Title: A *para*- to *meta*-isomerization of phenols

Authors: Simon Edelmann[1], Jean-Philip Lumb[1]*

Affiliations:

[1] Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, Quebec, H3A 0B8, Canada

*Corresponding author. Email: jean-philip.lumb@mcgill.ca

Abstract: Phenols and their derivatives are ubiquitous in nature and critically important industrial chemicals. Their properties are intimately linked to the relative substitution pattern of the aromatic ring, reflecting well-known electronic effects of the OH-group. Because of these *ortho*-, *para*-directing effects, *meta*-substituted phenols have historically been more difficult to synthesize, and an isomerization of the OH-group between isomers is unprecedented. Here, we describe a procedure to transpose phenols that hinges on a regioselective diazotization of the corresponding *ortho*-quinone. The procedure affords the *meta*-substituted phenol directly from its more common and accessible *para*-substituted isomer, and demonstrates good chemoselectivity that enables its application in late-stage settings. By changing the electronic effect of the OH group and its trajectory of hydrogen bonding, our transposition can be used to diversify natural products and existing chemical libraries, and potentially shorten the length and cost of producing underrepresented arene isomers.

Phenols are a common functional group of many natural products, biologically active molecules and materials.[1-3] In 2020 alone, ~60% of drugs approved by the Food and Drug Administration (FDA) contained a phenol or a phenolic ether, and their occurrence is similarly high amongst agrochemicals.[4] Naturally occurring phenols are also part of the human diet and are prevalent in fragrances and colorants. Their omnipresence reflects their diverse physical properties. Phenols are acidic and redox-active. They can both donate and accept hydrogen bonds and engage in π-interactions, making them critical participants in redox processes, acid-base chemistry and molecular recognition.[5-7] Phenols are also versatile synthetic intermediates from which a broad range of aromatic and non-aromatic products are made.[2,8-10] In all cases, the substitution pattern of a phenol has a pronounced impact on its physical properties, including the bond dissociation energy and acidity of the O–H group, and the redox properties of the attached aromatic ring.[11] These properties influence a molecule's ability to interact with its environment, including a biological target, creating an isomer effect that can have a pronounced influence on function. For example, the proteinogenic amino acid L-tyrosine is required for normal cellular function, whereas its *meta*-isomer is a toxin that inhibits cell growth and leads to miss-folded proteins.[12,13]

The synthesis of *meta*-substituted phenols is generally more challenging than the synthesis of *ortho*- or *para*-isomers, and frequently requires *de novo* synthesis of the aromatic ring or installation of the phenolic oxygen from a pre-existing functional group.[14-17] Strong π-donation of the oxygen lone pair localizes electron density to the *ortho*- and *para*-positions, leading to the well-known *ortho*-/*para*-directing effects of phenols in electrophilic aromatic substitution (EArS) reactions. Many examples of EArS are conducted on commodity scales and provide the primary supply of phenols for downstream industrial synthesis. Other phenol syntheses, including more modern C–H functionalization reactions, are also known, but with few exceptions,[19,20] these

provide *ortho*- or *para*-substituted products.[21-23] *Meta*-substituted phenols have remained more difficult to synthesize, and remain underrepresented in pharmaceutical libraries.[2,18]

A *para*- to *meta*-isomerization of phenols would be a welcome addition to the synthetic toolbox, but such a transformation faces several challenges (Fig. 1a). The C–O and C–H bonds of phenols are relatively strong (~110 kcal/mol), and for isomerization to occur selectively, they must be broken and reformed without a clear thermodynamic driving force to control regioselectivity. Similar challenges are faced by other arene isomerization reactions, including those of halogens, esters, or aryl groups,[24-26] which, remain underdeveloped as a general class of reactions. To our knowledge, the only two examples of isomerizing the substituents of a phenol are those of *tert*-butylphenols and brominated phenols,[27,28] but both require forcing conditions and afford mixtures of products. An isomerization that transposes the OH group under mild conditions would have potential applications in late-stage functionalization[29], where the *de novo* synthesis of a *meta*-isomer could be prohibitively lengthy or technically challenging. In synthetic planning, a synthesis of *meta*-substituted phenols from their more common *para*-isomers could shorten the synthesis of an intermediate, or it could be used to change the regiochemical bias of a phenol in EArS reactions.

For several years, our group has explored the dearomatization of phenols to *ortho*-quinones as a means of synthesizing polyfunctional arenes.[30-33] In the context of a phenol isomerization, we recognized that *ortho*-oxygenation accomplished two important tasks (Fig. 1b). It selectively installed the requisite oxygen atom at C2 (phenol numbering), and it differentiated the carbonyls at C1 and C2 of the resulting dienedione by the β-substituent at C4. For appropriate β-substituents, we speculated that nucleophilic attack would be disfavored at C2, thereby providing a means for selective deoxygenation of the carbonyl at C1. To implement this strategy, we needed to develop conditions for the challenging task of *ortho*-quinone deoxygenation that could avoid the promiscuous reactivity frequently observed for these redox-active, electrophilic species. Here, we report the development of these conditions, which have led to a *para*- to *meta*-isomerization of phenols compatible with complex substrates.

Results and Discussion: We began our reaction development by evaluating the regioselective diazotization of 4-benzyloxy-*ortho*-quinone (**2**), which we prepared from phenol **1** under the conditions of Pettus (Fig. 2a).[34] Thus, oxidation of **1** with a slight excess of 2-iodoxybenzoic acid (**3**, IBX) (1.2 equiv.) in dimethyl formamide (DMF) afforded a homogenous solution of **2** that was added to a solution of sulfonyl hydrazide (**5a-5c**) by cannula addition. Typical hydrazine-based reagents used to deoxygenate ketones or aldehydes under Wolff-Kishner conditions reduce *ortho*-quinones, setting off a deleterious series of redox reactions that lead to complex mixtures. After evaluating a range of electron-deficient hydrazides, we discovered that 2, 4, 6-triisopropylbenzenesulfonyl hydrazide (TPSH; **5c**) underwent selective condensation at C1 to provide diazoquinone **4** following α-elimination of sulfinic acid **8c** from hydrazone **7c** (see Inset Fig. 2a and Entry 3).[35] We highlight the selectivity of this process, since previous condensation reactions of *ortho*-quinones have been limited to sterically encumbered substrates. [30,32] Here, the steric and electronic properties of the sulfonyl hydrazide control several important factors. First is the rate of α-elimination from the hydrazone (**7a**-**7c**), which decreases for 4-methoxy-benezenesulfonyl hydrazide **5a**, such that imino-quinone **7a** remains intact under the conditions of condensation, and only affords diazoquinone **4** upon work-up (Entry 1). While the more electron-deficient 4-NO_2 derivative **5b** accelerates α-elimination, the resulting sulfinic acid **8b** undergoes an irreversible conjugate addition to *ortho*-quinone **2** that produces sulfone **6b** (Entry 2).[36] Ultimately, we found that the 2,4,6-triisopropylbenzene ring of **5c** balanced these two constraints

and facilitated α-elimination while disfavoring conjugate addition (Entry 3), to provide diazoquinone **4** in 81% yield, starting from phenol **1**.

Through the course of optimization studies, we discovered that the reaction pH and temperature had an important impact on the regioselectivity and yield of forming the diazoquinone (Fig. 2b). In the absence of acid, the reaction of hydrazide **5c** and 4-*tert*-butyl *ortho*-quinone **10** afforded a 4.0:1.0 mixture of isomeric diazoquinones **11a** and **11b** in a combined yield of only 44% (Entry 4). In the presence of trifluoracetic acid, the yield improved to 81%, but the regioselectivity decreased to 2.0:1.0 (Entry 5). Ultimately, we found that acetic acid improved both the yield and regioselectivity (Entry 6), and that by performing the condensation at −46 °C (Entry 7), we could obtain a 6.3:1.0 ratio of **11a** to **11b** in a combined yield of 94%.

To complete the formal isomerization, we needed conditions to reduce diazoquinone **11a** to 3-*tert*-butyl phenol (**12p** – see Table 1 for compound numbering) that would be compatible with the solvent and by-products of the first two steps. After surveying a range of conditions, we found that aqueous solutions of hypophosphorous acid (H_3PO_2) with catalytic amounts of tetrakis(acetonitrile)copper(I) hexafluorophosphate ($[(CH_3CN)_4Cu]PF_6$) (10 mol%) reduced the **11a/b** mixture to a 5.6:1.0 mixture of **12p** and **9**, in a combined yield of 97% (Entries 8-10). Mechanistically, we draw analogy to the reduction of aryl diazonium salts and believe that Cu(I) initiates a radical chain process by $1e^-$ reduction of the diazoquinone. Loss of dinitrogen (N_2) then affords an aryl radical that would evolve to the phenol by hydrogen atom transfer with H_3PO_2.[37] Based on these experiments, our optimized conditions for the *para*- to *meta*-isomerization of phenols consists of a sequential *ortho*-oxygenation, diazotization, and reduction, linked through a series of cannula transfers. In cases where the *meta*- and *para*-substituted phenols are separable, we report the yields of product based upon recovered starting material (BRSM); however, in cases where the phenols are currently inseparable, we report a combined yield of *meta*- and *para*-isomers, along with a ratio that reflects the regioselectivity of condensation and the relative efficiency of the diazoquinone reduction.

With these optimized conditions, we evaluated the scope of the process. Heteroatom substituents provided a strong electronic bias that led to generally high yields of the corresponding *meta*-substituted products as single regioisomers (Table 1). Methyl- **12a**, phenyl- **12b**, benzyl- **12c**, and allyl-ethers **12d** all performed well, although we noted a slight decrease in selectivity for the withdrawing pivalate ester **12e** that lead to small amounts of recovered starting material. These substrates demonstrated compatibility with a terminal olefin and activated C–H bonds that could be reactive towards quinones or aryl radicals. The isomerization of commercially available (*R*)-2-(hydroxyphenoxy)-propanoate afforded *meta*-isomer **12f** without erosion of enantiomeric excess (e.e.), and likewise, the isomerization of acetyl-protected β-arbutin proceeded smoothly to *meta*-isomer **12g** in 86% yield without epimerization at the anomeric carbon. Nitrogen substituents were also tolerated, and the isomerization of acetaminophen produced *meta*-isomer **12h** in 69% yield, while 2-pyrrolidinone **12i** and pyrrole **12j** returned their corresponding *meta*-isomers in yields of 76 and 85%, respectively. We did observe diminished yields for more basic nitrogen substituents, such as piperidine **12k**, but good reactivity was recovered for a thioether, as 4-(methylmercapto)phenol produced *meta*-isomer **12l** in 92% yield.

Aliphatic substituents presented several questions of chemoselectivity, including enolizable protons at the stage of the *ortho*-quinone that could lead to the formation of electrophilic *para*-quinone methides. The remote nature of the C4 position and the relatively modest electronic effects

of alkyl substituents also raised a question about their ability to control regioselectivity in the condensation. Nevertheless, we were pleased to observe good reactivity for 4-methyl-, ethyl- and isopropyl-phenols, which produced the corresponding *meta*-isomers **12m**-**12o** as inseparable mixtures with their *para*-isomers, in ratios of >7.0:1.0, and yields of 75, 85 and 88%, respectively. Likewise, 4-*tert*-butyl and 4-trityl-phenols underwent transposition in yields of 85 and 64%, albeit with slight decreases in regioselectivity (5.7:1.0 for **12p** and 1.5:1.0 for **12q**).

Next, we turned to substrates possessing pendant nucleophiles that could potentially react with the electrophilic *ortho*-quinone or diazoquinone intermediates (Table 1). Tethered oxygen and nitrogen nucleophiles are known to form 5-membered rings by a facile conjugate addition to *ortho*-quinones.[38,39] Nevertheless, the isomerization of phenols with either a 1° alcohol or 1° sulfonamide provided **12r** and **12s** in ratios of 5.7:1.0 and 1.7:1.0 favoring the *meta*-isomer, and yields of 72 and 50%, respectively. The isomerization of an acetanilide possessing a conformational bias towards cyclization was also successful,[40] and provided *meta*-isomer **12t** in 57% yield. Finally, the isomerization of a tetrahydroisoquinoline protected as its *tert*-butyl carbamate (Boc) yielded *meta*-isomer **12u** in a 5.3:1.0 ratio and 68% yield, demonstrating compatibility with a Boc protecting group. Substituents with C-sp^2 hybridization were also tolerated, and isomerization of 4-phenylphenol afforded a 68% yield of 3-phenyl phenol (**12v**) as a 6.3:1.0 mixture favouring the *meta*-isomer (Table 1). Likewise, isomerization of the natural product pterostilbene yielded *meta*-isomer **12w** as a 5.5:1.0 mixture of isomers in 70% yield, showing compatibility with the extended π-system of a stilbene.

In poly-substituted phenols, where there can be a combination of steric and electronic effects governing regioselectivity, we observed a consistent preference for condensation at the most sterically accessible position of the *ortho*-quinone (Table 1). For example, the isomerization of commercially available 3,5-dimethyl-4-chlorophenol led to 2,3,4-isomer **12x** in 68% yield, further demonstrating compatibility with a chlorine substituent that is activated for nucleophilic substitution at the stage of the *ortho*-quinone. In the case of fused aromatic systems, we observed isomerization towards the point of ring-fusion, such that 2-naphthol, 2-dibenzofuranol and *N*-protected-5-hydroxyindoles afforded **12y**-**12ab** as single regioisomers. We note that the reduction of these more substituted diazoquinones required heating to 60 °C, which may account for the decreased isolated yields.

To explore our isomerization in late-stage settings, we evaluated phenols for which the corresponding *meta*-isomer was either unknown or would require *de novo* synthesis (Fig. 3). For example, ezetimibe (**13**) is a commonly prescribed cholesterol-lowering pharmaceutical[41], but to the best of our knowledge, *meta*-ezetimibe (**14**) has not been reported, despite sharing many structural features with **13**. The preparation of **14** would require a *de novo* synthesis, likely comparable in length to the 8-steps needed to prepare **13** from *para*-hydroxybenzaldehyde,[42] and therefore, may have been overlooked or deprioritized as a viable candidate in the drug development process (Fig. 3a). Application of our isomerization directly on **13** provided **14** in serviceable yield, demonstrating chemoselectivity for isomerization in the presence of a β-lactam and an oxidatively sensitive 2° benzylic alcohol, creating an opportunity to explore the biological effects of the *para*- to *meta*-isomerization of a commonly used pharmaceutical. In certain cases, only the *para*-isomer of a naturally occurring phenol is available, requiring the de novo synthesis of the *meta*-isomer. For example, (*R*)-phenylephrine (**18**) is an α1-adrenergic receptor agonist that is synthesized in no less than 9 steps from acetophenone, including an asymmetric hydrogenation to install the 2° benzylic alcohol.[43] Its naturally occurring *para*-isomer (*R*)-synephrine (**15**) can be extracted from

citrus,[44] creating an opportunity to shorten the synthesis of **18** by applying our methodology. To this effect, we prepared and isomerized the corresponding Boc derivative (**16** to **17**) without erosion of e.e., further demonstrating chemoselectivity for a stereogenic 2° benzylic alcohol (Fig. 3b). Genistein (**19**) is a representative member of the flavone-family of natural products that display a range of biological activities, including as phytoestrogens. Interest in *meta*-isomer **20** as a potential cosmeceutical required the development of a 3-step *de novo* synthesis from **21** (Fig. 3c).[45] The successful isomerization of **19** into **18**, albeit with decreased regiocontrol, shortens the synthesis of the *meta*-isomer, and showcases notable chemoselectivity for phenolic isomerization in the presence of an unprotected resorcinol.[46] Finally, L-tyrosine and its derivatives are readily obtained from natural resources, but the relatively low natural abundance of *meta*-tyrosine requires its *de novo* synthesis, shown here in 4-steps from L-serine (**26**).[47] Application of our isomerization on commercially available Boc- (**22**) or Fmoc- (**23**) protected methyl esters of L-tyrosine afforded **24** and **25** in yields of 70 and 82%, respectively, in similar 4:1 ratios favoring the *meta*-isomers (Fig. 3d).

Because many late-stage functionalization reactions introduce phenols by EArS that are *ortho*- / *para*-selective, our isomerization creates an opportunity to extend these methods to the complimentary *meta*-isomer.[29] For example, Ritter's hydroxylation of the agrochemical pyriproxyfen (**27**)[23] is exceptionally selective for *para*-isomer **28**. Now, the corresponding *meta*-isomer **29** is available in 41% yield by using our isomerization, further demonstrating chemoselectivity with an electron-rich pyridine (Fig. 3e). In an alternative context, Stahl's synthesis of phenols by condensation of simple carbonyl compounds and aerobic oxidation is notable for providing *meta*-substitution patterns (Fig. 3f)[14]. Here, we use Stahl's method to prepare 3-phenyl-5-*tert*-butyl phenol (**30**), which we can then isomerize to a 2.4:1.0 mixture of isomers **31**/**32** in 58% yield. We attribute the slight preference for *ortho*-oxygenation of **30** at C2 over C6 to the steric effect of the *tert*-butyl substituent, and note that condensation is selective for C1 in both cases. Finally, 3-dihydrophenanthrol **33**, which is also prepared using Stahl's method, can now be used for the synthesis of sterically encumbered 4-phenanthrenols (e.g. **35**) by applying our previously reported conditions for the copper-catalyzed aerobic oxygenation/dehydrogenation of dihydrophenanthrenols.[48]

Conclusion: The discovery of a phenol isomerization creates new opportunities for the diversification of small molecules of pharmaceutical relevance. Moving forward, we see opportunities to apply these conditions on the tyrosine residues of increasingly complex substrates, including polypeptides or enzymes,[49] where a *para*- to *meta*-isomerization could have pronounced effects on function. Likewise, we anticipate opportunities to develop complexity generating transformations based upon the general principals of oxygenation and regioselective condensation, and believe that the synthesis of poly-substituted arenes, especially underrepresented isomers,[18] could be facilitated by the synthetic versatility of hydrazone and diazoquinone intermediates described herein.

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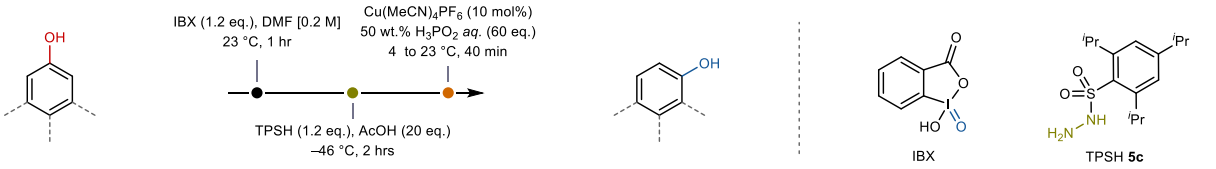
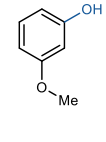
Author contributions: S.E. designed and conducted experiments, and collected and analyzed the data. J.-P.L. and S.E. conceptualized the project and wrote the manuscript. J.-P.L. supervised the research.

Competing interests: The other authors declare no competing interests.

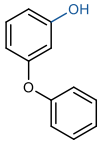
Table 1 | Scope of the 1,2-phenol transposition[a]



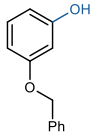
Heteroatom substitution



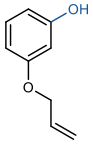
12a [73%][b] 38%



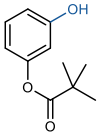
12b 80%



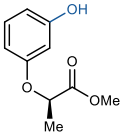
12c 71%



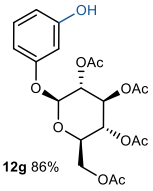
12d 72%



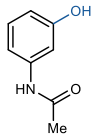
12e 67%
72% (BRSM)



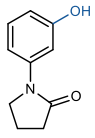
12f 97%
ee = >99%



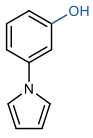
12g 86%



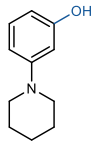
12h 69%



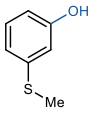
12i 76%



12j 85%

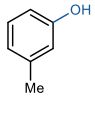


12k 20%[c]

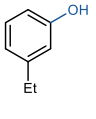


12l 92%

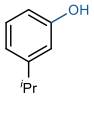
Alkyl and aryl substitution



12m [75%][b] 26%
m:*p* = 7.7:1.0



12n [85%][b] 57%
m:*p* = 7.7:1.0



12o [88%][b] 68%
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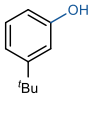
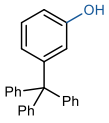
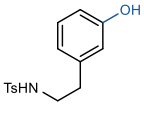


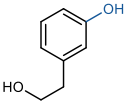
12p 87%
m:*p* = 5.7:1.0



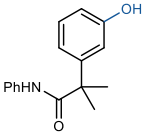
12q 64%[d]
m:*p* = 1.5:1.0



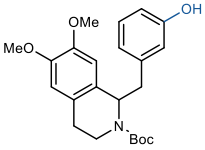
12r 72%
m:*p* = 5.7:1.0



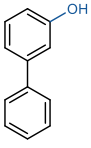
12s 50%
m:*p* = 1.7:1.0



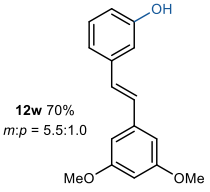
12t 57%
79% (BRSM)



12u 68%[c]
m:*p* = 5.3:1.0

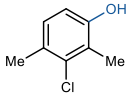


12v 68%
m:*p* = 6.3:1.0

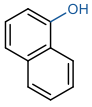


12w 70%
m:*p* = 5.5:1.0

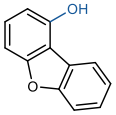
Polysubsituted substrates



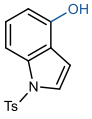
12x 68%



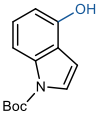
12y 27%[e] (62%)[f]



12z 25%[f]



12aa 23%[f]



12ab 54%[f]

[a]Standard Conditions: all reactions were carried out with the starting phenol (0.5 mmol), IBX (0.6 mmol) and DMF (2.5 mL) at room temperature for 1 hr, then cooled to –46 °C and added to TPSH (0.6 mmol), AcOH (10 mmol), and DMF (0.75 mL) for 2 hrs, then let warm to 4 °C and was added to $Cu(MeCN)_4PF_6$ (10 mol%), 50% wt. H_3PO_2 *aq.* (30 mmol) then stirred at room temperature over 40 min. [b]Due to the volatility of the product, yield was determined by ^{1}H-NMR using ethylene carbonate as an internal standard. [c]The reaction were conducted on a 0.2 mmol scale with respect to the starting phenol. [d]Addition to TPSH was conducted at 4 °C. [e]Reduction was conducted at 23 °C for 4 hrs. [f]Reduction was conducted at 60 °C for 40 min. BRSM, based on recovered starting material; Ac, acetyl; Ts, tosyl; Boc, *tert*-butyloxycarbonyl.

Fig. 1 | Challenges and development of a 1,2-phenol transposition. a, The *para* to *meta* isomerization of phenols is challenged by strong bonds and the lack of a clear thermodynamic driving force. **b,** This work employs *ortho*-oxygenation, regioselective diazotization and reductive aromatization to bring about a 1,2-transposition. IBX, 2-iodoxybenzoic acid; TPSH, 2, 4, 6-triisopropylbenzenesulfonyl hydrazide; AcOH, acetic acid.

Fig. 2 | Reaction development and optimization. **a,** Investigation of the condensation between sulfonyl hydrazides **5** and 4-benzyloxy *ortho*-quinone (**2**). **b,** Effects of pH and temperature on the condensation of sulfonyl hydrazide **5c** and 4-*tert*-butyl *ortho*-quinone (**10**). All reactions were conducted on a scale of 0.2 mmol according to the standard procedures described in the supporting information. [a]Yield determined by ^{1}H-NMR of reaction mixture using dimethyl terephthalate as an internal standard. [b]Yield determined by ^{1}H-NMR of reaction mixture using ethylene carbonate as an internal standard. [c]Yield determined by ^{1}H-NMR after 2 hours reaction time and 93% conversion of *ortho*-quinone (**10**). [d]Yield determined by ^{1}H-NMR using ethylene carbonate as an internal standard following work-up. DMF, dimethylformamide; TFA, trifluoroacetic acid.

Fig. 3 | Isomerization of complex substrates and complementarity with existing methodologies. a, Synthesis of *meta*-ezetimibe **b,** Streamlined synthesis of phenylephrine **c,** Isomerization of genistein **d,** Synthesis of *meta*-tyrosine **e,** Late-stage modification of pyriproxyfen. **f,** Extension of Stahl's phenol synthesis. [a]Standard Conditions: all reactions were carried out with the starting phenol (0.5 mmol), IBX (0.6 mmol) and DMF (2.5 mL) at room temperature for 1 hr, then cooled to –46 °C and added to TPSH (0.6 mmol), AcOH (10 mmol), and DMF (0.75 mL) for 2 hrs, then let warm to 4 °C and was added to $Cu(MeCN)_4PF_6$ (10 mol%), 50% wt. H_3PO_2 aq. (30 mmol) then stirred at room temperature over 40 min. If applicable, yields are reported for inseparable mixtures of regioisomers. [b]Conducted on 0.05 mmol scale with respect to **28**. [c]Reduction was conducted at 60 °C for 40 min. [d]Conducted on 0.2 mmol scale with respect to **34**. Fmoc, fluorenylmethyloxycarbonyl.

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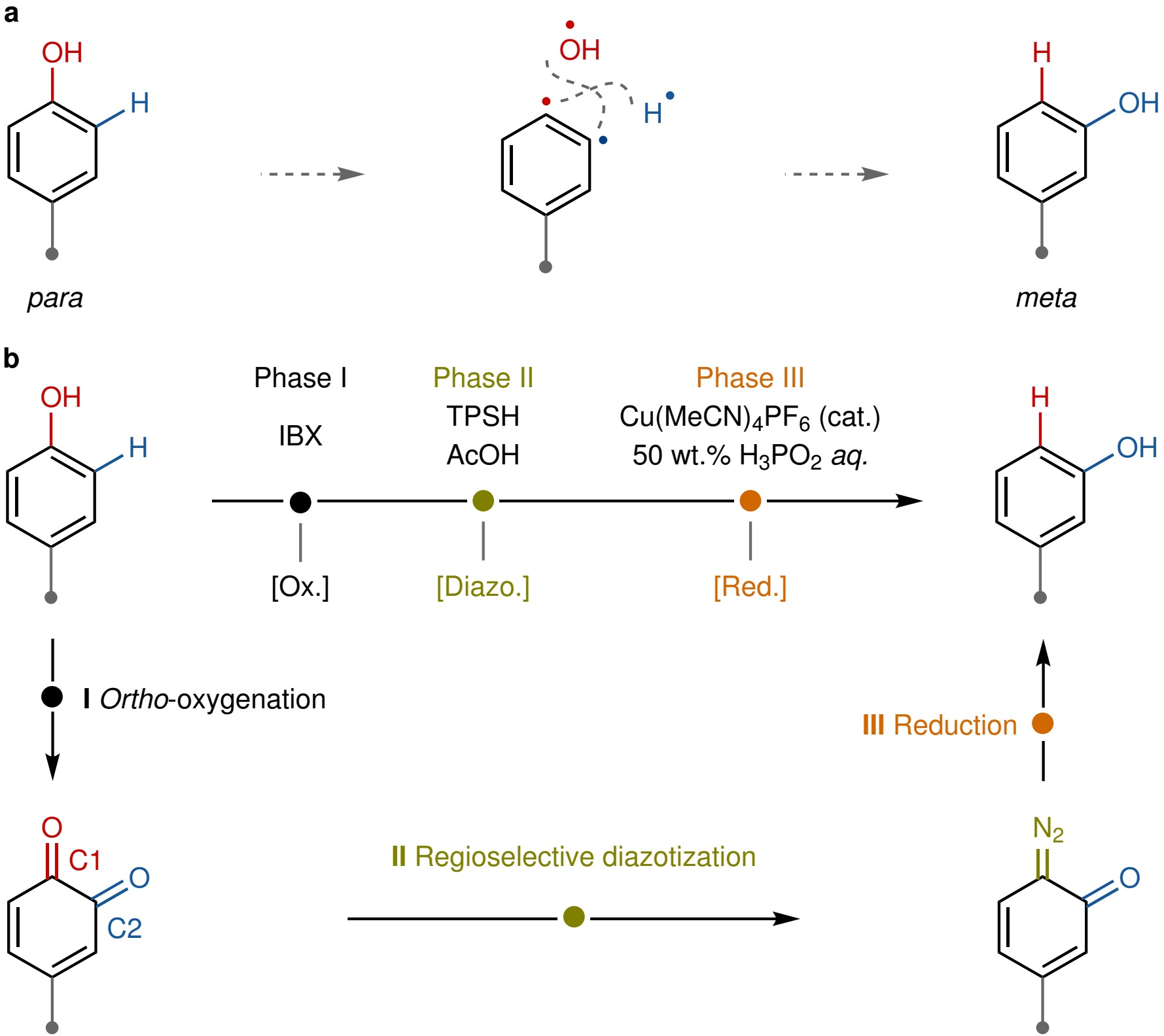
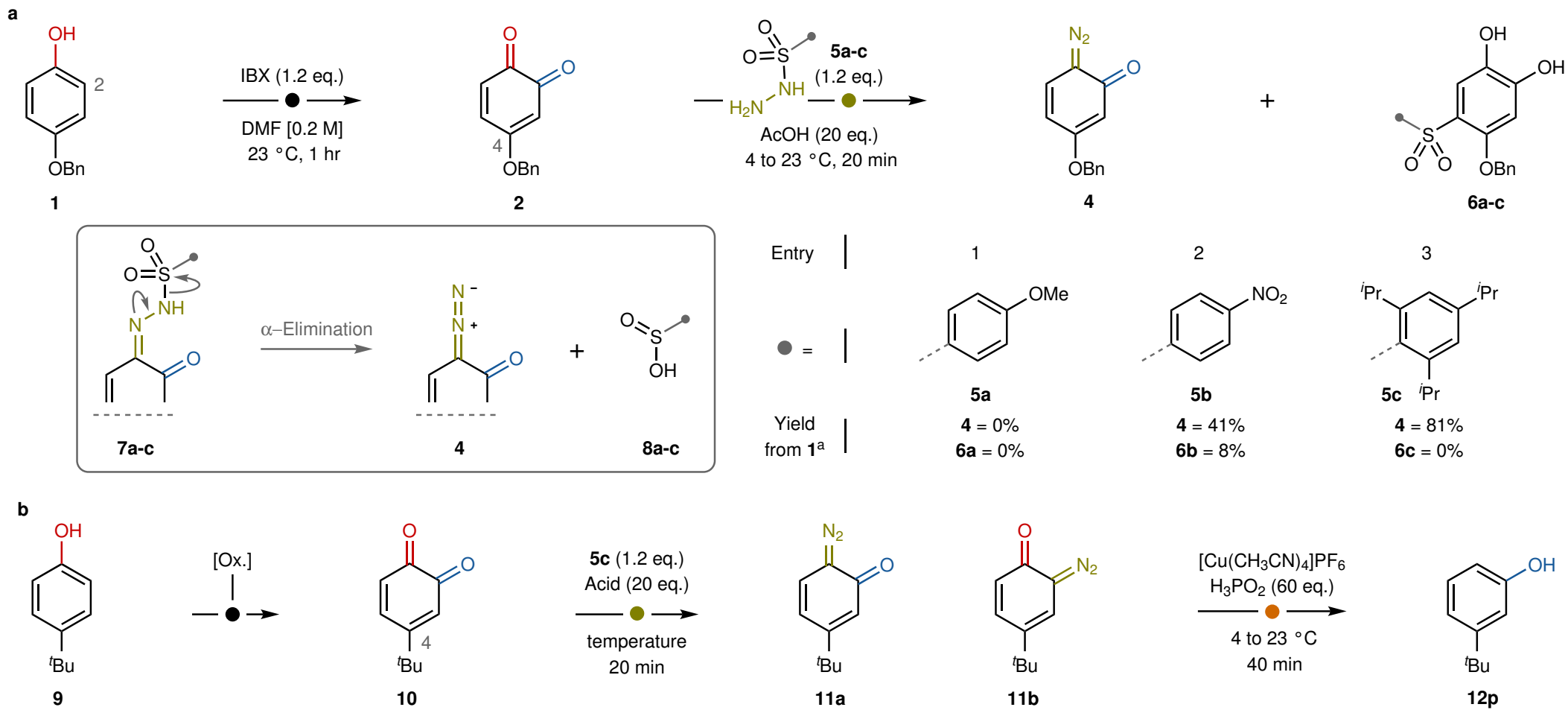
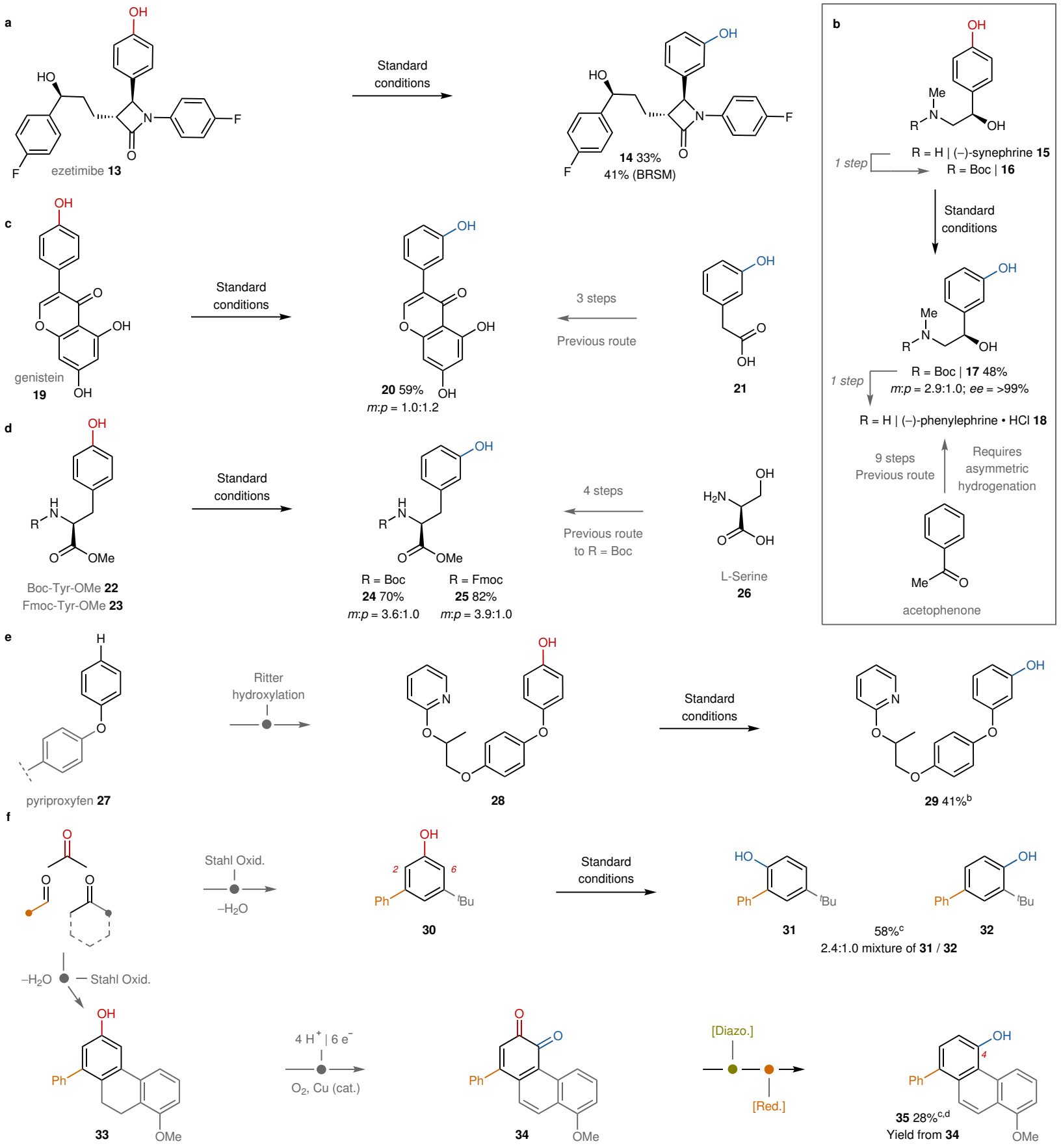
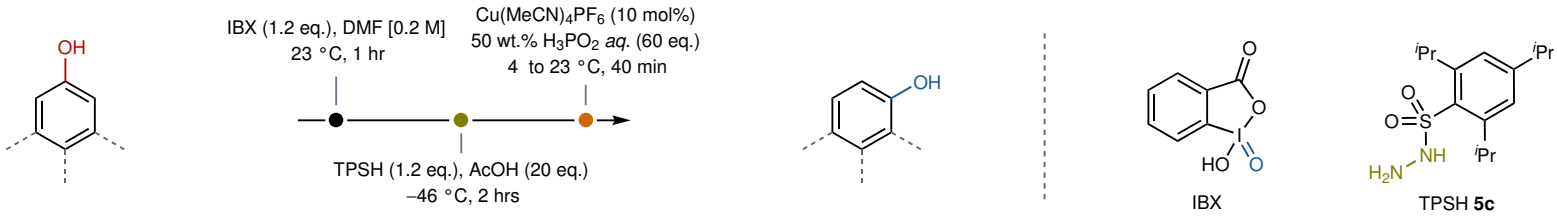
Methods: See the Supplementary Information for a detailed description of the methods.

Data Availability Statement: The data supporting the main findings of this study are available in the article, Supplementary Information and source data. Source data, including FIDs of all compounds, are available for download, free of charge, from the Open Science Framework (OSF) data repository at https://osf.io/e7q8n.

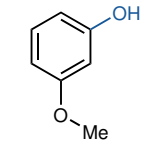

a
OH
H
para
OH
H
H
OH
meta
b
OH
H
Phase I
IBX
[Ox.]
Phase II
TPSH
AcOH
[Diazo.]
Phase III
Cu(MeCN)4PF6 (cat.)
50 wt.% H3PO2 aq.
[Red.]
H
OH
I Ortho-oxygenation
III Reduction
O
C1
O
C2
II Regioselective diazotization
N2
O


a
OH
2
OBn
1
IBX (1.2 eq.)
DMF [0.2 M]
23 °C, 1 hr
O
O
4
OBn
2
5a-c
(1.2 eq.)
AcOH (20 eq.)
4 to 23 °C, 20 min
N2
O
OBn
4
+
OH
OH
S
O
O
OBn
6a-c
α–Elimination
7a-c
4
8a-c
Entry
1
2
3
=
OMe
NO2
iPr
iPr
iPr
5a
5b
5c
Yield
from 1a
4 = 0%
6a = 0%
4 = 41%
6b = 8%
4 = 81%
6c = 0%
b
OH
tBu
9
[Ox.]
O
O
4
tBu
10
5c (1.2 eq.)
Acid (20 eq.)
temperature
20 min
N2
O
tBu
11a
O
N2
tBu
11b
[Cu(CH3CN)4]PF6
H3PO2 (60 eq.)
4 to 23 °C
40 min
OH
tBu
12p
Entry
4
5
6
7
Acid
N/A
TFA
AcOH
AcOH
Temperature
4 to 23 °C
4 to 23 °C
4 to 23 °C
–46 °C
[Red.]
Yield
from 9b
11a:11b = 4.0:1.0
11a+11b = 44%
11a:11b = 2.0:1.0
11a+11b = 81%
11a:11b = 3.7:1.0
11a+11b = 96%
11a:11b = 6.3:1.0c
11a+11b = 94%c
Entry
Cu
(mol%)
Yield
from 9d
Ratio
m : p
8
0
75%
5.6:1.0
9
5
86%
4.6:1.0
10
10
97%
5.6:1.0

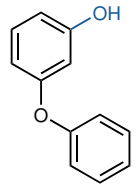

a
ezetimibe 13
Standard conditions
14 33%
41% (BRSM)
b
R = H | (–)-synephrine 15
1 step
R = Boc | 16
Standard conditions
R = Boc | 17 48%
m:p = 2.9:1.0; ee = >99%
1 step
R = H | (–)-phenylephrine • HCl 18
9 steps
Previous route
Requires asymmetric hydrogenation
acetophenone
c
genistein 19
Standard conditions
20 59%
m:p = 1.0:1.2
3 steps
Previous route
21
d
Boc-Tyr-OMe 22
Fmoc-Tyr-OMe 23
Standard conditions
R = Boc
24 70%
m:p = 3.6:1.0
R = Fmoc
25 82%
m:p = 3.9:1.0
4 steps
Previous route to R = Boc
L-Serine
26
e
pyriproxyfen 27
Ritter hydroxylation
28
Standard conditions
29 41%b
f
Stahl Oxid.
–H2O
30
Standard conditions
31
58%c
32
2.4:1.0 mixture of 31 / 32
–H2O
Stahl Oxid.
33
4 H+ | 6 e–
O2, Cu (cat.)
34
[Diazo.]
[Red.]
35 28%c,d
Yield from 34



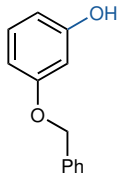
Heteroatom substitution



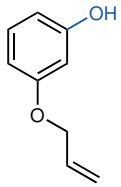
12a [73%][b] 38%



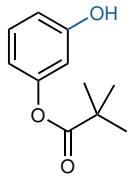
12b 80%



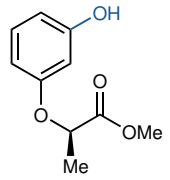
12c 71%



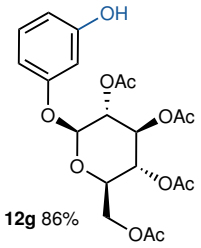
12d 72%



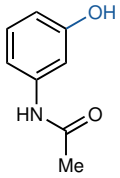
12e 67%
72% (BRSM)



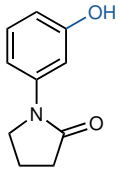
12f 97%
ee = >99%



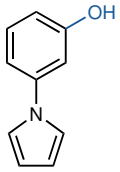
12g 86%



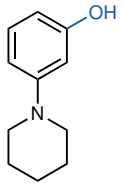
12h 69%



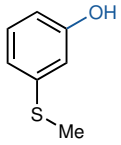
12i 76%



12j 85%

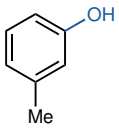


12k 20%[c]

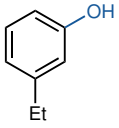


12l 92%

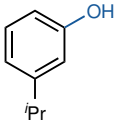
Alkyl and aryl substitution



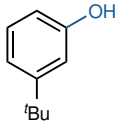
12m [75%][b] 26%
m:*p* = 7.7:1.0



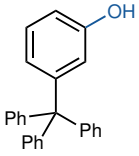
12n [85%][b] 57%
m:*p* = 7.7:1.0



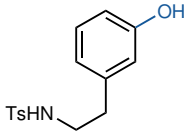
12o [88%][b] 68%
m:*p* = 7.7:1.0



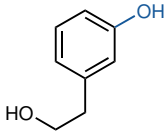
12p 87%
m:*p* = 5.7:1.0



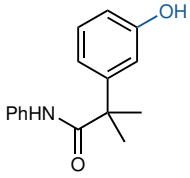
12q 64%[d]
m:*p* = 1.5:1.0



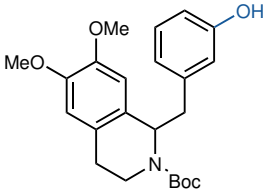
12r 72%
m:*p* = 5.7:1.0



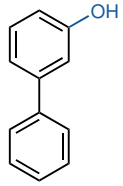
12s 50%
m:*p* = 1.7:1.0



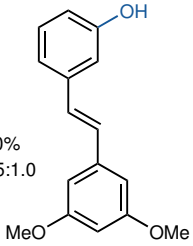
12t 57%
79% (BRSM)



12u 68%[c]
m:*p* = 5.3:1.0

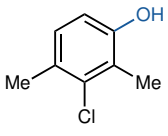


12v 68%
m:*p* = 6.3:1.0

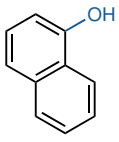


12w 70%
m:*p* = 5.5:1.0

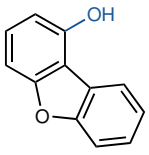
Polysubsituted substrates



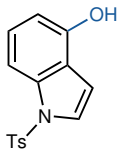
12x 68%



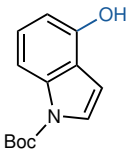
12y 27%[e] (62%)[f]



12z 25%[f]

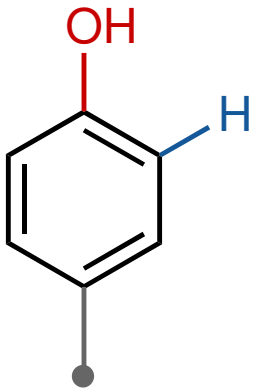


12aa 23%[f]



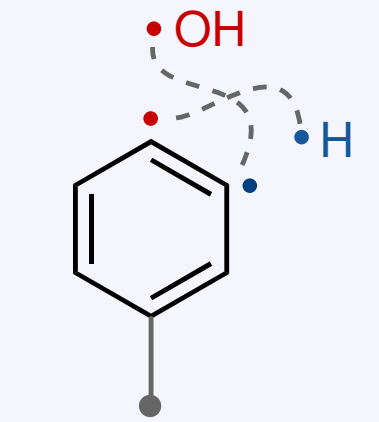
12ab 54%[f]

[a]Standard Conditions: all reactions were carried out with the starting phenol (0.5 mmol), IBX (0.6 mmol) and DMF (2.5 mL) at room temperature for 1 hr, then cooled to –46 °C and added to TPSH (0.6 mmol), AcOH (10 mmol), and DMF (0.75 mL) for 2 hrs, then let warm to 4 °C and was added to $Cu(MeCN)_4PF_6$ (10 mol%), 50% wt. H_3PO_2 *aq.* (30 mmol) then stirred at room temperature over 40 min. [b]Due to the volatility of the product, yield was determined by ^{1}H-NMR using ethylene carbonate as an internal standard. [c]The reaction were conducted on a 0.2 mmol scale with respect to the starting phenol. [d]Addition to TPSH was conducted at 4 °C. [e]Reduction was conducted at 23 °C for 4 hrs. [f]Reduction was conducted at 60 °C for 40 min. BRSM, based on recovered starting material; Ac, acetyl; Ts, tosyl; Boc, *tert*-butyloxycarbonyl.



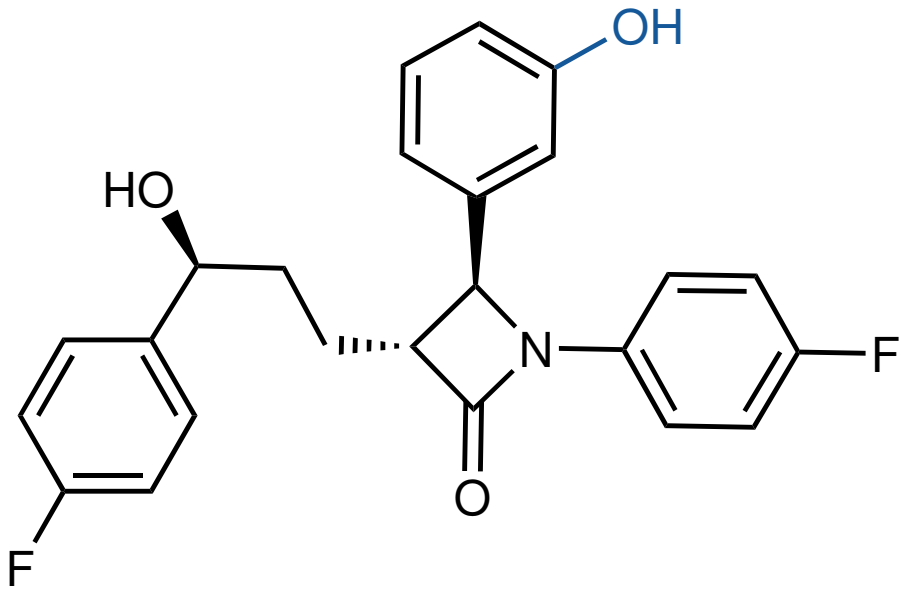
para

- naturally occurring
- commercially available
- readily synthesized



Challenges

- strong C–O / C–H bonds
- regioselectivity



meta-ezetimibe

- difficult to synthesize
- perturbed electronics
- H-bonding shifted