DOI: 10.1002/adsc.201200219

A Polymer-Supported Chiral Fluorinated Dirhodium(II) Complex for Asymmetric Amination of Silyl Enol Ethers

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Received: March 16, 2012; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200219.

Abstract: The immobilization of dirhodium(II) tetrakis[*N*-tetrafluorophthaloyl-(*S*)-*tert*-leucinate], [Rh_2(*S*-TFPTTL)$_4$], has been accomplished by copolymerization of a dirhodium(II) complex-containing monomer with styrene and 1,6-bis(4-vinylbenzyloxy)hexane as a flexible cross-linker. The polymer-supported chiral fluorinated dirhodium(II) complex catalyzed the amination of silyl enol ethers with [*N*-(2-nitrophenylsulfonyl)imino]phenyliodinane (NsN=IPh) to provide α-amino ketones in high yields with high levels of enantioselectivity and could be used up to 20 times as the catalyst readily withstood stirring in the presence of the solid reactant.

Keywords: asymmetric catalysis; heterogeneous catalysis; immobilization; nitrenes; rhodium

Chiral dirhodium(II) carboxylate and carboxamidate complexes are exceptional catalysts for a wide range of enantioselective metal carbene transformations with diazocarbonyl compounds, including cyclopropanation, C–H insertion, and rearrangement or cycloaddition *via* ylide generation.[1] Recently, they have also been recognized as effective catalysts in metal nitrene reactions such as C–H amination and olefin aziridination.[2–8] Although such reactions frequently proceed in high yield and with high levels of asymmetric induction, their practical applications in pharmaceutical production are hampered by the high costs of both rhodium[9] and chiral ligands as well as the difficulty in catalyst recovery and recycling. These drawbacks have stimulated a variety of efforts toward immobilization of chiral dirhodium(II) complexes.[10–16] While considerable advances have been made in selected catalytic asymmetric carbene processes, to the best of our knowledge, there is no immobilized dirhodium(II) catalyst available for nitrene reactions.[17,18]

Recently, we reported an effective immobilization of [Rh_2(*S*-PTTL)$_4$] (**1a**)[19–21] (Figure 1), which was achieved by preparation of a dirhodium(II) complex-containing monomer **2a** followed by copolymerization with styrene (**5a**) and 1,6-bis(4-vinylbenzyloxy)hexane (**6**) as a flexible cross-linker (Scheme 1).[22–25] The polymer-supported complex **7a** with no unreacted linkers or free ligands[26] catalyzed asymmetric C–H insertions with high enantioselectivities similar to those found with the homogeneous catalyst **1a** and could be used for up to 100 sequential applications with a low leaching level.[22] Very recently, a similar method proved to be beneficial for the immobilization of a chiral chlorinated dirhodium(II) complex.[27] The immobilized catalyst **7b** prepared by copolymerization of dirhodium(II) complex-containing monomer **2b** with 2-(trifluoromethyl)styrene (**5b**) and cross-linker **6** (Scheme 1) was successfully applied to intermolecular carbonyl ylide cycloaddition reactions under continuous flow conditions, where high yields as well as high levels of enantioselectivity (up to 99% *ee*) and turnover number (up to 11,700) were achieved.[27] Given that catalysts **7a** and **7b** were remarkably effective catalysts for metal carbene transformations, we were intrigued by the applicability of a polymer-supported dirhodium(II) complex to metal nitrene reactions. In this context, we previously demonstrated that dirhodium(II) tetrakis[*N*-tetrafluorophthaloyl-(*S*)-*tert*-leucinate], [Rh_2(*S*-TFPTTL)$_4$] (**1c**),[28] the fluorinated analogue of **1a**, is an effective catalyst for the enantioselective amination of silyl enol ethers derived from acyclic ketones or enones with [*N*-(2-nitrophenylsulfonyl)imino]phenyliodinane (NsN=IPh), in which high levels of asymmetric induction (up to 95% *ee*) were achieved when the reaction was conducted in CH_2Cl_2 at −40 °C.[28b] Toward this goal, however, a problem arose since NsN=IPh[29] is practically insoluble in

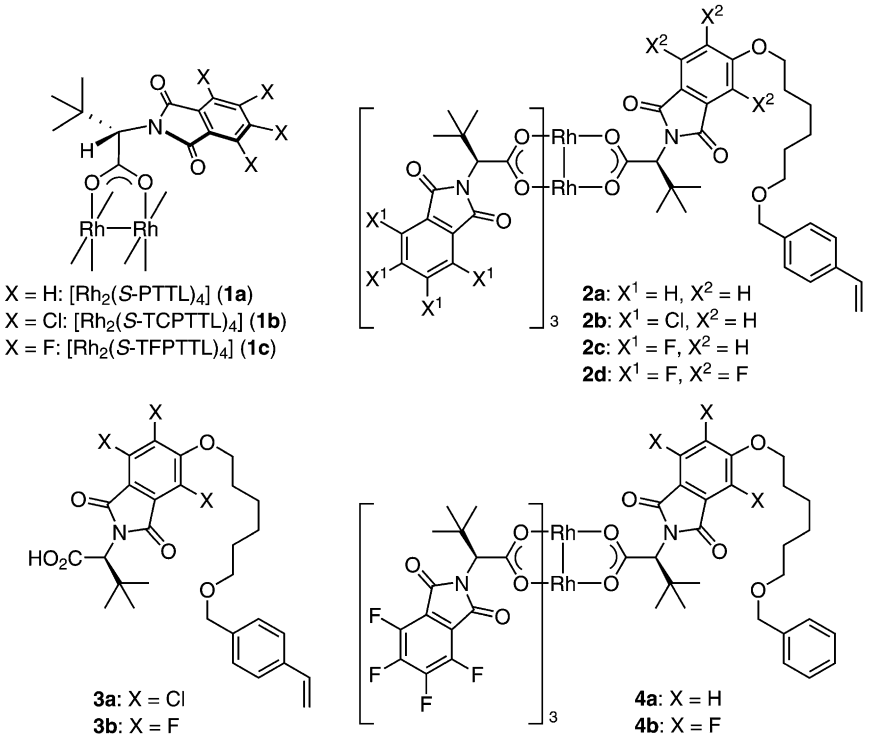
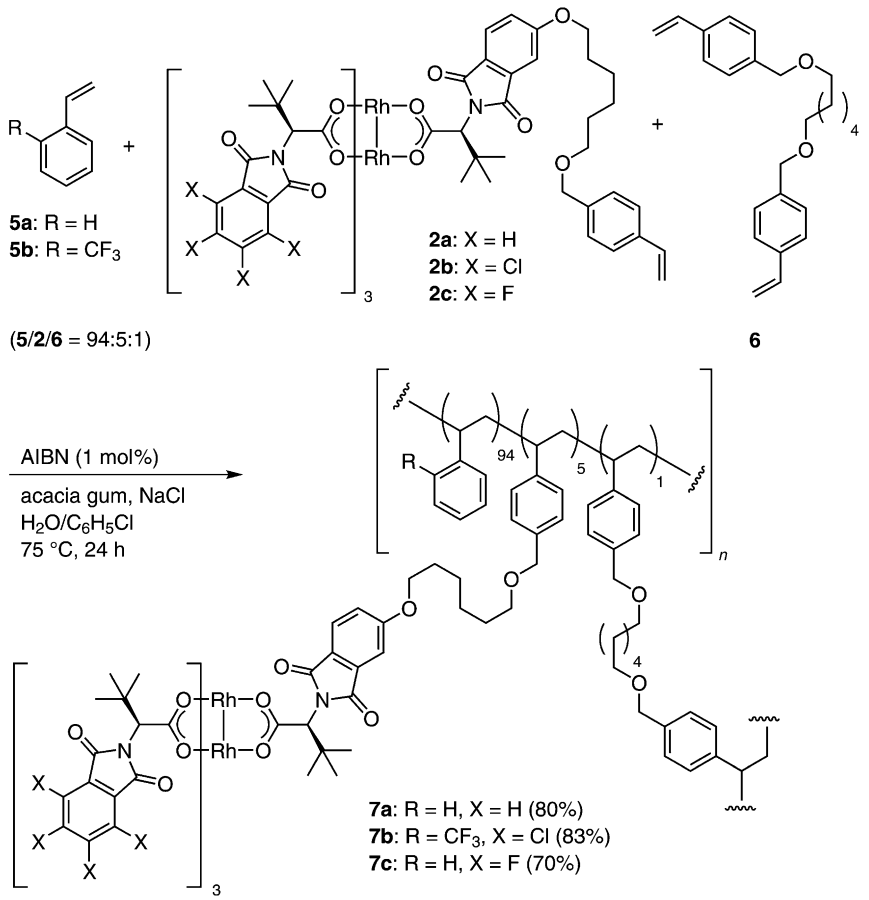


Figure 1. Chiral dirhodium(II) catalysts. PTTL = *N*-phthaloyl-*tert*-leucinate, TCPTTL = *N*-tetrachlorophthaloyl-*tert*-leucinate, TFPTTL = *N*-tetrafluorophthaloyl-*tert*-leucinate.



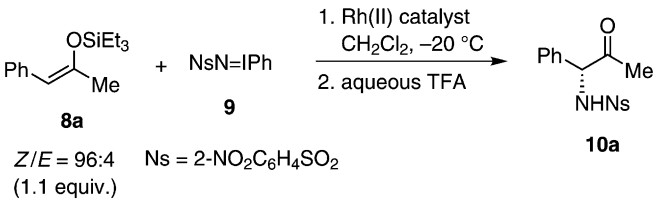
Scheme 1. Immobilization of chiral dirhodium(II) complexes.

most solvents[2c] including CH_2Cl_2, the optimal solvent for this transformation.[28b,30] Therefore, a major challenge was the development of polymer-supported dirhodium(II) catalysts that could readily withstand the dynamic contact with solid reactants. Herein, we report the immobilization of a chiral fluorinated dirhodium(II) complex and its use for enantioselective amination of silyl enol ethers.

In our previous work,[27] the immobilization of $[Rh_2(S\text{-TCPTTL})_4]$ (**1b**),[7,31–33] the chlorinated analogue of **1a**, was unsuccessful simply because nucleophilic substitution of tetrachlorophthalic acid with hydroxide ion failed to give the 4-hydroxy-3,5,6-trichlorophthalic acid required for the preparation of a replaceable ligand **3a**. Conveniently, however, the immobilized catalyst **7b** emerged as a surrogate for the unfinished goal (Scheme 1).[27] Thus, our initial study focused on the immobilization of a mixed dirhodium(II) complex **2c**,[34] one bridging ligand of which is *N*-4-[6-(4-vinylbenzyloxy)hexyl]oxyphthaloyl-(*S*)-*tert*-leucine. AIBN-initiated and acacia gum-stabilized suspension copolymerization of monomer **2c** with styrene (**5a**) and cross-linker **6** afforded a polymer-supported complex **7c** in 70% yield (Scheme 1).

The immobilized complex **7c** was examined for its catalytic performance in the amination of silyl enol ether **8a** (*Z*/*E* = 96:4) derived from phenylacetone with NsN=IPh (**9**) (Table 1).[28b] The reaction in the presence of 5 mol% of **7c** proceeded in CH_2Cl_2 at −20 °C for 20 h and, after separation of **7c** from the reaction mixture and subsequent treatment of the liquid phase with 90% aqueous trifluoroacetic acid (TFA), gave α-amino ketone **10a** in 94% yield with 79% *ee* (entry 2).[35] The enantioselectivity was substantially lower than that observed with $[Rh_2(S\text{-TFPTTL})_4]$ (**1c**) (94% *ee*, entry 1) but was found to be comparable to that obtained with the homogeneous reference catalyst **4a** (76% *ee*, entry 3). Although the *ee* value was unsatisfactory, this result indicates that the present method of immobilization had very little effect on the chiral environment around the immobilized catalyst.[36,37] At this point, we turned our attention to the performance of dirhodium(II) complex **4b**, a catalyst characterized by substitution of fluorine atoms for all phthalimido hydrogen atoms. Gratifyingly, the reaction using catalyst **4b** afforded **10a** in 91% yield with 91% *ee* (entry 4). This promising result had important implications for the design of an immobilized catalyst based on copolymerization of monomer **2d** that incorporates *N*-4-[6-(4-vinylbenzyloxy)hexyl]oxy-3,5,6-trifluorophthaloyl-(*S*)-*tert*-leucine (**3b**) as one of the bridging ligands.

Table 1. Rh(II)-catalyzed enantioselective amination of silyl enol ether **8a** with **9**.[a]



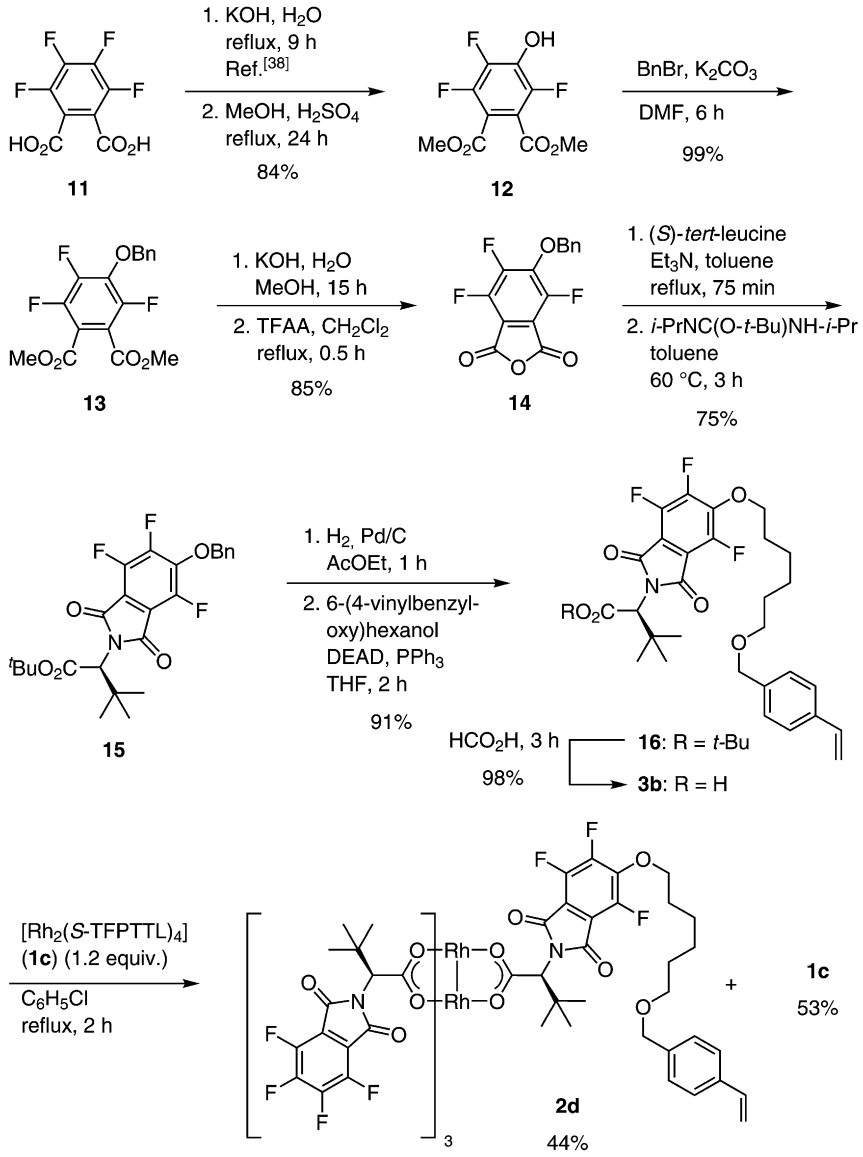
Entry	Rh(II)	mol%	Time [h]	Yield [%][b]	*ee* [%][c]
1	**1c**	2	3.5	93	94
2	**7c**	5	20	94	79
3	**4a**	2	5	94	76
4	**4b**	2	4	91	91

[a] All reactions were performed at −20 °C on a 0.1-mmol scale (0.1 M) with 1.1 equiv. of **8a**.
[b] Isolated yield.
[c] Determined by HPLC.

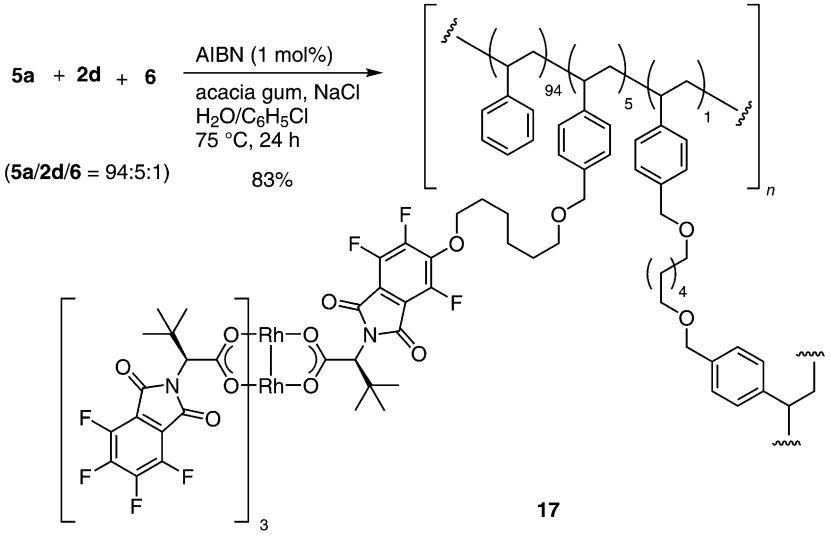
Dirhodium(II) complex-containing monomer **2d** was synthesized as shown in Scheme 2. 4-Benzyloxy-3,5,6-trifluorophthalic anhydride (**14**) was prepared in five steps from tetrafluorophthalic acid (**11**) *via* 4-hydroxy-3,5,6-trifluorophthalic acid[38] in 71% yield. Condensation of (*S*)-*tert*-leucine with **14** proceeded without racemization to form a carboxylic acid, which, upon treatment with *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea, afforded *tert*-butyl ester **15** in 75% yield. Hydrogenolysis of the benzyl ether followed by *O*-alkylation with 6-(4-vinylbenzyloxy)hexanol under Mitsunobu conditions and subsequent exposure to formic acid provided the targeted ligand **3b** in 89% yield. Treatment of $[Rh_2(S\text{-TFPTTL})_4]$ (**1c**) with **3b** in refluxing chlorobenzene gave an equilibrium mixture of dirhodium(II) complexes **2d** and **1c**, which were separable by gel permeation chromatography. The desired complex **2d** was isolated in 44% yield; **1c** was recovered in 53% yield. After a two-cycle sequence of ligand-exchange reactions of recovered **1c** and **3b**, complex **2d** was obtained in 60% combined yield.

Copolymerization of **2d** with styrene (**5a**) and **6** as a cross-linker gave a polymer-supported fluorinated dirhodium(II) complex **17** in 83% yield (Scheme 3). It is well known that the mechanical properties of the resin strongly depend on a homogeneous composition of the copolymer.[39] The chemical composition of **17** determined by elemental analysis and inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis was very close to the original monomer composition, indicating similar reactivity of the comonomers **2d**, **5a** and **6**. Furthermore, evidence for a uniform dispersion of dirhodium(II) complex in the polymer matrix was obtained from surface analysis of polymer **17** using scanning electron microscopy with an X-ray micro-analyzer (SEM-XMA).

Using 5 mol% of the immobilized catalyst **17**, we were gratified to find that the reaction of silyl enol ether **8a** with NsN=IPh (**9**) at −20 °C afforded α-amino ketone **10a** in 94% yield with high asymmetric induction (92% *ee*), though catalyst **17** displayed low reactivity relative to $[Rh_2(S\text{-TFPTTL})_4]$ (**1c**) (Table 2,

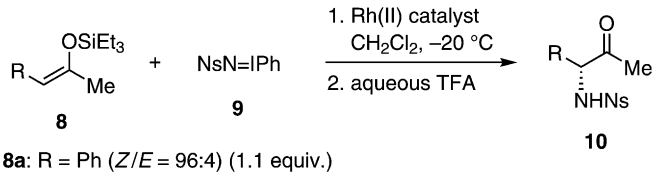


Scheme 2. Preparation of dirhodium(II)-complex-containing monomer **2d**.



Scheme 3. Immobilization of chiral dirhodium(II) complex.

Table 2. Rh(II)-catalyzed enantioselective amination of silyl enol ethers **8** with **9**.[a]



8 **9** **10**

8a: R = Ph (*Z*/*E* = 96:4) (1.1 equiv.)
8b: R = $PhCH_2$ (*Z*/*E* = >99:1) (1.1 equiv.)
8c: R = 4-$MeOC_6H_4CH_2$ (*Z*/*E* = 87:13) (1.3 equiv.)

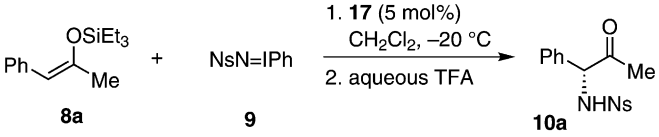
Entry	8	Rh(II)	Time [h]	Product	Yield [%][b]	*ee* [%][c]
1[d]	**8a**	**1c**	3.5	**10a**	93	94
2[e]	**8a**	**17**	20	**10a**	94	92
3[d]	**8b**	**1c**	1	**10b**	93	91
4[e]	**8b**	**17**	18	**10b**	91	88
5[d]	**8c**	**1c**	3	**10c**	87	82
6[e]	**8c**	**17**	30	**10c**	88	80

[a] All reactions were performed at –20 °C on a 0.1-mmol scale (0.1 M) with **8**.
[b] Isolated yield.
[c] Determined by HPLC.
[d] 2 mol% of $[Rh_2(S\text{-TFPTTL})_4]$ (**1c**) was used.
[e] 5 mol% of **17** was used.

entries 1 and 2). Furthermore, the reaction of benzyl-substituted silyl enol ethers **8b** and **8c** with catalyst **17** afforded the respective α-amino ketones **10b** and **10c**, a key intermediate in asymmetric formal synthesis of (–)-metazocine,[28b] in high yields and good to high enantioselectivities as found with **1c** (entries 3–6).[40]

Since the catalyst **17** displayed adequate activity and enantioselectivity, attention was next turned to

Table 3. Enantioselective amination of silyl enol ether **8a** with **9** catalyzed by immobilized Rh(II) complex **17**.[a]



8a **9** **10a**

Z/*E* = 96:4 (1.1 equiv.) Ns = 2-$NO_2C_6H_4SO_2$

Entry	Cycle	Time [h]	Yield [%][b]	*ee* [%][c]
1	1	20	94	92
2	2	20	93	92
3	5	24	93	90
4	10	30	94	90
5	15	48	94	90
6	20	72	95	91

[a] All reactions were performed at –20 °C on a 0.1-mmol scale (0.1 M) with 1.1 equiv. of **8a** in the presence of 5 mol% of Rh(II) catalyst **17**.
[b] Isolated yield.
[c] Determined by HPLC.

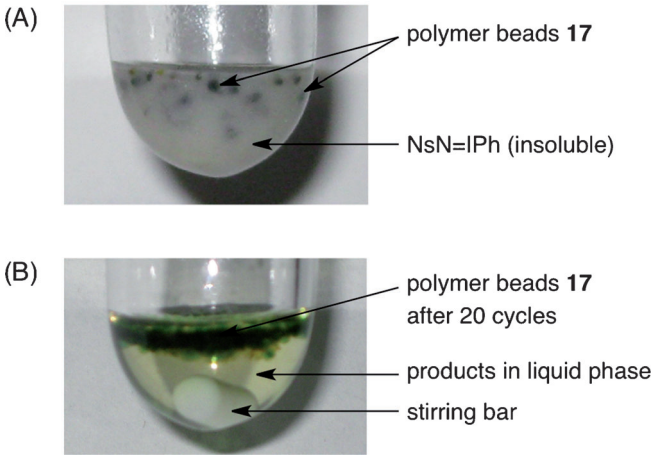


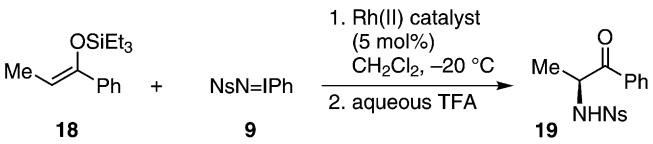
Figure 2. Photographs of the Rh(II) catalyst **17** (A) immediately after addition of NsN=IPh (**9**); (B) after 72 h of stirring (Table 3, entry 6).

the potency of its recovery and reuse (Table 3). After the amination of silyl enol ether **8a** with NsN=IPh (**9**) was complete, the liquid phase containing the product was easily separated from the solid catalyst **17** with a Pasteur pipette. The leaching level of rhodium atom was examined by ICP-MS. The liquid phase of the first cycle contained only 10 ppm rhodium, which corresponds to 0.04% of the initial catalyst charge. Indeed, the immobilized catalyst **17** could be used 20 times with virtually no drop in product yield or enantioselectivity, although reaction times were gradually prolonged with each subsequent recycling step (entries 2–6). The polymer-supported complex **17** is formed in beads that readily withstand stirring in the presence of practically insoluble solid reactant **9** (Figure 2). It is documented that the cross-link can have a profound effect on mechanical strength.[41] The mechanical stability of **17** can be attributed to its homogeneous composition and the choice of 1,6-bis(4-vinylbenzyloxy)hexane (**6**) as a flexible cross-linker.

The polymer-supported complex **17** was also found to be an effective catalyst for enantioselective amination of silyl enol ether **18** (*Z*/*E* = >99:1) derived from propiophenone with NsN=IPh (**9**) at –20 °C (Table 4).[28b] The catalysis with **17** afforded α-amino ketone **19** in virtually the same product yield and enantioselectivity as found with the $[Rh_2(S\text{-TFPTTL})_4]$ (**1c**) (entries 1 and 2).[42] The robust catalyst **17** could be recycled 20 times without compromising the product yield or enantioselectivity (entries 3–7).

In summary, we have accomplished the immobilization of a chiral fluorinated dirhodium(II) complex by copolymerization of a dirhodium(II) complex-containing monomer **2d** with styrene (**5a**) and 1,6-bis(4-vinylbenzyloxy)hexane (**6**) as a flexible cross-linker. The polymer-supported fluorinated dirhodium(II) complex

Table 4. Enantioselective amination of silyl enol ether **18** with **9** catalyzed by immobilized Rh(II) complex **17**.[a]



Entry	Rh(II)	Cycle	Time [h]	Yield [%][b]	*ee* [%][c]
1[d]	**1c**	–	3	95	91
2	**17**	1	10	92	90
3	**17**	2	10	91	91
4	**17**	5	12	92	91
5	**17**	10	14	93	90
6	**17**	15	18	91	90
7	**17**	20	22	92	90

[a] All reactions were performed at −20 °C on a 0.2-mmol scale (0.1 M) with 1.1 equiv. of **18** in the presence of 5 mol% of Rh(II) catalyst **17**.
[b] Isolated yield.
[c] Determined by HPLC.
[d] 2 mol% of $[Rh_2(S\text{-TFPTTL})_4]$ (**1c**) was used.

17 catalyzed the amination of silyl enol ethers to give α-amino ketones in high yields with high levels of asymmetric induction (up to 92% *ee*) and could be used up to 20 times. It was found that the substitution of fluorine atoms for all phthalimido hydrogen atoms is crucial for a high degree of enantioselectivity. To the best of our knowledge, this is the first example of metal nitrene reaction under catalysis by heterogeneous dirhodium(II) complexes. Further studies are currently in progress to extend the utility of this polymer-supported catalyst.

Experimental Section

Representative Procedure for the Enantioselective Amination of Silyl Enol Ether 8a with NsN=IPh (9) Catalyzed by Immobilized Rh(II) Complex 17 (Entry 1 in Table 3)

A reaction vessel was equipped with a stirring bar and charged with polymer-supported dirhodium(II) complex **17** (19.8 mg, 5 mol%), silyl enol ether **8a** (27.1 mg, 0.11 mmol, *Z*:*E* = 96:4) and CH_2Cl_2 (1 mL), and allowed to swell at room temperature for 0.5 h. NsN=IPh (**9**) (40.4 mg, 0.10 mmol) was added in one portion to the mixture at −20 °C. After 20 h of stirring at this temperature, the organic layer was separated from the solid catalyst **17** with a Pasteur pipette. The remaining resin was washed with an additional CH_2Cl_2 (1 mL), and the organic layer was combined with the crude reaction mixture. The catalyst **17** was reused without further treatments. The reaction mixture was treated with 90% aqueous TFA (*ca.* 0.1 mL) followed by stirring for 1.5 h at room temperature. The mixture was partitioned between EtOAc (15 mL) and pH 7.0 phosphate buffer (3 mL). The separated organic layer was washed with water (2 × 3 mL) and brine (2 × 3 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation furnished the crude product, which was purified by column chromatography on silica gel (2:1 hexane/EtOAc) to provide **10a** as a colorless viscous oil; yield: 31.4 mg (94%). The spectroscopic data were consistent with the previously reported data; $[\alpha]_D^{21}$: −328 (*c* 1.02, $CHCl_3$) for 92% *ee* [lit.[28b] $[\alpha]_D^{20}$: −340 (*c* 0.92, $CHCl_3$) for *R* 95% *ee* of **10a**]. The enantiomeric excess of **10a** was determined to be 92% by HPLC [Chiralpak AD-H column (3:1 hexane/*i*-PrOH, 1.0 mL min^{-1})]: t_R = 13.3 min for major enantiomer, t_R = 14.9 min for minor enantiomer.

Acknowledgements

This research was supported by a Grant-in Aid for Scientific Research on Innovative Areas "Organic Synthesis Based on Reaction Integration" (No. 2105) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We thank S. Oka and M. Kiuchi from the Center for Instrumental Analysis at Hokkaido University for technical assistance with mass spectrometry and elemental analysis.

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