for $C_{15}H_{19}N_2$ $(M + H)^+$ 227.1543, found 227.1542.

3-Isothiocyanatoisoquinoline (**9c**).[23] Thiophosgene (0.58 mL, 7.6 mmol) was slowly added to a mixture of isoquinolin-3-amine (1.0 g, 6.9 mmol) in water (25 mL) over a period of 5 min at 0 °C and the mixture was subsequently stirred at room temperature for 2 h before being diluted with water and extracted with EtOAc (25 mL × 3). The combined organic solution was dried over Na_2SO_4 and concentrated under reduced pressure with a rotary evaporator. Medium pressure liquid chromatography of the residue (10 – 20% EtOAc/hexanes) afforded 0.83 g (64%) of **9c** as a white solid (R_f = 0.30 in 10% EtOAc/hexanes, mp 64 – 65 °C). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.78 (s, 1H), 8.08 (d, *J* = 8.8 Hz, 1H), 7.98 (s, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.74 (t, *J* = 8.3 Hz, 1H), 7.61 (t, *J* = 8.8 Hz, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 148.0, 146.3, 138.7, 130.4, 130.2, 129.7, 128.1, 127.7, 127.6, 126.0. IR (ATR source): 2021 cm^{-1}. HRMS-ESI: calcd for $C_{10}H_7N_2S$ $(M + H)^+$ 187.0324, found 187.0342.

3-Isothiocyanato-5-phenylpyridine (**9e**). To a solution of 0.90 g (5.3 mmol) of 3-amino-5-phenylpyridine[24] dissolved in 15 mL of chloroform was added an equal volume of saturated aqueous $NaHCO_3$ at room temperature. The resulting solution was stirred and 0.50 mL (6.5 mmol) of thiophosgene in 5 mL of $CHCl_3$ was added dropwise. After 2 h, the reaction mixture was filtered and the aqueous layer was extracted with CH_2Cl_2 (25 mL × 2). The combined

organic material was dried over $MgSO_4$ and concentrated under reduced pressure with a rotary evaporator. Medium pressure liquid chromatography of the residue (5% EtOAc/hexanes) afforded 0.68 g (61%) of **9e** as a yellow solid (R_f = 0.15 in 10% EtOAc /hexanes, mp 51 – 52 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, *J* = 2.0 Hz, 1H), 8.50 (d, *J* = 2.5 Hz, 1H), 7.70 (dd, *J* = 2.0, 2.5 Hz, 1H), 7.56 (d, *J* = 7.4 Hz, 2H), 7.50 (t, *J* = 6.9 Hz, 2H), 7.45 (t, *J* = 6.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.2, 145.4, 139.5, 137.5, 136.1, 130.6, 129.7, 129.4, 128.9, 127.2. IR (ATR source): 2039 cm^{-1}. HRMS-ESI: calcd for $C_{12}H_9N_2S$ $(M + H)^+$ 213.0481, found 213.0494.

5-(4-tert-Butyl)phenyl-3-isothiocyanatopyridine (**9g**). To a solution of 0.25 g (1.1 mmol) of **8g** dissolved in 2.5 mL of chloroform was added an equal volume of saturated aqueous $NaHCO_3$ at room temperature. The resulting solution was stirred and 0.11 mL (1.4 mmol) of thiophosgene in 1 mL of $CHCl_3$ was added dropwise. After 2 h, the reaction mixture was filtered and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic material was dried over $MgSO_4$ and concentrated under reduced pressure. Medium pressure liquid chromatography of the residue (5 – 30% EtOAc/hexanes) afforded 0.17 g (57%) of **9g** as a yellow solid (R_f = 0.10 in 33% EtOAc/hexanes, mp 113 – 114 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.47 (s, 1H), 7.67 (s, 1H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.3, 146.1, 145.2, 139.4, 137.4, 133.2, 130.4, 129.7, 126.9, 126.4, 34.8, 31.4. IR (ATR source): 2067 cm^{-1}. HRMS-ESI: calcd for $C_{16}H_{17}N_2S$ $(M + H)^+$ 269.1107, found 269.1086.

3-Isothiocyanato-1-methylisoquinolinium iodide (**10c**). In a 6 dram vial, 40 mg (0.22 mmol) of **9c** was dissolved in 1 mL of EtOAc and 0.23 mL (3.7 mmol) of methyl iodide was added at 40 ^{o}C under argon. The reaction mixture was allowed to stir for 72 h and the resulting precipitate was filtered, washed with 1 mL of hexanes and dried under vacuum to afford 30 mg (42%) of

10c as a yellow solid (mp decomposed over 200 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.89 (s, 1H), 9.36 (s, 1H), 8.51 (d, *J* = 8.8 Hz, 1H), 8.40 (d, *J* = 7.8 Hz, 1H), 8.27 (dd, *J* = 7.3, 8.8 Hz, 1H), 8.08 (dd, *J* = 7.3, 7.8 Hz, 1H), 4.63 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 148.9, 141.2, 140.8, 136.4, 135.5, 130.7, 129.9, 128.6, 125.8, 119.2, 45.6. IR (ATR source): 2000 cm^{-1}. HRMS-ESI: calcd for $C_{11}H_9N_2S$.

General procedure for preparing 3-isothiocyanato-*N*-octylpyridinium ions 10b, 10d and 10f. In a 6 dram vial, 0.73 mmol of a 3-isothiocyanatopyridine derivative (**9a**,[25] **9c** or **9e**) was dissolved in 1 mL of CH_2Cl_2 and 0.39 g (1.47 mmol) of 1-octyl triflate[26] was added at room temperature under argon. The reaction mixture was allowed to stir overnight and concentrated under reduced pressure. The resulting residue was washed with 2 mL of pentane and dried under vacuum to afford the corresponding product.

3-Isothiocyanato-1-(1-octyl)pyridinium triflate (**10b**). An 86% yield (0.25 g) of this product was obtained as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (d, *J* = 6.3 Hz, 1H), 8.68 (s, 1H), 8.22 (d, *J* = 8.3 Hz, 1H), 8.07 (dd, *J* = 6.3, 8.3 Hz, 1H), 4.70 (t, *J* = 7.3 Hz, 2H), 2.00 (m, 2H), 1.20 - 1.40 (m, 10H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.3, 142.5, 141.7, 141.2, 134.9, 129.4, 120.5 (q, $J_{C\text{-}F}$ = 315 Hz), 63.0, 31.64, 31.58, 29.0, 28.9, 26.0, 22.6, 14.1. IR (ATR source): 2003 cm^{-1}. HRMS-ESI: calcd for $C_{14}H_{21}N_2S$ $(M - CF_3SO_2)^+$ 249.1420, found 249.1403.

3-Isothiocyanato-1-(1-octyl)isoquinolinium triflate (**10d**). This product was obtained in a 93% yield (0.30 g) as a yellow solid (mp 50 – 52 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.87 (s, 1H), 8.32 (d, *J* = 8.3 Hz, 1H), 8.30 (d, *J* = 8.3 Hz, 1H), 8.17 (t, *J* = 8.3 Hz, 1H), 7.93 (t, *J* = 8.3 Hz, 1H), 5.08 (t, *J* = 7.8 Hz, 2H), 2.02 (m, 2H), 1.01-1.49 (m, 10H), 0.80 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.7, 144.0, 141.9, 136.5, 136.0, 131.4, 130.8, 130.2,

128.2, 120.7 (q, $^{1}J_{F-C}$ = 321 Hz), 118.6, 59.2, 31.7, 30.3, 29.0, 26.4, 22.6, 14.8, 14.1. IR (ATR source): 1992 cm^{-1}. HRMS-ESI: calcd for $C_{18}H_{23}N_2S$ $(M - CF_3SO_2)^+$ 299.1576, found 299.1569.

3-Isothiocyanato-5-phenyl-1-(1-octyl)pyridinium triflate (**10f**). This product was obtained quantitatively (0.36 g) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.76 (s, 1H), 8.22 (s, 1H), 7.72 (m, 2H), 7.52 (m, 3H), 4.77 (t, *J* = 7.8 Hz, 2H), 1.98 (pentet, *J* = 7.4 Hz, 2H), 1.38-1.12 (m, 10H), 0.83 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.5, 142.8, 140.4, 139.1, 138.3, 135.0, 131.9, 131.3, 130.1, 127.7, 120.8 (q, *J* = 322 Hz), 63.4, 32.0, 31.8, 29.1, 26.1, 22.7, 14.8, 14.2. IR (ATR source): 2010 cm^{-1}. HRMS-ESI: calcd for $C_{20}H_{25}N_2S$ $(M - CF_3SO_2)^+$ 325.1733, found 325.1740.

General procedure for preparing 3-isothiocyanato-*N*-methylpyridinium ions 10e, 10g and 10h. In a 6 dram vial, 0.47 mmol of a 3-isothiocyanatopyridine derivative (**9e**, **9g** or **9h**)[27] was dissolved in 1 mL of EtOAc and 90 μL (1.4 mmol) of iodomethane was added at room temperature under argon. The reaction mixture was allowed to stir overnight and the resulting precipitate was filtered, washed with 2 mL of EtOAc and dried under vacuum to afford the corresponding product.

3-Isothiocyanato-1-methyl-5-phenylpyridinium iodide (**10e**). This product was obtained in a 60% yield (0.10 g) as a pale yellow solid (mp 154 – 155 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.36 (s, 1H), 9.26 (s, 1H), 9.01 (s, 1H), 7.92 (d, *J* = 6.9 Hz, 2H), 7.62 (m, 3H), 4.37 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 141.8, 141.4, 141.1, 139.4, 138.7, 132.2, 131.7, 130.5, 129.4, 127.5, 48.4. IR (ATR source): 2035 cm^{-1}. HRMS-ESI: calcd for $C_{13}H_{11}N_2S$ $(M - I)^+$ 227.0637, found 227.0643.

3-Isothiocyanato-1-methyl-5-(4-tert-butyl)phenylpyridinium iodide (**10g**). This product was obtained in a 77% yield (0.15 g) as a yellow solid (mp 205 – 207 °C). ^{1}H NMR (500 MHz,

DMSO-d_6) δ 9.33 (s, 1H), 9.23 (s, 1H), 8.97 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 4.36 (s, 3H), 1.33 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 153.4, 141.6, 141.2, 140.9, 139.3, 138.3, 131.7, 129.4, 127.3, 126.3, 48.4, 34.6, 30.9. IR (ATR source): 1989 cm^{-1}. HRMS-ESI: calcd for $C_{17}H_{19}N_2S$ $(M - I)^+$ 283.1263, found 283.1282.

4-Isothiocyanato-1-methylpyridinium iodide (**10h**). This product was obtained in a 66% yield (86 mg) as a yellow solid (mp 152 – 154 °C). ^{1}H NMR (500 MHz, CD_3CN) δ 8.60 (d, *J* = 5.9 Hz, 2H), 7.74 (d, *J* = 5.9 Hz, 2H), 4.23 (s, 3H). ^{13}C NMR (126 MHz, DMF-d_7) δ 149.6, 145.6, 126.7, 126.1, 66.3. IR (ATR source): 2017 cm^{-1}. HRMS-ESI: calcd for $C_7H_7N_2S$ $(M - I)^+$ 151.0324, found 151.0335; $(M - I)^+$ 201.0481, found 201.0459.

General procedure for preparing thiourea catalyst precursors 11a-h. In a 6 dram vial, 0.18 mmol of a 3-isothiocyanato-1-alkylpyridinium ion (**10a-h**) was dissolved in 2 mL of CH_3CN or CH_2Cl_2 and (1*S*,2*R*)-*cis*-1-amino-2-indanol (27 mg, 0.18 mmol) was added at room temperature under argon. The reaction mixture was allowed to stir overnight and was then either (a) concentrated under reduced pressure if no precipitate was present, or (b) filtered if precipitate was present. In the latter case the resulting residue was washed with 2 mL of pentane and dried under vacuum to afford the corresponding product.

3-(3-((1S,2R)-2-Hydroxy-2,3-dihydro-1H-inden-1-yl)thioureido)-1-methylpyridinium iodide **(11a)**. This compound was obtained in a 90% yield (70 mg) as a pale yellow solid (mp 175 – 178 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.47 (s, 1H), 8.70 (d, *J* = 5.9 Hz, 1H), 8.64 (d, *J* = 8.8 Hz, 1H), 8.62 (br s, 1H), 8.06 (dd, *J* = 5.9, 8.8 Hz, 1H), 7.10 - 7.35 (m, 4H), 5.80 (d, *J* = 3.9 Hz, 1H), 5.52 (d, *J* = 3.9 Hz, 1H), 4.57 (t, *J* = 4.4 Hz, 1H), 4.37 (s, 3H), 3.14 (dd, *J* = 4.4, 16.1 Hz, 1H), 2.87 (d, *J* = 16.1 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 180.6, 141.2, 140.6, 139.73, 139.68, 138.3,

136.9, 127.6, 127.0, 126.2, 125.1, 124.1, 71.7, 71.6, 61.5, 48.3. IR (ATR source): 3370, 3329, 3265 cm^{-1}. HRMS-ESI: calcd for $C_{16}H_{18}N_3OS$ $(M - I)^+$ 300.1165, found 300.1167.

3-(3-((1S,2R)-2-Hydroxy-2,3-dihydro-1H-inden-1-yl)thioureido)-1-(1-octyl)pyridinium triflate (**11b**). A 72% yield (71 mg) of **11b** was obtained as a pale yellow solid (mp 53 – 55 °C). ^1H NMR (500 MHz, $CDCl_3$) δ 9.98 (s, 1H), 9.69 (s, 1H), 8.38 (d, *J* = 8.3 Hz, 1H), 8.13 (d, *J* = 5.9 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.59 (dd, *J* = 5.9, 8.8 Hz, 1H), 7.37 (d, *J* = 6.4 Hz, 1H), 7.17 (m, 3H), 5.85 (dd, *J* = 4.4, 7.3 Hz, 1H), 4.75 (t, *J* = 4.4 Hz, 1H), 4.31 (t, *J* = 7.4 Hz, 2H), 3.11 (dd, *J* = 4.9, 16.6 Hz, 1H), 2.92 (d, *J* = 16.6 Hz, 1H), 1.91 (m, 2H), 1.27 (m, 10H), 0.86 (t, *J* = 4.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.2, 141.4, 140.5, 140.2, 137.0, 136.8, 136.4, 128.3, 127.5, 127.1, 125.4, 124.8, 120.3 (q, $J_{C\text{-}F}$ = 320 Hz), 73.3, 62.8, 39.8, 31.8, 31.2, 29.1, 29.0, 26.1, 24.3, 22.7, 14.2. IR (ATR source): 3372, 3266 cm^{-1}. HRMS-ESI: calcd for $C_{23}H_{32}N_3OS$ $(M - CF_3SO_2)^+$ 398.2261, found 398.2259.

3-(3-((1S,2R)-2-Hydroxy-2,3-dihydro-1H-inden-1-yl)thioureido)-1-methylisoquinolinium iodide (**11c**). This product was obtained in a 67% yield (58 mg) as a yellow solid (mp 157 – 159 °C). ^1H NMR (500 MHz, CD_3OD) δ 10.03 (s, 1H), 9.00 (s, 1H), 8.41 (d, *J* = 8.8 Hz, 1H), 8.31 (d, *J* = 8.3 Hz, 1H), 8.16 (dd, *J* = 7.3, 8.3 Hz, 1H), 7.98 (dd, *J* = 7.3, 8.8 Hz, 1H), 7.44 (d, *J* = 5.4 Hz, 1H), 7.26 (d, *J* = 5.4 Hz, 1H), 7.20 (m, 2H), 5.97 (d, *J* = 4.4 Hz, 1H), 4.74 (dd, *J* = 4.4, 4.9 Hz, 1H), 4.68 (s, 3H), 3.20 (dd, *J* = 4.9, 16.1 Hz, 1H), 2.98 (d, *J* = 16.1 Hz, 1H). ^{13}C NMR (126 MHz, CD_3OD) δ 184.2, 149.1, 142.1, 141.8, 138.2, 137.0, 136.1, 135.4, 131.5, 131.1, 131.0, 129.2, 127.9, 126.5, 125.6, 119.8, 66.9, 64.0, 46.7, 41.0. IR (ATR source): 3372, 3329, 3266 cm^{-1}. HRMS-ESI: calcd for $C_{20}H_{20}N_3OS$ $(M - I)^+$ 350.1322, found 350.1327.

3-(3-((1S,2R)-2-Hydroxy-2,3-dihydro-1H-inden-1-yl)thioureido)-1-(1-octyl)isoquinolinium triflate (**11d**). This product was obtained in a 64% yield (69 mg) as a yellow solid (mp 50 –

52 °C). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 10.16 (s, 1H), 9.91 (s, 1H), 8.46 (s, 1H), 8.02 – 8.10 (m, 3H), 7.99 (d, *J* = 7.3 Hz, 1H), 7.87 (t, , *J* = 6.9 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 7.3 Hz, 1H), 6.84 (t, *J* = 7.4 Hz, 1H), 6.64 (t, *J* = 7.4 Hz, 1H), 5.73 (t, *J* = 6.4 Hz, 1H), 4.94 (t, *J* = 4.4 Hz, 1H), 4.86 (m, 1H), 4.74 (m, 1H), 3.12 (dd, *J* = 3.9, 16.6 Hz, 1H), 2.97 (d, *J* = 16.6 Hz, 1H), 2.10 (m, 2H), 1.52 (m, 2H), 1.19 – 1.44 (m, 8H), 0.87 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 182.8, 147.2, 140.4, 140.1, 135.8, 134.9, 133.7, 130.4, 130.0, 129.8, 127.6, 126.5, 124.8, 124.6, 124.5, 120.5 (q, $^{1}J_{F\text{-}C}$ = 321 Hz), 116.3, 73.1, 63.0, 58.5, 39.9, 31.7, 29.8, 29.0, 26.6, 22.6, 18.6, 13.8. IR (ATR source): 3372, 3329, 3266 cm^{-1}. HRMS-ESI: calcd for $C_{27}H_{34}N_3OS$ $(M - CF_3SO_2)^+$ 448.2417, found 448.2396.

3-(3-((1S,2R)-2-Hydroxy-2,3-dihydro-1H-inden-1-yl)thioureido)-1-methyl-5-phenylpyridinium iodide (**11e**). This product was obtained in a 97% yield (88 mg) as a pale yellow solid (mp 160 – 162 °C). ^{1}H NMR (500 MHz, CD_3OD) δ 9.48 (s, 1H), 8.91 (s, 1H), 8.89 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 2H), 7.60 – 7.45 (m, 3H), 7.40 (d, *J* = 7.3 Hz, 1H), 7.28 – 7.11 (m, 3H), 5.94 (d, 1H), 4.71 (t, *J* = 4.4 Hz, 1H), 4.43 (s, 3H), 3.16 (dd, *J* = 4.4, 16.6 Hz, 1H), 2.95 (d, *J* = 16.7 Hz, 1H). ^{13}C NMR (126 MHz, CD_3OD) δ 182.6, 141.9, 141.8, 141.7, 141.4, 138.6, 137.3, 134.9, 134.6, 131.4, 130.7, 129.0, 128.5, 127.7, 126.3, 125.4, 73.6, 63.5, 49.7, 40.9. IR (ATR source): 3329, 3253 cm^{-1}. HRMS-ESI: calcd for $C_{22}H_{22}N_3OS$ $(M - I)^+$ 376.1478, found 376.1491.

3-(3-((1S,2R)-2-Hydroxy-2,3-dihydro-1H-inden-1-yl)thioureido)-1-(1-octyl)-5-phenylpyridinium triflate (**11f**). This product was obtained in a 85% yield (95 mg) as a pale yellow solid (mp 73 – 76 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 9.46 (s, 1H), 8.78 (s, 1H), 8.37 (s, 1H), 8.02 (d, *J* = 8.3 Hz, 1H), 7.63 (d, *J* = 5.4 Hz, 2H), 7.48 (m, 3H), 7.39 (d, *J* = 6.8 Hz, 1H), 7.20-7.10 (m, 3H), 5.89 (dd, *J* = 4.9, 6.9 Hz, 1H), 4.79 (t, *J* = 4.7 Hz, 1H), 4.39 (m, 2H), 3.97 (d, *J* = 5.9 Hz, 1H), 3.11 (dd, *J* = 4.9, 16.6 Hz, 1H), 2.88 (d, *J* = 16.6 Hz, 1H), 1.95 (t, *J* = 6.4 Hz, 2H), 1.40-

1.11 (m, 10H), 0.87 (t, J = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.4, 141.4, 140.9, 140.3, 139.8, 135.4, 134.8, 134.2, 132.8, 130.7, 129.9, 128.3, 127.4, 127.1, 125.3, 124.8, 120.3 (q, J = 320 Hz), 73.5, 63.0, 57.6, 39.5, 31.8, 31.4, 29.1, 26.1, 22.7, 14.8, 14.2. IR (ATR source): 3315 cm^{-1}. HRMS-ESI: calcd for $C_{29}H_{36}N_3OS$ $(M - CF_3SO_2)^+$ 474.2574, found 474.2558.

5-(4-tert-Butyl)phenyl-3-(3-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)thioureido)-1-methylpyridinium iodide (**11g**). This product was obtained in 75% (82 mg) as a pale yellow solid (mp 145 – 148 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.51 (s, 1H), 9.09 (s, 1H), 8.35 (s, 1H), 8.32 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 7.8 Hz, 2H), 7.54 (d, J = 7.8 Hz, 2H), 7.50 (d, J = 7.8 Hz, 1H), 7.21 – 7.10 (m, 4H), 5.86 (t, J = 4.9 Hz, 1H), 4.84 (t, J = 4.9 Hz, 1H), 4.23 (d, J = 5.9 Hz, 1H), 4.20 (s, 3H), 3.14 (dd, J = 4.9, 16.6 Hz, 1H), 3.00 (d, J = 16.6 Hz, 1H), 1.35 (s, 9H). ^{13}C NMR (126 MHz, $(CD_3)_2CO$) δ 181.9, 154.3, 141.8, 141.6, 140.1, 137.9, 135.6, 133.0, 131.4, 128.5, 127.9, 127.4, 127.2, 125.9, 125.4, 111.0, 73.4, 63.2, 49.8, 40.5, 35.4, 31.4. IR (ATR source): 3242 cm^{-1}. HRMS-ESI: calcd for $C_{26}H_{30}N_3OS$ $(M - I)^+$ 432.2104, found 432.2128.

4-(3-((1S,2R)-2-Hydroxy-2,3-dihydro-1H-inden-1-yl)thioureido)-1-methylpyridinium iodide (**11h**). This product was obtained in a 65% (50 mg) yield as a yellow solid (mp 138 – 140 °C). ^{1}H NMR (500 MHz, CD_3CN) δ 10.95 (s, 1H), 8.59 (d, J = 6.9 Hz, 2H), 8.56 (s, 1H), 8.26 (d, J = 7.3 Hz, 2H), 7.67 (d, J = 9.8 Hz, 1H), 7.41 (d, J = 7.3 Hz, 1H), 7.28 (t, J = 7.3 Hz, 1H), 7.22 (t, J = 7.3 Hz, 1H), 5.90 (dd, J = 4.9, 8.3 Hz, 1H), 4.71 (t, J = 4.9 Hz, 1H), 4.06 (s, 3H), 3.45 (s, 1H), 3.19 (dd, J = 4.9, 16.7 Hz, 1H), 2.94 (d, J = 16.6 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 179.4, 152.5, 145.1, 140.8, 140.7, 127.8, 126.3, 125.2, 124.2, 114.5, 71.6, 61.5, 46.0, 39.9. IR (ATR source): 3375, 3329, 3268 cm^{-1}. HRMS-ESI: calcd for $C_{16}H_{18}N_3OS$ $(M - I)^+$ 300.1165, found 300.1183.

General procedure for preparing thiourea catalysts 4a-h and 4a'. To a 6 dram vial, 21 mg (24 μmol) of sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate or 17 mg (24 μmol) of potassium tetrakis(pentafluorophenyl)borate, 24 μmol of a thiourea catalyst precursor (**11a, c-h**) and 1 mL of CH_2Cl_2 were added. This mixture was stirred at room temperature under an argon atmosphere until the solid material was totally dissolved and a cloudy suspension formed. Stirring was then stopped and the solution was left undisturbed until a white solid precipitated and a clear solution formed. The reaction mixture was then filtered and concentrated under reduced pressure. The resulting residue was washed with 2 mL of pentane and dried under vacuum to afford the corresponding product.

3-(3-((1S,2R)-2-Hydroxy-2,3-dihydro-1H-inden-1-yl)thioureido)-1-methylpyridinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (**4a**). The title compound was obtained in an 86% yield (24 mg) as a pale yellow solid (mp 70 – 73 °C). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 10.00 (s, 1H), 8.14 (s, 1H), 8.02 (d, J = 5.9 Hz, 1H), 7.75 (s, 8H), 7. 80 – 7.45 (m, 3H), 7.59 (s, 4H), 7.38 (d, J = 7.4 Hz, 1H), 7.28 (m, 3H), 5.96 (s, 1H), 4.78 (d, J =4.9 Hz, 1H), 4.31 (s, 3H), 3.26 (dd, J = 4.9, 16.7 Hz, 1H), 2.95 (d, J = 16.2 Hz, 1H) ^{13}C NMR (126 MHz, CD_2Cl_2) δ 180.8, 162.1 (q, $^1J_{B\text{-}C}$ = 49.5 Hz), 141.6, 140.1, 139.7, 137.9, 137.7, 136.8, 135.2 (q, $^2J_{B\text{-}C}$ = 31.3 Hz), 129.3 (qq, $^3J_{B\text{-}C}$ = 3.0 Hz and $^2J_{F\text{-}C}$ = 31.3 Hz), 128.4, 127.8, 127.7, 125.0, 124.9 (q, $^1J_{F\text{-}C}$ = 272 Hz), 124.7, 117.9 (q, $^3J_{F\text{-}C}$ = 2.0 Hz), 67.5, 62.9, 49.8, 40.4. IR (ATR source): 3334 cm^{-1}. HRMS-ESI: calcd for $C_{16}H_{18}N_3OS$ $(M - C_{32}H_{12}BF_{24})^+$ 300.1165, found 300.1181.

3-(3-((1S,2R)-2-Hydroxy-2,3-dihydro-1H-inden-1-yl)thioureido)-1-(1-octyl)pyridinium tetrakis (3, 5-bis(trifluoromethyl)phenyl)borate **(4b)**. This catalyst was obtained in an 81% yield (25 mg) as a pale yellow solid (mp 51 – 53 °C). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 10.23 (s, 1H), 8.93 (s, 1H), 7.80 (d, J = 5.9 Hz, 1H), 7.72 (s, 8H), 7.69 (s, 1H), 7.54 (s, 4H), 7.50 (m, 1H), 7.41 (dd, J =

5.9, 8.3 Hz, 1H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.20 – 7.33 (m, 3H), 5.95 (s, 1H), 4.81 (s, 1H), 4.35 (t, *J* = 6.8 Hz, 2H), 3.29 (d, *J* = 16.1 Hz, 1H), 2.98 (d, *J* = 16.0 Hz, 1H), 2.18 (br s, 1H), 2.02 (m, 2H), 1.10 – 1.40 (m, 10H), 0.88 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 181.0, 162.2 (q, $^{1}J_{B\text{-}C}$ = 49.1 Hz), 141.8, 140.1, 137.3, 136.9, 136.7, 136.6, 136.5, 136.3, 135.3 (q, $^{2}J_{B\text{-}C}$ = 35.3 Hz), 129.3 (qq, ^{3}JB-C = 3.0 Hz and ^{2}JF-C = 31.3 Hz), 128.4, 128.1, 125.9, 125.0 (q, $^{1}J_{F\text{-}C}$ = 273 Hz), 117.9 (q, $^{3}J_{F\text{-}C}$ = 2.0 Hz), 74.2, 63.9, 40.4, 31.9, 31.6, 29.2, 29.1, 26.3, 22.9, 22.8, 14.2. IR (ATR source): 3427, 3300 cm^{-1}. HRMS-ESI: calcd for $C_{23}H_{32}N_3OS$ $(M - C_{32}H_{12}BF_{24})^+$ 398.2261, found 398.2251.

3-(3-((1S,2R)-2-Hydroxy-2,3-dihydro-1H-inden-1-yl)thioureido)-1-methylisoquinolinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (**4c**). This product was obtained in an 86% yield (25 mg) as a yellow solid (mp 75 – 77 °C). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 9.95 (s, 1H), 9.35 (s, 1H), 8.74 (s, 1H), 8.00 – 8.15 (m, 3H), 7.92 (t, *J* = 6.9 Hz, 1H), 7.80 (s, 1H), 7.75 (s, 8H), 7.57 (s, 4H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.00 – 7.24 (m, 3H), 5.97 (s, 1H), 4.79 (s, 1H), 4.52 (s, 3H), 3.23 (dd, *J* = 4.4, 16.6 Hz, 1H), 2.94 (d, *J* = 16.1 Hz, 1H), 2.92 (br s, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 182.4, 162.1 (q, $^{1}J_{B\text{-}C}$ = 49.1 Hz), 146.1, 140.2, 137.3, 135.7, 135.2 (q, $^{2}J_{B\text{-}C}$ = 32.7 Hz), 134.6, 131.5, 131.3, 130.5, 130.3, 129.8, 129.2 (qq, $^{3}J_{B\text{-}C}$ = 3.0 Hz and $^{2}J_{F\text{-}C}$ = 32.8 Hz), 127.6, 127.5, 125.8, 125.1 (q, $^{1}J_{F\text{-}C}$ = 276 Hz), 125.0, 124.7, 117.9 (q, $^{3}J_{F\text{-}C}$ = 2.0 Hz), 74.3, 68.3, 46.3, 40.2. IR (ATR source): 3411, 3317 cm^{-1}. HRMS-ESI: calcd for $C_{20}H_{20}N_3OS$ $(M - C_{32}H_{12}BF_{24})^+$ 350.1322, found 350.1298.

3-(3-((1S,2R)-2-Hydroxy-2,3-dihydro-1H-inden-1-yl)thioureido)-1-(1-octyl)isoquinolinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (**4d**). This product was obtained in a 67% yield (21 mg) as a yellow solid (mp 56 – 58 °C). ^{1}H NMR (500 MHz, CD_3OD) δ 10.14 (s, 1H), 8.80 (s, 1H), 8.41 (d, *J* = 8.8 Hz, 1H), 8.24 (d, *J* = 7.9 Hz, 1H), 8.09 (t, *J* = 7.4 Hz, 1H), 7.88 (t, *J* = 7.8 Hz,

1H), 7.64 (s, 8H), 7.60 (s, 4H), 7.42 (s, 1H), 7.31 - 7.00 (m, 4H), 5.98 (s, 1H), 5.04 (t, J = 6.8 Hz, 2H), 4.74 (d, J = 4.9 Hz, 1H), 3.19 (dd, J = 4.4, 16.1 Hz, 1H), 2.99 (d, J = 16.1 Hz, 1H), 2.12 (m, 2H), 2.01 (br s, 1H), 1.52 (m, 2H), 1.42 – 1.14 (m, 8H), 0.82 (t, J = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 184.4, 163.0 (q, $^{1}J_{B\text{-}C}$ = 50.5, Hz) 148.8, 142.1, 141.8, 138.1, 136.4, 136.0, 135.4, 131.6, 131.4, 130.6 (qq, $^{3}J_{B\text{-}C}$ = 3.0 Hz and $^{2}J_{F\text{-}C}$ = 33.3 Hz), 129.2, 128.0, 127.9, 126.6, 126.5, 125.9 (q, $^{1}J_{F\text{-}C}$ = 273 Hz), 125.5, 119.6, 118.6 (q, $^{1}J_{F\text{-}C}$ = 3.0 Hz), 73.9, 64.1, 59.6, 41.0, 32.9, 31.1, 30.8, 30.3, 27.7, 23.7, 14.5. IR (ATR source): 3287 cm^{-1}. HRMS-ESI: calcd for $C_{27}H_{34}N_3OS$ $(M - C_{32}H_{12}BF_{24})^+$ 448.2417, found 448.2427.

3-(3-((1S,2R)-2-Hydroxy-2,3-dihydro-1H-inden-1-yl)thioureido)-1-methyl-5-phenylpyridinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (**4e**). This product was obtained in an 89% yield (26 mg) as a yellow solid (mp 68 – 71 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.63 (s, 1H), 9.24 (s, 1H), 8.49 (s, 1H), 8.10 (s, 1H), 7.71 (s, 8H), 7.65 (s, 1H), 7.56 – 7.41 (m, 5H), 7.53 (s, 4H), 7.32 (d, J = 6.9 Hz, 1H), 7.28 – 7.13 (m, 3H), 5.93 (s, 1H), 4.76 (s, 1H), 4.19 (s, 3H), 3.22 (d, J = 16.2 Hz, 1H), 2.87 (d, J = 15.6 Hz, 1H), 2.53 (s, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 180.7, 161.8 (q, $^{1}J_{B\text{-}C}$ = 50.5, Hz), 142.4, 141.3, 139.8, 139.4, 135.4, 135.3, 134.8 (q, $^{2}J_{B\text{-}C}$ = 31.3 Hz), 134.3, 132.1, 131.5, 131.1, 130.3, 129.9, 128.9 (qq, $^{3}J_{B\text{-}C}$ = 3.0 Hz and $^{2}J_{F\text{-}C}$ = 33.3 Hz), 127.3, 126.9, 124.6 (q, $^{1}J_{F\text{-}C}$ = 273 Hz), 124.5, 117.5 (q, $^{3}J_{F\text{-}C}$ = 3.0 Hz), 74.0, 62.6, 49.5, 40.1. IR (ATR source): 3336 cm^{-1}. HRMS-ESI: calcd for $C_{22}H_{22}N_3OS$ $(M - C_{32}H_{12}BF_{24})^+$ 376.1478, found 376.1479.

3-(3-((1S,2R)-2-Hydroxy-2,3-dihydro-1H-inden-1-yl)thioureido)-1-(1-octyl)-5-phenylpyridinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (**4f**). This product was obtained in an 87% yield (28 mg) as a yellow solid (mp 58 – 61 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.95 (s, 1H), 9.28 (s, 1H), 8.25 (s, 1H), 8.17 (s, 1H), 7.71 (s, 9H), 7.51 (s, 4H), 7.55-7.40 (m, 5H), 7.36 (d, J = 7.4 Hz,

1H), 7.32-7.20 (m, 3H), 5.98 (s, 1H), 4.79 (s, 1H), 4.44 (t, J = 6.9 Hz, 2H), 3.27 (d, J = 15.6 Hz, 1H), 2.94 (d, J = 15.6 Hz, 1H), 2.68 (br s, 1H), 2.08 (t, J = 7.3 Hz, 2H), 1.44-1.18 (m, 10H), 0.87 (t, J = 4.9 Hz, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 183.0, 162.9 (q, $^{1}J_{B\text{-}C}$ = 50.5, Hz), 142.4, 142.3, 141.7, 137.5, 137.2, 135.8, 135.3, 134.7, 131.5, 130.8, 130.4 (qq, $^{3}J_{B\text{-}C}$ = 3.0 Hz and $^{2}J_{F\text{-}C}$ = 32.3 Hz), 129.1, 128.5, 127.7, 126.4, 126.0, 125.8 (q, $^{1}J_{F\text{-}C}$ = 272 Hz), 125.4, 118.5 (q, $^{3}J_{F\text{-}C}$ = 3.0 Hz), 73.6, 63.6, 47.9, 40.9, 32.8, 32.4, 30.1, 30.0, 27.2, 23.6, 14.3. IR (ATR source): 3340, 3163 cm^{-1}. HRMS-ESI: calcd for $C_{29}H_{36}N_3OS$ $(M - C_{32}H_{12}BF_{24})^+$ 474.2574, found 474.2572.

3-(3-((1S,2R)-2-Hydroxy-2,3-dihydro-1H-inden-1-yl)thioureido)-1-methyl-5-(4-tert-butyl)-phenylpyridinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (**4g**). This product was obtained in an 88% yield (27 mg) as a yellow solid (mp 70 – 72 °C). ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 10.22 (s, 1H), 9.72 (s, 1H), 9.15 (s, 1H), 8.94 (s, 1H), 8.27 (s, 1H), 7.81 (s, 8H), 7.77-7.62 (m, 4H), 7.69 (s, 4H), 7.43 (d, J = 6.9 Hz, 1H), 7.29-7.19 (m, 3H), 6.02 (s, 1H), 4.79 (t, J = 5.4 Hz, 1H), 4.71 (s, 3H), 4.55 (s, 1H), 3.25 (dd, J = 4.4, 16.6 Hz, 1H), 2.99 (d, J = 16.6 Hz, 1H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, $(CD_3)_2CO$) δ 182.3, 162.6 (q, $^{1}J_{B\text{-}C}$ = 49.5, Hz), 154.7, 141.7, 141.6, 141.0, 138.7, 137.4, 135.5, 135.0, 131.5, 130.0 (qq, $^{3}J_{B\text{-}C}$ = 3.0 Hz and $^{2}J_{F\text{-}C}$ = 31.3 Hz), 128.7, 128.0, 127.6, 127.4, 127.3, 126.1, 125.4 (q, $^{1}J_{F\text{-}C}$ = 273 Hz), 125.3, 118.5 (q, $^{3}J_{F\text{-}C}$ = 3.0 Hz), 73.4, 63.2, 49.7, 44.0, 41.0, 31.3. IR (ATR source): 3325, 3163 cm^{-1}. HRMS-ESI: calcd for $C_{26}H_{30}N_3OS$ $(M - C_{32}H_{12}BF_{24})^+$ 432.2104, found 432.2107.

4-(3-((1R,2S)-2-Hydroxy-2,3-dihydro-1H-inden-1-yl)thioureido)-1-methylpyridinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (**4h**). This product was obtained in a 73% yield (20 mg) as a pale yellow solid (mp 109 – 111 °C). ^{1}H NMR (500 MHz, CD_3OD) δ 8.49 (d, J = 6.9 Hz, 2H), 8.43 (d, J = 7.4 Hz, 2H), 7.60 (s, 12H), 7.37 (d, J = 7.3 Hz, 1H), 7.29-7.06 (m, 3H), 5.96 (d, J = 4.9 Hz, 1H), 4.74 (t, J = 4.9 Hz, 1H), 4.16 (s, 3H), 3.22 (dd, J = 4.9, 16.6 Hz, 1H),

2.98 (d, J = 16.6 Hz, 1H). ^{13}C NMR (126 MHz, CD_3OD) δ 181.4, 162.9 (q, $^{1}J_{B\text{-}C}$ = 49.4, Hz), 155.1, 145.8, 141.8, 141.5, 135.8, 130.4 (qq, $^{3}J_{B\text{-}C}$ = 3.0 Hz and $^{2}J_{F\text{-}C}$ = 31.3 Hz), 129.2, 127.8, 126.4, 125.8 (q, $^{1}J_{F\text{-}C}$ = 272 Hz), 125.3, 118.5 (q, $^{3}J_{F\text{-}C}$ = 3.0 Hz), 115.9, 73.5, 63.3, 46.6, 41.0. IR (ATR source): 3229 cm^{-1}. HRMS-ESI: calcd for $C_{16}H_{18}N_3OS$ (M – $C_{32}H_{12}BF_{24}$)$^+$ 300.1165, found 300.1176.

3-(3-((1S,2R)-2-Hydroxy-2,3-dihydro-1H-inden-1-yl)thioureido)-1-methylpyridinium tetrakis(pentafluorophenyl)borate (**4a'**). This product was obtained in an 87% yield (20 mg) as a pale yellow solid (mp 74 – 77 °C). ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 10.16 (br s, 1H), 9.89 (s, 1H), 8.80 (d, J = 6.4 Hz, 1H), 8.73 (d, J = 8.3 Hz, 1H), 8.22 (s, 1H), 8.16 (dd, J = 5.9, 8.4 Hz, 1H), 7.40 (d, J = 7.4 Hz, 1H), 7.30-7.09 (m, 3H), 5.98 (s, 1H), 4.77 (t, J = 4.9 Hz, 1H), 4.65 (s, 3H), 4.57 (s, 1H), 3.23 (dd, J = 4.9, 16.6 Hz, 1H), 2.98 (J = 16.6 Hz, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 180.9, 148.4 (d, $J_{o\text{-}FC}$ = 241 Hz), 140.9 (d, $J_{p\text{-}FC}$ = 196 Hz), 139.5, 137.3, 136.6 (d, $J_{m\text{-}FC}$ = 242 Hz), 136.3, 136.2, 128.9, 128.2, 127.9, 127.6, 125.9, 124.9, 124.7 (*ipso*-C), 124.0, 74.6, 62.9, 49.6, 40.2. IR (ATR source): 3331 cm^{-1}. HRMS-ESI: calcd for $C_{16}H_{18}N_3OS$ (M – $C_{24}BF_{20}$)$^+$ 300.1165, found 300.1185.

Representative procedure for the catalytic enantioselective Friedel-Crafts alkylation of *trans*-β-nitroalkenes with indoles (see Eq. 2). Oven-dried NMR tubes were charged with 0.050 mmol of a trans-ß-nitroalkene, 0.15 mmol of the desired indole and 0.005 mmol (10 mol%) of the catalyst in 0.6 mL of $CDCl_3$ at -35 ˚C under an inert atmosphere. Reaction conversions were obtained at different times by ^{1}H NMR using the indole and the alkylation product resonances as indicated in Table S1. Second-order rates constants were obtained using the integrated rate law (i.e., $\ln([\text{indole}][\beta\text{-nitrostyrene}]_0/[\beta\text{-nitrostyrene}][\text{indole}]_0) = k([\text{indole}]_0 - [\beta\text{-nitrostyrene}]_0)t$) where $[\beta\text{-nitrostyrene}]_0$ and $[\text{indole}]_0$ are the initial concentrations and [β-nitrostyrene] and

[indole] are the concentrations at different times. The resulting kinetic data are given in Table S2. The catalyst can be recovered by normal phase MPLC using CH_2Cl_2/MeOH (95 : 5).

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Supporting Information Available: Kinetic data, NMR spectra, and HPLC traces. This material is available free of charge via the internet at http://pubs.acs.org.

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