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Asymmetric C–C bond formation using organometallic chemistry

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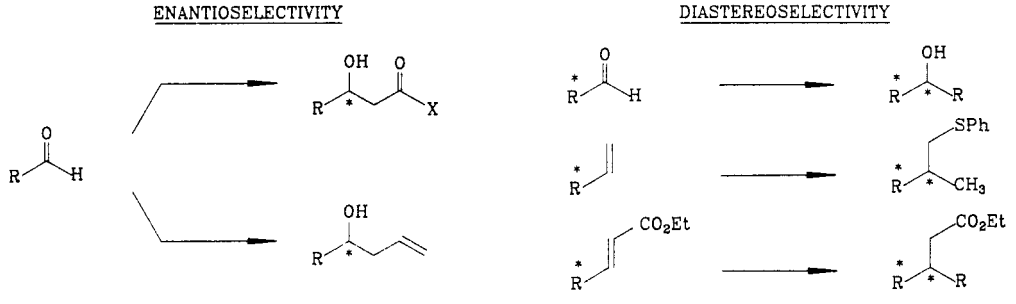
Abstract - Boron enolates having C_2-symmetric ligands (cf. 11) add to aldehydes high enantioselectively, as do chirally modified allylboron reagents 21. Diastereofacial selective Grignard and aldol additions to α-aminoaldehydes 28 are possible with chelation or non-chelation control, depending upon the type of protective group and nature of the organometallic reagent. Using the proper organometallic reagents, electrophilic or nucleophilic additions to chiral olefins occur diastereoselectively.

INTRODUCTION

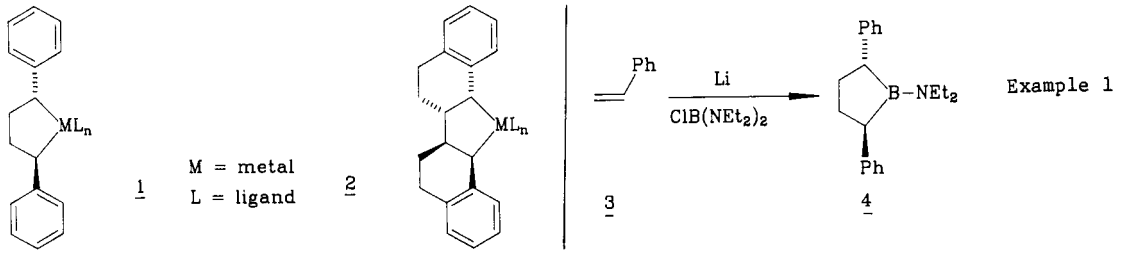
Organometallic reagents provide a unique means to perform a variety of stereoselective C-C bond forming reactions. The present progress report summarizes our recent efforts directed toward controlling a) enantioface differentiation in aldol-type addition reactions of aldehydes and b) diastereofacial selectivity in addition reactions of chiral aldehydes, non-activated olefins and activated olefins.



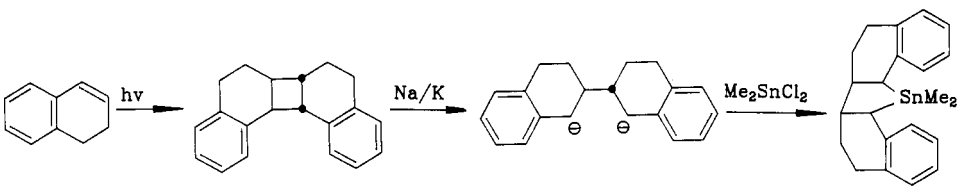
ENANTIOSELECTIVE ALDOL-TYPE ADDITIONS

For some time we have been interested in optically active C_2-symmetric organometallic compounds of the type 1 and 2 for two reasons. Firstly, displacement of a ligand L by a carbon nucleophile such as an enolate should provide reagents useful in stoichiometric enantioselective reactions (ref. 1,2). Secondly, 1 and 2 may function as chiral Lewis acid catalysts for enantioselective C-C bond formation (ref. 1,2).

Access to such metallacycles is easier than one might expect. Two examples are shown below (racemates shown in one arbitrary enantiomeric form):

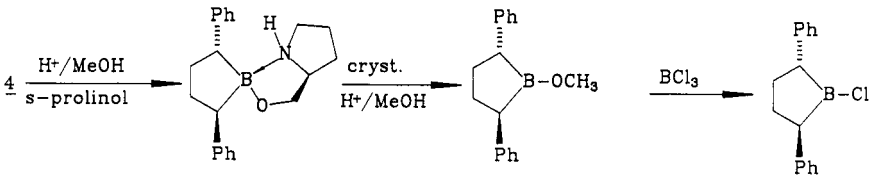


1 2 3 4



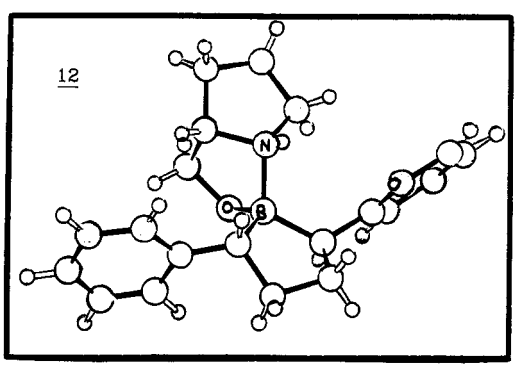
5 6 7 8 Example 2

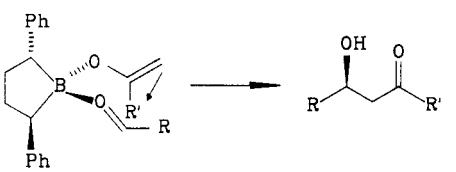
Boracycle 4 is formed as a cis/trans mixture from which the trans form crystallizes in 40-45% yield (ref. 1,2), whereas the tin compound 8 is generated as a single diastereomer (68-74% yield following recrystallization from pentane) (ref. 3). Compound 4 was transformed into the optically active boron chloride 11 using a method related to that employed by Masamune (ref. 4) in the antipode separation of a 2,5-dimethyl analog. The absolute configuration of compounds 10/11 originating from the material which crystallizes first from the diastereomeric mixture 9 is R,R as shown in the formulae (see X-ray analysis below).



9 10 11

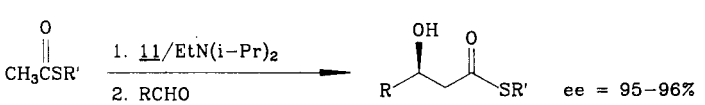
The borylating agent 11 undergoes a Si/B exchange reaction with O-silyl ketene ketals (e.g., $Me_2C{=}C(OMe)OSiMe_3$) as shown by ^{13}C- and ^{11}B-NMR spectroscopy. Such boron enolates add to aldehydes enantioselectively (ee ≈ 90%) (ref. 2). Alternatively, ketones can be O-borylated with 11 in the presence of Hünig bases. The aldol adducts 14 in such cases have lower ee-values, an exception being the enolate from cyclohexanone (ee = 92% in the addition to PhCHO). The aldol products have the absolute configuration indicated in 14. Since 11 has the (R,R)-configuration as shown by X-ray analysis (cf. prolinol adduct 12) (ref. 5), transition state 13 explains the observed enantioface differentiation of the aldol addition.





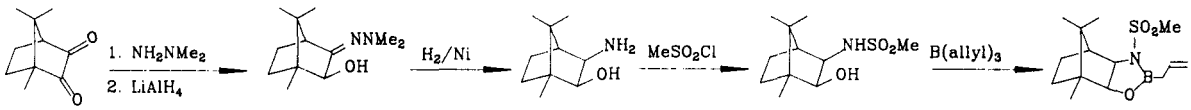
13 14

We have recently used 11 to perform highly enantioselective aldol additions of the thioester 15 (ref. 6). Since the ee-values are >95%, this system constitutes one of the most efficient enantioselective aldol additions currently available (ref. 7).



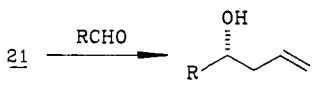
15 (R' = CEt_3) 16 (R = n-C_6H_{13} ; CH_2CHMe_2)

The enantioselective addition of chiral allylboron reagents was pioneered by Hoffmann (ref. 8) and improved by others (ref. 9). We have synthesized a chiral auxiliary 20 starting from campherquinone 17 (available in both optically active forms) which is the basis of the most efficient enantioselective allylboron reagent 21 currently known (ref. 3).



17 18 (79%) 19 (71%) 20 (74%) 21 (>95%)

The Grignard-type allyl additions of 21 to aldehydes proceed with ee-values of 88-96%. In some cases the isolated yield is low due to the volatility of the product.



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R	yield(%)	% ee
CH_3	47	96
Et	90	92
n-Pr	78	96
i-Pr	51	94
t-Bu	80	88
i-Bu	69	90
Ph	91	88

The X-ray structural analysis of a derivative having a tosyl group at nitrogen and a methoxy substituent at boron shows that the top side of the molecule is sterically shielded (cf. 23). This may well mean that aldehydes add to 21 from the bottom side leading to transition state 24.

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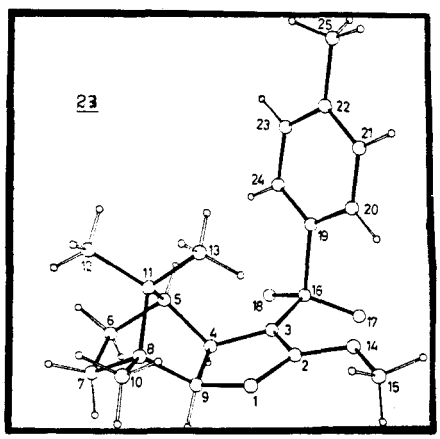

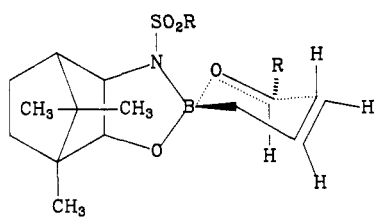

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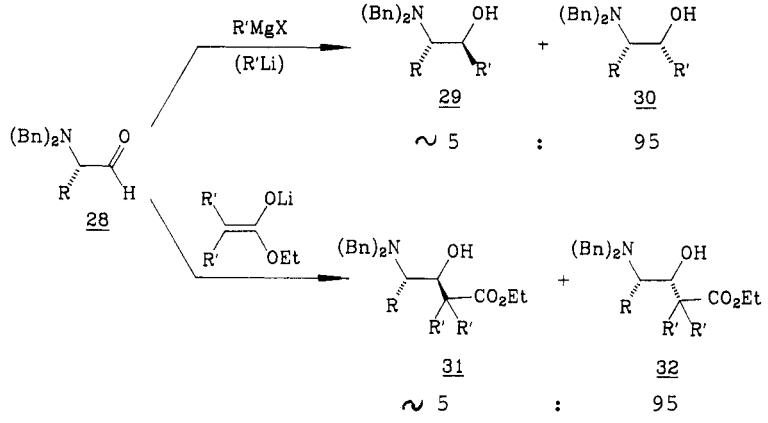
DIASTEREOFACIAL ADDITIONS TO α-AMINO ALDEHYDES

The chiral pool of natural L-α-amino acids provides a convenient source of optically active compounds which have been utilized by organic chemists for various purposes (ref. 10). One possibility is to convert them into the corresponding N-protected α-amino aldehydes, since these are potentially useful building blocks in such C-C bond forming reactions as Grignard and aldol additions. The problem is to find ways to control diastereofacial selectivity which allow the formation of either of the two possible diastereomers on an optional basis. Although several successful examples of stereoselective additions to certain protected α-amino aldehydes have been reported, the vast majority of reported examples involve the formation of mixtures of diastereomers (ref. 11). Generally, the BOC protective group has been used, but this causes another problem, namely the difficulty in handling the aldehydes due to the relative ease of enantiomerization. Although the 9-phenyl-9-fluorenyl protective group leads to fairly stable aldehydes, Grignard and aldol additions afford mixtures of diastereomers (ref. 12).

Our approach to the solution of both problems makes use of N,N-dibenzyl amino aldehydes 28, which are readily accessible from the amino acids 25 (ref. 13).

25 26 27 28

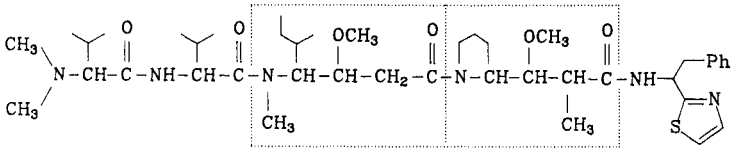
Since the chiral center in 28 bears a heteroatom with lone electron pairs, Grignard-type additions can occur either with chelation or non-chelation control (ref. 14) to form the diastereomers 29 or 30, respectively. Surprisingly, RMgX and RLi add with non-chelation control (29:30 ≈ 5:95). No signs of enantiomerization are observed. The same applies to aldol additions of Li-enolates (ref. 13). Removal of the N-benzyl groups is best performed using Pd-black (ref. 13).



28 → 29 : 30 ~ 5 : 95

28 → 31 : 32 ~ 5 : 95

It is interesting to note that dolastatin-10 (cf. 33), the most powerful antineoplastic compound known to date (G.R.Pettit),contains the structural unit of an O-methylated aldol. Although the absolute and relative configuration is currently not known, we have prepared one of the stereoisomers in the form of the ester 35 by performing a non-chelation controlled aldol addition (>97% stereoselective) to the aldehyde 34 derived from L-isoleucine (ref. 15).



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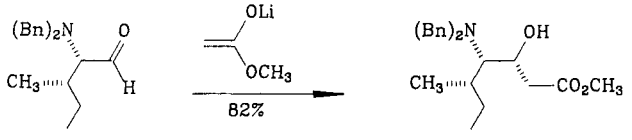
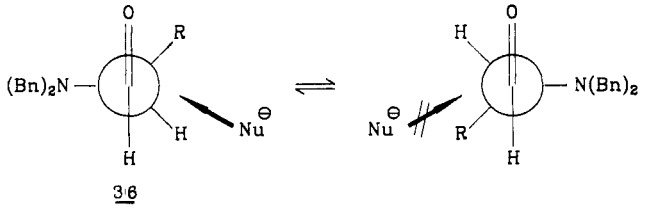


34 >96% pure 35

Non-chelation control can be explained by the Felkin-Anh model (cf. 36) or on the basis of ground state arguments. Concerning the latter, force field calculations show 37 to be the most stable conformer (ref. 16).



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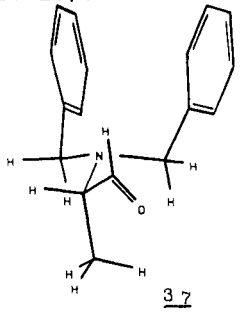
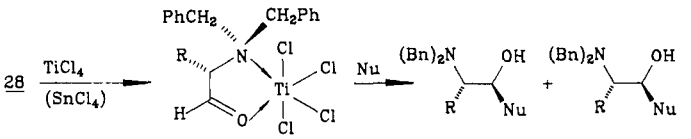
IS π^*_{C-N} — σ^*_{C-N} CONJUGATION LARGE ENOUGH ?



37

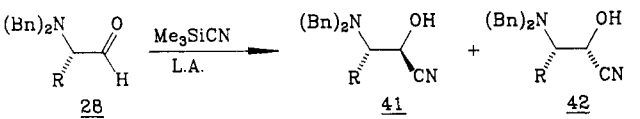
In contrast to α-alkoxy aldehydes (ref. 14), chelation control in reactions of α-amino aldehydes is more difficult. Reagents such as $SnCl_4/CH_2{=}CHCH_2SiMe_3$ or $TiCl_4/(CH_3)_2Zn$ allow for 80-90% chelation control. The reason for the lower degree of diastereoselectivity has to do with the fact that $SnCl_4$ or $TiCl_4$ do not form discrete 5-membered chelates 38 as the sole complexes. Rather, NMR-studies show that at least three species are formed (ref. 17). Open chain adducts are probably also involved, leading to a lower degree of chelation control. This led us to employ smaller protective groups in combination with cuprates, which in fact results in efficient chelation control (ref. 13).



38 39 40

R	Reagent	Yield (%)	39 : 40
CH_3	$TiCl_4/(CH_3)_2Zn$	82	94 : 6
CH_3	$SnCl_4/CH_2{=}CHCH_2SiMe_3$	85	84 : 16
CH_2Ph	$SnCl_4/CH_2{=}CHCH_2SiMe_3$	79	87 : 13
CH_2CHMe_2	$SnCl_4/CH_2{=}CHCH_2SiMe_3$	78	90 : 10
$CHMe_2$	$TiCl_4/(CH_3)_2Zn$	66	(65 : 35)
$CHMe_2$	$SnCl_4/CH_2{=}CHCH_2SiMe_3$	79	95 : 5

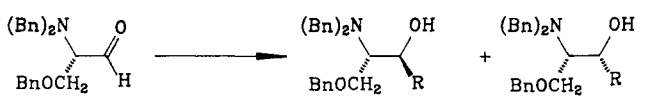
An interesting influence of the nature of the Lewis acid on stereoselectivity is observed in cyanohydrin formation using Me_3SiCN. This methodology opens the way to the rational synthesis of low molecular weight peptides such as amastatin, epiamastatin, bestatin and epibestatin (ref. 17).



28 41 42

$ZnBr_2$	5	:	95
$MgBr_2$	80	:	20

Amino acids bearing additional functional groups such as serine can also be converted into the corresponding protected amino aldehydes (ref. 18). Here again no special measures must be taken to ensure non-chelation control. The products 45 have the absolute and relative configuration which occurs in natural sphingoid bases. Reversal of diastereoselectivity is also possible using Lewis acid reagents.

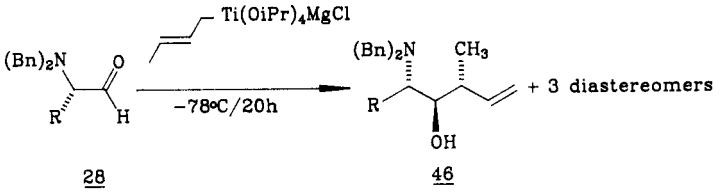


43 44 45

CH_3MgI	5	:	95
$TiCl_4/(CH_3)_2Zn$	>95	:	<5
EtMgBr	<5	:	>95
PhMgBr	<5	:	>95
$C_{15}H_{31}MgBr$	<5	:	>95

If the carbon nucleophile is prochiral, diastereofacial selectivity and simple diastereoselectivity are relevant, leading to a maximum of four diastereomers. We have begun to develop methods which allow the selective

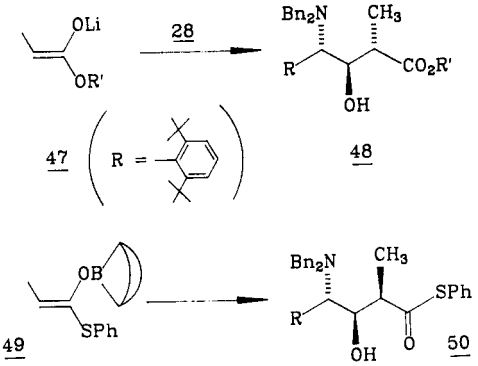
formation of a particular diastereomer (ref. 19). For example, crotyltitanium-ate complexes (ref. 20) react with non-chelation control, simple diastereoselectivity being the expected anti-type (cf. 46).



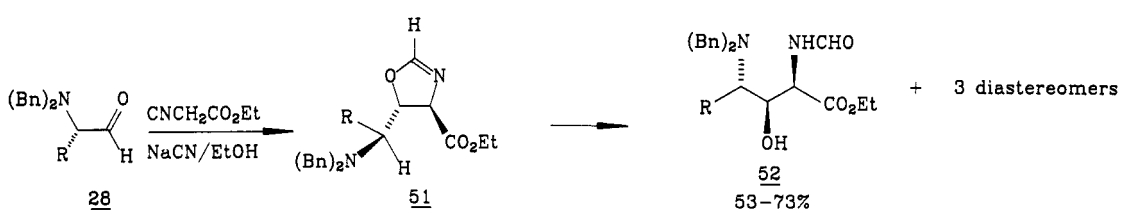
28 46

R = CH_3	90	:	10
R = $PhCH_2$	94	:	6
R = Me_2CHCH_2	96	:	4
R = Me_2CH	99	:	1

Similarly, aldol additions of known anti-selective enolates 47 or of syn-selective enolates 49 afford single diastereomers (non-chelation/anti or non-chelation/syn, respectively) in high yield (ref. 19).



Applying Schöllkopf's oxazoline chemistry (ref. 21) to the amino aldehydes, we obtained stereoselectively the interesting new class of compounds 52, which are regioselectively protected α,γ-diamino-β-hydroxy acids. These may turn out to be useful as isosteric compounds in synthetic peptides. This aldol-type of addition is an interesting example in which diastereofacial selectivity (non-chelation control) is kinetically controlled and simple diastereoselectivity is thermodynamically controlled (trans in 51), both in one reaction.



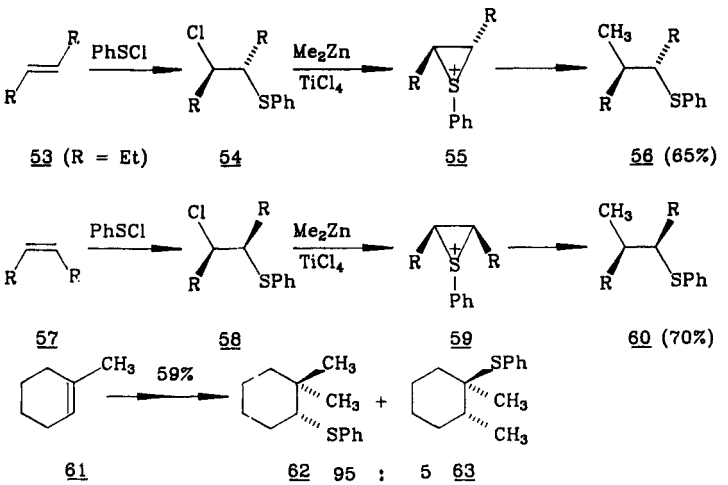
28 51 52

53–73%

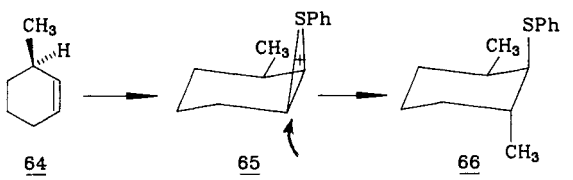
R = CH_3	84	:	16
R = $PhCH_2$	84	:	16
R = Me_2CH	87	:	13

DIASTEREOFACIAL ELECTROPHILIC AND NUCLEOPHILIC ADDITIONS TO OLEFINS

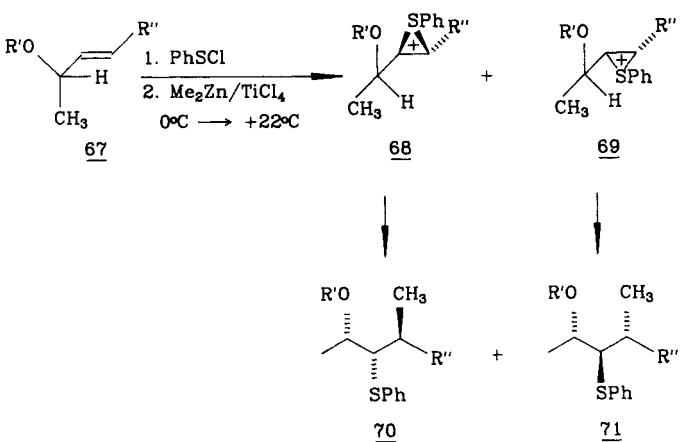
We have recently described the trans-stereospecific electrophilic carbosulfenylation of olefins (ref. 22). Intermediate episulfonium ions (e.g. 55) are attacked by the organometallic reagent in an S_N2-process. Unsymmetrical olefins react regioselectively (e.g. 61 → 62).



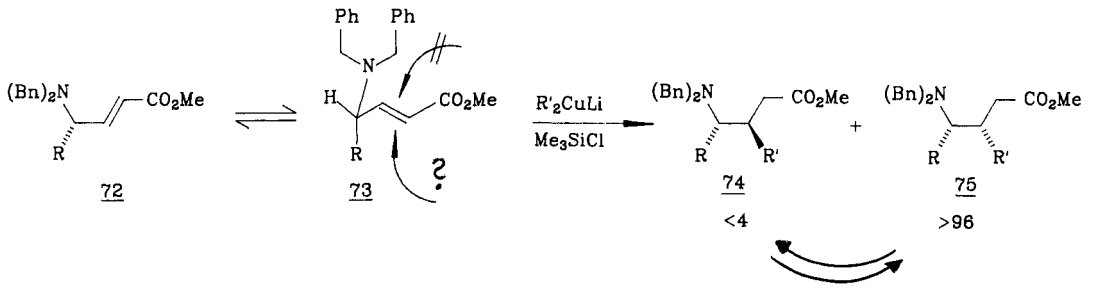
If the olefin bears a neighboring chiral center, diastereofacial selectivity is relevant, e.g., 64 deliveres essentially only 66.



Acyclic allylic derivatives 67 also react stereoselectively, depending upon the nature of the protected group. Although the formation of 70 can be explained by the models suggested by Hehre (ref. 23) or Houk (ref. 24), a different phenomenon appears to be involved. Of the two possible episulfonium intermediates 68 and 69, the latter is selectively destroyed via nucleophilic attack of the organometallic reagent at sulfur with formation of olefin and CH_3SPh (ref. 25). One of the applications of this methodology is the control of 1,3-stereorelation following the removal of sulfur by Raney-nickel.



$R'' = CH_3$			
$R' = CH_3$	99	:	1
$= CH_2Ph$	85	:	15
$= SiMe_3$	84	:	16
$= Si(t\text{-}Bu)Me_2$	47	:	53
$R'' = C_2H_5$			
$R' = CH_3$	99	:	1



Concerning nucleophilic additions to chiral olefins, compounds 72 prepared via Horner-Wittig olefination of 28 react stereoselectively with a variety of nucleophiles, e.g., cuprates (ref. 26). Although the configuration has not been determined with certainty, a direction of attack (cf. 73) analogous to that in the reactions of aldehydes 28 would mean that 75 is the major isomer. Compounds of the type 72 are expected to be useful optically active building blocks in other reactions as well. An example is the conversion to the corresponding amine oxides using m-chloro-perbenzoic acid; these undergo rapid 2,3-sigmatropic rearrangements with a high degree of chirality transfer (ref. 27).

Acknowledgements

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