

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

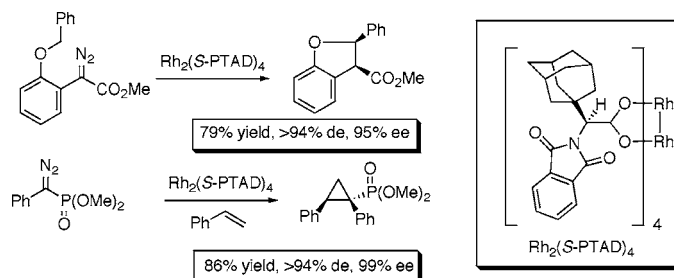
Ravisekhara P. Reddy, Gene H. Lee, and Huw M. L. Davies*

Department of Chemistry, University at Buffalo, State University of New York,
Buffalo, New York 14260-3000

hdavies@acsu.buffalo.edu

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ABSTRACT



The dirhodium tetracarboxylate, Rh₂(S-PTAD)₄, derived from adamantylglycine, is a very effective chiral catalyst for carbenoid reactions. High asymmetric induction was obtained in Rh₂(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 tetraproline Rh₂(S-DOSP)₄ or the bridged variant Rh₂(S-bi-TISP)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 Rh₂(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 Rh₂(S-PTTL)₄⁵ and the new adamantyl variant Rh₂(S-PTAD)₄ developed by us are very effective backup chiral catalysts when Rh₂(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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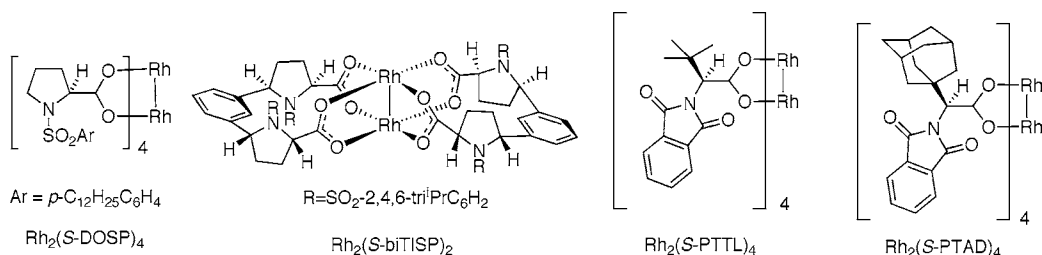


Figure 1. Chiral dirhodium tetracarboxylates.

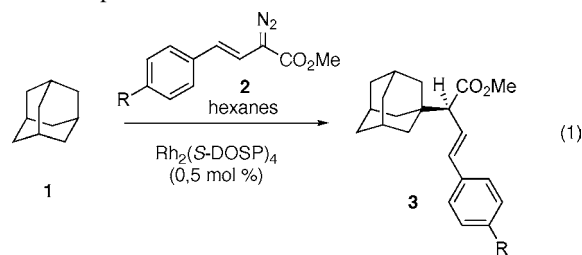
catalyst.⁶ In recent years, the ready accessibility of *tert*-leucine has made the *tert*-butyl group a very popular unit to incorporate into chiral catalysts, especially as the enantio-induction is often much improved compared to catalysts containing smaller groups.⁷ Hashimoto has successfully used the *tert*-butyl group in the carbenoid field in the design of his rhodium phthalimidocarboxylate catalysts, where in most instances the *tert*-butyl derivative $\text{Rh}_2(\text{S-PTTL})_4$ 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 chemistry¹⁰ would allow us enantioselective access to adamantylglycine.¹¹ Therefore, in evaluating the potential of using $\text{Rh}_2(\text{S-PTTL})_4$ as a backup chiral catalyst for $\text{Rh}_2(\text{S-DOSP})_4$, we expanded the study to include the adamantyl catalyst $\text{Rh}_2(\text{S-PTAD})_4$.

The key step in the synthesis of $\text{Rh}_2(\text{S-PTAD})_4$ is an intermolecular C–H functionalization of adamantane by means of a metal carbenoid-induced C–H insertion. The $\text{Rh}_2(\text{S-DOSP})_4$ -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 $\text{Rh}_2(\text{S-DOSP})_4$ -catalyzed reaction of the vinyl-diazoacetates **2** with adamantane (**1**) using hexanes as solvent are summarized in Table 1. Selective C–H functionalization

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Table 1. Optimization of Adamantane C–H Activation



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

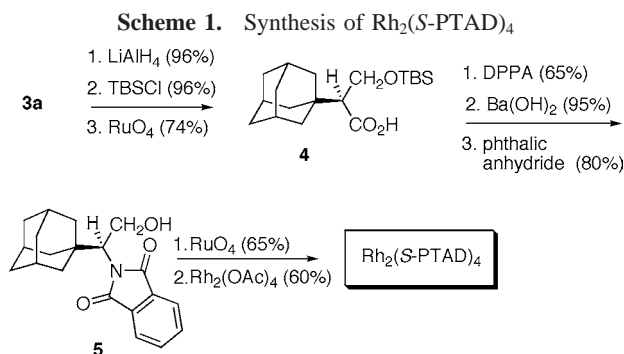
at the tertiary C–H bond occurs because this is electronically favored and is not sterically encumbered.¹³ Optimization studies were conducted with three vinyl diazoacetates **2a–c**. The *p*-bromo derivative **2b** gave the highest enantioselectivity under refluxing conditions (95% ee), and this could 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 phenylvinylidiazooacetate **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 $\text{Rh}_2(\text{S-PTAD})_4$ is readily achieved using conventional steps (Scheme 1). LiAlH_4 -mediated



reduction of the ester **3** followed by protection of the alcohol and oxidative cleavage¹⁴ 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 tetraacetate¹⁵ resulted in the formation of $\text{Rh}_2(\text{S-PTAD})_4$. A similar sequence beginning with a $\text{Rh}_2(\text{R-DOSP})_4$ -catalyzed C–H activation of adamantane generated $\text{Rh}_2(\text{R-PTAD})_4$.

The first set of experiments compared $\text{Rh}_2(\text{S-PTAD})_4$ to the two standard catalysts, $\text{Rh}_2(\text{S-DOSP})_4$ and $\text{Rh}_2(\text{S-PTTL})_4$. $\text{Rh}_2(\text{S-DOSP})_4$ 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 $\text{Rh}_2(\text{S-DOSP})_4$ -catalyzed reaction is not highly enantioselective and $\text{Rh}_2(\text{S-PTTL})_4$ results in higher enantioinduction.¹⁶ One such system is the intramolecular C–H insertion of the aryldiazooacetate **6**, which generates the benzodihydrofuran **7** (Table 2).^{16a,b} The $\text{Rh}_2(\text{S-PTTL})_4$ -catalyzed reaction^{16b} of **6** proceeds with much higher but opposite enantioinduction than $\text{Rh}_2(\text{S-DOSP})_4$,^{16a} but $\text{Rh}_2(\text{S-PTAD})_4$ outperforms both of the standard catalysts. The $\text{Rh}_2(\text{S-PTAD})_4$ -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

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Table 2. Enantioselective Intramolecular C–H Insertion

catalyst	temp, °C	yield, %	dr	ee, %
$\text{Rh}_2(\text{S-DOSP})_4$	23	60	1.5 : 1	38 ^a
$\text{Rh}_2(\text{S-PTTL})_4$ ^{12b}	23	78	>30 : 1	70
$\text{Rh}_2(\text{S-PTTL})_4$ ^{12b}	-60	87	>30 : 1	90
$\text{Rh}_2(\text{S-PTAD})_4$	23	83	>30 : 1	87
$\text{Rh}_2(\text{S-PTAD})_4$	-60	79	>30 : 1	95

^a ent-**7** is the major enantiomer.

synthesis, the $\text{Rh}_2(\text{S-DOSP})_4$ -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, %
$\text{Rh}_2(\text{S-DOSP})_4$ ^{13b}	23	72	2:3	–	32
$\text{Rh}_2(\text{S-PTTL})_4$	23	79	13:1	57 ^a	–
$\text{Rh}_2(\text{S-PTTL})_4$	0	71	14:1	65 ^a	–
$\text{Rh}_2(\text{S-PTAD})_4$	23	83	14:1	65 ^a	–
$\text{Rh}_2(\text{S-PTAD})_4$	0	72	14:1	79 ^a	–
$\text{Rh}_2(\text{R-PTAD})_4$	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.

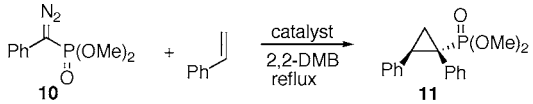
obtained only when a combination of $\text{Rh}_2(\text{S-DOSP})_4$ and a chiral auxiliary was used.¹⁷ This gave rise to the desired trans stereoisomer, with an asymmetric induction of 86% de.¹⁷ The $\text{Rh}_2(\text{S-PTTL})_4$ - or $\text{Rh}_2(\text{S-PTAD})_4$ -catalyzed reactions described in this current study were much more stereoselective than the $\text{Rh}_2(\text{S-DOSP})_4$ -catalyzed reaction. Under the opti-

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mized conditions, the Rh₂(*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 Rh₂(*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 Rh₂(*S*-DOSP)₄-catalyzed

Table 4. Enantioselective Intramolecular Cyclopropanation



catalyst	yield, %	dr	ee, %
Rh ₂ (<i>S</i> -DOSP) ₄ ¹⁵	69	>30 : 1	34 ^a
Rh ₂ (<i>S</i> -biTISP) ₂ ¹⁵	89	>30 : 1	88
Rh ₂ (<i>S</i> -PTTL) ₄	85	>30 : 1	97
Rh ₂ (<i>S</i> -PTAD) ₄	86	>30 : 1	99

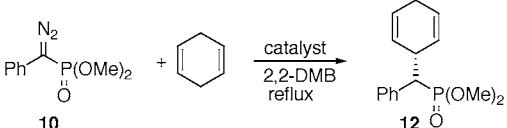
^a ent-**11** is the major enantiomer.

cyclopropanation of styrene results in the formation of **11** in 34% ee.¹⁸ The bridged prolinato catalyst Rh₂(*S*-biTISP)₂ results in 88% ee.¹⁸ In the current study, we demonstrate that Rh₂(*S*-PTTL)₄ or Rh₂(*S*-PTAD)₄ is far superior, with Rh₂(*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 Rh₂(*S*-DOSP)₄-catalyzed reaction generated the C–H activation product **12** in 41% ee, whereas with Rh₂(*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 (<i>S</i> -DOSP) ₄	62	41 ^a
Rh ₂ (<i>S</i> -biTISP) ₄	57	72
Rh ₂ (<i>S</i> -PTTL) ₄	67	89
Rh ₂ (<i>S</i> -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 Rh₂(*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 Rh₂(*S*-PTTL)₄ and Rh₂(*S*-PTAD)₄ are promising backup catalysts for Rh₂(*S*-DOSP)₄. Even though Rh₂(*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 Rh₂(*S*-PTTL)₄ and Rh₂(*S*-PTAD)₄ can perform extremely well in these problem systems with the adamantyl catalyst Rh₂(*S*-PTAD)₄ generally giving slightly higher enantioselectivity than the established *tert*-butyl catalyst, Rh₂(*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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