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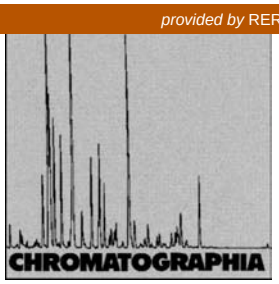
Enantioselective Gas Chromatographic Analysis of Cyclopropane Derivatives



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Dedicated to Professor Volker Schurig on the occasion of his 65th birthday

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Abstract

Chirasil-β-Dex was used as chiral stationary phase for the enantioselective gas chromatographic analysis of several new chiral cyclopropane derivatives. The GC method provides information about the chemical yields of the cyclopropane products, enantioselectivity, substrate specifity, and catalytic activity of the chiral catalysts used in the inter- and intra-molecular cyclopropanation reactions and avoids time-consuming work-up procedures.

Keywords

Gas chromatography
Enantiomeric excess
Chirasil-β-Dex
Rhodium complexes
Cyclopropanes

Introduction

Naturally-occurring and synthetic cyclopropanes bearing simple functionalities are endowed with a large spectrum of biological properties ranging from enzyme inhibitions to insecticidal, antifungal, herbicidal, antimicrobial, antibiotic, antibacterial, antitumor and antiviral activities [1, 2]. Thus, they constitute a common structure motif in pyrethroids [3], the antidepressant tranylcypromine [4], papain and cystein protease inhibitors [5], the potential anti-psychotic substances [6], anti-HIV agents [7, 8], and marine lactones [9]. Accordingly, a great deal of effort has been developed over the last two decades to make the stereo-controlled synthesis of substituted cyclopropanes more appealing to organic chemists [10–13]. Besides the resolution of their racemates [14], a number of synthetic methodologies including asymmetric Simmons-Smith reaction, metal-catalyzed reaction of diazo compounds with olefins, and asymmetric ylide cyclopropanation have been developed to access to the enantiomerically pure or enriched cyclopropanes [15,16]. The utility of the ylide approaches is directly related to the level of selectivity of the process, which is believed to proceed in via metal carbenes as intermediates [17,18].

Metal carbene complexes (cf. Fig. 1) have been proposed as the active species in such cyclopropanation and olefins metathesis reactions catalyzed by transition metals. Such species, which are usually obtained from the decomposition of diazo compounds by transition metal complexes, contain a carbene unit, which can be transferred to the substrates (olefins) to afford the cyclopropane products. The ways in which efficiency and practicality of this procedure are defined is depending on a large number of factors. Among these factors are suitable catalyst, scale, reagent costs, time allotted and required, suitable equipments and reliable methods used in the determination of the enantiomeric excess (ee) of the resulting cyclopropanes. The development of accurate non-chiroptic methods for the determination of enantiomeric purity has been critical for the development of enantioselective catalysis. Thus, a prerequisite in the metal-catalyzed asymmetric synthesis is a precise and reliable assessment of the enantiomeric purity of the resulting products [19]. Among these methods are: polarimetric methods, gas

Fig. 1. Metal carbene complex

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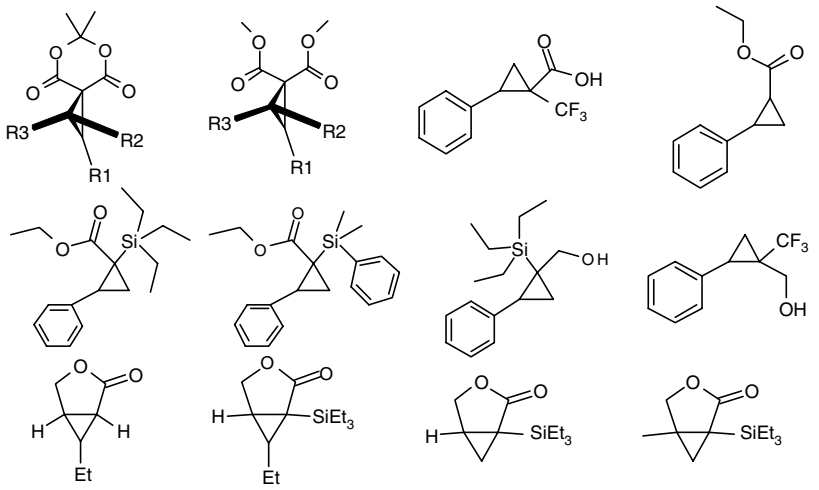

Fig. 2. A set of cyclopropane derivatives prepared and separated by GC

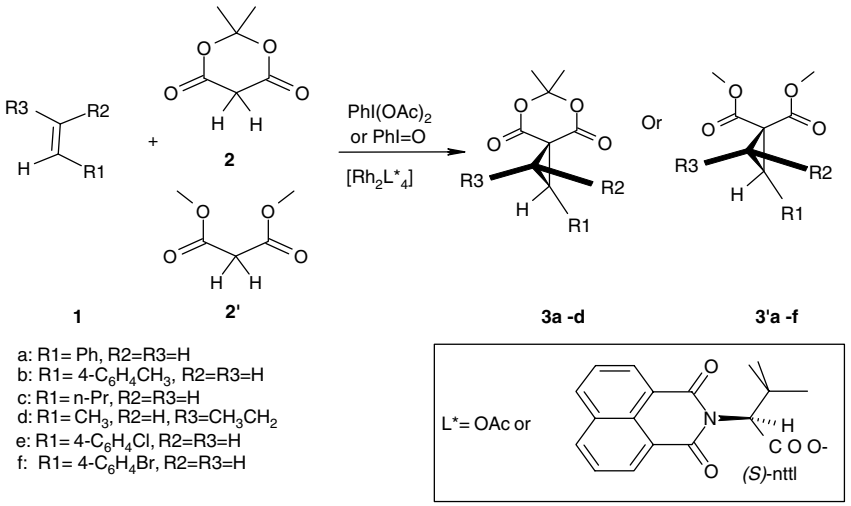

Fig. 3. One pot synthesis of cyclopropane derivatives **3** and **3′** using either Meldrum's acid **2** or dimethyl malonate **2′** and $PhI(OAc)_2$ or PhI = O, respectively in the presence of rhodium (II) catalyst

chromatographic methods, liquid chromatographic methods and NMR spectroscopy. The modern and most sensitive methods used in the determination of enantiomeric purity of the outcome of metal-catalyzed reactions, allowing a detection as little as 0.1% of one enantiomer in the presence of another, are chiral GC and HPLC methods. For an efficient monitoring of the reaction progress, enantioselective gas chromatography (GC) was the method of choice for the determination of the enantiomeric excess of the resulting cyclopropane derivatives.

Although a large number of chiral stationary phases (CSPs) have been developed [20–24], the choice of an appropriate column is still difficult. Chirasil-β-Dex, a polysiloxane-anchored permethylated β-cyclodextrin with 3, 5 and 8 spacer have been successfully used as CSP in GC [20]. In this contribution, we report on the synthesis of a different class of cyclopropane derivatives (cf. Fig. 2) and their chiral analysis using Chirasil-β-Dex as CSP in GC.

Experimental

Chemicals and Instrumentation

All chemicals were commercially available. Olefin substrates were used as purchased. Solvents were dried prior to use. The catalysts and diazo compounds were synthesized according to [25–27].

Representative Procedure for the Intermolecular Cyclopropanation of Olefins Using Meldrum's Acid (3a–d)

Dichloromethane (10 mL) was added through syringe into a 50 mL round bottom flask containing a mixture of Meldrum's acid (**2**,10 mmol, 1 equiv.), $PhI(OAc)_2$ (1.4 equiv.), $[Rh_2(OAc)_4]$ or $[Rh_2\{(S)\text{-nttl}\}_4]$ (5 mol%), Al_2O_3 (2.3 equiv.) and molecular sieves 4 Å (250 mg), followed by the addition of the olefin (10 equiv.). The reaction mixture was thermostatted in an oil bath to 30°C and stirred under argon. 100 µL samples were taken after several time intervals. The samples were filtered using a syringe filter holder (0.2 µm pore size) and the organic layer was diluted with 100 µL of dichloromethane and analysed by GC. The reaction progress was monitored qualitatively and quantitatively by GC-MS using *n*-dodecane as an internal standard. When maximum conversion was reached, the reaction was terminated by filtration through celite. The residue on the celite was washed twice with dichloromethane. Evaporation of the combined filtrates under reduced pressure followed by chromatography on silica gel column with *n*-pentane/ethyl acetate (2:1 *v*/*v*) as eluent afforded the desired cyclopropane derivatives.

Synthesis of Iodosyl Benzene, PhI=O

To finely powdered diacetoxyiodobenzene (32.2 g, 0.10 mol) was added NaOH 3N (150 mL) in 5 min with vigorous stirring, and the lumps of solid, which formed where macerated with a spatula. The reaction mixture was stirred for 45 min and then diluted with H_2O (100 mL). The crude yellow solid was collected by filtration, washed with H_2O (3×100 mL) and dried under vacuum. It was suspended in $CHCl_3$ (75 mL), macerated and separated by filtration. The crude PhI = O was air-dried and used without further purification.

General Procedure for the Intermolecular Cyclopropanation of Olefins Using Dimethyl Malonate as a Carbene Precursor (3′a–f)

Dimethyl malonate (0.01 mol) is added to a mixture of iodosyl benzene (1.4 equivalent), olefins (10 equivalent), MgO (2.3 equivalent), rhodium (II) catalyst (5 mol%) and 250 mg molecular sieves 4 Å in dichloromethane (10 mL). The reaction mixture is stirred under argon for 24 h. 100 µL samples were taken after several time intervals. The samples were filtered using a syringe filter holder (0.2 µm pore size) and the organic layer was diluted with 100 µL of dichloromethane for the GC analysis. The reaction progress was monitored qualitatively and quantitatively by GC-MS using *n*-dodecane as an internal standard. When maximum conversion was reached, the reaction was terminated by filtration through celite. The residue on the celite was washed twice with dichloromethane. Evaporation of the combined filtrates under reduced pressure followed by chromatography on silica gel column with *n*-heptane/ethyl acetate (5:1 *v*/*v*) as eluent afforded the desired cyclopropane derivatives.

Rh(II)-catalyzed Intermolecular Cyclopropanation of Styrene with Silylated Diazoacetate (5, 9)

To the Rh(II)-catalyst (2 mol %) was added styrene (920 µL, 8.0 mmol) under argon and the silylated diazoacetate **4** or **8** (0.85 mmol). The mixture was heated until the decomposition of the diazo ester was completed (*ca.* 2 h). The solvent was evaporated and the crude cyclopropane was purified by flash chromatography [25].

Desilylation of (cis- and trans-2-phenyl-1-(triethylsilyl)-1-hydroxymethylcyclopropane 5 (cis/trans-6)

To an 82:18 mixture of *trans* (48% ee) and *cis* (30 % ee) of **5** (142 mg, 0.56 mmol) in THF (3.0 mL) was added 1M TBAF (1.0 mL) in THF at −78°. The temperature was allowed to reach r.t. After stirring for 2–4 h the mixture was quenched with H_2O (2.0 mL) and extracted with CH_2Cl_2. The organic layer was evaporated, dried

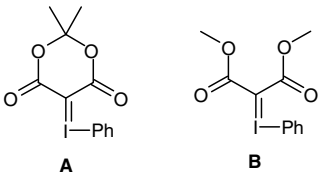

Fig. 4. The phenyliodonium ylide **A** and **B** generated in *situ* in the one pot synthesis of cyclopropane derivatives **3** and **3′** respectively

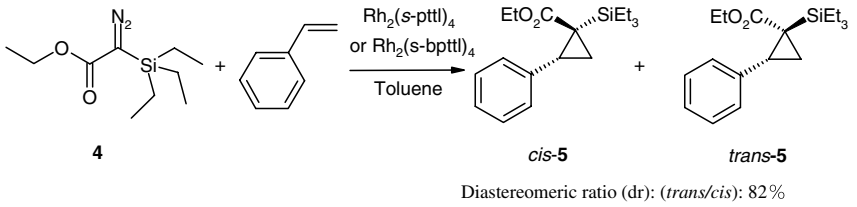

Fig. 5. Intermolecular cyclopropanation of styrene using ethyl diazo(triethylsilyl)acetate **4**

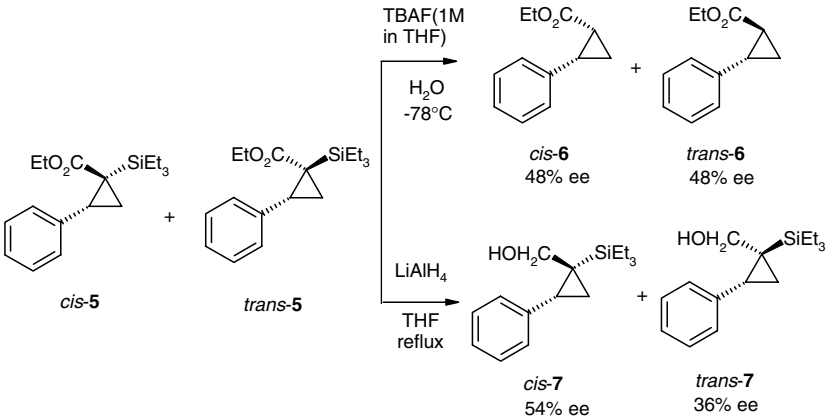

Fig. 6. The desilylation and reduction of ethyl *cis*- and *trans*-1-(triethylsilyl)-2-phenylcyclopropane-1-carboxylate (*cis*/*trans*-**5**)

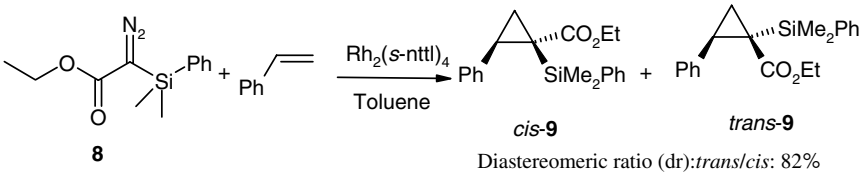

Fig. 7. Intermolecular cyclopropanation of styrene using ethyl diazo(dimethylphenylsilyl)acetate **8**

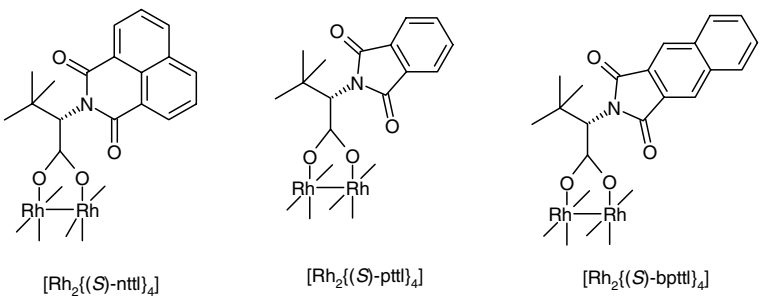

Fig. 8. Structure of the rhodium (II) catalysts used in the asymmetric synthesis of cyclopropane derivatives

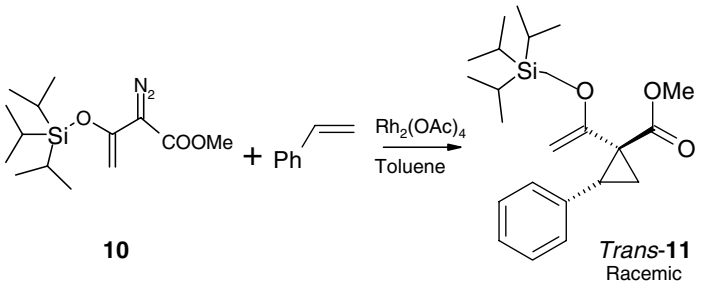

Fig. 9. Intermolecular cyclopropanation of styrene with methyl-3-(tri(isopropyl)silanyloxy)-2-diazo-but-3-enoate

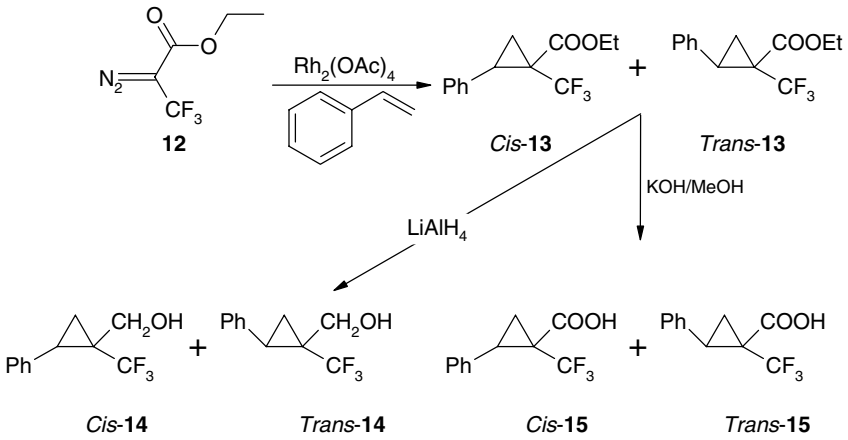

Fig. 10. Intermolecular cyclopropanation of styrene using ethyl 3,3,3-trifluoro-2-diazopropionate **12**

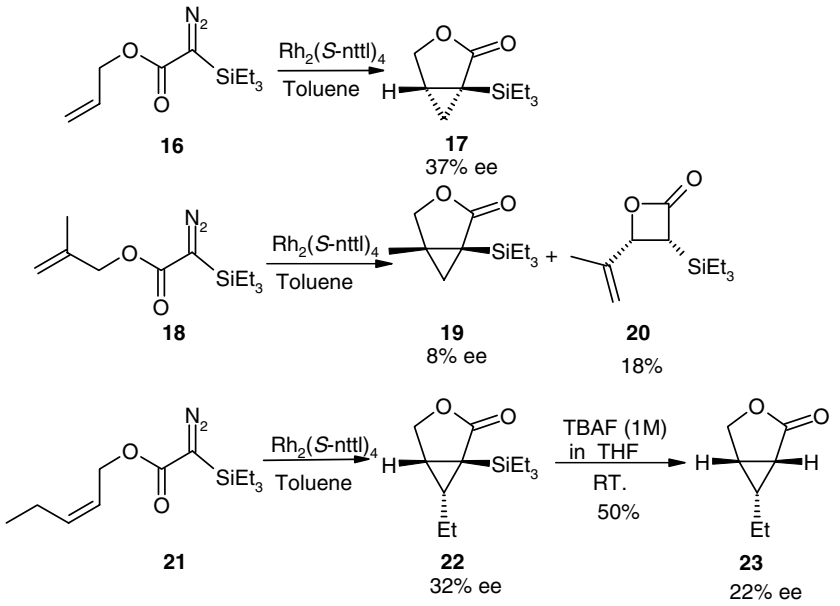

Fig. 11. Rhodium (II)-catalyzed intramolecular cyclopropanation with Allyl diazo(triethylsilyl)acetates

($MgSO_4$), and the residue was purified by flash chromatography (SiO_2, pentane/AcOEt 97:3) to afford a 70:30 mixture of ethyl cis- and trans-2-phenylcyclopropane-1-carboxylate *(**6**)*, (1*S*,2*S*)-*trans*-**6** (48 % ee) and (1*R*,2*S*)-*cis*-**6** (48% ee) in 81% yield (cf. Fig. 14C and D) [25].

Reduction of (*cis*- and *trans*-2-Phenyl-1-(triethylsilyl)-1-hydroxymethylcyclopropane 5 (cis/trans-7)

To $LiAlH_4$ (2 equiv.) in THF (2.0 mL) was added, under argon, the *cis*/*trans* mixture of **5** (0.80 mmol) in THF (4.0 mL). The mixture was stirred overnight at r.t. The excess of $LiAlH_4$ was decomposed by the addition of ethylene diamine (2 mL), followed by 8% NaOH (2.0 mL) and H_2O. The crude product was extracted with Et_2O (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The separation of the diasteroisomers by flash chromatography (SiO_2, CH_2Cl_2/*n*-pentane 80:20) afforded the alcohol *cis*/*trans*-**7** [25].

Rh(II)-catalyzed Intermolecular Cyclopropanation of Styrene with Methyl-3-(tri(isopropyl)silanyloxy)-2-diazo-but-3-enoate (trans-11)

The rhodium catalyst (0.008 mmol) was activated by heating in *vacuo*, and dissolved in toluene (3 mL). After addition of styrene (7 mmol), the mixture was cooled to 0°C, and the methyl-3-(tri(isopropyl)silanyloxy)-2-diazo-but-3-enoate **10** (0.70 mmol) in toluene (2 mL) was added dropwise. After the addition, stirring was continued for 1 h. The solvent was evaporated and the residue was purified by flash chromatography (SiO_2/Et_2O/*n*-pentane 5:95) to afford methyl-2-phenyl-1-(tris(isopropyl)silanyloxy)-vinyl)-cyclopropanecarboxylate *trans*-**11** in 60% yield [26].

General Procedure for the Rh(II)-catalyzed Carbene Transfer with Ethyl 3,3,3-trifluoro-2-diazopropionate (cis/trans-13)

The diazo **12** (92 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) was added to the olefin (5 mmol) in CH_2Cl_2 (5 mL) containing the appropriate catalyst (5 mol%) within 8 h at room temperature. After completion of the reaction, the reaction mixture was passed through short plug of silica gel, which was subsequently washed with CH_2Cl_2 (20 mL). The solvent was removed in *vacuo* and the crude product was purified by flash chromatography to afford the desired cyclopropanes *cis*/*trans*-**13**. The reduction and hydrolysis of *cis*/*trans*-**13** to *cis*/*trans*-**14** and **15**, respectively were performed according to lit. procedure [27].

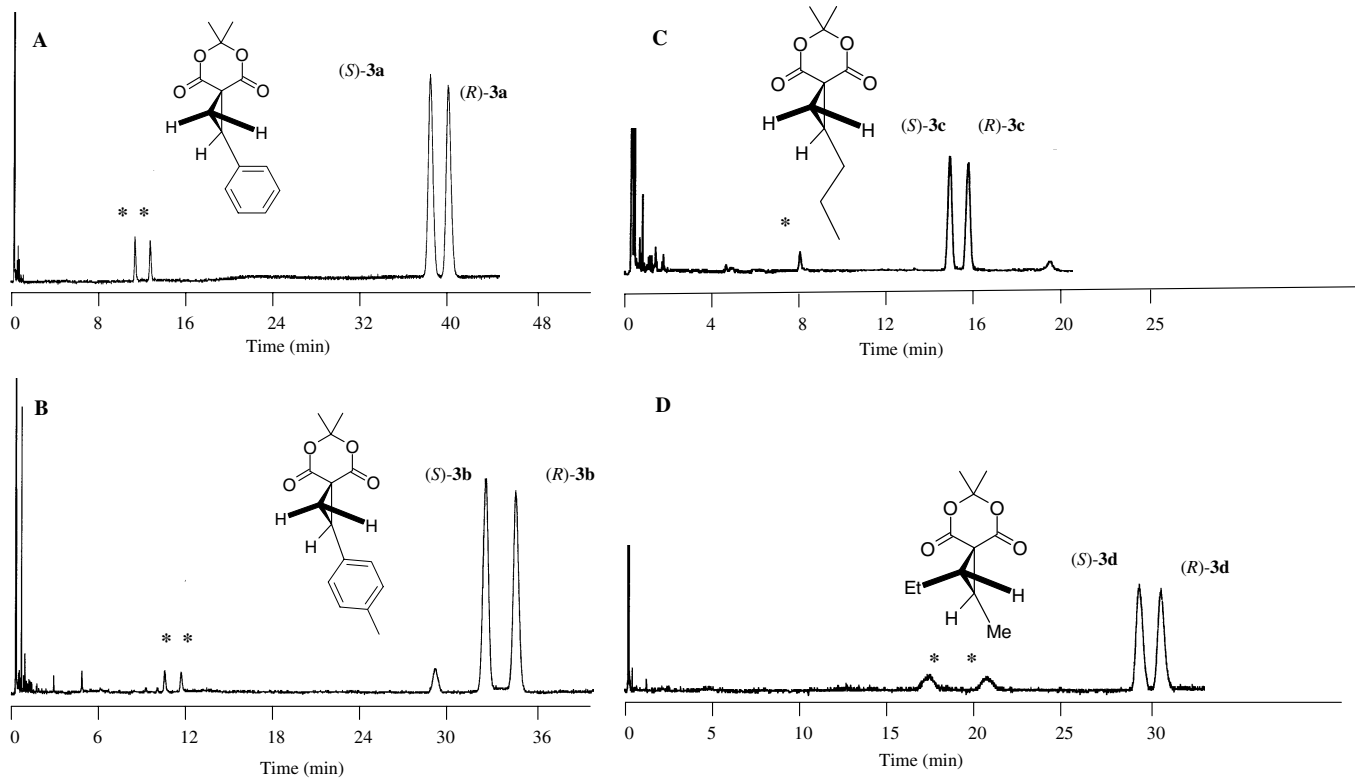

Fig. 12. Gas chromatographic enantiomers separation of cyclopropanes derived from Meldrum's acid showing products' decomposition in GC to afford the corresponding dicarboxylic acid (*). The latter is baseline separated in some cases (A, B, and D) and other not (C)

General Procedure for the Intramolecular Cyclopropanation of Allyl diazo(triethylsilyl)acetates (17, 19, 22)

To the Rh(II)-catalyst (2% with respect to the allyl diazo(triethylsilyl)acetates) was added the diazosilane **16**, **18** or **21** (0.40 mmol) under argon in 5 min. The mixture was stirred during 2 h at r.t. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography to afford the desired cyclopropanes [25].

General procedure of the Desilylation of 1-(Triethylsilyl)-3-oxabicyclo[3.1.0]hexan-2-ones (23)

A solution of TBAF (1M in THF, 1mL) was added dropwise to the appropriate bicyclohexane **22** (0.56 mmol) at room temperature. After stirring for 2–4 h, H_2O (2.0 mL) was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography afforded **23**.

Enantioselective Gas Chromatographic Analysis

A gas chromatograph (HP 580, Agilent Technologies, Waldbronn, Germany) equipped with a flame ionization detector (FID) was used for the chiral analysis of cyclopropane derivatives. The chiral stationary phase permethylated-5-pent-1-enyl-β-cyclodextrin, 20% (w/w) was coated on a 20 m × 0.25 mm fused silica capillary column (0.25 μm film thickness) according to literature procedure [20]. The analytical conditions were: injector temperature, 200 °C; FID temperature, 250 °C; oven temperature is varying depending on the structure of cyclopropane. Dihydrogen was used as the carrier gas (150 KPa column head pressure).

Results and Discussion

Intermolecular Cyclopropanation

Diazo Free One Pot Procedure

A set of cyclopropanes derived from Meldrum's acid and dimethyl malonate were prepared using a user-friendly diazo free one-pot procedure. Thus, the cyclopropanation of olefins (**1a–f**) in the presence of either Meldrum's acid (**2**) or dimethyl malonate (**2′**) and $PhI(OAc)_2$ or PhI = O and 5 mol% of rhodium (II) catalyst [$Rh_2(OAc)_4$] afforded the racemic cyclopropane derivates **3** and **3'**, respectively with high yield (up to 85%) (cf. Fig. 3, 12 and 13). The phenyliodonium ylides **A** and **B** (cf. Fig. 4), respectively were generated and decomposed by the appropriate rhodium catalyst *in situ* [17]. Attempts to use a chiral rhodium (II) catalyst [Rh_2 (*s*-nttl)$_4$] instead of $Rh_2(OAc)_4$ afforded the enantioenriched cyclopropanes **3a**, **3b**, **3c** and **3d** derived from Meldrum's acid with 57%, 51%, 70% and 33% ee, respectively. While the cyclopropane **3'a** derived from dimethyl malonate was afforded in 37% ee.

Cyclopropanation with Isolated Diazo Compounds

The intermolecular cyclopropanations were carried out with ethyl diazo(triethyl)- and (dimethylphenyl)-silylacetate **4** and **8**, respectively. Their decomposition with chiral rhodium (II) catalyst [Rh_2(*s*-pttl)$_4$] or [Rh_2(*s*-bpttl)$_4$] and [Rh_2(*s*-nttl)$_4$] in refluxing toluene and 10 equiv. of styrene afforded the ethyl *cis*/*trans*-1-(triethylsilyl)-2-phenylcyclopropane-1-carboxylate

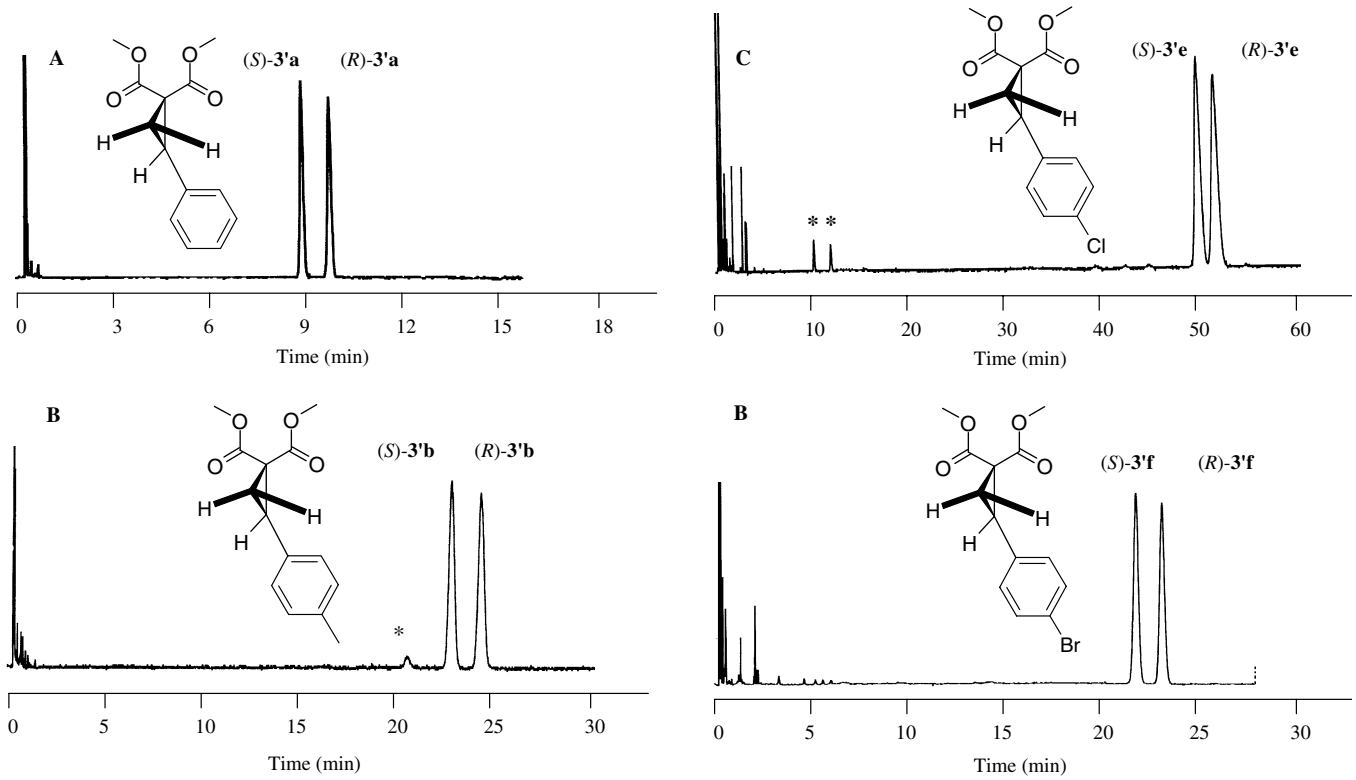

Fig. 13. Gas chromatographic enantiomers separation of cyclopropanes derived from dimethyl malonate showing products' decomposition in GC to afford the corresponding dicarboxylic acid (*). The latter is baseline separated in one case (C) and other not (B) while not shown in A and D

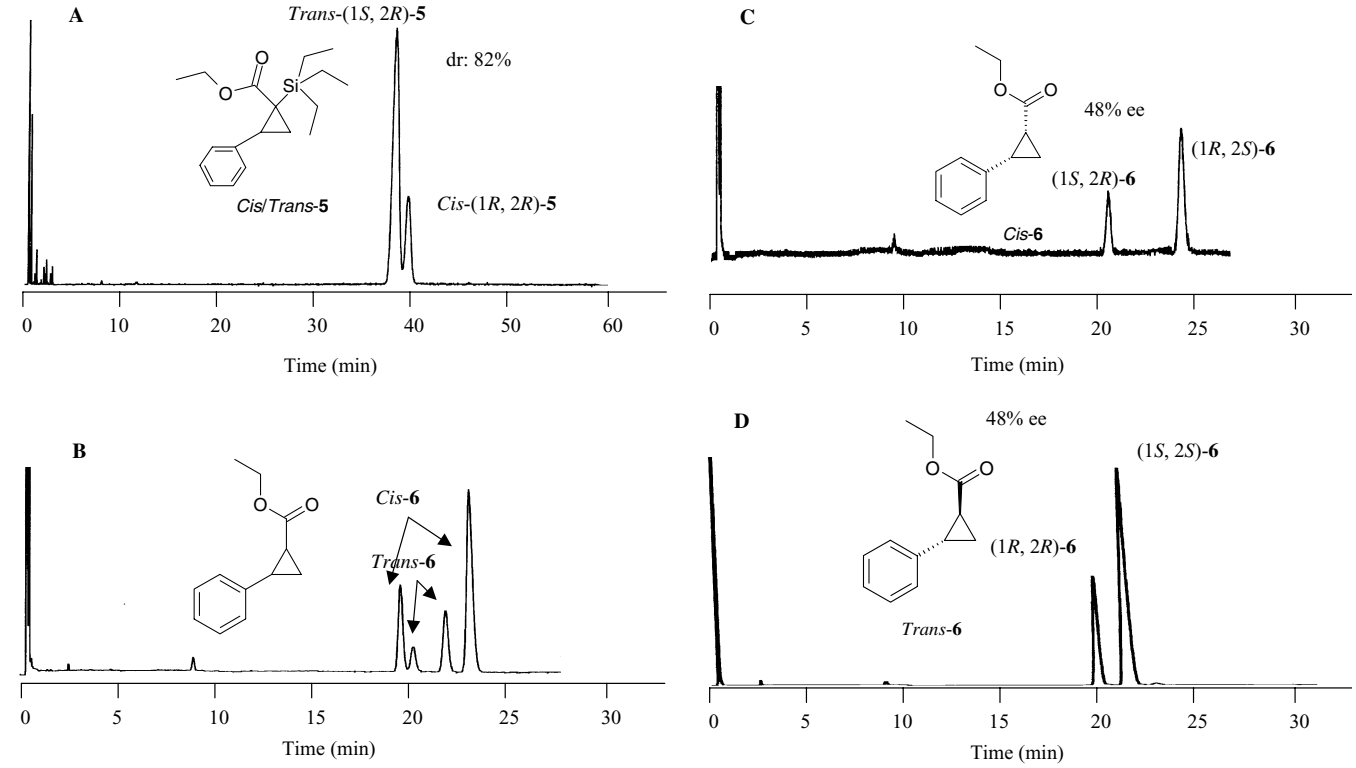

Fig. 14. Gas chromatographic diastereomers (A and B) and enantiomers separation (C and D) of silylated (A) and desilylated cyclopropanes (B, C and D) resulted from the intermolecular cyclopropanation of diazo compounds. The effect of the silyl moiety on the separation should be noted (enantiomers of silylated *cis*/*trans* **5** were not separated, while those of **6** were baseline separated)

(*cis*/*trans*)-**5** and the ethyl cis/trans-1-(dimethylphenylsilyl)-2-phenylcyclopropane-1-carboxylate (*cis*/*trans*)-**9**, respectively with similar diastereomeric ratio (82% *trans*/*cis*) isomers (cf. Fig. 5–8 and 14–16).

The preference for formation of *trans*-**5** where the phenyl and ethoxycarbonyl groups are *cis* (cf. Fig. 5) is of some interest since in the cyclopropanation with ethyl diazoacetate the *trans*-isomer usually predominates. However, upon protiodesilylation with TBAF, epimerization occurred and the desilylated cyclopropane **6** was isolated in equal ratio 48:48 *trans*/*cis* mixture (cf. Fig. 6), even when the reaction was carried out at −78°. The enantioselective GC separation of the enantiomers of the cyclopropanes (*cis*/*trans*)-**5** failed, but could be achieved upon their reduction with $LiAlH_4$ to a diastereomeric mixture of the alcohol **7**. The relative configuration of the diastereoisomers of **7** was verified by comparison of the NMR signals of the hydroxymethyl group with those reported in the literature for its trimethylsilyl analogues [25]. The latter failed to undergo protiodesilylation upon exposure to TBAF even upon prolonged reaction times (cf. Fig. 6).

By analogy, the intermolecular cyclopropanation of styrene with (silanoxyvinyl)-diazoacetate **10** was performed using achiral rhodium catalyst $[Rh_2(OAc)_4]$ to afford methyl-2-phenyl-1-(tris(isopropyl)silanyloxy)-vinyl)-cyclopropanecarboxylate *trans*-**11** in 60% yield. The diastereoselecivity is typical for Rh(II)-catalyzed cyclopropanations with vinyldiazoacetate esters [23] (cf. Fig. 9 and 17).

Another set of cyclopropane derivatives were prepared via Rh(II)-catalyzed asymmetric cyclopropanation of styrene using 3,3,3-trifluoro-2-diazopropionate **12** to afford a mixture of (*cis*/*trans*)-**13** in good yield [27]. The simultaneous reduction of **13** afforded the alcohol **14** while the hydrolysis afforded the acid **15** (cf. Fig. 10 and 18).

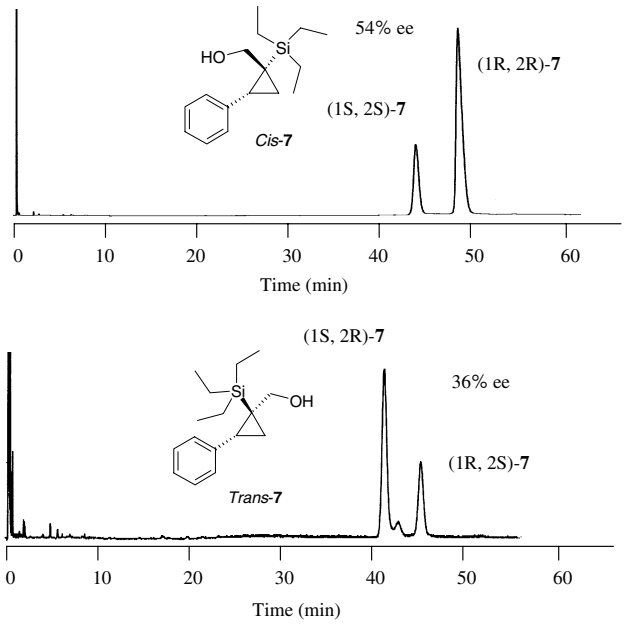

Fig. 15. Gas chromatographic enantiomers separation of cyclopropanes resulted from the intermolecular cyclopropanation of styrene using silylated diazoacetate **4** followed by reduction

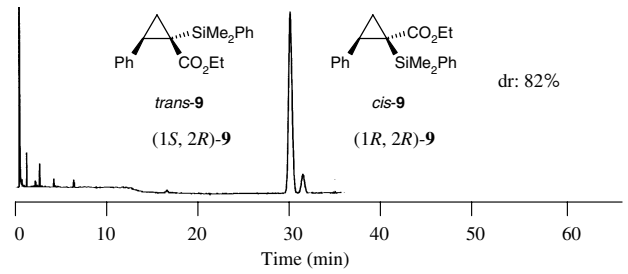

Fig. 16. Gas chromatographic enantiomers separation of ethyl *cis*-and *trans*-1-(dimethylphenylsilyl)-2-phenylcyclopropane-1-carboxylate (*cis*/*trans*-**9**)

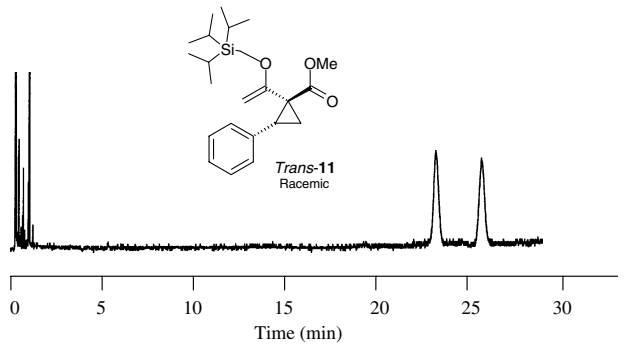

Fig. 17. Gas chromatographic enantiomers separation of methyl-2-phenyl-1-(tris(isopropyl)silanyloxy)-vinyl)-cyclopropanecarboxylate (*trans*-**11**)

Intramolecular Cyclopropanation

The intramolecular cyclopropanation of triethylsilyl-substituted allyl diazoacetates **16**, **18** and **21** were carried out in the presence of chiral rhodium (II) catalyst $[Rh_2(s\text{-nttl})_4]$ in toluene to afford the corresponding cyclopropanes **17**, **19** and **22** with 37%, 8% and 32% ee, respectively (cf. Fig. 11 and 19) [25]. The diazo decomposition of **16** was accompanied by secondary products, the structure which could not be established. However, a β-lactone may be implicated (see below). The diazo decomposition of 2-methyl substituted diazoacetate **18**, in turn, proceeded to **19** in mediocre yield of ca. 20% with up to 8% ee, and was accompanied by formation of the β-lactone **20** in the range of 15 to 18% yield. In contrast, the reaction proceeded well with the *cis*-pent-2-enyl diazoester **21** and resulted in yields of *ca.* 70% of cyclopropane **22** with 32% ee. The structure of **22** was confirmed *via* its protiodesilylation

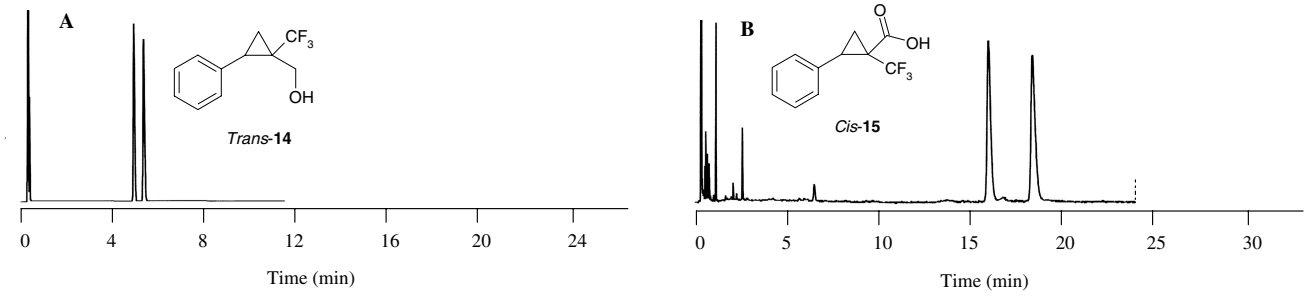

Fig. 18. Gas chromatographic enantiomers separation of trifluoro-substituted cyclopropane derivatives *trans*-**14** and *cis*-**15**.

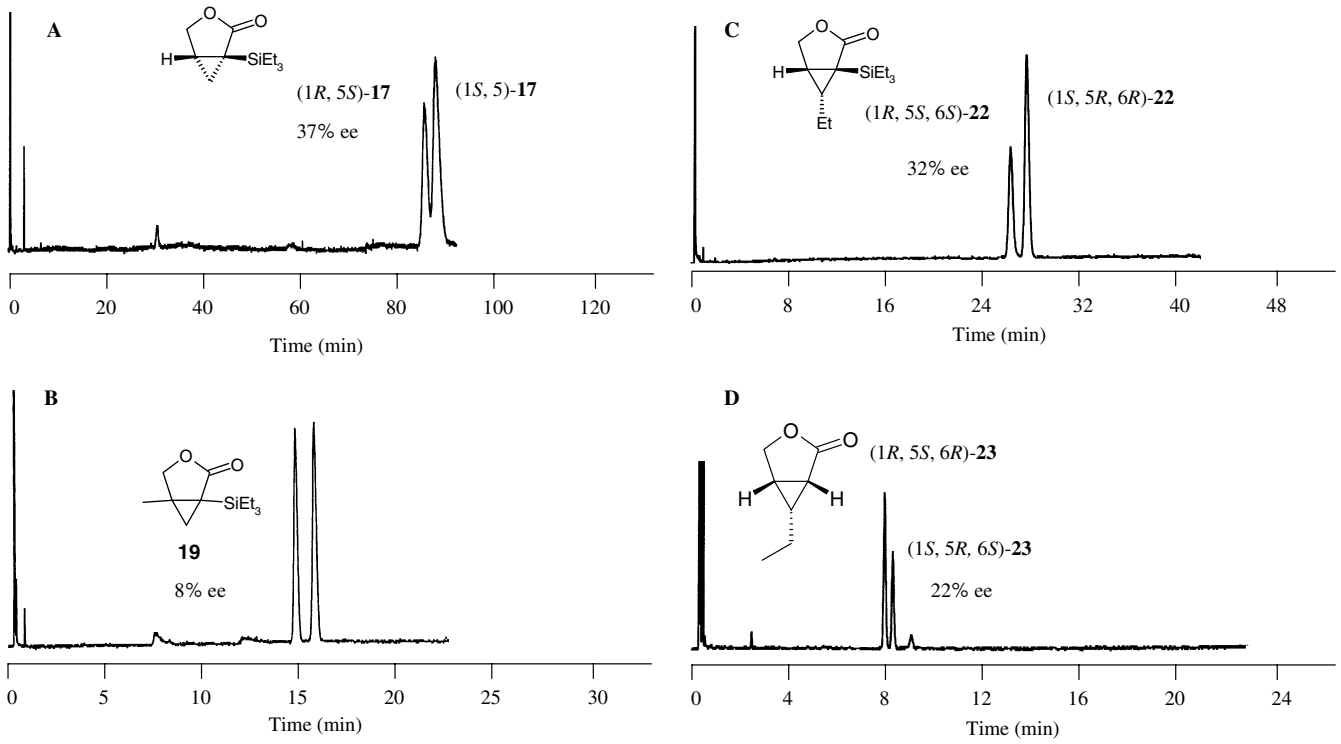

Fig. 19. Gas chromatographic enantiomers separation of cyclopropanes resulted from the intramolecular cyclopropanation of allyl diazo(triethylsilyl)acetates. The effect of the silyl moiety on the separation should be noted (C and D)

with TBAF in THF to afford known **23** with 22% ee, which was used for the determination of the ee. The absolute configuration of **22** was determined according to literature procedure [25].

Enantioselective Separation of Cyclopropane Derivatives

The chiral separation of the cyclopropane derivatives is demonstrated using Chirasil-β-dex as a chiral stationary phase (CSP) for enantioselective gas chromatography [20]. In all cases of cyclopropanes prepared, the reactions were monitored qualitatively and quantitatively using GC-MS with *n*-dodecane as internal standard. Thus, from a single run and with a simple filtration, information regarding the yield of the resulting cyclopropane derivatives and the selectively of the catalyst can be provided without further work up. Although, a baseline gas chromatographic separation was achieved for all cyclopropanes prepared, some of them especially those derived from Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) **3** (cf. Fig. 3) decomposed in GC affording the corresponding dicarboxylic acid cyclopropane derivatives in approximately 16% yield. The latter has been identified qualitatively and quantitatively using GC-MS. (cf. Fig. 12). The enantiomers of the dicarboxylic acid cyclopropane derivatives resulting from the thermal decomposition in GC are baseline separated in some cases (cf. Fig. 12a, b, d) while other derivatives were not resolved (cf. Fig. 12c). Surprisingly, those derived from dimethyl malonate **3′** (cf. Fig. 3) showed also decomposition but to a less extent (cf. Fig. 13b, c). The effect of silyl moiety on the chiral separation was noticed in case of the silylated cyclopropane derivatives **10** and the corresponding desilylated one **11** (cf. Fig. 14c, d). Only the silylated diastereomers of **13** (*cis*/*trans*) could be separated, however, their enantiomers were not (cf. Fig. 15a). The four enantiomers of *cis*/*trans* desilylated version of **13** (*cis*/*trans*-**14**) were baseline separated (cf. Fig. 15b, c and d). Other cyclopropane derivatives containing an alcoholic moiety were successfully resolved with reasonable resolution and

separation factor (cf. Fig. 16 and 18). Among the different classes of cyclopropane derivatives separated by GC, **3′**a, **11** and *trans*-**22** were the fast eluted enantiomers with a resolution (R_s) 4.29, 1.80, 3.37 and a separation factor (α) 1.10, 1.04 and 1.08, respectively. The latter can be used in the high throughput screening to discover the best enantioselective catalyst in a combinatorial approach. Results are summarized in Table 1.

Table 1. Oven temperature (T), retention time (t_R), resolution (R_s) and the separation factor (α) of the simultaneous baseline separation of racemic cyclopropane derivatives

Compounds	Oven temperature[1]	t_R (*S*)	t_R (*R*)	R_s	α
3a	130 °C	37.2	38.8	1.89	1.04
3b	140 °C	33.0	35.1	2.84	1.06
3c	100 °C	14.8	15.7	2.33	1.05
3d	85 °C	28.7	29.9	1.63	1.04
3e	130 °C	21.9	23.1	2.22	1.26
3′a	130 °C	8.7	9.6	4.29	1.10
3′b	120 °C	22.6	24.1	2.65	1.06
3′c	–	–	–	–	–
3′d	–	–	–	–	–
3′e	115 °C	48.5	50.2	1.45	1.03
3′f	140 °C	22.4	23.8	2.60	1.06
Cis/*Trans*-**5**	125 °C	37.4 (*Trans*)	38.6 (*Cis*)	1.05	1.03
Trans-**6**	100 °C	19.7	21.3	3.28	1.08
Cis-**7**	130 °C	42.4	46.7	3.80	1.10
Trans-**7**	130 °C	41.6	45.6	3.71	1.09
Cis/*Trans*-**9**	150 °C	29.4 (*Trans*)	30.7 (*Cis*)	1.77	1.04
Trans-**11**	130 °C	23.2	25.7	4.89	1.10
Trans-**14**	120 °C	4.8	5.2	3.37	1.08
Cis-**15**	150 °C	15.4	17.7	5.46	1.14
17	80 °C	83.7	85.9	1.14	1.02
19	110 °C	14.9	15.9	2.66	1.06
22	105 °C	25.9	27.2	1.93	1.05
23	100 °C	7.7	8.0	1.80	1.04

[1]The head pressure is 150 KPa, the injector temperature is 200 °C and the FID temperature is 250 °C

Conclusion

The utility of polysiloxane-anchored permethylated β-cyclodextrins (chirasil-β-dex) as CSP in GC was demonstrated in the gas chromatographic enantiomeric separation of a set of different class of cyclopropane derivatives prepared *via* inter- and intra-molecular cyclopropanation procedures. The GC method is used for the reaction monitoring and provides chemical yields of the cyclopropane products, enantioselectivity, substrate specifity, and catalytic activity of the chiral catalysts used in the asymmetric cyclopropanation reactions and avoids time-consuming work-up procedures.

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References

1. Liu HW, Walsh CT (1997) In: Rappoport Z (ed) The Chemistry of the Cyclopropyl Group; Wiley, New York, pp. 959–1025
2. Salaün J (2000), Top Curr Chem 207:1–6
3. Nishii Y, Maruyama N, Wakasugi K, Tanabe Y (2001) Bioorg Med Chem 9:33–39
4. Csuk R, Schabel MJ, von Scholz Y (1996) Tetrahedron Asymmetry 7:3505–3512
5. Kumar JS, Roy S, Datta A (1999) Bioorg Med Chem Lett 9:513-514
6. Zhang X, Hodgetts K, Rachwal S, Zhao H, Wasley JWF, Craven K, Brodbeck R, Kieltyka A, Hoffman D, Bacolod MD, Girard B, Tran J, Thurkauf A (2000) J Med Chem 43:3923–3932
7. Csuk R, Kern A, Mohr KZ (1999) Naturforsch: 1463–1468
8. Högberg M, Engelhardt P, Vrang L, Zhang H (2000) Biorg Med Chem Lett 10:265–268.
9. Mohapatra DK, Datta A (1998) J Org Chem 63:642–646
10. Doyle MP, McKervey MA, Ye T (1998) Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides; Wiley-Interscience, New York
11. Dörwald FZ (1998) Metal Carbenes in Organic Synthesis, Wiley-VCH New York,
12. Doyle MP. (1995) In: Headegeus LS (ed) Comprehensive Organometallic Chemistry II Pergamon Press, New York, (1995); Vol. 12; chapters 5.1 and 5.2
13. Pfaltz A (1999) In: Jacobsen EN, Pfaltz A, Yamamoto H (eds) Comprehensive Asymmetric Catalysis. Springer, Berlin, Vol. II, Chapter 16.1, pp. 513–538
14. Rosen TC, Haufe G, (2002) Tetrahedron Asymmetry 13:1397–1405
15. Ressig H-H (1996) Angew Chem Int Ed Engl 35:971–973
16. Müller P, Fernandez D, Nury P, Rossier J-C (1998) J Phys Org Chem 11: 321–333
17. Müller P, Ghanem A (2003) Synlett 12:1830–1833
18. Müller P, Ghanem A (2004) Org Lett in press
19. Ghanem A, Ginatta C, Jiang Z, Schurig V (2003) Chromatographia 57:S275–S281
20. Schurig V, Nowotny HP (1990) Angew Chem Int Ed Engl 29:939
21. Schurig V (2001) J Chromatography A 906:275–299
22. Dietrich A, Maas B, Messer W, Bruche G, Karl V, Kaunzinger A, Mosandl A (1992) J High Resolut Chromatogr 15:590–593
23. Koenig WA, Lutz S, Mischnick-Luebbecke P,Brassat B, Wenz G (1988) J Chromatogr 441–471
24. Armstrong DW, Li WY, Pirha J (1990) Anal Chem 62:217
25. Müller P, Lacrampe, F (2004) Tetrahedron Asymmetry in press
26. Müller P, Bernardinelli G, Allenbach Y, Ferri M, Flack HD (2004) Org Lett 6 (11):1725–1728
27. Müller P, Grass S, Shahi SP, Bernardinelli, G (2004) Tetrahedron 60:4755–4763