A *para*-to-*meta* Isomerization of Phenols

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Phenols are a common functional group of many important molecules, including the amino acid tyrosine and its many derivatives, secondary metabolites from across the tree of life, and a plethora of industrial chemicals, including many that are essential to pharmaceutical, agrochemical and materials industries. Phenols are defined by an aromatic ring with a hydroxy substituent (-OH group), whose properties are intimately linked to neighbouring substituents. Phenol isomers localize electron density differently, have different dipoles, acidities, redox potentials and abilities to engage in hydrogen bonding or π-interactions. The resulting substituent effect could be strategic to explore as a 'late-stage' or 'peripheral' (*J. Med. Chem.* **2024**, *67*, 11459–11466) modification, but a phenol isomerization faces a number of formidable challenges (Figure 1a). These include the need to both break and reform strong bonds with high chemo- and regioselectivity, often without a clear thermodynamic bias for a given isomer. "There are only two related examples in which the substituents of a phenol, namely substituents other than the -OH group, were isomerized, but both methods required forcing conditions and exhibited limited scope (*J. Org. Chem.* **1968**, *33*, 3415–3418; *Tetrahedron Lett.* **1982**, *23*, 1673–1676)," explained Professor Jean-Philip Lumb, from McGill University (Canada).

To bring about a chemo- and regioselective isomerization of phenols, Professor Lumb, together with PhD student Simon Edelmann, capitalized on the intermediacy of an *ortho*-quinone. Professor Lumb told SYNFORM: "An electrophilic and redox-active oxidation product of phenols has been a topic of study in our group for a number of years (*Angew. Chem. Int. Ed.* **2014**, *53*, 5877–5881; *J. Am. Chem. Soc.* **2014**, *136*, 7662–7668). *ortho*-Quinones can be accessed from phenols by *ortho*-oxygenation under a variety of conditions, including those of Pettus and co-workers (*Org. Lett.* **2002**, *4*, 285–288) using 2-iodoxybenzoic acid (IBX) (Scheme 1a). For the purposes of a 1,2-isomerization, oxygenation introduces the requisite oxygen atom at C2 with complete regiocontrol, and also differentiates the oxygen atoms at C1 and C2 of the quinone by virtue of substituent effects. What remains is a method for the selective reductive deoxygenation of an *ortho*-quinone **2** that would provide *meta*-phenol **3** to complete the isomerization form *para*-phenol **1** (Scheme 1a)."

According to Professor Lumb, while *ortho*-quinones are relatively uncommon intermediates in synthetic methodologies, they can be versatile coupling partners with a variety of nucleophiles, including with amines (*ACS Catal.* **2017**, *7*, 3477–3482; *Chem. Eur. J.* **2017**, *23*, 8596–8600; *Chem* **2017**, *2*, 533–549). "This precedent led us to investigate hydrazine-based reagents for the reductive deoxygenation of **2**, following a Wolff–Kischner like mechanism," explained Professor Lumb. He continued: "Here, a note regarding reagent selection is merited. Whereas typical hydrazine-based reductants are relatively electron rich, a suitably deactivated reagent was required for condensation with *ortho*-quinone **2** to avoid undesired reduction to either semi-quinone or catechol oxidation states. Promiscuous redox is a perennial challenge when working with *ortho*-quinones, and a likely reason they are not more widely utilized. Nevertheless, we found that commercially available sulfonyl hydrazide **8** (TPSH), possessing a 2,4,6-triisopropyl arene, was ideally suited to react with *ortho*-quinone **2**, affording diazoquinone **6** following a cascade of condensation and α-elimination (see **4** in Scheme 1b). The selection of TPSH reflects the numerous elements of reactivity

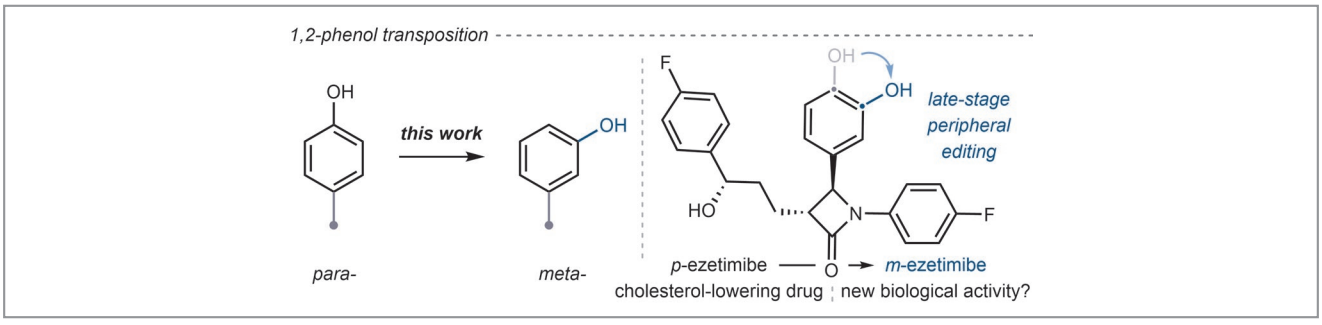

Figure 1 Transposition of *para*-phenols into *meta*-phenols for late-stage peripheral editing of bio-active molecules

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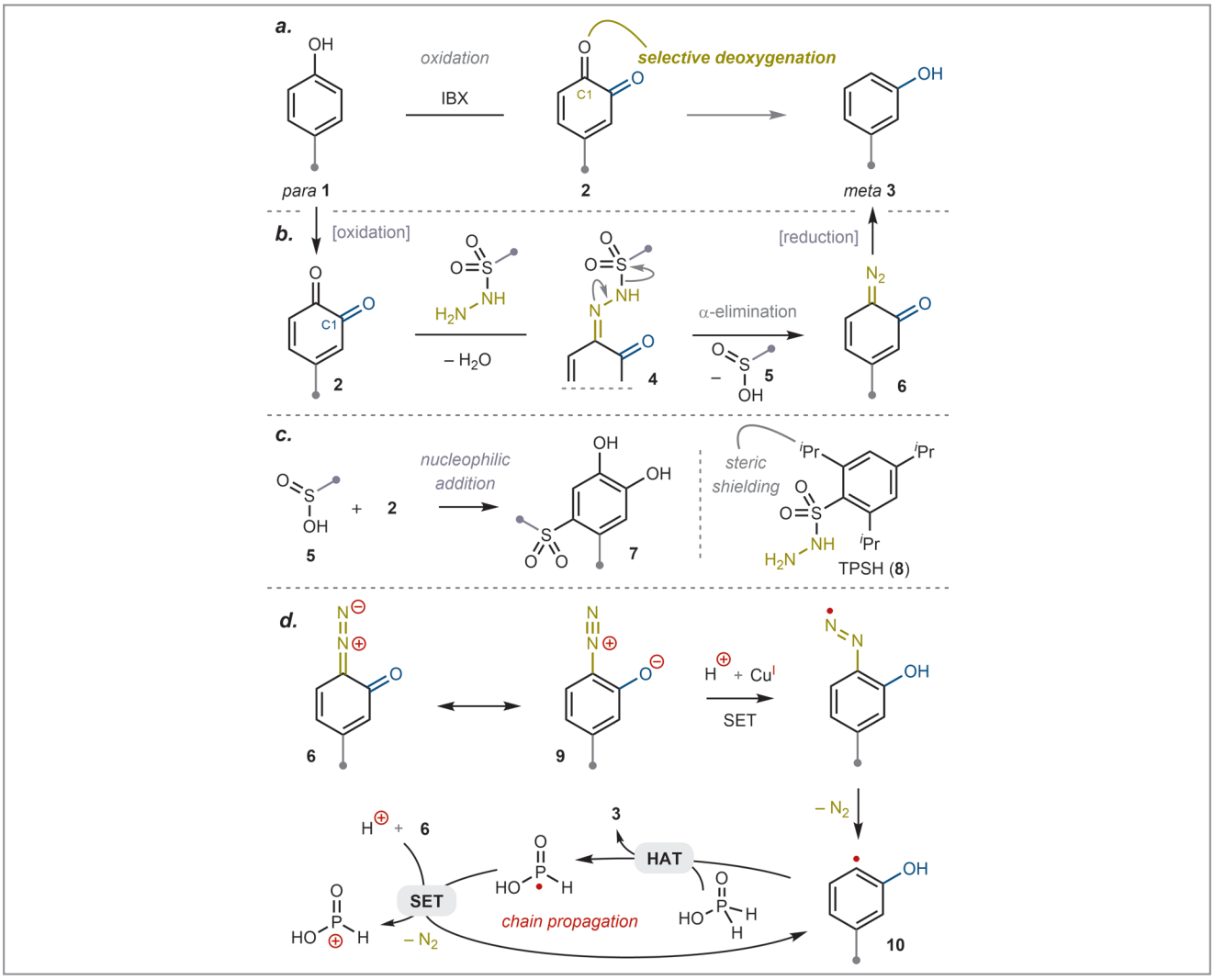


Scheme 1 (a) and (b) Overall strategy for the isomerization. (c) Problematic addition of the sulfinic acid byproduct. (d) Proposed mechanism for reduction of the diazoquinone.

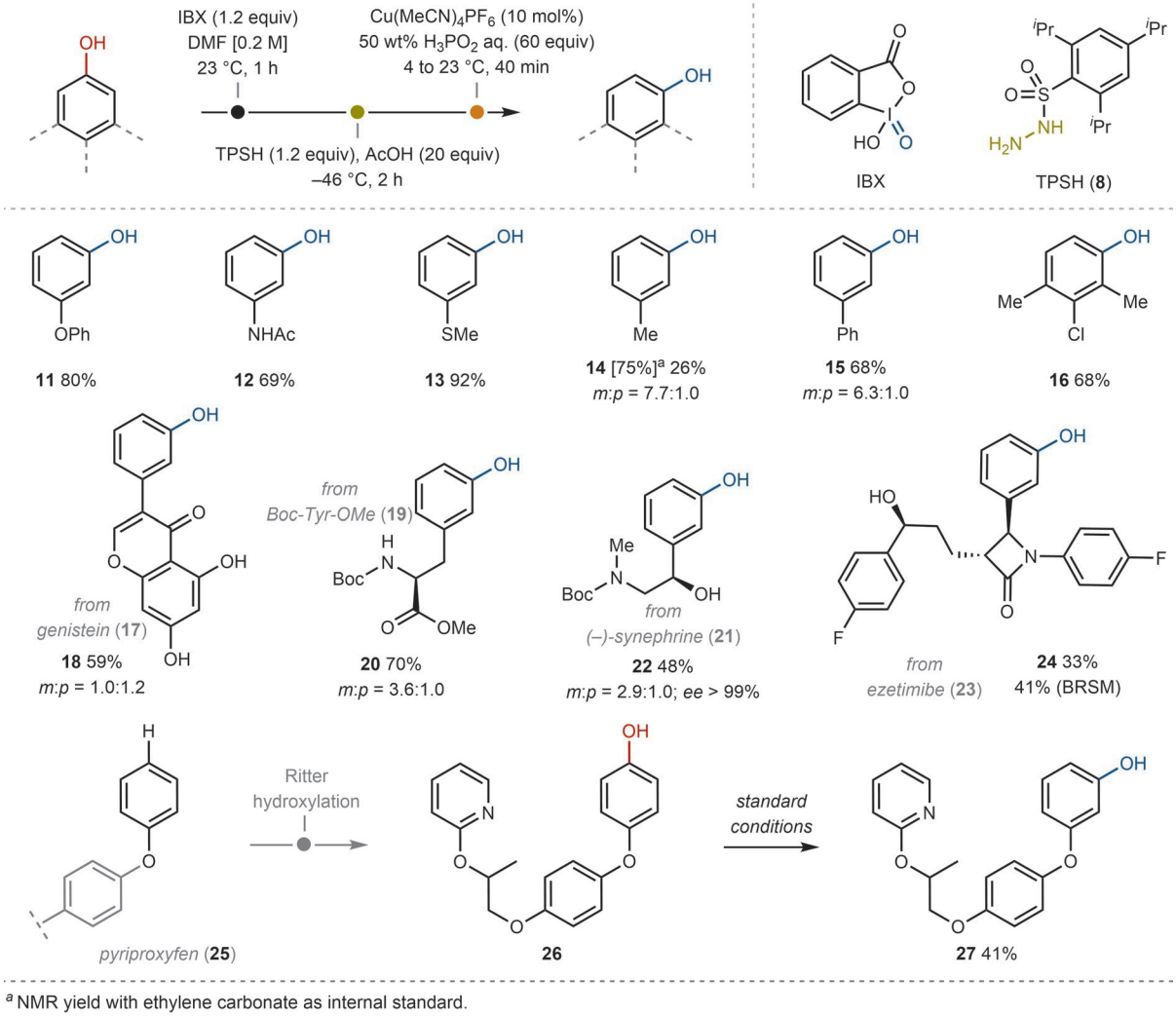
that needed to be balanced, including selectivity for condensation over electron transfer, regioselectivity for condensation at C1 over C2, the rate of α-elimination to ensure a one-pot protocol, and finally, the reactivity of sulfinic acid **5** that is formed as a byproduct. For less sterically demanding derivatives of TPSH, we observed competitive conjugate addition to *ortho*-quinone **2**, leading to catechol **7** as an undesirable addition product (Scheme 1c)."

Finally, to convert diazoquinone **6** into *meta*-phenol **3**, the authors explored classical conditions for the reduction of diazonium salts, recognizing their similarities to the zwitterionic resonance structure of **9**. "We found that a combination of hypophosphorous acid (H_3PO_2) and a Cu(I) salt effected chemoselective reduction, drawing inspiration from Kornblum (*J. Am. Chem. Soc.* **1950**, *72*, 3013–3021)," remarked Professor Lumb, adding: "We suspect that this process involves a radical-chain mechanism that is initiated by Cu(I) and that leads to the liberation of N_2 and an aryl radical **10**. Hydrogen atom transfer (HAT) with H_3PO_2 would then propagate the radical chain, while providing product **3** (Scheme 1d)."

As a one-pot, sequential process, in which the reaction mixture is progressively transferred to reagents by cannula additions, the isomerization exhibits good functional group tolerance and generally affords high yields. Heteroatom substituents, including oxygen, nitrogen and sulfur (**11**–**13**) are particularly effective at directing the isomerization to afford

single regioisomers, but even relatively simple aliphatic substituents, such as methyl (**14**), are tolerated and provide synthetically useful ratios of products (Scheme 2). "We illustrated the versatility of the reaction on natural products, including genistein (**17**) and tyrosine derivative **19**, to provide *meta*-isomers **18** and **20** in short order from commercially available starting materials," said Professor Lumb. He went on: "Finally, we showed the utility of our method in the late-stage diversification of (–)-synephrine (**21**) and ezetimibe (**23**), along with the agrochemical pyriproxyfen (**25**), to provide isomers that would otherwise be difficult to prepare from commercial sources (Scheme 2)."

In summary, the authors have developed a method to isomerize phenols that should facilitate the synthesis of isomers which could otherwise be difficult or costly to prepare. "Generally speaking, *meta*-substituted phenols are more difficult to make and less abundant than their *para*-isomers because of the well-known directing effects of phenols in most bond-forming reactions," said Professor Lumb, who concluded: "This new tool could benefit synthetic, medicinal and materials scientists by facilitating the diversification of readily available feedstocks, to explore a substituent effect that should have a dramatic impact on properties and thus performance. Related methods of scaffold editing have gained



[a] NMR yield with ethylene carbonate as internal standard.

Scheme 2 Selected examples of reaction scope

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recent attention (*Nat. Synth.* **2022**, *1*, 352–364), particularly from medicinal chemists, as they create new opportunities to diversify chemical space. We see many opportunities to apply a phenol isomerization to this objective."

About the authors

S. Edelmann

Simon Edelmann obtained his B.Sc. at the University of British Columbia Okanagan, Canada (2019) where he worked on the synthesis of fluorescent dyes and kainic acid analogues for the study of neuroreceptors under the guidance of Prof. Frederic Menard. Simon joined the Lumb group as a PhD student in 2019 and is working on developing methods to better utilize *ortho*-quinones in organic synthesis.

Prof. J-P Lumb

Jean-Philip Lumb is an Associate Professor of Chemistry at McGill University (Canada). He obtained his Ph.D. from the University of California, Berkeley (USA) in 2008 working with Dirk Trauner before completing a postdoctoral fellowship at Stanford University (USA) with Barry Trost. His group is interested in oxidation chemistry, and often applies the tactics of biomimicry and catalysis to facilitate the synthesis of complex organic molecules. In 2019, Professor Lumb was awarded the Keith Fagnou Award from the Canadian Chemical Society, and in 2023, he received the X–Chem Research Excellence Award, also from the Canadian Chemical Society.

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