Russian Journal of Organic Chemistry, Vol. 39, No. 3, 2003, pp. 436–452. From Zhurnal Organicheskoi Khimii, Vol. 39, No. 3, 2003, pp. 463–480.

REVIEW

Dedicated to Full Member of the Russian Academy of Sciences I.P. Beletskaya on Her Jubilee

Application of Bis-Sulfonamides in Asymmetric Catalysis. Addition of Diethylzinc to Prochiral Aldehydes*

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Received December 20, 2002

Abstract—The review summarizes the authors' and published data on the Ti(OPr-*i*)$_4$-catalyzed addition of diethylzinc to prochiral aldehydes in the presence of bis-sulfonamides. The effect of bis-sulfonamide structure and other factors on the enantioselectivity of formation of secondary alcohols is discussed.

Chiral enantiopure bis-sulfonamides have found wide application in asymmetric catalysis. They have been successfully applied in aluminum-catalyzed Diels–Alder [1] and ketene aldehyde cycloadditions [2] to afford six- and four-membered rings with excellent enantioselectivity. High enantioselectivity was also observed in the magnesium bis-sulfonamide-catalyzed amination of enolates [3]. Bis-sulfonamides are also known to promote the Simmons–Smith cyclopropanation of allyl alcohols [4]. Moreover, stoichiometric amounts of boron bis-sulfonamide were used in the allylation of aldehydes [5], Ireland–Claisen rearrangement [6], and aldol reaction [7]. A variety of titanium bis-sulfonamides have found application as efficient promotors for the addition of diethylzinc to prochiral aldehydes.

Addition of diethylzinc to prochiral aldehydes. Chiral secondary alcohols are integral parts of biologically active compounds and are versatile intermediates for further transformations. The two most obvious ways of synthesizing such alcohols from achiral starting materials involve enantioselective reduction of the corresponding ketones or addition of an organometallic reagent to the corresponding aldehyde. The advantage of adding an organometallic reagent is that a carbon–carbon bond is formed and that the carbon skeleton is thus extended during the process.

The first highly enantioselective addition of an organometallic reagent to an aldehyde was reported by Mukaiyama *et al.* in 1979 [8]. Butyllithium and diethylmagnesium were added to benzaldehyde in the presence of lithium salt **1** of the proline-derived amino alcohol, resulting in secondary alcohols with an enantiomeric excess (ee) of 92–95%. The disadvantage of using lithium and magnesium reagents was their propensity to add to aldehydes in the absence of a ligand even at low temperature. Even though coordination of donor atoms like nitrogen and oxygen to an organometallic species normally increases their nucleophilicity, the rate acceleration is often too low to compete with the nonstereoselective path, and excess ligand is necessary to achieve an acceptable enantioselectivity [9]. To circumvent this problem, attention was turned to organozinc reagents. Frankland was the first to describe organozinc reagents as early as 1848 [10], but they were considered to be alternatives to lithium and magnesium reagents only after Mukaiyama *et al.* [8] discovered that β-amino alcohols catalyzed their addition to aldehydes. The advantage of using alkylzinc reagents was that they did not add to aldehydes at room temperature in the absence of coordinating molecules. However, excess deprotonated amino alcohol **1** failed to induce any chirality and it was not until 1984 that the first enantioselective addition of diethylzinc to benzaldehyde (**2**) was reported by Oguni and Omi [11] (Scheme 1). Secondary alcohol **3** was obtained with 49% ee in the presence of 2 mol % of (*S*)-2-amino-4-methyl-1-pentanol (**4**).

The success of (*S*)-leucinol as promotor in the alkylation of aldehydes was soon followed by other reports on β-amino alcohols which showed excellent enantioselectivity in the alkylation reactions. Noyori and co-workers [12] applied DAIB [(–)-*exo*-3-di-

* The original article was submitted in English.

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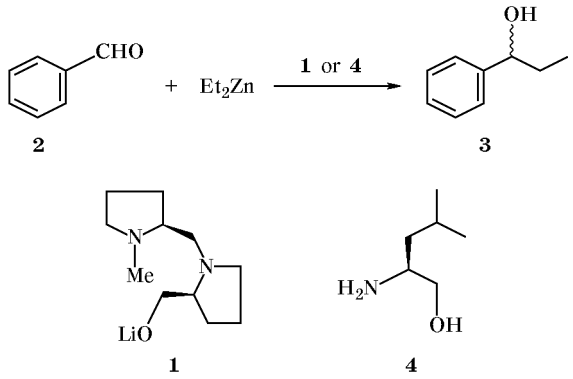
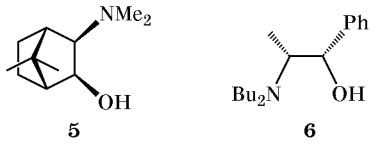
Scheme 1.



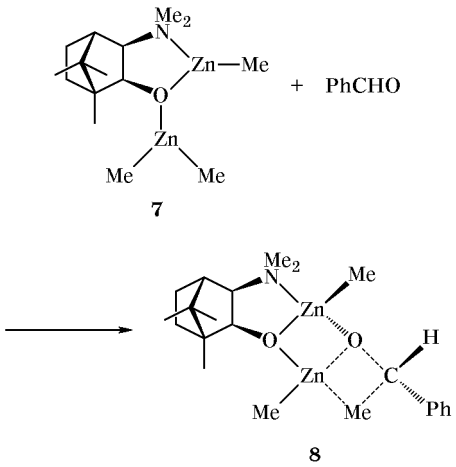
1, 400 mol %, ee 0%; **4**, 2 mol %, ee 49%.

methylaminoisoborneol (**5**)] which worked well with aromatic aldehydes, and Soai *et al.* [13] introduced the norephedrine-derived ligand DBNE [(1*S*,2*R*)-(–)-2-dibutylamino-1-phenyl-1-propanol (**6**)], which gave secondary alcohols with excellent ee values when aliphatic aldehydes were used as substrates. Noyori and co-workers [14] also demonstrated that DAIB exhibited a positive nonlinear effect in the alkylation reaction. Secondary alcohol **3** with 95% ee was obtained with the use of 8 mol % of DAIB (ee 15%) as catalyst.

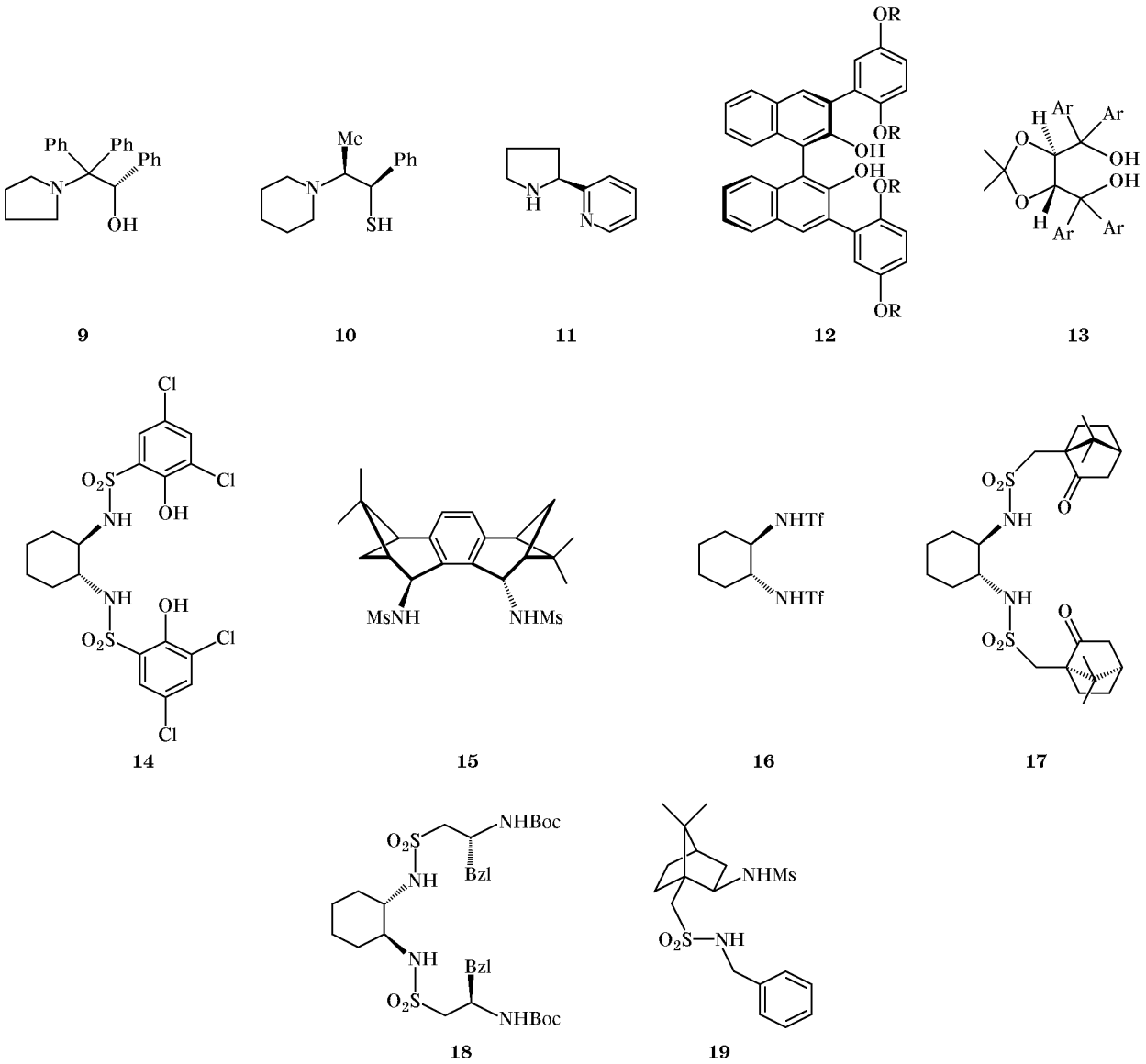


Monomeric dialkylzinc compounds have a linear geometry around the zinc atom; this makes the zinc–alkyl bond nonpolar and the alkylzinc reagent nonreactive toward aldehydes. When an amino alcohol is treated with an alkylzinc reagent, the nitrogen and oxygen donor atoms coordinate to the zinc atom, yielding a difunctional catalyst **7** which is incapable of acting as alkyl donor [14] (Scheme 2). The zinc atom in the five-membered chelate ring of **7** is a Lewis acid which coordinates the aldehyde molecule through the oxygen nonbonding orbital, and the carbonyl carbon atom is activated for nucleophilic attack. Electrons in one of the lone pairs on the oxygen atom in **7** coordinate to the zinc atom in the zinc reagent, and this Lewis basic coordination changes the geometry of the zinc reagent from linear to bent; the zinc–carbon bond in Me_2Zn is elongated, resulting in increased nucleophilicity. The geminal methyl groups in the ligand backbone direct the aldehyde to *endo* coordination. Theoretical study of the reaction mechanism and possible transition state structures shows that aldehyde coordinates to the zinc atom in an *anti-trans* fashion (structure **8**), i.e., the two terminal rings in the zinc-containing tricyclic system thus formed (the ligand backbone excluded) are arranged *anti*, and the aldehyde coordinates to the zinc atom with the lone pair *trans* to the phenyl ring of benzaldehyde (Scheme 2) [15]. The alkyl group is then transferred to the *Si* face of the aldehyde producing the product alkoxide. The product alkoxide is removed from the catalyst as an alkylzinc alkoxide, and the formation of a stable tetramer is the driving force for reconstitution of the catalyst which is believed to be monomeric [16].

Scheme 2.



A large variety of efficient catalytic systems for enantioselective addition of zinc reagents to aldehydes are now known, and the diversity of structures which have been evaluated as ligands in the alkylation reaction is impressing. These include pyridyl alcohols, amino thiols, amines, diols, and bis-sulfonamides [17]. Two distinct alternatives exist for the addition of diethylzinc to aldehydes; the addition can be performed in the presence or in the absence of $Ti(OPr\text{-}i)_4$. An amino alcohol acts as a Lewis base which activates the zinc reagent and forms a Lewis acidic zinc species, e.g., **7**, which activates the aldehyde. Bis-sulfonamide or diol with $Ti(OPr\text{-}i)_4$ forms a Lewis acidic ligand–titanium complex which activates the aldehyde. Excess $Ti(OPr\text{-}i)_4$ which is normally used probably assists the alkyl transfer to the aldehyde. Structures **9**–**19** shown below turned out to be effective ligands both in the presence and in the absence of $Ti(OPr\text{-}i)_4$. Table 1 compares the above ligands on the basis of reaction time, reaction temperature, amount of the catalyst, and enantioselectivity with respect to benz-



9 **10** **11** **12** **13**

14 **15** **16** **17**

18 **19**

12, R = *n*-C_6H_{13}; **13**, Ar = β-naphthyl.

aldehyde substrate. In addition, the data are given for some aromatic, α,β-unsaturated, and aliphatic aldehydes from which the corresponding secondary alcohols were obtained with a 90% ee or higher [18]. The alkylation in the presence of $Ti(OPr\text{-}i)_4$ is generally much faster, and it can be performed at a lower temperature. As seen from Table 1, aromatic aldehydes afford higher enantioselectivity than aliphatic aldehydes. Diols **12** and **13** stand out as two of the most general promotors for alkylation of a broad range of aldehydes, including substituted benzaldehydes, linear and branched aliphatic aldehydes, and α,β-unsaturated aldehydes. Bis-sulfonamide **16** is an attractive alternative due to its straightforward preparation and a remarkable catalytic activity at a low concentration. The substrate-to-catalyst ratio can be as high as 2000 while an excellent enantioselectivity is still maintained. The extensive work by Knochel *et al.* [19] showed the generality of **16** as promotor for alkylation of aldehydes. The substrate tolerance is as impressive as that of **12** and **13**, and a number of aldehydes and functionalized organozinc reagents can be employed.

Bis-sulfonamides as ligands in the alkylation of aldehydes: background. The work on bis-sulfonamides as ligands in the asymmetric addition of diethylzinc to aldehydes was pioneered by Yoshioka and co-workers in 1989 [30]. The authors sought for

Table 1. Catalytic systems for enantioselective addition of diethylzinc to aldehydes

Ligand no.	Ti(OPr-*i*)$_4$,[a] equiv	ee,[a] %	Time,[a] h	Temperature,[a] °C	C/I[a]	Arom.[b]	α,β-Unsat.[c]	Aliph.[d]	Reference
9	–	97	3	0	17	13	2	5	[20]
10	–	100	12	0	20	8	0	2	[21]
11	–	100	18	–10	17	5	1	1	[22]
12	–	>99	4	0	20	11	6	5	[23]
13	1.2	99	30	–25	5	9	6	5	[24]
14	1.4	99	4	–23	5	8	3	1	[25]
15	1.2	98	16	–40	100	1	0	3	[26]
16	1.2	98	2	–20	2000	1[e]	1[e]	2[e]	[30]
17	1.4	91	10	27	5	2	0	0	[27]
18	1.2	96	16	–20	25	2	0	1	[28a]
19	1.3	64	2	–20	5	0	0	3	[29]

[a] With benzaldehyde as substrate.

[b] The number of aromatic aldehydes from which the corresponding secondary alcohols were obtained with ee > 90%.

[c] The number of α,β-unsaturated aldehydes.

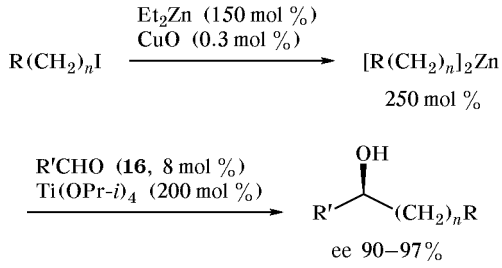
[d] The number of aliphatic aldehydes.

[e] Only those aldehydes were taken into account, which were reported in original papers. More than 50 aldehyde–organozinc combinations were reported in [19].

a class of promotors containing stronger electron-withdrawing elements than those present in amino alcohols in order to accelerate the catalytic reaction. They identified the sulfonyl group as a suitable candidate in this respect and prepared sevaral ligands by reacting (*R*,*R*)-1,2-diaminocyclohexane with various sulfonyl chlorides. However, the resulting bis-sulfonamides produced secondary alcohol **3** (Scheme 1) with a moderate enantioselectivity (36–83% ee), and only a weak acceleration was observed even when bis-sulfonamide **16** was employed [31]. A suitable metal partner was sought to increase the rate, and various Lewis acidic metal alkoxides were evaluated in the reaction between diethylzinc and benzaldehyde. Among the metal alkoxides tested, titanium(IV) isopropoxide was found to stand out. At a concentration of 2 mol %, it was able to catalyze the alkylation of benzaldehyde in 80% yield in 12 h at room temperature. A combination of bis-sulfonamide **16** (4 mol %) with titanium(IV) isopropoxide (4.8 mol %) was highly successful: alcohol **3** was produced with 98% ee in 2 h at 0°C. It was possible to use as little as 0.05 mol % of ligand **16** in combination with 120 mol % of Ti(OPr-*i*)$_4$ and still obtain an excellent enantiomeric excess (98%). However, the introduction of Ti(OPr-*i*)$_4$ complicated the alkylation reaction since Ti(OPr-*i*)$_4$ alone catalyzed the reaction in a nonselective fashion. It was surprising to note that alcohol **3** could be obtained with high ee value despite the use of a large excess of Ti(OPr-*i*)$_4$. The role of excess Ti(OPr-*i*)$_4$ was attributed to replacing the product alkoxide in the titanium–bis-sulfonamide complex and thus reconstituting the active catalyst.

Knochel extended the scope of application of asymmetric alkylation by introducing functionalized dialkylzinc reagents [32]. These reagents were prepared from the corresponding alkyl iodides via copper-catalyzed iodine–zinc exchange reaction [33]. The asymmetric alkylation catalyzed by **16** and Ti(OPr-*i*)$_4$ tolerated the presence of functional groups such as ester and chlorides, if the ester group or chlorine atom is separated by at least four carbon atoms from the zinc atom; alcohols with excellent ee values were thus obtained (Scheme 3). This methodology was also extended to include β-stannylated saturated and α,β-unsaturated aldehydes, as well as β-silylated α,β-unsaturated aldehydes and acetylenic aldehydes [33–35].

Scheme 3.

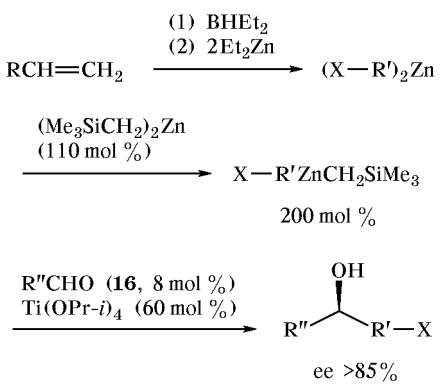


R = Me, Cl, OCOR″.

The products obtained from such substrates could be modified further in a number of ways.

An alternative and milder path to functionalized organozinc reagents starts from alkenes [36]. The one-pot procedure includes hydroboration of alkene to the corresponding borane which readily undergoes boron–zinc exchange with diethylzinc to give organozinc reagent (Scheme 4).

Scheme 4.

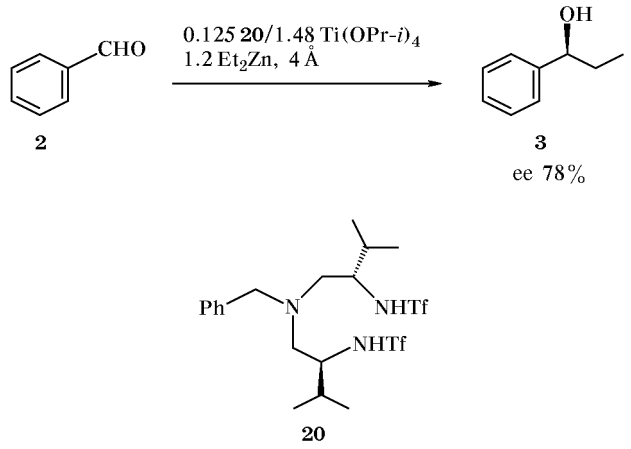


X = COOR, Alk_3Si, $CH_2=CHCOO$, I, Br.

The tolerance of functional groups is impressive: ester groups, silyl ethers, acrylates, alkyl iodides, and alkyl bromides can be involved in the alkylation reaction provided that they are separated from the zinc atom by at least three carbon atoms. A disadvantage of these zinc reagents is that an excess (2–3 equiv) is required to attain a good chemical yield and high enantioselectivity. Moreover, only one of the alkyl groups bound to zinc is transferred to the aldehyde. The problems can be avoided by treating the organozinc reagent with $(Me_3SiCH_2)_2Zn$ to obtain a new organozinc reagent in which the trimethylsilylmethyl moiety behaves as a nontransferrable group [37]. These mixed organozinc reagents can be used in smaller amounts but at the expense of the reaction rate, and a smaller excess of titanium(IV) isopropoxide must be used to suppress the background reaction. Different combinations of functionalized organozinc reagents, bis-sulfonamide **16**, and $Ti(OPr\text{-}i)_4$ can be successfully employed in the syntheses of complex structures [38].

Bis-sulfonamides obtained by ring opening of chiral aziridines as catalysts. Optimization of the reaction conditions. When bis-sulfonamide **20** was used as ligand in the addition of diethylzinc to benzaldehyde (Scheme 5), the reaction enantioselectivity was found to strongly depend on the conditions [39]. The amount of $Ti(OPr\text{-}i)_4$ was an important factor;

Scheme 5.



the optimal ratio benzaldehyde–**20**–$Ti(OPr\text{-}i)_4$–Et_2Zn was 1 : 0.125 : 1.48 : 1.2, and the presence of activated 4Å molecular sieves was necessary. These conditions ensured formation of 1-phenyl-2-propanol (**3**) with an enantiomeric excess of 78%.

Further variation of the amount of $Ti(OPr\text{-}i)_4$ was performed to obtain a clear pattern of its effect on the catalytic reaction, as well as on the competing nonselective background process [40]. In the absence of $Ti(OPr\text{-}i)_4$, the reaction was slow and nonselective. Presumably, it involved formation of a zinc complex with bis-sulfonamide, and alcohol **3** was obtained with a low ee value. This is consistent with the results obtained with ligand **16** and its derivatives: in the absence of $Ti(OPr\text{-}i)_4$, alcohol **3** is formed with modest ee values [31]. The *R* enantiomer of the product dominated when ligand **20** and $Ti(OPr\text{-}i)_4$ were present in equimolar amounts during the catalytic reaction, but the ee value was still low, and the reaction was very slow. Raising the amount of $Ti(OPr\text{-}i)_4$ considerably changed the enantioselectivity and increased the reaction rate. It was surprising that the major enantiomer formed in the presence of excess titanium(IV) isopropoxide was opposite to the major enantiomer obtained when equimolar amounts of $Ti(OPr\text{-}i)_4$ and ligand **20** were used. The maximal ee value (59%) was reached at about 1.5 equiv of $Ti(OPr\text{-}i)_4$. Seebach and co-workers observed a similar pattern, but even to a greater extent, in the reaction with TADDOL and 4-methoxybenzaldehyde as substrate. The *R* enantiomer was obtained with 98% ee using 2 equiv of TiL_2 in the absence of titanium(IV) isopropoxide, while the corresponding *S*-enantiomer was formed with 94% ee when 0.1 equiv of the same catalyst was used in the presence of 1.2 equiv of $Ti(OPr\text{-}i)_4$ [41]. In the latter case, the precatalyst is

likely to form a Ti(OPr-*i*)$_2$L species in the presence of Ti(OPr-*i*)$_4$.

The reaction rate also increased to an appreciable extent when the amount of Ti(OPr-*i*)$_4$ is raised; the complete conversion was reached in 15 min in the presence of 0.68 equiv of Ti(OPr-*i*)$_4$. As noted above, the alkylation of aldehydes is complicated by introduction of Lewis acidic titanium(IV) isopropoxide since the titanium can catalyze the reaction in a nonselective way. However, the background reaction is too slow to compete with the ligand-catalyzed path, so that it should not affect the stereochemical output of the reaction.

The alkylation catalyzed by bis-sulfonamide like **20** is ligand-accelerated, presumably due to the presence of strongly electron-withdrawing sulfonyl groups [42]. Seebach *et al.* [43] presumed that the role of excess titanium(IV) isopopoxide is to replace the product alkoxide on the catalyst by isopropoxide and thus reconstitute the catalyst. The presence of Ti(OPr-*i*)$_4$ is crucial when the catalyst is a TADDOL–titanium complex containing enantiomerically pure 1-phenylpropoxides coordinating to titanium. Excess titanium(IV) isopropoxide (1.2 equiv) affords secondary alcohol **3** with much higher ee value than that observed in the absence of Ti(OPr-*i*)$_4$ [43]. A large excess of Ti(OPr-*i*)$_4$ (1.2 to 1.8 equiv) is commonly employed in the bis-sulfonamide-catalyzed addition of alkylzinc reagents to aldehydes. For example, bis-sulfonamide **14** (Fig. 1) and 0.2% of Ti(OPr-*i*)$_4$ (equimolar amount) give alcohol **3** with an ee value of 4%, whereas with 1.4 equiv of Ti(OPr-*i*)$_4$, 99% ee was obtained [25a].

Activated 4 Å molecular sieves are sometimes used in asymmetric catalysis, especially when d^0 early transition metals such as titanium is the metal source [44]. The role of molecular sieves in different reactions may be different; the sieves may serve to trap water [45] or as sources of limited amounts of water [46]. The structure and the water content of molecular sieves may be factors determining the outcome and reproducibility of a catalytic reaction [47]. Molecular sieves can also assist complex formation between ligand and metal [48]. The presence of water can largely influence the enantioselectivity in titanium bis-sulfonamide-mediated alkylation reactions [49].

The effect of activated 4 Å molecular sieves was studied in the reaction with bis-sulfonamide **20** and 1.2 equiv of Et$_2$Zn. Alcohol **3** was obtained with 59% ee both in the presence and in the absence of activated 4 Å molecular sieves, and the reaction rate did not change. The background reaction was also unaffected by the presence of molecular sieves. The use of nonactivated 4 Å molecular sieves considerably attenuated the reaction rate, yet the enantioselectivity was improved slightly compared to the affect of activated 4 Å molecular sieves.

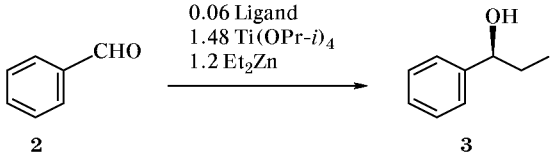
According to the ^{1}H and ^{13}C NMR data, no titanium–bis-sulfonamide complex is formed on heating of bis-sulfonamide **20** and titanium(IV) isopropoxide in toluene at 60°C. The acidic sulfonamide protons were still visible in the ^{1}H NMR spectrum, and addition of activated 4 Å molecular sieves did not assist ligand exchange. Analogous patterns were observed by Walsh and co-workers [50] with derivatives of **16**, and the authors presumed that Et$_2$Zn is required to deprotonate the bis-sulfonamide for ligand exchange to occur. In fact, improved enantioselectivity was observed when ligand **20**, titanium(IV) isopropoxide, and diethylzinc were mixed at –78°C and were then allowed to slowly reach room temperature; the mixture was maintained at that temperature before addition of the aldehyde.

The enantioselectivity remained almost unchanged when the amount of **20** was reduced from 12 to 6 mol %; however, the reaction rate decreased [40]. Very similar results were obtained with 4 mol % of ligand **20**; further reduction in its amount to 2 mol % led to decreased enantioselectivity which however increased as the conversion rose. A competition with the nonselective background reaction was probably responsible for the reduced enantioselectivity. Interestingly, the enantioselectivity increases with the conversion when 6 mol % or a smaller amount of the ligand was used. The chiral alkoxide formed is likely to coordinate to the catalytically active species and affect the enantioselectivity. Variation in the enantioselectivity with the conversion was also observed in the alkylation of benzaldehyde in the presence of some derivatives of ligand **16** [51].

Sulfonamides as promotors for the addition of diethylzinc to benzaldehyde. Ligands **21**–**42** were also assessed in the enantioselective addition of diethylzinc to benzaldehyde in order to elucidate how structural differences in the ligands affect the outcome of the catalytic reaction [40]. The conditions found to be optimal for bis-sulfonamide **20** were employed, i.e., the ligand–benzaldehyde–Ti(OPr-*i*)$_4$–Et$_2$Zn ratio was 0.06 : 1 : 1.48 : 1.2 (Scheme 6).

Monosulfonamide **21** afforded low enantioselectivity and low conversion in the alkylation reaction (Table 2). Presumably, the ligand-catalyzed pathway cannot compete with the nonselective background reaction. The alkylation was much faster in the presence of bis-sulfonamide **22**. The enantioselectivity

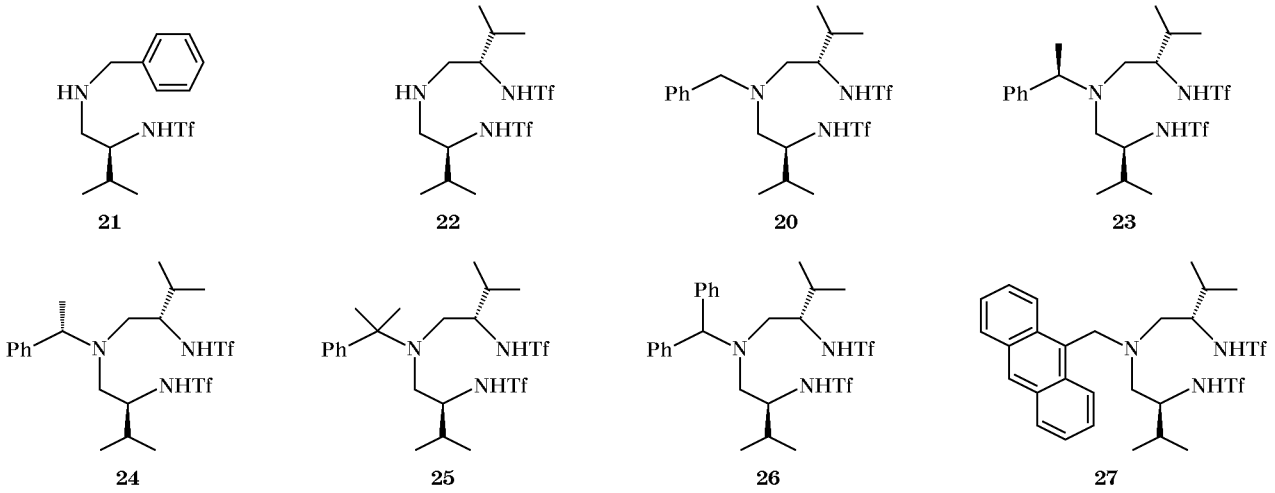
Scheme 6.



changed with conversion, and ee value for alcohol **3** was 10% when the conversion was complete. As follows from the results of the above optimization study, replacement of hydrogen in the secondary amine by benzyl group ensures even higher reaction rate and considerably improves the enantioselectivity. The latter does not increase on lowering the temperature from –35 to –78°C. The complete conversion is achieved after additional 90 min at –55°C, and the ee value of **3** increases. Introduction of a bulkier group into the ligands (e.g., as in **23** and **24**) slightly improves both the reaction rate and its enantioselectivity. However, the enantioselectivity increases toward the *S* enantiomer at either configuration of the additional chiral center. The reaction was exceptionally fast in the presence of ligands **23** and **24**, and the conversion was complete within 15 min. The enantioselectivity was not improved when ligands **25** and **26** having an additional steric bulk at the benzylic position were used in the alkylation. A slower and less selective reaction occurred on replacement of toluene as solvent by THF where ligand **25** was completely soluble. Ligand **26** showed as strong acceleration effect as that observed with compounds **23** and **24**, and the consumption of benzaldehyde was complete within 15 min. The enantiomeric excess of **3** increased with rise in the conversion when ligand **25** and anthracene derivative **27** were applied.

Ligand **28** derived from (*S*)-alaninol was inferior to its (*S*)-valinol analog **20** as promotor for the addition of diethylzinc to benzaldehyde: both enantioselectivity and conversion were lower (Table 3). Ligand **29** containing less electron-acceptor *p*-tolylsulfonyl groups (as compared to trimethylsulfonyl groups, as in **20**) interestingly favored formation of the *R* enantiomer of **3** [52], but the catalytic reaction slowed down. Lower enantioselectivity of the catalytic reaction was observed in the presence of hydroxy-containing ligands **30** and **31**. The low selectivity may be explained by coordination of the hydroxy groups to the titanium atom in the catalytic species and increased steric hindrance. Walsh and co-workers [53], as well as Seebach and co-workers [43], observed reduced enantioselectivity with sterically encumbered derivatives of **16** and **13**, while tetradentate ligand **14** afforded an excellent enantioselectivity [25]. The alkylation was faster and more selective with *O*-methyl derivative **32** than with its hydroxy analog **31**. In the presence of ligands **28** and **29**, the enantioselectivity increased with conversion, whereas the use of ligand **30** caused decrease in the selectivity with conversion. Diastereoisomeric ligands **33** and **34** showed a behavior similar to that of ligand **32** in the catalytic reaction. Unstable ligands **33** and **34** might have decomposed to ligand **32**; alternatively, the planarily chiral arene moiety is too distant from the catalytic center to affect the enantioselectivity. Better enantioselectivity was achieved with ligands **28** and **31** (67 and 60% ee, respectively) under the conditions used in our earlier study [39]. Specifically, the pre-catalyst was obtained by heating equimolar amounts of the ligand and Ti(OPr-*i*)$_4$, and activated 4 Å molecular sieves were used in the catalytic reaction, but the mixture was not kept at room temperature before addition of the aldehyde. These results indicate that optimal conditions might be found for each particular ligand. Tetradentate ligands **35** and **36** favor formation of the *R* enantiomer of **3** at similar rates of conversion. The selectivity was higher with the use of ligand **35** in the catalytic reaction (Table 4). Reduction of the enantioselectivity with conversion was observed in the alkylation in the presence of **35**; with ligand **36**, the enantioselectivity changed in parallel with the conversion. 1,2-Diaminocyclohexane derivatives **37** and **38** did not mediate the addition of diethylzinc to benzaldehyde to an appreciable extent, and only racemic products were obtained. The rate of the reaction was low, indicating that a considerable amount of the secondary alcohol was formed via the Ti(OPr-*i*)$_4$-catalyzed pathway. The poor solubility of ligands **37** and **38** in toluene was not responsible for the lack of enantioselectivity, for similar results were obtained in THF where these ligands were completely soluble. Axially chiral ligands **39** and **40** afforded a low enantioselectivity in the catalytic reaction, the ee value for (*R*)-**3** was 5 to 9%. Increase in the reaction rate in the presence of ligands **39** and **40** suggests that the background reaction did not influence the enantioselectivity. Low selectivity was achieved in the alkylation with C_3-symmetric tris-sulfonamide ligands **41** and **42**. Interestingly, two (*S*)-valinol derivatives, **41** and **42**, afforded alcohol **3** with opposite absolute configurations. Ligand **42** containing electron-withdrawing *p*-tolylsulfonyl group promoted formation of the *R* enantiomer of **3**, whereas triflate analog **41** gave rise to the *S* enantiomer, though the *R* enantiomer dominated at a low conversion. These data are consistent with the results obtained for *p*-tolylsulfonyl

Table 2. Addition of diethylzinc to benzaldehyde, promoted by bis-sulfonamides **21**–**27**[a]



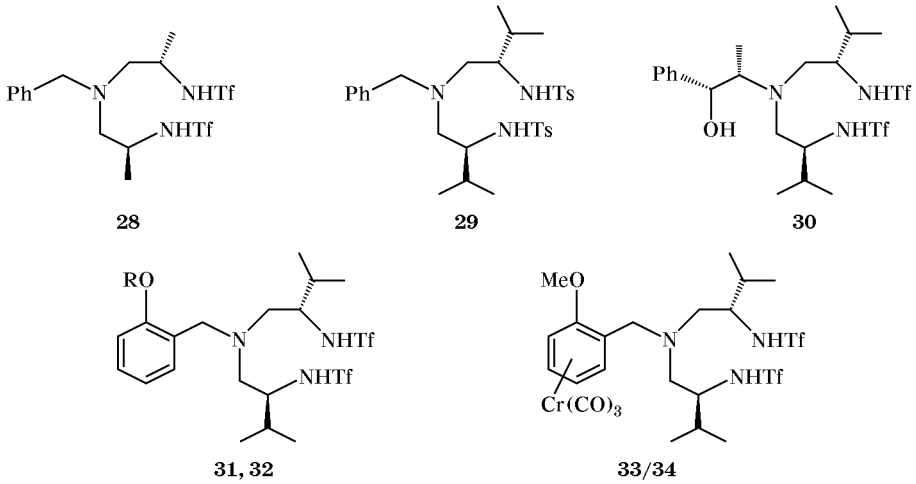
Ligand	Time,[b] h	Conversion,[c] %	ee,[c] %	Yield,[d] %	Conversion,[e] %
21	19	95	3 (*S*)	88	36
22	0.25	44	0		
	1.33	94	8 (*S*)		
	2.7	100	10 (*S*)	100	44
20	0.25	86	67 (*S*)		
	1	97	71 (*S*)	90	86
20	3[f]	10	50 (*S*)		
	4.5[g]	97	69 (*S*)	–	0
23	0.25	97	75 (*S*)	97	97
24	0.25	99	76 (*S*)	93	99
25	0.25	42	48 (*S*)		
	2.5	95	56 (*S*)	91	42
25[h]	0.25	14	12 (*S*)	–	14
26	0.25	96	69 (*S*)	93	96
27	0.25	73	56 (*S*)		
	2.33	98	63 (*S*)	98	73

[a] Ratio ligand–benzaldehyde–Ti(OPr-*i*)$_4$–Et$_2$Zn 0.06 : 1 : 1.48 : 1.2; the reaction mixture was kept at room temperature before addition of benzaldehyde.
[b] At –35°C.
[c] Determined by GLC.
[d] Determined by GLC using external standard technique.
[e] Conversion in 15 min at –35°C.
[f] At –78°C.
[g] 3 h at –78°C and 1.5 h at –55°C.
[h] In THF.

derivative **29** which favor formation of the *R* enantiomer, while triflate analog **20** favors formation of the *S* enantiomer.

With a few exceptions, benzaldehyde and related aromatic aldehydes are substrates for which the highest enantioselectivity was achieved in asymmetric alkylation. A considerable difference between the small hydrogen atom and relatively large phenyl group, as well as the absence of acidic protons, makes benzaldehyde a perfect substrate for alkyl group addition, even though the synthetic utility is limited. It is generally difficult to achieve excellent enantioselectivities with aliphatic aldehydes, but greater ee values can often be obtained if an aliphatic aldehyde

Table 3. Addition of diethylzinc to benzaldehyde, promoted by bis-sulfonamides **28**–**34**[a]



31, R = H; **32**, R = Me.

Ligand	Time,[b] h	Conversion,[c] %	ee,[c] %	Yield,[d] %	Conversion,[e] %
28	0.25	11	7 (*S*)		
	1.5	67	17 (*S*)		
	3.5	89	23 (*S*)		
	19.3	100	19 (*S*)	97	11
29	0.25	18	31 (*R*)		
	1	65	49 (*R*)		
	4.5	99	50 (*R*)	99	18
30	0.25	30	41 (*S*)		
	18	96	29 (*S*)	92	30
31[f]	4.5	93	20 (*S*)	90	22
32	1.67	98	61 (*S*)	90	86
33	1.67	95	65 (*S*)	78	74
34	1.67	94	65 (*S*)	78	76

[a] Ratio ligand–benzaldehyde–Ti(OPr-*i*)$_4$–Et$_2$Zn 0.06 : 1 : 1.48 : 1.2; the reaction mixture was kept at room temperature before addition of benzaldehyde.

[b] At –35°C.

[c] Determined by GLC.

[d] Determined by GLC using external standard technique.

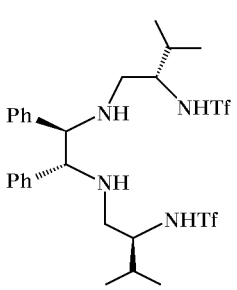
[e] Conversion in 15 min at –35°C.

[f] In the presence of 5 mol % of the ligand.

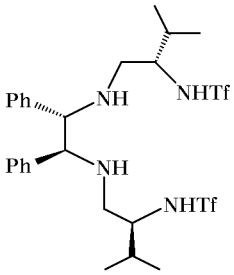
contains a substituent in the α-position. The addition of diethylzinc to cyclohexanecarbaldehyde **43** in the presence of ligand **20** under the optimal conditions (see above) gives alcohol **44** with a low enantiomeric excess (25%; Scheme 7). The reaction time is notably longer than in the reaction with benzaldehyde, and 90% conversion is attained in 36 h.

Possible scheme of the catalytic cycle. Some features of the intermediates involved in the bis-sulfonamide-promoted enantioselective alkylation of aldehydes are known, even though suggestions regarding possible transition state structures are rare [54]. The structure of the zinc–bis-sulfonamide complex obtained from Et$_2$Zn and bis-sulfonamide derivative **45** (Scheme 8) was determined by X-ray analysis. The zinc atom is linked to both nitrogen atoms of the sulfonamide in such a way that the C_2 symmetry is preserved [55]. The NH protons in sulfonamide are acidic (pK_a 7–10) [56], and bis-sulfonamides are readily deprotonated by the action of diethylzinc.

Table 4. Addition of diethylzinc to benzaldehyde, promoted by bis-sulfonamides **35**–**42**[a]



35



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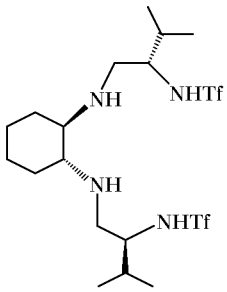

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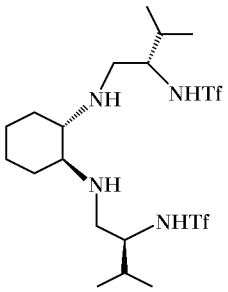

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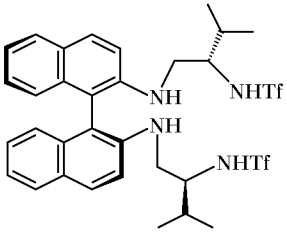

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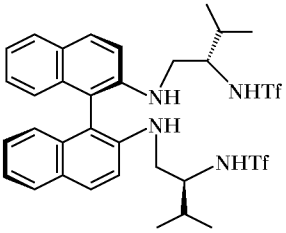

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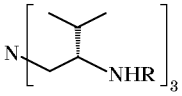


41, 42

41, R = Tf; **42**, R = Ts.

Ligand	Time,[b] h	Conversion,[c] %	ee,[c] %	Yield,[d] %	Conversion,[e] %
35[f]	0.25	29	80 (*R*)		
	1.67	73	65 (*R*)		
	5	87	59 (*R*)	79	29
36[f]	5.25	87	12 (*R*)	87	27
37[g]	18.25	93	0	89	5
38	18	98	0	95	4
39	3.67	95	9 (*R*)	83	25
40	3.33	94	5 (*R*)	84	35
41[h]	0.25	29	17 (*R*)		
	1.75	91	9 (*S*)		
	3.3	97	11 (*S*)	89	29
42	0.25	20	25 (*R*)		
	18	96	31 (*R*)	91	20

[a] Ratio ligand–benzaldehyde–Ti(OPr-*i*)$_4$–Et$_2$Zn 0.06 : 1 : 1.48 : 1.2; the reaction mixture was kept at room temperature before addition of benzaldehyde.

[b] At –35°C.

[c] Determined by GLC.

[d] Determined by GLC using external standard technique.

[e] Conversion in 15 min at –35°C.

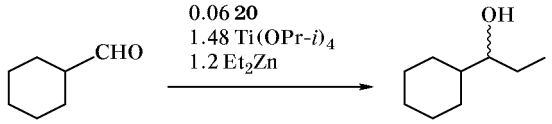
[f] In the presence of 5 mol % of the ligand.

[g] Analogous results were obtained in THF.

[h] A mixture of THF with toluene (1 : 7) was used to dissolve the ligand.

Walsh and co-workers [53] showed that mixing of ligand **46** with excess Ti(OPr-*i*)$_4$ gives no titanium complex **47**. Nevetheless, this complex is formed by reaction of **46** with Ti(OPr-*i*)$_2$(NMe$_2$)$_2$ (Scheme 8). The X-ray diffraction data indicate that the titanium atom has a distorted octahedral configuration and that one oxygen atom of each sulfonyl group is coordinated to the titanium center, thus fixing a rigid

Scheme 7.



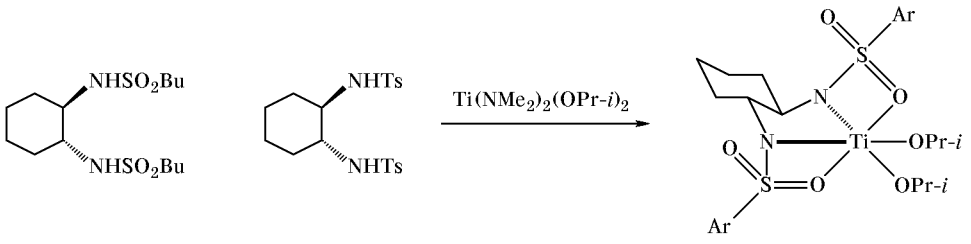
43 **44**

C_2-symmetric structure of the complex [50, 57]. Furthermore, the use of a mixture of ligand **46** with Ti(OPr-*i*)$_4$ and Et_2Zn gives the same results in the alkylation reaction as those obtained with complex **47** under the same conditions. Presumably, diethylzinc serves to deprotonate **46**, and the bis-sulfonamide–zinc complex reacts with Ti(OPr-*i*)$_4$ *in situ* to form **47**. However, the driving force of this reaction remains unclear. The absence of nonlinear effects in the presence of ligand **46** suggests that the catalytic species is monomeric [25b, 50]. The enantioselectivity observed in the alkylation with titanium complexes containing two bis-sulfonamide ligands (TiL_2) is lower than with analogous complex containing one sulfonamide ligand. It follows that the active species has a stoichiometry of Ti(OPr-*i*)$_2$L [51]. It is important that the C_2-symmetric *trans* conformation of the aryl groups in catalyst **47** is maintained during the reaction [53]. Catalysts in which a short tether forces the aryl groups into a *syn* conformation (**48**, n = 6) are inferior to those in which a longer tether (**48**, n = 22) allows a *trans* conformation to be maintained during the reaction (Scheme 8).

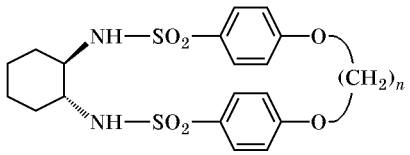
It is not clear whether the ethyl group is transferred from zinc or from titanium atom and whether the transfer occurs inter- or intramolecularly. ^{1}H NMR studies on a mixture of Et_2Zn with Ti(OPr-*i*)$_4$ revealed a concentration-dependent equilibrium where no monomeric Et_2Zn species was present but signals from at least two ethyl groups were observed [30, 31]. The results of these studies on ligand **16** led Yoshioka and co-workers to presume TiL(Et)(*i*-PrO) species [31] to be the key intermediate from which ethyl group transfer is faster than from any other ethyl-containing species [58]. Paquette and Zhou [26] also proposed that the ethyl group is transferred intramolecularly from titanium to the aldehyde. However, it seems unlikely that the strong Ti–O bond is replaced by weaker Ti–C bond, even though the Ti–C bond is stronger than the corresponding Zn–C bond [59]. Moreover, intramolecular transfer would result in an unfavorbale angle of approach of the ethyl group. It is more probable that a bimetallic complex is formed which includes Et_2Zn, titanium, and the ligand and that ethyl group transfer from the zinc atom occurs intramolecularly [25, 34, 43].

Scheme 9 shows a mechanistic scenario based on the results of our experiments with bis-sulfonamide **20** and published data. Treatment of **20** with diethylzinc is accompanied by gas evolution (ethane), presumably leading to intermediate **49**, in which the tertiary nitrogen atom is coordinated to zinc. Intermediate **49** catalyzes addition of diethylzinc to benzaldehyde, which is slow and nonselective: the conversion is only 58% in 4 days (ee 21%). This means that complex **49** is not a catalytically active species when the reaction is carried out in the presence of Ti(OPr-*i*)$_4$. Instead, zinc complex **49** is likely to react with Ti(OPr-*i*)$_4$ to form a titanium complex like Ti(bis-sulfonamide)(OPr-*i*)$_2$, which is active in the catalytic process. According to the X-ray diffraction data for the aluminum complex of **20**, the tertiary nitrogen atom coordinates to aluminum; analogous coordination may be expected in the titanium complex

Scheme 8.



45 **46** **47**



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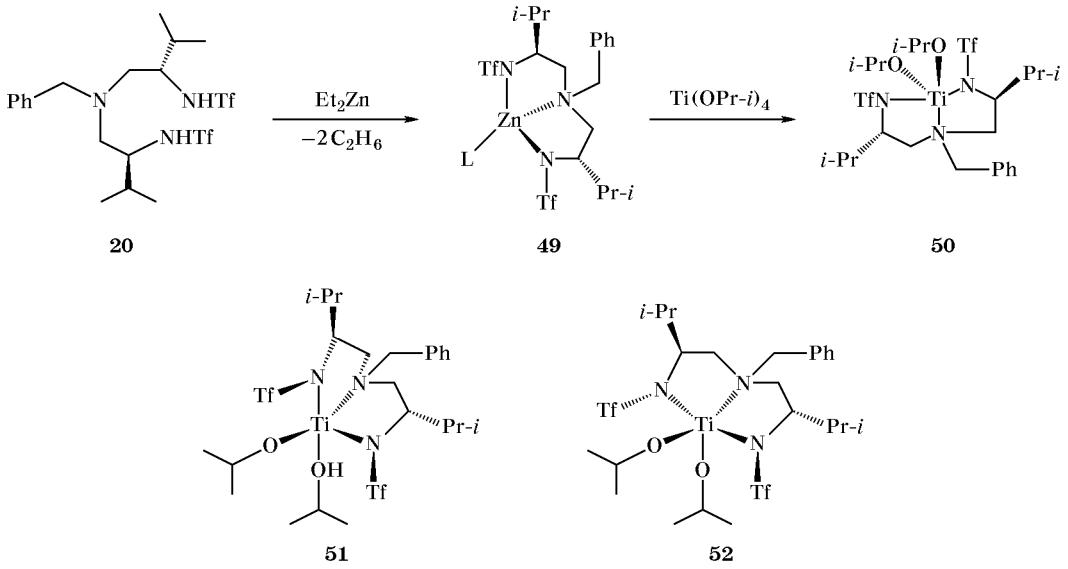
Scheme 9.



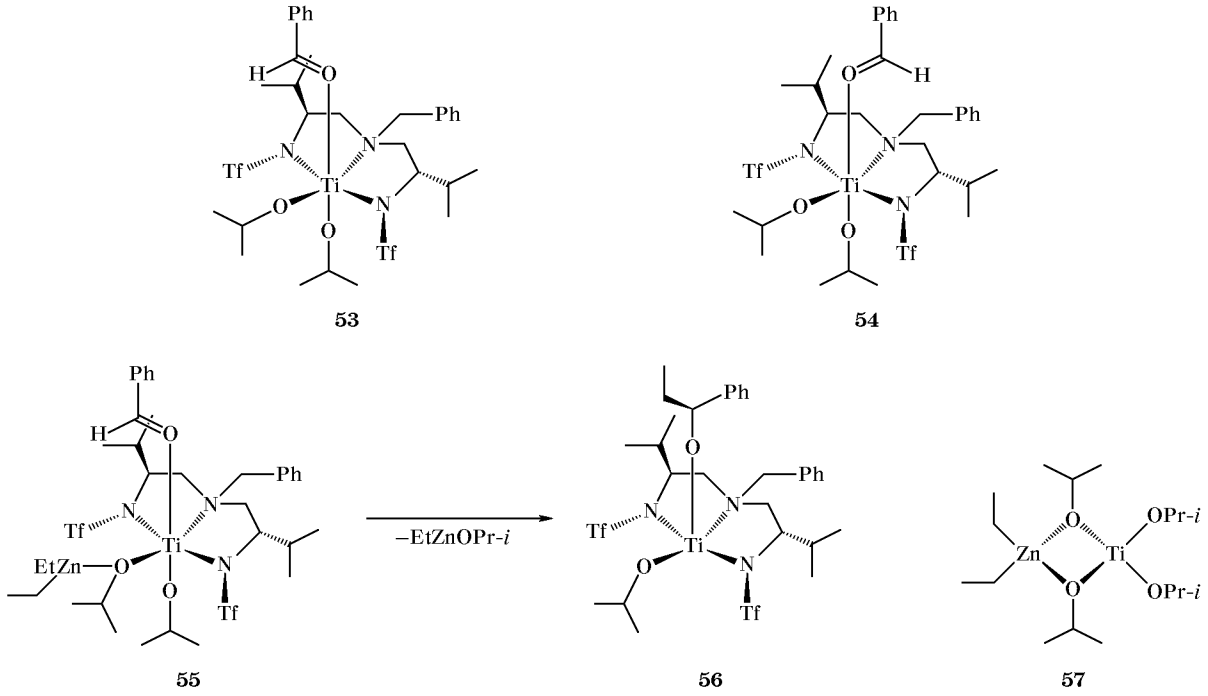
[60]. By analogy with a similar achiral bis-sulfonamide ligand, a distorted trigonal bipyramidal (**50**) or octahedral geometry is possible [61]. Octahedral coordination of ligand **20** could give rise to two complexes with either a facial or a meridional coordination of the bis-sulfonamide (complexes **51** and **52**, respectively). It is difficult to predict the exact structures and relative stability of the octahedral complexes, as well as to conclude whether or not there is an interaction between the sulfonyl oxygen atom and titanium center. The sulfonamide nitrogen atoms are expected to have a planar geometry [50], and each isopropyl group in the ligand should force the sulfonamide group to occupy the *trans* position. This should destabilize facially coordinated structure **51** since the two bulky sulfonamide groups would then be in close proximity. We did not succeed in obtaining spectroscopic evidence for any of these intermediates.

Benzaldehyde is a weak ligand which prefers to coordinate to titanium *trans* with respect to the strong isopropoxide ligand in **52**, resulting in complex **53** (Scheme 10) [62]. A coordination mode like that in complex **54** is also possible if the benzyl group resides below the plane. Corey and co-workers recently presumed [63] that hydrogen bonding between an aldehyde proton and an alkoxide ligand bound to titanium can be invoked to explain the stereochemical outcome of asymmetric transformations. In our system such interaction is improbable since hydrogen bond between the aldehyde proton and the oxygen atom of the equatorial isopropoxide group in **53** will bring the sulfonamide, which is located above the plane, and the benzaldehyde moieties too close to each other [64]. Hydrogen bond to the highly electron-deficient sulfonamide nitrogen atom is also improbable, even though, in keeping with the proposed model, the position of the aldehyde proton would be nearly optimal. Our model then predicts that the ethyl group attacks the aldehyde from the *Si* face at the same time as the isopropoxide ligand *trans* to the aldehyde leaves the catalyst (see structure **55**), presumably yielding *i*-PrOZnEt [65]. This model predicts the observed formation of (*S*)-alcohol (**56**). A possible mode of activation of diethylzinc is seen from structure **55** where the the equatorial titanium isopropoxide oxygen coordinates to the zinc atom of Et_2Zn or, alternatively, intermolecular ethyl group transfer from the ethylzinc species like **57** can be envisaged. The two scenarios imply that the aldehyde is attacked at a favorable angle.

Excess Ti(OPr-*i*)$_4$ replaces the alkoxide residue from intermediate **56** (Scheme 10), thus reconstituting intermediate **52** (Scheme 9). The nonlinearity between the conversion and enantiomeric excess, which is observed with some our ligands in the alkylation reaction, indicates that the catalyst does not remain unchanged during the catalytic process. It is possible that structure **56** acts as catalyst in the alkylation reaction and that chiral alkoxide residue coordinates to the titanium atom in **56** in a favorable or unfavorable way, causing increase or decrease, respectively, in the enantiomeric excess.

Effect of chiral additives on the enantioselectivity of the addition of diethylzinc to benzaldehyde. Even though the exact structure of catalytically

Scheme 10.



active species in the bis-sulfonamide-mediated addition of diethylzinc to benzaldehyde is unknown, it is clear that the formation of a neutral bis-sulfonamide–titanium(IV) complex requires coordination of two anionic ligands. Such ligands may be two isopropoxide molecules, even though the presence of an ethyl group on the titanium atom is assumed (see above). The structure of alkoxides which coordinate to titanium can have a decisive effect on the outcome of asymmetric alkylation. According to Knochel *et al.* [66], enantiomeric excess of the product increases from 0 to 93% on replacement of Ti(OPr-*i*)$_4$ by bulkier Ti(OBu-*t*)$_4$. However, the task of finding the optimal size of the titanium alkoxide employed is delicate. Another study by Knochel and co-workers [35] revealed that the optimal enantioselectivity is produced by an equimolar mixture of Ti(OPr-*i*)$_4$ and Ti(OBu-*t*)$_4$. According to Yus *et al.* [29], Ti(OPr-*i*)$_4$ affords higher enantioselectivity than does Ti(OBu-*t*)$_4$ or Ti(OEt)$_4$. A moderate enantioselectivity was obtained when achiral bis-sulfonamides were used as ligands in combination with titanium bound to (*S*)-1-phenyl-1-propanol (**3**) [67]. Our observation of nonlinearity between the enantiomeric excess and the conversion in the asymmetric alkylation reaction (see above) indicates that the enantioselectivity can be affected by the presence of chiral coordinating alkoxides. This means that the enantioselectivity in the alkylation promoted by bis-sulfonamide **20** can be improved by introduction of chiral coordinating groups as additives [68]. Chiral amines, amino alcohols, and alcohols have now been used in the presence of bis-sulfonamide **20** and Ti(OPr-*i*)$_4$ [69].

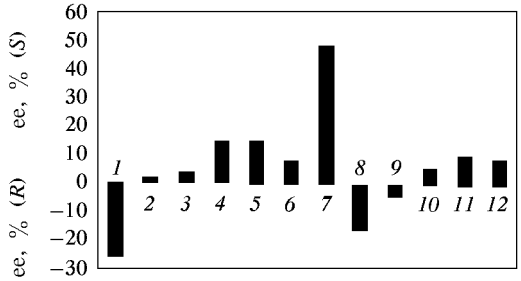


Fig. 1. Effect of amines and amino alcohols on the enantioselectivity in the addition of diethylzinc to benzaldehyde: (*1*) no additive, (*2*) (*R*)-1-phenylethylamine; (*3*) (*S*)-1-phenylethylamine, (*4*) (1*R*,2*R*)-1,2-diaminocyclohexane, (*5*) (1*S*,2*S*)-1,2-diaminocyclohexane; (*6*) *cis*-1,2-diaminocyclohexane, (*7*) (1*R*,2*R*)-1,2-diamino-1,2-diphenylethane, (*8*) (1*S*,2*S*)-1,2-diamino-1,2-diphenylethane, (*9*) (*R*)-1,1′-binaphthyl-2,2′-diamine, (*10*) (–)-sparteine, (*11*) (*R*)-2-phenylglycinol, and (*12*) (*S*)-phenylalaninol.

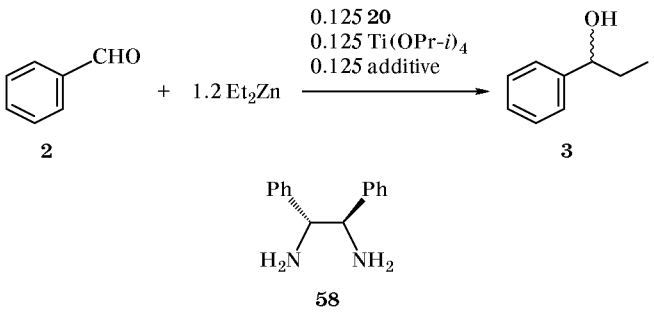
A ligand **20**–additive–Ti(OPr-*i*)$_4$ ratio of 1 : 1 : 1 (12.5 mol % of each) was used in the alkylation reaction, and it was believed to favor formation of a titanium complex containing one molecule of ligand **20** and one molecule of the additive; however, other combinations are also possible [70]. The mixture was

heated for 90–160 min in toluene at 60°C, and diethylzinc and benzaldehyde were added at –78°C. The reaction was quenched after ~90 h at –35°C. The ee values of the catalytic reactions in the presence of chiral mono- and diamines [71] and amino alcohols are given in Fig. 1. Figure 1 shows ee values obtained in the catalytic reactions in the presence of chiral mono- and diamines and amino alcohols. In all cases, except for amino alcohols, the conversion was greater than 87%. In the absence of additive, the ee value for alcohol **3** was 26% in favor of the *R* enantiomer (Fig. 1, *1*). Both enantiomers of 1-phenylethylamine favored formation of the *S* enantiomer of **3**, but the ee values were very poor (Fig. 1, *2* and *3*). The two 1,2-diaminocyclohexane enantiomers also afforded the *S* enantiomer, but again with low enantioselectivity (Fig. 1, *4* and *5*). The highest enantioselectivity, 49% (*S*), was observed when (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine (**59**) was used as additive, whereas its enantiomer favored formation of *R* enantiomer with 16% ee (Fig. 1, *7* and *8*). The axially chiral diamine, (*R*)-1,1′-binaphthyl-2,2′-diamine, (–)-sparteine, and two amino alcohols, (*R*)-2-phenylglycinol and (*S*)-phenylalaninol, showed a low enantioselectivity in the alkylation reaction (Fig. 1, *9–12*).

The results obtained under analogous conditions with mono- and bidentate alcohols as additives are summarized in Fig. 2. With a few exceptions, the conversion was greater than 90%. All monodentate alcohols favor formation of the *R* enantiomer of **3**, whereas bidentate alcohols, except for (*R*)-BINOL, favor formation of (*S*)-**3**. The *R* enantiomer of **3** was formed as the major product when 2 equiv of monodentate L-menthol was added. The maximal enantioselectivity (ee 46%) was observed with (–)-TADDOL [72]. In the presence of a slight excess of Ti(OPr-*i*)$_4$, (*S*)-BINOL favored formation of (*S*)-**3** (ee 92%). This result partially explains the enantioselectivity observed with BINOL additives [73].

The results obtained with enantiomeric pairs as additives indicate participation of diastereoisomeric

Scheme 11.



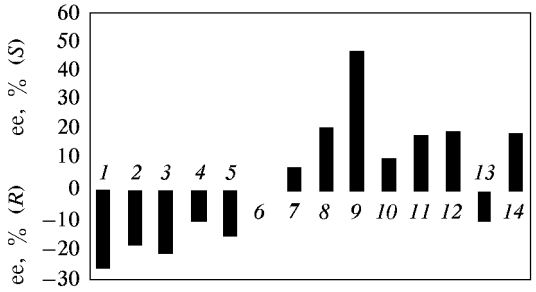


Fig. 2. Effect of mono- and bidentate alcohols on the enantioselectivity of the addition of diethylzinc to benzaldehyde: (*1*) no additive, (*2*) D-menthol, (*3*) L-menthol, (*4*) 2 equiv of L-menthol, (*5*) (1*S*,2*S*,5*S*)-(–)-myrtanol, (*6*) (*S*)-(+)-mandelic acid methyl ester, (*7*) *cis*-1,2-cyclohexanediol, (*8*) dimethyl L-tartrate, (*9*) (–)-TADDOL, (*10*) (2*R*,5*R*)-2,5-hexanediol, (*11*) (2*S*,5*S*)-2,5-hexanediol, (*12*) (1*S*,2*S*)-1,2-di-*o*-tolylethane-1,2-diol, (*13*) (*R*)-(+)-BINOL, (*14*) (*S*)-(–)-BINOL.

complexes in the alkylation process. If titanium complexes containing only one additive and no ligand determine the stereochemical outcome of the alkylation reaction, then (1*R*,2*R*)-1,2-diaminocyclohexane, for example, would favor formation of the opposite enantiomer to that obtained with (1*S*,2*S*)-1,2-diaminocyclohexane, but with the same ee value. Of course, various combinations of Ti(OPr-*i*)$_4$, ligand **20**, and additive are possible, and in each case the enantioselectivity, the relative concentration, and the reaction rate must be considered.

Attempts to improve the enantioselectivity of the catalytic reaction in the presence of diamine **58** (Scheme 11) were made by optimizing the reaction conditions. Increase in the amount of Ti(OPr-*i*)$_4$ from 0.125 to 1.35 equiv resulted in appreciable reduction of the enantioselectivity, probably due to competition with the background reaction. It was surprising that the complete conversion was not attained despite prolonged reaction time and large excess of Ti(OPr-*i*)$_4$. The enantioselectivity was sligthly improved when the reaction mixture was kept at room temperature before addition of aldehyde. Under analogous conditions, raising the amount of Et_2Zn did not increase the enantioselectivity. The reaction with a 1:1 mixture of diamine **58** and Ti(OPr-*i*)$_4$ in the absence of ligand **20** was slow, and the *S* enantiomer of **3** was obtained with a low ee value (3%). In the absence of **20** and Ti(OPr-*i*)$_4$, diamine **58** favored formation of (*R*)-**3**, though the reaction was even slower.

Conclusions. Sulfonamides are efficient promotors in the titanium-catalyzed addition of diethylzinc to prochiral aldehydes, which in many cases affords secondary alcohols with high enantioselectivity.

Sulfonamides obtained by ring opening of chiral aziridines promote titanium-mediated addition of diethylzinc to benzaldehydes. The structure of the promotor was found to be important for both the enantioselectivity and the rate of addition of diethylzinc to benzaldehyde, although only moderate ee values were obtained. Reaction conditions strongly affect the outcome of the reaction, and a large excess of titanium(IV) isopropoxide usually favors increased reaction rate and enantioselectivity. Chiral amines and alcohols have a decisive effect on the ee values. Versatility of sulfonamides as ligands for asymmetric catalysis was shown by Nelson *et al.* in the ketene aldehyde cycloaddition, and sulfonamides should be evaluated as promotors for other types of Lewis acid-mediated processes such as Diels–Alder reactions.

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