Asymmetric Catalysis

International Edition: DOI: 10.1002/anie.201511555
German Edition: DOI: 10.1002/ange.201511555

Organocatalysis by Networks of Cooperative Hydrogen Bonds: Enantioselective Direct Mannich Addition to Preformed Arylideneureas

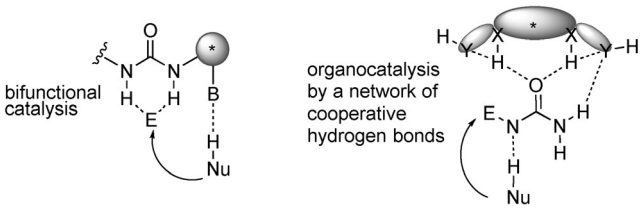
*Victor J. Lillo, Javier Mansilla, and José M. Saá**

Dedicated to Professor Carmen Nájera on the occasion of her 65th birthday

Abstract: *The concept of noncovalent organocatalysis by means of networks of cooperative hydrogen bonds (NCHB organocatalysis) has been explored. Arylideneureas were chosen as ideal substrates because of their powerful donor–acceptor properties. We have examined their uncatalyzed, direct Mannich reaction with acetoacetates in comparison with that catalyzed by a number of salan derivatives capable of providing a network of cooperative hydrogen bonds. Catalyst* ***D*** *[(R,R)-N,N′-bis(salicyl)cyclohexane-1,2-diamine] was found to drive the above direct Mannich reaction in an enantioselective manner, thereby allowing the synthesis of several Biginelli dihydropyrimidinones with high enantioselectivity. DFT calculations (B3LYP-D-PCM/6-31+G*//B3LYP/6-31+G*) revealed that the NCHB organocatalyst lowers the energy barrier of the reaction. The NCHB organocatalysts appear to function as biomimetic catalysts.*

Inspired by the mechanisms of biocatalysts,[1] chemists have realized that noncovalent organocatalysts displaying appropriately located double hydrogen-bond donors[2] can promote catalysis by lowering the energy of the transition state more effectively than that of the ground state.[3] This rapidly emerging field should lead to "greener" methodology for asymmetric synthesis,[4] thereby revolutionizing the otherwise slowly evolving field of "green" chemistry.[5]

Urea, thiourea, and related functional groups have been incorporated by catalyst designers into chiral scaffolds, in most cases together with an additional Brønsted base motif for the purpose of also activating incoming acidic nucleophiles.[6] This strategic plan paved the way for the early development of enantioselective bifunctional catalysis.[7,8] In this scenario, these moieties play the role of powerful double hydrogen-bond donors towards the electrophile. Nevertheless, it is well-known that they could also act as powerful acceptors.[9] By switching the standard roles of the nucleophile, electrophile, and catalyst in bifunctional catalysis (Scheme 1, left) we did not want to change the outcome of the reaction (E + NuH → EH–Nu*) but rather to explore new possibilities in the search for bioinspired organocatalysts. It occurred to us that by putting the urea moiety not in the catalyst but in the prochiral electrophile unit E, we would perhaps make the electrophile able to activate the reagent NuH through the intermediate formation of an ion pair (EH^+/Nu^-) en route to the final EH–Nu product. If so, we envisaged that appropriately designed chiral catalysts displaying a network of cooperative hydrogen bonds (NCHB) could act as pure noncovalent, bioinspired organocatalysts[10] to drive the above direct reaction in an enantioselective manner (Scheme 1, right).



Scheme 1. General mode of action of a bifunctional catalyst (left) and a NCHB catalyst (right) for a reaction of the type NuH + E → Nu–EH*.

Arylideneureas **1** were chosen as ideal candidates to explore this hypothesis, as these substrates possess an electron-withdrawing group presumably capable of activating the otherwise quite unreactive imine unit.[11] Furthermore, we speculated that arylideneureas could act as a base towards the incoming NuH reaction partner.[12] On the other hand, arylideneureas were expected to behave as both hydrogen-bond donors and hydrogen-bond acceptors towards chiral catalysts containing complementary systems (Scheme 1, right). Accordingly, we believed that NCHB organocatalysts would be adaptable to a particular reaction.[13] We found that preformed arylideneureas **1** react in a direct manner at room temperature under neutral conditions with common β-ketoesters, an issue of relevance to the mechanism of the Biginelli reaction.[14] Herein, we report that this reaction takes place in the presence of a substoichiometric amount of a chiral, bioinspired NCHB organocatalyst and provides, after acid treatment, enantiomerically enriched Biginelli dihydropyrimidinones.[15]

To the best of our knowledge, arylideneureas **1** have not been prepared or described previously,[16] with one exception.[17] Unfortunately, the application of the reported methodology[17] to common aldehydes was not successful. Therefore, we investigated a viable synthesis of **1** by recourse to the

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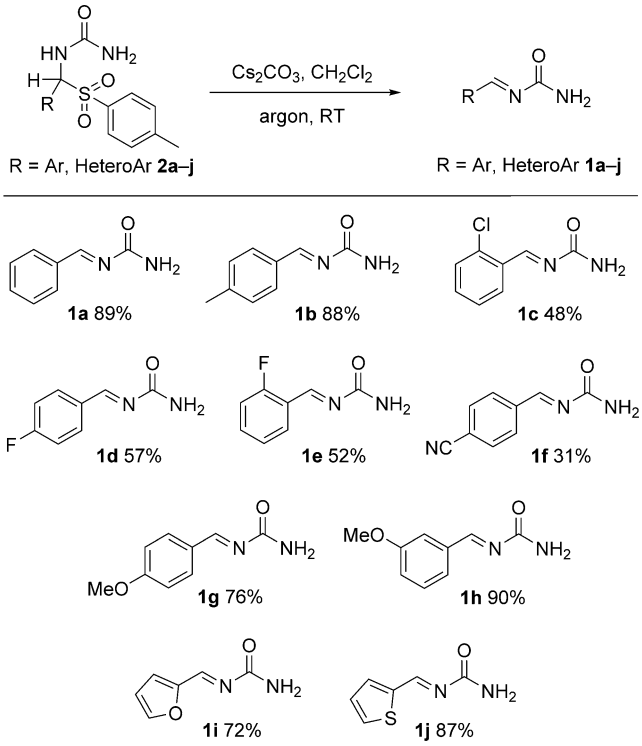
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201511555.

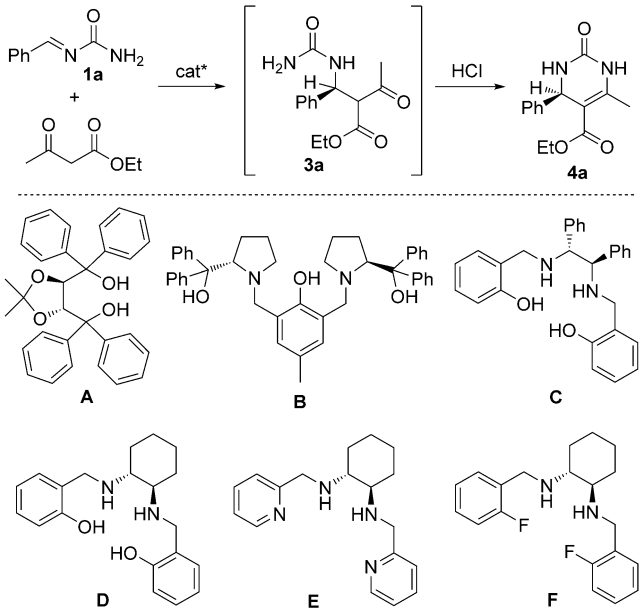
standard two-step methodology for accessing *N*-acyl imines[18] via α-ureidosulfone intermediates **2**.[19,20] The treatment of compounds **2** with dried cesium carbonate led to the formation of aryl- and heteroarylideneureas **1a–j** as solids, which were stable for up to 7 days if kept dry in the cold under an inert atmosphere (Scheme 2).[21]



Scheme 2. Arylidene and heteroarylideneureas **1a–j** prepared from α-ureidosulfones **2**. Reactions were conducted on a 1 mmol scale.[21] Yields are for the isolated product.

Following the lead of Johnston and co-workers,[22] we first explored the monosalts generated in situ from several chiral diamines (**B** and **C** with 1 equivalent of CCl_3COOH, CF_3COOH, aqueous HCl, or AcOH) as enantioselective catalysts for the Mannich addition of ethyl acetoacetate to **1a** (Scheme 3). Unfortunately, we were frustrated by the hydrolysis of **1a**. Obliged to put aside catalysts capable of full proton transfer, we focused our search on a fine-tuning study of hydrogen-bond donors capable of simultaneously complexing the electrophile and the nucleophile NuH (Scheme 1, right).[23]

We surmised that ideal catalysts should display a complementary network of cooperative hydrogen-bond donors (Scheme 1). We used reported X-ray crystallographic data as well as data from DFT (B3LYP-D/6-31 + G**) calculations to select C_2-symmetric scaffolds with a network of cooperative hydrogen-bond donors (XH) and acceptors (YH) with XH–HX distances in the 2.3–2.6 Å range.[24] Besides TADDOL (**A**)[25] and the bisaminophenol **B** developed by Trost and Ito,[26] secondary aminophenols **C** and **D** of the "salan" family (*N*,*N*′-bis(*o*-hydroxybenzyl)-1,2-diaminoethane derivatives) and analogues **E** and **F** were considered



Scheme 3. Direct addition of ethylacetoacetate to **1a** with organocatalysts **A**–**F**: Enantioselective synthesis of the Biginelli dihydropyrimidinone **4a**.

(Scheme 3).[27] Both salen[28] and salan[29] ligands have been reported as chiral ligands in metal-based catalysis; however, as far as we are aware, they have not been explored as NCHB organocatalysts.

The readily available salan ligand **C** yielded product **4a** in high yield, but with moderate enantioselectivity only (Table 1, entry 4). The rigid analogue **D** afforded higher enantioselectivity (Table 1, entry 5) and thus became our catalyst of choice for further development. Being *o*-hydroxybenzylamines, we reasoned that catalysts **C** and **D** could provide a NCHB system for binding in which the phenol groups might play a significant role not only in rigidifying the structure but also in acidifying the N–H bonds and concomitantly basifying the

Table 1: Catalyst screening for the direct, enantioselective addition of ethyl acetoacetate to **1a** to give **4a** (after acid treatment).[a]

Entry	Catalyst (10 mol%)	Solvent	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	none	CH_2Cl_2	25	5	–
2	**A**	CH_2Cl_2	25	<10	nd
3	**B**	CH_2Cl_2	25	21	0
4	**C**	CH_2Cl_2	25	87	42
5	**D**	CH_2Cl_2	25	67	58
6	**E**	CH_2Cl_2	25	58	0
7	**F**	CH_2Cl_2	25	54	3
8	**D**	**CH_2Cl_2**	**−78**	**93**	**94**
9	**D**	acetone	−78	98	60
10	**D**	THF	−78	77	30
11	**D**	toluene	−78	88	27
12	**D**	$CHCl_3$	−78	86	82

[a] Reactions were conducted on a 0.2 mmol scale (molar ratio arylideneurea/ethyl acetoacetate/catalyst 1:1.1:0.1). [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC with a Daicel Chiralpak OD-H column.

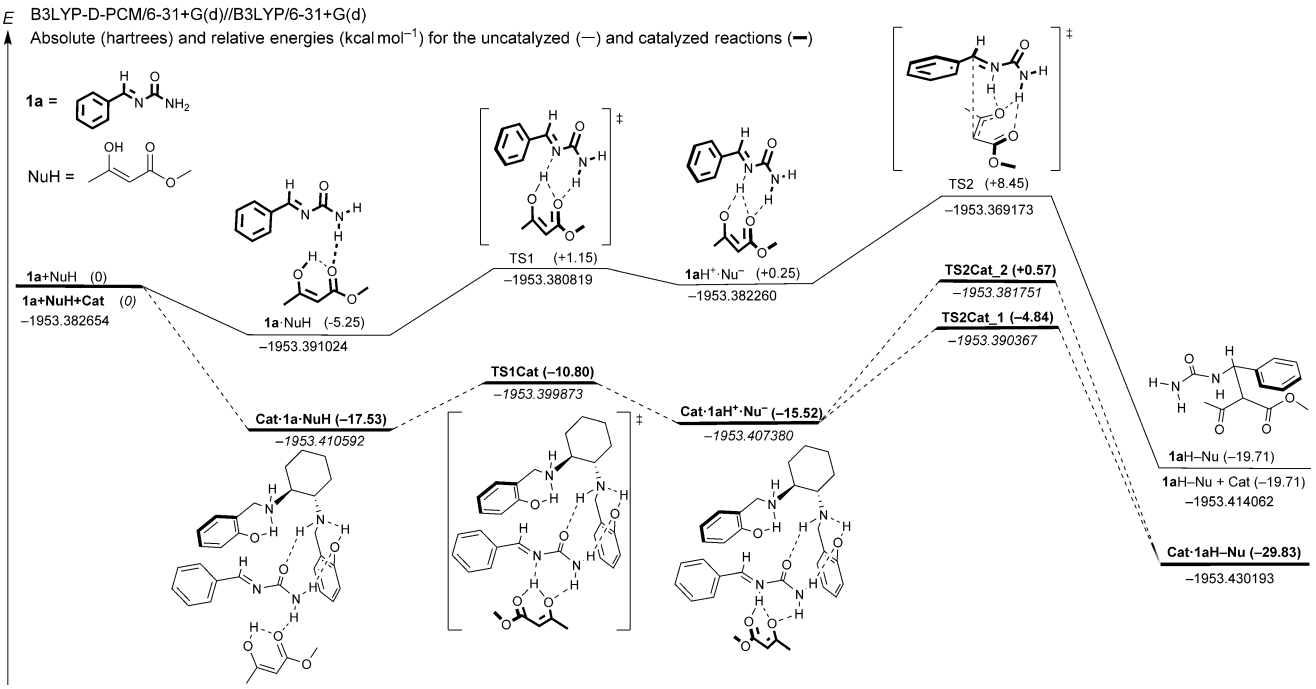


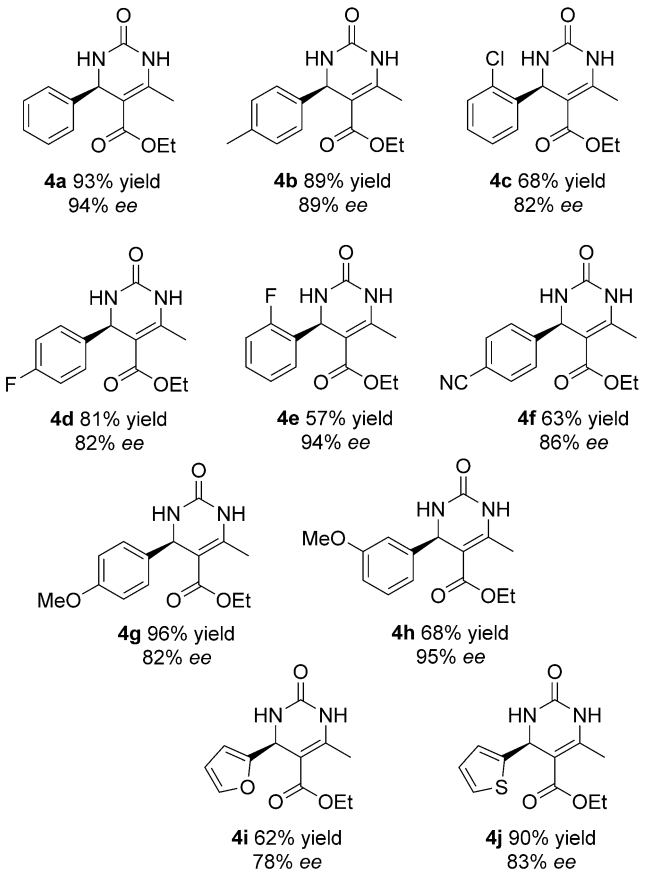
Figure 1. Absolute and relative free energies (B3LYP-D-PCM/6-31 + G*//B3LYP/6-31 + G*) of the species involved in the catalyzed (bold lines) and uncatalyzed reaction **1a** + NuH (methyl acetoacetate, enol form).

OH oxygen atoms for an ideal host–guest interaction. In fact, removal of the OH group as in catalyst **E**,[30] or its substitution by a fluorine atom as in catalyst **F**,[31] led to no or insignificant enantioselectivity.

We optimized the reaction by fine-tuning the experimental variables with catalyst **D**. The best overall results in terms of yield and enantioselectivity were obtained with dichloromethane as the solvent at −78 °C (Table 1, entry 8). The scope of this two-step method for the synthesis of enantiomerically enriched dihydropyrimidinones **4** was then explored (Scheme 4). The absolute configuration of **4a** was assigned on the basis of literature data.[32] That of the related products **4b–j** was assigned by analogy.

As suggested previously,[12] we examined the catalytic mechanism by means of a DFT computational study with (*S*,*S*)-**D** as the catalyst.[33] Geometries were optimized at the B3LYP/6-31 + G* level in the gas phase. For the purpose of analyzing the chemistry taking place in solution, we performed single-point calculations within the Tomasi continuum solvent model IEFPCM (dichloromethane)[34] with a dispersion correction as described by Grimme et al.[35]

For both uncatalyzed and catalyzed pathways we found two routes differing in the moment at which hydrogen transfer occurs. For the sake of simplicity, only the lowest-energy route is illustrated in Figure 1.[21] This route involves proton transfer from NuH to **1a** via TS1 to give an intermediate ion pair **1a**H$^+$·Nu$^-$, which then collapses to the Mannich adduct **1a**H–Nu via TS2. The computed data for the catalyzed reaction (Figure 1) clearly show that the role performed by the NCHB catalyst is to lower the energy (B3LYP-D-PCM/6-31 + G*//B3LYP/6-31 + G*) of complex **1a**·NuH (by 12.28 kcal mol^{-1}), the ion-pair intermediate



Scheme 4. Dihydropyrimidinones **4a–j** obtained by the addition of ethyl acetoacetate to arylideneureas **1a–j** with the organocatalyst **D**.

1a$H^+ \cdot Nu^-$ (by 15.77 kcal mol^{-1}), the transition structure TS1 (by 11.95 kcal mol^{-1}), and, most importantly, **TS2Cat_1** (by 13.29 kcal mol^{-1}, *Re* attack) and **TS2Cat_2** (by 7.88 kcal mol^{-1}, *Si* attack) relative to the uncatalyzed reaction (Figure 2). The sign of the enantioselectivity is in full agreement with experiment.[33]

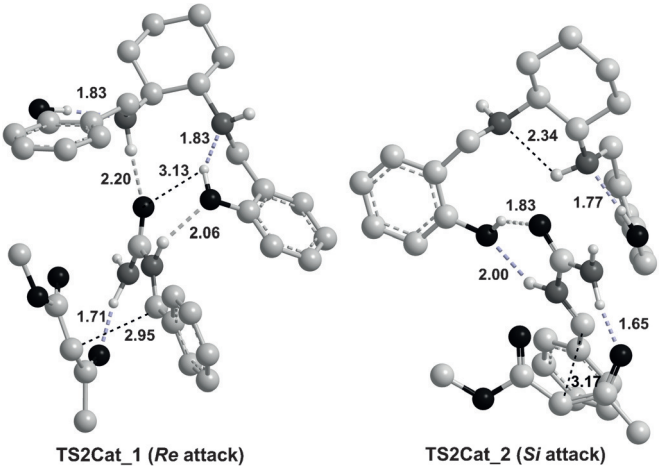


Figure 2. Transition-state structures (B3LYP/6-31+G*) corresponding to *Re* and *Si* attack (CH hydrogen atoms omitted for clarity).

The network of cooperative hydrogen bonds present in catalyst **D** is thus playing the role of an enzyme in lowering the energy barrier of the reaction by stabilizing the rate-determining transition state (**TS2**) more strongly than the ground state **1a·NuH**. Thus, as put down by Anslyn and Dougherty,[1] we can conclude that we are dealing with a catalytic event by an NCHB organocatalyst.

In summary, arylideneureas **1** are a new kind of imine derivative capable of reacting in a direct manner through the intermediate formation of an ion pair en route to the Mannich addition product. This behavior has been shown to be amenable to enzyme-like catalysis by organocatalysts displaying a network of cooperative hydrogen bonds. It is our belief that other enantioselective, direct reactions of the type E+NuH→EH–Nu* promoted by organocatalysts NCHB are awaiting discovery.

Acknowledgements

Support has been provided by the Ministerio de Ciencia e Innovación (MICINN, grant number CTQ2010-17339), Spain. Thanks are due to the UIB (Universidad de las Islas Baleares) for the allocation of computing time. We also thank Dr. A. Frontera (UIB) for helpful discussions.

Keywords: asymmetric catalysis · cooperative hydrogen bonds · dihydropyrimidinones · Mannich reaction · organocatalysis

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 4312–4316
Angew. Chem. **2016**, *128*, 4384–4388

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Received: December 12, 2015
Revised: January 27, 2016
Published online: February 25, 2016

