Organic & Biomolecular Chemistry

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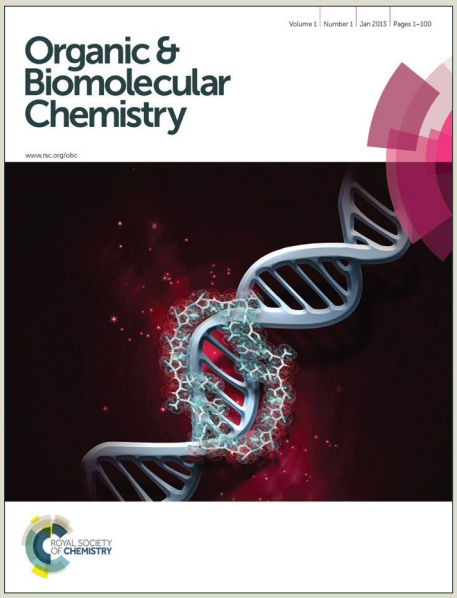

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DOI: 10.1039/C6OB00160B

Journal Name

ARTICLE

Deracemizing Organocatalyzed Michael Addition Reactions of 2-(Arylthio)cyclobutanones with β-Nitrostyrenes

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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Organocatalyzed Michael addition reactions of 2-(arylthio)cyclobutanones with *trans*-β-nitrostyrenes have been carried out using a bifunctional thiourea-primary amine catalyst, providing diastereoisomerically and enantiomerically enriched 2-alkyl-2-(arylthio)cyclobutanones having two contiguous stereocenters of which one is a chiral quaternary center. The absolute configuration of these novel adducts was assigned by X-ray diffraction analysis and a transition-state model is proposed to explain the observed stereoselectivities.

Dedicated to Dr Jean Ollivier, a mentor and a friend, on the occasion of his retirement

Introduction

Cyclobutanones are a family of strained small-ring carbocyclic molecules which are stable yet chemically reactive and are recognised as powerful intermediates for the stereo- and enantioselective synthesis of natural and/or biologically-active products.[1] The interest on this class of compounds arises from both the α-proton acidity and the marked carbonyl group electrophilicity.[2] These intrinsic characteristics have been used advantageously in synthesis, for the construction of highly functionalized building blocks containing quaternary stereogenic centres.[3] Over the years, cyclobutanone derivatives have been exploited in various synthetic applications such as ring-opening,[4] ring-expansion,[5] and ring-contraction reactions.[6] while useful intramolecular cyclization reactions[7] and oxidation protocols[8] have been established. More recently, metal-catalyzed and organocatalytic procedures have been developed in order to facilitate controlled selective transformations of cyclobutanones, including α-alkylation,[9] aldolization[10] and Mannich reactions[11] of cyclobutanone itself; aldolization,[12] nitrogen insertion,[13] and α-amination[14] of 2-hydroxycyclobutanone; and the aldol-desymmetrization of prochiral 3-substituted cyclobutanones.[15]

Concerning organocatalyzed Michael addition reactions, Ley and co-workers were the first to consider (unsubstituted) cyclobutanone in reactions with β-nitrostyrenes, employing L-proline derivatives as catalysts.[16] Since then, however, little development of this type of reaction has been reported. In one significant result in the field, reported by Rodriguez and co-workers, hydrogen bond-forming 2-carboxamide derivatives of cyclobutanone were engaged successfully in straightforward enantio- and diastereoselective Michael addition reactions with β-nitrostyrenes using bifunctional organocatalysts.[17] Our own recent work in this area revealed that 3-substituted cyclobutanones can be desymmetrized in Michael addition reactions with nitroalkenes in mild organocatalyzed conditions, yielding the corresponding α-functionalized adducts with high selectivity.[18] However, reaction times were long and many cyclobutanone derivatives are moisture and air sensitive,[19] so we considered that further exploration of Michael reactions of cyclobutanones was warranted.

Our rationale for the developments described in this paper is based on the added synthetic value of using cyclobutanones bearing an α-sulfanyl group as substrates. With such compounds, we anticipated an enhanced reactivity of the cyclobutanone α-proton and an improved stability of the intermediates during the enolization processes. Indeed, the literature concerning β-ketosulfides shows that the enolate of α-(phenylthio)cyclobutanone has a pronounced pro-nucleophilic character, comparable with ketoamides and 1,3-dicarbonyl compounds (pK_a (DMSO) = 16–19).[20] It is also known that α-(phenylthio)cyclobutanones show a strong tendency to enolize in the presence of triethylamine/Ac_2O, generating the corresponding stable enolthioether.[21] These β-ketosulfides, as well as their enolthioethers derivatives, have been described in a number of synthetic applications[22] but to the best of our knowledge they have never been used in

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Electronic Supplementary Information (ESI) including ^1H and ^{13}C NMR spectra, HPLC traces, CIF data for compound **5a** and additional experimental procedures available: DOI: 10.1039/x0xx00000x

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DOI: 10.1039/C6OB00160B

enantioselective procedures. The chemical versatility of sulfur-containing building blocks should also facilitate the use of such compounds in a wide number of subsequent transformations. For all of these reasons, we undertook a study of 2-(arylthio)cyclobutanone derivatives as nucleophiles in new organocatalyzed Michael addition reactions with β-nitrostyrenes.

Results and discussion

To begin, a catalyst screening was conducted. The catalysts examined are illustrated in Figure 1 and fall into four categories: L-Proline derivatives **I-V**, cinchona alkaloid derivatives **VI-VII**, thiourea–amine derivatives **VIII-XII**, and two squaramide derivatives **XIII-XIV**. The model Michael addition reaction between (±)-2-(phenylthio)cyclobutanone **1a**[23] and *trans*-β-nitrostyrene **2a** was selected to examine using each of these catalysts in appropriate solvents at room temperature for 2 days.

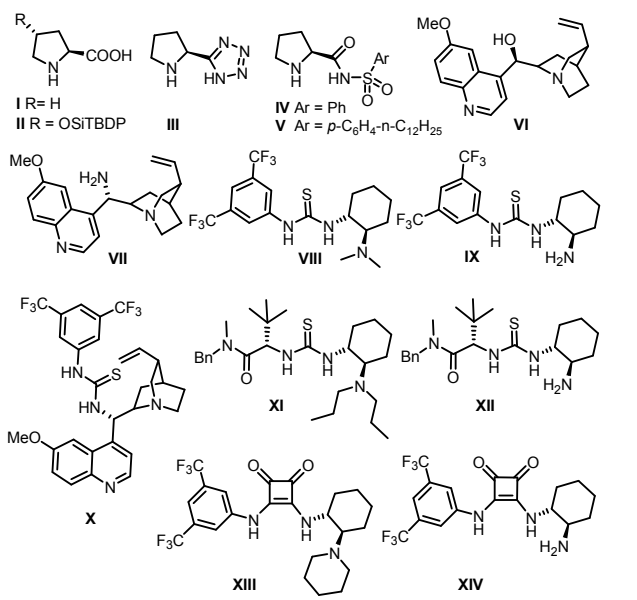

Figure 1. Catalysts **I-XIV** studied in this work.

The first series of experiments was conducted in the presence of 20 mol% of a proline derivative (Table 1). The use of L-proline **I** itself in DMSO (entry 1) led to the formation of two Michael adducts in a 10:1 ratio and a combined yield of 44%. The major product was isolated and ^{1}H NMR and NOESY analysis revealed that its structure was *iso*-**3a**, obtained with a notable 10:1 diastereoselectivity. The quaternary regioisomeric adduct **3a** was identified as the minor product (configuration not determined). Formation of this product is rationalized by the hypothesis that the reaction proceeds preferentially via the formation of the less-hindered enamine (implicating the C4 center) due to the steric bulk of the PhS group.[24] Improved results were achieved using catalyst **II** in DMSO (entry 2), which provided a higher conversion of **1a**, an excellent product selectivity in favour of *iso*-**3a**, and a very high diastereoselectivity for this compound. In toluene (entry 3) the high selectivities observed using catalyst **II** were maintained but the conversion was diminished; the reaction failed to proceed in dichloromethane (entry 4). The use of catalysts **III-V** in DMSO (entries 5-7) progressed with lower conversions and reduced selectivities. While several aspects of this first-round study were encouraging, unfortunately all of the isolated samples of the main product *iso*-**3a** were close to racemic. Likewise, HPLC analysis of the recovered unreacted cyclobutanone **1a** showed this material to be racemic indicating no kinetic or dynamic resolution was operating.

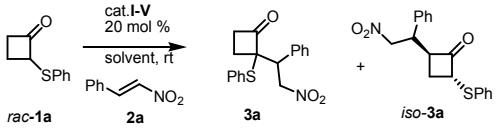

Table 1. Michael addition reaction of cyclobutanone **1a** with *trans*-β-nitrostyrene **2a** using catalysts **I-V**.[a]

Entry	Cat.	Solvent	Y(**3a**+*i*-**3a**)(%)[b]	**3a**:*i*-**3a**[c]	*i*-**3a** *d.r.*[c]	*i*-**3a** *e.r.*[d]
1	**I**	DMSO	44	17:83	9:91	57:43
2	**II**	DMSO	62	2:98	2:98	55:45
3	**II**	toluene	25	4:96	4:96	53:47
4	**II**	CH_2Cl_2	–[e]			
5	**III**	DMSO	35	26:74	21:79	52:48
6	**IV**	DMSO	28	23:77	16:84	59:41
7	**V**	DMSO	30	19:81	13:87	43:57

[a] Reactions were carried out in a 5 mL vial with **1a** (0.56 mmol), **2a** (0.56 mmol), cat. **I-V** (20 mol %) in the reported solvents (1.5 mL) at room temperature (48 h). [b] Yields were determined by weight after chromatography. [c] **3a**:*iso*-**3a** ratios and *iso*-**3a** *d.r.* values were determined by ^{1}H NMR analysis ($CDCl_3$) of the crude reaction mixtures. [d] *iso*-**3a** *e.r.* values were determined by chiral HPLC. [e] No reaction.

Unsatisfied with these results, we turned our attention to the model reaction of **1a** with **2a** in the presence of 20 mol % of the other catalysts **VI-XIV**; toluene was a more convenient solvent for these reactions (Table 2). The cinchona-derived catalysts **VI** and **VII** induced the formation of the quaternary Michael adduct **3a** (implicating reaction at the C2 center) in low yields and diastereoselectivities (entries 1 and 2). When the reaction was carried out in the presence of thiourea–tertiary amines **VIII** or **X** (entries 3 and 5) the yields of **3a** were improved although diastereoselectivities remained low. The related thiourea-primary amine **IX** performed less well, providing **3a** in a lower yield and with a comparable diastereoselectivity; however, in contrast to its tertiary amine congeners, **IX** provided sample of the major diastereomer of **3a** with a more encouraging enantiomeric ratio, better than 4:1 (entry 4). Further improvements were obtained using catalyst **XI** which gave **3a** in 68% yield and a better than 7:1 diastereoselectivity; the diastereoselection in this case was in favour of the *syn*-**3a** isomer (entry 6).[25] The best result in this series of test experiments was achieved using the thiourea–primary amine catalyst **XII**, which afforded *anti*-**3a**, in 84% yield, almost exclusively as a single diastereomer which had an enantiomeric ratio of 99:1 (entry 7). The catalyst screening was

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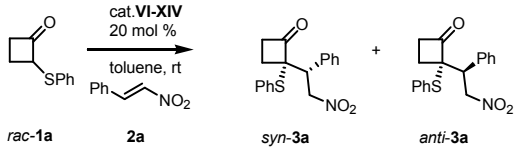
completed by examining the squaramide derivatives **XIII** and **XIV** which gave disappointing results in terms of both product yields and selectivities (entries 8 and 9). The *anti* configuration observed for the major diastereoisomer in all these experiments (with the exception of entry 6) is attributed here on the basis of the x-ray diffraction analysis described later in this manuscript. *Anti*- and *syn*-stereoisomers showed quite similar ^{1}H NMR spectra, although one of the four cyclobutanone ring protons showed a configuration-dependent chemical shift, appearing at 2.31 ppm in *anti*-**3a** and at 1.95 ppm for *syn*-**3a**.



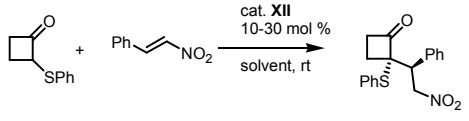
rac-**1a** **2a** *syn*-**3a** *anti*-**3a**

Table 2. Michael addition reaction of cyclobutanone **1a** with *trans*-β-nitro styrene **2a** using catalysts **VI-XIV**.[a]

Entry	Cat.	Yield **3a** (%)[b]	*syn:anti* **3a**[c]	*anti*-**3a** *e.r.*[d]
1	**VI**	16	42:58	23:77
2	**VII**	12	24:76	–[e]
3	**VIII**	64	31:69	53:47
4	**IX**	21	22:78	19:81
5	**X**	50	27:73	52:48
6	**XI**	68	88:12	90:10[f]
7	**XII**	84	1:99	1:99
8	**XIII**	49	14:86	8:92
9	**XIV**	26	20:80	18:82

[a] Reactions were carried out in a 5 mL vial with **1a** (0.56 mmol), **2a** (0.56 mmol), cat. **VI-XIII** (20 mol %) in toluene (1.5 mL) at room temperature (48 h). [b] Yields were determined by weight after chromatography. [c] **3a** *d.r.* values were determined by ^{1}H NMR analysis ($CDCl_3$) of the reaction crude mixtures. [d] *anti*-**3a** *e.r.* values were determined by chiral HPLC. [e] Not determined. [f] The value is given for the major *syn*-**3a** adduct.

The pleasing results obtained using the thiourea–amine **XII** inspired us to pursue studies with this catalyst and explore different reaction conditions in which the solvent, the reagent stoichiometry, the reaction time and the catalyst loading were varied, with a view to optimization (Table 3).



rac-**1a** **2a** *anti*-**3a**

Table 3. Michael addition reaction of cyclobutanone **1a** with *trans*-β-nitro styrene **2a** using catalyst **XII** in different conditions.[a]

Entry	Solv.	Cat.(mol%)	**1a**:**2a**	time(h)	**3a** Y(%)[b]	**3a** *d.r*[c]	**3a** *e.r.*[d]
1	*n*-hexane	20	1:1	168	27	1:99	10:90
2	EtOAc	20	1:1	48	20	1:99	10:90
3	*m*-xylene	20	1:1	48	19	7:93	–[e]
4	CH_2Cl_2	20	1:1	36	13	13:87	13:87
5	$CHCl_3$	20	1:1	72	29	10:90	9:91
6	dioxane	20	1:1	48	22	28:72	–[e]
7	THF	20	1:1	48	20	21:79	22:78
8	toluene	20	1:1	48	80	1:99	1:99
9	toluene	10	1:1	120	48	4:96	3:97
10	toluene	15	1:1	48	72	1:99	2:98
11	toluene	30	1:1	48	71	2:98	2:98
12	toluene	15	1:3	48	81	1:99	2:98
13	toluene	15	3:1	48	49	4:96	4:96
14	toluene	15	1:6	48	63	2:98	3:97
15	toluene	15	1:10	48	28	8:92	7:93

[a] Reactions were carried out in a 5 mL vial with **1a** (0.56 mmol), **2a** (0.56 mmol), cat. **XII** (15-30 mol %) in the appropriate solvent (1.5 mL) at room temperature. [b] Yields were determined by weight after chromatography. [c] **3a** *d.r.* values were determined by ^{1}H NMR analysis ($CDCl_3$) of the reaction crude mixtures. [d] *anti*-**3a** *e.r.* values determined by chiral HPLC. [e] Not determined.

Firstly, the effect of the solvent was assessed in reactions using 20 mol% catalyst and 1 equivalent each of **1a** and **2a**. In *n*-hexane the diastereoselectivity was high but the reaction was very slow and inefficient; after seven days, compound **3a** was obtained in only 27% yield (entry 1). Reactions remained sluggish in several other solvents (entries 2-7) and in some cases selectivity was compromised. We therefore returned to toluene as the solvent of choice for the evaluation of the reagent stoichiometry and catalyst loading parameters. Using 20 mol% catalyst and 1 equivalent each of **1a** and **2a** the adduct **3a** was obtained in 80% yield after 48 hours with excellent diastereo- and enantioselectivity (entry 8). When the catalyst loading was reduced to 10 mol%, the reaction was considerably slower, giving **3a** in 48% yield only after 5 days (entry 9). On the other hand, an increased catalyst loading of 30 mol% did not provide any benefit in terms of yield or selectivity (entry 11). A 72% yield of **3a** with very high selectivity was achieved in 2 days, when 15 mol% of catalyst **XII** was employed (entry 10). The use of a 3-fold excess of the cyclobutane substrate **1a** reduced the yield of the adduct **3a** somewhat (entry 13), whereas the use of an 3-fold excess of *trans*-β-nitrostyrene **2a** resulted in an increase of the yield of **3a** to 81%, still characterized by high diastereo- and enantioselectivities (entry 12) and considered by us the best reaction condition for this transformation. Further increases in the excess of the nitrostyrene did not improve on this result (entries 14 and 15). The optimized protocol was therefore concluded as being the use of 15 mol% of catalyst **XII** in toluene at room temperature for 2 days with a 1:3 **1a**/**2a** ratio.
We then turned our attention to the **XII**-catalyzed Michael addition reactions involving other 2-(arylthio)cyclobutanones in order to establish the reaction scope and to evaluate the electronic effects, if any, of substituents present on the sulfanyl aromatic moiety. For these purposes, a panel of *p*-substituted derivatives of racemic 2-(phenylthio)cyclobutanone **1b-g** was prepared[23] and each was submitted to a Michael addition reaction with *trans*-β-

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nitrostyrene **2a** to afford the corresponding C2 quaternary cyclobutanone **3b-g** (Table 4). In each case, the Michael adduct **3b-g** was obtained in good yield, with very high *anti* diastereoselectivity, and with high enantiomeric enrichment. The major *anti* configuration was suggested by the uniformly low-field chemical shift values (>2.2 ppm) observed for the cyclobutanone proton discussed above for **3a**. Only marginal differences in the terms of yield and selectivity were observed across the substrate panel, suggesting no significance of the electronic effects present in the arylthio moiety for either the formation of the intermediate enamine or the progress of the reaction.

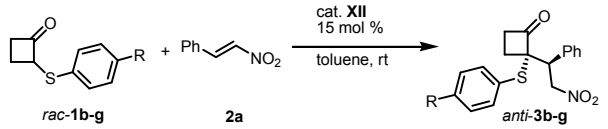
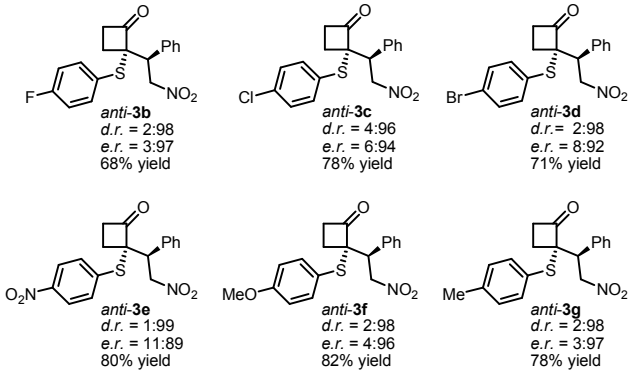


Table 4. Michael addition reactions of cyclobutanones **1b-g** with *trans*-β-nitrostyrene **2a** using catalyst **XII** in optimized conditions.[a-d]



[a] Reactions were carried out in a 5 mL vial with **1b-g** (0.56 mmol), **2a** (1.68 mmol), cat. **XII** (15 mol %) in toluene (1.5 mL), room temperature (48 h). [b] *d.r.* values were determined by ^{1}H NMR analysis ($CDCl_3$). [c] Yields were determined by weight after chromatography. [d] *e.r.* values determined by chiral HPLC.

In the next series of experiments, we evaluated the scope of the reaction and the significance, if any, of the electronic and steric effects prevalent in the *trans*-β-nitrostyrene component. For this purpose, a panel of differently substituted β-nitrostyrene derivatives **2b-l** was selected and each was submitted to a Michael addition reaction with racemic 2-(phenylthio)cyclobutanone **1a**, using the optimized reaction conditions established above, to afford the corresponding C2 quaternary cyclobutanones **4b-l** (Table 5). Compound **1a** reacted smoothly with the *p*-substituted *trans*-β-nitrostyrene derivatives **2b-g**, bearing either an electron-donating or an electron-withdrawing group, affording the corresponding *anti* derivatives **4b-f** (showing low-field chemical shift values for the relevant cyclobutanone proton in ^{1}H NMR spectra) with good yields (57-78%) and with excellent diastereoselectivities and *e.r.* values. The reaction with the *m,p*-methylenedioxy derivative **2h** to give **4h** worked equally well, and the reaction also proceeded with the *o,p*-disubstituted and *o,o*-disubstituted *trans*-β-nitrostyrenes, **2i** and **2j**, with only marginally lower yields and unaffected high stereoselectivities. These observations gratifyingly illustrated a general tolerance of electronic and steric effects on the aryl moiety of the *trans*-β-nitrostyrene component.

To probe the limits of the reaction scope, cyclobutanone **1a** was placed with nitroalkenes **2k** and **2l** in the standard Michael addition conditions. The reaction failed to proceed with these substrates and almost complete recovery of the unchanged starting materials was observed. This result is in line with comparable observations, reported previously by Wennemers and co-workers,[26] of the low reactivity of α- or β-substituted β-nitrostyrenes with sterically hindered nucleophiles in C–C bond-forming reactions.

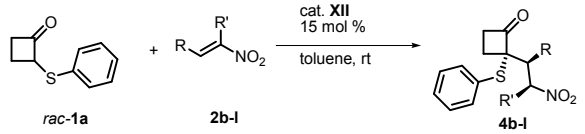
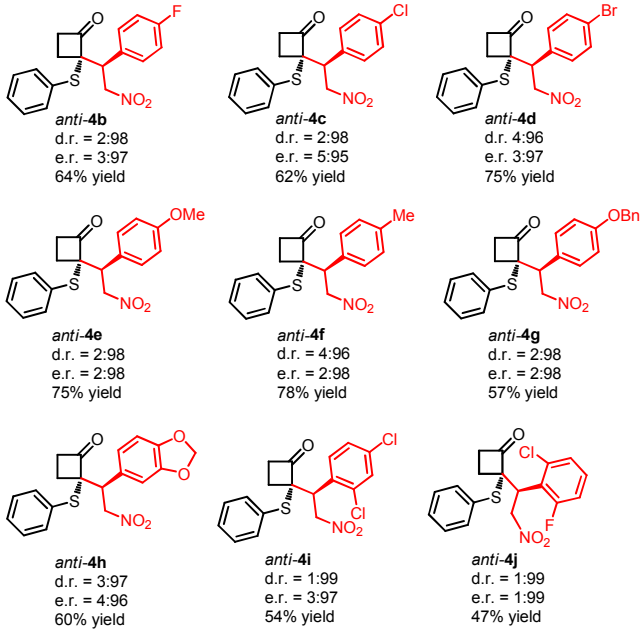
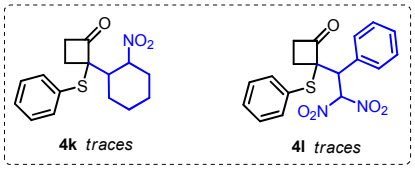


Table 5. Michael addition reactions of cyclobutanone **1a** with *trans*-β-nitrostyrene derivatives **2b-l** using catalyst **XII** in optimized conditions.[a-d]





[a] Reactions were carried out in a 5 mL vial with **1a** (0.56 mmol), nitrostyrene **2b-l** (1.68 mmol), cat. **XII** (15 mol %) in toluene (1.5 mL) at room temperature (48 h). [b] *d.r.* values of compounds **4b-j** were determined by ^{1}H NMR analysis ($CDCl_3$) of the reaction crude mixtures. [c] Yields were determined by weight after chromatography. [d] *e.r.* values determined by chiral HPLC.

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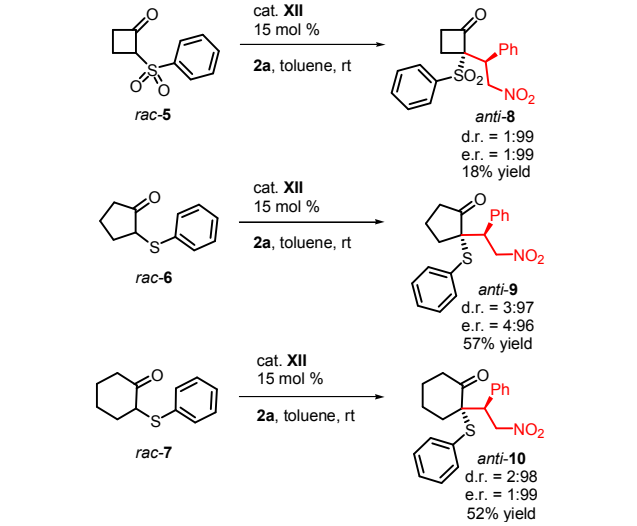
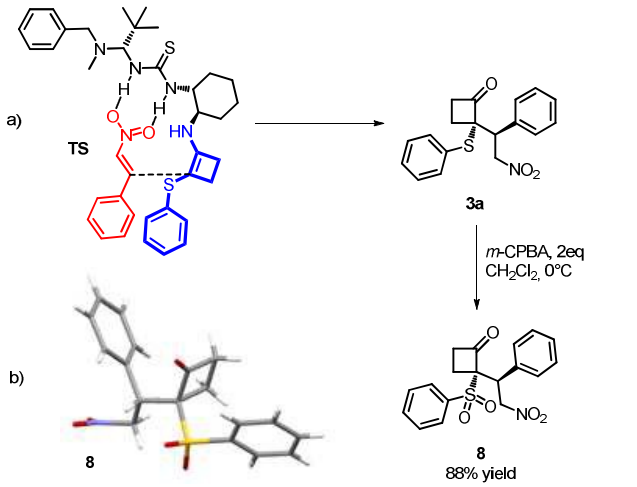
Satisfied with the results obtained thus far in our investigation, we extended the methodology by applying it to other related ketone substrates (Scheme 1). The α-sulfonyl cyclobutanone (±)-**5** reacted only very slowly with *trans*-β-nitrostyrene **2a** in the presence of catalyst **XII**, yielding the quaternary Michael adduct *anti*-**8** in low yield as a single diastereoisomer. The α-sulfanyl cyclopentanone and cyclohexanone substrates, (±)-**6** and (±)-**7**, both reacted with *trans*-β-nitrostyrene **2a** in the standard conditions to provide the single diastereoisomeric adducts *anti*-**9** and *anti*-**10**, in 57 % (*e.r.* 4:96) and 52 % (*e.r.* 1:99) yields, respectively.



Scheme 1. Reaction of other cyclic ketone substrates **5-7** with *trans*-β-nitrostyrene **2a** using catalyst **XII** in optimized conditions.

In order to establish the stereochemical profile of the Michael addition reactions described in this work, the major diastereoisomer of **3a** (described in Table 2) was oxidized using *m*-CPBA in dichloromethane, to give sulfone **8**, in 88% yield (Scheme 2). This compound was spectroscopically identical (superimposable ^{1}H and ^{13}C NMR spectra, same sign for specific rotation) with the sample of **8** obtained in Scheme 1. X-Ray diffraction analysis of a single crystal of the new sample of **8** revealed the *anti* diastereoisomeric structure with the *R* configuration at the quaternary cyclobutanone C2 center and the *S* configuration at the new exocyclic stereogenic center (Scheme 2).[27] This observation is in good agreement with our previous work using catalyst **XII** for Michael addition reactions of 3-substituted cyclobutanones with *trans*-β-nitrostyrenes, which exhibited the same stereochemical selectivities at the two above-mentioned sereocenters.[18] On the basis of the similarities in the ^{1}H and ^{13}C-NMR spectroscopic signatures it is proposed by extension that the same configuration pattern prevails for the major stereoisomer throughout the series of compounds **3a-g**, **4b-j**, **8-10** prepared in this work.

A plausible transition state model, which explains the formation of the major *anti*-cyclobutanone adducts **3a-g** and **4a-i** with the attributed stereochemistry, is illustrated in Scheme 2. In this representation, cyclobutanone **1a** interacts with catalyst **XII** leading to the formation of an enamine intermediate able to interact with the β-nitrostyrene **2a** bound to the thiourea moiety of the catalyst via hydrogen-bonding interactions.[17,18] The geometrical alignment of the two reactive entities in the transition state for the formation of the new C-C bond is therefore responsible for the observed enantioselectivity of the reaction, leading to the isomer (2*R*,1'*S*)-**3a** after hydrolytic liberation of the ketone from the catalyst manifold.



Scheme 2. a) Plausible transition state (TS) model for the formation of cyclobutanone **3a**. b) Oxidation of adduct **3a** to sulfone **8** and ORTEP plot of the single crystal X-ray structure of this compound (see the Supporting Information for details).

Conclusions

In summary, we have developed a new, deracemizing organocatalyzed Michael addition reaction between 2-(arylthio)cyclobutanones and *trans*-β-nitrostyrenes which provides access to a selection of new C2 quaternary cyclobutanone derivatives in good yields and with excellent regio-, diastereo- and enantio-selectivities. The extent of substrate tolerance in both the electrophile and the nucleophile, the successful preliminary extensions to other cyclic ketone substrates, the reactivity potential embedded in the highly-functionalized adducts, and the general simplicity and feasibility of this C–C bond-forming reaction make it a useful addition to the existing inventory of organocatalyzed reactions currently available as tools for fine organic synthesis.

Acknowledgements

The authors gratefully acknowledge R.A.S. "Sardinia Regional Government" for financial support (P.O.R. Sardegna F.S.E. Operational Programme of the Autonomous Region of Sardinia, European Social Fund 2007-2013-Axis IV Human Resources, Objective l.3, Line of Activity l.3.1) and C.I.N.M.P.I.S. (Consorzio Interuniversitario Nazionale di Ricerca

View Article Online
DOI: 10.1039/C6OB00160B

in Metodologie e Processi Innovativi di Sintesi). Funding by the Université Paris-Sud, the CHARM3AT LabEx, and the Ile-de-France Region (SESAME program 2012 N°12018501) for Instrument resources is acknowledged.

Experimental section

General information

^{1}H NMR spectra were recorded on 400 and 500 MHz Varian spectrometers at 27 °C using $CDCl_3$, DMF-d_7, acetone-d_6 or DMSO-d_6 as solvent. ^{13}C NMR spectra were recorded at 100 and 125 MHz at 27 °C using $CDCl_3$, DMF-d_7 or DMSO-d_6 as solvent. Chemical shifts (δ) are given in ppm. Coupling constants (*J*) are reported in Hz. Infrared spectra were recorded on a FT-IR Bruker spectrophotometer and are reported in wavenumbers. High resolution mass spectra (HRMS) were obtained using positive mode Electrospray ionization (ESI). Optical rotation values were recorded with a PolAAr 32 instrument. Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 70-200 mesh silica gel. Yields refer to chromatographically and spectroscopically pure materials. Enantiomeric ratios (*e.r.*) of Michael adduct cyclobutanones reported in the text were determined by analytical HPLC using a Diacel Chiralpak AD-H, a Chiracel OJ, a Chiracel AS-H or a Phenomenex Lux Cellulose-1 analytical column, with *i*-PrOH/Hexane as the moble phase. Authentic racemic samples were used for reference comparisons. All 2-(arylthio)cycloalkanones **1a-g**, **6** and **7** were prepared using the recent literature protocol.[23] β-Nitrostyrene and its derivatives **2a-l** were purchased from Sigma-Aldrich or Alfa-Aesar and used without further purification. Catalyst **XII** was purchased from Sigma-Aldrich or prepared according to the literature procedure.[28]

Synthesis of *2-(phenylsulfonyl)cyclobutanone* 5.
To a stirred solution of cyclobutanone **1a** (300 mg, 1.68 mmol) in $CHCl_3$ (20 mL) cooled to –20 °C, commercial *m*-CPBA (70% pure; 752 mg, 3.36 mmol), was added portion-wise over 20 min. The reaction mixture was monitored by TLC and stirred until the reaction was complete (5 h). The resulting suspension was filtered through a pad of celite, which was washed through with $CHCl_3$. The organic layer was washed successively with saturated aqueous $NaHCO_3$ solution, water, then brine. It was then dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes:diethyl ether, gradient 90:10 to 50:50) affording the pure product **5** as a pale yellow solid, in 78% yield. Mp = 68-70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85-7.80 (m, 2H), 7.64-7.58 (m, 1H), 7.55-7.47 (m, 2H), 4.72-4.61 (m, 1H), 3.23 (dddd, *J* = 18.3, 11.1, 7.2, 2.8 Hz, 1H), 3.14-3.02 (m, 1H), 2.57 (ddt, *J* = 12.8, 11.1, 6.4 Hz, 1H), 2.35 (dtd, *J* = 12.7, 9.8, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.0, 137.9, 134.2, 129.3, 128.5, 78.8, 47.6, 13.6. This compound was prepared previously using a different method.[29]

General procedure for the organocatalyzed Michael reactions of ketones 1a-g and 5-7 with nitrostyrenes.

In a 5 mL vial, a solution of the appropriate ketone (0.56 mmol), the appropriate nitrostyrene (1.68 mmol) and catalyst **XII** (15 mol %), in dry toluene (1.5 mL) was stirred for 36 h at room temperature. The reaction mixture was directly purified by flash chromatography (hexanes:diethyl ether, gradient 95:5 to 50:50) to affording the corresponding pure product.

*(2R,1'S)-2-(2-nitro-1-phenylethyl)-2-(phenylthio)cyclobutanone anti-***3a**. Yellow oil. FTIR (neat) ν: 2952, 2342, 1790, 1566, 1051 cm^{-1}; $[\alpha]^{25}_D$ = +19.2 (*c*. 0.36, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.51-7.48 (m, 2H), 7.39-7.34 (m, 1H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.23 (dt, *J* = 6.9, 6.2 Hz, 3H), 7.19-7.15 (m, 2H), 5.25 (dd, *J* = 13.4, 3.8 Hz, 1H), 4.88 (dd, *J* = 13.3, 11.9 Hz, 1H), 3.89 (dd, *J* = 11.8, 3.7 Hz, 1H), 2.88 (ddd, *J* = 17.9, 10.6, 7.3 Hz, 1H), 2.44 (ddd, *J* = 17.9, 10.3, 5.6 Hz, 1H), 2.31 (ddd, *J* = 12.3, 10.4, 7.4 Hz, 1H), 1.76 (ddd, *J* = 12.4, 10.7, 5.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.2, 136.2, 133.9, 130.1, 129.5, 129.2, 129.2, 129.0, 128.5, 75.0, 72.6, 45.2, 43.6, 21.2; HRMS (ESI): calcd for $C_{18}H_{17}NNaO_3S$: 350.0827 (M+Na$^+$), found: 350.0829. HPLC analysis (Phenomenex Lux-1 column, *i*-PrOH/Hexane 5:95, 1.0 mL/min. λ = 254 nm, t_R (major) = 20.78 min, t_R (minor) = 18.44 min.

*2-(2-nitro-1-phenylethyl)-2-(phenylthio)cyclobutanone syn-***3a** Colourless oil. FTIR (neat) ν: 2994, 2344, 1791, 1542, 1048 cm^{-1}; $[\alpha]^{25}_D$ = +19.2 (*c*. 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.50-7.47 (m, 2H), 7.40-7.32 (m, 3H), 7.27-7.19 (m, 3H), 7.08-7.04 (m, 2H), 5.27 (dd, *J* = 13.3, 3.8 Hz, 1H), 5.06 (dd, *J* = 13.2, 11.5 Hz, 1H), 3.79 (dd, *J* = 11.4, 3.8 Hz, 1H), 2.85 (ddd, *J* = 18.2, 10.5, 7.6 Hz, 1H), 2.39 (ddd, *J* = 18.3, 10.2, 5.8 Hz, 1H), 1.95 (ddd, *J* = 16.5, 10.7, 5.8 Hz, 1H), 1.87 (ddd, *J* = 12.4, 10.3, 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 205.8, 136.1, 135.7, 131.9, 129.9, 129.5, 129.1, 128.6, 128.5, 76.7, 73.7, 48.9, 43.7, 22.0; HRMS (ESI): calcd for $C_{18}H_{17}NNaO_3S$: 350.0827 (M+Na$^+$), found: 350.0831. HPLC analysis (chiral pack AD-H column, *i*-PrOH/Hexane 25:75, 1.0 mL/min. λ = 254 nm, t_R (major) = 24.18 min, t_R (minor) = 22.62 min.

(2*R*,1'*S*)-*2-(4-fluorophenylthio)-2-(2-nitro-1-phenylethyl) cyclobutanone anti-***3b.** Yellow solid. Mp = 135-137 °C; FTIR (KBr) ν: 2993, 2357, 1789, 1555, 1053 cm^{-1}; $[\alpha]^{25}_D$ = +69.2 (*c*. 0.87, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (dd, *J* = 8.5, 5.3 Hz, 2H), 7.36-7.25 (m, 3H), 7.23 (d, *J* = 7.7 Hz, 2H), 7.09 (t, *J* = 8.5 Hz, 2H), 5.31 (dd, *J* = 13.3, 3.7 Hz, 1H), 5.01-4.89 (m, 1H), 3.91 (dd, *J* = 11.7, 3.7 Hz, 1H), 2.97 (ddd, *J* = 17.7, 10.6, 7.2 Hz, 1H), 2.56-2.47 (m, 1H), 2.44-2.35 (m, 1H), 1.87-1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.8, 165.2, 138.4 (d, *J* = 8.5 Hz), 133.4 (d, *J* = 29.0 Hz), 129.0, 128.9, 128.4, 124.3, 116.5 (d, *J* = 21.9 Hz), 74.7, 72.4, 45.0, 43.5, 20.7; HRMS (ESI): calcd for $C_{18}H_{16}FNNaO_3S$: 368.0727 (M+Na$^+$), found: 368.0714. HPLC analysis (Phenomenex Lux-1 column, *i*-PrOH/Hexane 5:95, 1.0 mL/min. λ = 254 nm, t_R (major) = 21.51 min, t_R (minor) = 23.97 min.

*(2R,1'S)-2-(4-chlorophenylthio)-2-(2-nitro-1-phenylethyl)cyclobutanone anti-***3c.** Yellow solid. Mp = 91-94

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DOI: 10.1039/C6OB00160B

°C; FTIR (KBr) ν: 2984, 2344, 1789, 1557, 1060 cm^{-1}; $[\alpha]^{22}_D$ = +107.4 (*c*. 0.48, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.50 (d, *J* = 8.4 Hz, 2H), 7.42-7.35 (m, 2H), 7.34-7.27 (m, 3H), 7.24 (t, *J* = 7.5 Hz, 2H), 5.29 (dd, *J* = 13.4, 3.7 Hz, 1H), 4.95 (t, *J* = 12.5 Hz, 1H), 3.93 (dd, *J* = 11.7, 3.6 Hz, 1H), 3.00 (ddd, *J* = 17.7, 10.5, 7.1 Hz, 1H), 2.60-2.46 (m, 1H), 2.45-2.34 (m, 1H), 1.90-1.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.7, 161.8, 137.3, 133.5, 129.6, 129.0, 128.9, 128.5, 127.6, 74.7, 72.4, 45.0, 43.5, 20.8; HRMS (ESI): calcd for $C_{18}H_{16}ClNNaO_3S$: 384.0432 ($M+Na^+$), found: 384.0415. HPLC analysis (Phenomenex Lux-1 column, *i*-PrOH/Hexane 5:95, 1.0 mL/min. λ = 254 nm, t_R (major) = 27.01 min, t_R (minor) = 24.15 min.

(2R,1'S)-2-(4-bromophenylthio)-2-(2-nitro-1-phenylethyl)cyclobutanone anti-**3d.** White solid. Mp = 132-133; FTIR (KBr) ν: 2949, 2350, 1790, 1563, 1064 cm^{-1}; $[\alpha]^{20}_D$ = +39.8 (*c*. 0.10, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.45 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.27-7.19 (m, 3H), 7.17-7.14 (m, 2H), 5.21 (dd, *J* = 13.4, 3.8 Hz, 1H), 4.87 (dd, *J* = 13.3, 11.8 Hz, 1H), 3.86 (dd, *J* = 11.7, 3.7 Hz, 1H), 2.92 (ddd, *J* = 17.9, 10.6, 7.2 Hz, 1H), 2.45 (ddd, *J* = 18.0, 10.4, 5.7 Hz, 1H), 2.33 (ddd, *J* = 12.4, 10.4, 7.2 Hz, 1H), 1.75 (ddd, *J* = 12.5, 10.6, 5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 202.8, 137.6, 133.7, 133.7, 132.7, 129.1, 129.0, 128.6, 125.0, 74.6, 72.5, 45.1, 43.7, 21.0; HRMS (ESI): calcd for $C_{18}H_{16}BrNNaO_3S$: 427.9926 ($M+Na^+$), found: 427.9907. HPLC analysis (Phenomenex Lux-1 column, *i*-PrOH/Hexane 5:95, 1.0 mL/min. λ = 254 nm, t_R (major) = 32.83 min, t_R (minor) = 28.65 min.

(2R,1'S)-2-(4-nitrophenylthio)-2-(2-nitro-1-phenylethyl)cyclobutanone anti-**3e.** Yellow oil. FTIR (neat) ν: 2997, 2340, 1790, 1576, 1478, 1242 cm^{-1}; $[\alpha]^{20}_D$ = +31.7 (*c*. 0.26, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 8.24 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 4.5 Hz, 3H), 7.14–7.11 (m, 2H), 5.19 (dd, *J* = 13.2, 4.2 Hz, 1H), 5.11-5.01 (m, 1H), 3.97 (dd, *J* = 10.7, 4.2 Hz, 1H), 3.18 (ddd, *J* = 18.2, 10.4, 7.6 Hz, 1H), 2.73-2.61 (m, 1H), 2.29-2.15 (m, 1H), 2.14-2.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.1, 139.0, 134.6, 133.7, 133.3, 129.3, 129.1, 128.7, 124.3, 74.8, 44.9, 43.7, 22.7, 20.9; HRMS (ESI): calcd for $C_{18}H_{16}N_2NaO_5S$: 395.0678 ($M+Na^+$), found: 395.0683. HPLC analysis (Phenomenex Lux-1 column, *i*-PrOH/Hexane 5:95, 1.0 mL/min. λ = 254 nm, t_R (major) = 35.90 min, t_R (minor) = 41.57 min.

(2R,1'S)-2-(4-methoxyphenylthio)-2-(2-nitro-1-phenylethyl) cyclobutanone anti-**3f.** Colourless solid. Mp = 123-124 °C; FTIR (ATR) ν: 2934, 2345, 1790, 1556, 1052 cm^{-1}; $[\alpha]^{20}_D$ = +68.5 (*c*. 1.342, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.22 (ddt, *J* = 18.5, 11.7, 4.2 Hz, 6H), 7.10-7.04 (m, 2H), 6.94-6.85 (m, 1H), 5.24 (dd, *J* = 13.4, 3.8 Hz, 1H), 4.87 (dd, *J* = 13.2, 12.0 Hz, 1H), 3.92 (dd, *J* = 11.8, 3.8 Hz, 1H), 3.75 (s, 3H), 2.91 (ddd, *J* = 17.7, 10.6, 7.2 Hz, 1H), 2.42 (ddd, *J* = 17.8, 10.3, 5.5 Hz, 1H), 2.30 (ddd, *J* = 12.3, 10.4, 7.2 Hz, 1H), 1.75 (ddd, *J* = 12.3, 10.8, 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.2, 130.2, 130.0, 129.0, 128.8, 128.4, 127.9, 120.4, 116.3, 74.8, 72.3, 55.4, 44.9, 43.5, 20.9; HRMS (ESI): calcd for $C_{19}H_{19}NNaO_4S$: 380.0927 ($M+Na^+$), found: 380.0915. HPLC analysis (Phenomenex Lux-1 column, *i*-PrOH/Hexane 5:95, 1.0 mL/min. λ = 254 nm, t_R (major) = 27.82 min, t_R (minor) = 25.75 min.

(2R,1'S)-2-(p-tolylthio)-2-(2-nitro-1-phenylethyl)cyclobutanone anti-**3g.** White solid. Mp = 83-85 °C; FTIR (ATR) ν: 2989, 2354, 1790, 1585, 1440 cm^{-1}; $[\alpha]^{21}_D$ = +71.0 (*c*. 1.07, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.37 (d, *J* = 8.0 Hz, 2H), 7.26-7.20 (m, 3H), 7.20-7.14 (m, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.26 (dd, *J* = 13.4, 3.8 Hz, 1H), 4.88 (dd, *J* = 13.3, 12.0 Hz, 1H), 3.87 (dd, *J* = 11.8, 3.7 Hz, 1H), 2.89 (ddd, *J* = 17.9, 10.5, 7.3 Hz, 1H), 2.43 (ddd, *J* = 17.9, 10.3, 5.6 Hz, 1H), 2.31 (s, 1H), 2.30-2.24 (m, 1H), 1.75 (ddd, *J* = 12.4, 10.7, 5.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.0, 140.4, 136.2, 133.9, 130.1, 129.0, 128.8, 128.3, 125.5, 74.9, 72.5, 45.0, 43.5, 21.3, 20.9; HRMS (ESI): calcd for $C_{19}H_{19}NNaO_3S$: 364.0978 ($M+Na^+$), found: 364.0965. HPLC analysis (Phenomenex Lux-1 column, *i*-PrOH/Hexane 5:95, 1.0 mL/min. λ = 254 nm, t_R (major) = 37.25 min, t_R (minor) = 32.88 min.

(2R,1'S)-2-(1-(4-fluorophenyl)-2-nitroethyl)-2-(phenylthio) cyclobutanone anti-**4b.** Colourless oil. FTIR (neat) cm^{-1} ν: 2889, 2350, 1789, 1562, 1436, 1257 cm^{-1}; $[\alpha]^{20}_D$ = +61.2 (*c*. 0.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.49 (d, *J* = 6.9 Hz, 1H), 7.41-7.30 (m, 4H), 7.20-7.13 (m, 2H), 6.94 (dd, *J* = 11.9, 5.2 Hz, 2H), 5.25 (dd, *J* = 13.4, 3.7 Hz, 1H), 4.87-4.78 (m, 1H), 3.87 (dd, *J* = 11.9, 3.6 Hz, 1H), 2.99-2.88 (m, 1H), 2.53-2.43 (m, 1H), 2.31-2.19 (m, 1H), 1.78 (ddd, *J* = 12.5, 10.7, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.9, 162.5 (d, *J* = 248.3 Hz), 136.1, 130.7 (d, *J* = 8.1 Hz), 130.1, 129.5, 129.4, 128.9, 115.9 (d, *J* = 21.6 Hz), 74.9, 72.3, 44.5, 43.5, 20.9; HRMS (ESI): calcd for $C_{18}H_{16}FNNaO_3S$: 368.0727 ($M+Na^+$), found: 368.0716. HPLC analysis (Phenomenex Lux-1 column, *i*-PrOH/Hexane 5:95, 1.0 mL/min. λ = 254 nm, t_R (major) = 17.63 min, t_R (minor) = 18.64 min.

(2R,1'S)-2-(1-(4-chlorophenyl)-2-nitroethyl)-2-(phenylthio) cyclobutanone anti-**4c.** Yellow oil. FTIR (neat) ν: 2967, 2340, 1789, 1558, 1442, 1378 cm^{-1}; $[\alpha]^{25}_D$ = +53.4 (*c*. 0.22, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.48-7.45 (m, 2H), 7.40-7.35 (m, 5H), 6.95 (d, *J* = 8.4 Hz, 2H), 5.23 (dd, *J* = 13.4, 3.9 Hz, 1H), 5.00 (dd, *J* = 13.3, 11.6 Hz, 1H), 3.76 (dd, *J* = 11.5, 3.7 Hz, 1H), 2.92 (ddd, *J* = 18.3, 10.5, 7.7 Hz, 1H), 2.45 (ddd, *J* = 18.3, 10.1, 5.6 Hz, 1H), 1.96 (ddd, *J* = 12.4, 10.7, 5.6 Hz, 1H), 1.86 (ddd, *J* = 12.5, 10.2, 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 205.2, 136.1, 134.7, 132.3, 130.3, 130.0, 129.5, 129.3, 122.6, 76.4, 73.3, 48.1, 43.7, 21.9; HRMS (ESI): calcd for $C_{18}H_{16}ClNNaO_3S$: 384.0432 ($M+Na^+$), found: 384.384.0426. HPLC analysis (Phenomenex Lux-1 column, *i*-PrOH/Hexane 5:95, 1.0 mL/min. λ = 254 nm, t_R (major) = 25.41 min, t_R (minor) = 21.935 min.

(2R,1'S)-2-(1-(4-bromophenyl)-2-nitroethyl)-2-(phenylthio) cyclobutanone anti-**4d.** Yellow solid, Mp = 121-124 °C; FTIR (ATR) ν: 2923, 2356, 1790, 1460, 1045 cm^{-1}; $[\alpha]^{26}_D$ = +63.4 (*c*. 0.43, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.46 (m, 2H), 7.39-7.34 (m, 5H), 6.95 (d, *J* = 5.0 Hz, 2H), 5.23 (dd, 1H, *J* = 5.0, 10.0 Hz), 5.00 (dd, *J* = 10.0, 15.0 Hz, 1H), 3.76 (dd, *J* = 5.0, 15.0 Hz, 1H), 2.95-2.89 (m, 1H), 2.47-2.45 (m, 1H), 1.99-1.93 (m, 1H), 1.91-1.85 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 205.2, 136.1, 134.7, 132.3, 130.3, 130.0, 129.5, 129.3, 122.6,

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DOI: 10.1039/C6OB00160B

76.4, 73.3, 48.1, 43.7, 21.9; HRMS (ESI): calcd for $C_{18}H_{16}BrNNaO_3S$: 427.9926 ($M+Na^+$), found: 427.9913. HPLC analysis (Chiralpack AD-H column, *i*-PrOH/Hexane 10:90, 1.0 mL/min. λ = 254 nm, t_R (major) = 43.98 min, t_R (minor) = 41.76 min.

*(2R,1'S)-2-(1-(4-methoxyphenyl)-2-nitroethyl)-2-(phenylthio) cyclobutanone anti-***4e.** Yellow oil. FTIR (neat) ν: 2996, 2354, 1790, 1554, 1033 cm^{-1}; $[\alpha]^{21}_D$ = +74.3 (*c*. 1.22, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.52-7.48 (m, 2H), 7.38-7.29 (m, 3H), 7.09 (d, *J* = 8.7 Hz, 2H), 6.77-6.73 (m, 2H), 5.22 (dd, *J* = 13.2, 3.9 Hz, 1H), 4.82 (dd, *J* = 13.2, 12.0 Hz, 1H), 3.83 (dd, *J* = 11.9, 3.8 Hz, 1H), 3.69 (s, 2H), 2.88 (ddd, *J* = 18.0, 10.6, 7.3 Hz, 1H), 2.44 (ddd, *J* = 18.0, 10.3, 5.7 Hz, 1H), 2.29 (ddd, *J* = 12.3, 10.3, 7.3 Hz, 1H), 1.75 (ddd, *J* = 12.4, 10.6, 5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.5, 159.6, 136.2, 130.3, 130.0, 129.4, 125.7, 114.4, 107.4, 75.2, 72.7, 55.3, 44.5, 43.6, 21.0; HRMS (ESI): calcd for $C_{19}H_{19}NNaO_4S$: 380.0927 ($M+Na^+$), found: 380.0925. HPLC analysis (Phenomenex Lux-1 column, *i*-PrOH/Hexane 2:98, 1.0 mL/min. λ = 254 nm, t_R (major) = 43.07 min, t_R (minor) = 39.23 min.

*(2R,1'S)-2-(2-nitro-1-p-tolylethyl)-2-(phenylthio)cyclobutanone anti-***4f.** Yellow solid, Mp = 92-95 °C; FTIR (ATR) ν: 2899, 2348, 1790, 1380, 1061 cm^{-1}; $[\alpha]^{27}_D$ = +26.5 (*c*. 0.62, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.59-7.48 (m, 1H), 7.38 (ddd, *J* = 10.6, 6.4, 2.2 Hz, 2H), 7.08 (s, 2H), 5.26 (dd, *J* = 13.3, 3.8 Hz, 1H), 4.89 (dd, *J* = 13.3, 11.9 Hz, 1H), 3.88 (dd, *J* = 11.8, 3.8 Hz, 1H), 2.91 (ddd, *J* = 17.7, 10.6, 7.2 Hz, 1H), 2.47 (ddd, *J* = 17.8, 10.3, 5.6 Hz, 1H), 2.39-2.30 (m, 1H), 2.26 (s, 2H), 1.79 (ddd, *J* = 12.4, 10.6, 5.6 Hz, 1H), 0.86 (ddt, *J* = 10.3, 6.5, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.4, 138.3, 136.2, 130.8, 130.0, 129.7, 129.4, 129.0, 75.1, 72.6, 44.8, 43.6, 21.2, 21.1; HRMS (ESI): calcd for $C_{19}H_{19}NNaO_3S$: 364.0983 ($M+Na^+$), found: 364.1035. HPLC analysis (Phenomenex Lux-1 column, *i*-PrOH/Hexane 5:95, 1.0 mL/min. λ = 254 nm, t_R (major) = 23.38 min, t_R (minor) = 20.80 min.

*(2R,1'S)-2-(1-(4-(benzyloxy)phenyl)-2-nitroethyl)-2-(phenylthio) cyclobutanone anti-***4g.** White solid. Mp = 62-63 °C; FTIR (ATR) ν: 2964, 1791, 1586, 1253 cm^{-1}; $[\alpha]^{27}_D$ = +31.2 (*c*. 0.71, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.47 (d, *J* = 6.4 Hz, 2H), 7.38-7.24 (m, 8H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.25 (dd, *J* = 13.2, 3.8 Hz, 1H), 5.01 (dd, *J* = 22.2, 9.2 Hz, 1H), 4.93 (s, 2H), 3.74 (dd, *J* = 11.5, 3.8 Hz, 1H), 2.82 (ddd, *J* = 18.2, 10.2, 7.9 Hz, 1H), 2.39 (ddd, *J* = 18.3, 9.9, 6.2 Hz, 1H), 2.00-1.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.3, 158.9, 136.7, 136.2, 130.0, 129.9, 129.7, 129.6, 128.7, 128.2, 127.8, 127.6, 115.4, 76.8, 73.9, 70.2, 48.3, 43.8, 22.1; HRMS (ESI): calcd for $C_{25}H_{23}NNaO_4S$: 456.1240 ($M+Na^+$), found: 456.1286. HPLC analysis (chiralpack-OJ column, *i*-PrOH/Hexane 25:75, 1.0 mL/min. λ = 254 nm, t_R (major) = 31.18 min, t_R (minor) = 46.53 min.

*(2R,1'S)-2-(1-(benzo[d][1,3]dioxol-6-yl)-2-nitroethyl)-2-(phenylthio) cyclobutanone anti-***4h.** Yellow oil. FTIR (neat) ν: 2994, 1791, 1378, 1256 cm^{-1}; $[\alpha]^{24}_D$ = +78.6 (*c*. 0.54, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.52 (dd, *J* = 7.5, 6.0 Hz, 1H), 7.40-7.31 (m, 2H), 7.04 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.96 (d, *J* = 1.6 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.71-6.65 (m, 2H), 5.90 (s, 2H), 5.23 (dd, *J* = 13.3, 3.8 Hz, 1H), 4.81 (dd, *J* = 13.2, 12.1 Hz, 1H), 3.83 (dd, *J* = 11.9, 3.8 Hz, 1H), 3.00-2.86 (m, 1H), 2.62-2.49 (m, 1H), 2.33 (ddd, *J* = 12.4, 10.3, 7.5 Hz, 1H), 1.81 (ddd, *J* = 12.4, 10.7, 5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.2, 147.9, 147.6, 136.0, 129.9, 129.3, 129.1, 127.3, 122.5, 109.3, 108.4, 101.3, 75.1, 72.4, 44.9, 43.5, 21.1; HRMS (ESI): calcd for $C_{19}H_{17}NNaO_5S$: 394.0720 ($M+Na^+$), found: 394.0701. HPLC analysis (Phenomenex Lux-1 column, *i*-PrOH/Hexane 5:95, 1.0 mL/min. λ = 254 nm, t_R (major) = 16.99 min, t_R (minor) = 26.84 min.

*(2R,1'S)-2-(1-(2,4-dichlorophenyl)-2-nitroethyl)-2-(phenylthio) cyclobutanone anti-***4i.** Yellow viscous oil. FTIR (neat) ν: 2996, 2360, 1788, 1436, 1058 cm^{-1}; $[\alpha]^{26}_D$ = +47.4 (*c*. 0.33, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.64-7.55 (m, 2H), 7.49-7.40 (m, 4H), 7.27-7.22 (m, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 5.44 (dd, *J* = 13.8, 3.9 Hz, 1H), 5.21 (dd, *J* = 13.8, 11.4 Hz, 1H), 4.62 (dd, *J* = 11.4, 3.9 Hz, 1H), 3.05 (ddd, *J* = 18.4, 10.7, 7.7 Hz, 1H), 2.51 (ddd, *J* = 18.2, 10.2, 5.6 Hz, 1H), 2.16-2.08 (m, 1H), 1.79 (ddd, *J* = 12.5, 10.2, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 205.0, 136.8, 136.3, 135.0, 132.4, 130.4, 130.3, 129.7, 129.3, 128.8, 128.1, 107.5, 75.6, 73.5, 44.1, 43.9, 22.1; HRMS (ESI): calcd for $C_{18}H_{15}Cl_2NNaO_3S$: 418.0042 ($M+Na^+$), found: 418.0025. HPLC analysis (Phenomenex Lux-1 column, *i*-PrOH/Hexane 3:97, 1.0 mL/min. λ = 254 nm, t_R (major) = 30.23 min, t_R (minor) = 40.38 min.

*(2R,1'S)-2-(1-(2-chloro-6-fluorophenyl)-2-nitroethyl)-2-(phenylthio) cyclobutanone anti-***4j.** Yellow oil. FTIR (neat) ν: 2999, 2355, 1789, 1484, 1258 cm^{-1}; $[\alpha]^{24}_D$ = +38.2 (*c*. 0.22, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.62 (d, *J* = 7.8 Hz, 2H), 7.45 (dd, *J* = 10.7, 3.8 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.17 (dd, *J* = 11.2, 4.9 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.97 (dd, *J* = 11.4, 8.2 Hz, 1H), 5.27 (dd, *J* = 13.2, 4.3 Hz, 1H), 5.19 (t, *J* = 11.5 Hz, 1H), 4.65 (dd, *J* = 10.8, 4.3 Hz, 1H), 3.34-3.23 (m, 1H), 2.80 (dd, *J* = 10.2, 5.4 Hz, 1H), 2.76-2.67 (m, 1H), 1.93-1.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.5, 163.0, 160.5, 136.7, 130.2, 130.1, 129.2, 126.6, 120.6 (d, *J* = 16.1 Hz), 115.1 (d, *J* = 24.6 Hz), 73.5 (d, *J* = 8.6 Hz), 72.4, 43.5, 39.8, 21.1 (d, *J* = 9.4 Hz); HRMS (ESI): calcd for $C_{18}H_{15}ClFNNaO_3S$: 402.0337 ($M+Na^+$), found: 402.0324. HPLC analysis (Chiralpack OJ column, *i*-PrOH/Hexane 5:95, 1.0 mL/min. λ = 254 nm, t_R (major) = 20.78 min, t_R (minor) = 18.44 min.

*(2R,1'S)-2-(2-nitro-1-phenylethyl)-2-(phenylsulfonyl)cyclobutanone anti-***8.** White solid, Mp = 160-162 °C; FTIR (ATR) ν: 3000, 1790, 1480, 1440 cm^{-1}; $[\alpha]^{23}_D$ = +51.4 (*c*. 0.51, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 8.00 (d, *J* = 7.5 Hz, 2H), 7.82 (t, *J* = 7.5 Hz, 1H), 7.70 (t, *J* = 7.8 Hz, 2H), 7.28 (d, *J* = 1.5 Hz, 1H), 7.27 (d, *J* = 1.7 Hz, 2H), 7.09 (dd, *J* = 6.5, 2.8 Hz, 2H), 5.42 (dd, *J* = 13.7, 3.7 Hz, 1H), 4.99 (dd, *J* = 13.6, 12.0 Hz, 1H), 4.07 (dd, *J* = 11.9, 3.7 Hz, 1H), 3.08-2.99 (m, 1H), 2.99-2.90 (m, 1H), 2.61-2.52 (m, 1H), 2.48-2.38 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 197.4, 135.1, 134.7, 132.3, 130.3, 129.5, 129.2, 129.0, 128.7, 88.9, 74.3, 46.8, 42.9, 15.3; HRMS (ESI): calcd for $C_{18}H_{17}NNaO_5S$: 382.0725 ($M+Na^+$), found: 382.0718; HPLC analysis (Chiralpack AD-H column, *i*-PrOH/Hexane 5:95, 1.0 mL/min. λ = 254 nm, t_R (major) = 22.35 min, t_R (minor) = 19.57 min.

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*(2R,1'S)-2-(2-nitro-1-phenylethyl)-2-(phenylthio) cyclopentanone anti-***9.** Yellow oil. FTIR (neat) ν: 2998, 1747, 1485, 1254 cm^{-1}; $[\alpha]^{27}_D$ = +42.3 (*c*. 0.12, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.51-7.46 (m, 2H), 7.42 (d, *J* = 7.5 Hz, 2H), 7.26-7.15 (m, 5H), 5.71 (dd, *J* = 13.2, 3.4 Hz, 1H), 4.99 (t, *J* = 12.8 Hz, 1H), 4.04 (dd, *J* = 12.4, 3.3 Hz, 1H), 2.44 (dd, *J* = 18.3, 8.3 Hz, 1H), 2.37-2.29 (m, 1H), 2.17-2.05 (m, 1H), 1.86 (dd, *J* = 13.6, 6.7 Hz, 1H), 1.79 (dd, *J* = 13.6, 8.6 Hz, 1H), 1.72 (dd, *J* = 18.9, 9.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 204.9, 135.0, 131.8, 128.3, 128.0, 127.1, 126.3, 125.9, 109.9, 74.0, 60.8, 43.0, 34.0, 28.7, 16.0; HRMS (ESI): calcd for $C_{19}H_{19}NNaO_3S$: 364.0978 ($M+Na^+$), found: 364.0969. HPLC analysis (Chiralpack AD-H column, *i*-PrOH/Hexane 5:95, 1.0 mL/min. λ = 254 nm, t_R (major) = 30.50 min, t_R (minor) = 24.96 min.

*(2R,1'S)-2-(2-nitro-1-phenylethyl)-2-(phenylthio) cyclohexanone anti-***10.** White solid. Mp = 92-94 °C; FTIR (ATR) ν: 2964, 1732, 1556, 1261 cm^{-1}; $[\alpha]^{27}_D$ = +37.8 (*c*. 0.30, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.41-7.29 (m, 4H), 7.25-7.06 (m, 6H), 5.49 (dd, *J* = 13.0, 3.2 Hz, 1H), 4.84 (t, *J* = 12.7 Hz, 1H), 4.16 (dd, *J* = 12.4, 3.1 Hz, 1H), 2.99 (ddd, *J* = 15.8, 13.9, 6.3 Hz, 1H), 2.31-2.19 (m, 1H), 2.18-2.10 (m, 1H), 2.06-1.93 (m, 1H), 1.87 (ddd, *J* = 25.0, 11.0, 2.7 Hz, 1H), 1.70-1.61 (m, 2H), 1.39-1.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.5, 135.8, 134.8, 131.8, 130.9, 130.2, 129.4, 128.1, 127.7, 64.6, 56.4, 46.3, 37.8, 32.5, 25.0, 20.7; HRMS (ESI): calcd for $C_{20}H_{21}NNaO_3S$: 378.1134 ($M+Na^+$), found: 378.1172. HPLC analysis (Chiralpack AD-H column, *i*-PrOH/Hexane 5:95, 1.0 mL/min. λ = 254 nm, t_R (major) = 20.61 min, t_R (minor) = 19.18 min.

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DOI: 10.1039/C6OB00160B

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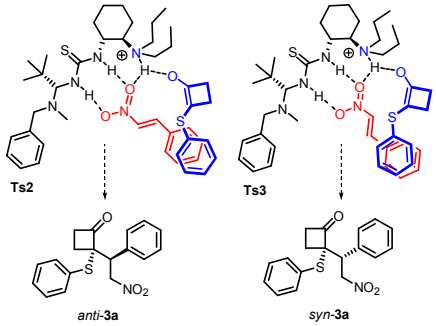

Scheme 3. Hypothetic transition states evoked for the formation of *anti*-**3a** (Ts2) and *syn*-**3a** (Ts3) using catalyst **XI.**

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