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Asymmetric domino reactions. Part B: Reactions based on the use of chiral catalysts and biocatalysts

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Contents

Keywords: Asymmetric Domino reactions; Chiral catalysts; Biocatalysts.

Abbreviations used: Ac, acetyl; Acac, acetylacetone; Ala, alanine; Ar, aryl; BINAP, 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; BINOL, 1,1′-bi-2-naphthol; $BF_3{\cdot}Et_2O$, boron trifluoride etherate; Bn, benzyl; Boc, *tert*-butoxycarbonyl; BQ, benzoylquinine; Bu, butyl; Bz, benoyl; c, cyclo; Cbz, benzyloxycarbonyl; CMP, cytosine monophosphate; Cob, cobyrinic acid; COD, cyclooctadiene; Cp, cyclopentadienyl; dba, (*E*,*E*)-dibenzylideneacetone; de, diastereomeric excess; dr, diastereomeric ratio; DAIB, dimethylamino isoborneol; DEAD, diethyl azodicarboxylate; DIB, *o*-diiodobenzene; DIOP, 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane; DMF, dimethylformamide; DMSO, dimethylsulphoxide; DMTC, 5,5-dimethyl thiazolidinium-4-carboxylate; DUPHOS, 1,2-bis(phospholano)benzene; ee, enantiomeric excess; Et, ethyl; EWG, electron-withdrawing; FMOC, 9-fluorenylmethoxycarbonyl; Fu, furan; Hex, hexyl; Me, methyl; Ms, mesyl; MOM, methoxymethyl; Nbd, norbornadiene; NMDPP, (neomenthyl)-diphenylphosphane; Np, naphthyl; Nu, nucleophile; ONf, nonaflate; PBG, phorphobilinogen; PCC, pyridinium chlorochromate; Pent, pentyl; Ph, phenyl; Pr, propyl; py, pyridine; quinap, 1-(2-diphenylphosphino-1-naphthyl)-isoquinoline; salen, 1,2-bis(salicylidenamino)ethane; SAM, *S*-adenosylmethionine; TADDOL, $\alpha,\alpha\alpha'\alpha'$-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol; TBAF, tetra-*n*-butylammonium fluoride; TBDMS, *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; Tf, trifluoromethanesulphonyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; THP, tetrahydropyranyl; TMS, trimethylsilyl; TMSOTf, trimethylsilyl trifluoromethanesulphonate; Tol, toluene; Tr, triphenylmethyl(trityl); Ts, 4-toluenesulphonyl(tosyl); UDP, uridine-5′-diphosphate.

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1. Introduction

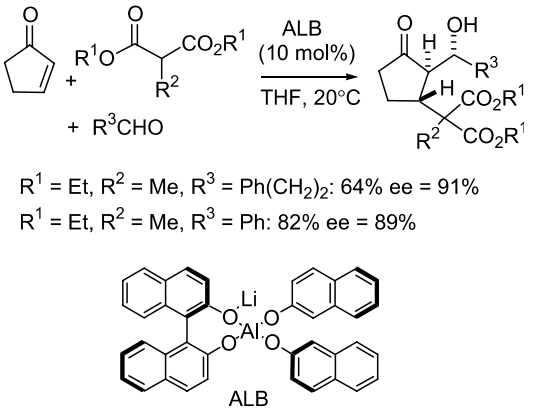
Tietze has defined a domino reaction as involving two or more bond-forming transformations, which take place under the same reaction conditions, without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step.[1] Domino reactions can be classified according to the mechanism of the single steps, which may be of the same or different types (cationic, anionic, radical, pericyclic, or transition-metal-catalysed transformations). The quality and importance of a domino reaction can be correlated to the number of bonds generated in such a process and the increase in complexity. The reactions can be performed as single-, two- and multicomponent transformations. Thus, most, but not all, of the known multicomponent processes can be defined as a subgroup of domino reactions. The use of domino and domino multicomponent reactions in asymmetric synthesis is increasing constantly. Such single-step reactions allow the synthesis of a wide range of complex molecules in an economically favourable way by using processes that are reasonably simple. Domino reactions have gained wide acceptance, because they increase synthetic efficiency by decreasing the number of laboratory operations required and the quantities of chemicals and solvents used. The proliferation of domino reactions is evidenced by the number of recent reviews covering the literature through 1992.[2] The asymmetric aspect of the domino methodology has not, however, been reviewed (excepted for multicomponent reactions[3]) and, with this report, the author would like to fill this gap. The synthesis of optically active chiral compounds, which play an important role in medicine and materials, is one of the most fascinating aspects of modern organic synthesis. Of the methods available for preparing such compounds, catalytic asymmetric synthesis has attracted most attention. The economical interest in combinations of chiral catalytic processes with domino reactions is obvious. As in Part A of this review, the domino reactions are catalogued on the basis of the reaction intermediates or, in some cases, the reaction types involved in the first two synthetic steps. It is, of course, impossible to locate all the published examples of asymmetric domino reactions, since many of these are incorporated in total syntheses described under different keywords. The examples cited in this review have been selected to highlight the most promising applications of asymmetric domino reactions to organic synthesis. In order to facilitate presentation, the review has been divided into two parts. Part A[4] deals with domino reactions using chiral auxiliaries, whereas Part B includes domino reactions catalysed by chiral catalysts and biocatalysts.

2. Chiral catalysts

The catalytic asymmetric formation of chiral building blocks represents an increasingly important field in organic chemistry, owing to the usefulness of these products in further synthetic transformations. The catalytic enantioselective formation of C–C bonds is a widely developed method for achieving this goal and a number of reactions and methodologies have been developed.[5] Among the various asymmetric C–C bond-forming reactions, the direct catalytic domino reactions are of particular interest, as multiple stereogenic centres can be formed in a single reaction. To the best of the author's knowledge, no examples are known for cationic sequences catalysed by chiral catalysts.

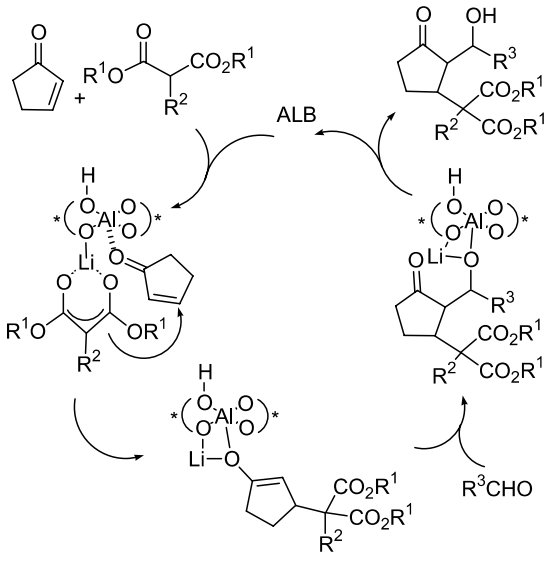
2.1. Anionic primary step

2.1.1. Anionic–anionic reactions. The first catalytic asymmetric domino Michael aldol reaction was reported by Shibasaki et al. in 1996.[6] This domino reaction was promoted by the catalytic use of a heterobimetallic multifunctional asymmetric complex, for example, AlLibis[(*R*)-binaphthoxide] complex (ALB) (Scheme 1). The usefulness of this methodology was demonstrated by its further application to the catalytic asymmetric synthesis of 11-deoxy-$PGF_{1\alpha}$.[7]



Scheme 1. Catalytic asymmetric Michael aldol reaction promoted by AlLi-(*R*)-binaphthoxide complex.

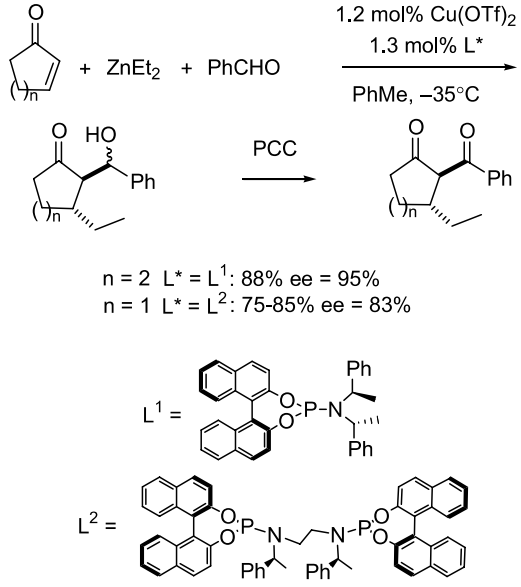
In addition, these authors have described the reaction pathway in this three-component coupling reaction as follows (Scheme 2). The reaction of diethyl malonate with AlLi-(*R*)-binaphthoxide complex gives the corresponding lithium enolate. This latter enolate then reacts with cyclopentenone, which is pre-coordinated to the aluminium, to give an aluminium enolate enantioselectively. Further



Scheme 2. Possible mechanism for asymmetric domino Michael aldol reaction catalysed by ALB.

reaction of this latter enolate with aldehyde would lead to an alkoxide. Although it is unclear whether the aluminium or lithium alkoxide is generated, the resulting alkoxide then abstracts a hydrogen atom from an acidic OH group to give the three-component coupling product and regenerates the ALB complex, which completes the catalytic cycle.

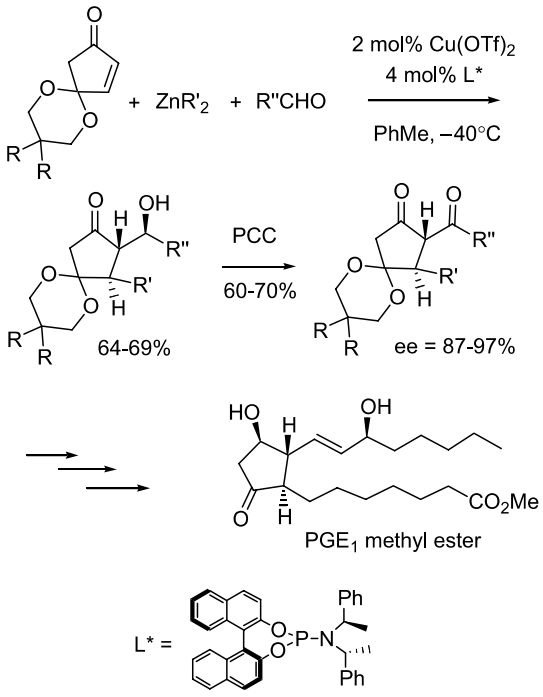
First reported in 1996 by Noyori et al.,[8] the catalytic enantioselective domino 1,4-addition-enolate trapping reaction of dialkylzinc reagents to enones was re-investigated by Feringa et al. in the presence of new copper complexes of bidentate chiral phosphoramidites prepared from TADDOL and BINOL.[9] Thus, these ligands were successfully involved in the copper-catalysed enantioselective conjugate addition aldol reaction of diethylzinc to 2-cyclopentenone in the presence of benzaldehyde (Scheme 3). Other enantioselective Michael aldol reactions have been reported such as those involving the Michael addition of silyl phenyl selenide or sulphide derivatives to vinyl ketone derivatives mediated by a chiral acyloxyborane.[10] Hayashi et al. have shown that it was also possible to use various 9-aryl-9-borabicyclo[3.3.1]-nonanes as a source of nucleophile activated by a chiral rhodium complex.[11] In 2004, a new domino Michael aldol reaction was introduced, in which the addition of diethylaluminium iodide to propiolate derivatives in the presence of aldehydes was catalysed by chiral salen-type ligands.[12]



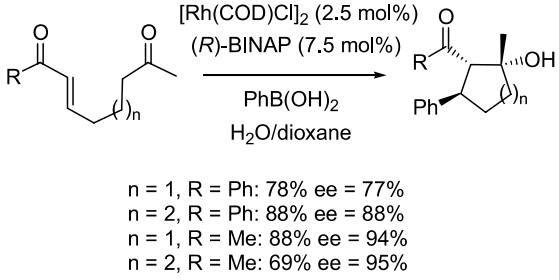
Scheme 3. Asymmetric domino conjugate addition aldol reaction with cyclic enones.

The usefulness of this methodology was illustrated by its application to cyclopenten-3,5-dione monoacetals, suppling the key step in the total synthesis of (−)-prostaglandin E_1 methyl ester (Scheme 4).[13] The reactions depicted in Schemes 1, 3 and 4 involve three-components and, consequently, could also be included in Section 2.6.

In 2003, Krische et al. reported a domino conjugate addition-aldol cyclisation reaction based on an enantioselective catalytic carbometallative aldol cycloreduction of aromatic and aliphatic mono-enone mono-ketone derivatives, providing five- and six-membered ring products (Scheme 5).[14]



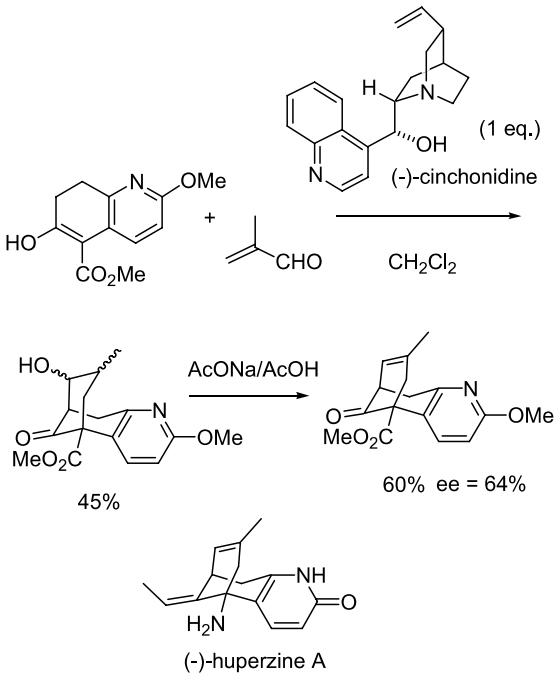
Scheme 4. Synthesis of PGE_1 methyl ester by enantioselective domino 1,4-addition aldol reaction.



Scheme 5. Catalytic enantioselective domino carbometallative aldol cycloreduction reaction.

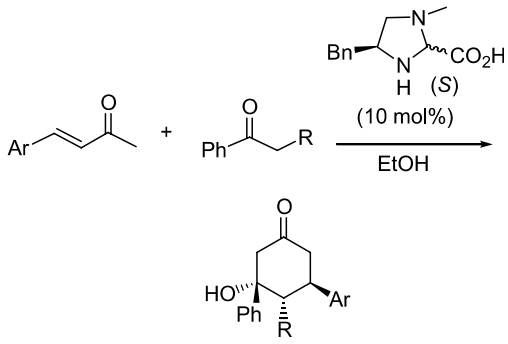
Chiral amine catalysts such as *Cinchona* alkaloids have been shown to catalyse an enantioselective domino Michael aldol reaction of a β-ketoester with methacrolein. This reaction was the key step to construct the 5,9-methanocycloocta[*b*]pyridine system characterising the tricyclic structure of (−)-huperzine A (Scheme 6).[15] Thus, it was demonstrated that simple chiral organic molecules could be alternatives to metal-based catalysts.

In 2005, Gryko reported the asymmetric domino Michael aldol reaction of 1,3-diketones with methyl vinyl ketone in the presence of L-proline, providing highly substituted chiral cyclohexanones.[16] This family of chiral catalysts was also used by Hatakeyama et al. for the development of an asymmetric version of the Baylis–Hillman reaction.[17] More recently, Jorgensen et al. achieved the first highly enantio- and diastereoselective organocatalytic domino Michael aldol reaction of β-diketones, β-ketosulphones, and β-ketoesters with α,β-unsaturated ketones.[18] This reaction was catalysed by an imidazolidine catalyst, easily prepared from phenylalanine. The very mild conditions, inexpensive catalyst, and chromatography-free procedure made this



Scheme 6. Asymmetric domino Michael aldol reaction promoted by *Cinchona* alkaloids.

domino reaction an attractive approach to optically active cyclohexanone building blocks (Scheme 7 and Table 1).

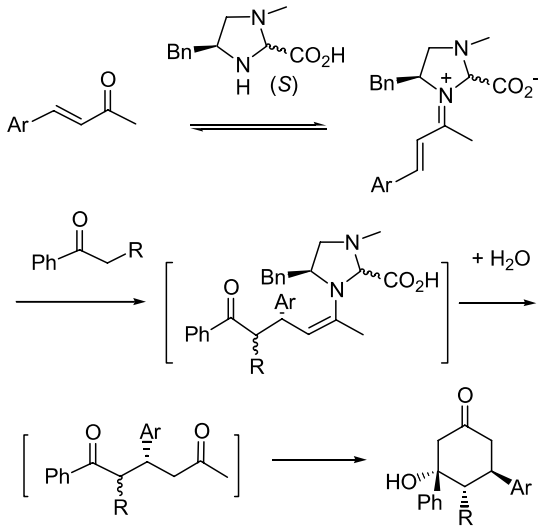


Scheme 7. Enantioselective organocatalytic domino Michael aldol reaction.

Table 1.

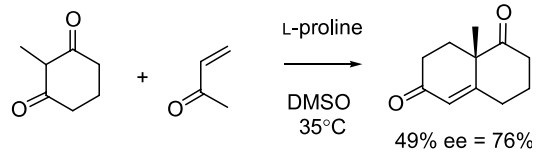
Ar	R	Yield (%)	de (%)	ee (%)
Ph	CO_2Et	60	>94	88
Ph	CO_2Bn	80	>94	95
p-ClC_6H_4	CO_2Bn	60	>94	93
2-Pyrimidyl	CO_2Bn	84	>94	89
Ph	COPh	56	>95	91
p-$NO_2C_6H_4$	COPh	47	>95	87
2-Furyl	SO_2Ph	59	>95	85
Ph	SO_2Ph	93	>95	96
p-ClC_6H_4	SO_2Ph	95	>95	94
p-HOC_6H_4	SO_2Ph	87	>95	98
2-Furyl	SO_2Ph	77	>95	94

As shown in Scheme 8, the catalyst was believed to have three roles during the reaction: (1) activation of the Michael acceptor by iminium ion formation, (2) deprotonation of the Michael donor, and (3) acting as a base catalyst for the intramolecular aldol step.



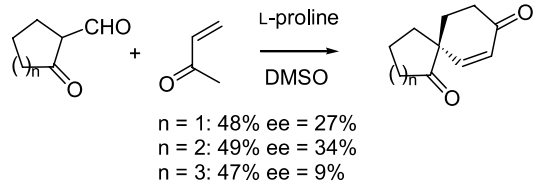
Scheme 8. Mechanism of chiral imidazoline-catalysed domino Michael aldol reaction.

In 2000, Barbas et al. showed that L-proline could act as an efficient catalyst of the one pot Robinson annulation reaction, providing the enantiopure Wieland–Miescher ketone, which has proved to be a particularly useful synthon for the construction of a variety of biologically active compounds (Scheme 9).[19]



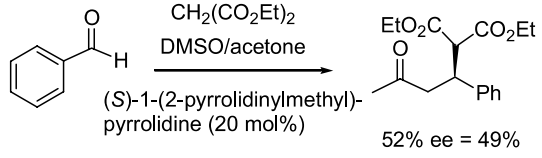
Scheme 9. Proline-catalysed asymmetric domino Robinson annulation reaction.

In addition, Swaminathan et al. have extended this methodology to annulation of a number of 2-formylcyclononones and have obtained the corresponding optically active spiroenediones (Scheme 10).[20]



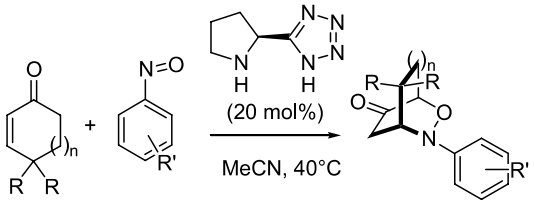
Scheme 10. Asymmetric domino Robinson annulation of formylcyclononones.

On the other hand, asymmetric domino Michael-terminated processes are also present in the literature such as the one pot Knoevenagel Michael reaction reported by Barbas that directly converted an aldehyde into the final Michael adduct via chiral amine catalysis of both steps (Scheme 11).[21]



Scheme 11. (*S*)-1-(2-Pyrrolidinylmethyl)-pyrrolidine-induced domino Knoevenagel Michael reaction.

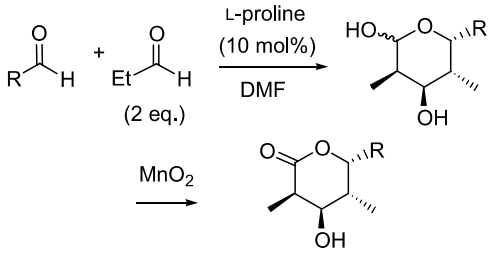
Another example of an enantioselective Michael-terminated process was reported by Yamamoto et al. in 2004.[22] This domino *O*-nitroso aldol Michael reaction catalysed by a pyrrolidine-based tetrazole gave rise to nitroso Diels–Alder adducts (Scheme 12).



n = 1, R = Me, R' = H: 64% ee = 99%
n = 1, R = R' = H: 34% ee = 99%
n = 1, R = Ph, R' = H: 56% ee = 99%
n = 1, R,R = (OCH_2CH_2O), R' = H: 61% ee = 98%
n = 1, R = Me, R' = 3,5-Me_2: 52% ee = 98%
n = 1, R = Me, R' = 4-Br: 50% ee = 99%
n = 2, R = Me, R' = H: 14% ee = 99%

Scheme 12. Enantioselective domino *O*-nitroso aldol Michael reaction.

L-Proline-catalysed direct asymmetric assembly reactions involving three aldehyde components were developed in 2002, providing the remarkably simple preparation of polyketides in an enzyme-like assembly process.[23] This asymmetric double aldol reaction led to the formation of pyranoses, which were further converted into the corresponding δ-lactones by oxidation (Scheme 13). At the same time, Barbas et al. reported the proline-catalysed one-step asymmetric synthesis of 5-hydroxy-(2*E*)-hexenal from the self-aldol reaction of acetaldehyde.[24]

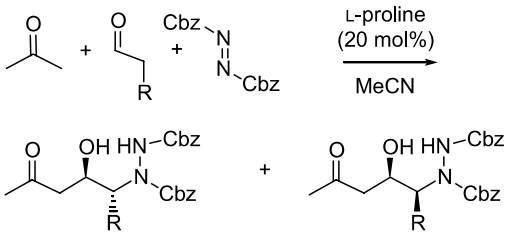


R = Et: 53% ee = 47%
R = *i*-Pr: 32% ee = 12%
R = *i*-Bu: 24% ee = 11%

Scheme 13. L-Proline-catalysed asymmetric double aldol reaction.

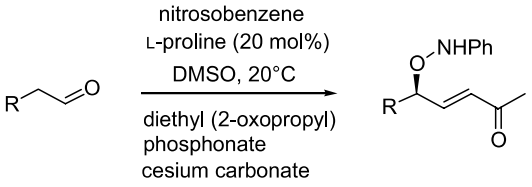
In order to extend the above methodology, Chowdari et al. developed this assembly reaction in the presence of aldehydes, ketones, and azodicarboxylic acid esters to provide optically active β-aminoalcohols.[25] This result was the first example of assembly reactions that used directly both aldehydes and ketones as donors in one pot (Scheme 14).

In addition, L-proline was involved in an enantioselective synthesis of *O*-amino-substituted allylic alcohols by an asymmetric domino aminoxylation olefination reaction of aldehydes under ambient conditions (room temperature, air and moisture were tolerated).[26] Indeed, the process enabled reactive α-aminoaldehydes to be trapped in situ by Wadsworth–Emmons–Horner olefination (Scheme 15).



R = Me: 82% *anti:syn* = 28/72 ee (*anti:syn*) = 98:78
R = Bn: 83% *anti:syn* = 45/55 ee (*anti:syn*) = 99:91
R = *n*-Pent: 82% *anti:syn* = 44/56 ee (*anti:syn*) = 99:61
R = Me: 85% *anti:syn* = 54/46 ee (*anti:syn*) = 99:34

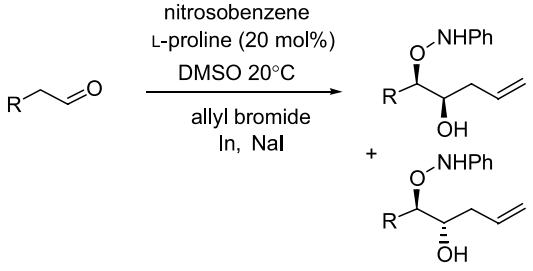
Scheme 14. Proline-catalysed asymmetric assembly reactions of acetone, dibenzyl azodicarboxylate and aldehydes.



R = *i*-Pr: 74% ee = 98%
R = Me: 56% ee = 98%
R = Bn: 81% ee = 97%
R = *n*-Bu: 69% ee = 99%
R = *n*-Pr: 70% ee = 97%
R = allyl: 71% ee = 98%

Scheme 15. L-Proline-promoted asymmetric domino aminoxylation olefination reaction of aldehydes.

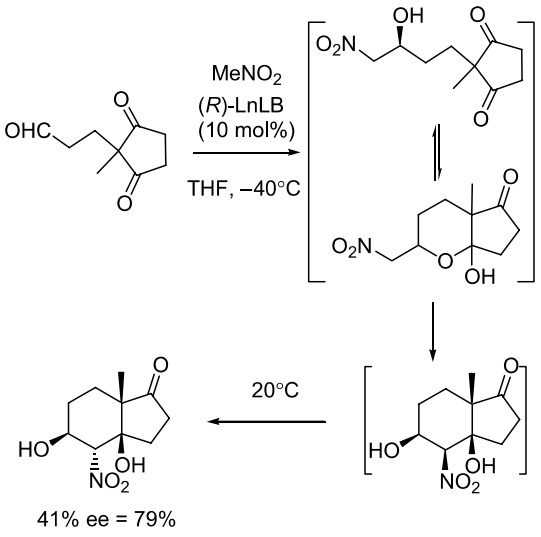
The same conditions were applied to the domino aminoxylation allylation reaction of aldehydes in order to prepare enantiopure mono-substituted 1,2-diols (Scheme 16).[27] The proline-catalysed α-aminoxylation of aldehydes was followed by in situ indium-promoted allylation.



R = *i*-Pr: 71% dr(*syn:anti*) = 5:3 ee(*syn:anti*) = 99%:97%
R = Me: 80% dr(*syn:anti*) = 3:2 ee(*syn:anti*) = 98%:98%
R = *n*-Pr: 65% dr(*syn:anti*) = 3:2 ee(*syn:anti*) = 98%:98%
R = Bu: 82% dr(*syn:anti*) = 3:2 ee(*syn:anti*) = 98%:98%
R = Bn: 74% dr(*syn:anti*) = 3:2 ee(*syn:anti*) = 99%:99%

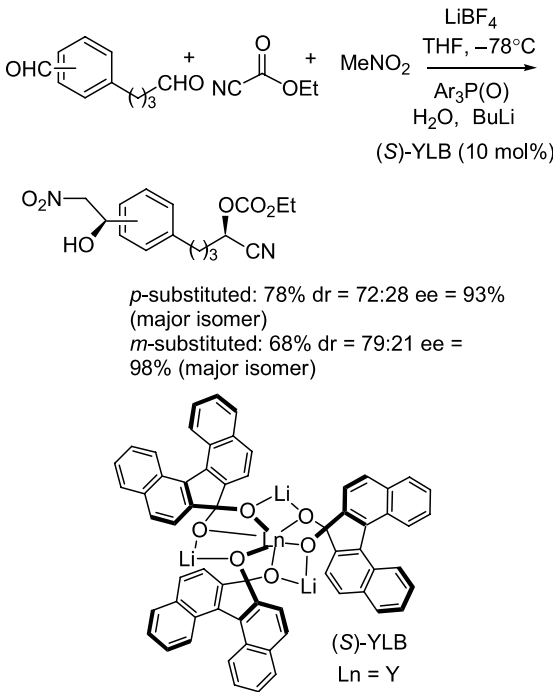
Scheme 16. L-proline-promoted asymmetric domino aminoxylation allylation reaction of aldehydes.

The first domino inter-intramolecular catalytic asymmetric nitroaldol reaction using a $LnLi_3${*tris*[(*R*)-binaphthoxide]} complex (LnLB; Ln: lanthanoid) was developed by Shibasaki et al., providing easy access to optically active 3α,5-dihydroxy-7α-methyl-4-nitro-3α,4,5,6,7,7α-hexahydro-1-indanones (Scheme 17).[28]



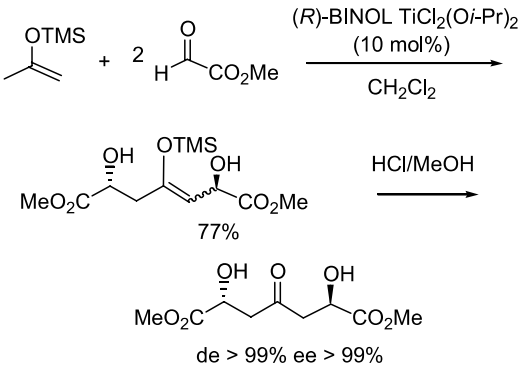
Scheme 17. Chiral lanthanoid complex-promoted domino inter-intramolecular nitroaldol reaction.

In the same context, the first asymmetric domino cyanation nitroaldol reaction using a YLi_3{*tris*[(−)-binaphthoxide]} single catalyst component was performed by these authors. Tuning the chiral environment in YLB with achiral additives such as $Ar_3P(O)$ and $LiBF_4$ had a key role in this reaction (Scheme 18).[29] This reaction, which involves three-components, could also be included in Section 2.6.



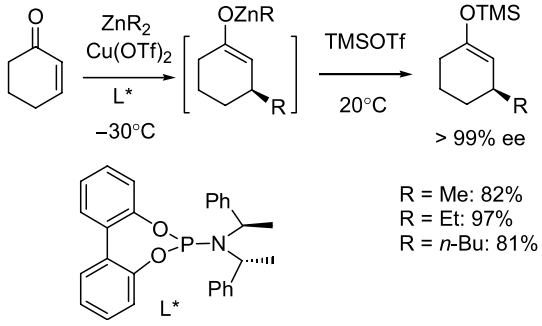
Scheme 18. Domino catalytic cyanation nitroaldol reaction.

A binaphthol-derived chiral titanium complex has been used as the catalyst of the first domino and two-directional asymmetric catalysis of the Mukaiyama aldol reaction.[30] Indeed, upon addition of an excess amount of an aldehyde, the Mukaiyama aldol reaction of a silyl ether proceeded in a tandem and two-directional fashion to give the corresponding silyl enol ether in >99% ee (Scheme 19).



Scheme 19. Asymmetric catalytic domino two-directional Mukaiyama aldol reaction.

Domino conjugate addition-silylation and addition-cyclopropanation reactions were developed by Alexakis et al. in 2002.[31] Both of these reactions were copper catalysed in the presence of chiral phosphoramidate ligands. In the former reaction, zinc enolates, resulting from the copper-catalysed conjugate addition of dialkylzinc reagents to enones, could be trapped as silyl enol ethers with TMSOTf (Scheme 20). Similarly, these zinc enolates could be trapped by various electrophiles such as acetals, ketals or orthoesters.[32]

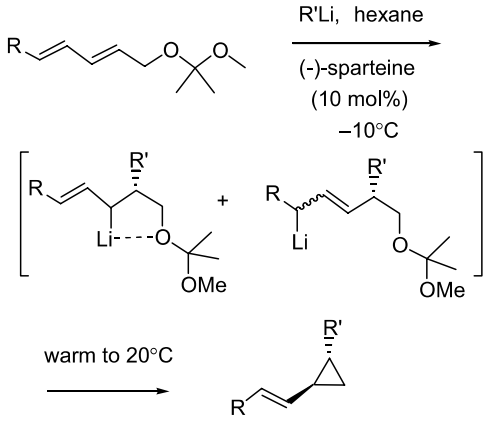


Scheme 20. Domino asymmetric conjugate addition silylation reaction of zinc enolates.

In order to prepare chiral vinylcyclopropanes, Marek et al. developed the first domino catalytic asymmetric carbolithiation reaction of dienyl systems, followed by 1,3-intramolecular elimination.[33] This reaction, catalysed by (−)-sparteine, involved (1) the enantiofacial choice of a dienyl system by the chiral organolithium, and (2) the stereoselective 1,3-elimination into the corresponding cyclopropane. This method represented one of the first syntheses of vinylcyclopropanes with substoichiometric amounts of chiral ligands (Scheme 21).

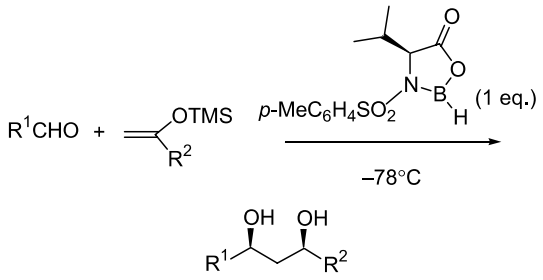
In 1994, Kiyooka et al. reported a domino aldol reaction reduction in which the double asymmetric inductions were effectively accomplished by only one promoter.[34] Indeed, a chiral borane turned out to successively promote the asymmetric aldol reaction of aldehydes with silyl enol ethers and the following asymmetric reduction in one pot, to afford chiral *syn*-1,3-diols (Scheme 22).

Finally, an enantioselective synthesis of aziridines was based on the asymmetric one pot aziridination of imines with alkyl bromides via the imino Corey–Chaykovsky



R = *c*-Hex, R' = *n*-Bu: 70% ee = 72%
R = *n*-Hex, R' = *c*-Hex: 61% ee = 50%
R = *n*-Bu, R' = Ph: 53% ee = 83%
R = *n*-Hex, R' = Ph: 45% ee = 73%
R = TMS, R' = *n*-Bu: 60% ee = 55%
R = TMS, R' = *n*-Hex: 52% ee = 52%
R = *i*-Pr, R' = *n*-Bu: 60% ee = 54%

Scheme 21. Asymmetric domino carbolithiation elimination reaction.



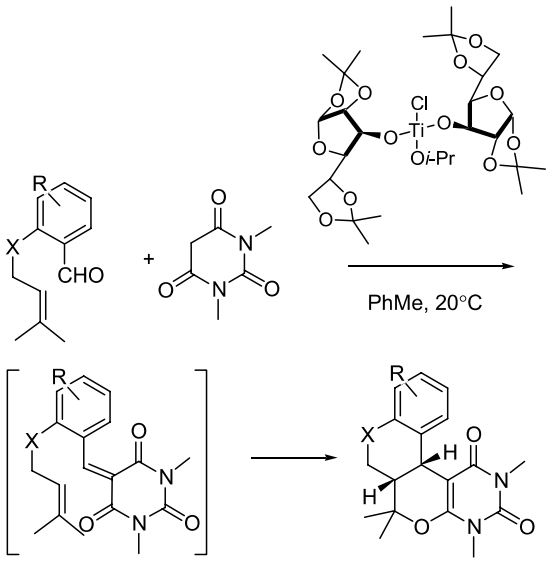
R^1 = *i*-Pr, R^2 = Ph: 60% ee = 94%
R^1 = *i*-Pr, R^2 = $BnO(CH_2)_2$: 55% ee = 86%
R^1 = *i*-Pr, R^2 = *n*-Hex: 70% ee = 99%
R^1 = *n*-Pr, R^2 = Ph: 63% ee = 96%
R^1 = *n*-Pr, R^2 = *n*-Hex: 66% ee = 98%
R^1 = C_6H_5, R^2 = *n*-Hex: 53% ee = 85%

Scheme 22. Asymmetric domino aldol reduction reaction.

reaction mediated by chiral sulphide. The use of a camphor-derived chiral sulphide mediator allowed high enantioselectivities (≤98% ee).[35]

2.1.2. Anionic–pericyclic reactions. In 1992, Tietze et al. reported an enantioselective domino Knoevenagel hetero Diels–Alder reaction, which was actually the first enantioselective domino reaction.[36] A chiral titanium Lewis acid was a potent mediator for the intramolecular hetero Diels–Alder reaction of 1-oxa-1,3-butadienes prepared in situ by a Knoevenagel condensation of aromatic aldehydes and *N*,*N*′-dimethylbarbituric acid (Scheme 23).

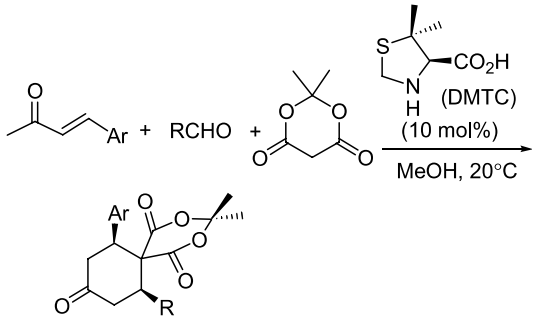
In the same context, Barbas et al. reported in 2003 the first organocatalytic asymmetric domino Knoevenagel Diels–Alder reaction that produced highly substituted spiro[5,5]-undecane-1,5,9-triones from commercially available 4-substituted-3-buten-2-ones, aldehydes, and 2,2-dimethyl-



R = H, X = O: 81% ee = 68%
R = 3-OMe, X = O: 68% ee = 75%
R = 4-OMe, X = O: 72% ee = 80%
R = 5-OMe, X = O: 86% ee = 88%
R = 3-Me, X = O: 58% ee = 71%
R = H, X = CH_2: 55% ee = 68%

Scheme 23. Enantioselective domino Knoevenagel hetero Diels–Alder reaction.

1,3-dioxane-4,6-dione in the presence of a catalytic amount of a chiral amino acid such as 5,5-dimethyl-thiazolidinium-4-carboxylate (DMTC) (Scheme 24).[37] This three-component reaction could also be included in Section 2.6.

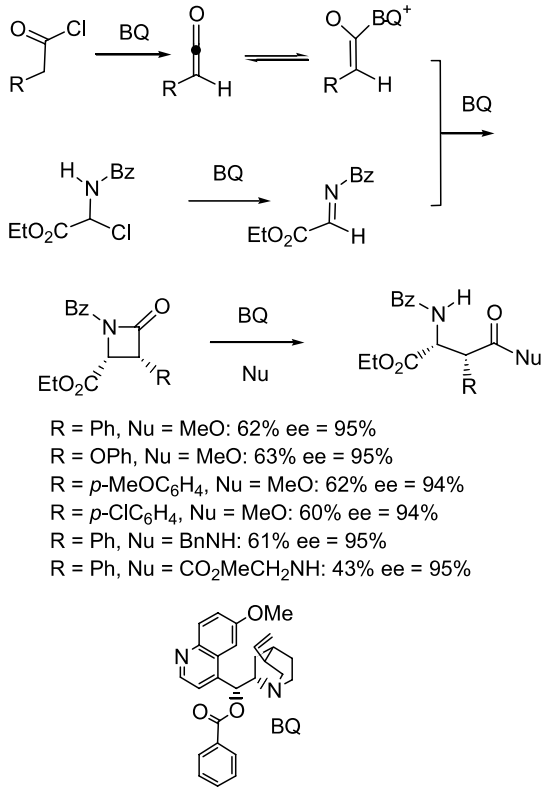


Ar = Ph, R = *p*-$NO_2C_6H_4$: 88% ee = 86%
Ar = Ph, R = *p*-CNC_6H_4: 80% ee = 84%
Ar = 1-naphthalenyl, R = *p*-$NO_2C_6H_4$: 93% ee = 99%
Ar = 2-furanyl, R = *p*-$NO_2C_6H_4$: 85% ee = 88%
Ar = 2-thiophenyl, R = *p*-$NO_2C_6H_4$: 75% ee = 99%

Scheme 24. DMTC-catalysed domino Knoevenagel Diels–Alder reaction.

On the other hand, the same authors have developed amine-catalysed domino Diels–Alder reactions between α,β-unsaturated ketones with nitro-olefins.[38] Either (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine or L-proline catalysed the in situ-generation and reaction of 2-amino-1,3-dienes, to provide cyclohexanone derivatives in good yield (≤87%) in one-step with modest enantioselectivity (≤38% ee). Another chiral amine, for example, benzoylquinine (BQ), was involved as catalyst in the asymmetric synthesis of β-substituted aspartic acid derivatives through a four-stage,

one pot procedure.[39] It was demonstrated that this nucleophilic catalyst served up to four discrete roles in the procedure: catalytic dehydrogenation of acid chlorides to form ketenes; catalytic dehydrohalogenation of α-chloroamines to form the corresponding imines; catalytic [2+2]-cycloaddition to produce intermediate acyl β-lactams; and, finally, nucleophilic ring opening to afford the optically active aspartic acid derivatives (Scheme 25). It must be noted that the first example of an enantioselective one pot synthesis of β-lactams was reported by Cinquini et al., in 1995, using an *N*-methylephedrine derivative as a chiral ligand of BCl_3. This latter chiral catalyst induced the reaction of enolates of 2-pyridylthioesters with achiral imines.[40]

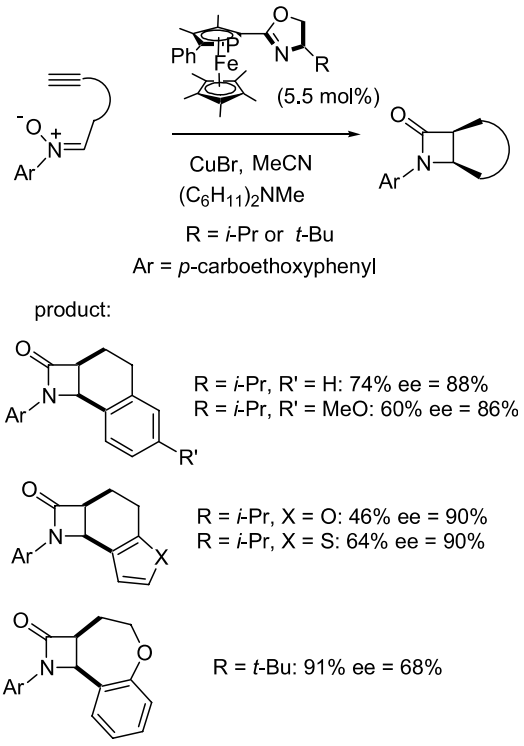


Scheme 25. One pot asymmetric domino synthesis of aspartic acid derivatives.

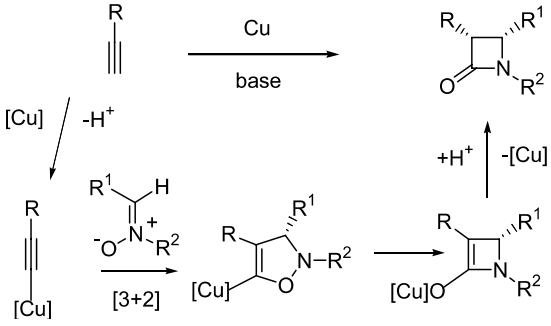
In addition, these authors developed a bifunctional catalyst system in which a chiral nucleophile was paired with an achiral Lewis acidic metal salt to effect a similar asymmetric synthesis of β-lactams.[41] Other chiral β-lactams were prepared by copper-catalysed intramolecular Kinugasa reactions and interception of an intermediate (enolate) in the reaction cascade.[42] The reaction was carried out in the presence of catalytic amounts of planar-chiral phosphaferrocene-oxazolines (Scheme 26).

An outline of a possible mechanism for the Kinugasa reaction is depicted in Scheme 27.

Asymmetric cascade 1,3-dipolar cycloaddition reactions of imines were studied by Grigg in 1995, allowing successful approaches to various chiral pyrrolidines by using metals



Scheme 26. Asymmetric intramolecular Kinugasa reactions.

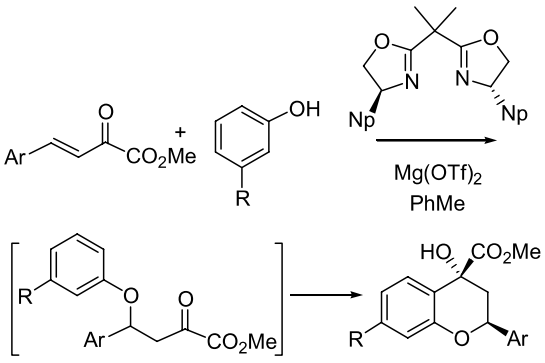


Scheme 27. Possible mechanism for Kinugasa reaction.

such as Mn(II) or Co(II) in combination with chiral ligands.[43]

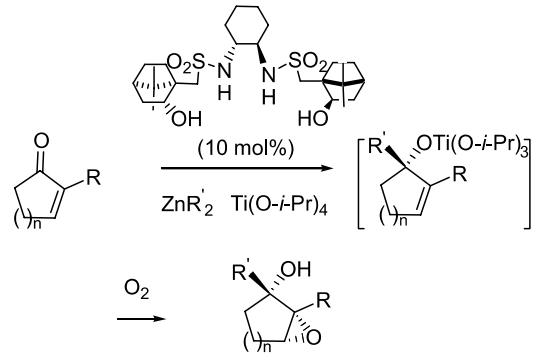
2.1.3. Anionic–miscellaneous reactions. In 2003, Jorgensen et al. reported the synthesis of optically active functionalised chromanes by a catalytic asymmetric domino oxa-Michael addition Friedel-Crafts alkylation reaction.[44] Bisoxazolines were involved as the chiral ligands in combination with $Mg(OTf)_2$ (Scheme 28).

In 2003, Walsh et al. performed a one pot enantioselective ketone alkylation diastereoselective epoxidation reaction.[45] The protocol consisted simply of capping the reaction with a balloon of dioxygen when the asymmetric addition of ZnR_2 to the enone was complete (Scheme 29). Very recently, this methodology was applied to the one pot asymmetric synthesis of acyclic chiral epoxyalcohols via a domino vinylation epoxidation reaction.[46]



R = OMe, Ar = Ph: 77% ee = 80%
R = OMe, Ar = *p*-BrC_6H_4: 45% ee = 66%
R = OMe, Ar = *p*-ClC_6H_4: 39% ee = 74%
R = NMe_2, Ar = *p*-ClC_6H_4: 95% ee = 18%

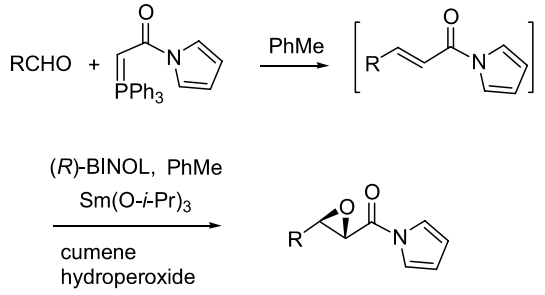
Scheme 28. Asymmetric domino oxa-Michael addition Friedel-Crafts alkylation reaction.



R = Me, R' = Me, n = 2: 82% ee = 99%
R = Me, R' = Et, n = 2: 80% ee = 99%
R = Me, R' = Me, n = 1: 50% ee = 98%
R = Me, R' = Et, n = 1: 60% ee = 97%
R = Pent, R' = Me, n = 1: 67% ee = 99%
R = Pent, R' = Et, n = 1: 60% ee = 99%

Scheme 29. Asymmetric domino alkylation epoxidation reaction.

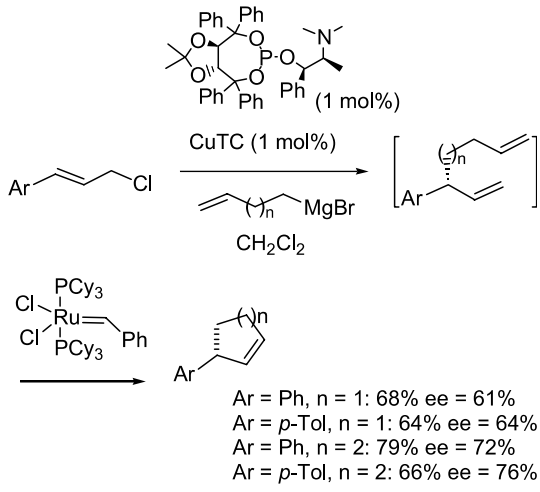
In 2004, Shibasaki et al. developed a domino Wittig olefination catalytic asymmetric epoxidation reaction, providing efficient one pot access to optically active epoxides from various aldehydes (Scheme 30).[47]



R = Ph: 96% ee = 99.5%
R = naphthalene: 100% ee = 99%
R = *p*-MeC_6H_4: 92% ee = 99%
R = *p*-$MeOC_6H_4$: 87% ee = 98%
R = *p*-ClC_6H_4: 100% ee = 99%

Scheme 30. Domino Wittig olefination asymmetric epoxidation reaction.

In 2002, Alexakis et al. showed that Grubbs' catalyst was compatible with excess Grignard reagent and copper salts by developing the first enantioselective domino substitution metathesis.[48] Thus, Grignard reagents underwent enantioselective copper-catalysed S_N2' substitution on achiral allylic chlorides, and the resulting terminal alkene could be submitted to metathesis, providing new chiral synthons (Scheme 31).

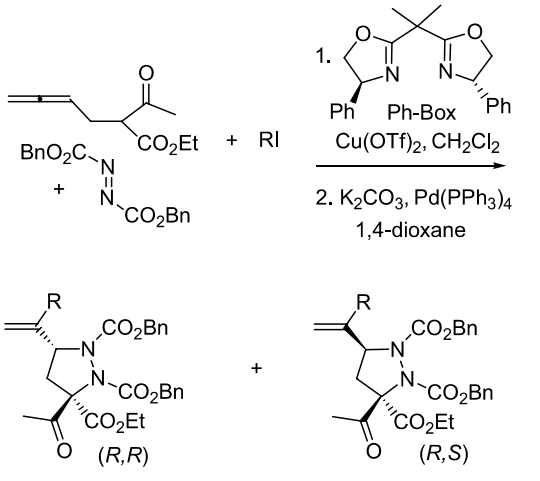


Ar = Ph, n = 1: 68% ee = 61%
Ar = *p*-Tol, n = 1: 64% ee = 64%
Ar = Ph, n = 2: 79% ee = 72%
Ar = *p*-Tol, n = 2: 66% ee = 76%

CuTC: copper thiophene-2-carboxylate

Scheme 31. Asymmetric domino substitution metathesis reaction.

Optically active pyrazolidine derivatives have been constructed by the Cu- and Pd-catalysed asymmetric domino addition cyclisation reaction of 2-(2′,3′-dienyl)-β-ketoesters, organic halides, and dibenzyl azodicarboxylate (DBAD) (Scheme 32).[49] This three-component reaction could also be included in Section 2.6.

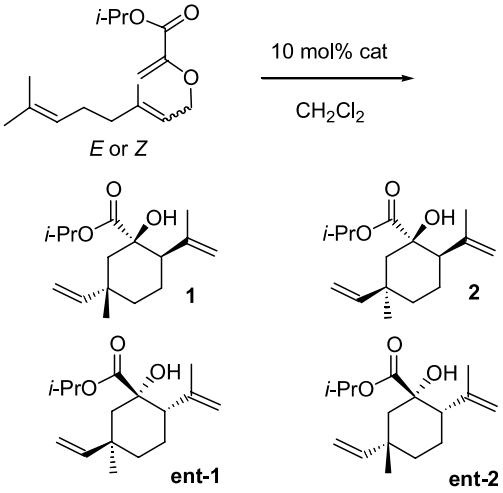


R	Yield (%)	dr (*R*,*R*:*R*,*S*)	ee (*R*,*R*) (%)	ee (*R*,*S*) (%)
p-Tol	85	33:67	98	98
p-$MeOC_6H_4$	95	34:66	98	98
p-BrC_6H_4	94	36:64	97	98
p-$NO_2C_6H_4$	97	40:60	98	99
thiophen-2-yl	71	36:64	91	99

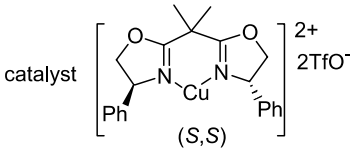
Scheme 32. Asymmetric domino addition cyclisation reaction.

2.2. Pericyclic primary step

The first catalytic processes including Claisen rearrangements had been planned as domino reactions. An initial enantioselectively catalysed step generated the allyl vinyl backbone for the consecutive sigmatropic rearrangement. The first successful enantioselective catalytic Claisen rearrangement for the construction of newly defined C–C bonds was published by Hiersemann et al.[50] This domino Claisen rearrangement intramolecular carbonyl-ene reaction was catalysed by chiral copper(II) bis(oxazolines) (Scheme 33).

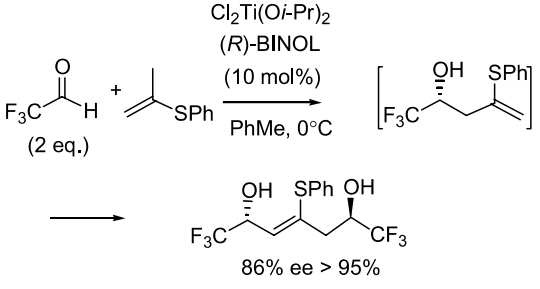


Substrate	Catalyst	Yield (%)	dr	ee (%)
E	(*S*,*S*)	98	**1**:**2** = 89:11	98
E	(*R*,*R*)	92	**ent-1**:**ent-2** = 89:11	99
Z	(*S*,*S*)	93	**1**:**2** = 19:81	99
Z	(*R*,*R*)	93	**ent-1**:**ent-2** = 20:80	99



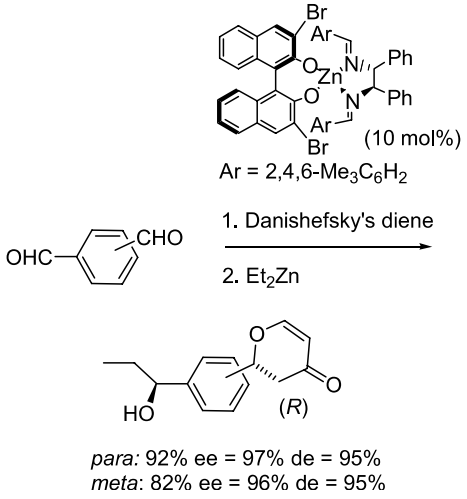
Scheme 33. Catalytic asymmetric domino Claisen rearrangement carbonyl-ene reaction.

Mikami et al. have demonstrated that a binaphthol-derived chiral titanium complex could promote a domino and two-directional asymmetric fluoral-ene reaction, providing a new type of antiferroelectric liquid crystalline molecules (Scheme 34).[51]



Scheme 34. Asymmetric domino two-directional carbonyl-ene reaction with fluoral.

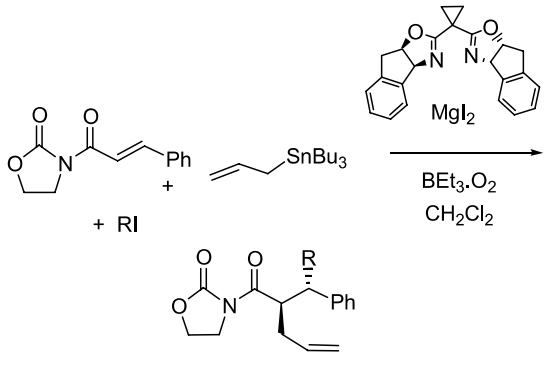
In addition, Ding et al. have achieved the integration of two asymmetric reactions in one pot with the promotion of a single catalyst for the hetero Diels–Alder reaction of Danishefsky's diene and diethylzinc addition to aldehydes (Scheme 35).[52] Indeed, this strategy demonstrated the ability of a single catalyst to promote two distinct enantioselective reactions in one pot. This three-component reaction could also be included in Section 2.6.



Scheme 35. Asymmetric domino hetero Diels–Alder diethylzinc addition reaction.

2.3. Radical sequences

The first examples where two C–C bonds were formed with high stereocontrol by nucleophilic radical addition to an enolate followed by trapping with an allylstannane were reported by Sibi et al. in 2001.[53] In these unusual domino three-component intermolecular addition intermolecular trapping reactions involving acyclic systems, chirality was established at both β- and α-centres with control over both absolute and relative stereochemistry (Scheme 36).

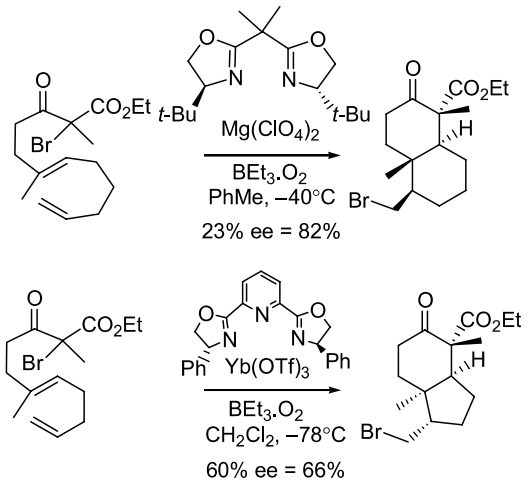


R = *c*-Hex: 80% de = 96% ee = 92%
R = *i*-Pr: 93% de = 94% ee = 93%
R = *t*-Bu: 84% de = 98% ee = 97%
R = Et: 79% de = 94% ee = 77%

Scheme 36. Enantioselective domino radical reaction.

Other chiral Lewis acid-promoted enantioselective atom-transfer radical tandem cyclisation reactions were developed by Yang et al., providing excellent methods for

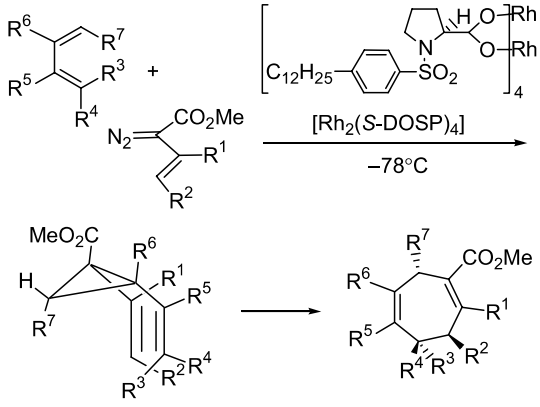
the construction of polycyclic ring skeletons under mild and neutral conditions (Scheme 37).[54]



Scheme 37. Enantioselective atom-transfer radical tandem cyclisation reactions.

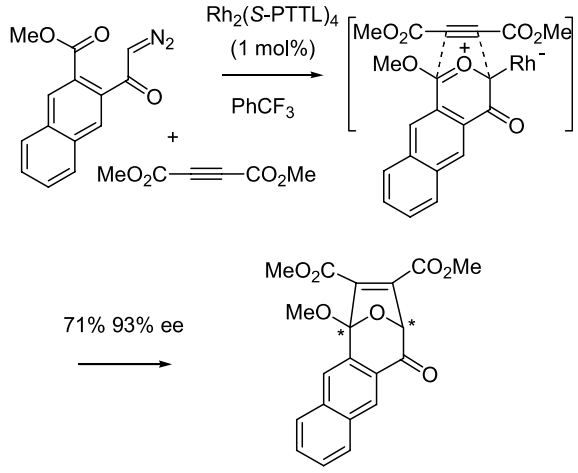
2.4. Carbene sequences

In 1998, Davies et al. reported a domino asymmetric cyclopropanation Cope rearrangement reaction using rhodium(II) (*N*-dodecylbenzenesulphonyl)prolinate [Rh_2-(*S*-DOSP)$_4$].[55] In this process, decomposition of vinyl diazoacetates by the chiral catalyst in the presence of dienes resulted in a direct and highly enantioselective method for the formation of *cis*-divinylcyclopropanes. A combination of this process with a subsequent Cope rearrangement resulted in a highly enantioselective synthesis of a variety of cycloheptadienes containing multiple stereogenic centres (Scheme 38). The same methodology was extended to the enantioselective synthesis of various fused cycloheptadienes,[56] allowing the total synthesis of 5-*epi*-tremulenolide.[57]



Scheme 38. Asymmetric domino cyclopropanation Cope rearrangement reaction.

The domino carbonyl ylide formation and 1,3-dipolar cycloaddition methodology extensively advanced by the Padwa group with dirhodium(II) carboxylate catalysts is rapidly becoming recognised as a potentially powerful means for the construction of highly substituted oxygen-containing heterocycles.[58] Hashimoto et al. have shown that enantioselective 1,3-dipolar cycloaddition of the ester-carbonyl ylides derived from methyl 2-(diazoacetyl)-benzoate and 3-(diazoacetyl)-2-naphthoate with dipolarophiles could be effected with the aid of dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate] [Rh_2(*S*-PTTL)$_4$], affording the cycloadducts in up to 93% yield (Scheme 39).[59]

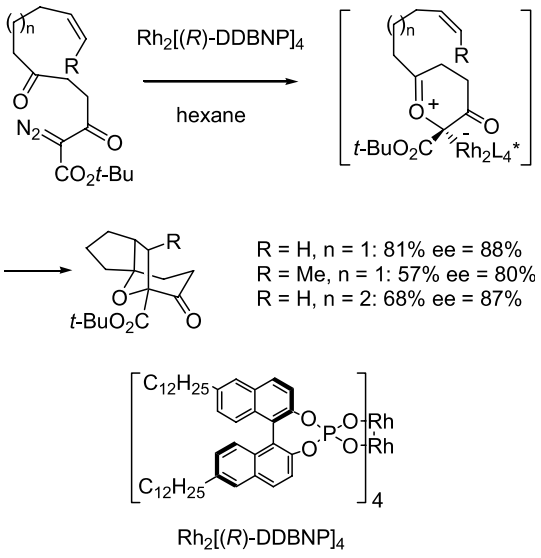


Scheme 39. Enantioselective domino intermolecular 1,3-dipolar cycloaddition reaction of ester-carbonyl ylides.

Hodgson et al. have extended the scope of this reaction to dipolarophiles, which did not contain electron-withdrawing substituents on the reacting π-bond such as phenylacetylene, or strained alkene dipolarophiles, in the presence of 2-diazo-3,6-diketoester-derived carbonyl ylides.[60] Various chiral rhodium catalysts were involved to promote the reaction, giving values for ee ≤92%. In 2003, an intramolecular version of this reaction was developed by these authors.[61] They demonstrated that enantioselective intramolecular 1,3-dipolar cycloadditions of unsaturated 2-diazo-3,6-diketoester-derived carbonyl ylides showed a promising scope in terms of asymmetric induction as the tethered alkene/alkyne dipolarophile component was varied (Scheme 40). In order to develop a better understanding of the factors affecting asymmetric induction in this emerging asymmetric process, the same methodology was successfully applied to α-aryl-α-diazodiones.[62] The results showed that electronic effects clearly played a role in determining the level of asymmetric induction, since the more electron-deficient cycloaddition precursor delivered the higher enantioselectivity.

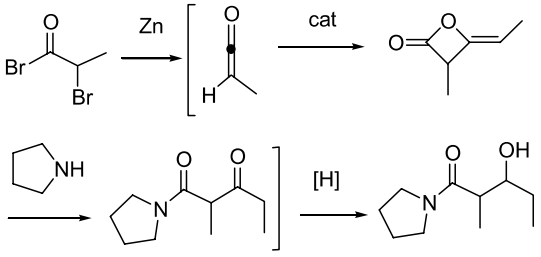
2.5. Miscellaneous sequences

In 1998, Calter et al. reported one pot, catalytic, asymmetric syntheses of all four stereoisomers of a dipropionate synthon, based on a chiral amine-catalysed dimerisation of methylketene, generated in situ from α-bromopropionyl bromide (Scheme 41).[63] Trapping of the ketene dimer with a



Scheme 40. Asymmetric domino carbonyl ylide formation intramolecular [3+2] cycloaddition reaction.

secondary amine, followed by reduction under the appropriate conditions, affords either diastereomer of the dipropionate synthon.

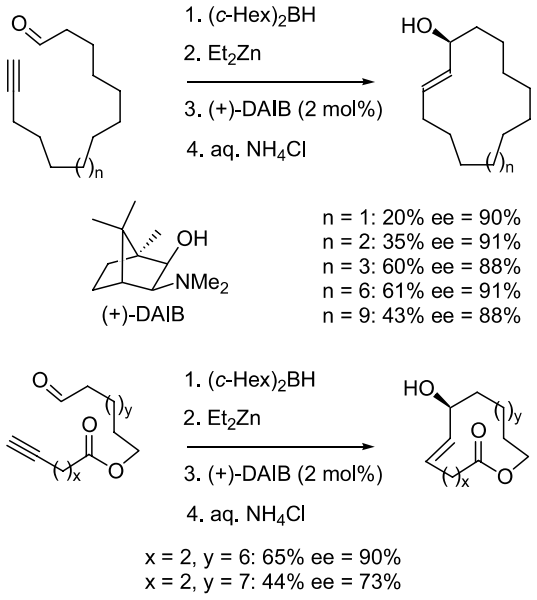


Catalyst	Reduction conditions	Yield (%)	ee (%) (confign)
quinidine	$KB(H)Et_3$	48	98 (2*S*,3*S*)
quinidine	$Zn(OTf)_2$ $NaBH_4$	42	99 (2*S*,3*R*)
trimethylsilyl quinine	$KB(H)Et_3$	48	96 (2*R*,3*R*)
trimethylsilyl quinine	$Zn(OTf)_2$ $NaBH_4$	42	96 (2*R*,3*S*)

Scheme 41. In situ generation and asymmetric dimerisation of ketene.

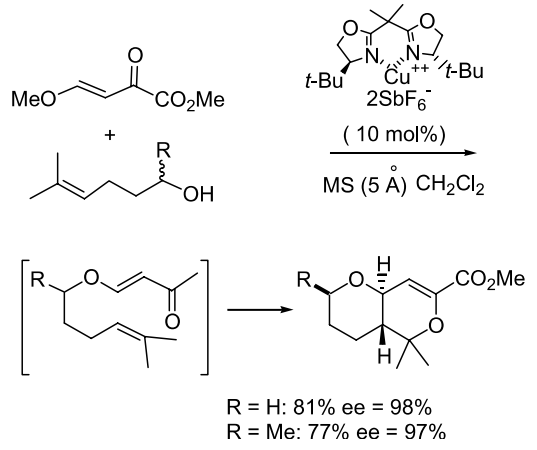
An asymmetric synthesis of macrocyclic (*E*)-allylic alcohols was elaborated by Oppolzer et al., starting from ω-alkynals via intramolecular 1-alkenylzinc/aldehyde additions.[64] This one pot procedure involved, successively, akyne monohydroboration, boron- to -zinc transmetallation, and [(+)-DAIB]-catalysed enantioselective intramolecular ring closure to the aldehyde function (Scheme 42). This methodology offered an efficient approach to various naturally occurring chiral carbocycles and macrolides.

An efficient catalytic double asymmetric induction during a new type of catalytic domino transetherification intramolecular hetero Diels–Alder reaction has been developed, leading to enantiomerically enriched *trans*-fused hydropyranopyran derivatives by using methyl (*E*)-4-methoxy-2-oxo-3-butenoate and δ,ε-unsaturated alcohols in the



Scheme 42. Asymmetric domino hydroboration transmetallation intramolecular ring closure.

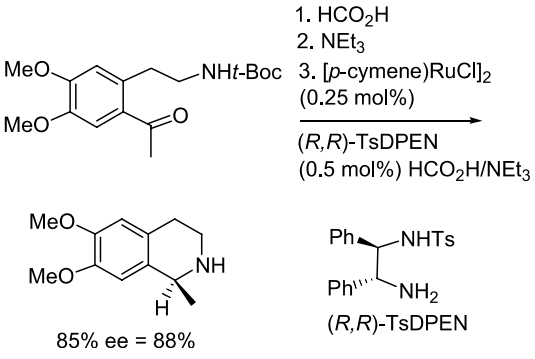
presence of (*S*,*S*)-*t*-Bu-bis(oxazoline)-$Cu(SbF_6)_2$ and molecular sieves (5 Å) (Scheme 43).[65]



Scheme 43. Asymmetric domino transetherification intramolecular hetero Diels–Alder reaction.

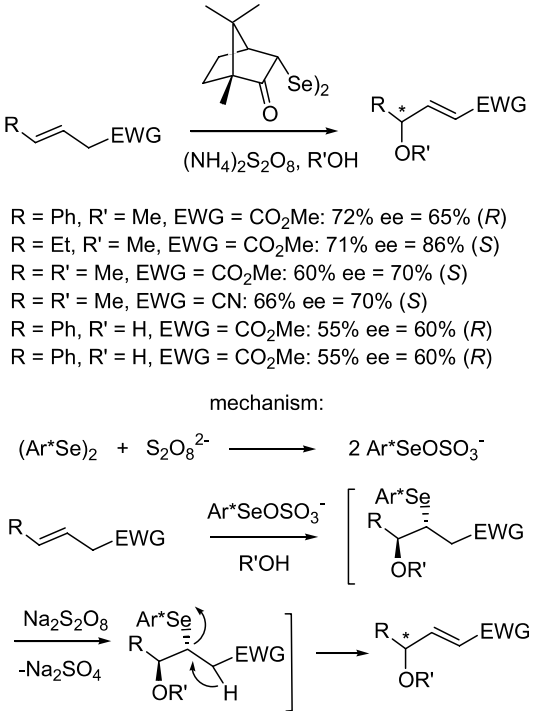
In 2003, Wills et al. reported a one pot process for the enantioselective synthesis of amines via reductive amination under transfer hydrogenation conditions.[66] Indeed, a chiral bicyclic amine could be prepared directly from a *t*-Boc-protected amino ketone by a one pot deprotection/formation of imine/cyclisation/reduction sequence (Scheme 44). A chiral monotosylated diamine (TsDPEN) was adopted as the optimal ligand for this process when used in formic acid/triethylamine, which acted both as the solvent and the hydrogen source.

In 1998, Wirth et al. showed that only catalytic amounts of chiral selenium reagents were necessary to achieve a one pot sequence of methoxyselenenylation and oxidative β-hydride elimination of alkenes.[67] Tiecco et al. applied this domino reaction to various β,γ-unsaturated esters and nitriles, which afforded, by treatment with chiral



Scheme 44. Asymmetric domino deprotection/formation of imine/cyclisation/reduction process.

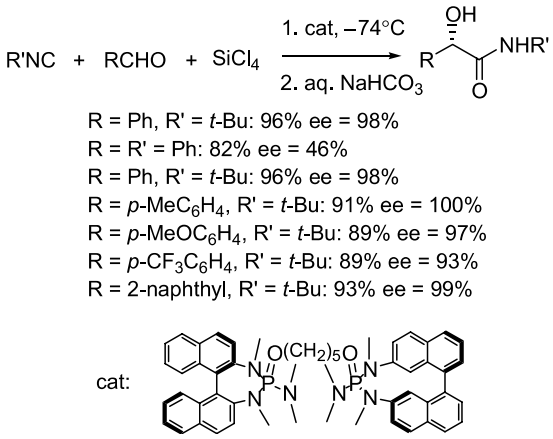
diselenides, the corresponding enantiomerically enriched γ-alkoxy- or γ-hydroxy-α,β-unsaturated derivatives (Scheme 45).[68]



Scheme 45. Asymmetric domino oxyselenenylation deselenenylation reaction.

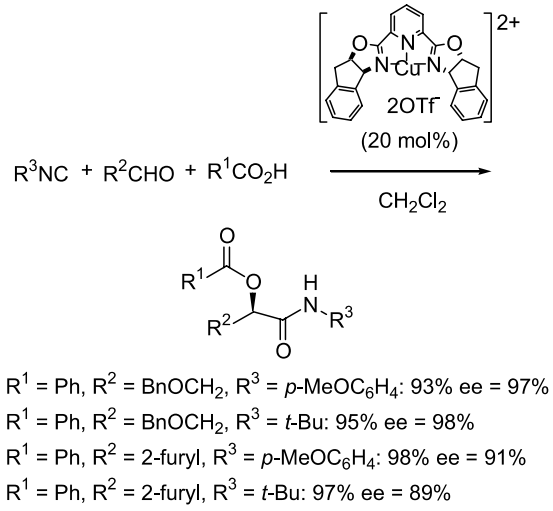
2.6. Domino multicomponent reactions

Despite intense interest, there are still few reports of enantioselective multicomponent reactions (MCRs) for the synthesis of stereochemically complex polycyclic compounds.[69] The most prominent of the isocyanide-based MCRs[70] are the Passerini reaction of isocyanides, oxo components and carboxylic acids, and the Ugi reaction involving isocyanides, oxo components, primary amines, and carboxylic acids, respectively. The first example of an enantioselective Passerini MCR using a chiral Lewis acid catalyst was reported by Dömling et al. in 2003.[71] Better enantioselectivities were obtained in the case of Passerini-type reactions by using a chiral biphosphoramide-$SiCl_4$ system as catalyst (Scheme 46).[72]



Scheme 46. Lewis-base-catalysed enantioselective Passerini-type reaction.

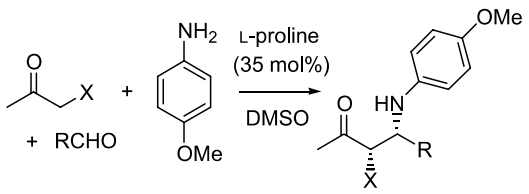
A very efficient catalytic asymmetric version of the Passerini reaction was reported by Schreiber et al. in 2004 using a tridentate bis(oxazolinyl)pyridine (pybox)-Cu(II) Lewis acid with substrates capable of bidentate coordination (Scheme 47).[73]



Scheme 47. (Pybox)-Cu(II)-catalysed Passerini reaction.

The Mannich reaction is enormously useful for the construction of nitrogenous molecules. In this transformation, three-components, a ketone, an aldehyde, and an amine, react to form a β-aminoketone.[74] The first direct catalytic asymmetric Mannich reaction reported in 1999 by Shibasaki et al. was based on the use of a heterobimetallic complex, for example, AlLibis(binaphthoxide) and $La(OTf)_3 \cdot nH_2O$.[75] Although the yields (≤16%) and the ees (≤64%) were modest, these authors have succeeded in extending the reaction to aminomethyl ethers. Jorgensen et al. have developed direct asymmetric Mannich reactions involving activated ketones as donors, which were catalysed by chiral copper(II) bisoxazoline (box) complexes.[76] Kobayashi et al. have employed zirconium alkoxides in the presence of 6,6-dibromobinaphthol to catalyse the Mannich reaction of a protected hydroxyaldehyde, a silyl enol ether derived from ethyl thioacetate, and an aniline derivative, providing the corresponding chiral β-aminothioester.[77] Highly enantioselective three-component

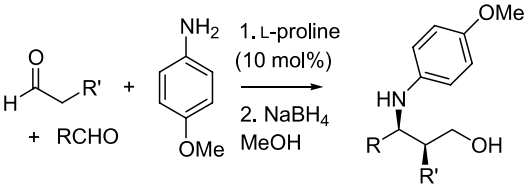
Mannich reactions were reported for the first time by List et al., involving proline as catalyst (Scheme 48).[78]



X = H, R = *p*-$NO_2C_6H_4$: 50% ee = 94%
X = H, R = 2-naphthyl: 35% ee = 96%
X = H, R = *i*-Bu: 90% ee = 93%
X = H, R = CH_2OBn: 82% ee = 75%
X = OH, R = *i*-Pr: 57% ee = 65%
X = OH, R = *p*-$NO_2C_6H_4$: 92% ee = 99%
X = OH, R = *p*-$NO_2C_6H_4$: 92% ee = 99%
X = OMe, R = *p*-BrC_6H_4: 90% ee = 98%

Scheme 48. Proline-catalysed direct Mannich reaction.

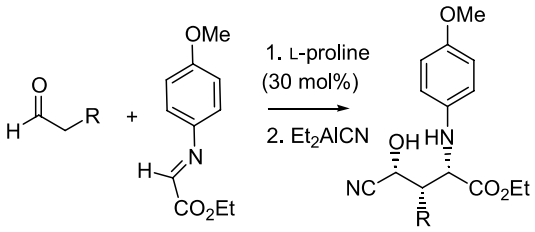
In 2001, Barbas et al. reported equivalent results for the same organocatalytic reactions performed in the presence of the penicillamine derivative, L-5,5-dimethylthiazolidine-4-carboxylic acid, instead of L-proline.[79] Similarly, Cordova et al. disclosed direct organocatalytic Mannich reactions between aqueous formaldehyde and ketones that furnished under the same conditions the corresponding optically active α-aminomethylated ketones with yields of up to 94% and >99% ee.[80] These authors, together with Hayashi's group, developed at the same time the first direct asymmetric Mannich reactions of aldehydes.[81] Such a system would comprise a Mannich reaction in which one aldehyde was employed as the Mannich donor and the other was used as a component of the Mannich acceptor to afford a synthetically versatile intermediate, a β-aminoaldehyde. Since this latter compound decomposed during purification by chromatography on silica gel, it was isolated after reduction with $NaBH_4$ to the corresponding β-aminoalcohol (Scheme 49).



R = Ph, R' = Me: 90% ee = 98%
R = Ph, R' = Et: 85% ee = 97%
R = *p*-BrC_6H_4, R' = Me: 85% ee = 95%
R = *p*-$NO_2C_6H_4$, R' = Me: 93% ee = 99%
R = *p*-ClC_6H_4, R' = Me: 91% ee = 98%
R = *p*-MeC_6H_4, R' = Me: 95% ee = 86%

Scheme 49. Direct asymmetric Mannich reaction with aldehydes.

On the other hand, one pot asymmetric Mannich hydrocyanation reactions were described by Barbas et al.[82] Indeed, L-proline-catalysed reaction of aldehydes with protected α-imino ethyl glyoxylate followed by the addition of $AlEt_2CN$ provided highly enantiomerically pure β-cyano-hydroxymethyl α-amino acid derivatives (Scheme 50).

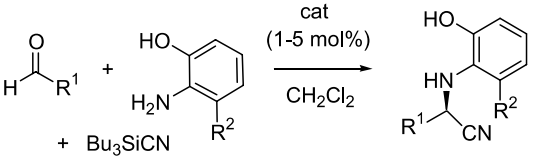


R = *n*-Bu: 60% ee = 93%
R = *n*-Pent: 68% ee = 98%
R = *n*-Hex: 65% ee = 98%
R = Bn: 62% ee = 99%

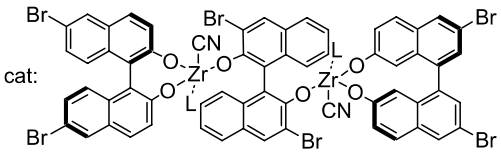
Scheme 50. One pot asymmetric domino Mannich hydrocyanation reaction.

In addition, these authors have developed one pot Mannich indium-promoted allylation reactions by treating the intermediate Mannich product with allyl bromide in the presence of indium.[83] The corresponding optically active γ-allyl-substituted α-amino acid derivatives were obtained in ≤99% ee.

The Strecker amino acids synthesis consists of the treatment of aldehydes with ammonia and hydrogen cyanide (or their equivalents), and subsequent hydrolysis of the intermediate α-amino nitriles, providing the α-amino acids. In 2000, Kobayashi et al. reported a highly efficient catalytic asymmetric Strecker reaction of aldimines with tributyltin cyanide, proceeding smoothly in the presence of a chiral zirconium catalyst (Scheme 51).[84]



R^1 = Ph, R^2 = H: 80% ee = 86%
R^1 = $Ph(CH_2)_2$, R^2 = Me: 85% ee = 94%
R^1 = C_8H_{17}, R^2 = Me: 93% ee = 91%
R^1 = *i*-Bu, R^2 = Me: 99% ee = 94%
R^1 = *c*-C_6H_{11}, R^2 = Me: 95% ee = 94%
R^1 = *t*-Bu, R^2 = Me: 100% ee = 88%



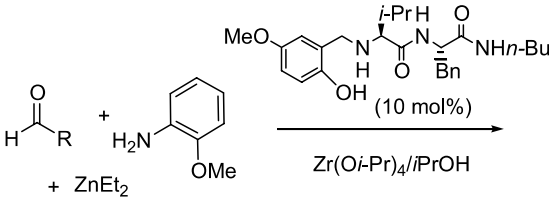
L = *N*-methylimidazole

Scheme 51. Chiral zirconium-catalysed Strecker reaction.

The cyanation of pyridines, the Reissert–Henze reaction, may be considered as a variant of the Strecker reaction. An asymmetric multicomponent version of this reaction has been performed with different functionalised quinoline derivatives and a chiral binaphthol in the presence of diethylaluminium chloride, TMSCN and a carbonyl chloride.[85] The same methodology was applied to the cyanation of different 1-substituted isoquinolines, yielding the corresponding α,α-disubstituted aminonitriles.[86]

The synthetic utility of this methodology was demonstrated by its application to the formal synthesis of the dopamine D_4 receptor-selective antagonist, CP-293019.[87]

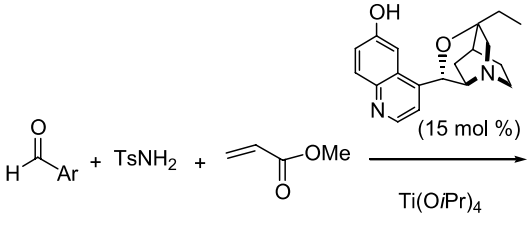
Zirconium-catalysed asymmetric multicomponent reactions were developed in 2001 by Hoveyda et al., involving the addition of alkylzincs to aliphatic imines in a single vessel and avoiding the isolation of the unstable imine (Scheme 52).[88]



R = Bu: 69% ee = 97%
R = Hex: 62% ee = 97%
R = $Ph(CH_2)_2$: 98% ee = 94%
R = $Br(CH_2)_5$: 57% ee = 95%
R = $(CH_2)_3OH$: 64% ee = 97%
R = *c*-Pr: 83% ee = 98%

Scheme 52. Asymmetric three-component catalytic synthesis of aliphatic amines.

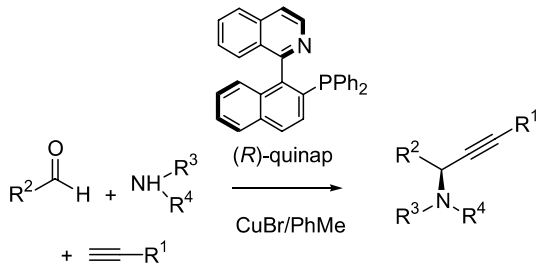
Various chiral allylamines have been obtained by the reaction of 1-phenylpropyne, triethylborane, and *N*-methyl aryl imines catalysed by a nickel complex and a chiral phosphane.[89] The enantioselectivity of this reaction could be improved by the use of a chiral ferrocenyl monophosphane instead of a chiral phosphane.[90] An in situ formation of imine was also involved in an asymmetric one pot version of a three-component aza-Baylis–Hillman reaction reported by Adolfsson et al.[91] Chiral quinuclidine derivatives were employed to catalyse the reaction between arylaldehydes, tosylamide and alkyl acrylates or acrylonitrile (Scheme 53).



Ar = Ph: 78% ee = 68%
Ar = *m*-$NO_2C_6H_4$: 94% ee = 63%
Ar = *p*-$NO_2C_6H_4$: 95% ee = 61%
Ar = *m*-ClC_6H_4: 95% ee = 67%
Ar = furyl: 95% ee = 74%

Scheme 53. Asymmetric three-component aza-Baylis–Hillman reaction.

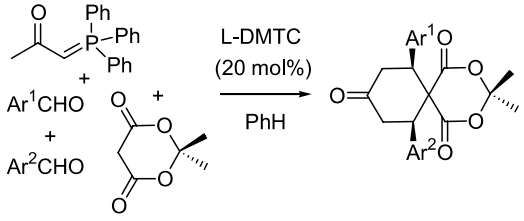
In order to prepare chiral propargylamines, Knochel et al. have examined a new three-component reaction between an alkyne, an aldehyde, and a secondary amine in the presence of CuBr and (*R*)-quinap (Scheme 54).[92] Carreira et al. have proposed an alternative ligand, a new chiral biaryl ligand derived from phthalazine, for this reaction, which gave similar results.[93]



R^1 = Ph, R^2 = *i*-Bu, R^3 = Bn: 98% ee = 86%
R^1 = *p*-BrC_6H_4, R^2 = *i*-Pr, R^3 = Bn: 99% ee = 83%
R^1 = TMS, R^2 = *i*-Pr, R^3 = Bn: 87% ee = 92%
R^1 = TMS, R^2 = *c*-Hex, R^3 = Bn: 99% ee = 92%
R^1 = TMS, R^2 = 1-Et-Pr, R^3 = Bn: 72% ee = 96%

Scheme 54. Enantioselective three-component synthesis of propargylamines.

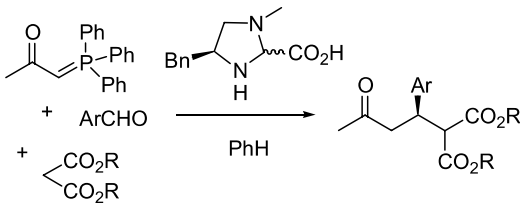
In 2004, Barbas et al. reported an organocatalytic asymmetric four-component Wittig Knoevenagel Diels–Alder reaction sequence, in order to generate an enantioselective synthesis of spirolactones in one pot.[94] Thus, the L-DMTC (L-5,5-dimethyl thiazolidinium-4-carboxylate)-catalysed reaction of *trans*-enone, aldehydes, and Meldrum's acid led to the formation of optically active substituted spiro[5.5]undecanes (Scheme 55).



Ar^1 = Ph, Ar^2 = *p*-$NO_2C_6H_4$: 83% ee = 69%
Ar^1 = *p*-$NO_2C_6H_4$, Ar^2 = Ph: 80% ee = 42%
Ar^1 = Ph, Ar^2 = *p*-CNC_6H_4: 85% ee = 70%

Scheme 55. Asymmetric four-component Wittig Knoevenagel Diels–Alder reaction.

Additionally, these authors studied the asymmetric three-component Michael reaction of phosphorane, benzaldehyde, and malonate under chiral imidazolidine catalysis (Scheme 56).[94]



Ar = Ph, R = Et: 65% ee = 90%
Ar = *o*-$NO_2C_6H_4$, R = Bn: 84% ee = 91%

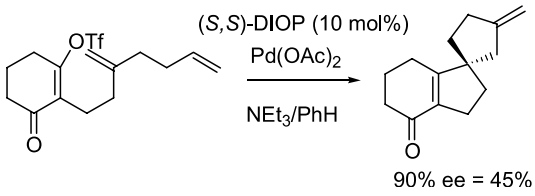
Scheme 56. Asymmetric three-component Michael reaction.

In 2004, Hopkins et al. reported a new multicomponent reaction involving the coupling of arylboronic acids with

allenes and aldehydes, giving rise to various homoallylic alcohols.[95] This reaction was catalysed by a chiral π-allylpalladium complex, but gave only a low enantioselectivity. Finally, D,L-proline was found to catalyse efficiently the one pot trimolecular condensation of indoles, a sugar hydroxyaldehyde, and Meldrum's acid, followed by intramolecular cyclisation with the evolution of carbon dioxide and elimination of acetone, to afford perhydrofuro[3,2-*b*]pyran-5-ones in high diastereoselectivity.[96]

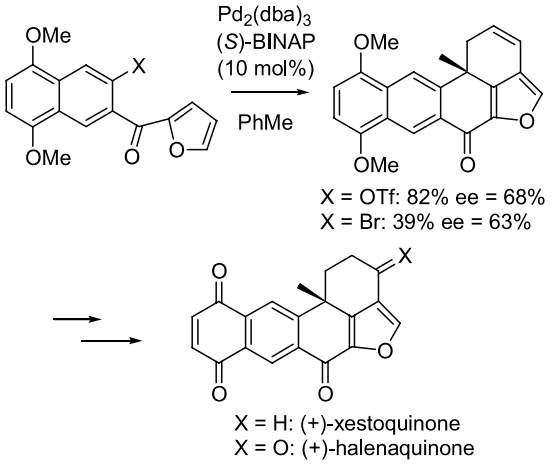
2.7. Transition-metal-catalysed sequences

2.7.1. Domino reactions including a Heck reaction. A powerful extension of palladium-catalysed transformations, also of economic interest, is the development and use of multiple Pd-catalysed transformations, which may be performed in a domino fashion.[97,98] The possibility of extending the scope of intramolecular enantioselective Heck reactions to inclusion in Pd-mediated domino polyene cyclisation was demonstrated in 1989 by Overman in his first report on the generation of a quaternary chiral centre from a triene, to give the corresponding spirocycle (Scheme 57).[99]



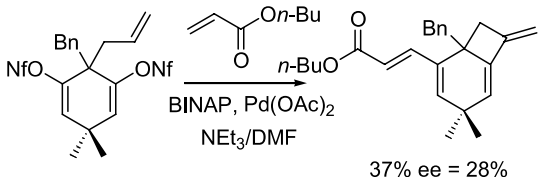
Scheme 57. Asymmetric domino intramolecular Heck reaction.

Keay et al. have recently reported the asymmetric synthesis of (+)-xestoquinone from a pentacyclic intermediate, which was obtained via a one pot cyclisation of a triflate under enantioselective Heck reaction conditions, thus demonstrating the feasibility of a domino asymmetric Heck reaction (Scheme 58).[100] A similar methodology was applied to the synthesis of (+)-halenaquinone.[101,102,103,104] A remote substituent effect on the enantioselectivity was demonstrated by Keay et al., since a surprisingly higher ee (≤96%) was obtained when the aryl group became phenyl instead of naphthyl.



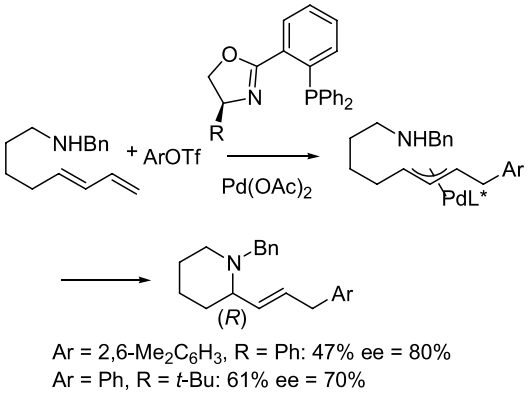
Scheme 58. Synthesis of (+)-xestoquinone via domino intramolecular Heck reaction.

Bräse has reported the palladium-catalysed enantioselective desymmetrisation of a bisnonaflate on reaction with butyl acrylate in the presence of BINAP to give the corresponding bicyclic tetraene with a quaternary carbon centre (Scheme 59).[105]



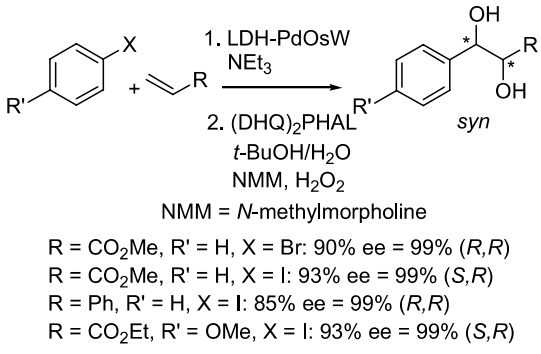
Scheme 59. Asymmetric domino intramolecular Heck reaction of bisnonaflate.

A novel enantioselective two-component domino Heck-allylic amination reaction of an α,ω-amino-1,3-diene to give the corresponding chiral piperidine derivative has recently been described by Helmchen et al. in the presence of chiral phosphino–oxazoline ligands (Scheme 60).[106]



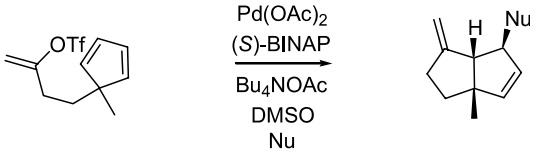
Scheme 60. Asymmetric domino Heck-allylic amination reaction of α,ω-amino-1,3-diene.

In 2003, Choudary et al. reported a one pot biomimic synthesis of chiral diols via Heck coupling N-oxidation asymmetric dihydroxylation mediated by a recyclable trifunctional heterogeneous catalyst (layered double hydroxides (LDH)-PdOsW) consisting of active palladium, tungsten, and osmium species embedded in a single matrix (Scheme 61).[107] This protocol involving a Sharpless chiral ligand, for example, [(DHQD)$_2$PHAL] [1,4-bis(9-*O*-dihydroquinidinyl)phthalazine], was applied to the synthesis of diltiazem and the taxol side chain.



Scheme 61. Heck coupling N-oxidation asymmetric dihydroxylation reaction.

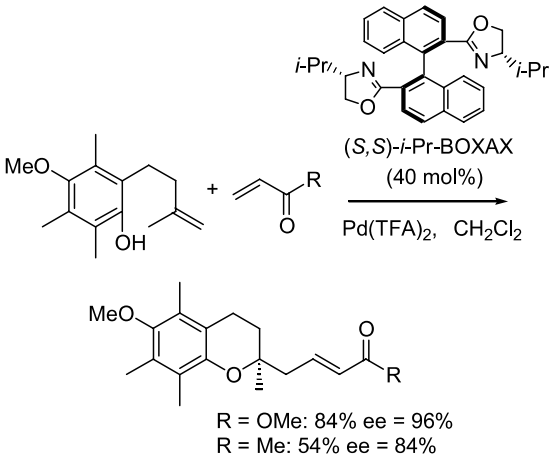
An asymmetric Heck reaction carbanion capture process was achieved for the first time by Shibasaki et al., making possible the catalytic asymmetric synthesis of various functionalised bicyclo[3.3.0]octane derivatives (Scheme 62).[108]



Nu = $NaCH_2(CO_2Me)_2$: 92% ee = 83%
Nu = $Na(CO_2Et)_2CH(CH_2)_2OTBDPS$: 77% ee = 87%
Nu = $NaCH_2(SO_2Ph)_2$: 83% ee = 94%
Nu = $NaCH_2(COMe)(CO_2Me)$: 74% ee = 83%
Nu = $NaCH_2(CO_2Me)(COCH_2Cl)$: 67% ee = 80%
Nu = $NaCH_2(COPh)_2$: 90% ee = 80%
Nu = NaOAc: 89% ee = 80%
Nu = NaNHBn: 76% ee = 81%

Scheme 62. Asymmetric Heck reaction carbanion capture process.

Very recently, Tietze et al. developed a palladium-catalysed enantioselective domino reaction for the efficient synthesis of vitamin E.[109] This sequence comprised an enantioselective Wacker oxidation and a subsequent Heck reaction catalysed by $Pd(TFA)_2$ in the presence of the chiral ligand, (*S*,*S*)-*i*-Pr-BOXAX, depicted in Scheme 63.



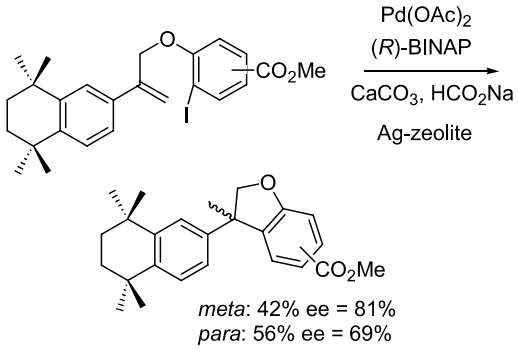
R = OMe: 84% ee = 96%
R = Me: 54% ee = 84%

Scheme 63. Asymmetric domino Wacker oxidation Heck reaction.

In 1998, Diaz et al. developed an enantioselective domino reaction consisting of an intramolecular Heck cyclisation hydride-capture process in order to prepare novel conformationally restricted retinoids in the presence of Pd-(*R*)-BINAP (Scheme 64).[110]

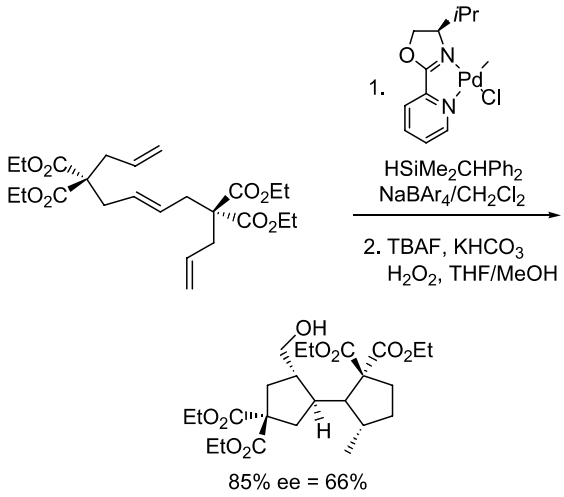
2.7.2. Other transition-metal-catalysed reactions. In 2001, Pei et al. reported an asymmetric domino cyclisation hydrosilylation reaction of a triene, forming the corresponding tethered bicyclopentane, using a chiral pyridine–oxazoline–Pd complex (Scheme 65).[111]

In 2001, Arai et al. reported a highly efficient enantioselective Pd-catalysed asymmetric domino cyclisation employing a dialkyl carbinol substrate, leading to the corresponding bicyclic compound (Scheme 66).[112] These authors suggested a domino oxy- and carbopalladation process as a plausible mechanism for this unprecedented reaction.



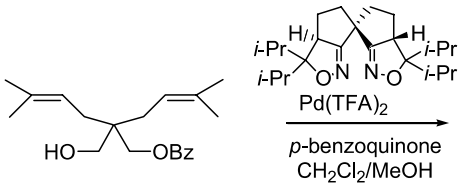
meta: 42% ee = 81%
para: 56% ee = 69%

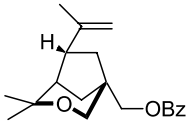
Scheme 64. Asymmetric domino Heck reductive cyclisation reaction.



85% ee = 66%

Scheme 65. Asymmetric domino cyclisation hydrosilylation reaction.



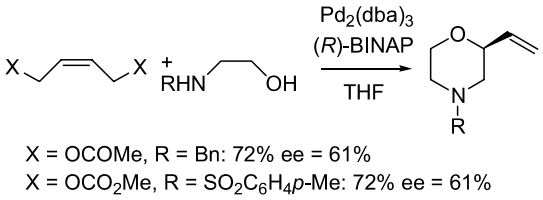


89% ee = 82%

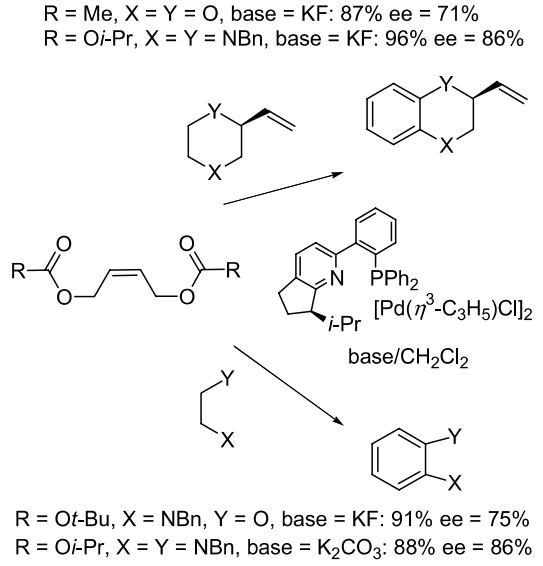
Scheme 66. Asymmetric domino Wacker-type cyclisation reaction.

Palladium-catalysed asymmetric tandem allylic substitutions using chiral ligands [(*R*)-BINAP] were developed in 1993 by Hayashi et al., in order to prepare optically active morpholines (Scheme 67).[113]

Better results were recently obtained by Ito et al. using a chiral 2-(phosphinophenyl)pyridine ligand for the palladium-catalysed domino allylic substitution[114] of 1,4-diacyloxy- or 1,4-bis(alkoxycarbonyloxy)-2-butenes using a 1,2-heterofunctionalised compound as nucleophile (Scheme 68).[115]

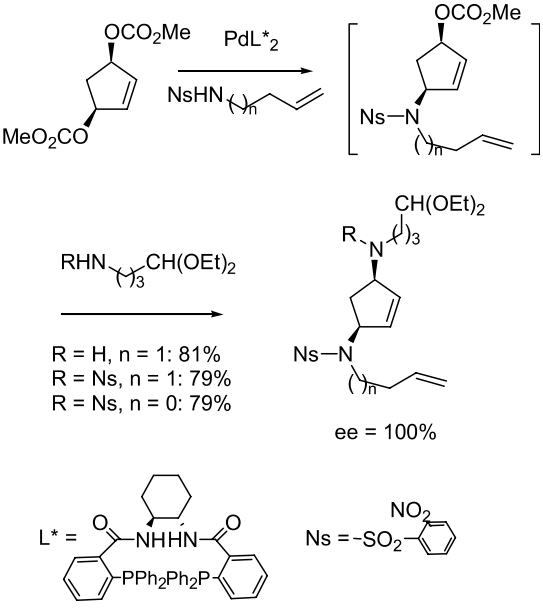


Scheme 67. Asymmetric Pd-catalysed domino allylic substitution reaction.



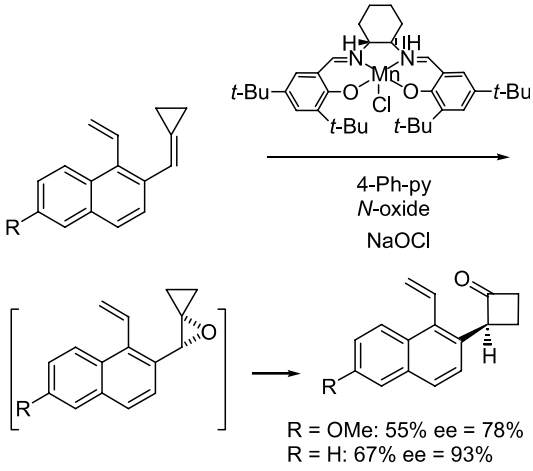
Scheme 68. Asymmetric Pd-catalysed domino allylic substitution reactions.

An asymmetric palladium-catalysed domino three-component allylic alkylation reaction of a chiral dicarbonate has given access to chiral tetraponerines with an all-cis stereochemistry and to all of the desired ring sizes.[116] The catalyst (PdL^*_2) was prepared from a chiral diphosphine (L*) and a tris(dibenzylideneacetone)dipalladium(0) chloroform complex in THF (Scheme 69).



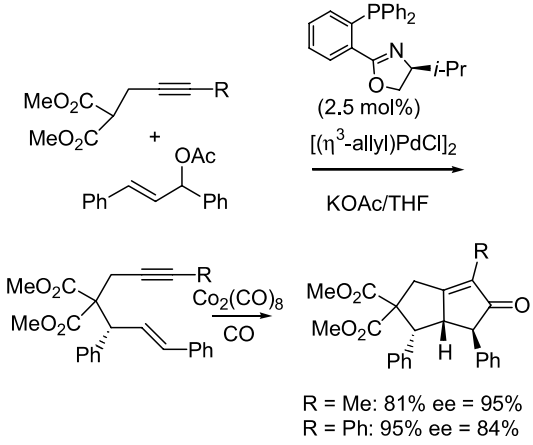
Scheme 69. Asymmetric Pd-catalysed domino allylic alkylation reaction.

On the other hand, a cascade asymmetric epoxidation ring-expansion reaction of cyclopropylidene was examined by Ihara et al (Scheme 70).[117] This procedure was catalysed by a chiral (salen)Mn^{III} complex and applied to the total synthesis of (+)-equilenin.



Scheme 70. Asymmetric domino epoxidation ring-expansion reaction.

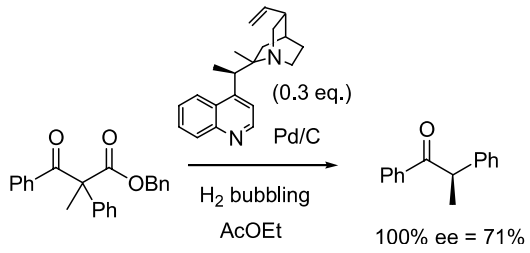
A tandem action of a homogeneous chiral Pd(II) catalyst and a heterogeneous Co/C catalyst led to a two-step, one pot highly enantioselective Pauson–Khand-type reaction, depicted in Scheme 71.[118]



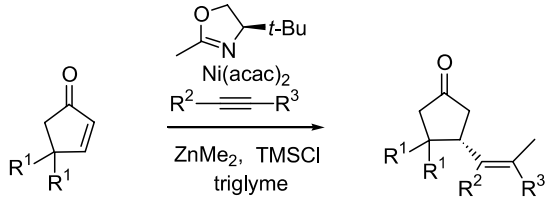
Scheme 71. Asymmetric domino Pd-catalysed allylic alkylation Pauson–Khand-type reaction.

An unusual one pot catalytic deprotection decarboxylation asymmetric tautomerisation of β-ketoesters was studied by Muzart et al., providing an easy access to various chiral ketones.[119] This palladium-induced procedure was performed in the presence of chiral β-aminoalcohols and allowed the synthesis of either cyclic ketones such as indanones, tetralones, and chromanones, or linear ketones (Scheme 72).

Simple chiral monodentate oxazolines have been employed as chiral ligands in a nickel-catalysed asymmetric multiple-component reaction involving cyclic enones, alkynes, $ZnMe_2$, and Me_3SiCl (Scheme 73).[120]

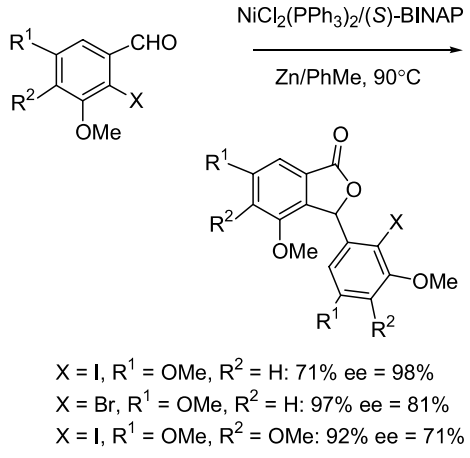


Scheme 72. One pot deprotection decarboxylation asymmetric tautomerisation of β-ketoesters.



Scheme 73. Nickel-catalysed asymmetric multiple-component coupling.

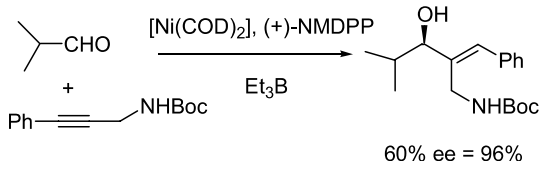
Nickel was also used for the catalysis of an asymmetric domino addition cyclisation reaction performed in the presence of chiral bidentate ligands such as BINAP, providing a useful method to synthesise optically active halogen-substituted phthalides (Scheme 74).[121]



Scheme 74. Nickel-catalysed asymmetric domino addition cyclisation reaction.

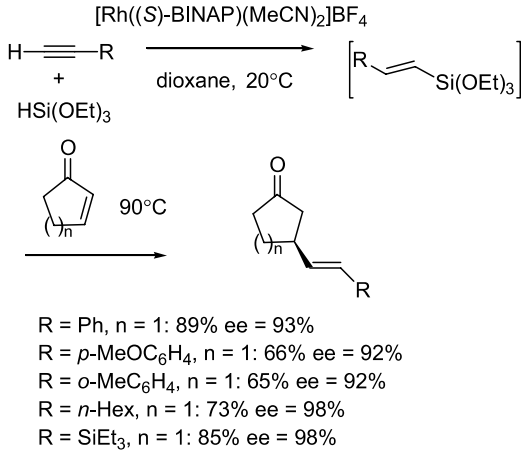
More recently, Ikeda et al. reported the enantioselective reductive coupling of aldehydes and alkynes using Et_3B.[122] When (+)-(neomenthyl)diphenylphosphane (NMDPP) was treated as a chiral ligand in this catalytic reaction, a trisubstituted allylic alcohol was obtained in 96% ee with high regio- and stereoselectivities (Scheme 75).

Hayashi et al. have shown that chiral rhodium complexes catalysed the 1,4-addition of alkenylsilanes, in situ generated by the hydrosilylation of alkynes, via a one pot procedure in which a rhodium/(*S*)-BINAP complex induced the two successive reactions (Scheme 76).[123] The same



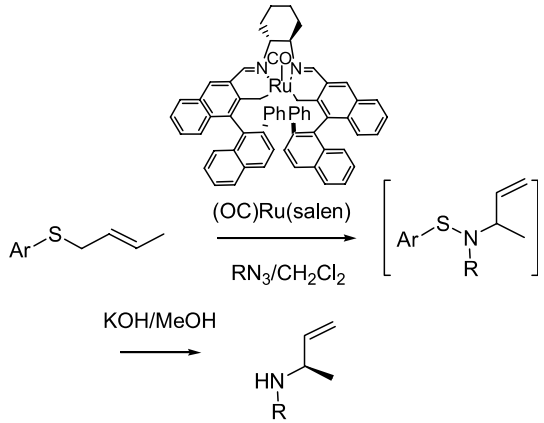
Scheme 75. Nickel-catalysed enantioselective reductive coupling of aldehyde and alkyne.

methodology was applied to the 1,4-addition of alkenylboranes in situ generated by the hydroboration of alkynes.[124]



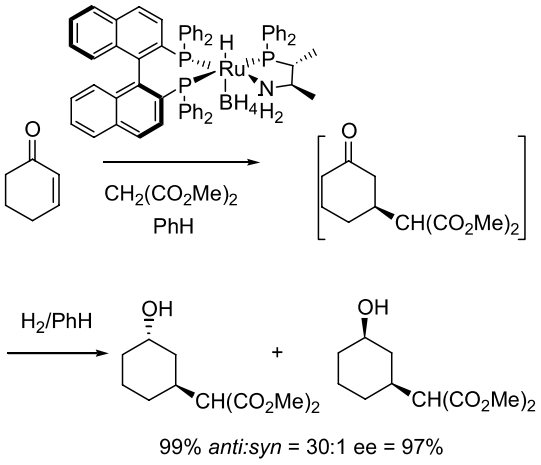
Scheme 76. Asymmetric domino rhodium-catalysed hydrosilylation 1,4-addition reaction of alkynes.

Asymmetric C–N bond formation could be achieved in a highly enantioselective manner by using (OC)Ru(salen)-catalysed domino sulphimidation [2,3]sigmatropic rearrangement reactions of allyl aryl sulphides with *p*-toluenesulphonyl azide, followed by hydrolysis, leading to *N*-allyl arylsulphonamides (Scheme 77).[125]



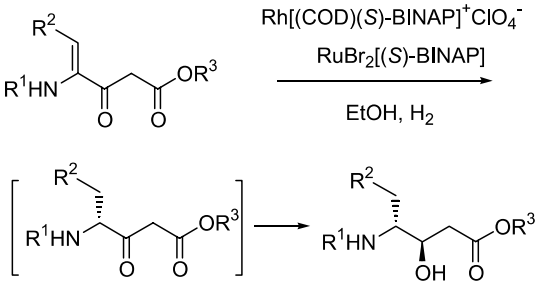
Scheme 77. Asymmetric domino sulphimidation [2,3]sigmatropic rearrangement reaction of allyl aryl sulphides.

Very recently, Morris et al. demonstrated that ruthenium hydride borohydride complexes containing β-aminophosphine ligands could promote, in the same flask, an enantioselective Michael addition and a hydrogenation reaction (Scheme 78).[126]



Scheme 78. Asymmetric domino Michael addition hydrogenation reaction.

A double asymmetric hydrogenation was performed in the presence of both rhodium(I) and ruthenium(II) chiral phosphine complexes.[127] Thus, the domino asymmetric hydrogenation reaction of γ-(acylamino)-γ,δ-unsaturated-β-ketoesters provided the two possible corresponding statin analogues in the presence of both Rh(I) and Ru(II) chiral catalysts (Scheme 79).

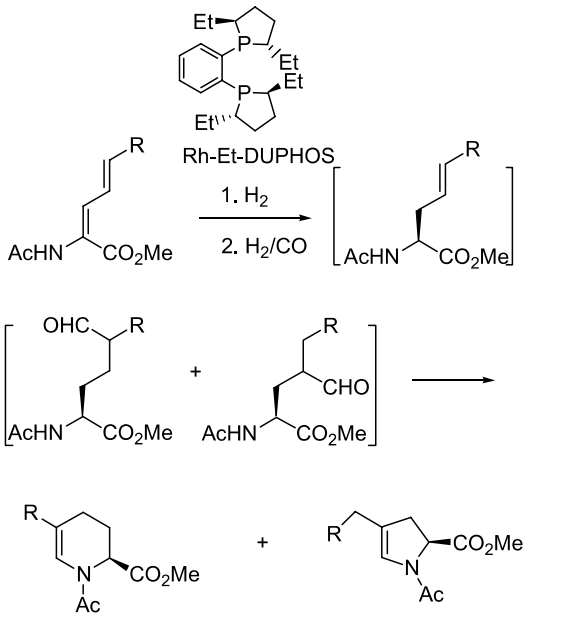


R1 = Ac, R2 = Ph, R3 = Et: 99% ee = 95%
R1 = Ac, R2 = Ph, R3 = Me: 99% ee = 95%
R1 = Boc, R2 = Ph, R3 = Et: 99% ee = 95%
R1 = Ac, R2 = *p*-ClC6H4, R3 = Et: 90% ee = 95%

Scheme 79. Rh(I)- and Ru(II)-catalysed asymmetric domino hydrogenation reaction.

Another asymmetric hydrogenation involving the synthesis of cyclic amino acids was incorporated in a domino hydrogenation hydroformylation reaction.[128] In this case, only one catalyst system promoted successively the reaction of prochiral dienamide esters with H_2, followed by H_2/CO, using Rh(I)-Et-DUPHOS (Scheme 80).

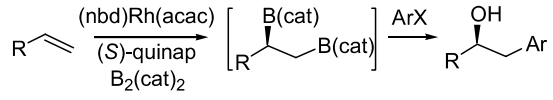
In 2004, Morken et al. developed a catalytic asymmetric carbohydroxylation of alkenes by a domino diboration Suzuki cross-coupling oxidation reaction.[129] Chiral



R = H: 91% piperidine:pyrrolidine dr = 54:46 % ee = 95:99
R = Me: 81% piperidine:pyrrolidine dr = 56:44 % ee = 95:99

Scheme 80. Asymmetric domino hydrogenation hydroformylation reaction.

nonsymmetric 1,2-diboron adducts, generated by catalytic enantioselective diboration, reacted in situ with aryl halides in which the less hindered C–B bond participated in cross-coupling. The remaining C–B bond was then oxidised (Scheme 81).



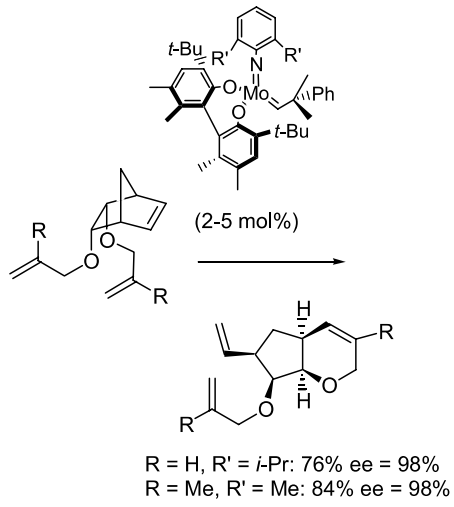
nbd = norbornadiene

R = *t*-Bu, ArX = PhOTf: 76% ee = 94%
R = *t*-Bu, ArX = *p*-BrC6H4NO2: 62% ee = 94%
R = *t*-Bu, ArX = *m*-BrC6H4OMe: 77% ee = 95%
R = BnOCH2(Me)2C, ArX = *m*-Br-py: 58% ee = 93%
R = *p*-TolCH2(Me)2C, ArX = *p*-BrC6H4CHO: 48% ee = 76%

Scheme 81. Asymmetric domino diboration Suzuki coupling oxidation reaction.

Domino metatheses are combinations of ring-opening metatheses (ROMs), ring-closing metatheses (RCMs), and cross metatheses (CMs). Catalytic asymmetric versions of these reactions have been recently developed such as those involving strained disubstituted cyclic alkenes promoted by chiral Mo complexes (Scheme 82).[130]

The application of domino metathesis reactions to *N*-alkylated derivatives of 2-azanorbornenones allowed the enantioselective synthesis of pyrrolizidine, quinolizidine, pyrrolidinoazepine, and pyrrolidinoazocine derivatives in a straightforward process.[131] In addition, Fürstner et al. reported a catalytic approach to (*R*)-(+)-muscopyridine, based on an iron-catalysed alkyl–aryl cross-coupling method.[132]



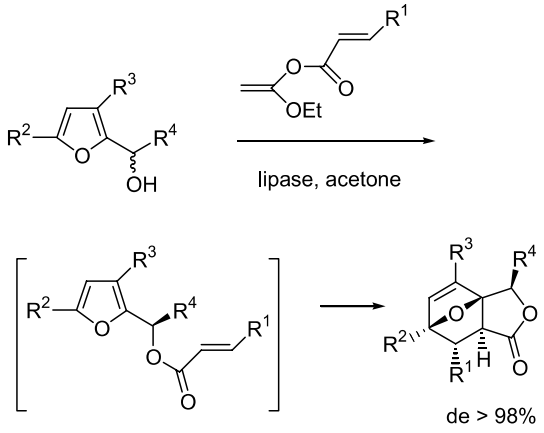
Scheme 82. Asymmetric domino Mo-catalysed asymmetric ring-opening metathesis ring-closing metathesis reaction.

3. Asymmetric biocatalysed domino reactions

Since the prototypes of domino processes are the sequential transformations catalysed in nature by biocatalysts, the incorporation of enzymatic transformations in a series of sequential nonenzymatic reactions could open up new and promising opportunities for organic synthesis. The first successful combination of enzymatic with nonenzymatic transformations in a nonasymmetric domino reaction sequence was reported by Waldmann et al. in 1996.[133] Asymmetric biocatalysed domino reactions can be divided into two categories of reactions, that is, the asymmetric enzyme-triggered domino reactions,[134] and the asymmetric multienzymatic one pot reactions.

3.1. Asymmetric enzyme-triggered domino reactions

In contrast with the traditional asymmetric chemo-catalysed domino reactions, only a few examples of asymmetric domino reactions have been reported in which the initiation of the reaction cascade consisted of a biotransformation. The synthetic potential to conduct the domino processes in an asymmetric fashion may conveniently be achieved by making use of the unparalleled chemo-, stereo-, and enantioselectivity of enzymes.[135] Thus, in the case of the sequence of events being triggered by a biocatalyst, the cascade may proceed in a highly asymmetric fashion to furnish products in a nonracemic form. In the first step, the enzyme modifies an enzyme-labile trigger group within the starting material, for example, via oxidation, hydrolysis of an ester or epoxide, transesterification of an alcohol, etc., giving access to a reactive intermediate. This latter intermediate may bear a liberated negative charge, which can deliver electrons to a π-system, or may act as a nucleophile. Consequently, the intermediate immediately undergoes a subsequent domino reaction, which may consist of a fragmentation, a rearrangement, or a cyclisation such as a Diels–Alder reaction. An elegant asymmetric domino Diels–Alder reaction following an enzymatic kinetic resolution using a 1-ethoxyvinyl ester was reported by Kita et al. in 1998.[136] Kinetic resolution of racemic furfuryl alcohol derivatives was accomplished via acyl transfer catalysed by a *Pseudomonas* sp. lipase preparation, employing an enol ester as acyl donor in the first step. In this way, the diene and dienophile were linked on to each other and, at the same time, asymmetry was introduced into the system by means of kinetic resolution. The second step constituted of intramolecular Diels–Alder reaction, providing the corresponding optically active 7-oxabicyclo[2.2.1]heptene derivative (Scheme 83).

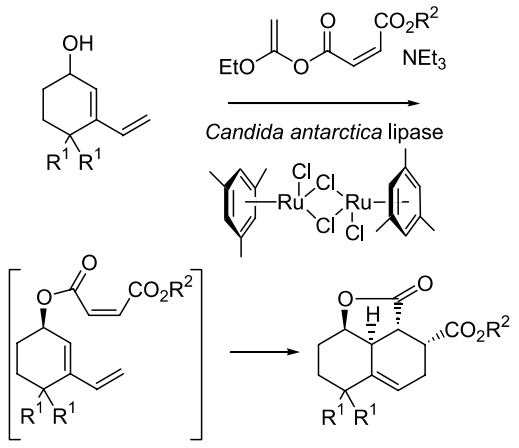


$R^1 = CO_2Me$, $R^2 = H$, $R^3 = R^4 = Me$: 43% ee = 84%
$R^1 = CO_2Me$, $R^2 = H$, $R^3 = Me$, $R^4 = Et$: 45% ee = 99%
$R^1 = CO_2Me$, $R^2 = Me$, $R^3 = Br$, $R^4 = Et$: 35% ee = 95%
$R^1 = CO_2Me$, $R^2 = CH_2OMe$, $R^3 = Br$, $R^4 = Et$: 43% ee = 94%
$R^1 = CO_2Et$, $R^2 = H$, $R^3 = Me$, $R^4 = Et$: 46% ee = 99%
$R^1 = CO_2Et$, $R^2 = H$, $R^3 = Br$, $R^4 = Et$: 43% ee = 96%
$R^1 = CO_2Et$, $R^2 = Me$, $R^3 = Br$, $R^4 = Et$: 30% ee = 95%
$R^1 = CO_2Et$, $R^2 = CH_2OMe$, $R^3 = Br$, $R^4 = Et$: 45% ee = 96%
$R^1 = COMe$, $R^2 = H$, $R^3 = Br$, $R^4 = Et$: 40% ee = 99%
$R^1 = COMe$, $R^2 = Me$, $R^3 = Br$, $R^4 = Et$: 34% ee = 99%
$R^1 = COMe$, $R^2 = CH_2OMe$, $R^3 = Br$, $R^4 = Et$: 36% ee = 93%

Scheme 83. Asymmetric enzyme-triggered Diels–Alder reaction.

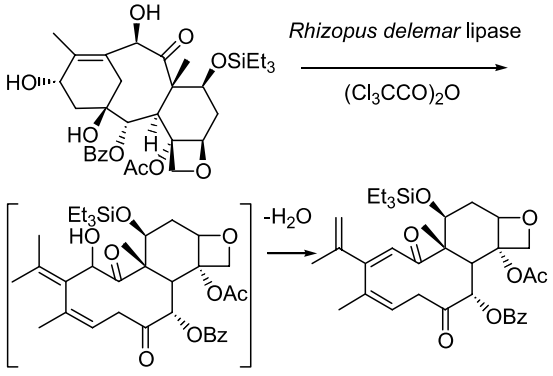
More recently, these authors have reported a combination of the domino reaction concept and the dynamic kinetic resolution (DKR) protocol[137] comprising the first lipase-catalysed domino process that combined the DKR of racemic alcohols by using 1-ethoxyvinyl esters and the Diels–Alder reaction of the intermediates. Their finding that ruthenium catalysts produced a rapid racemisation of the slow-reacting (*S*)-enantiomers was the key to the success of this process, which provided useful chiral intermediates for natural products such as compactin and forskolin (Scheme 84).

Other enzyme-triggered rearrangements such as an enzymatic dehydration-initiated rearrangement have been observed during the development of a new strategy for the synthesis of paclitaxel.[138] The 7-triethylsilyl derivative of 10-deacetylbaccatine III served as the starting material for this cascade reaction. The 13-hydroxy group of this latter substrate was regioselectively acylated by *Rhizopus delemar* lipase in the presence of trichloroacetic anhydride as the acyl donor. It was assumed that, after the first dehydration rearrangement had formed the intermediate α-hydroxyketone, the latter underwent a second dehydration (Scheme 85).



R^1 = H, R^2 = Et: 86% ee = 95%
R^1 = H, R^2 = Me: 83% ee = 93%
R^1 = R^2 = Me: 81% ee = 91%
R^1,R^1 = $S(CH_2)_3S$, R^2 = Et: 69% ee = 93%

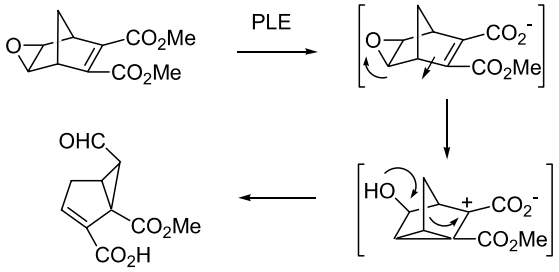
Scheme 84. Asymmetric enzyme-triggered Diels–Alder reaction combined with DKR.



Scheme 85. Enzymatic selective dehydration and skeletal rearrangement of paclitaxel precursors.

Domino reactions initiated by an enzymatically liberated (negative) charge have an enzyme-catalysed hydrolytic starting step in common, during which a carboxy ester moiety is cleaved. The latter leads to the liberation of an anion, which does not participate in the subsequent reaction, but donates electrons into the molecule, initiating a domino reaction involving fragmentation or rearrangement. As an example, an enzyme-triggered asymmetric rearrangement was reported by Ohno et al.[139] This unusual enzyme-triggered asymmetric rearrangement was observed when attempting to hydrolyse a symmetric tricyclic diester in an asymmetric fashion using porcine liver esterase (PLE), the expected chiral monoester not being obtained, but, rather, the product turned out to be a bicyclo[3.1.0]hexane framework (Scheme 86). Actually, a hemiester was, indeed, first formed by hydrolysis, but this immediately underwent a Meinwald rearrangement to furnish the final enantiomerically enriched product.

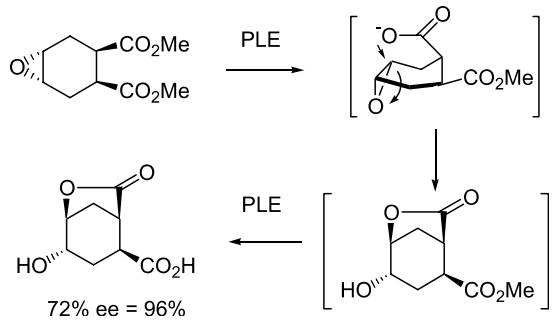
Other types of enzyme-triggered domino reactions are those initiated by an enzymatically liberated nucleophile. Instead



100% ee = 48%

Scheme 86. Asymmetric enzyme-triggered Meinwald rearrangement.

of undergoing a fragmentation or rearrangement reaction, the carboxylate or hydroxy group, formed during (enzymatic) ester hydrolysis or epoxide ring opening, can also act as a nucleophile by attacking an electrophile during the cascade reaction. The electrophile usually consisted of an epoxide or a related species such as a halide. Domino reactions of this type can start with the enzymatic hydrolysis of an ester or epoxide to liberate a nucleophile ($-CO_2^-$ or –OH), which opens an epoxide in an intramolecular S_N2 reaction in the second step. Thus, the final product formed is a lactone ($-CO_2^-$ acting as nucleophile) or a (hydroxy)-tetrahydrofuran (–OH acting as nucleophile). Such a cascade reaction was observed upon asymmetric hydrolysis of a *meso*-epoxy diester using PLE (Scheme 87).[140] It was found that the more accessible (equatorial) carboxy ester moiety was selectively hydrolysed, liberating an intermediate carboxylate anion, which, in turn, acted as a nucleophile for opening the epoxide moiety to furnish the corresponding hydroxy-γ-lactone. In order to undergo lactone formation, the intermediate epoxycarboxylate has to undergo a conformational change, which converted the second (remaining) axial ester moiety into the more accessible equatorial position. As a consequence, it could now be additionally hydrolysed by PLE and this led to the final chiral product.

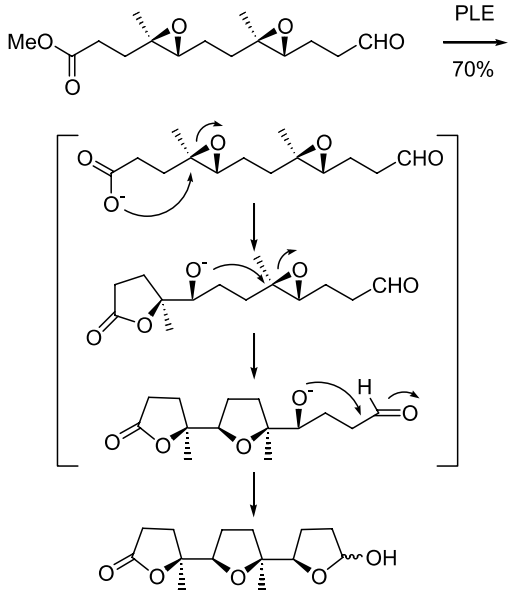


72% ee = 96%

Scheme 87. γ-Lactone formation initiated by enzymatically liberated nucleophile ($-CO_2^-$).

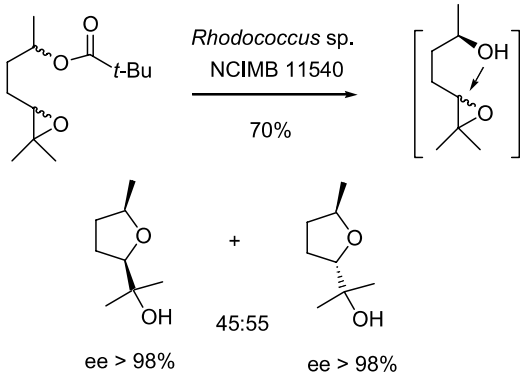
A related, but even more complex, domino reaction is depicted in Scheme 88. Again, the cascade was started by the enzymatic hydrolysis of an ester liberating a nucleophile ($-CO_2^-$), which opened an epoxide to furnish the corresponding lactone, together with a free alkoxy moiety in the δ-position. The latter alkoxide underwent another (intramolecular) nucleophilic attack on the second epoxide

to furnish a tetrahydrofuran derivative. At the end of this cascade, the resulting alkoxide was trapped by forming a hemiacetal with an aldehyde, bringing the cascade to a halt.[141]



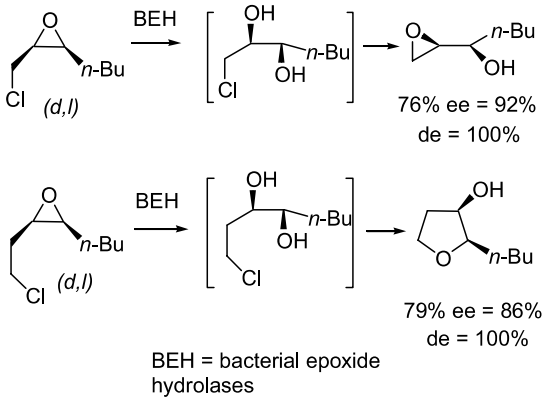
Scheme 88. Enzymatic liberation of nucleophile ($-CO_2^-$) followed by three-step S_N2 cascade involving two epoxy groups.

Instead of an enzymatically generated carboxylate anion, an alcohol group (derived from a biocatalysed ester or epoxide hydrolysis) may also serve as the nucleophile to open an epoxy moiety in a cascade reaction (Scheme 89), for example, treatment of a diastereomeric mixture of an epoxyester with a crude immobilised enzyme preparation (Novo SP 409), or whole lyophilised cells of *Rhodococcus erythropolis* NCIMB 11540, gave the corresponding intermediate alcohol via kinetic resolution of the secondary alcohol moiety. The latter spontaneously opened the epoxide in an S_N2 fashion to furnish the corresponding diastereomeric tetrahydrofuran derivatives, which could be separated by column chromatography.[142] Both compounds were bioactive constituents of bark beetle pheromones.



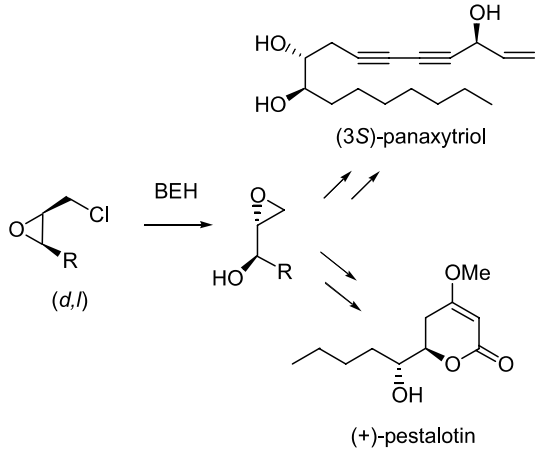
Scheme 89. Cyclisation initiated by enzymatically generated nucleophile (–OH) attacking an epoxide.

In all of the cases described above, the nucleophile acting during the cascade was liberated by hydrolysis of an ester. In the following example, the nucleophile was generated by enzymatic hydrolysis of an epoxide to form the corresponding diol. This involved the biohydrolysis of racemic 2,3-disubstituted *cis*-chloroalkyl-epoxides, which turned out to initiate a cascade reaction (Scheme 90). First, both enantiomers of the racemic epoxide were hydrolysed by bacterial epoxide hydrolases (BEH) (*Mycobacterium paraffinicum* NCIMB 10420) in an enantioconvergent fashion to furnish the expected corresponding diols, which, however, underwent spontaneous ring closure to yield the corresponding cyclic products. The cyclisation reaction showed some resemblance to a Payne-type rearrangement.[143]



Scheme 90. Enzyme-triggered cyclisation of haloalkyl-oxiranes catalysed by epoxide hydrolases.

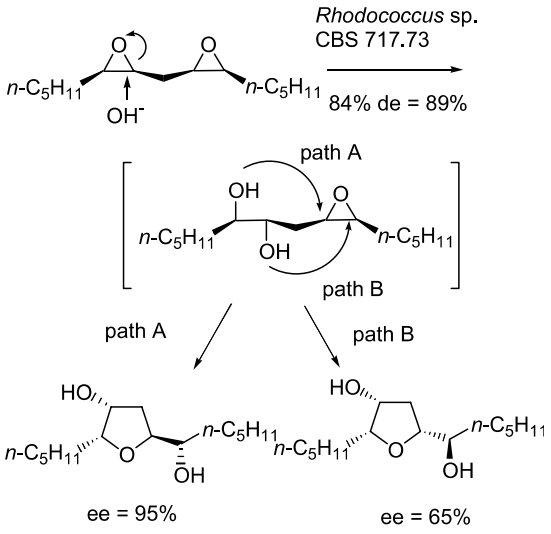
The synthetic potential of these building blocks was demonstrated by the asymmetric synthesis of four bioactive compounds, such as (3*S*)-panaxytriol (Scheme 91),[144] an antileukemic constituent of ginseng roots, (+)-pestalotin (Scheme 91),[145] a phytohormone, pityol,[146] a pheromone, and a natural bicyclic acetal.[146]



Scheme 91. Synthetic applications of enzyme-triggered cascade reactions.

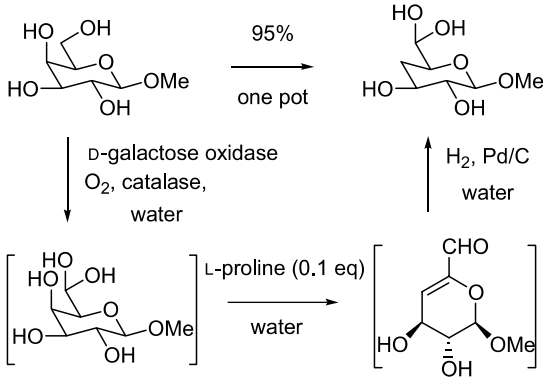
In order to test the limits of the stereocontrol, the enzyme-triggered cyclisation of bis-epoxides was investigated (Scheme 92).[147] In this study, four enzymatic trigger

pathways were leading to four possible stereoisomeric tetrahydrofuran products through two secondary pathways. Careful elucidation of the products obtained showed that the *meso-cis-cis*-oxirane was converted through an enzyme-triggered cascade via a single dominant pathway into a chiral dihydroxy-tetrahydrofuran derivative containing four stereogenic centres as the sole product. Compounds of this type constitute the central core of *Annonaceous* acetogenins, which exhibit a range of biological effects, such as antitumour, antimalarial, pesticidal, and immunosuppressive activities.



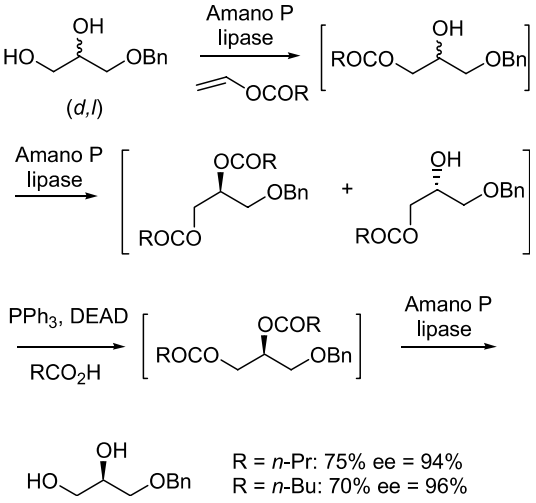
Scheme 92. Enzyme-triggered rearrangement of *meso*-bis-epoxides.

In addition, in certain cases, asymmetric hydrolysis of thioesters, liberating thiols, has been accomplished using esterases/lipases.[148] In 2002, Kieboom et al. developed consecutive catalytic oxidation (oxygen, D-galactose oxidase), dehydration (L-proline) and reduction (hydrogen, palladium) of methyl β-D-galactoside in water at neutral pH, yielding methyl 4-deoxy-6-aldehydo-β-D-glucoside without any intermediate recovery steps, demonstrating the potential power of a multicatalytic approach, using both bio- and chemo-catalysts, for carbohydrate conversions without the use of protective groups or stoichiometric amounts of reagents (Scheme 93).[149]



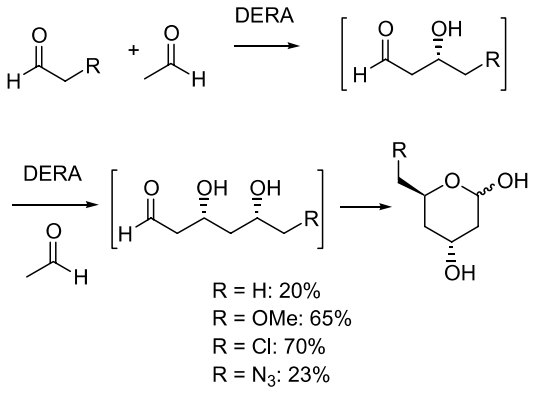
Scheme 93. One pot bio- and chemo-catalysed reactions of D-galactose derivative.

On the other hand, a new efficient chemoenzymatic enantioselective methology for the production of 3-*O*-benzyl-glycerol has been developed.[150] This one pot procedure was based on the sequential enzymatic acylation-Mitsunobu inversion-enzymatic hydrolysis (Amano P lipase) of racemic 1-*O*-benzylglycerol, which has been performed without isolation of the intermediates (Scheme 94).



Scheme 94. One pot chemoenzymatic enantioselective synthesis of 3-*O*-benzyl-glycerol.

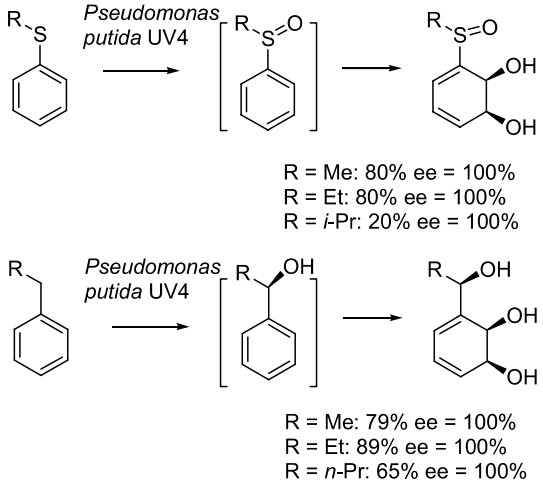
In 1994, Wong et al. reported an asymmetric domino aldol reaction involving three aldehyde substrates catalysed by 2-deoxyribose-5-phosphate aldolase (DERA).[151] The reaction started with a stereospecific addition of acetaldehyde to a substituted acetaldehyde to form a 3-hydroxy-4-substituted-butyraldehyde, which subsequently reacted with another acetaldehyde to form a 2,4-dideoxyhexose derivative, also in a stereospecific manner (Scheme 95). The enzymatic products constituted useful chiral synthons of HMG-CoA reductase inhibitors and 1,3-polyol systems (the enantiomeric purity was not detailed).



Scheme 95. Asymmetric domino aldol reaction catalysed by DERA.

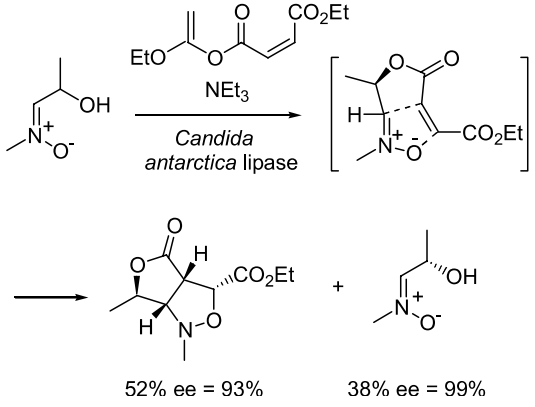
In 2002, Boyd et al. reported the domino dioxygenase-catalysed trioxygenation of alkyl phenyl sulphides, yielding the corresponding enantiopure *cis*-dihydrodiol sulphoxides via a domino monosulphoxidation *cis*-dihydroxylation reaction.[152] The same conditions employing whole cells of

Pseudomonas putida UV4 as source of toluene dioxygenase (TDO) were applied to alkylbenzenes, providing the corresponding chiral triols (Scheme 96).



Scheme 96. Domino dioxygenase-catalysed trioxygenation reaction of alkyl phenyl sulphides and alkylbenzenes.

In the course of developing a concise asymmetric total synthesis of (−)-rosmarinecine, Kita et al. developed, in 2005, a lipase-catalysed domino kinetic resolution of α-hydroxynitrone intramolecular 1,3-dipolar cycloaddition reactions (Scheme 97).[153]

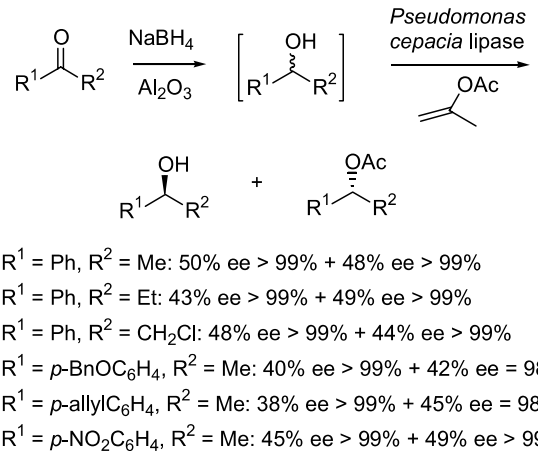


Scheme 97. Lipase-catalysed domino kinetic resolution of α-hydroxynitrone intramolecular 1,3-dipolar cycloaddition reaction.

In contrast, a few examples of domino chemoenzymatic reactions have involved the chemical reaction as the first step of the sequence. As an example, Kamal et al. have developed domino reactions involving the reduction of acetophenones with sodium borohydride in the presence of neutral alumina followed by enantioselective acylation catalysed by *Pseudomonas cepacia* lipase in one pot (Scheme 98).[154] This new protocol for lipase-mediated resolution involved for the first time the use of lipases in the presence of borohydride.

3.2. Asymmetric multienzymatic one pot reactions

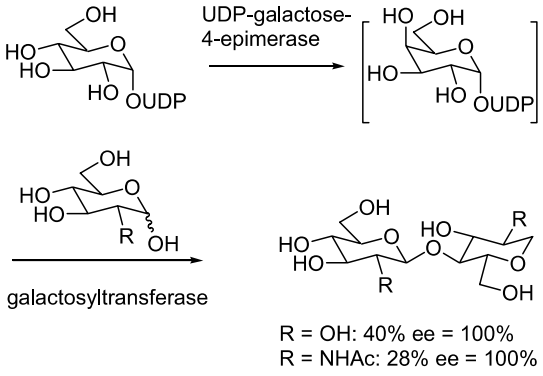
A highly interesting approach in the application of domino reactions is the use of a multienzyme cocktail to catalyse



Scheme 98. Domino lipase-catalysed synthesis of chiral alcohols from carbonyl compounds.

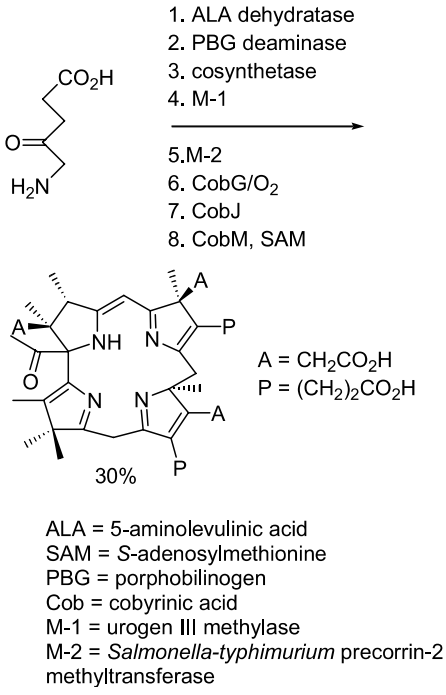
different reactions. It is now evident that the multienzyme synthesis of natural products has passed from feasibility to practical reality and that there is no limit to the number of enzymes that can be combined in a single reactor to produce a complex structure in good yield and in a domino fashion. What is truly remarkable is the lack of product/substrate inhibition, which is probably due to the irreversible nature of many of the later steps in a given sequence. As an early example, Längström et al. reported, in 1990, the multienzymatic synthesis of carboxy-^{11}C-labelled L-tyrosine, L-DOPA, L-tryptophan and 5-hydroxy-L-tryptophan starting from racemic [1-^{11}C]alanine with enantiomeric purities higher than 99%.[155] The enzymatic reactions were performed using, simultaneously, D-amino acid oxidase, catalase, glutamic-pyruvic transaminase, and β-tyrosinase (for L-tyrosine and L-DOPA), or tryptophanase (for L-tryptophan and 5-hydroxy-L-tryptophan), in a one pot reaction. In 1991, Gygax et al. described the synthesis of β-D-glucuronides by a one pot multienzyme system with in situ regeneration of uridine 5′-diphosphoglucuronic acid.[156] This stereoselective simple reaction involved the use of glucose-1-phosphate as a donor of the glucuronic acid moiety and phosphoenolpyruvate and NAD (nicotinamide adenine dinucleotide) as co-substrates. On the other hand, Thiem et al. have shown that galactosyltransferase catalysed the galactosylation of oligosaccharides terminated by glucose and by 2-acetamido-2-deoxy-glucopyranose, respectively.[157] The glycosyl donor, uridine-5′-diphospho-galactose, was generated in situ by the treatment of UDP-glucose with UDP-galactose-4-epimerase. In the presence of a glycosyl acceptor and galactosyltransferase, the corresponding galactosylated oligosaccharide was obtained (Scheme 99).

In 1993, Wong et al. reported a multienzyme system for a one pot synthesis of sialyl oligosaccharides through a combined use of β-galactosidase and α(2,6)-sialyltransferase coupled with regeneration in situ of CMP-sialic acid.[158] Thus, the synthesis of sialyl oligosaccharides has been achieved with a β-galactosidase-catalysed galactosylation of an acceptor followed by a sialyltransferase-catalysed sialylation with regeneration in situ of CMP-sialic acid. In 1994, another multienzyme cocktail was used for the domino synthesis of precorrin-5, starting from



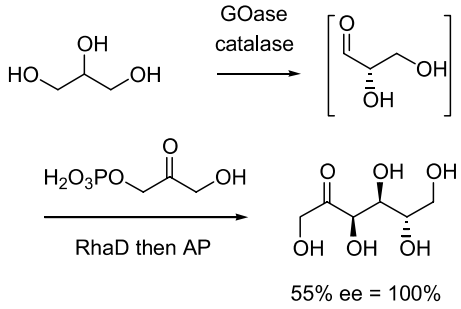
Scheme 99. Synthesis of galactose-terminated oligosaccharides by multienzyme system.

δ-aminolevulinic acid. In this transformation, eight different enzymes have been used including ALA-dehydratase to form porphobilinogen (PBG) as well as PBG deaminase and cosynthetase to give the tetracyclic uroporphyrinogen III (Scheme 100).[159]



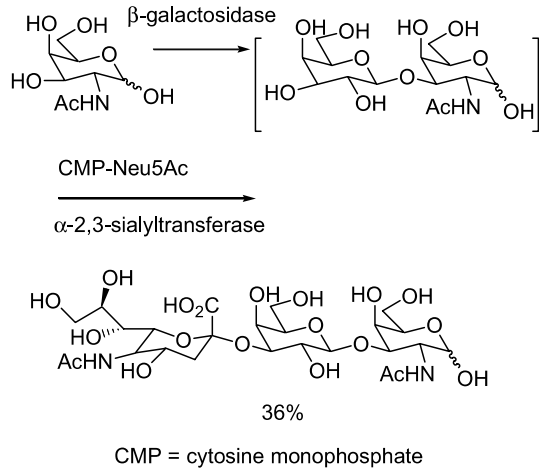
Scheme 100. Multienzyme cocktail for domino synthesis of precorrin-5.

In 1995, Wong et al. reported a domino aldol reaction catalysed by the aldolases, 2-deoxyribose 5-phosphate aldolase (DERA) and fructose 1,6-diphosphate aldolase (RAMA). This multienzyme system was used to catalyse a ternary crossed aldol between an α-substituted acetaldehyde derivative, acetaldehyde, and dihydroxyacetone phosphate.[160] At the same time, these authors have developed an enzymatic synthesis of enantiomerically pure L-fructose from dihydroxyacetone phosphate (DHAP) and L-glyceraldehyde, carried out by a multienzyme system comprising rhamnulose-1-phosphate aldolase (RhaD) and acid phosphatase (AP) using a stereospecific aldol addition reaction by this aldolase.[161] This latter methodology suffered, however, from two limitations. Firstly, L-glyceraldehyde is not commercially available and, secondly, this starting material is known to be thermodynamically metastable and decomposes easily. In this way, L-glyceraldehyde could be produced in situ from glycerol in the presence of galactose oxidase (GOase), catalase, rhamnulose-1-phosphate aldolase (RhaD), and acid phosphatase (AP) (Scheme 101).[162]



Scheme 101. Multienzyme system for domino synthesis of L-fructose.

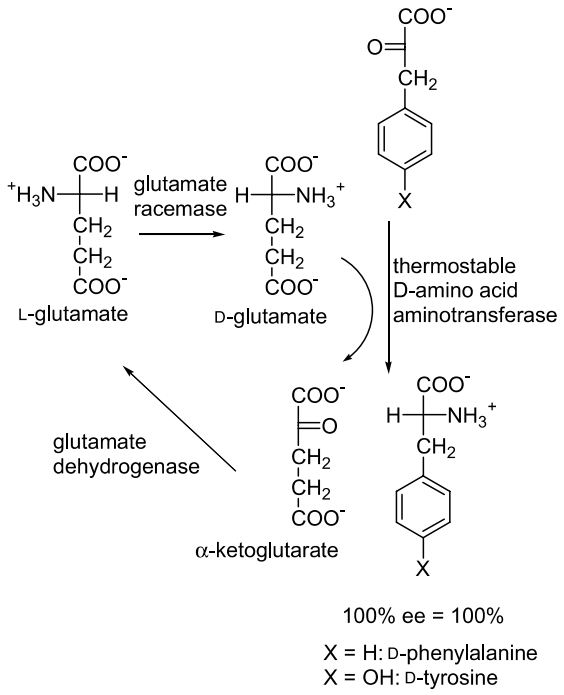
Kren et al. have developed a sequential multienzyme one pot system with cofactor regeneration in order to prepare rather complicated hetero-oligoglycosides such as the sialylated antigen T-epitope (Scheme 102).[163]



Scheme 102. One pot synthesis of sialyl T-antigen via multienzyme system.

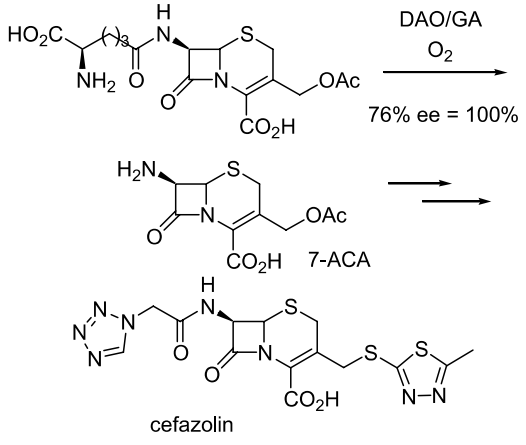
In another example, Duggan et al. supplied erythrose-4-phosphate and the unnatural substrate, 3-fluorophosphoenolpyruvate, to enzymes of the shikimate biosynthetic pathway to produce unnatural (*R*)- and (*S*)-6-fluoro analogues of shikimic acid, potentially useful as antibiotics.[164] In 1999, Sung et al. reported the production of aromatic D-amino acids from α-ketoacids and ammonia by the coupling of four enzyme reactions.[165] The multienzyme system composed of glutamate racemase, thermostable D-amino acid aminotransferase, glutamate dehydrogenase and formate dehydrogenase was employed for the synthesis of the enantiomerically pure D-amino acids, D-phenylalanine and D-tyrosine, from the corresponding α-ketoacids, phenylpyruvate and hydroxyphenylpyruvate, respectively (Scheme 103).

In 1997, Guisàn et al. reported the enzymatic deacylation of cephalosporin C in one batch by the simultaneous use of D-amino acid oxidase (DAO) from *Trigonopsis variabilis*,



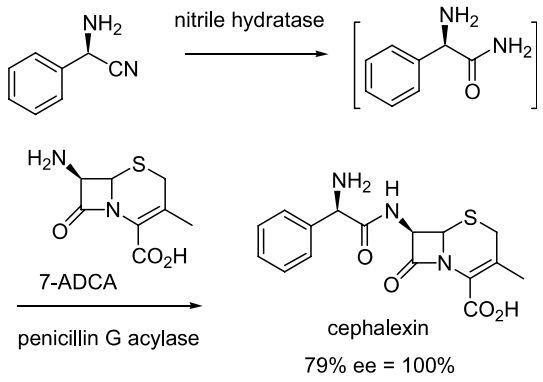
Scheme 103. Multienzyme synthesis of D-amino acids.

glutaryl acylase (GA) from *Acetobacter* sp., and a continuous flow of O_2.[166] This domino enzymatic reaction was included in a one pot, three-step chemoenzymatic synthesis of 3′-functionalised cephalosporins (e.g., cefazolin) involving three consecutive biotransformations catalysed by DAO and GA at the same time, and then by penicillin G acylase in a fully aqueous medium. DAO is known to catalyse the oxidative deamination of the α-aminoadipic side chain of cephalosporin C to give the α-ketoadipic derivative. A further decarboxylation in the presence of O_2 gives the glutaryl analogue, which is then deacylated by GA to obtain 7-aminocephalosporanic acid (7-ACA) (Scheme 104).



Scheme 104. Multienzyme cocktail for domino synthesis of cefazolin.

In 2002, Sheldon et al. reported a two-step, one pot enzymatic synthesis of cephalexin from D-phenylglycine nitrile.[167] The nitrile hydratase-catalysed hydration of D-phenylglycine nitrile to the corresponding amide was combined with the penicillin G acylase-catalysed acylation of 7-ADCA with the in situ-formed amide to afford a two-step, one pot synthesis of cephalexin (Scheme 105).



Scheme 105. Synthesis of cephalexin via one pot cascade of two enzymatic reactions.

4. Conclusions

This review clearly demonstrates the power and economic interest of asymmetric catalysed domino reactions in the field of synthetic organic chemistry. The development of new asymmetric processes such as asymmetric catalysed domino reactions for producing chiral elaborate structures in a rapid, atom-economic, and efficient manner has become an important area of research in organic synthesis. In addition, this review demonstrates that, by making use of the asymmetric catalytic potential of biocatalysts, enzyme-triggered cascade reactions may be turned into highly efficient protocols for the asymmetric synthesis of bioactive materials.

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Biographical sketch

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