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Universal Strategy for the Immobilization of Chiral Dirhodium Catalysts

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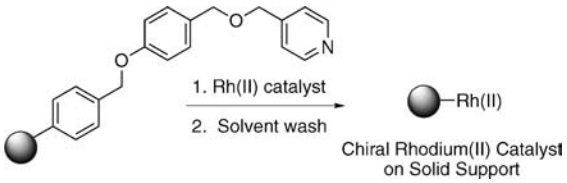
ABSTRACT



Chiral rhodium(II) catalysts used in asymmetric carbenoid chemistry can be efficiently heterogenized using a novel immobilization strategy. The immobilized catalysts display similar reactivity and stereoselectivity to their homogeneous counterparts and can be effectively recycled with limited loss in stereoselectivity.

Over the past few years, we have explored the chemistry of dirhodium tetraprolinates, Rh_2(*S*-DOSP)$_4$ (**1**), Rh_2(*S*-TBSP)$_4$ (**2**), **3**, and Rh_2(*S*-biTISP)$_2$ (**4**), as effective chiral catalysts for reactions of donor/acceptor-substituted carbenoids.[1] The success of the dirhodium tetraprolinates led us to develop these catalysts as solid-supported reagents using pyridine coordination as an immobilization strategy.[2] The immobilized catalysts have been very effective for the asymmetric intermolecular cyclopropanation[2a] and asymmetric intermolecular C−H activation reactions[2b] of donor/acceptor-substituted carbenoids. The immobilization strategy does not require ligand derivatization, and so a potential advantage of this approach is the ability to immobilize any chiral rhodium(II) catalyst, independent of its ligand structure. Herein, we report our efforts to demonstrate a universal immobilization system for chiral dirhodium catalysts and its application to a broad array of enantioselective rhodium carbenoid reactions.

Chiral catalyst development within the dirhodium core has mainly centered around the use of chiral carboxylate and carboxamidate ligands.[3] In most cases, C_1 symmetric ligands from simple amino acids are coordinated around the dirhodium core to give the chiral rhodium catalysts. Doyle has introduced chiral carboxamidate ligands, which coordinate to the dirhodium core through amide bonds. Generally these catalysts, for example, Rh_2(*S*-MEPY)$_4$ (**5**) and Rh_2(*S*-MEAZ)$_4$ (**6**), are more electron-rich than the tetracarboxlyates and have a very different reactivity profile.[3] Ikegami and Hashimoto have developed phthalimide-protected tetracarboxylate catalysts such as Rh_2(*S*-PTTL)$_4$ (**7**), which use amino acids such as valine and *tert*-leucine as the chirality source.[4] A very interesting variation to this approach has been the use of C_2 symmetric binaphthoyl phosphates as ligands to give catalysts such as Rh_2(*R*-BNP)$_4$ (**7**), which was developed by Pirrung and Zhang.[5] The main challenge for developing a universal immobilization method is to ensure compatibility with the different electronic and steric features of each catalyst system. We therefore, selected the

(1) (a) Davies H. M. L.; Beckwith, R. J. W. *Chem. Rev.* **2003**, *103*, 2861. (b) Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1.

(2) (a) Nagashima, T.; Davies, H. M. L. *Org. Lett.* **2002**, *4*, 1989. (b) Davies, H. M. L.; Walji, A. M. *Org. Lett*. **2003**, *5*, 479. (c) Davies, H. M. L.; Walji, A. M.; Nagashima, T. *J. Am. Chem. Soc.* **2004**, *126*, 4271.

(3) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. In *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998. (b) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911.

(4) (a) Hashimoto, S.; Watanabe, N.; Sato, T.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* **1993**, *34*, 5109. (b) Takahashi, T.; Tsutsui, H.; Tamura, M.; Kitagaki, S.; Nakajima, M.; Hashimoto, S. *Chem. Commun.* **2001**, 1604.

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Rh_2(*S*-MEPY)$_4$, Rh_2(*S*-MEAZ)$_4$, Rh_2(*S*-PTTL)$_4$, and Rh_2(*R*-BNP)$_4$ catalysts, as representative examples of the most effective rhodium catalysts, for evaluation of our immobilization strategy.

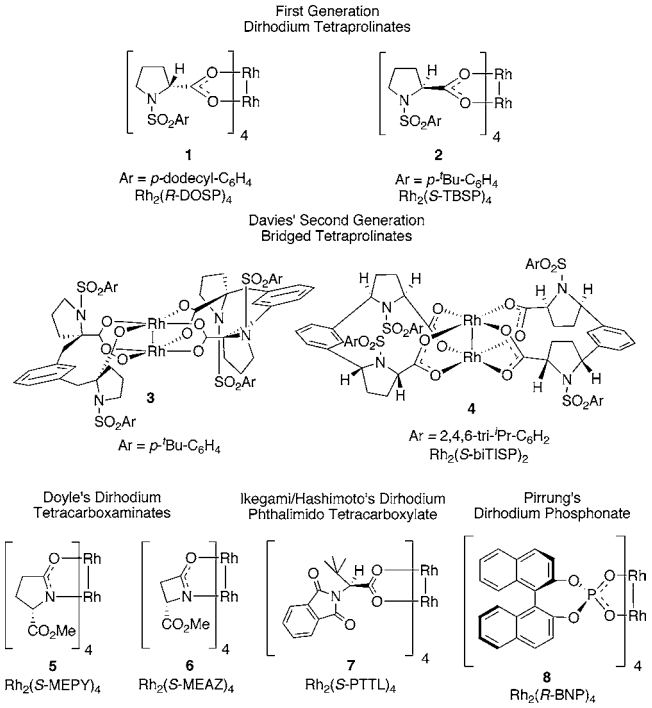
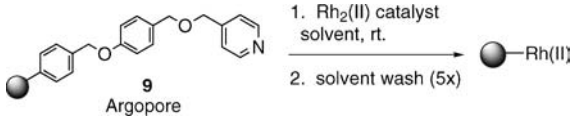


Figure 1. Popular chiral rhodium(II) catalysts used in carbenoid chemistry.

The immobilization procedure was similar to that used for the dirhodium tetraprolinate catalysts.[2c] Agitation of a suspension of resin **9** in solvent (toluene or dichloromethane) in the presence of the homogeneous catalysts resulted in efficient catalyst immobilization (Table 1). This was visually observed by a change in the color of the solid support from yellow to purple, indicating coordination of the rhodium catalysts to the pyridine linker. After the resin beads were washed, ICP-AES analysis for percent rhodium was used to calculate the amount of catalyst immobilization (%) and loading (mmol/g) (Table 1). These results indicated that all the catalysts were effectively immobilized using the solid support **9**.

Asymmetric cyclopropanation of alkenes with diazo compounds has been used as the benchmark reaction to evaluate new heterogeneous catalysts for carbenoid reactions.[1b,6] Therefore, we initiated studies to test the immobilized catalysts using the standard asymmetric intermolecular cyclopropanation of styrene with methyl phenyldiazoacetate (**10**). Although the chosen catalysts are not well suited to give high asymmetric induction in this reaction,[1b] the preliminary screen gave excellent indications regarding the catalytic activity of the immobilized catalysts. Except for the immobilized Rh_2(*S*-MEPY)$_4$ catalyst, the homogeneous variant of which is known to be a poor catalyst for the decomposition of **10**,[6d] the immobilized catalysts gave virtually identical enantioselectivities compared to their homogeneous variants (Table 2). Immobilized Rh_2(*S*-MEPY)$_4$ was tested in the cyclopropanation of styrene with ethyl diazoacetate. In this case, the diastereoselectivity was also recorded and compared to that of the homogeneous catalyst. Immobilized Rh_2(*S*-MEPY)$_4$ catalyst, previously reported by Doyle,[6c] has also been tested in this reaction,

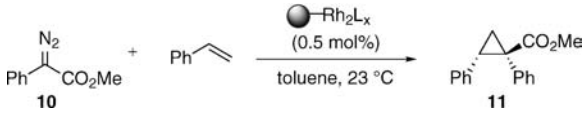
Table 1. Immobilization of Rhodium(II) Catalysts Using Resin **9**



catalyst	loading (mmol/g)[b]	immobilization (%)	immobilized catalyst
3	0.13	87	**9a**−**3**
Rh_2(*S*-MEPY)$_4$	0.12[c]	60	**9a**−Rh_2(*S*-MEPY)$_4$
Rh_2(*S*-MEAZ)$_4$	0.12	61	**9a**−Rh_2(*S*-MEAZ)$_4$
Rh_2(*S*-PTTL)$_4$	0.14	77	**9a**−Rh_2(*S*-PTTL)$_4$
Rh_2(*R*-BNP)$_4$	0.14	81	**9a**−Rh_2(*R*-BNP)$_4$

[a] Amount (mmol) of catalyst was varied to maintain 1.3 equiv of resin **9** with respect to the catalyst. [b] Loading determined by ICP analysis for Rh (mmol/g). [c] Loading determined by change in mass resin after drying.

Table 2. Standard Asymmetric Cyclopropanation of Styrene with Methyl Phenyldiazoacetate (**10**) Using Immobilized Catalysts



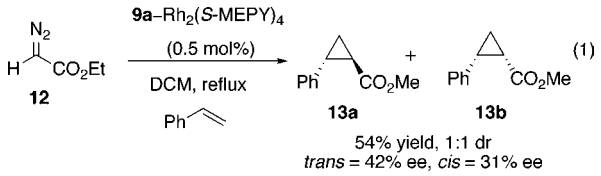
catalyst	time (min)	yield (%)	ee (%)	ee (%)[b]
9a−**3**	12	80	53	53
9a−Rh_2(*R*-BNP)$_4$	15	85	40	42
9a−Rh_2(*S*-MEAZ)$_4$[a]	>3 h	76	68	69
9a−Rh_2(*S*-PTTL)$_4$	12	82	10	13

[a] Dichloromethane was used as the solvent. [b] Enantioselectivity using homogeneous catalyst.

(5) (a) Pirrung, M. C.; Zhang, J. *Tetrahedron Lett.* **1992**, *33*, 5987. For Hodgson's derivatives of Pirrung's catalyst, see: (b) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *J. Chem. Soc., Chem. Commun.* **1999**, 2185. (c) Hodgson, D. M.; Stupple, P. A.; Pierard, F. Y. T. M.; Labande, A. H.; Johnstone, C. *Chem. Eur. J.* **2001**, *7*, 4465. (d) Hodgson, D. M.; Glen, R.; Redgrave, A. J. *Tetrahedron Lett.* **2002**, *43*, 3927.

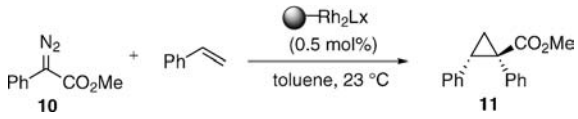
(6) (a) Doyle, M. P.; Eismont, M. Y.; Bergbreiter, D. E.; Gray, H. N. *J. Org. Chem.* **1992**, *57*, 6103. (b) Doyle, M. P.; Timmons, D. J.; Tumonis, J. S.; Gau, H.-M.; Blossey, E. C. *Organometallics* **2001**, *21*, 1747. (c) Doyle, M. P.; Yan, M.; Gau, H.-M.; Blossey, E. C. *Org. Lett.* **2003**, *5*, 561. (d) Doyle, M. P.; Zhou, Q.-L.; Charnsangavej, C.; Longoria, M. A.; McKervey, M. A.; Garicia, C. F. *Tetrahedron Lett.* **1996**, *37*, 4129.

and the results can be used for comparison between the immobilized catalysts. The homogeneous Rh_2(*S*-MEPY)$_4$ (**5**) gives a diastereomeric ratio of 1.3:1 (trans 58% ee:cis 33% ee) and 59% yield (Figure 1).[1c] Previously, Doyle's covalently bound Rh_2(*S*-MEPY)$_4$ catalyst on solid support showed an improvement in the overall stereoselectivity in this reaction, as the product was formed in a 2.1:1 mixture of diastereomers favoring the trans isomer (trans 66% ee: cis 49% ee).[6c] In contrast, noncovalently bound **9a**−Rh_2(*S*-MEPY)$_4$ gives the product as a 1:1 mixture of diastereomers (trans 42% ee:cis 31% ee) (eq 1). These results indicate that the noncovalent immobilization strategy has a minimal effect on the chiral environment around the immobilized catalysts, as results similar to those found for the homogeneous catalyst are obtained.



The best assessment of this immobilization technology would be to evaluate the immobilized catalysts in reactions in which their homogeneous counterparts routinely give high asymmetric induction. Therefore, a few of the best applications of these catalysts that have been reported in the literature were chosen and repeated using the homogeneous catalysts. Since catalysts **3** and Rh_2(*R*-BNP)$_4$ (**8**) have not been reported to give enantioselectivities >85%, they were further tested in the asymmetric cyclopropanation of styrene with methyl phenyldiazoacetate (**10**). The catalysts were recycled five times, and the reaction time and enantioselectivity was recorded for every other cycle. Interestingly, in both these systems the enantioselectivity was maintained with minimal loss compared to the first cycle (Table 3).

Table 3. Asymmetric Cyclopropanation of Styrene with Methyl Phenyldiazoacetate (**10**) Using Immobilized Catalysts **9a**−**3** and **9a**−Rh_2(*R*-BNP)$_4$[a]

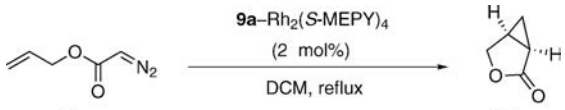


	9a−**3**		**9a**−Rh_2(*R*-BNP)$_4$	
cycle	time (min)	ee (%)	time (min)	ee (%)
1	12	53	15	40
3	15	50	30	39
5	25	48	60	38

[a] Reaction yields determined by ^{1}H NMR, using DMAP as the internal standard, or isolated yields; in all cases, values were greater than 70%. See Experimental Section.

One of the earliest applications of the Rh_2(*S*-MEPY)$_4$ catalyst was the intramolecular cyclopropanation of allyl diazoacetates such as **14**.[7] When 2 mol % immobilized **9a**−Rh_2(*S*-MEPY)$_4$ was used, allyl diazoacetate **14** underwent highly enantioselective intramolecular cyclopropanation to give product **15** in 81% yield and 95% ee (Table 4). The

Table 4. Asymmetric Intramolecular Cyclopropanation of Allyl Diazoacetate **14** Using Immobilized Catalyst **9a**−Rh_2(*S*-MEPY)$_4$[a]



	–Rh_2(*S*-MEPY)$_4$	
cycle	yield (%)	ee (%)
1	81	95
2	75	95
3	72	95

[a] Homogeneous reaction: 79% yield, 95% ee. Reported reaction (ref 7): 75% yield, 95% ee.

catalyst was recycled three times with virtually no loss in enantioselectivity. The enantioselectivity is identical to the homogeneous control and reported homogeneous reactions.

Oxazetidinone-based catalysts such as Rh_2(*S*-MEAZ)$_4$ (**6**) have been very successful for reactions with acceptor/acceptor- and donor/acceptor-substituted carbenoids.[8] The best application of Rh_2(*S*-MEAZ)$_4$ is the intramolecular cyclopropanation of phenyldiazoacetate **16** to give the cyclopropane lactone **17**.[8] In the presence of immobilized **9a**−Rh_2(*S*-MEAZ)$_4$ (2 mol %), the cyclopropane product is formed in 80% yield and 88% ee (Table 5). The enantioselectivity in the initial cycle is comparable to that of the homogeneous control reaction (86% ee) and the reported homogeneous reaction (84% ee). Recycling the catalyst showed that after three reaction cycles, the enantioselectivity gradually drops to 70% ee.

One of the most notable examples of the enantioselective reactions of the Rh_2(*S*-PTTL)$_4$ catalyst is the intramolecular C−H activation of substituted aryldiazoacetates such as **18** to form dihydrobenzofurans.[9] Recently, Fukuyama and coworkers used a similar C−H activation reaction as the key step in the total synthesis of (−)-ephedradine A.[10] The room-temperature reaction using Rh_2(*S*-PTTL)$_4$ in the intramolecular C−H activation of aryldiazoacetate **18** has been reported in hexane, giving **19** in 78% yield, 99:1 dr, and 70% ee.[9] Conducting the reaction in toluene with homoge-

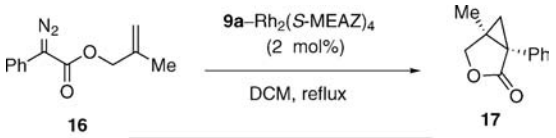
(7) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763.

(8) Doyle, P. M.; Davies, B. S.; Hu, W. *Org. Lett.* **2000**, *2*, 1145.

(9) Saito, H.; Oishi, H.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Org. Lett.* **2002**, *4*, 3887.

(10) (a) Kurosawa, W.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8112. (b) Kurosawa, W.; Kan, T.; Fukuyama, T. *Synlett* **2003**, 1028.

Table 5. Asymmetric Intramolecular Cyclopropanation of Phenyldiazoacetate **16** Using Immobilized **9a**−Rh_2(*S*-MEAZ)$_4$[a]

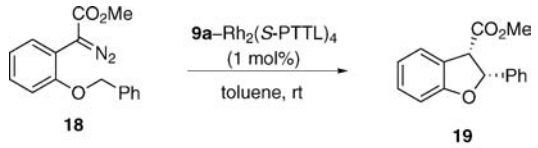


	—Rh_2(*S*-MEAZ)$_4$	
cycle	yield (%)	ee (%)
1	80	88
2	81	72
3	77	70

[a] Homogeneous reaction: 80% yield, 86% ee. Reported reaction (ref 8): 82% yield, 84% ee.

neous Rh_2(*S*-PTTL)$_4$ gave **19** in 72% yield, >94% de, and 82% ee (Table 6). When immobilized **9a**−Rh_2(*S*-PTTL)$_4$ was

Table 6. Asymmetric Intramolecular C−H Activation of Phenyldiazoacetate **18** Using Immobilized **9a**−Rh_2(*S*-PTTL)$_4$[a]



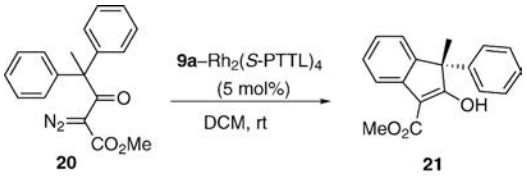
	—Rh_2(*S*-PTTL)$_4$	
cycle	yield (%)	ee (%)
1	67	83
2	70	75
3	68	75

[a] De > 94% was determined by H^1 NMR for all three cycles. Homogeneous reaction: 72% yield, >94% de, 82% ee (toluene). Reported reaction (ref 9): 78% yield, >99:1 dr, 70% ee (hexane).

used, the dihydrobenzofuran **19** was obtained in 67% yield, >94% de, and 83% ee. After three cycles, the enantioselectivity was maintained at 75% ee.

Another interesting application of the Rh_2(*S*-PTTL)$_4$ catalyst is the intramolecular aryl C−H activation to form substituted indanones with a quaternary chiral center.[11] The reaction of α-diazo *β*-ketoester **20** catalyzed by Rh_2(*S*-PTTL)$_4$ is reported to give the cyclic ketoester **21** in 93% ee. Ketoester **21** was converted via demethoxycarbonylation to the corresponding indanone, which was a key intermediate in the asymmetric synthesis of FR115427.[11b] When 5 mol % immobilized **9a**−Rh_2(*S*-PTTL)$_4$ catalyst was used, α-diazo *β*-ketoester **20** underwent enantiotopic aryl C−H activation to give **21** in 80% yield and 93% ee (isolated as its enol tautomer) (Table 7). The catalyst was efficiently recycled

Table 7. Asymmetric Intramolecular Aryl C−H Activation of **20** Using Immobilized **9a**−Rh_2(*S*-PTTL)[4]



	—Rh_2(*S*-PTTL)$_4$	
cycle	yield (%)	ee (%)
1	80	93
2	75	93
3	75	93

[a] Homogeneous reaction: 80% yield, 94% ee. Reported reaction (ref 11): 87% yield, 93% ee.

three times without loss in enantioselectivity. The homogeneous reaction with Rh_2(*S*-PTTL)$_4$ also gives the product in 93% ee.

In conclusion, we have demonstrated that our noncovalent immobilization technology has the potential to be a universal system for the heterogenization of chiral dirhodium catalysts. The immobilization is very effective, as a diverse range of rhodium(II) complexes can be immobilized. No derivatization of the chiral ligands is necessary because, in each case, pyridine coordination occurs to immobilize the catalyst. The enantioselectivity of the heterogeneous and homogeneous reactions is virtually the same, especially in the first cycle. The immobilized rhodium catalysts exhibit all the reactivity features of the homogeneous catalysts, with the advantage of excellent recyclability. The immobilization strategy demonstrates remarkable versatility for a diverse range of rhodium(II) catalysts and carbenoid reactions.

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Supporting Information Available: Experimental procedures for the immobilization and evaluation of immobilized catalysts. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) Tsutsui, H.; Yamaguchi, Y.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2003**, *14*, 817. (b) Watanabe, N.; Ogawa, T.; Ohtake, Y.; Ikegami, S.; Hashimoto, S. *Synlett* **1996**, 85.