Mimicking Enzymes: Asymmetric Induction Inside a Carbamate-Based Steroidal Cleft.

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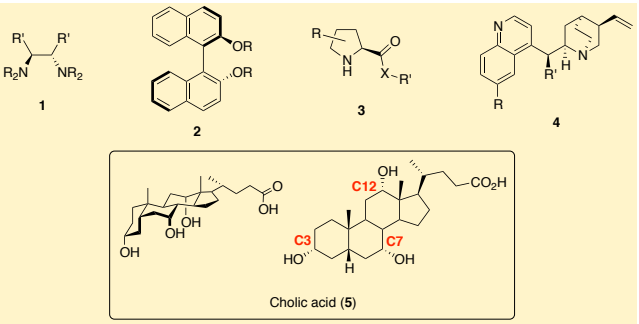
Supporting Information Placeholder

ABSTRACT: A novel tripodal carbamate-based steroidal architecture works as an efficient catalyst on the Michael-type addition reaction between dimethyl malonate and nitrostyrene. Its action mode has been disclosed by quantum chemical calculations. It comprises the preorganization and confinement of the reagents within the active chiral cavity of the steroid, which are held together by means of cooperative H-bond contacts.

Organocatalysis consists in the acceleration of chemical reactions employing small organic frameworks typically assembled from C, H, O, N, S and P atoms.[1] Some privileged structures have been widely used for building up asymmetric organocatalysts: derivatives of 1,2-diamines, **1**, BINOL, **2**, proline or other natural amino acids, **3**, and cinchona alkaloids, **4** (Figure 1). Alternative chiral scaffolds are extensively sought after. Herein we describe the ability of a steroidal platform, based on cholic acid, **5**, to work as an enantioselective organocatalyst that makes use of cooperative weak H-bonding interactions.

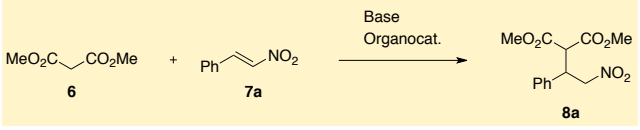
Figure 1. General structure of derivatives of 1,2-diamine, **1**, BINOL, **2**, proline, **3**, and cinchona alkaloids, **4**, typically used as organocatalysts. Structure of cholic acid, **5**, with its numbering (in red).



Along the last decades the group of Davis,[2] and others,[3] have demonstrated ways in which cholid acid, **5**, the archetypal bile acid scaffold, can be converted into receptors for anions and carbohydrates. However, to our knowledge, steroidal derivatives have never been employed in organocatalysis.[4] Cholic acid is a cheap, naturally occurring molecule, being one of the major bile acids produced by the liver of mammals. Moreover, it is inherently chiral. It would be remarkable transforming this architecture into an organic framework capable of operating as an efficient asymmetric catalyst.

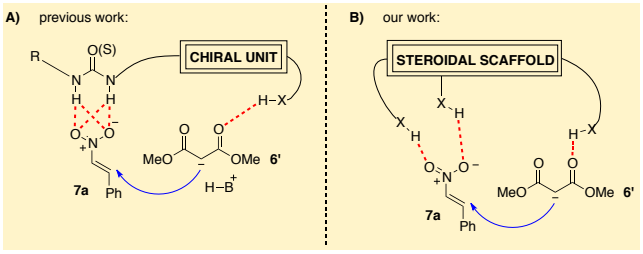
As a proof of concept we have examined the Michael-type addition of dimethyl malonate, **6**, to nitrostyrene, **7a**, in the presence of a base, to render the corresponding adduct **8a** (Scheme 1). This particular reaction is recognized as a playground to evaluate the capabilities of organocatalysts.

Scheme 1. General reaction scheme for the Michael-type addition of dimethyl malonate **6** to nitrostyrene **7a** to render product **8a**.



The organocatalysts previously employed on the reaction displayed on Scheme 1, normally constructed from backbones **1**-**4**, are equipped with guanidinium,[5] urea/thiourea,[6] squaramide moieties,[7] or 2-aminobenzimidazoles.[8] These motifs are capable of activating nitrostyrene **7a** through the formation of an array consisting of two parallel and contiguous H-bond contacts. Upon complexation the electrophilicity of **7a** is increased, becoming susceptible for the attack of a malonate anion (**6'**) previously generated from **6** by the action of a base.[9] Figure 2A represents this activation mode taking as an example an urea/thiourea motif.

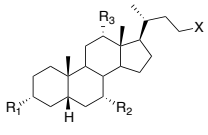
Figure 2. General activation mode of nitrostyrene **7a** by H-bonding with organocatalysts containing, for example, a urea or thiourea moiety. Malonate anion **6'** attacks on the activated alkene (**A**, left). Activation of nitrostyrene **7a** by multiple cooperative H-bond contacts established from a steroidal scaffold (**B**, right).



Avoiding the incorporation of the above mentioned double H-bond-donor motifs we decided to investigate the ability of steroidal polyols and carbamates as catalysts for the reaction displayed on Scheme 1. We envisioned these frameworks activating nitrostyrene through the establishment of simultaneous and cooperative, but spatially segregated, H-bond contacts triggered by the preorganization of the cholate platform (Figure 2, **B**). Such an approach resembles the activation mode of enzymes, which can fit and activate substrates within their active sites by means of multiple enzyme-substrate contacts, normally far apart in space.

Accordingly, triol **9** (methyl cholate) and diols **10-14** were readily prepared from cholic acid making use of previously described methodologies, or by conventional syntheses. Diol **15** corresponds to methyl deoxycholate, and **16** to methyl chenodeoxycholate. Phenyl carbamates **17-21** were easily afforded from some of these polyols (Figure 3).

Figure 3. Chemical structures of potential steroid-based catalysts **9-21**.

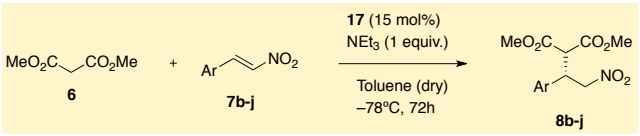


X = CO_2Me, R_1 = R_2 = R_3 = OH, **9**
X = CO_2Me, R_1 = OAc, R_2 = R_3 = OH, **10**
X = CO_2Me, R_1 = OBz, R_2 = R_3 = OH, **11**
X = CO_2Me, R_1 = OPiv, R_2 = R_3 = OH, **12**
X = CO_2Me, R_1 = OTBDMS, R_2 = R_3 = OH, **13**
X = CH_3, R_1 = H, R_2 = R_3 = OH, **14**
X = CO_2Me, R_1 = OH, R_2 = H, R_3 = OH, **15**
X = CO_2Me, R_1 = OH, R_2 = OH, R_3 = H, **16**

X = CO_2Me, R_1 = R_2 = R_3 = OC(O)NHPh, **17**
X = CO_2Me, R_1 = OAc, R_2 = R_3 = OC(O)NHPh, **18**
X = CH_3, R_1 = H, R_2 = R_3 = OC(O)NHPh, **19**
X = CO_2Me, R_1 = OC(O)NHPh, R_2 = H, R_3 = OC(O)NHPh, **20**
X = CO_2Me, R_1 = R_2 = OC(O)NHPh, R_3 = H, **21**

To our delight, after a profound screening of experimental parameters (see Supporting Information (SI) for details, Table SI_1 to SI_7) we found optimal conditions for the tripodal triscarbamate **17**. Thus, in the presence of steroid **17**, when a solution of **7a** in dry toluene, at –78ºC, was treated with **6** and dry NEt_3 the desired product **8a** was rendered in quantitative conversion and 91% *ee* (Table 1, entry 1). The stereochemical configuration of **8a** was confirmed as (*S*)-(+) by comparison with previously published HPLC data.[10] The stereoselectivity of the reaction is a consequence of a chiral relay from the cholic acid scaffold. More importantly, here we report for the first time the use of carbamate units as catalytic sites in organocatalysis. In the absence of steroid **17** the reaction between **6** and **7a** is inefficient (Table 1, entry 2). Catalyst **17** can be prepared in multigram scale from cholic acid **5** in two synthetic steps, with an overall yield of 71%.

Table 1. Synthesis of Michael adducts **8a-8j** catalyzed by cholic acid-derived steroidal triscarbamate **17**.[a]



entry	Ar	yield (%)[b]	*ee* (%)[c]
1	**7a**: C_6H_5	94	91
2[d]	**7a**: C_6H_5	3	-
3	**7b**: 4-F-C_6H_4	84	90
4	**7c**: 4-Cl-C_6H_4	99	89
5[e]	**7d**: 4-Br-C_6H_4	80	90
6[e]	**7e**: 4-OMe-C_6H_4	76	80
7[e]	**7f**: 4-Me-C_6H_4	65	85
8[e]	**7g**: 4-NO_2-C_6H_4	98	82
9[e]	**7h**: 4-Ph-C_6H_4	99	85
10	**7i**: 3-Cl-C_6H_4	96	86
11[e]	**7j**: 2-furyl	71	73

[a] General reaction conditions: aromatic nitroalkene **7a-j** (0.2 mmol), and organocatalyst **17** (0.03 mmol) were dissolved in dry toluene (1.6 mL), at –78 °C, before dimethyl malonate **6** (0.6 mmol) and dry NEt_3 (0.2 mmol) were added. The reaction mixtures were stirred for 72 h, then quenched with NH_4Cl (aq., sat.); [b] Isolated yield of analytically pure products **8a-j**; [c] Enantiomeric excess of analytically pure products **8a-j** as determined by chiral HPLC; [d] Reaction carried out without steroid **17**. [e] Reaction stirred for 7 days.

To establish the scope of our protocol a selection of aromatic nitroalkenes **7b-j**, bearing diverse functional groups and substitution patterns, were reacted with dimethyl malonate **6** under our best reaction conditions (Table 1, entries 3-11). All these reactions proceeded smoothly. The corresponding products **8b-j** could be isolated in good to high yield with reliable *ee* figures, ranging from 73 to 90%. Heteroaromatic nitroalkene **7j** was a suitable substrate for the steroidal catalyst (Table 1, entry 11). Some substrates required longer reaction times to achieve good conversions as a consequence of the limited solubility of the aromatic nitroalkenes in the reaction media (Table 1, entries 5-9, 11).

Aiming to shed light on the action mode of **17**, we next considered carrying out a series of quantum chemical

calculations employing both Density Functional (DFT) and Hartree-Fock (HF) levels of theory.

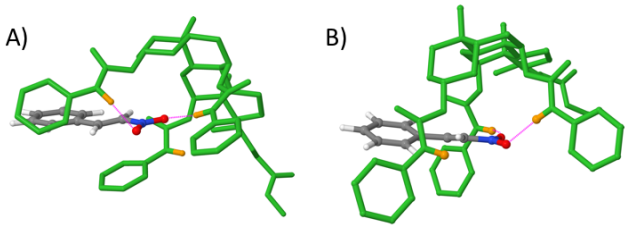
Initially, a study was undertaken to validate a set of functionals (B3LYP, M06-2X) and basis sets (cc-pVDZ, 6-31G*) in our system, employing the Gaussian09 program[11]. The M06-2X[12]/cc-pVDZ[13] combination afforded the best results, thus it was chosen for the rest of the study (see SI for details).All calculation were carried out in gas phase since the experimental solvent, toluene has a small dielectric constant.

For the non-catalyzed Michael-type addition reaction between **6** and **7a** a mean activation energy of +3.3 kcal/mol was computed for the formation of either (*R*)- or (*S*)-**8a** in the gas phase (SI).[14] In the case of the catalyzed reaction the catalytic effect as well as the stereo-preference of triscarbamate **17** towards the formation of product (*S*)-**8a** were studied by theoretical means.

The tripodal catalyst **17** displays an architecture resembling that of cholic acid, in which the steroidal backbone is barely altered. The carbamate moieties are oriented towards the inner part of the steroid, giving rise to the formation of a chiral cavity. Within this cavity there are three H-bond donating groups that constitute the active site of triscarbamate **17**, which is supposed to be responsible for its observed catalytic activity (SI, Figure SI_1).

With the aim of rationalizing the experimentally observed stereoselectivity for the addition reaction between **6** and **7a** in the presence of the steroidal catalyst, the binding energies of triscarbamate **17** and the species involved in the reaction were analyzed. DFT calculations revealed that nitrostyrene **7a** docks inside the cavity of **17** adopting two possible minimum energy conformations: supramolecular complex **I** and **II**, sustained by H-bond contacts and π-π stacking interactions (Figure 4). The net binding energies of the steroid with nitrostyrene **7a** account for –21.46 kcal/mol and –14.88 kcal/mol, for complex **I** and **II** respectively. This implies that complex **I** is significantly more stable than complex **II**. Nevertheless, as it can be observed from Figure 4, upon the formation of complex **I** the cavity of the steroid gets partly closed, causing a significant steric hindrance, which overall prevents the methyl malonate anion **6'** form approaching nitrostyrene in a favorable conformation. As a consequence, the Michael-type addition reaction proceeds *via* complex **II**, rendering preferentially product (*S*)-**8a** resulting from the attack of **6'** to the available *si*-face of nitrostyrene **7a**, which is in agreement with the experimental observations.

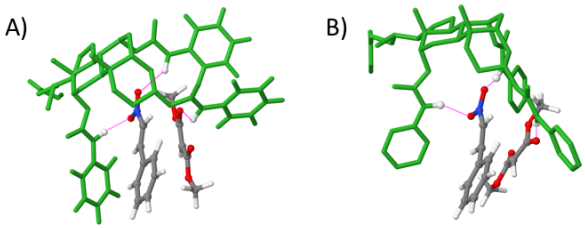
Figure 4. Representations of the optimized structures of supramolecular complexes [**7a•17**] **I** and **II** (M06-2X/cc-pVDZ). A) complex **I**. B) complex **II**. The steroidal backbone is colored green (H atoms are omitted for clarity). C atoms are colored grey, O atoms are colored red, N atoms are colored blue, H atoms are colored white. Carbamate H atoms are colored orange. H-bonds are represented by dashed lines.



The influence of steroid **17** in the reactivity and in the activation energy of the Michael addition was also evaluated. IRC calculations showed a large decrease in the activation energy in the presence of the catalyst, leading to a virtually barrierless process (see SI). This finding supports the catalytic effect of the steroid.

Figure 5B presents the minimum energy transition state (TS) found for the attack of dimethyl malonate anion **6'** to nitrostyrene **7a** in the presence of the steroidal catalyst **17**. Besides the two H-bond contacts established between the NO_2 moiety of nitrostyrene **7a** and the N-H motifs of the carbamates borne on C7 and C12, which are preserved, there is also a H-bond interaction between the N-H of the C3 carbamate and one carbonyl O atom of anion **6'**.

Figure 5. A) Calculated geometry for the pre-oganized reagents **6'** and **7a** inside the cavity of steroidal triscarbamate **17**. B) Calculated TS for the reaction between dimethyl malonate anion **6'** and nitrostyrene (**7a**) catalyzed by steroid **17**. Coloring as in Figure 4.



The nature of the catalytic phenomenon can be characterized by considering the initial disposition of the reagents within the active cavity. As it can be observed from Figure 4, the formation of complex **II** [**7a•17**] arranges the steroidal cavity leaving space for anion **6'**, which can be accommodated by a further H-bond contact between the NH proton of the C3 carbamate and anion **6'**. By these means, anion **6'** and **7a** get confined and pre-organized inside the cavity of **17** prior to the C-C bond-forming process (Figure 5A). In this process, the reactivity of **7a** towards a nucleophilic attack**,** as revealed through its electrophilicity index (SI, Table X) is markedly enhanced. Altogether, These reagents disposition is strikingly close to the one compelled by the TS (Figure 5B). Accordingly, tripodal steroid **17** presents a significant conformational plasticity: the rotation and folding of its C3, C7 and C12 carbamate appendages allow reagents **6'** and **7a** to reach the TS in a near-attack-conformation. This operational

mode resembles that of some enzymes, such as chorismate mutase.[15]

To conclude, a steroidal scaffold has been elaborated into an asymmetric catalyst for the first time. It consists of a cholic acid derivative decorated with three carbamate appendages. Remarkably, this is also the first occasion in which carbamate units have been disclosed as active sites for organocatalytic transformations. As a proof of concept, our steroidal catalyst has proved its ability on the Michael-type addition reaction between nitrostyrene and dimethyl malonate. The corresponding products are rendered with high yield and enantioselectivity. The working principle of our catalyst has been elucidated with the aid of quantum chemical calculations. It implies the preorganization and confinement of the reagents within the chiral cavity of the steroid in a conformation close to the TS, held up by three cooperative H-bond contacts. We are currently applying our steroidal catalyst **17**, and others, in different asymmetric organic transformations. Results will be reported in due course.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

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