# Enantioselective Synthesis of Homoallylic Amines by Addition of Allylmetal Reagents to Imines Derived from (S)-Valine Esters

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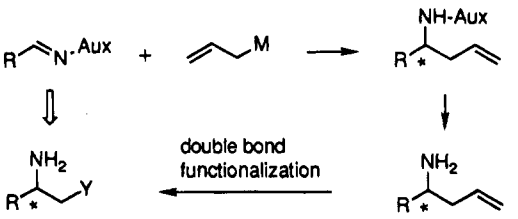
Grignard and Barbier procedures have been applied to the addition of allylmetal (Zn, Cu, Pb, Bi, Al, In) species to imines derived from (S)-valine esters, principally the methyl ester. The Zn-mediated, $CeCl_3$- or $SnCl_2$-catalyzed "Barbier" reactions of the imines with allyl bromide in THF in Ar atmosphere at room temperature proved particularly convenient, efficient and selective, providing the secondary homoallylic amines with excellent to perfect diastereoselectivity. The *si* face of the imine was attacked preferentially in every case. The addition of allylzinc bromide to aromatic imines was affected by reversibility, which caused the lowering of the diastereoisomeric ratio with increasing the reaction time. However, the *retro*allylation reaction could be avoided by performing the reaction in the presence of trace amounts of water, or by using $CeCl_3 \cdot 7H_2O$ as the catalyst, although at the expense of the reaction rate. The bimetal redox systems Al–$PbBr_2$, –$SnCl_2$, –$TiCl_4$, and –$BiCl_3$ were applied to the allylation of the imines derived from methyl valinate, but satisfactory results were achieved only with Al–$BiCl_3$ and –$TiCl_4$ systems. However, the use of the Al(Hg) and Al–$PbBr_2$ system afforded almost perfect chemo- and diastereoselectivity on the benzaldehyde imine derived from *tert*-butyl (*S*)-valinate. The synthesis of (*S*)-1-phenyl-3-butenamine from the corresponding secondary homoallylic amine was accomplished by a two-step sequence, consisting of the controlled reduction of the methyl ester with $LiAlH_4$ and subsequent oxidative cleavage with $H_5IO_6$–$MeNH_2$.

## Introduction

Optically active primary homoallylic amines can be prepared through the diastereoselective addition of allylmetal compounds[1] to imines prepared by the condensation of aldehydes with optically active amines, provided that the chiral auxiliary group (the nitrogen substituent) can be subsequently removed.[2–5] A variety of α-substituted alkyl amines are then available by the functionalization of the C=C bond of the N-protected homoallylic amine, e.g. by electrophilic or electrophile-mediated addition and oxidative cleavage reactions (Scheme 1). The analogous allylation of chiral cyclic iminium ions[6] (formed *in situ* from α-amino ethers, including N-substituted 1,3-oxazolidines), nitrones,[7] and hydrazones[8] has also been reported. The chiral auxiliary group was contributed generally[9] by optically active 1-arylethanamines,[2,6a–c] β-amino alcohols and ethers,[3,6d–f,7] α-amino acid esters,[4] and amino sugars.[5]

**Scheme 1**




The efficiency and the diastereoselectivity of the imine allylation reactions were found dependent on the nature of both the imine and the organometallic reagent. For example, allyl-9-BBN was the reagent of choice for the allylation of the imines prepared from 1-phenylethanamine and 2-methylpropanal,[2a] as well as butyl glyoxylate.[2b] The reactions of allylsilanes and -stannanes in the presence of $SnCl_4$ were efficient and diastereoselective (up to 99% de) with the imines derived from α-glycosylamines and aromatic aldehydes, but not aliphatic aldehydes.[5] The organometallic species obtained from allylmagnesium chloride and cerium trichloride[3a] and the functionalized allylzinc reagent derived from *tert*-butyl 2-bromomethyl acrylate[3c] were used for the allylation of the benzaldimines derived from phenylglycinol and alaninol. Following the Torii's seminal experiment on the Barbier allylation of the benzaldimine derived from methyl (*S*)-valinate (**1a**) by using allyl bromide and the bimetal redox system Al–$TiCl_4$,[4a] the addition of

† Allaye Bocoum, native of Mali, deceased prematurely in Bologna on 9 January 1994. We dedicate this paper to his memory.

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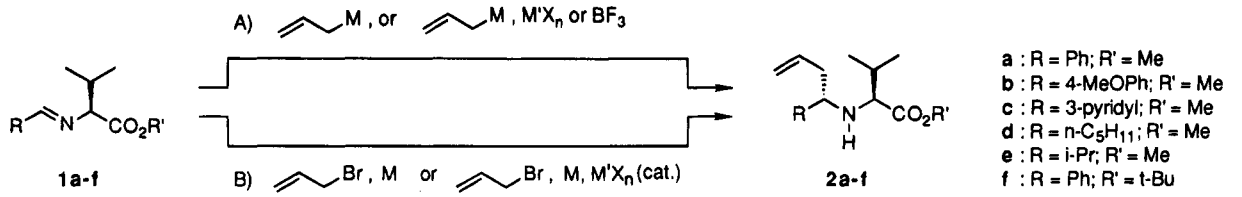
**Scheme 2. Grignard (A) and Barbier (B) Allylation of Imines**




allylchromium[4c] and -bismuth species[4d] and the allylzinc reagent mentioned above were successively reported.[4b]

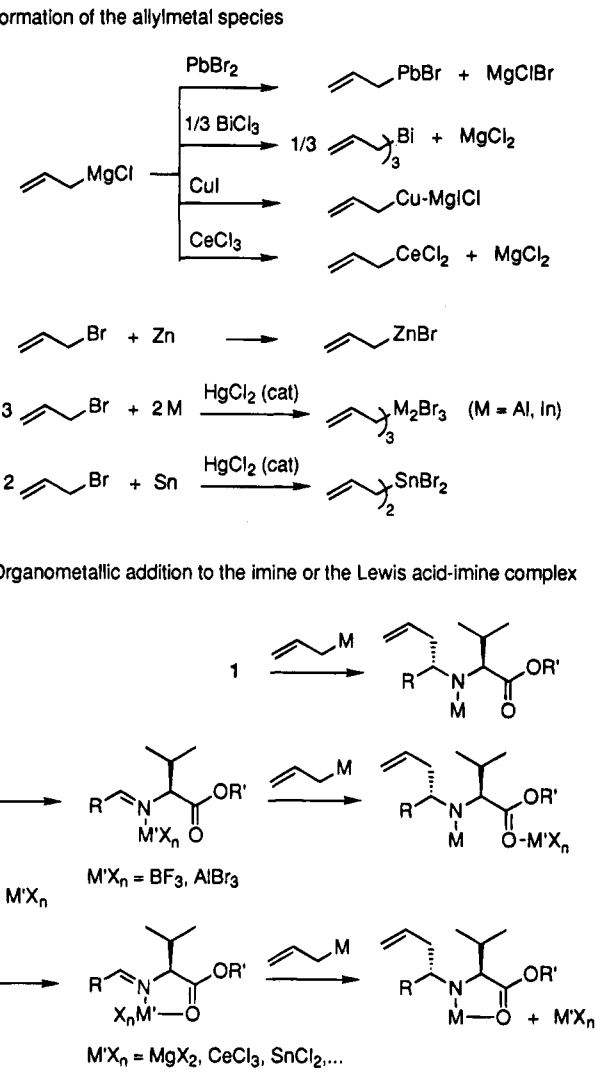
## Results and Discussion

We describe herein the results obtained in the addition of allylmetal species to aromatic and aliphatic imines **1a–f** derived from (*S*)-valine esters, principally the methyl ester, affording the secondary homoallylic amines **2a–f**.[10] Toward this purpose we have applied either Grignard and Barbier procedures (Scheme 2, routes A and B, respectively). For the Grignard procedure, usually adopted in organometallic reactions, we prepared a suitable allylmetal species and then added it to the imine (or *vice versa*). The imine can be activated by complexation with a Lewis acid, coming from the preparation of the allylmetal species ($M'X_n$) or added separately ($BF_3$·$Et_2O$). On the other hand, we followed several Barbier procedures,[11] where the imine and allyl bromide were added simultaneously to a suitable metal (M) or metal–metal salt system ($M/M'X_n$), the salt being used in catalytic amount.

**Grignard Procedure.** The Grignard procedure allows the reaction of the allylmetal species with the imine to be performed at low temperature, so that better chemo- and diastereoselectivity should be accomplished with respect to the Barbier procedure, which requires generally room temperature for the formation of the allylmetal species *in situ*. The organometallic reagent must discriminate the imine and ester functions of **1**, so we performed the transmetalation of allylmagnesium chloride with $PbBr_2$, $BiCl_3$,[12] $CeCl_3$,[3a] and CuI in THF, to prepare the corresponding allylmetal species. Furthermore, allylzinc bromide,[13] allylaluminum sesquibromide,[14] and diallyltin dibromide[15] were obtained by treatment of allyl bromide with Zn powder, Al(Hg) foil (i.e. in the presence of a catalytic amount of $HgCl_2$), and Sn(Hg) in THF. The reactions with **1a,d** were performed at different temperatures. The steps involved are described in Scheme 3[16] and the results of the organometallic reactions are reported in Table 1.

The addition of $BF_3$ etherate was necessary to activate the imine **1a** toward the allyllead and -bismuth species.

**Scheme 3. Mechanisms of Allylation of the Imines 1 ($M'X_n$ = nonreducible metal salt)**




The nature and the reactivity of the allyllead and -bismuth species were affected by the Grignard/salt ratio. These observations allowed us to discern the nature of the reactive organometallic species. Both allyllead bromide and diallyllead were prepared, but only the former was reactive, although the desired homoallylic amine **2a** was accompanied by products coming from the allylation of the ester group of **2a**.[17,18] Conversely, in the case of the bismuth species, the reaction performed with triallylbismuth gave better yields of **2a**, with respect to the reactions carried out by using a lower ratio allylmagnesium chloride/$BiCl_3$, according to the reported reactivity

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**Table 1. Addition of Allylmetal Compounds to the Imines (*S*)-1a,d[a]**

| imine | reagents[b] (equiv) | temp (°C) | time (h) | product | yield (%)[b] | dr (%)[b] |
|---|---|---|---|---|---|---|
| **1a** | $CH_2$=$CHCH_2PbBr$·MgBrCl (2.5), $BF_3$ (1)[c] | −78 | 5 | (*S,S*)-**2a** | 72[d] | >99:1 |
| **1a** | $(CH_2$=$CHCH_2)_3Bi$·3$MgCl_2$ (2),[e] $BF_3$ (1)[c] | −30 | 12 | (*S,S*)-**2a** | 78 | >98:2 |
| **1a** | $CH_2$=$CHCH_2Cu$·MgICl (2.5) | −78 | 3 | (*S,S*)-**2a** | 96 (78)[f] | 98:2 |
| **1a** | $(CH_2$=$CHCH_2)_2CuMgCl$·MgICl (3) | −78 | 3 | (*S*,4S)-**2a** | 100 | 98:2 |
| **1d** | $CH_2$=$CHCH_2Cu$·MgICl (2.5) | −78 | 3 | (*R,S*)-**2d** | 100 | <1:99 |
| **1a** | $(CH_2$=$CHCH_2)_3Al_2Br_3$ (0.5)[g] | −78 | 1.5 | (*S,S*)-**2a** | 70[d,h] | 97:3 |
| **1a** | $CH_2$=$CHCH_2ZnBr$ (2) | 25 | 1 | (*S,S*)-**2a** | 100 | 99:1 |
| **1a** | $CH_2$=$CHCH_2ZnBr$ (2) | 0 | 1 | (*S,S*)-**2a** | 100 | 100:0 |

[a] The reactions were carried out on 1−2 mmol of the imine in THF. [b] Determined by GC-MS analysis. The dr is reported according to the order of elution of the diastereoisomers. [c] $BF_3$ was added to the allylmetal reagent before adding **1a**. No product was obtained in the absence of $BF_3$, even at 0 °C. [d] Products derived by addition to the ester group were observed by GC-MS analysis. [e] By lowering the ratios Grignard/$BiCl_3$ organometallic reagent/**1a**, the yield and the diastereoselectivity decreased. [f] Yield of product isolated and purified by flash chromatography. [g] Solvent was $Et_2O$. [h] Unreacted **1a** (17%) was present.

of the different allylbismuth halides with carbonyl compounds.[12] The reaction of triallylbismuth was plagued by the waste of allyl groups, as a quantitative conversion of the imine was not obtained even with 2 equiv of triallylbismuth.

On the other hand, the use of allylcopper reagents in moderate excess allowed us to obtain **2a** and **2d** in almost quantitative yield and excellent diastereoselectivity from the aromatic and aliphatic imines **1a** and **1d**, respectively (Table 1). The addition of $BF_3$ etherate was unnecessary and did not affect the selectivity. On the other hand, the allylmetal species generated by treatment of allylmagnesium chloride with cerium trichloride was found unreactive toward **1a** at 0 °C, despite the reported reactivity with the benzaldimine derived from phenylglycinol.[3a] Similarly, diallyltin dibromide was unreactive toward **1a,e** at 25 °C.

Allylaluminum sesquibromide proved to be reactive and moderately selective on **1a** at −78 °C. However, we realized subsequently that the use of allylzinc bromide was most convenient, especially because the reaction with **1a** proceeded with almost perfect control of the chemo- and diastereoselectivity even at 0−25 °C (Table 1).

The composition of the diastereoisomeric mixtures of **2a** was determined by GC-MS and $^1$H-NMR analyses and by comparison with the authentic mixture of (*S,S*)- and (*R,S*)-**2a** (90:10) prepared by a reported procedure.[4a] As the addition of the allylmetal species occurred to the *si* face of **1a**, affording (*S,S*)-2a, we assumed that the same sense of asymmetric induction should be observed in the allylation of **1d**, so affording prevalently (*R,S*)-**2d**. As a matter of fact, the order of GC-MS elution of the diastereoisomers of **2a** (major isomer eluted first) was opposite to that of **2d** (minor isomer eluted first).

**Barbier Procedure. (A) Zn-, Al-, and In-Mediated Reactions.** The Barbier procedure,[11] involving the formation of the allylmetal reagent *in situ*, can be applied to the preparation of homoallylic amines, provided that the metal (e.g. Zn, Al, In) is unreactive toward the imine. In these conditions, the mechanism of reaction is not different from that involved in the Grignard procedure.

At first, the mixtures of the imine (**1a−f**), the metal (Zn, Al(Hg), In), and allyl bromide were stirred magnetically in anhydrous THF at room temperature and in argon atmosphere (Table 2).[19] The prevalent formation of (*S,S*)-**2a−c,e,f** and (*R,S*)-**2d** was assumed, consistent with the order of elution of the diastereoisomers in the GC-MS analysis. The Zn-mediated reaction was rapid and complete within 1.5 h, but the diastereoisomeric ratio was found to decrease with time. In fact, by quenching samples of the reaction mixture after increasing times, the (*S,S*/*R,S*) ratio of **2a** decreased from >99:1 (0.5 h, incomplete reaction of **1a**) to 94:6 (1.5 h, complete reaction), and further to 62:38 (48 h). The same observation was made by following the Grignard procedure, i.e. by adding **1a** to allylzinc bromide at −78 °C and quenching the reaction after stirring for several hours at 25 °C.

**Table 2. Reaction of (*S*)-1a−f with Allyl Bromide and Metals[a]**

| imine | metal | time (h) | product | yield (%)[b] | dr.(%)[b] |
|---|---|---|---|---|---|
| **1a** | Zn | 0.5 | (*S,S*)-**2a** | 80 | >99:1 |
| | | 1.5 | | 100 | 94:6 |
| | | 32 | | 100 | 52:48 |
| **1a** | Zn[c] | 7 | (*S,S*)-**2a** | 60 | 100:0 |
| | | 24 | | 100 (92)[d] | 100:0 |
| **1a** | Al(Hg) | 3 | (*S,S*)-**2a** | 37[e,f] | 81:19 |
| | | 24 | | 57[f,g] | 97:3 |
| | | 72 | | 52 | 94:6 |
| **1a** | In | 2.5 | (*S,S*)-**2a** | 50 | 76:24 |
| | | 12 | | 71 | 77:23 |
| | | 36 | | 100 | 75:25 |
| **1b** | Zn | 0.5 | (*S,S*)-**2b** | 100 | 100:0 |
| | | 48 | | 100 | 71:29 |
| **1c** | Zn | 2 | (*S,S*)-**2c** | 100 | >99:1 |
| | | 24 | | 100 | >94:6 |
| | | 48 | | 100 | 91:9 |
| **1d** | Zn[h] | 1 | (*R,S*)-**2d** | 100 | 5:95 |
| | | 48 | | 100 | 5:95 |
| **1e** | Zn | 12 | (*S,S*)-**2e** | 47[f,g] | 76:24 |
| **1e** | Zn[h] | 1.5 | (*S,S*)-**2e** | 88[f,g] | 87:13 |
| **1f** | Al(Hg) | 12 | (*S,S*)-**2f** | 100 | >99:1 |

[a] The reactions were performed in THF on 1−2 mmol of imine by using an excess of metal (1.5 equiv) and allyl bromide (1.2 equiv). [b] As in Table 1. [c] Reaction performed in the presence of 0.7 equiv of $H_2O$. [d] Yield of product isolated and purified by flash chromatography. [e] **1a** (34%) was present. [f] Byproducts coming from the allylation of the ester group were observed. [g] The conversion of **1a** was complete. [h] 1.05 Equiv of allyl bromide was used.

(17) Allylead bromide, generated from allyl bromide and Pb in the presence of $Bu_4NBr$ in DMF, was found unreactive toward esters: Tanaka, H.; Yamashita, S.; Hamatani, T.; Ikemoto, Y.; Torii, S. *Chem. Lett.* **1986**, 1611.

(18) When the allylation reactions were plagued by the addition to the ester group of **2**, the two diastereoisomers of **2** displayed a different reactivity, so that the final diastereoisomeric ratios were generally different from the original ones.

(19) The Barbier reactions were performed on 1−2 mmol of imine by using an excess of metal (1.5 equiv), and allyl bromide (1.2 equiv), to achieve a complete conversion of the imine. However, the $CeCl_3$-catalyzed Zn-mediated reactions with the aliphatic imines **1d,e** gave excellent results when performed with the stoichiometric amount of allyl bromide. Anhydrous THF, inert atmosphere, and room temperature were necessary either in the Zn- and Al/$PbBr_2$-mediated reactions. No reaction occurred when the mixture **1a**−Al−$PbBr_2$ was stirred at 0 °C in THF, and in MeOH, MeCN, and $Et_2O$ at 25 °C. When scaling up the reactions, care should be taken to cool the reaction flask with an external ice bath and to add slowly the organic reagents to the suspension of the metal or bimetal system, in order to get reproducible selectivities.

Furthermore, a sample of pure (S,S)-**2a** (>99%) underwent epimerization by treatment with a catalytic amount of $ZnCl_2$ in THF, whereas $SnCl_2$ and $CeCl_3$ were ineffective.

These observations are best rationalized by assuming that the addition of allylzinc bromide to (S)-**1a** is reversible at room temperature, as it was found for the addition of $\gamma$-substituted allyllzinc compounds to imines,[20] where the *syn/anti* ratio of the products was dependent on the reaction time. As an alternative, the epimerization could have occurred at the chiral center next to the ester group. However, this possibility could be excluded by the following experiments. The previously epimerized **2a** (52:48 mixture of diastereoisomers) was converted by carefully controlled removal of the valine auxiliary group to the primary homoallylic amine, which was optically inactive. Furthermore, after hydrogenation of the allyl moiety of **2a** ($H_2$, Pd/C, MeOH, 25 °C), no epimerization of the saturated product occurred by treatment with a catalytic amount of $ZnCl_2$ in THF.

By performing the reaction with **1a** using allyl bromide and Zn in the presence of 0.7 equiv of $H_2O$, we observed that the homoallylic amine **2a** was produced slowly but with perfect stereocontrol, even when quenching the reaction mixture after 24 h (Table 2). We suppose that $H_2O$ acts as a proton source for the reaction adduct, i.e. the zinc salt of **2a**, affording *in situ* **2a** and a less acidic zinc hydroxide species.

The Al(Hg)- and In-mediated Barbier procedure on **1a** did not show the character of reversibility (Table 2). However, the Al-mediated reaction was plagued by the formation of byproducts derived by the allylation of the ester function,[18] and the In-mediated Barbier allylation[15] was poorly diastereoselective, similarly to the analogous reaction performed on the imine derived from 1-phenylethylamine.[2d] Conversely, the Al(Hg)-mediated allylation of **1f**, derived from *tert*-butyl valinate, displayed essentially perfect chemo- and diastereoselectivity.

The Zn-mediated reaction with the imines derived from methyl valinate was superior in terms of rate, chemoselectivity, and diastereoselectivity with respect to the other metal-mediated reactions, provided that it was quenched in timely fashion or carried out in the presence of a little of water; it compares favorably also to the allylation of **1a** with allyl bromide, Bi and $Bu_4NBr$ in MeCN.[4d] The Zn-mediated procedure was applied to other aromatic and aliphatic imines (Table 2). Starting from **1b**, complete conversion and perfect diastereoselectivity for **2b** were observed after 0.5 h, but epimerization of **2b** occurred if the reaction mixture was not quenched, and a 71:29 diastereoisomeric ratio was observed after 48 h. The epimerization was much slower for **2c**[21] and did not occur with the aliphatic imines **1d,e**, demonstrating that the nature of group R of the imine has a prominent role in the process. Compound **1e** underwent the competitive allylation of the ester function, probably because even the attack to the imine group is impeded by the bulky i-Pr group, and the dr of **2e** was consistently lower.[18]

**(B) Al/M'X$_n$ (Bimetal Redox System)-Mediated Reactions.** Stimulated by recent reports of Barbier procedures exploiting bimetal redox systems for the synthesis of homoallylic amines,[4a,22] we investigated analogous Barbier allylation of the imines derived from methyl (*S*)-valinate. The method is based on the following principle. A bimetal redox system, constituted by a reducing metal (M) and a reducible metal salt (M'X$_n$) in catalytic amount is used to generate *in situ* the active metal (M') (eq 1), the direction of the redox reaction being

$$n\mathrm{M} + m\mathrm{M'X}_n \rightarrow n\mathrm{MX}_m + \mathrm{mM'} \qquad \text{(eq 1)}$$

determined approximately by the standard reduction potentials of the cations:[23] in aqueous solution the metal M is able to reduce the metal salt M'X$_n$ when the potential of $M^{+m}$ is more negative than that of $(M')^{+n}$.

The electrode reduction potentials of some cations have been measured in several organic solvents: it was apparent that the order of reducing ability of the metals was not modified by the solvent, which affected only the absolute values of the potentials.[24] Hence, the trend determined in water should be valid also in THF, at least when the standard reduction potentials of the cations differ largely.

We choose Al as the reducing metal, owing to the very negative potential ($Al^{+3}/Al$), assuming that it would be able to reduce $PbBr_2$, $BiCl_3$, $InCl_3$, and $SnCl_2$ to the zerovalent metals (Pb, Bi, In, Sn) in active form. The reaction should then proceed through the formation of the corresponding allylmetal species from the metals and allyl bromide, and the organometallic addition to the imine, activated by complexation with the aluminum halide formed in the redox reaction. On the other hand, the formation of either $Ti^0$ or $Ti^{+2}$ can be envisaged in the redox reaction of Al and $TiCl_4$.[23]

The redox bimetal systems Al/$PbBr_2$,[22] Al/$TiCl_4$,[4a] Al/$BiCl_3$[25] have been recently employed in the "Barbier" allylation of carbonyl compounds and imines with allyl bromide. The results we have obtained in the experiments performed on **1a,c,f** with these bimetal redox systems are reported in Table 3.

**Table 3. Reaction of (*S*)-1a,c,f with Allyl Bromide–Al–M'X$_n$[a]**

| imine | M'X$_n$ | time (h) | product | yield (%)[b] | dr (%)[b] |
|---|---|---|---|---|---|
| **1a** | $PbBr_2$ | 3 | (*S,S*)-**2a** | 56[c] | 96:4 |
| **1a** | $TiCl_4$ | 24 | (*S,S*)-**2a** | 83[c] | 90:10 |
| **1a** | $BiCl_3$[d] | 12 | (*S,S*)-**2a** | 100 | 93:7 |
| **1a** | $InCl_3$ | 0.08 | (*S,S*)-**2a** | 70[c,e] | 88:12 |
| | | 5 | (*S,S*)-**2a** | 79[c] | 87:13 |
| **1a** | $SnCl_2$[d] | 8 | (*S,S*)-**2a** | 53[e] | 78:22 |
| | | 48 | (*S,S*)-**2a** | 75[c] | 72:28 |
| **1c** | $PbBr_2$ | 4 | (*S,S*)-**2e** | 69[c] | 98:2 |
| **1f** | $PbBr_2$ | 12 | (*S,S*)-**2f** | 100 (86)[f] | >99:1 |

[a] The reactions were performed in THF on 1–2 mmol of imine by using an excess of metal (1.5 equiv) and allyl bromide (1.2 equiv), and a catalytic amount (0.1 equiv) of salt. [b] As in Table 1. [c] Byproducts derived from the allylation of the ester group of **2a,c** were formed. [d] $HgCl_2$ (0.5 mmol) was preliminarly added to the suspension of finely cut Al foil (2 mmol). [e] **1a** (25%) was present. [f] Yield of product isolated and purified by flash chromatography.

(20) Mauzé, B.; Miginiac, L. *Bull. Soc. Chim. Fr.* **1973**, 1832.

(21) In the preliminary communication,[10b] we erroneously reported the fast epimerization of **2c**, but we later realized that the imine **1a** was used, rather than **1c**, in that experiment.

(22) Imines have been allylated with allyl bromide, Al, $PbBr_2$ (cat.) and $BF_3$ in $Et_2O$: Tanaka, H.; Yamashita, S.; Ikemoto, Y.; Torii, S. *Chem. Lett.* **1987**, 673.

(23) CRC Handbook of Chemistry and Physics, 68th ed.; CRC Press: Boca Raton: FL, 1987. The following standard reduction potentials (V *vs* SHE) are of concern for the bimetal systems we used: $Ce^{+3}/Ce$, −2.483; $Al^{+3}/Al$, −1.662; $Zn^{+2}/Zn$, −0.762; $In^{+3}/In$, −0.338; $Sn^{+2}/Sn$, −0.137; $Pb^{+2}/Pb$, −0.126; $BiCl_4^-/Bi$, +0.160. For titanium, the following potentials are known: $TiO^{+2} + 2H^+/Ti + H_2O$, -0.882; $Ti(OH)^{+3} + H^+/Ti^{+3} + H_2O$, −0.055; $Ti^{+2}/Ti$, −1.628; $Ti^{+3}/Ti^{+2}$, −0.368.

(24) Headridge, J. B. *Electrochemical Techniques for Inorganic Chemists*; Academic Press: London, 1969; p 75. For example, the potentials (V *vs* aqueous SCE) of $Pb^{+2}$ and $Zn^{+2}$ in $H_2O$, DMSO, DMF, in the order are: $Pb^{+2}/Pb$, −0.38, −0.47, −0.42; $Zn^{+2}/Zn$, −1.00, −0.98, −0.98.

(25) Wada, M.; Ohki, H.; Akiba, K. *Bull. Chem. Soc. Jpn* **1990**, *63*, 1738.

**Table 4. Reaction of (S)-1a,c–e with Allyl Bromide–Zn–M'X$_n$[a]**

| imine | M'X$_n$ | time (h) | product | yield (%)[b] | dr (%)[b,c] |
|---|---|---|---|---|---|
| **1a** | $CeCl_3$ | 0.08 | (*S,S*)-**2a** | 100 | 100:0 |
| | | 2.5 | | 100 | 93:7 |
| | | 24 | | 100 | 64:36 |
| **1a** | $CeCl_3 \cdot 7H_2O$ | 0.5 | (*S,S*)-**2a** | 100 | >99:1 |
| | | 4 | | 100 | >99:1 |
| | | 20 | | 100 | >99:1 |
| **1a** | $SnCl_2$ | 0.1 | (*S,S*)-**2a** | 100 | 100:0 |
| | | 0.5 | | 100 | 98:2 |
| | | 12 | | 100 | 90:10 |
| | | 24 | | 100 | 64:36 |
| **1a** | $SnCl_2$[c] | 0.5 | (*S,S*)-**2a** | 40 | 100:0 |
| | | 24 | | 100 | 98:2 |
| **1c** | $CeCl_3$ | 0.16 | (*S,S*)-**2c** | 90 | 100:0 |
| | | 0.5 | | 100 | 100:0 |
| **1c** | $CeCl_3 \cdot 7H_2O$ | 2.5 | (*S,S*)-**2c** | 100 | 100:0 |
| **1d**[d] | $CeCl_3 \cdot 7H_2O$ | 0.75 | (*R,S*)-**2d** | 100 | 0:100 |
| **1e**[d] | $CeCl_3$ | 0.08 | (*S,S*)-**2e** | 100 | 98:2 |
| | | 24 | | 100 | 98:2 |
| **1e**[d] | $CeCl_3 \cdot 7H_2O$ | 0.25 | (*S,S*)-**2e** | 100 | 98:2 |
| **1e**[d] | $SnCl_2$ | 2 | (*S,S*)-**2e** | 50[e] | 100:0 |

[a,b] As in Table 3. [c] Reaction performed in the presence of 0.7 equiv of $H_2O$. [d] 1.05 Equivalents of allyl bromide was used. When using more allyl bromide (1.2 equiv), the attack to the ester group of **2e** occurred, lowering also the dr.[18] [e] Unidentified higher boiling organic compounds and an allyltin compound were present in the reaction mixture.

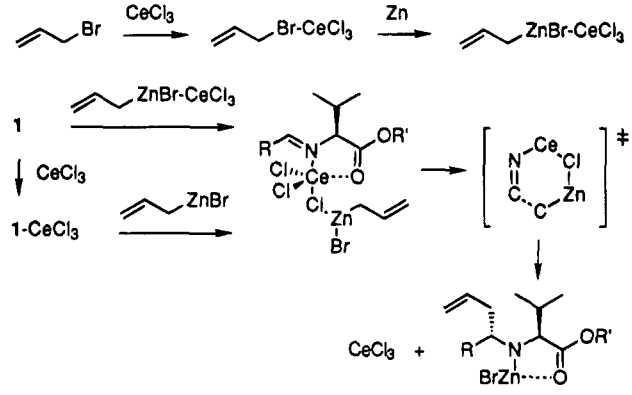
By comparison with the results obtained in the uncatalyzed Al(Hg)-mediated reaction (Table 2) and considering that unactivated Al is not reactive toward allyl bromide, it was evident that especially $InCl_3$ increased markedly the reaction rate even by using unactivated Al. On the other hand, $PbBr_2$ and $TiCl_4$ had a less pronounced effect, and $SnCl_2$ and $BiCl_3$ required the use of Al(Hg). Owing to the use of an excess of allyl bromide and metal, in the Al(Hg)-mediated allylation of **1a** and the Zn-mediated allylation of **1e** (Table 2), as well in the reactions with **1a,c** employing Al–$PbBr_2$, –$InCl_3$, –$TiCl_4$, and –$SnCl_2$ (Table 3), byproducts were formed by the addition of the allylmetal species to the ester group of the homoallylic amines. Conversely, the clean formation of **2a** was obtained with the Al(Hg)/$BiCl_3$ system, which also provided better diastereoselectivity (94% de): these results pointed against the involvement of allylaluminum sesquibromide as the reactive allylmetal compound, as the uncatalyzed Al(Hg)-mediated Barbier reaction was considerably less chemo- and diastereoselective.

Owing to the more satisfactory results obtained by the Zn-mediated Barbier procedure, the metal salt-catalyzed Al-mediated reactions was not applied further to the aliphatic imines **1d,e**. However, perfect chemo- and diastereoselectivity were achieved by the application of the Al/$PbBr_2$-mediated Barbier procedure to the imine **1f**, derived from *tert*-butyl (*S*)-valinate, affording the homoallylic amine **2f** (Scheme 2, Table 3).

**(C) Zn/$CeCl_3$- and Zn/$SnCl_2$-Mediated Reactions.** We examined the effect of a catalytic amount of a metal salt (M'Xn) added to the mixture of imines (*S*)-**1a,c–e**, allyl bromide and Zn, and found that anhydrous $CeCl_3$ and $SnCl_2$ gave excellent results (Table 4). The reaction rates were enhanced markedly, the reactions with **1a** being complete within 10 min, whereas the uncatalyzed reactions required >0.5 h for completion (Table 2). Furthermore the homoallylic amine **2a** was formed with perfect diastereoselectivity.

Again, we observed the extensive epimerization of **2a**, but not of **2c–e**, when quenching of the reaction mixture was delayed. By analogy with the uncatalyzed Zn-mediated Barbier reactions, the epimerization of **2a** was suppressed when the $SnCl_2$-catalyzed reaction was performed in the presence of 0.7 equiv of $H_2O$, or when using $CeCl_3 \cdot 7H_2O$. Although the presence of $H_2O$ in the salt or in the solvent caused the decrease of the reaction rate, the reactions were faster than those performed without the salt in anhydrous solvent (Table 2).

**Scheme 4. Mechanism of Zinc-Mediated, $CeCl_3$-Catalyzed Barbier Allylation of Imines 1**




The presence of a catalytic amount of $CeCl_3$ had a dramatic effect in the allylation of the hindered imine **1e**, where the chemo- and diastereoselectivity were greatly enhanced, by comparison with the corresponding uncatalyzed reaction (Table 2). Conversely, the use of $SnCl_2$ in the allylation of **1e** provided a more complex reaction mixture containing unidentified high-boiling products and an allyltin compound (GC-MS analysis).

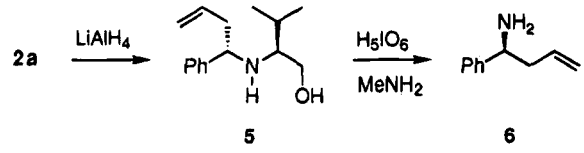
At our knowledge, the combined use of Zn–$CeCl_3$ and Zn–$SnCl_2$ in organic synthesis has never been reported, so that we examined the possibility for different mechanisms to be operating in such reactions.[26] No redox reaction can occur between Zn and $CeCl_3$, but Zn should be capable to reduce $SnCl_2$ to active Sn.[23] The intermediacy of allylcerium dichloride and diallyltin dibromide as the reactive organometallic species is unlikely, because these organometallic compounds were found unreactive toward **1a** and **1e**, respectively, by following the "Grignard" procedure at 0–25 °C.

A plausible mechanism of the $CeCl_3$-catalyzed, Zn-mediated reaction is shown in Scheme 4. The salt undoubtedly acts as a Lewis acid, activating the imine toward the addition of allylzinc chloride. However, we believe that it may have a role in the preliminary activation of allyl bromide toward the oxidative addition of Zn.[27] The addition of the allyzinc bromide–$CeCl_3$ complex to the imine **1**, or the addition of allylzinc bromide to **1**–$CeCl_3$, should take place through the formation of a three component complex, where $CeCl_3$ plays the double role of Lewis acid (Ce toward **1**) and Lewis base (Cl toward Zn of allylzinc bromide). Then the homoallylic amine should be delivered through a cyclic six-membered transition state (Scheme 4). This mechanism is analogous to that proposed by Evans for the metal

(26) Other M-$CeCl_3$ system did not prove as effective as Zn–$CeCl_3$ with **1a**. In fact, no product was obtained by substitution of Zn with Al, and the reaction with Al(Hg) was almost complete within 1 h, but was plagued by the competitive attack to the ester group. Furthermore, by the use of In–$CeCl_3$, **2a** was obtained with 71% yield and 78:22 dr after 8 h.

(27) Cerium trichloride acted as a Lewis acid in Friedel–Crafts reactions of benzyl and alkyl halides: (a) Olah, G. A.; Kobayashi, S.; Tashiro, M. *J. Am. Chem. Soc.* **1972**, *92*, 7448. (b) Mine, N.; Fujiwara, Y.; Yaniguchi, H. *Chem. Lett.* **1986**, 357. (c) Amer, I.; Alper, H. *J. Am. Chem. Soc.* **1989**, *111*, 927. (d) Grushin, V. V.; Alper, H. *Organometallics* **1993**, *12*, 3846.

**Scheme 5**




salt-catalyzed or -mediated addition of organometallic reagents to carbonyl compounds,[28] and applied recently to rationalize some $YbCl_3$-[29] and $CeCl_3$-[30] catalyzed reactions of Grignard reagents.

On the other hand, the $SnCl_2$-catalyzed, Zn-mediated Barbier reaction can proceed through two concomitant reactions of Zn: the oxidative addition to allyl bromide, affording the reactive allylzinc bromide, and the redox reaction with $SnCl_2$, producing Sn and $ZnCl_2$ (eq 1). Unreactive allyltin species should be produced in part from Sn and allyl bromide. On the other hand, either $SnCl_2$ and/or $ZnCl_2$ should be able to activate the imine toward the organometallic addition, through the formation of a chelated complex, similarly to $CeCl_3$.

**Removal of the Auxiliary Group. Synthesis of Primary Homoallylic Amines.** In order to confirm the stereochemistry assigned to the secondary homoallylic amines, as well as to give synthetic potential to the described allylation reactions, we faced the conversion of **2a** to the optically active primary homoallylic amine (S)-**6**. A two-step procedure to prepare (*S*)-**6** from (*S,S*)-**2a** has been reported, involving the preliminary basic hydrolysis of the ester group, followed by electrochemical oxidative decarboxylation.[4a] Alternatively, a multistep procedure could be followed from the acid, involving the Curtius rearrangement of the corresponding acyl azide as the key step.[31] However, we did not succeed to find satisfactory conditions for the electrochemical decarboxylation, whereas the other procedure was tedious and afforded a modest yield.

We devised a two-step procedure, consisting of the reduction of the ester function with $LiAlH_4$ to afford the $\beta$-hydroxy amines **5**, followed by the oxidative cleavage with periodic acid in the presence of methylamine[7] (Scheme 5). However, after performing the reduction of (*S,S*)-**2a** with $LiAlH_4$ overnight at room temperature, we isolated **6** with an ee consistently lower than the de of starting **2a**. We realized that in the reduction step the intermediate aluminum salt of **5** underwent a *retro*allylation–allylation reaction, resulting in the epimerization of the stereogenic center α to the phenyl group, as evidenced by $^1$H-NMR spectroscopy.[32] This interpretation was supported also by the observed reversibility of the Zn-mediated allylation of (*S*)-*N*-benzylidenevalinol.[10b] However, by performing the reduction step of **2a** at low temperature (<0 °C), followed by the oxidative cleavage, the primary homoallylic amine **6** was obtained optically pure in 86% overall yield, avoiding any purification of the intermediate **5**.

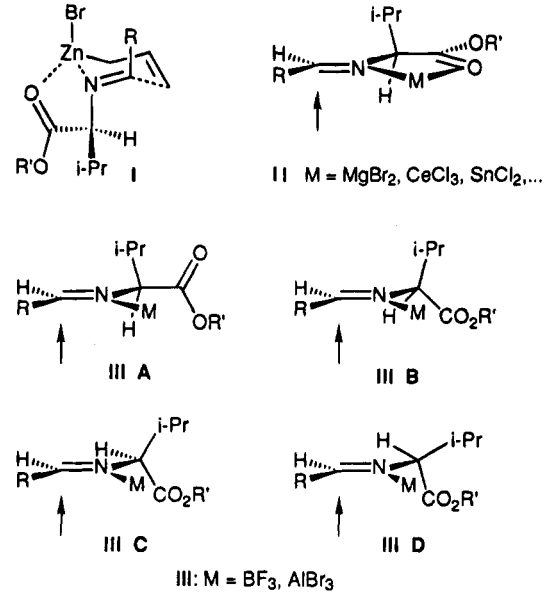



**Figure 1.**

**Stereochemical Models for the Asymmetric Induction.** The sense of asymmetric induction in the addition of allylmetal species to the imines **1a–f** was unaffected by many factors: the nature of the imine (the group R), the procedure followed (Grignard or Barbier), the nature of the metal in the reactive allylmetal species, the presence and the nature of a metal salt, which can form a chelated or nonchelated complex with the imine. As a matter of fact, the *si* face of the imine was always attacked, although with variable stereoselectivity.

The stereochemical models which provide explanation of the observed diastereoselectivity are shown in Figure 1. A cyclic chair transition state is envisaged in the addition of allylzinc bromide, or any allylmetal compound, to the imines **1** in the absence of Lewis acid, and the maximum stabilization is attained in **I**, where Zn (metal) is coordinated by the ester group and the bulky i-Pr group is disposed externally. In the case of reactions mediated by a Lewis acid which can form a chelated complex with the N and O heteroatoms of the imine, the stereocontrol is determined by steric factors, as the nucleophile adds to the rigid planar structure **II** *anti* to the i-Pr group, may be through a cyclic transition state as in Scheme 4.[28-30] Conversely, when the organometallic addition is promoted or catalyzed by $BF_3$ or $AlBr_3$, which can link to the imine nitrogen only, the conformations **IIIA–D**, obtained by progressive rotation around the N–C* bond, should be considered. The diastereoselectivity could be governed by either steric and stereoelectronic factors. In **IIIA**, where the planar imine and ester groups are disposed orthogonally one to eachother, the attack of the nucleophile is extremely favored from the side of the H substituent, rather than from the side of the i-Pr group.

The Felkin-type models **IIIB** and **IIID** allow the attainment of the maximum overlap of the $\pi^*$ (C=N) and allylic $\sigma^*$ (i-Pr-C* and $MeO_2C$-C*, respectively) orbitals, so lowering the energy of the LUMO of the imine and of the transition state for the nucleophilic addition, according to the Anh–Eisenstein rationale for the asymmetric

(28) Evans, D. A. *Science* **1988**, *240*, 420.
(29) Utimoto, K.; Nakamura, A.; Matsubara, S. *J. Am. Chem. Soc.* **1990**, *112*, 8189.
(30) (a) Bartoli, G.; Marcantoni, E.; Petrini, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1061. (b) Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Palmieri, G.; Petrini, M. *J. Chem. Soc., Chem. Commun.* **1994**, 715.
(31) Waldmann, H.; Braun, M. *J. Org. Chem.* **1992**, *57*, 4444. An *anti*-Felkin–Anh model was instead proposed to explain the diastereoselectivity of cycloaddition reactions of **1f** and analogous imines with Brassard's diene: Waldmann, H.; Braun, M.; Drager, M. *Tetrahedron: Asymmetry* **1991**, *2*, 1231.
(32) When **2a** was reduced with $LiAlH_4$ at 20 °C overnight, **5** was obtained as a 75:25 mixture of (*S,S*) and (*R,S*) epimers, as shown by the $^1$H NMR spectrum, where absorptions of (*R,S*)-**5** were observed at δ 5.22–5.10 (m, $CH_2$=CH), 3.33 (2 d, $J$ = 4.4 and 10.5 Hz, 1 H, $CH_2$-OH) and 3.19 (2 d, $J$ = 8.2 Hz and 10.5 Hz, 1 H, $CH_2$OH).

induction in nucleophilic addition to α-chiral carbonyl compounds.[33] In **IIIB** the stereodifferentiation is a consequence of the bulkiness of the i-Pr group, which then occupies the orthogonal position and dictates the *anti* addition of the nucleophile, which interacts with the small H group. However, the conformation **IIID** is also appealing, owing to the low-lying $\sigma^*$ orbital of the C*–$CO_2R'$ bond, but the observed sense of asymmetric induction is not in accord with the expected *anti* addition of the nucleophile. Instead, it may be conceived that the nucleophilic addition occurs *syn* to the $CO_2R'$ group. In fact, it has been calculated that secondary orbital interactions facilitate the *syn* addition of hydride ion to $C_1$ of propene (with respect to the allylic C–H bond).[34] Furthermore, *syn* addition of the nucleophile to the C=N bond of **IIID** proceeds through a transition state and gives an adduct in which the (developing) nitrogen lone pair has the preferred *anti* relationship with respect to the electron-withdrawing allylic substituent. Similar arguments, based on *ab initio* calculations, have been advanced to rationalize the *syn* stereochemistry of $S_N2'$ allylic substitution reactions, and the favored *syn* stereochemistry for nucleophilic addition reactions was predicted too.[34b]

The structural feature of the valine auxiliary group does not allow the easy empirical rationalization of the diastereoselectivity. The *anti*-periplanar attack with respect to an allylic orthogonal substituent at the chiral center is generally assumed, but the choice of the orthogonal group is a matter of controversy. For example, in a Lewis acid-catalyzed addition of Danishefsky's diene to **1a** the Felkin–Anh model with orthogonal $CO_2R'$ group has been proposed.[31] Conversely, in the epoxidation of α-chiral alkenes (R*CH=C) having the carbon framework (R*) of methyl valinate ($R^*NH_2$), preference was given to the model with orthogonal i-Pr group.[35] On the other hand, the *syn* addition to the orthogonal electron-withdrawing substituent ($CO_2R$) has never been considered a plausible alternative.

Finally, it should be noted that several authors prefer to explain the 1,3-asymmetric induction in addition reactions to chiral imines or iminium ions simply by evaluating the ground state conformation of the substrate, which generally possesses an allylic H–C* bond in the plane of the C=N bond and assuming the approach of the reagent to the least hindered face.[36] On this ground, the preferred conformation of the imine **1** should be **IIIC** (Figure 1) and the allylmetal compound should attack the C=N bond from below the plane. However, in our opinion the high degree of diastereoselectivity observed in the allylation of the valine-derived imines **1a–f** can be hardly explained by this model, based merely on the different steric properties of the i-Pr and $CO_2R$ groups.

(33) (a) Nguyen, T. A.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (b) Nguyen, T. A. *Top. Curr. Chem.* **1980**, *88*, 145. (c) Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1987**, *109*, 908. (d) Lodge, E. P.; Heathcock, H. C. *J. Am. Chem. Soc.* **1987**, *109*, 3353.

(34) (a) Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438. (b) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G. *J. Mol. Struct.* **1983**, *103*, 197. See also: Seebach, D.; Calderari, G.; Knochel, P. *Tetrahedron* **1985**, *41*, 4861.

(35) Matsumoto, T.; Terao, H.; Ishizuka, N.; Usui, S.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1761.

(36) For example, see: (a) Polniaszek, R. P.; McKee, J. A. *Tetrahedron Lett.* **1987**, *28*, 4511. (b) David, D. M.; Kane-Maguire, L. A. P.; Pyne, S. G. *J. Chem. Soc., Chem. Commun.* **1990**, 888. (c) David, D. M.; Kane-Maguire, L. A. P.; Pyne, *J. Organomet. Chem.* **1990**, *390*, C6. (d) Abraham, H.; Stella, L. *Tetrahedron* **1992**, *48*, 9707.

## Concluding Remarks and Perspectives

The study performed on the Grignard and Barbier allylation of imines derived from esters of (S)-valine allowed determination of the optimum conditions for perfect chemo- and diastereoselectivity. The secondary homoallylic amine derived from the benzaldimine is easily converted by a two-step sequence to optically pure (*S*)-1-phenyl-3-butenamine. The overall process demonstrates the usefulness of the valine esters as chiral auxiliaries in the addition of allylmetal compounds to the derived chiral imines. Therefore, it should be desirable to develope efficient procedures for the addition of other organometallic species (alkyl, vinyl, aryl, alkynyl) to the same imines. The problem is again to conciliate reactivity and chemoselectivity. At the moment, we have performed only a few experiments on **1a** by using an excess of methylcopper and dimethylcuprate species in the presence of $BF_3$, as these reagents reacted satisfactorily with imines derived from (*S*)-1-phenylethanamine;[37] however, we recovered **1a** unchanged or obtained with very poor yield unidentified, nonisolated products.

β-Amino alcohols derived from α-amino acids can be used as an alternative to valine esters as chiral auxiliaries, especially allowing the use of very reactive organometallic reagents not compatible with the ester function. In the preliminary communication[10b] we have described that the reaction of the benzaldimine derived from (*S*)-valinol with the allyl bromide–Zn–$CeCl_3 \cdot 7H_2O$ system afforded **5** with 100% diastereoselectivity, although the reaction required approximately 24 h for completion. On the other hand, a lower stereocontrol was obtained on the benzaldimine derived from (*S*)-phenylglycinol (unpublished results). Further work is in progress on this matter.

## Experimental Section

IR spectra of neat compounds are expressed by wavenumber ($cm^{-1}$). Optical rotations were measured on a digital polarimeter in methanol solution in a 1-dm cell. Chemical shift of $^1$H-NMR spectra taken at 300 MHz in $CDCl_3$ are indicated as s, singlet; t, triplet; q, quartet; m, multiplet; br, broad peak. GC-MS analyses were performed at an ionizing voltage of 70 eV. Melting points are uncorrected. Chromatographic purification was done with 240–400 mesh silica gel.

The organometallic reactions were performed in flame-dried apparatus in Ar atmosphere. Solvents were distilled in Ar atmosphere prior to use: THF over Na-$Ph_2CO$ ketyl and successively over $LiAlH_4$, and $CH_2Cl_2$ over $P_2O_5$. The imine **1a** and the amine **2a** are known compounds,[4a] but their spectroscopic properties have not been previously described.

**General Protocol for the Preparation of Imines.** To a solution of methyl (*S*)-valinate hydrochloride (50 mmol) in THF (50 mL) at 0 °C was added anhydrous $MgSO_4$ (10 g), the aldehyde (50 mmol), and triethylamine (50 mmol), and the mixture was stirred by a magnetic bar for 3 h. The solid phase was filtered off and the organic solvent was evaporated under reduced pressure. Anhydrous pentane (10 mL) was added to the residue, and the eventually formed precipitate was filtered off. The filtrate was concentrated at reduced pressure to leave the crude imine, which was obtained generally in almost quantitative yield and in pure state, as inferred by GC-MS and $^1$H-NMR analyses, presumably with *E* geometry. The imines were immediately used in the subsequent reaction. Only **2a** (for analytical purpose) and **2d** (owing to the presence of high boiling condensation products in consistent amounts) were distilled at reduced pressure.

**Methyl *N*-Benzylidene-(*S*)-valinate (1a)**: bp 96–98°/0.02 mmHg; $[\alpha]^{25}_D$ −126.8° (*c* 2.18, MeOH); IR 1640; $^1$H-NMR δ 8.25

(37) Boga, C.; Savoia, D.; Umani-Ronchi, A. *Tetrahedron: Asymmetry* **1990**, *1*, 291.

(s, 1), 7.80 (m, 2), 7.43 (m, 3), 3.76 (s, 3), 3.67 (d, $J$ = 7.2 Hz, 1), 2.39 (m, 1), 0.97 and 0.93 (2 d, $J$ = 6.7 Hz, 6); GC-MS $m/z$ (relative intensity) 160 (100), 204 (2).

**Grignard Allylation of Imines. Preparation of Methyl *N*-[(4*S*)-4-Phenylbut-1-en-4-yl)]-(*S*)-valinate (2a). (A) Reaction of 1a with Allylcopper.** To a suspension of CuI (99.999%, 0.47 g, 2.5 mmol) in THF (10 mL), cooled at −30 °C and stirred magnetically, was added allylmagnesium chloride (2 M in THF, 1.25 mL, 2.5 mmol). A yellow precipitate was formed. After 15 min the stirred mixture was cooled at −78 °C, then the solution of **1a** (0.219 g, 1 mmol) in THF (3 mL) was added over 10 min. The mixture was stirred for 30 min and then quenched with 10% aqueous NaOH (5 mL). The organic phase was extracted with $Et_2O$ (20 mL × 3), washed with brine, dried over $Na_2SO_4$, and concentrated at reduced pressure to leave **2a** as an oil (0.256 g, 96% pure, dr 98:2 by GC-MS analysis). Flash-chromatography (cyclohexane−$Et_2O$, 80:20) afforded pure (*S,S*)-**2a** (0.205 g, 78%): $[\alpha]^{25}_D$ −113.5° (*c* 2.98, $CH_2Cl_2$); $^1$H-NMR $\delta$ 7.2−7.4 (m, 5), 5.85−5.68 (m, 1), 5.20−5.08 (m, 2), 3.72 (s, 3, $CO_2Me$), 3.56−3.48 (m, 1), 2.80 (d, $J$ = 6.1 Hz, 1, $CHCO_2Me$), 2.48−2.26 (m, 2), 1.98 (br, 1), 1.90−1.76 (m, 1), 0.92 and 0.87 (2 d, J = 6.7 Hz, 6); GC-MS $m/z$ (relative intensity) 220 (100), 160 (54). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.39; H, 9.00; N, 5.37. By stirring a solution of (*S,S*)-**2a** with anhydrous $ZnCl_2$ (0.1 equiv) in THF, almost racemic **2a** was obtained; from the $^1$H-NMR spectrum the absorption of the $CHCO_2Me$ protons of (*R,S*)-**2a** were determined at $\delta$ 3.50 (s) and 3.04 (d).

**(B) Reaction of 1a with Allyllead Bromide and $BF_3$.** To a suspension of $PbBr_2$ (0.92 g, 2.5 mmol) in THF (5 mL), cooled at −78 °C and stirred magnetically, was added allylmagnesium chloride (2 M in THF, 1.25 mL, 2.5 mmol). After 30 min, $BF_3$−$Et_2O$ (0.12 mL, 1 mmol) and a solution of **1a** (0.219 g, 1 mmol) in THF (3 mL) were added. The mixture was stirred at −78 °C for 5 h, quenched with 10% aqueous NaOH, and analyzed by GC-MS spectroscopy.

**(C) Reaction of 1a with Triallylbismuth and $BF_3$.** To a suspension of $BiCl_3$ (0.42 g, 2 mmol) in THF (10 mL), cooled at −78 °C and stirred magnetically, was added allylmagnesium chloride (2 M in THF, 3 mL, 6 mmol). The reaction mixture was stirred for 30 min, and then $BF_3$−$Et_2O$ (0.12 mL, 1 mmol) and a solution of **1a** (0.219 g, 1 mmol) in THF (3 mL) were added. The reaction mixture was stirred for 12 h at −40 °C, quenched with 10% aqueous NaOH, and analyzed by GC-MS spectroscopy.

**(D) Reaction of 1a with Allylaluminum Sesquibromide.** Allylaluminum sesquibromide was prepared as described previously[13] by stirring a suspension of finely cut Al foil (0.054 g, 2 mmol), allyl bromide (0.364 g, 3 mmol), and $HgCl_2$ (0.054 g, 0.2 mmol) in $Et_2O$ (10 mL). The solution was cooled at −78 °C, and **1a** (0.219 g, 1 mmol) was added. After stirring for 1.5 h at −78 °C, the reaction was quenched with 10% NaOH and analyzed by GC-MS spectroscopy.

**Barbier Allylation of Imines. (A) Zinc-Mediated Reactions. General Procedure.** To a suspension of Zn powder (0.13 g, 2 mmol) in THF (3 mL), stirred magnetically and cooled with an ice bath, was added $CeCl_3$·$7H_2O$ (0.037 g, 0.1 mmol) and then a solution of the imine (1 mmol) and allyl bromide (0.182 g, 1.5 mmol) in THF (3 mL) was added. The same procedure was applied as well in the absence of the salt. The reactions in the presence of anhydrous salts were carried out as follows. The salts (ca 0.1 mmol) were dried and weighed in the same apparatus used for the subsequent reaction: $SnCl_2$ was heated *in vacuo* at 120 °C for 30 min, and anhydrous $CeCl_3$ was obtained by heating $CeCl_3$·$7H_2O$ at 150 °C for 2 h. To the salt was added THF (3 mL), Zn, and the organic reagents as above. The progress of the reactions was followed by GC-MS analysis, and after usual quenching and workup the products were isolated generally in quantitative yield with satisfactory purity for subsequent use. Only for analytical purpose the products were purified by flash-chromatography on $SiO_2$ (cyclohexane−$Et_2O$).

**Methyl *N*-[4(*S*)-4-(4′-Methoxyphenyl)but-1-en-4-yl]-(*S*)-valinate (2b)**: $^1$H-NMR $\delta$ 7.22 and 6.84 (2 d, $J$ = 7.3 Hz, 4), 5.80−5.65 (m, 1), 5.17−5.05 (m, 2), 3.80 (s, 3), 3.70 (s, 3), 3.52−3.43 (m, 1), 2.77 (d, $J$ = 6 Hz, 1), 2.42−2.24 (m, 2), 1.88−1.75 (m, 1); 0.90 and 0.84 (2 d, $J$ = 6.6 Hz, 6); GC-MS $m/z$ (relative intensity) 250 (100), 161 (48), 190 (48). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.31; H 8.63; N, 4.80.

**Methyl *N*-[(4*S*)-4-(3′-Pyridyl)but-1-en-4-yl]-(*S*)-valinate (2c)**: $^1$H-NMR $\delta$ 8.48 (m, 2), 7.65 (m, 1), 7.22 (m, 1), 5.77−5.60 (m, 1), 5.12−5.04 (m, 2), 3.55−3.46 (m, 1), 2.68 (d, $J$ = 5.8 Hz, 1), 2.40−2.25 (m, 2), 1.87−1.73 (m, 1), 0.86 and 0.81 (2 d, $J$ = 6.6 Hz, 6); GC-MS $m/z$ (relative intensity) 221 (100), 161 (72), 203 (15). Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.51; H, 8.47; N, 10.70.

**Methyl *N*-[(4*R*)-1-Nonen-4-yl)]-(*S*)-valinate (2d)**: $^1$H-NMR $\delta$ 5.87−5.65 (m, 1), 5.18−5.0 (m, 2), 3.70 (s, 3), 3.08 (d, $J$ = 9.2 Hz, 1), 2.5−1.78 (m, 5), 1.5−1.2 (m, 8), 1.05−0.85 (m, 9); GC-MS $m/z$ (relative intensity) 214 (100), 154 (40), 196 (13), 184 (8). The (*R,S*) diastereoisomer gave absorption at $\delta$ 3.00 (d) for the $CHCO_2Me$ proton. Anal. Calcd for $C_{15}H_{29}NO_2$: C, 70.71; H, 11.43; N, 5.49. Found: C, 70.84; H, 11.41; N, 5.51.

**Methyl *N*-[(4*S*)-5-Methylhex-1-en-4-yl)]-(*S*)-valinate (2e)**: $^1$H-NMR $\delta$ 5.80−5.65 (m, 1), 5.16−5.0 (m, 2), 3.68 (s, 3), 3.00 (d, $J$ = 6.1 Hz, 1), 2.20−2.05 (m, 3), 1.85−1.65 (m, 2), 0.94, 0.90, 0.86, and 0.85 (4 d, $J$ = 6.9 Hz, 12); GC-MS $m/z$ (relative intensity) 186 (100), 126 (69), 184 (60), 168 (20). The minor diastereoisomer (*S,S*)-**2e** showed an absorption at $\delta$ 3.04 (d, $J$ = 6.1 Hz) for the $CHCO_2Me$ proton. Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.63; H, 11.09; N, 6.17. Found: C, 68.70; H, 11.10; N, 6.15.

**(B) Al/$PbBr_2$-Mediated Reactions. General Procedure. Preparation of *tert*-Butyl *N*-[(4*S*)-4-Phenylbut-1-en-4-yl]-(*S*)-valinate (2f).** To the stirred suspension of finely cut Al foil (0.054 g, 2 mmol) and $PbBr_2$ (0.036 g, 0.1 mmol) in THF (5 mL) was added **1f** (0.261 g, 1 mmol) and allyl bromide (0.13 mL, 1.5 mmol). After stirring for 12 h and usual workup, the crude product was flash-chromatographed on a short column of $SiO_2$ (cyclohexane−$Et_2O$, 80:20) to obtain (*S,S*)-**2f** as an oil (0.258 g, 86%): IR 1720; $^1$H-NMR $\delta$ 7.4−7.2 (m, 5), 5.85−5.70 (m, 1), 5.20−5.07 (m, 2), 3.59−3.51 (m, 1), 2.63 (d, $J$ = 6.1 Hz, 1), 2.45−2.28 (m, 2), 2.0 (br, 1), 1.88−1.75 (m, 1), 1.5 (s, 9), 0.92 and 0.87 (d, $J$ = 6.7 Hz, 6); GC/MS $m/z$ (relative intensity) 72 (100), 131 (89), 206 (78), 91 (71), 160 (50). Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.21; H, 9.63; N, 4.62. Found: C, 75.22; H, 9.63; N, 4.61.

**Preparation of (*S*)-1-Phenyl-3-butenamine (6).** To the stirred suspension of $LiAlH_4$ (0.767 g, 2 mmol) in THF (5 mL), cooled at −5 °C, was added during 15 min a solution of (*S,S*)-**2a** (0.261 g, 1 mmol) in THF (3 mL). After stirring for 1 h at -5−0 °C, the mixture was quenched with 10% aqueous NaOH and further stirred for 15 min. After usual workup, **5** was obtained as an oil (0.219 g, 98%): $^1$H-NMR[32] $\delta$ 7.40−7.22 (m, 5), 5.80−5.65 (m, 1), 5.12−5.0 (m, 2), 3.75 (t, 1), 3.63 and 3.39 (2 dd, $J$ = 4.2 Hz, $J$ = 10.6 Hz, 2), 2.55−2.35 (m, 2), 2.28 (m, 1), 1.71 (m, 1), 1.44 (s, 2), 0.89 and 0.84 (2 d, $J$ = 6.9 Hz, 6); GC-MS m/z (relative intensity) 192 (100), 131 (50), 91 (50), 202 (20). To a solution of **5** (1.90 g, 8.2 mmol) in MeOH (50 mL) was added 40% aqueous $MeNH_2$ (7 mL) and $H_5IO_6$ (6.75 g, 29.6 mmol) dissolved in $H_2O$ (10 mL). The mixture was stirred magnetically over 1 h, 10% aqueous NaOH (25 mL) was added, MeOH was removed at reduced pressure, and the organic phase was extracted with $Et_2O$ (20 mL × 3). Drying and concentration afforded crude (*S*)-**6** (1.065 g, 88%), >99% pure by GC-MS analysis: $[\alpha]^{25}_D$ −42° (*c* 0.5, $CH_2Cl_2$) (lit.[4a] $[\alpha]^{22}_D$ 44.6°, probably owing to a typographical error); $^1$H-NMR $\delta$ 7.40−7.20 (m, 5), 5.85−5.68 (m, 1), 5.18−5.03 (m, 2), 3.99 (m, 1), 1.60 (br, s); GC-MS $m/z$ (relative intensity) 106 (100), 79 (34), 77 (16). The N-Boc derivative of (*S*)-**6** was prepared in 91% yield by the reported procedure:[5] mp 70 °C; $[\alpha]^{25}_D$ -48.4° (*c* 1, $CHCl_3$) (lit.[5] $[\alpha]^{22}_D$ −48.4° (*c* 1, $CHCl_3$).

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**Supplementary Material Available:** Optical rotation, and $^1$H-NMR and MS spectroscopic data for the imines **1b−f** (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.