COMMUNICATION

Hypoiodite-catalysed oxidative homocoupling of arenols and tandem oxidation/cross-coupling of hydroquinones with arenes

Muhammet Uyanik, Dai Nagata and Kazuaki Ishihara*

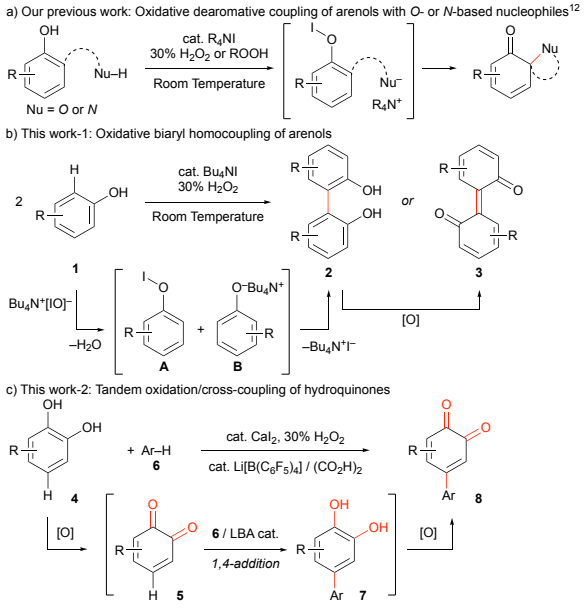
Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

We report the hypoiodite-catalyzed oxidative C–C homocoupling of arenols to the biarenols or biquinones using aqueous hydrogen peroxide as an oxidant. In addition, by combining hypoiodite catalysis and lipophilic Lewis acid-assisted Brønsted acid catalysis under aqueous conditions, we achieved a tandem oxidation/cross-coupling reaction of hydroquinones with electron-rich arenes. These results highlight the substantial scope of hypoiodite/acid co-catalysis for use in oxidative coupling reactions.

Biarenols and biquinones are found in several polyketide-derived natural products, biologically active compounds, and functional organomaterials.[1,2] Biaryl compounds are conventionally synthesized by the transition metal-catalysed C–C coupling reaction of aryl compounds pre-activated as halogen or metal derivatives. Oxidative C–H/C–H coupling of arenols is an attractive method for synthesizing biaryl compounds. Transition-metal complexes are often required as catalysts or reagents.[2,3] Several transition metal-free methods using inorganic or organic oxidants[4–7] as well as chemical oxidant-free electrochemical synthesis[8] have also been reported. Recently, hypervalent organoiodine-catalysed oxidative coupling of arenols has been reported by Kita and colleagues.[9] Oxidative arenol–arenol or arenol–arene cross-coupling reactions have been achieved in chemo- and regioselective manners. However, oxone was required as a relatively strong oxidant under acidic conditions in expensive fluorinated solvents.[9]

On the other hand, we have developed a quaternary ammonium hypoiodite-catalyzed[10,11] oxidative dearomative cyclization of arenols with *O*- or *N*-based nucleophiles such as carboxylic acids, alcohols, sulfonamides, or azide (Scheme 1a).[12] Hypoiodite (IO^-) active species could be easily generated *in situ* by oxidation of the corresponding iodide (I^-) with hydrogen peroxide or alkyl hydroperoxides under mild conditions. Intra- or intermolecular coupling would then proceed via umpolung of arenols activated electrophilically through *O*-iodination. We were interested in applying IO^-/H_2O_2 catalysis to the oxidative biaryl C–C coupling of arenols via a similar umpolung strategy. We envisioned that ammonium hypoiodite active species ($Bu_4N^+IO^-$) might react with two arenol molecules **1** to give intermediates **A** (acceptor) and **B** (donor) via electrophilic and nucleophilic activation, respectively (Scheme 1b).[12] Intermolecular C–C coupling of these two intermediates might then produce biarenols **2** after rearomative tautomerization. If biarenols **2** are oxidized much faster[3,6] than the starting arenols **1** in a chemoselective manner (i.e., no oxidative decomposition), the corresponding biquinones **3** could be obtained selectively. We also achieved a tandem oxidation/cross-coupling process including oxidation of hydroquinones **4** to quinones **5** followed by 1,4-addition of electron-rich arenes **6** and further oxidation of aryl hydroquinones **7** to arylquinones **8** by the combination of hypoiodite oxidation catalysis and lipophilic Lewis acid-assisted Brønsted acid (LBA)[13] catalysis (Scheme 1c).



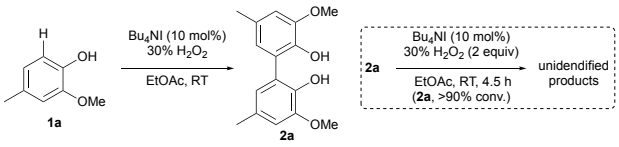
Scheme 1 Hypoiodite-catalysed oxidative coupling of arenols.

We commenced our investigation by examining the oxidative homocoupling of 2-methoxy-4-methylphenol (**1a**) (Scheme 2). The use of 1.2 equivalents of a 30% aqueous solution of

Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa, Nagoya 464-8603, Japan. E-mail: ishihara@cc.nagoya-u.ac.jp

†Electronic Supplementary Information (ESI) available: Additional information, experimental details and characterization data. See DOI: 10.1039/x0xx00000x

hydrogen peroxide as an oxidant in the presence of 10 mol% of Bu_4NI in ethyl acetate gave the desired biphenol **2a** in 45% yield along with a small amount of several unidentified side products, and the rest of the unreacted **1a** (ca. 40%) was recovered (Scheme 2, entry 1). On the other hand, the use of two equivalents of hydrogen peroxide gave a complex reaction mixture, in which **2a** was obtained in lower yield along with several unidentified side products and some of the unreacted **1a** (Scheme 2, entry 2). These results suggested that, as the desired reaction from **1a** to **2a** proceeded, a competitive oxidative decomposition of **2a** proceeded in the presence of a higher amount of oxidant, which was also confirmed by a control reaction of **2a** under similar oxidative conditions (Scheme 2, dashed box). Interestingly, when one equivalent of K_2CO_3 was added, a white precipitate was observed as the reaction proceeded (initially, K_2CO_3 powder was almost dissolved in an aqueous hydrogen peroxide phase), and the chemical yield of **2a** was increased to 87% (Scheme 2, entry 3 versus entry 1). On the other hand, the use of an aqueous solution of K_2CO_3 dramatically decreased the chemical yield of **2a** (Scheme 2, entry 4 versus entry 3), suggesting that the salt precipitation during the reaction is crucial to improving the chemoselectivity. Although the role of K_2CO_3 is not yet fully understood, we speculated that unselective over-reactions of **2a** might be suppressed by the selective precipitation of 2,2'-biphenol **2a** as a potassium salt under these conditions.

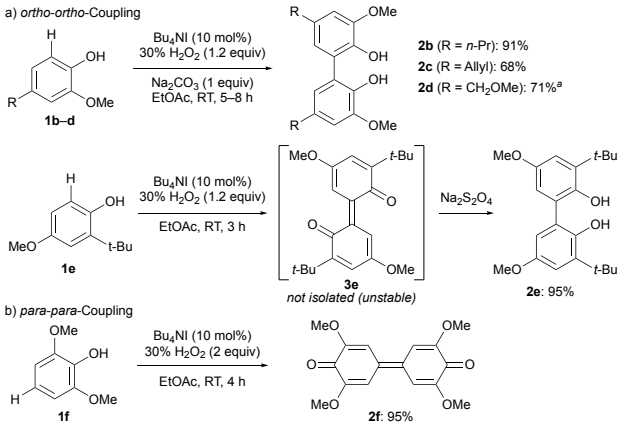


entry	H_2O_2 (equiv)	additive (equiv)	time (h)	**2a**, yield (%)[a]
1	1.2	–	3	45
2	2	–	3	30
3	1.2	K_2CO_3 (1)	4	87[b]
4	1.2	K_2CO_3 aq. (1)[c]	24	26

Scheme 2 Investigation of the oxidative homocoupling of 1a. [a] ^{1}H NMR analysis. [b] Isolated yield. [c] 1 *M* in H_2O. For further investigation of additives, see Table S1, ESI$^+$.

We examined the oxidative homocoupling of several electron-rich phenols (Scheme 3). Oxidative biaryl coupling of 4-substituted 2-methoxyphenols **1b**–**d** using Na_2CO_3 as an optimal inorganic base gave the corresponding 2,2'-biphenols **2b**–**d** in good to high yield (Scheme 3a). On the other hand, no inorganic base additives were required for the oxidation of 2-*tert*-butyl-4-methoxyphenol (**1e**) since no oxidative decomposition was observed. A chemoselective tandem oxidative coupling of **1e** proceeded smoothly to give 2,2'-biphenoquinone **3e** quantitatively as a detectable but non-isolable product, which was then converted to 2,2'-biphenol **2e** after a reductive workup (Scheme 3a). Notably, a bulky substituent is required at the *ortho*-position of 4-methoxyphenols to achieve a chemoselective oxidative biaryl coupling since oxidation of an *ortho*-methyl analogue gave a complex reaction mixture. Although a chemoselective *ortho*-*ortho*-coupling of 2,4-dimethoxyphenol failed, probably due to the inherent instability of the corresponding 2,2'-biphenoquinone,[14] *para*-*para*-coupling of 2,6-dimethoxyphenol (**1f**) proceeded smoothly to give 4,4'-biphenoquinone **2f** as a stable product (Scheme 3b).

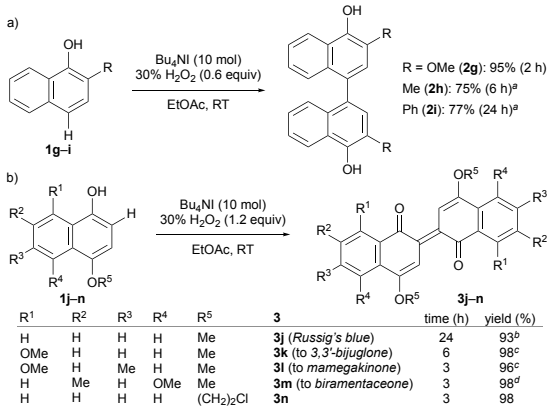
On the other hand, no regioselectivity was observed for the oxidation of 2-methoxyphenol that could couple at either the *ortho* or *para* position, and a complex mixture was obtained. Currently, our oxidative coupling is limited to electron-rich phenols bearing an alkoxy group at the *ortho*- or *para*-position, and phenols without alkoxy substituents could not be oxidized under these mild conditions (see Scheme S1 for unsuccessful examples, ESI$^+$).



Scheme 3 Oxidative homocoupling of phenols. [a] Na_2CO_3 (2 equiv) in $(MeO)_2CO$ at 50 °C.

Chemoselective oxidative homocoupling of 2-substituted 1-naphthols **1g**–**i** gave the corresponding 4,4'-binaphthols **2g**–**i** in high yield (Scheme 4a). Because almost no overoxidation or oxidative decomposition of these 4,4'-binaphthols was observed, inorganic base additives were not required, and 0.6 equivalents (1.2 equivalents per homocoupling reaction) of oxidant were enough to complete the oxidation. On the other hand, chemoselective over-oxidation of the corresponding 2,2'-binaphthols to the corresponding quinones was much faster than oxidative coupling of the starting 1-naphthols.[3b] Thus, a chemoselective tandem oxidative homocoupling of 4-alkoxy-substituted 1-naphthols **1j**–**n** gave the corresponding 2,2'-binaphthoquinones **3j**–**n**, including Russig's blue (**3j**, gram-scale),[15] and synthetic intermediates of several natural products such as 3,3'-bijuglone (**3k**),[16] mamegakinone (**3l**)[1a] and biramentaceone (**3m**),[1a] in high yield (Scheme 4b). These compounds were synthesized previously by using metal-based oxidants.[1a,3b,3c] However, in sharp contrast to 1-naphthols, oxidation of 2-naphthols was sluggish and gave complex mixtures along with the desired products in low yield (ESI$^+$).

Control experiments (Table S6, ESI$^+$) revealed that *in situ*-generated ammonium hypoiodite might be a catalytic active species for the present oxidative homocoupling reactions, as in our previous oxidative coupling reactions.[10,12] In addition, no reaction was observed by the protection of hydroxyl group of phenol **1** as methyl ether (Scheme S2, ESI$^+$), suggesting that the hydroxyl group might be essential to react with I^+ species to give an aryl hypoiodite species such as intermediate **A** shown in Scheme 1. Moreover, the addition of radical trapping agents such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or *N*-*tert*-butyl-α-phenylnitrone (PBN) did not influence the yield in the oxidative dimerization of **1**, suggesting that a free-radical pathway might be ruled out (Scheme S2, ESI$^+$).



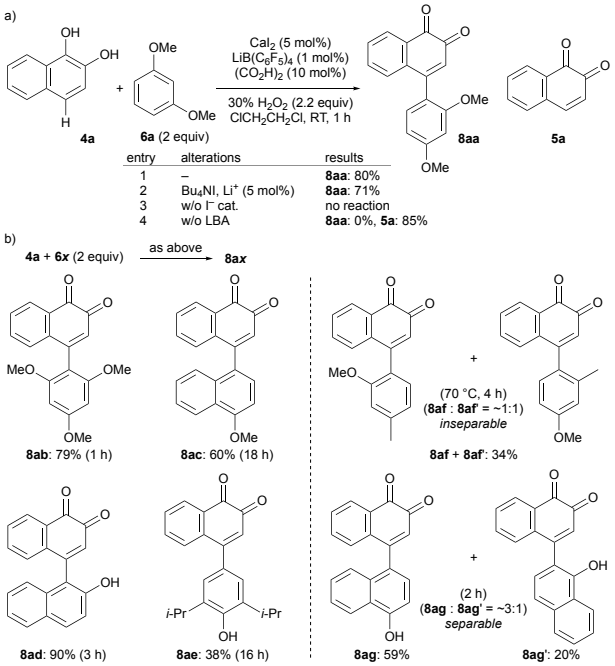
R^1	R^2	R^3	R^4	R^5	3	time (h)	yield (%)
H	H	H	H	Me	**3j** (*Russig's blue*)	24	93[b]
OMe	H	H	H	Me	**3k** (to *3,3'-bijuglone*)	6	98[c]
OMe	H	Me	H	Me	**3l** (to *mamegakinone*)	3	96[c]
H	Me	H	OMe	Me	**3m** (to *biramentaceone*)	3	98[d]
H	H	H	H	$(CH_2)_2Cl$	**3n**	3	98

Scheme 4 Oxidative homocoupling of 1-naphthols. [a] In CH_2Cl_2. [b] 1.7-gram scale, Bu_4NI (1 mol%). [c] 30% H_2O_2 (1.5 equiv). [d] Bu_4NI (5 mol%).

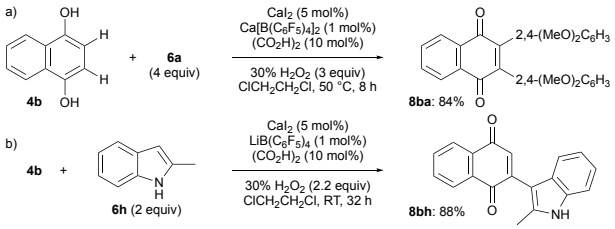
Unfortunately, cross-coupling of two different arenols or arenols with arenes failed due to preferential homocoupling or other unidentified side reactions. This issue will be a future challenge, and we were next interested in the tandem oxidation/cross-coupling of hydroquinones **4** with electron-rich arenes **6** to arylquinones **8** (Scheme 1c). Arylquinone skeletons are useful molecular structures in biologically active compounds and functional organic materials.[17] Conventionally, these compounds are synthesized by the transition metal-catalysed Minisci-type coupling of quinones with activated arenes (i.e., arylboronic acids or aryldiazonium salts)[18] or acid-catalysed 1,4-addition of electron-rich arenes to quinones followed by oxidation (**5** to **7** to **8**).[19] Recently, hypervalent iodine compounds were also used as a stoichiometric oxidant.[20] On the other hand, to the best of our knowledge, little is known about the tandem oxidative cross-coupling of hydroquinones (**4** to **8**), which relies on transition metal catalysis.[21]

Previously, we reported a highly efficient and selective Baeyer–Villiger oxidation using aqueous hydrogen peroxide as an oxidant.[13] The use of highly lipophilic borate salts such as $LiB(C_6F_5)_4$ or $Ca[B(C_6F_5)_4]_2$ with oxalic acid to generate Lewis-acid assisted Brønsted acid (LBA) catalysts[22] showed excellent activities under aqueous conditions. We envisioned that these lipophilic LBA catalysts might be used to mediate the 1,4-addition step of the tandem oxidation/cross-coupling of hydroquinones with electron-rich arenes under the present aqueous oxidative conditions.

We examined the hypoiodite/LBA-co-catalysed tandem oxidation/cross-coupling of 1,2-dihydroxynaphthalene (**4a**) with two equivalents of 1,3-dimethoxybenzene (**6a**) in dichloroethane as a less polar organic solvent required for lipophilic LBA catalysis under aqueous conditions[13] (Scheme 5a). Commercially available $LiB(C_6F_5)_4$ was used as a Lewis acid catalyst. The use of CaI_2 as an iodide catalyst gave superior results and desired arylquinone **8aa** was obtained in 80% yield (Scheme 5a, entry 1 versus entry 2). Notably, no reaction was observed in the absence of iodide catalyst, and only 1,2-naphthoquinone (**5a**) was obtained in the absence of LBA catalyst (Scheme 5a, entries 3 and 4). These results indicated that hypoiodite and LBA catalysis are required for the oxidation and 1,4-addition steps, respectively. Several electron-rich arenes **6b**–**g** were then examined as coupling partners with **4a** to give the corresponding arylquinones **8ab**–**ag** in moderate to high yield (Scheme 5b, for unsuccessful examples see Scheme S1, ESI^+). While no regioselectivity was observed for the reaction of 3-methoxytoluene (**6f**), oxidative coupling with 1-naphthol (**6g**) afforded two separable regiomers **8ag** and **8ag'** with reasonable regioselectivity.



Scheme 5 Tandem oxidation/cross coupling of **4a** with arenes **6a**–**6g** to arylquinones **8aa**–**8ag**. For details, see Table S3, ESI^+.

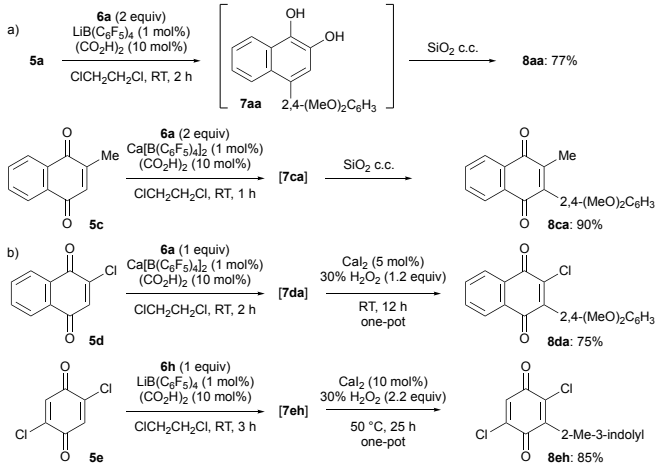


Scheme 6 Tandem oxidative coupling of **4b** with arenes **6**.

Tandem oxidation/cross-coupling of 1,4-dihydroxynaphthalene (**4b**) with **6a** afforded a mixture of mono- and di-arylquinones (ESI^+). 2,3-Diarylquinone **8ba** could be selectively obtained in 84% yield by using four equivalents of **6a** in the presence of $Ca[B(C_6F_5)_4]_2$ as a Lewis acid catalyst (Scheme 6a). However, selective synthesis of monoarylquinone failed under these conditions since the second 1,4-addition was found to proceed even with the lower amount of **6a** used (ESI^+). On the other hand, oxidative coupling with 2-methyl indole **6h** gave the corresponding mono coupling product **8bh** selectively in 88% yield, probably by suppressing the second 1,4-addition by a sterically bulkier indolyl group (Scheme 6b).

We finally examined the reaction of quinones **5** with electron-rich arenes **6**. LBA-catalysed 1,4-addition of **6a** to 1,2- and 1,4-naphthoquinones **5a** and **5c** gave the corresponding aryl hydroquinones **7aa** and **7ca**, which were converted to the

corresponding arylquinones **8aa** and **8ca** by air oxidation during column chromatography on silica-gel (Scheme 7a). On the other hand, hypoiodite catalysis was required for oxidation of the electron-withdrawing group-substituted hydroquinones **7da** and **7ea**, which were obtained from coupling of the corresponding 1,4-quinones **5d** and **5e** with arenes **6a** and **6e**, respectively (Scheme 7b). Notably, no reaction was observed in the absence of either Li salt or oxalic acid, suggesting that the use of both was crucial to generate LBA as an active acid catalyst[13] for 1,4-addition (Tables S4 and S5, ESI†).



Scheme 7 Tandem reaction of quinones **5** with arenes **6**.

In conclusion, we achieved the hypoiodite-catalysed chemoselective oxidative C–C homocoupling of electron-rich arenols using aqueous hydrogen peroxide as an oxidant under mild conditions. The corresponding biarenols or their over-oxidation products, biquinones, were obtained selectively in good to excellent yield, depending on the oxidizing susceptibility of arenol substrates and biarenol products. In addition, by combining hypoiodite oxidation catalysis with lipophilic LBA acid catalysis, we achieved the first transition metal-free protocol for the tandem oxidation/cross-coupling reaction of hydroquinones with electron-rich arenes. These results highlight the substantial scope of hypoiodite/acid co-catalysis for use in oxidative coupling reactions.

Financial support for this project was provided by JSPS.KAKENHI [15H05755 (to K.I.), 25620078 and 18H01973 (to M.U.)].

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) H. Laatcsch, *Liebigs Ann. Chem.*, 1980, **4**, 1321; (b) A. K. Jen, Y. Liu, Q. S. Hu and L. Pu, *Appl. Phys. Lett.*, 1999, **75**, 3745; (c) K. Dodou, *Expert Opin. Investig. Drugs*, 2005, **14**, 1419.

2 Selected recent reviews: (a) G. Bringmann, T. Gulder, T. A. M. Gulder and M. Breuning, *Chem. Rev.*, 2011, **111**, 563; (b) M. Grzybowski, B. Sadowski, H. Butenschön and D. T. Gryko, *Angew. Chem. Int. Ed.*, 2020, **59**, 2998.

3 Selected examples: (a) X. Li, J. Yang and M. C. Kozlowski, *Org. Lett.*, 2001, **3**, 1137; (b) T. Takeya, H. Doi, T. Ogata, I. Okamoto and E. Kotani, *Tetrahedron*, 2004, **60**, 9049; (c) B. C. Maiti, O. C. Musgrave, D. Skoyles, *Tetrahedron*, 2005, **61**, 6568; (d) Q.-X. Guo, Z.-J. Wu, Z.-B. Luo, Q.-Z. Liu, J.-L. Ye, S.-W. Luo, L.-F. Cun and L.-Z. Gong, *J. Am. Chem. Soc.*, 2007, **129**, 13927; (e) H. Egami, K. Matsumoto, T. Oguma, T. Kunisu and T. Katsuki, *J. Am. Chem. Soc.*, 2010, **132**, 13633; (f) K. V. N. Esguerra, Y. Fall, L. Petitjean, J. P. Lumb, *J. Am. Chem. Soc.* 2014, **136**, 7662; (g) H. Shalit, A. Libman and D. Pappo, *J. Am. Chem. Soc.*, 2017, **139**, 13404; (h) T. Horibe, K. Nakagawa, T. Hazeyama, K. Takeda, K. Ishihara, *Chem. Commun.*, 2019, **55**, 13677.

4 Using NaOCl: R. Neelamegam, M. T. Palatnik, J. Fraser-Rini, M. Slifstein, A. Abi-Dargham and B. Easwaramoorthy, *Tetrahedron Lett.*, 2010, **51**, 2497.

5 Using $K_2S_2O_8$: N. Y. More and M. Jeganmohan, *Chem. Commun.*, 2017, **53**, 9616.

6 Selected examples using quinones: (a) T. Takeya, H. Kondo, T. Otsuka, H. Doi, I. Okamoto and E. Kotani, *Chem. Pharm. Bull.*, 2005, **53**, 199; (b) H. Kondo, T. Otsuka, K. Tomita, I. Okamoto, O. Tamura and T. Takeya, *Org. Lett.*, 2007, **9**, 2807.

7 Selected examples using hypervalent organoiodine reagents: (a) S. K. R. Parumala and R. K. Peddinti, *Org. Lett.*, 2013, **15**, 3546; (b) K. Morimoto, K. Sakamoto, Y. Ohnishi, T. Miyamoto, M. Ito, T. Dohi and Y. Kita *Chem. Eur. J.*, 2013, **19**, 8726.

8 A recent review: B. Gleede, M. Selt, R. Franke and S. R. Waldvogel, *Chem. Eur. J.*, 2021, **27**, 8252.

9 (a) M. Ito, H. Kubo, I. Itani, K. Morimoto, T. Dohi and Y. Kita, *J. Am. Chem. Soc.*, 2013, **135**, 14078; (b) K. Morimoto, K. Sakamoto, T. Ohshika, T. Dohi and Y. Kita, *Angew. Chem. Int. Ed.*, 2016, **55**, 3652.

10 (a) M. Uyanik, H. Okamoto, T. Yasui and K. Ishihara, *Science*, 2010, **328**, 1376; (b) M. Uyanik, H. Hayashi and K. Ishihara, *Science*, 2014, **345**, 291.

11 Selected reviews: (a) M. Uyanik and K. Ishihara, *ChemCatChem*, 2012, **4**, 177; (b) P. Finkbeiner and B. J. Nachtsheim, *Synthesis*, 2013, **45**, 979; (c) R. Chen, J. Chen, J. Zhang and X. Wan, *Chem. Rec.*, 2018, **18**, 1292.

12 (a) M. Uyanik, N. Sasakura, E. Kaneko, K. Ohori and K. Ishihara, *Chem. Lett.*, 2015, **44**, 179; (b) M. Uyanik, T. Kato, N. Sahara, O. Katade and K. Ishihara, *ACS Catal.*, 2019, **9**, 11619; (c) M. Uyanik, K. Nishioka, R. Kondo and K. Ishihara, *Nat. Chem.*, 2020, **12**, 353.

13 M. Uyanik, D. Nakashima and K. Ishihara, *Angew. Chem. Int., Ed.*, 2012, **51**, 9093.

14 F. R. Hewgill, B. La Greca, F. Legge and P. E. Roga, *J. Chem. Soc. Perkin Trans. 1*, 1983, 131.

15 F. Russig, *J. Prakt. Chem.*, 1900, **62**, 30.

16 K. Hirakawa, E. Ogiue, J. Motoyoshiya and M. Yajima, *Phytochemistry*, 1986, **25**, 1494.

17 R. H. Thomson, *Naturally Occurring Quinones IV*; Blackie Academic: London, 1997.

18 Y. Fujiwara, V. Domingo, I. B. Seiple, R. Ginatassio, M. D. Be and P. S. Baran, *J. Am. Chem. Soc.*, 2012, **133**, 3292.

19 Selected examples: (a) M. C. Pirrung, Y. Liu, L. Deng, D. K. Halstead, Z. Li, J. F. May, M. Wedel, D. A. Austin, G. Webster, *J. Am. Chem. Soc.*, 2005, **127**, 4609; (b) C. Yu and F. W. Patureau, *Angew. Chem. Int. Ed.*, 2019, **58**, 18530; (c) Y. H. Chen, H. H. Li, X. Zhang, S. H. Xiang, S. Li and B. Tan, *Angew. Chem. Int. Ed.*, 2020, **59**, 11374.

20 S. Sharma, S. K. R. Parumala and R. K. Peddinti, *J. Org. Chem.*, 2017, **82**, 9367.

21 (a) S. Zhang, F. Song, D. Zhao and J. You, *Chem. Commun.*, 2013, **49**, 4558; (b) J. Guo, Y.-W. Xu, K. Li, L.-M. Xiao, S. Chen, K. Wu, X.-D. Chen, Y.-Z. Fan, J.-M. Liu and C.-Y. Su, *Angew. Chem. Int. Ed.*, 2017, **56**, 3852.

22 H. Yamamoto and K. Futatsugi, *Angew. Chem. Int. Ed.*, 2005, **44**, 1924.