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Use of TADDOLs and their derivatives in asymmetric synthesis

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Abbreviations: Ac, acetyl; Acac, acetylacetone; Anth, anthracen-9-yl; Ar, aryl; Bar_F, tetrakis[3,5-bis(trifluoromethyl)phenyl]borate; BINOL, 1,1′-bi-2-naphthol; BIPOL, biphenol; Bn, benzyl; Boc, *tert*-butoxycarbonyl; Box, bisoxazoline; BSA, bis-(trimethylsilyl)acetamide; BTPP, *tert*-butylimino-tri(pyrrolidino)phosphorane; BTSP, bis(trimethylsilyl)peroxide; Bu, butyl; Bz, benzoyl; C, cyclo; Cbz, benzyloxycarbonyl; Cod, cyclooctadiene; Cp, cyclopentadienyl; CPG, controlled-pore glass; Cy, cyclohexyl; Dba, (*E*,*E*)-dibenzylideneacetone; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCE, 1,2-dichloroethane; de, diastereomeric excess; DME, 1,2-dimethoxyethane; DMF, dimethylformamide; ee, enantiomeric excess; EPR, electron paramagnetic resonance; Et, ethyl; Fu, furyl; Hex, hexyl; L, ligand; Me, methyl; Menth, menthyl; MOM, methoxymethyl; Naph, naphthyl; Nbd, norbornadiene; NCS, *N*-chlorosuccinimide; NFSI, *N*-fluorobenzenesulfonimide; NIPAAm, *N*-isopropylacrylamide; NOBIN, 2-amino-2-hydroxy-1,1′-binaphthalene; Non, nonyl; Nu, nucleophile; Pent, pentyl; Ph, phenyl; PMB, *p*-methoxybenzoyl; PMP, *p*-methoxyphenyl; POM, polyoxometalate; Pr, propyl; PS, polystyrene; SET, single-electron transfer; TADDOL, α,α,α′,α′-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol; TBS, *tert*-butyldimethylsilyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; Thio, thiophene; TMEDA, tetramethylethylenediamine; TMS, trimethylsilyl; Tol, tolyl; Ts, 4-toluenesulfonyl (tosyl).

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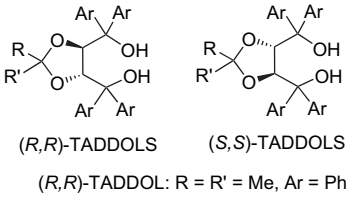
1. Introduction

The enantioselective production of compounds is a central theme in current research, mainly in connection with the fact that most natural products are chiral and their physiological or pharmacological properties depend upon their recognition by chiral receptors, which will interact only with molecules of the proper absolute configuration. The use of chiral drugs in enantiopure form is now a standard requirement for virtually every new chemical entity, and the development of new synthetic methods to obtain enantiopure compounds has become a key goal for pharmaceutical companies.[1] Indeed, the growing economic importance of chiral compounds has spurred major research efforts towards the selective preparation of chiral compounds. For example, in 2002, single-enantiomer drugs comprised 37% ($152 billion) of the total market of ~$400 billion. Since 2002, this number has still increased steadily, such that chiral drugs are projected to constitute a market of >$200 billion by 2008. Indeed, 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. Over the last 25 years an explosive growth of research in the field of asymmetric synthesis has occurred.[2] Asymmetric synthesis constitutes one of the main strategies to gain access to enantio-enriched compounds, involving the use of either chiral auxiliaries or catalysts derived preferentially from cheap chiral pool sources. In particular, asymmetric catalysis of organic reactions to provide enantiomerically enriched products is of central importance to modern synthetic and pharmaceutical chemistry.[3] In this context, the development of chiral ligands is one of the most fascinating methods to achieve high enantioselectivity of a given catalytic asymmetric reaction. Therefore, the need for the design of novel chiral ligands has been an eternal theme for organic chemists. Apart from the success of BINOL,[4] TADDOL is one of the most efficient chiral backbones for asymmetric synthesis. Tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs), containing two adjacent diarylhydroxymethyl groups in a trans relationship on a 1,3-dioxolane ring (Scheme 1), were introduced, in 1987, by Seebach et al.[5] TADDOLs are easily prepared from chiral acetals or ketals of tartrate esters by reaction of the latter with aromatic Grignard reagents.



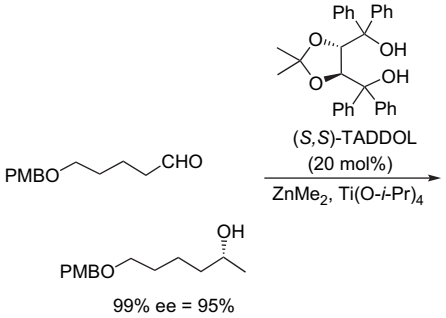
Scheme 1. Structure of TADDOLs.

Within the molecule of TADDOL, one of the hydrogen atoms of the alcohol group participates in an intramolecular hydrogen bond and the other is free for intermolecular interactions. These unique features have been confirmed by X-ray crystallographic analysis. The crystal structure analyses have revealed that the heteroatoms on the diarylmethyl groups are almost always in close proximity to each other, joined together by H-bonds, and predisposed to form chelate complexes in which the metallic centres reside in propeller-like chiral environments. TADDOLs and their derivatives are extraordinarily versatile chiral auxiliaries, which can be used as stoichiometric chiral reagents, chiral ligands for both stoichiometric and catalytic asymmetric reactions as well as, more recently, chiral organocatalysts. In addition, a number of simple optical resolutions of racemic compounds by inclusion complexation with a TADDOL derivative as a chiral host have been developed in recent years, furnishing an alternative and attractive approach to obtain optically active compounds. Moreover, crystalline inclusion complexes of guest compounds with TADDOLs have been useful as media for various selective reactions in the solid state. The use of TADDOL derivatives in asymmetric synthesis was previously reviewed by Seebach et al., in 2001.[6] The goal of the present review is to cover the recent advances in the use of TADDOLs in asymmetric synthesis, focussing on those published since 2001. This review is subdivided into six sections, according to the different types of asymmetric reactions based on the use of TADDOLs and their derivatives, such as nucleophilic additions to C=O bonds, nucleophilic conjugate additions to electron-deficient C=C double bonds, nucleophilic substitutions, cycloaddition reactions, oxidation and reduction reactions and miscellaneous reactions, including those occurring by inclusion complexation. In addition, the efficiency of TADDOLs as powerful resolving agents of various species is extensively illustrated.

2. Nucleophilic additions to C=O double bonds

2.1. Organozinc additions to aldehydes

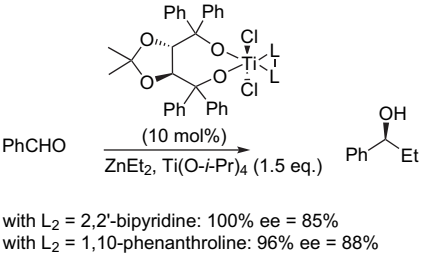
One of the most powerful methods for the catalytic asymmetric generation of C–C bonds is the enantioselective addition of organometallic reagents to aldehydes or ketones. Since the initial report of Oguni and Omi on the reaction of diethylzinc with benzaldehyde in the presence of a catalytic amount of (*S*)-leucinol with moderate enantioselectivity (49% ee) in 1984[7] research on asymmetric organozinc additions to carbonyl compounds has grown dramatically.[3b] In particular, Seebach et al. have carried out an extensive study on using titanium complexes of TADDOLs for the asymmetric organozinc addition.[8] Seebach's conditions (Me_2Zn and Ti(O-*i*-Pr)$_4$ in the presence of a TADDOL ligand) have been used by Takemoto et al. in the course of developing a total synthesis of macrolactin A, a 24-membered polyene macrolide antibiotic, having a strong activity against B16–F10 murine tumour cells and HIV-1.[9] Thus, the asymmetric methylation of the PMB aldehyde derived from 1,5-pentanediol led, in these conditions, to the formation of the corresponding chiral alcohol in almost quantitative yield with high enantioselectivity, as shown in Scheme 2.



Scheme 2. Methylation of PMB aldehyde.

In 2004, Gau and Sheen reported the synthesis of titanium–TADDOLate complexes containing bidentate nitrogen donors, such as 2,2′-bipyridine or 1,10-phenanthroline.[10] These six-coordinate complexes, $TiCl_2$(TADDOLate)(L_2) (L_2=2,2′-bipyridine or 1,10-phenanthroline), were prepared by the reaction of $TiCl_4$ with a TADDOL ligand, followed by the addition of the bidentate ligand. These novel complexes have shown good reactivities in asymmetric ethylation reactions of benzaldehyde with low-to-moderate enantioselectivities (≤52% ee). It was demonstrated, however, that, with the addition of an excess of Ti(O-*i*-Pr)$_4$, the enantioselectivities

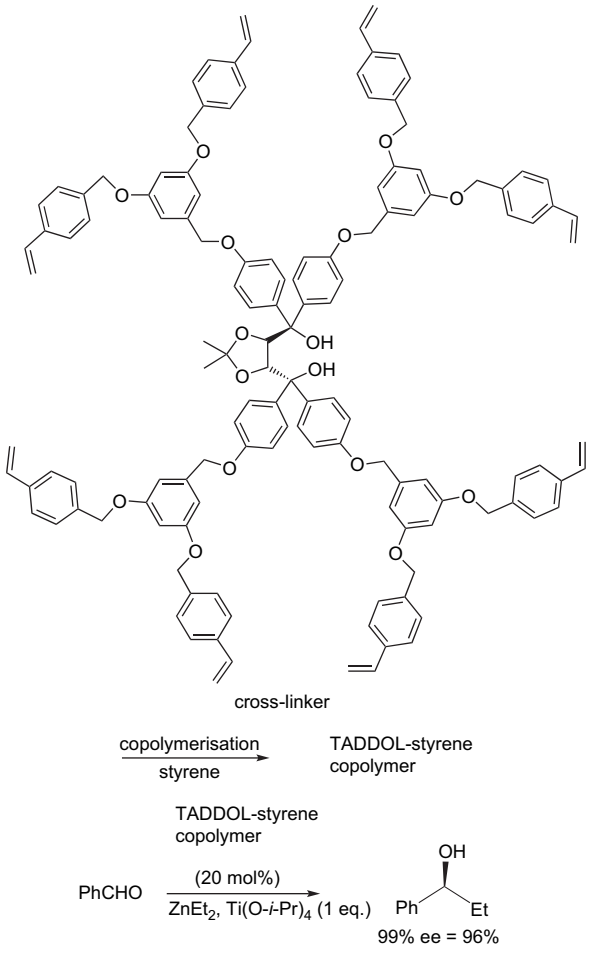
improved dramatically up to 88% ee, as shown in Scheme 3. Indeed, the asymmetric diethylzinc addition to aldehyde catalysed by chiral titanium(IV) complexes is a complicated catalytic system, since an excess of Ti(O-*i*-Pr)$_4$ is required in order to achieve the best enantioselectivity. The excess of Ti(O-*i*-Pr)$_4$ has been suggested to facilitate the removal of the product from the metal centre or to react with the chiral complex to give an active dimeric species with a Ti/chiral ligand ratio of 2:1.



Scheme 3. Ethylation of benzaldehyde in the presence of titanium-TADDOLate complex containing bidentate nitrogen donor.

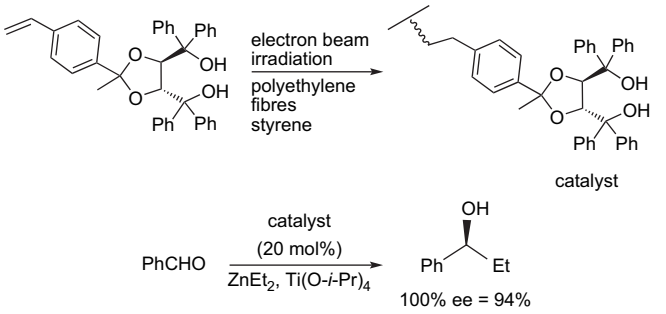
Macromolecular chiral catalysts have become a very attractive research subject in recent years, because these materials offer the advantages of simplified product isolation, easy recovery of the generally quite expensive or toxic chiral catalysts, potential use for continuous production, as well as, in many cases, enhanced stability of the polymer-bound catalyst, as compared to its soluble analogue.[11] The architecture and properties of the polymeric support play an important role in determining the catalytic performance. The immobilisation of a chiral auxiliary onto a polymeric matrix can be achieved by two alternative methodologies, grafting and copolymerisation. The most common type of polymeric support is cross-linked polystyrene beads, prepared by suspension copolymerisation of a polymerisable ligand together with styrene and a suitable cross-linker, such as divinylbenzene. Alternatively, the ligands can be grafted onto an existing cross-linked polystyrene resin containing properly functionalised reactive groups. The degree of cross-linking and the structure of the cross-linking agent strongly influence the activity and selectivity of the catalyst. Various heterogeneous TADDOL catalysts have been subsequently prepared, for instance by immobilising TADDOLs to a Merrifield resin,[12] dendritic macromolecules,[13] glass,[14] monolithic polymer rods[15] or by copolymerising TADDOLs with styrene in the presence or absence of a cross-linking agent. As an example, TADDOL-based polymers[16] and dendrimers[17] have been prepared by Seebach et al., providing very high and stable enantioselectivities for the diethylzinc addition to benzaldehyde, even after many cycles. In 2002, these workers reported a new method to immobilise chiral ligands on polystyrene, based on the copolymerisation of a TADDOL dendrimer with styrene, followed by loading with titanate, affording polymer-bound Ti–TADDOLate complexes with unprecedented stability and activity during recycling.[18] This novel approach was the first example of the use of dendrimers as cross-linkers in polystyrene. These dendritic polymer-embedded Ti–TADDOLate complexes were employed as catalysts in the addition of $ZnEt_2$ to benzaldehyde in the presence of Ti(O-*i*-Pr)$_4$, providing excellent conversions and enantioselectivities of up to 98% ee, as shown in Scheme 4. In addition, it was demonstrated that these polymers maintained a constant swelling ability during recycling, which could be the reason for their excellent performance.

The practical drawbacks of cross-linked polystyrene supports are their low mechanical strength and restricted thermooxidative stability. If the spherical beads are not sufficiently stable to withstand stirring over a long period of time, their breakdown will result in the formation of a fine powder, which severely limits their handling during filtration and recycling of the supported catalyst. Likewise, grafting of functionalised ligands to chemically modified polystyrene resins may result in undesired side reactions and incomplete grafting. Moreover, functionalities may remain in the support material that could reduce the effectiveness of the polymeric catalyst. Thus, the development of other approaches for facile anchoring of chiral catalysts to mechanically stable, inert polymeric supports is of special interest. In this context, Leino et al. have reported the immobilisation of TADDOLs on chemically inert, mechanically stable polyethylene fibres by electron beam-induced preirradiation grafting, using styrene as a comonomer.[19] These polymer-supported chiral ligands were employed as catalysts in the asymmetric addition of $ZnEt_2$ to benzaldehyde, providing a quantitative conversion of benzaldehyde with high enantioselectivity (Scheme 5). The catalyst was successfully regenerated and employed in subsequent reactions with retention of high enantioselectivities.

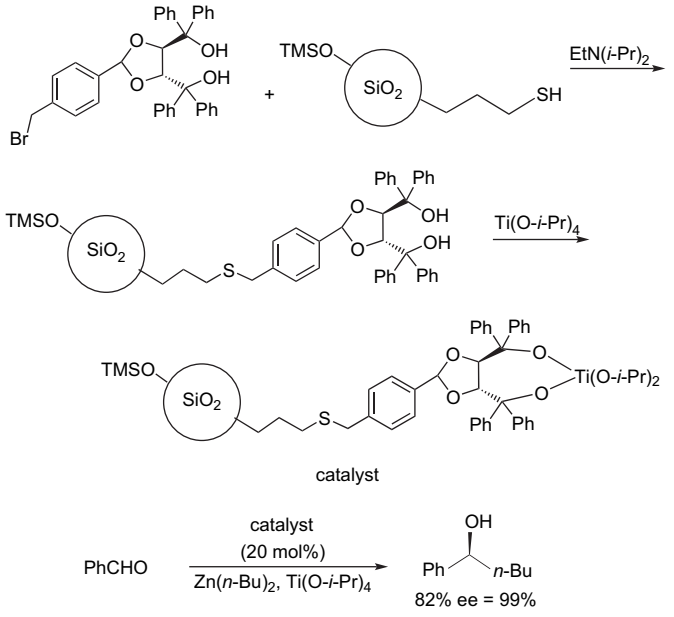


Scheme 4. Ethylation of benzaldehyde in the presence of polymer-bound Ti–TADDOLate.

On the other hand, Seebach and Heckel have demonstrated that TADDOLs could be immobilised on hydrophobic controlled-pore glass (CPG) silica gel.[20] Indeed, CPG is a rigid support that offers an open and accessible pore structure in all possible solvents and over a wide temperature and pressure range. These novel CPG-immobilised catalysts were prepared, as summarised in Scheme 6, and then applied to the condensation of Zn(*n*-Bu)$_2$ onto benzaldehyde. Excellent yields and enantioselectivities were observed, thus demonstrating that these catalysts were, in many ways, superior to their polymer-bound or -incorporated analogues.

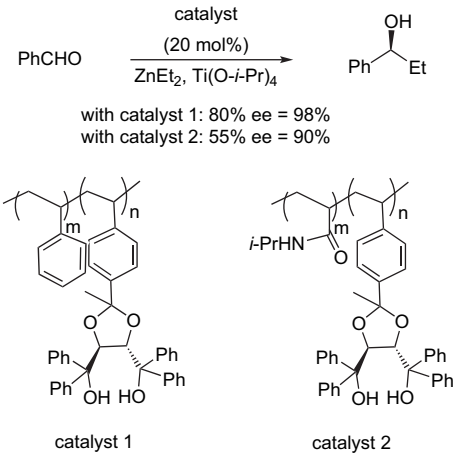


Scheme 5. Ethylation of benzaldehyde in the presence of fibre-bound Ti–TADDOLate.



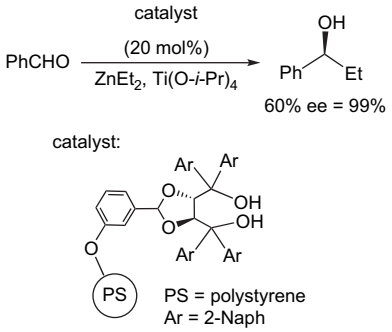
Scheme 6. Butylation of benzaldehyde in the presence of CPG-immobilised Ti–TADDOLate.

Homogeneous catalysts have advantage over heterogeneous catalysts since it often provide a better enantioselectivity and a better accessibility of the catalytic sites, avoiding the dependence of the catalytic activity on the swelling of the polymer. In this context, Rosling et al. reported, in 2005, the preparation of novel soluble TADDOL-bearing polymers on the basis of copolymerising the styryl derivative of TADDOL with styrene (catalyst 1, Scheme 7) or *N*-isopropylacrylamide, NIPAAm (catalyst 2, Scheme 7).[21] The efficiency of these complexes with Ti(IV) as catalysts in the enantioselective addition of $ZnEt_2$ to benzaldehyde has been investigated. The copolymer with styrene gave a very high yield and an excellent enantioselectivity, while the copolymer with NIPAAm afforded a slightly lower yield, along with a high ee, as shown in Scheme 7.



Scheme 7. Ethylation of benzaldehyde in the presence of soluble TADDOL-bearing polymers.

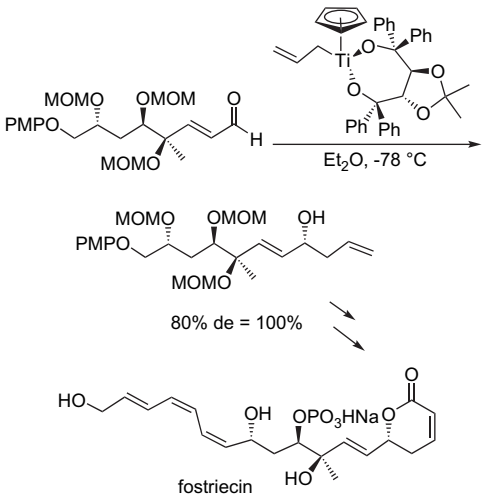
In addition, Luis et al. developed, in 2006, polymeric monolithic resins containing TADDOL subunits by polymerisation of the corresponding functional monomers.[22] The corresponding columnar polymeric monoliths containing Ti–TADDOLate functionalities were involved as catalysts of the addition reaction of $ZnEt_2$ to benzaldehyde. The catalyst bearing 2-naphthyl groups at the α-positions gave the best result when used under flow conditions, but could also be used in batch processes (Scheme 8). This new type of supported Ti catalysts has shown an extraordinary long-term stability, being active for at least one year.



Scheme 8. Ethylation of benzaldehyde in the presence of monolithic resin Ti–TADDOLate.

2.2. Allylations

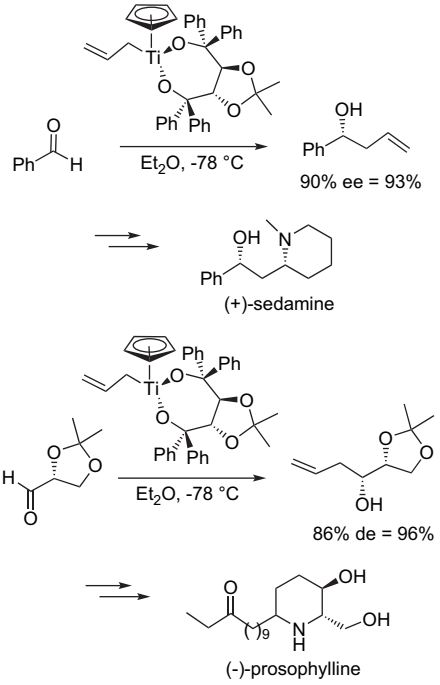
The allylmetallation of aldehydes and ketones, leading to products with a maximum of two new stereocentres and versatile functionalities for further transformations, is an important example of acyclic stereocontrol. In this context, TADDOLs have been demonstrated to be excellent chiral ligands in asymmetric allylations of aldehydes.[23] As an example, Cossy et al. reported, in 2001, an enantioselective allyltitanation applied to a polyfunctionalised aldehyde derived from (*S*)-glycidol, as depicted in Scheme 9.[24] The allylation was performed in the presence of a chiral TADDOL-derived allyltitanium complex, providing the corresponding



Scheme 9. Synthesis of C1–C12 fragment of fostriecin via allyltitanation reaction.

homoallylic alcohol with complete diastereoselectivity. The key factor for this successful enantioselective allyltitanium reagent was a single cyclopentadienyl ligand, providing a stable steric arrangement and the appropriate reactivity. The resulting homoallylic alcohol could be further converted into the C1–C12 fragment of fostriecin, a potential clinical antitumour agent (Scheme 9).

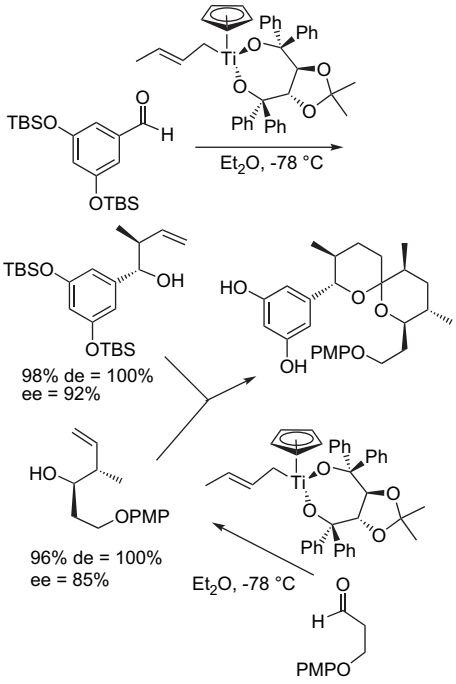
In addition, the same methodology was applied by these workers to the total syntheses of two piperidine alkaloids, (+)-sedamine and (−)-prosophylline.[25] In the synthesis of (+)-sedamine, the key step was the allyltitanation of benzaldehyde, which led to the formation of the corresponding homoallylic alcohol in excellent yield and enantioselectivity in the presence of the catalyst depicted in Scheme 9 (Scheme 10). This alcohol was further converted in 11 steps into (+)-sedamine with an overall yield of 20%. In the synthesis of (−)-prosophylline, the key enantioselective allyltitanation was performed in the presence of a D-glyceraldehyde acetonide, providing the corresponding homoallylic alcohol in excellent yield and diastereoselectivity, as shown in Scheme 10. This alcohol was subsequently converted into (−)-prosophylline in 14 steps with an overall yield of 9%.



Scheme 10. Syntheses of (+)-sedamine and (−)-prosophylline via allyltitanation reactions.

In 2004, Floreancig and Wang extended the scope of this methodology to the asymmetric crotylation of aromatic aldehydes.[26] The reaction was performed in the presence of Hafner's crotyltitanium–TADDOLate,[23] which led to the formation of the corresponding homoallylic alcohols with essentially complete diastereocontrol and in excellent yield and high enantioselectivity, as depicted in Scheme 11. Starting from these alcohols, a synthesis of the spiroketal unit of the HIV-integrase inhibitor, integramycin, was elaborated in an efficient and convergent manner.

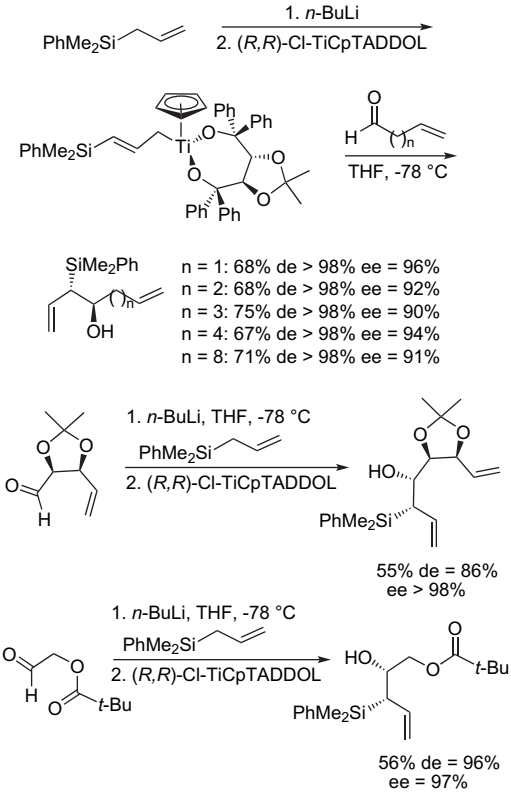
On the other hand, Ghosez et al. have developed asymmetric reactions between unsaturated aldehydes and a silyl-substituted allyltitanate reagent, generated from allyldimethylphenylsilane, *n*-BuLi and (*R*,*R*)-Cl-TiCpTADDOL.[27] These reactions gave the corresponding *anti*-β-hydroxyallylsilanes in good yields and high diastereo- and enantioselectivity, as depicted in Scheme 12. This methodology could also be applied to the allyltitanations of an acetonide-protected aldehyde and to an aldehyde derived from



Scheme 11. Synthesis of C16–C35 fragment of integramycin via crotyltitanation reactions.

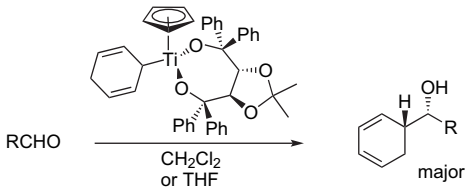
solketal, providing the corresponding β-hydroxyallylsilanes (Scheme 12).[28]

In 2004, Studer et al. reported the synthesis of a TADDOL-derived cyclohexadienyl-titanium complex and involved this chiral metallated cyclohexadiene in highly diastereo- and enantioselective allylations of both aromatic and aliphatic aldehydes,

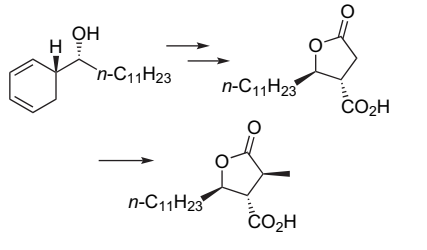


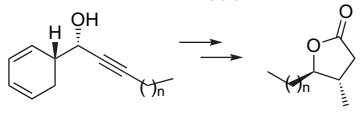
Scheme 12. Allyltitanation reactions of aldehydes with silyl-substituted allyltitanate reagent.

providing the corresponding *syn*-cyclohexadiene as the major product, as depicted in Scheme 13.[29] This methodology gave rise to various chiral functionalised 1,3-cyclohexadienes, which were useful building blocks for the preparation of biologically important γ-butyrolactones. Thus, this novel methodology was applied to the short efficient syntheses of (+)-nephrosteranic acid, (+)-*trans*-whisky lactone and (+)-*trans*-cognac lactone.



R = Ph: 83% de > 98% ee = 96%
R = *p*-Tol: 82% de > 98% ee = 90%
R = *p*-MeOC$_6$H$_4$: 63% de > 98% ee > 98%
R = *p*-BrC$_6$H$_4$: 94% de > 98% ee = 94%
R = *m*-MeOC$_6$H$_4$: 58% de > 98% ee = 94%
R = *o*-MeOC$_6$H$_4$: 61% de > 98% ee > 98%
R = *o*-Tol: 56% de > 98% ee = 92%
R = *o*-BrC$_6$H$_4$: 92% de > 98% ee > 98%
R = 1-Naph: 96% de > 98% ee > 98%
R = 2-Naph: 81% de > 98% ee = 80%
R = 2-Fu: 72% de = 96% ee = 86%
R = Ph-C≡C: 86% de > 98% ee = 98%
R = Et: 40% de > 98% ee = 82%
R = *n*-C$_{11}$H$_{23}$: 79% de > 98% ee = 86%
R = *n*-C$_9$H$_{19}$-C≡C: 83% de > 98% ee = 97%
R = Et-C≡C: 66% de > 98%
R = *n*-Pr-C≡C: 57% de > 98%

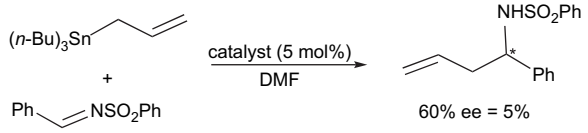


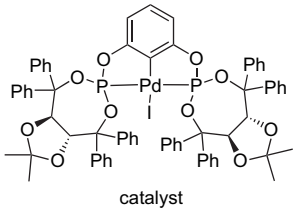


n = 3: (+)-*trans*-whisky lactone
n = 4: (+)-*trans*-cognac lactone

Scheme 13. Allylation of aldehydes with cyclohexadienyl-titanium complex.

Finally, Szabo et al. have studied asymmetric allylations of sulfonimines with allyltributylstannane performed in the presence of a TADDOL-based complex (Scheme 14).[30] The novel chiral C_2-symmetrical pincer complex was prepared on the basis of coupling the TADDOL moiety with iodoresorcinol, followed by oxidative addition of palladium(0). The corresponding chiral homoallylic amines were, however, obtained with a very low enantioselectivity (≤5% ee), while good enantioselectivities of up to 59% ee were observed by using BINOL units as chiral ligands in the same study. Although this reaction does not involve a nucleophilic addition to a C=O double bond, it was decided, however, to include it in this section.

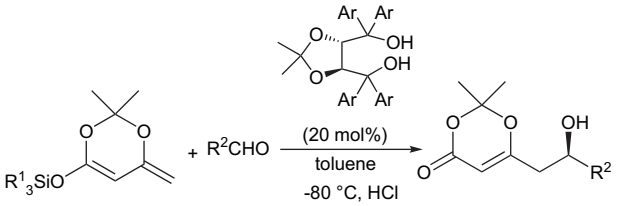




Scheme 14. Allylation of sulfonimine with pincer-complex catalyst.

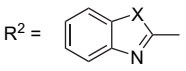
2.3. Aldol-type reactions

The asymmetric aldol reaction is one of the most important topics in modern catalytic synthesis. A new class of catalytic asymmetric aldol reactions have been developed in the last few years with the use of chiral organocatalysts,[31] becoming one of the most advanced types of synthesis in the field of organocatalysis. In comparison to the well-studied application of chiral diols as ligands, the emergence of TADDOLs and their derivatives as effective general organocatalysts is a very recent development. An indirect aldol reaction, such as the vinylogous Mukaiyama aldol reaction, has proved to be a powerful method for complex molecule synthesis, as it provides rapid access to polyketide derivatives. In 2005, Rawal et al. reported the successful use of 1-naphthyl-TADDOL as an organocatalyst in the enantioselective vinylogous Mukaiyama aldol reaction of silyldienol ethers with a range of aldehydes, giving regiospecifically the addition products in good-to-excellent yields and with ee values as high as 90% (Scheme 15).[32]



Ar = 1-Naph

R^1 = *n*-Bu, R^2 = CO$_2$Et: 60% ee = 87%
R^1 = *n*-Bu, R^2 = CO$_2$*t*-Bu: 54% ee = 84%
R^1 = *n*-Bu, R^2 = CH=CH-CO$_2$Et: 66% ee = 71%
R^1 = *n*-Bu, R^2 = *o*-O$_2$NC$_6$H$_4$: 58% ee = 75%
R^1 = *n*-Bu, R^2 = F$_5$C$_6$: 57% ee = 67%
R^1 = Me, R^2 = CO$_2$Et: 82% ee = 81%

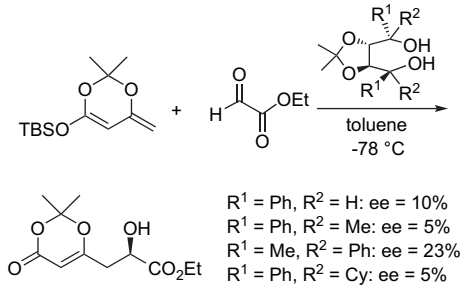


R^1 = *n*-Bu, X = O: 55% ee = 83%
R^1 = *n*-Bu, X = S: 73% ee = 90%

Scheme 15. Vinylogous Mukaiyama aldol reaction.

In 2006, Prasad and Chandrakumar studied the vinylogous Mukaiyama aldol reaction of a silyldienol ether with ethyl glyoxalate in the presence of novel TADDOL analogues.[33] These catalysts were prepared by reduction of the 1,4-diketones derived from (+)-tartaric acid with selectride, or by Grignard reagent addition to these 1,4-diketones. The vinylogous Mukaiyama aldol reaction catalysed by these new TADDOL ligands afforded the corresponding alcohols in low enantioselectivities (≤23% ee), as shown in Scheme 16.

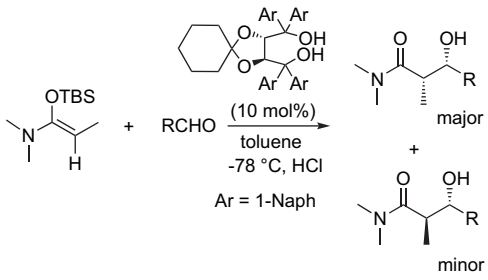
Among the many permutations of Mukaiyama aldol reactions, the reaction of silylated enolates of amides with aldehydes is of particular interest, since the presence of the enamine unit is expected to render these compounds highly nucleophilic. In 2006, Rawal et al. developed highly diastereo- and enantioselective



R^1 = Ph, R^2 = H: ee = 10%
R^1 = Ph, R^2 = Me: ee = 5%
R^1 = Me, R^2 = Ph: ee = 23%
R^1 = Ph, R^2 = Cy: ee = 5%

Scheme 16. Vinylogous Mukaiyama aldol reaction with ethyl glyoxalate.

Mukaiyama aldol reactions of *O*-silyl-*N*,*O*-ketene acetals mediated by a cyclohexylidene-TADDOL derivative as organocatalyst.[34] The catalysed reaction was effective for a range of aldehydes, giving the corresponding amide aldol products in useful yields and selectivities, as shown in Scheme 17.

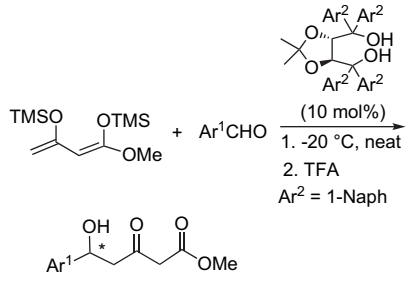


R = Ph: 94% de = 88% ee (major) = 98%
R = *p*-$O_2NC_6H_4$: 93% de = 86% ee (major) = 94%
R = *p*-ClC_6H_4: 86% de = 90% ee (major) = 97%
R = *p*-$CF_3C_6H_4$: 84% de > 92% ee (major) = 96%
R = *p*-Tol: 77% de = 88% ee (major) = 97%
R = *m*-Tol: 77% de = 80% ee (major) = 96%
R = *m*-BrC_6H_4: 84% de = ee (major) = 80%
R = 3,4-$(Cl)_2C_6H_3$: 71% de = ee (major) = 80%
R = *m*-$MeOC_6H_4$: 81% de = 86% ee (major) = 97%
R = *o*-$MeOC_6H_4$: 50% de = 78% ee (major) = 91%
R = 2-Naph: 50% de = 82% ee (major) = 97%
R = *n*-Pr: 47% de = 80% ee (major) = 91%

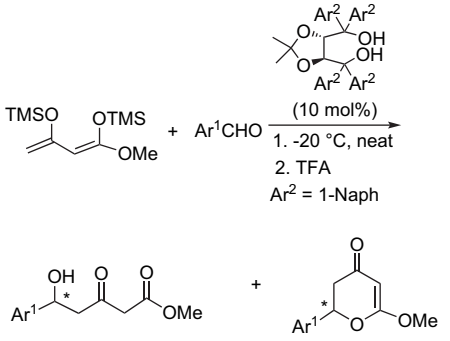
Scheme 17. Mukaiyama aldol reaction of *O*-silyl-*N*,*O*-ketene acetals.

In 2007, the enantioselective vinylogous aldol reaction of Chan's diene[35] with a range of aromatic and heteroaromatic aldehydes was developed by Villano et al., using TADDOLs as organocatalysts.[36] The corresponding vinylogous aldols were obtained as exclusive products in complete γ-selectivity and in moderate efficiency and enantioselectivity (≤61% ee). The results, reported in Scheme 18, indicated a strong dependence of the efficiency and enantioselectivity on the pattern of the substitution of the aromatic nucleus. Conversely, aliphatic aldehydes, such as *n*-decanal, were shown to be completely unreactive under similar conditions. On the other hand, the presence of an electron-withdrawing substituent on the aromatic ring caused a significant modification in the behaviour of the aldehydic substrates. Indeed, electron-poor aromatic aldehydes showed an enhanced reactivity, and a competing asymmetric hetero Diels–Alder reaction took place in comparable (or higher) yields and ees, leading to the corresponding pyrone derivatives (Scheme 18).

In addition to organocatalysed aldol-type reactions, Schneider and Hansch reported, in 2003, the first zirconium-catalysed enantioselective aldol–Tishchenko reactions involving ketone aldols as enol equivalents.[37] Thus, a chiral zirconium–TADDOLate complex was found to catalyse the aldol–Tishchenko reaction of ketone aldol adducts with a range of aldehydes, giving rise to differentiated



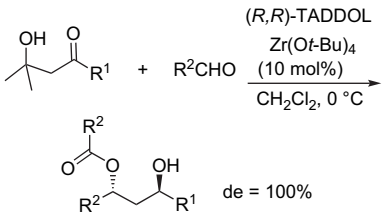
Ar^1 = Ph: 42% ee = 61%
Ar^1 = *p*-Tol: 39% ee = 57%
Ar^1 = 2-Fu: 40% ee = 37%
Ar^1 = *p*-$MeOC_6H_4$: 18% ee = 11%
Ar^1 = *o*-$MeOC_6H_4$: 57% ee = 40%



Ar^1 = *p*-$NO_2C_6H_4$: 39% ee = 54% + 32% ee = 57%
Ar^1 = *o*-$NO_2C_6H_4$: 32% ee = 46% + 30% ee = 60%
Ar^1 = *p*-$CF_3C_6H_4$: 52% ee = 31% + 38% ee = 51%
Ar^1 = *o*-CNC_6H_4: 46% ee = 56% + 39% ee = 59%

Scheme 18. Vinylogous aldol reactions of Chan's diene.

1,3-*anti*-diol monoesters in good-to-excellent yields, complete diastereocontrol and with up to 57% enantiomeric excess, as depicted in Scheme 19. This strategy differed from the conventional methodology, which typically employed silyl enolates as enol equivalents and featured the catalytic in situ generation of a chiral metal enolate undergoing an enantioselective aldol reaction with a subsequent Tishchenko reduction in a domino-type reaction.



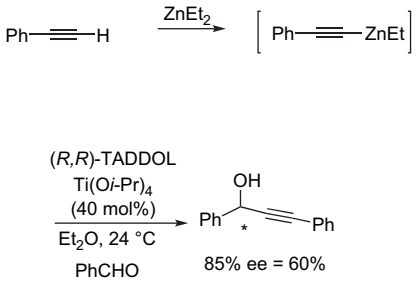
R^1 = *i*-Pr, R^2 = *n*-Hex: 86% ee = 30%
R^1 = R^2 = *i*-Pr: 82% ee = 44%
R^1 = *t*-Bu, R^2 = *n*-Hex: 88% ee = 42%
R^1 = *t*-Bu, R^2 = *i*-Pr: 84% ee = 57%
R^1 = *t*-Bu, R^2 = Cy: 75% ee = 50%

Scheme 19. Aldol–Tishchenko reaction with ketone aldols as enol equivalents.

2.4. Miscellaneous reactions

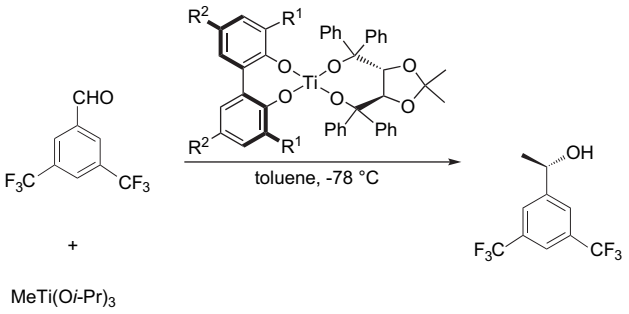
In recent years, there has been a considerable interest in asymmetric catalytic addition reactions of terminal alkynes to aldehydes,[38,39] since optically active propargylic alcohols represent versatile precursors for the synthesis of many chiral organic compounds. The acidity of a terminal alkynyl proton makes it easy to

prepare alkynylmetallic reagents as good functional carbon nucleophiles and the resulting products, chiral propargylic alcohols, are important precursors to many chiral organic compounds.[40] Thus, the asymmetric addition of alkynylzinc reagents to aldehydes is an important method of producing such compounds.[38,39,41] As an example, (*R*,*R*)-TADDOL has been employed as a ligand by Singh and Kamble for the enantioselective phenylacetylene addition to benzaldehyde, providing the corresponding propargylic alcohol in good yield and enantioselectivity, as depicted in Scheme 20.[42] It was demonstrated that the enantioselectivity decreased drastically, down to 4% ee, when the reaction was carried out in the absence of Ti(O-*i*-Pr)$_4$.



Scheme 20. Phenylacetylene addition to benzaldehyde.

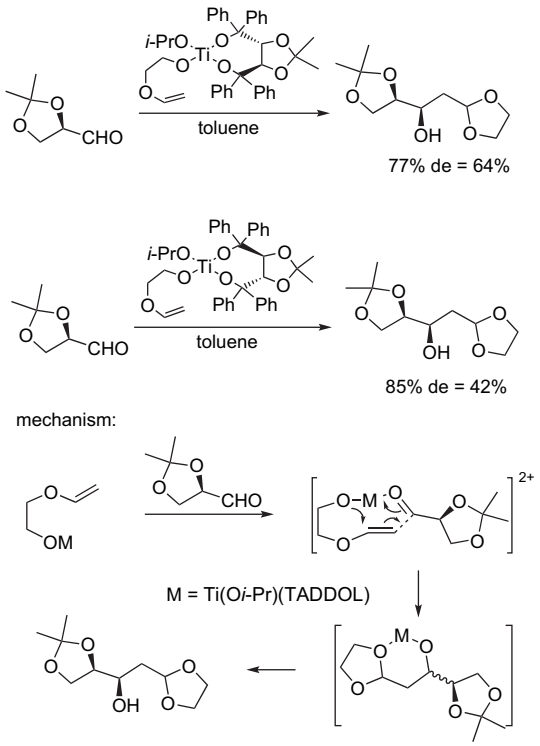
In 2001, Mikami et al. reported the synthesis of novel chiral titanium complexes, which were composed of 3,3′-modified biphenolate (BIPOLate) ligands atropisomerically controlled by (*R*,*R*)-TADDOLs.[43] These 3,3′-modified BIPOLate/TADDOLate–Ti complexes were prepared by treatment of Ti(O-*i*-Pr)$_4$ with (*R*)-BIPOL, giving Ti(O-*i*-Pr)$_2$(BIPOLate)$_2$, which, upon addition of TADDOL, led to the expected BIPOLate/TADDOLate–Ti complex. This type of complex proved to be highly enantioselective Lewis acid catalysts for the methylation reaction of aldehydes, giving enantioselectivities of up to 100% ee, as shown in Scheme 21.



R^1 = Ph, R^2 = H: 36% ee = 69%
R^1 = Me, R^2 = H: 56% ee = 88%
R^1 = *o*-MeOC$_6$H$_4$, R^2 = H: 40% ee = 65%
R^1 = MeO, R^2 = Me: 60% ee = 100%

Scheme 21. Methylation of aldehyde with 3,3′-modified BIPOLate/TADDOLate–Ti complexes.

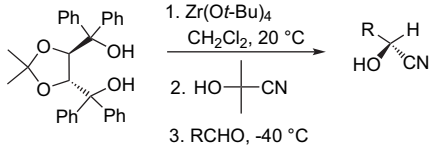
Vinyloxy ethoxides, in the presence of a Lewis acidic and/or a coordinating counterion, react with aldehydes to yield the corresponding β-hydroxy-1,3-dioxolanes. These reactions proceed via a transition state in which the metal coordinates the adducts in a cyclic nine-membered arrangement, resulting in C–C and C–O σ-bond formations. In 2005, Redlich et al. developed this type of reaction in the presence of chiral TADDOL-modified vinyloxides, providing the corresponding β-hydroxy-1,3-dioxolanes in good yields and moderate diastereoselectivities (Scheme 22).[44] Thus, these workers have modified the basic reagent, vinyloxyethoxytitanium triisopropyloxide, by replacing two of the isopropyloxides with (*R*,*R*)- or (*S*,*S*)-TADDOL, and condensing these reagents onto chiral 2,3-*O*-isopropylidene-D-glyceraldehyde to give the corresponding open-chain pentose derivatives. Interestingly, both enantiomeric reagent systems derived from (*R*,*R*)- and (*S*,*S*)-TADDOL led to the predominant formation of the (*R*)-product. This result is consistent with the suggestion that a very bulky reagent, such as the TADDOLato-modified complex, might, independently from its stereochemical assignment, approach the substrate predominantly from a less-hindered side, indicating a predominant substrate control.



Scheme 22. Reactions of TADDOL-modified vinyloxy ethoxides with 2,3-*O*-isopropylidene-D-glyceraldehyde.

Since cyanohydrins are generally recognised as versatile synthetic intermediates for the preparation of a variety of useful compounds, the development of methods for the enantioselective formation of cyanohydrins from achiral aldehydes has attracted considerable attraction.[45] In this context, a new procedure for asymmetric cyanohydrin synthesis was developed by Maruoka et al., in 2001, employing (*R*,*R*)-TADDOL as a chiral ligand and acetone cyanohydrin as the cyanide source.[46] Thus, in the presence of this chiral ligand, Zr(O-*t*-Bu)$_4$ could serve as an effective promoter for the Meerwein–Ponndorf–Verley cyanation of a range of aldehydes, giving rise to the corresponding cyanohydrins in good yields and enantioselectivities (Scheme 23).

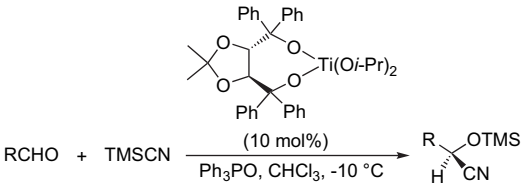
In 2001, Ward et al. studied the enantioselective hydrocyanation of α-alkoxy aldehydes performed in the presence of TMSCN as the cyanide source, (*R*,*R*)-TADDOL as a chiral ligand and TiCl$_2$(O-*i*-Pr)$_2$.[47] It was demonstrated that TMSCN could react with Ti(IV) reagents to produce the corresponding 'TiCN' reagents. These reagents induced the hydrocyanation of α-alkoxy aldehydes with low enantiotopic group selectivity (<2:1). It was established that the 'TiCN' reagents were capable of hydrocyanation, but with low substrate-controlled diastereoselectivity in reactions with α-alkoxy aldehydes. The poor enantiotopic group selectivity observed could be rationalised as resulting from this low diastereoselectivity, despite the respectable



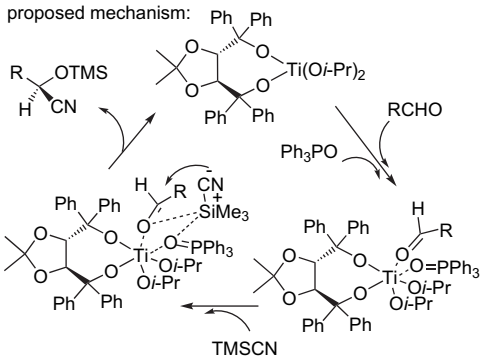
R = $BnCH_2$: 63% ee = 85%
R = *n*-Non: 63% ee = 84%
R = Cy: 55% ee = 79%
R = *t*-Bu: 36% ee = 72%
R = Bn: 47% ee = 59%
R = Ph: 45% ee = 63%
R = 2-Fu: 30% ee = 61%
R = 2-Thio: 28% ee = 54%
R = (*E*)-Ph-CH=CH: 25% ee = 29%

Scheme 23. Zirconium-mediated Meerwein–Ponndorf–Verley cyanation of aldehydes.

levels of enantioface selectivity associated with these reagents in the hydrocyanation of aldehydes. On the other hand, Kim et al. developed, in 2006, a highly efficient double activation catalysis by TADDOL/Ti(O-*i*-Pr)$_4$ and Ph_3PO for the enantioselective cyanosilylation of various aldehydes.[48] This cyanosilylation reaction took place under mild conditions, producing the corresponding trimethylsilyl ethers in excellent yields and moderate-to-good enantioselectivities (≤60% ee), as depicted in Scheme 24. A possible mechanism and transition state in this reaction are also given in Scheme 24.

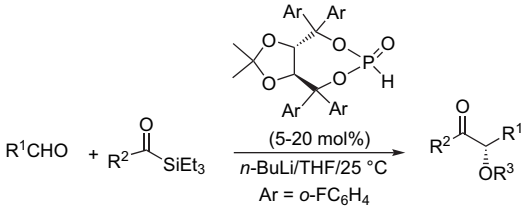


R = Ph: 95% ee = 50%
R = *p*-Tol: 97% ee = 57%
R = *p*-$MeOC_6H_4$: 94% ee = 40%
R = *p*-(*t*-Bu)C_6H_4: 96% ee = 60%
R = 3,4-(F,MeO)C_6H_3: 91% ee = 42%
R = 2-Naph: 87% ee = 52%
R = *m*-$MeOC_6H_4$: 92% ee = 40%
R = 2-Fu: 65% ee = 40%
R = (*E*)-Ph-CH=CH: 92% ee = 44%
R = $BnCH_2$: 95% ee = 59%



Scheme 24. Trimethylsilylcyanation of aldehydes.

The benzoin condensation is the archetypal catalytic reaction in which the carbonyl polarity is inverted via an intermediate, which functions as an acyl anion equivalent. The α-hydroxy carbonyls, which result from benzoin or acyloin condensations are desirable building blocks and comprise a structural motif, which is common among a number of natural products. In 2004, Johnson et al. demonstrated that TADDOL-derived metallophosphites could be useful umpolung catalysts for the enantioselective cross-silyl benzoin reaction.[49] In this reaction, the chiral lithium phosphite formed in situ, via the deprotonation of the corresponding phosphite with *n*-BuLi, catalysed the cross-silyl benzoin reaction between an acyltriethylsilane and an aldehyde to afford the corresponding silyloxy benzoin product. The tetra(*o*-fluorophenyl)-TADDOL phosphite provided the best combination of enantiocontrol and reactivity, while the presence on the catalyst of more powerful electron-withdrawing groups caused a dramatic drop in reactivity, and all other variations on the TADDOL phosphite backbone led to a decrease in selectivity relative to the fluorinated catalyst. This catalyst was applied to the cross-benzoin reaction between a number of acylsilanes and aldehydes, providing high yields and enantioselectivities, as depicted in Scheme 25.



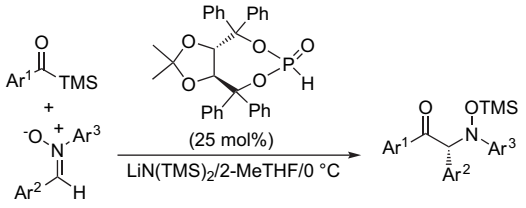
R^1 = R^2 = Ph, R^3 = $SiEt_3$: 84% ee = 82%
R^1 = Ph, R^2 = *p*-ClC_6H_4, R^3 = $SiEt_3$: 75% ee = 82%
R^1 = *p*-ClC_6H_4, R^2 = Ph, R^3 = $SiEt_3$: 82% ee = 87%
R^1 = Ph, R^2 = *p*-$MeOC_6H_4$, R^3 = $SiEt_3$: 87% ee = 91%
R^1 = *p*-$MeOC_6H_4$, R^2 = Ph, R^3 = $SiEt_3$: 83% ee = 88%
R^1 = *p*-ClC_6H_4, R^2 = *p*-$MeOC_6H_4$, R^3 = $SiEt_3$: 83% ee = 90%
R^1 = *p*-$MeOC_6H_4$, R^2 = *p*-ClC_6H_4, R^3 = H: 79% ee = 83%
R^1 = Ph, R^2 = *p*-$(Me_2N)C_6H_4$, R^3 = H: 80% ee = 81%
R^1 = *p*-$(Me_2N)C_6H_4$, R^2 = Ph, R^3 = $SiEt_3$: 86% ee = 86%
R^1 = Ph, R^2 = 2-Fu, R^3 = $SiEt_3$: 65% ee = 85%
R^1 = Ph, R^2 = *i*-Pr, R^3 = $SiEt_3$: 78% ee = 73%
R^1 = Ph, R^2 = *n*-Hex, R^3 = $SiEt_3$: 88% ee = 41%
R^1 = *n*-Hex, R^2 = Ph, R^3 = $SiEt_3$: 72% ee = 67%

Scheme 25. Cross-silyl benzoin reaction.

In 2007, the same workers extended the scope of the preceding methodology to the enantioselective 1,3-silylacylation of a range of nitrones, providing access to the corresponding enantiomerically enriched *N*-aryl α-amino ketones in good yield and with high enantioselectivity of up to 97% ee (Scheme 26).[50] In this case, the reactions were catalysed by (*R*,*R*)-TADDOL phosphite in the presence of $LiN(TMS)_2$ as a base and 2-MeTHF as a solvent. It must be noted that these results constituted the first example of direct enantioselective C-acylation of nitrones.

3. Nucleophilic conjugate additions to electron-deficient C=C double bonds

The enantioselective conjugate addition is a fundamentally important transformation in asymmetric synthesis.[51] In particular, the asymmetric conjugate addition of a dialkylzinc compound to prochiral α,β-unsaturated systems is one of the most powerful synthetic tools in organic chemistry.[52] In this context, Alexakis and Benhaim reported, in 2001, the use of a series of TADDOL-derived chiral phosphorus ligands for the asymmetric conjugate addition of dialkylzinc reagents to alkylidene malonates in the presence of copper triflate as a catalyst.[53] The best enantiomeric excesses were obtained in the presence of ligands in which the TADDOL moiety was not the only asymmetric centre, since these ligands provided an additional chirality at the exocyclic moiety. As an example, the



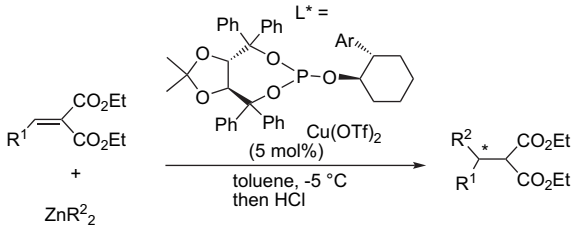
$Ar^1 = Ar^2 = Ph$, $Ar^3 = o\text{-}MeOC_6H_4$: 68% ee = 94%
$Ar^1 = p\text{-}MeOC_6H_4$, $Ar^2 = Ph$, $Ar^3 = o\text{-}MeOC_6H_4$: 77% ee = 97%
$Ar^1 = Ph$, $Ar^2 = p\text{-}MeOC_6H_4$, $Ar^3 = o\text{-}MeOC_6H_4$: 84% ee = 94%
$Ar^1 = Ar^2 = p\text{-}MeOC_6H_4$, $Ar^3 = o\text{-}MeOC_6H_4$: 94% ee = 97%
$Ar^1 = Ph$, $Ar^2 = p\text{-}N(Me)_2C_6H_4$, $Ar^3 = o\text{-}MeOC_6H_4$: 76% ee = 93%
$Ar^1 = p\text{-}MeOC_6H_4$, $Ar^2 = p\text{-}N(Me)_2C_6H_4$, $Ar^3 = o\text{-}MeOC_6H_4$: 36% ee = 94%
$Ar^1 = Ph$, $Ar^2 = o\text{-}Tol$, $Ar^3 = o\text{-}MeOC_6H_4$: 77% ee = 94%
$Ar^1 = p\text{-}MeOC_6H_4$, $Ar^2 = o\text{-}Tol$, $Ar^3 = o\text{-}MeOC_6H_4$: 86% ee = 96%
$Ar^1 = Ar^2 = p\text{-}ClC_6H_4$, $Ar^3 = o\text{-}MeOC_6H_4$: 82% ee = 96%
$Ar^1 = p\text{-}MeOC_6H_4$, $Ar^2 = p\text{-}ClC_6H_4$, $Ar^3 = o\text{-}MeOC_6H_4$: 93% ee = 97%
$Ar^1 = p\text{-}MeOC_6H_4$, $Ar^2 = Ph$, $Ar^3 = 2\text{-}CF_3\text{-}3\text{-}MeOC_6H_3$: 76% ee = 96%
$Ar^1 = p\text{-}MeOC_6H_4$, $Ar^2 = Ph$, $Ar^3 = p\text{-}ClC_6H_4$: 65% ee = 90%

Scheme 26. C-Acylation of nitrones.

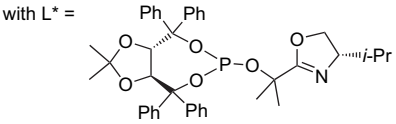
use of ligands containing a chiral substituted cyclohexanol skeleton allowed the corresponding products to be obtained in quantitative yields and good enantioselectivities of up to 73% ee, as depicted in Scheme 27. When similar reactions were carried out in the presence of triethylaluminium instead of dialkylzinc reagents, no enantioselectivity was, however, observed with any of the alkylidene malonates.

In 2001, Feringa et al. reported the synthesis of new chiral bidentate phosphoramidites derived from TADDOL, and involved these dimeric ligands in the copper-catalysed asymmetric addition of $ZnEt_2$ to cyclic α,β-enones.[54] The best results were obtained for 2-cyclohexenone, which gave moderate enantioselectivities (≤38% ee). An asymmetric tandem conjugate addition–aldol reaction, involving 2-cyclopentenone in the presence of benzaldehyde, was also developed in similar conditions, but provided the corresponding product in low diastereoselectivities (≤18% de), as shown in Scheme 28.

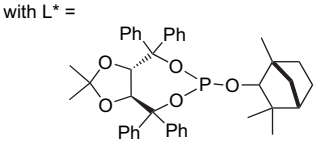
In 2004, Schrader et al. reported a mechanistic study on the conjugate addition of $ZnEt_2$ to cyclohexenone catalysed by various P(III) ligands, providing new insights into its mechanism.[55] These workers postulated a catalytic cycle, depicted in Scheme 29, having as the key steps the oxidative addition of the organocopper(I) species **I** to the enone double bond, followed by the rate-determining reductive elimination of the catalytic copper(I) complex **II** with simultaneous alkyl transfer to the γ-carbon of the enone. The resulting enolate **III** leads to the final product by quenching with water. In this work, a complete in situ conversion of the catalytic amount of $Cu(OTf)_2$ into a Cu(I) species by an excess of $ZnEt_2$ was demonstrated by EPR spectroscopy. Furthermore, experimental evidence was presented in favour of a critical ternary 1:1:1 complex between the enone, $ZnEt_2$ and catalyst, supporting a rate-limiting reductive elimination or carbocupration from a preformed mixed Cu/Zn cluster carrying one ligand when using TADDOL as ligand. The P(III) ligand firmly bound to Cu(III) seemed to lower the activation energy barrier for this process. With TADDOL as a ligand, an extremely powerful 1:1 complex between TADDOL and Cu(I)



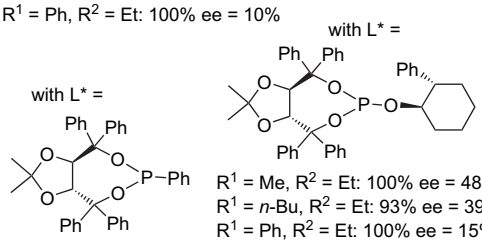
with Ar = Ph:
$R^1 = Me$, $R^2 = Et$: 87% ee = 58%
$R^1 = Me$, $R^2 = n\text{-}Bu$: 86% ee = 50%
$R^1 = n\text{-}Bu$, $R^2 = Et$: 91% ee = 56%
$R^1 = n\text{-}Bu$, $R^2 = Me$: 82% ee = 30%
$R^1 = Ph$, $R^2 = Et$: 93% ee = 52%
with Ar = 1-Naph:
$R^1 = Me$, $R^2 = Et$: 100% ee = 30%
$R^1 = n\text{-}Bu$, $R^2 = Et$: 100% ee = 40%
with Ar = 2-Naph:
$R^1 = Me$, $R^2 = Et$: 89% ee = 65%
$R^1 = n\text{-}Bu$, $R^2 = Et$: 93% ee = 73%



$R^1 = Me$, $R^2 = Et$: 100% ee = 19%
$R^1 = n\text{-}Bu$, $R^2 = Et$: 62% ee = 6%
$R^1 = Ph$, $R^2 = Et$: 100% ee = 22%



$R^1 = Me$, $R^2 = Et$: 100% ee = 10%
$R^1 = n\text{-}Bu$, $R^2 = Et$: 100% ee = 30%
$R^1 = Ph$, $R^2 = Et$: 100% ee = 10%



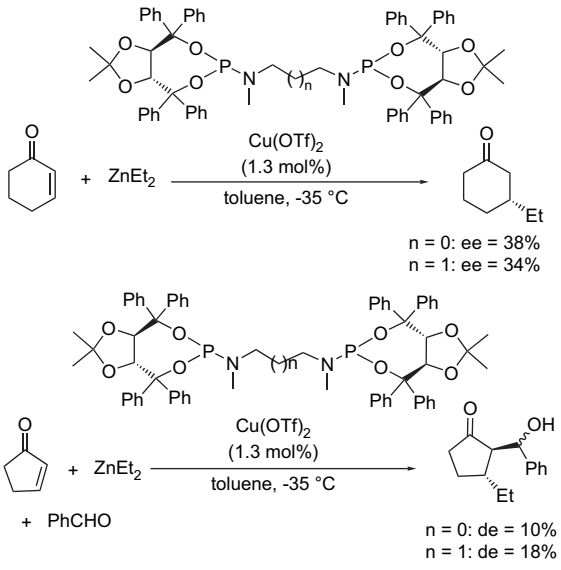
$R^1 = Me$, $R^2 = Et$: 100% ee = 48%
$R^1 = n\text{-}Bu$, $R^2 = Et$: 93% ee = 39%
$R^1 = Ph$, $R^2 = Et$: 100% ee = 15%

$R^1 = Me$, $R^2 = Et$: 100% ee = 20%
$R^1 = n\text{-}Bu$, $R^2 = Et$: 55% ee = 8%
$R^1 = Ph$, $R^2 = Et$: 100% ee = 15%

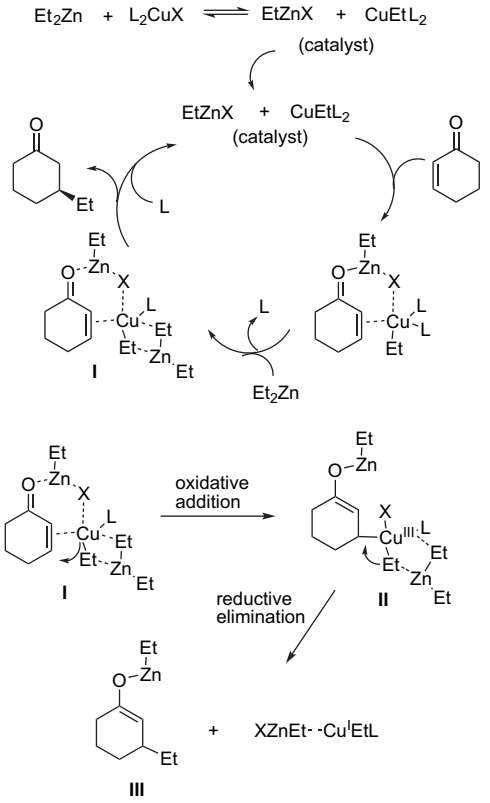
Scheme 27. Conjugate additions of dialkylzinc reagents to alkylidene malonates.

was formed. The high preference for 1:1 complexes could explain the superior performance of TADDOL with respect to the reaction rate and stereoselectivity, since, in the catalytically active species, steric hindrance around the central copper atom was minimised.

In 2006, Palacios and Vicario developed the Cu-catalysed asymmetric conjugate addition of $ZnEt_2$ to α,β-unsaturated imines derived from α-amino acids. The reaction was performed in the presence of a TADDOL-derived phosphoramidite complex, affording the corresponding chiral α-dehydroamino esters bearing a stereogenic centre in the γ-position.[56] Enantioselectivities of up to 88% ee were obtained, along with good yields, as shown in Scheme 30. On the basis of the previously mentioned mechanistic studies, concerning the conjugate addition of organozincs to enones (Scheme 29),[55] these workers proposed the catalytic cycle presented in Scheme 30, involving an initial alkyl transfer from $ZnEt_2$ to the copper salt, followed by the formation of the

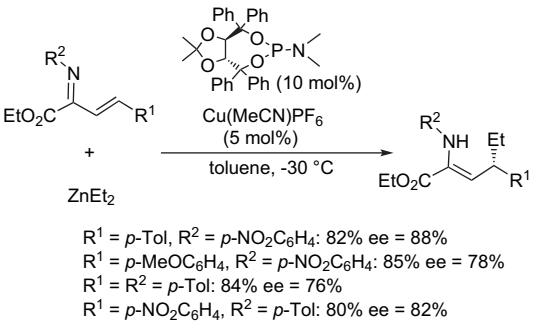


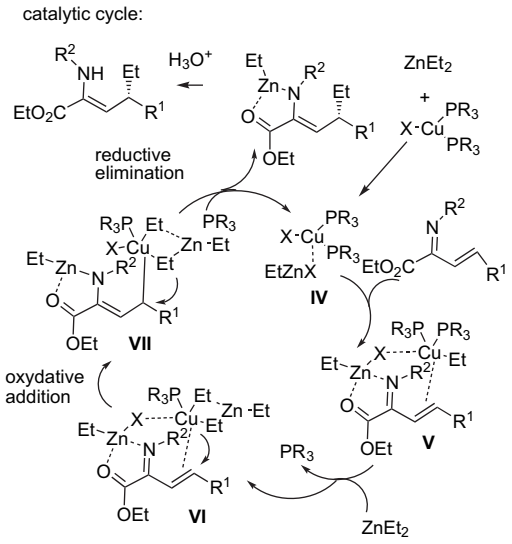
Scheme 28. Conjugate additions of $ZnEt_2$ to cyclic α,β-enones.



Scheme 29. Mechanism of Cu(I)-catalysed conjugate addition of $ZnEt_2$ to cyclohexenone.

π-complex **IV** between the soft Cu species and the double bond of the α,β-unsaturated imine, where the imine nitrogen and the carbonyl oxygen are chelated with the hard Lewis acid, EtZnX, forming a five-membered ring. The coordination of both copper and zinc with the counteranion in species **V** would be essential for the exclusive formation of the *Z*-enamine, since, by means of such coordination, the necessary less stable pseudo-cis-configuration is fixed in the α,β-unsaturated system. Then, a second molecule of $ZnEt_2$ is captured by the Cu species with simultaneous release of one of the phosphoramidite ligand molecules to form a highly

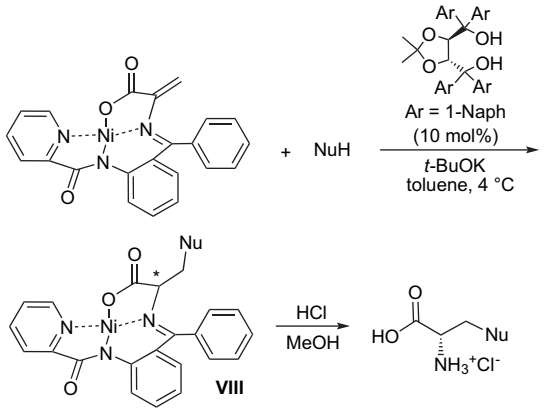




Scheme 30. Conjugate addition of $ZnEt_2$ to α,β-unsaturated imines.

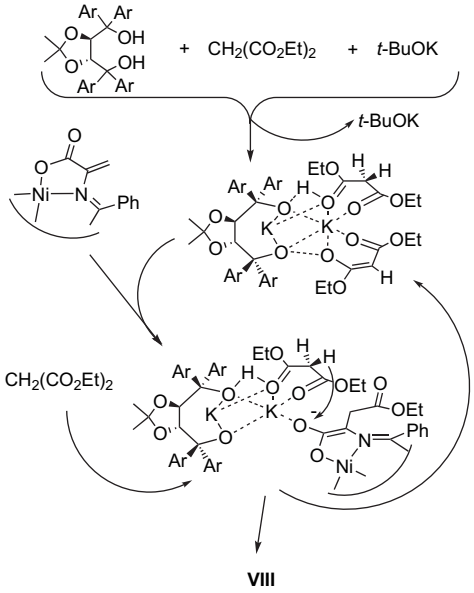
nucleophilic Cu/Zn cluster **VI**, which undergoes an oxidative addition of the organocopper reagent to the double bond to afford the σ-complex **VII**. Finally, a reductive elimination with concomitant formation of the C–C bond yields the enolate **VIII** (probably in the thermodynamically more stable dimeric form), which is then quenched with water to give the final α-dehydroamino ester.

With the aim of developing a novel route to amino acids, Seebach et al. have reported the synthesis of a new type of substrate based on an achiral Ni(II) complex of a Schiff base of dehydroalanine.[57] An efficient catalytic method of asymmetric conjugate addition of CH acids to these novel Michael acceptors was successfully developed, using TADDOLs as catalysts and providing the corresponding chiral amino acids after hydrolysis of the intermediate nickel complexes (Scheme 31). A series of TADDOL derivatives were tested as catalysts, showing that the TADDOL derivative bearing 1-naphthyl groups invariably led to the best enantioselectivities, when using *t*-BuOK and toluene as the base and solvent of choice, respectively. The best enantioselectivities of up to 80% ee were obtained in the presence of nucleophiles such as malonic ester derivatives, whereas nucleophiles, such as thiophenol or amines, reacted with the Schiff base of dehydroalanine without any detectable enantioselectivity. In these reactions, the enantioselectivity was determined in the protonation step of the intermediate enolate. In order to explain the enantioselectivity of the process, these workers have proposed a speculative mechanism, as depicted in Scheme 31, which might include the formation of a mixed chelate of TADDOL and malonic ester, with the latter functioning to deliver a proton to quench the intermediate enolate of **VIII**. The function of TADDOL might be to increase the malonic ester acidity by hydrogen bonding and forming a chiral



NuH = $CH_2(CO_2Et)_2$: 80% ee = 80%
NuH = $AcNHCH(CO_2Et)_2$: 65% ee = 78%
NuH = $BocNHCH(CO_2Et)_2$: 56% ee = 64%
NuH = PhSH: 64% ee < 1%

proposed mechanism for Michael addition of malonic ester:

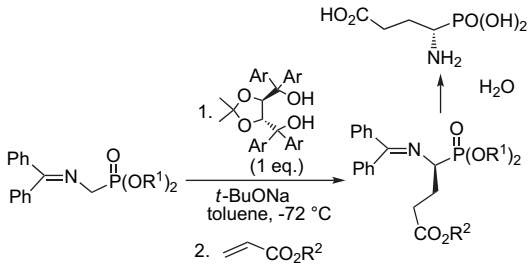


Scheme 31. Conjugate addition of nucleophiles to Schiff base Ni(II) complex of dehydroalanine.

environment for recognition of the enantiotopic enolate of **VIII** responsible of proton transfer.

α-Aminophosphonic acids, the phosphonic analogues of amino acids, have a potential biological importance as the tetrahedral structure of the phosphonic moiety mimics the tetrahedral transition state of the peptide hydrolysis. In this context, Jaszay et al. have successfully developed a novel approach in the synthesis of chiral phosphoglutaminic acid derivatives on the basis of a catalytic enantioselective Michael addition of a protected phosphoglycine synthon, a very weak CH acid.[58] Indeed, the Schiff base of the aminomethylphosphonic acid ethyl or *tert*-butyl ester could be condensed onto ethyl or *tert*-butyl acrylate in the presence of NaO-*t*-Bu as a base and a TADDOL derivative as a chiral ligand, providing the corresponding chiral phosphonic analogues of glutaminic acid derivatives in moderate-to-good enantioselectivities, as shown in Scheme 32 (≤72% ee).

The conjugate addition of acyl anion equivalents to α,β-unsaturated carbonyl compounds is a useful and direct approach to the synthesis of 1,4-dicarbonyl compounds, which can

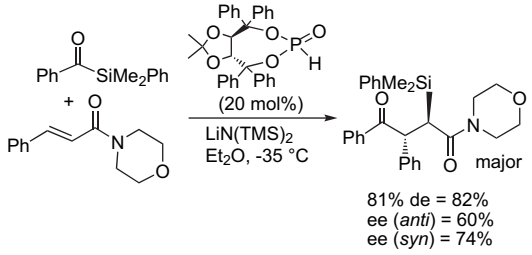


R^1 = Et, R^2 = *t*-Bu, Ar = Ph: 95% ee = 72%
R^1 = R^2 = Et, Ar = 2-Naph: 100% ee = 59%
R^1 = *i*-Pr, R^2 = *t*-Bu, Ar = Ph: 60% ee = 50%

Scheme 32. Conjugate addition of aminomethylphosphonic acid ethyl and *tert*-butyl esters to acrylates.

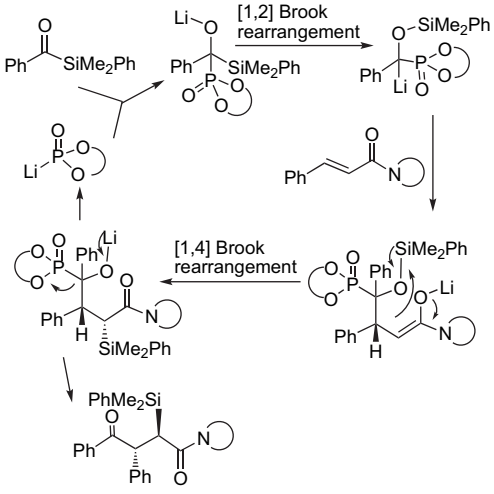
simultaneously introduce two new stereocentres.[59] In parallel with the development of aldehydes as acyl donors for conjugate additions, acylsilanes have shown promise as suitable pronucleophiles in conjugate addition reactions. As an example, Johnson et al. have achieved an enantioselective metallophosphite-catalysed conjugate addition of an acylsilane, such as benzoyldimethylphenylsilane, to an unsaturated amide, giving rise to the corresponding 1,4-diketone with high diastereoselectivity and moderate enantioselectivity (Scheme 33).[60] The proposed catalytic cycle, as depicted in Scheme 33, was initiated by the addition of the TADDOL-derived phosphite and a [1,2] Brook rearrangement. The catalyst release was apparently triggered after conjugate addition by an unusual diastereoselective retro [1,4] Brook rearrangement.

The scope of this methodology was extended, in 2006, by the same workers, who selected a menthone-derived TADDOL phosphite as the most efficient catalyst for the enantioselective addition of *p*-methoxybenzoylcyclohexyldimethylsilane to a variety of aryl



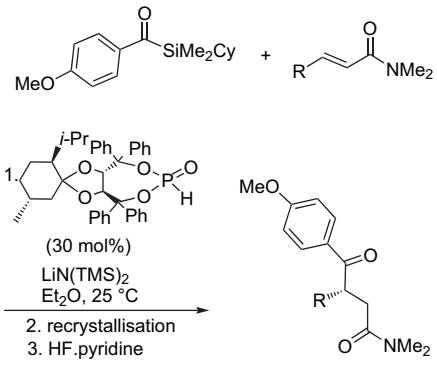
81% de = 82%
ee (*anti*) = 60%
ee (*syn*) = 74%

proposed mechanism:



Scheme 33. Conjugate addition of benzoyldimethylphenylsilane to unsaturated amide.

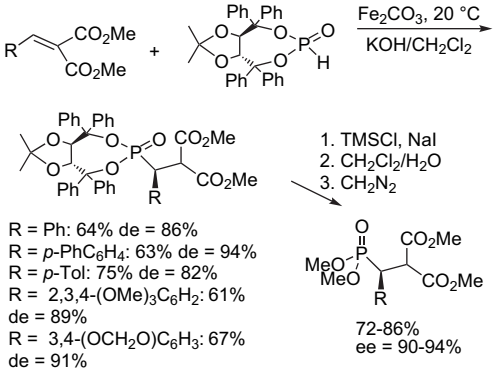
and alkyl *N*,*N*-dimethylacrylamide derivatives.[61] The corresponding chiral diketones were obtained in good yield and high enantioselectivity under mild reaction conditions and after desilylation (Scheme 34). Thus, the structural features of the menthone-modified catalyst resulted in enhancing the enantiocontrol of the reaction. An X-ray diffraction study of the catalyst revealed that the isopropyl group of the menthone ketal influenced the position of the *syn*-pseudoaxial phenyl group in the TADDOL structure.



R = Ph: 68% ee = 99%
R = *p*-$MeOC_6H_4$: 63% ee = 92%
R = *p*-Tol: 78% ee = 90%
R = *m*-Tol: 67% ee = 99%
R = 2-Fu: 15% ee = 24%
R = *p*-ClC_6H_4: 66% ee = 98%
R = *p*-$CF_3C_6H_4$: 80% ee = 90%
R = 2-Naph: 66% ee = 97%
R = Me: 56% ee = 86%
R = Et: 82% ee = 71%
R = *N*-tosylindol-3-yl: 60% ee = 97%

Scheme 34. Conjugate addition of *p*-methoxybenzoylcyclohexyldimethylsilane to unsaturated amides.

In addition, the ready access to, and the easy recovery of, TADDOLs allow their use as stoichiometric additives or reagents. As an example, Enders et al. have described the diastereoselective Fe_2O_3-mediated Michael addition of a chiral TADDOL-derived phosphite to α,β-unsaturated malonates.[62] This reaction constituted the first example of an asymmetric P–C bond formation under heterogeneous conditions. The easy cleavage of the chiral auxiliary from the addition products led to the corresponding optically active β-substituted β-phosphonomalonates in good yields and high enantioselectivities. This inexpensive and readily accessible Fe_2O_3/KOH system could be successfully applied under mild conditions to a range of aromatic α,β-unsaturated malonates, as depicted in Scheme 35, but, however, only unsatisfactory diastereoselectivities (15–30% des) were observed when using α,β-unsaturated



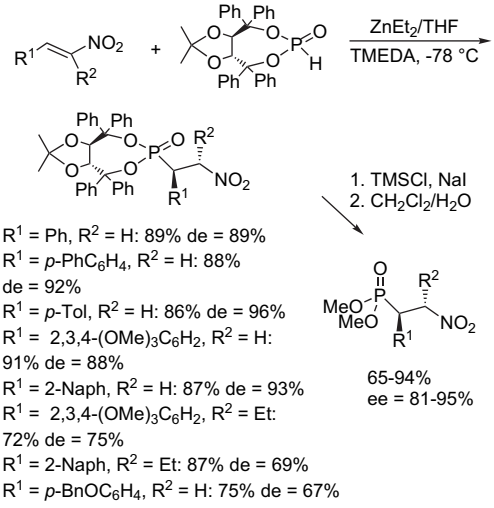
R = Ph: 64% de = 86%
R = *p*-PhC_6H_4: 63% de = 94%
R = *p*-Tol: 75% de = 82%
R = 2,3,4-$(OMe)_3C_6H_2$: 61% de = 89%
R = 3,4-$(OCH_2O)C_6H_3$: 67% de = 91%

72-86%
ee = 90-94%

Scheme 35. Conjugate addition of TADDOL-derived phosphite to α,β-unsaturated malonates.

malonates bearing an aliphatic substituent, such as a cyclohexyl or an isopropyl group.

Since only a few methods for the asymmetric synthesis of enantiomerically pure phosphonates have been described,[63] due to the difficulty of forming the P–C bond and in spite of the biological importance of these compounds,[64] this novel methodology constituted the first broadly applicable method of asymmetric P–C bond formation via conjugate addition. The extension of this methodology to the use of nitroalkenes as Michael acceptors was reported by the same workers, in 2006, providing the corresponding α-substituted β-nitrophosphonates.[62] In this case, the reactions were carried out in the presence of $ZnEt_2$ and a chelating amine, such as TMEDA. Under these conditions, high yields and diastereoselectivities were obtained, as shown in Scheme 36. The racemisation-free cleavage of the auxiliary led to the corresponding α-substituted β-nitrophosphonates in high yields and enantioselectivities. In addition, this method could be applied to the synthesis of α,β-disubstituted β-nitrophosphonates, bearing two new neighbouring stereogenic centres, in good yields and moderate diastereoselectivities, by using α,β-disubstituted nitroalkenes (Scheme 36).



R^1 = Ph, R^2 = H: 89% de = 89%
R^1 = *p*-PhC_6H_4, R^2 = H: 88% de = 92%
R^1 = *p*-Tol, R^2 = H: 86% de = 96%
R^1 = 2,3,4-$(OMe)_3C_6H_2$, R^2 = H: 91% de = 88%
R^1 = 2-Naph, R^2 = H: 87% de = 93%
R^1 = 2,3,4-$(OMe)_3C_6H_2$, R^2 = Et: 72% de = 75%
R^1 = 2-Naph, R^2 = Et: 87% de = 69%
R^1 = *p*-$BnOC_6H_4$, R^2 = H: 75% de = 67%

65-94%
ee = 81-95%

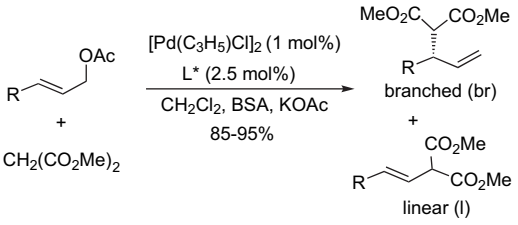
Scheme 36. Conjugate addition of TADDOL-derived phosphite to nitroalkenes.

4. Nucleophilic substitutions

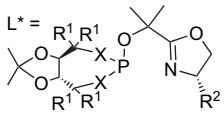
4.1. Allylic substitutions

Allylic compounds have been of synthetic, mechanistic and biological importance for over 50 years. Asymmetric allylic substitution is a fundamental transformation in organic synthesis and is one of the most powerful tools for the formation of carbon–carbon and carbon–heteroatom bonds.[65] Mild reaction conditions and high tolerance of functional groups are important advantages, which make these reactions potentially useful methods for the preparation of a wide range of chiral molecules. The vast majority of the studies reported apply palladium as the metal catalyst of choice, involving a plethora of ligands, mainly with phosphorus and/or nitrogen donor atoms.[65a] Thus, a number of highly efficient chiral *P*,*N*-bidentate ligands have been developed in recent years, and applied to the asymmetric allylic substitution reaction. As an example, Pfaltz and Hilgraf reported, in 2005, the synthesis of a series of novel P,N-ligands containing a chiral oxazoline ring and a cyclic phosphite group derived from TADDOL as a second chiral unit.[66] These TADDOL phosphite-oxazoline ligands were successfully employed in palladium-catalysed allylic alkylations of

unsymmetrical substituted allyl substrates with dimethyl malonate, providing a mixture of the corresponding branched and linear regioisomers in high yields. In most cases, the reaction occurred with good regiocontrol and gave good-to-high enantioselectivities of up to 94% ee, as shown in Scheme 37.



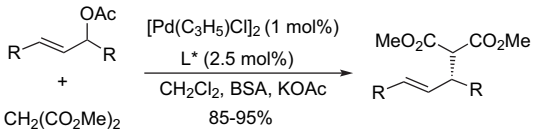
R = Ph, L* = L^3: br/l = 21/79 ee = 97%
R = 2-Naph, L* = L^1: br/l = 66/34 ee = 94%
R = Me, L* = L^3: br/l = 33/67 ee = 39%
R = *n*-Pr, L* = L^3: br/l = 8/92 ee = 62%



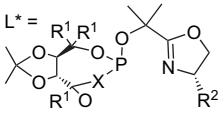
L^1: R^1= Ph, R^2 = *t*-Bu, X = O
L^2: R^1= R^2 = Ph, X = O
L^3: R^1= Ph, R^2 = *t*-Bu, X = NMe

Scheme 37. Allylic alkylation of unsymmetrical allyl acetates.

In addition, these ligands were investigated in the palladium-catalysed allylic alkylation of symmetrically substituted allyl substrates, providing, in similar conditions, only moderate enantioselectivities, as depicted in Scheme 38.[66]



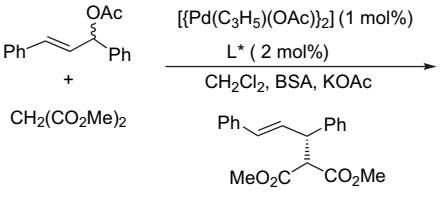
R = Ph, L* = L^2: ee = 56%
R = Et, L* = L^1: ee = 61%

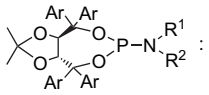


L^1: R^1= Ph, R^2 = *t*-Bu
L^2: R^1= R^2 = Ph

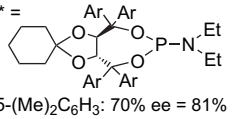
Scheme 38. Allylic alkylation of symmetrical allyl acetates.

On the other hand, the number of chiral monodentate ligands that have been studied in palladium-catalysed asymmetric allylic transformations is still rather limited. The reports on the application of chiral monodentate ligands in allylic alkylations deal almost without exception with chiral phosphines and, especially, chiral phosphoramidite and phosphite ligands, which have become increasingly important, because of their synthetic availability, high resistance to oxidation and low cost. Additionally, in comparison with traditional phosphines, chiral phosphoramidites and phosphites seem to be more versatile ligands. In this context, van Leeuwen et al. showed, in 2004, that bulky monodentate phosphoramidite ligands, based on TADDOL backbones, could be successfully employed in the palladium-catalysed allylic alkylation reaction with carbon nucleophiles, such as dimethyl malonate.[67] Indeed, the results obtained with these ligands show interesting features, which differ considerably from the results generally obtained with symmetrical bidentate ligands, especially with respect to regioselectivity. From the studies on isolated complexes, it was concluded that, in the allylpalladium complexes, only one ligand could coordinate to the metal centre. The most important feature of the reaction seemed to be the bulkiness of the ligand, resulting in the enforced monocoordination to palladium, which led to the enhanced reaction rates and high enantioselectivities. Due to this monocoordination, high enantioselectivities of up to 93% ee could be obtained for the allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in the presence of these bulky chiral phosphoramidites. The enantioselectivities of the reactions were, however, significantly lower for unsymmetrically substituted allyl compounds, as shown in Scheme 39.

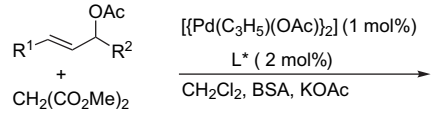


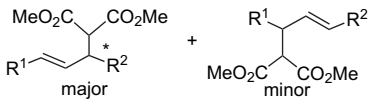
with L* = 

R^1 = R^2 = Et, Ar = 3,5-$(Me)_2C_6H_3$:
> 99% ee = 89%
R^1 = Me, R^2 = (*R*)-CH(Me)Ph, Ar = 3,5-$(Me)_2C_6H_3$:
> 99% ee = 87%
R^1 = Me, R^2 = (*S*)-CH(Me)Ph, Ar = 3,5-$(Me)_2C_6H_3$:
> 99% ee = 92%
R^1 = R^2 = *i*-Pr, Ar = Ph:
> 99% ee = 73%
R^1 = R^2 = Et, Ar = 2-Naph:
86% ee = 61%
R^1,R^2 = $(CH_2)_2$-N(Me)-$(CH_2)_2$, Ar = 3,5-$(Me)_2C_6H_3$:
ee = 83%

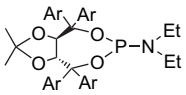
with L* = 

Ar = 3,5-$(Me)_2C_6H_3$: 70% ee = 81%





R^1 = Ph, R^2 = Me: > 95% > 99:1 ee (major) = 32%
R^1 = H, R^2 = Ph: > 99% > 94:6 ee (major) = 18%

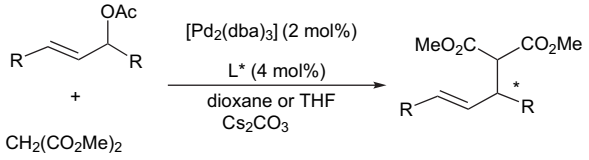
with L* = 

Ar = 3,5-$(Me)_2C_6H_3$

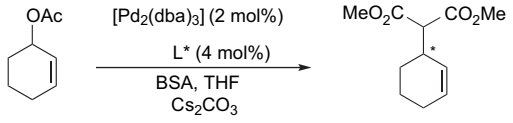
Scheme 39. Allylic alkylations of symmetrical and unsymmetrical allyl acetates.

More recently, Alexakis et al. reported the use of chiral monodentate TADDOL-derived phosphites in the asymmetric allylic alkylation of a range of symmetrical allyl acetates with dimethyl

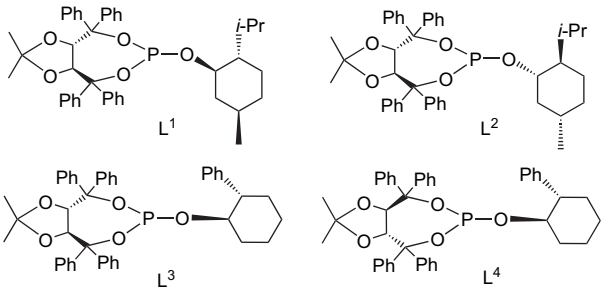
malonate.[68] As shown in Scheme 40, the combination of Cs_2CO_3 as base and dioxane or THF as the solvent allowed moderate-to-good enantioselectivities to be achieved. The ligands prepared from (−)- and (+)-menthol gave better enantioselectivities than those bearing a chiral cyclohexane.



R = Ph, L* = L^1: 100% ee = 79% (*R*)
R = Ph, L* = L^2: 100% ee = 38% (*R*)
R = Ph, L* = L^3: 100% ee = 22% (*S*)
R = Ph, L* = L^4: 100% ee = 6% (*R*)
R = Me, L* = L^1: 93% ee = 46% (*R*)
R = Me, L* = L^2: 78% ee = 45% (*R*)
R = Me, L* = L^3: 69% ee = 4% (*R*)
R = Me, L* = L^4: 35% ee = 29% (*S*)



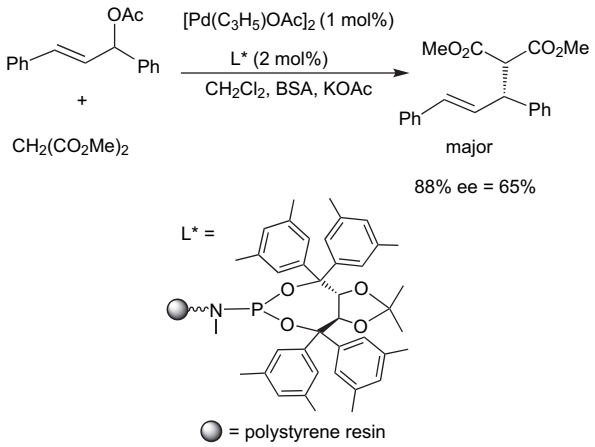
L* = L^1: 100% ee = 40% (*S*)
L* = L^2: 94% ee = 49% (*S*)
L* = L^3: 45% ee = 34% (*S*)
L* = L^4: 77% ee = 36% (*R*)



Scheme 40. Allylic alkylations of symmetrical allyl acetates.

Very recently, Jiang and Meng have applied polymer-supported TADDOL-based phosphoramidites to the palladium-catalysed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate, affording the corresponding chiral product with a good enantioselectivity and a high yield.[69] It was shown that the enantioselectivity of the reaction was very sensitive to the modification of the aryl substituents in the TADDOL backbone. The best enantioselectivity (65% ee) was obtained by using a resin-supported bulky monodentate phosphoramidite ligand, as depicted in Scheme 41, which could be recycled three times without a substantial decrease in the conversion and enantioselectivity. Moreover, when the reaction was carried out with allylic substrates containing smaller substituents, such as cinnamyl or α-vinylbenzyl acetate, both the conversion and the enantioselectivity were very low.

In addition, the asymmetric palladium-catalysed allylic amination reaction of allyl carbonates has been developed by Takacs et al., using self-assembled chiral TADDOL-derived bidentate P,P-ligands.[70] These chiral diphosphites were prepared starting from a racemic mixture of monosubstituted (*R*,*R*)- and (*S*,*S*)-bisoxazoline (box) ligands, which was reacted with $Zn(OAc)_2$, resulting in the

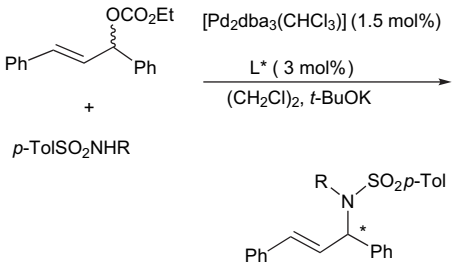


Scheme 41. Allylic alkylation in the presence of resin-supported TADDOL-based phosphoramidite.

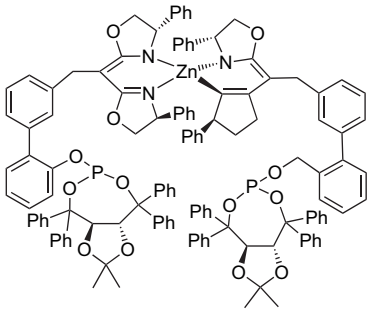
formation of the corresponding neutral $(box)_2Zn$ complex. This complex provided to be a quite remarkable compound, providing an extraordinarily simple and efficient method to prepare new chiral bidentate P,P-ligands. Thus, a series of monosubstituted box derivatives were prepared, each member bearing a pendant TADDOL-derived monophosphite. This metal-directed self-assembly has allowed a library of novel chiral diphosphites to be prepared. The chiral heterobimetallic catalyst of the allylic amination reaction employed zinc as an important structural element and palladium as a catalyst metal, offering a remarkably flexible and effective approach to catalyst design. As shown in Scheme 42, excellent yields and enantioselectivities were obtained for the allylic amination reaction of 1,3-diphenyl-2-propenyl ethyl carbonate with a range of *N*-substituted sulfonamides.

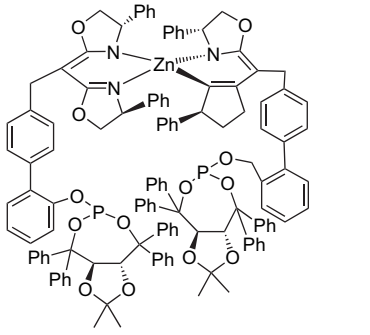
Metals other than palladium have also been involved in catalysing the asymmetric allylic substitution reaction. As an example, Helmchen et al. have reported the asymmetric iridium(I)-catalysed allylic alkylation of monosubstituted allylic acetates with a chiral TADDOL-derived phosphoramidite as a ligand.[71] Symmetrical, as well as unsymmetrical, allyl acetates provided, however, only low yields combined with very low enantioselectivities, as shown in Scheme 43. It must be noted that in this study, based on the use of iridium as metal, much better enantioselectivities of up to 94% ee were obtained in the presence of chiral phosphoramidites derived from 2,2′-binaphthol.

In addition, the copper(I)-catalysed allylic substitution reaction has generated a great deal of interest in recent years and several methods have been developed for the control of both regio- and stereochemistry in this reaction. An advantage of this approach is that a broad range of organometallic compounds, such as organolithium, Grignard and organozinc reagents, can be used in the allylic substitutions. In 2001, Alexakis et al. reported highly efficient enantioselective copper-catalysed S_N2' allylic substitutions of cinnamyl chloride with a range of Grignard reagents, using a series of chiral phosphorus ligands.[72] Among these, a ligand derived from (*R*,*R*)-TADDOL and (−)-*N*-methylephedrine showed a remarkably increased asymmetric induction over the other ligands tested, achieving enantioselectivities of up to 73% ee (Scheme 44). In this study, it was shown that the choice of the leaving group carried by the allyl substrate was critical to the regio- and enantioselectivity. Therefore, the use of cinnamyl bromide instead of cinnamyl chloride caused a significant drop in enantioselectivity (38% ee instead of 73% ee for the reaction with EtMgBr), while, with cinnamyl acetate, no asymmetric induction was observed. On the other hand, alkylmagnesium bromides were clearly preferable to other Grignard salts, giving greatly increased enantiomeric excesses (Scheme 44).

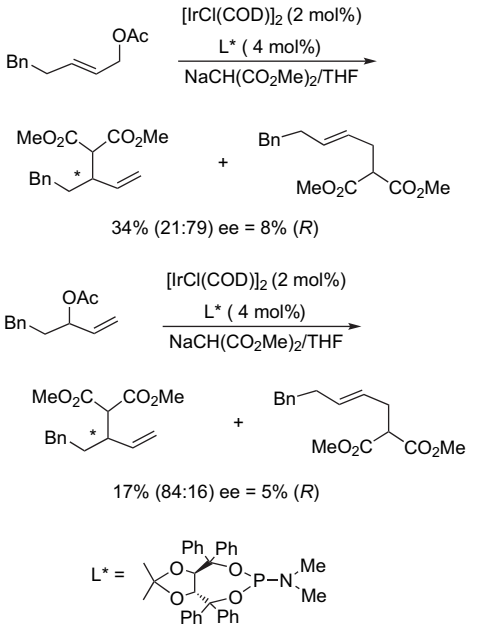


R = Me, L* = L^2: 88% ee = 87%
R = *n*-Bu, L* = L^1: 83% ee = 90%
R = *i*-Pr, L* = L^2: 74% ee = 95%
R = Ph, L* = L^1: 92% ee = 88%

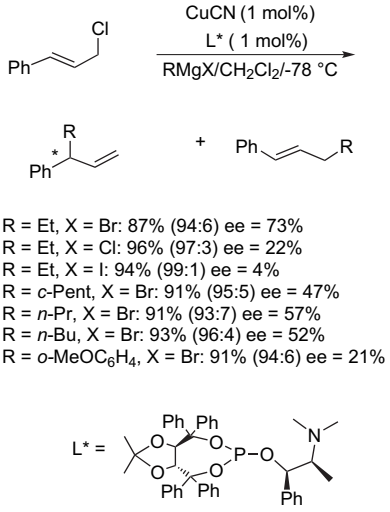




Scheme 42. Allylic amination of 1,3-diphenyl-2-propenyl ethyl carbonate.



Scheme 43. Ir(I)-catalysed allylic alkylations of allyl acetates.

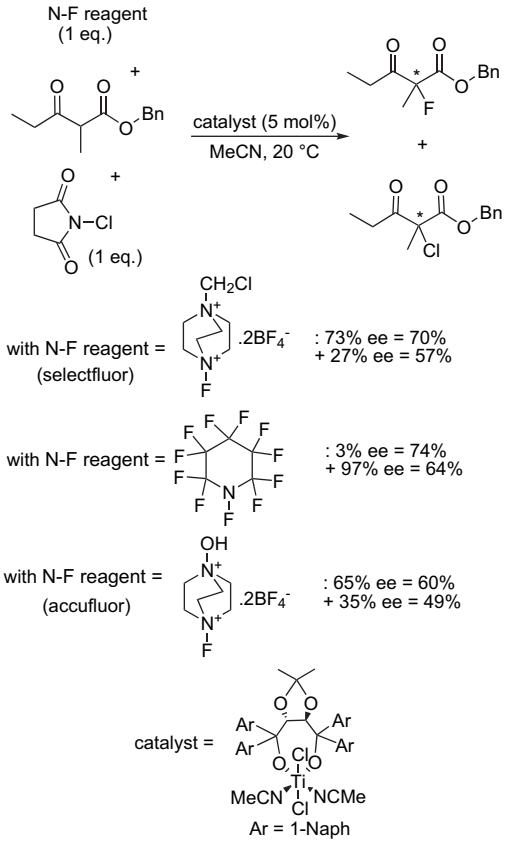


R = Et, X = Br: 87% (94:6) ee = 73%
R = Et, X = Cl: 96% (97:3) ee = 22%
R = Et, X = I: 94% (99:1) ee = 4%
R = *c*-Pent, X = Br: 91% (95:5) ee = 47%
R = *n*-Pr, X = Br: 91% (93:7) ee = 57%
R = *n*-Bu, X = Br: 93% (96:4) ee = 52%
R = *o*-$MeOC_6H_4$, X = Br: 91% (94:6) ee = 21%

Scheme 44. Cu(I)-catalysed allylic substitution of cinnamyl chloride with Grignard reagents.

4.2. α-Halogenations of carbonyl compounds

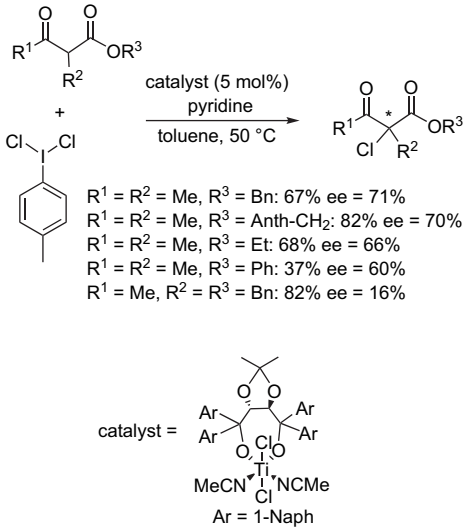
Although organic molecules containing fluorine are extremely rare in nature,[73] organocompounds are becoming increasingly important in medicinal chemistry and as crop-protection agents.[74] Consequently, the discovery of efficient stereoselective C–F bond-forming reactions is one of the most fascinating aspects of modern organofluorine chemistry.[75] A reason for the great interest in this topic is the far-reaching implications in terms of reactivity, solubility and stability of fluorinated organic compounds. Indeed, even a single *F*-substituent may be responsible for the improved resistance against metabolic degradation of biologically active compounds, in particular drugs and crop-protection agents. A wide collection of reagents and synthetic methods is currently available for the selective introduction of fluorine into organic molecules. In particular, TADDOLs have been demonstrated to be excellent chiral ligands in asymmetric halogenations, such as fluorinations.[76] The first catalytic enantioselective electrophilic fluorination, described by Togni and Hintermann in 2000, concerned to the fluorination of β-keto esters performed with selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate)) as the fluorinating agent in the presence of a [$TiCl_2$(TADDOLato)] catalyst (with TADDOL-bearing 1-naphthyl groups), providing up to 90% ees, along with excellent yields (85–95%).[76a,77] In addition, these workers studied the chlorination of β-keto esters in similar conditions, but with *N*-chlorosuccinimide as the chlorinating agent instead of selectfluor, which gave comparable enantioselectivities of up to 88% ee combined with excellent yields (83–97%).[76b] In contrast, the analogous bromination performed with *N*-bromosuccinimide was much less selective (≤25% ee).[76b] In order to assess the relative fluorinating activity of various electrophilic N–F reagents (containing an N–F bond), Togni et al. developed, in 2004, catalytic fluorination/chlorination competition experiments of a β-keto ester in the presence of a [$TiCl_2$(TADDOLato)] catalyst.[78] These halogenation experiments were conducted in the presence of a mixture of 1 equiv of *N*-chlorosuccinimide and 1 equiv of a chosen fluorinating agent, as shown in Scheme 45. The most powerful fluorinating reagent tested was selectfluor, with enantioselectivities of 70% and 57% ee for the corresponding fluorinated and chlorinated products, respectively (Scheme 45). This fluorinating agent, selectfluor, was shown to react more than 100-fold faster than undecafluoropiperidine.



Scheme 45. Competitive halogenations of β-keto esters.

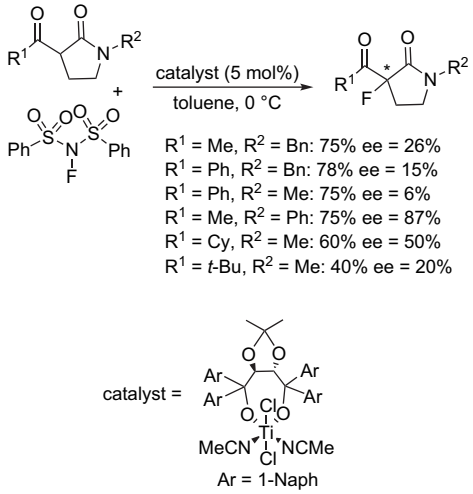
In 2004, these workers showed for the first time that highly reactive hypervalent dichloro(4-methyl phenyl)iodine could be employed in the catalytic asymmetric chlorination of β-keto esters in the presence of the same [$TiCl_2$(TADDOLato)] catalyst.[79] Good yields of the corresponding chlorinated products were obtained in these conditions, along with enantioselectivities of up to 71% ee, as shown in Scheme 46. It was noted that the enantioselectivity of the reaction showed a remarkable temperature dependence, with the maximum selectivity being obtained at 50 °C.

Due to their structure and versatile functional groups, α-acyl-γ-lactams are extremely interesting, since they may act as valuable building blocks for the synthesis of molecules with potentially



Scheme 46. Chlorination of β-keto esters with hypervalent iodine compound.

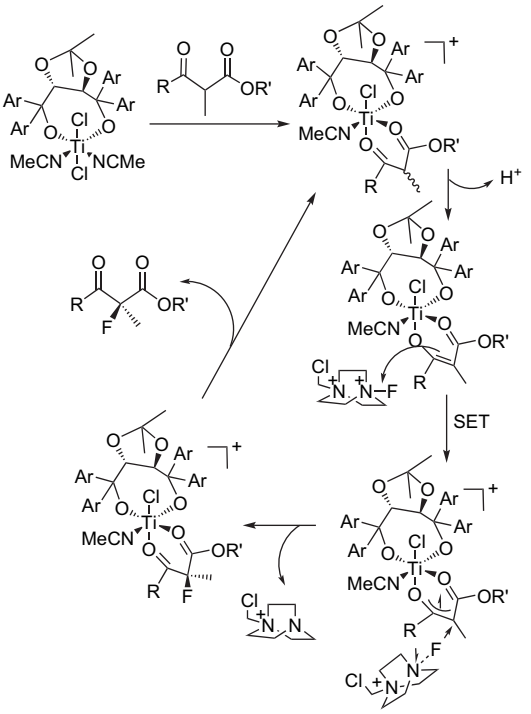
useful biological activity. In this context, Togni et al. developed, in 2006, the enantioselective fluorination of α-acyl-γ-lactams performed in the presence of *N*-fluorobenzenesulfonimide (NFSI) as the fluorinating agent and a [$TiCl_2$(TADDOLato)] catalyst.[80] The reaction achieved the corresponding fluorinated products in moderate-to-good enantioselectivities, as shown in Scheme 47.



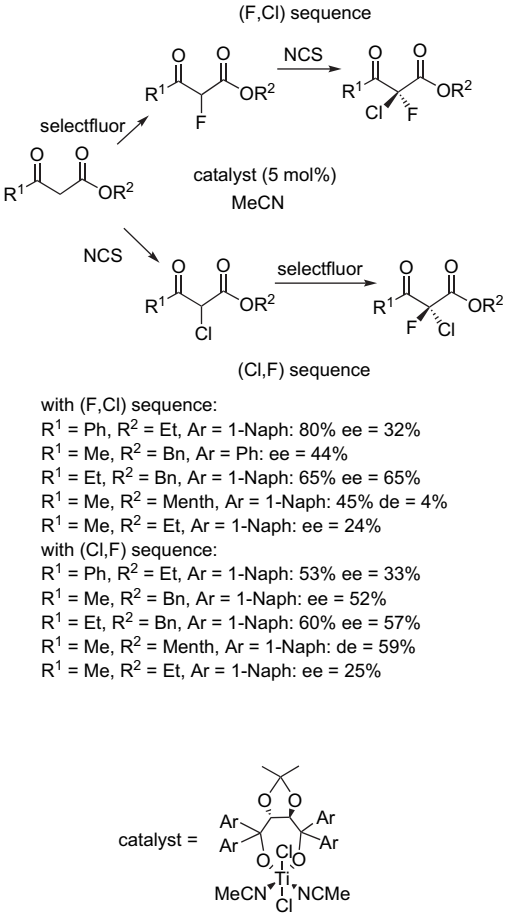
Scheme 47. Fluorination of α-acyl-γ-lactams.

There was a long-standing debate about the reaction mechanism for the electrophilic fluorination reaction with N–F reagents. In particular, it was controversial whether the reaction occurred via a single-electron transfer (SET) or a simple nucleophilic substitution (S_N2) at the fluorine atom. On the basis of QM/MM studies of the fluorination reaction, the same workers have shown that the C–F bond-forming step involved a single-electron transfer. A second important aspect revealed by the calculations concerned the structure of the intermediates and the specific role of the 1-naphthyl substituents on the chiral ligand in determining the stereochemical course of the reaction.[80,81] This feature explains the fact that, in all these asymmetric halogenations involving 1,3-dicarbonyl compounds, the most selective catalyst contains a TADDOL-bearing 1-naphthyl groups, and all other ligands tested gave much lower enantioselectivities. As shown in Scheme 48, the β-keto ester coordinates to the catalyst as an enolate and substitutes one of the two chlorides and one of the acetonitrile molecules. The resulting octahedral monochloro Ti(carbonylenolato) complex is the reactive species, which undergoes a single-electron transfer with the fluorinating agent.

In addition, this concept was further extended to the asymmetric α-heterodihalogenation of β-keto esters, providing the corresponding α-chloro-α-fluoro-β-keto esters according to two protocols.[82] In the first protocol (F,Cl), a fluorination reaction performed with selectfluor in the presence of a [$TiCl_2$(TADDOLato)] catalyst was achieved to form a fluorinated intermediate. This intermediate was then enantioselectively chlorinated by *N*-chlorosuccinimide. In the second protocol (Cl,F), the halogenation sequence was inverted. Although the selectivities of the reactions were not very high (≤65% ee), the most important finding of this study was that the sequence of addition of the halogenating agents determined the sense of the chiral induction. Thus, it was possible to form either enantiomer of the product preferentially, just by choosing the order of the two halogenation steps in this one-pot tandem process (Scheme 49). This very rare observation in asymmetric catalysis was explained by assuming that the first halogen was introduced in a nonstereoselective manner and that the overall



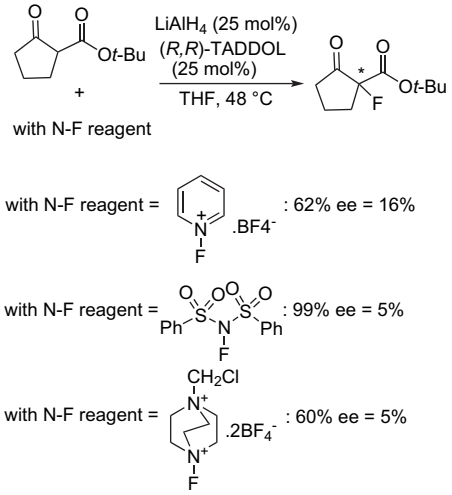
Scheme 48. Mechanism for Ti-catalysed fluorination of β-keto esters.



Scheme 49. α-Heterodihalogenations of β-keto esters.

stereochemical outcome was solely determined by the second halogenation step.

Finally, Cahard and Ma have screened various metals to catalyse the fluorination of β-keto esters in the presence of TADDOL.[83] In particular, heterobimetallic Al–Li–TADDOL complexes in the presence of a fluorinating agent, such as *N*-fluoropyridinium tetrafluoroborate, allowed the corresponding α-fluoro-β-keto esters to be obtained in good-to-excellent yields, but with low enantioselectivities (≤16% ee), as depicted in Scheme 50.

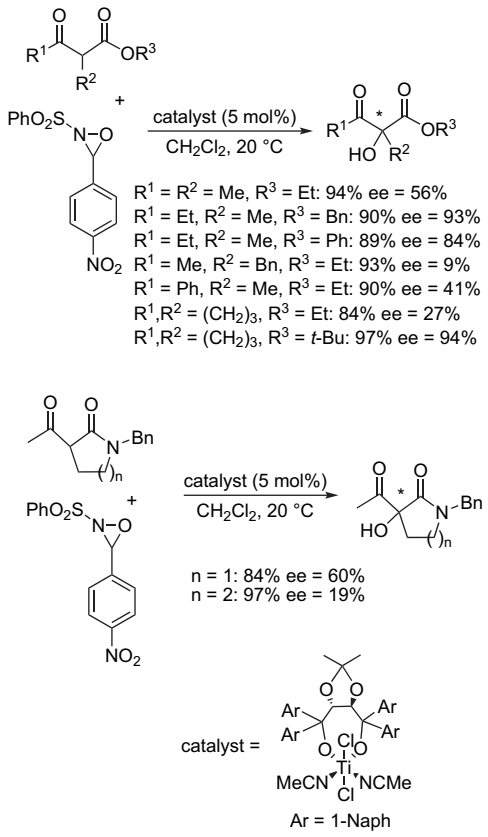


Scheme 50. α-Fluorination of β-keto ester using $LiAlH_4$ as metal catalyst.

4.3. Miscellaneous substitutions

Although the α-hydroxy carbonyl functional unit is ubiquitous in natural products and bioactive compounds, such as carbohydrates, antibiotics and antitumour agents, the enantioselective formation of a quaternary stereogenic centre coinciding with a hydroxylation process is still a very rare reaction from a homogeneous catalytic point of view. In this context, Togni et al. have successfully expanded the scope of the methodology previously applied to the α-fluorination of β-keto esters to the asymmetric hydroxylation of these compounds.[84] Therefore, a [$TiCl_2$(TADDOLato)] catalyst was used to promote the α-hydroxylation of a range of β-keto esters in the presence of 2-(phenylsulfonyl)-3-(4-nitrophenyl)oxaziridine as the oxidising agent, leading to the corresponding chiral hydroxylated products in high yields and enantioselectivities of up to 94% ee, as depicted in Scheme 51. Thus, besides affording an efficient enantiocontrol with several substrates, this new catalytic approach also afforded high chemo- and regioselectivity. As already observed in the analogous fluorination reaction, the enantioselectivity of the hydroxylation increased with increasing steric bulk of the ester residue. The methodology was also applied to the α-hydroxylation of structurally related acyl lactams, providing moderate enantioselectivities (Scheme 51).

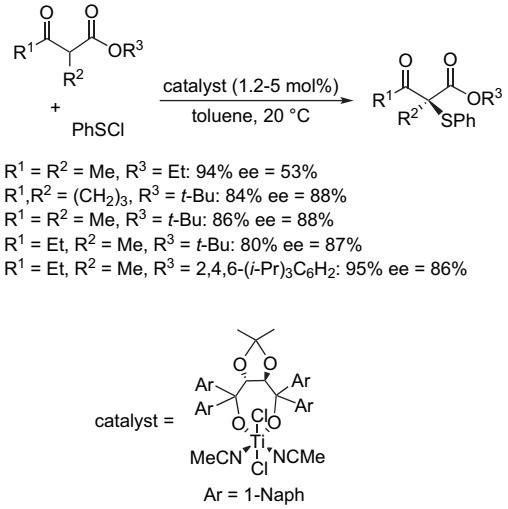
Optically active compounds containing sulfur functionalities have been recognised as important auxiliaries, as well as ligands, the importance of which has been growing over the past decade.[85] For these reasons, the development of selective and efficient methods for the direct generation of a stereogenic C–S bond is of considerable importance. In this context, Togni and Jereb have developed a highly efficient, direct, enantioselective, catalytic sulfenylation of β-keto esters, using a similar methodology to that applied for the analogous hydroxylation and fluorination reactions.[86] Indeed, the use of the [$TiCl_2$(TADDOLato)] catalyst depicted in Scheme 51, in the presence of phenylsulfenyl chloride, allowed the corresponding chiral α-sulfenylated β-keto esters to be obtained in high yields and



Scheme 51. α-Hydroxylations of β-keto esters and β-acetyl lactams.

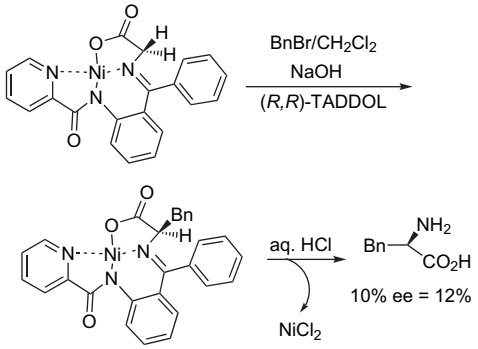
enantioselectivities of up to 88% ee (Scheme 52). The reaction was carried out without the need to add any base to neutralise the hydrogen chloride formed during the reaction. Thus, the catalyst compatibility towards the acidic byproduct under the reaction conditions was a noticeable advantage with respect to alternative methods.

Moreover, TADDOLs have been demonstrated, in the past, to be excellent chiral ligands in asymmetric alkylations.[87] With the aim of developing a novel catalytic access to chiral α-amino acids, Belokon et al. have employed TADDOL to promote the asymmetric phase-transfer alkylation of achiral nickel(II) complexes of glycine-derived Schiff bases in the presence of benzyl bromide (Scheme 53).[88] The corresponding alkylated nickel complexes could be



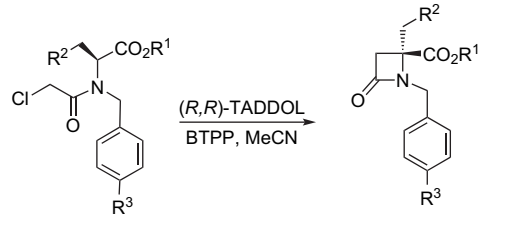
Scheme 52. α-Sulfenylation of β-keto esters.

obtained, but in much lower yields and enantioselectivities than those obtained with the use of NOBIN as catalyst in the same study.



Scheme 53. Phase-transfer-catalysed alkylation of nickel(II) complex.

Even though transition-metal-catalysed enantioselective reactions will certainly continue to play a central role in synthetic organic chemistry in the future, the last few years have, however, seen an increasing trend in the use of metal-free catalysts. Indeed, enantioselective organocatalytic processes have reached maturity in recent years with an impressive and steadily increasing number of publications.[31] In comparison to the well-studied application of chiral diols as ligands, the emergence of TADDOLs as effective general organocatalysts is very recent. In 2006, Gonzalez-Muniz et al. studied the intramolecular base-promoted alkylation of *N*-chloroacetyl derivatives of several amino acids carried out in the presence of TADDOL, giving rise to the corresponding enantiomerically enriched β-lactams.[89] Actually, this study demonstrated that TADDOL did not work as a true catalyst, but could be considered to act like a memory of chirality enhancer. Processes occurring with memory of chirality are characterised by an initial unique stereogenic element, which is destroyed during the generation of the corresponding reactive intermediates, but these intermediates are able to retain the information about the configuration of their precursors to transfer the chirality to the final compounds.[90] Most of the memory of chirality transformations can be found among the chemistry of α-amino acids with the α-alkylation reaction. The results, reported by Gonzalez-Muniz et al., constituted the first examples of the TADDOL-promoted enhancement of the enantioselectivity due to memory of chirality. Their experiments have shown that the degree of the selectivity improvement in the intramolecular α-alkylation of *N*-benzyl-*N*-chloroacetyl amino acid derivatives was dependent on the solvent and base used and, most importantly, on the nature of the amino acid side chain, that should be aromatic. On the other hand, the extent and sign of the enantioselectivity in the β-lactam formation were practically independent of the configuration of TADDOL. The principal results are collected in Scheme 54. A hypothetical mechanism to rationalise



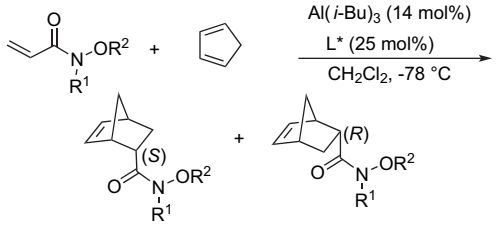
Scheme 54. Intramolecular alkylation of *N*-chloroacetyl derivatives of amino acids.

the function of TADDOL in these reactions could involve the formation of complexes between the starting amino acid derivative, or its enolate intermediate, and the chiral additive, through H-bonds and π–π interactions.

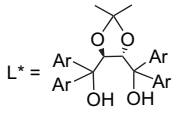
5. Cycloaddition reactions

5.1. Diels–Alder reactions

The Diels–Alder reaction plays a pivotal strategic role in the synthesis of a large number of important building blocks and intermediates in the total synthesis of natural products. In the last 25 years, the use of Lewis acids to catalyse the Diels–Alder reaction has become very popular, since it allows both accelerating the reaction and enhancing the selectivity.[91] Chiral diols, such as TADDOLs, have been demonstrated to be excellent chiral ligands in enantioselective Diels–Alder reactions.[92] As an example, Renaud and Corminboeuf demonstrated, in 2002, that *N*-alkoxyacrylates were suitable substrates for enantioselective Diels–Alder reactions performed in the presence of TADDOLs.[93] High enantioselectivities of up to 92% ee were achieved for a range of *N*-alkoxyacrylates, using a very simple chiral Lewis acid prepared from $(i\text{-Bu})_3$Al and 1-naphthyl-TADDOL (Scheme 55).

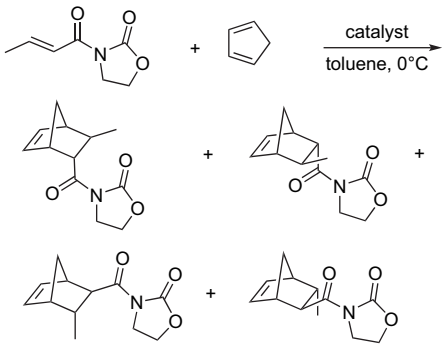


R^1 = Ph, R^2 = O*t*-Bu: *endo*:*exo* > 98:2 ee (*endo*) = 92% (*S*)
R^1 = Ph, R^2 = Me: *endo*:*exo* = 96:4 ee (*endo*) = 72% (*S*)
R^1 = Ph, R^2 = Et: *endo*:*exo* = 95:5 ee (*endo*) = 75% (*S*)
R^1 = Ph, R^2 = *i*-Pr: *endo*:*exo* = 97:3 ee (*endo*) = 89% (*S*)
R^1 = Ph, R^2 = Bn: *endo*:*exo* = 95:5 ee (*endo*) = 69% (*S*)
R^1 = R^2 = Me: *endo*:*exo* = 92:8 ee (*endo*) = 23% (*S*)
R^1 = *t*-Bu, R^2 = Me: ee (*endo*) = 21% (*R*)

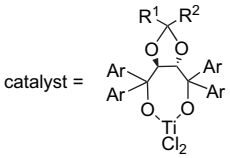


Scheme 55. Diels–Alder reaction of *N*-alkoxyacrylates with cyclopentadiene.

Luis et al. have used another type of dienophile, such as (*E*)-3-butenoyl-1,3-oxazolidin-2-one, in the Diels–Alder reaction with cyclopentadiene performed in the presence of various TADDOL–$TiCl_2$ complexes.[94] The reaction was studied with different [dienophile]/[catalyst] ratios, and different concentrations of reagents and catalysts. The enantioselectivity of some of the reactions depended on these factors, which indicated the participation of intermediate complexes with different catalyst and dienophile compositions (1:1, 1:2 and 2:1). The best results were obtained under conditions that favoured the formation of an equimolecular intermediate, whereas the conditions favouring the formation of intermediates containing two molecules of dienophile and one of catalyst gave rise to lower enantiomeric excesses. The main conclusion which could be drawn from this study was that there was a clear influence of the [reagent]/[catalyst] molar relationship on the enantioselectivity, and that this showed the existence of competitive mechanisms involving reactive intermediates with different compositions, which led to different enantioselectivities. In one case, however, the asymmetric induction was not dependent on the above factors, meaning that the effect described strongly depended on the structure of the chiral ligand, which did not contain aryl groups at the dioxolane moiety in this example. The best results are collected in Scheme 56.

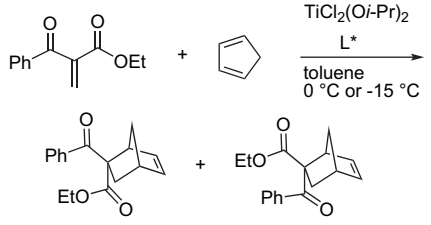


Ar = 3,5-$(Me)_2C_6H_3$, R^1 = H, R^2 = *p*-$BzOC_6H_4$
[dienophile]/[catalyst] = 10, [diene]/[dienophile] = 22:
99% *endo*/*exo* = 82:18 ee (*endo*) = 50%
[dienophile]/[catalyst] = 1, [diene]/[dienophile] = 21:
99% *endo*/*exo* = 81:19 ee (*endo*) = 7%
Ar = 2-Naph, R^1 = H, R^2 = *p*-$BzOC_6H_4$
[dienophile]/[catalyst] = 11, [diene]/[dienophile] = 30:
97% *endo*/*exo* = 76:24 ee (*endo*) = 62%
Ar = 2-Naph, R^1 = H, R^2 = *p*-$BzOC_6H_4$
[dienophile]/[catalyst] = 1, [diene]/[dienophile] = 22:
92% *endo*/*exo* = 76:24 ee (*endo*) = 22%
Ar = Ph, R^1 = R^2 = Me
[dienophile]/[catalyst] = 5, [diene]/[dienophile] = 20:
98% *endo*/*exo* = 82:18 ee (*endo*) = 29%
Ar = Ph, R^1 = R^2 = Me
[dienophile]/[catalyst] = 1, [diene]/[dienophile] = 20:
100% *endo*/*exo* = 85:15 ee (*endo*) = 21%

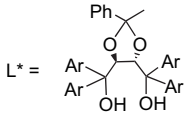


Scheme 56. Diels–Alder reaction of (*E*)-3-butenoyl-1,3-oxazolidin-2-one with cyclopentadiene.

On the other hand, the catalytic Diels–Alder reaction of 2-methylene-1,3-dicarbonyl compounds with cyclopentadiene in the presence of Ti–TADDOL complexes was investigated by Yamauchi et al. in 2001.[95] As shown in Scheme 57, both *exo*-selectivities and



Ar = Ph: 65% *exo*:*endo* = 82:18 ee (*exo*) = 24%
Ar = *p*-$MeOC_6H_4$: 65% *exo*:*endo* = 87:13 ee (*exo*) = 24%

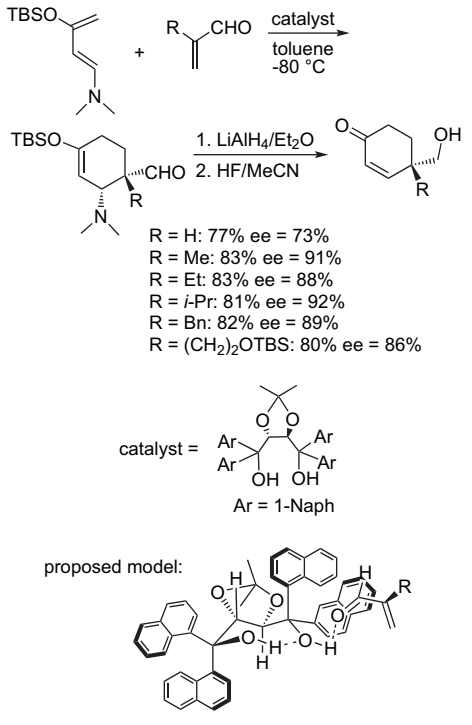


Scheme 57. Diels–Alder reaction of ethyl 2-benzoylacrylate with cyclopentadiene.

enantioselectivities were moderate and poor for a dienophile, such as ethyl 2-benzoylacrylate.

In addition, Luis et al. have developed novel routes for the preparation of several silica-bound TADDOL derivatives, which were further treated with $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ to give the corresponding complexes.[96] These complexes were then checked as catalysts for the Diels–Alder reaction of 3-crotonoyl-1,3-oxazolidin-2-one with cyclopentadiene, providing a low activity (≤40% yield), an *endo*/*exo* selectivity of about 4, along with very low enantioselectivities (≤10% ee). On the other hand, these workers reported, in 2006, the preparation of a range of polymeric monoliths containing TADDOL subunits by polymerisation of the corresponding functional monomers.[22] The corresponding monolithic Ti–TADDOLates were investigated to catalyse the same Diels–Alder reaction as discussed above, giving enantioselectivities of up to 61% ee and *endo*/*exo* ratios of up to 85:15. The Diels–Alder reaction was carried out in the presence of these polymer-bound systems more efficiently in batch rather than under flow conditions. Indeed, enantioselectivities of up to 25% ee were obtained for the same reaction performed under flow conditions.

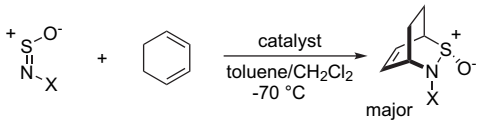
For a long time, it was not known that organocatalysts could be used to catalyse the Diels–Alder reactions, and base-catalysed Diels–Alder reactions, especially, were regarded as uncommon. In recent years, however, several different types of organocatalysts have been developed. In this context, Rawal et al. reported, in 2004, an excellent example of using TADDOLs as organocatalysts for the Diels–Alder reaction of aminosiloxydienes with acrolein dienophiles to afford the corresponding products in good yields and high enantioselectivities of up to 92% ee (Scheme 58).[97] The results are consistent with the model shown in Scheme 58, in which TADDOL is expected to exist in a well-defined, internally hydrogen-bonded arrangement. The dienophile is expected to complex with TADDOL through a two-point interaction. First, the free hydroxyl group on TADDOL is expected to form a strong intermolecular hydrogen bond to the carbonyl group of the dienophile, which provides the necessary lowering of the lowest unoccupied molecular orbital energy through a Lewis acid-like mechanism. Second, the complexed electron-deficient carbonyl double bond is expected to be stabilised through a π–π donor–acceptor interaction with the electron-rich π system of the proximal equatorial 1-naphthyl ring, which would selectively shield one face of the dienophile.



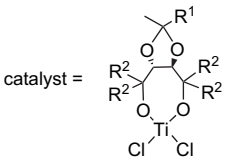
Scheme 58. Organocatalysed Diels–Alder reaction.

5.2. Hetero Diels–Alder reactions

Although less studied than the all-carbon version, the hetero Diels–Alder reaction has attracted greater attention over the past decades and constitutes nowadays an extremely useful reaction. It provides a versatile regio- and stereoselective approach towards heterocyclic compounds from heterodienes or heterodienophiles. This class of six-membered partly saturated heterocycles has found extensive use as starting materials for the total synthesis of many natural products and other highly functionalised heterocycles.[98] As an example, 1,2-thiazine 1-oxides, which are precursors of unsaturated vicinal aminoalcohols and homoallylic amines, have found application in the total synthesis of a number of natural products and biologically active compounds, such as benzodiazepines and benzothiadiazepines, can be prepared by asymmetric hetero Diels–Alder reactions using *N*-sulfinyl compounds as dienophiles. Thus, Gautun et al. reported, in 2002, the enantioselective hetero Diels–Alder reactions of cyclohexadiene with two *N*-sulfinyl dienophiles promoted by chiral Ti(IV)-based Lewis acids prepared from Me_2TiCl_2 and TADDOLs.[99] In almost all cases, the major diastereomer resulted from an *endo* approach of the reagents and was obtained with up to 83% yield and 69% ee, as shown in Scheme 59.



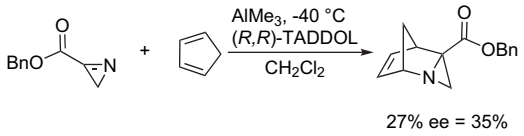
X = Cbz, R^1 = Me, R^2 = Ph: 63% *endo:exo* > 95:5
ee (*endo*) = 40%
X = Cbz, R^1 = R^2 = Ph: 70% *endo:exo* > 95:5
ee (*endo*) = 58%
X = Cbz, R^1 = Ph, R^2 = 3,5-$(Me)_2C_6H_4$: 69%
endo:exo = 92:8 ee (*endo*) = 37%
X = Ts, R^1 = Me, R^2 = Ph: 63% *endo:exo* = 92:8
ee (*endo*) = 59%
X = Ts, R^1 = R^2 = Ph: 83% *endo:exo* = 94:6
ee (*endo*) = 69%
X = Ts, R^1 = Ph, R^2 = 3,5-$(Me)_2C_6H_4$: 68%
endo:exo = 50:50 ee (*endo*) = 37%



Scheme 59. Hetero Diels–Alder reaction of *N*-sulfinyl dienophiles.

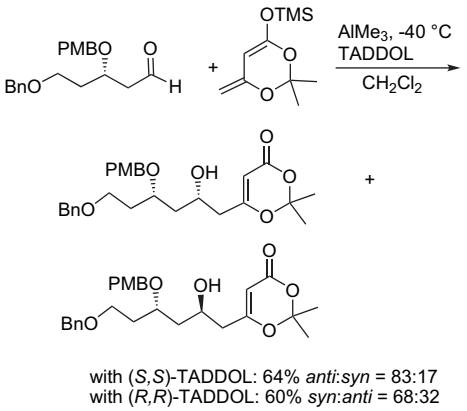
Other nitrogen-containing dienophiles have been involved in asymmetric hetero Diels–Alder reactions.[100] As an example, Somfai and Timen have developed enantioselective hetero Diels–Alder reactions of azirines with cyclopentadiene in the presence of a Lewis acid and TADDOL as chiral ligand.[101] These reactions afforded the corresponding products comprising a fused tetrahydropyridine–aziridine moiety in low yield and enantioselectivity, when using $AlMe_3$ as Lewis acid (Scheme 60).

On the other hand, TADDOL has also been used to catalyse hetero Diels–Alder reactions, involving oxygen-containing dienophiles. As an example, Jiang et al. have studied the hetero Diels–Alder reaction of benzaldehyde with Danishefsky's diene in the presence of $Ti(O\text{-}i\text{-}Pr)_4$ and TADDOL, which provided the



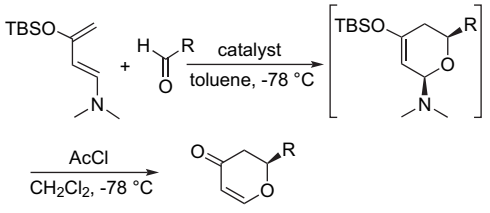
Scheme 60. Hetero Diels–Alder reaction of azirine.

corresponding cycloadduct in low yield (10%) and enantioselectivity (6% ee).[102] In the course of developing a novel synthesis of the spongistatin AB spiroketal, Crimmins and Smith have employed a hetero Diels–Alder reaction of a functionalised aldehyde with a silyldienolate, giving rise in the presence of TADDOL and Ti(O-*i*-Pr)$_2$Cl$_2$ to the corresponding dioxinone.[103] It was shown that the use of (*S*,*S*)-TADDOL delivered an 83:17 mixture favouring the *anti* diastereomer, whereas the use of (*R*,*R*)-TADDOL gave a 67:33 preference for the *syn* diastereomer, as depicted in Scheme 61.



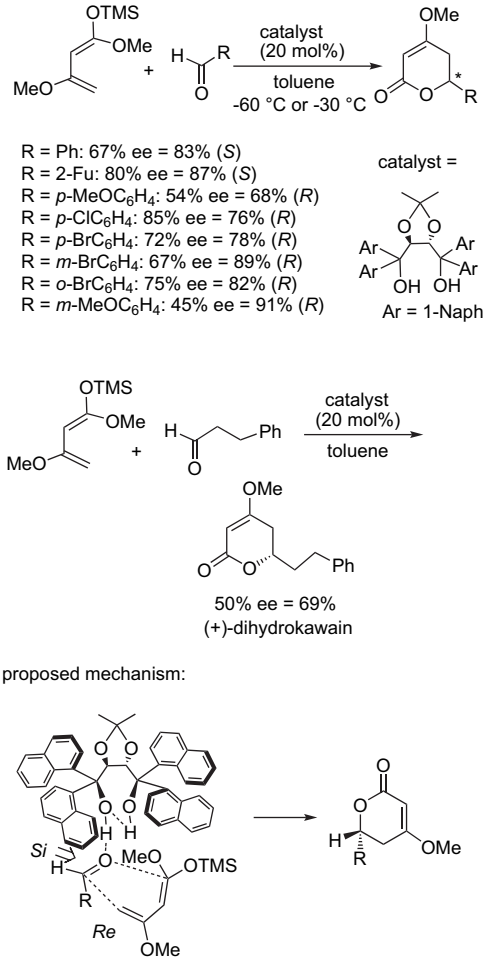
Scheme 61. Hetero Diels–Alder reaction of aldehyde.

In recent years, several organocatalytic enantioselective hetero Diels–Alder reactions have been developed, becoming a topic of interest in asymmetric organocatalysis.[31] Of these reactions, one of the most existing developments is the 1-naphthyl-TADDOL-promoted reaction of 1-amino-3-siloxybutadiene with aldehydes, which was reported by Rawal et al., in 2003.[104] Thus, these cycloadditions proceeded smoothly to furnish the cycloadducts highly enantioselectively after treatment with AcCl, as depicted in Scheme 62.



Scheme 62. Organocatalytic hetero Diels–Alder reaction of aminosiloxydiene.

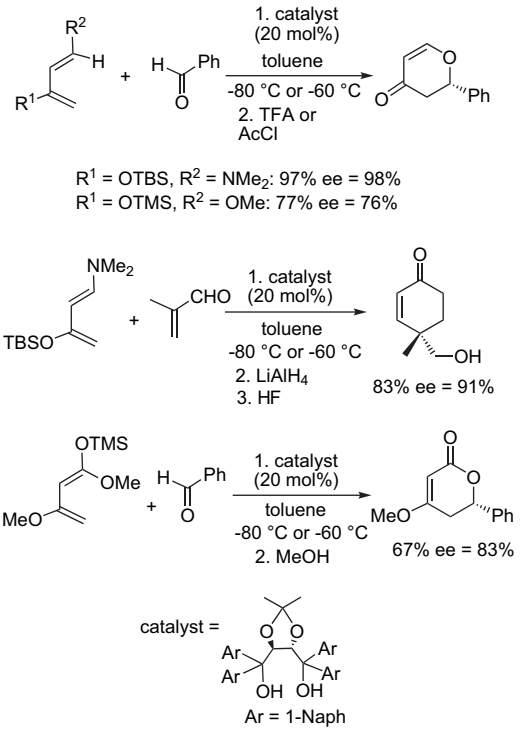
In 2004, the TADDOL derivative depicted above was employed by Ding et al. to induce the hetero Diels–Alder reaction of an aldehyde with Brassard's diene, affording the corresponding δ-lactone derivative highly enantioselectively (Scheme 63).[105] The usefulness of this methodology was demonstrated by its application in the total synthesis of the natural product, (+)-dihydrokawain. In order to explain the asymmetric induction of the reaction, these workers have proposed a possible mechanism, as outlined in Scheme 63. In this (*S*,*S*)-catalytic system, the steric hindrance of the naphthyl moiety shields the *Si* face of the aldehyde, while the *Re* face is available to accept the attacking diene to give the products with the *R* configuration, as expected. It is evident that the strength of the intermolecular hydrogen bonding between the catalyst and the substrate, the greater steric hindrance of the 1-naphthyl group and the π–π interaction between the naphthyl ring and the carbonyl group of the substrate all play important roles in the control of the enantioselectivity of the catalytic reactions.



Scheme 63. Organocatalytic hetero Diels–Alder reactions of Brassard's diene.

In 2005, Mikami and Tonoi observed a low enantioselectivity (5% ee, 55% yield) for the hetero Diels–Alder reaction of butyl glyoxylate with Danishefsky's diene in the presence of TADDOL as organocatalyst.[106] In the same context, Ding et al. have investigated enantioselective hetero Diels–Alder reactions of this diene and its analogues with various aldehydes in the presence of a range of TADDOL derivatives.[107] An interesting phenomenon was found, namely that naphth-1-TADDOL exhibited a remarkably superior performance compared to that of its analogues, such as simple phenyl-TADDOL or naphth-2-TADDOL, in several hetero Diels–Alder reactions in terms of both activity and enantioselectivity. Indeed, the α,α′-aryl substituents in the TADDOL molecules were found to exert a significant impact on both the activity and the

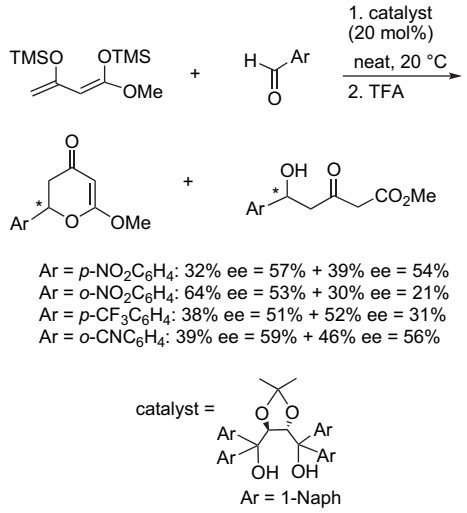
enantioselectivity of the catalysis. Thus, the use of naphth-1-TADDOL as organocatalyst allowed high enantioselectivities of up to 98% ee to be obtained, as shown in Scheme 64. In addition, the mechanism of the reaction was studied theoretically, using the ONIOM (B3LYP/6-31G*:PM3) method with *trans*-1,3-dimethoxy-1,3-butadiene as the model for Danishefsky's diene, indicating that the reaction evolved via a concerted mechanism through an asynchronous and zwitterionic transition structure, as depicted in Scheme 63. The carbonyl group of the aldehyde was activated by forming an intermolecular hydrogen bond with one of the hydroxy groups of TADDOL. Meanwhile, the intramolecular hydrogen bond between the two hydroxyl groups in TADDOL was found to facilitate the intermolecular hydrogen bonding with the aldehyde. The involvement of highly polarised transition states was confirmed by a computational study of the diol-catalysed hetero Diels–Alder reactions of Rawal-type dienes reported by Houk et al., in 2007.[108] It was shown that the 1,4-butanediol model systems for catalysis by TADDOLs were consistent with a cooperative hydrogen-bonding arrangement.



Scheme 64. Organocatalytic hetero Diels–Alder reactions of Danishefsky's diene and analogues.

In the course of investigating the viability of the enantioselective vinylogous aldol reaction of Chan's diene in the presence of naphth-1-TADDOL as organocatalyst, Villano et al. have found that the involvement of electron-poor aromatic aldehydes in this reaction enhanced the reactivity, and made a competing asymmetric hetero Diels–Alder reaction take place in comparable (or higher) yields and enantioselectivities under solvent-free conditions (Scheme 65).[36]

Recent publications outline the development of a novel computational procedure, reverse-docking, which has proved to be a useful tool for studying the enantioselectivity of several organocatalysed reactions.[109] In this procedure, a large flexible organocatalyst is docked around rigid transition-state models of catalyst-free reactions generated by ab initio transition-state optimisation calculations. The resulting reverse-docking arrangements represent simplified models for the transition states of the organocatalysed



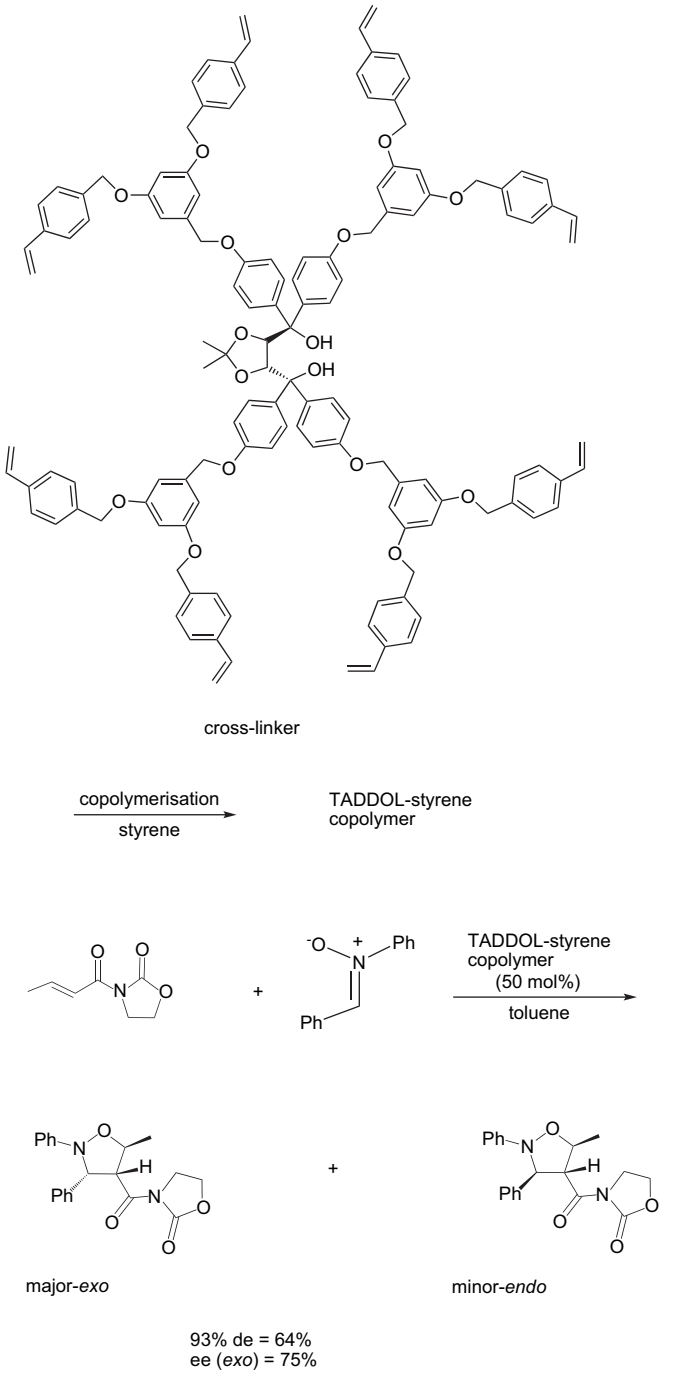
Scheme 65. Organocatalytic hetero Diels–Alder reaction of Chan's diene.

hetero Diels–Alder reaction. Therefore, Deslongchamps et al. described, in 2007, the reverse-docking of a TADDOL catalyst to rigid-state models of catalyst-free reactions (TS models) for an asymmetric hetero Diels–Alder reaction.[110] In previous reports, the reverse-docking of similar organocatalysts to rigid TS models has shown promise for generating transition-state models for the catalysed reaction, and revealed clear energetic trends favouring the experimentally preferred product enantiomers. Although the results indicated a mode of catalysis consistent with the experimental data, relative docking energies between TS model enantiomers were too great to allow an in silico correlation to experimentally observed ees. Thus, several changes were made to the reverse-docking algorithm, EM-Dock, permitting the first reported correlation with experimentally reported ee values based solely on reverse-docking and molecular mechanic energies.

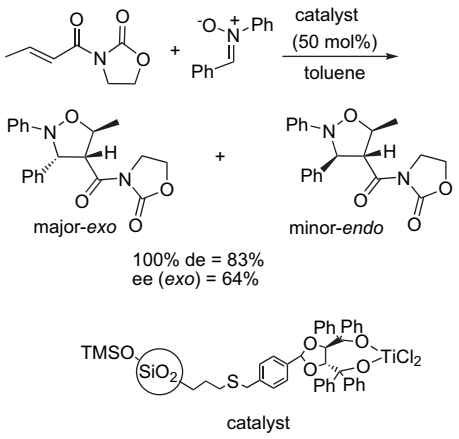
5.3. Miscellaneous cycloadditions

TADDOLs have been demonstrated to be excellent chiral ligands in asymmetric 1,3-dipolar cycloadditions,[111] even immobilised on polystyrene, as demonstrated by Seebach et al., in 2002.[18] These workers achieved the copolymerisation of a TADDOL dendrimer with styrene, followed by loading with titanate. The resulting dendritically polymer-bound Ti–TADDOLate complex was used to catalyse the asymmetric 1,3-dipolar cycloaddition[112] of diphenyl nitrone to 3-crotonoyl-1,3-oxazolidinone, providing the corresponding cycloadducts with preferential formation of the *exo* cycloadduct, as shown in Scheme 66. The degree of diastereo- and enantioselectivity remained unchanged during four catalytic cycles and was comparable to that obtained under homogeneous conditions.

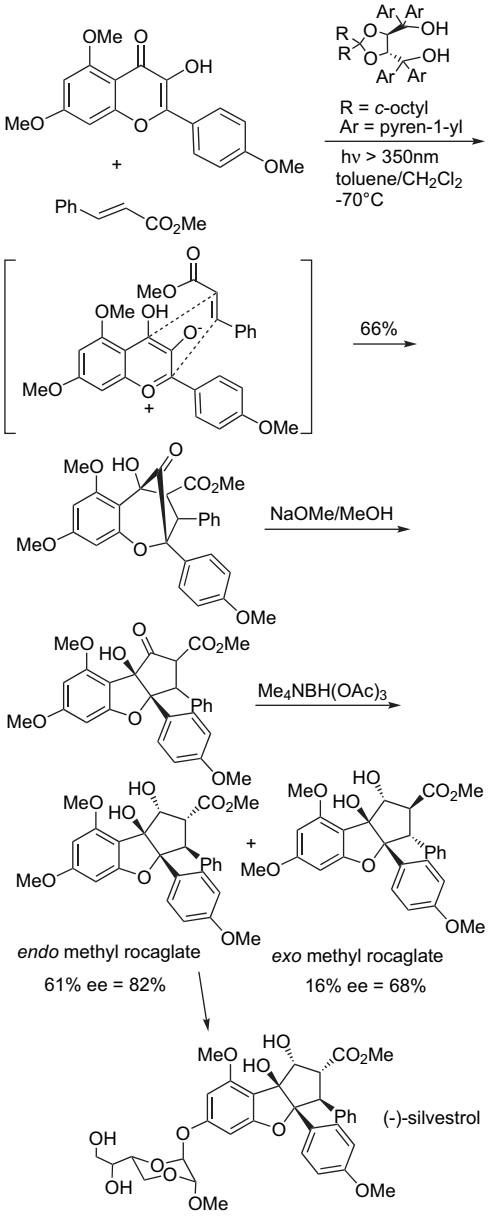
Since catalysts immobilised on hydrophilic silica gel often give superior performances to their polymer-bound or polymer-incorporated analogues for multiple applications, Seebach and Heckel have performed a similar reaction to that described above in the presence of TADDOLs immobilised on hydrophobic controlled-pore glass (CPG) silica gel, allowing good results to be obtained, as depicted in Scheme 67.[20] A seasoning of the catalyst material was shown in this reaction. Indeed, even if necessary to use 0.5 equiv of the immobilised catalyst initially in order to match performance, after three runs, the reaction rate and the enantio- and diastereoselectivity dropped considerably. An acidic washing after each subsequent run completely restored the performance, so that, after a total of seven runs, the amount of catalyst could be reduced to 0.4,



Scheme 66. 1,3-Dipolar cycloaddition in the presence of polymer-bound Ti–TADDOLate.



Scheme 67. 1,3-Dipolar cycloaddition in the presence of CPG-immobilised Ti–TADDOLate.



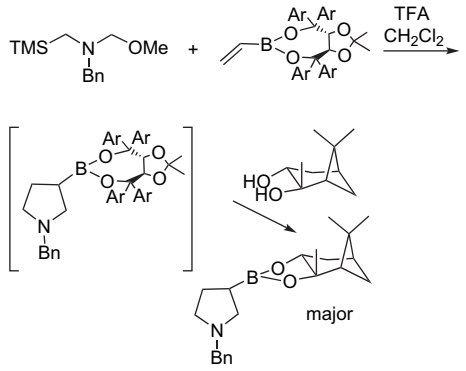
Scheme 68. Organocatalysed 1,3-dipolar photocycloaddition.

0.3, 0.2 and 0.1 equiv in the following runs, with identical good results.

In 2006, Porco et al. developed an asymmetric synthesis of rocaglamides on the basis of an enantioselective 1,3-dipolar cycloaddition of an oxidopyrylium species derived from excited-state intramolecular proton transfer of a 3-hydroxyflavone, using specifically functionalised TADDOL derivatives as chiral organocatalysts.[113] As shown in Scheme 68, the 1,3-dipolar photocycloaddition of a 3-hydroxyflavone in the presence of methyl cinnamate gave rise to the corresponding cycloadduct in good yield, which was further transformed into a mixture of the expected *endo* methyl rocaglate with high enantioselectivity and its corresponding *exo* isomer by employing a base-mediated α-ketol rearrangement/

hydroxyl-directed reduction sequence. In 2007, the same workers reported the conversion of *endo* methyl rocaglate into the complex natural rocaglate (−)-silvestrol, exhibiting a very potent cytotoxic activity against human lung cancer cells, which was comparable with that of the anticancer agent, paclitaxel (taxol).[114]

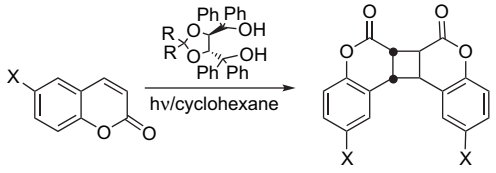
In addition, an asymmetric 1,3-dipolar cycloaddition of azomethine ylides, using alkenylboronic esters equipped with TADDOLs as chiral auxiliaries, was developed by Zong in 2005.[115] The cycloaddition gave rise to the corresponding cycloadduct intermediates, which were then transformed into the more stable corresponding (+)-pinanylboronic ester-substituted pyrrolidine derivatives through transesterification with (+)-pinanediol, since pinanylboronic esters were stable enough to be isolated. As shown in Scheme 69, the diastereoselectivity of the reaction was somewhat influenced by the type of aromatic group borne by the TADDOL moiety.



Ar = Ph: 75% de = 60%
Ar = 3,5-$(Me)_2C_6H_3$: 70% de = 46%
Ar = *o*-Tol: 75% de = 42%
Ar = 1-Naph: 70% de = 60%
Ar = 2-Naph: 74% de = 42%
Ar = 3,5-$(Ph)_2C_6H_3$: 73% de = 50%

Scheme 69. 1,3-Dipolar cycloaddition of TADDOL-derived chiral auxiliaries.

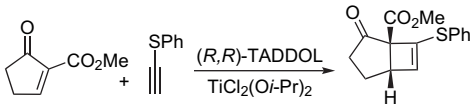
The [2+2]-cycloaddition reaction has been recognised as a powerful tool for the construction of a functionalised four-membered ring system, proceeding either under photoirradiation or under Lewis acid (also Bronsted acid)-catalysed conditions.[116] In 2005, Tanaka and Fujiwara described the highly enantioselective [2+2]-photodimerisation reaction of coumarins in solution in the presence of a TADDOL derivative as a chiral host compound providing the corresponding optically active anti-head-to-head dimers.[117] Upon irradiation of a solution of an equimolar mixture of the TADDOL derivative and the coumarin, a crystalline 2:1 inclusion complex of the TADDOL derivative and the cycloadduct was gradually precipitated as the reaction proceeded, providing an enantioselectivity of up to 95% ee (Scheme 70).



X = H, R = Me: 70% ee = 85%
X = Me, R,R = $(CH_2)_5$: 60% ee = 95%

Scheme 70. [2+2]-Photodimerisation reaction of coumarins.

More recently, Iguchi et al. reported the catalytic enantioselective [2+2]-cycloaddition reaction of 2-methoxycarbonyl-2-cyclopenten-1-one with thioacetylene derivatives in the presence of a chiral catalyst.[118] When the reaction was carried out in the presence of TADDOL and $TiCl_2$(O-*i*-Pr)$_2$, the expected cycloadduct was obtained in moderate yield and low enantioselectivity, as shown in Scheme 71.



53% ee = 22%

Scheme 71. [2+2]-Cycloaddition of 2-methoxycarbonyl-2-cyclopenten-1-one.

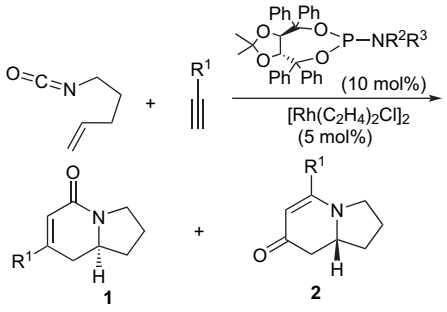
In 2006, Rovis and Yu developed a regio- and enantioselective rhodium-catalysed [2+2+2]-cycloaddition of alkenyl isocyanates with terminal alkynes, affording the corresponding bicyclic lactams and/or vinylogous amides, using TADDOL-derived phosphoramidites as chiral ligands.[119] The cycloaddition generally proceeded cleanly to furnish the cycloadducts in high yields and enantioselectivities and in a highly regioselective manner. Scheme 72 summarises the scope of the cycloaddition of pentenyl isocyanate with a variety of either aromatic or aliphatic acetylenes. In order to explain the selectivity of the reaction, these workers proposed a mechanism in which an initial oxidative cyclisation between the isocyanate and the alkyne occurred in an orientation where a C–N bond was formed, thus providing the metallacycle **A**. A CO migration to the metallacycle **B**, followed by olefin insertion and reductive elimination, furnished the vinylogous amides (pathway A, Scheme 72). In a different orientation, the metallacycle **D** was formed with a C–C bond formation (pathway B, Scheme 72). The subsequent olefin insertion and reductive elimination provided the corresponding lactams. The synthetic utility of this methodology was demonstrated in an expedient asymmetric total synthesis of (+)-lasubine II.

In 2001, Charette et al. reported the use of a titanium–TADDOLate complex for the asymmetric cyclopropanation of a wide variety of allylic alcohols, providing modest-to-excellent yields and enantioselectivities (Scheme 73).[120] The best results (up to 94% ee) were obtained with 3-aryl- or 3-heteroaryl-substituted allylic alcohols, while alkyl-substituted allylic alcohols gave modest yields and enantiomeric excesses (≤74% ee).

In order to extend the scope of the cyclopropanation reaction, the same group developed in 2006, a new family of chiral phosphates derived from TADDOL.[121] The use of these ligands in the asymmetric Simmons–Smith cyclopropanation of both functionalised and unfunctionalised olefins led to the formation of the desired cyclopropanes in good yields and good-to-moderate enantioselectivities, as shown in Scheme 74.

6. Oxidation and reduction reactions

The asymmetric epoxidation of olefins is one of the most useful and challenging reactions in modern organic chemistry,[122] due to the fact that chiral epoxides constitute versatile building blocks, and that many biologically active compounds and natural products contain epoxide functionalities.[123] In this area, Seebach and Aoki have reported the preparation of an optically active TADDOL-derived hydroperoxide, TADOOH, from H_2O_2 and TADDOL, by replacement of one OH group in TADDOL by an OOH group.[124] This new stable chiral hydroperoxide has been tested as a chiral oxidant in several asymmetric oxidations, such as the epoxidation of enones in base catalysis. As shown in Scheme 75, treatment of a range of enones with TADOOH in the presence of *n*-BuLi led to the formation of the corresponding epoxy ketones in high yields and variable enantioselectivities (up to 97% ee).



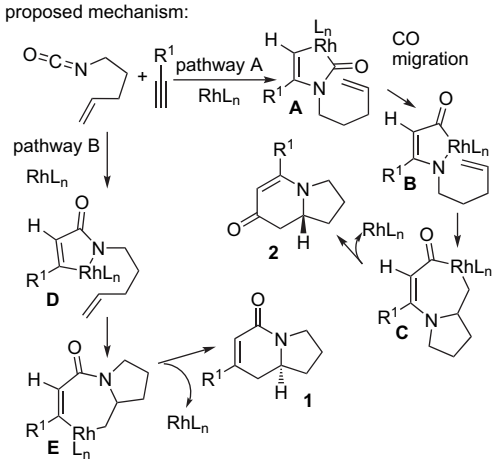
with $R^2,R^3 = (CH_2)_4$:

R^1 = 3,4-$(OMe)_2C_6H_3$: 72% **1**:**2** < 5:95 ee (**2**) = 94%
R^1 = *p*-$OMeC_6H_4$: 70% **1**:**2** < 5:95 ee (**2**) = 90%
R^1 = *o*-$OMeC_6H_4$: 64% **1**:**2** < 5:95 ee (**2**) = 94%
R^1 = *p*-$(NMe_2)C_6H_4$: 78% **1**:**2** < 5:95 ee (**2**) = 87%
R^1 = *m*-Tol: 65% **1**:**2** = 11:89 ee (**2**) = 94%
R^1 = 2-Thio: 64% **1**:**2** = 10:90 ee (**2**) = 86%
R^1 = Ph: 86% **1**:**2** = 12:88 ee (**1**) = 89% ee (**2**) = 94%
R^1 = *p*-BrC_6H_4: 72% **1**:**2** = 24:76 ee (**1**) = 90% ee (**2**) = 89%
R^1 = *p*-ClC_6H_4: 65% **1**:**2** = 21:79 ee (**1**) = 93% ee (**2**) = 90%
R^1 = *p*-$CF_3C_6H_4$: 50% **1**:**2** = 71:29 ee (**1**) = 94%

with $R^2,R^3 = (CH_2)_5$:

R^1 = *n*-Hex: 78% **1**:**2** = 83:17 ee (**1**) = 80%
R^1 = CH_2Bn: 47% **1**:**2** > 5:95 ee (**2**) = 84%
R^1 = Bn: 50% **1**:**2** > 5:95 ee (**2**) = 84%
R^1 = $(CH_2)_2OTBS$: 65% **1**:**2** > 5:95 ee (**2**) = 87%
R^1 = CH_2OMe: 46% **1**:**2** > 5:95 ee (**2**) = 76%
R^1 = $(CH_2)_4CO_2Me$: 65% **1**:**2** = 85:15 ee (**1**) = 80%

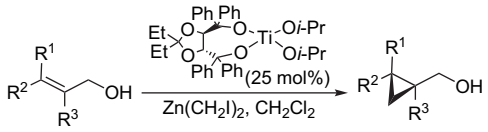
proposed mechanism:



Scheme 72. [2+2+2]-Cycloaddition of alkenyl isocyanate with terminal alkynes.

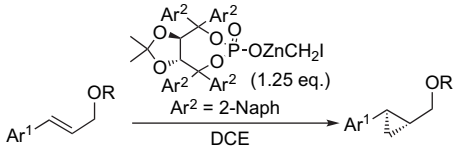
In 2003, Vogl et al. investigated the vanadium(V)-catalysed epoxidation of allylic alcohols in the presence of TADOOH as a chiral oxygen source.[125] Thus, treatment of a range of allylic alcohols with an achiral vanadium catalyst and TADOOH allowed the corresponding chiral epoxides to be obtained in up to 72% ee (Scheme 76). From a mechanistic study, it was proposed that this novel enantioselective oxygen transfer took place via a hydrogen-bonded template, held together by the vanadium metal. The transition structure depicted in Scheme 76 was proposed to be favoured, because, in this template, steric repulsions with the hydroperoxide were minimised.

Similar reactions were also successfully performed by Zhang et al. in the presence of an achiral oxovanadium(IV)-substituted polyoxometallate (POM) and TADOOH.[126] Thus, the use of this resistant oxovanadium sandwich-type POM, $[ZnW(VO)_2(ZnW_9O_{34})]$,[12] achieved chemo-, regio- and stereoselective epoxidations of allylic alcohols by TADOOH with very high

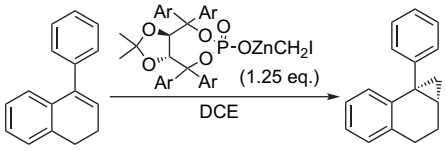


$R^1 = R^3$ = H, R^2 = Ph: 85% ee = 94%
R^1 = Ph, $R^2 = R^3$ = H: 62% ee = 72%
R^1 = Me, R^2 = Ph, R^3 = H: 80% ee = 88%
R^1 = H, R^2 = Ph, R^3 = Me: 80% ee = 50%
$R^1 = R^3$ = H, R^2 = 3,5-$(Me)_2C_6H_3$: 86% ee = 92%
$R^1 = R^3$ = H, R^2 = 2-Naph: 81% ee = 92%
$R^1 = R^3$ = H, R^2 = 1-Naph: 80% ee = 84%
$R^1 = R^3$ = H, R^2 = *p*-$OMeC_6H_4$: 90% ee = 92%
$R^1 = R^3$ = H, R^2 = *p*-ClC_6H_4: 81% ee = 82%
$R^1 = R^3$ = H, R^2 = *n*-Pr: 68% ee = 74%
R^1 = *n*-Pr, $R^2 = R^3$ = H: 87% ee = 48%
$R^1 = R^3$ = H, R^2 = $BnCH_2$: 63% ee = 60%
$R^1 = R^3$ = H, R^2 = Cy: 60% ee = 66%
$R^1 = R^2$ = Me, R^3 = H: 89% ee = 72%
$R^1 = R^3$ = H, R^2 = 2-Fu: 73% ee = 88%
$R^1 = R^3$ = H, R^2 = (*E*)-CH=CH-Ph: 75% ee = 84%

Scheme 73. Cyclopropanation of allylic alcohols in the presence of titanium–TADDOLate complex.

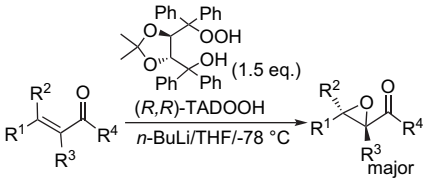


Ar^1 = Ph, R = Bn: 96% ee = 69%
Ar^1 = Ph, R = Me: 69% ee = 73%
Ar^1 = *p*-$MeOC_6H_4$, R = Bn: 87% ee = 69%
Ar^1 = *m*-$MeOC_6H_4$, R = Bn: 97% ee = 75%
Ar^1 = $Ph(CH_2)_2$, R = Bn: 88% ee = 69%

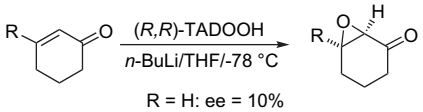


Ar = Ph: 38% ee = 40%
Ar = 2-Naph: 6% ee = 31%

Scheme 74. Cyclopropanations in the presence of TADDOL-derived phosphate ligands.

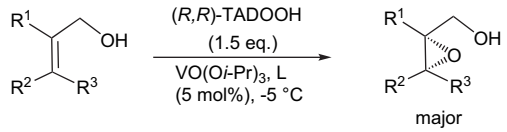


$R^1 = R^4$ = Ph, $R^2 = R^3$ = H: 80% ee = 97%
R^1 = Ph, $R^2 = R^3$ = H, R^4 = Me: ee = 78%
$R^1,R^3 = (CH_2)_4$, R^2 = H, R^4 = Me: ee = 40%

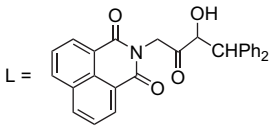


R = H: ee = 10%
R = Me: ee = 82%

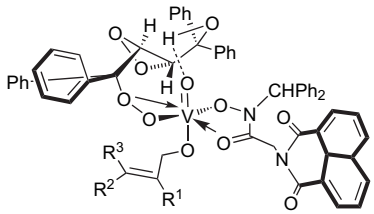
Scheme 75. Epoxidations of enones with TADOOH.



$R^1 = R^3 = H$, $R^2 = Ph$: 89% ee = 52%
$R^1 = Me$, $R^2 = Ph$, $R^3 = H$: 73% ee = 67%
$R^1 = R^2 = Ph$, $R^3 = H$: > 95% ee = 72%
$R^1 = R^2 = H$, $R^3 = Ph$: 30% ee = 41%
$R^1 = Ph$, $R^2 = R^3 = H$: 94% ee = 44%

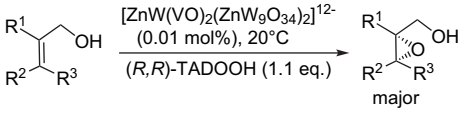


proposed transition structure:



Scheme 76. Vanadium-catalysed epoxidation of allylic alcohols with TADOOH.

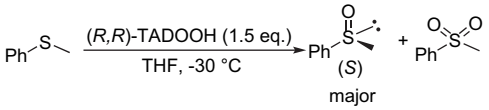
catalytic efficiency (up to 42,000 TON), allowing enantioselectivities of up to 90% ee to be obtained (Scheme 77).



$R^1 = R^2 = Ph$, $R^3 = H$: 90% ee = 90%
$R^1 = Me$, $R^2 = Ph$, $R^3 = H$: 92% ee = 84%
$R^1 = Me$, $R^2 = p\text{-}MeOC_6H_4$, $R^3 = H$: 86% ee = 70%
$R^1 = R^3 = H$, $R^2 = Ph$: 88% ee = 50%
$R^1 = Ph$, $R^2 = R^3 = H$: 93% ee = 44%
$R^1 = H$, $R^2 = (Me)_2C{=}CH\text{-}(CH_2)_2$, $R^3 = Me$: 96% ee = 18%

Scheme 77. Oxovanadium sandwich-type POM-catalysed epoxidation of allylic alcohols with TADOOH.

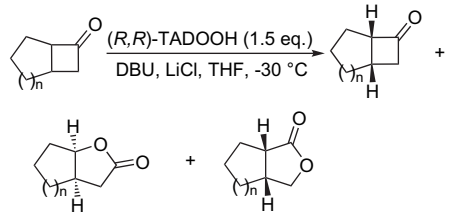
In recent years, it has been recognised that chiral sulfur compounds were of great value in asymmetric synthesis, since many reactions may be efficiently stereocontrolled by chiral sulfur auxiliaries, which later are easily removable under mild conditions by reductive or eliminative methods. In particular, chiral sulfoxides belong to the class of chiral organosulfur compounds, which are most widely used in asymmetric synthesis.[85b] Their application as chiral synthons has now become a well-established and reliable strategy, and a large number of asymmetric syntheses using chiral sulfoxides have been investigated in a wide range of reactions.[127] In this area, the efficient chiral hydroperoxide, TADOOH, has been applied as a chiral oxidant, by Seebach and Aoki, to an enantioselective oxidation of methyl phenyl sulfide.[124] As outlined in Scheme 78, TADOOH oxidised methyl phenyl sulfide without any catalysis, giving rise to the corresponding (*S*)-sulfoxide in good yield and high enantioselectivity. In this type of reaction, there is usually the formation, besides that of the expected sulfoxide, of the corresponding sulfone by overoxidation. Thus, there is the interesting implication that a chiral oxidant will react faster with one of the enantiomeric sulfoxides than with the other, so that a kinetic resolution of the primarily formed sulfoxide can complicate the assignment of the enantioselectivity of the actual sulfoxidation step. According to the result obtained by using TADOOH as oxidant, it can be concluded that the sulfoxide enantiomer, which is formed faster in the sulfoxidation step, is converted into the sulfone more slowly.



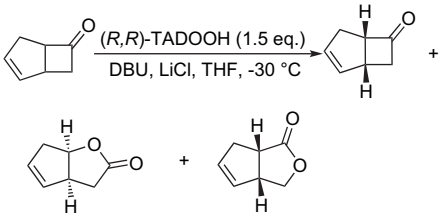
73% ee = 86% + 23%

Scheme 78. Oxidation of methyl phenyl sulfide with TADOOH.

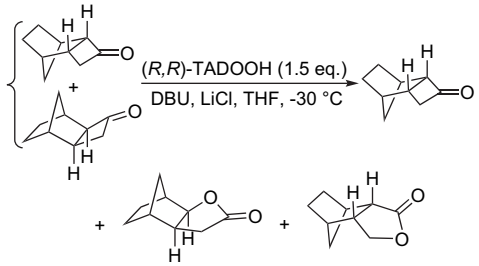
In addition, this chiral oxidant has been applied to the asymmetric Baeyer–Villiger oxidation of bicyclic and tricyclic cyclobutanones with kinetic resolution.[124] In the presence of DBU and LiCl, the cyclobutanone was oxidised into the normal Baeyer–Villiger product, along with the enantiomerically enriched unreacted cyclobutanone and, in some cases, the abnormal Baeyer–Villiger product (Scheme 79). Thus, these results, providing enantioselectivities of up to 99% ee, demonstrated that TADOOH turned out to be an enantiomer-differentiating, and also regioselective, stoichiometric oxidant in the Baeyer–Villiger reaction of cyclobutanones.



n = 2: 26% ee = 99% + 65% ee = 75% + 1%
n = 1: 30% ee = 99% + 51% ee = 84% + 19% ee = 99%



30% ee = 95% + 46% ee = 90% + 16% ee = 99%

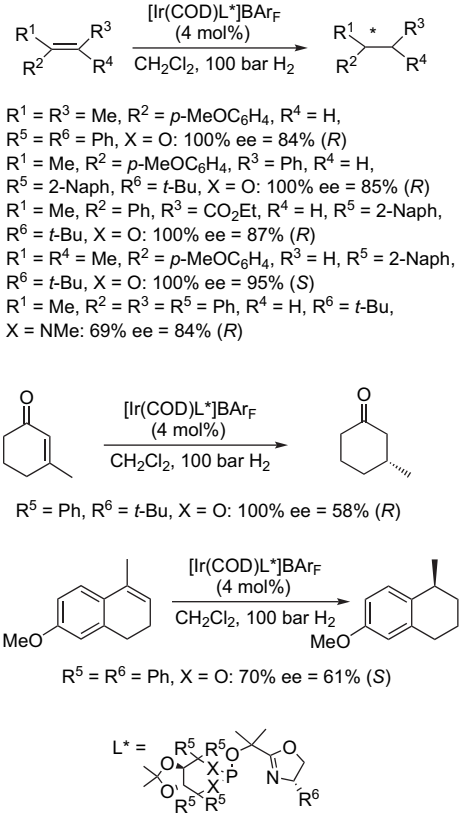


23% ee = 59% + 45% ee = 88% + 26% ee = 99%

Scheme 79. Baeyer–Villiger oxidations of bicyclic and tricyclic cyclobutanones with TADOOH.

On the other hand, the asymmetric hydrogenation of unsaturated organic compounds is currently becoming a standard procedure in both academic laboratories and industrial applications.[128] The enantioselective hydrogenation of olefins with chiral rhodium or ruthenium catalysts is the best-established and most widely used method in asymmetric catalysis.[129] Meanwhile,

unfunctionalised olefins are still particularly difficult substrates, because, in general, a polar group adjacent to the C=C bond, which can coordinate to the metal catalyst, is required for high catalyst activity and enantioselectivity. Indeed, there are very few examples of highly enantioselective hydrogenations of olefins lacking such a polar group. In order to overcome these limitations, Pfaltz and Hilgraf have found a new class of asymmetric hydrogenation catalysts, showing exceptionally high activity with unfunctionalised olefins and giving, in many cases, excellent enantioselectivity of up to 95% ee.[66,130] These highly efficient catalysts are iridium complexes of chiral P,N-ligands derived from TADDOL. As shown in Scheme 80, several types of olefins could be hydrogenated with high enantioselectivity and full conversion, in almost all cases, by using these chiral iridium complexes as their BAr_F salts (BAr_F=tetrakis[3,5-bis(trifluoromethyl)phenyl]borate).

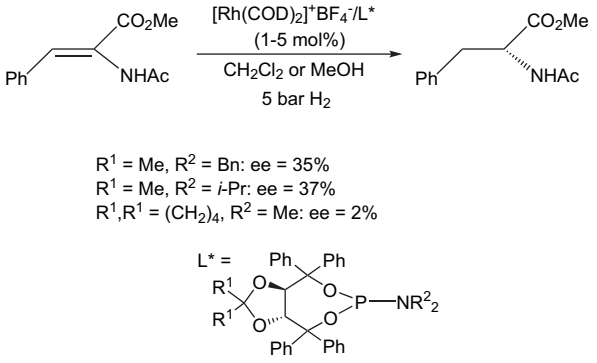


Scheme 80. Iridium-catalysed hydrogenations of olefins.

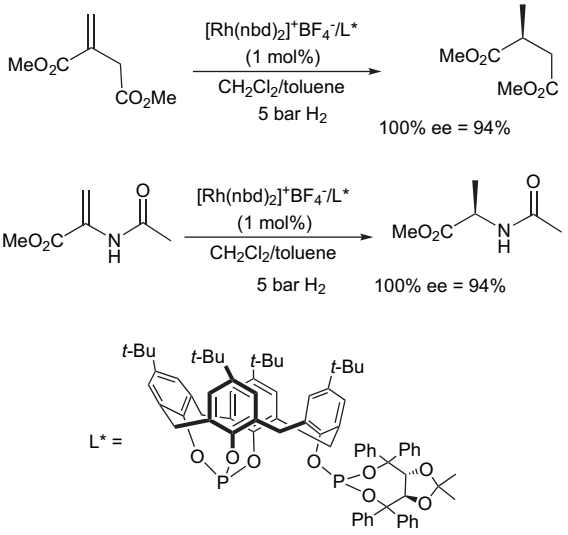
On the other hand, de Vries et al. have studied another type of chiral TADDOL-derived ligand, such as monodentate phosphoramidites bearing a TADDOL skeleton, for the rhodium-catalysed hydrogenation of dehydroamino esters.[131] As shown in Scheme 81, low enantioselectivities were observed for all ligands of this type for the hydrogenation of a dehydroamino ester.

On the other hand, high enantiomeric excesses of up to 94% ee combined with good activities were obtained, in 2007, by van Leewen et al. in the rhodium-catalysed hydrogenation of olefins, such as dimethyl itaconate and methyl α-acetamidoacrylate (Scheme 82).[132] In this work, the chiral ligands were calix[4]arene-based TADDOL-containing diphosphites, which demonstrated for the first time that calix[4]arene-based C_1-symmetric diphosphites could be successfully applied in metal-catalysed asymmetric transformations.

The enantioselective reduction of imines to obtain chiral amines still represents a challenging topic in asymmetric synthesis.



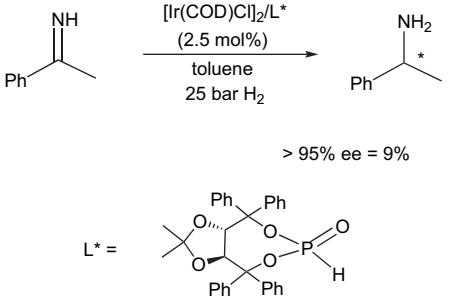
Scheme 81. Rhodium-catalysed hydrogenation of dehydroamino ester.



Scheme 82. Rhodium-catalysed hydrogenations of olefins with chiral calixarene-modified ligand.

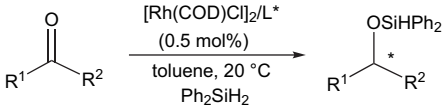
Although many highly enantioselective hydrogenations of ketones and alkenes are known, only less effective reductions of imines are available. Indeed, the development of efficient catalysts giving high enantioselectivity has proved to be much more difficult for imines, compared with alkenes and ketones. As an example, de Vries et al. have obtained a low enantioselectivity for the asymmetric iridium(I)-catalysed imine hydrogenation performed in the presence of a chiral monodendate secondary phosphine oxide derived from TADDOL (Scheme 83),[133] although better enantioselectivities of up to 83% ee were obtained by these workers by using other chiral secondary phosphine oxides in the same study.

In 2003, Finn et al. reported the asymmetric rhodium-catalysed hydrosilylation of ketones, based on the use of a chiral phosphite

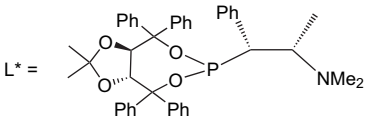


Scheme 83. Iridium-catalysed hydrogenation of imine.

P,N-ligand derived from TADDOL and (+)-*N*-methylephedrine.[134] An excellent level of asymmetric induction was observed for a variety of ketones, as depicted in Scheme 84.

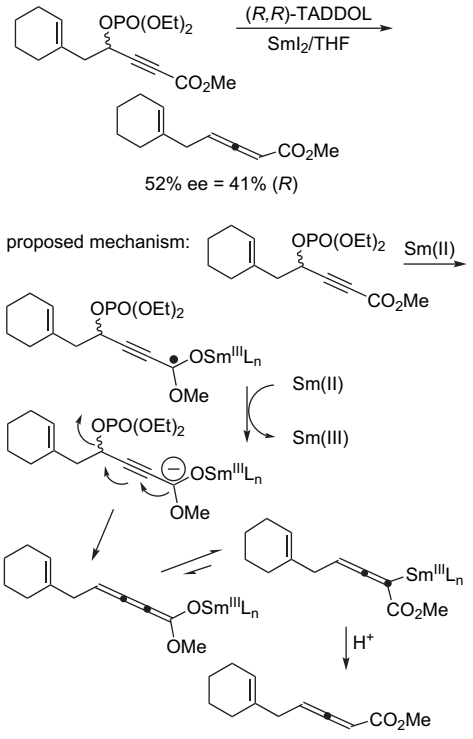


R^1 = 1-Naph, R^2 = Me: ee = 82%
R^1 = Ph, R^2 = Me: ee = 80%
R^1 = 2-Naph, R^2 = Me: ee = 94%
R^1 = Me, R^2 = CO_2Et: ee = 89%
R^1 = Ph, R^2 = Et: ee = 36%
R^1 = Ph, R^2 = *i*-Pr: ee = 15%



Scheme 84. Rhodium-catalysed hydrosilylation of ketones.

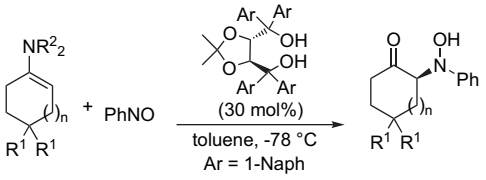
In addition, Mikami and Yoshida have developed an asymmetric synthesis of allenic esters on the basis of an enantioselective samarium(II)-mediated reduction of propargylic phosphates bearing alkoxycarbonyl groups at the acetylene terminus (Scheme 85).[135] The involvement of a chiral proton source, such as TADDOL, in this system, allowed enantio-enriched allenic esters to be obtained through dynamic kinetic protonation of anionic allenylsamarium(III) species without the involvement of chirality transfer or destruction of one enantiomer. This efficient asymmetric protonation could be attained, due to the chelation of TADDOL with samarium(III) possessing strong Lewis acid acidity and oxophilicity. In the course of this study, it was additionally demonstrated that enantioselectivities of up to 95% ee could be obtained in similar conditions, but using pantolactone instead of TADDOL as the chiral proton source.



Scheme 85. Samarium-mediated reduction of propargylic phosphate.

7. Miscellaneous reactions

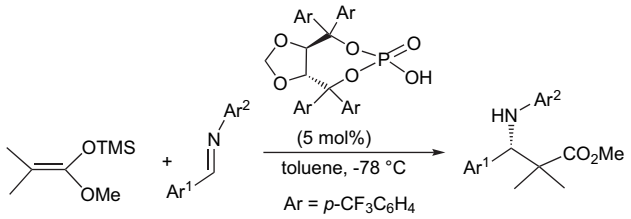
The α-oxycarbonyl group is a common feature of many natural and biologically active compounds. Furthermore, this functionality is an obvious precursor in the synthesis of other important building blocks, such as diols. Among the already existing methods for the asymmetric synthesis of chiral α-hydroxy carbonyl compounds, the direct organocatalysed enantioselective α-aminoxylation of carbonyl compounds is one of the most important strategies for achieving this purpose. Nitroso compounds, such as nitrosobenzene, are useful electrophiles for performing this type of reaction, although the nitrogen versus oxygen reactivity should be carefully controlled through the selection of appropriate catalysts and reaction conditions.[136] In this context, Yamamoto and Momiyama reported, in 2005, regio- and enantioselective nitroso aldol reactions, in which a piperidine enamine of cyclohexanone reacted with nitrosobenzene with an enantioselectivity of up to 91% ee in the presence of (*S*,*S*)-1-naphthyl-TADDOL as catalyst, leading selectively to the *N*-nitroso aldol reaction product (Scheme 86).[137] The scope of this reaction was extended in 2006 by Greck et al., confirming the exclusive formation of the *N*-regioisomers in a highly enantioselective manner with up to 93% ee.[138]



R^1 = H, R^2,R^2 = $(CH_2)_5$, n = 1: 81% ee = 83%
R^1 = H, R^2,R^2 = $(CH_2)_2O(CH_2)_2$, n = 1: 91% ee = 79%
R^1 = H, R^2,R^2 = $(CH_2)_2S(CH_2)_2$, n = 1: 88% ee = 77%
R^1 = H, R^2,R^2 = $(CH_2)_4$, n = 1: 69% ee = 70%
R^1 = H, R^2,R^2 = $(CH_2)_5$, n = 1: 77% ee = 92%
R^1,R^1 = (OCH_2CH_2O), R^2,R^2 = $(CH_2)_5$, n = 1: 83% ee = 93%
R^1 = H, R^2,R^2 = $(CH_2)_6$, n = 1: 89% ee = 91%
R^1 = Me, R^2,R^2 = $(CH_2)_5$, n = 1: 78% ee = 82%
R^1 = H, R^2,R^2 = $(CH_2)_5$, n = 2: 67% ee = 65%

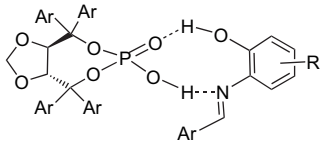
Scheme 86. *N*-Nitroso aldol reaction of enamines with PhNO.

Chiral α-branched amines are common substructures within biologically active materials and hence attract broad interest, particularly in the areas of synthetic methodology, bioorganic and medicinal chemistry and natural product synthesis. Additions of carbon fragments to C=N bonds of imines and related compounds build up the carbon framework in the same operation as asymmetric induction, so that this approach is one of the more attractive entries to chiral amines.[139] In this context, the Mannich reaction is a widely applied means of producing β-amino carbonyl compounds starting from cheap and readily available substrates, an aldehyde, an amine and a ketone, reacting in a three-component, one-pot synthesis.[140] As an alternative strategy, the reaction can also be performed as a nucleophilic addition of a *C*-nucleophile to a preformed imine, which is prepared starting from the aldehyde and an amine source. In recent years, a number of organocatalysed Mannich reactions have been successfully developed. As an example, Akiyama et al. have reported enantioselective Mannich-type reactions of a ketene silyl acetal with a range of aldimines catalysed by a novel chiral phosphate having the TADDOL scaffold, which gave rise to the corresponding β-amino acid esters with high enantioselectivities (Scheme 87).[141] Based on these results, these workers have surmised that the Mannich-type reaction took place



Ar^1 = Ph, Ar^2 = *o*-HOC_6H_4: 97% ee = 73%
Ar^1 = Ph, Ar^2 = 2-OH-*m*-Tol: 83% ee = 76%
Ar^1 = Ph, Ar^2 = 2-OH-*p*-Tol: 100% ee = 89%
Ar^1 = *p*-ClC_6H_4, Ar^2 = 2-OH-*p*-Tol: 81% ee = 85%
Ar^1 = *p*-FC_6H_4, Ar^2 = 2-OH-*p*-Tol: 95% ee = 92%
Ar^1 = *p*-$MeOC_6H_4$, Ar^2 = 2-OH-*p*-Tol: 85% ee = 89%
Ar^1 = *p*-Tol, Ar^2 = 2-OH-*p*-Tol: 96% ee = 92%

proposed transition state:

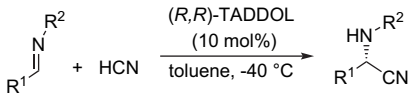


Scheme 87. Mannich-type reaction of ketene silyl acetal with aldimines.

through a nine-membered transition state, wherein the phosphate hydrogen activated the imine and the phosphoryl oxygen interacted with the hydrogen of the imine hydroxyl group by hydrogen bonding, as shown in Scheme 87.

The Strecker reaction, starting from an aldehyde, ammonia and a cyanide source, is an efficient method for the preparation of α-amino acids and their derivatives. A popular version for asymmetric purposes is based on the use of preformed imines and a subsequent nucleophilic addition of HCN or TMSCN in the presence of a chiral catalyst.[142] Intense investigation of the asymmetric Strecker-type reaction has continued over many years, due to the importance of α-amino acid building blocks in medicinal chemistry.[142,143] Interestingly, a number of completely different types of chiral organocatalysts have been found to have catalytic hydrocyanation properties. Among these molecules is TADDOL, which has been very recently implicated in the enantioselective hydrocyanation of aldimines by Rueping et al.[144] Although the enantioselectivities obtained were moderate, the results, collected in Scheme 88, demonstrated the feasibility of chiral diols, such as TADDOL, as promising enantioselective catalysts for the Strecker reaction, but more importantly showed that hydrogen-bond activation could be achieved not only for aldehydes but also for the first time for aldimines.

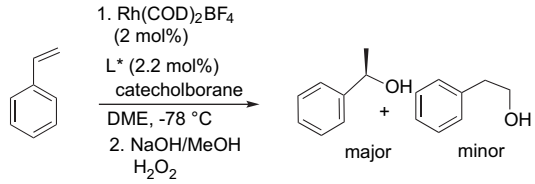
In 2002, Schmalz et al. reported the preparation of a library of chiral bidentate P,P-ligands derived from TADDOL, which were



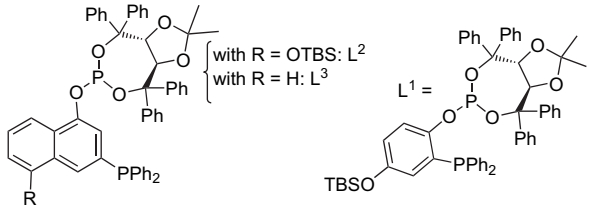
R^1 = 4-OMe-1-Naph, R^2 = Bn: 69% ee = 56%
R^1 = *p*-Tol, R^2 = Bn: 68% ee = 30%
R^1 = *p*-$MeOC_6H_4$, R^2 = Bn: 93% ee = 22%
R^1 = *p*-ClC_6H_4, R^2 = Bn: ee = 32%
R^1 = *p*-$MeOC_6H_4$, R^2 = *p*-$MeOC_6H_4$-CH_2: ee = 8%
R^1 = *p*-$MeOC_6H_4$, R^2 = *p*-FC_6H_4-CH_2: ee = 16%
R^1 = *p*-$MeOC_6H_4$, R^2 = *p*-ClC_6H_4-CH_2: ee = 22%
R^1 = *p*-$MeOC_6H_4$, R^2 = *p*-BrC_6H_4-CH_2: ee = 14%

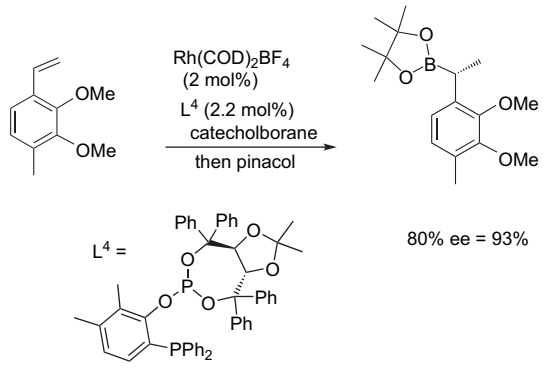
Scheme 88. Strecker reaction of aldimines.

further tested as catalysts for the enantioselective rhodium-catalysed hydroboration of styrene to give 1-phenylethanol in up to 91% ee.[145] In addition, it was demonstrated that small, even subtle, variations of the ligand structure led to rather dramatic and unpredictable consequences for both the activity and the selectivity of the in situ-generated rhodium complexes. The catalysts, which gave the best performance are depicted in Scheme 89. In 2007, this methodology was applied to an efficient and highly stereoselective synthetic entry to a *trans*-7,8-dimethoxycalamenene, a projected intermediate for the total synthesis of marine biologically active serrulatane and amphilectane diterpenes.[146] Indeed, the key step of this synthesis was the rhodium-catalysed hydroboration of a styrene derivative in the presence of a chiral TADDOL-derived ligand, which afforded the corresponding boronate in 93% ee (Scheme 89).



with L* = L^1: 98% major/minor = 98/2 ee = 81%
with L* = L^2: 97% major/minor = 96/4 ee = 88%
with L* = L^3: 63% major/minor = 95/5 ee = 91%

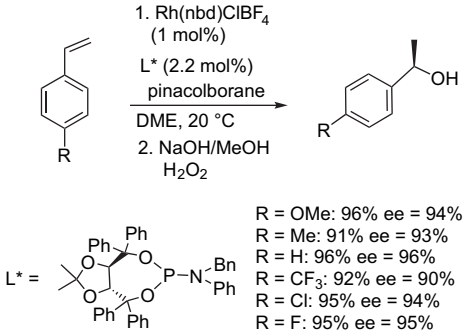




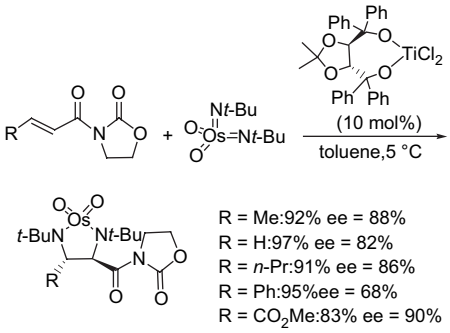
Scheme 89. Rhodium-catalysed hydroborations of styrene derivatives.

In addition, Takacs et al. have extended the scope of this enantioselective rhodium-catalysed hydroboration to a wide range of either electron-donating or -withdrawing substituted styrenes, and by using very simple TADDOL-derived monodentate ligands.[147] In this case, the best results, collected in Scheme 90, were obtained by using pinacolborane.

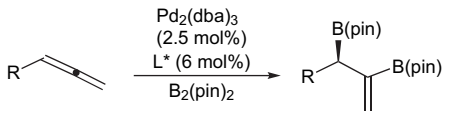
In 2005, Morken et al. involved a closely related ligand to those depicted above to induce chirality in a palladium-catalysed enantioselective diboration of allenes, providing a reactive chiral allylboron intermediate, which was a versatile reagent for the allylation of aldehydes.[148] On the basis of the high level of enantioselectivity obtained for the diboration reaction, a one-pot diboration/allylboration/oxidation cascade process was elaborated, giving rise to

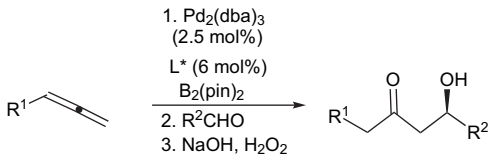


Scheme 90. Rhodium-catalysed hydroboration of 4-substituted styrenes.

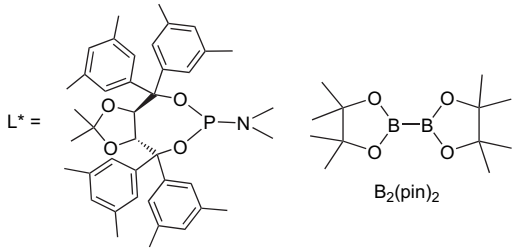


Scheme 92. Diamination of oxazolidinones.





R^1 = Ph, R^2 = *n*-Pr: 85% ee = 94%
R^1 = Ph, R^2 = *i*-Pr: 89% ee = 95%
R^1 = R^2 = Ph: 81% ee = 93%
R^1 = *n*-decyl, R^2 = *n*-Pr: 88% ee = 91%
R^1 = *n*-decyl, R^2 = Ph: 96% ee = 87%
R^1 = Cy, R^2 = *n*-Pr: 89% ee = 86%
R^1 = Cy, R^2 = *i*-Pr: 83% ee = 87%
R^1 = Cy, R^2 = Ph: 83% ee = 84%

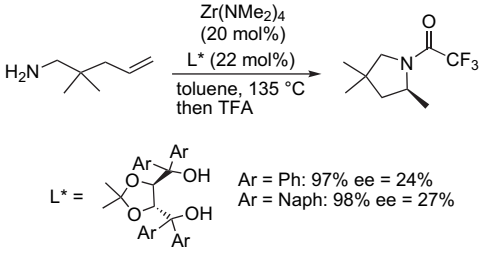


Scheme 91. Palladium-catalysed diboration and sequential diboration/allylboration/oxidation reactions.

β-hydroxy ketones with high enantioselectivity, as shown in Scheme 91.

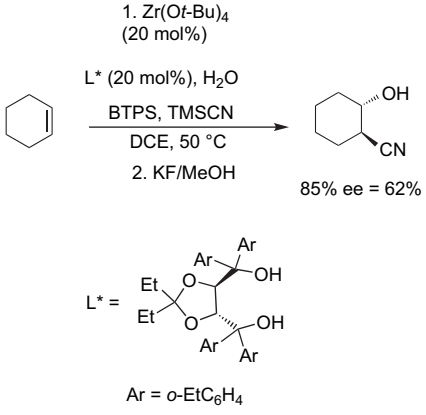
In 2005, a new method for the asymmetric diamination of alkenes was developed by Muniz and Nieger by using a bisimidoosmium reagent in the presence of a catalytic amount of a chiral titanium-TADDOLate.[149] In particular, the reaction of a variety of oxazolidinones allowed the corresponding enantiomerically enriched osmaimidazolidinones to be formed in high yields, as depicted in Scheme 92.

On the other hand, low enantioselectivities (≤27% ee) were obtained in the zirconium-catalysed asymmetric intramolecular alkene hydroamination developed by Bergman et al., in 2006 (Scheme 93).[150] Indeed, the use of a TADDOL derivative as a chiral ligand led to the formation of the expected pyrrolidines in quantitative yields, but with low enantioselectivities, whereas enantioselectivities of up to 80% ee were observed when using chiral diphosphinic amides as chiral ligands in the same study.



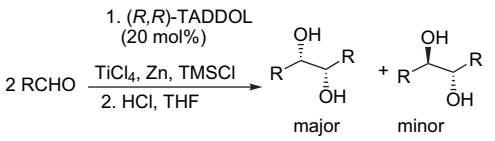
Scheme 93. Zirconium-catalysed intramolecular alkene hydroamination.

A TADDOL derivative has been employed as a chiral ligand by Shibasaki et al. in another asymmetric zirconium-catalysed reaction, providing the corresponding enantiomerically enriched *trans*-β-cyanohydrin of cyclohexene with moderate enantioselectivity (Scheme 94).[151] In this one-pot reaction, the zirconium catalyst promoted the epoxidation of the alkene with bis(trimethylsilyl) peroxide (BTSP) and the subsequent epoxide-opening step performed by treatment with TMSCN.



Scheme 94. Zirconium-catalysed one-pot synthesis of *trans*-β-cyanohydrin.

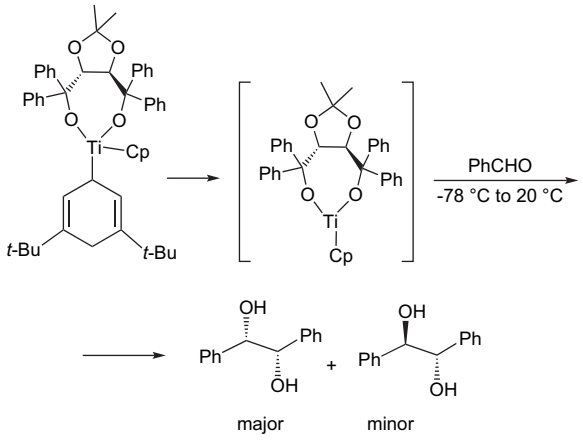
The pinacol coupling of aldehydes to give diols is an important method for constructing vicinally functionalised C–C bonds. In recent years, TADDOL has been successfully exploited, as its corresponding in situ-generated titanium complex, in an asymmetric pinacol coupling reaction of aldehydes, providing the corresponding chiral diols with excellent diastereoselectivities and moderate-to-good enantioselectivities (Scheme 95).[152]



R = Ph: 88% de = 98% ee (major) = 71%
R = *p*-Tol: 93% de = 100% ee (major) = 74%
R = *p*-$MeOC_6H_4$: 92% de = 98% ee (major) = 73%
R = *o*-ClC_6H_4: 82% de = 66% ee (major) = 49%
R = *p*-ClC_6H_4: 86% de = 78% ee (major) = 58%
R = 2,4-$(Cl)_2C_6H_3$: 76% de = 28% ee (major) = 51%
R = 1-Naph: 89% de = 96% ee (major) = 68%

Scheme 95. Titanium(IV)-catalysed pinacol coupling reaction of aldehydes.

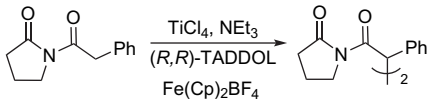
In 2005, similar reactions were developed by Studer and Knoop by using, for the first time, a chiral Ti(III)–TADDOLate.[153] In this study, it was demonstrated that cyclohexadienyl-Ti(IV) complexes underwent thermal Ti–C bond homolysis to generate the corresponding Ti(III) complexes. These Ti(III) complexes could be used in the reductive dimerisation of benzaldehyde, yielding the corresponding diol in moderate yield and stereoselectivity (Scheme 96).



48% de = 50% ee (major) = 56%

Scheme 96. Titanium(III)-catalysed pinacol coupling reaction of benzaldehyde.

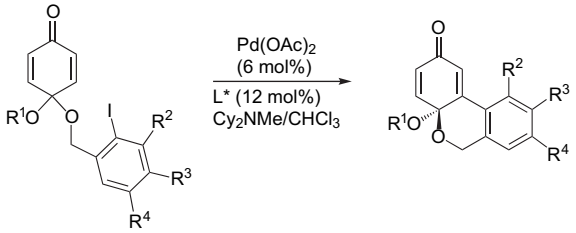
On the other hand, TADDOL has also been involved as a chiral ligand in an enantioselective oxidative coupling of the titanium enolate of 3-phenylacetyl-2-oxazolidinone with a ferrocenium cation as oxidant, affording the corresponding chiral dimer with high yield, moderate diastereoselectivity and good enantioselectivity, as shown in Scheme 97.[154]



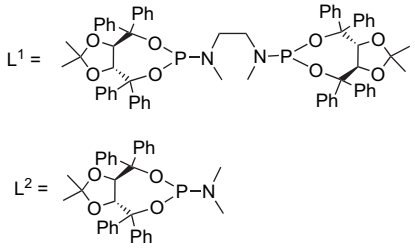
91% *dl* : *meso* = 25:75
ee = 76%

Scheme 97. Oxidative coupling of titanium enolate with $Fe(Cp)_2BF_4$.

In the last 28 years, the asymmetric Heck reaction has received considerable attention, providing high enantioselectivities, which have been reached by using chiral bidentate ligands.[155] As an example, Feringa et al. have developed a highly enantioselective intramolecular Heck reaction of cyclohexadienone monoacetals, as new substrates, performed in the presence of a bidentate TADDOL-based phosphoramidite as a chiral ligand, as shown in Scheme 98.[156] Moreover, these workers have made the remarkable finding that chiral monodentate phosphoramidites, such as those derived from TADDOL and depicted in Scheme 98, were effective ligands for this highly enantioselective reaction with up to 96% ee.

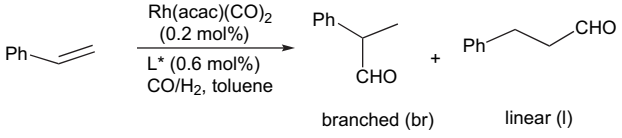


with L* = L^1:
R^1 = Me, R^2 = R^3 = R^4 = OMe: 100% ee = 90%
R^1 = *i*-Pr, R^2 = R^3 = R^4 = H: 90% ee = 73%
R^1 = R^2 = Me, R^3 = R^4 = H: 98% ee = 70%
R^1 = Me, R^2 = OMe, R^3 = R^4 = H: 87% ee = 92%
R^1 = Me, R^2 = R^3 = R^4 = OMe: 80% ee = 83%
with L* = L^2:
R^1 = Me, R^2 = R^3 = R^4 = OMe: 100% ee = 96%
R^1 = *i*-Pr, R^2 = R^3 = R^4 = H: 89% ee = 78%
R^1 = R^2 = Me, R^3 = R^4 = H: 95% ee = 73%
R^1 = Me, R^2 = OMe, R^3 = R^4 = H: 83% ee = 94%
R^1 = Me, R^2 = R^3 = R^4 = OMe: 84% ee = 87%

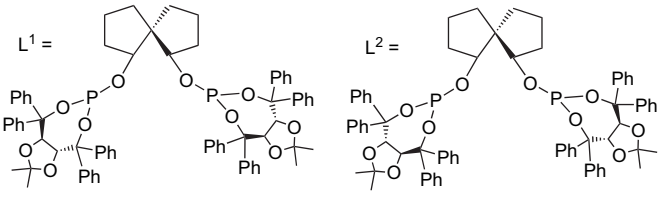


Scheme 98. Intramolecular Heck reaction of cyclohexadienone monoacetals.

In a different context, Xue and Jiang have reported a rhodium-catalysed asymmetric hydroformylation of styrene performed in the presence of a chiral diphosphite derived from TADDOL.[157] Therefore, the use of a chiral diphosphite, derived from a (1*R*,5*S*,6*R*)-*trans*,*trans*-spirol and (*R*,*R*)-TADDOL or (*S*,*S*)-TADDOL, allowed moderate enantioselectivities to be obtained, as shown in Scheme 99. The fact that the pair of diastereomeric ligands gave the opposite configuration of the product implied that the sense of enantioface selection was mainly dictated by the configuration of the terminal group on the ligand.

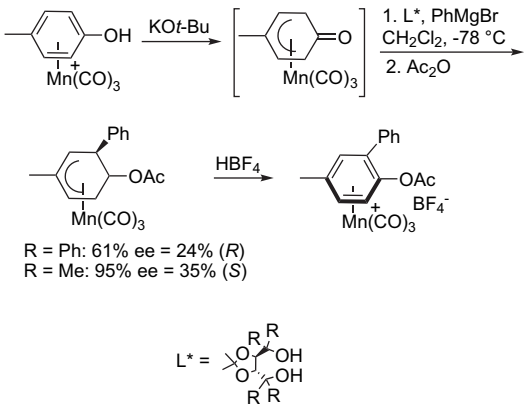


at 40 °C:
with L* = L^1: 19% br/l = 82/18 ee = 32% (*S*)
with L* = L^2: 62% br/l = 77/23 ee = 47% (*R*)
at 50 °C:
with L* = L^2: 38% br/l = 75/25 ee = 49% (*R*)



Scheme 99. Hydroformylation of styrene.

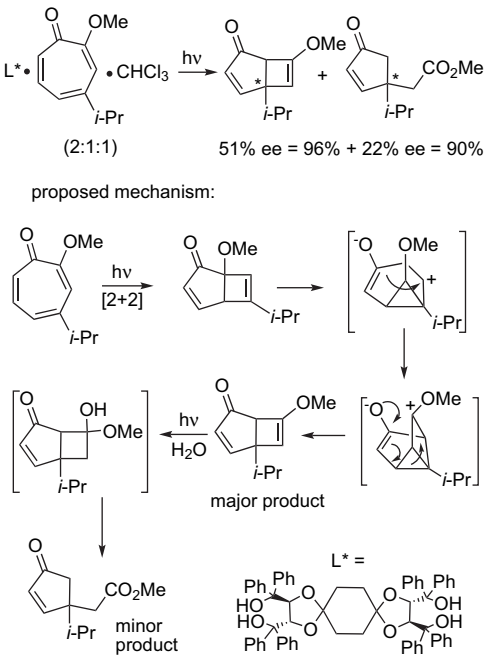
In 2002, Chung et al. described the first example of the synthesis of planar chiral (1,3-disubstituted arene)$Mn(CO)_3^+$ cations by the reaction of (*p*-cresol)$Mn(CO)_3^+$ with *t*-BuOK, followed by the addition of nucleophiles and subsequent quenching with electrophiles in the presence of a chiral ligand, such as a TADDOL derivative.[158] A final treatment with HBF_4 generated the expected planar chiral (1,3-disubstituted arene)$Mn(CO)_3^+$ cations. As shown in Scheme 100, only a moderate enantioselectivity was induced in this sequential nucleophile/electrophile addition to the prochiral manganese complex, while the involvement of (*S*)-BINOL as a ligand provided up to 98% ee, as shown in the same study.



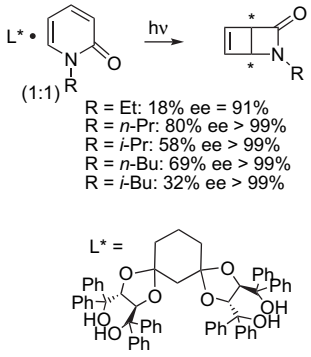
Scheme 100. Synthesis of planar chiral (1,3-disubstituted arene)$Mn(CO)_3^+$ cation.

TADDOLs are known to crystallise especially well in the presence of hydrogen-bond acceptors, with which they also form inclusion compounds. Pioneering research in the area of chiral recognition by TADDOL derivatives has proved that these compounds were efficient resolving agents for a variety of basic species, such as amines, alcohols, carbonyl compounds and sulfoxides, through the formation of H-bonded inclusion compounds.[159] These observations provided the impetus for the subsequent development of enantioselective reactions, employing inclusion complexes of prochiral guest molecules with TADDOL hosts.[160] Therefore, when racemic guest molecules are arranged in a chiral form in their inclusion crystal with a chiral host compound, such as TADDOL, its chirality can be fixed by a photochemical or chemical reaction to give optically active products. As an example, Tanaka et al. have developed the enantioselective photocyclisation of 4-isopropyltropolon-2-yl methyl ether in inclusion crystals with a chiral host compound, such as a TADDOL derivative.[161] Thus, the irradiation of a 2:1 (host/guest) inclusion complex led to the formation of the expected bicyclic cyclopentenone in up to 96% ee, along with another chiral cyclopentenone in up to 90% ee, which might have been obtained by photochemical addition of water in the atmosphere to the double bond of the former cyclopentenone, followed by ring opening during photoirradiation (Scheme 101). Concerning the formation of the major cyclopentenone, a Chapman mechanism was supposed to occur, in which a first disrotatory photocyclisation of the tropolone occurred enantioselectively to give the first-formed cyclopentenone, which was further converted into the major product.[162]

In 2002, the scope of this methodology was extended to the highly enantioselective photocyclisation of 1-alkyl-2-pyridones to the corresponding β-lactams.[163] In this case, a 1:1 inclusion complex of a chiral TADDOL-derived host compound and the pyridinone was photoirradiated in the solid state, giving rise to the expected chiral β-lactams in good yield and high enantioselectivities of 91–99% ee, as shown in Scheme 102.



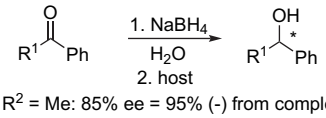
Scheme 101. Photocyclisation of 4-isopropyltropolon-2-yl methyl ether by inclusion complexation.



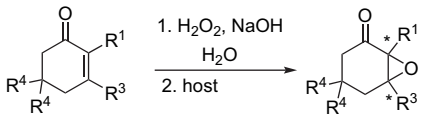
Scheme 102. Photocyclisation of 1-alkyl-2-pyridones by inclusion complexation.

Indeed, crystalline inclusion complexes of guest compounds with chiral hosts, such as TADDOLs, are useful as media for molecular recognitions and various selective reactions in the solid state. In this area, Toda et al. have developed a one-pot preparation of optically active alcohols, epoxides and sulfoxides on the basis of a combination of synthesis and enantiomeric resolution with TADDOLs as chiral hosts in a water suspension medium.[164] This process is based on the combination of a solid-state reaction in a water suspension medium and an enantioselective inclusion complexation of the product with a chiral host compound, such as a TADDOL derivative, in the same aqueous medium. This novel simple, economical and ecological method consisted of the preparation of a racemic compound by carrying out a chemical reaction in a water suspension medium, followed by the addition of a chiral host to the medium to give an inclusion complex with one enantiomer of the racemic product. From the inclusion complex, an optically active compound was obtained. The successful application of this methodology to the synthesis of chiral alcohols, epoxides and sulfoxides in high enantioselectivities of up to 100% ee is summarised in Scheme 103.

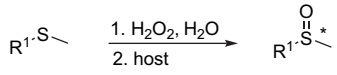
Thermodynamic resolution through the formation of inclusion complexes with chiral hosts, such as TADDOLs, has been studied as



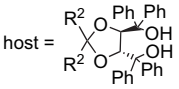
$R^1 = R^2$ = Me: 85% ee = 95% (-) from complex +
70% ee = 77% (+) from filtrate
R^1 = Et, R^2 = Me: 96% ee = 62% (-) from complex +
50% ee = 52% (+) from filtrate
R^1 = *o*-Me-py, $R^2,R^2 = (CH_2)_4$: 44% ee = 99% (-) from complex +
100% ee = 40% (+) from filtrate
R^1 = *m*-Me-py, R^2 = Me: 88% ee > 99% (+) from complex +
86% ee = 73% (-) from filtrate
R^1 = *p*-Me-py, $R^2,R^2 = (CH_2)_4$: 80% ee = 77% (+) from complex +
82% ee = 36% (-) from filtrate
R^1 = 2-Fu, R^2 = Me: 76% ee = 93% (+) from complex +
96% ee = 50% (-) from filtrate
R^1 = 2-Thio, R^2 = Me: 84% ee = 86% (-) from complex +
61% ee = 43% (+) from filtrate



$R^1 = R^3 = R^4$ = H, $R^2,R^2 = (CH_2)_4$: 38% ee = 100% (+)
from complex + 78% ee = 51% (-) from filtrate
$R^1 = R^4$ = H, R^3 = Me, $R^2,R^2 = (CH_2)_4$: 61% ee = 97% (+)
from complex + 89% ee = 78% (-) from filtrate
R^1 = Me, $R^3 = R^4$ = H, $R^2,R^2 = (CH_2)_4$: 63% ee = 63% (-)
from complex + 100% ee = 31% (+) from filtrate



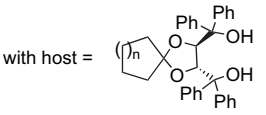
R^1 = Ph, $R^2,R^2 = (CH_2)_5$: 82% ee = 57% (+)
from complex + 73% ee = 54% (-) from filtrate
R^1 = *p*-Tol, $R^2,R^2 = (CH_2)_5$: 75% ee = 98% (+)
from complex + 78% ee = 51% (-) from filtrate
R^1 = *c*-Pent, $R^2,R^2 = (CH_2)_5$: 89% ee = 78%
R^1 = Cy, $R^2,R^2 = (CH_2)_5$: 55% ee = 49% (-)
from complex + 100% ee = 31% (+) from filtrate

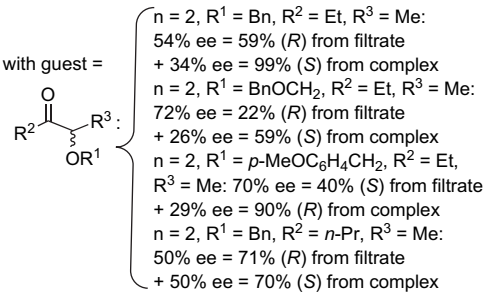


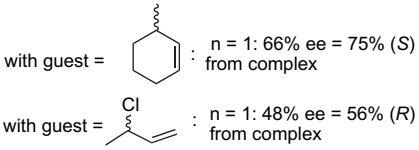
Scheme 103. Combinations of synthesis and enantiomeric resolution by inclusion complexation.

an attractive approach to obtain various optically active compounds. In this context, a number of simple optical resolutions by inclusion complexation with a TADDOL derivative as a chiral host have been developed in recent years. Indeed, the inclusion complexation methodology using TADDOLs as chiral hosts is also a useful and straightforward procedure for the preparation of optically active compounds by simple optical resolution. The selectivity of this process, based on the formation of a molecular complex between a neutral chiral host (TADDOL) and just one enantiomer from a racemate, is a function of host versatility, character of guest (size, polarity, solubility and capability of H-bond formation) and resolution conditions. This type of optical resolution has been applied to various racemic guest compounds, such as hydrocarbons, with moderate enantioselectivities,[164b] and acyclic α-hydroxy ketone derivatives,[165] with enantioselectivities of up to 99% ee, along with a quantitative recovery of the chiral host in each case (Scheme 104).

In 2003, Vinogradov et al. reported a highly efficient resolution of α-cyclopropylethanol on the basis of the crystallisation of its inclusion complexes with a chiral host, providing the corresponding (*R*)-enantiomer in >98% ee by using (*S*,*S*)-TADDOL as the chiral

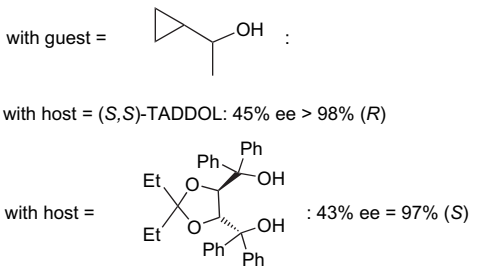






Scheme 104. Optical resolutions of α-hydroxy ketones and hydrocarbons by inclusion complexation.

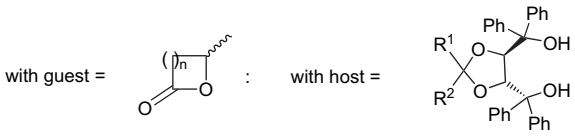
host, or the (*S*)-enantiomer in 97% ee by using a chiral (*R*,*R*)-TADDOL derivative as the chiral host (Scheme 105).[166] Moreover, the starting chiral host could be almost quantitatively recovered. In 2006, the optical resolution of another alcohol, 1-phenylethanol, was studied by Livingston et al. In this study, these workers developed a novel chiral separation process, which used a combination of the enantioselective inclusion complexation methodology and organic solvent nanofiltration.[167] In this process, a racemate was added to a chiral host suspended in a resolution solvent. The (*S*)-enantiomer enantioselectively co-crystallised with the chiral host, while the (*R*)-enantiomer remained in the liquid. Nanofiltration of the resulting resolution suspension eluted the (*R*)-enantiomer, retaining the chiral host and the chiral host–(*S*)-enantiomer complex. A decomplexation solvent was then added to dissolve and dissociate the complex into the (*S*)-enantiomer and host. This solution was subsequently nanofiltered to elute the (*S*)-enantiomer, while the soluble host was retained by the membrane. Exchanging the decomplexation solvent caused the host to recrystallise, and it was returned quantitatively to the next cycle. This novel technology was investigated, using 1-phenylethanol as the guest and (*R*,*R*)-TADDOL as the chiral host, providing enantioselectivities of up to 93% ee.



Scheme 105. Optical resolution of α-cyclopropylethanol by inclusion complexation.

On the other hand, Tanaka et al. have reported the optical resolution of a series of medium-sized lactones by inclusion complexation with TADDOLs as the chiral hosts.[168] Interestingly, a remarkable odd–even effect on the enantioselectivity in the

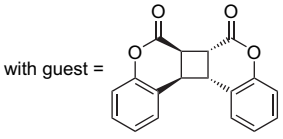
inclusion complexation was observed during the course of this study. For example, an (*R*,*R*)-TADDOL derivative (R^1,R^2=$(CH_2)_4$, Scheme 106) included the (*S*)-enantiomer of the four- and six-membered ring lactones, whereas this host included the (*R*)-enantiomer of the corresponding five- and seven-membered ring lactones (Scheme 106).



n = 1, R^1 = R^2 = Me: 15% ee = 59% (*S*)
n = 2, R^1 = R^2 = Me: 22% ee = 38% (*S*)
n = 3, R^1 = R^2 = Me: 23% ee = 45% (*R*)
n = 1, R^1,R^2 = $(CH_2)_4$: 9% ee = 52% (*S*)
n = 2, R^1,R^2 = $(CH_2)_4$: 22% ee = 38% (*R*)
n = 3, R^1,R^2 = $(CH_2)_4$: 19% ee = 80% (*S*)
n = 4, R^1,R^2 = $(CH_2)_4$: 7% ee = 44% (*R*)
n = 1, R^1,R^2 = $(CH_2)_5$: 21% ee = 44% (*S*)
n = 2, R^1,R^2 = $(CH_2)_5$: 26% ee = 11% (*R*)
n = 3, R^1,R^2 = $(CH_2)_5$: 20% ee = 17% (*S*)

Scheme 106. Optical resolution of medium-sized lactones by inclusion complexation.

In 2003, Ding and Zhao achieved a highly efficient optical resolution of an anti-head-to-head racemic coumarin dimer by molecular complexation with (*R*,*R*)-TADDOL, providing the enantiopure enantiomers in 99% ee each (Scheme 107).[169] These chiral products were further used as starting materials for the synthesis of a new type of C_2-symmetric biphosphine ligand.

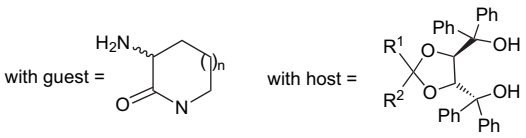


with host = (*R*,*R*)-TADDOL: 70% ee = 99% (*S*,*S*,*S*,*S*)
from complex + 75% ee = 99% (*R*,*R*,*R*,*R*) from filtrate

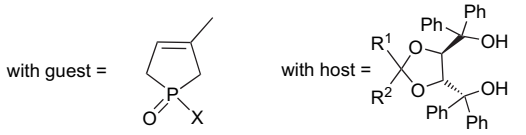
Scheme 107. Optical resolution of anti-head-to-head racemic coumarin dimer by inclusion complexation.

In 2007, Tanaka et al. reported a highly efficient optical resolution of α-aminolactams by selective complexation with TADDOL-derived hosts.[170] In this study, it was shown that the presence of the amino substituent on the lactam ring played an essential role in efficient chiral recognition in the inclusion crystals. The best results are collected in Scheme 108. In addition, 1-substituted 3-methyl-3-phospholene 1-oxides have been successfully resolved by the same methodology by Novak et al., using (*R*,*R*)-TADDOL as the chiral host.[171] As shown in Scheme 108, excellent enantioselectivities of up to 99% ee were obtained for the resolution of both cyclic phosphine oxides and phosphinates.

In addition to its application to the simple optical resolution of racemic compounds, the host–guest inclusion complexation technique has been applied to the deracemisation of racemic compounds, such as α-substituted ketones, under basic conditions. Therefore, Tsunoda et al. have demonstrated that the deracemisation of 2-alkylcycloalkanones by using a TADDOL-derived host was a convenient and excellent method, especially for the preparation of optically active α-substituted cyclohexanones, as shown in Scheme 109.[172] In 2007, the scope of this methodology was extended by Matsumoto et al. to an efficient approach to chiral acyclic α-hydroxy ketones by dynamic resolution.[173] In this case, K_2CO_3 was employed as the standard base, providing enantioselectivities of up to 96% ee, as depicted in Scheme 109.

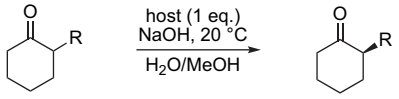


n = 1, R^1,R^2 = $(CH_2)_5$: ee > 99% (*S*)
n = 2, R^1,R^2 = $(CH_2)_5$: ee > 99% (*S*)
n = 2, R^1 = R^2 = Me: ee > 99% (*S*)

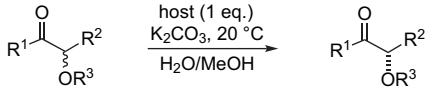


R^1 = R^2 = Me, X = Ph: 44% ee = 97% (*S*)
R^1,R^2 = $(CH_2)_5$, X = Ph: 29% ee > 99% (*S*)
R^1 = R^2 = Me, X = *n*-Pr: 35% ee = 95% (*R*)
R^1,R^2 = $(CH_2)_5$, X = *o*-Tol: 41% ee > 99% (*S*)
R^1,R^2 = $(CH_2)_5$, X = *p*-Tol: 30% ee > 99% (*S*)
R^1,R^2 = $(CH_2)_5$, X = 1-Naph: 55% ee > 99%
R^1,R^2 = $(CH_2)_5$, X = *n*-Pr: 30% ee = 89% (*S*)
R^1,R^2 = $(CH_2)_5$, X = OEt: 50% ee = 95% (*R*)
R^1,R^2 = $(CH_2)_5$, X = O*i*-Pr: 37% ee > 99% (*R*)

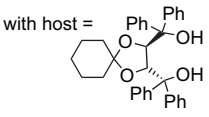
Scheme 108. Optical resolutions of α-aminolactams and 3-methyl-3-phospholene 1-oxides by inclusion complexation.



R = Bn: 100% ee = 74%
R = *m*-TolCH_2: 98% ee = 86%
R = *p*-TolCH_2: 96% ee = 82%
R = $CH_2CH{=}C(Me)_2$: 97% ee = 90%
R = $(CH_2)_2OMe$: 96% ee = 94%



R^1 = Et, R^2 = Me, R^3 = Bn: 100% ee = 96%
R^1 = *n*-Pr, R^2 = Me, R^3 = Bn: 99% ee = 95%
R^1 = *n*-Bu, R^2 = Me, R^3 = Bn: 95% ee = 63%
R^1 = CH=CH-C≡CH, R^2 = Me, R^3 = Bn: 94% ee = 61%
R^1 = R^2 = Me, R^3 = Bn: 96% ee = 52%
R^1 = Ph, R^2 = Me, R^3 = Bn: 86% ee = 98%
R^1 = R^2 = Et, R^3 = Bn: 95% ee = 71%
R^1 = Et, R^2 = Me, R^3 = *p*-$MeOC_6H_4CH_2$: 100% ee = 72%



Scheme 109. Deracemisations of 2-alkylcyclohexanones and α-hydroxy ketones by inclusion complexation.

N-Nitrosamines are known to be strong carcinogenic and mutagenic agents and, consequently, are the subject of continuing interest for biological chemists. In this area, Polonski et al. have showed that several *N*-nitrosopiperidines could be resolved to enantiomers by inclusion crystallisation with a TADDOL-derived host.[174] The chirality of these compounds resulted solely from the restricted N–N rotation and the interconversion between the

enantiomers occurred by rotation of the nitroso group. Since the corresponding energy barrier was relatively high (23–25 kcal/mol), it was reasonable to expect isolation of the enantiomers at ambient temperature. A range of *N*-nitrosamines were successfully resolved, with yields of the resolution, exceeding 50% in all cases. For example, the (*S*)-enantiomer of 1-nitroso-4-phenylpiperidine was obtained in 78% yield.

8. Conclusions

Since its introduction by Seebach, TADDOL has generated a great diversity of readily accessible derivatives, which have become among the most widely used ligands for both stoichiometric and catalytic asymmetric reactions. This review updates the principal and highly versatile reactions, which employ TADDOLs and their derivatives as chiral ligands as well as chiral auxiliaries, reported in the literature since 2001, and has illustrated in depth the diversity of useful products that can be obtained through the use of these powerful versatile chiral reagents. Indeed, the last seven years have witnessed significant developments in the efficiency and scope of using TADDOLs and their derivatives as chiral inductors. In particular, the varied utility and ability of TADDOL as a catalyst in a number of asymmetric reactions established TADDOL as one of the most privileged ligands.[175] In addition, a number of enantioselective organocatalysed reactions involving TADDOLs and their derivatives as organocatalysts have recently appeared in the literature. Moreover, a number of simple optical resolutions of racemic compounds by inclusion complexation with a TADDOL derivative as a chiral host have been developed in recent years, furnishing an alternative and attractive approach to obtain optically active compounds. Finally, a number of crystalline inclusion complexes of guest compounds with TADDOLs have been useful as media for various selective reactions in the solid state.

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Biographical sketch

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