


 Cite this: *Chem. Commun.*, 2020, 56, 8202

 Received 12th February 2020,
 Accepted 19th May 2020

DOI: 10.1039/d0cc01118e

rsc.li/chemcomm

Gold-catalyzed intermolecular [4+1] spiroannulation *via* site-selective aromatic C(sp²)-H functionalization and dearomatization of phenol derivatives†

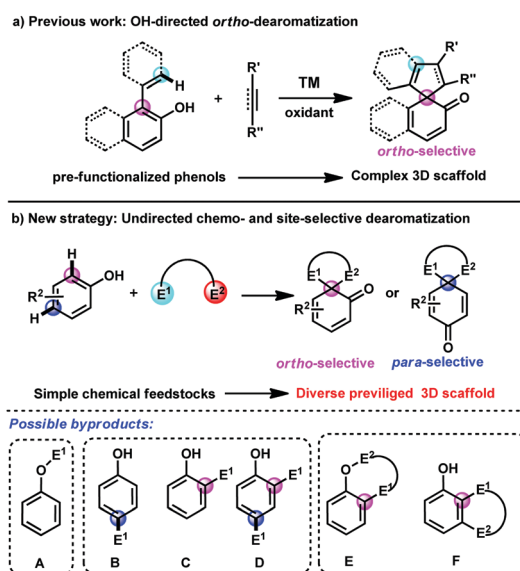
 Yongfeng Li,^a Zhiqiong Tang,^a Junliang Zhang ^{*b} and Lu Liu ^{*ac}

Herein, we have developed a novel and simple protocol to realize the C–H bond functionalization/dearomatization of naphthols and phenols with *ortho*-alkynylaryl- α -diazoesters under gold(I) catalysis. In this protocol, various spirocyclic molecules could be obtained in good yields with excellent chemo- and regioselectivity and moderate to good diastereoselectivity.

Phenols and naphthols are among the most readily available chemical feedstocks in industry and possess multiple reactive sites, which make them versatile building blocks for the synthesis of biologically active molecules, natural products and pharmaceuticals.¹ Recently, the dearomatization reactions of phenols and naphthols have received great attention and emerged as one of the most efficient and straightforward approaches for the rapid construction of highly complex three-dimensional scaffolds from these planar aromatic molecules, which tremendously increases diversification in synthetic science.^{2,3} Several elegant examples in transition-metal-catalyzed dearomatization of phenols and naphthols have been developed,^{4,5} which provide an efficient route to construct the spirocycles.⁶ Nevertheless, most of these reactions still rely on intramolecular dearomatizations or intermolecular transformations of pre-functionalized starting materials. With the advance of transition-metal-catalysed C–H bond functionalization,⁷ a cooperative approach combining C–H bond functionalization and sequential dearomatization of arenes represents a step- and atom-economical tool to access the spirocycles. In this regard, Luan, You, Mascareñas and Gulías, Lam and others have reported several elegant

transition-metal-catalyzed [3+2] and [2+2+1] spiroannulations of 2-naphthol or phenol derivatives and C–C multiple bonds by aromatic or vinyl C(sp²)-H bond functionalization/dearomatization cascade reactions (Scheme 1a).⁸ However, there are still several limitations of these reactions, including the single reaction site (only at *ortho*-position of hydroxyl), narrow substrate scope and harsh conditions. Thus, the development of more novel approaches for diverse and straightforward C–H bond functionalization/dearomatization reactions of commercially available phenols and naphthols is urgently desirable.

To address this daunting challenge, we hypothesized that the reaction of phenols and naphthols with bis-electrophiles may be achieved by the tandem C–H bond functionalization/dearomatization reactions, which will provide a straightforward approach to construct diverse spirocycles (Scheme 1b). However, this approach poses several considerable challenges. (1) The free phenolic hydroxyl group is active, which typically results in O–H



Scheme 1 C–H bond functionalization/dearomatization reactions.

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

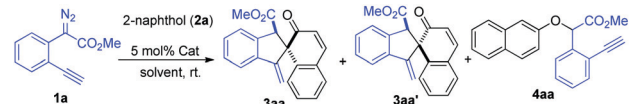
^c Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, East China Normal University, Shanghai, 200062, P. R. China

† Electronic supplementary information (ESI) available. CCDC 1915415, 1915417 and 1915418. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0cc01118e

bond functionalization with electrophile E1 rather than C–H bond functionalization (A, Scheme 1b). (2) Both the *para*- and *ortho*-sites on the phenyl ring are nucleophilic, typically leading to mixtures of *ortho*- and *para*-substituted products with various electrophiles (B–D, Scheme 1b). (3) After achieving the first site-selective C–H bond functionalization, how to control the following competing O–H substitution and C–H substitution is still challenging (E and F, Scheme 1b).

Recently, we have developed a gold-catalyzed⁹ site-selective aromatic C(sp²)–H bond functionalization of phenols, naphthols and toluene derivatives with diazo compounds.¹⁰ In addition, You and Zhang reported a highly efficient gold-catalyzed intramolecular dearomatization reaction of naphthols *via* 5-*endo*-dig cyclization.¹¹ Thus, we envisioned that alkynyl diazo compound **1a** should be a suitable bis-electrophile to achieve direct dearomatization of unmodified phenol derivatives by gold-catalyzed sequential C(sp²)–H functionalization/5-*endo*-dig carbocyclisation. It must be noted that the tandem C(sp²)–H functionalization/5-*endo*-dig cyclisation^{10f} occurred when the internal alkynyl diazo compounds being similar to **1a** reacted with phenols under the catalysis of the gold complex.

To test this hypothesis, our investigation began with the reaction of methyl *o*-alkynylaryl- α -diazoester **1a** and β -naphthol **2a** as the model substrates. The gold-complexes derived from PPh₃ and (2,4-*t*-Bu₂C₆H₃O)₃P, which are commonly used in C(sp²)–H bond functionalization with diazo compounds, could not produce the desired product (Table 1, entries 1 and 2). IPrAuCl/AgNTf₂ only gave a trace amount of the desired product. To our delight, the desired dearomatizative product **3aa/3aa'** was obtained in 75% total yield (51%/24%) with 2.1:1 diastereo-selectivity and 12.5:1 chemo-selectivity in the presence of JohnPhosAuCl (5 mol%) and AgNTf₂ (5 mol%) in DCM, in which the O–H bond insertion product **4aa** was detected in 6% yield (Table 1, entry 4). Encouraged by this result, the screening of various phosphine ligands was conducted (Table 1, entries 5–17). Gratifyingly, 2-(diphenylphosphino)pyridine (**L9**) proved to be the most suitable ligand, affording the desired products **3aa/3aa'** in 94% total NMR yield with 4.5:1 diastereoselectivity and 47:1 chemoselectivity (Table 1, entry 17). The counteranion effect of the halide scavenger was then investigated. The combination of **L9AuCl** and NaBAR_F displayed the highest reactivity (96% total yield), chemo-selectivity (2% of **4aa**) and diastereo-selectivity (7.7:1) compared to those of AgNTf₂ and AgBF₄ (Table 1, entries 17–19). Further attempts to modify the pyridine-based phosphine ligands **L10–L12** failed to improve the yield and diastereoselectivity (Table 1, entries 17–19). The solvent screening of, *e.g.*, toluene and DCE could not give better results (Table 1, entries 23, 24 and Table S1 in the ESI†). The introduction of diazo compound **1a** in one portion led to a lower yield (Table 1, entry 25). A series of other catalysts, such as Cu(OTf)₂, AgOTf, and (C₆F₅)₃B, which are commonly used in the transformation of diazo compounds, was also tested, and they showed very low catalytic activity and selectivity in this case (Table S1 in the ESI†). The structure and the relative configuration of

Table 1 Optimization of reaction conditions^a


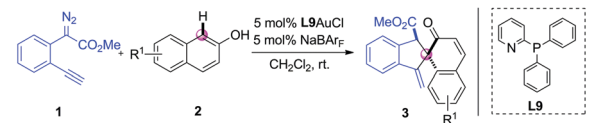
L1AuCl: R = 2-Me₂N, R' = Cy
 L2AuCl: R = 4-Me, R' = C₆H₅
 L3AuCl: R = 2-Me, R' = Cy
 L4AuCl: R = 2-C₆H₅, R' = C₆H₅
 L7AuCl: R = H, R' = Cy
 L8AuCl: R = CHO, R' = C₆H₅
 L10AuCl: R = H, R' = H
 L11AuCl: R = H, R' = H
 L12AuCl: R = H, R' = H

Entry	Cat. (5 mol%)	Solvent	Yield ^b (%) 3aa/3aa'/4aa
1	(2,4- <i>t</i> -Bu ₂ C ₆ H ₃ O) ₃ PAuCl/AgNTf ₂	DCM	Messy
2	PPh ₃ AuCl/AgNTf ₂	DCM	Messy
3	IPrAuCl/AgNTf ₂	DCM	Trace
4	JohnPhosAuCl/AgNTf ₂	DCM	51/24/6
5	^t Bu ₃ PAuCl/AgNTf ₂	DCM	59/16/5
6	Ph ₂ MePAuCl/AgNTf ₂	DCM	56/16/8
7	L1AuCl /AgNTf ₂	DCM	Trace
10	L2AuCl /AgNTf ₂	DCM	15/45/5
11	L3AuCl /AgNTf ₂	DCM	48/24/6
12	L4AuCl /AgNTf ₂	DCM	39/17/13
13	L5AuCl /AgNTf ₂	DCM	Trace
14	L6AuCl /AgNTf ₂	DCM	32/8/12
15	L7AuCl /AgNTf ₂	DCM	46/24/9
16	L8AuCl /AgNTf ₂	DCM	59/12/5
17	L9AuCl /AgNTf ₂	DCM	77/17/2
18	L9AuCl /AgBF ₄	DCM	36/18/9
19	L9AuCl /NaBAR _F	DCM	85/11/2
20	L10AuCl /NaBAR _F	DCM	79/11/3
21	L11AuCl /NaBAR _F	DCM	55/16/3
22	L12AuCl /NaBAR _F	DCM	80/17/2
23	L9AuCl /NaBAR _F	DCE	61/10/0
24	L9AuCl /NaBAR _F	Toluene	45/14/3
25 ^c	L9AuCl /NaBAR _F	DCM	59/8/—

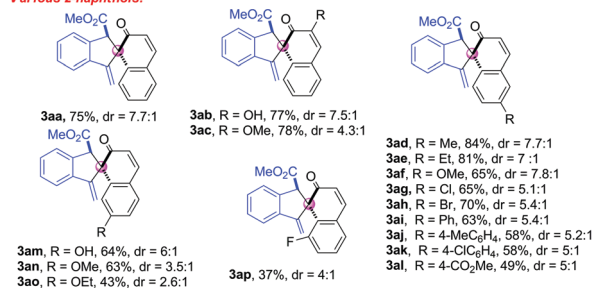
^a A solution of **1a** (0.4 mmol) in 1 mL of CH₂Cl₂ was introduced to a mixture of **2a** (0.6 mmol) and catalyst (5 mol%) in solvent (5 mL) by syringe in 20 min, and the reaction mixture stirred for 6 h. ^b NMR yield. ^c The solution of **1a** was added directly. Johnphos = 2-(di-*tert*-butylphosphino)biphenyl; IPr = 1,3-bis(2,6-di-*i*-propyl-phenyl)imidazol-2-ylidene.

products *cis*-**3aa** and *trans*-**3aa'** were further confirmed by single crystal X-ray diffraction analysis.¹²

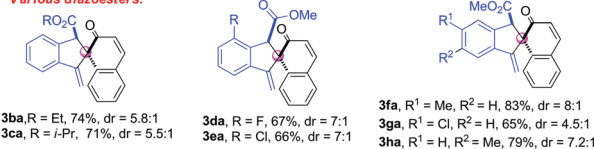
With the optimal reaction conditions in hand (Table 1, entry 19), we next investigated the substrate scope of the 2-naphthols **1**. As shown in Scheme 2, a diverse range of 2-naphthols were suitable substrates for this tandem C–H bond functionalization/5-*exo*-dig carbocyclisation reaction, affording the corresponding spirocyclic products in moderate to good yields with excellent chemo- and site-selectivity and good diastereoselectivity. Various commonly encountered functional groups such as hydroxyl, alkoxy, alkyl, chloro, bromo and aryl at C3 and C6-position were well tolerated (**3aa–3ak**). Gratifyingly, 2-naphthol **2l** with the strong electron-withdrawing group also reacted with alkynyl diazoester **1a** smoothly to give the corresponding spirocyclic product **3al** in 49% yield and 5:1 dr. The lower yield should be attributed to the weaker nucleophile of **2l** with the ester group that slows down the C–H bond



Various 2-naphthols:



Various diazoesters:



^aA solution of **1** (0.4 mmol) in 1 mL of CH₂Cl₂ was introduced to the mixture of **2** (0.6 mmol), L9AuCl (0.02 mmol) and NaBARF (0.02 mmol) in CH₂Cl₂ (3 mL) by syringe in 20 mins, and the reaction mixture stirred for 6-12 h. ^bIsolated yield.

Scheme 2 Spiroannulation of 2-naphthols and diazoesters.^{a,b}

functionalization and the sequential cyclisation. C7-substituted substrates **2m–2o** were compatible under the reaction conditions, giving the spirocyclic **3am–3ao** in good yields with good dr ratios. It was noteworthy that the reaction of C8-substituted 2-naphthol showed lower reactivity, probably due to the bulky allylic 1,3-strain (**3ap**). Subsequently, a variety of *o*-alkynylaryl- α -diazoesters **1b–1h** were prepared and tested. All the reactions of **2a** with **1b–1h**, which were equipped with various ester groups and phenyl rings, worked smoothly, delivering the corresponding dearomatization products **3ba–3ha** in good yields with good diastereoselectivity (Scheme 3). It was noteworthy that all the [4+1] spiroannulations were highly chemoselective and *ortho*-selective.



Next, the dearomatization of 1-naphthol was also investigated. The combination of 1-naphthol **2q** and *o*-alkynylaryl- α -diazoester **1a** underwent tandem *ortho*-selective C–H bond functionalization/dearomatization cyclisation reaction under the standard conditions, giving the corresponding spirocycle product **3aq** in 58% yield with 6:1 dr (eqn (1)). The structure of the product **3aq** was further confirmed by single crystal X-ray diffraction analysis.¹²

Finally, we wondered whether phenols were applicable to the present spiroannulation, which was more challenging because the energy barrier of dearomatization of phenols is significantly higher than that of naphthols.¹³ Unfortunately,



^aA solution of **1a** (0.3 mmol) in 1 mL of CH₂Cl₂ was introduced to the mixture of **2** (0.45 mmol) and 5 mol% (2,4-^tBu₂C₆H₃O)₃PAuCl/AgOTf in CH₂Cl₂ (4 mL) by syringe in 20 mins, and the reaction mixture stirred for 6-12 h. ^bIsolated yield.

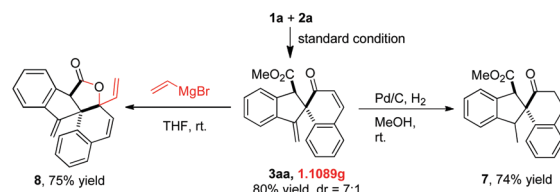
^cUsed Cy₂P(*o*-MePh)AuCl/AgOTf as a catalyst.

Scheme 3 Substrate scope of phenols.^{a,b}

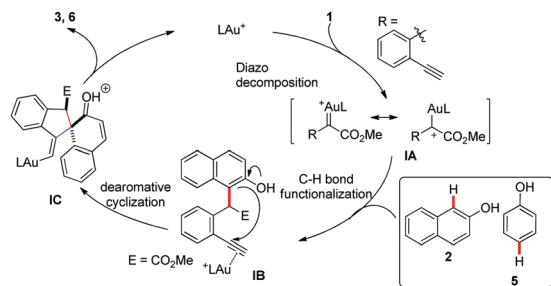
the reaction of phenol **5a** with alkynyl diazoester **1a** gave a complicated mixture under the standard conditions. From our previous work, we knew that the gold catalysts for C–H bond functionalization of phenols and naphthols were very different. After switching the ligand, to our delight, (2,4-^tBu₂C₆H₃O)₃PAuCl/AgOTf could enable the reaction of phenol **5a** with **1a** to give the corresponding dearomatization product **6a** in moderate yield. This high *para*-selectivity was consistent with our previous studies.^{10e} When the phenols **5b–5g** with various substituents such as alkyls, alkoxy *etc.* were used, the corresponding *para* C–H bond functionalization/dearomatization products **6b–6g** were isolated in moderate to good yields (Scheme 3). Unfortunately, the reaction of *p*-methyl phenol with **1a** cannot give the *ortho*-spiroannulation product but afforded the O–H insertion product.

It should be noted that this gold(I)-catalyzed cascade C–H functionalization/dearomatization of naphthols with *o*-alkynylaryl- α -diazoesters was easy to scale-up. A gram-scale reaction of 5 mmol of **1a** and **2a** was carried out under standard conditions, furnishing 1.1089 g of **3aa** in 70% isolated yield and **3aa'** in 10% isolated yield (Scheme 4). To demonstrate the synthetic value of this protocol further, transformations of **3aa** were performed (Scheme 4). The reduction of the exocyclic double bond of **3aa** would produce the corresponding product **7** in 74% yield. The reaction of **3aa** with vinyl magnesium bromide afforded the multi-fused lactone **8** in 75% yield *via* the tandem 1,2-addition/lactonization.

Based on the above results and previously reported work, a proposed mechanistic pathway accounting for this transformation is illustrated in Scheme 5. The gold(I) carbene intermediate **IA**, which was formed from *o*-alkynylaryl α -diazoesters **1** with the gold catalyst, would react with the nucleophilic naphthols **2** or



Scheme 4 Gram scale-up and transformation of product.



Scheme 5 Proposed catalytic cycle.

phenols **5** to afford *ortho*- or *para*-selective C–H bond functionalization product **IB**. The following 5-*exo*-dig carbocyclization of naphthols or phenols onto the terminal alkynes activated by the gold catalyst afforded the alkenyl gold intermediate **IC**. Finally, **IC** underwent the following deprotonation and protodeauration to produce the target spiroannulation products **3** or **6**.

To conclude, we have developed a conceptually simple, but highly unusual protocol for achieving dearomatization of readily available phenols and naphthols. Upon treatment with the gold complex, highly chemo- and site-selective C–H bond functionalization of phenols and naphthols with *o*-alkynylaryl α -diazoesters occurs, delivering the alkenyl phenol derivatives, which can undergo the following carbocyclisation dearomatization reaction. This protocol provides a straightforward access to diverse highly complex three-dimensional spirocyclic molecules in good to excellent yields with high chemo- and regioselectivity and good diastereo-selectivity. Moreover, this work will broaden the application of diazo compounds in organic synthesis and open a new door for the design of dearomatization of arenes.

We are grateful to the NSFC (No. 21971066 and 21772042) and the STCSM (18JC1412300) for financial support.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- 1 *Synthetic and Natural Phenols*, ed. J. H. P. Tyman, Elsevier, 1996.
- 2 For selected books and reviews, see: reviews: (a) *Asymmetric Dearomatization Reactions*, ed. S.-L. You, Wiley-VCH, Weinheim, Germany, 2016; (b) A. R. Pape, K. P. Kaliappan and E. P. Kündig, *Chem. Rev.*, 2000, **100**, 2917–2940; (c) S. P. Roche and J. Porco, Jr., *Angew. Chem., Int. Ed.*, 2011, **50**, 4068; (d) C. Zheng and S.-L. You, *Chem*, 2016, **1**, 830.
- 3 For selected reviews of dearomatization of phenols and naphthols, see: (a) H. Wang and X. Luan, *Org. Biomol. Chem.*, 2016, **14**, 9451–9455; (b) W.-T. Wu, L. Zhang and S.-L. You, *Chem. Soc. Rev.*, 2016, **45**, 1570–1580; (c) W. Sun, G. Li, L. Hong and R. Wang, *Org. Biomol. Chem.*, 2016, **14**, 2164–2176.
- 4 For selected examples of intramolecular dearomatization of phenols and naphthols to construct spirocycles, see: (a) T. Nemoto, Y. Ishige,

- M. Yoshida, Y. Kohno and Y. Hamada, *Org. Lett.*, 2010, **12**, 5020–5023; (b) S. Rousseaux, J. Garcia-Fortanet, M. A. Del Aguila Sanchez and S. L. Buchwald, *J. Am. Chem. Soc.*, 2011, **133**, 9282–9285; (c) Q.-F. Wu, W.-B. Liu, C.-X. Zhuo, Z.-Q. Rong, K.-Y. Ye and S.-L. You, *Angew. Chem., Int. Ed.*, 2011, **50**, 4455–4458; (d) R.-Q. Xu, Q. Gu, W.-T. Wu, Z.-A. Zhao and S.-L. You, *J. Am. Chem. Soc.*, 2014, **136**, 15469–15472; (e) H. Nakayama, S. Harada, M. Kono and T. Nemoto, *J. Am. Chem. Soc.*, 2017, **139**, 10188–10191.
- 5 For intermolecular spiroannulation, see: (a) L. Yang, H. Zheng, L. Luo, J. Nan, J. Liu, Y. Wang and X. Luan, *J. Am. Chem. Soc.*, 2015, **137**, 4876–4879; (b) H. Zheng, L. Bai, J. Liu, J. Nan, Z. Zuo, L. Yang, Y. Wang and X. Luan, *Chem. Commun.*, 2015, **51**, 3061–3064; (c) Z. Zuo, J. Wang, J. Liu, Y. Wang and X. Luan, *Angew. Chem., Int. Ed.*, 2020, **59**, 653–657.
- 6 For selected recent reviews on synthesis of spirocycles, see: (a) P.-W. Xu, J.-S. Yu, C. Chen, Z.-Y. Cao, F. Zhou and J. Zhou, *ACS Catal.*, 2019, **9**, 1820–1882; (b) E. M. Carreira and T. C. Fessard, *Chem. Rev.*, 2014, **114**, 8257–8322.
- 7 (a) C. Cheng and J. F. Hartwig, *Chem. Rev.*, 2015, **115**, 8946; (b) G. Song and X. Li, *Acc. Chem. Res.*, 2015, **48**, 1007; (c) K. Shin, H. Kim and S. Chang, *Acc. Chem. Res.*, 2015, **48**, 1040; (d) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754–8786.
- 8 For [3+2] dearomatization of 2-naphthol derivatives, see: (a) J. Zheng, S.-B. Wang, C. Zheng and S.-L. You, *J. Am. Chem. Soc.*, 2015, **137**, 4880–4883; (b) C. Zheng, J. Zheng and S.-L. You, *ACS Catal.*, 2016, **6**, 262–271; (c) G. Duarah, P. P. Kaishap, B. Sarma and S. Gogoi, *Chem. – Eur. J.*, 2018, **24**, 10196–10200; (d) I. Khan, S. R. Chidipudi and H. W. Lam, *Chem. Commun.*, 2015, **51**, 2613–2616; (e) J. Nan, Z. Zuo, L. Luo, L. Bai, H. Zheng, Y. Yuan, J. Liu, X. Luan and Y. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 17306–17309; (f) L. Han, H. Wang and X. Luan, *Org. Chem. Front.*, 2018, **5**, 2453–2457. For [3+2] dearomatization of phenol derivatives, see: (g) A. Seoane, N. Casanova, N. Quiñones, J. L. Mascareñas and M. Gulías, *J. Am. Chem. Soc.*, 2014, **136**, 7607–7610; (h) P.-P. Lin, X.-L. Han, G.-H. Ye, J.-L. Li, Q. Li and H. Wang, *J. Org. Chem.*, 2019, **84**, 12966–12974; (i) S. Kujawa, D. Best, D. J. Burns and H. W. Lam, *Chem. – Eur. J.*, 2014, **20**, 8599–8602. For [2+2+1] dearomatization of 2-naphthol, see: (j) S. Gu, L. Luo, J. Liu, L. Bai, H. Zheng, Y. Wang and X. Luan, *Org. Lett.*, 2014, **16**, 6132–6135.
- 9 For reviews on gold-catalyzed transformation of diazo compounds, see: (a) L. Liu and J. Zhang, *Chem. Soc. Rev.*, 2016, **45**, 506; (b) F. Wei, C. Song, Y. Ma, L. Zhou, C.-H. Tung and Z. Xu, *Sci. Bull.*, 2015, **60**, 1479; (c) M. R. Fructos, M. M. Díaz-Requejo and P. J. Pérez, *Chem. Commun.*, 2016, **52**, 7326; (d) B. Ma, L. Liu and J. Zhang, *Asian J. Org. Chem.*, 2018, **7**, 2015–2025.
- 10 For reviews, see: (a) M. P. Doyle, R. Duffy, M. Ratnikov and L. Zhou, *Chem. Rev.*, 2010, **110**, 704; (b) M. M. Díaz-Requejo and P. J. Pérez, *Chem. Rev.*, 2008, **108**, 3379; (c) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire and M. A. McKerverey, *Chem. Rev.*, 2015, **115**, 9981; (d) L. Liu and J. Zhang, *Chin. J. Org. Chem.*, 2017, **37**, 1117–1126. For examples of our group, see: (e) Z. Yu, B. Ma, M. Chen, H.-H. Wu, L. Liu and J. Zhang, *J. Am. Chem. Soc.*, 2014, **136**, 6904; (f) B. Ma, Z. Chu, B. Huang, Z. Liu, L. Liu and J. Zhang, *Angew. Chem., Int. Ed.*, 2017, **56**, 2749; (g) Y. Liu, Z. Yu, J. Z. Zhang, L. Liu, F. Xia and J. Zhang, *Chem. Sci.*, 2016, **7**, 1988; (h) Z. Yu, Y. Li, P. Zhang, L. Liu and J. Zhang, *Chem. Sci.*, 2019, **10**, 6553–6559; (i) Z. Yu, H. Qiu, L. Liu and J. Zhang, *Chem. Commun.*, 2016, **52**, 2257; (j) B. Ma, Z. Wu, B. Huang, L. Liu and J. Zhang, *Chem. Commun.*, 2016, **52**, 9351; (k) B. Ma, J. Wu, L. Liu and J. Zhang, *Chem. Commun.*, 2017, **53**, 10164–10167.
- 11 (a) W.-T. Wu, R.-Q. Xu, L. Zhang and S.-L. You, *Chem. Sci.*, 2016, **7**, 3427. For reviews, see: (b) W.-T. Wu, L. Zhang and S.-L. You, *Acta Chim. Sin.*, 2017, **75**, 419–438.
- 12 CCDC 1915415 (**3aa**), 1915417 (**3aa'**), 1915418 (**3aq**).
- 13 T. Oguma and T. Katsuki, *J. Am. Chem. Soc.*, 2012, **134**, 20017–20020.