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Selectivity Enhancement in the Rh(II)-Catalyzed Cyclopropanation of Styrene with (Silanyloxyvinyl)diazoacetates

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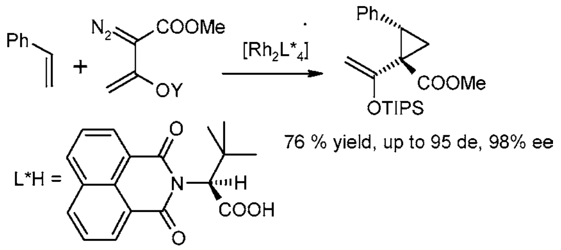
ABSTRACT



76 % yield, up to 95 de, 98% ee

The cyclopropanation of styrene with (silanyloxyvinyl)diazoacetates proceeds with exceptional diastereo- and enantioselectivity in the presence of chiral Rh(II) catalysts. 1,8-Naphthoyl-protected amino acids are the most effective Rh(II) ligands for these transformations.

The intermolecular cyclopropanation of olefins with phenyl-[1] and vinyldiazoacetate[2] esters in the presence of the [$Rh_2\{(S)\text{-dosp}\}_4$] catalyst of Davies[3] proceeds with remarkable diastereo- and enantioselectivities. The dosp catalyst is, however, less suited for intermolecular cyclopropanations with (silanyloxyvinyl)diazoacetates. Thus, an ee of only 26% has been reported for the cyclopropanation of *n*-butyl vinyl ether, although the selectivity for cyclopropanation of 2,3-dihydrofuran and β-methoxystyrene reached 67 and 71% de, respectively, when pantolactone was used as a chiral auxiliary in conjunction with [$Rh_2\{(S)\text{-dosp}\}_4$].[4] Recently, we have examined the suitability of (*S*)-*N*-1,8-naphthoyl-*t*-leucine as ligand for Rh(II)-catalyzed asymmetric carbene transfer. Encouraging enantioselectivities of up to 79% were observed with the resulting [$Rh_2\{(S)\text{-nttl}\}_4$] catalyst in intramolecular CH insertions of α-silylated diazoacetate esters.[5]

We have now investigated the intermolecular cyclopropanation of styrene (**1a**) with the (silanyloxyvinyl)-diazoacetates **2a** and **2b** in the presence of Rh(II) catalysts. Reaction of **2a** (X = TBDMS) with catalytic [$Rh_2(OAc)_4$] in CH_2Cl_2 afforded *trans*-**3a** in 59% yield. The cis config-

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(1) (a) Davies, H. M. L.; Bruzinski, P. R.; Fall, M. J. *Tetrahedron Lett.* **1996**, *37*, 4133−4136. (b) Doyle, M. P.; Thou, Q.-L.; Charnsagevej, C.; Longoria, M. A.; McKervey, M. A.; Garcia, C. F. *Tetrahedron Lett.* **1996**, *37*, 4129−4133.

(2) (a) Davies, H. M. L. *Aldrichimica Acta* **1997**, *30*, 107−114. (b) Davies, H. L. M.; Xiang, B.; Kong, N.; Stafford, D. G. *J. Am. Chem. Soc.* **2001**, 123, 7461−7462. (c) Davies, H. M. L.; Boebel, T. A. *Tetrahedron Lett.* **2000**, 41, 8189−8193. (d) Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1−326.

(3) (a) Davies, H. L. M.; Hutcheson, D. K. *Tetrahedron Lett.* **1993**, *34*, 7243−7247. (b) Davies, H. L. M.; Bruzinski, P. R.; Lake, D. H.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897−6907.

(4) Davies, H. M. L.; Ahmed, G.; Calvo, R. L.; Churchill, M. L.; Churchill, D. G. *J. Org. Chem.* **1998**, *63*, 2641−2645.

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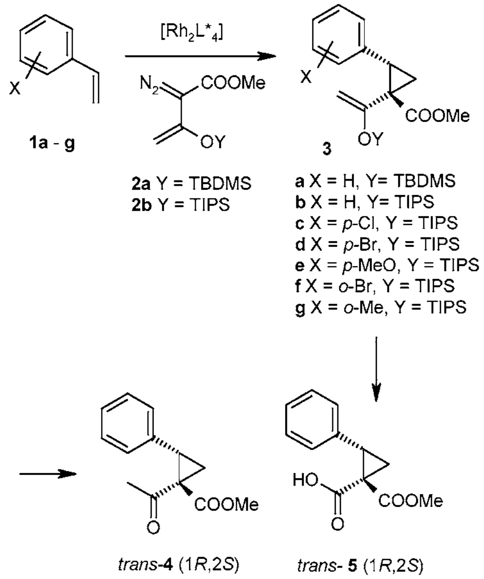
uration of the vinyl group with respect to the phenyl ring in **3a** was assigned by desilylation to *trans*-**4** of known configuration.[6] This diastereoselectivity is typical for Rh(II)-catalyzed cyclopropanations with vinyldiazoacetate esters.[2a]

Scheme 1. Cyclopropation of styrenes **1a**−**g** with silanoxyvinyldiazoacetates **2a**,**b**



A selection of chiral nonracemic Rh(II) catalysts were screened, and the results are summarized in Table 1. With [Rh_2\{(*S*)-nttl\}$_4$], the reaction proceeded with 83% ee in CH_2Cl_2, but the selectivity increased significantly to 91% in toluene. The cis isomer of **3a** could not be detected in the reaction mixture.

Table 1. Cyclopropanation of Styrene (**1a**) with **2a** (y = TBDMS) in the Presence of Rh(II) Catalysts[a]

solvent	catalyst	yield (%)	ee (%)
CH_2Cl_2	[$Rh_2OAc)_4$]	**3a** 59	
CH_2Cl_2	[Rh_2\{(*S*)-nttl\}$_4$]	**3a** 49	83
$PhCH_3$	[Rh_2\{(*S*)-nttl\}$_4$]	**3a** 60	91
CH_2Cl_2	[Rh_2\{(*R*)-ntv\}$_4$]	**3a** 69	83[b]
CH_2Cl_2	[Rh_2\{(*S*)-pttl\}$_4$]	**3a** 70	62
CH_2Cl_2	[Rh_2\{(*S*)-ptpa\}$_4$]	**3a** 82	41
CH_2Cl_2	[Rh_2\{(*S*)-bnp\}$_4$]	**3a** 65	32

[a] Conditions: 8.7 mmol of **1a**, 0.6 mmol of **2a** in the appropriate solvent (5.0 mL), 2 mol % catalyst, 25 °C. [b] *ent*-**3a**.

Other Rh(II) catalysts were less selective with **2a**; however, a new catalyst, [Rh_2\{(*R*)-ntv\}$_4$], which uses (*R*)-*N*-1,8-naphthoyl valinate as a ligand, was as efficient as [Rh_2\{(*S*)-nttl\}$_4$] and afforded the enantiomer of **3a** with 94%. The selectivity of [Rh_2\{(*R*)-ntv\}$_4$] is remarkable; apparently, the additional methyl group of [Rh_2\{(*S*)-nttl\}$_4$] is not significant for enantioselectivity in this particular reaction.

Replacement of the TBDMS in **2a** by the sterically more demanding TIPS group (i.e., **2b**) afforded the cyclopropanes **3b** in yields ranging from 72 to 86% (Table 2). As with **2a**, the reaction was highly diastereoselective, although the trans isomer of **3b** was detectable by NMR and GC. The stereoisomers of **3b** were not separable, so the ee and de of the reaction were determined with *trans*-**4**,[6] after cleavage of the silyl group with TBAF. The TIPS group led to an enantioselectivity of 94% ee in CH_2Cl_2 with [Rh_2\{(*S*)-nttl\}$_4$] at 0 °C, but no further improvement occurred when the reaction was carried out in toluene or in neat styrene. However, the ee increased to 98% (with 95% de) when the reaction was initiated at −78 °C and allowed to warm to room-temperature overnight. [Rh_2\{(*S*)-pttl\}$_4$] and [Rh_2\{(*S*)-ptpa\}$_4$] performed significantly better with **2b** than with **2a**, while [Rh_2\{(*R*)-ntv\}$_4$] was as effective as [Rh_2\{(*S*)-nttl\}$_4$] and gave 94% ee and 92% de. [Rh_2\{(*S*)-dosp\}$_4$], in turn, resulted in a significantly lower enantioselectivity of 81%, but with the highest de of 98.5%.

Table 2. Cyclopropanation of Styrene (**1a**) with **2b** (y = Tips) in the Presence of Rh(II) Catalysts[a]

solvent	catalyst	yield (%)	ee (%)	de (%)
$PhCH_3$	[Rh_2\{(*S*)-nttl\}$_4$]	**3b** 77	94	91
styrene[b]	[Rh_2\{(*S*)-nttl\}$_4$]	**3b** 72	94	nd
$PhCH_3$(c)	[Rh_2\{(*S*)-nttl\}$_4$]	**3b** 76	98	95
CH_2Cl_2	[Rh_2\{(*S*)-nttl\}$_4$]	**3b** 84	95	nd
styrene	[Rh_2\{(*R*)-ntv\}$_4$]	**3b** 77	94[d]	92[d]
$PhCH_3$	[Rh_2\{(*S*)-pttl\}$_4$]	**3b** 86	94	93
$PhCH_3$	[Rh_2\{(*S*)-ptpa\}$_4$]	**3b** 86	88	95
$PhCH_3$	[Rh_2\{(*S*)-dosp\}$_4$]	**3b** 84	81	98.5

[a] Conditions: 8.7 mmol of **1a**, 0.6 mmol of **2b** in the appropriate solvent (5.0 mL), 2 mol % catalyst, 0 °C. [b] In neat styrene (**1a**). [c] At −78 °C. [d] *ent*-**3b**.

Ozonolysis of a sample of *trans*-**3b** having 84% ee afforded the acid **5** with $[\alpha]^{24}_{D}$ −77 (c = 1.12, PhH, for

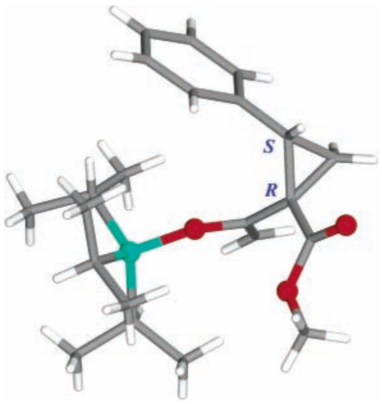


Figure 1. X-ray structure of **3b**.

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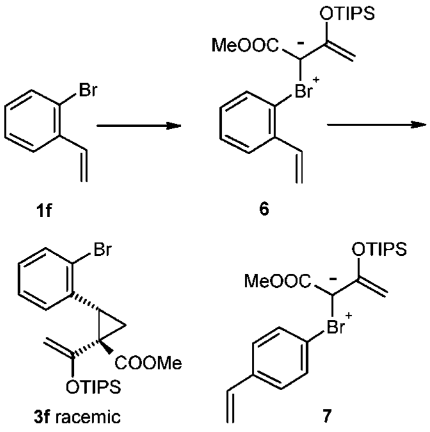
(6) (a) Batsila, C.; Kostakis, G.; Hadjarapoglou, L. P. *Tetrahedron Lett.* **2002**, 43, 5997−6000**.** (b) Jacoby, D.; Celerier, J.-P.; Haviari, G.; Petit, H.; Lhommet, G. *Synthesis* **1992**, 884−887.

Scheme 2. Cyclopropanation of *o*-Bromostyrene (**1f**) and *p*-Bromostyrene (**1d**) with **2b**



84% ee). The optical rotation of (1*R*,2*S*)-**5**, according to the literature is $[\alpha]^{24}_D$ −104 (*c* = 1.12, PhH, for >99% ee),[7] which allows assignment of the (1*R*,2*S*)-configuration to the cyclopropanes **3a** and **3b**, except the ones resulting from reaction with [Rh$_2${(*R*)-ntv}$_4$], where it is (1*S*,2*R*)-. The cyclopropane **3b**, resulting from reaction with [Rh$_2${(*S*)-nttl}$_4$], was subjected to X-ray analysis to confirm both relative and absolute configurations.[8,9]

Introduction of para substituents in the styrene had only a minor effect on the enantioselectivity. Thus, the *p*-chloro and the *p*-bromostyrenes were converted to the cyclopropanes **3c** and **3d** with 94 and 92% ee, respectively, in the presence of [Rh$_2${(*S*)-nttl}$_4$], while the *p*-methoxy substituent led to a slightly lower ee of 89% (Table 3). Surprisingly, however, a bromo substituent in ortho position of the styrene resulted in an almost racemic cyclopropane **3f**. Initially, we attributed this loss of selectivity to a steric effect. However, this hypothesis had to be abandoned when it was found that the cyclopropane **3g** resulting from reaction with *o*-methylstyrene (**2g**) had an ee of 91%. Thus, the low selectivity observed in the case of **3f** should not have a steric origin. Conceivably, an unselective competitive pathway could involve reaction of the metal-complexed carbene with the bromo substituent instead of the double bond, with formation of an intermediate ylide **6** that may dissociate from the metal.[10] The formation of ylides between carbenes and organohalides is well documented.[11] If direct intramolecular transfer of the carbene from ylide **6** to the double bond occurs without intervention of the chiral catalyst, the resulting cyclopropane **3f** will be racemic. The analogous reaction of *p*-bromostyrene (**1d**) may afford the ylide **7**. Since the cyclopropanation of **1d** is enantioselective, this suggests that either the pathway involving **7** is not significant or carbene transfer of **7** must involve the catalyst. Asymmetric carbene transfer from isolable phenyliodonium ylides, although not from bromonium ylides, has been reported in the past with Rh(II) and Cu(I) catalysts.[12]

Table 3. Cyclopropanation of Substituted Styrenes (**1c**−**g**) with **2b** (y = Tips) in the Presence of [Rh$_2${(*S*)-nttl}$_4$] as the Catalyst[a]

compd	X	catalyst	yield (%)	ee (%)[b]
1c	*p*-Cl	[Rh$_2${(*S*)-nttl}$_4$]	**3c** 77	94
1d	*p*-Br	[Rh$_2${(*S*)-nttl}$_4$]	**3d** 70	92
1e	*p*-MeO	[Rh$_2${(*S*)-nttl}$_4$]	**3e** 80	89
1f	*o*-Br	[Rh$_2${(*S*)-nttl}$_4$]	**3f** 71	11
1g	*o*-Me	[Rh$_2${(*S*)-nttl}$_4$]	**3g** 84	91

[a] Conditions: 8.7 mmol of **1a**−**g**, 0.6 mmol of **2b** in PhCH$_3$ (5.0 mL), 2 mol % catalyst, 0 °C. [b] Cis isomer not identified.

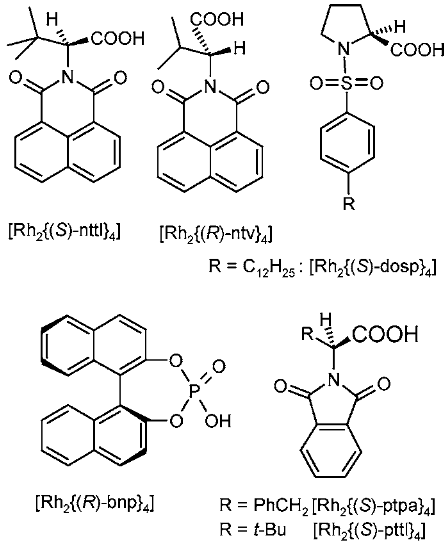


Figure 2. Ligands L*H for Rh(II)-catalyzed cyclopropanations.

The performance of the vinyldiazoacetate **2** in conjunction with [Rh$_2${(*S*)-nttl}$_4$] may be appreciated in the light of

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[7] Corey, E. J.; Gant, T. G. *Tetrahedron Lett.* **1994**, *35*, 5373−5376.

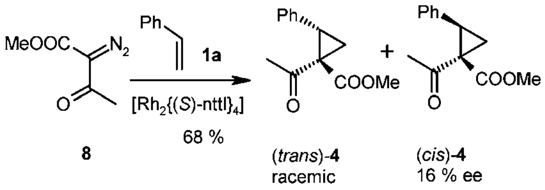
[8] Crystal data for **3b**: $C_{22}H_{34}O_3Si$, M_r = 374.6; μ = 0.12 mm^{-1}, d_x = 1.132 g/cm^3, trigonal, *P*32, Z = 3, *a* = 15.3674(9), *c* = 8.0593(4) Å, *V* = 1648.3(2) Å^3; *F*(000) = 612, θ_{max} = 26.02°, crystal size = 0.17 × 0.21 × 0.28 mm. Cell dimensions and intensities were measured at 200 K on a Stoe IPDS diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). Data were corrected for Lorentz and polarization effects and for absorption (T_{min}, T_{max} = 0.9690, 0.9854). The structure was solved by direct methods (SIR97). A total of 20 679 reflections collected and 16 215 reflections with $I > 2u(I)$, not merged (on account of twinning), were used in the full-matrix least-squares (|*F*|2) refinement (SHELXL97), *S* = 0.862, R_1 = 0.0348 (all data = 0.0498), wR_2 = 0.0694 (all data) for 242 parameters. Largest residual peak (hole) 0.169 (−0.127) e/Å^3. The crystal shows twinning by a 180° rotation about $[\bar{1}10]$ and displaying a volume ratio of 0.564(1)/0.436(1) of the two domains. The Flack parameter (*x* = 0.05(6)) was estimated from a refinement taking into account the eight possible twin laws associated to the space group *P*3$_2$ with respect to its holohedry as described by H. D. Flack and G. Bernardinelli.[9] Full details are given in the CIF file (CCDC 230695) containing the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.; fax: (+ 44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[9] Flack, H. D.; Bernardinelli, G. *Acta Crystallogr.* A **1999**, *55*, 908−915.

[10] Hodgson, D. M. *Chem. Soc. Rev.* **2001**, 30, 50−61.

[11] (a) Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 5094−5102. (b) Doyle, M. P.; *Acc. Chem. Res.* **1986**, *19*, 348−356.

Scheme 3. Cyclopropanation of Styrene (**1a**) with Methyl 2-Diazoacetoacetate (**8**)



carbene transfer from methyl diazoacetoacetate **8** to styrene (**1a**) with the same catalyst. The reaction afforded a 68% yield of a diastereoisomeric mixture of racemic *trans*-**4** and enantioenriched *cis*-**4** with 16% ee, in a 1:8 ratio.

These results demonstrate again the high enantioselectivity that may be achieved in carbene transfer with diazoacetates carrying electron-donating substituents.[13] Further applications of these carbene precursors with Rh(II) catalysts based on 1,8-naphthoyl imides are in progress in our laboratory.

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Supporting Information Available: Experimental procedure, product characterizaion, and synthesis of [Rh_2{(R)-ntv}$_4$]. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) Müller, P.; Allenbach, Y.; Robert, E. *Tetrahedron: Asymmetry* **2003**, 14, 779−785. (b) Müller, P.; Boléa, C. *Helv. Chim. Acta* **2001**, *84*, 1093−1111. (c) Müller, P.; Bolea, C. *Synlett.* **2000**, 826−828. (d) Müller, P. Acc. Chem. Res. 2004, in press.

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