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Chiral Benzimidazoles as Hydrogen Bonding Organocatalysts

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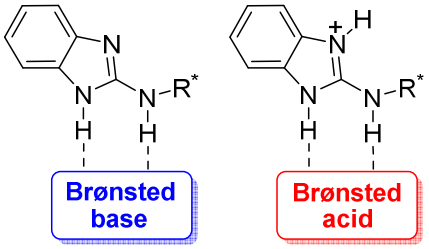


Abstract

Several bifunctional organocatalysts bearing the 2-aminobenzimidazole unit have been designed in order to act as bifunctional systems by hydrogen bonding. Chiral 2-aminobenzimidazoles are conformational rigid guanidines able to catalyze enantioselectively Michael reaction, direct S_N1 of alcohols and aldol reactions. Some of these organocatalysts can be easily recovered by simple isolation methods and reused without loss of catalytic activity. Related (2-aminoalkyl)benzimidazoles have been used as chiral organocatalysts in aldol and amination reactions of carbonyl compounds.

1. Introduction

Benzimidazole, firstly described by Hobrecker in 1872, is an important heterocyclic motif[1] present in many natural products,[2] in material science fuel cells,[3] in ionic liquids,[4] and in pharmaceutical industry,[5] as for instance in the proton pump inhibitor esomeprazole **1**, which also is an antiulcer and antiviral drug (Figure 1). Molecules containing the benzimidazole unit are important in medicinal chemistry due to antiarrythmic, antihistamine, anticancer, fungicidal, antihelmintical, and ionotropic activities, and in many biological processes.[6] Recently, chiral benzimidazole derivatives have enmerged as valuable structures in asymmetric catalysis either as metal ligands or as organocatalysts. The main features of benzimidazole are the basic character (pK_a = 5.4),[6] high stability, facile synthesis of derivatives,[1] and its capability to form hydrogen bonding. In 2005, Göbel's group discovered that 2-aminobenzimidazoles were good

candidates for acid/base catalysis and can substitute guanidinium groups in receptor molecules designed as phosphoryl transfer catalysts.[7] Thus, amine **2** (Figure 1) was able to cleave RNA by phosphate activation by means of hydrogen bonding under neutral conditions. In supramolecular chemistry, the combination of two benzimidazole units bonded to 4,5-diamino-9,9-dimethylxanthene **3** (Figure 1) provided an excellent receptor for neutral guests with oxygen atom such as sulfoxides, ketones and alcohols.[8] In addition, carboxylic acids and carboxylates are also suitable substrates for this receptor by hydrogen bond formation.

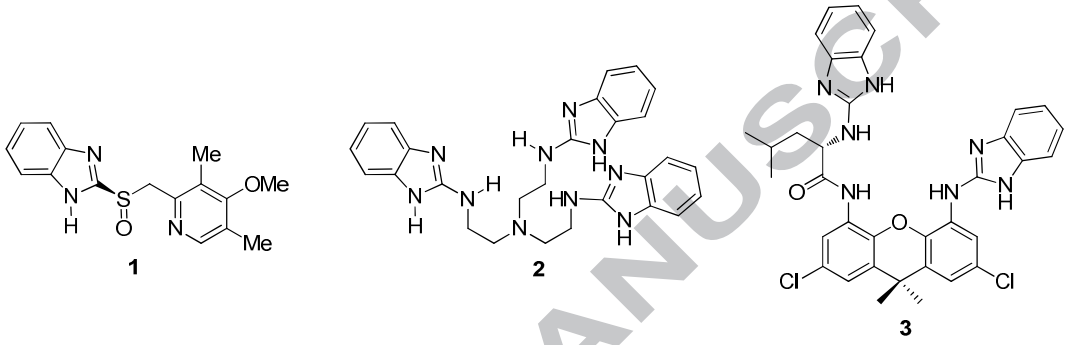


Figure 1. Selected benzimidazole derivatives.

Asymmetric organocatalysis by chiral hydrogen bonding (HB) has become an efficient activation mode in many enantioselective synthesis.[9] Among different HB moieties, thiourea such as **4**,[10] quinazolines **5**,[11] and benzothiadiazines **6**,[11] developed by Takemoto's group (Figure 2) are privileged structures and specially thioureas have been applied in a plethora of enantioselective reactions. Other HB-catalysts have been developed, such as sulfinylureas **7**[12] by Ellman's group and squaramides **8a-c**[13,14] by Rawal's group (Figure 2). In all these compounds **4**-**8**, the presence of an additional amino group, gave them a bifunctional character able to work both as Brønsted acid and base for the activation of the electrophilic and the nucleophilic partners. In this Digest we compile the recent achievement using organocatalysts bearing a benzimidazole unit, which can activate the substrates not only as hydrogen donor but also as acceptor, in enantioselective processes.

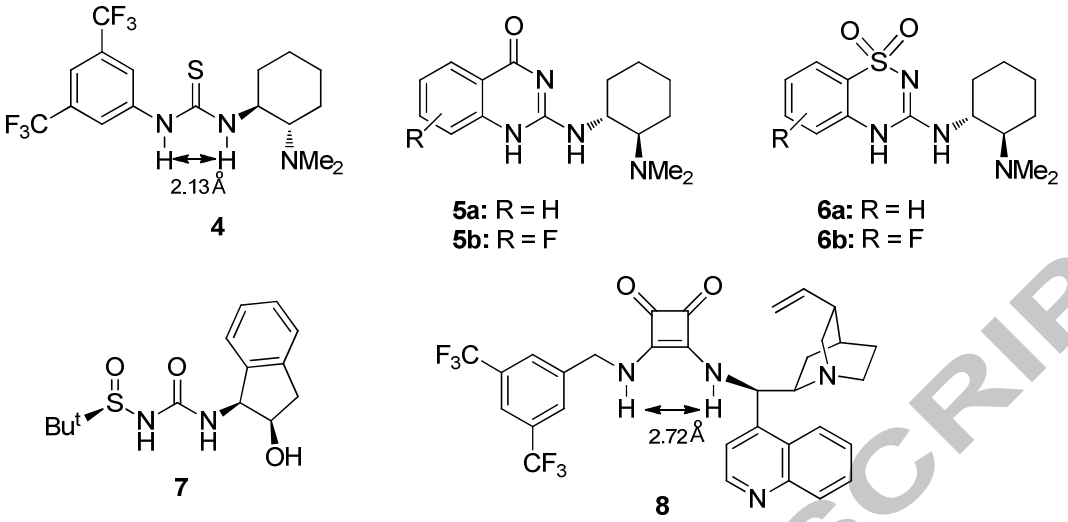


Figure 2. Hydrogen bonding organocatalysts.

2. 2-Aminobenzimidazoles

The 2-aminobenzimidazole structural unit is conformationally more rigid than guanidines and can form dual hydrogen bonding (HB) like thioureas and squaramides acting as Brønsted acid. On the other hand, the presence of an amino group at the 2-position would increase the basic character of the benzimidazole unit (pK_a ~7).[7] They can be easily prepared by nucleophilic substitution of 2-chlorobenzimidazoles with amines. Independently, in 2009 our group and Park's group reported new organocatalysts, bearing the 2-aminobenzimidazole unit, **9**[15] and **10**-**11**[16] as excellent HB derivatives (Figure 3). The observed distances between the two hydrogens in the case of 2-aminobenzimidazoles **9a-c** are in between the reported ones for thiourea **4**[10] and squaramide **8**[13a] derived organocatalysts (Figure 2). From the crystalographic and computational data of catalyst **9a** the distances are between 2.41 and 2.61 Å, respectively.[15] Therefore, the designed organocatalysts should be privileged structures acting as bifuctional catalysts bearing a Brønsted base and a HB donor units.

Conjugate addition of 1,3-dicarbonyl compounds to nitroalkenes is a model process for this type of dual activation. For the Michael reaction of diethyl malonate with β-nitrostyrene the efficiency of organocatalysts **9-11** was evaluated (Scheme 1 and Table 1). In addition, several bifunctional double HB catalysts **4**-**6** and **8** have been included in Table 1 for comparison purposes. All 2-aminobenzimidazole derived organocatalysts

gave similar results than thiourea at room temperature but lower enantioselection than squaramide **8**.

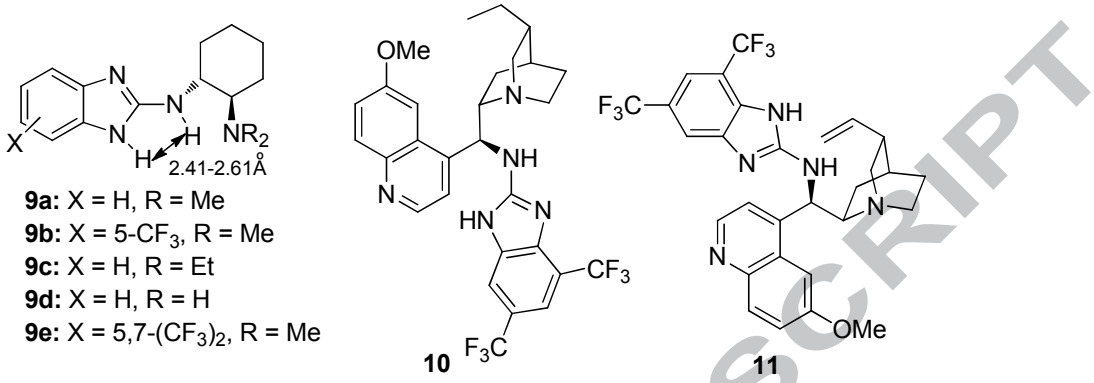
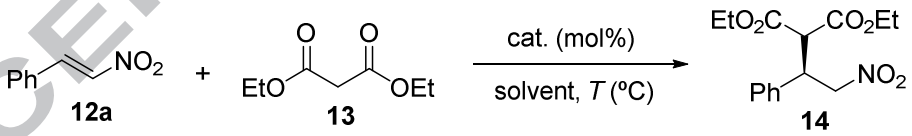


Figure 3. Bifunctional 2-aminobenzimidazoles bearing an amino group.

In the case of the *trans*-cyclohexane-1,2-diamine derived catalyst **9a**, the presence of trifluoroacetic acid (TFA) as cocatalyst was crucial to achieve 92% ee (Table 1, entry 6). The presence of trifluoromethyl groups in the benzimidazole, such in the case of **9b**,[16b] allows to perform the reaction under neutral conditions (Table 1, entry 7). Pseudoenantiomeric *Cinchona* derived organocatalysts **10** and **11** also worked under neutral conditions affording the adduct (*S*)-**14** and (*R*)-**14**, respectively (Table 1, entries 8 and 9).[16a] In these two cases working at -20 ºC was possible to obtain compound **14** in 95 and 97 % ee, respectively.



Scheme 1. Michael reaction of diethyl malonate with nitrostyrene organocatalyzed by organocatalysts **4-6** and **8-11**.

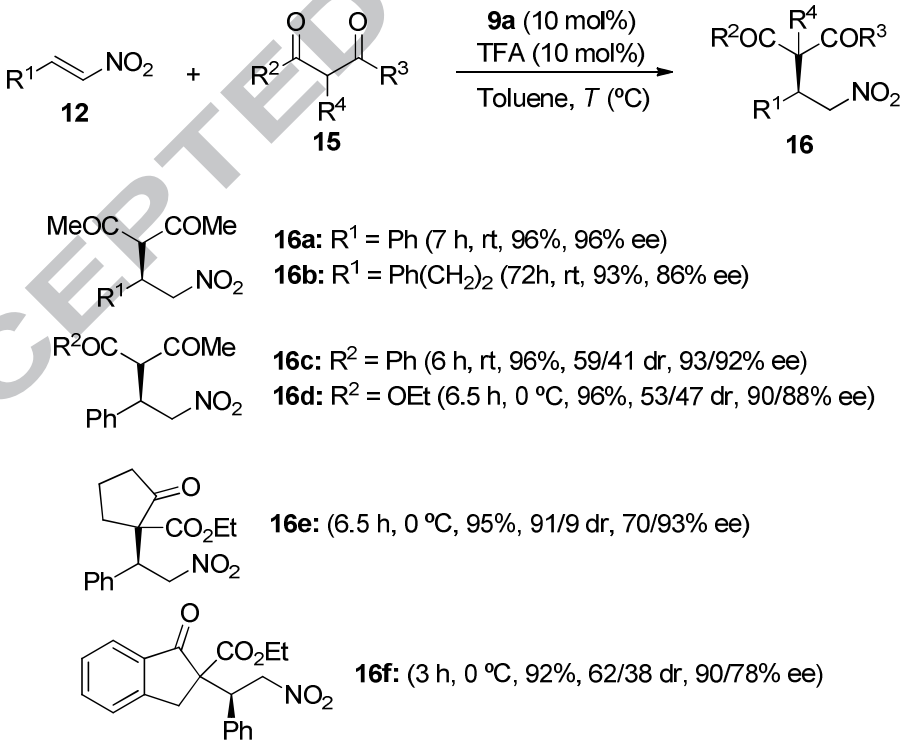
Table 1

Michael addition of diethyl malonate to nitrostyrene

Ent.	Cat. (mol%)	Solvent	*T* (ºC)	*t* (h)	Yield (%)	ee (%)	Ref.
1	**4** (10)	Toluene	25	24	83	92	10
2	**5a** (10)	Toluene	25	24	70	85	11
3	**6a** (10)	Toluene	25	24	65	78	11
4	**8** (0.5)	CH_2Cl_2	25	9	98	97	13a
5	**9a** (10)	Toluene	25	24	99	78	15
6	**9a** (10)[a]	Toluene	25	48	97	92	15
7	**9b** (10)	CH_2Cl_2	25	6	99	90[b]	16b
8	**10** (2)	CH_2Cl_2	25	7	99	93	16a
9	**11** (2)	CH_2Cl_2	25	6	99	90	16a

[a] TFA (10 mol%) was added.
[b] For the (*S*)-**14**.

The simplest 2-aminobenzimidazole **9a** can be recovered in 94% yield after simple acid-base extractive workup. These organocatalysts afforded products of the type **14** derived from different nitroalkenes in 95-98% yields and 87-94% ee.[15] Its efficiency as organocatalysts in Michael additions of 1,3-dicarbonyl compounds such as 1,3-diketones and β-keto esters **15** has been evaluated (Scheme 2). Pentane-2,4-dione gave compounds **16a** and **16b** in high yields and in 96 and 86% ee, respectively. In the case of 1-phenylbutane-1,3-dione and other β-keto esters, diastereomeric mixtures of compounds **16c**-**16f** were obtained in high ee. The best dr 91/9 was obtained in the case of ethyl 2-oxocyclopentanecarboxylate giving **16e** in 70 and 93% ee.



Scheme 2. Michael reaction of 1,3-dicarbonyl compounds with nitroalkenes organocatalyzed by **9a**.

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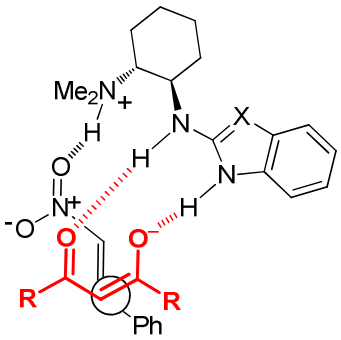
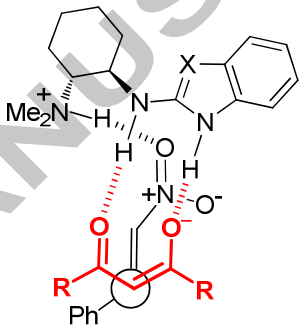
Mechanistic studies were carried out using DFT calculations at B3LYP/6-311++G**//B3LYP/6-31G* level for the conjugate addition of dimethyl malonate and acetylacetone to β-nitrostyrene (Figure 4).[15] Two possible scenarios have been postulted for thiourea catalysis: (a) nitrostyrene activation through binding to the Brønsted acidic NH moieties by Takemoto[10] or (b) alternative binding of the two NH moieties to malonate according to DFT calculations by Pápai.[17] In our case, either under neutral or in the presence of TFA the results are very similar (Figure 4).



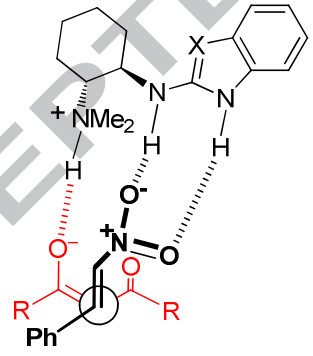
TSa-*R* (X = N)
R = OMe; 0; (0)
R = Me; 0; (0)

TSa-H$^+$-*R* (X = $^+$NH)
R = OMe; 0; (0)
R = Me; 0; (0)



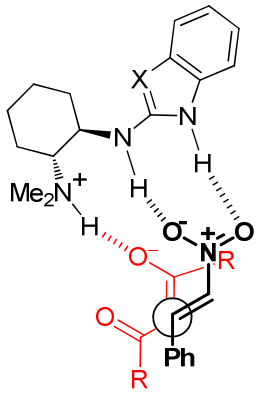
TSa-*S* (X = N)
R = OMe; 2.6; (3.2)
R = Me; 2.8; (4.3)

TSa-H$^+$-*S* (X = $^+$NH)
R = OMe; 1.9; (2.1)
R = Me; 6.6; (7.3)



TSb-*R* (X = N)
R = OMe; 1.9; (3.0)
R = Me; 2.6; (3.6)

TSb-H$^+$-*R* (X = $^+$NH)
R = OMe; 3.9; (4.8)
R = Me; 5.1; (5.7)



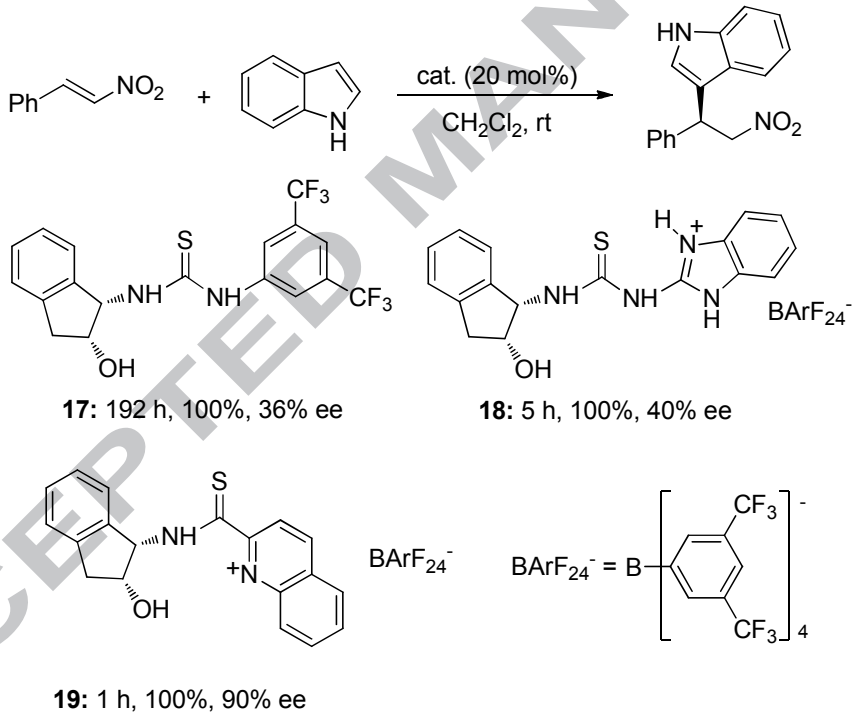
TSb-*S* (X = N)
R = OMe; 2.4; (3.7)
R = Me; 4.4; (6.1)

TSb-H$^+$-*S* (X = $^+$NH)
R = OMe; 2.3; (4.4)
R = Me; 5.2; (6.9)

Figure 4. Representation of the computed transition states for the Michael reaction of 1,3-dicarbonyl compounds with nitrostyrene. Single-point values in a toluene model (IEF-PCM) are shown in parenthesis.[15]

The lowest energy transition states TSa correspond to the formation of two hydrogen bonds between the nucleophile and the 2-aminobenzimidazole and one hydrogen bond between the nitroalkene and the protonated tertiary amine. In general, the other possible ones TSb are 2-6 Kcal/mol higher in energy. In addition, only the nucleophile-aminobenzimidazole interaction confirms the observed enantioselective bias since *R*-TSa lies an average of 3.8 Kcal/mol lower in energy than *S*-TSa. However, for the other TSb similar energies E_S-E_R = 0.6 Kcal/mol, were calculated predicting the formation of *quasi*-racemic compounds.

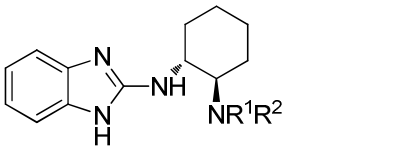
For the Michael addition of indol to nitroalkenes with the thiourea derived from *cis*-1-amino-2-indanol, the 3,5-bis(trifluoromethyl)phenyl moiety **17**[18a] has been substituted by quinoline, pyridine, and benzimidazole units. The latest one **18** accelerates the reaction but in lower enantioselection than the quinoline derivative **19** (Scheme 3).[18b]



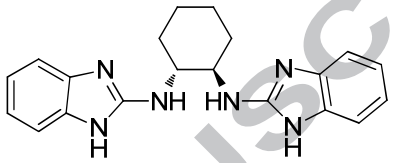
Scheme 3. Michael reaction of indol with nitrostyrene catalyzed by **17-19**.

The asymmetric organocatalyzed addition to maleimides is a straightforward strategy for the synthesis of enantioenriched succinimide derivatives.[19] Further applications of 2-aminobenzimidazoles **9** in the conjugate addition of 1,3-dicarbonyl compounds to maleimides were evaluated.[20] In the case of using different organocatalysts with a tertiary **9a,c-e** and a primary amine **9f** (Figure 5) for the addition of acetylacetone to the

challenging maleimide very poor enantioinduction was observed in the presence of TFA. Unexpectedly, the C_2-symmetric bis(2-aminobenzimidazole) **20**, which failed in the previous described Michael addition of diethyl malonate to β-nitrostyrene,[21,16b] provided the adduct **21a** in 94% yield and 97% ee in the presence of TFA (10 mol%) and only 51% ee under neutral conditions (Scheme 4).[20] Surprisingly, when 20 mol% of TFA was used the reaction failed. The addition of acetylacetone to maleimide can be also performed with only 1 mol% loading of **20**/TFA affording product **21a** in 96% yield and 93% ee.

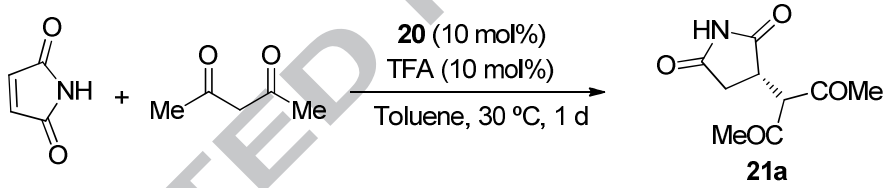


9a: $R^1 = R^2 = Me$
9c: $R^1 = R^2 = Et$
9d: $R^1 = R^2 = H$
9f: R^1- R^2 = 2,5-dimethylpyrrol-1-yl
9g: R^1- R^2 = piperidin-1-yl



20

Figure 5. Benzimidazole-derived organocatalysts **9** and **20.**



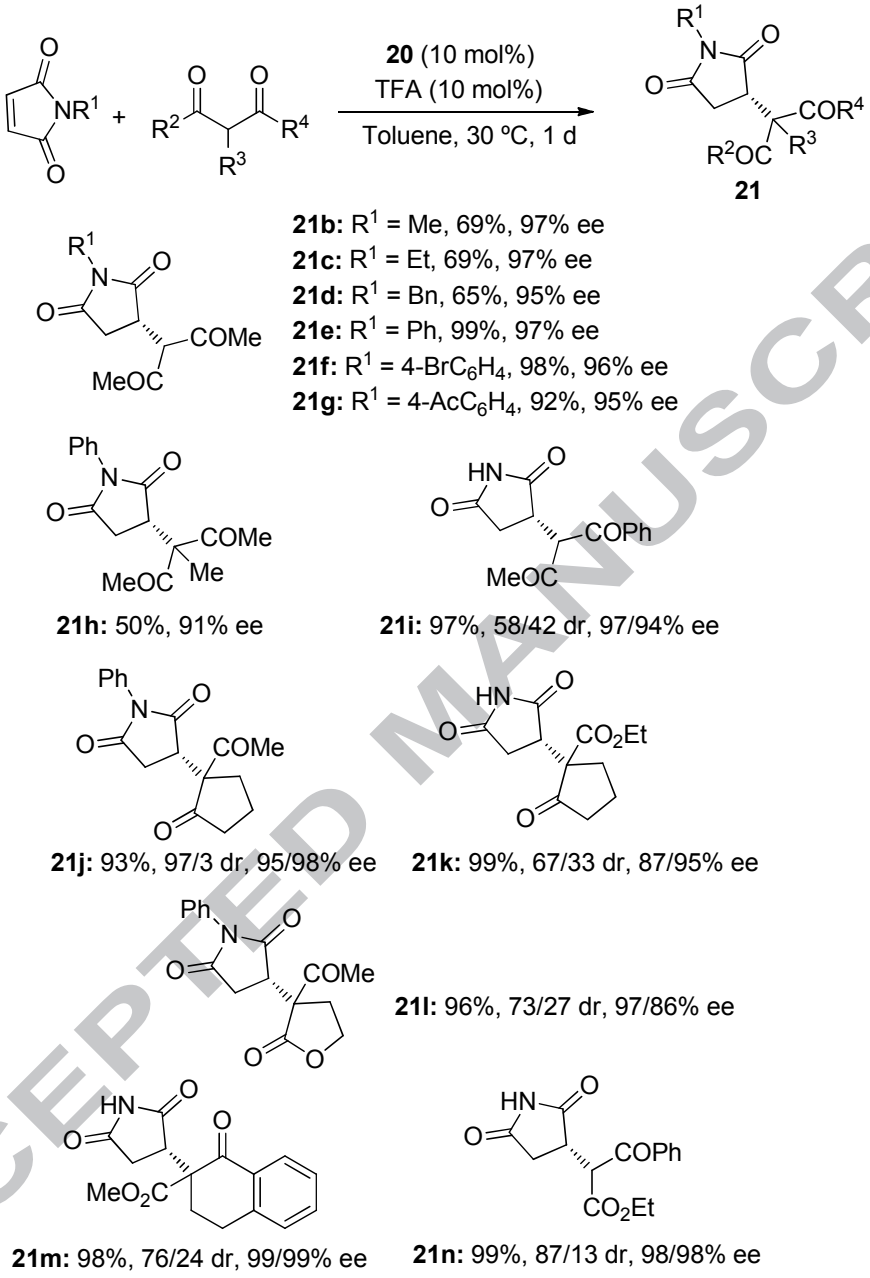
21a

Scheme 4. Michael reaction of acetylacetone with maleimide catalyzed by **20**.

Additional studies on catalyst concentration revealed that ee values were consistent with the diffusion coefficients (*D*) of **20**/TFA. This fact indicates that the degree of hydrogen bonds self-association of the catalyst in solution plays a crucial role in the enantioselectivity of this Michael addition.

The study of the scope of the conjugate addition of 1,3-diketones to different maleimides indicates a high degree of enantioselectivity affording products **21** in good yields (Scheme 5). The absolute configuration was determined by X-ray analysis of the bromo-substituted derivative **21f**.[20a] In the case of unsymmetrical diketones such as 1-phenylbutane-1,3-dione the product **21i** was obtained in low dr. However, the cyclic 2-acetylcyclopentanone gave product **21j** in 97:3 dr and in 93% ee for the major

diastereomer. Several β-ketoesters were assayed yielding succinimides derivatives **21k-n** in moderate dr and high ee (Scheme 5).

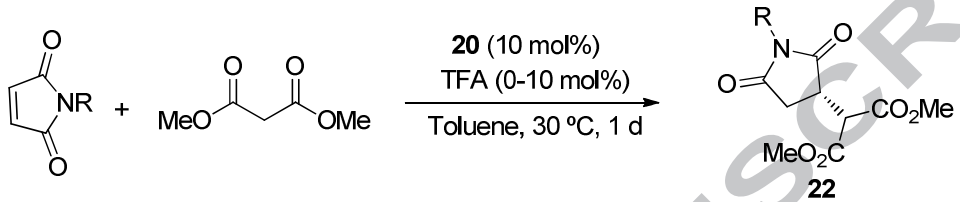


Scheme 5. Michael reaction of 1,3-dicarbonyl compounds with maleimides organocatalyzed by **20**.

Several experiments were performed on gram-scale (5-40 mmol of maleimides) providing the corresponding succinimides **21a**, **21d**, **21g**, and **21k** as optically pure compounds in 81-89% yields just by simple filtration from the crude reaction mixture, and only with 2-5 mol% of organocatalysts **20**/TFA. The recovery of the catalyst was performed in the case of **21f** by treatment of the crude reaction mixture with

isopropanol. In the precipitate, the product **21f** was isolated in 90% yield and 97% ee and from the isopropanol solution **20**/TFA was obtained in 99% yield, which was used in a second run without purification giving product **21f** in 99% yield and 93% ee.

The conjugate addition of diethyl malonate to maleimides was performed in the presence and in the absence of TFA yielding the corresponding products **22** in better results under neutral conditions (Scheme 6). In general, lower yields were obtained in the presence of TFA as well as enantioselectivities.



22a: R = H, 23%, 74% ee (TFA)
22a: R = H, 81%, 78% ee
22b: R = Me, 7%, 90% ee (TFA)
22b: R = Me, 99%, 99% ee
22c: R = Ph, 40%, 83% ee (TFA)
22c: R = Ph, 83%, 99% ee

Scheme 6. Michael reaction of dimethyl malonate with maleimides organocatalyzed by **20**.

DFT computational studies for the Michael addition of acetylacetone to maleimide assumed that the reaction was initiated by deprotonation of the nucleophile by the organocatalyst forming an enolate/protonated catalyst binary complex, which was taken as the ground $G = 0$ energy level (Figure 6). Further hydrogen bonding with maleimides provides a ternary complex which evolves to the final products.

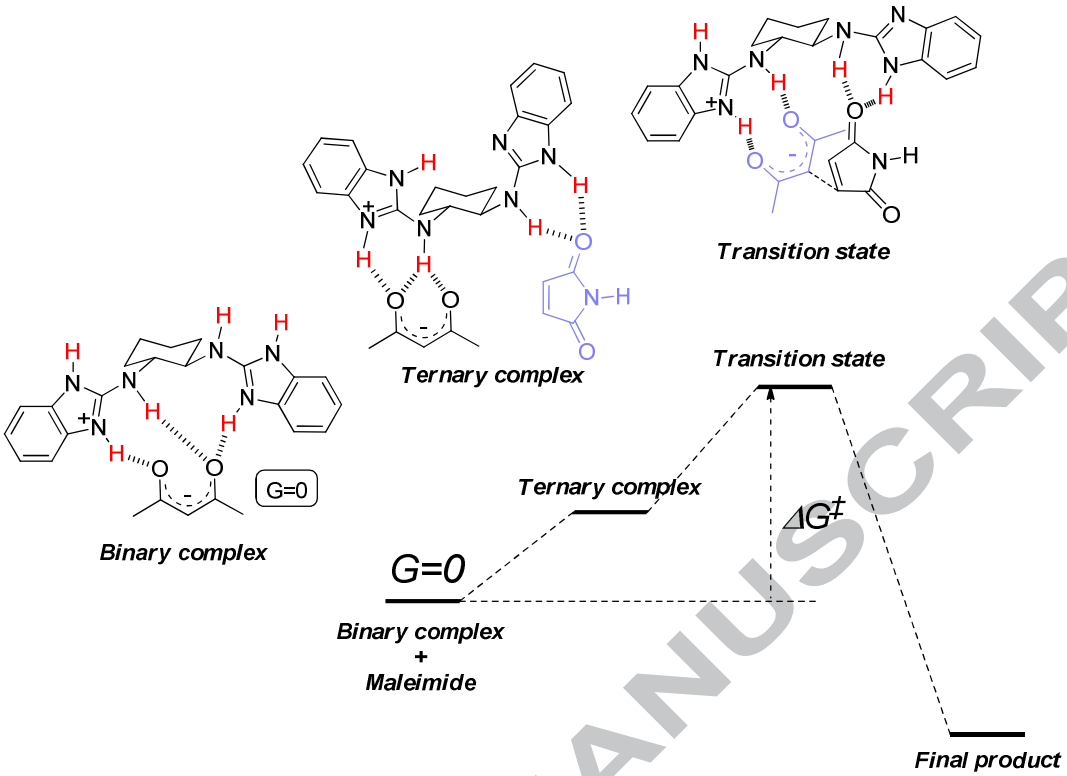


Figure 6. Main structures proposed along the reaction coordinate for the Michael reaction of acetylacetone with maleimide.

Three possible mechanistic alternatives were evaluated: A) in the absence of acid, B) partial protonation (1 equiv) of the organocatalyst, and C) double protonation of the catalyst. The calculated difference in energy in model A for the $TS_{A2}(S)$ and $TS_{A2}(R)$ is 1.7 Kcal/molar in agreement with the 51% ee obtained in the absence of TFA (Figure 7). For the model B the difference is 4.6 Kcal/mol in agreement with the experimental 97% ee. The inclusion of a second molecule of TFA gave <5% yield due to the cancelation of the basic character of the organocatalyst suppressing the deprotonation of the nucleophile observing a high computed activation energy (46.3 Kcal/mol).[20b]

In the case of the addition of dimethyl malonate to maleimides, the TFA-protonated catalyst (mechanism B, Figure 7) is a disfavored process (Figure 8).[20b] Therefore, the mechanism A with a computed 86% ee in fair agreement with the experimental 74-78% ee, although at different rates with and without TFA.

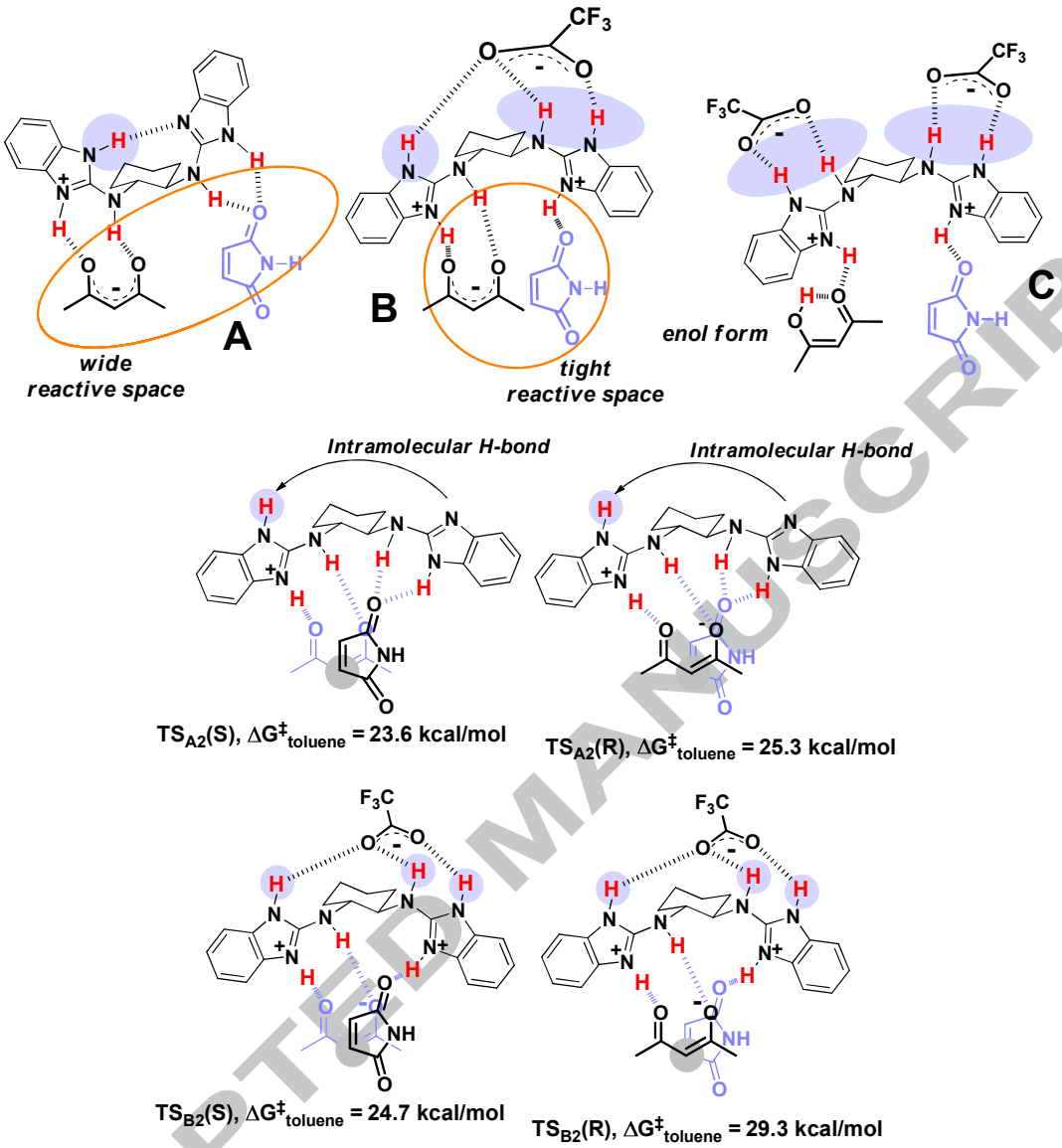


Figure 7. Computed mechanism alternatives A-C and main transition structures computed in models A and B.

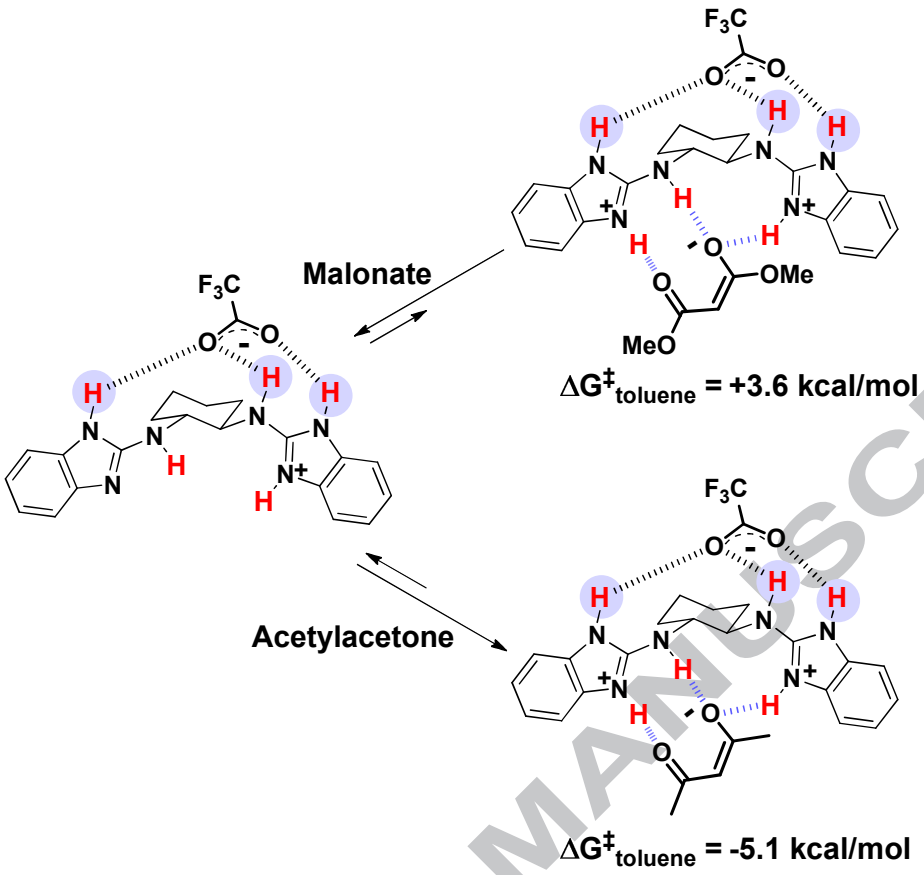
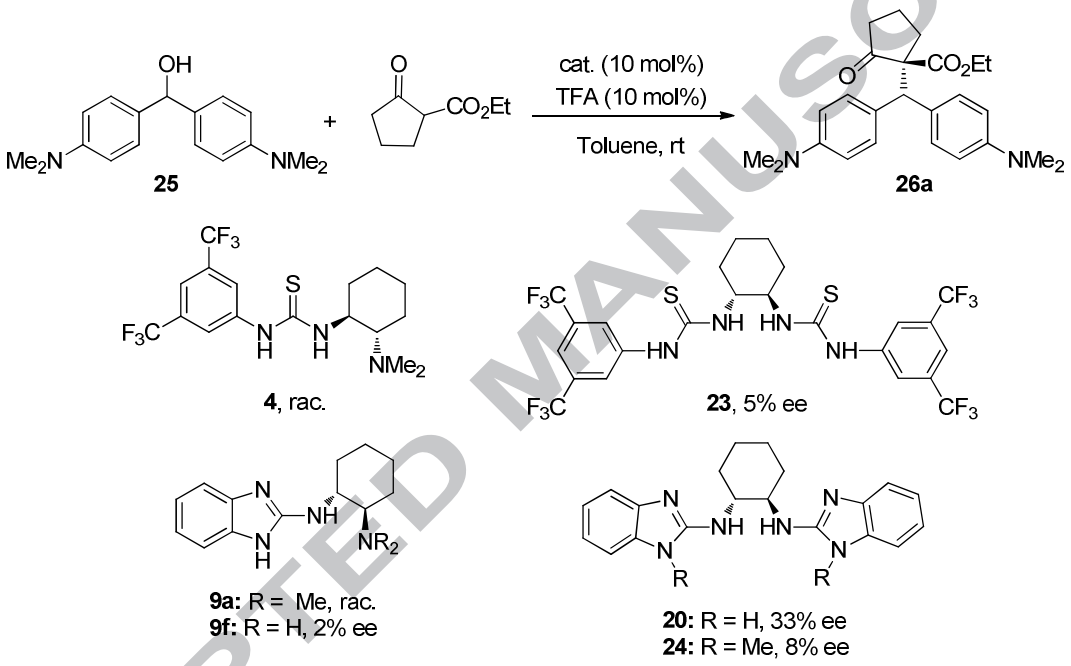


Figure 8. Different binding properties of the computed nucleophiles acetylacetone and dimethyl malonate with organocatalyst **20**.

The enantioselective catalytic alkylation of carbon nucleophiles using activated alcohols, instead of organic halides or sulfonates, through a S_N1 mechanism, is a new strategy for carbon-carbon bonds formation which generates only water as byproduct.[22] Pioneer work on this field has been performed with copper(II) triflate and BOX-ligands as catalysts for the reaction of benzydrylic alcohols with β-ketophosphonates[23] and 1,3-dicarbonyl compounds.[24] Cozzy's group has described the organocatalyzed asymmetric α-alkylation of aldehydes with alcohols through an enamine activation mode.[25] We envisaged a possible strategy for S_N1 alkylation of 1,3-dicarbonyl compounds based on dual hydrogen bonding activation of both components.

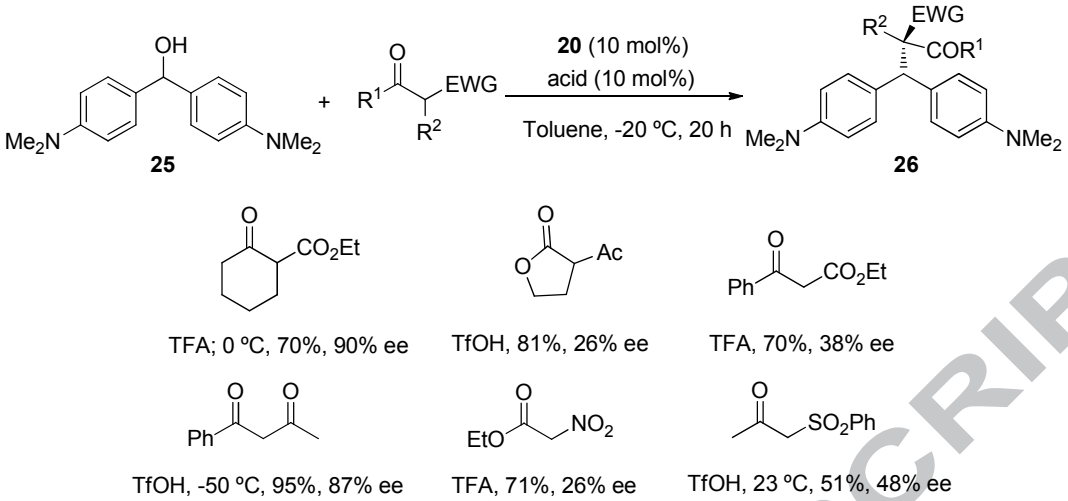
For the model reaction between benzylic alcohol **25** and ethyl 2-oxocyclopentanecarboxylate different hydrogen donor organocatalysts such as thioureas **4** or **23** and 2-aminobenzimidazoles **9a**, **9f**, **20**, and **24**, derived from *trans*-cyclohexane-1,2-diamine, were tested (Scheme 7).[26] The reactions were performed at

room temperature in toluene and in the presence of TFA as cocatalyst, and only the bis(2-aminobenzimidazole) **20** gave product **26a** in a modest 33% ee. Further studies with organocatalysts **20** in the presence of TFA or triflic acid (TfOH) at -20 ºC afforded product **26a** in 85% or 90% yield and in 64 and 67% ee, respectively (Scheme 8). Also in these cases, when the amount of acid was 20 mol% the ee decreased dramatically. Concerning evidences about a S_N1 mechanism, a deep blue color was observed just after addition of the alcohol **25** and the acid due to the formation of cationic species (Michler's hydrol blue).[27] The scope of this alkylation was studied with other carbon nucleophiles (Scheme 8).



Scheme 7. Asymmetric alkylation of ethyl 2-oxocyclopentanecarboxylate with benzylic alcohol **25** organocatalyzed by different hydrogen donors.

Several β-ketoesters, 1,3-diketones, ethyl nitroacetate and α-phenylsulfonylacetone were allowed to react with the alcohol **25** using **20**/TFA and **20**/TfOH as organocatalysts, the best results being summarized in Scheme 8.



Scheme 8. Asymmetric alkylation of β-ketoesters with benzylic alcohol **25** organocatalyzed by **20**.

Other alcohols such as bis(4-methoxyphenyl)methanol, xanthydrol and thioxanthydrol gave racemic compounds. Only the later alcohol gave product **27a** and **27b** in modest to good enantioselectivities at rt (Figure 9). On the other hand, in the case of the allylic alcohol (*E*)-1,3-bis(4-methoxyphenyl)prop-2-en-1-ol (**28**) it only reacted

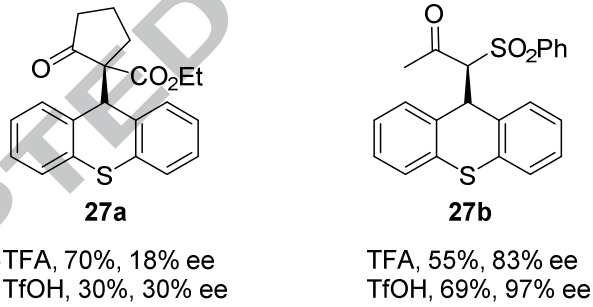
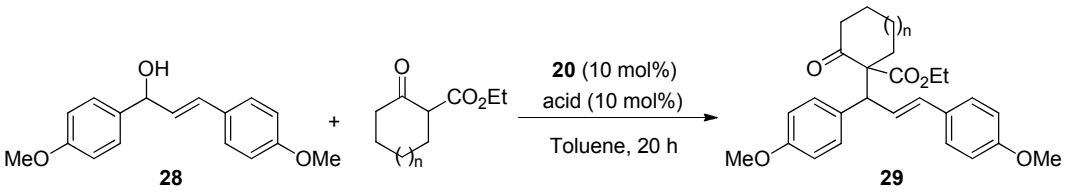


Figure 9. Products **27** from the asymmetric alkylation of activated methylene compounds with thioxanthydrol organocatalyzed by **20**.

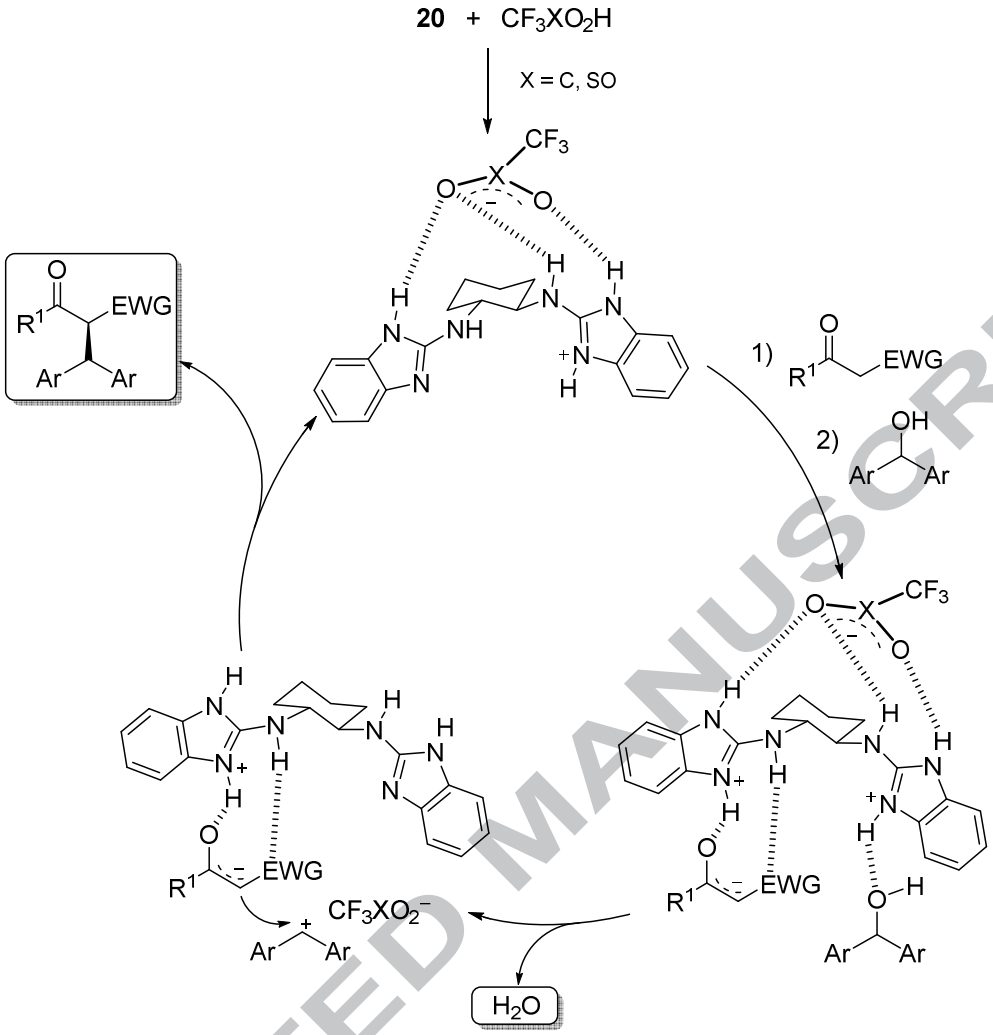
with cyclic β-ketoesters affording the corresponding products **29** with modest diastereo- and enantioselectivities (Scheme 9).



29a: n = 0, -50 ºC, TFA, 64%, 70/30 dr, 26/24% ee
29a: n = 0, -50 ºC, TfOH, 72%, 25/75 dr, 40/30% ee
29b: n = 1, -20 ºC, TFA, 67%, 63/37 dr, 5/10% ee
29b: n = 1, -20 ºC, TfOH, 55%, 52/48 dr, 5/25% ee

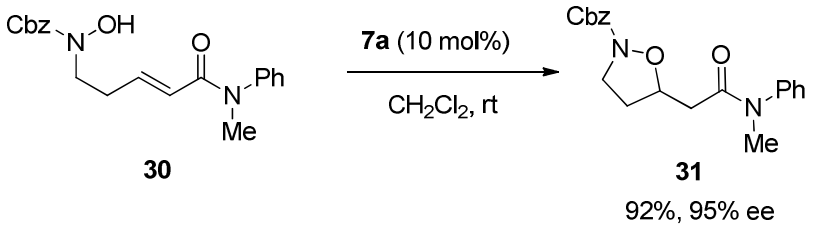
Scheme 9. Asymmetric alkylation of β-ketoesters with allylic alcohol **28** organocatalyzed by **20**.

According to previous DFT calculations performed for the **20**/TFA catalyzed Michael addition of 1,3-dicarbonyl compounds to maleimides,[20b] the proposed mechanism is based on the ability of the 2-aminobenzimizadole unit to deprotonate and to bond to the enolate derived from the 1,3-dicarbonyl compound. The other 2-aminobenzimizadole unit, which is protonated by the acid, bonds the alcohol generating the cationic species, which can form an ionic pair with the enolate. After final alkylation the product is released and the bifunctional catalyst is recovered (Scheme 10). By using the reaction of alcohol **25** and ethyl 2-oxocyclopentanecarboxylate at 1 mmol scale, the organocatalyst **20** could be recovered after extractive work-up in 62% yield and was reused giving the same results.



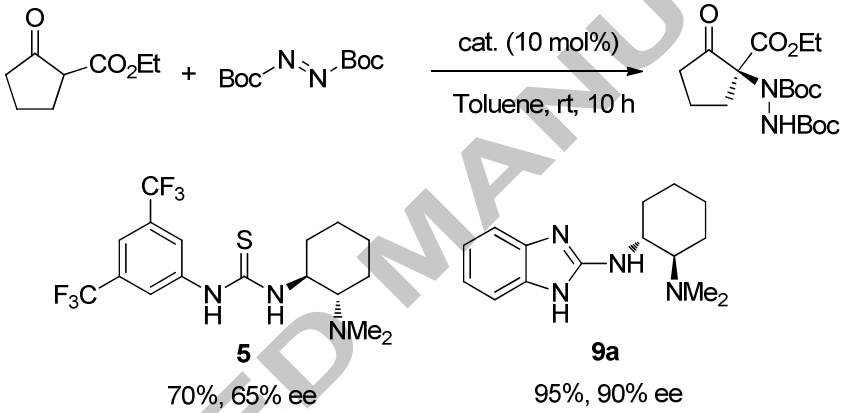
Scheme 10. Proposed reaction mechanism for the asymmetric alkylation of β-ketoesters with benzylic alcohols organocatalyzed by **20**.

Intramolecular enantioselective oxa-Michael reaction of α,β-unsaturated amides of the type **30** has been carried out using different HB-donor organocatalysts such as thiourea **4**, squaramide **8**, 2-aminobenzimidazole **9a**, quinazoline **6a** and benzothiadiazine **7a** (Scheme 11).[28] The process was carried out at rt in dichloromethane obtaining the product **31** in 92% yield and 95% ee with the latest organocatalyst **7a**. However, the 2-aminobenzimidazole derivative **9a** failed in this reaction.



Scheme 11. Intramolecular enantioselective oxa-Michael reaction of α,β-unsaturated amides **30**.

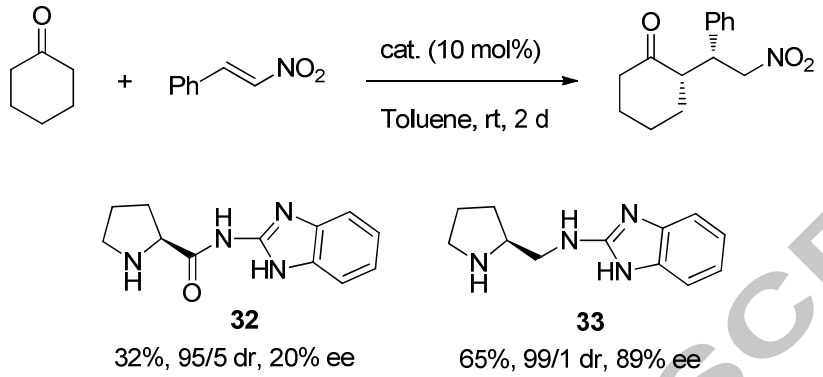
On the other hand, **9a** has shown a better catalytic activity than thiourea **4** in the amination reaction of ethyl 2-oxocyclopentanecarboxylate with di-*tert*-butylazodicarboxylate (Scheme 12).[29] However, modest results were obtained with other 1,3-dicarbonyl compounds.



Scheme 12. Enantiocatalyzed amination of ethyl 2-oxocyclopentanecarboxylate with di-*tert*-butylazodicarboxylate.

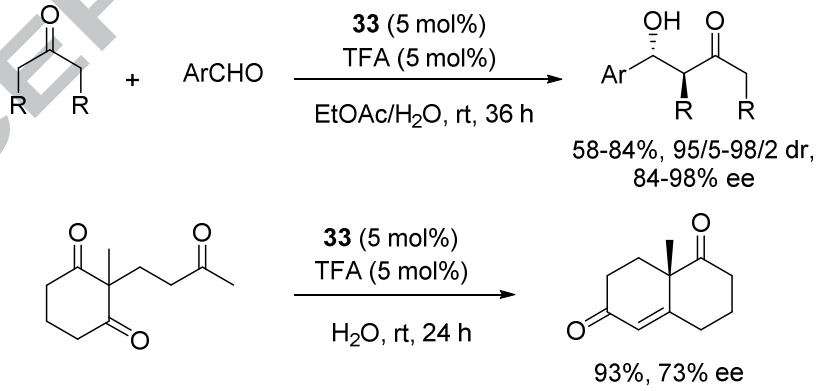
Different chiral pyrrolidine-2-aminobenzimidazole bifunctional organocatalysts have been designed for the asymmetric Michael addition of ketones to nitroalkenes through enamine formation and hydrogen bond activation of the nitro group.[30] The best results have been obtained with the pyrrolidine-2-aminobenzimidazole **33** (compared to the prolinamide derivative **32**) for the conjugate addition of cyclohexanone to β-nitrostyrene (Scheme 13). Further screening of the reaction conditions with organocatalyst **33** revealed that the use of 4-methoxybenzoic acid as cocatalyst (10 mol%) and brine as solvent gave the corresponding adduct in only 9 hours in 93% yield, 99/1 dr and 98% ee with only 2 equivalents of cyclohexanone. The process has been extended to different nitroalkenes in excellent results concluding that the 2-

aminobenzimidazole unit is a better HB-donor than amides, azoles, sulfonamides and thioureas, which are the most commonly used in pyrrolidine derivatives.[30]



Scheme 13. Asymmetric Michael addition of cyclohexanone to nitrostyrene organocatalyzed by **32** and **33**.

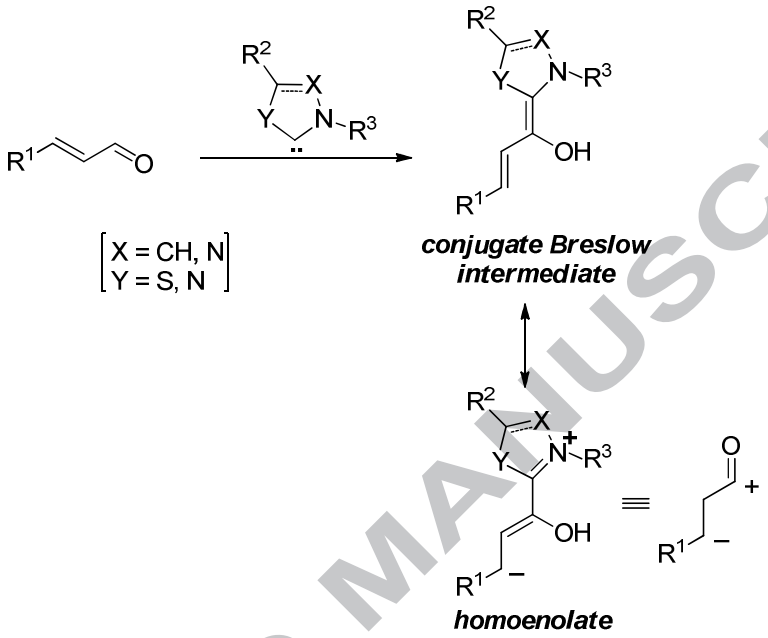
The pyrrolidine-2-aminobenzimidazole derivative **33** has been further used as organocatalyst in enantioselective intermolecular aldol reaction of ketones with aromatic aldehydes and for the synthesis of the Wieland-Miescher ketone by an intramolecular process.[31] In this case, TFA was used as cocatalyst in a 1/1 mixture of EtOAc/H_2O at room temperature giving the corresponding aldol products in good yields, 95/5-98/2 *anti*/*syn* ratios, and high ee (Scheme 14). However, the Hajos-Parrish-Wiechert-Eder-Sauer (HPWES) aldol reaction took place in 93% yield and in a moderate 73% ee.



Scheme 14. Enantioselective aldol reactions organocatalyzed by **33**.

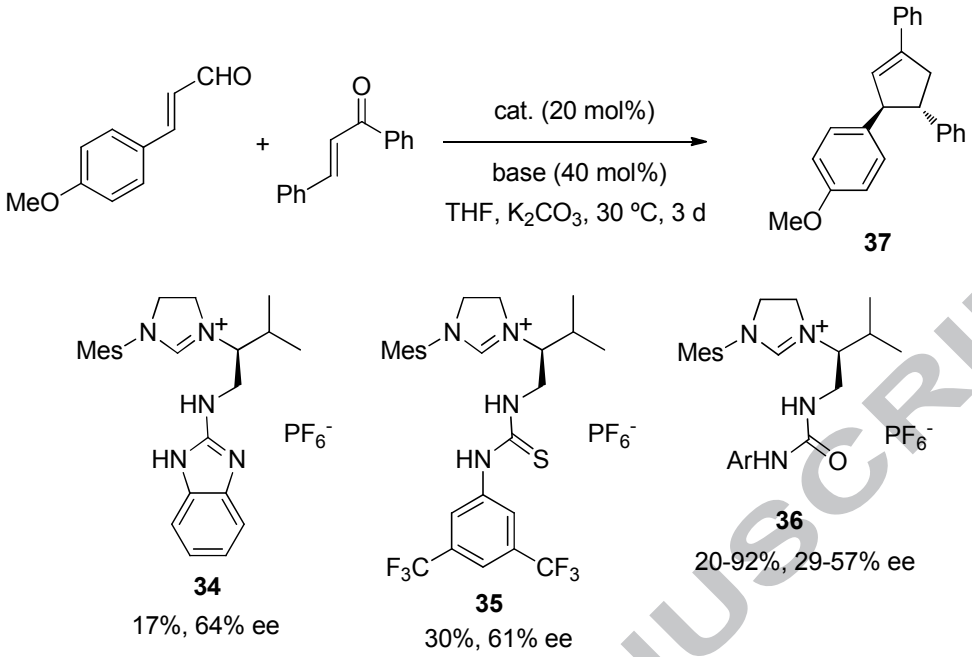
N-Heterocyclic carbenes (NHCs) functionalized with hydrogen bond donor moieties have been evaluated as bifunctional organocatalysts involving homoeneolate

intermediates.[32] Enals can react with NHCs forming a conjugate Breslow intermediate[33] in which the β-position behaves as nucleophile and the carbonyl group is prone to suffer nucleophilic substitution liberating the NHC catalyst (Scheme 15).[33] Several chiral hydroxyl-functionalized imidazolium salts[35] were selected to prepare the corresponding



Scheme 15. Breslow's mechanism for the generation of homoenolates by N-heterocyclic carbenes from enals.

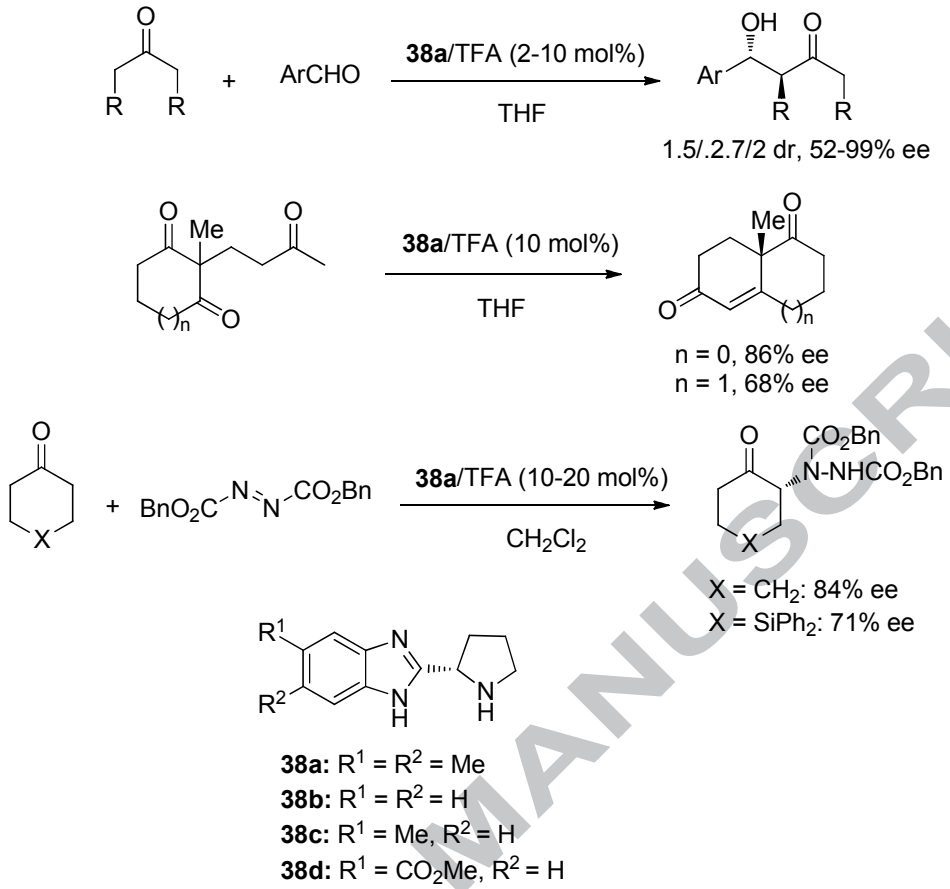
amino-imidazolium salts, which were transformed into the benzimidazole **34**, the thiourea **35**, and ureas **36** (Scheme 16). These precatalysts failed in the enantioselective Michael addition of β-ketoamides to methyl vinyl ketone.[35] However, the cyclopentannulation with chalcones previously described by Nair's group in the racemic series,[36] and by Bode's group in the enantioselective version,[37] afforded cyclopentene **37** in modest yields and moderate ee (Scheme 16).



Scheme 16. Enantioselective cyclopentannulation of enals with chalcone organocatalyzed by chiral N-heterocyclic carbenes **34-36**.

3. 2-(Aminoalkyl)benzimidazoles

Benzimidazole-pyrrolidines **38** (BIP) have been used as bifunctional chiral organocatalysts in aldol and amination reactions. This type of catalysts can be prepared by heating of (*S*)-proline and the corresponding substituted 1,2-diaminobenzene under acidic conditions.[38] Compound **38a** crystallized incorporating a water molecule, which bonded two molecules of BIP through four hydrogen bonds, the distance between the two NH group being 2.71Å, larger than in the 2-aminobenzimidazole derivatives **9**. The presence of TFA increased notably the catalytic efficiency in direct aldol processes allowing the use of equimolecular amounts of ketone donor and aldehyde acceptor (Scheme 17). For the intramolecular HPWES reaction the corresponding bicyclic diketones were obtained in 86% (n = 0) and in 68% ee (n = 1) for the Wieland-Miescher ketone. In the case of the amination of cycloalkenones with dibenzyl-diazodicarboxylate (DBAB) the corresponding α-hydrazino products were obtained in 65-92% yields and in 66-71% ee (Scheme 17).[38]



Scheme 17. Asymmetric aldol and amination reactions of ketones organocatalyzed by **38a**.

Related chiral benzimidazole-pyrrolidine derivatives **38b-d** have been used in the aldol reaction of acetone with aromatic aldehydes in *N*-methylpyrrolidone (NMP) at room temperature giving in the case of **38d** (15 mol%) the aldol products in modest 27-49% ee.[39] For the conjugate addition of cyclohexanone to different β-nitroalkenes in methanol the corresponding adducts were isolated in 11-49% ee.[39]

Several chiral prolinamides with tetrazole **39**-**41** and benzimidazole units **42**-**43** have been evaluated as organocatalysts in the direct intermolecular aldol reactions under neutral conditions (Figure 10).[40] For the reaction of acetone with aromatic aldehydes in DMF at room temperature, the best results were obtained with the catalyst **40** (10 mol%) (up to 96% ee) and **43** (5-10 mol%) in neat acetone (up to 96% ee).

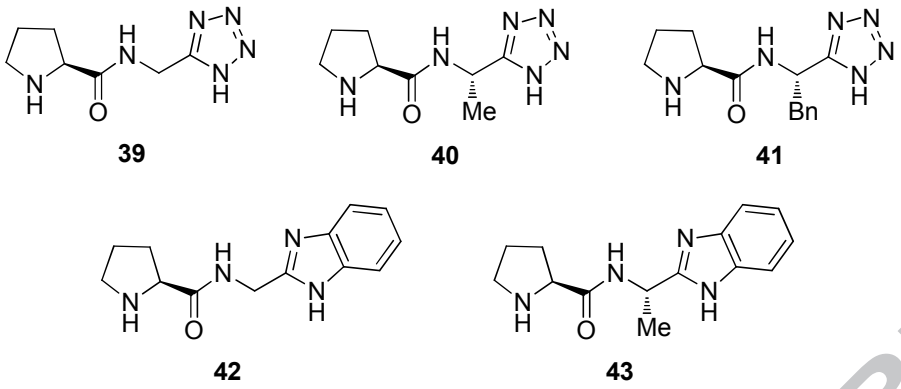


Figure 10. Chiral prolinamides with tetrazole **39**-**41** and benzimidazole units **42**-**43** used as organocatalysts in aldol reactions.

Recently, benzimidazole functionalized chiral thioureas **44** have been evaluated biologically giving high antibacterial and anticancer activity (Figure 11).[40] Thioureas (*S*)-**44** showed antibacterial activity towards various Gram-positive and Gram-negative bacterial strains, whereas its enantiomers were inactive. Moreover, both showed promising activity against cell lines A549, DU145, and HeLa.

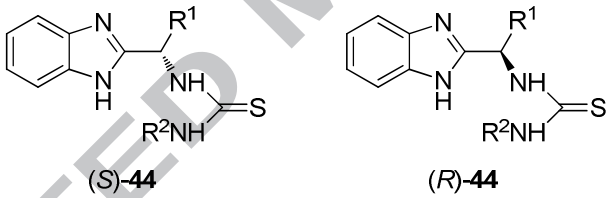


Figure 11. Benzimidazole-derived thioureas **44** with antibacterial and anticancer activity.

Conclusions

We have shown that 2-aminobenzimidazoles anchored to a chiral skeleton are excellent organocatalysts able to work as hydrogen donors with different substrates like thioureas and squaramides. They can be prepared easily just by reaction of a chiral amine with 2-chlorobenzimidazole. They can be considered as rigid guanidines and are able to catalyze enantioselective Michael-type reactions, direct nucleophilic substitution of alcohols, amination reactions, and aldol reactions. The homologous 2-(aminoalkyl)benzimidazoles have been used as chiral organocatalysts only in aldol and amination reactions of carbonyl compounds. We think that the benzimidazole unit has a promising potential as hydrogen donor in asymmetric organocatalysis.

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