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Synthesis, structure, and stereochemistry of the bora derivatives of 1-[(2-hydroxy-1-naphthyl)methyl]proline

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Abstract—Novel chiral bora derivatives of 1-[(2-hydroxy-1-naphthyl)-methyl]proline have been synthesized in over 98% diastereoselectivity. Their structures and stereochemistry were elucidated by means of 2D NMR spectra as well as quantum-mechanical calculation.

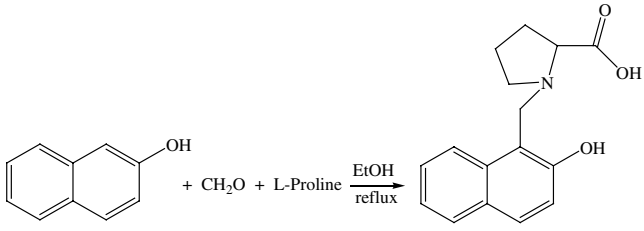
1. Introduction

Presently, boro organic compounds play a significant role in chemistry and are frequently employed for the preparation of optically active drugs and in other applications in modern organic synthesis.[1–4] The acidity of the boron atom causes its interactions with heteroatoms possessing lone pairs. This results in coordination between the boron atom and its partner, which is particularly strong in the case of a nitrogen atom, and makes it possible to form many interesting heterocyclic compounds.[5–9] Such a coordination changes the physicochemical properties and structures of the constituent ligands. Many examples of this with biologically significant molecules have already been reviewed.[10]

Herein, we report the synthesis, structure, and stereochemistry of novel bora derivatives of 1-[(2-hydroxy-1-naphthyl)methyl]proline **1**. Compound **1** was synthesized via a Mannich reaction of β-naphthol, formaldehyde, and L-proline (Scheme 1) in 80% yield, by refluxing the reaction mixture in ethanol.

2. Results and discussion

The thus formed tridentate ligand **1** having both a hydroxy group and carboxy group as well as a lone electron pair at the nitrogen atom was subjected to 'clipping' with the selected boron compounds $R_1R_2R_3B$ shown in



Scheme 1.

Table 1 with the resulting products of this reaction shown in Scheme 2.

Table 1.

	R_1	R_2	R_3
a	OH	OH	Ph
b	OH	OH	3-Cl-C_6H_5
c	OH	OH	3,5-Br_2-C_6H_4
d	OH	OH	OH
e	OMe	OMe	OMe

In the case of phenylboronic acid derivatives, toluene was used as a solvent, which made it possible to remove water formed during the reaction azeotropically. In the case of the oxygen compounds of boron, acetonitrile was used. In all cases, the diastereoselectivity was greater than 98%. The yields of particular products and their physicochemical data are summarized in Table 2.

During the reaction apart from the stereogenic center present at L-proline, new stereogenic centers are

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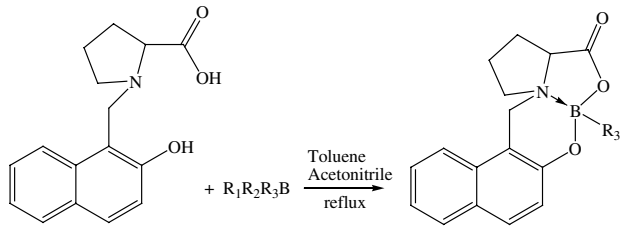

Scheme 2.

Table 2. The yields of the products **2a**–**e**, and their physicochemical data

Product	Yield (%)	Melting point (°C)	Specific rotation
2a	87	205–207	−61.0 (*c* 1.72, $CHCl_3$)
2b	90	265–267	−25.0 (*c* 0.35, CH_2Cl_2)
2c	89	274–275	−49.7 (*c* 0.63, CH_2Cl_2)
2d	80	223–225	−126.73 (0.32, DMSO)
2e	75	187–188	−168.40 (1.66, $CHCl_3$)

generated at the boron and nitrogen atoms. Theoretically, this may lead to formation of four diastereoisomers having the following stereogenic centers: (1) C(*S*)–N(*S*)–B(*S*); (2) C(*S*)–N(*S*)–B(*R*); (3) C(*S*)–N(*R*)–B(*S*); (4) C(*S*)–N(*R*)–B(*R*). However, as mentioned above, the reaction is highly diastereoselective. In order to determine, which one of these diastereoisomers is formed in this reaction, we performed quantum-mechanical calculations of the enthalpy of formation of particular diastereoisomers for all products **2**, using the AM1 semiempirical method.[11] The calculation results are presented in Table 3.

The calculation results demonstrate that the C(*S*)–N(*S*)–B(*S*) configuration results in the most stable diastereoisomers of products **2a**–**c**. The most stable configuration for the products **2d**–**e** was C(*S*)–N(*S*)–B(*R*). In order to ascertain the actual structure of the obtained products, the 2D NMR (^1H–^1H COSY, ^1H–^1H NOESY) spectra were recorded for all products **2** and compared with the results of the quantum-mechanical calculation. Figure 1 shows a fragment of the NOESY spectrum for **2a** and the interactions through space between the closely located protons: H_1–H_8, H_6–H_7, H_6–H_8. Analysis of the spatial arrangement for all four theoretically possible diastereoisomers indicates that the observed interactions between protons exist only in the configuration C(*S*)–N(*S*)–B(*S*). This conclusion is in full agreement with our quantum-mechanical calculation results, which suggest that the diastereoisomer that has the C(*S*)–N(*S*)–B(*S*) configuration is the energetically most stable.

From the results in Table 3, the most stable diastereoisomers of **2d** and **2e** have the C(*S*)–N(*S*)–B(*R*) configuration. These results are confirmed by the analysis of the NOESY spectrum for **2d** (see Fig. 2). The following protons interact through the space: H_1–H_8, H_6–H_7, H_6–H_8. Analysis of the spatial arrangement for all four possible diastereoisomers indicates that the observed interactions between protons exist only in the configuration C(*S*)–N(*S*)–B(*R*).

3. Conclusion

In conclusion, the coordination of 1-[(2-hydroxy-1-naphthyl)methyl]proline with boron compounds proceeds with high diastereoselectivity. Based on the analysis of two-dimensional NMR spectra as well as the results of quantum-mechanical calculation, we have demonstrated that, in the cases of the derivatives of phenylboronic acids **2a**–**c**, the reaction leads to formation of the diastereoisomers having the following C(*S*)–N(*S*)–B(*S*) configuration. In the cases of using trimethoxyborane and boronic acid, one obtains the diastereoisomers, which had the stereogenic centers of the C(*S*)–N(*S*)–B(*R*) configuration were obtained.

4. Experimental

^1H and ^{13}C NMR spectra were recorded with a Bruker AC 400 (400 MHz). Melting points were determined with a Büchi B-540 melting point apparatus and are uncorrected. Reagents and solvents were obtained from Fluka and Merck and used as received. Chromatographic separations were performed on a Silica Gel 60 (Merck, particle size 0.040–0.063 mm, 230–240 mesh).

4.1. 1-[(2-Hydroxy-1-naphthyl)methyl]proline 1

A mixture of 42 mmol (6.0 g) of β-naphthol and 42 mmol (4.8 g) of L-proline was heated in 120 ml of ethanol after which 46 mmol (2.4 g) of formaldehyde was added. The reaction mixture was gently refluxed overnight and then a white precipitate formed, which was filtered off and thoroughly washed with ethanol. ^1H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 1.69 (m, 1H, H5), 1.86 (m, 1H, H4), 1.94 (m, 1H, H3), 2.26 (m, 1H, H2), 2.87 (k, J = 8.0 Hz, 1H, H7), 3.16 (m, 1H, H6), 3.67

Table 3. AM1 quantum-mechanical calculation of the enthalpy of formation of all theoretically possible diastereoisomeric products **2**

Product	Enthalpy of formation (kcal/mol)			
	C(*S*)–N(*R*)–B(*R*)	C(*S*)–N(*R*)–B(*S*)	C(*S*)–N(*S*)–B(*R*)	C(*S*)–N(*S*)–B(*S*)
2a	−59.8345078	—[a]	−62.9492928	**−79.0107190**
2b	−67.4288195	—[a]	−72.1717550	**−89.0900865**
2c	−50.1262125	—[a]	−55.1010650	**−72.0074449**
2d	—[a]	−169.9676326	**−191.6246427**	−177.7995619
2e	—[a]	−155.8165960	**−178.6960419**	−165.5137471

[a] Labile structures, which transformed into other diastereoisomers during the calculation.

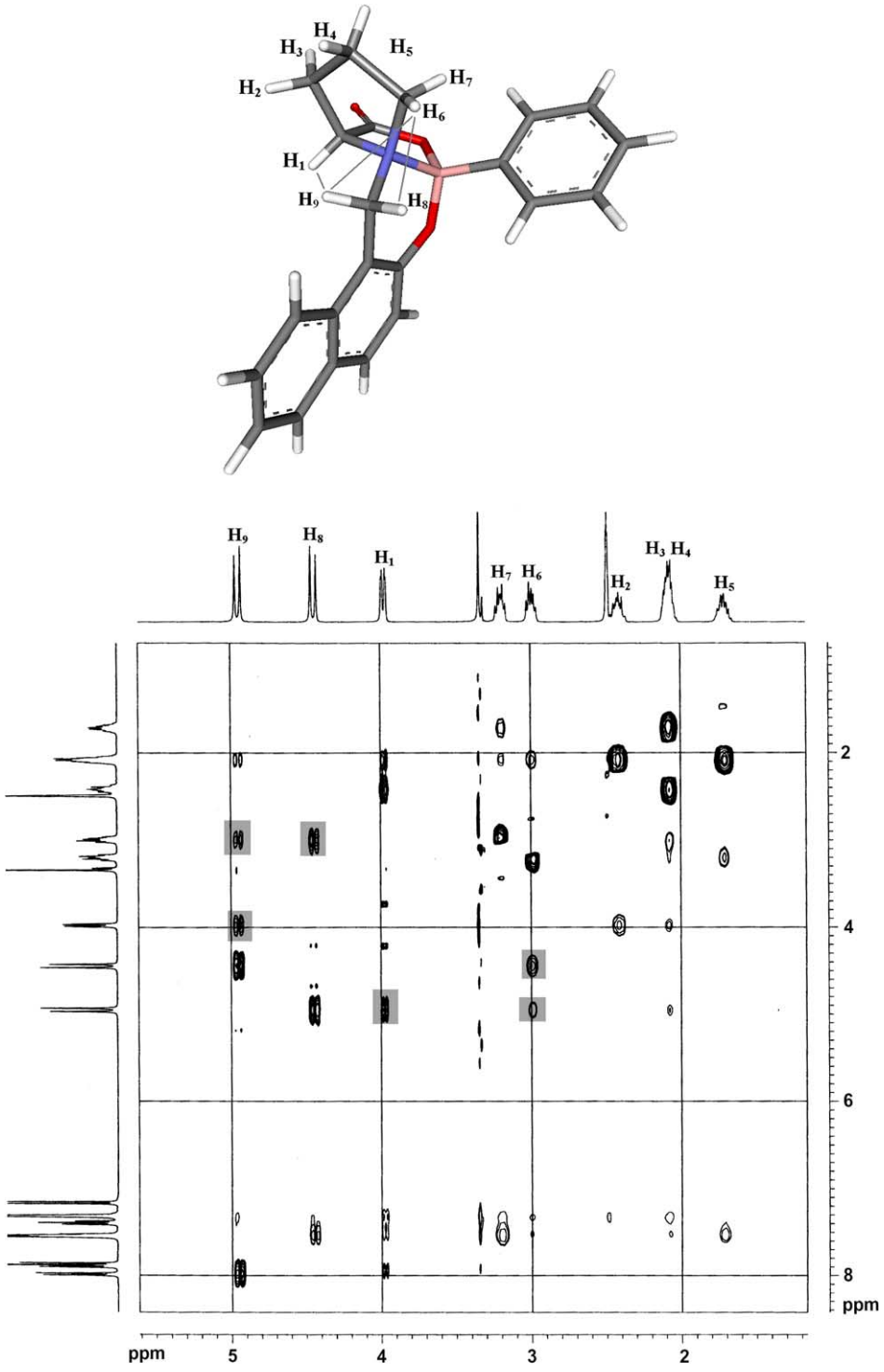

Figure 1. Fragment of the ^{1}H–^{1}H NOESY spectrum for the product **2a** in DMSO-d_6. The proton couplings are marked. The drawing at the top shows the structure of product **2a** corresponding to the diastereoisomer having the C(*S*)–N(*S*)–B(*S*) configuration. Labels denote the numbering of the interacting protons.

(dd, J = 8.0, 4.0 Hz, 1H, H1), 4.48 (d, J = 16.0 Hz, 1H, H8), 4.55 (d, J = 12.0 Hz, 1H, H9), 7.19 (m, 1H, ArH), 7.31 (m, 1H, ArH), 7.48 (m, 1H, ArH), 7.80 (m, 2H, ArH), 8.20 (m, 1H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C): 23.05, 28.57, 38.90, 39.11, 39.32, 39.53, 39.74, 39.95, 39.99, 40.15, 48.98, 48.99, 53.00, 67.28, 118.21, 122.41, 122.65, 126.83, 127.92, 128.45, 130.30, 133.25, 155.20, 155.22, 171.52.

4.2. The general method of the preparation of bora derivatives 2a–e

A mixture of 3.7 mmol of 1-[(2-hydroxy-1-naphthyl)methyl]proline **1** and 4.1 mmol of the corresponding derivative of phenylboronic acid was heated in 50 ml of dry toluene. The reaction mixture was refluxed for 4 h. After approximately 1 h, a white precipitate was

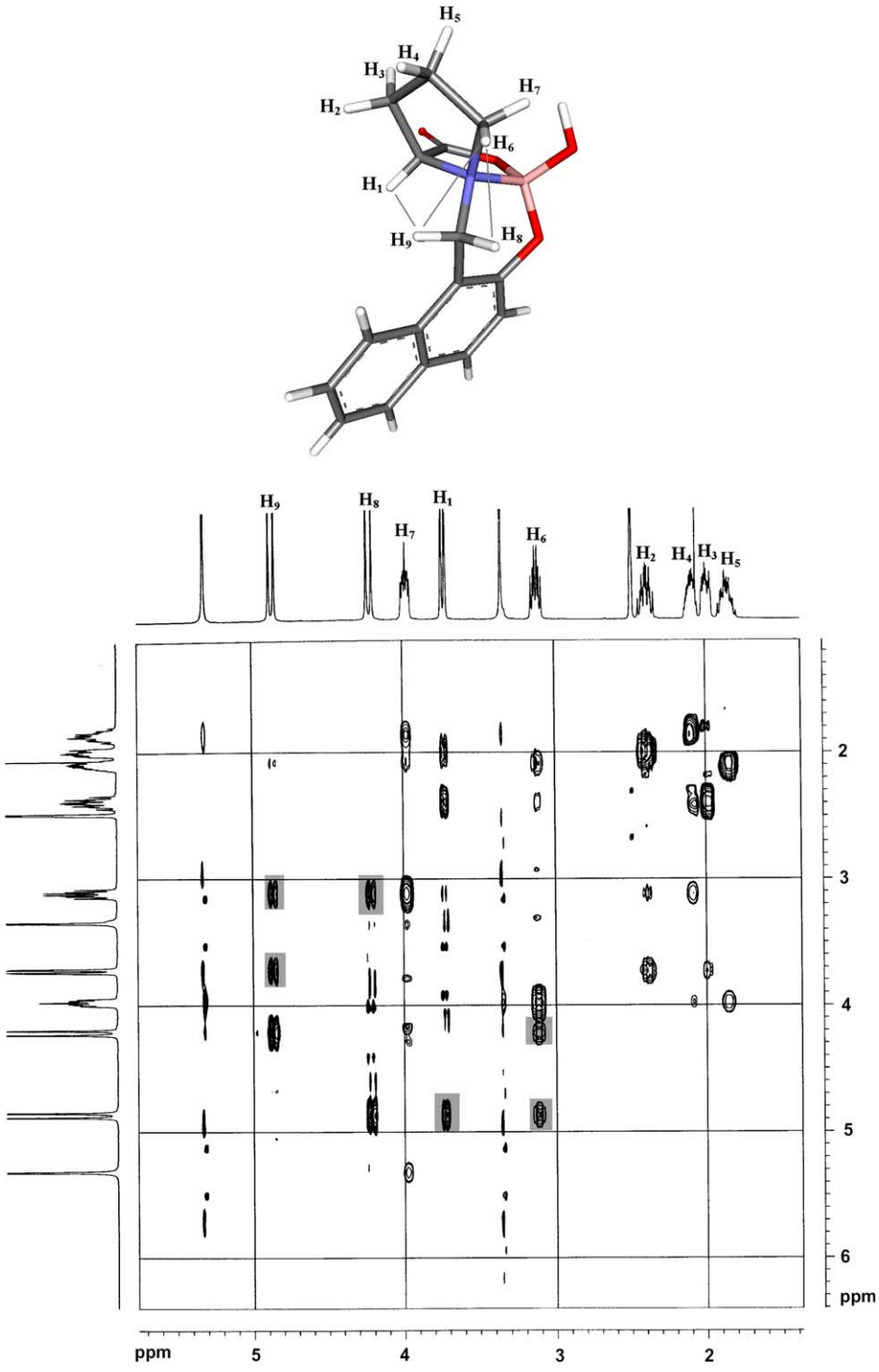

Figure 2. Fragment of the ^{1}H–^{1}H NOESY spectrum for product **2d** in DMSO-d_6. The proton couplings are marked. The drawing at the top shows the structure of product **2d** corresponding to the diastereoisomer having the configuration C(*S*)–N(*S*)–B(*R*). Labels denote numbering of the interacting protons.

formed. Following cooling, the precipitate was filtered off and purified by crystallization. In the cases of using trimethoxyborane and boric acid, the reaction was carried out in acetonitrile, and the reaction mixture was refluxed for 4 h.

4.2.1. Compound 2a. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.71 (m, 1H, H5), 2.08 (m, 1H, H4), 2.42 (m, 1H, H3), 2.49 (t, J = 1.66 Hz, 1H, H2), 2.99 (m, 1H, H7), 3.20 (m, 1H, H6), 3.98 (dd, J = 2.36, 9.65 Hz, 1H, H1), 4.44 (d, J = 14.63 Hz, 1H, H8), 4.95 (d, J = 14.66 Hz, 1H, H9), 7.16 (d, J = 8.79 Hz, 1H, ArH), 7.31 (m, 3H, ArH), 7.39 (t, J = 7.44 Hz, 1H, ArH), 7.54 (m, 3H, ArH), 7.89 (m, 2H, ArH), 7.99 (d, J = 8.48 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C): δ = 23.56, 27.55, 52.49, 60.73, 68.29, 111.74, 121.79, 123.75, 127.20, 127.82, 128.46, 128.84, 128.95, 130.57, 131.85, 132.47, 153.93, 173.68.

4.2.2. Compound 2b. Crystallized from a mixture of acetone–ethyl acetate: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.96 (m, 1H, H5), 2.08 (m, 1H, H4), 2.30 (m, 1H, H3), 2.46 (m, 1H, H2), 2.80 (m, 1H, H7), 3.38 (m, 1H, H6), 3.99 (dd, J = 2.82, 12 Hz, 1H, H1), 4.44 (d, J = 13.28 Hz, 1H, H8), 4.55 (d, J = 13.81 Hz, 1H, H9), 7.25 (m, 3H, ArH), 7.39 (m, 1H, ArH), 7.54 (m, 2H, ArH), 7.680 (m, 2H, ArH), 7.85 (m, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C): δ = 23.46, 27.01, 52.66, 60.48, 67.40, 109.37, 119.24, 120.82, 123.44, 127.11, 128.58, 129.15, 129.19, 130.04, 131.08, 131.98, 134.08, 154.12, 172.49.

4.2.3. Compound 2c. Crystallized from a mixture of acetone–ethyl acetate: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.96 (m, 1H, H5), 2.13 (m, 1H, H4), 2.30 (m, 1H, H3), 2.42 (m, 1H, H2), 2.94 (q, J = 7.5 Hz, 1H, H7), 3.36 (dt, J = 7.5 Hz, 1H, H6), 3.97 (dd, J = 3.13, 12.00 Hz, H1), 4.42 (d, J = 12.0 Hz, 1H, H8), 4.58 (d, J = 16.0 Hz, 1H, H9) 7.25 (m, 1H, ArH), 7.43 (m, 1H, ArH), 7.54 (m, 1H, ArH), 7.66 (m, 2H, ArH), 7.75 (m, 2H, ArH), 7.85 (m, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C): δ = 23.82, 27.23, 52.91, 60.81, 67.67, 109.75, 119.50, 120.90, 123.32, 123.84, 127.46, 129.22, 129.40, 131.29, 131.52, 133.77, 134.20, 154.13, 172.36.

4.2.4. Compound 2d. Purified via column chromatography using ethyl acetate–hexane as an eluent: ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 1.87 (m, 1H, H5), 2.00 (m, 1H, H4), 2.15 (m, 1H, H3), 2.39 (m, 1H, H2), 3.16 (m, 1H, H7), 3.35 (s, 1H, OH), 3.73 (dd, J = 2.54, 9.81 Hz, 1H, H1), 3.98 (m, 1H, H6), 4.22 (d, J = 13.89 Hz, 1H, H8), 4.87 (d, J = 13.92 Hz, 1H, H9), 7.12 (d, J = 8.77 Hz, 1H, ArH), 7.37 (m, 1H, ArH), 7.52 (m, 1H, ArH), 7.85 (m, 2H, ArH), 8.02 (d, J = 9.37 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C): δ = 24.12, 28.76, 52.65, 58.56, 68.45, 113.51, 120.30, 121.48, 123.35, 126.77, 128.57, 130.15, 131.45, 154.25, 171.92.

4.2.5. Compound 2e. Purified via column chromatography using acetone–ethyl acetate as an eluent: ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 1.83 (m, 1H, H5), 1.99 (m, 1H, H4), 2.16 (m, 1H, H3), 2.39 (t, J = 1.66 Hz, 1H, H2), 3.21 (m, 1H, H7), 3.34 (m, 1H, H6), 3.46 (s, 1H, OH), 3.84 (m, 1H, H1), 4.36 (d, J = 14.00 Hz, 1H, H8), 4.90 (d, J = 14.00 Hz, 1H, H9), 7.17 (d, J = 8.40 Hz, 1H, ArH), 7.38 (m, 1H, ArH), 7.53 (t, J = 7.20 Hz, 1H, ArH), 7.87 (m, 2H, ArH), 8.01 (d, J = 8.40 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C): δ = 6.72, 21.38, 24.25, 49.91, 66.05, 107.88, 118.64, 119.396, 121.21, 124.82, 126.25, 126.65, 127.90, 129.57, 151.33, 171.57.

Acknowledgments

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References

1. Brown, H.; Zaidlewicz, M. *Organic Synthesis Via Boranes, Vol. 2. Recent Developments;* Aldrich Chemical Company, 2001.
2. Abel, E. W.; Stone, F. G. A. *Comprehensive Organometallic Chemistry II: Main-Group Metal Organometallics in Organic Synthesis*; Elsevier Science: Oxford, 1995.
3. *Houben–Weyl Methods of Organic Chemistry, E21: Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme Verlag: Stuttgart, 1996.
4. (a) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986; (b) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650.
5. Woodgate, P. D.; Horner, G. M.; Maynard, N. P.; Rickard, E. R. *J. Organomet. Chem.* **2000**, *595*, 215.
6. Thormeier, S.; Carboni, B.; Kaufmann, D. E. *J. Organomet. Chem.* **2002**, *657*, 136.
7. Farfan, N.; Haepl, H.; Barba, V.; Ochoa, M. E.; Santillan, R.; Gomez, E.; Gutierrez, A. *J. Organomet. Chem.* **1999**, *581*, 70.
8. Sanchez, M.; Sanches, O.; Haepl, H.; Ochoa, M. E.; Castillo, D.; Farfan, N.; Rojas-Lima, S. *J. Organomet. Chem.* **2004**, *689*, 811.
9. Sanchez, M.; Sanches, O.; Haepl, H.; Ochoa, M. E.; Farfan, N.; Santillan, R.; Rojas-Lima, S. *Chem. Eur. J.* **2002**, *6*, 612.
10. Flores-Rosa, A.; Contreras, R. *Coord. Chem. Rev.* **2000**, *196*, 85.
11. *HyperChem 5.0*, Hypercube Inc, 115 NW 4th Street, Gainville, FL, USA.