

Palladium-Catalyzed Tetrakis(dimethylamino)ethylene-Promoted Reductive Coupling of Aryl Halides

Manabu Kuroboshi, Yoko Waki, and Hideo Tanaka*

Department of Applied Chemistry, Faculty of Engineering, Okayama University, Tsushima-naka 3-1-1, Okayama, Okayama 700-8530, Japan

tanaka95@cc.okayama-u.ac.jp

Received December 17, 2002

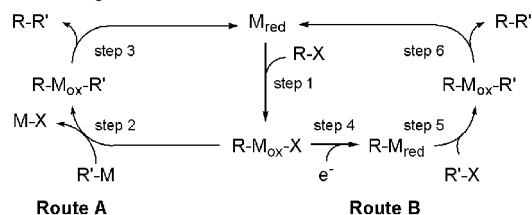
Tetrakis(dimethylamino)ethylene (TDAE)/cat. PdCl₂(PhCN)₂-promoted reductive coupling of aryl bromides having either electron-donating or electron-withdrawing groups on their para- and/or meta-position proceeded smoothly to afford the corresponding biaryls in good to excellent yields. Notably, TDAE is such a mild reductant that easily reducible groups, such as carbonyl and nitro groups, are tolerate. A similar reductive coupling of ortho-substituted aryl bromides did not occur at all. The proper choice of palladium catalysts is essential for the reductive coupling; thus, PdCl₂(PhCN)₂, PdCl₂(MeCN)₂, Pd(hfacac)₂, Pd₂(dba)₃, PdCl₂, and Pd(OAc)₂ were used successively for this reaction, but phosphine-ligated palladium catalysts such as Pd(PPh₃)₄, PdCl₂(PPh₃)₂, and Pd(dppp) did not promote the reaction. The reductive coupling did not occur with nickel catalysts such as NiBr₂, NiCl₂(bpy), and Ni(acac)₂. The TDAE/cat. palladium-promoted reductive coupling of aryl halides having electron-withdrawing groups took place more efficiently than that of aryl halides substituted with electron-donating groups. A plausible mechanism of TDAE/cat. palladium-promoted reaction is discussed.

Introduction

Biaryl compounds are useful compounds because of the excellent physical and chemical properties. Indeed, biaryls are widely used as monomers of conductive polymers,¹ chiral phosphine ligands,² chiral host molecules for inclusion compounds,³ chirality-recognition reagents for chromatography,⁴ and core structures for liquid crystals.⁵ Biaryl skeletons are also found in many important natural bioactive products⁶ such as (–)-ancistrocladine, (–)-gossypol, and (–)-steganone. Recently, supramolecules having biaryl moieties have been synthesized.⁷

There have been reported many methods to prepare biaryls. For example, cross-coupling reactions of aryl halides with arylmetals in the presence of Pd(0) and/or Ni(0) catalysts have been developed. Arylboronic acids,⁸

SCHEME 1. Catalytic Cycle of Transition Metal-Catalyzed Reaction



arylstannanes,⁹ and arylzinc¹⁰ derivatives as well as aryl Grignard reagents¹¹ are frequently used as arylmetal reagents. In these reactions, oxidative addition of organic halide or *pseudo*-halide to low-valent metal reagent M_{red} forms organometallic reagent R-M_{ox}-X (Scheme 1, Route A, step 1). Subsequent reaction of R-M_{ox}-X with organometallic reagent R'-M generates R-M_{ox}-R' (step 2). Reductive elimination of R-M_{ox}-R' produces R-R' and regenerates M_{red} (step 3). These methods are effective, but require more than an equimolar amount of organometallic reagent, R'-M.

Reductive dimerization of aryl halide is considered to be a more convenient and straightforward method for the synthesis of symmetrical biaryls. Historically, Ullmann coupling has been used for this purpose.^{12,13} However,

(1) (a) Schulz, E.; Fahmi, K.; Lemaire, M. *Acros Org. Acta* **1995**, *1*, 10. (b) Papiion, J.; Schulz, E.; Gélinas, S.; Lessard, J.; Lemaire, M. *Synth. Metals* **1998**, *96*, 155–160. (c) Zhu, S. S.; Swager T. M. *Adv. Mater.* **1996**, *8*, 497. (d) Yamamoto, T.; Maruyama, T.; Zhou, Z.; Ito, T.; Fukada, T.; Yoneda, Y.; Begum, F.; Ikeda, T.; Sasaki, S.; Takezoe, H.; Fukada, A.; Kubota, K. *J. Am. Chem. Soc.* **1994**, *116*, 4832.

(2) Noyori, R. *Chem. Soc. Rev.* **1989**, *18*, 187.

(3) Chao, Y.; Weisman, G. R.; Sogah, G. D. Y.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 515.

(4) Mikes, F.; Boshart, G. *J. Chromatogr.* **1978**, *149*, 455.

(5) Yamamura, K.; Ono, S.; Tabushi, I. *Tetrahedron Lett.* **1988**, *29*, 1797.

(6) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977.

(7) *Supramolecular Chemistry*, 1st ed.; Lehn, J. M., Ed.; VCH Verlagsgesellschaft: Weinheim, Germany, 1995.

(8) (a) Liebeskind, L. S.; Peña-Cabrera, E. *Tetrahedron Lett.* **1995**, *36*, 2191. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2454.

(9) Wallow, T. I.; Norak, B. M. *J. Org. Chem.* **1994**, *59*, 5034.

(10) Miller, J. A.; Farrell, R. P. *Tetrahedron Lett.* **1998**, *39*, 6441.

(11) Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153.

(12) (a) Ullman, F. *Chem. Ber.* **1903**, *36*, 2389. (b) Fanta, E. *Synthesis* **1974**, 9.

TABLE 1. Reductive Coupling Reaction of *p*-Bromoanisole

entry	cat.	time/h	yield of 2a / ^a %
1	PdCl ₂ (PhCN) ₂	4	98
2	PdCl ₂ (MeCN) ₂	8	96
3	Pd(hfacac) ₂	5	98
4	Pd ₂ (dba) ₃	24	75
5	PdCl ₂	14	98
6	Pd(OAc) ₂	10	80
7	PdCl ₂ (PPh ₃) ₂	6	— ^b
8	Pd(PPh ₃) ₄	4	— ^b
9	PdCl ₂ (dppb)	6	— ^b
10	NiBr ₂	10	— ^b
11	NiCl ₂ (bpy)	10	— ^b
12	Ni(acac) ₂	10	— ^b

^a Isolated yields. ^b Most of the starting material **1a** was recovered.

Results and Discussion

Reductive coupling of *p*-bromoanisole (**1a**) was carried out by use of TDAE/cat. PdCl₂(PhCN)₂ combination. A typical procedure is as follows (Table 1, Entry 1): To a solution of **1a** (1 mmol) and a catalytic amount of PdCl₂(PhCN)₂ (0.05 mmol) in freshly distilled DMF (5 mL) was added TDAE (2 mmol) in one portion. The reaction mixture turned dark brown immediately after the addition of TDAE. The mixture was stirred under argon atmosphere at 50 °C and the reaction was monitored by HPLC. After most of the starting material **1a** was consumed (4 h), the usual workup followed by recrystallization from hexanes–ethyl acetate afforded the corresponding biaryl compound **2a** in 98% yield.²⁹

Proper choice of the catalyst is essential for this reaction (Table 1). When PdCl₂(MeCN)₂, Pd(hfacac)₂ (hfacac = hexafluoroacetylacetonato), and Pd₂(dba)₃ (dba = dibenzylacetone) were used in place of PdCl₂(PhCN)₂, the reductive coupling reaction of **1a** proceeded in a similar manner to give the desired biaryl compound **2a** in excellent to good yields (Entries 2–4). Palladium catalysts bearing no ligands, such as PdCl₂ and Pd(OAc)₂, could also promote the reductive coupling reaction to give **2a** in good yield (Entries 5 and 6). These results are reasonably understood by assuming that TDAE would act as a ligand as well as a reductant; thus, TDAE would coordinate to palladium with its nitrogen atoms to suppress the deposition of Pd metal. Two-electron transfer from TDAE to the Pd(II) would take place efficiently through this kind of coordination.

In contrast, phosphine-ligated palladium complexes, such as PdCl₂(PPh₃)₂, Pd(PPh₃)₄, and PdCl₂(dppb), did not promote the reductive coupling reaction at all, and most of the substrate **1a** was recovered (Entries 7–9). In these reactions, no color change of the reaction mixture was observed, suggesting that phosphine ligands would coordinate to Pd(II) so tightly that TDAE could scarcely interact with the palladium metal. It is also very likely

(29) After extraction, byproducts derived from TDAE were not detected at all. Though there is no evidence, TDAE might turn into water-soluble degradation products.

that donation of the lone pair of the phosphine to Pd(II) would prevent the electron transfer from TDAE to the Pd(II). Indeed, redox potentials of ArPdCl(PPh₃)₂ are around –2 V³⁰ vs SCE in DMF, while the redox potential of TDAE is –0.62 V vs SCE in DMF. Therefore, TDAE could not reduce the phosphine-coordinated arylpalladium complex to generate an active low-valent Pd(0) species.

A similar reductive coupling reaction of **1a** with Ni(II) complexes such as NiCl₂(bpy), NiBr₂, and Ni(acac)₂ did not proceed at all (Entries 10–12). It is likely that reduction of Ni(II) with TDAE cannot effectively proceed.³¹ In contrast, zinc metal can generate active low-valent palladium and nickel species from PdCl₂(PPh₃)₂^{14f} and NiCl₂(PPh₃)₂,^{14a–d} respectively, which promote the reductive coupling of aryl halides. From these phenomena, TDAE is found to be a very mild and selective reductant, and is expected to promote chemoselective reactions.

The TDAE/cat. PdCl₂(PhCN)₂ system can be successfully applied to the reductive coupling of various aryl halides. The representative results are summarized in Table 2. Aryl bromides having an electron-donating group such as methoxy (**1a**, Entry 1), methyl (**1d**, Entry 4), and *N,N*-dimethylamino (**1e**, Entry 5) groups at the para-position gave the corresponding biaryls (**2a**, **2d**, **2e**) in good yield. *p*-Methoxyphenyl iodide (**1b**) gave the corresponding biaryl compounds quantitatively (Entry 2), whereas the reductive coupling with *p*-methoxyphenyl chloride (**1c**) did not proceed at all, and most of the starting material was recovered (Entry 3). Nonsubstituted bromobenzene (**1f**) gave biphenyl (**2f**) in moderate yield (Entry 6).³²

Similar reductive coupling reactions proceeded smoothly with substrates having electron-withdrawing groups, such as formyl (**1g**, Entry 7), cyano (**1h**, Entry 8), and ester groups (**1i** and **1j**, Entries 9 and 10), and these functional groups were not affected during the course of these reactions. The reductive coupling of nitrophenyl halides is very difficult because the nitro group is reduced very easily. Indeed, the reductive coupling of 4-bromonitrobenzene (**1k**) with use of zinc or magnesium as a reductant did not yield 4,4'-dinitrobiphenyl (**2k**). The desired **2k**, however, was obtained by use of this TDAE/cat. palladium system in 92% yield (Entry 10). TDAE may work as a very mild reductant and it is very likely that TDAE would reduce Pd(II) complexes selectively without reduction of the nitro group. Similarly, *p*-iodonitrobenzene gave **2k** in a quantitative yield with 60 mol % of TDAE (Entry 12).

Reductive coupling of 2-bromopyridine (**1m**) proceeded smoothly and was completed within 2 h to give the corresponding bipyridyl compound **2m** in 83% yield

(30) Amatore, C.; Carré, E.; Jutand, A.; Tanaka, H.; Ren, Q.; Torii, S. *Chem. Eur. J.* **1996**, *2*, 957.

(31) Although aluminum is a more powerful reductant than zinc, aluminum/nickel catalyst-promoted reductive coupling of aryl halides only proceeded in the presence of a catalytic amount of PbBr₂ in methanol.^{3a} The redox potential of TDAE is close to that of zinc, but TDAE could not reduce nickel reagents. It is difficult to discuss the reaction between the transition metal reagents and the electron source from the viewpoint of the redox potential, and further investigation is needed.

(32) The substrate **1a** was not detected after 10 h. A part of biaryl **2a** seems to be lost during workup and/or purification processes due to its high volatility.

TABLE 2. Reductive Coupling Reaction of Aryl Halides with PdCl₂(PhCN)₂/TDAE

		Ar-X 1 (1 mmol)		PdCl ₂ (PhCN) ₂ (0.05 mmol) TDAE (2 mmol) DMF (5 mL), 50 °C		Ar-Ar 2	
Entry	Aryl Halide 1	Time (h)	Yield 2 (%) ^a	Entry	Aryl Halide 1	Time (h)	Yield 2 (%) ^a
1		4	98 (89)	13		2	75 (83)
2	X = I 1b	5	70	14		24	- ^b
3	X = Cl 1c	24	trace	15	HCl ·	6	92
4		10	89(83)	16		24	- ^b
5		8	90 (81)	17		24	- ^b
6		12	68(84)	18		24	- ^b
7		2	88 (90)	19		24	- ^b
8		2	89 (94)	20		24	trace ^b
9		3	87 (90)	21		42	trace ^b
10		3	81 (79)				
11	X = Br 1k	2	92 (98)				
12	X = I 1l	24	(93)				

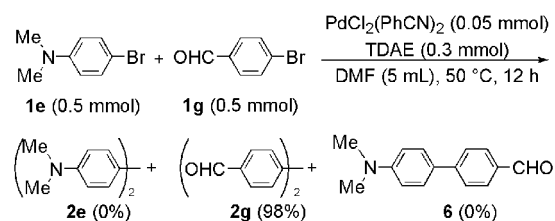
^a Isolated yield. Yields in parentheses were obtained from reactions with 60 mol % (0.6 mmol) of TDAE. ^b Most of the starting material was recovered.

(Entry 13). Upon similar conditions, 3-bromopyridine (**1n**) was not converted into the corresponding reductive coupling product **2n**, and most of the substrate **1n** was recovered (Entry 14). These results are probably due to the electronic nature of the pyridine ring, that is, the 2-position and the 4-position of pyridine are relatively electron deficient, while the 3-position is relatively electron rich. The reductive coupling of 4-bromopyridine hydrochloride (**1o**) was performed by use of an excess amount (200 mol %) of TDAE to afford **2o** in 92% yield (Entry 15), wherein TDAE would act not only as a reductant of Pd(II) but also as a base to neutralize hydrochloric acid. In all experiments (vide supra), no detectable amount of protonolysis products, Ar-H, was obtained from this TDAE/cat. palladium-promoted coupling reaction. A small excess (0.6 mmol) amount of TDAE was found to be enough to complete the reductive coupling of most of the aryl halides (Table 2, Entries 1, 2, 3, 6, 7, 8, 9, 10, and 20), indicating that electron transfer from TDAE to palladium(II) occurs efficiently.

Bromobenzenes bearing hydroxyl (**1p**, Entry 16), amino (**1q** and **1r**, Entries 17 and 18), and hydroxycarbonyl (**1s**, Entry 19) substituents did not give the corresponding

coupling products, presumably because so tight an interaction between palladium and these substituents would disturb the oxidative addition of aryl halides. On the other hand, aryl bromides possessing an ortho substituent (**1t**) afforded only a trace amount of the desired products (Entry 20). Naphthyl bromide (**1u**) did not undergo the reductive coupling reaction and most of **1u** was recovered (Entry 21). It is not clear at present but the steric hindrance of the ortho substituent would prevent the formation of intermediary arylpalladium complexes.

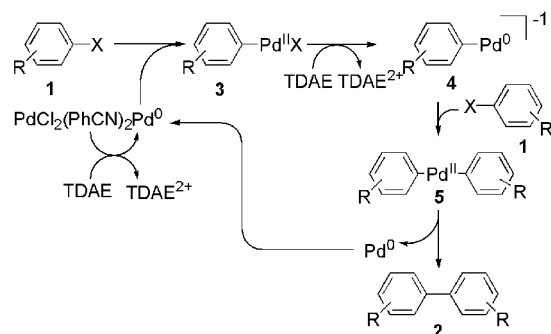
To obtain more insight of the TDAE/cat. palladium biredox system, the cross-coupling reaction of *p*-bromo-*N,N*-dimethylaniline (**1e**) and *p*-bromobenzaldehyde (**1g**) was investigated. The reaction was carried out as follows: To a mixture of **1e** (0.5 mmol), **1g** (0.5 mmol), and PdCl₂(PhCN)₂ (0.05 mmol) in DMF was added 0.3 mmol of TDAE, and the mixture was stirred at 50 °C for 12 h. After the usual workup, only the biaryl **2g** was produced in 98% yield, and **1e** was recovered quantitatively (eq 2). These results indicate that, in the TDAE/cat. palladium biredox system, aryl halides with an electron-



withdrawing group (CHO) are more reactive than those with an electron-donating group (NMe_2) (Scheme 1, steps 1 and 5).

A plausible mechanism of the TDAE/cat. palladium-promoted reductive coupling reaction of aryl halides is shown in Scheme 2. The reductive coupling reaction would be initiated with reduction of Pd(II) with TDAE generating Pd(0) species. Oxidative addition of aryl halide Ar-X **1** to thus generated Pd(0) could form Ar-Pd^{II}-X **3**. The Pd complexes Ar-Pd^{II}-X **3** would be reduced with TDAE to give [Ar-Pd(0)]⁻ **4**. Subsequent reaction of [Ar-Pd(0)]⁻ **4** with Ar-X would afford Ar-Pd^{II}-Ar **5**. Finally, reductive elimination of **5** would produce biaryl Ar-Ar **2** and active Pd(0) species to complete the catalytic cycle.^{18,30,33}

SCHEME 2. A Plausible Mechanism of the TDAE/Palladium Cat.-Promoted Reductive Coupling



In conclusion, the TDAE/cat. palladium-promoted reductive coupling reaction of aryl halides having both an electron-donating group and an electron-withdrawing group proceeded effectively. In the TDAE/palladium biredox system, the coupling of aryl halides having an electron-withdrawing group proceeds more efficiently than that of aryl halides having an electron-donating group. TDAE has a mild reducing ability and hardly reduces formyl, ester, and even nitro groups, and the reductive coupling reaction of aryl halides having these substituents can be performed successfully.

Experimental Section

All reactions were conducted under argon atmosphere. Unless otherwise noted, materials were obtained from commercial suppliers and reagent grade materials were used without further purification. Reaction solvents were distilled immediately before use.

Reductive Coupling Reaction of Aryl Halides in TDAE/Palladium Cat. Systems: A typical procedure (Table 1,

(33) For zinc/nickel catalyst-promoted reaction, disproportionation of Ar-Ni-X to Ar₂Ni and NiX₂ and subsequent reductive elimination from Ar₂Ni affording Ar₂ was proposed as a plausible mechanism.¹⁴

Entry 1) is as follows: To a solution of *p*-bromoanisole (**1a**, 187 mg, 1.00 mmol) and $\text{PdCl}_2(\text{PhCN})_2$ (19 mg, 0.05 mmol) in DMF (5 mL) was added TDAE (403 mg, 2.01 mmol) in one portion under argon atmosphere. The mixture was stirred under argon atmosphere at 50 °C for 5 h. The reaction was monitored by HPLC. After most of the starting material was consumed, the reaction mixture was poured into iced water and extracted with ether (10 mL × 4). The combined extracts were washed with aq NaHCO₃ and brine, successively, dried over Na₂SO₄, and concentrated under reduced pressure. Most of the desired biaryl **2a** was obtained from recrystallization (hexane, AcOEt). The mother liquor was concentrated, and purification of the residue by silica gel column chromatography (hexane/AcOEt 1/1) also gave the desired biaryl **2a**. Totally, 105 mg (0.489 mmol, 98%) of **2a** was obtained as a white solid: ^{20e} *R*_f 0.86 (hexane/AcOEt 1/1); ¹H NMR (200 MHz, CDCl₃) δ 3.84 (s, 6H), 6.96 (d, *J* = 8 Hz, 4H), 7.48 (d, *J* = 8 Hz, 4H); IR (KBr) 3036, 3002, 2954, 2835, 1609, 1498, 1275, 1048, 754 cm⁻¹.

In a similar manner, the reductive coupling reactions of aryl halides, Ar-X **1** (X = Br, I, Cl) were carried out in the presence of several palladium and nickel catalysts in DMF. The results are shown in Tables 1 and 2.

4,4'-Dimethylbiphenyl (2d):³⁴ a white solid; *R*_f 0.88 (hexane/AcOEt 3/1); ¹H NMR (200 MHz, CDCl₃) δ 2.42 (s, 6H), 7.23 (d, *J* = 8 Hz, 4H), 7.57 (d, *J* = 8 Hz, 4H); IR (KBr) 3024, 2916, 1502, 1450, 803 cm⁻¹.

4,4'-(*N,N*-Dimethylamino)biphenyl (2e):³⁵ a white solid; *R*_f 0.65 (toluene/AcOEt 10/1); ¹H NMR (200 MHz, CDCl₃) δ 2.42 (s, 12 H), 7.23 (d, *J* = 8 Hz, 4H), 7.57 (d, *J* = 8 Hz, 4H); IR (KBr) 3090, 3013, 2992, 2910, 1500, 1250, 780 cm⁻¹.

Biphenyl (2f):^{20e} a white solid; *R*_f 0.52 (hexane); ¹H NMR (200 MHz, CDCl₃) δ 7.3–7.6 (m, 10H); IR (CCl₄) 3072, 3065, 3033, 2953, 2924 cm⁻¹.

4,4'-Diformylbiphenyl (2g):³⁶ a white solid; *R*_f 0.22 (toluene); ¹H NMR (200 MHz, CDCl₃) δ 7.81 (d, *J* = 8 Hz, 4H), 8.01 (d, *J* = 8 Hz, 4H), 10.1 (s, 2H); IR (KBr) 2841, 2747, 1694, 1604, 1391 cm⁻¹.

4,4'-Dicyanobiphenyl (2h):³⁷ a white solid; *R*_f 0.57 (toluene/AcOEt 10/1); ¹H NMR (200 MHz, CDCl₃) δ 7.69 (d, *J* = 8 Hz, 4H), 7.79 (d, *J* = 8 Hz, 4H); IR (KBr) 2228, 818 cm⁻¹.

Biphenyl-4,4'-dicarboxylic acid dimethyl ester (2i):^{20e} a white solid; *R*_f 0.42 (hexane/AcOEt 5/1); ¹H NMR (200 MHz, CDCl₃) δ 3.95 (s, 6H), 7.69 (d, *J* = 9 Hz, 4H), 8.13 (d, *J* = 9 Hz, 4H); IR (KBr) 3016, 2960, 2920, 2853, 1722, 1610, 1434, 1285 cm⁻¹.

Biphenyl-3,3',4,4'-tetracarboxylic acid tetramethyl ester (2j):³⁸ a white solid; *R*_f 0.72 (hexane/AcOEt 1/1); ¹H NMR (200 MHz, CDCl₃) δ 3.94 (s, 6H), 3.95 (s, 6H), 7.77 (d, *J* = 8 Hz, 2H), 7.87 (d, *J* = 8 Hz, 2H), 7.95 (s, 2H); IR (KBr) 3030, 3008, 2954, 1713, 1434, 1257 cm⁻¹.

4,4'-Dinitrobiphenyl (2k):^{20e} a yellow solid; *R*_f 0.67 (toluene); ¹H NMR (200 MHz, CDCl₃) δ 7.76–7.81 (m, 4H), 8.34–8.39 (m, 4H); IR (KBr) 3088, 1517, 1344, 852 cm⁻¹.

2,2'-Bipyridyl (2m):^{20e} a white solid; *R*_f 0.20 (toluene/AcOEt 5/1); ¹H NMR (200 MHz, CDCl₃) δ 7.27–7.34 (m, 2H), 7.35–7.87 (m, 2H), 8.40 (d, *J* = 8 Hz, 2H), 8.69 (d, *J* = 5 Hz, 2H); IR (KBr) 3087, 3055, 1579, 1558, 1452, 1416, 757 cm⁻¹.

4,4'-Bipyridyl (2o):³⁹ a white solid; *R*_f 0.18 (hexane/AcOEt 2/1); ¹H NMR (200 MHz, CDCl₃) δ 7.53–7.56 (m, 4H), 8.73–8.77 (m, 4H); IR (KBr) 3076, 3028, 1636, 1592, 807 cm⁻¹.

JO0207473

(34) Kende, A. S.; Liebeskind, L. S.; Braitsch, D. M. *Tetrahedron Lett.* **1975**, 3375.

(35) Brune, H. A.; Ertl, J. *Liebigs Ann. Chem.* **1980**, 928.

(36) Iyoda, M.; Otsuka, H.; Sato, K.; Nisato, N.; Oda, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 5908.

(37) Semmelhack, M. F.; Helquist, P. M.; Jones, L. D. *J. Am. Chem. Soc.* **1971**, *93*, 5908.

(38) Itatani, H.; Yoshimoto, H. *J. Org. Chem.* **1973**, *38*, 76.

(39) Fort, Y.; Backer, S.; Caubere, P. *Tetrahedron* **1994**, *50*, 11893.