ORGANIC
LETTERS

2003
Vol. 5, No. 9
1403−1406

Dirhodium Tetraprolinate-Catalyzed Asymmetric Cyclopropanations with High Turnover Numbers

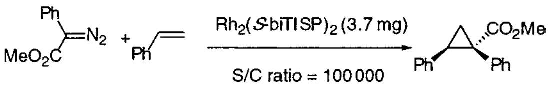
Huw M. L. Davies* and Chandrasekar Venkataramani

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

hdavies@acsu.buffalo.edu

Received January 2, 2003

ABSTRACT



crude: 46 g, 92% yield 85% ee
recrystallized: 37.8 g, 75% yield 99.3% ee

The bridged dirhodium tetraprolinate Rh_2(*S*-biTISP)$_2$ (2) catalyzes the asymmetric cyclopropanation reaction between methyl phenyldiazoacetate and styrene at room temperature with high turnover number (92 000) and turnover frequency (4000 per h).

The metal-catalyzed decomposition of diazo compounds to transient metal carbenoids is a very versatile reaction in organic synthesis.[1] A wide variety of catalysts have been developed leading to highly enantioselective cyclopropanations,[2] C−H insertions,[3] and dipolar cycloadditions.[4] Carbenoids containing an electron acceptor ester group and a donor group such as aryl, vinyl, or alkynyl are much more chemoselective than the traditional carbenoids.[5] They are far less susceptible to carbene dimerization,[6] routinely result in highly diastereoselective cyclopropanation,[7] and are capable of highly regioselective intermolecular C−H activation by means of carbenoid-induced C−H insertion.[3b] Furthermore these carbenoids are very effective in solid-phase chemistry.[8] In this paper, we report that donor/acceptor carbenoids can also undergo intermolecular cyclopropanation with very high catalyst turnover number (TON).

One of the most important future goals of transition metal-catalyzed asymmetric reactions will be the development of catalysts that are capable of very high TON. This will not only improve the economy of the catalytic process but also limit the problems of product contamination. Certain reactions such as catalytic asymmetric hydrogenation[9] can be conducted with very low catalyst loadings, but the majority of catalytic asymmetric reactions are still conducted with at least 1 mol % catalyst. The metal-catalyzed transformations of diazo compounds appear to be ideally suited for low catalyst loading because many of the catalysts are very active and have good stability, while product inhibition is generally not an issue. Even so, 1 mol % catalyst tends to be used in metal carbenoid reactions, and reports of much lower catalyst loading are rare.[10,11]

In our own experience, dirhodium tetracarboxylates are kinetically very active initially, but this high activity may

---

[1] (a) Doyle, M. P.; McKervey, M. A.; Ye, T. In *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998; pp 112−162. (b) Mass, G. In *Topics in Current Chemistry*; Springer-Verlag: New York; 1987; Vol. 137, pp 75−254.

[2] Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *59*, 1−302.

[3] (a) Sulikowski, G. A.; Cha, K. L.; Sulikowski, M. M. *Tetrahedron: Asymmetry* **1998**, *9*, 3145. (b) Davies, H. M. L. *J. Mol. Catal. A* **2002**, *189*, 125.

[4] Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50.

[5] Davies, H. M. L.; Panaro, S. A. *Tetrahedron* **2000**, *56*, 4871.

[6] Davies, H. M. L.; Hodges, L. M.; Matasi, J. J.; Hansen, T.; Stafford, D. S. *Tetrahedron Lett.* **1998**, *39*, 4417.

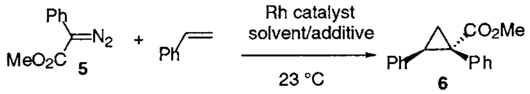
[7] Davies, H. M. L.; Clark, T. J.; Church, L. A. *Tetrahedron Lett.* **1989**, *30*, 5057.

[8] (a) Nagashima, T.; Davies, H. M. L. *J. Am. Chem. Soc.* **2001**, *123*, 2695. (b) Nagashima, T.; Davies, H. M. L. *Org. Lett.* **2002**, *4*, 1989. (c) Davies, H. M. L.; Walji, A. M. *Org. Lett.* **2003**, *5*, 479.

[9] Ohkuma, T.; Koizumi, M.; Muniz, K.; Hilt, G.; Kabuto, C.; Noyori, R. *J. Am. Chem. Soc.* **2002**, *124*, 6508.

10.1021/ol034002a CCC: $25.00

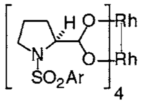
Table 1. Optimization of Cyclopropanation with Low Catalyst Loading



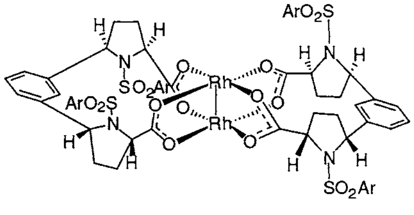
entry	catalyst (solvent)	substrate/catalyst ratio	additive[b]	yield, %	ee, %	time, h
1	**1** (hexanes)	1000	A	98	90	1
2	**1** (hexanes)	1000	B	97	91	1
3	**1** (hexanes)	10 000	A	62	25	>60[a]
4	**1** (hexanes)	10 000	B	96	85	16
5	**1** (hexanes)	100 000	A	15	11	>192[a]
6	**1** (hexanes)	100 000	B	14	10	>192[a]
7	**2** (CH_2Cl_2)	1000	A	72	89	1
8	**2** (CH_2Cl_2)	1000	B	82	89	1
9	**2** (CH_2Cl_2)	10 000	A	80	89	6
10	**2** (CH_2Cl_2)	10 000	B	79	89	3
11	**2** (CH_2Cl_2)	100 000	A			>144[a]
12	**2** (CH_2Cl_2)	100 000	B			>144[a]
13	**2** (CH_2Cl_2)	100 000	C	82	65	42
14	**2** (CH_2Cl_2)	100 000	**D**	**85**	**83**	**28**
15	**2** (CH_2Cl_2)	1 000 000	C	63	62	>240[a]
16	**2** (CH_2Cl_2)	1 000 000	D	75	74	>240[a]

[a] Reaction did not go to completion. [b] A: no additives. B: methyl benzoate (1 equiv). C: 4 Å molecular sieves. D: methyl benzoate (1 equiv) and 4 Å molecular sieves.

not continue throughout the reaction. Rhodium prolinates such as Rh$_2$(*S*-DOSP)$_4$ **1** and the bridged structure Rh$_2$(*S*-biTISP)$_2$ **2** are exceptional catalysts for the cyclopropanation chemistry of donor/acceptor carbenoids, active even at −50 °C.[12] The vast majority of our studies with these catalysts have used 1 mol % catalyst. In one brief study with Rh$_2$(*S*-DOSP)$_4$, the problems with the use of lower catalyst loading were demonstrated (Scheme 1).[13] Increasing the substrate/catalyst ratio to 1000 instead of 100 in the cyclopropanation of the vinyldiazoacetate **3** to form **4** resulted in a drop in enantioselectivity from 92 to 87% ee.[13] The effect was even more severe when a substrate/catalyst ratio of 10 000 was used, as this resulted in an incomplete transformation and a large drop in enantioselectivity to 50% ee.[13] These results indicate that the catalyst is being slowly modified under the reaction conditions to some other species that catalyzes the reaction with very different enantioselectivity. Although, the mechanism for catalyst degeneration is not known, one possibility would be the dissociation of the carboxylate ligands. Therefore, we considered that a comparison of the catalytic efficiency of Rh$_2$(*S*-DOSP)$_4$ and Rh$_2$(*S*-biTISP)$_2$ would be worthwhile, because the bridging ligands in Rh$_2$(*S*-biTISP)$_2$ may make it a more robust catalyst.



1 Rh$_2$(*S*-DOSP)$_4$: Ar = *p*-$C_{12}H_{25}C_6H_4$



2 Rh$_2$(*S*-biTISP)$_2$: Ar = 2,4,6-tri-*i*-PrC$_6$H$_2$

The test reaction that was used to evaluate the limitations of catalyst loading was the cyclopropanation of styrene (2 equiv) with methyl phenyldiazoacetate (**5**) at 23 °C to form **6** (Table 1). The reaction catalyzed by Rh$_2$(*S*-DOSP)$_4$ (**1**) in hexane[14] was very successful (98% yield, 90% ee) when a substrate catalyst ratio of 1000 was used, but the yield and

---

(10) For examples of asymmetric carbenoid reactions using < 1 mol % catalyst loading, see (a) Che, C.-M.; Huang, J.-S.; Lee, F.-W.; Li, Y.; Lai, T.-S.; Kwong, H.-L.; Teng, P.-F.; Lee, W.-S.; Lo, W.-C.; Peng, S.-M.; Zhou, Z.-Y. *J. Am. Chem. Soc.* **2001**, *123*, 4119. (b) Doyle, M. P.; Dyatkin, A. B.; Tedrow, J. S.; *Tetrahedron Lett.* **1994**, *35*, 3853. (c) Doyle, M. P.; Zhou, Q. −L. *Tetrahedron: Asymmetry* **1995**, *6*, 2157. (d) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martins, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763. (e) Doyle, M. P.; Kalinin, A. V. *J. Org. Chem.* **1996**, *61*, 2179. (f) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726.

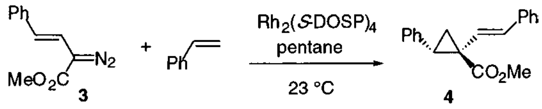
(11) While preparing this manuscript, we became aware of a study by Hashimoto on asymmetric intramolecular C−H insertion using low catalyst loading: Tsutsui, H.; Yamaguchi, Y.; Kitagaki, S.; Nakamura, S.; Ananda, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2003**, in press.

(12) Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, 2459.

(13) Davies, H. M. L.; Bruzinski, P.; Hutcheson, D. K.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.

(14) Hydrocarbons are the optimum solvent for high enantioselectivty for Rh$_2$(*S*-DOSP)$_4$-catalyzed reactions, while CH_2Cl_2 is the ideal solvent for Rh$_2$(*S*-biTISP)$_2$-catalyzed reactions. The Rh$_2$(*S*-DOSP)$_4$-catalyzed reactions give preferentially the (2*S*)-cyclopropanes, while the Rh$_2$(*S*-biTISP)$_2$-catalyzed reactions give preferentially the (2*R*)-cyclopropanes: see ref 12 for details.

Scheme 1[a]



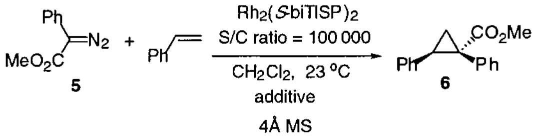
substrate/catalyst ratio	ee, %
100	92
1000	87
10 000	50[a]

[a] Reaction did not go to completion.

enantioselectivity dropped considerably (62% yield, 25% ee) when a substrate/catalyst ratio of 10 000 was used. Prior to our development of chiral catalysts for the donor/acceptor carbenoids, we had found that α-hydroxyesters were exceptional chiral auxiliaries for these carbenoid systems[15] and, furthermore, the ester of the auxiliary enhanced the carbenoid chemoselectivity.[16] On the basis of this phenomenon, we explored the effect of methyl benzoate as an additive on this chemistry. Addition of 1 equiv of methyl benzoate greatly enhanced the catalytic reaction because at a substrate/catalyst ratio of 10 000, the reaction was complete in 16 h and **6** was formed in 96% yield and 85% ee. Attempts at further lowering of the Rh_2(*S*-DOSP)$_4$ loading failed because the reaction using a substrate/catalyst ratio of 100 000 was not effective with or without methyl benzoate.

The cyclopropanation reactions of Rh_2(*S*-biTISP)$_2$ (**2**) were even more impressive as illustrated in Table 1 (entries 7−16). Reactions using a substrate/catalyst ratio of 10 000 in CH_2Cl_2[14] were uniformly effective with or without methyl benzoate. A further improvement was obtained by conducting the reaction in the presence of molecular sieves, as this enabled an efficient reaction to be conducted using a substrate/catalyst ratio of 100 000. The presence of both methyl benzoate and molecular sieves as additives was optimal, and under these conditions, **6** could be obtained in 85% yield and 83% ee. Indeed, **6** was formed in 75% yield and 74% ee when a substrate/catalyst ratio of 1 000 000 was used, but with this low loading, the reaction did not reach completion even after 10 days. Rh_2(*S*-biTISP)$_2$ has also been shown to be more robust than Rh_2(*S*-DOSP)$_4$ when used as a recoverable solid-supported catalyst.[8b,c]

Table 2. Comparison of Additive Effects on Cyclopropanation

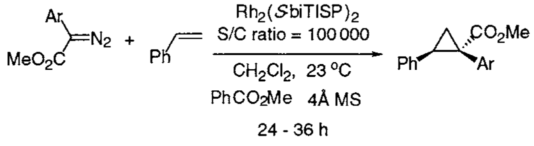


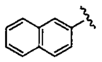
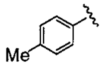
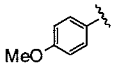
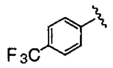
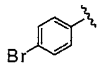
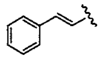
entry	additive	yield, %	ee, %	time, h
1	none	82	65	42
2	$PhCO_2Me$	**85**	**83**	**28**
3	$(Me_2N)_2C{=}O$	48	74	>36[a]
4	(i-Pr)$_2$NEt	5		>36[a]
5	OP(Oct)$_3$	36	78	>36[a]

[a] Reaction did not go to completion.

Additives have been used previously to optimize various carbenoid transformations. Nelson and co-workers reported that the yield in a rhodium carbenoid-mediated intermolecular O−H insertion reaction was considerably enhanced by addition of tetramethyl urea (TMU) or diisopropylethylamine (DIPEA).[17] Jessop and co-workers have described that the enantioselectivity of dirhodium tetraprolinate-catalyzed cyclopropanations under slightly hydrous conditions is greatly improved by the addition of tri-*n*-octylphosphine oxide (OP(Oct)$_3$).[18] A comparison of the effect of these additives with methyl benzoate revealed that methyl benzoate was far superior. DIPEA virtually blocked the catalytic process, while the reaction in the presence of TMU or OP(Oct)$_3$ was considerably slower. Although the actual role of methyl benzoate in these reactions is uncertain, it is possible that it stabilizes the rhodium carbenoid complex either by coordination to the carbenoid or to the other rhodium center.

Table 3. Asymmetric Cyclopropanation by Various Aryldiazoacetates



entry	Ar	product	yield, %	ee, %
1		**7a**	86	94
2		**7b**	91	80
3		**7c**	91	80
4		**7d**	76	87
5		**7e**	87	86
6[a]		**4**	77	85

[a] S/C ratio = 10 000.

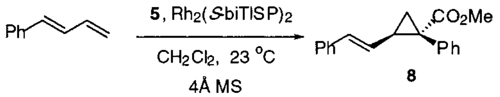
---

(15) Davies, H. M. L.; Huby, N. J. S.; Cantrell, W. R., Jr.; Olive, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 9468.

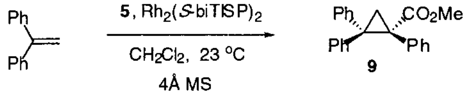
(16) Davies, H. M. L.; Matasi, J. J.; Thornley, C. *Tetrahedron Lett.* **1995**, *36*, 7205

(17) Nelson, T. D.; Song, Z. J.; Thompson, A. S.; Zhao, M.; DeMarco, A.; Reamer, R. A.; Huntington, M. F.; Grabowski, E. J. J.; Reider, P. J. *Teterahedron Lett.* **2000**, *41*, 1877.

Table 4. Cyclopropanation of Other Substrates



S/C ratio	$PhCO_2Me$	yield, %	ee, %	time, h
100	No	90	78	<1
100 000	No	86	79	36
100 000	**Yes**	**92**	**78**	**28**



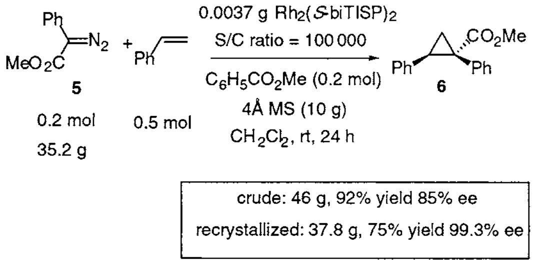
S/C ratio	$PhCO_2Me$	yield, %	ee, %	time, h
100	No	88	78	<1
100 000	No	85	76	36
100 000	**Yes**	**89**	**79**	**24**

The asymmetric cyclopropanation with low catalyst loading (substrate/catalyst ratio of 100 000) may be applied to various aryldiazoacetates as illustrated in Table 3 (entries 1−5). In all instances, the reactions were complete in 24−36 h and the cyclopropanes were obtained in good yield (76−91%) and enantioselectivity (80−94% ee). In the case of the phenylvinyldiazoacetate cyclopropanation (entry 6), the lowest effective catalyst loading was 10 000:1. This may be due to the fact that methyl phenylvinyldiazoacetate slowly undergoes a 6π electrocyclization to a pyrazole,[15] and a pyrazole is likely to partially poison the catalyst. This improvement in catalyst loading is significant because the resulting vinylcyclopropane **4** has been used for the asymmetric synthesis of phenylcyclopropane amino acids[13] and the antidepressant (+)-sertraline.[19]

Two other examples of the cyclopropanation with low catalyst loading are the reactions with 1-phenylbutadiene and 1,1-diphenylethylene in Table 4. These reactions give comparable results in terms of yield and enantioselectivity to the standard reaction with 1 mol % catalyst. Once again, the reactions are faster when methyl benzoate is used as an additive. These examples indicate that low catalyst loading could be used in the asymmetric [3 + 4] cycloaddition between vinyldiazoacetates and dienes,[20] and in the asymmetric synthesis of cyclopropane amino acids[21] as well as cyclopropyl analogues of tamoxifen.[22]

The cyclopropanation chemistry is applicable to large-scale synthesis as illustrated in Scheme 2. The $Rh_2(S\text{-biTISP})_2$ catalyzed cyclopropanation can be readily carried out on a 0.2 mol scale with 0.001 mol % catalyst. Under these conditions the green catalyst is so dilute that it appears colorless in solution. The reaction can be monitored by simply observing the gradual disappearance of the yellow color of methyl phenyldiazoacetate. As carbene dimerization is rarely a problem with the donor/acceptor carbenoids, there is no need to use very slow addition of the diazo compound. The reaction is complete in 24 h, which means that the catalyst is operating at very high TON (92 000) and turnover frequency (4000 per h). After filtration of the molecular sieves and removal of volatiles, no contaminants are visible in the NMR of the crude material, which can be readily enriched by recrystallization to give **6** in 75% isolated yield and 99.3% ee.

Scheme 2



crude: 46 g, 92% yield 85% ee

recrystallized: 37.8 g, 75% yield 99.3% ee

In summary, the bridged prolinate catalyst $Rh_2(S\text{-biTISP})_2$ has been shown to be a superior catalyst over our first generation catalyst $Rh_2(S\text{-DOSP})_4$ in terms of low catalyst loading. This may indicate that the design of new high TON catalysts for carbenoid chemistry would benefit from the use of bridging dicarboxylate ligands. Molecular sieves and methyl benzoate have a beneficial effect on the stability of the catalyst under the reaction conditions. Under optimized conditions, room temperature cyclopropanations with a substrate/catalyst ratio of 100 000 are readily achieved.

Acknowledgment. Financial support of this work by the National Science Foundation (CHE-0092490) is gratefully acknowledged. We thank Qihui Jin for his preliminary studies with methyl benzoate in C-H activation reactions, which encouraged us to use it as an additive in this study.

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

OL034002A

---

[18] Wynne, D. C.; Olmstead, M. M.; Jessop, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 7638.

[19] Corey, E. J.; Grant, T. J. *Tetrahedron Lett.* **1994**, *35*, 5373.

[20] Davies, H. M. L.; Stafford, D. G.; Doan, B. D.; Houser, J. H. *J. Am. Chem. Soc.* **1998**, *120*, 3326.

[21] Moye-Sherman, D.; Welch, M. B.; Reibenspies, J.; Burgess, K. *J. Chem. Soc., Chem. Commun.* **1998**, 2377.

[22] Davies, H. M. L.; Nagashima, T.; Klino, J. L., III. *Org. Lett.* **2000**, *2*, 823.