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The First Solid-Phase Synthesis of Bis(oxazolinyl)pyridine Ligands

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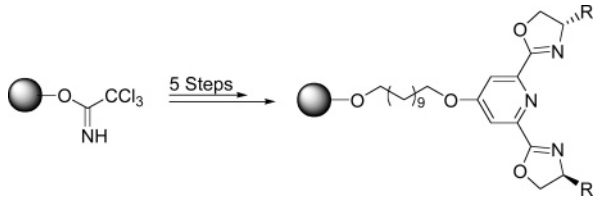

Chiral Pybox (pyridine-2,6-bis(oxazoline)) ligands can be cleanly and efficiently prepared on polystyrene support via a five-step solid-phase synthetic sequence. Cu(I)-complexed polymer-bound Pybox was used as a catalyst in the first heterogeneously catalyzed asymmetric addition of alkynes to imines. Best enantioselectivity was observed with ^{t}Bu-substituted oxazolines.

In recent years, supported catalysts, based on well-defined catalytic units tethered to an insoluble matrix, have become the subject of intense research activity. Such heterogeneous substitutes of homogeneous catalystic systems demonstrated promising results in a number of important transformations.[1] Herein, we report the preparation of the polymer-supported tridentate Pybox ligands and the enantioselective addition of alkynes to imines, catalyzed by supported Pybox-copper complexes. Both the synthesis and catalysis are first examples of their kind.

Development of methods for the enantioselective preparation of chiral compounds, particularly the introduction of chiral catalysts, is currently one of the core subjects of organic synthesis. Pybox ligands, which demonstrate great versatility in complexation of the transition metals, have attracted increased attention in recent years.[2] The interest in Pybox ligands was inspired by a number of remarkable, highly enantioselective catalytic processes, such as hydrosilylation, the reductive aldol reaction, and the ring opening of meso epoxides, performed by their complexes.[3] Only two examples of immobilization of a bis(oxazoline)pyridine (Pybox) ligand have thus far been reported.[4] Mayoral et al. reported preparation of an immobilized Pybox ligand via copolymerization of styrene and divinylbenzene with a soluble vinyl-bearing Pybox monomer, which had to be prepared via a 12%-yielding six-step sequence.[4a] Moberg et al. prepared the immobilized ligand through grafting of a soluble Pybox containing a remote carboxylate or hydroxyl onto a suitably functionalized polymer.[4b] The preparation of the precursor in solution in this case involved a 51%- and 59%-yielding five-step sequence. It is noteworthy that the immobilization of related bis(oxazoline) (Box) ligands was also always achieved via grafting or polymerization of the ligand precursors pre-synthesized in solution.[5] On the other hand, we recently presented an alternative approach for the synthesis of bis(oxazolinyl) ligands—stepwise solid-phase synthesis.[6] This approach was applied for the synthesis of supported Box and Phebox (phenyl-2,6-bis(oxazoline)) ligands and bears potential advantages, such as technical simplicity and more easily attainable diversity, over the two existing methods. The synthetic methodology was recently extended to the synthesis of Pybox ligands as we report herein.

The synthetic procedure starts with the immobilization of a long spacer, 11-bromoundecan-1-ol, on Wang trichloroacetimidate resin (Scheme 1). Dimethyl ester of chelidamic acid, which can easily be prepared from the commercially available acid,[7] is then efficiently anchored to the spacer. The key step of the synthesis is the base-induced aminolysis of the ester groups with β-amino alcohols that we recently introduced.[6a] In the case of the Pybox ligand precursors, this reaction proceeds cleanly and efficiently for all substituents. The synthesis was accomplished via chlorodehydroxylation and base-induced cyclization steps. Both steps are highly efficient and clean for amino alcohols with aliphatic substituents. However, for phenylglycinol, the last step produces only a small amount of a significantly contaminated ligand. To overcome this problem, we applied an alternative oxazoline-forming procedure, direct cyclization of the hydroxyamide precursor **1g** with Burgess reagent (Scheme 2). This method was previously applied in solution, and we recently adapted the procedure for the solid-phase synthesis of oxazolines derived from serine or threonine.[8,9]

The acidolytic cleavage of ligands **3**, followed by ^{1}H NMR, reveals high overall yields (66%−90%) and purity (80%−95%). Although the oxazolines are hydrolyzed under cleavage conditions, formation of the characteristic protonated bis(aminoester) hydrolysis product clearly demonstrates the existence of oxazolines prior to the cleavage.[10] Formation of the expected Pybox products is

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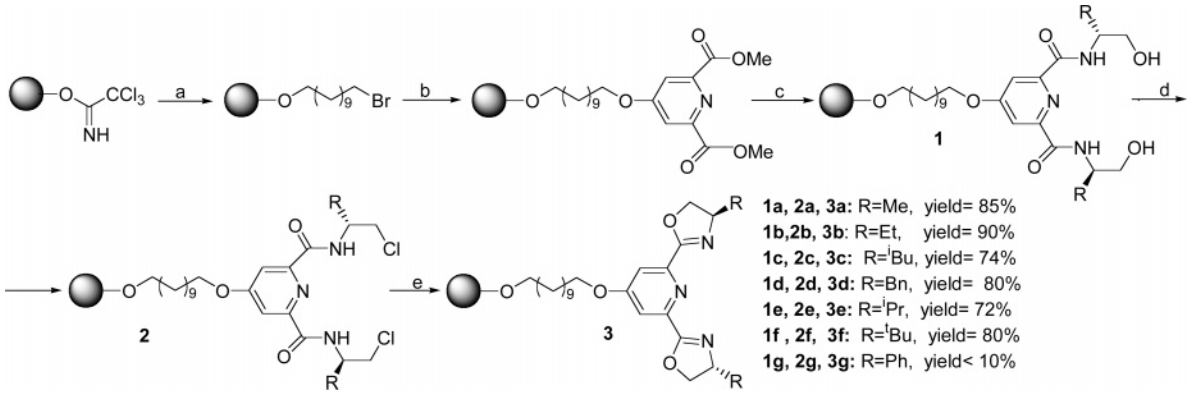
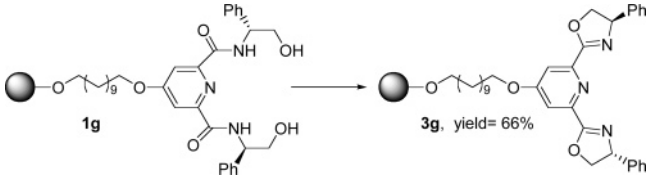
SCHEME 1. Synthesis of Polymer-Bound Pybox Ligands[a]



[a] Reagents and conditions: (a) 11-bromoundecan-1-ol, $BF_3{\cdot}OEt_2$, cyclohexane/CH_2Cl_2, rt; (b) dimethyl ester of chelidamic acid, LiH, DMF, 60 °C; (c) β-amino alcohol, LDA, DMF, 50 °C; (d) PPh_3, C_2Cl_6, THF, rt; (e) DBU, THF, 60 °C.

SCHEME 2. Synthesis of 3g[a]

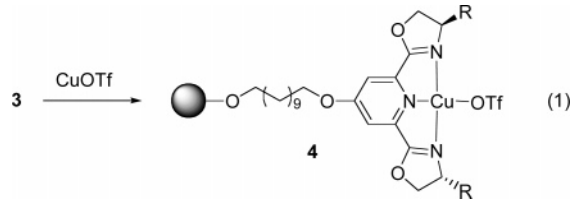


[a] Reagents and conditions: Burgess reagent, dioxane, 100 °C.

also confirmed by gel-phase ^{13}C NMR. Thus, characteristic changes are observed upon comparison of the spectra of β-chloroamides with those of oxazolines (the last synthetic step). For instance, the signals of two carbons, α and β to the nitrogen, are shifted from 45 and 56 ppm in the chloroamide **2f** to 69 and 76 ppm, respectively, in the corresponding Pybox ligand **3f**.

The prepared Pybox ligands were tested in an enantioselective alkynylation of imines. Chiral propargylamines are important building blocks that are used in the synthesis of drug candidates and natural products.[11] Although a number of stoichiometric routes to enantiopure propargylamines are known, catalytic routes to this type of compounds are scarce.[12] Only recently was a successful reaction, based on homogeneous catalysis with copper complexes of Pybox, reported.[13] Accordingly, we decided to test the supported Pybox ligands for the first heterogeneously catalyzed chiral addition of alkynes to imines leading to propargylamines.

Thus, the resin-bound Pybox were incubated with a dichloromethane solution of CuOTf, filtered, and washed, yielding a light brown polymer (eq 1). The polymer-bound

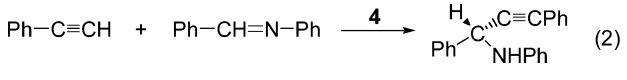


catalysts were tested in a model alkyne addition reaction between phenylacetylene and benzylideneaniline (eq 2, Table 1). Our experiments revealed the steric bulk of the oxazoline substituent strongly influences the enantioselectivity. The low ee obtained with **4a** (R = Me) (entry 1, ee = 8%) could be increased in parallel with the increase in steric size of the substituent, reaching 83% for **4f** (R = ^{t}Bu, entry 5). Surprisingly, the complex **4g**, derived from the Ph-substituted ligand, the analogue of which demonstrated high enantioselectivity in solution,[13] exhibited disappointing reactivity and formed a practically racemic product (entry 7). The catalyst recovered after one catalytic cycle exhibited diminished reactivity, while the enantioselectivity was unaffected (entry 6). The reason for the reduced reactivity is, most probably, the strong propensity of the catalytic complex to undergo oxidation and, possibly, some leaching of the metal. A separate experiment demonstrated that Cu^{II} complexes of **3** are not catalytically active in the model reaction. The remaining Pybox−Cu^I complex is responsible for the residual activity as well as preservation of the enantioselectivity.

TABLE 1. Reaction of Phenyl Acetylene and Benzilideneaniline in the Presence of 4[a]

entry	catalyst	solvent	yield[b] (%)	ee (%)
1	**4a**	CH_2Cl_2	90	8
2	**4b**	CH_2Cl_2	85	20
3	**4d**	CH_2Cl_2	77	44
4	**4e**	CH_2Cl_2	87	52
5	**4f**	CH_2Cl_2	63	83
6[c]	**4f**	CH_2Cl_2	20	82
7	**4g**	CH_2Cl_2	traces	<5
8	**4f**	THF	80	54
9[d]	**4f**	THF	77	55
10[e]	**4f**	THF	56	60
11	**4f**	THF	80, 78, 78[f]	<5

[a] Reaction conditions: 1 equiv of *N*-benzilideneaniline, 1.5 equiv of phenylacetylene, 10% of **4**, 40 °C, 24 h. [b] NMR-determined yield. [c] Catalyst recovered from entry 5. [d] Catalyst recovered from entry 8. [e] Catalyst recovered from entry 9. [f] Three consecutive runs in the presence of ascorbic acid.



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In an attempt to improve the recyclability of the catalyst, the reaction was carried out in solvents other than dichloromethane. Indeed, in THF, the ability to recycle the catalyst **4f** was markedly improved (entries 8−10). Although the ee was lower than in dichloromethane and the yields somewhat decreased during the three consecutive cycles, the yield in the first run was higher and the enantioselectivity through the cycles improved. The trend of decrease in yields, while the enantioselectivity is preserved, was also observed in the two other supported Pybox catalytic systems reported.[4] The addition of ascorbic acid, as a sacrificial reducing agent, to the reaction mixture produced a fully recyclable catalytic system (no change in yield in three consecutive runs), but the enantioselectivity was lost (entry 11).

It is noteworthy that the tridentate coordination of Cu^{I} seems essential for chiral induction. Both in solution (according to the literature) and with a supported catalyst (as observed by us), the use of bidentate oxazoline-containing ligands leads to a racemic product.[5,9]

In conclusion, we developed a technically simple and efficient methodology for the preparation of polymer-supported Pybox ligands, demonstrating the advantages of stepwise solid-phase ligand synthesis. We successfully exploited the catalytic system derived from such ligands for the first heterogeneously catalyzed chiral addition of an alkyne to an imine. Investigation of additional asymmetric transformations based on supported Pybox ligands is underway.

Experimental Section

Polymer-Bound 11-Bromoundecan-1-ol. The solution of 11-bromoundecan-1-ol (2 equiv) in CH_2Cl_2 (20 mL/g resin) was added dropwise to a suspension of Imidate Wang resin in cyclohexane (20 mL/g resin). The mixture was stirred at room temprature for 5 min. Then, a catalytic amount of boron trifluoride etherate (0.1 equiv) was added, and the suspension was stirred at room temprature for another 10 min. The resin was filtered, washed with CH_2Cl_2, THF, and CH_2Cl_2, and then dried under vacuum. Following acidolytic cleavage: ^{1}H NMR (200 MHz, $CDCl_3$/TFA 1:1) δ 4.41 (t, J = 6.8 Hz, 2H), 3.42 (t, J = 6.8 Hz, 2H), 1.70−1.90 (m, 4H), 1.32−1.35 (m, 14H).

Polymer-Bound Dimethyl Ester of Chelidamic Acid. Polymer-bound 11-bromoundecan-1-ol was suspended in anhydrous DMF (20 mL/g resin). In another flask, LiH (8 equiv) was added to a solution containing the dimethyl ester of chelidamic acid (5 equiv) in a minimal amount of dry DMF. After 5 min of stirring, the solution was cannulated to the resin suspension, a catalytic amount of tetrabutylammonium iodide was added, and the reaction mixture was stirred for 36 h at 60 °C. The resin was filtered, washed with DMF, DMF/H_2O, H_2O, THF, and CH_2Cl_2, and then dried under vacuum. Following acidolytic cleavage: ^{1}H NMR (200 MHz, $CDCl_3$/TFA 1:1) δ 8.12 (s, 2H), 4.54 (t, J = 6.4 Hz, 2H), 4.43 (t, J = 6.6 Hz, 2H), 4.21 (s, 6H), 1.77−2.05 (m, 4H), 1.36−1.39 (m, 14H).

Polymer-Bound Bis-β-hydroxy Chelidamic Amides (1a−g). The polymer-bound dimethyl ester of chelidamic acid was suspended in anhydrous DMF (20 mL/g resin). In another flask, LDA (20 equiv) was added dropwise to the solution of β-amino alcohol (22 equiv) in a minimal amount of dry DMF at 10 °C. This solution was mixed for 5 min, cannulated into the suspension in the first flask and stirred overnight at 60 °C. The resin was filtered, washed with DMF, DMF/H_2O, H_2O, THF, and CH_2Cl_2, and then dried under vacuum. The resin-bound species were usually characterized after the chlorodehydroxylation step, due to substantial simplification of the spectra upon conversion of the hydroxyamides to chloroamides.

Representative hydroxyamide characterization: **1e**. Following acidolytic cleavage: ^{1}H NMR (200 MHz, $CDCl_3$/TFA 1:1) δ 8.40 (d, J = 9.2 Hz, 2H), 7.85 (s, 2H) 4.82 (m, 2H), 4.57 (m, 2H), 4.45 (t, J = 6.4 Hz, 2H), 4.37 (m, 2H), 4.27 (t, J = 6.4 Hz, 2H), 1.70−2.09 (m, 6H), 134−1.36 (m, 14H), 1.09 (d, J = 6.8 Hz, 6H) 1.05 (d, J = 6.8 Hz, 6H); partial ^{13}C NMR (100 MHz, $CDCl_3$/TFA 1:1) δ 171.0, 128.1, 112.7, 71.0, 69.3, 67.3, 56.1, 29.4, 29.0, 28.7, 28.1, 27.7, 25.1, 18.0.

Polymer-Bound Bis-chloro Amides (2a−f). Polymer-bound bis-β-hydroxy amide (**1a**−**f**) resins were suspended in anhydrous THF (20 mL/g resin) for 10 min. In a second flask, PPh_3 (10 equiv) and C_2Cl_6 (10 equiv) were dissolved in dry THF. This solution was cannulated to the resin suspension, and the reaction mixture was stirred overnight at room temperature. The resin was filtered, washed with THF and CH_2Cl_2, and then dried under vacuum.

2b: partial gel-phase ^{13}C NMR (100 MHz, C_6H_6) δ 150.0, 144.7, 71.9, 69.4, 68.0, 50.5, 47.2, 29.2, 25.9, 25.2, 24.7, 9.6. Following acidolytic cleavage: ^{1}H NMR (200 MHz, $CDCl_3$/TFA 1:1) δ 8.17 (d, J = 8.0 Hz, 2H), 7.92 (s, 2H), 4.34−4.40 (m, 6H), 3.68−3.79 (m, 4H), 1.67−1.88 (m, 4H), 1.29−1.32 (m, 14H), 1.00 (t, J = 6.0 Hz, 6H).

2c. Following acidolytic cleavage: ^{1}H NMR (200 MHz, $CDCl_3$/TFA 1:1) δ 8.24 (d, J = 8.8 Hz, 2H), 7.95 (s, 2H), 4.53−4.59 (m, 2H), 4.42 (t, J = 6.6 Hz, 2H), 4.35 (m, 2H), 3.65−3.84 (m, 4H), 1.60−1.89 (m, 8H), 1.34−1.36 (m, 14H), 0.97 (d, J = 4.6 Hz, 12H).

2d: partial gel-phase ^{13}C NMR (100 MHz, C_6H_6) δ 157.9, 149.9, 69.4, 68.1, 50.7, 46.2, 37.0, 29.1, 25.8, 25.2. Following acidolytic cleavage: ^{1}H NMR (200 MHz, $CDCl_3$/TFA 1:1) δ 8.42 (d, J = 8.6 Hz, 2H), 7.82 (s, 2H), 7.27−7.38 (m, 10H), 4.68−4.71 (m, 2H), 4.42 (t, J = 6.6 Hz, 2H), 4.26 (m, 2H), 3.71−3.90 (m, 4H), 3.09 (d, J = 7.4 Hz, 4H), 1.74−1.94 (m, 4H), 1.34−1.37 (m, 14H).

2e: partial ^{13}C NMR (200 MHz, $CDCl_3$/TFA 1:1) δ 147.2, 128.1, 112.7, 71.1, 69.3, 67.3, 56.1, 29.4, 29.0, 28.7, 28.1, 27.7, 25.1, 18.0. Following acidolytic cleavage: ^{1}H NMR (200 MHz, $CDCl_3$/TFA 1:1) δ 8.27 (d, J = 9.2 Hz, 2H), 7.80 (s, 2H), 4.36−4.46 (m, 4H), 4.21 (m, 2H), 3.82 (m, 4H), 1.77−2.09 (m, 6H), 1.34−1.36 (m, 14H), 1.09 (d, J = 6.6 Hz, 6H) 1.05 (d, J = 6.6 Hz, 6H).

2f: partial gel-phase ^{13}C NMR (100 MHz, C_6H_6) δ 158.7, 145.6, 71.9, 69.4, 68.0, 56.2, 45.1 34.6, 29.18.0, 26.1, 25.2. Following acidolytic cleavage: ^{1}H NMR (200 MHz, $CDCl_3$/TFA 1:1): δ 8.13 (d, J = 9.8 Hz, 2H), 8.00 (s, 2H), 4.30−4.47 (m, 6H), 3.93−4.00 (m, 2H), 3.66−3.71 (m, 2H), 1.78−1.99 (m, 4H), 1.36−1.37 (m, 14H), 1.11 (m, 18H).

Polymer-Bound Pybox Ligands (3a−f). Polymer-bound bis-chloro amide (**2a**−**f**) resins were suspended in anhydrous THF (20 mL/g resin) to which DBU (100 equiv) was added. The reaction mixture was stirred for 48 h at 60 °C. The resin was filtered, washed with DMF, DMF/H_2O (1:1), H_2O, THF, and CH_2Cl_2, and then dried under vacuum.

3a: partial gel-phase ^{13}C NMR (100 MHz, C_6H_6) δ 161.8, 148.3, 114.0, 111.4, 73.3, 72.0, 69.5, 67.5, 61.7, 29.2, 25.7, 25.3, 20.7. Following acidolytic cleavage: ^{1}H NMR (200 MHz, $CDCl_3$/TFA 1:1) δ 7.88 (s, 2H), 5.43 (m, 2H) 4.98 (m, 4H), 4.39 (t, J = 6.6 Hz, 2H), 4.25 (t, J = 6.2 Hz, 2H), 1.79 (m, 4H), 1.71 (d, J = 5.8 Hz, 6H), 1.33 (m, 14H).

3b: partial gel-phase ^{13}C NMR (100 MHz, C_6H_6) δ 162.0, 148.3, 114.2, 111.6, 71.9, 69.4, 67.6, 29.2, 28.2, 26.0, 25.3, 9.6. Following acidolytic cleavage: ^{1}H NMR (200 MHz, $CDCl_3$/TFA 1:1) δ 7.92 (s, 2H), 5.48 (t, J = 9.8 Hz, 2H), 4.93 (t, J = 9.2 Hz, 2H), 4.83 (m, 2H), 4.38 (t, J = 6.6 Hz, 2H), 4.22 (t, J = 6.4 Hz, 2H), 1.90 (m, 8H), 1.31 (m, 14H), 1.05 (t, J = 7.2 Hz, 6H).

3c: partial gel-phase ^{13}C NMR (100 MHz, C_6H_6) δ 166.9, 152.8, 114.3, 111.8, 72.9, 69.7, 67.7, 64.7, 44.9, 29.2, 28.2, 26.0, 24.8, 22.4, 21.8. Following acidolytic cleavage: ^{1}H NMR (200 MHz, $CDCl_3$/TFA 1:1) δ 7.91 (s, 2H), 5.51 (t, J = 9.6 Hz, 2H), 5.05 (t, J = 9.0 Hz, 2H), 4.88 (m, 2H), 4.42 (t, J = 6.6 Hz, 2H), 4.26 (t, J = 6.4 Hz, 2H), 1.74−1.97 (m, 10H), 1.35 (m, 14H), 1.02 (m, 12H).

3d: partial gel-phase ^{13}C NMR (100 MHz, C_6H_6) δ 162.4, 148.5, 137.5, 114.1, 111.7, 71.6, 69.4, 67.5, 40.9, 40.2, 29.2, 25.3, 22.9.

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Following acidolytic cleavage: ^{1}H NMR (200 MHz, $CDCl_3$/TFA 1:1) 7.87(s, 2H), 7.20−7.37 (m, 10H), 5.15−5.36 (m, 6H), 4.42 (t, J = 6.6 Hz, 2H), 4.22 (t, J = 6.2 Hz, 2H), 3.22 (m, 4H), 1.80 (m, 4H), 1.34 (m, 14H).

3e: partial gel-phase ^{13}C NMR (100 MHz, C_6H_6) δ 161.9, 148.5, 111.6, 72.4, 70.3, 67.7, 32.5, 29.3, 26.1, 25.2, 18.2. Following acidolytic cleavage: ^{1}H NMR (200 MHz, $CDCl_3$/TFA 1:1) δ 7.94 (s, 2H), 5.38 (t, J = 10.2 Hz, 2H), 5.19 (dd, J = 10.2, 7.4 Hz, 2H), 4.70 (m, 2H), 4.43 (t, J = 6.6 Hz, 2H), 4.28 (t, J = 6.4 Hz, 2H), 2.22 (m, 2H), 1.87 (m, 4H), 1.35 (m, 14H), 1.10 (d, J = 6.8 Hz, 6H), 1.06 (d, J = 6.8 Hz, 6H).

3f: partial gel-phase ^{13}C NMR (100 MHz, C_6H_6) δ 162.1, 148.4, 114.2, 111.7, 75.8, 71.9, 69.4, 68.5, 67.6, 33.1, 29.2, 28.3, 26.0, 25.2. Following acidolytic cleavage: ^{1}H NMR (200 MHz, $CDCl_3$/TFA 1:1) δ 7.95 (s, 2H), 5.30 (m, 4H), 4.62 (dd, J = 10.4, 7.0 Hz, 2H), 4.43 (t, J = 6.6 Hz, 2H), 4.28 (t, J = 6.4 Hz, 2H), 1.84 (m, 4H), 1.35 (m, 14H), 1.08 (m, 18H).

Procedure for the Transformation of 1g to 3g. Compound **1g** was suspended in sodium-dried dioxane. Burgess reagent (4 equiv) was then added, and the reaction was refluxed for 4 h. The resin was filtered and washed with THF, MeOH, THF, and CH_2Cl_2 and then dried under vacuum.

3g: partial gel-phase ^{13}C NMR (100 MHz, C_6H_6): δ 163.1, 150.5, 114.1, 74.5, 71.9, 69.5, 68.0, 29.1, 25.9, 25.2. Following acidolytic cleavage: ^{1}H NMR (200 MHz, $CDCl_3$/TFA): δ 7.95 (s, 2H), 7.30−7.50 (m, 10H), 5.83 (m, 4H), 5.35 (m, 2H), 4.44 (t, J = 6.6 Hz, 2H), 4.28 (t, J = 6.4 Hz, 2H), 2.01 (m, 2H), 1.84 (m, 2H), 1.31 (m, 14H).

General Procedure for Complexation of Polymer-Bound Pybox Ligands. Copper(I) triflate (1.2 equiv) was dissolved in a minimum amount of CH_2Cl_2. In another flask, the resin-bound Pybox ligand (1 equiv) was suspended in CH_2Cl_2. The solution of the first flask was cannulated to the resin suspension, and the mixture was stirred for 24 h at room temprature. The resin was filtered, washed with THF and CH_2Cl_2, and dried under vacuum.

General Procedure for the Catalysis. *N*-Benzilideneaniline (1 equiv) and phenylacetylene (1.5 equiv) were added to the suspension of the catalyst (0.1 equiv). The mixture was heated to 50 °C for 24 h. Then the resin was filtered and washed twice with CH_2Cl_2. The crude obtained after evaporation of the solvent from the combined solution was separated on a silica gel column (Et_2O/hexanes 1:10) to obtain the pure product. Enantioselectivity was determined by HPLC using a Chiralcel OD column (hexanes/2-propanol 95:5, flow rate 0.5 mL/min, detection wavelength 254 nm); t_R = 14.4 min, t_R = 17.7 min.

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Supporting Information Available: General experimental methods, ^{1}H NMR of cleavage solutions of resins **2** and **3**, and gel-phase ^{13}C NMR of ligands (**3a**−**f**). This material is available free of charge via the Internet at http://pubs.acs.org.

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