[S1-2] [4/18/2002(Thur) 14:30-15:20/Hall A]

Enantioselective Intramolecular C-H Insertion Reactions Catalyzed by Dirhodium(II) Carboxylates.Catalytic Asymmetric Synthesis of Carbocycles and Heterocycles.

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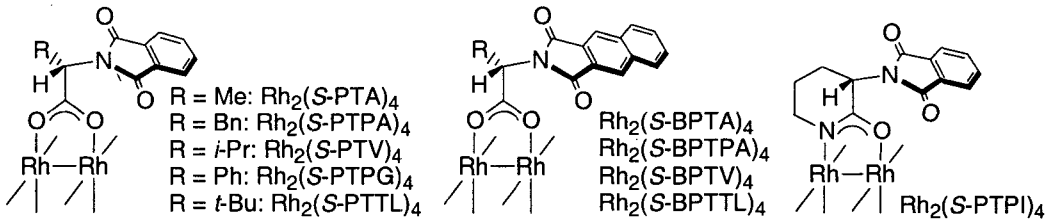
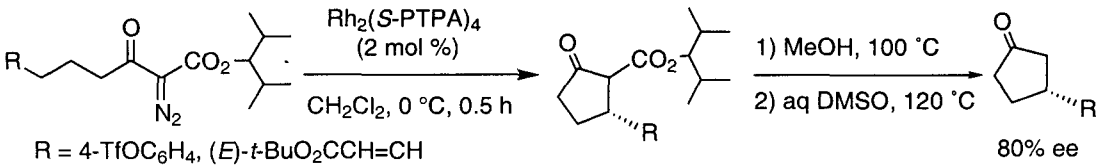
The development of an enantioselective version of rhodium(II) carbene transformations including C-Hinsertion,cyclopropanation,andrearrangementorcycloaddition*via*ylidegenerationhasrecently been the subject of intensive investigations in the field of asymmetric synthesis.[1] Consequently, a great deal of effort has been focused on the design, synthesis and evaluation of chiral dirhodium(II) catalysts.[2] Our efforts in this area have led to the development of dirhodium(II) carboxylates, particularly dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-phenylalaninate], Rh_2(*S*-PTPA)$_4$, and dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-PTTL)$_4$, and dirhodium(II) carboxamidates exemplified by dirhodium(II) tetrakis[3(*S*)-phthalimido-2-piperidinonate], Rh_2(*S*-PTPI)$_4$.Inhighlyenantioselectivereactionsmediatedbythesecatalysts,[3-5] twophthalimidogroups in a pair of adjoining ligands orienting to an axial coordination site of each octahedreal rhodium have been considered to play a pivotal role as enantiocontrollers.[6]
Ithasbeenwelldocumentedthatdirhodium(II)complexesdistinguishthemselvesbytheirsuperiority in C-H insertion reactions.This lecture will focus on enantioselective intramolecular C-H insertion reactions catalyzed by our dirhodium(II) carboxylates and their applications.



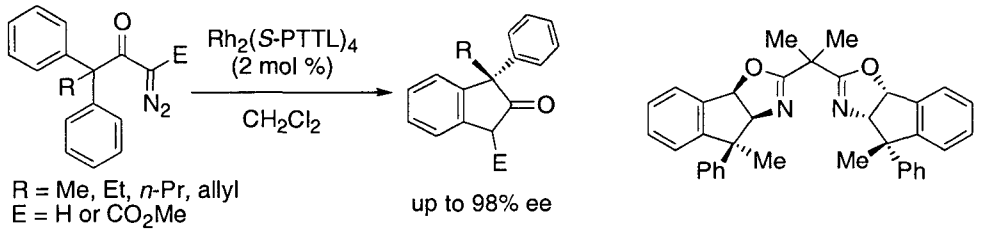
1. Enantioselective Synthesis of 3-Substituted Cyclopentanones

Intramolecular C-H insertion reactions of α-diazo β-keto esters are mediated by Rh_2(*S*-PTPA)$_4$ to afford, after a removal of the ester group, optically active 3-substituted cyclopentanones of up to 80% ee, in which the combinational use of a bulky 2,4-dimethyl-3-pentyl ester and electron-withdrawing substituents at the insertion site has proven to be crucial for high levels of enantioselectivity.[7]



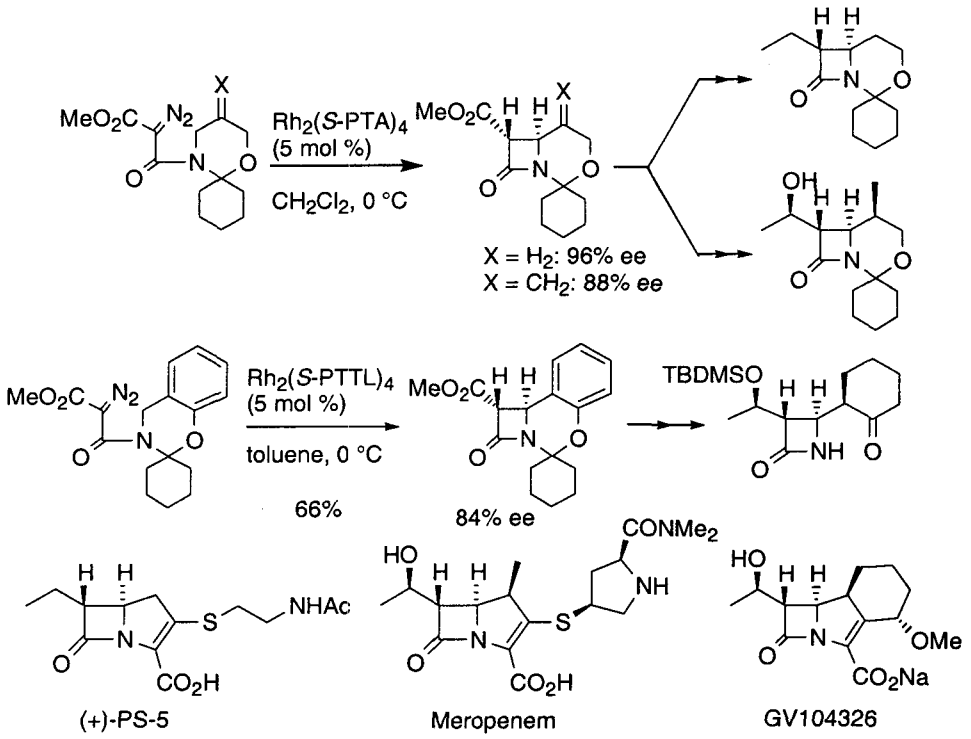
2. Asymmetric Creation of Quaternary Carbon Centers by Enantiotopically Selective Aromatic C-H Insertion Reactions

Rh_2(*S*-PTTL)$_4$ catalyzes aromatic C-H insertion reactions of 3-alkyl-substituted 1-diazo-3,3-diphenyl-2-propanones to give (*S*)-1-alkyl-1-phenyl-2-indanones containing a chiral quaternary carbon atom in up to 98% ee.[8] The present protocol has been successfully exploited for the synthesis of new chiral bis(oxazoline) ligand containing a rigid indan backbone, the potential of which has been demonstrated in copper-catalyzed enantioselective Diels-Alder reactions.[9]



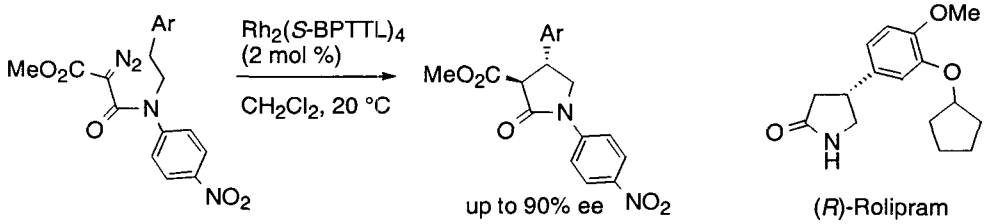
3. Enantioselective Construction of the Key Intermediates for the Synthesis of Carbapenem Antibiotics

Rh_2(*S*-PTA)$_4$ has been demonstrated to be useful for the decomposition of α-methoxycarbonyl-α-diazoacetamide derivatives bearing a tetrahydro-1,3-oxazine system, producing the key synthetic intermediates for 1-unsubstituted and 1 β-methylcarbapenem antibiotics in up to 96% ee.[10] Further extention of the present protocol to the diazoacetamide derivative bearing a benzene ring enabled the synthesis of the pivotal intermediate for trinem antibiotics, in which Rh_2(*S*-PTTL)$_4$ displayed the highest enantioselectivity (84% ee) of our catalysts.[11] It is worthy of note that all the 2-azetidinone derivatives obtained here, upon a single recrystallization, produced the optically pure samples.



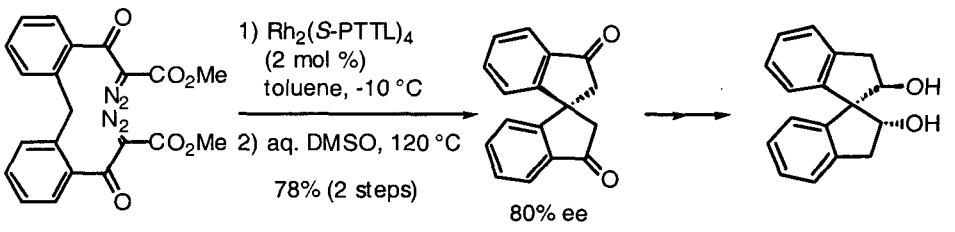
4.Site- and Enantioselective Construction of 2-Pyrrolidinones

Apart from enantiocontrol, site-control has remained a major challenge in the enantioselective construction of heterocycles *via* an intramolecular C-H insertion process in an acyclic system.Site- and enantioselective intramolecular C-H insertion of α-methoxycarbonyl-α-diazoacetamides has been achieved by exploiting *p*-nitrophenyl group as *N*-substituent and Rh_2(*S*-BPTTL)$_4$ as catalyst, leading to the formation of 4-substituted 2-pyrrolidinone derivatives of up to 90% ee.[12] The effectiveness of the present protocol has been verified well by the first catalytic asymmetric synthesis of (*R*)-(-)-rolipram.[13]



5.Enantioselective Double Intramolecular C-H Insertion Process

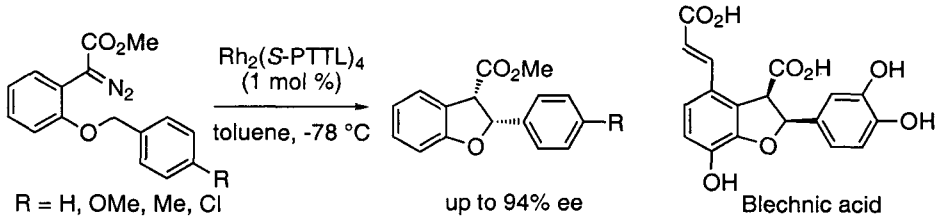
A highly efficient synthesis of optically active 1,1'-spirobiindan-3,3'-dione (up to 80% ee) has been achieved by exploiting double intramolecular C-H insertion reaction of dimethyl



2,2'-methylenebis(α-diazo-β-oxobenzenepropanoate) under the influence of Rh_2(*S*-PTTL)$_4$.[14] The potentiality of the opticaly pure *cis*,*cis*-1,1'-spirobiindane-2,2'-diol as a precursor to useful chiral ligands for metal catalyzed enantioselective reactions is being investigated.

6.Enantioselective Construction of Dihydrobenzofurans

We have recently found that intramoleculat C-H insertion of phenyldiazoacetates bearing a benzyloxy group at the ortho position in the presence of Rh_2(*S*-PTTL)$_4$ proceeds quite smoothly even at -78°C to give thermodynamically less stable *cis*-dihydrobenzofurans as the sole product in up to 94% ee.[15] The applicability of the present protocol to the synthesis of natural dihydrobenzofuran neolignans is currently in progress.



References

1. Doyle, M. P.; McKervey, M. A.; Ye, T. "Modern Catalytic Methods for Organic Synthesis with Diazo Compounds", Wiley-Interscience, New York, 1998.
2. Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911.
3. For enantioselective intermolecular cyclopropanations, see: (a) Watanabe, N.; Matsuda, H.; Kuribayashi, H.; Hashimoto, S. *Heterocycles* **1996**, *42*, 537. (b) Kitagaki, S.; Matsuda, H.; Watanabe, N.; Hashimoto, S. *Synlett* **1997**, 1171.
4. For enantioselective intermolecular 1,3-dipolar cycloaddition via carbonyl ylide generarion, see: (c) Kitagaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S. *J. Am. Chem. Soc.* **1999**, *121*, 1417. (d) Kitagaki, S.; Yasugahira, M.; Anada, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron Lett.* **2000**, *41*, 5931.
5. For enantioselective rearrangement via onium ylide generation, see: (e) Kitagaki, S.; Yanamoto, Y.;Okubo,H.;Nakajima,M.;Hashimoto,S.*Heterocycles***2001**,*54*,623.(f)Kitagaki,S.;Yanamoto, Y.; Tsutsui, H.; Anada, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron Lett.* **2001**, *42*, 6361. (g) Tsutsui, H.; Matsuura, M.; Makino, K.; Nakajima, M.; Kitagaki, S.; Hashimoto, S.; *Isr. J. Chem.*

in press.
6. Hashimoto, S.; Watanabe, N.; Anada, M.; Ikegami, S. *J. Synth. Org. Chem., Jpn. (in English)* **1996**, *54*, 988.
7. (a) Hashimoto, S.; Watanabe, N.; Sato, T.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* **1993**, *34*, 5109; (b) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Synlett* **1994**, 353.
8. (a) Watanabe, N.; Ohtake, Y.; Hashimoto, S.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* **1995**, *36*, 1491; (b) Watanabe, N.; Ogawa, T.; Ohtake, Y.; Ikegami, S.; Hashimoto, S. *Synlett* **1996**, 85.
9. Otani, S.; Yonehara, Y.; Tamura, M.; Kitagaki, S.; Nakamura, S.; Nakajima, M.; Hashimoto, S. Unpublished results.
10. Anada, M.; Watanabe, N.; Hashimoto, S. *Chem. Commun.* **1998**, 1517.
11. Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **1998**, *39*, 9063.
12. (a) Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **1998**, *39*, 79; (b) Anada, M.; Hashimoto, S. Unpublished results.
13. Anada, M.; Mita, O.; Watanabe, H.; Kitagaki, S.; Hashimoto, S. *Synlett* **1999**, 1775.
14. Takahashi,T.;Tsutsui,H.;Tamura,M.;Kitagaki,S.;Nakajima,M.;Hashimoto,S.*Chem.Commun.* **2001**, 1604.
15. Saito, H.; Oishi, H.; Kitagaki, S, Nakamura, S.; Anada, M.; Hashimoto, S. Unpublished results.