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Novel axially chiral bis-arylthiourea-based organocatalysts for asymmetric Friedel–Crafts type reactions

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Abstract—It has been shown that catalytic amounts (10–20 mol %) of novel axially chiral bis-arylthioureas promote the asymmetric organocatalytic Friedel–Crafts type addition of indole and *N*-methylindole to nitroolefins. The optimum catalyst is capable of promoting the reaction between challenging substrates such as *N*-methylindole and nitroolefins bearing aliphatic β-substituents with enantioselectivity unprecedented for an organocatalytic system.

The addition of π-excessive heteroaromatic compounds to activated olefins (a process analogous to the Friedel–Crafts alkylation reaction[1,2]) is a reaction of considerable synthetic utility, which can provide access to valuable precursors to compounds of biological and medicinal interest.[3] Over the past five years, a number of transition-metal complexes incorporating either chiral bis-oxazoline[4–12] or salen[13] ligands have been shown to serve as efficient catalysts for asymmetric variants of such processes, with the enantioselective addition of indoles to a wide variety of α,β-unsaturated electrophiles being the subject of particularly intensive investigation. McMillan and co-workers first demonstrated the feasibility of complementary organocatalytic strategies with the development of chiral imidazolidinone salts for the promotion of enantioselective Friedel–Crafts (FC) alkylations of pyrroles[14a] and indoles[14b] with α,β-unsaturated aldehydes via iminium ion catalysis, however, since these seminal studies, the rate of expansion of the scope of the reaction with respect to the electrophilic component has been relatively slow.

In this context, the addition of indoles to nitroolefins is an attractive target for asymmetric organocatalyst design as, (a) the analogous uncatalysed reaction generally requires solvent-free conditions/elevated temperatures and is characterised by variable yields and polymerisation of the olefin component,[15] (b) the presence of two Lewis-basic oxygen atoms potentially allow for activation of the olefin by the acceptance of two hydrogen bonds from a suitably designed catalyst[16,17] and, (c) the versatile nitro moiety is readily amenable to subsequent modification (e.g., reduction to yield substituted chiral tryptamines).

Ricci et al. have found that bis-arylthioureas **1** (Fig. 1) effectively promote the addition of π-excessive aromatic compounds to nitroolefins.[18a] Very recently the same group demonstrated that bifunctional catalyst **2** (20 mol %, Fig. 1) promoted the addition of indoles to nitrostyrenes with high levels of stereoinduction, however, the corresponding *N*-alkylated indoles not susceptible to bifunctional catalysis gave near-racemic products under optimised low-temperature conditions.[18b] As this report emerged we were engaged in the design of chiral thioureas for the enantioselective promotion of FC reactions involving challenging *N*-alkyl indoles and nitroolefins. A recent report from Jørgensen and co-workers[19] describing the development of a highly active bis-sulfonamide catalyst **3** (Fig. 1) capable of promoting the asymmetric addition of *N*-methylindole to nitrostyrenes with up to 50% ee prompted us to report our preliminary results in this area.

Our catalyst design-rationale is straightforward; from both previous studies in our laboratory on the catalysis of the Baylis–Hillman reaction[20] using thiourea derivatives such as **1** and seminal work by Schreiner[21] on the promotion of Diels–Alder reactions by the same class of

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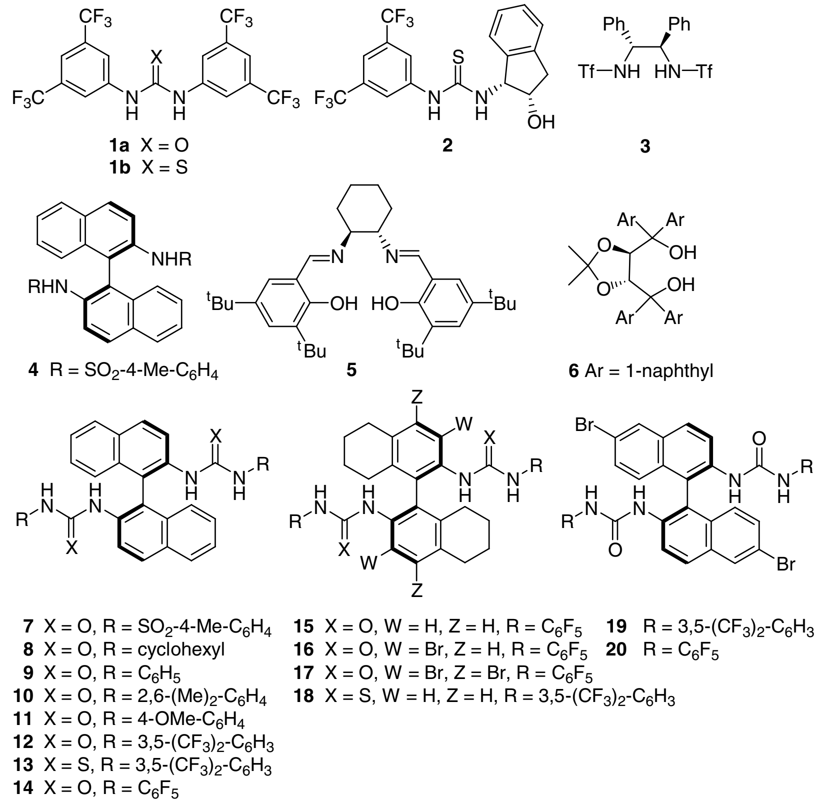


Figure 1. Hydrogen bond donating organocatalysts.

compound[22]—it is clear that replacement of either one, or both *N*-aryl substituents with an aliphatic moiety results in greatly attenuated catalyst activity;[23,24] we therefore designed and prepared axially chiral catalysts **4** and **7**–**20**, which retain the bis-*N*-aryl structural *motif*. The catalysts were devised to probe the influence of the steric and electronic characteristics of *both* the chiral and achiral *N*-aryl substituents on catalyst efficacy and enantioselectivity. Catalysts **4**–**17** were evaluated in the asymmetric FC addition of the traditionally challenging substrate *N*-methylindole (**21**) to (*E*)-β-nitrostyrene (**22**) at ambient temperature in $CDCl_3$.[25] The results of these studies are presented in Table 1.

In the absence of catalyst, only trace levels of FC adduct **23** were observable after 3 days reaction time (Table 1, entry 1). The catalytic importance of the thiourea moiety is evident from both the clear superiority (in terms of efficacy) of **7** over (*R*)-bis-*N*-tosyl-BINAM-derivative **4** (Table 1, entries 2 and 5), and the catalytic inactivity of diols **5** and **6**.[26] Disappointingly, catalysis with tosyl-urea **7** was completely unselective. Bis-*N*-arylthiourea-based catalysts incorporating either aliphatic- or electron-rich/sterically hindered aromatic substituents (**8**–**11**, entries 6–9) did furnish **22** with low enantioselectivity, however these materials were decidedly slow promoters of the reaction. In contrast, analogues bearing electron-deficient aromatic substituents (**12**–**14**) proved considerably more active and marginally more selective catalysts.

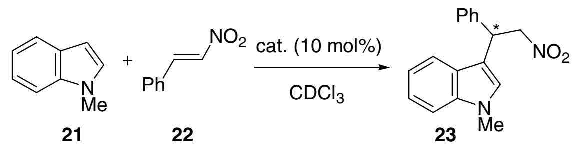
While urea **12** and its thiourea analogue **13** afforded the product with similar levels of stereoinduction at room temperature (entries 10 and 11), at −30 °C the significantly more active **13** gave much improved levels of selectivity. The superiority (in terms of selectivity) of decafluoro-catalyst **14** to either **12** or **13** is of interest—to the best of our knowledge the *N*-pentafluorophenyl moiety has not previously been evaluated as a substituent in *N*-aryl urea-based catalysts,[17] regrettably this is concomitant with a reduction in activity which renders **14** less convenient to utilise than **12** at lower temperatures (entries 8–15).

Our attention next turned to the chiral bis-naphthyl moiety. Although alteration of this catalyst sector did (as expected) influence both catalyst efficacy and selectivity, no single modification led to appreciable improvements in both concurrently. Octahydro-analogues of **13** and **14** (**15** and **18**, respectively) were significantly less efficient (yet reasonably selective) catalysts, while mono- and di-bromo derivatives of **15** (**16** and **17**, respectively) gave racemic products (entries 16–19). It is noteworthy that the activity of urea-based catalyst **12** could be substantially augmented via the installation of bromo substituents at C-6 and C-6′ (catalyst **19**, entries 20 and 21).

The results of these studies allow the identification of the simple thiourea **13** as the catalyst structure possessing the most practical balance of properties in terms of both catalytic activity and stereoinductive capability.

To probe the compatibility of the catalyst with substrates with a variety of steric and electronic characteristics we investigated the addition of **21** to both aromatic and aliphatic nitroalkenes **24**–**29** catalysed by **13** at low

Table 1. Catalysis of the addition of **21** to **22** by **4**–**20**



Entry	Catalyst	Concn (M)	Temperature (°C)	Time (h)	Conversion (%)[a]	ee (%)[b]
1	—	0.36	rt	72	<2	—
2	**4**	0.36	rt	72	<2	—
3	**5**	0.36	rt	72	<2	—
4	**6**	0.36	rt	72	<2	—
5	**7**	0.36	rt	20	80 (100)[c]	0
6	**8**	0.36	rt	113	2	7
7	**9**	0.36	rt	113	2	4.5
8	**10**	0.36	rt	113	14	10
9	**11**	0.36	rt	113	4	8
10	**12**	0.36	rt	113	100	11
11	**13**	0.36	rt	20	66 (100)[d]	12
12	**13**	0.36	−30	64	88	30
13	**14**	0.36	rt	113	55 (93)[c]	15
14	**14**	0.36	−20	167	42	34
15	**14**	0.72	−20	70	80	28
16	**15**	0.36	rt	65	23	20
17	**16**	0.36	rt	113	29	0
18	**17**	0.36	rt	113	46	0
19	**18**	0.36	−30	113	15	28
20	**19**	0.36	rt	22	100	5
21	**19**	0.36	−20	70	100	8
22	**20**	0.36	rt	167	93	16
23	**20**	0.72	−30	167	38	23

[a] Determined by ^1H NMR spectroscopy.
[b] Determined by HPLC using a Chiralpak AD-H column (250 × 4.6 mm).
[c] Conversion after 166 h in parenthesis.
[d] Conversion after 160 h.

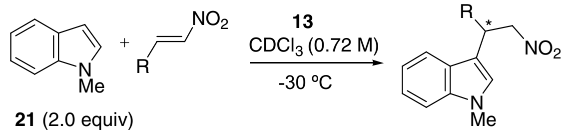
temperature (Table 2). Aromatic nitroalkenes bearing electron-withdrawing functionality (entries 2–3) and sterically hindering *ortho*-substitution (entry 4) gave FC adducts **30**–**32** with similar enantioselectivity to that obtained using the parent styrene **22**, while the electron-rich heterocyclic analogue **27** underwent conversion to **33** at an appreciable rate at ambient temperature only. Contrary to the trend observed by Jørgensen using bis-sulfonamide **3**,[19] nitroolefins with aliphatic substituents (often more difficult substrates in asymmetric organocatalytic Michael reactions)[16,19] *underwent FC addition with improved enantioselectivity relative to their aromatic counterparts in the presence of* **13** (entries 6 and 7). Interestingly, the FC addition of indole itself to **22** catalysed by **13** proceeded slowly, however, adduct **37** was isolated with 10% ee (Scheme 1) after chromatography due in part to a demonstrable silica-catalysed FC reaction[19] which can be problematic in cases involving the purification of reaction mixtures where conversion is incomplete.

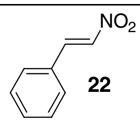
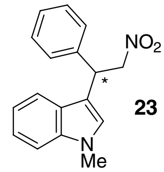
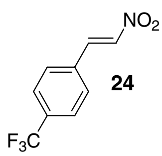
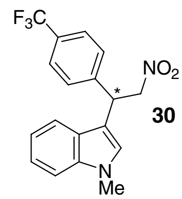
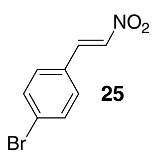
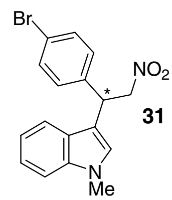
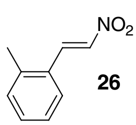
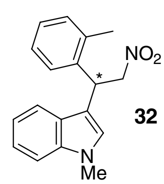
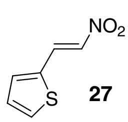
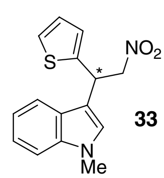
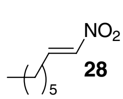
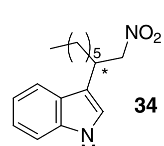
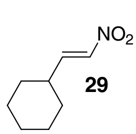
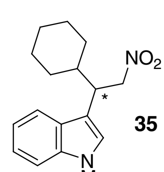
With a view towards better understanding both the catalyst mode of action and the origins of the stereoselectivity in these reactions we determined the X-ray crystal structure of **13**.[27] To our surprise the structure indicated that the preferred conformation of the thiourea moiety is *s-trans*, *cis*[28] and not the expected[21,29,30] *s-cis*, *cis* isomer (Fig. 2).

Naturally this unusual thiourea structure (if indicative of the active conformation in solution) precludes a substrate binding scenario in which the nitroolefin (and by extension the transition state of the rate determining addition step) accepts two hydrogen bonds from a *single thiourea moiety*. Binding of the electrophile nitro functionality between thiourea moieties is also unlikely as the most suitably oriented hydrogen atoms (i.e., H_a and H_b, Fig. 2) are separated by 3.53 Å,[27] while the O–O distance in the nitrostyrene is considerably shorter (ca. 2.15 Å). These preliminary studies therefore support the intriguing possibility that the catalytic activity of **13** could be derived from the binding of the substrate/transition state nitro group *to a single thiourea hydrogen atom*.[19]

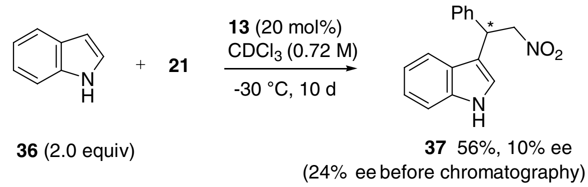
In summary, we have prepared and evaluated a small library of novel thiourea-based axially chiral organocatalysts for the asymmetric addition of *N*-methylindole to nitroolefins. Initial screening studies led to the identification of the relatively simple and readily prepared[31] (*S*)-**13** as the optimal structure. While **13** is less active than the prototype literature organocatalyst **3**,[19] it is capable of the promotion of the addition of *N*-methylindole **21** to nitrostyrenes in good yield and with comparable (albeit lower) levels of enantioselectivity. An advantage associated with the use of **13** in these reactions is its compatibility with challenging nitroolefin substrates

Table 2. Asymmetric addition of **21** to nitroalkenes catalysed by **13**: reaction scope



Entry	Substrate	mol % (catalyst)	Product	Time (h)	Yield[a] (%)	ee[b] (%)
1	 **22**	10	 **23**	117	98	30
2	 **24**	10	 **30**	140[c]	89	36
3	 **25**	20	 **31**	287	54	28
4	 **26**	10	 **32**	115	78	28
5	 **27**	10	 **33**	140[d]	60[e]	12
6	 **28**	20	 **34**	69	76	50
7	 **29**	20	 **35**	120	65	43

[a] Isolated yield.
[b] Determined by HPLC-Chiralpak AD-H or AS column (250 × 4.6 mm).
[c] Reaction concn 0.36 M.
[d] At rt.
[e] Refers to conversion.



Scheme 1. Asymmetric addition of indole to **21**.

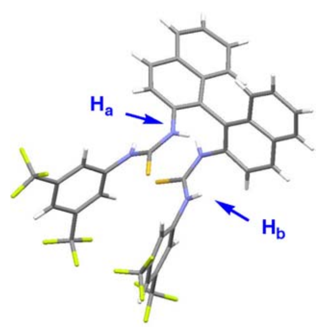


Figure 2.

incorporating β-aliphatic substituents, which undergo FC addition with **21** in the presence of thiourea **13** with considerably higher enantioselectivity than the literature benchmark for an organocatalytic system.[19] Investigations to determine the solution-phase structure of the catalyst in order to facilitate further optimisation, and the evaluation of **13** (and **7**–**20**) as organocatalysts in other asymmetric carbon–carbon bond forming transformations are underway.

Acknowledgements

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30. The X-ray crystal structure of cyclohexyl-substituted urea-based catalyst **8** exhibited an *s-cis,cis* urea conformation. The distance between the urea hydrogen atoms is 2.12 Å.
31. In a 10 cm^3 flask fitted with a stirring bar under an atmosphere of N_2 (balloon), bis-3,5-trifluoromethylphenyl isothiocyanate (276 μL, 1.5 mmol) was added via syringe

to a solution of (*S*)-1,1′-binaphthyl-2,2′-diamine (205 mg, 0.72 mmol) in CH_2Cl_2 (1.2 cm^3). The resulting solution was left to stir overnight at room temperature. Removal of the solvent in vacuo and purification of the product by column chromatography gave (*S*)-**13** as a white solid (546 mg, 91%), mp 137–138 °C, $[\alpha]_D^{20}$ −126 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.24 (br s, 2H), 8.10 (d, *J* = 8.7 Hz, 2H), 7.97 (d, *J* = 8.3 Hz, 2H), 7.88 (d, *J* = 8.7 Hz, 2H), 7.71 (br s, 2H), 7.68 (s, 4H), 7.68 (s, 2H), 7.50 (m, 2H), 7.29 (m, 2H), 7.13 (d *J* = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) 179.8, 138.6, 133.4, 132.6, 132.2, 131.7 (q, *J* = 33.7 Hz), 130.5, 128.6, 128.0, 127.3, 126.9, 125.2, 124.6, 124.2, 122.6 (q, *J* = 272.9 Hz), 119.5. IR (film) ν 3265, 1688, 1498, 980 cm^{-1}. HRMS (ESI) calcd for $[C_{38}H_{22}F_{12}N_4S_2{+}Na]^+$ requires 849.0992. Found 849.1013.