Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

Ligand-free copper-catalyzed *O*-arylation of arenesulfonamides with phenols: An unusual approach to biaryl ether synthesis

Junmin Chen, Junmin Wang, Xida Chen, Yuming Huang & Pu Shouzhi

To cite this article: Junmin Chen, Junmin Wang, Xida Chen, Yuming Huang & Pu Shouzhi (2019): Ligand-free copper-catalyzed *O*-arylation of arenesulfonamides with phenols: An unusual approach to biaryl ether synthesis, Synthetic Communications, DOI: 10.1080/00397911.2019.1574833

To link to this article: https://doi.org/10.1080/00397911.2019.1574833

Published online: 16 Feb 2019.

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2019.1574833

Taylor & Francis
Taylor & Francis Group

Ligand-free copper-catalyzed *O*-arylation of arenesulfonamides with phenols: An unusual approach to biaryl ether synthesis

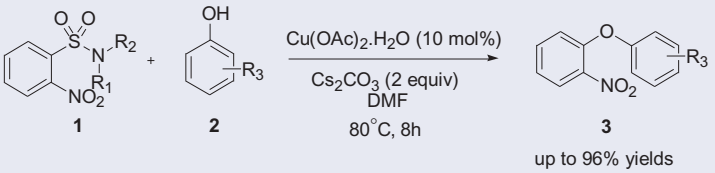
Junmin Chen[a,b], Junmin Wang[b], Xida Chen[b], Yuming Huang[b], and Pu Shouzhi[a]

[a]Jiangxi Key Laboratory of Organic Chemistry, Jiangxi Science & Technology Normal University, Nanchang, Jiangxi, P. R. China; [b]Key Laboratory of Functional Small Organic Molecules Ministry of Education and College of Chemistry & Chemical Engineering, Jiangxi Normal University, Nanchang, Jiangxi, P. R. China

ABSTRACT

An unprecedented ligand-free copper-catalyzed *O*-arylation of arenesulfonamides with phenols has been developed. Thus, a range of unsysmmetric biaryl ethers were synthesized in excellent yields. The reaction occurs efficiently with excellent regioselectivity through the cleavage of C_{ary}–S bond and with a good tolerance of functional groups on the phenyl ring of phenols. The reaction is appreciated for its readily accessible substrates, mild conditions, and simple operation under air.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 16 August 2018

KEYWORDS
Arenesulfonamides; biaryl ether synthesis; copper-catalyzed; C–O bond-forming

Introduction

Diaryl ethers represent an important and versatile structure motif that is frequently present in natural products; materials, pharmaceuticals, and other biologically active molecules.[1–6] Because of their great importance, a wide variety of synthetic methodologies have been developed for the synthesis of diaryl ethers. Conventionally, the classic Ullmann ether synthesis is carried out under relatively harsh conditions, such as high temperatures (125–220 °C) and stoichiometric amounts of copper reagents.[7] In the last few decades, much progress has been made using Pd/ligand systems.[8–10] Although Pd-catalyzed systems show high efficacy in terms of turnover in cross-coupling reactions, costly and toxic Pd limits its applications to large scale production.[11] Significantly, Cu-catalyzed Ullmann coupling between an aryl halide and phenol has been successfully developed under mild conditions by using some special ligands.[12–18] Although

CONTACT Pu Shouzhi pushouzhi@tsinghua.org.cn Jiangxi Key Laboratory of Organic Chemistry, Jiangxi Science & Technology Normal University, Nanchang, Jiangxi, P. R. China.

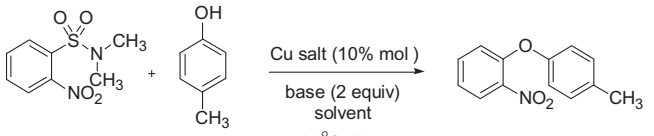
Supplemental data for this article can be accessed on the publisher's website.

significant progress has been achieved in the ether formation reaction, there remain some limitations. For example, the electrophilic coupling partners only were limited to aryl halides and some auxiliary ligands were needed to promote the transformation.[19] To increase the applicability of the method, there is interest in extending cross-coupling reactions to a broader range of electrophiles. Recently, Wu et al. reported for first time nitroarenes as a powerful electrophilic coupling partner and unsymmetrical diaryl ethers were obtained *via* Rh-catalyzed coupling of nitroarenes with arylboronic acids.[20] Latterly, some Pd and Cu catalyst were also found to activate the Ar-NO_2 bonds of nitroarenes towards cross-coupling with arylboronic acids[21,22] and phenols.[23–26] Similarly, arenesulfonamides are valuable intermediates in synthetic organic chemistry and were extensively used as pharmaceutical agents because of their diverse biological properties. To our knowledge, arenesulfonamides as coupling partners were less investigated, the reactions mainly focused on the development of C–C bond-forming transformations through the cross-coupling of vinyl sulfones or aryl sulfonates with Grignard reagents.[27–31]. Recently, we have successfully developed the copper(I)-catalyzed cross-coupling of 2-nitro benzenesulfonamides with thiol to form unsymmetrical sulfides under mild conditions with excellent yields.[32] Inspired by our previous work, we envision the C–O bond-forming transformations can be carried out *via* copper-catalyzed *O*-arylation of arenesulfonamides with phenols through the cleavage of C_{ary}–S bonds. In our continuation of efforts to develop arenesulfonamides as a new coupling partner in cross-coupling reactions, we wish to report the new protocol of copper-catalyzed synthesis of unsymmetrical diaryl ethers *via* direct coupling reaction of arenesulfonamides with phenols, which could be a synthetically alternative route that is environmentally friendly, avoiding the use of halides.

Results and discussion

To test the validity of the proposed Ulmman coupling reactions, we chose 2-nitro benzylsulfonamide (**1a**) and 4-methylphenol (**2a**) as the model substrates to optimize the reaction conditions (Table 1). In our initial investigation, the reaction was performed with $Cu(OAc)_2{\cdot}H_2O$ (10% mol), Na_2CO_3 (2 equiv) in DMF, at 80 °C for 8 h under air, which is the similar conditions used by Chen et al.[32] To our delight, the target product (**3a**) was obtained with 67% yield (Table 1, entry 1). It should be noted that this reaction is highly regioselective and the NO_2 group was not cleaved. Subsequently, we optimized the conditions by varying the Cu salt, solvent, base, and temperature. Firstly, we explored the effects of the base in the arylation coupling reaction. The results revealed that the use of K_2CO_3 or LiO^tBu as a base in the presence of $Cu(OAc)_2.H_2O$ can also perform the desired arylated product **3a** in 62% or 71% yield, respectively (Table 1, entries 2 and 3). However, the trace amount of product **3a** was obtained by using K_3PO_4 or KOAc as a base (Table 1, entries 4 and 5). Significantly, the excellent yield was obtained when Cs_2CO_3 was used under similar conditions (Table 1, entry 6). To further optimize the reaction conditions, the various copper courses were screened in the presence of Cs_2CO_3 (2 equiv.) with DMF as solvent at 80 °C for 8 h under air. However, CuO, CuI, CuI, $CuSO_4$, $CuCl_2$ and Cu_2O produced the desired product **3a** in moderate to good yields (Table 1, entries 7–11) and none of them were superior to

Table 1. Optimization of conditions.



1a **2a** **3a**

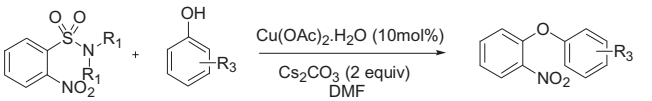
Entry[a]	Copper salt	Base	Solvent	Yield (%)[b]
1	$Cu(OAc)_2.H_2O$	Na_2CO_3	DMF	67
2	$Cu(OAc)_2.H_2O$	K_2CO_3	DMF	62
3	$Cu(OAc)_2.H_2O$	LiO^tBu	DMF	71
4	$Cu(OAc)_2.H_2O$	K_3PO_4	DMF	Trace
5	$Cu(OAc)_2.H_2O$	KOAc	DMF	Trace
6	$Cu(OAc)_2.H_2O$	Cs_2CO_3	DMF	93
7	CuO	Cs_2CO_3	DMF	78
8	CuI	Cs_2CO_3	DMF	47
9	$CuSO_4$	Cs_2CO_3	DMF	78
10	$CuCl_2$	Cs_2CO_3	DMF	82
11	Cu_2O	Cs_2CO_3	DMF	51
12	$Cu(OAc)_2.H_2O$	Cs_2CO_3	DMSO	66
13	$Cu(OAc)_2.H_2O$	Cs_2CO_3	CH_3CN	47
14	$Cu(OAc)_2.H_2O$	Cs_2CO_3	1,4-Dioxane	34
15	$Cu(OAc)_2.H_2O$	Cs_2CO_3	H_2O	35
16[c]	$Cu(OAc)_2.H_2O$	Cs_2CO_3	DMF	53
17[d]	$Cu(OAc)_2.H_2O$	Cs_2CO_3	DMF	14
18[e]	$Cu(OAc)_2.H_2O$	Cs_2CO_3	DMF	73
19	/	Cs_2CO_3	DMF	Trace
20	$Cu(OAc)_2.H_2O$	/	DMF	Trace

[a]Reaction conditions: 2-nitro benzylsulfonamide (**1a**) (0.25 mmol), 4-methylphenol (**2a**) (0.30 mmol), copper salt (10 mol%), base (0.5 mmol), and solvent (0.5 mL), at 80 °C for 8 h.
[b]Isolated yield.
[c]Reaction at 50 °C.
[d]Reaction at 25 °C.
[e]In the presence of 5 mol% $Cu(OAc)_2.H_2O$.

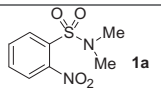
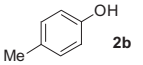
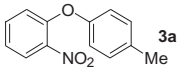
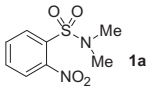
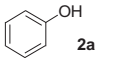
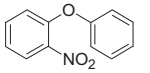
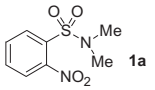
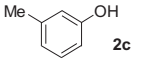
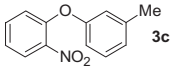
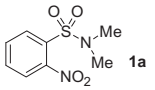
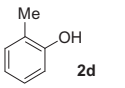
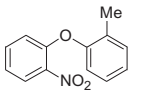
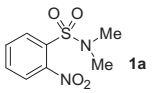
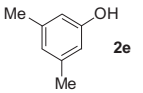
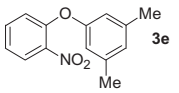
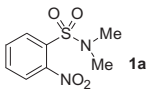
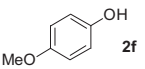
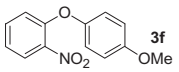
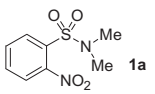
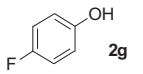
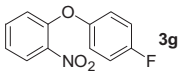
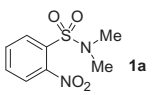
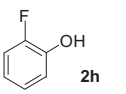
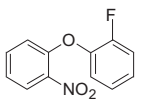
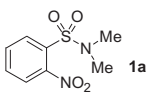
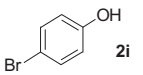
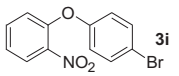
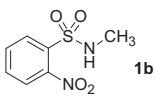
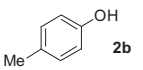
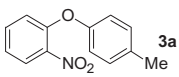
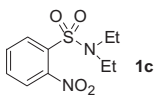
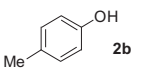
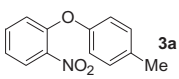
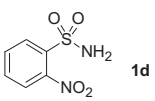
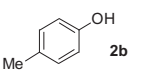
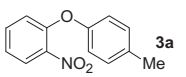
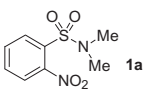
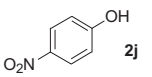
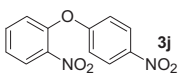
$Cu(OAc)_2{\cdot}H_2O$ (Table 1, entry 6). Secondly, the solvents were screened. It was found that reaction works in various solvents including DMSO, CH_3CN, H_2O or 1,4-dioxane, however, the yields are less efficient compared to DMF under the similar conditions (Table 1, entries 12–15). The temperature had an obvious effect on the reaction efficiency. When the reaction was proceeded at 50 and 25 °C respectively, the yields reduced to 53%, and 14%, respectively (Table 1, entries 16 and 17). Additionally, lowering the amount of the Cu source (5 mol %) led to the formation of **3a** in a drastically decreased yield (Table 1, entry 18). Finally, control experiment confirmed that a trace amount of desired product **3a** were observed without the Cu source or base (Table 1, entries 19 and 20). which also further proved that the present reaction was not classic aromatic nucleophilic substitution (SN_{Ar}) reactions. Thus, the optimized reaction conditions were as follows: 10 mol% of $Cu(OAc)_2.H_2O$, and 2 equiv. of Cs_2CO_3 in DMF (as a solvent) reacting at a temperature of 80 °C for 8 h under air.

With the optimized reaction conditions in hand, we set out to explore the scope of the ligand-free copper-catalyzed transformation of arenesulfonamides **1** with phenol **2** to unsymmetrical diaryl ethers **3** (Table 2). Primarily, we set on to evaluate 2-nitro benzenesulfonamide **1a** and various phenols **2**. Phenols with electron-neutral, electron-donating or electron-withdrawing groups reacted smoothly with 2-nitro benzenesulfonamide **1a**, and high to excellent yields were achieved (Table 2, entries 1–11). For

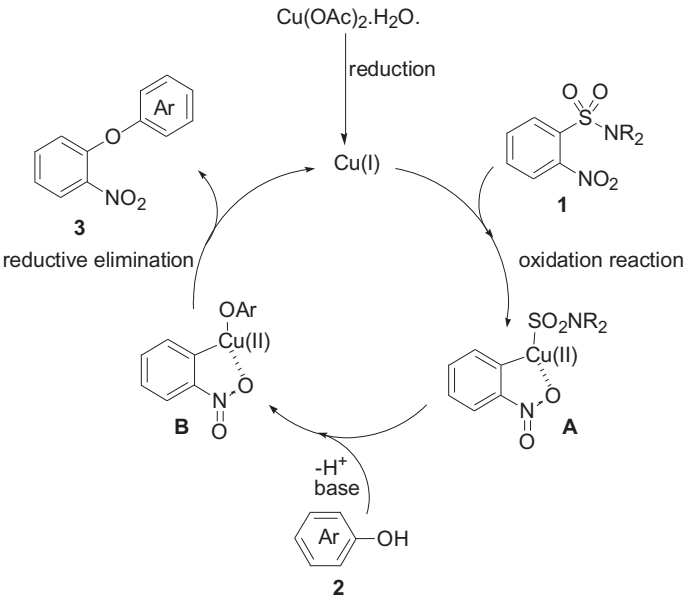
Table 2. Copper-catalyzed cross coupling of 2-nitro benzenesulfonamide **1** with various phenols **2**.



1 **2** **3**

Entry[a]	Substrate **1**	Substrate **2**	Product **3**	Yield (%)[b]
1	 **1a**	 **2b**	 **3a**	93
2	 **1a**	 **2a**	 **3b**	91
3	 **1a**	 **2c**	 **3c**	89
4	 **1a**	 **2d**	 **3d**	87
5	 **1a**	 **2e**	 **3e**	83
6	 **1a**	 **2f**	 **3f**	86
7	 **1a**	 **2g**	 **3g**	84
8	 **1a**	 **2h**	 **3h**	81
9	 **1a**	 **2i**	 **3i**	83
10	 **1b**	 **2b**	 **3a**	91
11	 **1c**	 **2b**	 **3a**	96
12	 **1d**	 **2b**	 **3a**	23
13	 **1a**	 **2j**	 **3j**	trace

[a]Reaction conditions: 2-nitro benzenesulfonamides (**1**) (0.25 mmol), phenol (**2**) (0.30 mmol), $Cu(OAc)_2.H_2O$ (10 mol%), Cs_2CO_3 (0.5 mmol), and DMF (0.5 mL), at 80 °C for 8 h under air.
[b]Isolated yield.



Scheme 1. Plausible reaction mechanism.

example, the reacted with unsubstituted phenol **2b** to give the desired product **3b** in 91% yield (Table 2, entry 2). The steric effects of substituents on the phenyl ring of phenols had no some effect on the reaction, for example, *meta* and *ortho*-methyl substituted phenols **2b** and **2c** were proved to be good substrates for this transformation, affording the corresponding products **3c**, and **3d** in excellent yields (Table 2, entries 3 and 4). Para-methoxyl substituted phenol **3e** can afford the desired coupling product **3e** in 86% yield (Table 2, entry 5). Moreover, the two methyl-substituted phenol **3f** was proved to be good substrate and afforded the desired **3f** in a very high yield (Table 2, entry 6). It should be mentioned that halo-substituted phenols have tolerated well to give the corresponding products, for example, *para,* and *ortho*-halgon substituted phenols **2g**, **2h**, and **2i** can offer the corresponding product **3g**, **3h**, and **3i** in 84, 81, and 83% yields, respectively (Table 2, entries 7–9), which could offer platforms for further functionalization as they contain halogens. Furthermore, the secondary 2-nitro benzenesulfonamide derivative **1b** served as a suitable substrate and provided the corresponding product **3b** in excellent yield (Table 2, entry 10). The 2-nitro benzenesulfonamide derivative **1c** bearing a diethyl amino group can perform the desired product in 91% yield (Table 2, entry 11). Curiously, the primary 2-nitro benzenesulfonamide **1d**, which is a good substrate in C-S bond-forming transformations, [32] only gave the desired product **3b** in a very low yield (Table 2, entry 12). Furthermore, a very low yield of product **3j** was observed by TLC when 4-nitro phenol was used as a substrate with 2-nitro benzenesulfonamide derivative **1a**, and no attempt was made to isolate the product from this reaction (Table 2, entry 13). However, we attempted to use various benzenesulfonamide **1** bearing nitro group at *meta*- or *para* position as the substrate with 4-methylphenol (**2a**), and only trace amount of the desired product was obtained. Based on these results, we concluded that the NO_2 groups at *ortho* position play a coordination directing and

electron-withdrawing double roles for controlling the regioselectivity and reactivity in this C–O bond coupling reaction.

We have formulated a possible mechanism based on previously reported mechanism of copper-catalyzed O-arylation reactions (Scheme 1).[33] Firstly, the Cu(II) salt was reduced to form Cu(I) species, and the subsequent oxidative addition of 2-nitro benzenesulfonamides **1** formed a chelated five-membered reactive species **A**, in which the oxygen of the NO_2 group may coordinate to Cu to provide additional stabilization. Secondly, in the presence of a base, the non-nucleophilic phenol **2** could be converted to intermediate **B** by nucleophile displacement of a sulfonamide group. Finally, the reductive elimination of **B** gave the diaryl ether **3** and regenerated the copper catalyst.

Conclusion

In summary, an efficient, ligand-free copper-catalyzed method for the O-arylation of arenesulfonamides with phenols was developed. This protocol provided a new avenue for developing C-O bond-forming reactions and led to access unsymmetrical diaryl ethers. Notably, this method furnished the direct synthesis of unsymmetrical diaryl ethers through the regioselective cleavage of C_{ary}–S bond without the cleavage of C_{ary}-N bond. Efforts to extend the applications of arenesulfonamides as a new coupling partner to other types of trans-metal-catalyzed coupling reactions are currently underway in our laboratory and will be reported in due course.

Experimental

All reactions were performed under air. Chemicals were purchased from Aldrich, Acros, or Alfa Asar, and, unless otherwise noted, were used without further purification. Flash chromatography was performed on silica gel (silica gel, 200–300 mesh). 1H NMR spectra were recorded on Bruker 400 MHz spectrometers with $CDCl_3$ as the solvent. Compounds **1a-c** were prepared according to the literature.[31]

General procedure for the synthesis of unsymmetrical diaryl ethers 3

A mixture of 2-nitro benzylsulfonamide 1 (0.25 mmol), phenol 2 (0.30 mmol), $Cu(OAc)_2.H_2O$ (0.025 mmol, 5 mg), Cs_2CO_3 (0.5 mmol,163 mg), and DMF (0.5 mL) was placed in a 25-mL roundbottom flask. The mixture was stirred at 80 °C for 8 h under air. Then, the reaction mixture was cooled, diluted with ethyl acetate, filtered through celite, and concentrated in *vacuo*. The residue was purified by silica gel column chromatography with ethyl acetate/petroleum ether to afford the desired product **3**.

Funding

We are grateful for the financial support from the National Natural Science Foundation of China [Grant No. 21762022] and Foundation of Jiangxi Educational Committee [Grant No. GJJ160287].

References

[1] Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2700–2704. DOI: 10.1002/(SICI)1521-3773(19981016)37:19<2700::AID-ANIE2700>3.0.CO;2-P.

[2] Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 5400–5449. DOI: 10.1002/anie.200300594.

[3] In, J.-K.; Lee, M.-S.; Yang, J.-E.; Kwak, J.-H.; Lee, H.; Boovanahalli, S. K.; Lee, K.; Kim, S. J.; Moon, S. K.; Lee, S.; et al. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1799–1802. DOI: 10.1016/j.bmcl.2006.12.048.

[4] Zenitani, S.; Tashiro, S.; Shindo, K.; Nagai, K.; Suzuki, K.; Imoto, M.. *J. Antibiot.* **2003**, *56*, 617–621. DOI: 10.7164/antibiotics.56.617.

[5] Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337–2764. DOI: 10.1016/j.ccr.2004.09.014.

[6] Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 3096–3099. DOI: 10.1002/anie.200703209.

[7] Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853–854. DOI: 10.1002/cber.190403701141.

[8] Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818. DOI: 10.1021/ar9600650.

[9] Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 10718–10719. DOI: 10.1021/ja002543e.

[10] Harkel, S.; Kumar, K.; Michalik, D.; Zapf, A.; Jackstell, R.; Rataboul, F.; Riemeier, T.; Monsees, A.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 3237–3240. DOI: 10.1016/j.tetlet.2005.03.033.

[11] D.; Mann, G, B.; Hartwig, J. F. *Curr. Org. Chem.* **1997**, *1*, 287–305.

[12] Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539–10540. DOI: 10.1021/ja971901j.

[13] Ma, D.; Cai, Q. *Org. Lett.* **2003**, *5*, 3799–3802. DOI: 10.1021/ol0350947.

[14] Cai, Q.; Zou, B.; Ma, D. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 1276–1279. DOI: 10.1002/anie.200503538.

[15] Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 643–646. DOI: 10.1021/ol062904g.

[16] Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863–3867. DOI: 10.1021/jo070443m.

[17] Zhang, Q.; Wang, D.; Wang, X.; Ding, K. *J. Org. Chem.* **2009**, *74*, 7187–7190. DOI: 10.1021/jo9012157.

[18] Tye, J. W.; Weng, Z.; Giri, R.; Hartwig, J. F. *Angew. Chem. Int. Ed. Engl.* **2010**, *49*, 2185–2189. DOI: 10.1002/anie.200902245.

[19] Yong, F.-F.; Teo, Y.-C.; Yan, Y.-K.; Chua, G.-L. *Synlett.* **2012**, 101–106.

[20] Zheng, X.; Ding, J.; Chen, J.; Gao, W.; Liu, M.; Wu, H. *Org. Lett.* **2011**, *13*, 1726–1729. DOI: 10.1021/ol200251x.

[21] Mondal, M.; Bharadwaj, S. K.; Bora, U. *New J. Chem.* **2015**, *39*, 31–37. DOI: 10.1039/C4NJ01293C.

[22] Peng, D.; Yu, A.; Wang, H.; Wu, Y.; Chang, J. *Tetrahedron* **2013**, *69*, 6884–6889. DOI: 10.1016/j.tet.2013.05.112.

[23] Chen, J.; Wang, X.; Zheng, X.; Ding, J.; Liu, M.; Wu, H. *Tetrahedron* **2012**, *68*, 8905–8907. DOI: 10.1016/j.tet.2012.08.032.

[24] Phan, N. T. S.; Nguyen, T. T.; Nguyen, V. T.; Nguyen, K. D. *ChemCatChem.* **2013**, *5*, 2374–2381. DOI: 10.1002/cctc.201300032.

[25] Wang, H.; Yu, A.; Cao, A.; Chang, J.; Wu, Y. *Appl. Organomet. Chem.* **2013**, *27*, 611–614.

[26] Maity, T.; Bhunia, S.; Das, S.; Koner, S. *RSC Adv.* **2016**, *6*, 33380–33386. DOI: 10.1039/C6RA04409C.

[27] Wenkert, E.; Ferreira, T. W.; Michelotti, E. L. *J. Chem. Soc. Chem. Commun.* **1979**, 637–638. DOI: 10.1039/C39790000637.

[28] Okamura, H.; Miura, M.; Takei, H. *Tetrahedron Lett.* **1979**, *20*, 43–46. DOI: 10.1016/S0040-4039(01)85876-7.

[29] Clayden, J. J.; Cooney, A. Julia, *J. Chem. Soc, Perkin Trans. 1* **1995**, 7–14. DOI: 10.1039/p19950000007.
[30] Cho, C.-H.; Yun, H.-S.; Park, K. *J. Org. Chem.* **2003**, *69*, 3017–3025. DOI: 10.1021/jo026449n.
[31] Milburn, R. R.; Snieckus, V. *Angew. Chem. Int. Ed.* **2004**, *43*, 888–891. DOI: 10.1002/anie.200352633.
[32] Chen, J.; Zhang, K.; Zhao, Y.; Pu, S. *Synth. Commun.* **2018**, *48*, 1316–1323. DOI: 10.1080/00397911.2018.1441420.
[33] Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120–4121. DOI: 10.1021/ja050120c.