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# Efficient Synthesis of α-Aryl-/Heteroaryl-Substituted β-Amino Acids via Ni(II) Complex through the Suzuki Coupling Reaction

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*Received March 4, 2009*

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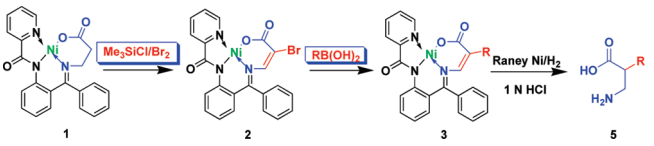
Published on June 10, 2009 on http://pubs.acs.org | doi: 10.1021/jo900469d




We described a synthesis method by first using chlorotrimethylsilane as the activator to brominate the Ni(II) complex of the β-alanine Schiff's base [β-AlaNi(II)-PABA] **1** and developed it to prepare β-amino acids **5**. The procedure involves a Suzuki coupling reaction between boric acids and the bromoenone **2**, followed by hydrogenation and hydrolysis. This is the first report of the application of the Ni (II) complex [β-AlaNi(II)-PABA], which represents an attractive route to afford α-aryl-/heteroaryl-substituted β-amino acids.

α-Substituted β-amino acids ($\beta^2$-amino acids) are important structural motifs in many natural products and medicinal agents.[1] They have also been shown to display interesting structural effects as constituents of β-peptides.[2] Therefore, a number of potential methods have been developed for the synthesis of these compounds. To date, the Mannich reaction[3] and the alkylation of β-alanine derivatives[4] have received the most attention as synthetic routes to $\beta^2$-amino acids; other routes such as Arndt−Eistert homologation,[5] conjugate additions,[6] Curtius rearrangement,[7] and reduction of unsaturated esters or nitriles[8] have also been reported. However, to our knowledge, only a few examples of the synthesis of α-aryl or heteroaryl β-amino acids were reported in the literature. Huw et al.[9] reported an intermolecular C−H insertion of substituted carbenoids catalyzed by [$Rh_2$(S-DOSP)$_4$] to synthesize α-aryl β-amino acids. Akkari et al.[10] used (*S*)-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)acetic acid as a solid-phase protocol for the preparation of amino acids. Beddow[6] reported a conjugate addition of lithium dibenzylamide to (*S*)-*N*-acryloyl-4-isopropyl-5,5-dimethyloxazolidin-2-one and alkylation of the resulting lithium β-amino enolate affords various β-amino acids. Recently, Martin et al.[11] described an approach for α-aryl-substituted β-amino acids via hydrogenation of β-nitro esters, which were prepared from a catalytic asymmetric conjugate reduction. Though all these efforts have been made, development of a synthesis method that is both practical and efficient remains a challenge in synthetic chemistry.

Recently, the applications of the Ni(II) complex of the glycine Schiff's base for the synthesis of α-amino acid derivatives have received much attention.[12,13] In addition, we have previously[14] demonstrated a convenient one-pot, two-step protocol to generate novel nucleophilic β-alanine equivalent 2-[*N*-(α-picolyl)amino]benzophenone (PABA) derived Ni(II) complex [β-AlaNi(II)PABA] **1**. It features attractive physicochemical characteristics such as excellent solubility in many organic solvents and good crystallinity

(1) (a) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991–8035. (b) Trimurtula, G.; Ohtani, I.; Patterson, G. M. L.; Moore, R. E.; Corbett, T. H.; Valeroite, F. A.; Demchik, L. *J. Am. Chem. Soc.* **1994**, *116*, 4729–4737. (c) Shih, C.; Gossett, L. S.; Gruber, J. M.; Grossman, C. S.; Andis, S. L.; Schulz, R. M.; Worzalla, J. F.; Corbett, T. H.; Metz, J. T. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 69–74. (d) Schmidt, J.; Langner, J. *Chem. Commun.* **1994**, 2381–2382. (e) Pratt, L. M.; Beckett, R. P.; Davies, S. J.; Launchbury, S. B.; Miller, A.; Spavold, Z. M.; Todd, R. S.; Whittaker, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2585–2588.

(2) (a) Hintermann, T.; Seebach, D. *Synlett* **1997**, *5*, 437–438. (b) Juan, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1595–1597.

(3) (a) Davis, F. A.; Szewczyk, J. M.; Reddy, R. E. *J. Org. Chem.* **1996**, *61*, 2222–2225. (b) Davis, F. A.; Reddy, G. V.; Liang, C. H. *Tetrahedron Lett.* **1997**, *38*, 5139–5142. (c) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12–13. (d) Coídova, A.; Watanabe, S. I.; Tanaka, F.; Notz, W.; Barbas, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1866–1867. (e) Christopher, J.; Rhonda, L.; Dennis, C. *J. Org. Chem.* **2008**, *73*, 1264–1269.

(4) (a) Gutiêrrez-Garcîa, V. M.; Lòpez-Ruiz, H.; Reyes-Rangel, G.; Juaristi, E. *Tetrahedron* **2001**, *57*, 6487–6496. (b) Tessier, A.; Lahmar, N.; Pytkowicz, J.; Brigaud, T. *J. Org. Chem.* **2008**, *73*, 3970–3973.

(5) Yang, H.; Foster, K.; Stephenson, C. R. J.; Brown, W.; Roberts, E. *Org. Lett.* **2000**, *2*, 2177–2179.

(6) Beddow, J. E.; Davies, S. G.; Ling, K. B.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 2812.

(7) Sibi, M. P.; Deshpande, P. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1461–1466.

(8) Jun, D.; Xiang, H.; Jia, H.; Sai, Y.; Dao, W.; Zheng, D.; Zhuo, Z. *J. Org. Chem.* **2008**, *73*, 2015–2017.

(9) Huw, M. L. D.; Chandrasekar, V. *Angew. Chem., Int. Ed.* **2002**, *41*, 2197–2199.

(10) Akkari, R.; Calmes, M.; Di Malta, D.; Escale, F.; Martinez, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1223.

(11) Martin, N. J. A.; Cheng, X.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 13862–13863.

(12) (a) Tararov, V. I.; Savel'eva, T. F.; Kuznetsov, N. Y.; Ikonnikov, N. S.; Orlova, S. A.; Belokon, Y. N.; North, M. *Tetrahedron: Asymmetry* **1997**, *8*, 79–83. (b) Xu, P. F.; Chen, Y. S.; Lin, S. I.; Lu, T. J. *J. Org. Chem.* **2002**, *66*, 2309–2314.

(13) (a) Belokon, Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Larionov, O. V.; Harutyunyan, S. R.; Vyskocil, S.; North, M.; Kagan, H. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 1948–1951. (b) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *J. Org. Chem.* **2000**, *65*, 6688–6696. (c) Ellis, T. K.; Martin, C. H.; Ueki, H.; Soloshonok, V. A. *Tetrahedron Lett.* **2003**, *44*, 1063–1066.

(14) (a) Deng, G.; Wang, J.; Zhou, Y.; Jiang, H.; Liu, H. *J. Org. Chem.* **2007**, *72*, 8932–8934. (b) Wang, J.; Shi, T.; Deng, G.; Jiang, H.; Liu, H. *J. Org. Chem.* **2008**, *73*, 8563–8570.



Published on Web 06/10/2009 DOI: 10.1021/jo900469d

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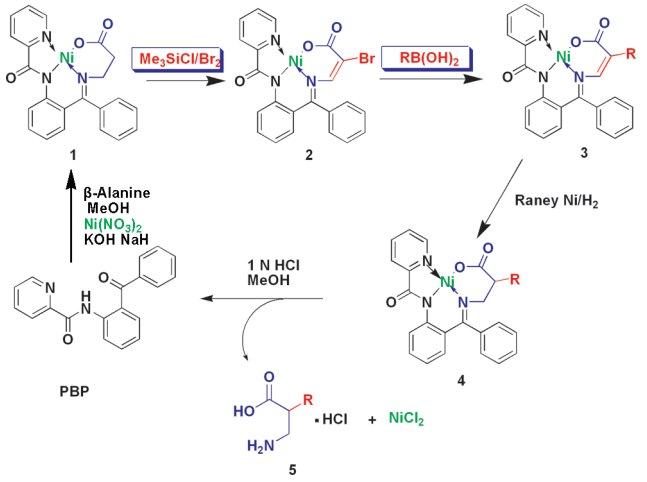
**SCHEME 1. Synthesis of α-Substituted β-Amino Acids via a Ni (II) Complex with Boric Acids**




leading to good operation in the chemical reaction and convenient purification. The notable merits of the Ni(II) complex render it an attractive strategy for practical synthesis in industrial settings.

Accordingly, we proposed the use of the Ni(II) complex [β-AlaNi(II)PABA] **1** as a novel and efficient β-amino acid equivalent for the synthesis of α-substituted β-amino acids. Remarkably, we demonstrated that bromination of β-AlaNi-(II)PABA directly afforded the bromoenone of the Ni(II) complex **2**, which is followed by Suzuki coupling with boric acids, hydrogenation, and hydrolysis (Scheme 1). This is the first example of the preparation of α-substituted β-amino acids from the Ni(II) complex [β-AlaNi(II)PABA].

We initiated our studies by the synthesis of key intermediate bromoenone **2** and various reaction conditions for the bromination of [β-AlaNi(II)PABA] **1** were examined. By using *N*-bromosuccinimide or $Br_2$ as the bromination reagents combined with different bases such as TEA, NaOH, NaH, *t*-BuONa, *t*-BuOK, or LDA in various solvents, the reaction could not be conducted and only the starting material **1** was recovered. However, we obtained the product **2** in a low yield (10%) when $Br_2$ along with 5 equiv of chlorotrimethylsilane (TMSCl) was applied in THF (Table 1, entry 1). It is the first time using TMSCl as the activator to brominate the Ni(II) complex [β-AlaNi(II) PABA].[15] Subsequently, we screened different solvents; the results showed that $CH_2Cl_2$ is the optimal solvent and a 54% of product yield was obtained under the same bromination conditions (Table 1, entries 2−5). Furthermore, variation of the amounts of TMSCl was also probed in $CH_2Cl_2$ at −40 °C, and the investigations revealed that the product **2** was afforded in 95% yield when 10 equiv of TMSCl was used (Table 1, entries 6−9). Finally, the reaction temperature was found to be an important factor on this transformation, and we only obtained bromoenone **2** in 11% and 50% yields with reaction at −20 and −60 °C, respectively. The product **2** was recrystallized from $CH_2Cl_2$ and petroleum ether, which was characterized crystallographically (Figure 1).

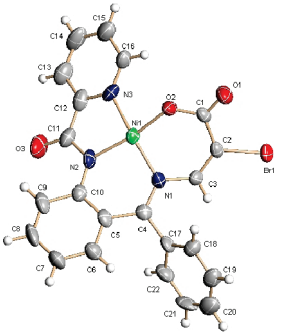
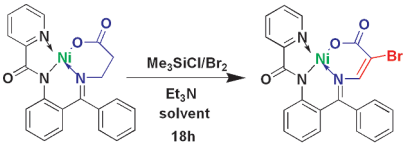


**FIGURE 1.** The crystal structure of **2** by X-ray analysis.

**TABLE 1. Optimization of the Bromination of the Ni(II) Complex 1**[a]




| entry | solvent | equiv of TMSCl | temp (°C) | yield (%) |
|---|---|---|---|---|
| 1 | THF | 5 | −40 | 10 |
| 2 | DMF | 5 | −40 | 16 |
| 3 | $CH_3OH$ | 5 | −40 | 21 |
| 4 | $C_6H_5CH_3$ | 5 | −40 | 0 |
| 5 | $CH_2Cl_2$ | 5 | −40 | 54 |
| 6 | $CH_2Cl_2$ | 3 | −40 | 32 |
| 7 | $CH_2Cl_2$ | 8 | −40 | 72 |
| 8 | $CH_2Cl_2$ | 10 | −40 | 95 |
| 9 | $CH_2Cl_2$ | 11 | −40 | 90 |
| 10 | $CH_2Cl_2$ | 10 | −20 | 11 |
| 11 | $CH_2Cl_2$ | 10 | −60 | 50 |

[a] Reactions were run with 2.3 mmol of **1**, 23 mmol of bromide reagent in 40 mL of the solvent, and 10 mL of triethylamine with TMSCl.

Under our optimized reaction conditions (2.3 mmol of **1**, 23 mmol of $Br_2$, 23 mmol of TMSCl, 10 mL of TEA, 40 mL of $CH_2Cl_2$, −40 °C, 18 h), the key intermediate bromoenone **2** was synthesized efficiently, which was subsequently used for the preparation of compounds **3a**−**p** by Suzuki coupling reactions.[16] The reaction proceeded satisfactorily when reacting **2** with various boric acids in the presence of $Pd(PPh_3)_4$ and $Na_2CO_3$ in toluene and water under microwave irradiation. As shown in Table 2, a variety of aromatic boric acids can participate in the reaction to afford the corresponding products **3a**−**o** in moderate to excellent yields. Both electron-rich and electron-poor substituted phenyl boric acids were tolerated (Table 2, entries 2−11), while a relatively lower yield was obtained in the case of *o*-$CF_3$-substituted phenyl boric acid, presumably due to steric effect (42%, Table 2, entry 6). Additionally, we further probed the substrate scope in application to heteroaryl boric acids. Reactions of 2-benzofuran and 2-dibenzofuran boric acids also proceeded in high yields (Table 2, entries 12 and 13). However, the corresponding products of *N*-heteroaryl boric acids were obtained in lower yields (Table 2, entries 14 and 15). Lastly, the limitation of the scope is also realized. Only trace product **3p** was obtained when alkyl boric acid was used (Table 2, entry 16).

(15) For the proposed mechanism for the preparation of the Ni(II) complex **2** see the Supporting Information.

(16) Perron, J.; Joseph, B.; Merour, J.-Y. *Tetrahedron* **2003**, *59*, 6659–6666.

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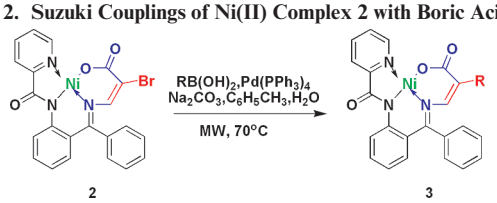
**TABLE 2. Suzuki Couplings of Ni(II) Complex 2 with Boric Acids[a]**




2 3

| entry | R group | | yield (%) |
|---|---|---|---|
| 1 | Ph | **3a** | 84 |
| 2 | 2-MeO-$C_6H_4$ | **3b** | 86 |
| 3 | 3-MeO-$C_6H_4$ | **3c** | 86 |
| 4 | 4-MeO-$C_6H_4$ | **3d** | 87 |
| 5 | 4-$CF_3$-$C_6H_4$ | **3e** | 83 |
| 6 | 2-$CF_3$-$C_6H_4$ | **3f** | 42 |
| 7 | 3-$CF_3$-$C_6H_4$ | **3g** | 72 |
| 8 | 2,4-dimethoxy-$C_6H_3$ | **3h** | 74 |
| 9 | 3,5-bis(trifluoromethyl)-$C_6H_3$ | **3i** | 80 |
| 10 | 4−F-$C_6H_4$ | **3j** | 82 |
| 11 | 4-biphenyl | **3k** | 81 |
| 12 | 2-benzofuran | ***3l*** | 66 |
| 13 | 2-dibenzofuran | **3m** | 72 |
| 14 | 4-pyridine | **3n** | 54 |
| 15 | 8-quinoline | **3o** | 53 |
| 16 | *n*-Bu | **3p** | trace |

[a] Reactions were run with 1.31 mmol of **2**, 3.9 mmol of boric acids, 3.9 mmol $Na_2CO_3$ in 5 mL of toluene and 2 mL of water with 0.014 mmol of $Pd(PPh_3)_4$ at 70 °C under microwave irradiation.

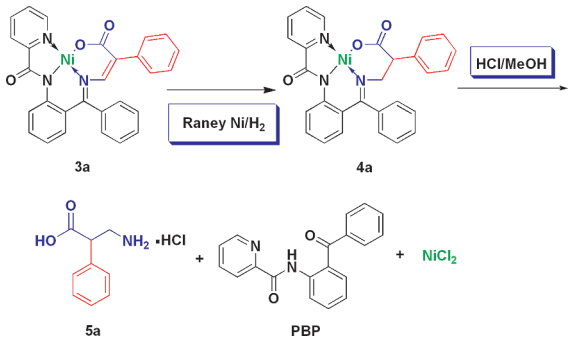
Hydrogenation of the C=C segment of **3a** was attempted under several conditions (Pd/C, $NaBH_4$, and Raney Ni). However, only Raney Ni catalyzed hydrogenation of **3a** to produce **4a** in high yield (90%). Heating a suspension of **4a** in methanol/1 N HCl yielded the target amino acid 3-amino-2-phenylpropionic acid **5a** in 96% yield and the PBP was recovered quantitatively (Scheme 2).

In conclusion, we have successfully synthesized bromoenone of the Ni(II) complexes of *β*-alanine Schiff's base and developed a practical and highly efficient route to α-aryl- and α-heteroaryl-substituted *β*-amino acids using the Suzuki coupling reaction. A broad range of aryl and heteroaryl substituents may be employed under operationally simple and effective conditions. The absolute configuration of the bromoenone product **2** was determined. Furthermore, this is the first efficient application of the Ni(II) complexes of *β*-alanine Schiff's base equivalents. Further studies will focus on mechanistic aspects and applications of the Ni(II) complex [*β*-AlaNi(II)PABA] in other important carbon−carbon bond forming reactions. The results thereof will be reported in due course.

## Experiment Section

**General Procedures for the Synthesis of 2.** A solution of chlorotrimethylsilane (23 mmol) in dichloromethane (10 mL) was added dropwise to a stirred solution of [*β*-AlaNi(II)PABA] **1** (2.3 mmol) in dichloromethane (20 mL) and triethylamine (10 mL) at −40 °C. After 0.5 h, a solution of bromine (23 mmol) in dichloromethane (10 mL) was slowly added to the mixture. The resulting mixture was then stirred at −40 °C for 18 h. Hydrolysis was performed by addition of aq sat. $NH_4Cl$. After extraction with dichloromethane (50 mL), the combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The crude residue was purified by column chromatography on silica gel (dichloromethane/methanol = 20/1) to give **2** as a black solid. $^1$H NMR (300 MHz, $CDCl_3$): *δ* 8.45 (d, *J* = 9 Hz, 1H), 8.23 (d, *J* = 3.3 Hz, 1H), 8.01 (m, 1H), 7.90 (m, 1H), 7.44−7.63 (m, 4H), 7.26−7.41 (m, 1H), 7.12−7.24 (m, 2H), 6.97 (s, 1H), 6.78−6.83 (m, 2H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): *δ* 173.8, 169.2, 151.9, 145.3, 143.5, 140.7, 135.6, 135.3, 134.9, 131.9, 131.4, 129.4, 129.1, 127.7, 127.0, 124.1, 123.3, 121.5 ppm; MS (ESI, *m*/*z*) 506 $[M+H]^+$; HRMS(ESI) calcd for $C_{22}H_{14}BrN_3O_3NaNi$ $[M+Na]^+$ 527.9470, found 527.9454.

**SCHEME 2. Hydrogenation and Decomposition of Ni(II) Complex 3 To Release Amino Acids and Recovery of the Ligand PBP**




3a 4a 5a PBP

**General Procedures for the Synthesis of 3a−p.** To a stirred solution of compound **2** (1.31 mmol) in toluene (5 mL) and water (2 mL) was added freshly prepared tetrakis(triphenylphosphine)palladium (0.014 mmol). Boronic acid (3.9 mmol) and $Na_2CO_3$ (3.9 mmol) were then added. The heterogeneous solution was stirred at 70 °C for 40 min under microwave irradiation. Brine solution was then added, the two layers were separated, and the aqueous phase was extracted with dichloromethane (5 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The crude residue was purified by column chromatography on silica gel (dichloromethane/methanol = 20/1) to give the desired compound. Selected example, compound **3a**: $^1$H NMR (300 MHz, $CDCl_3$): *δ* 8.56 (d, *J* = 8.4 Hz, 1H), 8.35 (d, *J* = 5.7 Hz, 1H), 7.97 (m, 1H), 7.91 (m, 1H), 7.49−7.63 (m, 4H), 7.36−7.42 (m, 1H), 7.15−7.23 (m, 7H), 6.83−6.86 (m, 2H), 6.67 (s, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): *δ* 173.5, 152.5, 145.7, 143.8, 140.6, 140.3, 136.3, 136.1, 135.3, 134.5, 132.0, 131.2, 129.5, 129.1, 128.9, 128.1, 126.8, 124.0, 123.3, 121.4 ppm; MS (ESI, *m*/*z*) 504 $[M+H]^+$; HRMS (EI) calcd for $C_{28}H_{19}N_3O_3NaNi$ $[M+Na]^+$ 526.0678, found 526.0660. (For details, please see the Supporting Information.)

**General Procedures for the Synthesis of 4a.** In a hydrogenation flask was placed compound **3a** and 10 mL of methanol under a nitrogen atmosphere before the addition of Raney-Ni suspended in 10 mL of water. The resulting mixture was pressurized to hydrogen and mechanically stirred at room temperature for 30 min. The reaction mixture was filtered and the filtrate was concentrated in a rotary evaporator to afford the crude product. The crude residue was purified by column chromatography on silica gel (dichloromethane/methanol = 20/1) to give **4a** as a red solid in 90% yield. $^1$H NMR (300 MHz, $CDCl_3$): *δ* 8.45 (d, *J* = 8.7 Hz, 1H), 8.39 (d, *J* = 4.8 Hz, 1H), 7.98 (t, *J* = 8.7 Hz, 1H), 7.85 (d, *J* = 6.9 Hz, 1H), 7.42−7.51 (m, 3H), 7.23−7.34 (m, 7H), 7.07−7.09 (m, 1H), 6.59−6.76 (m, 2H), 6.12 (d, 1H), 3.70−3.78 (m, 3H) ppm; $^{13}$C NMR (75 MHz, $DCl_3$): *δ* 176.0, 174.3, 169.3, 152.8, 145.8, 142.1, 140.5, 137.3, 135.4, 134.4, 133.1, 129.7, 129.0, 128.2, 127.4, 127.1, 126.6, 123.8, 123.7, 121.4 ppm; MS (ESI, *m*/*z*) 506 $[M+H]^+$; HRMS (ESI) calcd for $C_{28}H_{21}N_3O_3NaNi$ $[M+Na]^+$ 528.0834, found 528.0844.

**General Procedures for the Synthesis of 5a.** The complex **4a** was decomposed by a suspension in a mixture of aqueous 1 N HCl (1 mL) and MeOH (15 mL) for half an hour until the red color of the solution disappeared. The reaction was cooled to room temperature and then evaporated to dryness.

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Water (20 mL) was added to the residue to form a clear solution then this solution was separated by column chromatography on $C_{18}$-reversed phase (230−400 mesh) silica gel. Pure water as eluent was employed to remove the green $NiCl_2$ and excess HCl, then MeOH/water (1/1) was used to obtain the product **5a**.The ligand PBP decomposed from **4a** was recovered by MeOH eluent (96%), and the column chromatograph was washed with 100 mL of MeOH for further use.

**Acknowledgment.** We gratefully acknowledge financial support from the National Natural Science Foundation of China (Grants 20721003 and 20872153), International Collaboration Projects (Grants 2007DFB30370 and 20720102040), and the 863 Hi-Tech Program of China (Grants 2006AA020602 and 2006AA020402).

**Supporting Information Available:** Detailed experimental procedures, characterization data, copies of $^{1}H$ and $^{13}C$ NMR spectra for all products, and crystallographic information files (CIF) of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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