Pergamon

Tetrahedron 57 (2001) 3069–3073

TETRAHEDRON

A general palladium-catalysed synthesis of aromatic and heteroaromatic thioethers

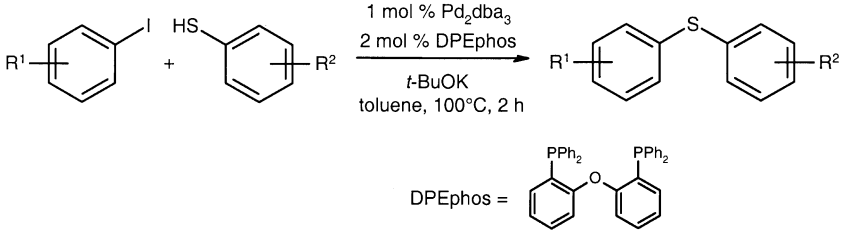
Ulrich Schopfer* and Achim Schlapbach

Novartis Pharma AG, Preclinical Research, Lichtstrasse, CH-4002 Basel, Switzerland

Received 8 January 2001; accepted 31 January 2001

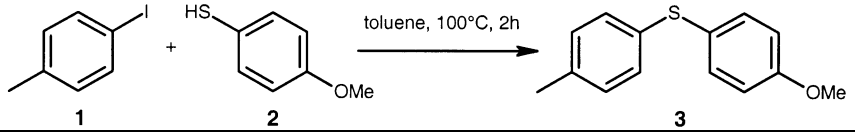
Abstract—Thioethers can be efficiently prepared via palladium-catalysed cross-coupling of arene- or heteroarene thiols with arene- or heteroarene iodides. A simple, cheap and robust catalytic system is described that couples a broad range of electron-deficient as well as electron-rich substrates in high yield.

Thioethers, especially when they contain heterocyclic rings, are common features in many natural products and pharmacologically important molecules.[1] While the palladium-catalysed formation of diaryl amines[2] and diaryl ethers[3] has received considerable interest recently, much less attention has been focused on the formation of diaryl thioethers. The direct nucleophilic substitution[4] of unactivated aryl halides with thiols typically requires temperatures over 150°C or photoinitiation[5] and the use of polar aprotic solvents. This is still true when the reaction is promoted by



Scheme 1.

Table 1. Effect of Pd source, ligand and base on the coupling reaction of aryl iodides with aromatic thiols



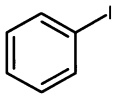
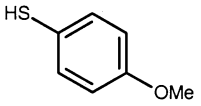
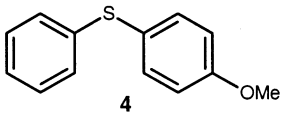
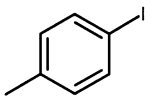
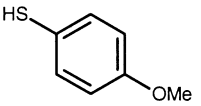
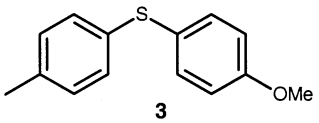
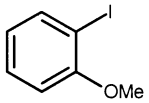
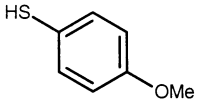
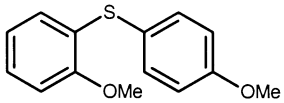
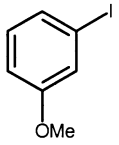
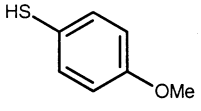
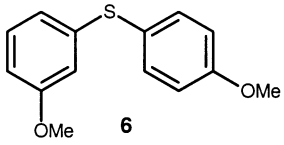
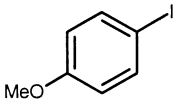
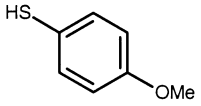
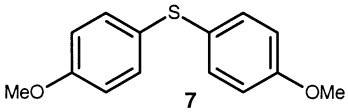
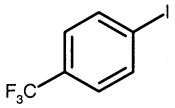
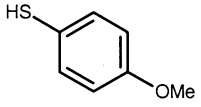
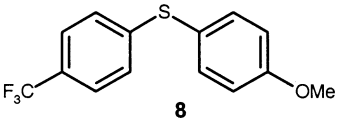
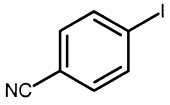
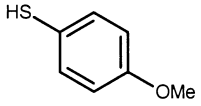
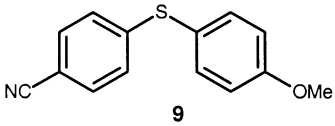
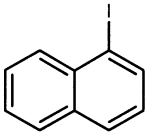
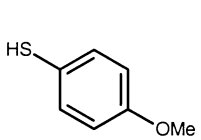
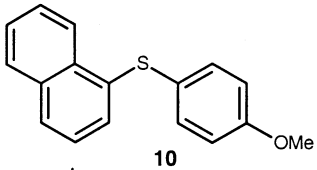
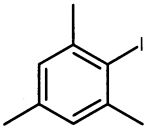
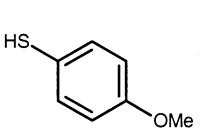
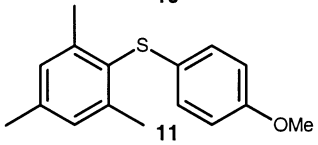
1 2 3

Entry	Catalyst precursor	mol%	Ligand	mol%	Base (1.1 equiv.)	Isolated yield (%)
1	Pd_2dba_3	4	DPEphos	10	*t*-BuOK	94
2	Pd_2dba_3	1	DPEphos	2	*t*-BuOK	90
3	Pd_2dba_3	1	DPEphos	1	*t*-BuOK	81
4	Pd_2dba_3	1	DPEphos	2	*t*-BuONa	82
5	Pd_2dba_3	1	DPEphos	2	Cs_2CO_3	23
6	Pd_2dba_3	1	DPEphos	2	Phosphazene-P_4	65
7	Pd_2dba_3	1	PPh_3	4	*t*-BuOK	<5
8	$Pd(OAc)_2$	1	DPEphos	2	*t*-BuOK	13
9	–		DPEphos	2	*t*-BuOK	<5

Keywords: diaryl thioethers; palladium; cross-coupling; homogeneous catalysis; heterocycles.
* Corresponding author. Tel.: +41-61-324-4951; fax: +41-61-324-9794; e-mail: ulrich.schopfer@pharma.novartis.com

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00157-0

Table 2. Pd-catalysed formation of aromatic thioethers

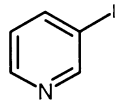
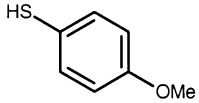
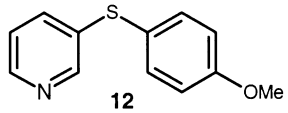
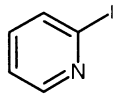
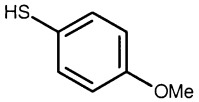
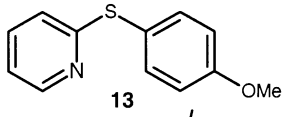
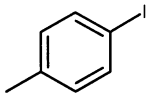
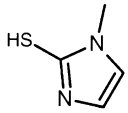
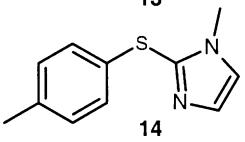
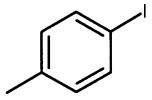
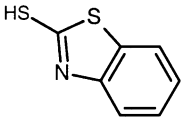
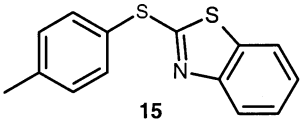
Entry	Halide	Thiol	Thioether	Isolated yield (%)[a]
1			 **4**	74
2			 **3**	90
3			 **5**	99
4			 **6**	80
5			 **7**	99
6			 **8**	84
7			 **9**	93
8			 **10**	94
9			 **11**	35 (35)[b]

[a] All reactions were conducted in toluene at 100°C in the presence of 1 mol% Pd_2dba_3, 2 mol% DPEphos and 1.1 equiv. *t*-BuOK for 2 h.
[b] Reaction time 4 h.

copper additives,[4a,6] although it was shown recently that the use of Schwesinger's phosphazene bases allows the formation of a broad range of diaryl sulfides in toluene.[7] After early reports by Murahashi[8] and Migita,[9] only a few examples of nickel- and palladium-catalysed carbon–sulfur bond-forming reactions have been reported in the literature.[10] A general study of the scope and limitations of this reaction has been lacking to date. Recently, Hartwig has made considerable inroads into this underdeveloped field and showed that the stoichiometric reaction of isolated Pd(II) aryl halide complexes with thiolates provided aryl sulfides.[11]

Bidentate ligands have been shown to be very efficient in a variety of aryl–heteroatom coupling reactions. Thus, recently DPEphos was introduced by van Leeuwen[12] and was later used efficiently by Buchwald for Pd-catalysed amination reactions.[13] Herein, the potential of DPEphos, which is readily available from commercial sources (e.g. Aldrich, $120/5 g), for the promotion of intermolecular coupling reactions of aryl iodides and aryl thiols was evaluated. We wish to report a catalytic system with cheap and readily available components that couples a broad range of activated and deactivated aryl iodides with thiols in high yields (Scheme 1). We anticipate that the

Table 3. Pd-catalysed formation of heteroaromatic thioethers

Entry	Halide	Thiol	Thioether	Isolated yield (%)[a]
1			 **12**	87
2			 **13**	77[b]
3			 **14**	88
4			 **15**	43

[a] All reactions were conducted in toluene at 100°C in the presence of 1 mol% Pd_2dba_3, 2 mol% DPEphos and 1.1 equiv. *t*-BuOK for 2 h.
[b] Under otherwise identical conditions, reaction without Pd_2dba_3 gave 7% of 2-thiopyridine.

extension of the reaction to heterocyclic coupling partners will be useful for the synthesis of many biologically active molecules.

For the optimisation of reaction parameters, we chose a model reaction with electron-rich coupling partners (Table 1). Hartwig showed that electron-donating groups on the aryl halide decelerate the reaction[11] and we were confident that reaction conditions optimised for these difficult cases would prove generally applicable. We also felt that an useful reaction should deliver high yields of thioether from only one equivalent of each aryl halide and thiol. We found that the reaction of *p*-tolyl iodide (**1**) with 4-methoxythiophenol (**2**) in the presence of Pd_2dba_3, DPEphos and *t*-BuOK proceeded in excellent yield (Table 1, entries 1 and 2). The catalyst loading could be reduced to 1 mol% without significant reduction in yield, while 2 mol% of ligand was beneficial. We were interested in developing reaction conditions using 'reagent' grade toluene without drying or degassing in order to make this reaction useful in parallel synthesis. We therefore did not attempt to minimise catalyst loadings by scrupulous purification of solvent or reactants.

The choice of the base is critical (entries 2, 4–6). Contrary to our expectations, we found that bases forming more soluble thiolates like Cs_2CO_3 or the phosphazene-P_4 base led to lower yields. Control experiments (entries 7–9) showed that DPEphos is a better ligand than triphenylphosphine, Pd_2dba_3 is a better catalyst precursor than $Pd(OAc)_2$ and that palladium-catalysis is needed for the reaction to proceed.

A wide range of substituted aryl iodides were subjected to the optimised reaction conditions (Table 2). Substituted aryl iodides carrying electron-withdrawing groups as well as electron-donating groups gave equally good yields. The substitution pattern in *ortho*-, *meta*- or *para*-substituted aryl iodides did not greatly influence yields (entries 3–5). In concurrence with Hartwig's observations[11b] however, *ortho*-disubstitution (entry 9) led to lower yields, presumably due to the prevention of reductive elimination.

Finally, we applied these optimised reaction conditions to heterocyclic substrates (Table 3). Heteroaromatic iodides (entries 1 and 2) as well as heterocyclic thiols (entries 3 and 4) were efficiently converted into the corresponding thioethers. To our knowledge, this has not been achieved before. Considering the privileged position of heteroaromatic compounds in medicinal chemistry, we feel that the catalytic system reported here will prove useful in the synthesis of bioactive molecules.

In summary, we have developed a general method for the synthesis of thioethers starting from aromatic iodides and aryl thiols. The reaction uses Pd_2dba_3 and DPEphos as the catalyst precursors, both cheap and readily available, *t*-BuOK as base and can be performed in 'reagent' grade toluene without any special precautions.

1. Experimental

1.1. Representative procedure for mixed aryl sulfides

1.1.1. 1-Methyl-2-(*p*-tolylsulfanyl)-1*H*-imidazole (14). A solution of 10.0 mg (10 μmol) Pd_2dba_3 and 10.8 mg (20 μmol) DPEphos in 8 ml toluene was stirred under argon atmosphere for 3 min. After addition of 0.22 g (1.0 mmol) *p*-tolyl iodide, 0.11 g (1.0 mmol) 1-methyl-2-mercaptoimidazole and 0.12 g (1.1 mmol) *t*-BuOK, the mixture was stirred at 100°C for 2 h. The reaction mixture

was filtered over Celite, evaporated, and the residue was purified by flash chromatography yielding 180 mg (0.88 mmol) 1-methyl-2-(*p*-tolylsulfanyl)-1*H*-imidazole. ^{1}H NMR (400 MHz, $CDCl_3$): 2.29 (s, 3H), 3.62 (s, 3H), 7.04 (d, 1H), 7.06–7.12 (m, 4H), 7.16 (d, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 21.0, 33.8, 123.6, 128.7, 129.9, 130.0, 130.9, 136.8, 138.7. MS (EI, *m/z*): 204 (100%). HRMS (ESI): $C_{13}H_{15}NaSN_3$ [M+Na+CH_3CN], calcd: 268.0884, found: 268.0886.

1.1.2. 1-Methoxy-4-[(4-methylphenyl)thio]benzene (3). 103 mg (0.45 mmol, 90%) of a colourless oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): 2.29 (s, 3H), 3.79 (s, 3H), 6.86 (d, 2H), 7.05 (d, 2H), 7.12 (d, 2H), 7.36 (d, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 20.9, 55.2, 114.8, 125.6, 128.2, 129.3, 129.7, 134.3, 136.0, 159.4. (In agreement with lit.[10e])

1.1.3. 1-Methoxy-4-(phenylthio)benzene (4). 81 mg (0.37 mmol, 74%) of a colourless oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): 3.77 (s, 3H), 6.88 (d, 2H), 7.05–7.22 (m, 5H), 7.39 (d, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 55.3, 114.9, 124.3, 125.7, 128.5, 128.9, 135.3, 138.6, 159.8. (In agreement with lit.[14])

1.1.4. 1-Methoxy-2-[(4-methoxyphenyl)thio]benzene (5). 121 mg (0.49 mmol, 99%) of a colourless oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): 3.86 (s, 3H), 3.93 (s, 3H), 6.80–6.95 (m, 5H), 7.15 (m, 1H), 7.49 (d, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 55.3, 55.8, 110.3, 114.7, 121.1, 124.3, 122.7, 126.5, 127.3, 128.0, 128.9, 136.0, 155.6, 159.9. (In agreement with lit.[15])

1.1.5. 1-Methoxy-3-[(4-methoxyphenyl)thio]benzene (6). 98 mg (0.40 mmol, 80%) of a colourless oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): 3.78 (s, 3H), 3.86 (s, 3H), 6.68–6.80 (m, 3H), 6.94 (d, 2H), 7.19 (t, 1H), 7.49 (d, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 55.1, 55.3, 111.2, 113.3, 114.9, 120.1, 123.7, 129.6,135.6, 140.0, 159.9. MS (EI, *m/z*): 246 (100%). HRMS (FAB): $C_{14}H_{14}O_2S$, calcd: 246.0714, found: 246.0711.

1.1.6. 1,1′-Thio-bis[4-methoxy]-benzene (7). 122 mg (0.49 mmol, 99%) of a colourless oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): 3.83 (s, 6H), 6.88 (d, 4H), 7.44 (d, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 55.3, 114.6, 127.4, 132.6, 159.0. (In agreement with lit.[15])

1.1.7. 1-[(4-Methoxyphenyl)thio]-4-(trifluoromethyl)benzene (8). 119 mg (0.42 mmol, 84%) of colourless crystals after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): 3.83 (s, 3H), 6.95 (d, 2H), 7.14 (d, 2H), 7.44 (d, 2H), 7.47 (d, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 55.4, 115.4, 121.6, 125.4, 126.4, 136.7, 160.7. Mp 82–83°C (lit.[16] Mp 79–80°C).

1.1.8. 4-[(4-Methoxyphenyl)thio]benzonitrile (9). 112 mg (0.46 mmol, 93%) of slightly yellow crystals after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): 4.01 (s, 3H), 7.14 (d, 2H), 7.25 (d, 2H), 7.57–7.68 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 55.4, 108.0, 115.6, 118.9, 120.3, 126.0, 132.2, 137.1, 147.4, 161.0. Mp 90–91°C (lit.[17] Mp 87°C).

1.1.9. 1-[(4-Methoxyphenyl)thio]naphthalene (10). 125 mg (0.47 mmol, 94%) of slightly brownish crystals after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): 4.01 (s, 3H), 7.10 (d, 2H), 7.54–7.60 (m, 4H), 7.75 (q, 2H), 7.95 (d, 1H), 8.08 (d, 1H), 8.60 (d, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 55.3, 115.0, 124.9, 125.1, 125.7, 126.3, 126.5, 127.4, 128.5, 132.2, 133.8, 134.0, 134.6, 159.4. Mp 106–107°C. MS (EI, *m/z*): 266 (100%). HRMS (FAB): $C_{17}H_{14}OS$, calcd: 266.0765, found: 266.0761.

1.1.10. 1-[(4-Methoxyphenyl)thio]-2,4,6-trimethylbenzene (11). 45 mg (0.17 mmol, 35%) of a colourless oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): 2.30 (s, 3H), 2.38 (s, 6H), 3.74 (s, 3H), 6.73 (d, 2H), 6.88 (d, 2H), 6.96 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 21.1, 21.8, 55.3, 114.6, 127.6, 128.3, 129.0, 129.3, 138.9, 143.4, 157.4. MS (EI, *m/z*): 258 (100%). HRMS (FAB): $C_{16}H_{18}OS$, calcd: 258.1078, found: 258.1087.

1.1.11. 3-[(4-Methoxyphenyl)thio]-pyridine (12). 188 mg (0.87 mmol, 87%) of a pale yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): 3.83 (s, 3H), 6.92 (d, 2H), 7.14 (dd, 1H), 7.39–7.42 (m, 1H), 7.43 (d, 2H), 8.37 (dd, 1H), 8.43 (d, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 55.4, 115.2, 122.5, 123.6, 135.3, 135.7, 136.0, 146.7, 148.8, 160.2. MS (EI, *m/z*): 217 (100%). HRMS (ESI): $C_{12}H_{12}NOS$ [M+H], calcd: 218.0640, found: 218.0640.

1.1.12. 2-[(4-Methoxyphenyl)thio]-pyridine (13). 168 mg (0.77 mmol, 77%) of a white solid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): 3.86 (s, 3H), 6.78 (d, 1H), 6.94–6.98 (m, 1H), 6.98 (d, 2H), 7.40–7.45 (m, 1H), 7.54 (d, 2H), 8.40 (dd, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 55.4, 115.3, 119.4, 120.3, 121.0, 136.6, 137.3, 149.4, 160.6, 162.8. MS (EI, *m/z*): 217 (70%), 216 (100%). Mp 50–51°C. (In agreement with lit.[18])

1.1.13. 2-[(4-Methylphenyl)thio]-benzthiazole (15). 110 mg (0.43 mmol, 43%) of a colourless oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): 2.44 (s, 3H), 7.26 (t, 1H), 7.30 (d, 2H), 7.40 (t, 1H), 7.61–7.67 (m, 3H), 7.88 (d, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 21.5, 120.7, 121.8, 124.1, 126.1, 126.2, 130.8, 135.4, 135.6, 141.2, 154.0, 170.9. MS (EI, *m/z*): 257 (70%), 256 (100%). HRMS (ESI): $C_{14}H_{12}NS_2$ [M+H], calcd: 258.0411, found: 258.0413.

References

1. Recent examples: (a) Potin, D.; Parnet, V.; Teulon, J.-M.; Camborde, F.; Caussade, F.; Meignen, J.; Provost, D.; Cloarec, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 805–809. (b) Webber, S.; Bartlett, C. A.; Boritzki, T. J.; Hilliard, J. A.; Howland, E. F.; Johnston, A. L.; Kosa, M.; Margosiak, S. A.; Morse, C. A.; Shetty, B. V. *Cancer Chemother. Pharmacol.* **1996**, *37*, 509–517.
2. (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125–146. (c) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046–2067.
3. (a) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224–3225. (b) Mann, G.;

Hartwig, J. F. *Tetrahedron Lett.* **1997**, *38*, 8005–8008. (c). Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395–3396.
4. Recent examples: (a) Caruso, A. J.; Colley, A. M.; Bryant, G. L. *J. Org. Chem.* **1991**, *56*, 862–865. (b) Nabeshima, T.; Iwata, S.; Furukawa, N.; Morihashi, K.; Kikuchi, O. *Chem. Lett.* **1988**, *8*, 1325–1328.
5. Pierini, A. B.; Baumgartner, M. T.; Rossi, R. A. *J. Org. Chem.* **1991**, *56*, 580–586.
6. Van Bierbeek, A.; Gingras, M. *Tetrahedron Lett.* **1998**, *39*, 6283–6286.
7. Palomo, C.; Oiarbide, M.; López, R.; Gómez-Bengoa, E. *Tetrahedron Lett.* **2000**, *41*, 1283–1286.
8. Murahashi, S.-I.; Yamamura, M.; Yanagisawa, K.-I.; Mita, N.; Kondo, K. *J. Org. Chem.* **1979**, *44*, 2408–2417.
9. Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.-I.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn* **1980**, *53*, 1385–1389.
10. For recent reviews see: (a) Kondo, T.; Mitsudo, T.-A. *Chem. Rev.* **2000**, *100*, 3205–3220. (b) Barañao, D.; Mann, G.; Hartwig, J. F. *Current Org. Chem.* **1997**, *1*, 287–305. Further leading references: (c) Takagi, K. *Chem. Lett.* **1987**, 2221–2224. (d) Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.-I.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn* **1980**, *53*, 1385–1389. (e) Still, I. W. J.; Toste, F. D. *J. Org. Chem.* **1996**, *61*, 7677–7680. (f) Pinchart, A.; Dallaire, C.; Gingras, M. *Tetrahedron Lett.* **1998**, *39*, 543–546. (g) Zheng, N.; McWilliams, J. C.; Fleitz, F. J.; Armstrong III, J. D.; Volante, R. P. *J. Org. Chem.* **1998**, *63*, 9606–9607.
11. (a) Mann, G.; Barañao, D.; Hartwig, J. F.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 9205–9219. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852–860. (c) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11598–11599. (d) Barañao, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 2937–2938.
12. Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081–3089.
13. Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, *39*, 5327–5330.
14. Takeuchi, H.; Oya, H.; Yanase, T.; Itou, K.; Adachi, T.; Sugiura, H.; Hayashi, N. *J. Chem. Soc., Perkin Trans. 2* **1994**, 827–834.
15. Elothmani, D.; Do, Q. T.; Simonet, J.; Le Guillanton, G. *Bull. Soc. Chim. Fr.* **1994**, *131*, 779–788.
16. Kozachuk, D. N.; Serguchev, Y. A.; Kremlev, M. M.; Fialkov, Y. A.; Yagupolskii, L. M. *J. Org. Chem. USSR (Engl. Transl.)* **1974**, *10*, 1239–1243.
17. Petit, L.; Sonnier, M. *Bull. Soc. Chim. Fr.* **1974**, 477–478.
18. Nagasaki, I.; Matsumoto, M.; Yamashita, M.; Miyashita, A. *Heterocycles* **1999**, *51*, 1015–1024.