Catalytic olefination of carbonyl compounds. A new versatile method for the synthesis of alkenes*

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The review is devoted to a new catalytic olefination reaction (**COR**) discovered by the authors. This is the reaction between *N*-unsubstituted hydrazones of carbonyl compounds with dihalides $CHal_2XY$ in the presence of copper(I) chloride to give substituted alkenes. Catalytic olefination is versatile. Variation of the carbonyl and olefinating components opens up the way for the synthesis of various classes of unsaturated compounds including those containing functional groups. The reaction mechanism is discussed and a catalytic cycle describing the process is proposed. A model for estimating and predicting the reactivity of halogen-containing compounds in the **COR** is developed. The relationship between the structure of the carbonyl substrates and their behavior in the title reaction is elucidated.

Key words: catalysis, transition metals, copper salts, carbonyl compounds, hydrazones, polyhaloalkanes, olefination, alkenes, electrophilicity, metal carbene complexes.

Introduction

The formation of new carbon—carbon bonds is among the most important reactions in organic synthesis. The vigorous development of catalysis by metal complexes has given rise to a large number of reagents and catalysts based on transition metals that allow the formation of carbon—carbon bonds.[1,2]

Olefination of carbonyl compounds, *i.e.*, the transformation of the carbonyl group into a double carbon—carbon bond (Scheme 1), represents a versatile approach to the synthesis of substituted alkenes.[3] Variation of the carbonyl component and the olefinating reagent provides the route to a broad range of unsaturated compounds with specified structures.

Scheme 1

Numerous methods of olefination using various reagents have been developed to date.[1,3] Methods based on the addition of heteroatom-stabilized carbanions to carbonyl compounds have found the most extensive use in synthetic practice. The heteroatoms include phosphorus (Wittig reaction[4,5] and its versions[6,7]), sulfur (Julia olefination,[8] Johnson methylenation[9,10]), silicon (Peterson reaction[11—16]), and some other. A number of olefination methods based on reductive coupling of carbonyl compounds with various reagents in the presence of transition metals in low oxidation states have been proposed.[1,3] The reducing agents used include zinc,[17—19] chromium,[20—22] and titanium[23—26] compounds. The McMurry reaction is often used for the synthesis of symmetrical alkenes from carbonyl compounds.[27—32] However, all these methods require an equimolar amount or an excess of organoelement compounds or reducing metals. As a rule, the reactions must be carried out under inert atmosphere in anhydrous solvents. Therefore, development of new methods for olefination of carbonyl compounds, especially catalytic ones, alternative to the classical routes remains topical.

In 1999, we discovered the catalytic olefination reaction (**COR**).[33] We found that hydrazones of carbonyl compounds can be transformed into substituted alkenes $R^1R^2C{=}CXY$ upon the reaction with *gem*-dihalo-con-

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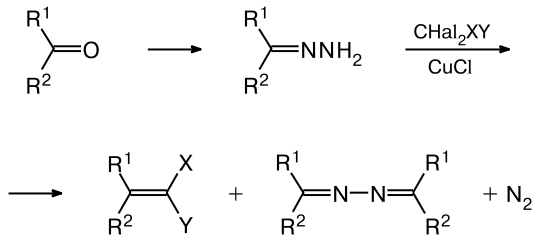
taining reagents $CHal_2XY$ in the presence of catalytic amounts of copper(I) chloride (Scheme 2). Thus, the carbon—nitrogen bond of the hydrazone is converted into the olefin carbon—carbon bond. The reaction of hydrazones with the $CHal_2XY$ reagents is accompanied by nitrogen evolution, symmetrical azines of carbonyl compounds being formed as the only by-products of hydrazine transformation (see Scheme 2). Subsequently, we used the term "olefination products" in relation to both alkenes and azines, as both products are formed *via* the same intermediates within the same catalytic process. The catalytic olefination we discovered is an absolutely atypical reaction of both hydrazones of carbonyl compounds and polyhaloalkanes.

Scheme 2



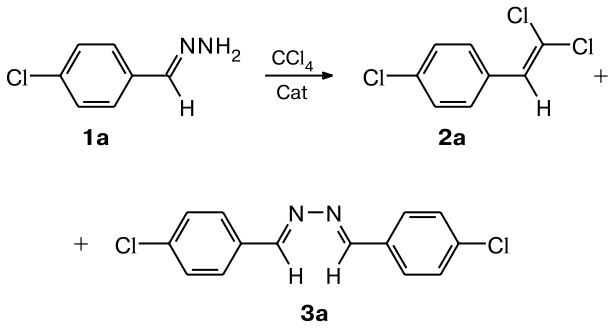
Development of new general methods for the synthesis of unsaturated compounds from aldehydes and ketones is important; therefore, a new catalytic olefination reaction is of theoretical and practical interest. This reaction does not require an inert atmosphere or anhydrous solvents; it smoothly proceeds at room temperature. The **COR** is the first example of catalytic olefination that does not require the use of equimolar amounts of exterior reducing agents or organoelement compounds. On the basis of this reaction, we developed convenient methods for the synthesis of substituted alkenes of various types.

This review summarizes the results of our studies (1999—2003) dealing with the regularities, the mechanism, and the synthetic potential of **COR**, which were carried out in the trends as follows: (i) investigation of the factors influencing the reaction route between hydrazones and polyhaloalkanes; (ii) study of the reaction mechanism; (iii) analysis of the effect of the structure of carbonyl compounds on the reaction route; (iv) determination of the reactivity of halogen-containing reagents in the **COR**; (v) study of the synthetic potential of this reaction and its use for the synthesis of various types of unsaturated compounds.

The factors influencing the route of reaction of hydrazones with polyhaloalkanes

The reaction of hydrazones with aromatic carbonyl compounds with CCl_4, resulting in dichloroalkenes, was studied as the model reaction (Scheme 3). 4-Chlorobenzaldehyde hydrazone (**1a**) was taken as the model substrate. Without a catalyst, hydrazone **1a** is slowly oxidized by CCl_4 to 4-chlorobenzaldehyde azine **3a** (the degree of conversion of **1a** over 3 days is 10%), whereas the expected olefination product, *gem*-dichloroalkene **2a**, is not formed.

Scheme 3



Cat is catalyst

We studied the catalytic activity of Group IB—VIII transition metal chlorides in the reaction of hydrazone **1a** with CCl_4 in DMSO in the presence of ammonia. Chlorides of metals (in lower oxidation states, whenever possible), except for the cases when these chlorides are unstable, were used as catalysts (Table 1).*

It was found that all transition metal compounds we studied do catalyze the reaction of hydrazone **1a** with CCl_4. In all cases, the starting model hydrazone **1a** is completely converted to give only alkene **2a** and azine **3a**, *i.e.*, the **COR** products (see Scheme 3). In most cases, the total yield of these compounds is nearly quantitative. As a rule, on passing from lighter to heavier elements within the same Group, the yield of dichloroalkene **2a** decreases, while the yield of azine **3a** increases. In some cases, namely, when zinc, titanium, and ruthenium compounds are used as catalysts, the total yield of **COR** products was less than 70%, due to the side resinification processes taking place in the system.

Copper(I) chloride proved to be the catalyst of choice for the synthesis of dichloroalkenes by this reaction. The results obtained stipulated the necessity for additional investigation of the dependence of the yield of dichloroalkene **2a** and azine **3a** on the copper oxidation state and the nature of the counter-ion. To this end, we carried out the reaction of hydrazone **1a** with CCl_4 under standard conditions using a number of copper(I) and copper(II) salts (Table 2).[34] In all cases, olefination gave the same products **2a** and **3a** in a nearly quantitative total yield.

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Table 1. Effect of the catalyst nature on the yields of the products of reaction of hydrazone **1a** with CCl_4

Catalyst	Group of the Periodic Table	Product yield (%)		
		2a	**3a**	**2a** + **3a**
CuCl	IB	82	18	100
AgCl	IB	20	76	96
$HAuCl_4$	IB	11	86	97
$ZnCl_2$	IIB	20	47	67
$CdCl_2$	IIB	13	80	93
$HgCl_2$	IIB	5	87	92
$LaCl_3$	IIIB	22	69	91
$Ce(NO_3)_3 \cdot 6H_2O$	IIIB	15	73	88
$TiCl_3 \cdot 3THF$	IVB	17	37	54
$ZrCl_4$	IVB	6	84	90
$NbCl_5$	VB	8	87	95
$TaCl_5$	VB	10	90	100
$CrCl_2$	VIB	Traces	73	73
$MoCl_5$	VIB	Traces	76	76
WCl_6	VIB	Traces	92	92
$MnCl_2 \cdot 4H_2O$	VIIB	20	73	93
$FeCl_3$	VIII	25	58	83
$CoCl_2 \cdot 6H_2O$	VIII	22	62	84
$NiCl_2 \cdot 6H_2O$	VIII	10	62	72
$RuCl_3 \cdot 3H_2O$	VIII	15	80	95
$RhCl_3 \cdot 3H_2O$	VIII	5	29	34
$PdCl_2$	VIII	17	66	83
H_3IrCl_6	VIII	Traces	95	95
K_2PtCl_4	VIII	25	73	98

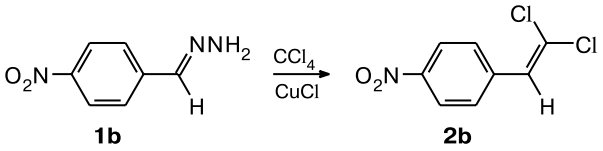
Table 2. Effect of the copper oxidation state and the counter-ion of the copper salt on the product yield in the reaction of hydrazone **1a** with CCl_4

Catalyst	Product yield (%)		
	2a	**3a**	**2a** + **3a**
CuCl	82	18	100
$CuCl_2$	73	27	100
$CuSO_4 \cdot 5H_2O$	68	19	87
$Cu(OAc)_2 \cdot 2H_2O$	75	20	95
$Cu(OTf)_2$	74	22	96
CuCN	20	65	85

Thus, both Cu^I and Cu^{II} compounds are suitable as catalysts of the **COR**. In the reaction with CuCN, the yield of alkene **2a** decreases to 20%, azine **3a** being the major product. Probably, this is due to the fact that the cyanide ion is a strong complexing species firmly associated to the Cu atom. In addition, the complexation with the cyanide ion increases the stability of Cu^I ions against oxidation.[35] With counter-ions weakly bound to Cu (halide, sulfate, acetate, and triflate ions), the reaction direction depends little on the counter-ion used. Subsequently, we used CuCl as the catalyst; the low cost and ready availability of this catalyst are its essential advantages.

The effect of the amount of the catalyst on the yield of alkenes in the olefination has been studied[36] for the reaction of 4-nitrobenzaldehyde hydrazone **1b** with CCl_4 (Scheme 4).

Scheme 4



1b **2b**

It was found that dichloroalkene **2b** is formed even when the amount of the catalyst is 0.1 mol.% (the yield of **2b** is 68%). The highest yield of the alkene is attained in the presence of 5—10 mol.% of the catalyst. When the catalyst concentration is higher, the yield starts to decrease, apparently, due to the more vigorous reaction behavior accompanied by heat evolution (Fig. 1). In subsequent experiments, we used the catalyst in a concentration of 10 mol.% with respect to the substrate.

The formation of dichlorostyrene requires one mole of CCl_4 per mole of the hydrazone. However, on treatment of hydrazone **1b** with an equimolar amount of CCl_4, the yield of dichlorostyrene **2b** was only 44%. An increase in the amount of CCl_4 with the amount of the catalyst remaining constant (10 mol.%) results in a higher yield of the target product.[36] By using a fivefold excess of CCl_4 with respect to **1b**, we were able to increase the yield of alkene **2b** to 79% (Fig. 2).

The nature of the solvent used in the reaction has also a pronounced influence on the product yields (Table 3).[36] We studied systematically the reaction of hydrazone **1b** with CCl_4 using protic, dipolar aprotic, low-polarity and nonpolar solvents.[37]

It can be seen from Table 3 that almost in all polar solvents including alcohols, amides, acetonitrile, DMSO, HMPA, nitromethane, and sulfolane, complete conversion of hydrazone is observed and the target dichloro-

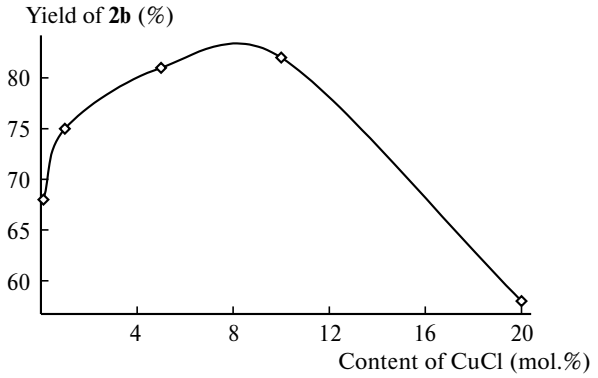


Fig. 1. Effect of the amount of CuCl on the yield of alkene **2b**.

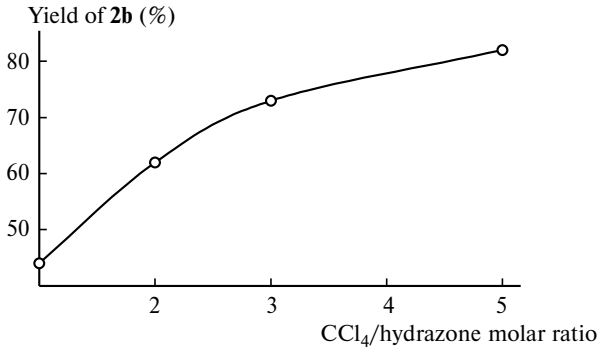


Fig. 2. Effect of the amount of CCl_4 on the yield of alkene **2b**.

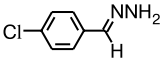
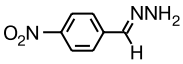
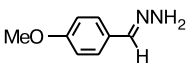
Table 3. Effect of the nature of the solvent on the product yield in the reaction of hydrazone **1a** with CCl_4

Solvent	ε_r[a]	μ[b]·10^{30} /C m	Conversion of **1b**	Yield of **2b**
			(%)	
Formamide	111.0	11.2	100	48
Water	78.3	5.9	0	0
Ethylene glycol	37.7	7.7	100	59
Methanol	32.66	5.7	100	61
N-Methylformamide	182.4	12.9	100	63
Ethanol	24.55	5.8	100	59
Isopropyl alcohol	19.92	5.5	100	53
Nitromethane	35.94	11.9	100	58
Acetonitrile	35.94	11.8	100	57
DMSO	46.45	13.5	100	79
Sulfolane	43.3	16.0	100	57
DMF	36.71	10.8	100	57
N-Methylpyrrolidone	32.2	13.6	100	12
Tetramethylurea	23.6	11.7	100	64
HMPA	29.6	18.5	100	47
THF	7.58	5.8	100	27
Dimethoxyethane	7.20	5.7	75	10
CH_2Cl_2	8.93	5.2	0	0
CCl_4	2.23	0.0	0	0
Benzene	2.27	0.0	81	12
Hexane	1.88	0.0	77	8

[a] Relative dielectric constant.
[b] Dipole moment.

styrene **2b** is formed in a high yield. In water, the reaction does not take place, probably, because the reactants and the catalyst are water-insoluble. In low-polarity and nonpolar solvents such as benzene, THF, and hexane, the target product is formed in a low yield, and in some cases, the starting hydrazone has also been isolated. The reaction does not take place in polyhalomethanes (CH_2Cl_2, CCl_4). Apparently, these results are due to inefficient solvation of the catalyst and the polar hydrazone by solvents with low polar. The dipolar aprotic DMSO solvent, which efficiently solvates cations, proved to be the medium of choice for this reaction.

Table 4. Yields of the products in the reactions of hydrazones **1a—c** with CCl_4

Hydrazone	The yield of **COR** product (%)		
	Dichloroalkene	Azine	The sum of products
 (**1a**)	82	17	99
 (**1b**)	79	17	96
 (**1c**)	49	44	93

It should be noted that the reaction occurs only in the presence of aqueous ammonia. Probably, its role is both to be complexed with the catalyst and to trap two acid molecules formed.

Thus, the course of the reaction of hydrazones of carbonyl compounds with CCl_4 is influenced by the nature of the catalyst (transition metal compounds), the catalyst and reactant concentrations, and the nature of the solvent.

The mechanism of catalytic olefination

The formation of dichloroalkenes **2a,b** and azines **3a,b** on treatment of 4-chlorobenzaldehyde (**1a**) and 4-nitrobenzaldehyde (**1b**) hydrazones with CCl_4 in the presence of CuCl has been previously unknown for hydrazones. The reaction of 4-methoxybenzaldehyde hydrazone **1c** with CCl_4 occurs in a similar way to give dichlorostyrene **2c** and azine **3c** as the only products (Table 4)[38].

For any of the studied substrates, the total yield of the **COR** products is nearly quantitative. No other transformation products of hydrazones, nor even in trace amounts have been found in the reaction mixture by GC/MS analy-

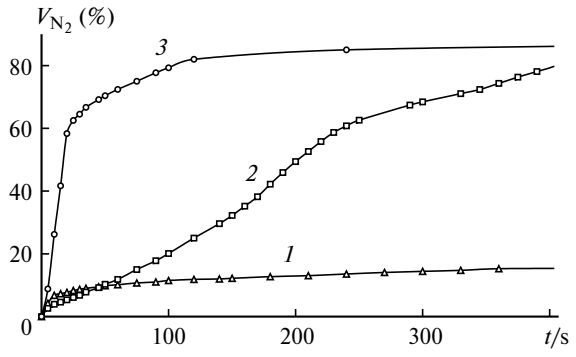
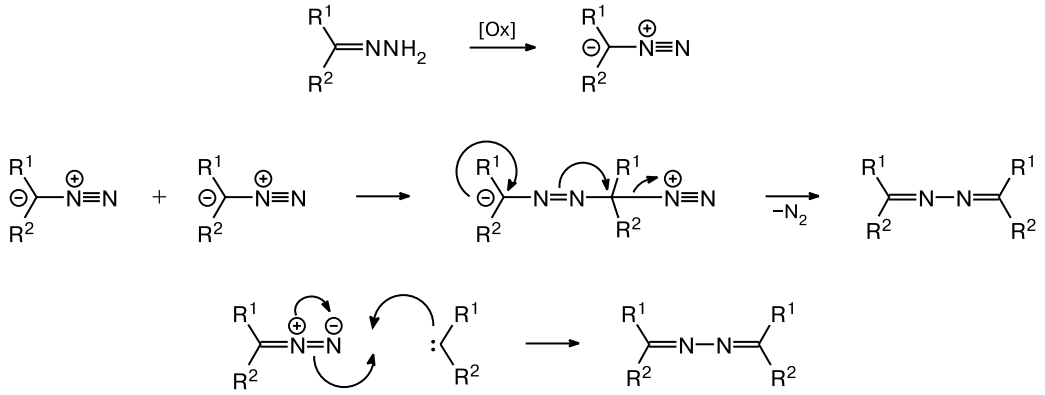


Fig. 3. Gas evolution rate in the reaction of hydrazones **1a—c** with CCl_4: 4-nitrobenzaldehyde hydrazone (*1*), 4-chlorobenzaldehyde hydrazone (*2*), and 4-methoxybenzaldehyde hydrazone (*3*). The nitrogen volume is indicated in percent of the theoretical volume.

Scheme 5



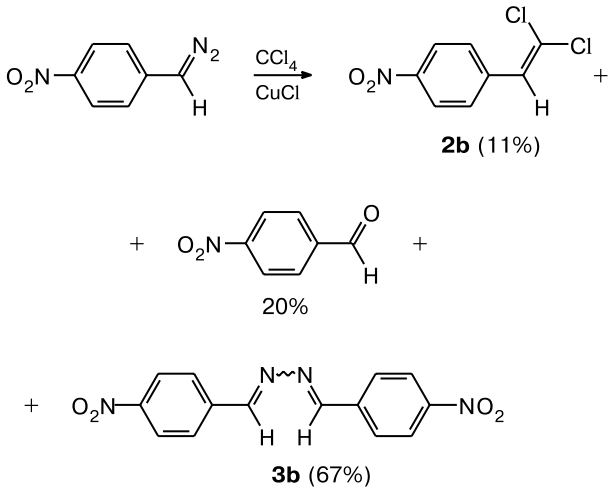
sis. These data attest to an exceptionally high chemoselectivity of hydrazone transformation under the reaction conditions.

Since the reaction of hydrazones with CCl_4 is accompanied by nitrogen evolution, the rate of gas evolution can be used to estimate the relative reactivities of substrates. It was found that the rate of nitrogen evolution and the yield of reaction products depend appreciably on the nature of the substituent in the aromatic ring of hydrazones **1a—c** (Fig. 3). An electron-withdrawing substituent, *e.g.*, the nitro group in substrate **1b**, results in a lower rate of nitrogen evolution. The highest gas evolution rate was found for hydrazone **1c**, which contains the strong electron-releasing methoxy group; however, the yield of dichloroalkene **2c** (49%) was much lower than those with hydrazones **1a,b**. The highest yield of azine **3c** (44%) was observed for hydrazone **1c**.

On treatment with oxidants, *N*-unsubstituted hydrazones of carbonyl compounds are known[39] to be converted, most often, into the corresponding diazoalkanes and then into products of their transformations and in symmetrical azines. Compounds of transition metals in higher oxidation states, halogens, *N*-bromosuccinimide, or peroxo acids can be used as oxidants. Depending on the nature of the oxidant, azine can be produced by two routes, *via* the intermediate diazo compound or *via* the hydrazonyl radical; if metal compounds in higher oxidation states are used as oxidants, the reaction normally proceeds through diazoalkanes.[39] Azines are formed from diazo compounds upon ejection of a nitrogen molecule[39,40] or upon the reaction of carbenes with diazo compounds[39] (Scheme 5).

The formation of azines may imply that diazoalkanes participate in the catalytic olefination. To confirm this assumption, 4-nitrophenyldiazomethane prepared beforehand[36] was introduced in the reaction. The reaction of 4-nitrophenyldiazomethane with CCl_4 (5 equiv.) under standard olefination conditions (in a DMSO solution in the presence of an aqueous solution of ammonia and 10 mol % CuCl) was found to give the same products (alkene **2b** and azine **3b**) as obtained with 4-nitrobenzaldehyde hydrazone **1b**. However, the yield of alkene **2b** has markedly decreased and the yield of azine **3b** has increased (Scheme 6).

Scheme 6



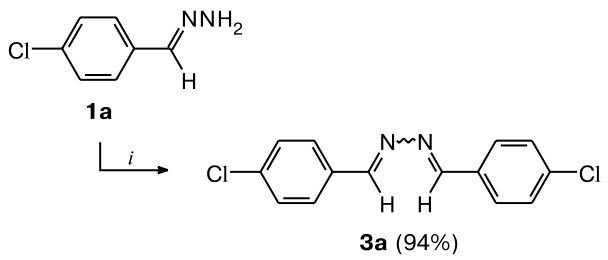
A by-product resulting from noncatalytic transformations of diazoalkane, 4-nitrobenzaldehyde, which is not produced from hydrazone **1b** under the **COR** conditions, has also been isolated (it is known[41—43] that carbonyl compounds are formed from diazoalkanes when they react with the oxidants present in the system, *viz.*, DMSO, oxygen).

The rate of nitrogen evolution during the reaction of 4-nitrophenyldiazomethane with CCl_4 is higher than in the reaction of hydrazone **1b**. Thus, the oxidation of hydrazone to diazoalkane proceeds more slowly than decomposition of diazoalkane during the **COR**. This ensures a low concentration of diazoalkane compared to CCl_4 when using hydrazones. An increase in the diazoalkane con-

centration promotes dimerization (the formation of azine) and oxidation (the formation of aldehyde). Apparently, hydrazones are oxidized in the first step to diazoalkanes with copper(II), resulting from oxidation of CuCl with carbon tetrachloride. According to the reaction pattern, the formation of azine requires two diazoalkane molecules, whereas the formation of dichloroalkene requires one molecule of the diazo compound and one CCl_4 molecule. Therefore, an increase in the amount of CCl_4 entails an increase in the content of dichloroalkene in the reaction products. The factors that enhance the susceptibility of hydrazones for oxidation are favorable for the increase in diazoalkane concentration and, hence, gas evolution rate; this should increase the yield of azines, which is really the case for electron-releasing hydrazone **1c**. Thus, on the basis of analysis of published and experimental data, we demonstrated that azines **3a—c** are formed upon oxidation of hydrazones **1a—c** with Cu^{II} compounds to the corresponding diazoalkanes, which then react with each other with nitrogen ejection.

When an equimolar amount of Cu^{II} is used for oxidation (the reaction is carried out in DMSO in the presence of an aqueous solution of ammonia without CCl_4), azine **3a** is formed in 94% yield as the only transformation product of hydrazone **1a** (Scheme 7). Apparently, the intermediate diazo compound cannot be isolated, as it rapidly decomposes in the presence of copper compounds.

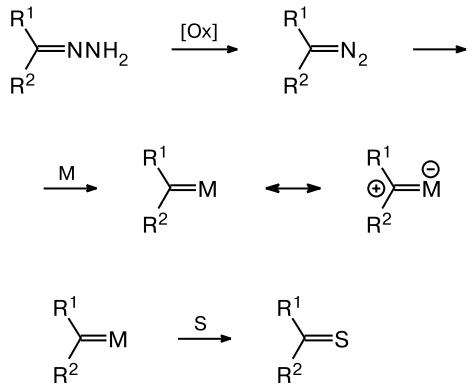
Scheme 7



i. $CuCl_2$ (2 equiv.).

Thus, the synthesis of dichloroalkenes and azines during olefination can involve the intermediate formation of diazoalkanes.[36] Diazoalkanes are widely used in synthetic organic chemistry; their properties have been the subjects of fundamental reviews and monographs.[41—43] They are able to undergo diverse transformations both with nitrogen evolution and with nitrogen retention in the molecule. For example, diazo compounds decompose under the action of some transition metals, first of all, copper and rhodium to give metal carbene complexes. The carbene complexes of copper, rhodium, and other metals are generally recognized intermediates of carbene transfer reactions such as cyclopropanation of alkenes[44] and the synthesis of oxiranes (Scheme 8).[45]

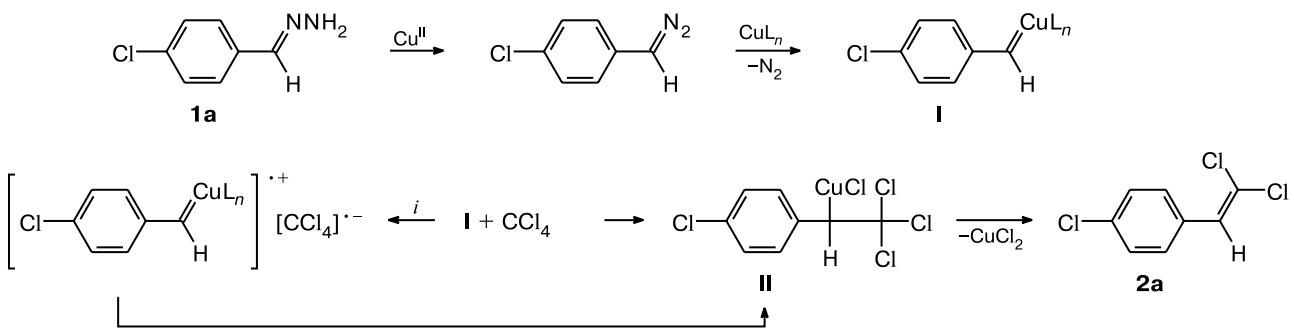
Scheme 8



M = Cu, Rh; S is substrate

We assumed that the synthesis of dichloroalkenes in the reaction of hydrazones with CCl_4 also involves a copper carbene complex as an intermediate.[38,46,47] The oxidation of hydrazone **1a** affords aryldiazomethane, which further undergoes copper-catalyzed decomposition to give copper carbene complex **I** (Scheme 9). We have postulated complex **I** to be the key intermediate of the **COR**. The subsequent addition of CCl_4 to carbene complex **I**

Scheme 9

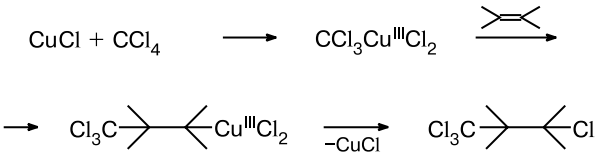


i. Single-electron transfer.

gives rise to organocopper compound **II**. This reaction proceeds presumably as the insertion of the Cu atom into the C—Cl bond, although a mechanism including preliminary single-electron transfer from the copper carbene complex to CCl_4 is also possible. This yields a radical anion/radical cation pair, which is subsequently converted into intermediate **II**. Elimination of $CuCl_2$ from intermediate **II** gives dichlorostyrene **2a**.

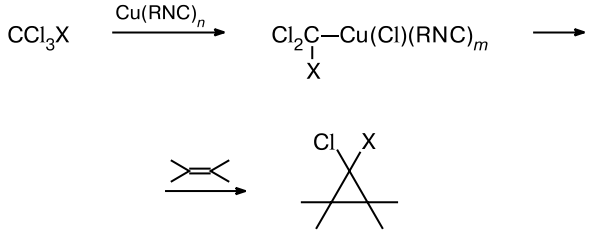
A number of reactions including the oxidative addition of copper to the C—Hal bond have been reported. Thus the addition of CCl_4 and other polyhaloalkanes to the C=C bonds in the presence of CuCl to give 1 : 1 adducts has been studied in detail (Scheme 10).[48—50] The reaction is assumed to follow a radical mechanism[51] or to involve the intermediate formation of Cu^{III} compounds.[50]

Scheme 10



The synthesis of carbenoid complexes of copper in the oxidative addition of isonitrile copper complexes to trichloromethyl-containing compounds has been documented (Scheme 11). The carbenoid complexes add to alkenes to furnish cyclopropanes.[52,53] We believe that the reaction of copper carbene complex **I** with CCl_4 under the **COR** conditions proceeds as described in the literature and includes the oxidative addition of copper to the C—Hal bond to give the C—Cu—Hal fragment.

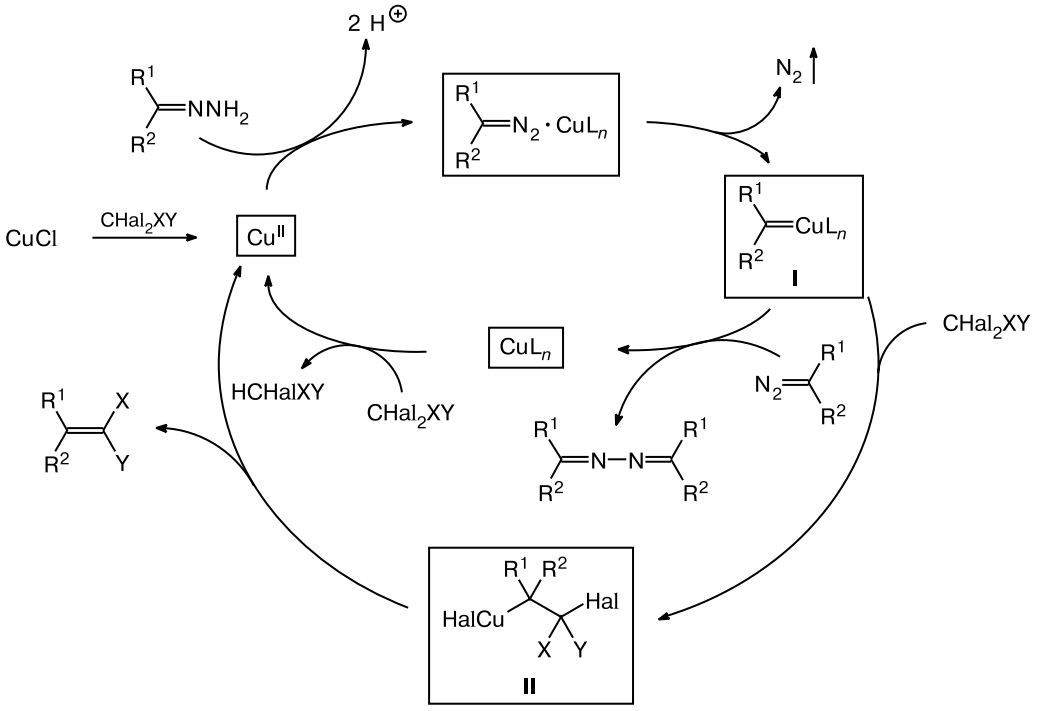
Scheme 11



X = Ph, CO_2R, CN

The results obtained in a study of the model reaction of hydrazones with CCl_4, together with the published data allow one to construct a unified catalytic cycle of the **COR** which would describe the transformations taking place in the system and account for the formation of unsaturated compounds and azines under these conditions (Scheme 12). The reaction is initiated by the oxidation of CuCl with halogen compounds $CHal_2XY$ to give Cu^{II}, which then oxidizes hydrazones to diazoalkanes, the acid formed being trapped with ammonia. The subsequent copper-catalyzed decomposition of diazoalkanes with nitrogen evolution results in copper carbene com-

Scheme 12



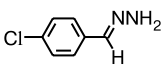
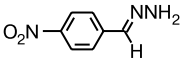
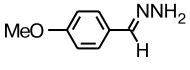
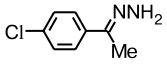
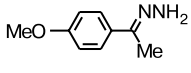
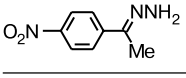
plex **I**, which is the key intermediate of the **COR**. The subsequent transformation of the copper carbene complex follows two routes. The reaction of the complex with $CHal_2XY$ results in substituted alkenes and regeneration of the catalyst, Cu^{II} (external cycle). The side reaction giving rise to azines proceeds *via* dimerization of diazoalkanes with Cu catalysis or through the reaction of the copper carbene complex with another diazoalkane molecule (internal cycle). The low-valence copper compounds thus formed should be oxidized by polyhaloalkanes to give partial reduction products.

Both catalytic cycles (the external and internal ones) include the same states of the Cu catalyst. The ratio of the hydrazone transformation products, alkenes and azines, is determined by the competing transformations of the copper carbene complex **I**.

Effect of the structure of carbonyl substrates

In order to determine the scope of synthetic application of **COR** in the series of carbonyl substrates and to compare the reactivities of different hydrazones, we studied the reactions of hydrazones derived from aromatic aldehydes, alkyl aryl ketones, and diaryl ketones with CCl_4 in the presence of CuCl (Table 5).[38] Detailed analysis of the transformation products has shown that in all cases, except for the hydrazones of diaryl ketones (fluorenone and benzophenone), the two expected **COR** products (dichloroalkenes and *symm*-azines) are formed in a nearly quantitative total yield. Thus, catalytic olefination is a general reaction, which can involve both aromatic aldehydes and ketones. This opens up the way for the synthesis of a broad range of alkenes from carbonyl precursors.

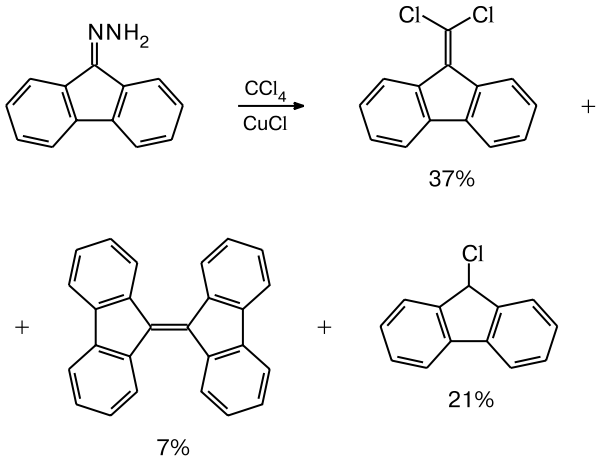
Table 5. Yields of the products in the reactions of hydrazones with CCl_4

Hydrazone	Yield (%)		
	$Ar(R)C{=}CCl_2$	$Ar(R)C{=}N{-}N{=}C(R)Ar$	Σ*
	74	19	93
	79	17	96
	49	44	93
	82	14	96
	88	7	95
	58	32	90

* The sum of products.

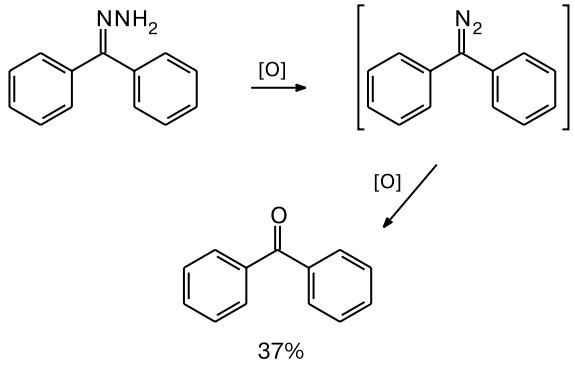
In the case of fluorenone hydrazone, "abnormal" products, bis-fluorenylidene and 9-chlorofluorene, have been obtained together with the expected 9-dichloromethylenefluorene (Scheme 13). The corresponding fluorenone azine could not be isolated.

Scheme 13



When benzophenone hydrazone is used in the reaction, benzophenone is isolated as the only product (yield 37%); this product results from oxidative cleavage of the C=N bond of diazoalkane under reaction conditions (Scheme 14).

Scheme 14



Thus, the behavior of hydrazones of aromatic aldehydes and alkyl aryl ketones is fully consistent with the proposed **COR** scheme, whereas diaryl ketone hydrazones show an abnormal behavior. It was found[38] that the increase in the amount of abnormal products is correlated with enhancement of the stability of the diazoalkanes involved and with the increase in the steric hindrance of the hydrazone group in the case of diaryl ketone derivatives. The enhancement of the stability of the inter-

mediate diazoalkanes and, as a consequence, a decrease in the formation rate of the copper carbene complex lead the diazoalkane out of the **COR** catalytic cycle; hence, it participates in side reactions (both those catalyzed by copper salts and those proceeding without catalysts).

The identification of the general scope of the reaction and the relationship between the structure and the **COR** behavior of the carbonyl compound suggest that olefination can occur for a broad range of various carbonyl compounds. Therefore, the **COR** can be used to synthesize alkenes of different structural types.

Determination of the reactivities of halogen-containing reagents under the COR conditions

According to the general **COR** pattern (see Scheme 2), apart from CCl_4, other $CHal_2XY$ compounds containing a *gem*-dihalomethylene fragment or a trihalomethyl group as well as tetrahalomethanes can also act as olerfinating reagents.

We have studied the influence of the nature of the halogen-containing reagents on the route of their reaction with hydrazones. According to the proposed **COR** mechanism (see Scheme 12), the olefinating reactivity of a polyhaloalkane should be determined by the step where this compound reacts with copper carbene complex **I** to give organocopper compound **II** (see Scheme 9), *i.e.*, by its ability to function as an electron acceptor and by the strength of the C—Hal bond, which is going to be cleaved upon the oxidative addition of the copper carbene complex to the halogen-containing reagent. An increase in the olefination reactivity of polyhaloalkanes should result in higher yields of the target products, *i.e.*, alkenes, and lower yields of the by-products, *i.e.*, azines, because these reaction routes compete with each other.

Polyhaloalkanes behave as typical electrophiles with respect to electron donors.[54] Previous studies[55,56] revealed correlations between the reactivity and some characteristics of polyhaloalkanes, namely, the half-wave electroreduction potential, electron affinity, bond energy, and the energy of the lower unoccupied molecular orbital (LUMO). As a rule, the electron affinity increases with an increase in the number of halogen atoms (except for polyfluoroalkanes).[57] In recent years, the global reactivity index ω has been often used to estimate the reactivity of chemical compounds. This is a semiempirical parameter reflecting the energy of electron transfer to the LUMO of the given molecule.[58,59] The global electrophilicity index of the molecule is determined from the formula $\omega = \mu^2/2\eta$, where μ is the electron chemical potential ($\mu = 0.5(E_{HOMO} + E_{LUMO})$, E_{HOMO} is the energy of the higher occupied molecular orbital), η is the chemical rigidity ($\eta = E_{LUMO} - E_{HOMO}$). This parameter takes into account both the acceptor and donor properties of the molecule and is well correlated with experimental data on the electrophilicity of various compounds.[58,59]

Table 6. Global electrophilicity indices (ω) and LUMO (E_{LUMO}) and HOMO (E_{HOMO}) energies for a number of halogen-containing compounds

Reagent	$-E_{HOMO}$	$-E_{LUMO}$	ω
	eV		
CBr_3NO_2	7.24	3.93	4.70
CCl_3COCF_3	7.48	3.94	4.60
CBr_4	7.02	3.73	4.38
CCl_3NO_2	7.61	3.86	4.38
CBr_3Cl	7.02	3.59	4.10
CBr_2Cl_2	7.13	3.43	3.76
CCl_3CHO	7.06	3.27	3.52
$CHBr_2CN$	7.50	3.26	3.42
$CBrCl_3$	7.34	3.22	3.39
CBr_3COMe	6.63	3.12	3.38
$CHBr_2COMe$	6.46	3.03	3.29
$CHBr_3$	6.91	3.03	3.19
CBr_2F_2	7.35	2.98	3.06
CCl_4	7.73	2.99	3.03
CCl_3CN	8.09	2.96	2.98
$CHBr_2CO_2Me$	6.87	2.88	2.97
$CHCl_2COMe$	6.47	2.80	2.93
$CHBr_2Cl$	7.03	2.85	2.92
CH_2BrCN	7.44	2.74	2.76
$CHCl_2CN$	8.12	2.69	2.69
$CHBr_2SO_2Me$	7.13	2.66	2.68
$CHBrCl_2$	7.21	2.62	2.64
CCl_3CO_2Me	7.03	2.61	2.63
CCl_3F	7.76	2.62	2.62
CH_2BrCO_2Me	6.57	2.58	2.62
CCl_3SO_2Me	7.41	2.57	2.57
$CHCl_2COOMe$	6.92	2.51	2.52
$CCl_3—CF_3$	7.84	2.52	2.52
$CH_2BrCOMe$	6.15	2.46	2.51
$CF_3—CHBrCl$	7.49	2.43	2.43
$CCl_3—CCl_3$	7.46	2.43	2.43
$CCl_3—CCl_2H$	7.42	2.38	2.39
CCl_3OMe	7.30	2.35	2.35
CCl_3CONH_2	6.70	2.34	2.34
$PhCHBr_2$	6.38	2.30	2.31
$CCl_3—CH_2OH$	7.19	2.25	2.26
$CHCl_3$	7.53	2.25	2.26
CH_2Br_2	6.97	2.24	2.24
CCl_2F_2	8.04	2.18	2.23
CCl_3CONMe_2	6.34	2.21	2.21
$CCl_2F—CClF_2$	8.08	2.15	2.21
$PhCH_2Br$	6.31	2.13	2.13
$CClF_3$	8.55	1.50	1.79
CH_2Cl_2	7.37	1.52	1.69
CH_3Br	6.68	1.33	1.50
CH_4	9.42	0.36	1.32
CH_3Cl	7.09	0.84	1.26

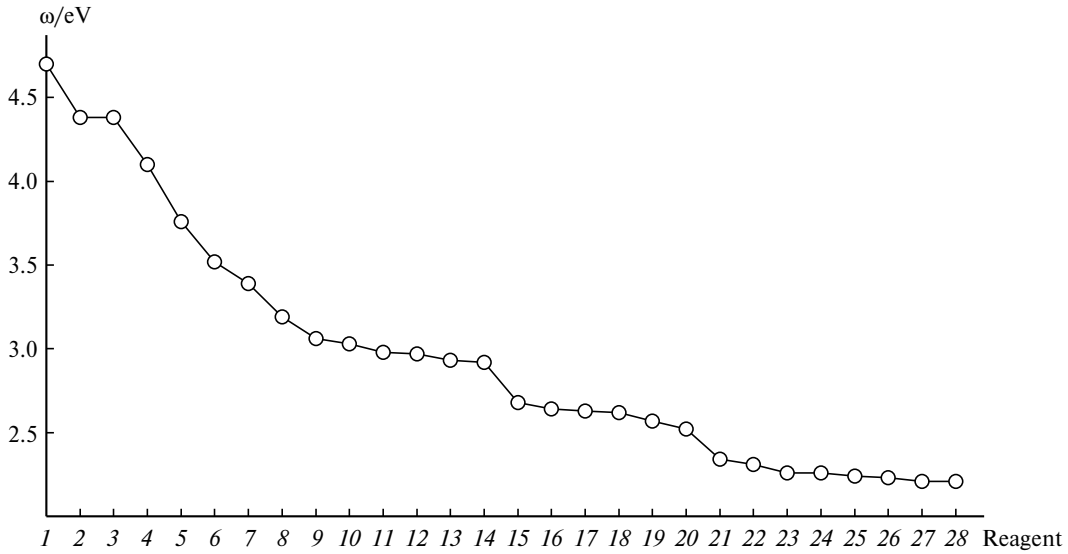


Fig. 4. Variation of the global electrophilicity index (ω) in the series of reagents CBr_3NO_2 (*1*), CBr_4 (*2*), CCl_3NO_2 (*3*), CBr_3Cl (*4*), CBr_2Cl_2 (*5*), CCl_3CHO (*6*), $CBrCl_3$ (*7*), $CHBr_3$ (*8*), CBr_2F_2 (*9*), CCl_4 (*10*), CCl_3CN (*11*), $CHBr_2CO_2Me$ (*12*), $CHCl_2COMe$ (*13*), $CHBr_2Cl$ (*14*), $CHBr_2SO_2Me$ (*15*), $CHBrCl_2$ (*16*), CCl_3CO_2Me (*17*), CCl_3F (*18*), CCl_3SO_2Me (*19*), $CCl_3—CF_3$ (*20*), CCl_3CONH_2 (*21*), $PhCHBr_2$ (*22*), $CCl_3—CH_2OH$ (*23*), $CHCl_3$ (*24*), CH_2Br_2 (*25*), CCl_2F_2 (*26*), CCl_3CONMe_2 (*27*), and $CCl_2F—CClF_2$ (*28*).

Table 7. Bond energies (E_b) for a number of halogen-containing compounds

Reagent	E_b/kcal mol^{-1}		Reagent	E_b/kcal mol^{-1}		Reagent	E_b/kcal mol^{-1}	
	C—Br	C—Cl		C—Br	C—Cl		C—Br	C—Cl
CCl_3COCCl_3	—	54.28	CBr_3CONH_2	50.76	—	CCl_3F	—	74.32
CCl_3COCF_3	—	55.45	CBr_3CONMe_2	50.86	—	CCl_2F_2	—	80.74
CCl_3CN	—	58.38	CBr_3NO_2	49.56	—	CBr_2F_2	66.93	—
CCl_3CO_2Me	—	61.73	CBr_4	53.67	—	$CHBr_3$	63.19	—
CCl_3CONH_2	—	62.85	CBr_3Cl	54.09	65.89	$CHBr_2Cl$	63.28	75.18
CCl_3NO_2	—	63.00	CBr_2Cl_2	54.49	66.31	$CHBrCl_2$	63.31	75.30
CCl_3CONMe_2	—	63.48	$CBrCl_3$	54.87	66.71	$CHCl_3$	—	75.35
CH_2ClCN	—	72.61	$PhCHBr_2$	56.30	—	CH_2Br_2	71.15	—
CCl_3OMe	—	72.74	CBr_3OMe	59.44	—	CH_2Cl_2	—	82.51
$CH_2ClCOMe$	—	76.96	$PhCH_2Br$	63.14	—	$CCl_3—CCl_3$	—	65.82
CH_2ClCO_2Me	—	77.10	CH_2BrCN	62.28	—	$CCl_3—CCl_2H$	—	66.47 (CCl_3)
CH_2ClNO_2	—	80.64	$CH_2BrCOMe$	65.83	—			73.49 (CCl_2H)
CBr_3CN	46.91	—	CH_2BrCO_2Me	65.93	—	$CCl_3—CF_3$	—	68.86
CBr_3CO_2Me	49.35	—	CH_2BrNO_2	68.78	—	$CCl_2F—CClF_2$	—	76.33 (CCl_2F)
CBr_3COCF_3	44.13	—	CCl_4	_	67.07			82.95 ($CClF_2$)

By DFT calculations* with the PBE 96 functional[60] using the PRIRODA program,[61] we determined the LUMO and HOMO energies, the global electrophilicity indices (Table 6, Fig. 4), and the C—Hal bond energies for a number of halogen-containing compounds (Table 7).[34] The resulting values were used for qualitative estimation and prediction of the reactivity of various polyhalogen-containing compounds potentially able to act as olefinating reagents.

The calculation results allow one to determine the regular features of the variation of global electrophilicity indices and the bond energies as functions of reagent nature. The C—Hal bond energy in halomethanes CH_nHal_{4-n} varies over a broad range depending on the number of halogen atoms (see Table 7).[34,62] It can be seen that the bond energy decreases and, hence, the bond be-

* The PBE calculation was carried out using a large orbital basis set of compressed Gaussian type basis functions with the contraction scheme (5,3×1/3×1/2×1) for H, (7,7×1/5,3×1/3×1/2×1) for C, (7,7×1/5,3×1/3×1/2×1) for F, (8,12×1/7,8×1/3×1/2×1) for Cl, and (8,17×1/6,13×1/6,8×1/3×1) for Br.

comes more prone to rupture with an increase in the degree of methane halogenation. On passing from trihalomethanes $CHBr_nCl_{3-n}$ to tetrahalomethanes CBr_nCl_{4-n}, the C—Br and C—Cl bond energies decrease by 8—10 kcal mol^{-1}. The calculated data suggest that the behaviors of bromine-containing tetrahalomethanes CBr_4, CBr_3Cl, CBr_2Cl_2, and $CBrCl_3$ in this reaction would be virtually the same, because the reactivity of polyhaloalkanes is dictated by the strength of the weakest C—Br bond, which is the first to be cleaved in the oxidative addition of the copper carbene complex (Fig. 5), while the reactivity of CCl_4 in the **COR** should be much lower. The relative reactivities of $CHBr_3$, $CHBr_2Cl$, and $CHBrCl_2$ should be similar for the same reasons, while the reactivities of chloroform (E_{C-Cl} = 75.35 kcal mol^{-1}) and dihalomethanes are expected to be substantially lower than those of bromine-containing trihalomethanes or CCl_4 (Figs. 5 and 6).

In the case of other halogen-containing compounds $CH_nHal_{3-n}G$ (G is a functional group), the bond energy depends appreciably both on the degree of halogenation of the reaction centers and on the nature of the functional group. The introduction of electron-withdrawing substituents ensures a substantial decrease in the C—Cl and C—Br bond energy. The replacement of Cl or Br atoms by F results in a higher strength of the C—Hal bond. In all cases, the C—Cl bond energy in compounds with analogous structures is several kcal mol^{-1} higher than the C—Br bond energy. The global electrophilicity indices of the corresponding halogen-containing reagents increase in parallel with the decrease in the C—Hal bond energy.

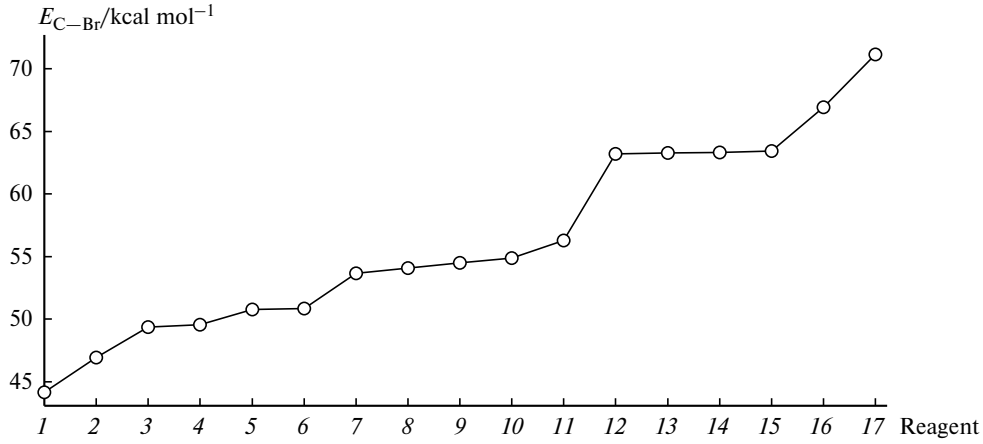


Fig. 5. Variation of the C—Br bond energy in the series CBr_3COCF_3 (*1*), CBr_3CN (*2*), CBr_3CO_2Me (*3*), CBr_3NO_2 (*4*), CBr_3CONH_2 (*5*), CBr_3CONMe_2 (*6*), CBr_4 (*7*), CBr_3Cl (*8*), CBr_2Cl_2 (*9*), $CBrCl_3$ (*10*), $PhCHBr_2$ (*11*), $CHBr_3$ (*12*), $CHBr_2Cl$ (*13*), $CHBrCl_2$ (*14*), $PhCH_2Br$ (*15*), CBr_2F_2 (*16*), and CH_2Br_2 (*17*).

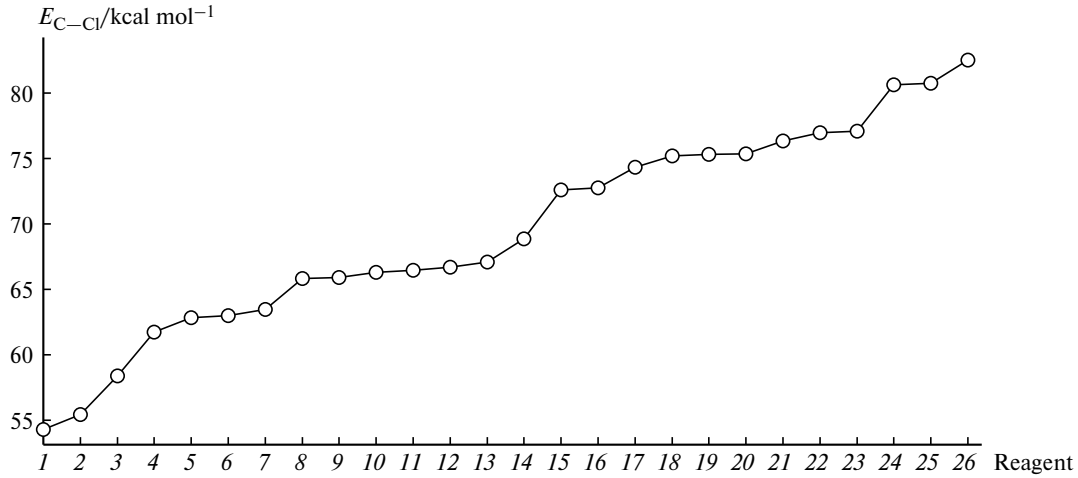
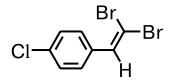
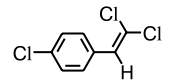
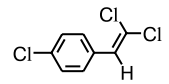
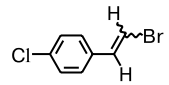
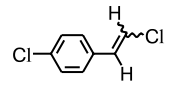
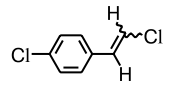
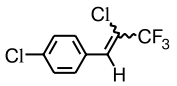
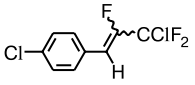


Fig. 6. Variation of the C—Cl bond energy in the series CCl_3COCCl_3 (*1*), CCl_3COCF_3 (*2*), CCl_3CN (*3*), CCl_3CO_2Me (*4*), CCl_3CONH_2 (*5*), CCl_3NO_2 (*6*), CCl_3CONMe_2 (*7*), CCl_3—CCl_3 (*8*), CBr_3Cl (*9*), CBr_2Cl_2 (*10*), CCl_3—CCl_2H (*11*), $CBrCl_3$ (*12*), CCl_4 (*13*), CCl_3—CF_3 (*14*), CH_2ClCN (*15*), CCl_3OMe (*16*), CCl_3F (*17*), $CHBr_2Cl$ (*18*), $CHBrCl_2$ (*19*), $CHCl_3$ (*20*), CCl_2F—$CClF_2$ (*21*), $CH_2ClCOMe$ (*22*), CH_2ClCO_2Me (*23*), CH_2ClNO_2 (*24*), CCl_2F_2 (*25*), and CH_2Cl_2 (*26*).

Table 8. Olefinating ability of polyhaloalkanes

Reagent	Prepared alkene	Yield (%)		
		Alkene	Azine **3a**	Σ*
CBr_4		89	7	96
$CBrCl_3$		71	20	91
CCl_4		82	17	99
$CHBr_3$		67	26	93
$CHBrCl_2$		44	52	96
$CHCl_3$		0	52	52
CH_2Br_2	—	—	78	78
CH_2Cl_2	—	—	63	63
$CCl_3—CF_3$		63	21	84
$CCl_2F—CClF_2$		20	21	41

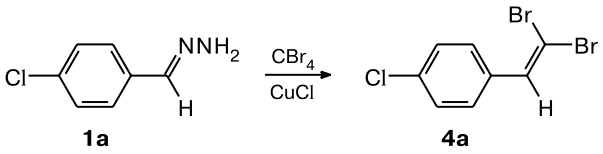
* The sum of products.

To confirm the hypothesis stating that the global electrophilicity index and the C—Hal bond energy allow one to predict the behavior of polyhaloalkanes in the catalytic olefination and to estimate their olefinating reactivity, we studied the reactions of a number of polyhaloalkanes with model 4-chlorobenzaldehyde hydrazone **1a**. It was found that with any of the above reagents, the transformation of hydrazone **1a** gives the corresponding alkenes and azine **3a** as the only products (Table 8).[34]

The tetrahalomethanes CBr_nCl_{4-n} serve as excellent olefinating reagents, the corresponding β,β-dihalostyrenes being isolated in high yields (71—89%). Azine is the minor product, the total yield of dihaloalkenes and azine being nearly quantitative. When CBr_4 is used, hydrazone **1a** is converted into the corresponding dibromostyrene **4a** (Scheme 15). In the case of bromotrichloromethane or CCl_4, dichlorostyrene **2a** is formed.

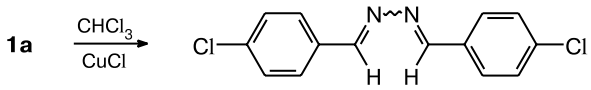
The reaction of haloforms with hydrazone **1a** in the presence of CuCl proceeds in a similar way to give vinyl halides **5a** and **6a**, together with azine **3a**. No β-chlorostyrene was detected upon the reaction with chloroform, which is due to its low global electrophilicity index and markedly higher C—Cl bond energy compared to those of tetrahalomethanes. Azine **3a** was the only reaction product in this case (Scheme 16).

Scheme 15



1a **4a**

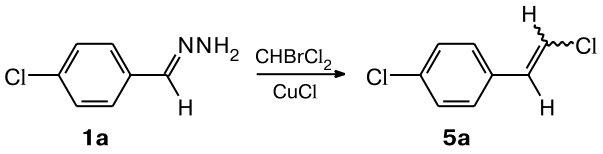
Scheme 16



3a (52%)

However, the replacement of one Cl atom by Br (the use of $CHBrCl_2$) results in the stereoselective formation of the target β-chlorostyrene **5a** in a high yield (Scheme 17). The *E*-isomer of the alkene is formed as the major product. Thus, the use of bromodichloromethane $CHBrCl_2$ as the olefinating reagent opens up a convenient preparative route to β-chlorostyrenes. These results serve as a convincing proof of the fact that the strength of the C—Hal bond is an important factor determining the reactivity of polyhaloalkanes under **COR** conditions.

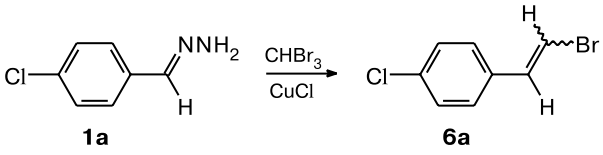
Scheme 17



1a **5a**

Bromoform can be used in the **COR** as a C_1-building block. This gives the corresponding vinyl bromide **6a** (Scheme 18).

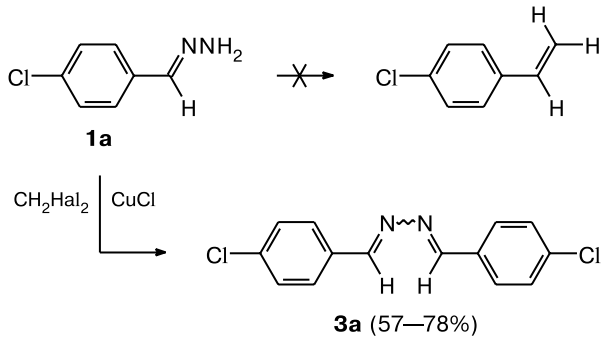
Scheme 18



1a **6a**

Dihalomethanes, *viz.*, diiodomethane, dibromomethane, and dichloromethane, are insufficiently active in the **COR** (Scheme 19). No expected unsubstituted styrene 4-$ClC_6H_4CH=CH_2$ is formed, azine **3a** being the only product.

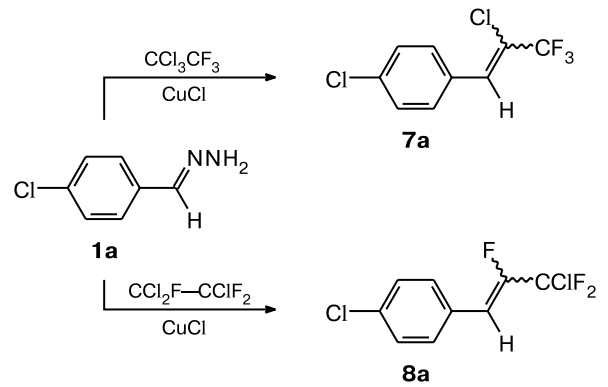
Scheme 19



Hal = Cl, Br, I

Freon isomers $C_2Cl_3F_3$ react with hydrazones to give fluorine-containing alkenes **7a** and **8a** (Scheme 20). The olefinating reactivity of $CCl_3—CF_3$ (Freon 113a) proved to be much higher than that of isomeric $CCl_2F—CClF_2$. Alkene **7a** was obtained in 63% yield, whereas the yield of alkene **8a** was only 20%. This is due to the fact that the reactivity of the trichloromethyl reaction center at the key step of the olefination, *i.e.*, insertion of the copper carbene complex at the C—Hal bond, is much higher than that of the dichlorofluoromethyl group, as the C—Cl bond energy is much lower and the global electrophilicity index is higher for $CCl_3—CF_3$ than for $CCl_2F—CClF_2$.

Scheme 20



Thus, we demonstrated the possibility of using catalytic olefination of hydrazones for the synthesis of substituted alkenes of various types. These data indicate that the general scheme of the formation of olefins and azines describes adequately the reactions of diverse polyhaloalkanes with hydrazones. The predicted dependence of the reactivity on the global electrophilicity indices and the C—Hal bond energies fully correspond to the observed results. This allows the use of calculated data for predicting the olefinating reactivity of various halogen-containing compounds. The reagents whose global electrophilicity indices are higher than that of chloroform (for chlorine-containing reagents) or dibromomethane (for bromine-containing reagents) are expected to enter into the **COR** to give substituted alkenes.

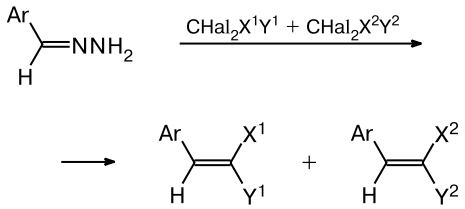
Table 9. Olefination of 4-chlorobenzaldehyde hydrazone (**1a**) with reagent mixtures

Reagents	Composition of the products*	Total yield of alkenes (%)
CBr_4/CCl_4	**4a**	65
$CBr_4/CHBr_3$	**4a** + **6a** (50 : 1)	98
$CCl_4/CHBr_3$	**2a** + **6a** (6 : 1)	72
CCl_4/CCl_3CF_3	**2a** + **7a** (33 : 1)	63
$CHBr_3/CHBrCl_2$	**6a** + **5a** (3 : 2)	74
$CBr_4/CBrCl_3$	**2a** + **4a** (2 : 3)	84

* Determined by ^{1}H NMR.

To verify once again the hypothesis stating that the global electrophilicity indices and the C—Hal bond energies allow one to predict the behavior of polyhaloalkanes in the catalytic olefination, we studied the relative olefinating reactivities of a series of polyhaloalkanes toward the model hydrazone **1a** by the competing reaction technique (Scheme 21, Table 9).

Scheme 21



Ar = 4-ClC_6H_4

When a mixture of CBr_4 and CCl_4 is used, β,β-dibromostyrene **4a** is formed as the only olefination product, *i.e.*, the reactivity of CBr_4 is much higher, which is in good agreement with the relative stabilities of the C—Cl and C—Br bonds. Comparison of the activities of the CCl_4/CCl_3CF_3 and $CBr_4/CHBr_3$ pairs can serve as convincing evidence for higher reactivity of tetrahaloalkanes with respect to trihaloalkanes.

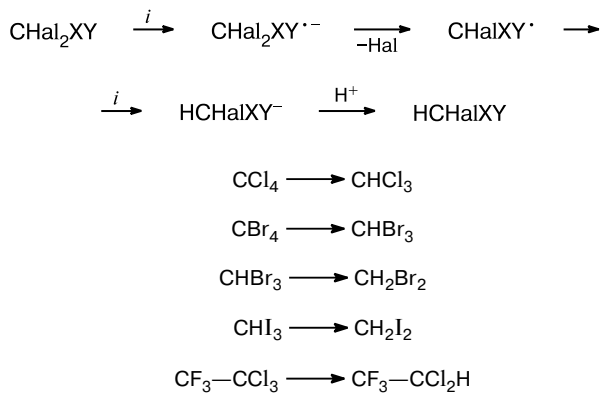
The reactivities of bromoform and bromodichloromethane are similar. β-Bromostyrene **6a** and β-chlorostyrene **5a** were obtained in 3 : 2 ratio, which is in line with the similarity of the C—Br bond energies in bromoform and bromodichloromethane. Analogous results have been obtained in the reaction with a $CBr_4/CBrCl_3$ mixture. This confirms our assumption that polyhalomethanes characterized by close energies of the weakest C—Hal bond should also have similar reactivities.

On the basis of the results obtained, we composed the following reactivity sequence for polyhaloalkanes with respect to hydrazone **1a** in the DMSO—aqueous ammonia reaction system: $CBr_4 \approx CBrCl_3 \gg CCl_4 > CHBr_3 \approx \approx CHBrCl_2 > CCl_3CF_3$.

The regularities we discovered are consistent with those predicted on the basis of calculated global electrophilicity indices (see Table 6) and bond energies (see Table 7). These results serve as additional evidence for the catalytic cycle of the **COR**.

Analysis of the compositions of reaction mixtures by GC/MS and NMR showed the presence of the products of partial reduction of polyhaloalkanes under the **COR** conditions (Scheme 22). The formation of such products during the oxidation of hydrazones to azines was predicted on the basis of analysis of the catalytic cycle (see Scheme 12, internal cycle). It was shown that the reduction of tetrahalomethanes results in haloforms, while the reduction of haloforms gives diahalomethanes. Presumably, this process is a sequence of two single-electron transfer steps. The transfer of one electron to a polyhaloalkane results in the formation of a radical anion, which then decomposes with the ejection of a halide ion. The subsequent single-electron transfer to the generated radical gives an anion, which adds a proton from the medium to give the final reduced product.

Scheme 22

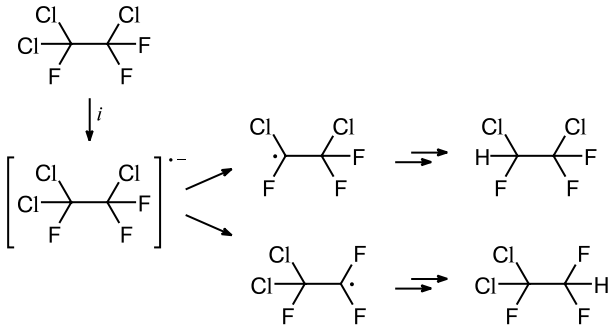


i. Single-electron transition.

Olefination with Freon-113 may give two isomeric dichlorotrifluoroethanes, $CHClF—CClF_2$ and $CHF_2—CCl_2F$, corresponding to elimination of different Cl atoms during decomposition of the radical anion, formed upon single-electron transition to the $CCl_2F—CClF_2$ molecule (Scheme 23). Indeed, both products were detected in the reaction system by GC/MS.

The detection of partial reduction products of polyhaloalkanes predicted on the basis of the catalytic cycle serves as additional evidence for the proposed reaction mechanism.

Scheme 23



i. Single-electron transfer.

Synthetic potential of the COR. Synthesis of various halo-substituted unsaturated compounds

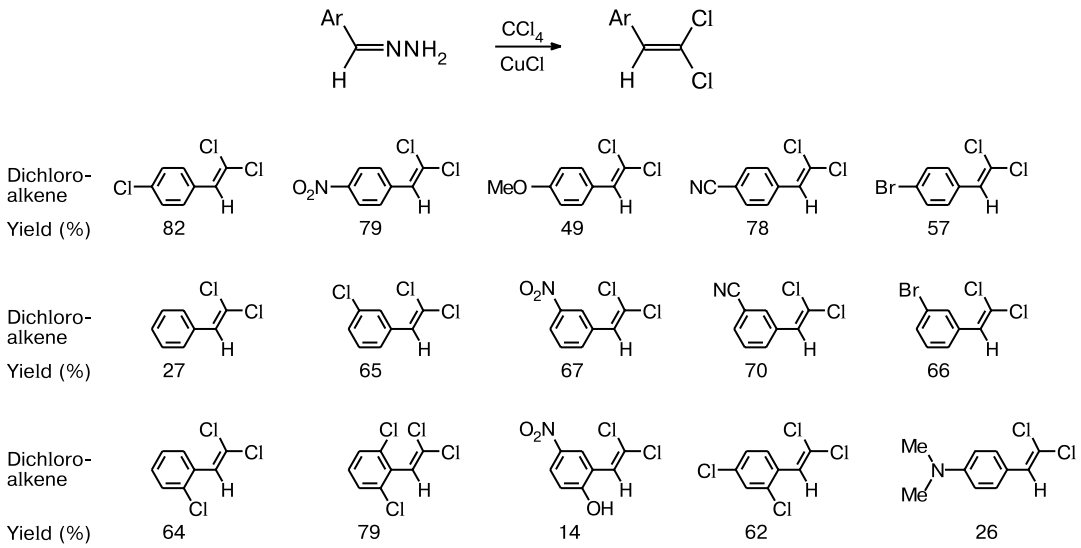
Relying on the calculations predicting the applicability of a broad range of halo-containing compounds as olefinating reagents, we proceeded to investigating the synthetic potential of the **COR** and developed new methods for the synthesis of various types of halo-substituted unsaturated compounds.

Synthesis of dichloroalkenes. On the basis of catalytic olefination, we developed a new method for the synthesis of β,β-dichlorostyrenes from hydrazones of aromatic aldehydes.[33,36] To elucidate the role of substrates, the reaction was performed with hydrazones of substituted benzaldehydes containing diverse substituents in the aromatic ring, namely, chloro, bromo, nitro, cyano, and dimethylamino groups (Scheme 24). All these substrates react with CCl_4 to be converted into the corresponding dichlorostyrenes.

Substrates containing electron-withdrawing substituents in the aromatic nucleus are converted into the target β,β-dichlorostyrenes in high yields. In the case of hydrazones with electron-releasing substituents and benzaldehyde hydrazone, the yields of dichloroalkenes are much lower. The behavior of hydrazones of substituted benzaldehydes depends little on the position of substituents in the nucleus or steric restrictions. In the reaction with 2,6-dichlorobenzaldehyde hydrazone, the corresponding alkene was obtained in 79% yield.

N-Unsubstituted hydrazones of many aldehydes are known[39] to be rather unstable compounds, being prone to oxidative dimerization. The tendency of hydrazones containing electron-releasing substituents for oxidation, and, hence, the formation of pronounced amounts of azine is mainly responsible for the low yield of dichlorostyrenes in these cases. For avoiding rather laborious isolation and purification of hydrazones and increasing the yield of dichloroalkenes, we have developed[46] a new procedure

Scheme 24

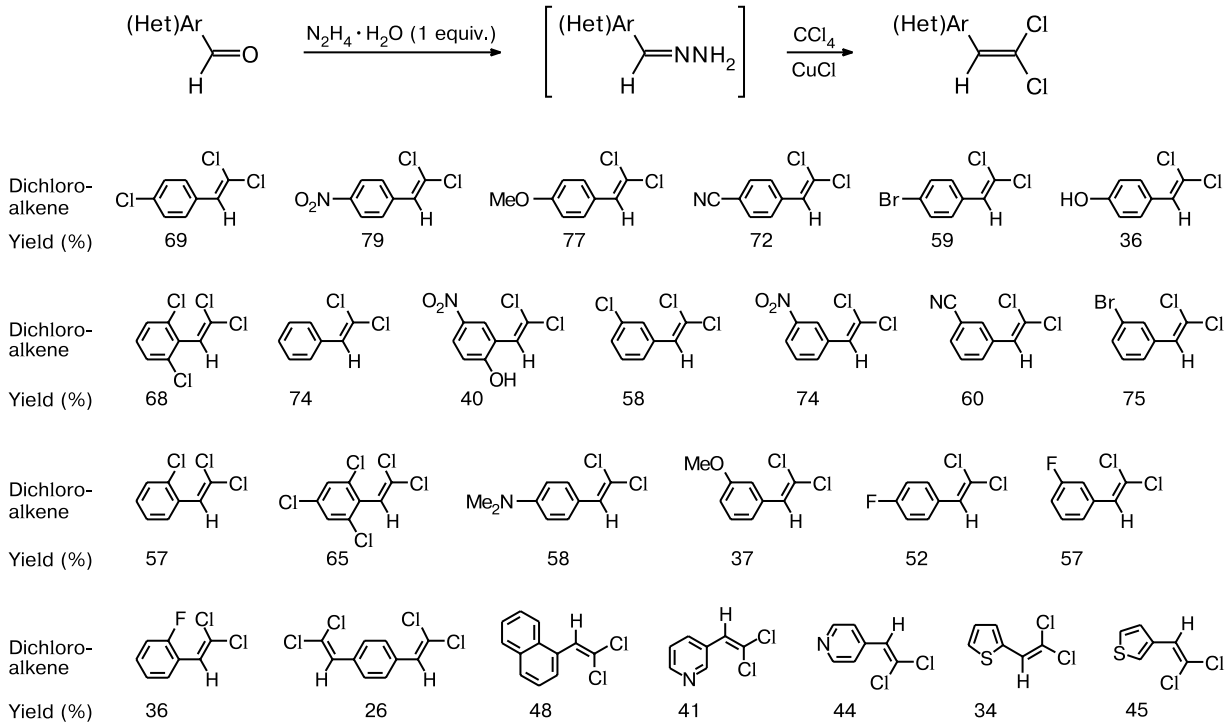


for the preparation of dichloroalkenes without intermediate isolation of the hydrazone (Scheme 25). This is a general procedure that allows the synthesis of dichlorostyrenes both with electron-releasing and electron-withdrawing substituents.[46]

Comparison of the two versions of dichlorostyrene synthesis we developed, one using hydrazones of aromatic aldehydes prepared beforehand and one using those prepared *in situ*, shows that the latter route is preferred for most of aromatic substrates; in the case of substrates with electron-releasing substituents and benzaldehyde, the yields of the target alkenes substantially increased. Along with aromatic aldehydes, heteroaromatic aldehydes of the thiophene and pyridine series were used in the reaction.

The scope of synthetic application of the catalytic olefination is not limited to aromatic aldehydes. The re-

Scheme 25



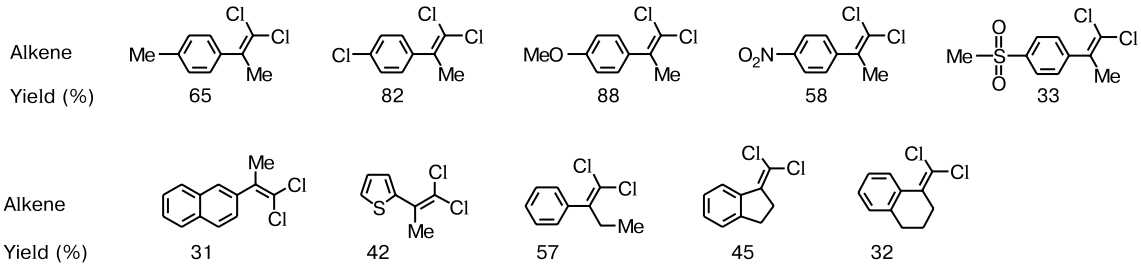
actions of alkyl aryl ketone hydrazones with CCl_4 affords[62] the corresponding tetrasubstituted dichloroalkenes, which are presented below.

Polycyclic and heterocyclic hydrazones can also be introduced into the olefination.

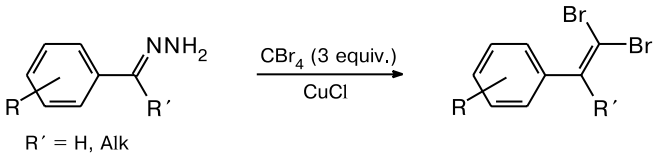
Thus, we developed a new, in principle, approach to the preparation of tri- and tetrasubstituted alkenes containing a *gem*-dichlorovinyl group based on olefination of hydrazones of aromatic aldehydes and ketones with CCl_4. By varying the structure of the starting carbonyl compounds, it is possible to obtain diverse dichloroalkenes containing alkyl, aryl, and hetaryl substituents at the double bond. The olefination is compatible with a large number of functional groups such as the sulfonyl, nitro, cyano, alkoxy, and hydroxy groups. The modified one-pot procedure is suitable for the synthesis of dichloroalkenes from both electron-releasing and electron-withdrawing substrates.

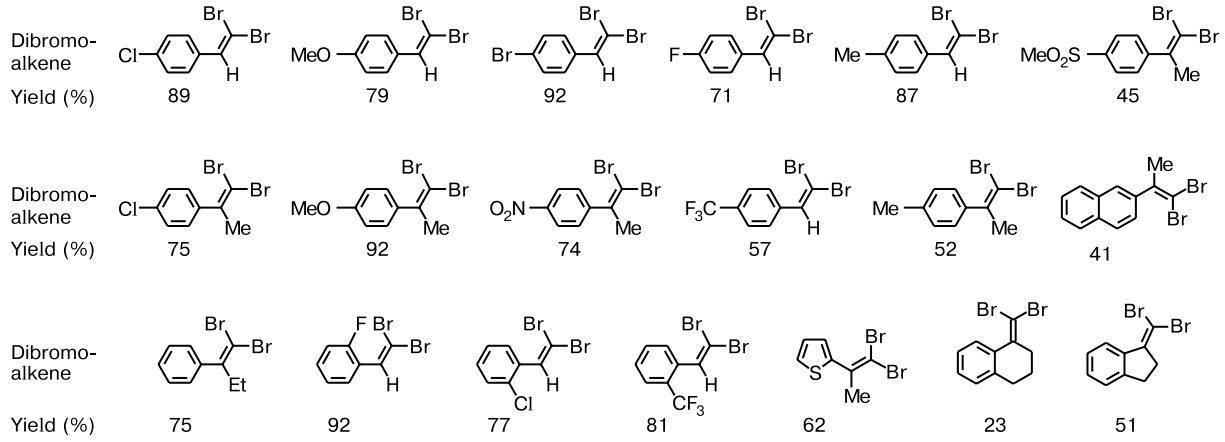
Dichloroalkenes have found extensive application in organic chemistry as precursors of acetylenes and chloroacetylenes and some other classes of compounds.[63,64] The key methods for the synthesis of *gem*-dichloroalkenes include (i) reduction of α-trichloromethylarylcarbinols or their acetates,[65—67] (ii) the Wittig[64] and the Horner—Emmons—Wadsworth reactions,[68] (iii) [2+2]-cycloaddition of dichloroketene to aldehydes followed by thermal decarboxylation of the resulting lactone,[69] (iv) reductive addition of CCl_4 to aldehydes in the presence of the lead—aluminum bimetallic system[70] or low-valence titanium compounds.[23] The necessity of using equimolar amounts or large excesses of phosphorus compounds or reducing metals is an essential drawback of these methods. As a rule, these reactions are to be carried out in an inert atmosphere using anhydrous solvents. The method of synthesis of dichloroalkanes we proposed is free from these drawbacks, which makes it rather promising.

The synthesis of dibromoalkenes. Calculations of the bond energies and global electrophilicity indices show that not only CCl_4 but also other polyhalogen-containing compounds can be used as olefinating reagents. By varying polyhaloalkanes, one can synthesize a broad spectrum of alkenes containing various substituents at the double bond. In particular, when CBr_4 is used as the olefinating

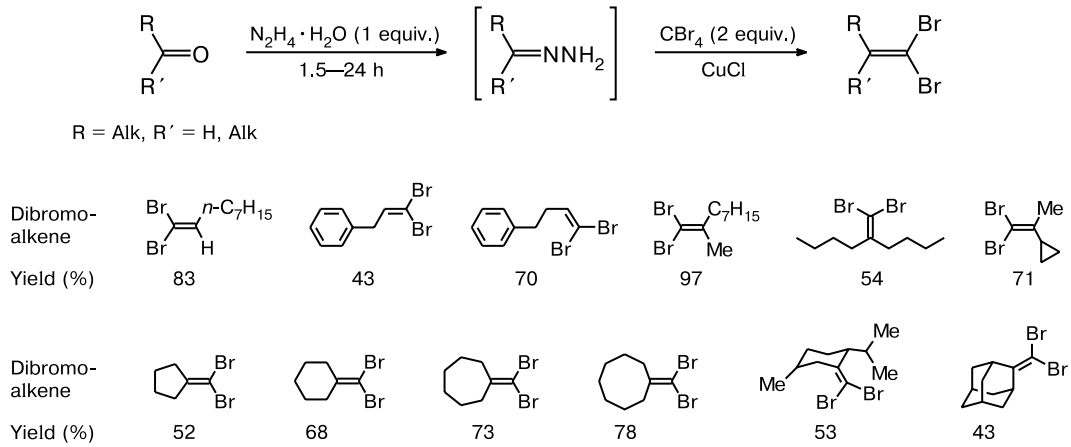


Scheme 26





Scheme 27



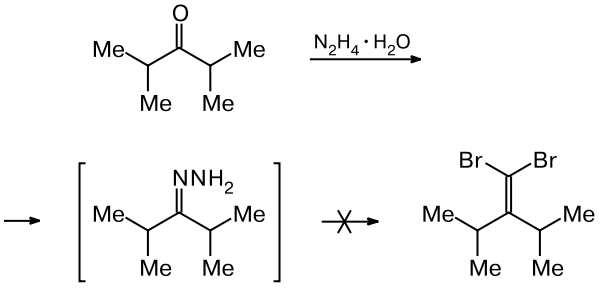
reagent, hydrazones of carbonyl compounds are converted into dibromoalkenes in high yields (Scheme 26).[71]

Unlike olefination of hydrazones of aromatic aldehydes with CCl_4, the reaction with CBr_4 proceeds in high yields even with donor substrates. Hydrazones of the series of alkyl aryl ketones behave in a similar way; the reaction gives the corresponding tetrasubstituted dibromoalkenes.[62]

The catalytic olefination reaction is very general; aliphatic aldehydes and ketones can also be used as the substrates of **COR**.[72] We have developed a procedure for direct transformation of aliphatic substrates into the corresponding 1,1-dibromoalkenes without intermediate isolation of hydrazones (Scheme 27).[72]

This reaction can be carried out for open-chain aldehydes and ketones and cyclic carbonyl compounds, which allows one to prepare both trisubstituted and tetrasubstituted *gem*-dibromoalkenes of various structures. The yields of dibromoalkenes are markedly affected by steric and electronic factors. Thus olefination of nonan-2-one gave the alkene in 97% yield, while isomeric nonan-5-one is converted into dibromoalkene in 54% yield. With even more sterically hindered ketones, diisopropyl ketone, pinacoline, and dicyclohexyl ketone, the expected dibromoalkenes have not been isolated at all (Scheme 28).

Scheme 28

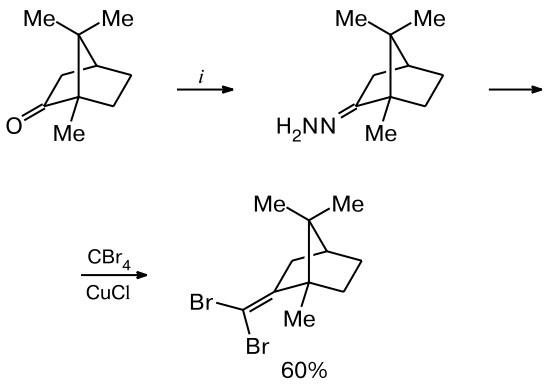


Apparently, the presence of bulky substituents near the reaction center prevents the reaction of the key intermediate, copper carbene complex with CBr_4.

It should be noted that in the reaction involving methyl cyclopropyl ketone, the cyclopropyl group is retained and the reaction gives dibromovinylcyclopropane. The possibility of using olefination for the synthesis of halovinylcyclopropanes is of particular interest, because this fragment is a part of many pyrethroids, which are widely used insecticides.[73] We also studied olefination of a number of cyloalkanones with five- to eight-membered rings. In all cases, dibromomethylene derivatives of cycloalkanes were obtained, the product yield increasing monotonically with an increase in the ring size.

The introduction in the reaction of adamantanone and camphor hydrazone furnished the corresponding alkenes, in which the alkene fragment is attached to a cage structure, in good yields (Scheme 29).

Scheme 29



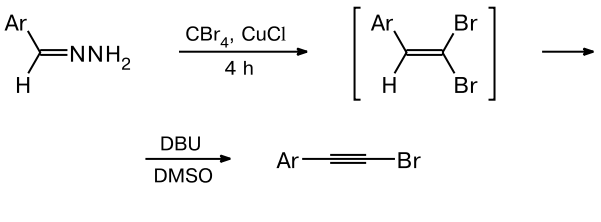
i. $N_2H_4 \cdot H_2O$ (2 equiv.), Bu^nOH, refluxing for 24 h.

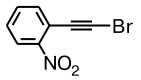
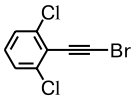
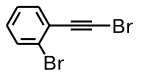
Thus, catalytic olefination is a versatile reaction in which any carbonyl compounds — aliphatic, aromatic,

and heteroaromatic aldehydes and ketones — can be used as **COR** substrates and converted into the target alkenes in high yields. The general method for the synthesis of dibromoalkenes from carbonyl compounds we developed represents a convenient alternative to the methods for the synthesis of dibromoalkenes reported in the literature. A modified Wittig reaction, *i.e.*, treatment of carbonyl compounds with CBr_4 in the presence of excess triphenylphosphine, has now remained the most general method for the synthesis of *gem*-dibromoalkenes.[74,75].

In some cases, olefination of hydrazones of aromatic aldehydes with CBr_4 is accompanied by partial dehydrobromination of the resulting *gem*-dibromoalkenes with the base present in the reaction mixture, *i.e.*, an aqueous solution of ammonia.[71] Therefore, we developed the procedure for direct transformation of the hydrazones of *ortho*-substituted benzaldehydes into terminal bromoacetylenes.[71] The reactions of dibromoalkenes obtained *in situ* with DBU results in HBr elimination to yield terminal bromoakynes (Scheme 30).

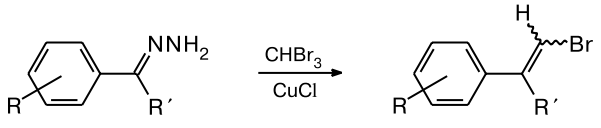
Scheme 30



Bromoacetylene	Yield (%)	Bromoacetylene	Yield (%)
	66		43
	71		

Synthesis of bromoalkenes. The use of trihalomethanes (haloforms) as olefinating reagents in the **COR** should afford monohaloalkenes. The reactions of hydrazones of aromatic aldehydes with $CHBr_3$ in the presence of CuCl give β-bromostyrenes.[76] The reaction is stereoselective, the sterically less shielded *E*-alkene being formed predominantly (Scheme 31). The *E*-/*Z*-isomer ratio for bromoalkenes is at least 5 : 1; the dependence of the isomer ratio on the nature and positions of substituents in the aromatic nucleus is ambiguous (Table 10). In the case of sterically most shielded substrate, 2,6-dichlorobenzaldehyde hydrazone, only the *E*-isomer of the vinyl bromide derivative is formed.

Scheme 31



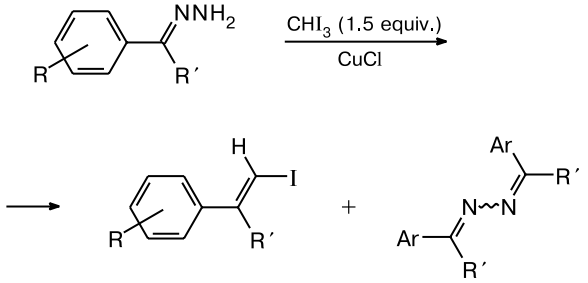
R′ = H, Me

This reaction provides a route to bromostyrenes containing either electron-donating (methoxy group) or electron-withdrawing substituents (trifluoromethyl or nitro group). The yield of vinyl bromides is usually high. The reactions of alkyl aryl ketone hydrazones with bromoform proceed in a similar way; however, the stereoselectivity of alkene formation is lower, which is due to the smaller difference between the steric volumes of substituents at the carbonyl group in ketones compared to that in aldehydes (see Table. 10).[76]

Bromoalkenes have found wide use in the stereospecific synthesis of substituted alkenes[77—81] and in the total synthesis of natural products and antibiotics.[77,82] The classical methods for the preparation of bromostyrenes include debromodecarboxylation of dibromocinnamic acids,[83] various modifications of the Hunsdiecker—Borodin reaction,[84,85] and the Wittig reaction.[86]

Synthesis of vinyl iodides. The use of iodoform as an olefinating reagent opens up a new way for the transformation of carbonyl compounds into iodoalkenes,[87] which are important reagents in the palladium-catalyzed cross-coupling.[88] We studied the reactions of a number of hydrazones of aromatic aldehydes and ketones with iodoform and showed that they are converted into iodoalkenes (Scheme 32). The reaction proceeds stereoselectively to give sterically less hindered *E*-iodoalkene as the major product (Table 11).[87]

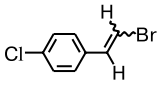
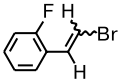
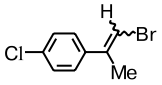
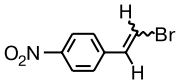
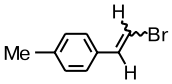
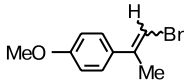
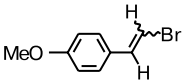
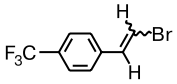
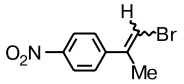
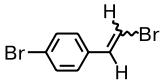
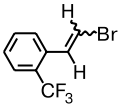
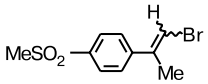
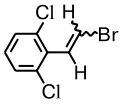
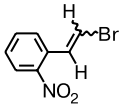
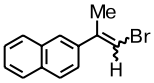
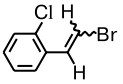
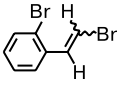
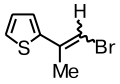
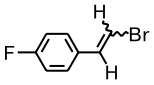
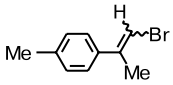
Scheme 32



R′ = H, Me

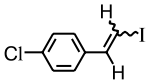
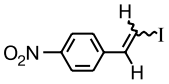
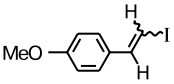
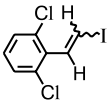
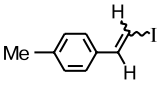
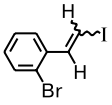
The yield of iodoalkenes is usually relatively low, azines being the major reaction products. The total yield of alkenes and azines is, most often, nearly quantitative. The yield of alkenes and the stereoselectivity of the reaction are markedly influenced by the nature of substituents in the aromatic ring and steric factors. For example, the presence of *ortho*-substituents relative to the hydrazone group favors the predominant formation of *E*-isomers.

Table 10. Synthesis of bromoalkenes

Bromostyrene	*E* : *Z**	Yield (%)	Bromostyrene	*E* : *Z**	Yield (%)	Bromostyrene	*E* : *Z**	Yield (%)
	6 : 1	67		5 : 1	84		1.4 : 1	73
	20 : 1	56		5 : 1	64		2 : 1	54
	5 : 1	60		9 : 1	29		1.3 : 1	47
	10 : 1	73		6 : 1	84		1 : 1	21
	*E*	31		5 : 1	19		3 : 1	39
	8 : 1	53		13 : 1	57		2 : 1	60
	10 : 1	52		1.3 : 1	55			

* The isomer ratio was determined from ^{1}H NMR data.

Table 11. Synthesis of iodostyrenes from hydrazones of aromatic aldehydes

Iodostyrene	*E* : *Z**	Yield (%)	
		iodostyrene	azine
	4.2 : 1	40	55
	2 : 1	28	45
	3.7 : 1	15	77
	2.8 : 1	21	69
	3 : 1	28	58
	5.2 : 1	23	—

* The isomer ratio was determined from ^{1}H NMR data.

Thus, this reaction also obeys the general **COR** pattern. Analysis of the catalytic cycle suggests a reason for the relatively low yield of the target iodoalkenes. The oxidation of hydrazones in the catalytic cycle is induced by copper(II), which is able to oxidize iodide ions present in the reaction system to elemental iodine.[34] This results in lower yields of the catalytic reaction products, namely, iodoalkenes and azines, due to the side oxidation and iodination of hydrazones.[89] Despite the relatively low yields of the target products, this reaction can serve as a convenient alternative to the methods described in the literature.

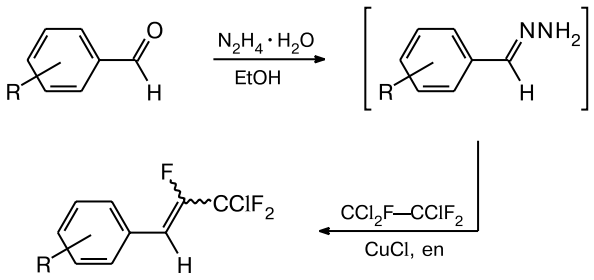
The classical methods for the preparation of iodoalkenes from carbonyl compounds are represented by the Wittig reaction[90] and the reductive coupling of aldehydes and ketones with iodoform in the presence of $CrCl_2$ as the reducing agent.[20,91] Most often, this yields mixtures of *E*- and *Z*-iodoalkenes. Stereochemically pure *E*- or *Z*-iodoalkenes can be prepared from acetylenes by multistage procedures *via* intermediate vinylsilanes[92—94] or vinylboronic acids.[95]

Synthesis of fluoro-substituted alkenes. Further research into the synthetic applications of the **COR** resulted in the development of methods for the preparation of fluorine-containing alkenes. The development of methods for the selective introduction of F atoms or fluorine-containing groups is an important task of organic chemis-

try.[96] This is due to the high physiological activities of many fluorine-containing compounds.[97] The use of chlorofluoroalkanes (Freons) and bromofluoroalkanes as olefinating reagents in the **COR** underlies a pathway to fluorine-containing alkenes. In addition, utilization of toxic and environmentally hazardous Freons and their transformation into valuable synthetic products remains a topical task. It should be noted that the presence of F atoms in the molecule of the polyhalogen-containing reagent results in pronounced strengthening of all of the C—Hal bonds (see Table 7) and in a noticeable decrease in the global electrophilicity index (see Table 6), which makes fluorine-containing compounds chemically inert. It was found that activation of Freons as olefinating reagents implies modification of the reaction conditions, in particular, ethanol is used as the solvent and 1,2-ethylenediamine is used as the base. Probably, this pronounced effect of the solvent and the base is related to the higher solubility of Freons in alcohol than in DMSO and to stronger complexation of the copper catalyst with ethylenediamine, resulting in a higher catalytic activity and a change in the redox potential.

A series of substituted aromatic aldehydes have been converted into (3-chloro-2,3,3-trifluoroprop-1-enyl)arenes by the reaction with 1,1,2-trichloro-1,2,2-trifluoroethane $CCl_2F—CClF_2$ (Scheme 33).[98] The alkenes obtained in this way have both a F atom and a $CClF_2$ group at the double bond. Compounds of this type have been unknown before. The active Cl atom in the allylic position in these molecules provides a pathway to further functionalization of the products. The yields of fluorine-containing alkenes vary over a broad range, from 19 to 66% (Table 12).[98] Using this approach, substrates containing electron-releasing groups, those containing electron-withdrawing groups, and 1-naphthaldehyde have been introduced in the reaction.

Scheme 33

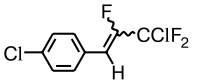
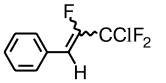
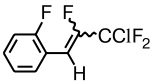
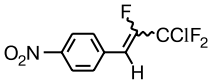
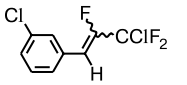
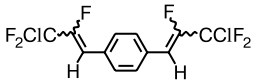
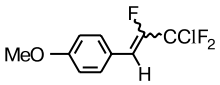
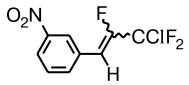
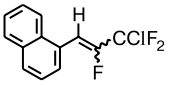
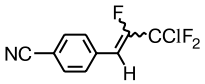
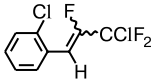
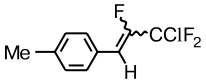
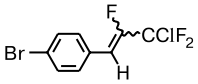
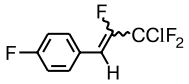


en is 1,2-ethylenediaine

The synthesis of fluoroalkenes proceeds stereoselectively to give mainly the sterically less shielded *Z*-alkene, the ratio of alkene isomers being directly related to the nature of the aromatic system. The highest stereoselectivity is observed for 1-naphthaldehyde (only *Z*-isomer is formed) and 4-methoxybenzaldehyde (the *Z*-/*E*-isomer ratio is 19 : 1). In the case of substrates containing electron-withdrawing groups, the selectivity of alkene formation decreases.

In addition to Freon-113, $CCl_2F—CClF_2$, we attempted to use the isomeric 1,1,1-trichloro-2,2,2-trifluoroethane, $CCl_3—CF_3$, as a C_2-building block providing a carbonyl substrate molecule with a trifluoromethyl

Table 12. Synthesis of (3-chloro-2,3,3-trifluoroprop-1-enyl)arenes

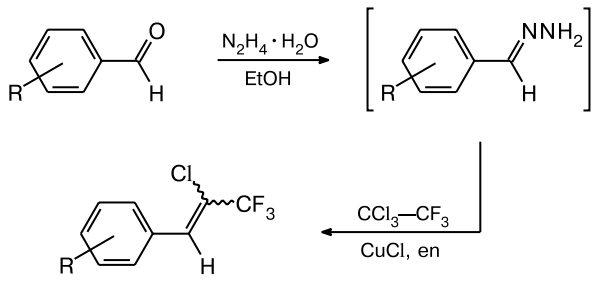
Alkene	*E* : *Z**	Yield (%)	Alkene	*E* : *Z**	Yield (%)	Alkene	*E* : *Z**	Yield (%)
	10 : 1	46		13 : 1	39		4 : 1	33
	6 : 1	63		11 : 1	48		7 : 1**	19
	19 : 1	49		4 : 1	63		*Z*	48
	6 : 1	35		7 : 1	24		16 : 1	66
	6 : 1	55		13 : 1	36			

* The isomer ratio was determined from ^{1}H NMR data.

** (*Z*,*Z*)- and (*Z*,*E*)-isomer mixture.

group (Scheme 34).[98] Development of new methods for the synthesis of trifluoromethyl-containing alkenes is very important. Indeed, many synthetic pyrethroids, highly active and widely used insecticides, contain a trifluoromethylchlorovinyl fragment.[73] Previously, these alkenes have been synthesized most often by reductive coupling of aldehydes with $CCl_3—CF_3$ or $CHClBrCF_3$ in the presence of zinc or triphenylphosphine.[99—101]

Scheme 34



en is 1,2-ethylenediaine

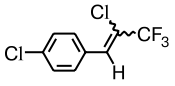
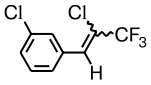
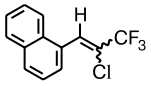
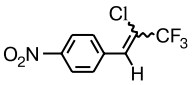
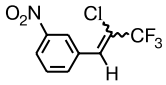
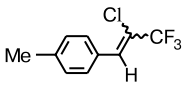
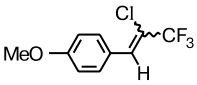
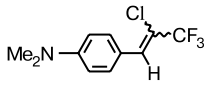
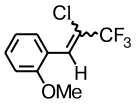
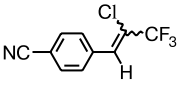
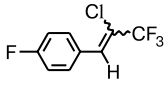
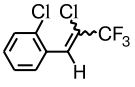
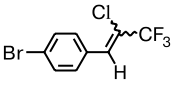
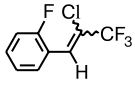
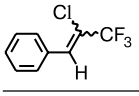
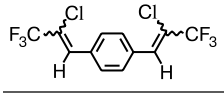
As a rule, the reactions proceed in high yields for both electron-releasing and electron-withdrawing substrates (Table 13).[98] However, the proposed method for the synthesis of trifluoromethylstyrenes is sensitive to steric restrictions in the substrate. The presence of *ortho*-substituents relative to the carbonyl group in the ring results in a pronounced decrease in the yields of target alkenes. Probably, this is due to the large bulk of the reagent, Freon $CCl_3—CF_3$, which entails enhanced steric requirements to the substrate.

The formation of trifluoromethyl-containing alkenes is stereoselective, giving predominantly the *Z*-isomer with a *trans*-arrangement of the aromatic system and the CF_3 group. The *Z*- to *E*-isomer ratio of the alkenes obeys the same regularities as those found previously for the reactions of hydrazones with the Freon $CCl_2F—CClF_2$. The presence of electron-releasing substituents promotes the predominant formation of *Z*-olefin. The best stereoselectivity (a *Z*-/*E*-isomer ratio of 10 : 1) is attained for substrates containing a methoxy group or a naphthalene system, and in the case of dimethylaminobenzaldehyde, only the *Z*-isomer of alkene is produced.

Most often, the yields of the target alkenes for the same substrates are higher with $CCl_3—CF_3$ than with isomeric $CCl_2F—CClF_2$. However, the stereoselectivity of formation of alkenes $CH=C(Cl)—CF_3$ from $CCl_3—CF_3$ is normally somewhat lower than that for the formation of isomeric alkenes $CH=C(F)—CClF_2$ from $CCl_2F—CClF_2$. This can be easily understood, because the steric requirements of the substituents at the double bond (the Cl atom and the trifluoromethyl group) are less different than those of the F atom and the chlorodifluoromethyl group.

We also used the trichlorofluoromethane CCl_3F (Freon-11) as a fluorine-containing C_1-building block.[102] The reactions give the corresponding chlorofluorostyrenes

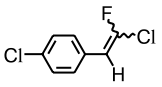
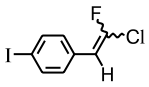
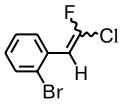
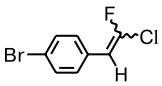
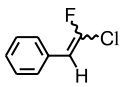
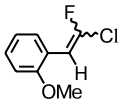
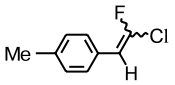
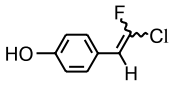
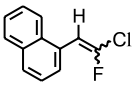
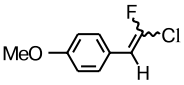
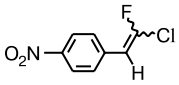
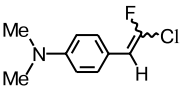
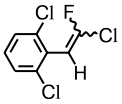
Table 13. Synthesis of trifluoromethyl-containing alkenes

Alkene	*E* : *Z**	Yield (%)	Alkene	*E* : *Z**	Yield (%)	Alkene	*E* : *Z**	Yield (%)
	7 : 1	73		4 : 1	57		10 : 1	47
	7 : 1	67		3 : 1	57		6 : 1	72
	10 : 1	56		*Z*	31		6 : 1	22
	3 : 1	61		4 : 1	34		4 : 1	40
	6 : 1	63		3 : 1	32			
	6 : 1	27		2 : 1**	24			

* The isomer ratio was determined from ^1H NMR data.

** (*Z*,*Z*)- and (*Z*,*E*)-isomer mixture.

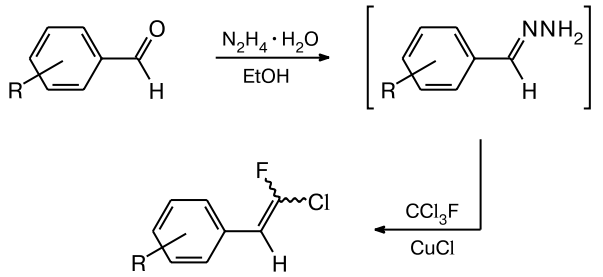
Table 14. Synthesis of fluorochloroalkenes

Alkene	*E* : *Z**	Yield (%)	Alkene	*E* : *Z**	Yield (%)	Alkene	*E* : *Z**	Yield (%)
	2.6 : 1	78		2.5 : 1	55		2.7 : 1	81
	2.4 : 1	68		2.8 : 1	62		3.2 : 1	61
	3.3 : 1	65		3.5 : 1	54		5 : 1	57
	4 : 1	50		2 : 1	52			
	4.2 : 1	35		10 : 1	68			

* The isomer ratio was determined from ^{1}H NMR data.

(Scheme 35). The product yields are usually high, thermodynamically more stable *E*-isomers being formed predominantly (Table 14)[102].

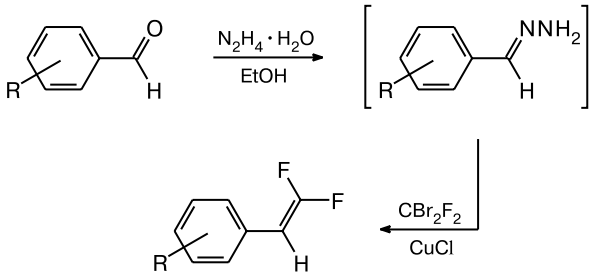
Scheme 35

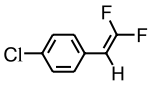
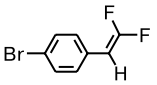
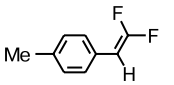
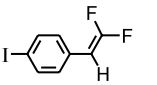
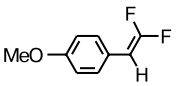
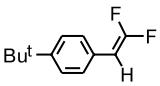
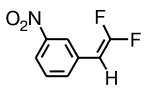


Bromofluoroalkenes and chlorofluoroalkenes are used in palladium-catalyzed cross-coupling reactions.[103] Previously,[104–107] these chlorofluoroalkenes were obtained by the Wittig reaction using chlorofluoromethylenephosphorane $CClF{=}PPh_3$.

By using dibromodifluoromethane CBr_2F_2 as the olefinating reagent, one can transform hydrazones of carbonyl compounds into valuable *gem*-difluorostyrenes (Scheme 36).[108] The relatively low yields of the olefination products[108] can be attributed to rather high energy of the C—Br bond in dibromodifluoromethane and to the low global electrophilicity index of this compound caused by the presence of two F atoms in the reagent molecule. Nevertheless, owing to mild reaction conditions, this method is a convenient alternative to the classical syntheses of difluoroalkenes.

Scheme 36



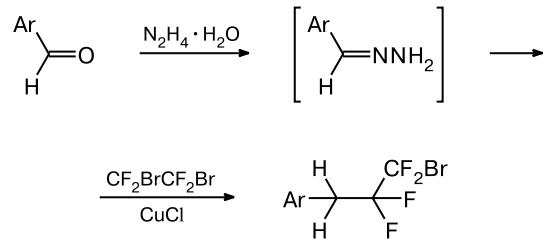
Difluorostyrene	Yield (%)	Difluorostyrene	Yield (%)
	36		31
	26		33
	20		29
	20		

gem-Difluoroalkenes have found extensive use in the synthesis of various fluorine-containing compounds.[109] They are usually prepared by the Wittig reaction with the difluoromethylenephosphorane $CF_2{=}PPh_3$.[110,111] 2,2-Difluorostyrenes have also been prepared by the palladium-catalyzed cross-coupling of aryl halides with 2,2-difluoro-

vinylzinc[112] or by thermal decarboxylation of α,α-difluoro-β-lactones.[113]

The reactions of hydrazones of aromatic aldehydes with $CBrF_2—CBrF_2$ follow an abnormal route (Scheme 37). They give no unsaturated compounds, but afford instead arylbromotetrafluoropropanes.

Scheme 37



This unusual reaction route is nevertheless quite consistent with the proposed general mechanism of the **COR** (see Scheme 12). Copper carbene complex **I** reacts with $CBrF_2—CBrF_2$ to give the organocopper intermediate **II**, which can hardly be expected to split off CuBrF due to the high strength of the C—F bond (Scheme 38). The formal hydrolysis of intermediate **II** appears to be more likely; therefore, only a saturated compound is produced. On the basis of this reaction, we developed a method for the synthesis of arylbromotetrafluoropropanes, representing a previously unknown type of organic compounds (see Scheme 38).*

These compounds can be used to prepare a broad range of other fluorine-containing products. Thus treatment of arylbromotetrafluoropropanes with an alcohol solution of alkali results in stereospecific elimination of one HF molecule to give previously unknown (3-bromo-2,3,3-trifluoroprop-1-en-1-yl)arenes in almost quantitative yields (Scheme 39).*

Treatment with a stronger base, potassium *tert*-butoxide, induces elimination of two HF molecules giving rise to arylacetylenes containing a bromodifluoromethyl group (Scheme 40).* This reaction also gives high product yields.

It is noteworthy that both types of previously unknown fluoro-containing compounds contain a highly active Br atom in allylic or propargylic positions, respectively; therefore, it appears quite pertinent to study the synthetic potential of these products.

The reactions of arylbromotetrafluoropropanes with butyllithium lead to the synthesis of a new type of fluorine-substituted unsaturated compounds containing a trifluoroallyl system (Scheme 41).* The putative mechanism of this reaction includes the replacement of Br by Li followed by β-elimination of LiF.

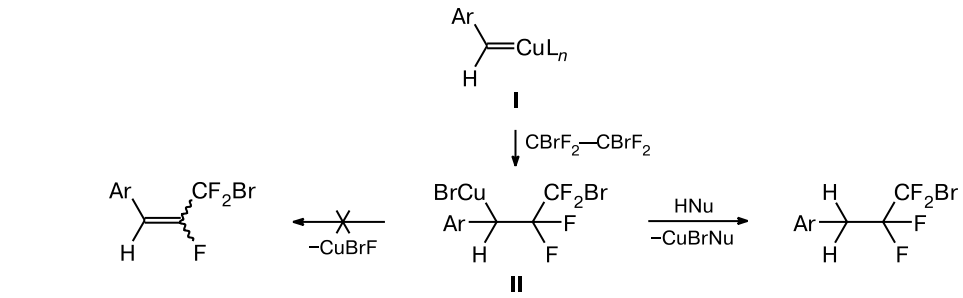
Thus, new approaches to the synthesis of various classes of fluoro-containing alkanes, alkenes, and alkynes using various Freons as the C_1 and C_2 building blocks have been developed on the basis of the **COR**.

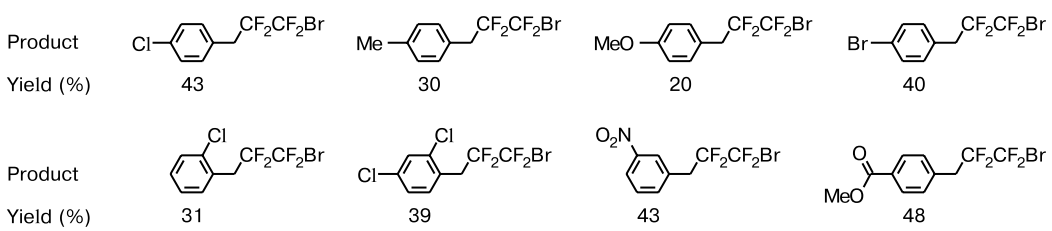
Synthesis of functionally substituted unsaturated compounds. As shown by calculations of the bond energies (see Table 7) and global electrophilicity indices (see

* V. G. Nenaidenko, G. N. Varseev, V. N. Korotchenko, A. V. Shastin, and E. S. Balenkova, *J. Fluorine Chem.*, the paper is being prepared for publication.

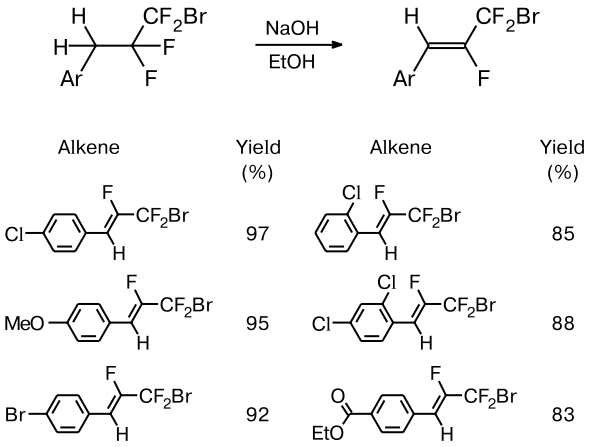
* V. G. Nenaidenko, G. N. Varseev, V. N. Korotchenko, A. V. Shastin, and E. S. Balenkova, *J. Fluorine Chem.*, the paper is being prepared for publication.

Scheme 38





Scheme 39



Scheme 40

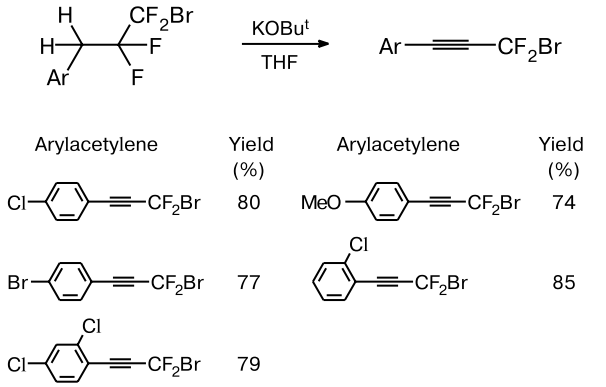
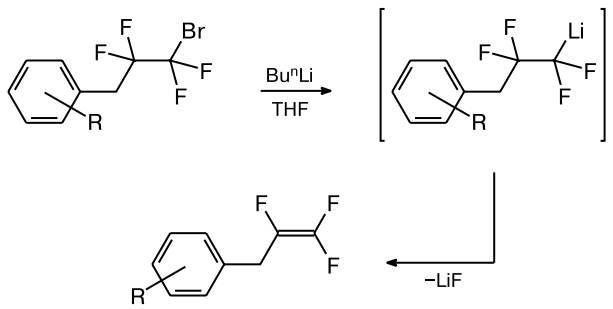


Table 6), the introduction of electron-withdrawing functional groups (NO_2, CN, COOR, $CONR_2$) into the molecule of an olefinating reagent is expected to increase their reactivity toward the **COR**. The use of polyhalogen-containing compounds with functional groups as olefinating reagents appears especially promising, as it allows one to prepare alkenes with diverse functional groups.

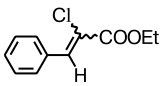
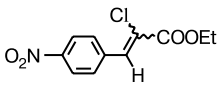
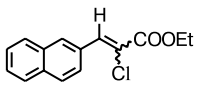
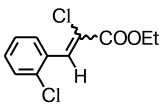
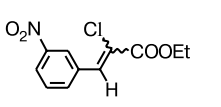
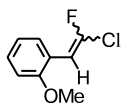
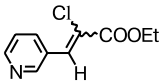
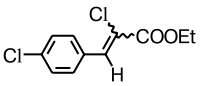
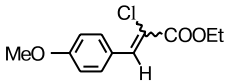
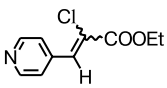
Scheme 41



The reactions of aromatic aldehyde hydrazones with ethyl trichloroacetate in the presence of catalytic amounts of $CuCl_2$ afford ethyl α-chlorocinnamates (Scheme 42). These unsaturated compounds are widely used as building blocks in the synthesis of amino acids, aziridines, and some other heterocyclic systems.[114–118] Previously, these α,β-unsaturated esters have been prepared by the Wittig and Horner—Emmons—Wadsworth reactions,[119] the Knoevanagel condensation of aldehydes with halo-substituted CH acids,[120] carbonylation of vinyl halides in the presence of transition metals,[121] chlorination of alkyl cinnamates,[122] and reductive coupling of ethyl trichloroacetate with carbonyl compound in the presence of zinc.[123]

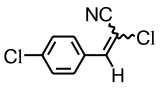
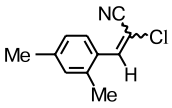
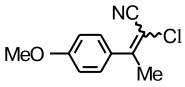
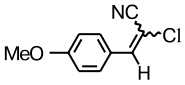
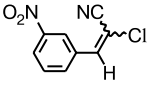
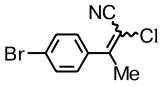
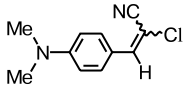
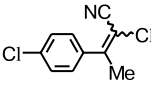
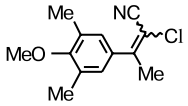
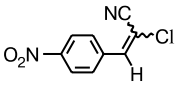
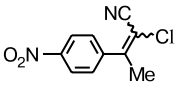
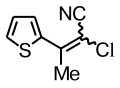
The product yields are high with both electron-releasing and electron-withdrawing substrates (Table 15).[124] The stereoselectivity of formation of α,β-unsaturared esters is also rather high. This makes this method a convenient alternative to conventional methods for the synthesis of such compounds.

Table 15. Synthesis of alkyl α-chlorocinnamates

Product	*E* : *Z**	Yield (%)	Product	*E* : *Z**	Yield (%)	Product	*E* : *Z**	Yield (%)
	6 : 1	58		6 : 1	49		6 : 1	41
	5 : 1	41		5 : 1	60		5 : 1	40
	5 : 1	57		6 : 1	60		9 : 1	53
	9 : 1	36						

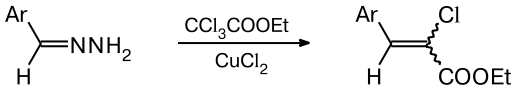
* *E*- : *Z*-isomer ratio.

Table 16. Synthesis of α-chlorocinnamonitriles

Product	*E* : *Z**	Yield (%)	Product	*E* : *Z**	Yield (%)	Product	*E* : *Z**	Yield (%)
	4 : 1	51		2.3 : 1	57		1.3 : 1	78
	1.6 : 1	66		1.5 : 1	37		1.8 : 1	63
	1.2 : 1	40		1.6 : 1	74		1.5 : 1	61
	2.2 : 1	29		3.8 : 1	52		2 : 1	44

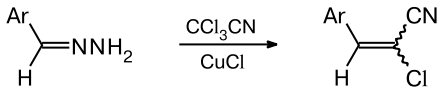
* *E*- : *Z*-isomer ratio.

Scheme 42



When trichloroacetonitrile is used as the olefinating reagent, the reaction gives α,β-unsaturated chlorocinnamonitriles (Scheme 43, Table 16),[125] which are also widely used to prepare N-, S-, and O-containing heterocycles.[117] Previously, such nitriles have been prepared by the Wittig reaction,[126,127] chlorine addition to cinnamonitriles followed by elimination of HCl,[128] the reactions of alkyl α-cyanocinnamates with chlorine followed by decarboxylation,[129] and the reaction of carbonyl compounds with 1-chloro-1-cyanoketene.[130]

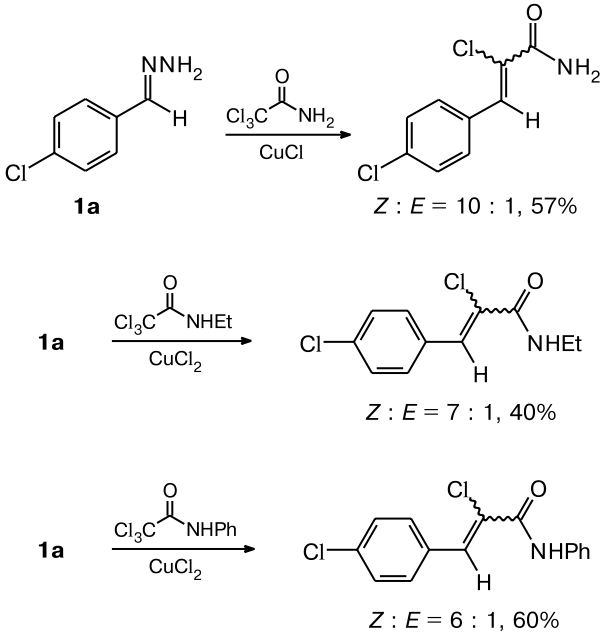
Scheme 43



This reaction also gives products in acceptable yields; however, the reaction stereoselectivity is relatively low, which is related to similar steric requirements of the Cl atom and the nitrile group. The *E*-alkene in which the Cl atom and the aromatic system are located in the *trans*-positions relative to each other is formed as the major product, which is due to the smaller volume of the cyano group with respect to the Cl atom (the conformational energies are 0.17 and 0.43 kcal mol^{-1}, respectively).[131]

The use of other olefinating reagents containing functional groups is also of considerable interest. The reaction of hydrazone **1a** with trichloroacetamide or with substituted amides furnishes the corresponding α,β-unsaturated amides (Scheme 44).* The reaction is highly stereoselective; the products formed can also serve as promising precursors of various heterocyclic systems.

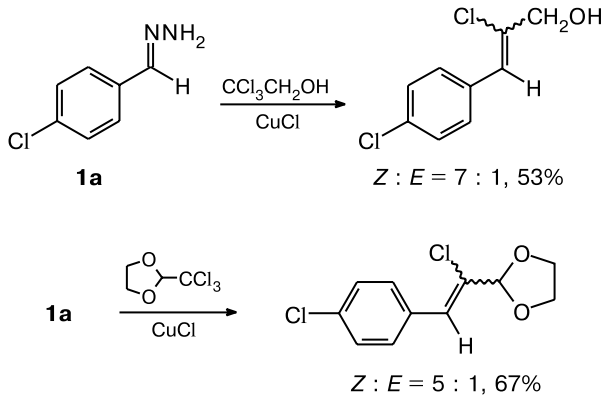
Scheme 44



The use of trichloroethanol and 2-(trichloromethyl)-1,3-dioxolane also results in the synthesis of unsaturated compounds, allyl alcohol and chlorocinnamic aldehyde acetal, respectively (Scheme 45).*

* V. G. Nenaidenko, A. V. Shastin, O. N. Lenkova, and E. S. Balenkova, unpublished data.

Scheme 45

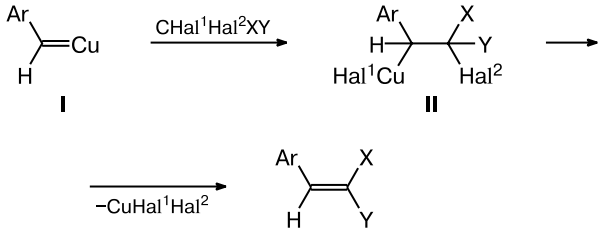


The use of functionally substituted reagents in the **COR** provides the routes to a broad range of unsaturated compounds with various functions, both electron-withdrawing and electron-releasing ones. The products thus formed are exceptionally promising building blocks for further transformations, especially in the synthesis of heterocycles.

Chemo- and stereoselectivity of alkene formation

When the polyhaloalkane molecule contains simultaneously different halogen atoms, they may split off competitively under the reaction conditions, which may give rise to different types of alkenes. However, practically, reactions with these "mixed" reagents give predominantly or exclusively only one of the possible types of alkene

Scheme 46



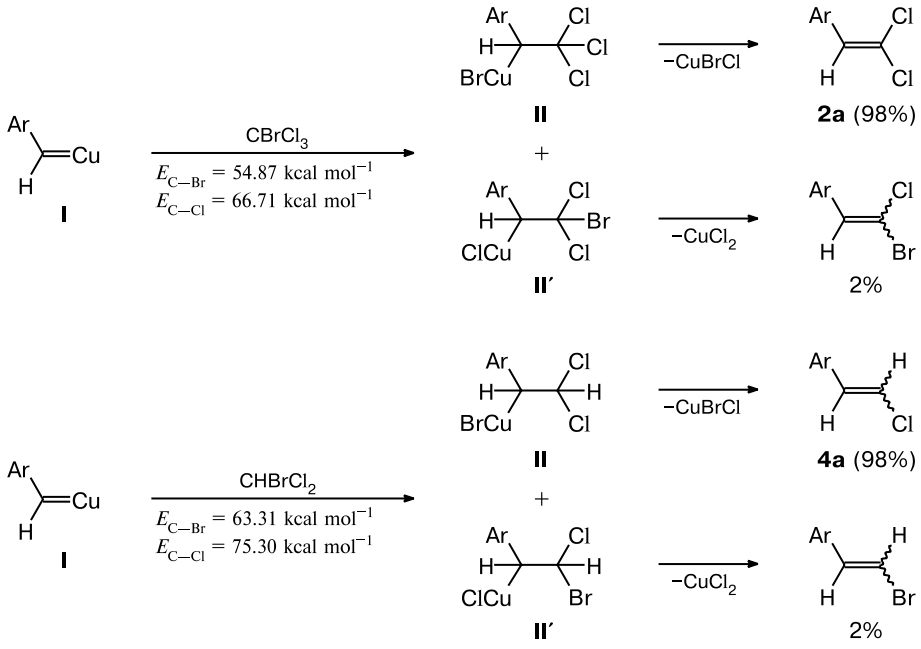
Ar = 4-ClC_6H_4

$E_{C-Hal^1} < E_{C-Hal^2}$

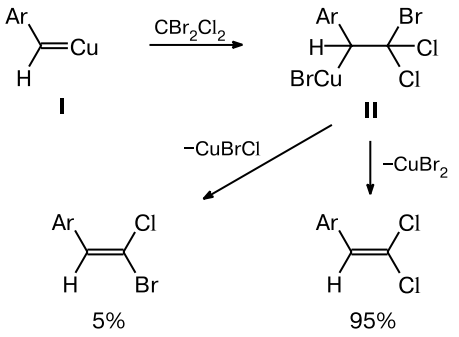
(Scheme 46). In the discussion of the reaction mechanism (see Scheme 12), we demonstrated that oxidative addition of the copper carbene complex **I** to polyhaloalkanes to give intermediates of type **II** is the key reaction step. The subsequent elimination of the Cu^{II} salt from these intermediates yields alkenes. If the polyhaloalkane contains different halogen atoms, the first step should be insertion of the Cu atom into the least strong C—Hal bond (see Scheme 46).[132] Thus, the oxidative addition step should proceed with high chemoselectivity, thus determining the chemoselectivity of the whole transformation.

However, detailed analysis of the composition of the resulting products formed from reagents containing both Cl and Br atoms demonstrated that mono- and polybromine-containing reagents react with different chemoselectivities. The studies were carried out in relation to a model substrate, 4-chlorobenzaldehyde hydrazone **1a**.

Scheme 47



Scheme 48



The reagents containing only one Br atom ($CBrCl_3$, $CHBrCl_2$) react with copper carbene complex **I** to give predominantly intermediate **II**, the subsequent β-elimination of CuBrCl from which gives alkenes **2a** and **4a** containing no Br (Scheme 47).

Analysis of the composition of the reaction products by GC/MS showed the presence of trace amounts of bromine-substituted alkenes formed from intermediate **II´**, resulting from copper insertion into the C—Cl bond of the starting reagent.

If the starting reagent contains more than one Br atom (CBr_2Cl_2, $CHBr_2Cl$), the subsequent elimination of the Cu^{II} salt can occur in two ways to give two different alkenes, the proportion of bromine-containing products being higher (Scheme 48).

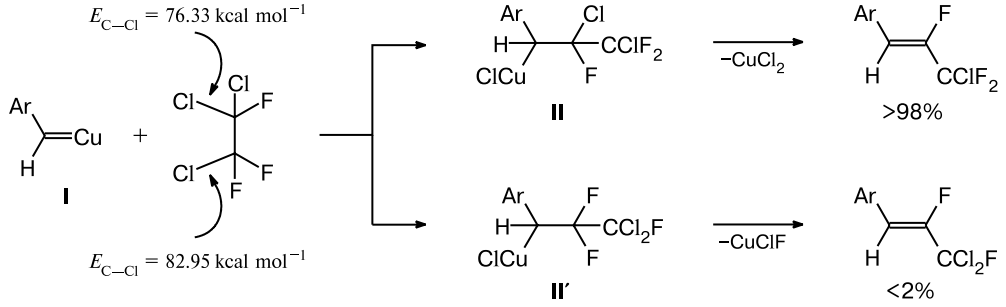
The exceptional chemoselectivity of the olefination with Freons CCl_3F and CCl_3CF_3 (no even traces of anomalous alkenes resulting from elimination of the F atoms were detected) is also due to the much higher strength of the C—F bond compared to the C—Cl bond (see Table 7). However, nonsymmetrical Freon CCl_2F—$CClF_2$ can react with the copper carbene complex **I** at either of the two ends of the molecule to give two different intermediates **II** and **II´** (Scheme 49).

The subsequent elimination of $CuHal_2$ from intermediates **II** and **II´** yields two different alkenes, although the expected alkene **7a** is formed predominantly. This is consistent with the assumption of the preferred cleavage of the weaker C—Cl bond, resulting in the organocopper intermediate **II**.

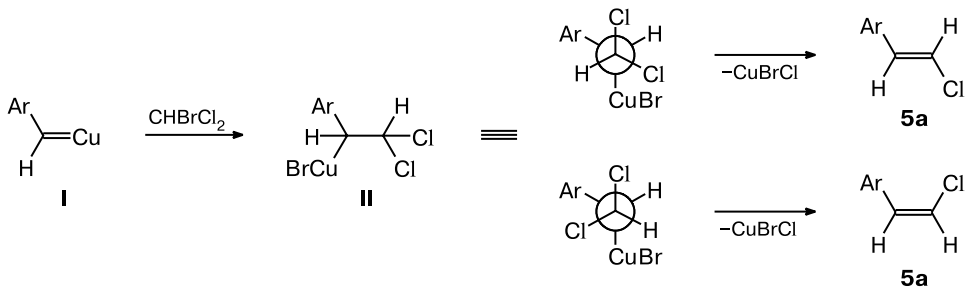
Thus, in the olefination of hydrazones with polyhaloalkanes containing different halogen atoms, the tendency of halogen atoms for elimination varies in the sequence Br > Cl ≫ F, which is consistent with the variation of the C—Hal bond energy in polyhaloalkanes.

The formation of alkenes $R^1R^2C{=}CXY$ in the olefination is stereoselective if X and Y are different substituents. We studied the factors that determine the stereochemistry of the formation of alkenes. For predicting the stereoselectivity, the conformational energy of intermediate **II**, resulting from the addition of polyhaloalkanes to the copper carbene complex **I**, was calculated for the model sub-

Scheme 49



Scheme 50



Ar = 4-ClC_6H_4

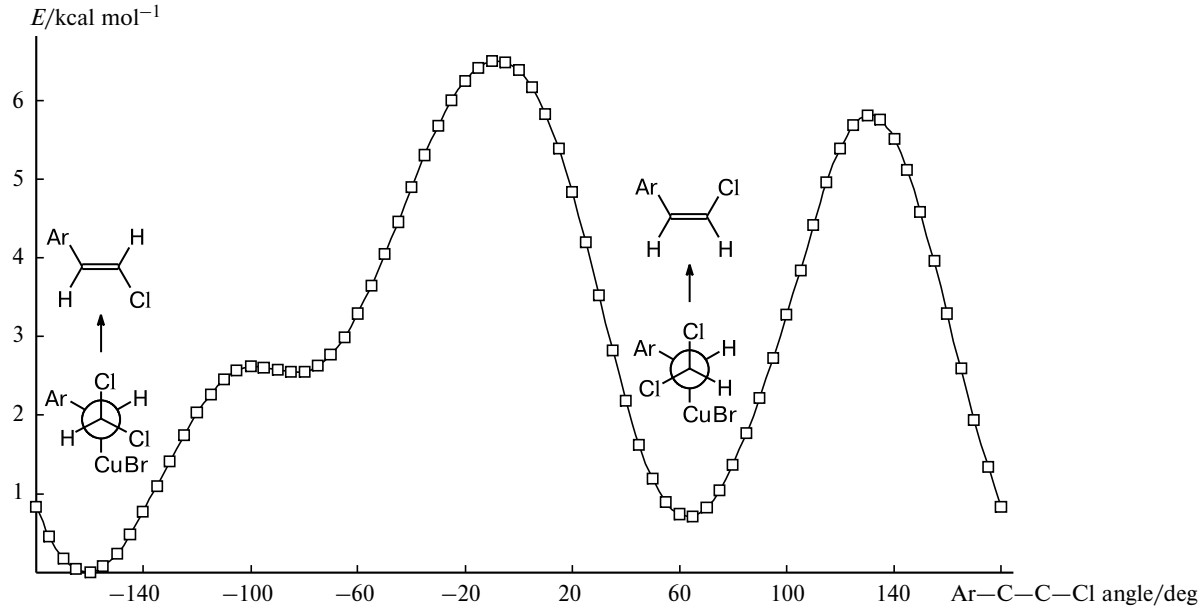
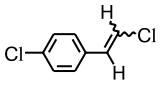
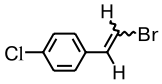
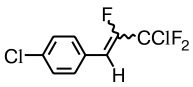
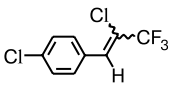


Fig. 7. Conformational energy of the intermediate **II** resulting from the addition of bromodichloromethane to the copper carbene complex **I**.

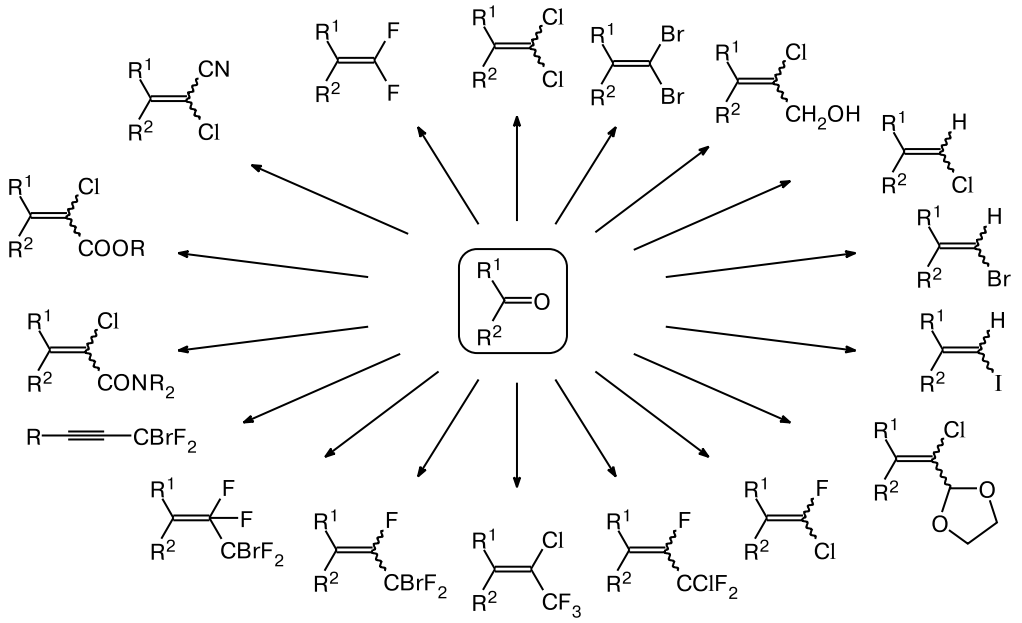
strate, 4-chlorobenzaldehyde hydrazone **1a**.[133] In the case of addition of $CHBrCl_2$, the organocopper intermediate **II** can exist as two conformers (Fig. 7), the *anti*-elimination of CuBrCl from each conformer giving rise to two geometric isomers of chlorostyrene **5a** (Scheme 50). The energy difference between two antiperiplanar conformers corresponding to minima in the conformation curves, which give two alkene isomers, should determine the ratio of the alkene isomers and the stereoselectivity of the reaction. A similar calculation was carried out for the conformational energies of the intermediates formed upon the addition of bromoform and Freons $CCl_2F—CClF_2$ and $CCl_3—CF_3$ to the copper carbene complex.

The energy differences between the conformers were used to calculate the theoretical isomer ratios for the alkenes with the assumption that conformers **II** occur in a thermodynamic equilibrium. The calculation was carried out using the formula $K = \exp[-\Delta E/(RT)]$, where ΔE is the energy difference between the corresponding minima in the conformational curves, K is the conformer ratio. Comparison of the calculated and experimental isomer ratios has shown that the results of calculations are in good agreement with experimental data. The calculations allow one to predict properly, on a qualitative level, the predominant formation of the thermodynamically more stable isomers of alkenes and the isomer ratio (Table 17).[133]

Table 17. Stereochemistry of formation of alkenes in the olefination

Reagent	Alkene	ΔE /kcal mol^{-1}	*E*-/*Z*-isomer ratio	
			Calculation	Experiment
$CHBrCl_2$		0.71	77 : 23	93 : 7
$CHBr_3$		0.67	71 : 29	86 : 14
$CCl_2F—CClF_2$		1.21	11 : 89	14 : 86
$CCl_3—CF_3$		1.89	4 : 96	12 : 88

Scheme 51



R^1 = Alk, Ar, HetAr; R^2 = H, Alk

Conclusion

Thus, we found a new highly selective catalytic olefination reaction (**COR**) of carbonyl compounds consisting of the reaction of *N*-unsubstituted hydrazones of aldehydes or ketones with polyhalogen-containing compounds in the presence of catalytic amounts of copper salts. The mechanism of catalytic olefination has been studied and the catalytic cycle describing the transformations that take place in the reaction system is proposed. The key intermediate of the reaction is a copper carbene complex. A model describing the reaction of polyhaloalkanes with the copper carbene complex and providing explanation for the observed chemo- and stereoselectivity has been proposed.

The relationship between the polyhaloalkane nature and behavior in the catalytic olefination has been identified. It was shown that the behavior of polyhaloalkanes as olefinating reagents can be predicted using a number of parameters, namely, the global electrophilicity index and the C—Hal bond energy.

The scope of synthetic application of the catalytic olefination was studied. It was shown that aliphatic, aromatic, and heteroaromatic aldehydes and ketones can be used as the carbonyl substrates and fluoro-, chloro-, bromo-, and iodoalkanes and some functionally substituted compounds are suitable as olefinating reagents. New convenient methods for the synthesis of a broad range of di-, tri-, and tetrasubstituted olefins have been developed on the basis of this reaction (Scheme 51). The simple procedures for the reaction and product isolation, mild conditions, and compatibility with a broad range of functional groups are obvious advantages of this approach to the synthesis of olefins from carbonyl compounds, which makes it a convenient tool of organic synthesis.

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