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# Enamides and dienamides in phosphoric acid-catalysed enantioselective cycloadditions for the synthesis of chiral amines

Thomas Varlet and Géraldine Masson\*

Chiral substituted cyclic amines are ubiquitous among biologically active molecules and natural products and are valuable intermediates in organic synthesis. Straightforward enantioselective synthetic methods toward these motifs are highly sought after. Cycloaddition reaction is considered as one of the direct and efficient strategy for the construction of cyclic amines. In particular, chiral phosphoric acid catalysed formal cycloadditions involving enamides and dienamides as partners have contributed significantly in this field. This feature article showcases the remarkable versatility of these cycloadditions to access chiral cyclic amines with different ring sizes ranging from 5- to 7-membered rings, with an emphasis on biologically active natural products.

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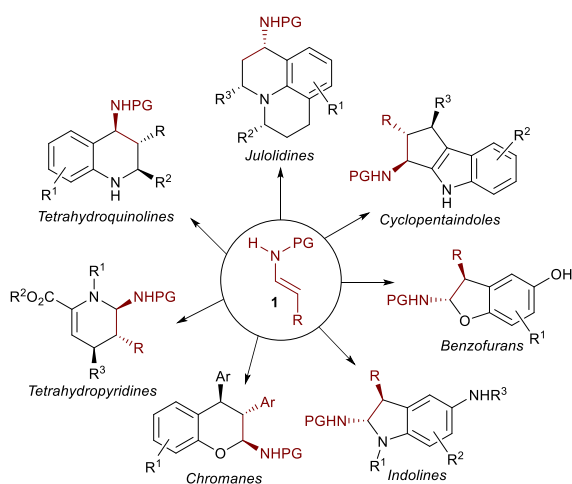
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## 1. Introduction

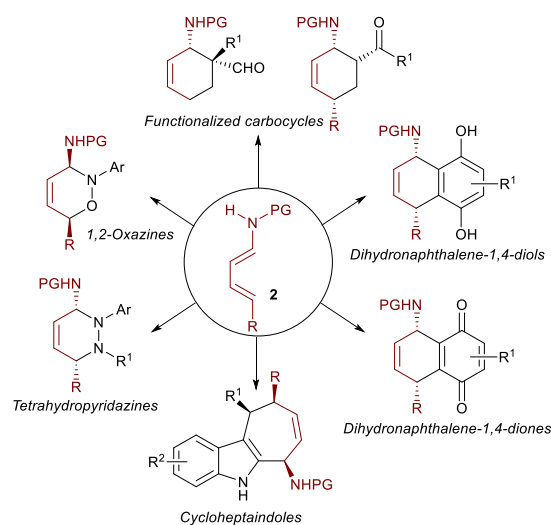
Chiral substituted cyclic amines are valuable motifs widely found in an array of natural products, and biologically active substances. Thus, the development of efficient methods for their effective construction has been intensively pursued by the organic synthetic community. Among them, the cycloaddition reactions of enamides constitute one of the most direct, powerful and atom-economical procedures. In these approaches, the polarized enamides react with various electrophilic dienes or dienophiles in inverse-electron demand

(formal) cycloadditions to generate 5- and 6-membered cyclic amines (Scheme 1).

Similarly, vinylogous dienamides can also participate as electron rich dienes in normal-electron demand (formal) cycloaddition reactions to lead to 6- and 7-membered cyclic amines (Scheme 2).



Scheme 1 Selection of chiral cyclic amines structures obtained from enamides.



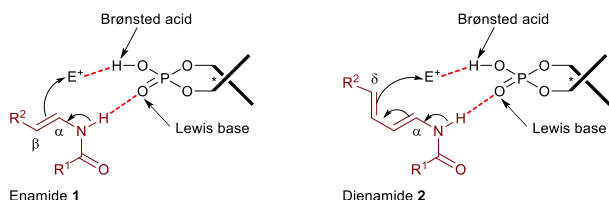
Scheme 2 Selection of chiral cyclic amines structures obtained from dienamides.

However, in contrast to asymmetric cycloadditions involving enamines or dienamines,<sup>1</sup> the development of catalytic enantioselective versions with enamides and dienamides has received less attention. This is in part due to their lower nucleophilic character and their tendency to isomerize into the corresponding imine derivatives under acidic conditions.

Since the pioneering works of Akiyama<sup>2</sup> and Terada,<sup>3</sup> chiral phosphoric acid (CPA) catalysis has emerged as a powerful strategy for many important enantioselective transformations.<sup>4</sup> In many cases, their effectiveness relies on their bifunctional character, since the electrophile and the nucleophile can be

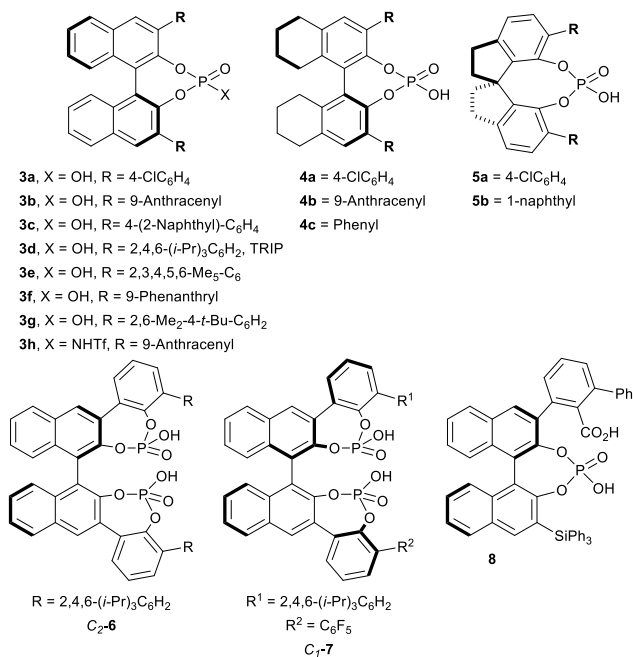
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synergistically activated through hydrogen-bonding interactions to ensure high enantioselectivity and reactivity. In particular, they have proven to be particularly well-adapted catalysts for the development of enantioselective cycloadditions with secondary enamides and dienamides. Indeed, these derivatives bearing an NH moiety can form a hydrogen bond with the Lewis base of phosphoric acid while the latter form the required hydrogen bond with the electrophile (Scheme 3).



**Scheme 3** Bifunctional catalytic activation of enamides and dienamides by phosphoric acid.

This strategy combining a chiral phosphoric acid (Scheme 4) and secondary enamides as well as dienamides has proven to be successful for the construction of various cyclic nitrogen-containing products with high regio-, chemo-, and enantioselectivity. In this feature article, we will first summarize recent advances in the enantioselective (formal) cycloadditions of enamides which allow efficient access of

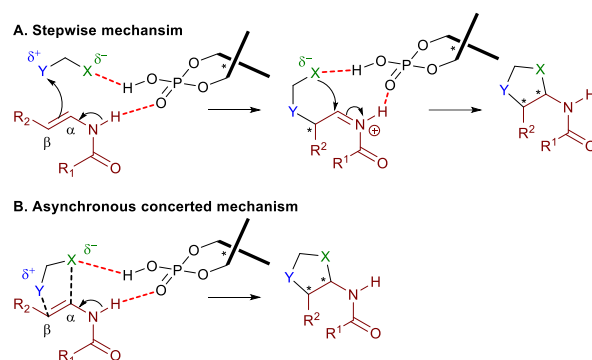


**Scheme 4** Scaffolds of the chiral phosphoric acid catalysts used throughout this article. **3**, BINOL; **4**, Octahydrogenated BINOL; **5**, SPINOL. The chirality of phosphoric acids **3**, **4** and **5** is indicated for each example along this article.

optically active 5- and 6-membered amino-heterocycles. In the second part, we will focus on enantioselective (formal) cycloadditions of dienamide derivatives leading to a diverse range of complex amino-heterocycles and amino-carbocycles.

## 2. Inverse-electron-demand cycloaddition of Encarbamates

Cycloaddition of electron rich enamides<sup>5</sup> with electron-poor dienes or dipoles can be considered as an inverse electron-demand (IED) cycloaddition. Due to the polarized nature of both reactants, these reactions can occur either through a stepwise mechanism involving an iminium intermediate (Scheme 5A) or, alternately, through an asynchronous concerted mechanism (Scheme 5B).

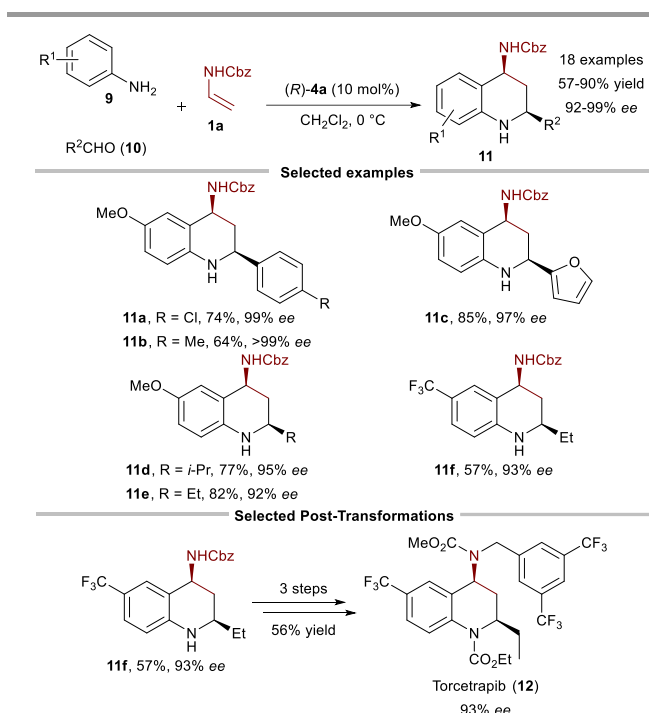


**Scheme 5** Mechanistic possibilities for phosphoric acid catalysed cycloadditions of enamides.

### 2.1 (4 + 2) Cycloaddition with 2-azadienes

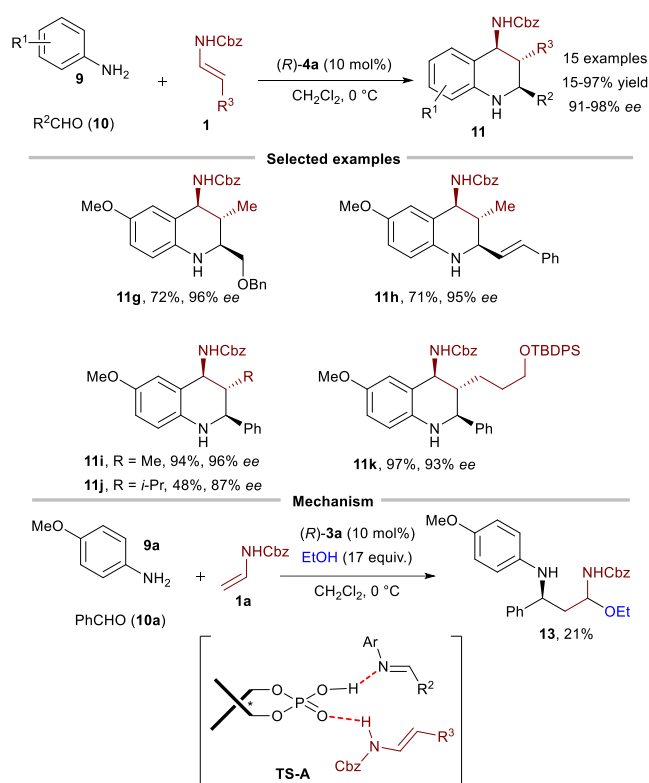
*N*-arylimines have proven to be versatile 2-azadienes in IED aza-Diels-Alder (aza-DA) reaction, also known as Povarov reaction,<sup>6</sup> for the preparation of biologically important tetrahydroquinolines.<sup>6c,7</sup> The first examples of catalytic enantioselective Povarov reaction, catalysed by chiral ytterbium complex and aminodiol-titanium (IV) complexes, were respectively reported by Kobayashi<sup>8</sup> and Sundararajan.<sup>9</sup> Ten years later, Akiyama *et al.*<sup>10</sup> disclosed the first organocatalytic asymmetric Povarov reaction promoted by chiral phosphoric acid catalysts. In these seminal works, enol ethers were mainly used as dienophiles affording an efficient access to 4-alkoxy-tetrahydroquinolines with high diastereo- and enantioselectivity. Inspired by these studies, we investigated the use of encarbamates as dienophiles<sup>11</sup> in 3-component<sup>4l,12</sup> Povarov reaction catalysed by chiral phosphoric acids.<sup>13</sup> Delightedly, we found that the secondary encarbamate **1a** was a suitable partner to react with  $\alpha$ -aryl-substituted imines generated *in situ* in the presence of the H8-BINOL-based chiral phosphoric acid (*R*)-**4a**. This IED aza-DA provided an efficient and easy access to 4-amino-1,2,3,4-tetrahydroquinolines **11** (a common substructure found in biologically active compounds and drug candidates)<sup>6g,7b,11b,14</sup> with high enantio- and diastereoselectivities. Various anilines and aromatic aldehydes were suitable components to afford *cis*-2,4-disubstituted tetrahydroquinolines **11** in high yield with up to >99% *ee*. Aliphatic aldehydes, which are challenging substrates due to the tautomerization of the *in situ* formed imines, effectively delivered the desired cycloadducts **11** with excellent enantio- and diastereoselectivities. We later accomplished the synthesis of the antihypercholesterolemic

drug candidate Torcetrapib **12**,<sup>11a,14d,e,15</sup> in a three-step sequence, employing as a key-step this enantioselective phosphoric acid-catalysed 3-component Povarov reaction (Scheme 6).



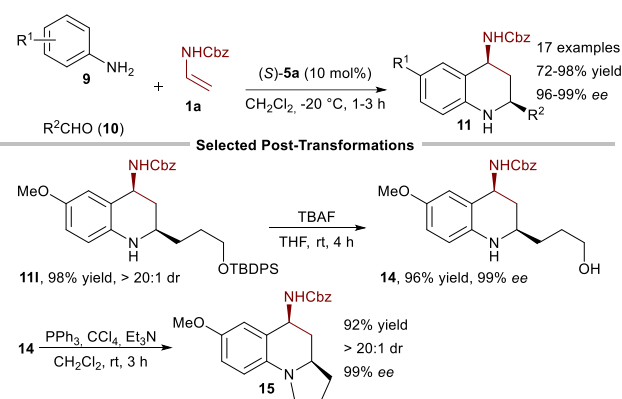
**Scheme 6** Conditions for the asymmetric 3-component Povarov reaction

Shortly after, we expanded our study to  $\beta$ -substituted enecarbamates.<sup>16a</sup> Under the same conditions, various (*E*)-enecarbamates **1** reacted smoothly and gave the corresponding 2,3- and 3,4-*trans* tri-substituted tetrahydroquinolines **11** as the major isomers with excellent enantioselectivities. The catalyst loading could be reduced to 1 mol%, giving the cycloadduct **11i** ( $R^1 = \text{OMe}$ ,  $R^2 = \text{Me}$  and  $R^3 = \text{Ph}$ ) with the same efficiency and selectivity. (*Z*)-enecarbamate (*Z*)-**1a** was much less reactive than its *E* isomer affording cycloadduct **11i** in 32% yield as a mixture of two diastereoisomers (9:1 dr). Surprisingly, the major diastereoisomer was found to be the same 3,4-*trans* cycloadduct as that derived from (*E*)-**1a**. A slow isomerization of enecarbamate (*Z*)-**1a** to (*E*)-**1a** *via* the N-acyliminium intermediate, in the presence of phosphoric acid, could explain this observation. Evidence for a stepwise mechanism was provided by isolation of the iminium intermediate, which was trapped by ethanol under the form of the hemiaminal **13**.<sup>16b</sup> Low chiral induction was observed with tertiary endocyclic enecarbamates, leading us to propose a well-organized transition state **TS-A** wherein the phosphoric acid acts as a bifunctional catalyst to activate both enecarbamate and N-arylimine *via* hydrogen-bonding network (Scheme 7).



**Scheme 7** Asymmetric 3-component Povarov reaction involving  $\beta$ -substituted enecarbamates

This asymmetric 3-component Povarov reaction was studied as well by Lin *et al.* in 2013.<sup>17</sup> They focused on using challenging aliphatic aldehydes. SPINOL-derived phosphoric acid catalyst (*S*)-**5a** was chosen as the best catalyst. Running the reaction at  $-20\text{ }^\circ\text{C}$  furnished the corresponding cycloadducts **11** in excellent yields and almost enantiomerically pure products. The authors solely used unsubstituted enecarbamate **1a**. Their strategy was successfully applied to the synthesis of chiral benzo[*e*]indolizidine **15** in three steps without erosion of enantioselectivity (Scheme 8).

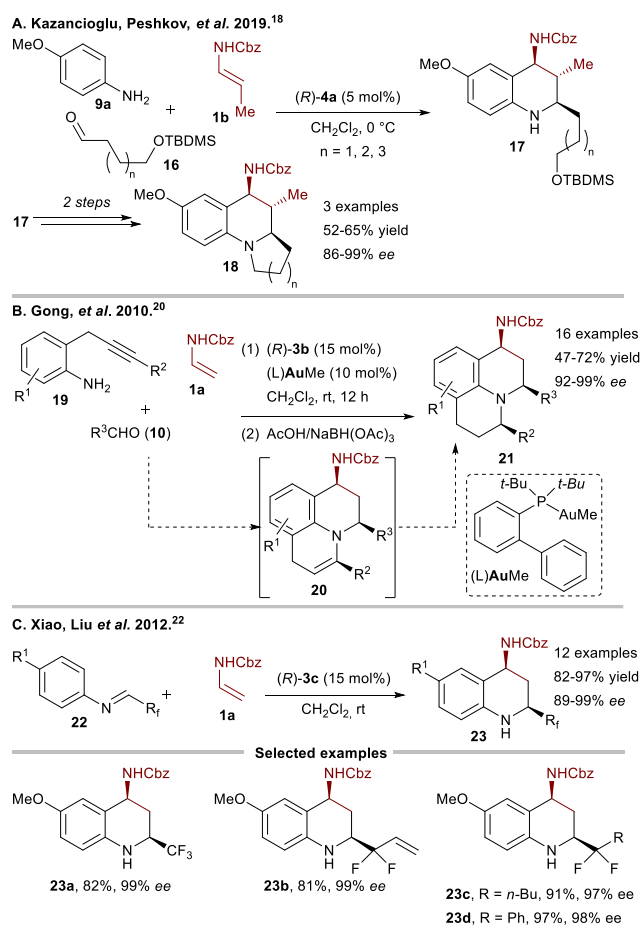


**Scheme 8** Conditions for the asymmetric 3-component Povarov reaction and application to the synthesis of chiral benzo[*e*]indolizidine.

Very recently, Kazancioglu, Peshkov *et al.*<sup>18</sup> applied this 3-component Povarov reaction to the synthesis of tricyclic

tetrahydroquinoline motifs found in a range of bioactive alkaloids.<sup>12b,19</sup> They used appropriate aldehydes **16** bearing protected hydroxyl group on aliphatic chains. The reaction with anisidine **9a**, enecarbamate **1b** and phosphoric acid catalyst (*R*)-**4a** afforded tetrahydroquinolines **11** in excellent enantiomeric excess. Removal of silyl protecting group followed by cyclization under Appel conditions led to the desired tricyclic derivatives **18** without any erosion of enantioselectivity (Scheme 9A).

In 2010, Gong *et al.*<sup>20</sup> described an elegant cascade reaction consisting of CPA-catalysed 3-component Povarov reaction with the  $\beta$ -unsubstituted enecarbamate **1a** and Au(I)-catalysed hydroamination of alkynes. The expected cycloadduct **20**, too unstable to be isolated, was reduced *in situ* using NaBH(OAc)<sub>3</sub> in the presence of acetic acid. Through the sequence, diverse optically enriched tri-substituted julolidine derivatives **21** were produced in high yields. Control experiments revealed that chiral phosphoric acid (*R*)-**3b** was the effective catalyst for the Povarov reaction and that chiral gold phosphate<sup>21</sup> generated *in situ* was the active catalyst in the hydroamination reaction (Scheme 9B).



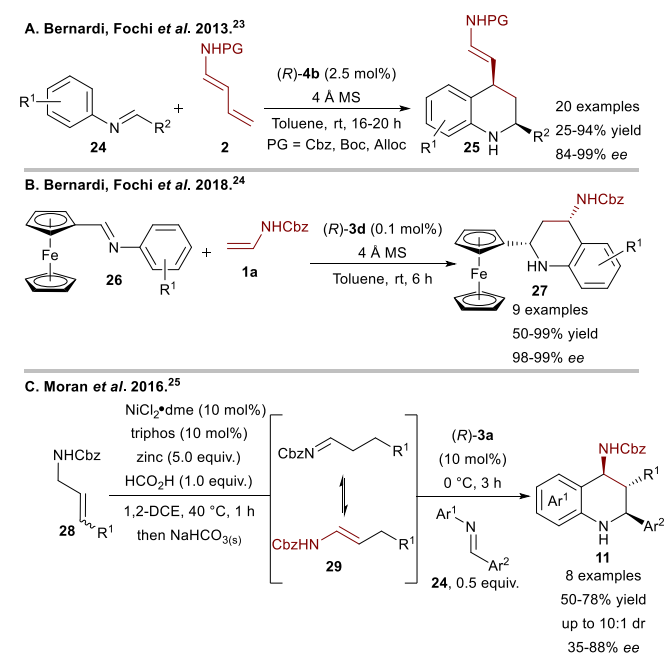
**Scheme 9** Examples of Povarov reactions to access biologically active structures.

Afterward, Xiao, Liu *et al.*<sup>22</sup> reported an asymmetric synthesis of trifluoromethylated and difluoromethylated tetrahydroquinolines **23**. Chiral phosphoric acid catalyst (*R*)-**3c**, with extensive 4-(2-naphthyl)-phenyl 3,3'-substituents gave the best results in terms of yields and *ee*. Under the optimized

conditions, various perfluorinated *N*-arylimines **22** reacted smoothly with  $\beta$ -unsubstituted enecarbamate **1a** in good to high yield with excellent *cis*-diastereo- and enantioselectivity (Scheme 9C).

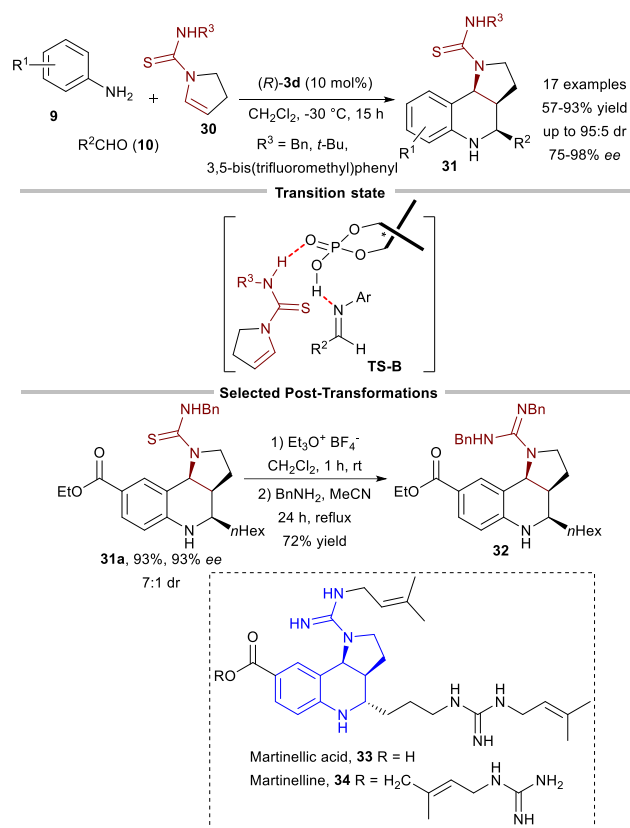
In 2013, Bernardi, Fochi *et al.*<sup>23</sup> reported the first enantioselective vinylogous Povarov reaction using non-substituted dienecarbamates **2** as electron-rich dienophiles instead of enecarbamates. The best stereochemical result was attained with phosphoric acid (*R*)-**4b** derived from octahydro-(*R*)-BINOL to produce the *cis*-tetrahydroquinolines **25** in high yields. The Povarov reaction proceeded with a high level of enantioselectivity and exclusive chemoselectivity for the more distant double bond of the diene. This remains the sole example so far of such a reactivity for dienecarbamates (Scheme 10A). Later,<sup>24</sup> the same authors devised a strategy to access tetrahydroquinolines substituted with a ferrocenyl moiety **27**, in order to combine interesting biological properties of tetrahydroquinoline motif and ferrocenyl functionality. The ferrocenyl was successfully introduced by using ferrocenecarbaldehyde-derived imines **26**. Using 3,3'-bis(2,4,6-triisopropylphenyl)binol phosphoric acid (TRIP)-catalyst (*R*)-**3d** and unsubstituted enecarbamate **1a**, a range of ferrocenyl-substituted tetrahydroquinolines were accessed in high yields and excellent enantioselectivities, showing the remarkable compatibility of ferrocene with these conditions (Scheme 10B).

In 2016, Moran *et al.*<sup>25</sup> developed a cascade isomerization of *N*-allylcarbamate **28**<sup>26</sup> into *N*-propenylcarbamate **29** in presence of the NiCl<sub>2</sub>/TRIPHOS/Zn/HCO<sub>2</sub>H catalytic system followed by chiral phosphoric acid (*R*)-**3a**-catalysed Povarov reaction. Although the enantio- and diastereoselectivity were lower, this protocol avoided the synthesis of enecarbamates through Curtius rearrangement of the corresponding unsaturated carboxylic acids (Scheme 10C).<sup>5</sup>



**Scheme 10** Examples of asymmetric Povarov reaction.

In 2012, we described the analogous cycloaddition using cyclic dienophiles for enantioselective synthesis of hexahydropyrrolo[3,2-*c*]quinolines.<sup>27</sup> Since the presence of the free NH function on the dienophile was crucial for the enantioselectivity, the enethiourea **30**,<sup>28</sup> incorporating an NH donor group was selected in order to conserve hydrogen bond interaction between the dienophile and the phosphoric acid catalyst. Indeed, high enantio- and diastereoselectivity were achieved in a three-component Povarov reaction by employing the bulky (*R*)-**3d** TRIP catalyst. The scope of the reaction was then studied and aliphatic aldehydes as well as  $\alpha,\beta$ -unsaturated aldehydes, aromatic aldehydes, and heteroaromatic aldehydes, were appropriate substrates, giving the corresponding cycloadducts **31** in good yields and excellent diastereo- and enantioselectivities. A wide range of diversely functionalized anilines was also employed in this reaction, and we noted that the best enantioselectivity was obtained for electron-poor substrates. The synthetic utility of these hexahydropyrrolo[3,2-*c*]quinolines was further demonstrated. For instance, the thiocarbamoyl group **31a** was converted to the guanidine containing pyrroloquinoline **32**, giving access to a valuable intermediate for the synthesis of analogues of martinellie acid **33** martinelline **34**.<sup>29</sup> (Scheme 11).



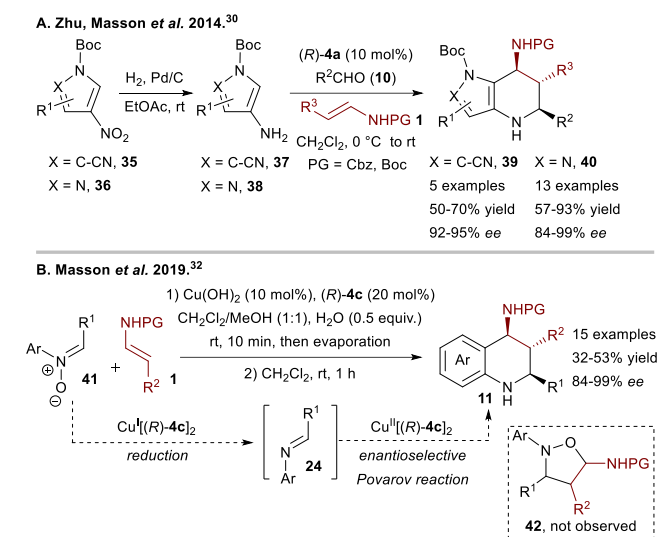
**Scheme 11** Asymmetric 3-component Povarov reaction with cyclic enethioureas.

We implemented an enantioselective Brønsted acid catalysis for the 3-component Povarov reaction of enecarbamates with heteroazadienes generated *in situ* from aldehydes and 3-aminopyrrols **37** or 4-aminopyrazoles **38**.<sup>30</sup> However, these aminoheterocycles were particularly difficult to

manipulate due to their propensity to isomerize into their imine forms under acidic conditions.<sup>31</sup> To solve the problem, they were synthesized *in situ* through the hydrogenation of the corresponding nitro heterocycles **35** and **36**. The reaction with 4-nitro-pyrazoles **38** proceeded smoothly with aromatic,  $\alpha,\beta$ -unsaturated and aliphatic aldehydes. Regarding 4-nitro-2-cyano-pyrroles **37**, the reaction worked best with aromatic aldehydes, either electron-rich or electron-poor. A range of substituted (*E*)-enecarbamates **1** was well suited and Boc protecting group worked as well as Cbz in terms of yields and enantioselectivity. The N-protecting groups have no significant influence on the reactivity and enantioselectivity. The corresponding cycloadducts were obtained as the major *trans*, *trans*-isomer in moderate to good yields with high *ee* (Scheme 12A).

Recently, an alternative strategy for a stereoselective synthesis of tetrahydroquinolines **11** was disclosed by our group.<sup>32</sup> During our study on the development of enantioselective (3 + 2) cycloadditions between enecarbamates **1** and nitrones **41**, an unexpected result was observed when a copper-phosphate salt  $\text{Cu}^{\text{II}}[(R)\text{-4c}]_2$  was employed as catalyst. The only product formed was not the expected isoxazolidines **42** but, to our surprise, the 4-aminotetrahydroquinolines **11** in excellent enantio- and diastereoselectivity. This result was reasoned to arise from a copper(I)-promoted deoxygenation of the nitron to afford the corresponding aryl-imine **24**.<sup>33</sup> The latter underwent enantioselective Povarov reaction with enecarbamates in the presence of the resulting copper(II) complex catalyst<sup>34</sup> in a DCM/MeOH (1:1) mixture. The catalyst  $\text{Cu}^{\text{II}}[(R)\text{-4c}]_2$  was prepared *in situ* from  $\text{Cu}(\text{OH})_2$  and chiral phosphoric acid (*R*)-**4c** in a ratio 1:2 respectively. The resulting copper(II) complex can be reduced by *N*-arylhydroxylamine (generated during partial hydrolysis of **41**) to form copper(I) complex  $\text{Cu}^{\text{I}}[(R)\text{-4c}]_2$  which catalysed the deoxygenation of nitrones. The presence of water was thus required to generate the active catalyst species. A wide range of tri-substituted tetrahydroquinolines **11** were obtained in moderate yields and high diastereo- and enantioselectivities starting from either electron-rich or electron-poor aryl imines, with diversely  $\beta$ -alkylated enecarbamates **1**, including linear and bulkier branched ones (Scheme 12B).

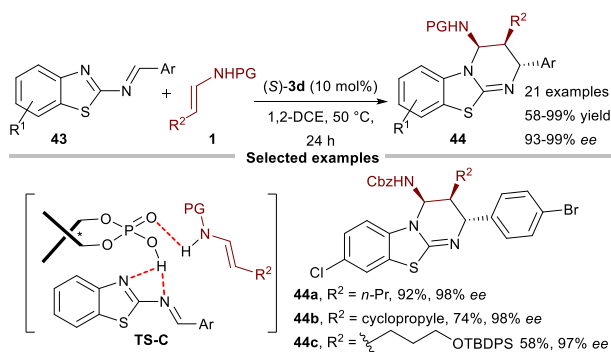




Scheme 12 Examples of asymmetric Povarov reaction with nitrones.

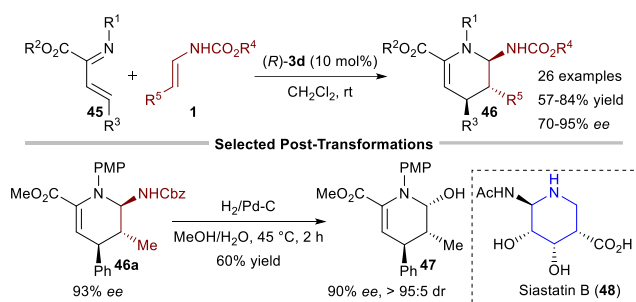
## 2.2 (4 + 2) Cycloaddition with hetero-2-azadienes

Based on the work of Enders *et al.*, we found that 2-benzothiazolimines<sup>35</sup> were useful hetero-2-azadienes in the phosphoric acid catalysed asymmetric IED aza-DA reaction with enecarbamates.<sup>36</sup> The more bulky TRIP phosphoric acid catalyst (*S*)-**3d** proved to be the most effective, delivering tri-substituted *trans-cis* benzothiazolopyrimidines **44** with excellent diastereo- and enantioselectivity albeit with moderate yields due to catalyst deactivation with the basic isothioureia group of **44**. After extensive optimisation studies, we found that the cycloaddition proceeded smoothly at 50 °C when 3 equiv. of enecarbamates were used. The reaction showed broad substrate scope with both enecarbamates **1** and 2-benzothiazolimines **43**. Various benzothiazolopyrimidines **44** (also named homobenzotetramisoles) that may constitute a novel family of Lewis base catalysts<sup>37</sup> were produced in high yields and selectivities. Based on DFT calculations, we proposed a stepwise mechanism of the aza-DA reaction that includes Mannich addition of enecarbamates **1** to imines **43** followed by intramolecular amination. To explain the observed stereoselectivity, a tentative model was proposed where phosphoric acid activates both enecarbamate and imine *via* hydrogen bonds forming the complex **TS-C** (Scheme 13).

Scheme 13 Synthesis of chiral HBTMs *via* asymmetric aza-DA reaction.

## 2.3 (4 + 2) Cycloaddition with 1-azadienes

The IED aza-DA reaction of 1-aza-butadienes<sup>6d,38</sup> is one of the most direct approaches for the preparation of highly substituted tetrahydropyridines.<sup>39</sup> However, organocatalytic enantioselective examples<sup>6d,f,h,38a,b,40</sup> are scarcer compared with that of 2-aza-dienes.<sup>6a,b,d,e,38b,d,e</sup> In continuation of our works, we developed the first enantioselective aza-DA reaction of *N*-aryl  $\beta,\gamma$ -unsaturated  $\alpha$ -iminoesters **45** with  $\beta$ -substituted enecarbamates **1** catalysed by the highly hindered BINOL phosphoric acid (*R*)-**3d** (TRIP catalyst).<sup>41</sup> Under optimum conditions, 6-amino-1,4,5,6-tetrahydropyridine derivatives **46** were isolated in moderate to good yields with high level of diastereo- and enantioselectivities. This provides an efficient access to cyclic motifs found in a range of biologically natural products such as Siastatin B **48**, a potent neuraminidase inhibitor.<sup>42</sup> The presence of the ester group on the azadiene was found to be crucial to control the regioselectivity of the cycloaddition. Indeed, the sterically bulky substituent prevents the attack of enecarbamate at the C2 position (as reported *N*-aryl-1-azabutadiene **11h**, Scheme 7) and the reaction occurs only at the C4-position. Various  $\beta,\gamma$ -unsaturated  $\alpha$ -iminoesters **45** bearing electron-donating and electron-withdrawing aromatic substituents, as well as heteroaromatic rings at the  $\gamma$ -position, reacted smoothly to afford the tri-substituted tetrahydropyridines **46** in good yields with excellent diastereo- and enantioselectivities. To illustrate the synthetic interest of this methodology, a key precursor<sup>43</sup> of a variety of chiral piperidines was synthesized with a Pd/C-catalysed hydrogenolysis of the NHCbz function to yield the hemiaminal adduct **47** in 60% yield with a slight erosion of enantioselectivity (Scheme 14).

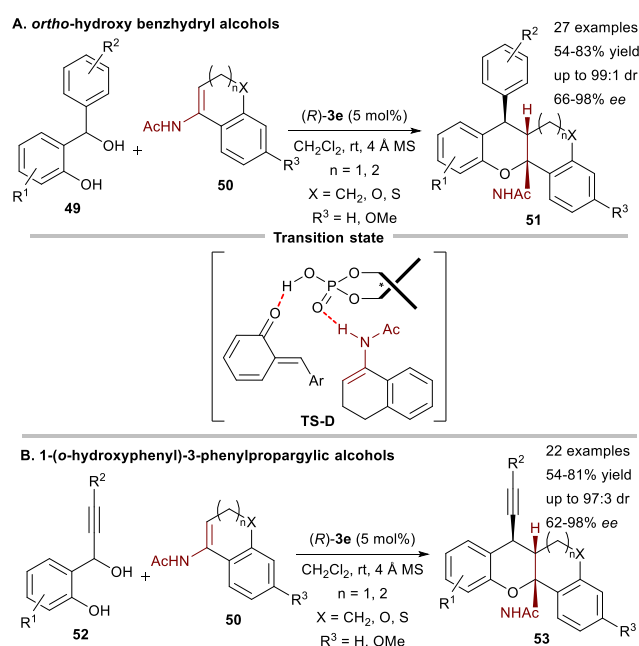


Scheme 14 Conditions for asymmetric aza-DA reaction involving 1-aza-dienes.

## 2.4 (4 + 2) Cycloaddition with *ortho*-quinone methide

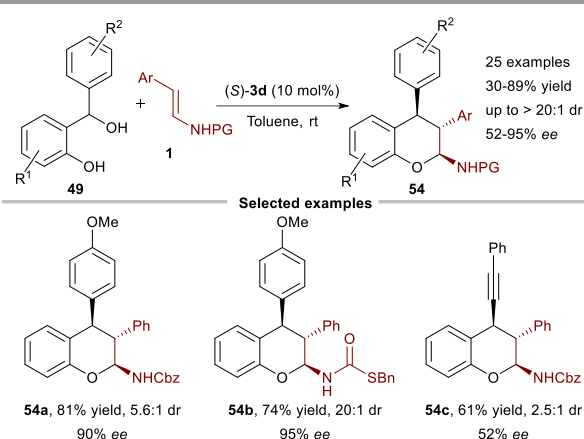
Catalytic asymmetric IED oxa-DA reaction of *ortho*-quinone methides (a special class of 1-oxadienes) is a powerful method for constructing tetrahydroxyxanthenes found in a range of pharmaceutical compounds.<sup>44</sup> In 2005, Schneider *et al.*<sup>45</sup> found that *ortho*-quinone methides<sup>46</sup> generated *in situ* from *ortho*-hydroxybenzhydryl alcohols **49** and chiral phosphoric acid (*R*)-**3e**, underwent IED oxa-DA reaction with cyclic enamides **50** to form various tetrahydroxyxanthenes **51** in high yields and enantioselectivities. The addition of 4 Å molecular sieves was beneficial to the yields, preventing the undesired hydrolysis of the enamide partners under acidic conditions. The reaction was

sensitive to electronic features of the  $\beta$ -aryl substituents of **49**. Lower yields were obtained with electron-poor aromatic rings. Diverse carbocyclic (6- to 7-membered rings) and heterocyclic (chromene and thiochromene derivatives) enamides were well tolerated, although the use of 7-membered cyclic enamides resulted in lower *ee* and diastereoselectivity. Overall, complex polycyclic structures **51** were obtained in good yields and consistently high *ee* values. The authors proposed a well-organized transition state model **TS-D** to explain the stereochemical outcome of the cycloaddition (Scheme 15A). Schneider's group extended this work to 1-(*o*-hydroxyphenyl)propargylic alcohols **52** using the same bulky phosphoric acid catalyst (*R*)-**3e** to synthesize 7-alkynyl-12 $\alpha$ -acetamido benzo(*c*)xanthene derivatives **53**.<sup>47</sup> (Scheme 15B).



**Scheme 15** Asymmetric oxa-DA reaction with cyclic enamides.

Later on, Pan *et al.*<sup>48</sup> extended this strategy to acyclic enecarbamates **1**, for the synthesis of chiral tri-substituted chromans, recurring motifs in natural products and bioactive agents.<sup>49</sup> In the presence of bulky TRIP phosphoric acid (*S*)-**3d**, chroman derivatives **54** were obtained in high yields with moderate to high diastereoselectivity and excellent enantioselectivity for the major diastereoisomer. The reaction was quite sensitive towards steric parameters: bulkier *ortho*-substituted  $\beta$ -aryl substituents gave the corresponding cycloadducts **54** in higher yields and *ee* values, with a total diastereoselectivity (>20:1 dr). Interestingly, enethiocarbamate **1c** (PG = C(O)SBn) afforded the chroman cycloadduct **54b** in better *ee* (95%) and dramatically increased dr (20:1) than the corresponding enecarbamates (Scheme 16).



**Scheme 16** Asymmetric oxa-DA reaction involving acyclic enecarbamates

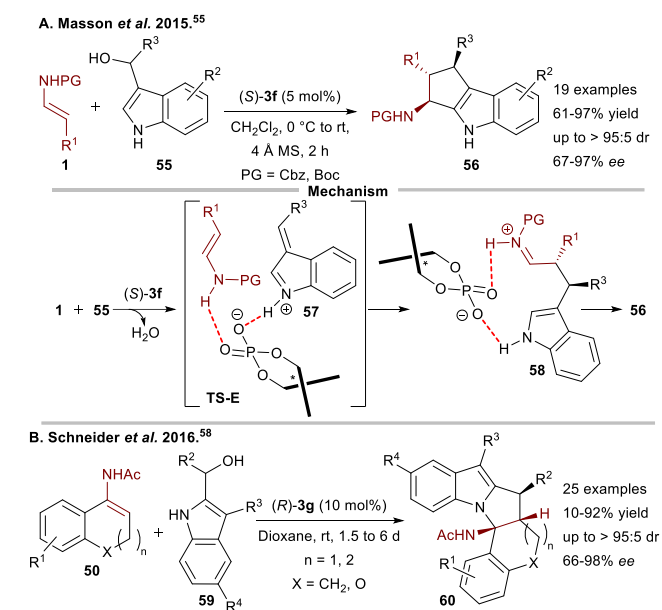
## 2.5 (3 + 2) Cycloaddition with vinylindolinium

Although less developed than the (4 + 2) analogs,<sup>5</sup> type III (3 + 2)-cycloadditions<sup>50</sup> are also powerful methods to react with enamide derivatives and construct highly substituted 5-membered carbo- and heterocycles.<sup>51</sup> For instance, inspired by previous studies on the enantioselective (3 + 2)-cycloaddition with 3-indolylarylmethanols reported by Guo<sup>52</sup> and Shi,<sup>53</sup> we realized the first example of formal (3 + 2)-cycloaddition of *in situ* formed vinylindolinium ion **57** with  $\beta$ -substituted enecarbamates **1**.<sup>55</sup> In the presence of chiral phosphoric acid (*S*)-**3f**, this reaction provided a direct access to biologically important aminocyclopenta[*b*]indoles<sup>56</sup> **56** with three contiguous stereogenic centers in good yields with high diastereoselectivities (>98:2 dr) and up to 99% *ee*. The reaction showed broad substrate scope. Enecarbamates **1** bearing linear or bulkier alkyl  $\beta$ -substituents were well accommodated. No influence of the electronic properties of the aryl moiety, or the indole core, was observed. The cycloadducts with either heteroaromatic (2-thienyl) or alkyl substituents (isopropyl, *n*-butyl) instead of the aryl substituent could also be synthesized albeit in slightly lower yields and decreased *ee*. The free NH group of indoles **55** was crucial for the enantioselectivity. Racemic cycloadduct was isolated when a corresponding *N*-benzylated analogue was used as dipole under the standard conditions. A control experiment showed that the cycloaddition occurred *via* a stepwise mechanism, with isolation of the iminium intermediate trapped by ethanol. Based on these investigations and previous reports,<sup>53g,i,57</sup> a plausible reaction mechanism was proposed in Scheme 17A. In presence of phosphoric acid, indolylarylmethanols **55** was *in situ* transformed to the vinylindolinium ion **57**. Then, the reaction of enecarbamate **1** with the vinyliminium intermediate **57** provided the iminium intermediate **58**. Finally, the C2 alkylation of indole with iminium **58** furnishes the aminocyclopenta[*b*]indoles **56**. To explain the high stereoinduction, a bifunctional activation mode *via* the formation of the active complex **TS-E** was suggested, thereby favouring the *Si* face attack on **57**.

Afterwards, Schneider *et al.*<sup>58</sup> developed a similar strategy to access chiral cyclopenta[*a*]indoles **60**,<sup>59</sup> using cyclic enamides



**50** as dipolarophiles in the reaction with 2-indolylarylmethanols **59**. The formal (3 + 2) cycloaddition proceeded most efficiently in dioxane in the presence of chiral phosphoric acid (*R*)-**3g** bearing 2,6-dimethyl-4-tert-butyl phenyl groups at 3,3'-positions to produce polyheterocycles **60** in generally high yields and excellent stereoselectivity. The reaction was compatible with a variety of functional groups, and demonstrated a broad substrate scope. Mechanistic studies realized by the authors also suggested a stepwise mechanism. Similarly, free NH of indoles plays a pivotal role in the activation and preorganization of the substrates (Scheme 17B).

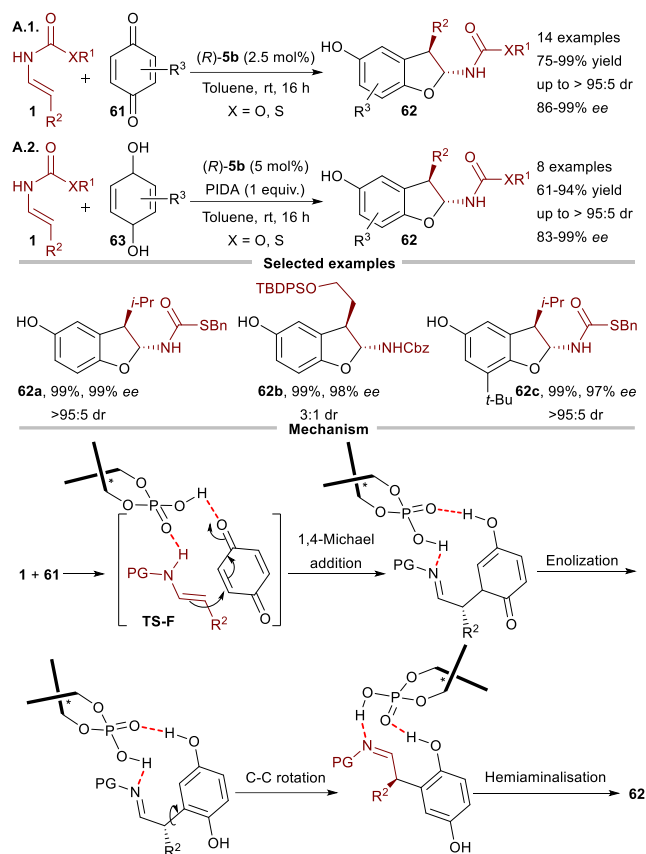


**Scheme 17** Synthesis of chiral cyclopentaindoles *via* asymmetric (3 + 2) cycloaddition.

## 2.7 (3 + 2) Cycloaddition with benzoquinone derivatives

Quinones have been extensively used in (3 + 2)-cycloaddition reactions<sup>60</sup> for the synthesis of dihydrobenzofurans which are common fragments in a number of biologically active molecules and natural products.<sup>61</sup> In 2015, based on previous reports, we developed a (3 + 2)-cycloaddition of quinones **61** with  $\beta$ -substituted ene- and thioencarbamates **1**.<sup>62</sup> The best stereocontrol was achieved by (*R*)-3,3'-(1-naphthyl)-SPINOL phosphoric acid (*R*)-**5b** which provided densely substituted 2,3-disubstituted 2,3-dihydrobenzofurans **62** with excellent regio- and enantioselectivity. However, the diastereoselectivity was strongly dependent of the nature of the protecting group of the dipolarophile. (*E*)-Enthiocarbamate gave systematically higher *trans* diastereoselectivity (Scheme 18A.1). We also reported a more practical process which involved *in situ* oxidation of dihydroxybenzoquinones **63** to quinones with phenyliodine diacetate (PIDA) in presence of encarbamates and chiral phosphoric acid (*R*)-**5b**. However, enantioselectivity in this oxidative condition was noticeably lower due to the formation of acetic acid generated from PIDA.<sup>62a,l,63</sup> Pleasingly, the selectivity was restored when the catalyst loading was

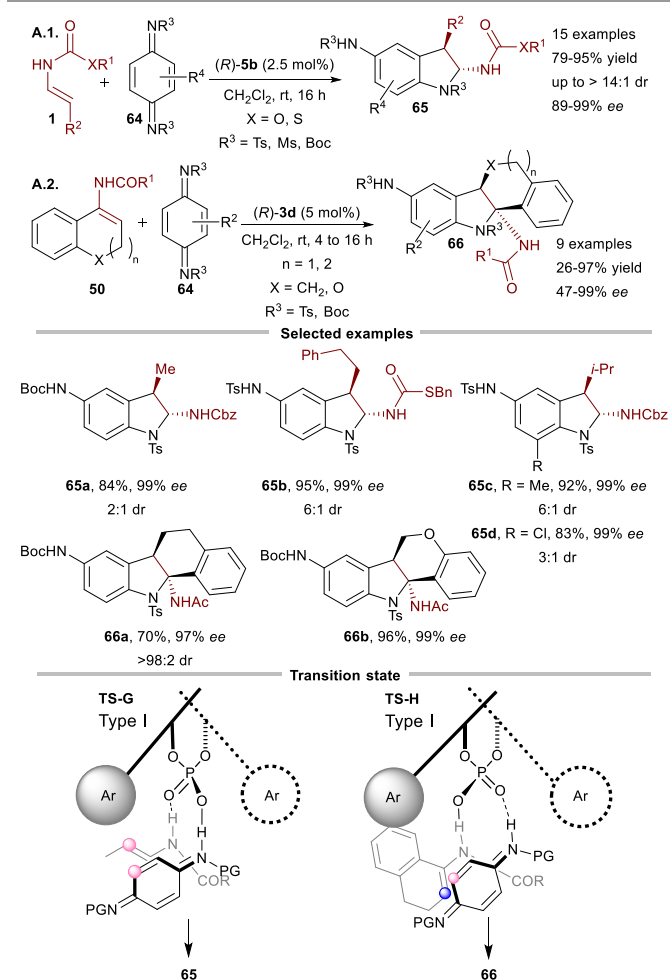
increased from 2.5 to 5 mol%. Under these conditions, various substituted hydroquinones **61** whose corresponding benzoquinones are not commercially available smoothly underwent the (3 + 2) cycloaddition in high yields with good to excellent enantioselectivities (Scheme 18A.2). Mechanistic studies suggested a stepwise mechanism which includes enantioselective 1,4-Michael addition of electron-rich enamide to **61** followed by enolization and C-C rotation of the imine moiety and the intramolecular hemiaminalisation over the transition state **TS-F** (Scheme 18).



**Scheme 18** Conditions for the asymmetric (3 + 2) cycloaddition with quinones.

Very recently, we further extended the developed (3 + 2)-cycloaddition reactions to the quinone diimines **64**,<sup>64</sup> providing an efficient manner to a wide range of 2,3-disubstituted indolines **65** and **66**.<sup>65</sup> In the presence of chiral phosphoric acid catalysts with BINOL or SPINOL backbones, quinone diimines **64** reacted with  $\beta$ -substituted encarbamates **1** and with cyclic enamides **50** to produce a diversity of highly enantiomerically enriched indolines in high yield with moderate to excellent diastereoselectivity. In addition, a highly chemoselective cycloadditions occurred from heteroprotected quinone diamine giving cycloadducts **65a** and **66a**, hereby demonstrating the ability of the catalyst to differentiate two nitrogen protecting groups. Based on the work of Goodman concerning the prediction of the stereochemistry of phosphoric acid-catalysed reactions of imines,<sup>66</sup> two transition states **TS-G** and **TS-H** were proposed respectively for the two types of enamides **1** or **50**. In each one, both substrates are activated by the catalyst, with

formation of a double hydrogen bonding. The inversion of enantioselectivity observed between acyclic enecarbamates **1** and cyclic enamides **50** was explained by the minimization of steric clash between phosphoric acid 3,3'-substituents and enamide derivatives. Accordingly, acyclic enecarbamates **1** favour the *Re* face attack on quinone diimide **64** (TS-G) while cyclic enamides **59** favour the *Si* face attack on **64** (TS-H) (Scheme 19).

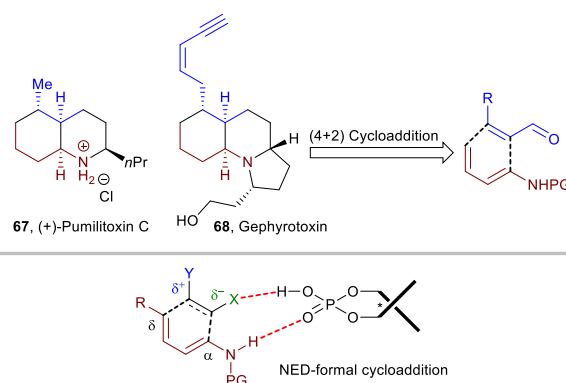


**Scheme 19** Conditions for the asymmetric (3 + 2) cycloaddition with quinones diimides.

### 3. Normal-electron-demand cycloaddition of dienecarbamates

Dienecarbamates, vinylogous version of enecarbamates, have been used for the first time by Overman in 1978 in (4 + 2) cycloadditions to access several nitrogen containing natural products showing interesting biological properties.<sup>67</sup> Similar to enamide derivatives, secondary dienamides and dienecarbamates can also be activated by the chiral phosphoric acids through hydrogen bond interaction between the Lewis base site (P=O) of the catalyst and the free NH of the diene (Scheme 20). This activation increases the nucleophilic character of the  $\delta$ -carbon and enables their enantioselective

difunctionalisations at their  $\alpha$ - and  $\delta$ -positions. Such transformations using electrophiles tethered to nucleophiles can be seen as normal electron-demand (NED) cycloadditions, occurring either by a concerted or stepwise process. This strategy has become a powerful method for the construction of numerous 6-membered carbocycles and heterocycles, as well as less usual 7-membered carbocycles.



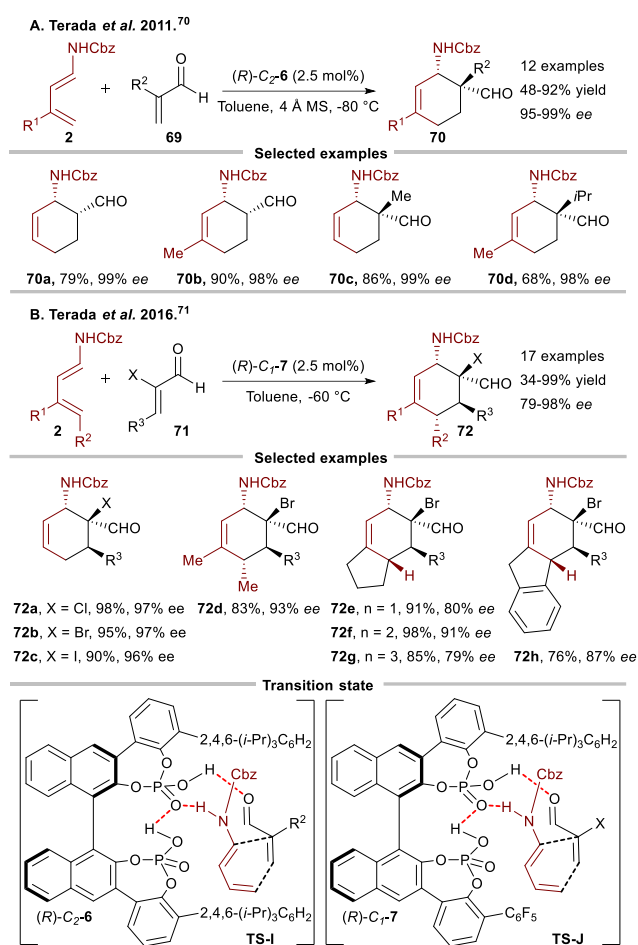
**Scheme 20** Natural bioactive products synthesized *via* DA reaction with dienecarbamates.

#### 3.1 (4 + 2) Cycloaddition with carbonyls

$\alpha,\beta$ -Unsaturated carbonyls are an important class of dienophiles for enantioselective DA reaction.<sup>68</sup> However, chiral phosphoric acid-catalysed enantioselective DA version has received less attention, partly because the activation of carbonyl compounds<sup>4e</sup> by such catalyst has been less successful.<sup>69</sup> Terada *et al.*<sup>70</sup> described the pioneering enantioselective NED-DA reaction in which dienecarbamates were used. In the presence of carefully designed chiral bis-phosphoric acid (*R*)-C<sub>2</sub>-**6** bearing two phosphoric acid motifs, these dienes **2** were able to react with acrolein derivatives **69** yielding exclusively *cis*-diastereomers of chiral substituted cyclic formylcarbamates **70** in high enantioselectivities. The higher acidity of the catalyst (*R*)-C<sub>2</sub>-**6** (compared to that of mono-phosphoric), thanks to intramolecular conjugated double hydrogen, was proven crucial for reactivity (TS-I). Diversely  $\gamma$ -substituted dienecarbamates **2** and unsubstituted acrolein derivatives **69** were well tolerated achieving the desired cycloadducts **70** in high yields and enantioselectivity. However,  $\alpha$ -alkylated acroleins gave corresponding cycloadducts in lower yields but still excellent *ee* (Scheme 21A).

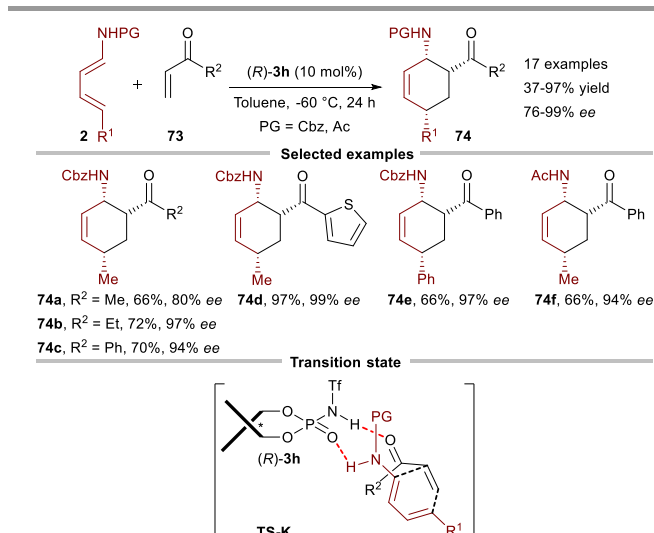
In a follow-up work by the same group,<sup>71</sup> the authors found that a new C<sub>1</sub>-symmetric bis-phosphoric acid (C<sub>1</sub>-BISPA) (*R*)-C<sub>1</sub>-**7**, exhibiting higher acidity than (*R*)-C<sub>2</sub>-**6**, was required for the cycloaddition of dienecarbamates **2** with challenging less basic  $\alpha$ -haloacroleins<sup>72</sup> **71**. Under the optimized conditions, various acrolein derivatives such as bromo-, chloro- and iodo-acroleins underwent NED-DA reaction to furnish cycloadducts **72** in good yields and high enantioselectivities. Again, the acidity of the catalyst was found to be the key factor for the success of this transformation (TS-J).<sup>4h,73</sup> The X-ray diffraction analysis data and computational studies allowed demonstrating the higher

acidity of the phosphoric acid proton near the TRIP substituent (Scheme 21B).



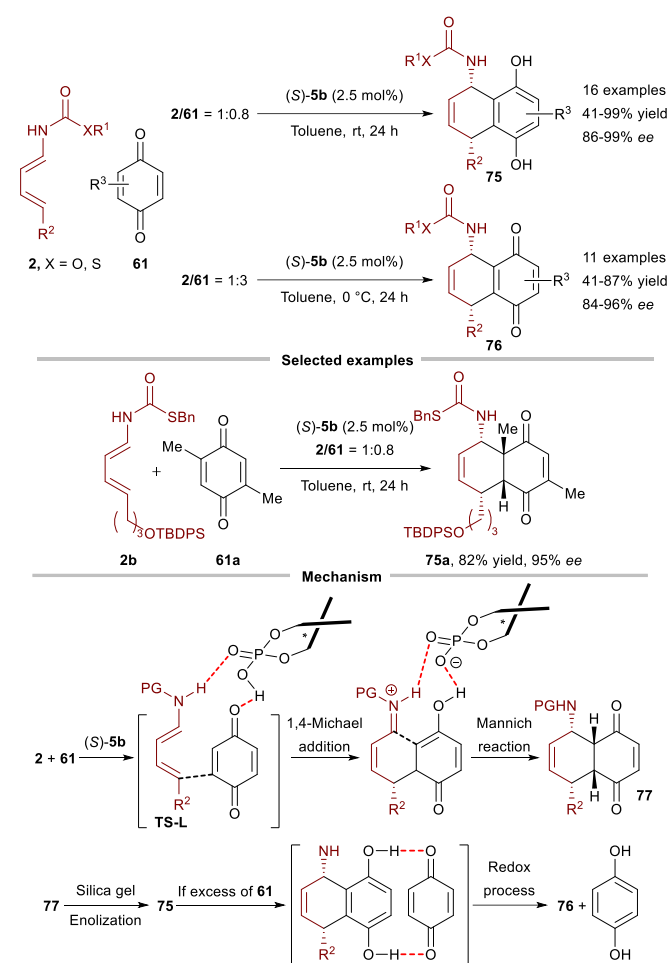
**Scheme 21** Examples on asymmetric DA reaction involving acroleins.

In 2014, Kong *et al.*<sup>74</sup> successfully disclosed a challenging asymmetric DA cycloaddition between dienecarbamates **2** and aryl vinyl ketones **73**. The authors identified that the more acidic chiral *N*-triflyl phosphoramidate (developed by Yamamoto)<sup>72a,75</sup> was the most efficient catalyst. Interestingly, BINOL-derived phosphoric acids were completely inactive in this case. It was found that (*R*)-3,3'-bis-9-anthracenyl-BINOL phosphoramidate (*R*)-**3h** was the best catalyst and the yield was dramatically increased by slowly adding the  $\delta$ -substituted dienecarbamates **2** to the reaction media. Under the optimized conditions, a range of aryl vinyl ketones **73** and  $\delta$ -substituted methyl- and phenyl-dienecarbamates reacted to give *endo*-cycloadducts **74** in overall good yields and high *ee*. However, due to high instability, the reaction employing the unsubstituted dienecarbamate was inefficient, furnishing the final cycloadduct in low yield. It is noteworthy that no reaction occurred for the diene bearing the *N*-methylated carbamate group. This supported the crucial role of the NH proton in the NED-DA reaction. Based on this, the authors proposed a bifunctional activation, where the catalyst activates both the dienecarbamate and the vinyl ketone by hydrogen-bonding (TS-K, Scheme 22).



**Scheme 22** Conditions for the asymmetric DA reaction involving vinyl ketones.

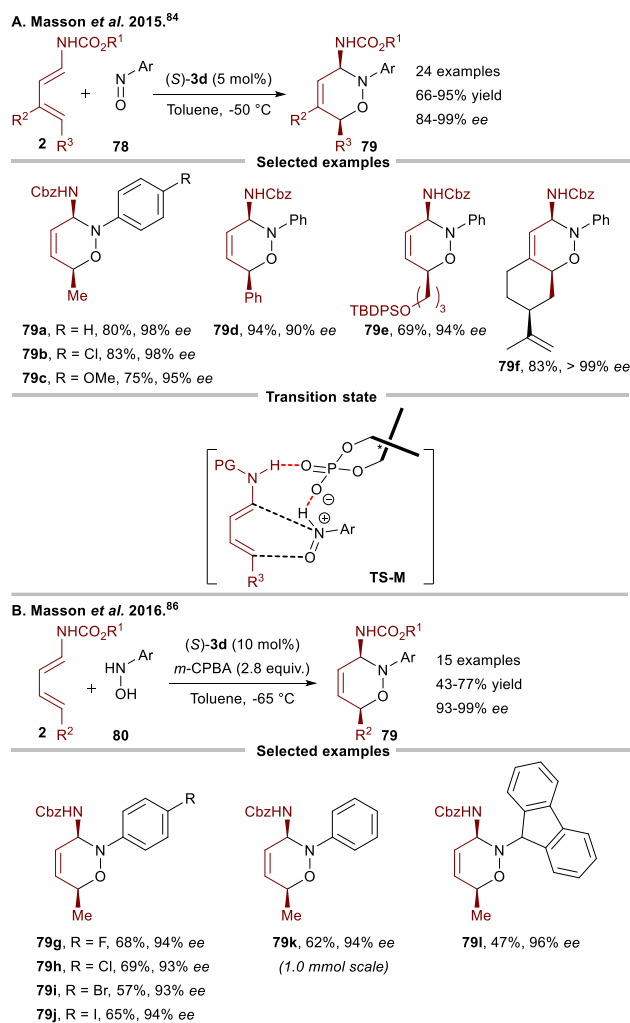
Following our work on the asymmetric (3 + 2) cycloaddition between enecarbamates and quinones,<sup>76</sup> we found that thiodienecarbamates could effectively react with quinones in an enantioselective (4 + 2)-cycloaddition with (*S*)-SPINOL (*S*)-**5b** as chiral phosphoric acid catalyst.<sup>77</sup> Interestingly, a divergent synthesis of redox isomers, dihydronaphthalene-1,4-diols **75** and tetrahydronaphthalene-1,4-diones **76**,<sup>75b,78</sup> was controlled by adequate amount of the quinones employed. The enantioselectivity was found to be highly dependent on the protecting group of the diene. Indeed, the thiodienecarbamates **2** (X=S) underwent NED-DA, giving products with high *ee* while dienecarbamates **2** (X=O) gave the corresponding adducts with much less enantioselectivity. The developed protocol with thiodienecarbamates provided a facile access of both redox isomers in moderate to high yields with excellent regio-, enantio-, and diastereoselectivities. A wide range of diversely substituted thiodienecarbamates **2** suited the reaction. Electron-donating group substituents on the quinones favoured the catalytic transformation, affording the corresponding cycloadducts **75** and **76** in higher yields. Challenging symmetrical disubstituted 2,5-dimethyl-benzoquinone **61a** provided the desired cycloadduct **75a** with a complete control of all four stereocenters (95% *ee*). Based on control experiments and DFT calculations, we proposed a stepwise mechanism that includes activation of both quinones **61** and thiodienecarbamates **2** by the phosphoric acid catalyst (*S*)-**5b** (TS-L). Subsequent Michael addition of diene to the activated quinone followed by intramolecular Mannich cyclization afforded hexahydronaphthalene-1,4-dione intermediate **77**. The latter aromatized on silica to deliver dihydronaphthalene-1,4-diol **75**. In presence of excess of quinone, the intermediate **77** underwent a double oxidation to generate tetrahydronaphthalene-1,4-dione **76**.<sup>79</sup> It is worth to notice a reversible redox switching between the redox isomers was developed.<sup>80</sup> Various transformations of **75** and **76** to different functionalities were accomplished with success, demonstrating the value of this methodology (Scheme 23).



### 3.2 (4 + 2) Cycloaddition with nitrosoarenes

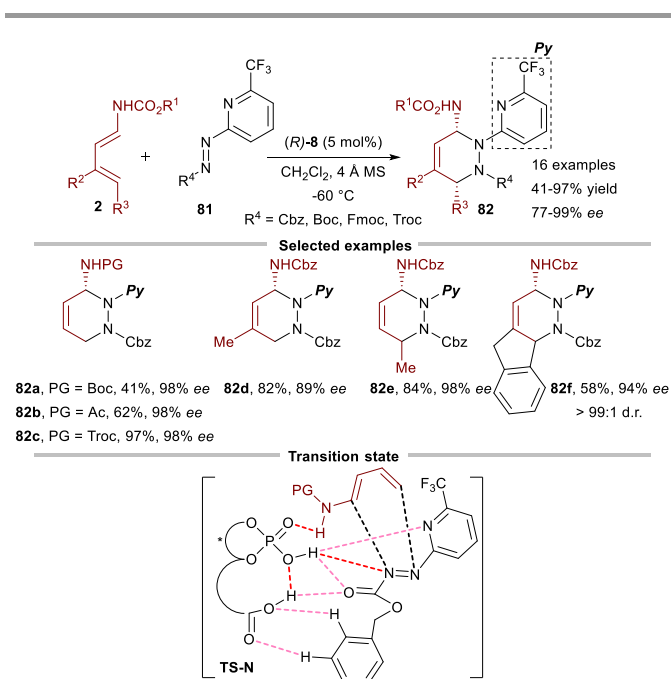
Nitroso compounds are recognized as important and highly useful heterodienophiles for the synthesis of dihydro-1,2-oxazines motifs, which are found in many biologically active compounds and can serve as key intermediates for the synthesis of diverse natural products.<sup>5f,81</sup> The first enantioselective nitroso-DA reaction was presented in 2004 by Yamamoto.<sup>82</sup> It opened up the way for further development using metal or organic catalysts.<sup>83</sup> In 2015, we developed a chiral phosphoric acid-catalysed enantioselective nitroso-DA reaction with dienecarbamates.<sup>84</sup> The bulky TRIP phosphoric acid (*S*)-**3d** proved to be the most effective, providing the desired enantioenriched cycloadduct **79** in high yields and with complete *O*-regioselectivity<sup>79c,85</sup> and excellent diastereoselectivity in favour of the *cis*-diastereomer. The (4 + 2) cycloaddition was applicable to a wide range of dienecarbamates and nitrosoarenes compounds **78** delivering 3,6-dihydro-1,2-oxazines **79** with excellent enantioselectivity. Different protecting groups in dienes (Cbz, Fmoc, Alloc, Acetate) appeared suitable for the cycloaddition. DFT calculations supported that the cycloaddition did occur *via* an asynchronous concerted mechanism. The high regioselectivity was explained in terms of directing effect of the phosphoric acid through hydrogen bond with nitrogen atom of the nitroso. Based on

these studies, a model was proposed where the phosphoric acid protonated the nitroso dienophile and formed H-bonding with the dienes, resulting in a well-organized transition state **TS-M**. Later, we were able to expand the scope of this cycloaddition by developing enantioselective oxidative nitroso-DA reaction of *N*-arylhydroxylamines **80** with dienecarbamates **2**.<sup>86</sup> The method used *m*-CPBA as a stoichiometric oxidant in combination with 10 mol% of (*S*)-TRIP catalyst (*S*)-**3d** to oxidize **80** into nitrosoarenes **78** as well as promote the enantioselective cycloaddition. The process simplified access to this important heterocyclic motif<sup>81</sup> because preparation of unstable nitrosoarene partners was avoided. Under optimized conditions, a wide variety of *N*-arylhydroxylamines reacted smoothly, giving the corresponding *cis*-3,6-disubstituted dihydro-1,2-oxazines **79** in excellent regio-, diastereo-, and enantioselectivity. It is worth noting that, *N*-arylhydroxylamines whose corresponding nitroso compounds are known to be unstable were successfully engaged in this oxidative enantioselective reaction. Scalability of the process was also demonstrated by performing the oxidative nitroso-DA reaction up to a gram scale on compound **79k** (Scheme 24).



### 3.3 (4 + 2) Cycloaddition with diazenes

Similarly to nitrosoarenes, diazenes can be used as dienophiles in DA reactions to form biologically interesting piperazines which appears in many important bioactive natural products and drugs.<sup>87</sup> However, due to the high electrophilic nature of diazodicarboxylates, the development of enantioselective DA version with such dienophiles proved particularly challenging.<sup>88</sup> To address this issue, Terada *et al.*<sup>89</sup> judiciously designed a chiral phosphoric acid having two different acidic sites, carboxylic acid and phosphoric acid. In their studies, the 2-azopyridinecarboxylates **81** was identified as the dienophiles of choice to perform an enantioselective DA reaction with dienecarbamates in presence of catalyst (*R*)-**8**. Different dienecarbamate partners, with substituents on either  $\gamma$ - or  $\delta$ - positions were tested with success. Overall, a broad range of cycloadducts was synthesized in good yield and with excellent regio-, enantio- and diastereoselectivity. The pyridine group on the diazenes was required for high selectivity, leading the authors to postulate a transition state wherein the carboxylic acid-assisted phosphoric acid forms hydrogen bonds with both the pyridine and the diazene functions. Meanwhile, a hydrogen bond was also formed between the phosphoryl oxygen and the NH moiety of **2**. Both control experiments and DFT calculations supported the transition state model (**TS-N**). (Scheme 25).



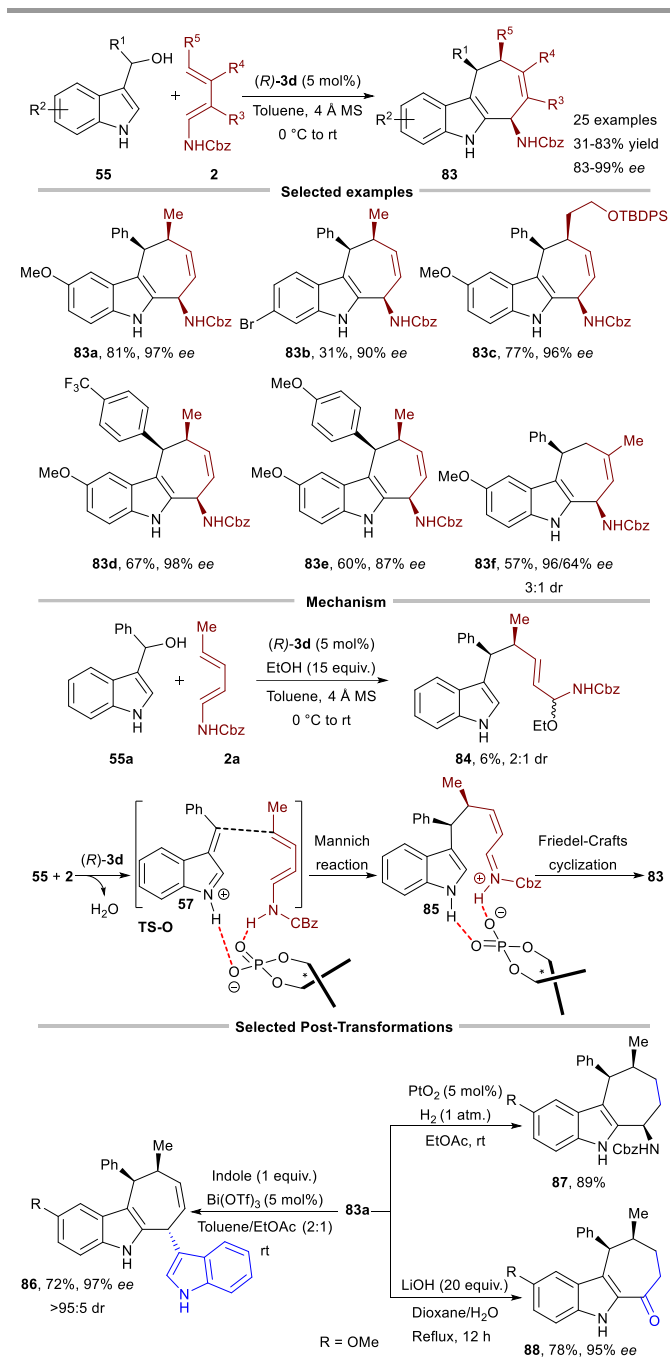
**Scheme 25** Conditions for the asymmetric azo-DA reaction.

### 3.4 (4 + 3) Cycloaddition with indolylmethanols

Shortly after our work on the asymmetric (3 + 2) cycloaddition between 3-indolylarylmethanols and enecarbamates,<sup>54</sup> we realized the first enantioselective synthesis of chiral cyclohepta[*b*]indoles *via* the (4 + 3)-cycloaddition of vinylindoliniminium ions **57** with dienecarbamates **2**.<sup>90</sup> The developed methodology provided

facile access to biologically important cyclohepta[*b*]indoles **83** (found in a large number of natural products and pharmaceutical drugs)<sup>91</sup> with perfect diastereoselectivity and excellent enantioselectivity under chiral phosphoric catalysis. The scope, with regard to  $\delta$ -3-indolylarylmethanols **55**, was studied and showed that substituents at different positions were well-tolerated. Nevertheless, better yields were achieved with indoles bearing electron-rich group. We proposed a stepwise mechanism for this reaction, including successive vinylogous addition of dienecarbamates to vinyliminium **57** followed by Friedel–Crafts cyclization step which was supported by isolation of intermediate **84** trapped by nucleophilic ethanol. The synthetic utility was demonstrated by facile conversion of cycloadduct **83a** into various enantiomerically enriched cyclohepta[*b*]indoles. For instance, nucleophilic displacement of carbamate moiety was achieved using Bi(OTf)<sub>3</sub> Lewis acid and indole, furnishing the cyclohepta[*b*]indole **86** with complete inversion of the chiral centre bearing the indole moiety. The endocyclic olefin of **83a** was chemoselectively reduced with Adams' catalyst giving **87** in 89% yield. Submitting **83a** to basic aqueous conditions with LiOH resulted in the hydrolysis of the carbamate to form the corresponding ketone derivative **88** in high yield and without erosion of enantiomeric excess (Scheme 26).





**Scheme 26** Conditions for the asymmetric (4 + 3)-cycloaddition reaction.

## Conclusions

Over the past two decades, significant progress has been made in the enantioselective synthesis of cyclic amines via cycloaddition reactions using enamides and dienamides as key nitrogen partners to incorporate the nitrogen atoms into the ring. By employing easy to synthesize and to handle enamides and dienamides, chiral phosphoric acid-catalysed cycloaddition reactions enable the direct synthesis of useful and complex cyclic amines. In this feature article some elegant examples have been presented demonstrating the synthetic potential of

enamides and dienamides for the preparation of a panel of natural products and biologically active molecules.

Despite such great achievements, most of efforts were focused on the construction of 6-membered cyclic amines. 5-membered rings were achieved using activated electrophiles and only one example providing access to 7-membered ring was reported. At the current state of the art, it is expected that more developments will emerge. For instance, the use of less reactive electrophilic partners with enamides and dienamides will afford an access to collections of structurally diverse compounds to populate unexplored chemical space. In addition, the development of enantioselective cycloadditions allowing the construction of large rings would be useful for the synthesis of various number of complex natural products and important biologically active products

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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## Notes and references

- For selected reviews on asymmetric cycloadditions involving enamines, see: (a) S. Meninno, C. Volpe and A. Lattanzi *ChemCatChem* 2019, **11**, 3716–3729; (b) G. J. Reyes-Rodriguez, N. M. Rezayee, A. Vidal-Albalat, K. A. Jorgensen, *Chem. Rev.* 2019, **119**, 4221–4260; (c) B. S. Donslund, T. K. Johansen, P. H. Poulsen, K. S. Halskov, K. A. Jorgensen, *Angew. Chem. Int. Ed.* 2015, **54**, 13860–13874; (d) P. Renzi, J. Overgaard and M. Bella, *Org. Biomol. Chem.* 2010, **8**, 980–983; (e) S. Mukherjee, J. Woon Yang, S. Hoffmann and B. List *Chem. Rev.* 2007, **107**, 5471–5569; For selected reviews on asymmetric cycloadditions involving dienamines, see: (f) D. B. Ramachary and Y. V. Reddy, *Eur. J. Org. Chem.*, 2012, 865–887; (g) V. Marcos and J. Alemán, *Chem. Soc. Rev.*, 2016, **45**, 6812–6832; (h) K. Anebuselvy, D. B. Ramachary and I. Kumar, *Dienamine Catalysis for Organic Synthesis*, Royal Society of Chemistry, Cambridge, 2018. Albert Moyano\*

and

- Ramon Rios\*

*Chemical Reviews* 2011, 111, 8, 4703-4832 (

- 1
- 2 T. Akiyama, J. Itoh, K. Yokota and K. Fuchibe, *Angew. Chem. Int. Ed.*, 2004, **43**, 1566-1568.
- 3 D. Uraguchi and M. Terada, *J. Am. Chem. Soc.*, 2004, **126**, 5356-5357.
- 4 For reviews on catalysis by chiral phosphoric acids, see: (a) T. Akiyama, J. Itoh and K. Fuchibe, *Adv. Synth. Catal.*, 2006, **348**, 999-1010; (b) T. Akiyama, *Chem. Rev.*, 2007, **107**, 5744-5758; (c) M. Terada, *Synthesis*, 2010, 1929-1982; (d) D. Kampen, C. M. Reisinger and B. List, *Top. Curr. Chem.*, 2010, **291**, 395-456; (e) M. Rueping, A. Kuenkel and I. Atodiresei, *Chem. Soc. Rev.*, 2011, **40**, 4539-4549; (f) M. Rueping, B. J. Nachtsheim, W. leawsuwan and I. Atodiresei, *Angew. Chem. Int. Ed.*, 2011, **50**, 6706-6720; (g) D. Parmar, E. Sugiono, S. Raja and M. Rueping, *Chem. Rev.*, 2014, **114**, 9047-9153; (h) T. James, M. van Gemmeren and B. List, *Chem. Rev.*, 2015, **115**, 9388-9409; (i) R. Maji, S. C. Mallojjala and S. E. Wheeler, *Chem. Soc. Rev.*, 2018, **47**, 1142-1158; (j) A. Rahman and X. Lin, *Org. Biomol. Chem.*, 2018, **16**, 4753-4777; (k) J. Merad, C. Lalli, G. Bernadat, J. Maury and G. Masson, *Chem. – Eur. J.*, 2018, **24**, 3925-3943; (l), P. S. G. Nunes, H. D. A. Vidal and A. G. Corrêa, *Org. Biomol. Chem.*, 2020, **18**, 7751-7773; (m) Y.-D. Shao and D.-J. Cheng, *ChemCatChem*, 2020, **12**, DOI:10.1002/cctc.202001750.
- 5 For selected reviews on utilisation of enamides, see: (a) R. Matsubara and S. Kobayashi, *Acc. Chem. Res.*, 2008, **41**, 292-301; (b) K. Gopalaiah and H. B. Kagan, *Chem. Rev.*, 2011, **111**, 4599-4657; (c) N. Gigant, L. Chausset-Boissarie and I. Gillaizeau, *Chem. – Eur. J.*, 2014, **20**, 7548-7564; (d) F. Beltran and L. Miesch, *Synthesis*, 2020, **52**, 2497-2511; (e) T. Zhu, S. Xie, P. Rojsitthisak and J. Wu, *Org. Biomol. Chem.*, 2020, **18**, 1504-1521
- 6 For recent reviews on aza-DA reactions, see: (a) V. V. Kouznetsov, *Tetrahedron*, 2009, **65**, 2721-2750; (b) D., Bello, R. Ramón and R. Lavilla, *Curr. Org. Chem.*, 2010, **14**, 332-356; (c) V. Sridharan, P. A. Suryavanshi and J. C. Menéndez, *Chem. Rev.*, 2011, **111**, 7157-7259; (d) G. Masson, C. Lalli, M. Benohoud and G. Dagousset, *Chem. Soc. Rev.*, 2013, **42**, 902-923; (e) M. Fochi, L. Caruana and L. Bernardi, *Synthesis*, 2014, **46**, 135-157; (f) V. Eschenbrenner-Lux, K. Kumar and H. Waldmann, *Angew. Chem. Int. Ed.*, 2014, **53**, 11146-11157; (g) O. Ghashghaei, C. Masdeu, C. Alonso, F. Palacios and R. Lavilla, *Drug Discovery Today*, 2018, **29**, 71-79; (h) S. Zlotin, M. G. Vinogradov and O. V. Turova, *Adv. Synth. Catal.*, 2021, **363**, DOI:10.1002/adsc.202001307.
- 7 For recent reviews on tetrahydroquinolines, see: (a) J. S. Bello Forero, J. J. Junior and F. M. da Silva, *Curr. Org. Synth.*, 2016, **13**, 157-175; (b) I. Muthukrishnan, V. Sridharan, and J. C. Menéndez, *Chem. Rev.*, 2019, **119**, 5057-5191.
- 8 H. Ishitani and S. Kobayashi, *Tetrahedron Lett.*, 1996, **37**, 7357-7360.
- 9 G. Sundararajan, N. Prabakaran and B. Varghese, *Org. Lett.*, 2001, **3**, 1973-1976.
- 10 T. Akiyama, H. Morita and K. Fuchibe, *J. Am. Chem. Soc.*, 2006, **128**, 13070-13071.
- 11 The first examples of Povarov reactions using enamide derivatives, see: (a) P. D. Leeson, R. W. Carling, K. W. Moore, A. M. Moseley, J. D. Smith, G. Stevenson, T. Chan, R. Baker, A. C. Foster, S. Grimwood, J. A. Kemp, G. R. Marshall and K. Hoogsteen, *J. Med. Chem.*, 1992, **35**, 1954-1968; (b) M. Hadden and P. J. Stevenson, *Tetrahedron Lett.*, 1999, **40**, 1215-1218; (c) R. A. Batey, P. D. Simoncic, D. Lin, R. P. Smyj and A. J. Lough, *Chem. Commun.*, 1999, 651-652.
- 12 For recent reviews on asymmetric 3-component reactions, see: (a) J. Zhu and H. Bienaymé, *Multicomponent Reactions*, Wiley-VCH, Weinheim, 2005; (b) C. M. R. Volla, I. Atodiresei and M. Rueping, *Chem. Rev.*, 2014, **114**, 2390-2431; (c) D. J. Ramón and M. Yus, *Angew. Chem. Int. Ed.*, 2005, **44**, 1602-1634.
- 13 H. Liu, G. Dagousset, G. Masson, P. Retailleau and J. Zhu, *J. Am. Chem. Soc.*, 2009, **131**, 4598-4599.
- 14 (a) C. Xia, L. Heng and D. Ma, *Tetrahedron Lett.*, 2002, **43**, 9405-9409; (b) D. A. Powell and R. A. Batey, *Org. Lett.*, 2002, **4**, 2913-2916; (c) M. Bazin and C. J. Kuhn, *J. Comb. Chem.*, 2005, **7**, 302-308; (d) D. B. Damon, R. W. Dugger, G. Magnus-Aryitev, R. B. Ruggeri, R. T. Wester, M. Tu and Y. Abramov, *Org. Process Res. Dev.*, 2006, **10**, 464-471; (e) D. B. Damon, R. W. Dugger, S. E. Hubbs, J. M. Scott and R. W. Scott, *Org. Process Res. Dev.*, 2006, **10**, 472-480.
- 15 (a) D. B. Damon and R. W. Dugger, *Eur. Pat. Appl.* EP1125929, 2001 and *US Patent* 6,313,142, 2001; (b) D. B. Damon, R. W. Dugger and R. W. Scott, *US Patent* 6,689,897, 2004; (c) M. Guinó, P. H. Phua, J.-C. Caille and K. K. Hii, *J. Org. Chem.*, 2007, **72**, 6290-6293.
- 16 (a) G. Dagousset, J. Zhu and G. Masson, *J. Am. Chem. Soc.*, 2011, **133**, 14804-14813. (b) G. Dagousset, F. Drouet, G. Masson and J. Zhu, *Org. Lett.*, 2009, **11**, 5546-5549.
- 17 D. Huang, F. Xu, T. Chen, Y. Wang and X. Lin, *RSC Adv.*, 2013, **3**, 573-578.
- 18 M. Z. Kazancioglu, E. Kalay, E. A. Kazancioglu and V. A. Peshkov, *ChemistrySelect*, 2019, **4**, 8797-8799.
- 19 (a) M. Hadden, M. Nieuwenhuyzen, D. Osborne, P. J. Stevenson, N. Thompson and A. D. Walker, *Tetrahedron*, 2006, **62**, 3977-3984; (b) S. Ikeda, M. Shibuya and Y. Iwabuchi, *Chem. Commun.*, 2007, 504-506; (d) B. B. Snider, Y. Ahn and B. M. Foxman, *Tetrahedron Lett.*, 1999, **40**, 3339-3342; (e) C. J. Lovely, and H. Mahmud, *Tetrahedron Lett.*, 1999, **40**, 2079-2082.
- 20 C. Wang, Z.-Y. Han, H.-W. Luo and L.-Z. Gong, *Org. Lett.*, 2010, **12**, 2266-2269.
- 21 For selected reviews on chiral gold-phosphate catalysts, see: (a) S. M. Inamdar, A. Konal and N. T. Patil, *Chem. Commun.*, 2014, **50**, 15124-15135; (b) M. Jia and M. Bandini, *ACS Catal.*, 2015, **5**, 1638-1652.
- 22 J.-H. Lin, G. Zong, R.-B. Du, J.-C. Xiao and S. Liu, *Chem. Commun.*, 2012, **48**, 7738-7740.
- 23 L. Caruana, M. Fochi, S. Ranieri, A. Mazzanti and L. Bernardi, *Chem. Commun.*, 2013, **49**, 880-882.
- 24 D. Stevanović, G. Bertuzzi, A. Mazzanti, M. Fochi and L. Bernardi, *Adv. Synth. Catal.*, 2018, **360**, 893-900.
- 25 E. Richmond, I. U. Khan and J. Moran, *Chem. – Eur. J.*, 2016, **22**, 12274-12277.
- 26 For nickel-catalysed allylamine carbamate isomerization, see: (a) L. Wang, C. Liu, R. Bai Y. Pan and A. Lei, *Chem. Commun.*, 2013, **49**, 7923-7925; (b) S. Krompiec, M. Pigulla, M. Krompiec, S. Baj, J. Mrowiec-Bialon and J. Kasperczyk, *Tetrahedron Lett.*, 2004, **45**, 5257-5261.
- 27 G. Dagousset, P. Retailleau, G. Masson and J. Zhu, *Chem. – Eur. J.*, 2012, **18**, 5869-5873.
- 28 The first exemple of povarov reaction using ene-urea derivatives, see: R. A. Batey and D. A. Powell, *Chem. Commun.*, 2001, 2362-2363.
- 29 (a) K. M. Witherup, R. W. Ransom, A. C. Graham, M. J. Bernard, A. M. Salvatore, W. C. Lumma, P. S. Anderson, S. M. Pitzenger and S. L. Varga, *J. Am. Chem. Soc.*, 1995, **117**, 6682-6685; (b) A. H. Gentry and K. Cook, *J. Ethnopharmacol.* 1984, **11**, 337-343; (c) J. S. Blakeney, R. C. Reid, G. T. Le and D. P. Fairlie, *Chem. Rev.*, 2007, **107**, 2960-3041.
- 30 J. Brioché, T. Courant, L. Alcaraz, M. Stocks, M. Furber, J. Zhu and G. Masson, *Adv. Synth. Catal.*, 2014, **356**, 1719-1724.
- 31 (a) M. De Rosa, R. P. Issac and G. Houghton, *Tetrahedron Lett.*, 1995, **36**, 9261-9264; (b) G. Cirrincione, A. M. Almerico, P. Diana, P. Barraja, F. Mingoia, S. Grimaudo, G. Dattolo and E. Aiello, *J. Heterocycl. Chem.*, 1996, **33**, 161-168; (c) M. De Rosa,

- R. P. Issac, M. Marquez, M. Orozco, F. J. Luque and M. D. Timken, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1433-1438.
- 32 C. Gelis, G. Levitre, V. Guérineau, D. Touboul, L. Neuville and G. Masson, *Eur. J. Org. Chem.*, 2019, **31**, 5151-5155.
- 33 For recent selected examples of copper catalysed-deoxygenation of *N*-oxides, see: (a) S. K. Singh, M. S. Reddy, M. Mangle, K. R. Ganesh, *Tetrahedron*, 2007, **63**, 126-130; (b) J. Jeong, D. Lee and S. Chang, *Chem. Commun.*, 2015, **51**, 7035-7038; (c) R. Odani, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2015, **80**, 2384-2391; (d) B. Du, P. Qian, Y. Wang, H. Mei, J. Han and Y. Pan, *Org. Lett.*, 2016, **18**, 4144-4147; (e) C.-S. Wang, T. Roisnel, P. H. Dixneuf and J.-F. Soulé, *Org. Lett.*, 2017, **19**, 6720-6723; (f) S. Yu, H. L. Sang and S. Ge, *Angew. Chem. Int. Ed.*, 2017, **56**, 15896-15900; (g) Y. Kong, Y. Liu, B. Wang, S. Li, L. Liu, W. Chang, J., Li, *Adv. Synth. Catal.*, 2018, **360**, 1240-1252.
- 34 For selected example using chiral copper(II) phosphate catalyst, see: (a) K. Saito, Y. Kajiwara and T. Akiyama, *Angew. Chem. Int. Ed.* **2013**, **52**, 13284-13288; (b) V. Rauniyar, Z. J. Wang, H. E. Burks and F. D. Toste, *J. Am. Chem. Soc.*, **2011**, **133**, 8486-8489.
- 35 For selected examples of the use of 2-benzothiazolines, see: (a) H.-X. He and D.-M. Du, *RSC Adv.*, 2013, **355**, 1137-1148; (b) H.-X. He and D.-M. Du, *Eur. J. Org. Chem.*, 2014, 6190-6199; (c) Q. Ni, X. Song, J. Xiong, G. Raabe and D. Enders, *Chem. Commun.*, 2015, **51**, 1263-1266.
- 36 L. Jarrige, D. Glavač, G. Levitre, P. Retailleau, G. Bernadat, L. Neuville and G. Masson, *Chem. Sci.*, 2019, **10**, 3765-3769.
- 37 (a) J. Merad, J.-M. Pons, O. Chuzel and C. Bressy, *Eur. J. Org. Chem.*, 2016, **34**, 5589-5610; (b) S. Vellalath and D. Romo, *Angew. Chem. Int. Ed.*, 2016, **55**, 13934-13943; (c) J. E. Taylor, S. D. Bull and J. M. J. Williams, *Chem. Soc. Rev.*, 2012, **41**, 2109-2121; (d) N. De Rycke, F. Couty and O. R. P. David, *Chem. – Eur. J.*, 2011, **17**, 12852-12871.
- 38 (a) M. Behforouz and M. Ahmadian, *Tetrahedron*, 2000, **56**, 5259-5288; (b) S. Jayakumar, M. P. S. Ishar and M. P. Mahajan, *Tetrahedron*, 2002, **58**, 379-471; (c) B. Groenendaal, E. Ruijter and R. V. A. Orru, *Chem. Commun.*, 2008, 5474-5489; (d) J.-C. M. Monbaliu, K. G. R. Masschelein and C. V. Stevens, *Chem. Soc. Rev.*, 2011, **40**, 4708-4739; (e) G. Blond, M. Gulea and V. Mamane, *Curr. Org. Chem.*, 2016, **20**, 2161-2210.
- 39 (a) M. Rubiralta, E. Giralt and A. Diez, *Piperidine: Structure, Preparation, Reactivity and Synthetic Applications of Piperidine and Its Derivatives*, in *Studies in Organic Chemistry*, Elsevier: New-York, 1991, vol. 43; (b) J. P. Michael, *The Alkaloids*, Cordell, G. A., Ed., Academic Press: San Diego, 2001, vol. 55; (c) P. D. Bailey, P. A. Millwood and P. D. Smith, *Chem. Commun.*, 1998, 633-640; (d) V. H. Lillelund, H. H. Jensen, X. F. Liang and M. Bols, *Chem. Rev.*, 2002, **102**, 515-554; (e) P. M. Weintraub, J. S. Sabol, J. M. Kane and D. R. Borchering, *Tetrahedron*, 2003, **59**, 2953-2989; (f) M. G. P. Buffat, *Tetrahedron* 2004, **60**, 1701-1729; (g) F.-X. Felpin and J. Lebreton, *Curr. Org. Synth.* 2004, **1**, 83-109; (h) N. Zanatta, L. da S. Fernandes, F. M. Nachtigall, H. S. Coelho, S. S. Amaral, A. F. C. Flores, H. G. Bonacorso and M. A. P. Martins, *Eur. J. Org. Chem.*, 2009, 1435-1444; and references cited therein; (g) X. Huang, A. Zhang, D. Chen, Z. Jia, X. Li, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 2859-2863. (h) P. R. Girling, T. Kiyoi and A. Whiting, *Org. Biomol. Chem.*, 2011, **9**, 3105-3121.
- 40 For selected reviews, see: (a) J. K. Whitesell and M. A. Whitesell, *Synthesis*, 1983, 517-536; (b) D. L. Boger and S. M. Weinreb, *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic Press, San Diego, 1987, chap. 2, pp 34-70; chap. 9, pp 239-299, and references therein; (c) J. Xianxing and W. Rui, *Chem. Rev.*, 2013, **113**, 5515-5546; (d) M. Xie, L. Lin and X. Feng, *Chem. Rec.*, 2017, **17**, 1184-1202; (e) Y. Dudognon, J. Rodriguez, T. Constantieux and X. Bugaut, *Eur. J. Org. Chem.*, 2018, **2018**, 2432-2442; For selected examples of asymmetric aza-DA using 1-azadiene, see: (f) M. E. Jung and J. J. Shapiro, *J. Am. Chem. Soc.*, 1980, **102**, 7862-7866; (g) J. Esquivias, R. G. Arrayás and J. C. Carretero, *J. Am. Chem. Soc.*, 2007, **129**, 1480-1481; (h) B. Han, J.-L. Li, C. Ma, S.-J. Zhang and Y.-C. Chen, *Angew. Chem. Int. Ed.*, 2008, **47**, 9971-9974; (i) X. Jiang, X. Shi, S. Wang, T. Sun, Y. Cao and R. Wang, *Angew. Chem. Int. Ed.*, 2012, **51**, 2084-2087; (j) Y. Deng, L. Liu, R. G. Sarkisian, K. Wheeler, H. Wang, and Z. Xu, *Angew. Chem. Int. Ed.*, 2013, **52**, 3663-3667; (k) X. Feng, Z. Zhou, C. Ma, X. Yin, R. Li, L. Dong and Y.-C. Chen, *Angew. Chem. Int. Ed.*, 2013, **52**, 14173-14176; (l) S. He, H. Gu, Y.-P. He and X. Yang, *Org. Lett.*, 2020, **22**, 5633-5639.
- 41 L. He, G. Laurent, P. Retailleau, B. Folléas, J.-L. Brayer and G. Masson, *Angew. Chem. Int. Ed.*, 2013, **52**, 11088-11091.
- 42 (a) Y. Nishimura, T. Satoh, H. Adachi, S. Kondo, T. Takeuchi, M. Azetaka, H. Fukuyasu and Y. Iizuka, *J. Med. Chem.*, 1997, **40**, 2626-2633; (b) S. Knapp and D. Zhao, *Org. Lett.*, 2000, **2**, 4037-4040; (c) E., Shitara, Y. Nishimura, K. Nerome, Y. Hiramoto and T. Takeuchi, *Org. Lett.*, 2000, **2**, 3837-3840.
- 43 (a) J.-P. Wan, C. C. J. Loh, F. Pan and D. Enders, *Chem. Commun.*, 2012, **48**, 10049-10051; (b) B. Han, J.-C. Li, C. Ma, S.-J. Zhang and Y.-C. Chen, *Angew. Chem. Int. Ed.*, 2008, **120**, 9971-9974.
- 44 For biological properties of xanthenes and derivatives, see: (a) H. N. Hafez, M. I. Hegab, I. S. Ahmed-Farag and A. B. A. El-Gazzar, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4538-4543; (b) R. W. Lambert, J. A. Martin, J. H. Merrett, K. E. B. Parkes and G. J. Thomas, CT Int. Appl. WO9706178, 1997; (c) T. Hideo and J. Teruomi, (Sankyo CO.), Jpn. Patent, 56005480, 1981; (d) J. P. Poupelin, G. Saint-Ruf, O. Foussard-Blanpin, G. Narcisse, G. Uchida-Ernouf and R. Lacroix, *Eur. J. Med. Chem.*, 1978, **13**, 67-71.
- 45 S. Saha and C. Schneider, *Chem. – Eur. J.*, 2015, **21**, 2348-2352.
- 46 For reviews, see: (a) Y. Chiang, A. J. Kreesge and Y. Zhu, *Pure Appl. Chem.*, 2000, **72**, 2299-2308; (b) R. W. van de Water and T. R. R. Pettus, *Tetrahedron*, 2002, **58**, 5367-5405; (c) S. E. Rokita, *Quinone Methides*, John Wiley and Sons, 2009; (d) T. P. Pathak and M. S. Sigman, *J. Org. Chem.*, 2011, **76**, 9210-9215; (e) N. J. Willis and C. D. Bray, *Chem. – Eur. J.*, 2012, **18**, 9160-9173; (f) W.-J. Bai, J. G. David, Z.-G. Feng, M. G. Weaver, K.-L. Wu and T. R. R. Pettus, *Acc. Chem. Res.*, 2014, **47**, 3655-3664; (g) M. S. Singh, A. Nagaraju, N. Anand and S. Chowdhury, *RSC Adv.*, 2014, **4**, 55924-55959; (h) A. A. Jaworski and K. A. Scheidt, *J. Org. Chem.*, 2016, **81**, 10145-10153.
- 47 S. Saha and C. Schneider, *Org. Lett.*, 2015, **17**, 648-651.
- 48 C. Gharui, S. Singh and S. C. Pan, *Org. Biomol. Chem.*, 2017, **15**, 7272-7276.
- 49 (a) S. R. Trenor, A. R. Shultz, B. J. Love and T. E. Long, *Chem. Rev.*, 2004, **104**, 3059-3078; (b) M. C. Breschi, V. Calderone, A. Martelli, F. Minutolo, S. Rapposelli, L. Testai, F. Tonelli and A. Balsamo, *J. Med. Chem.*, 2006, **49**, 7600-7602; (c) S. Khelili, X. Florence, M. Bouhadja, S. Abdelaziz, N. Mechouch, Y. Mohamed, P. D. de Tullio, A. Lebrun and B. Pirotte, *Bioorg. Med. Chem.*, 2008, **16**, 6124-6130; (d) A. Coi, A. M. Bianucci, V. Calderone, L. Testai, M. Digiacomio, S. Rapposelli and A. Balsamo, *Bioorg. Med. Chem.*, 2009, **17**, 5565-5571.
- 50 R. Sustmann, *Pure and Applied Chemistry*, 1974, **40**, 569-593.
- 51 (a) Y. Xing and N.-X. Wang, *Coord. Chem. Rev.*, 2012, **256**, 938-952; (b) T. Hashimoto and K. Maruoka, *Chem. Rev.*, 2015, **115**, 5366-5412.
- 52 C. Zhang, L.-X. Zhang, Y. Qiu, B. Xu, Y. Zong and Q.-X. Guo, *RSC Adv.*, 2014, **4**, 6916-6919.
- 53 W. Tan, X. Li, Y.-X. Gong, M.-D. Ge and F. Shi, *Chem. Commun.*, 2014, **50**, 15901-15904.

- 54 For selected reviews on vinylindoles and vinylindoliniums, see: (a) S. M. Weinreb and P. M. Scola, *Chem. Rev.*, 1989, **89**, 1525-1534; (b) B. E. Maryanoff, H.-C. Zhang, J. H. Cohen, I. J. Turchi and C. A. Maryanoff, *Chem. Rev.*, 2004, **104**, 1431-1628; (c) A. Yazici and S. G. Pyne, *Synthesis*, 2009, 339-368; (d) A. Yazici and S. G. Pyne, *Synthesis*, 2009, 513-541; (e) A. Palmieri, M. Petrini and R. R. Shaikh, *Org. Biomol. Chem.*, 2010, **8**, 1259-1270; (f) B. Yin, Y. Zhang and L.-W. Xu, *Synthesis*, 2010, 3583-3595; (g) A. O. Kataja and G. Masson, *Tetrahedron*, 2014, **70**, 8783-8815; (h) E. Rossi, G. Abbiati and V. Pirovano, *Eur. J. Org. Chem.*, 2017, **31**, 4512-4529; (i) Y.-C. Zhang, F. Jiang and F. Shi, *Acc. Chem. Res.*, 2020, **53**, 425-446.
- 55 C. Lebé, A. O. Kataja, F. Blanchard and G. Masson, *Chem. – Eur. J.*, 2015, **21**, 8399-8402.
- 56 For selected examples of biological properties of cyclopenta[b]indoles, see: (a) P. S. Steyn and R. Vleggar, *Fortschr. Chem. Org. Naturst.*, 1985, **48**, 1-80; (b) Y. C. Kong, K. F. Cheng, R. C. Cambie and P. G. Waterman, *J. Chem. Soc. Chem. Commun.*, 1985, 47-48; (c) A. Park, R. E. Moore and G. M. L. Patterson, *Tetrahedron Lett.*, 1992, **33**, 3257-3260; (d) J. P. Springer, J. Clardy, J. M. Wells, R. J. Cole and J. W. Kirksey, *Tetrahedron Lett.*, 1975, **16**, 2531-2534; (e) B. J. Wilson, T. Hoekman and W. D. Dettbarn, *Brain Res.*, 1972, **40**, 540-544; (f) G. N. Belofsky, J. B. Gloer, D. T. Wicklow and P. F. Dowd, *Tetrahedron*, 1995, **51**, 3959-3968.
- 57 (a) T. courant, S. Kumarn, L. He, P. Retailleau and G. Masson, *Adv. Synth. Catal.*, 2013, **355**, 836-840.
- 58 K. Bera and C. Schneider, *Org. Lett.*, 2016, **18**, 5660-5663.
- 59 For selected examples of biological properties of cyclopenta[a]indoles, see: (a) F. Tillequin, M. Koch, M. Bert and T. Sevenet, *J. Nat. Prod.*, 1979, **42**, 92-95; (b) B. S. Iyengar, W. A. Remers and W. T. Bradner, *J. Med. Chem.*, 1986, **29**, 1864-1868; (c) E. O. M. Orlemans, W. Verboom, M. W. Scheltinga, D. N. Reinhoudt, P. Lelieveld, H. H. Fiebig, B. R. Winterhalter, J. A. Double and M. C. Bibby, *J. Med. Chem.*, 1989, **32**, 1612-1620; (d) J. J. Vepsäläinen, S. Auriola, M. Tukiainen, N. Ropponen and J. C. Callaway, *Planta Med.*, 2005, **71**, 1053-1057; (e) U. Galm, M. H. Hager, S. G. V. Van Lanen, J. Ju, J. S. Thorson and B. Shen, *Chem. Rev.*, 2005, **105**, 739-758; (f) T. Sasae, H. Yamada, K. Sakoda, N. Imagawa, T. Abe, M. Ito, S. Sagawa, M. Tanaka and M. Matsushita, *Diabetes, Obes. Metab.*, 2005, **7**, 586-594; (g) L. S. Fernandez, M. S. Buchanan, A. R. Carroll, Y.-J. Feng, R. J. Quinn and V. M. Avery, *Org. Lett.*, 2009, **11**, 329-332.
- 60 (a) G. Büchi and P.-S. Chu, *J. Org. Chem.*, 1978, **43**, 3717-3719; (b) T. A. Engler, M. A. Letavic, R. Iyengar, K. O. LaTessa and J. P. Reddy, *J. Org. Chem.*, 1999, **64**, 2391-2405; (c) K. L. Jensen, P. T. Franke, L. T. Nielsen, K. Daasbjerg and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2010, **49**, 129-133; (d) X.-X. Sun, H.-H. Zhang, G.-H. Li, L. Meng and F. Shi, *Chem. Commun.*, 2016, **52**, 2968-2971; (e) Q. Yu, Y. Fu, J. Huang, J. Qin, H. Zhuo, Y. Wu and F. Zhong, *ACS Catal.*, 2019, **9**, 7285-7291.
- 61 (a) S. Apers, D. Paper, J. Bürgermeister, S. Baronikova, S. Van Dyck, G. Lemiè, A. Vlietinck and L. Pieters, *J. Nat. Prod.*, 2002, **65**, 718-720; (b) B. M. Trost, O. R. Thiel and H.-C. Tsui, *J. Am. Chem. Soc.*, 2003, **125**, 13155-13164; (c) M. Lachia and C. J. Moody, *Nat. Prod. Rep.*, 2008, **25**, 227-253; (d) T. Shen, X.-N. Wang and H.-X. Lou, *Nat. Prod. Rep.*, 2009, **26**, 916-935; (e) L. Pieters, S. Van Dyck, M. Gao, R. Bai, E. Hamel, A. Vlietinck and G. Lemiè, *J. Med. Chem.*, 1999, **42**, 5475-5481; (f) J. S. Shin, Y. M. Kim, S. S. Hong, G. S. Kang, Y. J. Yang, D. K. Lee, B. Y. Hwang, J. S. Ro and M. K. Lee, *Arch. Pharm. Res.*, 2005, **28**, 1337-1340; (g) S. K. Manna, J. S. Bose, V. Gangan, N. Raviprakash, T. Navaneetha, P. B. Raghavendra, B. Babajan, C. S. Kumar and S. K. Jain, *J. Biol. Chem.*, 2010, **285**, 22318-22327.
- 62 C. Gelis, M. Bekkaye, C. Lebé, F. Blanchard and G. Masson, *Org. Lett.*, 2016, **18**, 3422-3425.
- 63 For a selected review on dearomatization followed by enantioselective organocatalysed reactions, see: (a) Z.-L. Xia, Q.-F. Xu-Xu, C. Zheng and S.-L. You, *Chem. Soc. Rev.*, 2019, **49**, 286-300; For selected examples of oxidative dearomatization followed by enantioselective organocatalysed reactions, see: (b) Q. Liu and T. Rovis, *J. Am. Chem. Soc.*, 2006, **128**, 2552-2553; (c) N. T. Vo, R. D. M. Pace, F. O'Har and M. J. Gaunt, *J. Am. Chem. Soc.*, 2008, **130**, 404-405; (d) K. L. Jensen, P. T. Franke, L. T. Nielsen, K. Daasbjerg and K. A. Jørgensen, *Angew. Chem Int. Ed.*, 2010, **49**, 129-133; (e) Q. Gu, Z.-Q. Rong, C. Zheng and S.-L. You, *J. Am. Chem. Soc.*, 2010, **132**, 4056-4057; (f) Q. Gu and S.-L. You, *Org. Lett.*, 2011, **13**, 5192-5195; (g) Q. Gu and S.-L. You, *Chem. Sci.*, 2011, **2**, 1519-1522; (h) R. Leon, A. Jawalekar, T. Redert and M. J. Gaunt, *Chem. Sci.*, 2011, **2**, 1487-1490; (i) M.-Q. Jia and S.-L. You, *Chem. Commun.*, 2012, **48**, 6363-6365; (j) D. M. Rubush, M. A. Morges, B. J. Rose, D. H. Thamm and T. Rovis, *J. Am. Chem. Soc.*, 2012, **134**, 13554-13557; (k) M.-Q. Jia, C. Liu and S.-L. You, *J. Org. Chem.*, 2012, **77**, 10996-11001; (l) F. Portalier, F. Bourdreux, J. Marrot, X. Moreau, V. Coeffard and C. Greck, *Org. Lett.*, 2013, **15**, 5642-5645; (m) J. Zhang, S.-X. Lin, D.-J. Cheng, X.-Y. Liu and B. Tan, *J. Am. Chem. Soc.*, 2015, **137**, 14039-14042; (n) G. Zhu, G. Bao, Y. Li, J. Yang, W. Sun, J. Li, L. Hong and R. Wang, *Org. Lett.*, 2016, **18**, 5288-5291.
- 64 W.-Y. Ma, C. Gelis, D. Bouchet, P. Retailleau, M. Xavier, L. Neuville and G. Masson, *Org. Lett.*, 2021, **23**, 442-448.
- 65 For reviews on indolines properties, see: (a) N. R. Candeias, L. C. Branco, P. M. P. Gois, C. A. M. Afonso and A. F. Trindade, *Chem. Rev.*, 2009, **109**, 2703-2802; (b) D. Liu, G. Zhao and L. Xiang, *Eur. J. Org. Chem.*, 2010, **2010**, 3975-3984; (c) D. Zhang, H. Song and Y. Qin, *Acc. Chem. Res.*, 2011, **44**, 447-457; (d) T. S. Silva, M. T. Rodrigues, H. Santos, L. A. Zeoly, W. P. Almeida, R. C. Barcelos, R. C. Gomes, F. S. Fernandes and F. Coelho, *Tetrahedron*, 2019, **75**, 2063-2097.
- 66 J. Reid, L. Simon and J. A. Goodman, *Acc. Chem. Res.*, 2016, **49**, 1029-1041.
- 67 (a) L. E. Overman and P. J. Jessup, *J. Am. Chem. Soc.*, 1978, **100**, 5179-5185; (b) L. E. Overman, R. L. Freerks, C. B. Petty, L. A. Clizbe, R. K. Ono, G. F. Taylor and P. J. Jessup, *J. Am. Chem. Soc.*, 1981, **103**, 2816-2822; (c) L. E. Overman, D. Lesuisse and M. Hashimoto, *J. Am. Chem. Soc.*, 1983, **105**, 5373-5379.
- 68 For reviews on Lewis-acid catalyzed DA reactions of  $\alpha,\beta$ -unsaturated carbonyls, see: (a) F. Fringuelli and A. Taticchi, *The Diels-Alder Reaction: Selected Practical Methods*, John Wiley and Sons, 2002, chap. 3, pp 99-142; (b) S. Iwasa and H. Nishiyama, in *Acid Catalysis in Modern Organic Synthesis*, ed. H. Yamamoto, K. Ishihara, Wiley-VCH, Weinheim, 2008, ch. 16, pp 859-901; For selected reviews on proline-catalyzed DA reactions of  $\alpha,\beta$ -unsaturated carbonyls, see: (a) V. Marcos and J. Alemán, *Chem. Soc. Rev.*, 2016, **45**, 6812-6834; (b) K. Anebuselvy, D. B. Ramachary and I. Kumar, *Dieneamine Catalysis for Organic Synthesis*, CPI Group, Croydon, 2018.
- 69 For selected examples of asymmetric DA reactions with  $\alpha,\beta$ -unsaturated aldehydes using chiral Lewis acid catalysts, see: (a) Y. Huang, T. Iwama and V. H. Rawal, *J. Am. Chem. Soc.*, 2000, **122**, 7843-7844; (b) Y. Huang, T. Iwama and V. H. Rawal, *Org. Lett.*, 2002, **4**, 1163-1166. For other selected examples of asymmetric DA reactions with  $\alpha,\beta$ -unsaturated aldehydes, see: (c) K. A. Ahrendt, C. J. Borths and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2000, **122**, 4243-4244; (d) A. B. Northrup and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2002, **124**, 2458-2460; (e) S. A. Selkälä, J. Tois, P. M. Pihko and A. M. P. Koskinen, *Adv. Synth. Catal.*, 2002, **344**, 941-945; (f) M. Lemay and W. W. Ogilvie, *Org. Lett.*, 2005, **7**, 4141-4144; (g) R. M. Wilson, W. S. Jen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 11616-11617; (h) T. Kano, Y. Tanaka and K. Maruoka, *Org. Lett.*, 2006, **8**, 2687-2689; (i) M. Lemay, L. Aumand and W. W. Ogilvie, *Adv. Synth. Catal.*, 2007, **349**, 441-447; (j) T. Kano, Y.

- Tanaka and K. Maruoka, *Chem. Asian J.*, 2007, **2**, 1161-1165; (k) H. He, B.-J. Pei, H.-H. Chou, T. Tian, W.-H. Chan and A. W. M. Lee, *Org. Lett.*, 2008, **10**, 2421-2424; (l) C. Gioia, A. Hauville, L. Bernardi, F. Fini and A. Ricci, *Angew. Chem. Int. Ed.*, 2008, **47**, 9236-9239; (m) H. Nakano, K. Ozone, M. Takeshita, E. Kwon, C. Seki, H. Matsuyama, N. Takano and Y. Kohari, *Chem. Commun.*, 2010, **46**, 4827-4829; (n) B. Tan, G. Henández-Torres and C. F. Barbas III, *J. Am. Chem. Soc.*, 2011, **133**, 12354-12357; (o) K. S. Halskov, B. S. Donslund, S. Barfusser and K. A. Jørgensen, *Angew. Chem. Int. Ed.* 2014, **53**, 4137-4141; (p) M. E. Abbasov, B. M. Hudson, D. J. Tantillo and D. Romo, *J. Am. Chem. Soc.*, 2014, **136**, 4492-4495; (q) Y. Hayashi, B. P. Bondzic, T. Yamazaki, Y. Gupta, S. Ogasawara, T. Taniguchi and K. Monde, *Chem. – Eur. J.*, 2016, **22**, 15874-15880; For a review, see: (r) H. Pellissier, *Tetrahedron*, 2012, **68**, 2197-2232.
- 70 N. Momiyama, T. Konno, Y. Furiya, T. Iwamoto and M. Terada, *J. Am. Chem. Soc.*, 2011, **133**, 19294-19297.
- 71 N. Momiyama, K. Funayama, H. Noda, M. Yamanaka, N. Akasaka, S. Ishida, T. Iwamoto and M. Terada, *ACS. Catal.*, 2016, **6**, 949-956.
- 72 For selected examples of catalytic enantioselective DA reactions of  $\alpha$ -haloacrolein, see: (a) E. J. Corey and T.-P. Loh, *J. Am. Chem. Soc.*, 1991, **113**, 8966-8967; (b) E. J. Corey and T.-P. Loh, *Tetrahedron Lett.*, 1993, **34**, 3979-3982; (c) M. Hatano, T. Mizuno, A. Izumiseki, R. Usami, T. Asai, M. Akakura and K. Ishihara, *Angew. Chem. Int. Ed.*, 2011, **50**, 12189-12192.
- 73 (a) C. H. Cheon and H. Yamamoto, *Chem. Commun.*, 2011, **47**, 3043-3056; (b) N. Momiyama, T. Narumi, and M. Terada, *Chem. Commun.*, 2015, **51**, 16976-16979; (c) T. Akiyama and K. Mori, *Chem. Rev.*, 2015, **115**, 9277-9306.
- 74 L. Kong, X. Han and P. Jiao, *Chem. Commun.*, 2014, **50**, 14113-14116.
- 75 D. Nakashima and H. Yamamoto, *J. Am. Chem. Soc.*, 2006, **128**, 9626-9627.
- 76 For selected reviews on Quinone-DA reactions, see: (a) K. C. Nicolaou, S. A. Snyder, T. Montagnon and G. Vassilikoginnakis, *Angew. Chem. Int. Ed.*, 2002, **41**, 1668-1698; (b) C. C. Nawrat and C. J. Moody, *Angew. Chem. Int. Ed.*, 2014, **53**, 2056-2077.
- 77 T. Varlet, C. Gelis, P. Retailleau, G. Bernadat, L. Neuville and G. Masson, *Angew. Chem. Int. Ed.*, 2020, **59**, 8491-8496.
- 78 M. A. Colucci, G. D. Couch and C. J. Moody, *Org. Biomol. Chem.*, 2008, **6**, 637-656.
- 79 For selected examples of oxidation via quinhydrone complex, see: (a) J. M. Miguel del Corral, M. Gordaliza, M. A. Castro, M. M. Mahiques, P. Chamorro, A. Molinari, M. D. García-Grávalos, H. B. Broughton and A. San Feliciano, *J. Med. Chem.*, 2001, **44**, 1257-1267; (b) R. J. Radel, J. M. Sullivan and J. D. Hatfield, *Ind. Eng. Chem. Prod. Res. Dev.*, 1982, **21**, 566-570; (c) P. Guin, S. Das and P. C. Mandal, *Int. J. Electrochem.*, 2011, **1**, 1-23; (d) F. Wöhler, *Justus Liebigs Ann. Chem.*, 1844, **51**, 125-129.
- 80 For selected examples of chiral molecular redox switch, see: (a) B. L. Feringa, R. A. van Delden, N. Koumura and E. M. Geertsema, *Chem. Rev.*, 2000, **100**, 1789-1816; (b) D. Schweinfurth, M. Zalibera, M. Kathan, C. Shen, M. Mazzolini, N. Trapp, J. Crassous, G. Gescheidt and F. Diederich, *J. Am. Chem. Soc.*, 2014, **136**, 13045-13052; (c) G. Storch, B. Kim, B. Q. Mercado and S. J. Miller, *Angew. Chem. Int. Ed.*, 2018, **57**, 15107-15111.
- 81 For reviews of synthetic applications of Nitroso-DA products, see: (a) B. S. Bodnar and M. J. Miller, *Angew. Chem. Int. Ed.*, 2011, **50**, 5630-5647; (c) S. Carosso and M. J. Miller, *Org. Biomol. Chem.*, 2014, **12**, 7445-7468; (d) J. Streith and A. Defoin, *Synthesis*, 1994, **1994**, 1107-1117.
- 82 Y. Yamamoto and H. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 4128-4129.
- 83 (a) Y. Yamamoto, N. Momiyama and H. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 5962-5963; (b) Y. Yamamoto and H. Yamamoto, *Angew. Chem. Int. Ed.*, 2005, **44**, 7082-7085; (c) N. Momiyama, Y. Yamamoto and H. Yamamoto, *J. Am. Chem. Soc.*, 2007, **129**, 1190-1195; (d) C. K. Jana and A. Studer, *Angew. Chem. Int. Ed.*, 2007, **46**, 6542-6544; (e) C. K. Jana, S. Grimme and A. Studer, *Chem. – Eur. J.*, 2009, **15**, 9078-9084.
- 84 J. Pous, T. Courant, G. Bernadat, B. Iorga, F. Blanchard and G. Masson, *J. Am. Chem. Soc.*, 2015, **137**, 11950-11953.
- 85 For discussions of regioselectivity in Nitroso-DA reaction, see: (a) J. Sauer and R. Sustmann, *Angew. Chem. Int. Ed. Engl.*, 1980, **19**, 779-807; (b) D. L. Boger, M. Patel and F. Takusagawa, *J. Org. Chem.*, 1985, **50**, 1911-1916; (c) A. Defoin, H. Frits, C. Schmidlin and J. Streith, *Helv. Chim. Acta*, 1987, **70**, 554-569; (d) A. G. Leach and K. N. Houk, *J. Org. Chem.*, 2001, **66**, 5192-5200; (e) G. Galvani, R. Lett and C. Kouklovsky, *Chem. – Eur. J.*, 2013, **19**, 15604-15614; (f) J. M. Janey, *Angew. Chem. Int. Ed.*, 2005, **44**, 4292-4300; (g) M. Lu, Y. Lu, D. Zhu, X. Zeng, X. Li and G. Zhong, *Angew. Chem. Int. Ed.*, 2012, **49**, 8588-8592.
- 86 A. Dumoulin and G. Masson, *J. Org. Chem.*, 2016, **81**, 10154-10159.
- 87 For representative examples of enantioselective azo-hetero-DA reactions, see: (a) P. S. Aburel, W. Zhuang, R. G. Hazell and K. A. Jørgensen, *Org. Biomol. Chem.*, 2005, **3**, 2344-2349; (b) B. Liu, K.-N. Li, S.-W. Luo, J.-Z. Huang, P. Huan and L.-Z. Gong, *J. Am. Chem. Soc.*, 2013, **135**, 3323-3326; (c) B. Liu, T.-Y. Liu, S.-W. Luo and L.-Z. Gong, *Org. Lett.*, 2014, **16**, 6164-6167; For selected examples of synthetic applications of DA with diazenes products, see: (a) H. Yamamoto and M. Kawasaki, *Bull. Chem. Soc. Jpn.*, 2007, **80**, 595-607; (b) R. Chingle and W. D. Lubell, *Org. Lett.*, 2015, **17**, 5400-5403; (c) G. W. Starkey, J. J. Parlow and D. L. Flynn, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2385-2390.
- 88 For selected examples of non-catalysed azo-DA reactions, see: (a) L. Xiao, Y. Chen and K. Zhang, *Macromolecules*, 2016, **49**, 4452-4461; (b) S. Billiet, K. De Bruycker, F. Driessen, H. Goossens, V. Van Speybroeck, J. M. Winne and F. E. Du Prez, *Nat. Chem.*, 2014, **6**, 815-821; For an example with dienecarbamates, see: (c) T. Varlet, G. Levitre, P. Retailleau and G. Masson, *Bioorg. Med. Chem.*, 2019, **27**, 2438-2443.
- 89 N. Momiyama, H. Tabuse, H. Noda, M. Yamanaka, T. Fujinami, K. Yamanishi, A. Izumiseki, K. Funayama, F. Egawa, S. Okada, H. Adachi and M. Terada, *J. Am. Chem. Soc.*, 2016, **138**, 11353-11359.
- 90 C. Gelis, G. Levitre, J. Merad, P. Retailleau, L. Neuville and G. Masson, *Angew. Chem. Int. Ed.*, 2018, **57**, 12121-12125.
- 91 For selected reviews, see: (a) E. Stempel and T. Gaich, *Acc. Chem. Res.*, 2016, **49**, 2390-2402; (b) R. R. Gataullin, *Russ. J. Org. Chem.*, 2016, **52**, 1227-1263; (c) E. Yamuna, R. A. Kumar, M. Zeller and K. J. R. Prasad, *Eur. J. Med. Chem.*, 2012, **47**, 228-238; (d) B.-Y. Liu, C. Zhang, K.-W. Zeng, J. Li, X.-Y. Guo, M.-B. Zhao, P.-F. Tu and Y. Jiang, *Org. Lett.*, 2015, **17**, 4380-4383; (e) A. R. Carrol, E. Hyde, J. Smith, R. J. Quinn, G. Guymer, P. I. Forster, *J. Org. Chem.*, 2005, **70**, 1096-1099; (f) M. Andriantsiferana, R. Besselièvre, C. Riche, H. P. Husson, *Tetrahedron Lett.*, 1977, **18**, 2587-2590; (g) P. J. Gritsch, E. Stempel, T. Gaich, *Org. Lett.*, 2013, **15**, 5472-5475.