ChemComm



COMMUNICATION

View Article Online



Cite this: Chem. Commun., 2020, 56 9485

Received 30th June 2020, Accepted 9th July 2020

DOI: 10.1039/d0cc04495d

rsc.li/chemcomm

Copper-catalysed ortho-selective C-H bond functionalization of phenols and naphthols with α -aryl- α -diazoesters†

Ben Ma, Dab Zhiqiong Tang, Junliang Zhang * and Lu Liu * * ab

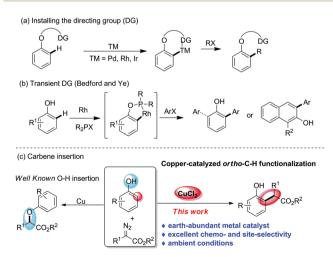
Herein, we reported the first copper-catalyzed highly efficient C(sp²)-H functionalization of unprotected naphthols and phenols with α -aryl- α -diazoesters. In this transformation, CuCl₂ efficiently promoted the highly chemo- and site-selective C-H bond functionalization under mild conditions, furnishing diverse phenol derivatives in moderate to excellent yields from readily available starting materials.

Phenol and naphthol motifs are prevalent in natural products, dyes, medicines, bioactive compounds, functional materials, and privileged chiral ligands, and they also represent the most readily available chemical feedstocks and versatile building blocks for diverse transformations in chemical science. Thus, the development of straightforward strategies to synthesize phenol derivatives via the direct site-selective C-H bond functionalization of free phenols is highly attractive to the synthetic community. However, chemo- and site-selective C-H functionalization of unprotected phenols poses considerable challenges, because there are four possible reaction sites, including the chemoselectivity of oxygen or carbon and the site-selectivity of the *ortho*-, *meta*- or *para*-position.²

In the past decade, with the advance of transition-metalcatalysed directed C-H bond functionalization,³ many strategies have been developed to achieve ortho-selective functionalization of phenols. In this regard, a directing-group-assisted approach, which requires directing groups to be installed on the oxygen atom to ensure ortho selectivity, as well as to protect the hydroxyl group, has emerged as one of the most efficient

Recently, the catalytic carbene transfer reaction, typically using diazo compounds,⁶ has emerged as one of the most powerful strategies for aromatic C(sp2)-H bond functionalization.7 Nonetheless, most of the commonly used catalysts are based on noble metals, including rhodium, gold, palladium and iridium, which are becoming more and more expensive and scarce because they are derived from dwindling resources.8 The development of effective and abundant catalysts to replace the rare and toxic transition metals is a long-term need. Copper, which is an earth abundant, readily available, inexpensive, environmentally benign, and less toxic metal, represents an ideal catalyst in organic synthesis.9 Although Cu-catalysed carbene transfer reactions have

[†] Electronic supplementary information (ESI) available. CCDC 1834202. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/



Scheme 1 Ortho-selective C-H functionalization of phenols.

and popular solutions to address the ortho-selectivity problem (Scheme 1a).4 However, this extra operation of installing and removing such directing groups limits the utilization of this approach in organic synthesis. Recently, Bedford and Ye et al. realized an alternative way for direct ortho-selective C-H bond arylation of phenols and naphthols by using P-containing ligands R₂PX as transient directing groups (Scheme 1b). Unfortunately, this strategy is still limited to a few examples.

^a School of Chemistry and Molecular Engineering, East China Normal University, 500 Dongchuan Road, Shanghai, 200241, P. R. China. E-mail: lliu@chem.ecnu.edu.cn

^b Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, East China Normal University, Shanghai 200062, P. R. China

^c Department of Chemistry, Fudan University, 2005 Songhu Road, Shanghai 200438, P. R. China. E-mail: junliangzhang@fudan.edu.cn

Communication ChemComm

been in use for over half a century, compared with the wellestablished O-H bond insertion of phenols with coppercarbene, 10 the analogous C(sp2)-H bond functionalization is still unknown. 11 Very recently, Nemoto and we have reported the ortho-C-H functionalization of naphthols and phenols with diazoesters. 12 However, these methods require the use of expensive catalysts, gold complexes or B(C₆F₅)₃. In addition, gold catalysts 12b,c were suitable for naphthols, but were not compatible with phenols, and $B(C_6F_5)_3^{12a}$ showed the opposite trend. A general approach to achieve ortho-alkylation of both phenols and naphthols has not been developed so far. Herein, we reported the unprecedented CuCl₂-catalysed highly chemoand ortho-selective C-H bond functionalization of phenols and naphthols with diazoesters (Scheme 1c).

Initially, we performed the reaction of 1-naphthol 1a with α-phenyl-α-diazoacetate 2a in the presence of 5 mol% Cu(ClO₄)₂. 6H₂O in DCM at room temperature. To our delight, the desired ortho-C-H functionalization products, including 3aa and the corresponding lactone 11 from 3aa, were obtained in 60% yield with 30:1 C-H/O-H selectivity and regio-specific ortho-selectivity (Table 1, entry 1). Encouraged by this result, various copper salts were then screened, and finally CuCl₂ was observed to be the best catalyst, affording the ortho-selective C-H bond alkylation product in 85% yield with excellent chemo- and site-selectivity after 6 h at room temperature (Table 1, entries 2-7). Solvent screening showed that DCE, toluene and THF could not improve the yield (Table 1, entries 10-12).

Next, the scope of the copper-catalysed ortho-selective C-H functionalization of 1-naphthol with various α -aryl- α -diazoacetates was explored using CuCl₂ (5 mol%) in DCM at room temperature. As shown in Scheme 2, this reaction proved to be applicable to a wide range of α -aryl- α -diazoacetates and the desired 2-alkylated

Table 1 Optimization of reaction conditions^a

Entry	Cat. (5 mol%)	Yield ^a (%)	
		3/4/5/6	
1	Cu(ClO ₄) ₂ ⋅6H ₂ O	$60 (12)^b/0/2/38$	
2	Cu(CH ₃ CN) ₄ PF ₆	$60(18)^{b}/0/2/38$	
3	CuOAc	$68 (10)^b/0/1/31$	
4	CuOTf	$54 (24)^b/0/0/46$	
5	CuCl	$72(4)^b/0/0/22$	
6	CuCl ₂	$85(2)^b/0/2/3$	
7	CuF_2	$70(12)^b/0/2/24$	
8^c	$CuCl_2$	$76(2)^b/0/5/5$	
9^d	$CuCl_2$	53/0/3/35	
10^e	$CuCl_2$	25/0/5/31	

Reaction conditions: a solution of 2a (0.4 mmol) in 1 mL of solvent was introduced into 1a (0.6 mmol) and the catalyst (5 mol%) in solvent (1 mL) at room temperature via a syringe over a period of 15 min. a NMR yield. ^b The corresponding lactone 11 from 3aa was detected. ^c DCE instead of DCM. d Toluene instead of DCM. e THF instead of DCM.

Scheme 2 Ortho C-H bond functionalization of 1-naphthols.

1-naphthols were obtained in good to excellent yields with excellent chemo- and site-selectivity. The steric hindrance of the ester group had no effect on this reaction (3ab-3ad). Various commonly encountered functional groups such as chloro, bromo, methyl, methoxyl, and CF3 at various positions of the phenyl rings of α-aryl-α-diazoacetates were well tolerated (3ae-3at). Strong electrondonating groups (OMe) could facilitate this reaction (3ah and 3ao), while strong electron-withdrawing groups (CF3) would slow down this reaction (3am). Furthermore, several substituted 1-naphthols 1b-1e were tested in this transformation, delivering the corresponding ortho-selective C-H functionalization products 3ba-3ea in moderate to excellent yields (68% to 97%). It must be noted that all the reactions exhibited 100% ortho-selectivity.

Subsequently, we investigated the substrate scope of the CuCl2-catalyzed ortho-selective C-H bond functionalization of 2-naphthols. All the reactions of 2-naphthols 7 with various diazoacetates 2 proceeded smoothly under standard conditions, affording the corresponding ortho-selective products in 58% to 98% yields with excellent chemo- and site-selectivity (Scheme 3).

Furthermore, we wondered whether phenols were applicable to this copper-catalysed ortho-C-H functionalization, which was

Scheme 3 Ortho C-H bond functionalization of 2-naphthols.

ChemComm Communication

Scheme 4 Ortho C-H bond functionalization of phenols.

more challenging because the nucleophilicity of phenols was much lower than that of naphthols. Indeed, all attempts to realize the ortho-C-H alkylation of unsubstituted phenol failed. To our delight, CuCl2 could enable the ortho-C-H bond functionalization of alkoxyl-substituted phenols 9 with α-arylα-diazoacetates 2 to give the corresponding products 10a-10d in good to excellent yields with excellent site-selectivity (Scheme 4).

To demonstrate the practicality of this transformation, a gram-scale reaction was carried out (Scheme 5). To our delight, the ortho-selective alkylation was easy to scale up to a gramscale with only 1 mol% catalyst loading, affording the desired product 3aa (1.61 g, 92%). To demonstrate the utility of this method further, transformations of the products were also performed. As shown in Scheme 5, TFA-catalyzed lactonization of 3aa and 10c could afford the corresponding cyclized products 11 and 12 in 99% and 95% yields, respectively. The structure of 12 was further confirmed by single-crystal X-ray analysis.13

OMe
$$Ph$$
 Ph
 CO_2Me
 CO_2Me
 $CH_2Cl_2, r.t.$

14, trace

OMe Ph
 CO_2Me
 CO_2Me
 CO_2Me

To further gain mechanistic insight into this copper-catalysed ortho-C-H alkylation of phenols, 1-methoxynaphthalene 13 was reacted with diazoester 2a in the presence of CuCl₂, which only delivered a trace amount of ortho-selective C-H bond functionalization products (eqn (1)). This result indicated that the hydroxyl group was vital not only for site-selectivity but also for reactivity, and the interaction between the hydroxyl group and the copper catalyst could give rise to the *ortho*-selectivity.

Based on the aforementioned results, two possible catalytic cycles accounting for this transformation are depicted in Scheme 6. Path A is the Cu-carbene process. The Cu(II)-carbene intermediate IA was formed from α-aryl-α-diazoesters 2 with CuCl₂, ¹⁴ which results in the formation of intermediate **IB** via coordination. The electrophilic addition of copper-carbene at the ortho-position of the phenols generated IC, which then underwent aromatization and protonation to produce the target ortho-C-H bond functionalization products 3, 8 or 10 and regenerate the copper catalyst. In path B, CuCl2 serves as a Lewis acid to coordinate the nitrogen of α -aryl- α -diazoesters 2 to form the carbocation intermediate IA', which would further

Gram-scale reactions and transformations of products

coordinate the oxygen of the phenols to generate IB'. The following electrophilic addition of the copper-carbocation at the ortho-position of the phenols generated IC', which then underwent aromatization, denitrogenation and protonation to produce the target *ortho*-C-H bond functionalization products and regenerate the copper catalyst. Further mechanistic studies indicated that these two processes occurred in this reaction.¹⁵

To conclude, we have described the first example of a CuCl₂catalyzed direct C-H functionalization of unprotected phenols and naphthols with α -aryl- α -diazoacetates under mild conditions, leading to diverse phenol derivatives with convertible functional groups. This work broadens the application scope of copper catalysts in carbene transfer reactions. The salient features of this reaction include an inexpensive catalyst, readily available starting materials, unprecedented C-H functionalization rather than O-H insertion, a good substrate scope, mild conditions, and diverse convenient transformations of the products. Further studies on the mechanism and the application of this protocol in organic synthesis are currently underway in our laboratory.

Communication

We are grateful to the National Natural Science Foundation of

China (No. 21971066, 21772042) and the STCSM (18JC1412300) for financial support.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- 1 (a) Synthetic and Natural Phenols, ed. J. H. P. Tyman, Elsevier, 1996; (b) F. H. Fiege, H.-W. Voges, T. Hamamoto, S. Umemura, T. Iwata, H. Miki, Y. Fujita, H.-J. Buysch, D. Garbe and W. Paulus, Phenol derivatives, in Ullmann's Encyclopedia of Industrial Chemistry, Wiley VCH, Weinheim, 2000; (c) J. M. Brunel, Chem. Rev., 2005, 105, 857.
- 2 For recent reviews on phenol functionalization, see: (a) D.-G. Yu, F. de Azambuja and F. Glorius, Angew. Chem., Int. Ed., 2014, 53, 7710; (b) G. Rousseau and B. Breit, Angew. Chem., Int. Ed., 2011, 50, 2450; (c) Z. Huang and J.-P. Lumb, ACS Catal., 2019, 9, 521; for recent examples, see: (d) K. Kobayashi, M. Arisawa and M. Yamaguchi, J. Am. Chem. Soc., 2002, 124, 8528; (e) D.-H. Lee, K.-H. Kwon and C. S. Yi, J. Am. Chem. Soc., 2012, 134, 7325; (f) C. Yu and F. W. Patureau, Angew. Chem., Int. Ed., 2018, 57, 11807; (g) G. Wang, L. Gao, H. Chen, X. Liu, J. Cao, S. Chen, X. Cheng and S. Li, Angew. Chem., Int. Ed., 2019, 58, 1694; (h) J.-L. Dai, N.-Q. Shao, J. Zhang, R.-P. Jia and D.-H. Wang, J. Am. Chem. Soc., 2017, 139, 12390; (i) S. Agasti, U. Sharma, T. Naveen and D. Maiti, Chem. Commun., 2015, 51, 5375; (j) P. Feng, G. Ma, X. Chen, X. Wu, L. Lin, P. Liu and T. Chen, Angew. Chem., Int. Ed., 2019, 58, 8400; (k) M. Murai, M. Yamamoto and K. Takai, Org. Lett., 2019, 21, 3441.
- (a) C. Cheng and J. F. Hartwig, *Chem. Rev.*, 2015, **115**, 8946; (b) O. Daugulis, J. Roane and L. D. Tran, *Acc. Chem. Res.*, 2015, 48, 1053; (c) Y. Segawa, T. Maekawa and K. Itami, Angew. Chem., Int. Ed., 2015, 54, 66; (d) S. A. Girard, T. Knauber and C.-J. Li, Angew. Chem., Int. Ed., 2014, 53, 74; (e) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, Chem. Rev., 2012, 112, 5879; (f) B.-J. Li and Z.-J. Shi, Chem. Soc. Rev., 2012, 41, 5588.
- 4 For selected recent examples, see: (a) T. A. Boebel and J. F. Hartwig, J. Am. Chem. Soc., 2008, 130, 7534; (b) C. Huang and V. Gevorgyan, J. Am. Chem. Soc., 2009, 131, 10844; (c) C. Huang, B. Chattopadhyay and V. Gevorgyan, J. Am. Chem. Soc., 2011, 133, 12406; (d) B. Xiao, Y. Fu, J. Xu, T.-J. Gong, J.-J. Dai, J. Yi and L. Liu, J. Am. Chem. Soc., 2010, 132, 468; (e) X. Zhao, C. S. Yeung and V. M. Dong, J. Am. Chem. Soc., 2010, 132, 5837; (f) T. Patra, S. Bag, R. Kancherla, A. Mondal, A. Dey, S. Pimparkar, S. Agasti, A. Modak and D. Maiti, Angew. Chem., Int. Ed., 2016, 55, 7751-7755; (g) Y. Wu, Z. Chen, Y. Yang, W. Zhu and B. Zhou, J. Am. Chem. Soc., 2018, 140, 42.
- 5 (a) R. B. Bedford, S. J. Coles, M. B. Hursthouse and M. E. Limmert, Angew. Chem., Int. Ed., 2003, 42, 112; (b) R. B. Bedford and M. E. Limmert, J. Org. Chem., 2003, 68, 8669; (c) J.-F. Yang, R.-H. Wang, Y.-X. Wang, W.-W. Yao, Q.-S. Liu and M. Ye, Angew. Chem., Int. Ed., 2016, 55, 14116; (d) Q.-S. Liu, D.-Y. Wang, J.-F. Yang, Z.-Y. Ma and M. Ye, Tetrahedron, 2017, 73, 3591.
- 6 For selected reviews, see: (a) H. M. L. Davie and J. R. Manning, Nature, 2008, 451, 417; (b) M. M. Díaz-Requejo and P. J. Pérez, Chem. Rev., 2008, 108, 3379; (c) M. P. Doyle, R. Duffy, M. Ratnikov and L. Zhou, Chem. Rev., 2010, 110, 704; (d) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire and M. A. Mckervey, Chem. Rev., 2015, 115, 9981; (e) F. Wei, C. Song, Y. Ma, L. Zhou, C.-H. Tung and Z. Xu, Sci. Bull., 2015, 60, 1479; (f) M. R. Fructos, M. M. Díaz-Requejo and P. J. Pérez, Chem. Commun., 2016, 52, 7326; (g) Y. Xia, D. Qiu and J. Wang, Chem. Rev., 2017, 117, 13810; (h) L. Liu and J. Zhang, Chem. Soc. Rev., 2016, 45, 506.

- 7 For selected reviews on aromatic C-H bond functionalization with diazo compounds, see: (a) B. Ma, L. Liu and J. Zhang, Asian J. Org. Chem., 2018, 7, 2015; (b) L. Liu and J. Zhang, Chin. J. Org. Chem., 2017, 37, 1117; for rhodium catalysts: (c) W. W. Chan, S. F. Lo, Z. Zhou and W.-Y. Yu, J. Am. Chem. Soc., 2012, 134, 13565; (d) T. K. Hyster, K. E. Ruhl and T. Rovis, J. Am. Chem. Soc., 2013, 135, 5364; (e) H. Qiu, M. Li, L.-Q. Jiang, F.-P. Lv, L. Zan, C.-W. Zhai, M. P. Doyle and W.-H. Hu, Nat. Chem., 2012, 4, 733; (f) B. Xu, M.-L. Li, X.-D. Zuo, S.-F. Zhu and Q.-L. Zhou, J. Am. Chem. Soc., 2015, 137, 8700; (g) A. DeAngelis, V. W. Shurtleff, O. Dmitrenko and J. M. Fox, J. Am. Chem. Soc., 2011, 133, 1650; (h) C. M. Qin and H. M. L. Davies, J. Am. Chem. Soc., 2014, 136, 9792; (i) T. Miura, Q. Zhao and M. Murakami, Angew. Chem., Int. Ed., 2017, 56, 16645; (j) D. Best, D. J. Burns and H. W. Lam, Angew. Chem., Int. Ed., 2015, 54, 7410; for palladium catalysts: (k) D. Zhang, H. Qiu, L. Jiang, F. Lv, C. Ma and W. Hu, Angew. Chem., Int. Ed., 2013, 52, 13356; (1) X. Gao, B. Wu, W.-X. Huang, M.-W. Chen and Y.-G. Zhou, Angew. Chem., Int. Ed., 2015, 54, 11956; for gold catalysts: (m) G. Xu, K. Liu and J. Sun, Org. Lett., 2018, 20, 72; (n) Y. Xi, Y. Su, Z. Yu, B. Dong, E. J. McClain, Y. Lan and X. Shi, Angew. Chem., Int. Ed., 2014, 53, 9817; (o) B. Ma, Z. Chu, B. Huang, Z. Liu, L. Liu and J. Zhang, Angew. Chem., Int. Ed., 2017, 56, 2749; (p) B. Ma, J. Wu, L. Liu and J. Zhang, Chem. Commun., 2017, 53, 10164; (q) Y. Liu, Z. Yu, J. Z. Zhang, L. Liu, F. Xia and J. Zhang, Chem. Sci., 2016, 7, 1988; (r) Z. Yu, H. Qiu, L. Liu and J. Zhang, Chem. Commun., 2016, 52, 2257; (s) B. Ma, Z. Wu, B. Huang, L. Liu and J. Zhang, Chem. Commun., 2016, 52, 9351; (t) Y. Li, Z. Tang, J. Zhang and L. Liu, Chem. Commun., 2020, 41, DOI: 10.1039/D0CC01118E; (u) Z. Yu, B. Ma, M. Chen, H.-H. Wu, L. Liu and J. Zhang, J. Am. Chem. Soc., 2014, 136, 6904; for iridium catalysts: (v) Y. N. Aher, D. M. Lade and A. B. Pawar, Chem. Commun., 2018, 54, 6288; for others: (w) A. Conde, G. Sabenya, M. Rodríguez, V. Postils, J. S. Luis, M. M. Díaz-Requejo, M. Costas and P. J. Pérez, Angew. Chem., Int. Ed., 2016, 55, 6530; (x) B. Wang, I. G. Howard, J. W. Pope, E. D. Conte and Y. Deng, Chem. Sci., 2019, 10, 7958.
- 8 E. Nakamura and K. Sato, Nat. Mater., 2011, 10, 158.
- 9 For selected reviews, see: (a) X.-X. Guo, D.-W. Gu, Z. Wu and W. Zhang, Chem. Rev., 2015, 115, 1622; (b) C. Zhang, C. Tang and N. Jiao, Chem. Soc. Rev., 2012, 41, 3464; for selected examples, see: (c) T. Naveen, A. Deb and D. Maiti, Angew. Chem., Int. Ed., 2017, **56**, 1111; (*d*) S. Jana, A. Ashokan, S. Kumar, A. Verma and S. Kumar, Org. Biomol. Chem., 2015, 13, 8411.
- 10 For selected books and reviews on O-H insertion reactions, see: (a) Modern Catalytic Methods for Organic Synthesis with Diazo Compounds, ed. M. P. Doyle and M. A. McKervey, Wiley, New York, 1998; (b) S.-F. Zhu and Q.-L. Zhou, Acc. Chem. Res., 2012, 45, 1365; (c) X. Guo and W. Hu, Acc. Chem. Res., 2013, 46, 2427; For recent Cu-catalyse O-H insertion of phenols and naphthols, see: (d) T. C. Maier and G. C. Fu, J. Am. Chem. Soc., 2006, 128, 4594; (e) X.-G. Song, S.-F. Zhu, X.-L. Xie and Q.-L. Zhou, Angew. Chem., Int. Ed., 2013, 52, 2555; (f) C. Chen, S.-F. Zhu, B. Liu, L.-X. Wang and Q.-L. Zhou, J. Am. Chem. Soc., 2007, 129, 12616; (g) T. Osako, D. Panichakul and Y. Uozumi, Org. Lett., 2012, 14, 194.
- 11 P. Yates, J. Am. Chem. Soc., 1952, 74, 5376. In Yates' report, the reaction of phenols with diazo compound catalyzed by copper gave the ortho C-H bond functionalization product as a minor one.
- 12 For $B(C_6F_5)_3$ -catalysed *ortho*-selectivity of phenols, see: (a) Z. Yu, Y. Li, J. Shi, B. Ma, L. Liu and J. Zhang, Angew. Chem., Int. Ed., 2016, 55, 14807; for Au(1)-catalysed ortho-selectivity of naphthols, see: (b) Z. Yu, Y. Li, P. Zhang, L. Liu and J. Zhang, Chem. Sci., 2019, **10**, 6553–6559; (c) S. Harada, C. Sakai, K. Tanikawa and T. Nemoto, Tetrahedron, 2019, 75, 3650.
- 13 CCDC 1834202 (12)†.
- 14 F. Li, J. Z. Zhang and F. Xia, J. Phys. Chem. A, 2020, 124, 2029.
- 15 According to the reviewer's suggestion, we did several control experiments to understand the mechanism. Because of the page limitation, all the details were in the ESI.† We thank the reviewer for his/her helpful suggestion.