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DFT analysis of a key step in the cinchona-mediated organocatalytic Michael-addition of nitromethane to 1,3-diphenylpropenone

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ABSTRACT

The potential of a series of cinchona-based organocatalyst candidates was investigated by comparative DFT analysis of the crucial bond-forming step of the enantioselective Michael addition of nitromethane to 1,3-diphenylpropenone. It was shown that the applied methods are feasible to investigate the influence of functional groups on the activation electron energy. Besides the well known interaction of the substrates with the urea and quinuclidine moiety the significance of π stacking- and H-bonding interactions between the electrophilic component and the catalyst are also pointed out. Due to the π stacking the replacement of the widely appreciated trifluoromethyl groups by nitro groups allows the interacting rings to get closer lowering the activation barrier of the crucial C–C bond formation step.

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1. Introduction

Organocatalysts have an advantage over the metal-based catalysts mainly due to their pronounced "greener" character. Moreover, the members of this catalyst family are generally non toxic, readily available, robust, convenient and easy-to-handle alternatives to the appropriate metal-containing counterparts with similar range of activities. For their biomimetic behavior they are often referred as artificial enzymes.

Three decades ago Wynberg and Hiemstra [1] demonstrated that the application of cinchona-based molecules as asymmetric organocatalysts is a promising choice of synthetic approaches in the field of enantioselective transformations. A number of easily available cinchona derivatives are known to efficiently catalyze a wide variety of reactions [2] due to their bifunctional character associated with the presence of suitably positioned Lewis-base (HOMO-elevating) and Lewis-acid (LUMO-lowering) regions in close proximity surrounded by chiral environment [3]. Since Curran and Kuo [4] developed a class of organocatalysts with diarylurea- and thiourea structures which were successfully employed in stereoselective radical allylation reactions. The robust, tunable and easily accessible catalysts are capable of bonding *via* two H-bonds [5] to the electrophilic component with Lewis base functionality lowering the energy of its LUMO [6]. Since nitroaromatics inhibit radical processes, trifluormethyl group was the suitable choice to be introduced into the aromatic ring enhancing the desired acidic character of the catalyst. N-Arylthioureas bearing electron-withdrawing substituents at the meta- and para-positions have a somewhat rigid conformation making the entropic effect more favorable in molecular recognition [7]. Wittkopp and Schreiner [8] has demonstrated that the activity of the catalyst can easily be fine-tuned by varying the N-aryl substituent. It has been shown that inside the N-3,5-*bis*-trifluoromethylphenyl substituted model the rigidity of the thiourea linker is enhanced by a hydrogen bond formed between the aryl hydrogen atom at position 2 and the negatively polarized sulfur centre [8]. In addition, the electron withdrawing substituents on the aryl moiety may also increase the acidity of the N–H groups in these models.

The first cinchona-based amine-thiourea catalysts were prepared parallel in four research groups [9] and it became evident that they promote a variety of asymmetric reactions like Michael-addition [10], aza-Henry reaction [11], Diels–Alder reaction [12], Mannich reaction [13] and interrupted Feist-Bénary reaction [14]. Moreover, the use of amine-thiourea catalysts proved to be highly beneficial in the total syntheses of natural products, e.g. rolipram [15] and nakadomarin A [16]. Although this class of catalysts has been quickly recognized and exploited by several researchers, to the best of our knowledge only a narrow range of aryl groups (phenyl [17], trifluoromethyl-phenyl [18] and the well-referred *bis*(trifluoromethylphenyl) were introduced in the catalyst candidates subjected to extensive evaluation. There are some examples for urea-based catalyst which are superior to their thiourea analogue [19] but they are of minor importance due to their decreased acidity and increased flexibility of the urea moiety.

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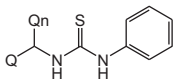
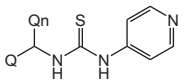
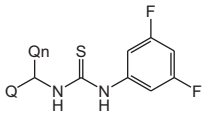
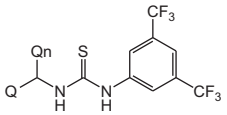
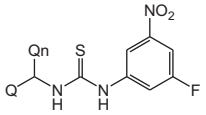
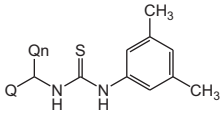
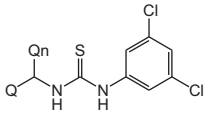
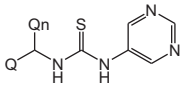
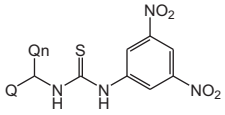
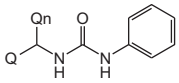
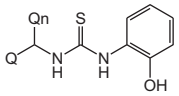
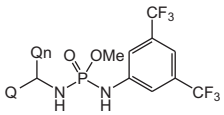
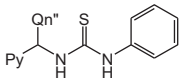
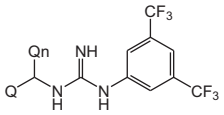
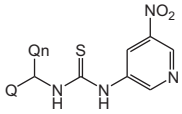
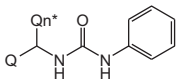
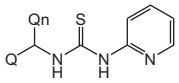
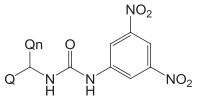
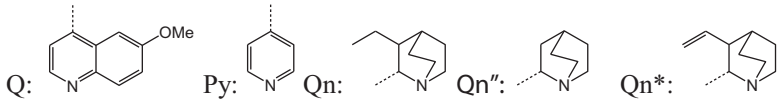
Table 1
Calculated activation energies (in kJ/mol) for the catalyst systems on three different levels.

Structure	Nr.	E_1	E_2	E_3	Structure	Nr.	E_1	E_2	E_3
	**1**	38.3	45.1	37.9		**10**	38.4	45.0	38.1
	**2**	35.2	42.5	35.0		**11**	32.4	39.8	32.2
	**3**	32.9	40.2	32..2		**12**	38.9	45.3	36.8
	**4**	35.5	42.6	35.5		**13**	34.6	41.9	33.9
	**5**	18.7	27.1	18.8		**14**	37.4	43.9	35.2
	**6**	75.5	82.2	74.2		**15**	57.7	64.3	55.0
	**7**	38.8	45.4	37.5		**16**	45.3	53.4	43.3
	**8**	30.3	37.9	30.0		**17**	37.5	44.1	35.5
	**9**	55.8	62.9	56.4		**19**	***26.5***	***34.3***	***25.4***

Abbrev.:



$E_1 = E_{act[6\text{-}311G(d)]}$ $E_2 = E_{act[6\text{-}311G(2df,p)]}$ $E_3 = E_{act[6\text{-}311G(d)IEFPCM]}$.

The field of cinchona-based amine-thiourea catalysts have profusely been reviewed by Connon [2] and Takemoto [20].

In this field the first mechanistic study on the addition of nitromethane to 1,3-diphenylpropenone catalyzed by cinchona organocatalysts was performed by Hamza et al. [21]. They suggested that the activation of the electrophilic component is achieved through the hydrogen bond interaction with the protonated quinuclidine ring, while the thiourea moiety is bonded to the nucleophilic methylene-nitronate. A year later confirming their former statements, the same research group published a further paper [22] on the recalculation of the activation energies associated with the same geometries by other DFT functionals and *ab initio* methods using more extended basis sets.

2. Computational details

Our primary purpose was to monitor some novel cinchona based organocatalyst candidates in a model reaction and make a proposal in which direction should these catalysts be improved. In order to reveal structure–reactivity relationships of basic importance we performed modeling study on the formation of the C–C bond, most important step of the overall reaction. First we searched for stationary points belonging to the catalyst-bonded complexes of the reactants and the products, respectively. For these calculations the aforementioned assembly of TS structures [21] and the coordinates of our minimal system **7** (Table 1) were chosen as starting points according to which our model systems were constructed. With the local minima in hands the transition states (TS) were located by QST3 method. In each case the intrinsic reaction coordinate (IRC) route was traced to make sure that the TS obtained by QST3 method really belongs to the targeted C-C bond forming channel. All of these calculations were made at the B3LYP/6-31G(d) level [23] of density functional theory. For the identified stationary points we performed single-point energy calculations using a reliable method (M06-2X/6-311G(d)) [22,24] in order to obtain more accurate electron energy values. To analyse the energy

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