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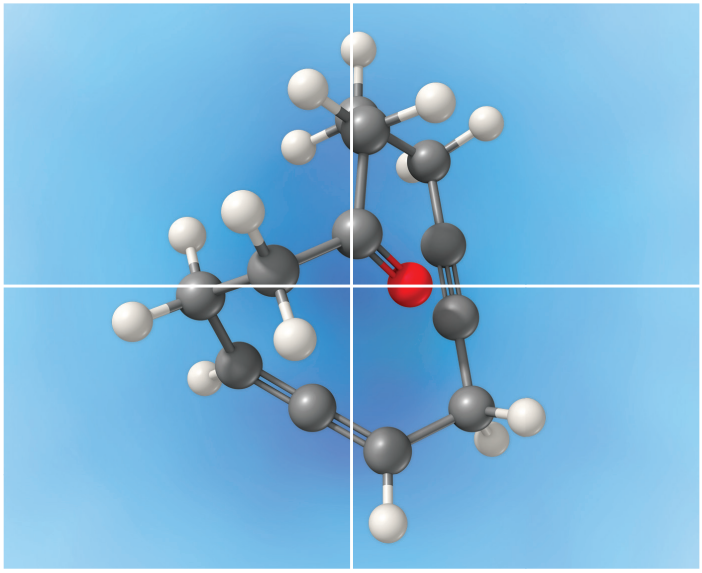

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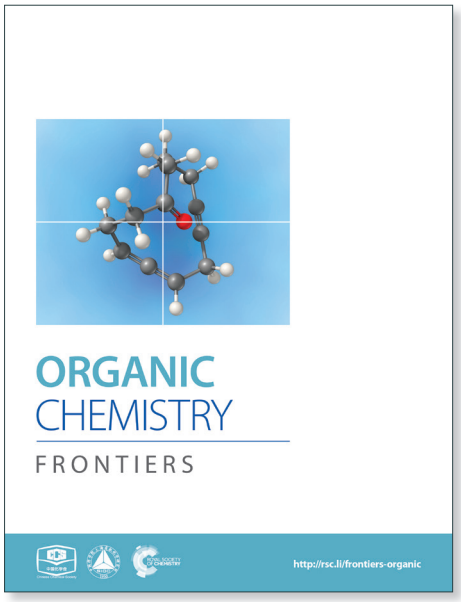

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ARTICLE

Palladium-Catalyzed Direct ortho C-O Bond Construction of Azoxybenzenes with Carboxylic Acids and Alcohols

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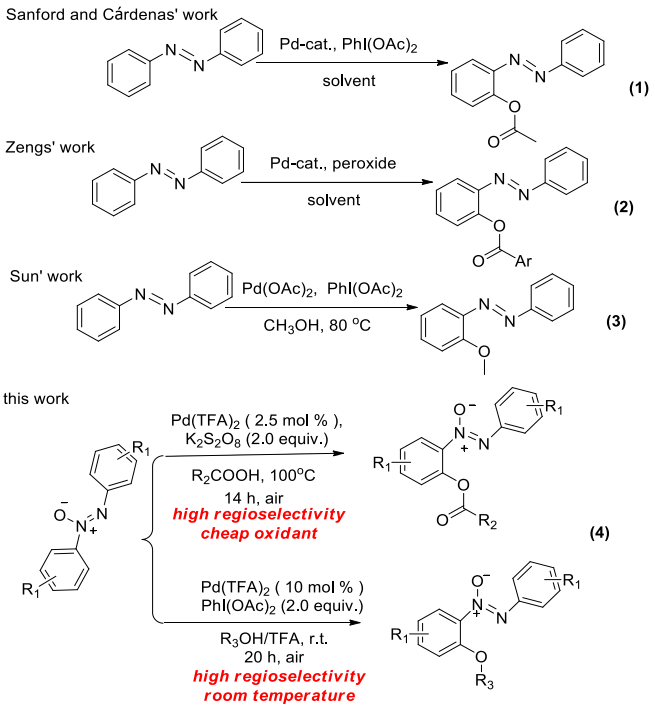
A Pd(II) catalyzed C-O bond formation of azoxybenzenes has been developed. N-atom served as a directing group was confirmed by the single crystal X-ray diffraction analysis of the palladium complex. The products were obtained in moderate to excellent yields for 29 examples. This protocol features high regioselectivity, wide functional group tolerance and atomic economy.

Introduction

Azoxybenzenes are widely applied in pharmaceuticals,[1a] oxidants,[1b-d] photochemistry,[1e] spectroscopy,[1f-g] polymer inhibitors and stabilizers.[1h] In light of their importance, the development of azoxybenzene derivatives has been a hot topic. Nowadays direct C-H bond functionalization has been established to build various azoxybenzene derivatives. The transition-metal-catalyzed *ortho*-halogenation,[2] *ortho*-acylation,[3] *ortho*-arylation,[4] *ortho*-alkoxylation,[5] *ortho*-acyloxyation,[6] *ortho*-amidation,[7] *ortho*-sulfonylation,[8] *ortho*-phosphorylation,[9] *ortho*-nitration[10] and cyclization[11] of azobenzenes have been developed rapidly. Compared with the formation of C-C, C-S and C-N bonds, the reports on the C-O bond formation based metal-catalyzed C-H bonds activation are less well established, maybe due to the electronegativities of the oxygen atom as well as its strong coordination with metal.[5a,12] To the best of our knowledge, there are only three examples to build C-O bond of azobenzenes in the literature shown in Scheme 1. Acyloxyation of the azobenzene was reported by Sanford[6a] and Cárdenas groups[6b] via palladium-catalyzed C-H acyloxyation of azobenzene with $PhI(OAc)_2$. And, Zeng[6d] obtain the acyloxylated azobenzene via palladium-catalyzed acyloxyation of azobenzene with aryl acylperoxides. Sun[5a] presented an alkoxylation of the azobenzene via palladium-catalyzed alkoxylation of azobenzene with methanol. Additionally, the previous work of Wang,[13] Zang[14] and our group[15] indicated that introduction of azoxy group into the azobenzenes can not only bring a high regioselectivity, but also enhance the reactivity of the target C-H bond. In continuation of our effort on C-H functionalization of azoxybenzenes, we embark on development of a simple and efficient procedure for various acyloxyazoxybenzenes and alkoxylazoxybenzenes based on palladium-catalyzed direct C-H bond activation with high efficiency and regioselectivity under the mild conditions. Compared to azobenzenes, azoxybenzenes exhibited higher regioselectivity and resulted in milder reaction conditions as substrates.



Scheme 1. Palladium-Catalyzed Direct C-O Bond Construction of Diazobenzenes.

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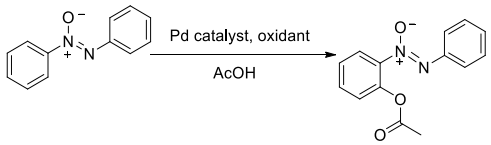
Electronic Supplementary Information (ESI) available: [The supporting information, including the preparation of azoxybenzene, the spectral data for all products and crystallographic data for **3q**, **4l** and **complex I** (CIF)]. See DOI: 10.1039/x0xx00000x

Results and discussion

Initially, the cross-coupling of azoxybenzene **1a** and acetic acid **2a** was chosen as a model reaction to screen various reaction parameters. The results were summarized in Table 1. When the reaction was carried out in carboxylic acids at 100 °C with 10 mol% $Pd(OAc)_2$ as a catalyst and $K_2S_2O_8$ (2.0 equiv) as an oxidant, the desired *o*-acyloxyazoxybenzene **3a** was afforded in 79% yield (entry 1, Table 1). Subsequently, a further screening $Pd(dba)_2$, $PdCl_2$, $Pd(TFA)_2$ salts indicated that $Pd(TFA)_2$ was the best catalyst and could provide **3a** in 86% yield (entries 1-4, Table 1). Other oxidants, such as TBHP, DTBP, Ag_2CO_3, $AgNO_3$, Ag_2O and AgOAc, turned out to be inferior to $K_2S_2O_8$ (entries 5-10, Table 1). When prolonging the reaction time to 10 hours, the yield was not improved significantly (entry 11, Table 1). The catalyst loading was reduced to 2.5 mol% and the reaction time was 14 hours, the product **3a** was obtained in 86% yield (entry 12, Table 1). After surveying the reaction parameters, the optimal reaction conditions were determined as follows: azoxybenzene (0.2 mmol), $Pd(TFA)_2$ (2.5 mol%), $K_2S_2O_8$ (2.0 equiv) in acetic acid (2.0 ml) at 100 °C oil bath under air for 14 hours.

Table 1. Optimizing reaction conditions for the Pd-catalyzed cross-coupling of azoxybenzene **1a** with acetic acid **2a**[a].

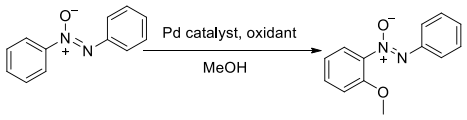


Entry	Catalyst	Oxidant	Time	Yield %[b]
1	$Pd(OAc)_2$	$K_2S_2O_8$	6h	79
2	$Pd(dba)_2$	$K_2S_2O_8$	6h	16
3	$Pd(Cl)_2$	$K_2S_2O_8$	6h	7
4	$Pd(TFA)_2$	$K_2S_2O_8$	6h	86
5	$Pd(TFA)_2$	TBHP	6h	nr
6	$Pd(TFA)_2$	DTBP	6h	nr
7	$Pd(TFA)_2$	$AgNO_3$	6h	trace
8	$Pd(TFA)_2$	Ag_2CO_3	6h	nr
9	$Pd(TFA)_2$	Ag_2O	6h	nr
10	$Pd(TFA)_2$	AgOAc	6h	nr
11	$Pd(TFA)_2$	$K_2S_2O_8$	10h	89
12[c]	$Pd(TFA)_2$	$K_2S_2O_8$	14h	86

[a] Reaction conditions: azoxybenzene (**1a**) (0.2 mmol), acetic acid (**2a**) (2.0 ml), catalyst (10 mo l%), oxidant (2.0 equiv), under air, 100 °C, [b] Isolated yield based on **1a**, [c] $Pd(TFA)_2$ (2.5mol%).

The alkoxylation of azoxybenzene with alcohols was investigated. Changing the coupling partner to methanol, methoxyazoxybenzene was achieved in 22% yield (entry 1, Table 2). When the loading of $Pd(TFA)_2$ was increased to 10 mol%, the product **4a** was obtained in 34% yield (entry 2, Table 2). Inspired by the previous studies, suitable additives might bring crucial effects on the C-H bond activation.[16] When 1.2 mmol (6.0 equiv) of CF_3COOH were added, the yield was improved to 50% (entry 3, Table 2). Compared to $K_2S_2O_8$, $PhI(OAc)_2$ was better (entry 3 *vs* entry 4, Table 2). To our surprised, when the reaction underwent at room temperature, the yield was not significant change (entry 5, Table 2). When the TFA loading was increased to 12.0 equiv. and 18.0 equiv., the product **4a** was obtained in 73% and 80% yields, respectively (entries 6-7, Table 2). So, the optimal reaction conditions were determined: azoxybenzene (0.2 mmol), $Pd(TFA)_2$ (10 mol %), $K_2S_2O_8$ (2.0 equiv), TFA (18.0 equiv.) in methanol (2.0 ml) at room temperature under air for 20 hours.

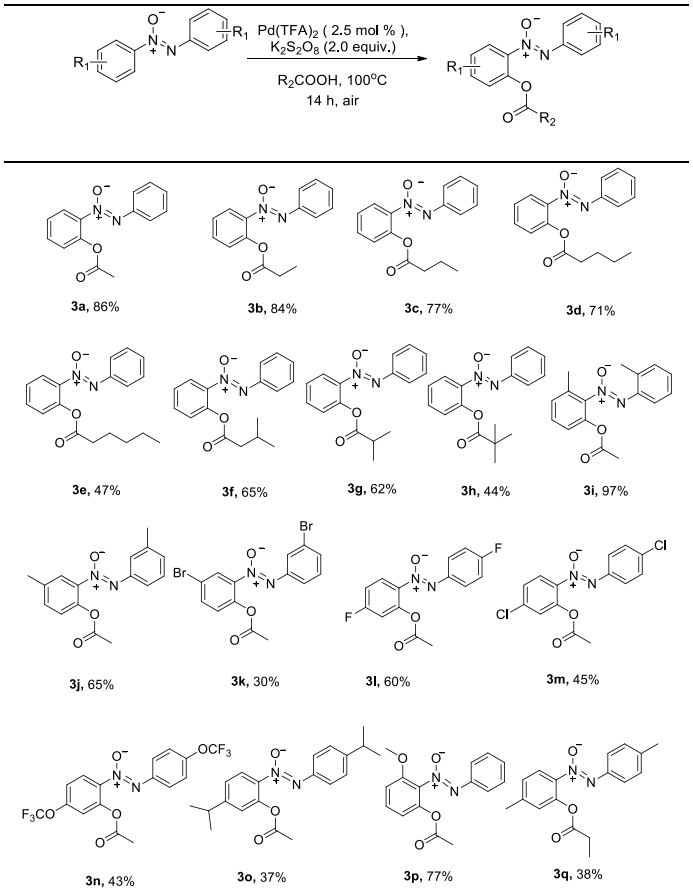
Table 2. Optimizing reaction conditions for the Pd-catalyzed cross-coupling of azoxybenzene **1a** and methanol[a].



Entry	Oxidant	Additive	T	Yield %[b]
1[c]	$K_2S_2O_8$	none	100	22
2	$K_2S_2O_8$	none	100	34
3	$K_2S_2O_8$	TFA (6.0 equiv)	100	50
4	$PhI(OAc)_2$	TFA (6.0 equiv)	100	57
5[d]	$PhI(OAc)_2$	TFA (6.0 equiv)	R.T.	58
6[d]	$PhI(OAc)_2$	TFA (12.0 equiv)	R.T.	73
7[d]	$PhI(OAc)_2$	TFA (18.0 equiv)	R.T.	80

[a]Reaction conditions: azoxybenzene (**1a**) (0.2 mmol), MeOH (**2a'**) (2.0 ml), $Pd(TFA)_2$ (10 mol%), oxidant (2.0 equiv), under air, 20 h. [b]Isolated yield based on **1a**. [c]$Pd(TFA)_2$ (2.5 mol%). [d]room temperature.

With the optimized reaction conditions in hand, the scope of the reaction between azoxybenzene and carboxylic acids was assessed under the optimized conditions (Table 1). A variety of linear carboxylic acids could be coupled with azoxybenzene (**1a**), affording the *ortho*-acyloxyation azoxybenzenes in 47-86% yields (**3a-3e** Scheme 2). The carboxylic acids with α or β steric hindrances were suitable substrates. For example, isovaleric acid, isobutyric acid and trimethylacetic acid gave the corresponding products in 65%, 62% and 44% yields, respectively (**3f-3h** Scheme 2). Next, we explored the azoxybenzenes substrates, and found that the procedure can be widely applied. The 2,2'-dimethyl could promote this reaction and give the desired products in 97% yield (**3i** Scheme 2). While the 3,3'-dimethyl azoxybenzene provided the product in 65% yield and 3,3'-dibromo azoxybenzene provided the product 30% yield (**3j-3k** Scheme 2). The successful conversion of 4,4'-difluoro, 4,4'-dichloro, 4,4'-ditrifluoromethoxy and 4,4'-diisopropyl azoxybenzenes showed that electron-withdrawing and electron-donating groups substituted in substrates are tolerated (**3l-3o** Scheme 2). It is worthy of note that these standard reaction conditions were applied to the unsymmetrically azoxybenzene, affording the corresponding product with only one isomer in 77% yield (**3p** Scheme 2). When the 4,4'-dimethyl azoxybenzene reacted with propionic acid, the 38% yield was obtained (**3q** Scheme 2). The structure of **3q** was confirmed by singlecrystal X-ray diffraction and shown in Fig. 1 in the Supporting Information.

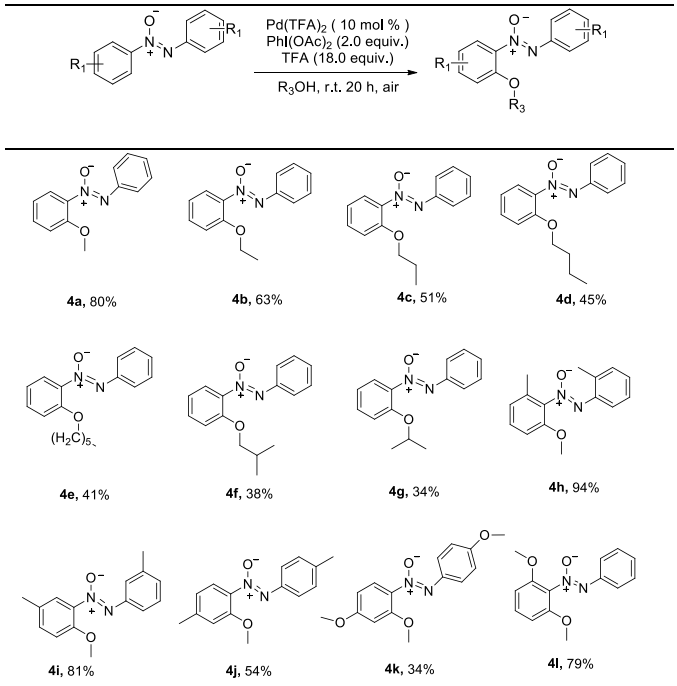


[a]Reaction conditions: azoxybenzenes (0.2 mmol), $Pd(TFA)_2$ (2.5 mol%), $K_2S_2O_8$ (2.0 equiv), carboxylic acids (2.0 ml), 100 °C, under air for 14 hours. Isolated yield.

Scheme 2 The Scope of Palladium-Catalyzed *ortho* C-O Formation of Azoxybenzenes with Carboxylic Acids.[a]

The similar rule to azoxybenzene (**1a**) coupled with alcohols. A variety of linear or branched alcohols could react with azoxybenzenes(**1a**) to give products **4a-4g**. Linear alcohols, such as methanol, ethanol, propanol, butanol and hexylalcohol could be coupled well with azoxybenzene (**1a**), affording products in 41-80% yields (**4a-4e**, Scheme 3). The branched alcohols with steric hindrance of isobutanol and isopropanol did not significantly affect this transformation, providing the desired products in 38% and 34% yields (**4f-4g** Scheme 3). Moreover, the steric effect was observed when methyl-substituted azoxybenzenes at their *ortho*-, *meta*- and *para*-positions were also suitable substrates and successfully afforded the desired products in 94%, 81% and 54% yields, respectively (**4h-4j** Scheme 3). The more electron-donating groups on the *para*-positions, the lower yield was obtained (**4j** *vs* **4k** Scheme 3). As an unsymmetrical substrate, 2-OCH_3 azoxybenzene also proceeded well with excellent regioselectivity and gave the product in 79% yield (**4l** Scheme 3). The structure of **4l** was confirmed by singlecrystal X-ray diffraction and shown in Fig. 1 in the Supporting Information.

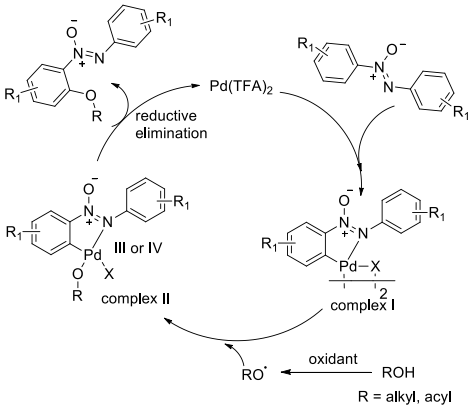
To clarify the reaction mechanism, 4.0 equiv. of TEMPO was added to the reactions under the optimized conditions,



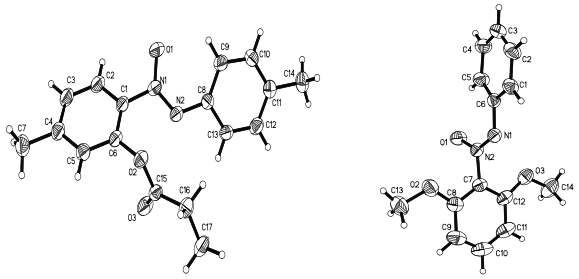
[a]Reaction conditions: azoxybenzenes (0.2 mmol), alcohols (2.0 ml), $Pd(TFA)_2$ (10 mol%), $PhI(OAc)_2$ (2.0 equiv), TFA (18.0 equiv.), room temperature, under air for 20 h. Isolated yield.

Scheme 3 The Scope of Palladium Catalyzed ortho C-O Formation of Azoxybenzenes with Alcohols.[a]

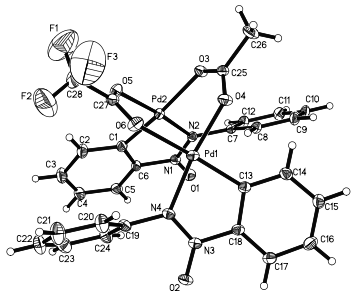
respectively. And no desirable products were detected. Therefore, it suggested that these reactions involve a free radical pathway. Although the details of the mechanism of this C-O formation remain to be elucidated, a possible mechanism is outlined based on earlier literature and our preliminary studies.[17] The coordination of the nitrogen atom in azoxybenzene **1a** firstly reacted with $Pd(TFA)_2$ to form palladacycle **complex I** (Fig. 1.) through the *ortho*-C–H bond activation, which accounted for the high regioselectivity in the reactions. Next, the palladium(II) intermediate was reacted with the alkoxyl radical[18] or carbonyl oxygen radicals[6d,19] to form a palladium(III) or palladium(IV) complex II[20]. Reductive elimination of complex II gave the C-O coupled product accompanied by the regeneration of the palladium(II) catalyst.



Scheme 4. Proposed Reaction Mechanism.



X-ray Molecular Structure of **3q** X-Ray Molecular Structure of **4l**



X-Ray Molecular Structure of Complex I

Fig. 1 The X-ray Molecular structures of **3p**, **4l** and complex **I**.

Conclusions

In summary, we have developed a Pd(II) catalyzed C-O bond formation of azoxybenzenes with carboxylic acids and alcohols. N-atom served as a directing group was confirmed by the singlecrystal X-ray diffraction analysis. Both of acyloxyazoxybenzenes and alkoxylazoxybenzenes were obtained smoothly by these processes. This protocol features high regioselectivity, wide functional group tolerance and atomic economy. Further investigations to expand the substrate scope and application of such chemistry in organic synthesis are underway.

Acknowledgements

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Notes and references

1 For applications of azoxybenzenes, see: (a) H. Takahashi, T. Ishioka, Y. Koiso, M. Sodeoka, Y. Hashimoto, *Biol. Pharm. Bull.* 2000, **23**, 1387; (b) V. M. Dziomko, K. A. Dunaevskaya, *Zh. Obshch. Khim.* 1961, **31**, 3385; (c) L. Giuseppe, R. Amerigo, *Ann. Chim*. 1956, **46,** 296; (d) A. F. Worth, L. Kenneth, *Trans. Kansas Acad. Sci.* 1932, **35**, 146; (e) Ōkubo, M.; H. Hyakutake, N. Taniguchi, *Bull. Chem. Soc. Jpn.* 1988, **61**, 3005; (f) A. Barth, J. E. T. Corrie, M. J. Gradwell, Y. Maeda, W. Mäntele, T. Meier, D. R. Trentham, *J. Am. Chem. Soc.* 1997, **119,** 4149; (g) M. A. Berwick, R. E. Rondeau, *J. Org. Chem.* 1972, **37**, 2409; (h) J. M. Huang, J. F. Kuo, C. Y. Chen, J. *Appl. Polym. Sci.* 1995, **55,** 1217

2 X. T. Ma, S. K. Tian, *Adv. Synth. Catal.* 2013, **355**, 337

3 (a) H. Y. Song, D. Chen, C. Pi, X. L. Cui, Y. J. Wu, *J. Org Chem.* 2014, **79**, 2955; (b) H. J. Li, P. H. Li, Q. Zhao, L. Wang, *Chem. Commun.* 2013, **49**, 9170; (c) Z. Y. Li, D. D. Li, G. W. Wang, *J. Org. Chem.* 2013, **78,** 10414; (d) F. Xiong, C. Qian, D. E. Lin, W. Zeng, X. X. Lu, *Org. Lett.* 2013, **15,** 5444; (e) H. J. Li, P. H. Li, L. Wang, *Org. Lett.* 2013, **15,** 620; (f) H. Tang, C. Qian, D. E. Lin, H. F. Jiang, W. Zeng, *Adv. Synth. Catal.* 2014, **356**, 519

4 S. Miyamura, H. Tsurugi, T. Satoh, M. Miura, *J. Organomet. Chem.* 2008, **693**, 2438.

5 (a) Z. W. Yin, X. Q. Jiang, P. P. Sun, *J. Org. Chem.* 2013, **78**, 10002; (b) S. Shi, C. Kuang, *J. Org. Chem.* 2014, **79**, 6105.

6 (a) A. R. Dick, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* 2004, **126,** 2300; (b) F. Tato, A. García-Domínguez, D. J. Cárdenas, *Organometallics* 2013, **32,** 7487; (c) B. C. Kocher, C. Weder, P. Smith, *Adv. Funct. Mater.* 2003, **13**, 427; (d) C. Qian, D. G. Lin, Y. F. Deng, X. Q. Zhang, H. F. Jiang, G. Miao, X. H. Tang, W. Zeng, *Org. Biomol. Chem*., 2014, **12**, 5866.

7 X. F. Jia, J. Han, *J. Org. Chem.* 2014, **79**, 4180.

8 D. Zhang, X. L. Cui, Q. Q. Zhang, Y. J. Wu, *J. Org. Chem.* 2015, **80,** 1517

9 G. Hong, D. Mao, S. Y. Wu, L. M. Wang, *J. Org. Chem.* 2014, **79,** 10629

10 J. W. Dong, B. Jin, P. P. Sun, *Org. Lett*. 2014, **16,** 4540

11 (a) K. Takagi, M. Al-Amin, N. Hoshiya, J. Wouters, H. Sugimoto, Y. Shiro, H. Fukuda, S. Shuto, M. Arisawa, *J. Org. Chem.* 2014, **79,** 6366; (b) J. Y. Jo, H. Y. Lee, W. J. Liu, A. Olasz, C. H. Chen, D. Lee, *J. Am. Chem. Soc*. 2012, **134,** 16000; (c) D. B. Zhao, Q. Wu, X. L. Huang, F. J. Song, T. Y. Lv, J. S. You, *Chem. Eur. J.* 2013, **19,** 6239; (d) K. Muralirajan, C. H. Cheng, *Chem. Eur. J.* 2013, **19,** 6198; (e) A. Alberti, N. Bedogni, M. Benaglia, R. Leardini, D. Nanni, G. F. Pedulli, A. Tundo, G. Zanardi, *J. Org. Chem.* 1992, **57**, 607; (f) X. L. Huang, X. Y. Chen, S. Ye, *J. Org. Chem.* 2009, **74,** 7585; (g) S. S. Mochalov, M. I. Khasanov, A. N. Fedotov, E. V. Trofimova, *Chem. Heterocycl. Compd.* 2008, **44**, 229

12 (a) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* 2011, **473,** 470.

13 (a) H. J. Li, P. H. Q. Li, Zhao, L. Wang, *Chem. Commun.* 2013, **49**, 9170; (b) H. Li, X. Y. Xie, L. Wang, *Chem. Commun.* 2014, **50**, 4218.

14 M. Sun, L. K. Hou, X. X. Chen, X. J. Yang, W. Sun, Y. S. Zang, *Adv. Synth. Catal.* 2014, **356**, 3789

15 M. L. Yi, X. L. Cui, C. W. Zhu, C. Pi, W. M. Zhu, Y. J. Wu, *Asian J. Org. Chem.* 2015, **4,** 38.

16 (a) B. Xiao, Y. Fu, J. Xu, T. J. Gong, J. J. Dai, J. Yi, L. Liu, *J. Am. Chem. Soc.* 2010, **132**, 468; (b) B. Xiao, T. J. Gong, J. Xu, Z. J. Liu, L. Liu, *J. Am. Chem. Soc.* 2011, **133,** 1466; (c) R. Giri, J. K. Lam, J. Q. Yu, *J. Am. Chem. Soc.* 2010, **132,** 686.

17 (a) X. Chen, K. M. Engle, D. H. Wang, J. Q. Yu, *Angew. Chem., Int. Ed.* 2009, **48,** 5094; (b) L. M. Xu, B. J. Li, Z. Yang, Z. J. Shi, *Chem. Soc. Rev*. 2010, **39**, 712; (c) K. M. Engle, T. S. Mei, M. Wasa, J. Q. Yu, *Acc. Chem. Rev.* 2012, **45,** 788. (d) V. S. Thirunavukkarasu, S. I. Kozhushkov, L. Ackermann, *Chem. Commun.*, 2014, **50**, 29.

18 (a) G. S. Georigiev, E. B. Kamenska, N. V. Tsarevsky, L. K. Christov, *Polym. Int.* 2001, **50,** 313; (b) R. Amorati, L. Valgimigli, P. Dinér, K. Bakhtiari, M. Saeedi, L. Engman, *Chem. Eur. J.* 2013, **19**, 7510.

19 (a) Y. Siddaraju. M. Lamni, K. R. Prabhu, *J. Org. Chem*. 2014, **79**, 3856; (b) X. Mi, C. Y. Wang, M. M. Huang, Y. S. Wu, Y. J. Wu, *J. Org. Chem.* 2015, **80,** 148.

20 (a) D. C. Powaers, M. A. L. Geibel, J. E. M. N. Klein, T. Ritter, *J. Am. Chem. Soc.* 2009, **131,** 17050; (b) D. C. Powers, T. Ritter, *Nat. Chem.* 2009, **1,** 302; (c) J. M. Racowski, A. R. Dick, M. S. Sanford, *J. Am. Chem. Soc.* 2009, **131**, 10974; (d) N. R. Deprez, M. S. Sanford, *J. Am. Chem. Soc*. 2009, **131**, 11234