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# DIASTEREOSELECTIVE ALLYLATION OF CHIRAL IMINES. NOVEL APPLICATION OF ALLYLCOPPER REAGENTS TO THE ENANTIOSELECTIVE SYNTHESIS OF HOMOALLYL AMINES

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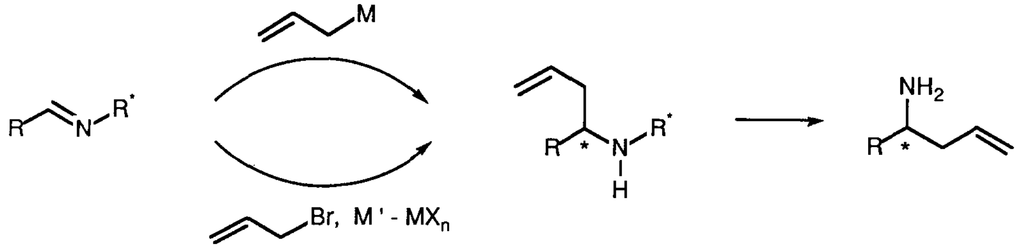
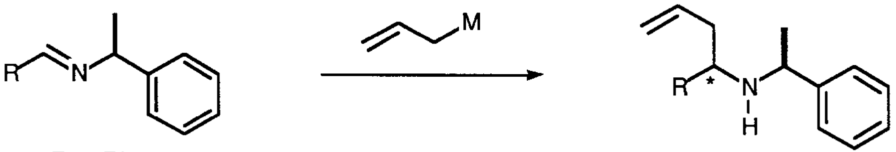
*Abstract:*.The addition of allylcopper reagents to imines derived from S-valine occurs with excellent diastereoselectivity (e.e. 98 %).

Homoallyl amines are useful precursors of a variety of compounds, especially β-amino acids and β-lactam antibiotics,[1] by functionalization of the double bond. An attractive strategy for their synthesis rests on the organometallic allylation of chiral imines carrying the stereogenic centre on the nitrogen substituent, which can be successively removed.[2] As a useful alternative, the "Barbier-type" electroreductive allylation has been developed by Torii, where the allyl metal species is prepared in the presence of the imine from allyl bromide and a metal-redox couple.[3,4] The use of aluminum or zinc (sacrificial anodes), lead(II) halides in catalytic amount, and allyl bromide has been at first described for the "electrochemical" (<1 F/mol is needed) allylation of N-benzyl imines;[3] successively, the metal-redox couple Al-$TiCl_4$ has been used for the allylation of imines derived from S-valine with high diastereoselectivity.[4]



We report here the results we have obtained on the analogous allylation reaction of chiral imines, making use of organometallic reagents. The results obtained on the imines **1 a, b** derived from (S)-phenylethylamine by using allylmagnesium, allylcopper[5] and allylcopper-boron trifluoride reagents are reported in Table 1. A satisfactory diastereoselectivity could not be generally obtained, adversely to the analogous addition of methylcopper- and dimethylcuprate-boron trifluoride reagents.[6] It can be also observed that the R or S configuration[7] of the new chiral center is prevalently obtained depending on the solvent and the nature of the organometallic reagent, and that slightly better results are obtained from **1 b** than from **1 a.**



**1 a**, R = Ph
**b**, R = o-anisoyl

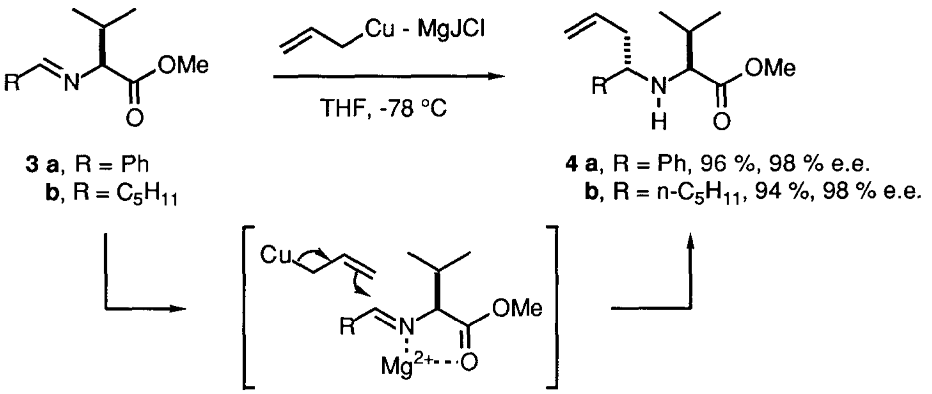
**2 a**, R = Ph
**b**, R = o-anisoyl

Table 1: Reaction of imines **1 a, b** with allylmagnesium and allylcopper reagents.

| imine | allylmetal | equiv. of allyl-M | solvent | **2** (yield %)[b] | diastereom. ratio[b] |
|---|---|---|---|---|---|
| **1 a** | allylMgBr | 1.5 | Et$_2$O | 100 | 43:57 |
| " | allylMgCl | " | THF | " | 64:36 |
| **1 b** | " | " | Et$_2$O-THF | " | 30:70[c] |
| **1 a** | allylCu-MgJBr | 3 | Et$_2$O | " | 40:60 |
| " | allylCu-MgJCl | " | THF | " | 40:60 |
| " | (allyl)$_2$CuMgBr-MgJBr | " | Et$_2$O | " | 41:59 |
| " | (allyl)$_2$CuMgCl-MgJCl | " | THF | " | 65:35 |
| " | allylCu-MgJCl-BF$_3$ | 2 | " | 42 | 38:62 |
| " | (allyl)$_2$CuMgCl-MgJCl-BF$_3$ | 3 | " | 100 | 43:57 |
| **1 b** | allylCuMgJCl | " | " | " | 24:76[c] |
|  | (allyl)$_2$CuMgCl-MgJCl | " | " | " | 17:83[c] |

(a) Allylcopper reagents were prepared in the usual way, then the imine (1 mmol) was added at -78°C and the reaction mixture was stirred for 1.5-2 h, before quenching with 10% aqueous NaOH and extraction with diethyl ether. (b) The yields and diastereomeric ratios (S,S:R,S) were determined by GC-MS analysis. (c) The configuration of the two diastereomers has not been determined.

Aiming to obtain a more satisfactory diastereoselectivity, we investigated the behaviour ot the imines derived from S-valine toward the same organometallic reagents, and we were gratified to find that allylcopper and diallylcuprate reagents (2.5 equivalents), prepared from allylmagnesium chloride and copper iodide in THF, allowed an almost quantitative conversion of **3 a**, **b** (1 mmol) to the homoallyl amines **4 a**, **b** with very high diastereoselectivity.[8]



**3 a**, R = Ph
**b**, R = $C_5H_{11}$

**4 a**, R = Ph, 96 %, 98 % e.e.
**b**, R = n-$C_5H_{11}$, 94 %, 98 % e.e.

The S,S-configuration of the major diastereoisomer **4 a** was ascertained by GC comparison with the reaction mixture obtained by the reported Barbier-type allylation procedure by using the metal redox couple Al-$TiCl_4$, which produces a 20:1 mixture of the S,S- and R,S-diastereomers, since the major diastereomer was converted to S-1-phenylbutylamine.[4] It should be observed that allylcopper reagents afford a higher diastereoselectivity. We suppose that the reaction pathway involves the addition of the allylcopper species to the rigide chelated complex formed between the imino-ester and magnesium ion; the organometallic reagent should attack the same enantioface of both the imines **3 a**, **b** to produce S,S-**4 a** and R,S-**4 b**.

Reaction of imine 3 a with allylcopper: A suspension of copper iodide (Aldrich, 99.999 %, 0.47 g, 2.5 mmol) in anhydrous THF (10 ml), is cooled to -30 °C under argon atmosphere. Allylmagnesium chloride (2 M solution in THF, 1.25 ml, 2.5 mmol) is added with stirring. After 15 min the reaction mixture is cooled to -78 °C, and the solution of the imine **3 a** (0.22 g, 1 mmol) in THF ( 5 ml) is added dropwise. After stirring for 30 min, the reaction mixture is quenched with aqueous sodium hydrogen carbonate, then filtered on Celite, and the organic phase is extracted with ether.(3 X 20 ml) The ether solution is washed with brine, and dried over magnesium sulfate. Evaporation of the solvent at reduced pressure leaves an oil, the crude homoallylamine **4 a** as an oil, 94 % pure by GC analysis. The pure S,S-diastereomer is obtained by flash-chromatography on silica gel, eluting with cyclohexane-ether (80:20): 205 mg (78 %); [α] D$^{28}$ -113.5° (c 2.98 $CH_2Cl_2$); $^1H$-NMR (300 MHz, $CDCl_3$, TMS) $\delta$ 7.2-7.4 (m, 5H, Ph), 5.65-5.82 (m, 1H, CH=), 5.05-5.18 (m, 2H, $CH_2$=) 3.70 (s, 3H, OMe), 3.45-3.55 (m, 1H, C$\underline{H}$Ph), 2.80

(d, 1H, $CHCO_2$), 2.24-2.45 (m, 2H, $CH_2C$=), 1.98 (broad s, 1H, NH), 1.77-1.89 (m, C<u>H</u>$Me_2$), 0.90 (d, 3H, Me), 0.85 ppm (d, 3H, Me); $^{13}C$-NMR (300 MHz, $CDCl_3$) $\delta$ 176.5, 143.8, 135.5, 128.4, 127.7, 127.2, 117.8, 64.2, 60.6, 51.1, 43.7, 31.5, 19.2, 18.2 ppm.
**4 a**-Hydrochloride: m.p.160-163 °C (ether-methanol); $[\alpha]$ $D^{28}$ -21.8° (c 1.84, MeOH; $^1H$-NMR d 10.65 and 9.87 (two broad s, $NH_2^+$), 7.65-7.75 (m, 2H, Ph), 7.40-7.50 (m, 3H, Ph), 5.32-5.50 (m, 1H, CH=), 4.90-5.10 (m, 2H, $CH_2$=), 4.2-4.35 (m, 1H, $CHCO_2$), 3.80 (s, 3H, OMe), 3.71-3.87 (m,1H,C<u>H</u>Ph), 3.2-3.36 (m,2H, $CH_2C$=), 2.7-2.84 (m, 1H, C<u>H</u>$Me_2$), 1.13 (d, 3H, Me), 1.05 ppm (d, 3H, Me).

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## Notes and References

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(2) Y. Yamamoto, T. Komatsu, K. Maruyama, *J. Am. Chem. Soc.* 1984, <u>106</u>, 5031; Y. Yamamoto, S. Nishii, K. Maruyama, T. Komatsu and W. Ito, *ibid.* 1986, <u>108</u>, 7778.
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(4) H. Tanaka, K. Inoue, U. Pokorski, M. Taniguchi and S. Torii, *Tetrahedron Letters* 1990, 3023.
(5) The conjugate addition of allylcopper species has only recently been described: B. H. Lipshutz, E. L. Ellsworth, S. H. Dimock and R.A.J. Smith, *J. Am. Chem. Soc.* 1990, <u>112</u>, 4404.
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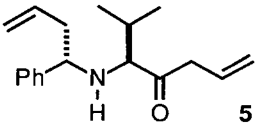
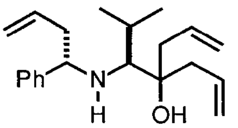
(7) We could demonstrate that the diastereomer of 2 a having the lower GC retention time has the S,S-configuration: in fact the allyl chain hydrogenation of 2 a (65:35 mixture of diastereoisomers) afforded a reaction mixture which was compared (GC, 1H-NMR) with that obtained by reaction of 1 a with $Pr_2CuMgBr$-MgJBr-$BF_3$, which affords a 76:24 ratio of S,S and R,S diastereomers, by analogy with the reaction with methyl copper-boron trifluoride reagents.[5]
(8) Compounds **5** and **6,** as diastereomeric mixtures, coming from the allylation of the ester group, are present in little amounts which increase when 3-5 equivalents of organometallic reagent are used.


**5**


**6**

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