

FIRST DIASTEREOSELECTIVE ASYMMETRIC CARBOMETALLATION OF CHIRAL VINYL METALS.

Denis Brasseur^a, Hadi Rezaei^a, Alain Fuxa^a, Alexandre Alexakis^a, Pierre Mangeney^a, Ilan Marek^{*b}, Jean F. Normant^{*a}

^aLaboratoire de Chimie des Organoéléments, associé au CNRS, Tour 44-45
Université P. et M. Curie, 4 Place Jussieu, 75252 Paris Cedex 05, France.

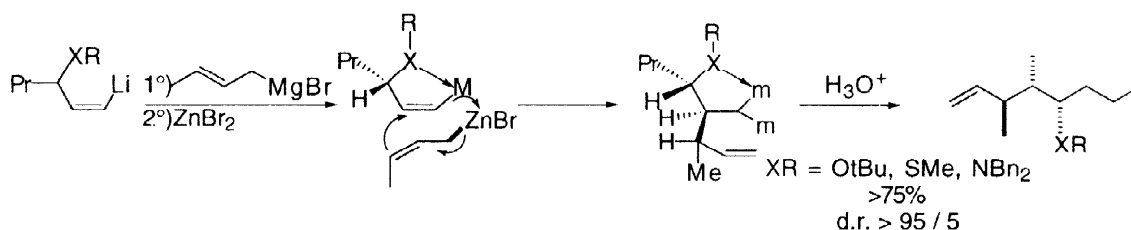
^bDepartment of Chemistry, Technion Institute of Technology, Technion City, 32000 Haifa, Israël.

Received 16 March 1998; accepted 4 May 1998

Abstract : Addition of substituted allylzinc reagents to chiral (*Z*) metallated allyl amines (or amina) 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.

Keywords : amines; asymmetric induction; chelation; zinc reagents.

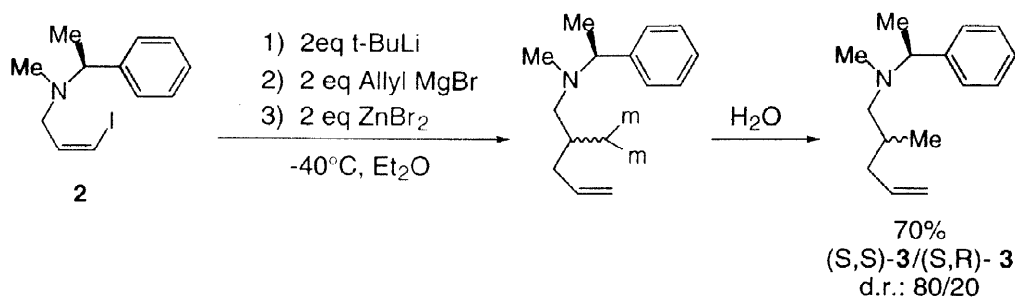
We have recently shown that the carbometallation of vinylmetals, by various allyl and propargyl zinc reagents, was stereoselective when the former reagents display a heteroatom (O,N,S) [1] in allylic or homoallylic position [2], whose chelation to the vinylmetal induces a diastereodifferentiation of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



Scheme 1

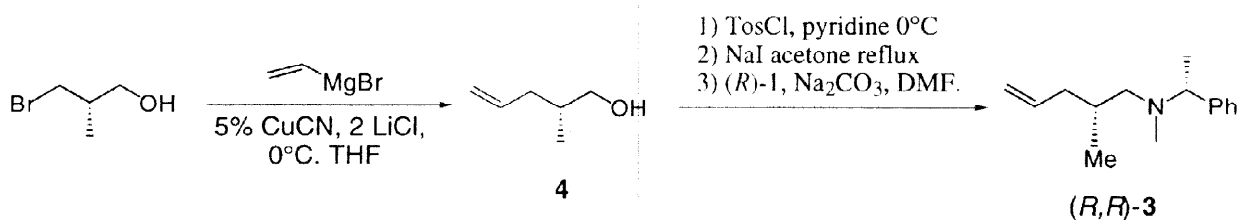
This route for the synthesis of geminated organobismetallic compounds is an easy and straightforward method for the preparation of several stereocenters in a one-pot operation [3] (see Scheme 1). If an efficient method was available to render such a process asymmetric, it would acquire a tremendous utility 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.

*Fax : 330144277567 ; e-mail : normant@c.c.r.jussieu.fr



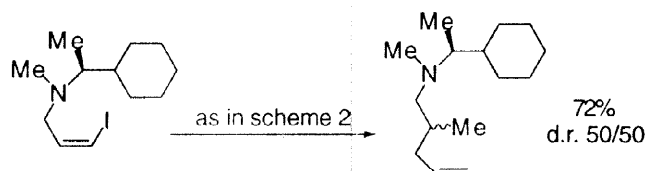
Scheme 2

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.



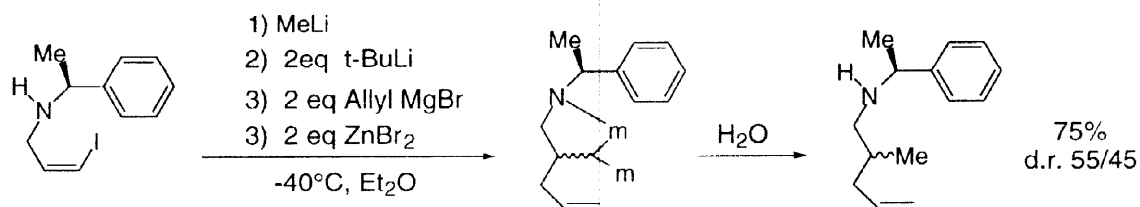
Scheme 3

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).



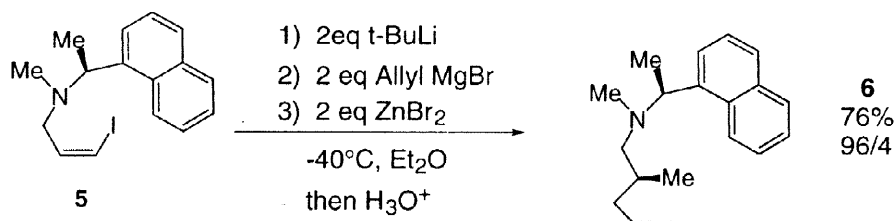
Scheme 4

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



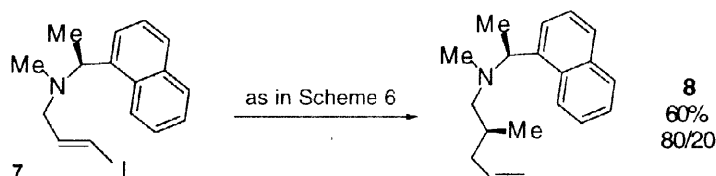
Scheme 5

In order to improve the π -stacking, we turned to the corresponding chiral naphthylamines. Amine **5** was prepared as was **2**, starting from (*S*)-1-(1-naphthyl)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.



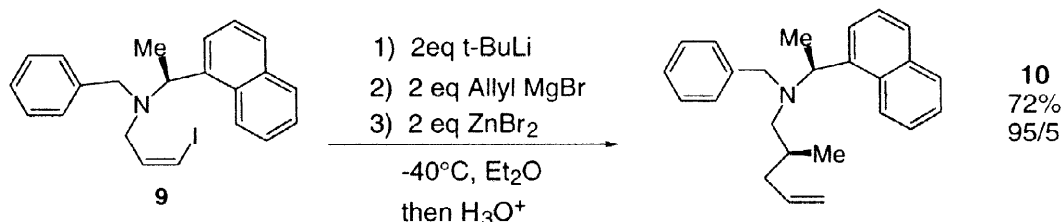
Scheme 6

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 (scheme 7).



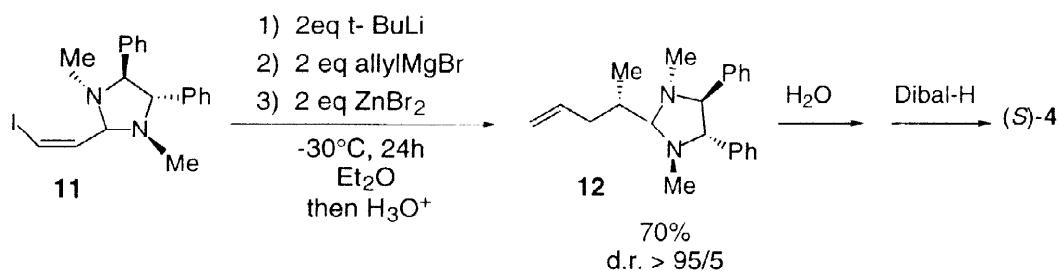
Scheme 7

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 naphthyl 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 naphthyl 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)



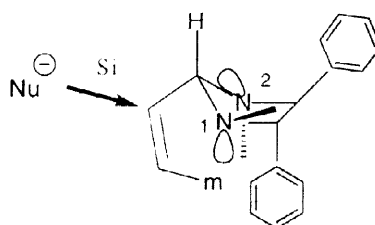
Scheme 8

Finally, the use of chiral aminals of C₂ 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** ($[\alpha]_D^{25} = -2$, $c = 0.2$ CHCl₃) [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 N¹ (and not N²) [12], thus promoting the shielding of the *Re* face by the methyl group on N² (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.

References and Notes.

- [1] Brasseur D, Marek I, Normant J.F. *Tetrahedron* **1996**; 52: 7235-7250.
- [2] Bahr A, Marek I, Normant J.F. *Tetrahedron Lett.* **1996**; 37: 5873-5876.
- [3] Marek I, Normant J.F. *Chem. Rev.* **1996**; 96: 3241-3267.
- [4] Marek I, Normant J.F. *Carbometallation Reactions. In Metal Catalyzed Cross-Coupling Reactions* Editors Diederich F, Stang P.J. Weinheim Wiley-VCH. **1998**: 271-337.
- [5] Marek I, Beruben D, Normant J.F. *Tetrahedron Lett.* **1995**; 36: 1263-1266.
- [6] Beruben D, Marek I, Normant J.F, Platzer N *J. Org. Chem.* **1995**; 60: 2488-2501.
- [7] Lorthiois E, Marek I, Normant J.F. *Tetrahedron Lett.* **1997**; 38: 89-92.
- [8] Marek, I.; Meyer, C.; Normant, J.F. *Org. Synth.* **1995**; 74 : 194-204.
- [9] Davies S.G., Ichihara O, Walters I.A.S. *Synlett* **1993**; 461-462.
- [10] For a general review on aminals in asymmetric synthesis, see Alexakis A, Mangeney P in: *Advanced Asymmetric Synthesis* Editor Stephenson GR. Chapman & Hall, London, **1996**: 93-110.
- [11] Gramatica P, Manitto P, Monti D, Speranza G. *Tetrahedron* **1988**; 44 : 1299-1304.
- [12] Alexakis A, Lensen N, Tranchier JP, Mangeney P. *J.Org.Chem.* **1992**; 57: 4563-4565.