

Cite this: *Chem. Sci.*, 2024, 15, 15819

All publication charges for this article have been paid for by the Royal Society of Chemistry

# *meta*-C–H functionalization of phenylethyl and benzylic alcohol derivatives via Pd/NBE relay catalysis†

Hua-Chen Shen,<sup>a</sup> Jian-Jun Li,<sup>a</sup> Peng Wang<sup>✉</sup>\*<sup>abc</sup> and Jin-Quan Yu<sup>✉</sup>\*<sup>d</sup>

The transition metal-catalyzed *meta*-C–H functionalization of alcohols and their hydroxylamine derivatives remains underdeveloped. Herein, we report an efficient *meta*-C–H arylation of both phenylethyl and benzylic alcohols and their hydroxylamine derivatives using a readily removable oxime ether directing group. Using electronically activated 2-carbomethoxynorbornene as the transient mediator and 3-trifluoromethyl-2-pyridone as the enabling ligand, this reaction features a broad substrate scope and good functional group tolerance. More importantly, with this oxime-directed *meta*-C–H functionalization, this method provides a dual approach for efficient access to both *meta*-substituted alcohols and hydroxylamines using two sets of simple deprotection conditions. This protocol leads to the efficient synthesis of bioactive compounds possessing promising reactivities for the treatment of pulmonary fibrosis.

Received 10th June 2024  
Accepted 3rd September 2024

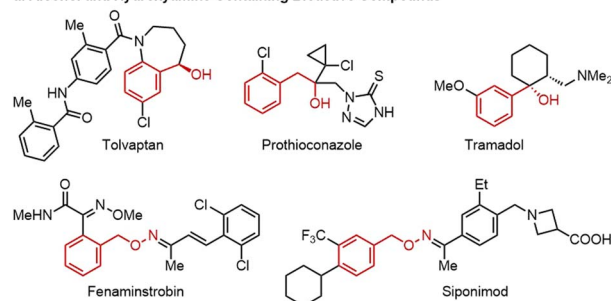
DOI: 10.1039/d4sc03802a

rsc.li/chemical-science

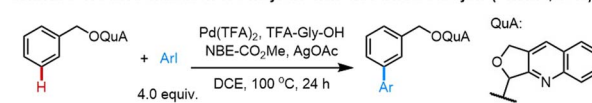
## Introduction

Phenylethyl and benzylic alcohols and their hydroxylamine derivatives are commonly found in a wide range of bioactive molecules, including tolaptan, prothioconazole, tramadol, fenaminstrobil, siponimod *etc.* (Scheme 1a).<sup>1</sup> In addition, they are also significant and widely utilizable synthetic building blocks that can engage in many fundamental transformations<sup>2</sup> and heterocycle constructions.<sup>3</sup> Thus, developing general and practical C–H transformations of alcohols and their hydroxylamine derivatives are highly valuable for late-stage diversification of alcohol or hydroxylamine containing bioactive scaffolds. Although transition metal catalyzed *ortho*-C–H functionalization of aryl alcohols has been well studied,<sup>4</sup> diverse *meta*-C–H functionalizations of those substrates are relatively less common and inefficient in both substrate and coupling partner scope<sup>5,6</sup> in spite of significant progress in the field of transition

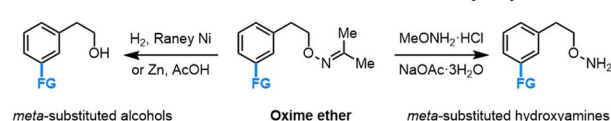
### a. Alcohol and Hydroxylamine Containing Bioactive Compounds



### b. *meta*-C–H Functionalization of Benzyl alcohols via Pd/NBE Catalysis (Ferreira, 2017)



### c. One Stone Two Birds: Access to *meta*-Substituted Alcohols and Hydroxylamines



### d. *meta*-C–H Functionalization of Alcohols and Hydroxylamines



Scheme 1 *meta*-C–H functionalization of alcohol and hydroxylamine via Pd/NBE relay catalysis.

<sup>a</sup>State Key Laboratory of Organometallic Chemistry and Shanghai-Hong Kong Joint Laboratory in Chemical Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, CAS 345 Lingling Road, Shanghai 200032, P. R. China. E-mail: pengwang@sioac.ac.cn

<sup>b</sup>School of Chemistry and Materials Science, Hangzhou Institute for Advanced Study, University of Chinese Academy of Sciences, 1 Sub-lane Xiangshan, Hangzhou 310024, P. R. China

<sup>c</sup>College of Material Chemistry and Chemical Engineering, Key Laboratory of Organosilicon Chemistry, and Material Technology of Ministry of Education, Hangzhou Normal University, Hangzhou 311121, P. R. China

<sup>d</sup>The Scripps Research Institute (TSRI), 10550 North Torrey Pines Road, La Jolla, CA 92037, USA. E-mail: yu200@scripps.edu

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d4sc03802a>



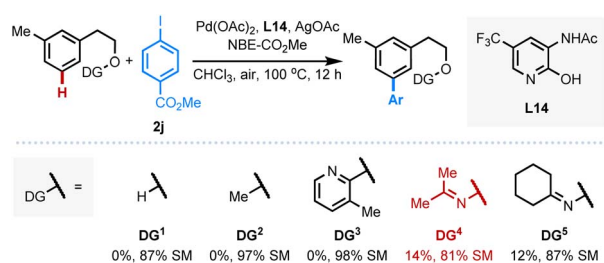
metal catalyzed *meta*-C–H activation.<sup>7–10</sup> Taking advantage of the Pd/NBE relay approach<sup>6,9</sup> for efficient *meta*-C–H functionalization, the only example of *meta*-arylation of benzylic alcohol derivatives has been reported by the Ferreira group (Scheme 1b). However, this reaction is limited to benzylic alcohols and a large excess of aryl iodides (4.0 equiv.) is required to give synthetically useful yields.<sup>6</sup> Furthermore, the preparation of the directing group in this reaction is not straightforward. Herein, we report a palladium-catalyzed *meta*-C–H functionalization of oxime ethers using 2-carbomethoxynorbornene (NBE-CO<sub>2</sub>Me) as a transient mediator and commercially available 3-trifluoromethyl-2-pyridone as the ligand (Scheme 1d). This reaction features a broad substrate scope and good functional group tolerance. More importantly, with this oxime-directed *meta*-C–H functionalization, this method provides a “one

stone two birds” approach (Scheme 1c) for efficient access to *meta*-substituted alcohols and hydroxylamines by the removal of the directing group under different conditions.

## Results and discussion

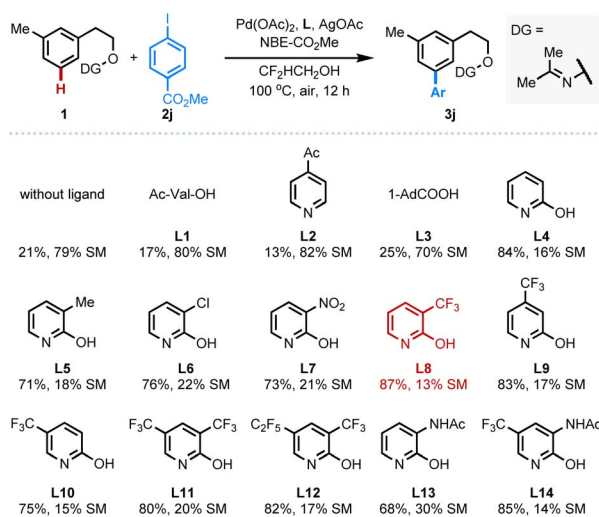
Our group has reported palladium-catalyzed hydroxy-directed *ortho*-C–H olefination of tertiary phenethyl alcohols with the assistance of an MPAA ligand.<sup>4a–c</sup> However, directed *meta*-C–H arylation using the native hydroxy group under our previous

**Table 1** Directing group evaluation for *meta*-C–H functionalization of alcohol derivatives<sup>ab</sup>



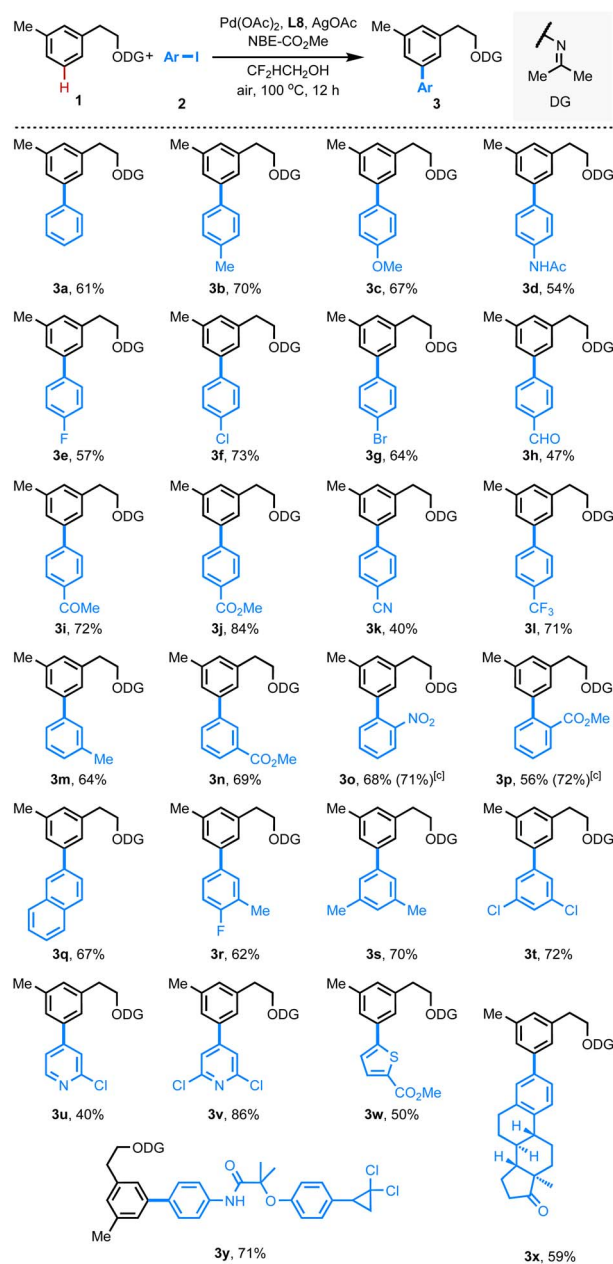
<sup>a</sup> Reaction conditions: substrate (0.1 mmol), **2j** (52.4 mg, 0.2 mmol), Pd(OAc)<sub>2</sub> (2.2 mg, 10 mol%), **L14** (4.4 mg, 20 mol%), AgOAc (25.0 mg, 0.15 mmol), NBE-CO<sub>2</sub>Me (22.8 mg, 0.15 mmol), CF<sub>2</sub>HCH<sub>2</sub>OH (0.1 mL), air, 100 °C, 12 h. <sup>b</sup> The yield was determined by <sup>1</sup>H NMR analysis of the crude product using CH<sub>2</sub>Br<sub>2</sub> as the internal standard.

**Table 2** Ligand evaluation for Pd-catalyzed *meta*-C–H functionalization of oxime ethers<sup>ab</sup>



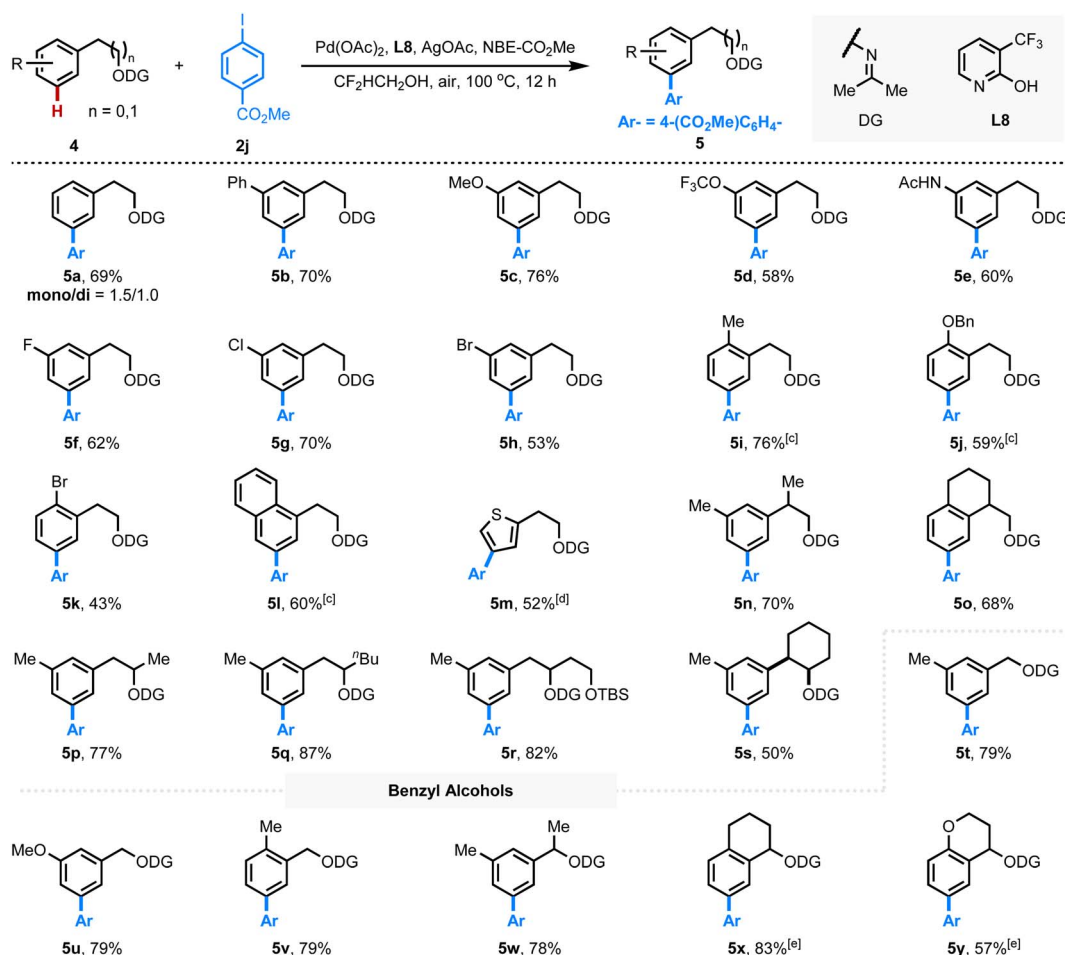
<sup>a</sup> Reaction conditions: **1** (19.1 mg, 0.1 mmol), **2j** (52.4 mg, 0.2 mmol), Pd(OAc)<sub>2</sub> (2.2 mg, 10 mol%), **L** (20 mol%), AgOAc (25.0 mg, 0.15 mmol), NBE-CO<sub>2</sub>Me (22.8 mg, 0.15 mmol), CF<sub>2</sub>HCH<sub>2</sub>OH (0.1 mL), air, 100 °C, 12 h. <sup>b</sup> The yield was determined by <sup>1</sup>H NMR analysis of the crude product using CH<sub>2</sub>Br<sub>2</sub> as the internal standard.

**Table 3** Scope of aryl iodides<sup>abc</sup>



<sup>a</sup> Reaction conditions: **1** (38.3 mg, 0.2 mmol), **2** (0.4 mmol), Pd(OAc)<sub>2</sub> (4.5 mg, 10 mol%), **L8** (6.5 mg, 20 mol%), AgOAc (50.1 mg, 0.30 mmol), NBE-CO<sub>2</sub>Me (45.7 mg, 0.30 mmol), CF<sub>2</sub>HCH<sub>2</sub>OH (0.2 mL), 100 °C, 12 h. <sup>b</sup> Isolated yield. <sup>c</sup> Ar–Br was used instead of Ar–I.



Table 4 Scope of acetone oxime ethers<sup>abcde</sup>

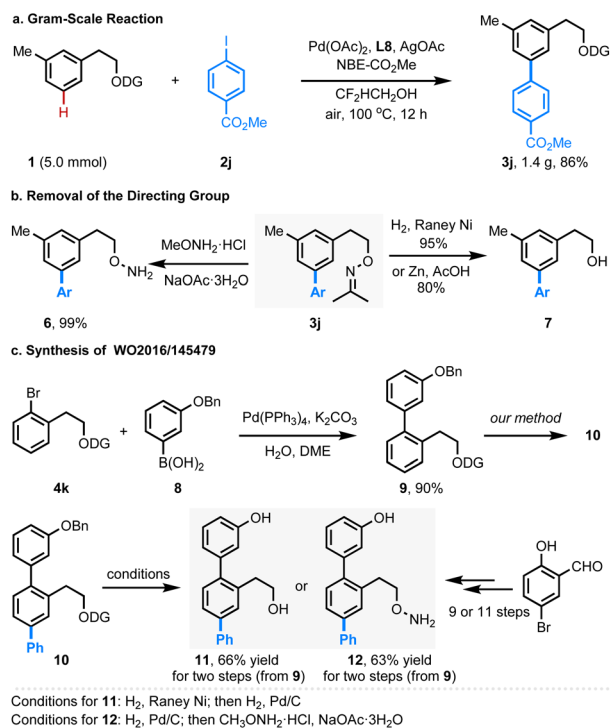
<sup>a</sup> Reaction conditions: **4** (0.2 mmol), **2j** (104.8 mg, 0.4 mmol),  $\text{Pd}(\text{OAc})_2$  (4.5 mg, 10 mol%), **L8** (6.5 mg, 20 mol%),  $\text{AgOAc}$  (50.1 mg, 0.30 mmol),  $\text{NBE-CO}_2\text{Me}$  (45.7 mg, 0.30 mmol),  $\text{CF}_2\text{HCH}_2\text{OH}$  (0.2 mL),  $100\text{ }^\circ\text{C}$ , 12 h. <sup>b</sup> Isolated yield. <sup>c</sup> TFE was used. <sup>d</sup>  $\text{AgOAc}$  (100.1 mg, 0.60 mmol) was used. <sup>e</sup> **L14** was used instead of **L8**.

*meta*-C–H arylation conditions resulted in no reaction and the slight decomposition of the primary alcohol. Despite methyl ether ( $\text{DG}^2$ ) being stable under these conditions, no desired product was observed either. Although the pyridine directing group  $\text{DG}^3$  is inert, we are pleased to find that the acetone oxime directing group ( $\text{DG}^4$ ) could provide the desired *meta*-arylated product in 14% NMR yield. Cyclohexanone oxime ether ( $\text{DG}^5$ ) also showed similar reactivity (Table 1). Following this finding, systematic evaluation of reaction parameters was conducted to further improve the outcomes using the acetone oxime ether as the directing group (Table 2). Notably, fluorinated alcohols can raise the yield drastically, and 2,2-difluoroethanol was identified as the most efficient solvent for this reaction due to the better mass balance (for more details, see the ESI<sup>†</sup>). With 2,2-difluoroethanol as the optimal solvent, the ligand effect was further evaluated, and we are pleased to find that the pyridone ligands are superior to the mono-protected amino acid (MPAA) ligand (**L1**), pyridine ligand (**L2**), and bulky carboxylic acid (**L3**). In general, both electron-rich (**L4**, **L5**) and electron-deficient (**L6–8**) 2-pyridone ligands could dramatically improve the yield

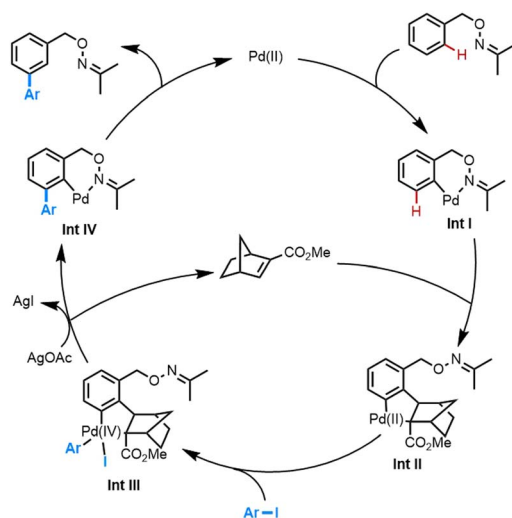
of this reaction, in which commercially available 3-trifluoromethyl-2-pyridone **L8** gave the best outcome (87% yield). Switching the  $\text{CF}_3$  group to other positions at the 2-pyridone scaffold (**L9**, **L10**) or more electron-deficient 2-pyridone ligands (**L11**, **L12**) cannot further enhance the reactivity. The mono-protected 3-amino-2-pyridone ligands (**L13**, **L14**) also provide the desired product in 68% and 85% yields, respectively. It is worth mentioning that the control experiments indicate the pyridone ligand is crucial for accelerating this *meta*-arylation of phenethyl alcohol-derived oxime ether, and only 21% NMR yield of the desired product was obtained in the absence of ligand.

Under the optimal conditions, the scope of aryl iodides was evaluated using 2-(*m*-tolyl)ethan-1-ol derived acetone oxime **1** as the model substrate (Table 3). In general, *para*-substituted aryl iodides containing both electron-rich substituents (**2b–d**) and electron-deficient substituents (**2e–l**) were all suitable coupling partners, providing the desired *meta*-arylated products in 40–84% yields. The 3-substituted (**2m**, **2n**) aryl iodides showed similar reactivities in comparison to the *para*-substituted aryl





Scheme 2 Gram-scale reaction and synthetic applications.



Scheme 3 Proposed mechanism.

iodides. Under the highly acidic conditions, 2-substituted aryl iodides are highly active, resulting in more side products *via* the classic Catellani reaction pathway. Accordingly, less reactive aryl bromides (**2o**, **2p**) provide higher yields than the corresponding aryl iodides. Multiple substituted aryl iodides (**3q–t**) were also evaluated, affording the desired products in good yields. Notably, the heteroaryl iodides, containing pyridine (**2u**, **2v**) and thiophene (**2w**) motifs, were well tolerated with this procedure. Aryl iodides derived from estrone (**2x**) and ciprofibrate (**2y**) were also investigated, which further demonstrated the generality of this reaction towards the complex scaffold.

Next, we turned our attention to check the breadth of aromatic oxime substrates (Table 4). The simple phenethyl alcohol-derived acetone oxime ether (**4a**) gave a mixture of mono- and di-products in 69% total yield with a mono/di ratio of 1.5/1.0. The phenethyl alcohol-derived oxime ethers bearing both electron-donating and electron-withdrawing substituents at the 3-position (**4b–h**), such as phenyl, methoxy, trifluoromethoxy, and acetylamino groups and halides, were all tolerated, providing the desired products in high efficiency. For *ortho*-substituted phenethyl alcohol derivatives (**4i–l**), 2,2,2-trifluoroethanol (TFE) was found to be a more efficient solvent than CF<sub>2</sub>HCH<sub>2</sub>OH, giving the arylated products in 43–76% yields. The *meta*-C–H bond on the thiophene ring could also be arylated (**4m**) with a lower yield probably due to the stability of the substrate under the reaction conditions.

To our delight, phenethyl alcohols bearing both  $\alpha$ - (**4n–o**) and  $\beta$ -substituents (**4p–r**) were tolerated with this procedure (**4n–s**), indicating the great potential of the current method for late-stage modification of complex primary and secondary alcohols. Less challenging benzylic alcohol derivatives with various substituents on the aromatic ring (**4t–v**) and the benzylic position (**4w–y**) were also investigated. Generally, the benzylic alcohol derived substrates showed higher reactivities than phenethyl alcohols.

The scalability of this reaction was demonstrated by conducting this reaction on a 5.0 mmol scale, affording the desired arylated product **3j** in 86% yield (Scheme 2a). Gratifyingly, the acetone oxime directing group could be selectively converted to alcohol **7** and hydroxylamine **6** in high yields under reductive conditions and mild hydrolysis conditions, respectively. The newly developed protocol could not only provide an efficient strategy for the late-stage installation of functionalities at the *meta*-position of the aromatic alcohols and their hydroxylamine derivatives, but also paved a new way for the synthesis of bioactive compounds. For example, the 2,5-diaryl substituted phenylethanol **11** and its hydroxylamine derivative **12**, both possessing promising reactivities for the treatment of pulmonary fibrosis,<sup>11</sup> could be prepared in high efficiency within three steps by leveraging our method as the key synthetic step (Scheme 2c). For comparison, those compounds were prepared in nine (for **11**) or eleven steps (for **12**) starting from 5-bromo-2-hydroxybenzaldehyde.<sup>11</sup>

Based on the previous works on the *meta*-C–H activation *via* Pd/NBE relay catalysis,<sup>9</sup> a proposed mechanism is depicted in Scheme 3. Firstly, oxime directed *ortho*-C–H activation occurs to give **Int I**, followed by the migration insertion of NBE-CO<sub>2</sub>Me, and sequential *meta*-C–H activation to generate **Int II**. The *meta*-functionalization happened *via* the oxidative addition with aryl iodide and reductive elimination. NBE-CO<sub>2</sub>Me could be regenerated by  $\beta$ -C elimination, and the product was formed *via* protodemetalation of **Int IV**.

## Conclusions

In summary, a Pd-catalyzed *meta*-functionalization of oxime ethers was realized by using Pd/NBE relay catalysis. The 3-trifluoromethyl pyridone ligand was identified as the enabling



ligand, which could significantly enhance the efficiency of this *meta*-functionalization. This procedure features a broad substrate scope and remarkable functional group compatibility, thus paving a practical way for the construction of *meta*-substituted alcohols and their hydroxylamine derivatives.

## Data availability

The data supporting this article have been included as part of the ESI.†

## Author contributions

H.-C. S. and J.-J. L. performed the experiments and analysed the data. P. W. guided the experiments. P. W. and J.-Q. Y. conceived this concept and prepared this manuscript with feedback from H.-C. S. and J.-J. L.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We gratefully acknowledge the National Key R&D Program of China (2023YFF0723900), National Natural Science Foundation of China (22371293, 22171277, 22101291), Strategic Priority Research Program of the Chinese Academy of Sciences (XDB0610000), Program of Shanghai Academic/Technology Research Leader (23XD1424500), Shanghai Institute of Organic Chemistry (SIOC), and State Key Laboratory of Organometallic Chemistry for financial support. We also thank J.-P. Wang at SIOC for verifying the reproducibility of this work.

## Notes and references

- (a) R. W. Schrier, P. Gross, M. Gheorghide, T. Berl, J. G. Verbalis, F. S. Czerwiec and C. Orlandi, *N. Engl. J. Med.*, 2006, **355**, 2099–2112; (b) J. E. Parker, A. G. Warrilow, H. J. Cools, C. M. Martel, W. D. Nes, B. A. Fraaije, J. A. Lucas, D. E. Kelly and S. L. Kelly, *Appl. Environ. Microbiol.*, 2011, **77**, 1460–1465; (c) W. Richter, H. Barth, L. Flohe and H. Giertz, *Arzneimittelforschung*, 1985, **35**, 1742–1744; (d) M. Ishaque, G. Schnabel and D. D. Anspaugh, WO2009/153231A2, 2009; (e) P. Gergely, B. Nuesslein-Hildesheim, D. Guerini, V. Brinkmann, M. Traebert, C. Bruns, S. Pan, N. Gray, K. Hinterding, N. Cooke, A. Groenewegen, A. Vitaliti, T. Sing, O. Luttringer, J. Yang, A. Gardin, N. Wang, W. Crumb, M. Saltzman, M. Rosenberg and E. Wallström, *Br. J. Pharmacol.*, 2012, **167**, 1035–1047.
- R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, Wiley-VCH, New York, 2nd edn, 1989.
- For selected examples, see: (a) T. Kondo, S. Yang, K.-T. Huh, M. Kobayashi, S. Kotachi and Y. Watanabe, *Chem. Lett.*, 1991, **20**, 1275–1278; (b) J. Zhou and J. Fang, *J. Org. Chem.*, 2011, **76**, 7730–7736; (c) H.-J. Li, C.-C. Wang, S. Zhu, C.-Y. Dai and Y.-C. Wu, *Adv. Synth. Catal.*, 2015, **357**, 583–588.
- For free hydroxyl group directed *ortho*-C–H activation, see: (a) Y. Lu, D.-H. Wang, K. M. Engle and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 5916–5921; (b) X. Wang, Y. Lu, H.-X. Dai and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 12203–12205; (c) Y. Lu, D. Leow, X. Wang, K. M. Engle and J.-Q. Yu, *Chem. Sci.*, 2011, **2**, 967–971; (d) K. Morimoto, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2011, **76**, 9548–9551; (e) L. Li, Q. Liu, J. Chen and Y. Huang, *Synlett*, 2019, **30**, 1366–1370; (f) D. A. Strassfeld, C.-Y. Chen, H. S. Park, D. Q. Phan and J.-Q. Yu, *Nature*, 2023, **622**, 80–86; For selected examples of *ortho*-C–H activation with a directing group, see: ; (g) E. M. Simmons and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 17092–17095; (h) K. Guo, X. Chen, M. Guan and Y. Zhao, *Org. Lett.*, 2015, **17**, 1802–1805; (i) Z. Ren, J. E. Schulz and G. Dong, *Org. Lett.*, 2015, **17**, 2696–2699; (j) L.-Y. Shao, C. Li, Y. Guo, K.-K. Yu, F.-Y. Zhao, W.-L. Qiao, H.-W. Liu, D.-H. Liao and Y.-F. Ji, *RSC Adv.*, 2016, **6**, 78875–78880; (k) B. J. Knight, J. O. Rothbaum and E. M. Ferreira, *Chem. Sci.*, 2016, **7**, 1982–1987; (l) Y.-J. Mao, S.-J. Lou, H.-Y. Hao and D.-Q. Xu, *Angew. Chem., Int. Ed.*, 2018, **57**, 14085–14089.
- (a) D. S. Leow, G. Li, T.-S. Mei and J.-Q. Yu, *Nature*, 2012, **486**, 518–522; (b) S. Lee, H. Lee and K. L. Tan, *J. Am. Chem. Soc.*, 2013, **135**, 18778–18781; (c) L. Chu, M. Shang, K. Tanaka, Q. H. Chen, N. Pissarnitski, E. Streckfuss and J.-Q. Yu, *ACS Cent. Sci.*, 2015, **1**, 394–399; (d) L. Zhang, C. Zhao, Y. Liu, J. Xu, X. Xu and Z. Jin, *Angew. Chem., Int. Ed.*, 2017, **56**, 12245–12249; (e) S.-D. Li, H. Wang, Y.-X. Weng and G. Li, *Angew. Chem., Int. Ed.*, 2019, **58**, 18502–18507; (f) H. Xu, M. Liu, L.-J. Li, Y.-F. Cao, J.-Q. Yu and H.-X. Dai, *Org. Lett.*, 2019, **21**, 4887–4891.
- Q. Li and E. M. Ferreira, *Chem.–Eur. J.*, 2017, **23**, 11519–11523.
- For a review on template-directed *meta*-C–H functionalization, see: (a) G. Meng, N. Y. S. Lam, E. L. Lucas, T. G. Saint-Denis, P. Verma, N. Chekshin and J.-Q. Yu, *J. Am. Chem. Soc.*, 2020, **142**, 10571–10591. For selected examples, see: ; (b) L. Wan, N. Dastbaravardeh, G. Li and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 18056–18059; (c) R. Tang, G. Li and J.-Q. Yu, *Nature*, 2014, **507**, 215–220; (d) Y. Kuninobu, H. Ida, M. Nishi and M. Kanai, *Nat. Chem.*, 2015, **7**, 712–717; (e) H. J. Davis, M. T. Mihai and R. J. Phipps, *J. Am. Chem. Soc.*, 2016, **138**, 12759–12762; (f) Z. Zhang, K. Tanaka and J.-Q. Yu, *Nature*, 2017, **543**, 538–542.
- For a review on ruthenium(II)-catalyzed *meta*-C–H functionalization by *ortho*-cyclometallation, see: (a) J. A. Leitch and C. G. Frost, *Chem. Soc. Rev.*, 2017, **46**, 7145–7153; for selected examples, see: (b) O. Saidi, J. Marafie, A. E. W. Ledger, P. M. Liu, M. F. Mahon, G. Kociok-Köhn, M. K. Whittlesey and C. G. Frost, *J. Am. Chem. Soc.*, 2011, **133**, 19298–19301; (c) N. Hofmann and L. Ackermann, *J. Am. Chem. Soc.*, 2013, **135**, 5877–5884; (d) C. J. Teskey, A. Y. W. Lui and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2015, **54**, 11677–11680; (e) Z. Fan, J. Ni and



- A. Zhang, *J. Am. Chem. Soc.*, 2016, **138**, 8470–8475; (f) C. C. Yuan, X. L. Chen, J. Y. Zhang and Y. S. Zhao, *Org. Chem. Front.*, 2017, **4**, 1867–1871; (g) Y. Wang, S. Chen, X. Chen, A. Zangarelli and L. Ackermann, *Angew. Chem., Int. Ed.*, 2022, **61**, e202205562; (h) J. Wu, N. Kaplaneris, J. Pöhlmann, T. Michiyuki, B. Yuan and L. Ackermann, *Angew. Chem., Int. Ed.*, 2022, **61**, e202208620.
- 9 For selected examples on *meta*-C–H arylation using a palladium/norbornene relay process, see: (a) X.-C. Wang, W. Gong, L.-Z. Fang, R.-Y. Zhu, S. Li, K. M. Engle and J.-Q. Yu, *Nature*, 2015, **519**, 334–338; (b) Z. Dong, J. Wang and G. Dong, *J. Am. Chem. Soc.*, 2015, **137**, 5887–5890; (c) P.-X. Shen, X.-C. Wang, P. Wang, R.-Y. Zhu and J.-Q. Yu, *J. Am. Chem. Soc.*, 2015, **137**, 11574–11577; (d) P. Wang, M. E. Farmer, X. Huo, P. Jain, P.-X. Shen, M. Isohey, J. E. Bradner, S. R. Wisniewski, M. D. Eastgate and J.-Q. Yu, *J. Am. Chem. Soc.*, 2016, **138**, 9269–9276; (e) P. Wang, G.-C. Li, P. Jain, M. E. Farmer, J. He, P.-X. Shen and J.-Q. Yu, *J. Am. Chem. Soc.*, 2016, **138**, 14092–14099; (f) H. Shi, P. Wang, S. Suzuki, M. E. Farmer and J.-Q. Yu, *J. Am. Chem. Soc.*, 2016, **138**, 14876–14879; (g) J. Han, L. Zhang, Y. Zhu, Y. Zheng, X. Chen, Z.-B. Huang, D.-Q. Shi and Y. Zhao, *Chem. Commun.*, 2016, **52**, 6903–6906; (h) H. Shi, A. N. Herron, Y. Shao, Q. Shao and J.-Q. Yu, *Nature*, 2018, **558**, 581–585; (i) L.-Y. Liu, J. X. Qiao, K.-S. Yeung, W. R. Ewing and J.-Q. Yu, *J. Am. Chem. Soc.*, 2019, **141**, 14870–14877; (j) R. Li, Y. Zhou, X. Xu and G. Dong, *J. Am. Chem. Soc.*, 2019, **141**, 18958–18963; (k) V. Sukowski, M. van Borselen, S. Mathew and M. Á. Fernández-Ibáñez, *Angew. Chem., Int. Ed.*, 2022, **61**, e202201750.
- 10 For *meta*-C–H functionalization by either steric or electronic influences: (a) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 390–391; (b) J.-Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka Jr and M. R. Smith III, *Science*, 2002, **295**, 305–308; (c) Y. Saito, Y. Segawa and K. Itami, *J. Am. Chem. Soc.*, 2015, **137**, 5193–5198; (d) R. Bisht and B. Chattopadhyay, *J. Am. Chem. Soc.*, 2016, **138**, 84–87; (e) B. Ramadoss, Y. Jin, S. Asako and L. Iles, *Science*, 2022, **375**, 658–663; (f) R. J. Phipps and M. J. Gaunt, *Science*, 2009, **323**, 1593–1597; (g) Y.-H. Zhang, B.-F. Shi and J.-Q. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 5072–5074. For an example using a traceless directing group relay strategy: ; (h) J. Luo, S. Preciado and I. Larrosa, *J. Am. Chem. Soc.*, 2014, **136**, 4109–4112.
- 11 K. A. Duggan, WO2016/145479A1, 2016.

