DOI: 10.1002/ejoc.200800523

Hydrosilanes Are Not Always Reducing Agents for Carbonyl Compounds but Can Also Induce Dehydration: A Ruthenium-Catalyzed Conversion of Primary Amides to Nitriles

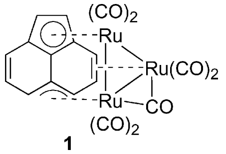
Shiori Hanada,[a] Yukihiro Motoyama,[b] and Hideo Nagashima*[b]

Keywords: Amides / Dehydration / Cyanides / Hydrosilanes / Ruthenium

A practical procedure for production of nitriles is offered by the triruthenium carbonyl cluster catalyzed dehydration of primary carboxamides with hydrosilanes under neutral conditions. This is the first example that a transition-metal-catalyzed activation of Si–H bonds does not lead to the reduction of carbonyl compounds but to dehydration. Possible mechanisms for the dehydration is discussed on the basis of NMR spectroscopic detection of intermediary species.

Introduction

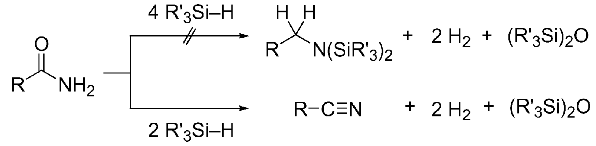
For hydrosilylation reactions, it is well known that the Si–H bond in hydrosilanes is added across an unsaturated bond with the aid of transition-metal catalysts.[1] Application of hydrosilylation to the reduction of C=O and C=N functional groups has been actively studied in organic synthesis, as the process has advantages over conventional hydride reductions; hydrosilanes are easy to handle and environmentally problematic waste is not formed. Furthermore, possibilities in catalyst design can lead to high reactivity and high selectivity of the reduction processes.[2] We have reported the triruthenium carbonyl cluster, ($\mu_3,\eta^2,\eta^3,\eta^5$-acenaphthylene)$Ru_3(CO)_7$ (**1**), to be one of the most reactive catalysts for the catalytic reduction of aldehydes, ketones, and carboxylic acid derivatives with hydrosilanes (Figure 1).[3]



1

Figure 1. ($\mu_3,\eta^2,\eta^3,\eta^5$-Acenaphthylene)$Ru_3(CO)_7$ (**1**).

Perhaps, the reduction of tertiary amides is the most useful example to show the utility of complex **1**. The reaction proceeds at ambient temperature under neutral conditions,[3b,3c] and a facile removal of both the silicone waste and the metal residues is achieved.[3d] The reduction of less-reactive secondary amides was also carried out by an appropriate choice of hydrosilanes.[3e] Within this context, we expected that primary amides would also reduce to the corresponding amines by an appropriate choice of hydrosilanes and reaction conditions. *To our astonishment, the reaction that actually occurred was not the reduction of amides to primary amines as expected, but a dehydration of amides to nitriles as shown in Scheme 1.* To the best of our knowledge, this is the first example of a transition-metal-catalyzed activation of Si–H bonds that does not lead to the reduction of carbonyl compounds but to dehydration.



Scheme 1. Reactions of primary amides with hydrosilanes.

Results and Discussion

When *p*-toluamide (**2a**) was treated with hydrosilanes listed in Table 1 in the presence of a catalytic amount of **1** at room temperature, hydrogen gas evolved, which lead to the dehydrogenative silylation of **2a** to give silylated amides (vide infra). Aqueous workup of the reaction mixture resulted in hydrolysis of the silylated amides to give complete recovery of **2a**. In contrast, dehydration of **2a** proceeded smoothly at higher temperatures to give *p*-tolunitrile (**3a**). Table 1 shows the yield of **3a** when **2a** (0.5 mmol) was treated with hydrosilanes (Si–H: 1.25 mmol) in dimethoxyethane (DME) in the presence of **1** (2.5 mol-% to **2a**) at

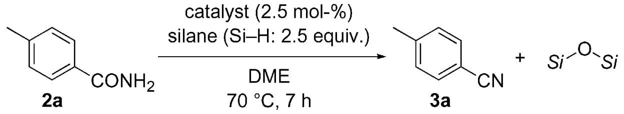
---

[a] Graduate School of Engineering Sciences, Kyushu University,
Kasuga, Fukuoka 816-8580, Japan
[b] Institute for Materials Chemistry and Engineering, Kyushu University,
Kasuga, Fukuoka 816-8580, Japan
Fax: +81-92-583-7819
E-mail: nagasima@cm.kyushu-u.ac.jp

Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

70 °C for 7 h. Several trialkylhydrosilanes and hydrosiloxanes can be used for the present dehydration, and hydride reduction of the C≡N group formed is not observed under these conditions. However, the yield of nitrile **3a** is sensitive to the structure of the organosilane used (Entries 1–8). Among the hydrosilanes we have examined, a bifunctional organosilane, 1,2-bis(dimethylsilyl)ethane (BDMSE),[4] provided the best results, as listed in Table 1. After 7 h, the conversion of **2a** reached ca. 60%, where **3a** was formed as a single product in 61% yield (Entry 8). A longer reaction time (12 h) resulted in complete conversion of the amide **2a** to afford the nitrile **3a** in 90% isolated yield (Entry 9). In our previous papers, we reported that reduction of amides with poly(methylhydrosiloxane) (PMHS) by catalyst **1** resulted in gelation of PMHS, and all of the ruthenium species are soaked up.[3d] The reaction of **2a** with PMHS in the presence of **1** led to a vigorous evolution of gas, and the silicone gel containing ruthenium was obtained within 10 min. However, the corresponding nitriles were isolated only in 10% yield (Entry 6). Presumably, **2a** was bonded with the silicone gel by either Si–O or Si–N bonds (vide infra). Although with a lower catalytic activity, other ruthenium carbonyl complexes, $Ru_3(CO)_{12}$ and $[RuCl_2(CO)_3]_2$, also catalyzed the dehydration reaction under similar conditions (Entries 10 and 11). In contrast, **3a** was not formed when either other ruthenium complexes $\{(\eta^5\text{-}C_5H_5)RuCl(PPh_3)_2$, $[(\eta^6\text{-}C_6Me_6)RuCl_2]_2$, and $[(\eta^6\text{-}C_6Me_6)RuCl(MeCN)_2](PF_6)\}$ or other late transition metals such as $Co_2(CO)_8$, $RhH(CO)(PPh_3)_3$, and $IrCl(CO)(PPh_3)_2$ were used as the catalyst (see Supporting Information).

Table 1. Dehydration of *p*-toluamide **2a** by various silanes and ruthenium complexes.[a]

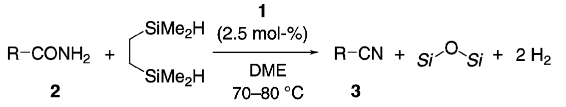


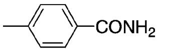
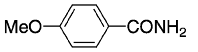
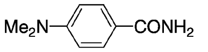
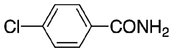
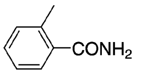
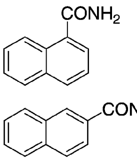
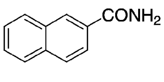
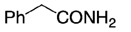
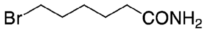
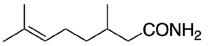
Entry	Catalyst	Silane	Yield [%][b]
1	**1**	Et_3SiH	<2
2	**1**	$(EtO)_2MeSiH$	<2
3	**1**	$(n\text{Octyl})Me_2SiH$	46
4	**1**	$Me_3SiOSiMe_2H$	36
5	**1**	$HMe_2SiOSiMe_2H$	10
6	**1**	PMHS	10
7	**1**	$1,2\text{-}(HMe_2Si)_2C_6H_4$	<2
8	**1**	$HMe_2Si(CH_2)_2SiMe_2H$	61
9[c]	**1**	$HMe_2Si(CH_2)_2SiMe_2H$	>95 (90)[d]
10	$Ru_3(CO)_{12}$	$HMe_2Si(CH_2)_2SiMe_2H$	51
11	$[RuCl_2(CO)_3]_2$	$HMe_2Si(CH_2)_2SiMe_2H$	19

[a] Reaction conditions: **2a** (0.5 mmol), ruthenium complex **1** (2.5 mol-% to **2a**), DME (0.25 mL), hydrosilanes (Si–H: 1.25 mmol), 70 °C, 7 h, under nitrogen atmosphere. [b] Determined by ^1H NMR spectroscopy analysis with dibenzyl ether as an internal standard. [c] For 12 h. [d] The yield in parentheses was the isolated yield by silica gel chromatography.

Table 2 shows the results obtained for the dehydration of various primary carboxamides (**2a**–**2k**) with BDMSE (Si–H: 2.5 equiv. to the amide). In the presence of 2.5–5 mol-% of the triruthenium carbonyl cluster **1**, the reactions of aromatic and aliphatic amides generally occurred at 70–80 °C to give the desired nitriles as a single product. The yield of the nitriles as determined by NMR spectroscopy was found to be over 95% after 12–24 h. After purification of the crude product, dehydration of the *para*-substituted benzamide derivatives **2a**–**2c** proceeded smoothly to give the corresponding benzonitriles **3a**–**3c** in 88–90% isolated yields (Entries 1–3). The electron-withdrawing chloro substituent retards the reaction, and a twofold amount of **1** was needed for effective conversion of the amide **2d** (Entry 4). In the reactions of *o*-toluamide (**2e**) and α- and β-naphthamides (**2f** and **2g**, respectively), the yield of the product was found to improve at slightly higher temperatures (80 °C, Entries 5–7). Neither reduction of a carbon–bromine bond nor elimination of hydrogen bromide occurred in the reaction of 6-bromohexanamide (**2j**) to give the desired 6-bromohexanenitrile **3j** in 95% isolated yield (Entry 10). The present system was also effective for the dehydration of amides containing a tri-substituted alkenyl moi-

Table 2. Dehydration of various primary amides with BDMSE catalyzed by triruthenium carbonyl cluster **1**.[a]

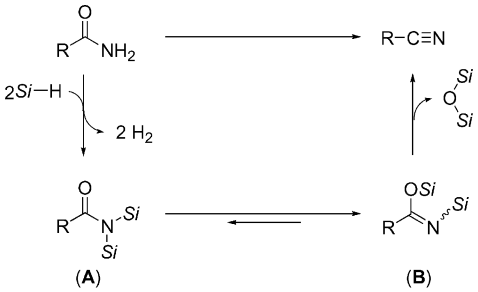


Entry	Amide	Temp. [°C]	Time [h]	Yield[b][%]
1	 **2a**	70	12	>95 (90)
2	 **2b**	70	18	>95 (90)
3	 **2c**	70	18	>95 (88)
4[c]	 **2d**	70	24	>95 (72)[d]
5	 **2e**	80	24	>95 (88)
6	 **2f**	80	20	>95 (92)
7	 **2g**	80	24	>95 (96)
8	$C_{10}H_{21}CONH_2$ **2h**	70	18	>95 (84)
9	 **2i**	70	20	>95 (61)[d]
10	 **2j**	80	20	>95 (95)
11	 **2k**	80	20	>95 (60)[d]

[a] Reaction conditions: primary amide (**2a**–**2k**: 1.0 mmol), ruthenium complex **1** (16.3 mg, 2.5 mol-%), DME (0.5 mL), 1,2-bis(dimethylsilyl)ethane (246 µL, 1.25 mmol, Si–H: 2.5 equiv. to **2**), under nitrogen atmosphere. [b] Determined by ^1H NMR spectroscopy analysis. The yield in parentheses was the isolated yield by silica gel chromatography. [c] 5.0 mol-% of **1** was used. [d] The lower yield was caused by substantial loss of the product in the purification process.

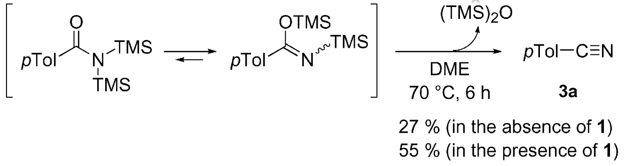
ety, e.g. the reaction of citronellamide **2k** at 80 °C for 20 h gave citronellyl nitrile **3k** as a single product. Hydrosilylation towards the C=C bond did not occur (Entry 11). In contrast, reduction of the C=C bond, presumably through 1,4-hydrosilylation of the α,β-unsaturated nitriles formed, is a major side reaction in the reaction of α,β-unsaturated carboxamides.[5] *Trans*-cinnamamide was converted mainly to dihydrocinnamonitrile, which was obtained in ca. 50% yield.

An intriguing feature of this new reaction is the role of hydrosilanes as dehydrating reagents; hydrosilanes usually act as reducing reagents in this particular catalytic reaction. In fact, the present catalytic system is effective for the reduction of tertiary and secondary amides.[3] A clue towards understanding the mechanism is the reaction of N–H groups of primary amides with hydrosilanes to give H_2, which facilely takes place in the presence of **1**. A plausible mechanism is shown in Scheme 2. The reaction of a primary amide with two equivalents of an Si–H group gives an equilibrium mixture, bis(silyl)amide **A** and *N*,*O*-bis(silyl)imidate **B**.[6] It is known that the bis(silyl)imidate **B** facilely eliminates a siloxane molecule to form the corresponding nitrile under thermal conditions (200–250 °C).[7]



Scheme 2. Possible reaction mechanism.

Formation of **A** and **B** was actually confirmed by ^1H and ^{29}Si NMR spectroscopy analysis of the reaction mixture. In the reaction of **2a** with BDMSE (Si–H: 2.2 equiv. to **2a**) in the presence of **1** (2.5 mol-%) in [D$_6$]benzene at 70 °C, the N–H protons of amide **2a** were completely consumed within 1 h, and the ^{29}Si NMR spectrum of the reaction mixture showed four signals at δ = 10.1, 14.0, 15.7, and 23.9 ppm. These signals are the same as those for the bis-silylated compounds prepared from *p*-toluoyl chloride and lithium 2,4-bis(dimethylsilyl)-1-azacyclopentane according to the literature methods[8] and support the presence of both *N*,*N*- and *O*,*N*-silylated species.[9] As the reaction progressed, ^1H resonances from *p*-tolunitrile and a ^{29}Si signal at δ = 8.59 ppm from 2,5-bis(dimethylsilyl)-1-oxacyclopentane arise. The ^{29}Si signal at δ = 8.59 ppm slowly diminished to give many peaks at 8–10 ppm, which suggest that ring-opening polymerization of 2,5-bis(dimethylsilyl)-1-oxacyclopentane occurs.[10] We observed that the catalysis by **1** accelerates the reaction. Thermal decomposition of a mixture of **A** and **B**, which were prepared from *p*-toluoyl chloride and LiN(TMS)$_2$,[8] in DME at 70 °C for 6 h gave *p*-tolunitrile **3a** in only 27%. In contrast, the yield is increased to 55% in the presence of ruthenium complex **1** (Scheme 3).



Scheme 3. Thermal decomposition of bis(trimethylsilyl)amide derivatives.

Conclusions

The present reaction, which presents the effective use of hydrosilanes as dehydrating reagents under catalysis by **1**, provides an important new aspect in organic chemistry. It is known that halosilanes and alkoxysilanes are useful in dehydration reactions in organic synthesis because of the strong affinity of Si and O.[11] However, an intramolecular esterification reported by Mukaiyama is the only precedence for an organohydrosilanes behaving as dehydrating reagents, in which a substrate containing two acidic protons and an oxygen atom reacts with a hydrosilane with the aid of a rhodium catalyst and a strong Lewis acid, which leads to the elimination of a siloxane. Synthesis of nitriles by dehydration of primary amides conventionally requires strongly acidic and vigorously reactive reagents[12] such as phosphorus pentoxide,[12c] titanium tetrachloride,[12d] or thionyl chloride.[12e] Although several dehydrating reagents that can be used under milder conditions have been devised recently,[13] only a few reactions occur under neutral conditions.[14] They all have drawbacks. The present report clearly demonstrates the utility of catalytic activation of hydrosilanes in the dehydration of primary amides to nitriles, which leads to a new process that proceeds under neutral conditions and does not give intractable waste. Further investigation on transition-metal catalysis inducing dehydration with hydrosilanes is underway.

Experimental Section

General Remarks: ^1H, ^{13}C, and ^{29}Si NMR spectra were measured on JEOL GSX-270 (270 MHz) and ECA 600 (600 MHz) spectrometers. Chemical shifts for ^1H NMR spectroscopy are expressed in parts per million downfield from tetramethylsilane as an internal standard (δ = 0 ppm) in CDCl$_3$, unless otherwise noted. Chemical shifts for ^{13}C NMR spectroscopy are expressed in parts per million in CDCl$_3$ as an internal standard (δ = 77.1 ppm), unless otherwise noted. Chemical shifts for ^{29}Si NMR spectroscopy are expressed in parts per million downfield from tetramethylsilane as an external standard. IR spectra were measured on a JASCO FT/IR-4200 spectrometer. Analytical thin-layer chromatography (TLC) was performed on glass plates precoated with silica gel (Merck, Kieselgel 60 F$_{254}$, layer thickness 0.25 mm). Visualization was accomplished by UV light (254 nm), iodine, and phosphomolybdic acid. (μ_3,η^2,η^3,η^5-Acenaphthylene)Ru$_3$(CO)$_7$ (**1**)[3c] and 1,2-(HMe$_2$Si)$_2$-C$_6$H$_4$[4a] were prepared by methods reported previously. Ru$_3$(CO)$_{12}$[15] and [RuCl$_2$(CO)$_3$]$_2$[16] were prepared by the literature methods.

Synthesis of 1,2-Bis(dimethylsilyl)ethane (BDMSE):[17] To a suspension of lithium aluminum hydride (3 g, large excess) in tetraglyme

(30 mL) was slowly added 1,2-bis(chlorodimethylsilyl)ethane (10 g, 23.2 mmol) at 0 °C; the mixture was then stirred at 50 °C for 3 h. Purification by direct distillation from the resultant suspension under reduced pressure (64 °C/90 Torr) gave 1,2-bis(dimethylsilyl)ethane (BDMSE) in 81% yield (5.5 g). Colorless liquid. ^{1}H NMR (270 MHz, CDCl$_3$): δ = 0.07 (d, J = 3.6 Hz, 12 H), 0.53 (t, J = 1.7 Hz, 4 H), 3.84 (t of sept., J = 1.7, 3.6 Hz, 2 H) ppm. ^{13}C NMR (67.8 MHz, CDCl$_3$): δ = –4.7, 7.2 ppm. IR (neat): $\nu_{\text{Si–H}}$ = 2116 cm^{-1}.

Typical Dehydration Procedure: To a stirred solution of *p*-toluamide (**2a**) (1.0 mmol) and ($\mu_3,\eta^2,\eta^3,\eta^5$-acenaphthylene)Ru$_3(CO)_7$ (**1**) (16.3 mg, 2.5 mol-%) in dimethoxyethane (0.5 mL) was slowly added 1,2-bis(dimethylsilyl)ethane (246 µL, Si–H: 2.5 equiv. to **2a**). At this time, the evolution of hydrogen gas was observed. After the mixture was stirred at 70 °C for 12 h, the cooled reaction mixture was diluted with diethyl ether and quenched by the addition of sodium hydrogen carbonate. After it was stirred at room temperature for 30 min, the resultant mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/ether = 20:1) gave *p*-tolunitrile (**3a**) in 90% yield. Colorless liquid. ^{1}H NMR (270 MHz, CDCl$_3$): δ = 2.42 (s, 3 H), 7.27 (d, J = 8.2 Hz, 2 H), 7.54 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR (67.8 MHz, CDCl$_3$): δ = 21.9, 109.4, 119.2, 129.9, 132.1, 143.7 ppm. IR (neat): $\nu_{\text{C}\equiv\text{N}}$ = 2222 cm^{-1}.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and characterization data of both the primary amides and the nitriles formed are presented.

Acknowledgments

This work was partially supported by a Grant-in Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. S. H. is thankful for a Research Fellowship from the Japan Society for the Promotion of Science for Young Scientists.

---

[1] a) I. Ojima in *The Chemistry of Organic Silicon Compounds* (Ed.: S. Patai, Z. Rappoport), John Wiley & Sons, New York, **1989**, part 2, ch. 25, pp. 1479–1526; b) B. Marciniec, *Comprehensive Handbook on Hydrosilylation*, Pergamon Press, Oxford, **1992**; c) B. Marciniec in *Applied Homogeneous Catalysis with Organometallic Compounds* (Eds.: B. Cornils, W. A. Herrmann), Wiley-VCH, Weinheim, **1996**, vol. 1, ch. 2.

[2] a) H. Nishiyama, K. Itoh in *Catalytic Asymmetric Synthesis, 2nd ed.* (Ed.: I. Ojima), Wiley-VCH, New York, **2000**, pp. 111–143; b) J.-F. Carpentier, V. Bette, *Curr. Org. Chem.* **2002**, *6*, 913–936; O. Riant, N. Mostefaï, J. Courmarcel, *Synthesis* **2004**, 2943–2958.

[3] a) H. Nagashima, A. Suzuki, T. Iura, K. Ryu, K. Matsubara, *Organometallics* **2000**, *19*, 3579–3590; b) K. Matsubara, T. Iura, T. Maki, H. Nagashima, *J. Org. Chem.* **2002**, *67*, 4985–4988; c) Y. Motoyama, C. Itonaga, T. Ishida, M. Takasaki, H. Nagashima, *Org. Synth.* **2005**, *82*, 188–195; d) Y. Motoyama, K. Mitsui, T. Ishida, H. Nagashima, *J. Am. Chem. Soc.* **2005**, *127*, 13150–13151; e) S. Hanada, T. Ishida, Y. Motoyama, H. Nagashima, *J. Org. Chem.* **2007**, *72*, 7551–7559.

[4] Rate enhancement by proximate dual Si–H groups is often seen in transition-metal-catalyzed hydrosilylation reactions, see: a) H. Nagashima, K. Tatebe, Y. Ishibashi, A. Nakaoka, J. Sakakibara, K. Itoh, *Organometallics* **1995**, *14*, 2868–2879; b) S. Hanada, Y. Motoyama, H. Nagashima, *Tetrahedron Lett.* **2006**, *47*, 6173–6177, and ref.[3a]

[5] In the reaction of *trans*-cinnamonitrile with BDMSE, dihydrocinnamonitrile was obtained in ca. 60% yield by [1,4]-addition, followed by hydrolysis.

[6] a) K. Itoh, M. Katsuda, Y. Ishii, *J. Chem. Soc. B* **1970**, 302–304; b) B. Dejak, Z. Lasocki, *J. Organomet. Chem.* **1983**, *246*, 151–158; c) M. S. Samples, C. H. Yoder, *J. Organomet. Chem.* **1987**, *332*, 69–73.

[7] a) C. Kruger, E. G. Rochow, U. Wannagat, *Chem. Ber.* **1963**, *96*, 2138–2143; b) W. E. Dannis, *J. Org. Chem.* **1970**, *35*, 3253–3255; c) B. Rigo, C. Lespagnol, M. Pauly, *Tetrahedron Lett.* **1986**, *27*, 347–348.

[8] a) J. Pump, E. G. Rochow, *Chem. Ber.* **1964**, *97*, 627–635, and ref. 6a.

[9] A. R. Bassindale, T. B. Posner, *J. Organomet. Chem.* **1979**, *175*, 273–284.

[10] K. Matsubara, J.-I. Terasawa, H. Nagashima, *J. Organomet. Chem.* **2002**, *660*, 145–152.

[11] a) H. Vorbrüggen, *Silicon-Mediated Transformations of Functional Groups*, Wiley-VCH, Weinheim, **2004**; b) T. Tozawa, Y. Yamabe, T. Mukaiyama, *Chem. Lett.* **2005**, *34*, 1334–1335; T. Tozawa, Y. Yamabe, T. Mukaiyama, *Chem. Lett.* **2005**, *34*, 1586–1587, and references therein.

[12] Reviews, see; a) D. T. Mowry, *Chem. Rev.* **1948**, *42*, 189–283; b) R. C. Larock, *Comprehensive Organic Transformations*, VCH, New York, **1989**; c) D. B. Reisner, E. C. Horning, *Org. Synth., Coll. Vol. IV*, **1963**, p. 144–145; d) W. Lehnert, *Tetrahedron Lett.* **1971**, *12*, 1501–1504; e) J. A. Krynitsky, H. W. Carhart, *Org. Synth., Coll. Vol. IV*, **1963**, p. 436–438; f) F. Campagna, A. Carotti, G. Casini, *Tetrahedron Lett.* **1977**, *18*, 1813–1815.

[13] a) C. Kuo, J. Zhu, J. Wu, C. Chu, C. Yao, K. Shia, *Chem. Commun.* **2007**, 301–303; b) A. V. Narsaiah, K. Nagaiah, *Adv. Synth. Catal.* **2004**, *346*, 1271–1274; c) N. Nakajima, M. Saito, M. Ubukata, *Tetrahedron* **2002**, *58*, 3561–3577.

[14] a) R. T. Ruck, R. G. Bergman, *Angew. Chem. Int. Ed.* **2004**, *43*, 5375–5377; b) S. Kim, K. Yi, *Tetrahedron Lett.* **1986**, *27*, 1925–1928; c) C. Ressler, H. Ratzkin, *J. Org. Chem.* **1961**, *26*, 3356–3360.

[15] M. I. Bruce, C. M. Jensen, N. L. Jones, *Inorg. Synth.* **1990**, *28*, 216–220, and references therein.

[16] A. Mantovani, S. Cenini, *Inorg. Synth.* **1976**, *16*, 51–53.

[17] P. Pawluc, B. Marciniec, I. Kownacki, H. Maciejewski, *Appl. Organomet. Chem.* **2005**, *19*, 49–54.

Received: May 29, 2008