DE GRUYTER Pure Appl. Chem. 2016; 88(6): 561–578

Conference paper

Carmen Nájera*, José Miguel Sansano and Enrique Gómez-Bengoa

Heterocycle-based bifunctional organocatalysts in asymmetric synthesis

DOI 10.1515/pac-2016-0403

Abstract: Different chiral bifunctional organocatalysts derived from *trans*-cyclohexane-1,2-diamine bearing different types of guanidine units able to form-hydrogen bonding activation have been designed. Conformational rigid 2-aminobenzimidazoles bearing a tertiary amino group have been used in enantioselective Michael type reactions of activated methylene compounds to nitroalkenes. The C_2 symmetric bis(2-aminobenzimidazole) derivatives the appropriate organocatalyst for the conjugate addition of 1,3-dicarbonyl compounds to maleimides as well as for the S_N1 reaction of benzylic alcohols with carbon nucleophiles. 2-Aminobenzimidazoles bearing a primary amino group have shown excellent catalytic activity in the Michael reaction of aldehydes to maleimides and nitroalkenes. Diastereomeric 2-aminopyrimidines bearing a prolinamide unit have been incorporated in the *trans*-cyclohexane-1,2-diamine scaffold and have been used for the inter- and intra-molecular direct aldol reaction under solvent-free conditions. For the Michael reaction of aldehydes with maleimides the primary amine 2-aminopyrimidine has shown excellent efficiency as organocatalyst. The bifunctional character of these organocatalysts has been demonstrated by means of DFT calculations.

Keywords: aldols; asymmetric synthesis; bifunctional catalysis; carbenium ions; 1,3-dicarbonyl compounds; hydrogen bonding; nitro compounds; succinimides; TRAMECH VIII.

Introduction

The crucial role of hydrogen-bonding (HB) interactions in biological systems have inspired the recent development of small organic molecules able to act as chiral hydrogen-bond donors and acceptors in asymmetric organocatalysis [1–5]. Chiral ureas [6–8] and thioureas [9–11] **1** with pKa = 27 and 21 in DMSO [12], respectively, have emerged as the most successful catalysts due to their ability to form two hydrogen bonds with nucleophiles and electrophiles (Fig. 1). Rigid guanidines have been employed as chiral bases also capable of forming hydrogen bonds [13–19]. However, acyclic guanidines due to conformational free rotation, according to DFT calculations, are able to form only one hydrogen bond with electrophiles [20–22]. Other systems able to form two-hydrogen bonds such as aminophosphonium [23–25], thioamides [26], squaramides [27, 28] and sulfonamides [29]. Concerning heterocyclic based organocatalysts 2-aminopyridinium ions **2** [30–35] with pKa = 6 in DMSO [36] have been used as chiral catalysts [26, 30–35]. Another 2-amino heterocyclic systems

Article note: A collection of invited papers based on presentations at the Trans Mediterranean Colloquium on Heterocyclic Chemistry (TRAMECH VIII) in Anatalya, Turkey, 11–15 November 2015.

***Corresponding author: Carmen Nájera,** Departamento de Química Orgánica and Centro de Innovación en Química Avanzada (ORFEO-CINQA), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain, e-mail: cnajera@ua.es
José Miguel Sansano: Departamento de Química Orgánica and Centro de Innovación en Química Avanzada (ORFEO-CINQA), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain
Enrique Gómez-Bengoa: Departamento de Química Orgánica I, Facultad de Química, Universidad del País Vasco, Apdo. 1072, E-20018 San Sebastián, Spain

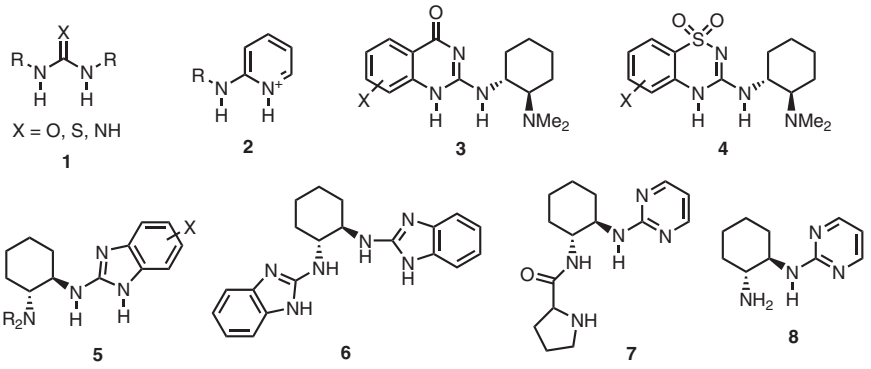


Fig. 1: Dual hydrogen-bonding systems.

bearing a quinozaline **3** related to guanine, or benzothiadiazines **4** skeletons [37, 38] have shown excellent bifunctional catalytic properties acting as dual hydrogen-bond donors (Fig. 1). We envisaged that 2-aminobenzimidazoles and 2-aminopyrimidines can behave as rigid guanidines and should be appropriate units to form double hydrogen bonds. This article compiles our contribution on bifunctional heterocyclic organocatalysts **5–8** (Fig. 1) by using the *trans*-cyclohexane-1,2-diamine as a chiral scaffold.

Chiral 2-aminobenzimidazoles

2-Aminobenzimidazoles and 2-aminopyridines with similar pKa (7.0 and 6.2) have shown very good acid/base catalytic features substituting guanidinium moieties as phosphoryl transfer catalysts [39]. However, only tris(2-aminobenzimidazoles) **9** led to active RNA cleavers by means of HB with phosphates under neutral conditions being promising candidates as site specific artificial ribonucleases (Fig. 2). More recently, Moran et al. have designed a xanthenes-2-aminobenzimidazole receptor **10** able to form multiple hydrogen bonds with sulfoxides, ketones or alcohols and strongly with carboxylic acids and chloride anion [40]. The 2-aminobenzimidazole is an important unit in medicinal chemistry due to the broad spectrum of pharmacological applications such as the antihelmintic mebendazole and albendazole and the antihistaminic astemizole [41–47]. Ganesh and Seidel [26] described a thiourea bearing a protonated 2-aminobenzimidazole unit **11**, which has been used as chiral organocatalysts in the enantioselective addition of indole to nitroalkenes with amoderate 40 % ee. Further development of chiral 2-aminobenzimidazoles has demonstrated the outstanding ability of these units as dual HB donor [48].

We initially designed and synthetized different 2-aminobenzimidazoles **5** starting from both enantiomers of *trans*-cyclohexane-1,2-diamine by reaction with 2-chlorobenzimidazole [49]. From X-ray diffraction analysis data and DFT calculations the distances of both hydrogens in the NH groups could be determined. They are in the range of 2.41–2.61 Å, whereas in related thiourea **12** [9–11] and squaramide **13** [27] are 2.13 Å and 2.72 Å, respectively (Fig. 3).

As a benchmark reaction the conjugate addition of diethyl malonate to β-nitrostyrene catalyzed by compounds **5** bearing a primary amine **5a** (R = H, X = H), a tertiary amine **5b** (R = Me, X = H), **5c** (R = Et, X = H) and **5d** (R = Me, X = 6-CF_3) in different solvents and in the presence and absence of trifluoroacetic acid (TFA) as cocatalyst was studied [49]. From the screening of these reaction conditions it could be deduced that toluene as a solvent, organocatalysts **5b** (10 mol %), TFA (10 mol %) at room temperature during 2 days gave the best performance (Scheme 1). This organocatalyst could be recovered in 94 % yield by extractive work-up with 10 % aqueous NaOH. The Michael adducts were obtained in 95–98 % yield and 87–94 % ee (Scheme 1). When β-keto esters were used as nucleophiles moderate to high diatereoselectivities were observed (up to 82 %) with in general high enantioselectivity for each diastereomer (70–93 % ee). Acetylacetone afforded the corresponding Michael adducts in 93–96 % yield and 86–99 % ee under the same reaction conditions.

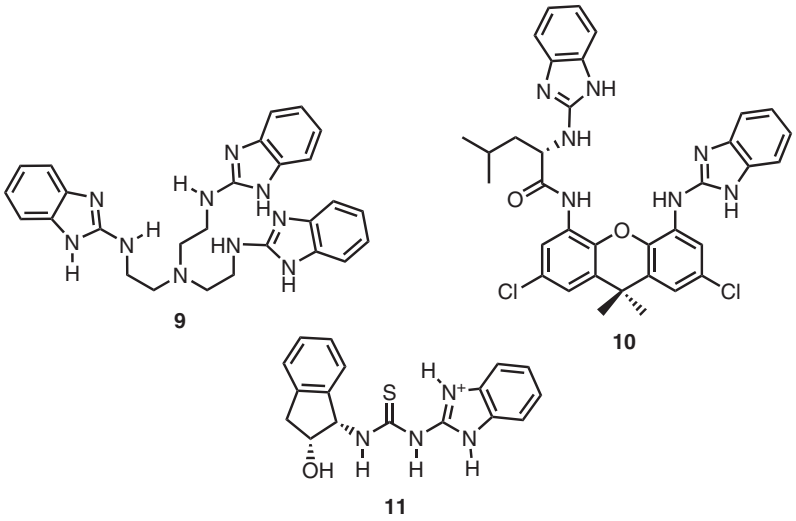


Fig. 2: Selected 2-aminobenzimidazoles.

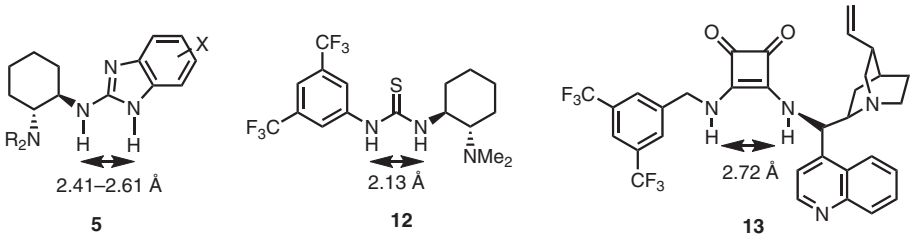
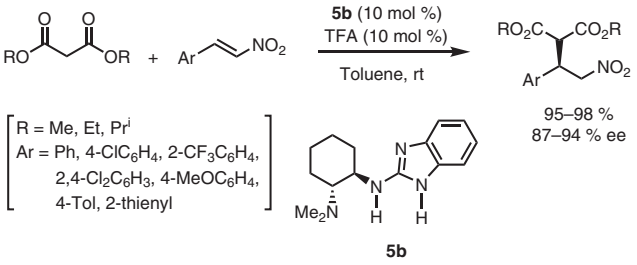


Fig. 3: Hydrogen distances for organocatalysts **5**, **12** and **13**.



Scheme 1: Conjugate addition of malonates to nitrostyrenes.

From DFT calculations at the B3LYP/6-311++G**//B3LYP/6-31G* level for the conjugate addition of dimethyl malonate or acetylacetone to β-nitrostyrene two possible activation modes were considered with the neutral and the protonated organocatalyst (Fig. 4). The most favored activation mode is in agreement with Papai et al. calculations for the same reaction catalyzed by thiourea **12** [50], the formation of the two hydrogen bonds from the 2-aminobenzimidazole unit with the 1,3-dicarbonyl compound.

Transition state TSa for the *R*-enantiomer in the case of malonate is 1.9 kcal/mol more stable than for the *S*-enantiomer. However, the other interaction gave the opposite enantioselection and only a 0.6 kcal/mol difference in energy for both TS producing quasi-racemic products [49] (Fig. 5). These calculations not only supported the dual HB but also the bifunctional character of this catalyst and the participation of TFA as a cocatalyst. On the other hand, the protonated dimethylamino group form a hydrogen bond with one of the oxygen of the nitro group.

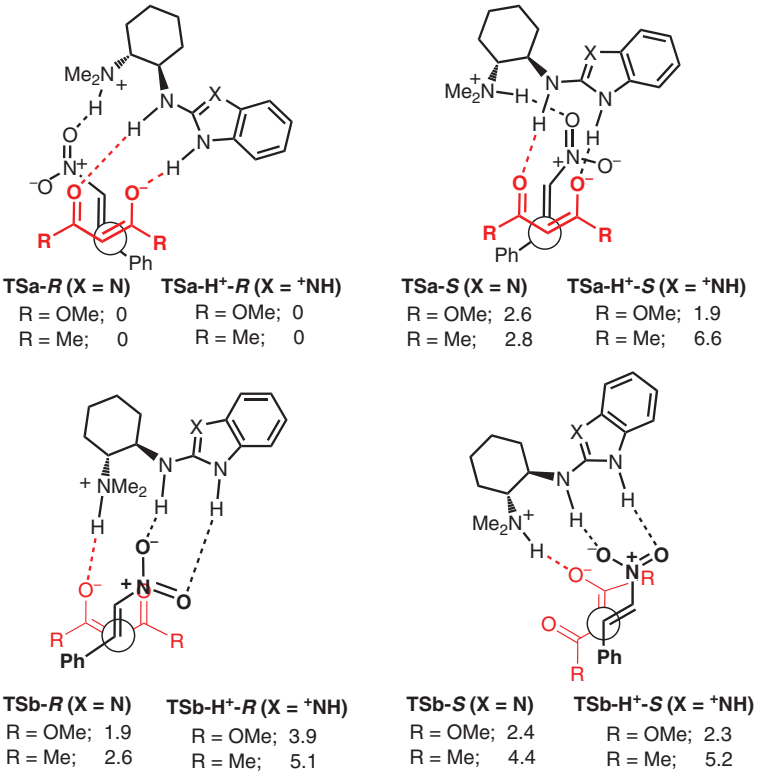


Fig. 4: Values correspond to Gibss free energies (G, kcal/mol) relative to **TSa-*R*** (G = 0) computed at B3LYP/G-311++G** level for the conjugate addition of dimethyl malonate and acetylacetone to β-nitrostyrene.

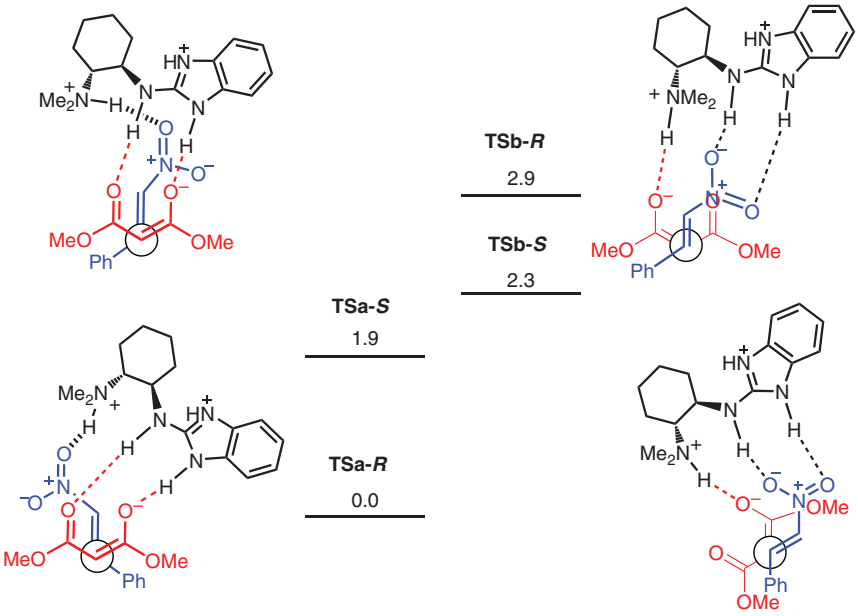


Fig. 5: Energy differences of the transition states for the Michael addition of dimethylmalonate to β-nitrostyrene.

Independently, the Park and Jew groups [51] described that related 2-aminobenzimidazoles **14** and **15** (Fig. 6), derived from dihydroquinidine and quinidine as chiral bases, were very efficient organocatalysts for the Michael addition of dimethyl malonate to nitroalkenes. Under neutral conditions by using 2 mol %

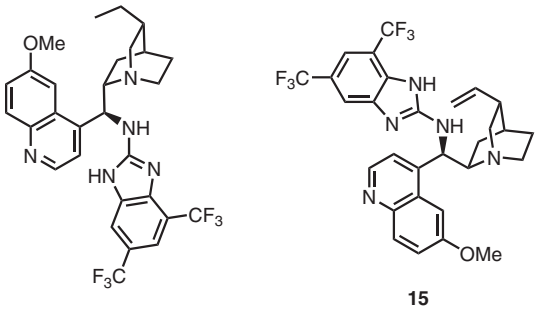
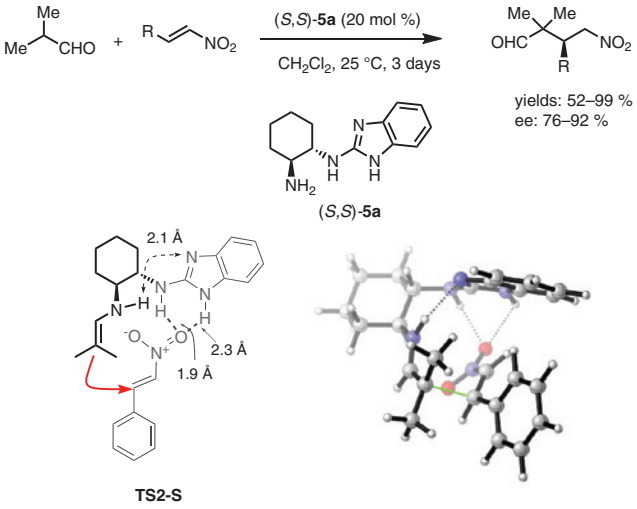


Fig. 6: *Cinchona* alkaloids derived 2-aminobenzimidazole organocatalysts.

of catalyst loading in dichloromethane (DCM) as solvent at –20 °C during 40–96 good yields (67–99 %) and ee (91–99 %) were obtained. Further contribution from this group with 10 mol % of *trans*-cyclohexane-1,2-diamine organocatalyst **5e** (R = Me, X = 5,7-$(CF_3)_2$) revealed that under neutral conditions, the addition of dimethyl malonate in DCM at 0 °C gave 90–96 % ee [52]. They proposed that the nitro group is activated by double HB with the 2-aminobenzimidazole unit and confirmed that in the absence of CF_3 groups in the benzimidazole **5b** needs the presence of TFA and proposed the same interaction mode in agreement with our results. When organocatalyst **5b** was employed in enantioselective intramolecular oxa-Michael addition, the reaction failed. However, organocatalyst **4** gave high yields and enantioselectivities [38]. In the case of the α-amination of 1,3-dicarbonyl compounds with diazodicarboxylates only ethyl cyclopentanecarboxylate gave, in the presence of 10 mol % of **5b**, a 92 % ee [53].

For the conjugate addition of isobutyraldehyde to nitroalkenes the presence of a primary amine in the 2-aminobenzimidazole (*S*,*S*)-**5a** (20 mol %) in DCM at 25 °C during 3 days allowed the synthesis of γ-nitroaldehydes in moderate to high yields and enantioselectivities (Scheme 2) [54]. DFT calculations [M06-2X/6-31+G(d,p) level] support the approaching of nitrostyrene behind the enamine and the two NH of the 2-aminobenzimidazole unit are forming two HB with one oxygen atom of the nitro group with 1.9 Å and 2.3 Å distances (Scheme 2). In addition, the sp^2 nitrogen of the benzimidazole acts as hydrogen acceptor of the enamine hydrogen being the distance 2.1 Å. These calculations corroborate the bifunctional character of this organocatalyst.

Enantioenriched succinimides can be prepared by asymmetric conjugate addition to maleimides [55]. The succinimide unit is present in natural products such as moramide B and andrimid and in some drugs

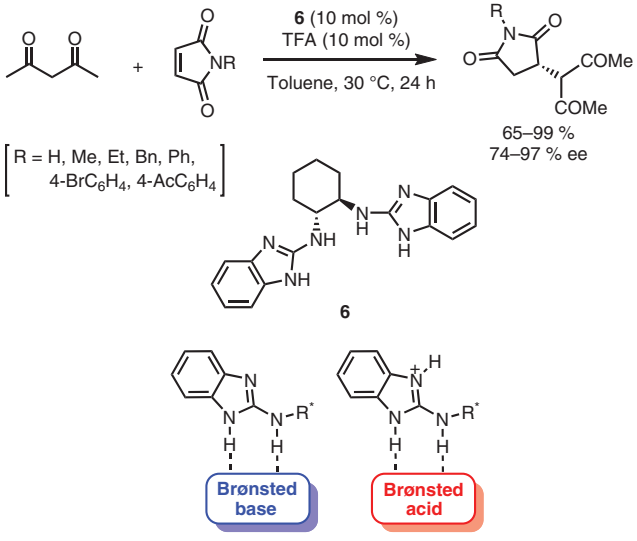


Scheme 2: Michael addition of isobutyraldehyde to nitroalkenes catalyzed by the primary amine-2-aminobenzimidazole (*S*,*S*)-**5a**.

such as phensuximide, ethosuximide and palasimide [56–61]. In addition, succinimides can be transformed into γ-lactams or pyrrolidines by partial or total reduction, and in succinic acid derivatives by acid or basic hydrolysis [62, 63]. Initial studies on the conjugate addition of acetylacetone to maleimide were assayed with different organocatalysts of the type **5** (10 mol %) and TFA (10 mol %) in toluene at rt afforded low ee (13–41 %) [64, 65]. However, when the C2 symmetric bis(2-aminobenzimidazole) **6** (10 mol %) and TFA (10 mol %) as cocatalyst were used the addition took place quantitatively in 97 % ee. The scope of the reaction was studied with different maleimides giving the corresponding adducts in general high yields (65–99 %) and enantioselectivities (74–97 % ee) (Scheme 3) [64, 65]. This catalytic behavior can be explained accepting that one 2-aminobenzimidazole unit is acting as a Brønsted base and the other, which is protonated by TFA, is acting as a Brønsted acid.

In the case of unsymmetrical 1,3-diketones and β-keto esters, modest to high diastereomeric ratios (58/42–97/3) and modest to high enantioselections (24–99 % ee) were obtained (Fig. 7). When these processes were scaled up to gram scale in 5–20 mmol, excellent results were achieved (Fig. 7). For the recovery of the organocatalysts **6** the reaction of acetylacetone and 4-(bromophenyl)maleimide was chosen. After the reaction was complete, isopropanol was added and the corresponding succinimide precipitated and was filtered off. From the solution **6**, as trifluoroacetate salt, was isolated after evaporation of the solvents in 99 % yield and was used in a second run without further purification giving the succinimide in 99 % yield and 93 % ee [65]. The presence of one equivalent of TFA was crucial to obtain good yields and enantioselectivities. Notably, a complete deactivation of the catalyst was observed when using a twofold excess (20 mol %) of cocatalyst. Also, dependence of the enantioselectivity of the process on catalyst loading was observed. However, at high concentrations, product racemization due to thermodynamic control of the process was discharged, as the enantioselectivity of the reaction was kept constant within the course of the experiment when a 0.1 M catalyst concentration was used in the conjugate addition. The ee values obtained at different catalyst concentrations were fairly consistent with the diffusion coefficients of **6**·TFA, strongly indicating that the degree of hydrogen-bonded self-association of bifunctional organocatalyst in solution plays a crucial role in determining the enantioselectivity of the process.

The excellent catalytic activity of **6** was unexpected because this compound failed in the previously described Michael addition of dimethyl malonate to nitrostyrenes [52, 66]. However, the addition of dimetyl malonate to maleimides took place under neutral conditions (Scheme 4). This was probably due to the lower acidity of the nucleophile compared to 1,3-diketones and β-keto esters, thus requiring a catalyst with an stronger basic character.



Scheme 3: Conjugate addition of acetylacetone to maleimides organocatalyzed by **6**.

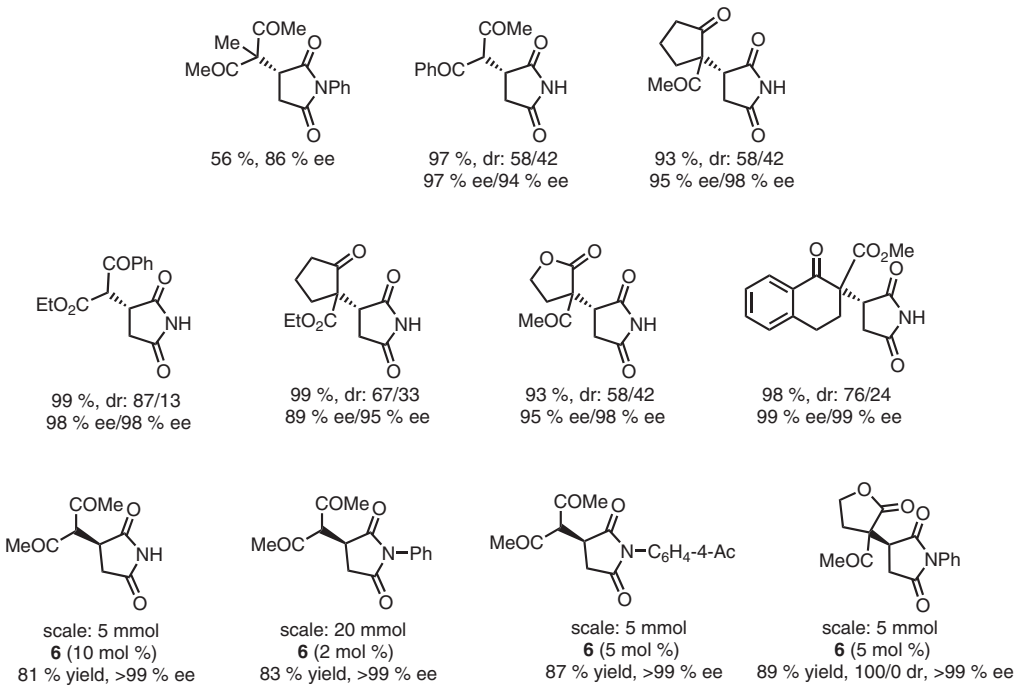
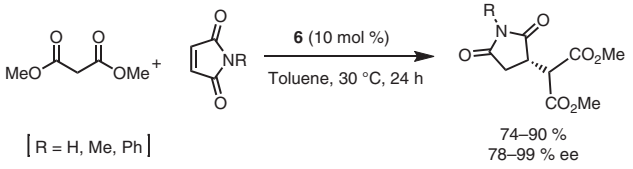


Fig. 7: Selected examples on the Michael addition of 1,3-dicarbonyl compounds to maleimides.



Scheme 4: Conjugate addition of dimethyl malonate to maleimides catalyzed by **6**.

DFT computational studies carried out in a solvent model (IEFPCM, toluene) at B3LYP/6-311++G** level, were conducted aimed at detailing the H-bond network between catalyst, nucleophile and maleimide responsible for the observed reactivity/enantioselectivity. It was assumed that the reaction is initiated with the deprotonation of the pronucleophile (2,5-pentadione) by one of the 2-aminobenzimidazole units to form an enolate/protonated catalyst binary complex. Further hydrogen bonding with the maleimide renders a ternary complex that evolves to the final products through the corresponding transition state [65].

Three possible mechanistic scenarios were considered: a) in the absence of acid, the basic catalyst deprotonates and binds the nucleophile (**A**, Fig. 8). Four NH groups are available for Nu/maleimide activation, arranged in a flexible and open reactive site; b) if partial protonation (1 equiv of acid) of the catalyst is considered, the neutral portion of the catalyst deprotonates the nucleophile leading to structure **B**, which possesses a tighter reactive space decorated with three or four NH groups for reagent activation; c) further protonation of the catalyst with a second molecule of acid would cancel the basicity of the catalyst, and only the enol form of the nucleophile could act as a nucleophile, like in structure **C**, lowering its reactivity [65].

After an extensive conformational search, the calculated energies for the optimal transition states in model **A** predict a high reactivity and a moderate selectivity [1.7 kcal/mol energy difference between $\mathbf{TS}_{A2}$(S) and $\mathbf{TS}_{A2}$(R), Fig. 9], which is in fair agreement with the experimental results in the absence of acid (>99 % conversion, 51 % ee). The privileged transition structures for each enantiomer [$\mathbf{TS}_{A2}$(S) and $\mathbf{TS}_{A2}$(R)] bear an intramolecular H bond between the protonated and the neutral benzimidazole portions of the catalyst. As a consequence, a very open reaction space is formed, in which the remaining four NH bonds are involved

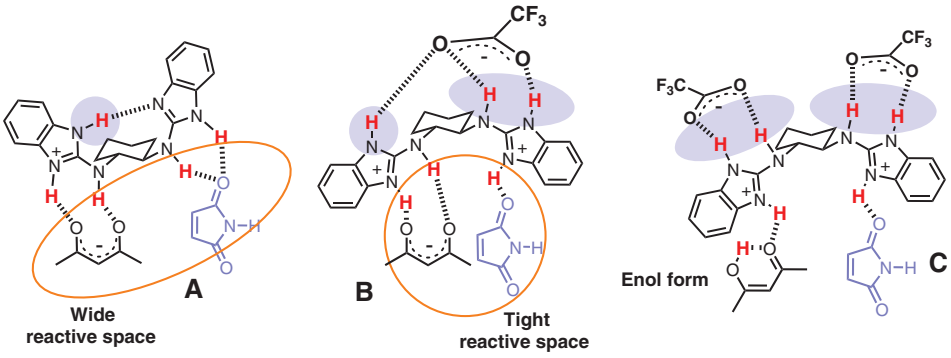
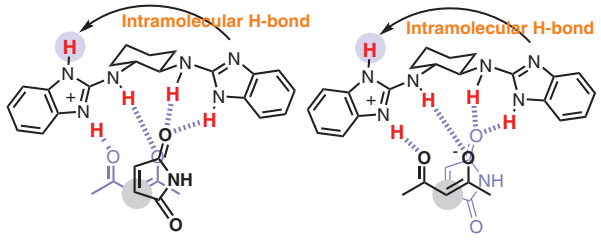
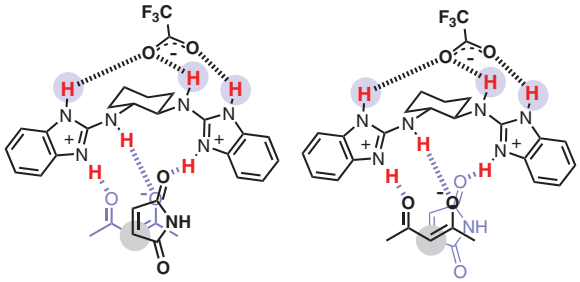


Fig. 8: Computed mechanistic alternatives **A–C**.



TS_{A2}(S), $\Delta G^{\ddagger}_{toluene}$ = 23.6 kcal/mol TS_{A2}(R), $\Delta G^{\ddagger}_{toluene}$ = 25.3 kcal/mol



TS_{B2}(S), $\Delta G^{\ddagger}_{toluene}$ = 24.7 kcal/mol TS_{B2}(R), $\Delta G^{\ddagger}_{toluene}$ = 29.3 kcal/mol

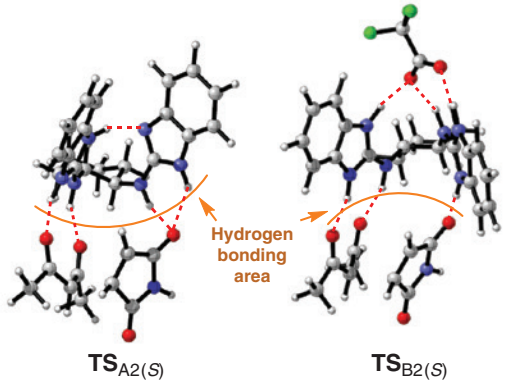


Fig. 9: Main transition structures computed in models **A** and **B**.

in a low-selective binding of the nucleophile and electrophile. In contrast, the inclusion of one molecule of trifluoroacetic acid might produce a fast protonation of the catalyst (model **B**). The CF_3COO^- anion is able to bind the two imidazole units, eliminating the possibility of an intramolecular H-bonding between them. The optimal transition structures were found, in which three of the NH groups are exposed to the trifluoroacetate anion and solvent. In this structure, the activation of the maleimide is achieved by a single NH bond, and

two other NH groups bind the nucleophile, in a tight, concave reaction site. This effect increases the energy difference between the diastereomeric forms $TS_{B(S)}$ and $TS_{B(R)}$ (24.7 and 29.3 kcal/mol, respectively), predicting a high reactivity and very good enantioselectivity, as experimentally found (>99 % conversion, 94 % ee). As previously mentioned these calculations confirm the bifunctional nature of this organocatalyst **6** [65].

Finally, the distinct outcome shown by the malonates as nucleophiles might be related to the lower basicity of dimethyl malonate *versus* acetylacetone (pKas in DMSO are 15.7 and 13.3, respectively). In fact, the deprotonation of dimethyl malonate by the TFA-protonated catalyst (mechanism B) is computed to be a disfavored process (Fig. 10). Thus, both reactions of malonate in the presence or absence of TFA proceed through mechanism **A**, with a computed 86 % ee, in fair agreement with the experimental 78–81 % ee, and at different rates, since the acid exerts the negative effect of lowering the available amount of the necessary free benzimidazole [65].

The conjugate addition of aldehydes to maleimides were performed in the presence of the primary amine-benzimidazole catalyst (*S*,*S*)-**5a** (15 mol %) in toluene at 15 °C during 4 days under neutral conditions (Scheme 5) [54]. The corresponding succinimides were isolated in 47–99 % yield and 55–89 % ee. DFT calculations were performed at M06-2X/6-31+G(d,p) level for the addition of isobutyraldehyde to *N*-phenylmaleimide (Scheme 5). They showed the bifunctional properties of this organocatalysts confirming that the approach of maleimide takes place by the opposite side than the enamine by formation of two hydrogen bonds of the 2-aminobenzimidazole unit with the carbonyl group (2.0 Å and 2.1 Å). An extra hydrogen bond is formed between the enamine and the sp^2 N of the benzimidazole unit as occurred in the addition of isobutyraldehyde to nitrostyrene (Scheme 2). The difference in energy between TS(*S*) and TS(*R*) being 1.8 kcal/mol.

The ability of organocatalysts **6**·TFA to act as chiral Brønsted acid prompted us to study the enantioselective alkylation of carbon nucleophiles with benzylic alcohols. This asymmetric S_N1 reaction [67–70] was previously performed with benzylic alcohols and β-keto phosphonates [71] and 1,3-dicarbonyl compounds [72] by using copper(II) triflate–Box complexes as catalysts. Initial organocatalyst screening [73] was performed with hydrogen donors such as thioureas **12** and **16**, 2-aminobenzimidazoles **5a**, **5b**, **6** and **17** in the presence of TFA for the alkylation of ethyl 2-oxocyclopentanecarboxylate with bis[4-(dimethylamino)phenyl]methanol, which is a precursor of a very stable carbenium ion (E = –7.02) [74] called Michler's blue [75]. Only in the case of using **6**·TFA as organocatalysts a moderate 33 % ee was observed (Scheme 6). Lowering the temperature to –20 °C either with TFA or TfOH the corresponding alkylated β-keto ester was obtained in 85 % and 88 % yield and in 64 % and 67 % ee, respectively.

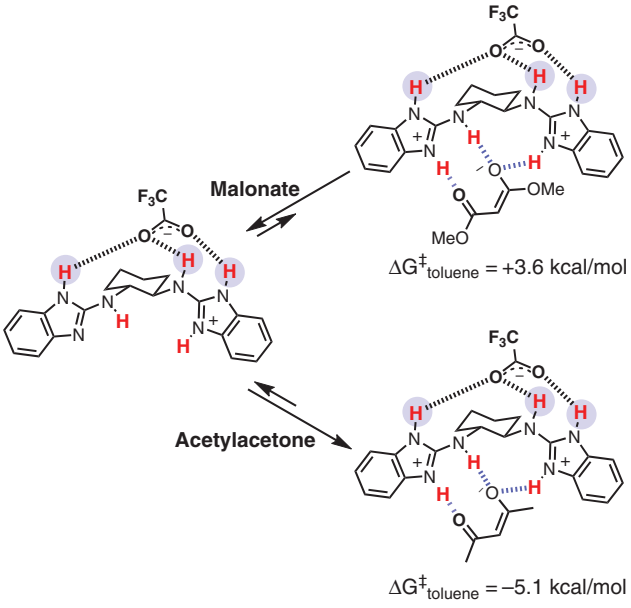
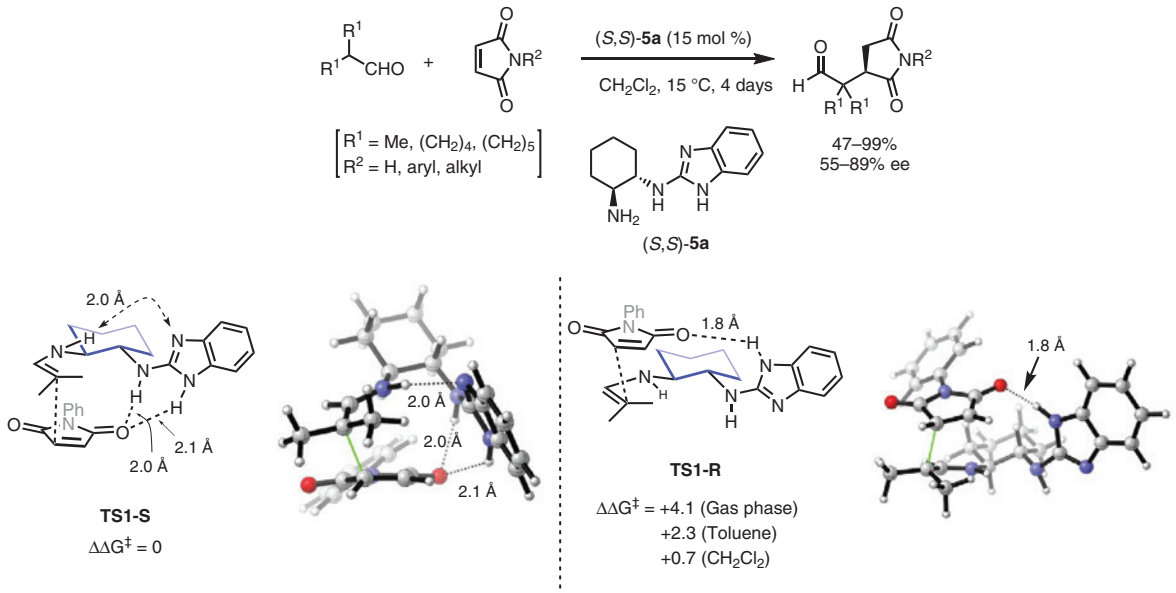
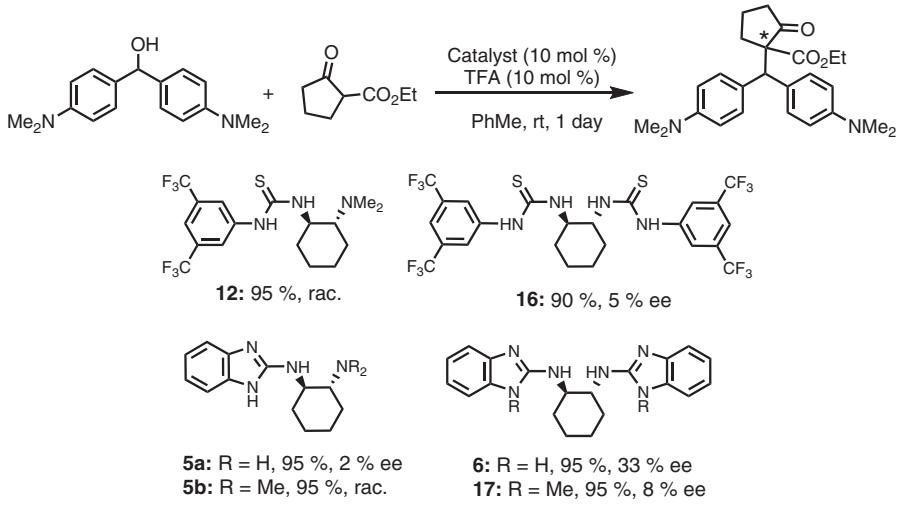


Fig. 10: Different binding energies of the computed nucleophiles for mechanism **B**.



Scheme 5: Conjugate addition of aldehydes to maleimides catalyzed by the primary amine-2-aminobenzimidazole (*S*,*S*)-**5a**.



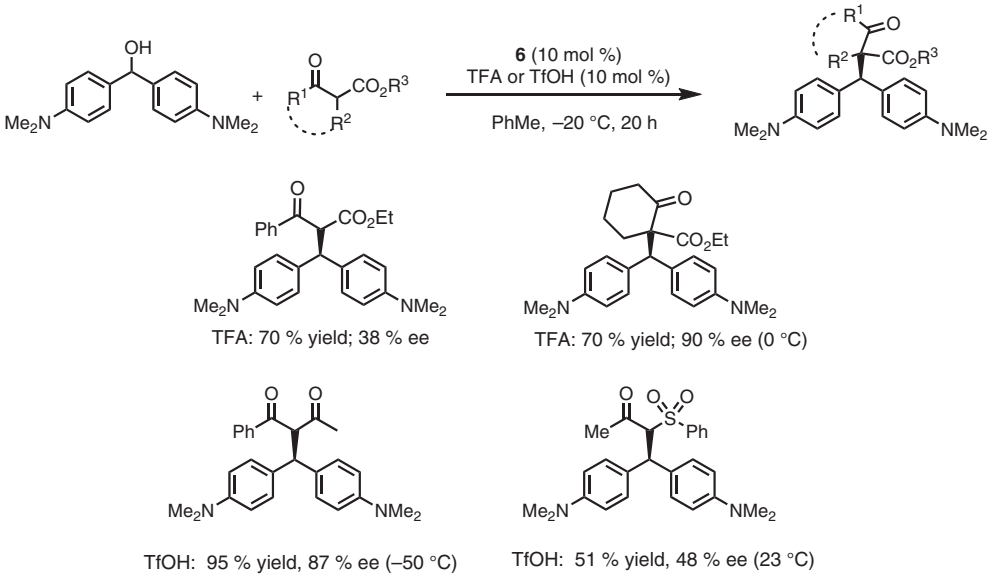
Scheme 6: Organocatalyst screening for the alkylation of ethyl 2-oxocyclopentanecarboxylate with a benzylic alcohol.

When other carbon nucleophiles were assayed with Mischler's blue and **6** as organocatalyst in the presence of 1 equiv. of TFA or TfOH, variable results were obtained (26–90 % ee) (Scheme 7) [73].

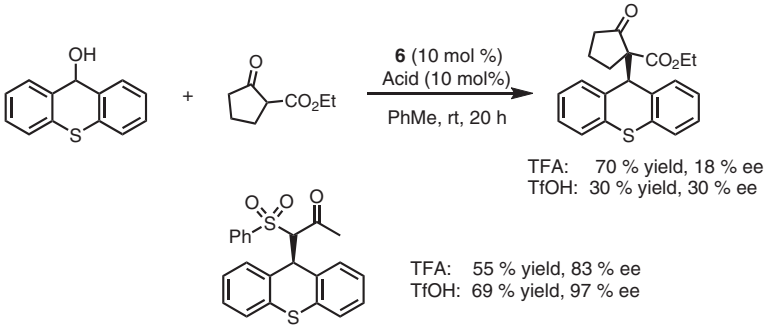
With respect to other benzylic alcohols only thioxanthydrol gave moderate to high enantioselectivities (18–97 % ee) (Scheme 8) [73].

In this case, the proposed mechanism is based on previous calculations performed with organocatalyst **6**·TFA for the Michael addition of 1,3-dicarbonyl compounds to maleimides (Fig. 9). The bifunctional feature of **6**·TFA could be explained by the formation of a intermediate B by formation of two hydrogen bonds with the β-keto ester of one of the 2-aminobenzimidazole unit and one hydrogen bond of the protonated 2-aminobenzimidazole unit with the benzylic alcohol. After formation of the carbenium ion and therefore the corresponding ion pair, takes place the enantioselective S_N1 reaction (Fig. 11) [73].

Recently, a prolinamide **18** and a pyrrolidine **19** bearing a 2-aminobenzimidazole unit were employed as chiral organocatalysts for the conjugate addition of cyclohexanone to β-nitrostyrene affording the corresponding adduct in 20 % and 98 % ee, respectively [75]. However, **18** has shown excellent catalytic



Scheme 7: Enantioselective alkylation of carbon nucleophiles with bis[4-(dimethylamino)-phenyl]methanol.



Scheme 8: Enantioselective alkylation of carbon nucleophiles with thioxanthydrol.

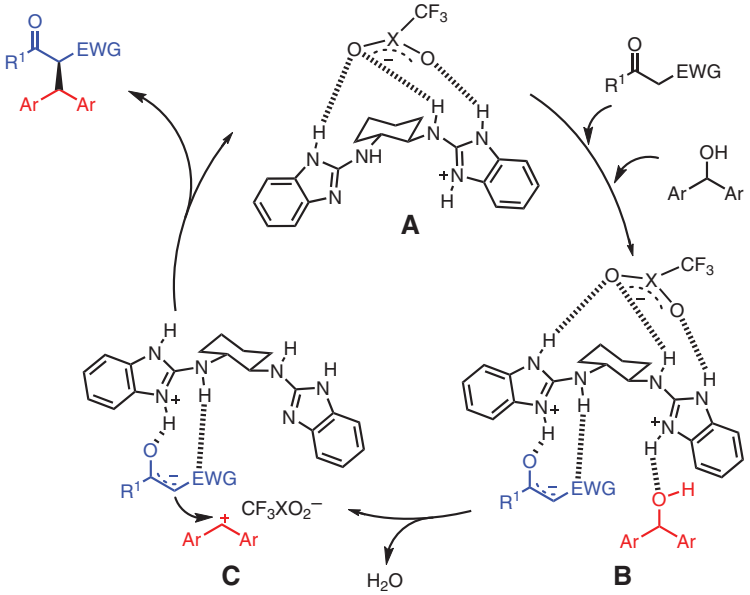


Fig. 11: Proposed mechanism for the enantioselective S_N1 reaction with benzylic alcohols.

activity in the aldol reaction much better than other related prolinamide-guanidine type derivatives **20–22** (Fig. 12) [76].

Chiral 2-aminopyrimidines

The development of rigid guanidine-type hydrogen bonding bifunctional organocatalysts move us to design 2-aminopyrimidines bonded to *trans*-cyclohexane-1,2-diamines as a chiral scaffold. We have synthesized two type of 2-aminopyrimidine organocatalysts **7** [77] and **8** [78] in order to study their catalytic activity in aldol reactions and in conjugate additions, respectively (Fig. 1). Diastereomeric prolinamides **7a** and **7b** were prepared by reaction of *N*-Boc protected (*R*,*R*)- and (*S*,*S*)-*trans*-cyclohexane-1,2-diamine with 2-chloropyrimidine followed by Boc-deprotection. Subsequent amidation with *N*-Boc-(*S*)-proline in the presence of ethyl chloroformate and final *N*-Boc deprotection provide these prolinamide-pyrimidines in 40 % overall yield (Scheme 9) [77].

As a benchmark reaction cyclohexanone was allowed to react with 4-nitrobenzaldehyde. This direct aldol reaction was performed under solvent-free conditions [79] in the presence of hexanedioic acid (HDA, 10 mol %) as cocatalyst. 12 equiv. of H_2O at 10 °C during 1 day. Both organocatalysts **7a** and **7b** (10 mol %) gave the corresponding aldol in similar yields and diastereomeric ratios, being **7b** (97 % ee) slightly better than **7a** (90 % ee) (Scheme 10). Therefore, the absolute configuration of the aldol was determined mainly by the prolinamide unit. For the recovery of catalyst **7b** the reaction was scaled up to 1 g scale giving, after extractive work-up with 2 M NaOH, the aldol in 51/1 *anti/syn* ratio and the *anti* isomer in 95 % ee and the organocatalysts in 87 % yield were isolated [77].

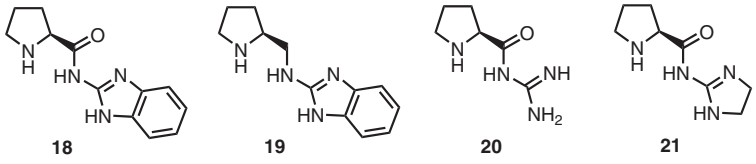
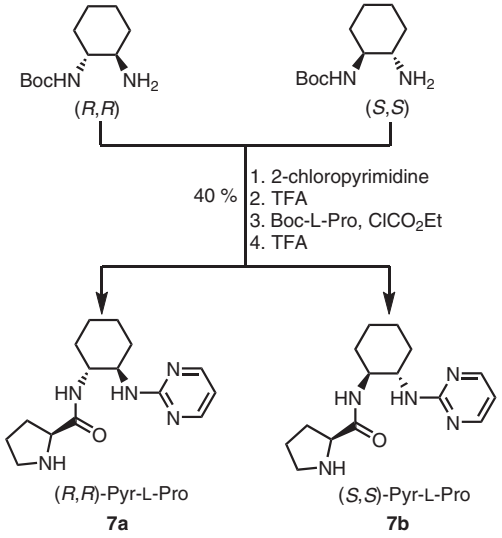
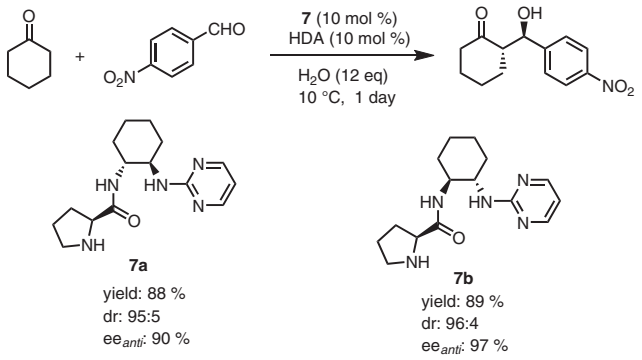


Fig. 12: Proline-guanidine type organocatalysts.



Scheme 9: Synthesis of prolinamide-pyrimidine organocatalysts **7**.

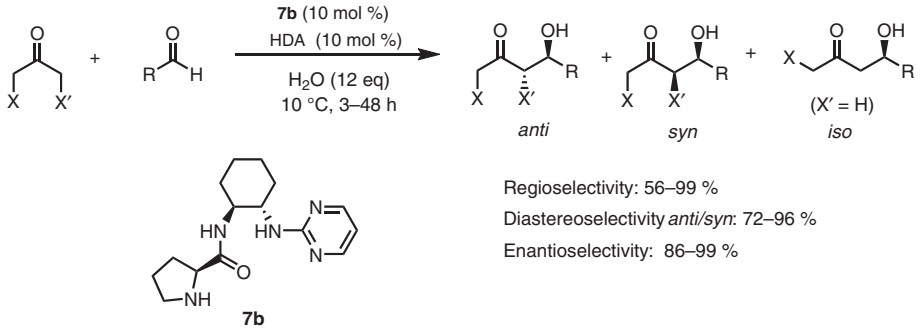


Scheme 10: Intermolecular direct aldol reaction organocatalyzed by **7a** and **7b**.

The scope of the intermolecular aldol reaction was studied with organocatalyst **7b** using different ketones as donors and aldehydes as acceptors obtaining the aldols in 56–99 % regioselectivity range, 72–96 % *anti*/*syn*-diastereoselectivity and 86–99 % enantioselectivity (Scheme 11). The selected example is, the protected D-*erythro*-pentos-4-ulose (68 % yield, 90 % de, 89 % ee_{anti}) obtained from protected 1,3-dihydroxyacetone and 2,2-dimethoxyacetaldehyde in better yield and enantioselectivity than with L-Pro under the same reaction conditions (47 %, 90 % de, 83 % ee) [77].

From DFT calculations the distances between the two hydrogens in the 2-aminopyrimidine unit are variable in the range of 2.1–3.0 Å. Calculations for the reaction of cyclohexanone with 4-nitrobenzaldehyde, in order to obtain insight about the mechanism and the origin of the enantioselectivity with both catalysts, were designed. Geometry optimization was performed at the B3LYP/6-31+G** level of theory [80–82] in a solvent model system (CPCM, water as solvent) [83, 84]. Single point energies were obtained for the optimized structures at the M06-2X/6-311+G** level [85]. The computed Ha–O and Hc–O bond distances (1.8 Å and 1.6 Å, respectively) are very similar in both structures TSA-*anti* and TSA-*syn* for enamine A formed with organocatalysts **7a** (Fig. 13). The difference in energy is 0.7 or 2.7 kcal/mol depending on the computational model, M06-2X/6-311+G** M06-2X/6-311+G** or B3LYP, respectively. In the case of enamine B formed with organocatalyst **7b** a different orientation of the NH groups was observed, being Ha and Hb better suited for carbonyl activation by hydrogen bonding than Ha and Hc. In this case, the energy difference is significantly increased to 4.4 and 7.7 kcal/mol. In the late case the 2-aminopyrimidine unit forms only one hydrogen bond [77].

For the intramolecular aldol Hajos–Parrish–Eder–Sauer–Weichert (HPESW) reaction, the Wieland–Mischer ketone, a valuable intermediate for steroid synthesis, was prepared using both diastereomeric organocatalysts **7** under solvent-free conditions (Scheme 12) [77]. The enantioselectivity was slightly better with **7a** (89 %) than with **7b** (86 %) and shorter reaction time was observed (10 h towards 20 h). In this case, **7a** was recovered in 79 % yield after extractive work-up. Another examples of this HPESW reaction by using organocatalyst **7a** are shown in Scheme 12.



Scheme 11: Intermolecular aldol reaction with organocatalyst **7b**.

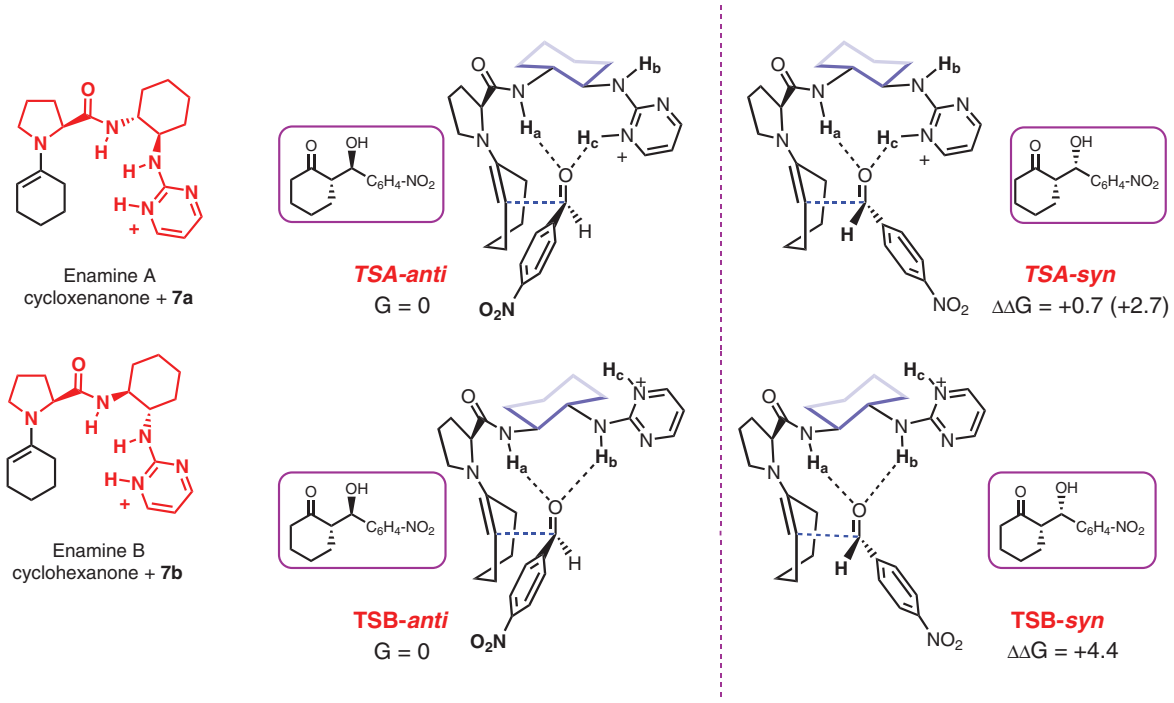
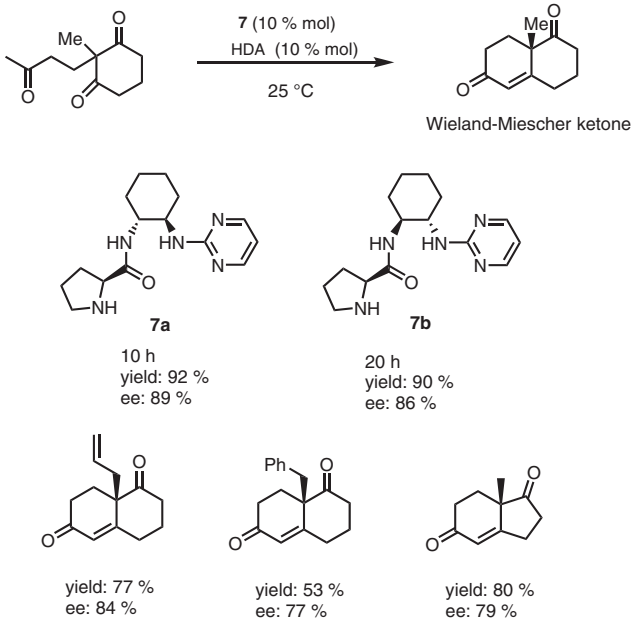


Fig. 13: Transition states for the aldol reaction of cyclohexanone with 4-nitrobenzaldehyde organocatalyzed by **7a** and **7b**.

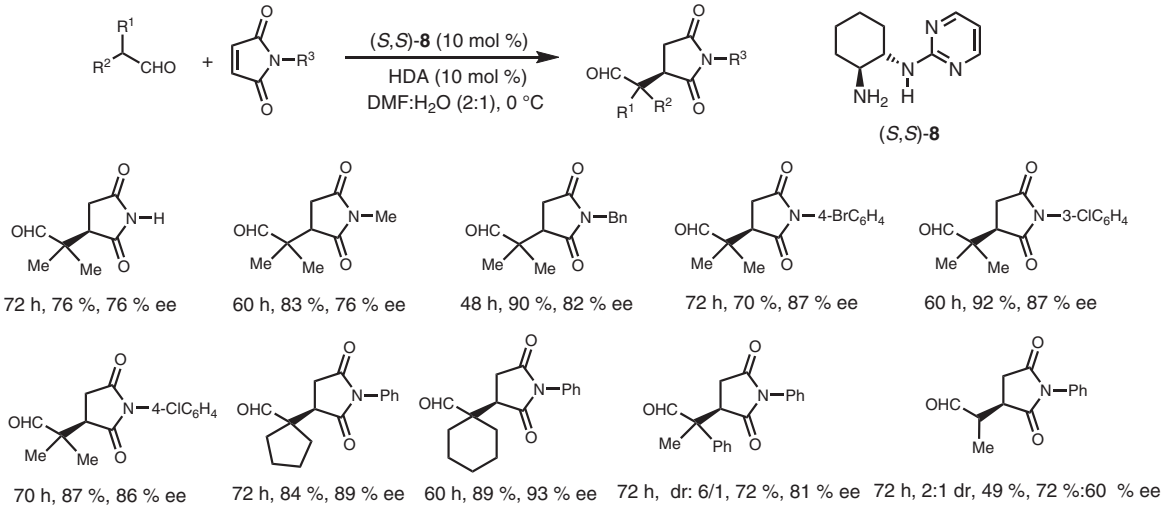


Scheme 12: Intramolecular aldol reactions with organocatalysts **7**.

The primary amine-2-aminopyrimidine organocatalysts **8**, prepared according to the procedure described in Scheme 9 in 65 % yield, were assayed in the conjugate addition of aldehydes to maleimides. For the optimization of the reaction conditions the addition of isobutyraldehyde to *N*-phenylmaleimide was chosen as the benchmark reaction. It was found that aqueous DMF at 0 °C gave the corresponding enantiomeric adducts in 83 % yield and 88 % ee by using the (*R*,*R*)-**8** or the (*S*,*S*)-**8** (10 mol %) and HDA (10 mol %) as a co-catalyst.

The scope of the reaction was studied with different aldehydes and maleimides affording the resulting succinimides in 70–92 % yield and 78–93 % ee (Scheme 13) [78]. These results were better than those results with (*S*,*S*)-**5a** (Scheme 5).

For the DFT calculations, the structures were initially optimized by using density functional theory (DFT) with the B3LYP [80–82] as implemented in Gaussian 09, combined with the 6-31G** basis set. Further re-optimization at M06-2X/6-311++G** level of theory [83] were carried out, including polarization functions for a better description of the hydrogen bond activations. It was found that no internal hydrogen bonds are taking place in this conjugate addition due to the use of aqueous solvents. Furthermore, a number of transition states lacking any internal H-bond were located, and the two lowest in energy among them, are shown in Fig. 4. Both structures lead to the formation of the *R*-enantiomer. Their charge separation (developing negative charge in the carbonyl oxygen and positive in the enamine-nitrogen) is very high, inducing a polar structure, that would be better stabilized in polar solvents. The energy differences between gas phase and water, ca. 2 kcal/mol, are significant and could justify an increase reactivity of around two orders of magnitude. Also, the two values for **TS-R$_1$** are lower than the corresponding values for **TS-R$_2$**, indicating that the former is operative in the mechanism leading to the *R*-enantiomer. Thus, in this case the 2-aminopyrimidine unit shows only steric hindrance in the transition state (Fig. 14) [78].



Scheme 13: Conjugate addition of aldehydes to maleimides organocatalyzed by the primary amine-2-aminopyrimidine (*S*,*S*)-**8**.

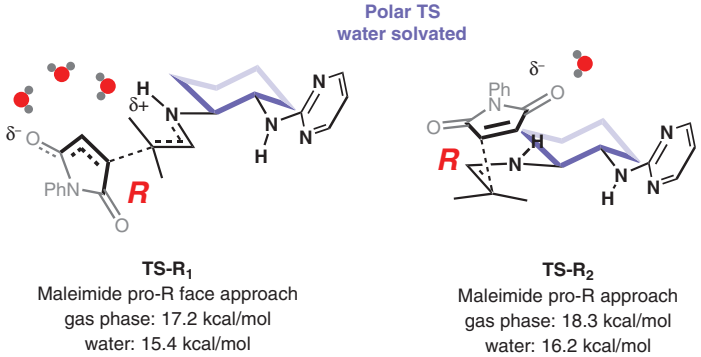


Fig. 14: Computed activation energies for the transition states **TS-R$_1$** and **TS-R$_2$** in the gas phase and water models for the addition of isobutyraldehyde to *N*-phenylmaleimide organocatalyzed by (*S*,*S*)-**5a**.

Conclusions

The 2-aminobenzimidazole unit has shown excellent dual hydrogen bonding capability as a Brønsted base. In the case of enantio-catalyzed conjugate additions or S_N1 reactions, the 1,3-dicarbonyl compound is deprotonated by this 2-aminobenzimidazole fragment. With respect to the electrophile, for the conjugate addition to nitroalkenes, the protonated dimethylamino unit forms a hydrogen bond with the nitro group, in the case of maleimides a hydrogen bond is formed with the protonated 2-aminobenzimidazole unit. For the S_N1 reaction the protonated 2-aminobenzimidazole unit could form the corresponding benzylic carbocation acting as a Brønsted acid. According to the calculations the conjugate addition of aldehydes to nitroalkenes and maleimides takes place by enamine formation and double hydrogen bonding with the Michael acceptor by the 2-aminobenzimidazole unit. However, in the case of the aldol reaction organocatalyzed by 2-aminopyrimidine prolinamides the activation of the aldehyde acceptor occurs by formation of one hydrogen bond from the protonated prymidine and the other from the prolinamide. However, the 2-aminopyrimidine unit in the enantio-catalyzed conjugate addition of aldehydes to maleimides, no hydrogen bonds were observed acting as a face blocking group in the TS. The presence of the chiral *trans*-cyclohexane-1,2-diamine scaffold controls the enantioselectivity of all the described processes.

Acknowledgments: The Spanish Ministerio de Ciencia e Innovación (MICINN) (projects CTQ2010-20387, and Consolider Ingenio 2010, CSD2007-00006), the Spanish Ministerio de Economía y Competitividad (MINECO) (projects CTQ2013-43446-P and CTQ2014-51912-REDC), FEDER, the Generalitat Valenciana (PROMETEO 2009/039 and PROMETEOII/2014/017), the Basque Government (GV Grant IT-291-07), the FP7 Marie Curie Actions of the European Commission via the ITN ECHONET network (MCITN-2012-316379) and the Universities of Alicante and Basque Country are gratefully acknowledged for financial support. We also thank for technical and human support provided by IZO-SGI SGIker of UPV-EHU and European funding (ERDF and ESF). We thank all the collaborators that have participate in this subject.

References

[1] M. S. Taylor, E. N. Jacobsen. *Angew. Chem. Int. Ed*. **45**, 1520 (2006).
[2] X. Xu, W. Wang. *Chem. Asian J*. **3**, 516 (2008).
[3] M. Petri, M. Pihko (Eds.). *Hydrogen Bonding in Organic Synthesis*, Wiley-VCH, Weiheim (2009).
[4] K. Maruoka (Ed.). *Science of Synthesis, Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysts, and Additional Topics*, Thieme, Stuttgart (2012).
[5] L. Albrecht, H. Jiang, K. A. Jørgensen. *Chem. Eur. J.* **20**, 358 (2014).
[6] C. L. Cao, M.-C. Ye, X.-L. Sun, Y. Tang. *Org. Lett.* **8**, 2401 (2006).
[7] Y.-J. Cao, H.-H. Lu, Y.-Y. Lai, L.-Q. Lu, W.-J. Xiao. *Synthesis* 3795 (2006).
[8] Y.-J. Cao, Y.-Y. Lai, X. Wang, Y.-J. Li. W.-J. Xiao. *Tetrahedron Lett.* **48**, 21 (2007).
[9] T. Okino, Y. Hoashi, Y. Takemoto. *J. Am. Chem. Soc.* **125**, 12672 (2003).
[10] T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto. *J. Am. Chem. Soc.* **127**, 119 (2005).
[11] For a review, see: O. V. Serdyuk, C. M. Heckel, S. S. Tsogoeva. *Org. Biomol. Chem.* **11**, 7051 (2013).
[12] A. G. Doyle, E. N. Jacobsen. *Chem. Rev.* **107**, 5713 (2007).
[13] R. Chinchilla, C. Nájera, P. Sánchez-Agulló. *Tetrahedron: Asymmetry* **5**, 1393 (1994).
[14] E. J. Corey, H. J. Grogan. *Org. Lett*. **1**, 157 (1999).
[15] T. Ishikawa, T. Isobe. *Chem. Eur. J.* **8**, 553 (2002).
[16] D. Leow, C.-H. Tan, *Synlett* 1589 (2010).
[17] T. Ishikawa. *Chem. Pharm. Bull*. **58**, 1555 (2010).
[18] K. Nagasawa, Y. Sohtome. *Science of Synthesis, Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysts, and Additional Topics*, K. Maruoka (Ed.), Thieme, Stuttgart (2012).
[19] P. Selig. *Synthesis* **45**, 703 (2013).
[20] A. Ávila, R. Chinchilla, C. Nájera. *Tetrahedron: Asymmetry* **23**, 1625 (2012).
[21] A. Ávila, R. Chinchilla, E. Gómez-Bengoa, C. Nájera. *Eur. J. Org. Chem*. 5085 (2013).
[22] A. Ávila, R. Chinchilla, B. Fiser, E. Gómez-Bengoa, C. Nájera. *Tetrahedron: Asymmetry* **25**, 462 (2014).
[23] D. Uraguchi, Y. Ueki, T. Ooi. *J. Am. Chem. Soc.* **130**, 14088 (2008).
[24] D. Uraguchi, Y. Ueki, T. Ooi. *Science* **326**, 120 (2009).

[25] D. Uraguchi, D. Nakashima, T. Ooi. *J. Am. Chem. Soc.* **131**, 7242 (2009).
[26] M. Ganesh, D. Seidel. *J. Am. Chem. Soc.* **130**, 16464 (2008).
[27] J. P. Malerich, K. Hagihara, V. H. Rawal. *J. Am. Chem. Soc.* **130**, 14416 (2008).
[28] Y. Zhu, J. P. Malerich, V. H. Rawal. *Angew. Chem. Int. Ed*. **49**, 153 (2010).
[29] W. Zhuang, T. B. Poulsen, K. A. Jørgensen. *Org. Biomol. Chem.* **3**, 3284 (2005).
[30] T. Schuster, M. Kurz, M. W. Göbel. *J. Org. Chem.* **65**, 1697 (2000).
[31] B. M. Nugent, R. A. Yoder, J. N. Johnston. *J. Am. Chem. Soc.* **126**, 3418 (2004).
[32] Z. Tang, L.-F. Cun, X. Cui, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong. *Org. Lett.* **8**, 1263 (2006).
[33] N. Takenaka, R. S. Sarangthem, S. K. Seerla. *Org. Lett.* **9**, 2819 (2007).
[34] A. Singh, R. A. Yoder, B. Shen, J. N. Johnston. *J. Am. Chem. Soc.* **129**, 3466 (2007).
[35] A. Singh, J. N. Johnston. *J. Am. Chem. Soc.* **130**, 5866 (2008).
[36] A. S. Hess, R. A. Yoder, J. N. Johnston. *Synlett* 147 (2006).
[37] T. Inokuma, M. Furukawa, T. Uno, Y. Suzuki, K. Yoshida, Y. Yano, K. Matsuzaki, Y. Takemoto. *Chem. Eur. J.* **17**, 10470 (2011).
[38] Y. Kobayashi, Y. Taniguchi, N. Hayama, T. Inokuma, Y. Takemoto. *Angew. Chem. Int. Ed*. **52**, 11114 (2013).
[39] U. Scheffer, A. Strick, V. Ludwig, S. Peter, E. Kalden, M. W. Göbel. *J. Am. Chem. Soc.* **127**, 2211 (2005).
[40] F. M. Muñiz, V. Alcázar, F. Sanz, L. Simón, A. L. Fuentes de Arriba, C. Raposo, J. R. Morán. *Eur. J. Org. Chem*. 6179 (2010).
[41] F. Janssens, J. Torremans, M. Janssen, R. A. Stok-Broekx, M. Luyckx, P. A. Janssen. *J. Med. Chem*. **28**, 1925 (1985).
[42] W. Nawrocka. *Bull. Chim. Farm*. **135**, 18 (1996).
[43] P. Winstanley. *Lancet* **352**, 1080 (1998).
[44] A. Carpio, *J. Neurol., Neurosurg. Psychiatry* **66**, 411 (1999).
[45] R. J. Snow, M. G. Cardozo, T. M. Morwick, C. A. Busacca, Y. Dong, R. J. Eckner, S. Jacober, S. Jakes, S. Kapadia, S. Lukas, M. Panzenbeck, G. W. Peet, J. D. Peterson, A. S. Prokopowicz, III, R. Sellati, R. M. Tolbert, M. A. Tschantz, N. Moss. *J. Med. Chem*. **45**, 3394 (2002).
[46] A. Kling, G. Backfisch, J. Delzer, H. Geneste, C. Graef, W. Hornberger, U. Lange, A. Lauterbach, W. Seitz, T. Subkowski. *Biorg. Med. Chem*. **11**, 1319 (2003).
[47] C. G. O'Neill, D. Slipetz, J. Wang. *Biorg. Med. Chem. Lett*. **14**, 3195 (2004).
[48] For a review on chiral benzimidazoles, see: C. Nájera, M. Yus. *Tetrahedron Lett.* **56**, 2623 (2015).
[49] D. Almaşi, D. A. Alonso, E. Gómez-Bengoa, C. Nájera. *J. Org. Chem*. **74**, 6163 (2009).
[50] A. Hamza, G. Schubert, I. Pápai. *J. Am. Chem. Soc.* **128**, 13151 (2006).
[51] L. Zhang, M.-M. Lee, S.-M. Lie, J. Lee, M. Cheng, B.-S. Jeong, H.-g. Park, S.-s. Jew. *Adv. Synth. Catal*. **351**, 3063 (2009).
[52] M. Lee, L. Zhang, Y. Park, H.-g. Park. *Tetrahedron* **68**, 1452 (2012).
[53] P. Trillo, M. Gómez-Martínez, D. A. Alonso, A. Baeza. *Synlett* **26**, 95 (2015).
[54] T. de A. Fernandes, P. Vizcaíno-Milla, J. M. J. M. Ravasco, A. Ortega-Martínez, J. M. Sansano, C. Nájera, P. R. R. Costa, B. Fiser, E. Gómez-Bengoa. *Tetrahedron: Asymmetry* **27**, 118 (2016).
[55] For a recent review, see: P. Chauhan, J. Kaur, S. S. Chimni. *Chem. Asian J.* **8**, 328 (2013).
[56] A. Fredenhagen, S. Y. Tamura, P. T. M. Kenny, H. Komura, Y. Naya, K. Nakanishi, K. Nishiyama, M. Sugiura, H. Kita. *J. Am. Chem. Soc.* **109**, 4409 (1987).
[57] C. Malochet-Grivois, C. Roussakis, N. Robillard, J. F. Biard, D. Riou, C. Debitus, J. F. Verbist. *Anti-Cancer Drug Des*. **7**, 493 (1992).
[58] Y. Ando, E. Fuse, W. D. Figg. *Clin. Cancer Res*. **8**, 1964 (2002).
[59] C. Freiberg, N. A. Brunner, G. Schiffer, T. Lampe, M. Polmann, D. Habich, K. Ziegelbauer. *J. Biol. Chem*. **279**, 26066 (2004).
[60] M. Isaka, N. Rugseree, P. Maithip, P. Kongsaeree, S. Prabpai, Y. Thebtaranonth. *Tetrahedron* **61**, 5547 (2005).
[61] J. Uddin, K. Ueda, E. R. O. Siwu, M. Kita, D. Uemura. *Biorg. Med. Chem*. **14**, 6954 (2006).
[62] For selected examples, see: E. J. Yoo, M. Wasa, J.-Q. Yu. *J. Am. Chem. Soc.* **132**, 17378 (2010).
[63] S. Das, D. Addis, L. R. Knöpke, U. Bentrup, K. Junge, A. Brückner, M. Beller. *Angew. Chem. Int. Ed*. **50**, 9180 (2011).
[64] E. Gómez-Torres, D. A. Alonso, E. Gómez-Bengoa, C. Nájera. *Org. Lett.* **13**, 6106 (2011).
[65] E. Gómez-Torres, D. A. Alonso, E. Gómez-Bengoa, C. Nájera. *Eur. J. Org. Chem*. 1434 (2013).
[66] D. Almaşi. PhD Thesis, University of Alicante (2009).
[67] J. Muzart. *Eur. J. Org. Chem*. **2007**, 3077 (2007).
[68] E. Emer, R. Sinisi, M. Guiteras-Capdevilla, D. Petruzzielo, F. DeVicentis, P. G. Cozzi. *Eur. J. Org. Chem*. **2011**, 647 (2011).
[69] B. Biannic, A. Aponick. *Eur. J. Org. Chem*. 3605 (2011).
[70] A. Baeza, C. Nájera. *Synthesis* **46**, 25 (2014).
[71] M. Shibata, M. Ikeda, K. Muyoyama, Y. Miyake, Y. Nishibayashi. *Chem. Commun*. **48**, 9528 (2012).
[72] P. Trillo, A. Baeza, C. Nájera. *Adv. Synth. Catal*. **355**, 2815 (2013).
[73] P. Trillo, A. Baeza, C. Nájera. *Synthesis* **46**, 3399 (2014).
[74] Electrophilicity parameter in Mayr's scales: S. Minegishi, H. Mayr. *J. Am. Chem. Soc.* **125**, 286 (2003).
[75] J. Lin, H. Tian, Y.-J. Jiang, W.-B. Huang, L.-Y. Zheng, S.-Q. Zhang. *Tetrahedron: Asymmetry* **22**, 1434 (2011).
[76] G. Tang, U. Gün, H.-J. Altenbach. *Tetrahedron* **68**, 10230 (2012).
[77] P. Vizcaíno-Milla, J. M. Sansano, C. Nájera, B. Fiser, E. Gómez-Bengoa. *Eur. J. Org. Chem*. 2614 (2015).
[78] P. Vizcaíno-Milla, J. M. Sansano, C. Nájera, B. Fiser, E. Gómez-Bengoa. *Synthesis* **47**, 2199 (2015).

[79] A. Bañón-Caballero, G. Guillena, C. Nájera. *Mini-Rev. Org. Chem*. **11**, 118 (2014).
[80] C. Lee, W. Yang, R. G. Parr. *Phys. Rev. B* **37**, 785 (1988).
[81] A. D. Becke. J. *Chem. Phys*. **98**, 5648 (1993).
[82] W. Kohn, A. D. Becke, R. G. Parr. *J. Phys. Chem*. **100**, 12974 (1996).
[83] E. Cancés, B. Mennucci, J. Tomasi. *J. Chem. Phys*. **107**, 3032 (1997).
[84] J. Tomasi, B. Mennucci, E. Cancés. *J. Mol. Struct.: THEOCHEM* **464**, 211 (1999).
[85] Y. Zhao, D. G. Truhlar. *Theor. Chem. Acc*. **120**, 215 (2008).