Symmetry **2011**, *3*, 220-245; doi:10.3390/sym3020220

OPEN ACCESS

symmetry

ISSN 2073-8994

www.mdpi.com/journal/symmetry

Review

Organocatalytic Enantioselective Henry Reactions

Yolanda Alvarez-Casao [1], Eugenia Marques-Lopez [1] and Raquel P. Herrera [1,2,*]

[1] Laboratory of Asymmetric Synthesis, Department of Organic Chemistry, Institute of Synthetic Chemistry and Homogeneous Catalysis (ISQCH), University of Zaragoza-CSIC, E-50009 Zaragoza, Spain; E-Mails: yalvarezcasao@gmail.com (Y.A.-C.); mmaamarq@unizar.es (E.M.-L.)

[2] ARAID, Aragon I+D Foundation, E-50004 Zaragoza, Spain

* Author to whom correspondence should be addressed. E-Mail: raquelph@unizar.es; Tel.: +34 976762281; Fax: +34 976762075.

Received: 29 March 2011; in revised form: 10 May 2011 / Accepted: 11 May 2011 / Published: 23 May 2011

Abstract: A large number of interesting organocatalytic enantioselective protocols have been explored and successfully applied in the last decade. Among them, the Henry (nitroaldol) reaction represents a powerful carbon-carbon bond-forming procedure for the preparation of valuable synthetic intermediates, such as enantioenriched nitro alcohols, which can be further transformed in a number of important nitrogen and oxygen-containing compounds. This area of research is still in expansion and a more complex version of this useful process has recently emerged, the domino Michael/Henry protocol, affording highly functionalized cycles with multiple stereogenic centers.

Keywords: Henry; nitroaldol; organocatalysis; enantioselective; nitroalkanes; domino Michael/Henry

---

1. Introduction

The reaction between an *in situ* generated nitronate species and a carbonyl compound, known as Henry (nitroaldol) reaction, is an important carbon-carbon bond-forming method in organic synthesis [1]. This process represents a powerful and useful tool for the synthesis of valuable β-nitroalcohols [2], providing, after further transformation of the β-nitroalcohols, efficient access to interesting and highly functionalized intermediates like nitroalkenes, 1,2-amino alcohols and α-hydroxy carboxylic acids [3,4].

In the last decade a new discipline: *asymmetric organocatalysis*, has attracted much attention by many research groups [5–7]. Very interesting progresses have been achieved in this intriguing area,

with the development of an incredible number of new processes, such as epoxidations [8], reductions [9], aza-Henry [10], Morita-Baylis-Hillman [11], aldol reaction [12], Pudovick [13], Strecker [14], Friedel-Crafts [15,16], Michael addition [17–21], Diels-Alder [22], and Mannich reactions [23]. In the context of this novel field, appealing advances have been also accomplished in the enantioselective synthesis of very complex molecules [24,25].

The Henry reaction may be promoted under many different conditions and using diverse catalytic systems providing from moderate-to-good enantioselectivities. This review will focus on the current progress of the Henry reaction in the field of asymmetric organocatalysis. The most significant contributions since 2007 will be discussed and illustrated, since earlier examples have been extensively reported in other main works dedicated to this process [26,27], although in some cases references to the pioneering models will be necessary.

2. Enantioselective Henry Reaction with Aldehydes

In spite of the significant importance of controlling the absolute stereochemistry in the final Henry adducts, limited organocatalytic methods have been reported so far in the literature for this purpose, and the reaction still presents some limitations. Among the key catalysts used with this aim we can find Cinchona alkaloids, phase transfer catalysts, thioureas and guanidines.

The first organocatalytic enantioselective example of this reaction was published in 1994 by Nájera *et al.* [28]. They used enantiomerically pure guanidines **1** and **2** as catalysts, affording enantiomeric excess up to 54%. Following this report, many efforts have been initiated and different kinds of organocatalysts have been designed in order to improve those pioneering results (Figure 1). In this context, further chiral guanidines were developed, such as guanidinium salt **3** synthesized by Murphy *et al*. [29], however lower enantiomeric excesses were obtained in comparison with those previously reported and catalyst **4** used in a diastereoselective Henry reaction [30]. Moreover, in 2005, Nawasaga *et al*. [31–34] developed the novel bifunctional catalyst **5** bearing guanidine and thiourea moieties in the same skeleton. Compound **5** catalyzed the reaction of nitromethane with α-branched aldehydes reaching enantioselectivities up to 88%, although the induction was lower in the case of unbranched aldehydes (55% *ee*) [31]. The use of KI in the reaction seemed to be crucial for the inhibition of the retro-nitroaldol reaction observed by the authors, and the achievement of better values of enantioselectivity.

In addition, the same authors extended the application of guanidine **5** as catalyst to a variety of nitroalkanes with different aldehydes, obtaining high *syn* diastereoselectivities and enantioselectivities (Table 1) [33,34].

In order to explain the major *syn* selectivity obtained in the final products of this reaction, the authors suggested three plausible transition states (**TSI**-**TSIII**) (Figure 2). Among them, the *anti*, *anti*-conformational transition state **TSI** (nitro group and R_1 are in an *anti* relationship, carbonyl group and R_2 are *anti*), is considered to be more favorable since it avoids steric repulsion [33,34].

Figure 1. Guanidine: Efficient catalysts to promote the Henry reaction with aldehydes.

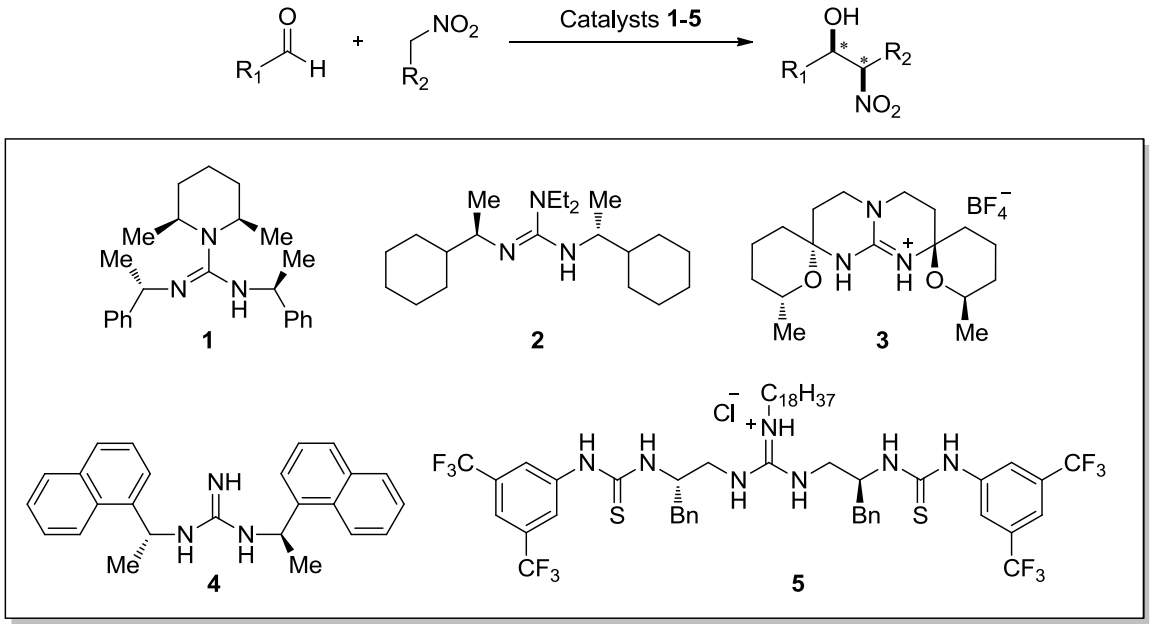
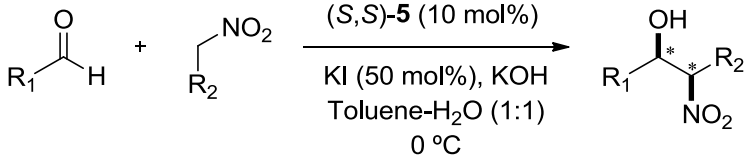


Table 1. Enantio- and *syn*-selective Henry reaction of aldehydes with nitroalkanes in presence of catalyst **5**.

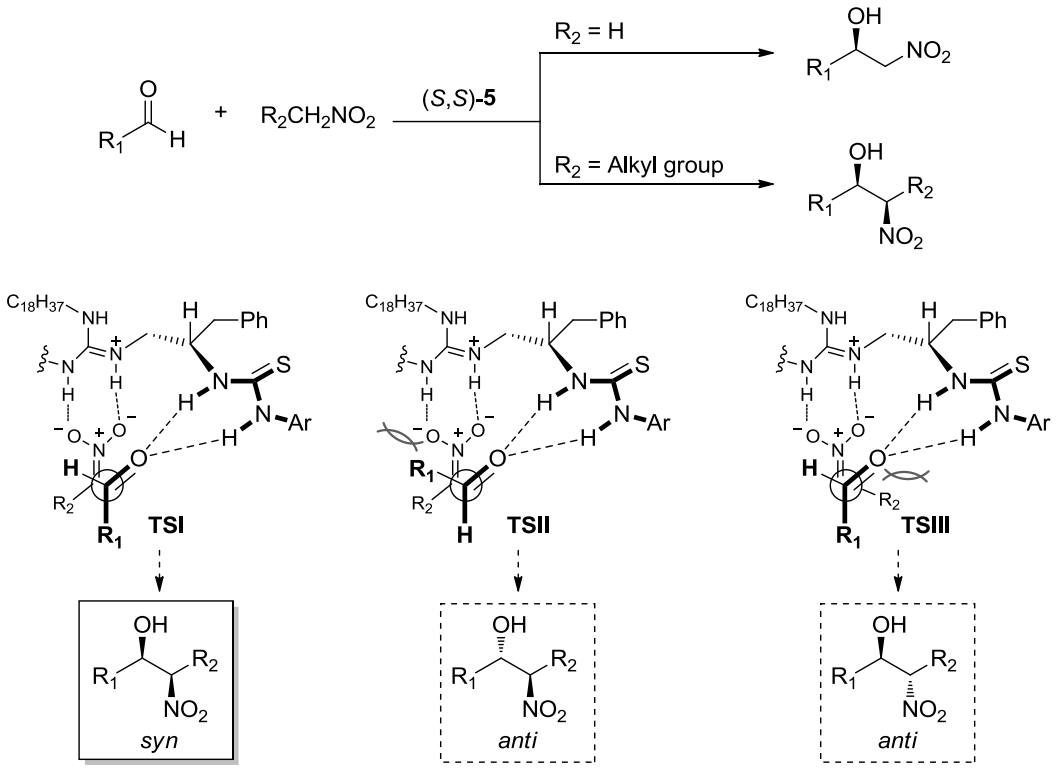


R_1	R_2	KOH (mol%)	Time (h)	Yield (%)	*syn*:*anti*	*ee* (*syn*) (%)
$CH_3(CH_2)_2$	$CH_3(CH_2)_2NO_2$	5	48	63	90:10	85
$CH_3(CH_2)_2$	$TBSO(CH_2)_2NO_2$	3	48	51	97:3	87
$CH_3(CH_2)_2$	$TIPSO(CH_2)_2NO_2$	3	24	58	92:8	87
$CH_3(CH_2)_2$	$PhCH_2NO_2$	10	24	70	91:9	87
c-C_6H_{11}	$CH_3(CH_2)_2NO_2$	5	40	61	99:1	95
c-C_6H_{11}	$TBSO(CH_2)_2NO_2$	7	48	63	99:1	90
c-C_6H_{11}	$TIPSO(CH_2)_2NO_2$	6	48	60	99:1	90
c-C_6H_{11}	$PhCH_2NO_2$	7	48	67	99:1	95

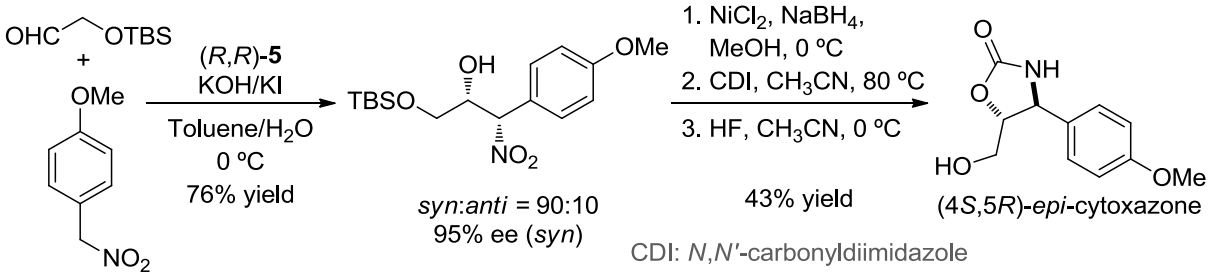
The synthetic utility of this methodology was demonstrated by the straightforward synthesis of (4*S*,5*R*)-*epi*-cytoxazone (Scheme 1) and cytoxazone [33,34].

More recently, Terada *et al*. [35] designed novel axially chiral guanidine bases and applied them as efficient chiral Brønsted base catalysts in the Henry reaction between nitroalkanes and aldehydes (Scheme 2 and Table 2). After an extensive screening of promising catalyst structures, catalyst **6**, having 3,5-bis(trifluoromethyl)phenyl groups introduced in the 3,3'-positions of the binaphthyl backbone, was found to be the best in terms of both enantioselectivity and catalytic activity.

Figure 2. Possible transition state models (**TSI-TSIII**) of enantioselective Henry reaction in the presence of catalyst **5**.



Scheme 1. Synthesis of (4*S*,5*R*)-*epi*-cytoxazone.



Scheme 2. Henry reaction catalyzed by axially chiral guanidine base **6**.

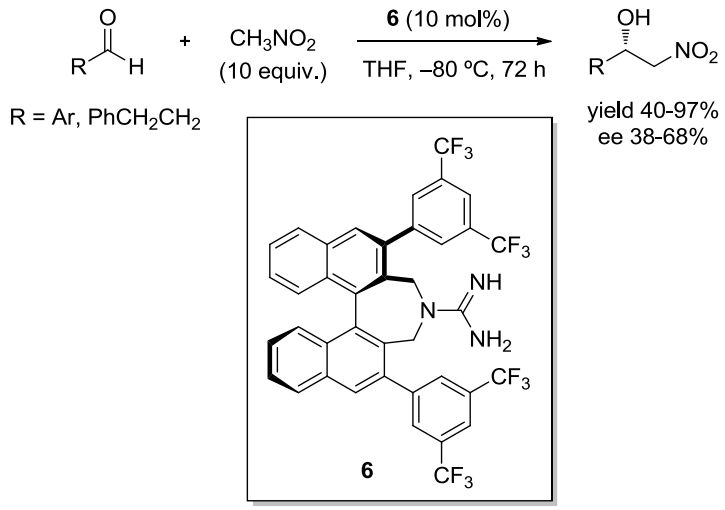
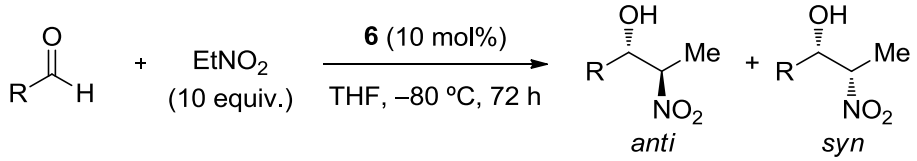
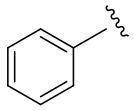
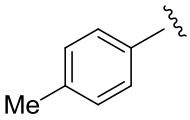
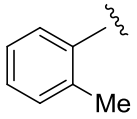
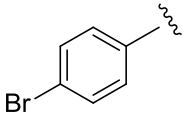
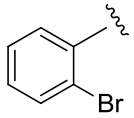


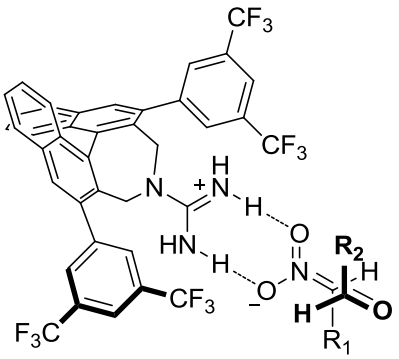
Table 2. Henry reaction of nitroethane with aldehydes catalyzed by guanidine **6**.



R	Yield (%)	*anti:syn*	*ee* (*anti*) (%)	*ee* (*syn*) (%)
	72	79:21	78	87
	56	76:24	81	89
	75	94:6	69	74
	81	80:20	58	57
	66	87:13	56	10

On the basis of these experimental results, the activation was envisioned to occur between the nitronate specie and the chiral guanidinium ion through the two hydrogen bonds as shown in Figure 3.

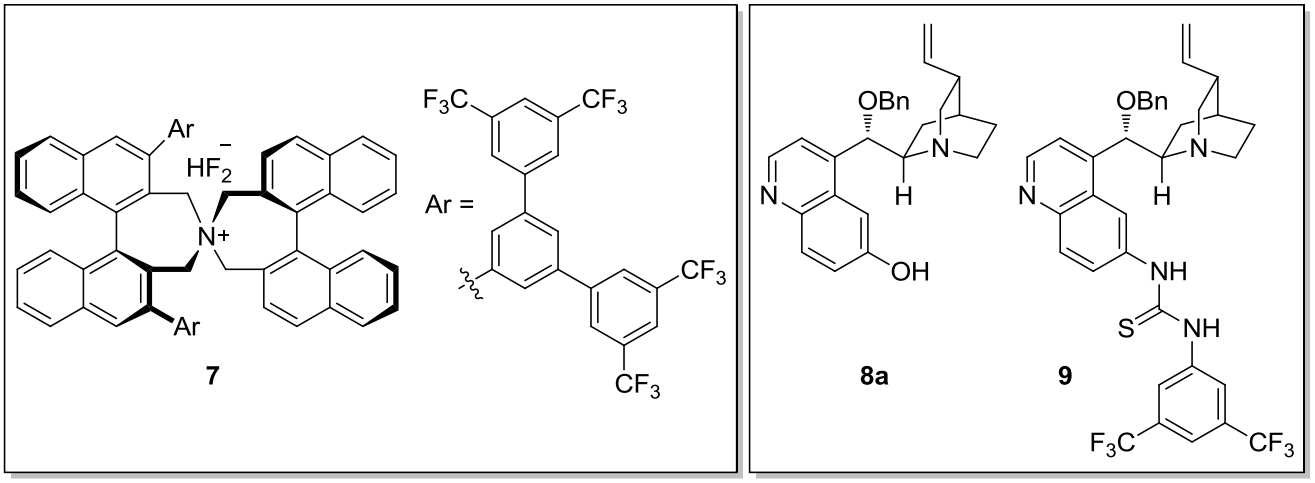
Figure 3. Plausible transition state model for catalyst **6**.



In agreement with the *anti* selectivity observed by the authors in the final adducts, the transition state is assumed to proceed through an acyclic extended transition state, where the substituents in the nitronate ion and in the aldehyde would be orientated in order to avoid unfavorable steric interactions. The substituents in the 3,3'-positions would drive the appropriate attack of the aldehyde by its *si*-face affording the established (*S*)-configuration.

Furthermore, the *N*-spiro C_2-symmetric chiral quaternary ammonium bifluoride **7** was successfully applied by Maruoka *et al*. as efficient phase transfer catalyst in the reaction of silyl nitronates with aldehydes (Figure 4) [36].

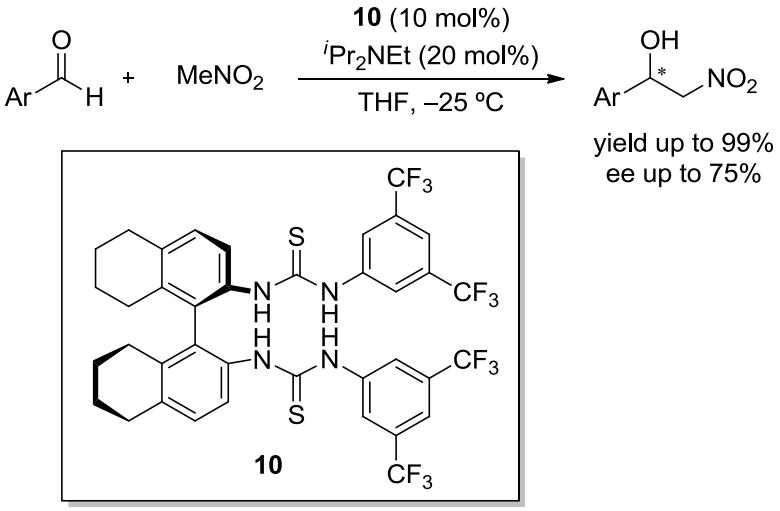
Figure 4. Appropriated catalysts to promote the Henry reaction.



In addition, cinchona alkaloid derivatives have been also used as suitable asymmetric catalysts in the Henry reaction (Figure 4). Hiemstra *et al*. reported moderate results with the bifunctional estructure **8a** [37]. Later, they found that the replacement of the phenol moiety on compound **8a** with a better hydrogen bond donor, such as a thiourea moiety, resulted in a more powerful catalyst **9** [38]. In fact, this organocatalyst promoted the direct enantioselective nitroaldol reaction of aromatic and heteroaromatic aldehydes with nitromethane with very good yields and enantioselectivities, improving the results obtained previously with catalyst **8a**.

The thiourea moiety is also present in the catalyst (**10**) designed by Shi *et al*. in 2007 (Scheme 3) [39]. The used of this axially chiral bis(arylthiourea)-based organocatalyst in the enantioselective Henry reaction of aromatic aldehydes with nitromethane provided the corresponding adducts with good yields and moderate enantioselectivities.

Scheme 3. Henry reaction catalyzed by bis(arylthiourea) **10**.



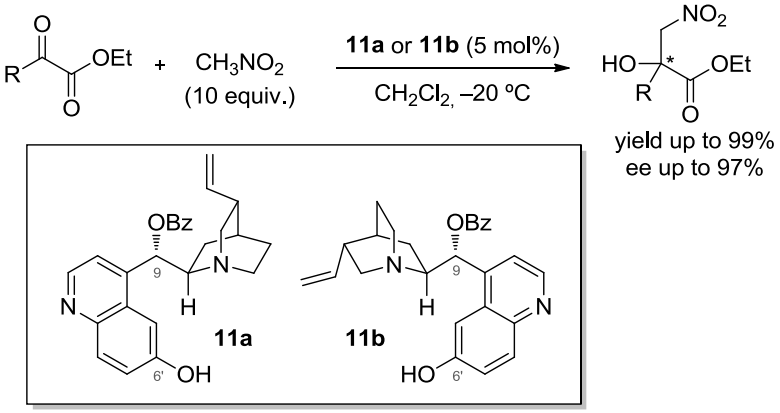
3. Enantioselective Henry Reaction with Ketones

The use of ketones as suitable substrates for this reaction has been less well explored compared to the use of aldehydes, perhaps due to the lesser reactivity shown by ketones. However, the obtainment of tetrasubstituted chiral carbons is, in general, a demanding task in organic chemistry [40]. Additionally, the preparation of chiral tertiary alcohols is potentially attractive for the synthesis of medicinal targets [41]. For these reasons, it remains a challenge in synthetic chemistry, and a few examples concerning this interesting area will be detailed below.

3.1. Henry Reaction with α-Ketoesters

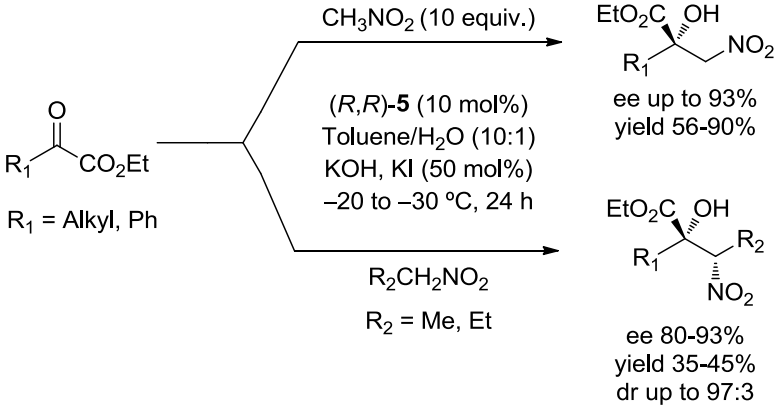
In 2007, Deng *et al*. [42] described the first efficient organocatalytic enantioselective nitroaldol reaction with α-ketoesters (Scheme 4). In this case, C6'-OH cinchona alkaloids **11a** and **11b** were used as catalysts, obtaining very good results at low temperature.

Scheme 4. Enantioselective addition of nitromethane to α-ketoester catalyzed by cinchona alkaloids **11a** and **11b**.



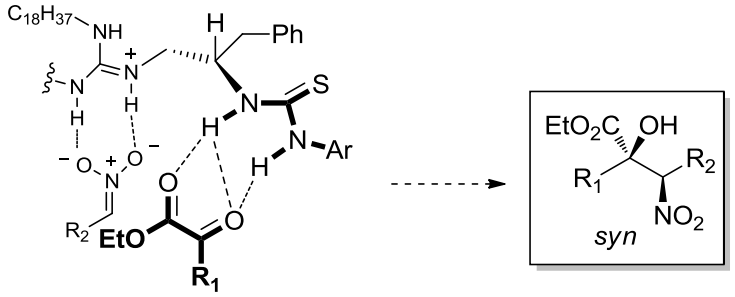
After this pioneering example, Nagasawa's group [43] explored the same asymmetric nitroaldol reaction of α-ketoesters using guanidine–thiourea bifunctional organocatalyst **5** at temperatures below the freezing point of water. Various cyclic, branched-type and linear α-ketoesters, afforded chiral *tert*-nitroaldols with very good enantioselectivities and moderate yields (Scheme 5).

Scheme 5. Enantioselective addition of nitromethane to α-ketoester catalyzed by **5**.



The authors invoked a transition state based on a bifunctional mode of action of the catalyst to explain the absolute stereochemistry observed in the final products (Figure 5). In this plausible transition state, the larger substituents belonging to the nitronate ion and the α-ketoester are preferentially placed in an *anti*-relationship in order to minimize steric repulsion.

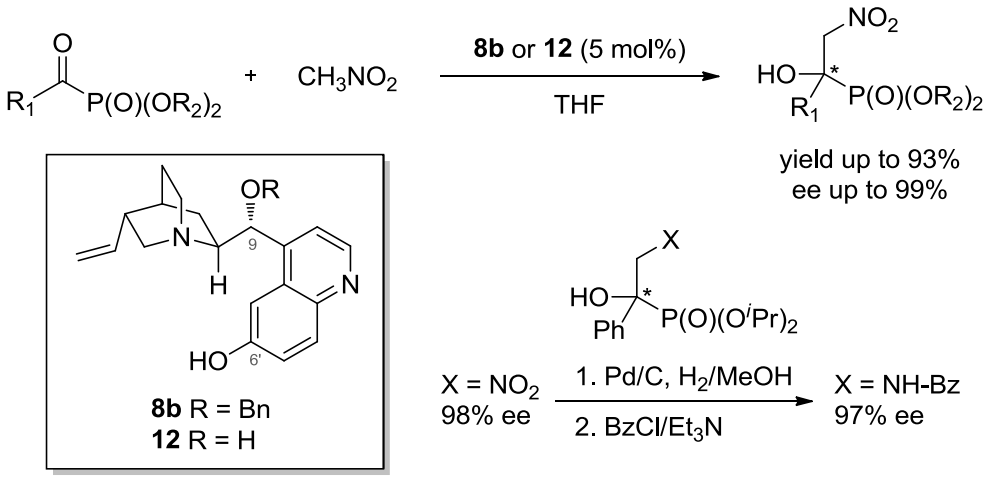
Figure 5. Invoked transition state using catalyst (*S*,*S*)-**5**.



3.2. Henry Reaction with α-Ketophosphonates

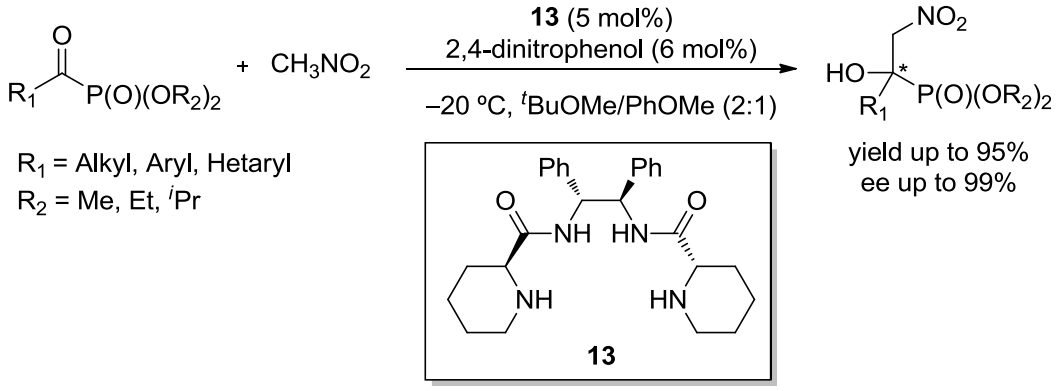
Zhao *et al*. [44] carried out the first organocatalytic highly enantioselective nitroaldol reaction of α-ketophosphonates and nitromethane using cupreine (**12**) or 9-*O*-benzylcupreine (**8b**) as catalysts at a low catalyst loading (5 mol%) (Scheme 6). The resulting α-hydroxy-β-nitrophosphonates, obtained with good yields and excellent enantioselectivities, were transformed in β-amino-α-hydroxyphosphonates without loss of the enantioselectivity.

Scheme 6. Enantioselective addition of nitromethane to α-ketophosphonates catalyzed by compounds **8b** and **12**.



Later, Hu *et al*. [45] reported the secondary amine amide **13** as efficient catalyst in the asymmetric Henry reaction of α-ketophosphonates (Scheme 7). Excellent enantioselectivities and moderate-to-high yields were achieved for a variety of α-ketophosphonates using a low catalyst loading (5 mol%). Preliminary theoretical calculations supported hydrogen-bond interactions between catalyst **13** and the substrates, which could be crucial for the reactivity and enantioselectivity of this process.

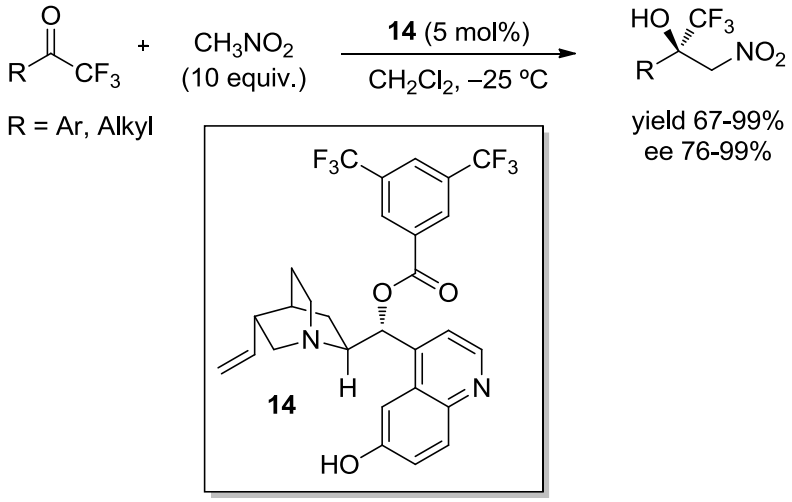
Scheme 7. Enantioselective addition of nitromethane to α-ketophosphonates catalyzed by secondary amine amide **13**.



3.3. Henry Reaction with Fluoromethylketones

The first organocatalytic enantioselective nitroaldol reaction of fluoromethylketones was described in 2008 by Umani-Rochi *et al.* (Scheme 8) [46]. They used as catalyst the novel cupreine derivative **14** bearing electron-withdrawing groups in the benzoyl moiety. The corresponding fluorinated β-nitroalcohol adducts were isolated with high yield and excellent enantiomeric excesses, using aromatic and aliphatic substrates and being tolerant to different electronic groups.

Scheme 8. Enantioselective addition of nitromethane to fluoromethylketones catalyzed by cupreine derivative **14**.



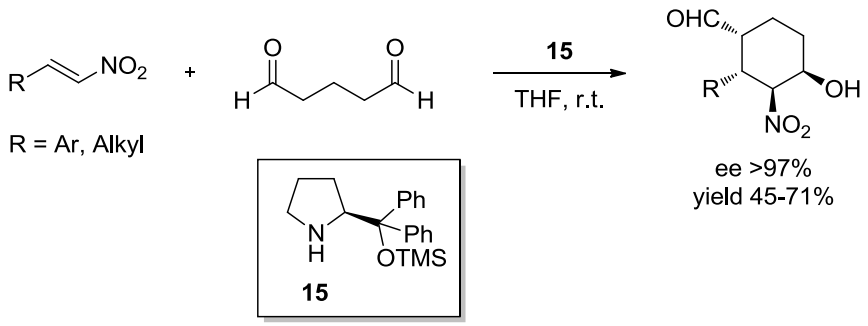
4. Enantioselective Domino Michael/Henry Reactions

During the last decade, the design of more complex processes and structures has become a significant synthetic challenge in organic chemistry. In this sense, great efforts have been motivated in the discovery of new multicomponent [47,48], and domino reactions [49–51], which lead to highly functionalized molecules with multiple stereogenic centers. The importance of this protocol relies on the synthesis of valuable chiral building blocks, which are motifs present in biologically active compounds.

4.1. Aminocatalysis

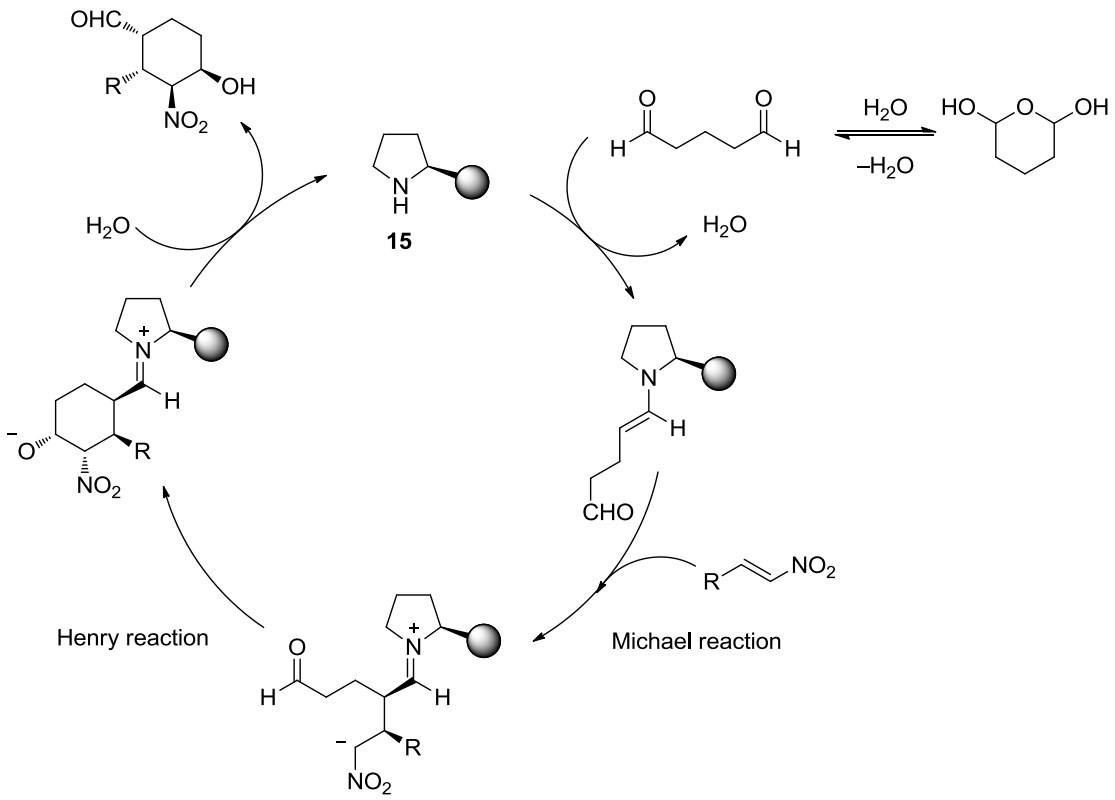
The first example of this combined process was reported in 2007 by Hayashi *et al*. They developed a highly diastereo- and enantioselective tandem Michael/Henry reaction catalyzed by diphenylprolinol silyl ether **15** (Scheme 9) [52]. They obtained very good results in terms of both enantio- and diastereoselectivity and moderate yields in a single step involving several 2-substituted nitroalkenes and pentane-1,5-dial. This procedure renders substituted chiral nitrocyclohexanecarbaldehydes derivatives with control of four stereogenic centers with the formation of two carbon-carbon bonds.

Scheme 9. Catalytic asymmetric tandem Michael/Henry reaction catalyzed by diphenylprolinol silyl ether **15**.



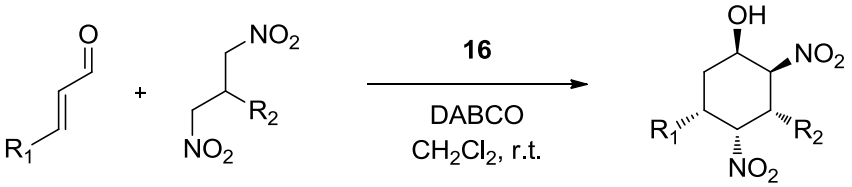
The formation of the final adducts can be explained by the mechanistic hypothesis proposed in Scheme 10, where, after the first Michael addition reaction via enamine activation, an intramolecular Henry reaction occurs affording final cyclic products with four stereogenic centers.

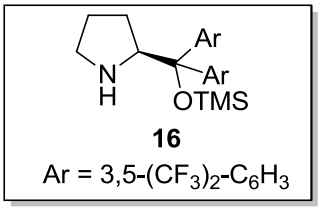
Scheme 10. Invoked reaction mechanism.



Concurrently, Jørgensen *et al*. [53] developed the Michael addition of dinitroalkanes to α,β-unsaturated aldehydes followed by an intramolecular Henry reaction using catalyst **16** (Table 3). This was the first example of one-pot asymmetric formation of five contiguous streocenters by an intermolecular two-component reaction. The final pentasubstituted cyclohexanols were furnished with moderate-to-good yields and high diastereo- and enantioselectivities.

Table 3. Scope of the organocatalytic nitro-Michael/Henry reaction catalyzed by chiral secondary amine **16**.





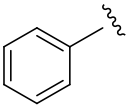
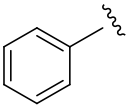
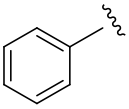
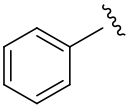
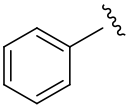
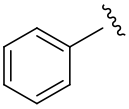
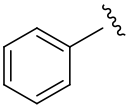
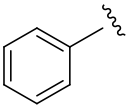
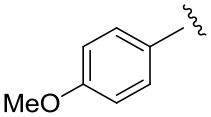
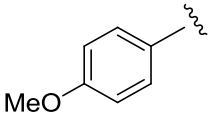
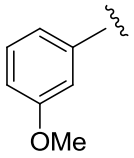
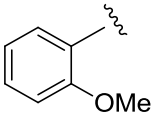
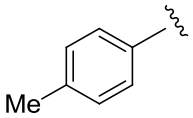
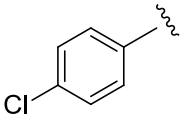
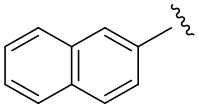
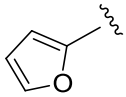
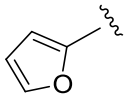
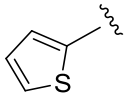
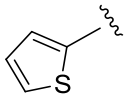
R_1	R_2	Yield (%)	*dr*	*ee* (%)
Et		45	4:2:1	90
Me		43	4:1:1	75
n-Pr		44	4:2:1	86
i-Pr		38	3:1:1	90
n-Bu		43	4:2:1	87
CH_2OTIPS		56	3:1:0	94
cis-C_6H_{11}		52	4:2:1	86
C_7H_{16}		50	4:2:1	87
Et		48	4:2:1	92

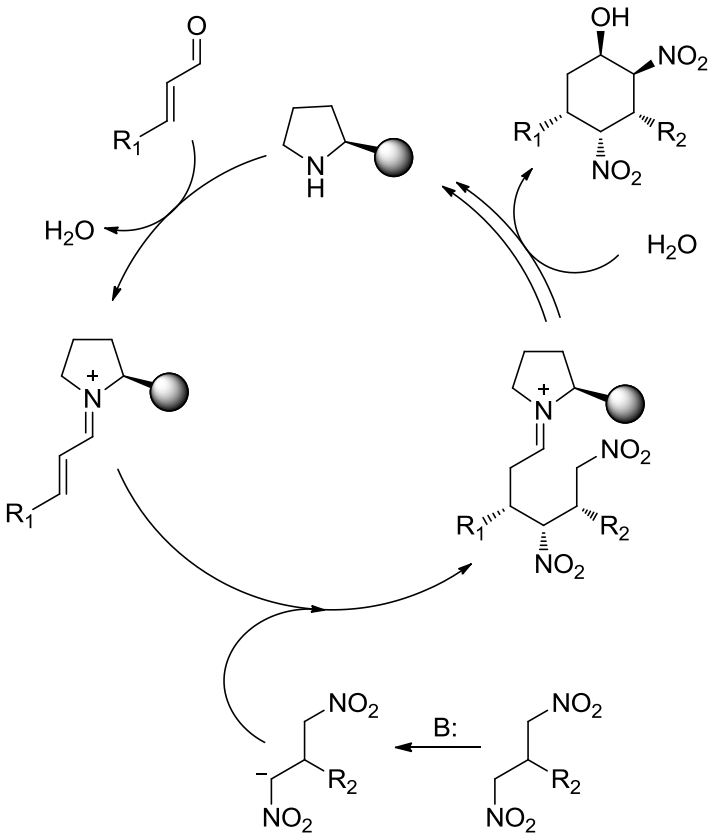
Table 3. *Cont.*

R_1	R_2	Yield (%)	*dr*	*ee* (%)
i-Pr		53	5:1:1	89
i-Pr		65	12:2:3	90
i-Pr		48	5:2:1	90
i-Pr		40	5:1:1.2	84
i-Pr		47	5:1:1	88
i-Pr		61	5:0:1	88
Et		60	4:2:1	86
i-Pr		43	6:1:0	88
Et		42	4:0:1	80
i-Pr		43	5:1:1	90

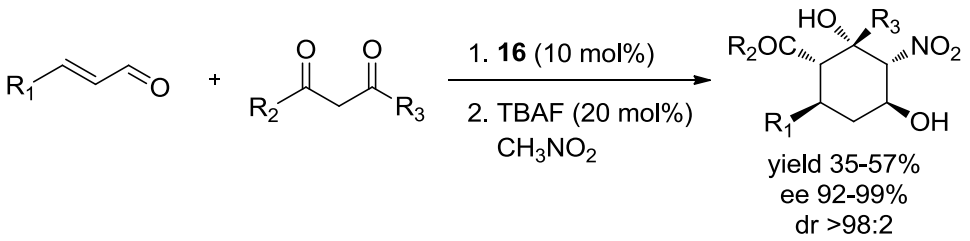
In this case, the first step would be the Michael addition reaction of the deprotonated nitroalkane over an iminium ion resulted from the initial activation of the α,β-unsaturated aldehyde with the catalyst, followed by an intramolecular Henry reaction to render the final nitroalcohol derivatives with very good enantioselectivity (Scheme 11).

More recently, Ruano, Alemán *et al*. [54] have shown that the appropriate combination of two catalysts, diarylprolinol silyl ether **16** and TBAF, in a one-pot process resulted in an effective synthesis of cyclohexanes with five chiral centers starting from α,β-unsaturated aldehydes, β-dicarbonyl compounds and nitromethane (Scheme 12).

Scheme 11. Proposed mechanism for the organocatalyzed asymmetric domino nitro-Michael/Henry reaction.



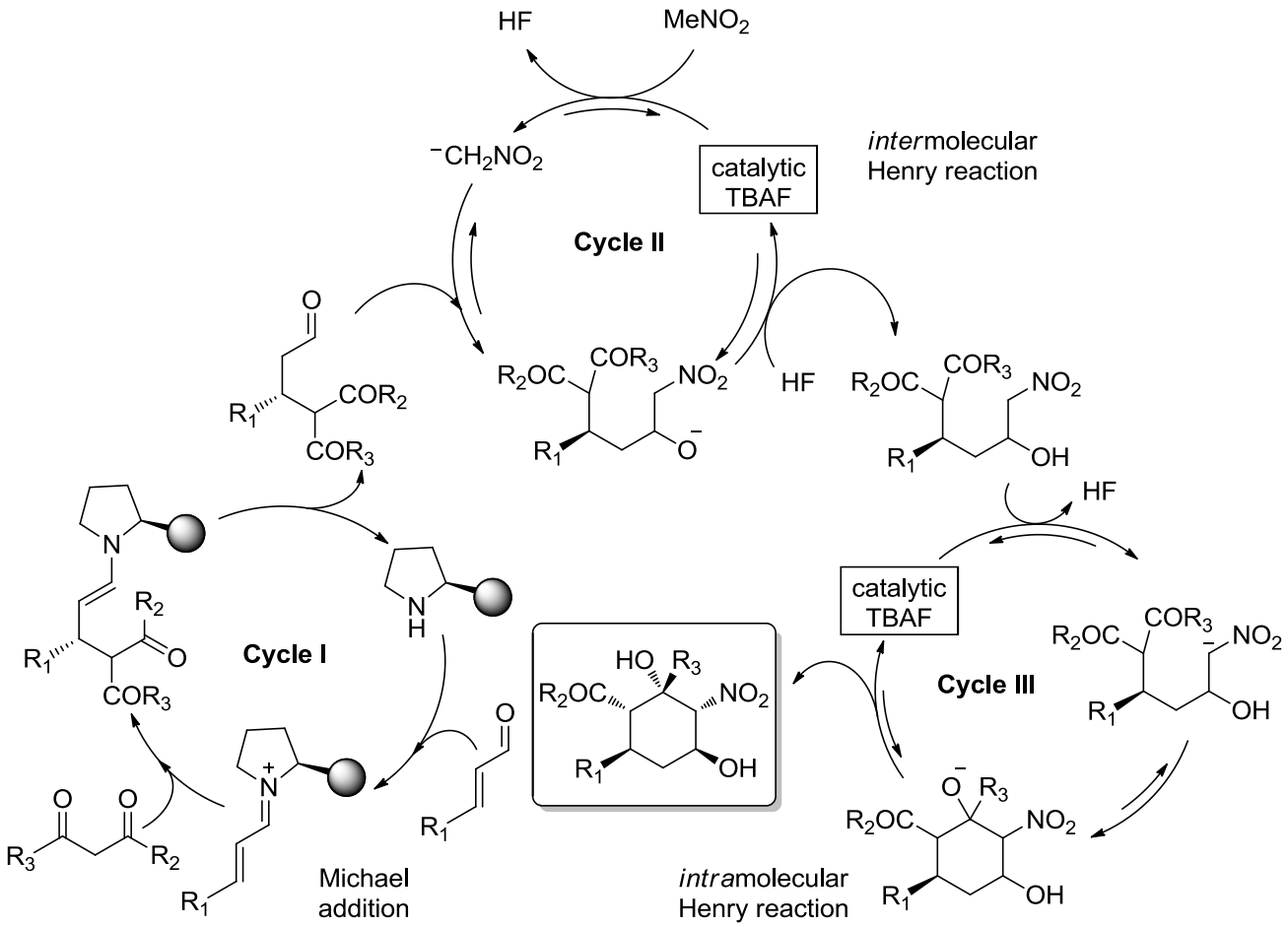
Scheme 12. Tandem Michael/inter-intra double Henry reaction.



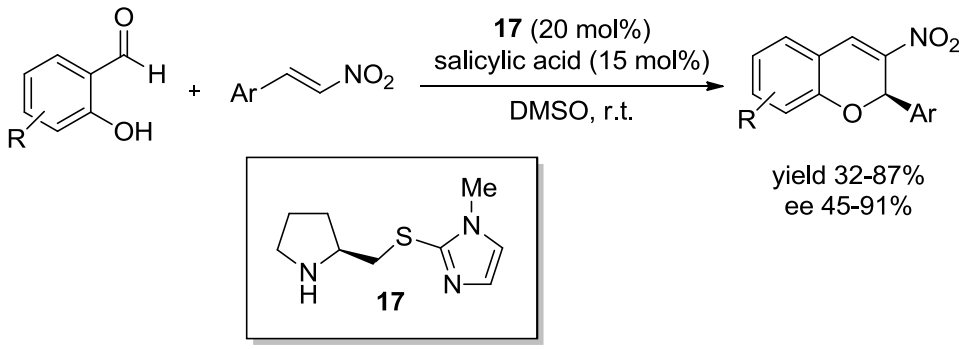
The authors invoked a complex mechanism formed by three cycles in order to explain the formation of the highly functionalized cyclohexane adducts (Scheme 13). The first cycle would be a Michael addition reaction over the activated α,β-unsaturated aldehydes. The second one would be an intermolecular Henry reaction, and the third one an intramolecular Henry reaction, closing the cycle and furnishing the final product with excellent enantioselectivity.

In order to synthesize interesting chromene derivatives, Xu *et al.* applied this tandem methodology using the chiral secondary amine organocatalyst **17** with salicylaldehydes and β-nitrostyrenes via a domino oxa-Michael/Henry reaction (Scheme 14) [55]. The mechanism proposed by the authors explains the isolated final adducts. It involves a first oxa-Michael reaction followed by an intramolecular Henry attack to the activated iminium ion, thus, the elimination of the catalyst closes the catalytic cycle (Scheme 15). This work represents the first example of the activation of aromatic aldehydes involving an iminium ion.

Scheme 13. Proposed mechanism for the one-pot Michael/Henry reaction.



Scheme 14. Enantioselective tandem oxa-Michael/Henry reaction of salicylaldehydes with various β-nitrostyrenes.



Very recently, Hong *et al*. discovered an unprecedented asymmetric domino Michael/acetalization/Henry reaction that allows the synthesis of tetrahydro-6*H*-benzo[*c*]chromen-6-ones with excellent enantioselectivity (Table 4) [56]. The formation of four contiguous chiral centers in a three-bond-forming cascade is especially remarkable, although the methodology is only applied to a small number of examples.

Scheme 15. Mechanism proposed for the enantioselective tandem oxa-Michael/Henry reaction using catalyst **17**.

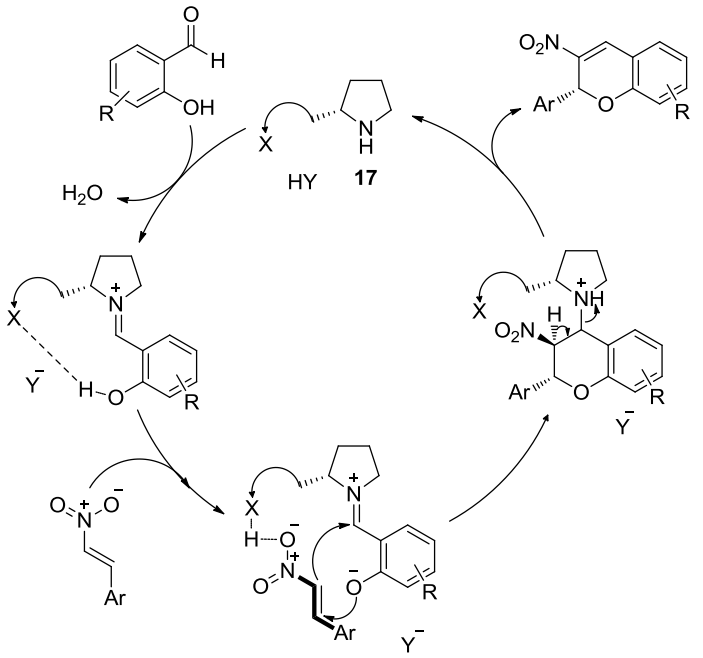
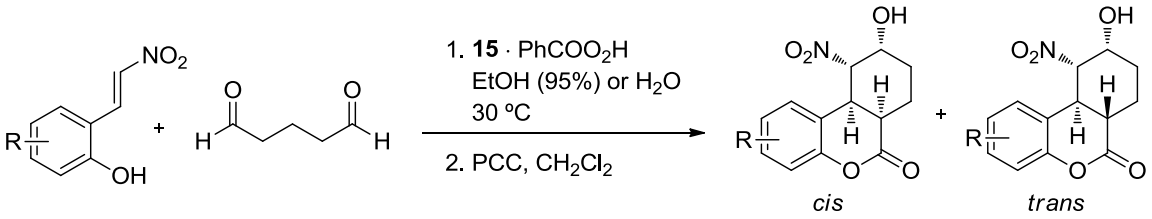
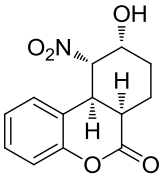
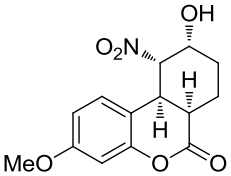
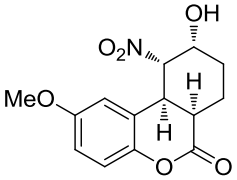


Table 4. Synthesis of tetrahydro-6*H*-benzo[*c*]chromen-6-ones via an asymmetric domino Michael/acetalization/Henry reaction.

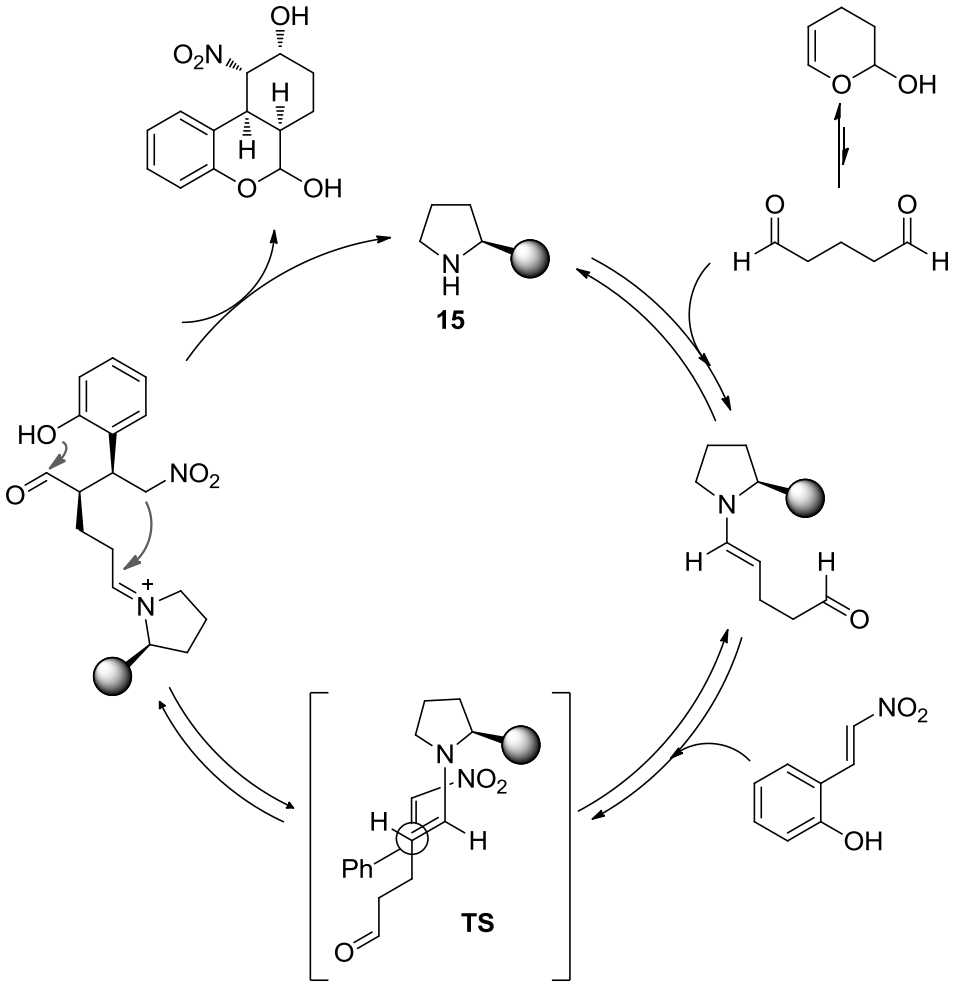


R	in EtOH (95%)		in H_2O		Yield (%) [b]	*ee* (%) [c]
	t (h)	*cis*:*trans* [a]	t_2 (h)	*cis*:*trans* [a]		
	42	88:12	24	81:19	50 (76)	>99
	45	86:14	24	88:12	63 (77)	>99
	46	87:13	30	80:20	65 (81)	>99

[a] Determined by ^{1}H NMR after oxidation. [b] Isolated yield (Tandem Michael/acetalization/Henry reaction (oxidation)). [c] The ee of the major oxidation product (*i.e.*, *cis*-isomer).

In order to explain the high enantioselectivity obtained, a plausible mechanism was suggested by the authors (Scheme 16). After the formation of the enamine from the glutaraldehyde and the catalyst, a Michael addition with nitrostyrene occurs through the transition state (**TS**), depicted in the scheme. Then, the formed *cis* iminium intermediate is further subject to the intramolecular Henry reaction and acetalization to produce the corresponding chromanol.

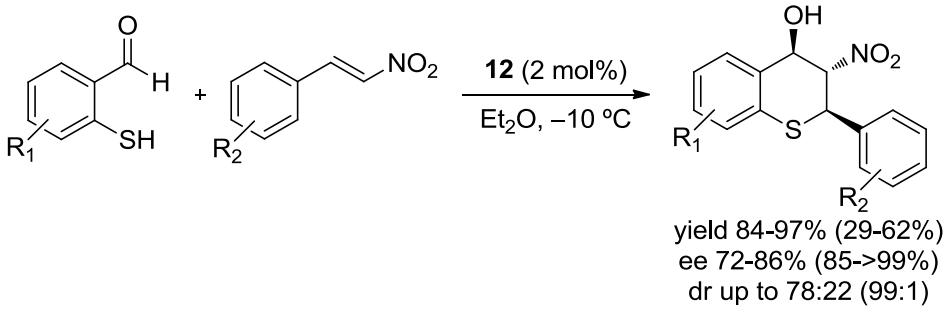
Scheme 16. Proposed mechanism for the organocatalytic tandem Michael/acetalization/ Henry reaction.



4.2. Cinchona Alkaloids

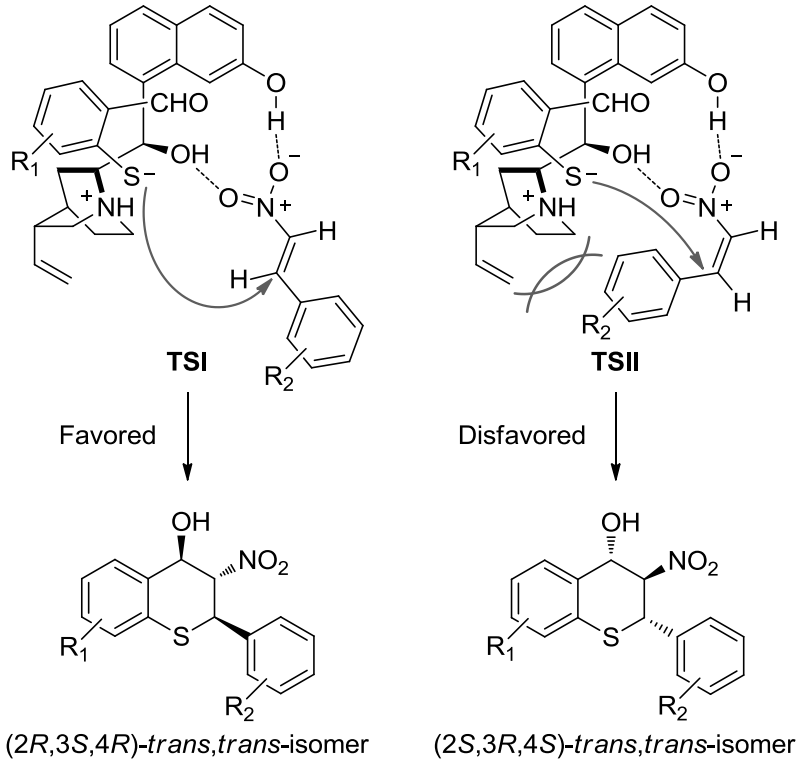
Zhao *et al*. [57] reported another example of tandem Michael/Henry reaction for the interesting preparation of thiochromanes, like suitable important targets with possible biological activities, using cupreine **12** as catalyst and starting from 2-mercaptobenzaldehydes and β-nitrostyrenes (Scheme 17). In this protocol, the authors synthesized chiral 2-aryl-3-nitrothiochroman-4-ols with good diastereomeric ratios and enantioselectivities after recrystallization, using a very low catalyst loading (2 mol%).

Scheme 17. Enantioselective tandem Michael/Henry reaction of 2-mercaptobenzaldehydes with various β-nitrostyrenes. (Values in parantheses are those of the recrystallized products).



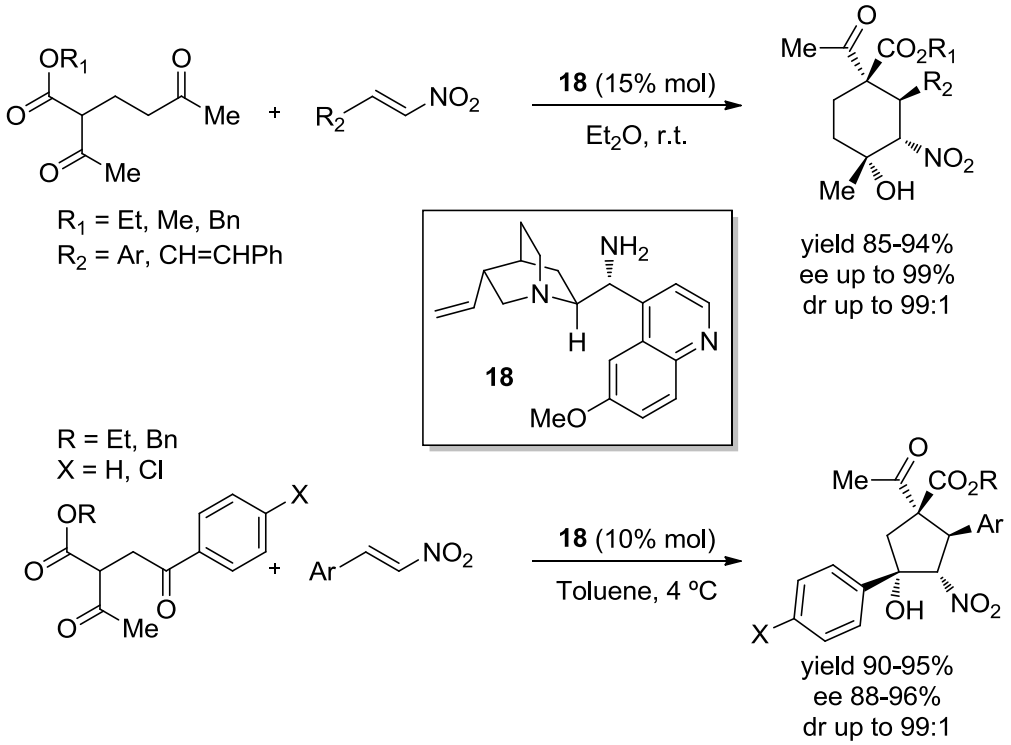
The authors proposed two different transition states (**TSI**-**TSII**) to justify the formation of the major (2*R*,3*S*,4*R*)-*trans*,*trans*-isomer (Figure 6). **TSI** is the preferred state, since it avoids steric interaction between the aromatic substituent of the nitroalkene and the catalyst.

Figure 6. Proposed transition states (**TSI**-**TSII**) for the formation of thiochromanes.



The same group developed two novel organocatalytic tandem Michael/Henry reactions consecutively, efficiently catalyzed by 9-amino-9-deoxyepiquinine **18** to give highly functionalized chiral cyclohexanes [58] and cyclopentanes [59] in good-to-excellent yields, high diastereoselectivities and excellent enantioselectivities (Scheme 18). The final products have four stereogenic centers containing two quaternary stereocenteres in both cases.

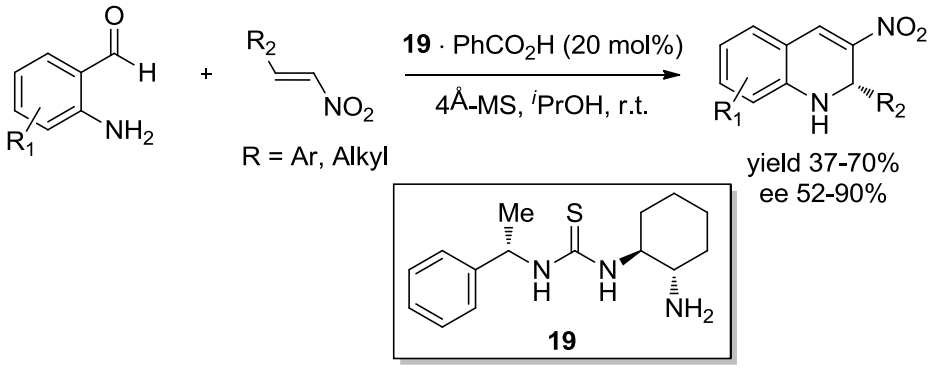
Scheme 18. Tandem Michael/Henry reaction of diketoesters and nitroolefins catalyzed by catalyst **18**.



4.3. Thiourea Catalysts

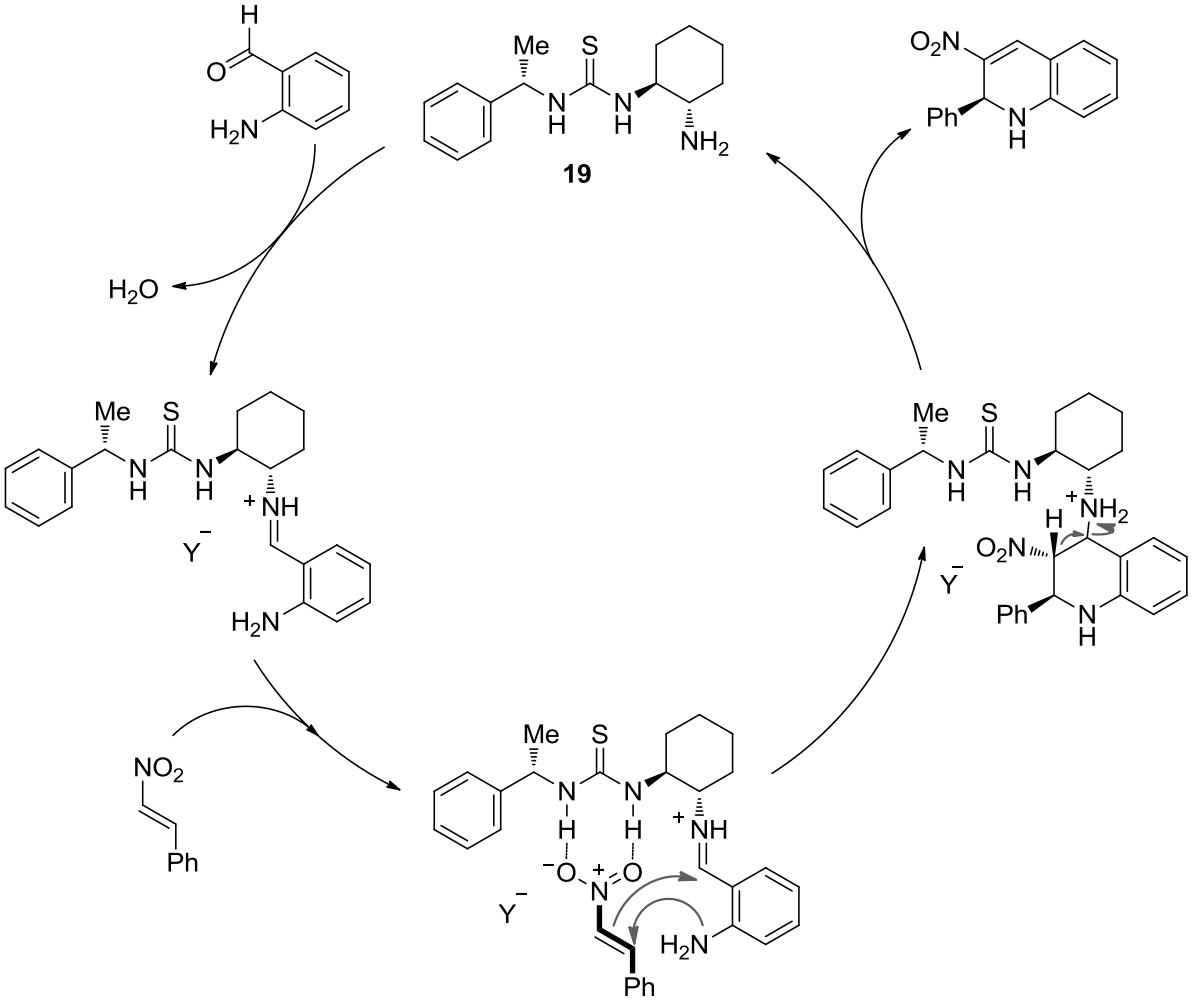
More recently, Xu *et al*. described an efficient enantioselective domino aza-Michael/Henry reaction of 2-aminobenzaldehydes and aromatic and aliphatic nitroolefins, catalyzed by chiral thiourea **19**, to generate synthetically versatile 3-nitro-1,2-dihydroquinoline in moderate yields and from moderate-to-high enantioselectivities (Scheme 19) [60].

Scheme 19. Domino aza-Michael/Henry reactions promoted by thiourea **19**.



The thiourea catalyst **19** is proposed to react as a bifunctional catalyst by generating an iminium ion with the primary amine and the aldehyde, and at the same time, approaching the nitroalkene via hydrogen bonds with the thiourea moiety in order to facilitate the domino aza-Michael/Henry reaction as depicted in Scheme 20.

Scheme 20. Proposed mechanism for the reaction catalyzed by thiourea **19**.



In 2010, Barbas *et al*. presented a simple methodology for the asymmetric synthesis of pyranosa derivatives with talo- and manno- configurations from simple achiral precursors through organocatalytic asymmetric intermolecular Michael/Henry reaction sequences [61]. The procedure was applied for a variety of nitroalkenes and catalyzed by the bifunctional thiourea catalyst **20** rendering the final adducts with very high enantioselectivities (Tables 5 and 6).

Table 5. Domino Michael/Henry reaction to give 3,4-dideoxy-D-talose derivatives catalized by thiourea **20**.

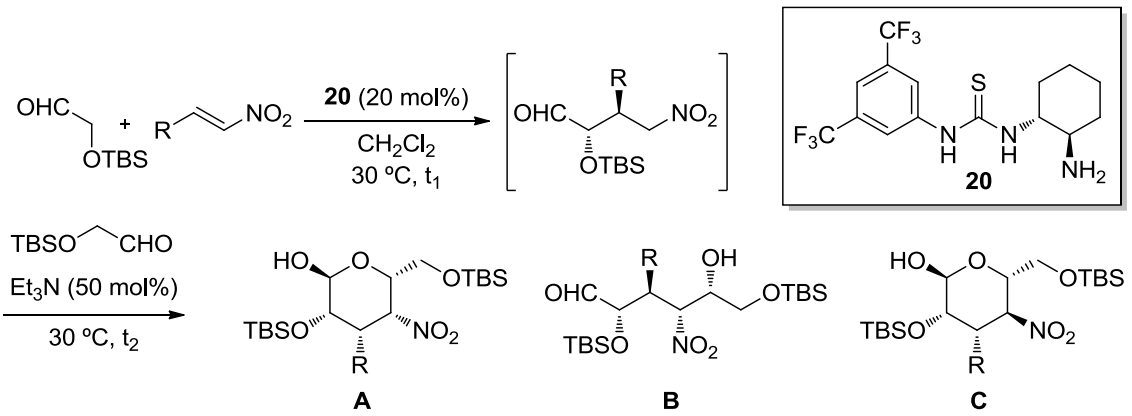


Table 5. *Cont.*

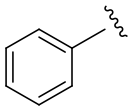
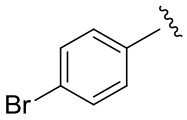
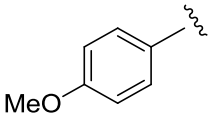
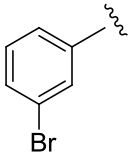
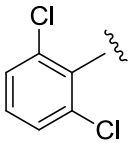
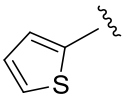
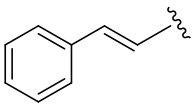
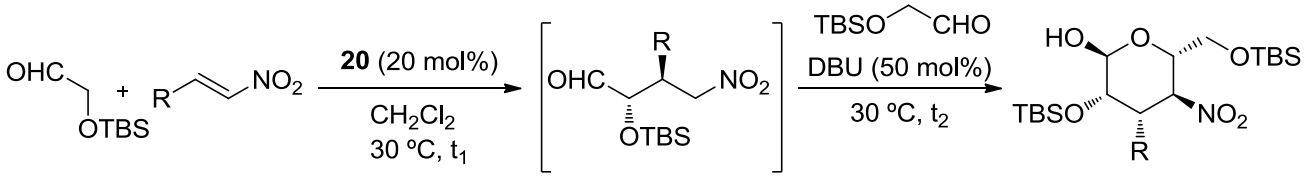
R	t_1 (h)	t_2 (h)	Yield (%)	*dr*		*ee* (%)
				A+**B**:**C**	**A**:**B**	
	4	1	68	>10:1	3:1	98
	4	0.5	62	>10:1	4:1	98
	4	1.5	76	>10:1	3:1	97
	5	0.5	68	>10:1	6:1	97
	16	4	37	1:0	0:1	99
	7	0.5	63	7:1	13:1	97
	6	0.3	43	6:1	1:0	93
C_7H_{15}	5	18	44	>10:1	1:0	96

Table 6. Domino Michael/Henry reaction to give dideoxy-D-mannopyranose derivatives catalized by thiourea **20**.



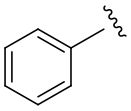
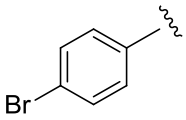
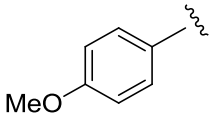
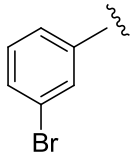
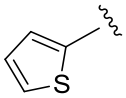
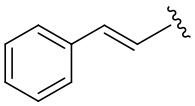
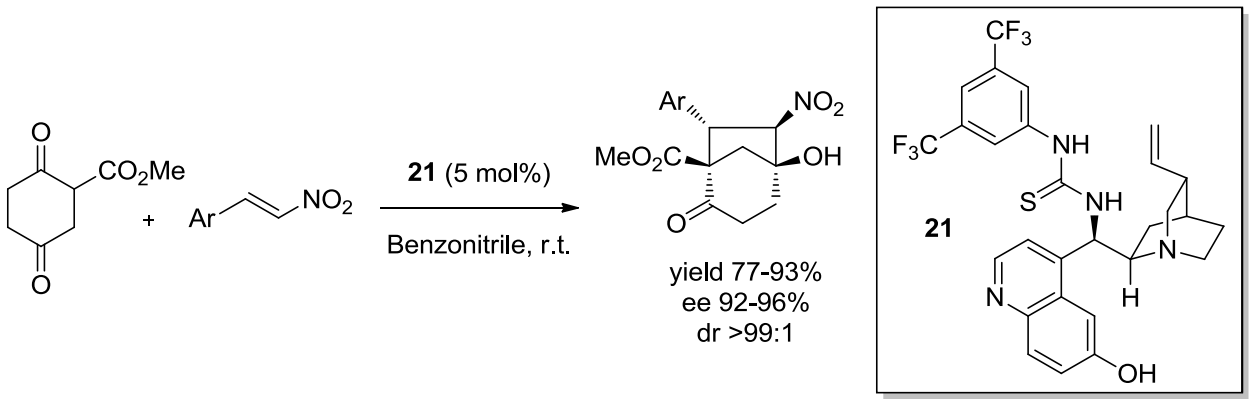
R	t_1 (h)	t_2 (h)	Yield (%)	*ee* (%)
	4	1	51	98
	4	1	65	96
	23	1	48	95

Table 6. *Cont.*

R	t_1 (h)	t_2 (h)	Yield (%)	*ee* (%)
	5	1	57	98
	7	1	59	96
	20	2	66	93
C_7H_{15}	5	1	50	96

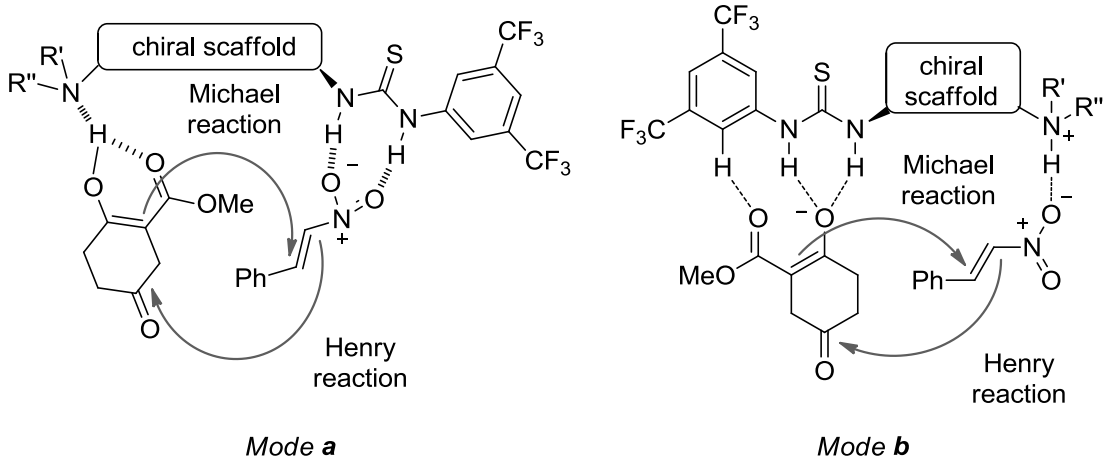
Morover, Zhong *et al*. developed a highly enantio- and diastereoselective organocatalytic domino Michael/Henry process for the preparation of medicinally important byciclo[3.2.1]octane derivatives with four stereogenic centers, including two quaternary stereocenters (Scheme 21) [62].

Scheme 21. Domino Michael/Henry reaction of nitroolefins catalyzed by catalyst **21**.



In addition, a new catalytic model for this domino reaction was proposed (Figure 7). The thiourea catalyst **21** is invoked to react according to a dual activation model, where the two substrates involved in the reaction are activated simultaneously. However, two different modes of activation were suggested, for which, after a Michael addition over the nitroalkene, a subsequent Henry reaction takes place, resulting in a highly enantioselective product. Between the two different modes of activation depicted in Figure 7, DFT computational calculations supported *Mode **b*** as the more suitable transition state for this process.

Figure 7. Proposed activation modes of catalyst **21**.



*Mode **a*** *Mode **b***

5. Conclusions

In this work we have compiled significant examples concerning the organocatalytic enantioselective Henry reaction from three different points of view: the addition of nitroalkane to aldehydes, and to ketones, and, in a more complex approach, via domino Michael/Henry reactions. In a variety of protocols, several kinds of organocatalysts have been efficiently employed, such as chiral thioureas, guanidines, cinchona alkaloids derivatives and phase transfer organocatalysts. This is a very interesting and useful reaction in organic synthesis proven by the growing interest and efforts focused in this area. However, in spite of its importance, investigation of this key reaction is still needed, and we expect that, in the near future, new, efficient and more complex examples regarding the nitroaldol reaction will be reported.

Acknowledgements

We thank the Spanish Ministry of Science and Innovation (Projects CTQ2009-09028 and CTQ2010-19606) and the Government of Aragón (Project PI064/09 and Research Groups, E-10) for financial support of our research. E. M.-L. thanks CSIC for a JAE-Doc postdoctoral contract. R. P. H. thanks the Aragón I + D Foundation for her permanent position.

References

1. Luzzio, F.A. The Henry Reaction: Recent Examples. *Tetrahedron* **2001**, *57*, 915–945.
2. Henry, L. Nitro-alcohols. *Compt. Rend. Hebd. Séances Acad. Sci.* **1895**, *120*, 1265–1268.
3. *The Nitro Group in Organic Synthesis*; Ono, N., Ed.; Wiley-VCH: New York, NY, USA, 2001.
4. Bergmeier, S.C. The Synthesis of Vicinal Amino Alcohols. *Tetrahedron* **2000**, *56*, 2561–2576.
5. Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VHC: Weinheim, Germany, 2004.
6. *Enantioselective Organocatalysis*; Dalko, P.I., Ed.; Wiley-VCH: Weinheim, Germany, 2007.
7. *Organocatalysis*; Reetz, M.T., List, B., Jaroch, S., Weinmann, H., Eds.; Springer-Verlag: Berlin, Germany, 2008.

8. Wong, O.A.; Shi, Y. Chiral Ketones and Iminium Catalysts for Olefin Epoxidation. *Top. Curr. Chem.* **2010**, *291*, 201–232.
9. Guizzetti, S.; Benaglia, M. Trichlorosilane-Mediated Stereoselective Reduction of C=N Bonds. *Eur. J. Org. Chem.* **2010**, *2010*, 5529–5541.
10. Marqués-López, E.; Merino, P.; Tejero, T.; Herrera, R.P. Catalytic Enantioselective aza-Henry Reactions. *Eur. J. Org. Chem.* **2009**, *15*, 2401–2420.
11. Masson, G.; Housseman, C.; Zhu, J. The Enantioselective Morita-Baylis-Hillman Reaction and its aza Counterpart. *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 4614–4628.
12. Pihko, P.M.; Majander, I.; Erkkilä, A. Enamine Catalysis. *Top. Curr. Chem.* **2010**, *291*, 29–75.
13. Merino, P.; Marqués-López, E.; Herrera, R.P. Catalytic Enantioselective Hydrophosphonylation of Aldehydes and Imines. *Adv. Synth. Catal.* **2008**, *350*, 1195–1208.
14. Merino, P.; Marqués-López, E.; Tejero, T.; Herrera, R.P. Organocatalyzed Strecker Reactions. *Tetrahedron* **2009**, *65*, 1219–1234.
15. Marqués-López, E.; Diez-Martinez, A.; Merino, P.; Herrera, R.P. The Role of the Indole in Important Organocatalytic Enantioselective Friedel-Crafts Alkylation Reactions. *Curr. Org. Chem.* **2009**, *13*, 1585–1609.
16. Terrasson, V.; de Figueiredo, R.M.; Campagne, J.M. Organocatalyzed Asymmetric Friedel-Crafts Reactions. *Eur. J. Org. Chem.* **2010**, *2010*, 2635–2655.
17. Almaşi, D.; Alonso, D.A.; Nájera, C. Organocatalytic Asymmetric Conjugate Additions. *Tetrahedron: Asymmetry* **2007**, *18*, 299–365.
18. Vicario, J.L.; Badía, D.; Carrillo, L. Organocatalytic Enantioselective Michael and Hetero-Michael Reactions. *Synthesis* **2007**, *14*, 2065–2092.
19. Tsogoeva, S.B. Recent Advances in Asymmetric Organocatalytic 1,4-Conjugate Additions. *Eur. J. Org. Chem.* **2007**, 1701–1716.
20. *Catalytic Asymmetric Conjugate Reactions*; Córdova, A., Ed.; Wiley-VCH: Weinheim, Germany, 2010.
21. Roca-López, D.; Sadaba, D.; Delso. I.; Herrera, R.P.; Tejero, T.; Merino, P. Asymmetric Organocatalytic Synthesis of γ-Nitrocarbonyl Compounds through Michael and Domino Reactions. *Tetrahedron: Asymmetry* **2010**, *21*, 2561–2601.
22. Merino, P.; Marqués-López, E.; Tejero, T.; Herrera, R.P. Enantioselective Organocatalytic Diels-Alder Reactions. *Synthesis* **2010**, *1*, 1–26.
23. Verkade, J.M.M.; van Hemert, L.J.C.; Quaedflieg, P.J.L.M.; Rutjes, F.P.J.T. Organocatalysed Asymmetric Mannich Reactions. *Chem. Soc. Rev.* **2008**, *37*, 29–41.
24. De Figueiredo, R.M.; Christmann, M. Organocatalytic Synthesis of Drugs and Bioactive Natural Products. *Eur. J. Org. Chem.* **2007**, *2007*, 2575–2600.
25. Marqués-López, E.; Herrera, R.P.; Cristmann, M. Asymmetric Organocatalysis in Total Synthesis—a Trial by Fire. *Nat. Prod. Rep.* **2010**, *27*, 1138–1167.
26. Boruwa, J.; Gogoi, N.; Pratim, Saikia, P.P.; Barua, N.C. Catalytic Asymmetric Henry Reaction. *Tetrahedron: Asymmetry* **2006**, *17*, 3315–3326.
27. Palomo, C.; Oiarbide, M.; Laso, A. Recent Advances in the Catalytic Asymmetric Nitroaldol (Henry) Reaction. *Eur. J. Org. Chem.* **2007**, *2007*, 2561–2574.
28. Chinchilla, R.; Nájera, C.; Sánchez-Agulló, P. Enantiomerically Pure Guanidine-Catalysed Asymmetric Nitroaldol Reaction. *Tetrahedron: Asymmetry* **1994**, *5*, 1393–1402.

29. Allingham, M.T.; Howard-Jones, A.; Murphy, P.J.; Thomas, D.A.; Caulkett, P.W.R. Synthesis and Applications of C_2-Symmetric Guanidine Bases. *Tetrahedron Lett.* **2003**, *44*, 8677–8680.
30. Ma, D.; Pan, Q.; Han, F. Diastereoselective Henry Reactions of *N*,*N*-Dibenzyl α-Amino Aldehydes with Nitromethane Catalyzed by Enantiopure Guanidines. *Tetrahedron Lett.* **2002**, *43*, 9401–9403.
31. Sohtome, Y.; Hashimoto, Y.; Nawasaga, K. Guanidine-Thiourea Bifunctional Organocatalyst for the Asymmetric Henry (Nitroaldol) Reaction. *Adv. Synth. Catal.* **2005**, *347*, 1643–1648.
32. Sohtome, Y.; Takemura, N.; Toshitsugu, I.; Hashimoto, Y.; Nawasaga, K. Diastereoselective Henry Reaction Catalyzed by Guanidine-Thiourea Bifunctional Organocatalyst. *Synlett* **2006**, *1*, 144–146.
33. Sohtome, Y.; Hashimoto, Y.; Nawasaga, K. Diastereoselective and Enantioselective Henry (Nitroaldol) Reaction Utilizing a Guanidine-Thiourea Bifuntional Organocatalyst. *Eur. J. Org. Chem.* **2006**, *2006*, 2894–2897.
34. Sohtome, Y.; Takemura, N.; Takada, K.; Takagi, R.; Toshitsugu, I.; Nawasaga, K. Organocatalytic Asymmetric Nitroaldol Reaction: Cooperative Effects of Guanidine and Thiourea Functional Groups. *Chem. Asian J.* **2007**, *2*, 1150–1160.
35. Ube, H.; Terada, M. Enantioselective Henry (Nitroaldol) Reaction Catalyzed by Axially Chiral Guanidines. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3895–3898.
36. Ooi, T.; Doda, K.; Maruoka, K. Designer Chiral Quaternary Ammonium Bifluorides as an Efficient Catalyst for Asymmetric Nitroaldol Reaction of Silyl Nitronates with Aromatic Aldehydes. *J. Am. Chem. Soc.* **2003**, *125*, 2054–2055.
37. Marcelli, T.; van der Haas, R.N.S.; van Maarseveen, J.H.; Hiemstra, H. Cinchona Derivatives as Bifunctional Organocatalysts for the Direct Asymmetric Nitroaldol (Henry) Reaction. *Synlett* **2005**, *18*, 2817–2819.
38. Marcelli, T.; van der Haas, R.N.S.; van Maarseveen, J.H.; Hiemstra, H. Asymmetric Organocatalytic Henry Reaction. *Angew. Chem. Int. Ed.* **2006**, *45*, 929–931.
39. Liu, X.; Jiang, J.; Shi, M. Development of Axially Chiral Bis(arylthiourea)-based Organocatalysts and their Application in the Enantioselective Henry Reaction. *Tetrahedron: Asymmetry* **2007**, *18*, 2773–2781.
40. Bella, M.; Gasperi, T. Organocatalytic Formation of Quaternary Stereocenters. *Synthesis* **2009**, *10*, 1583–1614.
41. Riant, O.; Hannodouche, J. Asymmetric Catalysis for the Construction of Quaternary Carbon Centres: Nucleophilic Addition on Ketones and Ketimines. *Org. Biomol. Chem*. **2007**, *5*, 873–888.
42. Li, H.; Wang, B.; Deng, L. Enantioselective Nitroaldol Reaction of α-Ketoesters Catalyzed by Cinchona Alkaloids. *J. Am. Chem. Soc.* **2006**, *128*, 732–733.
43. Takada, K.; Takemura, N.; Cho, K.; Sohtome, Y.; Nawasaga, K. Asymmetric Organocatalytic Nitroaldol Reaction of α-Ketoesters: Stereoselective Construction of Chiral Tertiary Alcohols at Subzero Temperature. *Tetrahedron Lett.* **2008**, *49*, 1623–1626.
44. Mandal, T.; Samanta, S.; Zhao, C. Organocatalytic Highly Enantioselective Nitroaldol Reaction of α-Ketophosphonates and Nitromethane. *Org. Lett.* **2007**, *9*, 943–945.

45. Chen, X.; Wang, J.; Zhu, Y.; Shang, D.; Gao, B.; Liu, X.; Feng, X.; Su, Z.; Hu, C. A Secondary Amine Amide Organocatalyst for the Asymmetric Nitroaldol Reaction of α-Ketophosphonates. *Chem. Eur. J.* **2008**, *14*, 10896–10899.
46. Bandini, M.; Sinisi, R.; Umani-Ronchi, A. Enantioselective Organocatalyzed Henry Reaction with Fluoromethyl Ketones. *Chem. Commun.* **2008**, *36*, 4360–4362.
47. Guillena, G.; Ramón, D.J.; Yus, M. Organocatalytic Enantioselective Multicomponent Reactions (OEMCRs). *Tetrahedron: Asymmetry* **2007**, *18*, 693–700.
48. Bonne, D.; Coquerel, Y.; Constantieux, T.; Rodriguez, J. 1,3-Dicarbonyl Compounds in Stereoselective Domino and Multicomponent Reactions. *Tetrahedron: Asymmetry* **2010**, *21*, 1085–1109.
49. Enders, D.; Grondal, C.; Hüttl, M.R.M. Asymmetric Organocatalytic Domino Reactions. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581.
50. Yu, X.; Wang, W. Organocatalysis: Asymmetric Cascade Reactions Catalysed by Chiral Secondary Amines. *Org. Biomol. Chem.* **2008**, *6*, 2037–2046
51. Alba, A.N.; Companyó, X.; Viciano, M.; Rios, R. Organocatalytic Domino Reactions. *Curr. Org. Chem.* **2009**, *13*, 1432–1474.
52. Hayashi. Y.; Okano, T.; Aratake, S.; Hazelard, D. Diphenylprolinol Silyl Ether as Catalyst in an Enantioselective, Catalytic, Tandem Michael/Henry Reaction for the Control of Four Stereocenters. *Angew. Chem. Int. Ed.* **2007**, *46*, 4922–4925.
53. Reyes, E.; Jiang, A.; Milelli, A.; Elsner, P.; Hazell, R.T.; Jørgensen, K.A. How to Make Five Contiguous Stereocenters in One Reaction: Asymmetric Organocatalytic Synthesis of Pentasubstituted Cyclohexanes. *Angew. Chem. Int. Ed.* **2007**, *46*, 9202–9205.
54. García Ruano, J.L.; Marcos, V.; Suanzes, J.A.; Marzo, L.; Alemán, J. One-Pot Synthesis of Pentasubstituted Cyclohexanes by a Michael Addition Followed by a Tandem Inter-Intra Double Henry Reaction. *Chem. Eur. J.* **2009**, *15*, 6576–6580.
55. Xu, D.Q.; Wang, Y.F.; Luo, S.P.; Zhang, S.; Zhong, A.G.; Chen, H.; Xu, Z.Y. A Novel Enantioselective Catalytic Tandem oxa-Michael/Henry Reaction: One-pot Organocatalytic Asymmetric Synthesis of 3-Nitro-2*H*-chromenes. *Adv. Synth. Catal.* **2008**, *350*, 2610–2616.
56. Hong, B.C.; Kotame, P.; Liao, J.H. Enantioselective Organocatalytic Domino Michael-Acetalization-Henry Reactions of 2-Hydroxynitrostyrene and Aldehydes for the Synthesis of Tetrahydro-6*H*-benzo[*c*]chromenones. *Org. Biomol. Chem*. **2011**, *9*, 382–386.
57. Dodda, R.; Goldman, J.J.; Mandal, T.; Zhao, C.G.; Broker, G.A.; Tiekink, R.T. Synthesis of 2,3,4-Trisubstituted Thiochromanes Using an Organocatalytic Enantioselective Tandem Michael/Henry Reaction. *Adv. Synth. Catal.* **2008**, *350*, 537–541.
58. Tan, B.; Chua, P.J.; Li, Y.; Zhong, G. Organocatalytic Asymmetric Tandem Michael/Henry Reactions: a Hihgly Stereoselective Synthesis of Multifunctionalized Cyclohexanes with Two Quaternary Stereocenters. *Org. Lett.* **2008**, *10*, 2437–2440.
59. Tan, B.; Chua, P.J.; Zeng, X.; Lu, M.; Zhong, G.A. Highly Diastereo- and Enantioselective Synthesis of Multisubstituted Cyclopentanes with Four Chiral Carbons by the Organocatalytic Domino Michael/Henry Reaction. *Org. Lett.* **2008**, *10*, 3489–3492.

60. Wang, Y.F.; Zhang, W.; Luo, S.P.; Li, B.L.; Xia, A.B.; Zhong, A.G.; Xu, D.Q. One-Pot Organocatalytic Asymmetric Synthesis of 3-Nitro-1,2-dihydroquinolines by a Dual-Activation Protocol. *Chem. Asian J.* **2009**, *4*, 1834–1838.
61. Uehara, H.; Imashiro, R.; Hernández-Torres, G.; Barbas, C.F., III. Organocatalytic Asymmetric Assembly Reactions for the Syntheses of Carbohydrate Derivatives by Intermolecular Michael/Henry Reactions. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20672–20677.
62. Tan, B.; Lu, Y.; Zeng, X.; Chua, P.J.; Zhong, G. Facile Domino Access to Chiral Bicyclo[3.2.1]Octanes and Discovery of a New Catalytic Activation Mode. *Org. Lett.* **2010**, *12*, 2682–2685.