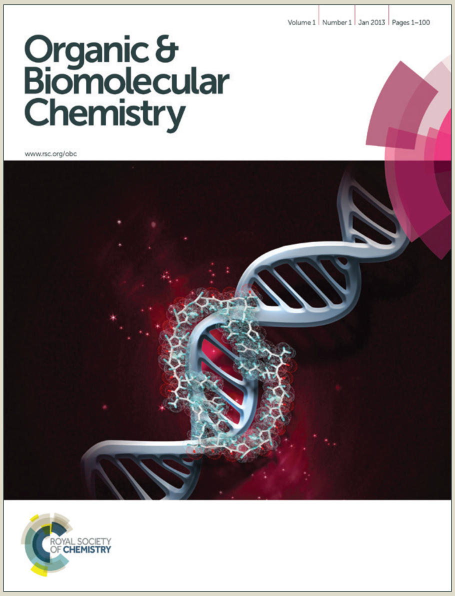
Organic & Biomolecular Chemistry

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Organic & Biomolecular Chemistry

Dynamic Article Links ►

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Copper-catalyzed bis-arylations of alkenes leading to oxindole derivatives †

Liangliang Shi, Yuyuan Wang, Haijun Yang and Hua Fu*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

A simple and practical copper-catalyzed approach to oxindole derivatives by copper-catalyzed bis-arylation of *N*-alkyl-*N*-phenylacrylamides with diaryliodonium triflates has been developed under mild conditions, and the method is of tolerance towards some functional groups in the substrates.

Oxindoles widely occur in natural products with unique biological activity, they are the privileged scaffolds for design and discovery of drugs, and many of them exhibit potent biological activities, such as anticancer, antibacterial, antifungal, antiviral and antiangiogenic properties.[1] As shown in Figure 1, the cyclopropane-containing oxindole (**A**) is a potent HIV-1 nonnucleoside reverse transcriptase inhibitor,[2] and Sunitinib (SU11248, **B**) is used as the orally active receptor tyrosine kinase (RTK) inhibitor marketed by Pfizer as Sutent.[3] The 3-amino-substituted oxindole AG-041R (**C**) is of a variety of interesting biological properties including induction of systemic cartilage hyperplasia in rats,[4] and the 3-hydroxy oxindole SM-130686 (**D**) is a growth hormone secretagogue.[5] Recently, there is great progress on transition metal-catalyzed difunctionalization of alkenes[6] such as dioxygenation,[7] aminooxygenation,[8] diamination,[9] aminohalogenation[10] and fluoroamination,[11] and various interesting and useful oxindole derivatives were constructed via the difunctionalization strategy[12] (Very recently, Fu and co-workers reported a visible-light-mediated diarylation of *N*-arylacrylamides with aryl diazonium salts under catalysis of $Ru(bpy)_3$[12o]).

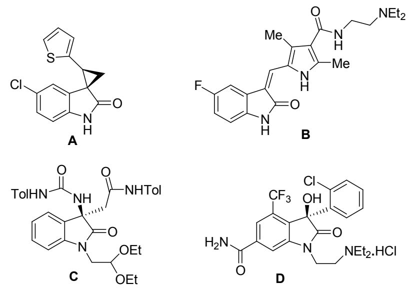
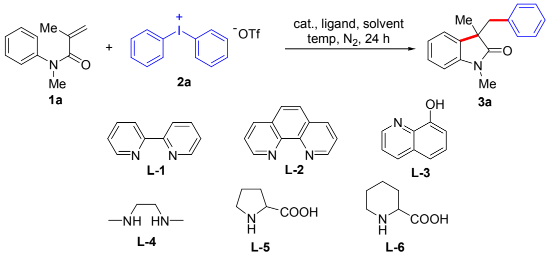


Figure 1 Representative examples for pharmacologically active compounds with the oxindole framework.

On the other hand, diaryliodonium salts have attracted much attention as powerful electrophilic arylation reagents,[13,14] and they have been used in metal-catalyzed[15] and metal-free arylation reactions.[16] Recently, copper-catalyzed organic reactions have attracted considerable attention because of low cost, low toxicity and high efficiency of copper-catalysts,[17,18] and some efficient copper-catalyzed methods for synthesis of heterocycles has been developed by us[19] and other groups.[20] Herein, we report an easy copper-catalyzed bis-arylations of alkenes leading to oxindole derivatives via reactions of *N*-alkyl-*N*-phenylacrylamides with diaryliodonium triflates.

Reaction conditions including catalysts, ligands, solvents and temperature were first investigated for synthesis of 3-benzyl-1,3-dimethylindolin-2-one (**3a**) via copper-catalyzed reaction of *N*-methyl-*N*-phenylmethacrylamide (**1a**) with diphenyliodonium triflate (**2a**). As shown in Table 1, six ligands (20 mol% amount relative to **1a**) were screened applying 10 mol% of CuI as the catalyst, and dichloroethane (DCE) as the solvent at 100 °C under nitrogen atmosphere (entries 1-6), and 2-(pyridin-2-yl)pyridine provided the highest yield (entry 1). It was worthwhile to note that the reaction gave the similar yield to entry 1 in the absence of ligand (entry 7). Other copper salts were attempted (entries 8-13), and they afforded lower yields than CuI. No target product was observed without addition of copper catalyst (entry 14). Effect of solvents were investigated, and DCE was suitable (compare entries 7, 15-19). Lower reactivity was observed when temperature was changed (compare entries 7, 20 and 21).

Table 1 Investigation of conditions for synthesis of 3-benzyl-1,3-dimethylindolin-2-one (**3a**) via copper-catalyzed reaction of *N*-methyl-*N*-phenylmethacrylamide (**1a**) with diphenyliodonium triflate (**2a**)[a]



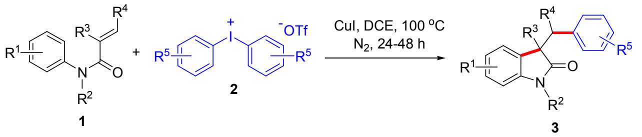
Entry	Cat.	Ligand	Solvent	Temp. (°C)	Yield (%)[b]

1	CuI	L-1	DCE	100	70
2	CuI	L-2	DCE	100	48
3	CuI	L-3	DCE	100	62
4	CuI	L-4	DCE	100	17
5	CuI	L-5	DCE	100	56
6	CuI	L-6	DCE	100	66
7	**CuI**	**-**	**DCE**	**100**	**71**
8	CuCl	-	DCE	100	57
9	CuBr	-	DCE	100	60
10	Cu_2O	-	DCE	100	68
11	CuSCN	-	DCE	100	64
12	$Cu(OAc)_2$	-	DCE	100	56
13	$Cu(OTf)_2$	-	DCE	100	46
14	-	-	DCE	100	0
15	CuI	-	toluene	100	51
16	CuI	-	dioxane	100	45
17	CuI	-	MeCN	100	Trace
18	CuI	-	THF	100	61
19	CuI	-	DMSO	100	Trace
20	CuI	-	DCE	80	49
21	CuI	-	DCE	120	66

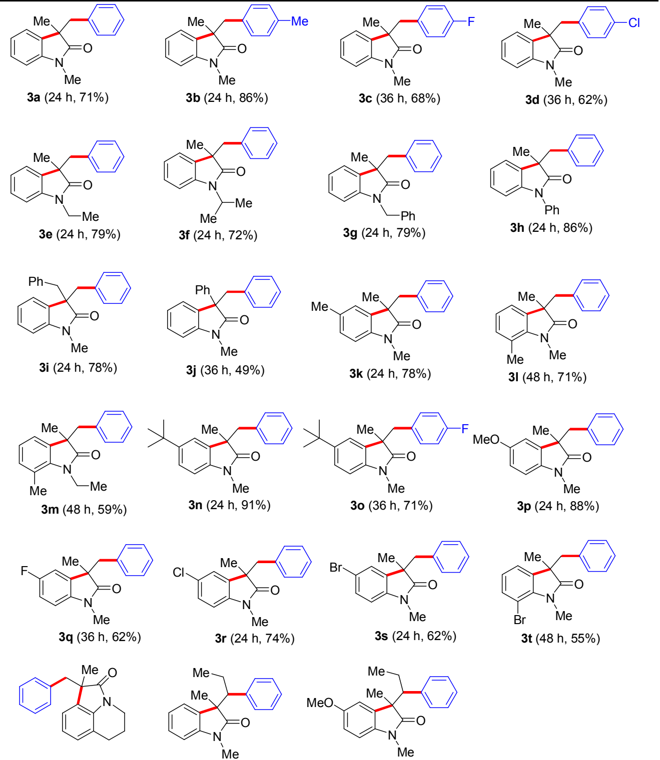
[a] Reaction conditions: *N*-methyl-*N*-phenylmethacrylamide (**1a**) (0.25 mmol), diphenyliodonium triflate (**2a**) (0.75 mmol), catalyst (0.025 mmol), ligand (0.05 mmol), solvent (2.5 mL), temperature (80-120 °C) under nitrogen atmosphere. Reaction time (24 h). [b] Isolated yield.

The substrate scope on copper-catalyzed bis-arylation of *N*-alkyl-*N*-phenylacrylamides (**1**) was investigated under our optimized conditions (using 10 mol % of CuI as the catalyst and DCE as the solvent at 100 °C under nitrogen atmosphere). As shown in Table 2, the tested substrates gave moderate to good yields. For *N*-alkyl-*N*-phenylacrylamides (**1**), reactivity of the substrates decreased when substituents R^1 were at *ortho*-site of nitrogen on phenyl (**3l**, **3m** and **3t**), so a long time was required. The substrates containing electron-donating groups (R^1) provided higher yields than those with electron-withdrawing groups. When R^2 was phenyl the substrate displayed higher reactivity (**3h**). However, the substrate with phenyl for R^3 afforded a low yield for the steric hindrance (see **3j**). The reactivity decreased when R^4 was ethyl (**3v** and **3w**), and a pair of diastereoisomers were observed by ^1H NMR for the presence of a new chiral carbon during the first arylation. For diaryliodonium triflates, the substrates containing electron-withdrawing groups exhibited lower reactive activity than those with electron-donating groups. The bis-arylation above could tolerate some functional groups including C-F bonds (**3c**, **3o** and **3q**), C-Cl bond (**3d** and **3r**), C-Br bond (**3s** and **3t**), ether (**3p** and **3w**), *N*-heterocycle (**3u**) and amide (**3a-w**) in the substrates.

Table 2 Copper-catalyzed synthesis of oxindole derivatives[a]



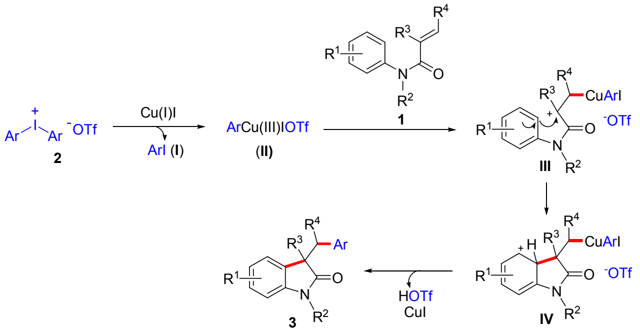
2 (Time, Yield[b])



3a (24 h, 71%)
3b (24 h, 86%)
3c (36 h, 68%)
3d (36 h, 62%)
3e (24 h, 79%)
3f (24 h, 72%)
3g (24 h, 79%)
3h (24 h, 86%)
3i (24 h, 78%)
3j (36 h, 49%)
3k (24 h, 78%)
3l (48 h, 71%)
3m (48 h, 59%)
3n (24 h, 91%)
3o (36 h, 71%)
3p (24 h, 88%)
3q (36 h, 62%)
3r (24 h, 74%)
3s (24 h, 62%)
3t (48 h, 55%)
3u (48 h, 82%)
3v (48 h, 46%)
3w (36 h, 53%)

[a] Reaction conditions: *N*-alkyl-*N*-phenylacrylamide (**1**) (0.25 mmol), diaryliodonium triflate (**2**) (0.75 mmol), CuI (0.025 mmol), DCE (2.5 mL), temperature (100 °C) under nitrogen atmosphere. Reaction time (24-48 h). [b] Isolated yield.

A possible mechanism for synthesis of oxindole derivatives is proposed as shown in Scheme 1 according to the result above and the previous references.[6d,12p] First, treatment of diaryliodonium triflate (**2**) with Cu(I) salt gives Cu(III) complex (**II**) leaving ArI (**I**), then arylation of alkenyl in **1** with **II** yields intermediate **III**, and intramolecular arylation of **III** provides **IV**. Finally, desorption of CuI and HOTf from **IV** affords the target product (**3**).



Scheme 1 Possible mechanism for copper-catalyzed synthesis of oxindole derivatives.

In summary, we have developed a simple and efficient copper-catalyzed method for synthesis of oxindole derivatives. The protocol uses inexpensive CuI as the catalyst, readily available *N*-alkyl-*N*-phenylacrylamides and diaryliodonium triflates as the starting materials, and bis-arylations of *N*-alkyl-*N*-phenylacrylamides were performed well under mild conditions. The method is of high tolerance towards various functional groups in the substrates, and the synthesized compounds will is helpful for screening of diverse biological molecules.

The authors wish to thank the National Natural Science Foundation of China (Grant Nos. 21172128, 21372139 and 21221062), and the Ministry of Science and Technology of China (Grant No. 2012CB722605) for financial support.

Notes and references

Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, P. R. China. Fax: (+86) 10-62781695; E-mail: fuhua@mail.tsinghua.edu.cn

† Electronic Supplementary Information (ESI) available: Full experimental details, characterization and NMR spectra of the target products are provided. See DOI: 10.1039/b000000x/

1 For reviews on oxindoles see: (*a*) J. E. M. N. Klein and R. J. K. Taylor, *Eur. J. Org. Chem.,* 2011, 6821; (*b*) A. Millemaggi and R. J. K. Taylor, *Eur. J. Org. Chem.,* 2010, 4527; (*c*) F. Zhou, Y.-L. Liu and J. Zhou, *Adv. Synth. Catal.*, 2010, **352**, 1381; (*d*) B. M. Trost and M. K. Brennan, *Synthesis,* 2009, 3003; (*e*) C. V. Galliford and K. A. Scheidt, *Angew. Chem. Int. Ed.,* 2007, **46**, 8748; (*f*) C. Marti and E. M. Carreira, *Eur. J. Org. Chem.,* 2003, 2209.

2 (*a*) T. Jiang, K. L. Kuhen, K. Wolff, H. Yin, K. Bieza, J. Caldwell, B. Bursulaya, T. Y.-H. Wu and Y. He, *Bioorg. Med. Chem. Lett.,* 2006, **16**, 2105; (*b*) T. Jiang, K. L. Kuhen, K. Wolff, H. Yin, K. Bieza, J. Caldwell, B. Bursulaya, T. Tuntland, K. Zhang, D. Karanewsky and Y. He, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2109.

3 C. Le Tourneau, E. Raymond and S. Faivre, *Ther. Clin. Risk Manag.*, 2007, **3**, 341.

4 H. Kitamura, A. Kato and T. Esaki, *Eur. J. Pharmacol., 2001*, **418**, 225.

5 T. Tokunaga, W. E. Hume, T. Umezome, K. Okazaki, Y. Ueki, K. Kumagai, S. Hourai, J. Nagamine, H. Seki, M. Taiji, H. Noguchi and R. Nagata, *J. Med. Chem.,* 2001, **44**, 4641.

6 (*a*) K. Muñiz, *Angew. Chem. Int. Ed*., 2009, **48**, 9412; (*b*) S. R. Chemler, *Org. Biomol. Chem*., 2009, **7**, 3009; (*c*) R. I. McDonald, G. Liu and S. S. Stahl, *Chem. Rev*., 2011, **111**, 2981; (*d*) C. Feng and T.-P. Loh, *Chem. Sci*., 2012, **3**, 3458.

7 (*a*) Y. Li, D. Song and V. M. Dong, *J. Am. Chem. Soc*., 2008, **130**, 2962; (*b*) A. Wang, H. Jiang and H. Chen, *J. Am. Chem. Soc*., 2009, **131**, 3846.

8 (*a*) E. J. Alexanian, C. Lee and E. J. Sorensen, *J. Am. Chem. Soc*., 2005, **127**, 7690; (*b*) G. Liu and S. S. Stahl, *J. Am. Chem. Soc*., 2006, **128**, 7179; (*c*) L. V. Desai and M. S. Sanford, *Angew. Chem. Int. Ed*., 2007, **46**, 5737; (*d*) R. Zhu and S. L. Buchwald, *Angew. Chem. Int. Ed*., 2012, **51**, 1926.

9 (*a*) J. Streuff, C. H. Hövelmann, M. Nieger and K. Muñiz, *J. Am. Chem. Soc*., 2005, **127**, 14586; (*b*) K. Muñiz, *J. Am. Chem. Soc*., 2007, **129**, 14542; (*c*) P. A. Sibbald, C. F. Rosewall, R. D. Swartz and F. E. Michael, *J. Am. Chem. Soc*., 2009, **131**, 15945; (*d*) B. Zhao, X. Peng, S. Cui and Y. Shi, *J. Am. Chem. Soc*., 2010, **132**, 11009.

10 (*a*) A. Lei, X. Lu and G. Liu, *Tetrahedron Lett*., 2004, **45**, 1785; (*b*) F. E. Michael, P. A. Sibbald and B. M. Cochran, *Org. Lett.,* 2008, **10**, 793.

11 T. Wu, G. Yin and G. Liu, *J. Am. Chem. Soc*., 2009, **131**, 16354.

12 For selected papers, see: (*a*) A. Pinto, Y. Jia, L. Neuville and J. Zhu, *Chem. Eur. J.,* 2007, **13**, 961; (*b*) X. Han and X. Lu, *Org. Lett*., 2009, **11**, 2381; (*c*) G. An, W. Zhou, G. Zhang, H. Sun, J. Han and Y. Pan, *Org. Lett*., 2010, **12**, 4482; (*d*) T. Wu, X. Mu and G. Liu, *Angew. Chem. Int. Ed.,* 2011, **50**, 12578; (*e*) G. Broggini, V. Barbera, E. M. Beccalli, E. Borsini, S. Galli,G. Lanza and G. Zecchi, *Adv. Synth. Catal.,* 2012, **354**, 159; (*f*) K. Matcha, R. Narayan and A. P. Antonchick, *Angew. Chem. Int. Ed.,* 2013, **52**, 7985; (*g*) W.-T. Wei, M.-B. Zhou, J.-H. Fan, W. Liu, R.-J. Song, Y. Liu, M. Hu, P. Xie and J.-H. Li, *Angew. Chem. Int. Ed.,* 2013, **52**, 3638; (*h*) D. C. Fabry, M. Stodulski, S. Hoerner and T. Gulder, *Chem. Eur. J.,* 2012, **18**, 10834; (*i*) S.-L. Zhou, L.-N. Guo, H. Wang and X.-H. Duan, *Chem. Eur. J.*, 2013, **19**, 12970; (*j*) J. Xie, P. Xu, H. Li, Q. Xue, H. Jin, Y. Cheng and C. Zhu, *Chem. Commun.,* 2013, **49**, 5672; (*k*) Y.-M. Li, X.-H. Wei, X.-A. Li and S.-D. Yang, *Chem. Commun*., 2013, **49**, 11701; (*l*) M.-B. Zhou, R.-J. Song, X.-H. Ouyang, Y. Liu, W.-T. Wei, G.-B. Deng and J.-H. Li, *Chem. Sci.,* 2013, **4**, 2690; (*m*) W. Kong, M. Casimiro, E. Merino and C, Nevado, *J. Am. Chem. Soc.,* 2013, **135**, 14480; (*n*) P. Xu, J. Xie, Q. Xue, C. Pan, Y. Cheng and C. Zhu, *Chem. Eur. J.,* 2013, **19**, 14039; (*o*) W. Fu, F. Xu, Y. Fu, M. Zhu, J. Yu, C. Xu and D. Zou, *J. Org. Chem*., 2013, **78**, 12202; (*p*) A similar paper was published after our submission to another journal (*Chem. Commun.*), see: B. Zhou, W. Hou, Y. Yang, H. Feng and Y. Li, *Org. Lett.,* 2014, **16**, 1322.

13 For reviews on diaryliodonium salts, see: (*a*) P. J. Stang and V. V. Zhdankin, *Chem. Rev.,* 1996, **96**, 1123; (*b*) V. V. Zhdankin and P. J. Stang, *Chem. Rev.,* 2002, **102**, 2523; (*c*) V. V. Zhdankin and P. J. Stang, *Chem. Rev*., 2008, **108**, 5299; (*d*) E. A. Merritt and B. Olofsson, *Angew. Chem, Int. Ed.,* 2009, **48**, 9052.

14 For selected papers, see: (*a*) P. J. Stang, V. V. Zhdankin and R. Tykwinski and N. S. Zefirov, *Tetrahedron Lett.,* 1991, **32**, 7497; (*b*) M. D. Hossain, Y. Ikegami and T. Kitamura, *J. Org. Chem.,* 2006, **71**, 9903; (*c*) M. Bielawski, D. Aili and B. Olofsson, *J. Org. Chem.,* 2008, **73**, 4602.

15 For selected papers, see: (*a*) D. Kalyani, N. R. Deprez, L. V. Desai and M. S. Sanford, *J. Am. Chem. Soc.,* 2005, **127**, 7330; (*b*) R. J. Phipps and M. J. Gaunt, *Science,* 2009, **323**, 1593; (*c*) R. B. Bedford, R. L. Webster and C. J. Mitchell, *Org. Biomol. Chem.,* 2009, **7**, 4853; (*d*) A. E. Allen and D. W. C. MacMillan, *J. Am. Chem. Soc.,* **2011**, *133*, 4260; (*e*) A. Bigot, A. E. Williamson and M. J. Gaunt, *J. Am. Chem. Soc.,* 2011, **133**, 13778; (*f*) C.-L. Ciana, R. J. Phipps, J. R. Brandt, F.-M. Meyer and M. J. Gaunt, *Angew. Chem. Int. Ed.,* 2011, **50**, 458.

16 For selected papers, see: (*a*) Y. Kita, K. Morimoto, M. Ito, C. Ogawa, A. Goto and T. Dohi, *J. Am. Chem. Soc.,* 2009, **131**, 1668; (*b*) T. Dohi, M. Ito, N. Yamaoka, K. Morimoto, H. Fujioka and Y. Kita, *Angew. Chem. Int. Ed.,* 2010, **49**, 3334; (*c*) N. Jalalian, T. B. Petersen and B. Olofsson, *Chem. Eur. J.,* 2012, **18**, 14140.

17 For recent reviews on copper-catalyzed cross couplings, see: (*a*) S. V. Ley and A. W. Thomas, *Angew. Chem. Int. Ed*., 2003, **42**, 5400; (*b*) K. Kunz, U. Scholz and D. Ganzer, *Synlett,* 2003, 2428; (*c*) I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev*., 2004, **248**, 2337; (*d*) D. Ma and Q. Cai, *Acc. Chem. Res.,* 2008, *41*, 1450; (*e*) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.,* 2008**, 108**, 3054; (*f*) F. Monnier and M. Taillefer, *Angew. Chem. Int. Ed*., 2009, **48**, 6954; (*g*) D. S. Surry and S. L. Buchwald, *Chem. Sci.,* 2010, **1**, 13; (*h*) H. Rao and H. Fu, *Synlett,* 2011, 745 and references cited therein.

18 For selected papers, see: (*a*) D. Ma, Y. Zhang, J. Yao, S. Wu and F. Tao, *J. Am. Chem. Soc*., 1998, **120**, 12459; (*b*) A. Klapars, J. C. Antilla, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.,* 2001, **123**, 7727; (*c*) A. Klapars, X. H. Huang and S. L. Buchwald, *J. Am. Chem. Soc*., 2002, **124**, 7421; (*d*) A. S. Gajare, K. Toyota, M. Yoshifuji and F. Yoshifuji, *Chem. Commun.,* 2004, 1994; (*e*) L. Zhu, L. Cheng, Y. Zhang, R. Xie and J. You, *J. Org. Chem*., 2007, **72**, 2737; (*f*) H. Rao, Y. Jin, H. Fu, Y. Jiang and Y. Zhao, *Chem. Eur. J.,* 2006, **12**, 3636; (*g*) X. Guo, H. Rao, Y. Jin, H. Fu, Y. Jiang and Y. Zhao, *Adv. Synth. Catal.,* 2006, **348**, 2197; (*h*) D. Jiang, H. Fu, Y. Jiang and Y. Zhao, *J. Org. Chem.,* 2007, **72**, 672; (*i*) L. Jing, J. Wei, L. Zhou, Z. Huang, Z. Li and X. Zhou, *Chem. Commun.,* 2010, **46**, 4767.

19 (*a*) F, Wang, H. Fu, Y. Jiang and Y. Zhao, *Green Chem.,* 2008, **10**, 452; (*b*) X. Gong, H. Yang, H. Liu, Y. Jiang, Y. Zhao and H. Fu, *Org. Lett.,* 2010, **12**, 3128. (*c*) J. Lu, X. Gong, H. Yang and H. Fu, *Chem. Commun.,* 2010, **46**, 4172; (*d*) C. Wang, S. Li, H. Liu, Y. Jiang and H.

Fu, *J. Org. Chem*., 2010, **75**, 7936; (*e*) W. Xu, Y. Jin, H. Liu, Y. Jiang and H. Fu, *Org. Lett*., 2011, **13**, 1274; (*f*) J. Lu, Y. Jin, H. Liu, Y. Jiang and H. Fu, *Org. Lett*., 2011, **13**, 3694; (*g*) W. Xu and H. Fu, *J. Org. Chem*., 2011, **76**, 3846; (*h*) X. Wang, Y. Jin, Y. Zhao, L. Zhu, H. Fu, *Org. Lett*., 2012, **14**, 452; (*i*) H. Xu and H. Fu, *Chem. Eur. J*., 2012, **18**, 1180.

20 For selected papers, see: (*a*) S. Ueda and H. Nagasawa, *Angew. Chem. Int. Ed*., 2008, **47**, 6411; (*b*) G. Brasche and S. L. Buchwald, *Angew. Chem. Int. Ed.,* 2008, **47**, 1932; (*c*) S. Ueda and H. Nagasawa, *J. Am. Chem. Soc.,* 2009, **131**, 15080; (*d*) P. Saha, T. Ramana, N. Purkait, M. A. Ali, R. Paul and T. Punniyamurthy, *J. Org. Chem*., 2009, *74*, 8719; (*e*) Y.-F. Wang, H. Chen, X. Zhu and S. Chiba, *J. Am. Chem. Soc*., 2012, **134**, 11980; (*f*) C. Wan, J. Zhang, S. Wang, J. Fan and Z. Wang, *Org. Lett.,* 2010, **12**, 2338; For a review: see: (*g*) T. Liu and H. Fu, *Synthesis,* 2012, **44**, 2805.