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Dirhodium Tetracarboxylate Derived from Adamantylglycine as a Chiral Catalyst for Carbenoid Reactions

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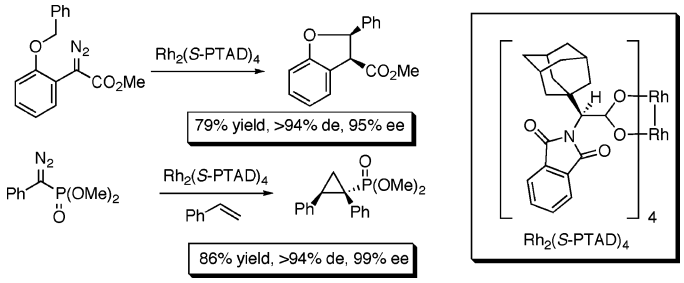
ABSTRACT



The dirhodium tetracarboxylate, Rh_2(*S*-PTAD)$_4$, derived from adamantylglycine, is a very effective chiral catalyst for carbenoid reactions. High asymmetric induction was obtained in Rh_2(*S*-PTAD)$_4$-catalyzed intramolecular C–H insertion (94% ee), intermolecular cyclopropanation (99% ee), and intermolecular C–H insertion (92% ee).

Rhodium-catalyzed reactions of diazo compounds have broad application in organic synthesis.[1] In recent years, it has become recognized that donor/acceptor-substituted diazo compounds generate carbenoids capable of highly regio- and stereoselective reactions.[2] The most commonly utilized types of donor/acceptor carbenoids have been derived from either methyl aryldiazoacetates or methyl vinyldiazoacetates. These precursors are capable of highly enantioselective transformations when catalyzed by the dirhodium tetraprolinate Rh_2(*S*-DOSP)$_4$ or the bridged variant Rh_2(*S*-biTISP)$_2$.[2,3] High enantioselectivity is maintained with a broad range of functionality on the donor group, leading to powerful methods for asymmetric cyclopropanation, [4 + 3] cycloaddition, C−H insertion, and ylide formation.[2] Ironically, the acceptor group has very stringent requirements for high asymmetric induction with Rh_2(*S*-DOSP)$_4$, and a methyl ester is by far the optimum functionality.[4] To broaden the scope of enantioselective reactions of donor/acceptor-substituted carbenoids, the acceptor group and the chiral catalysts need to be carefully matched. In this paper, we describe that Hashimoto's phthalimido catalyst Rh_2(*S*-PTTL)$_4$[5] and the new adamantyl variant Rh_2(*S*-PTAD)$_4$ developed by us are very effective backup chiral catalysts when Rh_2(*S*-DOSP)$_4$ fails to give high asymmetric induction (Figure 1).

A common strategy in chiral catalyst design is to use sterically blocking groups to limit the number of reasonable orientations of the substrates as they interact with the

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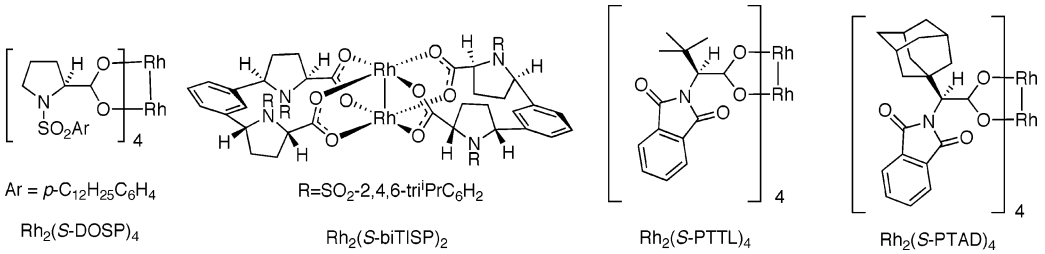
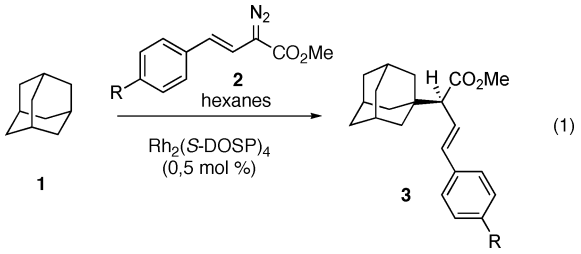


Figure 1. Chiral dirhodium tetracarboxylates.

catalyst.[6] In recent years, the ready accessibility of *tert*-leucine has made the *tert*-butyl group a very popular unit to incorporate into chiral catalysts, especially as the enantioinduction is often much improved compared to catalysts containing smaller groups.[7] Hashimoto has successfully used the *tert*-butyl group in the carbenoid field in the design of his rhodium phthalimidocarboxylate catalysts, where in most instances the *tert*-butyl derivative Rh_2(*S*-PTTL)$_4$ is far superior to other catalysts derived from amino acids with smaller side chains.[5] The use of ligands with stereogenic centers containing larger groups than *tert*-butyl, such as adamantyl, have rarely been incorporated into chiral catalysts,[8] although large groups away from the stereogenic centers have been used with good effect.[9] We recognized that our newly developed C−H activation chemistry[10] would allow us enantioselective access to adamantylglycine.[11] Therefore, in evaluating the potential of using Rh_2(*S*-PTTL)$_4$ as a backup chiral catalyst for Rh_2(*S*-DOSP)$_4$, we expanded the study to include the adamantyl catalyst Rh_2(*S*-PTAD)$_4$.

The key step in the synthesis of Rh_2(*S*-PTAD)$_4$ is an intermolecular C−H functionalization of adamantane by means of a metal carbenoid-induced C−H insertion. The Rh_2(*S*-DOSP)$_4$-catalyzed reactions of donor/acceptor-substituted carbenoids are particularly effective because highly regioselective and enantioselective C−H functionalization can be achieved.[12] Previous studies have demonstrated that a range of alkanes can be functionalized,[13] and in this paper, we use this reaction in the synthesis of adamantylglycine. The results of the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of the vinyldiazoacetates **2** with adamantane (**1**) using hexanes as solvent are summarized in Table 1. Selective C−H functionalization

Table 1. Optimization of Adamantane C−H Activation



(1)

compound	R	temp, °C	yield, %	ee, %
a	H	69	58	91
b	OMe	69	40	85
c	Br	69	57	95
c	Br	23	10	98

at the tertiary C−H bond occurs because this is electronically favored and is not sterically encumbered.[13] Optimization studies were conducted with three vinyldiazoacetates **2a**−**c**. The *p*-bromo derivative **2b** gave the highest enantioselectivity under refluxing conditions (95% ee), and this could be

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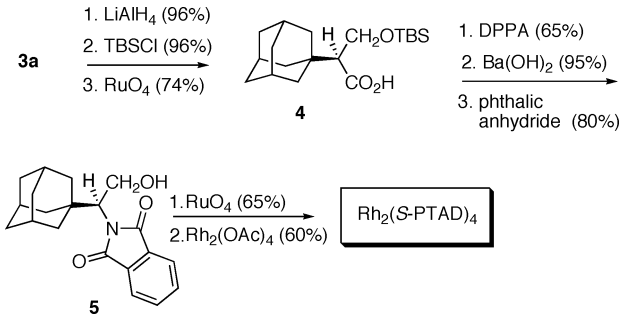
improved to 98% ee for a room-temperature reaction; however, the yield was greatly decreased. The most practical system was the phenylvinyldiazoacetate **2a** because the product was easily purified and enriched by recrystallization. The selectivity of the C−H activation is sufficiently high that the reaction can be carried out in hexanes as solvent. The reaction of **2a** has been conducted on a 40−50 g scale, and a single recrystallization enriches the product (*S*)-**3a** to >99% ee.

The conversion of **3** to Rh_2(*S*-PTAD)$_4$ is readily achieved using conventional steps (Scheme 1). $LiAlH_4$-mediated

Scheme 1. Synthesis of Rh_2(*S*-PTAD)$_4$

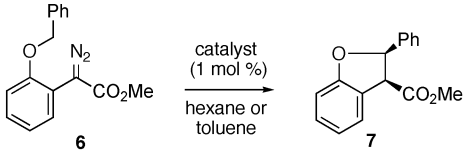


reduction of the ester **3** followed by protection of the alcohol and oxidative cleavage[14] of the alkene generated the acid **4**. A Curtius rearrangement on the acid **4**, followed by conversion of the amine to the phthalimide, generated the protected amino alcohol **5**. Oxidation of the alcohol **5** to the acid and then ligand exchange with dirhodium tetraacetate[15] resulted in the formation of Rh_2(*S*-PTAD)$_4$. A similar sequence beginning with a Rh_2(*R*-DOSP)$_4$-catalyzed C−H activation of adamantane generated Rh_2(*R*-PTAD)$_4$.

The first set of experiments compared Rh_2(*S*-PTAD)$_4$ to the two standard catalysts, Rh_2(*S*-DOSP)$_4$ and Rh_2(*S*-PTTL)$_4$. Rh_2(*S*-DOSP)$_4$ is the premier chiral catalyst for the reactions of the donor/acceptor-substituted carbenoids, especially when the acceptor group is a methyl ester.[10,12] In a few cases, however, the Rh_2(*S*-DOSP)$_4$-catalyzed reaction is not highly enantioselective and Rh_2(*S*-PTTL)$_4$ results in higher enantioinduction.[16] One such system is the intramolecular C−H insertion of the aryldiazoacetate **6**, which generates the benzodihydrofuran **7** (Table 2).[16a,b] The Rh_2(*S*-PTTL)$_4$-catalyzed reaction[16b] of **6** proceeds with much higher but opposite enantioinduction than Rh_2(*S*-DOSP)$_4$,[16a] but Rh_2(*S*-PTAD)$_4$ outperforms both of the standard catalysts. The Rh_2(*S*-PTAD)$_4$-catalyzed reaction formed **7** in 87% ee at room temperature and 95% ee at −60 °C.

A second example is a key step in the synthesis of a natural product (−)-ephedradine A (Table 3). In the published

Table 2. Enantioselective Intramolecular C−H Insertion

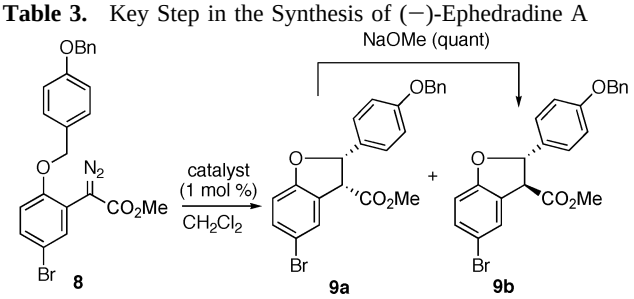


catalyst	temp, °C	yield, %	dr	ee, %
Rh_2(*S*-DOSP)$_4$	23	60	1.5 : 1	38[a]
Rh_2(*S*-PTTL)$_4$[12b]	23	78	>30 : 1	70
Rh_2(*S*-PTTL)$_4$[12b]	-60	87	>30 : 1	90
Rh_2(*S*-PTAD)$_4$	23	83	>30 : 1	87
Rh_2(*S*-PTAD)$_4$	-60	79	>30 : 1	95

[a] ent-**7** is the major enantiomer.

synthesis, the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of **8** generated **9a** and **9b** with poor diastereoselectivity (2:3 dr) and enantioselectivity (32% ee).[17b] Reasonable results were

Table 3. Key Step in the Synthesis of (−)-Ephedradine A



catalyst	temp, °C	yield, %	dr	**9a**, ee, %	**9b**, ee, %
Rh_2(*S*-DOSP)$_4$[13b]	23	72	2:3	–	32
Rh_2(*S*-PTTL)$_4$	23	79	13:1	57[a]	–
Rh_2(*S*-PTTL)$_4$	0	71	14:1	65[a]	–
Rh_2(*S*-PTAD)$_4$	23	83	14:1	65[a]	–
Rh_2(*S*-PTAD)$_4$	0	72	14:1	79[a]	–
Rh_2(*R*-PTAD)$_4$	0	49[b]	14:1	79	

[a] ent-**9a** is the major enantiomer. [b] Poor isolated yield was obtained in the reaction conducted on a very small scale.

obtained only when a combination of Rh_2(*S*-DOSP)$_4$ and a chiral auxiliary was used.[17] This gave rise to the desired trans stereoisomer, with an asymmetric induction of 86% de.[17] The Rh_2(*S*-PTTL)$_4$- or Rh_2(*S*-PTAD)$_4$-catalyzed reactions described in this current study were much more stereoselective than the Rh_2(*S*-DOSP)$_4$-catalyzed reaction. Under the opti-

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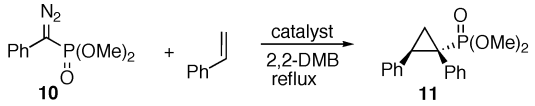
mized conditions, the Rh_2(*R*-PTAD)$_4$-catalyzed reaction of **8** generated preferentially the *cis* isomer **9a** in a 14:1 dr with 79% ee, without requiring the use of a chiral auxiliary. The *cis* isomer **9a** can be readily equilibrated to the desired *trans* isomer **9b** on treatment with sodium methoxide following Hashimoto's conditions.[16b]

Even though Rh_2(*S*-DOSP)$_4$ gives excellent enantioinduction with a range of donor substituents in the donor/acceptor-substituted carbenoids,[10] altering the acceptor group can have a profound effect on the level of enantioinduction.[4] This is clearly seen in the asymmetric cyclopropanation of the diazophosphonate **10** (Table 4). The Rh_2(*S*-DOSP)$_4$-catalyzed

Table 4. Enantioselective Intramolecular Cyclopropanation



catalyst	yield, %	dr	ee, %
Rh_2(*S*-DOSP)$_4$[15]	69	>30 : 1	34[a]
Rh_2(*S*-biTISP)$_2$[15]	89	>30 : 1	88
Rh_2(*S*-PTTL)$_4$	85	>30 : 1	97
Rh_2(*S*-PTAD)$_4$	86	>30 : 1	99

[a] ent-**11** is the major enantiomer.

cyclopropanation of styrene results in the formation of **11** in 34% ee.[18] The bridged prolinate catalyst Rh_2(*S*-biTISP)$_2$ results in 88% ee.[18] In the current study, we demonstrate that Rh_2(*S*-PTTL)$_4$ or Rh_2(*S*-PTAD)$_4$ is far superior, with Rh_2(*S*-PTAD)$_4$ resulting in the highest enantioselectivity (99% ee).

A similar enhancement in enantioselectivity can be achieved for intermolecular C−H activation of 1,4-cyclohexadiene by diazophosphonate **10** (Table 5). The Rh_2(*S*-DOSP)$_4$-catalyzed reaction generated the C−H activation product **12** in 41% ee, whereas with Rh_2(*S*-PTAD)$_4$ the opposite enantiomer was preferentially formed (92% ee). The

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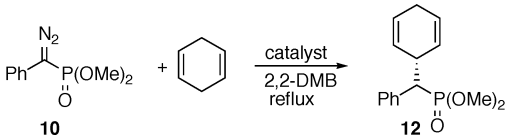
Table 5. Enantioselective Intermolecular C−H Insertion



catalyst	yield, %	ee, %
Rh_2(*S*-DOSP)$_4$	62	41[a]
Rh_2(*S*-biTISP)$_4$	57	72
Rh_2(*S*-PTTL)$_4$	67	89
Rh_2(*S*-PTAD)$_4$	83	92

[a] Opposite enantiomer preferentially formed.

absolute configuration of **12** has not been determined, but if the sense of asymmetric induction follows the trend of aryldiazoacetate C−H insertion,[19] the predicted configuration of **12** for the Rh_2(*S*-DOSP)$_4$-catalyzed reaction would be (*R*) and for the other catalysts it would be (*S*).

In summary, these studies demonstrate that the phthalimido catalysts Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-PTAD)$_4$ are promising backup catalysts for Rh_2(*S*-DOSP)$_4$. Even though Rh_2(*S*-DOSP)$_4$ has been very effective with a wide variety of substrates, it does have certain substrate limitations, especially when the acceptor group is not a methyl ester. Both Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-PTAD)$_4$ can perform extremely well in these problem systems with the adamantyl catalyst Rh_2(*S*-PTAD)$_4$ generally giving slightly higher enantioselectivity than the established *tert*-butyl catalyst, Rh_2(*S*-PTTL)$_4$.

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Supporting Information Available: Experimental data for the reported reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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