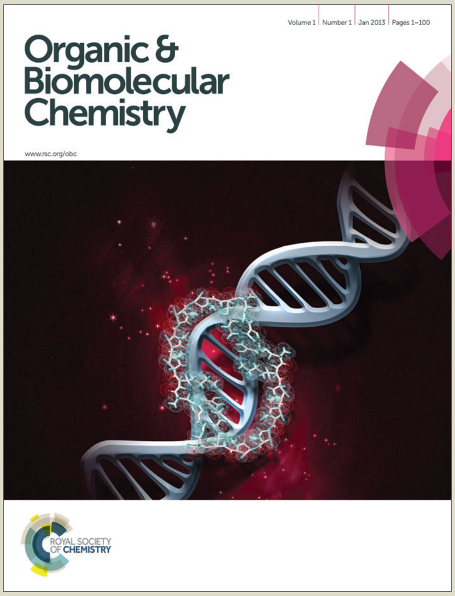
View Article Online
View Journal

Organic & Biomolecular Chemistry

This article can be cited before page numbers have been issued, to do this please use: S. Zhang and L. Huang, *Org. Biomol. Chem.*, 2015, DOI: 10.1039/C5OB01675D.



Journal Name
Organic & Biomolecular Chemistry
Dynamic Article Links ►
View Article Online
DOI: 10.1039/C5OB01675D

Cite this: DOI: 10.1039/c0xx00000x
www.rsc.org/xxxxxx
ARTICLE TYPE

Copper-catalyzed cyanation of aryl iodides with α-cyanoacetates via C-CN bond activation†

Song-Lin Zhang* and Lu Huang

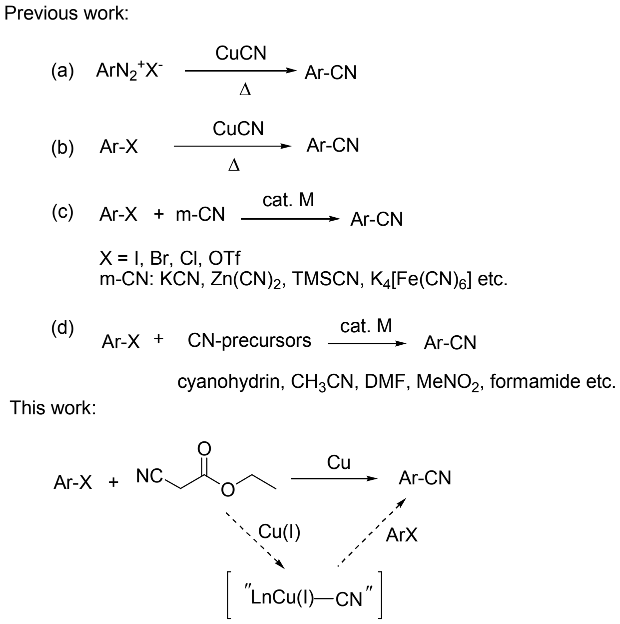
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A Cu(I)-catalyzed cyanation reaction of aryl iodides with α-cyanoacetates is reported herein, which uses α-cyanoacetates as the nontoxic and easy-handling CN source through copper-mediated C-CN bond cleavage. This reaction enables access to aryl nitriles with an array of functional groups on the aromatic ring in good to excellent yields.

1 Introduction

Aryl nitriles are important structural motifs in numerous compounds ranging from pharmaceuticals, agrochemicals, materials to dyes.[1] Aryl nitriles are also synthetic intermediates for an array of valuable functionalized compounds, e.g., amines, imines, ketones and *N*-heterocycles, taking advantage of the versatile conversion of cyano functional group.[2] Therefore, the search for efficient aromatic cyanation reactions has been a longstanding interest. Classic methods for the preparation of aryl nitriles are illustrated by Sandmeyer reaction[3] (Scheme 1a) and Rosenmund-von Braun reaction[4] (Scheme 1b) which exploit the cyanation of aryldiazonium salts or aryl halides by stoichiometric amounts of CuCN. In recent years, transition metal (typically Pd and Cu) catalyzed cyanation reactions have been developed to produce aryl nitriles by coupling of aryl halides with *inorganic* cyanide salts such as NaCN, KCN, CuCN, $Zn(CN)_2$, $K_4Fe(CN)_6$ etc (Scheme 1c).[5,6] For example, one breakthrough in this area is reported in 2003 by Buchwald et al. who achieved the efficient cyanation of aryl and heteroaryl bromides by NaCN in the presence of catalytic amount of KI under CuI/dimethylethylenediamine catalyst sytem.[6b] The use of relatively less toxic $K_4Fe(CN)_6$ as the CN source for cyanation also achieved impressive progress.[6f,6i] However, in these reports, the cyanide salts are highly toxic and hard to handle which greatly limits their widespread applications. The search for methods using safer and easily handling CN sources remains highly desirable. To this end, a number of CN-containing small *organic molecules* such as cyanohydrin,[7] CH_3CN,[8] as well as molecules without a CN group such as formamide,[9] DMF[10] and nitromethane,[11] have been shown to be effective CN sources for aromatic cyanation reactions (Scheme 1d).[5] In addition, more complicated strategies for generating CN group from combined sources have been reported to achieve aromatic cyanation reactions, e.g., DMF + NH_3,[12] DMF + NH_4I,[13] DMF + NH_4HCO_3 [14] and etc.[15]

In recent years, transition metal-mediated C-C bond activation reactions have emerged as a promising tool for organic synthesis due to the prevalence of C-C bond in organic molecules.[16] Among them, the activation of C-CN bond of nitriles by a transition metal complex (typically a Ni(0) or Rh(I) complex) has been well studied to yield TM-CN (TM denotes a transition metal complex) intermediates.[17] These TM-CN intermediates are known to be much less toxic than common cyanide salts that are extremely dangerous. Therefore, nitrile activation by a transition metal complex followed by coupling with aryl halides may provide an alternative and friendly route for the preparation of aryl nitriles (Scheme 1).



Scheme 1 Synthetic methods for the preparation of aryl nitriles

We set out our study by coupling of aryl halides with commercially readily available ethyl α-cyanoacetate as the CN source under copper catalysis. We anticipate that α-cyanoacetate may undergo more facile C-CN bond activation due to the stabilizing resonance of enolate structure in the in-situ generated $(CN)Cu(CH_2CO_2Et)$ type of intermediate. Additional advantages

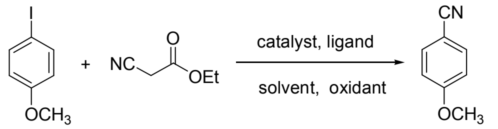
View Article Online
DOI: 10.1039/C5OB01675D

for the use of cyanoacetate are the ready availability, nontoxicity and easily handling characters. These properties are especially attractive from synthetic viewpoint compared to commonly used cyanide salts in cyanation chemistry. The selection of copper catalyst is attributed to two reasons. First, the classic Rosenmund-von Braun reaction demonstrated the feasibility of Cu-CN as the cyanation reagent to react with aryl halides. Second, copper salts are also readily available, non-toxic and operationally simple. To our knowledge, there is no precedent of aryl nitrile preparation using copper-catalyzed coupling of aryl halides with α-cyanoacetates although a Pd-catalyzed variant has been reported recently.[18]

2 Results and Discussion

2.1 Reaction development

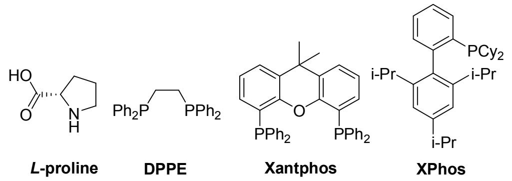
Table 1 Optimization of the reaction conditions [a]



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

entry	*Catalyst*	*Ligand*	*Solvent*	*oxidant*	*Yield (%)*[b]
1	Cu_2O		DMF	air	35
2	Cu_2O	PPh_3	DMF	air	44
3	Cu_2O	PPh_3	DMA	air	45
4	Cu_2O	PPh_3	NMP	air	53
5	Cu_2O	PPh_3	DMSO	air	30
6	Cu_2O	PPh_3	toluene	air	0
7	Cu_2O	PPh_3	NMP	N_2	0
8	**Cu_2O**	**PPh_3**	**NMP**	**O_2**	**70**
9	CuI	PPh_3	NMP	O_2	64
10	$(CH_3COO)_2Cu\cdot H_2O$	PPh_3	NMP	O_2	56
11	$Cu(NO_3)_2\cdot 3H_2O$	PPh_3	NMP	O_2	45
12	$(CuSO_4)\cdot 5H_2O$	PPh_3	NMP	O_2	35
13	CuO	PPh_3	NMP	O_2	12
14	Cu_2O	Phen	NMP	O_2	29
15	Cu_2O	*L*-Proline	NMP	O_2	48
16	Cu_2O	DPPE	NMP	O_2	42
17	Cu_2O	Xantphos	NMP	O_2	41
18	Cu_2O	Xphos	NMP	O_2	0
19	Cu_2O	PCy_3	NMP	O_2	45
20	Cu_2O	PPh_3	NMP	O_2	18[c]
21	**Cu_2O**	**PPh_3**	**NMP**	**O_2**	**80[d]**
22	Cu_2O	PPh_3	NMP	$AgNO_3$,O_2	74[d,e]
23	Cu_2O	PPh_3	NMP	TBHP,O_2	53[d,e]
24	Cu_2O	PPh_3	NMP	DTBP,O_2	69[d,e]
25	Cu_2O	PPh_3	NMP	H_2O_2, O_2	68[d,e]

[a] Reaction conditions: 4-iodoanisole (0.5 mmol), ethyl cyanoacetate (1.0 mmol), copper catalyst (0.1 mmol), ligand (0.2 mmol), and solvent (2 mL) stirred at 130°C under air or oxygen overnight. [b] Isolated yields after silica gel column chromatography. [c] Reaction performed at 100°C. [d] PPh_3 (0.1 mmol). [e] Co-oxidant (0.5 mmol); TBHP, tertbutylhydroperoxide; DTBP, ditertbutyl peroxide.



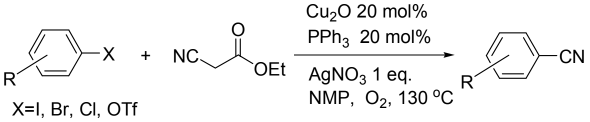
Initial screening of the reaction conditions (entries 1-4, Table 1) led to the discovery that in the presence of 20 mol% Cu_2O and 40 mol% PPh_3 ligand reaction of ethyl α-cyanoacetate (**2a**) with *para*-methoxyphenyl iodide (**1a**) gave the desired benzonitrile **3a** in 53% yield in *N*-methylpyrrolidinone (NMP) at 130°C under air (entry 4). NMP is a preferred solvent compared to other common solvents such as DMF, DMA, DMSO and toluene (entries 2-6), possibly due to the better solubility of the in-situ formed Cu-CN intermediate in NMP.[5a] Notably, oxygen is necessary for the reaction to occur; performing the reaction under N_2 atmosphere led to no reaction at all (entry 7). When an oxygen balloon was used, the reaction yield can increase significantly to 70% (entry 8). Furthermore, change of the catalyst precursors to other copper salts did not result in improved yields compared to Cu_2O (entries 9-13). A number of other ligands such as phenanthroline, *L*-proline, Xantphos, Xphos and PCy_3 etc were also examined, but gave reduced yields compared to PPh_3 (entries 14-19). The optimal reaction temperature was 130 °C; reaction at 100 °C largely reduced the yield to only 18% (entry 20). Interestingly, reducing the amount of PPh_3 ligand from 40 mol% to 20 mol% further improved the reaction yield to 80% (entry 21). Finally, addition of one equivalent $AgNO_3$ additive led to a 74% yield which may act as a co-oxidant assisting oxygen to achieve good catalytic turnovers (entry 22). This beneficial effect of co-oxidant is further demonstrated for some substrates in reaction scope study as discussed in Table 2 (*vida infra*). Other additives were also examined to show good promotion effect, including TBHP, H_2O_2 and DTBP, but they were slightly less effective than $AgNO_3$ (entries 23-25). However, for practical large-scale applications, they may be potential substitutes for $AgNO_3$ due to the low price.

2.2 Substrate scope

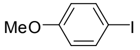
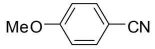
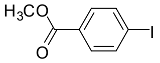
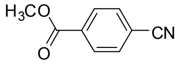
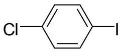
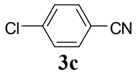
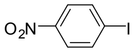
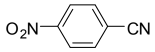
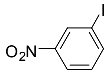
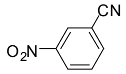
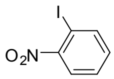
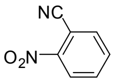
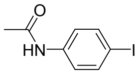
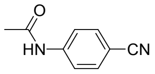
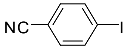
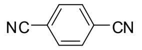
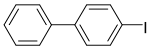
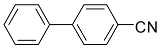
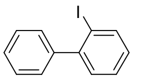
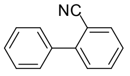
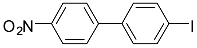
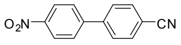
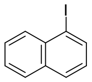
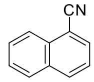
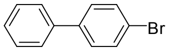
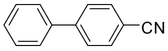
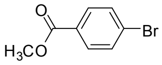
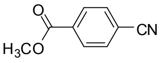
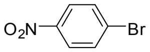
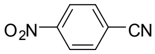
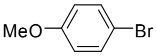
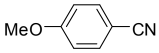
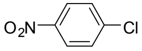
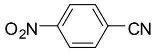
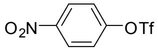
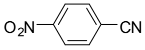
With the optimized reaction conditions in hand, we next studied the substrates scope for this cyanation reaction (Table 2). Various substituted aryl iodides with either electron-rich or -deficient substituents on the aryl ring were compatible with the optimized reaction conditions. Aryl iodides with methoxyl, methoxycarbonyl, chloride, nitro, amide and cyano were shown to be reactive and afford the desired coupling products in good to excellent yields (entries 1-8). Notably, phenyl iodide with *para*-chloride (**1c**) gave selectively the desired product **3c** at the C-I position with the C-Cl bond intact, which provides a handle for further functionalization of the product (entry 3).[19] Aryl iodides with a nitro group at either *ortho*, *meta* or *para* position were all reactive to produce the desired C-I cyanation products (entries 4-6). This is particularly significant considering that nitro group can hardly be tolerated in many cross-coupling reactions due to its unique electronic properties and that it is often difficult for aryl halides with *ortho* substituents to undergo cross-coupling reaction due to steric repulsion. Aryl iodide **1h** with a cyano group at the *para*-position gave the desired terephthalonitrile **3h** in good yields, which can be synthetic intermediate for biologically active compounds and materials with conjugated aromatic rings. Additionally, biaryl iodides and other fused aryl iodides such as **1i**, **1j**, **1k** and **1l** can be compatible with the reaction conditions, giving the desired aryl nitriles in good to excellent yields (entries 9-12).

View Article Online
DOI: 10.1039/C5OB01675D

Table 2 Substrate scope for copper-catalyzed aromatic cyanation [a]



1 2a 3

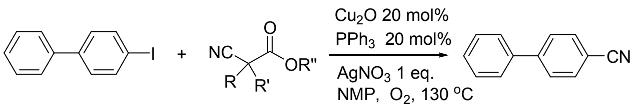
entry	ArX	Product	Yield(%)[b]
1[c]	 **1a**	 **3a**	80
2[c]	 **1b**	 **3b**	76
3[c]	 **1c**	 **3c**	70
4[c]	 **1d**	 **3d**	75
5	 **1e**	 **3e**	66
6	 **1f**	 **3f**	50
7	 **1g**	 **3g**	90
8	 **1h**	 **3h**	61
9	 **1i**	 **3i**	89
10	 **1j**	 **3j**	51
11	 **1k**	 **3k**	96
12	 **1l**	 **3l**	86
13[d]	 **1m**	 **3i**	45
14[d]	 **1n**	 **3b**	24
15[d]	 **1o**	 **3d**	31
16[d]	 **1p**	 **3a**	24
17[d]	 **1q**	 **3d**	0
18[d]	 **1r**	 **3d**	0

[a] Reaction conditions: aryl halide (0.5 mmol), ethyl cyanoacetate (1.0 mmol), Cu_2O (0.1 mmol), PPh_3 (0.1 mmol), $AgNO_3$ (0.5 mmol) and NMP (2 mL), 130 °C, under O_2 atmosphere. [b] Isolated yields using silica gel column chromatography. [c] without $AgNO_3$ salt. [d] Cu_2O (0.5 mmol).

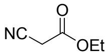
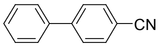
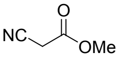
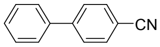
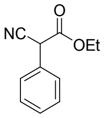
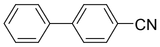
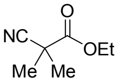
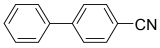
In addition to aryl iodides, aryl bromides can also react with α-cyanoacetate to deliver the desired aryl nitrile products. However, stoichiometric amounts of Cu_2O were generally required and much lower yields were obtained (entries 13-16). Aryl chlorides and triflates were also examined for this cyanation reaction, but no appreciable amounts of products could be obtained (entries 17,18). The reactivity of aryl halides follows an apparent trend of ArI > ArBr > ArCl. This strongly implies that aryl halide activation should be rate-limiting under the reaction conditions for this reaction. Further efforts are still required for these challenging substrates.

To further demonstrate the compability of this cyanation reaction, several commercially available cyanoacetates were examined to react with iodide **1i** under the optimized reaction conditions (Table 3). It was pleased to find that methyl cyanoacetate (**2b**) gave the desired product **3i** in 80% yield, which is a little lower than ethyl cyanoacetate (**2a**). Additionally, cyanoacetates **2c** and **2d** with either one phenyl or two methyls substituents at the α-C position were also reactive to give the desired **3i** in very good yields. These results demonstrate that an array of cyanoacetates are feasible CN sources for this cyanation reaction.

Table 3 Substrate scope for cyanoacetate sources [a]



1i 2 3i

entry	Cyanoacetate	Product	Yield (%)[b]
1	 **2a**	 **3i**	89
2	 **2b**	 **3i**	80
3	 **2c**	 **3i**	76
4	 **2d**	 **3i**	75

[a] Reaction conditions: aryl halide (0.5 mmol), cyanoacetate (1.0 mmol), Cu_2O (0.1 mmol), PPh_3 (0.1 mmol), $AgNO_3$ (0.5 mmol) and NMP (2 mL), 130 °C, under O_2 atmosphere. [b] Isolated yields using silica gel column chromatography.

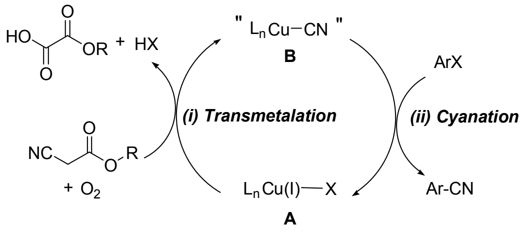
Finally, the synthetic potential of this reaction is further shown by the ready scale up of this reaction to gram levels. For example, reaction of 8 mmol **1i** with 16 mmol **2a** under the optimized reaction conditions gave the desired **3i** in a yield of 1.03 g (72% yield). This should be particularly attractive for practical synthetic applications because it is not practical to prepare aryl nitriles at gram levels using large quantity of common toxic

View Article Online
DOI: 10.1039/C5OB01675D

cyanide salts as the CN source.

2.3 Mechanistic aspects

To shed insights into the mechanistic aspects of this reaction, especially the fate of the CH_2CO_2Et and halide anion counterparts of the reactants, GC analyses of the crude product mixture were performed for the reaction in Table 1. GC analyses showed that aside from the desired products and the reactants recovered, there were no signals of organic compounds containing CH_2CO_2Et or halide anion counterparts, such as ICH_2CO_2Et conceived from reaction stoichiometry (please refer to ESI for details). Considering the fact that oxygen is crucial to this reaction (refer to discussions related to Table 1), it is possible that the CH_2CO_2Et part might be oxidized by oxygen to get oxalate derivatives, which may easily sublime from the reaction solution or further decompose to release CO_2 under the reaction conditions.[20] Additional evidence supporting this hypothesis is that the reaction mixture shown in Table 1 exhibits significant acidity (*p*H~5) while the reaction solution is basic (*p*H~9) before the reaction.[21]



Scheme 2 Plausible mechanism for this cyanation reaction

As a result, a plausible mechanism profile is suggested as shown in Scheme 2 for this copper-catalyzed cyanation reaction. A key L_nCu-CN intermediate **B** is generated initially via transmetalation of CN group from α-cyanoacetate to Cu center through C-CN bond cleavage which may probably be accompanied by oxidation of the methylene group (Scheme 2). Complex **B** reacts with aryl halide to produce the desired Ar-CN product and intermediate **A**. This step may possibly be rate-limiting because our experiments clearly show a reactivity trend of ArI > ArBr > ArCl. Aryl iodides are much more reactive than aryl bromides and chlorides and can achieve catalytic reactions in good to excellent yields. In contrast, aryl bromides need stoichiometric amount of copper to produce the desired products in low yields while aryl chlorides led to no reaction at all under either catalytic or stoichiometric amounts of copper. Finally, the regeneration of **B** from **A** via transfer of CN group from α-cyanoacetate to copper center completes the catalytic cycle. At present, it is unclear about the detailed mechanism for the reaction of intermediate **B** with aryl halide. Possible oxidative addition/reductive elimination, nucleophilic aromatic substitution, σ-bond metathesis, and single electron transfer mechanisms[22,23] may be operative. Additional efforts including computational studies may be required to obtain more information to distinguish between these candidates.

5 Conclusions

In summary, a reaction protocol for copper-catalyzed aromatic cyanation of aryl iodides has been reported, which uses readily available and friendly α-cyanoacetate as the CN source via C-CN bond cleavage. It provides an alternative and safe choice for the preparation of aryl nitriles to currently known methods using toxic cyanides salts. This reaction is operationally simple, free of manipulating toxic cyanide salts and can tolerate an array of functional groups on the aromatic ring, which render it very attractive for the practical synthesis of functionalized aryl nitriles. Further studies on the expansion of the substrate scope and understanding the mechanism of this reaction are ongoing in our laboratory.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Nos. 21472068, 21202062) and the Natural Science Foundation of Jiangsu Province (No. BK2012108).

Notes and references

The Key Laboratory of Food Colloids and Biotechnology, Ministry of Education, School of Chemical and Material Engineering, Jiangnan University, Wuxi 214122, Jiangsu Proince, China. Fax: +86-510-85917763; Tel: +86-510-85917763; E-mail: slzhang@jiangnan.edu.cn

† Electronic Supplementary Information (ESI) available: Experimental details, characterization data, ^1H, ^{13}C NMR spectra for all the products and GC analyses. See DOI: 10.1039/b000000x/

1 (a) A. Kleemann, J. Engel, B. Kutscher and D. Reichert, *Pharmaceutical Substance: Synthesis Patents, Applications*, 4th ed., Georg Thieme, Stuttgart, 2001; (b) J. S. Miller and J. L. Manson, *Acc. Chem. Res.*, 2001, **34**, 563; (c) F. F. Fleming and Q. Wang, *Chem. Rev.*, 2003, **103**, 2035.
2 (a) Z. Rappoport, *Chemistry of the Cyano Group*, Wiley, London, 1970; (b) R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, VCH, New York, 1989.
3 T. Sandmeyer, *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 1633.
4 K.W. Rosenmund and E. Struck, *Ber. Dtsch. Chem. Ges.*, 1919, **2**, 1749.
5 For reviews on transition metal-catalyzed cyanation reactions, see: (a) G. P. Ellis and T. M. Romney-Alexander, *Chem. Rev.*, 1987, **87**, 779; (b) J. Kim, H. J. Kim and S. Chang, *Angew. Chem., Int. Ed.*, 2012, **51**, 11948; (c) P. Anbarasan, T. Schareina and M. Beller, *Chem. Soc. Rev.*, 2011, **40**, 5049; (d) Q. Wen, J. Jin, L. Zhang, Y. Luo, P. Lu and Y. Wang, *Tetrahedron Lett.*, 2014, **55**, 1271.
6 For selected examples of copper-catalyzed cyanation of aryl halides, see: (a) J. X. Wu, B. Beck and R. X. Ren, *Tetrahedron Lett.*, 2002, **43**, 387; (b) J. Zanon, A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 2890; (c) H.-J. Cristau, A. Ouali, J.-F. Spindler and M. Taillefer, *Chem. —Eur. J.*, 2005, **11**, 2483; (d) T. Schareina, A. Zapf and M. Beller, *Tetrahedron Lett.*, 2005, **46**, 2585; (e) T. Schareina, A. Zapf, W. Magerlein, N. Müller and M. Beller, *Synlett*, 2007, 555; (f) T. Schareina, A. Zapf, W. Magerlein, N. Müller and M. Beller, *Chem. —Eur. J.*, 2007, **13**, 6249; (g) D. Wang, L. Kuang, Z. Li and K. Ding, *Synlett*, 2008, 69; (h) P. Y. Yeung, C. M. So, C. P. Lau and F. Y. Kwong, *Org. Lett.*, 2011, **13**, 648; (i) P. Y. Yeung, C. M. So, C. P. Lau and F. Y. Kwong, *Angew. Chem., Int. Ed.*, 2010, **49**, 8918; (j) P. Y. Yeung, C. P. Tsang and F. Y. Kwong, *Tetrahedron Lett.*, 2011, **52**, 7038.
7 (a) M. Sundermeier, A. Zapf and M. Beller, *Angew. Chem., Int. Ed.*, 2003, **42**, 1661; (b) T. Schareina, A. Zapf, A. Cott, M. Gotta and M. Beller, *Adv. Synth. Catal.*, 2011, **353**, 777; (c) K. Ouchaou, D. Georgin and F. Taran, *Synlett* 2010, 2083; (d) E. J. Park, S. Lee and S. Chang, *J. Org. Chem.*, 2010, **75**, 2760.
8 F.-H. Luo, C.-I. Chu and C.-H. Cheng, *Organometallics*, 1998, **17**, 1025.

View Article Online
DOI: 10.1039/C5OB01675D

9 (a) D. N. Sawant, Y. S. Wagh, P. J. Tambade, K. D. Bhatte and B. M. Bhanage, *Adv. Synth. Catal.*, 2011, **353**, 781; (b) K. Hosoi, K. Nozaki and T. Hiyama, *Org. Lett.*, 2002, **4**, 2849.

10 S. Ding and N. Jiao, *J. Am. Chem. Soc.*, 2011, **133**, 12374.

11 X. Chen, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 6790.

12 J. Kim and S. Chang, *J. Am. Chem. Soc.*, 2010, **132**, 10272.

13 (a) J. Kim, J. Choi, K. Shin and S. Chang, *J. Am. Chem. Soc.*, 2012, **134**, 2528; (b) K. V. V. K. Mohan, N. Narender and S. J. Kulkarni, *Tetrahedron Lett.*, 2004, **45**, 8015; (c) J. Kim, H. Kim and S. Chang, *Org. Lett.*, 2012, **14**, 3924.

14 (a) X. Ren, J. Chen, F. Chen and J. Cheng, *Chem. Commun.*, 2011, **47**, 6725; (b) G. Zhang, X. Ren, J. Chen, M. Hu and J. Cheng, *Org. Lett.*, 2011, **13**, 5004.

15 (a) Z. Zhang and L. S. Liebeskind, *Org. Lett.*, 2006, **8**, 4331; (b) P. Anbarasan, H. Neumann and M. Beller, *Chem.* —*Eur. J.*, 2010, **16**, 4725; (c) P. Anbarasan, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2011, **50**, 519; (d) Y. Yang, Y. Zhang and J. Wang, *Org. Lett.*, 2011, **13**, 5608.

16 For general reviews on C−C activation, see: (a) M. Murakami and Y. Ito, In *Topics in Organometallic Chemistry*; Murai, S., Ed.; Springer-Verlag: New York, 1999; pp 97−129; (b) B. Rybtchinski and D. Milstein, *Angew. Chem., Int. Ed.*, 1999, **38**, 870; (c) C. Perthuisot, B. L. Edelbach, D. L. Zubris, N. Simhai, C. N. Iverson, C. Muller, T. Satoh and W. D. Jones, *J. Mol. Catal. A*, 2002, **189**, 157; (d) C.-H. Jun, *Chem. Soc. Rev.*, 2004, **33**, 610; (e) Y. J. Park, J.-W. Park and C.-H. Jun, *Acc. Chem. Res.*, 2008, **41**, 222; (f) C. Najera and J. M. Sansano, *Angew. Chem., Int. Ed.*, 2009, **48**, 2452; (g) M. Murakami and T. Matsuda, *Chem. Commun.*, 2011, **47**, 1100; (h) K. Ruhland, *Eur. J. Org. Chem.*, 2012, 2683.

17 For a review on C−CN bond cleavage, see: M. Tobisu and N. Chatani, *Chem. Soc. Rev.*, 2008, **37**, 300.

18 S. Zheng, C. Yu and Z. Shen, *Org. Lett.*, 2012, **14**, 3644.

19 *Metal-Catalyzed Cross-Coupling Reactions*; A. de Meijere and F. Diederich, Eds.; Wiley: Weinheim, Germany, 2004.

20 Oxalic acid can greatly sublime at temperatures higher than 125 ºC. Additionally, it has been shown by Liu et al that decarboxylation of oxalate monoesters by a Pd complex can be achieved under relatively mild conditions, see: (a) R. Shang, Y. Fu, J.-B. Li, S.-L. Zhang, Q.-X. Guo and L. Liu, *J. Am. Chem. Soc.*, 2009, **131**, 5738; (b) R. Shang, D.-S. Ji, L. Chu, Y. Fu and L. Liu, *Angew. Chem., Int. Ed.*, 2011, **50**, 4470.

21 The p*H* value of the saturated CO_2 aequous solution at ambient temperature under 1 atm is about 5.6.

22 For mechanistic discussions on copper-catalyzed coupling reactions, see: (a) E. Sperotto, G. P. M. van Klink, G. van Koten and J. G. de Vries, *Dalton Trans.*, 2010, **39**, 10338; (b) G. Lefevre, G. Franc, A. Tlili, C. Adamo, M. Taillefer, I. Ciofini and A. Jutand, *Organometallics*, 2012, **31**, 7694; (c) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400; (d) F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6954.

23 (a) E. R. Strieter, D. G. Blackmond and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4120; (b) E. R. Strieter, B. Bhayana and S. L. Buchwald, *J. Am. Chem. Soc.*, 2009, **131**, 78; (c) J. W. Tye, Z. Weng, A. M. Johns, C. D. Incarvito and J. F. Hartwig, *J. Am. Chem. Soc.*, 2008, **130**, 9971; (d) R. Giri and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 15860; (e) S.-L. Zhang, L. Liu, Y. Fu and Q.-X. Guo, *Organometallics*, 2007, **26**, 4546.