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Enhancing the potential of the Michael addition reaction using Betti base-thiourea-derived organocatalysts for the one-pot synthesis of 2,4-disubstituted pyrroles

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A novel class of Betti base-thiourea-derived bifunctional organocatalysts have been synthesized. The hydroxy group of the naphthyl ring (Betti base) and substituted thiourea moiety effectively enhances the reactivity through hydrogen bonding and facilitates the Michael addition reaction of methyl ketones to nitroolefins, affording 2,4-disubstituted pyrroles, which are core structural motifs in pharmaceuticals and optoelectronic and agrochemicals materials. The comprehensive reaction optimization and broad substrate scope evaluation with moderate to high yields (75–93%) highlight the versatility and efficiency of this catalytic system under mild reaction conditions.

Introduction

Organocatalysis is one of the most thriving research domains in contemporary organic synthesis approaches after enzymatic and metal-based catalysis.[1] With the development of organocatalysis, substantial progress has been achieved in recent years in solving established synthetic difficulties by uncovering novel catalytic modes and beneficial integrations with various reaction types.[2] The approach of developing novel organocatalysts is growing into a dynamic activity, and the emergence of Brønsted acid catalysts that enabled increased activity for organic reactions is a prime example. A distinctive single key-activation mechanism recently paved the way to a more enzyme-like use of numerous interactions. The integration of different non-covalent interactions improved the activation methodologies of organocatalysts to obtain high selectivities.[3] In these organocatalysts, the activation approaches might lead to enhanced reactivities *via* H-donor acidity that could not be easily achieved by other means. The concept was found useful in many organic transformations.[4]

Among the different classes of organocatalysts, thiourea-based derivatives have attracted researchers; thus, the high hydrogen bonding activity of urea and thiourea derivatives has led to numerous studies in the field of molecular recognition. Through multi-hydrogen bonding, they have been utilised for detecting nitrate, sulfonic acid, carboxylic acid, and other substances.[5–7] According to recent reports from many groups, urea and thiourea can be used as excellent organocatalysts for synthesising various heterocyclic compounds[8–11] due to their ability to activate electrophiles *via* hydrogen bonding and offer a compelling alternative by stabilizing the transition state, thus facilitating a range of transformations enhancing both the yield and selectivity.

Many natural products and pharmaceutical molecules contain pyrrole moieties as the core structure (Fig. 1)[12,13] due to their vital role as key intermediates in the synthesis of various anticancer drugs, agrochemicals, and optoelectronic materials. Conventional pyrrole synthesis relies on classical condensation or multicomponent reactions, such as the Hantzsch, Huisgen, and Paal–Knorr syntheses, which require harsh conditions and extended reaction times and involve multistep processes with low atom economy, use of toxic reagents and reactions utilising gaseous reagents such as H_2 or CO at high pressures.[14]

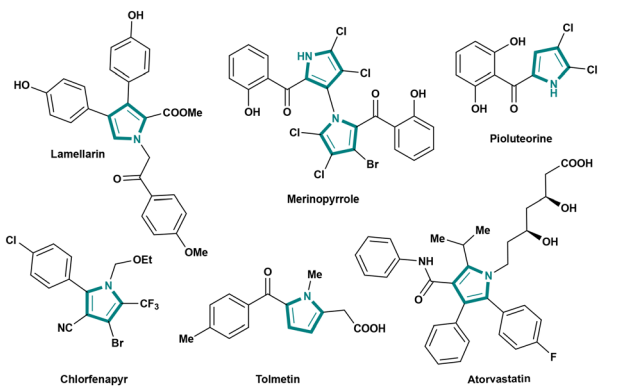

Fig. 1 Bio-active molecules containing a pyrrole moiety.

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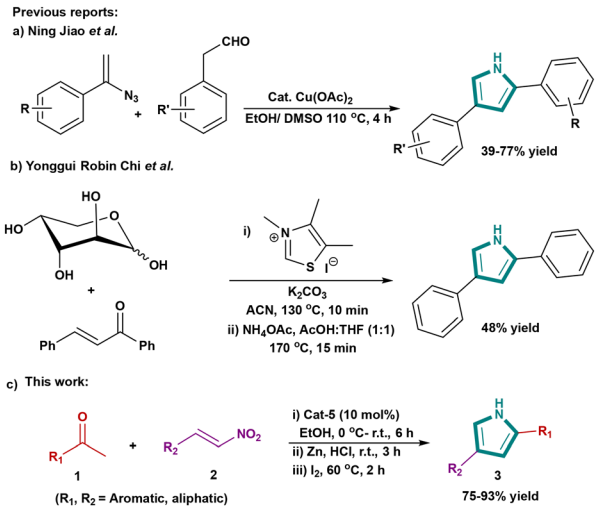
To overcome these challenges, various catalytic systems, including metal catalysts (*e.g.*, Pd, Cu, and Fe) and organocatalysts, have been reported for pyrrole synthesis, offering improved selectivity, use of milder conditions, and higher yields. Organocatalysis has developed into a compelling strategy in modern synthetic chemistry, such as for the Michael addition reaction of methyl ketones to nitroolefins, and the nitro functionality can be transformed into various functional groups, such as ketones, nitrile oxide, amines and carboxylic acids, which play vital roles in the synthesis of complex organic molecules, particularly in pharmaceuticals and natural product synthesis.[15]

In particular, the synthetic routes for preparing 2,4-diaryl-substituted pyrrole are underexplored. These methods include the reductive dimerization of phenacyl azides using samarium(II) iodide,[16] coupling of unactivated alkynes and amines with carbon monoxide using zirconocene-derived complexes,[17] hydrogenation of α-phenyl-β-benzoyl propionitrile followed by oxidation using selenium,[18] the condensation reactions like acyclic ketone with aziridine,[19] cyclo-condensation of aminoacetonitrile with different enones followed by dehydrocyanation,[20] copper-catalyzed reaction of aryl acetaldehydes with vinyl azides (Scheme 1b),[21] and formylation of 1,3-diphenyl prop-2-en-1-one using an N-heterocyclic carbene (NHC) catalyst followed by ammonium acetate under microwave irradiation (Scheme 1b).[22]

Continuing our interest in designing new synthetic methods[23] for biologically significant compounds such as imidazo[1,2-*a*]pyridines, 1,4-dihydro quinolines, 4-hydroxy coumarins, and tetrazoles, we present herein the synthesis of 2,4 disubstituted pyrroles *via* the Michael addition of nitrostyrene to the methyl ketone using Betti base-thiourea-derived bifunctional organocatalysts under mild reaction conditions (Scheme 1c).



Scheme 1 Previous reports (a and b) and this work (c).

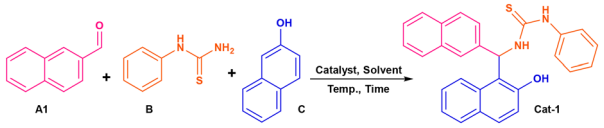
Results and discussion

Considering the significance of organocatalysts, we tried to design and synthesize Betti base-thiourea-derived bifunctional organocatalysts following the methods reported in the literature.[24] We obtained low to poor yields. Hence, various Lewis acids and reaction conditions were attempted to optimize the reaction, such as *p*-toluene sulfonic acid, ferric chloride, aluminium chloride, and titanium chloride, which afforded poor yield (Table 1, entries 2, 4, 5 and 7). While phosphorus pentoxide (Table 1, entry 3) failed to give the desired product, the best result was obtained with zinc chloride (Table 1, entry **6**). Then, different solvents were optimized. Among the solvents, ethanol at room temperature gave the highest product yield. Under the optimized condition, different organocatalysts were synthesized (Scheme 2).

To seek an efficient and optimal reaction condition for the one-pot synthesis of 2,4-disubstituted pyrroles under non-toxic and environmentally friendly conditions, we performed the reaction using acetophenone (0.5 mmol), nitrostyrene (0.5 mmol), and organocatalyst (0.05 mmol), as given in Table 2. We used L-proline, glycine, and boric acid, which afforded poor yields (Table 2, entries 2–4), while dextrose, urea, thiourea and phenylthiourea failed to give any products. Hence, different Betti base-thiourea-derived bifunctional organocatalysts were synthesized (Scheme 2) and used to optimize the proposed scheme (Table 2). Catalysts **1** to **6** were used, out of which catalyst **5** (**Cat-5**) gave the best results. For the solvent optimization, different solvents were used out of which ethyl acetate, dichloromethane, tetrahydrofuran and acetonitrile failed to give any products, while toluene, dichloroethane, methanol and DMSO gave poor yield (Table 2, entries 12–15).

The best result was observed with the ethanol solvent, and then the temperature was optimised as 0 °C in 6 hours (Table 2, entry **23**). Taking insights from the literature,[25a–c] UV-vis spectroscopy was performed to observe the interaction of starting materials with the organocatalyst **Cat-5**, for which **1a**, **2a** and **Cat-5** were taken in an equimolar ratio in ethanol, and the UV-vis spectra were recorded for individual samples as well as their cross combinations. Fig. 2 shows that **Cat-5** is interacting with both **1a** (blue curve) and **2a** (orange curve), while the red curve illustrates the bifunctional nature of the organocatalyst **Cat-5**, as it interacts with **1a** and **2a** simultaneously. The lower yield of the reaction with **Cat-1** as compared to **Cat-5** indicates that the hydroxy group on the aldehyde **A3** is enhancing the reactivity of the organocatalyst, as hydroxyl groups play a vital role by participating in hydrogen bonding and stabilising the transition state (Scheme 6),[25d–f] while **Cat-4** and **Cat-6**, having bulky chlorine attached at the *ortho*-position, provide hindrance for interaction with the starting materials, and hence, lower yields were observed. Catalyst recycling was then examined in Fig. 3, showcasing

Table 1 Optimization of the reaction conditions[a]

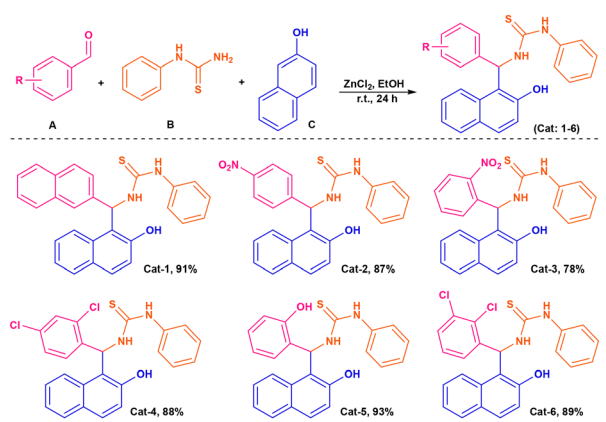


Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	% yield[b]
1.	—	EtOH	25	24	NR[c]
2.	*p*-TSA	EtOH	25	24	45
3.	P_2O_5	EtOH	25	24	NR
4.	$FeCl_3$	EtOH	25	24	8
5.	$AlCl_3$	EtOH	25	24	18
6.	**$ZnCl_2$**	**EtOH**	**25**	**24**	**91**
7.	$TiCl_3$	EtOH	25	24	9
8.	BBr_3	EtOH	25	24	Trace
9.	H_2SO_4	EtOH	25	24	5
10.	$ZnCl_2$	DCM	25	24	85
11.	$ZnCl_2$	Toluene	25	24	79
12.	$ZnCl_2$	DMSO	25	24	79
13.	$ZnCl_2$	MeCN	25	24	79
14.	$ZnCl_2$	EtOH	40	24	79
15.	$ZnCl_2$	EtOH	78	24	85

[a] Reaction conditions: (i) **A** (1.0 mmol), **B** (1.0 mmol), **C** (1.0 mmol), Catalyst (0.2 mmol) in 5.0 mL EtOH. [b] Isolated yield. [c] NR = no result.

that the organocatalyst can be easily reused (recovered from the reaction mixture using column chromatography) up to four times without any noticeable drop in conversion and yield of the product.

Under the optimised reaction conditions (Table 2, entry **23**), 2,4-disubstituted pyrroles were successfully synthesised using the dual interaction of the organocatalyst (**Cat-5**). Different methyl ketones and nitrostyrene derivatives, such as mono- and di-substituted, electron-withdrawing, and electron-donating groups, were investigated, and minor yield differences were observed (Scheme 3). Nitrostyrene having electron-withdrawing moieties, such as *p*-bromo, *p*-chloro, *p*-nitro and *o*-nitro afforded **3b**, **3c**, **3e** and **3j** in 87%, 89%, 69% and 55% yields, respectively, while the electron-donating groups such as *p*-methoxy, *p*-methyl, *o*-methyl and *o*-methoxy gave **3d**, **3q**, **3s** and **3ae** in 93%, 91%, 86% and 81% yields, respectively. Similarly, the aromatic methyl ketone having electron-withdrawing moieties such as *p*-chloro, *p*-bromo and *p*-nitro afforded **3f**, **3i** and **3l** in 88%, 90% and 68% yields, respectively. Aromatic methyl ketone gave **3z**, **3aa** and **3ad** in 90%, 88% and 91% yields, respectively. Di-substituted nitrostyrene and methyl ketones afforded **3m**, **3n**, **3o**, **3t**, **3v** and **3ag** in 87%, 92%, 89%, 90%, 80% and 77% yields, respectively. The biologically important moieties such as tetrazole and coumarin were integrated into the starting materials and afforded **3w**, **3x**, **3ah** and **3ai** in 79%, 75%, 81% and 76% yields, respectively. The lower yield of starting materials containing nitro groups confirmed that the interaction of nitrostyrene with the organocatalyst as the nitro group of starting materials hinders the nitrostyrene interaction. Following the optimized conditions, we also tried Scheme 4 but failed to obtain substrates **3aj**, **3aj** and **3ak** probably due to the steric hindrance and *cis–trans* geometry in the transition state **3** (**TS-3**) (Scheme 6). Similarly, to increase the substrate scopes, we also performed reactions with cinnamonitrile with methyl ketones. However, it failed to give the desired product, which might be due to less hydrogen bonding interaction with cinnamonitrile and a Betti base-thiourea-derived bifunctional organocatalyst. The scale-up reaction employing the ongoing scheme gave the desired products **3d** (1.02 g) and **3n** (1.44 g), with good yields of 82% and 81%, respectively (Scheme 5).

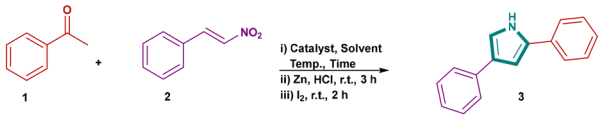


Scheme 2 Substrate scopes for the as-synthesized organocatalysts.

Plausible mechanism

Following the literature survey,[26] the plausible reaction mechanism proposed is the interaction of nitrostyrene (**2a**) with the organocatalyst (**Cat-5**) leading to the transition state **1** (**TS-1**) which further interacted with methyl ketone (**2a**) to form the transition state **2** (**TS-2**). The activated methene group in the transition state **3** (**TS-3**) attacked nitrostyrene,

Table 2 Optimization of the reaction conditions[a,b]



Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	% yield[c]
1.	—	EtOH	0	24	NR[d]
2.	L-Proline	EtOH	0	24	12
3.	Glycine	EtOH	0	24	8
4.	Boric acid	EtOH	0	24	14
5.	Di-PTU[e]	EtOH	0	24	Trace
6.	**Cat-1**	EtOH	0	24	67
7.	**Cat-2**	EtOH	0	24	75
8.	**Cat-3**	EtOH	0	24	81
9.	**Cat-4**	EtOH	0	24	74
10.	**Cat-5**	EtOH	0	24	93
11.	**Cat-6**	EtOH	0	24	79
12.	**Cat-5**	Toluene	0	24	21
13.	**Cat-5**	DCE	0	24	5
14.	**Cat-5**	MeOH	0	24	61
15.	**Cat-5**	DMSO	0	24	24
16.	**Cat-5**	EtOH	0	10	93
17.	**Cat-5**	EtOH	0	6	93
18.	**Cat-5**	EtOH	10	4	91
19.	**Cat-5**	EtOH	25	4	85
20.	**Cat-5**	EtOH	50	4	28
21.	**Cat-5**	EtOH	78	4	93
22.	**Cat-5** (5 mol%)	EtOH	0	6	57
23.	**Cat-5 (10 mol%)**	**EtOH**	**0**	**6**	**93**
24.	**Cat-5** (20 mol%)	EtOH	0	6	93

[a] Reaction conditions: (i) **1** (0.5 mmol), **2** (0.5 mmol), Catalyst (0.05 mmol) in 1.0 ml EtOH. (ii) Zn dust (1.0 mmol), HCl (0.5 ml). (iii) I_2 (0.5 mmol). [b] Catalysts dextrose, urea, thiourea and phenylthiourea did not give any reaction. Similarly, no reaction occurred in EtOAc, DCM, THF and CH_3CN solvents. [c] Isolated yield. [d] NR = no result. [e] Di-PTU = diphenylthiourea.

giving the intermediate-1 (**Int-1**) which was reduced to form the intermediate-2 (**Int-2**) using zinc and conc. HCl (ref. 27) and further aromatized using iodine[28] in one-pot synthesis that led to the desired product **3a** upon oxidation with iodine. Moreover, **Int-1** and **Int-2** were isolated separately and confirmed by ^{1}H and ^{13}C-NMR.

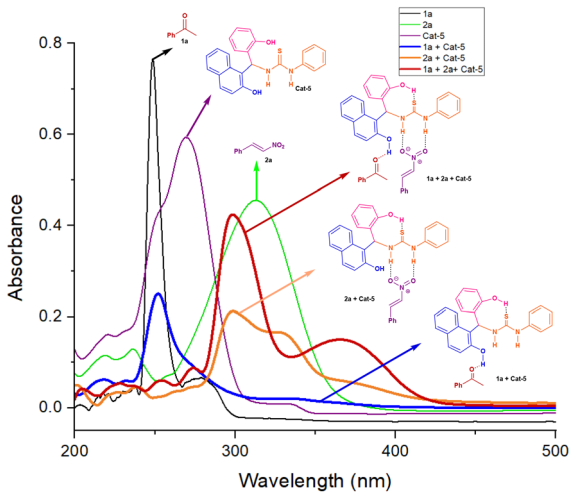


Fig. 2 Interaction of the starting materials with **Cat-5**.

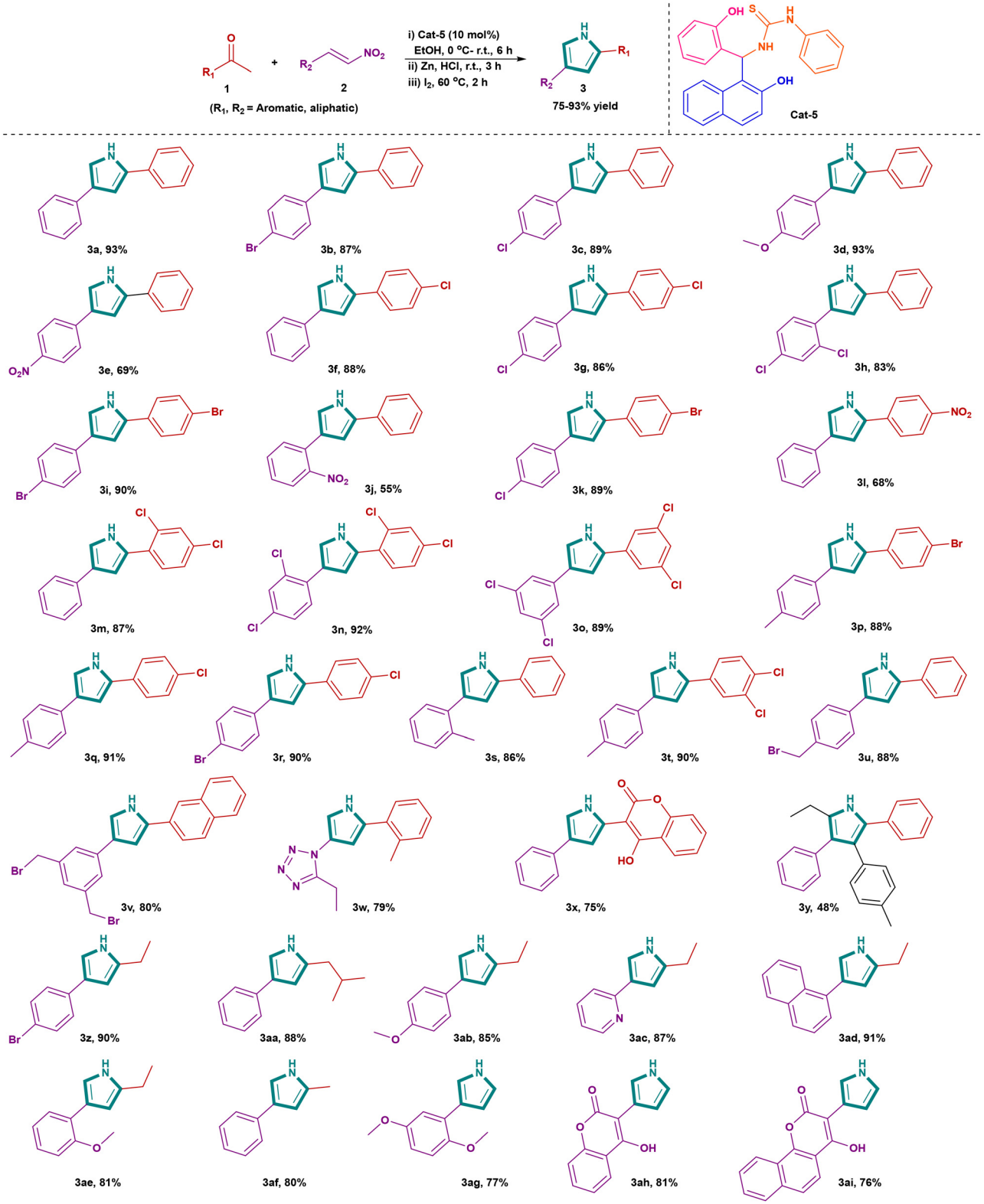
Conclusions

In this study, we have developed a novel Betti base-thiourea-derived bifunctional organocatalyst for promoting the Michael addition reaction of methyl ketones and nitrostyrenes for the synthesis of 2,4-disubstituted pyrroles. The thiourea catalyst-bearing hydrogen bonding sites efficiently facilitated the Michael addition through hydrogen-bonding activation, achieving good to excellent yields under mild reaction conditions, highlighting its versatility in heterocyclic chemistry. The mechanistic insights and a broad range of substrate scope evaluations further adduce the robustness and practical applicability of the catalytic system.

Experimental

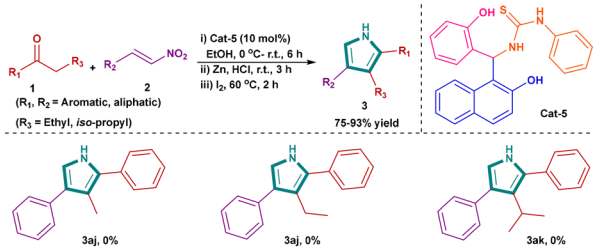
General procedure

(a) Synthesis of organocatalysts. First, 0.2 mmol of zinc chloride was added to a round-bottom flask containing a solution of 1.0 mmol of each of aldehyde, phenylthiourea and beta-naphthol in 5.0 ml of ethanol, and the resulting solution was stirred at room temperature for 24 hours. After completion of the reaction, 25.0 ml of cold water was added to afford the precipitate, which was filtered off and recrystallized using ethanol.

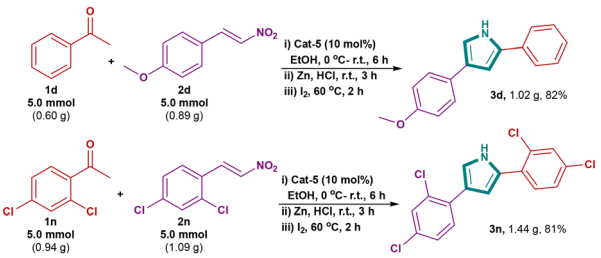


Scheme 3 Substrate scope of **Cat-5**.

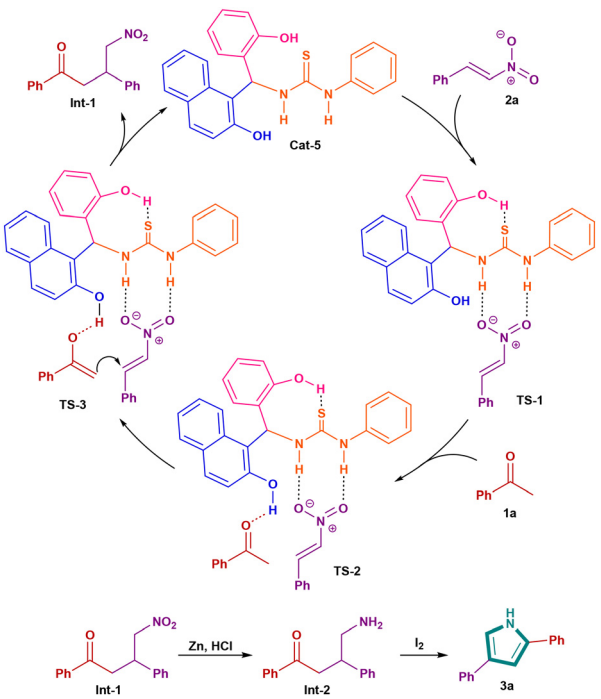
(b) Synthesis of 2,4-disubstituted pyrroles. First, 0.5 mmol of methyl ketone was added to a round-bottom flask containing a solution of nitrostyrene (0.5 mmol) and **Cat-5** (0.05 mmol) in 1.0 ml of ethanol kept at 0 °C and stirred for 6 h at room temperature. After consumption of the starting material, 1.0 mmol of zinc dust and 0.5 ml of HCl were added at the same temperature and stirred for 2 hours. Afterwards, 0.5 mmol of I_2 was added and stirred at 60 °C for



Scheme 4 Failed substrate scope.



Scheme 5 Scale-up synthesis.



Scheme 6 Plausible reaction mechanism.

3 hours to afford the final product, which was purified by column chromatography.

*2,4-diphenyl-1H-pyrrole (**3a**).* Yield 93%; brown solid; mp: 174–176 °C. ^{1}H NMR (500 MHz, CHLOROFORM-*D*) δ 8.49 (s, 1H), 7.49 (td, J = 8.4, 1.7 Hz, 4H), 7.43–7.21 (m, 6H), 7.11 (dd, J = 2.7, 1.7 Hz, 1H), 6.77 (dd, J = 2.8, 1.7 Hz, 1H). ^{13}C NMR (126 MHz, CHLOROFORM-*D*) δ 135.3, 132.1, 132.0, 131.0, 129.2, 128.8, 126.9, 126.0, 125.2, 125.1, 116.0, 104.4. IR spectrum (KBr), ν_{max}, cm^{-1}: 3448 (NH), 1549, 1422, 1434, 1173, 1094, 1076, 953, 706. HRMS analysis: $(M - H)^+$ = 218.0972. CHNS analysis ($C_{16}H_{13}N$): calculated: C (87.64%), H (5.98%), N (6.39%) found: C (87.68%), H (5.99%), N (6.32%).

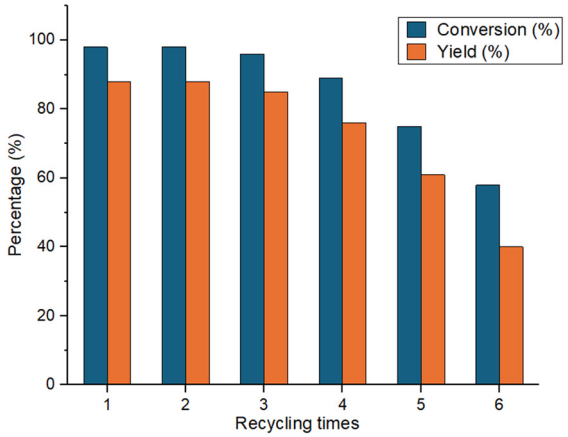


Fig. 3 Catalyst recovery cycles.

Author contributions

Rajeev Singh – experiments and original writing. Naseem Ahmed – conceptualization, editing and writing.

Conflicts of interest

There are no conflicts to declare.

Data availability

The authors declare that the data will be available as reported in this paper.

Supporting information for this article is available. See DOI: **https://doi.org/10.1039/D5CY00312A**.

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