nature chemistry

ARTICLES

PUBLISHED ONLINE: 16 SEPTEMBER 2012 | DOI: 10.1038/NCHEM.1450

Thiourea-catalysed ring opening of episulfonium ions with indole derivatives by means of stabilizing non-covalent interactions

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Small organic and metal-containing molecules (molecular mass <1,000) can catalyse synthetically useful reactions with the high levels of stereoselectivity typically associated with macromolecular enzymatic catalysts. Whereas enzymes are generally understood to accelerate reactions and impart selectivity as they stabilize specific transition structures through networks of cooperative interactions, enantioselectivity with chiral, small-molecule catalysts is rationalized typically by the steric destabilization of all but one dominant pathway. However, it is increasingly apparent that stabilizing effects also play an important role in small-molecule catalysis, although the mechanistic characterization of such systems is rare. Here, we show that arylpyrrolidino amido thiourea catalysts catalyse the enantioselective nucleophilic ring opening of episulfonium ions by indoles. Evidence is provided for the selective transition-state stabilization of the major pathway by the thiourea catalyst in the rate- and selectivity-determining step. Enantioselectivity is achieved through a network of attractive anion binding, cation-π and hydrogen-bond interactions between the catalyst and the reacting components in the transition-structure assembly.

Multifunctional urea and thiourea derivatives are known to promote enantioselective reactions of cationic species in nonpolar media by binding the corresponding counter-anion through hydrogen bonding[1–4], with selectivity imparted through a combination of electrostatic association and additional non-covalent interactions that differentiate the diastereomeric transition structures that lead to the product enantiomers[5–7]. We sought to extend the anion-binding catalysis concept to episulfonium ions, which are highly reactive electrophilic species that readily undergo diastereospecific bond-forming reactions with nucleophiles[8–11]. Recently, Toste and co-workers demonstrated enantioselective catalysis of the addition of alcohols to episulfonium ions using a chiral phosphoric acid catalyst[12]. On the basis of our previous work in anion-binding catalysis, we envisioned that a urea or thiourea could serve as a suitable host for an episulfonium ion formed *in situ* through interactions with the counteranion (Fig. 1). High enantioselectivity might be achieved if additional interactions between the catalyst and episulfonium intermediate could be incorporated to stabilize differentially the diastereomeric pathways. This hypothesis was investigated in the context of a Friedel–Crafts-type indole alkylation reaction[13].

Results and discussion

Reaction methodology development. Preliminary efforts to identify a suitable episulfonium-ion precursor revealed that a relatively non-nucleophilic leaving group was required to achieve the desired reactivity. Ultimately, we found that stable trichloroacetimidates of type **1a** (ref. 12) were particularly useful substrates (equation (1), see Table 1) that undergo protonolysis and substitution with a variety of strong Brønsted acids to form a *meso*-episulfonium ion with a counteranion that can be varied readily, based on the identity of the acid employed.

A wide variety of chiral urea and thiourea derivatives was evaluated in the model reaction (Table 1). Only arylpyrrolidine-derived thioureas of type **3** were found to induce reactivity above the background rate of **1a** and acid alone. A broad screen of Brønsted acids revealed a pronounced counterion effect. In conjunction with thiourea **3b**, mineral acids with a nucleophilic counteranion, such as HCl, produced only trace amounts of the desired indole addition product **2a** (entry 1, Table 1), and the corresponding chloride addition product predominated. In contrast, sulfonic acid co-catalysts afforded **2a** in useful yields and varying levels of enantioselectivity, with the most promising result provided by 4-nitrobenzenesulfonic acid (4-NBSA) (entry 5, Table 1). The identity of the aromatic substituent on the pyrrolidino amide portion of the catalyst also exerted a profound effect on reaction enantioselectivity (entries 5, 7–12, Table 1). Catalyst **3a**, which lacks an aryl group, induced little rate acceleration above that of the background reaction (entry 6, Table 1) and afforded a nearly racemic product. In contrast, catalysts **3c**–**3g**, which bear more-extended aromatic substituents, proved more enantioselective than catalyst **3b**. Correlation between enantiomeric excess (e.e.) and either the electronic properties of the aryl substituents or the polarizability of the aromatic ring occurs in other reactions using this family of catalysts[2,6,14]. However, in the present case no such straightforward relationship was observed. Instead, e.e. improved on expanding the aryl group from phenyl to phenanthryl (entries 5, 8–10, Table 1), and then to decrease slightly with more expansive

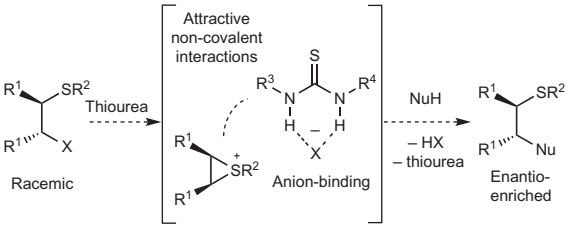

Figure 1 | Proposed thiourea-catalysed ring-opening of episulfonium ions with indole via anion binding.

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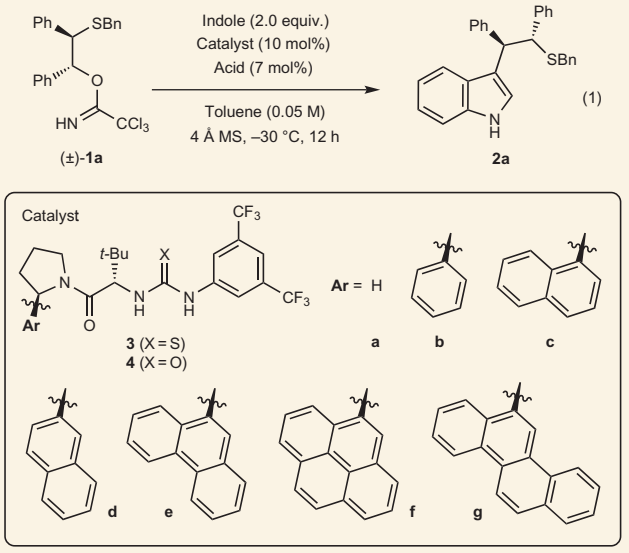
Table 1 | Reaction optimization.



Entry	Catalyst	Acid	Yield (%)*	e.e. (%)†
1	**3b**	HCl	10	5
2	**3b**	HOTf	73	32
3	**3b**	FSO_3H	78	19
4	**3b**	2,4-diNBSA	79	63
5	**3b**	4-NBSA	72	73
6	–	4-NBSA	7	n/a
7	**3a**	4-NBSA	16	12
8	**3c**	4-NBSA	84	84
9	**3d**	4-NBSA	80	85
10	**3e**	4-NBSA	93	93
11	**3f**	4-NBSA	91	91
12	**3g**	4-NBSA	97	88
13	**4e**	4-NBSA	98	92

Optimization reactions were performed on a 0.05 mmol scale. *Isolated yields of material purified chromatographically. †e.e. values determined by high-performance liquid chromatography analysis. MS = molecular sieves, 2,4-diNBSA = 2,4-dinitrobenzenesulfonic acid.

aryl substituents (entries 11–12, Table 1). Urea catalyst **4e** induced only a marginally lower e.e. than its thiourea counterpart (entries 10 versus 13, Table 1), which indicates that any mechanism wherein the thiourea sulfur is engaged productively as a Lewis base catalyst is not operative[15–18].

A variety of substrate combinations was evaluated to define the scope as well as gain insight into the mechanism of the reaction (equation (2), Table 2). Substrates bearing electronically and sterically diverse sulfur substituents (R^2) underwent enantioselective reactions (entries 1–9, Table 2), and *S*-benzyl-substituted derivatives afforded the highest e.e. values (entries 1 and 7, Table 2). Electron-potential maps calculated using density functional theory showed that the benzylic protons in the *S*-benzyl episulfonium ions bear a substantial amount of partial positive charge, which may serve to enhance attractive interactions between the cationic intermediate and an electronegative functionality on the catalyst (see below). Various indole derivatives with electron-donating and -withdrawing substituents at the 2-, 4-, 5- or 6-positions all underwent the addition reaction with high levels of enantioselectivity (entries 10–16, Table 2). In sharp contrast, *N*-methylindole provided the desired product **2p** with a moderate yield and in almost racemic form (entry 17, Table 2). This suggested that the indole N–H motif may be involved in a key interaction during the e.e.-determining transition state (see below). Benzotriazole also underwent an addition reaction to form a C–N bond with synthetically useful e.e. (entry 18, Table 2). Less nucleophilic heterocycles (for example, π-nucleophiles with Mayr nucleophilicity parameters $N < 4$) (ref. 19) proved unreactive. Variation of the substituents on the carbon backbone of the electrophile revealed that aryl groups with *meta*- and *ortho*-functionalities were compatible (entries 19–22, Table 2); substrates that carry a *para*-substituent, regardless of its steric and electronic properties, resulted in substantially lower enantioselectivity (entries 23–26, Table 2). Ongoing computational studies suggest that in the transition state leading to the major enantiomeric product, one of the *para*-C–H bonds is engaged in an attractive, electrostatic interaction with the thiourea-bound sulfonate. We reasoned that the lack of this interaction in the cases with *para*-substituted substrates might result in a less well-organized transition structure and reduced selectivity. Finally, three different acetimidate leaving groups displayed essentially the same reactivity and enantioselectivity, which suggests that the leaving group is not directly involved in the e.e.-determining step (entries 28–30, Table 2).

Elucidation of the rate- and enantio-determining step. Thiourea derivatives of type **3** bearing specific arylpyrrolidino residues are highly enantioselective catalysts for nucleophilic additions to a remarkable variety of cationic electrophilic intermediates, including oxocarbenium ions[2], acyliminium ions[6], acylpyridinium ions[20] and now episulfonium ions. Potentially, elucidation of the mechanisms that underlie catalytic activity and stereoinduction by these thioureas may serve as a foundation for the discovery of new reactions and provide broader insights into cooperative non-covalent pathways. We therefore undertook a detailed experimental and computational investigation of the indole addition to episulfonium ions promoted by **3e** and related catalysts. On the basis of the qualitative observations described above and previous studies that involved pathways for binding the thiourea anion, a simple catalytic cycle for the reaction of indoles with **1** mediated by **3e** can be advanced (Fig. 2). The absence of a dependence of enantioselectivity on the identity of the acetimidate group suggests that the reaction begins with protonation of the trichloroacetimidate substrate, followed by the formation of episulfonium ions in a step that may or may not be under the influence of the thiourea catalyst. A series of ^{1}H NMR studies of preformed episulfonium-ion derivatives[17] revealed that the episulfonium sulfonate most probably exists as a covalent adduct, both in the presence and the absence of the thiourea catalyst, so an endothermic ionization to the episulfonium-ion complex presumably takes place before addition of the indole nucleophile. Finally, re-aromatization to form the product and regenerate the acid closes the catalytic cycle. In the thiourea-promoted pathway, the chiral catalyst must therefore induce enantioselectivity through association with the charged intermediates and transition structures, indicated in Fig. 2 as taking place via direct binding to the sulfonate counterion.

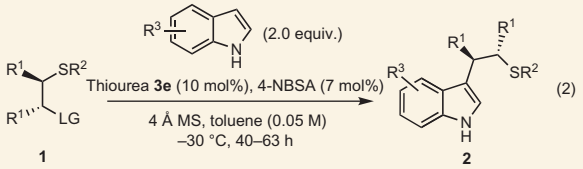
To identify the rate- and enantioselectivity-determining step in the catalytic mechanism, reaction-progress kinetic analysis[21] of the reaction that employed substrate **1a**, indole, thiourea **3e** and 4-NBSA in toluene at 0 °C was conducted with *in situ* infrared spectroscopy[22,23]. Using reaction rates measured over 10% to 60% conversion with 'different excess' experiments[22], the empirical rate equations were determined for both the racemic reaction catalysed by only 4-NBSA (equation (3)) and the asymmetric reaction co-catalysed by 4-NBSA and thiourea (equation (4)).

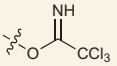
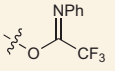
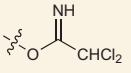
$$r_{rac} = d[\mathbf{1a}]/dt = k_{rac}[\text{4-NBSA}]_T[\text{indole}] \quad (3)$$

$$r_{asym} = d[\mathbf{1a}]/dt = k_{asym}[\text{4-NBSA}]_T[\mathbf{3e}]_T[\text{indole}] \quad (4)$$

Here, k_{rac} is the second-order rate constant for the racemic reaction and k_{asym} is the third-order rate constant for the asymmetric

Table 2 | Substrate scope of nucleophilic ring opening of episulfonium ions with indole derivatives.



Entry	R^1	R^2	LG	R^3	Product	Yield (%)	e.e. (%)
1		Bn			**2a**	99	93
2		Ph			**2b**	83	85
3*		Ph			**2b**	84	80
4		4-F-C_6H_4			**2c**	73	81
5	Ph	4-Me-C_6H_4		H	**2d**	76	87
6		2-naphthyl	(TCA)		**2e**	90	88
7		PMB			**2f**	>99	94
8		Me			**2g**	72	84
9		*t*-Bu			**2h**	89	87
10				5-Me	**2i**	97	91
11				5-MeO	**2j**	93	93
12				5-Br	**2k**	83	92
13				5-F	**2l**	88	95
14	Ph	Bn	TCA	6-F	**2m**	92	85
15				4-MeO	**2n**	83	91
16				2-Me	**2o**	95	79
17				*N*-Me	**2p**	54	3
18				Benzotriazole‖	**2q**	92	80
19†	3-MeO-C_6H_4				**2r**	85	93
20	3-F-C_6H_4				**2s**	97	95
21	3-Me-C_6H_4				**2t**	95	93
22	2-Me-C_6H_4				**2u**	>99	79
23	4-F-C_6H_4	Bn	TCA	H	**2v**	91	45
24	4-Me-C_6H_4				**2w**	89	60
25†	4-MeO-C_6H_4				**2x**	67	6
26	4-CF_3-C_6H_4				**2y**	18	5
27‡	-$(CH_2)_4$-				**2z**	16	9
28§			TCA		**2b**	87	87
29§	Ph	Ph		H	**2b**	91	85
30§					**2b**	85	85

Isolated yields of material purified chromatographically are reported. *With urea **4c**. †Yields determined by ^{1}H NMR are reported. Product isolated via flash column chromatography usually contains a small amount of **3e**. ‡R^2 = Ph, with HOTf. §With 20 mol% **3e** and 10 mol% 4-NBSA. ‖Benzotriazole as nucleophile instead of indole. PMB, *p*-methoxy benzyl.

reaction, and $[4\text{-NBSA}]_T$ and $[\mathbf{3e}]_T$ are the total initial concentrations of acid and thiourea, respectively.

The rate of the asymmetric reaction was accelerated by the chiral thiourea catalyst relative to the reaction catalysed by 4-NBSA alone. For instance, at 273 K, $[\mathbf{3e}]_T = 50$ mmol l^{-1}, the r_{asym}/r_{rac} at 10% conversion of **1a** is 43.4 ± 5.0. This rate acceleration corresponds to a lowering of the free energy of activation of the reaction by **3e** of 2.0 ± 0.1 kcal mol^{-1}.

The zeroth-order rate dependence on **1a** and first-order rate dependence on 4-NBSA indicate that quantitative protonation of the substrate occurs under the reaction conditions prior to the rate-determining step ($pK_{a(4\text{-NBSA})} \approx -7$, $pK_{a(\mathbf{1a})} \approx 2$) (ref. 24). In support of this conclusion, treatment of substrate **1a** with 1 equiv. of 4-NBSA resulted in an instantaneous complete consumption of **1a** and a concomitant, quantitative formation of trichloroacetamide (the by-product generated during episulfonium-ion formation) as determined by *in situ* infrared spectroscopy. The first-order dependence on indole in both the reaction catalysed by 4-NBSA alone or by 4-NBSA + **3e** reveals that indole is present in the rate-determining transition structure and that episulfonium·4-nitrobenzenesulfonate (existing predominantly as the covalent adduct) is the resting state of the substrate in the reaction. The kinetic data are consistent with a reaction with indole that involves either addition or reversible addition followed by slow re-aromatization as the rate-determining step (Fig. 2).

To distinguish between these two possibilities, studies of the linear free-energy relationships and kinetic isotope effects were carried out. In the racemic reaction catalysed by 4-NBSA alone, a linear correlation was observed between the reaction rate and Mayr's nucleophilicity parameter *N* for five different 5-substituted indoles ($\log(k_{rac})$ versus $s_N N$, $R^2 = 0.997$, where *N* is the Mayr nucleophilicity parameter and s_N is the nucleophile-specific parameter (see the Supplementary Information), and R^2 is the correlation coefficient), consistent with the indole addition step that results in nucleophilic ring opening of the episulfonium ion being the rate-limiting step[25]. A correlation between indole nucleophilicity and rate was also obtained in the thiourea-catalysed reaction ($\log(k_{asym})$ versus $s_N N$, $R^2 = 0.757$). As discussed below, a strict linear correlation is not observed in this case because the Brønsted acidity of the indole N–H group also influences the reaction rate in the thiourea-catalysed reaction. Evaluation of

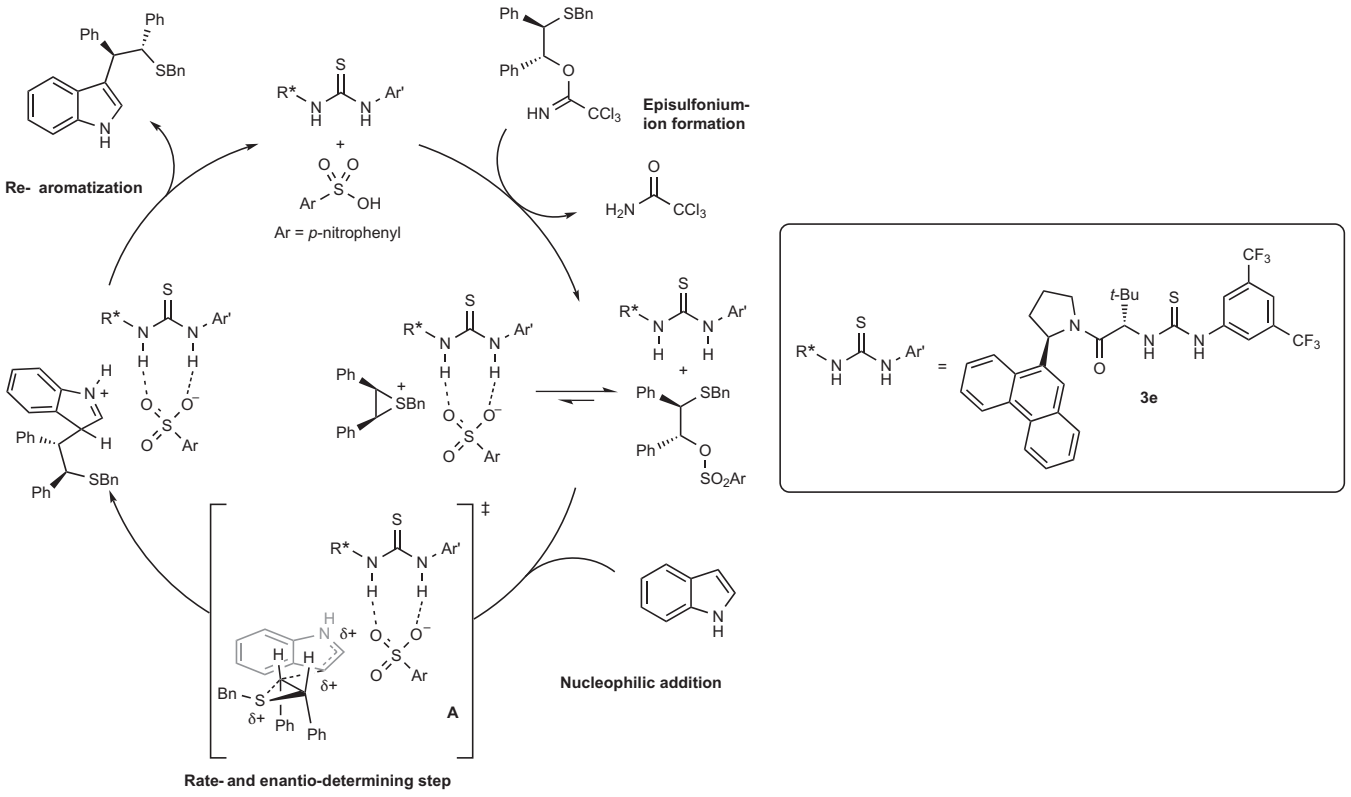


Figure 2 | Proposed catalytic cycle for thiourea-catalysed ring-opening of episulfonium ions with indole. R* denotes an unspecified chiral group.

3-deuterioindole in the thiourea-catalysed addition reaction revealed a very small effect of isotopic substitution ($k_H/k_D = 0.93 \pm 0.12$). This rules out re-aromatization as the rate-determining step, which would be expected to display a significant primary isotope effect ($k_H/k_D > 2.5$) (ref. 26), and is fully consistent with a rate-determining indole addition. It can be concluded that indole addition is enantio-determining as well, because the product's stereogenic centres are generated in this rate-determining step[27].

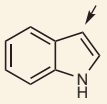
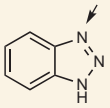
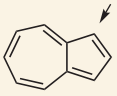
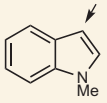
Elucidation of the catalyst–substrate interactions in the enantio-determining step. Although the kinetic studies served to define the stoichiometry of the transition structure in the rate- and e.e.-determining addition of indoles to **1**, they do not provide any direct insight into the specific manner by which the thiourea catalyst induces rate acceleration and enantioselectivity. This proved attainable, however, through the series of structure–reactivity and structure–enantioselectivity studies detailed below.

Thiourea dual hydrogen-bond donation to the sulfonate anion. Anion-binding catalysis is recognized as the primary mode of substrate activation in a variety of asymmetric reactions that involve hydrogen-bond donors[1]. In studies relevant to the system described here, sulfonate-ion associations with urea or thiourea derivatives via dual hydrogen-bond donation interactions were identified in both binding and reactivity studies[28,29]. To test whether such sulfonate binding operates in the current reaction, model binding studies and catalyst structure–activity studies were conducted. Titration of solutions of thiourea **3e** in d_8-toluene with dibenzylmethylsulfonium triflate $[(Bn_2MeS)^+(OTF)^-]$ (**5**) revealed the formation of a 1:1 complex, as determined by ^{1}H NMR spectroscopy. Resonances assigned to each of the thiourea N–H protons sharpened and shifted downfield on complexation, consistent with a dual hydrogen-bond interaction[29,30]. Perturbations to the chiral catalyst that diminished its ability to act as a hydrogen-bond donor, either by reduction of its acidity through substituent effects or by excision of one of the donor groups, led to strong or complete decreases in reactivity and enantioselectivity in the indole addition reaction (see Supplementary Section 4). These data, taken together with the strong e.e. dependence on the sulfonate counterion of the Brønsted acid (Table 1) suggest strongly that the thiourea–sulfonate interaction is a key element in the mechanism for catalysis and stereoinduction.

Hydrogen-bond interaction with the indole N–H group. As noted above, a striking difference in enantioselectivity was observed between the *N*–H indole and *N*–methylindole analogues in the addition reaction (93% versus 3% e.e. using catalyst **3e** in additions to **1a**). This suggests an important organizational role of the indole N–H bond in the stereoinduction mechanism, probably through hydrogen bonding to a Lewis basic functionality on the catalyst. To define the catalyst–indole interactions, a structure–reactivity and structure–enantioselectivity relationship study was undertaken with a series of π-nucleophiles (Table 3). In general, the absence of an N–H motif in a (1,3)-relationship with the reactive nucleophilic site led to very low levels of rate acceleration and enantioselectivity (entries 1 and 2 versus entries 3–5, Table 3).

To probe further into the role of hydrogen-bond interactions between the indole nucleophile and catalyst, various 5-substituted indoles were evaluated in competition experiments under both racemic and thiourea-catalysed reaction conditions. The degree of rate acceleration induced by thiourea **3e** was found to be linked directly to the acidity of the indoles, and a linear correlation between $\log(k_{asym}/k_{rac})$ and the pK_a of indoles was observed (Fig. 3). Therefore, in the presence of thiourea the rate of the reaction is correlated not only to the intrinsic nucleophilicity of the indole, but also to its hydrogen-bond donor properties. No correlation was observed between reaction enantioselectivity

Table 3 | Structure reactivity and enantioselectivity relationship of π-nucleophiles.

Entry	Nucleophile	Yield (%)*	e.e. (%)*	$r_{asym}/r^{\dagger}_{rac}$
1		93	93	43.4
2		92	80	n.d.
3		68	32	3.2
4		67	9	3.2
5		57	1	3.8

*Yields and enantiomeric excesses were obtained under reaction conditions described in equation (2). †The initial reaction rates with 4-NBSA alone (r_{rac}) and with 4-NBSA plus **3e** (r_{asym}) were determined directly by *in situ* infrared spectroscopy. The r_{asym}/r_{rac} value was not determined (n.d.) for benzotriazole (entry 2) because the kinetic analysis was complicated by the poor solubility of the nucleophile in the reaction medium.

and the acidity of the indoles, which indicates that this interaction probably exists to a similar degree in both the major and the minor pathways. The kinetic data are thus consistent with a general base activation of indole through an indole N–H–catalyst hydrogen-bond interaction in the rate-determining addition to episulfonium ions[31–34]. Catalyst **3e** possesses few Lewis-base functionalities (namely, the thiourea, the amide and perhaps the extended arene substituent) and therefore the possible catalyst hydrogen-bond acceptor sites are limited in number. The similar reactivity and enantioselectivity displayed with urea **4e** and thiourea **3e** appear to rule out a direct role of the thiourea sulfur atom. As discussed below, the extended aromatic plays a key role that can be tied to interactions with the episulfonium ion. Therefore, by this simple process of elimination we propose that the amide oxygen is the most likely hydrogen-bond acceptor site for the activation of the indole[35,36]. Consistent with this hypothesis, catalyst **3a** was found to be more reactive than the corresponding thioamide analogue in the model reaction (equation (2)). In addition, the reaction catalysed by **3a** is about four times as fast as the reaction with Schreiner's thiourea (1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea), which is a stronger H-bond donor, but lacks an amide appendage.

Stabilization of the cationic transition state through cation-π interactions. The strong correlation between reaction enantioselectivity and the identity of the arene on the catalyst suggests a direct role of the extended π-system in the mechanism of stereoinduction. In principle, this arene affect may be caused primarily either by an acceleration of the major pathway through transition-state stabilization or by inhibition of pathways that lead to the minor enantiomer through destabilizing interactions. This question was addressed through a kinetic analysis of the reaction, which takes advantage of the fact that the indole addition step is both rate- and e.e.-determining. The rate constant that corresponds to the major pathway ($k_{asym,major}$) could be deduced for catalysts **3a–3g** from *in situ* infrared-based kinetic measurements combined with enantiomeric ratio (e.r.) determinations. A strong correlation between this rate and reaction enantioselectivity was observed: a good linear fit was obtained in plots of $\ln(k_{asym,major})$ versus ln(e.r.) (Fig. 4a). This provides unambiguous evidence that enantioselectivity increases because variations of the aryl component of the catalyst **3** are, indeed, tied to stabilization of the major transition structure[14]. The rate of the pathway that leads to the minor enantiomer also displays a linear, positive correlation with the reaction e.r., which indicates that the minor transition structure is also stabilized selectively by the more enantioselective catalysts, albeit to a substantially lesser extent.

Insight into the nature of the transition-state stabilizing interactions that may be at play was provided through spectroscopic analyses of thiourea derivatives **3a** and **3e** complexed to a sulfonium-ion model system. The dibenzylmethylsulfonium ion triflate **5** was selected for these studies because episulfonium sulfonate could not be examined directly (see above) and the cation in **5** was found by computational methods to have a very similar charge distribution to that of the episulfonium ion (Fig. 4c). With thiourea **3e**, the resonances of the benzylic and methyl protons of **5** underwent a significant upfield shift (0.6–0.8 ppm) on formation of the 1:1 complex (Fig. 4b)[37]. In contrast, the chemical shift of these protons was barely perturbed to any measurable extent ($\Delta\delta <$ 0.05 ppm) on complexation of **5** with the thiourea derivative **3a**, which lacks an aryl substituent. This points to an attractive cation-π interaction between the π-face of the arene in catalyst **3e** and the sulfonium ion in the model system[38–42]. Such interaction in the transition structure of the indole addition to episulfonium ions could underlie the observed enantioselectivity effects, as the cation-π interactions are expected to increase in magnitude with more extended aromatic substituents[43,44]. Based on the kinetic and enantioselectivity data, we therefore propose that the difference in

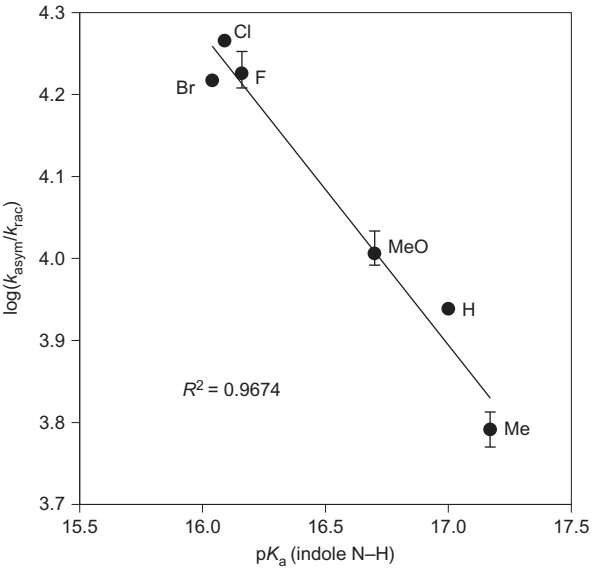


Figure 3 | Rate acceleration by 3e and acidity of the N–H motif of the 5-indole derivatives. Correlation between the degree of rate acceleration by **3e** over the background racemic reaction (k_{asym}/k_{rac}) and the acidity of the N–H motif of 5-substituted indole derivatives (pK_a). The rate data were obtained by *in situ* infrared and ^{1}H NMR spectroscopy (see Supplementary Section 14 for detailed experimental procedures and data analyses). Error bars reflect the range of experimental data from 2–3 individual measurements, and the line represents the least-squares fit.

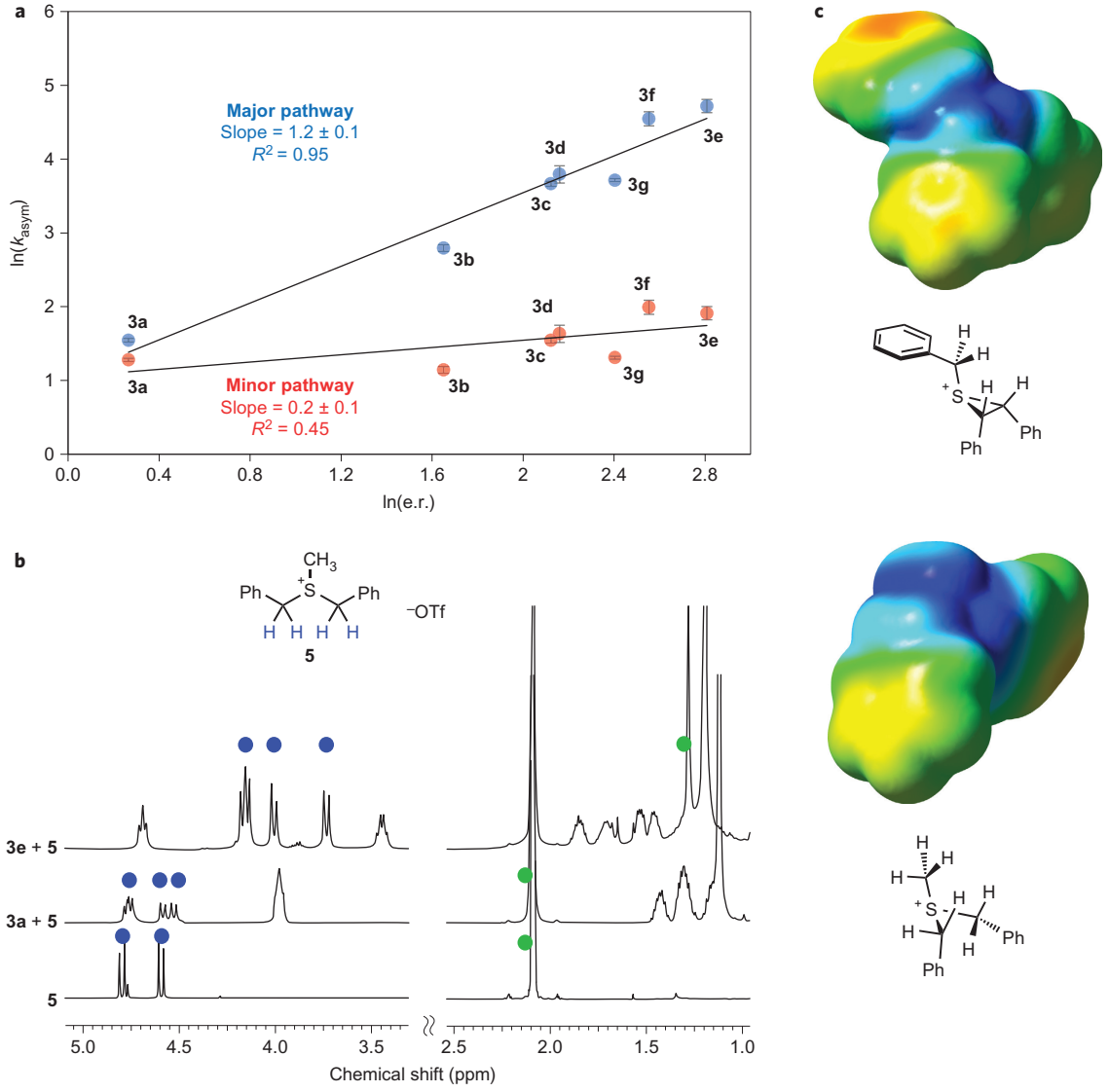


Figure 4 | Enantio-induction with thiourea catalysts through a selective, attractive cation-π interaction between the extended aromatic residue on the catalyst and the acidic α-protons in the episulfonium ion. a, Correlation between rate and enantioselectivity of reactions catalysed by thioureas **3a**–**3g**. Each data point represents the average rate determined from two individual kinetic experiments, and the error bar shows the range of the measurements. The rate constants for the major and the minor pathways ($k_{asym,major}$ and $k_{asym,minor}$, respectively) are calculated on the basis of the rate equations (equations (3), (4), $r_{asym} = r_{asym,major} + r_{asym,minor}$ and e.r. $= r_{asym,major}/r_{asym,minor}$). The lines represent least-square fits. **b**, A ^{1}H NMR binding study of thiourea and **5** in d_8-toluene showed attractive interactions between the aromatic group in **3e** and the α-protons in **5**. The resonances of the benzylic protons and the methyl protons in **5** are labelled with blue and green dots, respectively. In the bottom two spectra, the methyl resonance overlaps with the solvent peak, but can be identified in expanded displays. **c**, Electrostatic potential maps for fully optimized structures (B3LYP/6-31G(d)) of the episulfonium ion derived from **1a** and the sulfonium ion in **5** reveal a similar distribution of positive charge over the benzylic protons. Negative potentials are shown in red and positive potentials in blue.

the strength of the cation-π interaction between the major and minor pathways lies at the origin of the high reaction enantioselectivity observed[6,14,45]. On the basis of polarizability effects alone, which are known to correlate directly with cation-π binding ability[46], the most expansive aryl-substituted catalysts **3f** and **3g** might be expected to be the most enantioselective. However, these two thiourea derivatives afford slightly lower e.e. values (see Table 1) in the model reaction than the smaller phenanthryl catalyst **3e**. The reason for the lack of an exact correlation between the polarizability of the aromatic substituent and reaction enantioselectivity is not yet established. However, it seems reasonable to expect that any number of minor steric or conformational factors could attenuate the ability of the largest substituents to engage fully in the stabilizing cation-π interaction.

Taken together, the data presented above allow the construction of a detailed mechanistic model for the enantioselective reaction, wherein rate acceleration and enantioselectivity are induced by the thiourea catalyst through a network of attractive non-covalent interactions. In particular, we propose that the transition structure for the rate-determining addition of indole to the episulfonium ion is stabilized by a combination of anion binding of the thiourea to the sulfonate, general base activation of the indole via a catalyst amide–indole N–H interaction and a cation-π interaction between the arene of the catalyst and the benzylic protons of the episulfonium ion (Fig. 5). We anticipate that characterization of these enzyme-like non-covalent stabilizing elements with small-molecule catalysts such as **3e** may enable the future design and application of such biomimetic strategies in organic asymmetric synthesis.

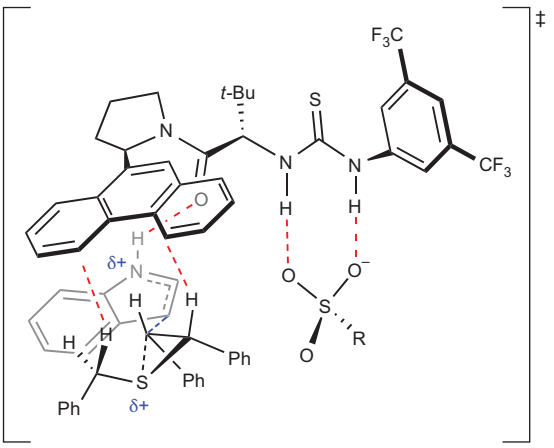


Figure 5 | Proposed transition-structure model. The transition structure for the rate-determining addition of indole to the episulfonium ion is stabilized by a combination of attractive, non-covalent interactions, which include anion binding of the thiourea to the sulfonate, general base activation of the indole via a catalyst amide–indole N–H interaction and a cation-π interaction between the arene of the catalyst and the benzylic protons of the episulfonium ion.

Methods

General procedure for thiourea 3e-catalysed nucleophilic ring opening of episulfonium ions with indole derivatives. An oven-dried 1.5 dram vial was charged with substrate **1** (0.05 mmol, 1.0 equiv.), **3e** (3.2 mg, 0.005 mmol, 0.1 equiv.), indole (11.7 mg, 0.1 mmol, 2.0 equiv.) and 4 Å molecular sieves (25 mg, powder, activated) under an atmosphere of N_2. The vial was cooled to –30 °C, and toluene (1 ml) was added with stirring. Once the reactants and catalyst had dissolved fully, the mixture was cooled to –78 °C and solid 4-NBSA (0.7 mg, 0.0035 mmol, 0.07 equiv.) was added at once against a counterflow of N_2. The resulting solution was stirred at –30 °C and the progress of the reaction was monitored by thin layer chromatography (see Supplementary Section 3). When the progress of the reaction was determined to be complete, triethylamine (~10 μl) was added at –30 °C. The resulting mixture was applied directly to a pipette column that contained 4–5 cm of silica gel, and the product was isolated by eluting hexanes/ethyl acetate (20:1 to 10:1) and solvent removal.

Detailed experimental procedures, syntheses of the substrates and catalysts, characterization data for all the new compounds, procedures and data for mechanistic investigations (including reaction-progress kinetic analysis, linear free-energy relationship studies with Mayr's reactivity parameters, kinetic isotope-effect studies, model binding studies by ^{1}H NMR spectroscopy and other experimental kinetic studies) are given in the Supplementary Information. Crystallographic information for compounds **2b**, **2g** and **2q** are deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 862750, CCDC 862751 and CCDC 862752, respectively).

Received 19 January 2012; accepted 31 July 2012; published online 16 September 2012

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Acknowledgements

This work was supported by the National Institute of General Medical Sciences (NIGMS) (P50 GM-69721 and RO1 GM-43214) and by a predoctoral fellowship to S.L. from Eli Lilly. We thank R. Knowles, K. Brak and H. Mayr for helpful discussions, A. Brown, D. Lehnherr and A. Hyde for the use of catalysts, and S-L. Zheng for crystal structure determinations.

Author contributions

S.L. conducted the experiments, S.L. and E.N.J. co-wrote the manuscript and E.N.J. guided the research.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permission information is available online at http://www.nature.com/reprints. Correspondence and requests for materials should be addressed to E.N.J.

Competing financial interests

The authors declare no competing financial interests.