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Catalytic Asymmetric Cyclopropanation Using Bridged Dirhodium Tetraprolinates on Solid Support

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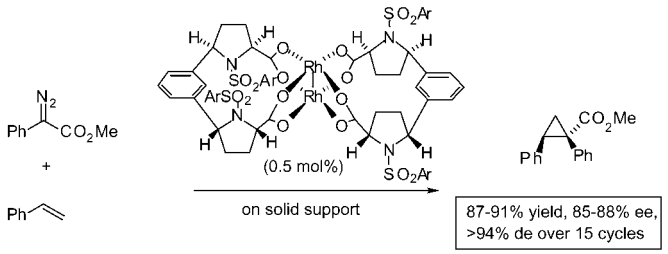
ABSTRACT



Dirhodium tetraprolinates in highly cross-linked macroporous polystyrene resins are very effective catalysts for asymmetric cyclopropanation using methyl aryldiazoaceates.

Polymer-supported reagents and catalysts are useful tools in synthesis because, in principle, they can be readily separated from the product and then recycled.[1] In recent years there has been considerable interest in the development of solid-supported catalysts for asymmetric cyclopropanation.[2] The vast majority of these are copper-based catalysts, although there has been one report on chiral dirhodium tetracarboxamidates.[2g] Major challenges with these systems include obtaining yields comparable to those of the homogeneous reactions and avoiding degradation in enantioselectivity with recycled catalyst. Considering that the dirhodium tetracarboxylates are the most generally useful catalysts for carbenoid transformations,[3] the development of solid-supported chiral catalysts of this class would be particularly worthwhile. The successful accomplishment of this goal using an unusual immobilization strategy is the basis of this paper.

Various chiral dirhodium carboxylates have been developed as homogeneous catalysts for carbenoid transformations.[3] *N*-(Arylsulfonyl)prolinate dirhodium complexes such as Rh_2(*S*-TBSP)$_4$ (**1**) and Rh_2(*S*-DOSP)$_4$ (**2**) are especially effective for the asymmetric cyclopropanations of aryl- and styryldiazoacetates.[4] Recently, a conformationally restricted catalyst, Rh_2(*S*-biTISP)$_2$ (**3**), was developed,[5] which was found to give high ee's in cyclopropanation reactions and in some C−H insertion reactions.[4a] Because of the broad utility of these catalysts and the high price of rhodium, the successful immobilization of these catalysts would be very desirable.

Immobilization of a dirhodium tetracarboxylate has been achieved by using a ligand exchange between $Rh_2(OAc)_4$

(1) For reviews, see: (a) Clapham, B.; Reger, T. S.; Janda, K. D. *Tetrahedron* **2001**, *57*, 4637. (b) Sherrington, D. C. *J. Polym. Sci. Part A: Polym. Chem.* **2001**, *39*, 2364. (c) 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.

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(3) Doyle, M. P.; McKervey, M. A.; Ye, T. In *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998.

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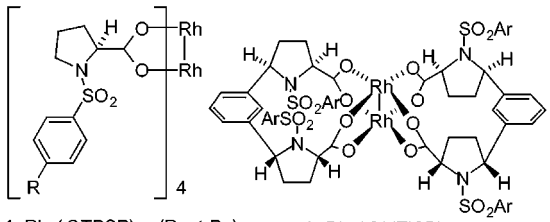
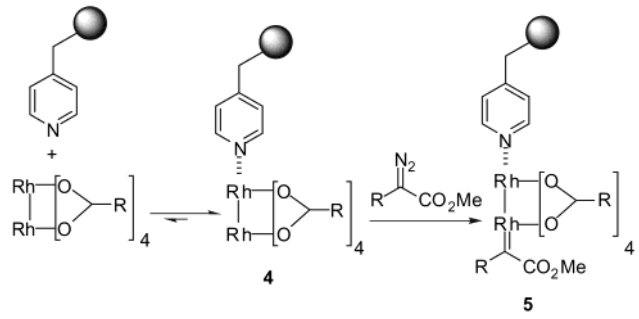


1 Rh_2(*S*-TBSP)$_4$ (R = t-Bu)
2 Rh_2(*S*-DOSP)$_4$ (R = $C_{12}H_{25}$)
3 Rh_2(*S*-biTISP)$_2$ (Ar = 2,4,6-tri-iPrC_6H_2)

and a solid-supported dicarboxylic acid, resulting in an active hydroformylation catalyst.[4a,6] Such an approach for a chiral catalyst would be problematic because it would alter the chiral environment around the catalyst. To immobilize chiral dirhodium teracarboxylate catalysts without resorting to ligand modification, we decided to study the use of polymer-supported pyridines (Scheme 1). Axial coordination of

Scheme 1

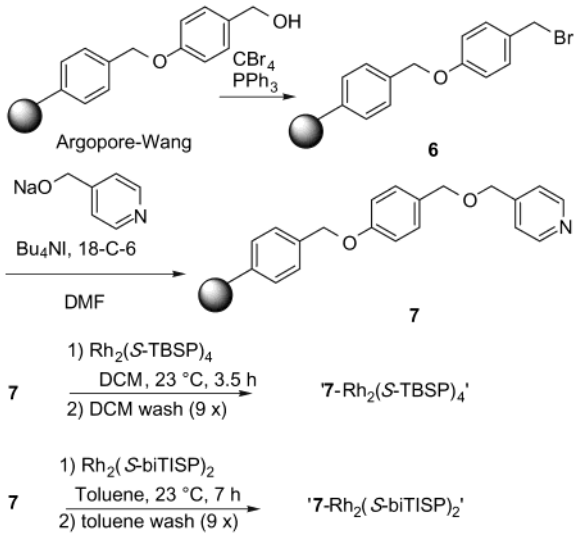


4 **5**

dirhodium tetracarboxylates to basic sites is well-known.[7] Thus the dirhodium complex could coordinate to the polymer-supported pyridine to form **4**, and the other rhodium center in **4** could react with diazo compounds to form the corresponding carbenoid **5**.

ArgoPore resin was chosen for this study because it is a highly cross-linked macroporous polystyrene and can be used with a variety of solvents. To prevent possible steric interaction between the ligands in the dirhodium complex and the polymer backbone, a benzyl group was used as a spacer between the pyridinyl group and the polystyrene. The hydroxy group in ArgoPore-Wang resin (hydroxyl loading = 0.65 mmol/g)[8] was converted to the bromide **6** with PPh_3 and CBr_4, and **6** was reacted with the sodium alkoxide of 4-pyridinylmethanol to give **7** (Scheme 2). To immobilize Rh_2(*S*-TBSP)$_4$, the pyridine resin **7** was gently stirred with Rh_2(*S*-TBSP)$_4$ in dichloromethane. The color of the resin changed from pale brown to purple, indicating the coordination of the pyridine to the rhodium metal. After the filtration of the solvent, the resin was washed with dichloromethane (nine times), and was dried under vacuum. In a similar way,

Scheme 2



Rh_2(*S*-biTISP)$_2$ was immobilized on the resin **7**. The loading of the rhodium complex was estimated by the increase of the weight of the resin. The loading of Rh_2(*S*-TBSP)$_4$ in **7** was 0.18 mmol/g, and that of Rh_2(*S*-biTISP)$_2$ was 0.17 mmol/g.

A standard cyclopropanation was used to evaluate the catalytic activity of "**7**−Rh_2(*S*-TBSP)$_4$" and "**7**−Rh_2(*S*-biTISP)$_2$". Dropwise addition of methyl phenyldiazoacetate to a solution of styrene (2 equiv) with the resin (0.5 mol % of dirhodium catalyst) in toluene as solvent resulted in efficient cyclopropanation. The rate of the reaction was found to depend on the rate of stirring, and so all reactions were run with approximately the same stirring rate. The end-point of the reaction was judged by the cessation of the evolution of nitrogen gas. The resin was rinsed with toluene (five times) and dried before reuse in the next cycle.

The cyclopropanation with **7**−Rh_2(*S*-TBSP)$_4$ gave the cyclopropanation product in good yield (92−89%) and diastereoselectivity (>94% de); however, the enantiomeric excess (ee) dropped steadily from 82% to 70% over four cycles (Table 1). The high diastereoselectivity is characteristic of aryldiazoacetate cyclopropanations.[9] A similar drop in enantioselectivity has been observed in solution-phase cyclopropanation with Rh_2(*S*-DOSP)$_4$ when using low catalyst loading (<0.1 mol %).[10] This indicates that the prolinate catalysts are undergoing slow degradation under the reaction conditions. This would also explain why there is a drop in enantioselectivity using recycled catalyst. In contrast, **7**−Rh_2(*S*-biTISP)$_2$ appears to be a very robust catalyst as the yield (87−91%) and the enantioselectivity (85−88% ee) remains steady over 15 cycles. The only change is the reaction time, which increases by a factor of 6 over the 15 cycles. As is

(6) Nowotny, M.; Maschmeyer, T.; Johnson, B. F. G.; Lahuerta, P.; Thomas, J. M.; Davies, J. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 955.
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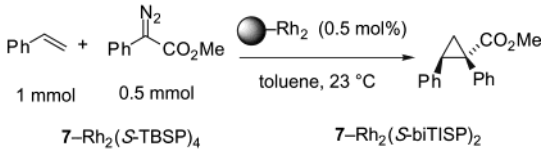
(10) Davies, H. M. L.; Bruzinski, P.; Hutcheson, D. K.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.

Table 1. Asymmetric Cyclopropanation of Styrene Using a Polymer Supported Catalyst

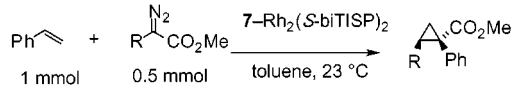


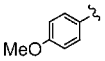
7−Rh_2 (*S*-TBSP)$_4$				7−Rh_2 (*S*-biTISP)$_2$			
cycle	time (min)	yield (%)	ee (%)	cycle	time (min)	yield (%)	ee (%)
1	10	92	82	1	18	91	85
2	17	91	78	2	23	91	86
3	14	89	73	3	26	90	87
4	14	89	70	4	36	90	87
				10	60	87	88
				15	92	89	88

well-established with the corresponding homogeneous catalysts,[9,10] **7**−Rh_2(*S*-TBSP)$_4$ gave the (*S*,*S*)-cyclopropane, whereas **7**−Rh_2(*S*-biTISP)$_2$ gave the (*R*,*R*)-cyclopropane.

The observation that the bridged prolinate catalyst Rh_2(*S*-biTISP)$_2$ is much more effective at maintaining high enantioselectivity compared to the unbridged catalyst may have a major impact on the future design of robust chiral dirhodium catalysts. To further evaluate the catalytic activity of **7**−Rh_2(*S*-biTISP)$_2$, the reactions of several diazo compounds using lower equivalents of the catalyst were examined. As shown in Table 2, the reaction with methyl

Table 2. Asymmetric Cyclopropanation of Styrene with Aryl- and Vinyldiazoacetates

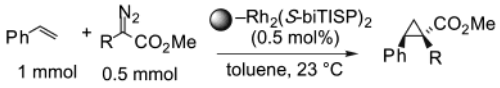


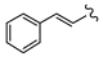
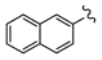
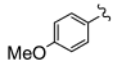
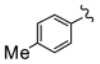
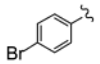
entry	R	time (min)	catalyst (mol%)	yield (%)	ee (%)
1		180	0.04	88	88
2		120	0.1	89	74
3		60	0.1	90	80
4		60	0.1	89	83
5		60	0.1	87	90
6		420	0.1	82	68

phenyldiazoacetate (entry 1) was similarly achieved (88% yield, 88% ee) with 0.04 mol % of **7**−Rh_2(*S*-biTISP)$_2$, but the reaction took 3 h to reach completion. With the other aryldiazoacetates (entries 2−5), when 0.1 mol % of the catalyst was used, high yields and enantioselectivities of the products were consistently obtained (entries 2−5). The styryldiazoacetate (entry 6) was also effective, but the reaction was slower than that of the aryldiazoacetates.

One of the attractive features of recoverable catalysts is that they can be useful for the preparation of compound libraries. To determine further this potential, a series of cyclopropanations was carried out using recycled catalyst (Table 3). The yields and the ee's are comparable to those

Table 3. Asymmetric Cyclopropanation of Styrenes with Various Aryl- and Styryldiazoacetates Using Recycled Catalyst



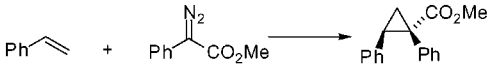
cycle	R	reaction time (min)	yield (%)	ee (%)
1		16	82	71
2		30	86	76
3		5	84	80
4		30	85	80
5		30	94	90

obtained with the fresh catalyst (see Table 2). With 0.5 mol % of the catalyst, all of the reactions were completed within 30 min. Furthermore, from the ^{1}H NMR spectra of the crude mixture, there was no cross-contamination between successive cyclopropanations. This would indicate that the product is efficiently washed from the polymer support between cycles even though the catalyst is retained.

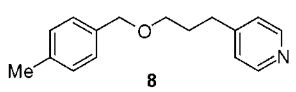
In some regards, the success of this chemistry is surprising because donor groups such as pyridine tend to deactivate dirhodium tetracarboxylates.[7] Therefore, control experiments were carried out to determine why **7**−Rh_2(*S*-biTISP)$_2$ was able to function as such an efficient catalyst. To study the effect of pyridine, both Rh_2(*S*-TBSP)$_4$ and Rh_2(*S*-biTISP)$_2$ were mixed with 1.5 equiv of 4-alkyl-pyridine **8** (Scheme 3). The cyclopropanation of styrene with phenyldiazoacetate using these catalysts was conducted in toluene. With Rh_2(*S*-TBSP)$_4$ coordinated to **8** the reaction was complete in 10 min but the yield was only 43%. Rh_2(*S*-biTISP)$_2$ coordinated to **8** showed very little catalytic activity. Even after 12 h the yield of cyclopropanation was only 18%, and many unidentified side products were observed by ^{1}H NMR of the crude mixture. In both cases, however, the enantioselectivity remained high. These results suggest that coordination of pyridine to Rh_2(*S*-biTISP)$_2$ greatly decreases its catalytic activity, and that in the **7**−Rh_2(*S*-biTISP)$_2$ catalyst, the "active" catalyst is not Rh_2(*S*-biTISP)$_2$ coordinated to the pyridine.

To further determine the importance of the pyridine group a second control experiment was undertaken. The analogous

Scheme 3



catalyst	time, min	yield, %	ee, %
Rh_2(*S*-TBSP)$_4$ /**8**	10	43	81
Rh_2(*S*-biTISP)$_2$ /**8**	720	18	88



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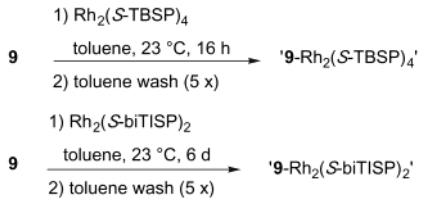
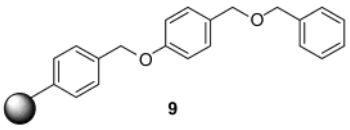
phenyl-substituted resin **9** was prepared, and it also could immobilize Rh_2(*S*-TBSP)$_4$ and Rh_2(*S*-biTISP)$_2$ (Scheme 4).

Scheme 4





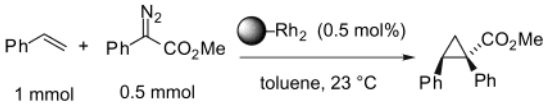
9

The resin **9** was treated with either Rh_2(*S*-TBSP)$_4$ or Rh_2(*S*-biTISP)$_2$ in toluene, and the resin was then washed with toluene (five times). The resulting green-colored resins contained 0.11 mmol/g of Rh_2(*S*-TBSP)$_4$ and 0.07 mmol/g of Rh_2(*S*-biTISP)$_2$, respectively.

With the phenyl-substituted resin catalysts, five cycles of cyclopropanation of styrene with methyl phenyldiazoacetate were tried. As shown in Table 4, the reaction with the phenyl resin **9**−Rh_2(*S*-TBSP)$_4$ gave the cyclopropanation product in good yields (90−92%); however, the enantioselectivity dropped slightly from 85% to 81% ee. The reaction with the phenyl-resin **9**−Rh_2(*S*-biTISP)$_2$ maintained the same level of enantioselectivity over four cycles; however, longer reaction times were required to complete the reaction.

These control experiments suggest that the actual catalyst in the pyridine-resin **7** is not the pyridine-coordinated

Table 4. Asymmetric Cyclopropanation of Styrene Using a Polymer-Supported Catalyst Lacking a Pyridine Linker



9−Rh_2 (*S*-TBSP)$_4$				**9**−Rh_2 (*S*-biTISP)$_2$			
cycle	time (min)	yield (%)	ee (%)	cycle	time (min)	yield (%)	ee (%)
1	21	92	85	1	24	85	82
3	19	91	83	3	37	84	84
5	15	90	81	5	57	83	84

dirhodium complex. The immobilization of these catalysts is most likely due to a microencapsulation effect,[11] although further studies are needed to determine all the controlling factors. The high molecular weight catalysts remain trapped on the highly cross-linked polymer and can be recycled 15 times, while the products are readily removed by solvent washing.

In summary, dirhodium tetraprolinates in highly cross-linked macroporous polystyrene resins are very effective catalysts in asymmetric cyclopropanation. Future studies are needed to determine the key structural features that govern this simple immobilization of the catalyst and if the approach is applicable to other catalyst systems. A further significant observation from this study is that the bridged prolinate catalyst Rh_2(*S*-biTISP)$_2$ is much more effective at maintaining high enantioselectivity than the unbridged catalyst. This will have important ramifications for the design of dirhodium catalysts capable of very high turnover numbers.

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Supporting Information Available: Experimental data for the synthesis of the solid supported catalysts and for the asymmetric cyclopropanation. This material is available free of charge via the Internet at http://pubs.acs.org.

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