

Enantioselective Synthesis of Homoallylic Amines. Evidence of Reversible Addition of Allylzinc Bromide to Aromatic Imines Derived from (*S*)-Valine Methyl Ester and (*S*)-Valinol

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The reaction of aromatic and aliphatic imines derived from (*S*)-valine methyl ester and (*S*)-valinol with allyl bromide and zinc in tetrahydrofuran affords homoallylic amines with up to 100% diastereoisomeric excess (d.e.), but in the case of the aromatic imines the diastereoselectivity is lowered by increasing the reaction time, owing to the reversibility of the allylation reaction.

As a part of an extensive research devoted to the preparation of optically active amines by the organometallic addition to imines carrying a homochiral substituent at nitrogen,¹ we performed some 'Barbier' allylation reactions on imines derived from (*S*)-valine methyl ester by using allyl bromide and zinc pulver in anhydrous tetrahydrofuran (THF) at room temperature and in argon atmosphere (Scheme 1).

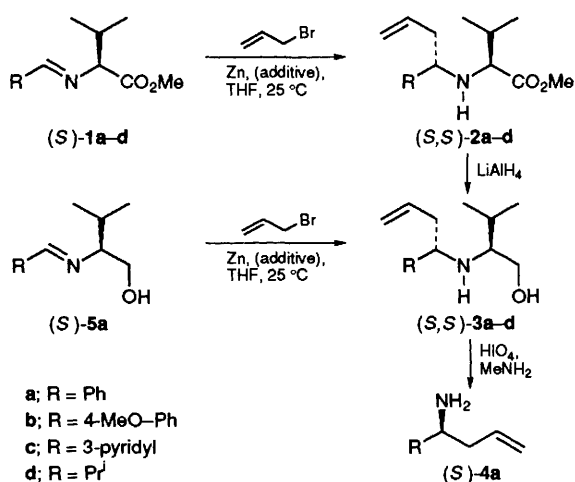
A clean reaction took place with the imine (*S*)-**1a**, affording essentially (*S,S*)-**2a** with 99% diastereoisomeric excess (d.e.) and with no contamination of products arising by the addition to the ester group. However, by following carefully the course of the reaction by GC-MS analysis, we could observe that the diastereoisomeric ratio (d.r.) decreased with increasing reaction time, even after the reaction was complete, unless the reaction mixture was quenched timely with water (Table 1, entry 1). Furthermore, the treatment of isolated, >99% pure

(*S,S*)-**2a** with a catalytic amount of zinc chloride in THF for 3 h lead to a 78:22 mixture of diastereoisomers.†

The (*S,S*) configuration of the prevalent diastereoisomer **2a** was determined by comparing the GC-MS elution times and ¹H NMR absorptions of the crude reaction mixture (d.r. = 99:1) with those exhibited by the mixture of (*S,S*)- and (*R,S*)-**2a** (90:10) prepared by the procedure described by Torii *et al.*,² making use of the redox system aluminium-titanium tetrachloride and presumably involving an allyl-titanium species.

The epimerization could also be observed by following the 'Grignard' procedure, *i.e.* by preparing preliminarily allylzinc bromide from allyl bromide and zinc in THF,³ then adding the imine to this solution. However, by performing the Grignard reaction at 0 °C a quantitative yield of (*S,S*)-**2a** with 100% d.e. was obtained after 75 min, and the rate of epimerization was reduced considerably.

These observations are likely rationalized by assuming that the addition of allylzinc bromide to (*S*)-**1a** is reversible, as it was found for the addition of crotylzinc species to imines, where the ratio of *syn* and *anti* diastereoisomers was depending on the reaction time.⁴ As an alternative, the epimerization could occur at the chiral centre next to the ester group, since in this case the ¹H NMR analysis cannot distinguish the (*S,R*) and (*R,S*) enantiomers of **2a**. This interpretation can be rejected since the epimerized **2a** (52:48 mixture of diastereoisomers) was converted by carefully controlled removal of the valine auxiliary group (as described in the following) to the primary homoallylic amine **4a** (Scheme 1), which was almost optically inactive, demonstrating that epimerization had occurred at the newly formed chiral centre.



Scheme 1

† The two diastereoisomers were clearly identified in the 300 MHz ¹H NMR spectrum: in particular the CH-CO₂CH₃ protons absorbed at δ 2.80 (d) and 3.72 (s) for (*S,S*)-**2a**, and at 3.04 (d) and 3.50 (s) for (*R,S*)-**2a**.

Table 1^a

Entry	Imine	Additive (equiv.)	React. time/h	Product	Yield ^b (%)	(<i>S,S</i>):(<i>R,S</i>) ^c
1	<i>(S)</i> -1a		0.5	2a	80	>99:1
			1.5		100	94:6
			4		100	93:7
			24		100	62:38
			32		100	52:48
2	<i>(S)</i> -1a	CeCl ₃ ·7H ₂ O (0.1)	0.5	2a	100	>99:1
			4		100	>99:1
			20		100	>99:1
3	<i>(S)</i> -1a	CeCl ₃ (0.1)	0.08	2a	100	100:0
			2.5		100	93:7
			24		95 ^d	64:36
4	<i>(S)</i> -1a	H ₂ O (0.1)	7	2a	60	100:0
			24		100	100:0
5	<i>(S)</i> -1b		0.5	2b	100	100:0
			48		77 ^d	71:29
6	<i>(S)</i> -1c	CeCl ₃ (0.1)	0.16	2c	90	100:0
			18		100	65:35
7	<i>(S)</i> -1c	CeCl ₃ ·7H ₂ O (0.1)	2.5	2c	100	100:0
			15		100	100:0
8	<i>(S)</i> -1d	CeCl ₃ ·7H ₂ O (0.1)	0.25	2d	100	94:6
			9		<i>(S)</i> -1d	CeCl ₃ (0.1)
3		94:6				
24		94:6				
10	<i>(S)</i> -5a	CeCl ₃ ·7H ₂ O (0.1)	24	3a	100	100:0
			11		<i>(S)</i> -5a	CeCl ₃ (0.1)

^a Unless otherwise indicated the reactions were carried out on 1 mmol of imine by using 1.5 equiv. of allyl bromide and 2 equiv. of zinc powder (THF, Ar, 25 °C). ^b The yields (GC) refer to products 2 and 3. ^c The ratios were determined by capillary GC-MS analysis (entries 1–5) and by 300 MHz ¹H NMR analysis (entries 6–11). ^d Products derived from allylation of both the imine and ester groups were formed. ^e The imine was fully consumed.

By examining the effect of several metal salts in the 'Barbier' reaction with zinc, we observed that the epimerization was suppressed in the presence of a catalytic amount of cerium trichloride heptahydrate, since (*S,S*)-2a was formed rapidly and quantitatively with almost complete diastereoselectivity (>99% d.e.), even on quenching the reaction mixture after 20 h (entry 2). On the other hand, (*S,S*)-2a was quantitatively and exclusively obtained within a few minutes by performing the reaction in the presence of anhydrous cerium chloride, but consistent epimerization was observed after a long time (entry 3). Furthermore, pure (*S,S*)-2a could be obtained by a slow reaction carried out without the cerium salt but in the presence of a little amount of water (entry 4).

We believe that in this reaction the cerium salt acts as a strong Lewis acid activating both allyl bromide towards zinc and the imine towards allylzinc bromide: the formation of allylzinc bromide from allyl bromide and zinc powder and the reaction of allylzinc bromide with the imines were quite slow in the absence of the cerium salt, both reactions requiring 2–3 h for completion. On the other hand, at the moment we think that water acts simply as a proton source for the organometallic-imine adduct to afford *in situ* the homoallylic amine 2 and a less acidic zinc hydroxide species.

The reversibility of the allylation reaction was also demonstrated for the aromatic imines (*S*)-1b, c (entries 5 and 6), and again the epimerization of (*S,S*)-2c was suppressed by using the hydrated cerium salt (entry 7). However, the reaction of the aliphatic imine (*S*)-1d lead to (*S,S*)-2d with a constant ratio of diastereoisomers (entries 8 and 9).

The preparation of the homoallylic amine (*S*)-4a involved the reduction of (*S,S*)-2a to β-amino alcohol (*S,S*)-3a and subsequent oxidative cleavage (Scheme 1). Surprisingly, the reduction of (*S,S*)-2a with lithium aluminum hydride in THF at room temp. afforded a mixture of (*S,S*)- and (*R,S*)-3a. Since the diastereoisomers were not separated by capillary GC and

GC-MS analyses, their ratio was evaluated by the 300 MHz ¹H NMR spectroscopic analysis of the crude reaction product.‡ To explain the loss of configurational purity during the reduction we supposed that the aluminum salt of (*S,S*)-3a produced underwent a *retro*-allylation reaction leading to the equilibration with (*R,S*)-3a through the corresponding imine (*S*)-5a. However, the configurational purity was preserved by performing the reduction at low temperature (<0 °C).† Finally, the treatment of (*S*)-3a with periodic acid in the presence of aqueous methylamine⁵ allowed the optically pure (*S*)-1-phenyl-2-butenamine (4a) to be obtained directly in 88% yield (Scheme 1).§

Alternatively, the homoallylic amine (*S,S*)-3a was obtained by applying the Barbier procedure to the imine (*S*)-5a derived from (*S*)-valinol, although the reaction was slow and required about 24 h for completion with either hydrated and anhydrous cerium trichloride (entries 10 and 11). Again, a complete diastereoselectivity was obtained by working in the presence of the hydrated salt, whereas a mixture of diastereoisomers, probably derived by a slow epimerization, was obtained on using the anhydrous salt.‡

To our knowledge the reversibility of the addition of allylic zinc compounds to homochiral imines has never been understood.^{7–9} We have shown that it affects the diastereoselectivity in the reactions of aromatic imines and suppose that the

‡ (*S,S*)- and (*R,S*)-3a exhibited absorptions for the CH₂OH protons in the 300 MHz ¹H NMR spectrum at δ 3.60 and 3.36 (dd), and 3.32 and 3.18 (dd), respectively.

§ The crude product (*S*)-4a had [α]_D²² –42 (c 0.5, CHCl₃); lit.²: [α]_D²⁵ + 44.6, probably owing to a mistake in the sign. In fact the *N*-Boc derivative of (*S*)-4a had the same optical rotation as the known compound: [α]_D²² –48.4 (c 1.2, CHCl₃); lit.⁶ [α]_D²² –48.4 (c 1.0, CHCl₃).

analogous reactions of benzylic and Reformatzky reagents may be reversible too.

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