Applied
Organometallic
Chemistry

Received: 6 October 2012 Revised: 4 December 2012 Accepted: 4 December 2012

(wileyonlinelibrary.com) DOI 10.1002/aoc.2958

$(BeDABCO)_2Pd_2Cl_6$ (1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride) as a highly active catalytic system for the Stille cross-coupling reaction under microwave irradiation

Abdol R. Hajipour[a,b]*, Narges Najafi[a] and Fatemeh Rafiee[a]

An efficient catalytic system using $(BeDABCO)_2Pd_2Cl_6$ was developed for the Stille cross-coupling reaction. The substituted biaryls were produced in excellent yields in short reaction times using a catalytic amount of this catalyst in DMF at 120 °C. The ionic character of homogeneous catalyst and microwave irradiation and also DMF as microwave-active polar solvent gave higher yields and shorter reaction times than conventional heating. Benzyl DABCO as an efficient ligand and also a quaternary ammonium salt had an efficient stabilizing effect on the Pd(0) species. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: palladium catalyst; Stille reaction; biaryls; microwave irradiation

Introduction

The palladium-catalyzed cross-coupling of organostannanes with electrophilic organic halides and triflates[1,2] has emerged as a potent tool for the formation of C–C coupling reactions in the production of new materials, natural products,[3] carbohydrate chemistry[4] and biological research.[5] This cross-coupling reaction has gained importance due to the growing availability of the organostannanes, excellent compatibility with a large variety of functional groups and their stability in moisture and air.[6–8] Stille coupling is a powerful route to the formation of biaryls. Biaryls are applied as the building block of a wide range of herbicides,[9] pharmaceuticals,[10] natural and bioactive products,[11] microelectrode array,[12] conducting polymers and liquid crystal materials.[13] In view of the importance of biaryls, a number of effective palladium catalytic systems have been developed for the Stille cross-coupling reaction. Generally, the combination of palladium catalysts with various phosphine ligands results in excellent yields and high efficiency.[14] However, most of the phosphine ligands are expensive and air sensitive, which places significant limits on their synthetic applications.[15] Thus the development of new and efficient phosphine-free palladium catalytic systems remains a potentially promising field for organic synthesis.[16] $Pd(OAc)_2$/1,4-diazabicyclo[2.2.2]octane (DABCO), as a stable, inexpensive and highly efficient catalyst system, is used in cross-coupling reactions and displays some properties as ligands to stabilize the reactive palladium intermediates. 1,4-Diazabicyclo[2.2.2]octane has a cage-like structure with high steric hindrance, and as a rigid ligand has an important place in organic synthesis.[17]

Transition-metal-catalyzed cross-coupling reactions usually need long reaction times and an inert atmosphere to complete with traditional heating. Microwave-assisted couplings under controlled conditions are generally quicker and cleaner than conventional heating, reducing reaction times, yielding products in high yields with fewer side products and increasing the selectivity. The use of homogeneous metal catalysts in conjunction with microwaves leads to an increased lifetime of the catalyst. High-speed Stille coupling reaction was carried out successfully under controlled microwave conditions.[18–20]

In continuation of our recent investigations on the synthesis of the palladium catalysts and application of these complexes in the microwave-assisted cross coupling reactions,[21] we now wish to report the extension of $(BeDABCO)_2Pd_2Cl_6$ homogeneous complex for the cross-coupling reaction of various aryl halides with phenyltributyltin under microwave irradiation.

Results and Discussion

1-Benzyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride ([BeDABCO]Cl) was prepared according to our previous work.[22] The reaction of [BeDABCO]Cl with $PdCl_2$ in 1:1 ratio in acetone reflux gave the $(BeDABCO)_2Pd_2Cl_6$ complex.[23] The structure of synthesized catalyst **A** was suggested as shown in Scheme 1.

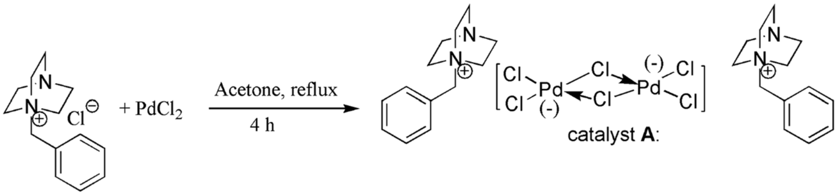
The effect of tetraalkylammonium salts on the activity and stability of palladium catalysts has been described by Jeffery.[24] $(BeDABCO)_2Pd_2Cl_6$ catalyst comprises both *N*-donor ligand and quaternary salt. Benzyl DABCO as an efficient ligand and also a quaternary ammonium salt has efficient stabilizing effect on the Pd(0) species and prevents aggregation of palladium metal.

---

* *Correspondence to: Abdol R. Hajipour, Pharmaceutical Research Laboratory, Department of Chemistry, Isfahan University of Technology, Isfahan 84156, Islamic Republic of Iran. E-mail: haji@cc.iut.ac.ir*

a *Pharmaceutical Research Laboratory, Department of Chemistry, Isfahan University of Technology, Isfahan, 84156, Islamic Republic of Iran*

b *Department of Pharmacology, University of Wisconsin, Medical School, Madison, WI 53706-1532, USA*



Scheme 1. Synthesis of catalyst **A** from *N*-benzyl DABCO chloride and palladium chloride.

The efficiency of this catalytic system was evaluated in Stille cross-coupling reaction under microwave irradiation. In order to investigate the efficiency of this catalytic system and optimize the reaction conditions, a series of screening experiments were carried out in cross-coupling of 4-bromobenzonitrile with phenyltributyltin in different solvents and bases under microwave irradiation. The monitoring system for temperature, pressure, power and reaction times in a microwave reactor allows for excellent control of reaction parameters which generally leads to rapid optimization and more reproducible reaction conditions. The direct control of reaction mixture temperature was carried out with IR sensors and results were summarized in Table 1.

The fluoride sources are potential activators for the organotin species and can facilitate Stille cross-couplings.[25] We investigated the efficacy of fluoride salts such as KF, LiF, NaF, and CsF as a base in this reaction (Table 1, entries 5–8). Among the selected bases, CsF was found to be the most effective. The other bases such as K_2CO_3, Cs_2CO_3 and NaOAc were less effective (Table 1, entries 1–4). Several different solvents such as DMF, *N*-methylpyrrolidone (NMP), toluene, acetonitrile, dioxane, THF and ethanol were examined. Among the tested solvents DMF as a microwave-absorbing polar aprotic solvent having the ability to additionally stabilize palladium species by weak coordination gave the best result. We also optimized the concentration of catalyst, employing various amounts of catalyst for this cross-coupling using CsF as base and DMF as solvent. The low palladium concentration usually led to a long period of reaction, as increasing the amount of palladium catalyst shortened the reaction time. The best result was obtained when the Stille coupling reaction was carried out with 0.19 mol% of catalyst **A** (Table 1, entry 12).

Table 1. Optimization of reaction conditions for Stille coupling under microwave irradiation[a]

Entry	Solvent	Base	Catalyst (mol%)	Temp. (°C)	Conversion (%)[b]
1	EtOH	K_2CO_3	0.2	60	70
2	DMF	K_2CO_3	0.2	120	86
3	DMF	Cs_2CO_3	0.2	120	40
4	DMF	NaOAc	0.2	120	60
5	DMF	KF	0.2	120	75
6	DMF	LiF	0.2	120	50
7	DMF	CsF	0.2	120	100
8	DMF	NaF	—	120	Trace
9	DMF	CsF	0.04	120	30
10	DMF	CsF	0.09	120	50
11	DMF	CsF	0.14	120	85
12	DMF	CsF	0.19	120	100
13	DMF	CsF	—	120	—
14	CH_3CN	CsF	0.2	80	80
15	THF	CsF	0.2	90	Trace
16	Toluene	CsF	0.2	100	65
17	1,4-Dioxane	CsF	0.2	100	53
18	NMP	CsF	0.2	130	60
19	EtOH	CsF	0.2	60	85

[a] Reaction conditions: 4-bromobenzonitrile (1 mmol), phenyltributyltin (1.2 mmol), base (2 mmol), solvent (2 ml), catalyst **A**, 500 W, 3 min.
[b] GC yield.

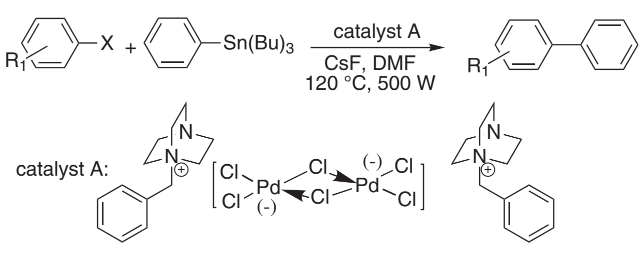
These optimized reaction conditions were applied in the Stille cross-coupling reaction of various aryl halides under microwave irradiation (Table 2). We examined the electronic and steric effects of various aryl halides bearing electron-donating and electron-withdrawing groups on the resulting yields and conversion times of the reactions. The substituent effects in the aryl iodides emerged to be less significant than in the aryl bromides and the reactivity of aryl bromides with electron-withdrawing substituent was higher than that of aryl bromides with electron-donating substituent. I- and Br-substituted aryl halides are most reactive; however, Cl analogues are cheaper and more readily available. As expected, the reactivity of aryl chlorides was lower than that of aryl iodides and bromides as the Stille coupling reactions of aryl chlorides required longer times and lower yields resulted (Table 2, entries 17–20). The steric hindrance of the procedure was examined using 2-, 3- and 4-bromoacetophenone as hindered substituted aryls (Table 2, entries 8–10). Increasing steric hindrance in the vicinity of the leaving group can cause a decrease in reaction conversion. 2-Bromoacetophenone showed slower reaction times and therefore only a reasonable yield was obtained. The chemoselectivity of the procedure was examined using chlorobromobenzene derivatives (Table 2, entries 11 and 12). In these reactions Br acted as the better leaving group. This catalytic complex was compatible with a wide range of functional groups such as nitro, cyano, methoxy, halogen and carbonyl on aryl halides.

Microwave irradiation, in comparison to conventional reflux conditions, led to dramatically reduced reaction times and higher yields (Table 3). The dramatic rate enhancement was due to the rapid and uniform heating of the reaction mixture and increased catalyst lifetime by the elimination of wall effects in microwave versus oil-bath heating. Microwave irradiation raises the temperature of the whole volume simultaneously (bulk heating), whereas in the oil-heated tube the reaction mixture in contact with the vessel wall is heated first.[26]

Conclusions

In this work a general protocol was applied to the microwave-promoted Stille reaction of various aryl halides using $(BeDABCO)_2PdCl_6$. The catalytic amounts of this ionic complex converted various aryl halides to the corresponding biaryls in excellent yields. The dipole characteristics of the catalyst translate into rapid excitation by microwaves and consequently faster reactions. The combination of homogeneous complex as catalyst, high dipole moment

Table 2. Stille reaction of various aryl halides with phenyltributyltin under microwave irradiation[a]



Entry	Ar-X	Biaryl product	Time (min)	Yield (%)[b]
1	Ph-I	Ph-Ph	1	98
2	*p*-MeO-Ph-I	*p*-MeO-Ph-Ph	4	92
3	*p*-O$_2$N-Ph-I	*p*-O$_2$N-Ph-Ph	3	93
4	Ph-Br	Ph-Ph	2	97
5	*p*-MeO-Ph-Br	*p*-MeO-Ph-Ph	6	90
6	*p*-O$_2$N-Ph-Br	*p*-O$_2$N-Ph-Ph	4	91
7	*p*-NC-Ph-Br	*p*-NC-Ph-Ph	3	97
8	*p*-MeOC-Ph-Br	*p*-MeOC-Ph-Ph	7	94
9	*m*-MeOC-Ph-Br	*m*-MeOC-Ph-Ph	9	74
10	*o*-MeOC-Ph-Br	*o*-MeOC-Ph-Ph	12	64
11	*m*-Cl-Ph-Br	*m*-Cl-Ph-Ph	1	98
12	*o*-Cl-Ph-Br	*o*-Cl-Ph-Ph	2	95
13	*p*-OHC-Ph-Br	*p*-OHC-Ph-Ph	5	85
14	1-Br-naphthalene	1-Ph-Naphthalene	7	83
15	9-Br-phenanthrene	9-Ph-phenanthrene	10	89
16	2-Br-pyridine	2-Ph-pyridine	10	82
17	Ph-Cl	Ph-Ph	12	78
18	*p*-OHC-Ph-Cl	*p*-OHC-Ph-Ph	10	75
19	*p*-MeOC-Ph-Cl	*p*-MeOC-Ph-Ph	12	86
20	*p*-O$_2$NPh-Cl	*p*-O$_2$N-Ph-Ph	12	80

[a] Reaction conditions: aryl halide (1 mmol), phenyltributyltin (1.2 mmol), CsF (2 mmol), DMF (2 ml), catalyst **A** (0.19 mol%), 120 °C, 500 W.

[b] Isolated yield.

of quaternary salt part and microwave irradiation increased the lifetime of the catalyst, improved the yields of the reactions and decreased reaction times.

Experimental

General

All melting points were taken on a Gallenkamp melting apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz in CDCl$_3$ solution at room temperature (tetramethylsilane was used as an internal standard) on a Bruker Avance 500 (Rheinstetten, Germany) and Varian 400 NMR instrument. FT-IR spectra were recorded on a spectrophotometer (Jasco 680, Japan). Spectra of solids were carried out using KBr pellets. Vibrational transition frequencies are reported as wavenumber (cm^{-1}). We used a Milestone microwave (ATC-FO 300, Microwave Labstation GmbH) for synthesis. We also used gas chromatography (BEIFIN 3420 gas chromatograph equipped a Varian CP SIL 5CB column: 30 m, 0.32 mm, 0.25 μm) for examination of reaction completion and yields. Palladium acetate, aryl halides and all chemicals were purchased from Merck and Aldrich and were used as received.

General Procedure for the Synthesis of Palladium Salt (Catalyst A):

To a mixture of 0.25 mmol (0.0597 g) *N*-benzyl DABCO chloride and 0.25 mmol (0.044 g) palladium chloride, 3 ml acetone was added in a round-bottom flask equipped with condenser and placed in an oil bath under reflux conditions. After 4 h the reaction mixture was filtered and the resulting solids were washed with water (5 ml) to remove the unreacted *N*-benzyl DABCO chloride. The yellow-brownish catalyst was air dried and weighed. The yield of catalyst **A** with this procedure was 70%. ^{1}H NMR (500 MHz, DMSO): δ_{ppm} 3.01 (t, 6H, $J = 6.8$ Hz, CH$_2$), 3.29 (t, 6H, $J = 6.8$ Hz, CH$_2$), 4.48 (s, 2H, CH$_2$), 7.48 (br s, 5H, H$_{\mathrm{arom}}$); ^{13}C NMR (125 MHz, DMSO): δ_{ppm} 45.67 (C$-$N$_{\mathrm{DABCO}}$), 52.55 (C$-$N$_{\mathrm{DABCO}}$), 67.54 (CH$_2$), 127.96 (C$_{\mathrm{arom}}$), 129.88 (C$_{\mathrm{arom}}$), 131.09 (C$_{\mathrm{arom}}$), 134.08 (C$_{\mathrm{arom}}$); FT-IR (KBr, cm^{-1}): *u* 3016, 2991, 1621, 1585, 1457, 1412, 1372, 1318, 1215, 1078, 1054, 906, 850, 808, 769, 709; UV–visible (DMSO, nm): 275, 309; decomp: 298 °C. Anal. Calcd for C$_{26}$H$_{38}$Cl$_6$N$_4$Pd$_2$: C 37.53, H 4.60, N 6.73; found C 37.10, H 4.37, N 6.41.

General Procedure for the Stille Reaction of Aryl Halides

A mixture of the aryl halide (1 mmol), phenyltributyltin (1.1 mmol) and CsF (2 mmol), (BeDABCO)$_2$PdCl$_6$ (0.19 mmol%) was added to DMF (2 ml) in a round-bottom flask equipped with condenser and placed in the Milestone microwave. Initially using a microwave power of 500 W, the temperature was ramped from room temperature to 120 °C, this taking approximately 40 s, and then held at this temperature until the reaction was completed. During this time, the power was modulated automatically to keep the reaction mixture at 120 °C. The mixture was stirred continuously using an appropriate magnet during the reaction. After the reaction was completed, the mixture was cooled to room temperature and diluted with water and *n*-hexane or diethyl ether. The organic layer was washed with saturated KF solution and dried over MgSO$_4$. The solution was then filtered and the solvent was evaporated using a rotary evaporator. The residue was purified by silica gel column chromatography (*n*-hexane or *n*-hexane–ethyl acetate (9:1). The biaryl products are known compounds and were characterized by comparing their IR, ^{1}H and ^{13}C NMR spectra with those found in the literature.[23,27]

Table 3. Stille reaction of various aryl halides with phenyltributyltin under conventional heating conditions using an oil bath[a]

Entry	Ar-X	Biaryl product	Time (h)	Yield (%)[b]
1	*p*-MeO-Ph-I	*p*-MeO-Ph-Ph	2	92
2	*p*-O$_2$N-Ph-I	*p*-O$_2$N-Ph-Ph	1	97
3	Ph-Br	Ph-Ph	1	95
4	*p*-MeO-Ph-Br	*p*-MeO-Ph-Ph	3	80
5	*p*-O$_2$N-Ph-Br	*p*-O$_2$N-Ph-Ph	2	85
6	*p*-NC-Ph-Br	*p*-NC-Ph-Ph	1.5	94
7	*p*-MeOC-Ph-Br	*p*-MeOC-Ph-Ph	5	95
8	*m*-MeOC-Ph-Br	*m*-MeOC-Ph-Ph	6	72
9	*o*-MeOC-Ph-Br	*o*-MeOC-Ph-Ph	8	61
10	9-Br-Phenanthrene	9-Ph-Phenanthrene	7	85

[a] Reaction conditions: aryl halide (1 mmol), phenyltributyltin (1.2 mmol), CsF (2 mmol), DMF (2 ml), catalyst **A** (0.19 mol%), 120 C.

[b] Isolated yield.

Acknowledgments

We gratefully acknowledge the funding support received for this project from the Isfahan University of Technology (IUT), IR Iran, and Isfahan Science and Technology Town (ISTT), IR Iran. Further financial support from the Center of Excellence in Sensor and Green Chemistry Research (IUT) is gratefully acknowledged.

References

[1] a) J. K. Stille, *Angew. Chem. Int. Ed Engl.* **1986**, *25*, 508; b) A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176.

[2] V. Farina, V. Krishnamurthy, W. J. Scott, The Stille Reactions: Organic Reactions, *Vol. 50*, Wiley, New York, **1997**, pp. 1–652.

[3] a) A. Demotie, I. J. S. Fairlamb, F.-J. Lu, N. J. Shaw, P. A. Spencer, J. Southgate, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2883; b) S. Burling, C. M. Crawforth, I. J. S. Fairlamb, A. R. Kapdi, R. J. K. Taylor, A. C. Whitwood, *Tetrahedron* **2005**, *61*, 9736.

[4] T. Kuribayashi, S. Gohya, Y. Mizuno, S. J. Satoh, *Carbohyd. Chem.* **1999**, *18*, 383.

[5] K. C. Nicolaou, N. P. King, M. R. V. Finlay, Y. He, F. Roschangar, D. Vourloumis, H. Vallberg, F. Sarabia, S. Ninkovic, D. Hepworth, *Bioorg. Med. Chem.* **1999**, *7*, 665.

[6] A. Scrivanti, U. Matteoli, V. Beghetto, S. Antonaroli, B. Crociani, *Tetrahedron* **2002**, *58*, 6881.

[7] V. Polshettiwara, C. Lenb, A. Fihri, *Coord. Chem. Rev.* **2009**, *253*, 2599.

[8] W. Su, S. Urgaonkar, J. G. Verkade, *Org. Lett.* **2004**, *6*, 1421.

[9] S. Peter, H. Gerhard, P. Michael, W. Karl-otto, Z. Cyrill, *Chimia* **2003**, *57*, 715.

[10] G. Bringmann, S. Rudenauer, T. Bruhn, L. Benson, R. Brun, *Tetrahedron* **2008**, *64*, 5563.

[11] A. Pouilhes, A. F. Amado, A. Vidal, Y. Langlois, C. Kouklovsky, *Org. Biomol. Chem.* **2008**, *6*, 1502.

[12] L. Hu, K. Maurer, K. D. Moeller, *Org. Lett.* **2009**, *11*, 1273.

[13] J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359.

[14] a) T. Weskamp, V. P. W. Böhm, W. A. Herrmann, *J. Organomet. Chem.* **1999**, *585*, 348; b) G. A. Grasa, S. P. Nolan, *Org. Lett.* **2001**, *3*, 119; c) H. Tang, K. Menzel, G. C. Fu, *Angew. Chem. Int. Ed.* **2003**, *42*, 5079.

[15] L. H. Pignolet, Homogeneous Catalysis with Metal Phosphine Complexes, Plenum, New York, **1983**.

[16] a) S. Minière, J.-C. Cintrat, *J. Org. Chem.* **2001**, *66*, 7385; b) W. A. Herrmann, *Angew. Chem. Int. Ed.* **2002**, *41*, 1290; c) B. M. Chouday, S. Madhi, N. S. Chowdari, M. L. Kantam, B. Sreedhar, *J. Am. Chem. Soc.* **2002**, *124*, 14127; d) C. Amatore, A. A. Bahsoun, A. Jutand, G. Meyer, A. N. Ntepe, L. Ricard, *J. Am. Chem. Soc.* **2003**, *125*, 4212; e) J. L. Davis, R. Dhawan, B. A. Arndtsen, *Angew. Chem. Int. Ed.* **2004**, *43*, 590.

[17] a) J. H. Li, W. J Liu, *Org. Lett.* **2004**, *6*, 2809; b) J. H. Li, Y. Liang, D. P. Wang, W. J. Liu, Y. X. Xie, D. L. Yin, *J. Org. Chem.* **2005**, *70*, 2832; c) J. H. Li, C. L. Deng, W. J. Liu, Y. X. Xie, *Synthesis* **2005**, 3039; d) J. H. Li, Q. M. Zhu, Y. X. Xie, *Tetrahedron* **2006**, *62*, 10888; e) J. H. Li, X. D. Zhang, Y. X. Xie, *Synthesis* **2005**, 804; f) J. H. Li, D. P. Wang, Y. X. Xie, *Synthesis* **2005**, 2193.

[18] S. Tierney, M. Heeney, I. McCulloch, *Synthetic Met.* **2005**, *148*, 195.

[19] M. Larhed, C. Moberg, A. Hallberg, *Acc. Chem. Res.* **2002**, *35*, 71.

[20] K. Olofsson, M. Larhed, in Microwave-Assisted Organic Synthesis (Eds: P. Lidström, J. P. Tierney), Blackwell, Oxford, **2004**, ch. 2.

[21] a) A. R. Hajipour, F. Rafiee, *Appl. Organomet. Chem.* **2011**, *25*, 542; b) A. R. Hajipour, F. Rafiee, *J. Organomet. Chem.* **2011**, *696*, 2669; c) A. R. Hajipour, F. Abrisham, Gh. Tavakoli, *Transition. Met. Chem.* **2011**, *36*, 725. d) A. R. Hajipour, K. Karami, A. Pirisedigh, *Inorg. Chim. Acta* **2011**, *370*, 531; e) A. R. Hajipour, K. Karami, Gh. Tavakoli, *J. Organomet. Chem.* **2011**, *696*, 819; f) A. R. Hajipour, K. Karami, A. Pirisedigh, *Appl. Organomet. Chem.* **2010**, *24*, 454; g) A. R. Hajipour, K. Karami, Gh. Tavakoli, *Appl. Organomet. Chem.* **2010**, *24*, 798; h) A. R. Hajipour, K. Karami, A. Pirisedigh, *Appl. Organomet. Chem.* **2009**, *23*, 504; i) A. R. Hajipour, K. Karami, A. Pirisedigh, *J. Organomet. Chem.* **2009**. *694*, 2548.

[22] A. R. Hajipour, N. Mahboubghah, *J. Chem. Res.-S* **1998**, *3*, 122.

[23] A. R. Hajipour, I. Mahboobi Dehbane, F. Rafiee, Appl. Organomet. Chem. **2012**, *26*, 743.

[24] T. Jeffery, *Tetrahedron* **1996**, *52*, 10113.

[25] A. F. Littke, L. Schwarz, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 6343.

[26] C. O. Kappe, *Angew. Chem. Int. Ed.* **2004**, *43*, 6250.

[27] K. Karami, C. Rizzoli, M. Mohamadi Salah, *J. Organomet. Chem.* **2011**, *696*, 940.