Green
Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: N. Jiao, Y. Liang, S. Song, L. Ai and X. Li, *Green Chem.*, 2016, DOI: 10.1039/C6GC02674E.

View Article Online
DOI: 10.1039/C6GC02674E

Green Chemistry

COMMUNICATION

Highly efficient metal-free approach to *meta*- and multiple-substituted phenols via a simple oxidation of cyclohexenones

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

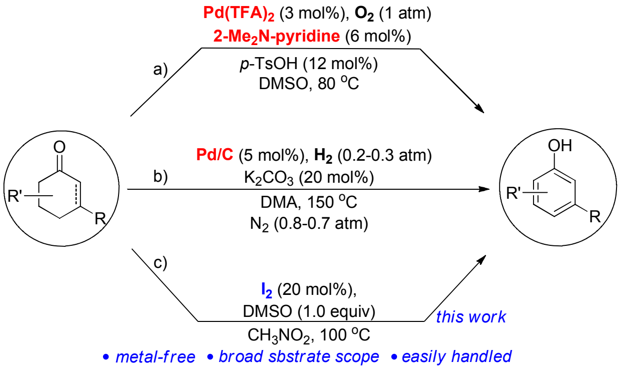
www.rsc.org/

Yu-Feng Liang,[a] Song Song,[a] Lingsheng Ai,[a] Xinwei Li,[a] and Ning Jiao[a,b]*

A novel and efficient metal-free approach to substituted phenols has been disclosed from simple and readily available cyclohexenones and cyclohexenones equivalents. Dimethyl sulfoxide (DMSO), the simple and common organic reagent, was employed as a mild oxidant in this I_2-catalysis, which significantly tolerates various substituents including some easily oxidizable or reducible functionalities. The challenging meta- and multiple-substituted phenols could be well prepared by this method. The metal-free and mild oxidation make this protocol very simple, practical, and easily handled.

Substituted phenols are common and important chemicals and are widely applied in the preparation of high-value pharmaceuticals, agrochemicals, polymers, biologically active compounds, as well as other fine and bulk chemicals.[1] In the past decades, the electrophilic[2] and nucleophilic[3] aromatic substitution, and the C-H hydroxylation of arenes,[4] have been developed for the preparation of substituted phenols.[5] Cyclohexenones and cyclohexanones are readily available, stable, easy to handle and widely used as bulk materials to prepare other important fine chemicals.[6,7] Although the transition-metal-catalyzed oxidative dehydrogenation[8] of cyclohexanones and cyclohexenones has been disclosed as an alternative approach to phenols,[9] most of these processes have been limited to the preparation of simple unsubstituted phenols, suffer from high temperature or stong acid employment. The classical electrophilic and nucleophilic aromatic substitution could hardly afford *meta*-substituted phenols because of the strong *ortho*/*para*-directing effect of the hydroxy group. Therefore, the efficient synthesis of *meta*- and multiple-substituted phenols is still a desirable and challenging issue.

Very recently, Stahl and his co-workers made a breakthrough on the oxidative dehydrogenation of cyclohexenones and cyclohexanones to diverse substituted phenols.[10] A Pd-catalyst combined with a pyridine ligand was employed in the highly efficient oxidative protocols (Scheme 1a). Alternatively, by using a general hydrogenation condition, an elegant Pd/C catalyzed dehydrogenation of cyclohexenones and cyclohexanones to substituted phenols was developed by Liu and co-workers (Scheme 1b).[11] Despite the significance, the active Pd/O_2[12] and Pd/H_2[13] catalysis are employed respectively in these protocols which might cause the undesirable overoxidation or hydrogenation of some functional groups and therefore limit the substrate scope. Furthermore, the heavy metal content in some fine chemicals and pharmaceutically active ingredients are typically strict, which cause a critical and difficult problem in the removal of Pd-catalyst from the products.[14] However, the metal-free catalysis for *meta*- and multiple-substituted phenols has not been well developed, yet. Therefore, it is still highly desired to improve on these shortcomings and discover a metal-free strategy for the transformation of cyclohexenones and cyclohexanones to substituted phenols.



Scheme 1 Catalytic oxidative dehydrogenation of cyclohexenones and cyclohexanones to *meta*- and multiple-substituted phenols.

We recently reported an I_2/DMSO system for the conversation of cyclohexanones, in which catehols were obtained as the products.[15] Herein, we present a metal-free I_2-catalyzed DMSO oxidative transformation of cyclohexenones and cyclohexenones equivalents,

---

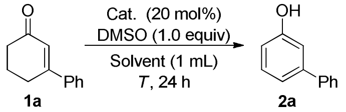
[a] State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Xue Yuan Road 38, Beijing 100191, China, Fax: (+86)-010-8280-5297, E-mail: jiaoning@pku.edu.cn; Homepage: http://sklnbd.bjmu.edu.cn/nj
[b] Shanghai Key Laboratory of Green Chemistry and Chemical Processes, Department of Chemistry, East China Normal University, Shanghai 200062, China
Electronic Supplementary Information (ESI) available: Detailed experimental procedures and spectroscopic data. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C6GC02674E

in contrast, *meta*- and multiple-substituted phenols were selectively generated (Scheme 1c). The simple and readily available I_2 catalyst, cheap and common DMSO oxidant, mild and easily handled conditions, makes this approach green and practical.

We initiated this dehydrogenative aromatization with the model reaction of 3-phenylcyclohexenone **1a**. Inspired by recent development of DMSO oxidative reactions,[16-18] we envisioned that oxidation of cyclohexenones to phenols could be accessed by DMSO oxidant. It was very interesting to obtain the expected 3-phenylphenol product **2a** in 5 % yield when NBS was employed as catalyst in the presence of only 1.0 equiv of DMSO in CH_3NO_2 at 100 °C (entry 1). The efficiency was significantly improved by the employment of NIS as catalyst, whereas NCS failed to produce the desired product (entries 2-3). In contrast, the reaction did not work in the presence of TBAB, KI or TBAI (entries 4-6). To our delight, the yield of **2a** could be improved to 92% when I_2 was employed as the catalyst (entry 7). Solvent screening demonstrated that the choice of solvent is crucial for this transformation. When DMF, dioxane, toluene or DMSO was employed as the solvent, the product was formed in lower yields (entries 8-11). It is noteworthy that this transformation underwent well under Ar atmosphere (entry 12). In contrast, the reaction failed to give **2a** in the absence of I_2 catalyst (entry 13).

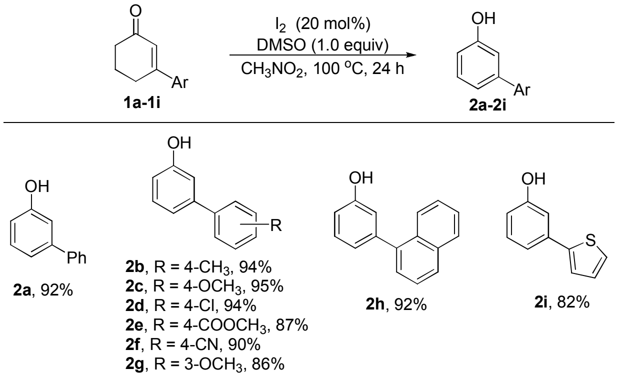
Table 1 Optimization of the reaction conditions[a]



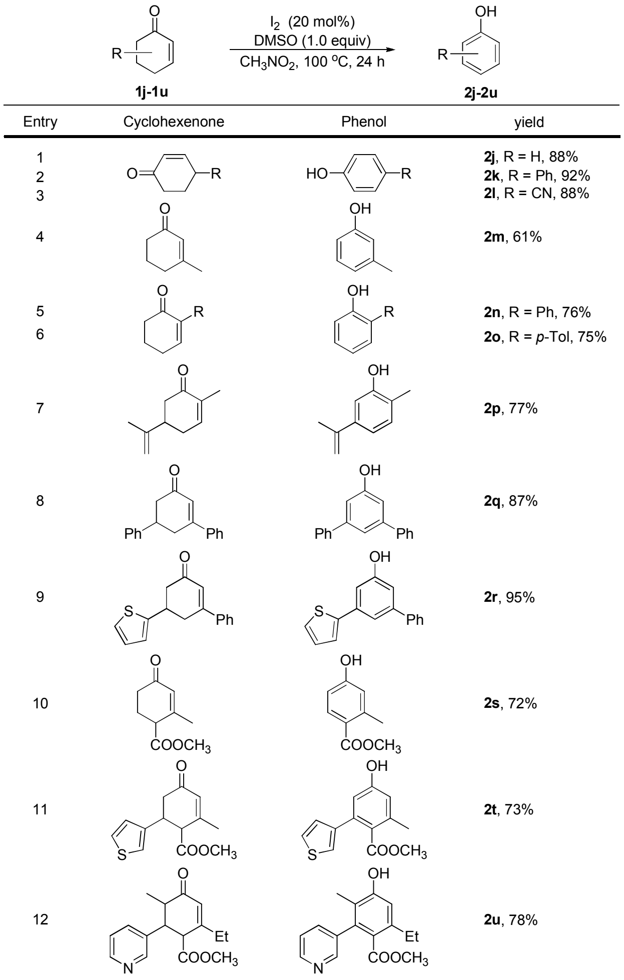
Entry	Cat. (20 mol%)	Solvent	Yield/%[b]
1	NBS	CH_3NO_2	5
2	NIS	CH_3NO_2	85
3	NCS	CH_3NO_2	0
4	TBAB	CH_3NO_2	0
5	KI	CH_3NO_2	0
6	TBAI	CH_3NO_2	0
7	I_2	CH_3NO_2	92
8	I_2	DMF	trace
9	I_2	dioxane	75
10	I_2	toluene	30
11	I_2	DMSO	24
12[c]	I_2	CH_3NO_2	90
13	--	CH_3NO_2	0

[a] Reaction conditions: **1a** (0.5 mmol), catalyst (0.1 mmol), Solvent (1 mL), stirred at 100 °C under air for 24 h. [b] Isolated yields. [c] The reaction was carried out under Ar (1 atm).

The optimized reaction conditions proved to be effective with a number 3-arylcyclohexenones for the preparation of *meta*-aryl substituted phenols (Scheme 2). The substrates with electron-donating and electron-withdrawing groups at the aromatic ring performed well with this reaction, affording the desired products **2b**-**2g** in good to excellent yields. Furthermore, 3-naphthyl and 3-thiophene substituted cyclohexenones were also suitable substrates for this protocol (**2h**-**2i**). From a practical perspective, the simple conditions, broad substrate scope, and easy operation would make this strategy extremely attractive in the development of efficient approaches to *meta*-phenols.

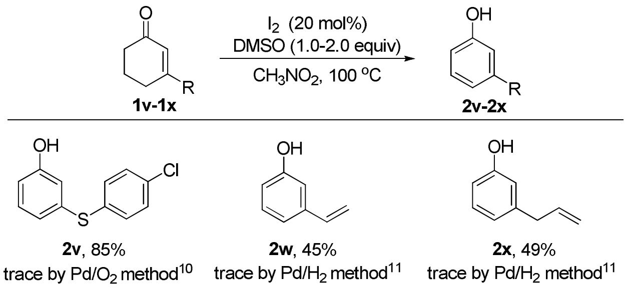


Scheme 2 Metal-free oxidative process for the preparation of *meta*-substituted phenols.



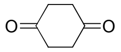
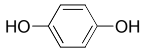
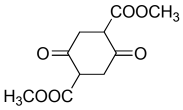
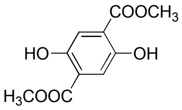
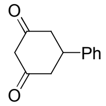
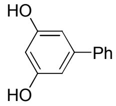
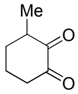
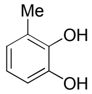
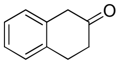
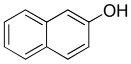
Scheme 3 Metal-free oxidative process for the preparation of diverse substituted phenols.

As the reaction conditions are mild, we subsequently expected that various substituted cyclohexenones would be applicable. To our delight, we could indeed show that a wide range of functional groups are tolerated under the reaction conditions (Scheme 3). The outcome of the dehydrogenation was not significantly affected by varying the position of the same substituent, for instance a phenyl group on the 2-cyclohexenones. Carvone, a widely used spice, could also be transformed to the corresponding phenol **2p** in good yield. 3,5-Diarylphenols **2q** and **2r** were obtained in excellent yield from the corresponding 3,5-diarylcyclohexenones. Moreover, ester, thiophene and pyridine moieties in products **2s**-**2u** were all compatible with this transformation.



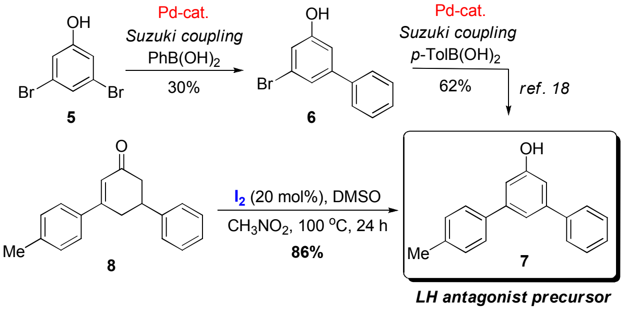
Scheme 4 Metal-free oxidative process for oxidation or reduction sensitive substrates.

It is noteworthy that under this simple and mild conditions, highly oxidation or reduction sensitive substrates with sulfide, vinyl, or allyl substituent afforded the corresponding phenols **2v**-**2x** in moderate to good yields, which are not obtained by the Pd/O_2[10] or Pd/H_2[11] catalysis (Scheme 4).

entry	substrate (**3**)	product (**4**)	yield
1			**4a**, 82%
2			**4b**, 87%
3			**4c**, 90%
4			**4d**, 26%
5			**4e**, 66%[a]

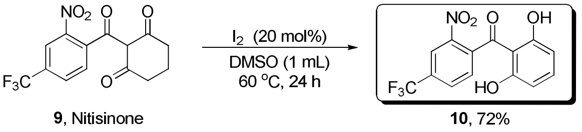
Scheme 5 Metal-free oxidative process for the preparation of phenols from cyclohexenones equivalents. Reaction conditions: **3** (0.5 mmol), I_2 (20 mol%), DMSO (1 mL) was stirred at 80 °C for 12 h. [a] 1-iodonaphthalen-2-ol (19%) was also obtained.

To further examine the scope and limitations of the reaction, we tested various cyclohexenones equivalents (Scheme 5). Interestingly, cyclohexanediones smoothly underwent the dehydrogenative aromatization to afford the corresponding benzenediols **4a-4d** with DMSO as the oxidant and solvent.[19] When 2-tetralone was employed as the substrate, a moderate yield was obtained for the 2-naphthol **4e**. The further iodination at the electron-rich α-position also occurred affording 1-iodonaphthalen-2-ol in 19% yield.[18a] Note that the iodination is not a problematic side reaction in other substrates.



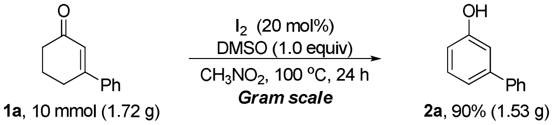
Scheme 6 Synthesis of 3-(4′-methylphenyl)-5-phenylphenol.

It should be mentioned that this protocol establishes more efficient and concise synthetic methodologies. For example, 3-(4′-methylphenyl)-5-phenylphenol **7**, the precursor of *O*-terphenylcarbamate which was identified as a potent antagonist for the human luteinizing hormone (LH) receptor, was prepared by traditional Suzuki coupling methods starting from 3,5-dibromophenol **5** through two steps with low total yield.[20] By the present simple metal-free protocol, **7** could be prepared from readily available **8** in 86% yield (Scheme 6). Notably, the boring and strictly Pd-catalyst removal is avoided by the current method.[10a]



(1)

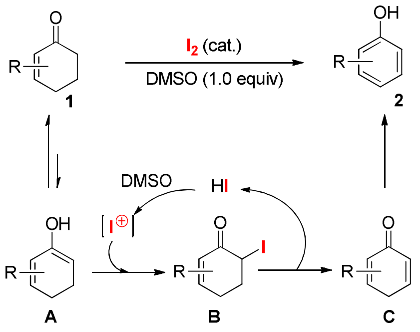
We next applied the present method to the diversification with bioactive molecul as the substrate. Remarkably, nitisibone **9**, a drug used to slow the effects of hereditary tyrosinemia type 1,[21] was proved to be competent to aromatize to afford phenol product **10** in 72% yield at 60 °C(eq . 1).[22] This protocol could be readily scalable, and when the transformation was scaled up to 10 mmol with a gram scale, the phenol product **2a** was isolated in 90% yield (eq. 2).



(2)

A possible reaction pathway is proposed for this dehydrogenative aromatization (Scheme 7). Initially, cyclohexenone undergoes keto-enol tautomerization to form **A**, followed by electrophilic iodization to afford α-iodo cyclohexenone **B**. The subsequent HI elimination took place to form cyclohexadienone intermediate **C**,[23] which should quickly tautomerize to the phenol product. Then HI could be oxidized by DMSO[17,18] to complete the catalytic cycle.[24]

View Article Online
DOI: 10.1039/C6GC02674E



Scheme 7 Proposed reaction mechanism.

Conclusions

In conclusion, we have demonstrated a novel and efficient metal-free oxidation of cyclohexenones and cyclohexenones equivalents to substituted phenols. Various substituents including some easily oxidizable or reducible functionalities such as sulfide, vinyl, or allyl group could be tolerated in this mild DMSO oxidation. The challenging *meta*-substituted phenols could be well prepared. The mild metal-free I_2-catalysis makes this protocol very simple, practical and easily handled. Further studies of DMSO as an oxidant or an oxygen source are ongoing in our group.

Acknowledgements

Financial support from National Basic Research Program of China (973 Program) (grant No. 2015CB856600), National Natural Science Foundation of China (Nos. 21325206, 21632001), the National Young Top-notch Talent Support Program, and the Peking University Health Science Center (BMU20150505) are greatly appreciated. We thank Kai Wu in this group for reproducing the results of **2g** and **4d**.

Notes and references

1 (a) J. H. P. Tyman, *Synthetic and Natural Phenols*, Elsevier, New York, 1996; (b) Z. Rappoport, *The Chemistry of Phenols*, Wiley-VCH, Weinheim, 2003; (c) P. M. Dewick, *Medicinal Natural Products: A Biosynthetic Approach*, Wiley-VCH, Weinheim, 2011; (d) S. D. Roughley, A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451.

2 (a) C. A. Fyfe, *The Chemistry of the Hydroxyl Group*, Wiley-Interscience, New York, 1971; (b) C. Hoarau and T. R. R. Pettus, *Synlett*, 2003, 127; (c) P. Hanson, J. R. Jones, A. B. Taylor, P. H. Walton and A. W. Timms, *J. Chem. Soc., Perkin Trans. 2*, 2002, 1135; (d) T. George, R. Mabon, G. Sweeny, J. B. Sweeney and A. J. Tavassoli, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2529.

3 For some examples of hydroxylation of aryl halides and aryl boric acids, see: (a) G. Mann, C. Incarvito, A. L. Rheingold and J. F. Hartwig, *J. Am. Chem. Soc.*, 1999, **121**, 3224; (b) Q. Shelby, N. Kataoka, G. Mann and J. F. Hartwig, *J. Am. Chem. Soc.*, 2000, **122**, 10718; (c) K. W. Anderson, T. Ikawa, R. E. Tundel and S. L. Buchwald, *J. Am. Chem. Soc.*, 2006, **128**, 10694; (d) T. Schulz, C. Torborg, B. Schäffner, J. Huang, A. Zapf, R. Kadyrov, A. Börner and M. Beller, *Angew. Chem., Int. Ed.*, 2009, **48**, 918; (e) A. Dumrath, X. F. Wu, H. Neumann, A. Spannenberg, R. Jackstell and M. Beller, *Angew. Chem., Int. Ed.*, 2010, **49**, 8988; (f) R. E. Maleczka, Jr, F. Shi, D. Holmes and M. R. Smith III, *J. Am. Chem. Soc.*, 2003, **125**, 7792; (g) Y.-Q. Zou, J.-R. Chen, X.-P. Liu, L.-Q. Lu, R. L. Davis, K. A. Jørgensen and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2012, **51**, 784.

4 For some examples of hydroxylation of Csp^2-H bonds, see: (a) X. Chen, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 6790; (b) Y.-H. Zhang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 14654; (c) I. Garcia-Bosch, A. Company, J. R. Frisch, M. Torrent-Sucarrat, M. Cardellach, I. Gamba, M. Güell, L. Casella, L. Q. Jr., X. Ribas, J. M. Luis and M. Costas, *Angew. Chem., Int. Ed.*, 2010, **49**, 2406; (d) Q. Liu, P. Wu, Y. Yang, Z. Zeng, J. Liu, H. Yi and A. Lei, *Angew. Chem., Int. Ed.*, 2012, **51**, 4666; (e) J. Gallardo-Donaire and R. Martin, *J. Am. Chem. Soc.*, 2013, **135**, 9350; (f) C. Yuan, Y. Liang, T. Hernandez, A. Berriochoa, K. N. Houk and D. Siegel, *Nature*, 2013, **499**, 192; (g) K. Ohkubo, A. Fujimoto and S. Fukuzumi, *J. Am. Chem. Soc.*, 2013, **135**, 5368; (h) Z.-J. Zhang, X.-J. Quan, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, *Org. Lett.*, 2014, **16**, 3292; (i) X. Li, Y.-H. Liu, W.-J. Gu, B. Li, F.-J. Chen and B.-F. Shi, *Org. Lett.*, 2014, **16**, 3904; (j) F. Yang, K. Rauch, K. Kettelhoit and L. Ackermann, *Angew. Chem., Int. Ed.*, 2014, **53**, 11285; (k) V. S. Thirunavukkarasu and L. Ackermann, *Org. Lett.*, 2012, **14**, 6206; (l) G. Shan, X. Yang, L. Ma and Y. Rao, *Angew. Chem., Int. Ed.*, 2012, **51**, 13070; (m) F. Mo, L. J. Trzepkowshi and G. Dong, *Angew. Chem., Int. Ed.*, 2012, **51**, 13075; (n) P. Y. Choy and F. Y. Kwong, *Org. Lett.*, 2013, **15**, 270; (o) Y. Yan, P. Feng, Q.-Z. Zheng, Y.-F. Liang, J.-F. Lu, Y. Cui and N. Jiao, *Angew. Chem., Int. Ed.*, 2013, **52**, 5827; (p) K. Seth, M. Nautiyal, P. Purohit, N. Parikh and A. K. Chakraborti, *Chem. Commun.*, 2015, **51**, 191; (q) J. Dong, P. Liu and P. Sun, *J. Org. Chem.*, 2015, **80**, 2925; (r) Y.-F. Liang, X. Wang, Y. Yuan, Y. Liang, X. Li and N. Jiao, *ACS Catal.*, 2015, **5**, 6148.

5 For a review, see: D. A. Alonso, C. Nájera, I. M. Pastor and M. Yus, *Chem. Eur. J.*, 2010, **16**, 5274.

6 M. T. Musser, *Cyclohexanol and Cyclohexanone in Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, 2005.

7 For some recent examples with cyclohexenones or cyclohexanones as starting materials, see: (a) M.-O. Simon, S. A. Girard and C.-J. Li, *Angew. Chem., Int. Ed.*, 2012, **51**, 7537; (b) M. Sutter, N. Sotto, Y. Raoul, E. Métay and M. Lemaire, *Green Chem.*, 2013, **15**, 347; (c) S. A. Girard, X. Hu, T. Knauber, F. Zhou, M.-O. Simon, G.-J. Deng and C.-J. Li, *Org. Lett.*, 2012, **14**, 5606; (d) S. Kambourakis and J. W. Frost, *J. Org. Chem.*, 2000, **65**, 6904; (e) N. Gigant and J.-E. Bäckvall, *Chem. Eur. J.*, 2014, **20**, 5890; (f) Y. Chen, F. Xiao, H. Chen, S. Liu and G.-J. Deng, *RSC Adv.*, 2014, **4**, 44621; (g) X. Jin, K. Taniguchi, K. Yamaguchi and N. Mizuno, *Chem. Sci.*, 2016, **7**, 5371; (h) Z. Chen, H. Zeng, H. Gong, H. Wang and C.-J. Li, *Chem. Sci.*, 2015, **6**, 4174; (i) Z. Chen, H. Zeng, S. A. Girard, F. Wang, N. Chen and C.-J. Li, *Angew. Chem., Int. Ed.*, 2015, **54**, 14487; (j) Y. Xie, J. Wu, X. Che, Y. Chen, H. Huang and G.-J. Deng, *Green Chem.*, 2016, **18**, 667; (k) X. Chen, J. S. Martinez and J. T. Mohr, *Org. Lett.*, 2015, **17**, 378.

8 For reviews, see: (a) M. T. Keβler and M. H. G. Prechtl, *ChemCatChem.*, 2012, **4**, 326; (b) S. A. Girard, H. Huang, F. Zhou, G.-J. Deng and C.-J. Li, *Org. Chem. Front.*, 2015, **2**, 279; and references cited therein.

9 (a) E. C. Horning and M. G. Horning, *J. Am. Chem. Soc.*, 1947, **69**, 1359; (b) D. Bondon, Y. Pietrasanta and B. Pucci, *Tetrahedron Lett.*, 1977, **18**, 821; (c) T. T. Wenzel, *J. Chem. Soc., Chem. Commun.*, 1989, 932; (d) M. Hayashi, K. Yamada and S. Nakayama, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1501; (e) T. Moriuchi, K. Kikushima, T. Kajikawa and T. Hirao, *Tetrahedron Lett.*, 2009, **50**, 7385; (f) C. S. Yi and D. W. Lee, *Organometallics*, 2009, **28**, 947; (g) P. F. Schuda and W. A.

View Article Online
DOI: 10.1039/C6GC02674E

Price, *J. Org. Chem.*, 1987, **52**, 1972; (h) K. Kikushima and Y. Nishina, *RSC Adv.*, 2013, **3**, 20150; (i) H.-C. Tong, K. R. Reddy and S.-T. Liu, *Eur. J. Org. Chem.*, 2014, 3256; (j) Z. Zhang, T. Hashiguchi, T. Ishida, A. Hamasaki, T. Honma, H. Ohashi, T. Yokoyama and M. Tokunaga, *Org. Chem. Front.*, 2015, **2**, 654; For a review, see: (j) J. Muzart, *Eur. J. Org. Chem.*, 2010, 3779.

10 (a) Y. Izawa, D. Pun and S. S. Stahl, *Science*, 2011, **333**, 209; (b) Y. Izawa, C. Zheng and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2013, **52**, 3672; (c) T. Diao, D. Pun and S. S. Stahl, *J. Am. Chem. Soc.*, 2013, **135**, 8205; (d) D. Pun, T. Diao and S. S. Stahl, *J. Am. Chem. Soc.*, 2013, **135**, 8213.

11 J. Zhang, Q. Jiang, D. Yang, X. Zhao, Y. Dong and R. Liu, *Chem. Sci.*, 2015, **6**, 4674.

12 For reviews, see: (a) S. S. Stahl, *Angew. Chem., Int. Ed.*, 2004, **43**, 3400; (b) K. M. Gligorich and M. S. Sigman, *Angew. Chem., Int. Ed.*, 2006, **45**, 6612; (c) Z. Shi, C. Zhang, C. Tang and N. Jiao, *Chem. Soc. Rev.*, 2012, **41**, 3381.

13 For reviews, see: (a) H. Sajiki and Y. Monguchi, *Development of Palladium Catalysts for Chemoselective Hydrogenation*, Wiley-VCH, Weinheim, 2011; (b) S. Nishimura, *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*, Wiley-Intersciences, New York, 2001.

14 (a) C. E. Garrett and K. Prasad, *Adv. Synth. Catal.*, 2004, **346**, 889; (b) C. J. Welch, J. Albaneze-Walker, W. R. Leonard, M. Biba, J. DaSilva, D. Henderson, B. Laing, D. J. Mathre, S. Spencer, X. Bu and T. Wang, *Org. Process Res. Dev.*, 2005, **9**, 198.

15 Y.-F. Liang, X. Li, X. Wang, M. Zou, C. Tang, Y. Liang, S. Song and N. Jiao, *J. Am. Chem. Soc.*, 2016, **138**, 12271.

16 For reviews that DMSO oxidative reactions, see: (a) X.-F. Wu and K. Natte, *Adv. Synth. Catal.*, 2016, **358**, 336; (b) W. W. Epstein and F. W. Sweat, *Chem. Rev.*, 1967, **67**, 247; (c) H. D. Martin, A. Weise and H.-J. Niclas, *Angew. Chem., Int. Ed.*, 1967, **6**, 318; (d) A. J. Mancuso and D. Swern, *Synthesis*, 1981, 165; (e) T. T. Tidwell, *Synthesis,* 1990, 857.

17 For some recent examples that DMSO as a reagent, see: (a) S. Liu, H. Xi, J. Zhang, X. Wu, Q. Gao and A. Wu, *Org. Biomol. Chem.*, 2015, **13**, 8807; (b) X. Gao, X. Pan, J. Gao, H. Jiang, G. Yuan and Y. Li, *Org. Lett.*, 2015, **17**, 1038; (c) J. Chen, G. Li, Y. Xie, Y. Liao, F. Xiao and G.-J. Deng, *Org. Lett.*, 2015, **17**, 5870; (d) T. Jia, A. Bellomo, S. Montel, M. Zhang, K. EL. Baina, B. Zheng and P. J. Walsh, *Angew. Chem., Int. Ed.*, 2014, 53, 260; (e) N. Mupparapu, S. Khan, S. Battula, M. Kushwaha, A. P. Gupta, Q. N. Ahmed and R. A. Vishwakarma, *Org. Lett.*, 2014, **16**, 1152; (f) Q. Gao, X. Wu, S. Liu and A. Wu, *Org. Lett.*, 2014, **16**, 1732; (g) X. Wu, Q. Gao, S. Liu and A. Wu, *Org. Lett.*, 2014, **16**, 2888; (h) R. Xu, J.-P. Wan, H. Mao and Y. Pan, *J. Am. Chem. Soc.*, 2010, **132**, 15531; (i) R. Tomita, Y. Yasu, T. Koike and M. Akita, *Angew. Chem., Int. Ed.*, 2014, **53**, 7144; (j) N. Battini, A. K. Padala, N. Mupparapu, R. A. Vishwakarma and Q. Naveed, *RSC. Adv.*, 2014, **4**, 26258; (k) R. N. Reddi, P. K. Prasad and A. Sudalai, *Angew. Chem., Int. Ed.*, 2015, **54**, 14150; (l) T. Jia, A. Bellomo, K. E. L. Baina, S. D. Dreher and P. J. Walsh, *J. Am. Chem. Soc.*, 2013, **135**, 3740.

18 For the development of DMSO oxidative reactions from our group, see: (a) S. Song, X. Sun and N. Jiao, *Org. Lett.*, 2015, **17**, 2886; (b) Y.-F. Liang, K. Wu, S. Song, X. Li, X. Huang and N. Jiao, *Org. Lett.*, 2015, **17**, 876; (c) S. Song, X. Li, X. Sun, Y. Yuan and N. Jiao, *Green. Chem.*, 2015, **17**, 3285; (d) S. Song, X. Huang, Y.-F. Liang, C. Tang, X. Li and N. Jiao, *Green Chem.*, 2015, **17**, 2727; (e) T. Shen, X. Huang, Y.-F. Liang and N. Jiao, *Org. Lett.*, 2015, **17**, 6186.

19 Only trace amount of phenols products were observed for cyclohexenones equivalents when DMSO (1.0 equivalent) was used as oxidant in CH_3NO_2 solvent.

20 L. H. Heitman, R. Narlawar, H. de Vries, M. N. Willemsen, D. Wolfram, J. Brussed and A. P. IJzermann, *J. Med. Chem.*, 2009, **52**, 2036.

21 P. Suwannarat, K. O'Brien, M. B. Perry, N. Sebring, I. Bernardini, M. I. Kaiser-Kupfer, B. I. Rubin, E. Tsilou, L. H. Gerber and W. A. Gahl, *Metabolism*, 2005, **54**, 719.

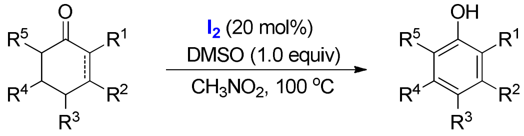
22 The reaction of nitisibone is sensitive the temperature. The yield decreased to 27% at 80 ^{o}C, and only trace amount of phenol product was obtained at 100 ^{o}C.

23 For a review on α,β-dehydrogenation by halogenation/elimination, see: S. S. Stahl and T. Diao, *Comp. Org. Synth.*, 2014, **7**, 178; and references cited therein.

24 Note that 1.0 equivalent of DMSO as oxidant is enough for cyclohexenones, while for cyclohexenones equivalents DMSO should be used as solvent.

View Article Online
DOI: 10.1039/C6GC02674E

Table of Contents



• metal-free • broad sbstrate scope • easily handled

The simple and readily available I_2 catalyst, cheap and common DMSO oxidant could be employed for the transformation of cyclohexenones to *meta*- and multiple-substituted phenols with various functional substituents tolerated.