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A Friedel–Crafts alkylation mechanism using an aminoindanol-derived thiourea catalyst†

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Computational calculations based on experimental results shed light on the mechanistic proposal for a Friedel–Crafts alkylation reaction between indole and nitroalkenes, catalysed by a chiral aminoindanol-derived thiourea. In our hypothesis both substrates are simultaneously coordinated to the catalyst in a bifunctional mode. This study elucidates the crucial role played by the hydroxyl group of the catalyst in the success of the reaction. The OH group seems to be involved in the preferential attack of the indole over the nitroalkene, affording the major enantiomer and stabilizing the resulting transition state by a concomitant coordination with the nitroolefin. The results obtained with other catalysts from the same family, and other indoles, are reported and discussed. Theoretical calculations are in agreement with the experimental outcomes and with our previously developed mechanism, displaying the pivotal role played by hydrogen bond interactions.

Introduction

In the last decade, catalysts acting through hydrogen bond interactions have attracted great interest, and they represent a noteworthy part of the organocatalytic field.[1–3] One of the main families of organocatalytic structure included in this large group are the thiourea/urea derivatives, and many efforts have been devoted to the design and synthesis of new ones as appropriate catalysts in a large number of interesting processes.[4] In the last few years, we have focused part of our investigation on the development of new thiourea-catalysed methods.[5]

The Friedel–Crafts alkylation reaction has received the attention of a great number of research groups, becoming an efficient tool for carbon–carbon bond-formation.[6] In fact, some of us pioneered the first thiourea-catalysed Friedel–Crafts alkylation reaction between indoles and nitroalkenes (**TSI**, Fig. 1).[5b] More recently, we have also reported some preliminary results concerning a new concept on the cooperative effect between a Brønsted acid additive and a chiral thiourea organocatalyst in the same process (**TSII**, Fig. 1).[5g] In these mechanisms, the essential function performed by hydrogen bond interactions was fundamental for the reactivity and enantioselectivity of the processes. In both cases, two enantiomers of the thiourea-aminoindanol derivative **1a** were the catalysts of choice to efficiently promote a Friedel–Crafts reaction between the indoles **2** and nitroolefins **3**. Transition states depicted in Fig. 1 (**TSI** and **TSII**) were postulated in order to explain the role of the catalyst and the major enantiomer observed.

Understanding the mechanism of a reaction is always an attractive and challenging task in order to improve the process and to promote further developments. Moreover, information about the catalyst's mode of action could help to understand its use in similar reactions. For this purpose, computational studies, reinforced with experimental results, have become an important tool in organocatalysis. In the last decade, it has allowed the proposition of interesting reaction mechanisms, and has provided remarkable insights into the origin of catalysis and the selectivity of the explored processes.[7]

The aminoindanol skeleton has been investigated several times in different interesting catalyst structures acting as a hydrogen bond promoter, following our pioneering work.[8] However, to the best of our knowledge only one work using the catalyst (1*R*,2*S*)-**1a** has been focused on computational calculations, in an aza-Michael addition reaction.[9]

In our previously reported works on this Friedel–Crafts reaction, a reasonable bifunctional mechanism was envisioned based on experimental results (**TSI** and **TSII**, Fig. 1).[5b,g] Herein we want to report our most recent studies on this mechanistic hypothesis, employing theoretical calculations.[10,11] Compu-

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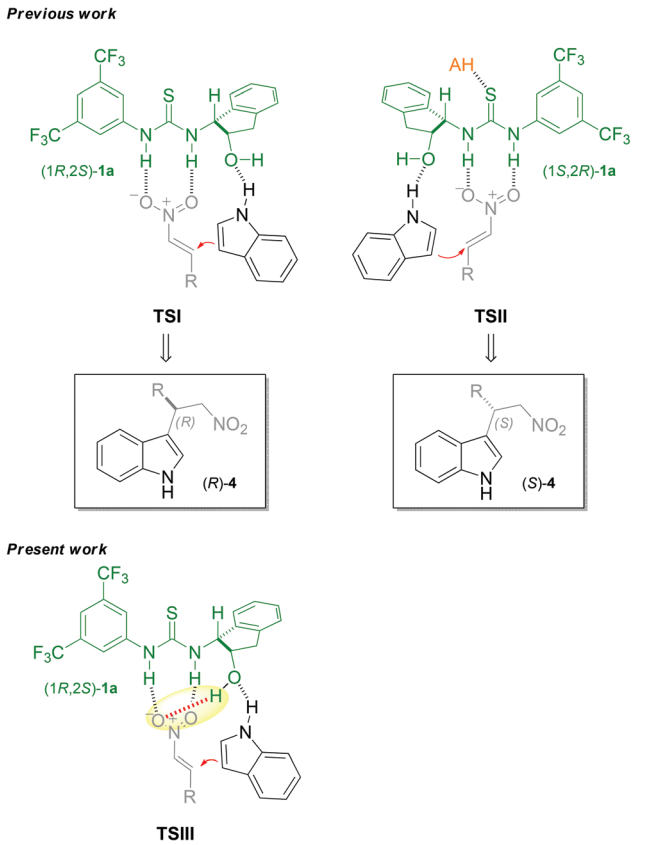
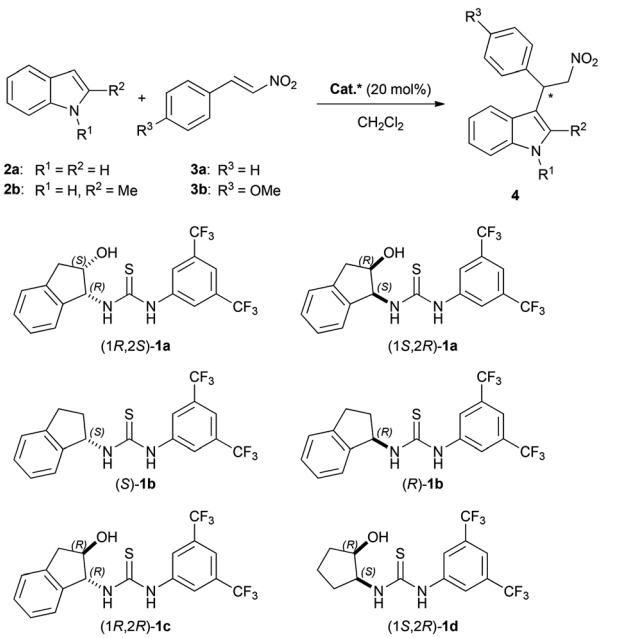


Fig. 1 Transition states proposed to explain the Friedel–Crafts alkylation reaction.

tational and experimental results underline the important role played by the hydroxyl group present in the aminoindanol structure, and the activation through hydrogen bonding of all species involved in the mechanism. This has been found to be crucial for the success of both reactions in terms of the reactivity and enantioselectivity (**TSIII**, Fig. 1).

Results and discussion

It has been accepted that the nucleophilic attack of the aromatic ring on the electrophile is the rate-determining step in the Friedel–Crafts reaction, causing the subsequent proton transfer to be a faster process.[12] To evaluate our proposed mechanistic hypothesis, we started the investigation by computationally studying the C–C bond formation pathway, founded on experimental results (some of those experiments are compiled in Scheme 1 and Table 1). Although we have already observed the importance of the hydroxyl group in the structure of catalyst **1a** for the Friedel–Crafts alkylation reaction,[5b,e,g] we have recently realised the importance of having the hydroxyl group in the correct position in the catalyst skeleton. For example, we did not observe either reactivity or enantioselectivity with catalyst (1*R*,2*R*)-**1c**,[5g] with the hydroxyl group in the *trans* position (Table 1, entries 6 and 7). This evidence supports the idea that the hydroxyl group must be in the



Scheme 1 Thiourea catalysts tested in the Friedel–Crafts alkylation reaction.

skeleton in the *cis* configuration, playing a crucial role in the enantioselectivity and the reactivity of the process. Therefore, even though the presence of the hydroxyl group in the structure is important, it must be also placed in the appropriate position, in order to efficiently drive the attack of the external nucleophile through hydrogen bond coordination, as shown in Fig. 1.[5b,e,g]

In our mechanistic proposals (Fig. 1), we hypothesised that the hydroxyl group would drive the attack of the indole over a preferential face of the nitroalkene to afford the desired product, with the corresponding configuration depending on the enantiomer of catalyst **1a** employed.[5b,g] The importance of the NH group in the indole molecule seems to be in concordance with a plausible hydrogen bond interaction between it and the OH group of the catalyst (H–O···H–N), which would help in the orientation of the attack of the nucleophile. Remarkably, using catalysts **1b** and **1c** (Table 1, entries 3–7),[5b,g] the results are very poor in terms of both reactivity and selectivity. **TSI** and **TSII** could explain the selectivity of this process; in the absence of a hydroxyl group the reaction affords a racemic mixture, since the indole can attack over both faces of the activated nitroolefin. However, they cannot explain the lack of reactivity, which makes us think that maybe the hydroxyl group is involved in another crucial interaction, performing dual modes of action (**TSIII**, Fig. 1). On the one hand, it would drive the attack of the indole over the nitroalkene as a conductor; and on the other hand, it should be also involved in the activation of the nitroalkene. In this sense, the OH could govern the reactivity of the process, explaining the lack of reactivity in its absence. These experimental observations encouraged us to study in depth, for the first time, the proposed dual role of the hydroxyl group in the transition state, and to

Table 1 Thiourea-catalysed Friedel–Crafts alkylation reactions[a]

Entry	Catalyst	Indole	T (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1[d]	(1*R*,2*S*)-**1a**	**2a**	−24	72	78	85 (ref. 5*b*) (*R*)-**4aa**
2	(1*S*,2*R*)-**1a**	**2a**	−25	72	40	82 (ref. 5*g*) (*S*)-**4aa**
3[d]	(*S*)-**1b**	**2a**	−24	72	15	Rac.[f] (ref. 5*b*)
4[e]	(*R*)-**1b**	**2a**	r.t	120	24	Rac.[f] (ref. 5*g*)
5	(*R*)-**1b**	**2a**	−25	72	n.d.[g]	Rac.[f] (ref. 5*g*)
6	(1*R*,2*R*)-**1c**	**2a**	r.t.	96	n.d.[g]	Rac.[f] (ref. 5*g*)
7	(1*R*,2*R*)-**1c**	**2a**	−25	120	n.d.[g]	10 (*S*)-**4aa**
8	(1*S*,2*R*)-**1d**	**2a**	−25	96	26	54 (*S*)-**4aa**
9[d]	(1*R*,2*S*)-**1a**	**2b**	−45	72	82	74 **4ba** (ref. 5*b*)
10[e]	(1*S*,2*R*)-**1a**	**2b**	r.t.	72	94	20 **4ba** (ref. 5*g*)

[a] Experimental conditions: to a mixture of catalyst **1a–d** (20 mol%) and nitroalkene **3a** (0.1 mmol) in CH_2Cl_2 (0.25 mL), indole **2a,b** (0.15 mmol) was further added, in a test tube at the corresponding temperature. After the reaction was complete, products **4aa** and **4ba** were isolated by flash chromatography. [b] Isolated yield. [c] Determined by chiral HPLC. [d] 0.1 mL CH_2Cl_2. [e] 0.5 mL CH_2Cl_2. [f] Racemic mixture. [g] Not determined.

elucidate the mechanism of this Friedel–Crafts alkylation reaction using catalyst **1a**.[13]

Theoretical calculations based on the real catalytic system

All the calculations were carried out at the PCM(CH_2Cl_2)/M06-2X/6-311G(d,p) level,[14] including minima, transition states, structure optimisations and frequencies analyses. The thermal and entropic contributions to the free energies were also obtained from the vibrational frequencies analyses, performed at −24 °C, which is the temperature at which the highest experimental enantiomeric excess was obtained. Although the mechanism of our reaction was initially studied in a simplified system, for more clarity we report here only the complete system with catalyst (1*R*,2*S*)-**1a**, indole (**2a**) and nitrostyrene (**3a**). This allows us to obtain a more accurate approach of our active system in the rate determining step.

To prove the robustness of our mechanism, different parameters were widely analysed. As such, the conformations of the catalysts, the attack through both faces of the nitroalkene, the possibility of bidentate or monodentate coordination through directional hydrogen bonding between the nitroalkene and the thiourea, the coordination of the hydroxyl group to the indole, and the approaching face of the indole were some key aspects of the comprehensive study. In order to test the accuracy of our proposed mechanism, we analysed different transition states for the C–C bond formation step – that is, the attack of indole **2** over the nitroalkene **3** activated with the thiourea catalyst (1*R*,2*S*)-**1a** through hydrogen bond interactions – using the complete catalytic system. The analysis of the global reactivity in terms of Fukui's indices for indole **2**, the nitroalkene **3** and the active catalytic complex were also calculated at the ground state (see ESI†).

In this respect, we focused this computational work on the study of all possible hydrogen bond interactions between all involved species, which are expected to stabilize the catalytic system in the transition state. Based on an extensive conformational search, we were able to find several transition states. Among all of the possibilities studied, only the most stable transition states calculated are shown in Fig. 2. In these states, the reaction occurs through a concomitant coordination of both reagents. Additionally, in Fig. 2 some relevant distances have been marked on the transition states, indicating the formation of a C–C bond and all plausible hydrogen bond interactions involved in the activation of the process. These values are related to the interactions between the NH of the thiourea **1** and the nitroalkene **3**, the C–C bond formation between the indole **2** and the nitroalkene **3**, the coordination between the OH of the catalyst **1** and the NH of indole **2**, and, even more interestingly, the interaction found between the hydroxyl group and one of the oxygen atoms of the nitroalkene **3** (O–H···O–N=O) (**TS1**, **TS2**, **TS5** and **TS6**). Furthermore, an additional relevant interaction has been found between the H atom of the hydroxyl group and the S atom of the thiourea (O–H···S), which is acting as a hydrogen acceptor (**TS3** and **TS4**).

We have also examined the energetic cost for the uncatalysed reaction represented in Scheme 1, between indole (**2a**) and nitrostyrene (**3a**), and found that it is 28 kcal mol^{-1}, in contrast to 11 kcal mol^{-1} for $\Delta G^{\ddagger}$ in the case of **TS1**, the most stable state for the catalysed reaction (Fig. 2). This outcome is consistent with the stabilizing effect promoted by the presence of the catalyst, and the subsequent acceleration of the reaction. Free energy values for the calculated transition states are given relative to the most stable, **TS1**, to which was assigned an energy value of 0.

Some interesting conclusions could be extracted from these outcomes (Fig. 2). In all cases, the oxygen atom in the hydroxyl group of the catalyst **1a** prefers to interact with the NH group of the indole (**2a**) through H–O···H–N, leading to the attack of the nucleophile over the nitroalkene **3**, as we previously predicted (Fig. 1).[5b,g] The small differences in activation barrier for the attack of the indole (**2a**) over the *Si* face of the nitrostyrene (**3a**) (**TS1**, 0.0 kcal mol^{-1}) and the *Re* face (**TS2**, 2.1 kcal mol^{-1}) could explain why the higher enantiomeric excess achieved was around 85% (Table 1, entries 1 and 2). According to the experiments, the most stable transition state **TS1** would afford the *R* enantiomer of the final product (*R*)-**4aa** obtained with (1*R*,2*S*)-**1a** (Table 1, entry 1).[5b] The opposite is true for the catalyst (1*S*,2*R*)-**1a**, which would afford the *S* enantiomer of **4aa** (Table 1, entry 2). To unambiguously establish the absolute

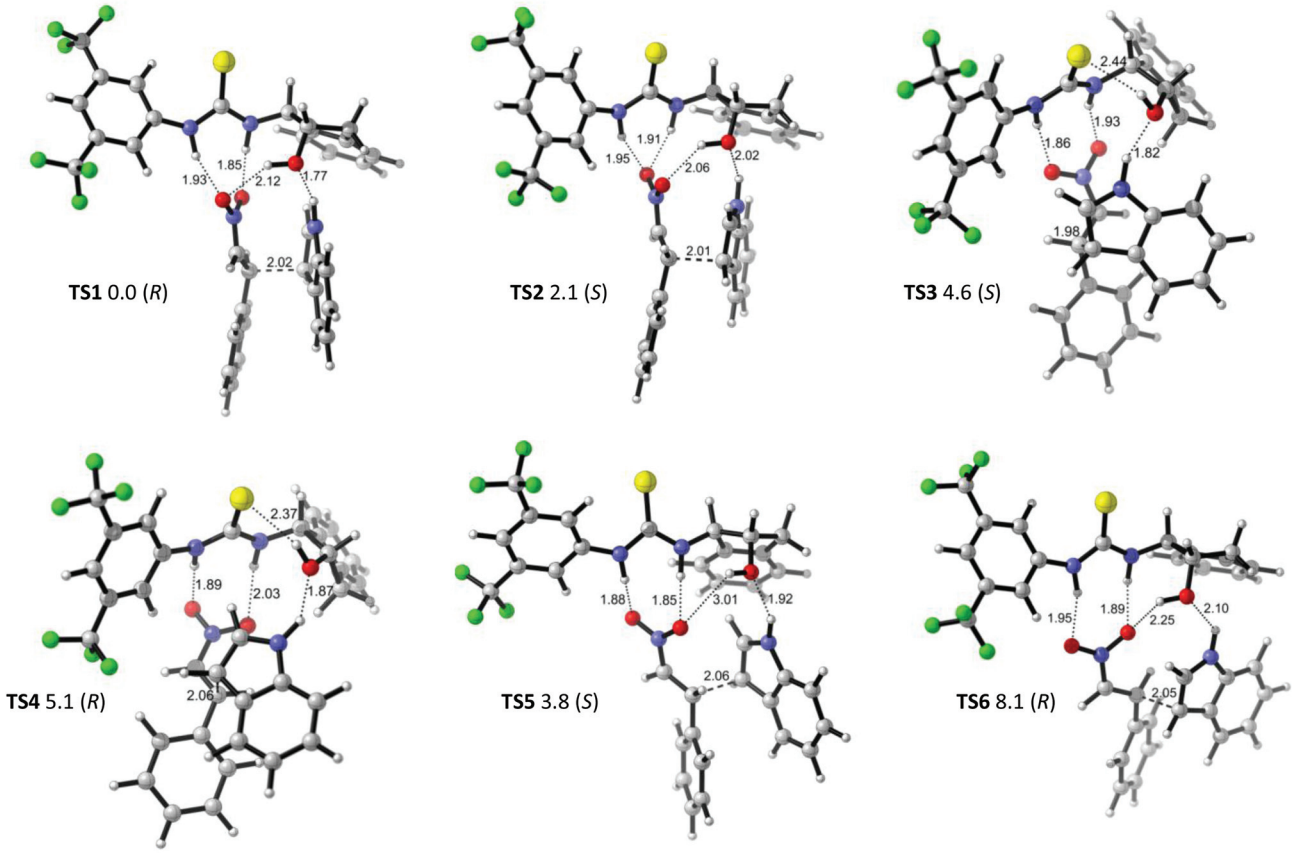


Fig. 2 Transition states for the Friedel–Crafts alkylation reaction using catalyst (1*R*,2*S*)-**1a**. Relative free energies are expressed in kcal mol^{-1}; distances are in Å.

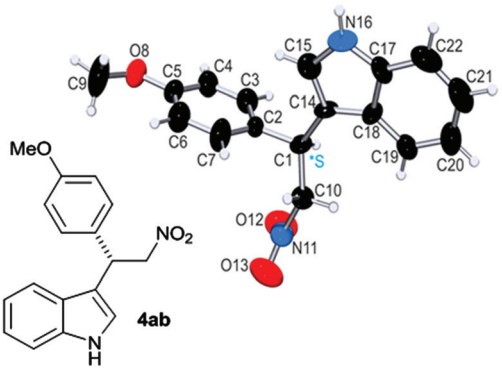


Fig. 3 X-ray crystal structure of (*S*)-**4ab**.

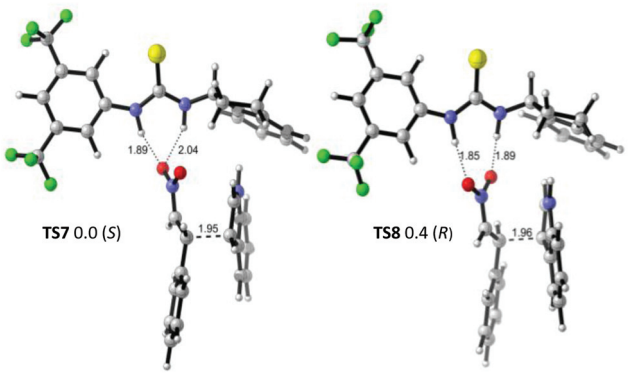


Fig. 4 Transition states for the Friedel–Crafts alkylation reaction using catalyst (*S*)-**1b**. Relative free energies are expressed in kcal mol^{-1}; distances are in Å.

configuration of the final Friedel–Crafts adducts **4** using catalyst (1*S*,2*R*)-**1a**, single crystals were grown from adduct **4ab**. As expected, the stereochemical outcome was determined to be *S* for the final product **4** (Fig. 3).[15]

Moreover, it is interesting to note that except in **TS2**, the nitroalkene **3** prefers to be coordinated through a bidentate coordination, as first observed by Etter and co-workers.[16] This bidentate coordination provides a more rigid TS among the three species, although previous works have also postulated a plausible monodentate coordination between a thiourea and a nitroalkene.[17] The stability of the more stable transition state **TS1** could be attributed to a less hindered packaging, since the indole (**2a**) is farther from the aromatic ring of the amino-indanol part of the catalyst than in **TS2**, which would cause stronger repulsions. In this sense, the indole–nitroalkene relative orientation plays a crucial role in determining the selectivity observed in the final products (**4**).

Having identified the most stable transition state **TS1**, we proceeded to vary the structure firstly of the catalyst **1** and then of the indole **2**. Centred on our experiments, we examined the

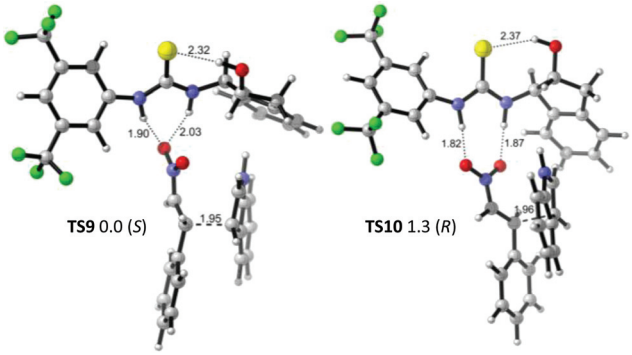


Fig. 5 Transition states for the Friedel–Crafts alkylation reaction using catalyst (1*R*,2*R*)-**1c**. Relative free energies are expressed in kcal mol^{-1}; distances are in Å.

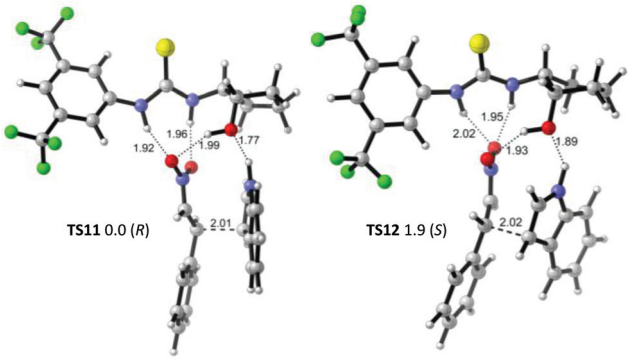


Fig. 6 Transition states for the Friedel–Crafts alkylation reaction using catalyst (1*R*,2*S*)-**1d**. Relative free energies are expressed in kcal mol^{-1}; distances are in Å.

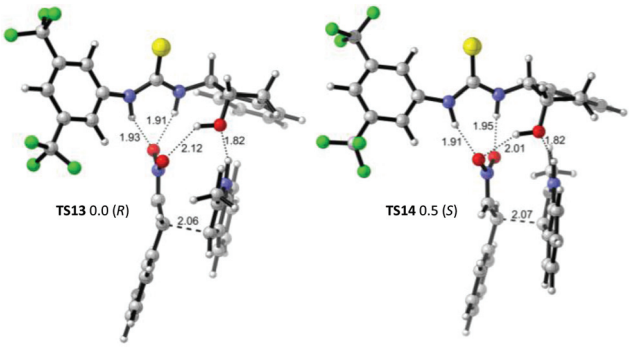


Fig. 7 Transition states for the Friedel–Crafts alkylation reaction of **2b** using catalyst (1*R*,2*S*)-**1a**. Relative energies are expressed in kcal mol^{-1}; distances are in Å.

TS for catalyst (*S*)-**1b** (Fig. 4). The outcome of replacing the OH in the catalyst with H was interesting. First of all, the energetic differences among the different conformations of the catalytic system which afford enantiomers (*R*)-**4** and (*S*)-**4** are reduced. This trend supports the observation of a racemic mixture being formed when catalyst **1b** is used (Table 1, entries 3–5).

The $\Delta G^{\ddagger}$ for **TS7** was found to be 17 kcal mol^{-1}, 6 kcal mol^{-1} more energetic than in the case of **TS1**. This demonstrates that the hydroxyl group not only has a driving effect in this process, orientating the attack of the indole **2**, but also has a stabilising effect. This is also in concordance with the experimental outcomes reached, since the reaction proceeds poorly and in a racemic way (Table 1, entries 3–5).

A similar effect is observed when catalyst (1*R*,2*R*)-**1c**, which has a *trans* configuration, is employed (Fig. 5). Interestingly, in this case a preferred hydrogen bond interaction between the hydroxyl group and the S atom of the thiourea is found (O–H···S). This coordination does not stabilise the TS more than in the absence of the hydroxyl group, since the $\Delta G^{\ddagger}$ for **TS9** was found to be 18 kcal mol^{-1}, the same order of energy as that obtained in **TS7** (17 kcal mol^{-1}). In both reactions, the high $\Delta G^{\ddagger}$ values fit with the almost complete lack of reactivity observed (Table 1, entries 6 and 7).

In this case, the obtainment of the same enantiomer (*R*)-**4aa** would be expected, since the configuration of the carbon bearing the NH group in the aminoindanol structure of the catalyst (1*R*,2*R*)-**1c** is the same as in catalyst (1*R*,2*S*)-**1a** (Table 1, entry 1). Remarkably, a variation in the final enantiomer is computationally predicted, because the attack of the indole **2** occurs preferentially by the *Re* face of the nitroalkene **3**, affording an *S* configuration in the final product **4**. This result is in accordance with the experimental outcome (Table 1, entry 7). Although the energetic difference between the two transition states (**TS9** and **TS10**) is small, the preferred *S* configuration could be due to a more congestive conformation in **TS10** between the indole **2** and the aminoindanole ring of the catalyst. In this case, we found preferential monodentate coordination between the nitrostyrene (**3a**) and the thiourea (1*R*,2*R*)-**1c** (**TS9**).

Furthermore, we analysed the effect of the catalyst in the absence of an aromatic ring in the aminoindanol skeleton, that is, using (1*R*,2*S*)-**1d** (Fig. 6). The most stable transition states (**TS11** and **TS12**) are similar to **TS1** and **TS2**, with the same differences in energy and the same favoured coordination by the hydroxyl group to the NH in the indole **2** (H–O···H–N) and to the O atom in the nitro group of the alkene **3** (O–H···O–N═O). The $\Delta G^{\ddagger}$ for **TS11** was found to be 12.5 kcal mol^{-1}, 1.5 kcal mol^{-1} more energetic than in the case of **TS1**. Although the absence of the aromatic ring seems not to have a great effect on the calculated energies, the experimental results are very different to those reached with catalyst **1a** (Table 1, entries 1, 2 and 8). In this case, the influence of the aromatic ring seems to be really important in the origin of the selectivity of the process. We can envision a strong steric effect of the aromatic ring in catalyst **1a**, avoiding an attack of the indole **2** by the other side, that does not exist in the case of catalyst **1d**.

After analysing the catalyst structure, we further considered varying the indole skeleton (Fig. 7). When we explored 2-methylindole (**2b**) as the nucleophile, the central core of the most stable transition states and all the hydrogen bonds remained unaltered compared with **TS1** and **TS2** (Fig. 2).

However, the difference in energy between **TS13** and **TS14** is very small. The ΔG is in agreement with the less enantioselective process observed (Table 1, entries 9 and 10). The $\Delta G^{\ddagger}$ for **TS13** was found to be 9.0 kcal mol^{-1}. The energy barrier is much lower (2.1 kcal mol^{-1}) than in the case of **TS1**, indicating a much higher reactivity. This behaviour agrees well with the higher reaction rate observed in this process. This is due to the inductive effect provided by the methyl group, which favours an attack through the third position of the indole **2b**.

It is worth noting that we found a preferred monodentate coordination between the thiourea and the nitroalkene **3** (**TS13**). The coordination of the hydroxyl group to the nitro group through O–H···O–N=O was also found in both transition states (**TS13** and **TS14**, Fig. 7).

With all these outcomes in mind, we have modified our previous two transition states **TSI** and **TSII** (Fig. 1), which were not far from the possible mechanistic activation. In order to better understand the experimental results, we have now included the crucial interaction between the OH group of the catalyst and an oxygen atom of the nitroalkene (O–H···O–N=O) (Fig. 1, **TSIII**). These theoretical calculations have underlined the essential role of hydrogen bonding in the success of the process.

Conclusions

We have reported an unprecedented theoretical study of the mechanism of a thiourea-catalysed Friedel–Crafts alkylation reaction for the addition of indoles **2** to nitroalkenes **3**. The catalyst at the centre of the study was the aminoindanol derived thiourea (1*R*,2*S*)-**1a** and its enantiomer (1*S*,2*R*)-**1a**. Some other catalysts derived from this crucial structure have been also considered. Our work sheds light on the experimental results obtained in this process and provides further support for them. The computational results are in accordance with our previously disclosed mechanisms (Fig. 1).

It is revealed that indole **2** is coordinated to the crucial hydroxyl group of the catalyst through a hydrogen bond (HO···H–N) and that the nitroalkene **3** is preferentially coordinated *via* bidentate hydrogen bonds with the thiourea **1**. Additionally, we have found an interesting interaction between the hydroxyl group of the catalyst **1** and an oxygen atom of the nitro group of the nitroalkene **3** (O–H···O–N=O), supporting the lack of reactivity when the OH function is not present in the catalyst structure or it is not placed in the correct position. Based on extensive computational studies, we can elucidate a preference in the attack of the indole **2** over the appropriate face of the nitroalkene **3**, affording the observed major enantiomer in each case. This clarifies the origin of the enantioselectivity in this Friedel–Crafts alkylation reaction for different catalyst structures and indoles. We think that our work could be an important theoretical study to explain the role of the aminoindanol skeleton in organocatalysts, especially the role of the hydroxyl group, and it could help to understand future mechanisms in which an aminoindanol structure is involved.

Experimental section

Materials

All commercially available solvents and reagents were used as received. CH_2Cl_2 was filtered through basic alumina prior to use, to avoid the presence of trace amounts of acid. The ^{1}H and ^{13}C NMR spectra for the catalysts (1*R*,2*S*)-**1a**,[5b] (1*S*,2*R*)-**1a**,[5g] (*S*)-**1b**,[18] (*R*)-**1b**,[5g] (1*R*,2*R*)-**1c**,[5g] and (1*S*,2*R*)-**1d**,[5e] and the final products **4aa**,[5g] **4ab**[5g] and **4ba**[5g] are consistent with values previously reported in the literature.

Representative procedure for a thiourea organocatalysed Friedel–Crafts alkylation reaction of indoles with nitroalkenes

To a mixture of catalyst **1a–d** (20 mol%) and nitroalkene **3a** or **b** (0.1 mmol) in CH_2Cl_2 (0.1, 0.25 or 0.5 mL), indole **2a** or **b** (0.15 mmol) was further added, in a test tube at low temperature. After the appropriate reaction time (see Table 1), the residue was purified by flash chromatography (SiO_2; hexane–EtOAc, 8 : 2) to afford the final adducts (**4**). Yields and enantioselectivities are reported in Table 1. Spectral and analytical data for compounds **4aa**, **4ab** and **4ba** are in agreement with those previously reported in the literature.[5g]

Computational methods

All calculations were performed using the Gaussian09 program.[14] Molecular geometries were optimized with the M06-2X functional[19] in conjunction with the 6-311G(d,p) basis set.[20] Analytical second derivatives of the energy were calculated to classify the nature of every stationary point, to determine the harmonic vibrational frequencies, and to provide zero-point vibrational energy corrections. The thermal and entropic contributions to the free energies were also obtained from the vibrational frequency calculations, using the unscaled frequencies, and a value of −24 °C for the temperature (as this is the temperature at which the highest experimental enantiomeric excess was obtained). Full optimization calculations have been carried out considering solvent effects (CH_2Cl_2) with the PCM model.[21]

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