TRANSITION METAL COMPLEX CATALYSIS IN FINE ORGANIC SYNTHESIS. A PERSONAL ACCOUNT

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The development of catalytic systems for palladium catalyzed C–C and C–heteroatom bond formation is overviewed. Attention is focused on the issues relevant for environmental and technological safety of the processes: high catalytic efficiency, reactions in the absence of expensive non-recoverable phosphine ligands, the use of water and aqueous media, atom efficient transformations, *etc.*

Keywords: Homogeneous catalysis; Transition metal complexes; Cross-coupling reactions; Palladium; Ligand-free reactions; Phosphine ligands; Aqueous conditions; Microemulsions.

During the last century chemistry has brought to life hundreds of thousands of new useful compounds, many of which are unknown in Nature, ranging from pharmaceuticals and household chemicals to new advanced materials shaping the technology of tomorrow. Still, from the layman's point of view, chemistry remains a dubious and unclean art, responsible for environmental pollution, endangering Nature and all what is considered natural. It should be admitted that this prejudice, though unjust, is not without reasons. Anyway, chemistry has to radically change its ways in order to meet the requirements of the 21st century. The gap between "natural" and "artificial" must be narrowed, in particular in what concerns the methods used for the production of indispensable chemical substances.

If we try to speculate on what makes a given chemical process green, several issues are of relevance. A good process must be atom-economical and atom-effective, *i.e.* it must involve the least possible amount of those reagents which are not transformed into the products, which implies that the reaction is catalytic; it must produce the least possible amount of by-products, which implies high selectivity of the reaction and a proper choice of the transformation pathway. The application of green solvents (such as water and aqueous media, supercritical fluids, *etc.*) is important for liquid-phase reactions[1].

Among many ways to make new chemistry "green" is the development and implementation of new catalytic processes, particularly those involving the extremely versatile and effective transition metal complexes in homogeneous catalytic reactions.

It is generally understood that homogeneous catalytic processes are superior to heterogeneous catalysis in the scope and versatility of applications, selectivity (particularly enantioselectivity), reaction rates, *etc.* Moreover, homogeneous processes allow for more thorough research and understanding of the intrinsic mechanisms, systematic trends in reactivity and selectivity, and thus can be precisely fine-tuned to a given application. The drawback making many valuable homogeneous processes so far uneconomical is associated mainly with the properties of the homogeneous catalyst itself contained in the same phase as reagents and products, from what follows the need for post-reaction isolation, recovery and reactivation of the catalyst. In many cases it is only the central metal of the catalysts which is recovered, which necessitates re-production of the active form before recharging the reactor. Expensive ligands in the majority of cases cannot be recovered and are lost.

It should be stressed that these immanent flaws of homogeneous catalysis are not fatal. The gap between homogeneous and heterogeneous catalysis is not so wide. A compromise between the two is the recyclable phase-separation catalysis[2]. Moreover, given that in any heterogeneous or recycleable catalytic system the catalyst is actually partially lost during the reaction (leaching of catalyst), designing the homogeneous system with high efficiency and small loading of catalyst may, in terms of consumption of the catalyst, be the same as designing heterogeneous or recyclable system.

The role of ligands in a given transition metal-catalyzed reaction may be multiple. There are many cases in which ligands are indispensable playing an important role in the mechanism of reaction, or performing, *e.g.*, chirality transfer. However, still many cases are not so strongly ligand-dependent. For example, many important palladium-catalyzed reactions allow for the so-called "ligand-free" or rather "phosphine-free" mode, that is these reactions do not require any specific ligands to be present in the coordination shell of metal. That is why so many different palladium-containing compounds may be used in particular reactions, while neither of them can be regarded as specific catalyst for the given type of process. Moreover, the addition of phosphine ligands or use of preformed phosphine complexes often leads to an apparent decrease in the rate of catalytic reaction and efficiency of the catalyst. But meanwhile, phosphine-free systems often fail with the substrates of lower reactivity. This paradox is a re-

flection of the fact that the dichotomy between regular phosphine-assisted and phosphine-free modes of catalysis can be regarded as a compromise between the stability of catalytic system and the reactivity of catalytic species. Phosphines and similar strongly bonded ligands play a non-specific role of stabilizing unstable catalytically active states of metal (*e.g.* zero-valent for Ni and Pd), while at the same time blocking coordination sites which should be free for the catalytic action to take place. In those cases when the rate of catalytic reaction is faster than the rate of decomposition of unstable catalytically active species, the reaction can be run in phosphine-free mode, and *vice versa*. Understanding the mechanisms of catalyst deactivation and factors influencing the stability of active complexes allows to increase the scope of phosphine-free and related processes.

Here we will attempt to show how the challenges of palladium catalyzed reactions outlined above can be approached, using as an example the work of the Laboratory of organoelement compounds of Moscow State University.

Aqueous Palladium Catalysis and Phosphine-Free Processes[3]

The story of palladium catalysis in organic synthesis as a versatile tool of C–C bond formation begins with the discovery of the cross-coupling reaction more than 30 years ago. While the first examples discovered independently by Corriu and Kumada[4,5] used organolithium or Grignard reagents (the Kumada–Tamao reaction), it was Stille's contribution introducing the organotin compounds which made the cross-coupling chemistry a true success[6]. The organotin compounds allowed much wider scope of substituents in the reagents thus making the method very versatile. Major problem, however, was associated with intrinsically low reactivity of organotins which required the use of highly polar coordinating solvents like DMSO or HMPA at high temperatures. In the mid-eighties Beletskaya *et al.* have discovered that this problem can be overcome in many cases by using phosphine-free catalytic systems which are effective at lower temperatures and in more trivial and less expensive solvents such as acetone[7]. Besides making the procedure cheaper this modification allows for simpler workup and product isolation. Similarly, the reactions of organotins with acyl halides were soon realized in phosphine-free mode to afford unsymmetrical ketones. Further elaboration of this strategy led to the development of a three-component reaction in which aryl halide reacted with organotin compound (of the type R'_3SnNu, where Nu = R, MeO, MeS, Me_2N, *etc.*) in the presence of CO to afford ketones or various acid derivatives[8]. Simple
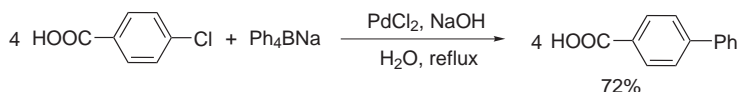
palladium salts and complexes such as LiPdCl$_3$ or [PdCl$_2$(MeCN)$_2$], *etc.* served as catalysts. Amides and esters were later shown to be formed also in the phosphine-free carbonylation of aryl iodides in the presence of phenolates or anilines thus avoiding toxic tin compounds[9,10].

The reactions of Me$_4$Sn with benzenediazonium salts have been carried in water containing a small amount of MeCN (refs[11,12]). Similarly, various organotin compounds can be coupled with iodonium salts in aqueous solutions. Even if the reaction mixtures was visually heterogeneous, the yields of coupling products were excellent[13].


Z = *o*-, *p*-NO$_2$; *p*-I, *p*-Br, *p*-MeO, *p*-Me

R = Me, *m*-MeC$_6$H$_4$; Z = H, *m*-NO$_2$
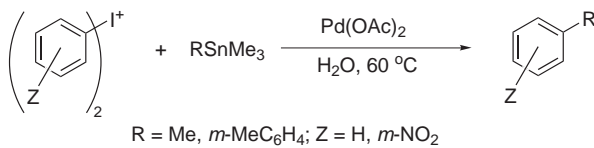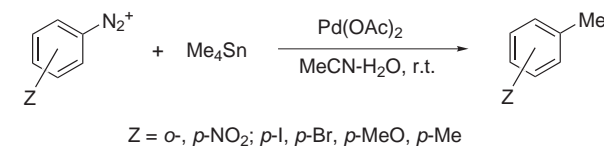
Main drawbacks of common organotin reagents, the loss of three out of four organic groups in the molecule of R′$_3$SnR and the formation of toxic waste R′$_3$SnX, can be overcome through the use of monosubstituted stannanes RSnX$_3$. In view of very low nucleophilicity of such compounds, the reaction can be carried out in water in the presence of base transforming the initial reagent into more nucleophilic water-soluble stannates RSn(OH)$_{3+n}^{n-}$ in the presence of a water-soluble phosphine[14]. It was cross-coupling with organoboron compounds, the Suzuki reaction, where the aqueous phosphine-free protocol really shone. This method allows in many cases to dramatically increase the yields, reduce the loading of palladium catalyst, avoid scrambling of aryls between the products and phosphine ligands. The latter is of particular interest when the reaction is applied for the preparation of advanced materials, in which any structure imperfection caused by scrambling leads to deterioration of desirable properties[15]. In the case of water-soluble substrates, the reaction can be carried out in neat water in the presence of simple inorganic bases and tiny amounts of trivial palladium salts under very mild conditions giving near to quantitative yields[16]. Sodium tetraphenylborate can be used in place of phenylboronic acid, all four phenyl groups being transferred in a very facile catalytic pro-

cess[17]. The reactivity of this catalytic system is so high, that the differences between iodo- and bromoarenes are insignificant. Moreover, the reaction made possible one of the rarest cases of phosphine-free reactions of aryl chlorides[18].

$$4 \ HOOC-\!\!\langle \ \rangle\!\!-Cl \ + \ Ph_4BNa \ \xrightarrow[\text{H}_2\text{O, reflux}]{\text{PdCl}_2, \text{NaOH}} \ 4 \ HOOC-\!\!\langle \ \rangle\!\!-Ph$$
<div align="center">72%</div>

Cross-coupling with acetylenes can also be accomplished in aqueous media in the presence of inorganic bases, though the addition of trialkyl-amines (up to 10 mole %) is required to achieve high yields[19].

Z = H, NO$_2$, CN, MeCO
R = Ph, n-C$_5$H$_{11}$, p-C$_9$H$_{19}$C$_6$H$_4$
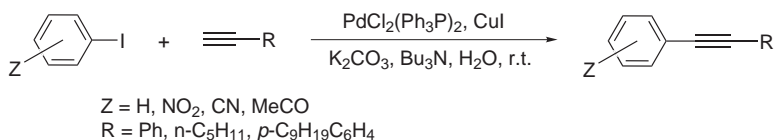
The best results were achieved with iodonium salts taken as arylating agents[20,21].

Similar conditions (heterogeneous system, stoichiometric amount of inorganic base and catalytic amount of trialkylamine) can be used to carry out the Heck reactions with water-insoluble compounds[22]. Heck reaction with water-soluble substrates is highly effective in water under phosphine-free conditions[23].

X = I, Br
Z = H, p-Cl, p-MeO, p-Me, p-Ac, p-NO$_2$, p-CHO, p-OH, m-COOH
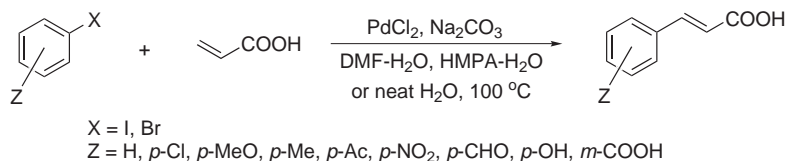
Water exerts marked accelerating effect on the Heck reaction. The addition of 15–25 vol.% water to DMF has been demonstrated to lead to the rate increase by an order of magnitude. The effect of further addition of water depends on whether the substrates are water-soluble or not. In the case of hydrophilic substrates the use of highly aqueous solvents or even neat water may be advantageous. For example, the arylation of allyl or vinyl-phosphonates runs in water much faster than in aprotic solvents at lower temperatures giving high yields of the target arylated products[24].

Aqueous media and phosphine-free conditions were found to be advantageous for substitutive carbonylation reactions, allowing to apply very mild

conditions. The reaction of aryl iodides and some reactive bromides can be accomplished at 1 atm of CO and room temperature in the presence of $Pd(OAc)_2$ giving high yields of the respective acids[25].

$$ArI \xrightarrow[\text{DMF-H}_2\text{O (2:1), 25–50 °C}]{\text{Pd(OAc)}_2,\ 1\ \text{atm CO, K}_2\text{CO}_3} ArCOOH$$
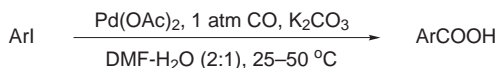
Ar = p-ZC_6H_4 (Z = NO_2, Cl, CN, Me, NH_2, *etc.*), 2-$C_{10}H_7$, 2-thienyl

Very high catalytic efficiency can be achieved. Thus, TON values of the 10^5 order of magnitude were observed in the carbonylation of water-soluble 4-iodobenzoic acid. Common aryl bromides can also be processed in aqueous media, though in the presence of phosphine ligands.

Aqueous conditions proved to be suitable for the C–P bond-forming cross-coupling reactions. For example, the reaction of aryl iodides with dialkylphosphites can be accomplished under phase-transfer conditions upon prolonged heating, while in water or aqueous MeCN the reaction is dramatically accelerated. Aryl iodides can react in the absence of phosphine ligands, while aryl bromides do require phosphines to be present[26].
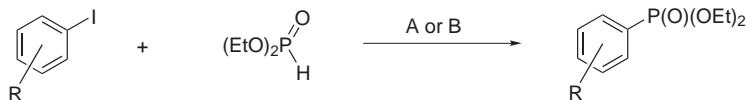
A: $Pd(OAc)_2$, TPPMS, NaOH, Bu_4NCl, PhH-H_2O, 60 °C
B: $Pd(OAc)_2$, TPPMS, Et_3N, MeCN-H_2O, r.t.

Catalytic amination at least in some cases can be accomplished in aqueous media. For example, the arylation of benzotriazole with diaryliodonium salts can be done in water. It is interesting that while both aryl groups of iodonium salt are transferred to the product, no reaction was observed under the same conditions with aryl iodide as arylating agent. The selectivity of the reaction, which gives a mixture of N^1 and N^2 substitution products can be radically improved by the addition of copper carboxylate co-catalyst[27].

Microemulsions and Related Media for Palladium-Catalyzed Reactions

The study of application of aqueous solvents to palladium-catalyzed reactions highlighted main limitation of homogeneous media with high contents of water, the solubility of reagents. The design of aqueous systems

with water as predominant component and suitable for wider scopes of organic reagents led to the exploitation of the solubilization phenomena. It is well known that aqueous solutions of surfactants are capable of enhancing the solubility of hydrophobic organic compounds as well as the solubility of water and aqueous solutions in hydrophobic liquids often generically referred to as oils for brevity and to pay tribute to the tradition. The molecules of solubilizate naturally do not form a true solution, but rather are absorbed by the micelles. Common ionic surfactants (like sodium dodecyl sulfate or cetyltrimethylammonium bromide, *i.e.* those consisting of a single ionic head group and a single non-branched hydrocarbon tail) form spherical micelles having very low solubilization capacity; typically, a single micelle built of several tens of surfactant molecules takes a few (1–5) molecules of solubilizate.

In order to increase the solubilizing ability of microheterogeneous system, the hydrophilic-lipophilic balance (HLB) of a surfactant system must be adjusted to counterweight hydrophilic and hydrophobic interactions. The adjustment of HLB is performed by a number of means including the use of special surfactants, or compound surfactant/co-surfactant systems. Further fine balancing is performed by varying the temperature and concentration of electrolytes. The resulting microheterogeneous media are characterized by very low interfacial tension between aqueous and oil phases, and is capable of solubilizing considerable amounts of water-insoluble organic compounds. Unlike macroemulsions, such media, the most well-known of which are called microemulsions, are thermodynamically stable systems, which are formed spontaneously and which do not require continuous mechanical agitation.

Such systems can be successfully applied for palladium catalyzed reactions with water-insoluble reagents. The simplest media of this type are formed by a combination of single-tail ionic surfactant and short-chain aliphatic alcohol as a co-surfactant, dispersed in water in an approximate molar ratio surfactant:ROH:water = 1:4:100–200. After fine balancing with electrolyte, which can simultaneously act, *e.g.*, as a base needed for a majority of catalytic reactions under discussion, these media solubilize organic reagents in amounts roughly equivalent to those commonly used in organic preparations in more conventional media (0.1–1 mol/l).

Such media can be used for all major types of palladium catalyzed reactions including carbonylation of aryl halides, hydrogenolysis, acetylenic coupling, *N*-arylation, Heck and Suzuki reactions, Wacker olefins oxidation, *etc.*[28–31]. Most of the reactions studied so far can be performed in the phosphine-free mode with high efficiency.

The study of Heck arylation and Suzuki cross-coupling provided experimental evidence of the involvement of palladium clusters in phosphine-free catalysis. These reactions in microemulsions turned out to actually run through a fast formation of palladium sols. Unlike the studies of the catalytic activity of palladium sols treated above where the nanoparticles were obtained in an independent way and then transferred to the reaction media, in solubilized systems nanoparticles are formed and survive, and thus perform catalytic functions in the native environment. The catalytic process itself proceeded in the presence of colloid palladium, which underwent no further evolution during the reaction. By carrying out the reactions in systems built with various types of surfactants (anionic carboxylates, phosphonates, sulfates, sulfonates of variable chain lengths, as well as cationic alkyltrimethylammonium salts) showed that the performance of catalytic systems changed in parallel with the ability of the media to assist in the formation of colloid and to sustain it). The reactions showed high turnover numbers (up to 50 000). This is not surprising as only a fraction of palladium atoms located at the surface of the cluster actually reacts; thus, lowering the initial concentration of palladium leads only to the formation of smaller particles having less of wasted palladium atoms in cluster interiors.

Thus, we may argue that the microphase of the solubilized system acts as another example of a self-sustained nanoreactor, the role of which is performed by the interfacial layers and surfactant-stabilized Pd clusters. Aqueous and oil phases act as feedstocks of hydrophilic and hydrophobic reagents, respectively, as, *e.g.*, in the Heck arylation. Unlike simple micelles, the solubilized systems possess much wider limits of stability, and thus, are quite tolerant to a profound change in the composition of reacting system during the process.

Solubilized systems can also be formed by non-ionic surfactants, the derivatives of oligo(ethylene)glycol $R(OCH_2CH_2)_nOH$. The balancing of such systems does not require a co-surfactant, but is performed by varying the number of ethylene oxide residues in the surfactant molecule, with further fine balancing achieved by temperature variation in the vicinity of the phase inversion point, at which the nature of system changes from more-hydrophilic to more-hydrophobic. Non-ionic surfactants and similar molecules exhibit another intriguing ability to effect local transport of ions, thus facilitating mass transfer of hydrophilic reagents to the interfacial nanoreactor.

The Atom Economical Route to Phosphines

One of the key principles of organic synthesis relevant from the "green" point of view is atom economy, which is the basis of development of true waste-free technologies. While any substitution reaction cannot fully satisfy this principle and thus is potentially problematic, the addition to double and triple bonds does meet this criterion. The addition of P-H and P-P reagents to triple bonds giving rise to mono- and diphosphines has been recently developed.
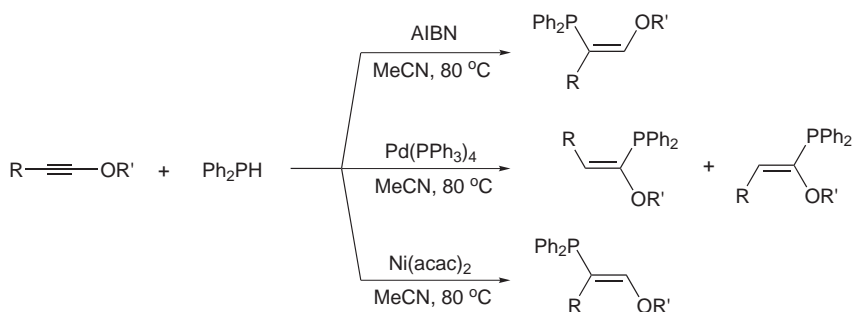
The addition of Ph$_2$PH has been shown to lead regiospecifically to either α- or β-adducts depending on conditions. The reactions can be catalyzed by Ni or Pd complexes and give exclusively syn-adducts. These reactions are an excellent route to various unsaturated mono- and diphosphines, which can be transformed by enantioselective hydrogenation into valuable chiral ligands[32].

REFERENCES

1. Beletskaya I. P., Cheprakov A. V. in: *Transition Metal Catalysed Reactions* (S. I. Murahashi and S. G. Davies, Eds). Blackwell, Oxford 1999.
2. Herrmann W. A., Cornils B.: *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1049.
3. Beletskaya I. P., Cheprakov A. V. in: *Organic Synthesis in Water* (P. Grieco, Ed.). Blackie, London 1998.
4. Corriu R. J. P., Masse J. P.: *J. Chem. Soc., Chem. Commun.* **1972**, 144.
5. Tamao K., Sumitani K., Kumada M.: *J. Am. Chem. Soc.* **1972**, *94*, 4374.
6. Stille J. K.: *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.
7. Bumagin N. A., Bumagina I. G., Beletskaya I. P.: *Dokl. Akad. Nauk SSSR* **1984**, *274*, 818.
8. Bumagin N. A., Gulevich Y. V., Beletskaya I. P.: *J. Organomet. Chem.* **1985**, *285*, 415.
9. Bumagin N. A., Nikitin K. V., Andryukhova N. P., Beletskaya I. P.: *Dokl. Akad. Nauk SSSR* **1991**, *318*, 1389.
10. Bumagin N. A., Nikitin K. V., Beletskaya I. P.: *Dokl. Akad. Nauk SSSR* **1991**, *320*, 887.

11. Bumagin N. A., Sukhomlinova L. I., Tolstaya T. P., Vanchikov A. N., Beletskaya I. P.: *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci.* **1990**, *39*, 2419.
12. Bumagin N. A., Sukhomlinova L. I., Tolstaya T. P., Beletskaya I. P.: *Zh. Org. Khim.* **1994**, *30*, 1524.
13. Bumagin N. A., Sukhomlinova L. I., Igushkina S. O., Vanchikov A. N., Tolstaya T. P., Beletskaya I. P.: *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci.* **1992**, *41*, 2128.
14. Roshchin A. I., Bumagin N. A., Beletskaya I. P.: *Tetrahedron Lett.* **1995**, *36*, 125.
15. Wallow T. I., Novak B. M.: *J. Am. Chem. Soc.* **1991**, *113*, 7411.
16. Bumagin N. A., Bykov V. V., Beletskaya I. P.: *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci.* **1989**, *38*, 2206.
17. Bumagin N. A., Bykov V. V., Beletskaya I. P.: *Dokl. Akad. Nauk SSSR* **1990**, *315*, 1133.
18. Bykov V. V., Bumagin N. A., Beletskaya I. P.: *Dokl. Akad. Nauk* **1995**, *340*, 775.
19. Bumagin N. A., Ponomarev A. B., Beletskaya I. P.: *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci.* **1984**, *33*, 1433.
20. Bumagin N. A., Sukhomlinova L. I., Luzikova E. V., Tolstaya T. P., Beletskaya I. P.: *Tetrahedron Lett.* **1996**, *37*, 897.
21. Sukhomlinova L. I., Luzikova E. V., Tolstaya T. P., Bumagin N. A., Beletskaya I. P.: *Russ. Chem. Bull.* **1995**, *44*, 769.
22. Bumagin N. A., Bykov V. V., Sukhomlinova L. I., Tolstaya T. P., Beletskaya I. P.: *J. Organomet. Chem.* **1995**, *486*, 259.
23. Bumagin N. A., More P. G., Beletskaya I. P.: *J. Organomet. Chem.* **1989**, *371*, 397.
24. Demik N. N., Kabachnik M. M., Novikova Z. S., Beletskaya I. P.: *Zh. Org. Khim.* **1995**, *31*, 64.
25. Bumagin N. A., Nikitin K. V., Beletskaya I. P.: *J. Organomet. Chem.* **1988**, *358*, 563.
26. Demik N. N., Kabachnik M. M., Novikova Z. S., Beletskaya I. P.: *Zh. Org. Khim.* **1994**, *30*, 876.
27. Beletskaya I. P., Davydov D. V., Moreno-Mannas M.: *Tetrahedron Lett.* **1998**, *39*, 5621.
28. Cheprakov A. V., Beletskaya I. P.: *Abstr. Pap. – Am. Chem. Soc.* **1993**, *206*, 332.
29. Cheprakov A. V., Ponomareva N. V., Beletskaya I. P.: *J. Organomet. Chem.* **1995**, *486*, 297.
30. Davydov D. V., Beletskaya I. P.: *Russ. Chem. Bull.* **1995**, *44*, 1141.
31. Davydov D. V., Beletskaya I. P.: *Russ. Chem. Bull.* **1995**, *44*, 965.
32. Kazankova M. A., Efimova I. V., Kochetkov A. N., Afanasiev V. V., Beletskaya I. P., Dixneuf P. H.: *Synlett* **2001**, 497.