RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

RSC Advances

COMMUNICATION

Facile synthesis of 2,2'-dinitrosubstituted biaryls through Cu-catalyzed ligand-free decarboxylative homocoupling of *ortho*-nitrobenzonic acids

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Zhengjiang Fu,[a] Zhaojie Li,[a] Qiheng Xiong,[a] and Hu Cai*[a]

A novel waste-free Cu-catalyzed decarboxylaitve homocoupling of *ortho*-nitrobenzoic acids has been developed, and diverse substituents on the phenyl core of the ortho-nitrobenzoic acid are compatible with the transformations. This method provides a practical alternative to synthesize valuable 2,2'-dinitrosubstituted biaryls from cheap and readily available *ortho*-nitrobenzoic acids.

It's well known that biaryls not only constitute important structural motifs in many functional materials, natural products and pharmaceuticals,[1] but also are usually employed as useful building blocks in organic catalysts and ligands in organic synthesis to construct complex molecules,[2] therefore, synthesis of biaryl scaffold has been a matter of great interest in organic synthesis community.[3] In this regard, considerable studies has been devoted into developing quantities of transformations to create various biaryl compounds, and transition metal-catalyzed coupling procedures have exhibited as preferential choice to synthesize biaryls for their straightforward and concise routes. Traditionally, great progress has been achieved through transition metal-catalyzed coupling of haloarenes or arylmetallic reagents, including well-known Ullmann coupling reaction.[3a-b] Nevertheless, the drawbacks including the prefunctionalization of arenes and generation of unwanted byproducts, to some extent, limit the widespread application of the protocols in organic synthesis and industrial production. To address these issues, reactions involving transition metal-promoted oxidative coupling of arene C-H bond activation have emerged as atom- and step-economic alternatives to synthesize biaryls. Thus, transition metal-promoted oxidative coupling of arene C-H bond activation is one of the most widely accepted green transformations to form biaryls.[4] In spite of effectiveness of direct functionalization of arene C-H bonds, the challenges associated with these transformations are the difficulty to control the regio- and chemoselectivity of arene C-H bond activation processes, as well as tedious procedure to remove or modify the directing groups in many cases. Consequently, these dilemmas have impeded to widely prepare biaryls via the above protocols, and have continued to stimulate the development of facile methods for the synthesis of biaryls with easily available substrates as well as good regio- and chemoselectivities.

Pioneered by Myers who reported a Pd-catalyzed decarboxylative Heck coupling of arene carboxylic acids with olefins,[5] carboxylic acids and transition metal-catalyzed decarboxylative reactions have been hot research topics in the field of catalysis and organic synthesis in the last decade,[6-10] because of ready availability and low cost of carboxylic acids as well as nontoxic carbon dioxide as by-product in the decarboxylative reactions. Therefore, transition metal-catalyzed decarboxylative coupling reactions of aryl carboxylic acids have recently emerged as an attractive and alternative approach to synthesis of biaryl compounds.[11] In this context, taking advantage of aromatic carboxylic acid as arylating partner to couple with aryl (pseudo)halides, arylboron reagents and even unfunctionalized (hetero)arenes to deliver biaryl compounds. Under transition-metal catalysis, the in situ generated aryl-metal intermediate from decarboxylation of aryl carboxylic acid can serve as either nucleophile or electrophile depending on the nature of the employed transition-metal catalyst, which demonstrates the potential of aromatic carboxylic acid as versatile coupling partner. In spite of the advantages of these decarboxylative coupling methods, and although biaryl compounds can be achieved in above elegant studies, however, there is still significant room for improvement for the unwelcome waste and/or reaction selectivity. Most notably, it's an ideal and much greener route to synthesize biaryls from the decarboxylative coupling reaction between aryl carboxylic acids, since the reaction only takes place at the original aryl position of the carboxylic acid group with high selectivity, and only innocuous carbon dioxide is extruded as by-product from the reaction. In the year of 2011, the group of Larrosa developed the first Pd/Ag-catalyzed decarboxylative homocoupling of substituted aromatic and heteroaromatic carboxylic acids to prepare symmetrical biaryls in good yields.[12] Tan, and Deng et al. further reported a Pd/Ag-mediated decarboxylative homo- and heterocoupling of substituted benzoic acids to deliver symmetrical and unsymmetrical biaryl compounds.[13] Remarkably, Su disclosed Pd/Ag-promoted decarboxylative cross coupling between various

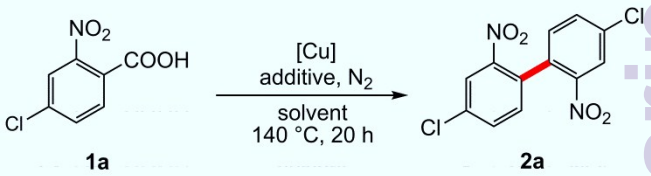
[a] College of Chemistry, Nanchang University, Nanchang, Jiangxi, China. E-mail: caihu@ncu.edu.cn, http://chem.ncu.edu.cn/Teacher_show.asp?id=13.

Electronic Supplementary Information (ESI) available: Copy of all the compounds ^{1}H, ^{13}C and ^{19}F spectra. See DOI: 10.1039/x0xx00000x

substituted arene carboxylic acids to synthesize asymmetrical biaryls exclusively in synthetically useful yields together with only trace amount of homocoupling by-products.[14] In view of high loading and expensiveness of silver salts in their protocols, Djakovitch developed copper as a replacement for silver salt in the above mentioned protocol for decarboxylative heterocoupling of substituted benzoic acids, although narrow in substrate scope and low in reaction yield.[15] Therefore, an efficient method for the formation of biaryls via decarboxylative coupling reaction between aryl carboxylic acids in the absence of noble metal catalyst is still highly desirable. Inspired by these works, aiming at pursuing our efforts to develop sustainable methods for the synthesis of biaryl compounds[16] and exploit new catalytic methods for environmentally friendly decarboxylative coupling,[17] herein, we firstly describe the reliable synthesis of valuable 2,2'-dinitrosubstituted biaryls through decarboxylative homocoupling of 2-nitrobenzonic acids with cheap CuI as the sole catalyst under Pd- or Ag-free conditions.

We commenced our investigation by taking decarboxylative homocoupling of 4-chloro-2-nitrobenzoic acid (**1a**) as the model reaction for the optimization studies. Table 1 presented some selected results from these optimization studies, which showed the effects of the catalyst, reaction temperature and other reaction parameters on the reaction outcome. Initially, in the presence of 2 equivalents of CuI as a mediator, the decarboxylative homocoupling of 4-chloro-2-nitrobenzoic acid (**1a**) was carried out in DMSO at 160 °C under nitrogen atmosphere and furnished desired product 4,4'-dichloro-2,2'-dinitrobiphenyl (**2a**) in 24% isolated yield (entry 1, Table 1). Remarkably, the influence of reaction temperature showed that lowering reaction temperature to 140 °C led to a much higher efficiency (82%), however, essential trace of the target product provided when the reaction was performed at 120 °C (entries 2 and 3). The result indicated the reaction temperature was an important factor to influence the overall yield. Then, the effect of different loading of CuI was elaborately evaluated. It's found that the reaction offered mild yield (45%) in the presence of a catalytic amount of 0.4 equiv of CuI. Pleasingly, the yield increased to 75% when 4 Å molecular sieves (MS) were introduced into the reaction system (entries 4 and 5). In this regard, MS presumably functioned as a water scavenger to avoid protonation of decarboxylative aryl-copper intermediate.[11a-b] Under otherwise identical conditions, decreasing the loading of CuI to 0.3 equivalents gave comparable yield (72%), nevertheless, further reducing CuI loading led to a slightly lower yield (61%) (entries 6 and 7). Subsequently, the influence of counterion of the Cu catalyst on the reaction was examined, and CuI was proved to be the best choice for this decarboxylative homocoupling transformation (entries 8-10). A brief survey of different solvent systems under otherwise equal conditions announced that the combination of CuI and DMSO was clearly the optimized selection for this catalytic system, because either inferior yield (11%) exhibited when the reaction carried out in DMF or no product was detected completely when employing NMP as the solvent (entries 11-12). Finally, studies indicated that the additional nitrogen ligands did not display any beneficial effect on the reaction (entries 13-14). On the basis of these results, we decided to perform decarboxylative homocoupling of 4-chloro-2-nitrobenzoic acid (**1a**) in the presence of 0.4 equiv of CuI in DMSO at 140 °C with 4 Å MS as additive under nitrogen atmosphere and use these conditions as our standard conditions.

Table 1 Selected results for decarboxylative homocoupling of 4-chloro-2-nitrobenzoic acid **1a** under nitrogen atmosphere[a]



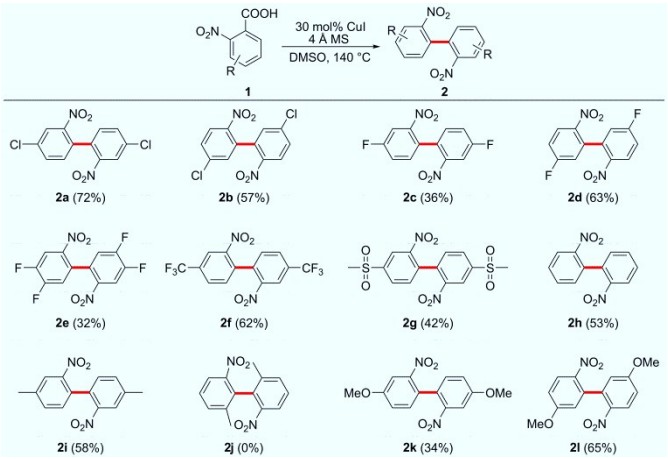
1a **2a**

Entry	Cu (equiv)	Additive	Solvent	Isolated yield (%)[b]
1[c]	CuI (2)		DMSO	24
2	CuI (2)		DMSO	82
3[d]	CuI (2)		DMSO	< 5
4	CuI (0.4)		DMSO	45
5	CuI (0.4)	4 Å MS	DMSO	75
6	**CuI (0.3)**	**4 Å MS**	**DMSO**	**72**
7	CuI (0.2)	4 Å MS	DMSO	61
8	Cu_2O (0.15)	4 Å MS	DMSO	32
9	CuBr (0.3)	4 Å MS	DMSO	37
10	CuOAc (0.3)	4 Å MS	DMSO	13
11	CuI (0.3)	4 Å MS	DMF	11
12	CuI (0.3)	4 Å MS	NMP	0
13[e]	CuI (0.3)	4 Å MS	DMSO	56
14[f]	CuI (0.3)	4 Å MS	DMSO	69

[a] Conditions: **1a** (0.2 mmol), solvent (2 mL), nitrogen atmosphere, 140 °C, 20 h. [b] Average of two runs. [c] Reaction conducted at 160 °C. [d] Reaction conducted at 120 °C. [e] 0.15 equiv of 1,10-phenanthroline was added into the reaction. [f] 0.15 equiv of 2,2'-bipyridine was added into the reaction.

We next evaluated the substrate scope of this novel Cu-catalyzed decarboxylative homocoupling protocol with respect to aromatic carboxylic acids. As depicted in Table 2, *ortho*-nitrobenzoic acid **1h** was an effective substrate to afford 53% isolated yield under the standard conditions, and all of the *ortho*-nitrobenzoic acids substrates bearing electron-deficient (**1a**-**g**) and -rich group (**1i**, **1k**-**l**) directly provided the corresponding symmetrical biaryl compounds in moderate or satisfactory yields. Generally speaking, this protocol worked for a variety of *ortho*-nitrobenzoic acids with electron-withdrawing (chloro, fluoro, bromo, trifluoromethyl, and sulfonyl) and electron-donating groups (methoxy and methyl). 4-Chloro-2-nitrobenzoic acid (**1a**) and its isomer 5-chloro-2-nitrobenzoic acid (**1b**) smoothly formed the hoped-for products (**2a** and **2b**) with the halogen moiety surviving from this catalytic system. Interestingly, the halogen moiety could be used for late-stage modification via the transformation of the C–Hal bond. Unlike its isomer 4-methyl-2-nitrobenzoic acid **1i**, 6-methyl-2-nitrobenzoic acid **1j** was an inert substrate toward this process in the presence of CuI catalyst, indicative of the sensitivity of this transformation to steric hindrance. Unfortunately, the attempt to employ a broad range of other benzoic acids in this transformation failed, regardless of the presence other groups (chloro, methoxy, fluoro, etc.) or absence o

Table 2 Synthesis of symmetrical biaryls via Cu-sataylzed decarboxylative homocoupling of *ortho*-nitrobenzoic acids[a]



[a] Conditions: **1** (0.2 mmol), CuI (30 mol %), 4 Å MS, DMSO (2 mL), nitrogen atmosphere, 140 °C, 20 h.

nitro group at the *ortho*-position of benzoic acid substrate, this result is consistent with our recent observation on the requirement for Pd/Cu-catalyzed decarboxylative methylthiolation reaction: namely, nitro group at the *ortho*-position of benzoic acid substrate is crucial for the decarboxylative process to stabilize the transition structure of decarboxylation procedure and enhance the formation rate of aryl-copper intermediate in the transformation.[17] It's worth noting that the desiredly formed nitro-containing biaryl products in this protocol can be converted into bioactive amino-substituted biaryls via selective reduction[18] and can be used as building blocks in various fields such as dyes, plastics, perfumes, explosives as well as pharmaceuticals.[19] Thus, the transformations endow the further potential application of this methodology in the research laboratory and industrial production.

Conclusions

In conclusion, we have developed a novel waste-free protocol for Cu-catalyzed decarboxylaitve homocoupling of *ortho*-nitrobenzoic acids under noble metal-free conditions. The method exhibited good functional tolerance with respect to both electron-donating and -withdrawing groups and furnished desired nitro-containing biaryl compounds in moderate or satisfactory yields with high selectivity. Thus, the procedure is complementary to the previously established methods for the preparation of symmetrical 2,2'-dinitrosubstituted biaryls. Investigation on Cu-catalyzed decarboxylative heterocoupling of different aromatic carboxylaic acids under palladium or silver-free conditions is currently in progress and will be reported in due course.

Acknowledgement

Financial support from the National Key Basic Research Program of MOST of China (2012CBA01204), National Natural Science Foundation of China (NSFC) (21301088 and 21162015), Natural Science Foundation of Jiangxi Province (20142BAB213001) and Science Foundation of State Key Laboratory of Structural Chemistry (20150022) is greatly appreciated.

Notes and references

1 (a) H. Meier, *Angew. Chem., Int. Ed.*, 2005, **44**, 2482-2506; (b) A. P. Degnan and A. I. Meyers, *J. Am. Chem. Soc.*, 1999, **121**, 2762-2769; (c) M. Vrettou, A. A. Gray, A. R. E. Brewer and A. G. M. Barrett, *Tetrahedron*, 2007, **63**, 1487-1536; (d) A. Markham and K. L. Goa, *Drugs*, 1997, **54**, 299-311; (e) K. F. Croom and G. M. Keating, *Am. J. Cardiovasc. Drugs*, 2004, **4**, 395-404.

2 (a) D. S. Surry and S. L. Buchwald, Chem. Sci., 2011, **2**, 27-50; (b) J. M. Brunel, *Chem. Rev.*, 2005, **105**, 857-897.

3 (a) "Copper-Mediated Aryl-Aryl Bond Formation Leading to Biaryls: A Century after the Ullmann Breakthrough": Y. Yamamoto, *Copper-Mediated Cross-Coupling Reactions*, (Ed.: G. Evano and N. Blanchard), John Wiley & Sons, 2013, p. 335-399; (b) "Transition Metal - Catalysed Direct Arylation of Unactivated Arenes with Aryl Halides": A. Lei and H. Zhang, *C-H and C-X Bond Functionalization : Transition Metal Mediation*, (Ed.: X. Ribas), RSC Catalysis Series, 2013, p. 310-327; (c) V. P. Mehta and B. Punji, *RSC Adv.*, 2013, **3**, 11957-11986; (d) L. J. Goossen, K. Goossen and C. Stanciu, *Angew. Chem., Int. Ed.*, 2009, **48**, 3569-3571.

4 (a) J.-Q. Yu and Z.-J. Shi, C-H activation; Springer: Berlin, Germany, 2010; (b) D. Liu and A. Lei, *Chem. Asian J.*, 2015, **10**, 806-823; (c) F. Zhang and D. R. Spring, *Chem. Rev.*, 2014, **43**, 6906-6919; (d) Y. Segawa, T. Maekawa and K. Itami, *Angew. Chem., Int. Ed.*, 2014, **53**, 66-81; (e) R. Kumar and E. V. Van der Eycken, *Chem. Soc. Rev.*, 2013, **42**, 1121-1146; (f) J. J. Mousseau and A. B. Charette, *Acc. Chem. Res.*, 2013, **46**, 412-424; (g) S. R. Neufeldt and M. S. Sanford, *Acc. Chem. Res.* 2012, **45**, 936-946; (h) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord and F. Glorius, *Angew. Chem., Int. Ed.*, 2012, **51**, 10236-10254; (i) X. Mu, T. Wu, H. Wang, Y. Guo and G. Liu, *J. Am. Chem. Soc.*, 2012, **134**, 878-881.

5 (a) A. G. Myers, D. Tanaka and M. R. Mannion, *J. Am. Chem. Soc.*, 2002, **124**, 11250-11251; (b) D. Tanaka, S. P. Romeril and A. G. Myers, *J. Am. Chem. Soc.*, 2005, **127**, 10323-10333.

6 For recent reviews, see: a) J. Cornella and I. Larrosa, *Synthesis*, 2012, **44**, 653-676; b) R. Shang and L. Liu, *Sci. China Chem.*, 2011, **54**, 1670-1687; c) N. Rodríguez and L. J. Goossen, *Chem. Soc. Rev.*, 2011, **40**, 5030-5048; d) L. J. Gooßen, N. Rodríguez and K. Gooßen, *Angew. Chem., Int. Ed.* 2008, **47**, 3100-3120; e) Z. Fu, Z. Li, Q. Xiong and H. Cai, *Chin. J. Org. Chem.*, 2015, **35**, 10.6023/cjo201409029.

7 (a) H.-P. Bi, W.-W. Chen, Y.-M. Liang and C.-J. Li, *Org. Lett.*, 2009, **11**, 3246-3249; (b) T. Patra, A. Deb, S. Manna, U. Sharma and D. Maiti, *Eur. J. Org. Chem.*, 2013, 5247-5250; (c) H. Yang, H. Yan, P. Sun, Y. Zhu, L. Lu, D. Liu, G. Rong and J. Mao, *Green Chem.*, 2013, **15**, 976-981; (d) X. Huang, W. Liu, J. M. Hooker and J. T. Groves, *Angew. Chem., Int. Ed.*, 2015, **54**, 5241-5245; (e) K. Yang, C. Zhang, P. Wang, Y. Zhang and ... Ge, *Chem. Eur. J.*, 2014, **20**, 7241-7244; (f) L. W. Sardzinski, W. C. Wertjes, A. M. Schnaith and D. Kalyani, *Org. Lett.*, 2015, **17**, 1256-1259.

8 For selected examples of Pd-catalyzed decarboxylative coupling reactions, see: (a) C. Wang, I. Piel and F. Glorius, *J. Am. Chem. Soc.*, 2009, **131**, 4194-4195; (b) L. Huang, J. Qi, Y. Wu, K. Huang and H. Jiang, *Org. Lett.*, 2013, **15**, 2330-2333; (c) Z. Fu, S. Huang, W. Su and M. Hong, *Org. Lett.*, 2010, **12**, 4992-4995; (d) C. Feng and T.-P. Loh, *Chem. Commun.*, 2010, **46**, 4779-4781; (e) Z. Duan, S. Ranjit, P. Zhang and X. Liu, *Chem. Eur. J.*, 2009, **15**, 3666-3669; (f) J. Lindh, P. J. Sjörberg and M. Larhed, *Angew. Chem., Int. Ed.*, 2010, **49**, 7733-7737;

(g) C. Wang, S. Rakshit and F. Glorius, *J. Am. Chem. Soc.*, 2010, **132**, 14006-4008; (h) R. Shang, Z.-W. Yang, Y. Wang, S.-L. Zhang and L. Liu, *J. Am. Chem. Soc.*, 2010, **132**, 14391-4393; (i) M. Kim, J. Park, S. Sharma, A. Kim, E. Park, J. H. Kwak, Y. H. Jung and I. S. Kim, *Chem. Commun.*, 2013, **49**, 925-927; (j) H. Li, P. Li, H. Tan and L. Wang, *Chem. Eur. J.*, 2013, **19**, 14432-14436; (k) K. Rouséé, C. Schneider, S. Couve-Bonnaire, X. Pannecoucke, V. Levacher and C. Hoarau, *Chem. Eur. J.*, 2014, **20**, 15000-15004.

9 For selected examples of Ag-catalyzed decarboxylative reactions, see: (a) Z. Wang, L. Zhu, F. Yin, Z. Su, Z. Li and C. Li, *J. Am. Chem. Soc.*, 2012, **134**, 4258-4263; (b) S. Bhadra, W. I. Dzik, L. J. Gooßen, *J. Am. Chem. Soc.*, 2012, **134**, 9938-9941; (c) F. Hu, X. Shao, D. Zhu, L. Lu and Q. Shen, *Angew. Chem., Int. Ed.*, 2014, **53**, 6105-6109; (d) S. Seo, M. Slater and M. F. Greaney, *Org. Lett.*, 2012, **14**, 2650-2653; (e) W.-M. Zhao, X.-L. Chen, J.-W. Yuan, L.-B. Qu, L.-K. Dun and Y.-F. Zhao, *Chem. Commun.*, 2014, **50**, 2108-2110; (f) R. Suresh, R. S. Kumaran, V. Senthilkumarb and S. Muthusubramanian, *RSC Adv.*, 2014, **4**, 31685-31688.

10 For selected examples of Cu-catalyzed decarboxylative coupling reactions, see: (a) H.-P. Bi, L. Zhao, Y.-M. Liang and C.-J. Li, *Angew. Chem., Int. Ed.*, 2009, **48**, 792-795; (b) Y. Yang, C. Xie, Y. Xie and Y. Zhang, *Org. Lett.*, 2012, **14**, 957-959; (c) L. Yu, P. Li and L. Wang, *Chem. Commun.*, 2013, **49**, 2368-2370; (d) Q. Song, Q. Feng and M. Zhou, *Org. Lett.*, 2013, **15**, 5990-5993; (e) D. L. Priebbenow, P. Becker, C. Bolm, *Org. Lett.*, 2013, **15**, 6155-6157; (f) G. Hu, Y. Gao and Y. Zhao, *Org. Lett.*, 2014, **16**, 4464-4467; (g) H. Yang, P. Sun, Y. Zhu, H. Yan, L. Lu, X. Qu, T. Li and J. Mao, *Chem. Commun.*, 2012, **48**, 7847-7949; (h) Z. He, R. Zhang, M. Hu, L. Li, C. Ni, J. Hu, *Chem. Sci.*, 2013, **4**, 3478-3483.

11 (a) L. J. Gooßen, G. Deng and L. M. Levy, *Science*, 2006, **313**, 662-664; (b) L. J. Gooßen, N. Rodríguez, B. Melzer, C. Linder, G. Deng and L. M. Levy, *J. Am. Chem. Soc.*, 2007, **129**, 4824-4833; (c) L. J. Goossen, N. Rodriguez, P. P. Lange and C. Linder, *Angew. Chem., Int. Ed.*, 2010, **49**, 1111-1114; (d) R. Shang, Y. Fu, Y. Wang, Q. Xu, H.-Z. Yu and L. Liu, *Angew. Chem., Int. Ed.*, 2009, **48**, 9350-9354; (e) P. Forgione, M.-C. Brochu, M. St-Onge, K. H. Thesen, M. D. Bailey and F. Bilodeau, *J. Am. Chem. Soc.*, 2006, **128**, 11350-11351; (f) F. Zhang and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2010, **49**, 2768-2771; (g) F. Pan, Z.-Q. Lei, H. Wang, H. Li, J. Sun and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2013, **52**, 2063-2067; (h) J. Kan, S. Huang, J. Lin, M. Zhang and W. Su, *Angew. Chem., Int. Ed.*, 2015, **54**, 2199-2203; (i) J.-B. Rouchet, C. Schneider, C. Spitz, J. Lefèvre, G. Dupas, C. Fruit and C. Hoarau, *Chem. Eur. J.*, 2014, **20**, 3610-3666.

12 J. Cornella, H. Lahlali and I. Larrosa, *Chem. Commun.*, 2010, **46**, 8276-8278.

13 K. Xie, S. Wang, Z. Yang, J. Liu, A. Wang, X. Li, Z. Tan, C.-C. Guo and W. Deng, *Eur. J. Org. Chem.*, 2011, 5787-5790.

14 P. Hu, Y. Shang and W. Su, *Angew. Chem., Int. Ed.*, 2012, **51**, 5945-5949.

15 N. Rameau, S. Cadot, A. Paquet, C. Pinel and L. Djakovitch, *Top. Catal.*, 2014, **57**, 1430–1437.

16 (a) Z. Fu, Q. Xiong, W. Zhang, Z. Li and H. Cai, *Tetrahedron Lett.*, 2015, **56**, 123-126; (b) Q. Xiong, Z. Fu, Z. Li and H. Cai, *Synlett*, 2015, **26**, 975-979.

17 Z. Fu, Z. Li, Q. Xiong and H. Cai, *Eur. J. Org. Chem.*, 2014, 7798-7802.

18 A. W. Czarnik, *Acc. Chem. Res.*, 1996, **29**, 112-113.

19 (a) G. K. S. Prakash and T. Mathew, *Angew. Chem., Int. Ed.*, 2010, **49**, 1726-1728; (b) G. Yan and M. Yang, *Org. Biomol. Chem.*, 2013, **11**, 2554-2566.