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Simple Strategy for the Immobilization of Dirhodium Tetraprolinate Catalysts Using a Pyridine-Linked Solid Support

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Abstract: Dirhodium tetracarboxylates are readily immobilized on agitation in the presence of highly cross-linked polystyrene resins with a pyridine attachment. A systematic study demonstrates that the polymer backbone, the linker, the terminal pyridine group, and the catalyst structure all contribute to the efficiency of dirhodium catalyst immobilization. The immobilization is considered to be due to the combination of ligand coordination and encapsulation. The dirhodium tetraprolinate catalysts, Rh_2(*S*-DOSP)$_4$ (**1a**), Rh_2(*S*-TBSP)$_4$ (**1b**), and Rh_2(*S*-biTISP)$_2$ (**2**), are all efficiently immobilized. The resulting heterogeneous complexes are very effective catalysts for asymmetric cyclopropanation between methyl phenyldiazoacetate and styrene, and under optimized conditions they can be recycled five times with virtually no loss in enantioselectivity. The three-phase test studies indicated that a very slow reaction occurs when both the catalyst and the diazo compound were immobilized, but the slow rate precluded the likelihood that the cyclopropanation was predominately occurring by a release-and-capture mechanism.

Introduction

The challenges of chiral catalyst immobilization have attracted the interest of a wide range of polymer and synthetic chemists.[1] Over the past few decades, the field of carbenoid chemistry has witnessed explosive growth in the development of chiral catalysts.[2,3] Some of the commonly used catalysts for asymmetric carbenoid reactions derived from copper, ruthenium, and rhodium(II) complexes have been immobilized on organic and inorganic supports.[4] Most immobilization strategies have relied on covalent attachments between chiral ligands and the solid supports.[4] In general, the method of immobilization, choice of polymer matrix, and point of attachment to the catalyst influence the chiral environment of the immobilized species.[1a,5]

Dirhodium tetraprolinate catalysts Rh_2(*S*-DOSP)$_4$ (**1a**), Rh_2(*S*-TBSP)$_4$ (**1b**), and Rh_2(*S*-biTISP)$_2$ (**2**) (Figure 1) developed in our laboratories have proven to be exceptional catalysts for homogeneous asymmetric intermolecular cyclopropanation and C−H activation reactions of donor/acceptor substituted carbenoids **3** (Figure 2).[6] Consequently, we have begun to explore the utilization of immobilized versions of these catalysts. The design strategy for effective asymmetric induction with these catalysts is based on the coordination of several identical chiral ligands of low symmetry to the central bimetallic core to produce a chiral complex of higher symmetry.[6d] Therefore, immobilization methods would be required that would avoid modification of any of the ligands because this would destroy the high-symmetry environment of the chiral catalyst.

We have communicated a novel approach for the immobilization of the dirhodium tetraprolinates using the general strategy shown in Scheme 1.[7,8] In this method, an appropriate polymer backbone functionalized with a pyridine group was used to coordinate to one rhodium while the other rhodium continued to be an active site for catalysis. This approach has been very

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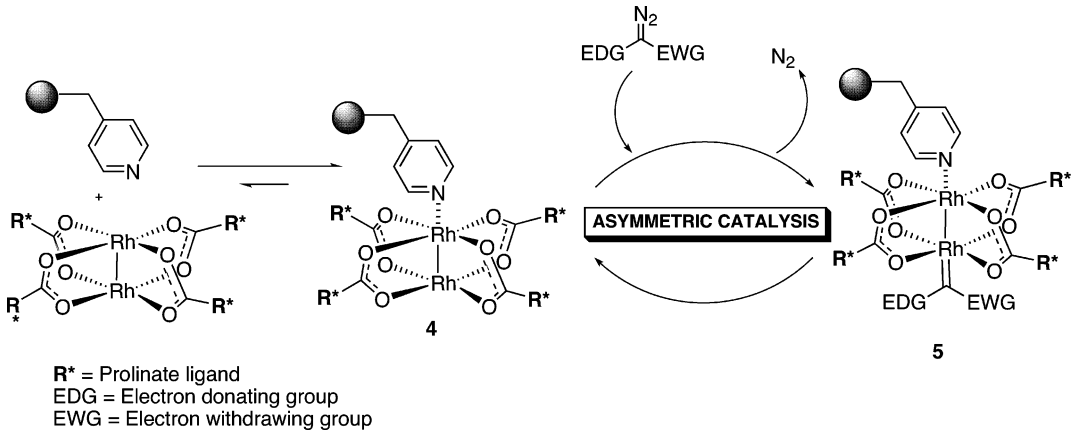
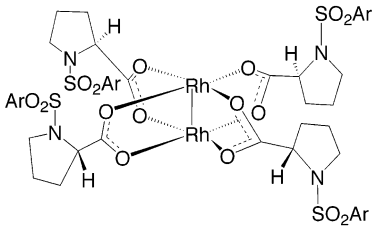
(1) (a) *Chiral Catalysts Immobilization and Recycling*; De Vos, D. E., Vankelecom I. F. J., Jacobs, P. A., Eds.; Wiley-VCH: Weinheim, Germany, 2000. (b) Clapham, B.; Reger, T. S.; Janda, K. D. *Tetrahedron* **2001**, *57*, 4637. (c) Sherrington, D. C. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 2364. (d) Flynn, D. L.; Devraj, R. V.; Parlow, J. J. In *Solid-Phase Organic Synthesis*; Burgess, K., Ed.; Wiley-Interscience: New York, 2000; pp 149−194. (e) de Miguel, Y. D.; Bryle, E.; Margue, R. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3085−3094.
(2) Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1−326.
(3) (a) Davies, H. M. L.; Beckwith, R. J. W. *Chem. Rev.* **2003**, *103*, 2861. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. In *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998.
(4) (a) Bergbreiter, D. E.; Chen, B.; Morvant, M. *Tetrahedron Lett.* **1991**, *32*, 2731. (b) Doyle, M. P.; Eismont, M. Y.; Bergbreiter, D. E.; Gray, H. N. *J. Org. Chem.* **1992**, *57*, 6103. (c) Burguette, M. I.; Fraile, J. M.; Garcia, J. I.; Garcia-Verdugo, E.; Luis, S. V.; Mayoral, J. A. *Org. Lett.* **2000**, *2*, 3905. (d) Burguette, M. I.; Fraile, J. M.; Garcia, J. I.; Garcia-Verdugo, E.; Luis, S. V.; Mayoral, J. A. *J. Org. Chem.* **2001**, *66*, 8893. (e) Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Perez, P. J. *Organometallics* **2000**, *19*, 285. (f) Glos, M.; Reiser, O. *Org. Lett.* **2000**, *2*, 2045. (g) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Pitillo, M. *J. Org. Chem.* **2001**, *66*, 3160. (h) Doyle, M. P.; Timmons, D. J.; Tumonis, S. J.; Gau, H.; Blossey, C. E. *Organometallics* **2002**, *21*, 1747. (i) Cornejo, A.; Fraile, J. M.; Garcia, J. I.; Garcia-Verdugo, E.; Gil, M. J.; Legarreta, G.; Luis, V. S.; Martinez-Merino, V.; Mayoral, J. A. *Org. Lett.* **2002**, *4*, 3927. For reviews, see: (j) Rechavi, D.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 3467. (k) Bergbreiter, D. E. In *Chiral Catalyst Immobilization and Recycling*; De Vos, D. E., Vankelecom, I. F. J., Jacobs, P. A., Eds.; Wiley-VCH: Weinheim, Germany, 2000; p 43.
(5) Altava, B.; Burguete, M. I.; Garcia-Verdugo, E.; Luis, S. V.; Vincent, M. J.; Mayoral, J. A. *React. Polym.* **2001**, *48*, 25.
(6) (a) Reference 3a. (b) Davies, H. M. L.; Antoulinakis, E. G. *J. Organomet. Chem.* **2001**, *617*−*618*, 47. (c) Davies, H. M. L. *J. Mol. Catal* **2002**, *189*, 125. (d) Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, 2459.
(7) Nagashima, T.; Davies, H. M. L. *Org. Lett.* **2002**, *4*, 1989.
(8) Davies, H. M. L.; Walji, A. M. *Org. Lett.* **2003**, *5*, 479.

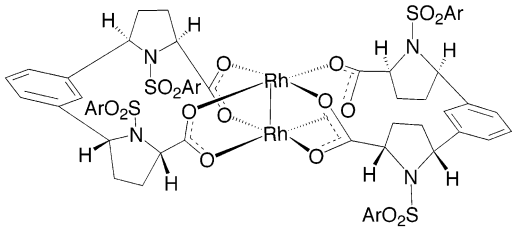
Scheme 1. Strategy for Catalyst Immobilization



successful for asymmetric intermolecular cyclopropanation[7] and asymmetric intermolecular C−H activation.[8] During the course of these studies, a number of puzzling observations were made.

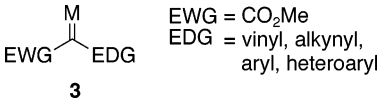


1a Rh_2(*S*-DOSP)$_4$: Ar = *p*-$C_{12}H_{25}C_6H_4$
1b Rh_2(*S*-TBSP)$_4$: Ar = *p*-^{t}BuC_6H_4



2 Rh_2(*S*-biTISP)$_2$:
Ar = 2,4,6-tri-^{i}PrC_6H_4

Figure 1. Dirhodium tetraprolinate catalysts.

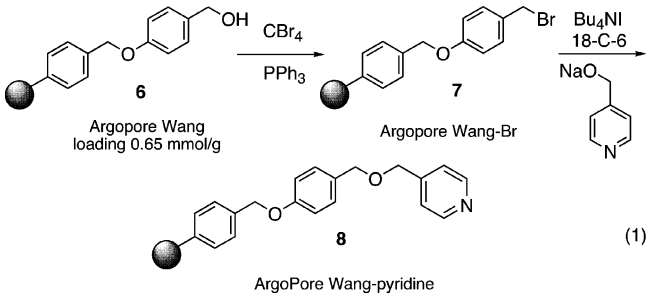


3

Figure 2. Donor/acceptor substituted carbenoids.

Pyridine coordination is known to deactivate dirhodium complexes, and control experiments of homogeneous reactions clearly revealed that the prolinate catalysts were deactivated by pyridine coordination.[7] Furthermore, replacement of the pyridine linker with benzene did not block the immobilization of the catalyst. Therefore, the exact mechanism of the immobilization process remained very uncertain. A further concern with the earlier studies was the utilization of an excess of the expensive catalysts. Herein, we describe a systematic study of the immobilized catalysts, which defines what features of the catalyst, polymer, linker, and terminal group are optimum for immobilization and catalytic activity. Furthermore, a more practical and cost-effective method for catalyst immobilization is described.

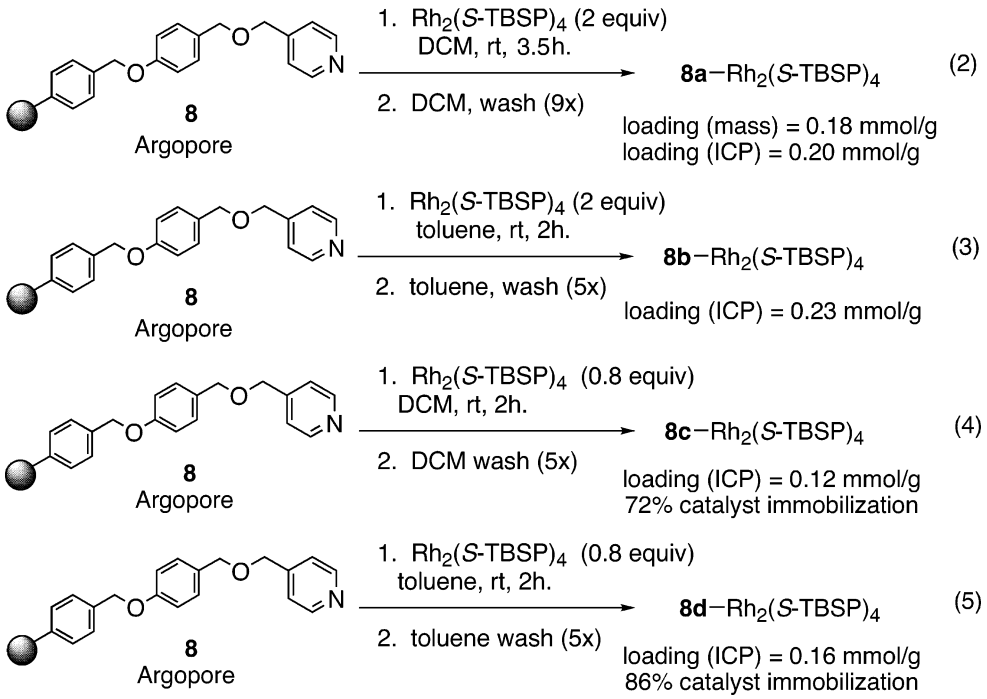
In the original studies[7,8] the Argopore[9] resin was chosen as the polymer backbone due to its rigid, highly cross-linked, macroporous polystyrene framework. Such a polymer would allow easy access for reagents into reaction sites without having to swell the beads.[10] Consequently, hydrocarbon solvents, which are ideal for high asymmetric induction in solution-phase reactions of donor/acceptor substituted carbenoids would be applicable for reactions with the immobilized catalysts.[6a] The Wang linker[11] was chosen because it should ensure sufficient spacing between the catalyst and the polymer to minimize unfavorable steric interactions. The basic approach to introduce the pyridine terminal group is shown in eq 1. The hydroxyl group of the Wang linker **6** was converted to the bromo derivative **7** and then reacted with 4-pyridyl carbinol to form the 4-benzyloxymethyl-pyridine resin **8**. The pyridine loading of the Argopore-Wang resin **8** was determined to be 0.30 mmol/g by cleavage of the 4-pyridyl carbinol using trifloroacetic acid/dichloromethane (1:1).



(1)

The first series of experiments were directed toward the development of optimum reaction conditions for catalyst immobilization. These test reactions were conducted using Rh_2(*S*-TBSP)$_4$ as catalyst. In our original communication,[7] the immobilization of Rh_2(*S*-TBSP)$_4$ on the resin **8** was carried out using dichloromethane as solvent. Gentle shaking of **8** in a solution of Rh_2(*S*-TBSP)$_4$ (2 equiv) in dichloromethane for 3.5 h caused the color of the resin to change from a pale yellow to purple. After extensive washing with dichloromethane (9×), the **8a**-Rh_2(*S*-TBSP)$_4$ resin remained purple, indicating the coordination of the catalyst to the pyridine and its immobilization

(9) Purchased from Argonaut Technologies (www.argotech.com).
(10) Dorwald, F. Z. In *Organic Synthesis on Solid Phase*; Wiley-VCH: Weinheim, Germany, 2000.
(11) Wang, S.-S. *J. Am. Chem. Soc.* **1973**, *95*, 1328.



onto the solid support (eq 2). The change in mass after drying the **8a**-Rh_2(*S*-TBSP)$_4$ was used to determine catalyst loading (0.18 mmol/g), and this has now been confirmed by ICP-AES analysis (0.20 mmol/g). A concern with this original method was the use of dichloromethane as solvent because dichloromethane is not the ideal solvent for high asymmetric induction with Rh_2(*S*-TBSP)$_4$.[6d] A modified immobilization method was developed in which toluene was used as the solvent in place of dichloromethane. This gave **8b**-Rh_2(*S*-TBSP)$_4$ with an ICP-AES determined catalyst loading of 0.23 mmol/g (eq 3). For immobilized catalysts **8a**-Rh_2(*S*-TBSP)$_4$ and **8b**-Rh_2(*S*-TBSP)$_4$, an excess amount of catalyst to resin was used in the immobilization step. To further improve this technology, the immobilization was attempted with the catalyst as the limiting reagent in both solvents. This process was also very effective as **8c**-Rh_2(*S*-TBSP)$_4$ (eq 4) and **8d**-Rh_2(*S*-TBSP)$_4$ (eq 5) were formed with catalyst loadings of 0.12−0.16 mmol/g, which corresponds to 72−86% catalyst immobilization.

In the original communication,[7] the evaluation of **8a**-Rh_2(*S*-TBSP)$_4$ was conducted in standard glassware, using the reaction of methyl phenyldiazoacetate with styrene as the standard reaction. All the work described in the current study has been conducted using an Argonaut Quest-210 parallel synthesizer. This allowed the agitation to be electronically controlled at a standard rate throughout all the experiments. The immobilized catalysts were recycled up to five times, and the yield, enantioselectivity, and reaction time were determined for every other cycle.[12] The rate of the reaction was easily monitored visually because the starting methyl phenyldiazoacetate is yellow and when the reaction reaches completion the solution becomes colorless.

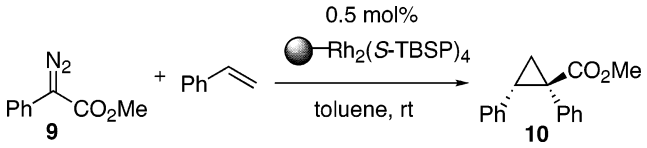
(12) Asymmetric cyclopropanations of aryldiazoacetates are routinely highly diastereoselective. Throughout these studies >92% de was observed and is therefore not reported for each reaction. (a) Davies, H. M. L.; Bruzinski, P. R.; Fall, M. J. *Tetrahedron Lett.* **1996**, *37*, 4133. (b) Doyle, M. P.; Zhou, Q.-L.; Charnsangavej, C.; Longoria, M. A.; McKervey, M. A.; Garcia, C. F. *Tetrahedron Lett.* **1996**, *37*, 4129.

Under these new reaction conditions, comparison of the new variants **8b**−**d**-Rh_2(*S*-TBSP)$_4$ with **8a**-Rh_2(*S*-TBSP)$_4$ revealed some very interesting trends (Table 1). The asymmetric induction in the reaction catalyzed by **8a**-Rh_2(*S*-TBSP)$_4$ was lower (82% ee) than the corresponding homogeneous reaction catalyzed by Rh_2(*S*-TBSP)$_4$ (87−90% ee). Furthermore, the enantioselectivity dropped to 70% ee in the fourth cycle using recycled **8a**-Rh_2(*S*-TBSP)$_4$. In contrast, **8b**-Rh_2(*S*-TBSP)$_4$ resulted in higher enantioselectivity in the first cycle (87% ee) and retained the value reasonably well over five cycles (87 to 81% ee). Catalysts **8c**-Rh_2(*S*-TBSP)$_4$ and **8d**-Rh_2(*S*-TBSP)$_4$ behaved very similarly to **8b**-Rh_2(*S*-TBSP)$_4$, which demonstrates that an effective immobilized catalyst is formed when Rh_2(*S*-TBSP)$_4$ is the limiting agent. Rhodium analysis by ICP-AES of the initial reaction cycles before product isolation was conducted to determine the extent of catalyst leaching between the systems. The reaction mixture (first cycle) from catalyst **8b**-Rh_2(*S*-TBSP)$_4$ contained 1000 ppm Rh, which corresponds to 30% of the initial catalyst charge. The reaction mixture (first cycle) with catalyst **8d**-Rh_2(*S*-TBSP)$_4$ contained 100 ppm Rh, which is 3% of the initial catalyst charge. The improved efficiency of the **8d**-Rh_2(*S*-TBSP)$_4$ is evident, which provides reduced product contamination without compromising catalyst activity and stereoselectivity.

The immobilization of the catalysts and the asymmetric cyclopropanation are very efficient procedures as illustrated in Figure 3. The creamy polymer (Figure 3a) rapidly became purple on exposure to the green solution of Rh_2(*S*-TBSP)$_4$ (Figure 3b). After being stirred for 40 min, the solution became colorless (Figure 3c), indicating that the catalyst was efficiently absorbed. Addition of methyl phenyldiazoacetate formed a yellow solution, which on gentle stirring caused rapid evolution of nitrogen (Figure 3d). Within minutes, the solution became colorless (Figure 3e), and the purple **8d**-Rh_2(*S*-TBSP)$_4$ was ready for filtering and recycling.

One of the most surprising aspects of the original immobilization studies was the discovery that effective im-

Table 1. Evaluation of Optimum Catalyst Immobilization Procedure[a]



	8a-Rh_2(*S*-TBSP)$_4$		**8b**-Rh_2(*S*-TBSP)$_4$		**8c**-Rh_2(*S*-TBSP)$_4$		**8d**-Rh_2(*S*-TBSP)$_4$	
cycle	time[b]	ee[c]	time[b]	ee[c]	time[b]	ee[c]	time[b]	ee[c]
1	10	82	10	87	10	86	10	86
3	14	73	10	83	10	84	10	83
5	14[d]	70[d]	15	81	15	82	15	81

[a] Reaction yields determined by ^{1}H NMR using DMAP as internal standard or isolated yields; in all cases the yields were greater than 74%. See Supporting Information. [b] In minutes. [c] In percent. [d] Fourth reaction cycle.

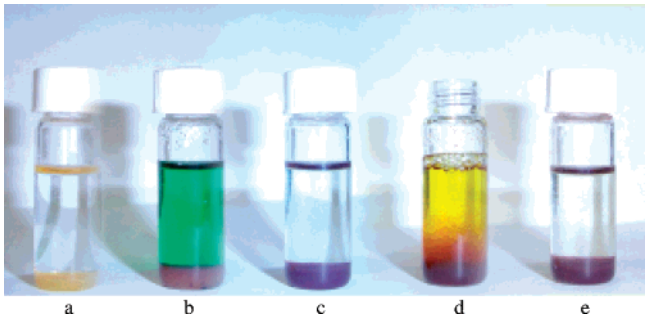


Figure 3. Visualization of the cyclopropanation chemistry of **8d**-Rh_2(*S*-TBSP)$_4$. (a) Resin **8** in toluene. (b) Resin in toluene immediately after addition of Rh_2(*S*-TBSP)$_4$. (c) **8d**-Rh_2(*S*-TBSP)$_4$ in toluene after being shaken for 40 min. (d) **8d**-Rh_2(*S*-TBSP)$_4$ in toluene immediately after addition of methyl phenyldiazoacetate. (e) **8d**-Rh_2(*S*-TBSP)$_4$/methyl phenyldiazoacetate after being shaken for 10 min.

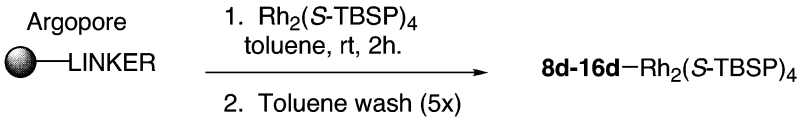
mobilization occurred when the terminal pyridine group was replaced by benzene.[7] Therefore, we have undertaken an extensive study to determine what characteristics of the polymer backbone, the linker, and the terminal group are required for effective immobilization of the dirhodium catalysts. First, the effect of non-pyridine-based linkers was tested, with and without the Wang linker (Table 2). Argopore-Wang phenyl resin **11** was included in the study with the Argopore-Wang resin **12** and Argopore-Wang Br resin **13**. The amount of catalyst immobilization was compared with the Argopore Cl resin **14** lacking the Wang linker. The presence of the Wang linker had a drastic effect on catalyst immobilization, as evident from the difference in catalyst loading obtained between catalysts **11d**-Rh_2(*S*-TBSP)$_4$ (75%)/**12d**-Rh_2(*S*-TBSP)$_4$ (71%)/**13d**-Rh_2(*S*-TBSP)$_4$ (70%) and **14d**-Rh_2(*S*-TBSP)$_4$ (12%). The positive effect of a pyridine group on catalyst immobilization was verified using the non-Wang-based pyridine linker **15**. Catalyst immobilization was observed by disappearance of the green color from the reaction mixture, giving high catalyst immobilization (92%). The corresponding phenyl linker **16** gave lower catalyst immobilization (29%) compared to its Argopore-Wang phenyl counterpart **11** (75%), which shows that the Wang linker has a positive effect on catalyst immobilization.

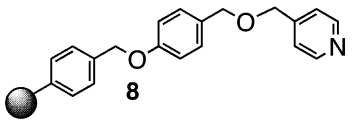
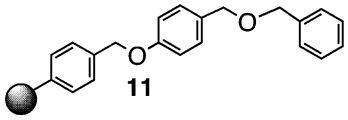
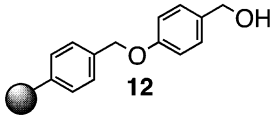
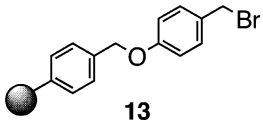
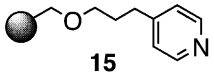
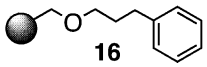
To determine catalyst efficiency and stereoselectivity, immobilized catalysts **11d**−**16d**-Rh_2(*S*-TBSP)$_4$ were tested in the standard asymmetric cyclopropanation reaction using 0.5 mol % catalyst (Table 3). In all cases in which the reaction went to completion the cyclopropane **10** was formed in >70% yield and >92% de favoring the *E* isomer. The Wang-based supported catalysts **11d**-Rh_2(*S*-TBSP)$_4$, **12d**-Rh_2(*S*-TBSP)$_4$, and **13d**-Rh_2(*S*-TBSP)$_4$ resulted in slightly lower enantioselectivities (84 to 80% ee) in the initial cycle compared to **8d**-Rh_2(*S*-TBSP)$_4$ (86% ee). These catalysts could be recycled five times, but there was a greater drop in enantioselectivity (71 to 68% ee) for the fifth cycle compared to **8d**-Rh_2(*S*-TBSP)$_4$ (81% ee). The reactions with non-Wang-based supported catalyst **14d**-Rh_2(*S*-TBSP)$_4$ resulted in a severe drop in enantioselectivity even after the second cycle (83 to 53% ee). Argopore pyridine-supported catalyst **15d**-Rh_2(*S*-TBSP)$_4$ regained activity and was the only system comparable to the Argopore-Wang pyridine catalyst **8d**-Rh_2(*S*-TBSP)$_4$. The catalyst could efficiently be recycled, with only a 9% drop in enantioselectivity between the first and fifth reaction cycles (86 to 77% ee). In comparison, the Argopore phenyl-supported catalyst **16d**-Rh_2(*S*-TBSP)$_4$ displayed a similar drop in cyclopropane enantioselectivity to the Argopore-Wang phenyl catalyst **11d**-Rh_2(*S*-TBSP)$_4$. Pyridine-functionalized solid supports **8d**-Rh_2(*S*-TBSP)$_4$ and **15d**-Rh_2(*S*-TBSP)$_4$ provided higher catalyst loading and appeared to retain more of the catalyst on repeated cycles. The positive effect of the pyridine terminal group and the Wang linker is evident from these experiments, since both elements are advantageous for maintaining stereoselectivity and high catalytic activity.

At this stage, all test systems employed the highly cross-linked Argopore[9] polymer matrix. Previously,[7] we proposed a microencapsulation effect[1a,13] due to this polymer, which would permit the bulky prolinate catalysts to be entrapped within the macroporous polystyrene framework. Therefore, the next series of experiments were designed to investigate the effect of the Argopore resin by substituting the polymer backbone with various solid supports (Table 4). Initially, immobilization of Rh_2(*S*-TBSP)$_4$ on 1% cross-linked polystyrene PS-Wang[14] pyridine resin **17** was attempted. This resin gave very similar catalyst immobilization (78%) to its Argopore variant **8** (86%), and a similar catalyst color disappearance was observed in the experiment. The difference between the Argopore resin and the 1% cross-linked polystyrene resin was more evident with the phenyl-substituted resin **18**. A considerably lower catalyst loading (46%) compared to the Argopore-Wang phenyl resin **11** (76%) was obtained. For further comparison, commercially available pyridine functionalized solid supports were tested. Ortho-substituted pyridine-functionalized silica gel **19**[14] gave

(13) (a) Kobayashi, S.; Endo, M.; Nagayama, S. *Org. Lett.* **2001**, *3*, 2649. (b) Kobayashi, S.; Endo, M.; Nagayama, S. *J. Am. Chem. Soc.* **1999**, *121*, 11229. (c) Nagayama, S.; Endo, M.; Kobayashi, S. *J. Org. Chem.* **1998**, *63*, 6094. (d) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1998**, *120*, 2985.
(14) Purchased from Aldrich Chemical Co. (www.sigma-aldrich.com).

Table 2. Catalyst Immobilization Studies on Argopore-Based Resins



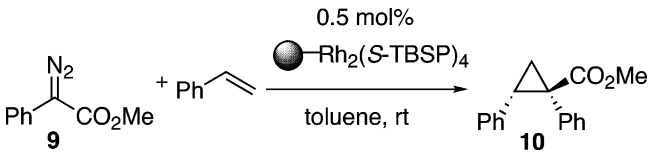
entry	Linker	Polymer (mmol)	Rh_2(*S*-TBSP)$_4$ (mmol)	Loading (mmol/g)[a]	Immobilization (%)	Catalyst
1	 **8**	0.018	0.014	0.16	86	**8d**−Rh_2(*S*-TBSP)$_4$
2	 **11**	0.017	0.014	0.13	75	**11d**−Rh_2(*S*-TBSP)$_4$
3	 **12**	0.040	0.014	0.12	71	**12d**−Rh_2(*S*-TBSP)$_4$
4	 **13**	0.039	0.014	0.12	70	**13d**−Rh_2(*S*-TBSP)$_4$
5	 **14**	0.065	0.014	0.02	12	**14d**−Rh_2(*S*-TBSP)$_4$
6	 **15**	0.030	0.014	0.16	92	**15d**−Rh_2(*S*-TBSP)$_4$
7	 **16**	0.030	0.014	0.05	29	**16d**−Rh_2(*S*-TBSP)$_4$

minimal catalyst immobilization (8%) while the 1% PS-DMAP resin **20**[9] and polypyridine *J*anda*J*el resin **21**[14] were not effective (<1%). To confirm whether the *J*anda*J*el polymer[15] support is a viable system for this immobilization method, the *J*anda*J*el Wang[14]-pyridine resin **22** was prepared and tested. With the presence of the Wang linker and the pyridine group, the system is now very efficient at catalyst immobilization (97%). The lack in catalyst immobilization displayed by the non-Wang pyridine polymers is very striking and would indicate that the chemical environment around the pyridine group is crucial for effective immobilization.

Evaluating these catalysts under the standard conditions quickly revealed that subtle factors were involved in the efficiency of the various solid supports (Table 5). Immobilized catalysts derived from the solid phase containing a terminal pyridine group on the Wang linker (**17d**-Rh_2(*S*-TBSP)$_4$ and **22d**-

(15) (a) Toy, P. H.; Janda, K. D. *Tetrahedron Lett.* **1999**, *40*, 6329. (b) Reger, T. S.; Janda, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 6929. (c) Garibay, P.; Toy, P. H.; Hoeg-Jensen, T.; Janda, K. D. *Synlett* **1999**, *9*, 1438. (d) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 6801. (e) Toy, P. H.; Reger, T. S.; Janda, K. D. *Aldrichimica Acta* **2000**, *33*, 87. (f) Toy, P. H.; Reger, T. S.; Garibay, P.; Garno, J. C.; Malikayil, J. A.; Liu, G.; Janda, K. D. *J. Comb. Chem.* **2001**, *3*, 117.

Table 3. Evaluation of Immobilized Catalysts on Argopore Resins **11**−**16**[a]

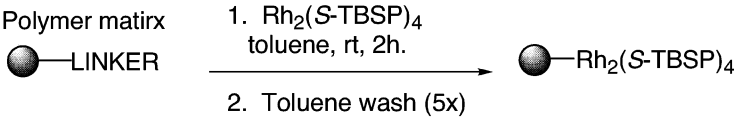


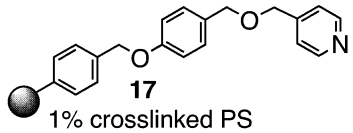
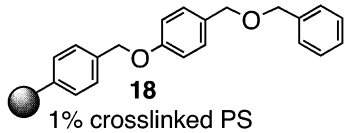
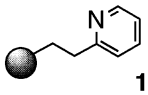
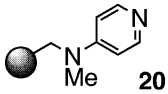
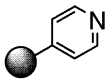
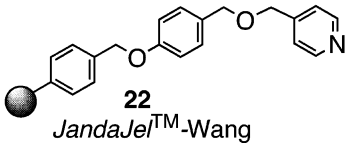
	11d-Rh_2(*S*-TBSP)$_4$		**12d**-Rh_2(*S*-TBSP)$_4$		**13d**-Rh_2(*S*-TBSP)$_4$	
cycle	time[b]	ee[c]	time[b]	ee[c]	time[b]	ee[c]
1	10	84	10	80	10	82
3	10	78	10	75	17	77
5	10	71	14	68	14	68

	14d-Rh_2(*S*-TBSP)$_4$		**15d**-Rh_2(*S*-TBSP)$_4$		**16d**-Rh_2(*S*-TBSP)$_4$	
cycle	time[b]	ee[c]	time[b]	ee[c]	time[b]	ee[c]
1	10	83	10	86	10	82
3	20[d]	53	20	79	22	72
5	nd[e]	nd[e]	20	77	30	67

[a] Reaction yields determined by ^{1}H NMR using DMAP as internal standard or isolated yields; in all cases yields were greater than 74%. See Supporting Information. [b] In minutes. [c] In percent. [d] Second reaction cycle. [e] nd = not determined (reaction incomplete overnight).

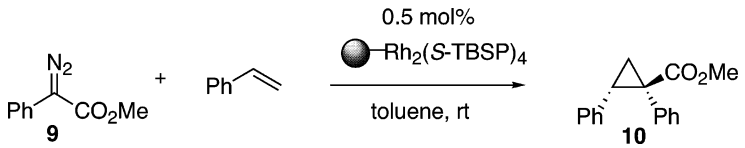
Table 4. Catalyst Immobilization Studies on Various Solid Supports



entry	Linker	Polymer (mmol)	Rh_2(*S*-TBSP)$_4$ (mmol)	Loading (mmol/g)[a]	Immobilization (%)	Catalyst
1	 **17** 1% crosslinked PS	0.017	0.014	0.14	78	**17d**−Rh_2(*S*-TBSP)$_4$
2	 **18** 1% crosslinked PS	0.017	0.014	0.08	46	**18d**−Rh_2(*S*-TBSP)$_4$
3	 **19** functionalized silica gel	0.077	0.014	0.01	8	**19d**−Rh_2(*S*-TBSP)$_4$
4	 **20** 1% PS-DMAP	0.084	0.014	0.0005	<1	**20d**−Rh_2(*S*-TBSP)$_4$
5	 **21** Polypypridine *Janda*Jel™	0.475	0.014	*b*	<1	**21d**−Rh_2(*S*-TBSP)$_4$
6	 **22** *JandaJel*™-Wang	0.02	0.014	0.17	97	**22d**−Rh_2(*S*-TBSP)$_4$

[a] Loading determined by ICP analysis for Rh (mmol/g). [b] ICP-AES analysis of the resin beads gave 1.04 ppm Rh, which corresponds to less than 1% immobilization.

Table 5. Evaluation of Immobilized Rh_2(*S*-TBSP)$_4$ on Various Polymer Supports[a]

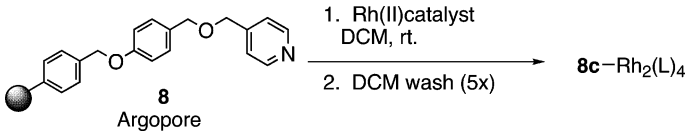


	17d-Rh_2(*S*-TBSP)$_4$		**18d**-Rh_2(*S*-TBSP)$_4$		**19d**-Rh_2(*S*-TBSP)$_4$		**22d**-Rh_2(*S*-TBSP)$_4$	
cycle	time[b]	ee[c]	time[b]	ee[c]	time[b]	ee[c]	time[b]	ee[c]
1	20	82	25	87	10	78	15	85
3	20	81	45[d]	77	120	66	15	79
5	35	74	overnight[e]	76	overnight[f]	54	20	77

[a] Reaction yields determined by ^{1}H NMR using DMAP as internal standard or isolated yields; in all cases yields were greater than 70%. See Supporting Information. [b] In minutes. [c] In percent. [d] Second reaction cycle. [e] Third reaction cycle. [f] Fourth reaction cycle.

Rh_2(*S*-TBSP)$_4$) displayed the best catalytic activity. These catalysts could be recycled five times, and the enantioselectivity is very comparable to the Argopore-Wang pyridine catalyst **8d**-Rh_2(*S*-TBSP)$_4$. Although catalyst **18d**-Rh_2(*S*-TBSP)$_4$ function-

Table 6. Immobilization of Achiral Catalysts on Argopore-Wang Pyridine **8**



catalyst	polymer (mmol)	catalyst (mmol)	loading (mmol/g)[a]	immobilization (%)	catalyst
$Rh_2(OAc)_4$	0.018	0.014	0.08	37	**8c**-$Rh_2(OAc)_4$
$Rh_2(acam)_4$	0.018	0.014	0.06	29	**8c**-$Rh_2(acam)_4$
$Rh_2(Oct)_4$	0.018	0.014	0.17	86	**8c**-$Rh_2(Oct)_4$
$Rh_2(OPiv)_4$	0.018	0.014	0.16	79	**8c**-$Rh_2(OPiv)_4$
$Rh_2(TFA)_4$	0.018	0.014	0.16	80	**8c**-$Rh_2(TFA)_4$
$Rh_2(TPA)_4$	0.018	0.014	0.13	71	**8c**-$Rh_2(TPA)_4$

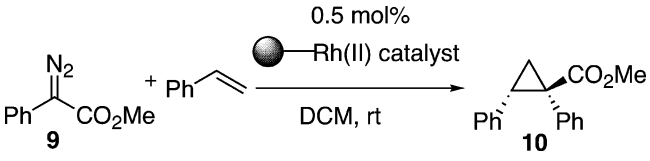
[a] Loading determined by ICP analysis for Rh (mmol/g).

alized with a phenyl group on the Wang linker furnished high enantioselectivity in the initial cycle, catalytic activity and enantioselectivity diminished by the third reaction cycle. The silica gel-based immobilized catalyst **19d**-Rh_2(*S*-TBSP)$_4$ was catalytically active but was not effectively recycled. The commercial pyridine-linked resins, PS-DMAP (**20**) and polypyridine *J*anda*J*el resin (**21**), were not effective at immobilizing Rh_2(*S*-TBSP)$_4$ and did not have sufficient rhodium catalyst immobilized for even one reaction cycle. The results from these catalyst immobilization and catalyst evaluation studies demonstrate that the Argopore-Wang pyridine resin **8** is ideally suited for immobilization and recovery of Rh_2(*S*-TBSP)$_4$.

From these studies, we have established that even though a pyridine group enhances catalyst immobilization, other factors are also involved. One possibility would be microencapsulation[1a,13] of the rhodium prolinate, which could explain why a highly cross-linked polymer such as the Argopore resin and specific linkers such as the Wang linker improve catalyst immobilization and recycling. The microencapsulation may be due to the large size of Rh_2(*S*-TBSP)$_4$. To test this possibility, the immobilization of a series of dirhodium catalysts of varying size was explored (Table 6). The catalysts were immobilized and evaluated for one reaction cycle in parallel. The small catalysts, $Rh_2(OAc)_4$ and $Rh_2(acam)_4$, show lower immobilization (29−37%) compared to the larger catalysts $Rh_2(Oct)_4$, $Rh_2(OPiv)_4$, and $Rh_2(TPA)_4$ (71−86%). $Rh_2(TFA)_4$ is the exception, giving better immobilization (80%) than the smaller catalysts probably due to its Lewis acidity. The immobilized small catalysts **8c**-$Rh_2(OAc)_4$ and **8c**-$Rh_2(acam)_4$ are not very effective catalysts because they require long reaction times to complete one reaction cycle (240 min; Table 7). Catalysts **8c**-$Rh_2(Oct)_4$, **8c**-$Rh_2(OPiv)_4$, and **8c**-$Rh_2(TPA)_4$ show better activity because the cyclopropanation reactions are complete within 20 min. Catalyst **8c**-$Rh_2(TFA)_4$ shows better reactivity than the other small catalysts (40 min), but this may be because this catalyst is more electrophilic than the others.

The detailed studies with Rh_2(*S*-TBSP)$_4$ indicated that Argopore-Wang pyridine solid phase **8** was optimum for catalyst immobilization. In the previous communications, Rh_2(*S*-biTISP)$_2$ was shown to be the most robust recoverable catalyst for asymmetric cyclopropanation[7] and Rh_2(*S*-DOSP)$_4$ was shown to be the most effective catalyst for asymmetric C−H activation.[8] The immobilized versions **8d**-Rh_2(*R*-DOSP)$_4$ and **8d**-Rh_2(*S*-biTISP)$_2$ were prepared by exposing **8** to the catalyst as the limiting agent in toluene (Table 8). Also, **8b**-Rh_2(*S*-biTISP)$_2$ was prepared by exposing **8** to an excess of the catalyst in toluene. **8d**-Rh_2(*R*-DOSP)$_4$ was a very effective catalyst for asymmetric cyclopropanation, capable of being recycled five times with virtually no drop in the enantioselectivity of the cyclopropanation. **8d**-Rh_2(*S*-biTISP)$_2$ was also effective at maintaining enantioselectivity over five cycles; however, higher catalyst loading (1 mol %) was necessary. Even better results were obtained with **8b**-Rh_2(S-biTISP)$_2$, which can be recycled up to 15 times without any drop in yield or enantioselectivity in the cyclopropanation (Table 9).[7]

Table 7. Evaluation of Achiral Immobilized Catalysts



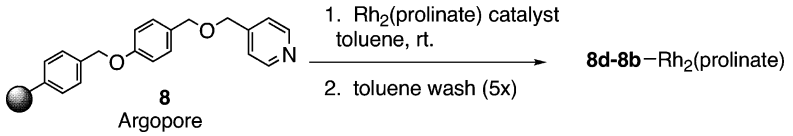
catalyst	time (min)	yield (%)
8c-$Rh_2(OAc)_4$	240	77
8c-$Rh_2(acam)_4$	240	76
8c-$Rh_2(Oct)_4$	20	82
8c-$Rh_2(OPiv)_4$	20	85
8c-$Rh_2(TFA)_4$	40	75
8c-$Rh_2(TPA)_4$	20	80

Pyridine coordination is generally considered to cause deactivation of dirhodium tetracarboxylates and so it is conceivable that either the polymer bound dirhodium complex or liberated dirhodium complex might be the catalytically active species. The release-and-capture mechanism[17a] is a distinct possibility in this system because it has been established that the dirhodium tetraprolinates are capable of catalyzing cyclopropanations with very high turnover numbers.[16] Furthermore, homogeneous control experiments with 4-alkyl-pyridine **23** confirm the adverse effect of pyridine coordination.[7] Under standard conditions, 1.5 equiv of 4-alkyl-pyridine **23** added to the reaction mixtures (Table 10) deactivates the rhodium catalysts. Product yields are lower in both cases, and the reaction rate is greatly affected in the Rh_2(*S*-biTISP)$_2$/**23** coordinated system.

To determine the phase of the active catalytic species, a Rebek-type three-phase test was conducted.[17] Our experimental

(16) Davies, H. M. L.; Venkataramani, C. *Org. Lett.* **2003**, *5*, 1403.
(17) (a) Davies, I. W.; Matty, L.; Hughes, D. L.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 10139. (b) Rebek, J.; Gavina, F. *J. Am. Chem. Soc.* **1974**, *96*, 7112. (c) Rebek, J.; Brown, D.; Zimmerman, S. *J. Am. Chem. Soc.* **1975**, *97*, 454. (d) Rebek, J., Jr. *Tetrahedron* **1979**, *35*, 723.

Table 8. Immobilization of Chiral Dirhodium Tetraprolinates Rh_2(*R*-DOSP)$_4$ and Rh_2(*S*-biTISP)$_2$



catalyst	polymer (mmol)	catalyst (mmol)	loading (mmol/g)[a]	immobilization (%)	catalyst
Rh_2(*R*-DOSP)$_4$	0.018	0.014	0.12	74	**8d**-Rh_2(*R*-DOSP)$_4$
Rh_2(*S*-biTISP)$_2$	0.018	0.014	0.11	68	**8d**-Rh_2(*S*-biTISP)$_2$
Rh_2(*S*-biTISP)$_2$	0.023	0.030	0.17[b]	*c*	**8b**-Rh_2(*S*-biTISP)$_2$

[a] Loading determined by ICP analysis for Rh (mmol/g). [b] Loading determined by mass gain. [c] Excess catalyst used for immobilization.

Scheme 2. Preparation of Phenyl Diazoacetate **26** on Solid Support

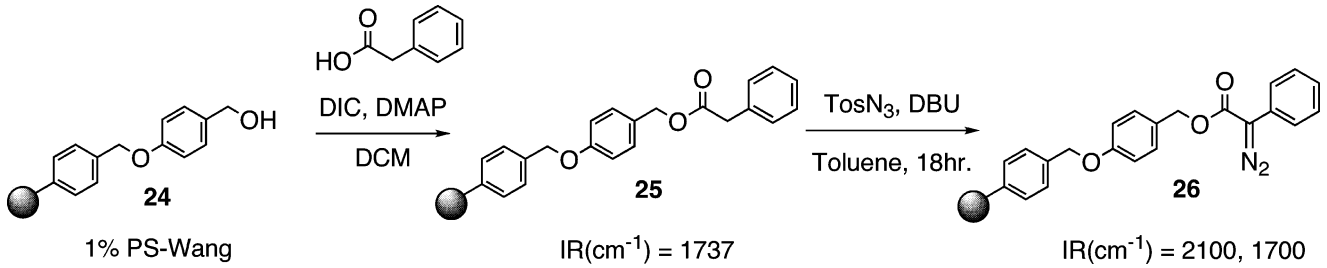
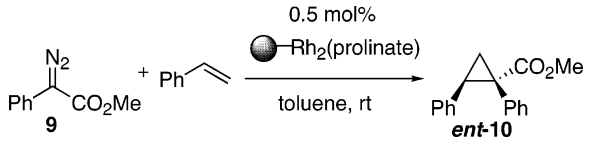


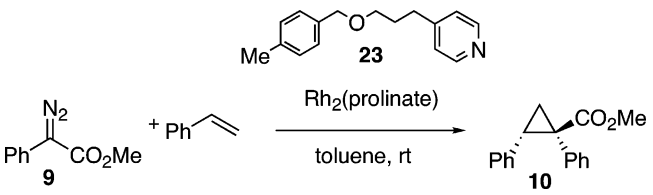
Table 9. Evaluation of Immobilized Rh_2(*R*-DOSP)$_4$ and Rh_2(*S*-biTISP)$_2$ [a]



	8d-Rh_2(*R*-DOSP)$_4$		**8d**-Rh_2(S-biTISP)$_2$ [b]		**8d**-Rh_2(S-biTISP)$_2$ [c]	
cycle	time[d]	ee[e]	time[d]	ee[e]	time[d]	ee[e]
1	15	84	40	86	18	85
3	20	85	75	86	26	87
5	45	86	140	86	30	86
15					92	88

[a] Reaction yields determined by ^{1}H NMR using DMAP as internal standard or isolated yields; in all cases yields were greater than 80%. See Supporting Information. [b] 1 mol % catalyst. [c] Reference 7. [d] In minutes [e] In percent.

Table 10. Control Experiments with Homogeneous 4-Alkyl-pyridine **23**[7]



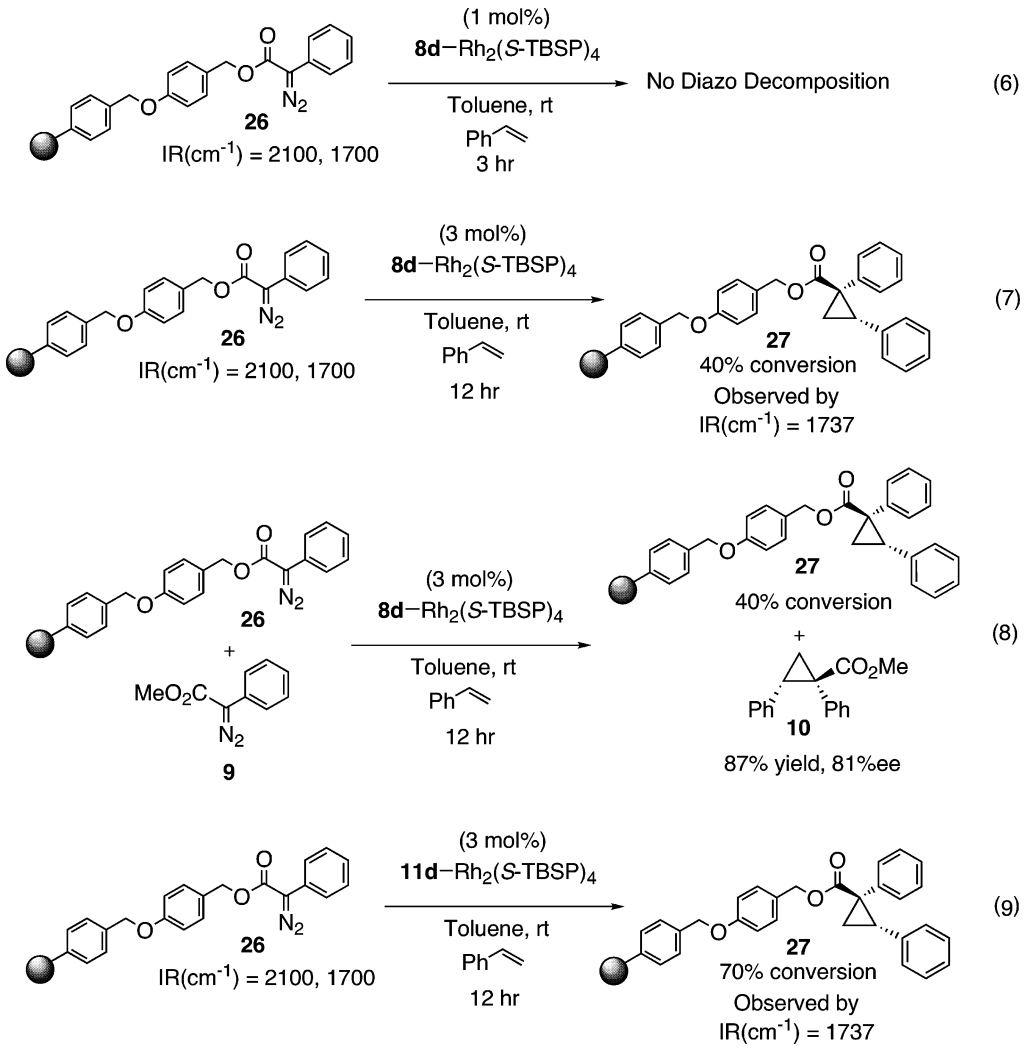
Rh_2(prolinate)	time, min	ee, %	yield, %
Rh_2(*S*-TBSP)$_4$/**23**	10	81	43
Rh_2(*S*-biTISP)$_2$/**23**	720	88	18[a]

[a] Enantiomer of **10** is formed.

design was to place the diazo compound on solid support[18] and add it to a reaction mixture of styrene and immobilized Rh_2-(*S*-TBSP)$_4$. Using the 1% cross-linked polystyrene resin PS-Wang **24**, we prepared solid supported phenyl diazoacetate **26** in two steps (Scheme 2). Carbodiimide coupling of phenyl acetic acid and PS-Wang, followed by standard diazo transfer with DBU and tosyl azide, gave the diazo compound **26**, which was characterized by FT-IR (2100 and 1700 cm^{-1}) and elemental analysis (0.95 mmol/g).

A typical asymmetric cyclopropanation of styrene using methyl phenyldiazoacetate catalyzed by immobilized catalyst **8d**-Rh_2(*S*-TBSP)$_4$ was complete within 10−15 min after diazo compound addition.[6d] The control solid-phase reaction with immobilized phenyldiazoacetate **26** catalyzed by homogeneous Rh_2(*S*-TBSP)$_4$ (1 mol %) required 60 min for complete diazo decomposition. The reaction can be qualitatively monitored by FT-IR (KBr), by comparing the appearance of the cyclopropane ester signal (∼1730 cm^{-1}) and disappearance of the diazo signal (∼2100 cm^{-1}). The three-phase test reaction was conducted using 1 mol % **8d**-Rh_2(*S*-TBSP)$_4$ and immobilized phenyl diazoacetate **26** and was allowed to agitate for 180 min (eq 6). Under these reaction conditions, no decomposition of the immobilized diazo compound **26** was observed by FT-IR (KBr). A 40% conversion of the immobilized diazo compound **26** to cyclopropane **27** was achieved by using higher catalyst loading (3 mol % **8d**-Rh_2(*S*-TBSP)$_4$) and prolonged reaction time (12 h) (eq 7). As a further test to determine if the immobilized catalyst system was operating via a release-and-capture mechanism, methyl phenyldiazoacetate **9** was added to the reaction mixture of **26** and **8d**-Rh_2(*S*-TBSP)$_4$ (eq 8). The homogeneous diazo compound **9** immediately reacted under these conditions (20 min), and the cyclopropane product was isolated in 87% yield and 81% ee. However, there was no obvious rate difference in the decomposition of the immobilized diazo compound **26** (40% conversion). On the basis of these results, we conclude that at least the majority of the reactivity of the immobilized catalyst is not by a release-and-capture mechanism. To further study the cooperative effect of pyridine coordination and

(18) (a) Clapham, B.; Spanka, C.; Janda, K. D. *Org. Lett.* **2001**, *3*, 2173. (b) Iso, Y.; Shindo, H.; Hamana, H. *Tetrahedron* **2000**, *56*, 5353−5361. (c) Gowravaram, M. R.; Gallop, M. A. *Tetrahedron Lett.* **1997**, *38*, 6973. (d) Zaragoza, F.; Petersen, S. V. *Tetrahedron* **1996**, *52*, 5000. (e) Cano, M.; Camps, F.; Joglar, J. *Tetrahedron Lett.* **1998**, *39*, 9819.



microencapsulation, the phenyl-substituted catalyst **11d**-Rh_2(*S*-TBSP)$_4$ was evaluated in the three-phase test (eq 9). As expected, this polymer was more active than **8d**-Rh_2(*S*-TBSP)$_4$ (70% conversion, 3 mol % catalyst) although the rate difference was relatively small. This shows that even in the case of the phenyl-substituted catalyst **11d**-Rh_2(*S*-TBSP)$_4$, the release-and-capture mechanism is not likely to be playing a major role.

In summary, the systematic studies described herein demonstrate that the polymer backbone, the linker, the terminal pyridine group, and the catalyst structure all contribute to the efficiency of dirhodium catalyst immobilization. The immobilization is considered to be due to a combination of ligand coordination and an encapsulation effect. The three-phase test studies indicated that a very slow reaction occurs when both the catalyst and the diazo compound were immobilized, but the slow rate precluded the likelihood that the cyclopropanation was predominately occurring by a release-and-capture mechanism. The most attractive feature of this immobilization strategy is the fact that the immobilized catalysts are generated by simply mixing the homogeneous catalysts with the polymer. Currently, we are studying the potential use of resin **8** as a universal solid support for immobilization of all the standard chiral dirhodium catalysts.

Experimental Section

General Method for the Immobilization of Rhodium(II) Catalysts. General procedure using Quest-210 parallel synthesizer: procedure for homogeneous catalyst as limiting agent.

To a 5-mL reaction vessel with stir bar was added resin (0.020 mmol, 1.2 equiv) and toluene (3.5 mL). The resin was agitated for 10 min, before the addition of rhodium(II) catalyst (0.017 mmol, 1 equiv). Extra toluene (1 mL) was used to wash down the sides of the reaction vessel. The mixture was agitated for 2−4 h, after which the solution was drained and the purple−green beads were washed with toluene (5×). Air was used to dry the beads before transferring them to a vial and dried under vacuum to give the solid supported catalyst which was analyzed by inductively coupled plasma emission spectroscopy (ICP-AES).

Standard Asymmetric Cyclopropanation of Styrene Using Solid Supported Catalysts and Methyl Phenyldiazoacetate.

To a 5-mL Quest 210 reaction vessel was added solid supported catalyst (0.0005 mmol, 0.5 mol %) and magnetic stirrer bar. The reaction vessel was inserted into the Quest 210 and purged with argon for 10 min. Toluene (3 mL), followed by styrene (0.2 mmol), was added to the reaction mixture and agitated for 10 min. A 1-mL toluene solution of methyl phenyldiazoacetate (0.1 mmol) was prepared and added dropwise via a syringe over 10 min to the agitating mixture. Endpoint of the reaction mixture was determined by cessation of nitrogen gas evolution and by disappearance of the yellow color from the diazo compound. The reaction mixture was agitated for 10 min after reaching the endpoint and drained. The resin was washed with toluene three to

four times with toluene and dried by pushing air through the reaction vessel. The reaction vessel was then purged with argon and filled with toluene (3 mL) for the next cycle. Excess styrene from drained reaction mixture was removed by evaporation under vacuum, and product yield was determined by ^{1}H NMR using DMAP as internal standard or by passing the crude reaction mixture through a short plug of silica gel (5:1 pentane/ether). HPLC, Whelk column, 2% 2-PrOH in hexanes, 1.0 mL/min, 1 mg/mL, t_R = 9.05 (minor) and 10.19 (major) min, UV 254 nm. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (m, 3 H), 7.04 (m, 5 H), 6.76 (m, 2 H), 3.65 (s, 3 H), 3.12−3.09 (dd, J = 4.0, 9.0 Hz, 1 H), 2.14−2.11 (dd, J = 5.0, 9.5 Hz, 1 H), 1.88−1.86 (dd, J = 5.0, 7.5 Hz, 1 H). The spectroscopic data are consistent with previously reported data.[12a]

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Supporting Information Available: Full experimental details for the preparation of resins **8**, **11**, **13**, **15**−**18**, **22**, **25**, **26**, detailed experimental procedures, and tables with enantioselectivities and yields (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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