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Methods for the synthesis of donor-acceptor cyclopropanes

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The interest in cyclopropane derivatives is caused by the facts that, first, the three-carbon ring is present in quite a few natural and biologically active compounds and, second, compounds with this ring are convenient building blocks for the synthesis of diverse molecules (acyclic, alicyclic and heterocyclic). The carbon – carbon bonds in cyclopropane are kinetically rather inert; hence, they need to be activated to be involved in reactions. An efficient way of activation is to introduce vicinal electron-donating and electron-withdrawing substituents into the ring; these substrates are usually referred to as donor-acceptor cyclopropanes. This review gives a systematic account of the key methods for the synthesis of donor-acceptor cyclopropanes. The most important among them are reactions of nucleophilic alkenes with diazo compounds and iodonium ylides and approaches based on reactions of electrophilic alkenes with sulfur ylides (the Corey – Chaykovsky reaction). Among other methods used for this purpose, noteworthy are cycloalkylation of CH-acids, addition of α-halocarbonyl compounds to alkenes, cyclization *via* 1,3-elimination, reactions of alkenes with halocarbenes followed by reduction, the Simmons – Smith reaction and some other. The scope of applicability and prospects of various methods for the synthesis of donor-acceptor cyclopropanes are discussed.
The bibliography includes 530 references.

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1. Introduction

The chemistry of strained organic molecules, first of all, cyclopropane derivatives is a rapidly developing area of modern organic chemistry. The interest in these compounds is caused by the fact that, on the one hand, a three-carbon ring is a part of many natural products and physiologically active compounds,[1–4] and, on the other hand, compounds with a three-carbon ring have now become convenient building blocks for the preparation of various acyclic, alicyclic and heterocyclic molecules; in particular, they are widely used in the total syntheses of diverse natural compounds and pharmaceuticals.[4–7] The three-carbon ring has a high strain energy (27.5 kcal mol^{-1}); therefore, ring opening can serve as the driving force for many transformations of cyclopropane derivatives. Nevertheless, the C–C bonds in cyclopropane are kinetically fairly inert. Therefore, reactions involving these bonds usually require additional activation, which may be attained by both the action of external factors (more drastic reaction conditions or more reactive reagents) and introduction of activating groups into the three-membered ring. The methods for cyclopropane activation by external factors have a limited synthetic potential, because drastic reaction conditions usually induce a variety of side reactions and, as a consequence, result in low yields of the target products. Conversely, the introduction of activating substituents often ensures high selectivity of reactions involving cyclopropanes. To date, there exists a large body of factual data on the effect of substituents on the three-carbon ring geometry[8] and, hence, reactivity. The highest reactivity is inherent in cyclopropanes **1a–d** with electron-donating and electron-withdrawing substituents in vicinal positions (Fig. 1).

Most popular electron-donating groups are heteroatomic (alkoxy, amino, alkylthio and silylmethyl groups) as well as aromatic, heteroaromatic and alkenyl groups capable of efficient stabilization of the positive charge. The most frequently used electron-withdrawing functional groups include alkoxycarbonyl, carbonyl, nitrile, sulfonyl and nitro groups, which stabilize the arising carbanionic centre. Currently, most attention is paid to the reactions of 2-alkenyl- and 2-aryl(hetaryl)cyclopropane-1,1-dicarboxylates, as they are easily accessible and highly reactive.

The concerted effect of substituents with opposite electronic properties provides a considerable polarization of the C–C bond between the atoms bearing these substituents; therefore, cyclopropanes can undergo various transformations accompanied by cleavage of this bond. These conclusions are supported by numerous experimental data.[9–11] Substituted cyclopropanes like **1b**,**c** usually exhibit the highest reactivity. These cyclopropanes can be additionally activated by Lewis acids, which are coordinated to the electron-withdrawing group(s) and thus increase polarization of the C–C bond up to complete bond cleavage to give 1,3-zwitterion.

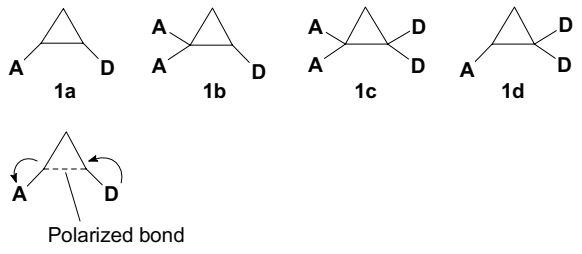


Figure 1. Cyclopropanes with donor-acceptor subsituents. **D** are electron-donating groups (OR, SR, NR_2, Ar, $C(R)=CR'R''$, CH_2SiR_3), **A** are electron-withdrawing groups [CO_2R, CN, C(O)R, SO_2Ph, $P(O)(OR)_2$, NO_2].

In 1980, Reissig and Hirsch[12] proposed the name 'donor-acceptor-substituted cyclopropanes' for these compounds, which was later transformed into 'donor-acceptor cyclopropanes' (DACs). In recent years, the chemistry of such activated cyclopropanes **1** has been studied very intensively and has formed a separate research area.[3]

Various ring-opening reactions, cycloaddition, annulation and rearrangements of DACs form the basis for preparative methods for the synthesis of various acyclic and carbo- and heterocyclic compounds. Lately, chemical transformations of DACs, in particular, 2-arylcyclopropane-1,1-dicarboxylates, have been markedly extended *via* conversion of the cyclopropanes to relatively stable 1,2-zwitterionic intermediates by treatment with anhydrous gallium trihalides (Scheme 1).[13,14]

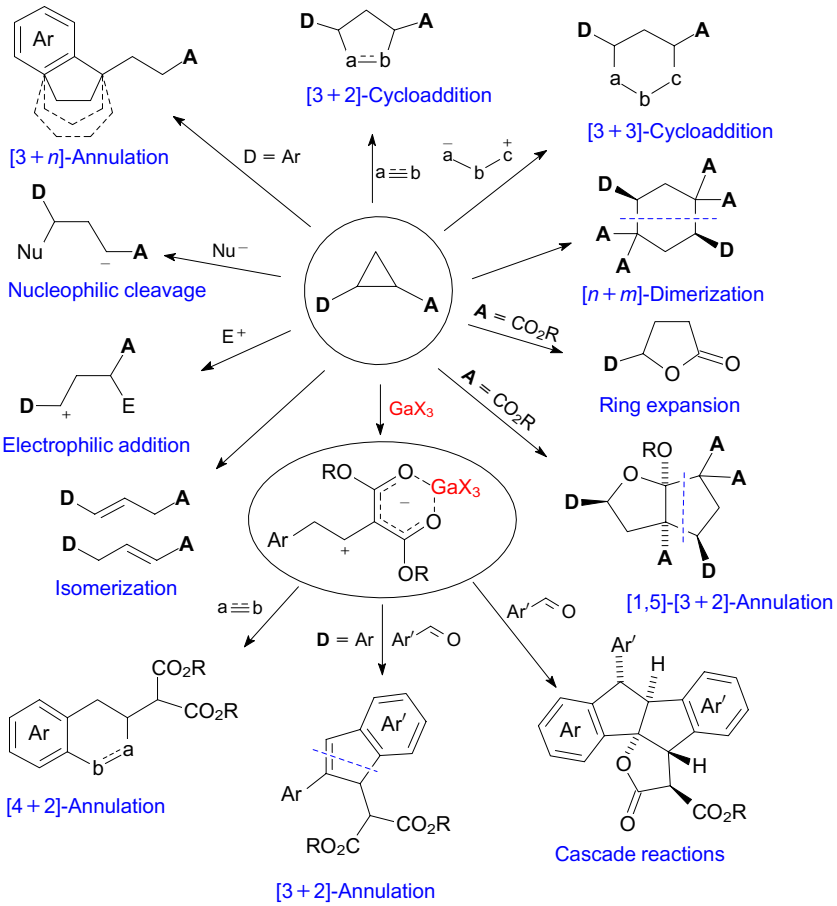
High reactivity and high synthetic potential of DACs account for the increased interest of researchers in these compounds. The first review[9] devoted to donor-acceptor cyclopropanes appeared back in 1988. During the last 10–15 years, a monograph[3] and quite a few reviews on various aspects of DAC chemistry have been published.[5,10,11,15–42]

Conversely, there is still no review dedicated to the methods for the synthesis of DACs; only two reviews[9,10] dealing with DAC chemistry, the more recent of which appeared in 2003, briefly summarize the information accumulated by that time on the major synthetic routes to these compounds. The reviews published in the last 15 years contain only sections devoted to particular classes of DACs or to particular methods of synthesis. For example, the preparation of optically active DACs is considered in some parts of two reviews[43,44] and in a monograph.[45] Several reviews that present methods for the synthesis of particular DACs are also noteworthy. Specifically, methods for DAC preparation from glycals have been integrated;[15,31] the synthesis of a number of substrates for intramolecular cross-cycloaddition has been reported;[23] several publications summarize the preparation methods for indole-based DACs,[37] DACs resulting from cyclopropanation of furans and pyrroles,[35] donor-acceptor aminocyclopropanes[29] and vinylcyclopropanes[46] and also DACs containing purine or pyrimidine donor substituents.[47] Finally, the data on the DAC synthesis reported in a recent limited edition monograph[3] are mainly historical, while currently the most demanded DACs, in particular, those containing two acceptor groups, are left beyond the scope of consideration.

Hence, review publications covering the modern methods for the synthesis of donor-acceptor cyclopropanes are virtually missing. Therefore, in this review, we summarize data on DAC preparation methods published in the last 15 years, primary attention being focused on DACs with one donor and two acceptor groups and DACs with one acceptor group and with aryl, alkoxy, amino and alkylthio groups as donor substituents.

The following designations and abbreviations are used in the review:

Scheme 1

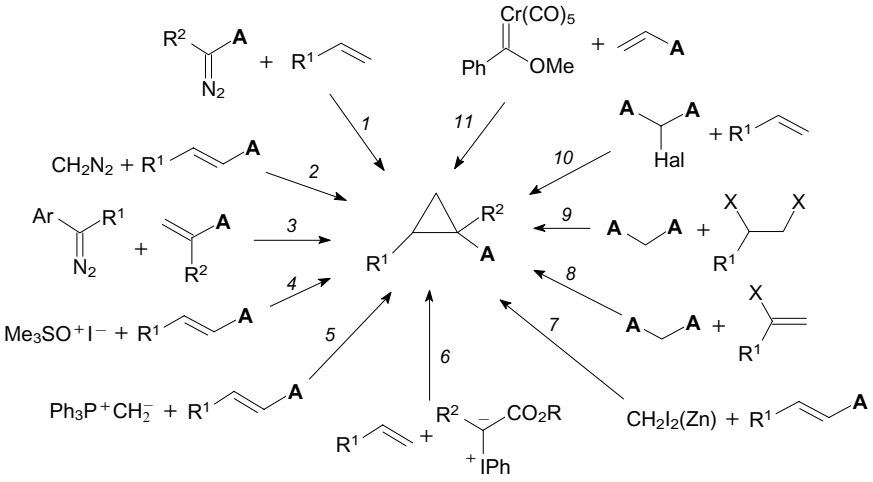


A — acceptor group;
acac — acetylacetonate;
Ad — adamantyl;
B: — base;
bmim — 1-n-butyl-3-methylimidazolium;
Boc — *tert*-butyloxycarbonyl;
m-CPBA — *m*-chloroperoxybenzoic acid;
Cy — cyclohexyl;
D — donor group;
DABCO — 1,4-diazabicyclo[2.2.2]octane;
DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene;
DCC — dicyclohexylcarbodiimide;
DCE — 1,2-dichloroethane;
DIPEA — diisopropylethylamine;
DMAP — 4-dimethylaminopyridine;
dr — diastereomeric ratio;
EDCI — 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide;
esp — α,α,α′,α′-tetramethylbenzene-1,3-dipropanoate;
EWG — electron-withdrawing group;
Fc — ferrocenyl;
Fu — furyl;
HMPA — hexamethylphosphoramide;
HOBt — 1-hydroxybenzotriazole;
IBX — iodoxybenzoic acid;
LG — leaving group;
LiHMDS — lithium hexamethyldisilazide;
MIRC — Michael initiated ring closure reaction;
MS — molecular sieves;
MW — microwave radiation;
Naph — naphthyl;
NBS — *N*-bromosuccinimide;
NMO — *N*-methylmorpholine *N*-oxide;
Ns — 4-nitrobenzenesulfonyl;
oct — octanoate;
PCC — pyridinium chlorochromate;
Piv — pivaloyl;
PMB — *p*-methoxybenzyl;
PMDETA — *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine;
Py — pyridyl;
rt — room temperature;
solv — solvent;
TBS — *tert*-butyldimethylsilyl;
Tf — trifluoromethanesulfonyl;
Th — thienyl;
TPAP — tetrapropylammonium perruthenate;
TPP-H_2 — *meso*-tetraphenylporphyrin;
Ts — *p*-toluenesulfonyl;
DAC — donor-acceptor cyclopropane.

2. General approaches to the synthesis of donor-acceptor cyclopropanes

Donor-acceptor cyclopropanes have now become convenient, readily accessible starting compounds in organic synthesis. This is possible, first of all, owing to the development of the chemistry of carbenes and small rings. The general approaches to the synthesis of functionally substituted cyclopropanes have been considered in monographs,[4, 48 – 53] collections,[54 – 61] reviews addressing DACs,[9, 10, 15, 17, 29, 62]

Scheme 2



R^1 = H or **D**; R^2 = H or **A**; X = Hal, SO_2Ar

general reviews on cyclopropane chemistry,[63–66] reviews devoted to particular methods of cyclopropane synthesis, in particular, methods involving organozinc compounds (Simmons – Smith reaction and its versions) [67,68] and sulfur ylides [69] and reactions of diazocarbonyl compounds,[70] and reviews [43,44,71–77] considering the synthesis of optically active cyclopropanes.

As regards particularly DACs, quite a number of general schemes have been proposed for their synthesis (see, for example, Refs 4, 9 and 10). Most of the reactions are general and are applicable to the preparation of numerous donor-acceptor cyclopropanes from reactive substrates containing electron-donating and electron-withdrawing substituents in different molecules, or both electron-donating and electron-withdrawing substituents in vicinal positions of one molecule. The use of chiral reagents and/or catalysts may serve for the preparation of optically active DACs.

One of widely applicable and available methods for the synthesis of DACs is catalytic cyclopropanation of alkenes with diazo compounds (Scheme 2, pathways *1–3*), especially diazo compounds with electron-withdrawing substituents (pathway *1*). Another approach is MIRC reactions (pathways *4–6*), which have been widely spread in recent years owing to the development of the Corey – Chaykovsky reaction (pathway *4*). Particularly these methods receive most attention in the review.

Some other methods are also used for the targeted synthesis of DACs such as synthetic protocols involving organozinc reagents (Simmons – Smith reaction, pathway *7*), cycloalkylation of CH-acids (pathways *8*, *9*), addition of halomalonates to styrenes (pathway *10*) and cyclopropanation with Fischer type carbene complexes (pathway *11*). However, most of these methods are not generally applicable or are occasionally used.

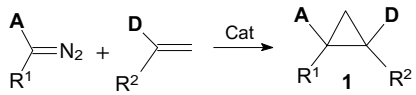
3. Cyclopropanation of alkenes with diazo compounds

Alkene cyclopropanation with diazo compounds (usually catalyzed by metal complexes) is widely used in organic synthesis to construct a three-carbon ring. Diazocarbonyl compounds and diazomethane are now the most widely employed diazo compounds. The reaction is carried out in the presence of catalysts that decompose the diazo compound with simultaneous addition of the carbene complexes thus formed to the double bonds of unsaturated substrates. Most often, compounds (complexes) of transition metals such as copper, rhodium, palladium, ruthenium and cobalt are used as catalysts. The cyclopropanation mechanism is determined by the nature of the catalyst metal. The general features of application of diazo compounds in organic synthesis and the key regularities of reactions in which they participate are described in monographs.[78,79]

3.1. Diazo compounds with electron-withdrawing substituents

The reaction of diazo compounds containing electron-withdrawing groups (in particular, diazo carbonyl compounds) with alkenes containing electron-donating substituents is one of the most versatile and widely used general methods for DAC synthesis. Most widely employed are alkyl diazoacetates and diazomalonates, which give rise to 2-aryl(hetaryl)cyclopropane-1-carboxylates (**1a**, R^1 = H, **A** = CO_2R) or -1,1-dicarboxylates (**1b**, R^1 = **A** = CO_2R), which are, in most cases, typical representatives of DACs (Scheme 3). The reaction is catalyzed by transition metal (Cu, Rh, Ru, Ir, Os, Co) compounds and smoothly gives target cyclopropanes in high yields.

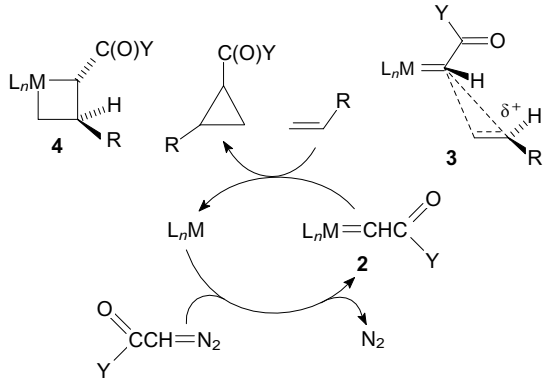
Scheme 3



A = CO_2R^3, C(O)R^3, CN, NO_2, *etc.*; **D** = Ar, OAlk, OAr, *etc.*; R^1 = H, **A**; R^2 = H, **D**

It is assumed (Scheme 4) that the reaction starts with the formation of metal-stabilized carbene complex **2**, which is then involved in the chemoselective intermolecular cyclopropanation *via* a metal carbene complex with the alkene (**3**) (but not the cyclobutane complex **4**).[73] In the case of chiral ligands (*e.g.*, porphyrins [80]), this method affords optically active cyclopropanes.[44,71,73,81] This scheme also accounts for the observed diastereoselectivity in favour of *trans*-

Scheme 4



M = Cu, Rh, Ru, Co, *etc.*

isomers of the cyclopropane products, as a result of steric factors in the transition state.

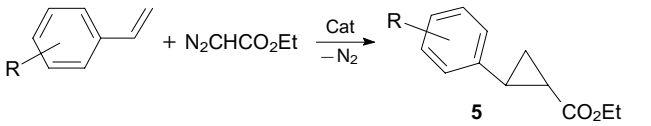
This scheme is consistent with the known effects of substituents at the alkene double bond on the cyclopropanation with various diazocarbonyl compounds in the presence of various catalysts (copper,[82–84] rhodium,[85,86] ruthenium[87] and iridium[88] compounds). The reaction rates were found to follow a linear Hammett correlation, which supports the mechanism with intermediate participation of an electrophilic metal carbene complex (see Scheme 4). Therefore, the introduction of acceptor substituents into the alkenes results, as expected, in decreasing reaction rates and decreasing cyclopropane product yields. Nevertheless, owing to the high reactivity of carbene complexes even with insufficiently nucleophilic alkenes, preparative yields can be attained for cyclopropanes by selecting appropriate catalysts. Indeed, the low yield of the products of 4-nitrostyrene cyclopropanation with ethyl diazoacetate in the presence of copper compounds could be increased to 84% by using iridium porphyrin complexes.[88] In these cases, the method for the synthesis of cyclopropanecarboxylate is virtually the only preparative method, because the alternative routes to compounds of this type (*e.g.*, the Corey – Chaykovsky reaction) do not lead to the desired outcome.

Obvious benefits of the alkene cyclopropanation with diazocarbonyl compounds are also ready accessibility and stability of the starting diazo compounds and the procedural simplicity.[89] This process has been implemented in industry, in particular, it is used in the production of pyrethroids, pharmaceuticals and other products of fine organic synthesis.[48,50] Lately, this method has been implemented in a continuous flow unit, which is also useful for its application on an industrial scale.[90–92]

3.1.1 Alkyl diazoacetates

Among diazocarbonyl compounds, alkyl diazoacetates are most important for preparative purposes. They are readily dediazotized on treatment with transition metal compounds, thus providing for the addition of the alkoxycarbonylcarbene moiety to the double bonds of unsaturated compounds giving cyclopropanecarboxylic acid derivatives (see Scheme 3). Currently, a wide range of transition metal compounds are known to catalyze decomposition of diazo compounds to give cyclopropanes, the metals being Cu, Rh, Ru, Co, Fe, Os, Pd, Pt, Cr, Ag and so on. Furthermore, Rh-, Ru-, Cu- and Co-based catalysts are most efficient for cyclopropanation of alkenes with electron-donating groups; in particular, soluble copper complexes [*e.g.*, $Cu(OTf)_2$ or $CuCl \cdot P(OR)_3$] and rhodium compounds, which allow conducting the reactions at room temperature, are used most often in DAC syntheses by reactions with alkyl diazoacetates.[93] Rhodium carboxylates are not reduced by diazo compounds, do not form π-complexes with alkenes and do not exchange the anion under usual conditions of catalysis. Cyclopropane adducts are formed in high yields, which depend little on the structure of the initial unsaturated compound[94] if the starting alkene does not contain a strong electron-withdrawing substituent. Among unsaturated compounds, styrene and its derivatives have been most studied in the reactions with alkyl diazoacetates (Scheme 5).

Scheme 5



R = H, 4-Me, 4-OMe, 4-F, 4-Cl, 4-Br, 4-CF_3, 4-NO_2, 3-NO_2, 2-NO_2, *etc.*

A multitude of catalytic systems have been tested in the key reaction of ethyl diazoacetate with styrene for both catalyst efficiency [yields of 2-phenylcyclopropanecarboxy-

Structures 6 – 8

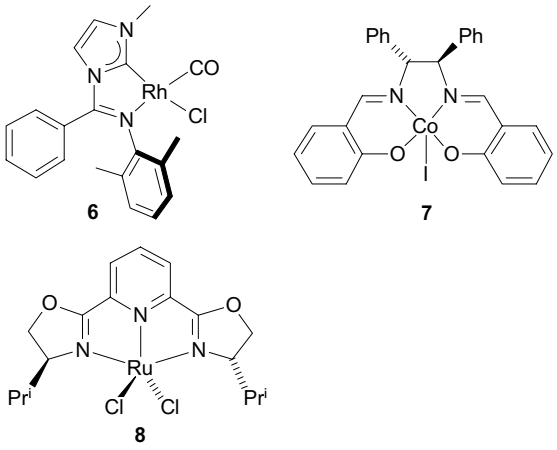


Table 1. Selected examples of the effect of catalysts on the yield and selectivity of styrene cyclopropanation with ethyl diazoacetate.

Catalyst	Yield of **5a** (%)	*trans* : *cis*	Ref.
[(N,C)RhCl] (**6**) + AgOTf	98	> 1 : 99	95
$Rh_2(OAc)_4$	93	62 : 38	96
$Cu(OTf)_2$	97	65 : 35	96
[Co(salen)I] (**7**)	76	98 : 2	97
[$RuCl_2$(Pibox-Pr^i)] (**8**)	73	91 : 9	98
[$Cp(CO)_2Fe(THF)]BF_4$ (see [a])	40	16 : 84	99
[$Sn^{IV}(TPP)(OTf)_2$]	95	> 99 : 1	100

[a] Cp = η^5-C_5H_5.

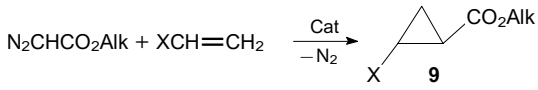
late **5a** (R = H) > 95%, see Scheme 5] and stereoselectivity. Although the *trans*-isomers somewhat predominate with most of the tested catalysts, some catalysts were found to ensure almost complete formation of either the *trans*- or *cis*-isomer (Table 1).

As noted above, substituted styrenes obey a linear correlation of the reaction rate according to the Hammett equation. Despite the decrease in the cyclopropanation rate upon the introduction of electron-withdrawing substituents into the styrene benzene ring, the yields of products usually depend only slightly on the nature of this substituent for most of the currently used catalysts.

As a result, by selecting the catalyst and the reaction conditions, one can obtain the desired cyclopropanes in high yields for virtually any substituted styrene. Even in the case of cyclopropanation of *p*-fluoro- and *p*-nitrostyrenes catalyzed by ruthenium perfluorophthalocyanine, the yields of cyclopropanecarboxylates **5b** (R = 4-F) and **5c** (R = 4-NO_2) are 86% and 83%, respectively, while the *trans* : *cis* isomer ratio is (4.5 – 5.0) : 1 (see Scheme 5).[101] A similar situation is observed when other catalysts are employed, for example, dicopper(II)-substituted silicotungstate with the γ-Keggin anion structure[102] or iridium(III) tetratolylporphyrin complexes.[88] It is noteworthy that the reactions of *para*-substituted methyl- and methoxystyrenes in the presence of the same catalysts gave the corresponding 2-arylcyclopropanecarboxylates also in the yields of about 86% – 90%.

The reactions of diazocarbonyl compounds with aryl and alkyl vinyl ethers, vinyl sulfides, enamines and other similar compounds are the key methods for the synthesis of DACs **9** (type of **1a**) (Scheme 6) in which a heteroatomic group acts as the donor substituent.

Scheme 6



X = OR, NRR′, SR (R, R′ = Alk, Ar)

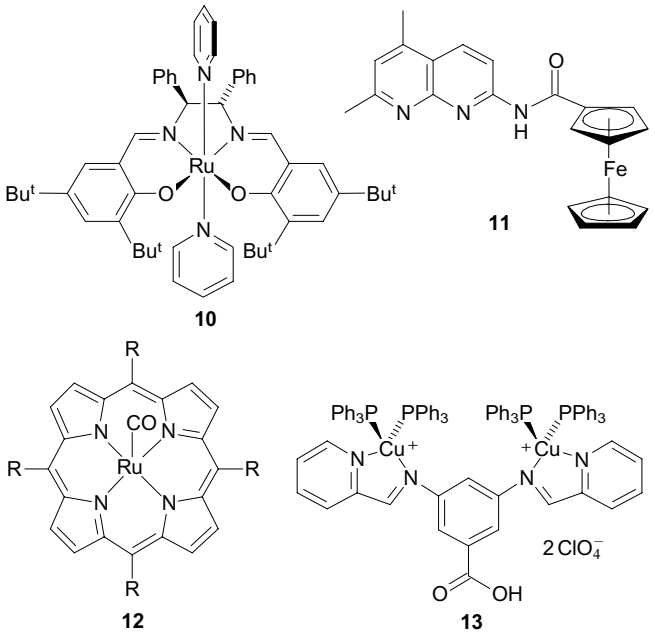
The reactions of ethyl diazoacetate with vinyl ethers, resulting in the preparation of DACs in up to 95% yields, have been most studied.[103] The reaction with ethyl vinyl ether (see Scheme 6, Alk = Et, X = OEt) for most of the applied catalysts gives, as in the case of styrene, a predominant amount of the *trans*-isomer of ethyl 2-ethoxycyclopropane-1-carboxylate (**9a**), with the yields of product **9a** being 70% – 90% (Table 2).

Table 2. Examples of the catalyst effect on the product yield and selectivity of cyclopropanation of ethyl vinyl ether with ethyl diazoacetate.

Catalyst	Yield of **9a** (%)	*trans* : *cis*	Ref.
[Ru^{II}(salen)(PyH)$_2$] (**10**)	91	79 : 21	104
$Rh_2(OAc)_4$	90	–	105
[{Cu(**11**)}$_2$](OTf)$_2$	90	55 : 45	106
Rh_2{OC(O)CPh$_3$}$_4$	89	53 : 47	107
[Ru^{II}(4-Glc-TPP)(CO)][a] (**12**)	86	5 : 1	108
$Rh_2(O_2PMe_2)_4$	81	1 : 2.6	109
13	69	74 : 26	110

[a] 4-Glc-TPP is the *meso*-tetrakis{4-(β-D-glucosyl)phenyl}porphyrin dianion.

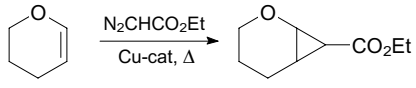
Structures 10 – 13



R = C_6H_4(glucopyranosyloxy)-4

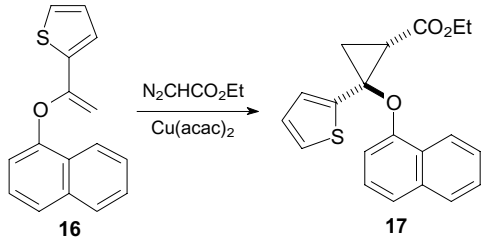
It should be borne in mind that some catalysts are inapplicable to cyclopropanation of vinyl ethers. For example, copper(II) triflate, which is an efficient catalyst of cyclopropanation, induces polymerization of the starting vinyl ethers and other side reactions.[96, 111] Nevertheless, examples of application of copper compounds as catalysts for DAC synthesis in the reactions of various vinyl ethers with ethyl diazoacetate have been reported.[103] 3,4-Dihydro-2*H*-pyran (**14**) was converted to DAC **15** with either $CuSO_4$ (62% yield, *exo*-isomer)[22] or CuOTf (90% yield, *exo* : *endo* = 95 : 5) being used as the catalyst (Scheme 7).[112]

Scheme 7



Similarly, the reaction of ethyl diazoacetate with enol ether **16** in the presence of copper acetylacetonate furnished

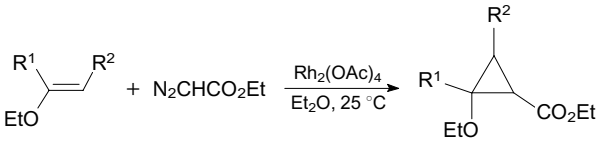
Scheme 8



cyclopropane-containing ether **17** (83% yield, *dr* = 2 : 1) (Scheme 8).[113]

Among other catalysts used in this reaction is rhodium carboxylate, which catalyzes the reaction of vinyl ethers with ethyl diazoacetate giving substituted 2-ethoxycyclopropanecarboxylates, which have been isolated and purified by flash chromatography on silica gel (no yields or stereochemistry are indicated) (Scheme 9).[114]

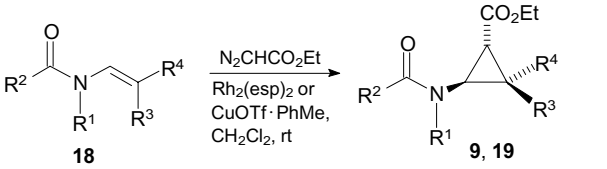
Scheme 9



$R^1 = (CH_2)_3CH{=}CH_2$, R^2 = H; R^2 = Bu^n: R^1 = H, Pr^n; $R^1-R^2 = (CH_2)_4$

Apart from ethers, a series of 2-aminocyclopropanecarboxylates **19** have been prepared in 36%–76% yields in a similar way by treatment of *N*-alkenylamides and -urethanes **18** with ethyl diazoacetate in the presence of the complex $Rh_2(esp)_2$ or copper(I) compounds (Scheme 10).[22, 115, 116]

Scheme 10

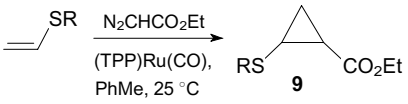


$R^3 = R^4$ = H (**9**); **19**: R^3 or $R^4 \neq$ H (**19**); $R^3 = R^4$ = H: R^1 = H, R^2 = OBn; R^1 = Bn, R^2 = OBn; $R^1-R^2 = (CH_2)_3$, $C(O)C_6H_4$, CH_2CH_2O; $R^1-R^3 = (CH_2)_3$, R^2 = OBn: R^4 = H, Et

Ruthenium[87, 117–120] and copper(II)[121] complexes are also efficient catalysts for these reactions.

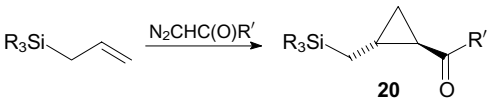
The reactions of ethyl diazoacetate with vinyl sulfides resulted in the synthesis of yet another group of DACs in which an alkyl- or arylsulfanyl group serves as the donor substituent (Scheme 11). The reaction is catalyzed by ruthenium porphyrin complexes, the yield of products **9** being 67% (*trans* : *cis* = 3.6) for R = Et and 61% (*trans* : *cis* = 1.8) for R = Ph.[87]

Scheme 11



R = Et, Ph

Scheme 12



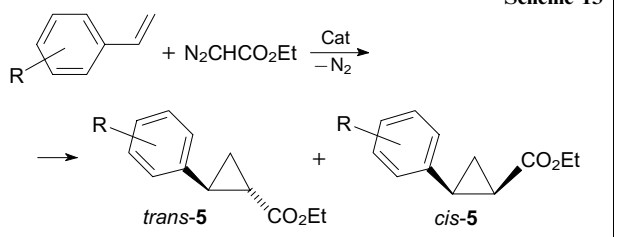
R_3Si = Bu^tPh_2Si; R′ = Ph, Bu^n, Bu^t

Finally, the same method with the use of diazo ketones was applied to prepare DACs **20** with the silylmethyl donor groups in 60%–75% yields [*dr* = (2–2.4) : 1] (Scheme 12).[122]

Thus, the reactions of diazoacetates with unsaturated compounds containing a donor substituent at the double bond can be considered as a general convenient method for the synthesis of DACs of type **1a**. Most often, these reactions give DACs mainly as *trans*-isomers; however, by selection of an appropriate catalyst, it is also possible to perform this reaction with high *cis*-selectivity.

The method based on the reaction of diazoacetates with unsaturated compounds can also be used to synthesize optically active DACs by application of chiral catalysts.[77, 123] The reaction of diazoacetates with styrene and its derivatives (Scheme 13) has also been used to investigate the dependence of the process enantioselectivity on the nature of the chiral catalyst of cyclopropanation; therefore, most experience has been gained in particularly this reaction. Several reviews[73, 123, 124] integrate data on the cyclopropanation enantioselectivity for a large number of chiral catalysts based on copper, rhodium, ruthenium, cobalt and iron compounds; some examples are given in Table 3.

Scheme 13



R = 4-MeO, 4-Me, 4-Hal, *etc.*

Thus, cyclopropanation of styrenes with alkyl diazoacetates catalyzed by chiral iron(II) complexes with tetraazamacrocyclic ligands (*e.g.*, ligand **21**) and porphyrins (**22**)[124, 125] gives high product yields and has high diastereoselectivity, but low enantioselectivity. When copper(I) complexes with 4,4′-bis(oxazoline) ligands (**23**, **24**) are used as catalysts, cyclopropanes are also formed with moderate enantioselectivity.[126] Meanwhile, the reactions of styrenes with alkyl diazoacetates in the presence of cobalt complex **25** afford the target 2-arylcyclopropanecarboxylates in high yields (up to 100%) and with high diastereo- and enantioselectivities (the *cis*-isomer is formed predominantly in a yield of up to 97% and with 93%–96% *ee*).[127] Even relatively unreactive 4-nitrostyrene is converted to the cyclopropane product under these conditions in 93% yield (*cis* : *trans* = 89 : 11, 93% *ee*).[127] In the case of ruthenium complex **26**, the *trans*-isomer is mainly formed with high enantioselectivity (see Table 3).

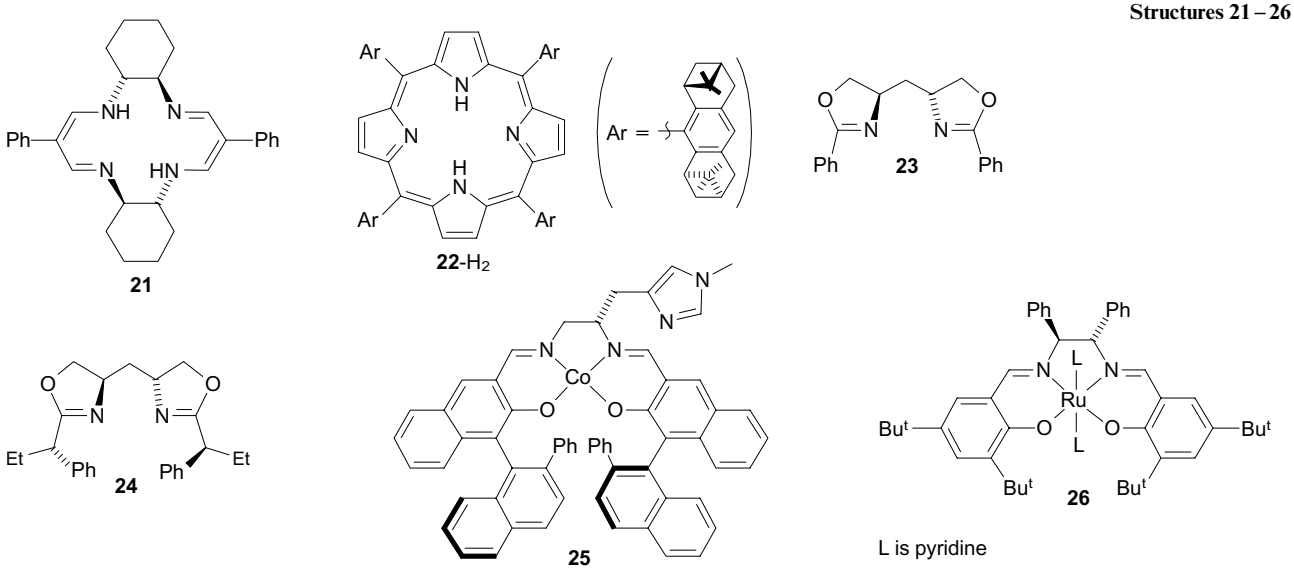
Among other chiral catalysts used for cyclopropanation of styrenes with alkyl diazoacetates, worth noting are the ruthenium and cobalt salen complexes[128] and ruthenium phenyloxazoline complexes supported on a polymer. The latter catalysts were found to retain the efficiency after being used many times.[118]

In addition, high yields of products, high *trans*-diastereoselectivity (up to 99 : 1) and moderate enantioselectivity ($\leqslant$87%) have been found for reactions of styrenes with

Table 3. Examples of the effect of chiral catalysts on the product yield and selectivity of cyclopropanation of styrene (R = H) with ethyl diazoacetate.

Catalyst	Yield of **5a** (%)	*trans* : *cis*	*ee trans* (%)	*ee cis* (%)	Ref.
[Fe^{II}(**21**)]	87	7.4	42	42	125
[Fe^{II}(**22**)]	99	21	45	21	125
[Cu^{I}(OTf)(**23**)]	99	60 : 40	32	16	126
[Cu^{I}(OTf)(**24**)]	67	37 : 63	61	64	126
25	99	3 : 97	93	96	127
26	95	77 : 23	> 99	> 99	104

Structures 21 – 26



alkyl diazoacetates carried out in the presence of iron(III) porphyrin complexes.[129]

Functionally substituted diazoacetates are also of certain value for the synthesis of cyclopropanecarboxylates. In some cases, they allow targeted synthesis of derivatives of cyclopropanecarboxylic acid esters.

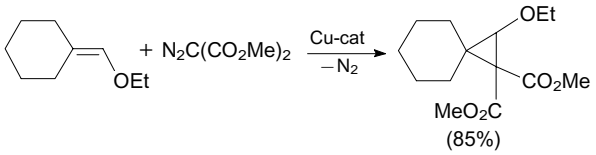
Cyclopropanation of alkenes with aryl diazoacetates is also known. It is worth noting that styrene cyclopropanation with aryl diazoacetates can proceed thermally, that is, without a catalyst, giving rise to cyclopropane products in 68% – 97% yields.[130] In the presence of various chiral catalysts, asymmetric cyclopropanation with aryl diazoacetates takes place, resulting in optically active cyclopropanes with high enantioselectivity.[131 – 136] Apart from the chiral copper, rhodium, ruthenium and cobalt complexes, this reaction can be efficiently catalyzed by chiral silver compounds.[137] Moreover, in this case, virtually no side products are formed, resulting from insertion into the C – H bond, as observed in the case of rhodium compounds.

3-Diazoindolin-2-ones, which can also be classified as aryl diazoacetate derivatives, react with substituted styrenes in the presence of rhodium compounds to give the corresponding cyclopropanes in up to 88% yields.[138]

3.1.2. Diazomalonic esters

Alkyl diazomalonates (ADM) (like alkyl diazoacetates) react with alkenes giving rise to cyclopropane adducts, and this is a convenient method for the synthesis of DACs, in particular, the most common 2-arylcyclopropane-1,1-dicarboxylates. Alkyl diazomalonates are thermally stable and were previously dediazotized by copper compounds.[50] This approach was especially efficient for cyclopropanation of substrates with electron-rich C=C bonds (Scheme 14).[62]

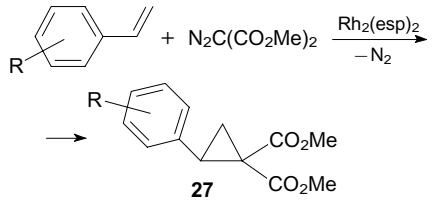
Scheme 14



However, in the presence of copper compounds, the formation of cyclopropane products was often accompanied by side reactions, *e.g.*, insertion of the carbene moiety into the C – H bonds. With advancement of the chemistry of donor-acceptor cyclopropanes, interest has revived in the development of convenient methods for the synthesis of cyclopropane-1,1-dicarboxylates, in particular, by reactions of diazomalonates with alkenes. Again, rhodium compounds, which successfully operate under very mild conditions, proved to be the most efficient catalysts. The benefits of rhodium catalysts include a minimized amount

of side products, the lack of necessity for slow addition of the diazo compound, the use of equivalent amounts of alkene and diazomalonate and low catalyst loading. For instance, a broad range of cyclopropane-1,1-dicarboxylates **27** have been prepared in high yields by the reaction of methyl diazomalonate with substituted styrenes in the presence of $Rh_2(esp)_2$ (Scheme 15).[22, 139 – 141]

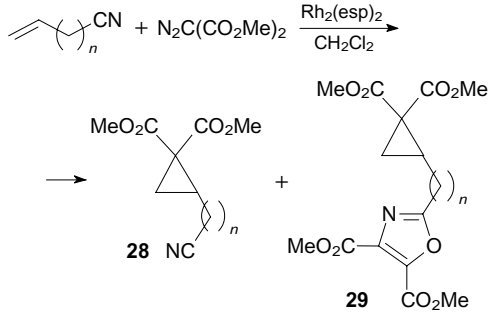
Scheme 15



R = H, 4-Me, 4-MeO, 4-Cl, 4-Br, 4-F, 4-AcNH, 4-AcO, 4-TBSO, 4-Fc, 4-F_3C , 4-NC, 3-Br, 2-MeO, 2-F, 2-Br, *etc.*

Apart from styrenes, cyclopropanation proceeds quite successfully with terminal alkenes, allyl ethers and cycloalkenes (72% – 91% yields). The cyclopropanation of internal alkenes proceeds with retention of the relative configuration of substituents; for example, (*Z*)-propenylbenzene is converted to 3-methyl-2-phenylcyclopropane-1,1-dicarboxylate in 87% yield, while the corresponding *E*-isomer gives the product in only 28% yield. In the case of unsaturated nitriles, the cyclopropanation is complicated by addition of the carbene moiety to the C≡N bond, resulting in the formation of not only cyclopropanes **28**, but also oxazoles **29** (Scheme 16).[139]

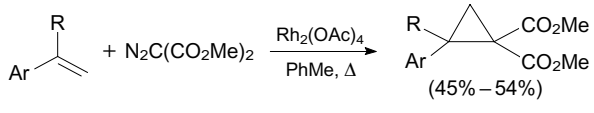
Scheme 16



n	Yield of **28** (%)	Yield of **29** (%)
1	38	23
3	52	17

A number of 2,2-disubstituted cyclopropane-1,1-dicarboxylates have been obtained in the presence of $Rh_2(OAc)_4$; however, the reaction was carried out in refluxing toluene at the alkene : ADM : catalyst molar ratio of 2.5 : 1 : 0.01 (Scheme 17).[142]

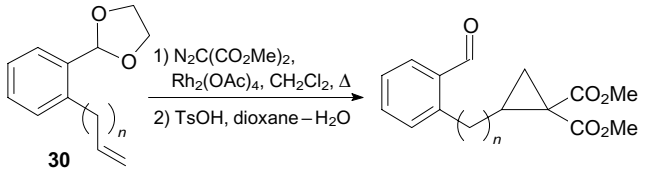
Scheme 17



R = Bn, Ar = Ph; R = Me: Ar = 4-NCC_6H_4 , 4-$MeOC_6H_4$

In the case of 2-phenylpenta-1,4-diene, the reaction was non-selective; nevertheless, the product of cyclopropanation at the disubstituted double bond predominated (70% total yield, 6 : 1 ratio of regioisomers). For cyclopropanation of unsaturated compounds containing a formyl group, this group must be protected (see, for example, substrate **30**), because diazo compounds react themselves with aldehydes (Scheme 18).[143]

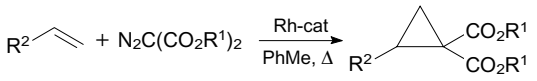
Scheme 18



n = 0 – 2

Donor-acceptor cyclopropanes containing an aryl, hetaryl, alk(aryl)oxyl or amide moiety as the donor were prepared by the reactions of diazomalonates with vinyl derivatives of various classes (Scheme 19).[115, 140, 144]

Scheme 19

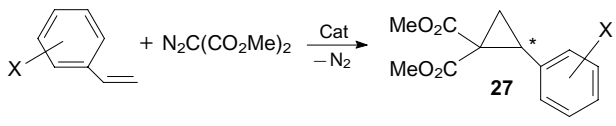


R^1 = Me, Et; R^2 = 2-Naph, 1,3-dimethylindol-2-yl, succinimido, phthalimido, PhO, BnO, Bu^nO, *etc.*

Note that cyclopropanation of *N*-vinylphthalimide with dimethyl and diethyl diazomalonates in the presence of 0.1 mol.% $Rh_2(esp)_2$ affords cyclopropanedicarboxylates in 78% and 90% yield, respectively.[145]

It is of interest to apply chiral catalysts in the synthesis of optically active DACs **27**.[146] Like in the case of alkyl diazoacetates, the use of chiral catalysts in the reactions of diazomalonates with unsaturated compounds leads to the synthesis of optically active cyclopropanes. When rhodium compounds are employed, cyclopropanedicarboxylates are obtained in high yields, the enantiomeric excess being dictated by the nature of the chiral anions (ligands) in the catalyst. For instance, cyclopropanation of styrene (X = H) with dimethyl diazomalonate in the presence of 0.1 mol.% $Rh_2(4S\text{-MEAZ})_4$ (**31**) affords cyclopropane **27** in a yield of up to 97% and with 44% *ee* (Scheme 20).[146] The same reaction in the presence of the diene complex RhCl(*R*,*R*)-L (**32**) and $NaBAr^F_4$ [Ar^F_4 = 3,5-$(CF_3)_2C_6H_3$] gives cyclopro-

Scheme 20



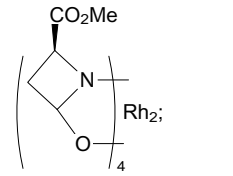
Cat = **31**, **32** + $NaBAr^F_4$, [Cu(**33**)]SbF_6; X = H, 2-Me, 3-Me, 4-Me, 4-MeO, 4-Cl, 4-F_3C

panedicarboxylate **27** in a somewhat lower yield (86%), but proceeds with a higher enantioselectivity (89% *ee*).[147]

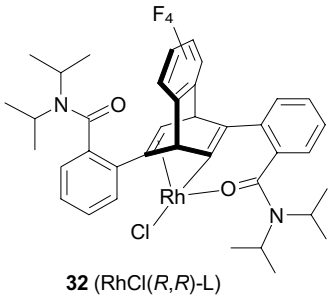
Among the catalysts based on copper(I) compounds, mention should be made of the $CuSbF_6$ complex with bis(oxazoline) ligand **33**; in the presence of this complex, the yield of 2-phenylcyclopropanedicarboxylate **27a** (X = H) was 88% and *ee* was 75%.[148]

The enantioselectivity of the reaction of substituted styrenes catalyzed by RhCl(*R*,*R*)-L (**32**) and $NaBAr^F_4$ was at a level of 80% – 90%. As expected, the yields of cyclopropanedicarboxylates decreased on going from electron-rich styrenes (4-$MeOC_6H_4CH{=}CH_2$, 96%) to electron-deficient ones (4-$F_3CC_6H_4CH{=}CH_2$, 57%) (see Scheme 20).[147]

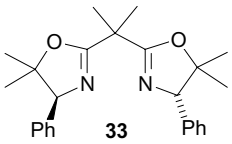
Structures 31 – 33



31 (Rh_2(4*S*-MEAZ)$_4$)



32 (RhCl(*R*,*R*)-L)



33

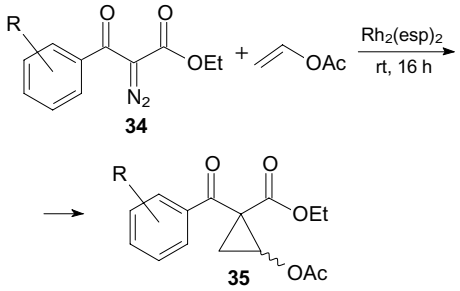
Other chiral rhodium complexes that efficiently catalyze the cyclopropanation with alkyl diazomalonates are also known.[148 – 153] The key principles of selection of the rhodium-based catalysts for the control of product yields and reaction enantioselectivity are formulated in a review.[154]

Apart from alkyl diazomalonates, rhodium-catalyzed cyclopropanation can also be carried out for fluoroalkyl diazomalonates [in particular, bis(2,2,2-trifluoroethyl) diazomalonate]. When $Rh_2(esp)_2$ is used instead of $Rh_2(OAc)_4$, the yields of DACs considerably increase and reach 94% in the case of styrene.[155]

If the diazo compound contains two different acceptor groups, the cyclopropanation generates a mixture of diastereomers, with the reaction diastereoselectivity being dependent on the natures of both the acceptor substituents in diazo compounds and the alkene. In some cases, the yields of DACs with the same unsaturated compounds proved to be lower than those attained with diazomalonates, as a result of some side transformations. Indeed, the reaction of α-aroyl diazoacetates **34** with vinyl acetate catalyzed by $Rh_2(esp)_2$ generates diastereomeric 1-aroyl-2-acetoxycyclopropanecarboxylates **35** in 16% – 87% yield (isomer ratio of ~6 : 1). The yields of cyclopropane products in these transformations were shown to follow an unusual dependence on the type of substituents in the aromatic ring, namely, the yields decrease on going to electron-donating substituents (Scheme 21).[156]

It is of interest that ethyl α-benzoyldiazoacetate reacts with ethyl and trimethylsilyl vinyl ethers to afford 5-trimethylsilyloxy(ethoxy)-2-phenyl-4,5-dihydrofuran-3-carboxylates instead of cyclopropanes.

Scheme 21

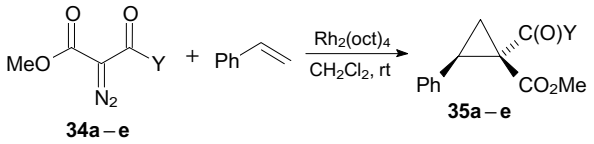


R = H (51% yield), 3-Cl (87%), 3-Br (86%), 3-Me (27%), 4-Me (16%), 4-Et (40%), 4-Pr^i (73%), 4-F (41%), 4-Cl (47%), 4-Br (53%)

The reactions of α-furoyl- and α-thienoyldiazoacetates with styrenes in the presence of $Rh_2(esp)_2$ give the corresponding DACs in 43% – 82% yields; in the case of reactions of 2- and 3-furoyldiazoacetates with 4-methoxystyrene, the predominant formation of *E*-isomers is observed (from 1.5 : 1 to 2.1 : 1).[157]

An attempt to explain the diastereoselectivity of the reactions of diazo compounds containing two different electron-withdrawing groups was made by Charette and co-workers[148] They found that the diastereoselectivity of styrene cyclopropanation with diazoacetates **34a – e** in the presence of $Rh_2(oct)_4$ is correlated with the carbonyl stretching frequency in analogous carbonyl derivatives of the MeC(O)Y type and varies in favour of the *cis*-isomer from 4 : 1 for acetyl diazoacetate to 30 : 1 for *N*,*N*-dimethylacetamide derivative (Scheme 22).

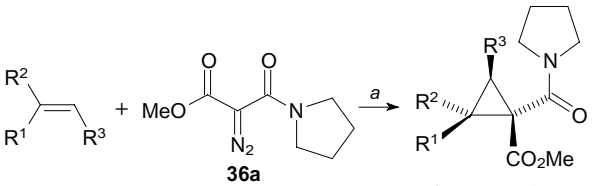
Scheme 22



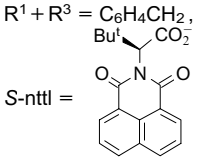
Compounds **34**, **35**	Y	Yield of **35** (%)	*dr* (*cis* : *trans*)	$\nu_{MeC(O)Y}$ /cm^{-1}
a	Me	69	4 : 1	1715
b	4-FC_6H_4	71	13 : 1	1689
c	Ph	65	14 : 1	1686
d	4-$MeOC_6H_4$	69	20 : 1	1672
e	Me_2N	62	> 30 : 1	1659

A high *trans*-directing ability of the amide group has been demonstrated for a broad series of α-carbamoyldiazoacetates (for example, compound **36a**), which have also exhibited high enantioselectivity in the reactions with styrenes, 3-vinylindoles, butyl vinyl ether and other unsaturated compounds in the presence of the chiral rhodium catalyst Rh_2(*S*-nttl)$_4$ (Scheme 23).[148, 149] Also, whereas in the case of styrenes, the diastereoselectivity was > 22 : 1, in the case of butyl vinyl ether, it was 9 : 1 and in the case of N-substituted 3-vinylindoles, it was only 1.2 : 1.

Scheme 23

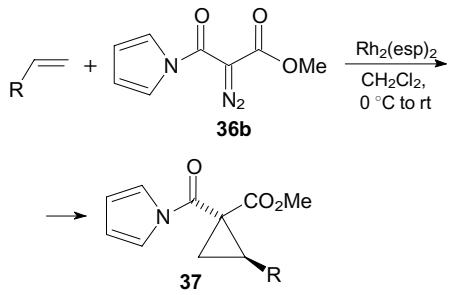


(*a*) Rh_2(*S*-nttl)$_4$ (1 mol.% – 2 mol.%), DCE, 25 °C;
$R^2 = R^3 = H$: R^1 = Bu^{n}O, Ph, 4-MeOC$_6$H$_4$, 4-Bu^{t}C$_6$H$_4$, 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, 3-MeOC$_6$H$_4$, 3-F$_3$CC$_6$H$_4$, 3-O$_2$NC$_6$H$_4$, 2-FC$_6$H$_4$, 2-ClC$_6$H$_4$, 2-BrC$_6$H$_4$, 1-Naph, 3,4,5-(MeO)$_3$C$_6$H$_2$, 3,5-(MeO)$_2$C$_6$H$_3$, 3-MeO-4-MeC$_6$H$_3$, *etc.*;
$R^1 + R^3 = C_6H_4CH_2$, R^2 = H; R^1 = Ph, R^2 = Me, R^3 = H



Similarly, the $Rh_2(esp)_2$-catalyzed reaction of diazomalonamide **36b** with alkenes afforded a series of 2-substituted 1-pyrrolocarbonylcyclopropane-1-carboxylates **37**. In this case, cyclopropanation of styrenes and phenyl vinyl ether occurs with yields varying from moderate to rather high (44% – 81%). Conversely, phenyl vinyl sulfide and allyl(*tert*-butyl)diphenylsilane give cyclopropanes in only 7% and 14% yields, respectively. Like monoamide **36a**, substrate **36b** reacts with substituted styrenes with the prevailing formation of diastereomer **37** with the *trans*-arrangement of the amide and donor moieties. Under the same conditions, 2-vinylfuran, 2-vinylnaphthalene and allyl(*tert*-butyl)diphenylsilane afford mixtures of DAC diastereomers in 9.1 : 1, 4.7 : 1 and 1 : 1 ratios, respectively (Scheme 24).[158]

Scheme 24

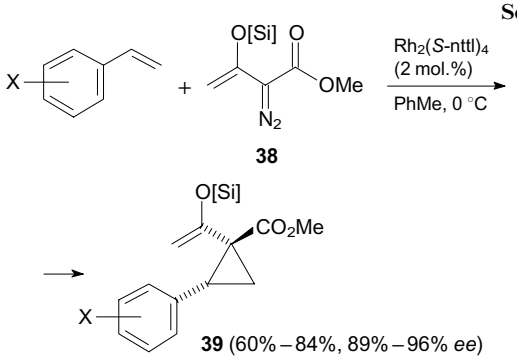


R = Ph, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 2-Naph, 2-Fu, PhS, PhO, Bu^{t}Ph$_2$SiCH$_2$

A high degree of asymmetric cyclopropanation was attained in the reaction of styrenes with (silyloxyvinyl)diazoacetates **38** in the presence of Rh_2(*S*-nttl)$_4$ or Rh_2(*R*-ntv)$_4$ [(*R*-ntv) is (*R*)-*N*-1,8-naphthaloyl valinate]. Owing to the triisopropylsilyl protection, DACs **39** were obtained with higher efficiency and enantioselectivity than in the case of *tert*-butyldimethylsilyl protection (Scheme 25). Low enantioselectivity (11% *ee*) was observed only in the cyclopropanation of *o*-bromostyrene.[159]

Recently, a method has been developed for the synthesis of DACs by the reaction of diazocarbonyl compounds (in the presence of ethyl diazoacetate) with donor alkenes in a continuous flow system, which opens up additional opportunities for the use of this process on a larger scale.[90]

Scheme 25

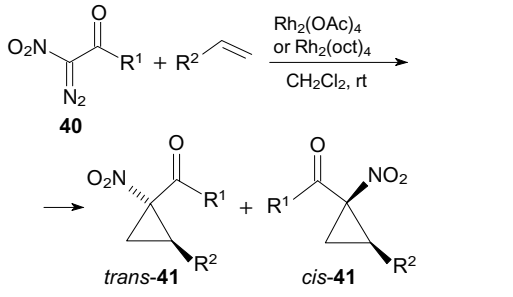


X = H, 4-Cl, 4-Br, 4-MeO, 2-Me, 2-Br; [Si] = SiPr$^i_3$, TBS

3.1.3. Miscellaneous diazocarbonyl compounds

Among diazo compounds with two electron-withdrawing substituents used to synthesize DACs, α-cyano- and α-nitrodiazocarbonyl compounds **40** are most studied. Due to the presence of two different electron-withdrawing substituents, the reactions of these diazo compounds with terminal alkenes may give two diastereomeric cyclopropanes **41**, and diastereoselectivity and enantioselectivity issues of these cyclopropanation reactions in the presence of chiral catalysts have gained a lot of attention of researchers. The carbonyl group in α-nitrodiazocarbonyl compounds was found to significantly affect the diastereoselectivity of styrene cyclopropanation catalyzed by rhodium carboxylates [151, 160 – 164] (Scheme 26, Table 4).

Scheme 26

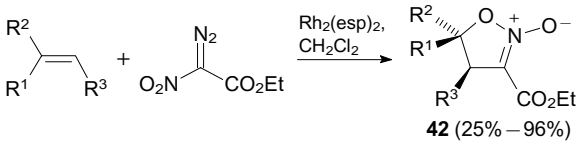


The reaction of 4-methoxystyrene (R^1 = C$_6$H$_4$OMe-4, $R^2 = R^3$ = H, Scheme 27) with α-nitrodiazoacetate in the presence of 0.1 mol.% $Rh_2(esp)_2$, as distinct from this reaction of styrene, does not stop after the cyclopropanation step, but the cyclopropane formed is converted under the reaction conditions to cyclic nitronate **42** (see Scheme 27). Alkyl(phenyl) vinyl ethers, enamides and ethyl vinyl sulfide react in a similar way; however, in the last-mentioned case, nitronate **42** is formed in only 25% yield, and phenyl vinyl sulfide is hardly cyclopropanated.[165]

Table 4. Examples of substituent effect in α-nitrodiazocarbonyl compounds on the product yield and selectivity of cyclopropanation of substituted styrenes.

R^1	R^2	Yield of **41** (%)	*dr* (*trans* : *cis*)	Ref.
OMe	1-Naph	86	95 : 5	162
OEt	Ph	75	89 : 11	164
OEt	Ph	90	93 : 7	162
OEt	Ph	80	88 : 12	151
Me	Ph	77	78 : 22	151
Me	1-Naph	52	79 : 21	160
cyclo-C_3H_5	Ph	69	76 : 24	160
Me	C_6H_4F-4	63	73 : 27	160
OMe	$(CH_2)_2Ph$	70	53 : 47	162
Ph	Ph	74	16 : 84	151
C_6H_4OMe-4	Ph	71	12 : 88	151

Scheme 27

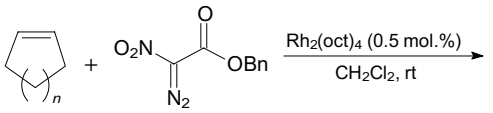


42 (25% – 96%)

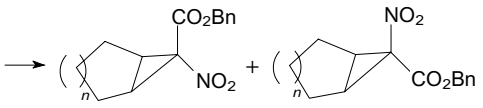
$R^2 = R^3 = H$: R^1 = OEt, OBu^n, OCy, OPh, SEt, C_6H_4OMe-4, phthalimido, 2-oxopyrrolidino; $R^3 = H$: R^1 = OMe, R^2 = Ph; $R^1 – R^2 = OCH_2CH_2$; R^1 = Ph, $R^2 = H$: R^3 = Ph, Me

Cyclopropanation of cycloalkenes with α-nitrodiazoacetates (*e.g.*, **40a**) has variable efficiency and affords nitrobicyclo[(*n* + 2).1.0]alkanecarboxylates **43** and **43′**, among which isomers **43** with the *exo*-positions of NO_2 groups predominate (Scheme 28).[162]

Scheme 28



40a

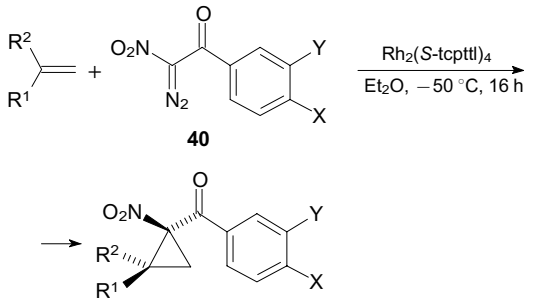


43a – c **43′a – c**

Compounds **43**, **43′**	*n*	Yield (%)	**43** : **43′**
a	1	81	87 : 13
b	2	39	86 : 14
c	4	66	80 : 20

For asymmetric cyclopropanation of alkenes with α-nitrodiazocarbonyl compounds **40**, high stereoselectivity has been achieved with the use of tetrakis[(2*S*)-3,3-dimethyl-2-(tetrachlorophthalimido)butyrato]dirhodium [Rh_2(*S*-tcpttl)$_4$]. This catalyst has been employed for cyclopropanation of a broad range of styrenes (Scheme 29). In most cases, one recrystallization was sufficient for DACs **44** to be formed as single diastereomers with high enantioselectivity. A low selectivity of the reaction with styrene was observed only for nitrodiazo-4-(trifluoromethyl)benzophenone, which afforded the desired cyclopropane in 80% yield, *dr* = 70 : 30, and 71% *ee*. A lower yield (38%), but a high selectivity (*dr* = 83 : 1, 96% *ee*) were observed in the case of nitrodiazo-4-(dimethylamino)benzophenone. Generally, the highest enantioselectivity in the reactions with various styrenes was found for diazonitro-4-methoxybenzophenone **40b** (Y = H, X = OMe) (*ee* > 91%).[151, 166]

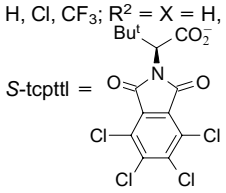
Scheme 29



40

44 (38% – 91%, from 70 : 30 to 99 : 1 *dr*, 71% – 98% *ee*)

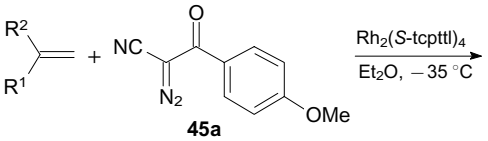
$R^2 = Y = H$, X = OMe: R^1 = Ph, 4-MeC_6H_4, 4-$Bu^tC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-$F_3CC_6H_4$, 4-$O_2NC_6H_4$, 3-$MeOC_6H_4$, 3-$F_3CC_6H_4$, 3-$O_2NC_6H_4$, 2-ClC_6H_4, 2-FC_6H_4, 1-Naph; R^1 = Ph: R^2 = Me, X = OMe, Y = H; $R^2 = Y = H$, X = NMe_2, OMe, H, Cl, CF_3; $R^2 = X = H$, Y = OMe;



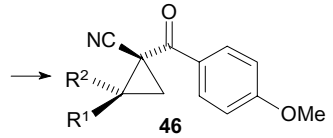
Heteroleptic chiral rhodium carboxylate complexes of the Rh_2A_3B type also showed good diastereo- and enantioselectivity in the reaction of α-nitrodiazo-4-methoxyacetophenone with styrene (*cis* : *trans* isomer ratio up to 94 : 6 and *ee* up to 96.4%).[167]

The use of Rh_2(*S*-tcpttl)$_4$ as a catalyst proved to be efficient also in the cyclopropanation of styrenes with diazo-4-methoxyacetophenone **45a** containing the α-cyano group. This reaction gave the target DACs **46** in high yields

Scheme 30



45a



46

$R^2 = H$: R^1 = Ph, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 3-$MeOC_6H_4$, 2-ClC_6H_4, 1-Naph, BzO; R^1 = Ph, R^2 = Me

(82% – 99%) and with good selectivity (*dr* from 84 : 16 to 99 : 1, *ee* of 73% – 94%) (Scheme 30).[151]

In the reactions of α-cyanodiazocarbonyl compounds **45** with styrene catalyzed by rhodium(II) octanoate, the highest diastereoselectivity was found for α-cyanodiazoacetamide (Scheme 31, Table 5).[160, 168]

Scheme 31

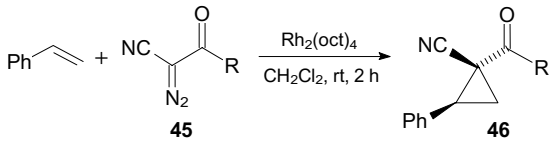
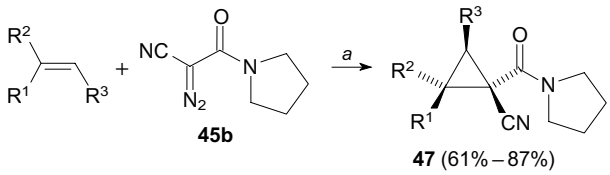


Table 5. Efficiency of styrene cyclopropanation with α-cyanodiazocarbonyl compounds.[160, 168]

R	Yield of **46** (%)	*trans* : *cis*
OEt	79	60 : 40
OCH_2CF_3	77	55 : 45
Bn	83	77 : 23
Ph	95	88 : 12
C_6H_4OMe-4	97	94 : 6
(*E*)-Styryl	96	57 : 43
NMe_2	61	91 : 9

These results were used for the development of a method for enantio- and diastereoselective cyclopropanation of various alkenes with diazocyanoacetamides. The best results were obtained for pyrrolidine derivative **45b**. The presence of 10 mol.% $TfNH_2$ as the co-catalyst increases both the yield of DACs **47** and reaction stereoselectivity. Meanwhile, the increase in the amount of the Rh catalyst from 1 mol.% to 5 mol.% increases the yield of cyclopropanes **47**, but barely affects the stereoselectivity. Under the proposed conditions, cyclopropanation of alkenes with α-cyanodiazo-1-pyrrolidinoethan-1-one (**45b**) affords DACs **47** with high diastereo- and enantioselectivities (*dr* up to 99 : 1; *ee* up to 98%) (Scheme 32).[150, 168]

Scheme 32

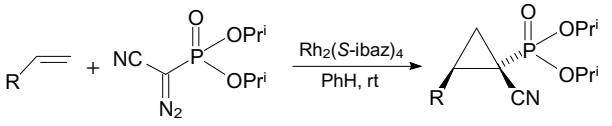


(*a*) Rh_2(*S*-nttl)$_4$ (1 – 5 mol.%), $TfNH_2$ (10 mol.%), PhMe, from −78 to 25°C, 16 h; $R^2 = R^3 = H$: R^1 = Ph, 4-Bu^{t}C$_6$H$_4$, 4-AcOC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 2-FC$_6$H$_4$, 2-ClC$_6$H$_4$, 2-BrC$_6$H$_4$, 2-MeC$_6$H$_4$, C$_6$F$_5$, Bu^n, $PhCH_2CH_2$, $PhCO_2$; $R^2 = H$: $R^1 – R^3 = (CH_2)_3$, $C_6H_4CH_2$; R^1 = Ph, R^2 = Me, $R^3 = H$

It is worth noting that the addition of $TfNH_2$ under similar conditions has virtually no effect on the stereoselectivity of styrene cyclopropanation with α-amidodiazoacetate.[150, 168]

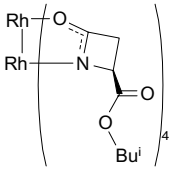
Good stereoselectivity of cyclopropanation of styrene and some other alkenes was attained in the dediazotization of α-cyanodiazomethylphosphonate **48a** catalyzed by Rh_2(*S*-ibaz)$_4$ (Scheme 33) or Rh_2(1-AdCO$_2^-$)$_4$; the latter provided somewhat lower diastereoselectivity for the obtained DACs **49**, but it was more efficient for the cyclopropanation of 1,1- and 1,2-disubstituted alkenes.[152]

Scheme 33



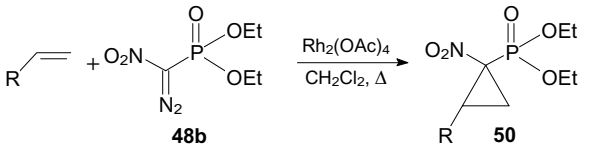
R = Ph, 4-AcOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 3-MeOC$_6$H$_4$, 3-O$_2$NC$_6$H$_4$, 2-BrC$_6$H$_4$, *N*-tosylindol-3-yl, $Ph_2C{=}CH$, $PhCH_2CH_2$, phthalimido;

Rh_2(*S*-ibaz)$_4$ =



α-Diazonitromethylphosphonate **48b** can also act as a cyclopropanating agent; when it reacts with styrene or hex-1-ene in the presence of rhodium acetate, 1-nitrocyclopropanephosphonates **50** are formed as mixtures of two diastereomers (Scheme 34). In the case of hexene, cyclopropane **50** is formed in a low yield as a result of the ene side reaction.[169]

Scheme 34

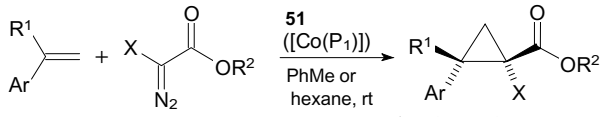


R = Ph (73% yield, *dr* = 59 : 41), Bu^n (25%, *dr* = 73 : 27)

Yet another efficient type of catalysts for the asymmetric cyclopropanation of alkenes with α-acetyl-,[170] α-nitro-[171] and α-cyanodiazoacetates[172] are cobalt porphyrin complexes (*e.g.*, complex **51a**) (Scheme 35). The reaction gives high yields of DACs with high diastereo- and enantioselectivities, with both the product yields and reaction stereoselectivity being higher for *tert*-butyl than for ethyl esters.

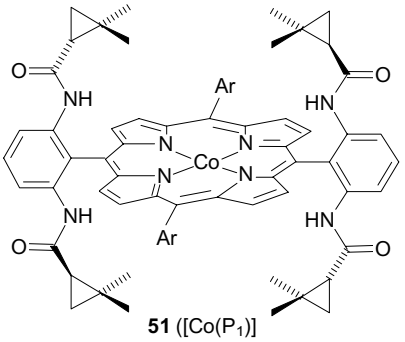
The data presented in this Section demonstrate that diazocarbonyl compounds (alkyl diazoacetates, dialkyl diazomalonates and some other) are fairly efficient cyclopropanating reagents, providing the synthesis of DACs with one or two acceptor groups, most often, ester groups.

Scheme 35



X = Ac, R^1 = H, R^2 = Bu^t: Ar = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-BrC_6H_4, 4-$F_3CC_6H_4$, 3-$O_2NC_6H_4$, 3-$HC(O)C_6H_4$, C_6F_5, (*E*)-styryl, *N*-Boc-indol-3-yl; R^1 = Me, Ar = Ph: R^2 = Et, Bu^t;
X = NO_2, R^1 = H: R^2 = Et, Bu^t; Ar = Ph, 4-MeC_6H_4, 4-$Bu^tC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$F_3CC_6H_4$, 3-$O_2NC_6H_4$, 3-MeC_6H_4, 2-MeC_6H_4, C_6F_5; R^1 = Me, Ar = Ph, R^2 = Et;
X = CN, R^1 = H: Ar = Ph, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, 3-$O_2NC_6H_4$, C_6F_5; R^2 = Et, Bu^t

Structure 51



51 ([Co(P1)])

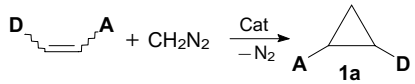
Ar = 3,5-$Bu^t_2C_6H_3$

Rhodium catalysts accomplish cyclopropanation under mild conditions at low temperatures, and the application of complex catalysts with chiral ligands enables the synthesis of optically active cyclopropanes.

3.2. Diazomethane

The catalyzed decomposition of diazomethane in the presence of copper or palladium compounds is a general method for carbene generation for alkene methylenation.[173, 174] For the preparation of DACs by this reaction, unsaturated compounds that contain both donor and acceptor substituents at the vicinal positions are utilized (Scheme 36).

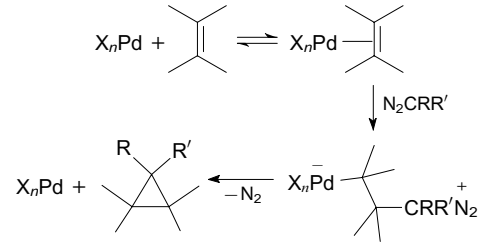
Scheme 36



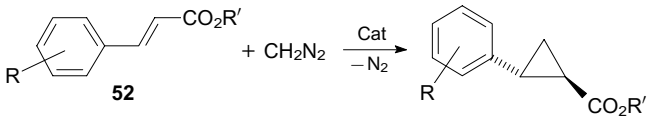
The most widely employed catalysts are palladium compounds. Initially, a complex is formed from the palladium compound and the alkene and then the complex reacts with the diazo compound (Scheme 37).[173, 175] Therefore, palladium compounds efficiently catalyze cyclopropanation only for those alkenes that are efficiently coordinated to a Pd atom.[173] This scheme also explains why palladium complexes with chiral ligands do not give optically active cyclopropanes (unlike analogous compounds of copper or rhodium).

This method can be used to obtain DACs with one acceptor group in 65% – 99% yields by reactions of *trans*-cinnamic acid esters **52** with diazomethane in the presence of palladium compounds or CuOTf.[176 – 179] The cyclopropane products are formed exclusively as *trans*-isomers (Scheme 38).

Scheme 37



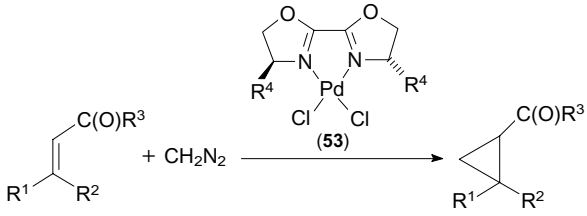
Scheme 38



R = H, 4-Me, 4-OMe, 4-OAc, 4-F, 4-Br, 4-CF_3, 4-CN, 4-NO_2, 2-Th, 3-Th, 2-Fu, 3-Fu, *etc.*; R′ = Me, Et, Pr^i, Bn, Ph

As has already been noted, the mechanism of catalysis by palladium compounds differs from these mechanisms for catalysts based on copper, rhodium, *etc*. This is clearly seen in the case of catalysts with chiral ligands. For example, the use of chiral bis(oxazoline) palladium(II) complexes **53** for diazomethane decomposition resulted in the corresponding cyclopropanes in high yields; however, the products proved to be racemic (the enantiomeric excess did not exceed 2%) (Scheme 39).[180]

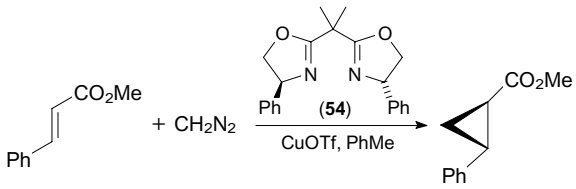
Scheme 39



Substrates: (*E*)-ethyl cinnamate, (*E*)-benzylideneacetone, cyclohexenone, *etc.*; R^4 = Pr^i, Bn

Optically active cyclopropanes were formed in this reaction when it was catalyzed by copper compounds, in particular, the chiral copper(I) bis(oxazoline) complex with ligand **54**. This distinction from the results obtained in the palladium-catalyzed reaction is attributable to generation of carbene complexes (Scheme 40).[179]

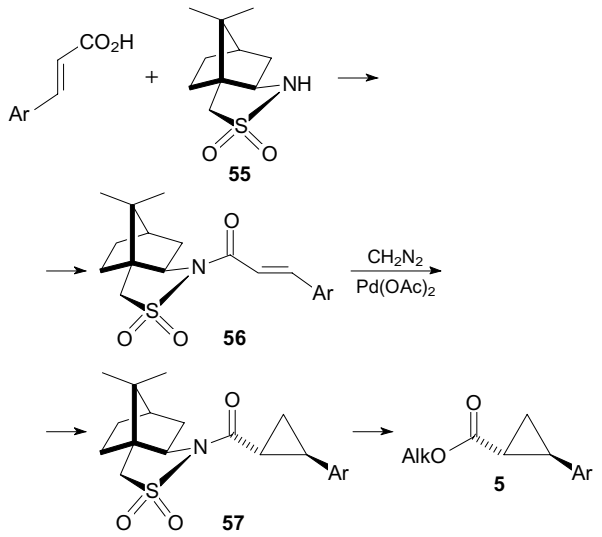
Scheme 40



(80%, 70% – 75% *ee*)

A different pathway was proposed for the synthesis of optically active cyclopropanes in the presence of palladium compounds as catalysts for diazomethane decomposition: first, the chiral ligand [(1*S*)-(−)-2,10-camphorsultam, **55**] is incorporated into the initial alkene molecule to give intermediate **56**, which is cyclopropanated with diazomethane in the presence of palladium acetate to form optically active DACs **57**. (1*R*,2*R*)-Cyclopropanes **5** were obtained by this method in preparative yields (Scheme 41).[181]

Scheme 41

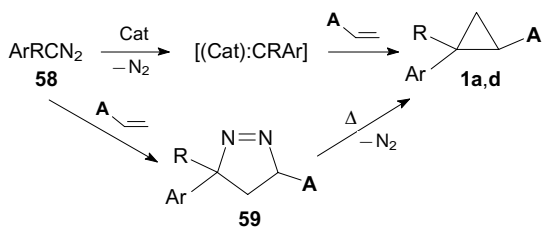


One more method that has been actively developed in recent years is direct catalytic cyclopropanation of unsaturated compounds with diazomethane generated *in situ*,[182–184] in particular, in the continuous mode. Owing to the absence of gaseous diazomethane, this is a convenient and safe preparative method. However, the scope of this method is limited to alkenes and catalysts stable to the action of concentrated alkali at room temperature. Furthermore, the nature of the ligand in the palladium-based catalyst considerably affects the regio- and stereoselectivity of reactions involving this catalyst.

3.3. Aryldiazomethanes

One more approach to the synthesis of DACs is the addition of arylcarbenes generated from aryldiazomethanes **58** to unsaturated compounds containing an acceptor substituent, or, alternatively, the 1,3-dipolar addition of aryldiazomethanes to alkenes to give pyrazolines **59**, which undergo thermal decomposition to form target DACs **1a**,**d** (Scheme 42).[50,185]

Scheme 42

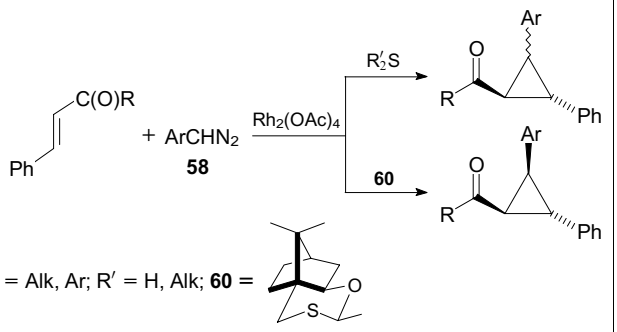


R = H, Ar

Phenyldiazomethane **58** (Ar = Ph, R = H) reacts with methyl methacrylate to give pyrazolines **59**, the thermal decomposition of which (in particular, under the action of molybdenum compounds) affords 2-phenylcyclopropanecarboxylates **1a**,**d** ($Z:E = 2.0$).[186] Similarly, 2,2-diphenylcyclopropanecarboxylate was obtained in 91% yield from diphenyldiazomethane and methyl acrylate.[187]

It was also shown that aryldiazomethanes **58** react with alkenes containing one acceptor substituent in the presence of the $Rh_2(OAc)_4$ catalyst and a catalytic amount of H_2S or an organic sulfide to give the expected cyclopropanes in good yields (Scheme 43).[188] The use of chiral 1,3-oxathiane **60** obtained from camphorsulfonyl chloride results in the formation of cyclopropanes in good yields and with high enantiomeric excess (*ee* > 97%).[188]

Scheme 43



Copper(II) acetylacetonate can also catalyze this reaction; however, the product yields are markedly lower in this case.[188] Other complexes of rhodium,[189] iron,[124,190] ruthenium,[191,192] iridium,[88] *etc.* can also catalyze the decomposition of aryldiazomethanes. Like in the case of alkyl diazoacetates, cyclopropanes are mainly formed as *trans*-isomers. It is of interest that the Lewis acid $[(\eta^5\text{-}C_5H_5)Fe^+(CO)_2(THF)][BF_4^-]$ present as the catalyst of reactions of phenyldiazomethane with alkenes produces *cis*-cyclopropanes with high selectivity.[193]

To make experimental procedures involving diazo compounds more facile and safe, methods for *in situ* generation of diazo compounds are being developed. In particular, such methods have been proposed for aryldiazomethanes.[194] However, the syntheses of DACs with the use of aryldiazomethanes have not become popular, first of all, because of their experimental complexity and lower yields of products as compared with other methods.

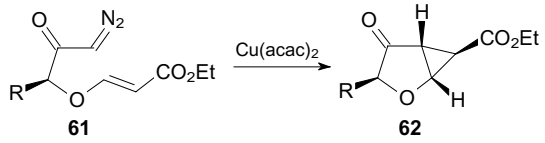
Finally, aryldiazomethanes are used in some cases in the synthesis of DACs, but they serve as the starting compounds rather than as sources of arylcarbenes; in particular, they are used as reactants in the synthesis of organometallic derivatives,[195,196] which are then employed for cyclopropanation.

3.4. Intramolecular reactions of diazo compounds

Intramolecular reactions of compounds in which the diazo group is bound to the C=C bond through a linker of an appropriate length usually afford the expected cyclopropanes with high stereoselectivity. For example, the intramolecular reaction of vinyl ethers **61** containing an α-diazocarbonyl moiety catalyzed by copper acetylaceto-

nate leads to cyclopropafuranones **62** in up to 80% yields (*dr* > 19 : 1) (Scheme 44).[197]

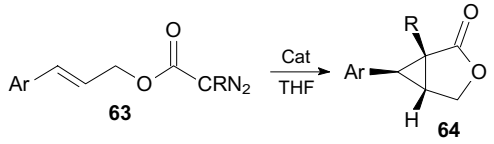
Scheme 44



R = Alk, Bn, Ph, $BnOCH_2$

Similarly in the presence of chiral cobalt or ruthenium salen complexes, cinnamyl diazoacetates **63** undergo, even at room temperature, the enantioselective intramolecular addition of the carbene carbon atom to the double bond to give 6-aryl-3-oxabicyclo[3.1.0]hexan-2-ones (**64**, R = H) in 60% – 78% yields (Scheme 45).[128]

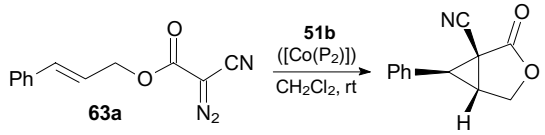
Scheme 45



R = H, Alk, CO_2Me

Examples of the synthesis of cyclic arylcyclopropanedicarboxylates by the intramolecular reaction of cinnamyl diazomalonates catalyzed by copper, cobalt, rhodium or ruthenium compounds have been reported.[118, 198, 199] This gives 6-aryl-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylates **64** (R = CO_2Me) in 62% – 99% yields (see Scheme 45). When chiral catalysts are used, the reaction is enantioselective. In particular, the intramolecular cyclopropanation of compound **63a** proceeds enantioselectively in the presence of optically active cobalt porphyrin complexes (*e.g.*, compound **51**) to form DAC **64a** in a high yield (Scheme 46).[198]

Scheme 46

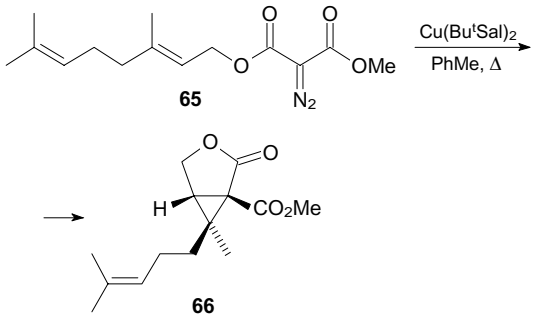


64a (99%, 55% *ee*)

Bicyclic lactone **66** was synthesized in this way in 80% yield by cyclopropanation of the nearest double bond of (*E*)-1-(3,7-dimethylocta-2,6-dienyl)-3-methyl-2-diazomalonate (**65**) (Scheme 47).[142]

Analogous intramolecular cyclopropanation reactions are also known for α-diazo-β-ketonitriles;[200] however, they all are of limited use in organic synthesis, in particular, for the preparation of DACs.

Scheme 47



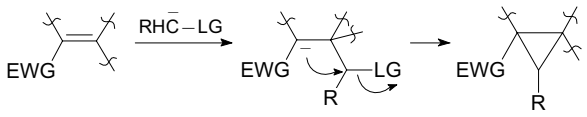
But Sal is *tert*-butylsalicylimine

4. Michael-initiated ring closure

This Section covers the methods for preparation of cyclopropane derivatives by the initial attack of a nucleophile on alkenes with electron-withdrawing substituents followed by intramolecular nucleophilic substitution with three-membered ring closure. This is possible provided that the nucleophile (or the electron-deficient alkene) contains a leaving group (LG) in an appropriate position. This type of reactions is called Michael-initiated ring closure reaction (MIRC) and is often used for the synthesis of cyclopropane derivatives.

The reactions of electron-deficient alkene with a nucleophile containing a leaving group are most significant for the synthesis of DACs. The resulting cyclopropane moiety contains two carbon atoms coming from the alkene and one from the nucleophile (Scheme 48). Particularly this type of transformations will receive the primary attention here.

Scheme 48

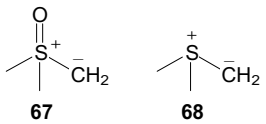


Sulfur ylides have found the most extensive use as reagents for the synthesis of DACs (Corey – Chaykovsky reaction). Phosphorus, arsenic, selenium, tellurium and iodonium ylides are also used. Also, a halogen atom often acts as the leaving group in the synthesis of cyclopropane derivatives, if the nucleophile is generated from compounds with an active methylene unit or from nitro compounds. α-Halo enolates are also used.

4.1. Corey – Chaykovsky reaction

In the 1960s, Corey and Chaykovsky[201, 202] proposed to use trimethylsulfoxonium [$Me_2S(O)CH_2$, **67**] and trimethylsulfonium (Me_2SCH_2, **68**) ylides as methylenating agents. Thorough investigation of their reactivity has shown that

Structures 67, 68

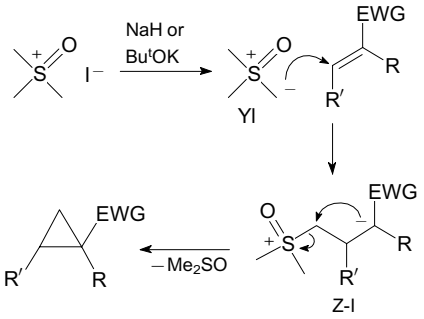


good results of cyclopropanation are achieved only for trimethylsulfoxonium ylide (**67**), which has acquired the name Corey ylide.[203, 204]

Owing to ready accessibility, relatively low cost and easy handling, this reagent is widely used to prepare a variety of esters of 2-aryl- and 2-hetarylcyclopropane-1,1-dicarboxylic acids and also some DACs with other acceptor groups, that is, particularly those DAC subclasses the reactivity of which is now attracting most attention. Indeed, using these substrates, [3 + 3]-,[205] [3 + 4]-,[206] [3 + 8]-[207, 208] and [3 + 1 + 1]-cycloaddition[209] reactions were discovered; unusual reactivity of DACs as synthetic equivalents of 1,2-zwitterions was found;[210, 211] [3 + 2]-,[212 – 214] [3 + 4]-[215] and [4 + 2]-annulation reactions[14, 216, 217] and numerous cyclodimerization reactions[14, 27, 218 – 221] were implemented.

The Corey – Chaykovsky reaction mechanism includes deprotonation of trimethylsulfoxonium iodide on treatment with the base to give ylide (Yl), Michael addition of the ylide to the electrophilic alkene and cyclization of the resulting zwitterion (Z-I) upon the attack of the anionic centre on the ylide methylene group with elimination of DMSO (Scheme 49).[202]

Scheme 49



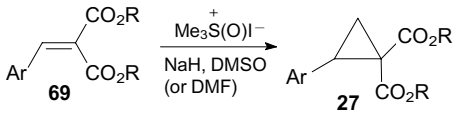
The Corey – Chaykovsky reaction of benzylidenemalonates **69** resulted in efficient synthesis of a broad range of cyclopropane-1,1-dicarboxylates **27** containing various aromatic and heteroaromatic donor substituents (Scheme 50).[14, 143, 170, 206, 214, 215, 222 – 254] It is noteworthy that the substituent in the aromatic moiety does not significantly affect the yields of the cyclopropane products. The variation of ester groups also has little effect: cyclopropanation reactions of methyl, ethyl, adamantyl and neopentyl esters are equally efficient. 2,2,2-Trifluoroethyl esters, which afford cyclopropanes in moderate yields, are exceptions.[250]

The reaction is usually carried out in DMSO or DMF, with sulfur ylide being generated immediately before cyclopropanation. Meanwhile, it has been found that the Corey ylide can be stored for long periods of time as a THF or dioxane solution, and the Corey – Chaykovsky cyclopropanation was performed, in some cases, in these solvents.

For the Corey – Chaykovsky cyclopropanation, it is important to use anhydrous solvents, since even traces of water induce the side reaction of hydrolysis of the cyclopropane-1,1-dicarboxylate product. It was noted, for example, that the reaction of alkene **69a** in wet DMF gives, together with the target 2-phenylcyclopropane-1,1-dicarboxylate **27a**, the corresponding monoester **27′a** in almost an equal amount (Scheme 51).[222]

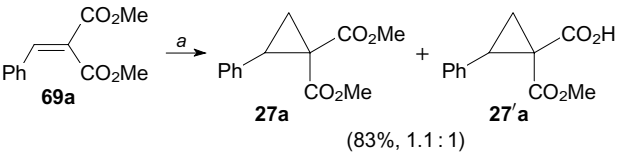
Whereas the yields of cyclopropanes depend little on the substituents in the aromatic moiety, the reaction time varies

Scheme 50



Ar = Ph, 4-MeOC$_6$H$_4$, 4-BnOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-Pr^{i}C$_6$H$_4$, 4-Bu^{t}C$_6$H$_4$, 4-PhC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-IC$_6$H$_4$, 4-piperidinophenyl, 4-pyrrolidinophenyl, 4-morpholinophenyl, 4-MeO$_2$CC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, 4-MeO$_2$SC$_6$H$_4$, 3-MeOC$_6$H$_4$, 3-MeC$_6$H$_4$, 3-ClC$_6$H$_4$, 2-(PhC≡CCH$_2$O)C$_6$H$_4$, 2-MeOC$_6$H$_4$, 2-MeC$_6$H$_4$, 2-ClC$_6$H$_4$, 2-BrC$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_3$, 3,4-(OCH$_2$CH$_2$O)C$_6$H$_3$, 3,4-(OCH$_2$O)C$_6$H$_3$, 3,4-Cl$_2$C$_6$H$_3$, 3,5-(MeO)$_2$C$_6$H$_3$, 3,5-Cl$_2$C$_6$H$_3$, 2,3-(MeO)$_2$C$_6$H$_3$, 2,3-(OCH$_2$O)C$_6$H$_3$, 2-BnO-3-MeOC$_6$H$_3$, 2-Br-4-O$_2$NC$_6$H$_3$, 2-Br-6-FC$_6$H$_3$, 2,5-(MeO)$_2$C$_6$H$_3$, 5-MeO-2-(CH$_2$=C(Me)CH$_2$)C$_6$H$_3$, 2-Br-5-MeOC$_6$H$_3$, 2-I-5-MeC$_6$H$_3$, 2-MeO-5-O$_2$NC$_6$H$_3$, 2-Me-5-O$_2$NC$_6$H$_3$, 2-Br-5-O$_2$NC$_6$H$_3$, 2-Br-4,5-(MeO)$_2$C$_6$H$_2$, 3,4,5-(MeO)$_3$C$_6$H$_2$, 2,3,4-(MeO)$_3$C$_6$H$_2$, 2,4,6-(MeO)$_3$C$_6$H$_2$, 2,4,6-Me$_3$C$_6$H$_2$, 2-Naph, 1-Naph, 2-Th, 3-Th, benzothiophen-2-yl, 2-Fu, 5-methylfuran-2-yl, 3-Fu, benzofuran-2-yl, 1-methylpyrrol-2-yl, 1-methylindol-4-yl, 3-Py, *etc.*; R = Me, Et, Bn, Pr^i, Bu^i, Bu^{t}CH$_2$, 2-Ad, CF$_3$CH$_2$

Scheme 51

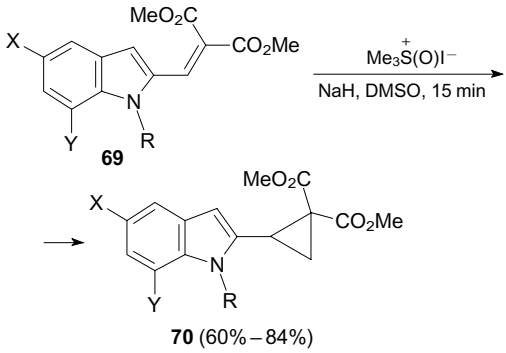


(*a*) Me$_3$S(O)I$^-$, NaH, wet DMF, 0 °C to rt

considerably depending on the electron-donating properties of this moiety: the more electron-donating the aromatic group, the shorter the time required for the complete substrate conversion, all other factors being equal. Keeping the reaction mixture for more time may be accompanied by some decrease in the yield of the target cyclopropane because of side reactions.

The monitoring of the extent of reaction is especially important for the synthesis of the most reactive DACs, for example, compounds **70**, in which 2-indolyl is the donor group (Scheme 52).[212, 215, 220, 233, 255]

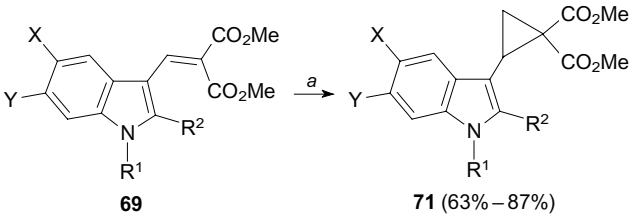
Scheme 52



R = Me, Bn, 4-MeOC$_6$H$_4$CH$_2$, EtOCH$_2$, Boc, Ts;
X = H, MeO, Cl, F; Y = H, Et

One more way to minimize the side reactions is slow addition of a solution of the substrate in DMSO or DMF to the ylide obtained by mixing of a suspension of NaH in an appropriate solvent with solid trimethylsulfoxonium iodide. Switching to this procedure is especially important for the synthesis of cyclopropanes **71** with the 3-indolyl donor group and some other highly reactive DACs (Scheme 53).[231, 238, 252, 256, 257]

Scheme 53

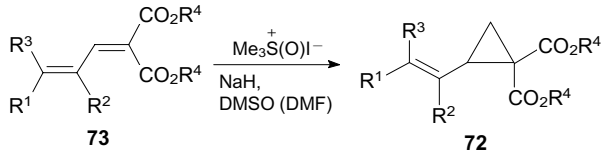


(*a*) $Me_3\overset{+}{S}(O)I^-$, NaH, DMSO; R^1 = Me, Bn, $Ph(CH_2)_3$, Boc, Ts, Ns; R^2 = H, Me; X = H, F, Cl, Br, CN; Y = H, F, Cl

Although the product yields upon cyclopropanation in DMSO and DMF differ little, the reactions in DMF are faster and give less side products than the reactions in DMSO. Therefore, the use of DMF is more beneficial.

The Knoevenagel reaction – Corey – Chaykovsky reaction sequence has also been used to prepare 2-alkenylcyclopropane-1,1-dicarboxylates **72** (Scheme 54).[222, 226, 238, 241, 245, 247, 251, 252, 258 – 260] Generally, the reactions gave high yields of products; however, in the cyclopropanation of *trans*-2-methylbut-2-enylidenemalonate (**73a**; $R^1 = R^2 = Me$, $R^3 = H$), the yield of the corresponding DAC **72a** was only 24%.[222]

Scheme 54

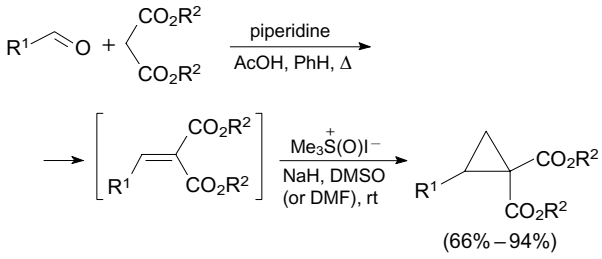


$R^2 = R^3$ = H: R^1 = Ph, 4-$MeOC_6H_4$, 3-MeC_6H_4; $R^1 = R^2$ = Me, R^3 = H; $R^1 – R^2 = C_6H_4CH_2CH_2$, R^3 = Br; R^4 = Me, 2-Ad, Bu^tCH_2

In some cases, the Knoevenagel condensation and Corey – Chaykovsky cyclopropanation have been carried out without isolation of the alkenes (Scheme 55).[14, 261, 262]

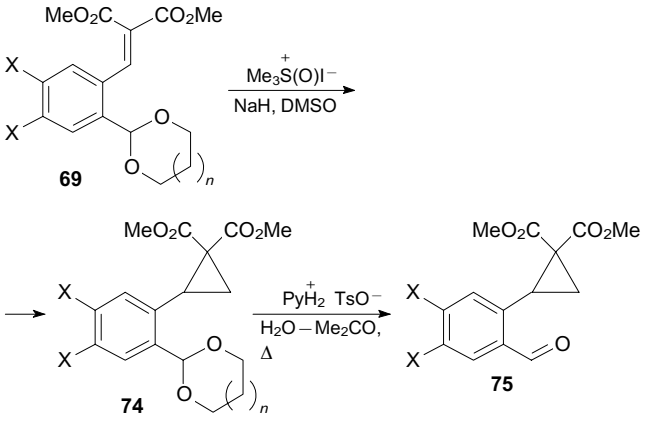
Corey ylide is highly reactive towards various groups and bonds,[203, 227] which in some cases hampers the formation of desired products because of side reactions. For example, $Me_2S(O)=CH_2$ (**67**) readily reacts with the carbonyl group of the aldehydes to give oxiranes; therefore, protecting groups are required for the Corey – Chaykovsky synthesis of DACs with such functional groups. Cyclopropanes containing an aldehyde group in the side chain are prepared *via* transformations of other 2-arylcyclopropanes. One example of such a sequence is shown in Scheme 56.[234]

Scheme 55



R^1 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-ClC_6H_4, 3-BrC_6H_4, 3,4,5-$(MeO)_3C_6H_2$, 2-Naph, 2-Fu, (*E*)-PhCH=CH, CH_2=CH; R^2 = Me, 2-Ad

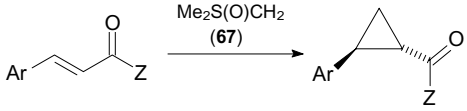
Scheme 56



Substituents	*n*	Yield of **74** (%)	Yield of **75** (%)
X = H	1	83	52
X – X = OCH_2O	2	72	91

The Corey – Chaykovsky reaction has also been used for cyclopropanation of α,β-unsaturated ketones (Z = Ar, Het, Alk),[263 – 278] esters (Z = OAlk)[178, 279 – 294] and amides ($Z = NR^1R^2$) (Scheme 57);[263, 284, 295 – 309] in the case of esters, the yields of products are usually moderate, while

Scheme 57

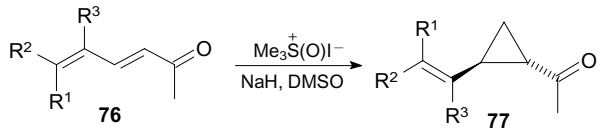


Z = Ar′, Het, Me, 1-Ad (Ar′ = Ph, 4-XC_6H_4 (X = Me, Bu^t, MeO, MeS, F, Cl, Br, F_3C, HO_2C, O_2N), 3-$MeOC_6H_4$, 3-ClC_6H_4, 2-IC_6H_4, 1-Naph; Het = 2-Th, 2-Fu, 2-Py *etc.*); Ar = Ph, 4-X′C_6H_4 (X′ = Me, MeO, MeS, Me_2N, O_2N, Cl, 4-$BrC_6H_4CH_2O$, 3,4-$Cl_2C_6H_3CH_2O$, *etc.*), 2,4-$(MeO)_2C_6H_3$, 3,4-$(MeO)_2C_6H_3$, 3-$O_2NC_6H_3$, 3-MeC_6H_4, 2-ClC_6H_4, 2-BrC_6H_4, 1-Naph, 2-Naph, 2-Th, 2-Fu, 3-Py, 4-Py, quinolin-3-yl, *etc.*; Z = OAlk (Alk = Me, Et, Bu^t); Ar = 4-YC_6H_4 (Y = Me, MeO, EtO, F_3C, O_2N, F_3CO, $MeOCH_2O$, F_3CCH_2O, *etc.*), 3-$MeOC_6H_4$, 3-FC_6H_4, 2-MeC_6H_4, 2-$MeOC_6H_4$, 1-Naph, 2-Th, 3-Th, 2-Fu, 3-Fu, *etc.*; $Z = NR^1R^2$ (R^1 = Me: R^2 = Me, MeO, Ph, *etc.*); Ar = Ph, 4-$Bu^tC_6H_4$, 4-$MeOC_6H_4$, 4-FC_6H_4, 3-$MeOC_6H_4$, 3-$Bu^tC_6H_4$, 3-FC_6H_4, 2-FC_6H_4, 2-BrC_6H_4, 3,4-$(MeO)_2C_6H_3$, 2,4-$(MeO)_2C_6H_3$, 3-HO-4-$MeOC_6H_3$, 1-Naph, quinolin-3-yl, isoquinolin-4-yl, 1-methylpyrazol-4-yl, *etc.*

for ketones and amides, they vary from moderate to quantitative.

The cyclopropanation of dienones **76** affords the corresponding 2-alkenylcyclopropyl ketones **77**. The yields of products in these reactions vary from 8% to 85% (Scheme 58).[267]

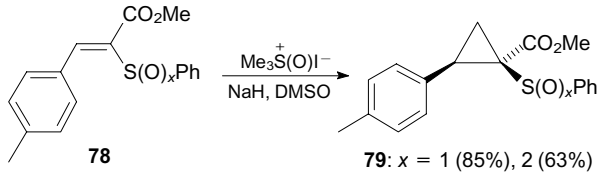
Scheme 58



R^3 = H: R^1 = R^2 = Me, Et; R^1 = H, R^2 = Bu^n; R^1 = Me,
R^2-R^3 = $(CH_2)_3CMe_2$; R^3 = H: R^1 = Me, R^2 = Et (mixture of isomers);
R^1 = Me, R^2 = $CH_2CH_2CH{=}CMe_2$ (mixture of isomers);
R^1 = H: R^2 = Et, Ph; R^3 = Me;
R^2-R^3 = $CH_2CH(CMe{=}CH_2)CH_2CH_2$

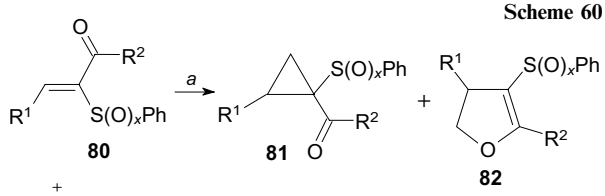
The use of the Corey–Chaykovsky reaction for cyclopropanation of Michael substrates containing two different acceptor groups proceeds more ambiguously. For example, the reaction of β-aryl-α-sulfonylacrylate **78** (x = 2) with the Corey ylide furnishes cyclopropane **79** as a mixture of *cis*- and *trans*-isomers in 1 : 1 ratio. Meanwhile, β-aryl-α-sulfinylacrylate **78** (x = 1) is converted under the same conditions only to isomer **79** with the *trans*-arrangement of Ar and CO_2Me groups, although comprising two diastereomers differing in configuration of the sulfur atom (Scheme 59).[310]

Scheme 59



It is worth noting that the major (or the only) products formed in the reaction of the Corey ylide with keto sulfones **80a–d** are dihydrofurans **82**, whereas in the case of keto sulfides **80g–r**, the predominant products are cyclopropanes **81** (Scheme 60, Table 6).[310,311]

Scheme 60



The cyclopropanation of sulfides **80f–r** leads exclusively to *cis*-cyclopropanes, whereas the cyclopropanes that are formed from sulfones **80c,d** have the *trans*-configuration. It was shown that sulfides **80j,k** can be efficiently oxidized to the corresponding sulfones, *i.e.*, in the general case, this approach is suitable for the preparation of 1-sulfonylcyclopropyl ketones as both *cis*- and *trans*-isomers. On the other hand, an attempted oxidation of compounds **81h,i** gave dihydrofurans **82**, instead of the expected cyclopropanes.[310,312]

Table 6. Reactions of Corey ylides with unsaturated ketones **80** (Scheme 60).

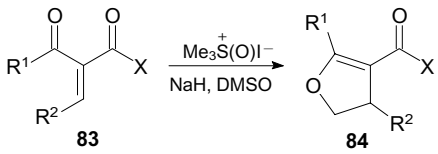
Compound **80**	R^1	R^2	x	Yield (%)	
				81	**82**
a	4-MeC_6H_4	Ph	2	0	90
b	Ph	Ph	2	0	71
c	Ph	Me	2	11 [a]	65
d	Pr^i	Me	2	27 [a]	63
e	Ph	Me	1	45 [b]	47
f	4-MeC_6H_4	4-ClC_6H_4	0	32 [c]	32
g	4-MeC_6H_4	Ph	0	65 [c]	21
h	4-MeC_6H_4	Me	0	85 [c]	0
i	4-$MeOC_6H_4$	Me	0	81 [c]	0
j	Ph	Me	0	68 [c]	0
k	2-Naph	Me	0	80 [c]	0
l	2-Fu	Me	0	70 [c]	0
m	2-Th	Me	0	76 [c]	0
n	Pr^i	Me	0	87 [c]	0
o	$PhCH_2CH_2$	Me	0	73 [c]	0
p	$PhCH_2CH_2$	Bu^n	0	91 [c]	0
q	Me	Bu^n	0	90 [c]	0
r	Pr^i	Ph	0	71 [c]	0

[a] *trans*-Isomer. [b] A mixture of two *trans*- and two *cis*-isomers in 1 : 1 ratio. [c] *cis*-Isomer.

Similarly, the treatment of α-phenylselenyl-α,β-unsaturated ketones with the Corey ylide generates either only cyclopropanes or their mixtures with dihydrofurans, depending on the nature of the substituent in the starting alkene.[313]

Dihydrofurans **84** are formed when the Corey ylide is reacted with Knoevenagel adducts **83** obtained from β-keto esters and 1,3-diketones (Scheme 61).[314] This reaction pathway is believed to be general for α,β-unsaturated ketones

Scheme 61

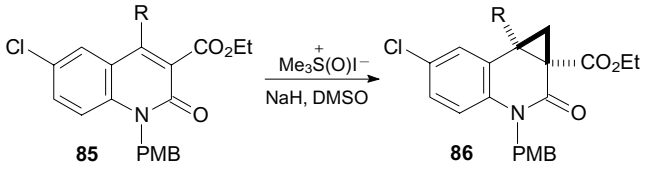


R^1 = Me, Et, Pr^i, Ph; R^2 = Ph, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, 4-PhC_6H_4, 3,4,5-$(MeO)_3C_6H_2$, 2,4,6-$(MeO)_3C_6H_2$, 4-FC_6H_4, 4-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 2-Fu, 2-Th, 2-Py, 1-benzylindol-3-yl, (*E*)-PhCH=C(Me), (*E*)-4-$MeOC_6H_4CH{=}CH$, Me;
X = Me, Et, Ph, OEt

containing an electron-withdrawing substituent (acyl, ester or sulfonyl group) in the α-position.[314]

If one of the two acceptor groups is a part of a cyclic system, the problem of formation of two diastereomers is eliminated. For example, the reaction of the Corey ylide with 3-alkoxycarbonylquinolin-2-ones **85** furnishes the corresponding cyclopropanes **86** in 51%–78% yields (Scheme 62).[315]

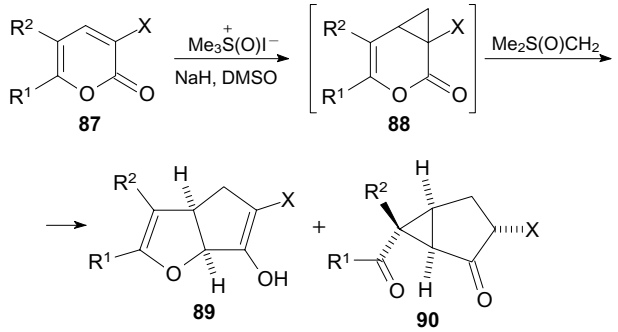
Scheme 62



R = Me, Et, Pr^n, Bu^n, n-C_5H_{11}, n-C_6H_{13}, Pr^i, Bu^i, cyclo-C_3H_5, cyclo-C_5H_9, Cy, Bn, $PhCH_2CH_2$, 4-PhC_6H_4

Conversely, the reaction of the Corey ylide with 3-(alkoxycarbonyl)coumarins and appropriate α-pyrones **87** gives only minor amounts, if any, of the expected cyclopropanes **88**. The sulfoxonium ylide attack on the cyclopropane **88** product induces its rearrangement to either cyclopentafuran **89** or bicyclo[3.1.0]hexane **90**, or to a mixture of these products (Scheme 63).[316–319]

Scheme 63



R^1 = Et, Pr^i, Bu^n, Ph, 2-Fu; R^2 = Ph, 4-$MeOC_6H_4$, 4-PhC_6H_4, 4-FC_6H_4, 4-$F_3CC_6H_4$, 4-$O_2NC_6H_4$, 2-Th, Pr^n;
R^1–R^2 = $(CH_2)_n$ (n = 2–6, 10), $(CH_2)_2N(CO_2Et)CH_2$, $(CH{=}CH)_2$, $[CH{=}C(OMe)]_2$, $CH{=}CHC_6H_4$, $C_6H_4OCH_2$;
X = CO_2Me, CO_2Et, CO_2Bu^t, C(O)Bu^t, C(O)Ph, CN, SO_2Ph

The Corey–Chaykovsky reaction has been successfully used to cyclopropanate 2′-hydroxy- and 2′-(tosylamino)-chalcones **91** (Scheme 64).[320, 321] The presence of a nucleophilic substituent in the *ortho*-position of the benzoyl moiety does not interfere with the target reaction.

The Corey–Chaykovsky reaction is rarely employed for the preparation of DACs that contain alkoxy, amino or alkylthio donor groups. Over the considered period of time, only one example of this reaction was published, in particular, ethyl 2-methyl-4-phenyl-4,5-dihydrofuran-3-carboxylate was converted to cyclopropane **92** in a 75% yield (Scheme 65).[314]

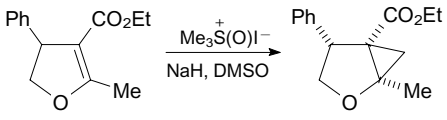
The catalytic asymmetric cyclopropanation of α,β-unsaturated ketones **93** with the Corey ylide was described for

Scheme 64



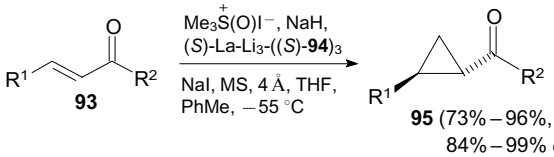
X = NTs: Ar = Ph, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2,4,6-$Me_3C_6H_2$, 2-Naph; X = O, Ar = Ph

Scheme 65



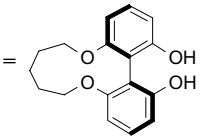
the first time in 2007.[322] For this purpose, a solution of the substrate in a mixture of THF and toluene was slowly added at −55 °C to a THF solution containing the pre-synthesized Corey ylide, the lanthanum lithium complex of substituted biphenyl-2,2′-diol **94**-H_2 and NaI, and the mixture was stirred at the same temperature for 24 h. The reaction resulted in DACs **95** in high yields and with high enantioselectivity except for alkyl styryl ketones, which afforded products in somewhat lower yields. (Scheme 66).[322]

Scheme 66



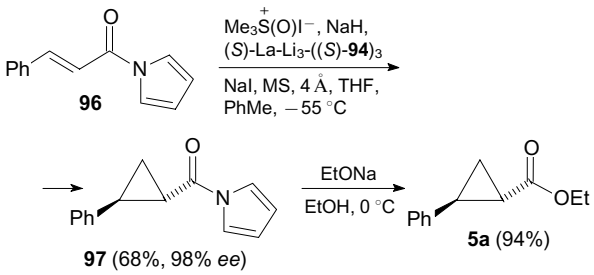
R^1 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-Th, 2-Fu, 4-Py, (*E*)-PhCH═CH; R^2 = Ph, 4-$MeOC_6H_4$, 4-$AllOC_6H_4$, 4-ClC_6H_4, Me, Pr^i;

(*S*)-**94**-H_2 =



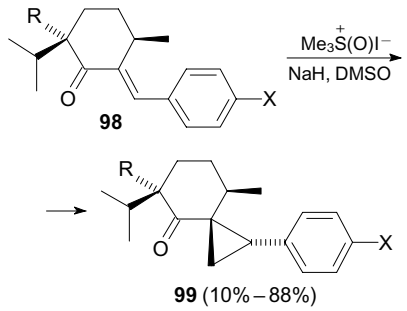
Under the same conditions, *N*-cinnamoylpyrrole (**96**), a heterocyclic ketone, is converted to cyclopropane **97** in 68% yield and with 98% *ee*, and then to the corresponding optically active cyclopropanecarboxylate **5a** (Scheme 67).[322]

Scheme 67



Optically active DACs are usually synthesized by the Corey–Chaykovsky reaction using enantiomerically enriched substrates. The reaction of the Corey ylide with optically active menthone-based substrates **98** is stereoselective, resulting only in products **99** (Scheme 68).[323, 324] It is noteworthy that cyclopropane **99a** (R = H, X = Ph) is formed in a considerably higher yield in DMF (60% in 1.5 h) than in DMSO (47% in 3 h).[323]

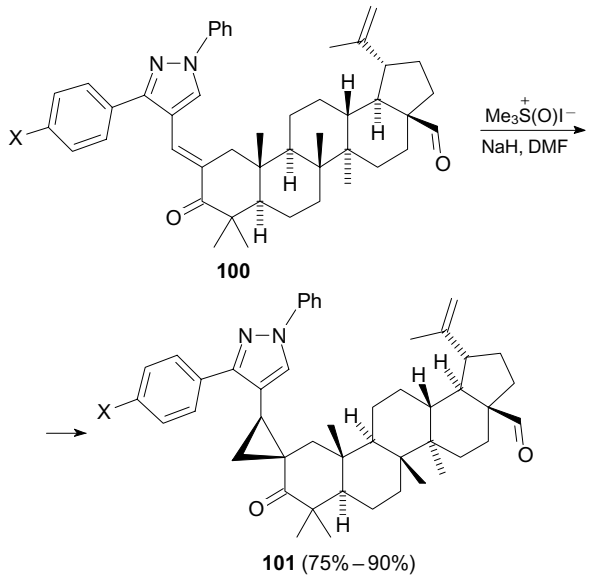
Scheme 68



R = H: X = Ph, 4-Pr^{n}OC$_6$H$_4$, F, Cl, Br; R = Me: X = Ph, Br

Conversely, the cyclopropanation of unsaturated ketones **100** based on betulinaldehyde gives a mixture of diastereomeric products **101** in 3 : 1 ratio (Scheme 69, the major isomer is shown).[325]

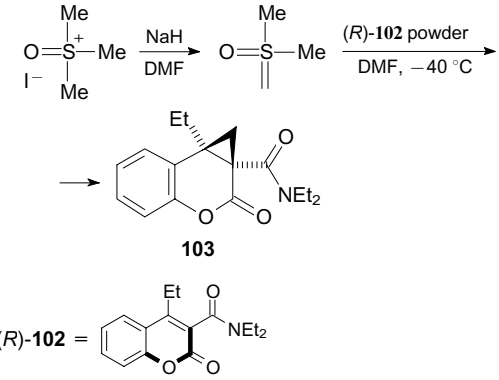
Scheme 69



X = Me, OMe

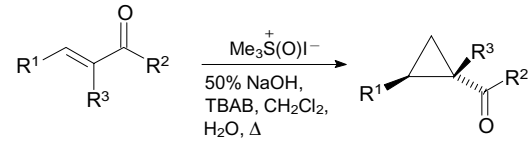
In 2016, the first example of asymmetric Corey–Chaykovsky cyclopropanation of an achiral substrate with so-called 'frozen' chirality was reported.[326] The method is based on the fact that after dissolution of chiral *N*,*N*,4-triethylcoumarin-3-carboxamide (**102**) crystals in cold DMF containing dimethylsulfoxonium methylide, the chiral conformation in which the molecule exists in the crystal is preserved for some period of time, which enables asymmetric synthesis. As a result, whereas dissolution of amide **102** at room temperature affords racemic cyclopropane **103**, the dissolution at −40 °C leads to cyclopropane **103** with 97% *ee*, although the substrate conversion is only 16% (Scheme 70).[326] Further development of this approach appears highly promising.

Scheme 70



Apart from the conventional procedures for the Corey–Chaykovsky reaction, phase transfer catalysis (PTC) is also used. According to this procedure, unsaturated ketone, trimethylsulfoxonium iodide and tetra-n-butylammonium bromide (TBAB) are dissolved in dichloromethane, aqueous NaOH is added, and the mixture is stirred at room temperature. The Corey ylide adds to the Michael acceptor (ketone) more rapidly than it reacts with water. This method can be used to prepare DACs in 51%–90% yields (Scheme 71).[327–330]

Scheme 71



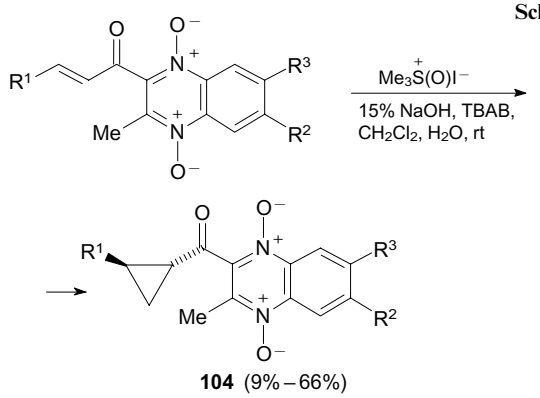
R^3 = H: R^1 = 4-ClC$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_3$, 3,4,5-(MeO)$_3$C$_6$H$_2$, 2-Th, 2-Fu, 5-methylfuran-2-yl, 1-methylpyrrol-2-yl; R^2 = 4-XC$_6$H$_4$ (X = F, 4-methylpiperazino, furfurylamino, Me$_2$N(CH$_2$)$_3$NH, morpholino, piperidino), 3-(4-methoxyphenyl)quinolin-2-yl, (MeS)$_2$C=CH, (MeS)$_2$C=CMe; R^1 = (*E*)-MeCH=CH, R^2–R^3 = (CH$_2$)$_3$

A similar PTC method was used to prepare 2-(2-arylcyclopropanoyl)quinoxalines **104** and **105**, which exhibit antimalarial activity (Scheme 72),[331] and dispiro ketones **106** (Scheme 73, the product yields or stereochemistry are not reported).[332]

In 2003, the Corey–Chaykovsky cyclopropanation in an ionic liquid was reported for the first time; this allows one to carry out this reaction using KOH as the base. Under these conditions a broad range of α,β-unsaturated ketones were converted into cyclopropanes in high yields; an example is the the conversion of aryl styryl ketones to the corresponding DACs (Scheme 74).[333]

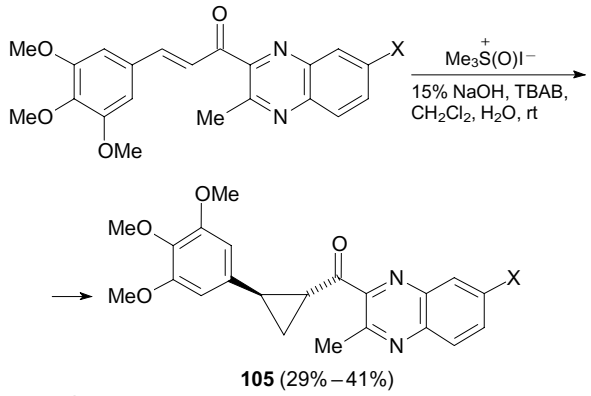
The solid-phase Corey–Chaykovsky cyclopropanation was also reported; for this purpose, 4-ferrocenylacetophenone (**107**) was first ground with NaOH and Al_2O_3; then aldehyde, trimethylsulfoxonium iodide, NaOH and Al_2O_3 were added successively with grinding, and finally the

Scheme 72



104 (9%–66%)

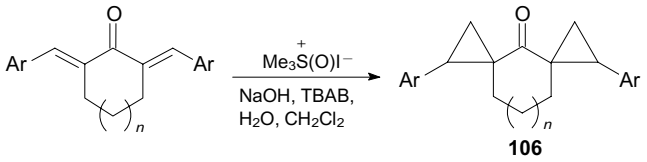
R^1 = 3,4,5-$(MeO)_3C_6H_2$, 2-Naph; R^2 = H, Me;
R^3 = H, Cl, Me, MeO



105 (29%–41%)

X = H, MeO

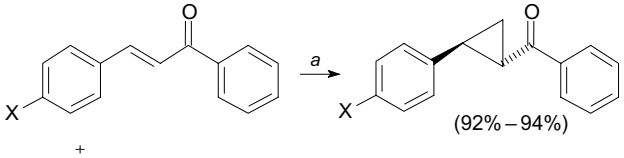
Scheme 73



106

Ar = 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-FC_6H_4, 3,4-$(MeO)_2C_6H_3$; *n* = 0, 1

Scheme 74

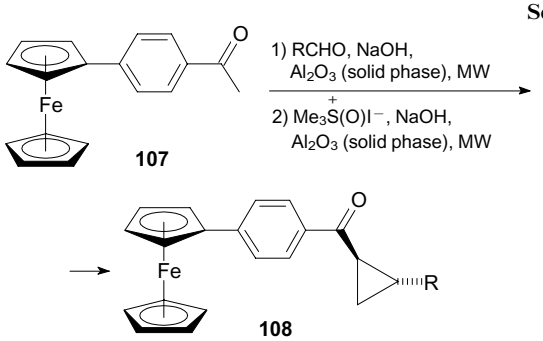


(*a*) $Me_3S(O)I^-$, KOH, $(bmim)PF_6$, rt; X = H, MeO

mixture was subjected to microwave irradiation. This afforded substituted cyclopropyl ketones **108** in yields of 85% to 99% (Scheme 75).[334]

One more unusual procedure of Corey–Chaykovsky cyclopropanation is to use a mixture of trimethylsulfoxonium iodide and a base (NaH or Bu^tOK), which is prepared

Scheme 75



107

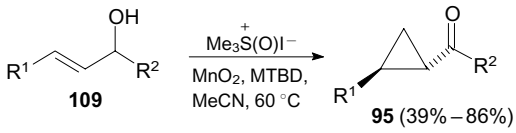
108

R = Ph, 4-$Me_2NC_6H_4$, 4-BrC_6H_4, 3-ClC_6H_4, 4-FcC_6H_4, 4-$O_2NC_6H_4$, 3,4-$(OCH_2O)C_6H_3$, 3-MeO-4-$(MeOCH_2O)C_6H_3$, 2-Fu, Fc, PhCH=CH, MeCH=CH

beforehand and stored dry without decomposition. This mixture was shown to be suitable for cyclopropanating various acceptor alkenes in yields not inferior to the yields obtained in reactions with successive addition of reactants.[335]

Mention should also be made of the oxidation–cyclopropanation tandem for allyl alcohols **109** based on simultaneous use of MnO_2, trimethylsulfoxonium iodide and 1-methyl-1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine (MTBD) (Scheme 76).[264] The reaction is regio- and diastereoselective and gives the corresponding cyclopropanes **95** only as *trans*-isomers.

Scheme 76



109 **95** (39%–86%)

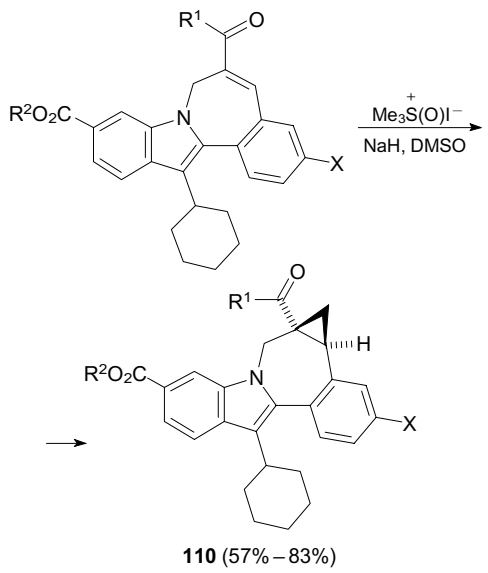
R^1 = Ph, 2-Th, 2-Fu, 2-Py, Me; R^2 = Ph, 2-Fu

The Corey–Chaykovsky reaction is actively used to construct the DAC moiety in the synthesis of physiologically active compounds; the syntheses of compounds **110** and **111** can be considered as examples. Compounds **110** are precursors or analogues of the agent BMS-791325 (**112**) developed for the treatment of hepatitis C (Scheme 77).[336–339] Analogues of cytisine **111** exhibit high affinity for nicotinic acetylcholine receptor $(\alpha4)_2(\beta2)_3$ (Scheme 78).[340]

Finally, related reactions involving other sulfoxonium ylides have been described. In particular, tris(isopropyl)sulfoxonium iodide reacts with α,β-unsaturated ketones, esters, sulfones, nitriles and nitro compounds to give the corresponding DACs in 33%–95% yields (Scheme 79).[341, 342]

It is of interest that *cis*-chalcone gives the same product as *trans*-chalcone under these conditions, thus demonstrating that in the case of a bulky ylide, the intermediate has a sufficient lifetime for rotation about the C–C bond to occur, resulting in the formation of the more stable cyclopropane with *trans*-positions of the acyl and aryl substituents.

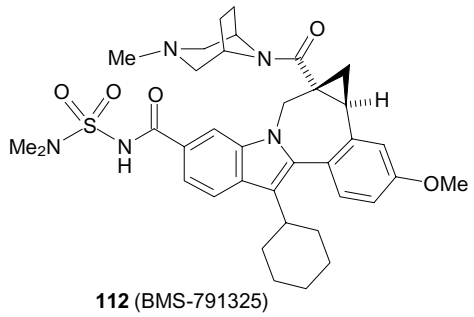
Scheme 77



110 (57%–83%)

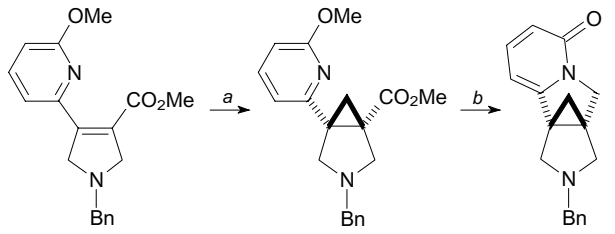
X = H, OMe; R^1 = OMe, morpholino; R^2 = Me, Bu^t

Structure 112



112 (BMS-791325)

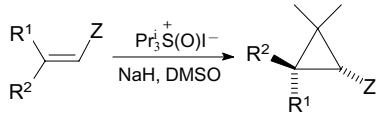
Scheme 78



111

(*a*) $Me_3\overset{+}{S}(O)I^-$, THF, rt (61% yield); (*b*) 4 steps

Scheme 79



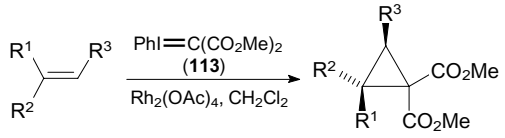
R^2 = H: R^1 = Ph, (*E*)-CH=CHPh, 2-Fu, 2-Py; Z = Ac, C(O)Ph, C(O)(2-Fu), C(O)CH=CHPh, CO_2Me, $CO_2C_6F_5$, SO_2Ph, NO_2, CN; R^2–Z = $OC_6H_4C(O)$, R^1 = H

4.2. Iodonium ylides

One more general method for the synthesis of DACs is cyclopropanation using iodonium ylides.[343,344] The key achievements of the iodonium ylide chemistry, including their synthetic application as reagents for cyclopropanation, have been integrated in a review.[344]

Iodonium ylides were employed for the first time for the cyclopropanation of alkenes in 1982.[345] Using this approach, ylides **113** (obtained from dimethyl malonates) were reacted with substituted styrenes to give a series of DACs **27** and **114** (Scheme 80).[346–349]

Scheme 80



27, **114** (39%–90%)

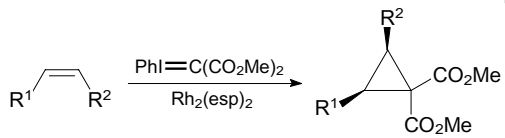
R^2 = R^3 = H (**27**), R^2 or R^3 ≠ H (**114**); R^2 = R^3 = H: R^1 = Ph, 4-MeC_6H_4, 4-$Bu^tC_6H_4$, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-$O_2NC_6H_4$, 3-$MeOC_6H_4$, 3-$O_2NC_6H_4$; R^1 = Ph, R^3 = H: R^2 = Me, Ph; R^1–R^3 = $C_6H_4CH_2$, R^2 = H

It was shown that the cyclopropanation rate depends on both the substituents in the benzene ring of styrene and the catalyst used. The relative rate constants of styrenes cyclopropanation obey the Hammett equation (σ^+ constants); in the case of rhodium(II) acetate, $\rho = -0.47$, while for copper(II) acetylacetonate, $\rho = -1.12$.[346]

When the ester function in the malonate is varied, the reaction efficiency depends appreciably on the type of ylide and the catalyst used. The cyclopropanation of styrene with phenyl iodonium ylide of dimethyl malonate in the presence of rhodium acetate occurs in up to 80% yield. However, diisopropyl malonate ylide generates cyclopropane in only 19% yield under the same conditions. The replacement of $Rh_2(OAc)_4$ by CuOTf increases the DAC yield to 91% in the former reaction[350] and up to 61% in the latter reaction.[351] The application of iodonium ylides also allows the use of other esters of malonic acid for styrene cyclopropanation [diethyl, di-*tert*-butyl, dibenzyl and mixed *tert*-butyl ethyl esters] in preparative yields.[351]

A considerable increase in the efficiency of alkene cyclopropanation with iodonium ylide of dimethyl malonate was attained by using $Rh_2(esp)_2$ as the catalyst (Scheme 81).[351,352]

Scheme 81

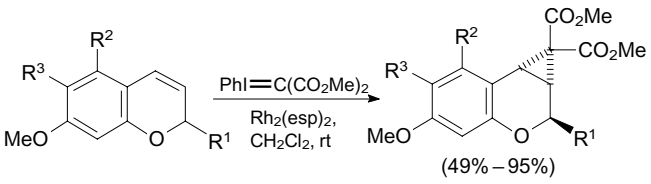


(78%–95%)

R^2 = H: R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, $PhCH_2CH_2$, $BnOCH_2$, Bu^n; R^1–R^2 = $C_6H_4CH_2$

The cyclopropanation of a number of chromene derivatives was carried out in the presence of $Rh_2(esp)_2$ (Scheme 82). Generally, the reaction was highly efficient; moderate yields (49% – 52%) were observed only for 2-(trimethoxyphenyl)chromenes, which tend to decompose even at room temperature. Note that the ylide obtained from *tert*-butyl methyl malonate does not produce target cyclopropanes under these conditions.[353]

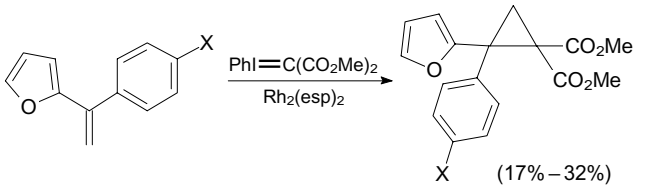
Scheme 82



R^1 = H, 4-$MeOC_6H_4$, 4-MeC_6H_4, 3,4,5-$(MeO)_3C_6H_2$, 2,4,6-$(MeO)_3C_6H_2$; R^2, R^3 = H, MeO

This method was also utilized to prepare 2-aryl-2-furylcyclopropane-1,1-dicarboxylates, although the product yields were moderate (Scheme 83).[354]

Scheme 83



X = H, OMe, CN, CF_3

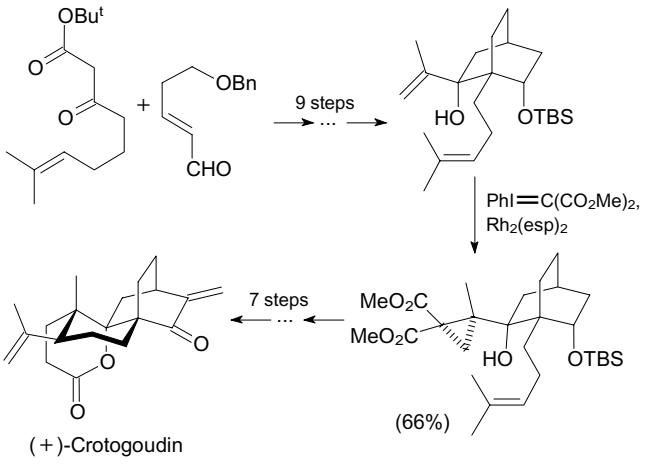
The cyclopropanation with iodonium ylide from dimethyl malonate in the presence of $Rh_2(esp)_2$ served as a key step in the total synthesis of the cytotoxic diterpene, (+)-crotogoudin (Scheme 84).[355]

Yet another way for increasing the efficiency of cyclopropanation is to use 2-alkoxyphenyliodonium ylides, *e.g.*, ylide **115**.[356] The reactions are catalyzed by rhodium or copper compounds, in particular, $Cu(acac)_2$ and $Rh_2(OAc)_4$. With this ylide and dirhodium tetraacetate as the catalyst, the yields of 2-arylcyclopropane-1,1-diesters **27** and **114** were comparable with the yields obtained in the reaction with phenyliodonium ylide in the presence of $Rh_2(esp)_2$ (Scheme 85).[356]

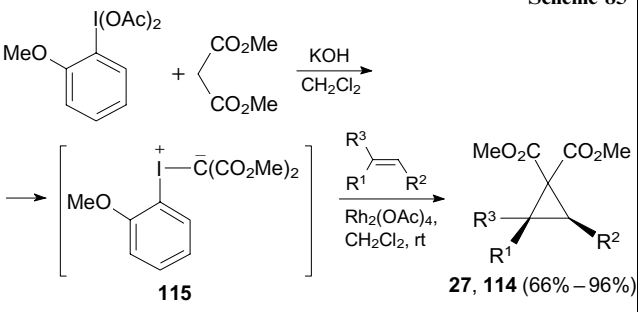
The cyclopropanation with iodonium ylides has also been used to prepare 2-alkenylcyclopropane-1,1-dicarboxylates **72**, **116** and 2-alkynylcyclopropane-1,1-dicarboxylates **117** by the reactions of dimethyl malonate-derived iodonium ylide with appropriate 1,3-dienes[347, 348] and with conjugated enynes (Scheme 86).[357 – 359]

As has already been noted, iodonium ylides obtained from alkyl malonates and acyclic 1,3-diketones are usually unstable; therefore, the domino version of this reaction was proposed without the isolation of the iodonium ylide

Scheme 84

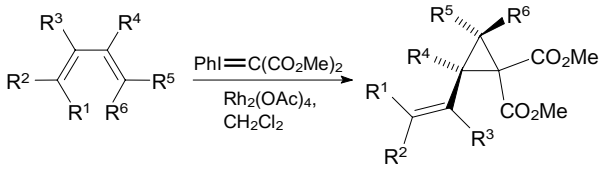


Scheme 85

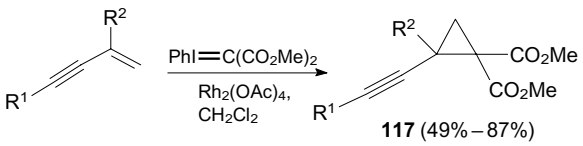


R^2 = R^3 = H: R^1 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-$F_3CC_6H_4$, 3-MeC_6H_4, 2-BrC_6H_4, n-C_6H_{13}, n-C_8H_{17};
R^3 = H: R^1 – R^2 = $C_6H_4CH_2$, $C_6H_4CH_2CH_2$, $CH_2CH_2CH{=}CH$,
R^1 = Ph: R^2 = H, R^3 = Me; R^2 = Me, R^3 = H

Scheme 86



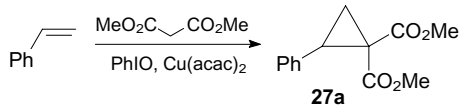
R^4 = R^5 = R^6 = H (**72**); R^4, or R^5, or R^6 ≠ H (**116**);
R^1 = R^2 = R^5 = R^6 = H: R^3 = R^4 = H, Me; R^3 = Me, R^4 = H;
R^2 = R^3 = R^4 = R^5 = H: R^1 – R^6 = CH_2, $C{=}CMe_2$, $(CH_2)_2$, $(CH_2)_4$, $CH_2CH{=}CH$



R^1 = Ph, Et, Pr^i, Bu^n, n-C_6H_{13}, Bn, $PhCH_2CH_2$, $Cl(CH_2)_3$, $Cl(CH_2)_4$, $TBSOCH_2CH_2$, $Bu^nO_2CCH_2CH_2$, cyclo-C_3H_5, Cy, Me_3Si, Bu^tPh_2Si;
R^2 = H, Me, Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$F_3CC_6H_4$, 4-NCC_6H_4, 4-$O_2NC_6H_4$, 3-MeC_6H_4, 3-$MeOC_6H_4$, 3-BrC_6H_4, 2-$MeOC_6H_4$, 2-ClC_6H_4, 2,4-$Me_2C_6H_3$, 2-Naph, 2-Th, 2-Fu, (*E*)-$PhCH{=}CH$

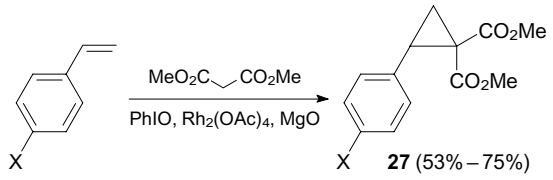
formed intermediately: treatment of styrene with dimethyl malonate and iodosobenzene in the presence of copper acetylacetonate directly led to DAC **27a** in 55% yield (Scheme 87).[360]

Scheme 87



The replacement of copper acetylacetonate by rhodium acetate increased the yield of 2-phenylcyclopropane-1,1-dicarboxylate **27a** to 75%. Meanwhile, the cyclopropanation of *p*-chloro- and *p*-bromostyrenes resulted in the yields of 53 and 54%, respectively (Scheme 88).[361, 362]

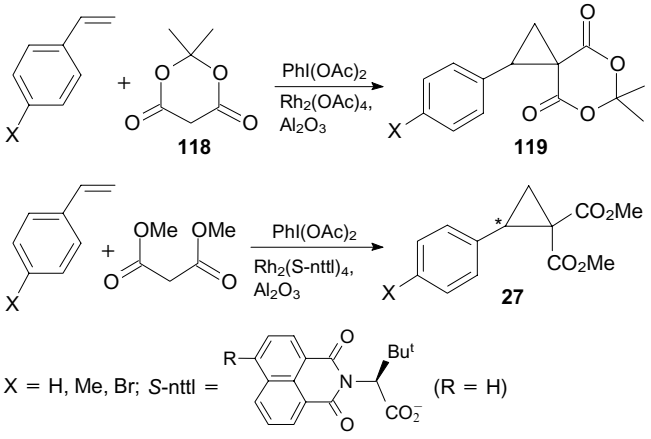
Scheme 88



X = H, Me, Cl, Br

In a similar reaction, $PhI(OAc)_2$ has also been used instead of PhIO; with this reagent, DACs have been obtained from Meldrum's acid (**118**) and dimethyl malonate in yields of up to 85% (Scheme 89).[361]

Scheme 89

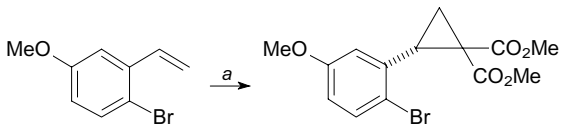


When chiral catalysts are used in these reactions, optically active DACs can be prepared. For example, the reaction carried out in the presence of Rh_2(*S*-nttl)$_4$ affords 2-arylcyclopropane-1,1-dicarboxylates **27** with a moderate enantiomeric excess (30% – 70% *ee*),[349, 363] while spirocyclopropanes **119** are formed with 30% to 57% *ee* (see Scheme 89). The enantioselectivity of the reaction increases if a chlorine atom (R = Cl) is attached to the C(4) atom of the naphthalene moiety of the chiral ligand. In this case, the *ee* values for cyclopropanes **27** and **117** are 66% – 70%.[361, 362] A further increase in the enantioselectivity of styrene cyclopropanation has been attained by using Rh_2(*S*-4-Br-nttl)$_4$ as the catalyst (R = Br). In the reaction with dimethyl malonate and PhIO, the yields of DACs **27** vary from 62% to 75% and *ee* are from 65% to 92% (for styrene and its 4-methyl-, 4-bromo-, 4-chloro and 4-trifluoromethyl derivatives), while in the reaction of styrene with Meldrum's acid, the target product **119** is formed in 76% yield with 92% *ee*.[364, 365]

When copper(I) hexafluoroantimonate in the presence of the chiral bis(oxazoline) ligand is used as the catalyst, the enantioselectivity of styrene cyclopropanation with ylide **113** reaches 75% *ee* (88% yield). With increasing size of the ester group in malonyl derivatives, the reaction enantioselectivity is usually lower under the same conditions. In the case of ylides derived from diethyl malonate and diisopropyl malonate, the enantiomeric excesses for the cyclopropane products were 34% and 35% (the yields of DACs were 23% and 41%, respectively). In the case of di(*tert*-butyl) ester, the *ee* was only 7% (77% yield), and in the case of mixed ethyl *tert*-butyl ester, cyclopropane was formed in a yield of 60% and *dr* = 85 : 15, the enantiomeric excess for the major isomer being 54%.[148]

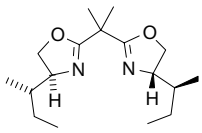
For asymmetric cyclopropanation of 2-bromo-5-methoxystyrene, $[Cu(MeCN)_4]PF_6$ and 2,2-bis{4-[(2*R*)-but-2-yl]-4,5-dihydrooxazol-2-yl}propane (**120**) were used as the catalysts (Scheme 90).[366]

Scheme 90



(*a*) PhI=C(CO$_2$Me)$_2$, $[Cu(MeCN)_4]PF_6$, **120**, CH_2Cl_2, −30 °C

120 =

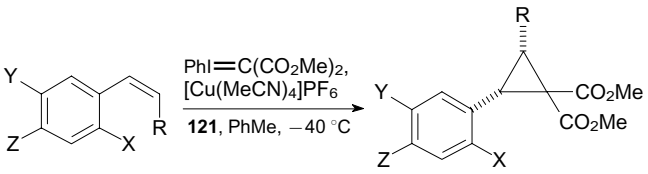


Excellent results in the asymmetric cyclopropanation of alkenes giving DACs have been obtained by using $[Cu(MeCN)_4]PF_6$ and 2,2-bis[(4*S*)-4-phenyl-4,5-dihydrooxazol-2-yl]-1,3-bis(4-*tert*-butylphenyl)propane (**121**). The reaction is diastereoselective, with the yields of cyclopropanes derived from substituted styrenes being 79% – 99% under these conditions and the enantiomeric purity being 87% – 99% (Scheme 91).[366]

Under the same conditions, high enantioselectivity was attained in the cyclopropanation of indenes and related compounds with six- and seven-membered rings (Scheme 92).[366]

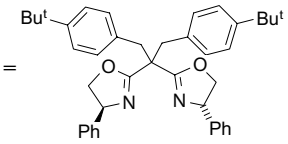
Similarly, in cyclopentadiene and cyclohexa-1,3-diene cyclopropanation, the corresponding DACs were formed with *ee* of 91% and 86%, but the yields of 2-alkenylcyclopropane-1,1-dicarboxylates were only 61%.[366]

Scheme 91

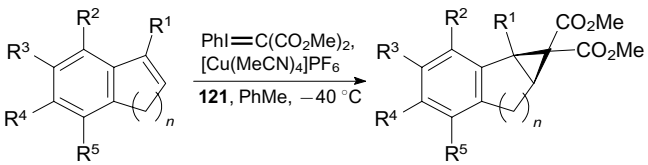


R = H, Me, Et; X = H, Me; Y = H, Me; Z = H, MeO, Me, Ph, Br, Cl, $ClCH_2$, F_3C;

121 =



Scheme 92

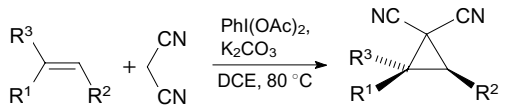


(70% – 99%, 95% – > 99% *ee*)

R^1, R^2, R^3, R^5 = H, Me; R^4 = H, Br, F; $R^3 – R^4$ = CH=CH–CH=CH; *n* = 1–3

The cyclopropanation with iodonium ylides can also be performed without transition metal derivatives. Heating of a mixture of alkene, malononitrile, $PhI(OAc)_2$ and K_2CO_3 affords DACs **122** in good yields (Scheme 93).[144, 367]

Scheme 93



122 (51% – 96%)

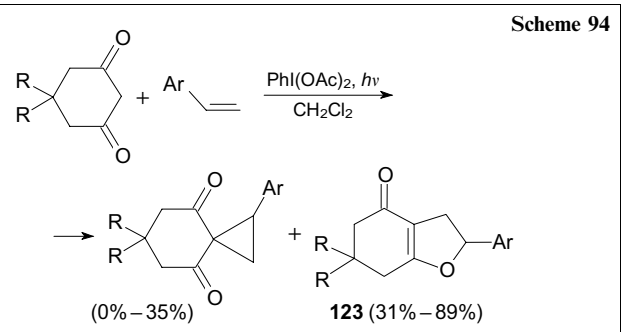
$R^2 = R^3$ = H: R^1 = Ph, 4-$Bu^tC_6H_4$, 4-BrC_6H_4, 2-Th, n-C_6H_{13}, 4-nitrophthalimido; R^1 = H, R^2 = C(O)Ph: R^3 = Ph, 4-MeC_6H_4, 3-$O_2NC_6H_4$, styryl; R^1 = H, R^2 = Ph: R^3 = Me, Ph; R^2 = H, R^3 = Me: R^1 = Ph, 3-CH_2=C(Me)C_6H_4; $R^1 – R^2 = (CH_2)_4$, R^3 = Ph; R^3 = H: $R^1 – R^2$ = $C_6H_4CH_2$, $C_6H_4CH_2CH_2$

It is noteworthy that this reaction occurs also in the absence of a base, but the product yields are low.[343]

The cyclopropanation of styrenes with *in situ* generated phenyliodonium ylides *via* photolysis in the absence of a catalyst gives, apart from cyclopropanes, dihydrofurans **123**, which are the major or the only products in most cases. The cyclopropanation of di- and trisubstituted alkenes and vinyl ethers and their thio analogues also produced only dihydrofurans (Scheme 94).[368, 369] According to control experiments, cyclopropanes quantitatively rearrange to dihydrofurans **123** upon irradiation.[369]

One more original procedure proposed for the cyclopropanation in the absence of metals consists in the treatment of alkenes with $PhI(OAc)_2$ (1 equiv.) and tetra-n-butylammonium iodide (30 mol.%) (Scheme 95).[370] The DAC yields in this reaction are highly variable; they decrease to traces in the case of ylides obtained from Meldrum's acid or acetylacetone; electron-rich styrenes produce dihydrofurans instead of cyclopropanes. Presumably, the reaction proceeds by the radical mechanism.

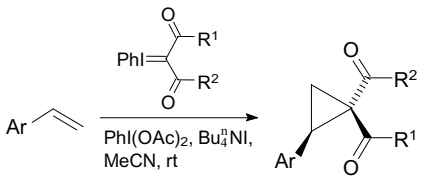
Scheme 94



(0% – 35%) **123** (31% – 89%)

Ar = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 3-$O_2NC_6H_4$, 2-ClC_6H_4; R = H, Me

Scheme 95



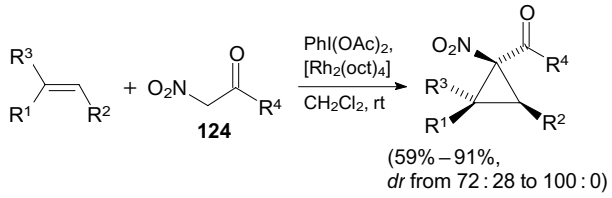
(17% – 89%)

Ar = Ph, C_6H_4Me-4, C_6H_4Cl-4, $C_6H_4NO_2$-3; R^1 = Me, Ph, OMe; R^2 = OMe, OBn, OPr^i, $OCHPh_2$; $R^1 – R^2 = (CH_2)_3$, $CH_2CMe_2CH_2$, NMeC(O)NMe

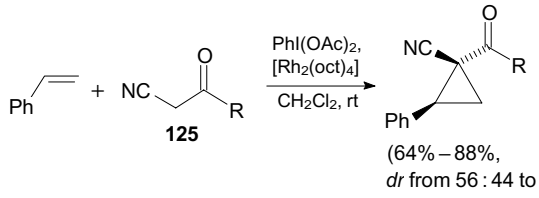
Iodonoium ylides are also used for the preparation of DACs with two different acceptor groups. Treatment of a mixture of styrene and α-nitro- (**124**)[160–162] or α-cyanocarbonyl compounds (**125**)[160] with (diacetoxy)iodobenzene in the presence of rhodium(II) carboxylates results in the formation of the corresponding DACs (Scheme 96). The best results are attained when rhodium octanoate or pivaloate is used, the stereoselectivity of this cyclopropanation (from 78 : 22 to 89 : 11 for arylethylenes) is comparable with the selectivity of their reactions with diazo compounds. However, the yields of products are usually somewhat lower, which is though counterbalanced by the lack of necessity of preliminary synthesis of diazo compounds. With the use of cyano ketones, the optimal yields of cyclopropanes can be increased by conducting the reaction in the presence of sodium carbonate and molecular sieves.[160] The diastereoselectivity of reactions involving benzoylnitromethane differs from the stereoselectivity of reactions of alkyl nitromethyl ketones: in the major isomer of the DAC product, the nitro group is located in the *cis*-position to the phenyl substituent.

The $PhI(OAc)_2$-induced cyclopropanation of alkenes with methyl nitroacetate also occurs in the absence of a Rh catalyst, but the product yield is much lower (49%, 50% and 73% for styrene, chalcone and norbornene, respectively).[367]

Scheme 96



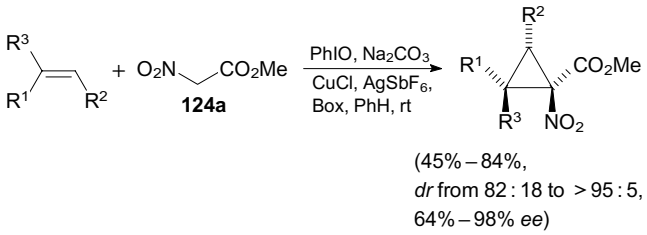
$R^2 = R^3 = H$: R^1 = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 1-Naph;
R^1 = Ph, R^2 = H, R^3 = Me; R^3 = H: $R^1–R^2$ = $C_6H_4CH_2$, $C_6H_4CH_2CH_2$; R^4 = Me, Pr^n, cyclo-C_3H_5, Ph, MeO, EtO, Pr^iO, $CH_2{=}CHCH_2O$, BnO



R = Ph, 4-$MeOC_6H_4$, Bn, (*E*)-PhCH=CH

A method for asymmetric cyclopropanation of diverse alkenes has been developed on the basis of phenyliodonium ylide generated from methyl 2-nitroacetate (**124a**) (Scheme 97). The reaction is highly diastereo- and enantioselective and gives the expected DACs with enantiomeric purity of up to 98%.[371,372]

Scheme 97

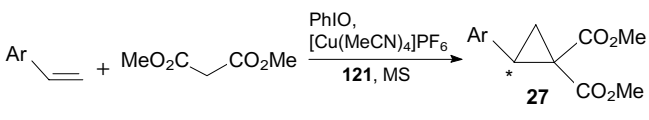


$R^2 = R^3 = H$: R^1 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$Bu^tC_6H_4$, 4-ClC_6H_4, 3-$MeOC_6H_4$, 2,4,6-$Me_3C_6H_2$, vinyl, 1-Naph, 2-Naph;
$R^1–R^2$ = $C_6H_4CH_2$, R^3 = H; R^1 = Me, R^2 = H, R^3 = $CH_2{=}CMe$;
Box = *ent*-**33** or **54**

When dimethyl malonate is used in this reaction, the yields of DACs **27** reach 99% (up to 95% *ee*) (Scheme 98).[366]

Finally, a publication of 2016 describes the cyclopropanation in a continuous flow reactor of 4-*tert*-butylstyrene on treatment with malononitrile or ethyl nitroacetate in the presence of (diacetoxy)iodobenzene or on treatment of a series of styrenes with ylide pre-generated from dimethyl malonate.[373] It is worth noting that the yields of cyclopropanes are generally lower in a flow reactor than under conventional reaction conditions.

Scheme 98

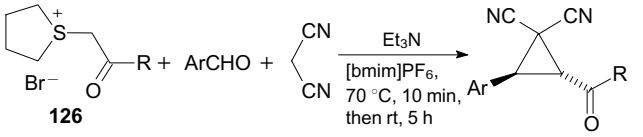


Ar = Ph, 4-XC_6H_4 (X = Br, Cl, $ClCH_2$, F_3C, Me, MeO, Ph), 2-MeC_6H_4, 3-MeC_6H_4

4.3. Miscellaneous ylides

Apart from dimethylsulfoxonium methylide (Corey–Chaykovsky ylide), other sulfur ylides can also participate in the cyclopropanation. For example, ylides generated from sulfonium salt **126** cyclopropanate the products of the Knoevenagel condensation of malononitrile and aromatic aldehyde in an ionic liquid, giving rise to 2-aryl-3-acylcyclopropane-1,1-dinitriles *trans*-**127** in high yields (Scheme 99).[374]

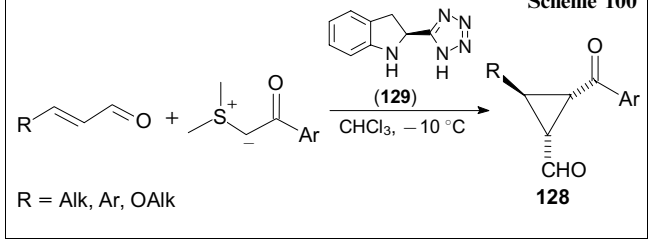
Scheme 99



R = Ph: Ar = 4-$MeOC_6H_4$, 2-FC_6H_4; R = 1-Ad: Ar = 2,3,4-$(MeO)_3C_6H_2$, 3,4-$F_2C_6H_3$

Other benzoyl-substituted cyclopropanes **128** have been synthesized in a similar way (Scheme 100). By using (*S*)-(−)-indolin-2-yl-1*H*-tetrazole (**129**) as a catalyst in this reaction, cyclopropanes **128** were obtained in high yields (> 73%) with high enantiomeric (99% *ee*) and diastereomeric (*de* > 95%) excess.[375,376]

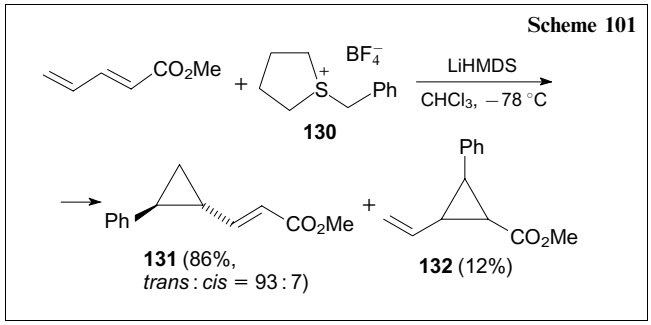
Scheme 100



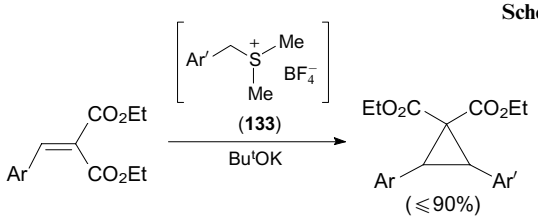
There are known examples of reactions of aryl- and vinyl-substituted sulfonium ylides with alkenes containing electron-withdrawing substituents.[377] Indeed, sulfonium ylide **130** reacts with methyl pentadienoate to give a mixture of cyclopropane adducts **131** and **132** (Scheme 101).[377]

Similarly, esters of arylidenemalonic acids react with 4-nitrophenyl- and 4-cyanophenyl-substituted sulfonium

Scheme 101



Scheme 102



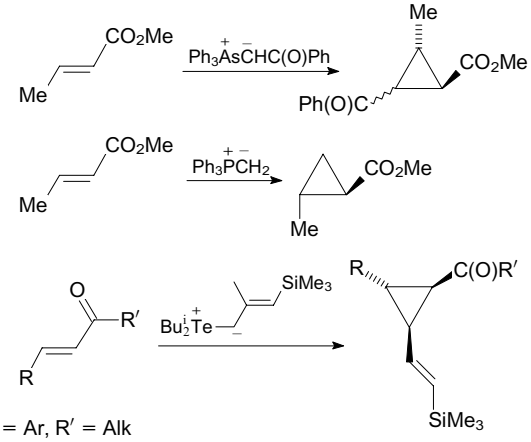
Ar = 4-$O_2NC_6H_4$, 4-NCC_6H_4, 3-ClC_6H_4; Ar′ = 4-$O_2NC_6H_4$, 4-NCC_6H_4

ylides **133** to give the expected cyclopropanes in up to 90% yields (Scheme 102).[227]

However, data on the synthesis of DAC using these sulfur ylides are scattered.

Apart from sulfur ylides, cyclopropanation can be carried out for other ylides (Scheme 103), in particular, iminium ylides (see a review [378]), ammonium [379] and telluronium ylides (see a review [380]) as well as arsenic and phosphorus ylides.[381]

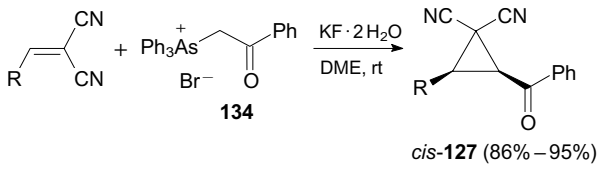
Scheme 103



R = Ar, R′ = Alk

For example, arsonium ylides **134** were employed to prepare a series of 2-aryl-3-benzoylcyclopropane-1,1-dinitriles *cis*-**127**. By using $KF \cdot 2H_2O$ as the base, it is possible to obtain DACs in higher yields than those obtained with K_2CO_3 (Scheme 104).[382]

Scheme 104

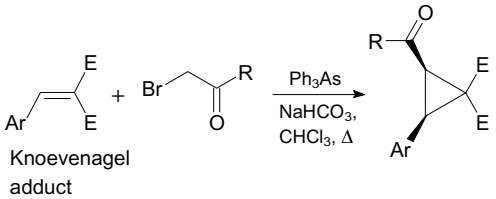


R = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$O_2NC_6H_4$, 2-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2,4-$(MeO)_2C_6H_3$, 3,4-$(OCH_2O)C_6H_3$

It was shown that cyclopropanation can be performed without isolation of arsonium ylide. For example, treatment of the Knoevenagel adduct with an α-bromocarbonyl compound, a base and triphenylarsine affords DACs in 74% – 90% yields over one synthetic step (Scheme 105).[383]

However, these ylides have only a limited use in the synthesis of DACs.

Scheme 105



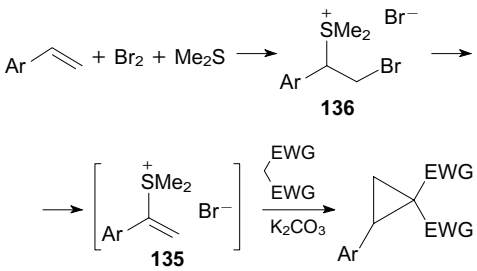
Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-$O_2NC_6H_4$, 2-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2,4-$(MeO)_2C_6H_3$, 3,4-$(OCH_2O)C_6H_3$;
R = Ph, OMe; E = CN; E – E = C(O)$OCMe_2$OC(O)

4.4. Reaction of alkyl malonates with the activated double bonds of styrenes

One more method based on the Michael addition followed by ring closure has been proposed for DAC synthesis *via* the reaction of malonic ester (and its derivatives) with styrenes with an activated C=C double bond. The double bond activation is attained most often by a sulfonium (selenonium) ion and other similar substituents (*e.g.*, SeO_2R), which act simultaneously as good leaving groups in the subsequent ring closure.

For example, a method has been developed for the synthesis of 2-aryl(hetaryl)cyclopropane-1,1-dicarboxylates based on styrylsulfonium ion **135** generated *in situ* from styrenes, bromine and dimethyl sulfide under the action of bases *via* the intermediate (1-aryl-2-bromoethyl)dimethylsulfonium bromide (**136**).[384, 385] The generated styrylsulfonium ion adds the malonate ion followed by intramolecular nucleophilic displacement of the sulfonium group. A variety of DACs have been obtained by this procedure in good yields (Scheme 106).[229, 384, 386 – 394]

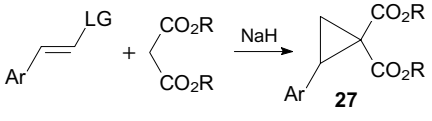
Scheme 106



Ar = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 2-ClC_6H_4, 2-Naph;
EWG = CO_2Alk, C(O)R, CN

Styrylselenonium derivatives [395] and styrylselenones [396, 397] react in a similar way to give the corresponding 2-arylcyclopropane-1,1-dicarboxylates **27** in high yields (Scheme 107).

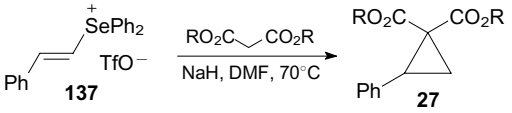
Scheme 107



Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4;
LG = $^{+}SePh_2$ TfO^-, SeO_2Ph

Thus, (β-styryl)diphenylselenonium triflate (**137**) reacts with malonic esters to give 2-arylcyclopropane-1,1-dicarboxylates **27** in 62% – 97% yields (Scheme 108).[395]

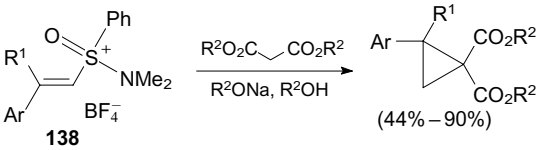
Scheme 108



R = Et, Bn

2-Arylcyclopropane-1,1-dicarboxylates are also prepared by reactions of malonates with *S*-styrylsulfoximine derivatives **138** (Scheme 109)[398] and styrylphenylselenones **139**.[397]

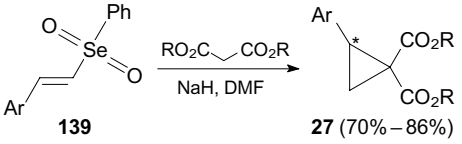
Scheme 109



Ar = Ph, 4-MeC_6H_4, 2-Fu; R^1 = H, Me, Ph; R^2 = Me, Et

In the case of styrylselenones **139**, the use of chiral bornyl and menthyl malonates furnishes a mixture of diastereomeric DACs **27**, which can be separated by chromatography (Scheme 110).[396]

Scheme 110



Ar = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$;
R = Me, (−)-bornyl, (−)-menthyl

5. Miscellaneous methods for the synthesis of donor-acceptor cyclopropanes

As has been noted in the beginning of the review, the chemistry of small rings has at hand quite a few methods for the synthesis of cyclopropanes with functional groups, including a number of versatile general approaches. However, only two approaches have become popular for the synthesis of donor-acceptor cyclopropanes — those based on diazo compounds and sulfur ylides (Corey – Chaykovsky reaction). Each of these approaches has both benefits and drawbacks or limitations.

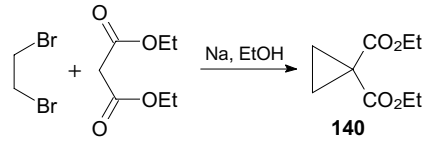
Other general methods for the synthesis of functionally substituted cyclopropanes have not found wide use in the synthesis of DACs and have been reported only as single examples. However, each of these methods has its strong points and can be applied with success in particular cases.

Below we consider the most promising of potentially general methods for the synthesis of cyclopropane compounds with functional groups. Also, we describe some other methods for donor-acceptor cyclopropane synthesis that are not general, but are convenient for the synthesis of particular DACs.

5.1. Cycloalkylation (double alkylation) of CH-acids

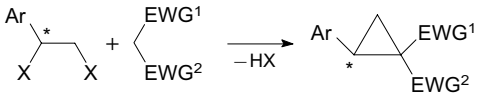
The cycloalkylation (double alkylation) of compounds with an activated CH_2 group (CH-acids), first of all, esters and nitriles of malonic acid, can serve as a general method for the synthesis of DACs with two geminal acceptor groups. This approach, particularly, the cycloalkylation of diethyl malonate with 1,2-dibromoethane, was used in 1884 to synthesize the first substituted cyclopropane — compound **140** (Scheme 111).[399]

Scheme 111



The alkylating agents used in these reactions are either 1,2-dihalides or other similar compounds with a good leaving group, in particular, sulfonic acid esters (tosylates, mesylates, benzenesulfonates, triflates, *etc.*). The key features of this reaction are similar to those of cyclopentadiene cycloalkylation to give spirocyclopropanes — spiro[2.4]-hepta-4,6-diene derivatives.[400, 401] The cycloalkylation of malonic acid esters and nitriles follows the S_N2 mechanism, which makes it possible to prepare optically active DACs; the reaction can occur under mild conditions in the presence of bases such as alkali metal carbonates (Scheme 112). A convenient version of this method is the synthesis of DACs under phase transfer catalysis.[402 – 405]

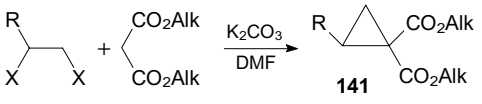
Scheme 112



X = Hal, OTs, OMs, OBz, OTf; EWG^1, EWG^2 = CO_2R, CN, C(O)R;
Ms = $MeSO_2$

Thus, cycloalkylation of alkyl malonates with 1,2-dihalides under the action of potassium carbonate in DMF affords cyclopropanes **141** in up to 85% yields (Scheme 113).[406] However, syntheses of 2-arylcyclopropane-1,1-dicarboxylates **27** from 1,2-dihalides by this method have not been reported, the existing examples of the synthesis of DACs by cycloalkylation being based on the esters of sulfonic acids (X = OMs, OTs).

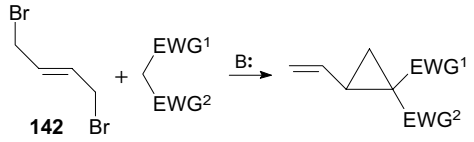
Scheme 113



X = Br, Cl, OMs, OTs; R = Alk

Vinylcyclopropanes containing two vicinal acceptor groups are prepared by alkylation of CH-acids with 1,4-dihalobut-2-enes (*e.g.*, dibromide **142**) (Scheme 114). The reaction is accompanied by allylic rearrangement and affords mainly vinylcyclopropane-1,1-dicarboxylates in preparative yields.[260, 407 – 410] In the case of *trans*-1,4-dibromobut-2-ene, the expected cyclopropane is formed as the only product.[411]

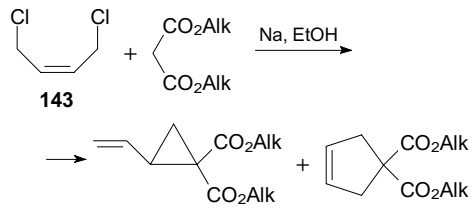
Scheme 114



EWG^1, EWG^2 = CO_2Alk, CN, Ts, SO_2Ph, $P(O)(OEt)_2$

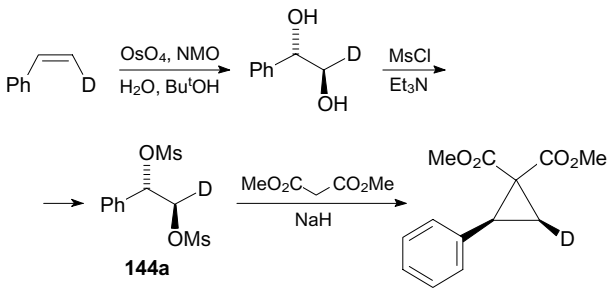
However, the reaction of alkyl malonates with *cis*-1,4-dichlorobut-2-ene (**143**) gives not only vinylcyclopropane-1,1-dicarboxylate, but also 1,1-disubstituted cyclopent-3-ene (Scheme 115).[411]

Scheme 115



Currently, sulfonates are often used instead of bromides, which makes cyclopropanation of malonates more efficient. Indeed, *cis*-deuteriostyrene is converted to dimesylate **144a**, which enantioselectively alkylates methyl malonate to give the corresponding cyclopropane (Scheme 116).[412]

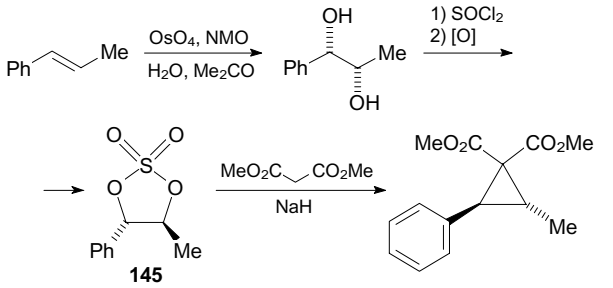
Scheme 116



Similarly, (*E*)-propenylbenzene is converted to the corresponding cyclic sulfate **145**, which reacts with dimethyl malonate to give dimethyl *trans*-3-methyl-2-phenylcyclopropane-1,1-dicarboxylate in the diastereomerically pure form (Scheme 117).[412]

It is noteworthy that the oxidation of cyclic sulfite to sulfate **145** is an important stage for efficient preparation of DACs. Indeed, it has been shown that the reaction of dimethyl malonate with cyclic sulfites prepared from 1-arylethane-1,2-diols and their 2-substituted analogues either

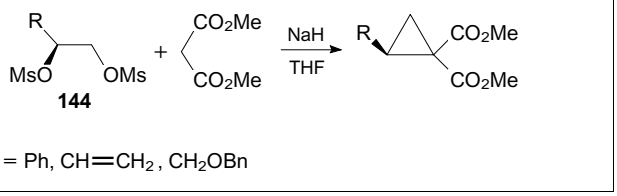
Scheme 117



does not produce cyclopropanes or gives them in low yields.[413]

Since the cycloalkylation of alkyl malonates follows the bimolecular nucleophilic substitution mechanism (S_N2), it is possible to prepare optically active DACs from chiral 1,2-dihalides (or from the appropriate ditosylates, dimesylates and so on). A series of optically active DACs have been obtained in up to 74% yields with enantiomeric excess of up to 97% by reactions of chiral dimesylates **144** with dimethyl malonate (Scheme 118).[414 – 417]

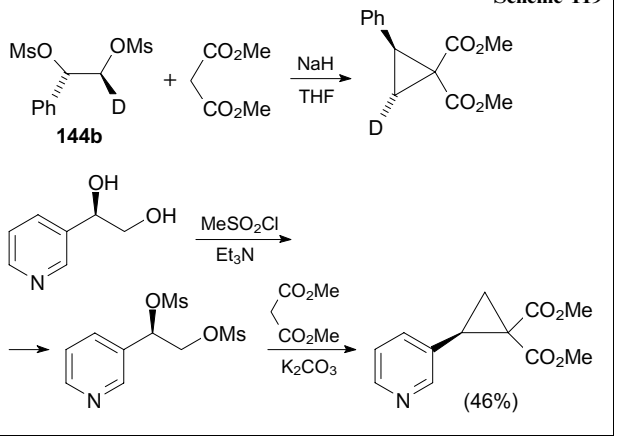
Scheme 118



R = Ph, CH=CH_2, CH_2OBn

Dimesylates **144a**,**b** prepared from *cis*- and *trans*-deuteriostyrenes, respectively, undergo cycloalkylation with dimethyl malonate to stereoselectively give deuterated 2-phenylcyclopropane-1,1-dicarboxylates in 66% yield (Schemes 116, 119).[168, 412] This method was used to prepare dimethyl 2-(but-3-enyl)- (Ref. 143) and 2-(3-pyridyl)cyclopropane-1,1-dicarboxylates (see Scheme 119).[229]

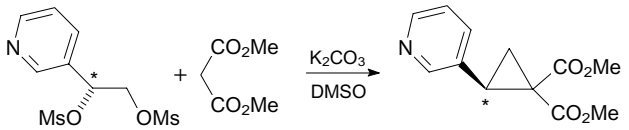
Scheme 119



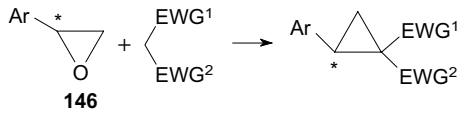
Similarly, the reaction of optically active dimesylate **144c** with dimethyl malonate results in pyridine-substituted DACs in a yield of 46%, with the enantiomeric ratio being 73 : 27 (Scheme 120).[229]

Aryloxiranes **146** can also act as alkylating agents (Scheme 121). High reactivity of oxiranes is caused by the

Scheme 120



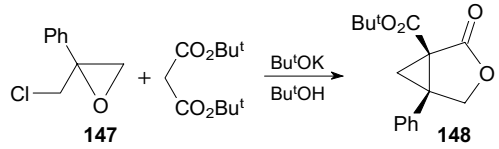
Scheme 121



high angular strain of the three-membered ring. The oxirane ring opening induced by nucleophiles follows the S_N2 mechanism, *i.e.*, the reaction is stereospecific with inversion of the configuration.

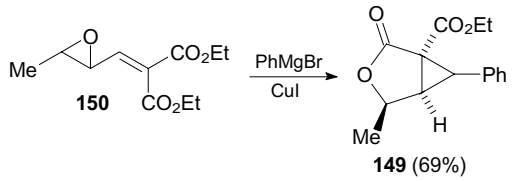
Among other reactions of oxiranes with malonic acid esters, note the reaction involving 2-chloromethyl-2-phenyloxirane (**147**), which affords lactone **148** in a yield of 54% (Scheme 122).[418, 419]

Scheme 122



Related lactone **149** was prepared by ring transformation of oxirane **150** on treatment with PhMgBr in the presence of CuI (Scheme 123).[420, 421]

Scheme 123

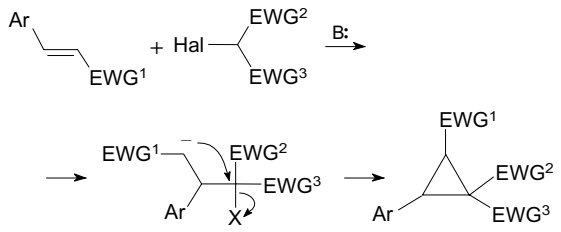


However, only few examples of the synthesis of DACs from oxiranes are available.

5.2. The addition of α-halocarbonyl compounds to alkenes

Yet another method for the synthesis of DACs based on the Michael addition of α-halocarbonyl compounds to alkenes followed by ring closure has been proposed (Scheme 124).

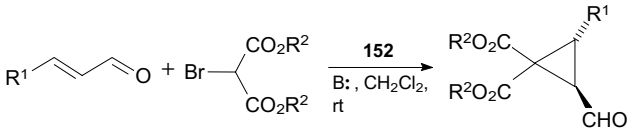
Scheme 124



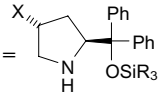
The α-halocarbonyl compounds used most often for the preparation of DACs are 2-halomalonates, although other α-halocarbonyl compounds are also employed.

This approach was applied for cyclopropanation of α,β-unsaturated aldehydes giving DACs **151**; when optically active bases were used, the enantioselectivity of cyclopropanation of cinnamaldehydes reached 99% (Scheme 125).[422 – 433]

Scheme 125



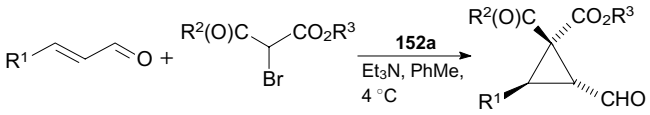
R^1 = Ph, 4-YC_6H_4 (Y = MeO, Me, Br, Cl, F, F_3C, MeO_2C, O_2N), 3-ClC_6H_4, 2-$MeOC_6H_4$, 2-ClC_6H_4, 2-$O_2NC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 3-MeO-4-$BnOC_6H_3$, 3,4-$(OCH_2O)C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, 2-Naph, 2-Fu, 3-Py, MeCH=CH, Pr^n, Me, $PhCH_2CH_2$;
R^2 = Me, Et, Pr^i, Bn;

152 = 

SiR_3 = $SiMe_3$, TBS, $SiEt_3$;
X = H, NMe_2, $OCH_2C_6H_4CH_2$-resin;
X = H, R = Me (**152a**)

This method has also been successfully used to prepare DACs **153** from 2-bromo-3-keto esters. The cyclopropanation results in the predominant formation of the diastereomer in which the ester group is located in the *cis*-position to the formyl group; however, the diastereoselectivity varies from relatively low in the reaction of cinnamaldehyde with methyl 2-bromoacetoacetate to the formation of only one isomer in the case of ethyl pivaloylbromoacetate. Generally, cyclopropanes are formed in high yields and with high enantioselectivity in the reactions of methyl and ethyl esters of bromo keto acids; *tert*-butyl 2-bromoacetoacetate not only reacts more slowly, but gives the products in a lower yield and with a moderate enantioselectivity (Scheme 126).[434, 435]

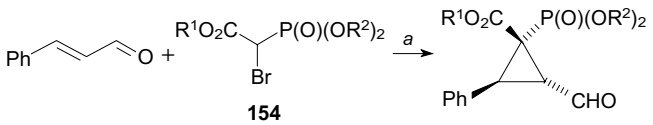
Scheme 126



R^1 = Ph, 4-BrC_6H_4, 4-NCC_6H_4, 4-$O_2NC_6H_4$, 3,4,5-$(MeO)_3C_6H_2$, Et, Bu^n;
R^2 = Me, Bu^t, Ph, 3,4,5-$(MeO)_3C_6H_2$, 3,4-$(OCH_2O)C_6H_3$;
R^3 = Me, Et, Bu^t

In the (*O*-trimethylsilyl)diphenylprolinol-catalyzed (**152a**) reaction of cinnamaldehyde with 2-bromo-2-phosphonoacetates **154**, the formation of the major product **155** was accompanied by the formation of the isomer with the *trans*-arranged aromatic moiety and ester group, but the

Scheme 127



154

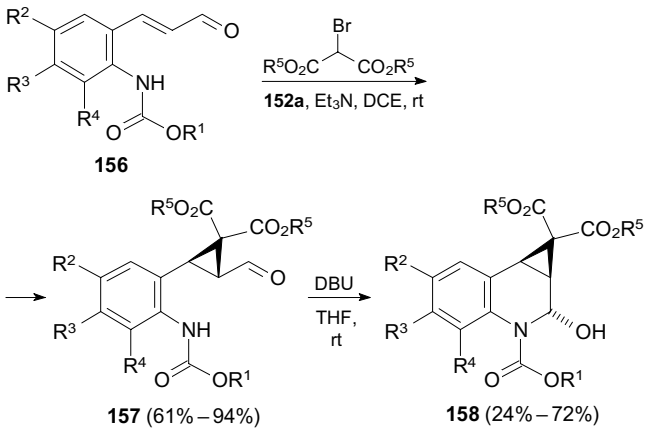
155 (47% – 89%, *dr* from 70 : 30 to 83 : 17, *ee* from 92% to > 99%)

(*a*) **152a**, Et_3N, MeOH, 0 °C; R^1 = Me, Et, Bu^t; R^2 = Me, Et, Pr^i

diastereoselectivity of cyclopropanation varied insignificantly (from 70 : 30 to 83 : 17), each isomer being obtained with high enantioselectivity (Scheme 127).[436]

When cinnamaldehydes **156** containing an *ortho*-carbamate group react with bromomalonates, cyclopropanes **157** are formed, which are readily converted to tetrahydrocyclopropa[*c*]quinolines **158** (Scheme 128).[437]

Scheme 128



156

157 (61% – 94%) **158** (24% – 72%)

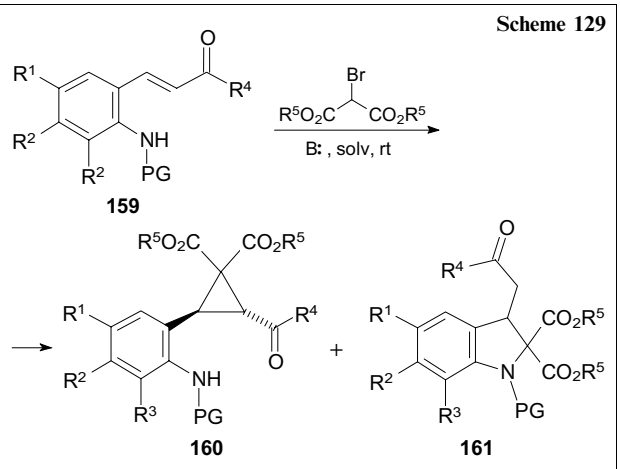
R^1 = Bu^t, Bn; R^2 = H, Me, Cl, Br; R^3 = H, Cl; R^4 = H, Me; R^5 = Me, Et, Bn

The efficiency of cyclopropanation of this type of substrates depends on the nature of the protecting group at nitrogen and reaction conditions. It was shown that treatment of β-[2-(alkoxycarbonylamino)phenyl]-α,β-unsaturated carbonyl compounds **159** with bromomalonate affords only 1-(2-aminophenyl)-2-acylcyclopropanes **160**, whereas in the case of 2-(tosylamino)phenyl derivatives **159**, the reaction gives 3-(2-oxoalkyl)-1-tosylindoline-2,2-dicarboxylates **161**, apart from cyclopropanes **160** (Scheme 129).[438]

The reactions of nitrostyrenes proceed less easily and give 2-aryl-3-nitrocyclopropane-1,1-dicarboxylates **162** in lower yields and with lower enantioselectivity when the reaction is catalyzed by diarylprolinols;[439,440] however, when cupreine (optically active 6′-demethylquinine, **163**) is used as the catalyst, an excellent enantioselectivity is attained (94% – 99% *ee*, except for the 1-naphthyl derivative, for which *ee* is 75%), although the yields are moderate (Scheme 130).[441]

When the bromine atom is replaced by chlorine, cyclopropanes are not formed under the same conditions. The cyclization occurs with a moderate yield only with the use of

Scheme 129



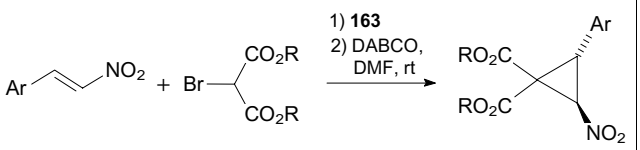
159

160 **161**

PG = CO_2Bn, Boc (59% – 70% yield, **160** : **161** > 20 : 1); PG = Ts (33% – 96%, **160** : **161** from 3 : 2 to 1 : 10)

R^1 = H, Cl, Br, Me; R^2 = H, Cl; R^3 = H, Me; R^4 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 2-Th, 2-Fu, Bu^t, cyclo-C_3H_5, Me, OEt; R^5 = Me, Et, Bn

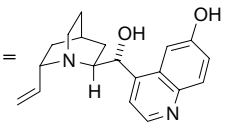
Scheme 130



162 (47% – 78%, 75% – 99% *ee*)

Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 4-$O_2NC_6H_4$, 2-$O_2NC_6H_4$, 2-Fu, 2-Th, 1-Naph; R = Alk;

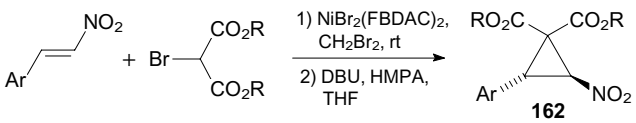
163 =



DBU in HMPA; however, the stereoselectivity markedly decreases in this case (14% – 47% *ee*).[441,442] Apparently, the reason is that the Michael addition becomes reversible, as a result of considerable retardation of the cyclization step and more drastic conditions.

When the nickel bromide complex with (1*R*,2*R*)-*N*,*N*′-bis(4-fluorobenzyl)-1,2-diaminocyclohexane (FBDAC) is used as the reagent, the reaction results in the synthesis of 2-aryl-3-nitrocyclopropane-1,1-dicarboxylates **162** in high yields (70% – 99%) with high enantioselectivity (85% – 99% *ee*) (Scheme 131).[443]

Scheme 131



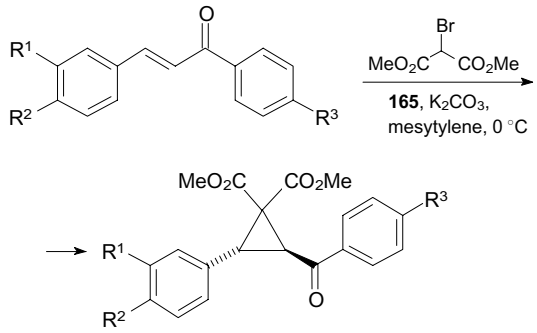
162

Ar = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 2-BrC_6H_4, 2-$O_2NC_4H_4$, 1-Naph, 2-Th, 2-Fu; R = Me, Et

The donor-acceptor cyclopropanes containing a nitro group as the substituent were also prepared by the reaction of cinnamaldehyde with bromonitromethane; however, this reaction proceeds with a moderate yield and moderate diastereo- and enantioselectivity.[444]

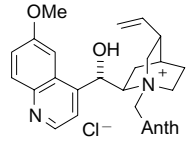
Optically active DACs **164** were also synthesized from bromomalonate and chalcones under phase transfer catalysis conditions using chiral catalysts obtained from the *Cinchona* alkaloids. It was shown that high product yields and high enantioselectivity are achieved in the presence of catalyst **165** obtained from quinidine and 9-(chloromethyl)-anthracene (Scheme 132).[445]

Scheme 132



164 (58% – 98%, 68% – 82% *ee*)

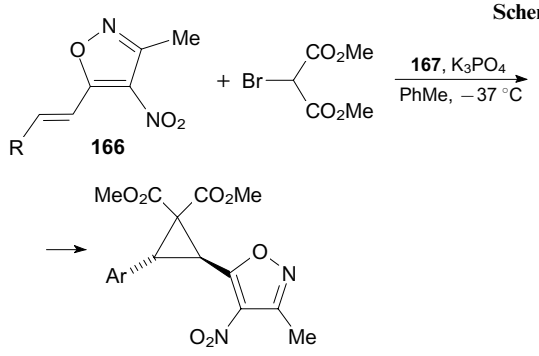
R^1 = H, NO_2; R^2 = H, Cl, NO_2; R^3 = H, Me, Cl, F;

165 = 

(Anth is 9-anthracenyl)

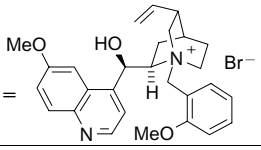
The reaction of chalcone with diethyl 2-bromomalonate catalyzed by aza-15-crown-5 ethers based on α-D-galactose or L-threitol proceeds with high enantioselectivity; however, the yield of cyclopropane in this case is only 28% – 35%.[446, 447] In the presence of similar crown ethers based on α-D-glucopyranose, this reaction also gives moderate product yields, with the enantioselectivity varying from 42% to 88%.[448] The phase transfer-catalyzed reaction of this type between dimethyl 2-bromomalonate and 4-nitro-5-styryloxazoles **166** in the presence of chiral catalyst **167** proceeds diastereoselectively and leads to DACs **168** in 91% – 99% yields with high enantioselectivity (up to 96%) (Scheme 133). This reaction can also be carried out using chloro-substituted malonates; however, the product yields decrease to 46%. When diethyl bromomalonate is employed, the enantioselectivity for the same conversion decreases, while in the case of diaryl esters, both characteristics of the reaction considerably decrease.[449]

Scheme 133



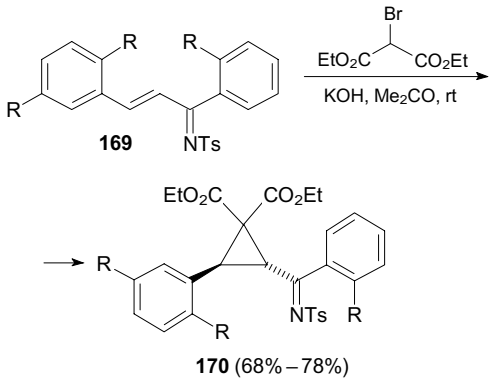
168 (91% – 99%, 84% – 96% *ee*)

R = Ph, 4-$MeOC_6H_4$, 4-FC_6H_4, 2-$MeOC_6H_4$, 2-BrC_6H_4, 2,4-$(MeO)_2C_6H_3$, 2,3-$(MeO)_2C_6H_3$, 2-Th, 2-Fu, n-C_7H_{15};

167 = 

N-Sulfonyl-2,4-diaryl-1-aza-1,3-dienes **169** also react with bromomalonates as unsaturated substrates, being converted to DACs **170** (Scheme 134).[450] However, when these substrates react with 2-bromo-1,3-diketones under the same conditions, only 2-aryl-3-[(α-tosylamino)benzylidene]-2,3-dihydrofurans are formed.

Scheme 134

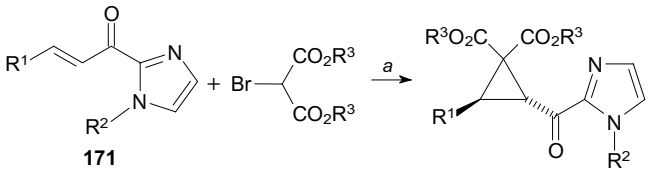


170 (68% – 78%)

R = H, Cl

Treatment of 2-cinnamoylimidazoles **171** with bromomalonates or appropriate keto esters in the presence of chiral rhodium complexes (*e.g.*, compound **172**) gave rise to 2-aryl-3-acylcyclopropane-1,1-dicarboxylates **173**, the reaction proceeding in high yields with high diastereo- and

Scheme 135

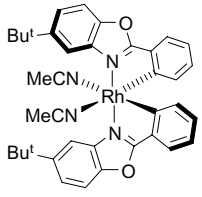


173 (70% – 99%, *dr* > 20 : 1, 93% – 99% *ee*)

(*a*) **172**, Et_3N, $CHCl_3$, rt;

R^1 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 3-MeC_6H_4, 2-BrC_6H_4, 2-MeC_6H_4, 1-Naph, 2-Th, 2-Fu, Me, EtO_2C; R^2 = Me, Pr^i, Ph;

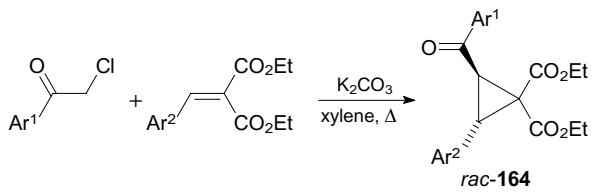
R = Et, Pr^i, Bn, Bu^t;

172 = 

enantioselectivity (Scheme 135). The same results were obtained for 2-cinnamoylpyridine under the same conditions. In the case of bromoacetoacetate and methyl *tert*-butyl-2-bromomalonate, the diastereoselectivity of cyclopropanation was relatively low.[451]

α-Halo ketones react similarly to bromomalonates. Phenacyl chlorides react with benzylidenemalonates to afford *trans*-3-aryl-2-aroylcyclopropane-1,1-dicarboxylates *rac*-**164** in 15% – 61% yields (Scheme 136).[452]

Scheme 136



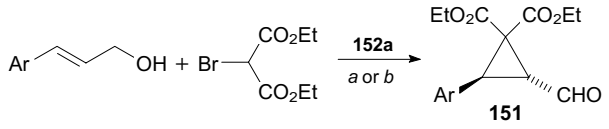
rac-**164**

Ar^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4; Ar^2 = Ph, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, 4-ClC_6H_4, 3,4-$(MeO)_2C_6H_3$, 2,4-$Cl_2C_6H_3$, 4-$O_2NC_6H_4$

Phenacyl chloride was also used for cyclopropanation of alkylidenemalononitriles catalyzed by cinchonidine; the reaction products were formed in variable yields with moderate enantioselectivity.[453]

The cinnamic alcohol oxidation – asymmetric cyclopropanation tandem has been proposed for the synthesis of formyl-substituted DACs; this method leads to compounds **151** in good yields with high stereoselectivity. Either tetrapropylammonium perruthenate[454] or MnO_2 was used as the oxidant (Scheme 137).[455]

Scheme 137

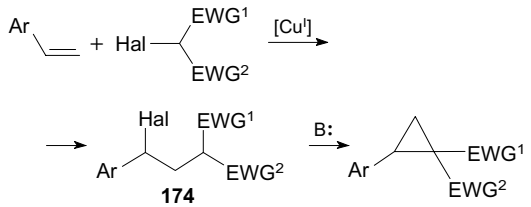


151

(*a*) TPAP, NMO, CH_2Cl_2, rt for Ar = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-$F_3CC_6H_4$, 4-$O_2NC_6H_4$, 2-$O_2NC_6H_4$ (66% – 89% yield, 92% – 95% *ee*); (*b*) MnO_2, $CHCl_3$, rt for Ar = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$F_3CC_6H_4$, 3-BrC_6H_4, 2-BrC_6H_4, 4-$O_2NC_6H_4$, 2-$O_2NC_6H_4$ (67% – 88% yield, 93% – 98% *ee*)

A different approach to alkene cyclopropanation with α-halocarbonyl compounds is based on copper salt-catalyzed radical addition of halomalonate to styrenes followed by cyclization of adduct **174** on treatment with a base (Scheme 138).

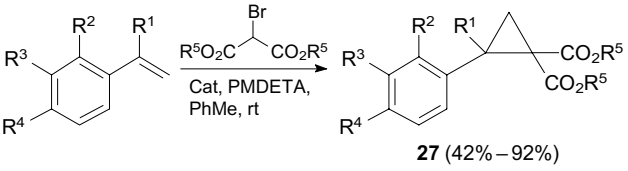
Scheme 138



174

The cyclopropanation *via* radical addition with halogen transfer was used in the synthesis of dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**27b**); for this purpose, 4-methoxystyrene was treated with bromomalonate and tetra-n-butylammonium bromide in the presence of CuI and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA) (Scheme 139).[456] It was shown that $[Cu(H_2O)_6](BF_4)_2$ is an efficient catalyst for the synthesis of DACs **27** (see Scheme 139).[457]

Scheme 139

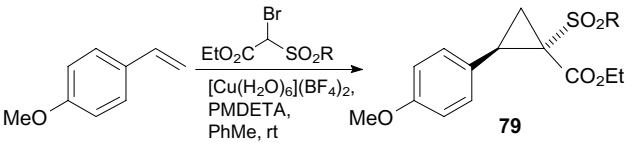


27 (42% – 92%)

Cat = $[Cu(H_2O)_6](BF_4)_2$; R^1 = H, Me; R^2 = H, MeO, Me; R^3 = H, MeO; R^4 = H, MeO, Me, Br, Cl, F, $MeCO_2$; R^5 = Me, Et, Pr^i, Bn; Cat = CuI, TBAB; R^1 = R^2 = R^3 = H, R^4 = MeO, R^5 = Me (**27b**, 67% yield)

Bulky substituents in the esters of bromomalonic acid prevent this reaction. When di(*tert*-butyl) bromomalonate or bromomalonic acid bis(*N*,*N*-dimethylamide) are used for the reaction, no DACs are formed. However, if one of the acceptor moieties is the sulfonyl group, the corresponding DACs **79** are produced in high yields (Scheme 140).[457]

Scheme 140

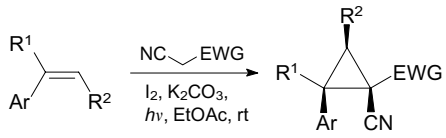


79

R = Me (92%, *dr* = 69 : 41), Ph (86%, *dr* = 85 : 15)

A version of this reaction is *in situ* generation of α-halosubstituted CH-acids under the action of iodine on irradiation (Scheme 141). This reaction proceeds for ethyl cyanoacetate, malononitrile, α-cyanoketones and diethyl malonate (the yield of DAC in the reaction with styrene is

Scheme 141



(21% – 95%, *dr* from 1.3 : 1 to 12 : 1)

EWG = CO_2Et, R^1 = R^2 = H: Ar = Ph, 4-$MeOC_6H_4$, 4-$Bu^tC_6H_4$, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 3-MeC_6H_4, 2-MeC_6H_4, 2-Py; EWG = CO_2Et, Ar = Ph: R^1 = Me, R^2 = H; R^1 = H, R^2 = Me, Ph; Ar = Ph, R^1 = R^2 = H: EWG = CO_2Me, C(O)Fu-2, $C(O)C_6H_4Me$-4, $C(O)Bu^t$, CN

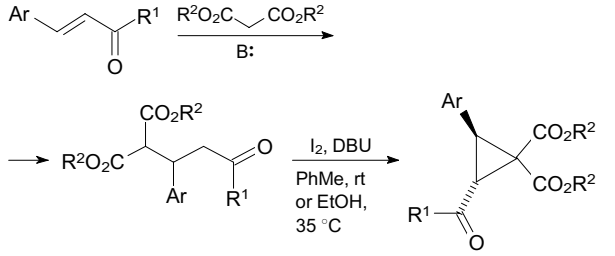
51% in this case). Conversely, when benzoylnitromethane is employed as the CH-acid, the yield of cyclopropane is only 8%, while in the case of phenylacetonitrile, cyclopropane is not formed at all.[458]

The replacement of elemental iodine by *N*-iodosuccinimide, also with irradiation, increases the product yields to 98%.[459]

5.3. Cyclizations upon 1,3-elimination

Another method for the synthesis of polysubstituted DACs, in particular, 3-aryl-2-aroylcyclopropane-1,1-dicarboxylates *rac*-**164**, is the addition of dialkyl malonate to chalcones followed by ring closure *via* 1,3-elimination on treatment of the Michael adduct with iodine and DBU (Scheme 142).[460, 461]

Scheme 142



rac-**164** (80% – 95%)

Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 3-$O_2NC_6H_4$; R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 2-Th, 2-Py; R^2 = Et, Bu^t

A study of the effect of the base on the efficiency of this reaction has demonstrated that the best results are obtained with DBU. The highest yield of cyclopropane is attained when DBU is used. When DBU is replaced by 4-(dimethylamino)pyridine, the yield slightly decreases; however, in this case, the reaction proceeds 10 times more slowly. Cyclopropane is also formed chemoselectively when NaOH, DABCO, Et_3N or Bu^tONa is used, but the yields of products are only 19% – 53%. In the presence of other bases, side products are often formed. For example, when Na_2CO_3 was employed, the reaction chemoselectivity completely changed, and only 3-aryl-4-acyloxetane-2,2-dicarboxylates were formed.[461]

A related method for the synthesis of cyclopropanes is the addition of the malonyl anion to electron-withdrawing vinyl bromide. The anion thus formed is more basic than the malonate anion. This induces fast proton transfer from the malonyl carbon atom and cyclization *via* 1,3-elimination of HBr (Scheme 143).[462, 463]

Similarly, 5-(2-aryl-1-bromovinyl)-3-methyl-4-nitroisoxazoles **175** are converted to cyclopropanes *rac*-**168** in 70% – 98% yields (Scheme 144).[462]

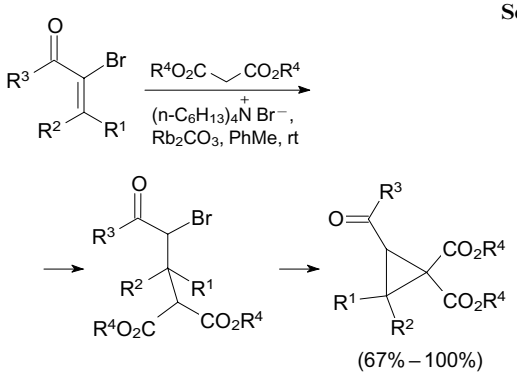
The cyclization of 2-(3-oxopropyl)malonate to give DAC *rac*-**164a** can also be induced with $PhI(OAc)_2$ in dioxane or acetonitrile (Scheme 145).[464, 465]

Similarly, the reaction of malonate with β-nitrostyrenes followed by cyclization of the Michael product gives rise to 2-aryl-3-nitrocyclopropane-1,1-dicarboxylates **162** in 5% – 98% yields. Methyl and ethyl esters cyclize with approximately equal efficiency to form only *trans*-DACs. However, di(*tert*-butyl) ester affords cyclopropane **162** in a yield of only 38% with diastereoselectivity of 88% (Scheme 146).[466]

A similar reaction can alo be induced by PhIO in methanol. This resulted in the synthesis of cyclopropanes *rac*-**164** in 75% – 98% yields (Scheme 147).[467]

Finally, trimethylsilyl bromide has been proposed as a reagent for leaving group introduction and three-membered ring closure in 2-(1-aryl-2-nitroethyl)malonates. However, in this case, the reaction produces 2-arylcyclopropane-1,1-dicarboxylates **176** (80% – 97% yield) containing the

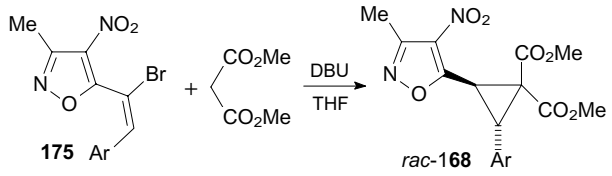
Scheme 143



(67% – 100%)

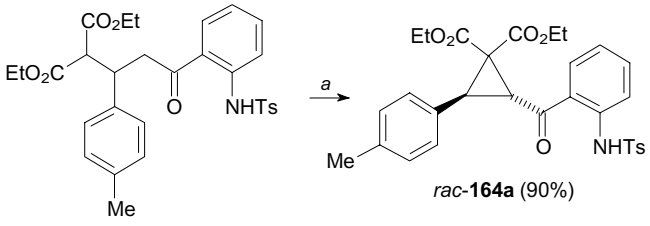
R^1 = H, Ph, Pr^i; R^2 = H; R^3 = Me, Ph; $R^2 – R^3$ = CH_2CH_2; R^4 = Pr^i, Bn

Scheme 144



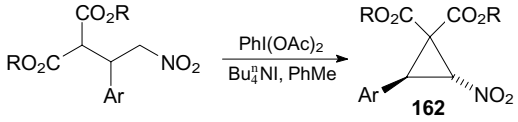
Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-Py

Scheme 145



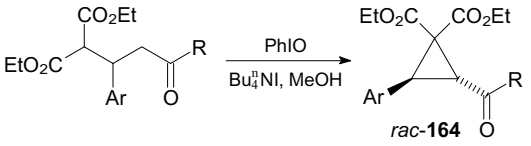
(*a*) $PhI(OAc)_2$, Bu^n_4NI

Scheme 146



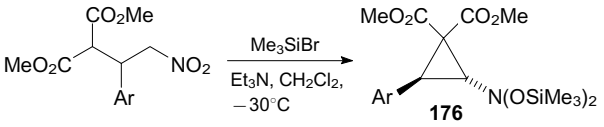
Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 2-BrC_6H_4, 4-$O_2NC_6H_4$, 1-Naph, 2-Fu, 2-Th, 2-Py; R = Me, Et, Bu^t

Scheme 147



Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-ClC_6H_4, 4-$O_2NC_6H_4$, 3-$O_2NC_6H_4$; R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$O_2NC_6H_4$

Scheme 148



Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 3-$O_2NC_6H_4$

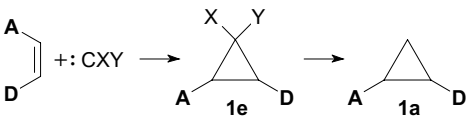
$N(OSiMe_3)_2$ moiety rather than a nitro group in position 3 (Scheme 148).[468, 469]

A drawback of this method is inapplicability for the preparation of 1,2-disubstituted DACs and also most demanded 2-arylcyclopropane-1,1-dicarboxylates.

5.4. Reactions of alkenes with halocarbenes and subsequent reduction

Combining halomethylenation with subsequent reduction of the halocyclopropanes thus formed is a general two-step method for the synthesis of cyclopropanes from alkenes (Scheme 149), which is in some cases more convenient and efficient than the above-indicated one-step processes for cyclomethylenation of alkenes (such as catalytic decomposition of diazomethane or the Simmons–Smith reaction).[50, 470–472] Although this two-step method is now barely used for the synthesis of donor-acceptor cyclopropanes, it still can be useful in some cases, in particular, when considerable amounts of DACs are required.

Scheme 149



X = Hal; Y = H, Hal

The first step in this synthetic method is the well-studied cycloaddition of mono- and dihalocarbenes to unsaturated compounds to give the corresponding mono- and dihalocyclopropanes **1e**. In the second step, the obtained halocyclopropanes are reduced to the target DACs **1a**.

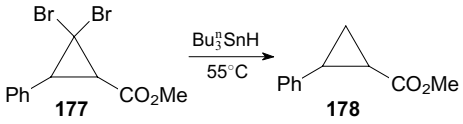
Among the products formed in the first step, most important are *gem*-dihalocyclopropanes **1e** (X, Y = Hal), which have now become cheap and readily accessible intermediates in organic synthesis, most of all, owing to the development of phase transfer catalysis.[402, 403, 473] Dihalocarbenes are usually generated from haloforms under the action of 50% aqueous NaOH or solid KOH in the presence of phase transfer catalysts (*e.g.*, benzyltriethylammonium chloride or crown ethers). The reaction does not require special conditions or anhydrous media, proceeds smoothly and gives the desired products in high yields.

The subsequent reductive dehalogenation of *gem*-dihalocyclopropanes, in which the three-carbon ring is preserved, results in the synthesis of DACs. The reduction of *gem*-dihalocyclopropanes is accomplished by metal–alcohol (water) and sodium–liquid ammonia systems or by metal hydrides; catalytic hydrogenation and electrochemical methods are also used.[50, 474–477]

In particular, dibromocyclopropane **177** was converted in this way to methyl 2-phenylcyclopropane-1-carboxylate (**178**) in a quantitative yield (Scheme 150).[478]

However, there are only a few examples of DAC synthesis by this method.

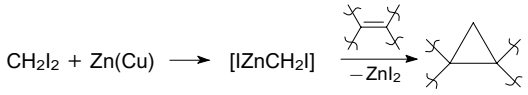
Scheme 150



5.5. Simmons–Smith reaction

The Simmons–Smith reaction is one of the most popular versatile laboratory methods for direct cyclopropanation of alkenes and their derivatives.[67, 68, 479, 480] The method comprises the reaction of the double bond of unsaturated compounds with diiodomethane and activated zinc dust to give cyclopropanes (Scheme 151).

Scheme 151



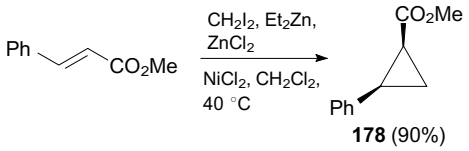
This reaction is stereoselective and occurs with retention of the configuration of the starting alkene. Presumably, the reactive species is iodomethylzinc iodide $IZnCH_2I$, which transfers the methylene group to the double bond.[480, 481] The key features of the reaction are surveyed in reviews[482–484] and in monographs devoted to carbene and cyclopropane chemistry (see, for example, Refs 4 and 50).

For the synthesis of DACs, modified Simmons–Smith reaction procedures are used, because the classical procedure provides too low product yields. Nevertheless, the modified procedures still retain all features and regular patterns inherent in the classical method.[4, 50]

Since the Simmons–Smith reagent behaves as a weak electrophile towards unsaturated compounds, the introduction of electronegative substituents into the substrate molecule retards the reaction. Therefore, unsaturated compounds with electron-withdrawing substituents (*e.g.*, CO_2R) are usually less reactive than hydrocarbons and give the expected cyclopropanes in yields not exceeding 25%.[50, 485–487] In the case of unsaturated ketones [C(O)R], the keto group usually has a markedly less pronounced retarding effect, and the corresponding cyclopropane adducts can be obtained in up to 80%–90% yields.[50] This reaction can be substantially accelerated and the product

yields can be increased (up to 90%–95%) by using, first, additional catalysts, in particular, nickel compounds, and, second, diethylzinc instead of the zinc–copper pair.[488,489] In this case, cinnamic acid esters, which do not react under the classical Simmons–Smith reaction conditions, can be converted to the corresponding DACs (*e.g.*, compound **178**) in high or preparative yields (Scheme 152).[488]

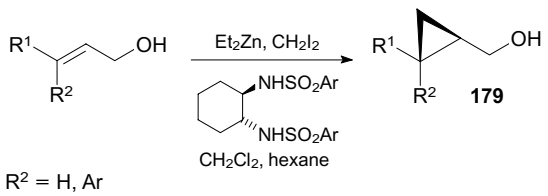
Scheme 152



178 (90%)

The Simmons–Smith reaction is also applied to the synthesis of optically active compounds by using chiral ligands.[485–487,490,491] The first reaction of this type was cyclopropanation of allyl alcohols in the presence of chiral disulfonamides; the yields of cyclopropanes **179** were 70%–92% (Scheme 153).[492] The oxidation of the alcohol group gives rise to DACs.

Scheme 153

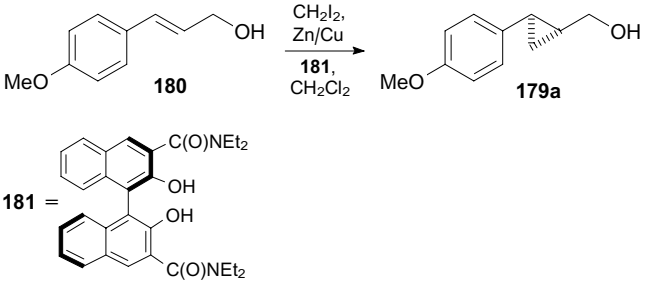


179

R^1, R^2 = H, Ar

Subsequently, other compounds were also used as chiral ligands. For example, the Simmons–Smith cyclopropanation of compound **180** in the presence of *N*,*N*,*N*′,*N*′-tetraalkyl-2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamides, for example, compound **181**, gives the corresponding cyclopropane **179a** in a yield of 78% with high optical purity (94% *ee*) (Scheme 154).[493]

Scheme 154



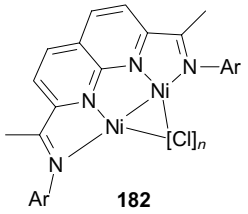
180 **179a**

181 =

The Simmons–Smith cyclopropanation of unsaturated alcohols and amines as well as vinyl and allyl ethers usually proceeds readily and gives products in good yields. This is due to the ability of these functional groups to form coordination bonds with organozinc reagents,[50] which accounts for the regioselectivity of cyclopropanation.[494] High reactivity in this reaction is also characteristic of esters and unsaturated trimethylsilyl ethers (ethers of the enol form of carbonyl compounds).[50]

A weak point of the Simmons–Smith reaction is diiodomethane. Recently, a less expensive and more readily available CH_2Cl_2 has been proposed as the source of methylene group; in this case, the reaction is catalyzed by binuclear Ni complexes with naphthyridine-diimine ligands,[495] for example, compound **182**.

Structures 182

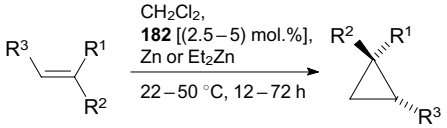


182

Ar = 2,6-$Pr^i_2C_6H_3$;
n = 1, 2

The reducing agents used are Zn and Et_2Zn; the yields of cyclopropane products can be nearly quantitative.[495] In the case of the synthesis of DACs, the yields of products are 70%–82% and the best results have been obtained with zinc metal (Scheme 155).

Scheme 155

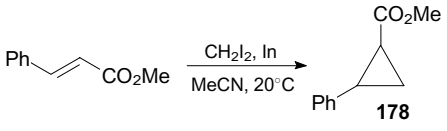


R^1, R^2, R^3 = Alk, Ar, C(O)R^4, CO_2R^4

This reaction is catalyzed also by mononuclear nickel complexes; however, the yields are considerably lower in this case (< 20%).[495] One more example of using dichloromethane as a source of methylene group in this reaction is known, but with dysprosium metal or dysprosium diiodide being used as the reducing agent.[496]

One more shortcoming of the Simmons–Smith reaction is the employment of the zinc–copper pair. Therefore, various substitutes have been proposed. For example, indium metal powder was found to be efficient; this makes it possible, for example, to prepare cyclopropane **178** from methyl cinnamate in a yield of 50% (Scheme 156).[497]

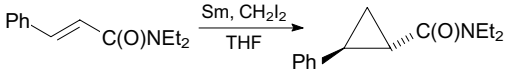
Scheme 156



178

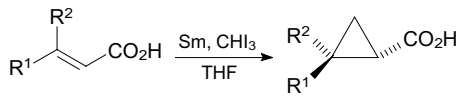
Among other metals applied as the reducing agents in the Simmons–Smith reaction, samarium should be mentioned.[498] The use of samarium made it possible in some cases to replace diiodomethane by chloroiodomethane and to make the yields of cyclopropanes nearly quantitative.[499] For example, cinnamic acid diethylamide is smoothly cyclopropanated on treatment with CH_2I_2 to give DAC in 79% yield (Scheme 157).[500]

Scheme 157



An interesting version of this reaction is the use of samarium metal and CHI_3 with sonication.[501] This provides cyclopropanation of unprotected organic acids, the reaction being highly diastereoselective. The *E*- and *Z*-isomers of carboxylic acids (in particular, cinnamic acids) are converted to cyclopropanecarboxylic acids in yields of up to 85% (Scheme 158).[501]

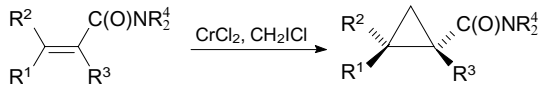
Scheme 158



R^1, R^2 = Ar, H

Finally, the $CH_2ICl-CrCl_2$ system was proposed as the reagent; as a result, α,β-unsaturated amides were converted to donor-acceptor cyclopropanes in 63%–98% yields (Scheme 159).[502]

Scheme 159



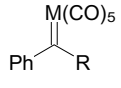
R^1 = Alk, Ar; R^2 = H, Alk, Ar; R^3 = H, Alk; R^4 = Alk

Thus, the Simmons–Smith reaction is a rather convenient and efficient method for direct methylenation of various unsaturated compounds. Generally, this reaction is widely used in laboratory practice, in particular, in the synthesis of various natural compounds.[503–505] However, this method is of limited use for the preparation of DACs.

5.6. Fischer carbene complexes

Among other methods for DAC synthesis, the reactions of alkenes with Fischer carbene complexes deserve attention.[506] These carbene complexes, in particular, compounds **183**–**187**,[507, 508] are convenient sources of carbenes able to undergo cyclopropanation. However, while reacting with alkenes, these complexes can not only give the corresponding cyclopropanes, but also initiate metathesis and other reactions.[509–511]

Structures 183–187

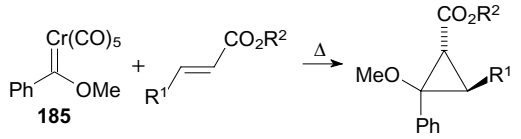


183–187

M = Cr: R = Ph (**183**), OMe (**185**);
M = W: R = H (**184**), OMe (**187**);
M = Mo, R = OMe (**186**)

The methoxyphenylcarbene pentacarbonylchromium complex (**185**), which is most studied in cyclopropanation, allows the preparation of DACs in 30%–60% yields (Scheme 160).[512]

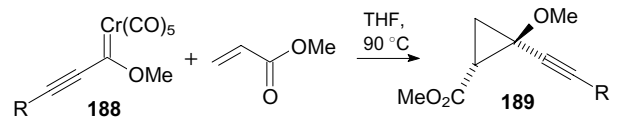
Scheme 160



R^1 = Me, Ar, CO_2Et; R^2 = Me, Et

On the basis of alkoxyalkynyl Fischer complexes **188**, a method has been developed for the synthesis of alkynyl-substituted DACs **189** in preparative yields and with high diastereomeric excess (95% and more) (Scheme 161).[513]

Scheme 161



R = Ar, TMS, Alk

Molybdenum and tungsten complexes behave in the cyclopropanation reactions in a similar way.[514]

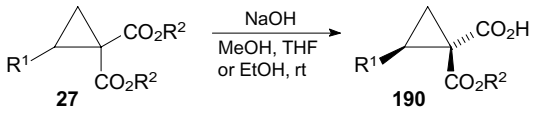
However, it should be noted that this method is rather experimentally cumbersome, therefore, it is not widely used in the synthesis of DACs. Nevertheless, in some cases, it may prove quite useful, for example, in the synthesis of *gem*-alkoxyaryl-substituted derivatives.

5.7. Modification of substituents in donor-acceptor cyclopropanes

Various methods for modification of the acceptor or donor substituent, *i.e.*, reactions that do not affect the three-membered ring, are widely used in the synthesis of DACs.

Among these transformations, modification of the acceptor substituent is employed more often for the preparation of DACs. Thus, partial hydrolysis of 2-arylcyclopropane-1,1-dicarboxylates **27** affords monoesters **190** (82%–98% yield); hydrolysis affects first of all the ester group located in the *trans*-position relative to the donor substituent (Scheme 162).[22, 228, 347]

Scheme 162



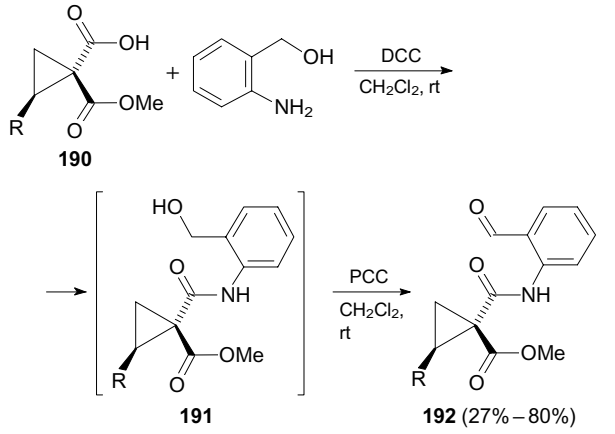
R^1 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 2-ClC_6H_4, 4-BrC_6H_4, 4-$(MeO_2S)C_6H_4$, 3,4-$(MeO)_2C_6H_3$, 2,3-$(MeO)_2C_6H_3$, 2,5-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, 2,3,4-$(MeO)_3C_6H_2$, 2-Fu, $PhCH_2CH_2$, Et, Pr^n, Pr^i, Bu^n, Bu^i, Et_2CH; R^2 = Me, Et

In turn, the dicyclohexylcarbodiimide-induced condensation of 2-arylcyclopropane-1,1-dicarboxylic acid monoesters **190** with 2-aminobenzyl alcohol followed by oxidation of intermediates **191** *in situ* resulted in aldehydes **192** (Scheme 163). The reactions of compounds **192** with various anilines were used to assemble the tricyclic core of martinellines and related alkaloids.[515]

In addition, DAC **193** with two different ester groups were prepared from 2-substituted cyclopropane-1,1-dicarboxylic acid monoesters **190**. These derivatives are important substrates to study the mechanisms of DAC reactions (Scheme 164).[347, 516]

One more transformation of the ester group is the reaction with nucleophiles. Although the reactions of most nucleophiles with 2-arylcyclopropane-1,1-dicarboxylates proceeds *via* the attack on the C(2) atom of the three-membered ring, examples of the attack on the carbonyl

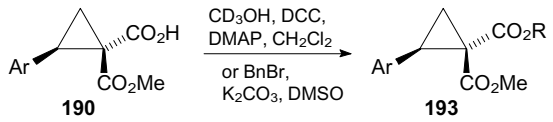
Scheme 163



190 **191** **192** (27% – 80%)

R = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-EtC_6H_4, 4-$MeOC_6H_4$, 3-MeC_6H_4, 3-ClC_6H_4, 3-BrC_6H_4, 2-ClC_6H_4, 2-Th, 2-Naph, CH_2═CH, (*E*)-CHPh═CH

Scheme 164



190 **193**

R = CD_3 or Bn

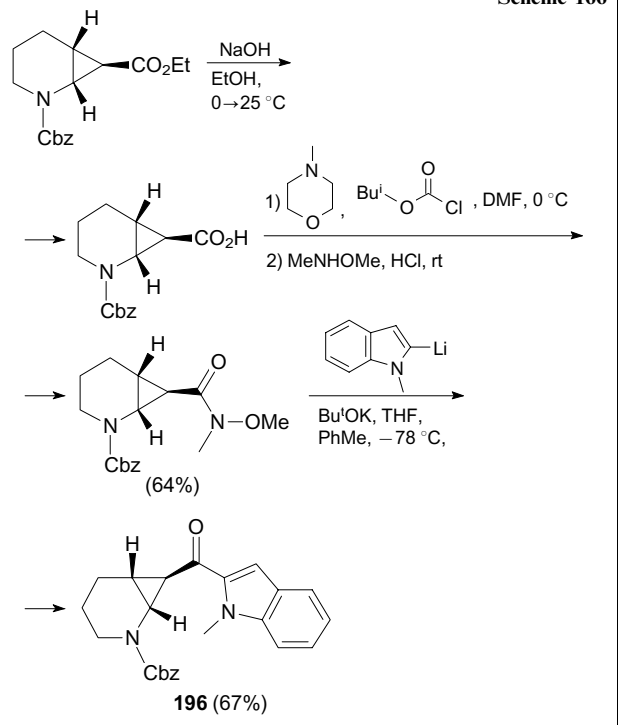
group, which can be used to convert DACs to one another, are also known. For example, treatment of DAC **27b** with dihydropyranyllithium (**194**) furnished isomeric 2-aryl-1-acylcyclopropanecarboxylates **195a**,**b**, with isomer **195a** being the major product (29% yield) (Scheme 165).[22]

It is noteworthy that DAC **195b** and related products with the *cis*-positions of the aromatic and acyl substituents can be obtained in preparative yields from monoesters (*e.g.*, compound **190a**), which are prepared from diesters by hydrolysis of one of the ester groups. The monoesters are first treated with alkenyllithium reagent **194** and then with methyl iodide and potassium carbonate (see Scheme 165).[22]

Similarly, 2-alkoxy- and 2-aminocyclopropanecarboxylates were converted to Weinreb amides and then to 2-aminocyclopropyl ketones **196**.[22, 116, 517] An example of such transformations is shown in Scheme 166.

Among other reactions, we would like to note the oxidation of cyclopropylmethanol **197** with 2-iodoxybenzoic acid (IBX), which was used to synthesize the corresponding carbonyl derivative (Scheme 167).[160]

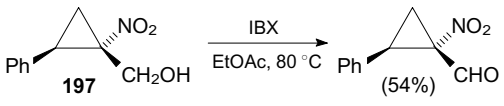
Scheme 166



(64%) **196** (67%)

Cbz = $PhCH_2OC(O)$

Scheme 167

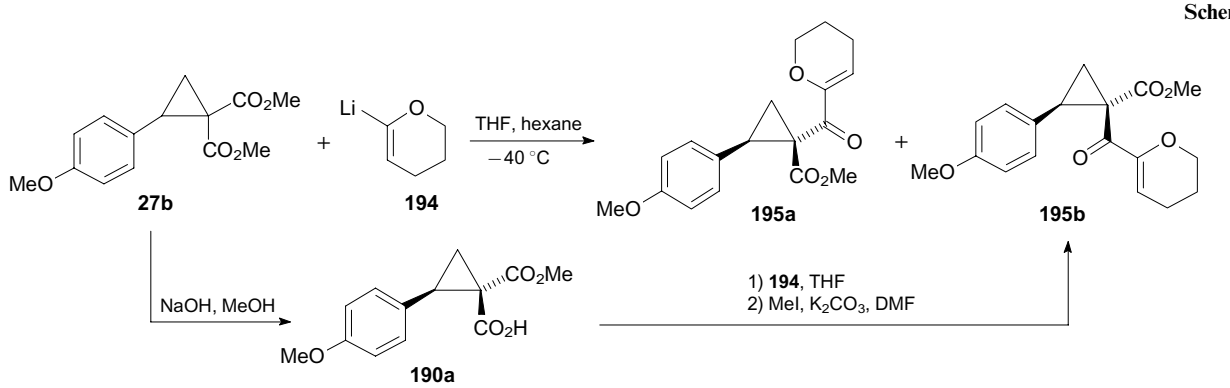


197 (54%)

Similarly, the oxidation of the *cis*- and *trans*-isomers of cyclopropylmethanol **198** served for the synthesis of 2-aryloxy-2-hetarylcyclopropanecarboxylic acids **199** in 73% and 68% yields, respectively (Scheme 168).[113]

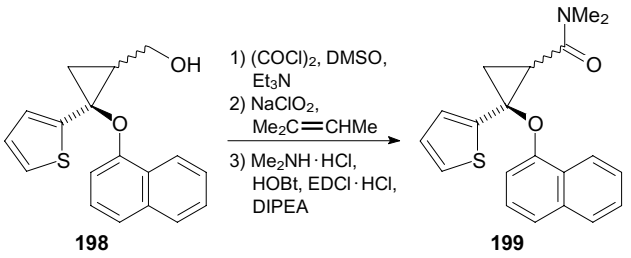
A protocol developed for the synthesis of optically active 2-aryl-2-methylcyclopropane-1,1-dicarboxylates **200** includes asymmetric cyclopropanation of α-methylstyrenes with styryldiazoacetate **201** followed by ozonation of intermediate compounds **200′** (Scheme 169).[142]

Scheme 165

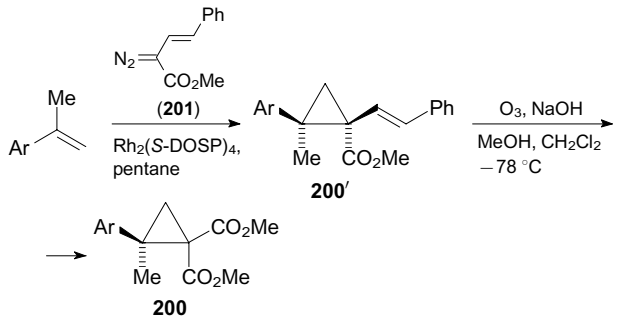


27b **194** **195a** **195b** **190a**

Scheme 168

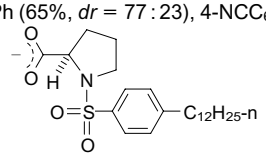


Scheme 169



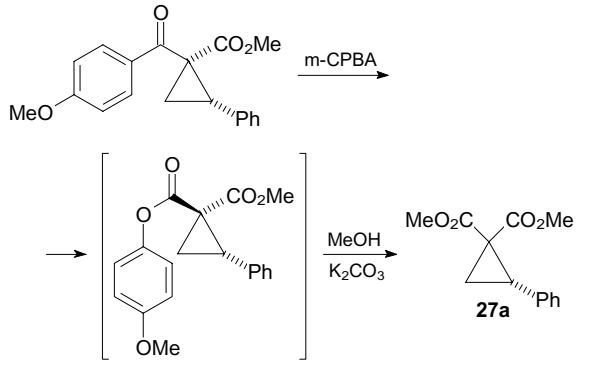
200′: Ar = Ph (65% yield, *dr* = 75 : 25, 90% *ee*), 4-NCC_6H_4 (47%, *dr* = 83 : 17, 90% *ee*);
200: Ar = Ph (65%, *dr* = 77 : 23), 4-NCC_6H_4 (83%, *dr* = 95 : 5);

S-DOSP =



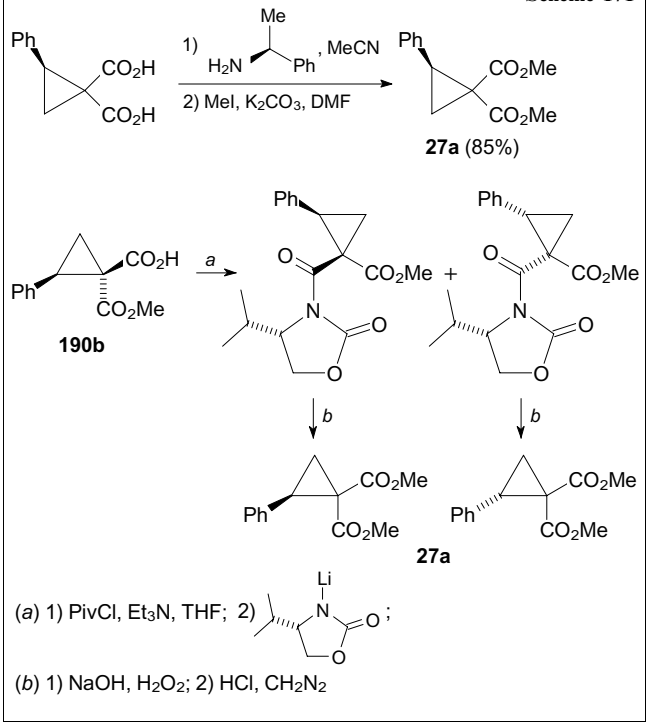
Since the asymmetric cyclopropanation of Knoevenagel adducts obtained from keto esters leads to cyclopropanes with a markedly higher enantioselectivity than the cyclopropanation of benzylidenemalonates, an indirect method has been proposed for the synthesis of optically active 2-arylcyclopropane-1,1-dicarboxylates (*e.g.*, compound **27a**) based on the Baeyer – Villiger oxidation of 2-aryl-1-aroylcyclopropanecarboxylates (Scheme 170).[151]

Scheme 170



In addition, optically active 2-arylcyclopropane-1,1-dicarboxylates (*e.g.*, compound **27a**) can be obtained from dicarboxylic acids[151,222] or their monoesters.[222,347] The crystallization-based separation of diastereomeric salts of 2-phenylcyclopropane-1,1-dicarboxylic acid with (*S*)-1-phenylethylamine followed by treatment of the pure diastereomer with methyl iodide[222] gives DAC **27a** (85% yield) (Scheme 171). The reaction of the monomethyl ester of 2-phenylcyclopropane-1,1-dicarboxylic acid (**190b**) with an optically active amine, separation of diastereomers, hydrolysis and methylation afford the final enantiomers of DAC **27a** (see Scheme 171).[518]

Scheme 171



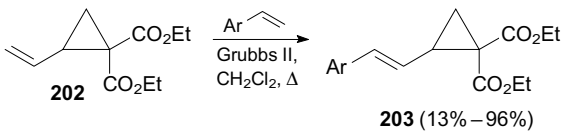
(*a*) 1) PivCl, Et_3N, THF; 2) ;

(*b*) 1) NaOH, H_2O_2; 2) HCl, CH_2N_2

Above in this Section we summarized the transformations of one DAC into another *via* modification of the acceptor substituent. Methods for the synthesis of new DACs by modification of the donor substituent have also been proposed.

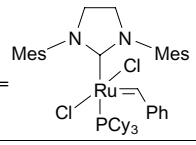
The first general method for these transformations is the metathesis involving vinylcyclopropanes **202**. It can be used to obtain cyclopropanes with alkenyl substituents, which are difficult to prepare by other methods. This pathway was applied for the synthesis of substituted 2-styrylcyclopropane-1,1-dicarboxylates **203** (Scheme 172).[260] The yields of the target products were markedly different depending on the substituent (13% for *p*-bromostyryl derivative; 55%,

Scheme 172



Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, 2-ClC_6H_4;

Grubbs II =

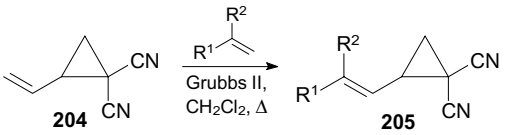


(Mes = 2,4,6-$Me_3C_6H_2$)

66% and 96% for *p*-methylstyryl, *p*-methoxystyryl and *o*-chlorostyryl analogues).

Using metathesis, 2-vinylcyclopropane-1,1-dicarbonitrile (**204**) was converted to cyclopropanes **205** with various alkenyl substituents in 10% – 60% yields (Scheme 173).[519]

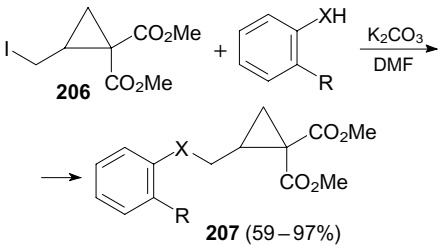
Scheme 173



$R^1 = R^2 = Me$; $R^2 = H$: $R^1 = Bu^n$, CO_2Me

One more approach to modification of the donor group is based on alkylation of (thio)phenols and related compounds with 2-(iodomethyl)cyclopropane-1,1-dicarboxylate **206** to give DACs **207** (Scheme 174).[143]

Scheme 174

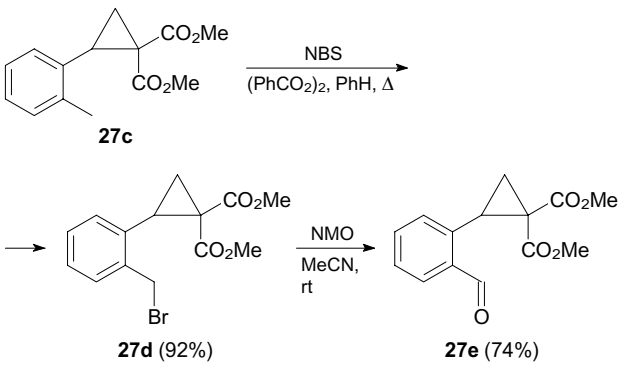


X = O, S; R = CHO, C(O)Me, CH_2OH

A similar alkylation of indole- and pyrrole-2-carbaldehydes resulted in the synthesis of the corresponding cyclopropanes in 50% and 77% yields, respectively.[143]

The bromination of 2-(*o*-tolyl)cyclopropane-1,1-dicarboxylate **27c** gave bromomethylphenyl-substituted cyclopropane **27d**, which was then converted to 2-(2-formylphenyl)cyclopropane-1,1-dicarboxylate **27e** (Scheme 175).[234]

Scheme 175

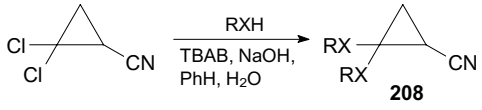


Thus, modification of either an acceptor or donor substituent in DACs is in some cases a convenient method for the synthesis of target donor-acceptor cyclopropanes.

5.8. Miscellaneous methods of synthesis

Among other methods for the preparation of DACs, note first of all the addition of various nucleophiles to substituted cyclopropenes. The use of the elimination – addition sequence provides the conversion of 2,2-dichlorocyclopropane-1-carbonitrile to DACs **208** with two donor and one acceptor groups in 58% – 80% yields (Scheme 176).[520, 521]

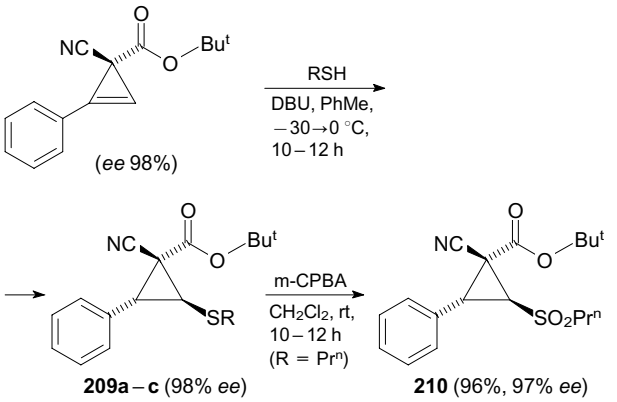
Scheme 176



RX = PhO, 4-MeC_6H_4O, 4-ClC_6H_4O, 4-$O_2NC_6H_4O$, MeO, EtO, PhS

In the synthesis of DACs containing one more substituent at the C(3) atom, the addition of nucleophiles to substituted cyclopropenes is also used. The key studies along this line performed before 2007 are summarized in a review.[522] In the subsequent years, additional publications appeared. Treatment with thiols of the products resulting from enantioselective cyclopropenation of alkynes with *tert*-butyl α-cyanodiazoacetate gave enantiomerically pure cyclopropanes **209a** – **c** containing two acceptor substituents at one carbon atom and a donor substituent at each of the other two carbon atoms. The oxidation of product **209a** to sulfone under the action of *m*-chloroperoxybenzoic acid affords DAC **210** with a sulfonyl group at C(3) (Scheme 177).[523]

Scheme 177



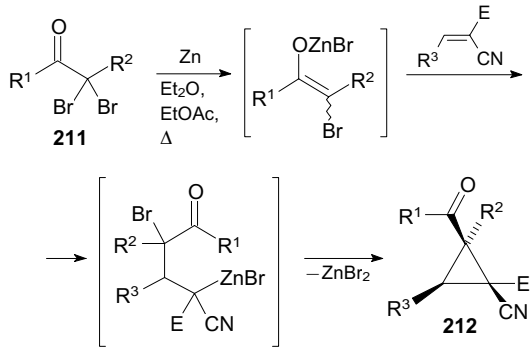
209: R = Pr^n (**a**, 98% yield), Pr^i (**b**, 88%), Bu^t (**c**, 54%)

Apart from reactions involving cyclopropenes, one more pathway to DACs is the reaction of dihalocarbonyl compounds with derivatives containing an activated double bond induced by organometallic reagents.

A process related to the Reformatsky reaction, consisting in treatment of Knoevenagel adducts, obtained from aldehyde and malononitrile or cyanoacetamide, with zinc and α,α-dibromocarbonyl compounds **211** furnished a series of DACs **212** in 43% – 80% yields (*dr* from 3 : 1 to > 99 : 1) (Scheme 178).[524 – 526]

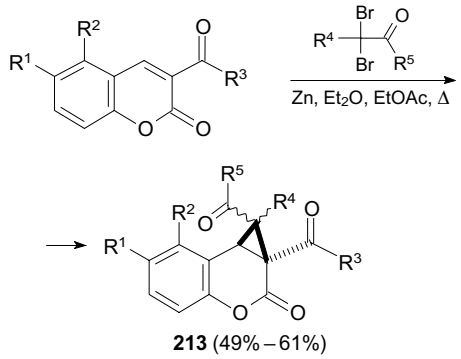
This approach has also been successfully applied to the synthesis of cyclopropa[*c*]coumarins **213**, which are difficult to obtain by other methods (Scheme 179).[525, 527]

Scheme 178



R^1 = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, Bu^t; R^2 = H, Me, Et; R^3 = Ph, 4-BrC_6H_4, 4-ClC_6H_4, 3,4-$(MeO)_2C_6H_3$, (*E*)-PhCH=CH; E = NC, BnNHC(O), 4-$MeC_6H_4NHC(O)$, 2-$MeC_6H_4C(O)$, CyNHC(O), BzNHC(O), 4-$BrC_6H_4CO_2$

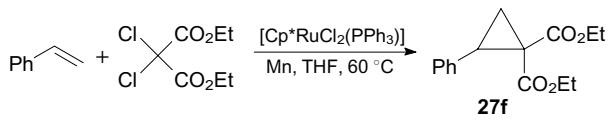
Scheme 179



R^2 = H: R^1 = H, Br; R^1–R^2 = CH=CH–CH=CH; R^3 = Me, Ph, 2-Fu, morpholino, piperidino; R^4 = H, Me, Et; R^5 = Bu^t, Ph, 4-MeC_6H_4, 4-EtC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4

The manganese-induced addition of diethyl 2,2-dichloromalonate to styrene catalyzed by the ruthenium complex [Cp*$RuCl_2(PPh_3)$] (Cp* = η^5-C_5Me_5) affording cyclopropane **27f** in 66% yield has been reported (Scheme 180).[528] The reaction proceeds, presumably, by a radical mechanism.

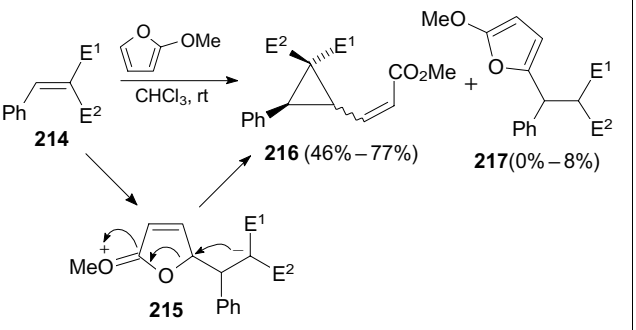
Scheme 180



Among other synthetic routes to DACs, note the reaction of 2-methoxyfuran with Knoevenagel adducts **214**. The reaction involves the formation of intermediate **215**, which may either lose a proton, being converted to cyclopropane **216**, or undergo intramolecular nucleophilic substitution (Scheme 181).[529, 530]

However, in the case of $E^1 = CO_2H$ or $C(O)NH_2$ (E^2 = CN) and for compounds **214**, obtained from malononitrile, diethyl malonate, acetoacetic acid or dibenzoylmethane, the reaction does not occur at all; if 3-benzylideneacetylacetone [$E^1 = E^2$ = C(O)Me] serves as the substrate, cyclopropane **216** is formed as a minor product (36%), whereas the Michael adduct **217** is the major product (51%).

Scheme 181



E^1 = CN, CO_2Et, C(O)Ph, C(O)Me, SO_2Ph; E^2 = CN, CO_2Et, C(O)Ph, C(O)Me

Finally, the kinetic resolution reactions, in which one cyclopropane enantiomer reacts with a partner, while the other enantiomer is recovered from the reaction mixture with a high optical purity, can also be considered as a method for the preparation of optically active DACs. For example, dimethyl 2-phenyl- and 2-(4-iodophenyl)cyclopropane-1,1-dicarboxylates (89%–90% *ee*) were isolated after a chiral copper complex-catalyzed reaction of dimethyl 2-arylcyclopropane-1,1-carboxylates with 1-benzyl-3-methylindole.[225]

6. Conclusion

Currently, the donor-acceptor cyclopropane chemistry experiences a boom. On the one hand, new reactions of DACs have been discovered, demonstrating their great synthetic potential. On the other hand, known transformations of DACs have been used to develop methods for the synthesis of acyclic and carbo- and heterocyclic compounds, which are employed, in particular, in the synthesis of biologically active natural products and their analogues. As a result of extensive studies of DACs, this subject has formed a separate research area of organic chemistry; the progress in this area was accompanied by improvement of the methods of DAC synthesis.

It follows from the data surveyed in the review that in the last 10–15 years, methods for the synthesis of DACs have been vigorously developed and general methods have appeared. First, new effective catalysts for cyclopropanation of alkenes with diazo compounds have been found, which made this method efficient and available for use. Second, methods for DAC synthesis based on the Michael-initiated ring closure have found wide use; most often, they employ the Corey–Chaykovsky reaction. This reaction, which was discovered in 1962 and was of low utility for a long time, is now a versatile general method for the synthesis of the most important DACs — 2-arylcyclopropane-1,1-dicarboxylates. Each of the general methods has benefits and limitations. For example, the Corey–Chaykovsky reaction is inapplicable to the cyclopropanation of 2-alkylidene-1,3-diones and the corresponding keto ethers or to cyclopropanation of compounds containing an active

hydrogen atom; conversely, the use of diazo compounds in these reactions is often efficient. Therefore, further investigation of these compounds would define more clearly the potential and the scope of applicability of each method.

Apart from the indicated general methods for the preparation of DACs, other approaches to their synthesis are being developed. For instance, the Simmons – Smith reaction, which was recently inapplicable to the synthesis of DACs, became suitable for this purpose owing to the appearance of new co-catalysts and reagents. Among other promising methods, note cycloalkylation of CH-acids to prepare DACs with two geminal acceptor groups, the addition of 2-halomalonates and their derivatives to styrenes followed by intramolecular ring closure dehydrohalogenation, and cyclization *via* 1,3-elimination. Considering the material presented in the review, these reactions can be treated as potential general methods for the synthesis of DACs, including those with new types of both donor and acceptor substituents and for the synthesis of DACs on an industrial scale. One can expect that further development of new preparative methods for the synthesis of DACs would pursue this strategy. It is evident that higher accessibility of DACs, including new derivatives, would stimulate further progress in this area.

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