Organometallics **2007,** *26,* 1571−1574

A Highly Reusable Catalyst for Enantioselective Ketone Hydrogenation. Catalyst−Organic Frameworks by Alternating ROMP Assembly

Corbin K. Ralph and Steven H. Bergens*

Department of Chemistry, University of Alberta, Edmonton, Alberta, T6G 2G2 Canada

Received February 4, 2007

*Summary: The alternating ROMP assembly of trans-RuCl$_2$((R)-5,5′-dinorimido-BINAP)(Py)$_2$ (**5**) and COE using RuCl$_2$(=CHPh)(PCy$_3$)$_2$ (**7**) as the catalyst resulted in an extended, three-dimensional catalyst−organic framework. The catalyst−organic framework was converted to contain Noyori-type active sites that were recycled for 25 times at low catalyst loadings without loss in enantioselectivity or activity and without detectable Ru leaching.*

We report a heterogenized chiral ketone hydrogenation catalyst that sustains a high number of reuses without detectable leaching of the catalyst metal center into the product. Hydrogenation is the most utilized, both in number and in scale, enantioselective catalytic reaction in the pharmaceutical, flavoring, fragrance, vitamin, and agrochemical industries.[1] This widespread application to hydrogenations and other catalytic reactions has encouraged a great deal of research aimed toward heterogenizing homogeneous enantioselective catalysts.[2] The objectives include the production of solid catalysts that are reusable, that do not leach toxic metal traces into the desired product, and that maintain the high activity and selectivity of their homogeneous procatalysts.[2e] The structures of solid catalysts can also provide benefits, including size selectivity and macroscopic chirality, that are not available to the homogeneous procatalysts. Among the notable recent advances in heterogenized chiral hydrogenation catalysts are a BINAP−polystyrene system (BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) used for the hydrogenation of ketones,[3] attachment of homogeneous catalysts to silica[4] and iron-nanoparticle surfaces,[5] preparation of self-supporting catalyst systems consisting of metal−organic frameworks,[6] and anchoring of cationic homogeneous catalysts onto heteropoly acid-modified supports.[7] These advances are significant, but they are vastly outnumbered by the number of reported systems that do not sustain more than a few reuses without loss in activity or selectivity. It remains a significant challenge in this field to develop practical heterogenized catalysts that sustain a large number of reuses under low hydrogen pressures in solvents best suited for the homogeneous catalytic reaction and, at the same time, provide high turnover numbers per run (TON/run), enantioselectivities (ee's), and rates without detectable catalyst leaching into the product.

In a previous publication, we reported the first polymeric asymmetric hydrogenation catalyst made by ROMP.[8] ROMP preparations of polymer-based catalysts are often able to utilize the metal complex directly as a monomer, and they offer good control over the resulting polymer's structure and length.[9] Using *trans*-RuCl$_2$(Py)$_2$((*R*,*R*)-Norphos) (**1**; ((*R*,*R*)-Norphos = (2*R*,3*R*)-2,3-bis(diphenylphosphino)bicyclo[2.2.1]hept-5-ene, Py = pyridine) as the monomer, we devised an alternating ROMP polymerization using cyclooctene (COE) as a spacer comonomer to prepare a polymeric catalyst that sustained 10 reuses without detrimental loss in activity or ee for the hydrogenation of 1′-acetonaphthone (TON/run = 500, 83% ee (*S*), rate = 40% of the rate of the homogeneous catalyst). To our knowledge, this remains the highest number of reuses of an insoluble, *polymer*-based hydrogenation catalyst without detrimental loss in ee or rate, that does not require a swelling cosolvent. We now report an alternating ROMP assembly of an extended, three-dimensional catalyst−organic framework with the catalyst complex as a high-loading, cross-linking monomer.

We chose BINAP as the preligand because it is the most influential of the so-called privileged ligands in enantioselective catalysis.[10] We prepared a ROMP-active version of BINAP in one step by condensation between the known precursor (*R*)-5,5′-diamino-BINAP[11] (**2**) and the *endo*-dicarboxylic anhydride

---

* To whom correspondence should be addressed. E-mail: steve.bergens@ualberta.ca.

(1) (a) *Asymmetric Catalysis on Industrial Scale*; Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, Germany, 2003. (b) *The Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, Germany, 2006. (c) Blaser, H. U.; Pugin, B.; Spindler, F. *J. Mol. Catal. A* **2005**, *231*, 1.

(2) (a) End, N.; Schoning, K. U. Immobilized catalysts in industrial research and application. *Top. Curr. Chem.* **2004**, *242*, 241. (b) Blaser, H. U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103. (c) Cole-Hamilton, D. J. *Science* **2003**, *299*, 1702. (d) Dioos, B. M. L.; Vankelecom, I. F. J.; Jacobs, P. A. *Adv. Synth. Catal.* **2006**, *348*, 1413. (e) Heitbaum, M.; Glorius, F.; Escher, I. *Angew. Chem., Int. Ed.* **2006**, *45*, 4732. (f) McMorn, P.; Hutchings, G. J. *Chem. Soc. Rev.* **2004**, *33*, 108. (g) Saluzzo, C.; Lemaire, M. *Adv. Synth. Catal.* **2002**, *344*, 915. (h) Song, C. E. *Annu. Rep. Prog. Chem., Sect. C, Phys. Chem.* **2005**, *101*, 143. (i) *Chiral Catalyst Immobilization and Recycling*; De Vos, D. E., Vankelecom, I. F. J., Jacobs, P. A., Eds.; Wiley-VCH: Weinheim, Gemany, 2000.

(3) (a) Bayston, D. J.; Fraser, J. L.; Ashton, M. R.; Baxter, A. D.; Polywka, M. E. C.; Moses, E. *J. Org. Chem.* **1998**, *63*, 3137. (b) Ohkuma, T.; Takeno, H.; Honda, Y.; Noyori, R. *Adv. Synth. Catal.* **2001**, *343*, 369. (c) Saluzzo, C.; Lamouille, T.; Herault, D.; Lemaire, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1841. (d) ter Halle, R.; Schulz, E.; Spagnol, M.; Lemaire, M. *Synlett* **2000**, 680. (e) Yu, H. B.; Hu, Q. S.; Pu, L. *Tetrahedron Lett.* **2000**, *41*, 1681. (f) Yu, H. B.; Hu, Q. S.; Pu, L. *J. Am. Chem. Soc.* **2000**, *122*, 6500.

(4) Steiner, I.; Aufdenblatten, R.; Togni, A.; Blaser, H. U.; Pugin, B. *Tetrahedron: Asymmetry* **2004**, *15*, 2307.

(5) Hu, A. G.; Yee, G. T.; Lin, W. B. *J. Am. Chem. Soc.* **2005**, *127*, 12486.

(6) (a) Hu, A. G.; Ngo, H. L.; Lin, W. B. *J. Am. Chem. Soc.* **2003**, *125*, 11490. (b) Liang, Y. X.; Jing, Q.; Li, X.; Shi, L.; Ding, K. L. *J. Am. Chem. Soc.* **2005**, *127*, 7694.

(7) (a) Augustine, R.; Tanielyan, S.; Anderson, S.; Yang, H. *Chem. Commun.* **1999**, 1257. (b) Burk, M. J.; Gerlach, A.; Semmeril, D. *J. Org. Chem.* **2000**, *65*, 8933.

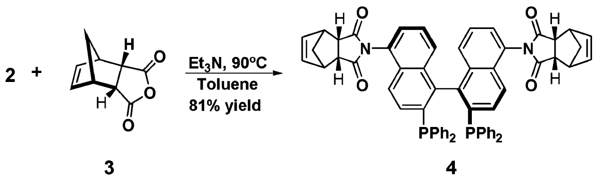
(8) Ralph, C. K.; Akotsi, O. M.; Bergens, S. H. *Organometallics* **2004**, *23*, 1484.

(9) (a) Buchmeiser, M. R. *Chim. Oggi* **2006**, *24*, 8. (b) Buchmeiser, M. R. Metathesis polymerization to and from surfaces. *Adv. Polym. Sci.* **2006**, *197*, 137. (c) Herndon, J. W. *Coord. Chem. Rev.* **2006**, *250*, 1889.

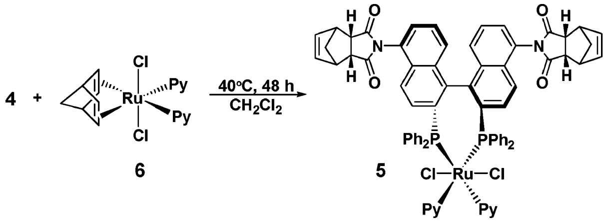
(10) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.

10.1021/om070109g CCC: $37.00

3 to give (*R*)-5,5′-*N*-bis(*cis*-5-norbornene-2,3-*endo*-dicarboximido)-2,2′-bis(diphenylphosphino)-1,1′-BINAP (**4**; (*R*)-5,5′-dinorimido-BINAP) in 81% yield (eq 1). The ligand **4** formed as a mixture of three NMR-distinct, diastereomeric atropisomers that differed in the relative rotameric orientations of the norimido groups about the arene−nitrogen bonds. Two of these diastereomeric atropisomers, *R,R,R* and *S,R,S*, were C_2 dissymetric, while the other, *R,R,S*, was not. Interestingly, the ligand **4** precipitated from 90 °C solutions of toluene as only one C_2 dissymetric diastereotopic atropisomer in 87% yield. This single atropisomer converted after 2 h at 22 °C in CD_2Cl_2 into the mixture of diastereomeric atropisomers in the same ratio as that from the preparation reaction. The catalyst monomer *trans*-Ru(**4**)Cl_2(Py)$_2$ (**5**) was prepared by replacing the norbornadiene (NBD) ligand in the compound *trans*-RuCl_2(Py)$_2$(NBD) (**6**) with **4** (eq 2).[12] As was the case for **4**, monomer **5** formed as a mixture of three diastereomers, two with a C_2 axis of rotation and one without, these being in a ratio similar to that of the free ligand **4**. Reaction between the ruthenium precursor **6** and the single C_2-dissymetric diastereotopic atropisomer of **4** obtained from hot toluene (vide supra) resulted in formation of **5** as a mixture of diastereomers.



(1)

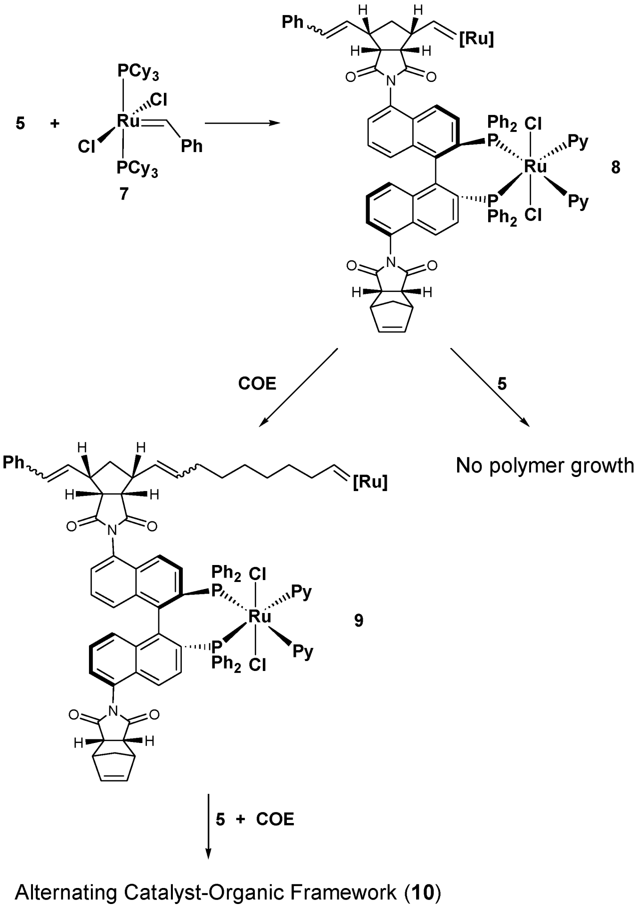


(2)

Catalytic ROMP did not occur with **5** using $RuCl_2(=CHPh)(PCy_3)_2$ (**7**) as catalyst (5 mol % **7**, CD_2Cl_2, 25 °C, 24 h). Instead, we utilized an alternating ROMP with COE as the spacer monomer.[8] The principles are that the strained norbornyl groups in **5** are intrinsically more reactive toward metathesis than COE, and **5** thereby reacts with **7** first to form a corresponding Ru−alkylidene species such as **8** (Scheme 1). The alkylidene **8** is too crowded to react with another molecule of **5**, but it is not too crowded to react with COE to generate **9**, with the corresponding Ru−alkylidene on the end of a C_8 spacer. This uncrowded alkylidene **9** now reacts with another molecule of **5**, then COE, and so on.

The following is evidence that this system reacts via such a sequence of steps. First, addition of COE (COE:**5** = 3.6:1) to a solution of **5** and **7** (5 mol % **7**, CD_2Cl_2, 25 °C) did initiate the polymerization, albeit slowly, at 22 °C. All of **5** and COE were consumed, however, after 40 h at 45 °C. Second, although the product NMR peaks were broad, and they overlapped with the peaks of the starting materials, a peak height analysis of a spectrum recorded after 4 h indicated that roughly 75% of **5** had reacted with COE to form the polymer. The ratio of reacted norbornyl groups in **5** to the amount of COE consumed at this point was ∼1:1. Considering that **5** does not undergo ROMP in the absence of COE, but COE does in the absence of **5**, the roughly equal decrease in both norbornyl groups in **5** and COE is strong evidence of an alternating, rather than a block ROMP process. A spectrum recorded after 24 h showed that all of **5** was consumed, while some free COE remained in solution. That the initial ratio of COE to norbornyl groups in **5** was 1.8:1 and that free COE remained after **5** was consumed shows that the ratio of COE to norbornyl groups in the ROMP product was less than 1.8:1, a result consistent with the peak height analysis (vide supra) that indicated the ratio was ∼1:1. The remaining COE was consumed ∼20 h later, showing that ROMP activity did not end when all of **5** had reacted. The ^{31}P NMR spectrum of the product consisted of a broad signal with the same chemical shift as for the starting material **5**, indicating that the immediate chemical environment of the ruthenium catalyst center was not significantly altered by the alternating ROMP.

Scheme 1. Alternating ROMP Assembly of 5 and COE



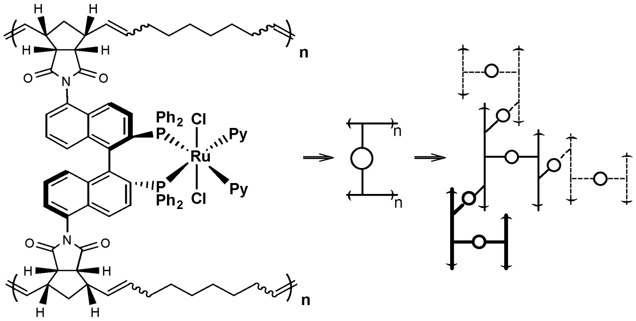
We designed the alternating ROMP between COE and both norbornyl groups in **5** to result in assembly of an extended, three-dimensional catalyst−organic framework with the catalyst complex as cross-linking units (**10**). In this way, catalyst leaching is minimized, and the cross-linking imparts a degree of rigidity to the framework. Scheme 2 shows a representation of the framework. On the basis of the preceding analysis, the ratio of COE to norbornyl groups in the framework is near 1:1 (at least less than 1.8:1) when **5** is consumed; thus, the loading of cross-linking catalyst complexes in the framework is high. This system thereby shares characteristics with the metal−organic frameworks.[6,13] One major difference is that metal−ligand covalent bonds are not part of the framework prepared by the alternating ROMP assembly of COE and **5**.

---

(11) Okano, T. K. H.; Akutagawa, S.; Kiji, J.; Konishi, H.; Fukuyama, K.; Shimano, Y. U.S. Patent 4 705 895, 1987.

(12) (a) Akotsi, O. M.; Metera, K.; Reid, R. D.; McDonald, R.; Bergens, S. H. *Chirality* **2000**, *12*, 514. (b) Leong, C. G.; Akotsi, O. M.; Ferguson, M. J.; Bergens, S. H. *Chem. Commun.* **2003**, 750.

Scheme 2. Schematic Representation of the Extended, Three-Dimensional Catalyst−Organic Framework 10



10

The Py ligands at the Ru centers of the framework were replaced in 100% yield by reaction with either (*R*,*R*)-dpen (dpen = 1,2-diphenylethylenediamine) or (*R*)-daipen (daipen = 1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine) that was added to the mixture after the alternating ROMP assembly was complete to result in catalyst−organic frameworks **11** and **12**, respectively.[12] These frameworks were then deposited as a thin film over BaSO$_4$ to provide mechanical stability to the system, to act as a filtration aid, and to improve mass transport at the active sites.[8]

The hydrogenation of 1′-acetonaphthone was used to evaluate the catalyst framework. The criteria for the turnover number (TON) of an enantioselective catalytic reaction before it can be applied to industrial small-scale production has been identified as ≥1000.[1c] We therefore chose 1000:1 as the ratio of substrate to catalyst for each run. We carried out the hydrogenation in 2-propanol solvent, under 10 atm of H$_2$, in the presence of 20 equiv of KO^{t}Bu per active site. These conditions are indigenous to the homogeneous reaction.[14] It was necessary to devise a method to preserve the catalyst between runs that was easily reversed during the subsequent catalytic hydrogenation. In a recent study, we prepared the intermediates proposed for these hydrogenations, and most are unstable at room temperature.[15] We also showed that the alkoxide *trans*-[((*R*)-BINAP)Ru(H)-(^{i}PrO)((*R*,*R*)-dpen)] (**13**) is relatively robust at room temperature and it is formed when several of the catalytic intermediates react with ^{i}PrOH. Further, **13** reacts rapidly even at ∼−80 °C with H$_2$ upon addition of base, e.g., ∼1 equiv of KO^{t}Bu, to form the active catalyst *trans*-[((*R*)-BINAP)Ru(H)$_2$((*R*,*R*)-dpen)]. These properties allowed us to protect the framework catalyst as the analogue of **13** between runs by keeping it under 2-propanol under an atmosphere of H$_2$ at all times between runs. The catalyst was regenerated for subsequent reuse by adding KO^t-Bu. The catalyst could be stored for days using this methodology without loss in activity or ee.

Figure 1 shows a graph plotting percent yield and percent ee vs number of recycles we obtained for the hydrogenation of 1′-acetonaphthone reusing a single sample of the catalyst framework **11**. The ee for each run was 95% (*S*).

Runs 1−4 were used to condition the framework and to optimize the reaction temperature and time. The increase in activity that occurred during these conditioning runs likely resulted from swelling of the catalyst framework and formation of the active catalyst from the ruthenium−chloride precursor. As run 3 (40 °C, 21 h) gave 100% yield, and run 4 (35 °C, 21 h) gave 80%, the subsequent runs were carried out at 40 °C. We reused the catalyst framework for a remarkable 25 further runs, with the catalyst operating for 25 days, without loss in catalytic activity or ee. A change in stirbar pitch was noted during run 29, and run 30 provided 91% yield without a change in ee, suggesting that a mechanical event occurred that diminished the activity of the catalyst during run 29. Runs 31−33 were carried out for 45 h with 100% yield, and run 34 was carried out with 2000 equiv of ketone, also for 45 h, and with 92% yield, suggesting no further decrease in catalyst activity occurred after run 29. When the steel reactor was opened, it was found that one side of the stirbar had worn flat, and ∼75% of the catalyst had splashed up the inner walls and lid of the vessel, leaving only ∼25% in contact with the reaction mixture.

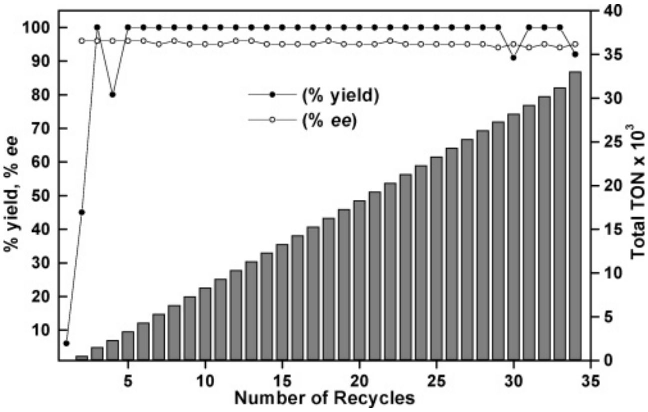


Figure 1. Recycles carried out under the experimental conditions described in Table 1.

The pressure drop in the sealed bomb corresponded to the amount of hydrogen consumed by each hydrogenation. Using this pressure drop as an indicator, the turnover frequency during the first 1 h of runs 5−29 was ∼750 h^{-1} at 75% conversion. This rate is comparable to that for the homogeneous hydrogenation, showing that mass transport did not significantly slow the framework catalyst.[14] Catalyst leaching was examined by reducing the colorless product solution to dryness, followed by sulfated ash treatment of the residues.[16] Control experiments revealed that an insoluble Ru mirror can result from the sulfated ash procedure; thus, each residue was further treated with 4 M KOH saturated in K$_2$S$_2$O$_8$[17] to dissolve any Ru before quantification by ICP-MS. A representative sampling of the runs contained less than the detectable limit of Ru, i.e., <4 ppb, corresponding to <0.00016 equiv of the Ru originally present in the catalyst framework.

Table 1 shows the ee's obtained using catalyst frameworks **11** and **12**. The ketones were hydrogenated sequentially using one sample of **11**. The ee's were typically over 90%; they were representative of those obtained from the homogeneous hydrogenations.[14] The microscopic chiral environment around the active sites in the catalyst organic framework therefore resembled that of the homogeneous procatalysts.

In summary, the majority of reported heterogenized chiral hydrogenation catalysts operate at less than practical TON/run values (i.e., <1000) and suffer from detrimental losses in activity by the third reuse. The only previous heterogenized hydrogenation catalyst systems that sustained more than 10 reuses at

---

[13] (a) Dai, L. X. *Angew. Chem., Int. Ed.* **2004**, *43*, 5726. (b) Ding, K. L.; Wang, Z.; Wang, X. W.; Liang, Y. X.; Wang, X. S. *Chem. Eur. J.* **2006**, *12*, 5188. (c) Lin, W. B. *J. Solid State Chem.* **2005**, *178*, 2486. (d) Seo, J. S.; Whang, D.; Lee, H.; Jun, S. I.; Oh, J.; Jeon, Y. J.; Kim, K. *Nature* **2000**, *404*, 982.

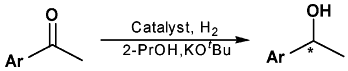
[14] Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40.

[15] Hamilton, R. J.; Bergens, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 13700.

[16] Gaines, P. Reliable Measurements-A Guidebook for Trace Analysts; online guide (http://www.ivstandards.com/tech/reliability/part14.asp).

[17] Wiel, V. D. *Chem. Weekbl.* **1952**, *48*, 597.

Table 1. Heterogeneous Hydrogenation of Aromatic Ketones[a]



	ee (%)	
Ar	cat. **11**	cat. **12**
1-naphthyl	95	97
2′-Me-Ph	89	97
4′-tBu-Ph	91	90

[a] All reactions were carried out at 40 °C under 10 atm pressure of H_2 at a substrate concentration of 1.0 M with substrate/KO^tBu/catalyst = 1000/20/1 for 21 h. ee values were determined by GC on a Supelco β-Dex120 column.

practical TON/run values without loss in activity or ee were the Ru(BINAP)-type complexes attached to magnetic nanoparticles prepared by Lin et al.[5] These catalysts sustained 14 reuses at TON/run = 1000 under 48 atm of H_2 for the hydrogenation of 1′-acetonaphthone. The catalyst−organic frameworks prepared here by alternating ROMP assembly sustained at least 25 reuses under mild pressures without detectable metal leaching. The general designs and concepts we present in this manuscript are adaptable to other asymmetric reactions. Research is underway in our laboratories to adapt this methodology to other reactions, to determine the precise structure of the catalyst−organic frameworks, and to examine further the origins of the high reusability of these systems.

Acknowledgment. We thank the University of Alberta and the NSERC for supporting this research.

Supporting Information Available: Text, tables, and figures giving experimental procedures for ligand and hetereogeneous catalyst preparation and use. This material is available free of charge via the Internet at http://pubs.acs.org.

OM070109G