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Enantioselective Synthesis of Cyclopropylphosphonates Containing Quaternary Stereocenters Using a D_2-Symmetric Chiral Catalyst Rh_2(*S*-biTISP)$_2$

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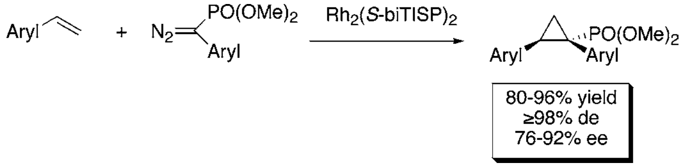
ABSTRACT



Rh_2(*S*-biTISP)$_2$-catalyzed reactions of dimethyl aryldiazomethylphosphonates generate donor/acceptor-substituted rhodium carbenoid intermediates capable of cyclopropanation of styrenes in high yields (85–96%), diastereoselectivity (≥98% de), and enantioselectivity (76–92% ee).

Cyclopropylphosphonates and cyclopropylphosphonic acids have been extensively studied, and several members display interesting biological activity. They have been used as mimics of 1-aminocyclopropane carboxylic acid (ACC) with a high inhibitory activity for the ACC-deaminase and alanine racemase,[1] as analogues of (−)-allonorcoronamic acid,[2] as structural moieties of nucleotides,[3] as potential herbicides or plant growth regulators,[4] as potential insecticides,[5] as phosphonic analogues of the antidepressant minalcipran,[6] and as a constrained analogue of the GABA antagonist phaclophen.[7]

A variety of methods have been developed to prepare cyclopropylphosphonates such as the phosphonylation of halogenated cyclopropanes,[8] the cyclopropanation of vinylphosphonates,[9] electrochemical methods,[10] the addition of phosphates to iminium salts,[11] fragmentation and rearrangement of epoxyethylphosphonates,[12] alkylation of benzylphosphonate carbanions with 1,2-dibromoethane,[13] and the addition of fumarates to phosphonylated sulfonium ylides.[14]

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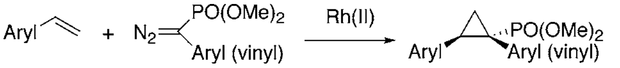
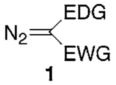
One very common method for the enantioselective synthesis of cyclopropanes, the meal-catalyzed decomposition of diazo compounds in the presence of alkenes,[15] has not been extensively applied to the synthesis of cyclopropylphosphonates.[16] A few publications exist on the racemic synthesis of cyclopropylphosphonates by means of copper-, rhodium-, or ruthenium-catalyzed cyclopropanations.[16a,g,h,i] Hanson and co-workers have explored enantioselective intramolecular cyclopropanations,[16c,d−f] but, as far as we are aware, only a single example of an enantioselective intermolecular cyclopropanation is known (reaction of diisopropyl diazomethylphosphonate with styrene resulting in cyclopropanation in 33% ee).[16j] In this paper, we describe a general method for the enantioselective synthesis of cyclopropylphosphonates containing a quaternary stereocenter using D_2-symmetric dirhodium complexes as catalysts (eq 1).



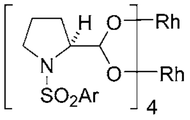
(1)

For some time, we have been exploring the chemistry of donor/acceptor-substituted rhodium-carbenoids (**1**) because these intermediates are capable of undergoing some spectacular transformations.[15,17] Unlike the more conventional carbenoids functionalized with only acceptor groups, these carbenoids undergo highly diastereoselective cyclopropanations[15] and chemoselective intermolecular C−H insertions[17] and are less prone to undergo formation of carbene dimers.[18] Furthermore, when the reactions are catalyzed by the rhodium prolinate catalyst $Rh_2(S\text{-DOSP})_4$ (**2**) or the second-generation bridged catalyst $Rh_2(S\text{-biTISP})_2$ (**3**), the reactions are generally highly enantioselective.[19] Due to the success of these donor/acceptor-substituted carbenoids, efforts have been made to expand the range of donor and acceptor groups that are compatible with this chemistry.[20] These studies demonstrate that the use of a dimethyl phosphonate group as the acceptor group instead of the usual methyl ester still enables highly stereoselective cyclopropanations to be achieved.



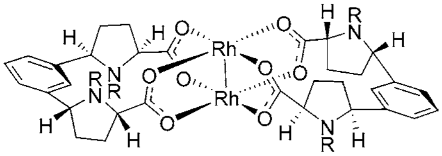
1

EDG = Aryl, vinyl, alkynyl
EWG = CO_2Me



Ar = p-$C_{12}H_{25}C_6H_4$

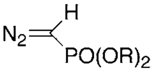
2: $Rh_2(S\text{-DOSP})_4$



R=SO_2-2,4,6-tri^{i}PrC_6H_2

3: $Rh_2(S\text{-biTISP})_2$

Even though most of the published cyclopropanation studies have been conducted with dialkyl diazomethylphosphonate (**4**), the seminal studies reported by Seyferth did also describe the reactions of dialkyl phenyldiazomethylphosphonate (**5**).[16a] The diastereoselectivity of the cyclopropanation with **5** was not measured; however, the reaction with **4** was found to be prone to undergo formation of carbene dimer, while the reaction with **5** was not. From our studies on donor/acceptor-substituted carbenoids,[15,17] it is now clear that the lack of dimer formation is a characteristic sign that the carbenoid derived from **5** is likely to be highly chemoselective.



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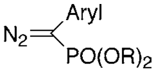
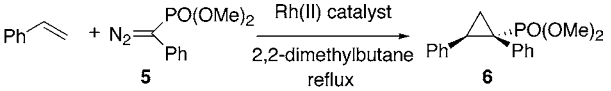


5

To evaluate the role of the phosphonate group, the rhodium-catalyzed decomposition of dimethyl phenyldiazomethylphosphonate (**5**) was examined in the presence of styrene. As $Rh_2(S\text{-DOSP})_4$-catalyzed reactions of donor/acceptor-substituted carbenoids tend to give the highest enantioselectivity when hydrocarbons are used as a solvent,[21] the reactions were conducted in 2,2-dimethylbutane. The phosphonate **5** is far less reactive toward metal-catalyzed nitrogen extrusion than the corresponding ester, which means the ideal reaction conditions required heating under reflux. Under these conditions, the $Rh_2(S\text{-DOSP})_4$-catalyzed cyclopropanation was effective (69% yield) and highly diastereoselective (95% de) but the enantioselectivity was poor (34% ee). Consequently, the reaction was repeated with $Rh_2(S\text{-biTISP})_2$, and this gave a much better result. The cyclopropane **6** was formed with much higher stereoselectivity (98% de, 88% ee) (Scheme 1).

Scheme 1



cat.	yield(%)	de(%)[a]	ee(%)[b]
$Rh_2(S\text{-DOSP})_4$	69	95	34
$Rh_2(S\text{-biTISP})_2$	89	98	88

[a] Determined by the ^1H NMR of the crude mixture. [b] Ee determined by chiral HPLC. See Supporting Information for details.

The reaction of **5** was applied to a range of alkenes as summarized in Table 1. Styrene derivatives and 1-phenyl-

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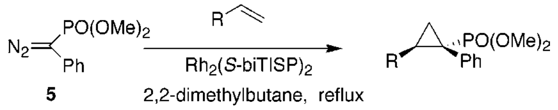
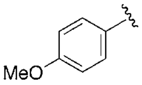
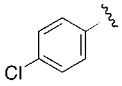
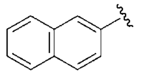
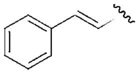
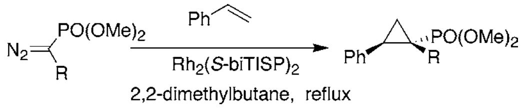
Table 1. Rh_2(*S*-biTISP)$_2$-Catalyzed Enantioselective Cyclopropanation by **5**

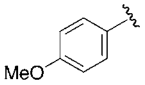
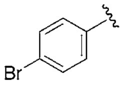
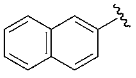
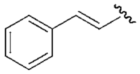


R	product	yield, %	de, %[a]	ee, %[b]
	**7**	93	98	89
	**8**	95	98	85
	**9**	93	98	87
	**10**	96	>98	83
$CH_3(CH_2)_3O$	**11**	91	44	86 (maj) 2 (min)
$CH_3(CH_2)_3$	**12**	6	98	98

[a] Determined by the ^1H NMR of the crude mixture. [b] Ee determined by chiral HPLC. See Supporting Information for details.

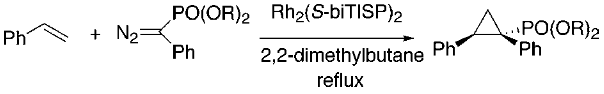
Table 2. Rh_2(*S*-biTISP)$_2$-Catalyzed Enantioselective Cyclopropanation of Styrene with Various Aryl- and Vinyldiazomethylphosphonates[22]



R	product	yield, %	de, %[a]	ee, %[b]
	**13**	84	>98	92
	**14**	80	98	89
	**15**	85	>98	76
	**16**	76	>98	68

[a] Determined by the ^1H NMR of the crude mixture. [b] Ee determined by chiral HPLC. See Supporting Information for details.

Scheme 2



R	product	yield(%)	de(%)[a]	ee(%)[b]
Me	**6**	89	98	88
Et	**17**	85	>98	75
i-Pr	**18**	61	>98	61

[a] Determined by the ^1H NMR of the crude mixture. [b] Ee determined by chiral HPLC. See Supporting Information for details.

butadiene were exceptional substrates resulting in the formation of the cyclopropanes **7**−**10** with very high yields (93−96%), diastereoselectivity (≥98% de), and enantioselectivity (83−89% ee). In contrast, the reaction with butyl vinyl ether was not highly diastereoselective and only the major diastereomer was produced in high enantioselectivity (86% ee). Electron-rich alkenes are required for effective cyclopropanation, as the reaction with 1-hexene was very low-yielding.

The cyclopropanation can be extended to a range of aryl- and vinyldiazophosphonates as illustrated in Table 2. Once again, all the reactions proceeded in high yield (76−85%) and diastereoselectivity (≥98% de), while the enantioselectivity varied from 68 to 92% ee.

One of the most distinctive features of the cyclopropanation chemistry of the vinyldiazoacetates is the effect of the size of the ester group on the stereoselectivity. The diastereoselectivity is not greatly influenced by ester size, but in the Rh_2(*S*-DOSP)$_4$-catalyzed cyclopropanations, the enantioselectivity decreases as the size of the ester increases.[21] Consequently, it was of interest to explore the effect of phosphonate size on the stereoselectivity of Rh_2(*S*-biTISP)$_2$-catalyzed reactions. As can be seen in Scheme 2, the steric influence in the phosphonate series runs parallel to the ester series. The diastereoselectivity is independent of the size of the phosphonate, while the enantioselectivity steadily decreases on increasing phosphonate size.

The relative configuration of the cyclopropanes is readily assigned on the basis of the distinctive shielding by a *cis*-aryl substituent on the adjacent dialkyl phosphonyl group. The high preference for the formation of the (*E*)-cyclopropanes is a distinctive characteristic of the donor/acceptor-substituted rhodium carbenoids.[21] The absolute configuration of **14** was determined by X-ray crystallography to be (1*S*,2*S*),[23] and the absolute stereochemistry of these cyclopropanations is the same as the Rh_2(*S*-biTISP)$_2$-catalyzed cyclopropanations of aryldiazoacetates.[24]

The cyclopropanation chemistry of vinyldiazoacetates with dienes is a very effective method for the construction of seven-membered carbocycles.[25] The styryldiazomethylphosphonate **19** is capable of a similar [4 + 3] cycloaddition as illustrated in the reaction with 1-phenylbutadiene (Scheme 3). The Rh_2(*S*-biTISP)$_2$-catalyzed generates the cyclohepta-

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(22) See Supporting Information for the synthesis of the diazomethylphosphonates.

(23) X-ray crystallographic data have been submitted to the Cambridge Structural Database [Gerlits, O. O.; Coppens, P. Private communication].

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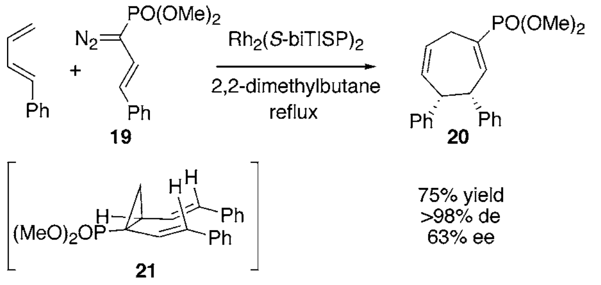
Scheme 3



diene **20** as a single diastereomer in 63% ee. The formation of a single diastereomer is readily rationalized by the involvement of **21**, the intermediate of a tandem cyclopropanation/Cope rearrangement.[25]

In summary, the asymmetric cyclopropanation chemistry of arylphosphonyldiazoalkanes catalyzed by Rh_2(*S*-biTISP)$_2$ occurs in a highly stereoselective manner. Additionally, the first example of a tandem asymmetric cyclopropanation/Cope rearrangement using a vinylphosphonyldiazoalkane has been achieved. These studies broaden the range of available donor/acceptor-substituted rhodium carbenoid systems.

Acknowledgment. Financial support of this work by the National Science Foundation (CHE-0350536) is gratefully acknowledged. We thank Miss Oksana O. Gerlits for the X-ray crystallographic analysis.

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

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