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Solvent-Free Enantioselective Michael Reactions Catalyzed by a Calixarene-Based Primary Amine Thiourea

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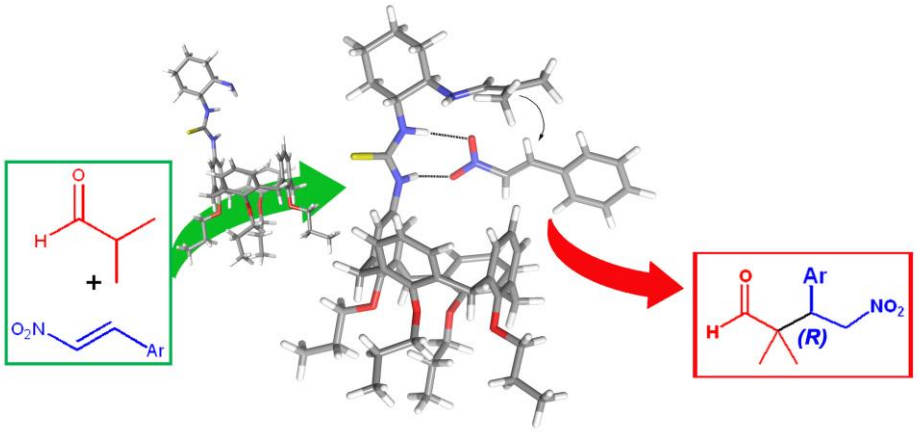

ABSTRACT: An upper-rim functionalized calix[4]arene based thiourea installed onto the (*R*,*R*)-1,2-cyclohexanediamine scaffold has been synthesized with a view to investigate its catalytic ability in enantioselective Michael additions. The reactions were found to conveniently proceed under solvent free conditions, observing good to high enantioselectivities. From this preliminary study, the calix[4]arene unit is likely to play a role in affecting the conversion and to a less extent to the stereochemical outcome of the reactions through van der Waals contacts and C–H···π interactions with the substrates.

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Introduction

One of the most powerful synthetic method for the enantioselective carbon-carbon bond formation from readily available carbonyl compounds is the Michael reaction.[1] In the last decades this fundamental synthetic process was intensively studied using bifunctional organocatalysts which can activate the reagents either via enamine or iminium ion intermediates (aminocatalysis)[2] and H-bonding interactions or under general acid-base catalysis.[3] Several examples illustrated the utility of proline and other chiral secondary and primary amine thioureas in stereoselective Michael reaction of aldehydes and ketones with different acceptors.[4] Most of the investigations reported focused on introduction of different chiral 1,2-diamine cores, bearing a thiourea moiety, often containing an electron-withdrawing-substituted phenyl group, with a view to enhance the H-bonding donor ability of the bifunctional promoter. Organocatalysts incorporating in the thiourea portion residues with a large van der Waals surface, able to display stabilizing secondary interactions with the substrate, were rarely investigated. Calixarene macrocycles[5a] are of interest in supramolecular chemistry where they have shown amazing supramolecular properties. The aromatic cavity of the calixarene skeleton, can be readily adorned with catalytically active groups, such as urea, or thiourea functions.[5a] In addition, examples of calixarene-based catalysts have been recently reported in literature, in which the aromatic cavity of the macrocycle has been exploited for stabilization of the catalyst-substrate complex,[5b-c] through secondary interactions (e.g.: π···π and C–H···π). Thus, some of us have shown that calixarene derivatives, bearing thiourea groups at the upper rim, were active in the catalysis of aldol reaction, through H-bond activation and molecular recognition of the substrates.[5b-c]

Thanks to their synthetic versatility, the calixarenes can be functionalized with chiral groups. Consequently, in the last decade, the use of chiral calixarenes as catalysts in enantioselective reactions, has been intensively investigated. Thus, inherently chiral calixarene-based organocatalysts[6] and calixarenes anchoring L-proline or 1,2-cyclohexyl amine were checked prevalently in enantioselective aldol reactions with limited examples in Michael reactions.[7] In the enantioselective Michael reactions of

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aldehydes catalyzed by calix[4]arene based primary amine thiourea **1**, two 1,2-cyclohexyl amine units were linked at lower rim, whereas two L-proline amines were likewise anchored at the upper rim of catalyst **2**, used in aldol reaction (Figure 1).

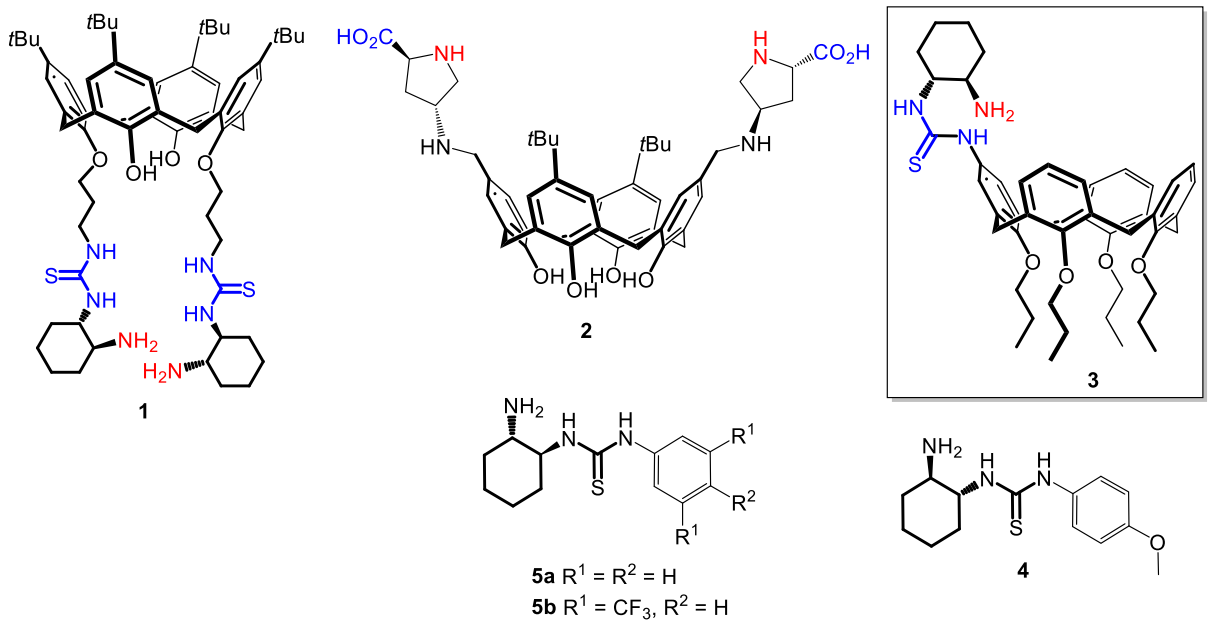

Figure 1. Representative calix[4]arenes and aryl based primary amine-thioureas applied in enantioselective aminocatalysis.

In catalysts **1** and **2**, the aromatic cavity of the calixarene was fixed relatively far from the two catalytic chiral units and in most of the examples reported so far, the chiral moieties were anchored at lower-rim (e.g. **1**). In those examples, the aromatic calixarene cavity cannot play some role in the complexation of the substrate.[8] We envisioned that additional non-covalent interactions (e.g.: van der Waals, π···π and C–H··π) involving the aromatic cavity of the calixarene macrocycle might have had an impact in the catalysis. Prompted by these considerations, we designed the calixarene-based amine-thiourea derivative **3,** containing the (*R*,*R*)-1,2-cyclohexanediamine moiety, bearing the thiourea group directly connected to a calix[4]arene backbone. In general, reported data, showed that the best activity provided by

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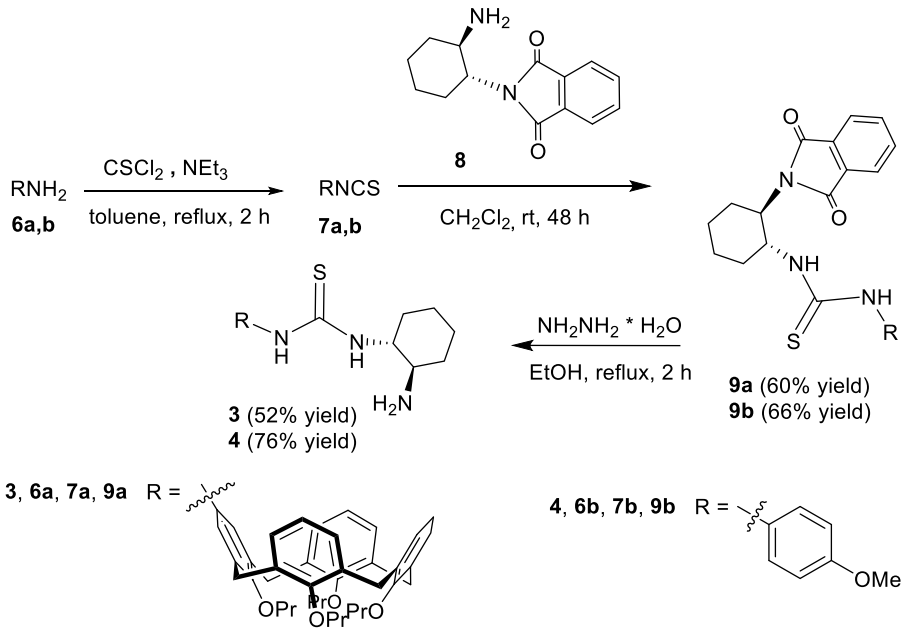
calixarene-based catalysts was achieved in water or organic solvents as the reaction medium and in the former case, hydrophobic effects were regarded to be responsible of increased catalytic performance.[5b-c] We wish to report here the synthesis of **3**, and results of our studies on the catalytic activity of **3** for solvent-free enantioselective Michael reactions.

Results and discussions

Catalyst **3** and the monomeric counterpart catalyst **4**[9] were synthesized according to standard procedures[10] with a more insight on the macrocycle's role in the catalysis by comparing their catalytic activities. The corresponding isothiocyanates **7a,b** were coupled with monoprotected (*R*,*R*)-1,2-cyclohexanediamine **8**, followed by deprotection (Scheme 1). Both catalysts were obtained in good overall yield.



Scheme 1. Synthetic approach to the calix[4]arene based amine-thiourea **3** and monomeric primary amine-thiourea **4**.

To have a comparative performance, catalyst **3** was initially employed in the enantioselective Michael reaction of isobutyraldehyde and *N*-phenylmaleimide under conditions previously reported by Wang

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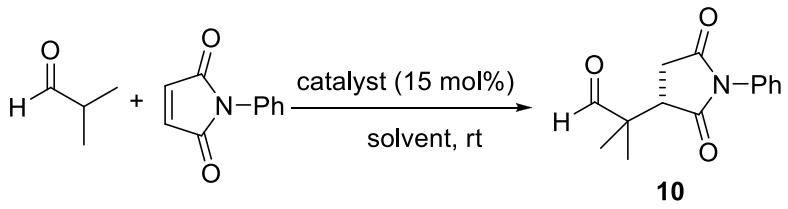
and coauthors in the presence of organocatalysts **5a** and **5b** (Table 1).[11] The monomeric catalyst **4**, which has a similar substitution pattern in the aromatic ring to catalyst **3**, was also checked. Simple primary amine thioureas **5a** and **5b** were both significantly more reactive than catalyst **3**, although the enantioselective induction was comparable in chloroform and water as additive (entries 1-3). It is interesting to note that in chloroform catalyst **1** was, as predictable, more effective than **3** in better conversion possibly due to two catalytic units present, but less enantioselective (entry 4). In pure water, catalysts **5a** and **3** afforded good conversion to product **10**, whereas the enantioselective induction was negatively affected, in particular for catalyst **5a** (entries 5, 6).

Table 1. Comparative enantioselective Michael reaction of isobutyraldehyde and *N*-phenylmaleimide in the presence of primary amine thioureas.



10

entry	catalyst	solvent	additive	time (min)	yield, *ee*[c]
1[a]	**5a**	$CHCl_3$	H_2O	40	93%, 97% (*S*)
2[a]	**5b**	$CHCl_3$	H_2O	40	96%, 94% (*S*)
3[b]	**3**	$CHCl_3$	H_2O	50	50%, 94% (*R*)
4[d]	**1**	$CHCl_3$	-	30	98%, 85% (*S*)
5[a]	**5a**	H_2O	-	30	89%, 62% (*S*)
6[e]	**3**	H_2O	-	35	85%, 78% (*R*)
7[e]	**3**	**-**	**-**	**30**	**98%, 88% (*R*)**
8[e]	**4**	-	-	30	98%, 72% (*R*)
9[e]	**5b**	-	-	30	98%, 91% (*R*)

[a]Data reported in ref. 11. [b]Molar ratios: aldehyde/maleimide 2/1 at C = 0.4 M and 15 mol% of H_2O). [c]Isolated yield after chromatography. The ee values determined by chiral HPLC analysis. [d]Data reported in ref. 8.[e]Molar ratio of aldehyde/maleimide 4/1.

As it appeared that hydrophobic effects might not play an active role in rate acceleration, but a deleterious effect on enantioselective induction, the reaction was performed without solvent (entry 7), using excess of aldehyde (4 equiv). Product **10** was rapidly observed with the enantioselective induction increased to a fairly good level. Under those conditions, the monomeric catalyst **4** proved to be equally

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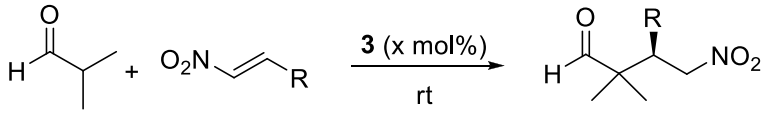
active, but significantly less enantioselective (entry 8). Finally, catalyst **5b** was also checked for the comparative performance with catalysts **3** and **4**. As expected, high conversion but a slightly decreased level of enantioselectivity were observed (entry 9) compared with the reaction carried out by Wang and coauthors in $CHCl_3$ and water as additive (entry 3). The data suggested that the calix[4]arene unit may guarantee the catalytic activity and high control of the enantioselectivity (compare entries 3 and 4). The highest activity is conveniently achieved under solvent-free conditions, where catalyst **3** achieved a satisfactory result (compared entries 7-9).

Prompted by those results and our long-standing interest in enantioselective organocatalytic Michael reactions,[12] we next investigated other reactions with a view to check the performance of catalyst **3** in a more general perspective. The reaction of isobutyraldehyde with *trans*-β-nitrostyrene using catalyst **3** was then investigated (Table 2) under the optimized conditions (Table 1, entry 7) and the adduct **11a** was isolated in excellent yield and 90% ee (entry 1). The addition of catalytic amount of dimethyl sulfoxide (DMSO), as competing H-bonding additive with respect to β-nitrostyrene, led to markedly reduced catalytic activity, but the level of enantioselectivity was maintained (entry 2).

Table 2. Solvent-free enantioselective Michael reaction of isobutyraldehyde and β-nitrostyrenes catalyzed by primary amine thiourea **3**.[a]



11

entry	R	**3** (x mol%)	time (h)	**11**	yield **11**(%)[b]	*ee* **11**(%)[c]
1	Ph	15	16	**11a**	98	90
2[d]	Ph	15	22	**11a**	40	92
3[e]	Ph	15	16	**11a**	50	92
4[f]	Ph	15	21	**11a**	35	92

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5[g]	Ph	15	20	**11a**	40	93
6[h]	Ph	10	60	**11a**	29	90
7[i]	Ph	15	8	**11a**	77	87
8	Ph	10	22	**11a**	29	92
9	4-$MeOC_6H_4$	15	52	**11b**	78	90
10[e]	4-$MeOC_6H_4$	15	48	**11b**	29	92
11	4-FC_6H_4	15	24	**11c**	91	91
12	2-ClC_6H_4	15	75	**11d**	57	93
13	3-BrC_6H_4	15	51	**11e**	53	90
14	4-BrC_6H_4	15	53	**11f**	52	89
15[e]	4-BrC_6H_4	15	49	**11f**	51	85
16	2-furyl	15	16	**11g**	53	90

[a]Molar ratios: aldehyde/ alkene 4/1. [b]Isolated yield after chromatography. [c]Determined by chiral HPLC analysis. [d]Reaction performed with 15 mol% of DMSO. [e]Reaction performed with catalyst **4**. [f]Reaction performed in $CHCl_3$ (C= 0.4 M). [g]Reaction performed in $CHCl_3$ (C= 0.4 M) with 15 mol% of H_2O. [h]Reaction performed in toluene (C= 0.2 M). [i]Reaction performed in water.

The monomeric catalyst **4** showed to be less active than catalyst **3**, although a similar level of enantioselectivity was observed (entry 3). Reactions performed with catalyst **3** in different solvents, such as chloroform, chloroform and water as additive or in toluene, proceeded sluggishly, demonstrating the best activity was only achieved under solvent-free conditions (entries 4-6). The reaction was performed in water, with 15 mol% of catalyst **3** in good conversion while a deleterious enantioselective induction (entry 7). Unfortunately, reduced catalytic loading of catalyst **3**, under neat conditions, markedly affected the activity and poor yield was observed with almost untouched enantioselectivity (entry 8).

Different nitroalkenes using 15 mol% of catalyst **3** under solvent-free conditions were then evaluated. Alkenes substituted within the phenyl group with either electron-donating or withdrawing groups or bearing heteroaromatic moiety were all converted into compounds **11** in satisfactory to good yields and high enantioselectivities (entries 9, 11-14 and 16).[13] For comparison, additional reactions with two differently substituted β-nitroalkenes were also carried out with monomeric catalyst **4** under the same conditions (entries 10 and 15). When the reaction mixtures are homogeneous (entries 9 and 10, 1 and 3) the calix[4]arene-based catalyst **3** showed to be significantly more efficient than **4**. Conversely, when

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the reaction mixtures are heterogeneous (entries 14 and 15) a comparable activity of both catalyst was observed, although promoter **3** provided the product with higher ee value. The different performances observed may not be simply rationalized by electronic effects and it is likely that aggregation state of the catalysts and solubility of the alkenes also play a significant role. Based on the data reported in Table 2 (entries 1, 2, 9, 10), the calix[4]arene macrocycle may help to markedly improve the conversion to the product, compared with monomeric catalyst **4**. To get some insight on the role played by the calix[4]arene skeleton in affecting the enantioselective induction, we have studied the complex in Figure 2 by DFT calculation.

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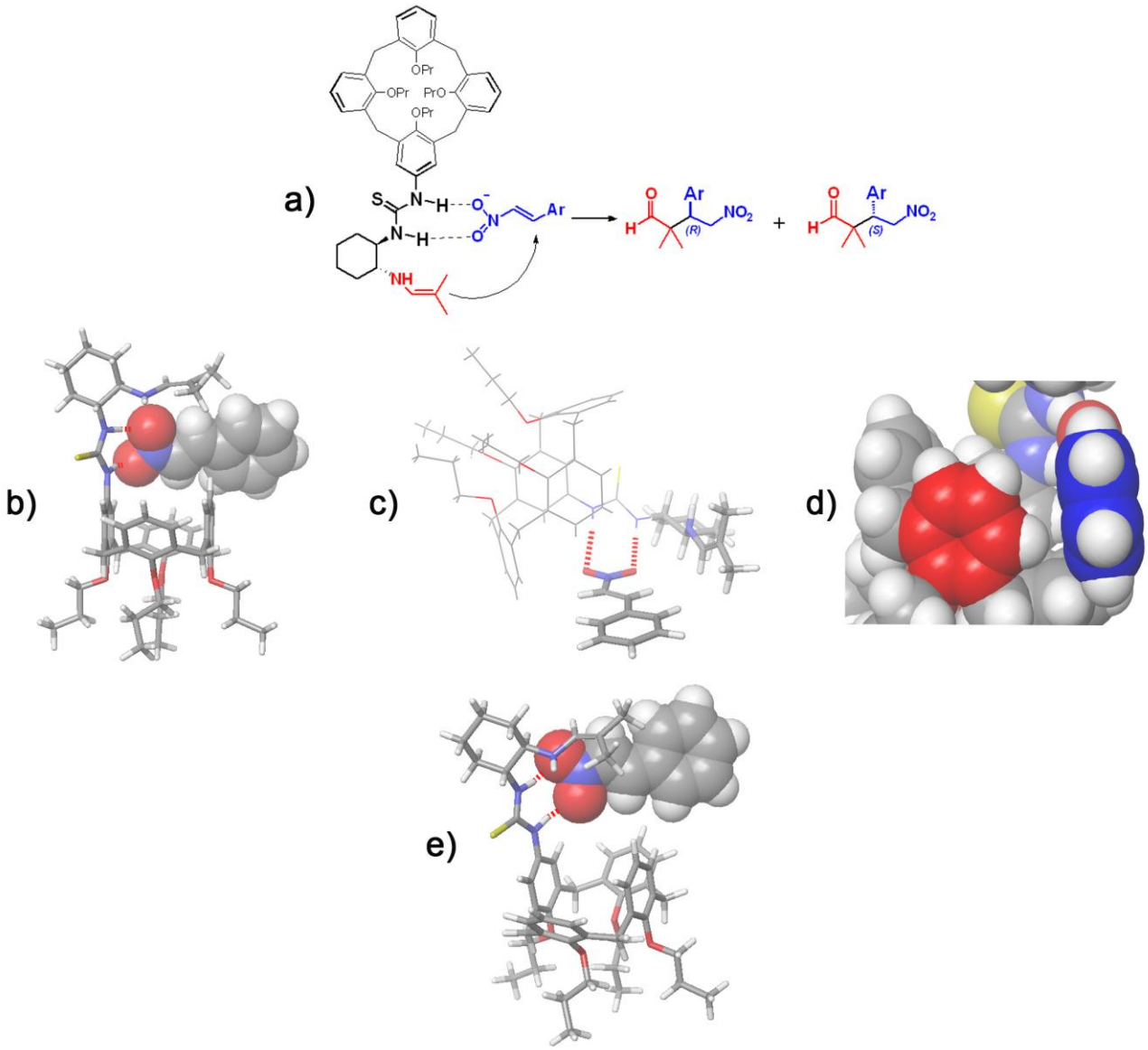

Figure 2. a) Model proposed for the attack of the calix-enamine (**3**+isobutyraldehyde) to *trans*-β-nitrostyrene. b and c) DFT-optimized structure of the complex with *trans*-β-nitrostyrene exposing the *Si* face at the attack of the enamine and d) particular stabilizing C–H···π (d = 4.0 Å, C–H···$\pi^{centroid}$) interactions between the calixarene skeleton and the aromatic ring of the *trans*- β-nitrostyrene. e) DFT-optimized structure of the complex with *trans*- β-nitrostyrene exposing the *Re* face at the attack of the enamine.

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The optimized structure of the complex in Figure 2a was obtained by DFT calculations at B3LYP/6-31G(d,p) level of theory and using Grimme's dispersion corrections (IOp(3/124 = 3). In Figure 2b the β-nitrostyrene exposes its *Si* face to the enamine in the complex, while in Figure 2e the *Re* face was exposed, affording, respectively, the formation of (*R*)-**11** and (*S*)-**11**. Stabilizing H-bonding interactions were detected between the thiourea group of the catalyst and the nitro-group in both cases. Single point calculations indicated that the *Si* orientation in Figure 2b was more stable by 0.28 kcal/mol with respect to the *Re* one in Figure 2e, in accordance with the preferential formation of the *R*-configured product.

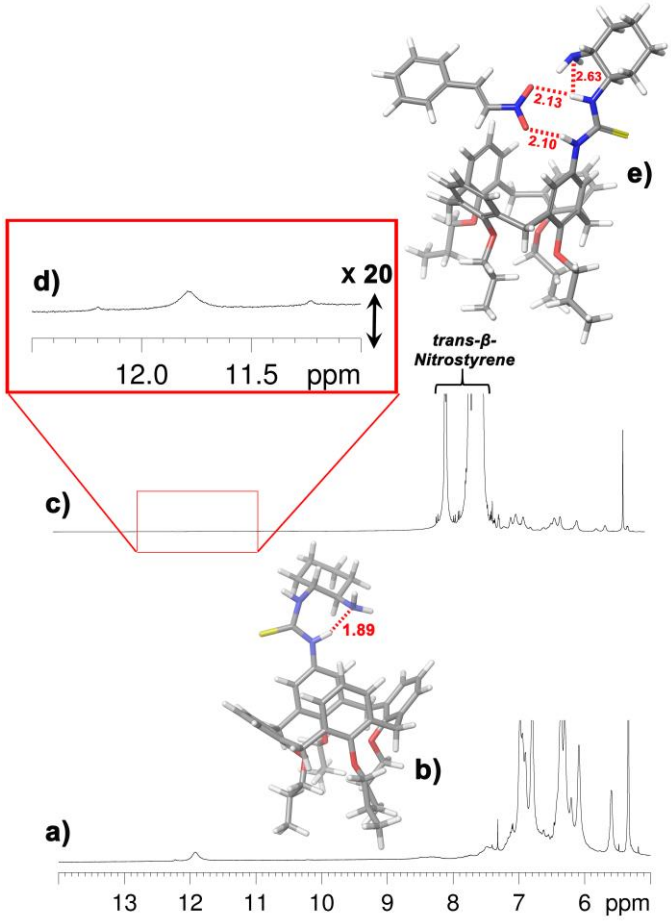

Figure 3. a) Significant portion of the ^{1}H NMR (CD_2Cl_2, 193 K, 600 MHz) spectrum of **3**; b) DFT-optimized (B3LYP/6-31G(d,p) level of theory) structure of derivative **3**, in which the conformation of the thiourea group is *trans-cis* (thiourea conformation is defined by the S-C-N-H torsion angle, *syn* 0°, *anti* 180°), Intramolecular N–H···N, H-bond distance 1.89 Å; c) Significant portion of the ^{1}H NMR (CD_2Cl_2, 193 K, 600 MHz) spectrum of a mixture (1:30) of derivative **3** and β-nitrostyrene (β-NS); d)

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enlargement of "c" and, e) DFT-optimized (B3LYP/6-31G(d,p) level of theory and using Grimme's dispersion corrections (IOp(3/124 = 3)) of the complex between **3** and β-NS. Intermolecular N–H···O, H-bond distances 2.10 and 2.13 Å.

Close inspection of the DFT-optimized structure of the complex in Figure 2a, reveals the presence of stabilizing van der Waals contacts between the calixarene aromatic skeleton and *trans*-β-nitrostyrene, in addition to C–H···π (in Figure 2d, d = 4.0 Å, C–H···$\pi^{centroid}$) interactions between the aromatic H-atoms of the calixarene catalyst and the aromatic ring of the substrate (Figure 2d). Based on those results we may conclude that the calixarene skeleton plays an important role on the stabilization of the complex between β-nitrostyrene and calixarene by van der Waals and C–H···π interactions. It is well-known that the H-bond donor abilities of the thiourea group plays a crucial role in organocatalyzed reactions with bifunctional systems.[14] In this regard, the presence of both amine and thiourea groups in bifunctional catalysts carries the possibility of intra- and intermolecular hydrogen bonds.[14] Following a procedure reported by Tárkányi and Soòs,[14b] a VT ^{1}H NMR study was performed in order to probe the presence of intramolecular H-bonding interactions in catalyst **3** (Figure 3). Accordingly, the ^{1}H NMR spectrum of **3** at 193 K evidenced the presence of a broad signal at 12 ppm (Figure 3a) attributable to thiourea N-H-atom interacting with the basic nitrogen atom (NH_2) (see DFT-optimized structure of **3** in Figure 3b). In agreement with previously reported data,[14b] the presence of intramolecular H-bonding between the more acidic thiourea N-H-atom and the basic amino groups (Figure 3b), stabilizes the *anti-syn* conformation (Figure 3b) of the thiourea group. It is known that the *anti-syn* orientation of the thiourea group in amine-thiourea organocatalysts favours the formation of self-assembled dimeric species by intermolecular H-bonds (Figure 4b). Interestingly, DOSY spectrum (see the Supporting Information) of catalyst **3** rules out the presence of self-assembled dimer of **3** (Figure 4b), probably because of steric repulsion between calix[4]arene skeletons. Those results clarify further the role of the sterically encumbered calixarene skeleton which prevents self-aggregation between amine-thiourea groups of **3**. The addition of *trans*-β-nitrostyrene to a $CDCl_3$ solution of **3** caused a shift of the thiourea N-H signal at

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12 ppm (Figure 3d), indicated the formation of H-bonds interactions between thiourea group of **3** and nitro group of the *trans*-β-nitrostyrene (Figures 3e and 4c). Those observations might also justify the higher activity observed for catalyst **3** under homogeneous conditions (Table 2) when compared with the monomeric catalyst **4**. Catalyst **3** would be more disposed to interact with the substrates, as it is less likely involved in self-assembled dimers, which are likely to occur in thiourea-amines of type **4**-**5a**,**b**.[14b]

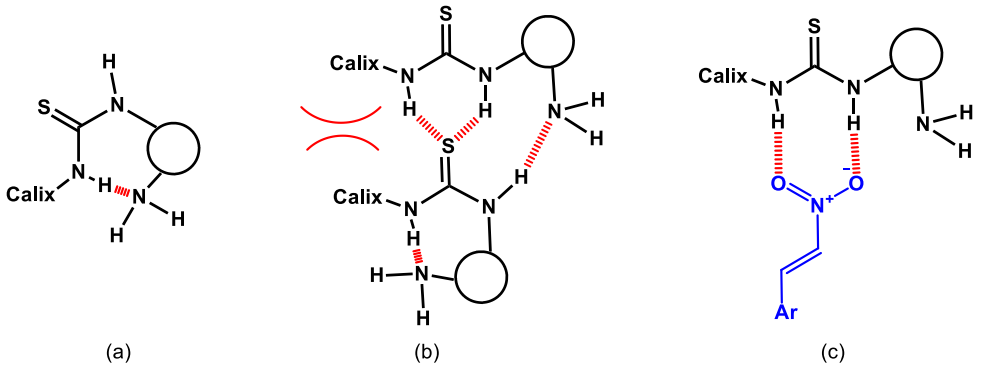

Figure 4. Models proposed for: (a) intramolecular H-bond, (b) intermolecular H-bond and self-aggregation between amine-thiourea based organocatalysts, (c) H-bonds between calixarene-organocatalyst **3** and *trans*-β-nitrostyrene.

Finally, catalyst **3** was evaluated in iminium activation of α,β-unsaturated ketones with dimethyl malonate as the nucleophile, under solvent-free conditions. Indeed, to the best of our knowledge calix[4]arene-based primary amine thioureas have been exclusively studied in enantioselective Michael reactions exploiting enamine activation of carbonyl compounds. To this end, benzylidene acetone was studied under similar conditions reported by Kwiatkowski and coworkers, in which catalyst **5b** and benzoic acid as co-catalyst in toluene at 50 °C were performed (Scheme 2).[15]

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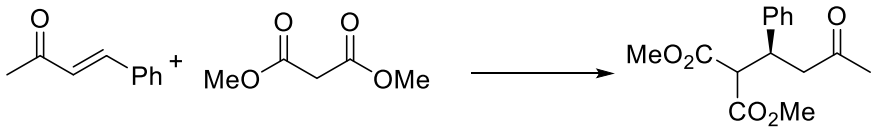

12 **13** **14**

5b (2 mol%)/benzoic acid (1 mol%), 50°C, 20 h, toluene	80%, 94% ee
3 (10 mol%)/benzoic acid (5 mol%), 50°C, 20 h, toluene	41%, 90% ee
3 (10 mol%)/benzoic acid (5 mol%), 40°C, 20 h, $CHCl_3$	36%, 69% ee
3 (15 mol%)/benzoic acid (7.5 mol%), rt, 16 h, solvent-free	88%, 80% ee
4 (15 mol%)/benzoic acid (7.5 mol%), rt, 16 h, solvent-free	90%, 75% ee

Scheme 2. Enantioselective Michael addition of dimethyl malonate to benzylidene acetone catalyzed by organocatalysts **3**, **4** and **5b**.

The reaction was performed with 10 mol% of catalyst **3** under those conditions or in chloroform at 40°C, proceeded slowly to the expected product **14**, which was recovered in significantly lowered ee in chloroform. Catalyst **3**, under solvent-free conditions at room temperature, afforded product **14** in high yield and good enantioselectivity, a better performance with respect to catalyst **4**.

In conclusion, we have demonstrated that a primary amine based on (*R*,*R*)-1,2-cyclohexanediamine bearing an upper-rim fixed calix[4]arene thiourea moiety was an effective aminocatalyst in Michael reactions under mild and solvent-free conditions. Our study has provided some more useful informations on the still underexplored calixarene-based catalysis, for further developments in aminocatalysis: 1) water and organic solvents are not the preferential media where they can be employed. Indeed, their catalytic activity can be significantly increased under solvent-free conditions, which are valuable for the development of more sustainable processes;[16] 2) Satisfactory catalytic activity is achieved by linking only one chiral unit to the calixarene platform, which clearly reduces both the costs and the loading of the chiral diamine; 3) DFT calculations and NMR investigations showed that the calix[4]arene unit may have an impact on the activity and stereoselectivity led by van der Waals contacts and C–H···π interactions with the substrates. Based on the few valuable data reported up to now in this area, the design of new calixarene-based organocatalysts will be necessary to elucidate their real catalytic potential, especially with a view to benefit from host-guest interactions among catalyst and the substrates.

Accepted Version doi: 10.1021/acs.joc.8b01454

EXPERIMENTAL SECTION

General Information. All reactions requiring dry or inert conditions were conducted in flame-dried glassware under a positive pressure of nitrogen. Molecular sieves (Aldrich Molecular Sieves, 4 Å, 1.6 mm pellets) were activated under vacuum at 200°C overnight. Reactions were monitored by thin layer chromatography (TLC) on Macherey-Nagel pre-coated silica gel plates (0.25 mm) and visualized by UV light and, when necessary, by ninhydrin, anisaldeide staining solutions. Flash chromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance-400, Bruker Avance-300 or Bruker Avance III HD 600 MHz in $CDCl_3$ as solvent at room temperature. Chemical shifts for protons are reported using residual solvent protons (^{1}H NMR: δ = 7.26 ppm for $CDCl_3$) as internal standard. Carbon spectra were referenced to the shift of the ^{13}C signal of $CDCl_3$ (δ =77.0 ppm). The following abbreviations are used to indicate the multiplicity in NMR spectra: s singlet; d doublet; t triplet; q quartet; dd – double doublet; m multiplet; br broad signal. Optical rotation of compounds was performed on a Jasco P-2000 digital polarimeter using WI (Tungsten-Halogen) lamp (λ=589 nm). FTIR spectra were recorded as thin films on KBr plates using Bruker Tensor 27 spectrometer and absorption maxima are reported in wavenumber (cm^{-1}). High resolution mass spectra (HRMS) were acquired using a Bruker solariX XR Fourier transform ion cyclotron resonance mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) equipped with a 7 T refrigerated actively-shielded superconducting magnet. The samples were ionized in positive ion mode using an electrospray (ESI) ionization source. Melting points were measured with a Stuart Model SMP 30 melting point apparatus and are uncorrected. Petrol ether (PE) refers to light petroleum ether (boiling point 40-60°C). Anhydrous toluene, methanol and all starting materials (unless otherwise noted) were purchased from Aldrich and used as received, all other solvents were dried over molecular sieves.

Enantiomeric excess of products **10**, **11a-g**, **14** was determined by HPLC (Waters-Breeze 2487, UV dual λ absorbance detector and 1525 Binary HPLC Pump) using Daicel chiral columns.

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Preparation of catalyst (9a)

To a stirred solution of amine **8**[10a] (198 mg, 0.809 mmol) in CH_2Cl_2 (3 mL) at 0 °C under nitrogen atmosphere was added dropwise a solution of isothiocianate **7a**[17] (492 mg, 0.809 mmol, 1 eq) in CH_2Cl_2 (3 mL). The resulting mixture was stirred at room temperature for 48 h, the solvent was removed under reduced pressure and the crude product was purified by flash cromatography on silica gel eluting with CH_2Cl_2/Et_2O (1:0 to 99:1) to afford compound **9a**. *1-((1R,2R)-2-(1,3-dioxoisoindolin-2-yl)cyclohexyl)-3-(1^2,3^2,5^2,7^2-tetrapropoxy-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5-yl)thiourea* (**9a**). Pale brown solid, 431 mg, yield 60%; mp 146–150 °C; $[\alpha]_D^{20}$ = - 51.79 (c = 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.85 (m, 2H), 7.74 (m, 2H), 6.94–6.92 (m, 2H), 6.87 (d, *J* = 6.2 Hz, 1H), 6.81 (t, *J* = 7.4 Hz, 1H), 6.66–6.62 (m, 3H), 6.35 (t, *J* = 7.4 Hz, 1H), 6.27 (d, *J* = 7.2 Hz, 1H) 6.24 (d, *J* = 7.2 Hz, 1H), 6.03 (s, 1H), 5.77 (s, 1H), 5.35 (d, *J* = 9.0 Hz, 1H), 4.97 (m, 1H), 4.45–4.39 (m, 4H), 3.95–3.80 (m, 7H), 3.70 (t, *J* = 7,0 Hz, 2H), 3.17–3.05 (m, 4H), 2.54 (m, 1H), 2.25 (m, 1H), 1.95–1.84(m, 9H), 1.78–1.74 (m, 2H), 1.49 (m, 1H), 1.28 (m, 1H), 1.10 (t, *J* = 7.4 Hz, 3H), 1.04 (m, 4H) 0.93–0.90, (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.9, 168.5, 157.4, 157.3, 156.8, 156.0, 155.4, 136.6, 136.5, 136.3, 135.6, 135.5, 135.3, 134.1, 134.0, 133.97, 129.1, 128.9, 128.7, 128.5, 128.2, 128.17, 128.0, 127.8, 125.2, 124.7, 123.4, 122.4, 122.2, 121.9, 121.4, 115.5, 76.75, 76.71, 76.69, 55.4, 54.2, 33.1, 31.1, 31.05, 31.0, 28.8, 25.5, 24.5, 23.6, 23.5, 23.2, 10.8, 10.7, 10.1; FT-IR 3363, 2960, 2934, 2874, 2354, 2333, 1710, 1586, 1530, 1463, 1388, 1374, 1247, 1215, 1087, 1068, 1037, 1005, 966, 844, 757, 718 cm^{-1}; HRMS (ESI+) calcd for $C_{55}H_{64}N_3O_6S$ $[M + H]^+$ 894.4510, found 894.4533.

Preparation of catalyst (3)

A solution of **9a** (416 mg, 0.465 mmol), and $NH_2NH_2 \cdot H_2O$ (0.6 mL) in ethanol (7 mL) was heated to reflux for 2 h, the solvent was removed under reduced pressure. The crude product was suspended in CH_2Cl_2 (10 mL) and washed with water (2 x10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL). The collected organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The product **3** was precipitated from CH_3CN and recovered by filtration. *1-((1R,2R)-2-aminocyclohexyl)-3-(1^2,3^2,5^2,7^2-tetrapropoxy-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5-yl)thiourea*

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(**3**). White solid, 186 mg, yield 52%; mp 95–97 °C; $[\alpha]_D^{20}$ = + 2.9 (c = 1.00, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 7.07–6.68 (m, 7H), 6.45–6.34 (m, 3H), 6.09 (br, 2H), 5.60 (br, 1H), 4.44–4.42 (m, 4H) 4.09 (br, 1H), 3.95–3.88 (m, 4H), 3.76–3.71 (m, 4H), 3.17–3.09 (m, 4H), 2.37 (br, 1H), 2.04–1.99 (m, 2H), 1.93–1.86 (m, 8H), 1.73–1.69 (m, 2H), 1.34–1.19 (m, 4H), 1.07–1.03 (m, 6H), 0.92–0.90, (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 180.2, 157.4, 156.1, 155.0, 136.6, 136.4, 135.5, 134.2, 129.2, 128.5, 128.4, 127.9, 127.87, 124.1, 123.8, 122.4, 121.6, 76.72, 61.7, 55.9, 34.9, 32.1, 31.2, 31.1, 31.08, 29.8, 25.1, 25.0, 23.5, 23.2, 10.7, 10.68, 10.1; FT-IR 3423, 3366, 2961, 2933, 2875, 2360, 2342, 1586, 1533, 1463, 1384, 1247, 1216, 1195, 1087, 1068, 1037, 1007, 966, 844, 757 cm^{-1}; HRMS (ESI+) calcd for $C_{47}H_{62}N_3O_4S$ $[M + H]^+$ 764.4456, found 764.4462.

Preparation of catalyst (**4**)

The same procedure described for catalyst **3** was followed, starting from crude **9b** (200 mg, 0.488 mmol), and $NH_2NH_2{\cdot}H_2O$ (0.63 mL) in ethanol (4 mL). *1-((1R,2R)-2-aminocyclohexyl)-3-(4-methoxyphenyl)thiourea* (**4**). White solid, 103 mg, yield 76%; mp 144-145 °C; $[\alpha]_D^{20}$ = + 34.9 (c = 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.04 (br, 1H), 7.21–7.19 (m, 2H), 6.93–6.91 (m, 2H), 5.92 (br, 1H), 4.13 (br, 1H), 3.81 (s, 3H), 2.42 (br, 1H), 2.12 (m, 1H), 1.93 (m, 1H), 1.72–1.70 (m, 2H), 1.35–1.21 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.5, 158.7, 127.4, 115.2, 62.0, 56.0, 55.7, 35.5, 32.2, 25.0, 25.0; FT-IR 3367, 2932, 2858, 2360, 2341, 1535, 1510, 1448, 1242, 1180, 1038, 830, 754, 526 cm^{-1}; HRMS (ESI+) calcd for $C_{14}H_{22}N_3OS$ $[M + H]^+$ 280.1478, found 280.1478.

General procedure for catalytic enantioselective Michael reaction of isobutyraldehyde with maleimide in water

To a suspension of N-phenylmaleimide (17.3 mg, 0.1 mmol) and catalyst **3** (11.5 mg, 0.015 mmol) in water (200 µL) isobutyraldehyde (36 µL, 0.4 mmol) was added. The suspension was stirred vigorously at room temperature for 40 minutes. The crude compound **10** was purified by flash chromatography (eluting from PE/ ethyl acetate 9:1 to 7:3).

General procedure for solvent-free catalytic enantioselective Michael reaction of isobutyraldehyde with maleimide

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A sample vial was charged with N-phenylmaleimide (17.3 mg, 0.1 mmol), catalyst **3** (11.5 mg, 0.015 mmol) and isobutyraldehyde (36 µL, 0.4 mmol). The reaction mixture was stirred at room temperature until completion, monitored by TLC (eluent PE/ ethyl acetate 7:3). The crude compound **10** was purified by flash chromatography (eluting from PE/ ethyl acetate 9:1 to 7:3).

*(R)-2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-methylpropanal (***10***)*[11,18] White solid, 24 mg, yield 98%; mp 103-106 °C;[19] ee 88% by HPLC Chiralcel OD-H *n*-hexane/2-propanol (75:25), flow 0.9 mL/min; UV = 220 nm, t_R = 29.2 min (major), 23.9 min (minor);[18] The absolute configuration was determined by comparison of the optical rotation with the literature.[11] $[\alpha]_D^{20}$ +1.6 (c = 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.52 (s, 1H), 7.51-7.26 (m, 5H), 3.15 (dd, *J* = 9.6, 5.4 Hz, 1H), 2.98 (dd, *J* = 20.0, 9.6 Hz, 1H), 2.63 (dd, *J* = 20.0, 5.0 Hz, 1H), 1.33 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.6, 176.9, 174.7, 131.7, 129.1, 128.7, 126.5, 48.5, 45.1, 31.9, 20.3, 19.5.

Catalytic enantioselective solvent-free Michael addition of isobutyraldehyde to nitroolefins

The nitroolefin (0.1 mmol), catalyst **3** (11.5 mg, 0.015 mmol) and isobutyraldehyde (36 µL, 0.4 mmol) were loaded in a capped vial. The reaction mixture was stirred at room temperature until completion, monitored by TLC (eluent PE/ ethyl acetate 9:1, visualized by UV light and by *p*-anisaldehyde staining solution). The residue was purified by flash chromatography (eluting from PE/ ethyl acetate 100:1 to 9:1). The absolute configurations were determined by comparison of the optical rotation with the literature.

*(R)-2,2-dimethyl-4-nitro-3-phenylbutanal (***11a***)*[20] Light yellow oil, 21.7 mg, yield 98%; ee 90% by HPLC Chiralpak IC *n*-hexane/2-propanol (90:10), flow 1.0 mL/min; UV = 220 nm, t_R = 26.3 min (major), 44.0 min (minor);[21] $[\alpha]_D^{24}$ +14.1 (c = 1.00, $CHCl_3$).[20b] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.53 (s, 1H), 7.33-7.29 (m, 3H), 7.21-7.09 (m, 2H), 4.85 (dd, *J* = 13.1, 11.3 Hz, 1H), 4.69 (dd, *J* = 13.1, 4.2 Hz, 1H), 3.75 (dd, *J* = 11.3, 4.2 Hz, 1H), 1.13 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.1, 135.3, 128.9, 128.5, 127.9, 76.1, 48.2, 48.0, 21.4, 18.6.

*(R)-3-(4-methoxyphenyl)-2,2-dimethyl-4-nitrobutanal (***11b***)*[20] White solid, 19.6 mg, yield 78%; mp 56-58°C;[20a] ee 90% by HPLC Chiralpak AD-H *n*-hexane/2-propanol (85:15), flow 1.0 mL/min; UV = 220

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nm, t_R = 8.1 min (major), 9.0 min (minor);[20b] $[\alpha]_D^{24}$ -8.7 (c = 1.00, $CHCl_3$).[20a,b,8b] ^1H NMR (400 MHz, $CDCl_3$): δ = 9.52 (s, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H), 4.80 (dd, *J* = 12.8, 11.4 Hz, 1H), 4.67 (dd, *J* = 12.8, 4.5 Hz, 1H), 3.79 (s, 3H), 3.73 (dd, *J* = 11.4, 4.5 Hz, 1H), 1.12 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.1, 159.8, 130.8, 127.7, 114.9, 77.1, 55.9, 49.0, 48.4, 22.2, 19.5.

*(R)-3-(4-fluorophenyl)-2,2-dimethyl-4-nitrobutanal (***11c***)*[20a,b,c]

Light yellow oil, 21.8 mg, yield 91%; ee 91% by HPLC Chiralpak AD-H *n*-hexane/2-propanol (85:15), flow 1.0 mL/min; UV = 220 nm, t_R = 7.1 min (major), 8.1 min (minor);[20b] $[\alpha]_D^{25}$ -8.2 (c = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.51 (s, 1H), 7.22–7.16 (m, 2H), 7.07–7.00 (m, 2H), 4.82 (dd, *J* = 13.0, 11.4 Hz, 1H), 4.69 (dd, *J* = 13.1, 4.0 Hz, 1H), 3.78 (dd, *J* = 11.4, 4.0 Hz, 1H), 1.13 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.1, 162.3 (d, *J* = 247 Hz), 131.0 (d, *J* = 3 Hz), 130.5 (d, *J* = 8 Hz), 115.6, (d, *J* = 22 Hz), 76.2, 48.1, 47.8, 21.7, 18.9.

*(S)-3-(2-chlorophenyl)-2,2-dimethyl-4-nitrobutanal (***11d***)*[20b]

Light yellow oil, 14.6 mg, yield 57%; ee 93% by HPLC Chiralpak AD-H *n*-hexane/2-propanol (98:2), flow 1.0 mL/min; UV = 220 nm, t_R = 15.6 min (major), 14.7 min (minor);[20b] $[\alpha]_D^{24}$ +15.0 (c = 0.52, $CHCl_3$).[20b] ^1H NMR (400 MHz, $CDCl_3$): δ = 9.56 (s, 1H), 7.44–7.40 (m, 1H), 7.30–7.22 (m, 3H), 4.87–4.81 (m, 1H), 4.72 (dd, *J* = 13.2, 3.6 Hz, 1H), 4.64 (d, *J* = 8.8 Hz, 1H), 1.17 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.8, 135.6, 133.8, 130.4, 129.1, 128.3, 127.1, 76.2, 49.0, 42.5, 20.8, 18.6.

*(R)-3-(3-bromophenyl)-2,2-dimethyl-4-nitrobutanal (***11e***)*[20a,d]

Yellow oil, 15.9 mg, yield 53%; ee 90% by HPLC Chiralcel OD-H *n*-hexane/2-propanol (90:10), flow 1.0 mL/min; UV = 220 nm, t_R = 20.0 min (major), 29.7 min (minor);[20a] $[\alpha]_D^{24}$ +1.9 (c = 0.53, $CHCl_3$).[8b] ^1H NMR (400 MHz, $CDCl_3$): δ = 9.50 (s, 1H), 7.46 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.38-7.34 (m, 1H), 7.24-7.18 (m, 1H), 7.17-7.12 (m, 1H), 4.83 (dd, *J* = 13.2, 11.2 Hz, 1H), 4.69 (dd, *J* = 13.2, 4.0 Hz, 1H), 3.76 (dd, *J* = 11.2, 4.0 Hz, 1H), 1.14 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.6, 137.9, 132.1, 131.3, 130.2, 127.7, 122.7, 76.0, 48.2, 48.0, 21.8, 18.8.

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*(R)-3-(4-bromophenyl)-2,2-dimethyl-4-nitrobutanal (***11f***)*[20,22]

White solid, 15.6 mg, yield 52%; mp 83- 85°C;[20a,23] ee 89% by HPLC Chiralpak AD-H *n*-hexane/2-propanol (85:15), flow 1.0 mL/min; UV = 220 nm, t_R = 7.6 min (major), 9.1 min (minor);[20b] $[\alpha]_D^{26}$ -29.0 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.45 (s, 1H), 7.45 (dd, *J* = 8.4, 1.8 Hz, 2H), 7.09 (dd, *J* = 8.4, 1.8 Hz, 2H), 4.81 (dd, *J* = 13.2, 11.4 Hz, 1H), 4.65 (dd, *J* = 13.2, 4.2 Hz, 1H), 3.70 (dd, *J* = 11.4, 4.2 Hz, 1H), 1.13 (s, 3H), 1.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.7, 134.5, 131.9, 130.8, 122.2, 76.1, 48.1, 47.9, 21.7, 18.9.

*(R)-3-(furan-2-yl)-2,2-dimethyl-4-nitrobutanal (***11g***)*[20a,b,23]

Pale yellow oil, 11.2 mg, yield 53%; ee 90% by HPLC Chiralpak AD-H *n*-hexane/2-propanol (95:5), flow 1.0 mL/min; UV = 220 nm, t_R = 9.0 min (major), 10.6 min (minor);[20b] $[\alpha]_D^{26}$ -18.1 (c = 1.00, $CHCl_3$).[20a,b] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.52 (s, 1H), 7.38 (dd, 1H, *J* = 2.0, 1.0 Hz), 6.33 (dd, 1H, *J* = 3.5, 2.0 Hz), 6.24 (dd, 1H, *J* = 3.5, 1.0 Hz), 4.76 (dd, 1H, *J* = 12.9, 10.9 Hz), 4.60 (dd, 1H, 13.1, 4.0 Hz), 3.93 (dd, 1H, *J* = 10.8, 4.0 Hz), 1.18 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.4, 149.7, 142.5, 110.4, 109.5, 74.3, 47.7, 41.8, 21.0, 19.0.

Catalytic enantioselective solvent-free addition of dimethyl malonate to benzylideneacetone

A sample vial was charged with benzylideneacetone (14.6 mg, 0.1 mmol), catalyst **3** (11.5 mg, 0.015 mmol), benzoic acid (0.9 mg, 0.0075 mmol) and dimethyl malonate (46 µL, 0.4 mmol). The reaction mixture was stirred at room temperature until completion, monitored by TLC (eluent PE/ ethyl acetate 8:2, visualized by UV light and by *p*-anisaldehyde staining solution). The crude compound **14** was purified by flash chromatography (eluting from PE/ ethyl acetate 9:1 to 7:3). The absolute configuration was determined by comparison of the optical rotation with the literature.[15]

(S)-Dimethyl 2-(3-oxo-1-phenylbutyl)malonate (**14**)

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White solid, 24.5 mg, yield 88%; mp 44- 46 °C;[24] ee 80% by HPLC Chiralpak AD *n*-hexane/2-propanol (98:2), flow 1.0 mL/min; UV = 225 nm, t_R = 33.9 min (major), 30.0 min (minor);[15] $[\alpha]_D^{16}$ +11.1 (c = 0.925, $CHCl_3$).[15] ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31-7.16 (m, 5H), 4.00-3.93 (m, 1H), 3.72 (d, *J* = 10.1 Hz), 3.71 (s, 3H), 3.48 (s, 3H), 3.00-2.87 (m, 2H), 2.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.8, 168.4, 168.0, 140.3, 128.4, 127.8, 127.2, 57.0, 52.6, 52.3, 47.1, 40.3, 30.2.

ASSOCIATED CONTENT

Supporting Information

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

Copies of ^1H NMR and ^{13}C NMR spectra of new compounds **3**, **4** and chiral HPLC traces of products **10**, **11a-g**, **14**. Details on the DFT calculations.

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