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Asymmetric organocatalytic synthesis of six-membered oxygenated heterocycles

Marta G. Núñez [a], Pilar García [b,†], Rosalina F. Moro [a], David Díez [a,*]

[a] Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad de Salamanca, Plaza de los Caídos 1-5, 37008 Salamanca, Spain
[b] Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470, Mülheim an der Ruhr, Germany

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Contents

1. Introduction

Six-membered oxygenated heterocycles (tetrahydropyrans, chromanes, flavanones, etc.) are probably one of the most common structural motifs found in natural products. Due to the rich array of functionalities and chiral centres that these heterocycles can incorporate, they are widely recognized as useful building blocks for the synthesis of biologically active compounds and, as such, the development of new catalytic methods for their preparation continues to be of major interest.[1]

Classical well-known methods for the asymmetric synthesis of six-membered oxygenated heterocycles include five-membered ring expansions, cycloaddition processes or intramolecular cyclizations.

Asymmetric organocatalysis has become a very attractive methodology in recent years, since environmentally friendly and metal-free transformations are desired.[2] A number of methods that make use of organocatalysts to enantioselectively synthesize six-membered oxygenated heterocycles that have appeared in literature over the last few years are reported in this review.

* Corresponding author. Tel.: +34 923 294474; fax: +34 923 294574.
E-mail address: ddm@usal.es (D. Díez).
† Present address: Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470, Mülheim an der Ruhr, Germany.

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This review is structured on the basis of the main transformation leading to the oxygenated heterocycle. Thus, organocatalytic carbon and oxygen nucleophile 1,2- and 1,4-additions (benzoin and Stetter reaction, tandem reactions) and organocatalytic *oxo*-hetero-Diels–Alder reactions are the main topics of this report.

With regard to the reaction mechanisms involved in these transformations, there are reviewed several modes of catalysis, such as: (i) Lewis base catalysis with secondary amines via enamine and iminium ions; (ii) Lewis base catalysis via carbenes; (iii) Lewis acid catalysis via phase-transfer catalysts; and (iv) Brønsted acid catalysis via hydrogen bonding. For each catalytic mode, a basic description of the general mechanism is included.

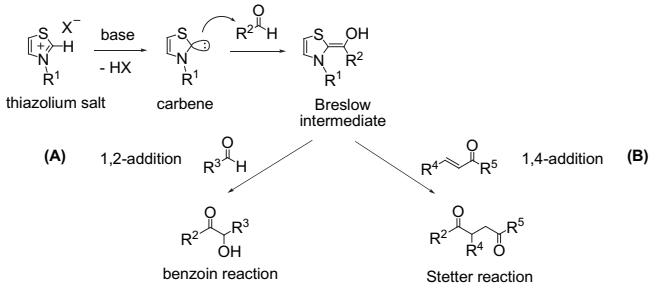
The aim of this review, which only includes organocatalytic asymmetric methods for the synthesis of mono-oxygenated six-membered rings, is to provide an overview of this exciting and rapidly growing field, emphasizing the structural and mechanistic features that contribute to such results. Only truly asymmetric reactions have been covered and diastereoselective approaches are not discussed.

2. 1,4- and 1,2-Additions of carbon nucleophiles

2.1. 1,4-Additions of carbon nucleophiles

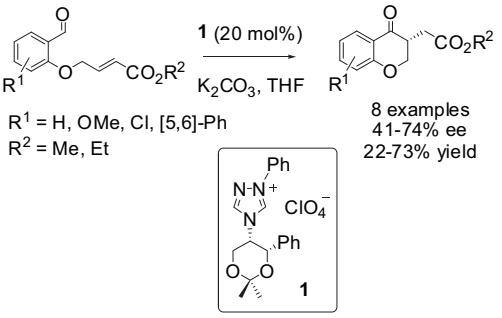
Over the last few years, interest in the field of asymmetric organocatalytic conjugate additions has increased spectacularly, with many new different catalysts showing remarkable results in terms of efficiency and selectivity. Here, the most important methods for the synthesis of six-membered oxygenated heterocycles that make use of organocatalytic conjugate additions of carbon nucleophiles as the main step for the construction of the heterocycle are described.

2.1.1. Stetter reaction. Aldehydes can be turned into acylanion equivalents (umpolung) through covalent activation with suitable nucleophiles, such as carbenes.[3] The 1,2-addition of these species with an acceptor aldehyde is referred to as the benzoin condensation (path A, Scheme 1). In the early 1970s, Stetter and Schreckenberg extended this concept to conjugate acceptors.[4] Since then, the 1,4-addition of aldehydes to α,β-unsaturated carbonyl compounds has been known as the Stetter reaction (path B, Scheme 1). Although it is a straightforward method for the formation of 1,4-dicarbonyl compounds, for many years its intramolecular version did not receive much attention. In 1995, Ciganek described the first example of an intramolecular Stetter reaction catalyzed by thiazolium salts for the synthesis of benzopyranones.[5]



Scheme 1. Benzoin and Stetter reactions catalyzed by thiazolium salts.

Soon after, the first asymmetric intramolecular Stetter reaction was reported by Enders et al. using the chiral triazolium salt **1** as precatalyst. In this manner, chroman-4-ones were synthesized by means of a new enantioselective pathway, although in moderate-to-good yields (22–73%) and ee of up to 74% (Scheme 2).[6] Since then, the cyclization of these salicylaldehyde derivatives to the corresponding chroman-4-ones has become a benchmark reaction to test the catalyst efficiency in asymmetric intramolecular Stetter reactions.



Scheme 2. First asymmetric organocatalyzed intramolecular Stetter reaction.

After these first results, not much attention was paid to this important methodology. During the last few years, however, Rovis et al. have achieved significant progress. Using triazolium salt **2b** (Fig. 1) as precatalyst and KHMDS as base, these authors discovered a significant improvement of the enantioselectivity of this reaction and a range of chroman-4-ones could be obtained in good yields (80–95%) and enantioselectivities (84–97%) (Scheme 3).[7]

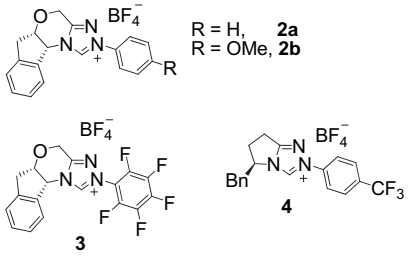
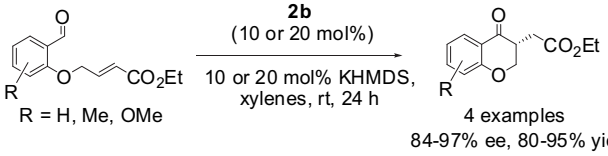


Figure 1. Triazolium salt precatalysts used by Rovis et al. in intramolecular Stetter reaction.

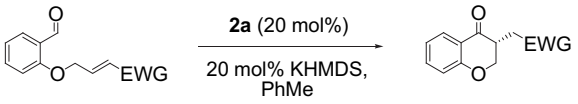


Scheme 3. Intramolecular Stetter reaction using chiral triazolium salt **2b** as precatalyst.

The electronic nature of the triazole precatalyst proved to be important for improving the yields, while maintaining high selectivities; an electron-rich catalyst, such as **2b**, bearing a 4-methoxy substituent in the phenyl group on the triazole nitrogen, is more nucleophilic and so facilitates the addition of the Breslow intermediate (Scheme 1) to the electron-deficient alkene.[7]

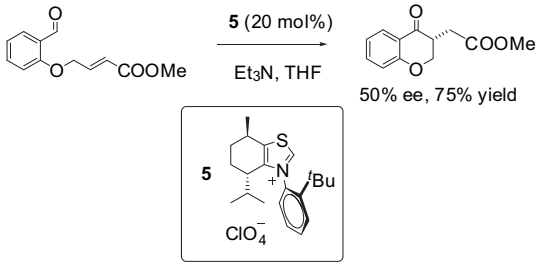
Further studies on the effect of the Michael acceptor in the organocatalyzed asymmetric intramolecular Stetter reaction were carried out by these authors. It was found that, while *E*-alkenes cyclized with good enantioselectivities and moderate yields, no reaction was observed in the case of *Z*-alkenes, even under stoichiometric reaction conditions when triazolium salt **2a** was used as precatalyst.[8] It was also demonstrated that various functional groups including esters, ketones and nitriles were effective in activating the Michael acceptor, while α,β-unsaturated amides, aldehydes and nitro compounds provided no products (Scheme 4).[8]

The concept of axial chirality was utilized by Bach et al. with the novel menthol-derived triazolium salt **5** (Scheme 5) in the asymmetric intramolecular Stetter reaction.[9] The use of 20 mol % of this



EWG	Yield (%)	ee (%)
$CONH_2$, CHO, NO_2	0	-
CO_2Et	58	95
CN	78	75
COEt	90	92

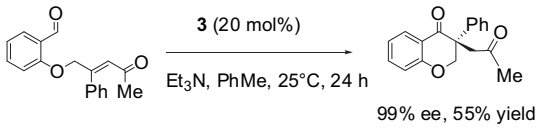
Scheme 4. Effect of Michael acceptor in intramolecular Stetter reaction using triazolium salt **2a** as precatalyst.



Scheme 5. Intramolecular Stetter reaction using menthol-derived triazolium salt **5** as precatalyst.

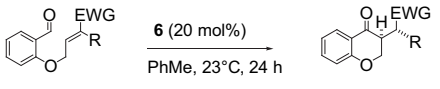
axially chiral precatalyst promoted the intramolecular Stetter reaction of the salicylaldehyde-derived substrate depicted in Scheme 5 to the corresponding chroman-4-one in 75% yield and 50% ee. Probably, an atropisomerization process during the reaction lowers the stereoselectivity.

The scope of the organocatalytic intramolecular Stetter reaction was later expanded by Rovis et al. to the synthesis of chiral compounds with quaternary stereocenters. A sole example for the synthesis of a chroman-4-one was reported (Scheme 6), and it was shown that the use of the electron-deficient triazolium salt **3** (Fig. 1) was essential to obtain a high enantioselectivity in the cyclization process.[10]

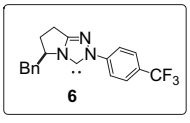


Scheme 6. Enantioselective formation of quaternary stereocenters via intramolecular asymmetric Stetter reaction.

The same group has also reported an enantio and diastereoselective variant of the intramolecular Stetter reaction using α,α-disubstituted Michael acceptors.[11] A variety of chroman-4-ones were synthesized with high enantioselectivities and moderate-to-high diastereoselectivities when using carbene **6** as catalyst (Scheme 7). In this case, the utilization of free carbenes is necessary to avoid epimerization of the cyclization product, thus affording reproducibly high enantio- and diastereoselectivities.

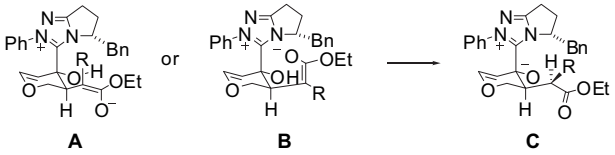


EWG	R	yield (%)	ee (%)	dr
CO_2Et	Me	94	95	30:1
CO_2Et	Et	95	92	35:1
CO_2Et	*n*-Bu	53	94	12:1
CO_2Et	Bn	80	84	20:1
CO_2Et	allyl	95	83	13:1



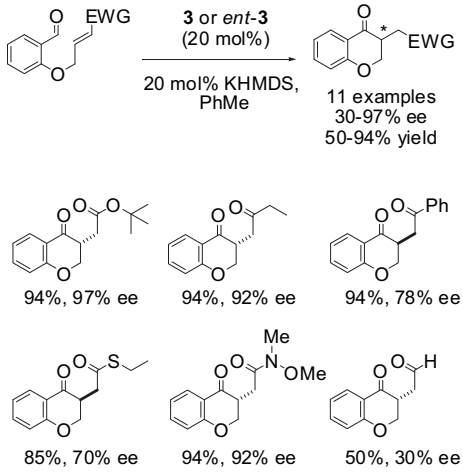
Scheme 7. Enantio- and diastereoselective intramolecular Stetter reaction catalyzed by carbene **6**.

The *syn*-selective formation of the new stereocenters was assumed to arise from a diastereoselective intramolecular proton transfer from two possible enolate rotamers **A** or **B**, resulting from the enantioselective C–C bond formation, to afford intermediate **C** (Scheme 8). This hypothetical intramolecular proton transfer was supported by the fact that the *E* and *Z* isomers afford complementary diastereoselectivity.[11]



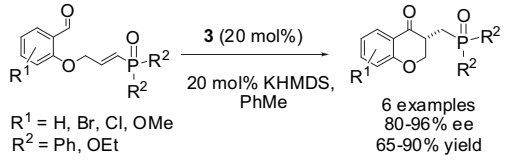
Scheme 8. Proposed transition-states for diastereo- and enantioselective Stetter reaction.

In more recent work, in which these authors report a full investigation on the scope of the organocatalyzed intramolecular Stetter reaction, comparing the effectiveness of different chiral triazolium salts, some of the limitations related to the effects of the Michael acceptor on the reactivity and selectivity (Scheme 4)[8] have been circumvented using precatalyst **3** and its enantiomer *ent*-**3** (Fig. 1).[12] The reaction is remarkably tolerant of a variety of Michael acceptors, such as α,β-unsaturated aldehydes, amides, nitriles, esters, thioesters, and ketones (Scheme 9). Cyclization of a *Z*-substrate (EWG=COOMe) was also achieved, although with low enantioselectivity (22% ee). Interestingly, when using the triazolium salt **4** (Fig. 1), the catalyst loading could be reduced to 3 mol% without significantly affecting the reactivity or selectivity of the reaction.[12]



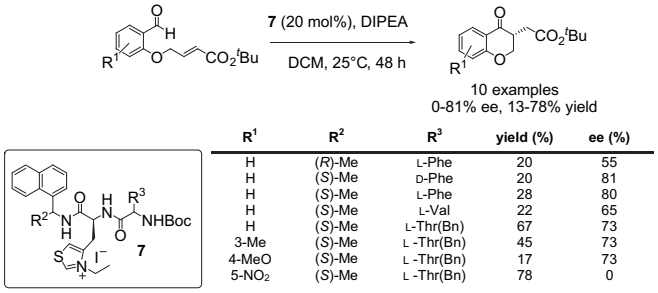
Scheme 9. Effect of Michael acceptor in intramolecular Stetter reaction.

Finally, Rovis and Cullen have extended the scope of electrophilic acceptors for the intramolecular Stetter reaction to vinylphosphine oxides and vinylphosphonates. When employing the triazolium salt precatalyst **3** (Fig. 1), this extension of the Stetter reaction led to interesting new enantioenriched scaffolds of phosphorus-containing compounds with good yields and enantioselectivities (Scheme 10).[13]



Scheme 10. Intramolecular Stetter reaction employing vinylphosphine oxides and vinylphosphonatesas electrophilic acceptors.

Miller et al. have carried out an intramolecular Stetter reaction for the synthesis of chroman-4-ones using a family of novel peptide precatalysts, which incorporate a thiazolylalanine (Taz) moiety in their structure.[14] The best results were obtained with the catalyst family **7**, bearing the Taz group in an internal position, although only low yields and moderate-to-good enantioselectivities were afforded (Scheme 11).



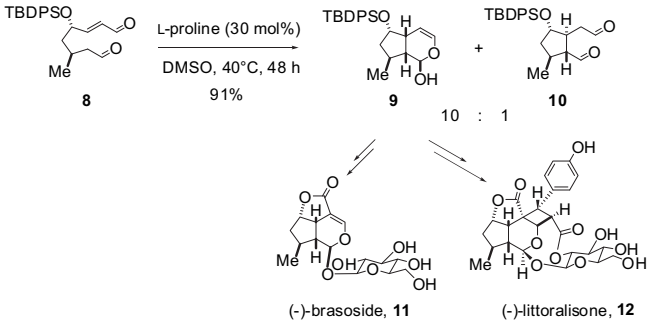
R^1	R^2	R^3	yield (%)	ee (%)
H	(*R*)-Me	L-Phe	20	55
H	(*S*)-Me	D-Phe	20	81
H	(*S*)-Me	L-Phe	28	80
H	(*S*)-Me	L-Val	22	65
H	(*S*)-Me	L-Thr(Bn)	67	73
3-Me	(*S*)-Me	L -Thr(Bn)	45	73
4-MeO	(*S*)-Me	L -Thr(Bn)	17	73
5-NO_2	(*S*)-Me	L -Thr(Bn)	78	0

Scheme 11. Thiazolyl alanine-catalyzed intramolecular Stetter reaction by Miller et al.

2.1.2. Tandem reactions. A number of asymmetric organocatalytic tandem reactions for the construction of six-membered oxygenated heterocycles, the first activation step of which is an organocatalytic Michael addition, have been reported in the last few years. The majority of these methods make use of enamine–iminium activation with pyrrolidine organocatalysts, although other organocatalysts, such as cinchona alkaloids and *N*-heterocyclic carbenes have also been used in these tandem reactions.

2.1.2.1. Tandem reactions catalyzed by proline-derived compounds. Recently, a number of studies that make use of asymmetric iminium ion catalysis for the synthesis of six-membered oxygenated heterocycles, such as benzopyrans, dihydropyrans or pyranonaphthoquinones have been published. This methodology is based on a tandem Michael addition/acetalization reaction catalyzed by proline-derived compounds.

Indeed, this type of cyclization was used by Macmillan and Mangion in 2005 as one of the key steps in the total synthesis of the natural products (−)-brasoside **11** and (−)-littoralisone **12**, using L-proline as organocatalyst.[15] This contra-thermodynamic intramolecular tandem Michael addition/acetalization provided the lactol intermediate **9** in 91% yield and with a 10:1 diastereoselectivity (**9**:**10**) from the formyl-enal substrate **8** (Scheme 12).

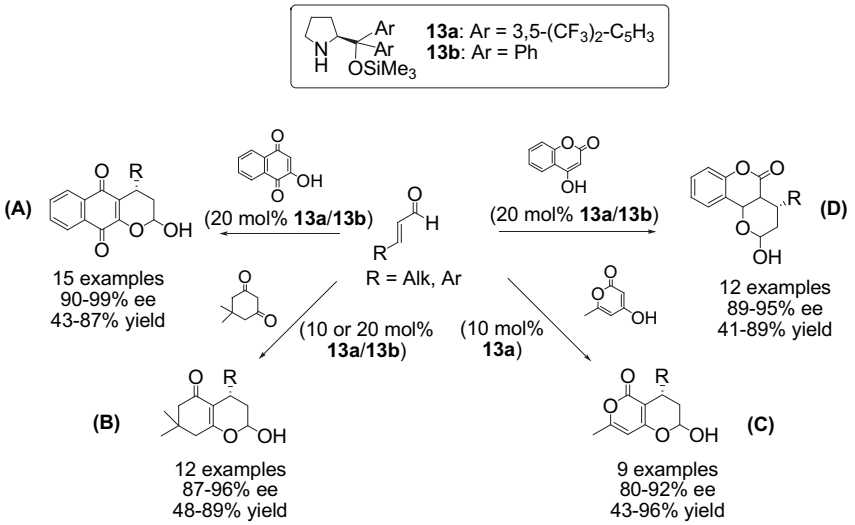


Scheme 12. Intramolecular Michael addition/acetalization reaction catalyzed by L-proline in synthesis of (−)-brasoside **11** and (−)-littoralisone **12**.

Rueping et al. have recently employed this tandem Michael addition/acetalization reaction for the enantioselective synthesis of different six-membered oxygenated heterocycles.[16–18] First, they studied the reaction of 2-hydroxy-1,4-naphthoquinone with aliphatic as well as aromatic α,β-unsaturated aldehydes catalyzed by diarylprolinol ethers **13** (Scheme 13, Path A). 1,4-Pyranonaphthoquinones were obtained in moderate-to-high yields (43–87%) and excellent enantioselectivities (up to 99% ee) when using diarylprolinol ether **13a** (20 mol %) as catalyst and dichloromethane as solvent.[16]

This procedure was later extended to the enantioselective synthesis of chromenones. When the 1,3-diketone dimedone (Scheme 13, Path B) was reacted with aliphatic and aromatic α,β-unsaturated aldehydes, the corresponding chromenones were obtained with yields in the range of 48–89% and enantioselectivities of up to 96% ee using 10 or 20 mol % of **13a** or **13b** as catalyst.[17]

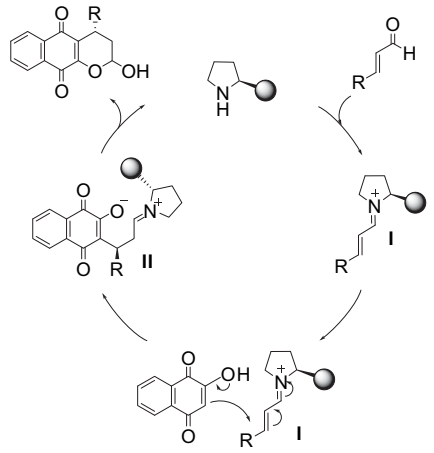
The potential of this organocatalytic transformation was explored further by the same authors and other cyclic 1,3-dicarbonyl compounds were tested. Again, aliphatic as well as aromatic α,β-unsaturated aldehydes were reacted with 4-hydroxy-6-methyl-2-pyrone and 4-hydroxycoumarin to obtain the corresponding cyclization products (Scheme 13, Paths C and D, respectively).[18] For the synthesis of pyranocoumarins (Scheme 13, Path D), good



Scheme 13. Tandem Michael addition/acetalization reactions for enantioselective synthesis of different six-membered oxygenated heterocycles by Rueping et al.

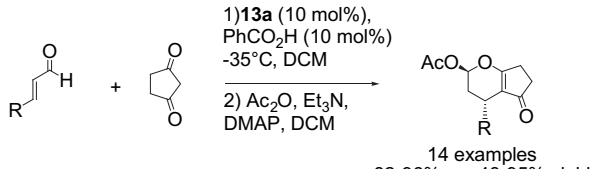
yields (41–89%) and enantioselectivities (89–95% ee) were achieved with both diarylprolinol ethers **13** (20 mol %). Evaluation of the reaction parameters for the cyclization of 4-hydroxy-6-methyl-2-pyrone (Scheme 13, Path C) revealed that the best results with regard to both the enantioselectivity and reactivity were achieved when the reaction was conducted with 10 mol % of diarylprolinol ether **13a**.

As mentioned before, all these transformations are based on a similar tandem Michael addition/acetalization mechanism, depicted in Scheme 14 for the synthesis of 1,4-pyranonaphthoquinones.[16] The reaction of the diarylprolinol ether catalyst with the corresponding α,β-unsaturated aldehyde results in the intermediary iminium ion **I**. Subsequent conjugate addition to 2-hydroxy-1,4-naphthoquinone followed by isomerization gives rise to the adduct **II**, which after hydrolysis and acetalization yields the desired 1,4-pyranonaphthoquinone with regeneration of the catalyst.



Scheme 14. Proposed mechanism of organocatalytic tandem Michael addition/acetalization reaction for synthesis of 1,4-pyranonaphthoquinones.

Jørgensen et al. have also studied the organocatalyzed tandem conjugate addition/acetalization reaction of 1,3-diketones with α,β-unsaturated aldehydes for the synthesis of 3,4-dihydropyrans.[19] The scope of this reaction was investigated with 1,3-cyclopentadione as the substrate and it was demonstrated that a broad range of different types of α,β-unsaturated aldehydes (R=aliphatic, aromatic, ester, heteroaromatic and alkene) are tolerated when using diarylprolinol ether **13a** as catalyst (10 mol %) and $PhCO_2H$ as additive (Scheme 15).

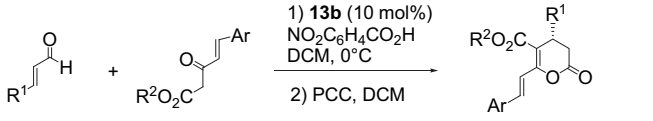


R	dr	yield (%)	ee (%)
Ph	3:1	85	90
p-F-Ph	7:2	82	88
2-thiophenyl	5:1	95	93
o-CF_3-Ph	5:2	69	91
Me	7:2	74	84
hex-3-en-1-yl	2:1	81	96
CO_2Et	> 20:1	48	88

Scheme 15. Tandem Michael addition/acetalization reaction for enantioselective synthesis of 3,4-dihydropyrans by Jørgensen et al.

Apart from varying the substituents in the α,β-unsaturated aldehydes, the ring size of the 1,3-diketone was also varied. Thus, the addition of 1,3-cyclohexanedione and 1,3-cycloheptanedione to cinnamaldehyde (R=Ph) using the reaction conditions described in Scheme 15, afforded the corresponding 3,4-dihydropyrans with a dr of 4:1 and >8:1, respectively, and with an enantioselectivity of 97% ee for the major diastereoisomer in both cases.[19]

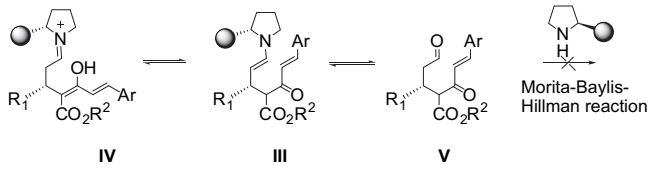
Another interesting example of the use of the diarylprolinol ether-catalyzed tandem Michael addition/acetalization methodology for the construction of dihydropyran derivatives has been reported by Gong et al. The employment of Nazarov reagents bearing an aryl group at C-5 as nucleophiles for the conjugate addition to α,β-unsaturated aldehydes and subsequent cyclization leads to vinyl-3,4-dihydropyrans (Scheme 16). A broad range of R^1- and R^2-aryl substituents are tolerated and moderate-to-good-yields (41–78%) and good-to-excellent enantioselectivities (79–97%) are achieved when using **13b** as catalyst.[20]



R^1	R^2	Ar	yield (%)	ee (%)
4-$NO_2C_6H_4$	Et	Ph	77	95
Ph	Et	Ph	54	84
4-MeC_6H_4	Et	Ph	41	83
COOEt	Et	Ph	63	97
4-$NO_2C_6H_4$	*t*-Bu	Ph	43	96
4-$NO_2C_6H_4$	Et	4-BrC_6H_4	72	93
4-$NO_2C_6H_4$	Et	2-$MeOC_6H_4$	51	92

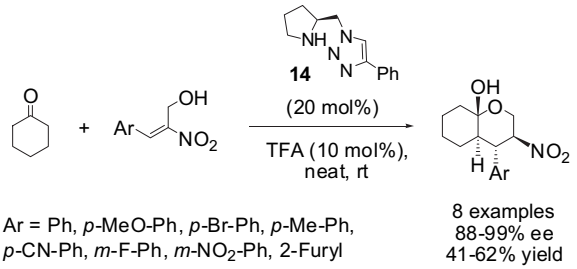
Scheme 16. Tandem Michael addition/acetalization reaction of α,β-unsaturated aldehydes with Nazarov reagents.

With regard to the mechanism, totally analogous to all of the previously mentioned examples of diarylprolinol ether-catalyzed tandem Michael addition/acetalization reactions, the intermediate **III** (Scheme 17), a Michael adduct of Nazarov reagent addition to the active iminium salts formed between the catalyst and α,β-unsaturated aldehydes, does not undergo a Morita–Baylis–Hillman reaction after being hydrolyzed to the intermediate **V**, due to the presence of the Ar substituent. It rather isomerizes to **IV**, which finally cyclizes to the corresponding vinyl-3,4-dihydropyrans (Scheme 17).



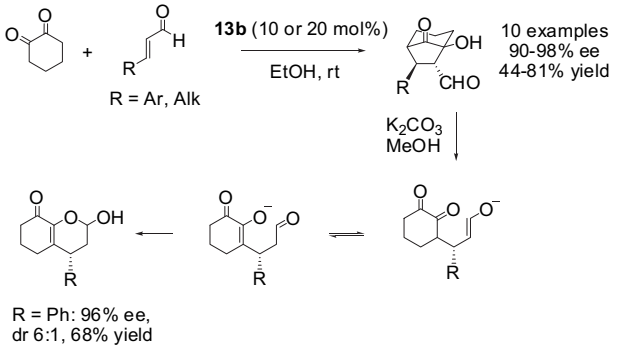
Scheme 17. Proposed mechanism for tandem Michael addition/acetalization reaction of α,β-unsaturated aldehydes with Nazarov reagents.

This enantioselective tandem Michael addition/ketalization strategy has been employed very recently by Chandrasekhar et al. for the construction of cycloalkane-fused tetrahydropyrans using cyclohexanone as nucleophile and hydroxymethyl nitroolefins as Michael acceptors. Among the catalysts screened, pyrrolidine–triazole **14** (20 mol %) together with TFA (10 mol %) gave the best results in terms of enantioselectivity (up to 99% ee), although only moderate yields (41–62%) were obtained (Scheme 18).[21]



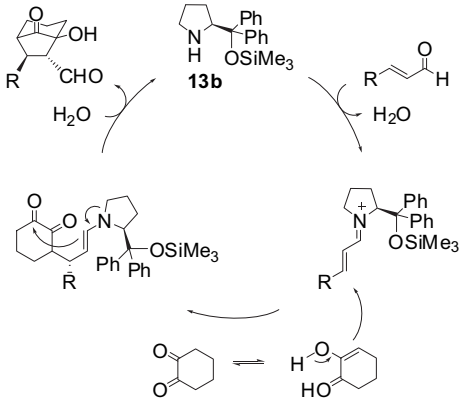
Scheme 18. Tandem Michael addition/ketalization reaction for enantioselective construction of cycloalkane-fused tetrahydropyrans.

Rueping et al. have recently used an indirect strategy for the enantioselective synthesis of tetrahydrochromenones. The diarylprolinol ether-catalyzed reaction of cyclohexane-1,2-dione with a variety of α,β-unsaturated aldehydes was examined and it was shown to result in the formation of bicyclic compounds with good yields and enantioselectivities of up to 98% ee when 10 or 20 mol % of catalyst **13b** was used in ethanol as solvent (Scheme 19).[22] These bicyclo[3.2.1]octane-6-carbaldehydes can be further transformed into tetrahydrochromenones by treatment with K_2CO_3 through a base-induced retro-aldol/cyclization reaction (Scheme 19).



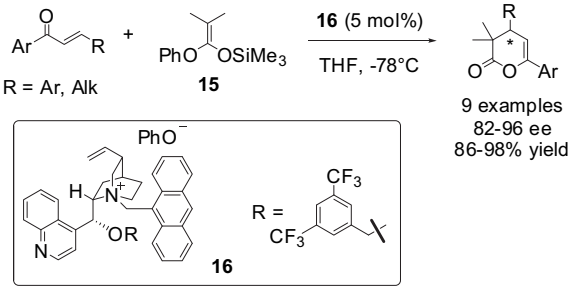
Scheme 19. Organocatalyzed Michael/aldol reaction followed by base-induced retro-aldol/cyclization reaction for asymmetric synthesis of tetrahydrochromenones.

Accordingly, and in contrast to the previously reported tandem Michael addition/acetalization reaction with 1,3-diketones as substrates, it was assumed that a tandem Michael addition/aldol reaction occurred by iminium/enamine activation, as depicted in Scheme 20.



Scheme 20. Proposed mechanism for diarylprolinol ether-mediated Michael/aldol reaction by Rueping et al.

2.1.2.2. Tandem reactions catalyzed by cinchona alkaloid-derived compounds. Mukaiyama et al. have described a new and efficient method for the enantioselective synthesis of optically active 3,4-dihydropyran-2-one derivatives via tandem Mukaiyama–Michael addition/lactonization between α,β-unsaturated ketones and the silyl enolate derived from phenyl isobutyrate **15** catalyzed by cinchona alkaloid-derived chiral quaternary ammonium phenoxides (Scheme 21).[23]

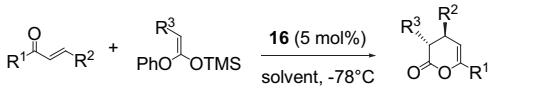


Scheme 21. Enantioselective synthesis of 3,4-dihydropyran-2-ones via tandem Mukaiyama–Michael addition/lactonization reaction catalyzed by **16**.

In this transformation, the phenoxy group contained in the silyl enolate **15** behaves as an effective leaving group to facilitate the intramolecular cyclization of the in situ-formed Michael adduct, and the liberated phenoxide ion also works as a Lewis base catalyst to activate the silyl enolate. A variety of chiral quaternary ammonium phenoxides were screened and catalyst **16** (Scheme 21) showed the best catalytic activity.

Interestingly, when *N*-arylmethylated cinchonidinium phenoxides with a hydroxyl group (R=H in **16**, Scheme 21) were employed, the absolute configuration of the product was proved to be *S*, which was the reversal of the case when using *N*,*O*-diarylmethylated cinchonidinium phenoxides (R=CH_2-3,5-$(CF_3)_2$-C_6H_3 in **16**, Scheme 21), under the same reaction conditions.[23c,e]

A further investigation on the diastereoselectivity of this organocatalyzed tandem reaction was carried out by the same authors. Significantly, when sterically more hindered silyl acetals were used (Scheme 22), the corresponding 3,4-dihydropyran-2-ones were produced in excellent yields with almost complete stereochemical control (*trans*/*cis*>99:1).[23b,c,e] This fact demonstrates that the alkyl substituents R^3 in the ketene silyl acetals play an important role in controlling both the diastereo- and enantioselectivity of this asymmetric reaction, and therefore the stereoselectivity improves as the bulk of R^3 increases.

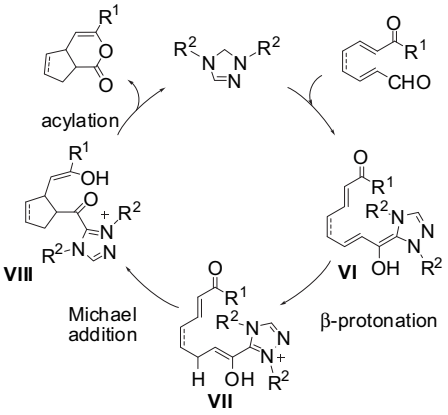


R^1	R^2	R^3	Yield (%)	*trans*/*cis*	ee (%)
Ph	4-$MeOC_6H_4$	Et	95	99:1	85
4-$MeOC_6H_4$	Ph	Et	97	99:1	87
Ph	4-FC_6H_4	^{i}Pr	98	99:1	95
4-FC_6H_4	Ph	^{i}Pr	92	99:1	94
Ph	4-$MeOC_6H_4$	^{i}Pr	93	99:1	94
4-$MeOC_6H_4$	4-BrC_6H_4	^{i}Pr	98	99:1	95

Scheme 22. Scope of tandem Mukaiyama-Michael addition/lactonization reaction for synthesis of 3,4-dihydropyran-2-ones catalyzed by **16**.

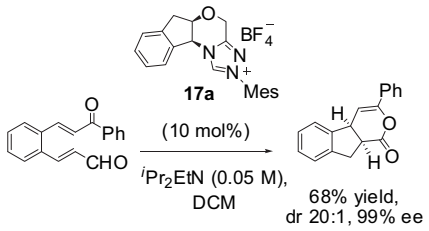
2.1.2.3. Tandem reactions catalyzed by N-heterocyclic carbene-derived compounds. Scheidt et al. have demonstrated that *N*-heterocyclic carbenes are highly selective catalysts for the intramolecular Michael reaction of dicarbonylic substrates, such as those depicted in Scheme 23 to afford bicyclic dihydropyranones through a proposed tandem Michael addition/acylation mechanism.[24] The addition of the *N*-heterocyclic carbene catalyst to the α,β-unsaturated aldehyde in the substrates affords the extended diene intermediate **VI**. A

subsequent β-protonation step leads to the key enol nucleophile intermediate **VII**, which undergoes a Michael addition to generate the enol **VIII**. An intramolecular acylation step releases the catalyst to afford the dihydropyranones, which can be converted into interesting dicarbonyl products after ring-opening on exposure to mild nucleophiles (Scheme 23).



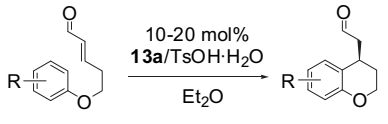
Scheme 23. Proposed tandem Michael addition/acylation mechanism for synthesis of dihydropyranones catalyzed by *N*-heterocyclic carbenes.

Both aryl and alkyl substituents are suitable for the reaction, and a high enantioselectivity is achieved when the chiral enantiopure triazolium salt **17a** and not Lewis basic solvents, such as DCM are used (Scheme 24).[24]



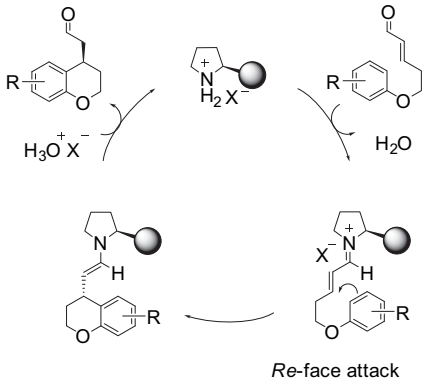
Scheme 24. *N*-heterocyclic carbene-mediated enantioselective tandem Michael addition/acylation reaction by Scheidt et al.

2.1.3. Other 1,4-additions of carbon nucleophiles. While organocatalyzed enantioselective intermolecular hydroarylations of electron rich arenes have been widely investigated, no example was available for the intramolecular version of this reaction until a recent report by Xiao et al.[25] The arylation of ω-aryloxy-tethered α,β-unsaturated aldehydes allows the production of functionalized chromans by using a combination of diarylprolinol ether **13a** and $TsOH\cdot H_2O$ as the catalytic system. Using electron-rich benzene frameworks as substrates, chromans are obtained in moderate-to-good yields and with enantioselectivities of up to 96% ee (Scheme 25).



Scheme 25. Organocatalytic intramolecular hydroarylation of ω-aryloxy-tethered α,β-unsaturated aldehydes.

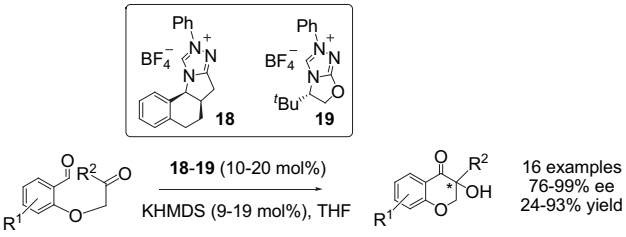
With regard to the mechanism, a *Re*-face attack of the electron-rich benzene framework on the previously formed iminium ion is assumed (Scheme 26).



Scheme 26. Proposed catalytic pathway for organocatalytic enantioselective intramolecular hydroarylation by Xiao et al.

2.2. 1,2-Additions of carbon nucleophiles

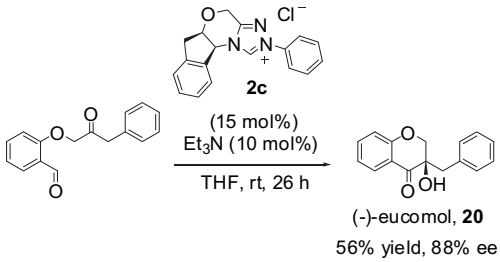
There are not many examples of organocatalytic 1,2-additions of carbon nucleophiles for the synthesis of six-membered oxygenated heterocycles in the recent literature. One example is the intramolecular cross-benzoin reaction, which has been used by Endres et al. for the enantioselective formation of 3-hydroxy-chroman-4-ones bearing a quaternary centre catalyzed by *N*-heterocyclic carbenes.[26] Yields of up to 93% and enantioselectivities of up to 99% were afforded using triazolium salts **18** and **19** as precatalysts, which generate enantiomeric configurations at the newly formed stereocenters (Scheme 27).



R^1	R^2	Precatalyst	T (°C)	yield (%)	ee (%)/config.
H	Et	**18**	5	88	94(*S*)
H	*i*-Bu	**18**	rt	78	92(*S*)
H	*i*-Bu	**18**	5	46	95(*S*)
2,4-dibromo	*i*-Bu	**19**	rt	87	86(*R*)
2,4-dibromo	*i*-Bu	**18**	0	93	92(*S*)
2-nitro	*i*-Bu	**19**	5	51	99(*R*)
2,3-methylendioxo	*n*-Pr	**18**	rt	24	91(*S*)

Scheme 27. Intramolecular cross-benzoin reaction for synthesis of chroman-4-ones.

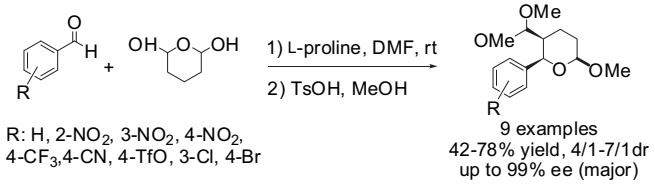
This crossed aldehyde–ketone benzoin cyclization has been used by Suzuki et al. for the enantioselective synthesis of the natural product (−)-eucomol **20** employing the triazolium salt **2c** as precatalyst and Et_3N as base in moderate yield (56%) and good enantioselectivity (88%) (Scheme 28).[27]



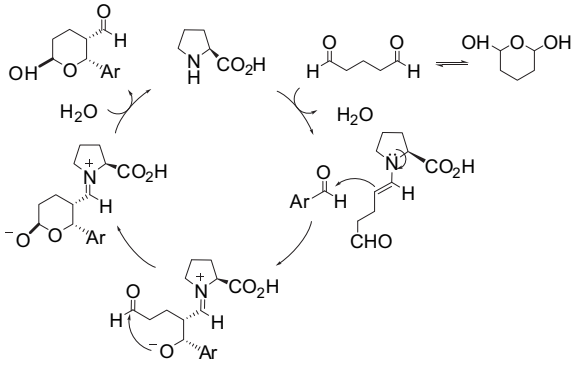
Scheme 28. Enantioselective synthesis of (−)-eucomol **20** through cross-benzoin cyclization.

A different strategy for the enantioselective synthesis of tetrahydropyrans that makes use of a 1,2-addition of a carbon nucleophile is the tandem proline-mediated aldol reaction/acetalization in aqueous media recently described by Hayashi et al.[28]

The proline-catalyzed reaction of pentane-1,5-dial, generated from aqueous tetrahydro-2*H*-pyran-2,6-diol under equilibrium conditions, with different benzaldehydes (Scheme 29) leads to optically active tetrahydropyrans in moderate yields and diastereoselectivities and good-to-excellent enantioselectivities through the mechanism depicted in Scheme 30. The quantity of L-proline needed to promote this transformations varies from 10 mol % for arylaldehydes with strong electron-withdrawing groups, such as 2-, 3- or 4-nitrobenzaldehyde and 4-trifluoromethyl-, 4-cyano- or 4-trifluoromethanesulfonylbenzaldehyde to 30 mol % for arylaldehydes, such as 2-chlorobenzaldehyde, 4-bromobenzaldehyde and benzaldehyde.

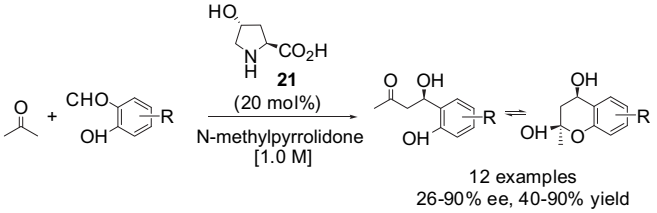


Scheme 29. Proline-mediated enantioselective synthesis of tetrahydropyrans via tandem aldol/acetalization reaction.



Scheme 30. Proposed mechanism for proline-mediated tandem aldol/acetalization reaction by Hayashi et al.

Very recently, Ramachary and Sakthidevi have made use of the tandem *trans*-4-OH-L-proline (**21**)-mediated aldol reaction/acetalization approach to the asymmetric synthesis of functionalized 2-methylchroman-2,4-diol products (Scheme 31).[29] A series of both electron-withdrawing and electron-donating substituted 2-hydroxybenzaldehydes was reacted with 14 equiv of acetone to obtain the corresponding aldol/lactol products, which co-exist in a fast dynamic equilibrium. The aldol/lactol ratios varied from 99:1 to 1:99, being 1:1 in most cases, and yields in the range 40–90% and enantioselectivities of up to 90% were achieved.



Scheme 31. *trans*-4-*OH*-L-Proline-mediated tandem aldol/aldol reaction by Ramachary et al.

3. 1,4-Additions of oxygenated nucleophiles

Similarly to Section 2.1, the most important organocatalytic methods for the synthesis of six-membered oxygenated heterocycles that use conjugate additions of oxygen nucleophiles (*oxa*-Michael additions) as the main step for the construction of the heterocycle are compiled in this section.

3.1. 1,4-Additions of oxygenated nucleophiles catalyzed by cinchona alkaloid-derived organocatalysts

Ishikawa et al. were the pioneers of the asymmetric intramolecular *oxa*-Michael addition reaction using quinine as organocatalyst for the construction of 2,3-dimethyl-4-chromanone rings.[30–32]

In an approach to the synthesis of (+)-calanolide A (**22a**, Fig. 2), a potential *anti*-HIV-active natural product, they observed that *O*-tigloylphenol **24a** (R=H) could be cyclized by a catalytic amount of (−)-quinine (**23a** in Fig. 2, 20 mol %) to afford a 1:1 mixture of *cis*-**25a** (87% ee) and *trans*-**25a** (0% ee) isomers (Scheme 32).[30] Further studies on this reaction showed significant solvent effects on both diastereo- and enantioselectivities; chlorobenzene was found to be

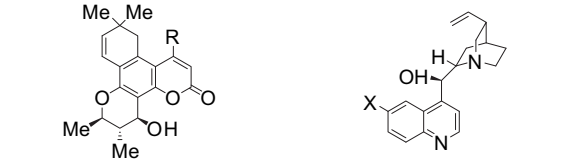
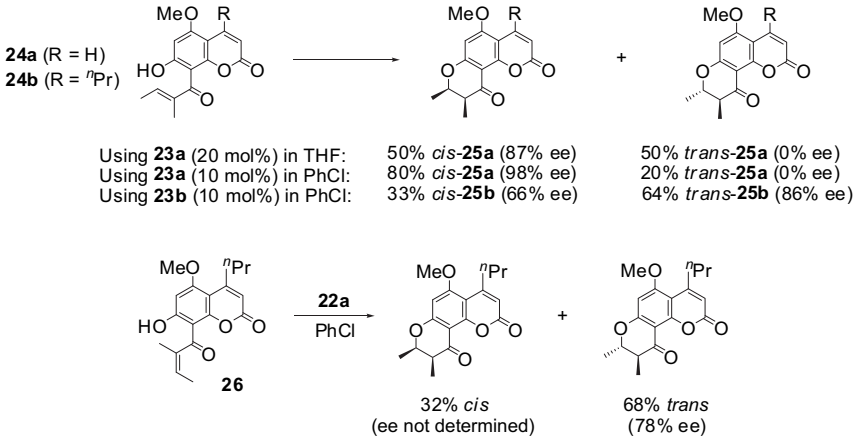


Figure 2. Calophyllum coumarins **22** and cinchona-derived compounds **23**.



Scheme 32. Intramolecular *oxa*-Michael addition of *O*-tigloylphenol and *O*-angeloylphenol catalyzed by cinchona alkaloids.

the solvent of choice, leading to the predominant production of *cis*-**25a** (80%) with 98% ee. Using the same solvent for the intramolecular *oxa*-Michael addition of *O*-angeloylphenol (**26** in Scheme 32) gave the *trans* isomer as the major product (68%), with 78% ee[31b]

The employment of other commercially available cinchona alkaloids, such as cinchonidine (**23b** in Fig. 2), lacking a methoxy function on the quinoline skeleton, as organocatalysts, resulted in the formation of the *trans*-**25b** isomer as the major product in 86% ee when using *O*-tigloylphenol **24b** (R=^{n}Pr) as substrate (Scheme 32). The fact that effective asymmetric induction was observed in the formation of one diastereoisomer, compared to the other, depending on the type of organocatalyst used (with or without a methoxy group on the quinoline scaffold), suggests that these cinchona alkaloid-catalyzed intramolecular *oxa*-Michael additions are not kinetically controlled by a normal 1,4-addition reaction, but through two independent reaction paths.[32]

These authors have employed the organocatalyzed intramolecular *oxa*-Michael addition reaction as the key step for the enantioselective synthesis of the *Calophyllum* coumarins (−)-calanolide A and (+)-inophyllum B (**22a** and **22b** in Fig. 2, respectively) in 16 and 5% overall yields, respectively, from commercially available substrates.[31a,32]

Merschaert et al. have also used cinchona alkaloid derivatives as catalysts in the first asymmetric 6-*exo*-*trig* *oxa*-Michael addition reaction of a phenolic nucleophile on an α,β-unsaturated ester for the synthesis of 2-substituted chromanes.[33]

Among the readily available cinchona alkaloids, the best results were obtained using cinchonine (10 mol %) as catalyst (**27** in Fig. 3). In an attempt to improve the moderate enantioselectivities obtained in the cyclizations depicted in Scheme 33, modifications around the chiral C9 in cinchonine **27** were carried out. After a broad screening of these modified catalysts, **28** was found to give the highest enantioselectivities for both *Z* (80% ee) and *E* (52% ee) isomers, although with a slight decrease in conversion.[33]

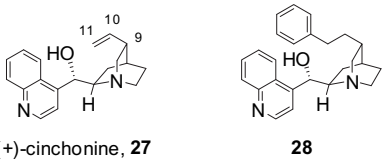
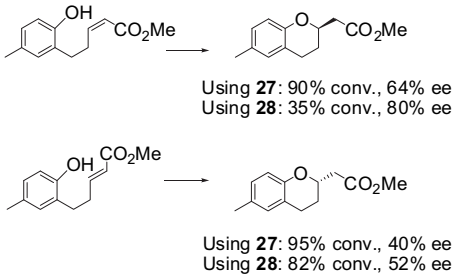
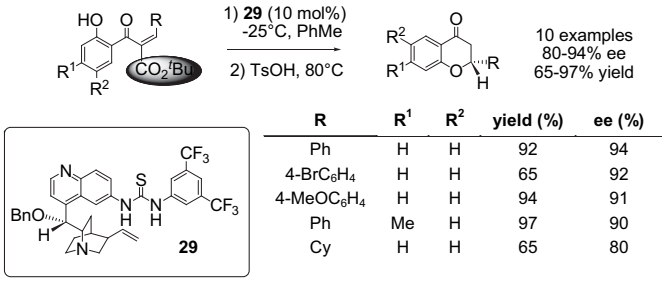


Figure 3. Cinchona alkaloid-derived catalysts employed by Merschaert et al.



Scheme 33. 6-*exo*-*trig* Cyclizations for synthesis of chromanes catalyzed by cinchona alkaloids.

The highly enantioselective cyclization of 2′-hydroxychalcones to flavanones catalyzed by the enzyme chalcone isomerise, is a well-known step in the biosynthesis of flavonoids. It cannot, however, be reproduced enantioselectively so far using asymmetric organocatalysis. Recently, Scheidt et al. have reported an indirect method to carry out this intramolecular 6-*endo*-*trig* *oxa*-Michael addition reaction by introducing an activating *tert*-butyl ester group at the C2 position of the hydroxychalcone substrates (Scheme 34)[34]; this additional electron-withdrawing group would increase the reactivity of the conjugate acceptor, favour the flavanone products over the acyclic chalcones and also provide a second Lewis basic site for potential interaction with the catalyst. Furthermore, this additional ester group can be easily removed without affecting the newly formed stereocentre at C2. In this manner, a series of different flavanones and chalcones were synthesized via a cyclization/decarboxylation single-pot reaction using bifunctional quinine-derived thiourea catalysts.[34]



R	R^1	R^2	yield (%)	ee (%)
Ph	H	H	92	94
4-BrC_6H_4	H	H	65	92
4-MeOC_6H_4	H	H	94	91
Ph	Me	H	97	90
Cy	H	H	65	80

Scheme 34. Enantioselective synthesis of chroman-4-ones catalyzed by bifunctional quinine-derived thiourea catalyst **29**.

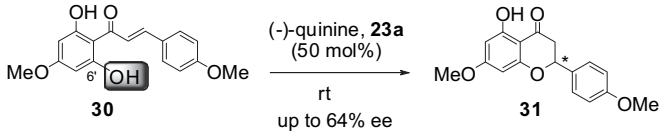
The best results were achieved with the chiral thiourea **29** (Scheme 34), obtaining yields in the 65–97% range and ees in the 80–94% range. Interestingly, the parent chalcones without the additional *tert*-butyl ester group did not undergo cyclization with any of the bifunctional catalysts tested, thus proving the importance of this functional group in the substrates.[34]

These authors propose a mechanism in which a hydrogen bond is formed between the β-ketoester substrate and the chiral thiourea moiety. The interaction between the quinuclidine nitrogen and the hydroxyl group of the phenol then promotes the enantioselective intramolecular *oxa*-Michael addition. It is worthy mentioning that a tertiary amine and a thiourea group together in a single catalyst are necessary to achieve a high enantioselectivity.

Hintermann et al. have also used cinchona alkaloids as catalysts for the synthesis of flavanones from 2′-hydroxychalcones.

Their strategy was based on the employment of ground-state destabilized 2′-hydroxychalcones bearing an additional hydroxyl group at the C6′ position as substrates.[35]

During their study of the catalytic cyclization of chalcone **30** to naringenin dimethyl ether **31** (Scheme 35), modest-to-high conversions and low-to-modest enantioselectivities (of up to 64% ee) were obtained using (−)-quinine (**23a**) as catalyst at high loadings (50 mol %) and PhCl as solvent at an optimal substrate concentration of 10 gL^{-1}.



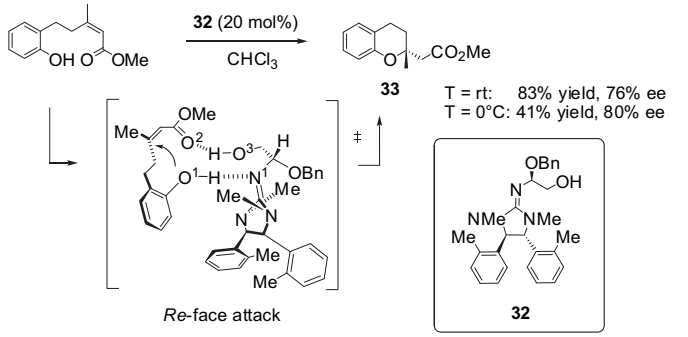
Scheme 35. Cinchona alkaloid-catalyzed cyclization of 2′-hydroxychalcones to flavanones.

3.2. 1,4-Additions of oxygenated nucleophiles catalyzed by guanidine-derived organocatalysts

Organocatalysts with a higher basicity than cinchona alkaloids, such as chiral guanidines have been employed by Ishikawa et al. for the asymmetric construction of 2,2-disubstituted chromane skeletons with a quaternary carbon centre.[36]

Similarly to the previously mentioned dihydrocinchonine-catalyzed 6-*exo*-*trig*-type intramolecular *oxa*-Michael addition reported by Merschaert et al.,[33] the use of the *Z* isomers instead of the *E* isomers results in improvements in the enantioselectivities.[36] The

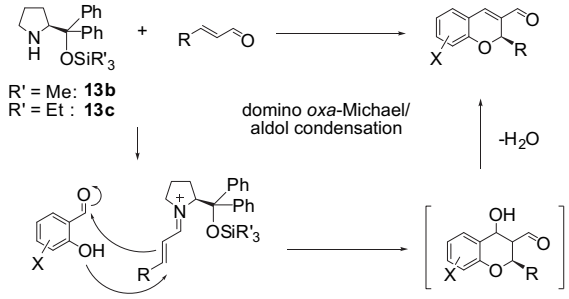
use of chiral guanidine **32** (Scheme 36) as catalyst, in $CHCl_3$ as solvent, gave chromane **33** in 83% yield and 76% ee, which can be increased to 80% ee when the reaction is carried out at 0 °C. This difference in asymmetric induction between the *E* and the *Z* isomers can be explained through the suggested Transition-State (TS) structure of the *oxa*-Michael addition (shown in Scheme 36): while in the TS corresponding to the *Z* isomer two hydrogen bonds between the substrate and the catalyst are formed, thus giving rise to the attack of the activated O^1 atom from the *Re*-face, in the alternative TS structure, which corresponds to *Si*-face attack leading to enantiomeric (*S*)-**33**, only a single hydrogen bond between O^1–H of the substrate and the guanidine N^1 atom is possible.



Scheme 36. Guanidine-catalyzed synthesis of chromanes by intramolecular *oxa*-Michael addition.

3.3. 1,4-Additions of oxygenated nucleophiles catalyzed by proline-derived organocatalysts

By taking advantage of the ability of chiral proline derivatives to undergo reversible formation of enamine and iminium intermediates, Arvidsson et al.,[37] Córdova et al.[38] and Wang et al.[39] have independently studied an enantioselective tandem *oxa*-Michael/aldol condensation reaction for the synthesis of chiral chromenes catalyzed by diarylprolinol ether catalysts. This chromene unit is formed through a tandem reaction involving the *oxa*-Michael attack of salicylic aldehyde derivatives on to α,β-unsaturated aldehydes, activated through an iminium ion with a diarylprolinol ether catalyst, followed by an intramolecular aldol reaction and the subsequent elimination of water (Scheme 37).



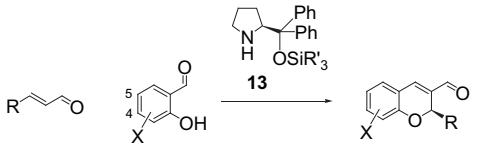
Scheme 37. Organocatalyzed asymmetric synthesis of chiral chromenes by tandem *oxa*-Michael/aldol condensation reaction.

Arvidsson et al. synthesized chromenes with aromatic substituents at the C2 position in up to 60% yield and 60% ee using diphenylprolinol ether **13b** (10 mol %) as catalyst in dichloromethane as solvent. The C2 aliphatic analogues were obtained in up to 90% ee, although in low-to-moderate yields (Table 1, method A).[37]

Córdova et al. improved the yields and enantioselectivities of this tandem reaction using the same diarylprolinol ether **13b** catalyst at a slightly higher loading (20 mol %) and toluene as solvent. The addition of a catalytic amount of 2-nitrobenzoic acid proved to be crucial to increase the enantioselectivity of this reaction: the ee of a test reaction was increased from 9 to 88% by the addition of 2-nitrobenzoic acid as co-catalyst. The use of molecular sieves (4 Å) for the removal of water also significantly enhanced the yields (of up to 95%) of this tandem reaction (Table 1, method B).[38]

Wang et al. also investigated this tandem *oxa*-Michael/aldol condensation reaction of α,β-unsaturated aldehydes and salicylaldehydes employing TES-protected diphenylprolinol **13c** (30 mol %), obtaining chiral chromenes in good yields (53–98%) and enantioselectivities (75–99%).[39] Enals with electron-withdrawing substituents were found to give the best results (Table 1, method C).

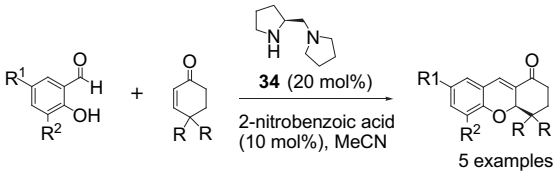
Table 1
Arvidsson et al.,[37] Córdova et al.[38] and Wang et al.[39] tandem *oxa*-Michael/aldol reactions of α,β-unsaturated aldehydes and salicylaldehydes



R	X	Method[a]	T (h)	T (°C)	Yield (%)	ee (%)
Ph	H	**A**	48	rt	63	60
		B[b]	16	rt	81	88
		C	60	0	87	88
4-$NO_2C_6H_4$	H	**A**	48	rt	36	48
		B[b]	24	rt	95	90
		C	24	0	96	95
4-$NO_2C_6H_4$	5-Me	**C**	18	0	98	96
2-$NO_2C_6H_4$	5-Cl	**C**	144	−15	82	>99
4-CNC_6H_4	H	**B**[b]	26	rt	81	90
4-ClC_6H_4	H	**B**[b]	31	rt	89	83
n-Pr	H	**A**	16	rt	14	77
		B	16	rt	57	87
n-Pr	5-MeO	**A**	16	rt	21	90
Me	5-MeO	**C**	48	0	84	85
CO_2Et	H	**B**	21	rt	70	96
CO_2Et	3-F	**B**	23	rt	72	98
CO_2Et	4-Me	**B**[b]	36	rt	70	98

[a] **A**: catalyst **13b** (10 mol %), dichloromethane, rt; see Ref. 37; **B**: catalyst **13b** (20 mol %), 2-nitrobenzoic acid (20 mol %), toluene, rt; see Ref. 38; **C**: catalyst **13c** (30 mol %), benzoic acid (30 mol %), molecular sieves (4 Å), 1,2-dichloroethane, see Ref. 39.
[b] Molecular sieves (4 Å) were added.

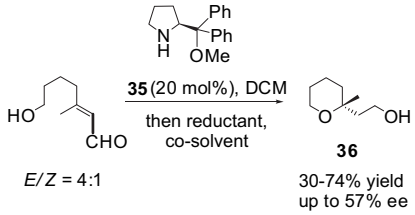
Apart from aldehydes, cyclic α,β-unsaturated ketones have also been used as substrates for this methodology by Córdova et al. Thus, they have reported the first organocatalytic asymmetric synthesis of tetrahydroxanthenones with moderate yields (up to 56%) and enantioselectivities in the range 85–91% ee when using pyrrolidine **34** as catalyst and 2-nitrobenzoic acid as additive (Scheme 38).[40]



R^1	R^2	R	yield (%)	ee (%)
H	H	H	52	89
Me	H	H	51	86
H	Me	H	53	87
H	F	H	56	85
H	Me	Me	51	88

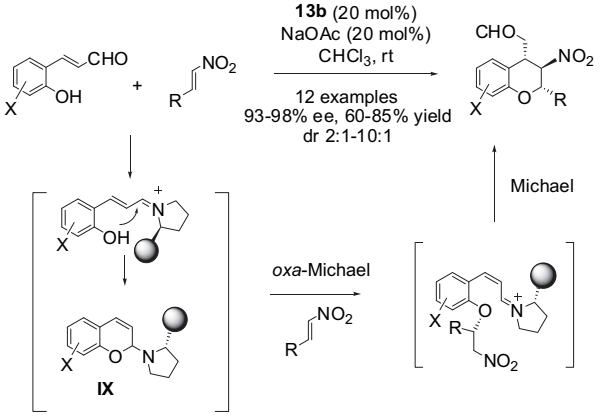
Scheme 38. Organocatalytic asymmetric tandem *oxa*-Michael/aldol condensations for synthesis of tetrahydroxanthenones.

Recently, we have described the first diarylprolinol ether-catalyzed synthesis of the alkyltetrahydropyran **36** by intramolecular *oxa*-Michael addition of a hydroxyl group to an α,β-unsaturated aldehyde (Scheme 39).[41] Diarylprolinol ether **35** was found to be the best catalyst for this transformation, obtaining *R*-**36** after in situ reduction as the major enantiomer in moderate-to-good yields (30–74%) and modest enantioselectivities (up to 57% ee).



Scheme 39. Organocatalyzed synthesis of alkyltetrahydropyran **36** by intramolecular *oxa*-Michael addition of hydroxyl group to α,β-unsaturated aldehyde.

In all the preceding organocatalyzed tandem *oxa*-Michael/aldol reactions reported by Arvidsson, Córdova and Wang,[37–39] only one stereogenic centre is generated in the products, due to the spontaneous dehydration of the β-hydroxy aldimine intermediate. Wang et al. have recently reported an organocatalyzed asymmetric tandem *oxa*-Michael/Michael reaction, which affords chiral highly functionalized chromans with the creation of three new stereogenic centres (Scheme 40).[42]

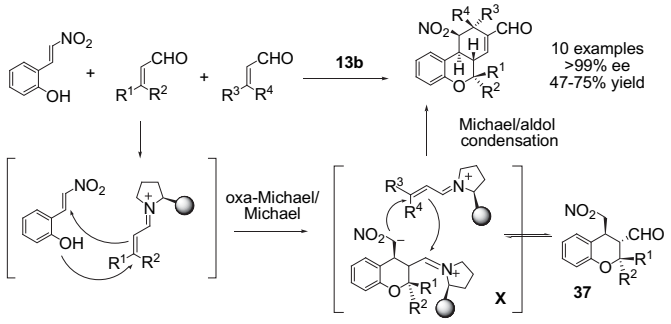


Scheme 40. Diphenylprolinol ether-catalyzed tandem *oxa*-Michael/Michael reaction for synthesis of highly functionalized chromans.

Mechanistically, this tandem reaction differs from the previous tandem *oxa*-Michael/aldol reactions in that an aminal intermediate (**IX** in Scheme 40) rather than a hydroxyl group, serves as an activated nucleophile for the first *oxa*-Michael addition.

This tandem *oxa*-Michael/Michael reaction catalyzed by diphenylprolinol ether **13b** has proved to be efficient between a variety of 2-hydroxy cinnamaldehydes and nitroolefins when using $CHCl_3$ as solvent and NaOAc as additive. In this way, chiral chromanes were obtained with excellent levels of enantiomeric excess (93–98% ee) and good-to-high diastereoselectivities (2:1–10:1).[42]

Very recently, Hong et al. have extended this methodology to the cascade *oxa*-Michael/Michael/Michael/aldol condensation reaction for the enantioselective synthesis of tetrahydro-6*H*-benzo[*c*]chromenes (Scheme 41).[43] The cascade sequence of the proposed mechanism starts in an analogous manner to that previously mentioned, although the first *oxa*-Michael step is followed by a second Michael addition to form the chromane unit. The intermediate **X** undergoes a new Michael attack of the nitro anion on to the α,β-unsaturated aldehydes, activated through an iminium ion with the diarylprolinol ether catalyst, followed by an intramolecular aldol reaction and subsequent elimination of water.

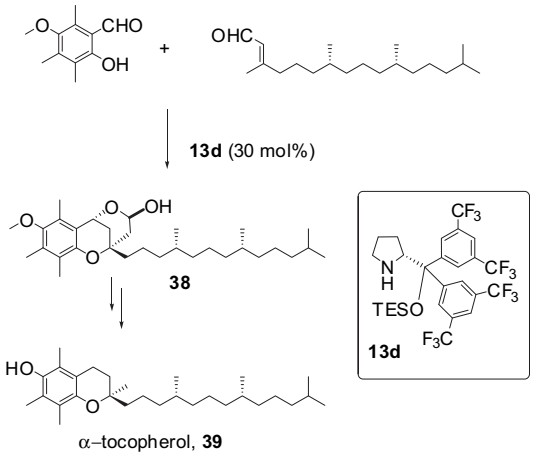


R^1	R^2	R^3	R^4	Yield (%)	ee (%)
Ph	H	Ph	H	75	> 99%
4-$MeOC_6H_4$	H	4-$MeOC_6H_4$	H	73	> 99%
4-BrC_6H_4	H	4-BrC_6H_4	H	55	> 99%
Me	Me	Ph	H	51	> 99%
Me	Me	4-$MeOC_6H_4$	H	54	> 99%
Me	Me	4-$NO_2C_6H_4$	H	47	> 99%

Scheme 41. Tandem *oxa*-Michael/Michael/Michael/aldol condensation reaction for enantioselective synthesis of tetrahydro-6*H*-benzo[*c*]chromenes.

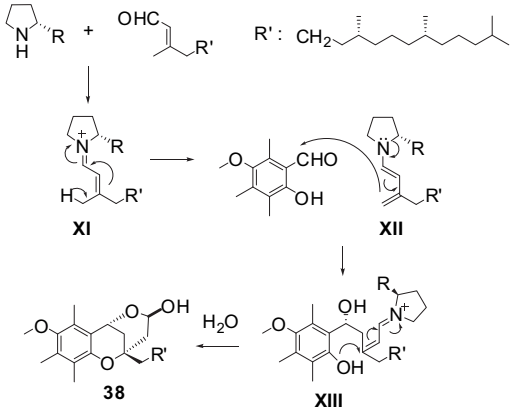
A series of arylacrylaldehydes were reacted with the nitrovinylphenol shown in Scheme 41 in the presence of pyrrolidine **13b** as catalyst and acetic acid as additive, obtaining tetrahydro-6*H*-benzo[*c*]chromenes in moderate-to-good yields and excellent diastereoselectivities (>30:1) and enantioselectivities (>99% ee). It is worth mentioning that, except for the observation of a trace amount of the intermediate **37**, only one enantiomer was observed in this reaction, probably due to the high enantio- and diastereoselective first *oxa*-Michael addition, the stereochemical outcome of which will dictate the stereochemistry of the following reactions. As can be seen in Scheme 41, this quadruple cascade organocatalytic reaction has also proved to be efficient for three-component reactions.

Recently, Woggon et al. have reported a diastereoselective tandem aldol/*oxa*-Michael reaction as the key step for the synthesis of the natural product α-tocopherol (**39** in Scheme 42) by using a diarylprolinol ether-derived catalyst **13d**. Despite the relatively high loading (30 mol%) of the organocatalyst, the reaction provided the tricyclic structure **38** with an embedded chiral chromane core with excellent diastereoselectivity (97%) and in 58% yield (Scheme 42).[44]



Scheme 42. Tandem aldol/*oxa*-Michael reaction for synthesis of α-tocopherol **39** catalyzed by diarylprolinol ether **13d**.

The formation of lactol **38** (Scheme 42) suggests a mechanism slightly different to that corresponding to the previous *oxa*-Michael/aldol condensation reactions of α,β-unsaturated aldehydes and salicylaldehydes (Scheme 37). In this case, the initially formed iminium salt **XI** leads to the subsequent dienamine **XII**, which reacts with the salicylaldehyde substrate in an aldol-type reaction to yield the intermediate **XIII** (Scheme 43). This compound then undergoes a diastereoselective intramolecular *oxa*-Michael addition, affording the lactol **38**.



Scheme 43. Proposed mechanism for tandem aldol/*oxa*-Michael reaction leading to lactol **38**.

4. Asymmetric organocatalyzed *oxo*-hetero-Diels-Alder reactions

The *oxo*-hetero-Diels–Alder (*oxo*-HDA) reaction appears to be the perfect tool for the enantioselective construction of six-membered oxygenated heterocycles. This is due to the well-known facets ascribed to all the Diels–Alder reaction variants, namely (a) ease of performance, (b) high regio- and stereoselectivity typically displayed by this cycloaddition and, more significantly, (c) the creation of up to four new stereocentres in the cyclic system.

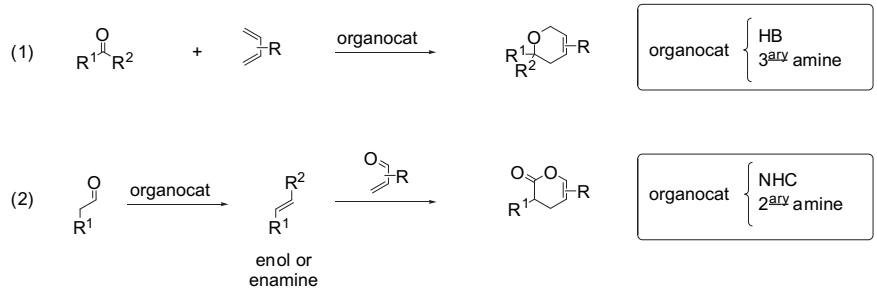
Applications of asymmetric organocatalysis in the *oxo*-HDA reaction are reported in this section. The exemplified transformation involves a carbonyl compound as the heterodienophile or the heterodiene (Scheme 44) to afford six-membered pyran derivatives.

The basic idea of performing these reactions in an organocatalytic enantioselective manner is to use the chiral organocatalyst to activate a carbonyl compound and also to control the stereochemical outcome of the cycloaddition by directing the three-dimensional approach of the diene or dienophile to one of the faces of the activated carbonyl compound. Hydrogen bonding of a simple chiral alcohol or amine to the carbonyl group has been exploited as a mode of activation for the *oxo*-HDA reactions (Scheme 44, Eq. 1). A different reaction pathway is found in the organocatalyzed inverse electron-demand *oxo*-HDA reactions, where the activation is achieved by enamine catalysis (Scheme 44, Eq. 2). This section will thus be organized on the basis of the activation mode performed by the catalyst, and is subdivided into four parts: Section 4.1. hydrogen bond (HB)-catalyzed *oxo*-HDA reactions, Section 4.2. Enamine catalysis in *oxo*-HDA reactions, Section 4.3. *oxo*-HDA reactions catalyzed by *N*-heterocyclic carbenes (NHC), and Section 4.4. *oxo*-HDA reactions catalyzed by chiral tertiary amines.

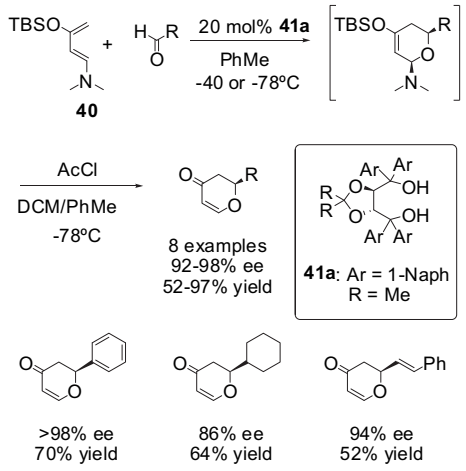
4.1. Hydrogen bond-catalyzed *oxo*-HDA reactions

The investigations in this field were initiated by Rawal and Huang. They observed that HB-donating solvents, such as dichloromethane or 2-butanol accelerate the *oxo*-HDA reaction of unactivated aldehydes[45] and ketones[46] with 1-amino-3-siloxybutadiene (**40** in Scheme 45).[47] Immediately after this study, the same group, explored the use of chiral alcohols as catalysts for the asymmetric transformation, finding that 20 mol % of 1-naphthyl-TADDOL **41a** (α,α,α′,α′-tetraaryl-1,3-dioxolan-4,5-dimethanol) promotes the cycloaddition of a variety of aldehydes with the so-called Rawal's diene **40** (Scheme 45). This reaction proceeded smoothly to furnish the corresponding dihydropyrones in good yields and excellent enantioselectivities after treatment with AcCl, as depicted in Scheme 45.[48] Remarkable is the broad substrate scope in the aldehyde component, as this transformation is found to be suitable for aromatic, as well as aliphatic and α,β-unsaturated aldehydes.

This exciting development achieved by Rawal et al. has been the origin of a vast amount of research, with efforts not only directed towards the expansion of substrate scope to less activated dienes and design of new HB catalysts, but also in the field of computational chemistry, where several reports account for mechanistic aspects of this particular transformation, as discussed below.

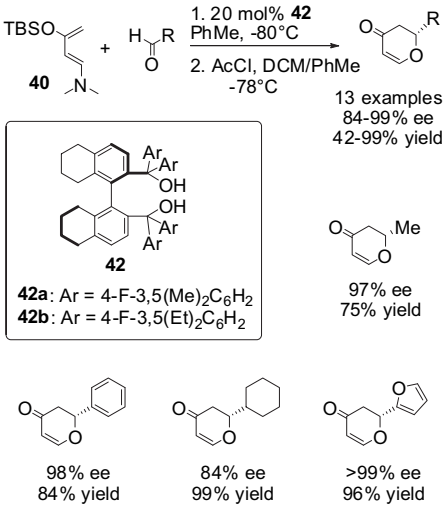


Scheme 44. Organocatalyzed *oxo*-HDA reactions of carbonyl compounds.



Scheme 45. TADDOL-catalyzed *oxo*-HDA reactions of aminosiloxydiene **40**.

Rawal, together with Yamamoto et al.,[49] introduced a new diol catalyst, **42**, having the axially chiral 1,1′-biaryl-2,2′-dimethanol (BAMOL) scaffold, which was demonstrated to be highly effective for the catalysis of the *oxo*-HDA reactions of a wide range of aliphatic and aromatic aldehydes with 1-amino-3-siloxybutadiene **40** (Scheme 46) and gave comparable results in terms of yield and enantioselectivity, to reactions catalyzed by TADDOL **41a**. This new motif shares with TADDOLs a bis-(diarylhydroxymethyl) functionality, in which the steric and electronic properties were readily tunable. The survey of different BAMOLs, revealed that diols **42a** and **42b** having the 4-fluoro-3,5-dimethylphenyl and 4-fluoro-3,5-diethylphenyl groups, respectively, afforded the best results for the cycloaddition of **40** to various aldehydes.



Scheme 46. BAMOL-catalyzed *oxo*-HDA reactions of aminosiloxydiene **40**.

An X-ray structure of the 2,2′-bis-(diphenylhydroxymethyl)binaphthylene–benzaldehyde complex (Fig. 4) not only shows a 1:1 association between the two molecules, but also reveals the presence of an intramolecular HB between the two hydroxyls and an intermolecular HB to the carbonyl oxygen of benzaldehyde. The complex suggests that carbonyl activation occurs through a single-point HB.

In 2004, the TADDOL derivatives **41a–d** were employed by Ding et al. to perform *oxo*-HDA reactions of aldehydes with Brassard's diene **43** (Scheme 47).[50] They reported the results

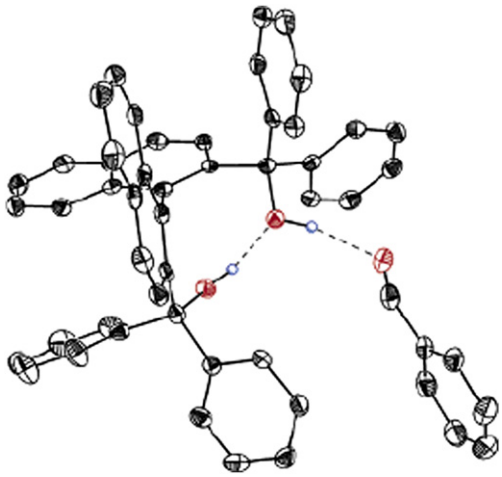
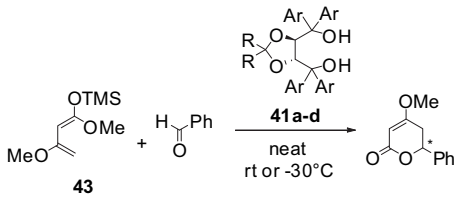


Figure 4. Crystal structure of the 2,2′-bis-(diphenylhydroxymethyl)binaphthylene–benzaldehyde complex.

obtained when using different substitution patterns in the TADDOL catalyst, concluding that 1-naphthyl-substituted TADDOLs (**41a–b**) exhibit a remarkably superior performance, compared to that of their analogues, such as simple phenyl-TADDOL **41c** or 2-naphthyl-TADDOL **41d**, in terms of both activity and enantioselectivity.

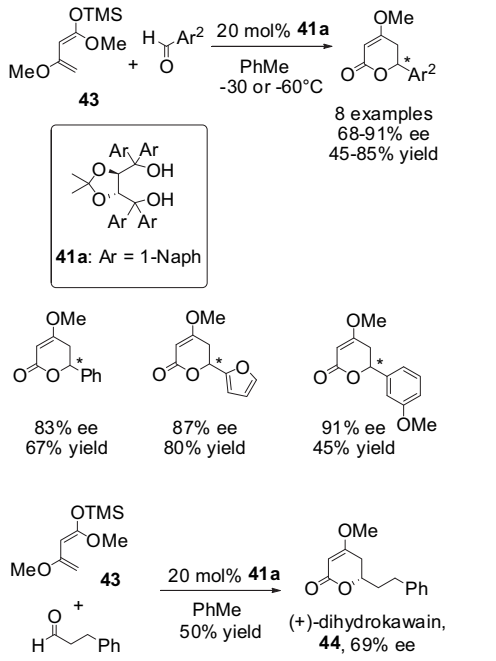


Scheme 47. TADDOL derivatives as catalysts in *oxo*-HDA reactions of Brassard's diene.

In this manner, they used catalyst **41a** to explore the aldehyde scope[50] in reactions with Brassard's diene, obtaining the corresponding *δ*-lactone derivatives highly enantioselectively (Scheme 48). The usefulness of this methodology was demonstrated in the total synthesis of the natural product (+)-dihydrokawain **44**.

These researchers proposed a possible mechanism and mode of action of the TADDOL catalyst based on an X-ray crystal structure analysis of the inclusion complex of TADDOL **41c** (having phenyl substituents) and dimethylformamide. This structure, shown in Figure 5, illustrates that the diol and the carbonyl group of the DMF associate via a single HB and that an intramolecular HB exists between the two hydroxy groups of the chiral diol (similar to that observed in the 2,2′-bis-(diphenylhydroxymethyl)binaphthylene–benzaldehyde complex depicted in Fig. 4).

With this information in hand, they proposed a mechanism, outlined in Scheme 49, for asymmetric induction in this catalytic system. When (*S*,*S*)-**41a** was used as the catalyst, the steric hindrance of the naphthyl moiety shields the *Si*-face of the aldehyde, while the *Re*-face is available to react with the diene, to give the product with the *R* configuration. Although this model cannot quantitatively explain the impact of the aryl groups of TADDOL



Scheme 48. TADDOL-catalyzed *oxo*-HDA reactions of Brassard's diene.

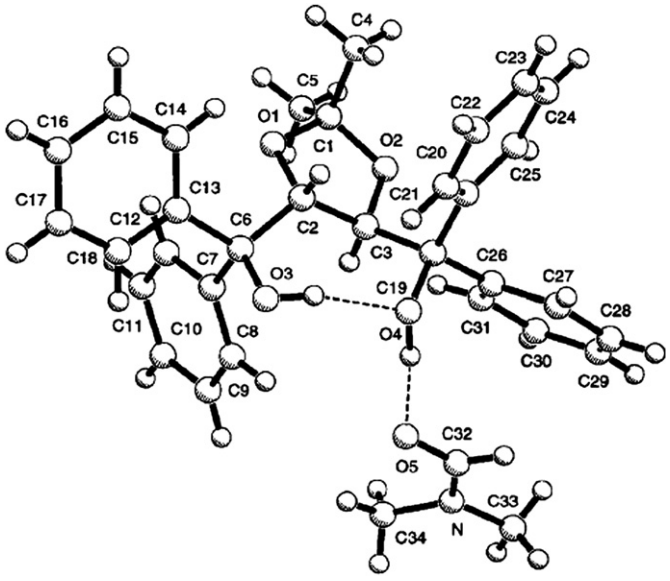
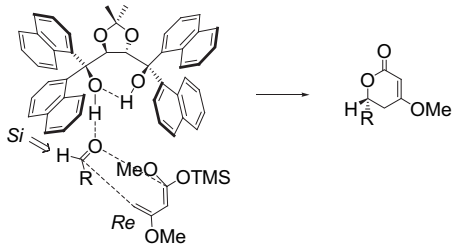


Figure 5. Crystal structure of (*R*,*R*)-TADDOL **41c**-DMF complex.

derivatives on their asymmetric induction in the reactions, it was evident that the strength of the intermolecular hydrogen bonding between the catalyst and the substrate, the greater steric hindrance of the 1-naphthyl group and the π–π interaction between the naphthyl ring and the carbonyl group of the substrate all played important roles in the control of the enantioselectivity of the catalytic reaction.

In the same context, the authors expanded their investigation,[51] and studied the mechanism of the reaction theoretically, using the ONIOM (B3LYP/6-31G*:PM3) method with *trans*-1,3-dimethoxy-1,3-butadiene as the model for Danishefsky's diene, indicating that the reaction evolved via a concerted mechanism through an asynchronous and zwitterionic transition structure, as depicted in Scheme 49. The carbonyl group of benzaldehyde is activated by



Scheme 49. Proposed mechanism for asymmetric induction in enantioselective *oxo*-HDA reaction between Brassard's diene and aldehydes.

forming an intermolecular HB with one of the hydroxyl groups of TADDOL. Meanwhile, the intramolecular HB between the two hydroxy groups in TADDOL is found to facilitate the intermolecular HB with benzaldehyde. The involvement of highly polarised transition-states was confirmed by a computational study of diol-catalyzed *oxo*-HDA reactions of Rawal's diene, by the group of Houk.[52] They showed that the 1,4-butanediol model systems for catalysis by TADDOLs were consistent with a cooperative hydrogen-bonding arrangement and also provided a model of selectivity[53] to predict the sense and relative magnitude of product stereoinduction for the TADDOL-promoted reaction, pointing out the orientation of the aldehyde by CH–π interaction between the aldehyde CH and the pseudoequatorial naphthalene ring of TADDOL **41a** (Fig. 6).

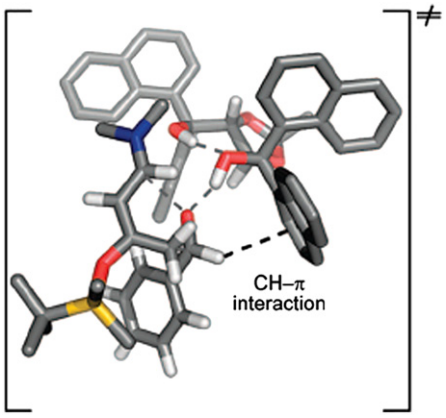
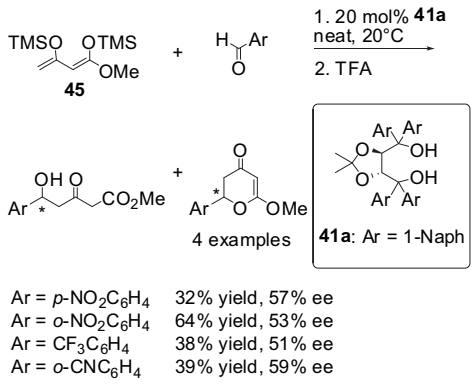


Figure 6. Proposed transition-state for TADDOL **41a**-catalyzed *oxo*-HDA reaction of Rawal's diene **40** and benzaldehyde.

Recent developments in computational procedures have come up with a reverse-docking methodology devised to rationalize the stereoselectivity of asymmetric reactions. In this procedure, a flexible organocatalyst is docked around a catalyst-free, transition-state representation of the asymmetric reaction. The resulting reverse docking represents a simplified geometric model of the TS for the catalyzed reaction and can provide an insight into the observed stereoselectivity. Deslongchamps and Harriman[54] studied the reverse docking of TADDOL catalyst **41a** to rigid transition-state representations of the *oxo*-HDA reaction reported by Rawal et al. in 2003,[48] revealing clear energetic trends favouring the experimentally preferred product enantiomers. The results indicated a mode of catalysis consistent with the experimental data, but the relative docking energies between the transition-state model enantiomers were too great to allow an in silico correlation with the experimentally observed ees. Thus, several changes were made to the reverse-docking algorithm, allowing the first reported[55] correlation with experimentally reported ee values, based solely on reverse docking and molecular mechanics energies.

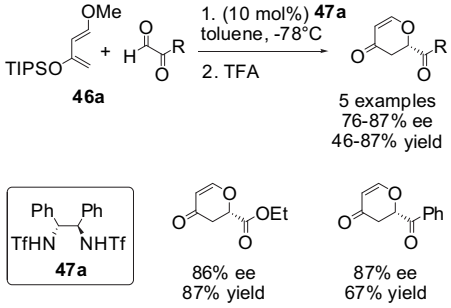
Chan's diene **45** has also been used in the TADDOL **41a**-catalyzed *oxo*-HDA reaction with aldehydes.[56] In this case, the cycloaddition

was found to be a competing transformation with the vinylogous aldol reaction when using electron-poor aromatic aldehydes under solvent-free conditions (Scheme 50). The cycloadducts are formed with a modest enantioselectivity of 51–59% ee at room temperature.



Scheme 50. TADDOL **41a**-catalyzed *oxo*-HDA reactions of Chan's diene, **45**.

Since the initial experiments with TADDOL and BAMOL catalysts, several other catalyst motifs have been demonstrated to promote the *oxo*-HDA reaction via hydrogen-bonding catalysis. In this regard, Mikami and Tonoi reported that a bis-triflylamide (**47a** in Scheme 51) is an active catalyst for the *oxo*-HDA reaction, promoting the reaction of TIPS-substituted Danishefsky's diene **46a** with glyoxylates and phenylglyoxals to afford dihydropyrones in 76–87% ee and good yield (Scheme 51).[57] Mikami also suggested that the bis-triflylamide catalyst **47a** acts as a double HB donor catalyst (differing from the mode of action proposed for TADDOL and BAMOL), basing this proposition on ^{1}H NMR titration experiments.

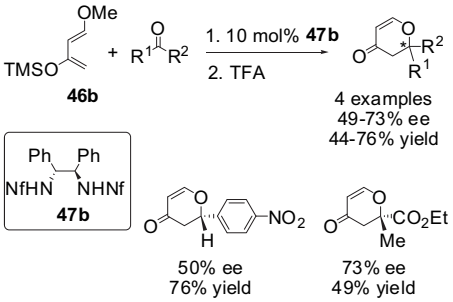


Scheme 51. Bis-sulfonamide-catalyzed *oxo*-HDA reactions of Danishefsky's diene.

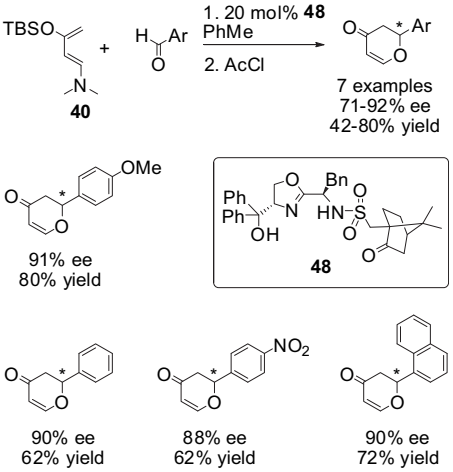
Shortly after Mikami's report, Jørgensen et al.[58] accounted for the same *oxo*-HDA reaction with the TMS-substituted Danishefsky's diene **46b**, using a slightly different catalyst, the bis-nonaflylamide **47b**, where the triflyl group had been replaced with the longer-chain nonaflyl group ($CF_3-(CF_2)_3-SO_2-$). The enantioselectivities achieved for the different dihydropyrones were in the range of 49–73% ee (Scheme 52).

Sigman and Rajaram[59] have designed another novel chiral organocatalyst (**48** in Scheme 53) with a rigid oxazoline backbone, bearing a sulfonylamide and a tertiary alcohol as the two HB-donating groups. Both HBs in the catalyst were necessary for effective catalysis. Scheme 53 shows that, in the presence of this catalyst, electron-rich and electron-poor arylaldehydes undergo cyclization with Rawal's diene **40**, to yield the corresponding dihydropyrones highly enantioselectively.

The group of Sigman continued with the studies on this organocatalyst scaffold and, in 2007,[60] reported the effect of the catalyst



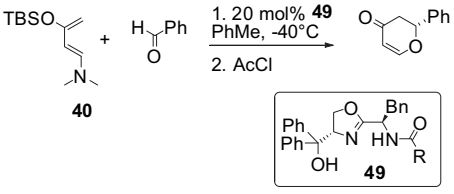
Scheme 52. Bis-sulfonamide-catalyzed *oxo*-HDA reactions of Danishefsky's diene.



Scheme 53. Sulfonamide-catalyzed *oxo*-HDA reactions of aminosiloxydiene **40**.

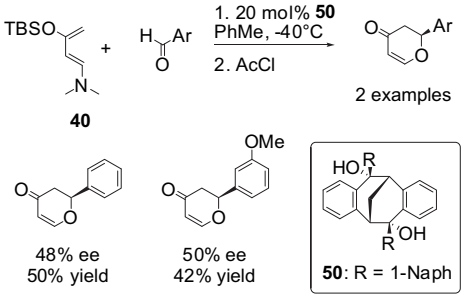
acidity on the enantioselectivity of the *oxo*-HDA reaction. Taking advantage of its modular nature, they prepared several oxazoline-core catalysts with a pendant alcohol and different halogenated acetamide groups (**49**, Scheme 54). Indeed, it was found that both the reaction rate and the enantioselectivity could be directly correlated with the catalyst acidity.

Cleft molecules[61] (**50** in Scheme 55) have also been tested as organocatalysts in the asymmetric *oxo*-HDA reaction of benzaldehydes and 1-amino-3-siloxybutadiene **40** (Scheme 55), providing both moderate yields and enantioselectivities (≤52% ee).



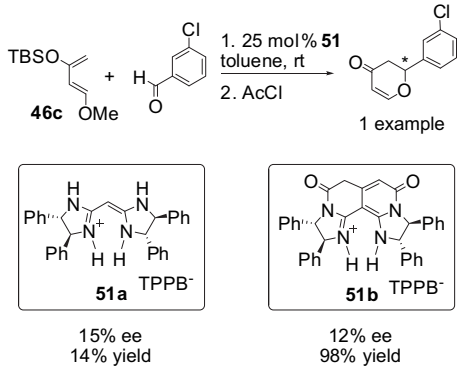
R	pk_a of RCO_2H	yield (%)	ee (%)
CF_3	-0.25	67	91
CCl_3	0.65	61	81
$CHCl_2$	1.29	53	75
CH_2F	2.66	17	62
CH_2Cl	2.86	32	52

Scheme 54. Effect of catalyst acidity on enantioselectiviy of *oxo*-HDA reaction.



Scheme 55. Cleft molecule-catalyzed *oxo*-HDA reactions of aminosiloxydiene **40**.

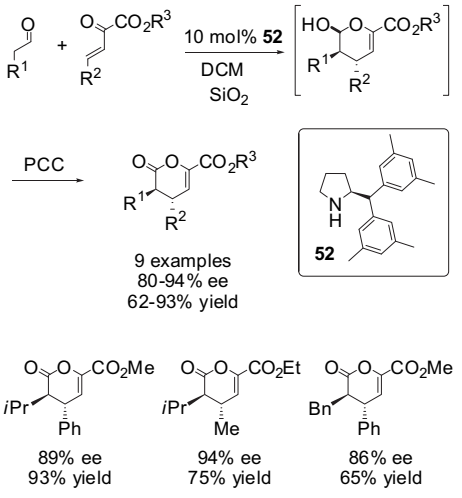
Göbel et al.[62] reported in 2007 the synthesis of C_2-symmetric bisamidines, (**51a**,**b** in Scheme 56), which in the monocationic form (and with weakly coordinating counterions), adopt a planar conformation with an almost convergent orientation of the two N–H groups, which looks ideal for electrophilic activation in HB-mediated host-guest complexes. They reported the acceleration of different reactions of simple ketones, nitroalkenes and aldehydes, such as the *oxo*-HDA of the TBS-substituted Danishefsky's diene **46c** and 3-chlorobenzaldehyde. The enantioinduction, however, is quite low, not surpassing 15% ee (Scheme 56).

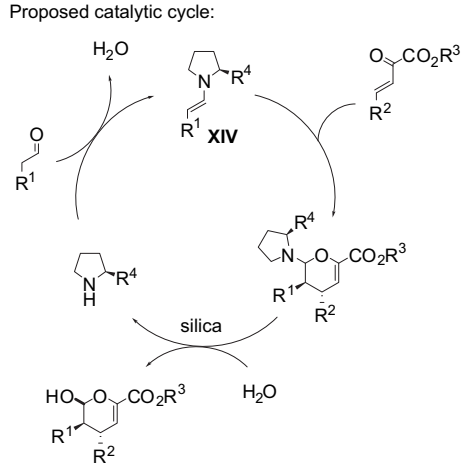


Scheme 56. Cleft-type molecule-catalyzed *oxo*-HDA reactions of Danishefsky's diene **46c**.

4.2. Enamine catalysis in *oxo*-HDA reactions

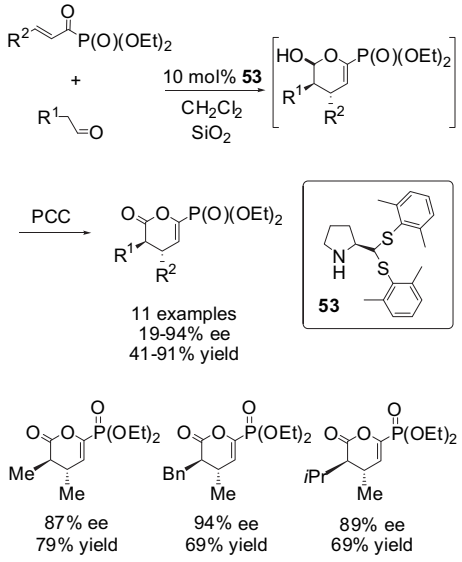
Jørgensen and Juhl[63] introduced this concept in 2003. It is based on the consideration that chiral enamines **XIV** (Scheme 57), generated from aldehydes and chiral pyrrolidines, such as **52**, can act as electron-rich alkenes and undergo an enantioselective *oxo*-HDA reaction with enones (in an inverse electron-demand fashion) to give the corresponding *oxo*-HDA cycloadducts, which, after hydrolysis of the aminal group in the presence of silica, gave the hemiacetal and released the chiral catalyst to complete the catalytic cycle, as outlined in Scheme 57. A further oxidation of the mixture of the two anomers yields the corresponding δ-lactone as a single diastereomer. The highly functionalized products are formed with excellent enantioselectivity and good-to-excellent yield, as depicted in Scheme 57.



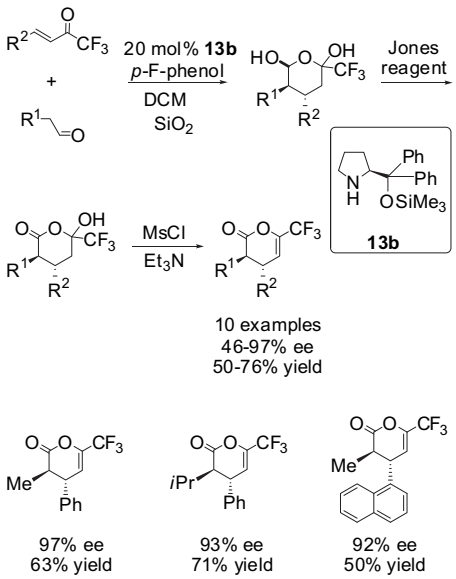


Scheme 57. Pyrrolidine-catalyzed *oxo*-HDA reactions of α,β-unsaturated acyl esters.

There are only a few more examples of using α,β-unsaturated carbonyl compounds in inverse electron-demand *oxo*-HDA reactions. Zhao et al. studied some novel prolinal dithioacetal derivatives as catalysts for the *oxo*-HDA reaction of enolizable aldehydes and β,γ-unsaturated α-ketophosphonates.[64] When the catalyst of choice was the more hindered catalyst **53**, shown in Scheme 58, the corresponding 5,6-dihydro-4*H*-pyran-2-ylphosphonates were obtained with good ee values (up to 94% ee). In all



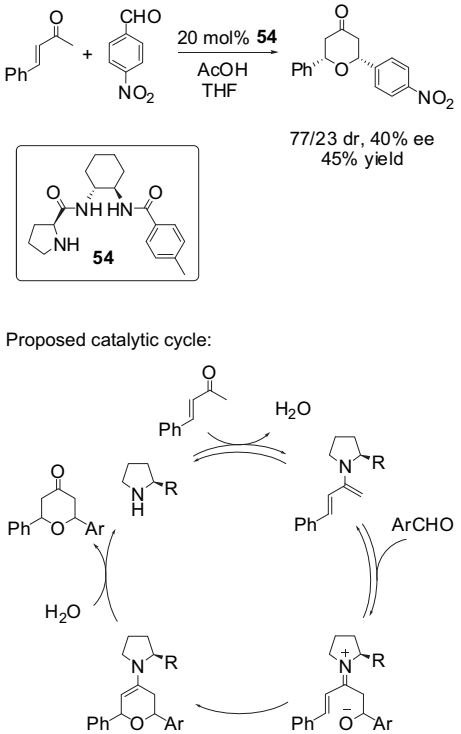
Scheme 58. Prolinal dithioacetal-catalyzed *oxo*-HDA reactions of β,γ-unsaturated α-ketophosphonates.



Scheme 59. Diarylprolinol ether-catalyzed *oxo*-HDA reactions of α,β-unsaturated trifluoromethyl ketones.

cases, only the *trans* diastereoisomer was isolated the oxidation of the mixture of the two anomeric stereoisomers.

Very recently, Liu et al. achieved, for the first time, the organocatalyzed asymmetric inverse electron-demand *oxo*-HDA reaction of aldehydes and α,β-unsaturated trifluoromethyl ketones.[65] The combination of a chiral diphenylprolinol ether **13b** and *p*-fluorophenol as catalysts allows the reaction to proceed under mild conditions to give the corresponding cyclic products, which were further oxidised to form the lactone derivatives. Due to their instability, these lactones were subsequently dehydrated with methanesulfonyl chloride and triethylamine. The final products were therefore isolated in moderate yields, for the three steps, with high diastereo- and enantioselectivities (Scheme 59).

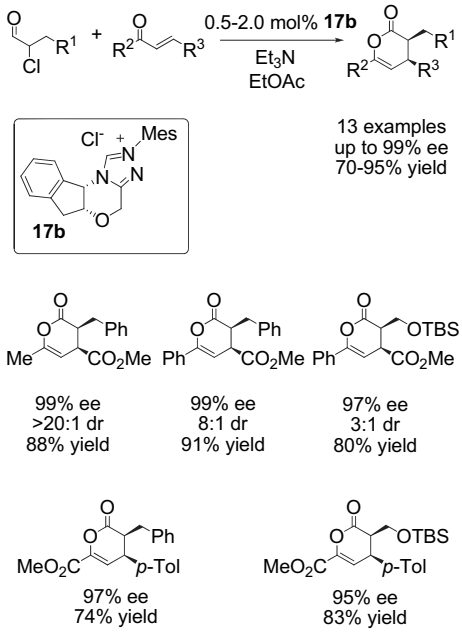


Scheme 60. Prolinamide-catalyzed *oxo*-HDA reactions of α,β-unsaturated ketones.

Xiao et al. described recently the organocatalytic *oxo*-HDA reaction of acyclic α,β-unsaturated ketones with aldehydes.[66] The catalysis is also achieved by an enamine intermediate, generated this time from the α,β-unsaturated ketone and a chiral prolinamide **54**. The electron-rich diene thus formed reacts with the non-enolizable aldehyde in a normal electron-demand *oxo*-HDA reaction (through a concerted or stepwise pathway), giving the corresponding cycloadduct, which upon imine hydrolysis, leads to the tetrahydropyran-4-one releasing the chiral catalyst to complete the catalytic cycle, as outlined in Scheme 60. Only one example is reported for the enantioselective transformation, and the cycloadduct is formed in moderate yield, and also moderate diastereo- and enantioselectivity.

4.3. *Oxo*-HDA reactions catalyzed by *N*-heterocyclic carbenes

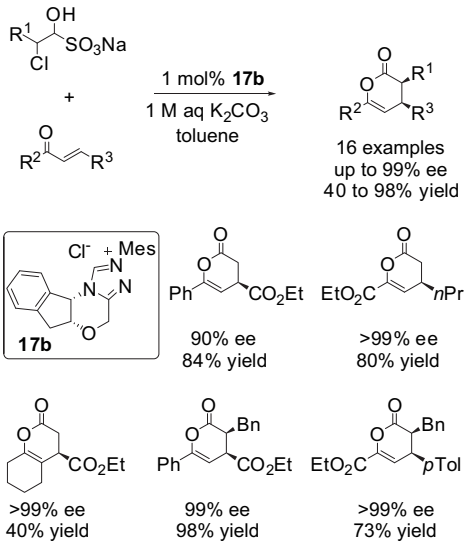
In 2006, Bode et al. published an asymmetric *N*-heterocyclic carbene (NHC)-catalyzed *oxo*-HDA reaction.[67] In this method, the enolate dienophile is formed from the racemic α-chloroaldehyde precursor reacting with the NHC, and can afterwards react with an enone as heterodiene in an *oxo*-HDA manner (Scheme 61). Different enones bearing electron-withdrawing groups as well as aromatic and aliphatic enoates were tested in the reaction, all



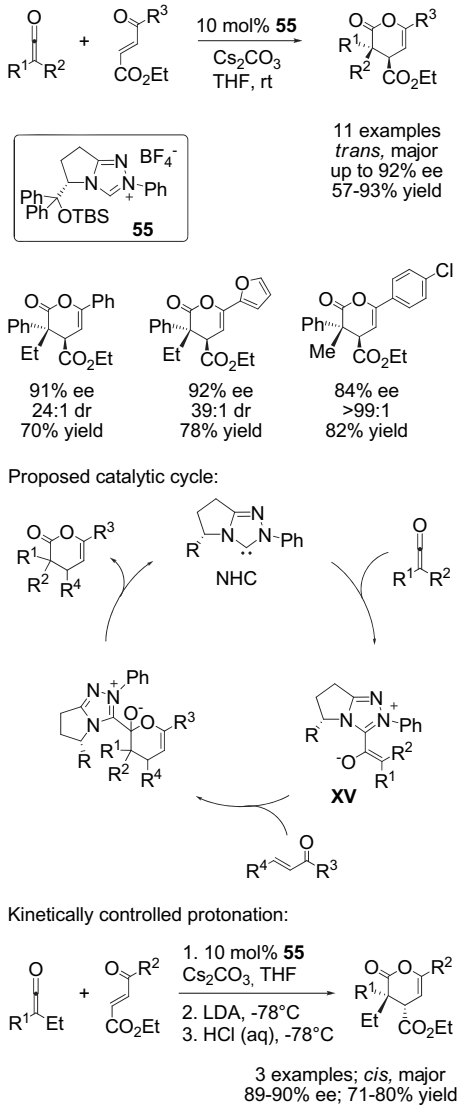
Scheme 61. NHC-catalyzed *oxo*-HDA reactions of α-chloroaldehydes.

providing high yields and enantioselectivities of up to 99% ee. Outstanding is the fact that the chiral triazolium salt is used in a remarkably low loading of 0.5 mol %.

The same group expanded this methodology to α-chloroaldehyde bisulfite salts as starting materials.[68] The chiral NHC-catalyzed *oxo*-HDA reaction was successfully carried out under biphasic reaction conditions with high levels of enantioselectivity, demonstrating, for the first time, water tolerance in this type of transformation (Scheme 62). The precatalyst **17b** is quite efficient at the low loading of 1 mol % and the procedure provides an innovative solution to enantioselective additions of acetate equivalents by using the inexpensive, commercially available bisulfite adduct of chloroacetaldehyde (R^1=H).



Scheme 62. NHC-catalyzed *oxo*-HDA reactions of α-chloroaldehyde bisulfite salts.

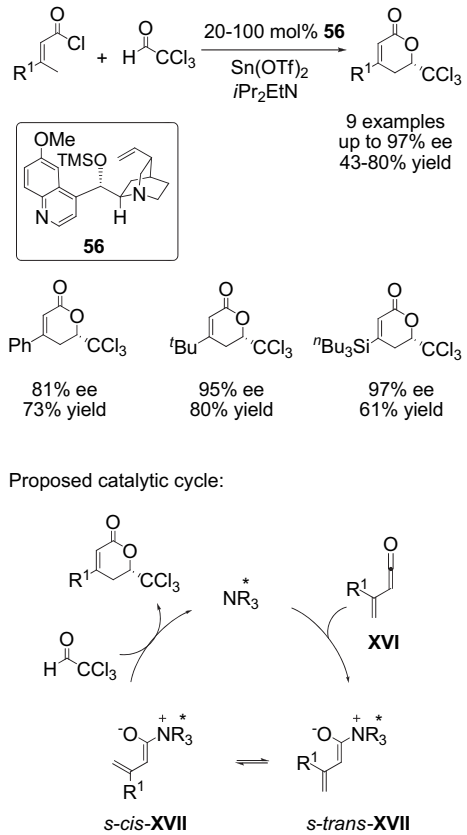


Scheme 63. NHC-catalyzed *oxo*-HDA reactions of ketenes.

Ye et al.[69] have reported, just recently, the NHC-catalyzed [4+2] cycloaddition of disubstitued ketenes with enones to give δ-lactones through the possible mechanism illustrated in Scheme 63. Precatalyst **55** was used for the generation of the NHC in the presence of Cs_2CO_3. The reaction is probably initiated by the nucleophilic addition of the NHC to the ketene to give the triazolium enolate intermediate **XV**, which reacts with the enone by an inverse electron-demand Diels–Alder reaction, forming the corresponding adduct. Subsequent NHC elimination furnishes the desired product and regenerates the NHC catalyst. Both the *trans* and *cis* isomers of the δ-lactones could be obtained in good yields with high diastereo- and enantioselectivities. The *trans* isomer is formed preferentially by an in situ thermodynamically controlled epimerization, using an excess of 20 mol % of Cs_2CO_3. It is noteworthy that the diastereomeric ratios and enantiomeric excess, although quite high, could be further improved by a single recrystallization. An in situ kinetically controlled protonation allows the *cis* isomer to be formed favourably with ee values of up to 90% (Scheme 63).

4.4. *Oxo*-HDA reactions catalyzed by chiral tertiary amines

Chiral tertiary amines have also been described as catalysts for asymmetric *oxo*-HDA reactions. In 2007, Peters and Tiseni[70] published the first and, so far, only, tertiary amine-catalyzed enantioselective [4+2] cycloaddition of α,β-unsaturated acid chlorides and the aldehyde chloral. The transformation probably proceeds through the in situ formation of a vinylketene **XVI** by dehydrohalogenation of the α,β-unsaturated acid chloride. The vinylketene is then trapped by the enantiopure tertiary amine, forming the zwitterionic dienolate **XVII** and, thus, the diene component of the Diels–Alder reaction (Scheme 64). The methodology necessitates the presence of a Lewis acid co-catalyst such as $Sn(OTf)_2$ that



Scheme 64. Tertiary amine-catalyzed *oxo*-HDA reactions of vinylketenes.

the authors claim facilitates the dehydrochlorination step and is not involved in the cycloaddition. The corresponding δ-lactone building blocks are formed in high ee values of up to 97% when the catalyst of choice was the trimethylsilylquinidine **56**.

5. Conclusions and overview

Organocatalysis has proved to be a very useful tool for enantioselective obtaining six-membered oxygen-containing heterocycles, which are important building blocks for the synthesis of enantiomerically pure, biologically active compounds. Notably, highly effective asymmetric organocatalytic 1,2- and 1,4-additions of carbon as well as oxygen nucleophiles to different electrophiles have been developed, among, which the intramolecular Stetter reaction has emerged as a powerful method for the synthesis of enantiopure chromen-4-ones, thanks to the development of new families of chiral nucleophilic carbenes. Another type of transformation leading to six-membered oxygenated heterocycles, which has experienced a considerable advance during recent years, is organocatalytic tandem reactions, the first activation step of which is an intermolecular organocatalytic Michael addition of a carbon nucleophile. A second intramolecular step of acetalization/ketalization (chiral pyrrolidine-catalyzed), lactonization (cinchona alkaloid-catalyzed) or acylation (*N*-heterocyclic carbene-catalyzed) has lead to a wide variety of enantiopure oxygenated heterocycles.

Chiral chromanes and chromanones have also been synthesized by 6-*exo*-*trig* and 6-*endo*-*trig* intramolecular *oxa*-Michael additions with cinchona alkaloid-derived as well as guanidine-derived organocatalysts. Enamine–iminium activation has also proved to be very useful in a range of tandem transformations leading to six-membered oxygen-containing heterocycles involving *oxa*-Michael additions, which in many cases, have provided excellent levels of asymmetric induction.

Organocatalyzed *oxo*-HDA reactions have emerged as a very efficient tool for the construction of chiral dihydropyranones. Over the last few years, these have become a benchmark in the growing field of hydrogen bond-catalyzed reactions and single-donor (TADDOL, BAMOL) as well as double-donor (bis-amides) modes of activation have been extensively studied. Again, enamine–iminium catalysis has been used in inverse as well as direct-electron-demand asymmetric *oxo*-HDA reactions leading to different six-membered oxygenated heterocycles.

In conclusion, the organocatalytic synthesis of chiral six-membered oxygen-containing heterocycles has become a very attractive topic for synthetic chemists in a relatively short period of time. There is however still much room for further investigations regarding these organocatalytic transformations, especially those that result in overcoming their major drawbacks, such as high catalyst loading or low substrate scope.

Acknowledgements

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References and notes

1. (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309–3362; (b) Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2301–2323; (c) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045–2053; (d) Tang, Y.; Oppenheimer, J.; Song, Z.; You, L.; Zhang, X.; Hsung, R. P. *Tetrahedron* **2006**, *62*, 10785–10813; (e) Larrosa, I.; Romea, P.; Urpí, F. *Tetrahedron* **2008**, *64*, 2683–2723.
2. For reviews on asymmetric organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726–3748; (b) List, B. *Tetrahedron* **2002**, *58*, 5573–5590; (c) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481–2495; (d) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (e) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724; (f) List, B. *Chem. Commun.* **2006**, 819–824; (g) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001–2011; (h) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496–7504; (i) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876–7880; (j) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8–27; (k) de Figueiredo, R. M.; Christmann, M. *Eur. J. Org. Chem.* **2007**, 2575–2600; (l) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581; (m) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797–5815; (n) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701–1716; (o) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299–365; (p) Vicario, J. L.; Badia, D.; Carrillo, L. *Synthesis* **2007**, 2065–2092; (q) Pellisier, H. *Tetrahedron* **2007**, *63*, 9267–9331; (r) Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2008**, *47*, 42–47; (s) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638–4660; (t) Enders, D.; Narine, A. A. *J. Org. Chem.* **2008**, *73*, 7857–7870; (u) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037–2046; (v) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632–653; (w) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583–1614; For special issues dealing with asymmetric organocatalysis, see: (x) *Acc. Chem. Res.*; Houk, K. N., List, B., Eds.; 2004; Vol. 37, pp 487–621; (y) *Tetrahedron*; Kočovský, P., Malkov, A. V., Eds.; 2006; 62, pp 255–502; (z) *Chem. Rev.*; List, B., Ed.; 2007; Vol. 107, pp 5413–5883.
3. (a) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326–1328; (b) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534–541.
4. (a) Stetter, H.; Schreckenberg, M. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 81; (b) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639–648.
5. Ciganek, E. *Synthesis* **1995**, 1311–1314.
6. Enders, D.; Breuer, K.; Runsik, J. *Helv. Chim. Acta* **1996**, *79*, 1899–1902.
7. Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298–10299.
8. Kerr, M. S.; Rovis, T. *Synlett* **2003**, 1934–1936.
9. Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* **2004**, 2025–2035.
10. (a) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876–8877; (b) Moore, J. L.; Kerr, M. S.; Rovis, T. *Tetrahedron* **2006**, *62*, 11477–11482.
11. Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284–6289.
12. Read de Alaniz, J.; Kerr, M. S.; Moore, J. L.; Rovis, T. *J. Org. Chem.* **2008**, *73*, 2033–2040.
13. Cullen, S. C.; Rovis, T. *Org. Lett.* **2008**, *10*, 3141–3144.
14. Mennen, S. M.; Blank, J. T.; Tran-Dubé, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195–197.
15. Mangion, I. K.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696–3697.
16. Rueping, M.; Sugiono, E.; Merino, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3046–3049.
17. Rueping, M.; Sugiono, E.; Merino, E. *Chem.—Eur. J.* **2008**, *14*, 6329–6332.
18. Rueping, M.; Merino, E.; Sugiono, E. *Adv. Synth. Catal.* **2008**, *350*, 2127–2131.
19. Franke, P. T.; Richter, B.; Jørgensen, K. A. *Chem.—Eur. J.* **2008**, *14*, 6317–6321.
20. Zhu, M.-K.; Wei, Q.; Gong, L.-Z. *Adv. Synth. Catal.* **2008**, *350*, 1281–1285.
21. Chandrasekhar, S.; Mallikarjun, K.; Pavankumarreddy, G.; Veeramohana Raob, K.; Jagadeeshb, B. *Chem. Commun.* **2009**, 4985–4987.
22. Rueping, M.; Kuenkel, A.; Tato, F.; Bats, J. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 3699–3702.
23. (a) Tozawa, T.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2006**, *35*, 56–57; (b) Tozawa, T.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2006**, *35*, 360–361; (c) Mukaiyama, T.; Nagao, H.; Yamane, Y. *Chem. Lett.* **2006**, *35*, 916–917; (d) Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2006**, *35*, 1398–1399; (e) Tozawa, T.; Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Asian. J.* **2007**, *2*, 123–134.
24. Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3107–3110.
25. Lu, H.-H.; Liu, H.; Wu, W.; Wang, X.-F.; Lu, L.-Q.; Xiao, W.-J. *Chem.—Eur. J.* **2009**, *15*, 2742–2746.
26. Enders, D.; Niemeier, O.; Raabe, G. *Synlett* **2006**, 2431–2434.
27. Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3492–3494.
28. Hazelard, D.; Ishikawa, H.; Hashizume, D.; Koshino, H.; Hayashi, Y. *Org. Lett.* **2008**, *10*, 1445–1448.
29. Ramachary, D. B.; Sakthidevi, R. *Chem.—Eur. J.* **2009**, *15*, 4516–4522.
30. Ishikawa, T.; Oku, Y.; Tanaka, T.; Kumamoto, T. *Tetrahedron Lett.* **1999**, *40*, 3777–3780.
31. (a) Tanaka, T.; Kumamoto, T.; Ishikawa, T. *Tetrahedron Lett.* **2000**, *41*, 10229–10232; (b) Tanaka, T.; Kumamoto, T.; Ishikawa, T. *Tetrahedron: Asymmetry* **2000**, *11*, 4633–4637.
32. Sekino, E.; Kumamoto, T.; Tanaka, T.; Ikeda, T.; Ishikawa, T. *J. Org. Chem.* **2004**, *69*, 2760–2767.
33. Merschaert, A.; Delbeke, P.; Daloze, D.; Dive, G. *Tetrahedron Lett.* **2004**, *45*, 4697–4701.
34. Biddle, M. M.; Lin, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3830–3831.
35. Dittmer, C.; Raabe, G.; Hintermann, L. *Eur. J. Org. Chem.* **2007**, 5886–5898.
36. Saito, N.; Ryoda, A.; Nakanishi, W.; Kumamoto, T.; Ishikawa, T. *Eur. J. Org. Chem.* **2008**, 2759–2766.
37. Govender, T.; Hojabri, L.; Moghaddam, F. M.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2006**, *17*, 1763–1767.
38. (a) Sundén, H.; Ibrahem, I.; Zhao, G.- L.; Eriksson, L.; Córdova, A. *Chem.—Eur. J.* **2007**, *13*, 574–581; (b) Ibrahem, I.; Sundén, H.; Rios, R.; Zhao, G.- L.; Córdova, A. *Chimia* **2007**, *61*, 219–223.
39. Li, H.; Wang, J.; E-Nunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. *Chem. Commun.* **2007**, 507–509.
40. Rios, R.; Sundén, H.; Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 2181–2184.
41. Díez, D.; Núñez, M. G.; Benéitez, A.; Moro, R. F.; Marcos, I. S.; Basabe, P.; Broughton, H. B.; Urones, J. G. *Synlett* **2009**, 390–394.
42. Zu, L.; Zhang, S.; Xie, H.; Wang, W. *Org. Lett.* **2009**, *11*, 1627–1630.
43. Kotame, P.; Hong, B.-C.; Liao, J.-H. *Tetrahedron Lett.* **2009**, *50*, 704–707.

44. Liu, K.; Chougnet, A.; Woggon, W.-D. *Angew. Chem., Int. Ed.* **2008**, *47*, 5827–5829.
45. Huang, Y.; Rawal, V. H. *Org. Lett.* **2000**, *2*, 3321–3323.
46. Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662–9663.
47. For DFT studies on the catalytic role of HB donor solvents in the *oxo*-HDA between acetone and Rawal's diene see: (a) Domingo, L. R.; Andrés, J. *J. Org. Chem.* **2003**, *68*, 8662–8668; (b) Polo, V.; Domingo, L. R.; Andrés, J. *J. Phys. Chem. A* **2005**, *109*, 10438–10444.
48. Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146.
49. Unni, A. K.; Takenak, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336–1337.
50. Du, H.; Zhao, D.; Ding, K. *Chem.—Eur. J.* **2004**, *10*, 5964–5970.
51. Zhang, X.; Du, H.; Wang, Z.; Wu, Y.-D.; Ding, K. *J. Org. Chem.* **2006**, *71*, 2862–2869.
52. Gordillo, R.; Dudding, T.; Anderson, C. D.; Houk, K. N. *Org. Lett.* **2007**, *9*, 501–503.
53. Anderson, C. D.; Dudding, T.; Gordillo, R.; Houk, K. N. *Org. Lett.* **2008**, *10*, 2749–2752.
54. Harriman, D. J.; Deslongchamps, G. *J. Mol. Model.* **2006**, *12*, 793–797.
55. Harriman, D. J.; Lambropoulos, A.; Deslongchamps, G. *Tetrahedron Lett.* **2007**, *48*, 689–692.
56. Villano, R.; Acocella, M. R.; Massa, A.; Palombi, L.; Scettri, A. *Tetrahedron Lett.* **2007**, *48*, 891–895.
57. Tonoi, T.; Mikami, K. *Tetrahedron Lett.* **2005**, *46*, 6355–6358.
58. Zhuang, W.; Poulse, T. B.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 3284–3289.
59. Rajaram, S.; Sigman, M. S. *Org. Lett.* **2005**, *7*, 5473–5475.
60. Jensen, K. H.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 4748–4750.
61. Friberg, A.; Olsson, C.; Ek, F.; Berg, U.; Frejd, T. *Tetrahedron: Asymmetry* **2007**, *18*, 885–891.
62. Akalay, D.; Dürner, G.; Bats, J. W.; Bolte, M.; Göbel, M. W. *J. Org. Chem.* **2007**, *72*, 5618–5624.
63. Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498–1501.
64. Samanta, S.; Krause, J.; Mandal, T.; Zhao, C.-G. *Org. Lett.* **2007**, *9*, 2745–2748.
65. Zhao, Y.; Wang, X.-J.; Liu, J.-T. *Synlett* **2008**, 1017–1020.
66. Lu, L.-Q.; Xing, X.-N.; Wang, X.-F.; Ming, Z.-H.; Wang, H.-M.; Xiao, W.-J. *Tetrahedron Lett.* **2008**, *49*, 1631–1635.
67. He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088–15089.
68. He, M.; Beahm, B. J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 3817–3820.
69. Zhang, Y.-R.; Lv, H.; Zhou, D.; Ye, S. *Chem.—Eur. J.* **2008**, *14*, 8473–8476.
70. Tiseni, P. S.; Peters, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 5325–5328.

Biographical sketch

David Diez received his B.Sc. in Chemistry in 1980 at the University of Salamanca in 1982. In 1986 he completed his PhD in the same University under the supervision of Professor J. G. Urones and Dr. I. S. Marcos. Then, he spent a postdoctoral stay (1988–1990, British Council Fellowship) with Professor Steven V. Ley at Imperial College of Science, Technology and Medicine (London). He became Associate Professor in 1991 at the University of Salamanca and full Professor in 2008 at the same University. He is co-author of more than 120 papers and he acts as referee for international scientific journals. His current research interests are focused in the transformation of natural products into biological active compounds, chemistry of cyclopropanes, sulfones, tetrahydropyrans, chiral amides and recently in organocatalysis.

Pilar García García was born in Salamanca and was graduated in the hometown University in 2000. She completed her Ph.D. in 2006 at the University of Salamanca, under the supervision of Prof. David Diez, Dr. N. M. Garrido and Prof. J. G. Urones. She spent postdoctoral stays with Professor David W. C. MacMillan in 2007 at Princeton University and with Professor Benjamin List in 2008 at Max-Planck Institut für Kohlenforschung. From 2005 till 2009, she was assistant professor in the Chemistry Department at the University of Salamanca. At present, she is working again in the group of Prof. Benjamin List. Her current research interest is focused on the development of asymmetric catalytic procedures.

Rosalina Fernández-Moro got her PhD in Organic Chemistry, Universidad de Salamanca in 1986 under the supervision of Professor J. G. Urones and Dr. P. Basabe. Then she carried out her postdoctoral research with Professor Steven V. Ley at Imperial College of Science, Technology and Medicine of London (1989–1991), obtaining the D.I.C. in September 1991. Currently she is Associate Professor in Organic Chemistry at the University of Salamanca, where she is researching on synthesis of bioactive compounds and organocatalysis.

Marta G. Núñez received her B.Sc in chemistry and her M.Sc in Organic Chemistry from the University of Salamanca, where she completed her Ph.D. on the synthesis and uses of chiral tetrahydropyrans and pyrrolidines under the supervision of Professor David Díez, Dr. R. F. Moro and Prof. J. G. Urones in 2008. Her research interests are focused on the development of new synthetic methodologies and their application to the stereoselective synthesis of natural products and biologically interesting targets.