

Alma Mater Studiorum Università di Bologna  
Archivio istituzionale della ricerca

Chemodivergent Preparation of Various Heterocycles via Phase-Transfer Catalysis: Enantioselective Synthesis of Functionalized Piperidines

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

*Published Version:*

Chemodivergent Preparation of Various Heterocycles via Phase-Transfer Catalysis: Enantioselective Synthesis of Functionalized Piperidines / Bertuzzi G.; Silvestrini F.; Moimare P.; Pecorari D.; Mazzanti A.; Bernardi L.; Fochi M.. - In: ADVANCED SYNTHESIS & CATALYSIS. - ISSN 1615-4150. - ELETTRONICO. - 362:5(2020), pp. 1167-1175. [10.1002/adsc.201901500]

*Availability:*

This version is available at: <https://hdl.handle.net/11585/787177> since: 2021-01-07

*Published:*

DOI: <http://doi.org/10.1002/adsc.201901500>

*Terms of use:*

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>).  
When citing, please refer to the published version.

(Article begins on next page)

This is the final peer-reviewed accepted manuscript of:

Chemodivergent Preparation of Various Heterocycles via Phase-Transfer Catalysis:  
Enantioselective Synthesis of Functionalized Piperidines

By

*Giulio Bertuzzi\*, Filippo Silvestrini, Pierluigi Moimare, Daniel Pecorari, Andrea  
Mazzanti, Luca Bernardi\* and Mariafrancesca Fochi\**

Advanced Synthesis and Catalysis, 2020, 362(5), 1167-1175.

The final published version is available online at:

<https://onlinelibrary.wiley.com/doi/full/10.1002/adsc.201901500>

Rights / License:

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

# Chemodivergent Preparation of Various Heterocycles *via* Phase-Transfer Catalysis: Enantioselective Synthesis of Functionalized Piperidines

Giulio Bertuzzi<sup>\*a</sup>, Filippo Silvestrini<sup>a</sup>, Pierluigi Moimare<sup>a</sup>, Daniel Pecorari<sup>a</sup>, Andrea Mazzanti<sup>a</sup>, Luca Bernardi<sup>\*a</sup> and Mariafrancesca Fochi<sup>\*a</sup>

<sup>a</sup> Department of Industrial Chemistry “Toso Montanari” & INSTM RU Bologna, Alma Mater Studiorum University of Bologna, V. Risorgimento 4, 40136 Bologna (Italy)  
E-mail: [giulio.bertuzzi2@unibo.it](mailto:giulio.bertuzzi2@unibo.it); [luca.bernardi2@unibo.it](mailto:luca.bernardi2@unibo.it); [mariafrancesca.fochi@unibo.it](mailto:mariafrancesca.fochi@unibo.it)

## Abstract.

In this work, a new chemodivergent domino approach for the preparation of various saturated heterocycles, based on phase-transfer catalysis (PTC) is presented. The versatile nature of doubly electrophilic substrates, showing both a Michael acceptor and a ketone, tethered by a heteroatom, enables three different domino reaction pathways. The nucleophile dictates the chemoselectivity of the reaction. Sulfa-Michael/aldol, cyanide addition/oxa-Michael and Michael/H-shift/aldol processes, along with the variation of the tethering heteroatom, results in the formation of six different classes of saturated heterocycles. DFT calculations account for the observed chemo- and diastereoselectivity of the two most productive processes. Moreover, an extensive investigation on the sulfa-Michael/aldol pathway was carried out, ultimately leading to the development of a new enantioselective domino approach to multi-substituted piperidines based on PTC.

**Keywords:** Phase-Transfer Catalysis; Heterocycles; Cascade Reactions; Asymmetric Synthesis; Sulfa-Michael addition

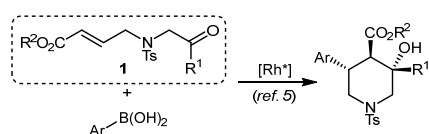
## Introduction

The importance of saturated heterocycles is demonstrated by the large number of biologically active and natural compounds as well as top-selling drugs displaying these motifs.<sup>[1]</sup> Great efforts are therefore dedicated in finding novel and convenient preparations of such scaffolds, with particular interest in the stereochemical control. Tandem and cascade (domino) processes effectively tackle the opportunity to build the desired heterocycle from simple substrates through multiple bond-forming events, in a rapid and efficient fashion.<sup>[2]</sup>

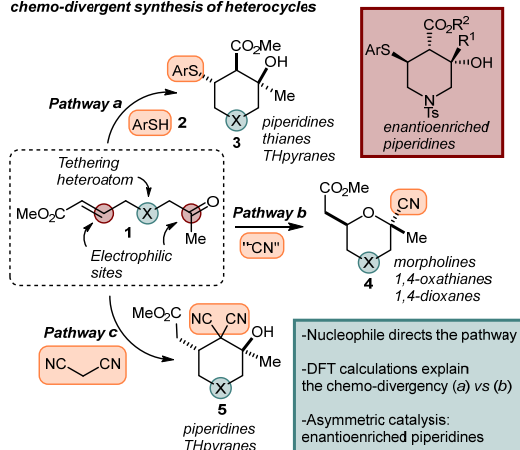
In connection with our interest in organocatalytic reactions aimed to the preparation of enantioenriched heterocycles,<sup>[3]</sup> including domino reactions,<sup>[4]</sup> substrates like **1** (Scheme 1, top) attracted our attention. These were recently engaged by Darses and co-workers in an efficient Rh-catalysed addition/carbocyclization cascade reaction with aryl boronic acids, resulting in the enantioselective

synthesis of piperidines.<sup>[5,6]</sup> The structural feature of substrates **1** (two electrophilic functionalities tethered by an heteroatom) intrigued us. We envisioned that such features could be generalized, providing a fertile ground for disclosing new six-membered heterocycle syntheses, beyond the piperidine framework (Scheme 1, bottom). Two electrophilic functionalities can give rise to divergent reactivity patterns;<sup>[7]</sup> within the same pattern, variation of the tethering heteroatom provides distinct heterocycles. To this aim, we initiated a study by exploring mildly acidic pro-nucleophiles, amenable to activation by organic catalysts, in reactions with substrates **1**. In this paper, we report three different domino reaction pathways (a-c in scheme 1) viable by using phase-transfer catalysis (PTC)<sup>[8]</sup> as enabling tool (Scheme 1, bottom). The pro-nucleophile (thiophenol **2a**, acetone cyanohydrin, malononitrile) dictates the pathway followed by the process, resulting in the chemo-divergent construction of saturated heterocycles (**3**, **4** or **5**) from substrates **1**, thus showing their “pluripotent” nature. For the most productive pathways (a) and (b), the reasons behind the chemo-divergency of the process were analysed and rationalised by DFT calculations. The use of a PTC approach lends itself to enantioselective reactions with chiral catalysts.<sup>[8d-g]</sup> Being such implementation non-trivial, an extensive investigation on pathway (a) was carried out, ultimately leading to the development of a new enantioselective domino approach to multi-substituted piperidines (bearing one quaternary carbon) based on PTC.

-Darses and co-workers: [Rh] catalysed addition-carbocyclisation domino reaction with substrates **1**:



-Exploiting the pluripotency of substrates **1** with PTC: chemo-divergent synthesis of heterocycles

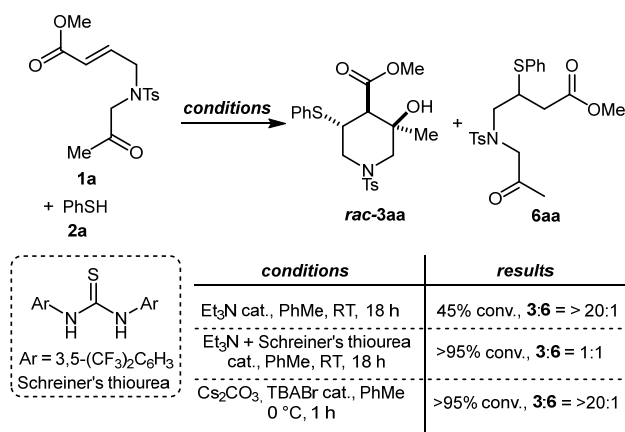


**Scheme 1.** Top, previous work: Metal-catalyzed domino reactions on substrates **1**. Bottom, this work: chemodivergent preparation of various heterocycles

## Results and Discussion

### Chemodivergent Preparation of Various Heterocycles

We initially investigated the reaction of substrate **1a** with thiophenol **2a** (Scheme 2). Despite the challenging nature of sulfa-Michael additions to  $\beta$ -substituted acrylates,<sup>[9]</sup> we hypothesised that a mild basic activation of **2a** could effectively promote a sulfa-Michael<sup>[10]</sup>/aldol domino reaction.<sup>[11]</sup> Indeed, by using simple triethylamine as promoter, the formation of the desired piperidine **rac-3aa**, displaying three contiguous stereocenters, was observed after 18 h at RT, although with moderate conversion. In an attempt to improve the electrophilicity of **1a**, Schreiner's thiourea<sup>[12]</sup> was employed in combination with triethylamine. Although the reactivity was improved, the formation of the desired piperidine **rac-3aa** was accompanied by substantial amounts of the open-chain product **6aa**, resulting from the interruption of the domino sequence after the sulfa-Michael step. Such product **6aa** could not be cyclized to **rac-3aa** using mild bases. After substantial experimentation, we ultimately found that PTC conditions promoted the domino process much more efficiently. After just one hour at 0 °C, **1a** was fully converted to **rac-3aa** in good yield and moderate diastereoselectivity using  $\text{Cs}_2\text{CO}_3$  as inorganic base, and the common tetra-*n*-butylammonium bromide (TBABr) as PTC catalyst.

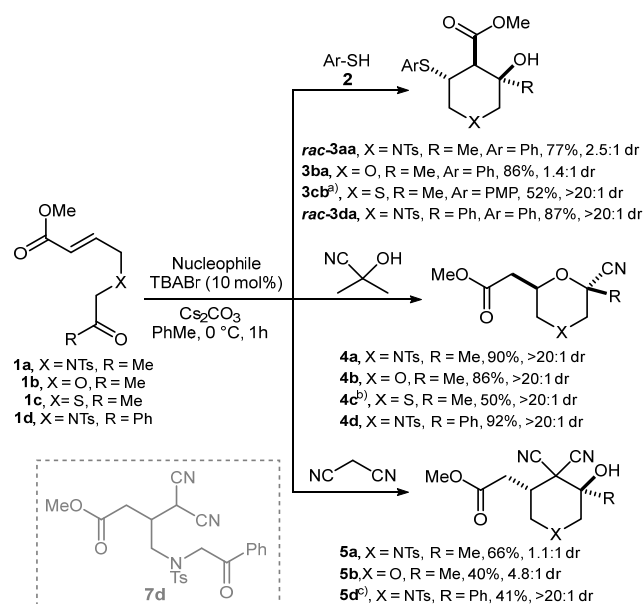


**Scheme 2.** Establishment of PTC as most efficient catalytic approach to the reaction between **1a** and **2a**.

Having established phase-transfer catalysis as efficient tool to trigger the sulfa-Michael/intramolecular aldol reaction, we decided to explore possible substrate variations (Scheme 3). Tetrahydropyran **3ba** and thiane **3cb** were obtained by applying the same methodology to oxygen- or sulfur-containing substrates **1b** and **1c**, respectively. This demonstrates the possibility to access diverse heterocycles, by varying part of the internal structure of the starting materials and keeping the same reaction sequence. The possibility of employing a phenyl ketone was also confirmed by the optimal reactivity of substrate **1d** in this reaction, delivering the corresponding product **rac-3da** as a single diastereoisomer in excellent yield. NMR analysis (see SI for details) allowed to assign the  $3R^*,4R^*,5R^*$  relative configuration to the major diastereoisomer of **rac-3aa** and the  $3R^*,4S^*,5S^*$  to the minor one. On the other hand, we envisioned that it could be possible to invert the order of the two steps of the cascade reaction (1,2-addition to the ketone followed by oxa-Michael cyclization), by changing the nucleophile.<sup>[13]</sup> With this approach, the oxygen of the carbonyl moiety will be embedded in the newly formed heterocycle, giving rise to different classes of compounds. We indeed found that the cyanide ion, conveniently generated *in situ* from acetone-cyanohydrin,<sup>[14]</sup> easily initiates such sequence under the same catalytic conditions reported above. Thus, reaction with substrates **1a-d** yielded morpholines **4a** and **4d**, 1,4-dioxane **4b** and 1,4-oxathiane **4c** respectively, as single diastereoisomers, in excellent yields, with  $2R^*,6S^*$  relative configuration for **4a**, and  $2R^*,6R^*$  for **4b** and **4c**.<sup>[15]</sup> Finally, we devised a variation of the 1,4/1,2-addition sequence by changing the intermediate nucleophile, responsible for the cyclization. Thus, when malononitrile was employed, double functionalization of the  $\text{CH}_2$ -moiety was observed,<sup>[16]</sup> generating piperidine **5a** and tetrahydropyran **5b** as equilibrating diastereomeric mixtures, with a substitution pattern different from compounds **rac-3aa** and **3ba**. In the reaction with malononitrile, substrate **1d** delivered product **5d** in moderate yield and as a single diastereoisomer, along with non-negligible amounts of intermediate **7d**, as the result of some instability during the purification process. In these reactions, the acidity

of the second proton of malononitrile favours its deprotonation after the first addition step. Other nucleophiles, such as: benzaldoxime, 4-nitrophenol, benzophenone imine, phthalimide, diphenylphosphoryl azide, ethyl acetoacetate, diethyl malonate, acetylacetone and indole, did not exert any reactivity with **1** under the optimized reaction conditions.

Thus, the possibility to obtain diverse chiral heterocycles displaying multiple stereocenters was demonstrated, by reacting different nucleophiles with the same substrate class and keeping the same catalytic strategy. This enlightens the capability of compounds **1** to adapt to the reactivity of various partners, changing the reaction course and products, in a fascinating pluripotent fashion.

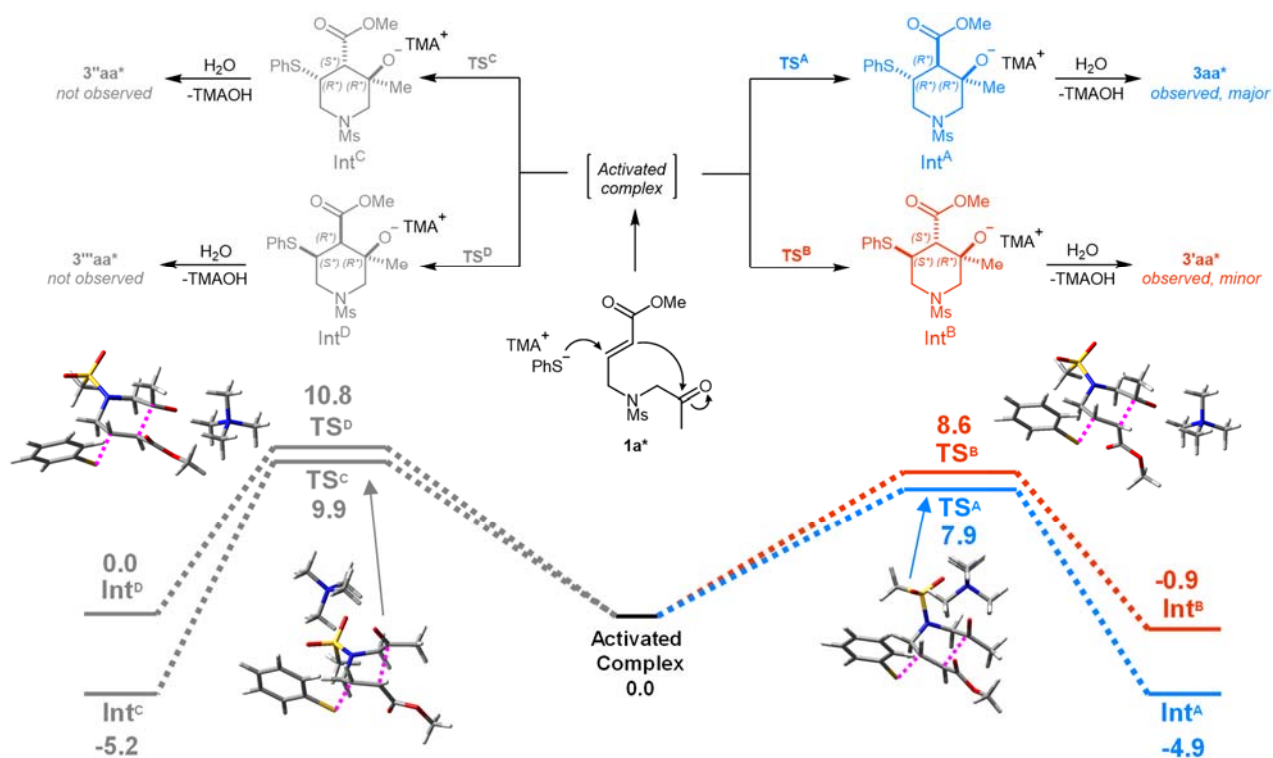


**Scheme 3.** Access to various heterocycles by phase-transfer organocatalytic chemodivergent cascade cyclizations. Reaction conditions: **1** (0.1 mmol), nucleophile (**2** equiv, 0.2

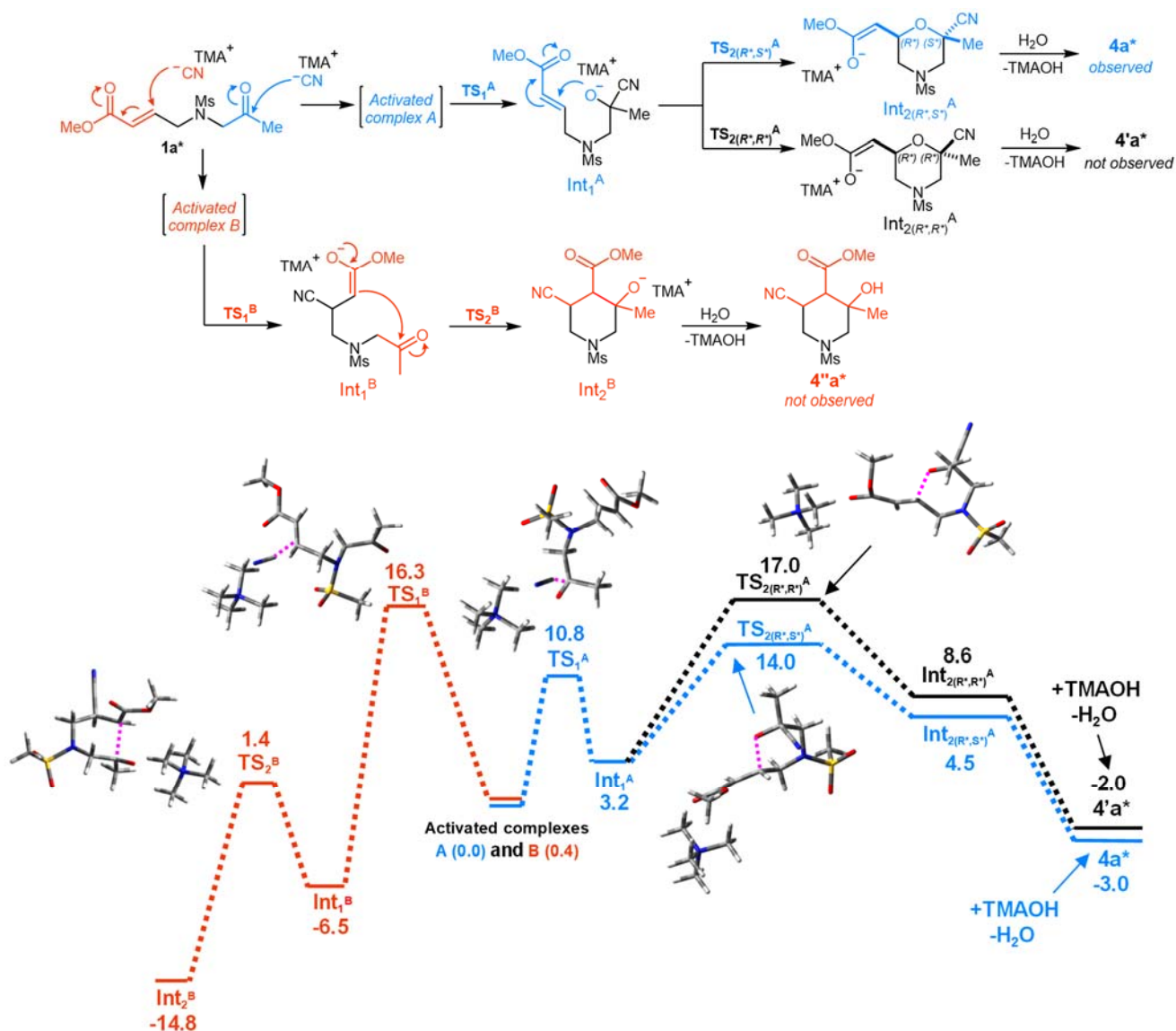
mmol),  $\text{Cs}_2\text{CO}_3$  (1.2 equiv, 1.2 mmol), TBABr (0.01 mmol), PhMe (500  $\mu\text{L}$ , 0.2 M), 18 h; dr determined on the crude mixture by  $^1\text{H}$  NMR analysis. a) aqueous  $\text{K}_2\text{CO}_3$  (10% wt.) was used instead of  $\text{Cs}_2\text{CO}_3$  and catalyst **F** (Table 1, *vide infra*) instead of TBABr; reaction time: 18 h. b) aqueous  $\text{K}_2\text{CO}_3$  (10% wt.) was used instead of  $\text{Cs}_2\text{CO}_3$ . c) Isolated in 1.3:1 mixture with **7d**.

## Computational investigations

A computational study based on DFT calculations was performed to rationalize the different outcomes of the reaction. In the case of piperidine **3**, derived from the sulfa-Michael/aldol process, the intramolecular transition state (TS) was searched starting from the cyclized compound (assuming  $3R^*, 4R^*, 5R^*$  configuration). This was performed by a relaxed scan of the potential energy surface (PES) that accounted for the elongation of the C3-C4 bond, followed by full optimization of the TS geometry (see SI). It was found that the reaction coordinate, related to the imaginary frequency, involved also the formation of the  $\text{S-C}_\beta$  bond. The C3-C4 distance in the TS is 2.32 Å and the C5-S is 1.91 Å. A relaxed IRC calculation confirmed that this TS effectively connects the cyclized compound and the starting reagents. Thus, it appears that the formation of the piperidine ring is due to a concerted, albeit asynchronous, reaction with a single TS (Figure 1). This is in agreement with the experimental outcomes, where intermediate **6aa** was never detected in reactions run under PTC. In the ground state (GS) of the cyclized compound the C3-C4 bond distance is 1.61 Å, whereas the C5-S is 1.86 Å, thus the C-S bond is almost already formed when the cyclization starts. Several attempts were made to localize the TS for the alternative pathway, where the thiolate nucleophile adds to the ketone, followed by cyclization to a morpholine derivative. However, we could not find any effective geometry for this TS. This is in accordance with similar cases known in the literature.<sup>[10,11]</sup>



**Figure 1.** Top: available reaction pathways for the formation of products **3**. A mesyl (Ms) group (**1a\***) was used instead of tosyl (**1a**) to reduce the computational time. Bottom: relative energies (in kcal/mol) of the four available TS for cyclization. TMA = tetramethylammonium (used in the calculation instead of TBA to save computational time).



**Figure 2.** Top: available reaction pathways for the formation of products **4**. A mesyl (Ms) group (**1a\***) was used instead of tosyl (**1a**) to reduce the computational time. Bottom: reaction pathway and relative energies (in kcal/mol) of the available TSs and intermediates. TMA = tetramethylammonium (used in the calculation instead of TBA to save computational time).

We then searched for the TS geometries leading to the three remaining diastereoisomers (Figure 1). The TS for the 3*R*\*,4*R*\*,5*R*\* configuration (TS<sub>A</sub>) was calculated as the most stable one. In agreement with the experimental outcome, the 3*R*\*,4*S*\*,5*S*\* TS (TS<sub>B</sub>) was calculated as the second in energy, with 0.7 kcal/mol difference with respect to the best one. This energy difference corresponds to a 78:22 ratio at 0 °C, in good agreement with the experimental dr. The two TSs leading to the remaining diastereoisomers (TS<sub>C</sub> and TS<sub>D</sub>) are higher in energy.

As for compounds **3**, two different reaction pathways have to be considered for the formation of compounds **4** (Figure 2). Pathway named A (blue and black pathways) leads to the formation of the observed compound, while pathway B (red pathway) would yield a piperidine derivative analogous to **3**. The first TS, where CN<sup>-</sup> adds to the ketone (TS<sub>1</sub><sup>A</sup>), was successfully localized, and subsequent relaxed IRC

calculation allowed to connect it with an activated complex and to intermediate **Int**<sub>1</sub><sup>A</sup>. The pathway to **Int**<sub>1</sub><sup>B</sup>, by way of TS<sub>1</sub><sup>B</sup> was also successfully localized, albeit its energy was calculated as 5.4 kcal/mol higher than that of TS<sub>1</sub><sup>A</sup>.

Subsequent cyclization from **Int**<sub>1</sub><sup>A</sup> and **Int**<sub>1</sub><sup>B</sup> leads to the anionic species (**Int**<sub>2</sub>) that are converted to morpholine or piperidine by protonation. The two possible diastereomeric TS, yielding the two diastereomeric morpholines, were found to have different energies. Comfortably, transition state TS<sub>2(R\*,S\*)</sub><sup>A</sup>, yielding the experimentally observed diastereoisomer, was found to be lower in energy with respect to TS<sub>1</sub><sup>B</sup>.

The main reason for the higher stability of TS<sub>2(R\*,S\*)</sub><sup>A</sup> compared to TS<sub>2(R\*,R\*)</sub><sup>A</sup> has to be assigned to the lower steric hindrance of the cyano group, with respect to the methyl, in the pseudo-axial position of the six-membered transition state.

## Organocatalytic enantioselective synthesis of piperidines

Among the diversified reaction pathways displayed by **1a** with different nucleophiles, we found the sulfa-Michael/aldol cascade reaction generating piperidines **3a** particularly worthy to be implemented to its enantioselective version, for a number of reasons. First, catalytic enantioselective sulfa-Michael addition<sup>[10]</sup> to  $\beta$ -substituted- $\alpha,\beta$ -unsaturated esters is a challenging process.<sup>[17]</sup> Besides the employment of activated substrates,<sup>[18]</sup> very few examples are known to proceed with high enantioselectivity on simple ester acceptors. Tomioka engaged chiral Li-base catalysts and encumbered thiophenols,<sup>[19]</sup> while Dixon employed a super-base organocatalyst to react aliphatic thiols with hindered esters.<sup>[9]</sup> Thus, a truly general enantioselective methodology for the sulfa-Michael addition of thiophenols to simple, unactivated  $\beta$ -substituted- $\alpha,\beta$ -unsaturated esters is missing in the present literature, rendering our methodology a relevant contribution. To the best of our knowledge, enantioselective sulfa-Michael additions under phase-transfer conditions are an extremely rare process, with only one example reported so far, showing a chiral crown-ether catalyzed sulfa-Michael/aldol cascade.<sup>[20]</sup> Finally, organocatalytic enantioselective sulfa-Michael initiated cascade cyclizations are well-established protocols.<sup>[10,21]</sup> However, sulfa-Michael/aldol processes are restricted to mercaptoaldehydes or ketones,<sup>[22]</sup> On the other hand, the employment of doubly electrophilic substrates such as **1** enables the use of simple thiols in complex stereoselective processes, opening a more general reactivity scenario.

Our initial investigation focused on the potential use of common chiral phase-transfer catalysts, such as quaternary ammonium salts derivatives of *Cinchona* alkaloids, in the reaction between **1a** and an excess (2 equiv) of thiophenol **2a** (Table 1). A diluted aqueous solution of  $K_2CO_3$  and toluene were preliminary used as biphasic reaction medium. We observed that a protected hydroxyl functionality on the alkaloid derivative was mandatory to impart some degree of enantioselectivity. The cinchonidine derivative **A** delivered product **3aa** with excellent diastereoselectivity but in a racemic form (entry 1), whereas the use of *O*-benzyl protected catalyst **B** resulted in low, yet promising, enantioselectivity at the expense of the diastereoselection (entry 2). At this point, different bases were preliminary tested (entries 3-5), confirming aqueous  $K_2CO_3$  was the most suitable one (for additional base screening see SI). On the other hand, a change in the reaction conditions, such as dilution of the organic medium and a lowering in the excess of **2a**, were beneficial for the stereoselectivity (entry 6). We then moved to screen different catalysts, focusing mainly on variations of the substituent at the 9-hydroxy moiety.

**Table 1.** Optimization of the enantioselective cascade reaction between substrate **1a** and thiophenol **2a**.<sup>a)</sup>

**A:** R = H

**B:** R = Bn

**C:** R = COPh

**D:** R = allyl

**E:** R =  $-(CH_2)_9$ -phenanthryl

**F:** R = benzhydryl

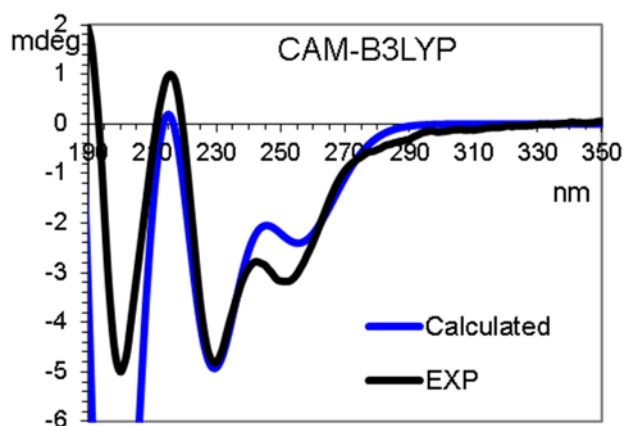
Entry	Cat.	Base	T (°C)	Conv. <sup>b)</sup> (%)	dr <sup>b)</sup>	ee <sup>c)</sup> (%)
1	<b>A</b>	$K_2CO_3$ <sup>d)</sup>	rt	90	>20:1	Rac
2	<b>B</b>	$K_2CO_3$ <sup>d)</sup>	rt	>99	3:1	23
3	<b>B</b>	$K_2CO_3$ <sup>e)</sup>	rt	>99	4.8:1	10
4	<b>B</b>	$NaH_2PO_4$ <sup>d)</sup>	rt	nr	-	-
5	<b>B</b>	$Na_2HPO_4$ <sup>d)</sup>	rt	80	3:1	23
6 <sup>f)</sup>	<b>B</b>	$K_2CO_3$ <sup>d)</sup>	rt	>99	6:1	50
7 <sup>f)</sup>	<b>C</b>	$K_2CO_3$ <sup>d)</sup>	rt	73	>20:1	22
8 <sup>f)</sup>	<b>D</b>	$K_2CO_3$ <sup>d)</sup>	rt	80	5:1	20
9 <sup>f)</sup>	<b>E</b>	$K_2CO_3$ <sup>d)</sup>	rt	nr	-	-
10 <sup>f)</sup>	<b>F</b>	$K_2CO_3$ <sup>d)</sup>	rt	>99	>20:1	35
11 <sup>f,g)</sup>	<b>G</b>	$K_2CO_3$ <sup>d)</sup>	rt	>99	4.6:1	65
12 <sup>f,g)</sup>	<b>G</b>	$K_2CO_3$ <sup>d)</sup>	0	>99	5.7:1	79
13 <sup>f,g)</sup>	<b>G</b>	$Cs_2CO_3$ <sup>e)</sup>	0	>99	8:1	88
14 <sup>f)</sup>	<b>G</b>	$Cs_2CO_3$ <sup>e)</sup>	-30	50	7.3:1	77

<sup>a)</sup> Reaction conditions: **1a** (0.05 mmol), **2a** (2 equiv, 0.1 mmol), base (*vide infra*), catalyst (0.005 mmol), PhMe (250  $\mu$ L, 0.2 M), 18 h. <sup>b)</sup> Determined on the crude mixture by <sup>1</sup>H NMR analysis. <sup>c)</sup> Determined on crude **3aa** by Chiral Stationary Phase (CSP) HPLC. <sup>d)</sup> Aqueous base (10% wt., 100  $\mu$ L). <sup>e)</sup> Solid base (0.06 mmol, 1.2 equiv). <sup>f)</sup> **2a** (1.2 equiv, 0.06 mmol), PhMe (1.0 mL, 0.05 M). <sup>g)</sup> Reaction time: 1 h.

Catalysts displaying an ester (**C**) or allyl (**D**) group gave a lower enantioselection than **B**, accompanied by mixed diastereoselectivities (entries 7-8), 9-phenanthrylmethyl substituted catalyst **E** failed to promote the reaction (entry 9), while dimeric structure **F** afforded product **3aa** as a single diastereoisomer, but with lower enantioselectivity (entry 10). Benzhydryl<sup>[23]</sup> derivative **G** was found to be the optimal catalyst, improving the stereoselectivity and enhancing the reaction rate considerably (entry 11). Additional screenings, involving variation at the quaternary *N*-moiety or the type of alkaloid did not exert any improvement (see SI). As a result of the high efficiency exhibited by catalyst **G**, a lowering in the reaction temperature was possible. It was thus observed that both the enantio- and the diastereoselectivity increased at 0 °C (entry 12). In order to further decrease the temperature, the possibility to exploit solid  $Cs_2CO_3$  was evaluated, as a commonly employed base for low-temperature phase-transfer catalysis. Pleasingly, the use of  $Cs_2CO_3$  as such resulted in very high values of enantio- and diastereoselection, even at 0 °C (entry 13, optimal conditions), while at -30 °C the reactivity dropped considerably as well as the stereoselectivity (entry 14).

The relative and absolute configuration of compound **3aa** was determined as 3*S*,4*S*,5*S* by means

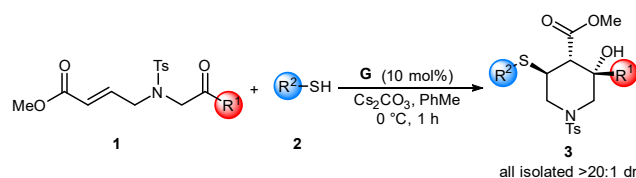
of TD-DFT simulation of the Electronic Circular Dichroism (ECD) spectrum (Figure 2, see SI for full details).<sup>[24]</sup>



**Figure 3.** Experimental and simulated ECD spectrum of **3aa**. Simulation at the CAM-B3LYP/6-311++G(2d,p) level was for the 3*S*,4*S*,5*S* absolute configuration.

With the best reaction conditions in hand, we moved to evaluate the generality of the reaction, by varying first the ketone group of the substrate. Pleasingly, substrate **1d** (Table 2, entry 2), displaying a phenyl-ketone moiety, afforded product **3da** as a single diastereoisomer and higher enantioselectivity (compared to **3aa**, entry 1). Other substrates exhibiting aryl ketones with different electronic properties (compounds **1e-f** entries 3 and 4) or heterocyclic moieties (**1g**, entry 5) productively underwent the desired cascade cyclization, providing piperidines **3ea-3ga** as single diastereoisomers but with slightly decreased efficiency. Conversely, a 2-naphthyl substituent (**1h**, entry 6) showed better performances. The scope in terms of thiol **2** variations was evaluated with substrate **1d**, for which a complete diastereoselection was observed in all cases. Both electron-donating (**2b**, entry 7) and electron-withdrawing (**2c-d**, entries 8 and 9) groups at the *para* position were perfectly tolerated, as well as substitution at the *meta* position (**2e**, entry 10). Sterically hindered *ortho*-substituted thiophenol **2f** required higher temperature and prolonged reaction time to afford product **3df** in useful yield (entry 11). The moderate enantiomeric excess highlights a certain tolerance of the process towards steric bulk. High yield and enantioselectivity were observed for 2-naphthalenethiol **2g** (entry 12), and the heteroaromatic group of thiol **2h** (entry 13) was well tolerated by the system. Finally, benzyl thiol **2i** was evaluated, in order to extend the process to aliphatic thiols. Despite product **3di** was formed in good yield (entry 14), the enantioselectivity dropped considerably.

**Table 2.** Optimization of the enantioselective cascade reaction between substrate **1a** and thiophenol **2a**.<sup>a)</sup>



Entry	R <sup>1</sup>	R <sup>2</sup>	<b>3</b> , yield <sup>b)</sup> (%)	ee <sup>b)</sup> (%)
1 <sup>d)</sup>	Me	Ph	<b>3aa</b> , 80	88
2	Ph	Ph	<b>3da</b> , 71	91
3	4-MeO-C <sub>6</sub> H <sub>4</sub>	Ph	<b>3ea</b> , 57	67
4	3-Br-C <sub>6</sub> H <sub>4</sub>	Ph	<b>3fa</b> , 65	59
5	2-thienyl	Ph	<b>3ga</b> , 66	67
6	2-naphthyl	Ph	<b>3ha</b> , 87	86
7	Ph	4-MeO-C <sub>6</sub> H <sub>4</sub>	<b>3db</b> , 70	81
8	Ph	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>3dc</b> , 57	89
9	Ph	4-F-C <sub>6</sub> H <sub>4</sub>	<b>3dd</b> , 74	91
10	Ph	3-Me-C <sub>6</sub> H <sub>4</sub>	<b>3de</b> , 71	91
11 <sup>e)</sup>	Ph	2-Br-C <sub>6</sub> H <sub>4</sub>	<b>3df</b> , 68	71
12	Ph	2-naphthyl	<b>3dg</b> , 84	94
13	Ph	2-thienyl	<b>3dh</b> , 71	83
14	Ph	Bn	<b>3di</b> , 67	37

<sup>a)</sup> Reaction conditions: **1** (0.1 mmol), **2** (1.2 equiv, 0.12 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.12 mmol), catalyst **G** (0.01 mmol), PhMe (2.0 mL, 0.05 M), 1 h. All products **3** displayed >20:1 dr both in the crude mixture and after purification unless otherwise stated. <sup>b)</sup> Isolated yield after column chromatography. <sup>c)</sup> Determined on isolated **3** by CSP HPLC. <sup>d)</sup> 8:1 dr in the crude mixture, isolation of major diastereoisomer was possible by column chromatography. <sup>e)</sup> Reaction run at rt for 18 h.

## Conclusion

In summary, we have developed a chemodivergent strategy for the preparation of various chiral saturated heterocycles, such as piperidines, tetrahydropyrans, thianes, morpholines, 1,4-dioxanes and 1,4-oxathianes in a racemic form. Three different domino reaction pathways are viable on the same doubly electrophilic substrate, using PTC as enabling tool. The nucleophile (thiophenol, cyanide or malononitrile) dictates the pathway followed by the process. A concerted asynchronous transition state for the formation of piperidines through sulfa-Michael/aldol domino processes was proposed following DFT calculations, accounting also for the observed diastereoselectivity. Moreover, for the cyanide-initiated cascade, leading to morpholines, both the chemo- and the diastereoselectivity were found to be the result of kinetic control. Finally, we developed a new enantioselective domino sulfa-Michael/aldol reaction based on PTC. The process represents a novel approach towards enantioenriched sulfur-containing piperidines and shows high yields and moderate to excellent diastereo- and enantioselectivities, with broad substrate scope.

## Experimental Section

**General Procedure for the synthesis of products *rac*-**3**, **4** and **5**.**

In a test tube, equipped with a magnetic stir bar, substrates **1** (0.1 mmol) and TBABr (3.2 mg, 0.01 mmol, 10 mol%) were suspended in toluene (500  $\mu$ L) and the reaction mixture was cooled to 0  $^{\circ}$ C. Then, Cs<sub>2</sub>CO<sub>3</sub> (40.0 mg, 0.12 mmol) and the corresponding nucleophile (0.12 mmol) were added in this order. The resulting suspension was vigorously stirred for 1 h at 0  $^{\circ}$ C, diluted with CH<sub>2</sub>Cl<sub>2</sub> (1 mL), passed through a small plug of silica, eluted with CH<sub>2</sub>Cl<sub>2</sub> (3x1 mL) and Et<sub>2</sub>O (3x1 mL) and evaporated *in vacuo*. The resulting crude mixture was analyzed by means of <sup>1</sup>H NMR spectroscopy to calculate the diastereomeric ratio and finally purified by column chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O mixtures) to obtain products *rac*-**3**, **4** or **5**.

**Methyl (2R\*,6S\*)-2-(6-cyano-6-methyl-4-tosylmorpholin-2-yl)acetate 4a.** Following the general procedure from substrate **1a** and acetone cyanohydrin, product **4a** (>20:1 dr after column chromatography and in the crude mixture) was obtained as a white solid in 90% yield after column chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O = 70:1). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.73 – 7.64 (m, 2H), 7.40 – 7.32 (m, 2H), 4.41 (dtd, *J* = 10.6, 6.3, 2.6 Hz, 1H), 3.83 (dd, *J* = 12.1, 1.6 Hz, 1H), 3.80 – 3.73 (m, 1H), 3.71 (s, 3H), 2.54 (dd, *J* = 15.9, 6.6 Hz, 1H), 2.45 (s, 3H) overlapped with 2.44 (dd, *J* = 15.9, 6.0 Hz, 1H), 2.29 (d, *J* = 12.1 Hz, 1H), 2.23 (dd, *J* = 11.7, 10.6 Hz, 1H), 1.55 (s, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 169.4, 144.5, 132.6, 130.0 (2C), 127.8 (2C), 117.7, 70.6, 70.3, 52.6, 52.1, 48.3, 37.6, 24.3, 21.6. HRMS: calculated for [C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>S + Na<sup>+</sup>]: 375.0985; found :375.0991.

**Methyl (3R\*,5R\*)- and (3R\*,5S\*)-2-(4,4-dicyano-5-hydroxy-5-methyl-1-tosylpiperidin-3-yl)acetate 5a.** Following the general procedure from substrate **1a** and malononitrile, product **5a** (1.1:1 dr after column chromatography and in the crude mixture) was obtained as a colorless oil in 66% yield after column chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O = 60:1). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 7.71 – 7.61 (m, 2H + 2H), 7.51 – 7.40 (m, 2H + 2H), 6.93 (s, 1H), 6.72 (s, 1H), 4.02 – 3.87 (m, 1H + 1H), 3.66 (dd, *J* = 12.2, 1.1 Hz, 1H) partially overlapped with 3.65 (s, 3H), 3.64 (s, 3H), 3.50 (dd, *J* = 12.2, 1.5 Hz, 1H), 3.01 (dddd, *J* = 11.2, 7.3, 6.1, 3.9 Hz, 1H), 2.82 (dddd, *J* = 10.8, 7.6, 5.4, 4.2 Hz, 1H), 2.63 – 2.52 (m, 2H + 2H), 2.40 (s, 3H), 2.39 (s, 3H) partially overlapped with 2.398 (d, *J* = 12.6 Hz, 1H), 2.31 (d, *J* = 12.7 Hz, 1H), 2.27 – 2.10 (m, 1H + 1H), 1.50 (s, 3H), 1.45 (s, 3H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 170.5, 170.4, 144.7, 144.4, 133.2, 132.8, 130.6 (2C), 130.5 (2C), 127.9 (2C), 127.8 (2C), 114.2, 114.0, 113.1, 112.8, 71.7, 71.2, 53.2, 52.51, 52.48, 52.2, 50.8, 48.6, 46.6, 46.1, 37.0, 35.3, 34.3, 34.2, 24.3, 22.8, 21.49, 21.46. All peaks are given without assignment. HRMS: calculated for [C<sub>18</sub>H<sub>21</sub>N<sub>3</sub>O<sub>5</sub>S - H<sup>+</sup>]: 390.1129; found :390.1124.

### General Procedure for the synthesis of enantioenriched piperidines **3**.

In a test tube, equipped with a magnetic stir bar, substrates **1** (0.1 mmol) and catalyst **G** (6.4 mg, 0.01 mmol, 10 mol%) were suspended in toluene (2 mL) and the reaction mixture was cooled to 0  $^{\circ}$ C. Then, Cs<sub>2</sub>CO<sub>3</sub> (40.0 mg, 0.12 mmol) and the corresponding thiophenol (0.12 mmol) were added in this order. The resulting suspension was vigorously stirred for 1 h at 0  $^{\circ}$ C, diluted with CH<sub>2</sub>Cl<sub>2</sub> (1 mL), passed through a small plug of silica, eluted with CH<sub>2</sub>Cl<sub>2</sub> (3x1 mL) and Et<sub>2</sub>O (3x1 mL) and evaporated *in vacuo*. The resulting crude mixture was analyzed by means of <sup>1</sup>H NMR spectroscopy to calculate the diastereomeric ratio and finally purified by column chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O mixtures) to obtain products **3** as white amorphous solids.

### Methyl (3S,4S,5S)-3-hydroxy-3-methyl-5-(phenylthio)-1-tosylpiperidine-4-carboxylate **3aa**

Following the general procedure from substrate **1a** and thiophenol **2a**, product **3aa** (> 20:1 dr after column chromatography, 8:1 in the crude mixture) was obtained as a white solid in 80% yield after column chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O = from 50:1 to 20:1). [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -89 (c = 0.7 in CHCl<sub>3</sub>) for 88% *ee*. <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN)

$\delta$  = 7.62 – 7.59 (m, 2H), 7.48 – 7.44 (m, 2H), 7.41 – 7.33 (m, 5H), 3.88 (ddd, *J* = 12.0, 4.7, 1.9 Hz, 1H), 3.71 (s, 3H), 3.58 (td, *J* = 12.0, 4.7 Hz, 1H), 3.50 (dd, *J* = 12.2, 1.9 Hz, 1H), 3.40 (bs, 1H), 2.43 (s, 3H), 2.33 (d, *J* = 12.4 Hz, 1H), 2.25 (t, *J* = 11.8 Hz, 1H) partially overlapped with 2.23 (d, *J* = 12.2 Hz, 1H). <sup>13</sup>C NMR (151 MHz, CD<sub>3</sub>CN)  $\delta$  = 171.5, 144.1, 133.5, 132.8 (2C), 132.4, 129.7 (2C), 129.3 (2C), 128.2, 127.5 (2C), 69.1, 55.4, 55.2, 51.5, 50.3, 43.2, 24.9, 20.5. HRMS: calculated for [C<sub>21</sub>H<sub>25</sub>NO<sub>5</sub>S<sub>2</sub> + Na<sup>+</sup>]: 458.1066; found: 458.1064. HPLC: OD-H (n-hexane/iPrOH 90:10, flow-rate 1.00 mL/min; t<sub>maj</sub> = 18.4 min; t<sub>min</sub> = 30.4 min).

## Acknowledgements

We acknowledge financial support from the University of Bologna (RFO program), MIUR (FFABR 2017), and F.I.S. (Fabbrica Italiana Sintetici). We thank Luca Zuppiroli (University of Bologna) for the HRMS analyses. We also thank Costanza Leonardi, Ana Ubide Botella, Eleonora Ridolfini and Pietro Viola for preliminary investigations and preparation of the starting materials.

## References

- [1] a) R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845-5859; b) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257-10274.
- [2] For reviews see: a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115-136; b) D. E. Fogg, D. N. dos Santos, *Coord. Chem. Rev.* **2004**, *248*, 2365-2379; Organocatalyzed cascade reactions: c) A. M. Walji, D. W. C. MacMillan, *Synlett* **2007**, 1477-1489; d) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167-178; e) L. Albrecht, H. Jiang, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2011**, *50*, 8492-8499; f) H. Pellissier, *Adv. Synth. Catal.* **2012**, *354*, 237-294; g) S. Goudedranche, W. Raimondi, X. Bugaut, T. Costantieux, D. Bonne, J. Rodriguez, *Synthesis* **2013**, 1909-1930; g) C. M. R. Volla, I. Atodiressei, M. Rueping, *Chem. Rev.* **2014**, *114*, 2390-2431; h) P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253-281; i) T. Chanda, J. C.-G. Zhao, *Adv. Synth. Catal.* **2018**, *360*, 2-79; Metal catalyzed cascade reactions: j) H. Pellissier, *Adv. Synth. Catal.* **2019**, *361*, 1733-1755.
- [3] Recent accounts and reviews: a) L. Bernardi, M. Fochi, M. Comes Franchini, A. Ricci, *Org. Biomol. Chem.* **2012**, *10*, 2911-2922; b) M. Fochi, L. Caruana, L. Bernardi, *Synthesis* **2014**, 135-157; c) L. Caruana, M. Fochi, L. Bernardi, *Molecules* **2015**, *20*, 11733-11764; d) L. Caruana, M. Fochi, L. Bernardi, *Synlett* **2017**, *28*, 1530-1543; e) G. Bertuzzi, L. Bernardi, M. Fochi, *Catalysts* **2018**, *8*, 632: doi:10.3390/catal8120632.
- [4] a) L. Caruana, M. Fochi, M. Comes Franchini, S. Ranieri, A. Mazzanti, L. Bernardi, *Chem. Commun.* **2014**, *50*, 445-447; b) S. Romanini, E. Galletti, L. Caruana, A. Mazzanti, F. Himo, S. Santoro, M. Fochi, L. Bernardi, *Chem. Eur. J.* **2015**, *21*, 17578-17582.
- [5] F. Serpier, J.-L. Brayer, B. Folléas, S. Darses, *Org. Lett.* **2015**, *17*, 5496-5499.
- [6] For additional examples of the utilization of substrates of type **1** in domino reactions, see: a) D. F. Cauble, J. D.

- Gipson, M. J. Krische, *J. Am. Chem. Soc.* **2003**, *125*, 1110-1111; b) P. M. Joensuu, G. J. Murray, E. A. F. Fordyce, T. Luebbers, H. W. Lam, *J. Am. Chem. Soc.* **2008**, *130*, 7328-7338; c) F. Serpier, B. Flamme, J.-L. Brayer, B. Folléas, S. Darses, *Org. Lett.* **2015**, *17*, 1720-1723. Substrates **1** have also been engaged in ketyl radical-olefin cyclisations, see: d) G. H. Lee, E. B. Choi, E. Lee, C. S. Pak, *J. Org. Chem.* **1994**, *59*, 1428-1443; e) K. T. Tarantino, P. Liu, R. R. Knowles, *J. Am. Chem. Soc.* **2013**, *135*, 10022-10025.
- [7] a) M. D. Burke, S. L. Schreiber, *Angew. Chem. Int. Ed.* **2003**, *43*, 46-58; for a recent exemplification: b) Q. Dai, N. K. Rana, J. C.-G. Zhao, *Org. Lett.* **2013**, *15*, 2922-2925; c) S. Caputo, L. Banfi, A. Basso, A. Galatini, L. Moni, R. Riva, C. Lambruschini, *Eur. J. Org. Chem.* **2017**, 6619-6628
- [8] a) C. Starks, C. Liotta, M. Halpern, *Phase-Transfer Catalysis: Fundamentals, Applications and Industrial Perspectives*, Chapman & Hall, New York, **1994**; b) E. V. Dehmlow, S. S. Dehmlow, *Phase-Transfer Catalysis*, 3rd Ed., Wiley-VCH, Weinheim, **1993**; c) M. Makosza, *Pure Appl. Chem.* **2000**, *72*, 1399-1403; d) *Asymmetric Phase-Transfer Catalysis* (Ed.: K. Maruoka), Wiley-VCH, **2008**; e) S. Shirakawa, K. Maruoka, *Angew. Chem. Int. Ed.* **2013**, *52*, 4312-4348; f) R. Herchl, M. Waser, *Tetrahedron* **2014**, *70*, 1935-1960; g) J. Tan, N. Yasuda, *Org. Proc. Res. Dev.* **2015**, *19*, 1731-1746; for a recent example of PTC work from our laboratory: h) L. Bernardi, M. Fochi, R. Carbone, A. Martinelli, M. E. Fox, C. J. Cobley, B. Kandagatla, S. Oruganti, V. H. Dahanukar, A. Carlone, *Chem. Eur. J.* **2015**, *21*, 19208-19222.
- [9] a) A. J. M. Farley, C. Sandford, D. J. Dixon, *J. Am. Chem. Soc.* **2015**, *137*, 15992-15995; b) J. Yang, A. J. M. Farley, D. J. Dixon, *Chem. Sci.* **2017**, *8*, 606-610.
- [10] a) D. Enders, K. Lüttgen, A. A. Narine, *Synthesis* **2007**, 959-980; b) P. Chauhan, S. Mahajan, D. Enders, *Chem. Rev.* **2014**, *114*, 8807-8864.
- [11] a) A. Kamimura, H. Mitsudera, S. Asano, A. Kakehi, M. Noguchi, *Chem. Commun.* **1998**, *18*, 1095-1096; b) M. Ono, K. Nishimura, Y. Nagaoka, K. Tomioka, *Tetrahedron Lett.* **1999**, *40*, 1509-1512; c) M. Ono, K. Nishimura, Y. Nagaoka, K. Tomioka, *Tetrahedron Lett.* **1999**, *40*, 6979-6982; d) A. Kamimura, H. Mitsudera, S. Asano, S. Kidera, A. Kakehi, *J. Org. Chem.* **1999**, *64*, 6353-6360; e) K. Nishimura, H. Tsubouchi, M. Ono, T. Hayama, Y. Nagaoka, K. Tomioka, *Tetrahedron Lett.* **2003**, *44*, 2323-2326.
- [12] P. R. Schreiner, A. Wittkopp, *Org. Lett.* **2002**, *4*, 217-220.
- [13] For related processes for the synthesis of tetrahydropyrans see: a) N. Yoneda, Y. Fujii, A. Matsumoto, K. Asano, S. Matsubara, *Nat. Commun.* **2017**, *8*, 1397; b) Y. Kurimoto, T. Nasu, Y. Fujii, K. Asano, S. Matsubara, *Org. Lett.* **2019**, *21*, 2156-2160.
- [14] a) R. P. Herrera, V. Sgarzani, L. Bernardi, F. Fini, D. Pettersen, A. Ricci, *J. Org. Chem.* **2006**, *71*, 9869-9872; b) L. Bernardi, F. Fini, M. Fochi, A. Ricci, *Synlett* **2008**, 1857-1961.
- [15] The different stereochemical descriptors are due to the different CIP priority of the endocyclic sulphur and oxygen (**4c** and **4b**) with respect to nitrogen (**4a**).
- [16] a) X.-M. Li, J.-M. Zhang, M. Yan, *Org. Lett.* **2011**, *13*, 374-377; b) C. De Fusco, A. Lattanzi, *Eur. J. Org. Chem.* **2011**, *2011*, 3728-3731; c) S. Maity, M. Saha, G. Hazra, P. Gorai, *Org. Lett.* **2017**, *19*, 5872-5875.
- [17] For a general overview on ester surrogates in organocatalysis: a) D. Monge, H. Jiang, Y. Alvarez-Casao, *Chem. Eur. J.* **2015**, *21*, 4494-4504.
- [18] 1,1,1,3,3,3-Hexafluoroisopropyl esters: a) X. Fang, J. Li, C.-J. Wang, *Org. Lett.* **2013**, *15*, 3448-3451;  $\beta$ -trifluoromethyl acrylates: b) X.-Q. Dong, X. Fang, C.-J. Wang, *Org. Lett.* **2011**, *13*, 4426-4429; alkylidene malonates: c) R. Dodda, T. Mandal, C.-G. Zhao, *Tetrahedron Lett.* **2008**, *49*, 1899-1902; alkylidene phosphonoacetates: d) A. R. Choudhury, S. Mukherjee, *Adv. Synth. Catal.* **2013**, *355*, 1989-1955.
- [19] a) K. Nishimura, M. Ono, Y. Nagaoka, K. Tomioka, *J. Am. Chem. Soc.* **1997**, *119*, 12974-12975; b) K. Tomioka, M. Okuda, K. Nishimura, S. Manabe, M. Kanai, Y. Nagaoka, K. Koga, *Tetrahedron Lett.* **1998**, *39*, 2141-2144.
- [20] M. Duan, Y. Liu, J. Ao, L. Xue, S. Luo, Y. Tan, W. Qin, C. E. Song, H. Yan, *Org. Lett.* **2017**, *19*, 2298-2301.
- [21] a) X. Tian, C. Cassani, Y. Liu, A. Moran, A. Urakawa, P. Galzerano, E. Arceo, P. Melchiorre, *J. Am. Chem. Soc.* **2011**, *133*, 17934-17941; b) P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253-281; c) W. Hou, Q. Wei, G. Liu, J. Chen, J. Guo, Y. Peng, *Org. Lett.* **2015**, *17*, 4870-4873; d) V. Corti, P. Camarero Gonzales, J. Febvay, L. Caruana, A. Mazzanti, M. Fochi, L. Bernardi, *Eur. J. Org. Chem.* **2017**, *2017*, 49-52.
- [22] In addition to reference 10 and references therein see: A. Przydacz, R. Kowalczyk, Ł. Albrecht, *Org. Biomol. Chem.* **2017**, *15*, 9566-9569.
- [23] For a recent example of O9-benzhydryl *Cinchona* catalyst, see: a) T. Martzel, J. Annibaleto, V. Levacher, J.-F. Brière, S. Oudeyer, *Adv. Synth. Catal.* **2019**, *361*, 995-1000. For similar catalysts in PTC promoted reactions see: b) L. Lykke, K. Søholm Halskov, B. D. Carlsen, V. X. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2013**, *135*, 4692-4695.
- [24] For reviews see: a) G. Pescitelli, L. Di Bari, N. Berova, *Chem. Soc. Rev.* **2011**, *40*, 4603-4625; b) A. Mazzanti, D. Casarini, *WIREs Comput. Mol. Sci.* **2012**, *2*, 613-641; c) S. Superchi, P. Scafato, M. Górecki, G. Pescitelli, *Curr. Med. Chem.* **2018**, *25*, 287-320; See also d) M. Mancinelli, R. Franzini, A. Renzetti, E. Marotta, C. Villani, A. Mazzanti *RSC Adv.* **2019**, *9*, 18165-18175; e) A. Pagano, E. Marotta, A. Mazzanti, G. Petrillo, C. Tavani, M. Mancinelli, *Synlett* **2018**, *29*, 2161-2166.

