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REVIEW

Catalytic Asymmetric Synthesis of Chiral Secondary Polyfunctional Alcohols Using Diorganozincs

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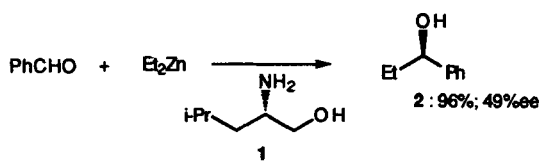
INTRODUCTION

Some ten years ago, Oguni[1] found that (*S*)-leucinol **1** catalyzes the enantioselective addition of Et_2Zn to benzaldehyde (96% yield; 49% ee; Eqn [1]). Since this important finding, a wide range of chiral 1,2-aminoalcohols and related compounds were found to catalyze the addition of Et_2Zn to aldehydes with excellent enantioselectivities [up to 99% ee (enantiomeric excess)][2,3] leading to secondary alcohols. Although optically active ethyl-substituted secondary carbinols such as **2** are worthwhile target molecules, an extension to other alkyl-substituted carbinols is desirable in order to confer some generality to this asymmetric synthetic method. This review covers the recent efforts made by our research group and others to accomplish the generalization of this enantioselective method to the preparation of polyfunctional secondary alcohols of type **3**. This goal can be achieved either by adding a polyfunctional diorganozinc [$(FG\text{-}R)_2Zn$; FG = functional group] to an aldehyde (RCHO) or by adding a diorganozinc (R_2Zn) to a polyfunctional aldehyde (FG-RCHO) (Eqn [2]).



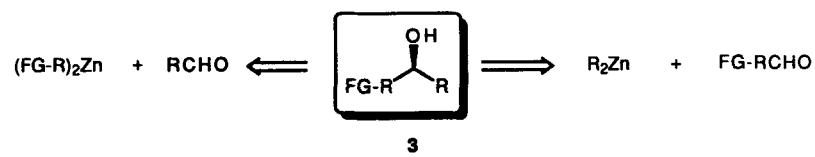
[1]

After the preparation methods for polyfunctional dialkylzincs [$(FG\text{-}R)_2Zn$] have been presented, the synthesis of functionalized chiral secondary alcohols via the two retrosynthetic pathways depicted in Eqn [2] will be discussed. Applications in the field of natural product synthesis will be given.

PREPARATION OF POLYFUNCTIONAL DIORGANOZINCS

The iodine–zinc exchange reaction

Only diorganozincs (R_2Zn) were found to be suitable zinc reagents for the catalytic asymmetric addition to aldehydes. The more easily prepared organozinc halides (RZnX) lead to only mediocre enantioselectivities.[2] Whereas diethyl-, dipropyl-, dibutyl- and dipentyl-zincs are readily prepared by the reaction of the corresponding lithium or magnesium organometallics with zinc halides, followed by distillation, higher dialkylzincs cannot be obtained salt-free by this method due to their thermal instability.[4] Interestingly, the transmetalation of alkylmagnesium halides with zinc chloride in ether followed by the addition of 1,4-



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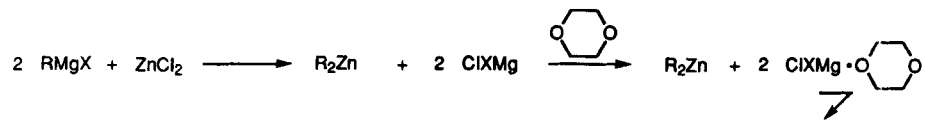

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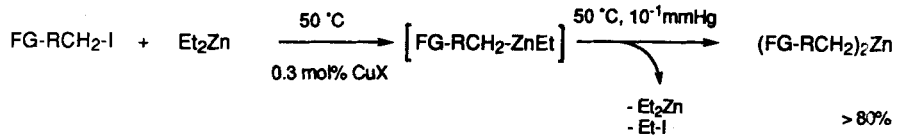
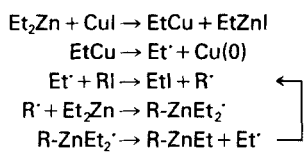


[4]

dioxane constitutes a convenient method for the preparation of higher salt-free dialkylzincs (Eqn [3]).[4,5] Although suitable for asymmetric reactions, this transmetalation does not give access to polyfunctional dialkylzincs. The most general approach to these reagents is an iodine–zinc exchange reaction (Eqn [4]).[6] This reaction, initially limited to di-iodomethane,[7] can be greatly extended. The treatment of Et_2Zn with various primary alkyl iodides at 50 °C for several hours provides the corresponding dialkylzincs and ethyl iodide via intermediate mixed dialkylzincs. Functional groups such as ester, nitrile, chloride, triflamide and boronic ester are tolerated in the organic moiety. The reaction is performed in the presence of catalytic amounts of copper(I) iodide or copper(I) cyanide (0.3 mol%) and may proceed via a radical mechanism (Scheme 1).[8] Secondary dialkylzincs and benzylic, allylic or aromatic diorganozincs cannot be prepared by this method.



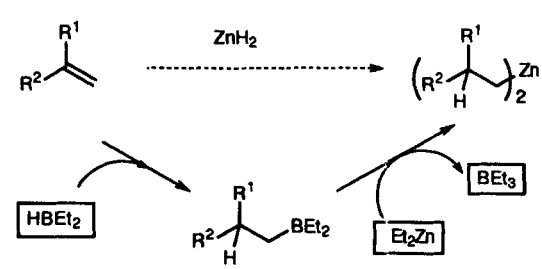
Scheme 1

The boron–zinc transmetalation

Organoboranes readily undergo transmetalation reactions with diorganozinc compounds.[4] The equilibrium of the reaction can be driven towards the right-hand side by distilling off the resulting borane (if R^1 = Me: trimethylborane, b.p. = −22 °C; Eqn [5]). This reaction constitutes

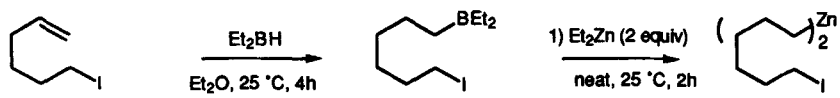
$$3R^1_2Zn + 2R^2_3B \rightleftarrows 3R^2_2Zn + 2R^1_3B \qquad [5]$$

an excellent method for the synthesis of diallyl- or dibenzyl-zincs (Eqn [6]). It formally allows the preparation of diorganozincs directly from olefins (Scheme 2). A range of diorganozincs not available by the iodine–zinc exchange reaction or by other methods can be prepared via the boron–zinc exchange. Thus functionalized primary dialkylzincs (Eqn [7]); secondary dialkylzincs (Eqn [8]) and benzylic zinc derivatives (Eqn [9]) have been prepared in high yields.[10,11] The reaction is also well suited for the preparation of dialkenylzincs of defined configuration. Thus the hydroboration of terminal alkynes with dicyclohexylborane (hexane, 0–25 °C) produces [(*E*)-1-alkenyl]boranes which can directly be transmetalated with Et_2Zn or Me_2Zn furnishing mixed alkenyl(alkyl)zincs.[12] Interestingly, the C_{sp^2}–Zn bond reacts preferentially over the C_{sp^3}–Zn bond with aldehydes. The method allows a unique preparation of polyfunctional alkenylzinc derivatives (Eqns [10]–[11]).[12,13]



Scheme 2

[6]



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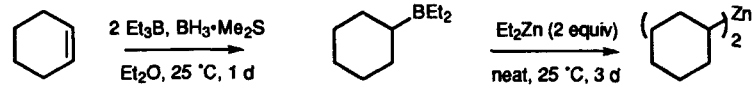

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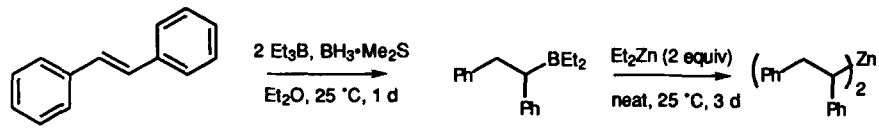

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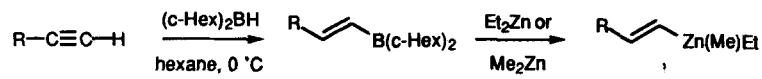

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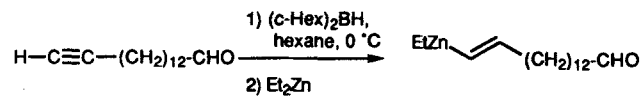
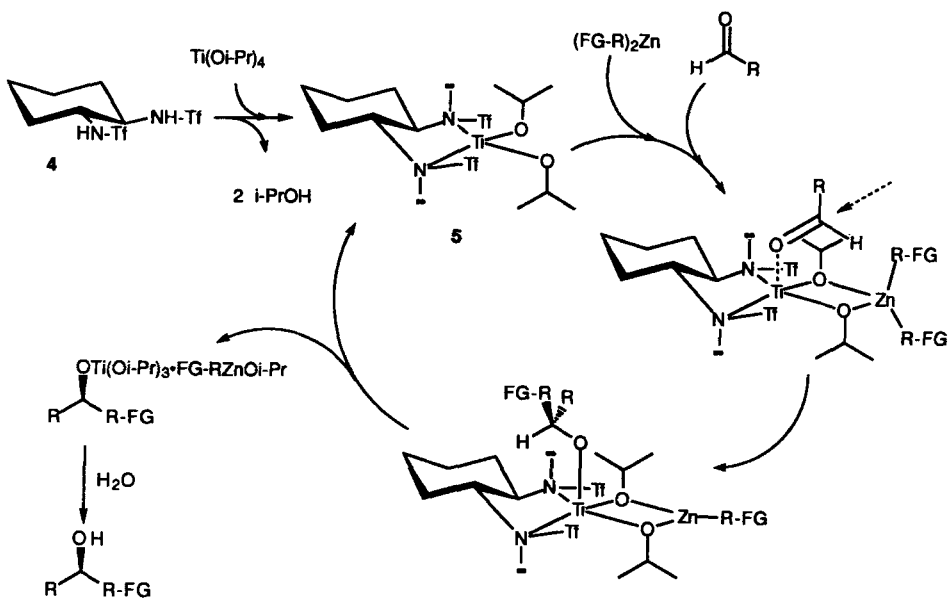


[11]

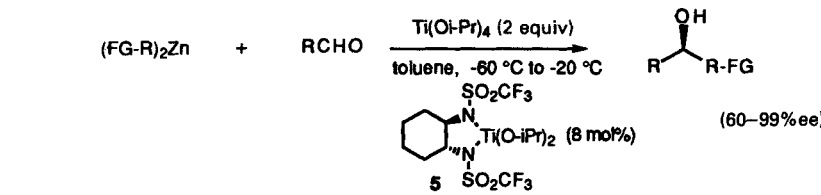
PREPARATION OF CHIRAL POLYFUNCTIONAL SECONDARY ALCOHOLS

Addition of functionalized diorganozincs to aldehydes

As mentioned above, the iodine–zinc exchange reaction allows a convenient synthesis of functionalized dialkylzincs. These reagents can be added to various aromatic and aliphatic aldehydes using (1*R*, 2*R*) - 1,2 - bis(trifluoremethanesulfonamido)-cyclohexane (**4**)[6, 14] as a catalyst (Eqn [12]). The addition of Ti(O-iPr)$_4$ (2 equiv.) is essential for the success of the reaction since it makes it possible to generate *in situ* the highly active titanium catalyst **5** and regenerates the catalyst continuously by removing the secondary alcohol



Scheme 3



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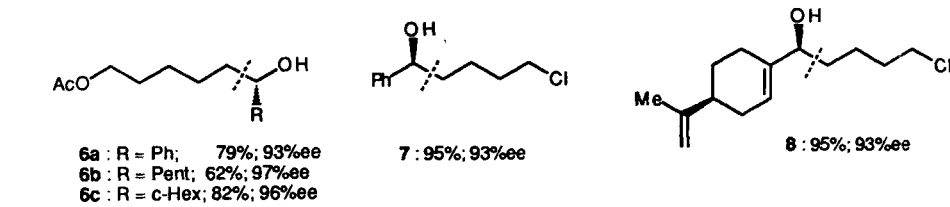
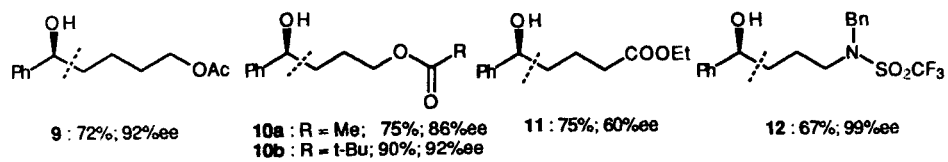
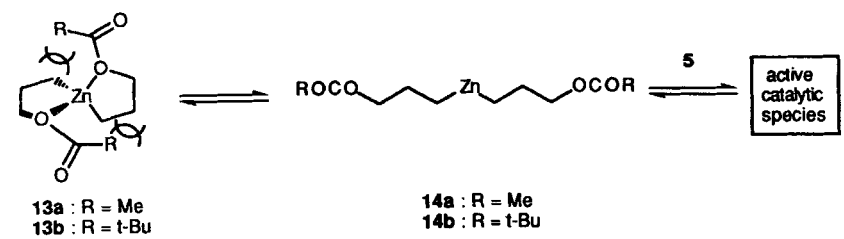


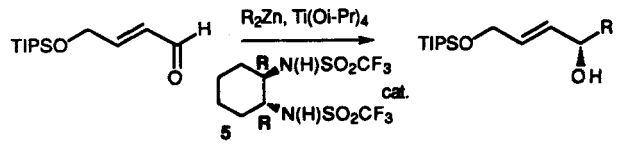




[13]

formed from the chiral titanium center, as represented in the tentative catalytic cycle depicted in Scheme 3 (Tf = SO_2CF_3).

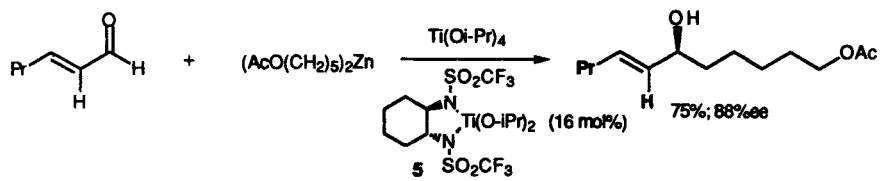
Various functionalized zinc reagents bearing an ester, chloride or triflamide functionality can be used (see the chiral products **6–12**; the new carbon–carbon bond formed is indicated by a dotted line). However, the presence of a cyano group in the diorganozinc compound inhibits the asymmetric addition, leading to the desired alcohol in low yield and mediocre enantioselectivity.[6] The presence of an ester function at a remote position (five carbon atoms away from the carbon–metal bond) does not interfere with the asymmetric addition and uniformly high enantioselectivities are obtained (see **6a–6c**); however, a closer substitution shows that the ester function is able to coordinate to the metal center. Thus bis(3-acetoxypropyl)zinc **13a** adds to benzaldehyde with a significantly lower enantioselectivity than the higher homologues (compare **6a–6c**, **9** and **10a**). This is explained by an intramolecular coordination of the carboxy group to the zinc center which hampers the formation of a complex of **13** with the catalyst **5** (Eqn [13]).[6] It is expected that by increasing the size of the ester function, the proportion of uncomplexed zinc reagent **14** capable of interacting with the catalyst would increase. This is observed and bis(3-pivaloxypropyl)zinc (**13b**) adds with a higher enantioselectivity to benzaldehyde (compare **10a** and **10b**). The rate of the addition reaction, as well as the enantioselectivity, is highly dependent on the reaction conditions. Thus the presence of traces of water or the use of impure titanium tetraisoproxide which may contain bridged titanium species ($(iPrO)_3TiOTi(OiPr)_3$) has a detrimental effect. A strong temperature dependence was also observed for the addition of $(FG\text{-}R)_2Zn$ to functionalized aldehydes. Whereas reactive dialkylzincs such as diethylzinc show a higher enantioselectivity at low temperatures, zinc rea-



	Et_2Zn		$(Oct)_2Zn$				
T (°C)	−75	−50	−75	−65	−50	−45	−45 to −25
ee (%)	94	85	42	60	83	90	90 (88% yield)

[a] Bath temperature.

Scheme 4



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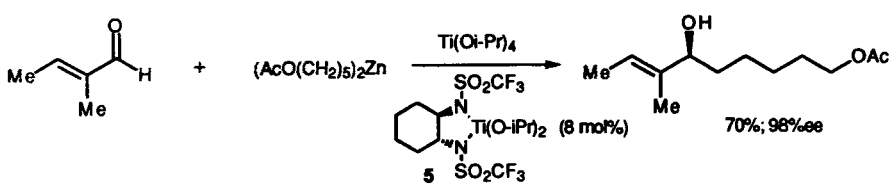
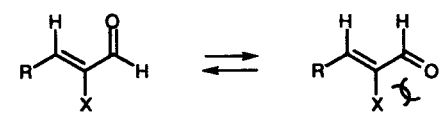


[15]

gents bearing a polar functionality such as an ester group or a long alkyl chain surprisingly display an inverse temperature effect (Scheme 4). As shown in Scheme 4, the method is also well suited to the preparation of secondary allylic alcohols.[12,15] Thus 2-hexenal adds bis(5-acetoxypentyl)zinc with 88% ee (75% yield) using 16 mol% of the catalyst (Eqn [14]). The presence of a substituent in the α- position enhances the enantioselectivity (Eqn [15]).[15] This may be explained by assuming that the presence of a substituent in position 2 favors the more reactive and sterically more demanding *s-cis* conformer **15** over the *s-trans* conformer **16** (Eqn [16]).[15] Thus, it was shown that unsaturated 2-bromoaldehydes add dialkylzincs with higher enenatioselectivity than the corresponding unsaturated aldehydes bearing only a hydrogen substituent in position 2 (compare **17a**, **b** and **18a**, **b**). This excellent enantioselectivity was exploited for the construction of a chiral C_3 triol **19** which may be of interest of the preparation of chiral catalysts (Scheme 5). Thus an addition–elimination sequence to (*E*)-2-pentenal provides an expeditive access to the 2-bromoaldehyde **20**, which adds Et_2Zn with 95% ee. Conversion of the bromine to a formyl group via a bromine–lithium exchange reaction affords the aldehyde **21**, which again adds Et_2Zn, furnishing the 1,3-diol **22** in 83% yield (>95% diastereomeric ratio). The hydroboration of **22** followed by an oxidation provides, with satisfactory diastereo-



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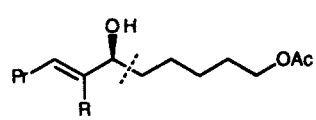
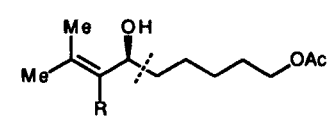
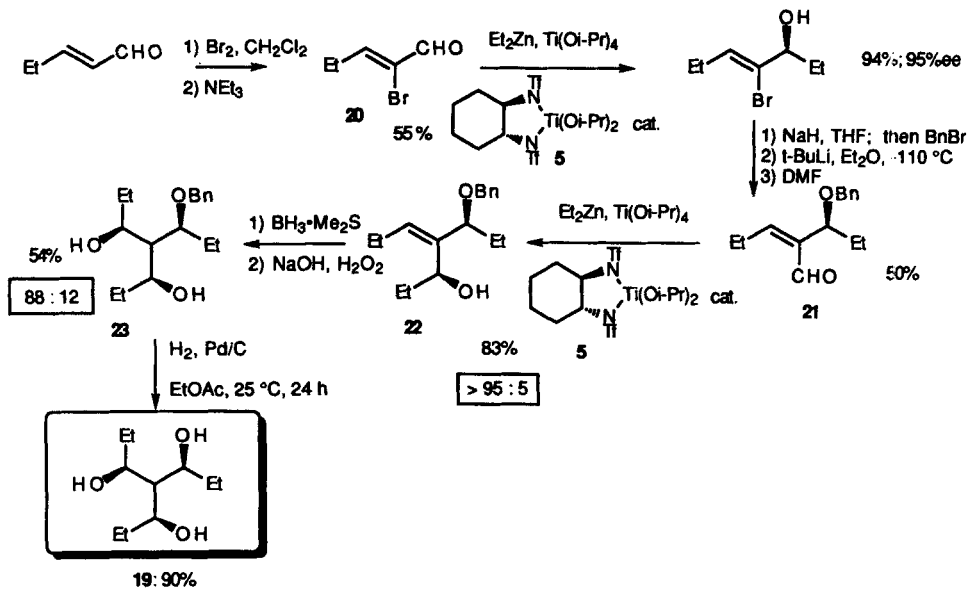


17a : R = H; 75%; 88%ee
17b : R = Br; 95%; 94%ee



18a : R = H; 95%; 30%ee; (addition of Oct_2Zn)
18b : R = Br; 68%; 68%ee

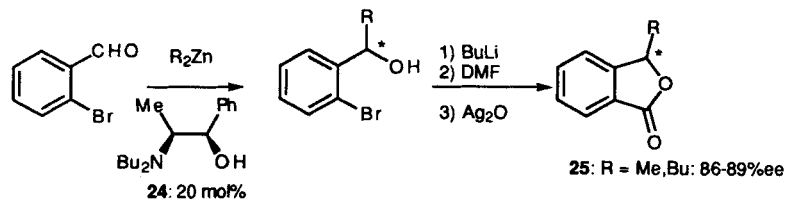


Scheme 5

selectivity (88:12), the protected triol **23**, which after hydrogenolysis furnishes the optically pure C_3 triol **19**.[16]

Addition of diorganozincs to functionalized aldehydes

The addition of diethylzinc to various functionalized aldehydes has been achieved with great success.[2] Thus the addition of diethylzinc (or dibutylzinc) to 2-bromobenzaldehyde in the presence of the 1,2-amino alcohol **24** produces alcohols (86–90% ee) which have been readily converted to optically active phthalides **25** (Eqn [17]).[17] A range of ketoaldehydes were shown to add dialkylzincs with high chemo- and enantioselectivity (Eqn [18]).[18,19] A ferrocene substituent is tolerated and the catalytic asymmetric addition of dialkylzincs to ferrocenecarboxaldehyde in the presence of (*R*)-3,3-dimethyl-1-piperidino-2-butanol **26** (5 mol%) proceeds with >96% ee providing, after a substitution reaction with dimethylamine, a new access to ferrocenyl-*N*,*N*-dimethylamino derivatives (Eqn [19]).[20] Several butyro- and valero-lactones can be prepared by the addition of Et_2Zn or Me_2Zn to esters bearing a remote aldehyde function followed by cyclization (Eqn [20]).[21] The very high enantioselectivity observed in the addition of Et_2Zn to phenylpropinal in the presence of TADDOL (**27**) is a very



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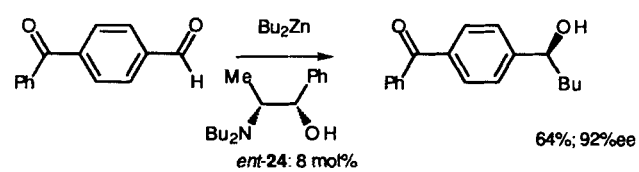

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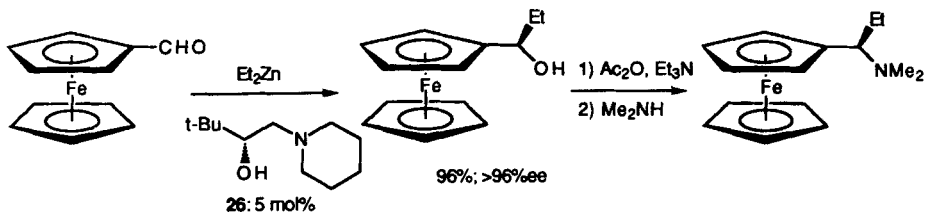

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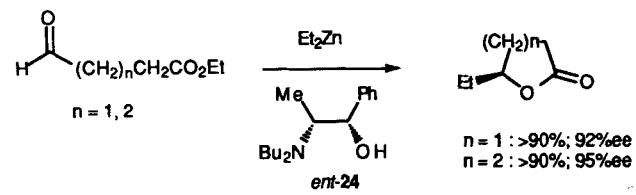
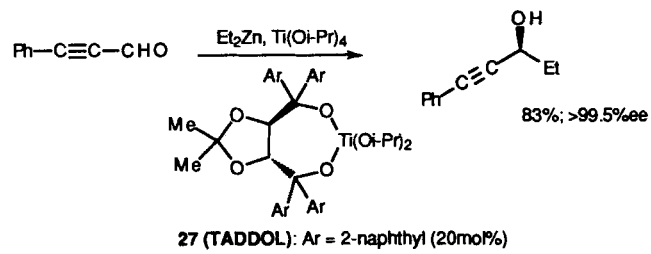


[20]

promising result with a great synthetic potential, since the resulting propargylic alcohols are key building-blocks in organic synthesis (Eqn [21]).[5] This catalytic system also makes it possible to prepare C_2-symmetrical benzylic alcohols such as **28** and **29**. By performing a stepwise addition of Et_2Zn and using the other enantiomer of TADDOL as catalyst (*ent*-**27**-, the *meso*-diol **30** can be prepared.[5]

The readily available γ-alkoxyaldehyde **31**[22] adds various diorganozincs [(FG-R)$_2$Zn] leading to 1,4-diol derivatives **32** in satisfactory yields and excellent stereoselectivity (Eqn [22]; TIPS = $(iPrO)_3Si$; PCC = pyridinium chlorochromate).[8,23] The compounds **32** are interesting chiral building blocks which give an efficient access to chiral γ-alkoxyenones **33** after standard transformations (Eq. [23]).[23] The γ-alkoxyaldehydes **34** prepared by this method add, in the presence of catalytic amounts of **4**, another equivalent of the dialkylzinc leading to C_2-symmetrical 1,4-diol derivatives **35** (Eqn [24], in which TFA = CF_3COOH; NMO = *N*-methylmorpholine *N*-oxide; TBDPS = $tBuPh_2Si$); see compounds **35a–e**). The diastereoselectivities obtained are excellent, showing that the second center is entirely induced by the configuration of the chiral catalyst and not by the configuration of the chiral center already present in **34**. Thus by using a chiral catalyst with the opposite configuration (*ent*-**5**-, the "*meso*"-1,4-diol derivative **36** is obtained with high diastereoselectivity (Eqn [25]).[23]

Whereas the addition of Me_2Zn under the



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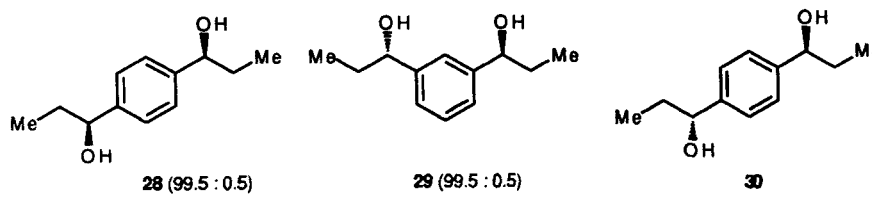

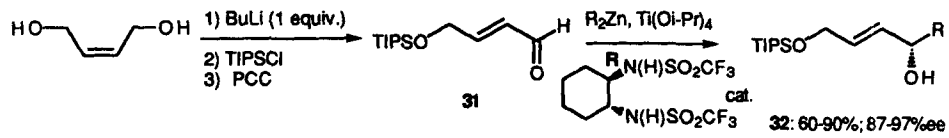

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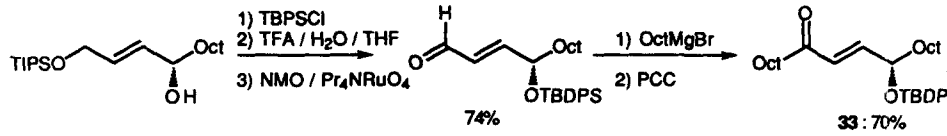

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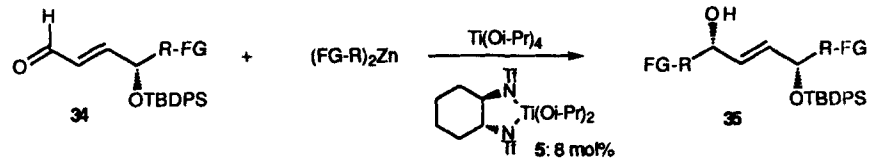

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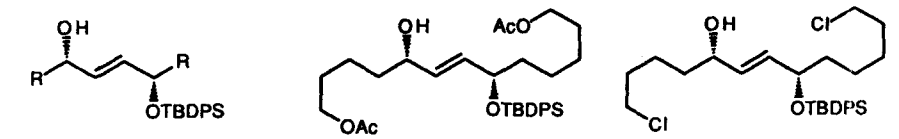

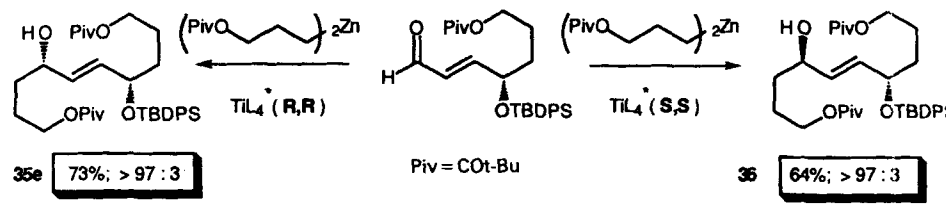

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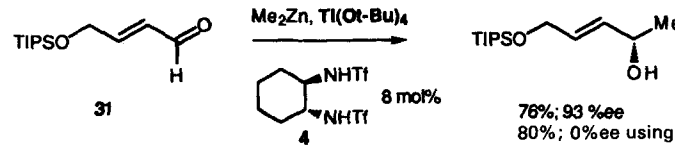
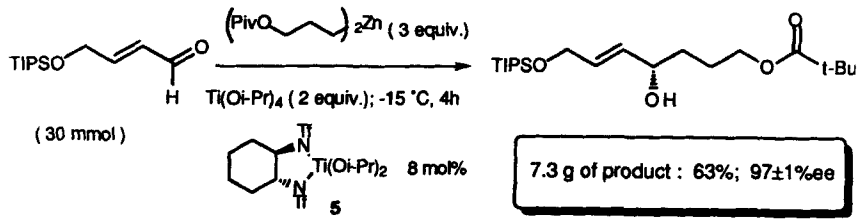


[26]



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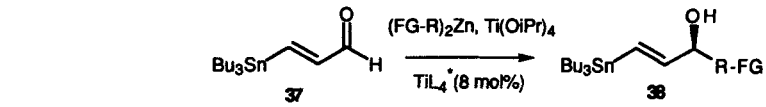

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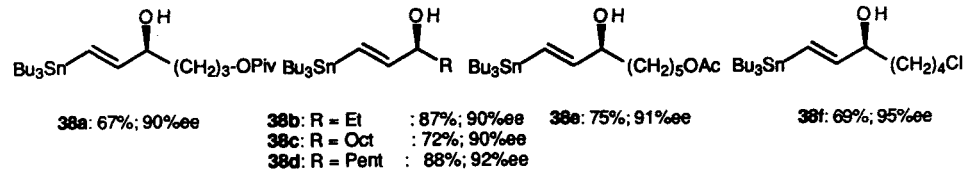
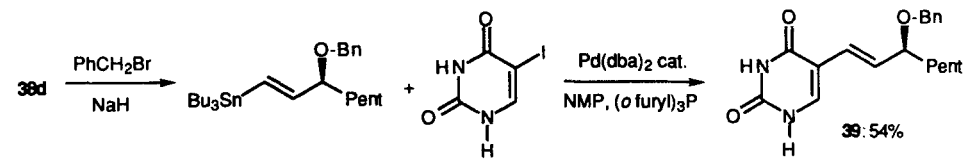


standard conditions proceeds with no enantioselectivity,[23b] it was found that the replacement of $Ti(OiPr)_4$ with $Ti(OtBu)_4$ leads to a remarkable increase in stereoselectivity (Eqn [26]). Furthermore, the general addition procedure has been well worked out, so that large-scale reactions (30 mmol) can be performed with satisfactory yields and excellent enantioselectivity (Eqn [27]).

The β-stannylated unsaturated aldehyde **37** is of special interest, since the addition of dipentylzinc to **37** in the presence of a chiral catalyst directly produces the side chain of prostaglandins.[24] In the presence of the chiral catalyst **5**, the addition of various dialkylzincs can be performed leading to unsaturated stannylated alcohols **38** (Eqn [28] and **38a–38f**).[25] After a protection step, these alcohols can be used for the preparation of the chiral uracil derivative **39** and of the γ-alkoxyenone **40** via a Stille coupling reaction (Eqns [29] and [30]; Pent = n-pentyl; Bn = benzyl; dba = dibenzylideneacetone; NMP = *N*-methyl-2-pyrrolidone; TBDMS = $tBuMe_2Si$; DMF = dimethylformamide).[25,26] The creation of new chiral center becomes more challenging when there is already a chiral center or a polar functionality in close proximity to the aldehyde function. Thus the reaction of 2-phenylpropanal with Et_2Zn in the presence of catalytic amounts of *ent*-**24** (10 mol%) produces 2-phenylpentan-3-ol as a *threo*/*erythro* 25:75 mixture. The enantiomeric excess for the two diastereoisomers, respectively, reaches 93 and 65%. The use of Bu_2Zn leads even to better selectivities (Eqn [31]).[27] By using TADDOL **27** as a chiral catalyst, a similar aldehyde (**41**) undergoes an asymmetric ethylation with complete reagent control. No influence of the chiral center at the α-position of **41** is observed. Thus with TADDOL **27**, the *anti*-alcohol **42** is obtained (97:3 diastereoselectivity), whereas with the enantiomeric catalyst (*ent*-**27**), the *syn*-alcohol **42** is produced with a similar stereoselectivity (>96:4; Eqn [32]).[5]

Aldehydes bearing a hydroxy group in the β-position to the carbonyl group are difficult substrates for the catalytic asymmetric addition, since after addition 1,3-diols with chelating abilities are obtained and a deactivation of the catalyst is usually observed. By using a bulky protecting group such as a $(iPrO)_3Si$ group (TIPS), the complexation of the hydroxy function can be greatly reduced and a catalytic asymmetric reaction is possible leading to chiral 1,3-diol derivatives of type **44**. After standard functional group



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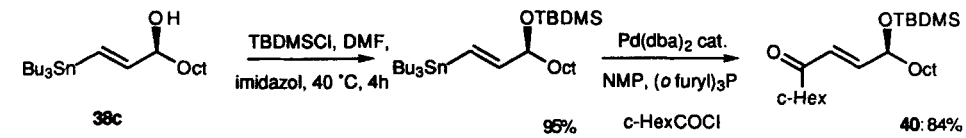
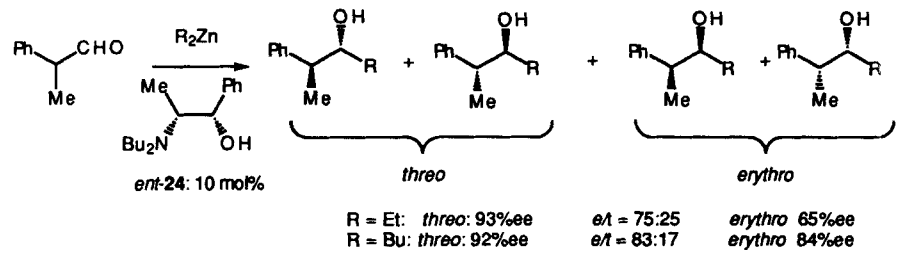
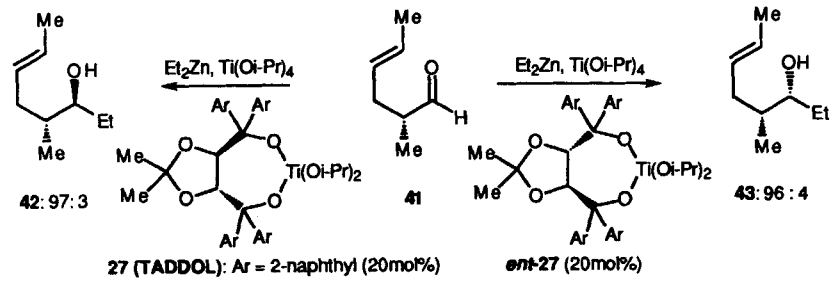


[30]



[31]



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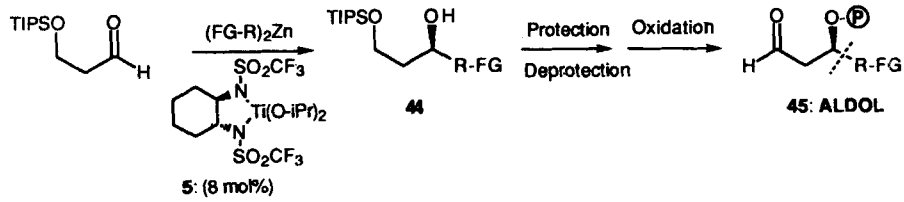
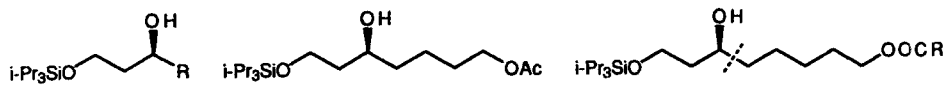


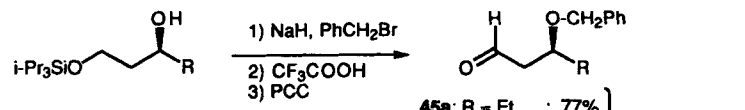
[33]



44a: R = Et : 92%, 93%ee
44b: R = Pent : 83%, 95%ee
44c: R = Oct : 82%, 93%ee

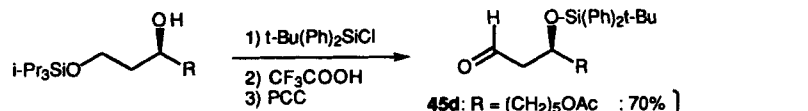
44d: 62%, 99%ee

44e: R = Me : 71%, 91%ee
44f : R = t-Bu : 72%, 91%ee



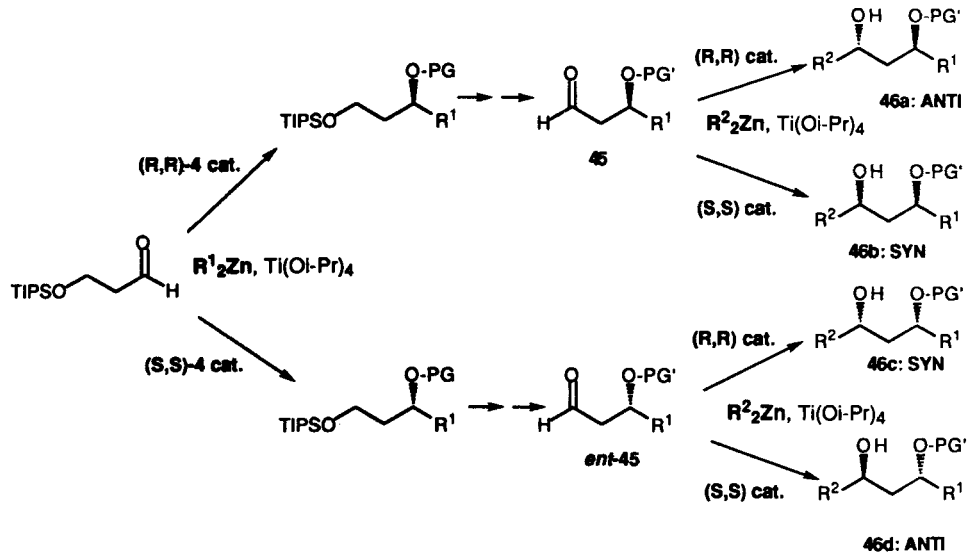
45a: R = Et : 77%
45b: R = Pent : 60%
45c: R = Oct : 64%
} **93%ee - 95%ee**

[34]



45d: R = $(CH_2)_5OAc$: 70%
45e: R = $(CH_2)_5OPiv$: 61%
45f : R = $(CH_2)_4OAc$: 54%
} **91%ee - 99%ee**

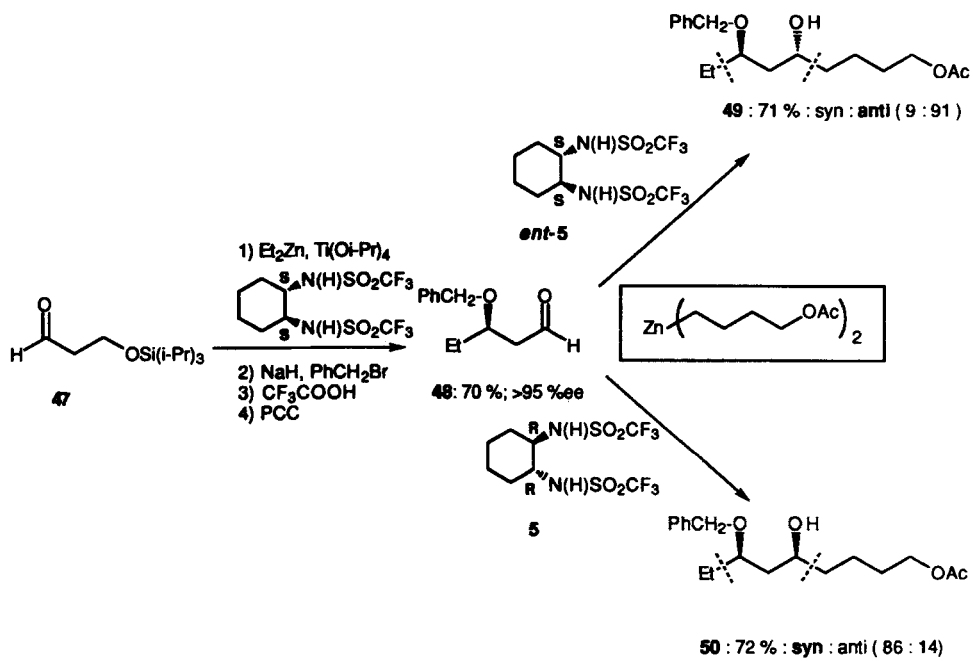
[35]



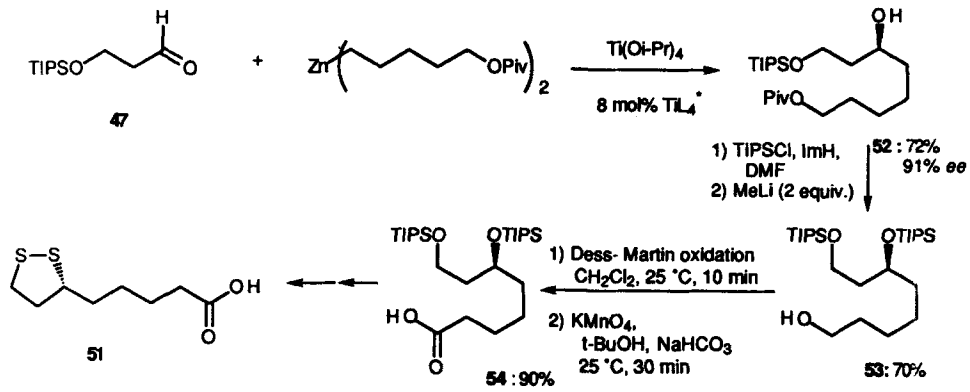
Scheme 6

interconversions, aldol products of type **45** are obtained (Eqn [33]).[28] The method allows the preparation of various polyfunctional 1,3-diol derivatives (see **44a–f**). Two sequences have been developed for converting the compounds **44** to the aldol products **45** (see **45a–45f**; Eqns [34] and [35]).[28] A further addition of a dialkylzinc to the aldols **45** may give an access to highly functionalized secondary 1,3-diols. By using the (*R*,*R*)-catalyst (**5**) or the (*S*, *S*)-catalyst (*ent*-**5**), all four 1,3-diols **46a–46d** can be selectively constructed (Scheme 6).[28, 29]

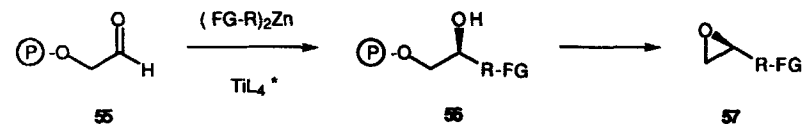
This is demonstrated in the following case. The addition of Et_2Zn to the aldehyde **47** affords, in



Scheme 7



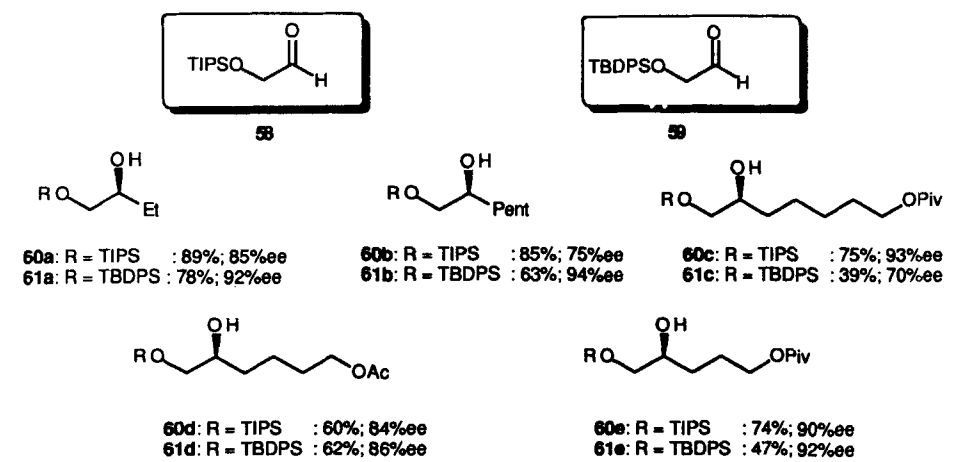
Scheme 8



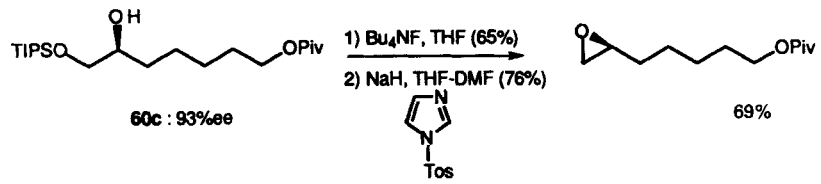
[36]

the presence of the catalyst (*ent*-**5**) and further functional group interconversions, the aldehyde **48** (70%; >95% ee), which adds bis(4-acetoxybutyl)zinc either in the presence of the (*S*,*S*)-catalyst (*ent*-**5**) furnishing selectively the *anti*-1,3-diol derivative **49** (*syn*/*anti* = 9:91) or in the presence of the (*R*,*R*)-catalyst (**5**) providing the *syn*-1,3-diol derivative **50** (*syn*/*anti* = 86:14) (Scheme 7). This strategy has been applied to a short formal synthesis of lipoic acid **51** (Scheme 8; ImH = imidazole).[30] Thus the addition of bis(5-pivaloxypentyl)zinc to the aldehyde **47** affords the desired secondary alcohol **52** (72%, 91% ee) which after two protection–deprotection steps leads to the primary alcohol **53** (70% yield). The oxidation of **53** produces the carboxylic acid **54** (90% yield), which has already been converted to lipoic acid **51**.[30, 31]

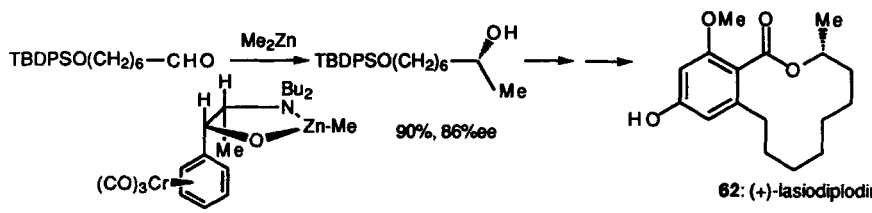
Epoxides are versatile chiral building blocks and the development of catalytic asymmetric synthesis of this class of compounds is therefore of special importance.[32] The addition of dialkylzincs ((FG-R)$_2$Zn) to protected α-hydroxyaldehydes **55** will lead to protected 1,2-diols **56**, which can be



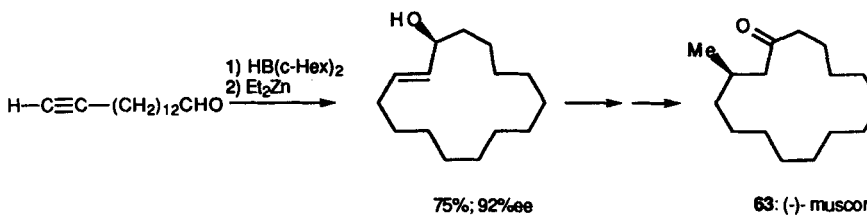
Scheme 9



[37]



[38]



[39]

easily converted to epoxides of type **57** (Eqn [36]). The choice of the protecting group for **55** proves to be crucial and the two silyl-protected hydroxyaldehydes **58** and **59** were found to give the best enantioselectivities leading to the 1,2-diols **60a–60e** and **61a–61e** with 75–94% ee (Scheme 9).[33] These 1,2-diol derivatives can be readily converted to chiral epoxides (Eqn [37]; THF = tetrahydrofuran; Tos = toluenesulfonyl).

The catalytic asymmetric addition of polyfunctional diorganozincs to aldehydes constitutes a powerful method for preparing various classes of chiral alcohols. Elegant applications to the preparation of natural products in enantiomerically enriched form such as (*R*)-(+)-lasiodiplodin, **62** (Eqn [38]),[34] and (−)-muscone, **63** (Eqn [39]),[13] demonstrate clearly the synthetic potential of this methodology.

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