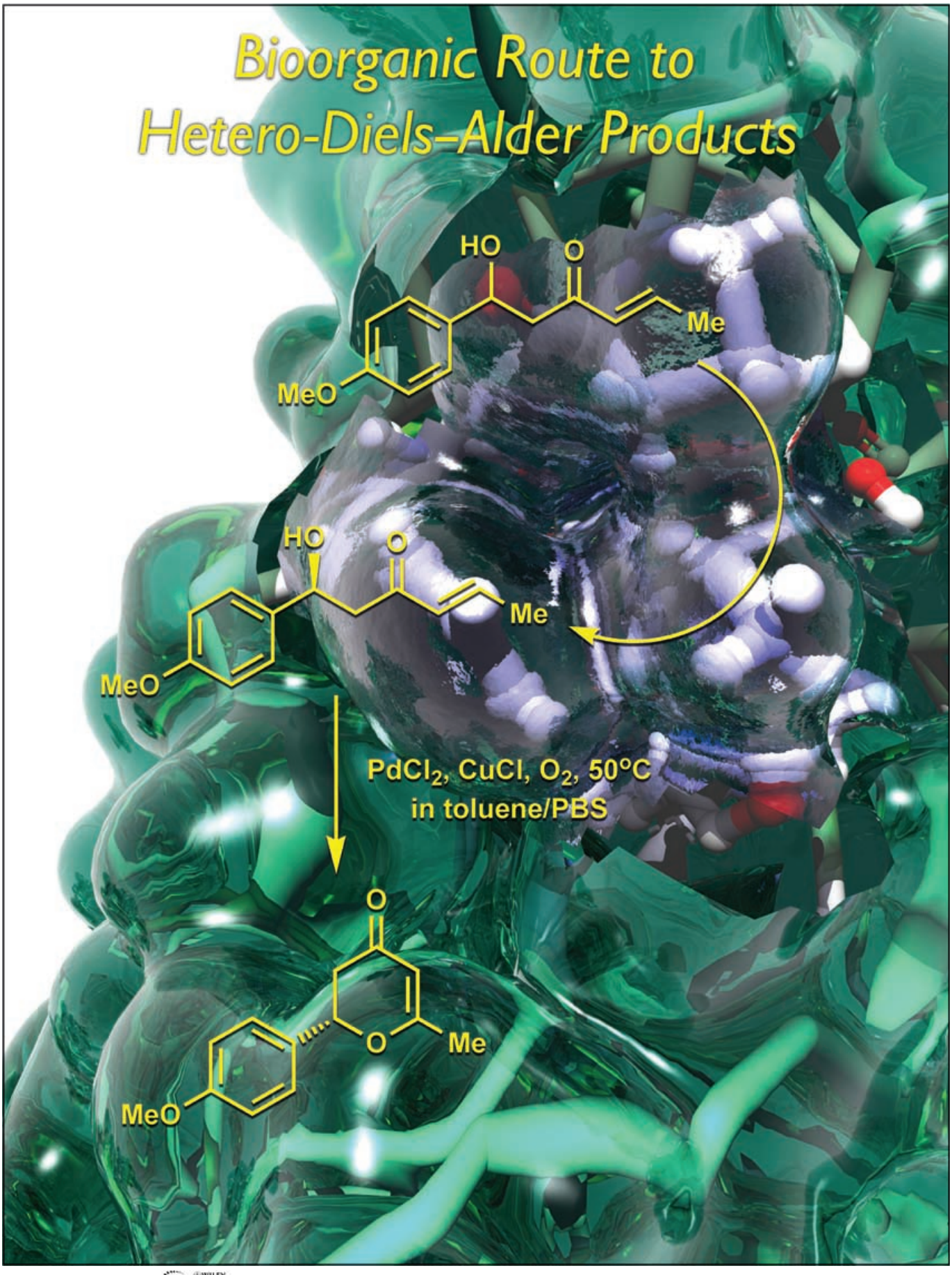

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Biocatalytic Approaches to Hetero-Diels–Alder Adducts of Carbonyl Compounds

Véronique Gouverneur* and Maud Reiter[a]

Abstract: Very little information is available on hetero-Diels–Alderases for the assembly of heterocyclic products despite the synthetic value of these [4+2] cycloadditions. Hetero-Diels–Alderase antibodies raised against a bicyclic transition state analogue have been generated for the cycloaddition of ethylglyoxylate with an all-carbon diene. More recently, a conceptually novel biocatalytic approach to hetero-Diels–Alder (HDA) adducts derived from carbonyl dienophiles has been developed mirroring a stepwise aldol Michael mechanism instead of a concerted pathway. In this approach, the two key steps are an antibody-mediated kinetic resolution of β-hydroxyenones and a subsequent ring-closure process. An attractive feature of this methodology is the possibility to convert the enantioenriched aldol intermediates into tetrahydropyranones or dihydropyranones. This bioorganic route is best applied for the preparation of enantioenriched HDA adducts derived from poorly electrophilic acceptors, therefore complementing existing catalytic routes to these adducts based on the use of small organocatalysts or chiral Lewis acids.

Keywords: antibodies · Diels–Alder reaction · enzyme catalysis · heterodienophiles · palladium

Introduction

Cycloaddition reactions involving carbonyl compounds as the heterodienophiles with all-carbon dienes have allowed the preparation of numerous six-membered oxygen-containing heterocycles. Typical products are substituted di- and tetrahydropyran rings, which are frequently occurring structural motifs in biologically active natural products.[1] In comparison with other short and efficient approaches to these compounds, such as the Prins cyclization,[2] it is the hetero-Diels–Alder (HDA) reaction that is the most widely used, probably because numerous studies have established its great synthetic value. This methodology allows for the construction of primary adducts possessing up to three stereogenic centres and as a result, numerous chiral HDA catalysts have been developed attempting to control the stereochemical outcome of the cycloadduct. Chiral Lewis acid catalysts based on aluminium, boron and copper have provided new opportunities for enantioselective cycloadditions allowing for the use of both activated and unactivated aldehydes as well as ketones.[1] Hydrogen bonding of a simple chiral alcohol to a carbonyl group can also be exploited as a mode of activation for HDA chemistry and complements alternative asymmetric catalytic strategies.[3] The Diels–Alder reaction had been regarded as one of the most powerful man-invented transformations until the mid-nineties, when an increasing amount of data suggested that nature had also evolved catalysts for this valuable transformation.[4] Today, we have unambiguous proof that natural enzymes are capable of catalyzing Diels–Alder reactions[4c] and an increasing number of publications have reported elegant biomimetic approaches to Diels–Alder type intermediates or products.[5] In addition, with the advent of catalytic antibody technology[6] and the discovery that RNA[7] can also act as a biocatalyst, biomolecules have been generated that are capable of catalyzing various Diels–Alder reactions and of controlling the stereochemical outcome of the products.[8] Surprisingly, only an extremely limited number of biocatalytic approaches to HDA adducts is known in comparison with the biocatalytic routes available for the preparation of all-carbon cycloadducts.

This article will first comment on the main strengths and weaknesses of small molecule or metal-mediated catalysts available for hetero-Diels–Alder chemistry, in which carbonyl compounds act as heterodienophiles. It will then go on to highlight how biocatalytic approaches can address some pending problems in HDA chemistry. The major conceptual

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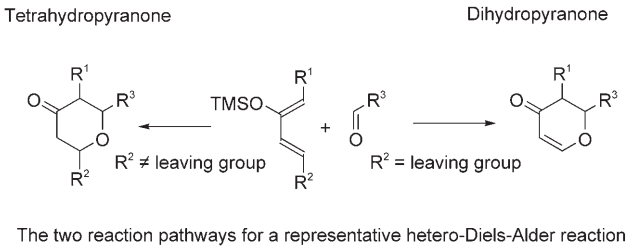
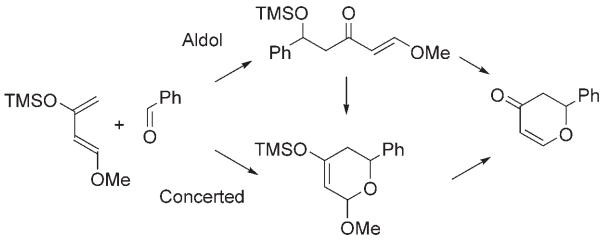
advance presented in this paper is the use of both metal and biological catalysts for the preparation of hetero-Diels–Alder adducts more difficult to access using alternative catalytic methods.

Lewis Acid-Mediated and Organocatalytic Hetero-Diels–Alder Reactions of Carbonyl Heterodienophiles

Two mechanisms can operate for asymmetric metal-catalyzed HDA reactions with carbonyl dienophiles; either a stepwise aldol Michael mechanism, featuring an enantioenriched aldol product as the key intermediate, or a concerted reaction, often involving an unsymmetrical transition state. Several parameters define which mechanism will take place and what the stereochemical outcome of the reaction product will be. These include the nature of the catalyst, the solvent and the structural features of the reactants (Scheme 1).[9]



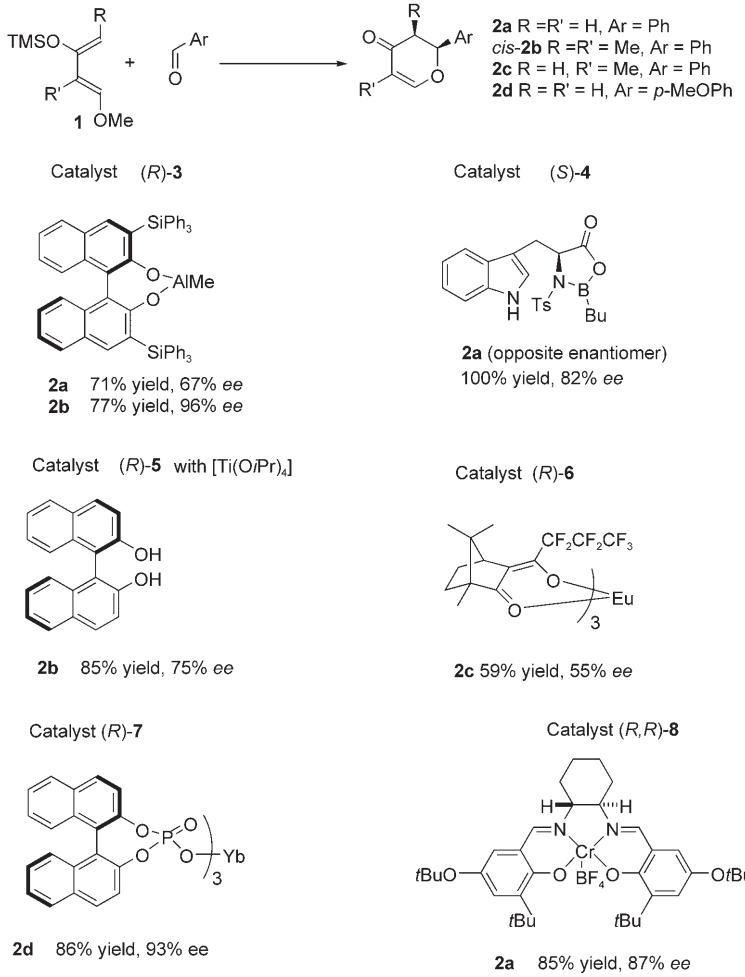
The two reaction pathways for a representative hetero-Diels-Alder reaction



Scheme 1. The products and the two mechanistic pathways for the hetero-Diels–Alder reaction of a carbonyl heterodienophile with a representative diene.

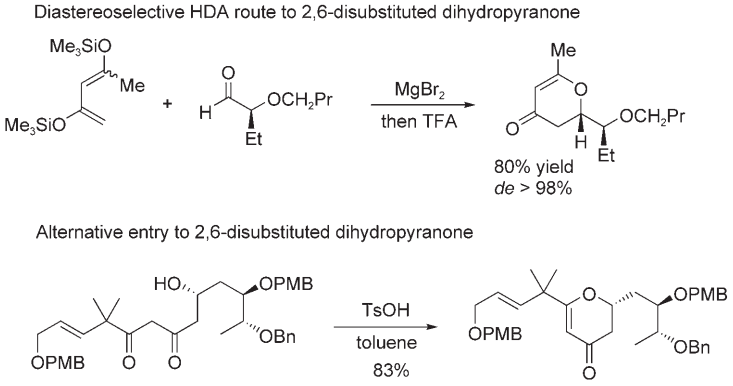
The extraordinary range of applications of enantiopure hetero-Diels–Alder adducts has stimulated the search for efficient chiral catalysts for cycloadditions between dienes and carbonyl dienophiles displaying various levels of reactivity. Many catalysts can accelerate the reaction of unactivated aldehydes with activated dienes (**1**), such as *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene) or *trans*-1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-pentadiene, which possess two strongly donating groups. The corresponding dihydropyranones (**2a**–**d**) were obtained in high yields and with excellent control of regio-, diastereo- and enantioselectivity. These catalysts (**3**–**8**), include chiral aluminium, boron, titanium and chromium complexes, as well as selected lanthanide complexes such as europium or ytterbium derivatives (Scheme 2).[10]

Examples reported in the literature led to dihydropyranones possessing more often one or two substituents. Fewer catalysts are known to deliver di- or trisubstituted dihydropyranones possessing a substituent on the sp^2-hybridized carbon atom attached to the endocyclic oxygen atom. This can be easily



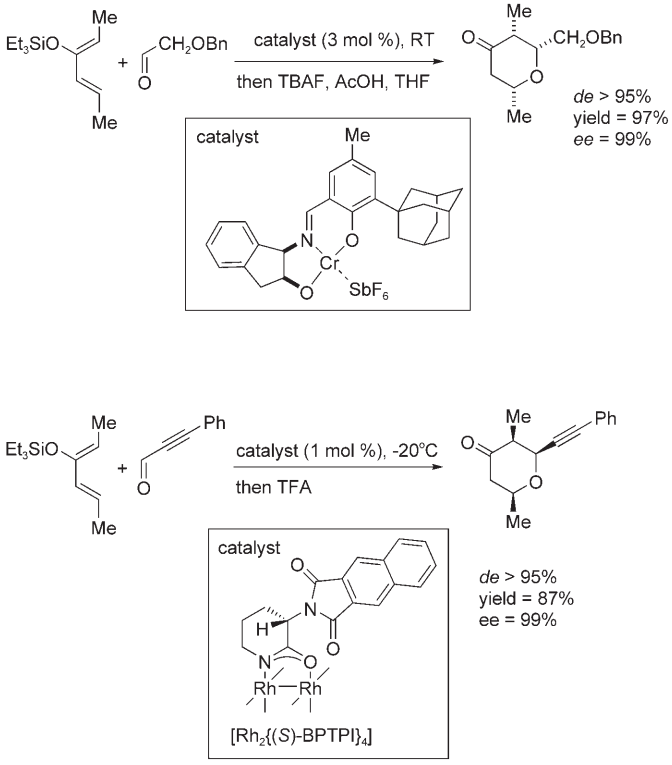
Scheme 2. Chiral Lewis acids for the HDA reaction of activated dienes.

explained by the lower reactivity of the corresponding dienes featuring a doubly substituted terminal carbon atom (one of the substituent being a suitable leaving group) and by the fact that these dienes are less readily available. These adducts are therefore usually prepared by using alternative approaches (Scheme 3).[11]



Scheme 3. Preparation of 2,6-dihydropyranones.

The chiral Lewis acid mediated cycloadditions between unactivated aldehydes with poorly nucleophilic dienes are very challenging and only limited studies have been devoted to solve this problem (Scheme 4). In this context, Jacobsen et al. have reported rare examples of cycloadditions involving various aldehydes with less nucleophilic dienes containing only one activating silyloxy group. They showed that



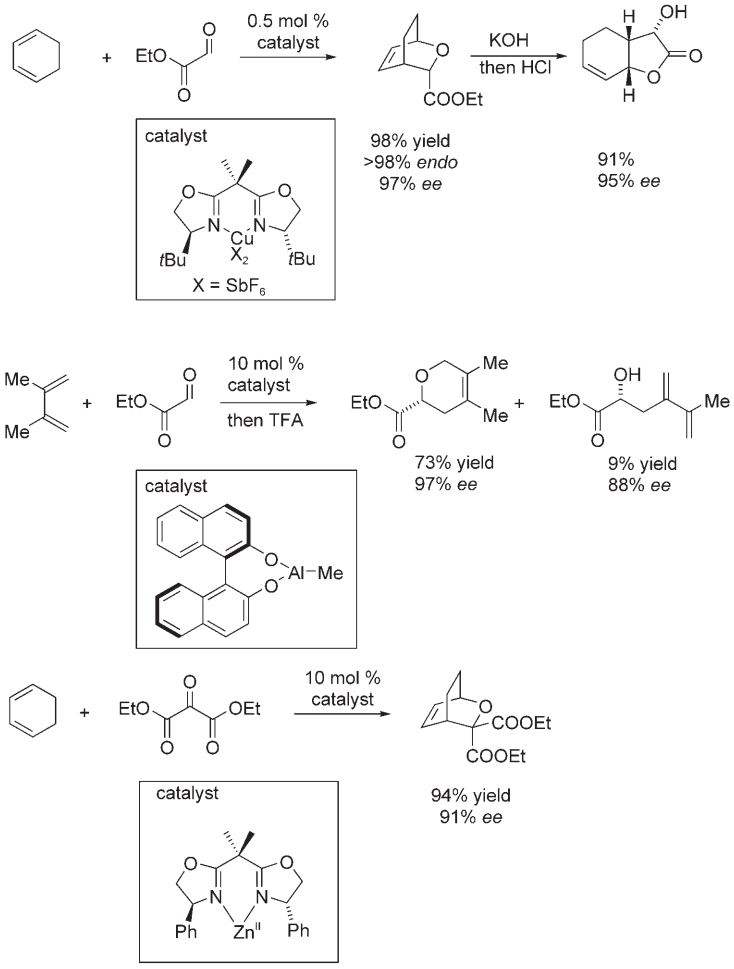
Scheme 4. Chiral chromium(III) and dirhodium(II) complexes as catalysts for HDA involving monooxygenated dienes.

chiral tridentate Schiff base chromium complexes catalyzed the formation of all *syn*-trisubstituted tetrahydropyranones with excellent yields and high diastereomeric and enantiomeric excesses.[12] An alternative catalytic system involving a carboxamidedirhodium(II) complex has also been found to be suitable, allowing for the preparation all-*syn* adducts tetrahydropyranones derived from poorly electrophilic aldehydes including representative alkynals.[13]

Activated aldehydes such as ethylglyoxylate and phenylglyoxal have been successfully engaged in hetero-Diels–Alder reactions and can be combined with electron-rich Danishefsky type dienes or less nucleophilic dienes such as 1,3-cyclohexadiene, isoprene or 2,3-dimethyl-1,3-diene. These reactions are often high yielding, but can give rise to side products resulting from a competitive ene reaction.[1] These activated dienophiles are set up for bidentate coordination and it is this structural feature that has been exploited for asymmetric catalysis. They form well-defined, distorted, square-planar, chiral bis(oxazolinyl) Cu^{II} complexes allowing for the formation of hetero adducts with excellent enantioselective induction.[14] In addition to these copper-based catalysts, chiral aluminum, boron or titanium complexes were found to be suitable catalysts for these activated substrates.[15] In comparison with cycloadditions involving aldehyde as the heterodienophiles, the Diels–Alder reactions of ketones is still a challenge to chemists. Since ketones are less reactive than aldehydes on both steric and electronic grounds, one needs to apply special reaction conditions for the cycloaddition to proceed.[16] Direct catalytic enantioselective hetero-Diels–Alder reactions of activated ketones are possible, making use of copper or zinc bisoxazoline complexes, whereas cycloadditions involving unactivated ketones with dienes are very rare (Scheme 5).[17]

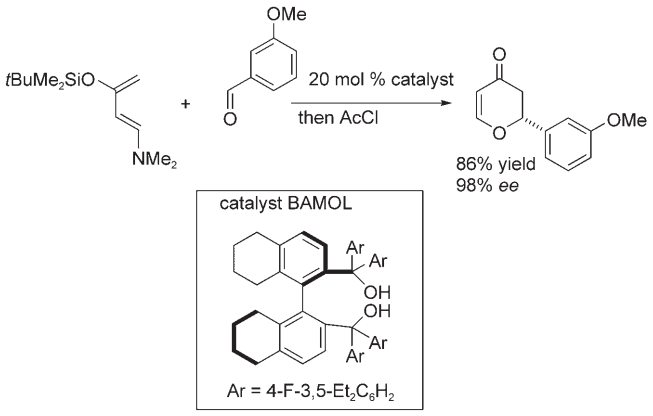
This brief survey reveals that additional catalysts are still to be found for the most demanding transformations featuring poorly activated reactants. The use of α,β-unsaturated carbonyl heterodienophiles is particularly challenging as they can potentially react either as C=C dienophiles or as C=O heterodienophiles. In addition, only limited examples of dihydropyranones possessing two substituents flanking the endocyclic oxygen have been prepared using Diels–Alder chemistry, as these adducts are the Diels–Alder products derived from dienes that are both less accessible and less reactive. Finally, catalysts for the preparation of structurally diverse enantioenriched tetrahydropyranones possessing multiple stereocentres are still rare.

Applying alternative concepts to achieve catalysis, diastereo- and enantioselective induction can potentially address these limitations. In this context, an exciting novel avenue of research has been uncovered by Rawal et al. who have demonstrated that small organic compounds such as TADDOL (TADDOL = tetraaryl-1,3-dioxolane-4,5-dimethanol) and axially chiral biaryl diols are suitable organocatalysts for enantioselective hetero-Diels–Alder reactions. These catalysts activate the heterodienophile through hydrogen bonding.[3,18] Enantiopure adducts derived from the addition of a representative aminosiloxydiene and numerous



Scheme 5. HDA of activated aldehydes and ketones.

electron-rich and electron-poor aldehydes were obtained. These results are significant as, despite its central importance as an organizational force in large biomolecules, the hydrogen bond is recognized as a weak interaction and only a few reports describe how it can be successfully used in asymmetric catalysis (Scheme 6).

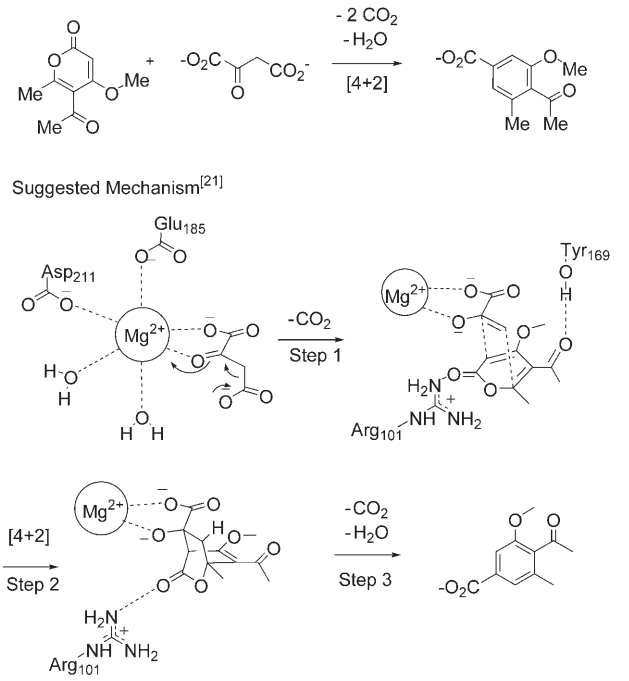


Scheme 6. Organocatalytic asymmetric HDA reaction catalyzed by BAMOL.

Biocatalytic Approaches to Hetero-Diels–Alder Adducts

Biocatalysts operate according to a multitude of mechanisms including metal-mediated activation and multiple noncovalent interactions (such as electrostatic, van der Waals contacts and hydrogen bonds), two modes of activation that were exploited successfully for the design of some of the catalysts outlined previously. Biocatalysts are therefore ideal candidates for the formation of enantioenriched hetero-Diels–Alder adducts, as they additionally provide a binding site that can lock the two reactants in their reactive conformation, therefore lowering the entropic energy barrier. Nevertheless, to date, only three purified or partially purified enzymes have been reported as naturally occurring Diels–Alderases and none of them promote a hetero-Diels–Alder process. Solanopyrone synthase catalyzes the conversion of prosolanopyrone II to solanopyrones A and D by oxidation and subsequent intramolecular Diels–Alder reaction.[19] Fungal lovastatin nonaketide synthase acts as a catalyst for the [4+2] cycloaddition of an intermediate hexaketide triene to generate the decalin system of lovastin.[20] The third example of natural Diels–Alderases is macrophomate synthase (MPS) that mediates the conversion of 2-pyrone derivatives into the corresponding benzoate analogues (Scheme 7).[21]

In addition to natural enzymes, many antibodies and nucleic acid hosts have been generated that catalyze Diels–Alder reactions involving all-carbon dienes and dienophiles, and several theoretical studies have provided quantitative comparisons of the reaction kinetics of these man-made cat-

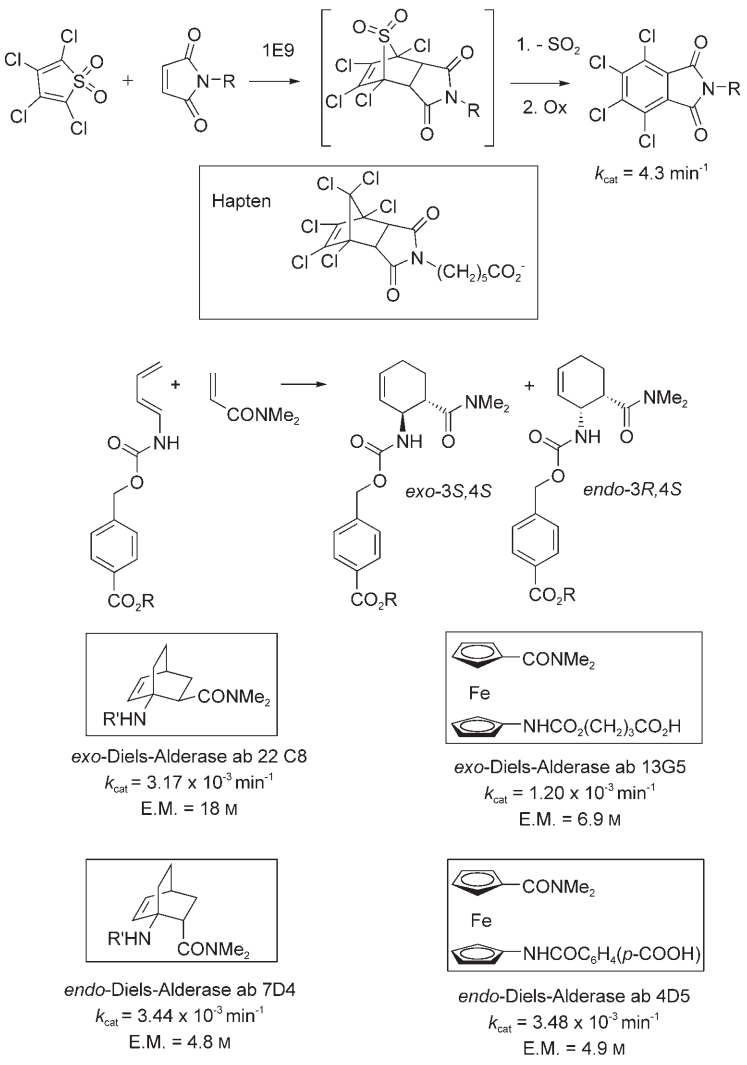


Scheme 7. Mode of action of macrophomate synthase, a natural enzyme displaying Diels–Alderase activity.

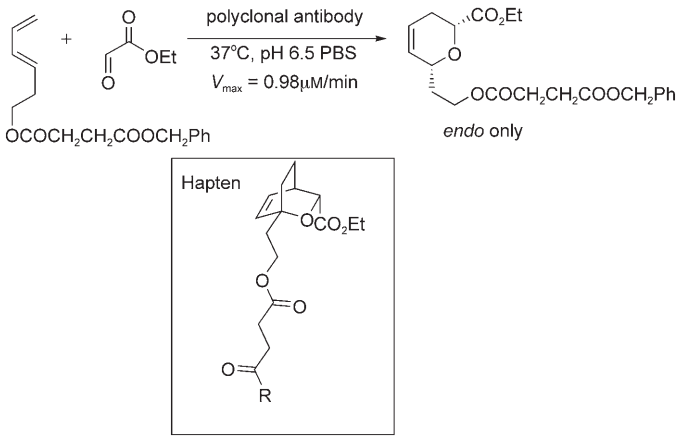
alysts.[22] The activity of modified RNA is entirely dependent on the nature of the base modification and the presence of cupric ion.[23] Antibodies featuring Diels–Alderase activity were obtained by challenging the immune system with transition state analogues.[8] These antibody-catalyzed reactions display Michaelis–Menten kinetics featuring unexceptional K_M values in the 10^{-3} M range for both the dienes and the dienophiles as expected for normal organic host–guest complexation in water. More importantly, it was found that most of these catalysts bind transition states to approximately the same degree as the substrates or more weakly. Most of them are not able to achieve significant specific binding of transition states, the hallmark of enzyme catalysis, and this is reflected in the lower catalytic efficiency of these antibodies and nucleic acid hosts. One exception is antibody 1E9, a Diels–Alderase biomolecule which catalyzes the [4π+2π] Diels–Alder reaction of thiophene dioxide and maleimide.[8a,b] The remarkable catalytic ability of this antibody has been explained by the high degree of shape and electrostatic complementarity with the transition state evidenced by hydrogen bonds and other polar interactions and by the presence of a key asparagine residue that can form a hydrogen bond with one of the carbonyls of the dienophile (Scheme 8).

Considering the number of existing antibodies or RNAses capable of catalyzing all-carbon Diels–Alder reactions, it is highly surprising that almost nothing is known about the existence of naturally occurring hetero-Diels–Alderase enzymes and about the generation of man-made hetero-Diels–Alderase biocatalysts. Few papers report the generation of antibodies capable of catalyzing hetero-Diels–Alder cycloadditions with just one example involving a carbonyl heterodienophile. Monoclonal antibodies have been successfully generated that catalyzed the hetero-Diels–Alder reaction of a nitroso heterodienophile with 1,3-pentadiene with good control of regio- and enantioselectivity.[24] Antibody-catalyzed retro hetero-Diels–Alder reactions have also been reported releasing HNO as the heterodienophile.[24c] It was Wu and co-workers who reported the only example of an antibody-catalyzed HDA reaction involving a carbonyl dienophile. They generated a mixture of polyclonal antibodies raised against a hapten mimicking an *endo* approach of ethylglyoxylate toward a poorly activated diene. The *endo* approach as programmed in the transition state analogue (TSA), resulted in the exclusive formation of the *cis*-3,4-dihydropyran derivative. Although showing moderate rate enhancement, the antibodies allowed for an excellent level of diastereocontrol in favour of the *cis* isomer. Regrettably, no enantiomeric excess for the product is provided.[25] The same authors also reported an example of an antibody-catalyzed aza-Diels–Alder reaction leading to the *trans*-adduct as programmed by the hapten, a TSA that was mimicking in this case an *exo* approach of the imino dienophile toward the diene (Scheme 9).[26]

Conceptually, the design of all the man-made biocatalysts reported so far relies on similar modes of actions. They lower the entropic activation by bringing together the reac-



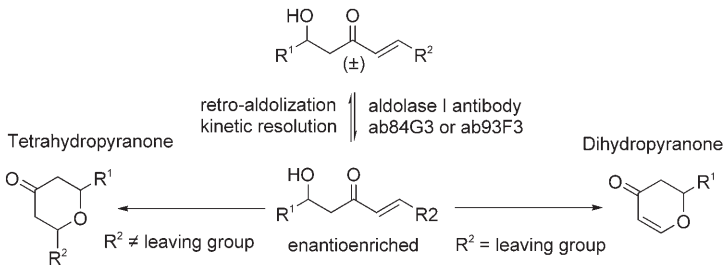
Scheme 8. Diels–Alderases for the formation of various carbocyclic adducts.



Scheme 9. Hetero-Diels–Alderases for the cycloaddition of an activated aldehyde.

tion partners in their reactive conformation and allow for enthalpic stabilization of the transition state relying on electrostatic and shape complementarity of the binding site for the transition state and on strategically positioned hydrogen-bonding interactions. So far, these strategies generated Diels–Alderase for cycloaddition processes involving more often moderately activated reaction partners, with one example of HDA reaction involving an activated carbonyl heterodienophile. Biocatalytic systems that will be best applied for the formation of enantiopure hetero-Diels–Alder adducts derived from unactivated dienes and dienophiles are still in demand. Recently, a novel concept has addressed this problem to some extent.

Combination of antibody and metal catalysts: Based on the two established mechanistic pathways for Lewis acid mediated hetero-Diels–Alder reactions, an alternative biocatalytic asymmetric route to hetero-Diels–Alder adducts of carbonyl compounds can be a nonconcerted stepwise approach relying on the production of enantioenriched aldol products derived from an α,β-unsaturated ketone donors, followed by a cyclization step leading to either dihydro- or tetrahydropyranones. This domino sequence will require a catalyst for the production of enantioenriched aldol intermediates and some optimization for the cyclization step, as little is known for this type of ring closure. The control of selectivity for both steps is critical for the success of the overall sequence.[27] Aldolase I antibodies were selected as catalysts for the first step as they are highly efficient catalysts, their mode of action is well-defined and they tolerate numerous structural variations of the donor and acceptor with substrate specificities that are different from those of the naturally existing enzymes.[28] The additional reason for selecting this class of catalysts is their ability to catalyze retro-aldolization processes in addition to forward aldolizations.[29] This is particularly significant as these retro-aldolizations can be anticipated to be more efficient for aldol products derived from less reactive aldehydes. In this stepwise strategy, the presence of a leaving group, such as the methoxy group, on the sp^2-hybridized carbon positioned β to the carbonyl in the aldol products is essential in order for the cyclization to give the corresponding dihydropyranones (Scheme 10). In the absence of this group, the enantioenriched tetrahydropyranones will be obtained instead.

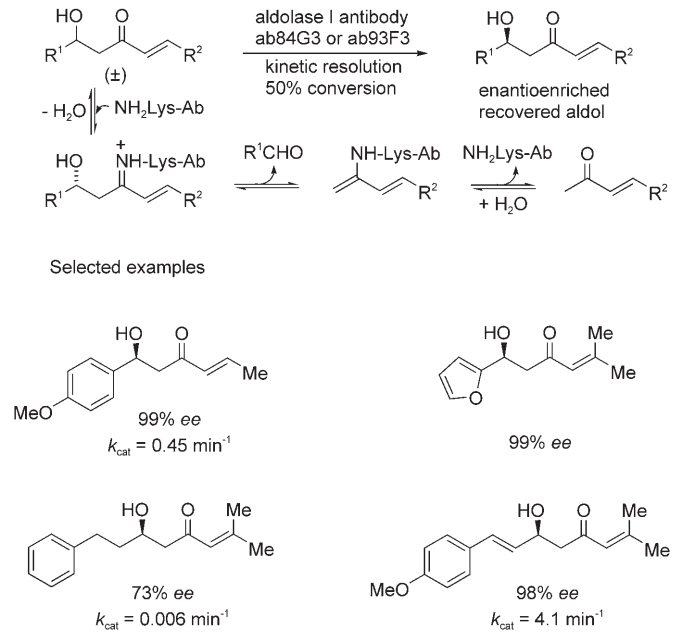


Scheme 10. Aldolase I antibody route to HDA adducts.

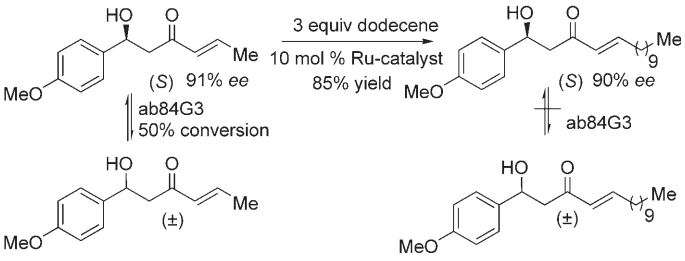
Antibodies 84G3 and 93F3[30] raised by reactive immunization against a hapten, featuring both a sulfone and a 1,3-diketone functionality, were found to be efficient catalysts for the kinetic resolution of various aldol products derived from α,β-unsaturated ketone donors, allowing for the recovery of the unreacted enantioenriched aldol products with enantiomeric excesses up to 99%. The catalytic mechanism relies on the presence of a key nucleophilic lysine residue at L_{89} of perturbed pK_a, as identified by site-directed mutagenesis and structural studies. These antibodies tolerate numerous structural variations for the part of the aldol product originally derived from the acceptor. Aldol products derived from 3-penten-2-one or 3-methylbutenone combined with various conjugated and unconjugated aldehydes were kinetically resolved in the presence of antibodies 84G3 or 93F3. These antibodies do not accept aldol products derived from α,β-unsaturated ketones possessing long-chain substituents β to the carbonyl group. The presence of an ethyl or a propyl group in place of a methyl group on that position slowed down the antibody-catalyzed retro-aldolization considerably, and no reaction was observed with aldols possessing a long-chain alkyl group. It was also found that aldol products derived from methylvinylketone and 4-methoxybutenone were non-substrates, but were acting as irreversible inhibitors. For these substrates, a Michael addition involving a nucleophilic residue of the antibody competed with the desired retro-aldolization and presumably led to the formation of an inactive covalently modified catalyst. The kinetic data suggested that, on selected substrates, these antibody-catalyzed reactions are extremely efficient with k_{cat} values up to 4.1 min^{-1}. The best k_{cat} value was obtained for the kinetic resolution of the aldol product derived from 4-methoxy-cinnamaldehyde, suggesting that this antibody approach is best applied to the preparation of hetero-Diels–Alder adducts derived from unactivated acceptors (Scheme 11).

The inability of antibodies 84G3 or 93F3 to resolve aldol products derived from a large number of structurally diverse enones was a potential drawback, but a general solution was found to address this limitation. Indeed, it was found that the alkenyl group of a representative enantioenriched aldol product ($ee = 91\%$) obtained by kinetic resolution with antibody 84G3 can be conveniently elongated in a single step process by cross-metathesis with dodecene to give the new enantioenriched elongated aldol product. No detectable epimerisation occurred upon metathesis. This sequential antibody-catalyzed retro-aldolization/Ru-mediated cross-metathesis process is potentially extremely versatile and should allow numerous structural variations, allowing for the preparation of aldol products that are valuable precursors for the synthesis of many natural product targets (Scheme 12).

Overall these data validate the first step of the proposed biocatalytic route to HDA adducts, the delivery of structurally diverse enantioenriched aldol products derived from α,β-unsaturated ketones, which upon cyclization will yield the enantioenriched cycloadducts. The retro-aldolization process led to the formation of the aldehyde and ketone



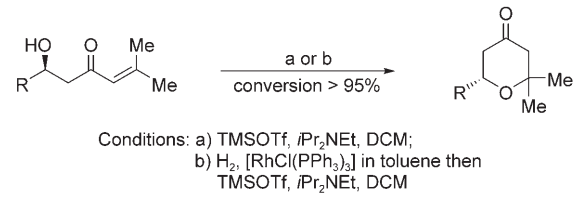
Scheme 11. Kinetic resolution of racemic aldol products using aldolase I antibodies 83G3 or 93F3.



Scheme 12. Cross-metathesis of enantioenriched aldol with dodecene.

starting materials. Since these can be reused to synthesize the racemic aldol product, the overall yield is good.

Direct cyclization of the recovered aldol products (*R*)-**9** and (*R*)-**10** was accomplished successfully in the presence of TMSOTf and *i*Pr$_2$NEt, affording the desired enantioenriched HDA adducts (*R*)-**12** and (*R*)-**13** with no detectable epimerization upon cyclization. The direct cyclization of compound (*S*)-**11** was not possible under these conditions as a competitive elimination occurred instead. For this type of substrate, a two-step sequence involving chemoselective hydrogenation of the allylic alcohol followed by cyclization afforded the tetrahydropyranone (*R*)-**14** with an enantiomeric excess greater than 99% (Scheme 13).

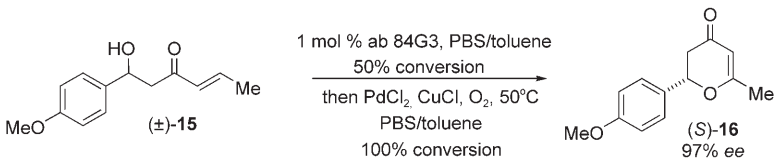


Aldol	*ee* [%]	Cond.	Product	*ee* [%]
(*R*)-**9** R = CH_2Ph(*p*-OMe)	83	a	(*R*)-**12** R = CH_2Ph(*p*-OMe)	83
(*R*)-**10** R = CH_2CH_2Ph	72	a	(*R*)-**13** R = CH_2CH_2Ph	72
(*S*)-**11** R = CH=CHPh(*p*-OMe)	>99	b	(*R*)-**14** R = CH_2CH_2Ph(*p*-OMe)	>99

Scheme 13. Preparation of enantioenriched trisubstituted tetrahydropyranones.

The major issue clouding the initial strategy to access dihydropyranones in addition to tetrahydropyranones was the inability of antibodies 84G3 or 93F3 to deliver enantioenriched aldol intermediates derived from 4-methoxybutenone. However the proposed strategy allows the possibility to correct this limitation by adapting the reaction condition of the cyclization process. Indeed, by replacing the standard intramolecular Michael addition by a Wacker oxidative cyclization process, the oxidation state of the sp^2-hybridized carbon positioned β to the ketone was restored allowing for the formation of the corresponding oxidized adduct.[31] The oxidative cyclizations were carried out in the presence of 10 mol% of $PdCl_2$ and 20 mol% of CuCl in a biphasic 1/1 mixture of toluene/PBS (PBS = phosphate-buffered saline), leading to the formation of the corresponding dihydropyranones in 60–70% isolated yields. Inspired by the antibody route to multigram scale preparation of other enantioenriched aldol products developed by Sinha, Lerner and Barbas III,[32] a convenient procedure was implemented for the direct conversion of the racemic aldol product **15** into the corresponding enantiopure dihydropyranone (*S*)-**16** (*ee* = 97%) with no purification of the intermediate enantiopure aldol product. In a typical transformation, a solution of the antibody (1 mol%) in PBS was added to a solution of the racemic aldol in toluene. The mixture was shaken until the desired *ee* was reached as monitored by HPLC. The reaction mixture was then cooled down, allowing for the separation of the organic layer containing the enantioenriched aldol product from the frozen aqueous antibody solution. PBS, $PdCl_2$ and CuCl were then added to the organic layer and the biphasic mixture was heated at 50 °C until complete conversion of the intermediate enantioenriched aldol into the desired dihydropyranone with no detectable epimerization (Scheme 14).

This strategy represents the first aldolase I antibody route to enantioenriched HDA adducts of carbonyl compounds by



Scheme 14. Conversion of aldol product (±)-**15** enantioenriched dihydropyranone (*S*)-**16**.

means of a stepwise pathway with an aldol product as the key intermediate. A remarkable feature of this approach is the particularly efficient preparation of adducts otherwise derived from less activated dienes possessing one oxygen-containing donating group and unactivated conjugated aldehydes substituted by an electron-donating group. This is because a retro-aldolization has been selected as key step for the delivery of the enantioenriched aldol intermediates. Another key feature relies on the possibility of taking advantage of the second step of this strategy as an opportunity to access both tetrahydropyranones and dihydropyranones. This can be achieved by simply modifying the reaction conditions of the ring-closure process. This procedure exemplifies how the combination of two types of catalysts, as illustrated here with an antibody catalyst and a transition metal catalyst, can address a challenging synthetic problem. The simultaneous use of protein and metal catalysts is not unprecendented. The coupling of enzymes and transition metals for the preparation of enantioenriched secondary alcohols has attracted considerable attention.[33] Here, the enzymes catalyzed an acylation process, whereas the metal catalyst, a ruthenium complex, mediated the in situ racemisation of the starting secondary alcohol, therefore allowing for an overall dynamic kinetic resolution process for the preparation of enantioenriched acylated alcohols. A related approach has recently been applied to the preparation of enantioenriched polysubstituted decalins resulting from an intramolecular all-carbon Diels–Alder cycloaddition.[34] The antibody–palladium approach detailed herein further expands the synthetic scope of this concept to the preparation of HDA adducts. In comparison with the one-pot strategy reported for the enzyme/metal catalytic process, the biphasic sequential approach reported herein presents the advantage of allowing easy separation of the protein-catalyst from the product for recycling purpose.

Conclusion

Catalysis involving biomolecules or metal centres plays a key role in synthesis. These two types of catalytic species are more often considered as part of two separate disciplines, but more recently semisynthetic and de novo proteins have allowed the formation of hybrid species that possess metal centers. The resulting catalytic species are various novel metalloenzymes or metalloantibodies possessing catalytic activity that can be potentially optimized chemically or by using directed evolution techniques.[35] An additional approach is to simply use both types of catalytic species simultaneously in a one-pot process as exemplified by the dynamic kinetic resolution of secondary alcohols or to use them in a versatile domino-type process. In this case, the two catalytic species display two distinct catalytic activities and both processes can be accelerated simultaneously or sequentially. The sequential approach has been exploited successfully for the implementation of an aldolase I antibody route to enantioenriched hetero-Diels–Alder products of various oxidation states. For the preparation of dihydropyranones, this approach relies on two catalytic species, an aldolase I antibody and palladium dichloride. A biphasic system was found particularly convenient for this process and proved extremely practical as it allowed for an easy purification of the HDA product and recovery of the catalyst. Synthetically, it led to hetero-Diels–Alder products derived from unactivated aldehydes and poorly nucleophilic dienes and therefore complements alternative asymmetric catalytic approaches based on the use of chiral Lewis acids. When a Michael addition is applied for the ring closure, trisubstituted tetrahydropyranones are obtained. These compounds are difficult to prepare from alternative Diels–Alder chemistry, as they are the products derived from less nucleophilic dienes and unactivated dienophiles. The antibody-mediated approach detailed in this paper could be biomimetic as the recent work of Jørgensen et al. carried out on macrophomate synthase (MPS) revealed that the stepwise Michael/aldol mechanism is the likely route used by this natural Diels–Alderase enzyme.[36,37]

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