Heterogeneous Catalysis

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A Polymer-Supported Chiral Dirhodium(II) Complex: Highly Durable and Recyclable Catalyst for Asymmetric Intramolecular C–H Insertion Reactions**

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Chiral dirhodium(II) complexes are highly effective catalysts for a diverse array of asymmetric carbene transformations of diazocarbonyl compounds, including cyclopropanation, C–H insertion, and rearrangement or cycloaddition via ylide generation.[1] Although a number of systems have been reported to provide enantioselectivities greater than 90% *ee*, the high cost of chiral dirhodium(II) complexes[2,3] and the difficulty in catalyst recovery and recycling are major limiting factors for their application in pharmaceutical production.

The potential benefits of heterogeneous catalysts include facilitation of catalyst separation from products and simplification of catalyst recycling. During the past few decades, a great deal of attention has been paid to developing methods for heterogenizing homogeneous chiral catalysts.[4] However, there have been limited reports on polymer-supported catalysts composed of several independent chiral ligands.[4,5] A significant challenge in grafting chiral dirhodium(II) complexes to supports is maintaining the chiral environment around the parent homogeneous catalysts.[6,7] In this context, Doyle et al. reported that immobilization of chiral dirhodium(II) carboxamidates such as $[Rh_2(5S\text{-MEPY})_4]$ (**1**; Figure 1), could be achieved on NovaSyn Tentagel hydroxy resin and Merrifield resin through an ester linkage to one of the pyrrolidinone ligands; this immobilization led to effective and reusable cyclopropanation catalysts with yields and selectivities comparable to those of the homogeneous catalysts.[8] Davies et al. developed a novel approach for the immobilization of chiral dirhodium(II) tetraprolinate catalysts such as $[Rh_2(S\text{-DOSP})_4]$ (**2**), by using a highly cross-linked macroporous polystyrene (Argopore) resin with a benzyloxymethylpyridine linker,[9] wherein the immobilization is considered to be a result of the cooperative effects of pyridine coordination and microencapsulation. The noncovalent immobilization strategy has not only realized the effective use of the immobilized $[Rh_2(S\text{-DOSP})_4]$ complex as a recyclable catalyst in asymmetric intermolecular cyclopropanation and C–H insertion reactions of donor/acceptor-substituted carbenoids, but has also demonstrated great versatility for a diverse range of chiral dirhodium(II) catalysts.[9d] Despite a great deal of work,[10–13] there still remains a need for development in terms of catalyst activity, selectivity, recyclability, and rhodium leaching. Herein, we report the immobilization of $[Rh_2(S\text{-PTTL})_4]$ (**3**),[14–17] the most generally effective catalyst of our dirhodium(II) carboxylate catalysts which incorporate *N*-phthaloyl-(*S*)-amino acids as bridging ligands, and its use as a highly selective, durable, and recyclable catalyst for asymmetric intramolecular C–H insertion reactions.

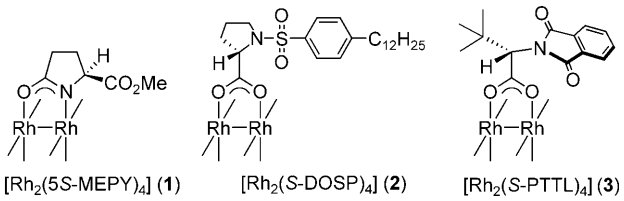

Figure 1. Chiral dirhodium(II) catalysts. MEPY = 5-methoxycarbonyl-2-oxopyrrolidinate, DOSP = *N*-(4-dodecylbenzenesulfonyl)prolinate, PTTL = *N*-phthaloyl-*tert*-leucinate.

We envisaged the immobilization of **3** by the preparation of dirhodium(II)-complex-containing monomer **4** and subsequent copolymerization (Scheme 1).[18,19] The design of polymer-supported chiral dirhodium(II) complex **5** is characterized by the following features: 1) a chiral dirhodium(II) complex is tethered to a polymer chain through one of the ligands in the monomer **4** so there would be no adverse effects on the chiral environment around the immobilized catalyst,[19a] 2) immobilization using the monomer **4** should produce polymer-supported complex **5** with no unreacted linkers or free ligands,[20] 3) a long spacer between the catalytic site and the polymer backbone would allow flexibility of the catalyst system,[21] and 4) copolymerization could lead to a uniform distribution of dirhodium(II) complex within the polymer matrix to allow unimpeded access of a substrate to the catalytic sites.[18,22]

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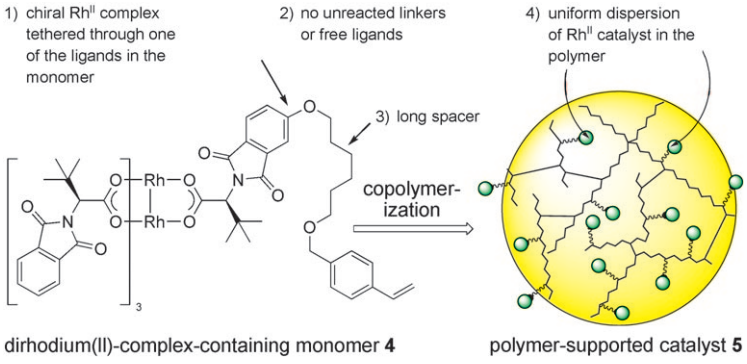
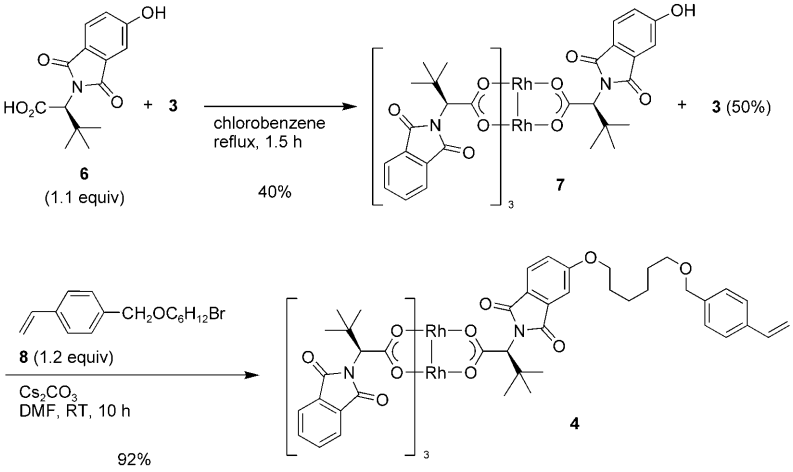


Scheme 1. Design of polymer-supported rhodium(II) complex **5**.

The synthesis of mixed dirhodium(II) tetracarboxylates with chiral ligands has not been previously reported. To the best of our knowledge, there are only a few reports on the synthesis of achiral $[Rh_2(R^1COO)_2(R^2COO)_2]$ species composed of four independent ligands.[23] Consequently, construction of chiral $[Rh_2(R^1COO)_3(R^2COO)]$ **4** became an objective. Toward this goal, we selected *N*-4-hydroxyphthaloyl-(*S*)-*tert*-leucine (**6**) as a replaceable ligand (Scheme 2). Treatment of **3** with **6** in refluxing chlorobenzene gave an equilibrium mixture of dirhodium(II) complex **7** and **3**, which were readily separable by column chromatography on silica gel. The desired complex **7** was isolated in 40% yield; **3** was recovered in 50% yield. A three-cycle sequence of ligand-exchange reactions of recovered **3** and **6** furnished complex **7** in 74% overall yield. O-alkylation of complex **7** with 6-(4-vinylbenzyloxy)bromohexane (**8**) afforded monomer **4** in 92% yield.

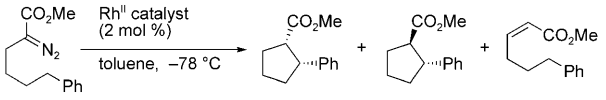


Scheme 2. Preparation of the rhodium(II)-catalyst-containing monomer **4**. DMF = *N*,*N*′-dimethylformamide.

The polymer-supported chiral dirhodium(II) catalyst **5** was prepared by suspension copolymerization[24] of **4** with styrene (**9**) and 1,6-bis(4-vinylbenzyloxy)hexane (**10**) as a cross-linker (Scheme 3). A survey of monomer ratios revealed that the most favorable composition of copolymer **5** was $\mathbf{9}_{94}$-$\mathbf{4}_5$-$\mathbf{10}_1$. A solution of monomers and AIBN in chlorobenzene was dispersed in an aqueous phase containing acacia gum and NaCl as stabilizers, and the mixture was heated at 75 °C for 24 hours. The crude polymer was filtered off, washed thoroughly with water, extracted with dichloromethane and ethyl acetate in a Soxhlet apparatus, and then dried under vacuum to provide **5** in 80% yield. The resultant resin **5** having flexible cross-linkage exhibited excellent swelling characteristics in several organic solvents (see the Supporting Information).[25] Elemental analysis indicated incorporation of 0.27 mmol dirhodium(II) complex per gram of **5**, corresponding to the composition of the monomer feed. The loading of rhodium on **5** was also confirmed by inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis. This observation suggests that copolymerization of styrene (**9**) with 4-vinylbenzyloxy groups in **4** and **10** produced a homogeneous composition of the monomer ratio, and this may be because of similar reactivity of the co-monomers.[26]

The polymer-supported complex **5** was examined for its catalytic performance in enantioselective C–H insertion of α-alkyl-α-diazo ester **11** (Table 1).[15g] Rhodium(II) carbene intermediates, generated from α-alkyl-α-diazo esters bearing a C–H bond adjacent to the diazo carbon atom, tend to form α,β-unsaturated esters via a 1,2-hydride shift.[27] Although it is documented that low reaction temperatures (−78 °C) are key to the suppression of β-hydride elimination,[15g,16,28] there is no immobilized dirhodium(II) catalyst available for carbene transformations below room temperature. The reaction of **11** with 2 mol% of the immobilized catalyst **5** proceeded at −78 °C to provide methyl *cis*-2-phenylcyclopentane-1-carboxylate (**12**) as the sole product in 94% *ee*, and there was no *trans* isomer **13** or alkene product **14**, even though catalyst **5** displayed low reactivity relative to **3** (Table 1, entry 1 versus 2).[29]

Table 1: Rhodium(II)-catalyzed enantioselective C–H insertion of α-diazo ester **11**.

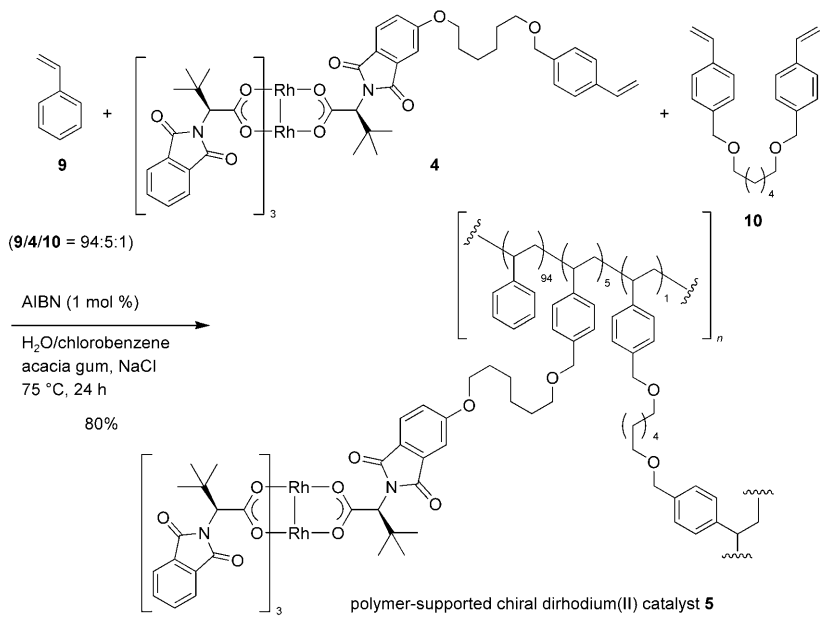


11 **12** **13** **14**

12/13/14 = >99:0:0

Entry	Rh^II	Cycle no.	*t* [h]	Yield [%][a]	*ee* [%][b]
1[c]	**3**	–	0.5	85	95
2	**5**	1	4	85	94
3	**5**	5	4	84	95
4	**5**	10	4	83	95
5	**5**	20	4	81	94

[a] Yield of isolated product **12**. [b] Determined by HPLC analysis. [c] 1 mol% of $[Rh_2(S\text{-PTTL})_4]$ (**3**) was used. See Ref. [15g].



Scheme 3. Preparation of the polymer-supported chiral rhodium(II) complex **5**. AIBN = 2,2′-azobisisobutyronitrile.

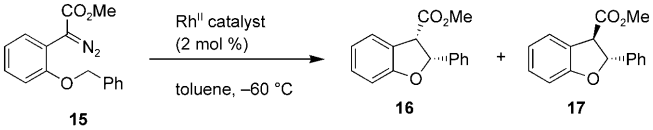
This result indicates that the present method of immobilization using monomer **4** produced very little effect on the chiral environment around the immobilized catalyst. Since catalyst **5** displayed adequate activity and selectivity, attention was next turned to the potency of its recovery and reuse (Table 1, entries 3–5). After the reaction was complete, the liquid phase containing the product was easily separated from the solid catalyst **5** by cannulation. The robust catalyst **5** could be used 20 times, under the same reaction conditions used for the first cycle, with virtually no drop in yield or enantioselectivity.

Another illustration of practical advantages of the immobilized catalyst **5** was provided through asymmetric intramolecular C–H insertion of aryldiazoacetate **15** to afford a dihydrobenzofuran neolignan system (Table 2).[9d,15f] The reaction of **15** in the presence of 2 mol% of **5** proceeded smoothly at −60 °C to afford *cis*-dihydrobenzofuran **16** as the sole product and in a similarly high yield and asymmetric induction as those found with the homogeneous catalyst **3** (Table 2, entry 1 versus 2). Furthermore, catalyst **5** was recyclable (15 times) with no apparent loss of reactivity or enantioselectivity (Table 2, entries 3–5). To determine the effect of the surface area upon the reaction rate, the reaction with pulverized polymer **5** was explored (Table 2, entry 6). Interestingly, the surface area of catalyst **5** had little effect upon the reaction time for full conversion. These results suggest that the reaction with **5** proceeds not only on the surface of the beads but also within the polymer matrix. Therefore, it seems likely that the swelling of polymer **5** in toluene provides free diffusion of the reactant and product to and from the catalytic sites.

Evidence for a uniform dispersion of dirhodium(II) complex in the polymer matrix was obtained from a cross-section analysis of polymer **5** using a scanning electron microscopy with an X-ray microanalyzer (SEM-XMA; see the Supporting Information). Thus, the efficiency of catalyst **5** may be attributed to the combination of good swelling properties and uniform dispersion of the dirhodium(II) complex within the polymer matrix.[30]

The utility of the immobilized catalyst **5** was additionally tested by employing enantioselective intramolecular aromatic C–H insertion of α-diazo-β-ketoester **18** to form substituted indanone **19**, which is a key intermediate in asymmetric synthesis of FR115427 (Table 3).[9d,15a] The reaction of **18** with 2 mol% of **5** at room temperature was conducted using an Argonaut quest-210 parallel synthesizer[31] for easy catalyst separation and catalyst recycling. The immobilized catalyst **5** exhibited essentially the same product yield and enantioselectivity as those found with the homogeneous catalyst **3**

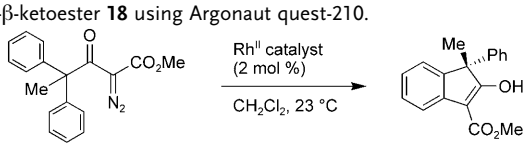
Table 2: Rhodium(II)-catalyzed enantioselective C–H insertion of aryldiazoacetate **15**.



Entry	Rh^{II}	Cycle no.	*t* [h]	Yield [%][a]	*ee* [%][b]
1[c]	**3**	–	0.5	87	90
2	**5**	1	2	83	91
3	**5**	5	2	84	91
4	**5**	10	2	84	91
5	**5**	15	2	80	90
6[d]	**5**	–	2	83	91

[a] Yield of isolated product **16**. [b] Determined by HPLC analysis. [c] 1 mol% of $[Rh_2(S\text{-PTTL})_4]$ (**3**) was used. See Ref. [15f]. [d] Pulverized catalyst **5** was used.

Table 3: Rhodium(II)-catalyzed enantioselective C–H insertion of α-diazo-β-ketoester **18** using Argonaut quest-210.



Entry	Rh^{II}	Cycle no.	*t* [min]	Yield [%][a]	*ee* [%][b]
1	**3**	–	5	89	91
2	**5**	1	20	86	91
3	**5**	10	20	90	91
4	**5**	50	20	90	91
5	**5**	100	20	88	92

[a] Yield of isolated product **19**. [b] Determined by HPLC analysis of the product after demethoxycarbonylation.

(Table 3, entry 1 versus 2). For pharmaceutically active ingredients, there are usually strict guidelines limiting the levels of heavy metals in the drug substance.[32] Therefore, the leaching level of rhodium was examined by ICP/mass spectrometry, which enables the measurement of elements at the parts-per-billion level. The liquid phase of the first cycle contained only 0.28 ppm rhodium, which corresponds to 0.0019 % of the initial catalyst charge. Indeed, the robust nature of catalyst **5** was demonstrated by the retention of full activity and enantioselectivity during 100 sequential applications (Table 3, entries 2–5). The high mechanical stability of catalyst **5** can be attributed to its homogeneous composition[26] and swelling properties.[33]

In conclusion, we have accomplished the immobilization of $[Rh_2(S\text{-PTTL})_4]$ (**3**) by copolymerization of dirhodium(II)-complex-containing monomer **4** with styrene (**9**) and the flexible cross-linker **10**. To the best of our knowledge, complex **4** is the first example of a chiral mixed dirhodium(II) tetracarboxylate. Tethering a chiral dirhodium(II) complex to a polymer chain through one of the ligands in **4** had no deleterious effect on the chiral environment around the immobilized catalyst. The immobilized catalyst **5** promoted asymmetric C–H insertions even at −78 °C with high enantioselectivity and could be used for up to 100 sequential applications with a low leaching level, a feature of which results from the combination of good swelling properties and uniform dispersion of catalytic sites within the polymer matrix. A similar method may prove beneficial for immobilization of homogeneous catalysts composed of several independent chiral ligands. Additional applications to other catalyst systems are currently being investigated.

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