Synthesis and X-ray Crystal Structure of *N,N*-Bis[(*S*)-1-phenylethyl]-(*R,R*)-4,5-diamino-1,7-octadiene

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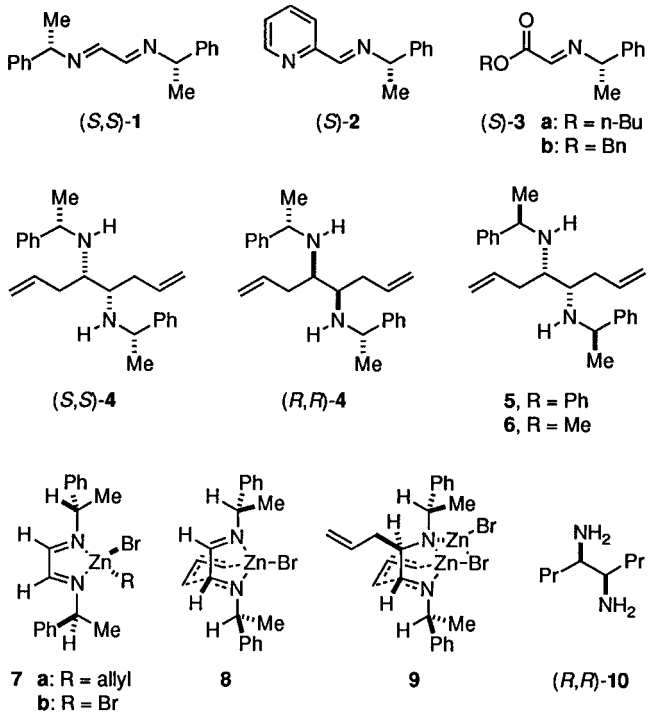
Introduction

The addition of organometallic reagents to the carbon−nitrogen double bond(s) of 1-aza-4-hetero-1,3-dienes **1**−**3** (Chart 1), derived from 1-phenylethylamine, is an attractive method for the preparation of optically active 1,2-diamines,[1] 1-(2-pyridyl)alkylamines,[2] and α-amino acids,[3] respectively. Apart from the reactions of allylboron and -aluminum compounds, which can coordinate only the imine nitrogen atom, the organometallic reactions likely proceed through the preliminary formation of a rigid chelate complex between the 1,4-heterodiene moiety and the metal center. This provides the activation of both the imine double bond and the metal−carbon bond and introduces a constraint that generally improves the stereocontrol with respect to the corresponding reactions of simple unactivated imines.

However, a clear picture of the asymmetric induction operating in these reactions has not been achieved yet. In fact, the addition of allylmagnesium chloride to the bis-imine (*S,S*)-**1** or (*R,R*)-**1** afforded the N,N-disubstituted 4,5-diamino-1,7-octadiene **4** (Chart 1) with good diastereoselectivity, only two of the three diastereomers being produced with 86:14 ratio.[1a] The *S* configuration of the newly formed stereocenters was assumed when using the *S* auxiliary, as shown in (*S,S*)-**4** (for sake of simplicity, we define only the configuration of the newly formed stereocenters). This assumption was based on the results of the addition of allylboron reagents to the imine prepared from (*R*)-1-phenylethylamine and isobutyraldehyde, as well as (*S*)-**3a**, where the *S* auxiliary produced the *S* chirality (*si* face addition), and *vice versa*.[3a,b] However, allyltin trichloride attacked the *re* face of (*S*)-**3a**.[3d] Moreover, the configuration of the product obtained through the addition of 2-(alkoxymethyl)allylzinc bromides to **3b** was not determined.[3c]

We have recently reported on allylmetalation reactions of imines derived from (*S*)-1-phenylethylamine, including (*S*)-**2**, to give (*R*)-α-aryl-substituted homoallylic amines.[2a] Particularly, we observed that allylzinc bromide added to the *re* face of (*S*)−**2** with better diastereoselectivity (dr 87:13) than other allylmetal reagents. Consequently, we predicted the 4*R*,5*R* configuration for the major diastereomer of the diamine **4**.[1a]

Chart 1



Results and Discussion

Herein we describe that allylzinc bromide adds to (*S*)-**1** with increased diastereoselectivity with respect to allylmagnesium chloride, and in both cases the major diastereomer possesses the *R* configuration of the newly formed stereocenters, as shown in (*R,R*)-**4**.

Allylzinc bromide was easily prepared from allyl bromide and zinc powder in THF and was used more conveniently than allylmagnesium chloride, for which the diastereoselectivity was dependent on stringent temperature control (−78 °C) and on the addition rate (syringe-controlled addition). The addition of allylzinc bromide (3 mol equiv) did not require particular care and afforded the amine **4** with excellent yield (GC, 98%; isolated yield, 92%) and a diastereomeric ratio (dr) of 93.5:3:3.5, reported in the order of elution determined by GC−MS analysis of the crude reaction mixture.[4] On the other hand, the addition of allylmagnesium chloride in the same conditions was unsatisfactory (GC, **4**, 92%; dr 65:17:18; unidentified high-boiling byproducts, 8%).

The crude product **4** obtained by the allylzincation reaction was chromatographed to obtain the prevalent diastereomer (>99% pure) with 76% yield. Fortunately, in an alternative attempt for purification, **4** crystallized from diethyl ether in crystals (57% yield) suitable for X-ray structure analysis. The molecular structure in the

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(1) (a) Neumann, W.; Rogic, M. M.; Dunn, T. J. *Tetrahedron Lett.* **1991**, *32*, 5865. (b) Bambridge, K.; Begley, M. J.; Simpkins, N. S. *Tetrahedron Lett.* **1994**, *35*, 3391.

(2) (a) Alvaro, G.; Boga, C.; Savoia, D.; Umani-Ronchi, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 875. (b) Alvaro, G.; Savoia, D.; Valentinetti, M. R. *Tetrahedron* **1996**, *52*, 12571.

(3) (a) Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778. (b) Yamamoto, Y.; Ito, W. *Tetrahedron* **1988**, *44*, 5415. (c) van der Heide, T. A. J.; van der Baan, J. L.; de Kimpe, V.; Bickelhaupt, F.; Klumpp, G. W. *Tetrahedron Lett.* **1993**, *34*, 3309. (d) Hallet, D. J.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1995**, 657.

(4) A minor product (<2% yield) was formed in all the reaction mixtures produced with allylzinc and -magnesium halides in different conditions. GC−MS analysis showed a retention time falling within the range of the three expected diastereomeric products **4** and, surprisingly, the identical mass spectral fragmentation. We suppose that it is a diastereomer of **4** resulting from the diallylation of (*R,S*)-**1**, most likely present in addition to (*S,S*)-**1**, due to the ascertained presence of small amounts of the *R* enantiomer in the starting (*S*)-1-phenylethylamine.

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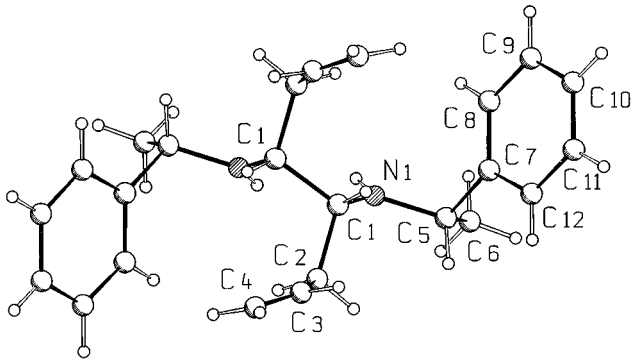

Figure 1. Molecular structure of (*R*,*R*)-**4** in the solid state, showing the labeling scheme. The crystallographic 2-fold axis passes through the C_1-$C_{1'}$ bond and is perpendicular to the plane of the picture. Relevant bond distances (in Å): N_1-C_1, 1.453(3); N_1-C_5, 1.460(3); $C_1-C_{1'}$, 1.531(4); C_1-C_2, 1.537(3); C_2-C_3, 1.446(6); C_3-C_4, 1.158(6) (see the Experimental Section); C_5-C_6, 1.528(6);C_5-C_7 1.502(4).

solid state is depicted in Figure 1, which shows the *R* configuration of the newly created stereocenters.

The diazaoctane chain in between the two methyl carbons C_6 and $C_{6'}$ of the auxiliary groups can be seen as constituted by two equivalent W-type fragments related by a crystallographic 2-fold axis passing through the C_1-$C_{1'}$ bond. The atoms of the chain are almost coplanar (maximum elevation from the average plane 0.28 Å), this resulting in a staggered arrangement of the substituents, i.e., the allyl groups at C_1 and $C_{1'}$ and the phenyl groups at C_5 and $C_{5'}$.

The *R*,*R* configuration of the C_1 and $C_{1'}$ carbon atoms is in agreement with the asymmetric induction observed in the addition of phenylmagnesium chloride to (*R*,*R*)-**1** in Et_2O at −78 °C (*si* face addition), which afforded **5** (Chart 1) with dr 90:10.[1b] The configuration of **5** was established by X-ray structure analysis, and its molecular features are similar to those of (*R*,*R*)-**4**; by analogy, the same stereochemical outcome was reasonably supposed for the preparation of **6** by the addition of methylmagnesium bromide to (*R*,*R*)-**1** (dr 70:30).[1b] Moreover, methyllithium added to the *re* face of (*S*)-**2**, although the *si* face addition mainly occurred with monodentate aromatic imines.[2b] Consequently, at the moment this sense of asymmetric induction (*re* face addition to the (*S*)-imine, and *vice versa*) appears to be general for the reactions of the bidentate imines derived from 1-phenylethylamine, as represented by **1**−**3**, with organometallic reagents capable of chelation.

The same asymmetric induction was also observed in the addition of the zinc enolates of esters and α-amino esters to the imines (*R*,*R*)-**1** and (*R*)-**2**, where the azetidinones were produced with the *S* configuration at C_4.[5] Notably, the reaction of the lithium enolate of methyl phenylacetate with (*R*,*R*)-**1** gave exclusively the N-alkylation product (1,2-diaminoethene) by a SET radical process[5b] that was also operating in the reaction of dialkylzinc compounds with 1,4-diazadienes.[6] The absence of the N-monoallylated product in the crude reaction mixture resulting from the addition of allylzinc bromide to (*S*,*S*)-**1** was assessed by GC−MS and ^{1}H-NMR analysis and pointed against the occurrence of the radical mechanism in the first allylation step.

As in our previous reports on the addition of allyl- and methylmetal reagents to bi- and tridentate imines derived from (*S*)-1-phenylethylamine[2] and methyl (*S*)-valinate,[7] we assume that the 1:1 complex **7a** (Chart 1) is preliminarily formed between (*S*,*S*)-**1** and allylzinc bromide and that the intramolecular nucleophilic transfer of the allyl group to one of the two C=N double bonds occurs through a six-membered cyclic transition state.

By analogy with previous observations on (*S*,*S*)-**2**,[2b] we demonstrated by ^{1}H-NMR spectroscopy and NOE experiments that the most stable conformation of the imine **1** is that in which the two azomethine groups are oriented *anti* to each other, as depicted in Chart 1, but with the H−C=N bond almost eclipsed with the H−C* bond of the auxiliary. In fact, irradiation of the azomethine proton gave a positive NOE response on the H−C* (15%) and Ph (3%) absorptions of the auxiliary. The orientation of the auxiliary was slightly modified by complexing the imine with anhydrous zinc bromide, i.e., in **7b**, as the same NOE experiment gave similar responses on the H−C* (9%) and Ph (6%) absorptions. This suggested that Ph was more inclined toward H−C=N to the detriment of H−C*; therefore, we postulate that in **7b**, and consequently in the organometallic complex **7a**, the methyl in the auxiliary group is approximately *anti* to H−C=N.

The two azomethine groups in **7a** are not equally leaned toward the intramolecular nucleophilic attack; however, they become equivalent by simple interchange of the allyl and bromide substituents at zinc. Considering the different steric properties of the H and Ph substituents of the auxiliary, the transfer of the allyl group will occur to the more accessible azomethine group. The bridged bicyclic transition state **8** (Chart 1) is then proposed for the first carbon−carbon bond-forming step.

A polar mechanism is reasonably assumed in the second allylation step, which is chelation-controlled, since the azomethine group has an α-zincioamido-substituted stereocenter. The *syn* relative configuration of the newly formed stereocenters is expected according to the Cram rule (1,2-asymmetric induction), and the stereocontrol is enforced by the 1,3-asymmetric induction of the auxiliary. In our opinion, (*R*,*R*)-**4** is produced through the bicyclic transition state **9** (Chart 1).

The higher degree of stereocontrol provided by allylzinc bromide with respect to allylmagnesium chloride in this reaction can be attributed to the lower reactivity of the zinc reagent, resulting in a later transition state, and to its higher Lewis acidity. Similarly, allylzinc halides and diallylzinc were preferred to Grignard reagents for the diastereoselective addition to C=O,[8] C=N,[2a,3c,7,9] and C=C groups.[10]

The cleavage of the auxiliary groups of (*R*,*R*)-**4** with concomitant hydrogenation of the C=C double bonds was accomplished by treatment with ammonium formate in the presence of palladium on carbon in methanol to afford the C_2-symmetric diamine (*R*,*R*)-**10** (Chart 1), which was isolated as the dihydrochloride salt in 85% yield.

The synthetic utility of the allylation reaction of the bis-imine **1** is increased by the possibility, only in part explored,[1a] to functionalize the C=C double bonds prior to removing the auxiliary. Moreover, substituted allylic

(5) (a) van der Steen, F. H.; Kleijn, H.; Britovsek, G. P.; Jastrzebski, J. T. B. H.; van Koten, G. *J. Org. Chem.* **1992**, *57*, 3906. (b) Kleijn, H.; van Maanen, L.; Jastrzebski, J. T. B. H.; van Koten, G. *Recl. Trav. Chim. Pay-Bas* **1992**, *111*, 497. (c) van Maanen, H. L.; Kleijn, H.; Jastrzebski, J. T. B. H.; Lakin, M. T.; Spek, A. L.; van Koten, G. *J. Org. Chem.* **1994**, *59*, 7839.

(6) Wissing, E.; Kleijn, H.; Boersma, J.; van Koten, G. *Recl. Trav. Chim. Pay-Bas* **1993**, *112*, 618. In this paper it was asserted that alkylzinc halides instead form stable complexes with 1,4-diazadienes.

(7) (a) Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1542. (b) Basile, T.; Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1994**, *59*, 7766. (c) Alvaro, G.; Savoia, D. *Tetrahedron: Asymmetry* **1996**, *7*, 2083.

zinc reagents, e.g., bearing functional groups that are incompatible with Grignard reagents, can be presumably exploited aiming to prepare structurally more complex molecules.

Experimental Section

General. General methods were described previously.[2a]

***N,N*-Bis-[(*S*)-1-phenylethyl]ethanediimine [(*S,S*)-1]**. The previously reported procedure starting from 40% aq glyoxal can be followed;[11] however, the following method is more convenient. In a dry apparatus, the mixture of glyoxal trimer dihydrate (Aldrich; 1.05 g, 15 mmol), $MgSO_4$ (7 g), and (*S*)-1-phenylethylamine (Fluka; ee ≥ 99%,[4] 3.63 g, 30 mmol) in anhydrous CH_2Cl_2 (30 mL) was stirred in N_2 atmosphere for 5 h and then filtered, and the solution was concentrated at reduced pressure to leave (*S,S*)-**1** as an oil: 3.96 g, 100% yield; $[\alpha]^{20}_D = -152$ (*c* 2.26, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (s, 2), 7.38−7.24 (m, 10), 4.53 (q, J = 6.7 Hz, 2), 1.60 (d, J = 6.7 Hz, 6); by irradiating at δ 8.07 (CH=N) positive NOE on the absorption at δ 7.35 (Ph, 3%) and 4.53 (C*H*Me, 15%) were observed; ^{13}C NMR ($CDCl_3$, 200 MHz) δ 160.6, 143.5, 128.5, 127.2, 126.6, 69.6, 23.9.

Complex 7b. To the solution of (*S,S*)-**1** (0.264 g, 1 mmol) in $CDCl_3$ (2 mL) was added anhydrous $ZnBr_2$ (0.225 g, 1 mmol), and the mixture was stirred until complete dissolution. A sample was analyzed by ^{1}H-NMR spectroscopy (200 MHz): δ 8.03 (s, 2), 7.40−7.23 (m, 10), 5.14 (q, J = 7 Hz, 2), 1.92 (d, J = 7 Hz, 6); by irradiating at δ 8.03 (CH=N) positive NOE at δ 7.37 (Ph, 6%) and 5.14 (C*H*Me, 9%) were observed; ^{13}C NMR ($CDCl_3$, 200 MHz) δ 157.1, 138.2, 129.2, 128.9, 128.0, 66.3, 22.2.

***N,N*-Bis[(*S*)-1-phenylethyl]-(*R,R*)-4,5-diamino-1,7-octadiene [(*R,R*)-4]**. Zinc powder (1.30 g, 20 mmol, previously heated for 5 min at 150 °C while stirring with a magnetic bar in N_2 atmosphere and then cooled to room temperature) was covered with anhydrous THF (15 mL). Freshly distilled allyl bromide (1.81 g, 15 mmol) was added, and the mixture was stirred for 2 h. Stirring was stopped, and excess zinc powder was allowed to deposit on the bottom of the flask; then the clear solution of allylzinc bromide was taken by a syringe and poured slowly (10 min) onto the stirred solution of (*S,S*)-**1** (1.32 g, 5 mmol) in anhydrous THF (15 mL) cooled at −78 °C. The mixture was stirred for a further 1.5 h; then the reaction was quenched with a solution obtained by mixing 1 M NH_4Cl (5 mL) and 30% NH_4OH (5 mL). The organic phase was separated, and the aqueous phase was extracted with Et_2O (20 mL × 3); the collected organic layers were dried over Na_2SO_4, filtered, and concentrated to leave **4** as a crystalline solid (1.60 g, 92%); high purity was assessed by ^{1}H NMR and GC−MS analysis, the latter indicating dr 93.5:3:3.5. The main diastereomer (*R,R*)-**4** was obtained pure with 76% yield by chromatography on a SiO_2 column (cyclohexane/ethyl acetate, 85:15) or by crystallization of the crude product from Et_2O. The latter procedure allowed to obtain with 57% yield crystals suitable for X-ray structure analysis: mp 68−70 °C; $[\alpha]^{20}_D = -126.8$ (*c* 2.04, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (m, 10), 5.46−5.35 (m, 2), 4.84−4.67 (m, 4), 3.74 (q, J = 6.6 Hz, 2), 2.22−2.03 (m, 6), 1.50 (br, 2), 1.26 (d, J = 6.6 Hz, 6); ^{13}C NMR (300 MHz, $CDCl_3$) δ 146.4, 136.4, 128.2, 127.1, 126.7, 116.3, 56.6, 56.0, 35.0, 25.1; GC−MS *m/z* (relative intensity) 105 (100), 174 (97), 70 (60), 307 (6). (*R,R*)-**4** corresponds to the previously prepared diastereomer of **4**, having $[\alpha]^{19.5}_D = -120$ (*c* 0.023, CH_2Cl_2), to which the wrong configuration was assigned.[1a]

Crystal Structure Determination of (*R,R*)-4. Diffraction intensities for compound (*R,R*)-**4** were collected at room temperature on an Enraf-Nonius CAD-4 diffractometer equipped with a graphite monochromator (Mo Kα radiation, l = 0.710 73 Å). The intensities were reduced to F_o^2, and the structure was solved by direct methods followed by difference Fourier and subsequent full-matrix least-squares refinement using the computer programs SHELX86[12a] and SHELXL92.[12b] All non-H atoms were allowed to vibrate anisotropically. The H atoms were added in calculated positions and refined riding on their respective carbon atoms. Results of thermal motion analysis[12c] showed that, on top of rigid-body libration of the whole molecule around an axis almost parallel to the cell α-axis, the C_3-C_4 group (numbering according to Figure 1) experiences a very large additional librational motion around the C_1-C_2 bond, both facts being responsible for the poorly resolved C_3-C_4 double-bond distance. SCHAKAL9[12d] was used for the graphical representation of the results. Crystal data and details of measurement: monoclinic, *C*2; a = 21.870(4), b = 6.675(4), c = 7.726(4) Å; β = 97.68(3)°, Z = 2, V = 1117.7(9) Å^3; ρ_{calcd} = 1.036 mg m^{-3}, 2θ-range = 2.5−25.0°; 2062 measured reflections, 1822 independent reflections used in the refinement, 119 refined parameters; $R1$ [$I > 2\sigma(I)$] = 0.0598, $R2_w$ (all data) = 0.1819. Tables of crystal data, atomic coordinates, and bond distances and angles have been deposited with the Cambridge Crystallographic Data Centre.[14]

(*R,R*)-4,5-Diaminooctane [(*R,R*)-10]. To the solution of the diamine (*R,R*)-**4** (1.05 g, 3 mmol) in anhydrous methanol (60 mL) were added Pd/C (0.06 g) and ammonium formate (1.14 g, 18 mmol). The mixture was magnetically stirred at reflux temperature for 2 h. After cooling, the reaction mixture was filtered and the solvent evaporated at reduced pressure to leave an oil (0.500 g), containing the diamine (*R,R*)-**10** and some ethylbenzene. To the mixture were added methanol (5 mL) and 37% hydrochloric acid (0.5 mL, 6 mmol). Benzene (10 mL) and methanol (10 mL) were added, then the solvents were removed at reduced pressure, and the operation was repeated twice. The residue was recrystallized from chloroform to give (*R,R*)-**10**·2HCl (0.550 g, 85%): mp 194−5 °C (lit.[13] mp 218−220 °C) (*d,l*); $[\alpha]^{20}_D = +31.4$ (*c* 2.04, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 3.46 (m, 2), 1.50 (m, 4), 1.39−1.14 (m, 8), 0.78 (t, 6); ^{13}C NMR (300 MHz, D_2O, MeOH as internal standard) δ 52.2, 28.9, 18.3, 12.9.

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Supporting Information Available: Crystal data and details of measurement, ORTEP drawing, tables of atomic coordinates, bond angles and distances, and anisotropic thermal parameters for (*R,R*)-**4** (6 pages). 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.

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(8) (a) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (b) Fronza, G.; Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G.; Zirotti, C. *Tetrahedron Lett.* **1982**, *23*, 4143. (c) Mulzer, J.; Angermann, A. *Tetrahedron Lett.* **1983**, *24*, 2843. (d) Fuganti, C.; Servi, S.; Zirotti, C. *Tetrahedron Lett.* **1983**, *24*, 5285. (e) Tamao, K.; Nakajo, E.; Ito, Y. *J. Org. Chem.* **1987**, *52*, 957. (f) Overly, K. R.; Williams, J. M.; McGarvey, G. J. *Tetrahedron Lett.* **1990**, *31*, 4573. (g) Taniguchi, M.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 645.

(9) (a) Dembélé, Y. A.; Belaud, C.; Hitchcock, P.; Villiéras, J. *Tetrahedron*: *Asymmetry* **1992**, *3*, 351. (b) Dembélé, Y. A.; Belaud, C.; Villiéras, J. *Tetrahedron*: *Asymmetry* **1992**, *3*, 511.

(10) (a) Kubota, K.; Nakamura, M.; Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1993**, *115*, 5867. (b) Nakamura, M.; Arai, M.; Nakamura, E. *J. Am. Chem. Soc.* **1995**, *117*, 1179. (c) Beruben, D.; Marek, I.; Normant, J.-F.; Platzer, N. *J. Org. Chem.* **1995**, *60*, 2488. (d) van der Baan, J. L.; van der Heide, T. A. J. ; van der Louw, J.; Klumpp, G. W. *Synlett* **1995**, 1.

(11) tom Dieck, H.; Dietrich, J. *Chem. Ber.* **1984**, *117*, 694.

(12) (a) Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467. (b) Sheldrick, G. M. *SHELXL92, Program for Crystal Structure Determination*; University of Göttingen: Göttingen, Germany, 1993. (c) Trueblood, K. N. *THMA11, Thermal motion analysis computer program*; University of California: Los Angeles, CA, 1990. (d) Keller, E. *SCHAKAL92, Graphical Representation of Molecular Models*; University of Freiburg: Germany, 1992.

(13) Jung, S.-H.; Kohn, H. *J. Am. Chem. Soc.* **1985**, *107*, 2931.

(14) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.