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Asymmetric Intermolecular C–H Activation, Using Immobilized Dirhodium Tetrakis((*S*)-*N*-(dodecylbenzenesulfonyl)-prolinate) as a Recoverable Catalyst

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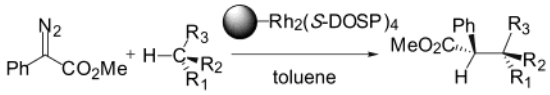
ABSTRACT



Heterogenization of dirhodium tetrakis((*S*)-*N*-dodecylbenzenesulfonyl)prolinate) (Rh_2(*S*-DOSP)$_4$) can be readily achieved on a pyridine functionalized highly cross-linked polystyrene resin. The immobilized complex is readily recycled and exhibits excellent catalytic activity for asymmetric intermolecular C–H activation by means of rhodium carbenoid induced C–H insertion.

Immobilization of chiral catalysts for asymmetric carbenoid transformations has attracted the interest of many research groups.[1] Several copper, ruthenium, and rhodium(II) complexes have been immobilized onto organic and inorganic supports and used as recoverable catalysts.[1] Asymmetric cyclopropanation[2] has been the standard reaction to evaluate these catalysts, with the exception of one study of asymmetric intramolecular C−H activation with dirhodium tetracarboxamidates.[1b] We have recently discovered a very general method for asymmetric intermolecular C−H activation by means of rhodium-carbenoid induced C−H insertion.[3−5] A requirement for a successful outcome in these C−H activations is the use of carbenoids containing both donor and acceptor groups.[3,4] As the method allows rapid access to a range of pharmaceutically relevant chiral building blocks, the availability of an effective immobilized chiral catalyst for this chemistry would broaden its utility for diversity synthesis. Herein we report the heterogenization of dirhodium tetrakis-

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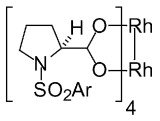
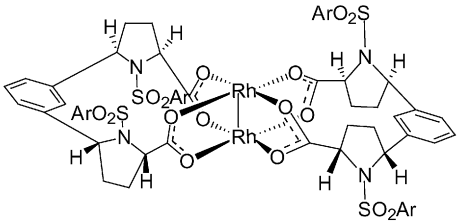
((*S*)-*N*-dodecylbenzenesulfonyl)prolinate) Rh_2(*S*-DOSP)$_4$ **1a** and its use as a highly efficient catalyst for asymmetric intermolecular C−H activation.



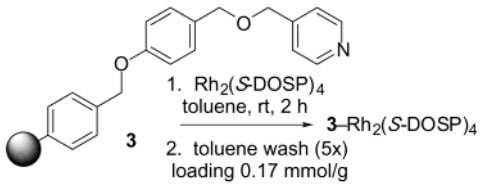
1a Rh_2(*S*-DOSP)$_4$: Ar = *p*-$C_{12}H_{25}C_6H_4$
1b Rh_2(*S*-TBSP)$_4$: Ar = *p*-^{t}BuC_6H_4



2 Rh_2(*S*-biTISP)$_2$:
Ar = 2,4,6-tri-^{i}PrC_6H_2

The highly crossed-linked polystyrene (Argopore)[6] resin with benzyloxymethyl-pyridine linker **3**[7] has been shown to be a remarkable system for immobilization of complexes Rh_2(*S*-TBSP)$_4$ **1b** and Rh_2(*S*-biTISP)$_2$ **2**.[1h] These immobilized catalysts are very effective for intermolecular cyclopropanations by donor/acceptor carbenoids.[1h] This led us to explore the similar heterogenization of Rh_2(*S*-DOSP)$_4$ **1a**, which is the most generally effective catalyst for intermolecular C−H activation.[3,4] Agitating a mixture of the resin and Rh_2(*S*-DOSP)$_4$ in toluene for 2 h gave, after filtration and washing, purple beads of **3**-Rh_2(*S*-DOSP)$_4$, indicating metal coordination to the pyridine. ICP analysis of the resin beads gave a measurement corresponding to 0.17 mmol/g catalyst loading (Scheme 1).

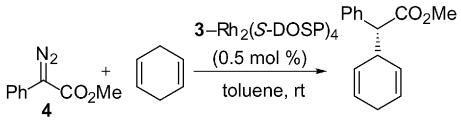
Scheme 1



To evaluate the catalytic activity of **3**-Rh_2(*S*-DOSP)$_4$ C−H activation of 1,4-cyclohexadiene was used as the standard reaction.[4f] With use of 0.5 mol % of **3**-Rh_2(*S*-DOSP)$_4$ in toluene and 5 equiv of 1,4-cyclohexadiene, dropwise addition of methyl phenyldiazoacetate **4** resulted in efficient intermolecular C−H activation. Even though the polymer support consists of polystyrene, it does not appear to interfere with the C−H activation process. The rate of agitation was electronically controlled and held constant, so any effects on the rate of the reaction would be consistent. Changes in the color of the solution after diazo addition and cessation of nitrogen gas evolution were used to determine the endpoint of the reaction. After filtration of the reaction mixture, the resin was washed with toluene (three times) and dried before reuse in the next cycle.

Ten cycles of C−H activation with **3**-Rh_2(*S*-DOSP)$_4$ were readily achieved and the products could be obtained in high purity by evaporation of the solvent and excess diene, followed by filtration. Good product yields (84−79%) and a slight drop in enantiomeric excess (ee) from 88% to 84% was observed over the 10 cycles (Table 1). The slight drop in enantioselectivity on recycling the catalyst is far less than had been previously reported for cyclopropanations induced by immobilized Rh_2(*S*-TBSP)$_4$.[1h]

Table 1. Asymmetric Intermolecular C−H Activation of 1,4-Cyclohexadiene with Immobilized Rh_2(*S*-DOSP)$_4$



cycle	time, min	yield, %[a]	ee, %
1	20	79 (81)	88
3	20	81 (81)	87
5	23	80 (83)	87
8	25	82	84
10	30	84	84

[a] Yields in parenthesis determined by NMR with DMAP as internal standard.

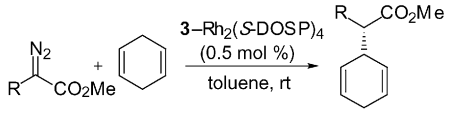
The activity of the catalyst was further tested by using recycled catalyst for a series of C−H insertions with several different aryldiazoacetates (Table 2). A final cycle with methyl phenyldiazoacetate (**4**) was used to confirm that the yields and ee values are comparable to those obtained with fresh catalyst. No cross contamination between successive cycles was observed from the ^{1}H NMR spectra of the crude reaction mixtures.

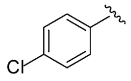
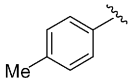
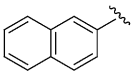
The C−H activation of 1,3- or 1,4-cyclohexadiene with the donor/acceptor carbenoids is useful for the synthesis of a number of pharmaceutical agents. Previously, we have utilized these reactions in the asymmetric syntheses of (+)-indatraline,[4j] (+)-cetiedil,[4k] and (+)-sertraline (Zoloft).[4b] The immobilized catalyst **3**-Rh_2(*S*-DOSP)$_4$ is also very effective at the asymmetric synthesis of these pharmaceutical agents, as the catalyst is able to furnish the key intermediates in high ee and purity (Scheme 2).

The C−H activation with the donor/acceptor carbenoids is a strategic reaction that can be considered as a surrogate of some of the classic organic synthesis reactions, such as the Michael reaction,[4h] the aldol reaction,[4c,g] the Mannich reaction,[4d] and the Claisen rearrangment.[4i] A series of reactions was explored to determine if the immobilized catalyst **3**-Rh_2(*S*-DOSP)$_4$ was effective in the full range of these surrogate reactions.

(6) Purchased from Argonaut Technologies (www.argotech.com).
(7) Derivatized from Argopore-Wang resin (hydroxyl loading 0.65 mmol/g).

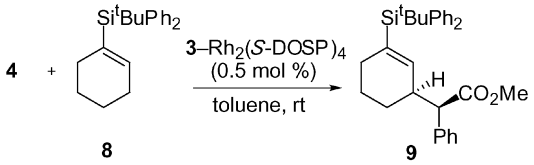
Table 2. Asymmetric C−H Activation of 1,4-cyclohexadiene with Various Aryl- and 3-Thienyldiazoacetates and Recycled Catalyst



cycle	R	time, (min)	yield, (%)	ee, (%)
1		20	82	87
2		20	85	85
3		23	78	82
4		24	60	87
5		20	82	86

An example of the Claisen rearrangement surrogate is the reaction of 1-(diphenyl-*tert*-butylsilyl)hexene (**8**) shown in Scheme 3.[4i] **3**-Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of **4** in the presence of **8** gave the C−H activation product **9** in 87% de and 94% ee. The high enantio-, diastereo-, and regioselectivity that has been observed with the homogeneous catalyst[4i] was similarly seen in the reaction catalyzed by **3**-Rh_2(*S*-DOSP)$_4$.

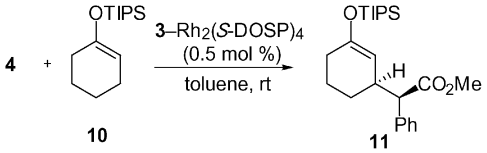
Scheme 3



87% de, 94%ee, 62%yield

The Michael reaction surrogate involved C−H activation of silyl enol ethers such as triisopropylsiloxycyclohexene (**10**).[4h] **3**-Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of **4** in the presence of **10** gave the C−H activation product as a mixture

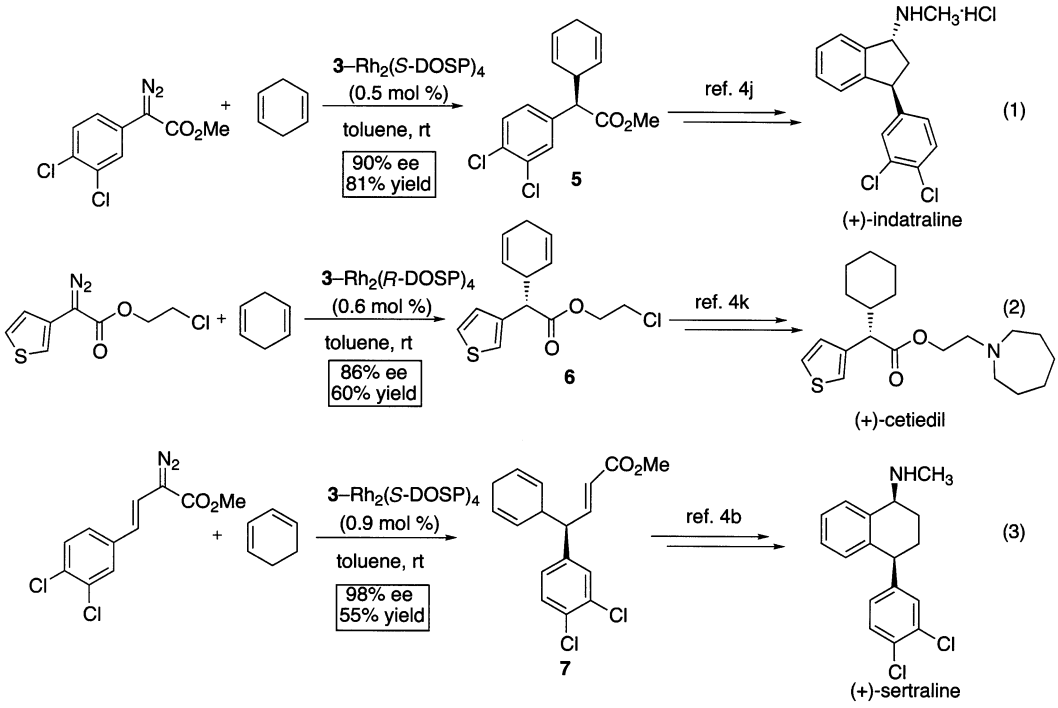
Scheme 4



89% ee, 60% yield, dr 63:37

of diastereomers (63:37 dr) in 60% yield, where the major diastereomer **11** was formed in 89% ee (Scheme 4). The

Scheme 2



preferential occurrence of C−H activation instead of cyclopropanation of the electron-rich double bond parallels the results obtained in the homogeneous reaction[4h] and is due to the demanding steric requirements of the donor/acceptor rhodium carbenoids.[3]

C−H activation α to O-silyl groups generates silyl-protected β-hydroxy esters and can be considered as a surrogate of the aldol reaction.[4g,c] The **3**-Rh_2(*S*-DOSP)$_4$-catalyzed reaction of **4** with tetraethoxysilane (**12**) as the substrate generates the *syn* product **13** in >90% de, 96% ee, and 72% yield (Scheme 5). Similarly, the **3**-Rh_2(*S*-DOSP)$_4$-catalyzed reaction of **4** with TBS-protected crotyl alcohol (**14**) was very effective. The *syn* product **15** was formed in 82% ee, >94% de, and 70% yield (Table 3). Repeating the reaction with recycled catalyst gave virtually identical results. The very high diastereoselectivity observed in these reactions matches the results obtained with homogeneous catalysis.[4g,c]

Scheme 5

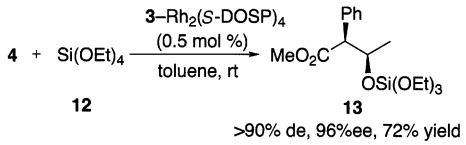
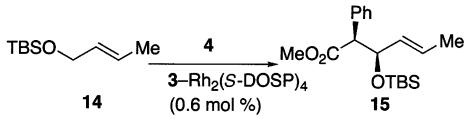


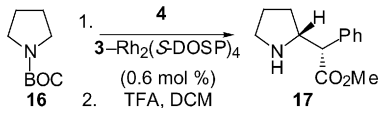
Table 3. Asymmetric C−H Activation as a Surrogate of the Aldol Reaction with Recycled Catalyst



cycle	de, %	ee, %	yield, %
1	>94	82	70
2	>94	82	68
3	>94	82	68

The C−H activation α to nitrogen is the Mannich reaction surrogate. An example of this reaction is the **3**-Rh_2(*S*-DOSP)$_4$-catalyzed reaction of **4** with *N*-BOC-pyrrolidine (**16**), which demonstrates the high diastereoselectivity and enantioselectivity that is possible with this chemistry. Three cycles were conducted without notable effect on the outcome of the reaction, as the C−H insertion product **17** was formed in 90% de, 88−86% ee, and 70−67% yield (Table 4). The stereoselectivity exhibited with **3**-Rh_2(*S*-DOSP)$_4$ is comparable to that obtained in the homogeneous reaction.[4d]

Table 4. Asymmetric C−H Activation as a Surrogate of the Mannich Reaction with Recycled Catalyst



cycle	de, %	ee, %	yield, %
1	90	88	70
2	90	88	67
3	90	86	68

The immobilization of Rh_2(*S*-DOSP)$_4$ has led to a highly efficient re-usable catalyst for asymmetric intermolecular C−H activation. The present study extends the applicability of asymmetric carbenoid transformations for diversity synthesis. In general the regio-, diastereo-, and enantioselectivity of these C−H activation processes are retained when using an immobilized catalyst instead of a homogeneous catalyst. A complete study directed toward understanding the various aspects of this catalyst immobilization is underway.

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Supporting Information Available: Experimental data for the synthesis of Rh_2(*S*-DOSP)$_4$ on solid support and for the asymmetric C−H activation. This material is available free of charge via the Internet at http://pubs.acs.org.

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