Professor Oleg G. Kulinkovich

A Tribute

Oleg Grigor'evich Kulinkovich was born May 11, 1948. He graduated from the Belarusian State University in Minsk in 1971. He obtained his Ph.D in 1975 and his Doctor of Science degree for his thesis "Activated Cyclopropyl Ketones: Methods for Their Preparation, Properties and Synthetic Application" in 1987 which entitled him to become a Full Professor of Chemistry. From 1993 through 2003 he was Head of the Department of Organic Chemistry at the Belarusian State University and, after a six month interruption, he became the Head of the Laboratory of Organoelement Synthesis at the same University. Professor Kulinkovich's research interests center on organic synthesis, including the development of new catalytic and non-catalytic synthetic methods based on transformations of strained organic or organometallic compounds. His pioneering work on titanium-catalyzed cyclopropanation of carboxylic esters with Grignard reagents bearing β-hydrogen atoms (Kulinkovich reaction) is very well known.

The first remarkable finding, which perhaps, defined the area of his scientific interests, occurred during the early 1970's. He found that *gem*-dichlorocyclopropyl ketones react with sodium alkoxides at low temperature to give 2,2-dialkoxy-2,3-dihydrofurans in excellent yields. The reaction conditions contrasted sharply with the harsh conditions required for the known reaction of nucleophilic substitution of halogen atoms in non-functionalized *gem*-dichlorocyclopropanes. He established that the reason for this difference was the presence of an acidic hydrogen atom in the cyclopropyl ring α to the carbonyl group and that the substitution reaction proceeded through an elimination-addition mechanism. In collaboration with his undergraduate and graduate students he was able to develop several convenient methods for the

preparation of dichlorocyclopropyl ketones and their efficacious conversion into esters and dialkylamides of γ-keto carboxylic acids, γ-diketones, γ-ketoaldehydes, ketenes dithioacetals, and inaccessible pyrrole, furan, and thiophene derivatives with heteroatom substituents in the α-position of the five-membered heterocycles. He elaborated convenient alternative methods for generation of cyclopropyl ketones, having activating heteroatom substituents in the three-membered ring based on 1,3-elimination reactions of 2-alkoxy(hydroxy)-3-haloalkyl ketones. He also revealed the advantage of using these intermediates as latent 1,4-dicarbonyl compounds.

The most outstanding achievement of Prof. Kulinkovich was the discovery of the above-mentioned cyclopropanation of carboxylic esters with Grignard reagents in the presence of titanium (IV) isopropoxide. He proposed that dialkoxititanacyclopropanes (titanium (II)-alkene complexes), which act as 1,2-dicarbanion equivalents, are the key intermediates in this unprecedented transformation. The development of new synthetic methods based on reactions of dialkoxytitanocyclopropane intermediates with unsaturated and saturated substrates remains one of the primary directions of his research. He discovered that dialkoxititanocyclopropane reagents are involved in exchange reactions with alkene ligands, as well as highly selective allylic ethylation reactions of allylic alcohols derivatives, reductive coupling of terminal homoallylic alcohols with unique head-to-head regioselectivity, reductive cleavage of nitrogen-oxygen single bonds and other synthetically useful transformations. He also carried out research towards the deeper understanding of the mechanisms of these reactions. The properties of dialkoxititanoacyclopropane compounds (Kulinkovich reagents) have been studied by other groups worldwide, leading to the discovery of new, synthetically useful applications of carbon-carbon bond formation and functional group transformations.

The area of his interests includes also the chemistry of cyclopropanols, many of which became available using the Kulinkovich reaction. His efforts towards the development of methodologies for the use of substituted cyclopropanols in organic synthesis led to convenient and effective approaches to the preparation of α-methyl and α-methylene ketones, β-haloketones, β-hydroxyketones, α,β-epoxyketones, 2-substituted allyl halides, *trans*-2,4-disubstituted butadienes, β-nitrosoketones and 5-substituted isoxazoles. Based on these transformations he continues to develop cyclopropanol methodologies for stereoselective synthesis of various biologically active compounds, primarily insect pheromones.

His students are co-authors of his publications; many of them continue their scientific research in Belarus and in western countries. He has published several reviews on the chemistry of activated cyclopropanes and titanocyclopropane reagents in peer-reviewed international journals and participated in representative international conferences (OMCOS-9 (1997), ICOS 13 (2000), ESOC 12 (2001), BOS (2002), Isoprenoids 25 (2005), ASOC (2006)) as an invited speaker. He is a member of the advisory board of Zh. Org. Khim. (Rus. J. Org. Chem.).

Dr. Vladimir I. Tyvorskii, Belarusian State University
Dr. Oleg. L. Epstein, Colorado State University

Selected Publications

Activated cyclopropylketones in 1,4-dicarbonyl compounds syntheses

1. "Reaction of 1-benzoyl-2,2-dichlorocyclopropane with sodium alcoholates" (with Tishchenko, I.G., Glazkov, Yu.V.) *Zh. Org. Khim.* **1975**, *11*, 581 (in Russian); *C. A.* **1975**, *83*, 28027.
2. "A new method for the synthesis of γ-ketoaldehydes" (with Tishchenko, I.G., Masalov, N.V.) *Synthesis* **1984**, 886.
3. "A new convenient synthesis of methyl-4-oxoalkanoates" (with Sorokin, V.L.) *Synthesis* **1994**, 361-362.
4. "A new synthesis of arylsubstituted 1,4-Diketones" (with Kel`in, A. V.) *Synthesis* **1996**, 330.

Other reactions of activated cyclopropyl carbonyl compounds

5. "Preparation of β-oxoketene dithioacetals by isomerisation of gem.-diphenylthiocyclopropyl ketones" (with Tishchenko, I.G., Roslik, N.A.) *Synthesis* **1982**, 931.
6. **"**Synthesis of 5-aryl-2-dialkylaminofurans" (with Tishchenko; I.G., Masalov, N.V.) *Khim. Geterotsikl. Soedin.* **1983**, 1028; *Chem.Heterocycl.Compd. (Engl.Transl.)* **1983**, *19,* 822.
7. "A convenient method for the preparation of 2-dialkylaminothiophenes" (with Sadovskii, O.L.) *Zh. Org. Khim.* **1993**, *29*, 1636; *Russ. J. Org. Chem. (Engl.Transl.)* **1993**, *29,* 1363.
8. "Eine bequeme Metode zur Herstellung 1,3-disubstituiert Pyrrole aus Acetalen von 3-Alkenalen" (with Sorokin, V.L., Azzuz, A., Sviridov, S.V., Masalov N.V.). *Synthesis* **1993**, 1059.

Titanium (IV) catalyzed cyclopropanation of esters with Grignard reagents

9. "Reaction of ethylmagnesium bromide with carboxylic esters in the presence of tetraisopropoxytitanium" (with Sviridov, S. V., Vasilevskii, D. A., Pritytskaya T. S.) *Zh. Org. Khim.* **1989**, *25*, 2244; *Russ. J. Org. Chem.(Engl.Transl.)* **1989**, *2,* 2027.
10. "Titanium(IV) isopropoxide-catalyzed formation of 1-substituted cyclopropanols in the reaction of ethylmagnesium bromide with methyl alkanecarboxylates" (with Sviridov, S.V., Vasilevski, D.A.) *Synthesis* **1991**, 234.
11. "Titanium (IV) isopropoxide-catalyzed reaction of ethylmagnesium bromide with ethylacetate in the presence of styrene" (with Savchenko, A.I., Sviridov, S.V., Vasilevski D.A.) *Mendeleev Commun.* **1993**, 230.
12. "On the mechanism of titanium-catalyzed cyclopropanation of esters with aliphatic organomagnesium compounds. Deuterium distribution in the reaction products of $(CD_3)_2CHMgBr$ with ethyl 3-chloropropionate in the presence of titanium

tetraisopropoxide" (with Epstein, O.L., Savchenko, A.I.) *Izv. Akad. Nauk. Ser. Khim.* **2000**, 376; *Russ. Chem. Bull*. **2000**, *49*, 378.

13. "Titanium(IV) isopropoxide-catalysed reaction of alkylmagnesium halides with ethyl acetate in the presence of styrene. Non-hydride mechanism of ligand exchange in the titanacyclopropanes" (with Epstein, O.L., Savchenko, A.I.) *Tetrahedron Lett.* **1999**, *40*, 5935.
14. "Advanced procedure for the preparation of *cis*-1,2-dialkylsubstituted cyclopropanols. modified ate complex mechanism for titanium-mediated cycloropanation of carboxylic esters with Grignard reagents" (with Kananovich D. G.) *Eur. J. Org. Chem.* **2007**, (accepted).

Other reactions of dialkoxititanacyclopropane reagents

15. "Regioselective carbon-carbon bond formation in titanium mediated reaction of ethylmagnesium bromide with allylic alcohols and allylic ethers" (with Epstein, O.L. Isakov, V.E. Khmel'nitskaya, E.A.) *Synlett* **2001**, 49.
16. "The head-to-head reductive coupling of homoallylic alcohols promoted by titanium(II)-olefin complexes" (with Isakov, V.E.) *Synlett* **2003**, 967.
17. "Alkylative reduction of titanium(IV) isopropoxide with EtMgBr: Convenient method for the generation of subvalent titanium alkoxide reagents and their reactivity in pinacol coupling reactions" (with Matiushenkov, E.A., Sokolov N.A.) *Synlett* **2004**, 77.
18. **"**A convenient and chemoselective method for the reductive ring cleavage of isoxazoles and isoxazolines with EtMgBr/Ti(O*i*-Pr)$_4$ reagent" (with Churykau, D. H., Zinovich V.G.) *Synlett* **2004**, 1949.

Cyclopropanols transformations

19. **"**A convenient method for the preparation of N-substituted 1-acetonylaminocyclopropanes from acetoacetic ester ethylene acetal" (with Raiman, M.V., Il'ina N.A.) **1999**, *Synlett*, 1053.
20. **"**A simple and efficient conversion of tertiary cyclopropanols to 2-substituted allyl halides" (with Kozyrkov, Y.Yu.) *Synlett* **2002**, 443.
21. "Synthesis of α,β-epoxy ketones from alkyl- and arylsubstituted cyclopropanols" (with Astashko, D.A., Tyvorskii, V.I., Ilyina, N.A. *Synthesis* **2001**, 1453.
22. "A convenient procedure for transformation of tertiary cyclopropanols into 5-substituted isoxazoles" (with Churykau D. H.). *Synlett* **2006**, 3427.

Cyclopropanol methodology for preparation of biologically active natural compounds

23. "Two-step synthesis of (±)-stigmolone, the pheromone of Stigmatella aurantiaca" (with Epstein, O.L.) *Tetrahedron Lett.* **2001**, *42*, 3757.

24. "Stereoselective synthesis of (7aS)-1-methylenehexahydro-1H-pyrrolizine and (-)-heliotridane from N-diphenylmethyl-(S)-proline ethyl ester" (with Lysenko, I.L.) *Zh. Org. Khim.* **2005**, *41*, 73; *Russ. J. Org. Chem. (Engl.Transl.)* **2005**, *41*, 70.
25. 25. "Transformation of esters into 2-substituted allyl halides via tertiary cyclopropanols: Application in the stereoselective synthesis of (2*S*,3*S*,7*S*)-3,7-dimethyl-2-pentadecyl acetate, the sex pheromone of the pine sawfly *Neodiprion sertifer*" (with Bekish, A.V. Prokhorevich K.N.) *Eur. J. Org. Chem.* **2006**, 5069.
26. "A cyclopropanol approach to the synthesis of the C13-C21 fragment of epothilones from diethyl (S)-malate" (with Bekish A.V., Isakov V.E.) *Tetrahedron Lett.* **2005**, *46,* 6979.

Reviews

27. "Activated cyclopropanes in the synthesis of five-membered carbocycles and heterocycles" *Uspekhi Khimii*, **1993**, *62*, 887; *Russ. Chem. Rev. (Engl.Transl.)* **1993**, *62*, 839.
28. "The chemistry of cyclopropanols" *Chem. Rev.* **2003**, *103*, 2597.
29. "Alkylation of carboxylic acid derivatives with dialkoxytitanacyclopropane reagents" *Izv. Akad. Nauk. Ser. Khim.* **2004**, *1022, Russ. Chem. Bull. (Engl.Transl.)* **2004**, *53*, 1065.
30. "Synthetic applications of intermolecular cyclopropanation of carboxylic esters with dialkoxytitanacyclopropane reagents" *Eur. J. Org. Chem.* **2004**, 4517.