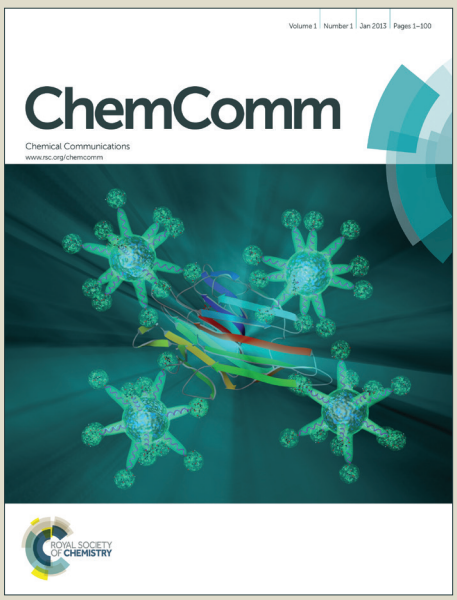
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Copper-mediated C-H(sp^2)/C-H(sp^3) coupling of benzoic acid derivatives with ethyl cyanoacetate: an expedient route to isoquinolinone scaffold †

Wei Zhu, Dengyou Zhang, Nan Yang, Hong Liu*

Received (in XXX, XXX) Xth XXXXXXXXX 200X, Accepted Xth XXXXXXXXX 200X

DOI: 10.1039/b000000x

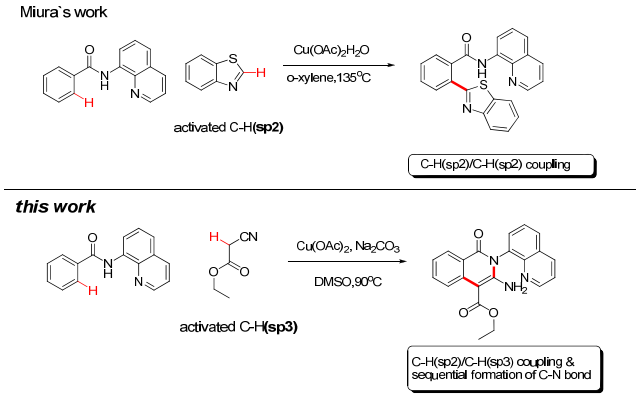
A facile, copper-mediated, direct C-H(sp^2)/C-H(sp^3) bond coupling of benzoic acid derivatives with ethyl cyanoacetate by the deployment of an 8-aminoquinoline moiety as a bidentate directing group is disclosed. Such a unique transformation provides a new strategy for the construction of isoquinolinone scaffold as one of privileged cores.

In the past decade, the metal-mediated functionalization of carbon-hydrogen bonds has emerged as a powerful and promising method for the formation of carbon-carbon and carbon-heteroatom bonds in a single synthetic operation.[1] In general, a wide range of noble metals including Pd,[2] Au,[3] Rh,[4] and Ru,[5] are highly active catalysts for C-H functionalization. From the point of practicality and applicability in academic and industrial communities, however, huge challenges still remain in the development of economical and efficient transformation systems for the inert C-H bond.

Among the various deployed metals, copper has attracted increasing attention because it is low-cost, environmentally-benign and abundant.[6] More recently, combinations of copper salts with bidentate directing groups, involving N, N`-dual coordinated sites, have emerged as an innovative strategy for the construction of carbon-heteroatom or carbon-carbon bonds through C-H cleavage.[7] Daugulis and Stahl successfully demonstrated that arene C-H bonds could be transformed into C-X bonds (X = S, O, N, F) with 8-aminoquilonines as directing groups.[8] By the employment of the similar approach, Miura disclosed an efficient copper-mediated C-H/C-H coupling of benzoic acid derivatives with 1,3-azoles bearing active sp^2 C-H groups (Scheme 1) .[9]

Despite these significant progress, to our knowledge, copper-mediated C-H(sp^2) / C-H(sp^3) coupling remains a great challenge for synthetic chemists. Previous studies have demonstrated the copper-mediated coupling of prefunctionalized aromatic derivatives with substrates bearing active methylenes[10] such as malonate,[11] 3-oxobutanoate[11a, 12] and 2-cyanoacetate[13] to the formation of C-C bonds. In light of these works, we desired to test such transformations via C-H cleavage, which might be facilitated by the employment of copper salts with bidentate directing groups. Herein, we revealed the copper-mediated, direct C-C bond construction of *ortho* C-H bond in an aromatic amide with ethyl cyanoacetate, along with simultaneous C-N bond formation. Such a unique transformation allows for the smooth construction of isoquinolinone scaffold, which stands for one of privileged moieties,which were ubiquitous in natural products and pharmaceuticals.[14]

We initiated our investigations by screening the reported bidentate directing groups (**A**, **B**, **C**, **D**) as they play a significant role in metal coordination (Table 1, entries 1-4). After extensive attempts, it was interesting to find that the 8-aminoquinoline-containing secondary amide (**A**) combined with copper salts enabled the direct C-H(sp^2)/C-H(sp^3) coupling with ethyl cyanoacetate, along with the sequential formation of the C-N bond, resulting in the construction of the isoquinolinone scaffold (entry 1). However, no reaction occurred when 8-aminoquinoline (**A**) was replaced with naphthalene (entry 5), indicating that coordination in an N, N` fashion is a key step in the reaction. Other substrates with active methylenes, such as malonate, 2-phenylacetonitrile, were also explored without the corresponding products observed. Further optimization of reaction conditions with respect to copper (II) salts, bases and solvents was summarized in Table 1. Using K_2CO_3 as the base and DMSO as the solvent at 110 °C, we found that the counter ions of copper(II) salts (entry 1 and entries 6-8) had a remarkable impact on the reaction yield; and the $Cu(OAc)_2$ gave the best yield. Subsequently, the evaluation of bases revealed that Na_2CO_3 was superior to the other alkali carbonates (entry1 and entries 9-11). The yield was further improved by lowering the temperature from



Scheme 1. Copper-mediated C-H/C-H coupling with with 8-amino-quilonines as directing groups

CAS Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, P. R. China. E-mail: hliu@mail.shcnc.ac.cn.

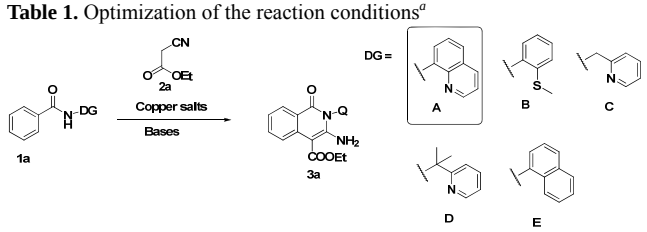
† Electronic supplementary information (ESI) available: Experimental procedures, compound characterizations, and 1H and 13C NMR spectra. See DOI: 10.1039/ b000000x

110°C to 90°C and reducing the reaction time to 4 h (entry 11). The effects of various solvents on the reaction were investigated. The use of aprotic solvent *i*PrOH (entry 13) and nonpolar solvent DCE (entry 14) was ineffective, while DMF (entry 15) was apparently inferior to DMSO. The yield was slightly decreased with the presence of TEMPO (entry 16).

With the optimized conditions identified, we next explored a series of 8-aminoquinoline benzamides to examine the scope and limitations of this process. As shown in Table 2, the desired products **3b-3r** were obtained in moderate to good yields (49%-86%) by the treatment of various benzamides (**1b-1r**) with ethyl cyanoacetate **2a**. The introduction of electron-donating groups (-Me, -OMe) at the *para*-position of the benzamides resulted in a slight reduction in yields of target compounds (**3b, 3c**), while substrates bearing electron-withdrawing substituents (-CF_3, -COOMe) afforded higher yields (**3d, 3e**). Notably, the halides such as fluorine (**3f**), chloride (**3g, 3l**) and bromide (**3h**) were tolerated under the standard reaction conditions, guaranteeing further transformation. The cleavage of C-H bonds in *meta*-substituted benzamides occurred predominantly at sterically less congested sites, irrespective of the electronic nature of the substituents (**3i-3l**). *Ortho*-substituted benzamides were also compatible, and gave good yields (**3m, 3n**). Naphthalene derivatives worked well, and the C-H functionalization of 2-naphthamide occurred predominantly at the less sterically-hindered β-site (**3o, 3p**). Benzamides bearing substituted quinoline rings also afforded good yields.

Next ,we investigated a variety of cyano-substrates as coupling partners (Table 3). Variation of the ester group had little effect on this transformation; isoquinolinone products were obtained in good yield (**3s-3u**), while the benzyl derivative gave moderate yield (**3v**). Apart from cyano substituted esters, we also tested cyano substituted amide, phosphonate and methylsulfonyl. Gratifyingly, the corresponding isoquinolinone products were obtained in good yields (**3w-3y**).

Table 1. Optimization of the reaction conditions[a]



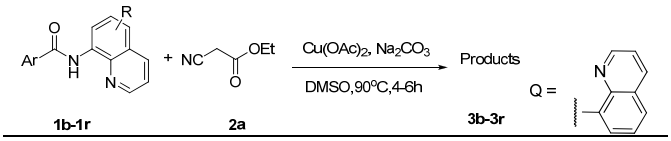
Entry	DG	Copper salts	Bases	Solvents	Yield (%)[b]
1	A	$Cu(OAc)_2$	K_2CO_3	DMSO	80
2	B	$Cu(OAc)_2$	K_2CO_3	DMSO	N.R.
3	C	$Cu(OAc)_2$	K_2CO_3	DMSO	N.R.
4	D	$Cu(OAc)_2$	K_2CO_3	DMSO	N.R.
5	E	$Cu(OAc)_2$	K_2CO_3	DMSO	N.R.
6	A	$Cu(OAc)_2H_2O$	K_2CO_3	DMSO	77
7	A	$Cu(OTf)_2$	K_2CO_3	DMSO	14
8	A	CuF_2	K_2CO_3	DMSO	35
9	A	$Cu(OAc)_2$	Li_2CO_3	DMSO	74
10	A	$Cu(OAc)_2$	Na_2CO_3	DMSO	82
11	A	$Cu(OAc)_2$	Cs_2CO_3	DMSO	71
12[c]	**A**	**$Cu(OAc)_2$**	**Na_2CO_3**	**DMSO**	**88**
13[c]	A	$Cu(OAc)_2$	Na_2CO_3	iPrOH	64
14[c]	A	$Cu(OAc)_2$	Na_2CO_3	DCE	25
15[c]	A	$Cu(OAc)_2$	Na_2CO_3	DMF	43
16[c, d]	A	$Cu(OAc)_2$	Na_2CO_3	DMSO	74

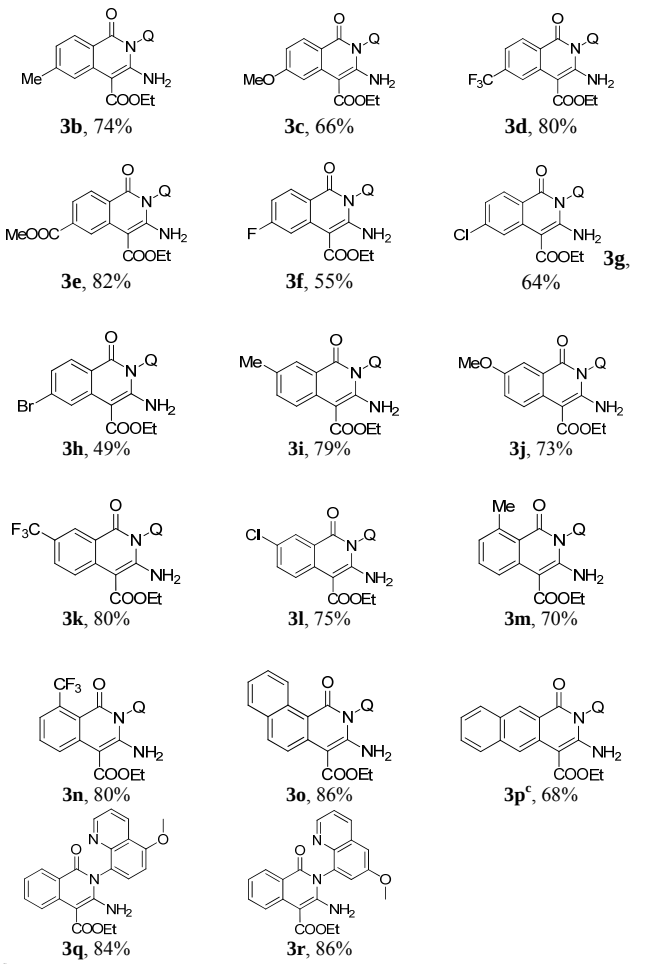
[a] Reaction conditions: **1** (0.4 mmol), Ethyl cyanoacetate (1.2 mmol), copper salts (1.2 mmol), 110 °C ,12 h, Ar. [b] Isolated yield. [c] 4 h, 90 °C, [d] 0.4 mmol TEMPO (1eq) was added

To get some insights into the mechanism of this cascade reaction, a series of controlled experiments were conducted. A stoichiometric amount of TEMPO, frequently used as radical scavenger in transition-metal-mediated reactions, had a slight effect on this transformation, indicating a free-radical pathway might be excluded (Table1, entry 16). 2-(cyanomethyl)-benzamide **4** could be smoothly transformed to the target molecule **3a** with high yield, while ortho-blocked benzamide 1m falied to generate neither the imino product **6** nor the enamine **7** under standard condition with 96% recovery of **1m**, which demonstrated that this tandem reaction first underwent the direct oxidative C(sp^2)−H/C(sp^3)−H cross-coupling followed by the intramolecular annulation to form the isoquinolinone scaffold (Scheme S1 in the ESI) .

Based on the above observations and considerations, a plausible reaction mechanism is proposed in Scheme 2. Firstly, cupation of the active menthene of ethyl cyanoacetate under base condition provided intermediate **M1**, which undergoes ligand exchange with **1a** to afford N,N-chelated copper(II) complex **M2**, followed

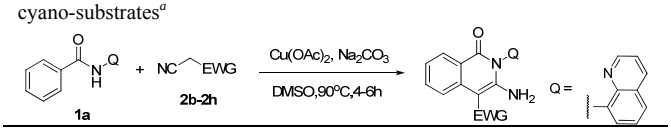
Table 2. Copper-mediated reaction of ethyl cyanoacetate with carboxylic acid derivatives[a, b]

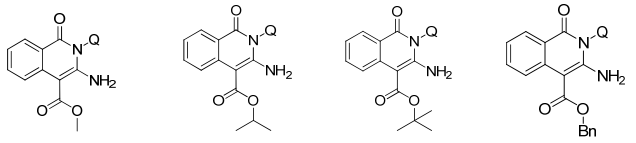




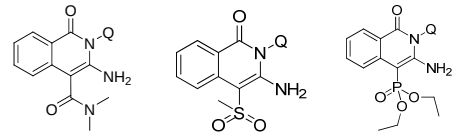
[a] Reaction conditions: **1** (0.4 mmol), Ethyl cyanoacetate (1.2 mmol), copper salts (1.2 mmol), 90 °C ,4-6 h, Ar. [b] Isolated yield. [c]α-isomer yield :11%

Table 3. Copper-mediated reaction of N-(quinolin-8-yl)benzamide with cyano-substrates[a]





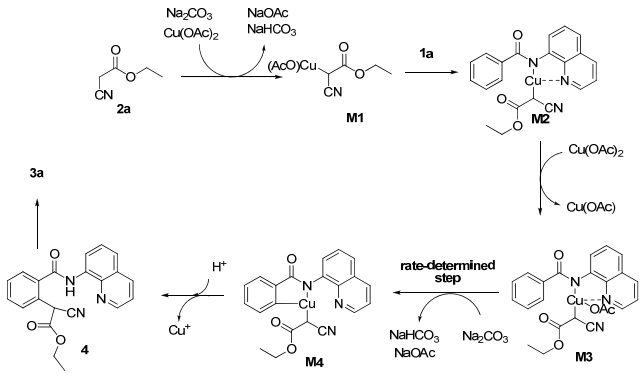
3s, 85% **3t,** 95% **3u,** 85% **3v,** 75%



3w, 77% **3x,** 84% **3y,** 89%

[a] Reaction conditions: **1** (0.4 mmol), cyano-substrates (1.2 mmol), copper salts (1.2 mmol), 90 °C ,4-6 h, Ar.

by the $Cu(OAc)_2$-promoted oxidation of **M2** to form copper(III) complex **M3**.[9] Intramolecular C−H cupration of the phenyl ring genrates the key intermediate **M4**,[15] which is speculated to be the rate-determined step with kinetic isotope effect (KIE) value of 3.65 (Scheme S2 in the ESI). The subsequent reductive elimination of **M4** and intramolecular annulation of **4** provides **3a**.[8e] This tentative passway also explains the necessity of excess $Cu(OAc)_2$ and Na_2CO_3 to realize a good conversion.



Scheme 2. Plausible reaction mechanism

In conclusion, we have developed a copper-mediated C-H / C-H coupling of benzoic acid derivatives and ethyl cyanoacetate, along with simultaneous C-N bond formation, under the aid of 8-aminoquinoline-based double N, N`-coordination strategy. The transformation exhibits wide generality, functional tolerance and high steric selectivity. It also provide a straightforward means for the construction of isoquinolinone scaffold, which is a privilege moiety and ubiquitous in natural products and pharmaceuticals. Further elucidation of the detailed mechanism and application of this transformation are under investigation in our laboratory.

We gratefully acknowledge financial support from the National Natural Science Foundation of China (Grants 21021063, 91229204, and 81025017), National S&T Major Projects (2012ZX09103101-072, 2013ZX09507-001, and 2014ZX0950 7002-001), Sponsored by Program of Shanghai Subject Chief Scientist (Grant 12XD1407100).

Notes and references

1 (a) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (b) C. J. Li, *Acc. Chem. Res,* 2009, **42**, 335; (c) I. V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173; (d) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev.*, 2011, **40**, 5068; (e) G. Y. Song, F. Wang and X. W. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651; (f) J. F. Hartwig, *Acc. Chem. Res,* 2012, **45**, 864; (g) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord and F. Glorius, *Angew. Chem. Int. Ed.,* 2012, **51**, 10236; (h) W. R. Gutekunst and P. S. Baran, *Chem. Soc. Rev.*, 2011, **40**, 1976.

2 (a) X. Chen, K. M. Engle, D. H. Wang and J. Q. Yu, *Angew. Chem. Int. Ed.*, 2009, **48**, 5094; (b) T. W. Lyons and M. S. Sanford, *Chem. Rev.,* 2010, **110**, 1147.

3 T. C. Boorman and I. Larrosa, *Chem. Soc. Rev.*, 2011, **40**, 1910.

4 (a) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (b) J. C. Lewis, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.,* 2008, **41**, 1013.

5 (a) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.,* 2012, **112**, 5879; (b) L. Ackermann and R. Vicente, *Top. Curr. Chem.,* 2010, **292**, 211.

6 (a) C. Zhang, C. H. Tang and N. Jiao, *Chem. Soc. Rev.,* 2012, **41**, 3464; (b) A. E. Wendlandt, A. M. Suess and S. S. Stahl, *Angew. Chem. Int. Ed.,* 2011, **50**, 11062.

7 (a) G. Rouquet and N. Chatani, *Angew. Chem. Int. Ed.,* 2013, **52**, 11726; (b) M. Corbet and F. De Campo, *Angew. Chem. Int. Ed.,* 2013, **52**, 9896.

8 (a) J. Roane and O. Daugulis, *Org. Lett.*, 2013, **15**, 5842; (b) T. Truong, K. Klimovica and O. Daugulis, *J. Am. Chem. Soc.*, 2013, **135**, 9342; (c) L. D. Tran, J. Roane and O. Daugulis, *Angew. Chem. Int. Ed.,* 2013, **52**, 6043; (d) L. D. Tran, I. Popov and O. Daugulis, *J. Am. Chem. Soc.*, 2012, **134**, 18237; (e) A. M. Suess, M. Z. Ertem, C. J. Cramer and S. S. Stahl, *J. Am. Chem. Soc.*, 2013, **135**, 9797.

9 M. Nishino, K. Hirano, T. Satoh and M. Miura, *Angew. Chem. Int. Ed.,* 2013, 52, 4457.

10 (a) F. Monnier and M. Taillefer, *Angew. Chem. Int. Ed.,* 2009, **48**, 6954; (b) D. Ma and Q. Cai, *Acc. Chem. Res.*, 2008, **41**, 1450.

11 (a) X. A. Xie, G. R. Cai and D. W. Ma, *Org. Lett.*, 2005, **7**, 4693; (b) S. F. Yip, H. Y. Cheung, Z. Y. Zhou and F. Y. Kwong, *Org. Lett.*, 2007, **9**, 3469.

12 X. A. Xie, Y. Chen and D. W. Ma, *J. Am. Chem. Soc.*, 2006, **128**, 16050.

13 (a) J. Y. Lu, X. Y. Gong, H. J. Yang and H. Fu, *Chem. Commun.*, 2010, **46**, 4172; (b) T. Liu, C. Y. Zhu, H. J. Yang and H. Fu, *Adv. Synth. Catal.*, 2012, **354**, 1579.

14 (a) B. D. Krane and M. Shamma, *J. Nat. Prod.,* 1982, **45**, 377; (b) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893; (c) W. Zhang, J. P. Mayer, S. E. Hall and J. A. Weigel, *J. Comb. Chem.*, 2001, **3**, 255; (d) S. B. Mhaske and N. P. Argade, *Tetrahedron,* 2006, **62**, 9787.

15 X. Ribas, D. A. Jackson, B. Donnadieu, J. Mahia, T. Parella, R. Xifra, B. Hedman, K. O. Hodgson, A. Llobet and T. D. P. Stack, *Angew. Chem. Int. Ed.*, 2002, **41**, 2991.