CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201102733

Continuous Flow System with a Polymer-Supported Dirhodium(II) Catalyst: Application to Enantioselective Carbonyl Ylide Cycloaddition Reactions

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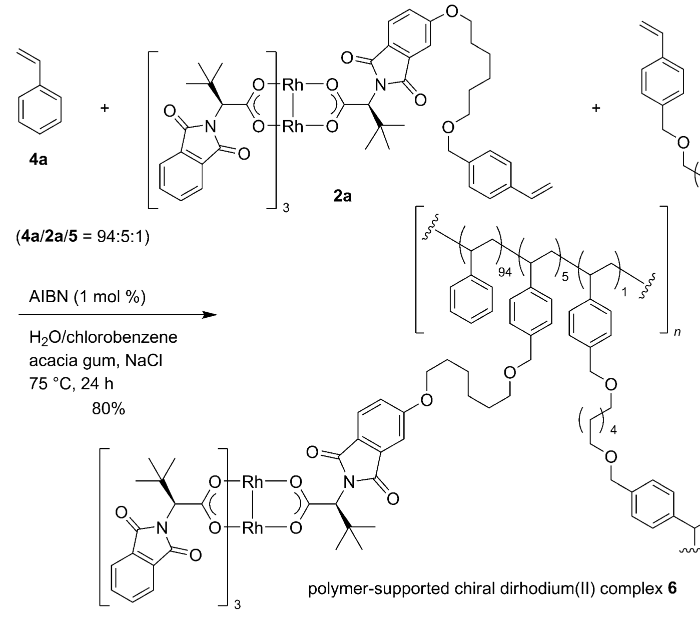
Dedicated to Professor Albert Padwa

Over the past two decades, the exceptional power of chiral dirhodium(II) carboxylate and carboxamidate catalysts has been demonstrated in a diverse array of enantioselective metal carbene transformations of diazocarbonyl compounds, including cyclopropanation, C–H insertion, and rearrangement or cycloaddition via ylide generation.[1] Although such reactions frequently proceed in high yield and with high levels of asymmetric induction, their practical applications in pharmaceutical production were often hindered due to high costs of both rhodium[2] and chiral ligands as well as the difficulty in catalyst recovery and recycling. To address this issue, several approaches toward immobilization[3] of chiral dirhodium(II) complexes have been explored, including covalent attachment to soluble[4] and insoluble supports,[5–8] use of biphasic systems,[9] and novel noncovalent immobilization using the combination of ligand coordination and encapsulation.[10] However, further improvements in catalyst activity, selectivity, recyclability, and rhodium leaching are still needed.[11]



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

Continuous flow reactors have found use as powerful synthetic tools enabling operational flexibility, reduced reaction times and system automation, resulting in a technique that is suitable for a high-throughput synthesis.[12] The application of heterogeneous catalysts in continuous flow mode offers advantages of suppressing the mechanical degradation of catalyst supports as well as easy catalyst separation and large-scale production.[13] Despite these potential benefits,[14] to the best of our knowledge, there is no immobilized dirhodium(II) catalyst available for a continuous flow process.[15]

Recently, we reported an effective immobilization of $[\mathrm{Rh}_2(S\text{-PTTL})_4]$ (**1a**)[16,17] (Figure 1) composed of four independent chiral ligands,[18,19] which relied on preparation of a dirhodium(II)-complex-containing monomer **2a** followed by copolymerization with styrene (**4a**) and 1,6-bis(4-vinylbenzyloxy)hexane (**5**) as a flexible cross-linker (Scheme 1).[8,20–22] The polymer-supported complex **6** with no unreacted linkers or free ligands[23] catalyzed asymmetric C–H insertions even at −78 °C with high enantioselectivities similar to those found with homogeneous **1a** and could be used for up to 100 sequential applications with a low leaching level (0.28 ppm),[8] a feature that results from the combination of good swelling properties and uniform dispersion of catalytic sites in the polymer matrix.[24] Given that the com-

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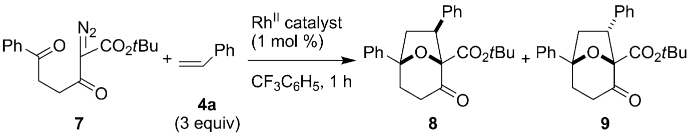
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201102733.

plex **6** was a remarkably effective catalyst for intramolecular C–H insertion reactions, we were intrigued by the applicability of a polymer-supported dirhodium(II) complex to intermolecular metal–carbene transformations. We previously reported that [Rh_2(*S*-TCPTTL)$_4$] (**1b**),[25–27] the chlorinated analogue of **1a**, is an exceptionally effective catalyst for enantioselective tandem carbonyl ylide formation-1,3-dipolar cycloaddition reactions of 2-diazo-3,6-diketoesters with arylacetylene, alkoxyacetylene, and styrene dipolarophiles, in which high levels of asymmetric induction (up to 99% *ee*) as well as perfect *exo* diastereoselectivity for styrenes were achieved.[26a,28,29] Herein, we report the immobilization of a chiral chlorinated dirhodium(II) complex and its use for enantioselective carbonyl ylide cycloaddition reactions under continuous flow conditions.

On the basis of our previous work, we considered that [Rh_2(*S*-TCPTTL)$_4$] (**1b**) could be immobilized by copolymerization of dirhodium(II)-complex-containing monomer **2b**, the chlorinated analogue of **2a**. However, all attempts to synthesize monomer **2b** were unsuccessful. At this point, we turned our attention to the catalytic performance of a mixed dirhodium(II) tetracarboxylate,[30] [Rh_2(*S*-PTTL)(*S*-TCPTTL)$_3$] (**3**), as a surrogate for **2b**. As a model reaction, intermolecular cycloaddition of carbonyl ylide derived from 2-diazo-3,6-diketoester **7** with styrene (**4a**) in α,α,α-trifluorotoluene ($CF_3C_6H_5$) was examined (Table 1).[26a] The reaction using 1 mol% of catalyst **3** afforded cycloadduct **8**[31] in high yield and asymmetric induction (99% *ee*) with perfect *exo* diastereoselectivity as found with [Rh_2(*S*-TCPTTL)$_4$] (**1b**) (entries 1 and 2). Examination of the temperature profile demonstrated that catalysis with **1b** or **3** performed well even at 60 °C (entries 4 and 5), in stark contrast to that with [Rh_2(*S*-PTTL)$_4$] (**1a**) (entries 3 and 6). Recently, Fox[32] and Charette[33] independently determined the X-ray crystal structure of [Rh_2(*S*-PTTL)$_4$] (**1a**) and other phthalimido-derived catalysts and showed that the four phthalimido groups are projected on the same face of the catalyst, thus providing a chiral crown conformation.[34] Charette and co-workers also proposed that [Rh_2(*S*-TCPTTL)$_4$] (**1b**), which could benefit from halogen-bonding interactions,[35] might be even more rigid in solution than [Rh_2(*S*-PTTL)$_4$] (**1a**).[33] Although one of the four ligands in [Rh_2(*S*-PTTL)(*S*-TCPTTL)$_3$] (**3**) is not chlorinated, variable temperature ^{13}C NMR experiments in C_6D_6 carried out on **3** indicated the rigid nature of such a chlorinated complex in solution as demonstrated by Charette[36] (see the Supporting Information for details). This observation, together with the great catalytic performance of **3**, had important implications for the design of a polymer-supported catalyst based on copolymerization of monomer **2c**.

Table 1. Enantioselective intermolecular cycloaddition of 2-diazo-3,6-diketoester **7** with styrene (**4a**) catalyzed by dirhodium(II) complexes.[a]



Entry	Catalyst	*T* [°C]	Yield [%][b]	**7**	*ee* of **8** [%][d]
1[e]	[Rh_2(*S*-TCPTTL)$_4$] (**1b**)	23	85	>99:1	99
2	[Rh_2(*S*-PTTL)(*S*-TCPTTL)$_3$] (**3**)	23	80	>99:1	99
3	[Rh_2(*S*-PTTL)$_4$] (**1a**)	23	50	95:5	90
4	[Rh_2(*S*-TCPTTL)$_4$] (**1b**)	60	88	>99:1	95
5	[Rh_2(*S*-PTTL)(*S*-TCPTTL)$_3$] (**3**)	60	86	>99:1	93
6	[Rh_2(*S*-PTTL)$_4$] (**1a**)	60	36	73:27	52

[a] All reactions were carried out as follows: a solution of **7** (61 mg, 0.2 mmol) and **4a** (3 equiv) in $CF_3C_6H_5$ (1 mL) was added over 1 h to a solution of Rh^{II} catalyst (1 mol%) in $CF_3C_6H_5$ (1 mL). [b] Combined yield of **8** and **9**. [c] Determined by ^{1}H NMR analysis of the crude product. [d] Determined by HPLC. [e] See ref. [26a].

Dirhodium(II)-complex-containing monomer **2c** was prepared according to the procedure developed for **2a** (Scheme 2).[8] Treatment of [Rh_2(*S*-TCPTTL)$_4$] (**1b**) with *N*-4-hydroxyphthaloyl-(*S*)-*tert*-leucine (**10**) in refluxing chlorobenzene gave an equilibrium mixture of dirhodium(II) complex **11** and **1b**, which were readily separable by column chromatography on silica gel. The desired complex **11** was isolated in 39% yield; **1b** was recovered in 50% yield. A three-cycle sequence of ligand-exchange reaction of recovered **1b** and **10** furnished complex **11** in 72% overall yield. *O*-Alkylation of complex **11** with 6-(4-vinylbenzyloxy)iodohexane (**12**) afforded monomer **2c** in 94% yield.

At the outset, we performed AIBN-initiated and acacia gum-stabilized suspension copolymerization[37] of **2c** with styrene (**4a**) and **5** as a cross-linker to give a polymer-supported complex **13a** in 80%

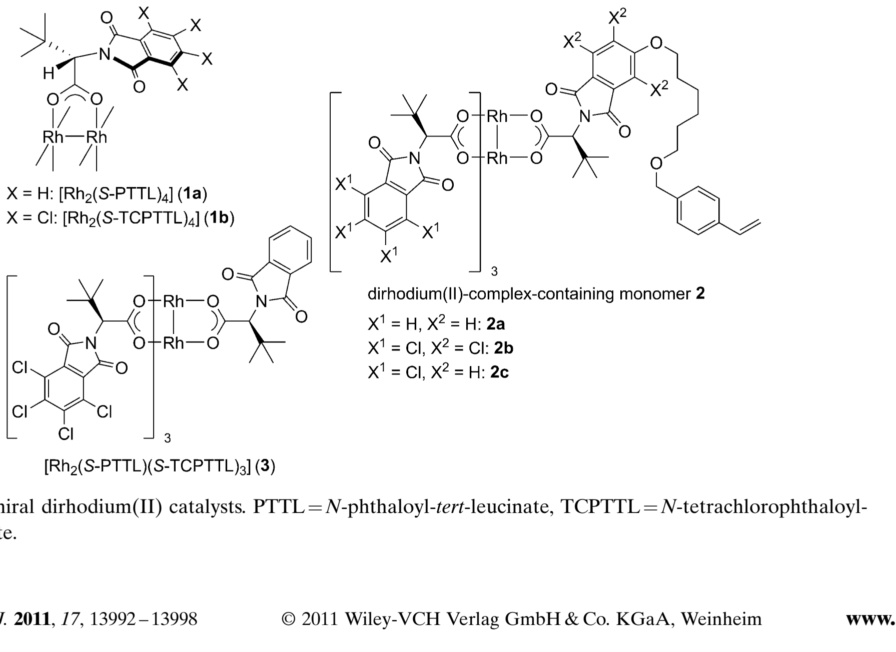
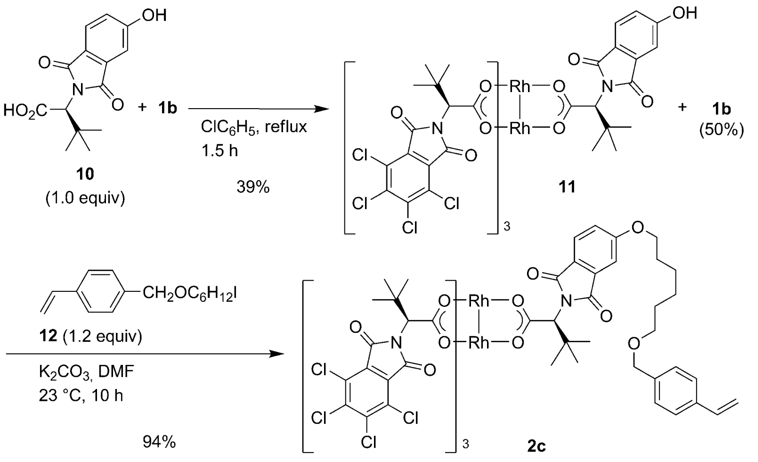


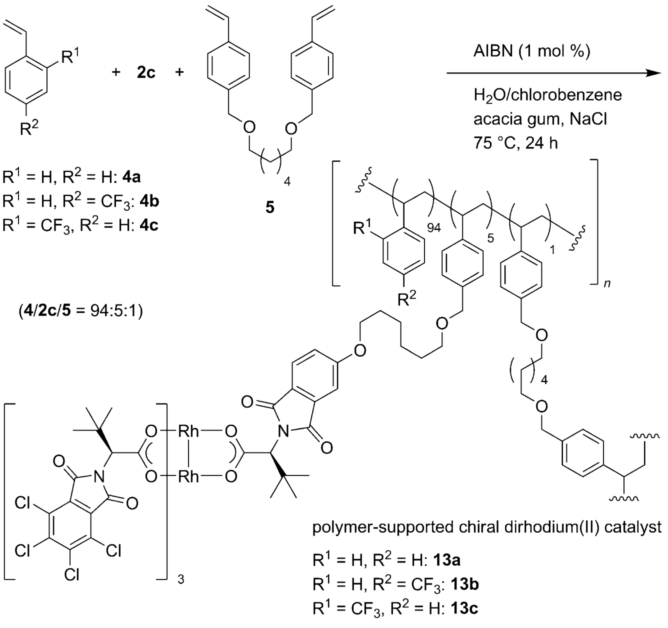
Figure 1. Chiral dirhodium(II) catalysts. PTTL = *N*-phthaloyl-*tert*-leucinate, TCPTTL = *N*-tetrachlorophthaloyl-*tert*-leucinate.



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

yield (Table 2, entry 1). The swelling volumes of resin **13a** were 7.8 $mL\,g^{-1}$ in $CF_3C_6H_5$ and 11.3 $mL\,g^{-1}$ in toluene (volumes were measured in syringes equipped with a filter; see the Supporting Information for details). An important general consideration for successful heterogeneous catalysis is swelling of the resin in the reaction medium.[24] In an attempt to achieve good swelling of **13a** in $CF_3C_6H_5$, the optimal solvent for enantioselective carbonyl ylide cycloaddition reaction,[38] we considered that attachment of trifluoromethyl moieties to polymer supports could be used as an alternative methodology. Thus, we conducted copolymerization with 4- or 2-trifluoromethyl-substituted styrenes **4b** and **4c** to provide resins **13b** and **13c** in 88 and 83 % yield, respectively (entries 2 and 3).[39] Pleasingly, both resins **13b** and **13c** showed a significant increase of swelling in $CF_3C_6H_5$ (**13b**, 10.7 $mL\,g^{-1}$; **13c**, 11.8 $mL\,g^{-1}$). Toluene was a better swelling solvent than $CF_3C_6H_5$ for **13a**, whereas $CF_3C_6H_5$ was a better solvating medium for **13b**, although both were exceptionally effective swelling solvents for **13c**. Elemental analysis of **13a–c** indicated that incorporation of dirhodium(II) complex in resin was close to the theoretical value in all cases, as also confirmed by inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis.

Table 2. Preparation of polymer-supported complexes **13**.



Entry	Polymer	Yield [%]	Loading [$mmol\,g^{-1}$]	Volume [$mL\,g^{-1}$] Dry	in $CF_3C_6H_5$	in toluene
1	**13a**	80	0.24	1.7	7.8	11.3
2	**13b**	88	0.18	1.9	10.7	8.0
3	**13c**	83	0.18	1.9	11.8	14.7

AIBN = 2,2′-azobisisobutyronitrile.

The polymer-supported complexes **13a–c** were evaluated for their catalytic performance in the reaction of diazodiketoester **7** with styrene (**4a**) (Table 3). The reactions with three types of complexes (3 mol %) resulted in high enantioselectivity (99 % *ee*) and perfect *exo* diastereoselectivity as found with $[Rh_2(S\text{-PTTL})(S\text{-TCPTTL})_3]$ (**3**), though the yields of cycloadduct **8** were diminished to 56, 64 and 69 %, respectively (entries 1–3). These results indicate that the present method of immobilization had very little effect on the chiral environment around the immobilized catalyst. This is the first example of carbonyl ylide cycloaddition with heterogeneous dirhodium(II) complexes. The reaction using **13a** was less efficient as reflected by the lower yield; this suggests that swelling of trifluoromethyl-substituted polymers **13b** and **13c** in $CF_3C_6H_5$ is important for the catalytic performance.

Table 3. Enantioselective intermolecular cycloaddition of 2-diazo-3,6-diketoester **7** with styrene (**4a**) catalyzed by polymer-supported dirhodium(II) complexes **13a–c**.[a]

Entry	Catalyst	Yield [%][b]	*ee* [%]
1	**13a**	56	99
2	**13b**	64	99
3	**13c**	69	99

[a] All reactions were carried out as follows: a solution of **7** (61 mg, 0.2 mmol) and **4a** (3 equiv) in $CF_3C_6H_5$ (1 mL) was added over 3 h to a solution of Rh^{II} catalyst (3 mol %) in $CF_3C_6H_5$ (1 mL). [b] Isolated yield. [c] Determined by HPLC.

We next explored the possibility of performing the reaction with catalysts **13b** and **13c** under continuous flow conditions, with particular emphasis on improvement in product yield and reduction in reaction times. The principal design of our flow reactor featured the need to make optimum use

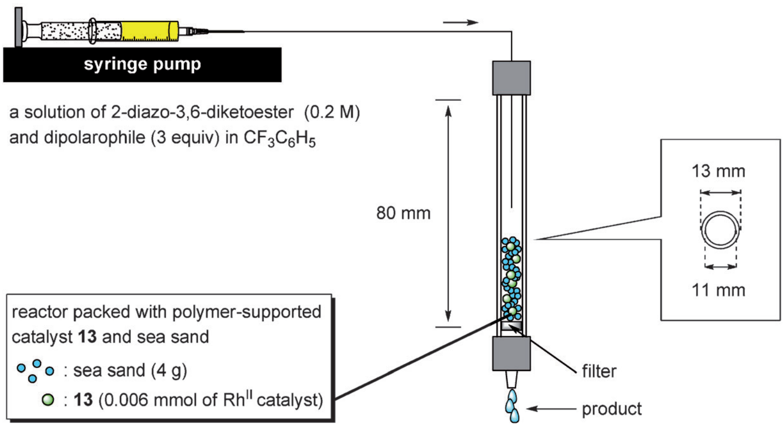


Figure 2. Schematic set up of the flow reactor.

of the cavity for operating without any pressurization. Toward this goal, a reaction vessel (80 mm in length and 11 mm in diameter)[13l] equipped with a filter was packed by injecting a slurry of catalyst (0.006 mmol of Rh^{II} catalyst) and sea sand (4 g)[40] in $CF_3C_6H_5$ (Figure 2). A solution of diazodiketoester **7** (0.2 M) and styrene (**4a**) (3 equiv) in $CF_3C_6H_5$ was passed through the flow reactor (0.34 mL h^{-1}, 3 h, 3 mol % of catalyst with respect to **7**) using a syringe pump (Table 4, entries 1 and 2). The continuous flow experiments gave higher yields than the reaction under batch conditions (cf. Table 3). A greatly improved yield of 80 % was obtained when the catalyst **13c** was used. It seems likely that the polymer matrix of **13c** has a high affinity for reactants as **13c** exhibited superior swelling characteristics not only in $CF_3C_6H_5$ but also in toluene (cf. Table 2).[41] A survey of flow rates revealed that full conversion with no apparent loss of product yield could be achieved at flow rates of up to 0.5 mL h^{-1}, whereby the reaction time was substantially reduced (entry 3). This result can be attributed to the close contact of the catalyst with the reactants and the high local concentration of the catalyst.[42] The leaching level of rhodium atom was examined by ICP-mass spectrometry. The reaction mixture contained only 2.1 ppm rhodium, which corresponds to 0.013 % of the initial catalyst charge. Indeed, the flow reactor could be operated under a steady state for a period of 60 h (entry 4). It is noteworthy that the extrusion of nitrogen gas from diazodiketoester had no deleterious effect on this continuous flow process.

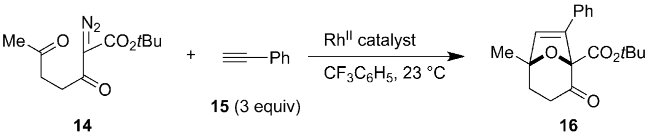
Table 4. Enantioselective intermolecular cycloaddition of 2-diazo-3,6-diketoester **7** with styrene (**4a**) under continuous flow conditions.[a]

Entry	Catalyst [mol %]	Flow rate [mL h^{-1}]	t [h]	Yield [%][b]	*ee* [%][c]
1	**13b**: 3	0.34	3	71	99
2	**13c**: 3	0.34	3	80	99
3	**13c**: 3	0.5	2	80	99
4	**13c**: 0.1	0.5	60	78	99

[a] All reactions were carried out as follows: a solution of **7** (0.2 M) and **4a** (3 equiv) in $CF_3C_6H_5$ was pumped through the flow reactor using a syringe pump at the indicated flow rate. [b] Isolated yield. [c] Determined by HPLC.

Another illustration of practical advantages of the flow reactor packed with **13c** was presented in the reaction of diazodiketoester **14** and phenylacetylene (**15**) in $CF_3C_6H_5$ (Table 5), in which the use of 1 mol % of $[Rh_2(S\text{-TCPTTL})_4]$ (**1b**) produced cycloadduct **16**[43] in 82 % yield with 97 % *ee* (entry 1).[26a] When the amount of **1b** was reduced from the standard 1 to 0.1 mol %, 27 and 6 % drops in yield and enantioselectivity, respectively, were observed (entry 2). In stark contrast, the flow reactor (0.1 mol % of catalyst with respect to **14**) provided **16** with virtually no drop in product yield or enantioselectivity at a flow rate of 30 mL h^{-1} (entries 3 and 4). To demonstrate the preparative utility of this process, the reaction was conducted on a 90 mmol scale (22 g of **14**) with the flow reactor (32 mg of **13c**) to afford 22 g (78 % yield) of **16** in 97 % *ee*, in which turnover numbers as high as 11 700 were achieved (entry 5). These results demonstrate that optimized reaction parameters developed on a small scale in the flow reactor could be transferred directly to large-scale production without the need for substantial further optimization.

Table 5. Enantioselective intermolecular cycloaddition of 2-diazo-3,6-diketoester **14** with phenylacetylene (**15**) under continuous flow conditions.



Entry	Catalyst [mol %]	t [h]	Yield [%][a]	*ee* [%][b]
1[c]	**1b**: 1	1	82	97
2	**1b**: 0.1	1	55	91
3[d]	**13c**: 1	0.1	75	98
4[d]	**13c**: 0.1	1	74	97
5[d]	**13c**: 0.0067	15	78	97

[a] Isolated yield. [b] Determined by HPLC. [c] See ref. [26a]. [d] The reaction was carried out as follows: a solution of **14** (0.2 M) and **15** (3 equiv) in $CF_3C_6H_5$ was pumped through the flow reactor at a flow rate of 30 mL h^{-1}.

In conclusion, we have accomplished the immobilization of $[Rh_2(S\text{-PTTL})(S\text{-TCPTTL})_3]$ (**3**) by copolymerization of dirhodium(II)-complex-containing monomer **2c** with styrenes **4** and the flexible cross-linker **5**. The polymer-supported dirhodium(II) complex **13c** derived from 2-(trifluoromethyl)styrene (**4c**) as a comonomer was successfully applied in tandem carbonyl ylide formation-cycloaddition reactions of 2-diazo-3,6-diketoesters with styrene (**4a**) and phenylacetylene (**15**) dipolarophiles in $CF_3C_6H_5$ under continuous flow conditions, where high yields and high levels of asymmetric induction (up to 99 % *ee*) similar to those found with [Rh_2(*S*-TCPTTL)$_4$] (**1b**) were achieved. The efficiency of **13c** is considered to be due to the combination of excellent swelling in $CF_3C_6H_5$ and good accessibility of the soluble reactants to the catalytic sites in the polymer matrix. The robust nature of the flow reactor was demonstrated by the retention of full activity and enantioselectivity for a number of hours (up to 60 h) with a low leaching level (2.1 ppm). Moreover, this flow system exhibited exceptionally high turnover numbers (up to 11 700) relative to the homogeneous catalyst system. To the best of our knowledge, this is the first example of a continuous flow system with heterogeneous dirhodium(II) complexes. Further application of the continuous flow method to other metal carbene transformations of diazocarbonyl compounds is currently in progress.

Experimental Section

Typical procedure for enantioselective carbonyl ylide cycloaddition under continuous flow conditions (Table 5, entry 5): A solution of diazodiketoester **14** (21.6 g, 90 mmol, 0.2 M) and phenylacetylene (**15**) (27.6 g, 270 mmol, 3 equiv) in $CF_3C_6H_5$ was passed through the flow reactor packed with polymer-supported dirhodium(II) complex **13c** (32 mg, 0.006 mmol of Rh^{II} catalyst) and sea sand (4 g) at 30 mL h^{-1} for 15 h. After complete addition, the flow reactor was washed with an additional $CF_3C_6H_5$ (2 mL). After evaporation of the solvent in vacuo, the residue was purified by column chromatography on silica gel (6:1 hexane/EtOAc) to provide cycloadduct **16** (22.0 g, 78 %) as a white solid. The enantiomeric excess of **16** was determined to be 97 % by HPLC with a Chiralpak OD column [9:1 hexane/*i*PrOH; flow: 1.0 mL min^{-1}; retention time: 7.9 min (minor enantiomer), 9.8 min (major enantiomer)].

Acknowledgements

This research was supported by a Grant-in Aid for Scientific Research on Innovative Areas “Organic Synthesis Based on Reaction Integration. Development of New Methods and Creation of New Substances” (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.

Keywords: asymmetric catalysis · continuous flow system · heterogeneous catalysis · immobilization · rhodium

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Received: September 1, 2011