Stereochemistry

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The Diaryl(oxy)methyl Group: More than an Innocent Bystander in Chiral Auxiliaries, Catalysts, and Dopants

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asymmetric synthesis · chirality · homogeneous catalysis · liquid crystals · synthetic methods

Dedicated to Professor Henri Kagan

Either as the free alcohol or deprotonated, a carbinol residue bearing gemial, identical aryl residues can at first sight be recognized as an achiral structural unit. When incorporated, however, into a chiral molecule, the two aryl groups become diastereotopic. Thus, they might contribute to an enhancement in stereoselectivity and do so in a variety of reactions. This Minireview highlights developments in stereochemistry when the diaryl(oxy)methyl group is involved, with emphasis given to the beneficial effect of this moiety. Of particular focus are auxiliaries, the stoichiometric use of metal complexes, metal and organocatalysts, and finally chiral dopants for liquid crystals, all featuring the diaryl(oxy)methyl group.

1. Introduction

When following the progress of asymmetric synthesis during the last few decades, keeping in mind the large variety of chiral auxiliaries, additives, ligands, and catalysts, one becomes aware of a recurring structural motif: the geminal diaryl group, attached to a carbon or a heteroatom.[1] Similar to the geminal dimethyl group, which is well known for exhibiting a Thorpe–Ingold effect,[2] the geminal diaryl counterpart favors cyclization and reduces dramatically the conformational mobility.[3] The group, when consisting of identical aryl residues—which is the case almost exclusively—is not a stereogenic unit per se. However, if it is incorporated in a chiral molecule, the two aryl rings become diastereotopic, thus creating an additional chiral environment. In reactions of such a compound, the relevant transition state has a fixed conformation, wherein the geminal diaryl pattern emerges as a temporary stereogenic unit.

The beneficial effect of diastereotopic phenyl groups in asymmetric synthesis was recognized early on in the form of diphenylphosphanyl groups on a chiral backbone and used as ligands for transitions metals. Noyori's binap–ruthenium(II) dicarboxylate complexes (Figure 1) became the most prominent examples.[4] Interestingly, the propeller shape of the geminal diphenyl motif had already been recognized in the 1970s by Kagan in a crystal structure of the [(diop)Ir(cod)Cl] complex[5] (Figure 1).

This Minireview, however, is concerned with the geminal diaryl motif when it is incorporated in the diarylhydroxymethyl or—in a more general form, including the deprotonated form—diaryl(oxy)methyl group and its use in asymmetric synthesis. In an alcohol, the replacement of α-hydrogen atoms or alkyl substituents by aryl residues will lead to an enhanced Brønsted acidity of the hydroxy group and Lewis acidity of a metal bound to the oxygen atom. One has to expect an influence on the strength of the hydrogen bridges in the alcohol as well as on the reactivity of metal complexes formed after deprotonation. It will be shown that a series of versatile and frequently applied reagents (both metal-bound and metal-free), stoichiometric auxiliaries, as well as catalysts take advantage of the beneficial effect of this group. Provided that the corresponding data are available, it will be indicated

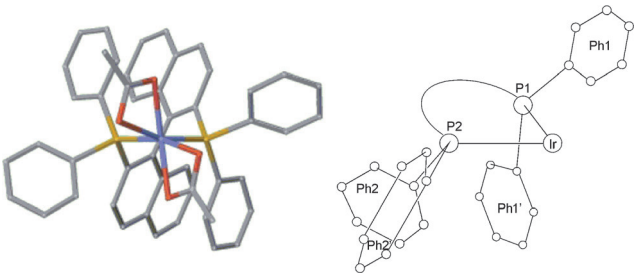

Figure 1. Structure of the complex [{(*S*)-binap}Ru(OAc)$_2$] (left: stick model, from Ref. [4]) and drawing of the complex [{(*S*,*S*)-diop}Ir-(cod)Cl] (cod = cycloocta-1,5-diene; right: from Ref. [5]).

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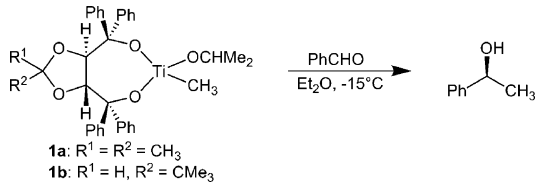
whether the geminal diaryl substitution pattern is crucial to the formation, reactivity, and selectivity of the relevant reagents or catalysts. In a similar way, the importance of the diarylhydroxymethyl or diaryl(oxy)methyl group for the efficiency of chiral dopants will be illustrated.

2. The Diaryl(oxy)methyl Group in Asymmetric Synthesis

2.1. Chiral Auxiliaries

Chronologically, the first report on the stoichiometric use of a reagent containing the diaryl(oxy)methyl motif in its deprotonated form is embedded in a short review on titanium reagents by Seebach et al. in 1983.[6] Therein, it is mentioned briefly that a methyl group was transferred from the titanium reagents **1a** or **1b** to benzaldehyde in an enantioselective manner, and 1-phenylethanol was obtained in 70 and 92% *ee*, respectively (Scheme 1). The chiral auxiliary group present as



Scheme 1. Enantioselective methyl transfer to benzaldehyde by using titanium TADDOLates.

a backbone in the titanium reagents **1** became well known as the prototype of TADDOLs **2**,[7] which became used as stoichiometric auxiliaries, chiral dopants for liquid crystals, as hosts in inclusion compounds, and highly efficient chiral mediators in both metal and organocatalysis. An immense number of applications underline the versatility of those chiral reagents derived from tartaric acid.[8] The superimposed structures of TADDOLs shown in Figure 2 reveal the propeller shape that is common to all TADDOL derivatives and their similarity to the chiral complexes shown in Figure 1.[8a]

Manfred Braun, born in 1948 in Schwalbach/Saar, studied chemistry at the University of Karlsruhe, and completed his PhD under Professor Dieter Seebach in Gießen in 1975. After postdoctoral research with Professor George H. Büchi at the Massachusetts Institute of Technology in 1975–1976, he joined Professor Hans Musso's research group at the University of Karlsruhe and completed his Habilitation there in 1981. Since 1985, he has been a professor of organic chemistry at the Heinrich-Heine-University Düsseldorf. His research interests include the development of new synthetic methods (especially for asymmetric synthesis), organometallic chemistry, development of metal complexes as smart materials, and syntheses of biologically active compounds.

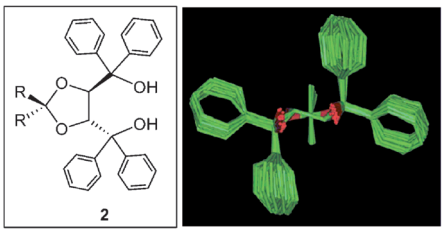
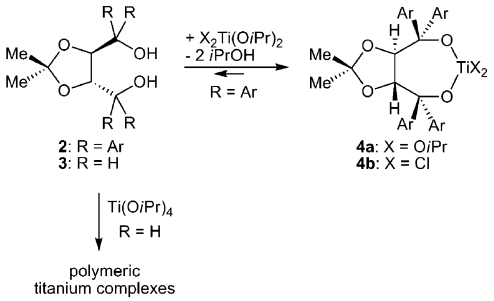


Figure 2. TADDOL prototype **2** (R = Me) and superimposition of crystal structures [R = Me, R-R = $(CH_2)_4$, R-R = $(CH_2)_5$]; from Ref. [8a].

In the formation of seven-membered cyclic titanium-TADDOLates, the geminal diaryl groups clearly favor the ring closure by acting in the sense of the Thorpe–Ingold effect and creating a conformation that is suitable for a chelation. Thus, as shown in Scheme 2, diol **3** which does not contain a



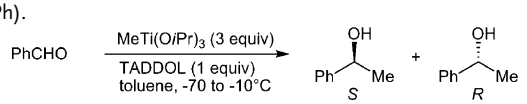
Scheme 2. The crucial role of geminal diaryl groups for the formation of titanium TADDOLates **4**.

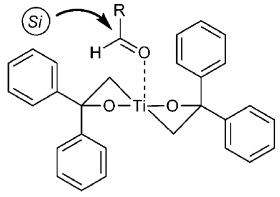
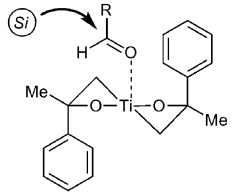
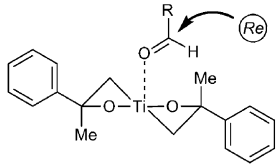
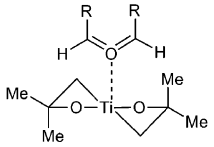
geminal diaryl or dialkyl substitution pattern leads to polymeric titanium alkoxides, whereas equilibria of TADDOLs **2** and $Ti(OiPr)_4$ or $Cl_2Ti(OiPr)_2$ lie on the side of the titanium TADDOLates **4a** and **4b**, respectively, and can be further shifted towards the products by removing 2-propanol with the solvent.[9] A spirocyclic bischelated titanium compound is another participant in the equilibria between TADDOLs and TiX_4.[10] Protocols for the selective and quantitative generation of the individual TADDOLates have been elaborated.[10,11] The various stoichiometric applications of TADDOLates are not discussed here, as they have already been reviewed comprehensively.[7,8]

The influence of the geminal substitution pattern of titanium TADDOLates on the enantioselectivity of the nucleophilic addition shown in Scheme 1 has been studied and rationalized on the basis of a model in which a precoordination of a molecule of benzaldehyde is postulated.[12] The results are shown in Table 1; for reasons of clarity, the dioxolane backbone is omitted. Benzaldehyde is attacked from the front side, either from the *Re* or *Si* face—depending on the geminal substitution pattern.

The highest enantioselectivity was reached with the TADDOL prototype **2** with the geminal diphenyl group (entry 1). The importance of the two quasiaxial phenyl groups is illustrated by the results given in entries 2 and 3: Substantial preference for attack at the *Si* face is maintained, as long as the phenyl groups are in the quasiaxial position, while the

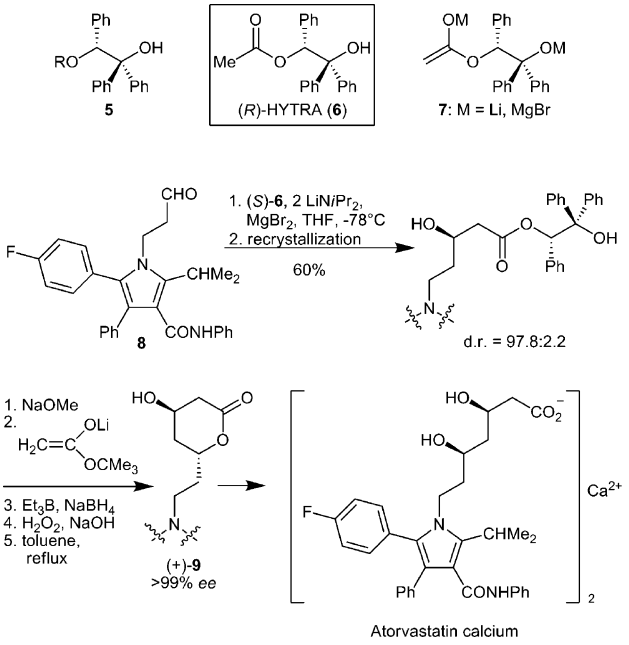
Table 1: Influence of the substitution pattern at the carbinol center in TADDOL derivatives on the stereochemistry of nucleophilic additions (R = Ph).



Entry	Titanium TADDOLate	1-Phenylethanol yield [%] (*S*/*R*)
1		72 (99:1)
2		81 (94:6)
3		90 (24:76)
4		66 (48:52)

quasiequatorial ones are replaced by methyl groups (entry 2). A comparison of entries 1 and 2 also indicates that electronic effects (replacement of a −I by a +I substituent) have only a minor influence on the enantioselectivity. When, however, the configurations at the carbinol centers are inverted, so that the phenyl groups adopt the quasiequatorial and the methyl groups the quasiaxial positions, the stereochemical outcome of the reaction is inverted, and (*R*)-2-phenylethanol forms as the main product (entry 3). Clearly, benzaldehyde switches from the left to the right side, thus avoiding the repulsive interaction between the formyl hydrogen atom and the quasiequatorial phenyl group, a repulsion that seems to be slightly more severe than that with the quasiaxial methyl group. As a consequence, the carbonyl group is attacked with not very high but significant selectivity at the *Re* face. When all the four phenyl groups are replaced by methyl groups, there is no preference for any one alternative way of coordination, so that a stereorandom outcome results (entry 4). The tetrabenzyl analogue of TADDOL **2** did not perform any better and was therefore called a "miserable ligand".[13] A deleterious effect on replacing the geminal diphenyl groups by dimethyl groups was also observed by Hafner, Duthaler et al. in the nucleophilic allylation in the presence of cyclopentadienyltitanium TADDOLate.[14]

Shortly after the first presentation of TADDOLs and TADDOLates in 1983, a simple chiral auxiliary was disclosed that features the diphenylhydroxymethyl group and offered a solution to the problem of the acetate aldol reaction: the ester HYTRA **6**,[15] which is readily accessible in both enantiomeric forms from mandelic acid through triphenylglycol **5**.[16] After double deprotonation, the dilithium or dimagnesium enolate **7** (Scheme 3) adds diastereoselectively to aldehydes. The removal of the auxiliary **5** (which can be recovered) by alkaline hydrolysis or transesterification leads to β-hydroxy carboxylic acids or esters in fair to high enantiomeric excess.[17]

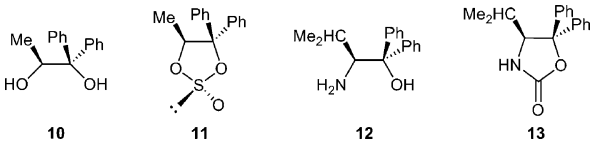


Scheme 3. The diphenylhydroxymethyl group in HYTRA (*R*)-**6**, a reagent for stereoselective acetate aldol reactions. Synthesis of Atorvastatin by stereoselective aldol addition with (*S*)-**6**.

At the time HYTRA was disclosed, a demand came for stereoselective acetate aldol reactions in the development of hydroxymethylglutaryl (HMG)-CoA-reductase inhibitors, which feature nonbranched β,δ-dihydroxy carboxylic acids or the corresponding δ-lactones as the pharmacophore. As illustrated in Scheme 3, the aldol addition of (*S*)-**6** to the heterocyclic aldehyde **8** serves as the key step in the synthesis of lactone **9**, the immediate precursor of the HMG-CoA-reductase inhibitor Atorvastatin calcium,[18] which was marketed as Lipitor, a "blockbuster" cholesterol-lowering drug.[19]

The (*S*)-lactate-derived diol **10**, which also features the diphenylhydroxymethyl group, served as the starting material for Kagan's cyclic sulfite **11**, which proved itself a versatile reagent for the enantioselective synthesis of sulfoxides. In consecutive nucleophilic substitutions at the sulfur center en route to sulfoxides, the geminal diphenyl group plays a crucial role in the stereochemical outcome (Figure 3).[20]

A practical advantage of various compounds containing the diphenyl(oxy)methyl group became evident in the applications of the chiral acetate **6**: they are, in general, readily crystallizing substances, and their recrystallization can be easily used for the enrichment of the main diastereomer.



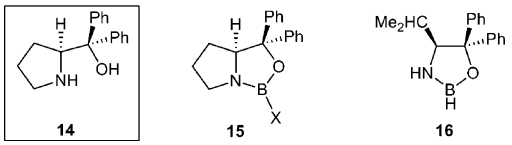
10 11 12 13

Figure 3. Incorporation of the geminal diphenyl group in heterocyclic auxiliaries: Kagan's cyclic sulfite **11** and Seebach's DIOZ (**13**) derived from diol **10** and diphenylvalinol **12**, respectively.

Guided by this idea, "a useful modification of the Evans auxiliary" was developed by Hintermann and Seebach: the heterocyclic auxiliary DIOZ **13**, derived from diphenylvalinol **12** (Figure 3).[21] After acylation, it permits not only Evans-like alkylations to be performed, but also Mannich-type reactions that lead to β-aminocarboxylic acids in high enantiomeric excess.[22] α,β-Unsaturated *N*-acyl-DIOZ derivatives have been used recently by Sorensen and co-workers in highly regioselective and diastereoselective Diels–Alder reactions in an approach directed towards hirsutellones.[23]

2.2. Metal Catalysis

Similar to the TADDOLs, an amino alcohol featuring the diphenylhydroxymethyl group—namely, diphenylprolinol **14**—became another "evergreen" chiral reagent. Before being discovered as an organocatalyst, it became prominent as the chiral backbone in the so-called CBS catalysts, which were initially developed for the enantioselective reduction of prochiral ketones to secondary alcohols by the Corey research group (Figure 4).[24] CBS catalysis, named after Corey, Bakshi, and Shibata,[25] was preceded by the work of Isuno et al., who

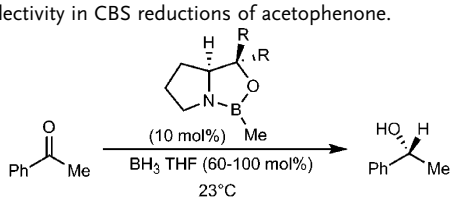


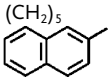
14 15 16

Figure 4. The Corey and Itsuno oxazaborolidines **15** and **16**, derived from amino alcohols **14** and **12**.

used the amino alcohol **12** (Figure 3) as an—initially stoichiometric—additive in the enantioselective reduction of prochiral ketones by boranes.[26] Corey et al. not only isolated and characterized the oxazaborolidines **15** and **16** derived from the amino alcohols **14** and **12**, respectively, they also elaborated a catalytic version of the enantioselective reduction.[25] Numerous variations of the residue R on the boron atom in diphenylprolinol-derived reagent **15** (H, alkyl, aryl), alterations to the oxazaborolidine, and, in particular, alternatives to the chiral backbone were created.[24c,d] In addition, various polymer-bound derivatives were described that permit the recovery and reuse of the catalyst.[27] Most of the CBS analogues were tested in the reduction of acetophenone to 1-phenylethanol. In this standard protocol, the effect of the substituents at the carbinyl center and the role of the geminal diphenyl group in CBS catalysts were studied. Selected results are given in Table 2.

Table 2: Influence of the substituent at the carbinyl center on the enantioselectivity in CBS reductions of acetophenone.



Entry	R	X	*ee* [%]	Ref.
1	Ph	Me	97	[24c]
2		Me	62	[24c]
3		Me	76	[24c]
4		Me	28	[24c]
5		Me	82	[24c]
6	*n*Bu	Me	55	[24c]
7	$(CH_2)_4$	H	67	[28a]
8	$(CH_2)_5$	H	71	[28a]
9		Me	98	[28b]
10		H	96	[24c]
11	H	H	>95	[29]
12	H	H	48	[30]
13	H	H	20–45	[31]
14	H	OMe	20–60	[31]
15	CF_3	*n*Pent	60	[24c]

It turns out that, compared with the parent system (entry 1), most of the alterations to the geminal substituents are deleterious to the enantioselectivity. This holds for the α-naphthyl (entry 2) and also for *ortho*-substituted aryl (entries 3 and 4) and 2-thienyl groups (entry 5). Not only the butyl (entry 6) but also cycloalkyl groups (entries 7 and 8) perform poorly. The enantioselectivity of the parent catalyst is only reached with the geminal β-naphthyl (entry 9) and the spiroindanyl substitution (entry 10) pattern. The reported highly enantioselective reduction (>95% *ee*) of acetophenone in the presence of prolinol (10 mol%; entry 11)[29] could not be reproduced by the research groups of Martens (entry 12)[30] and Xu (entries 13 and 14).[31] A detailed study revealed that the enantioselectivity increases with temperature, an effect that was rationalized by postulating an equilibrium between monomeric and dimeric oxazaborolidine.[31] In any case, prolinol-derived oxazaborolidines, which give enantiomeric excesses of 1-phenylethanol in the range of 20 to 60% *ee*, are definitely inferior and less efficient than diphenylprolinol-based oxazaborolidines.[32] The introduction of the strongly electron-withdrawing trifluoromethyl groups (entry 15) has a marginal effect compared to alkyl gropus such as butyl (entry 6). In reductions with related oxazaborolidines not derived from proline, however, electron tuning has

been observed—inasmuch as electron-withdrawing substituents on the geminal aryl groups led to an enhancement of enantioselectivity.[33] It seems that the higher Lewis acidity at the boron atom results in it forming a stronger bond to the ketone substrate in a tightened transition state.

The stereochemical outcome of the CBS-mediated reduction of acetophenone (i.e. the transfer of hydride from the *Si* face) has been rationalized by assuming the transition-state model **17** (Figure 5). Therein, the more accessible lone pair of electrons on the carbonyl oxygen atom (*cis* to the borane moiety) is coordinated to the oxazolidine boron atom. The opposite face is blocked not only by the proline ring but also by the *cis*-oriented phenyl group.[24c] The importance of the geminal diaryl substitution pattern has been rationalized by a series of early computational studies[34] as well as more recent DFT-B3LYP calculations.[35] These studies confirm the transition-state model **17** and predict the approach from the *Si* face to be favorable. Thus, the calculated and experimental enantioselectivity in favor of (*R*)-1-phenylethanol are in good agreement.

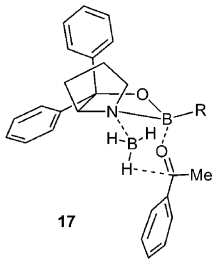
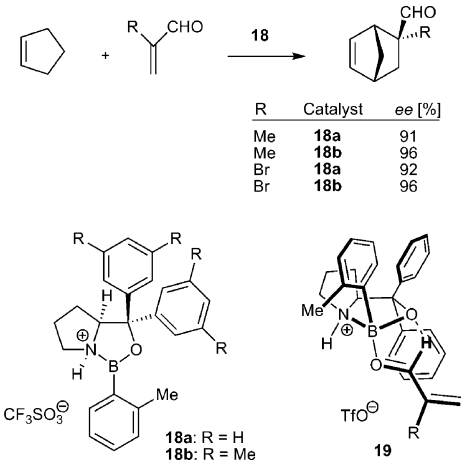


Figure 5. Postulated[25c] transition-state model for the CBS reduction of acetophenone, as confirmed by calculations.[35]

It was again the Corey research group who found that an additional, fruitful role of diphenylprolinol-derived oxazaborolidines results from protonation, preferably performed with trifluoromethanesulfonic acid. The protonated oxazaborolidines **18a** and **18b** thus obtained proved themselves to be highly efficient catalysts for stereoselective and regioselective Diels–Alder reactions.[36] A few selected, illustrative examples concerning enals (α-methyl and α-bromoacrolein)[37] are shown in Scheme 4. The model **19** that is thought to apply to these dienophiles postulates a coordination of the carbonyl group to the highly Lewis-acidic boron atom and an attractive electrostatic interaction between the formyl hydrogen atom and the oxygen atom of the oxazaborolidine ring. Furthermore, the geminal diaryl group plays a role: the aryl residue oriented *trans* to the B-aryl group exhibits a π–π interaction with the coordinated *s-trans* enal, thus completely shielding the rear side of the enal in the coordination complex **19**.[38] As a consequence, the approach of the diene is strongly directed to the front side. The fact that, in several cases, the 3,5-dimethyl substitution pattern in the geminal diaryl moiety is favorable to the enantioselectivity is easily explained by the enhanced π-electron density (compared to the unsubstituted phenyl rings), which leads to a closer π-stacking and enhanced shielding of the rear side.



Scheme 4. Selected examples of Diels–Alder reactions mediated by cationic oxazaborolidines **18**. The *endo*/*exo* ratio amounts to 91:9. Coordination complex **19** of **18a** with enals (formyl-CH···O interaction). The diene is postulated to approach from the front side, as the rear side is blocked by the geminal aryl rings.

The protocol has been successfully extended to other dienophiles such as α,β-unsaturated ketones, esters, and lactones as well as quinones.[39] More recently described variants of this type of catalysts, such as *N*-methyloxazaborolidinum cations and aluminum bromide activated oxazaborolidines as well as valine-derived oxazaborolidinium salts, also feature the geminal diaryl substitution pattern.[40]

Although the diphenyl(oxy)methyl group is not a typical structural motif in catalysis by late-transition metals, it was found to have a beneficial effect on the enantioselectivity in a rhodium-catalyzed hydrosilylation in the presence of pyridinyloxazolines,[41a] in bisoxazoline-mediated Meerwein arylation reactions of activated alkenes[41b] as well as in allylic alkylation[41c] and hydroformylation reactions.[41d] Cyclic phosphites, phosphoramidites, and phosphonites with a TADDOL backbone are also suitable ligands for late transition metals.[8a] The linkage of the diarylhydroxymethyl group to a suitably arranged nitrogen donor in an amine or imine group led to a variety of reagents being tested for their efficiency in terms of chemical yield and enantioselectivity in the addition of dialkylzinc to aldehydes to give the corresponding secondary alcohols.[42] A ferrocene moiety with planar (and in some cases additional central) chirality was often chosen as the backbone of the catalyst. A selection of ferrocene-based ligands **20a–e** is given in Figure 6.[43] The role of the geminal diaryl substitution pattern has not been elucidated in all cases. As a rule, the acidic diarylcarbinol group is deprotonated by

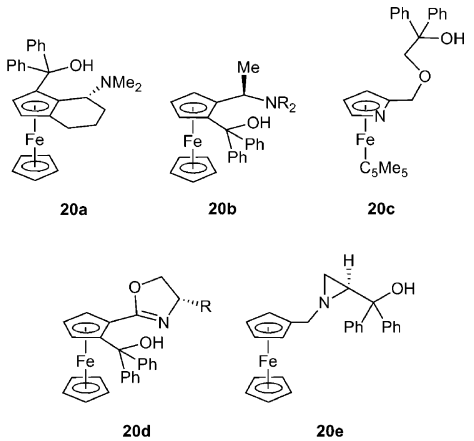
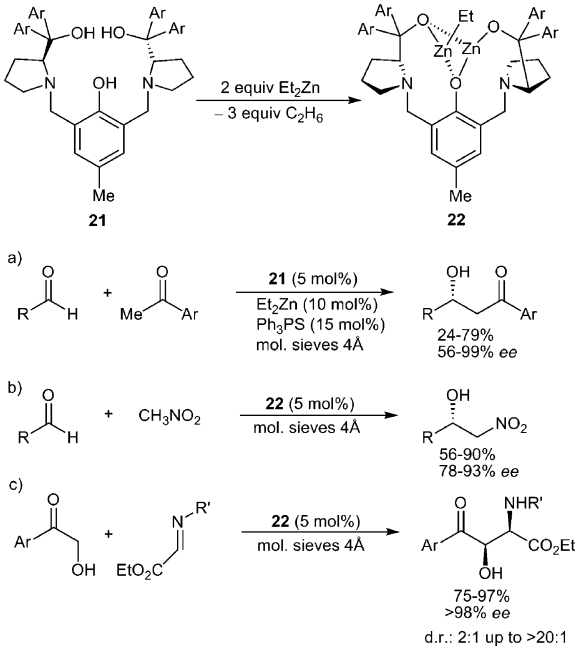


Figure 6. The diphenylhydroxymethyl moiety linked to a ferrocene-type backbone.

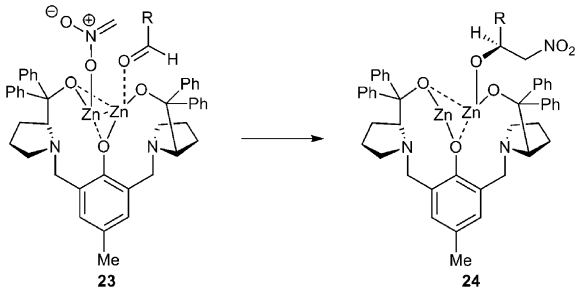
the dialkylzinc reagent to form a zinc alkoxide, where the metal is coordinated to the nitrogen atom. A remarkable catalytic reaction was reported with the ligand **20d**: the enantioselective, diethylzinc-mediated aryl transfer from boronic acids to aromatic aldehydes.[44]

The so-called Bis-Pro-Phenol ligand **21** developed by Trost et al. combines two homochiral diphenylprolinol units that are linked to the 2,6-positions of *p*-cresol.[45a] When treated with two equivalents of diethylzinc, the active bimetallic catalyst **22** forms, which might be considered a semi-crown ether.[46] The catalyst was first used in enantioselective aldol (Scheme 5a)[45a,b] and Henry (nitroaldol) reactions (Scheme 5b),[45c] as well as in diastereoselective and enantioselective Mannich reactions of α-hydroxy ketones (Scheme 5c).[45d,e] More recent applications of the Bis-Pro-Phenol ligands, or derivatives thereof, involve Friedel–Crafts-type alkylation reactions,[45f] desymmertization of *meso*-diols,[45g] additions of terminal alkynes to aldehydes,[45h,i] and various hydrophosphonylation reactions.[45j–l]



Scheme 5. Bis-Pro-Phenol ligand **21**, active bimetallic catalyst **22** (Ar = Ph), and their application in aldol (a), nitroaldol (b), and Mannich reactions (c).

According to the mechanism proposed for the aldol and nitroaldol reactions,[45a–c] the remaining ethyl group in the bimetallic catalyst is replaced by the C–H acidic component, whereas the second zinc atom coordinates to the carbonyl group of the aldehyde, which plays the role of the electrophile. In the selectivity-determining step from **23** to **24** (illustrated in Scheme 6 for the nitroaldol reaction), the nitronate moiety attacks the aldehyde from its *Re* face, thereby leading to the aldolate **24**. The preference for this topicity (observed also in the aldol reaction) has been postulated to originate from the conformational preferences of the diphenylcarbinol moieties.[45b]



Scheme 6. Proposed selectivity-determining step in the Bis-Pro-Phenol-mediated nitroaldol reaction.

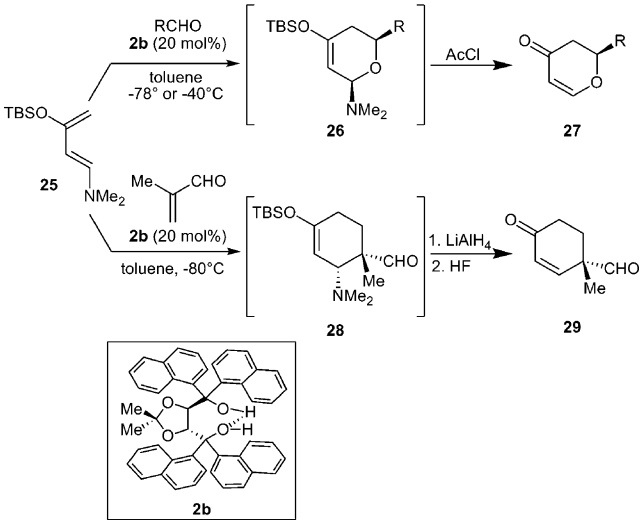
Variations to the aryl residues in ligand **21** have been studied in several cases. In the Henry reaction, the replacement of the phenyl groups in the catalyst by *p*-biphenyl (**21**, **22**: Ar = 4-PhC_6H_4) or *p*-fluorophenyl (**21**, **22**: Ar = 4-FC_6H_4) had only a modest effect on the enantioselectivity.[45m] In contrast, a beneficial effect of a *p*-biphenyl and the β-naphthyl group in place of the phenyl residues was observed in the Mannich reaction (Scheme 5c), inasmuch as both variants of the geminal diaryl pattern provided an enhanced diastereoselectivity, while maintaining the high enantiosectivity.[45d]

A recent DFT study of the Henry reaction[45n] mediated by the catalyst **22** addressed the origin of enantioselectivity. As a result, the *Re* face approach to benzaldehyde to give the *S*-configured nitro alcohol (Scheme 5b) is predicted (B3LYP) to be favored by 5.0 kcal mol^{-1}, a value that overestimates the selectivity compared with the experimentally determined value of 91 % *ee*. Interestingly, the calculation performed with the same functional for an analogous catalyst **22**, wherein the phenyl residues were replaced by methyl groups or hydrogen atoms, revealed that the preference for the *Re* face over the *Si* face decreased to 3.5 and 2.2 kcal mol^{-1}, respectively. By taking these data not as absolute values, one can estimate that the replacement of the diphenyl substituents by methyl groups or hydrogen atoms will have a deleterious effect on the enantioselectivity. Thus, according to the computational study, enantioselectivity originates from the steric repulsion between the phenyl groups of the benzaldehyde and the ligand; an experimental verification has not so far been provided.

2.3. Organocatalysis

In the past, titanium TADDOLates **4a** have been used as catalysts in nucleophilic additions to aldehydes, and Lewis-acidic titanium TADDOLates of type **4b** have largely been applied catalytically in stereoselective synthesis. The field has been reviewed comprehensively[6–8] and, therefore, does not need to be discussed in detail here. More recently, the recognition of the Brønsted-acidic character of TADDOLs **2** has led to them being used as organocatalysts.[47] The seminal work of Rawal and co-workers[47a,b] revealed that the hetero-Diels–Alder reaction between diene **25** and aldehydes was substantially accelerated by substoichiometric amounts of naphthyl-TADDOL **2b**. This resulted in cycloadducts **26** being formed smoothly and converted into dihydropyrones

27. More importantly, the reaction occurs with remarkable enantioselectvity: cycloadducts of aliphatic aldehydes formed with $\geq 83\,\%$ *ee*, while those of aromatic aldehydes were obtained in $\geq 95\,\%$ *ee*. In a homo-Diels–Alder reaction of the diene **25** with methacrolein, enone **29** was obtained in 91 % *ee* via cycloadduct **28** (Scheme 7).[47b]



Scheme 7. TADDOL **2b** as organocatalysts in Rawal's hetero-Diels–Alder reaction and Diels–Alder reaction. TBS = *tert*-butyldimethylsilyl.

TADDOL catalysis has been applied to Diels–Alder and hetero-Diels–Alder reactions with other electron-rich dienes[48] as well as to Mukaiyama aldol[49a] and vinylogous Mukaiyama aldol reactions.[49b] Another remarkable reaction that was mediated with TADDOL **2b** is the enantioselective N-nitroso aldol reaction of enamines.[50] In the Diels–Alder study, Rawal and co-workers proposed a model **30** (Figure 7)[47b] to explain the catalytic activity and selectivity: Based on crystal structure analyses, an intramolecular hydrogen bond is assumed to enhance the Brønsted acidity of the free hydrogen atom which, in turn, forms a strong hydrogen bond to the carbonyl group of the enal that serves as the dienophile.[51] The geminal diaryl pattern plays a role in a second, equally important, binding to the catalyst: a π–π donor–acceptor interaction between the electron-deficient carbon–carbon bond of the enal and the electron-rich neighboring quasiequatorial naphthyl ring, so that one face of the enal is shielded towards the attack of the diene. As a consequence, only the *Si* face of the enal is accessible to the approach of the diene.

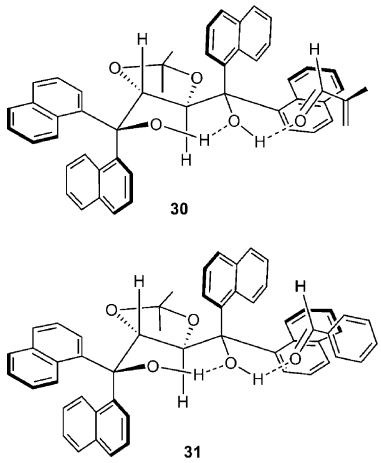


Figure 7. Proposed model for the TADDOL (**2b**) catalyzed Diels–Alder (top) and hetero-Diels–Alder (bottom) reaction. In both complexes, the diene approaches from the front side, while the rear side is blocked by the quasiequatorial naphthyl substituent.

This concept has been applied in analogy to the hetero-Diels–Alder reaction between the diene **25** and benzaldehyde, mediated by the TADDOL **2b**, and the model **31** has been proposed.[52a] Recent computational studies clearly reveal the crucial role of the geminal dinaphthyl groups for the stereochemical outcome. Aside from postulating that TADDOL **2b** forms a hydrogen bond to benzaldehyde, they emphasize π stacking with the quasiequatorial naphthyl residue[52] (as proposed by Rawal and co-workers), avoidance of steric hindrance,[53] or a formyl-H–π-interaction with the naphthyl residue.[54] Despite these differences, the relevance of the geminal diaryl substitution pattern is taken into account in all these calculations.

Derivatives of diarylprolinol developed into workhorses not only in metal catalysis but also in organocatalysis. Whereas hydrogen bonding of the carboxylic group of the first-generation organocatalyst, proline, is essential for catalytic activity and stereoselectivity,[55] the steric demand of the geminal diaryl group turned out to be the crucial feature, in particular in the form of the "obese"[56] diaryl(silyloxy)methyl group in the proline derivatives **32a** and **32b** reported by the research groups of Jørgensen[57] and—shortly after—Hayashi,[58] respectively. A multitude of reactions have been catalyzed by O-silyl-protected[59] diarylprolinols **32**, among them enantioselective aldol and Mannich reactions, Michael additions, vinologous additions of carbon and hetero nucleophiles to α,β-unsaturated aldehydes, and [4+2] cycloadditions of dienamides derived thereof.[60] The essential intermediates, from where the stereoselectivity-determining step starts in the catalytic cycles, are the nucleophilic enamines of type **33**, the electrophilic iminium ions **34**, or the dienamines **35** (Figure 8).

A comprehensive series of crystal structures obtained and collected recently by the Seebach research group clearly reveals the role of the diaryl(silyloxy)methyl side chain on the pyrrolidine skeleton.[56] The first function is to fix the conformation of the carbon chain attached to the nitrogen atom, as shown in structures **33**–**35**. The second function is the shielding of the front side through steric repulsion of the entering reactant, so that the approach of the corresponding reactant (i.e. an electrophile to the enamine **33**, a nucleophile to the iminium ion **34**, and the dienophile to the dienamine **35**) is forced to occur from the rear side. As a consequence, the corresponding intermediate products **36**, **37**, and **38**, respectively, form in a stereoselective manner. In the individual reaction types, the release of the catalyst and the formation of the final products take place by different reactions.

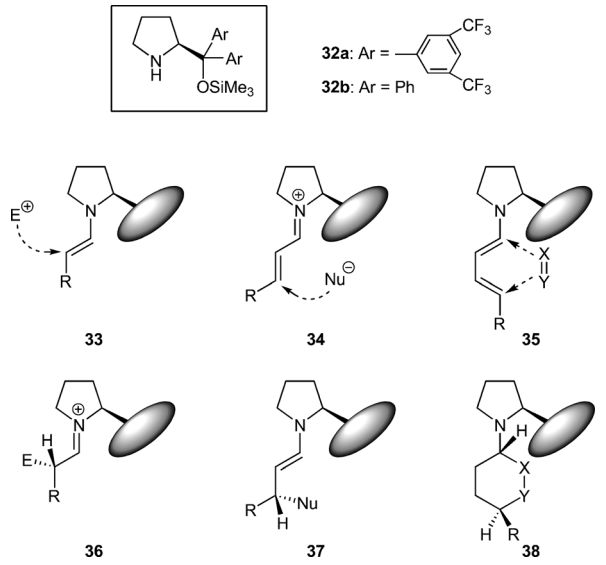


Figure 8. Organocatalysts **32** featuring the diaryl(trimethylsilyloxy)-methyl group and its influence on the stereochemical outcome of organocatalytic conversion.

A detailed computational study,[61] which may serve to illustrate the importance of the steric hindrance exhibited by the diaryl(silyloxy)methyl group, has been undertaken for the enantioselective conjugate addition of triazole to the iminium cation **34** (R = Et; Figure 9). First, the calculations at the

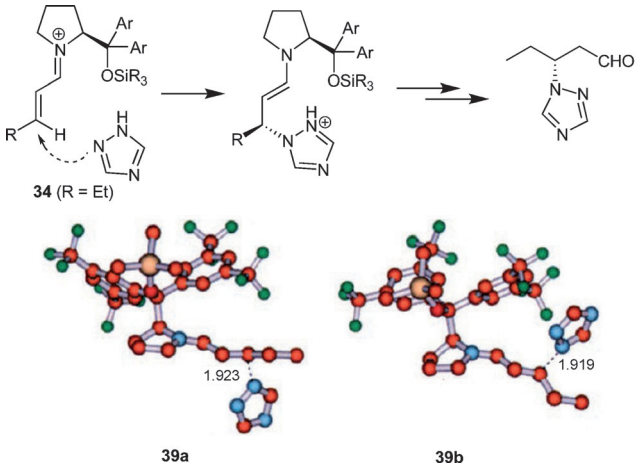


Figure 9. Addition of triazole to iminium cation **34**. Calculated transition states of bottom (left) and top (right) approach.

B3LYP/6-31G(d) level reveal the *E*-configured (concerning the carbon–nitrogen double bond) iminium cation **34** to be more stable than the *Z* isomer—a result that is in accordance with the X-ray study by Seebach and co-workers. The Gibbs free energies of the transition states **39a** (approach of the nucleophile from the bottom) and **39b** (approach from the top) were calculated. A comparison of the two transition-state models shows that in the second transition state, **39b**, the approach of the triazole will encounter severe steric repulsion form the bulky side chain. Thus, intuitively, one will expect **39b** to be disfavored compared to **39a**. Indeed, the calculations reveal transition state **39a**, which features a *Re* face attack, to be more stable by 2.0 kcal mol^{-1}. Taking into account the influence of the solvent [B3LYP/6-311G(d,p) level, using the CPCM model] the result is 1.8 kcal mol^{-1}. The former energy difference corresponds to an *ee* value of 94%, the latter to 90%. These calculated enantioselectivities are in good agreement with the experimental value of 92% *ee* of the final product 3-triazolylpentanal.

It is beyond the scope of this Minireview to discuss the large multitude of conversions that have been mediated by the organocatalysts **32**. Nevertheless, recent elegant domino reactions with silyl-protected diarylprolinols should be mentioned that proved themselves therein to be the key to high efficiency and stereoselectivity when combining enamine and iminium ion catalysis.[62]

3. The Diarylhydroxymethyl Group in Dopants for Liquid Crystals

Cholesteric liquid-crystalline compounds are considered as "smart materials" that find wide application as color-effect materials and essential components in displays and polarizers.[63] Although a variety of compounds have been found to form cholesteric phases, a particularly elegant method for the generation of a cholesteric phase is the addition of a small amount of a chiral dopant to a nematic phase so that it is converted into a cholesteric or chiral nematic phase (Figure 10). This concept is economically attractive, inasmuch as only a small amount of the precious dopant is required to

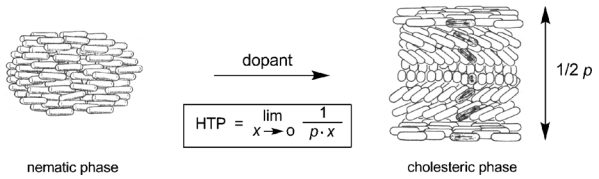


Figure 10. Conversion of a nematic into a cholesteric phase by the addition of a dopant.[63d] Definition of the helical twisting power (HTP) for small concentrations of the dopant; *p* is the pitch of the induced helix and *x* is the molar fraction of the dopant dissolved in the nematic phase.

transform a nematic phase (built from readily available, mostly commercial compounds) into a more valuable cholesteric phase. The doping also permits the pitch of the helix to be tuned so that its magnitude is in the range of visible light, which is desirable for most applications.[64]

Usually, it is the aim when developing efficient chiral dopants to use as small an amount of the dopant as possible to induce maximum helicity. The efficiency of the dopant is quantified by the so-called "helical twisting power" (HTP), which is defined (Figure 10) for small concentrations of the ligand, where *p* is the pitch of the induced helix, and *x* is the molar fraction of the dopant dissolved in the corresponding nematic phase. HTP values of a certain dopant depend slightly on the temperature, but to a much higher degree on

the individual nematic phase. A large variety of chiral natural products and derivatives thereof as well as resolved compounds have been applied as chiral dopants. HTP values in the range of 100 μm^{-1} are usually considered as "high".[65] As far as chiral dopants featuring the diarylhydroxymethyl motif are concerned, the TADDOLs again turned out to be a "Jack-of-all-trades," and the TADDOL derivative **40** became—at least for a while—the record-holder of HTP values, amounting to an impressive 534 μm^{-1} in so-called 5-CB, a nematic phase that features the cyanobiphenyl structure. (Figure 11).[7,66]

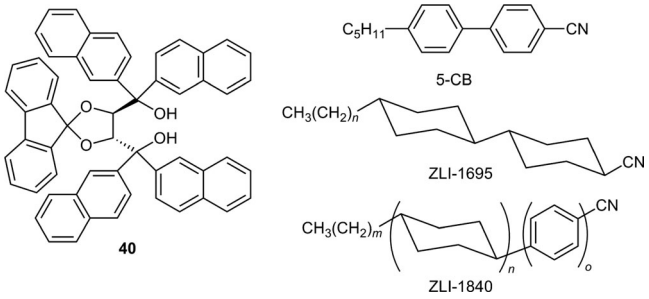
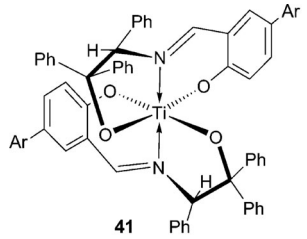
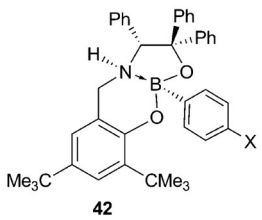


Figure 11. TADDOL derivative **40** used as a dopant. Selected nematic compounds 5-CB, ZLI-1695, and ZLI-1840.

We were guided by the idea that stable metal or half-metal complexes could be developed as efficient chiral dopants, not only because of the large variety and coordination geometries of the central metal atom as well as a multitude of ligands, but also by the possibility to "extend" the chirality of the metal to the periphery of the complex, where suitable residues should provide a maximum interaction with the molecules of the nematic compound.[67] (*R*)-2-Amino-1,1,2-triphenylethanol (readily available from D-phenylglycine) served, after condensation with aromatic *ortho*-hydroxy aldehydes to form the corresponding imines, as the chiral backbone in bis-(alkoxy)imine-titanium complexes. They formed with remarkable selectivity for the (*A*,*R*,*R*) diastereomers **41**, which feature a meridional coordination of the tridentate ligands (Figure 12).[68] The titanium complexes **41**, which proved themselves to be remarkably stable against air, protic solvents, and temperature, were tested as dopants in different



Ar	HTP [μm^{-1}]
4-ClC_6H_4	+ 101 (in ZLI-1695)
3-$CF_3C_6H_4$	+ 115 (in ZLI-1695)
2-Thienyl	+ 131 (in ZLI-1695)



X	HTP [μm^{-1}]
Cl	- 45 (in ZLI-1840)
Cl	- 67 (in 5-CB)
4-$EtOC_6H_4$	- 96 (in ZLI-1840)
4-$EtOC_6H_4$	- 115 (in 5-CB)

Figure 12. Selected titanium and boron complexes **41** and **42**, respectively, used as dopants, and HTP values obtained in different nematic phases.

commercial nematic phases: namely, 5-CB (as mentioned above), ZLI-1695, and ZLI-1840 (Figure 11). The HTP values of selected titanium complexes measured in the nematic phase ZLI-1695 are given in Figure 12.[69a,b] The sign of the induced helix is also given, where (−) indicates a left-handed, and (+) a right-handed helix. As generally observed in the doping of liquid crystals, the helical twisting power not only depends on the individual structure of the dopant but also on the nematic phase.[70]

To obtain insight into the interaction between the dopant, which can be considered to be the guest, and nematic host compounds on a molecular, structure-based level,[71] a library of boronate-amine complexes **42** was generated that are derived from 2-amino-1,1,2-triarylethanols. These complexes were shown to contain configurationally stable stereogenic boron and nitrogen atoms. Their HTP values, as shown in Figure 12, were determined in the nematic phases 5-CB and ZLI-1840.[69c] NMR spectroscopic studies in combination with crystal-structure analyses led to the identification of two different types of host–guest interactions: Firstly, a π–π stacking between the aryl residue at the boron atom and the aryl group of the nematic compounds **42** and, secondly, a hydrogen bridge between the coordinated NH group and the nitrile group of the nematic compounds. This led to a model being proposed[69c] that correlates the sign of the induced helix (−) with the structure of the dopant, as determined by crystal-structure analyses and known absolute configuration. It is assumed in this model that the arylboronic residue prevents the nematic compound from forming a stack towards the front side. Two directions then remain for stacking on the rear side. A turn to the right, however, is prohibited by the aryl groups of the amino alcohol moiety, in particular the one at the stereogenic amine carbon atom, and the *cis*-oriented one of the geminal phenyl groups.[72] As a consequence, the stacking turns to the left, "open" rear side of the complex. Thus, stacking to the left side can be interpreted as the first steps in the formation of the left-handed helix. The plausible correlation between the configuration of the boronate-amine complexes and the (−) helicity is illustrated in Figure 13.

4. Conclusion and Outlook

Admittedly, the development of stereochemistry during the last four decades[73] also brought us numerous auxiliaries and catalysts not featuring a diaryl(oxy)methyl group, but nevertheless acting in a highly efficient manner.[74] However,

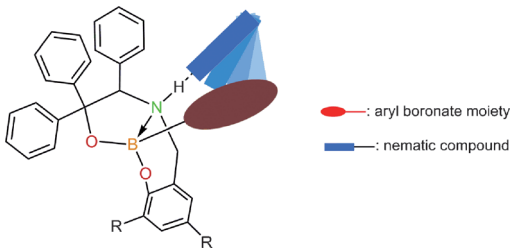


Figure 13. Model explaining the induction of a left-handed helix in the nematic phase by the dopant **42**.

the different examples collected in this Minireview demonstrate that this structural motif is more than an innocent spectator, and might encourage those who develop new, better tools for asymmetric synthesis to give the simple-looking, easily introduced diaryl(oxy)methyl group a try.

I would like to thank the enthusiastic co-workers of my group, and their contributions to this field are highly appreciated. The support provided for decades by the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

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[69] a) M. Braun, A. Hahn, M. Engelmann, R. Fleischer, W. Frank, C. Kryschi, S. Haremza, K. Kürschner, R. Parker, *Chem. Eur. J.* **2005**, *11*, 3405 – 3412; b) M. Engelmann, M. Braun, H.-G. Kuball, *Liq. Cryst.* **2007**, *34*, 73 – 77; c) S. Schlecht, W. Frank, M. Braun, *Eur. J. Org. Chem.* **2010**, 3721 – 3731.

[70] To give an example, titanium complexes **42** display HTP values in the range of 480 to 740 μm^{-1}, when used as dopants of [4-butyl-*N*-(4-methoxybenzylidene]aniline (so-called MBBA). This nematic phase is, however, purely "academic" and not applied industrially.

[71] Various attempts have been made to study the interaction between the dopant and nematic phase, most of them being based upon physical methods and theoretical calculations: W. J. A. Gossens, *Mol. Cryst. Liq. Cryst.* **1971**, *12*, 237 – 244; G.

Gottarelli, G. P. Spada, *Mol. Cryst. Liq. Cryst.* **1985**, *123*, 377 – 388; Y. K. Yarovoy, M. M. Labes, *Mol. Cryst. Liq. Cryst.* **1995**, *270*, 101 – 112; H.-G. Kuball, H. Brüning, *Chirality* **1997**, *9*, 407 – 423; G. Celebre, G. De Luca, M. Maiorino, F. Iemma, A. Ferrarini, S. Pieraccini, G. P. Spada, *J. Am. Chem. Soc.* **2005**, *127*, 11736 – 11744. See also ref. [64b,d, 67b,e].

[72] The importance of the diphenyl(oxy)methyl motif is here again illustrated by the fact that using an analogue of compound **43**, wherein two hydrogen atoms replace the geminal phenyl groups, results in the helical twisting power in 5-CB and ZLI-1840 vanishing almost completely; cf. Ref. [69c].

[73] The state of the art was reflected by the classic "Asymmetric Organic Reactions" by Morrison and Mosher that was considered comprehensive at that time: J. D. Morrison, H. S. Mosher, *Asymmetric Organic Reactions*, American Chemical Society, Washington, DC, **1976**.

[74] For a contemporary overview on asymmetric synthesis, see *Houben- Weyl* Volumes on Stereoselective Synthesis *Methods Org. Chem. (Houben-Weyl) 4th ed. 1952–*, *Vol. E 21a–e*, **1995** and the continuation and up-dating in the corresponding issues of *Science of Synthesis Stereoselective Synthesis.*

