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Silica-Immobilized Chiral Dirhodium(II) Catalyst for Enantioselective Carbenoid Reactions

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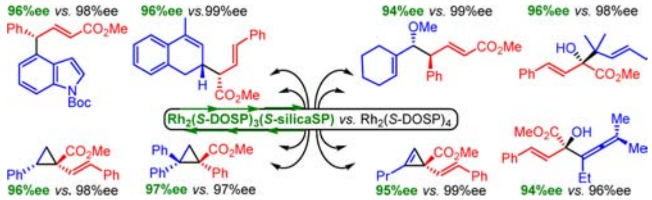
ABSTRACT



A silica-supported dirhodium(II) tetraprolinate catalyst was synthesized in four steps from L-proline and used in a range of enantioselective transformations of donor/acceptor carbenoids. These include cyclopropenation, cyclopropanation, tandem ylide formation/[2,3] sigmatropic rearrangement, and a variety of combined C−H functionalization/Cope rearrangement reactions. The products of these transformations were obtained in yields and levels of enantioselectivity comparable to those obtained with its homogeneous counterpart, Rh_2(*S*-DOSP)$_4$. The silica-supported Rh_2(*S*-DOSP)$_4$ derivative was successfully recycled over five reactions.

Dirhodium(II) complexes are versatile and powerful catalysts for reactions of diazo compounds, catalyzing a wide array of challenging synthetic transformations such as cyclopropanations, dipolar cycloadditions, ylide formations, and C−H, N−H, O−H, and Si−H insertion reactions.[1] Rh_2(*S*-DOSP)$_4$ is the most generally effective chiral dirhodium(II) catalyst for highly enantioselective transformations involving donor/acceptor carbenoid intermediates. These transformations include cyclopropanation,[2] cyclopropenation,[3] [3 + 4] and [3 + 2] cycloadditions,[4] tandem carbonyl ylide formation−1,3-dipolar cycloadditions,[5] tandem ylide formation/[2,3] sigmatropic rearrangements,[6] C−H insertions,[4] Si−H insertions,[7] combined C−H functionalization/Cope rearrangements (CHCR),[8a] CHCR followed by retro-Cope rearrangements,[8b] and CHCR−elimination reactions.[9] Several of

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these Rh$_2$(*S*-DOSP)$_4$-catalyzed transformations have been used as key steps in the syntheses of natural products.[4]

Despite its versatility, an effective strategy for recovery of Rh$_2$(*S*-DOSP)$_4$ is still lacking. Although considerable advances have been made in the immobilization of various dirhodium(II) catalysts,[10] efforts to alleviate the cost associated with Rh$_2$(*S*-DOSP)$_4$ by synthesis of reusable heterogeneous derivatives[10n] have been met with limited success.[10i,k,l,11] Immobilization of Rh$_2$(*S*-DOSP)$_4$ has been achieved by using a highly cross-linked polystyrene resin modified with pyridine linkers.[11] This polymer was effective for immobilizing a wide range of dirhodium catalysts by the cooperative effect of microencapsulation and coordination of the pyridyl nitrogen to one of the axial binding sites of dirhodium, leaving the remaining axial site uncoordinated and available for catalysis.[10k] A drawback to this immobilization strategy was the high level of rhodium leaching observed on recycling after the first reaction. We envisioned overcoming this complication by covalent attachment of a carboxylate ligand to a solid support in order to develop a broadly applicable and highly enantioselective immobilized variant of Rh$_2$(*S*-DOSP)$_4$ (Figure 1). Herein we present the successful immobilization, recycling, and application of covalently immobilized Rh$_2$(*S*-DOSP)$_4$ in a broad range of enantioselective transformations.

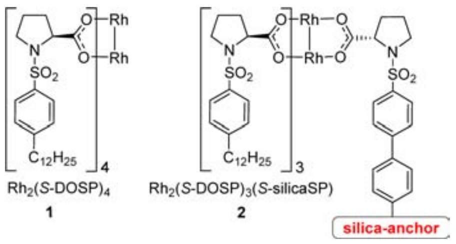
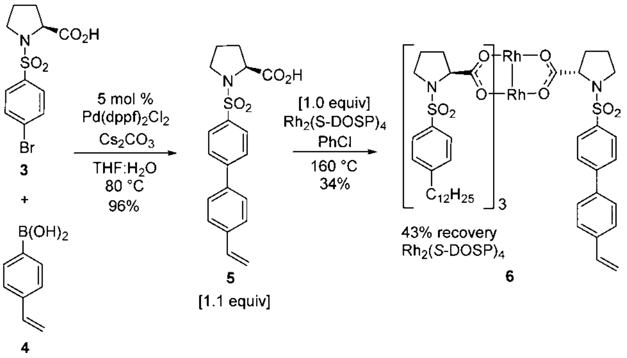


Figure 1. Chiral dirhodium(II) catalysts used in this study.

We sought to exchange a single ligand of Rh$_2$(*S*-DOSP)$_4$ with a ligand that could undergo a grafting reaction to a solid support. As immobilization by covalent attachment of a resin to a single ligand could break the high symmetry that is characteristic of these complexes, the attachment needed to be designed carefully to limit negative influence on the enantioselectivity of the resulting catalyst.[1a] Recently, Hashimoto reported immobilization of another dirhodium catalyst, Rh$_2$(*S*-PTTL)$_4$, containing a modified ligand, which was effective in intramolecular C$-$H insertion.[12] Inspired by these results, immobilization of Rh$_2$(*S*-DOSP)$_4$ was achieved by sulfonylation of L-proline with 4-bromobenzenesulfonyl chloride to provide **3** in 81% yield followed by Suzuki coupling of **3** with 4-vinylphenylboronic acid (**4**) to provide *N*-(arylsulfonyl)prolinate **5** in 96% yield which was subjected to single ligand exchange with Rh$_2$(*S*-DOSP)$_4$ (**1**) to provide **6** in 34% yield along with a 43% recovery of Rh$_2$(*S*-DOSP)$_4$ (Scheme 1).

Scheme 1. Synthesis of Rh$_2$(*S*-DOSP)$_4$ Derivative for Immobilization



While either polymer or silica supports could be used for immobilizing this ligand, a silica support was selected as these systems are typically recoverable in high yield post-reaction, do not require extensive washing, and often play a complementary role to polymer-supported catalysts.[13] Silica-supported catalysts can allow for faster reaction rates than conventional polymer resin-bound reagents, where the reaction is often slowed by the rate of diffusion through the polymer.[14] Also, silica neither swells nor shrinks in solvents, whereas, polymer-supported catalysts have the ability to swell, which can dramatically narrow the scope of solvents that can be used for a reaction.[15] Commercial silica (**7**) was functionalized with styrylethyltrimethoxysilane (**8**) to give **9** followed by capping the free hydroxyl groups with hexamethyldisilazane (HMDS) to provide **10**. Dirhodium complex **6** was then grafted to the functionalized silica (**10**) by AIBN-initiated radical coupling to provide Rh$_2$(*S*-DOSP)$_3$(*S*-silicaSP) (**2**), a Rh$_2$(*S*-DOSP)$_4$ derivative with three *S*-DOSP ligands and one silica-supported sulfonyl prolinate ligand (*S*-silicaSP)

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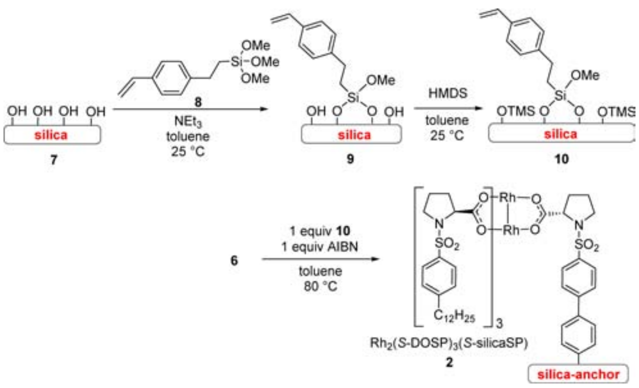
anchored to the silica surface through an organic linker (Scheme 2). The loading of **2** was determined to be 0.06 mmol/g by elemental analysis.

Scheme 2. Immobilization Strategy

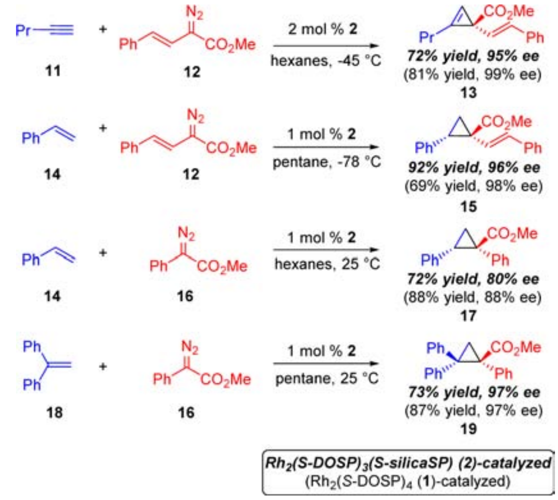


Initial comparison studies between Rh_2(*S*-DOSP)$_3$(*S*-silicaSP) (**2**) and Rh_2(*S*-DOSP)$_4$ were conducted with standard cyclopropenation and cyclopropanation reactions of donor/acceptor carbenoids. These studies were conducted with the most widely used donor/acceptor carbenoid precursors, styryl diazoacetate (**12**) and phenyl diazoacetate (**16**). The reactions were conducted using the optimal conditions developed previously for Rh_2(*S*-DOSP)$_4$-catalyzed reactions. Rh_2(*S*-DOSP)$_3$(*S*-silicaSP) (**2**)-catalyzed cyclopropenation of 1-pentyne (**11**) and cyclopropanation of styrene (**14**) with styryl diazoacetate **12** provided the corresponding cyclopropene **13** and cyclopropane **15** in ≥95% ee, comparable to the results obtained under Rh_2(*S*-DOSP)$_4$-catalyzed conditions (Scheme 3). Similarly, **2**-catalyzed cyclopropanation of styrene (**14**) or 1,1-diphenylethylene (**18**) with phenyl diazoacetate **16** gave comparable results to the Rh_2(*S*-DOSP)$_4$-catalyzed reactions. Cyclopropane **17** was formed in 80% ee with Rh_2(*S*-DOSP)$_3$(*S*-silicaSP) (**2**) vs 88% ee with Rh_2(*S*-DOSP)$_4$,[2c] whereas cyclopropane **19** was formed in 97% ee using either the immobilized or the homogeneous catalyst.[2a]

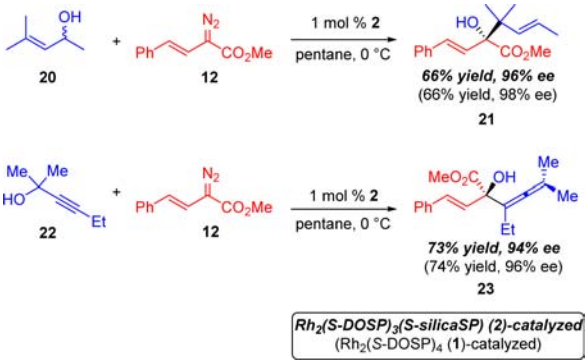
We then sought to determine the capability of Rh_2(*S*-DOSP)$_3$(*S*-silicaSP) (**2**) in more exotic reactions of donor/acceptor carbenoids. A new transformation for these intermediates is the tandem ylide formation/[2,3] sigmatropic rearrangements with allylic and propargylic alcohols.[6] Rh_2(*S*-DOSP)$_3$(*S*-silicaSP)-catalyzed reaction of allylic alcohol **20** with styryl diazoacetate **12** provided the corresponding rearrangement product **21** with a high level of asymmetric induction (96% ee), comparable to the results with Rh_2(*S*-DOSP)$_4$ (Scheme 4, 98% ee).[6a] Similarly, Rh_2(*S*-DOSP)$_3$(*S*-silicaSP)-catalyzed ylide formation/[2,3] sigmatropic rearrangement of propargylic alcohol **22** with **12** provided **23** with a high level of enantiocontrol.[6b]

Donor/acceptor carbenoids have been shown to be versatile reactants for stereoselective C–H functionalization. A particularly robust transformation is the combined C–H functionalization/Cope rearrangement (CHCR).

Scheme 3. Cyclopropenation and Cyclopropanation



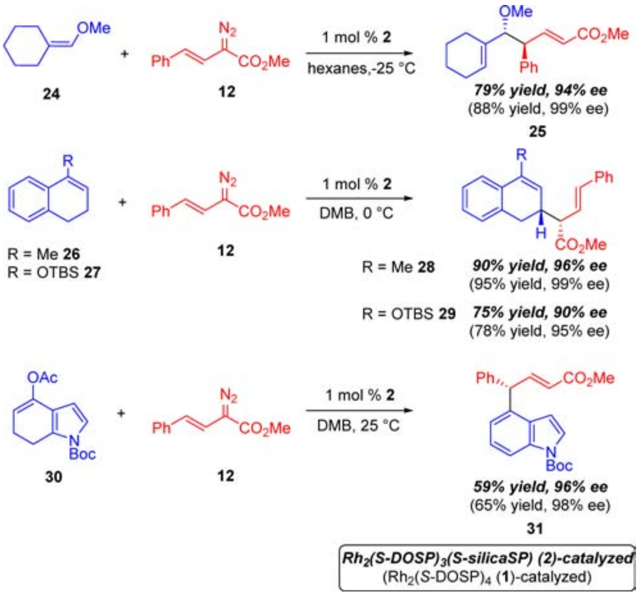
Scheme 4. Ylide Formation/[2,3] Sigmatropic Rearrangement



The Rh_2(*S*-DOSP)$_3$(*S*-silicaSP)-catalyzed reaction was applied to a range of CHCR reactions as illustrated in Scheme 5. The **2**-catalyzed CHCR reaction of (methoxymethylene)cyclohexane (**24**) with **12** provided **25** in 79% yield and 94% ee.[5,8a] The tandem CHCR/retro-Cope rearrangement of 1-methyl-3,4-dihydronaphthalene (**26**) with **12** provided **28** in 90% yield and 96% ee. The 1,2-dihydronaphthalene **27** performed similarly in the **2**-catalyzed CHCR/retro-Cope rearrangement cascade providing **29** in 75% yield and 90% ee.[8b] Finally, the CHCR reaction–elimination cascade of 4-acetoxy-6,7-dihydroindole (**30**) with **12** provided the indole **31** in 59% yield and 96% ee.[9] All of these reactions proceeded with levels of enantioinduction close to those obtained with Rh_2(*S*-DOSP)$_4$.

The promising activity and enantioselectivity of the immobilized complex led us to evaluate the robustness of the immobilization process via a filtration test to assess catalyst heterogeneity and stability. Conversion of substrate was monitored as a function of time, removing the solid catalyst by filtration while allowing the solid-free solution to continue to react.[16] Phenyl diazoacetate (**16**) was added to a

Scheme 5. C–H Functionalization



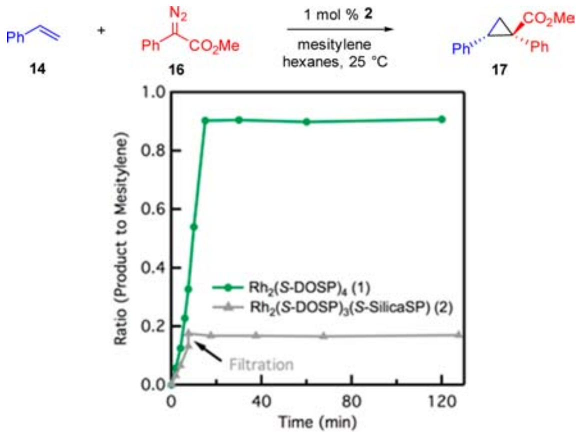
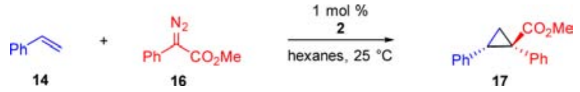


Figure 2. Filtration test demonstrating lack of activity in absence of solid catalyst.

Table 1. Catalyst **2** Recycling Study



cycle	yield (%)	ee (%)
1	72	80
2	78	81
3	75	79
4	76	77
5	78	79
Rh_2(*S*-DOSP)$_4$	88	88

mixture of **14**, catalyst **2**, and mesitylene in hexanes by syringe pump, stopping at 7.5 min. After filtering **2**, the filtrate was transferred to a new flask before addition of the second half of the solution of **16**. The amount of product in the filtrate remained constant after the filtration despite the additional phenyl diazoacetate addition, indicating robust immobilization of **2** on the silica surface (Figure 2).

The ultimate advantage of heterogeneous catalysts is their potential to be recycled over several consecutive reactions. We therefore sought to determine the recyclability of **2**. Thus, **2**-catalyzed cyclopropanation was repeated over five consecutive reactions using the same batch of catalyst and proved to provide a similar level of both yield and enantioinduction in each consecutive reaction (Table 1).

This study describes an effective method for covalent immobilization of a highly versatile and robust[17] dirhodium catalyst onto a silica support. Also, this represents the first successful immobilization, recycling, and application of an immobilized Rh_2(*S*-DOSP)$_4$ analogue in a broad range of enantioselective transformations with comparable enantioinduction to its homogeneous counterpart. It is anticipated that this catalyst may prove useful in flow reactors, which will be the subject of future investigation.

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Supporting Information Available. General experimental procedures, characterization of new compounds, and spectral data.This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.