DOI: 10.1002/ejoc.201100506

Enhanced Efficiency of Thiourea Catalysts by External Brønsted Acids in the Friedel–Crafts Alkylation of Indoles

Eugenia Marqués-López,[a] Ana Alcaine,[a] Tomás Tejero,[a] and Raquel P. Herrera*[a,b]

Keywords: Alkylation / Nitrogen heterocycles / Organocatalysis / Brønsted acids / Nitroalkenes

A novel study on the influence of external Brønsted acids on thiourea catalysts in the asymmetric Friedel–Crafts alkylation of indoles with nitroalkenes is reported. The final 3-substituted indole derivatives were synthesized with better results because of cooperative effects between the chiral thiourea and a Brønsted acid additive (**1a**·HA). The effects of diverse catalysts, different acid additives, solvents, and temperatures in the reaction were also explored. The high reactivity and selectivity of the reaction is presumptively attributed to an appropriate assembly between the Brønsted acid and the thiourea structure, affording a more acidic and rigid catalytic complex.

Introduction

In the last decades, the Friedel–Crafts alkylation reaction[1] has attracted much attention for the formation of new carbon–carbon bonds, and it has become a powerful tool in organic synthesis. In this field great efforts have been paid to develop new catalytic enantioselective variants.[2,3] In this context, the addition of indole derivatives to electron-deficient olefins enables direct access to 3-substituted indole analogues with potential applications, as the indole framework has been identified in a great number of natural and unnatural products and medicinal agents with interesting biological activities.[4] Therefore, the preparation of products with this privileged structural motif is nowadays a significant aim of investigation and the discovery of new catalytic enantioselective procedures is still an important challenge. Although this area of research has been more extensively explored using metal catalysis,[2] important organocatalytic enantioselective examples have been also reported.[3] Among the explored efficient electrophiles, nitroalkenes are one of the most attractive Michael acceptors in organic synthesis[5] due to their versatility to be readily transformed into a variety of different functionalities.[6] Nevertheless and in spite of their importance, the organocatalytic version of this process using nitroolefins remains scarcely explored.[7,8]

Recently, chiral thioureas have been shown to be versatile and efficient organocatalysts in many organic transformations.[9] In this context, during our ongoing studies on organocatalysis we have centered part of our research interest on the application of thiourea catalysts[7a,8a,10] for the discovery of new asymmetric procedures. In this area, efforts are now being devoted to the development of more reactive structures to overcome some drawbacks, such as high catalyst loadings and low turnover rates. A recent study revealed that both the reaction rate and the enantioselectivity were correlated to catalyst acidity, and it could be efficiently used for the modulation of catalyst structure in hydrogen-bond-catalyzed enantioselective reactions.[11] On the basis of this idea, other authors have designed new, more efficient catalysts by introducing internal acidic elements,[7d,12] different to the frequently used 3,5-bis(trifluoromethyl)phenyl group, in the (thio)urea skeleton (Figure 1).

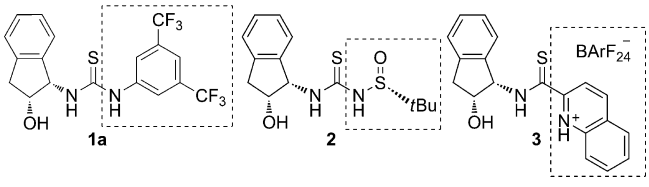


Figure 1. Representative examples of efficient thiourea catalysts.

We envisioned that higher enantioselectivity and reactivity might also be achieved by using a suitable and tunable external Brønsted acid additive (HA) with a chiral thiourea catalyst if appropriate assembly could be accomplished between them.[13] In this communication, we wish to report our preliminary results concerning this alternative approach to the establishment of cooperative effects between Brønsted acid additives and chiral thiourea organocatalysts, which may lead to the development of a novel activity pattern as a new promising concept (Figure 2).

[a] Laboratorio de Síntesis Asimétrica, Departamento de Química Orgánica, Instituto de Síntesis
Química y Catálisis Homogénea (ISQCH), CSIC – Universidad de Zaragoza,
50009 Zaragoza, Aragón, Spain
Fax: +34-976-762075
E-mail: raquelph@unizar.es
[b] ARAID, Fundación Aragón I+D,
50004 Zaragoza, Spain

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201100506.

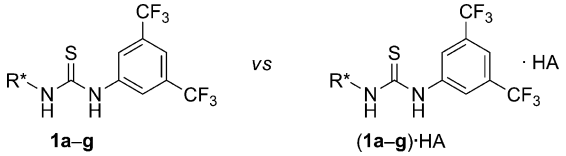
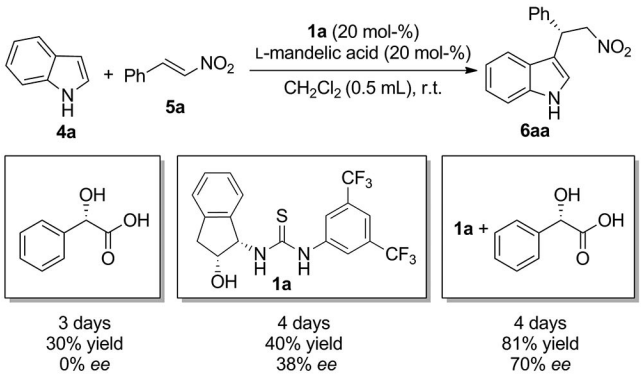


Figure 2. New concept explored. Brønsted acid assisted thiourea organocatalysts.

Results and Discussion

With the aim of increasing the acidity of chiral thioureas so that they can be more efficient catalysts, we thought that it would be easier to control and modulate the catalyst acidity by using an external additive instead of modifying the thiourea skeleton. The use of a carefully chosen acidic or basic additive has been extensively studied in aminocatalysis;[14] however, it has been less considered in the field of (thio)urea catalysis; in these few cases the thiourea was the additive in the catalytic system, and it was used to enhance the activity of the corresponding acid catalyst.[15] To evaluate the potential of this idea, we started our investigation by exploring the reactivity of thiourea **1a** with L-mandelic acid in a comparative study in the Friedel–Crafts alkylation reaction described in Scheme 1.

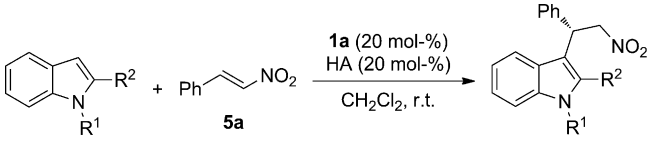


Scheme 1. L-Mandelic acid assisted thiourea **1a**.

To our surprise, the enantioselectivity of final adduct **6aa** in the presence of both L-mandelic acid and catalyst **1a** was quite a bit higher (70%*ee*) than that obtained in the absence of acid (38%*ee*). It is also remarkable that in presence of L-mandelic acid as the sole catalyst, the reaction leads to a racemic mixture, exemplifying that the synergic effect of both species is higher than the effect of each catalyst separately. This initial promising result encouraged us to examine this reaction more extensively by exploring other suitable acids and indole derivatives (Table 1).

We first tested D- and (±)-mandelic acid (Table 1, Entries 1 & 2) to study the match/mismatch effect, and the same results as those obtained with the enantiomeric L-form (Scheme 1) were achieved. Interestingly the sense of the stereoselection was the same as that when only thiourea **1a** was used. This fact shows that chirality is preferentially governed by catalyst **1a**, and this outcome prompted us to think that the acid activated the thiourea moiety rather than

Table 1. Screening of the cooperative effect of **1a**·HA.[a]



4a (R^1, R^2 = H)
4b (R^1 = H, R^2 = Me)
4c (R^1 = Me, R^2 = H)

Entry	HA	Indole	*t* [d]	Yield [%][b]	*ee* [%][c]
1	D-mandelic acid	**4a**	4	79	70
2	(±)-mandelic acid	**4a**	4	83	70
3	(*R*)-PhCH(OMe)CO_2H	**4a**	4	71	71
4	$PhCH_2CO_2H$	**4a**	4	65	58
5	$PhCO_2H$	**4a**	3	47	58
6	2-chloronicotinic acid	**4a**	3	39	44
7[d]	–	**4b**	3	94	20
8	L-mandelic acid	**4b**	3	95	38
9	D-mandelic acid	**4b**	3	95	38
10[d]	–	**4c**	4	58	rac.[e]
11	L-mandelic acid	**4c**	5	71	rac.[e]
12	D-mandelic acid	**4c**	5	70	rac.[e]
13	CH_3CO_2H	**4a**	4	90	65
14	CH_2ClCO_2H	**4a**	4	69	70
15	CF_3CO_2H	**4a**	4	96	49

[a] Experimental conditions: To a mixture of catalyst **1a** (0.02 mmol), HA (0.02 mmol), and nitroalkene **5a** (0.1 mmol) in a test tube at room temperature was added indole **4a**–**c** (0.15 mmol) and then CH_2Cl_2 (500 μL). After the reaction time, adduct **6** was isolated by flash chromatography. [b] Isolated yield. [c] Determined by chiral HPLC analysis (see Supporting Information). [d] Reaction performed in the absence of a Brønsted acid. [e] Racemic mixture.

assembling some of the reagents into the transition state by itself. In such a case, the stereochemistry in the acid might be determinant for the sign of the final enantiomer. On the other hand, catalyst complex **1a**·HA was significantly less effective when indole derivatives **4b** and **4c** were also considered (Table 1, Entries 7–12). It is noteworthy that better enantioselectivities were also achieved with 2-methylindole (**4b**; Table 1, Entries 8 & 9) compared with those obtained in the absence of acid (Table 1, Entry 7). However, with *N*-methylindole **4c**, the catalytic system afforded a racemic mixture regardless of whether the acid was present or not (Table 1, Entries 10–12). This suggests that the acid is able to improve the results when a thiourea catalyst renders final non-racemic mixtures. A variety of additives with differing levels of steric hindrance and acidity were then explored. Although the data do not display a clear correlation between steric factors and acidity (Table 1, Entries 1–6 and 13–15), the acidity could affect both the enantioselectivity and the reactivity of the process. In this respect, with a stronger acid, the acid-catalyzed reaction could compete with the **1a**·HA-promoted reaction (Table 1, Entry 15). Even if the presence of the OH group in mandelic acid seemed important for the enantioselectivity of the process (Table 1, Entry 1 vs. 4) similar and promising results were also obtained with (*R*)-PhCH(OMe)CO_2H (Table 1, En-

try 3) and CH_2ClCO_2H (Table 1, Entry 14). Our attention next turned to explore different synthesized thiourea catalysts **1b**–**g** under the same reaction conditions towards a better understanding of both the mode of action of the catalyst and the origin of the enantioselectivity in this process. To this purpose, different structural parameters were varied (Figure 3, Table 2).

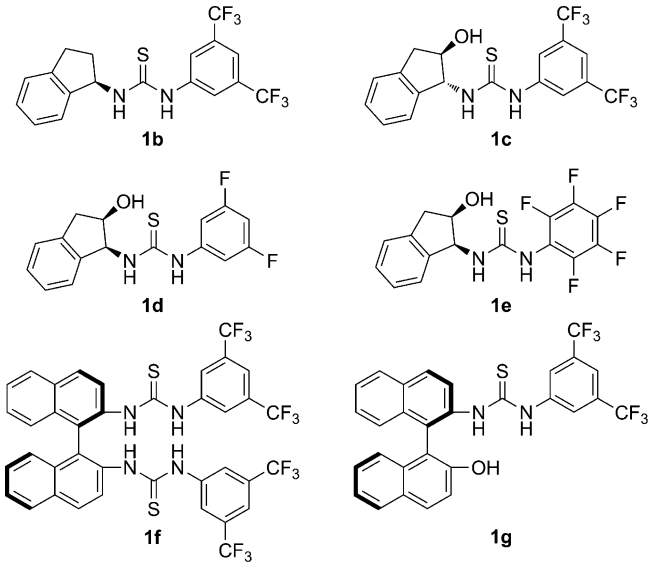
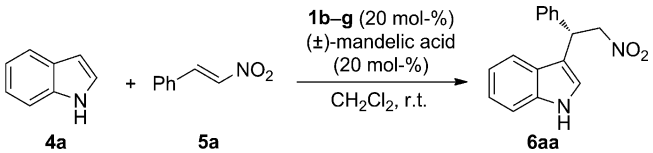


Figure 3. Chiral thioureas **1b**–**g** tested.

Although we could not improve the results achieved with **1a**·HA, several important aspects can be deduced from these results. The presence of an OH group in the skeleton of **1a** with *cis* configuration seems to be crucial for both the enantioselectivity and the reactivity as previously reported,[7a,10c] as catalysts **1b** and **1f** (Table 2, Entries 1 & 9) and catalysts **1c** and **1g** (Table 2, Entries 3 & 11) afforded poorer results compared with those obtained by using catalyst **1a**. This fact indicates that even though the presence of an OH group in the skeleton is important, the hydroxy group must be placed in the appropriate position to direct efficiently the attack of the external nucleophile, as previously reported.[7a,10c] The electronic effects of the CF_3 groups in the aromatic ring of thiourea catalyst **1a** seem to be also essential for the enantioselectivity, as catalysts **1d** and **1e** bearing different electron-withdrawing groups provided lower enantioinduction (Table 2, Entries 5 & 7). These results allowed the identification of system **1a**·HA as the most efficient in terms of enantioselectivity and reactivity. After these results, we decided to continue in the subsequent screening with catalyst **1a** and (±)-mandelic acid or CH_2ClCO_2H as additives. To optimize our cooperative catalyst system we also tested other parameters such as solvent, temperature, and variation in the concentration and equivalents of acid. On the basis of our experience we realized that solvent polarity might play an important role in governing the enantioselectivity of the reaction. In this context, we explored different solvents in the **1a**·HA-promoted Friedel–Crafts alkylation process (see Supporting Information). Among the solvents tested, $CHCl_3$ and CH_2Cl_2 allowed the obtainment of higher *ee* values. We decided to continue with CH_2Cl_2 in the ensuing screening.

Table 2. Screening of catalytic complexes (**1b**–**g**)·HA.[a]



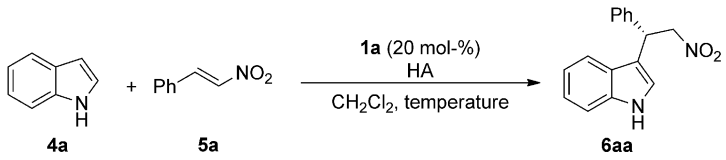
Entry	Catalyst	*t* [d]	Yield [%][b]	*ee* [%][c]
1	**1b**	5	24	rac.[d]
2[e]	**1b**	5	n.d.[f]	rac.[d]
3	**1c**	4	n.d.[f]	rac.[d]
4[e]	**1c**	4	n.d.[f]	rac.[d]
5	**1d**	7	68	60
6[e]	**1d**	7	24	45
7	**1e**	7	77	63
8[e]	**1e**	7	57	36
9	**1f**	6	30	8
10[e]	**1f**	7	21	14
11	**1g**	7	n.d.[f]	7
12[e]	**1g**	8	26	6

[a] Experimental conditions: To a mixture of catalyst **1b**–**g** (0.02 mmol), (±)-mandelic acid (0.02 mmol), and nitroalkene **5a** (0.1 mmol) in a test tube at room temperature was added indole **4a** (0.15 mmol) and then CH_2Cl_2 (500 μL). After the reaction time, compound **6aa** was isolated by flash chromatography. [b] Isolated yield. [c] Determined by chiral HPLC analysis (Chiralpak IA, flow hexane/*i*PrOH = 90:10, 1 mL/min). [d] Racemic mixture. [e] In the absence of (±)-mandelic acid. [f] Not determined.

By lowering the reaction temperature to –25 from 25 °C we could increase the enantioselectivity up to 89% (Table 3, Entries 11 & 15) although the reaction rate was lower. However, additional variations in the concentration and equivalents of acid did not lead to improved results. We tested the same reaction in the absence of acid at different temperatures under different conditions (Table 3, Entries 2, 4, 8, and 12), and in all cases lower values were obtained relative to those obtained with **1a**·HA in terms of enantioselectivity and reactivity. Unfortunately, the large differences achieved at room temperature between the reaction performed in the presence or absence of acid are not maintained at low temperature, and this may be due to a different mode of coordination between the thiourea catalyst and the acid. We realized that at low temperature the amount of active complex **1a**·HA could depend on the number of equivalents and the enantiomeric form used. Comparative experiments performed with (±)-, L-, and D-mandelic acid showed identical results, although 2 equiv. of D-mandelic acid gave slightly improved results in terms of enantioselectivity and reactivity (Table 3, Entry 15). Interestingly, in the absence of catalyst **1a**, the reaction did not proceed even after 4 d (Table 3, Entry 19), supporting the fact that the acid activates the catalyst more than one of the reagents.

Finally, with the optimal reaction conditions in hand, we investigated the scope of our protocol by using catalyst **1a**

Table 3. Screening of different reaction conditions using **1a**·HA.[a]



4a **5a** **6aa**

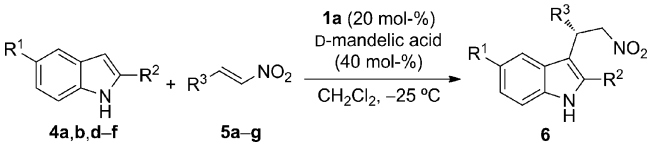
Entry	Volume of CH_2Cl_2 [μL]	HA (equiv.)[b]	Temperature [°C]	*t* [d]	Yield [%][c]	*ee* [%][d]
1	500	(±)-mandelic acid (1)	3	4	59	74
2	500	no acid	3	4	21	40
3	500	(±)-mandelic acid (1)	–10	4	32	82
4	500	no acid	–10	4	24	66
5	100	(±)-mandelic acid (1)	–25	3	61	87
6	250	CH_2ClCO_2H acid (1)	–25	4	64	84
7[e]	250	(±)-mandelic acid (1)	–25	4	45	88
8[e]	250	no acid	–25	4	34	77
9	250	(±)-mandelic acid (1)	–25	3	63	88
10	250	L-mandelic acid (1)	–25	3	55	88
11	250	D-mandelic acid (1)	–25	3	53	89
12	250	no acid	–25	3	40	82
13	250	(±)-mandelic acid (2)	–25	3	53	88
14	250	L-mandelic acid (2)	–25	3	56	88
15	250	D-mandelic acid (2)	–25	3	60	89
16	250	D-mandelic acid (0.5)	–25	4	55	87
17	250	D-mandelic acid (3)	–25	4	64	87
18	250	D-mandelic acid (5)	–25	4	67	86
19[f]	250	D-mandelic acid (2)	–25	4	n.r.[g]	n.r.[g]

[a] Experimental conditions: To a mixture of catalyst **1a** (0.02 mmol), HA (0.02 mmol), and nitroalkene **5a** (0.1 mmol) in a test tube at the indicated temperature was added indole **4a** (0.15 mmol) and then CH_2Cl_2 (the corresponding amount). After the reaction time, compound **6aa** was isolated by chromatography. [b] Equivalents of acid with respect to catalyst **1a**. [c] Isolated yield. [d] Determined by chiral HPLC analysis (Chiralpak IA, flow hexane/*i*PrOH = 90:10, 1 mL/min). [e] 10 mol-% of **1a**. [f] Reaction was performed in the absence of catalyst **1a**. [g] No reaction observed.

and D-mandelic acid in a comparative study by performing the reaction in the absence of an additive (Table 4, values in parentheses).

The reactions were stopped, even when they were not complete, after a reasonable number of days to compare the results with **1a**·HA to those obtained by using only catalyst **1a**. The procedure was successfully extended to different substituted nitroalkenes **5a**–**g** and indoles **4a**–**f**, furnishing corresponding adducts **6** in useful yields and very good enantioselectivities, as summarized in Table 4. Although in a few cases just slightly higher values were achieved in comparison to that obtained in the absence of acid (Table 4, Entries 7 & 10), in general the presence of acid provides better results in terms of both reactivity and enantioselectivity. Aromatic and heteroaromatic nitroolefins with electron-withdrawing and electron-donating groups reacted well with indole to afford alkylated adducts **6ab**–**ag** in good yields with high enantioselectivities (Table 4, Entries 1–6). Even though nitrostyrenes containing electron-donating groups showed a slightly lower reaction rate than the reaction of nitrostyrenes containing an electron-withdrawing group (Table 4, Entries 1–3 vs. Entries 4 & 6; except using 4-Br, Entry 5), the enantioselectivity was independent of the substituent on the aromatic ring. The electronic effects on the indole ring were also considered (Table 4, Entries 7–10). In this sense, when a Me group was introduced at the 2-position of the indole structure, the enantioselectivity dropped, although the reactivity was higher (Table 4, Entry 7). On the other hand, electron-withdrawing groups in the 5-position of the indole did not affect the enantioselectivity of the process, but the reaction rate was dramati-

Table 4. Final scope of the **1a**·HA-catalyzed Friedel–Crafts alkylation reaction.[a]



4a,**b**,**d**–**f** **5a**–**g** **6**

Entry	Indole; R^1,R^2	Nitroalkene; R^3	Product	*t* [d]	Yield [%][b]	*ee* [%][c]
1	**4a**; H,H	**5b**; 4-MePh	**6ab**	3	50 (39)	88 (62)
2	**4a**; H,H	**5c**; 4-MeOPh	**6ac**	3	45 (24)	84 (66)
3	**4a**; H,H	**5d**; 2-furyl	**6ad**	3	58 (27)	82 (68)
4	**4a**; H,H	**5e**; 4-ClPh	**6ae**	3	75 (33)	88 (75)
5	**4a**; H,H	**5f**; 4-BrPh	**6af**	3	30 (17)	87 (68)
6	**4a**; H,H	**5g**; 4-FPh	**6ag**	3	67 (42)	88 (64)
7	**4b**; H,Me	**5a**; Ph	**6ba**	4	94 (91)	58 (52)
8[d]	**4d**; Cl,H	**5a**; Ph	**6da**	5	25 (n.d.)	86 (70)
9	**4e**; F,H	**5a**; Ph	**6ea**	5	28 (12)	86 (72)
10	**4f**; MeO,H	**5a**; Ph	**6fa**	4	88 (74)	86 (82)

[a] Experimental conditions: To a mixture of catalyst **1a** (0.02 mmol), D-mandelic acid (0.04 mmol), and nitroalkene **5a**–**g** (0.1 mmol) in a test tube at low temperature (–25 °C) was added indole **4a**–**f** (0.15 mmol) and then CH_2Cl_2 (0.25 mL). After the reaction time, product **6** was isolated by flash chromatography. [b] Isolated yield. [c] Determined by chiral HPLC analysis (see Supporting Information). [d] 100 μL of solvent.

cally lower compared to that obtained with indoles bearing electron-donating groups (Table 4, Entries 8 & 9 vs. 7 & 10). The absolute configurations of adducts **6** were assigned by comparison of their optical rotation with those reported in the literature for the same products.[7]

Some authors have previously proposed active complexes **I**[15b–15d,16] and **II**[15a] (Figure 4) as suitable modes of interaction between an acid catalyst and a thiourea additive in the transition state. Although at this stage we cannot ensure the role of the acid in our mechanism, according to the experimental results we believe that in this reaction the mode of activation could be different to those previously invoked. Firstly, if **III** was the mode of activation in our mechanism, the chirality of the acid would influence which of the enantiomers is obtained, more than the catalyst chirality. Different signs and values of enantioselectivity should be expected using D-, L-, or (±)-mandelic acid as additives, but this is not the case. Moreover, **III** would not be in agreement with the good results obtained with (*R*)-PhCH(OMe)CO_2H (Table 1, Entry 3). On the basis of all these results we consider that the activation of the thiourea moiety with the acid **IV** in an upper face might explain the outcome better, although more experiments are necessary to clarify this mode of action. From the experimental results we can assume that the catalytic complex **1a**·HA is a more reactive species, maybe due to the lower pK_a of thiourea, therefore increasing the reaction rate. It is also remarkable that a stronger union between both species clearly worked against the independent activation of each one with the substrates. Furthermore, the improvement in the enantioselectivity could be explained by generating a more rigid assembly in the transition state, as a combination of both structures.

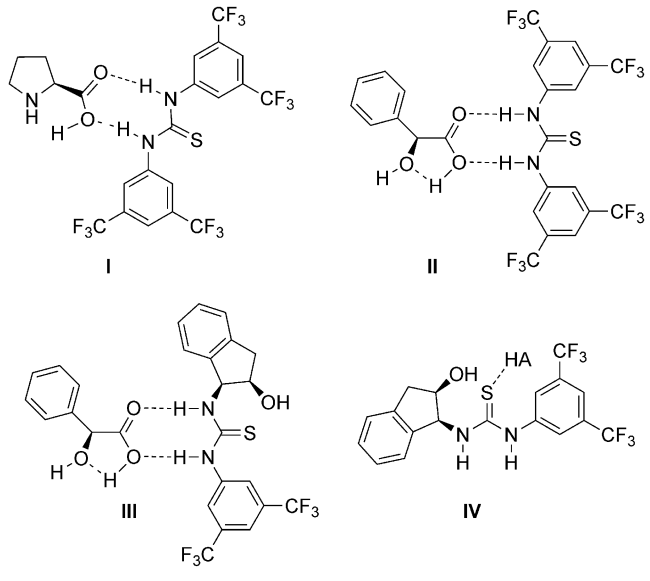


Figure 4. Hydrogen-bonding-mediated cooperative catalysis.

However, we cannot discard the possible simultaneous coordination of the acid and the thiourea moiety to one of the reagents involved in our reaction, as proposed by Shi and co-workers.[17] Additional computational calculations and NMR experiments[18] are being performed to shed light onto this interesting and novel reactivity, and the results will be published in due course.

Conclusions

The results show that Brønsted acid assisted thiourea catalysts are very effective catalyst complexes for the enantioselective Friedel–Crafts reaction of indoles with nitroalkenes. The synergic effect between both species is higher than the effect promoted by each one separately. Easy modulation of the nature of the acid allows the convenient alteration of the chiral environment and the pK_a of the donor hydrogen, which in our case is thiourea catalyst **1a**. These results could open a new interesting line of research related to the effect of additives in thiourea-catalyzed reactions, which is a concept that is scarcely considered in the literature. Moreover, this contribution could become an important starting point for further investigations. Additional studies to clarify our plausible mechanistic hypothesis by NMR spectroscopy and computational calculations, as well as its following application to other enantioselective thiourea-catalyzed systems, are in progress in our laboratories.

Experimental Section

General Information: Purification of reaction products was carried out by flash chromatography using silica gel (0.063–0.200 mm) or medium-pressure liquid chromatography using prepacked silica columns. Analytical thin-layer chromatography was performed on 0.25 mm silica gel 60-F plates. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra were recorded at 100 MHz by using $CDCl_3$ as solvent. Chemical shifts are reported relative to residual $CHCl_3$ (δ = 7.26 ppm) for ^{1}H NMR and relative to 77.0 ppm for ^{13}C NMR.

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. Chiral thiourea catalysts were obtained following literature procedures: **1a**,[10c] **1b**,[10c] **1c**,[19] and **1f**.[7c] Starting materials, yields, and spectroscopic data for compounds **1d**, **1e**, **1g**, and **6ea** are described in the Supporting Information. ^{1}H and ^{13}C NMR spectra for compounds **6aa**,[7a] **6ab**–**af**,[7d] **6ag**,[20] and **6ba**–**da**,**fa**[7a] are consistent with values previously reported in the literature.

General Procedure for the 1a·HA-Catalyzed Friedel–Crafts Alkylation Reaction: To a mixture of catalyst **1a** (20 mol-%), D-mandelic acid (40 mol-%), and nitroalkene **5a**–**g** (0.1 mmol) at low temperature (–25 °C) in a test tube was added indole **4a**–**f** (0.15 mmol) and then CH_2Cl_2 (0.25 mL). After the appropriate reaction time (see Table 4), the residue was purified by flash chromatography or medium-pressure liquid chromatography (SiO_2; hexane/EtOAc, 8:2) to afford final adducts **6**. Yields and enantioselectivities are reported in Table 4. Spectral and analytical data for compounds **6** are in agreement with those previously reported in the literature.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and characterization data for compounds **1d**, **1e**, **1g**, and **6ea** and HPLC chromatograms for all final products.

Acknowledgments

We thank the Ministry of Science and Innovation (MICINN), Madrid, Spain (Project CTQ2010-19606), and the Government of Aragón, Zaragoza, Spain (Project PI064/09 and Research Groups, E-10), for financial support of our research. We are also grateful to Prof. Luca Bernardi for useful comments. E.M.-L. thanks CSIC for a JAE-Doc postdoctoral contract. R.P.H. thanks the Aragón I+D Foundation for her permanent position.

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Received: April 10, 2011
Published Online: June 7, 2011

