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Dirhodium(II) Tetra(*N*-(dodecylbenzenesulfonyl)prolinate) Catalyzed Enantioselective Cyclopropenation of Alkynes

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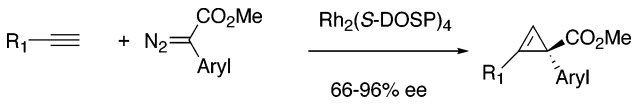
ABSTRACT



Dirhodium tetrakis((*S*)-*N*-(dodecylbenzenesulfonyl)prolinate) (Rh_2(*S*-DOSP)$_4$) is an effective chiral catalyst for the enantioselective cyclopropenation of alkynes by methyl aryldiazoacetates.

Strained ring systems such as cyclopropanes, aziridines, and epoxides are very versatile intermediates for organic synthesis.[1] The even more highly strained cyclopropene ring also undergoes a number of useful transformations, especially addition reactions across the strained double bond.[2] Cycloaddition reactions of various types are also highly favored, as well as free-radical-induced additions[2l,m] and transition-metal-catalyzed hydrogenation, hydrosilation,[2j] hydrostannation,[2j] and hydroboration.[2k] Addition reactions not commonly observed with electron-neutral double bonds such as reactions with Grignard reagents[2e,n] and organozinc,[2n,r] and organocupurate,[2p,q] and organolithium[2o] reagents are also very efficient.

To enhance the synthetic potential of cyclopropenes further, the development of methods for their utilization in enantioselective reactions is highly desirable. A very effective method has been the use of C_2 symmetric ketals of cyclopropenone as chiral building blocks.[3] More recently, effective catalytic methods for the desymmetrization of cyclopropenes have been developed such as hydrosilation,[2j] hydrostannation,[2j] and hydroboration.[2k]

An alternative strategy for the use of cyclopropenes in asymmetric synthesis would be to develop a practical method for the enantioselective synthesis of the cyclopropene build-

(1) (a) Reissig, H.-U.; Zimmer, R.; *Chem. Rev.* **2003**, *103*, 1151. (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (c) Li, A.; Dai, L.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341. (d) Binger, P.; Buch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. (e) Jennings, P. W.; Johnson, L. L. *Chem. Rev.* **1994**, *94*, 2241. (f) Protopopova, M. N.; Shapiro, E. A. *Russ. Chem. Rev.* **1989**, *58*, 667. (g) Maas, G. *Top. Curr. Chem.* **1987**, *137*, 75. (h) Park, C. S.; Kim, M. S.; Sim, T. B.; Pyun, D. K.; Lee, C. H.; Choi, D.; Lee, W. K.; Chang, J.-W.; Ha, H-J. *J. Org. Chem.* **2003**, *68*, 43. (i) Kim, B. M.; So, S. M.; Choi, H. J. *Org. Lett.* **2002**, *4*, 949. (j) Yan, Z.; Weaving, R.; Dauban, P.; Dodd, R. H. *Tetrahedron Lett.* **2002**, *43*, 7593. (k) Katsuki, T *Adv. Synth. Catal.* **2002**, *344*, 131.

(2) Reviews: (a) Halton, B.; Banwell, M. G. In *The Chemistry of the Cyclopropyl Group*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1987; p 1224. (b) Baird, M. S. *Top. Curr. Chem.* **1988**, *144*, 139. (c) Baird, M. S.; Schmidt, T. In *Carbocyclic Three-Membered Ring Compounds*; de Meijere, Ed.; Georg Thieme Verlag: Stuttgart, 1996; p 114. (d) Baird, M. S. Cyclopropenes: Transformations: Addition Reactions. In *Houben-Weyl*; Thieme: Stuttgart, 1997; E17 d/2, p 2794. Recent examples: (e) Fox, J. M.; Liao, L. *J. Am. Chem. Soc.* **2002**, *124*, 14322. (f) Delgado, A.; Castedo, L.; Mascarenas, J. L. *Org. Lett.* **2002**, *18*, 3091. (g) Suito, K.; Ono, K.; Ito, N.; Tada, N.; Ando, S. *Heterocycles* **2002**, *2*, 235. (h) Binger, P.; Wedemann, P.; Brinke, U. H. *Org. Synth.* **2000**, *77*, 254. (i) Ferjancic, Z.; Cekovic, Z.; Saicic, R. N. *Tetrahedron Lett.* **2000**, *16*, 2979. (j) Rubina, M.; Rubin, M.; Gevorggyan, V. *J. Am. Chem. Soc.* **2002**, *124*, 11566. (k) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198. (l) Nakamura, E.; Machii, D.; Imubushi, T. *J. Am. Chem. Soc.* **1989**, *111*, 6849. (m) Yamago, S.; Ejiri, S.; Nakamura, E. *Chem. Lett.* **1994**, 1889. (n) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978. (o) Kubota, K.; Mori, S.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **1998**, *120*, 13334. (p) Nakamura, E.; Isaka, M.; Matsuzawa, S. *J. Am. Chem. Soc.* **1988**, *110*, 1297. (q) Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1990**, *112*, 7428. (r) Nakamura, M.; Arai, M.; Nakamura, E. *J. Am. Chem. Soc.* **1995**, *117*, 1179. (s) Cho, S. H.; Liebeskind, L. S. *J. Org. Chem.* **1987**, *52*, 2631. (t) Marchueta, I.; Verdaguer, X.; Moyano, A.; Pericas, M. A.; Riera, A. *Org. Lett.* **2001**, *20*, 3193.

(3) Nakamura, M.; Isobe, H.; Nakamura, E. *Chem. Rev.* **2003**, *103*, 1295.

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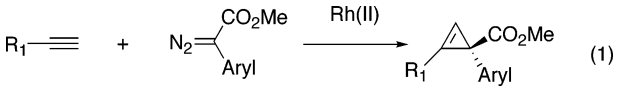
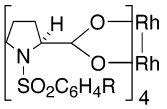
ing blocks, which then undergo reactions in a stereoselective manner. The most notable method to date for the enantioselective synthesis of cyclopropenes has been the metal-catalyzed cyclopropenation of alkynes by diazoacetates.[4] A number of chiral catalysts have been developed for this transformation, the most notable being Doyle's chiral dirhodium carboxamidates.[4a] These enantioselective cyclopropenations can be conducted on a range of alkynes, but the diazo compounds have been limited thus far to diazoacetates. In this paper, we describe procedures for the enantioselective cyclopropenation using aryldiazoacetates, which greatly expands the range of readily accessible chiral cyclopropenes to those containing a quaternary carbon center. Concurrently, Fox and co-workers have developed an alternative method to similar types of cyclopropenes by means of kinetic resolution strategies.[5]



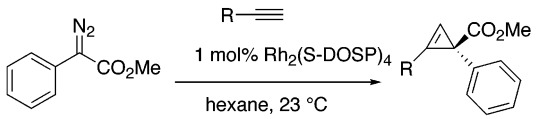
The metal-catalyzed decomposition of aryl diazoacetates and vinyl diazoacetates generates a distinctive class of transient-metal carbenoids, functionalized with both a donor and acceptor group.[6] The donor/acceptor-substituted carbenoids are more stabilized than the conventional carbenoids derived from diazoacetates. They are capable of remarkably stereoselective reactions, such as cyclopropanation,[7] [4 + 3] cycloaddition,[8] [3 + 2] cycloaddition[9] and intermolecular C−H insertion.[10] The most generally effective chiral catalyst for the various transformations of these donor/acceptor-substituted carbenoids has been the dirhodium(II) tetraprolinate Rh_2(*S*-DOSP)$_4$ (**1**).[11] In this paper, we show that Rh_2(*S*-DOSP)$_4$ is also an exceptional catalyst for enantioselective cyclopropenations.

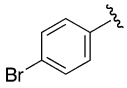
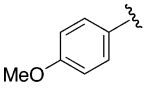
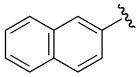
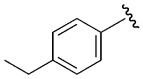


R =$C_{12}H_{25}$
Rh_2(*S*-DOSP)$_4$ (**1**)

To explore the scope of alkynes that would be amenable to Rh_2(*S*-DOSP)$_4$-catalyzed cyclopropenations, test reactions were conducted using methyl phenyldiazoacetate as the carbenoid precursor (Table 1). The optimum conditions were found to be slow addition of the diazo compound (over 5 h) to a hexane solution of Rh_2(*S*-DOSP)$_4$ (1 mol %) and the alkyne (10 equiv) at room temperature (23 °C). Under these conditions, the reaction with phenylacetylene generated the cyclopropene **2** in 62% yield and 90% ee (entry 1). Similar reactions were observed with various aromatic acetylenes (entries 2−5). An especially interesting substrate is the *p*-ethylbenzene derivative (entry 5) because this shows that cyclopropenation is favored over benzylic C−H insertion. An effective cyclopropenation of an enyne is also possible indicating selective cyclopropenation over cyclopropanation of the trisubstituted alkene (entry 6). The cyclopropenation

Table 1. Rh_2(*S*-DOSP)$_4$-Catalyzed Enantioselective Cyclopropenation with Methyl Phenyldiazoacetate[a]



entry	R	product	yield, %	ee, %
1		**2**	62	90
2		**3**	63	92
3		**4**	67	86
4		**5**	60	96
5		**6**	48	87
6		**7**	74	92
7	$(CH_2)_3CH_3$	**8**	51	84

[a] Reactions were performed by the addition of the diazo compound (1.0 mmol) in 5 mL of hexanes over a 5-h period to a solution of the alkyne (10.0 mmol) and catalyst (0.01 mmol) in 10 mL of hexanes. See the Supporting Information for details.

(4) (a) Doyle, M. P.; Protopopova, M. N.; Muller, P.; Shapiro, E. A. *J. Am. Chem. Soc.* **1994**, *116*, 8492. (b) Doyle, M. P.; Protopopova, M. N.; Muller, P.; Ene, D. *J. Am. Chem. Soc.* **1992**, *114*, 2755. (c) Doyle, M. P.; Eene, D.; Peterson, C. S.; Lynch, V. *Angew. Chem., Int. Ed.* **1999**, *38*, 700. (d) Müller, P.; Imogaï, H. *Tetrahedron: Asymmetry* **1998**, *9*, 4419. (e) Imogaï, H.; Bernardinelli, G.; Gränicher, C.; Moran, M.; Rossier, J.-C.; Müller, P. *Helv. Chim. Acta* **1998**, *81*, 1754. (f) Petiniot, N.; Anciaux, A. J.; Noels, A. F.; Hubert, A. J.; Teyssié, P. *Tetrahedron Lett.* **1978**, *14*, 1239.

(5) Concurrent with the work being reported here, Fox and co-workers have developed an alternative kinetic resolution strategy to cyclopropenes containing quaternary stereocenters: Fox, J. personal communication.

(6) Davies, H. M. L. *Curr. Org. Chem.* **1998**, *2*, 463.

(7) (a) Davies, H. M. L.; Bruzinski, P.; Hutcheson, D. K.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897. (b) Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1.

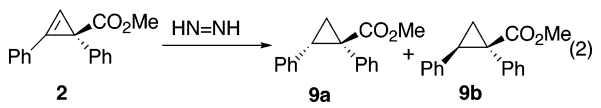
(8) Davies, H. M. L. In *Advances in Cycloaddition*; Haramata, M. E., Eds.; JAI Press: Greenwich, CT, 1999; Vol. 5, pp 119−164.

(9) Davies, H. M. L.; Xiang, B.; Kong, N.; Stafford, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 7461.

(10) (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (b) Davies, H. M. L. *J. Mol. Catal. A: Chem.* **2002**, *189*, 125.

(11) Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, *2459*, 9.

can also be conducted on 1-hexyne, but with slightly diminished yield and enantioselectivity (entry 7).

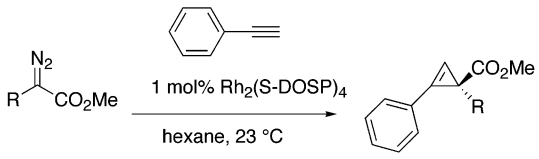


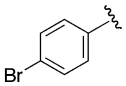
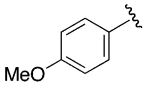
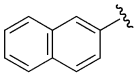
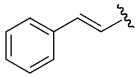
2 9a 9b

The absolute configuration of **2** was determined to be (*R*) by hydrogenation of **2** with diimide.[4a] Addition of hydrogen to **2** gave a 1:1 mixture of diastereomers **9a** and **9b**, in which the optical rotation for **9a** ($[\alpha]^{25}_{D}$ −20.0, *c* 0.15, $CHCl_3$, 90% ee) confirmed it was the (1*R*,2*R*) cyclopropane (lit.[7] $[\alpha]^{25}_{D}$ −28.5, *c* 1.1, $CHCl_3$, 89% ee). The absolute configuration of **3**−**8** is assigned as (*R*) by analogy to **2**.

The cyclopropenation can be extended to a range of aryldiazoacetates (Table 2). In most cases, the yields are in the 50−65% range, but the *p*-methoxy derivative **11** was formed in much lower yield (24%), presumably reflecting the lower reactivity of the *p*-methoxyphenyl carbenoid. Normally, the methyl styryldiazoacetate is an exceptional source of a donor/acceptor carbenoid,[7a] but its reaction with phenylacetylene failed to produce cyclopropene **14**. The failure of this reaction may be due to the instability of the product rather than an inherent problem with the reaction itself.

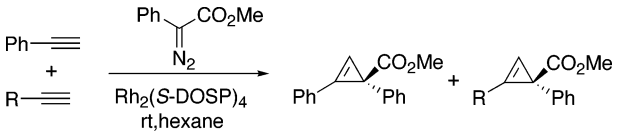
Table 2. Rh_2(*S*-DOSP)$_4$-Catalyzed Enantioselective Cyclopropenation of Phenylacetylene with Various Aryl- and Vinyldiazoacetates[12]



entry	R[a]	product	yield (%)	ee (%)
1		**2**	62	90
2		**10**	62	86
3		**11**	24[b]	66[b]
4		**12**	55	86
5		**13**	57	88
6		**14**	0	-

[a] 2.5−10 equiv of alkyne was used. See the Supporting Information for details. [b] 2 mol % catalyst was used.

Table 3. Relative Reactivity of Alkynes



R	relative rate vs phenylacetylene
p-$MeOC_6H_4$	5.9
p-EtC_6H_4	1.9
p-ClC_6H4	1.1
n-Bu	0.06

The cyclopropanation chemistry of donor/acceptor-substituted carbenoids is very distinctive because it is highly chemoselective.[7] A Hammett study on relative rates of reactivity of methyl phenyldiazoacetate with different styrenes showed a very close correlation to the σ^+ scale and indicated that buildup of positive charge at the benzylic carbon occurred in the transition state ($\rho = -1.0$).[13] To determine if the cyclopropenation reaction displayed a similar level of chemoselectivity, competition reactions were conducted between different alkynes (Table 3). The electron-rich *p*-methoxyphenylacetylene was the most reactive while 1-hexyne was 18 times less reactive than phenylacetylene. Thus, the electronic influence on cyclopropenation by the donor/acceptor-substituted carbenoids is very similar to the results observed for cyclopropanation.

A major mechanistic issue relating to the reactions of the donor/acceptor-substituted carbenoids is the trajectory of attack of the trapping species. In our earlier model for cyclopropanation by the donor/acceptor-substituted carbenoids, the alkene was considered to approach the rhodium carbenoid in a side-on manner,[7] but more recent kinetic isotope and modeling studies indicated that an end-on approach is more likely.[14] The cyclopropenation chemistry was considered to be a good test for the trajectory of approach of the alkyne because cyclopropenation of 1,2-disubstituted alkynes would appear to be impossible for a reaction occurring by an end-on approach because the alkyne substituent would collide with the catalyst surface, while the side-on approach would still be feasible (Figure 1).

To test this issue, cyclopropenation of 1-phenyl-1-propyne or 1,2-diphenylethyne was attempted. Neither substrate

(12) For the synthesis of diazo compounds, see: (a) Davies, H. M. L.; Huby, N. J. S.; Cantrell, W. R., Jr.; Olive, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 9468. (b) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063. (c) Davies, H. M. L.; Townsend, R. J. *J. Org. Chem.* **2001**, *66*, 6595.

(13) Davies, H. M. L.; Panaro, S. A. *Tetrahedron* **2000**, *56*, 4871.

(14) Nowlan, D. T.; Gregg, T. M.; Davies, H. M. L.; Singleton, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 15902.

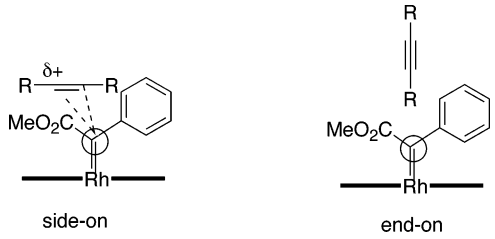
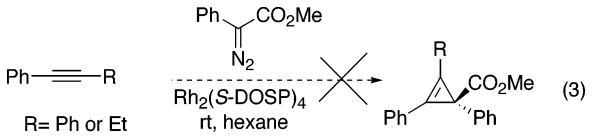


Figure 1. Comparison of side-on[7] and end-on[14] approaches for cyclopropenation.

generated any cyclopropene product. These results are in contrast to cyclopropenation reactions with ethyl diazoacetate, which does react with 1-phenylpropene.[4a,f] The total lack of reactivity of disubstituted alkynes is consistent with a reaction mechanism involving end-on approach.



In summary, these studies demonstrate that the Rh_2(*S*-DOSP)$_4$-catalyzed reactions of aryldiazoacetates with 1-substituted alkynes results in the enantioselective synthesis of cyclopropenes containing quaternary centers. This work expands the range of readily available chiral cyclopropenes, which can be used as chiral building blocks for organic synthesis.

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Supporting Information Available: Full experimental data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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