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Dirhodium Tetracarboxylates Derived from Adamantylglycine as Chiral Catalysts for Enantioselective C–H Aminations

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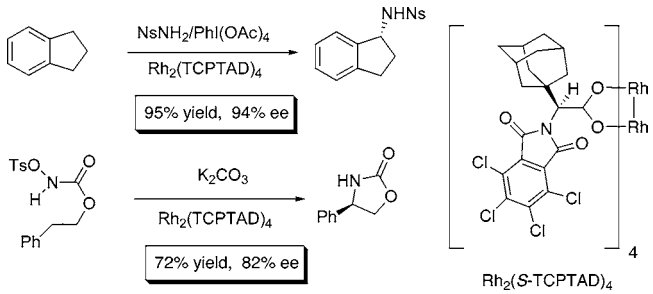
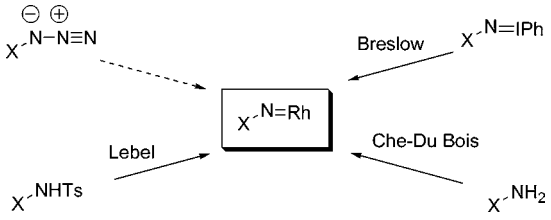
ABSTRACT



The dirhodium tetracarboxylate, Rh_2(*S*-TCPTAD)$_4$, derived from adamantylglycine, is an effective chiral catalyst for both inter- and intramolecular C–H aminations.

The development of practical catalytic methods for the functionalization of unactivated C−H bonds is an area of intense current interest.[1] Considerable advances have been made in recent years in many types of transformations, such as C−H oxidation,[2] C−H borylation,[3] C−H alkylation,[4] C−H arylation,[5] and C−H amination.[6] C−H amination has been greatly enhanced due to improved methods for the synthesis of rhodium nitrene intermediates (Scheme 1). The

Scheme 1. Generation of Rh Nitrene Intermediates



direct rhodium-catalyzed decomposition of azides is not an effective method for generating rhodium nitrenes. The first generally applicable method, pioneered by Breslow, was to use preformed iodinanes.[7] Che[8] and Du Bois[9] discovered an improved process, in which the iodinane is generated *in situ*, thereby opening up the chemistry to a range of primary amide and sulfonamide substrates. The synthetic potential of this

(1) (a) Sames, D.; Godula, K. *Science* **2006**, *312*, 67. (b) Davies, H. M. L.; Beckwith, E. J. *Chem. Rev.* **2003**, *103*, 2861. (c) Doyle, M.; McKervey, M.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998. (d) Davies, H. M. L. In *Comprehensive Asymmetric Catalysis (Supplement 1)*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; pp 83−94.

(2) (a) Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628. (b) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578. (c) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (d) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (e) Sigman, M. S.; Schultz, M. J. *Org. Biomol. Chem.* **2004**, *2*, 2551.

(3) (a) Ishiyama, T.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 3. (b) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056. (c) Hartwig, J. F. ACS Symposium Series; American Chemical Society: Washington, DC, 2004; p 136. (d) Bae, C.; Hartwig, J. F.; Chung, H.; Harris, N. K.; Switek, K. A.; Hillmyer, M. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6410. (e) Bae, C.; Hartwig, J. F.; Harris, N. K.; Long, R. O.; Anderson, K. S.; Hillmyer, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 767.

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process has been beautifully illustrated by Du Bois in the total synthesis of complex natural products such as tetrodotoxin[10] and saxitoxin.[11] Recently, Lebel reported that tosyloxycarbamates can be used as a nitrene precursor, and this approach also has great synthetic potential.[12]

The next natural extension for the C−H amination field is the development of effective chiral catalysts for this type of transformation. Chiral copper catalysts were successfully applied to intermolecular aziridination,[13] but dirhodium tetracarboxylates are the most widely used catalysts for the C−H amination chemistry.[6,7,9] Several chiral catalysts have been applied using preformed iodinanes as the nitrene precursor.[14] One of the most notable catalysts has been the rhodium phthalimide catalyst developed by Hashimoto, of which Rh_2(*S*-TCPTTL)$_4$ is considerably better at asymmetric C−H amination than the unchlorinated analogue Rh_2(*S*-PTTL)$_4$.[15] The related catalyst Rh_2(*S*-NTTL)$_4$ developed by Müller (Figure 1) also shows promise in this chemistry.[16]

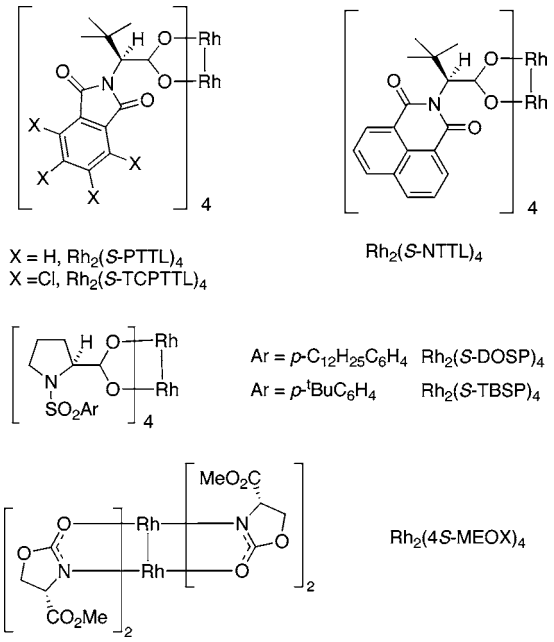


Figure 1. Chiral dirhodium catalysts.

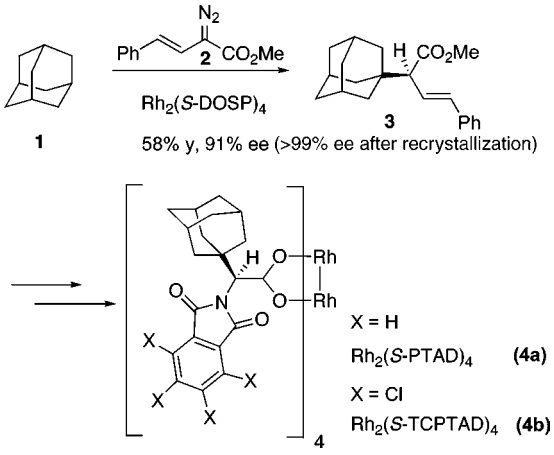
Other effective catalysts have been manganese salen catalysts developed by Katsuki[14e,f] and manganese porphyrin catalysts developed by Che.[8,14b−g] Che has also demonstrated that a ruthenium porphyrin catalyst is effective in C−H aminations where the iodinane is generated *in situ*.[17]

(4) (a) Fiedler, D.; Leung, D. H.; Bergman, R. G.; Raymond, K. N. *Acc. Chem. Res.* **2005**, *38*, 349. (b) Klei, S. R.; Tan, K. L.; Golden, J. T.; Yung, C. M.; Thalji, R. K.; Ahrendt, K. A.; Ellman, J. A.; Tilley, T. D.; Bergman, R. G. ACS Symposium Series; American Chemical Society: Washington, DC, 2004; p 885. (c) Kakiuchi, F.; Murai, S. Activation of C−H Bonds: Catalytic Reactions. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999; pp 47−79. (d) Muai, S.; Kakiuchi, F. *Acc. Chem. Res.* **2002**, *35*, 826.

(5) (a) Chen, X.; Li, J.; Hao, X.; Goodhue, C. E.; Yu, J. *J. Am. Chem. Soc.* **2006**, *128*, 78. (b) Li, Z.; Li, C. *J. Am. Chem. Soc.* **2006**, *128*, 56. (c) Miyura, N.; Suziki, A. *Chem. Rev.* **1995**, *95*, 2457. (d) Toure, B. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006**, *8*, 1979. (e) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581.

During our studies on enantioselective intermolecular C−H alkylation, we discovered that adamantane could be readily functionalized, and we have applied this chemistry to the synthesis of the adamantylglycine catalyst Rh_2(*S*-PTAD)$_4$ (Scheme 2).[18] This catalyst tends to give higher enantiose-

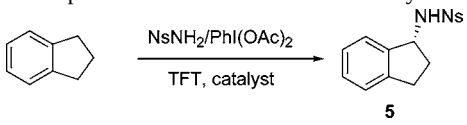
Scheme 2. Synthesis of Rh_2(*S*-PTAD)$_4$ and Rh_2(*S*-TCPTAD)$_4$



lectivity than Rh_2(*S*-PTTL)$_4$ in carbenoid reactions.[18] Therefore, we became interested to see how effective Rh_2(*S*-PTAD)$_4$ and its chlorinated derivative Rh_2(*S*-TCPTAD)$_4$ would be in C−H amination reactions.

The new catalysts were tested under the Che−Du Bois conditions where the nitrene precursors are generated *in situ*. As can be seen in the standard reaction for functionalizing indane, Rh_2(*S*-TCPTAD)$_4$ was the most effective catalyst studied (94% ee) (Table 1). Our traditional catalyst for

Table 1. Comparison of Chiral Dirhodium Catalysts

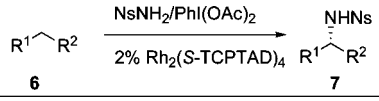


catalyst	yield, %	ee, %
Rh_2(OAc)$_4$	45	
Rh_2(*S*-TCPTAD)$_4$	95	94
Rh_2(*S*-PTAD)$_4$	86	59
Rh_2(*S*-TCPTTL)$_4$	88	79
Rh_2(*S*-PTTL)$_4$	81	43
Rh_2(*S*-DOSP)$_4$	49	(−) 11
Rh_2(*S*-TBSP)$_4$	25	(−) 31
Rh_2(*S*-NTTL)$_4$	56	34
Rh_2(*S*-MEOX)$_4$	12	10

carbenoid chemistry, Rh_2(*S*-DOSP)$_4$, resulted in low enantioselectivity (11% ee) as did Rh_2(*S*-MEOX)$_4$ (10% ee) and Rh_2(*S*-NTTL)$_4$ (34% ee). As expected from the literature,[15] Rh_2(*S*-TCPTTL)$_4$ gave relatively high asymmetric induction (79% ee) but did not match the results with Rh_2(*S*-TCPTAD)$_4$.

The Rh_2(*S*-TCPTAD)$_4$-catalyzed reactions were then examined with a range of substrates, and the results are summarized in Table 2. The most efficient conditions for carrying out these reactions were addition of a solution of $PhI(OAc)_2$ in trifluorotoluene to a solution of the substrate (5 equiv), $NsNH_2$, MgO, and the catalyst in trifluorotoluene at room temperature. This resulted in the formation of the products in good yields (65−92%) and reasonable enantioselectivities (62−78%). An excess of the substrate is optimal for these reactions as the efficiency of the reaction decreases considerably if less trapping agent is available. Because of solubility issues associated with the reagents used in this study, the reaction could not be improved by lowering the reaction temperature. The absolute configurations of **5a**, **7a**, and **7c** were shown to be (*R*) by comparison of optical rotation with literature values.[15] The absolute configurations of the other products are tentatively assigned to be (*R*) by analogy.

Table 2. Rh_2(*S*-TCPTAD)$_4$-Catalyzed Intermolecular C−H Amination[a]



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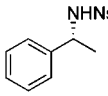
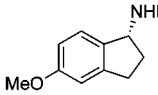
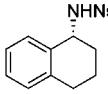
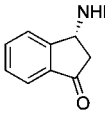
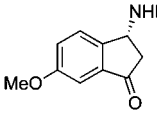
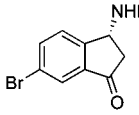
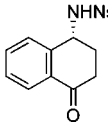
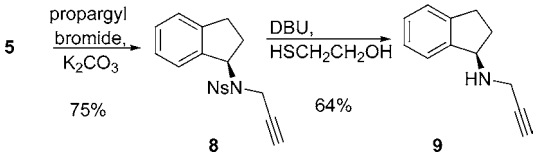
compound	product	yield, %	ee, %
a		86	74
b		92	62
c		82	73
d		75	76
e		85	74
f		70	73
g		65	78

[a] General procedure: A solution of $PhI(OAc)_2$ (1.5 equiv) in trifluorotoluene (10 mL) was added over 30 min to a solution of substrate (5 equiv), $NsNH_2$ (1 equiv), MgO (2.3 equiv), and the catalyst (2 mol %) in trifluorotoluene (15 mL) at 23 °C. The reaction mixture was sirred for 3 h and then filtered to remove the precipitated solids. The filtrate was concentrated, and the residue was purified by column chromatography.

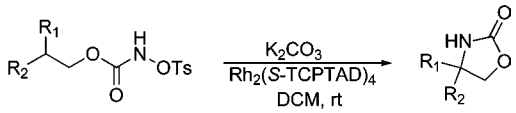
Selective C−H amination could be very useful for the rapid synthesis of pharmaceutical agents. An illustration of this potential is the enantioselective synthesis of the (*R*) enantiomer of the anti-Parkinson agent Rasagiline (**9**) shown in Scheme 3.[19] Alkylation of the sulfonamide **5a** with propargyl bromide to form **8**, followed by removal of the nosyl group in **8** using Fukuyama's protocol,[20] readily generates **9**. Both enantiomers of Rh_2(TCPTAD)$_4$ can be accessed,[18] and so, in principle, either enantiomer of **9** could be selectively formed.

Scheme 3. Synthesis of Rasagiline

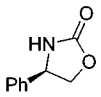
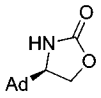
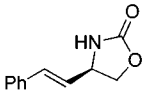
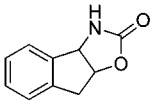


The Rh_2(*S*-TCPTAD)$_4$-catalyzed enantioselective C−H amination can be extended to intramolecular reactions as illustrated in Table 3. Lebel's method[12] was used for generating the nitrene precursors in these examples. Reaction

Table 3. Rh_2(*S*-TCPTAD)$_4$-Catalyzed Intramolecular C−H Amination[a]



10 11

compound	product	yield, %	ee, %
a		72	82
b		75	78
c		62	79
d		69	43

[a] General procedure: K_2CO_3 (1.5 mmol, 3 equiv) and the catalyst (2 mol %) were added to a solution of *N*-tosyloxycarbamate (0.5 mmol) in dichloromethane (10.0 mL) at 23 °C. The resulting suspension was stirred for 4 h. The mixture was filtered to remove the precipitate, and the solvent was removed under vacuum. The product was then purified by column chromatography.

(6) (a) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518. (b) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (c) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744. (d) Quan, Z.; Li, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889. (e) Espino, C. G.; Du Bois, J. In *Modern Rhodium Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley: New York, 2005; pp 379−416.

of the *N*-tosyloxycarbamates **10** generated the oxazolidinones **11** in good yields. With acyclic substrates **10a**−**c**, the enantioselectivity was quite reasonable (79−82% ee) but the C−H amination of the cyclic substrate **10d** was less enantioselective (43% ee).

In summary, these studies demonstrate that Rh_2(*S*-TCPTAD)$_4$ is an effective catalyst for enantioselective C−H amination. Further studies are in progress to refine the structure of this adamantyl-derived catalyst to achieve even higher enantioselectivity in both inter- and intramolecular C−H aminations.

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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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(7) (a) Breslow, R.; Gellman, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 6728. (b) Breslow, R.; Gellman, S. H. *J. Chem. Soc., Chem. Commun.* **1982**, 1400.

(8) (a) Liang, J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2002**, *4*, 4507. (b) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-g.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233. (c) Au, S.-M.; Zhang, S.-B.; Fung, W.-H.; Yu, X.-Q.; Che, C.-M.; Cheung, K.-K. *Chem. Commun*. **1998**, 2677. (d) Au, S.-M.; Huang, J.-S.; Che, C.-M.; Yu, W.-Y. *J. Org. Chem.* **2000**, *65*, 7858.

(9) (a) Fiori, K. W.; Fleming, J. J.; Du Bois, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 4349. (b) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598. (c) Espino, C. G.; Wehn, P.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935. (d) Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J. *Org Lett*. **2006**, *8*, 1073. (e) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc*. **2004**, *126*, 15378. (f) Wehn, P. M.; Lee, J.; Du Bois, J. *Org. Lett.* **2003**, *5*, 4823.

(10) Hinmann, A.; Du Bois, J. H. *J. Am. Chem. Soc.* **2003**, *125*, 11510.

(11) Fleming, J. J.; Du Bois, J. H. *J. Am. Chem. Soc.* **2006**, *128*, 3926.

(12) (a) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198. (b) Barani, M.; Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **1994**, *50*, 11235.

(13) (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742. (c) Sodergren, M. J.; Alanso, D. A.; Andersson, P. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3563. (d) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1993**, *115*, 5326. (e) Gillespie, K. M.; Sanders, C. J.; O'Shaughnessy, P.; Westmoreland, I.; Thickitt, C. P.; Scott, P. *J. Org. Chem*. **2002**, *67*, 3450.

(14) (a) Nageli, I.; Bernardinelli, G.; Jacquier, Y.; Moran, M.; Muller, P. *Helv. Chim. Acta* **1997**, *80*, 1087. (b) Leung, A. K.-Y.; Huang, J.-S.; Liang, J.-L.; Che, C.-M.; Zhou, Z.-Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 340. (c) Liang, J.-L.; Yu, X.-Q.; Che, C.-M. *Chem. Commun*. **2002**, 124. (d) Liang, J.-L.; Huang, J.-S.; Yu, X.-Q.; Zhu, N.; Che, C.-M. *Chem.*−*Eur. J*. **2002**, *8*, 1563. (e) Kohmura, Y.; Katsuki, T. *Tetrahedron Lett*. **2001**, *42*, 3339. (f) Omura, K.; Murakami, M.; Uchida, T.; Irie, R.; Katsuki, T. *Chem. Lett*. **2003**, *32*, 354. (g) Zhou, X.-G.; Yu, X.-Q.; Huang, J.-S.; Che, C.-M. *Chem. Commun.* **1999**. 2377.

(15) Yamawaki, M.; Tsutsui, H.; Kitagaki, S.; Anada, M.; Hashimoto, S. *Tetrahedron Lett*. **2002**, *42*, 9561.

(16) Fruit, C.; Muller, P. *Helv. Chim. Acta* **2004**, *87*, 1607.

(17) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, X.-Q.; Che, C.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465.

(18) Reddy, R. P.; Lee, G.; Davies, H. M. L. *Org. Lett*. **2006**, *8*, 3437.

(19) For the synthesis, see: (a) Graul, A.; Castaner, J. *Drugs Future* **1996**, *21*, 903. (b) Sterling, J.; Herzig, Y.; Goren, T.; Finkelstein, N.; Lerner, D.; Goldenberg, W.; Miskolczi, I.; Molnar, S.; Rantal, F.; Tamas, T.; Toth, G.; Zagyva, A.; Zekany, A.; Lavian, G.; Gross, A.; Friedman, R.; Razin, M.; Huang, W.; Krais, B.; Chorev, M.; Youdim, M. B.; Weinstock, M. *J. Med. Chem*. **2002**, *45*, 5260. (c) Lidor, R.; Bahar, E. US 563991, 1997.

(20) (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett*. **1995**, *36*, 6373. (b) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, *4*, 353.