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Metallocenium incorporated charge-enhanced thiourea catalysts†

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Several metallocenium derivatives were prepared including *N*-ferrocenium-*N*′-phenylthiourea tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate (BAr^F_4, 4a), *N*-methylferrocenium-*N*′-phenylthiourea BAr^F_4 (4b) and *N*-cobaltocenium-*N*′-phenylthiourea BAr^F_4 (5). These compounds are competent catalysts for the Friedel–Crafts alkylation of indoles with *trans*-β-nitrostyrenes, and are much more active than their reduced non-charged forms. The iron derivatives are less stable than the cobalt analog and were generated and used *in situ* whereas the cobalt-containing thiourea was isolated and characterized by X-ray crystallography. All three of these metallocenium salts have Lewis and Brønsted acidic sites which were exploited in tandem to afford charge-activated catalysts.

Introduction

Thioureas are prized catalysts for their ability to interact with a wide variety of substrates by forming complexes held together by two hydrogen bonds.[1] They are generally less active than metal-based Lewis acids, and the development of derivatives that lead to faster reactions are of considerable interest. The most notable species in this regard is *N*,*N*′-bis(3,5-bis(trifluoromethyl)phenyl)thiourea ($(3,5\text{-}(CF_3)_2C_6H_3NH)_2CS$), also known as Schreiner's thiourea (**1**).[2,3] It employs two 3,5-bis(trifluoromethyl)phenyl rings as electron-withdrawing groups to increase its acidity and improve its catalytic efficiency. Substitution of one of the aryl rings by a chiral group reduces the activity of the resulting catalyst, but it has proved to be an effective strategy for carrying out numerous enantioselective transformations.[4–9]

An alternative approach for increasing the efficacy of thiourea catalysts is to incorporate a positively charged substituent *in lieu* of a 3,5-bis(trifluoromethyl)phenyl ring.[10] One cationic center in the absence of additional electron-withdrawing groups such as in **2** (Fig. 1) was found to afford catalysts that outperform Schreiner's thiourea with its four electron-withdrawing CF_3 groups. Asymmetry was also exploited to carry out enantioselective transformations by replacing the phenyl ring in **2** with (1*S*,2*R*)-*cis*-1-amino-2-indanol to give **3**.[11,12]

Substituted metallocenium salts were recently reported, and these homogeneous Lewis acid catalysts are air and water tolerant.[13] This raised the possibility of appending an organocatalyst to the metallocenium framework to develop enhanced bi-, tri-, or multifunctional catalysts. In this study, we report our initial efforts in combining a thiourea with a metallocenium ion.[14] This includes the preparation of *N*-ferrocenium-*N*′-phenylthiourea tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate (BAr^F_4) (**4a**), *N*-methylferrocenium-*N*′-phenylthiourea BAr^F_4 (**4b**), and *N*-cobaltocenium-*N*′-phenylthiourea BAr^F_4 (**5**) (Fig. 2) along with their catalytic activity in the Friedel–Crafts alkylation of *trans*-β-nitrostyrenes with indoles.

Results and discussion

Thiourea **4a** was synthesized starting with ferrocene (**6**) as illustrated in Scheme 1. Iodination of **6** was carried out as described by Roemer and Nijhuis[15] but a more convenient work-up procedure adapted from Goeltz and Kubiak was used.[16] It involves the oxidation of residual ferrocene but not iodoferrocene by ferric chloride enabling the resulting ferrocenium ion to be removed by aqueous extraction. Substitution of the iodine in **7** by an amino group was subsequently accomplished using an iron and copper cocatalyst system developed by Gasser and coworkers.[17] This product (**8a**) was reacted with phenylisothiocyanate to afford the desired thiourea **9a**.

Oxidation of the metal center occurred readily, but isolation of clean material (**10**) proved to be difficult as indicated by a colorimetric change in the reaction solution from dark green to brown upon concentration. Salt metathesis of the resulting

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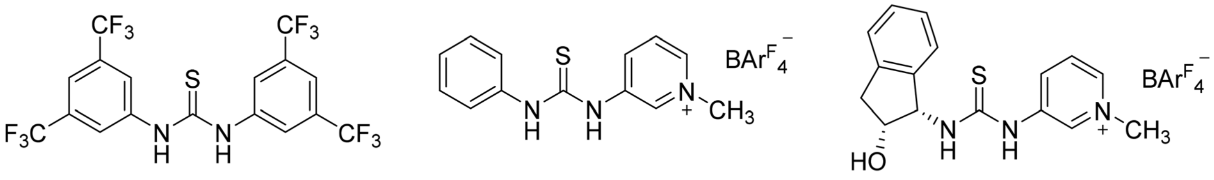
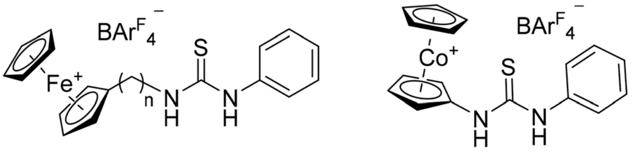


1 2 3

Fig. 1 Previously studied thiourea catalysts.



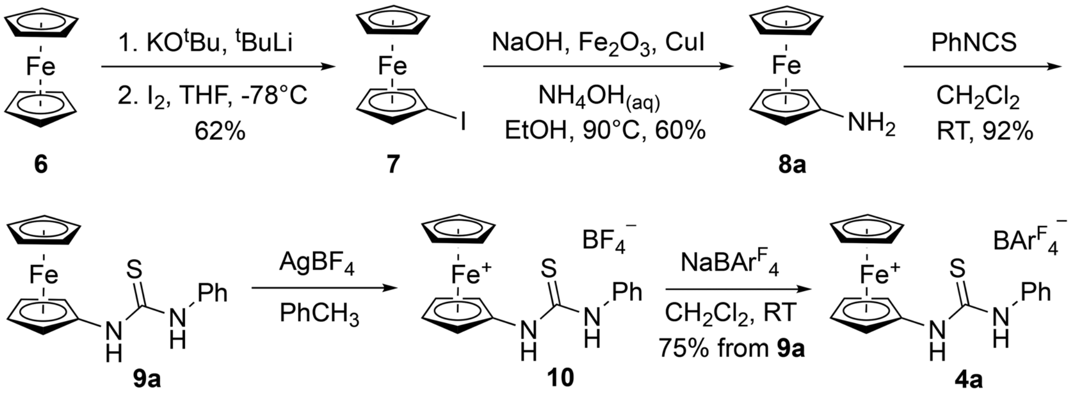
4a n = 0, **4b** n = 1 **5**

Fig. 2 Thiourea incorporated metallocenium salts explored in this work.

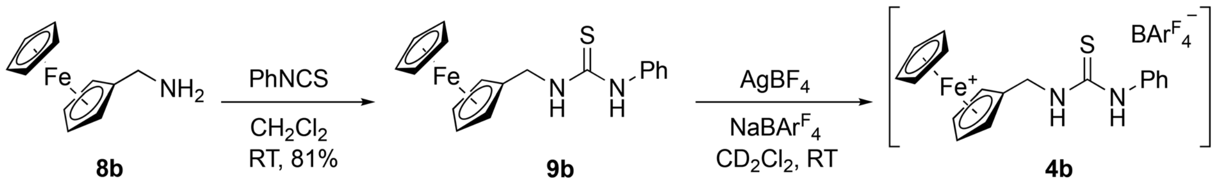
material with a slight excess (1.1 equiv.) of sodium BAr^F_4 afforded **4a** with varying purity. Consequently, *in situ* generation of this salt is preferred. This was accomplished by combining solid samples of $AgBF_4$, $NaBAr^F_4$, and **9a** under an argon atmosphere and then adding dry CH_2Cl_2 to dissolve the reactants. This enables the oxidation process to be conveniently monitored by a change in color from orange to dark green. After 5 min of stirring, the product solution was passed through a syringe filter and **4a** was ready for use in catalytic reactions.

To assess the effect of a methylene spacer between the thiourea and substituted cyclopentadienyl ring in **4a**, we decided to synthesize **4b**. This was accomplished by carrying out a reductive amination starting with commercially available ferrocenecarboxaldehyde. Conversion to its oxime followed by treatment with lithium aluminum hydride using previously reported procedures afforded ferrocenylmethylamine (**8b**).[18,19] It was transformed to *N*-ferrocenylmethyl-*N*'-phenylthiourea (**9b**) and oxidized *in situ* to the desired ferrocenium $BAr^F_4{}^-$ salt **4b** using the same methods as were used in the preparation of **4a** (Scheme 2). Isolation of the oxidized $BF_4{}^-$ and $BAr^F_4{}^-$ salts may be possible but *in situ* formation of **4b** *via* our general procedure is simpler and was sufficient for our needs.

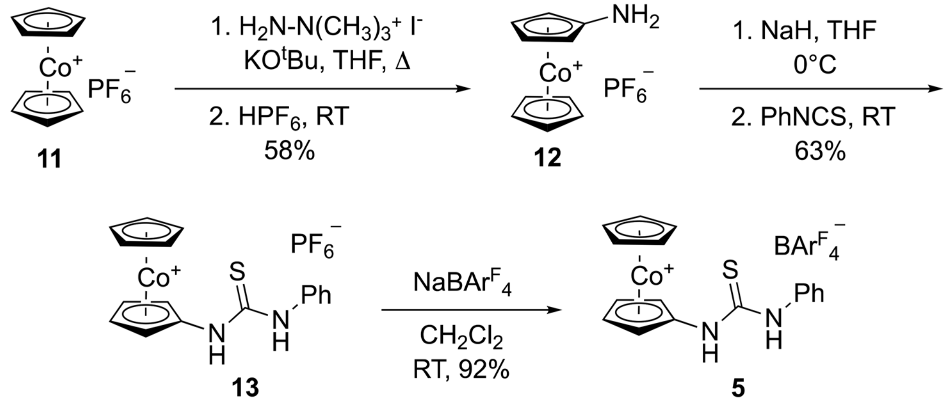
Cobaltocenium hexafluorophosphate (**11**) is a known compound which undergoes amination with 1,1,1-trimethylhydrazinium iodide to afford aminocobaltocenium hexafluorophosphate (**12**, Scheme 3).[20,21] The reduced nucleophilicity of this amine due to the positively-charged cobalt center accounts for why the desired thiourea **13** was not formed upon reaction with phenylisothiocyanate. This difficulty was overcome by



Scheme 1 Synthetic route for the preparation of *N*-ferrocenium-*N*′-phenylthiourea (**4a**).



Scheme 2 Synthetic route for the preparation of *N*-ferroceniummethyl-*N*′-phenylthiourea (**4b**).



Scheme 3 Synthetic route for the preparation of *N*-cobaltocenium-*N*′-phenylthiourea $BAr^F{}_4{}^-$ (**5**).

exploiting an approach by Heinze and coworkers for synthesizing bimetallocenes in which the aminocobaltocenium ion **12** is deprotonated with sodium hydride to give a more nucleophilic zwitterionic intermediate that can be trapped with electrophiles.[22] In this way, **12** was coupled to phenylisothiocyanate to yield the desired product, *N*-cobaltocenium-*N*′-phenylthiourea hexafluorophosphate (**13**). Salt metathesis with $NaBAr^F{}_4$ in dichloromethane enabled the $PF_6{}^-$ counteranion to be replaced by $BAr^F{}_4{}^-$, and upon trituration into hexanes, clean samples of **5** were obtained.

Suitable crystals of **13** for X-ray diffraction were grown by vapor diffusion of diethyl ether into a concentrated 1,2-dichloroethane solution of the cobaltocenium-derived thiourea over the course of several days. The unit cell of the crystallographic structure contains two unique forms of the ion pair, but for clarity only one of which is displayed in Fig. 3. In this structure the phenyl ring is rotated 50° relative to the plane defined by the thiouriedo group, and a smaller 6° twist is observed between the thiourea and its attached cyclopentadienyl ring. These angles are 42° and 12°, respectively, in the second structure that is omitted in the figure. Most notably, the sulfur atom interacts with an *ortho* hydrogen on the phenyl group (S⋯H = 2.504 Å) and α–H on the substituted cyclopentadienyl ring (S⋯H = 2.709 Å). These interactions are observed in both structures in the unit cell, moreover, similar bond networks were reported by Etter and coworkers in their studies on the solid state structures of a variety of phenyl-substituted (thio)ureas.[23,24] In addition, the enhanced reactivity of Schreiner's thiourea relative to derivatives without the electron-withdrawing trifluoromethyl groups is commonly attributed to similar interactions between the sulfur and an *ortho*-hydrogen on each aryl ring.[4,25] It is also worth noting that in the crystal structure there are two N–H hydrogen bond interactions with two fluorines of the hexafluorophosphate counteranion (*i.e.*, N–H⋯F distances of 2.109 and 2.564 Å are observed in the structure illustrated in Fig. 3).

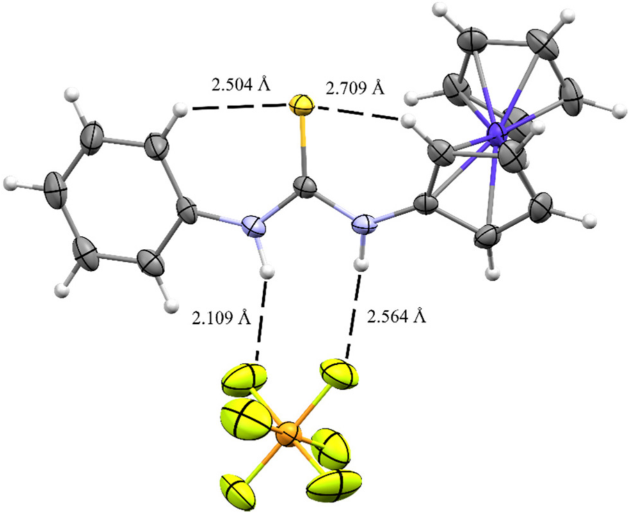
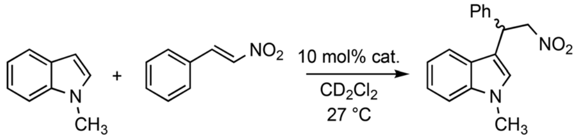


Fig. 3 X-ray crystallographic structure of **13**, where the hydrogen atoms are drawn as fixed size spheres and all other atoms are shown as thermal ellipsoids at the 50% probability level. A second structure in the unit cell is omitted for clarity, but the full unit cell is depicted in the ESI (Fig. S26†).

To assess the catalytic activity of **4a**, **4b**, and **5**, the Friedel–Crafts alkylation of *N*-methylindole with *trans*-β-nitrostyrene was examined under pseudo-first-order conditions (eqn (1)). This transformation is useful for the preparation of 3-substituted indoles and the synthesis of biologically active compounds.[6,26] It also has been used as a benchmark for a variety of catalysts including $BAr^F{}_4{}^-$ salts of ferrocenium ($FeCp_2{}^+$) and cobaltocenium ($CoCp_2{}^+$) ions.[13] Non-charged thiourea **9a** and $CoCp_2{}^+$ $BAr^F{}_4{}^-$ were not observed to be competent catalysts for the Friedel–Crafts reaction under the employed conditions. In contrast, **4a**, **4b**, and **5** were effective, and their rate constants for this process were subsequently determined (Table 1).



(1)

Multiple experiments with isolated samples of **4a** gave reaction half-lives spanning from 9.7 to 18 h. This variation is pri-

Table 1 Kinetic data for the catalyzed Friedel–Crafts reaction between *N*-methylindole and *trans*-β-nitrostyrene[a]

Catalyst	k (h^{-1})	$t_{1/2}$ (h)	k_{rel}
9a and $CoCp_2^+$ $BAr^F{}_4^-$ [b]	0.00019	3700	1.0
1	0.024	29	130
2	0.060	12	320
4a [c]	0.072	9.7	380
4b [c]	0.052	13	270
$FeCp_2^+$ $BAr^F{}_4^-$ [d]	0.048	14	250
5	0.043	16	230
$Co(C_5H_5)C_5H_4CO_2Me^+$ $BAr^F{}_4^-$ [d]	0.0028	250	15

[a] Reactions were carried out in CD_2Cl_2 at 27 °C with 10 mol% catalyst loadings and 50 and 500 mM concentrations of *N*-methylindole and *trans*-β-nitrostyrene, respectively. Rate constants are the average of 2 or 3 determinations. [b] No product was observed after 48 h with the cobalt catalyst and a 0.6% conversion was found with **9a** after 95 h. Consequently, the previously reported background rate (ref. 13) is given. [c] The catalyst was generated *in situ*. [d] Ref. 13.

marily due to the variable amount of catalyst decomposition that occurred upon its isolation. More reproducible and reliable data were obtained by generating **4a** *in situ*. This led to faster transformations and a narrower range of 9.1 to 10 h for the reaction half-life, which corresponds to a 400-fold rate enhancement relative to **9a** and the background reaction rate. It also represents a threefold improvement over Schreiner's thiourea and increases of 1.2 and 1.5 times relative to **2** and $FeCp_2^+$ $BAr^F{}_4^-$, respectively. Insertion of a methylene spacer between the cyclopentadienyl ring and the thiouriedo group leads to a modest reduction in rate, but the resulting catalyst is still a factor of two more active than **1**.

Cobaltocenium-containing thiourea **5** is marginally less active than the ferrocenium derived analogs. The latter species may be acting solely as Lewis acids that presumably bind to *trans*-β-nitrostyrene to activate it towards nucleophilic attack, but it appears that **5** is functioning as a hydrogen bond catalyst. This conclusion is based upon the observation that $CoCp_2^+$ $BAr^F{}_4^-$ does not promote the Friedel–Crafts test reaction and **5** is 15 times more active than $Co(C_5H_5)C_5H_4CO_2Me^+$ $BAr^F{}_4^-$, even though the latter species has an electron-withdrawing substituent that should increase the Lewis acidity of the metal. A plausible B3LYP/6-31G(d,p) transition structure for this process was computed in the absence of the weakly coordinating $BAr^F{}_4^-$ counteranion and is illustrated in Fig. 4. This structure is consistent with previous reports suggesting that thioureas electrophilically activate *trans*-β-nitrostyrene by forming hydrogen bonds with the nitro group.[27,28]

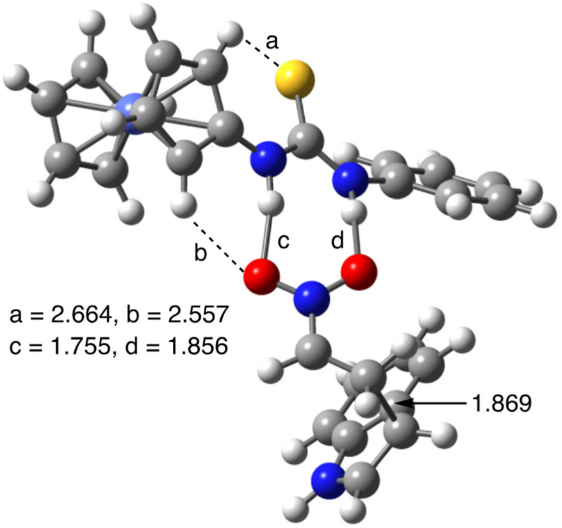


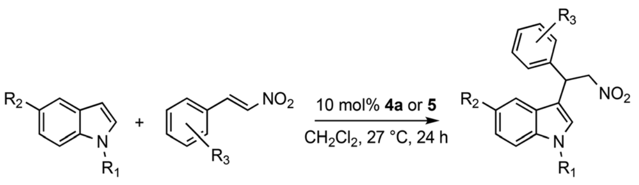
Fig. 4 Computed B3LYP/6-31G(d,p) transition structure for the Friedel–Crafts reaction of *trans*-β-nitrostyrene with indole catalyzed by **5**$^+$.

Table 2 Substrate scope for the Friedel–Crafts reaction of indoles and *trans*-β-nitrostyrenes using *in situ* generated ferrocenium catalyst **4a**

Reactants			Conv. (yield)[a]
R_1	R_2	R_3	
CH_3	H	H	81% (77%)
H	H	H	26% (22%)
H	OCH_3	H	45% (43%)
H	Cl	H	7% (6%)
H	H	2-Cl	51% (38%)
H	H	3-Br	35% (29%)
H	H	4-OCH_3	19% (14%)

[a] Yields were determined by qNMR and are given in parentheses.

To assess the broader reactivity and applicability of these catalysts, a substrate scope for the Friedel–Crafts reaction with several indoles and *trans*-β-nitrostyrene derivatives was carried out with **4a** and **5** (eqn (2)). The reaction conditions were not optimized, instead those used for the kinetic study were employed. Reaction conversions and yields by qNMR[29] were determined at 27 °C by ^1H NMR after 24 h with **4a** (Table 2). These clean transformations did not lead to noticeable byproducts but the catalyst is sensitive and undergoes varying amounts of decomposition over the course of the reaction as indicated by color changes from green or yellow-green at t = 0 to red or brown at t = 24 h. This also led to variable reaction conversions and product yields from experiment to experiment. Average values of 2 to 5 determinations for each entry are given in Table 2. The highest conversion (81%) to product was with *N*-methylindole and *trans*-β-nitrostyrene. Low to modest yields were obtained with the other substrates, but in general electron-donating substituents on the nucleophilic indole and electron-withdrawing groups on the electrophilic *trans*-β-nitrostyrene led to more efficient transformations.



(2)

Cobaltocenium thiourea **5** is more stable than **4a** and did not undergo any noticeable decomposition, which led to reprodu-

Table 3 Substrate scope for the Friedel–Crafts reaction of indoles and *trans*-β-nitrostyrenes using cobaltocenium thiourea **5**

Reactants			Conv.
R_1	R_2	R_3	
H	H	H	18% (no cat.)
H	H	H	91%
CH_3	H	H	97%
H	OCH_3	H	91%
H	Cl	H	35%
H	H	2-Cl	80%
H	H	3-Br	57%
H	H	4-OCH_3	8%

cible results from experiment to experiment. It is a less active catalyst, however, which led to a reduced product conversion for the alkylation of indole with *trans*-β-nitrostyrene (*i.e.*, 7% (**5**) *vs.* 26% (**4a**)). It was noted that a mixture of indole and *trans*-β-nitrostyrene forms a eutectic mixture that is partially liquid at room temperature, fortunately because this enables solvent-free reactions to be carried out (Table 3). A significant rate enhancement leading to a 91% conversion under solvent-free conditions was obtained in contrast to 18% when the catalyst was omitted. *N*-Methylindole is a slightly better substrate (97% conversion) and 5-methoxyindole (91%) is equally effective. An electron withdrawing chlorine atom at the 5-position of indole, however, reduces the efficiency of the reaction (35%). In contrast, electron withdrawing groups are more effective than electron donating substituents on the phenyl ring of *trans*-β-nitrostyrene (*i.e.*, R_3 = 2-Cl, 3-Br, and 4-MeO afford 80, 57, and 8% conversions, respectively).

Conclusions

In this work, robust synthetic methods for the generation of metallocenium-containing thioureas were developed. All compounds were found to be effective catalysts in a Friedel–Crafts alkylation reaction outperforming neutral analog **9a** and Schreiner's thiourea, a prized organocatalyst. *In situ* generated **4a** was the most active species studied, and when **4b** was used instead only a marginally slower reaction rate was observed despite the increased distance between the acidic N–H hydrogens and the charged iron center. Thiourea **5** provided greater rate enhancements compared to previously explored cobaltocenium derivatives, and it displayed better stability than the ferrocenium-containing species. It also functions as an organocatalyst that may exploit both Lewis and Brønsted acidic sites. This study lays the foundation for the development of charged-enhanced asymmetric thiourea catalysts with redox active metal centers for carrying out enantioselective transformations that exploit the rigidity and various modes of chirality that can be introduced into a metallocene.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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