

Diastereoselective Addition of Allylzinc Bromide to Imines Derived from (*R*)-Phenylglycine Amide

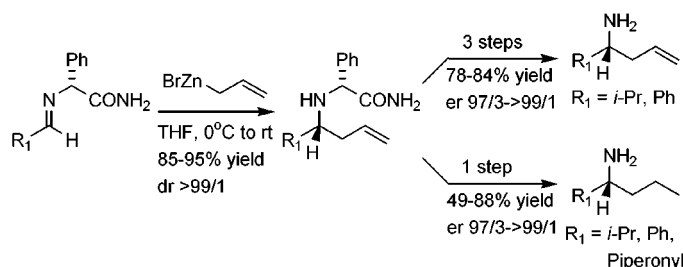
Marcel van der Sluis,[†] Jan Dalmolen,[‡] Ben de Lange,[§] Bernard Kaptein,[§]
Richard M. Kellogg,^{*,†} and Quirinus B. Broxterman^{*,§}

Syncom B.V., Kadijk 3, 9747 AT Groningen, The Netherlands, University of Groningen, Department of Organic and Molecular Inorganic Chemistry, Nijenborgh 4, 9747 AG Groningen, The Netherlands, and DSM Fine Chemicals-Advanced Synthesis and Catalysis, P.O. Box 18, 6160 MD Geleen, The Netherlands

rinus.broxterman@dsm.com

Received October 1, 2001

ABSTRACT



The highly diastereoselective addition of allylzinc bromide to imines derived from (*R*)-phenylglycine amide is reported. Homoallylamines with high enantiomeric purity are obtained from the adducts in three steps on removal of the chiral auxiliary by means of a nonreductive protocol. Removal of the auxiliary by hydrogenation leads to the saturated amines, also in high enantiomeric purity.

Chiral homoallylamines are valuable synthons for the preparation of topically interesting compounds such as β -amino acids, 1,3-amino alcohols, and 1-amino-3,4-epoxides.¹ Recently,^{2,3} homoallylamines proved to be key building blocks for the preparation of some pyrrolidines and piperidines via the ring-closing metathesis approach. The most frequently employed methodology for the synthesis of homoallylamines is the allylation of imines by allyl Si, Sn, Sm, Li, Mg, Zn, Ce, Cr, B, or Cr reagents.⁴

High 1,3-asymmetric induction during the addition can be achieved by using imines derived from chiral auxiliaries such

as α -arylethylamines,⁵ β -amino alcohols, β -alkoxy amines, and α -amino acid esters.⁶ A common feature of the latter three auxiliaries is the presence of a second heteroatom, which is capable of rigidifying the transition state of the 1,2-

(4) (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (b) Jones, P.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 186. (c) Wang, D.-K.; Zhou, Y.-G.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **1999**, *64*, 4233. (d) Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 2614. (e) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242. (f) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (g) Wang, D.-K.; Dai, L.-X.; Hou, X.-L.; Zhang, Y. *Tetrahedron Lett.* **1996**, *37*, 4187. (h) Negoro, N.; Yanada, R.; Okaniwa, M.; Yanada, K.; Fujita, T. *Synlett* **1998**, 835. (i) Itsuno, S.; Yokoi, A.; Kuroda, S. *Synlett* **1999**, 1987. (j) El-Shehawy, A. A.; Omara, M. A.; Ito, K.; Itsuno, S. *Synlett* **1998**, 367. (k) Yanada, R.; Negoro, N.; Okaniwa, M.; Ibuka, T. *Tetrahedron* **1999**, *55*, 13947. (l) Fang, X.; Johannsen, M.; Yao, S.; Gatherhood, N.; Hazel, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844.

(5) Juaristi, E.; Leon-Romo, J. L.; Reyes, A.; Escalante, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2441.

(6) (a) Alvaro, G.; Martelli, G.; Savoia, D. *J. Chem. Soc., Perkin Trans.* **1998**, *1*, 777. (b) Bocoum, A.; Savoia, D.; Umami-Ronchi, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1542 (b) Razavi, H.; Polt, R. *J. Org. Chem.* **2000**, *65*, 5693.

* E-mail for R.M.K.: r.m.kellogg@syncom.nl.

[†] Syncom B.V..

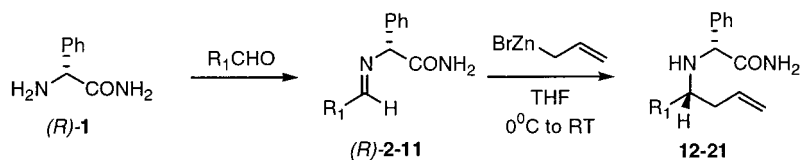
[‡] University of Groningen.

[§] DSM Fine Chemicals-Advanced Synthesis and Catalysis.

(1) Laschat, S.; Kunz, H. *J. Org. Chem.* **1991**, *56*, 5883.

(2) Felpin, F.-X.; Girard, S.; Vo-Thanh, G.; Robins, R. J.; Villieras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305.

(3) Wright, D. L.; Schulte, J. P., II; Page, M. A. *Org. Lett.* **2000**, *2*, 1847.

Table 1. Formation of (*R*)-phenylglycine Amide Imines **2–11** and the Formation of Homoallylamines **12–21** by Addition of Allylzinc Bromide

entry	imine	R ₁	yield ^a (%)	homoallylamine	yield ^a (%)	er (<i>R,R</i>)/(<i>S,S</i>)- 12–21 ^b	dr (<i>R,R</i>)/(<i>R,S</i>)- 12–21 ^c
1	2	phenyl	84	12	93	>99/1	>99/1
2	3 ^d	3-piperonyl	85	13	81	>99/1	>99/1
3	4	<i>p</i> -HOphenyl	90	14	90	nd	>99/1
4	5	2,5-(MeO) ₂ phenyl	87	15	93	nd	>99/1
5	6	3-pyridyl	90	16	43	nd	>99/1
6	7	2-furyl	89	17	88	nd	96/4
7	8	2-thiophene	80	18	90	nd	>99/1
8	9	<i>tert</i> -butyl	95	19	89	>99/1	>99/1
9	10	<i>i</i> -propyl	95	20	77	nd	99/1
10	11	<i>i</i> -butyl	86	21	94	nd	>99/1

^a Isolated yield. ^b Determined with HPLC. ^c dr values were determined with NMR spectroscopy. ^d In CHCl₃ with catalytic *p*-TolSO₃H for 2 h at reflux.

addition through chelation.⁵ This is also referred to as “chelation control”.⁷ Drawbacks are the limited availability and/or the need of removal of these auxiliaries by procedures unsuitable for large-scale preparations, i.e., oxidation with Pb(OAc)₄ or treatment with HIO₄/eNH₂.⁵

Recently, the use of optically pure (*R*)-phenylglycine amide (**1**) as highly efficient chiral auxiliary in the synthesis of α -amino acids was reported.⁸ Its application in the synthesis of chiral amines and homoallylamines based on diastereoselective allylation as the key step will be described here. Both reductive and nonreductive protocols for removal of the chiral auxiliary have been developed.

Aldimines (*R*)-**2–11** are obtained in 84–95% yield by stirring a mixture of **1** with the corresponding aldehyde (R₁-CHO) in CH₂Cl₂ overnight at room temperature. The formation of aldimine (*R*)-**3** required elevated temperatures and acid catalysis (Table 1). The addition of allylzinc bromide (1.5 equiv) to the imines in THF at 0 °C furnishes the homoallylamines (*R,R*)-**12–21** in yields up to 94% with diastereomeric ratios of >99/1 in most cases (Table 1). Allylzinc bromide proved to be the organometallic reagent of choice. It is easily prepared and is compatible with most organic groups.⁹

The phenylglycine amide chiral auxiliary in imines **2–11** contains a chiral center that could racemize under basic conditions. To determine if any racemization of this chiral center had occurred during the allylation reaction, we determined the (*R,R*)/(*S,S*) ratio of several adducts by HPLC (Table 1). The selected compounds contained only the (*R,R*)

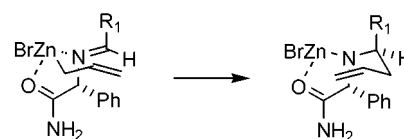
isomers, thereby establishing that the chiral auxiliary does not racemize under the reaction conditions employed.

The addition of allylzinc reagents to imines is reported to be limited to those that are nonenolizable or contain branched α -alkyl substituents.^{4f} This is not true for (*R*)-phenylglycine amide derived imines as shown by the allylation of **10** and **11** (entries 9 and 10).

The compatibility of allylzinc bromide with relatively acidic functionalities such as an amide or hydroxyl group is remarkable. In view of the approximate relative p*K*_a of **17** for amides,¹⁰ the basic allylzinc reagent could well be protonated by this group. The lack of reaction with an even more acidic functionality such as a phenolic hydroxyl group (p*K*_a 8–11) is even more striking (entry 3). The addition of 1.5 equiv of allylzinc bromide to (*R*)-**4** furnished the homoallylamine (*R,R*)-**14** as the only product in 90% isolated yield.

Reactions of **2** with, respectively, propylzinc bromide, *n*-butyllithium, benzylzinc bromide, or *p*-anisylmagnesium bromide failed to produce addition products. In all cases the starting material was recovered.

We postulate that the two heteroatoms of the (*R*)-phenylglycine amide-imine chelate the zinc atom of the allylzinc reagent to form a five-membered ring.^{5,7} Simultaneously, a six-membered chairlike transition state is formed

**Figure 1.** Chelation-controlled addition of allylzinc bromide to (*R*)-PGA imines.

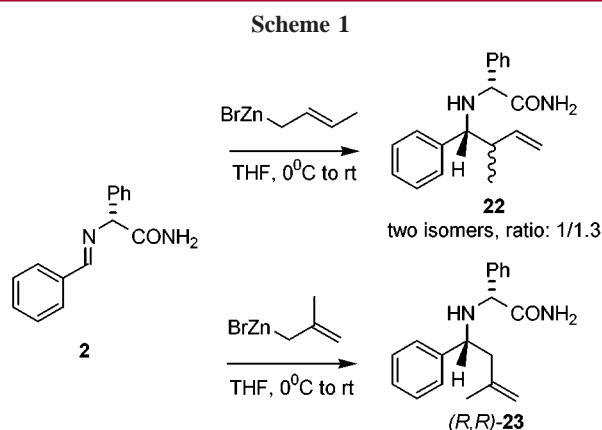
(7) Neuman, W. L.; Rogic, M. M.; Dunn, T. J. *Tetrahedron Lett.* **1991**, 32, 5865.

(8) (a) Boesten, W. H. J.; Seerden, J.-P. G.; de Lange, B.; Dielemans, H. J. A.; Elsenberg, H. L. M.; Kaptein, B.; Moody, H. M.; Kellogg, R. M.; Broxterman, Q. B. *Org. Lett.* **2001**, 3, 1121. (b) Boesten, W. H. J.; Seerden, J.-P. G.; de Lange, B.; van der Sluis, M.; Kaptein, B.; Moody, H. M.; Kellogg, R. M.; Broxterman, Q. B. PCT Int. Appl. WO 01 42,173.

(9) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, 93, 2117.

from the allylic system and the C=N double bond of the imine. The *re*-face 1,2-addition proceeds in a concerted fashion by an allylic rearrangement (Figure 1).

The allylic rearrangement was confirmed by the addition of crotylzinc bromide¹¹ to imine **2** (Scheme 1). Product **22**



was isolated in 98% yield (dr 99/1) as a mixture of two isomers in a ratio of 1:1.3. As a demonstration of the scope, the addition of methallyl bromide to **2** furnished *(R,R)*-**23** in 98% isolated yield (dr 99/1).

The α -substituted 1-aminobutanes *(R)*-**24**,¹² *(R)*-**25**,¹³ and *(R)*-**26**¹⁴ were obtained in 49–88% yield with enantiomeric ratios of 97/3 to >99/1 by catalytic hydrogenation of **12**, **20**, and **13**, respectively, under acidic conditions (Table 2). The high enantiomeric ratios of these chiral amines are in accord with the diastereoselectivity of the allylation reaction and lack of racemization of the phenylglycine amide moiety.

The observed signs of the optical rotations are in accord with the *(R)*-configuration (see Supporting Information). In accord with the model proposed in Figure 1, the absolute configuration of the adducts **12**–**21** should be *(R,R)*. This was unambiguously established by X-ray crystallographic analysis of **14**¹⁵ (Figure 2).

A demonstration of the synthetic value of this methodology is the preparation of *(R)*- α -propylpiperonylamine (*(R)*-**26**). This chiral butylamine is an important building block of the

(10) March, J. *Advanced Organic Chemistry*; John Wiley: New York, 1992; p 250.

(11) Crotylbromide was used consisting of a *cis/trans* (1:13) mixture (85%) and 3-bromo-1-butene (15%).

(12) (a) Bataille, P.; Paterne, M.; Brown, E. *Tetrahedron: Asymmetry*, **1998**, 9, 2181. (b) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, 120, 4242. (c) Yamamoto, Y.; Shimota, H.; Oda, J.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1976**, 49, 3247.

(13) Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, 108, 8, 4608.

(14) Cvetovich, R. J.; Chartrain, M.; Hartner, F. W.; Roberge, C.; Amato, J. S.; Grabowski, E. J. *J. Org. Chem.* **1996**, 61, 6575.

(15) X-ray data for **14** is available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, U.K. and was allocated the deposition number CCDC 154389.

(16) Cvetovich, R. J.; Chartrain, M.; Hartner, F. W., Jr.; Roberge, C.; Amato, J. S.; Grabowski, E. J. *J. Org. Chem.* **1996**, 61, 6575.

(17) (a) Moody, C. J.; Hunt, J. C. A. *Synlett* **1998**, 733. (b) Polniaszek, R. P.; Belmont, S. E.; Alvarez, R. *J. Org. Chem.* **1990**, 55, 215. (c) Laschat, S.; Kunz, H. *Synlett* **1990**, 51. (d) Hua, D. H.; Miao, S. W. M.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, 56, 4.

Table 2. Synthesis of Chiral Amines by Catalytic Hydrogenation of Homoallylamines

entry	homoallylamine	amine	yield (%) ^a	er (<i>R</i>)/(<i>S</i>)
1	12	<i>(R)</i> - 24	49	98/2 ^b
2	20	<i>(R)</i> - 25	64	97/3 ^c
3	13	<i>(R)</i> - 26	88	>99/1 ^b

^a Isolated yield. ^b Analysis by HPLC (Crownpak analytical column, 150 \times 4.6 mm; eluent aqueous HClO₄, pH = 2.0, 1.0 mL/min for 110 min) by integration of absorption at 216 nm. ^c Analysis by HPLC after tosylation with TosCl/Et₃N in dichloromethane (Chiralpak AS, 250 \times 4.6 mm; eluent heptane/EtOH/Et₂NH, 90/10/0.2, 1.0 mL/min for 20 min) by integration at 258 nm.

human leukocyte elastase inhibitor L-694,458, which was prepared earlier with an enantiomeric ratio of 97/3 via a three-step reaction sequence.¹⁶

Chiral homoallylamines are valuable synthons for the preparation of biologically active components including β -amino carboxylic acids or esters, obtained by oxidation of the allylic functionality.^{1,17} As removal of the chiral auxiliary by hydrogenation leads to the loss of the allylic functionality, we sought alternative routes for the conversion of the adduct into the “free” homoallylamines. Using adduct *(R,R)*-**12** and *(R,R)*-**20** as models, we developed the “retro-

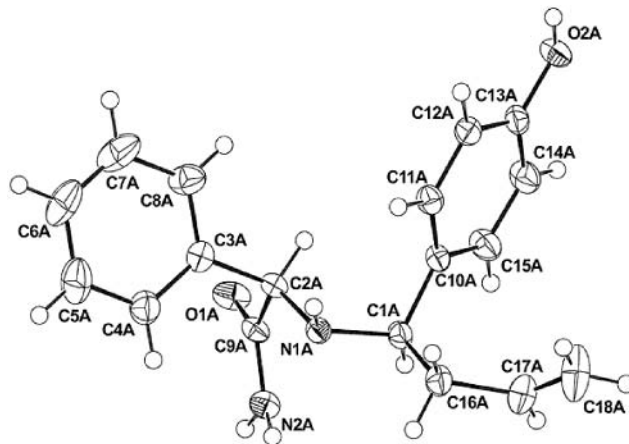
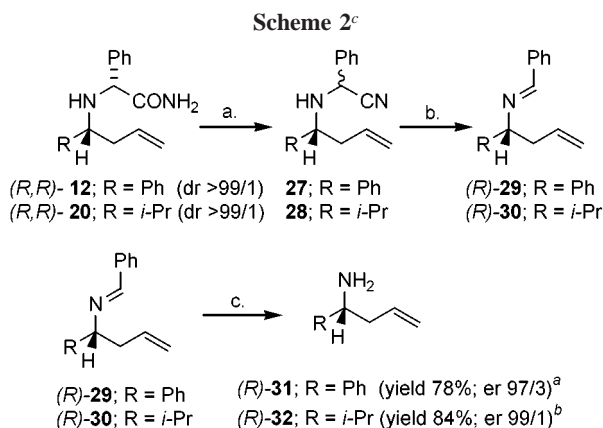


Figure 2. X-ray structure of *(R,R)*-**14**.

Strecker" method for the conversion of phenylacetamide protected homoallylamines into *N*-benzylidene protected homoallylamines (*R*)-**29** and (*R*)-**30**, respectively (Scheme 2).



^a Analysis by HPLC. ^b Analysis by HPLC after tosylation with TosCl/Et₃N in dichloromethane (Chiralpak AS, 250 × 4.6 mm; eluent heptane/EtOH/Et₂NH, 90/10/0.2, 1.0 mL/min for 20 min) by integration at 258 nm. ^c (a) Vilsmeier reagent, CH₂Cl₂, Et₃N (1 equiv), 0 °C to room temperature. (b) K₂CO₃ (2 equiv)/EtOH, reflux, 2 h. (c) NH₂OH·HCl, THF/H₂O, rt, overnight.

The amides were readily converted into the nitrile **27** and **28**, respectively, by dehydration of the amide moiety by the Vilsmeier reagent (ClCH=N(CH₃)₂⁺Cl⁻). Loss of HCN from the crude nitrile occurred on treatment with K₂CO₃ in ethanol to furnish (*R*)-**29** and (*R*)-**30**, respectively.

Acidic hydrolysis is usually the method of choice for the deprotection of benzylidene-protected amines.¹⁸ However, **29** and **30** are rather stable to exposure to aqueous HCl (6

M) at room temperature. At 80 °C in 10% aqueous HCl, the imine is hydrolyzed although aza-Cope rearrangement is a competitive reaction. A more effective method was treatment with hydroxylamine hydrochloride¹⁹ in aqueous THF, whereby (*R*)-**31**^{6b} and (*R*)-**32**²⁰ were obtained, respectively (Scheme 2). The homoallylamines were obtained with an enantiomeric ratio of 97/3 to 99/1 showing that the deprotection sequence proceeds with almost full retention of configuration. The overall yield of the deprotection is 78–84%.

The results presented here establish that (*R*)-phenylglycine amide is an excellent alternative for other chiral auxiliaries used for the preparation of chiral homoallylamines. Alkylation is readily accomplished via relatively cheap allylzinc bromide, and the chiral auxiliary is conveniently removed under either reductive or nonreductive conditions. Obviously, (*S*)-phenylglycine amide is also accessible and can be used for the preparation of the opposite isomer of the described products. Other applications of phenylglycine amide in asymmetric synthesis are under investigation.

Acknowledgment. The authors would like to thank Erik van Echten (Syncom B.V.) and Marc B. van Gelder (University of Groningen) for the HPLC analysis of the chiral amines.

Supporting Information Available: Complete experimental procedures and full characterization data of all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL016840F

(18) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Chemistry*; John Wiley: New York, 1999.

(19) Logers, M.; Overman, L. E.; Welmaker, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 9139.

(20) (a) Curran, D. P.; Gothe, S. A.; Cahoi, S.-M. *Heterocycles* **1993**, *35*, 1371. (b) Murakami, M.; Sugimoto, M.; Fujimoto, K.; Nakamura, H.; Andersson, P. G.; Ito, Y. *J. Am. Chem. Soc.* **1993**, *115*, 6487.