Enantioselective carbometallation of unactivated olefins

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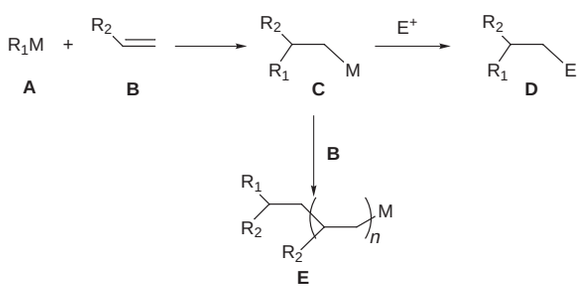
1 Introduction

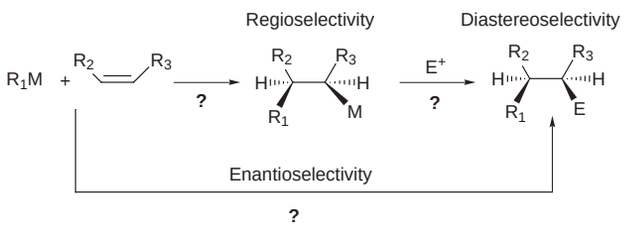
Carbon–carbon bond formation by means of organometallics, mainly began after the discovery of organomagnesium reagents by Grignard, and has commonly been achieved by their reactions with polar carbon electrophiles. In the search for new types of selective organometallic carbon–carbon bond formation, and following the pioneering Ziegler addition of some anionic initiators to non-polarized carbon–carbon bonds,[1] the controlled carbometallation reaction has emerged as a new tool. Since then, reactions which result in the addition of the carbon–metal bond of an organometallic **A** across a carbon–carbon double bond **B**, leading to a new organometallic **C** in which the *newly formed carbon–metal bond* of **C** *can be used for further synthetic transformations* to give **D** (see Scheme 1) are called carbometallation reactions.



Scheme 1

To be synthetically useful, the new organometallic **C** must have a reactivity different from that of **A** in order to avoid the polymerization (formation of **E**) of the carbometallated substrate.[2] So, the carbometallation ability of **A** must be higher than that of **C**, except in the case of an intramolecular carbometallation reaction. In the latter case, the entropy factors favor the mono-addition even if the starting organometallic and the product have similar reactivities (for example intramolecular 5-*exo-trig* cyclization produces a C–C bond, bond energy 370 kJ mol^{-1}, at the expense of a π-bond, bond energy 250 kJ mol^{-1}). Since this initial discovery an increasing number of organometallic additions to carbon–carbon double bonds in a racemic way have been reported and then reviewed.[3–5]

If the carbometallation is now performed on an α,β-disubstituted double bond, two regioisomers can be obtained and after reaction with an electrophile, two sp^3 stereogenic centers are created (see Scheme 2). So, in order to have a powerful reaction in synthetic organic chemistry, it will be necessary to control the regio- and the diastereoselectivity of this carbometallation (diastereoselectivity means that we have to control the configurational stability of sp^3 organometallic derivatives towards electrophiles). Moreover, if an efficient method was available to render such a process asymmetric, it would acquire significant utility as a method for the creation of asymmetric vicinal carbon atoms (see Scheme 2).

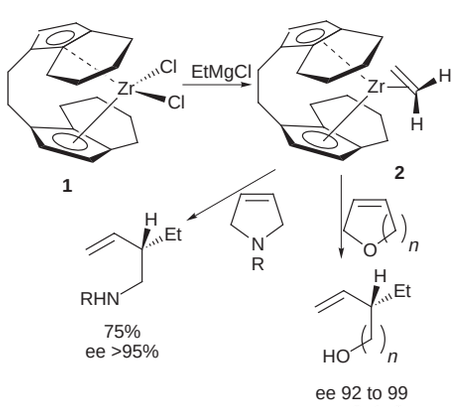


Scheme 2

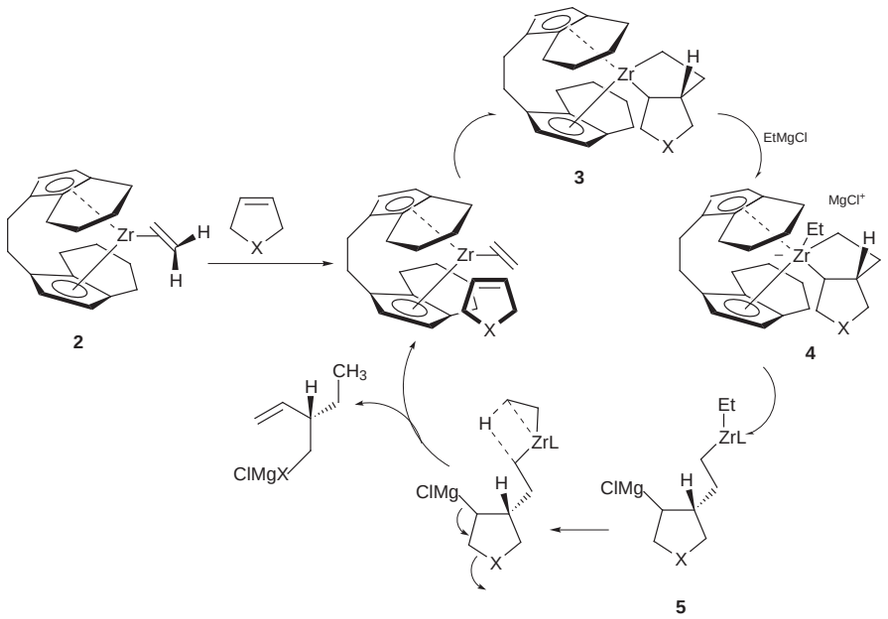
However, until now, such enantioselective carbometallation reactions are scarce due to the difficulty of enantiofacial differentiation of an unactivated alkene. This review will survey the enantioselective carbometallation chemistry of magnesium, aluminium, lithium, copper and zinc reagents. The reagents derived from titanium, palladium or nickel will not be addressed.

2 Asymmetric carbomagnesiation reactions

The regio- and stereoselective zirconocene-catalyzed addition of alkylmagnesium halides to alkenes, was investigated with ethylene-1,2-bis(η^5-4,5,6,7-tetrahydroinden-1-yl)zirconium dichloride [(ebthi)$ZrCl_2$] **1** or [(ebthi)Zr(binol)][6] as chiral zirconocene. Thus, treatment of 2.5 to 10% of **1** with ethylmagnesium chloride leads to the formation of the derived zirconocene alkene complex **2**, characterized by NMR spectroscopy,[7] which reacts with cyclic ethers or amines to lead respectively to the corresponding alcohols (n = 0,1,2) or amine in 92 to 99% ee and good overall yield[8] (Scheme 3).

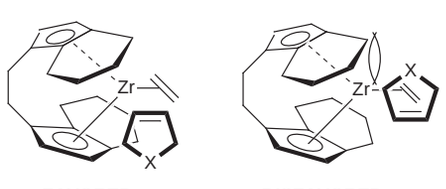


Scheme 3



Scheme 4

The rate of ethylmagnesiation of the remaining terminal double bonds of the reaction is sufficiently slower, so that unsaturated alcohols and amines can be isolated in high yield (the second alkylation is not generally stereoselective). The catalytic cycle proposed to account for the enantioselective ethylmagnesiation is shown in Scheme 4. The reaction is initiated by the chiral ziconocene-ethylene complex **2**, formed upon reaction of dichloride **1** (Scheme 3) with ethylmagnesium chloride. Coupling of the alkene substrate with **2** leads to the formation of the zirconacyclopentane intermediate **3**. Reaction of **3** with ethylmagnesium chloride affords zirconate **4**, which undergoes Zr–Mg ligand exchange to yield **5**. Subsequent β-hydride abstraction, accompanied by intramolecular magnesium–alkoxide elimination leads to the release of the carbomagnesiation product and regeneration of **2**. An important aspect of the carbomagnesiation of six-membered and larger heterocycles is that the intermediate metallacyclopentanes preferentially lead to reaction products in which the C–Zr bond is formed at the carbon α to the heterocycle C–X bond. It is plausible that the observed enantioselectivity arises from minimization of unfavorable steric and torsional interactions in the complex formed between **2** and the unsaturated heterocycle (Scheme 4). The alternative mode of addition illustrated in Scheme 5, would lead to costly steric repulsions between the heterocycle and the cyclohexyl group of the chiral ligand.

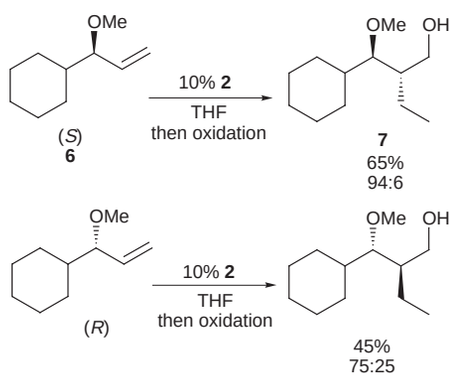


Scheme 5

Reactions in which higher magnesium alkyl halides are used, namely nPrMgCl and nBuMgCl, proceed less efficiently (35–40% yield) but with similarly high enantioselectivity (>90% ee).[8c] This methodology was successfully applied in a very elegant way to the enantioselective synthesis of the aglycon macrolactam of the antifungal agent Sch 38516.[9] The key step in this synthesis is the stereoselective ethylmagnesiation shown in Scheme 2 and further functionalization through three subsequent catalytic procedures yields the requisite synthon.

When racemic substituted pyrans are treated in THF, with the catalyst **2** at 70 °C for 30 min, a kinetic resolution leads to the unreacted pyran in >99% ee in approximately 35–40% yield.[10] Thus, the kinetic resolution of a variety of pyrans[10a] and cyclic allylic ethers[11] (six, seven and eight-membered vinyl systems)[8a] were investigated. In all cases, a very high enantioselectivity of the remaining starting materials was obtained. The first enantioselective total synthesis of (*S*,*R*,*R*,*R*)-nevivolol was successfully achieved *via* this zirconium-catalyzed kinetic resolution methodology of cyclic styrenyl ethers.[11b]

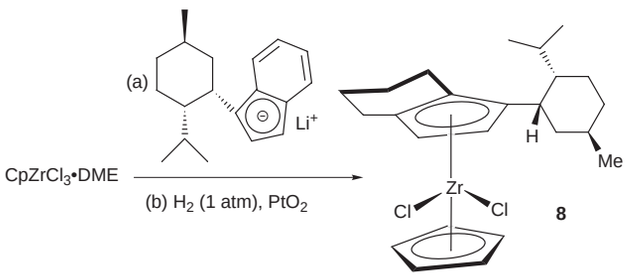
The transition metal–alkene complex **2** may also be employed as an effective catalyst in ethylmagnesiation of non-racemic allylic alcohols and ethers. These transformations proceed with varying levels of diastereochemical control, depending on which enantiomers of the chiral substrate is employed. Indeed, the reaction of chiral (*S*)-ether **6** (Scheme 6) in the presence of 10% of the (*R*)-complex **2** in THF affords the *anti* carbomagnesiation product (3*S*,4*R*)-**7** with 94:6 diastereocontrol whereas the (*R*)-chiral ether leads also to the *anti* isomer but with modest selectivity (75:25)[7,12] after oxidation with O_2 of the resulting organometallic derivatives. Thus, with the chiral catalyst, the (*S*)-ether **6** serves as the matched substrate, whereas the corresponding (*R*)-enantiomer has a mismatched interaction with the chiral catalyst.



Scheme 6

Recently, a novel C_i symmetric zirconocene dichloride $CpCp'ZrCl_2$ ($Cp = C_5H_5$, Cp' = 1-neomenthyl-4,5,6,7-tetrahydroindenyl) **8** was prepared, in which the alkene approaches mainly from one side. With this chiral ligand, the ethylmagnesiation of unsubstituted allylic amines or alcohols leads to

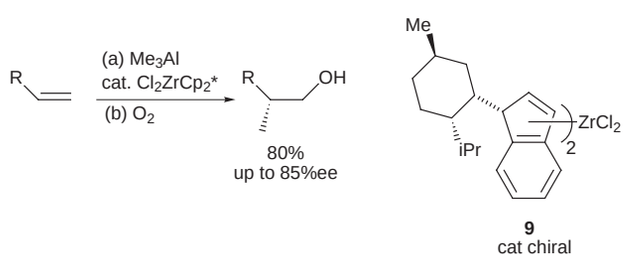
good enantioselectivities as described in Scheme 7[13] (the same reaction with 10% of **2** gives the carbometallated product in only 27% ee). However, Zr-catalyzed enantioselective alkylmetallation (with **1** or **8**) with higher alkylmetals was not promising and application of **8** to the kinetic resolution of 2-substituted dihydrofuran gave lower ee than reported for **1**.



Scheme 7

3 Asymmetric carboalumination reactions

The reaction of various monosubstituted alkenes containing hydrocarbon substituents as well as those containing heteroatom substituents with Me_3Al and a catalytic amount of a chiral dichlorobis(1-neomenthylindenyl)zirconium derivative **9**, provides after oxidation with O_2, 2-methylalkan-1-ols in high yields with up to 85% ee (typically 70–75%)[14] (Scheme 8).



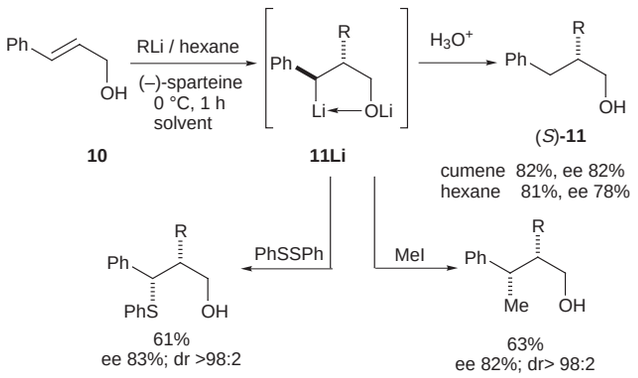
Scheme 8

The enantioselective methylalumination of monosubstituted alkenes with Me_3Al and a catalytic amount of **8** promises to be a reasonably general process with respect to the substituent in the starting alkenes.[14] Moreover, switching the solvent to CH_3CHCl_2 or CH_2Cl_2 in place of $(CH_2Cl)_2$ has allowed the addition with very good ee of higher alkyl metals such as Et_3Al, Pr_3Al, Oct_3Al in the presence of a catalytic amount of chiral zirconocene derivative **9**[15] (Scheme 9). More recently, asymmetric 2-aluminoethylalumination of monosubstituted alkenes and 2,5-dihydrofurans catalyzed by [(ebthi)Zr(binol)] or **8** (see Scheme 7) gave 30–99% enantiomeric excesses in moderate to good yields.[16]

Scheme 9

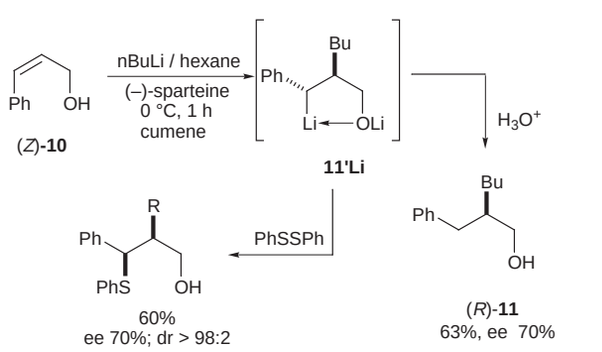
4 Asymmetric carbolithiation reactions

The addition of alkyllithiums to allylic alcohols, originally described by Felkin and Crandall and their co-workers[17] has received renewed interest due to the enantioselective carbometallation of cinnamyl derivatives. Indeed, asymmetric carbolithiation of (*E*)-cinnamyl alcohol **10** in hexane or cumene, in the presence of the readily available chiral diamine (−)-sparteine, leads to the carbometallated product (*S*)-**11** in 82% ee. Primary as well as secondary alkyllithiums lead to identical enantioselection.[18] The presence of a free alcohol is not a necessity as a similar ee is obtained with a *tert*-butyl ether or dialkylamines.[18] The chiral thermodynamically favored benzylic organolithium compound **11Li**, obtained after the carbometallation step, may react with a number of electrophiles in a highly diastereoselective manner with a formal inversion of configuration.[19,20] In all cases examined, the product is obtained in a diastereomeric ratio of >98 : 2 prior to purification and in 83% ee (see Scheme 10). Thus, two centers on an acyclic system have been created in a single pot operation.



Scheme 10

The stereochemistry of the olefin is crucial for the enantioselectivity of the carbolithiation. Whereas the asymmetric carbolithiation of (*E*)-cinnamyl alcohol **10** gives the (*S*)-alkylated product **11**, the reaction of the (*Z*)-isomer **10**, under the same experimental conditions, leads to **11′Li**, the enantiomer of **11Li** described in Scheme 10. After acidic hydrolysis, **11′Li** was converted to **11** with (*R*)-absolute configuration in 70% ee. Addition of diphenyl disulfide to **11′Li** leads to the formation of two vicinal chiral centers with a diastereoselectivity of 98 : 2 and an enantioselection of 70%[18] as described in Scheme 11. However a racemic product is obtained when the allylic alcohol is not substituted, as is the case with prop-2-en-1-ol. Thus, the two enantiomers of **11** can be synthesized from (−)-sparteine by switching from the (*E*)- to the (*Z*)-stereochemistry of the double bond of cinnamyl alcohol.[18] Since, cinnamyl derivatives were shown to be unreactive towards the addition of RLi in cumene at 0 °C without external diamine, the potential for catalysis was obvious. The results show that addition of these derivatives to nBuLi and catalytic amounts of (−)-sparteine (5%) also leads to good enantiomeric excess,[18] even on a large scale[21] (Scheme 12).

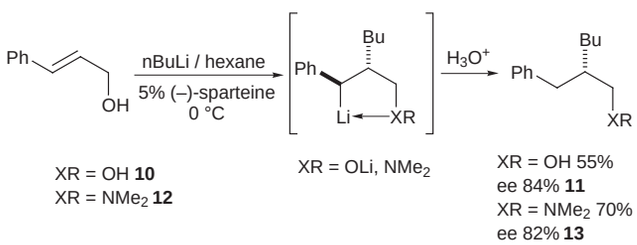


Scheme 11

Table 1 Enantioselective carbolithiation of propanal 2-(*E*)-cinnamyl 2-methyl acetal in the presence of (−)-sparteine

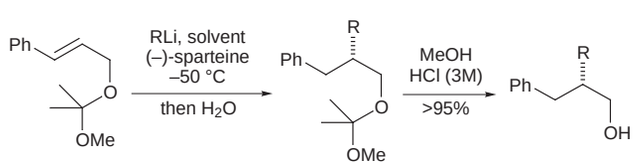
Entry[a]	RLi	(−)-sparteine (equiv.)[b]	Solvent	Yield (%)[c]	ee (%)[d]
1	nBuLi	1	cumene	72	95
2	nBuLi	1	hexane	77	94
3	HexLi	1	cumene	70	94
4	sBuLi[e]	1	cumene	80	90
5	HeptLi, LiBr	1	cumene	50	90
6	nBuLi	0.1	hexane	67	92
7	nBuLi	0.01	hexane	50	85
8	HexLi	0.1	hexane	65	92
9	sBuLi[e]	0.1	hexane	77	92

[a] The reactions were carried out by addition of the substrate to the RLi–sparteine mixture at −50 °C. [b] Based on the cinnamyl substrate. [c] Based on pure isolated product, after deprotection of the acetal (yield of the deprotection >95%). [d] ee was determined by ^{31}P NMR, see text. [e] As a mixture of 2 diastereomers from the use of sBuLi.



Scheme 12

Attempts to improve enantiomeric selectivity using different chiral ligands failed to provide enantioselectivities as high as (−)-sparteine. So, this problem was investigated following a different approach. Indeed, recent theoretical studies by Houk,[22] Schleyer[22] and Bailey and their co-workers[23] reveal that the initial step for the intermolecular as well as intramolecular carbometallation is an energetically favorable coordination of the lithium atom with the π-system[24] which serves to establish the geometry of the system prior to addition. Thus, in order to promote this initial π-chelation the authors decided to increase the association between the organolithium and the functional group of the substrate to enforce the proximity effect (called Complex Induced Proximity Effects,[25] CIPE). So, the dimethyl acetal of the (*E*)-cinnamyl alcohol was prepared and the enantioselective carbolithiation, in the presence of (−)-sparteine was studied, as described in Scheme 13.[26]



Scheme 13

Addition of the substrate to a solution of various alkyllithiums in hexane (or cumene) in the presence of 1 equiv. of (−)-sparteine leads, after hydrolysis, to the corresponding carbometallated products in good yield. After deprotection of the acetal moieties, the alcohols were obtained in very good enantiomeric excesses as determined according to Alexakis and Mangeney[27] (see Table 1). The use of the acetal allows the reaction to proceed at −50 °C instead of 0 °C for the carbolithiation of the corresponding alcohol (see Scheme 10). Primary [in the absence (entries 1, 2, 3) or in the presence (entry 5) of lithium salts] and secondary organolithiums (entry 4) undergo enantioselective carbolithiations in the presence of 1 equiv. of (−)-sparteine in hexane (or in cumene) *via* this simple method (Table 1). The results summarized in Table 1 show also that addition to this cinnamyl acetal in the presence of a catalytic amount of (−)-sparteine (10%) also leads to good enantiomeric excess (entries 6, 8, 9), even with 1% of chiral ligand (entry 7),

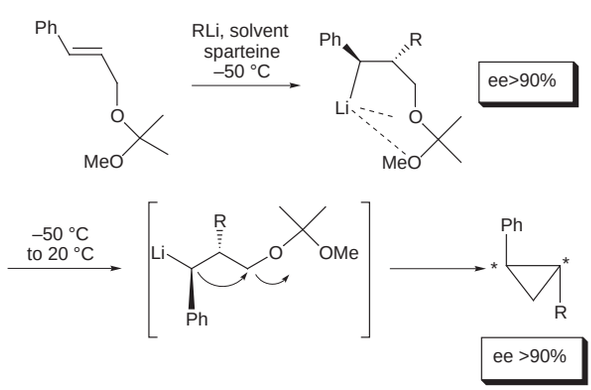
Table 2 Intramolecular reaction of chiral benzylic organolithium species

Entry[a]	RLi	(−)-sparteine (equiv.)[b]	Solvent	Yield (%)[c]
1	nBuLi	1	cumene	60
2	nBuLi	0.1	hexane	61
3	HexLi	0.1	hexane	59
4	sBuLi[d]	0.1	hexane	66

[a] After the carbometallation reaction, the mixture is rapidly warmed to room temperature. [b] Based on the cinnamyl substrate. [c] Based on pure isolated product and calculated from the cinnamyl substrate. [d] As a mixture of 2 diastereomers from the use of sBuLi.

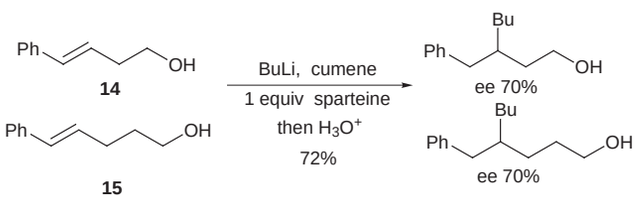
whatever the nature of the alkyllithium used (primary or secondary). Moreover, the product itself is not an enantioselective catalyst[28] since the hydrolysis of the reaction mixture after only 30% conversion leads to the same enantiomeric excess.

With the chiral benzylic organolithium in hand (before hydrolysis), the study of its reaction with an intramolecular electrophile, namely the acetal moiety, was investigated. Indeed, when the chelating moiety is a dimethyl(methoxy)methyl ether, the benzylic organolithium species formed is not stabilized but becomes thermally labile,[29] and when the reaction mixture is simply warmed to room temperature, a pure chiral *trans* disubstituted cyclopropane[30] is generated *via* an internal nucleophilic substitution, as illustrated in Scheme 14 and Table 2. The alkyl and phenyl groups in these cyclopropanes are *anti* to each other and may result from a W-shaped transition state.[31] Indeed, in this transformation, the initially formed stereogenic center C–R is invariant, when established during the carbolithiation reaction step, whereas the benzylic carbon is free to epimerize[18] and to promote the formation of the thermodynamically more stable *trans* cyclopropane.[32] Accordingly, the optical purities of the *trans* cyclopropanes thus obtained[33] are considered to be the same as those of the linear acetals described in Table 1.



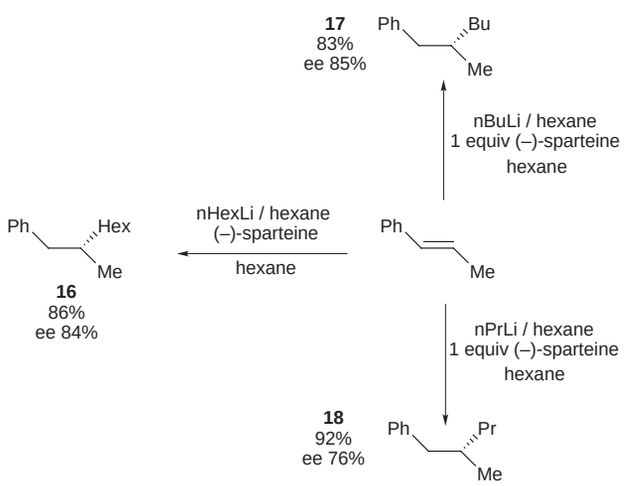
Scheme 14

These studies suggest that the intramolecular chelation of the benzylic organolithium by the heteroatoms is absolutely necessary to avoid polymerization and to increase the enantiomeric excess. However, the addition of an alkyllithium in the presence of (−)-sparteine to 4-phenylbut-3-en-1-ol **14** and to 5-phenylpent-4-en-1-ol **15** also leads to carbometallated products of unknown absolute configuration but in 70% ee without a trace of polymeric product (Scheme 15). These puzzling results led the authors to reconsider the basic idea on the necessary intramolecular chelation since in the carbolithiation reaction of **15**, an unfavorable seven-membered metallacycle should be formed before hydrolysis. Moreover, recent reports have shown that the carbolithiation reaction of a styrene derivative was also possible in good chemical yield without anionic polymerization.[34]



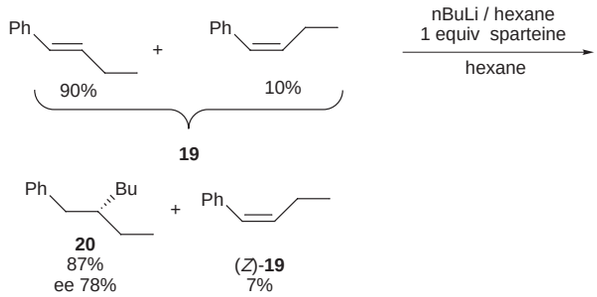
Scheme 15

So, the enantioselective carbolithiation of β-substituted, *non-functionalized* styrenes was investigated again. Addition of β-methylstyrene to a solution of various alkyllithiums (nHexLi, nBuLi, nPrLi) in hexane in the presence of 1 equiv. of (−)-sparteine for 4 hours at −15 °C leads, after hydrolysis, to the corresponding carbometallated product (**16** to **18**) in good yield and good enantioselectivity without polymerization as described in Scheme 16.[35] From this Scheme, we can deduce that intramolecular chelation is not necessary to prevent the polymerization (at least in hexane as solvent).



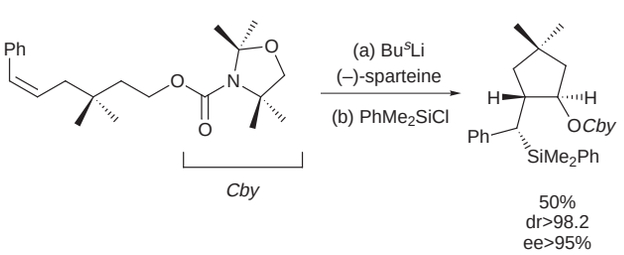
Scheme 16

A slightly lower enantiomeric excess, 70%, is obtained for **17** when the reaction is performed in the presence of a catalytic amount of (−)-sparteine (10%) after 12 hours at 0 °C. As previously described,[18] the stereochemistry of the olefin is crucial for the enantioselectivity of the carbolithiation. Indeed, whereas the carbometallation of the (*E*)-β-methylstyrene gives the (*S*)-alkylated product in 4 hours at −15 °C (see Scheme 16), the same reaction on the (*Z*)-β-methylstyrene leads to the opposite enantiomer (*R*) but with a lower enantiomeric excess (28%) in 50% yield after 8 hours at 0 °C. The fact that the carbometallation reaction on the (*Z*)-isomer (8 hours at 0 °C) differs markedly in rate from the carbometallation on the (*E*)-isomer (4 hours at −15 °C) led the authors to undertake a kinetic resolution of other β-alkylated styrene derivatives, such as β-ethylstyrene.[35] Indeed, the addition of nBuLi to **19** (*E*/*Z* = 90 : 10), leads to the carbometallated derivative at −10 °C. After hydrolysis, the corresponding carbometallated product **20** is obtained in 87% yield with an enantiomeric excess of 78%, and the (*Z*)-isomer (7%) is still present in the crude reaction mixture (see Scheme 17).

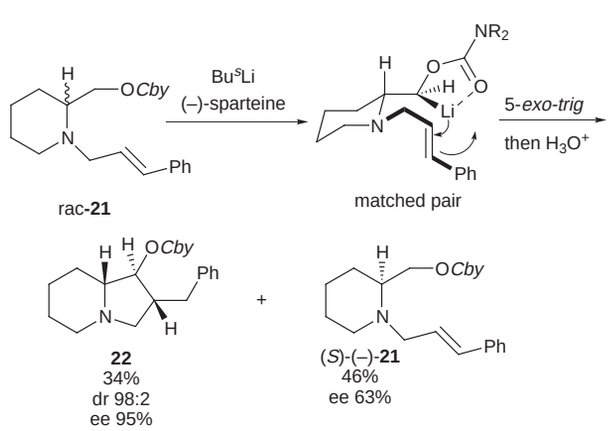


Scheme 17

The intramolecular version of this reaction was recently successfully applied to an enantioselective metallation in the α-position of a carbamate in the presence of (−)-sparteine followed by a diastereoselective carbocyclization onto a double (see Scheme 18)[36a,36b] or triple bond.[36c] This method was applied to the synthesis of heterocycles and particularly to the enantioselective synthesis of indolizidines. A kinetic resolution in the deprotonation step was performed on the racemic 2-(carbamoyloxy)methyl-*N*-cinnamylpiperidine **21** with (−)-sparteine, and the subsequent diastereoselective anionic 5-*exo-trig* cyclization gives the *trans*-fused five-membered heterocycle **22** with excellent diastereoselectivity[36d] (dr 98 : 2, ee 95%) (Scheme 19). The *cis*-fused heterocycles were not detected in any case. The anion emerging from the matched pair as well as the anion derived from the mismatched pair underwent *trans*-selective 5-*exo-trig* cyclization. Therefore, the two diastereomers resulted from incomplete differentiation within the deprotonation step and not within the cyclization step. Under these conditions, (*S*)-(−)-**21** was recovered in 46% yield and 63% ee (Scheme 19).

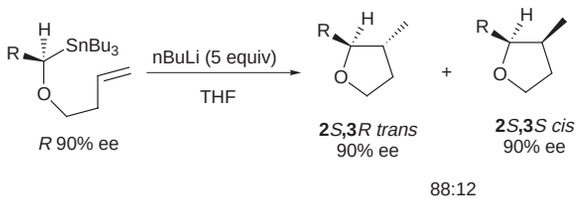


Scheme 18



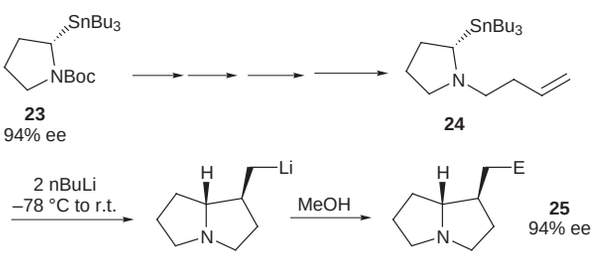
Scheme 19

It has also been shown that the steric course of intramolecular carbocyclization on the α-(homoallyloxy)alkyllithium proceeds with complete retention of configuration at the Li-bearing sp^3 carbon since the Sn to Li transmetallation occurs with complete retention of configuration[37] (Scheme 20). Of particular interest from a mechanistic point of view is that cyclization occurs with retention of stereochemistry but the structurally related Wittig rearrangement[38] occurs with inversion.



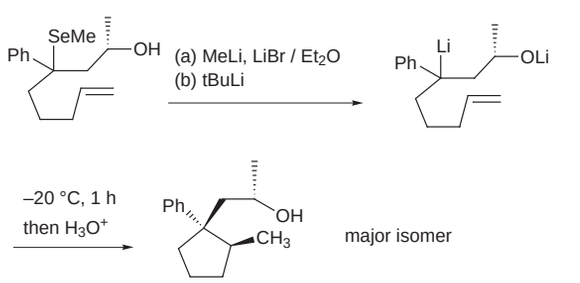
Scheme 20

A third asymmetric intramolecular anionic cyclization was obtained from a chiral α-aminoorganolithium, prepared by the Beak's methodology.[39] Thus, the stannane **23** (Scheme 21) was prepared in 94% ee and removal of the Boc group and trapping with but-3-enoyl chloride gave the amide, which was reduced to the amine **24**. Transmetallation of the amine **24** with nBuLi in hexane–Et_2O at low temperature and trapping the resulting organolithium with methanol gave the pyrrolizidine alkaloid (+)-pseudoheliotridane **25** as a single diastereomer[40] (Scheme 21). The anionic cyclization to give **25** proceeds with complete retention of configuration at the carbanion center.[40]



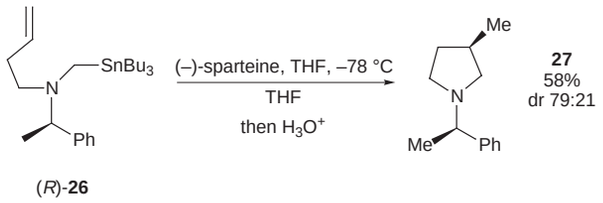
Scheme 21

A remote chiral center can also promote a diastereofacial differentiation of the olefin[41] in the carbocyclization step. Indeed metallation of the starting material with MeLi, LiBr[42] followed by the Se–Li exchange with tBuLi leads in 1 h at −20 °C in Et_2O to the cyclized product with a 82:8:7.5:2.5 diastereomeric ratio in 90% yield[41] (Scheme 22). The absolute configuration of the major isomer was ascertained by X-ray analysis,[41] and determined by chemical correlation.



Scheme 22

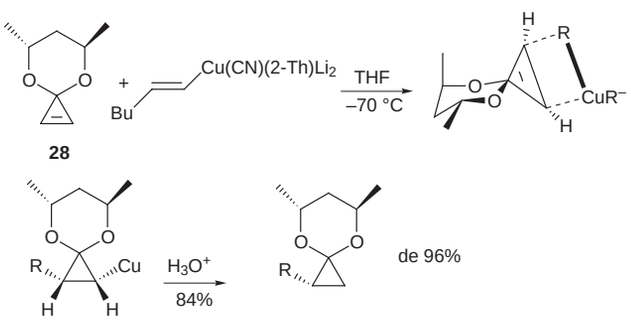
In the case of the cyclization of α-aminoorganolithiums **26** onto unactivated alkenes, the use of a α-methylbenzyl chiral auxiliary on the nitrogen atom gives rise to 3-substituted pyrrolidines **27** in the presence of (−)-sparteine with up to 58% de[43] (Scheme 23). In the absence of (−)-sparteine, a 48% diastereomeric ratio in 78% yield[43] is obtained.



Scheme 23

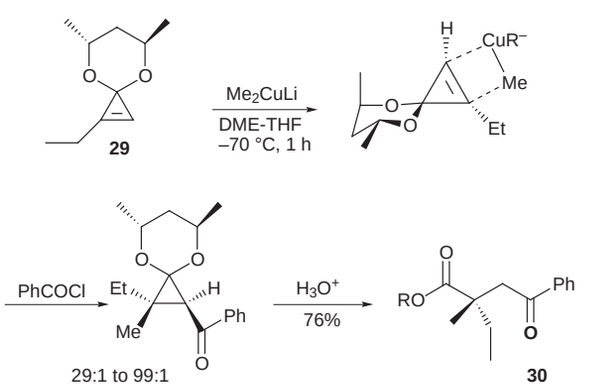
5 Asymmetric carbocupration reactions

A carbometallation of spirocyclic cyclopropenes has been described with a chiral ketal attached to the substrate. Thus, the addition of dialkyl cuprates to the chiral cyclopropene **28** at −70 °C showed very moderate stereoselectivity (*ca.* 70% de) to give the carbocupration product. However, the reaction of a bulkier "higher order" cuprate showed satisfactory selectivity (96% de)[44] and this selectivity profile suggested that the reaction takes place so that a bulkier group is oriented towards the equatorial carbon of the cyclopropene ring in the transition state shown below (Scheme 24).



Scheme 24

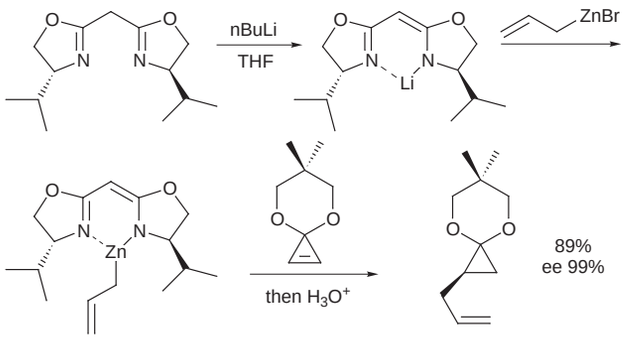
The stereoselectivity in the reaction of the 2-substituted cyclopropenes **29** is very high, favoring, after hydrolysis, the formation of the 2,2- *versus* 2,3-dialkyl adducts in a 29:1 to >99:1 ratio.[44] The reaction places the copper atom on the less sterically hindered position (Scheme 25). Substituted cyclopropene ketals react much more selectively than the unsubstituted one (R = H) and surprisingly the facial choice of the addition is from opposite sides in both cases. Removal of the chiral auxiliary under standard conditions gave the diester **30** in good overall yield.



Scheme 25

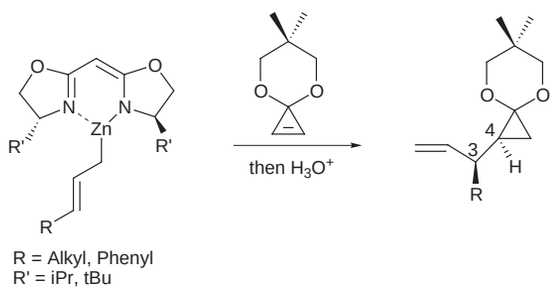
6 Asymmetric carbozincation reactions

Enantioselective allylmetallation of chiral cyclopropene ketal is possible[45] as well as the allylmetallation of achiral ketal but with the aid of chiral bisoxazoline (BOX) ligands (Scheme 26).[46] The chiral allylzinc reagents were much more reactive than the parent allylzinc bromide. The issue of double stereo-



Scheme 26

differentiation was also addressed with substituted allylzinc bromides (R = alkyl, phenyl) and leads to modest diastereoselectivity (Scheme 27). Indeed, the C(3)/C(4) diastereoselectivity was 73 : 27 with 60% ee, but the use of a bulkier BOX ligand (R′ = tBu) improved the latter to 97% ee whereas the C(3)/C(4) selectivity remained at 81 : 19.[46]

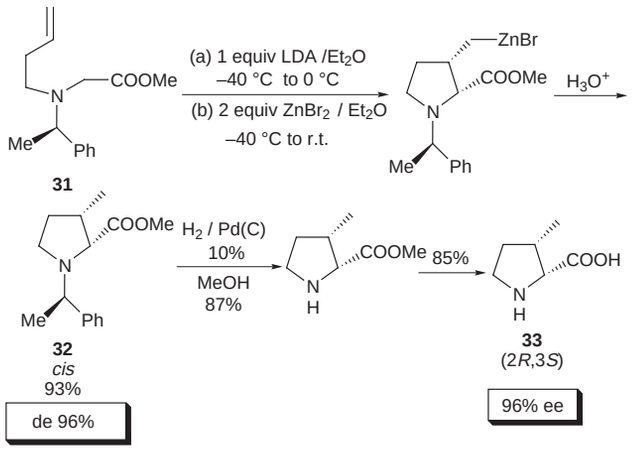


Scheme 27

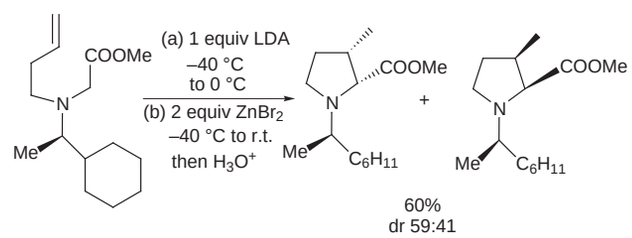
Several recent communications have revealed remarkable possibilities in enolate chemistry; namely zinc enolates cleanly add to unactivated olefins. The initial report dealt with an intramolecular addition of zincated ester.[47] Indeed, **31** prepared from the commercially available (*R*)-methylbenzylamine and subjected to the experimental procedure for the carbocyclization (lithium enolate formation by treatment of the ester with LDA—transmetallation into zinc bromide enolate—carbocyclization by warming to room temperature—hydrolysis after 2 hours at room temperature) gives the chiral β-methylproline **32** as a single *cis* diastereomer with a 98 : 2 diastereomeric ratio in 93% yield (Scheme 28). The (2*R*,3*S*) absolute configuration of **32** was determined[48] after hydrogenolysis to the secondary amine, saponification and comparison of the optical rotation of **33** with the known value for (2*R*,3*S*)-β-methylproline. Whereas the enantioselectivity of this reaction is 96% when 2 equiv. of zinc salt are used, a lower diastereoselection is obtained (50%) when the reaction is performed with only 1 equiv. of zinc salt (but still the *cis* diastereomer). Moreover, if the aromatic ring of the chiral inductor is replaced by a cyclohexyl ring, no diastereoselection is obtained as described in Scheme 29.

In light of the results quoted above, the authors postulate a π-chelation between the aromatic ring and the amino-zinc-enolate in the transition state. Knowing that some π-chelations between organozinc derivatives and unsaturated systems are described in the literature,[24,29] the excess of zinc salt, which is necessary for the high diastereoselection, is attributed as a relay between the aromatic ring and the amino-zinc-enolate as described in Scheme 30. From this simplistic point of view, the chiral inductor adopts a position in which the chiral methyl group has a lowered eclipsing strain with the two hydrogens in the α-position, for one particular face of the electrophilic carbon–carbon double bond relative to the other one.

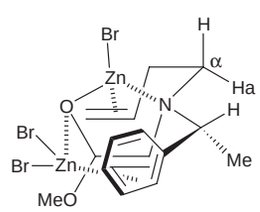
After these promising results, the study of the stereochemical effect of substituents on the carbon skeleton was undertaken.



Scheme 28

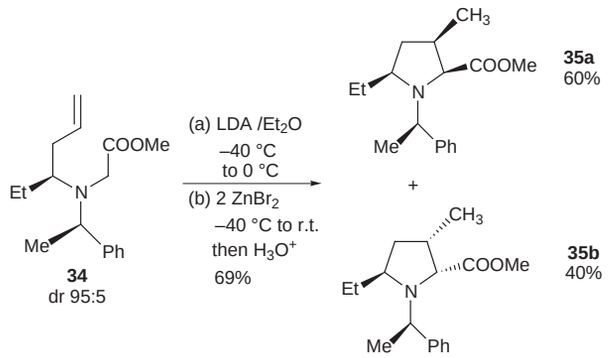


Scheme 29

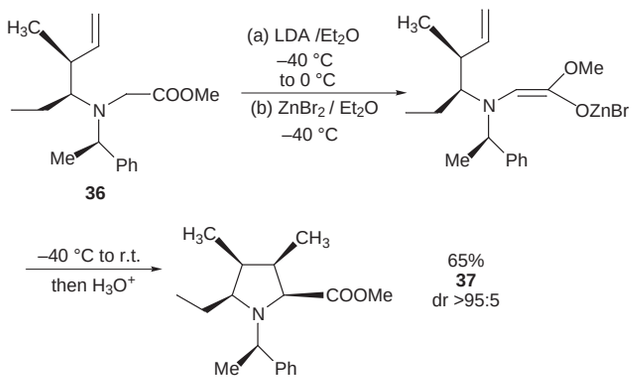


Scheme 30

For this reason, the corresponding chiral starting material **34** with a 90% diastereomeric excess[49] was prepared. So, the use of the (*R*)-1-benzylethylamine as chiral source gave, after hydrolysis, the product **34** in which the carbon bearing the ethyl substituent has the (*S*)-absolute configuration. However, according to the proposed model in Scheme 30, the carbocyclization reaction with the chiral (*R*)-α-methylbenzylamine will put the ethyl substituent on the pseudoaxial position in the chair-like transition state (Et instead of Ha), which is not a favorable transition state. Indeed, the substrate **34** was submitted to the *metallation–transmetallation–cyclization* reaction conditions (Scheme 31), and the two isomers were obtained in a 60 : 40 ratio, determined after a differential nuclear Overhauser effect.[50] The major isomer **35a** resulted from the transition state in which the ethyl substituent preferentially occupies the pseudoequatorial position whereas the minor isomer **35b** comes from the transition state laid down by the (*R*)-1-benzylethylamine chiral inductor (see Scheme 30). Hence, the ethyl substituent has a stronger effect on the stereochemical outcome than the chiral amino group (% of **35a** > % of **35b**). Finally, attention was turned to the synthesis of homochiral tetrasubstituted pyrrolidines starting from a chiral (*R*)-α-methylbenzylamine (Scheme 32). Amino ester **36** with two chiral centers[49] was subjected to the intramolecular carbometallation as described in Scheme 32.[50] The diastereoselection is very high (dr >95 : 5) and all the substituents of **37** are located on the same side, as described in Scheme 32. From this result, it can be deduced that the stereochemical outcome of the carbocyclization results from the substituents on the ring and not from the chiral benzyl methyl amino group.[50] Here again, the stereochemistry of the tetrasubstituted pyrrolidine is rationalized by the chair-like amino-



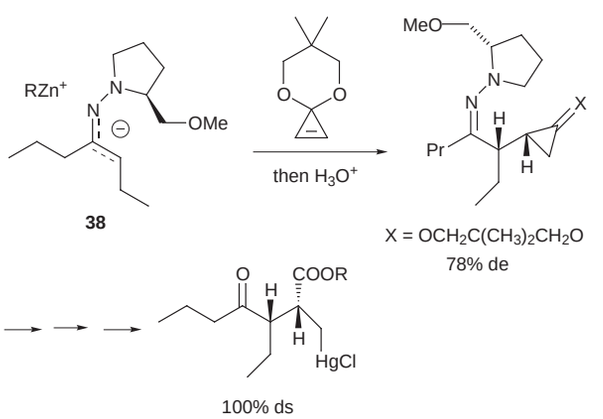
Scheme 31



Scheme 32

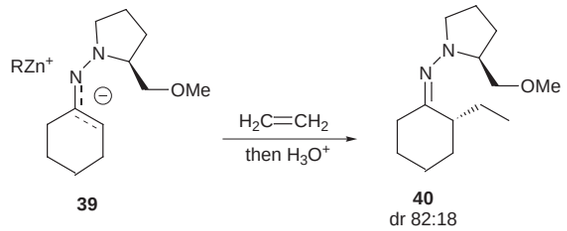
zinc-enolate transition state in which the ethyl group occupies a pseudoequatorial position and the methyl group, an axial position.[50]

Several other reports were published on the intermolecular addition of zincated chiral hydrazones to olefins. Thus optically active zincated heptan-4-one SAMP hydrazone **38** added with 100% 1,2-diastereoselectivity and 98% stereoselectivity to the cyclopropane ketal[51] (Scheme 33). The SAMP hydrazone **39**, which was made from cyclohexanone and optically active hydrazine, also reacted with excess ethylene under pressure to form the carbometallated product **40** in 42% yield and a diastereoselection of 82:18[52] (Scheme 34).

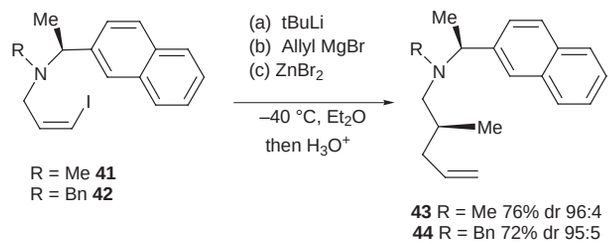


Scheme 33

One particular example of carbometallation of alkenes is the addition of alken-2-ylmetal to substituted vinylmetal to give the corresponding organo-*gem*-bismetallic derivatives.[53] Such allylmetallation reactions where the vinylic substrate is a metallated allylamine bearing a chiral substituent on the nitrogen is able to generate a π-chelation between the unsaturation and the vinyl metal as described in Scheme 35. In these cases, the carbometallated products **43** and **44** are obtained in respectively 92 and 90% de.[54] Of particular interest from a mechanistic

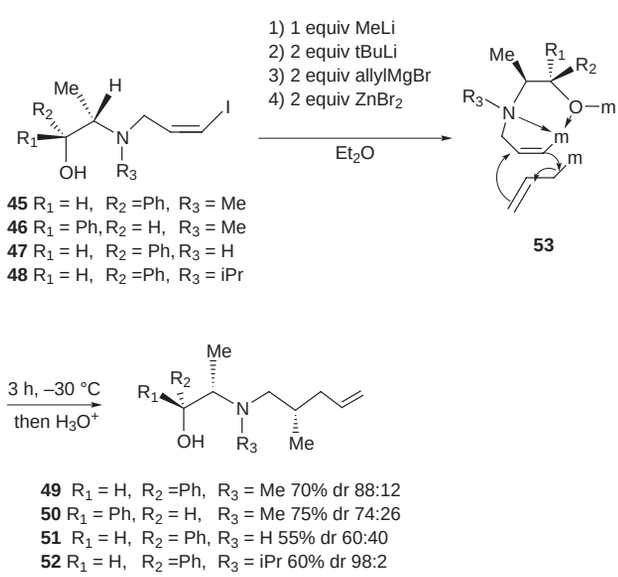


Scheme 34



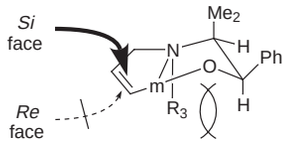
Scheme 35

point of view is that the π-stacking between the naphthyl moiety and the metal seems stronger than between the phenyl moiety and the metal (**44** is obtained with a high diastereoselectivity from **42**), and it is also stronger than the stacking of the two aromatic systems.[55] Although this reaction is highly diastereoselective, the use of chiral 1-(naphthyl)ethylamine as a chiral promoter is expensive and therefore precludes its synthesis on a large scale. For this reason, the authors have been interested to find an alternative chiral promoter and the choice was the use of commercial amino alcohols derived from ephedrine or pseudoephedrine as shown in Scheme 36. The different starting materials (**45** to **48**) were subjected to the classical experimental conditions to give the corresponding amines **49** to **52**. It was shown that the presence of a substituent on the nitrogen atom is responsible for the diastereoselectivity.[56] Indeed when applied to the secondary amine **51** (R_3 = H, dr 60:40), the diastereoselectivity is lower than for the tertiary amine **49** (R_3 = Me, dr 88:12) and **52** (R_3 = iPr, dr 98:2). From all the possible reacting conformers of the bicyclic chelated intermediates **53** (Scheme 36), the conformer **54** (Scheme 37) displays minimum interactions, and the allyl fragment reacts on the less shielded *Si* face of the vinylmetal[56] (*anti* to R_3 which is itself *anti* to Me_2).



Scheme 36

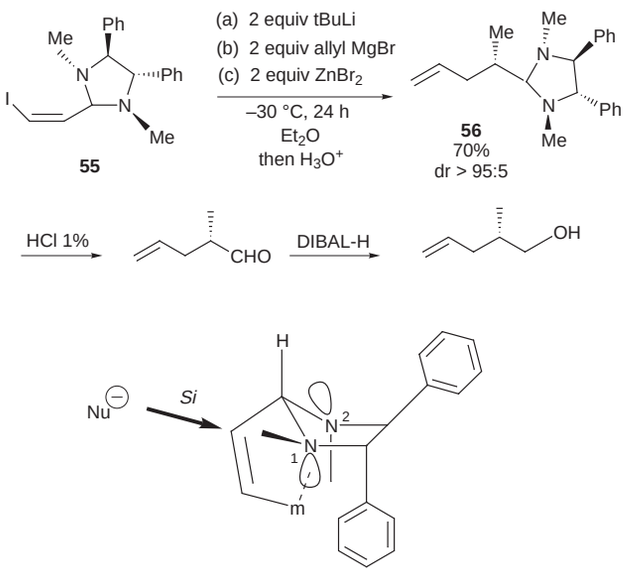
Finally, the use of chiral aminals of C_2 symmetry has been considered.[54] Thus aminal **55** was prepared by mixing the



54

Scheme 37

(*Z*)-β-iodoacrolein[57] with (2*S*,3*S*)-*N*,*N*′-dimethyldiphenylethanediamine[58] and subjected to the carbometallation conditions as described in Scheme 38. The corresponding aminal **56** is obtained as a unique diastereoisomer (dr >95 : 5) and is easily hydrolyzed to the parent aldehyde, which have been reduced to the known alcohol (ee > 98%). This high ratio is explained by considering the preference for an equatorial position of the vinyl group which allows coordination of the metal with the axial lone pair of N^1 (and not N^2)[59] promoting the shielding of the *Re* face by the methyl group on N^2.



Scheme 38

7 Conclusions

Asymmetric variants of the carbometallation of unactivated alkenes have been developed based on enantiofacial discrimination *via* chiral catalysis, diastereofacial discrimination arising from chiral substrates and chiral reagents. The scope, efficiency and stereoselectivity of the reactions suggest that they may be useful and practical tools in asymmetric synthesis.

8 Acknowledgements

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9 Notes and references

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