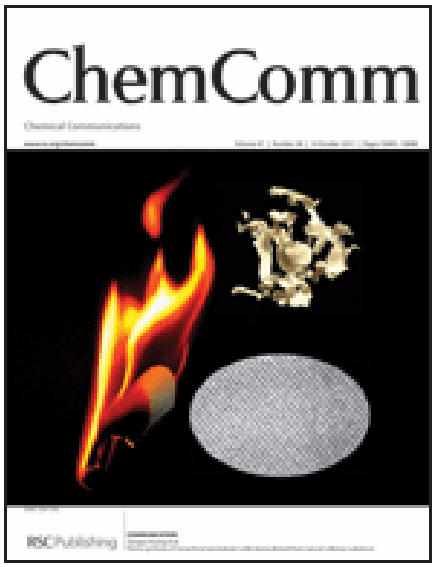

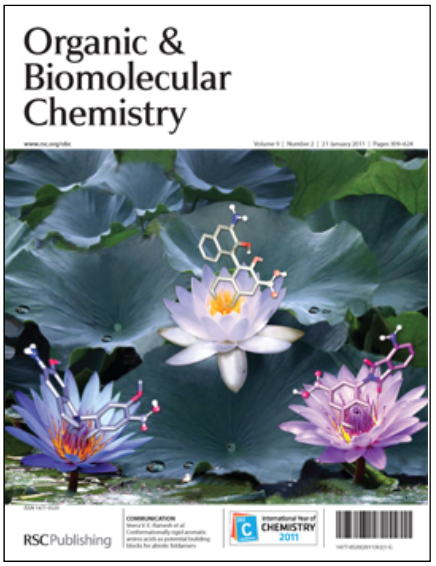

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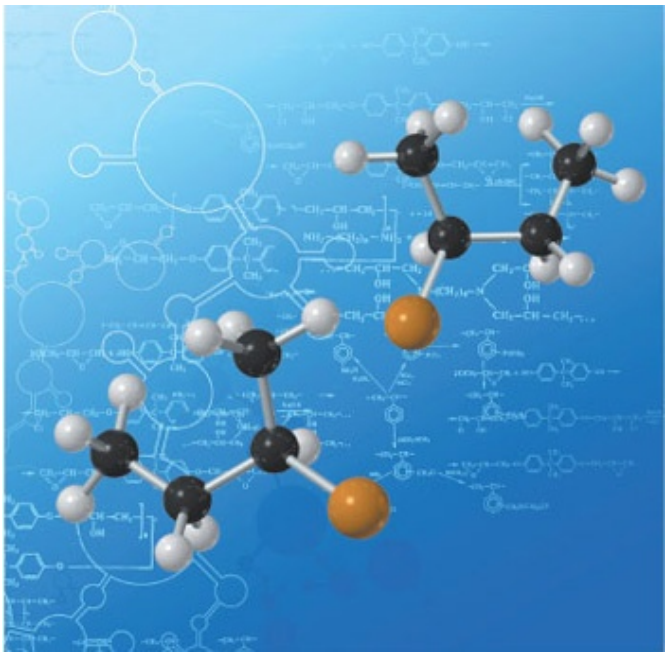

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EMERGING AREA

Asymmetric organocascades involving the formation of two C–heteroatom bonds from two distinct heteroatoms†

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In the vast and expanding world of enantioselective organocascades, the ones in which two C–heteroatom bonds are created from two distinct heteroatoms are rare. These fascinating domino processes constitutes real synthetic challenges and allow very convenient syntheses of diverse optically active heterocycles and also highly functionalised acyclic derivatives.

Introduction

The development of organocascades, *i.e.* organocatalytic domino reactions, is an exciting and very fast-growing area of research combining advantages in terms of synthetic efficiency and eco-compatibility.[1] Such chemical processes are conceptually the closest man-made transformations to the enzymes-mediated ones used by Nature for the synthesis of natural products.[2] While numerous successful organocascades involving the formation of several carbon–carbon (C–C) and carbon heteroatom (C–X) bonds have been developed so far,[3] enantioselective organocascades in which two C–X bonds are created from two distinct heteroatoms are rarely reported. Although less studied, these sequences are yet of high and general interest since they allow direct, efficient and selective access to important chiral building blocks or various heterocycles prevalent in complex natural products. Thus, their development constitutes a fascinating current challenge of general importance. Herein, we highlight the recent elegant and innovative contributions to this growing field starting from achiral precursors and involving various activation modes. Two major complementary strategies have been proposed depending on whether the two heteroatoms are provided by the same substrate or by two different heteroatomic partners.

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Damien Bonne was born in Epinal (France) in 1979. After studying chemistry at the Ecole Supérieure de Chimie de Lyon (CPE Lyon, France), he completed his PhD in 2006 under the supervision of Prof. Jieping Zhu working on isocyanide-based multicomponent reactions. He then moved to the University of Bristol (UK) to join the group of Prof. Varinder A. Aggarwal as a post-doctoral associate. Since 2007 he has been working as a assistant professor with Prof. Jean Rodriguez at the University Paul Cézanne in Marseille (France). His research interests include the development of new asymmetric organocatalysed methodologies and their application in stereoselective synthesis.

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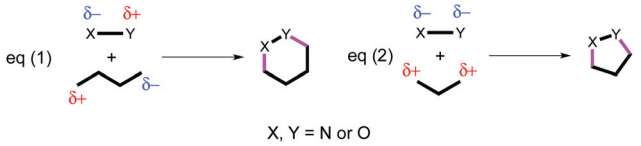
Thierry Constantieux was born in Pau, France, on 6 May 1968. After studying chemistry at the University Bordeaux I, he completed his PhD under the supervision of Dr J.-P. Picard and Dr J. Dunoguez in 1994. He completed his Habilitation in 2004, at the University Paul Cézanne, in Marseille, where he is currently Professor of Organic Chemistry. His main research interest is focused on the development of new eco-compatible synthetic methodologies, especially enantioselective organocatalyzed cascades and domino multicomponent reactions from 1,3-dicarbonyl compounds, and their applications in heterocyclic chemistry.



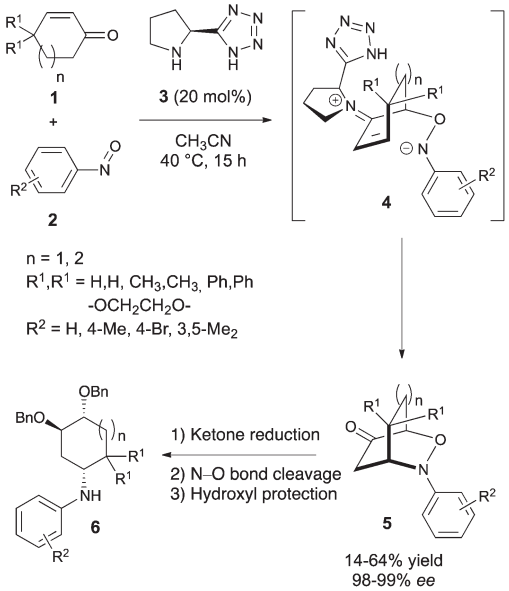
Scheme 1 Six- and five-membered rings by creation of two C–X bonds.

First strategy

The main strategy typically involves the consecutive creation of the two carbon–heteroatom bonds from a bi-heteroatomic reagent (X–Y) acting both as electrophile and nucleophile leading to six-membered rings (Scheme 1, eqn (1)), or as bis-nucleophile (Scheme 1, eqn (2)) giving rise to pentacyclic products.

The first very efficient example was reported by Yamamoto and co-workers in 2004 for the one-pot synthesis of 2-aza-3-oxa-bicycloketones **5** precursors of optically pure 1-amino-3,4-diols. They developed an asymmetric *O*-nitroso aldol/aza-Michael reaction from cyclohexenones **1** and aromatic nitroso compounds **2** as ambident *O*-electrophilic–*N*-nucleophilic reaction partners with proline-tetrazole **3** as catalyst under enamine/iminium activation (Scheme 2).[4] The bridged heterocycles **5** were thus synthesised by successive formation of a C–O and a C–N bonds with an excellent regioselectivity and a very high level of enantiocontrol. The products **5** could be easily transformed into 1-amino-3,4-diols **6** by sequential diastereoselective reduction of the ketone function followed by cleavage of the N–O bond.

Two years later, the same group reported that the regioselectivity of this cascade could be totally inverted by simply reacting preformed dieneamine **7** and nitroso derivatives **2** involving a Brønsted acid activation with the binol-based catalyst **8**. Thus,



Scheme 2 Enantioselective *O*-nitroso aldol/aza-Michael organocascade.

this asymmetric *N*-nitroso aldol/oxa-Michael cascade afforded the corresponding 3-aza-2-oxa-bicycloketones **9** with excellent regioselectivity and very good enantioselectivity (Scheme 3).[5] In this case, the phenolic protons of the catalyst coordinate the nitroso oxygen atom, leading consequently to the regioselective formation of the carbon–nitrogen bond first, followed by an intramolecular oxa-Michael reaction *via* the transient iminium ion **10**.

In 2008, Zhong and co-workers have applied elegantly the proline-catalysed *O*-nitroso aldol/aza-Michael sequence to the synthesis of functionalised tetrahydro-1,2-oxazines (THOs) **13a** (Scheme 4).[6a] Thus, aryl nitroso derivatives **2** were reacted with bifunctional enemalonate aldehydes **11a**, acting successively as

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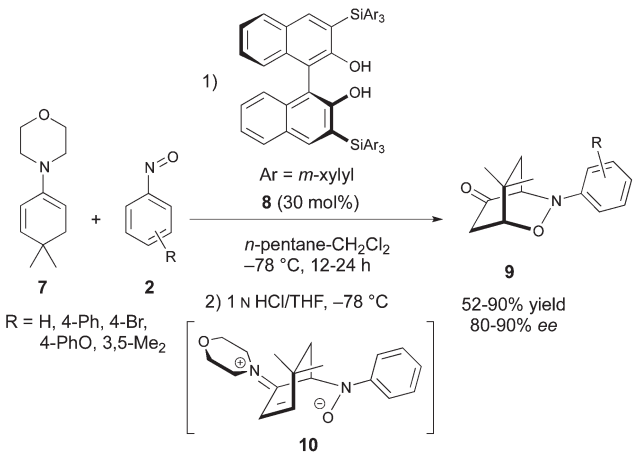
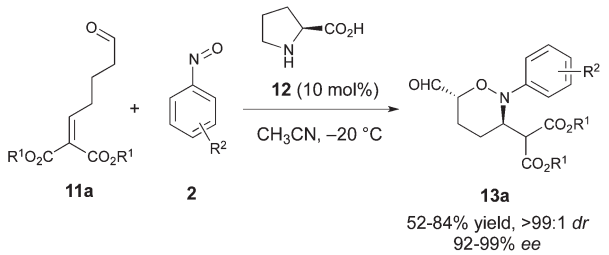
Yoann Coquerel was born in Rouen (France) in 1975. After studying chemistry at the University Joseph Fourier in Grenoble (France) where he completed his PhD in 2001 under the supervision of Prof. Jean-Pierre Deprés, he moved to Florida State University in Tallahassee (USA) to join the group of Prof. Robert A. Holton as a post-doctoral associate. Since 2003, he works as a CNRS researcher with Prof. Jean Rodriguez at Aix-Marseille Université (France). His research interests include the development of multiple bond-forming reactions, organocatalysis, and the total synthesis of natural products.

Jean Rodriguez

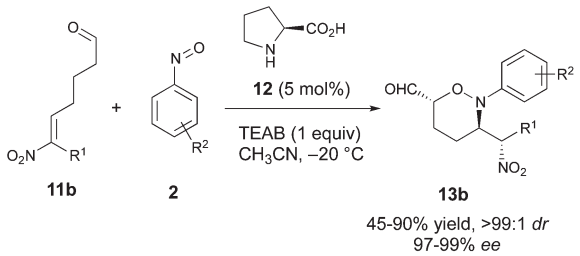
Jean Rodriguez was born in Cieza (Spain) in 1958. After studying chemistry at Aix-Marseille Université (France), he completed his PhD as a CNRS researcher with Prof. Bernard Waegell and Prof. Pierre Brun in 1987. He completed his Habilitation in 1992, at Marseille, where he is currently Professor and Director of the UMR-CNRS-7313-iSm2. His research interests include the development of domino and multicomponent reactions, and their application in stereoselective synthesis. In 1998 he was awarded the ACROS prize in Organic Chemistry, and in 2009 he was awarded the prize of the Division of Organic Chemistry from the French Chemical Society.



Scheme 3 Enantioselective *N*-nitroso aldol/oxa-Michael organocascade.



Scheme 4 Asymmetric aminoxylation/aza-Michael organocascade.

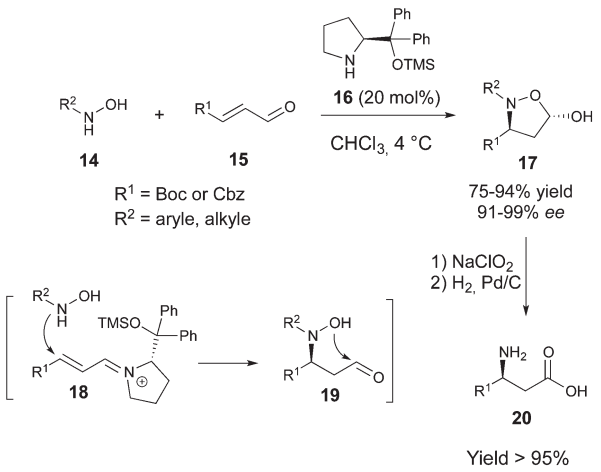


Scheme 5 Proline-catalysed *O*-nitroso aldol/aza-Michael organocascade for the enantioselective synthesis of THOs.

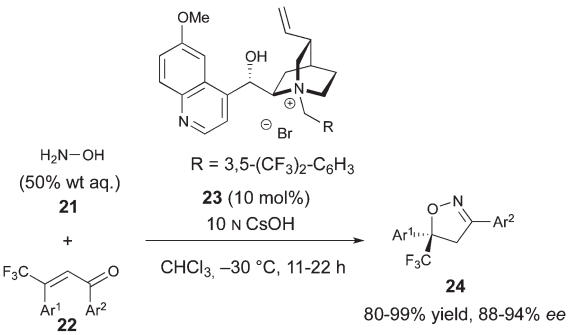
nucleophile *via* its enamine intermediate and as electrophile through the enemalonate moiety. The oxazine products **13a** bearing two stereogenic centres in a 1,4-*trans* relationship, could be obtained in good yields and excellent stereoselectivities.

Exploiting this domino heterocyclisation, the same research group demonstrated that the strategy was also very efficient replacing the enemalonate Michael acceptor by a conjugated nitroalkene moiety allowing the creation and control of a supplementary stereogenic center in the final THOs **13b** (Scheme 5).[6b]

As an alternative to the ambident reactivity of nitroso partners, the dual nucleophilicity of hydroxylamines has been exploited for the selective construction of valuable functionalised hydrooxazoles. Efficient entries to these heterocyclic building blocks have been developed following two complementary directions involving either aza- or oxa-Michael addition in the first step.



Scheme 6 Enantioselective aza-Michael/hemiacetalisation organocascade.

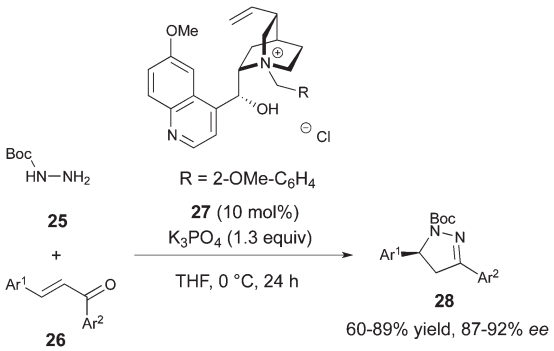


Scheme 7 Asymmetric oxa-Michael/5-*exo-trig* dehydrative cyclisation organocascade.

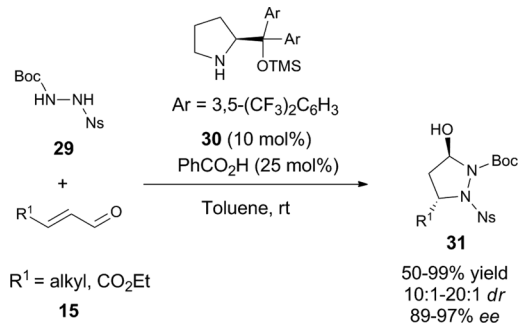
Thus, Córdova and co-workers proposed a simple and efficient chemo- and enantioselective access to 5-hydroxyisoxazolidines **17** based on iminium activation of unsaturated aldehydes **15** with diphenylprolinol silyl ether **16** as the organocatalyst (Scheme 6).[7] The domino reaction is initiated by an aza-Michael addition of *N*-protected hydroxylamines **14** to the iminium ions **18**, and subsequent hemiacetalisation of aldehyde intermediates **19**, giving the desired isoxazolidines **17**, which can easily be transformed into β-amino acids **20** in two steps.

Alternatively, Shibata's group synthesised optically active trifluoromethyl-substituted 2-isoxazolines **24** using a conceptually similar approach, but developed under phase transfer catalysis (PTC) conditions with the cinchona alkaloid salt **23** (Scheme 7).[8] In this case, the chiral ion pair formed with aqueous hydroxylamine (**21**) evolves by an oxa-Michael reaction to the β-trifluoromethyl enone **22** followed by a 5-*exo-trig* dehydrative cyclisation of the NH_2 moiety on the carbonyl function.

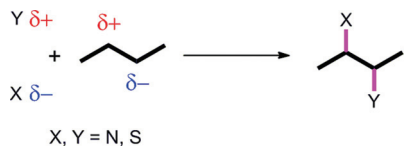
Contemporaneously, Brière and co-workers described a related PTC methodology with organocatalyst **27** for the synthesis of enantiomerically enriched pyrazolines **28**.[9,10] To access these biologically relevant important scaffolds in high yield and very good enantioselectivity, they disclosed the first organocatalytic activation of *N*-Boc hydrazines **25** reacting smoothly with



Scheme 8 Asymmetric aza-Michael/5-*exo-trig* dehydrative cyclisation organocascade.



Scheme 9 Enantioselective aza-Michael/hemiaminalisation organocascade.



Scheme 10 Alternative strategy for creating two C–X bonds from two distinct heteroatoms.

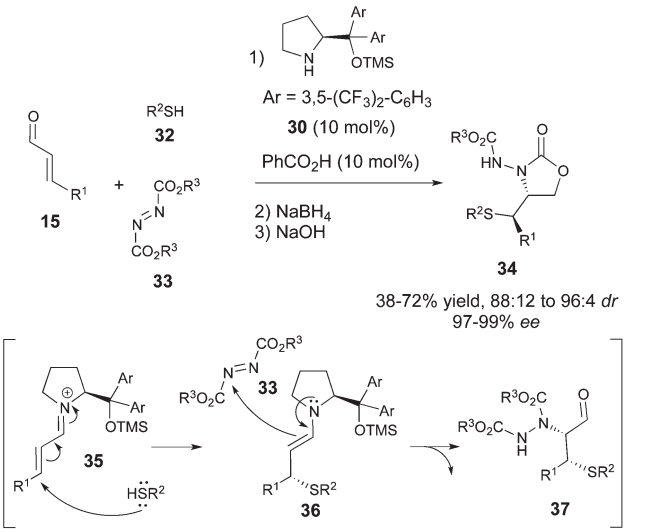
chalcones **26** through a similar asymmetric aza-Michael/cyclocondensation organocascade (Scheme 8).

A related approach to the pyrazolidine heterocycle has been reported very recently by Vicario and co-workers using α,β-unsaturated aldehydes **15** and *N*,*N*′-disubstituted hydrazines **29** under iminium activation with diarylprolinol silyl ether **30** as the organocatalyst (Scheme 9).[11] The domino enantioselective aza-Michael/hemiaminalisation reaction allowed the formation of the desired pyrazolidin-3-ol **31** in excellent yields, regio- and stereoselectivities. These products could be easily transformed into the corresponding pyrazoline by sequential deprotection/dehydration or oxidised to the pyrazolidin-3-ones.

Second strategy

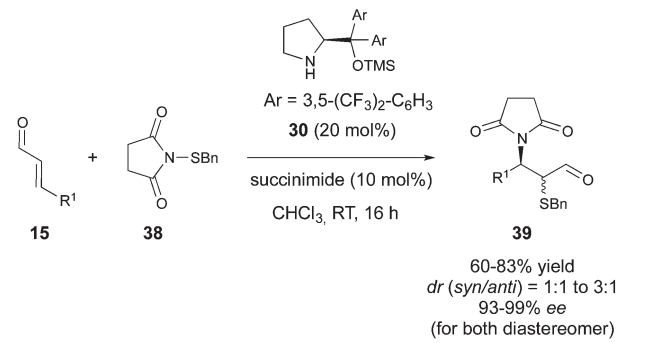
A conceptually different and complementary strategy for such organocascades consists in the use of two different nucleophilic or electrophilic hetero reactants that lead to the formation of the two different C–heteroatom bonds (Scheme 10). Notably, in the final products of these domino reactions, the heteroatoms X and Y are not bonded to each other as it was the case in the above methodologies.

Jørgensen and co-workers exploited this approach in 2005 by designing a three-component reaction involving iminium/enamine activation (Scheme 11).[12] They demonstrated that thiols **32** can initiate the sequence by a thia-Michael addition to the iminium intermediate **35** followed by *in situ* selective α-amination of the transient enamine **36** with azodicarboxylates **33**. The resulting α,β-difunctionalised aldehydes **37** were not isolated but directly reduced and cyclised to the corresponding oxazolidinones **34** in nearly optically pure form.



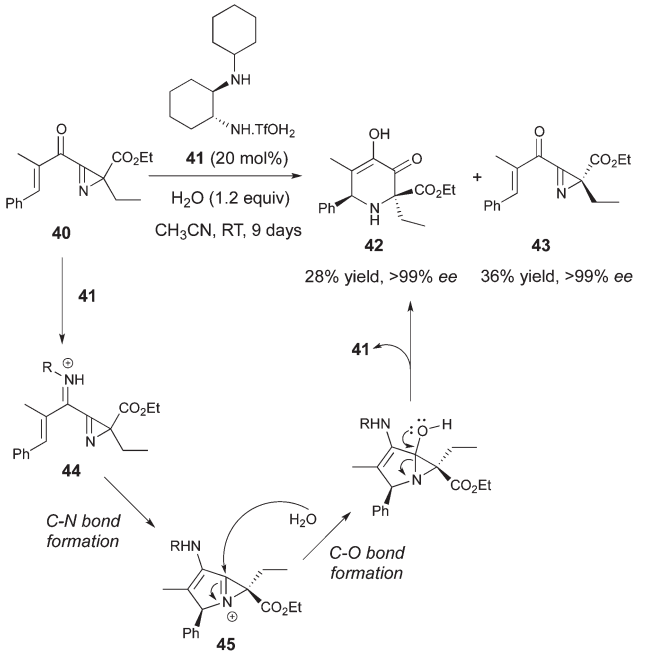
Scheme 11 Enantioselective thia-Michael/α-amination organocascade.

A related two-component α,β-difunctionalisation of enals **15** consists in linking both the nucleophilic and the electrophilic heteroatom as in *N*-(benzylthio)succinimide **38** (Scheme 12). Córdova and co-workers have described this achievement in 2008.[13] They developed an efficient aza-Michael initiated highly enantioselective β-amino-α-sulfenylation with diarylprolinol silyl ether organocatalyst **30** leading to the corresponding difunctionalised aldehydes **39** in good yields albeit with low diastereoselectivities.



Scheme 12 Enantioselective aza-Michael/sulfenylation organocascade.

Finally, the last domino reaction we present here is the unusual asymmetric aza-Nazarov cyclization of azirine **40**



Scheme 13 Organocatalytic asymmetric aza-Nazarov cyclisation.

organocatalysed by the 1,2-diaminocyclohexane derivative **41** described by Tius and co-workers in 2010 (Scheme 13).[14] The overall process conducted in the presence of water, ends with the formation of one C–N and one C–O bonds leading to functionalised piperidone **42** in only 28% yield but up to 99% ee, after an efficient kinetic resolution. The C–N bond is formed first by an intramolecular enantioselective aza-Michael reaction to the iminium intermediate **44** while the C–O bond results from trapping the transient cyclic iminium **45** by a molecule of water.

Conclusion

These contributions to the field of asymmetric organocascades involving the participation of two heteroatoms show the high synthetic potential of all the complementary strategies developed so far. A good control of the regioselectivity and a valuable chemical diversity can be reached by selection of specific activation modes, leading either to five- and six-membered rings or functionalised acyclic intermediates. The general interest of optically active scaffolds bearing two heteroatoms will help this field growing rapidly and many other ingenious organocascade reactions should appear in a near future.

Acknowledgements

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