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Parallel Solid-Phase Synthesis, Screening, and Encoding Strategies for Olefin-Polymerization Catalysts

Thomas R. Boussie, Vince Murphy, Keith A. Hall, Carla Coutard, Cameron Dales,
Miroslav Petro, Eric Carlson, Howard W. Turner, and Timothy S. Powers*

Symyx Technologies, 3100 Central Expressway,
Santa Clara, CA 95051, USA

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Abstract: A solid-phase protocol has been developed that allows for the parallel synthesis, screening, and chemical encoding of nickel (II) and palladium (II) olefin-polymerization catalysts. These catalysts display activity profiles comparable to the analogous homogeneous catalyst systems prepared by traditional methods. A chemical encoding strategy has also been developed which enables the chemical history of pooled solid-phase catalysts to be evaluated.

The application of combinatorial methods in the pharmaceutical industry has become standard practice for the discovery and optimization of novel drug-based molecules.[1] Similar methodology aimed towards the identification of new materials and catalysts, however, remains comparatively underdeveloped.[2] Recent reports have appeared describing the synthesis and screening of solid supported organometallic catalyst libraries examining a number of transformations, which include asymmetric C-H insertion reactions,[3] ring opening of epoxides,[4] ligand assisted addition of diethylzinc to aldehydes,[5] hydrogenations,[6] and asymmetric hydrocyanations of imines.[7] We have been exploring the application of combinatorial methods to the discovery and optimization of olefin polymerization catalysts,[8] which is an area that promises to be of major importance to the chemical industry that produces approximately 46 million metric tons of polyolefins annually.[9]

Since most commercial-scale polyolefin processes employ high surface area supports for immobilizing olefin polymerization catalysts, it is somewhat surprising that few reports have appeared examining the use of polystyrene as a catalyst support.[10] Fréchet and coworkers have recently shown that suitably modified cross-linked polystyrene can function as an efficient activator for group (IV) metallocene-based catalysts.[11] Cross-linked polystyrene not only functions as a more chemically compatible support for these types of polymerizations, but also provides a solution-like environment that more closely resembles the environment in which homogeneous metallocene catalysts generally function. In addition, a plethora of solid phase synthetic

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methodologies have appeared in recent years,[12] providing a broad knowledge base which ought to facilitate efforts in the field of olefin polymerization catalysis.

We chose to develop a parallel synthesis and screening protocol for solid supported analogs **1a-b** which closely resemble the homogeneous Ni (II) and Pd (II) olefin polymerization catalyst precursors **2a-b** recently reported by Brookhart (**Figure 1**).[13] These systems have recently sparked considerable interest in the polyolefins industry because of their high activity, ease of synthesis and handling, and tolerance toward functionalized olefins such as methacrylate and vinyl acetate compared to the metallocene-based catalysts currently being employed commercially. Herein we report a general synthetic methodology that allows for the parallel synthesis and screening of solid-supported Ni (II) and Pd (II) ethylene polymerization catalysts in a spatially addressable format.[14] Furthermore, we have discovered that it is possible to apply chemical encoding techniques to these catalysts and distinguish catalyst performance trends.[15]

Figure 1

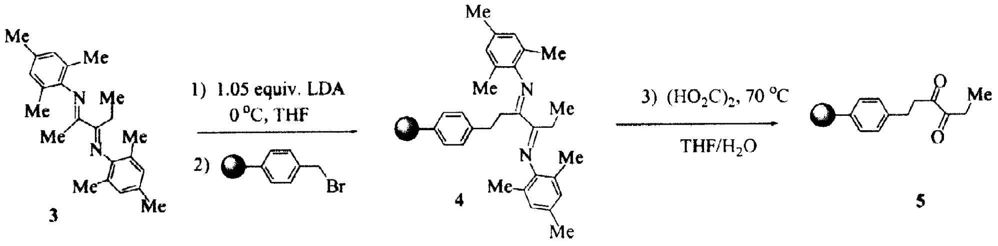
1a: M = Ni; L_1, L_2 = Br
1b: M = Pd; L_1 = CH_3, L_2 = Cl
● = 1% cross-linked polystyrene

2a: M = Ni; L_1, L_2 = Br
2b: M = Pd; L_1 = CH_3, L_2 = Cl

Parallel Synthesis of Solid-Supported Ni (II) and Pd (II) Complexes.

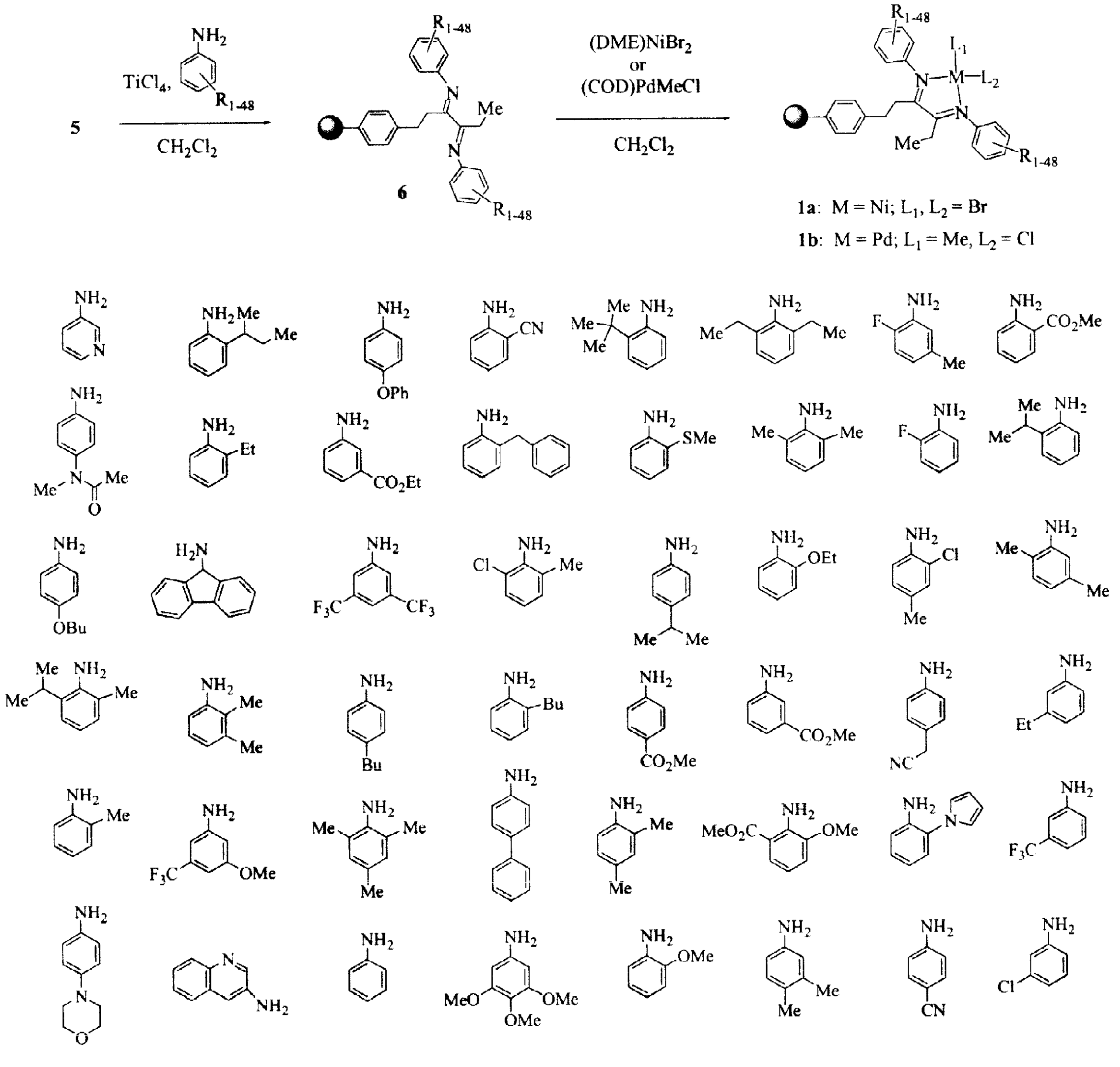
Since steric bulk on the 1,2-diimine aryl rings has been reported to play a dramatic role on polymer yield and molecular weight (M_w) in these catalytic systems, we chose to further examine this notion by synthesizing a small library of solid supported 1,2-diimine complexes of both Ni (II) and Pd (II). Our synthetic approach began with a regio-selective alkylation of an unsymmetrical 1,2-diimine **3**[16] with bromomethyl polystyrene to give the polystyrene grafted 1,2-diimine ligand **4** (**Scheme 1**). In order to incorporate a variety of functionalized aryl-substituted 1,2-diimines, a divergent approach was explored starting from diketone resin **5** which was obtained in high yield (>95% based on recovered 2,4,6-trimethyl aniline) from the hydrolysis of 1,2-diimine resin **4** with oxalic acid in THF/H_2O (5:1 v/v) at 70 °C for 12 hours. This transformation was monitored using single bead FTIR spectroscopy (C=N, ν = 1635 cm^{-1} versus C=O, ν = 1712 cm^{-1}).

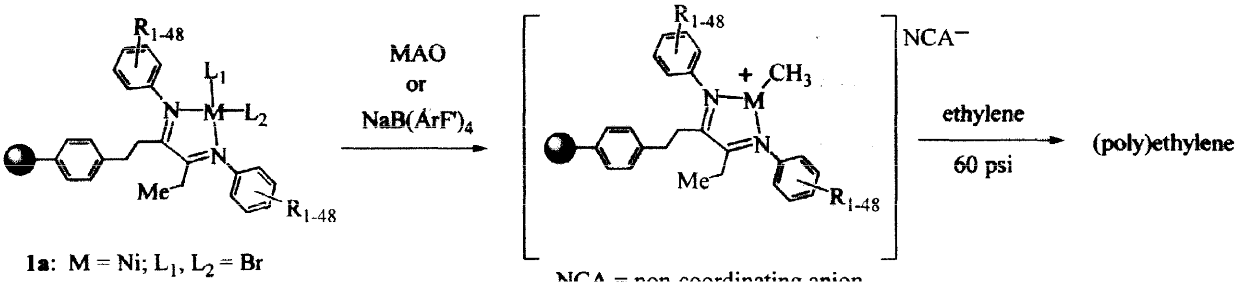
Scheme 1



A total of 48 commercially available anilines with varying steric and electronic substituents was then used to prepare the corresponding 1,2-diimine resins (**Scheme 2**). We found that we obtained the best results when employing $TiCl_4$ as a Lewis acid (15 equiv) with the appropriate aniline (30 equiv) to effect the formation of the 1,2-diimines **6**. A thorough washing protocol was implemented after this step to minimize excess aniline and titanium contamination of the library.

Scheme 2





1a: M = Ni; L_1, L_2 = Br
1b: M = Pd; L_1 = CH_3, L_2 = Cl

NCA = non-coordinating anion

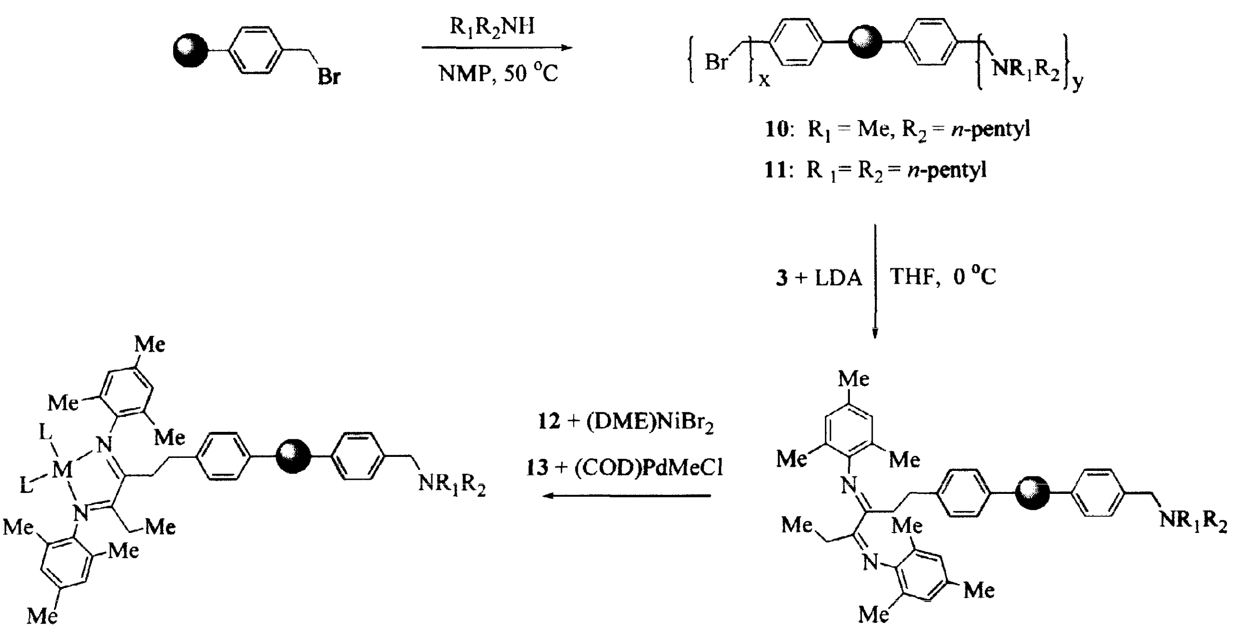
Table 1. Screening of Ni (II) and Pd (II) Catalysts **1** and **2**.[a]

Entry	M (II)	R	Polymer Yield (mg)	M_w	PDI
1	Pd	2-chloro-6-methyl	75	11,000[b]	d
2	Pd	2,6-dimethyl	109	12,000[b]	1.6
3	Pd	2,4,6-trimethyl	108	12,000[b]	1.9
4	Pd (solution-phase)	2,4,6-trimethyl	75	12,000[b]	1.7
5	Pd	3-ethyl	175	2,000[b]	d
6	Ni	2,4,6-trimethyl	608	59,000[c]	≤2.9
7	Ni (solution-phase)	2,4,6-trimethyl	800	213,000[c]	≤5.7
8	Ni	2-benzyl	190	46,000[c]	≤2.6
9	Ni	2,5-dimethyl	159	35,000[c]	<2.7
10	Ni	3-ethyl	215	10,000[c]	d
11	Ni	2-butyl	344	37,000[c]	≤2.7
12	Ni	2,4-dimethyl	301	35,000[c]	≤2.6
13	Ni	2-*t*-butyl	249	93,000[c]	≤7.0
14	Ni	2-methyl-6-isopropyl	171	85,000[c]	≤2.7

a. Conditions: 10 mg catalyst beads, Ni (II) beads activated with MAO (10% in toluene, 300 equiv.), Pd (II) beads activated with sodium tetrakis(3,5-bistrifluoromethyl)phenyl borate (5 equiv.), 23 °C for 1 hr, 60 psi ethylene. b. Determined by conventional GPC vs. polystyrene standards. c. Determined by rapid high temperature GPC vs. polystyrene standards. d Not determined.

In order to implement a chemical encoding strategy,[19-20] sub-stoichiometric amounts of secondary amine tags were added to bromomethyl-polystyrene (0.3 equiv. RR'NH, NMP, 50° C. **10**; R = Me, R' = *n*-pentyl. **11**; R = R' = *n*-pentyl) prior to attachment of the 1,2-diimine ligands (**Scheme 4**). The synthetic sequence above was then used to prepare the tagged, polystyrene supported Ni (II) **14** and Pd (II) **15** complexes. Catalysts **14** and **15** were pooled into a single reactor, activated with MAO and sodium tetrakis(3,5-bistrifluoromethyl)phenyl borate, respectively, and exposed to 60 psi ethylene for 30 minutes.[21] Upon workup, the product morphologies, viewed under a microscope, indicated the presence of two distinct sizes of polymer products (**Figure 3**).

Scheme 4



10: R_1 = Me, R_2 = *n*-pentyl
11: R_1 = R_2 = *n*-pentyl

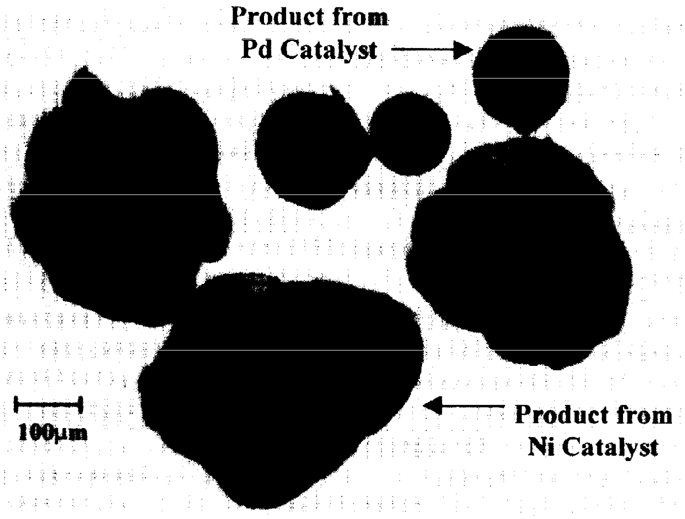
14: M = Ni; R_1 = Me, R_2 = *n*-pentyl
15: M = Pd; R_1 = R_2 = *n*-pentyl

12: R_1 = Me, R_2 = *n*-pentyl
13: R_1 = R_2 = *n*-pentyl

Five larger beads and five smaller beads were selected for decoding which consisted of an amine cleavage procedure coupled with HPLC and fluorescence detection. Specifically, the beads were first treated with α-chloroethyl chloroformate, a reagent known to cleave N-benzyl linked tertiary amines from solid supports. The cleaved secondary amine products were then derivatized with dansyl chloride prior to detection using HPLC with fluorescence detection. Importantly, the HPLC traces confirm (i) the presence of the secondary amine tags, and (ii) that the larger polymer granules were prepared from the nickel catalyst, in accordance with the known relative performance trends of 1,2-diimine Ni (II) and Pd (II) olefin polymerization catalysts.[13]

Thus, in these systems, olefin polymerization catalysts can be chemically encoded, pooled into a single reactor, and the resultant polymer granules can be decoded to deduce the synthetic history of the incipient polystyrene support.

Figure 3



The work described here demonstrates the feasibility of applying combinatorial techniques, including solid supported synthesis, on-bead screening, and the potential for deconvoluting pooled libraries of catalysts, for the discovery and optimization of new olefin-polymerization catalysts. It is noteworthy that the techniques described here could be applied to catalytic processes other than ethylene polymerization. With these techniques now realized, work is currently underway to fully examine the scope and utility of the methodology.

Experimental Section

Preparation of solution phase 1,2-diimine 7. To a cooled solution (0 °C) of 1,2-diimine **3** (2.00 g, 5.99 mmol) in 15 mL dry THF under nitrogen was added LDA (4.40 ml, 6.59 mmol, 1.5 M in THF). After stirring at 0 °C for 2 hr, benzyl bromide (0.86 mL, 7.19 mmol) was added and the resulting solution was stirred 3 hr at 0 °C and 10 hr at room temperature. The reaction mixture was concentrated on a rotavap and the remaining oily residue was taken up in 50 ml Et_2O and washed with H_2O (2 x 50 mL). The Et_2O layer was dried over $MgSO_4$, filtered, and concentrated. The crude material was passed through a plug of silica gel with CH_2Cl_2 and concentrated once more to afford 2.54 g of the compound **7** in 95 % yield as a yellow oil. ^{1}H NMR 300 MHz, ($CDCl_3$) δ 7.23-7.28 (m, 3H), 7.19 (d, 2H, J = 6.9 Hz), 6.98 (s, 2H), 6.94 (s, 2H), 2.87 (br s, 4H), 2.64 (q, 2H, J = 7.6 Hz), 2.37 (s, 3H), 2.35 (s, 3H), 2.14 (s, 6H), 2.06 (s, 6H), 1.12 (t, 3H, J = 7.6 Hz); ^{13}C NMR 75 MHz, ($CDCl_3$) δ

171.97, 169.97, 145.85, 145.56, 141.15, 132.28, 132.20, 128.66, 128.28, 128.15, 125.97, 124.37, 32.76, 31.28, 22.24, 20.67, 18.22, 18.06, 11.24; IR (C=N), 1635 cm^{-1}.

Preparation of solution phase complex 8. PEG polystyrene $NiBr_2$ resin (0.20 g, 0.90 mmol, 2.20 mmol/g) and 1,2-diimine **7** (0.17 g, 0.40 mmol) were combined under nitrogen and 10 mL dry CH_2Cl_2 was added. After stirring at room temperature for 12 hr, the mixture was filtered and the resin was washed with CH_2Cl_2. After concentrating, the reddish-brown residue was washed with hexane to give 0.26 g of the desired complex in 98% yield as a reddish-brown solid. Anal. Calcd for $C_{30}H_{36}N_2NiBr_2$: C 54.73; H 5.65; N 4.14. Found: C 55.88; H 5.62; N 4.34.

Preparation of solution phase complex 9. N,N,N-Trimethylpropylenediamine resin (0.20 g, 0.18 mmol, 0.91 mmol/g) and 1,2-diimine **7** (36 mg, 0.15 mmol) were combined under nitrogen and 3 mL dry CH_2Cl_2 was added. After stirring at room temperature for 4 hr, the mixture was filtered and the resin washed with CH_2Cl_2. After concentrating the filtrate, the orange-red residue was washed with hexane to give 48 mg of desired complex **9** in 98% yield as a orange-red solid. Anal. Calcd for $C_{31}H_{39}N_2PdCl$: C 64.02; H 6.76; N 4.81. Found: C 65.22; H 6.90; N 4.71.

Preparation of solid phase diketone 5. To a cooled solution (0 °C) of 1,2-diimine **1** (0.50 g, 1.49 mmol) in 15 mL dry THF under nitrogen was added LDA (1.09 mL, 1.49 mmol, 1.5 M in THF). After stirring at 0 °C for 2 hr, (bromomethyl)polystyrene (1.06 g, 0.75 mmol) was added and the resulting suspension was stirred for 3 hr at 0 °C and 10 hr at room temperature. The resin was filtered, washed with THF (2 x 10 mL), H_2O (2 x 20 mL), CH_2Cl_2 (2 x 20 mL), and dried under high vacuum to afford 0.60 g of 1,2-diimine resin **2**. The loading capacity of this resin was calculated to be 0.40 mmol/g based on nitrogen analysis (1.21% N). A strong absorbance at 1635 cm^{-1} (C=N) is observed by single bead FTIR. A stirring suspension of 1,2-diimine resin **2** (0.25 g, 0.09 mmol) and oxalic acid (42 mg, 0.47 mmol) in 10 mL THF/H_2O (5:1 v/v) was heated to 70 °C for 12 hr. After cooling to room temperature, the resin was filtered and washed with DMF (2 x 10 mL), H_2O (2 x 10 mL), and THF (2 x 10 mL) to yield 0.15 mg of diketone resin **5**. A strong absorbance at 1712 cm^{-1} (C=O) is observed by single bead FTIR.

General procedure for the solid phase synthesis of 1,2-diimine resins **6.** To a suspension of diketone resin **5** (0.10 g, 0.04 mmol) in 8 mL of dry CH_2Cl_2 was added the appropriate aniline (2.40 mmol) and $TiCl_4$ (1.20 mL, 1.20 mmol, 1.0 M in CH_2Cl_2) under nitrogen. The suspensions were shaken at room temperature for 24 hr upon which the resins were filtered and washed extensively with CH_2Cl_2 (3 x 10 mL), 10% $NaOCH_3$ in anhydrous THF/MeOH (3 x 10 mL), THF (3 x 10 mL), and dried under high vacuum to yield the desired 1,2-diimine resins **6**. Nitrogen analysis on a random sampling from the library revealed loading capacities to be approximately 0.38 mmol/g.

*General procedure for preparing the amine-tagged resins **10** and **11**.* (Bromomethyl)polystyrene (1.00g, 0.51 mmol, 0.51 mmol/g) and the appropriate secondary amine (0.15 mmol) were combined in 10 mL dry N-methylpyrrolidine and heated to 50 °C for 20 hr after which the resin filtered and washed extensively with N-methylpyrrolidine, 4:1 THF/saturated Li_2CO_3 in H_2O (2 x 20 mL), THF (2 x 20 mL), CH_2Cl_2 (2 x 20 mL), and Et_2O (2 x 20 mL). The resultant resins were dried under high vacuum to afford the amine tagged resins. Bromine analysis indicated that a maximum of 10 % of the (bromomethyl)polstyrene sites had reacted with the secondary amines.

*Preparation of solid phase complexes **1** and **2**.* Reactions were performed in glass tubes in a 48-cell parallel reactor. To a suspension of diketone resins **5** (0.10 g, 0.08 mmol) in 8 mL of dry CH_2Cl_2 was added the appropriate aniline (2.40 mmol) and $TiCl_4$ (1.20 mL, 1.20 mmol, 1.0 M in CH_2Cl_2) under nitrogen. The suspensions were shaken at room temperature for 24 hr upon which the resins were filtered and washed extensively with CH_2Cl_2 (3 x 10 mL), anhydrous $NaOCH_3$ in THF/MeOH (3 x 10 mL), THF (3 x 10 mL), and dried under high vacuum to yield the desired 1,2-diimine resins **6**. These resins were then split and converted to the corresponding complexes of Ni (II) **1** and Pd (II) **2** by the addition of (DME)$NiBr_2$ (30 mg, 0.10 mmol) and (COD)PdMeCl (27 mg, 0.10 mmol), respectively, in 10 mL CH_2Cl_2 and the reaction block was shaken for 12 hr. The resins were then washed with CH_2Cl_2 (4 x 10 mL) and dried under high vacuum to afford the desired resin bound complexes. Loading capacities for these resins were calculated to be approximately 0.35 mmol/g based on Ni and Pd analysis.

*Preparation of amine-tagged 1,2-diimine resins **12** and **13**.* To a cooled solution of 1,2-diimine **3** (0.17 g, 0.50 mmol) in 10 mL dry THF under nitrogen was added LDA (0.33 mL, 0.50 mmol, 1.5 M in THF). The resultant mixture was stirred at 0 °C for 45 min whereupon 0.50 g of the tagged (bromomethyl)polystyrene was added. The resulting suspension was stirred for 90 min at 0 °C and room temperature for 17 hr upon which the resins were filtered and washed extensively with THF (2 x 25 mL), H_2O (2 x 25 mL), THF (2 x 25 mL), and CH_2Cl_2 (2 x 20 mL). The bright yellow resins were then dried under high vacuum to afford the desired tagged 1,2-diimine resins **12** and **13**.

*Preparation of methylpentylamine tagged complex **14**.* 0.40 g of methylpentylamine tagged resin was combined with (DME)$NiBr_2$ (0.53 mmol) in 40 mL dry CH_2Cl_2 under nitrogen and the mixture was stirred at room temperature for 24 hr. The resultant resin was filtered and washed extensively with CH_2Cl_2 and dry acetone to give 0.40 g of the supported complex **14** as a red-brown resin. A catalyst loading of 0.40 mmol/g was obtained based on nickel analysis.

Preparation of dipentylamine tagged complex 15. 0.10 g of methylpentylamine tagged resin was combined with (1,5-cyclooctadiene)PdMeCl (0.38 mmol) in 10 mL dry CH_2Cl_2 under nitrogen and the mixture was stirred at room temperature for 4 hr. The resultant red-brown resin was filtered and washed extensively with CH_2Cl_2 (2 x 30 mL), toluene (2 x 30 mL), and pentane (2 x 30 mL) to give 0.10 g of supported catalyst **14** as a reddish-brown resin. A catalyst loading of 0.30 mmol/g was obtained based on palladium analysis.

General Decoding Procedure. In a typical experiment, 100 μL of α-(chloroethyl)chloroformate and 150 μL of CH_2Cl_2 were added to the sample beads. The resultant suspensions were agitated overnight at room temperature whereupon each sample evaporated to dryness. To each sample was then added 300 μL MeOH and the resultant suspensions were heated at 50°C overnight after which time the samples were evaporated to dryness. These samples were subjected to HPLC with fluorescence detection as previously described.

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21. The tagged catalysts were also run separately to assess relative performance trends.
22. The molecular weight values of high molecular weight polymers could be higher than the M_w values obtained by high temperature GPC since additional effects such as shear degradation may occur. See DeGroot, A. W.; Hamre, W. J. *J. Chromatogr.* **1993**, *648*, 33-39.