Ruthenium-Catalyzed Diastereoselective *syn*-Cyclopropanation of Trisubstituted Alkenes with Diazoacetates[1]

Thorsten Werle, Gerhard Maas*

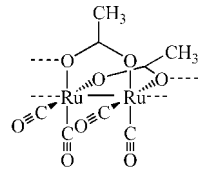
Division of Organic Chemistry I. Albert-Einstein-Allee 11, 89081 Ulm, Germany
Fax: +49 7 31 /5 02 27 90; e-mail: gerhard.maas@chemie.uni-ulm.de

Received June 19, 2000; Accepted July 19, 2000

Keywords: catalysts; cyclopropanes; diazo compounds; ruthenium; stereoselective reactions

Cyclopropanation of alkenes with diazo compounds in the presence of transition-metal catalysts is one of the important catalytic transformations in contemporary organic synthesis.[2] For intermolecular cyclopropanation, diazoacetates are particularly well suited. Dinuclear rhodium(II) complexes and copper complexes/salts prevail among the most efficient and versatile catalysts.[3,4] It is notable that, while several types of chiral catalysts have been developed for highly enantioselective cyclopropanation reactions,[2,5,6,7] satisfactory and general solutions for the control of diastereoselectivity have not yet been found. Cyclopropanation of monosubstituted alkenes with simple alkyl diazoacetates and catalysts such as $Rh_2(OAc)_4$ or copper(I) salts yield the thermodynamically favored *E*-diastereoisomer with an *E*:*Z* ratio typically in the range 2.5–1.1, and more highly substituted alkenes also form the sterically less congested cyclopropane preferentially.[4] High *E*-selectivities can be achieved, for example, with diazoacetates having bulky ester residues and with dinuclear rhodium(II) acetamidates rather than carboxylates as catalysts.[8] Furthermore, several catalysts bearing ligands with appropriate steric demands have been developed.[2,7,9] Directing the diastereoselectivity towards the sterically less favored *Z*-cyclopropanecarboxylate is more difficult. For the reaction of alkyl diazoacetates with styrene, suitable complexes with an appropriately designed ligand sphere around the catalyst metal (Rh[10], Ru[11], Cu[9i], Fe[12], Co[13]) have been developed.

Some time ago, we identified the polymeric ruthenium(I) complex $[Ru_2(CO)_4(OAc)_2]_n$ (**1**) and the derived dinuclear bis(acetonitrile) complex $[Ru_2(CO)_4(OAc)_2(CH_3CN)_2]$ as highly effective catalysts for cyclopropanation of alkenes with diazoacetates.[14] Mono- and 1,2-disubstituted C=C bonds were cyclopropanated with an *E*-(*anti*)-selectivity comparable to that obtained using $Rh_2(OAc)_4$ as catalyst, while 1,1-disubstituted alkenes gave *E*:*Z* ratios between 1.3 (2-methyl-1-butene) and 0.62 (α-methylstyrene). We now report that cyclopropanation of trisubstituted alkenes with diazoacetates catalyzed by **1** occur with a remarkably high *Z*-(*syn*)-diastereoselectivity.



1

Cyclopropanation reactions with trisubstituted alkenes **2a–f** were carried out by slow addition of an equimolar mixture of alkene and methyl diazoacetate (**3a**) to a dichloromethane solution containing an excess of alkene and catalyst **1** (1 mol %); these conditions keep the stationary concentration of **3a** low and help to limit the formation of formal carbene dimers. The dinuclear ruthenium complex, which is a coordination polymer in the solid state, becomes soluble after addition of some **3a**, indicating its depolymerization. Under these conditions, fair to good yields of cyclopropanes **4a**, **b**, **c**, **e** were achieved while the yields of **4d**, **f** were only low (Scheme 1 and Table 1). As expected, the chlorine substitution of alkenes **2d**, **f** lowers their reactivity towards the presumed electrophilic metal-carbene intermediate, and formation of the formal carbene dimers *E*- and *Z*-**5** takes over even under the chosen quasi-high dilution conditions.

Since the bulkiness of the ester residue often has an influence on the stereoselectivity, we tested the cyclopropanation of 2-methyl-2-butene (**2a**) with various diazoacetates (Scheme 2 and Table 2). Obviously, the different size of the alkyl groups (Me, Et, *t*-Bu) has no significant effect on the *Z*/*E* (*syn*/*anti*) ratio of cyclo-

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/asc/ or from the author.

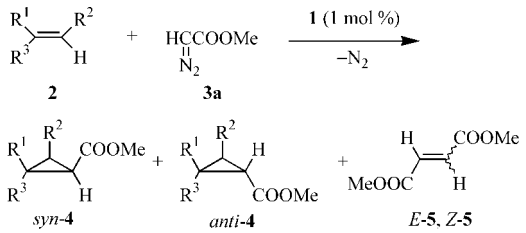
  1615-4150/01/34301-37–40 $ 17.50-.50/0

Table 1. Cyclopropanation of trisubstituted alkenes **2** with diazoacetate **3a** catalyzed by **1**

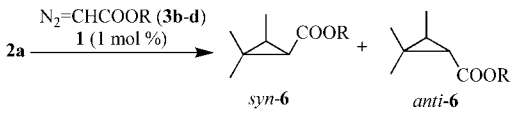
2,4	R^1	R^2	R^3	Yield of **4** [%][a]	Ratio[b],[c] (*syn* : *anti*)
a	Me	Me	Me	61	86 : 14
b	$-(CH_2)_4-$		Me	72	71 : 29
c	Me	CH_2CCl_3	Me	55	84 : 16
d	Me	Cl	Me	20[d]	91 : 9
e	Me	$CH{=}CMe_2$	Me	91	90 : 10
f	Me	$CH{=}CCl_2$	Me	30[e]	83 : 17

[a] Yields of isolated products are given.
[b] Determined by ^{1}H NMR integration of COO*Me* signals.
[c] *Syn/anti* corresponds to *Z/E* for **4a**, **c**, **d**, **e**, **f** and to *endo/exo* for **4b**.
[d] *Z*-**5** (55%) and *E*-**5** (19%) were also isolated.
[e] *Z*-**5** (48%) and *E*-**5** (18%) were also isolated.

propanes **6**. Use of a diazoacetate with an electron-withdrawing ester group (*N*-succinimidoyl) causes a marked lowering of the *Z*-selectivity, an effect which we correlate with an increased electrophilicity of the anticipated metal-carbene intermediate; this in turn would lead to an earlier transition state in which steric interactions between the metal-carbene complex and the alkene are less severe.[15]



Scheme 1.



Scheme 2.

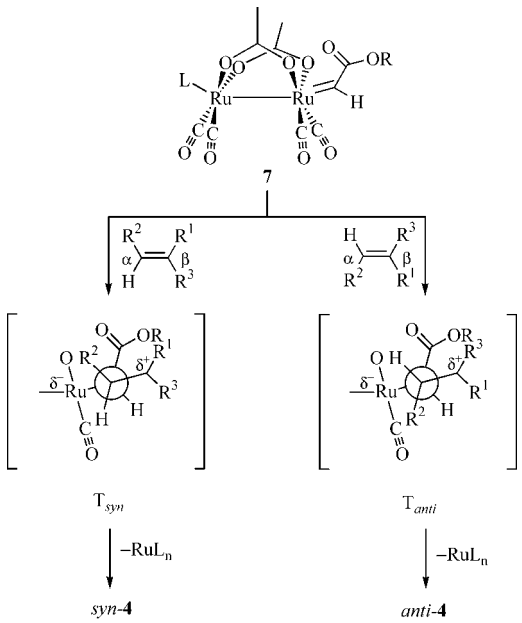
Catalyst **1** is unique in its ability to cyclopropanate all trisubstitued alkenes **2a–f** with remarkable *Z*- (*syn*)-selectivity and to provide at the same time a good chemical yield of the more nucleophilic alkenes: Most of the catalysts developed for *syn*-selective cyclopropanation seem not to have been tested with trisubstituted alkenes, others react to give only low yields or do not react at all. Aratani's chiral copper complexes with salicylaldimine-type ligands enabled the cyclopropanation of homoallylic chloride **2c** with a *syn*:*anti* ratio up to 85 : 15,[16] but gave a pronounced *anti*-selectivity when dienes **2e** and **2f** were cyclopropanated with the same diazoacetates.[17] Furthermore, the use of rhodium(II) pivalate or some ring-substituted rhodium(II) benzoates

Table 2. Cyclopropanation of 2-methyl-2-butene with various alkyl diazoacetates **3**

3,6	R	Yield of **6** [%][a]	*Z*-**6**/*E*-**6**[b]
a (**6a**=**4a**)	Me	61	86 : 14
b	Et	71[b]	84 : 16
c	*t*-Bu	75	87 : 13
d	*N*-succinimidoyl	72	68 : 32

[a] Yields of isolated products are given.
[b] Determined by integration of appropriate ^{1}H NMR signals.

gave cyclopropanecarboxylates derived from **2f** with a *syn*-selectivity of not more than about 60 : 40.[18] It should be recalled that certain esters of 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid (permethrinic acid) are powerful synthetic pyrethroids used as insecticides and that stereoselective syntheses of the more potent *syn*-diastereoisomer are of interest.[19]



Scheme 3. Proposed pathways for formation of cyclopropanes *syn*-**4** and *anti*-**4**

For an explanation of the observed *syn*-diastereoselectivity, we propose that a metal-carbene complex **7** is involved which has a geometry similar to $[Ru_2(CO)_4(\mu\text{-}OAc)_2L_2]$ (L = PPh_3),[20] but with the carbene moiety instead of PPh_3 as the axial ligand (Scheme 3; the exact nature of ligand L is not known). Important features of these dinuclear complexes are the sawhorse configuration (angles Ru–Ru–O < 90°, Ru–Ru–C > 90°) and the fact that the axial ligand is somewhat closer to the carboxylate oxygen atoms than to the carbonyl groups. Following generally accepted ideas about the mechanism of catalytic cyclopropanation reactions,[2] we can envi-

Table 3. ^{13}C chemical shifts of cyclopropanes **4** (100.6 MHz, $CDCl_3$, δ/TMS)[a]

Cyclopropane	*C*HCO	*C*R^{1}R^3	*C*HR^2	OMe	C=O	Other signals
Z-**4a**	28.4	25.3	27.6	50.6	172.0	7.9 (Me^2), 13.7 (Me^1), 28.7 (Me^3)
E-**4a**	33.7	27.4	28.4	51.1	173.2	12.6 (Me^2), 20.5 (Me), 20.8 (Me)
endo-**4b**	29.4	23.0	25.1	50.8	171.9	29.0 (Me); 18.6, 20.9, 21.0, 25.7 ($(CH_2)_4$)
exo-**4b**	30.2	27.5	27.8	51.1	173.5	20.6 (Me); 20.8, 21.0, 22.8, 31.7 ($(CH_2)_4$)
Z-**4c**	28.4	25.0	29.5	51.3	171.6	14.5 (Me), 28.2 (Me), 49.1 (CH_2), 99.9 (CCl_3)
E-**4c**	32.3	26.6	29.8	51.6	171.9	20.2 (Me), 21.9 (Me), 53.4 (CH_2), 99.1 (CCl_3)
Z-**4d**	29.5	25.5	43.6	51.3	168.4	14.6 (Me), 26.7 (Me)
E-**4d**	29.5	29.4	44.9	51.7	170.4	18.7 (Me), 21.7 (Me)
Z-**4e**	30.6[b]	26.0	31.9[b]	50.6	171.1	14.4, 17.9, 25.6, 28.4 (Me); 117.9 (=CH), 134.1 (=CMe_2)
E-**4e**	34.3	28.1	32.4	51.0	172.5	18.1, 20.1, 21.8, 25.2 (Me); 120.9 (=CH), 135.0 (=CMe_2)
Z-**4f**	31.5	27.2	32.4	51.3	170.7	14.7, 28.2 (Me); 120.4 (CCl_2), 124.8 (=CH),
E-**4f**	34.4	28.6	32.7	52.5	171.3	19.9, 22.4 (Me); 121.8 (CCl_2), 126.9 (=CH)

[a] Assignments for *C*HCO and *C*HR^2 were based on C,H correlation experiments.
[b] Assignments of signals at δ 30.6 and 31.9 may be interchanged.

sage the formation of open transition states T_{syn} and T_{anti}. Minimization of steric interactions between the approaching alkene and the "ligand face" around the catalyst metal would favor the population of T_{syn} over T_{anti}, and hence of *syn*-**4** over *anti*-**4**. This model implies that the steric interactions during the approach of the alkene to **7** are more important for stereocontrol than those in the transition state itself which is shown in an idealized antiperiplanar geometry of the C–Ru and C^{α}–C^{β} bonds. The minor importance of destabilizing steric interactions between COOR and alkene substituents R^1, R^2 in this proposal is in line with the observation that the size of the ester group in diazoacetates **3a–d** has no significant influence on the diastereoselectivity (see Table 2).

The dinuclear ruthenium(I) complex **1** is the first catalyst which provides a remarkably high *syn*-selectivity in the cyclopropanation of trisubstituted alkenes with diazoacetates. It appears that this property is due to the sawhorse configuration of **1** and of the derived intermediate metal-carbene complex **7**. In this configuration, the O–Ru–O face offers more space than the OC–Ru–CO face to accommodate a neighboring substituent (COOR in **7**) and to accept substituent R^2 of an approaching alkene $R^1R^3C{=}CHR^2$.

Experimental Section

Cyclopropanation of Alkenes 2, General Procedure
A mixture of diazoacetic ester **3** (20 mmol) and alkene **2** (20 mmol) was added, by means of a syringe pump, during 12 h to a solution of alkene (180 mmol) in dichloromethane (25 ml) in which catalyst **1**[21] (1 mol %) was suspended. When the evolution of molecular nitrogen had ceased (ca. 3 h), the solvent and low-boiling alkene were distilled off at 60 °C/800 mbar. The liquid residue was separated by column chromatography over silica gel. Thereby, residual alkene was eluted with pentane, the expected cyclopropane was obtained by elution with ether-pentane (1:8 to 1:11), and the carbene dimers *Z*- and *E*-**5** were eluted with ether. The cyclopropanes were purified further by bulb-to-bulb distillation. The *syn*- and *anti*-configurations of cyclopropanes **4** and **6** were determined from the magnitude of the ^3J(H,H) coupling constants of the two cyclopropane protons ($^3J_{cis} > {}^3J_{trans}$). If this was not possible due to signal overlap, the assignment was made based on the γ-effect on ^{13}C chemical shifts of carbon atoms attached to the cyclopropane ring (see, e. g., ref. [14]). A full comparison of the ^{13}C NMR chemical shifts is given in Table 3.

***N*-Succinimidoyl 2,2,3-trimethylcyclopropane-1-carboxylate (6d)**: Obtained from diazoacetate **3d**[22] and 2-methyl-2-butene; yield: 72%; mixture of diastereomers, *Z*:*E* = 68:32; m. p. 80 °C, b. p. 153–159 °C/0.001 mbar. ^1H NMR (400.1 MHz, $CDCl_3$): *Z*-**6d**: δ = 1.21 (s, 3H, 2-Me), 1.22 (d, 3H, *J* = 6.2 Hz, 3-Me), 1.24 (s, 3H, 2-Me), 1.54 (m, 1H, 3-H), 1.69 (d, 1H, *J* = 8.7 Hz, 1-H), 2.83 (s, 4H, CH_2); *E*-**6d**: δ = 1.18 (d, 3H, *J* = 6.3 Hz, 3-Me), 1.20 (s, 3H, 2-Me), 1.23 (s, 3H, 2-Me), 1.40 (d, 1H, *J* = 5.4 Hz, 1-H), 1.52 (m, 1H, 1-H), 2.83 (s, 4H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): *Z*-**6d**: δ = 7.6 (3-Me), 13.4 (2-Me), 25.2 (C-3), 25.3 (CH_2), 28.1 (2-Me), 28.5 (C-2), 29.9 (C-1), 166.2 (C=O), 169.6 (C=O); *E*-**6d**: δ = 12.5 (3-Me), 20.3 (2-Me), 20.4 (2-Me), 25.3 (CH_2), 29.8 (C-3), 30.0 (C-1), 30.5 (C-2), 167.7 (C=O), 169.4 (C=O); $C_{11}H_{15}NO_4$ (225.2): calcd. C 58.66, H 6.71, N 6.22; found C 58.7, H 6.7, N 5.9.

Spectral and physical data for all other cyclopropanes **4** and **6** are given in the Supporting Information.

Acknowledgments

Financial support of this work by the Volkswagen Foundation is gratefully acknowledged.

References

[1] Taken in part from the Doctoral Thesis of T. Werle, University of Kaiserslautern, **1996**.
[2] M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York, **1998**.
[3] (a) G. Maas, *Top. Curr. Chem.* **1987**, *137*, 77–253; (b) M. P. Doyle, *Chem. Rev.* **1986**, *86*, 919–939.

[4] M. P. Doyle, R. L. Dorow, W. E. Buhro, J. H. Griffin, W. H. Tamblyn, M. L. Trudell, *Organometallics* **1984**, *3*, 44–52.
[5] (a) M. P. Doyle, D. C. Forbes, *Chem. Rev.* **1998**, *98*, 911–935; (b) M. P. Doyle, M. N. Protopopova, *Tetrahedron* **1998**, *54*, 7919–7946; (c) M. P. Doyle, *Aldrichim. Acta* **1996**, *29*, 3–11.
[6] (a) H. M. L. Davies, *Eur. J. Org. Chem.* **1999**, 2459–2469; (b) H. M. L. Davies, *Aldrichim. Acta* **1997**, *30*, 107–114.
[7] A. Pfaltz, *Acc. Chem. Res.* **1993**, *26*, 339–345.
[8] M. P. Doyle, V. Bagheri, T. J. Wandless, N. K. Harn, D. A. Brinker, C. T. Eagle, K.-L. Loh, *J. Am. Chem. Soc.* **1990**, *112*, 1906–1912.
[9] (a) T. Aratani, *Pure Appl. Chem.* **1985**, *57*, 1839–1844; (b) D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726–728; (c) R. E. Lowenthal, S. Masamune, *Tetrahedron Lett.* **1991**, *50*, 7373–7376; (d) D. A. Smith, D. N. Reynolds, L. K. Woo, *J. Am. Chem. Soc.* **1993**, *115*, 2511–2513; (e) H. Nishiyama, Y. Itoh, Y. Sugawara, H. Matsumoto, K. Aoki, K. Itoh, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1247–1262; (f) S.-B. Park, N. Sakata, H. Nishiyama, *Chem. Eur. J.* **1996**, *2*, 303–306; (g) M. Frauenkron, A. Berkessel, *Tetrahedron Lett.* **1997**, *38*, 7175–7176; (h) M. Hagen, U. Lüning, *Chem. Ber./Recueil* **1997**, *130*, 231–234; (i) F. Löffler, M. Hagen, U. Lüning, *Synlett* **1999**, 1826–1828.
[10] (a) J. L. Maxwell, S. O'Malley, K. C. Brown, T. Kodadek, *Organometallics* **1992**, *11*, 645–652; (b) S. O'Malley, T. Kodadek, *Organometallics* **1992**, *11*, 2299–2302; (c) H. Ishitani, K. Achiwa, *Synlett* **1997**, 781–782; (d) M. P. Doyle, W. R. Winchester, M. N. Protopopova, P. Müller, G. Bernardinelli, D. Ene, S. Motallebi, *Helv. Chim. Acta* **1993**, *76*, 2227–2235.
[11] T. Uchida, R. Irie, T. Katsuki, *Synlett* **1999**, 1793–1795.
[12] W. J. Seitz, A. K. Saha, M. M. Hossain, *Organometallics* **1993**, *12*, 2604–2608.
[13] T. Niimi, T. Uchida, R. Irie, T. Katsuki, *Tetrahedron Lett.* **2000**, *41*, 3647–3651.
[14] G. Maas, T. Werle, M. Alt, D. Mayer, *Tetrahedron* **1993**, *49*, 881–888.
[15] The effect of the electrophilicity of the catalyst is supported by the observation of a similar decrease in *syn*-selectivity, when the combination of methyl diazoacetate and the trifluoroacetato analogue of catalyst **1** is used (ref. [1]).
[16] T. Aratani, Y. Yoneyoshi, T. Nagase, *Tetrahedron Lett.* **1982**, *23*, 685–688.
[17] T. Aratani, Y. Yoneyoshi, T. Nagase, *Tetrahedron Lett.* **1977**, 2599–2602.
[18] (a) A. Demonceau, A. F. Noels, A. J. Anciaux, A. J. Hubert, P. Teyssié, *Bull. Soc. Chim. Belges* **1984**, *93*, 949–952; (b) D. Holland, D. J. Milner, *J. Chem. Res. (S)* **1979**, 317; *(M)* 3734-3746.
[19] (a) M. Elliott, N. F. Janes, *Chem. Soc. Rev.* **1978**, 473–505; (b) K. Kondo, T. Takashima, A. Negishi, K. Matsui, T. Fujimoto, K. Sugimoto, C. E. Hatch III, J. S. Baum, *Pestic. Sci.* **1980**, *11*, 180–187; (c) D. Arlt, M. Jautelat, R. Lantzsch, *Angew.Chem.* **1981**, *93*, 719–840; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 703.
[20] K.-B. Shiu, S.-M. Peng, M. C. Cheng, *J. Organomet. Chem.* **1993**, *452*, 143–149.
[21] G. R. Crooks, B. F. G. Johnson, J. Lewis, I. G. Williams, G. Gamlen, *J. Chem. Soc. (A)* **1969**, 2761–2766.
[22] A. Ouihia, L. René, J. Guilhem, C. Pacard, B. Badet, *J. Org. Chem.* **1993**, *58*, 1641–1642.