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THE MAKOSZA REACTION — FORTY FIVE YEARS AFTER*

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After 45 years, the Makosza reaction has become an increasingly important instrument in the hands of an organic synthetic chemist. At the same time we are still far from a full understanding of the mechanism of the processes which take place in this reaction. The mechanism proposed by Makosza adequately illustrates the general procedures of the catalytic process, but in a manner which doesn't take into consideration the changes in the reaction process brought by the application of different ammonium salts. These phenomena which have been discovered over the past years not only increase the applicability of PTC, but are also of essential practical and academic value. It would still seem worthy to invest time and energy in a further investigation of this process forty five years after it was first brought to light. Refs 27. Figs 1. Tables 1.

Keywords: Makosza reaction, phase, transfer catalysis, mechanism, organic synthesis.

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РЕАКЦИЯ МАКОШИ — СОРОК ПЯТЬ ЛЕТ СПУСТЯ

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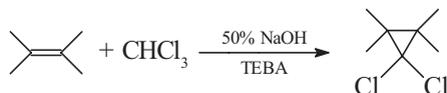
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Через 45 лет реакция Макоши стала важным инструментом в руках органиков-синтетиков. В то же время мы далеки от полного понимания механизма этих процессов. Механизм, предложенный Макошей, правильно отражает главные особенности каталитического процесса, но не пригоден к изменениям методики при использовании разных аммониевых солей. Библиогр. 27 назв. Ил. 1. Табл. 1.

Ключевые слова: реакция Макоши, межфазный катализ, механизм.

Dedicated to Professor Mieczysław Makosza on the occasion of his 80th birthday

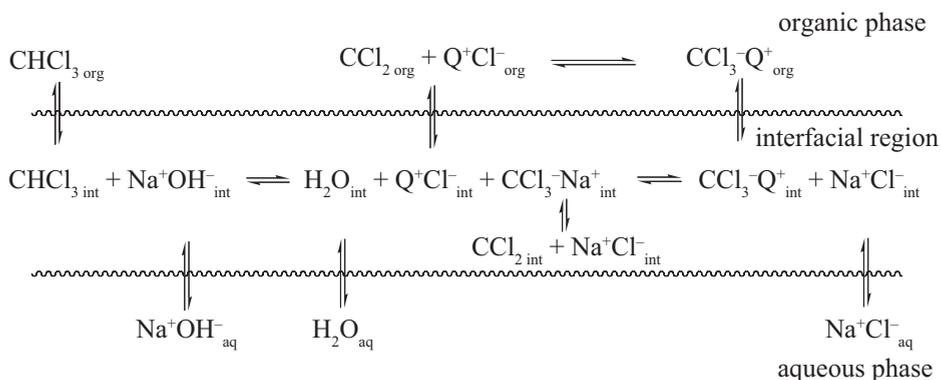
I. Introduction. One of the most important and unexpected applications of phase transfer catalysis (PTC [1–8]) is no doubt generation of dihalocarbenes from haloforms via α -elimination process, carried out in the presence of concentrated aqueous NaOH solution and lipophilic tetraalkylammonium (TAA) salt acting as a catalyst. Carbene thus formed can be trapped with alkenes with the formation of *gem*-dihalocyclopropane derivatives in high yields. This reaction, described in 1969 [9], is now commonly known as Makosza reaction.



I had the honor and pleasure to work with prof. Makosza since the discovery of the reaction, now bearing his name (I graduated at Faculty of Chemistry, Warsaw University of Technology in 1969). For many years under his direction and then on my own I worked on this fascinating field of chemistry and watched its rapid development, which has been made possible thanks to introduction of the PTC to the practice of organic synthesis.

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According to the commonly accepted mechanism of dichlorocarbene generation in two phase catalytic systems, proposed by Mąkosza in 1975 [10], deprotonation of chloroform occurs with high rate constant in the interfacial region of two immiscible phases: organic (chloroform, acceptor of carbene) and aqueous (concentrated NaOH solution). Sodium salts of the trichloromethyl anions thus formed cannot migrate neither to the organic, nor to the aqueous phase, but of course they can dissociate in the interfacial region to dichlorocarbene and chloride anions. Carbene, being strong electrophile, can react here rapidly with water or hydroxide anions with the formation of chloride and formate anions. Chloride anions accumulate in the interfacial region, surrounding dichlorocarbene and protecting it against further hydrolysis, but also against addition to alkenes. When a TAA salt (Q^+X^-) is present in the system, ion exchange proceeds in the interfacial region and lipophilic ion pairs “trichloromethyl anion — quaternary ammonium cation” are formed. These ion pairs, being fully organic can migrate into the organic phase where they dissociate to carbene and the catalyst is regenerated in this process.

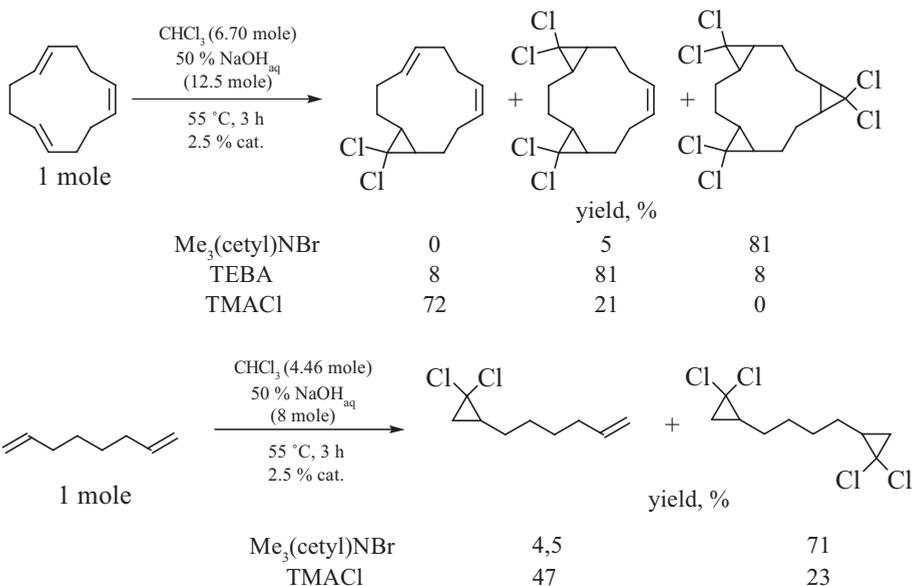


From this picture, which is now commonly accepted and supported by many observations, it is clear that the structure of the catalyst should not exert any significant effect on reaction course, providing it is lipophilic enough. It was shown however that this opinion, although in general correct, is oversimplified — the direction and selectivity of the reactions of haloforms with alkenes (especially with electrophilic ones) often depend significantly on the kind of catalyst and solvent used. Examples of such processes include: the selective preparation of *gem*-bromochlorocyclopropane derivatives from dibromochloromethane and alkenes, carried out in the presence of 50 % NaOH and dibenzo-18-crown-6 as a catalyst [11]; the synthesis of *gem*-dichlorocyclopropane derivatives from chloroform and electrophilic alkenes (50 % NaOH, tetramethylammonium, TMA, salt as a catalyst [12, 13]); syntheses of *gem*-dichlorocyclopropanes from 1-alkenyl esters and chloroform (50 % NaOH, TMA salt as a catalyst [14]), reactions of allyl halides with haloforms (addition of carbene vs. alkylation of trihalomethyl anion, depending on the kind of catalyst used [15]).

Basic principles, specific features and broad applications of PTC methodology in carbene chemistry were presented in many review papers [16–18] (see also [1–8]), so it is not necessary to repeat it here.

In this paper, we'd like to discuss two problems, which despite many trials are not fully solved yet, namely the influence of the catalyst structure on the reaction of unconjugated dienes with chloroform, carried on in PTC system, and possibility of generation of difluorocarbene and synthesis of *gem*-difluorocyclopropane derivatives in PTC reactions.

II. Reactions of unconjugated dienes with chloroform, carried out in PTC system. In 1982 Dehmlow has demonstrated for the first time: a) the possibility of applying a definitely hydrophilic catalyst — TMA chloride — for the synthesis of *gem*-dichlorocyclopropane derivatives under the PTC conditions, b) the possibility of a highly efficient synthesis of the products of monoaddition of dichlorocarbene to unconjugated di- and polyenes in the presence of this catalyst [19]. Dehmlow obtained these results by applying a considerable surplus of both chloroform (2.25×) and the base (4×) to each double bond in the di(poly)ene. Using cetyltrimethylammonium bromide as well as other lipophilic TAA salts as the catalyst he obtained polyadducts as main reaction products with high yields.



The analysis of Dehmlow's work leads to the following conclusions.

a. The results presented do not indicate that TMACl influences the reaction selectivity—conceivably we could also obtain polyaddition products in the presence of TMACl by conducting the reaction to a higher conversion.

b. Presumably, when lipophilic catalyst is used an addition of one dichlorocarbene molecule to a double bond of unconjugated diene (polyene) does not affect the reactivity of the remaining double bonds.

c. High yields of monoaddition products in reactions with the use of TMA salt are caused by the next double bond's lack of susceptibility to attack by dichlorocarbene. This speculation leads to the conclusion that the monoadduct might, by means of some unclear mechanism, be adsorbed on the surface of interfacial region by the cyclopropane fragment's end of the molecule. Such supposition is reinforced by the fact that Dehmlow achieved the best results (in the sense of monoaddition) using relatively "stiff" dienes — 1,5,9-cyclododecatriene or 4-vinylcyclohexene — whereas using 1,7-octadiene under the same conditions yielded a considerable amount of the diadduct in addition to the monoadduct.

We decided to experimentally examine the changes to the amount of the diene and the products of its reaction with dichlorocarbene as a function of the amount of dichlorocarbene added to double bonds. We used *cis,cis*-cycloocta-1,5-diene, octa-1,7-diene and deca-1,9-diene, which contains two double bonds with identical reactivity. We modeled the reaction

mathematically using the assumptions that: a) the carbene addition to the monoadduct happens at a speed k times higher than its addition to the diene and b) the carbene is supplied successively, i. e. each molecule is introduced after the previous one has been used. This last assumption is certainly satisfied under PTC conditions since in the organic phase the number of active carbene molecules is no greater than the number of the catalyst molecules used.

Let N_A , N_{AB} and N_{ABB} denote respectively the amount of diene (A), monoadduct (AB) and diadduct (ABB) in the organic phase, let N_B denote the amount of dichlorocarbene (B) which got added to the double bonds, and let N denote the initial amount of the substrate. Initially N_A , N_{AB} and N_{ABB} are equal to zero. The following formula is satisfied at all times:

$$N_B = N_{AB} + 2N_{ABB}.$$

The formulae describing the functions $N_A(N_B)$ and $N_{AB}(N_B)$ can be derived with the following reasoning.

Let's assume that one B molecule is introduced to the solution. It can encounter either an A molecule (with the probability $N_A/(N_A + N_{AB})$) or an AB molecule (with the probability $N_{AB}/(N_A + N_{AB})$). If it encounters A , the reaction $A \rightarrow AB$ may happen or not. Let's call the probability that this reaction happens p_1 . If the reaction doesn't happen, the situation does back to the beginning (i. e., B can again meet either A or AB with the previously given probabilities). If the B molecule encounters AB , the reaction $AB \rightarrow ABB$ may happen. Let's call the corresponding probability p_2 . We have assumed that B attaches itself to AB k times faster than to A , which is equivalent to saying that $p_2/p_1 = k$. As in the other case, if the reaction doesn't happen then we go back to the original situation. Let's denote the probability that the dichlorocarbene (B) eventually adds to A by $p_{A \rightarrow AB}$, and the probability that it eventually adds to AB by $p_{AB \rightarrow ABB}$. It can therefore be seen that

$$\begin{aligned} p_{A \rightarrow AB} &= \frac{N_A}{N_A + N_{AB}} p_1 + \frac{N_{AB}}{N_A + N_{AB}} (1 - p_2) p_{A \rightarrow AB} + \frac{N_A}{N_A + N_{AB}} (1 - p_1) p_{A \rightarrow AB}; \\ p_{A \rightarrow AB} \left(1 - \frac{N_A + N_{AB} - p_1 N_A - p_2 N_{AB}}{N_A + N_{AB}} \right) &= \frac{N_A}{N_A + N_{AB}} p_1; \\ p_{A \rightarrow AB} (p_1 N_A + p_2 N_{AB}) &= N_A p_1; \\ p_{A \rightarrow AB} &= \frac{N_A}{N_A + k N_{AB}}; \\ p_{AB \rightarrow ABB} = 1 - p_{A \rightarrow AB} &= \frac{k N_{AB}}{N_A + k N_{AB}}. \end{aligned}$$

Let's assume we add a very small amount of B , denoted by ΔN_B . Then $\Delta N_B p_{A \rightarrow AB}$ of A will be converted to AB , and $\Delta N_B p_{AB \rightarrow ABB}$ of AB will be converted to ABB . Therefore

$$\begin{aligned} \Delta N_{AB} &= \Delta N_B (p_{A \rightarrow AB} - p_{AB \rightarrow ABB}); \\ \Delta N_A &= -\Delta N_B p_{A \rightarrow AB}. \end{aligned}$$

Dividing both sides by ΔN_B and taking the limit $\Delta N_B \rightarrow 0$ we obtain the equations

$$\begin{aligned} \frac{dN_A}{dN_B} &= -\frac{N_A}{N_A + k N_{AB}}; \\ \frac{dN_{AB}}{dN_B} &= \frac{N_A}{N_A + k N_{AB}} - \frac{k N_{AB}}{N_A + k N_{AB}}. \end{aligned}$$

By solving this set of equations numerically for different values of k we can find which k fits any given set of experimental data best, i. e., we can find the value of k such that the sum

$$\sum_{i=1}^m \left[\left(N_{iA}^{\text{theoretic}} - N_{iA}^{\text{experimental}} \right)^2 + \left(N_{iAB}^{\text{theoretic}} - N_{iAB}^{\text{experimental}} \right)^3 + \left(N_{iABB}^{\text{theoretic}} - N_{iABB}^{\text{experimental}} \right)^2 \right]$$

is the least (where m is the number of the data points).

First we have examined experimentally the amounts of the substrate and the products of dichlorocarbene addition (generated under the PTC conditions in the presence of lipophilic catalysts) to *cis,cis*-cycloocta-1,5-diene, octa-1,7-diene and deca-1,9-diene. We used the same substrate proportions and reactions conditions as in Dehmlow work cited above.

Diene (0.1 mole), chloroform (0.446 mole, 53.5 g), 50 % NaOH (0.8 mole, 64 g) and the catalyst (2.5 mmole) were stirred at 50–55 °C, taking samples, the composition of which was analyzed using gas chromatography.

The experimental results were largely in agreement with the theoretical curves corresponding to the situation when the carbene adds with equal speed to the diene and to the monoadduct, i. e., the situation in which $1/k \approx 1$ (experimental results are given in the Table).

Diene	k^a			
	TEBA ^b	TBAB ^b	BTMA ^b	TMA·HSO ₄ ^c
<i>cis,cis</i> -cycloocta-1,5-diene	1.1	1.0	0.9	7.0
deca-1,9-diene	0.8	0.9	1.1	2.3
octa-1,7-diene	0.9	1.0	1.2	2.5

Note. TEBA: benzyltriethylammonium chloride; TBAB: tetrabutylammonium bromide; BTMA: benzyltrimethylammonium chloride; TMA·HSO₄: tetramethylammonium hydrogensulfate.

^a Average from three experiments. It should be noted that reproducibility of the experiments was rather poor, despite the fact we used the same reactor and stirrer. It is no doubts connected with the heterogeneity of the system.

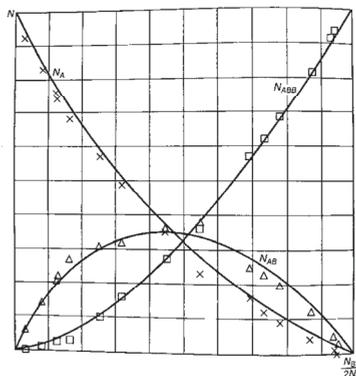
^b Full conversion of diene to bisadduct was observed.

^c We were unable to obtain full conversion of diene to bisadduct.

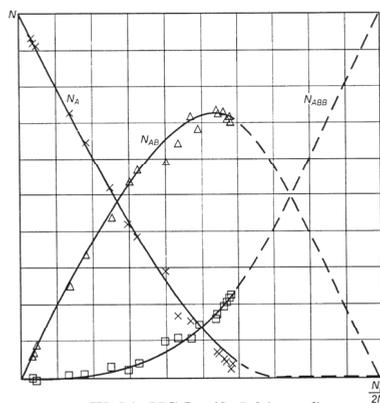
These results confirm the hypothesis that, in the presence of lipophilic catalysts, addition of one dichlorocarbene molecule to a diene's double bond doesn't change the reactivity of the other double bond.

In light of Dehmlow results cited above it is obvious that such agreement cannot take place when TMACl is used as a catalyst. Indeed the experimental results which we obtained in a reaction of the aforementioned dienes with chloroform conducted in the presence of TMA salt (2.5 % mol) are in agreement with theoretical curves corresponding to the situation when the second double bond enters the reaction slower than the first one. This could be caused by a significantly lower availability of the second double bond for the dichlorocarbene attack, caused by the presence of this bond deep in the organic phase, where dichlorocarbene, produced mainly in the interfacial region, cannot reach. However if this conjecture were true, one should expect a higher monoadduct yield (i. e., using all of the diene chiefly towards the generation of the monoadduct). In the experiments described however we did not manage

to conduct the reaction to complete conversion despite a very long reaction time. Typical graphs for the reactions of *cis,cis*-cycloocta-1,5-diene carried out in the presence of TEBA and TMA·HSO₄ are presented below, for designations see text.



TEBA (2.5 % mol)



TMA·HSO₄ (2.5 % mol)

Reagents (mole):

cis,cis-cycloocta-1,5-diene : CHCl₃ : 50 % NaOH = 1 : 4.5 : 8

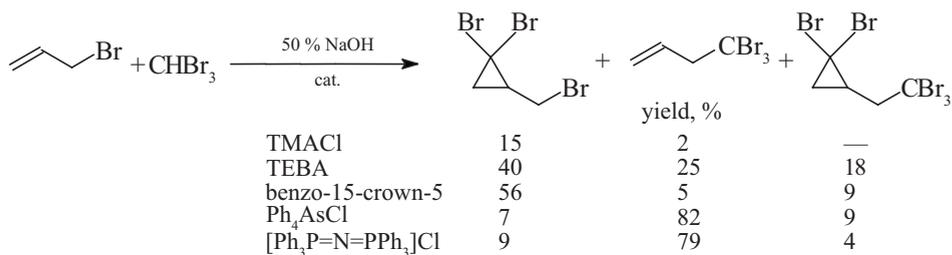
Based on this fact we can speculate that near the end of the reaction the substrate (diene) cannot get in contact with the carbene near the phases boundary, since the reaction is blocked by the monoadduct adsorbed there. Monoadduct of dichlorocarbene to *cis,cis*-cycloocta-1,5-diene in the reaction with 2.25 molar excess of chloroform, four molar excess of 50 % NaOH in the presence of TMA·HSO₄ catalyst formed diadduct with 54 % yield only. The same reaction carried out in the presence of TEBA leads to diadduct in quantitative yield. This result does not contradict the concept of adsorption of monoadduct in the interfacial region.

III. Trying to synthesize *gem*-difluorocyclopropane derivatives in PTC reactions. All attempts to prepare *gem*-difluorocyclopropanes from alkenes and difluorocarbene generated from chlorodifluoromethane in PTC systems failed till now. This is most probably due to instability of the chlorodifluoromethyl anion — the rates of deprotonation of haloform and dissociation of carbanion are similar, because of that chlorodifluoromethyl anion cannot be transferred as ion pair with the cation of the catalyst from interfacial region where it is formed into the bulk of organic phase. Instead difluorocarbene generated in the interfacial region undergoes fast hydrolysis.

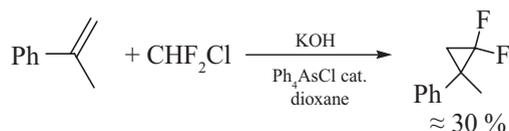
Trialkylamines are excellent catalysts of the generation of dichloro- and dibromocarbenes under PTC conditions [20]. Being strong nucleophiles they react irreversibly with these carbenes in the interfacial region with the formation of an ammonium ylide which acts as a base in the organic phase, deprotonating haloform [21]. However this approach turned out to be unsuccessful in the case of chlorodifluoromethane.

Dibromodifluoromethane enters halophilic bromination of carbanions generated from bromoform or methylene bromide in PTC system, producing in the organic phase bromodifluoromethyl anion, which dissociated here to difluorocarbene, which in turn adds to strongly nucleophilic alkenes giving difluorocyclopropanes in moderate yields [22, 23].

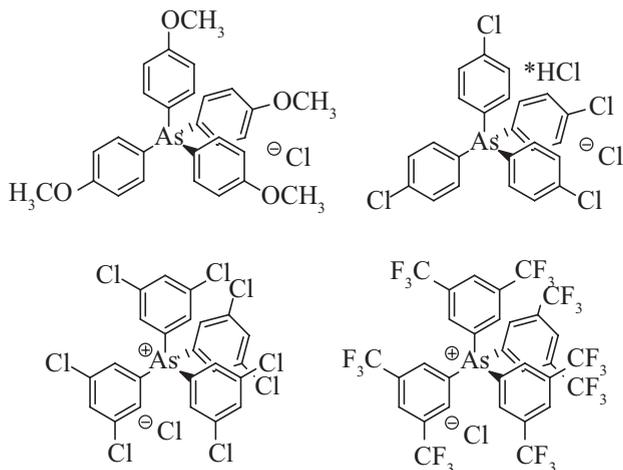
Dehmlow has found that in the reaction of allyl bromide with bromoform, carried out in PTC system, tetraphenylarsonium chloride (TPA) used as a catalyst favours processes with tribromomethyl anion participation [15].



We found that difluorocarbene generated from chlorodifluoromethane by the action of concentrated KOH in dioxane in the presence of TPA as a catalyst can be captured by nucleophilic alkenes, however the yields seldom exceed 30 %.



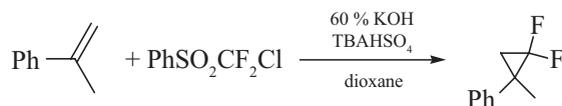
It is possible that the reversible reaction between the TPA cation and chlorodifluoromethyl anion that leads to pentacoordinated arsenic compound stabilizes the latter and permits its transportation into the bulk of the organic phase. We decided to synthesize modified tetraarylarsonium salts, containing electron donor or electron withdrawing groups in the aromatic ring in hope they will differ in their ability to coordinate chlorodifluoromethyl anion.



However despite many attempts, yields of adducts of difluorocarbene, generated from chlorodifluoromethane under different PTC conditions in the presence of the above mentioned catalysts, never exceeded 25–30 %.

At the end we turned our attention to chlorodifluoromethyl phenyl sulfone, easily available from thiophenol [24], as a potential difluorocarbene precursor in PTC reactions. It is known from the literature that in the reaction of trifluoromethyl phenyl sulfone with potassium tert-butoxide, trifluoromethyl anion is generated which reacts then as a nucleophile with carbonyl compounds leading to trifluoromethyl carbinols [25]. We hoped that replacement of one fluorine atom by chlorine in this sulfone should lead under PTC conditions to chlorodifluoromethyl anion which can dissociate to difluorocarbene and chloride

anion. Indeed in the reaction of chlorodifluoromethyl phenyl sulfone with α -methylstyrene carried out in the presence of 60 % KOH aqueous solution in dioxane as a solvent and catalytic amount of TBA·HSO₄, 1,1-difluoro-2-methyl-2-phenylcyclopropane was formed in yields ranging from 20 to 25 %.



However taking into account that boiling point of substrate (alkene) and product are similar and that alkene was used in threefold excess to carbene precursor, it is not easy to separate reaction product from the reaction mixture, therefore this method cannot be recommended as preparative procedure for obtaining *gem*-difluorocyclopropanes.

The utility of *gem*-difluorocyclopropanes as starting materials in organic synthesis, as well as key building blocks for biologically active molecules, is well documented [26]. Therefore a good, cheap and safe method for their preparation — PTC method — is still needed.

IV. Conclusion. In 2001 one of us (MF) published in *Modern Problems of Organic Chemistry* a paper “The Mąkosza Reaction — Thirty Years After” and we would like to repeat here the conclusion of this review which is in our opinion still relevant [27].

“After 30 (45) years, the Mąkosza reaction has become an increasingly important instrument in the hands of an organic synthetic chemist. At the same time we are still far from a full understanding of the mechanism of the processes which take place in this reaction. The mechanism proposed by Mąkosza adequately illustrates the general procedures of the catalytic process, but in a manner which doesn’t take into consideration the changes in the reaction process brought by the application of different ammonium salts. These phenomena which have been discovered over the past years not only increase the applicability of PTC, but are also of essential practical and academic value. It would still seem worthy to invest time and energy in a further investigation of this process thirty (forty five) years after it was first brought to light.”

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К о н т а к т н а я и н ф о р м а ц и я

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