ISSN 1070-4280, Russian Journal of Organic Chemistry, 2007, Vol. 43, No. 4, pp. 548–552. © Pleiades Publishing, Ltd., 2007.
Original Russian Text © Yu.V. Ageeva, S.A. Kurzeev, G.M. Kazankov, 2007, published in Zhurnal Organicheskoi Khimii, 2007, Vol. 43, No. 4, pp. 549–554.

Catalytic Hydrolysis of α-Amino Esters in the Presence of Chiral Palladacycles

Yu. V. Ageeva, S. A. Kurzeev, and G. M. Kazankov

Faculty of Chemistry, Moscow State University, Vorob'evy gory 1, Moscow, 119992 Russia
e-mail: g_kazankov@hotmail.com

Received March 30, 2006

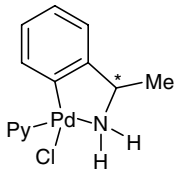
Abstract—The rate of hydrolysis of esters derived from optically active α-amino acids, catalyzed by chiral cyclopalladated benzylamines, depends on the configuration of chiral centers in the substrate and catalyst. The catalytic hydrolysis of sulfur-containing amino esters follows an intramolecular mechanism, and the difference in the reaction rates for the stereoisomers increases in going from *ortho*-palladated primary benzylamines (k_S/k_R = 1.1) to tertiary amines (k_S/k_R = 1.5); the strongest catalytic effect is observed for an ester and a complex with the same absolute configuration of the chiral centers. The efficiency of intermolecular catalysis is greater for a complex and ester with opposite absolute configurations of the chiral centers, and the rate constants of catalytic hydrolysis for two pairs of stereoisomers coincide within experimental error. The maximal difference in the reaction rates is observed for cyclopalladated secondary benzylamines; it reaches 2.3 for the phenylalanine ester.

DOI: 10.1134/S1070428007040100

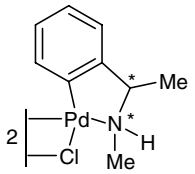
Systems based on cyclopalladated benzylamines, which are capable of catalyzing hydrolysis of amino acid derivatives [1–4], attract researchers' attention. Such complexes in aqueous medium acquire a strong nucleophilic center via coordination of hydroxo ligand at the *trans* position with respect to the aromatic carbon atom [5–7]. On the other hand, *ortho*-palladated benzylamines are convenient substrates for introduction of chiral centers. The use of optically active palladium complexes to catalyze hydrolysis of amino acid derivatives is expected to provide considerable differences in the reaction rates between different optically active isomers.

It is known that some metal complexes are capable of promoting enantioselective hydrolysis of biologically active compounds [8], including amino acid derivatives [4, 9, 10]. Design of fairly simple hydrolytic systems ensuring resolution of racemic mixtures into optical isomers is a quite promising method for separation of enantiomeric carboxylic acids and amino acids, which is important for both fine organic synthesis and large-scale production of biologically active substances.

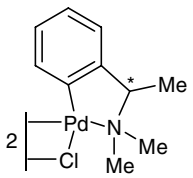
Separation of isomers in such systems is often based on the kinetic effect, i.e., the difference in the rates of hydrolysis of different enantiomers [8]. Kinetic resolution is widely used for synthetic purposes [11–15]; however, almost no systematic studies have been performed on the kinetics of the above reactions and their mechanism. Insofar as the isomer ratio in the kinetic resolution strongly depends on the conversion and reaction conditions, in the present work we examined reactions of optically active catalysts with pure enantiomers [4] with the goal of elucidating the mechanism of this process. As substrates we used *p*-nitrophenyl esters derived from N-protected optically active amino acids, and chiral palladium complexes **I**–**III** were taken as catalysts.



I

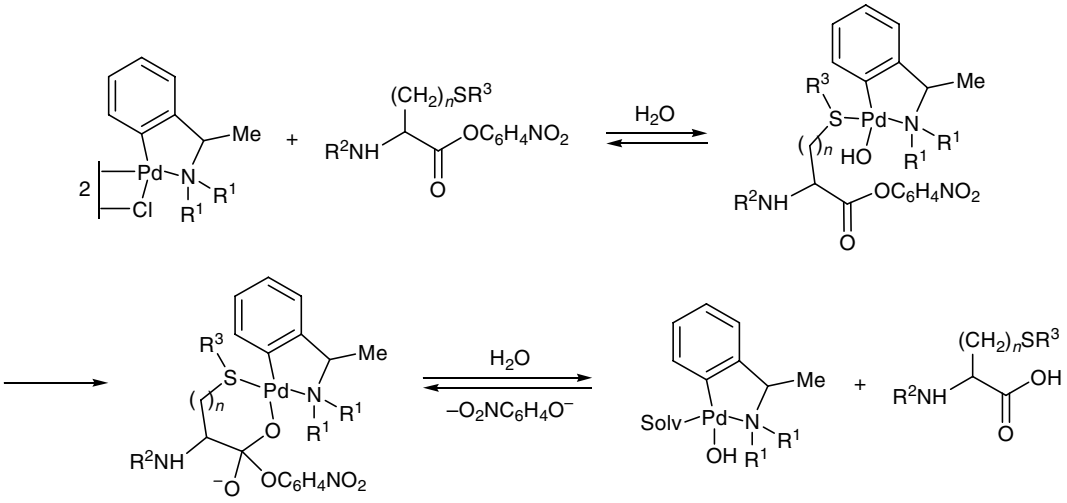


II



III

Scheme 1.



n = 1, 2; R^1 = H, Me; R^2 = Boc; R^3 = Me, $PhCH_2$.

ortho-Palladated 1-phenylethanamine (**I**) and *N*,*N*-dimethyl-1-phenylethanamine (**III**) catalyzed hydrolysis of methionine, *S*-benzylcysteine, leucine, and phenylalanine *p*-nitrophenyl esters. Methionine and *S*-benzylcysteine derivatives contain a side-chain sulfur atom which is a soft donor center and is capable of being coordinated to the metal atom in palladacycles. As shown previously [2], the hydrolysis of N-protected sulfur-containing amino acid esters, catalyzed by *ortho*-palladated benzylamines, follows an intramolecular mechanism. Initial coordination of the sulfur atom to palladium is followed by nucleophilic attack by the coordinated hydroxo ligand on the carbonyl carbon atom, and the reaction involves formation of cyclic intermediate (Scheme 1). The catalytic rate constants are given in table. Comparison of the rate constants shows the absence of a strong dependence of the rate of hydrolysis on the relative configuration of the chiral center in the palladium complex: the ratio of the catalytic rate constants $k_{cat}(S)/k_{cat}(R)$ is 1.17. A probable reason is that the chiral centers in the substrate and catalysts are strongly distant from each other; therefore, they weakly affect binding of sulfur to palladium and subsequent nucleophilic attack by the coordinated hydroxo ligand on the ester carbonyl carbon atom. The catalytic rate constants for the hydrolysis of *N*-*tert*-butoxycarbonyl-*S*-benzylcysteine *p*-nitrophenyl ester are smaller by an order of magnitude than those found for *N*-*tert*-butoxycarbonyl-*S*-methylcysteine *p*-nitrophenyl ester [1] and are twice as small as those for *N*-*tert*-butoxycarbonylmethionine *p*-nitrophenyl ester. Hydrolysis of cysteine derivatives analogous to methionine, i.e., of those containing a methyl group on the sulfur atom, in the presence of palladium complexes with benzylamines is characterized by much higher rate, as compared to methionine derivatives. This may

Catalytic rate constants k_{cat} (l mol^{-1} s^{-1}) and k_S/k_R ratios for the hydrolysis of N-protected optically active amino acid *p*-nitrophenyl esters in the presence of *S*- and *R*-isomeric *ortho*-palladated benzylamines; pH 8.0 (0.01 M phosphate buffer, 10% MeCN), 30°C

Amino acid	Complex **I**			Complex **II**			Complex **III**		
	S isomer	*R* isomer	k_S/k_R	*S* isomer	*R* isomer	k_S/k_R	*S* isomer	*R* isomer	k_S/k_R
R-Cysteine[a]	81±6	69±6	1.17						
S-Methionine[a]	188±8	166±8	1.1	134±7	94±6	1.7	3.6±0.2	2.4±0.1	1.5
R-Leucine	12.2±0.4	7.6±0.4	1.6	17±1	27±2	0.53	9.4±0.5	5.7±0.3	1.7
S-Leucine	6.4±0.4	9.8±0.3	0.65	28±2	16±1	2.16	5.5±0.3	9.0±0.4	0.61
S-Phenylalanine				10±1	19±1	0.44	5.5±0.4	9.1±0.4	0.60
R-Phenylalanine				21±2	11±1	2.28	9.3±0.4	5.7±0.3	1.63

[a] At 25°C.

be rationalized in terms of the mechanism shown in Scheme 1, where the key step is intramolecular attack by the coordinated hydroxo ligand on the carbonyl carbon atom with formation of a cyclic transition state [1]. In the reactions with the cysteine derivative, more thermodynamically favorable six-membered ring is formed, while the methionine derivative gives rise to a seven-membered ring. On the other hand, the hydrolysis of N-protected *S*-benzylcysteine *p*-nitrophenyl ester is much slower than the hydrolysis of analogous *S*-methylcysteine and methionine derivatives. This may be due to weaker coordination to palladium of the sulfur atom attached to benzyl radical, as compared to *S*-methyl analog, for steric reasons.

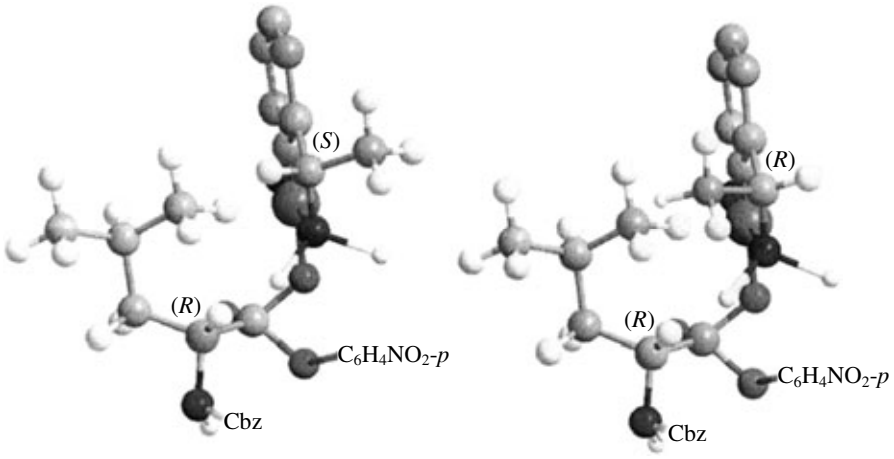
The results of hydrolysis of the *S* isomer of *N*-*tert*-butoxycarbonylmethionine *p*-nitrophenyl ester in the presence of complexes **I** and **III** show that the efficiency of catalysis decreases in going from primary *ortho*-palladated benzylamine to tertiary; here, the size of the substituent on the nitrogen atom affects coordination of the sulfur atom to palladium: bulkier substituents increase steric hindrances to the formation of cyclic transition state in the stage involving nucleophilic attack by the coordinated hydroxo ligand. On the other hand, the difference in the hydrolysis rate constants between the stereoisomers also increases: the ratio $k_{cat}(S)/k_{cat}(R)$ is 1.1 in the catalysis by chiral palladium complex derived from primary 1-phenylethanamine, while it is equal to 1.5 in the presence of the palladium complex with *N*,*N*-dimethyl-1-phenylethanamine.

In the hydrolysis of *R*- and *S*-isomeric *N*-benzyloxycarbonylleucine *p*-nitrophenyl esters (having no heteroatom capable of coordinating to palladium), the mechanism of catalysis by chiral complexes **I** and **III** is intermolecular. It also involves nucleophilic attack by the coordinated hydroxide ion on the ester carbonyl carbon atom of the substrate. The maximal catalytic effect is observed when the ester and catalyst have opposite absolute configurations of the chiral centers, and the catalytic rate constants for the two pairs of stereoisomers coincide within the experimental error, indicating stereospecificity of the process. This is related to steric hindrances to approach of the methyl group in the metal-containing ring to the isopropyl group in the leucine derivative (see figure). The ratio of the catalytic rate constants for hydrolysis of one stereoisomers of the substrate in the presence of different stereoisomers of the catalyst is 1.6 and 1.7 for complexes **I** and **III**, respectively. These values are larger than those found for the intramolecular mechanism of catalysis. Presumably, the reason is that *R* or *S* configuration of the α-carbon atom in the metal ring favors to greater or lesser extent appropriate mutual orientation of the substrate and catalyst at the stage of nucleophilic attack on the carbonyl carbon atom by the hydroxo ligand. By contrast, the transition state in the intramolecular reaction has a more rigid structure, and the effect of relatively distant α-methyl fragment is weaker.

Figure shows a probable mutual orientation of the substituent at the chiral center in stereoisomeric complexes (*R*)-**I** and (*S*)-**I** and the side-chain substituent in the (*R*)-leucine derivative. It is seen that the interaction between the amino ester and palladium complex having opposite absolute configurations is less sterically hindered.

Analogous results were obtained in the hydrolysis of *R*- and *S*-isomeric *N*-benzyloxycarbonylphenylalanine *p*-nitrophenyl esters in the presence of stereoisomeric complexes **III**. The ratios of the catalytic rate constants for the *R* and *S* isomers of **III** were k_S/k_R = 1.63 for the (*R*)-phenylalanine derivative and 0.60 for the *S* isomer. Here, the relation between the catalytic efficiency and configuration of the substrate and catalyst is the same as in the hydrolysis of leucine derivatives: the maximal catalytic effect is observed for the ester and the complex having opposite absolute configurations of the chiral centers.

ortho-Palladated *N*-methyl-1-phenylethanamine (**II**) contains a four-coordinate nitrogen atom linked to different substituents, i.e., complex **II** contains an additional chiral center on the nitrogen atom. In optically pure benzylamine, the configuration of the carbon atom is fixed, while the nitrogen atom in complex **II** may have both *R* and *S* configuration. In the ^{1}H NMR spectrum of complex **II** obtained from (*S*)-*N*-methyl-1-phenylethanamine we observed signals from both diastereoisomers, S_CS_N and S_CR_N. The ratio of these stereoisomers was estimated at 1:5 on the basis on the intensity ratio of the corresponding signals. The ^{1}H NMR spectrum of complex **II** derived from (*R*)-*N*-methyl-1-phenylethanamine displayed an analogous pattern with a similar ratio of the (R_CR_N)- and (R_CS_N)-diastereoisomers. It is known [16] that analogous complexes in which the nitrogen atom is linked to an isopropyl group are formed only as (S_CR_N)-diastereoisomers; therefore, we presumed that the major stereoisomers of complexes (*S*)-**II** and (*R*)-**II** have S_CR_N and R_CS_N configurations, respectively. We expected that catalysis by complex **II** having two chiral centers on the carbon and nitrogen atoms should pro-



Possible mutual orientations of the α-methyl fragment in the *R* and *S* isomers of complex **I** and the side-chain substituent in the (*R*)-leucine derivatives in the transition state for the hydrolysis of the ester group.

vide higher stereospecificity of the hydrolysis process, as compared to complexes **I** and **III**, for one of the chiral centers in **II** is located much more closely to the catalytic center.

The rate of hydrolysis of the methionine ester in the presence of complex **II** is lower than in the presence of **I** but higher than with the use of complex **III**. This is consistent with the above rationalization of the effect of the size of the substituent at the nitrogen atom on the coordination of sulfur to palladium and subsequent nucleophilic attack by the coordinated hydroxo ligand. The ratio of the catalytic rate constants for the S_CR_N and R_CS_N isomers of **II** is 1.7, i.e., the difference is greater than in the hydrolysis catalyzed by complexes **I** and **III**. We can conclude that *ortho*-palladated *N*-methyl-1-phenylethanamine **II** is the most promising among the three examined catalyst; this complex ensures fairly high reaction rate and higher stereospecificity, as compared to complexes **I** and **III** having only one chiral center.

Likewise, complex **II** turned out to be more effective than **I** and **III** in the hydrolysis of leucine and phenylalanine derivatives. In addition, the highest stereospecificity was attained in the hydrolysis catalyzed by complex **II**: the ratios k_S/k_R were 2.16 for the leucine ester and 2.28 for the phenylalanine ester. These findings can also be rationalized in terms of steric effect of a fairly large methyl substituent which, depending on the configuration of the nitrogen atom, interacts with bulky side-chain radicals in the amino acids to greater or lesser extent.

Our results indicate that the use of palladium complexes possessing a chiral nitrogen atom is the most promising from the viewpoint of attaining the maximal difference in the rates of hydrolysis of stereoisomeric optically active amino acid derivatives.

To conclude, the present study has shown that catalysts based on chiral palladacycles can be used to effect stereospecific hydrolysis of amino acid esters. We have also proposed a mechanistic explanation for the effect of mutual orientation of optically active centers in the catalyst and substrate on the efficiency of the process, which opens a way to purposeful design of palladium catalysts for hydrolysis of optically active substances.

EXPERIMENTAL

The NMR spectra were recorded on Varian UNITY-300 and Bruker CPX-200 spectrometers. Spectrophotometric studies were performed using Hitachi 150-20, Shimadzu UV-160A, and Pharmacia BioTech Ultrospec 1000 instruments equipped with a temperature-controlled unit. The optical rotations were measured on an Autopol II automatic polarimeter.

Procedure for kinetic measurements. The hydrolysis of amino acid *p*-nitrophenyl esters in the presence of *ortho*-palladated benzylamines was carried out in a 0.01 M phosphate buffer (pH 8.0) at 30°C. The kinetics of the process were monitored by spectrophotometry, following accumulation of *p*-nitrophenoxide ion at λ 400 nm. The reaction was initiated by adding in succession stock solutions of the complex and substrate in acetonitrile to a spectrophotometric cell. The reactant concentrations were $\sim 5\times10^{-5}$ M for the ester and 8×10^{-5} to 5×10^{-4} M for the catalyst. The concentration of acetonitrile in the reaction mixture was 10%.

The kinetic parameters were calculated by the nonlinear regression technique using SigmaPlot program. The apparent pseudofirst-order rate constants k_{ap} were calculated from the kinetic curve using the following equation:

$$D_\tau = D_\infty + (D_o - D_\infty)\exp(-k_{ap}\tau).$$

Here, D_τ, D_∞, and D_0 are the optical densities at a moment τ, by the end of the process, and in the initial moment, respectively. The kinetic curves are described by first-order equation for at least 5 half-conversion periods. From the dependence of the apparent rate constants on the concentration of palladium complexes we calculated the catalytic hydrolysis rate constants k_{cat} by the formula $k_{ap} = k_0 + k_{cat}[Pd(II)]$, where k_0 is the rate constant of hydrolysis in the absence of catalyst, and [Pd(II)] is the initial concentration of the palladium complex (calculated on the monomeric species).

(*R*)- and (*S*)-Chloro(1-phenylethanamine-*C*,*N*)-(pyridine)palladium(II) (I). The stereoisomeric complexes were synthesized according to the procedure described in [4] from di-μ-chlorobis(1-phenylethanamine-*C*,*N*)dipalladium(II) [17]. *R* Isomer: yield 91%, $[\alpha]_D^{20}$ = –24.3° (*c* = 0.85%, $CHCl_3$); *S* isomer: yield 97% $[\alpha]_D^{20}$ = +23.8° (*c* = 0.72%, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.63 d (CCH_3, *J* = 6 Hz), 3.40 and 4.70 br.d (NH_2), 4.44 q (CH, *J* = 6 Hz), 6.13 d (6-H, *J* = 8 Hz), 6.81 t (5-H, *J* = 8 Hz), 6.87 d (3-H, *J* = 8 Hz), 7.02 t (4-H, *J* = 8 Hz), 7.75 t (γ-H, *J* = 7 Hz), 8.67 d (α-H, *J* = 7 Hz); the signal from β-H in the pyridine ring was obscured by the solvent signal.

(*R*)- and (*S*)-Di(μ-chloro)bis(*N*-methyl-1-phenylethanamine-*C*,*N*)dipalladium(II) (II). The stereoisomeric complexes were synthesized from di-μ-acetobis-(*N*-methyl-1-phenylethanamine-*C*,*N*)dipalladium(II) [18] and sodium chloride according to the procedure for bridging ligand exchange [18–20]. *R* Isomer: yield 70%, $[\alpha]_D^{20}$ = –99° (*c* = 0.77%, CH_3CN); *S* isomer: yield 74%, $[\alpha]_D^{20}$ = +109° (*c* = 0.71%, CH_3CN). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.60 d (CCH_3, S_N), 1.72 d (CCH_3, R_N), 2.65 d (NCH_3, S_N), 2.89 d (NCH_3, R_N), 3.42 m (CH, S_N), 3.90 m (CH, R_N), 5.18 br.d (NH, S_N), 5.40 br.d (NH, R_N), 6.04 d (3-H, S_N), 6.10 d (3-H, R_N), 6.78 d.d (6-H), 6.89–6.98 m (4-H, 5-H).

(*R*)- and (*S*)-Di(μ-chloro)bis(*N*,*N*-dimethyl-1-phenylethanamine-*C*,*N*)dipalladium(II) (III). The complexes were synthesized according to the procedure described in [4] from K_2PdCl_4 and *N*,*N*-dimethyl-1-phenylethanamine. *R* Isomer: yield 86%, $[\alpha]_D^{20}$ = +57.3° (*c* = 1.85%, $CHCl_3$); *S* isomer: yield 83%, $[\alpha]_D^{20}$ = –42.8° (*c* = 0.71%, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: in $CDCl_3$: 1.59 d (CCH_3), 2.65 s and 2.92 s (NCH_3), 3.87 m (CH), 6.74–7.24 m (3-H, 4-H, 5-H, 6-H); in $CDCl_3$–pyridine-d_5: 1.64 d (CCH_3), 2.75 s and 2.97 s (NCH_3), 3.85 m (CH), 5.97 d.d (6-H), 6.73–6.96 m (3-H, 4-H, 5-H).

REFERENCES

1. Kurzeev, S.A., Kazankov, G.M., and Ryabov, A.D., *Russ. J. Org. Chem*., 2000, vol. 36, p. 1330.
2. Kurzeev, S.A., Kazankov, G.M., and Ryabov, A.D., *Inorg. Chim. Acta*, 2000, vol. 305, p. 1.
3. Kurzeev, S.A., Kazankov, G.M., and Ryabov, A.D., *J. Inorg. Biochem*., 2001, vol. 86, p. 304.
4. Ryabov, A.D., Kazankov, G.M., Kurzeev, S.A., Samuleev, P.V., and Polyakov, V.A., *Inorg. Chim. Acta*, 1998, vol. 280, p. 57.
5. Ryabov, A.D., Kazankov, G.M., Yatsimirsky, A.K., Kuz'mina, L.G., Burtseva, O.Y., Dvortsova, N.V., and Polyakov, V.A., *Inorg. Chem*., 1992, vol. 31, p. 3083.
6. Schmulling, M., Ryabov, A.D., and van Eldik, R., *J. Chem. Soc., Dalton Trans*., 1994, p. 1257.
7. Schmulling, M., Grove, D.M., van Koten, G., van Eldik, R., Veldman, N., and Spek, A.L., *Organometallics*, 1996, vol. 15, p. 1384.
8. Calmes, M., Glot, C., Michel, T., Rolland, M., and Martinez, J., *Tetrahedron: Asymmetry*, 2000, vol. 11, p. 737.
9. Scrimin, P., Tecilla, P., and Tonellato, U., *J. Org. Chem*., 1994, vol. 59, p. 4194.
10. Cleijg, M.C., Mancins, F., Scrimin, P., Tecillag, P., and Tonellato, U., *Tetrahedron*, 1997, vol. 53, p. 357.
11. Pellissier, H., *Tetrahedron*, 2003, vol. 59, p. 8291.
12. Cran, A.G., Gibson, C.L., and Handa, S., *Tetrahedron: Asymmetry*, 1995, vol. 6, p. 1553.
13. Bassas, O., Llor, N., Santos, M.M.M., Griera, R., Molins, E., Amat, M., and Bosch, J., *Org. Lett*., 2005, vol. 7, p. 2817.
14. Jitsukawa, K., Katoh, A., Funato, K., Ohata, N., Funahashi, Y., Ozawa, T., and Masuda, H., *Inorg. Chem*., 2003, vol. 42, p. 6163.
15. Makino, K., Goto, T., Hiroki, Y., and Hamada, Y., *Angew. Chem., Int. Ed*., 2004, vol. 43, p. 882.
16. Dunina, V.V., Golovan, E.B., and Gulyukina, N.S., *Tetrahedron: Asymmetry*, 1995, p. 2731.
17. Ryabov, A.D., Polyakov, V.A., and Yatsimirsky, A.K., *J. Chem. Soc., Perkin Trans. 2*, 1983, p. 1503.
18. Fuchita, Y., Tsuchiya, H., and Miyafuji, A., *Inorg. Chim. Acta*, 1995, vol. 233, p. 91.
19. Fuchita, Y., Yoshimura, Y., Hagino, Y., Kawano, H., and Kinoshita-Nagaoka, J., *J. Organomet. Chem*., 1999, vol. 580, p. 273.
20. Vicente, J., Saura-Llamas, I., and Palin, G., *Organometallics*, 1997, vol. 16, p. 826.