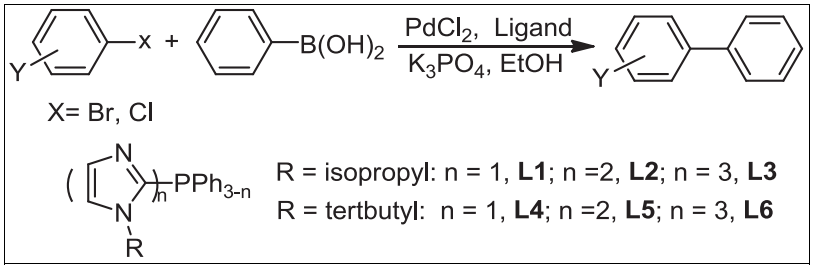
Ting Chen, Jin Tao Guan,* Zhi Yong Zhang, Jing Jing Chen, Fengyan Liu, and Xiaopei Liu

School of Chemical and Environmental Engineering, Wuhan Polytechnic University, Wuhan 430023, China
*E-mail: guanjintao@126.com
Received July 18, 2017
DOI 10.1002/jhet.3071
Published online 13 December 2017 in Wiley Online Library (wileyonlinelibrary.com).



Two series of alkylimidazole-based phosphines were conveniently synthesized in one step from the corresponding alkylimidazole by selective deprotonation and quenching with chlorodiphenylphosphine. The novel ligands are easily tunable and exhibit good-to-excellent performance in the palladium-catalyzed Suzuki coupling reaction.

J. Heterocyclic Chem., **55**, 551 (2018).

INTRODUCTION

Biaryls are of significant importance in organic chemistry and play an important role as intermediates for natural products, biologically active compounds, agrochemicals, and in materials science. As a widely used cross-coupling protocol, the Suzuki–Miyaura reaction allows the coupling of aryl boronic acids with aryl halides to biaryls under mild reaction conditions and with an excellent tolerance of a broad range of functional groups [1–6].

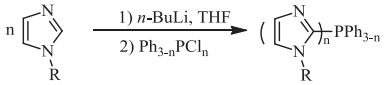
The Suzuki coupling reaction is efficiently catalyzed by a variety of Pd-based catalysts, and the efficacy of the catalytic system has been achieved by changing the ligand environment around palladium [7–10]. Therefore, numerous efforts have been made to design and develop more efficient and affordable ligands, especially phosphine ligands. As a result, various efficient ligands of different types and shapes have been explored and reported in the literature, such as tertiary phosphines, diadamantyl-type phosphines, hemilabile-type phosphines, sterically crowded biphenyl-type phosphines, bidentate-type dppp (1,3-bis(diphenylphosphino)propane) and dppf, polydentate-type Tedicyp, and other efficient phosphine ligands [11–23]. However, most ligands are very expensive, not easily available, and difficult to synthesize, giving rise to particular economic concerns, especially when large-scale operations are under consideration. Accordingly, searching for accessible ligands with a high activity and easy scale-up production has been one of the foremost missions for organic synthetic chemists.

N-Aryl-2(dialkylphosphino)imidazoles [24–28], which can be easily tuned and synthesized in one or two reaction steps on multi-g to multi-kg scale, showed excellent catalytic performance in the palladium-catalyzed Suzuki and Buchwald–Hartwig amination reactions.

As part of our ongoing project on palladium-catalyzed reaction [29–31], we investigated and reported the *N*-methylimidazole-based phosphines as the ligands in the palladium-catalyzed Suzuki reaction and found that the catalytic system showed excellent activity toward the Suzuki reaction. Encouraged by this result, we report herein further studies on the *N-iso*-propylimidazole and *N-tert*-butylimidazole-based phosphines as the ligands in the Pd-catalyzed Suzuki reaction.

RESULTS AND DISCUSSION

All the phosphine ligands were synthesized by deprotonation of the proton at the C-2 position in the imidazole ring using *n*-butyllitium and subsequent reaction with chlorophosphine according to the literature [25,28] (as shown in Fig. 1). The structures of the ligands were fully characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, and melting point. The ^{31}P NMR spectra of L1-L6 were −32.05, −48.56, −74.36, −23.4, −46.01, and −51.03 ppm, respectively. The ^{31}P NMR values shifted to higher field with the number of *N-iso*-propylimidazole

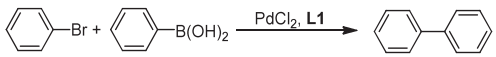


R = *iso*-propyl: n = 1, **L1**; n =2, **L2**; n = 3, **L3**
R = *tert*-butyl: n = 1, **L4**; n =2, **L5**; n = 3, **L6**

Figure 1. *N*-alkylimidazole-based phosphines.

Table 1

Effect of bases and solvents on the Suzuki reaction[a].

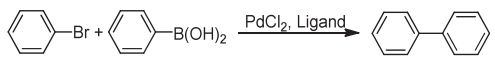


Entry	Base	Solvent	Yield (%)[b]
1	K_2CO_3	EtOH	23
2	Na_2CO_3	EtOH	53
3	K_3PO_4	EtOH	84
4	Et_3N	EtOH	69
5	K_3PO_4	1,4-Dioxane	11
7	K_3PO_4	DMF	22
8	K_3PO_4	Toluene	36
9	K_3PO_4	H_2O	80
10	K_3PO_4	THF	31
11	K_3PO_4	MeOH	82

[a]Reaction conditions are as follows: bromobenzene (2 mmol), phenylboronic acid (2.5 mmol), base (4 mmol), $PdCl_2$ (0.01 mmol), ligand (0.02 mmol), and solvent (3 mL) at 60°C for 0.5 h in a pressure tube.
[b]GC yields.

Table 2

Effect of ligands on the Suzuki reaction[a].



Entry	Ligand	Yield (%)[b]
1	L1	84
2	L2	73
3	L3	68
4	L4	92
5	L5	83
6	L6	76
7[c]	L4	85

[a]Reaction conditions are as follows: bromobenzene (2 mmol), phenylboronic acid (2.5 mmol), K_3PO_4 (4 mmol), $PdCl_2$ (0.01 mmol), ligand (0.02 mmol), and EtOH (3 mL) at 60°C for 0.5 h in a pressure tube;
[b]GC yields.
[c]L4 (0.01 mmol).

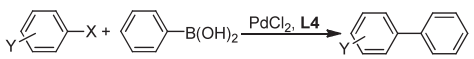
or *N-tert*-butylimidazole, and the ^{31}P NMR values shifted to lower field compared with *N-tert*-butyl-substituent L4 with *N-iso*-propyl substituent L1, which was the same as L5 with L2 and L6 with L3.

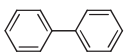
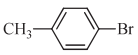
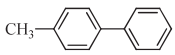
We then embarked on evaluating their activities on the Suzuki reaction. Initially, we investigated the effects of bases, solvents, and ligands on the Suzuki reaction of bromobenzene with phenylboronic acid using ethanol as solvent (Table 1, entries 1–4). Potassium phosphate appeared to be superior to the others (Table 1, entry 3). Next, we attempted various solvents for this reaction, and it was found that better yields were obtained in the strong polar protic solvents such as ethanol, methanol, and water (Table 1, entries 3, 9, and 11), and ethanol gave the highest yield. We also investigated the effects of ligands for this reaction (Table 2). The result showed that all the ligands exhibited good catalytic activity toward the reaction, and that the *N-tert*-imidazole ligand L4 showed the best yield at 92% (Table 2, entry 4). This can be reasoned by the fact that the *tert*-butyl-substituent L4 has a stronger electron-donating ability and sterical hindrance than the analogue *iso*-propyl substituent of L1; these are beneficial for the oxidative addition and reductive elimination, respectively. Additionally, the yield decreased with the number of imidazole rings. Perhaps because more imidazole rings can reduce the electron-donating ability, and this can be seen from the ^{31}P NMR values. At the same time, the sterical hindrance of L5 and L6 leads to the difficulties in oxidative addition. We lowered the ratio of $PdCl_2$/L4 to 1:1 and found that the yield of the model reaction decreased to 85% (Table 2, entry 7).

Thus, we studied the effects of the ligand L4 in the Suzuki reaction for a variety of aryl bromides and chlorides with phenylboronic acid in ethanol in the presence of K_3PO_4, and the results are summarized in Table 2. The reactions were performed smoothly for all the tested substrates, and expected products were obtained in moderate-to-excellent

Table 3

Suzuki reaction of aryl halides with phenylboronic acid[a].

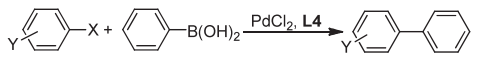


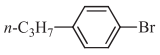
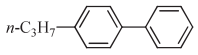
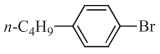
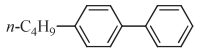
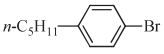
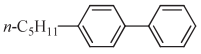
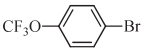
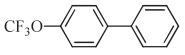
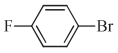
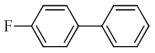
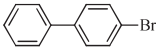
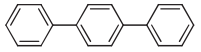
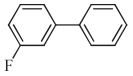
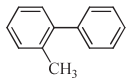
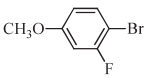
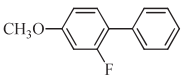
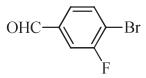
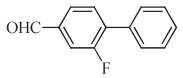
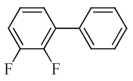
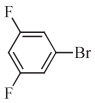
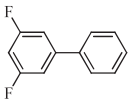
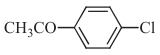
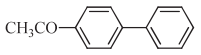
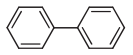
Entry	Aryl halides	Product	Yield (%)[b]
1			99
2			99

(*Continues*)

Table 3

(*Continued*)



Entry	Aryl halides	Product	Yield (%)[b]
3			96
4			95
5			96
6			88
7			98
8			79
9			97
10			96
11			92
12			96
13			53
14			55
15[c]			92
16[c]			41

[a]Reaction conditions are as follows: aryl halides (2 mmol), phenylboronic acid (2.5 mmol), K_3PO_4 (4 mmol), $PdCl_2$ (0.01 mmol), L4 (0.02 mmol), and EtOH (3 mL) at 60°C for 1 h in a pressure tube.
[b]Isolated yields.
[c]$PdCl_2$ (1 mol%), L4 (2 mol%), 80°C for 24 h, GC yield.

yields. As shown in Table 3, the para-substituted aryl bromides, regardless of them being electron-rich or electron-poor, reacted smoothly with phenylboronic acid to generate the desired products in excellent yields (Table 3, entries 2–7), except that a slightly lower yield was obtained for 4-bromobiphenyl (Table 3, entry 8, 79%). Fluorine-containing substrates also reacted in excellent yields to generate the desired products (Table 3, entries 9, 11, and 12), while moderate yields were obtained for difluorine-substituted substrates (Table 3, entries 13 and 14). Ortho-substituted 2-bromotoluene reacted with phenylboronic acid to give the desired product in excellent yield (Table 3, entry 10). In the case of low active aryl chlorides, 92% and 41% yields were obtained by reaction of 4-chloroacetophenone and 4-chlorobenzene with phenylboronic acid under longer time periods and higher catalyst loading, respectively (Table 3, entries 15 and 16). These results showed that a variety of important functional groups could be tolerated under the reaction conditions.

CONCLUSIONS

In summary, we described the synthesis, characterization of *N-iso*-propylimidazole and *N-tert*-butylimidazole-based phosphine ligands and their activities on the Suzuki reaction. The results showed that the ligand with one *N-tert*-butylimidazole substitute gave a better yield than that with one *N-iso*-propylimidazole substitute. Thus, the catalytic system of $PdCl_2$-L4 in the ethanol has been proven to be a practical and efficient system for the Suzuki reaction with an excellent tolerance of various functional groups.

EXPERIMENTAL

General information. All reactions were carried out under an atmosphere of highly purified nitrogen using standard Schlenk or vacuum-line techniques. All the reagents and chemicals were purchased from commercial sources. THF was distilled under nitrogen from sodium/benzophenone ketyl and bubbled for 15 min before use. Coupling reaction product yields were calculated by GC, using a 6890N Network GC system (Agilent Technologies). ^{1}H and ^{31}P NMR spectra were recorded on a Varian Mercury Plus spectrometer 400 MHz instrument, IR spectra were recorded on a Nicolet AVATAR 330 FTIR spectrophotometer, and mass spectroscopy (EI-MS) were recorded on an HP 5989B mass spectrometer.

2-(Diphenylphosphino)-N-iso-propylimidazole (L1). To a solution of *N-iso*-propylimidazole (11 g, 0.1 mol) in 120-mL anhydrous THF at −78°C was added n-BuLi (2.5*M*, in hexane, 48 mL, 0.12 mol) slowly. Chlorodiphenylphosphine (22.12 g, 0.1 mol) was added drop-wise after the mixture stirred for 1 h at −78°C. The reaction mixture was stirred for another 1 h and then warmed to room temperature slowly, and the mixture stirred continuously for another 1 h. The solvent was removed under vacuum to obtain a light yellow solid residue. The residue was dissolved in 100-mL dichloromethane and filtered through Celite to remove lithium chloride, then washed with water (50 mL), and dried over $MgSO_4$. After evaporation of solvent in vacuum, the obtained residue was recrystallized from CH_2Cl_2/Et_2O to yield **L1** as the white solid (12 g, 41%), mp 86–88°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ:1.28 (d, J = 6.8 Hz, 6H), 4.93–4.98 (m, J = 6.8 Hz, 1H), 7.11 (s, 1H), 7.28–7.47 (m, 11H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: (23.93, 48.57, 117.97, 128.56, 129.13, 131.66, 133.77, 135.46, 144.68)ppm; ^{31}P NMR (160 MHz, $CDCl_3$) δ: −32.05 ppm; MS (70 eV): m/z = 294 (M^+); *Anal*. Calcd for $C_{18}H_{19}N_2P$: C 73.45, H 6.51, N 9.52; found C 73.31, H 6.43, N 9.35.

Bis(N-iso-propyl-2-imidazolyl)phenylphosphine (L2). Synthesized as compound **L1**, using dichlorophenylphosphine (8.95 g, 0.05 mol) instead of chlorodiphenylphosphine, white solid (5.8 g, 36%), mp 116–117°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.13–1.18 (m, 12H), 4.79–4.87 (m, 2H), 7.15 (s, 2H), 7.26–7.52 (s, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: (23.71, 48.81, 118.73, 128.46, 128.91, 131.27, 132.54, 132.73, 141.68); ^{31}P NMR (160 MHz, $CDCl_3$) δ: −48.56 ppm, MS (70 eV): m/z = 326 (M^+), *Anal*. Calcd for $C_{18}H_{23}N_4P$: C 66.24, H 7.10, N 17.17; found C 66.11, H 7.02, N 17.09.

Tris(N-iso-propyl-2-imidazolyl)phosphine (L3). Synthesized as compound **L1**, using phosphorus trichloride (4.57 g, 0.03 mol) instead of chlorodiphenylphosphine, white solid (3.4 g, 28%), mp 206–208°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21–1.48 (m, 18H), 4.74–4.81 (m, 3H), 7.16–7.36 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: (23.67, 49.09, 119.32, 131.29, 139.21); ^{31}P NMR (160 MHz, $CDCl_3$) δ: −74.36 ppm, MS (70 eV): m/z = 358 (M^+), *Anal*. Calcd for $C_{18}H_{27}N_6P$: C 60.32, H 7.59, N 23.45; found C 60.13, H 7.42, N 23.39.

2-(Diphenylphosphino)-N-tert-butylimidazole (L4). Synthesized as compound **L1** [28], using *N-tert*-butylimidazole (12.4 g, 0.1 mol) instead of *N-iso*-propylimidazole, dichlorophenylphosphine (8.95 g, 0.05 mol) instead of chlorodiphenylphosphine, white solid (6.5 g, 37%), 133–134°C, IR (Vmax/cm^{-1}) (KBr) ν: 3035, 2979, 1476, 1433, 1245, 728, 696 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.72 (S, 9H, ─CH_3), 7.13 (t, 1H, ─C^4─H), 7.20 (d, 1H, ─C^5─H), 7.26 (d, 8H, Ar─H), 7.43 (t, 2H, Ar─H);^{13}C NMR (100 MHz, $CDCl_3$) δ:

(31.69, 57.13, 119.98, 128.41, 129.67, 133.65, 136.76, 144.76); ^{31}P NMR (160 MHz,$CDCl_3$) δ: −23.43 ppm; MS (70 eV): *m*/*z* = 308 (M^+); *Anal*. Calcd for $C_{19}H_{21}N_2P$:C 74.01, H 6.86, N 9.08; found C 73.92, H 6.83, N 9.11.

Bis(N-tert-butyl-2-imidazolyl)phenylphosphine (L5). Synthesized as compound **L1**, using *N-tert*-butylimidazole (12.4 g, 0.1 mol) instead of *N-iso*-propylimidazole, dichlorophenylphosphine (8.95 g, 0.05 mol) instead of chlorodiphenylphosphine, white solid (6.5 g, 37%), mp 165–166°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.66 (s, 18 H), 7.16 (s, 2H), 7.32–7.77 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: (25.13, 49.37, 118.65, 128.38, 128.96, 131.38, 132.61, 132.85, 142.64); ^{31}P NMR (160 MHz, $CDCl_3$) δ: −46.01 ppm; MS (70 eV): *m*/*z* = 354 (M^+), *Anal*. Calcd for $C_{20}H_{27}N_4P$: C 67.77, H 7.68, N 15.81; found C 67.63, H 7.62, N 15.70.

Tris(N-tert-butyl-2-imidazolyl)phosphine (L6). Synthesized as compound **L1**, using *N-tert*-butylimidazole (12.4 g, 0.1 mol) instead of *N-iso*-propylimidazole, phosphorus trichloride (4.57 g, 0.03 mol) instead of chlorodiphenylphosphine, white solid (3.7 g, 28%), mp 259–260°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.60 (s, 27 H), 7.16–7.28 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: (31.07, 56.64, 120.71, 129.84, 141.69); ^{31}P NMR (160 MHz, $CDCl_3$) δ: −51.03 ppm, MS (70 eV): *m*/*z* = 400 (M^+), *Anal*. Calcd for $C_{21}H_{33}N_6P$: C 62.98, H 8.31, N 20.98; found C 62.89, H 8.19, N 20.88.

General procedure for the Suzuki coupling reaction. A mixture of aryl halide (2 mmol), phenylboronic acid (292.6 mg, 2.4 mmol), $K_3PO_4{\cdot}3H_2O$ (2.13 g, 4 mmol), $PdCl_2$ (1.77 mg, 0.01 mmol), **L4** (6.17 mg, 0.02 mmol), and ethanol (3 mL) under nitrogen in a pressure tube was heated to given temperature and maintained for given time. Then it was cooled and extracted with diethyl ether (4 × 5.0 mL) and dried with Na_2SO_4. After evaporation under reduced pressure, the residue was purified on silica gel to give the desired product.

Large-scale application for the Suzuki coupling reaction. A mixture of bromobenzene (3.14 g, 20 mmol), phenylboronic acid (2.93 g, 24 mmol), $K_3PO_4{\cdot}3H_2O$ (21.3 g, 40 mmol), $PdCl_2$ (17.7 mg, 0.1 mmol), **L4** (61.7 mg, 0.2 mmol), and ethanol (20 mL) under nitrogen in a 50-mL two-necked flask was heated to 60°C and monitored using TLC. After completion (~3 h), the reaction mixture was diluted with brine (15 mL) and extracted with ether (3 × 15 mL). The combined organic extract was dried over anhydrous Na_2SO_4. After evaporation under reduced pressure, the residue was purified on silica gel (200–300 mesh, petroleum ether 60–90°C) to give biphenyl as the white solid (2.89 g, 94%).

Acknowledgment. We gratefully acknowledge financial support from Foundation of Hubei Provincial Department of Education (No. Q20111704 and No. B20111702) and Research and Innovation Initiatives of WHPU (No. 2016y19).

REFERENCES AND NOTES

[1] Suzuki, A. J Organomet Chem 1999, 576, 147.
[2] Burkhardt, E. R.; Matos, K. Chem Rev 2006, 106, 2617.
[3] Lennox, A. J. J.; Lloyd-Jones, G. C. Chem Soc Rev 2014, 43, 412.
[4] Tobisu, M.; Chatani, N. Angew Chem Int Ed 2009, 48, 3565.
[5] Hassan, Z.; Patonay, T.; Langer, P. Synlett 2013, 24, 412.
[6] Shi, S.; Meng, G.; Szostak, M. Angew Chem Int Ed 2016, 55, 6959.
[7] Alonso, D. A.; Nájera, C. Chem Soc Rev 2010, 39, 2891.
[8] Kranenburg, M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. Eur J Inorg Chem 1998 155.
[9] Martin, R.; Buchwald, S. L. Acc Chem Res 2008, 41, 1461.
[10] Bhattacharyya, P.; Woollins, J. D. Polyhedron 1995, 14, 3367.
[11] Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. Adv Synth Catal 2006, 348, 609.
[12] Dai, C.; Fu, G. C. J Am Chem Soc 2001, 123, 2719.
[13] Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. Angew Chem Int Ed 2002, 41, 4746.
[14] Li, H.; Zhong, Y.; Chen, C.; Ferraro, A. E. Wang Org Lett 2015, 17, 3616.
[15] Beare, N. A.; Hartwig, J. F. J Inorg Chem 2002, 67, 541.
[16] Old, D. W.; Wolfe, J. P.; Buchwald, S. L. J Am Chem Soc 1998, 120, 9722.
[17] Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. J Am Chem Soc 2001, 123, 2677.
[18] Schareina, T.; Kepme, R. Angew Chem Int Ed 2002, 41, 1521.
[19] Urgaonkar, S.; Nagarajan, M. Tetrahedron Lett 2002, 43, 8921.
[20] Biricik, N.; Durap, F.; Kayan, C.; Gumgum, B.; Gurbuz, N.; Ozdemir, I.; Ang, W. H.; Fei, Z.; Scopelliti, R. J Organomet Chem 2008, 693, 2693.
[21] Molander, G. A.; Canturk, B. Angew Chem Int Ed 2009, 48, 9240.
[22] Milde, B.; Schaarschmidt, D.; Rüffer, T.; Lang, H. Dalton Trans 2012, 41, 5377.
[23] Das, P.; Bora, U.; Tairai, A.; Sarmah, C. Tetrahedron Lett 2010, 51, 1479.
[24] Zapf, A.; Jackstell, R.; Rataboul, F.; Riermeier, T.; Monsees, A.; Fuhrmann, C.; Shaikh, N.; Dingerdissen, U.; Beller, M. Chem Commun 2004 38.
[25] Harkal, S.; Rataboul, F.; Zapf, A.; Fuhrmann, C.; Riermeier, T.; Monsees, A.; Beller, M. Adv Synth Catal 2004, 346, 1742.
[26] Schulz, T.; Torborg, C.; Schaffner, B.; Huang, J.; Zapf, A.; Kadyrov, R.; Borner, A.; Beller, M. Angew Chem Int Ed 2009, 48, 918.
[27] Gaillard, S.; Renaud, J. L. Dalton Trans 2013, 42, 7255.
[28] Sauerbrey, S.; Majhi, P. K.; Daniels, J.; Schnakenburg, G.; Brandle, G. M.; Scherer, K.; Streubel, R. Inorg Chem 2011, 50, 793.
[29] Guan, J. T.; Song, X. M.; Zhang, Z. Y.; Wei, B. M.; Dai, Z. Q. Appl Organomet Chem 2015, 29, 87.
[30] Guan, J. T.; Weng, T. Q.; Yu, G. A.; Liu, S. H. Tetrahedron Lett 2007, 48, 7129.
[31] Guan, J. T.; Yu, G. A.; Hou, J. G.; Yu, N.; Ren, Y.; Liu, S. H. Appl Organomet Chem 2007, 21, 355.