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Domino Reactions

Asymmetric Organocatalytic Domino Reactions**

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The current status of organic synthesis is hampered by costly protecting-group strategies and lengthy purification procedures after each synthetic step. To circumvent these problems, the synthetic potential of multicomponent domino reactions has been utilized for the efficient and stereoselective construction of complex molecules from simple precursors in a single process. In particular, domino reactions mediated by organocatalysts are in a way biomimetic, as this principle is used very efficiently in the biosynthesis of complex natural products starting from simple precursors. In this Minireview, we discuss the current development of this fast-growing field.

1. Introduction

For a long time, the field of asymmetric catalysis was dominated by metal and biocatalysis.[1,2] Since about the year 2000, the research area of asymmetric organocatalysis has grown rapidly to become one of the most exciting and current fields in organic chemistry.[3] Thus, asymmetric catalysis is now extended by this third discipline, asymmetric organocatalysis, in which small chiral organic molecules act as catalytically active species. These organocatalysts are metal-free, usually nontoxic, readily available, and often very robust. A significant advantage of many organocatalysts is the capability of promoting several types of reactions through different activation modes. A key role is played by chiral secondary amines, which are probably the most commonly used organocatalysts to date. They activate aldehydes either by enamine formation (raising the HOMO)[4] or α,β-unsaturated aldehydes by iminium-ion formation (lowering the LUMO).[5] This ability makes a catalyst ideal for application in domino reactions, which proceed consecutively and under the same reaction conditions to construct complex frameworks from simple precursors.[6] Organocatalytic domino reactions are characterized by high efficiencies and are in a way biomimetic, as the same principles are often found in the biosynthesis of natural products.[7] For this reason, it is not astonishing that domino processes represent a flourishing area in organic chemistry with characteristic advantages over the classical synthesis. Domino reactions avoid time-consuming and costly protection/deprotection processes as well as the purification of intermediates. They often proceed with excellent stereoselectivities and are environmentally friendly. The efficiency of asymmetric domino reactions can be judged by the number of bonds formed, the number of newly created stereocenters, and the increase in molecular complexity.

This Minireview illustrates the development of asymmetric organocatalytic domino reactions from its very beginning up to the present. The reactions are classified by their single activation steps, allowing a direct comparison of the different approaches. We have only covered truly asymmetric domino reactions; diastereoselective approaches are not discussed.

2. Amine-Catalyzed Domino Reactions

Organocatalytic domino reactions catalyzed by amines, especially secondary amines, are widespread, as secondary amines are capable of both enamine and iminium catalysis.[4] Also, the capability to tolerate numerous functional groups makes them ideal for the design of new asymmetric organocatalytic domino reactions, although their scope is mainly limited to carbonyl systems. In the following chapters we summarize the development in this area, sorted by their activation sequences.

2.1. Iminium–Enamine Activation

The iminium–enamine approach is currently the strategy most employed in developing new asymmetric organocata-

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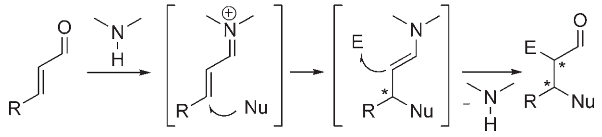
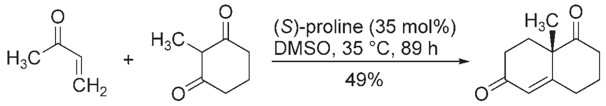
lytic domino reactions. All examples based on this concept have one thing in common—the use of enal or enone systems. These substrates are first activated through iminium-ion formation, using a secondary amine to initiate the nucleophilic conjugate addition. The resulting enamine can then undergo a second reaction with an electrophile to afford the double-substituted products, which in general contain two new stereocenters (Scheme 1).



Scheme 1. The concept of iminium–enamine activation.

An early example was reported by Barbas and Bui in 2000.[8] They reported a proline-catalyzed asymmetric Robinson annulation for the synthesis of the Wieland–Miescher ketone (WMK; **3**). They obtained the WMK (**3**) from methyl vinyl ketone (**1**) and the diketone **2** in 49 % yield and 76 % *ee* (Scheme 2). This Michael/aldol condensation sequence is triggered by iminium-ion formation of proline with **1**. After the conjugate addition of **2**, a 6-*enolendo* cyclization proceeds via enamine activation and is followed by condensation to afford the WMK (**3**).[9] The yield and enantioselectivity of **3** was similar to that obtained in the original two-step approach.[10]



1 **2** **3**
76% *ee*

Scheme 2. (*S*)-Proline-catalyzed asymmetric Robinson annulation. DMSO = dimethyl sulfoxide.

Dieter Enders, born in 1946 in Butzbach (Germany), completed his PhD at the Justus-Liebig-Universität Gießen in 1974 under the supervision of D. Seebach. After postdoctoral studies at Harvard University with E. J. Corey, he returned to Gießen and completed his habilitation in 1979. He became an associate professor at the University of Bonn in 1980 and moved to his present position as Professor of Organic Chemistry at the RWTH Aachen University in 1985. His research focuses on the asymmetric synthesis of biologically active compounds and the development of new synthetic methods.

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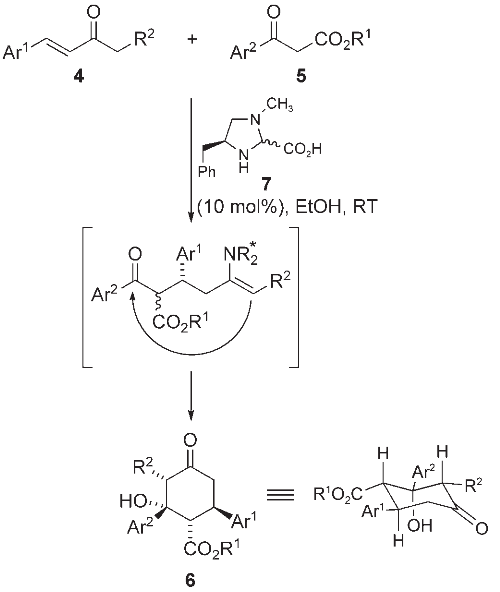
Matthias Hüttl was born in Augsburg (Germany) in 1977 and studied chemistry at the RWTH Aachen, where he received his diploma degree in 2004. He is currently studying for his PhD under the guidance of Professor D. Enders. His research interests include the development of new methods in asymmetric organocatalysis, in particular the organocatalytic α-fluorination of carbonyl compounds and multicomponent domino reactions.

A related approach was used by Jørgensen and coworkers for the assembly of optically active cyclohexanones **6** that bear up to four stereocenters.[11] This Michael/aldol reaction started with an iminium activation of the unsaturated ketone **4** by the imidazolidine catalyst **7**. After the conjugate addition of the β-ketoester **5** to **4**, the desired cyclohexanones **6** were obtained by an intramolecular aldol reaction (Scheme 3).



22–84%, 83–99% *ee*,
d.r. >97 : 3

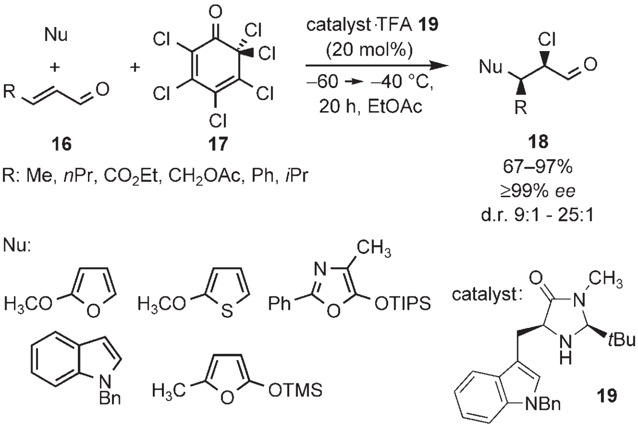
R^1: Me, Et, Bn
R^2: H, Me
Ar^1: Ph, 2-Np, 4-ClC_6H_4, 4-HOC_6H_4, 2-$NO_2C_6H_4$, 2-Furyl, 2-Thienyl, 2-Pyrimidyl
Ar^2: Ph, 4-FC_6H_4, 4-$MeOC_6H_4$

Scheme 3. Asymmetric Michael/intramolecular aldol reaction sequence. Bn = benzyl; Np = naphthyl.

An optimization revealed that catalyst **7** is excellent for this reaction proceeding in various solvents, in particular in protic solvents such as ethanol. In contrast to the moderate yields, the stereoselectivities were very good and only one diastereoisomer was formed during this reaction (83–99% *ee*). Moreover, this protocol tolerates a broad variety of residues and aryl substituents leading to polyfunctionalized chiral cyclohexanone building blocks. An extension of this reaction was the application of phenyl sulfonyl acetophenone instead of β-ketoester **5**.[12] The corresponding cyclohexanones were also obtained in good yields (31–95%) and with high diastereo- and enantioselectivities (d.r. > 97:3, 86–99% *ee*). In similar fashion, Gryko used 1,3-diketones instead of β-ketoesters **5** and methyl vinyl ketone in the presence of (*S*)-proline to synthesize disubstituted cyclohexanones. This variation gave good yields (39–93%) and moderate enantioselectivities (43–80% *ee*).[13]

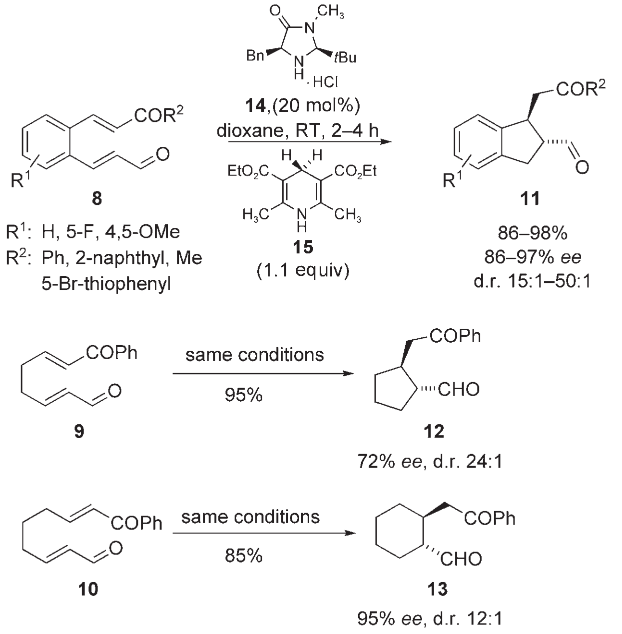
At nearly the same time, three independent contributions were reported on the iminium–enamine activation mode. The first of these, by List and co-workers, dealt with an asymmetric reductive Michael cyclization of enal enones **8–10** to form keto aldehydes **11–13** (Scheme 4).[14] The activated enal moiety is trapped by hydrogen nucleophiles derived from the Hantzsch ester **15**. The corresponding enamine then undergoes an intramolecular Michael addition to the enone to afford the cyclic keto aldehydes **11–13**. The imidazolidinone catalyst **14** turned out to be very efficient with respect to the reaction time, conversion, and stereoselectivity. The scope of this reaction is already broad: different substituted aromatic and aliphatic enal enones can be employed, with high diastereo- and enantiocontrol observed.

An intermolecular version of the iminium–enamine activation concept was described by MacMillan and co-workers.[15] They reported that a broad variety of aromatic π nucleophiles can undergo conjugate addition with several enals **16** (Scheme 5). The 1,4-addition is promoted by the imidazolidinone catalyst **19**. The resulting enamine intermediates can then take part in a catalytic cycle by reacting with halogen electrophiles (Cl, F). In nearly all cases, this reaction is accompanied by a high *syn* selectivity (*syn*/*anti* 9:1 to > 25:1; except 3:1 in one case) and excellent enantioselectivities (≥ 99% *ee*).

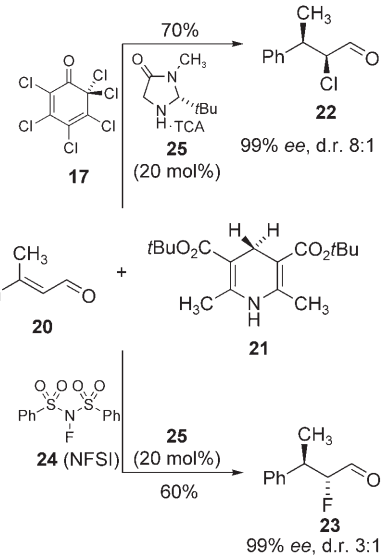


Scheme 5. Asymmetric Michael/intermolecular halogenation sequence. TFA = trifluoroacetic acid; TIPS = triisoproylsilyl; TMS = trimethylsilyl.

This work was extended by the application of Hantzsch ester **21** in combination with hexachlorocyclohexadienone **17** or *N*-fluorodibenzenesulfonamide (NFSI; **24**) and a trisubstituted olefin **20** as substrates, thus forming two new stereocenters. This cascade reaction represents the first formal asymmetric addition of HCl or HF to a trisubstituted olefin (Scheme 6). Interestingly, the addition of HCl proceeds with high *syn* selectivity whereas the addition of HF gives the



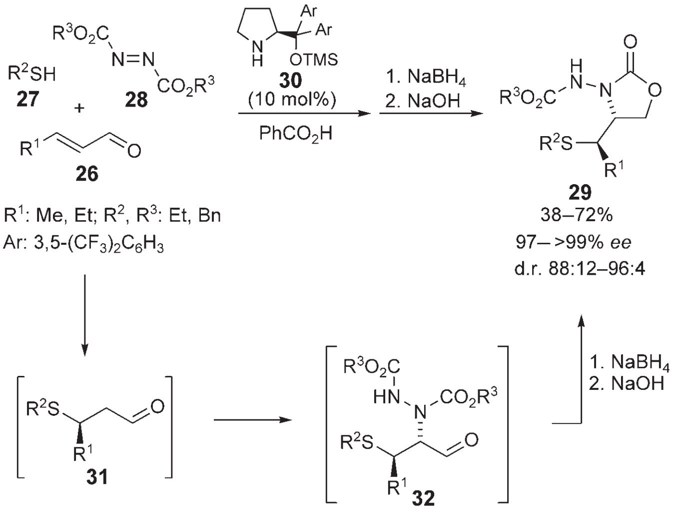
Scheme 4. Asymmetric reductive Michael cyclization.



Scheme 6. Diastereo- and enantioselective addition of HCl and HF to a trisubstituted olefin to afford halogenated aldehydes **22** and **23**. TCA = trichloroacetic acid.

anti product. The combination of discrete amine catalysts with cycle-specific selectivities can be employed to accomplish the *syn*- or *anti*-selective addition of HF.

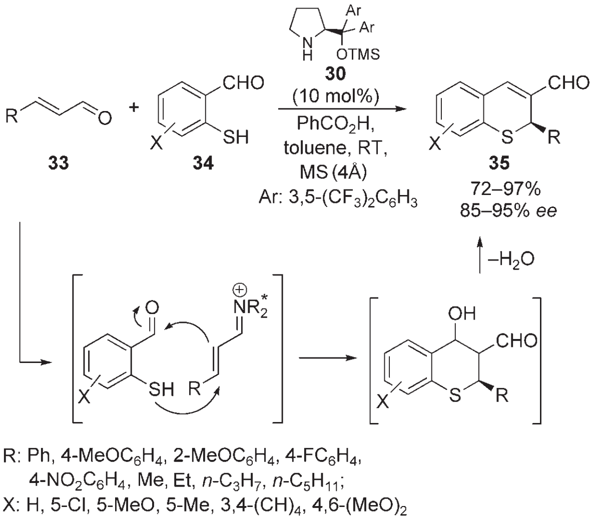
This concept was also used by Jørgensen and co-workers, who disclosed the first enantioselective, organocatalytic conjugate thiol addition/amination reaction.[16] They employed simple α,β-unsaturated aldehydes **26** in the presence of different thiols **27**, azodicarboxylates **28**, and the proline-derived catalyst **30**. First, the iminium-activated enal of **26** undergoes a conjugate addition with the soft thio nucleophile **27**. The resulting enamine of **31** is then trapped by **28** to afford the thio- and hydrazino-substituted aldehydes **32** with high diastereocontrol and very high enantiomeric purity (97 to >99 % *ee*; Scheme 7).



Scheme 7. Asymmetric conjugate thiol addition/amination sequence.

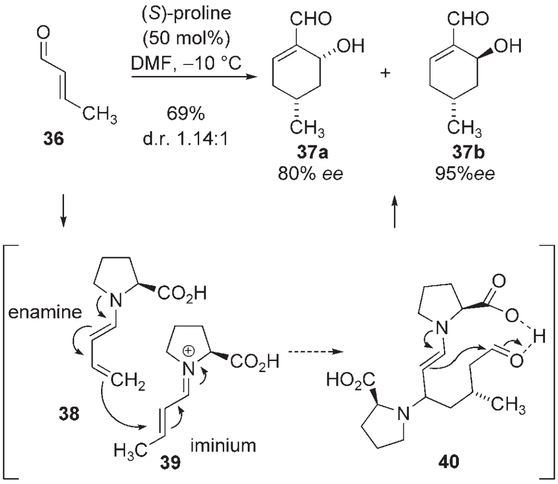
This domino reaction is then followed by in situ reduction of the aldehydes **32** with NaBH$_4$ and formation of the oxazolidinones **29** under basic conditions. The corresponding yields are quite good, as they result from a four-step one-pot procedure. It is important to mention that the reaction temperature has a great influence with regard to the stereoselectivity and the reaction rate. The sulfa-Michael addition is very fast at ambient temperature, but under these conditions the Michael product racemizes easily. If the reaction temperature is lowered to −15 °C, the racemization can be prevented but the reaction rate is strongly slowed down. The problem was solved by employing benzoic acid as a cocatalyst, which leads to higher reaction rates.

Wang et al. recently reported a sulfa-Michael addition followed by an intramolecular aldol condensation.[17] This sequence, catalyzed by prolinol derivative **30**, affords thiochromenes **35** from α,β-unsaturated enones **33** and *ortho*-mercaptobenzaldehydes **34** in generally high yields (72–97 %) and very good enantioselectivities (85–95 % *ee*). The reaction was performed between room temperature and 0 °C in toluene in the presence of benzoic acid (0.1 equiv) as additive (Scheme 8). The corresponding oxa-Michael/aldol condensation sequence was recently reported by Arvidsson and co-workers,[18] who obtained chromenes in 15–70 % yield and with 29–90 % *ee*.



Scheme 8. Sulfa-Michael/aldol condensation sequence.

A nice example of enamine and iminium activation operating with the same substrate in one reaction is found in a formal [3+3] cycloaddition of crotonaldehyde (**36**) to afford the cyclohexene carbaldehydes **37** (Scheme 9).[19]



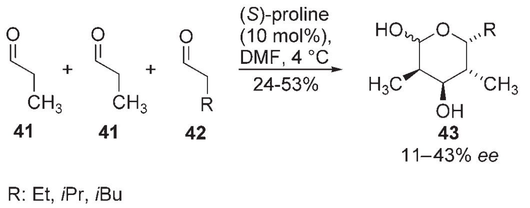
Scheme 9. Organocatalytic formal [3+3] cycloaddition of crotonaldehyde. DMF = *N*,*N*-dimethylformamide.

Screening of the solvent and catalyst revealed that this reaction proceeds best in DMF at −10 °C in the presence of 50 mol % (*S*)-proline. While the diastereoselectivity is low, the epimers **37** are formed in 69 % yield with 80 and 95 % *ee*, respectively. The authors proposed a Michael/Morita–Baylis–Hillman-type reaction. In the first step, one molecule of crotonaldehyde is activated by iminium formation and a second one is activated by enamine formation. The dienamine **38** then performs a vinylogous Michael-type addition to **39**, followed by a Morita–Baylis–Hillman-like reaction via the intermediate **40**.

Further examples of iminium–enamine-catalyzed tandem-like processes include the cyclopropanation reaction by MacMillan and Kunz[20] or the epoxidation by Jørgensen and co-workers.[21]

2.2. Enamine–Enamine Activation

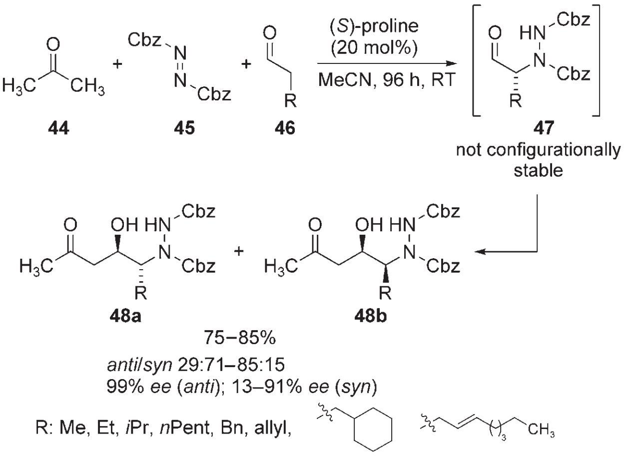
The concept of enamine–enamine activation is considerably less used in domino reactions than the iminium–enamine activation strategy. One of the first examples using this concept was reported by Barbas and co-workers, who described the self-aldolization of acetaldehyde to (+)-5-hydroxy-(2*E*)-hexenal with 90 % *ee*.[22] Shortly afterwards, they reported the proline-catalyzed trimerization of simple aldehydes to carbohydrates and polyketides (Scheme 10).[23]



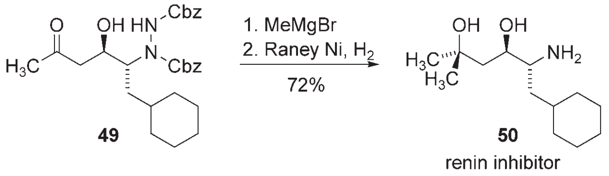
Scheme 10. Organocatalytic assembly of carbohydrates and polyketides.

This trimerization approach involves two consecutive aldol reactions between different aldehydes. The first reaction is a self-aldolization reaction between two propanal molecules (**41**). The second one comprises a cross-aldol reaction between two different aldehydes to achieve the lactols **43**. Although the yields and the enantioselectivities are generally low, this approach constitutes the first organocatalytic assembly of carbohydrates and polyketides.[24]

Barbas et al. later developed a proline-catalyzed three-component domino sequence for the synthesis of functionalized hydrazino alcohols **48**, employing acetone (**44**) in combination with different aldehydes **45** and the azodicarboxylate **46** (Scheme 11).[25] The first step involves an α-amination[26] to form the intermediate **47**, followed by an aldol reaction[27] with acetone. While the individual steps were already described, the combination of these in a domino process was new. Interestingly, the intermediate **47** undergoes a complete racemization before it is converted into the aldol product **48 a/b**. This phenomenon explains the moderate *anti*/*syn* selectivity of the final products, but the isomers can be separated by recrystallization. A screening of the solvent showed that different solvents have little effect on the yield and only a small influence on the diastereoselectivities. Furthermore, different aldehydes can be employed as substrates. The yields are quite good, whereas the *anti*/*syn* selectivities are moderate. The *anti* isomer can be obtained as a single enantiomer (> 99 % *ee*), but the *syn* enantioselectivity was only moderate to good (13–91 % *ee*). The potential of this reaction was demonstrated by application to the three-step synthesis of the known renin inhibitor **50** (Scheme 12).



Scheme 11. Proline-catalyzed three-component domino reaction for the synthesis of functionalized hydrazino alcohols **48**. Cbz = benzyloxycarbonyl.



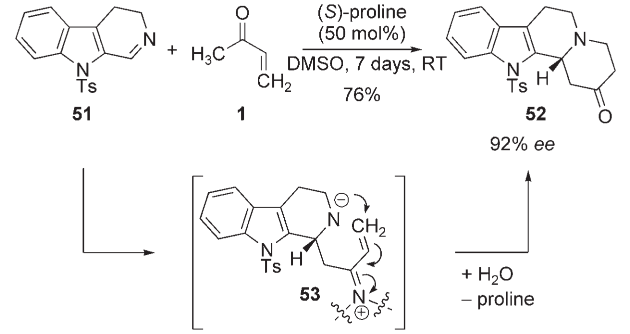
Scheme 12. Synthesis of the renin inhibitor **50**.

2.3. Enamine–Iminium Activation

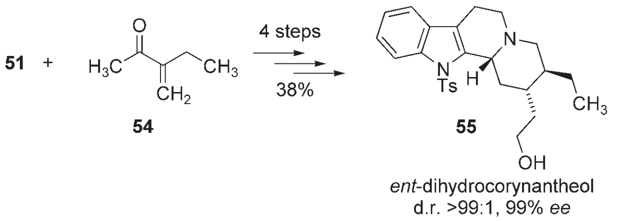
In principle, this concept is a reversion of the iminium–enamine activation. The substrate must be amenable to enamine formation, and after electrophilic substitution an iminium ion is formed subsequently. Prominent substrates are methyl vinyl ketones and derivatives. Alternatively, two different substrates can be employed with discrete activation modes.

Ohsawa and co-workers developed a proline-catalyzed Mannich/aza-Michael sequence for the D-ring construction of indole alkaloid building blocks.[28] Mixing of 9-tosyl-3,4-dihydro-β-carboline (**51**)—a *Z*-configured imine—and methyl vinyl ketone (**1**) affords the intermediate **53** through a proline-mediated Mannich-type reaction. The resulting iminium ion is then attacked by the negatively charged nitrogen center in an intramolecular aza-Michael reaction to close the D ring of **52** in 76 % yield and with a very good enantioselectivity of 92 % *ee* (Scheme 13). This sequence can also be regarded formally as a Diels–Alder reaction. Detosylated **52** has already been shown to be a valuable building block of various indole alkaloids.

Recently, this group applied their methodology in a straightforward synthesis of the alkaloid *ent*-dihydrocorynantheol (**55**).[29] A substituted methyl vinyl ketone **54** was employed, and two new stereocenters were created with excellent stereocontrol (d.r. > 99:1, > 99 % *ee*). The alkaloid **55** was synthesized in four steps in 38 % overall yield (Scheme 14).

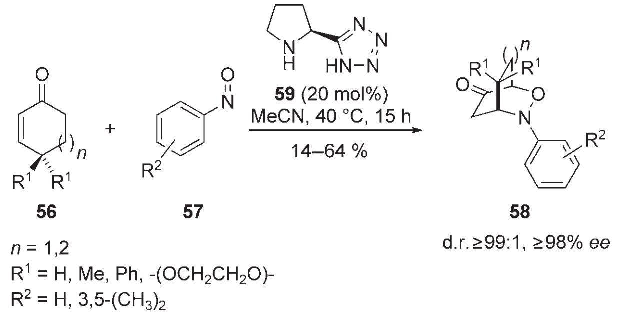


Scheme 13. Organocatalytic asymmetric synthesis of **52** through a Mannich/aza-Michael sequence. Ts = *para*-toluenesulfonyl.



Scheme 14. Asymmetric synthesis of *ent*-dihydrocorynantheol (**55**).

The combination of an organocatalytic α-aminohydroxylation reaction[30] and a Michael addition constitutes a synthetic alternative for the nitroso-Diels–Alder reaction. Yamamoto et al. employed cyclic enones **56**, nitrosobenzene or its derivatives **57** in such a tandem reaction (Scheme 15).[31]

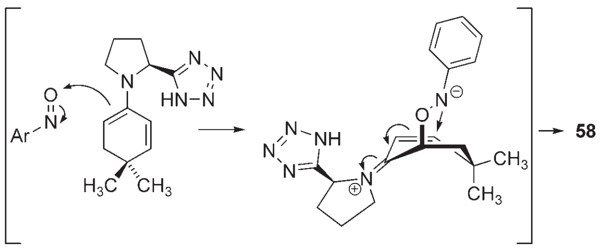


Scheme 15. α-Amino hydroxylation/aza-Michael reaction.

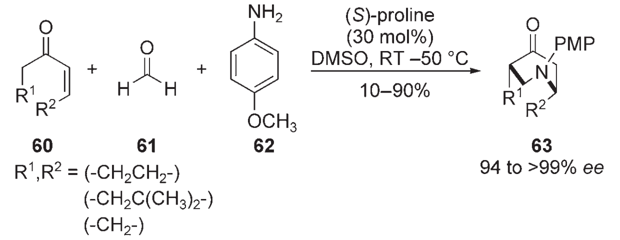
The proline-based tetrazole catalyst **59** was utilized because it shows higher activities than proline itself in the α-aminohydroxylation of ketones. The products **58** were formed with excellent diastereo- and enantioselectivies, ranging above 98% *ee*, and generally in good yields. The yield declined drastically in the case of cycloheptenone, but this could be compensated for by the use of proline as the organocatalyst.

The absolute configuration of **58** was confirmed by X-ray crystallography and is in total agreement with the expected relative topicity. Interestingly, these formal "Diels–Alder products" exhibit the opposite regiochemistry to normal nitroso-Diels–Alder products. This behavior results from the fact that first an α-aminohydroxylation reaction proceeds, followed by an intramolecular aza-Michael reaction (Scheme 16).

A similar sequence was carried out by Córdova and coworkers. They employed cyclic enones **60** and imines, formed in situ from formaldehyde (**61**) and *para*-anisidine (**62**), to mimic formally a direct aza-Diels–Alder reaction.[32] Solvent screening exposed that this reaction proceeds smoothly in DMSO between room temperature and 50 °C in low to very good yields (10–90%) and with excellent enantiomeric excesses (94 to > 99% *ee*; Scheme 17).



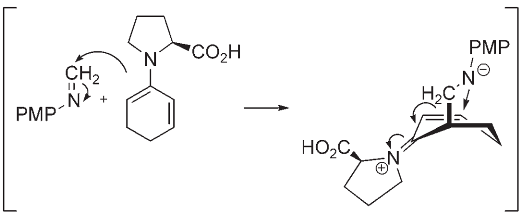
Scheme 16. Possible stepwise reaction pathway.



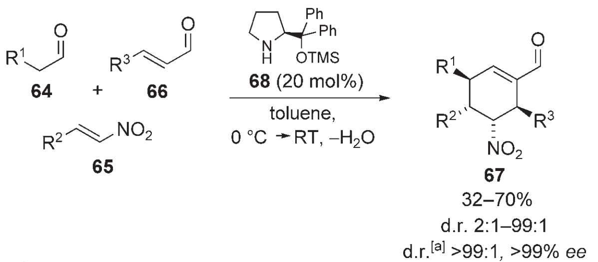
Scheme 17. Proline-catalyzed Mannich/aza-Michael reaction. PMP = *para*-methoxyphenyl.

Furthermore, proline or its tetrazole derivative **59** are the most appropriate catalysts in this reaction with respect to yields and enantioselectivities. A variation of the cyclic enone **60** showed that cyclohexenones and cycloheptenones are very good substrates for this reaction, whereas cyclopentenone is not suitable. Another limitation is the application of 3-substituted cyclohexenones, as the reaction stops after the Mannich reaction and no subsequent ring closure is observed. The absolute configuration of **63** was determined by X-ray crystal structure analysis and was in agreement with the expected stereochemical outcome and now allows the suggestion of a reaction pathway. A plausible assumption is a tandem Mannich/aza-Michael sequence, which explains the regio- as well as the stereoselectivity of the piperidone products **63** (Scheme 18).

A more complex example is the three-component triple cascade reaction for the construction of tetrasubstituted cyclohexene carbaldehydes **67** (Scheme 19).[33] This multicomponent reaction proceeds through a Michael/Michael/aldol condensation sequence that includes the consecutive and highly chemo-, regio-, and stereoselective formation of three C–C bonds. The pentasubstituted cyclohexenes **67** are constructed from three simple and readily available precur-



Scheme 18. Plausible stepwise reaction pathway.



R^1: Me, Et, CH_2OTBS, Bn, *i*Pr,
R^2: Ph, 2-ClC_6H_4, 4-$MeOC_6H_4$, 3-piperonyl, 2-Me-furyl
R^3: H, Ph, Me, *n*Bu
[a] after chromatographic epimer separation

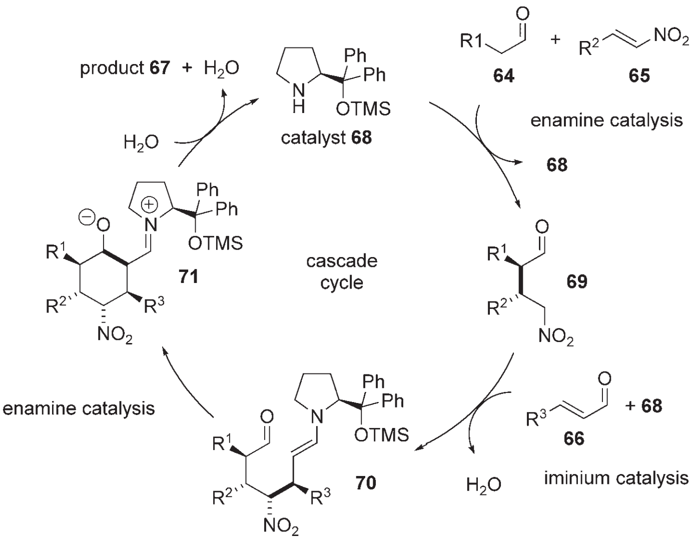
Scheme 19. Asymmetric organocatalytic triple cascade. TBS = *tert*-butyldimethylsilyl.

sors, namely enolizable aldehydes **64**, nitroalkenes **65**, and α,β-unsaturated aldehydes **66**. This triple cascade generates four new stereocenters. Thus, from 16 possible stereoisomers of **67** only two epimers located α to the nitro group are formed in a ratio ranging from 2:1 to 99:1 and the minor isomer can be easily separated by chromatography. An advantage of this approach is clearly the fact that R^1, R^2, and R^3 can be easily varied from aliphatic, aromatic, and heteroaromatic to functionalized residues by employing roughly a 1:1:1 ratio of the three substrates. The proline-derived catalyst **68** first activates the aldehyde **64** through enamine formation to achieve the first Michael-type addition to the nitroolefin **65**. Then, **68** forms an iminium ion with the enal **66** to catalyze the second conjugate addition of the nitroalkane **69** to form **70**. During this addition, an enamine intermediate is formed again which cyclizes through an intramolecular aldol condensation to afford the cyclohexenes **67** with moderate to good yields (30–58%) and complete enantioselectivity (≥ 99% *ee*; Scheme 20).

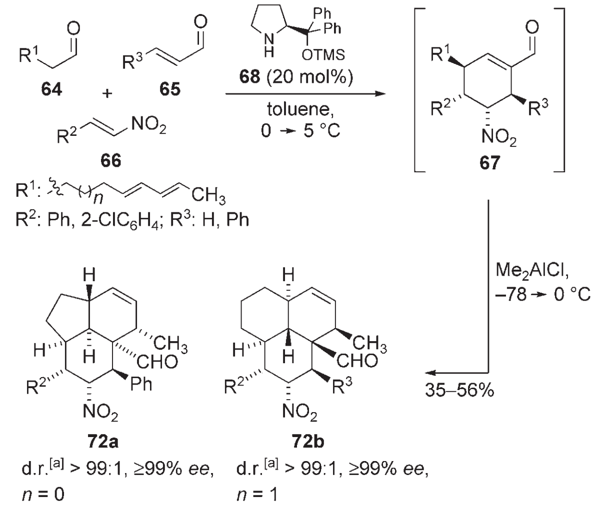
This multicomponent domino reaction was recently extended by a highly stereoselective intramolecular Diels–Alder reaction.[34] The domino reaction is followed by a Lewis acid mediated intramolecular [4+2] cycloaddition which leads to complex tricyclic frameworks **72a/b**. In this tetradomino reaction, five C–C bonds were formed with the diastereo- and enantioselective construction of up to eight new stereogenic centers in a one-pot operation (Scheme 21).

2.4. Other Amine-Catalyzed Domino Reactions

This section describes all the contributions on amine-catalyzed domino reactions which do not fit clearly into the three categories mentioned above (Sections 2.1–2.3). However, these examples are also based in principle on enamine and/or iminium-ion activation.



Scheme 20. Proposed catalytic cycle.

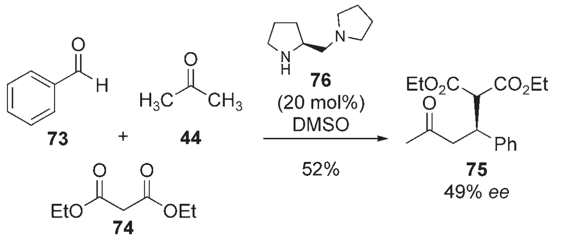


[a] after flash chromatography

Scheme 21. Michael/Michael/aldol condensation/Diels–Alder domino sequence.

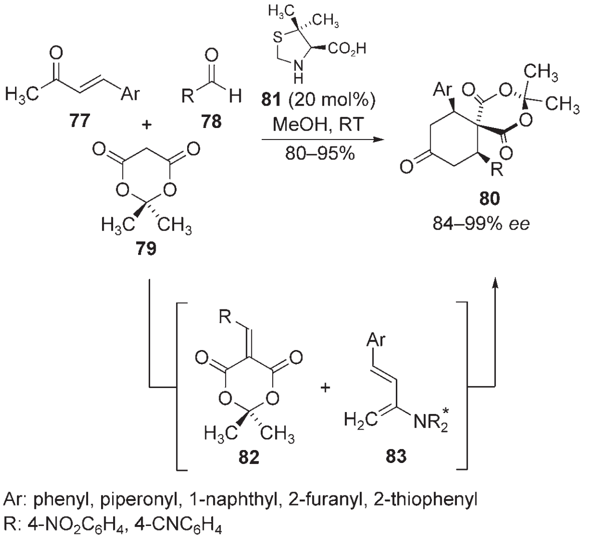
An asymmetric domino Knoevenagel/Michael reaction was performed with benzaldehyde (**73**), diethylmalonate (**74**), and acetone (**44**), catalyzed by (*S*)-1-(2-pyrrolidinylmethyl)-pyrrolidine (**76**; Scheme 22).[35] The chiral amine first catalyzes the formation of the alkylidene malonate, followed by an organocatalytic Michael reaction to afford the corresponding adduct **75** in moderate yield (52%) and enantioselectivity (49% *ee*).

The organocatalytic construction of spiro compounds was reported by Barbas and co-workers in 2003 with the development of an asymmetric three-component domino Knoevenagel/Diels–Alder reaction.[36] The spiro compounds **80** were assembled from three simple precursors, namely enones **77**,



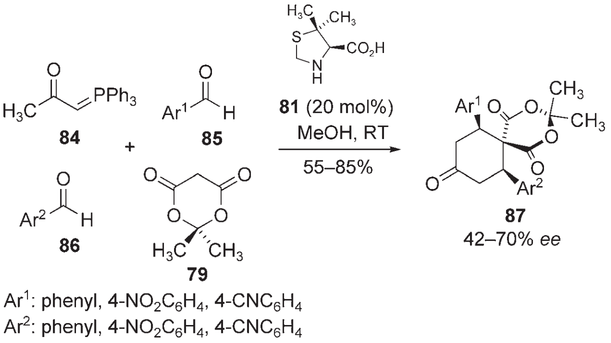
Scheme 22. Domino Knoevenagel/Michael reaction.

aldehydes **78**, and Meldrum's acid (**79**). First, the aldehyde **77** is transformed in a Knoevenagel reaction with **79** to the olefin **82**. In the second step, catalyst **81** activates the enone **77** by enamine formation to promote the subsequent Diels–Alder reaction. Hydrolysis then releases the products **80** and the catalyst **81** to enter the next cycle. This approach is characterized by good overall yields and regio- and enantioselectivities (Scheme 23). These spiro compounds are analogues of the antioxidative glucoside from oregano (*Origanum vulgare*).

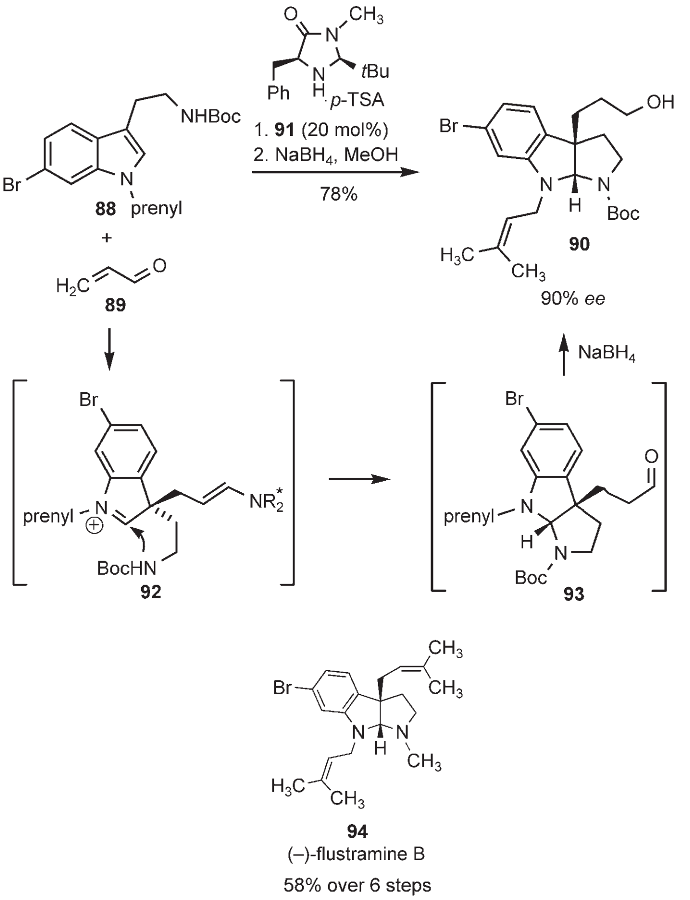


Scheme 23. Asymmetric Knoevenagel/Diels–Alder reaction for the synthesis of spiro compounds **80**.

Later on, this concept was extended to a four-component domino Wittig/Knoevenagel/Diels–Alder reaction.[37] The difference with respect to the initial approach is the application of a second aldehyde in the presence of a phosphorane **84** to generate the enone in situ (Scheme 24). The corresponding spiro compounds **87** are identical to those obtained above (**80**).

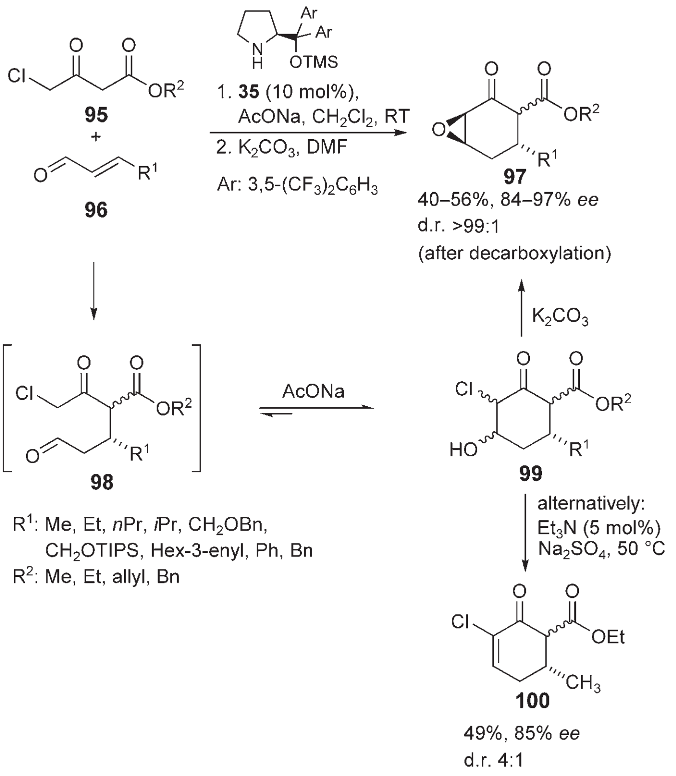


Scheme 24. Asymmetric Wittig/Knoevenagel/Diels–Alder reaction for the synthesis of spiro compounds **87**.



Scheme 25. Enantioselective key addition-cyclization of the total synthesis of (−)-flustramine B (**94**). Boc = *tert*-butyloxycarbonyl; *p*-TSA = *para*-toluenesulfonic acid.

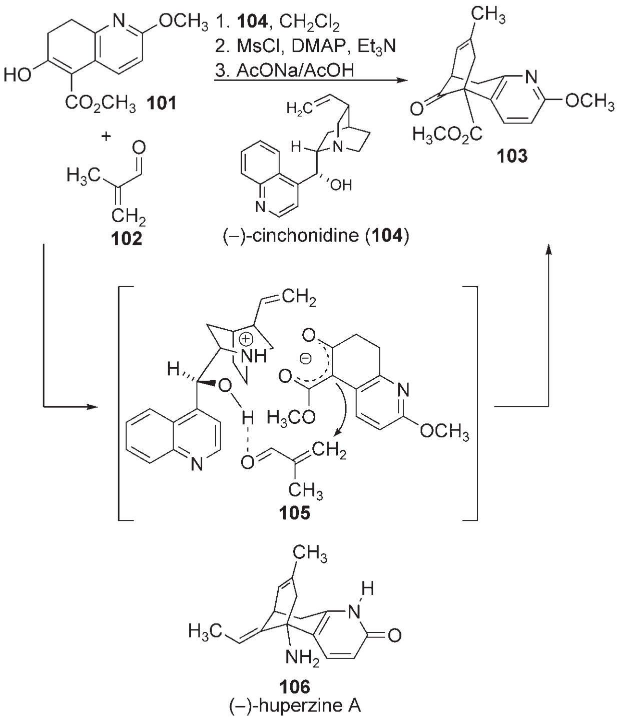
An impressive example of the application of organocatalytic domino reactions in natural product synthesis was demonstrated by the rapid construction of pyrroloindoline alkaloids through a conjugate addition/cyclization cascade (Scheme 25).[38] The key sequence of this synthesis of the alkaloid (−)-flustramine B (**94**) is characterized by a conjugate addition of the *N*-Boc-protected tryptamine **88** to acrolein **89**, catalyzed by the imidazolidinone **91**. The iminium-ion intermediate **92** is subsequently quenched by the Boc-protected amine through a 5-*exo*-heterocyclization to the tricyclic pyrroloindoline **93**, which is then reduced with $NaBH_4$ to the alcohol **90**. The cascade proceeds with good yield (78 %) and high stereocontrol. This elegant strategy afforded (−)-flustramine B (**94**), a biologically active marine alkaloid, in only six steps and with 58 % overall yield and clearly demonstrates the power and efficiency of domino reactions for the rapid construction of molecular complexity.



Scheme 26. Asymmetric Michael/Darzens reaction for the synthesis of epoxycyclohexanone derivatives **97**.

Highly functionalized epoxycyclohexanone derivatives **97** with up to four stereocenters can be obtained by a domino Michael/Darzens reaction (Scheme 26).[39] This process starts with a conjugate addition of the γ-chloro-β-ketoester **95** to the activated enal **96**. The Michael addition is followed by a Darzens reaction facilitated by NaOAc to promote first the aldol addition and then K_2CO_3 for the final intramolecular S_N2 displacement to form the epoxide. The overall yields and enantioselectivities are good, but the diastereocontrol is only moderate as the stereocenter between the ketone and ester is not configurationally stable, which explains the diastereomeric ratio (d.r. = 4:1 to 7:1) of the products **97**. However, after saponification and decarboxylation only one diastereomer is present (d.r. > 99:1). The high stereocontrol of the remaining stereocenters is a consequence of the intramolecular epoxide formation, as only one conformation of **99** is energetically favored. The authors postulated a reversible aldol addition whereby the diastereomers of **99** are in equilibrium and irreversible epoxide formation to afford the products in overall good yield. Alternatively, depending on the base the reaction can be directed towards the synthesis of 2-chlorocyclohex-2-enones **100**. The epoxycyclohexane derivatives **97** constitute characteristic structural features present in natural products, and they are very useful for further synthetic operations.

Back in 1998, Terashima and co-workers reported a domino Michael/aldol cyclization catalyzed by a chinchona alkaloid for the rapid and efficient construction of the core structure of huperzine A (**106**).[40] First, the β-ketoester **101** is deprotonated by the chiral tertiary amine to form the ionic complex **105**. The adjacent secondary alcohol of the catalyst then activates the enal **102** by directed hydrogen bonding to promote the Michael addition. Subsequent enolization affords the aldol cyclization to **103**. (−)-Cinchonidine (**104**) emerged as the most appropriate catalyst, promoting this reaction with 60 % yield and 64 % *ee* (Scheme 27).



Scheme 27. Asymmetric Michael/aldol cyclization as the key step for the synthesis of (−)-huperzine A (**106**). Ms = 2,4,6-trimethylphenyl; DMAP = 4-dimethylaminopyridine.

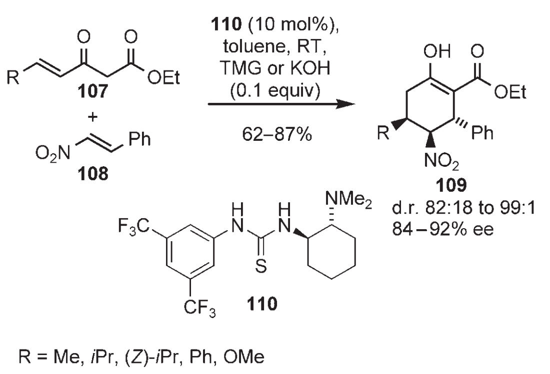
Other amine-catalyzed reactions that we have not categorized as true domino processes include the organocatalytic intramolecular cyclopropanation reactions of Ley, Gaunt, and co-workers[41] and the asymmetric synthesis of β-substituted aspartic acid derivatives through a four-stage, one-pot procedure by Lectka and co-workers.[42]

3. Brønsted Acid Catalyzed Domino Reactions

Asymmetric Brønsted acid catalysis has attracted much interest recently.[43] The activation of the substrate relies on the partial protonation or the formation of a strictly directed hydrogen bond by the catalyst. The interaction between the catalyst and the substrate is noncovalent, and the chiral ion pair is the intrinsic activated species. In particular, chiral thiourea-based derivatives and phosphoric acid derivatives are well known for their application as effective Brønsted acid organocatalysts. In contrast to amine-catalyzed domino reactions, the Brønsted acid catalyzed analogues are currently still in an early stage of development.

3.1. Thiourea-Catalyzed Domino Reactions

A thiourea-catalyzed Michael/Michael domino process was recently reported by Takemoto and co-workers, who disclosed a Michael addition of γ,δ-unsaturated-β-ketoesters **107** to nitrostyrene (**108**), followed by an intramolecular Michael addition to afford 4-nitrocyclohexenones **109** with three stereocenters.[44] This reaction proceeds with high yields (62–87 %), diastereoselectivities (d.r. = 82:18 to > 99:1), and enantioselectivities (84–92 % *ee*). They employed the bifunctional thiourea **110** as organocatalyst, but it was found that the use of 1,1,3,3-tetramethylguanidine (TMG) or KOH is necessary for the subsequent Michael addition (Scheme 28). This methodology was then applied for the total synthesis of the frog alkaloid (−)-epibatidine.

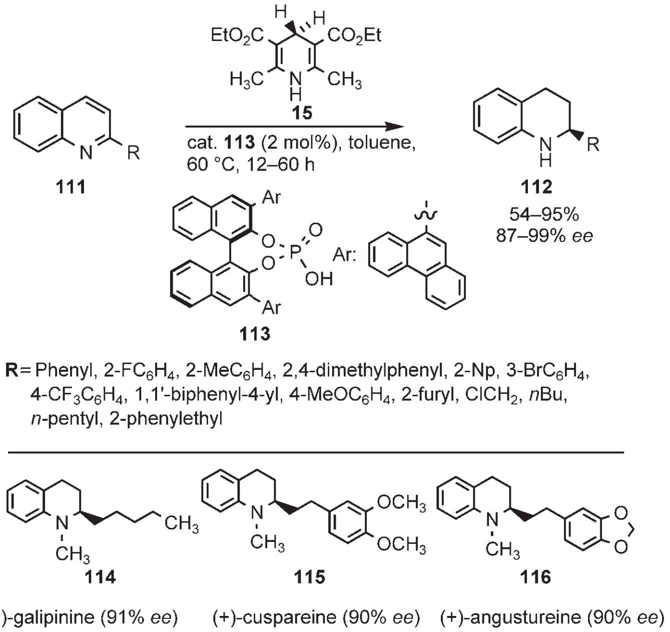


R = Me, *i*Pr, (*Z*)-*i*Pr, Ph, OMe

Scheme 28. Thiourea-catalyzed asymmetric tandem Michael/Michael reaction.

3.2. Phosphoric Acid Diester Catalyzed Cascade Reactions

The first and only example to date of an enantioselective phosphoric acid diester catalyzed domino reaction is an enantioselective cascade transfer hydrogenation established by Rueping et al. (Scheme 29).[45,46] They investigated the asymmetric transfer hydrogenation of 2-substituted quinoline derivatives **111** to tetrahydroquinolines **112** with the Hantzsch ester **15**. A screening of the reaction parameters revealed that the axial-chiral binol phosphate catalyst **113** is excellent for this hydrogenation cascade. However, nonpolar solvents are crucial for high enantioselectivities and aromatic solvents in particular gave the best results. The scope of the reaction is very broad, as demonstrated by the application of several 2-substituted quinolines with consistently high yields (54–95 %) and very high enantioselectivities (88 to > 99 % *ee*). This methodology allows a quick entry to several biologically active alkaloids such as galipinine (**114**), cuspareine (**115**), or angustureine (**116**). This cascade hydrogenation probably proceeds first by a 1,4-hydride addition to the protonated chinoline **117**, an iminium ion. This step is comparable to the iminium activation of an enal by a secondary amine and similar to the recently reported organocatalytic transfer hydrogenation of α,β-unsaturated aldehydes.[47] After 1,4-addition, the enamine intermediate **118** isomerizes to the iminium ion **121**, which is then transformed in a 1,2-addition to the amine **112**.[48] In principle, this sequence constitutes the combination of an iminium–iminium activation mode but with the important difference that the second iminium ion is the activated part of the last step and is reduced to an amine and not regenerated to its original form (Scheme 30).



R = Phenyl, 2-FC$_6$H$_4$, 2-MeC$_6$H$_4$, 2,4-dimethylphenyl, 2-Np, 3-BrC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 1,1'-biphenyl-4-yl, 4-MeOC$_6$H$_4$, 2-furyl, ClCH$_2$, *n*Bu, *n*-pentyl, 2-phenylethyl

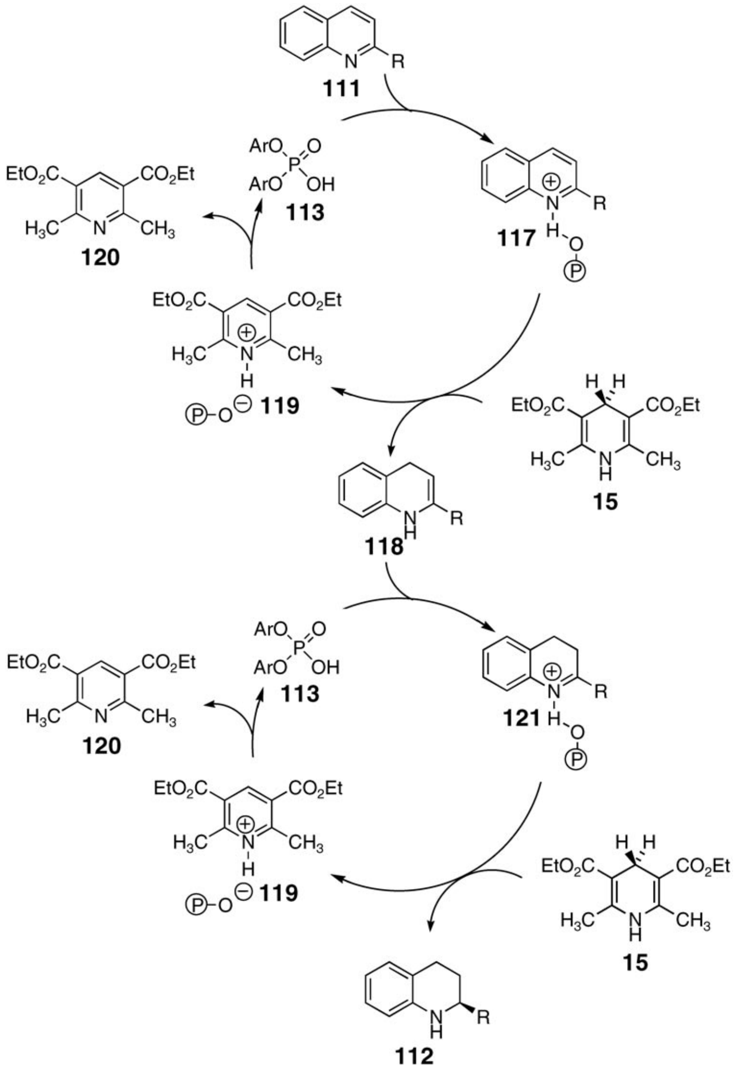
(+)-galipinine (91% *ee*) (+)-cuspareine (90% *ee*) (+)-angustureine (90% *ee*)

Scheme 29. Asymmetric phosphoric acid diester mediated cascade transfer hydrogenation of quinolines **111**.

4. Conclusion

In conclusion, asymmetric organocatalytic domino reactions have quickly become a powerful and efficient tool in organic chemistry. The combination of different activation modes allows the design of innovative domino sequences to afford high molecular complexity. Very often these organic cascades are accompanied by a high level of stereocontrol induced by the organocatalyst and often followed by chiral enhancement. Therefore, the generation of several stereocenters can be accomplished very easily without the problems that occur in classical syntheses. Currently, most approaches involve two-step cascades in which the first step is intermolecular and the second is intramolecular. The extension to fully intermolecular sequences and the combination of three and more steps will be the aim of further investigations. A future trend is definitely the application of this concept in natural product synthesis, as this approach is biomimetic-like and multistep syntheses can be reduced to short and efficient routes. Beyond that, the efficiency has to be optimized by structural variation of the organocatalysts to enable new strategies for domino reactions and bond formations.[49]

Received: August 2, 2006



Scheme 30. Proposed catalytic cycle of the cascade transfer hydrogenation of 2-substituted quinolines **111**.

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[48] For the asymmetric organocatalytic reduction of imines, see: a) M. Rueping, C. Azap, E. Sugino, T. Theissmann, *Synlett* **2005**, 2367; b) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, *Org. Lett.* **2005**, *7*, 3781; c) S. Hofmann, A. M. Seayad, B. List, *Angew. Chem.* **2005**, *117*, 7590; *Angew. Chem. Int. Ed.* **2005**, *44*, 7424; d) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84.

[49] Note added in proof (December 12, 2006): After submission of this Minireview, several new reports have appeared. a) For the synthesis of amino acid derivatives through a reductive Mannich-type domino reaction, see: G.-L. Zhao, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 7417; b) for the use of a domino Mannich/aldol reaction to synthesize highly functionalized tetrahydrothiophenes, see: S. Brandau, E. Maerten, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 14986; c) for the preparation of isochinuclidines through a Mannich/aza-Michael cascade, see: M. Rueping, C. Azap, *Angew. Chem.* **2006**, *118*, 7996; *Angew. Chem. Int. Ed.* **2006**, *45*, 7832; d) for the preparation of 2*H*-1-benzothiopyranes as well as a tetrahydrothioxanthenones using a domino Michael/aldol reaction, see: R. Rios, H. Sundén, I. Ibrahem, G.-L. Zhao, L. Erkisson, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 8547; Rios, H. Sundén, I. Ibrahem, G.-L. Zhao, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 8679.