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Diazo Compounds and Phenyliodonium Ylides in Inter- and Intramolecular Cyclopropanations Catalyzed by Dirhodium(II). Synthesis and Chiral Resolution by GC *versus* HPLC[#]

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Summary. The dirhodium(II)-catalyzed intermolecular cyclopropanation of a set of olefins with either diazo free phenyliodonium ylides or diazo compounds afforded cyclopropanes derived from *Meldrum*'s acid, dimethyl malonate, (silanoxyvinyl)diazoacetates, 3,3,3-trifluoro-2-diazopropionate, ethyl diazo(triethyl)- and (dimethylphenyl)silylacetate with moderate to high yield in either racemic or enantio-enriched forms. The intramolecular cyclopropanation of triethylsilyl-substituted allyl diazoacetates in the presence of the chiral rhodium(II) catalyst [Rh_2(*s-nttl*)$_4$] in toluene afforded the corresponding cyclopropanes with up to 37% *ee*. An efficient chiral separation method based on enantioselective GC and HPLC was developed. The 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 intramolecular cyclopropanation reactions and avoids time-consuming work-up procedures.

Keywords. Catalysts; Chiral resolution; Cyclopropanes; Gas chromatography; High performance liquid chromatography.

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[#] Dedicated to Prof. *P. Müller* on the occasion of his 65th birthday and retirement from the University of Geneva

Introduction

The cyclopropyl moiety has played an important role in organic chemistry for many years. Its strained structure, unusual and interesting bonding characteristics, and its use as internal mechanistic probe make it unique among cyclic hydrocarbons in its properties, synthesis, and reactions. Naturally occurring and synthetic cyclopropanes bearing simple or complex functionalities are endowed with a large spectrum of biological properties including enzyme inhibitions, insecticidal, antifungal, herbicidal, antimicrobial, antibiotic, antibacterial, antitumor, and antiviral activities [1]. Thus, they constitute a common structure motif in pyrethroids [2], the antidepressant tranylcyclopromine [3], papain and cystein protease inhibitors [4], the potential anti-psychotic substances [5], anti-HIV agents [6], and marine lactones [7]. 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 [8]. Besides the resolution of their racemates [9], a number of synthetic methodologies including asymmetric *Simmons-Smith* reaction and metal-catalyzed reactions of diazo compounds with olefins have been developed to access the enantiomerically pure or enriched cyclopropanes [10]. The latter proceeds *via* asymmetric carbene transfer reaction. Thus, the transition metal-catalyzed decomposition of the diazo precursor affords a metallocarbene as reactive intermediate, which then transfers the carbene moiety to an appropriate substrate. The enantioselectivity of the reaction may be controlled by chiral ligands surrounding the metal. Recently, phenyliodonium ylides were used as potential substitutes to diazo compounds. The utility of the ylide approaches is directly related to the level of selectivity of the process, which is believed to proceed also *via* metal carbenes as intermediates [11].

The ways in which efficiency and practicability of these procedures are defined is depending on a large number of factors. Among these factors are suitable catalyst, scale, reagent costs, time allotted and required, suitable equipment, 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 [12]. Among these methods are: polarimetric methods, gas 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 [13–17]. Here, we report on the synthesis of cyclopropanes derivatives *via* inter- and intramolecular cyclopropanations and their chiral analysis on either Chirasil-β-Dex as chiral selector in GC or cellulose tris(3,5-dimethylphenylcarbamate) [Chiralcel OD] coated on 10 µm silica-gel in High Performance Liquid Chromatography (HPLC).

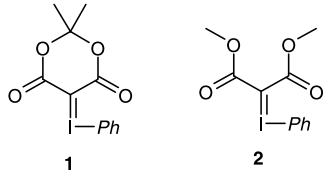
Results and Discussion

Intermolecular Cyclopropanation

A) Diazo Free One Pot Procedure

The conventional ylide approach used to prepare cyclopropanes consists of the intermolecular cyclopropanation of olefins using isolated phenyliodonium ylides **1** or **2** (*cf.* Fig. 1). The efficiency of this method is depending on how the ylide is convenient to handle and isolated in pure form.

To facilitate the procedure, a method was developed to generate the phenyl iodonium ylides **1** and **2** *in situ*. Thus, a set of cyclopropanes derived from *Meldrum*'s acid **4** and dimethyl malonate **5** were prepared using a user-friendly diazo free one-pot procedure. The intermolecular cyclopropanation of olefins **3a**–**3f** was carried out using either **4** or **5** and *Ph*I(O*Ac*)$_2$ (**6**) or *Ph*I=O (**7**) in the presence of 5 mol% of [Rh_2(O*Ac*)$_4$] (**8**) to afford the racemic cyclopropane derivates **11** and **12** with high yields (up to 85%) (*cf.* Fig. 2).



1 **2**

Fig. 1. The phenyliodonium ylide derived from *Meldrum*'s acid (**1**) and from dimethyl malonate (**2**) generated *in situ*

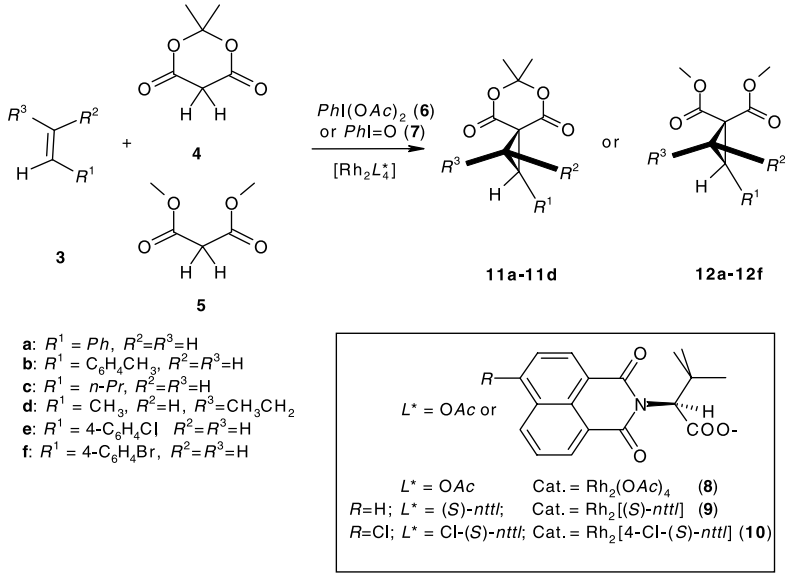


Fig. 2. One pot synthesis of cyclopropane derivatives **11** and **12** using either *Meldrum*'s acid **4** or dimethyl malonate **5** and *Ph*I(O*Ac*)$_2$ **6** or *Ph*I=O (**7**) in presence of either achiral [*L* = O*Ac*] **8** or chiral [*L* = (*S*)-*nttl* **9** or 4-Cl-(*S*)-*nttl* **10**] Rh(II) catalyst

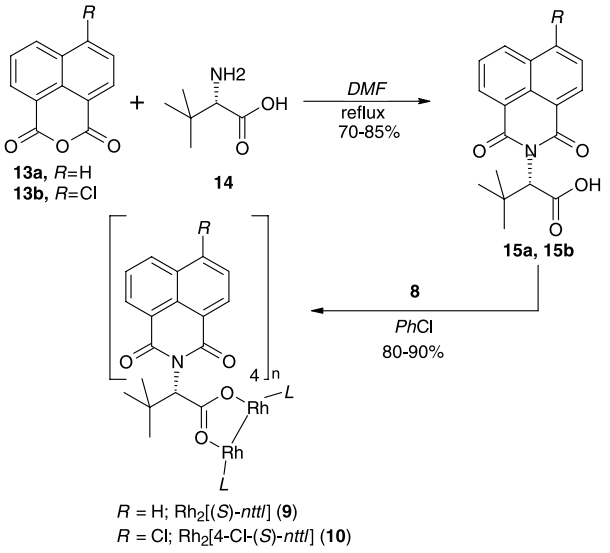


Fig. 3. Synthesis of chiral dirhodium(II) catalyst

The ylides **1** and **2** were generated and decomposed by the appropriate rhodium catalyst *in situ* to afford the cyclopropanes upon reaction with olefins [11]. Attempts to use the chiral rhodium(II) catalyst [Rh_2(*s-nttl*)$_4$] (**9**) (*cf.* Fig. 3) instead of **8** afforded the enantio-enriched cyclopropanes **11a**–**11d** and **11f** derived from **4** with 57%, 51%, 70%, 33%, and 30% *ee*. The cyclopropanation of styrene (**3a**) with **5** and **7** afforded the cyclopropane **12a** with only 37% *ee* whereas **12b**–**12f** were obtained with low *ee* ($<20\%$) (*cf.* Figs. 4–8).

The situation improved markedly, when a chloro substituent was introduced into the 4-position of the naphthalene ring to form Rh_2[4-Cl-(*s*)-*nttl*] (**10**), and the enantiomeric excess of **11a** resulting from the asymmetric cyclopropanation of **3a** with **4** and diacetoxyiodobenzene (**6**) in CH_2Cl_2 was 70% *ee* (81% yield) (*cf.* Fig. 4). Whereas it reached 66% *ee* (77% yield) in the cyclopropanation of **3a** with **5** and **7** in CH_2Cl_2 to afford **12a**. The cyclopropane **12e** was obtained with 56% *ee* (*cf.* Fig. 9). The catalysts **9** and **10** were prepared *via* condensation of the appropriate free or substituted 1,8-naphthalic anhydride **13a** or **13b** and the amino acid l-*tert*-leucine **14** in *DMF*. The ligands were easily prepared and afforded in high yield. Ligand exchange was carried out by refluxing [Rh_2(O*Ac*)$_4$] (**8**) with a 10 fold-excess of the ligand **15a** or **15b** in chlorobenzene. The acetic acid generated was absorbed in anhydrous Na_2CO_3 and the desired chiral dirhodium(II)-catalyst was obtained in 80–90% chemical yield (*cf.* Fig. 4).

B) Cyclopropanation with Isolated Diazo Compounds

The intermolecular cyclopropanations were carried out with either (silanoxyvinyl)-diazoacetates **16** (*cf.* Fig. 5) or 3,3,3-trifluoro-2-diazopropionate (**18**) (*cf.* Fig. 6) and achiral rhodium catalyst **8** to afford *trans*-**17** and a mixture of *cis*/ *trans*-**19** in 60% and 70% yield. The simultaneous reduction of **19** afforded the alcohol

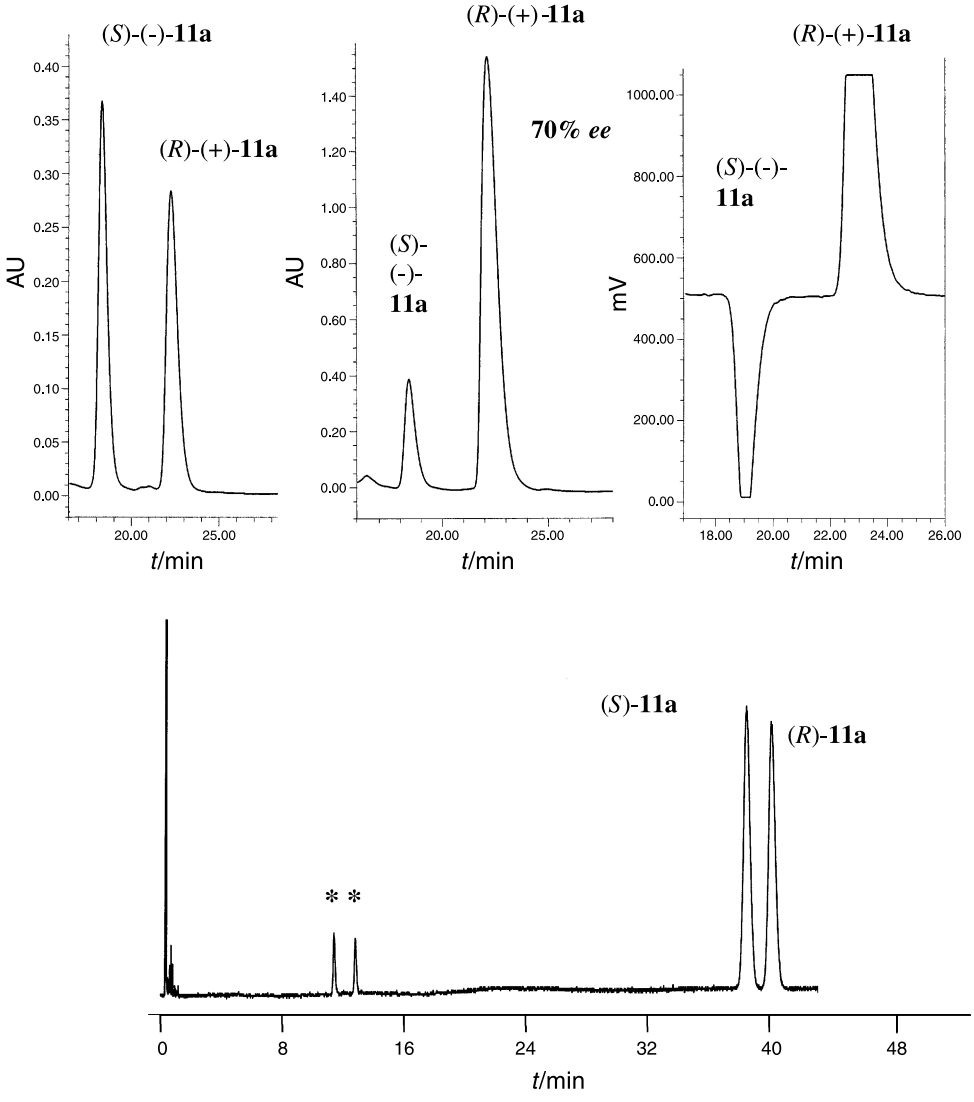


Fig. 4. HPLC versus GC analysis of **11a**

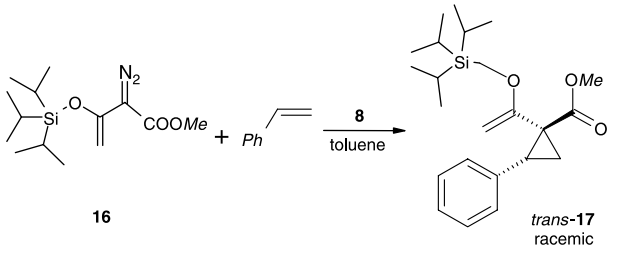


Fig. 5. Intermolecular cyclopropanation of styrene with methyl 3-(tri(isopropyl) silanyloxy)-2-diazobut-3-enoate (**16**)

20 whereas the hydrolysis gave the acid **21**. The esterification of *trans*-**20** with either 3,5-dinitrobenzoic acid or 4-nitrobenzoic acid afforded *trans*-**22** and **23** (*cf.* Fig. 7).

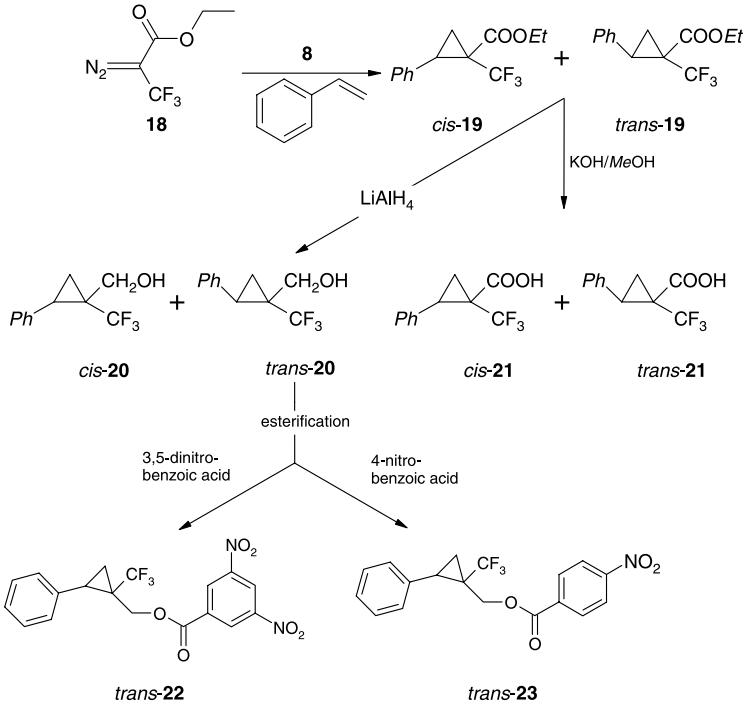


Fig. 6. Intermolecular cyclopropanation of styrene using ethyl 3,3,3-trifluoro-2-diazopropionate (**18**)

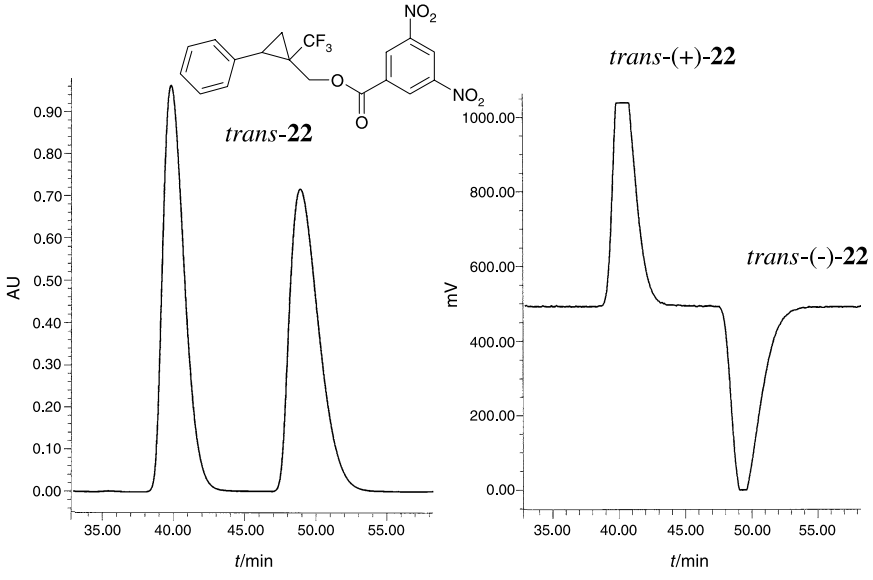


Fig. 7. HPLC analysis of *trans*-**22**

Up on using chiral rhodium(II) catalyst [Rh_2(*s-pttl*)$_4$] or [Rh_2(*s-bpttl*)$_4$] and [Rh_2(*s-nttl*)$_4$] in refluxing toluene, the intermolecular cyclopropanations of styrene with ethyl diazo(triethyl)- and (dimethylphenyl)silylacetate (**24a**) and (**24b**)

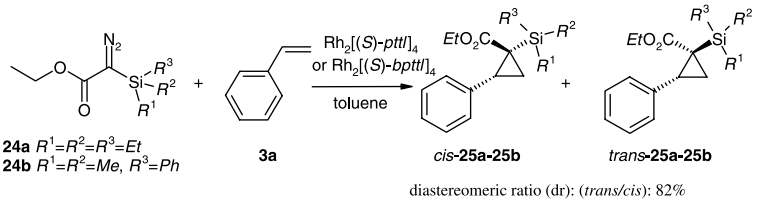


Fig. 8. Intermolecular cyclopropanation of styrene using ethyl diazo(triethylsilyl)acetate (**24a**) and ethyl diazo(dimethylphenylsilyl)acetate (**24b**)

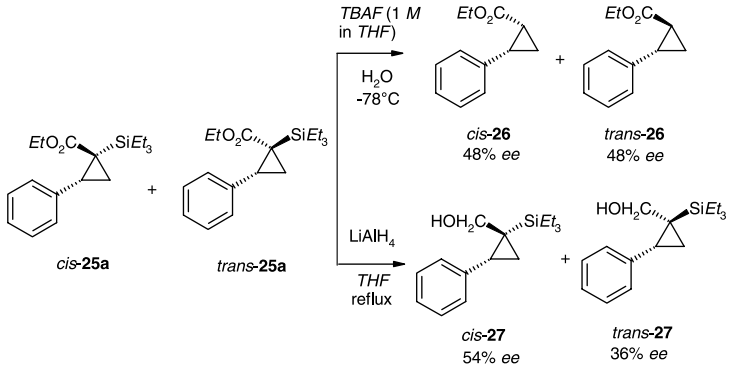


Fig. 9. The desilylation and reduction of ethyl *cis*- and *trans*-1-(triethylsilyl)-2-phenylcyclopropane-1-carboxylate (*cis*/*trans*-**25a**)

afforded the ethyl *cis*/*trans*-1-(triethylsilyl)-2-phenylcyclopropane-1-carboxylate ((*cis*/*trans*)-**25a**) and the ethyl *cis*/*trans*-1-(dimethylphenylsilyl)-2-phenylcyclopropane-1-carboxylate ((*cis*/*trans*)-**25b**) with similar diastereomeric ratio (82% *trans*/*cis* isomers, *cf.* Fig. 8).

The preference for formation of *trans*-**25** where the phenyl and ethoxycarbonyl groups are *cis* (*cf.* Fig. 8) is of some interest since in the cyclopropanation with ethyl diazoacetate the *trans*-isomer usually predominates [18]. However, upon protiodesilylation with *TBAF*, epimerization occurred and the desilylated cyclopropane **26** was isolated in an equal ratio 48/48 *trans*/*cis* mixture (*cf.* Fig. 9) even when the reaction was carried out at −78°C. The enantioselective GC separation of the enantiomers of the cyclopropanes (*cis*/*trans*)-**25** failed, but could be achieved upon their reduction with $LiAlH_4$ to a diastereomeric mixture of the alcohol **27**. The relative configuration of the diastereoisomers of **27** was verified by comparison of the NMR signals of the hydroxymethyl group with those reported in the literature for its trimethylsilyl analogues [18]. The latter failed to undergo protiodesilylation upon exposure to *TBAF* even upon prolonged reaction times (*cf.* Fig. 9).

Intramolecular Cyclopropanation

The intramolecular cyclopropanation of triethylsilyl-substituted allyl diazoacetates **28**, **30**, and **33** was carried out in the presence of **9** in toluene to afford the corresponding cyclopropanes **29**, **31**, and **34** with 37%, 8%, and 32% *ee* (*cf.* Fig. 10). The diazo decomposition of **28** was accompanied by secondary products, the structures of

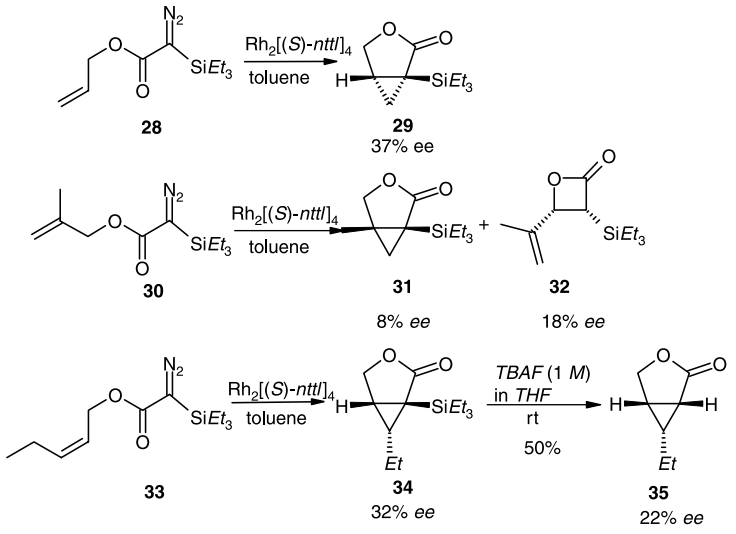


Fig. 10. Rhodium(II)-catalyzed intramolecular cyclopropanation with allyl diazo(triethylsilyl)acetates

which could not be established. However, a β-lactone may be implicated (see below). The diazo decomposition of 2-methyl substituted diazoacetate **30** in turn proceeded to **31** in mediocre yield of *ca.* 20% with up to 8% *ee*, and was accompanied by formation of the β-lactone **32** in the range of 15 to 18% yield. In contrast, the reaction proceeded well with the *cis*-pent-2-enyl diazoester **33** and resulted in yields of *ca.* 70% of cyclopropane **34** with 32% *ee*. The structure of **34** was confirmed *via* its protiodesilylation with *TBAF* in *THF* to afford known **35** with 22% *ee*, which was used for the determination of the *ee*. The absolute configuration of **34** was determined according to Ref. [18].

Enantioselective Separation of Cyclopropane Derivatives

Enantioselective Analysis (GC versus HPLC)

For an efficient monitoring of the reaction progress, enantioselective GC was first used for the determination of the enantiomeric excess of the resulting cyclopropane derivatives. The chiral resolution of the cyclopropane derivatives is demonstrated using a Chirasil-β-dex for enantioselective gas chromatography. The reactions were monitored qualitatively and quantitatively using GC/MS with *n*-dodecane as internal standard. Thus, from a simple filtration and a GC single run, information regarding the yield of the resulting cyclopropane derivatives and the selectivity of the catalyst can be provided without further work up. Albeit the baseline gas chromatographic separation, some of the cyclopropane derivatives derived from *Meldrum*'s acid **11** together with those derived from dimethyl malonate **12** undergo a thermal decomposition in GC to afford a secondary product consisting of the cyclopropane dicarboxylic acid derivatives (*cf.* Fig. 4) in approximately 16% yield. The latter has been identified qualitatively and quantitatively using GC/MS. Some cyclopropanes (*trans*-**22** and **23**) were not separated at all by GC. The effect of silyl moiety on the chiral separation was noticed in case of the silylated cyclopropane

derivatives **25** and the corresponding desilylated one **26**. Only the silylated diastereomers of **25** (*cis*/*trans*) could be separated, however, their enantiomers were not. The four enantiomers of *cis*/*trans* desilylated version of **25** (*cis*/*trans*-**26**) were baseline separated. Other cyclopropane derivatives containing an alcoholic moiety were successfully resolved with reasonable resolution and separation factor. Among the different classes of cyclopropane derivatives separated by GC, **12a**, **17**, and *trans*-**34** 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. The latter can be used in the high throughput screening to discover the enantioselective catalyst in a combinatorial approach. The chromatographic parameters including the separation factor (α) and the resolution (R_s) of the GC enantiomers separation of the cyclopropanes prepared are summarized in Table 1.

To avoid the thermal decomposition by GC and to achieve a base-line separation of all cyclopropanes together with the determination of the sign of their optical rotations, HPLC equipped with a sensitive optical rotation detector for monitoring the optical activity of racemic and enantio-enriched cyclopropanes resulted from the Rh(II)-catalyzed asymmetric carbene transfer reactions was used. The polysaccharide chiral selector consisted of cellulose tris(3,5-dimethylphenylcarbamate) [Chiralcel-OD] and the mobile phase was *n*-hexan/2-propanol (90/10 *v*/*v*) for the

Table 1. Oven temperature (T), retentiom time (t_R), resolution (R_s), and the separation factor (α) of the simultaneous GC separation of racemic cyclopropane derivatives on Chirasil-β-Dex

Compound	Oven temperature[a]/°C	t_R (*S*) / min	t_R (*R*) / min	R_s	α
11a	130	37.2	38.8	1.89	1.04
11b	140	33.0	35.1	2.84	1.06
11c	100	14.8	15.7	2.33	1.05
11d	85	28.7	29.9	1.63	1.04
11e	130	21.9	23.1	2.22	1.26
12a	130	8.7	9.6	4.29	1.10
12b	120	22.6	24.1	2.65	1.06
12c	80	13.7	15.9	1.14	1.02
12d	75	25.9	27.2	1.93	1.05
12e	115	48.5	50.2	1.45	1.03
12f	140	22.4	23.8	2.60	1.06
trans-**17**	130	23.2	25.7	4.89	1.10
trans-**20**	120	4.8	5.2	3.37	1.08
cis-**21**	150	15.4	17.7	5.46	1.14
trans-**22**	ns	ns	ns	ns	ns
trans-**23**	ns	ns	ns	ns	ns
cis/*trans*-**25a**	125	37.4 (*trans*)	38.6 (*cis*)	1.05	1.03
cis/*trans*-**25b**	150	29.4 (*trans*)	30.7 (*cis*)	1.77	1.04
trans-**26**	100	19.7	21.3	3.28	1.08
cis-**27**	130	42.4	46.7	3.80	1.10
trans-**27**	130	41.6	45.6	3.71	1.09

[a] The head pressure is 150 kPa, the injector temperature is 200°C, and the FID temperature is 250°C; ns: not separated by GC

Table 2. Retention time (t_R), resolution (R_s), and the separation factor (α) of the simultaneous HPLC separation of racemic cyclopropane derivatives on Chiralcel OD at room temperature

Compound	t_R (*S*)-(−) min	t_R (*R*)-(+) min	R_s	α
11a	18.4	22.1	3.19	1.21
11b	16.9	19.9	2.57	1.19
11c	27.1	29.2	2.61	1.20
11d	10.9	11.1	1.03	1.01
11e	19.7	24.1	3.24	1.23
12a	18.7	19.6	3.20	1.11
12b	24.3	25.9	2.62	1.02
12c	–	–	–	–
12d	–	–	–	–
12e	21.9	24.5	1.80	1.12
12f	25.3	26.7	2.64	1.05
trans-**17**	23.2 (1R, 2S)	25.7 (1S, 2R)	2.96	1.22
trans-**22**	38.4 (nd)	46.8 (nd)	2.19	1.22
trans-**23**	24.4 (nd)	29.1 (nd)	3.11	1.20

Mobile phase: 2-proponal/*n*-hexane (1/99 *v*/*v*), flow rate 0.3 cm^3/min; nd: the absolute configuration is not determined

cyclopropanes **11** and **12**) and (99/1 *v*/*v*) for the cyclopropanes **17**, **22**, and **23**. The flow rate was 0.3 cm^3/min and the UV detector was set at 270 nm. The chromatographic parameters of the enantioselective HPLC separation of cyclopropane derivatives are summarized in Table 2. The absolute configurations of **11**, **12**, and **17** were determined according to previously reported procedures, however, those of **22** and **23** are not yet known.

Conclusion

A set of cyclopropane derivatives were prepared *via* inter- and intramolecular cyclopropanation catalysed by achiral and chiral rhodium(II) catalysts. Both the diazo and ylide approach were utilized to access to cyclopropanes. The advantages of the liquid chromatographic separation of cyclopropanes' enantiomers over the gas chromatographic analysis of the same compounds were demonstrated. The results revealed that HPLC equipped with a chiralyzer might be a useful tool in the determination of the enantiomeric excess as well as helping in identifying the absolute configuration of cyclopropanes prepared *via* metal-catalyzed carbene transfer reaction.

Experimental

All olefins were commercially available and distilled prior use. *Meldrum*'s acid (2,2-dimethyl-1,3-dioxane-4,6-dione) (**4**), dimethyl malonate (**5**), diacetoxyiodobenzene [*Ph*I(O*Ac*)$_2$] (**6**), 1,8-naphthalic anhydride (**13a**) and its 4-Cl-substituted isomer **13b** were purchased from Acros Organics. Iodosyl benzene [*Ph*I=O] (**7**) was prepared according to Ref. [11b]. [Rh_2{(*S*)-*nttl*}$_4$] (**9**) and [Rh_2{4-Cl-(*S*)-*nttl*}$_4$] (**10**) were prepared as described below. Rh_2(O*Ac*)$_4$ (**8**) was purchased from Pressure Chemical (Pittsburgh, USA). Solvents were dried prior use. HPLC-grade *n*-hexane and 2-propanol were pur-

chased from Fluka. Diazo compounds were synthesized as described below [18–20]. Elemental analysis of **12a**–**12f** were in agreement with the calculated data.

Infrared (IR) spectra were measured on a Shimadzu FT-IR-9100 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker (400 MHz) spectrometer. Chemical shifts of ^{1}H NMR are expressed in ppm downfield relative to internal standard (*TMS*). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak and for IR w, weak; m, medium; s, strong.

The mobile phase for HPLC was filtered through a Millipore membrane filter (0.2 µm) from Nihon Millipore and degassed before use. The buffer was adjusted using a *pH*-meter from Orion Research (model 611). The HPLC system consisted of a Waters binary pump, Model 1525, equipped with a dual λ absorbance detector model 2487, an autosampler model 717plus, and an optical rotation detector (Chiralyzer, IBZ Messtechnik GmbH) operating at room temperature. The UV-detector was set at 245 nm. The Chiralcel OD column (4.6 × 250 mm ID coated on 10 µm silica-gel) was obtained from Daicel Chemical Industries Ltd. Collection of data was performed using Breeze Software from Waters. The gas chromatograph was a Hewlett Packard 580 equipped with a flame ionization detector (FID). The chiral selector permethylated-5-pent-1-enyl-β-cyclodextrin, 20% (w/w) was dissolved in dimethylpolysiloxane containing 5% Si-H groups (Gelest, ABCR GmbH & Co.) and coated on a 20 m × 0.25 mm mm fused silica capillary column (0.25 µm film thickness) according to Ref. [12]. The analytical conditions were: injector temperature, 200°C; FID temperature, 250°C; oven temperature is varying depending on the structure of cyclopropane. H_2 was used as the carrier gas (150 KPa column head pressure).

Synthesis of Substituted [Rh_2{(S)-nttl}$_4$] Catalyst (***10***)

A) Preparation of Ligands

N-4-Chloro-1,8-naphthoyl-(S)-tert-leucine (**15b**, $C_{18}H_{16}O_4NCl$)
A mixture of 1.01 g of l-*tert*-leucine (**14**, 7.72 mmol) and 2.0 g of 4-chloro-1,8-naphthalic anhydride (**13b**, 8.6 mmol) in 25 cm^3 *DMF* was heated to reflux for 1 h under N_2. The *DMF* was removed by distillation and the solid residue was purified by flash chromatography (SiO_2, *Et*OAc/*Me*OH 99/1) gave 2.56 g (86%) (*S*)-4-Cl-{*nttl*} (**15b**) as colorless solid, mp 122°C; $[\alpha]_D^{24} = -53^\circ$ cm^2 g^{-1} ($c = 0.1$, $CHCl_3$); IR (KBr): $\bar{\nu} = 3088$(w), 2956(w), 2912(w), 2862(w), 1736(m), 1703(m), 1660(s), 1585(m), 1569(m), 1366(s), 1341(s), 1234(s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.11$ (s, 9H), 5.48 (s, 1H), 7.69 (d, $J = 8$ Hz, 1H), 7.74 (t, $J = 8$ Hz, 1H), 8.40–8.45 (m, 1H), 8.44 (d, $J = 8$ Hz, 1H), 8.55–8.65 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.5$ (q), 36.1 (s), 59.8 (d), 124.2 (s), 124.9 (s), 128.9 (s), 129.1 (d), 130.7 (d), 130.8 (d), 131.7 (s), 131.8 (d), 132.3 (d), 132.7 (s), 163.8 (s), 164.1 (s), 173.6 (s) ppm; MS: m/z (%) = 345, 347 (M^+, 0), 289 (M^+–C_4H_8, 26), 273 (21), 272 (10), 271 (62), 245 (10), 241 (12), 216 (29), 214 (10), 190 (11), 188 (34), 160 (15), 126 (12), 73 (100), 57 (40); HR MS: $m/z = (C_{14}H_8O_4N^{35}Cl^+)$ calcd 289.0142 found 289.0168; ($C_{14}H_8O_4N^{37}Cl^+$) calcd 291.0112, found 291.0139.

B) Ligand Exchange

Dirhodium(II) tetrakis[N-4-chloro-1,8-naphtholyl-(S)-tert-leucinate]
[Rh_2{(S)-4-Cl-nttl}$_4$] (**10**, $C_{72}H_{60}N_4Cl_4O_{16}Rh_2$)
Dirhodium(II) acetate (**8**) (110 mg, 0.25 mol), 0.82 g **15b** (2.4 mmol), and 40 cm^3 of chlorobenzene were heated to reflux under N_2 in a *Soxhlet* apparatus fitted with a thimble containing dried Na_2CO_3 and sand in a 1:1 ratio. After 24 h the solvent was evaporated and the gummy residue was purified by flash chromatography (Al_2O_3 basic, *Me*OH) to afford 3.2 g **10** (85%) as green solid. $[\alpha]_D^{24} = +166^\circ$ cm^2 g^{-1} ($c = 0.1$, $CHCl_3$); IR (KBr): $\bar{\nu} = 295$(w), 1709(s), 1667(s), 1608(m), 1591(m), 1575(m), 1399(m), 1366(m), 1344(s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.31$ ((s), 9H), 5.79 ((s), 1H), 8.28–8.30 ((m), 2H), 8.32 (d, $J = 8$ Hz, 1H), 8.43 (d, $J = 8$ Hz, 1H), 8.51–8.60 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.8$ (q), 29.4 (q), 29.7 (q), 36.2 (s), 62.1 (d), 121.8 (s), 123.2 (s), 123.3 (s), 127.4 (d), 127.8 (d), 128.4 (d), 128.9 (s), 131.8 (d), 132.2 (d), 138.5 (s), 162.4 (s), 162.7 (s), 186.8 (s) ppm; MS (MALDI): $m/z = (C_{72}H_{60}{}^{35}Cl_4N_4O_{16}NaRh_2^+)$ calcd 1605.0768, found 1605.0680.

*Representative Procedure for the Intermolecular Cyclopropanation of Olefins Using Meldrum's Acids (**11a–11d**)*

Dichloromethane (10 cm^3) was added through a syringe into a 50 cm^3 round bottom flask containing a mixture of 2.1 mmol *Meldrum*'s acid (1 equiv), 2.9 mmol *Ph*I(O*Ac*)$_2$ (1.4 equiv), 5 mol% [Rh_2(O*Ac*)$_4$] or [Rh_2{(*S*)-*nttl*}$_4$], 2.3 equiv Al_2O_3 and 250 mg of molecular sieves 4 Å, followed by the addition of 10 equiv olefin. The reaction mixture was thermostated in an oil bath to 30°C and stirred under Ar. Samples (100 mm^3) were taken after time intervals. The samples were filtered using a syringe filter holder (0.2 µm pore size) and the organic layer was diluted with 100 mm^3 CH_2Cl_2 and analyzed 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 CH_2Cl_2. 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.

*General Procedure for the Intermolecular Cyclopropanation of Olefins Using Dimethyl Malonate as a Carbene Precursor (**12a–12f**)*

Dimethyl malonate (0.01 mol) is added to a mixture of 1.4 equiv 7, 10 equiv olefins, 2.3 equiv MgO, 5 mol% rhodium(II) catalyst, and 250 mg molecular sieves 4 Å in 10 cm^3 CH_2Cl_2. The reaction mixture is stirred under Ar for 24 h. Samples (100 mm^3) were taken after time intervals and filtered using a syringe filter holder (0.2 µm pore size), and the organic layer was diluted with 100 mm^3 CH_2Cl_2 for the GC analysis. The reaction progress was monitored qualitatively and quantitatively by GC-MS using *n*-dodecane as internal standard. When maximum conversion was reached, the reaction was terminated by filtration through celite. The residue on the celite was washed twice with CH_2Cl_2. 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.

The characterization of **12d** [10] as well as those derived from *Meldrum*'s acids **11a–11f** were in agreement with previously reported data [11].

Dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (**12a**, $C_{13}H_{14}O_4$)

Yield 1.75 g (75%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.71$ (dd, $J = 4$, 4 Hz, 1H), 2.18 (dd, $J = 4$, 4 Hz, 1H), 3.21 (t, $J = 8$ Hz, 1H), 3.34 (s, 3H), 3.76 (s, 3H), 7.19–7.28 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.1$ (t), 32.6 (d), 37.2 (s), 52.2 (q), 52.6 (q), 127.4 (d), 128.2 (d), 128.4 (d), 134.5 (s), 164.8 (s), 169.4 (s) ppm; HR MS: $m/z = (C_{13}H_{14}O_4^+)$ calcd 234.0892, found 234.0897.

Dimethyl 2-(4-methylphenyl)cyclopropane-1,1-dicarboxylate (**12b**, $C_{14}H_{16}O_4$)

Yield 1.78 g (72%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.79$ (dd, $J = 4$, 4 Hz, 1H), 2.18 (dd, $J = 8$, 8 Hz, 1H), 2.20 (s, 3H), 3.21 (t, $J = 12$ Hz, 1H), 3.42 (s, 3H), 3.81 (s, 3H), 7.15 (s, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.0$ (t), 20.9 (q), 32.3 (d), 37.0 (s), 52.0 (q), 52.6 (q), 128.1 (d), 128.7 (d), 131.3 (s), 136.9 (s), 166.9 (s), 170.1 (s) ppm; HR MS: $m/z = (C_{14}H_{16}O_4^+)$ calcd 248.10491, found 248.10530.

Dimethyl 2-propylcyclopropane-1,1-dicarboxylate (**12c**, $C_{10}H_{16}O_4$)

Yield 1.1 g (55%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.90$ (t, $J = 7$ Hz, 3H), 1.09–1.19 (m, 1H), 1.37–1.52 (m, 5H), 3.34 (s, 3H), 3.76 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.7$ (q), 21.5 (t), 22.2 (t), 28.2 (d), 30.6 (t), 33.9 (s), 52.2 (q), 52.4 (q), 168.8 (s), 171.4 (s) ppm; HR MS: $m/z = (C_{10}H_{16}O_4^+)$ calcd 200.2324, found 200.2321.

Dimethyl 2-(4-chlorophenyl)cyclopropane-1,1-dicarboxylate (**12e**, $C_{13}H_{13}ClO_4$)

Yield 1.4 g (53%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.72$ (dd, $J = 4$, 4 Hz, 1H), 2.13 (dd, $J = 8$ Hz, 1H), 3.16 (t, $J = 8$ Hz, 1H), 3.40 (s, 3H), 3.79 (s, 3H), 7.12 (d, $J = 8$ Hz, 2H), 7.23 (d, $J = 8$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.1$ (t), 30.7 (d), 36.2 (s), 51.9 (q), 52.4 (q), 127.6 (d), 129.0

(d), 132.1 (s), 132.3 (s), 165.8 (s), 168.9 (s) ppm; HR MS: $m/z = (C_{13}H_{13}O_4^{35}Cl^+)$ calcd 268.0502, found 268.0492.

Dimethyl 2-(4-bromophenyl)cyclopropane-1,1-dicarboxylate (**12f**, $C_{13}H_{13}BrO_4$)
Yield 1.6 g (54%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.75$ (dd, $J = 4$, 4 Hz, 1H), 2.15 (dd, $J = 8$, 8 Hz, 1H), 3.21 (t, $J = 8$ Hz, 1H), 3.42 (s, 3H), 3.81 (s, 3H), 7.08 (d, $J = 4$ Hz, 2H), 7.40 (d, $J = 8$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.1$ (t), 32.6 (d), 37.2 (s), 52.2 (q), 52.6 (q), 120.4 (s), 129.1 (d), 129.9 (d), 132.6 (s), 165.8 (s), 168.9 (s) ppm; MS: m/z (%) = 314 (M^+, 14), 312 (M^+, 14), 282 (82), 280 (28), 250 (20), 148 (19), 202 (19), 201 (100), 199 (69), 195 (26), 193 (26), 173 (20), 170 (27), 145 (27), 129 (13), 115 (62), 114 (23), 113 (10), 103 (12), 102 (10), 89 (16), 77 (14), 63 (17), 59 (45), 51 (10); HR MS: $m/z = (C_{13}H_{13}O_4^{79}Br^+)$ calcd 311.9997, found 312.0010; $(C_{13}H_{13}O_4^{81}Br^+)$ calcd 313.9977, found 313.9998.

*Rh(II)-catalyzed Intermolecular Cyclopropanation of Styrene (**3a**)*
*with Methyl-3-(tri(isopropyl)silanyloxy)-2-diazobut-3-enoate (trans-**17**)*
The rhodium catalyst (0.008 mmol) was activated by heating in *vacuo* and dissolved in 3 cm^3 of toluene. After addition of 7 mmol **3a**, the mixture was cooled to 0°C, and 0.70 mmol **16** in 2 cm^3 of toluene were 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*$_2$O/*n*-pentane 5/95) to afford *trans*-**17** in 60% yield, in agreement with previously reported data [19].

General Procedure for the Rh(II)-catalyzed Carbene Transfer
*with Ethyl 3,3,3-trifluoro-2-diazopropionate (cis/trans-**19**)*
The diazo compound **18** (92 mg, 0.50 mmol) dissolved in 5 cm^3 CH_2Cl_2 was added to 5 mmol olefin dissolved in 5 cm^3 CH_2Cl_2 containing 5 mol% of the appropriate catalyst 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 20 cm^3 CH_2Cl_2. The solvent was removed in *vacuo* and the crude product was purified by flash chromatography to afford the desired cyclopropanes *cis/trans*-**19**. The reduction and hydrolysis of *cis/trans*-**19** to *cis/trans*-**20** and **21** were performed according to Ref. [20].

Rh(II)-catalyzed Intermolecular Cyclopropanation of Styrene
*with Silylated Diazoacetate (**25a**, **25b**)*
To the Rh(II)-catalyst (2 mol%) was added 920 mm^3 **3a** (8.0 mmol) under Ar and 0.85 mmol silylated diazoacetate **24a** or **24b**. 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 according to Ref. [18].

Desilylation of cis- and trans-2-Phenyl-1-(triethylsilyl)-1-hydroxymethylcyclopropane
***25a** (cis/trans-**26**)*
To a 82:18 mixture of *trans*- (48% *ee*) and *cis* **5** (30% *ee*) (142 mg, 0.56 mmol) in 3.0 cm^3 *THF* was added 1 cm^3 *TBAF* (1 *M*) in *THF* at −78°C. The temperature was allowed to reach rt. After stirring for 2–4 h the mixture was quenched with 2 cm^3 H_2O and extracted with CH_2Cl_2. The organic layer was evaporated, dried ($MgSO_4$), and the residue was purified by flash chromatography (SiO_2, *n*-pentane/*Ac*O*Et* 97/3) to afford a 70:30 mixture of ethyl *cis*- and *trans*-2-phenylcyclopropane-1-carboxylate (**26**), (1*S*,2*S*)-*trans*-**26** (48% *ee*) and (1*R*,2*S*)-*cis*-**26** (48% *ee*) in 81% yield.

Reduction of cis- and trans-2-Phenyl-1-(triethylsilyl)-1-hydroxymethylcyclopropane
***5** (cis/trans-**27**)*
0.8 mmol *cis/trans* mixture of **25a** in 4.0 cm^3 *THF* was added to a suspension of 2 equiv $LiAlH_4$ in 2.0 cm^3 *THF* under Ar. The mixture was stirred overnight at rt. The excess of $LiAlH_4$ was decomposed by the addition of 2 cm^3 ethylene diamine, followed by 2 cm^3 8% NaOH and H_2O. The crude product

was extracted with 10 cm Et_2O, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The separation of the diastereoisomers by flash chromatography (SiO_2, CH_2Cl_2/*n*-pentane 80/20) afforded *cis*/*trans*-**27**.

*General Procedure for the Intramolecular Cyclopropanation of Allyl diazo(triethylsilyl)acetates (**29**, **31**, **34**)*

To the Rh(II)-catalyst (2% with respect to the allyl diazo(triethylsilyl)acetates) were added 0.40 mmol diazosilane **28**, **30**, or **33** under Ar in 5 min. The mixture was stirred during 2 h at rt. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography to afford the desired cyclopropanes according to Ref. [18].

*General Procedure for the Desilylation of 1-(Triethylsilyl)-3-oxabicyclo[3.1.0]hexan-2-ones (**35**)*

A solution of 1 cm^3 *TBAF* (1 *M* in *THF*) was added dropwise to 0.56 mmol of the appropriate bicyclohexane **34** at rt. After stirring for 2–4 h, 2 cm^3 H_2O were 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 **35**.

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