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FIRST DIASTEREOSELECTIVE ASYMMETRIC CARBOMETALLATION OF CHIRAL VINYL METALS.

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Abstract : Addition of substituted allylzinc reagents to chiral *(Z)* metallated allyl amines (or aminal) bearing a chiral aromatic moiety is face selective, and delivers β–methylated amines with good diastereomeric excess. © 1998 Published by Elsevier Science Ltd. All rights reserved.

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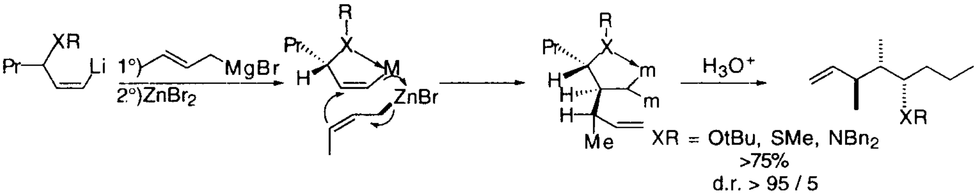
We have recently shown that the carbometallation of vinylmetals, by various allyl and propargyl zinc reagents, was stereoselective when the former reagents display a heteroatom (O,N,S) [1] in allylic or homoallylic position [2], whose chelation to the vinylmetal induces a diastereodifferenciation of the two faces of the C=C double bond.



Scheme 1

This route for the synthesis of geminated organobismetallic compounds is an easy and straightforward method for the preparation of several stereocenters in a one-pot operation [3] (see Scheme 1). If an efficient method was available to render such a process asymmetric, it would acquire a tremendous utility as a method for the creation of asymmetric vicinal carbon atoms [4]. As we have recently reported that a π-chelation between an olefinic site and a zinc atom governs the allylzincation reactions [5] and the 1,3-elimination reactions from organogembismetallic reagents [6], we have been able to prepare chiral pyrrolidines by using this π-chelation concept [7]. We now report on such allylmetallation reactions, where the vinylic substrate is a metallated allylamine bearing a chiral substituent on nitrogen, which is able to generate a π-chelation between the unsaturation and the vinylmetal. The starting material **2**, easily prepared from (*S*)-N-methyl methylbenzylamine **1** and (*Z*)-1-iodo-3-bromo-prop-1-ene [8], was submitted to our experimental conditions [1] as described in Scheme 2 to give the corresponding amine **3** in a 80/20 diastereomeric ratio.

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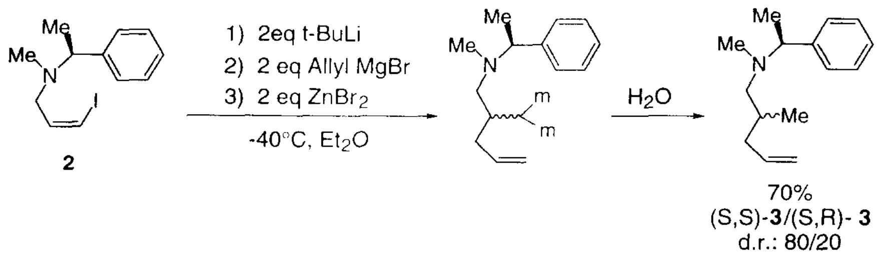
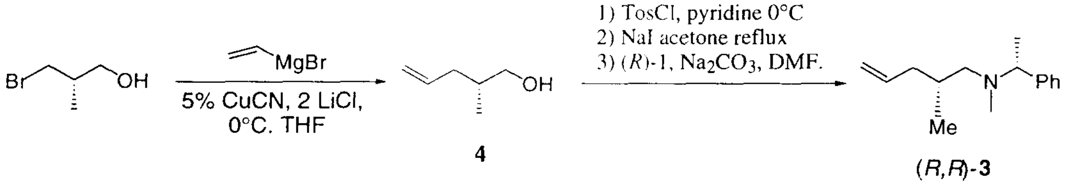


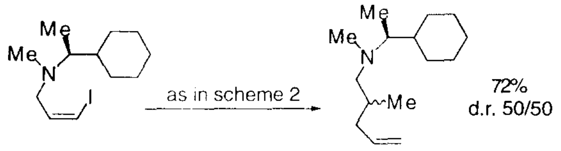
Scheme 2

The absolute configuration of the major diastereomer was established (following Scheme 3) from commercially available (*S*)-3-bromo-2-methyl- propan-1-ol, *via* vinylation and treatment of the corresponding iodide with (*R*)-**1**.The resulting (*R*,*R*)-**3** shows an NMR spectrum identical to that of the major diastereomer obtained in scheme 2, which is, hence, of (*S*,*S*) configuration.



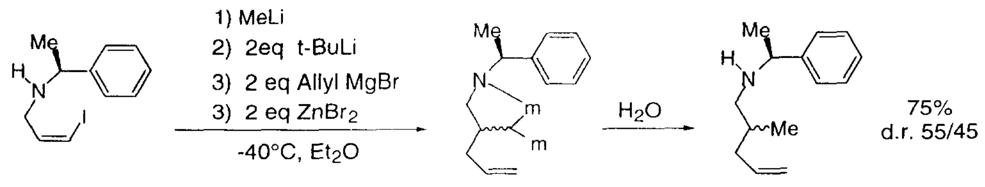
Scheme 3

The starting hypothesis of a π-stacking between the phenyl and the vinylzinc moieties seems to operate. Indeed, the replacement of the chiral aromatic moiety in **2**, by its saturated analog (*S*)-1-methylamino-1-cyclohexyl ethane, followed by the carbometallation reaction delivers the corresponding amine with no diastereoselection (Scheme 4).



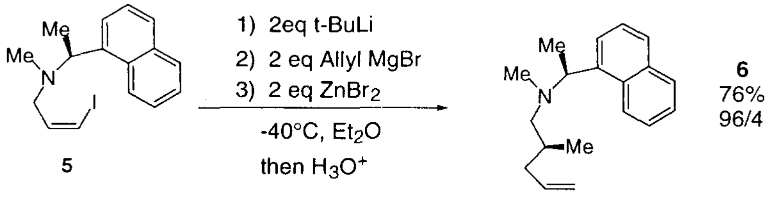
Scheme 4

Moreover if the starting amine is secondary, the corresponding amide is prone to allylmetallation, but the absence of the N-methyl group accounts for a very low diastereoselection.



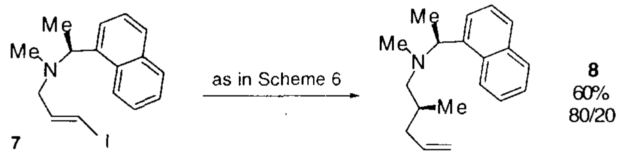
Scheme 5 .

In order to improve the π-stacking, we turned to the corresponding chiral naphtylamines. Amine **5** was prepared as was **2**, starting from (*S*)-1-(1-naphtyl)1-N-methyl ethylamine, and was submitted to the reaction sequence depicted in scheme 6 The corresponding amine **6** is now obtained in 76% yield as a 96/4 mixture of diastereomers, the major one being (*S,S*) as proved by a correlation similar to the preceding one in scheme 3.



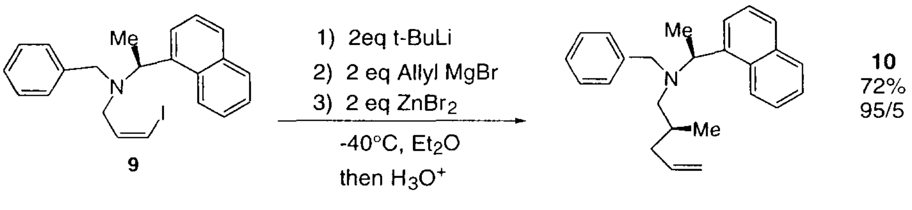
Scheme 6

When the chelation of the vinylmetal by both an aromatic substituent and the nitrogen lone pair cannot be attained, as is the case of **7** (*E* derivative), the diastereoselection drops (80/20) but still remains in favour of the *same* diastereomer (scheme7).



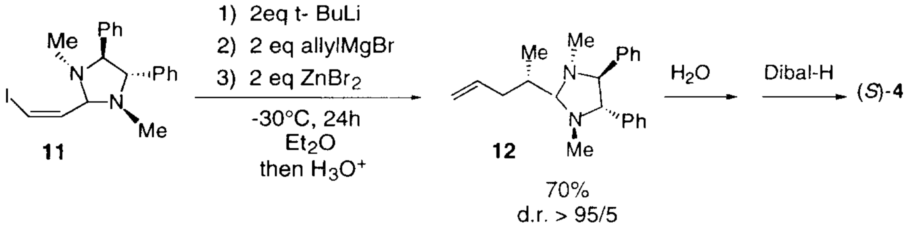
Scheme 7

This result points out the large efficiency of the π– stacking (in this case, due to the stereochemistry of the double bond, the π– stacking between the napthyl group and the vinylmetal is less operative). Now, if the N-methyl group, in **5** is replaced by a N-benzyl group (for a further elaboration into a primary amine), as in **9**, the carbometallation reaction delivers the corresponding amine **10** in 72% yield with a similar d.r. of 95/5. Thus, the π -stacking between the naphtyl moiety and the metal seems stronger than between the phenyl moiety and the metal, and also stronger than the stacking of the two aromatic systems [9] (scheme 8)



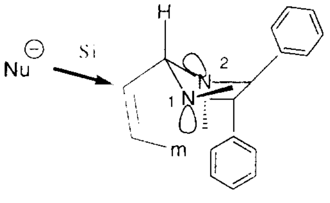
Scheme 8

Finally, the use of chiral aminals of C_2 symmetry has been considered. Thus aminal **11** was prepared by mixing the *Z*-β-iodo acrolein [8] with (*S,S*)-N,N'dimethyldiphenylethanediamine [10] and submitted to our carbometallation conditions as described in Scheme 9.



Scheme 9

The corresponding aminal **12** is obtained with excellent diastereoselection (d.r. > 95/5) and is easily hydrolyzed to the parent aldehyde, which has been reduced (Dibal-H) to the known alcohol (*S*)-**4** ($[\alpha]^D$ = -2, c = 0.2 $CHCl_3$) [11]. This high ratio is explained by considering the preference for an equatorial position of the allyl group which allows coordination of the metal with the axial lone pair of N^1 (and not N^2) [12], thus promoting the shielding of the Re face by the methyl group on N^2 (Scheme 10).



Scheme 10

In this case, if the chelation of the metal with nitrogen is made impossible (starting with *E* **11**), the diastereoselection drops to 70/30, but is still present.

In summary, metallated allylic amines bearing a chiral aromatic moiety on nitrogen are good candidates for a stereoselective allyl zincation.

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