Hydrogen bonds as an alternative activation

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1. Introduction

In the last decade a remarkable expansion of a new field has been accomplished, the *asymmetric organocatalysis*.^[1] This new discipline has appeared as an useful, complementary and alternative strategy between those previously and more broadly explored, the metal and enzymatic catalysis. In this context, an impressive number of highly enantioselective approaches have been successfully and efficiently developed for the most common organic reactions and the synthesis of new complex products has been also achieved.^[2]

The immense number of organocatalytic processes could be classified into four big groups depending on the catalyst activation nature as previously proposed by Dalko and Moisan:^[3] 1. Reactions via covalent activation complexes, such as those performed with chiral secondary or primary amines;^[4] 2. Reactions via non covalent activation transition states, using hydrogen bond catalysis;^[5] 3. Enantioselective phase-transfer reactions by chiral quaternary ammonium salts;^[6] 4. Asymmetric transformations in a chiral cavity.^[7] Among all of them and within the second group, catalysts acting by hydrogen bond interactions represent a significant contribution to this great area, receiving a special attention in the last decade.^[5] The main organocatalytic structures covering this large group are thiourea/urea derivatives,^[8] guanidines,^[9] TADDOL^[10] or BINOL analogues,^[11] “chiral proton catalysts”^[12] and chiral phosphoric acid derivatives.^[13] Some of these representative structures are illustrated in Figure 1.

Figure 1 Representative organocatalysts acting as hydrogen-bond donors

1.1 Chiral Thiourea/Urea Organocatalysts

Intensive efforts have been invested in studying the behavior of (thio)urea structures as suitable catalysts in a great number of efficient processes. In this respect, the center of inspiration for the subsequent reactions concerning this area was the work reported by Etter and co-workers where aryl urea **1** was able to form co-crystal complexes with a variety of hydrogen bond acceptors (Figure 2).[14]

Figure 2 Co-crystallized functional groups using urea **1**. Model of bidentate activation

Nevertheless, the first application of this kind of bidentate activation employing such structures was reported by Curran and co-workers, using urea catalyst **2**. They observed that the presence of urea **2** modified the rate and the stereochemical course of allylation reactions employing cyclic sulfinyl radicals as depicted in Scheme 1.[15] Moreover, urea **2** was also able to accelerate a Claisen rearrangement of electron rich allyl vinyl ethers.[16] Both studies became key works in this growing area and they were a main reference for the following research works using (thio)urea catalysts.

Scheme 1 Allylation reaction promoted by urea **2**

However the first examples using hydrogen bond catalysis promoted by bidentate motifs could be attributed to Hine's[17] and Kelly's groups,[18] although in these cases using biphenylenediol derivatives. Ensuing these original examples, a great number of chiral thioureas and several ureas have been developed and effectively applied in a large number of catalytic systems (Figure 3).[8]

Figure 3 Representative thiourea catalysts

This chapter will be focused on our own contribution to the emerging area of chiral thiourea catalysis. Our work will be illustrated and discussed by comparison with pioneering models concerning different explored reactions. Diverse developed strategies for the preparation of interesting building-blocks will be highlighted.

2. Thiourea catalysts

2.1 Friedel–Crafts alkylation reaction

Friedel–Crafts alkylation reaction has become one of the most powerful carbon-carbon bond-forming processes in organic synthesis, mainly by means of metal catalysis,[19] and more scarcely explored by organocatalytic procedures.[20] Among the most significant Friedel–Crafts reactions, those concerning the Michael addition of indoles to electron deficient alkenes have attracted a special attention.[20a] The indole is considered a privileged structure and it is a frequent motif in a great number of natural products (Figure 4)[21] for this reason the development of new enantioselective methodologies for its chiral synthesis is always an important achievement.

Figure 4 Indole motifs in natural products

In this context, we developed a pioneering example of organocatalyzed Friedel–Crafts alkylation reaction between nitroolefins and aromatic and heteroaromatic systems.[22] Until that moment, just metal catalyzed examples of this reactions using Lewis acids like $\text{Yb}(\text{OTf})_3 \cdot 3\text{H}_2\text{O}$,[23] $\text{Sc}(\text{OTf})_3$ [24] or $\text{Bi}(\text{OTf})_3$ [25] had been reported. We revealed by the first time the useful application of organocatalysis in this process using neutral hydrogen bond donors, urea- and thiourea-type catalysts **3** and **4** respectively (Scheme 2), in a comparative study where all examples were tested in toluene and solventless conditions affording very good yields.

Scheme 2 Organocatalyzed Friedel–Crafts alkylation reaction of aromatic and heteroaromatic systems

We also turned our attention to the Friedel–Crafts alkylation of indoles (Scheme 3), because only a practical and efficient InBr_3 -catalyzed addition of indoles to nitroalkenes in aqueous media had been formerly reported.[26]

Scheme 3 Friedel–Crafts alkylation reaction of indoles with nitroalkenes

The outcomes using thiourea organocatalyst **4** resulted superior in all cases with respect to those obtained employing urea **3**. This tendency was in agreement with the greater hydrogen-bond donor ability of thiourea derivatives supported by the enhanced differences in acidities (pK_{HA} thiourea = 21.0; pK_{HA} urea = 26.9).[27] Furthermore, the less tendency of sulfur atom to make self-association between the N-H group of one molecule with the thiocarbonyl group of another would justify the different results achieved with these catalysts.[28]

In order to explain the mode of activation, a similar double hydrogen-bond interaction between the (thio)urea-type derivatives with the nitro group was proposed in analogy to the hypothesis reported earlier for this functional group (Figure 5).[14]

Figure 5 Mechanistic hypothesis

More interesting was the original development of the enantioselective version of the latter Friedel–Crafts alkylation reaction.[29] For this purpose the synthesis of simple and easily accessible chiral (thio)urea catalysts was required. Initially we prepared and screened catalysts **7a-g** (Scheme 4), easily obtained in one step of reaction and in very good yields from the coupling reaction between 3,5-bis(trifluoromethyl)phenyl iso(thio)cyanate **5** or **6** and the corresponding chiral amines or amino alcohols, all commercially available.

Scheme 4 Synthesis of chiral (thio)ureas **7a-e**

In all cases an increased reactivity of *trans*- β -nitrostyrene against indole was achieved with every synthesized catalyst. However, only thiourea catalyst **7d** exhibited promising results in terms of both reactivity and enantioselectivity. After exploring different parameters and under the optimized reaction conditions, we extended our method to diverse indoles and nitroalkenes affording final adducts with very good yields and high enantioselectivities. The scope of the reaction is summarized in Scheme 5.

Scheme 5 Thiourea catalyzed Friedel–Crafts alkylation reaction

In order to demonstrate the synthetically valuable aspect of this process, the optically active adduct **8** was transformed into important compounds of biological interest such as tryptamine **9**[30] and 1,2,3,4-tetrahydro- β -carboline **11**[31] in very good yield and without racemization, as represented in Scheme 6. Moreover, derivatization of compound **8** in the corresponding *N*-tosylated tryptamine **10** allowed the assignment of the absolute configuration of the final products.

Scheme 6 Synthesis of tryptamine **9** and 1,2,3,4-tetrahydro- β -carboline **11**

In an attempt to understand the possible mode of action of novel catalyst **7d** in the activation complex that led to the observed enantioinduction in final products, we synthesized catalyst **7f**, lacking the alcoholic function, and **7g**, in which the hydroxy group was protected by a trimethylsilyl group. Both catalysts showed poorer results in comparison with **7d**, not only with regard to the enantioselectivity but also in terms of the catalyst activity, as shown in Figure 6.

Figure 6

This fact, in addition to the results obtained with different indoles in which the NH in the structure seemed to be also crucial, we envisioned that our catalyst could act as a bifunctional catalyst.[8f,32] Our proposal was that the thiourea would activate the nitro group through the N-H atoms, as previously reported, and the hydroxyl function would interact with the indolic proton by means of a weak hydrogen bond, approaching the nucleophile on the *Si* face of the nitroolefin as depicted in Figure 7. This attack would afford the absolute configuration observed in the final products.

Figure 7 Mechanistic proposal

The rigidity of the aminoindanol skeleton in catalyst **7d** seemed to be also crucial for the success of the process compared with the major flexibility expected by catalyst **7b** and **7c** in the transition state, in which the OH group was also present but affording poorer results overall in terms of enantioselectivities.

Concurrently to our original example, Jørgensen and co-workers[33] and more recently Connon's,[34] Seidel's[35] and Akiyama's[36] groups have developed attractive and efficient catalytic systems; which are bis-sulfonamide **12**, bis-thiourea **13**, quinolinium thioamide catalyst **14** and phosphoric acid silyl-derivative **15** respectively, for their applications as promoters in this Friedel–Crafts alkylation reaction (Figure 8).

Figure 8 Efficient catalysts for activating the Friedel–Crafts alkylation reaction

Chiral bis-arylthiourea **13** was employed in the study of the asymmetric organocatalytic Friedel–Crafts addition between *N*-methylindole and nitroolefines affording low enantioselectivities and good yields after long reaction time. However, with the other catalysts non *N*-substituted indoles were efficient nucleophiles against a range of nitroolefines, being the presence of the N-H moiety in the indole ring essential to achieve high yields and enantioselectivities. Interestingly in all cases a hydrogen donor catalyst was required to promote the reaction.

In spite of the importance of this process, it is still scarcely investigated and documented; therefore the searching for more effective catalysts is still open. Additional investigations are expected to arise in this area for the preparation of asymmetric attractive indole structures.

2.2 Michael addition reactions

Among the most significant and common reactions developed so far in organocatalysis, those concerning conjugate Michael additions of a nucleophile to an electron-deficient olefin, are the most relevant ones in this expanding area.[37] This strategy allows the stereoselective formation of carbon-carbon[38] or carbon-heteroatom bonds[39] and it has been successfully applied in a great number of reactions. Its synthetic potential has been demonstrated by application in total synthesis and in the obtention of molecules of high complexity.[2,40]

2.2.1 Michael addition reaction of *N,N*-dialkylhydrazones to nitroalkenes

Suitable but less explored nucleophiles are the *N,N*-dialkylhydrazones, which may exhibit an ambiphilic behavior: on the one hand demonstrating an aza-enamine character and reacting with electrophiles such as activated Michael acceptors under the appropriate conditions,[41] and on the other hand acting as imine surrogates against nucleophiles. Although, this aspect has been less considered,[42] contrary to the well-known electrophilic character of *N*-acylhydrazones.[43] As aza-enamines, formaldehyde *N,N*-dialkylhydrazones have been extensively used as synthetic equivalents of formyl and cyanide anions,[44] however and despite their diverse reactivity and synthetic versatility, these privileged species have been less considered in organocatalysis.[45]

In this context, another developed application of thiourea **4** is the activation of nucleophilic addition of *N,N*-dialkylhydrazones to diverse nitroolefines.[46] Formaldehyde *N,N*-dialkylhydrazones have been extensively investigated, in comparison with hydrazones synthesized with other aldehydes, which have been barely considered due to their inherent lower reactivity.[42b] We developed a new work in the field of conjugate

additions using less reactive aliphatic aldehyde hydrazones and nitroalkenes catalyzed by thiourea **4** and in absence of base, as depicted in Scheme 7.

Scheme 7 Michael addition reaction of *N,N*-dialkylhydrazones **16** to nitroalkenes **17**

Some remarkable aspects of this process should be underlined: Firstly, we were glad to observe that thiourea **4** promoted the reaction affording higher yield values at the same reaction time that the uncatalyzed reaction. Surprisingly, instead of the formation of the expected products from the attack by the azomethine carbon atom of the hydrazone, as it had been observed with formaldehyde hydrazone derivatives, we obtained the products resulting from the nucleophilic attack at the α -carbon of the hydrazone. This reactivity under non-basic conditions was totally unprecedented, and it had not been observed previously in the literature for enolizable hydrazones since the use of a strong base was always required *via* enamine formation and subsequently trapped by electrophiles.[47] To explain this surprising reactivity we suggested that the

hydrazones **16** should be in equilibrium with its ene-hydrazine form **19**, which would furnish the observed adducts by attacking the activated nitroalkene as represented in Scheme 8. Even when the presence of **19** could not be detected by NMR experiments, because the equilibrium is shifted to the more favorable hydrazone form **16**, the small amount of **19** in the medium was enough to allow the reaction and to move the equilibrium towards the appropriate direction.

Scheme 8 Proposed mechanism *via* hydrazone-ene-hydrazine equilibrium

We have illustrated a novel example of reactivity for thiourea **4** promoting an unprecedented conjugate addition of enolizable hydrazones to nitroalkenes, reacting at the α -carbon in absence of base and affording γ -nitrohydrazones in very good yields. This kind of reactivity is still open to be studied from an enantioselective point of view.

2.2.2 Michael addition reaction of formaldehyde *N,N*-dialkylhydrazones to β,γ -unsaturated α -keto esters

Among the different Michael addition approaches, the nucleophilic reactivity of formaldehyde dialkylhydrazones seems to be too low for reactions using weak electrophiles, such as α,β -unsaturated carbonyl compounds, and therefore, hydrazones have been rarely considered as formyl anion equivalents of synthetic value against these substrates.[48] Encouraged for the lack of catalytic examples and in order to contribute to this less explored field, we studied the viability of thiourea catalyzed Michael addition reaction of hydrazone **20** and β,γ -unsaturated α -ketoester **21** (Scheme 9).[49] After testing different parameters such as chiral catalysts, solvents, the dilution and temperature, we finally explored the scope of this new umpolung strategy with β,γ -unsaturated α -ketoester derivatives **21** and furnishing the corresponding adducts **22a-f** in suitable yields and good enantioselectivities at -40 or -60 °C (Scheme 9). In this process, thiourea **7d** was once more identified as the more promising catalyst for promoting this Michael addition.

Scheme 9 Organocatalytic Michael addition reaction using hydrazone pyrrolodine derivative **20**

The synthetic importance of these substrates lays in the possibility of further cleavage of the hydrazone moiety for regenerating the carbonyl function under a range of mild conditions, and the later transformation of final products into useful chiral building blocks. In this regard, the utility of adducts **22** was established by transforming the hydrazone group into some target compounds such as the corresponding nitriles **23a,b** by oxidative cleavage and into the succinate **24** resulting from oxidative decarboxylation of an unstable intermediate *in situ* generated under the specified conditions as described in Scheme 10. The latter allowed the assignment of the absolute configuration of product **22a** as *R*, and the same configuration was assumed for adducts **22b-f** by analogy.

Scheme 10 Syntheses of target compounds

In order to explain the absolute configuration obtained in the final products, we envisioned that catalyst **7d** would also act in a bifunctional way as previously mentioned in Figure 7.[29] Therefore, whereas the two thiourea hydrogen atoms would activate the carbonyl group, the free alcoholic function would interact with the hydrazone with a weak hydrogen bond, directing the attack of the incoming nucleophile on the *Re* face of the β,γ -unsaturated α -ketoester as illustrated in Figure 9.

Figure 9 Possible bifunctional mode of action

This synthetically useful class of hydrazones, from formaldehyde *N,N*-dialkylhydrazones or from enolizable aldehydes, represents an interesting type of umpolung carbonyl reagent or imine surrogates, respectively. Moreover, their neutral character as electrophiles or nucleophiles makes them compatible with many functional groups, being potential substrates in many catalytic approaches. Therefore, we expect that further efforts will be dedicated to the development of new applications based on the combination of organocatalysis and *N,N*-dialkylhydrazones, and a novel but promising area of research could grow up around these compounds.

2.2.3 Hydrophosphonylation reaction of nitroalkenes

Currently the stereoselective synthesis of α -[50] and β -aminophosphonic[51] acids and derivatives has attracted a particular interest due to their appealing biological activities as structurally analogues to α - and β -amino acids respectively, and because in general phosphorus compounds are important substrates in biochemical processes (Figure 10).

Figure 10 Biologically active β -amino phosphoric acid derivatives

However, although great progresses have been accomplished in the preparation of enantioenriched α -aminophosphonates,[50,52] the strategies for the access to β -aminophosphonic acids have been less explored,[51] and only a few examples based in organocatalytic protocols have been reported.[53] The Michael addition of phosphorus compounds to nitroalkenes[54,55] has been applied as an effective tool for the straightforward synthesis of P-C bonds, becoming a convenient method for the construction of functionalized β -aminophosphonates. In this respect, only three interesting and versatile methods concerning the organocatalytic conjugate addition of diphenyl phosphite to nitroalkenes have been reported using chiral guanidine **25**,[53a] quinine **26**[53b] and squaramide **27**[53c] (Figure 11). Therefore, the development of new catalytic methodologies to provide β -nitrophosphonates is still of notable importance.

Figure 11 Efficient catalysts for the synthesis of β -nitrophosphonates

Recently we explored this process using chiral thiourea catalysts as a new viable route to obtain the desired β -aminophosphonate adducts.[56] Among all the thioureas tested in a preliminary study to obtain the more efficient catalyst (Figure 12), only **31** afforded promising results in terms of both reactivity and enantioselectivity. It is noteworthy that with all catalysts shown in Figure 12 the addition of an external base ($i\text{Pr}_2\text{EtN}$) was always required in order to achieve reactivity in the explored reaction, except when using thiourea **31** which also has a Brønsted base moiety in its structure.

Figure 12 Thiourea catalysts tested

After an exhaustive exploration of different parameters such as solvents, various dialkylphosphites, temperature and reagent concentration, the best reaction conditions were accomplished with bifunctional thiourea **31** using CH_2Cl_2 and 10 mol% of catalyst at $-10\text{ }^\circ\text{C}$, and we extended the applicability of our developed procedure to a variety of aromatic and aliphatic nitroalkenes (Scheme 11).

Scheme 11 Thiourea catalyzed organocatalytic hydrophosphonylation of nitroalkenes

Our moderate results are comparable to those previously reported by Wang and co-workers,[53a] but in shorter reaction times because in our case it was not necessary to decrease the temperature to -55°C . However, we could not improve the excellent results reported by Terada's[53b] and Rawal's[53c] groups. Nevertheless, the accessibility to the commercially available thiourea **31**, support the simplicity and viability of our methodology. The absolute configuration of the Michael adducts **32a-l** was determined by comparison between the optical rotation values with those previously reported in the literature for the same products.[53] On the basis of the experimental results and comparing with other thioureas tested in our study, we envisioned that catalyst **31** could act following a bifunctional model as previously proposed in the literature

for the same structure.[57] In order to give additional support to this hypothesis we performed computational calculations using a DFT model: B3LYP/6-31+G*.[58] We have studied different approaches and the more stable **TS-1** is in agreement with the experimental results, since it would afford the observed enantiomer in our final adducts (Figure 13).

Figure 13 DFT calculations at B3LYP/6-31+G* level. Proposed transition state models

Even when this field has recently emerged, the growing interest for β -aminophosphonic acids showing biological activity or as useful intermediates for the preparation of peptidomimetic derivatives should stimulate further searches and provide achievements in this area.

2.3 Aza-Henry reaction

The addition of nitroalkanes to C=N bond (aza-Henry or nitro-Mannich reaction)[59] is an important synthetic procedure that affords C–C bond formation, and represents a simple route to achieve two different vicinal nitrogenated functionalities. The resulting β -nitroamine could be further transformed into a variety of valuable building blocks and interesting biological compounds such as 1,2-diamines[60] or α -amino acids.[61] Much attention has been paid to the catalytic asymmetric version of this reaction over the years,[59,62] but the search of new effective catalysts to promote highly selective processes is still remaining.

In this area we focused our research on the study of modified cinchona alkaloids[32,63] in order to explore the capability of these structures to promote the addition of nitromethane to a variety of protected aromatic and heteroaromatic imines (Scheme 12).[64] In a preliminary screening of a variety of catalysts (Figure 14), cinchona-based thiourea organocatalyst **43** proved to be the most efficient one.

Figure 14 Representative cinchona alkaloids screened in the aza-Henry reaction

Scheme 12 Organocatalytic aza-Henry reaction using cinchona-based thiourea **43**

The final adducts were isolated in moderate to good yields and high levels of enantioselectivity (up to 94%). Moreover, several protecting groups on the nitrogen atom were tested, including *N*-Boc, *N*-Cbz and *N*-Fmoc groups, and although the best results were obtained with *N*-Boc group, the high values achieved with the other two protecting groups confirmed the wide range of tolerance of this process to different *N*-carbamoyl groups and imines. Although mechanistic explanation was not given, we cannot rule out a possible bifunctional mode of action by the catalyst activating the reaction through the thiourea moiety and with the

quinuclidinic base function as previously suggested for this catalyst.[65] However we observed that catalysts with the OH group of quinine derivative protected via acetylation or carbamate formation, as derivatives **33** and **38**, or replaced by a benzomido moiety as in **34**, afforded the formation of the desired adducts with very poor yields. This fact supports the importance of the presence of the thiourea moiety in the backbone of the catalyst.

The products resulting from these strategies are very important motifs in biologically active compounds and in medicinal chemistry, for this reason this area of research has encouraged significant efforts in order to improve the previous published results, however several drawbacks have not been overcome yet, and this fact will prompt further investigations in this field.

3. Conclusions

In this chapter our small contribution in the huge field of organocatalysis in general and chiral thioureas in particular is reported. Different thiourea catalyzed processes have been illustrated, some of them original and pioneering in this area, which became a precedent for further explored reactions. Nevertheless, the exciting organocatalytic world is still in expansion and it is addressed to the development of new catalysts and more complex systems. We attend every day to the discovery of new amazing approaches and efficient catalysts, among them, thiourea catalysts still represent an interesting research area. In the next years improved and valuable catalysts will be reported and more complex versions of these and other useful processes will emerge. In fact, the searching for environmentally friendly catalysts is nowadays a challenge and one of the main goals in the scientific world, however its accomplishment will require further investigations.

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