Stereoselective construction of nitrile-substituted cyclopropanes†‡

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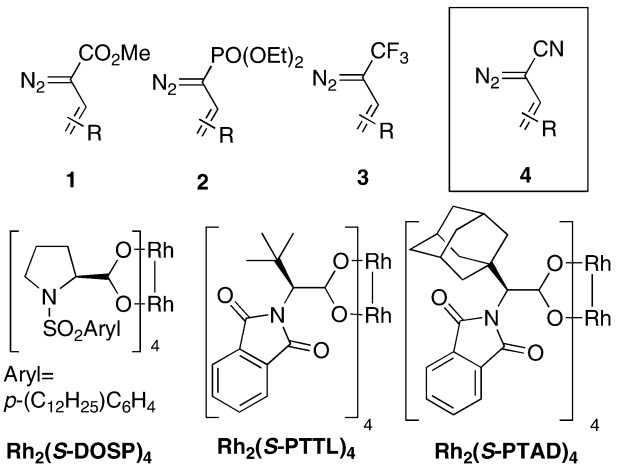
Nitrile-substituted cyclopropanes are readily synthesized in a stereocontrolled fashion from the intermolecular cyclopropanation between 2-diazo-2-phenylacetonitrile and electron-rich olefins, catalyzed by the chiral dirhodium complex, Rh_2(*S*-PTAD)$_4$.

Rhodium carbenoids, derived from diazo compounds, are versatile synthetic intermediates, capable of a range of useful transformations, such as cyclopropanation, C–H insertion and ylide formation.[1] It has become increasingly evident that the structure of the carbenoid greatly influences the outcome of this chemistry.[2] Most notably, donor/acceptor-substituted carbenoids are capable of a much wider range of selective transformations than the other classes of carbenoids.[3] A distinctive feature of the cyclopropanation chemistry of donor/acceptor-substituted carbenoids is the high diastereoselectivity exhibited with virtually all substrates.[4] Most of the early examples of donor/acceptor carbenoids use a methyl ester as the acceptor group,[2,4] and Rh_2(*S*-DOSP)$_4$ has been found to be an exceptional chiral catalyst for this system (**1**). Recent studies have been directed towards exploring the scope with other types of donor/acceptor systems such as the phosphonate **2**[5] and the trifluoromethyl derivative **3**.[6] Rh_2(*S*-DOSP)$_4$ is not an effective chiral catalyst with these systems but the new catalyst, Rh_2(*S*-PTAD)$_4$,[5b] circumvented this problem. In this communication, we describe the effect of chiral catalysts on the cyclopropanation reactions of donor/acceptor-substituted diazo compounds **4** where the acceptor group is a cyano group.



Donor/acceptor carbenoids containing a cyano group are not only of synthetic interest, but also offer further insight into the postulated mechanism of the cyclopropanation. Theoretical and kinetic isotope studies have led to the proposal that the cyclopropanation occurs in a concerted non-synchronous manner with the alkene approaching in a side-on manner (Fig. 1).[7] The high diastereoselectivity is considered to be due to the bulky nature of the electron-withdrawing group, which avoids destabilizing the electrophilic carbenoid by aligning out of the plane of the rhodium carbene π-bond.[7a] In the case of the diazo compounds **4**, the cyano group is not sterically bulky, and how this would influence the diastereoselectivity has been an interesting question.[7]

Several methods have been developed to synthesize nitrile-substituted cyclopropanes,[8] including the metal-catalyzed intermolecular cyclopropanation by α-diazoacetonitriles.[9] α-Diazoacetonitriles containing a donor group have not been extensively studied and the reported cyclopropanations with α-diazoacetonitriles lacking a donor group have proceeded with variable diastereoselectivity and up to 70% ee.[9c]

2-Diazo-2-phenylacetonitrile (**5**)[10] was used as the prototypical substrate in these studies. As a test reaction, the cyclopropanation of styrene was examined using the most generally effective chiral catalysts for the reactions of donor/acceptor substituted carbenoids, Rh_2(*S*-DOSP)$_4$, Hashimoto's Rh_2(*S*-PTTL)$_4$,[11] and Rh_2(*S*-PTAD)$_4$ (Table 1). All three catalysts gave high yield of the cyclopropane **6a** and good diastereocontrol (~95 : 5 dr), although the diastereoselectivity was lower than what had been observed with other types of donor/acceptor carbenoids.[4–6] Rh_2(*S*-DOSP)$_4$ gave relatively low enantioinduction (34% ee), while Rh_2(*S*-PTTL)$_4$, and Rh_2(*S*-PTAD)$_4$ gave far superior results (90% ee). The optimal conditions were 2 mol% of catalyst in toluene at −78 °C followed by slowly warming to room temperature. At higher temperature, the enantioselectivity was significantly lower, and erosion of enantioselectivity was also observed when just 1 mol% of catalyst was used.

The carbenoid reaction of **5** was applied to a range of olefins using Rh_2(*S*-PTAD)$_4$ as catalyst and the results are

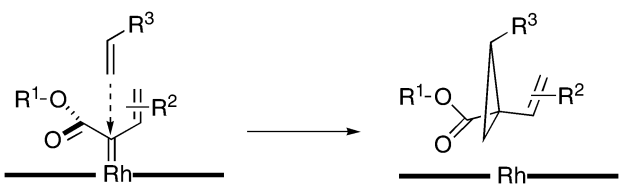


Fig. 1 The model for concerted non-synchronous cyclopropanation.

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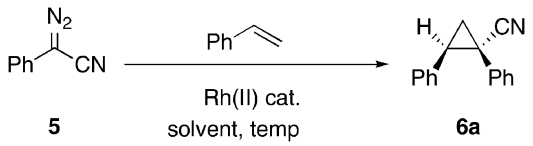
† CCDC 654356. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b719175h
‡ Electronic supplementary information (ESI) available: Experimental details for the synthesis of all new compounds. See DOI: 10.1039/b719175h

Table 1 2-Diazo-2-phenylacetonitrile in intermolecular cyclopropanation of styrene



5 6a

Rh(II) cat.	Loading	Solvent	Temp.	Yield[a] (%)	dr[b]	ee[c] (%)
Rh_2(*S*-PTAD)$_4$	2 mol%	TFT	rt	83	93 : 7	65
Rh_2(*S*-PTAD)$_4$	2 mol%	Toluene	rt	77	89 : 11	60
Rh_2(*S*-DOSP)$_4$	2 mol%	Toluene	−78 °C	85	95 : 5	34
Rh_2(*S*-PTTL)$_4$	2 mol%	Toluene	−78 °C	84	96 : 4	90
Rh_2(*S*-PTAD)$_4$	2 mol%	Toluene	−78 °C	86	97 : 3	90
Rh_2(*S*-PTAD)$_4$	1 mol%	Toluene	−78 °C	80	97 : 3	85

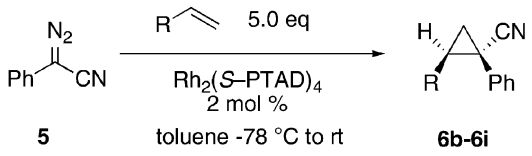
[a] Yield obtained after purification using flash chromatography. [b] Dr as judged by ^{1}H NMR spectroscopy before purification. [c] Ee as determined by chiral HPLC. TFT = α,α,α,-Trifluorotoluene.

summarized in Table 2. Styrenes were very effective substrates, generating cyclopropanes **6b–g** in high yields (80–89%), high diastereoselectivity (95 : 5 to >97 : 3 dr) and moderate to high enantioselectivity (78–90% ee). The lowest enantioselectivity was obtained with the most electron-rich styrene, which might be expected as this would be the most reactive substrate. The trend is the same as seen with vinyl diazoacetates and aryl diazoacetates.[4b,c] Extension of the study to *n*-butyl vinyl ether resulted in a dramatic drop in diastereoselectivity. The cyclopropane **6h** was formed as a 62 : 38 mixture of diastereomers, although the enantioselectivity remained moderate (80% ee (major) and 79% ee (minor)). Very low diastereoselectivity was also observed in the reaction with vinyl acetate, and indeed, in this case the slightly preferred diastereomer was the (*Z*) isomer of cyclopropane **6i**, while the enantioselectivity remained high (92% ee). The last result is markedly different from the reaction of the diazo compound **1**, which gave highly diastereoselective reactions with vinyl ethers.[4b,c] Attempted reactions with electron-neutral substrates such as 1-hexene gave very low yields of cyclopropanes.

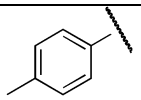
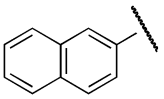
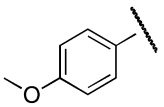
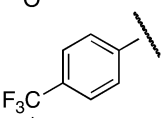
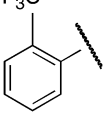
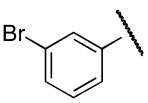
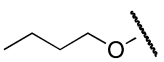
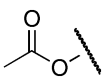
One of the most distinctive aspects of the cyclopropanation reactions with donor/acceptor carbenoids is that the diastereoselectivity is generally not sensitive to catalyst structure.[12] The reaction of **5** with 2,3-dihydrofuran did not follow this trend (Scheme 1).[12] The reaction catalyzed by Rh_2(*S*-PTAD)$_4$ gave the cyclopropane **7** in a 91 : 9 ratio of diastereomers while the reaction catalyzed by Rh_2(*S*-DOSP)$_4$ gave virtually a 1 : 1 dr of **7**. The enantioselectivity for the formation of **7** with either catalyst was very low (<15% ee).

Due to the variable stereoselectivity in these reactions, efforts were made to unambiguously verify the stereochemical assignments. The bromocyclopropane **6g** was enriched to >98% ee by recrystallization from absolute ethanol. X-Ray crystallographic analysis determined the relative and absolute configurations to be 1*S*,2*R* (Fig. 2).[13] The relative configuration of the other cyclopropanes were readily assigned by a distinctive 0.3–0.4 ppm shielding of the C-2 proton when *cis* to the C-1 phenyl. The absolute configuration of the other cyclopropanes is tentatively assigned by analogy to **6g**.

Table 2 Intermolecular cyclopropanation of electron-rich olefins

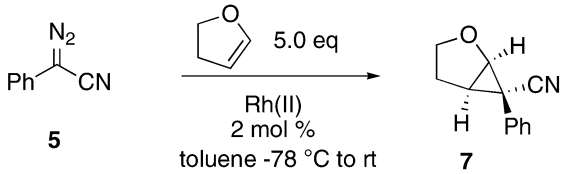


5 6b-6i

Entry	R	Yield[a] (%)	dr[b]	ee[c] (%)
6b		80	97 : 3	83
6c		89	>97 : 3	84
6d		82	95 : 5	78
6e		80	96 : 4	90
6f		83	95 : 5	83
6g		84	>97 : 3	90
6h		88[d]	62 : 38	80 (major), 79 (minor)
6i		90[d]	46 : 54	92 (major), 74 (minor)

[a] Yield obtained after purification using flash chromatography. [b] Dr (*E* : *Z*) as judged by ^{1}H NMR spectroscopy before purification. [c] Ee as determined by chiral HPLC. [d] Combined yield of diastereomers.

The diastereoselectivity observed in these studies offer interesting insights into rhodium carbenoid chemistry. The reactions with styrenes gave high diastereoselectivity, even though it would have been predicted that the small cyano acceptor group would be unable to influence the reaction in such a way.[7] In the case of alkenes lacking an aryl substituent the diastereoselectivity was very low. As the cyano group would



5 7

Rh_2(*S*-PTAD)$_4$: yield 84%; dr 91:9; 12% ee
Rh_2(*S*-DOSP)$_4$: yield 45%; dr 58:42; 9% ee

Scheme 1 Cyclopropanation of 2,3-dihydrofuran.

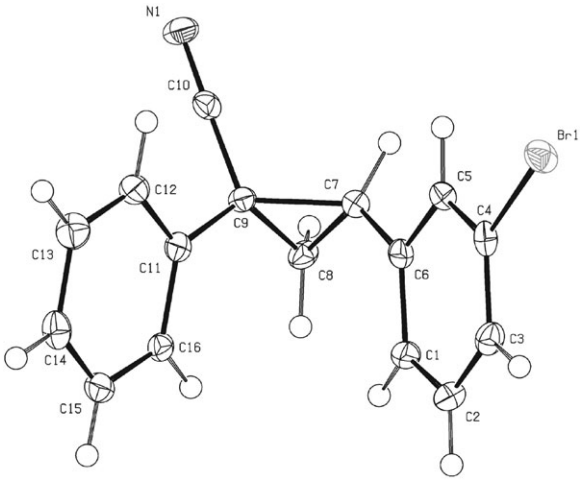


Fig. 2 X-Ray crystal structure of **6g**.

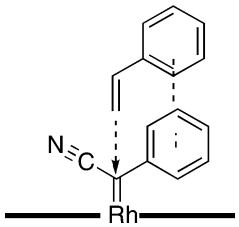


Fig. 3 The proposed charge-transfer complex.

not be blocking approach of the alkene, a reasonable explanation for the high diastereoselectivity with styrenes would be the occurrence of an attractive π stacking interaction between the aryl rings during the cyclopropanation (Fig. 3). This would also explain the extremely high diastereoselectivity observed in styrene cyclopropanations with diazo compounds **1–3**, as the carbenoid in these cases would block approach of the substrate over the acceptor group[7] *and* have an attracting π stacking interaction with the donor group.

In summary, the intermolecular cyclopropanation reactions of 2-diazo-2-phenylacetonitrile with various styrene derivatives afforded the nitrile-substituted cyclopropanes in high yield, high diastereoselectivity, and with moderate to high enantioselectivity. These studies underscore the importance of having both donor and acceptor groups on the carbenoid for diastereoselective cyclopropanation reactions, and suggest that even a small acceptor group such as cyano can be effective due to attractive π stacking interactions at the donor group.

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Notes and references

§ *General cyclopropanation procedure*: To a flame-dried round bottom flask under argon, equipped with a stir bar, was added toluene, the electron rich olefin (5.0 equiv., ~1.0 M solution), and the Rh(II) catalyst (2 mol%). The green solution was then cooled to −78 °C and the diazo compound solution of **5** (1.0 equiv. in toluene, ~0.1 M) was then added dropwise over 15 min. The resulting orange solution was then allowed to warm to room temperature over 6 h. After which, the resulting green solution was then concentrated *in vacuo* and the dr was determined by ^{1}H NMR. The crude cyclopropane was then further purified by column chromatography and the ee of the pure cyclopropane was determined by chiral HPLC.

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