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Chemical Equivalent of Arene Monooxygenases: Dearomative Synthesis of Arene Oxides and Oxepines

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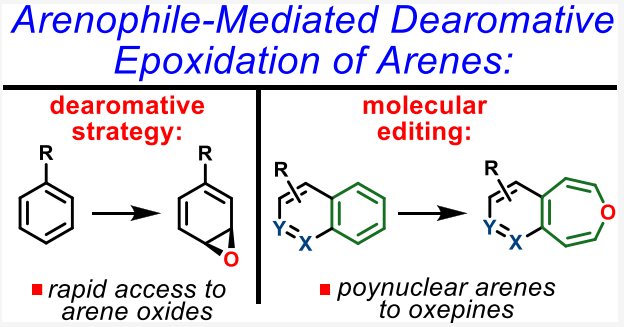
ABSTRACT: Direct epoxidation of aromatic nuclei by cytochrome P450 monooxygenases is one of the major metabolic pathways of arenes in eukaryotes. The resulting arene oxides serve as versatile precursors to phenols, oxepines, or *trans*-dihydrodiol-based metabolites. Although such compounds have an important biological and chemical relevance, the lack of methods for their production has hampered access to their utility. Herein, we report a general arenophile-based strategy for the dearomative synthesis of arene oxides. The mildness of this method permits access to sensitive monocyclic arene oxides without any noticeable decomposition to phenols. Moreover, this method enables direct conversion of polycyclic arenes and heteroarenes into the corresponding oxepines. Finally, these studies provided direct connection between simple aromatic precursors and complex small organic molecules via arene oxides and oxepines.



INTRODUCTION

One of the fundamental interests of biology, microbiology, and biochemistry is the metabolism of organic molecules by living organisms. This process often involves the incorporation of molecular oxygen into organic compounds catalyzed by oxidative enzymes.[1] Aromatic compounds are subject to such oxidative degradation, and their metabolism by both eukaryotic and prokaryotic systems has been extensively studied.[2] Notably, bacterial dioxygenases convert arenes into *cis*-dihydrodiols,[3] whereas mammalian and fungal monooxygenases lead to arene oxides (Figure 1A).[4] The latter intermediates are characterized by unique chemistry, including the valence tautomerization between arene oxide and oxepine forms.[5] Moreover, arene oxides are known for their instability,[6] often undergoing spontaneous and rapid [1,2]-hydride migration to phenols, known as the NIH shift.[7] Arene oxides are also subject to nucleophilic epoxide opening, delivering *trans*-dihydrodiol derivatives that are important precursors involved in biogenesis of primary and secondary metabolites, environmental degradation, and drug metabolism (Figure 1B). For example, dihydrodiol **4** is a phase-I metabolite of the antiepileptic drug phenytoin (**1**) that is derived from the hydrolysis of the corresponding arene oxide.[8] Gliotoxin (**5**) is an *Aspergillus fumigatus* produced mycotoxin that is derived from arene epoxidation of a phenylalanine precursor **2**.[9] Finally, perilloxin (**6**) is an oxepine-containing natural product that could be arising through arene oxidation of naphthalene **3**.[10]

Given the importance of biological arene oxidation processes, as well as the unique structural features of the resultant arene oxides that could be leveraged for further functionalization, significant efforts have been devoted to translating them to the field of synthetic chemistry. For example, the natural metabolic process of microbial arene oxidation has been implemented in laboratory settings utilizing whole-cell bacterial fermentations.[11] The resulting *cis*-dihydrodiols (*cis*-cyclohexadiene-1,2-diols) have proven to be versatile and key building blocks for the synthesis of many natural products and value-added intermediates.[12] Yet, no practical chemoenzymatic arene epoxidations exist, likely because of the instability of arene oxides. Thus, the preparation of arene oxides and co-occurring oxepines has been limited to only a few synthetic strategies. For example, the most common preparation of monocyclic arene oxides involves the Birch reduction[13] or bacterial arene oxidation as the initial dearomative step (Figure 2A).[14] On the other hand, the preparation of oxepines is even less developed, as documented with only a few examples of the synthesis of 3-benzoxepine (Figure 2B). Thus, phthalaldehyde was converted to the corresponding 3-benzoxepine by means of a double Wittig reaction.[15] The same product can be obtained also from

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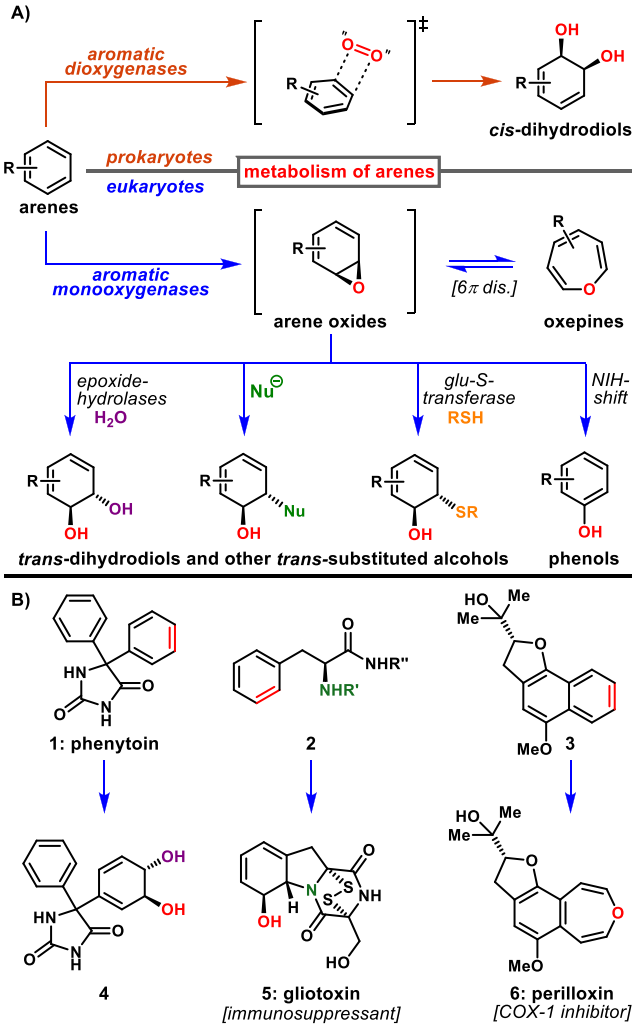

Figure 1. (A) Representative arene oxidation pathways in Nature. (B) Selected metabolites derived from arene oxides.

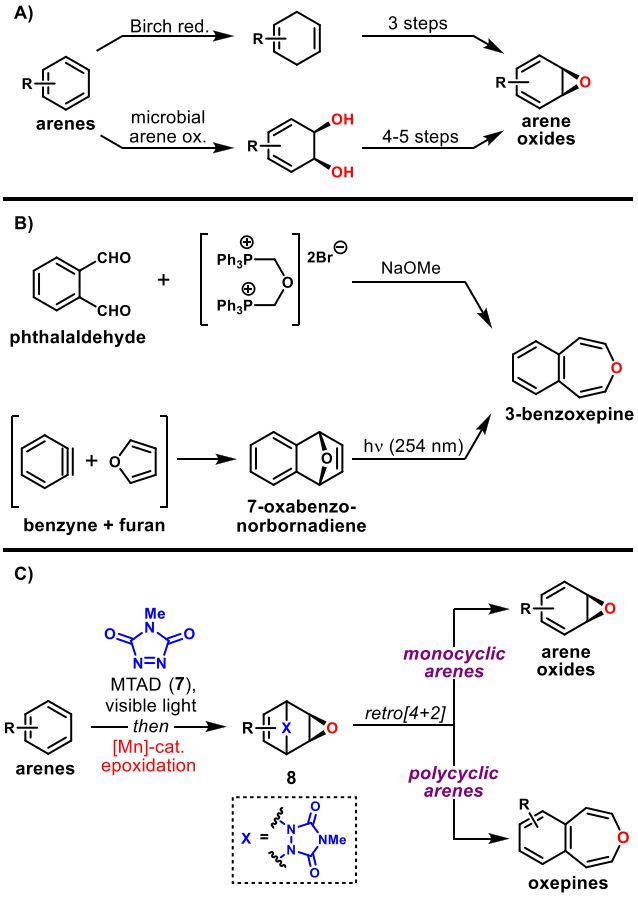

Figure 2. (A) Established preparation of arene oxides. (B) Previous preparations of 3-benzoxepine. (C) This work: arenophile-mediated synthesis of arene oxides and oxepines.

photochemical isomerization of 7-oxabenzonorbornadiene,[16] which can be prepared from benzyne and furan.

More straightforward and mild methods for the generation of arene oxides would significantly expand their synthetic utility and general applicability.[17] Considering the lack of methods for the direct epoxidation of arenes, we set out to develop an alternative preparation of arene oxides and oxepines based on an arenophile-mediated dearomative platform. Herein, we report the successful realization of this plan. Through the use of a Mn-catalyzed epoxidation as the olefin functionalization step (Figure 2C), a range of aromatic and heteroaromatic compounds delivered arene oxides and polycyclic oxepines, which are complementary to those obtained by other established strategies. Finally, the synthetic utility of this method was demonstrated through the preparation of several functionalized small molecules.

RESULTS AND DISCUSSION

Optimization of Reaction Conditions. We have recently reported a series of dearomative functionalizations based on the arenophile 4-methyl-1,2,4-triazoline-3,5-dione (**7**, MTAD),[18] which undergoes a visible-light-promoted *para*-cycloaddition with arenes. Subsequent in situ manipulation of the resulting cycloadducts gives rise to a diverse collection of dearomatized products.[19] One of the possible functionalization strategies involves the application of olefin chemistry, providing bicycles that reveal dienes after [4 + 2]-cycloreversion of the arenophile moiety. Overall, this sequence can be formally seen as an arenophile-assisted isolation of a single π-component from an aromatic system. On the basis of this concept, we initially developed a dearomative dihydroxylation, a chemical method to complement arene dioxygenases.[18] Interestingly, the corresponding epoxidation proved to be quite elusive despite a considerable number of attempts. The subjection of the arene-arenophile *para*-cycloadducts derived from benzene to numerous benchmark epoxidizing agents, such as peracetic acids and dioxiranes did not result in the detection of even trace amounts of the desired products (see Supporting Information for details). Ultimately, we evaluated transition-metal-mediated epoxidations and discovered that Stack's Mn-catalyzed epoxidation methodology[20] provided encouraging results.

Accordingly, our optimization commenced with screening of Mn-based epoxidation conditions with benzene-derived cycloadduct (Table 1; see also Supporting Information, Table S1, for full optimization details). The initial examination (entries 1−5) of commonly used ligands **10**−**12** for this process revealed that 1,10-phenanthroline (**12**) performed favorably. Though pyridine-oxazoline-type ligand **11** provided promising conversion (entry 3), further manipulations of reaction parameters to increase the yield of **8a** failed, which was traced back to the overoxidation/decomposition of the ligand.

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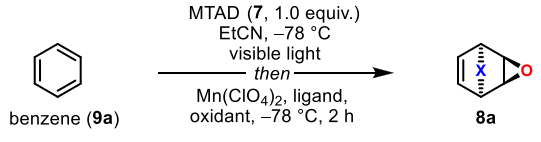
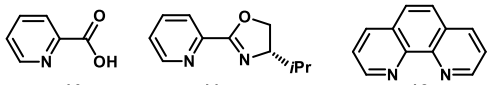
Table 1. Selected Optimization Studies for the Epoxidation of the Benzene-MTAD Cycloadduct[a]



entry	[Mn] (mol%)	ligand (mol%)	oxidant (equiv.)	yield (%, dr)[b]
1	20	**10** (100)	CH_3CO_3H (1.0)	NR
2	20	**10** (100)	CH_3CO_3H (1.0)	18 (3:1)[c]
3	20	**11** (40)	CH_3CO_3H (2.0)	23 (3:1)
4	20	**12** (40)	CH_3CO_3H (2.0)	20 (4:1)
5	20	**12** (40)	CH_3CO_3H (6.0)	25 (3:1)
6	5	**12** (10)	CH_3CO_3H[d] (4.0)	11 (3:1)
7	10	**12** (20)	CH_3CO_3H[d] (4.0)	23 (3:1)
8	20	**12** (40)	CH_3CO_3H[d] (3.0)	40 (3:1)
9	25	**12** (50)	CH_3CO_3H[d] (3.0)	45 (3:1)
10	40	**12** (80)	CH_3CO_3H[d] (3.0)	45 (3:1)

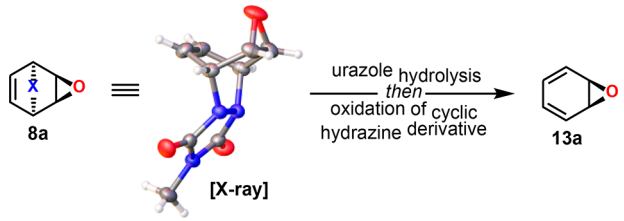
LIGANDS:



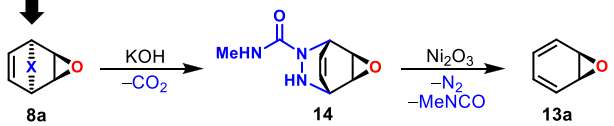
10 **11** **12**

[a]Standard reaction conditions: MTAD (**7**, 0.5 mmol, 1.0 equiv), benzene (**9a**, 5.0 mmol, 10 equiv), EtCN (0.10 M), visible light, −78 °C, 12 h, and then addition of a solution of catalyst [$Mn(ClO_4)_2$/ligand in MeCN], CH_3CO_3H, −78 °C, 2 h. [b]Reported yields are of isolated products and the ratio of diastereoisomers (in parentheses) was determined by ^1H NMR of the crude reaction mixtures. [c]After addition of catalysts and oxidant, the reaction was warmed to 25 °C over the course of 2 h. [d]Freshly prepared, H_2SO_4-free solution of CH_3CO_3H was used.

Table 2. Selected Cycloreversion Optimization Studies

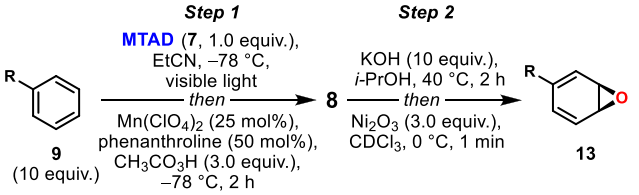


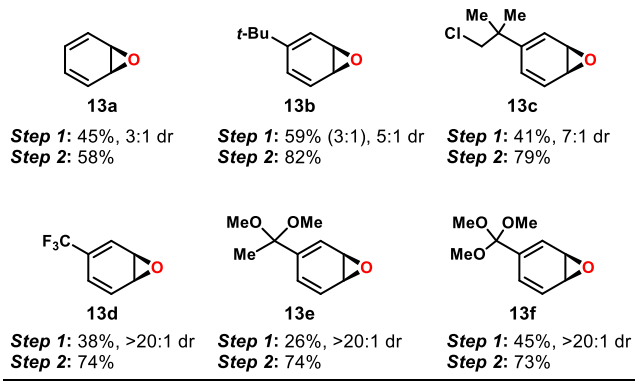
entry	conditions	result
1	KOH (10 equiv.), *i*-PrOH (0.1 M),100 °C, 16 h; then neutralization (AcOH aq.) and addition of $CuCl_2$ (2.0 equiv.), 0 °C, 20 min	decomp.
2	N_2H_4 (10 equiv.), 100 °C, 16 h; then removal of N_2H_4 and addition of $CuCl_2$ (2.0 equiv.), H_2O, 0 °C, 20 min	decomp.
3	KOH (10 equiv.), *i*-PrOH (0.1 M), 40 °C, 16 h; then neutralization (AcOH aq.) and addition of $CuCl_2$ (2.0 equiv.), 0 °C, 20 min	phenol
4	KOH (10 equiv.), *i*-PrOH (0.1 M), 40 °C, 16 h; then neutralization (AcOH aq.) and addition of Ni_2O_3 (3.0 equiv.), 0 °C, 1 min	product **13a** (58% yield)[a]



[a]Reported yield is based on ^1H NMR integration relative to the internal standard ($MeNO_2$).

Table 3. Preparation of Monocyclic Arene Oxides (13)[a]





[a]Standard reaction conditions. ***Step 1***: MTAD (7, 1.0 mmol, 1.0 equiv), arene (**9**, 10 mmol, 10 equiv), EtCN (0.1 M), visible light, −78 °C, 12 h; then addition of $Mn(ClO_4)_2$/phenanthroline (25/50 mol %) in MeCN and CH_3CO_3H (3.0 mmol, 3.0 equiv), −78 °C, 2 h. ***Step 2***: epoxide **8** (0.2 mmol, 1.0 equiv), KOH (2.0 mmol, 10 equiv), 40 °C, 2 h; then workup and exposure of crude to Ni_2O_3 (0.6 mmol, 3.0 equiv), $CDCl_3$ (0.1 M), 0 °C, 1 min. Reported yields of **8** (step 1) are of isolated products and the ratio of diastereoisomers and constitutional isomer (bracket) were determined by ^1H NMR of the crude reaction mixtures. Reported yields of **13** (step 2) are based on ^1H NMR integration relative to the internal standard ($MeNO_2$).

Furthermore, we also observed the decomposition of the product under reaction conditions due to the low pH of the commercial samples of peracetic acid, likely because of the presence of sulfuric acid. This hurdle was surmounted by using a freshly prepared solution of peracetic acid that was free of any inorganic acids (entries 6−10). By screening different catalyst loadings and using an optimal 1:2 ratio of [Mn]/[**12**] (entries 6−10), we found that the addition of a manganese(II) perchlorate/phenanthroline complex (25/50 mol %) with peracetic acid (3.0 equiv) as an oxidant provided epoxidized product **8a** in 45% yield, after chromatography and as a 3:1 mixture of diastereoisomers (entry 9).

With epoxidized cycloadduct **8a** in hand, we turned our attention toward cycloreversion (Table 2). In our previous studies[21] the urazole motif could be removed through a one-pot protocol involving hydrolysis to a cyclic hydrazine and oxidation to a cyclic diazine that readily extruded nitrogen to reveal the desired diene functionality. Unfortunately, the application of these established protocols to epoxidized cycloadduct **8a**, using KOH or neat hydrazine at 100 °C followed by $CuCl_2$ oxidation, resulted only in decomposition (entries 1 and 2). After several attempts, and with inspiration from the literature,[22] we discovered that partial urazole hydrolysis/decarboxylation (KOH in *i*-PrOH, 40 °C) provided a stable cyclic semicarbazide intermediate **14**, which could be further oxidized. Although $CuCl_2$ was not a suitable oxidant, providing only a phenol (entry 3), this result inspired the search for a milder oxidant, as the phenol was derived from the desired arene oxide via NIH shift. After screening a variety of

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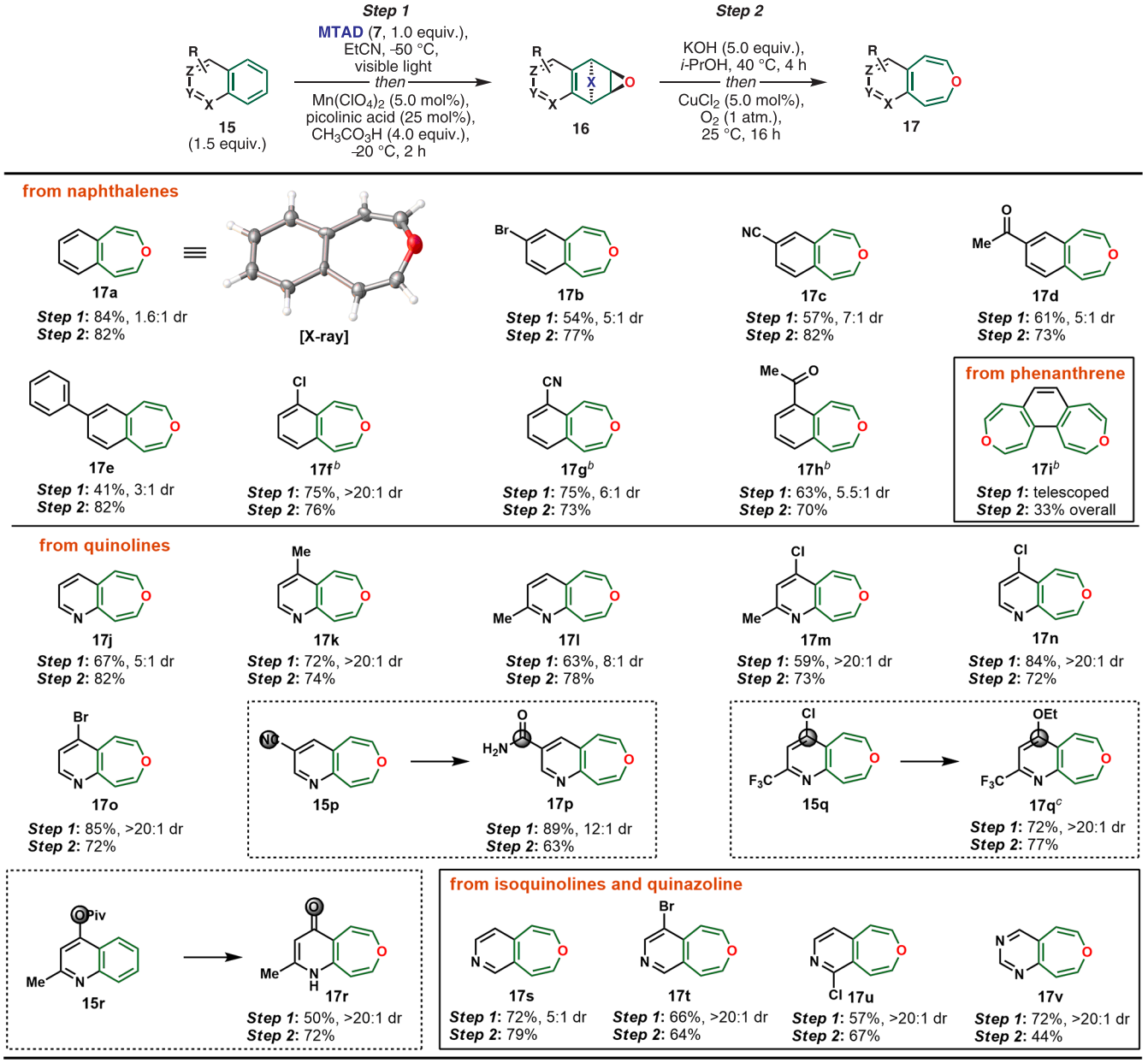
Table 4. Preparation of Oxepines (17)[a]



[a]Standard reaction conditions. ***Step 1***: MTAD (**7**, 1.0 mmol, 1.0 equiv), arene (**15**, 1.5 mmol, 1.5 equiv), EtCN (0.1 M), visible light, −50 °C, 12 h; then $Mn(ClO_4)_2$/picolinic acid (5/25 mol %) in MeCN and CH_3CO_3H (4.0 mmol, 4.0 equiv), −20 °C, 2 h. Reported yields are of isolated products. ***Step 2***: epoxide **16** (0.2 mmol, 1.0 equiv), KOH (1.0 mmol, 5.0 equiv), *i*-PrOH (1.0 M), 40 °C, 4 h; then workup and exposure to $CuCl_2$ (5.0 mol %) under O_2 atm. [b]Identical cycloaddition conditions to standard conditions; then $Mn(ClO_4)_2$/picolinic acid (20/100 mol %) in MeCN and CH_3CO_3H (6.0 mmol, 3.0 equiv), −78 °C, 2 h. [c]Ethanol was used instead of *i*-PrOH.

oxidants, we found that through the use of nickel(III) oxide, arene oxide **13a** could be obtained, virtually free of phenol byproducts.

Synthesis of Arene Oxides. With both epoxidation and cycloreversion strategies developed for benzene (**9a**), we examined the general applicability of these conditions toward benzene derivatives (Table 3). First, the challenging epoxidation also proved viable for other monocyclic arenes, delivering products **8b**−**8f** in 26−45% yields. Thus, benzene derivatives containing alkyl substituents such as *tert*-butyl (**8b**), a chlorinated alkyl side chain (**8c**), and a CF_3 (**8d**) all provided the desired products. Although electron-deficient benzene derivatives do not undergo cycloaddition with MTAD (**7**), the corresponding ketal of acetophenone (**8e**) and the orthoester of benzoic acid (**8f**) successfully underwent cycloaddition and epoxidation. Overall, high chemoselectivity was observed, as only *tert*-butylbenzene (**9b**) gave a minor constitutional isomer (3:1). Importantly, though epoxidation of these substrates resulted in diastereoisomeric mixtures ranging from 3:1 to >20:1, this proved inconsequential for the next step involving the preparation of arene oxides. Thus, all monocyclic epoxidized precursors **8a**−**8f** were rapidly converted to arene oxides **13a**−**13f** with yields ranging from 58% to 82% based on ^1H NMR (measured using an internal standard). Although it was not possible to isolate or purify these compounds, the

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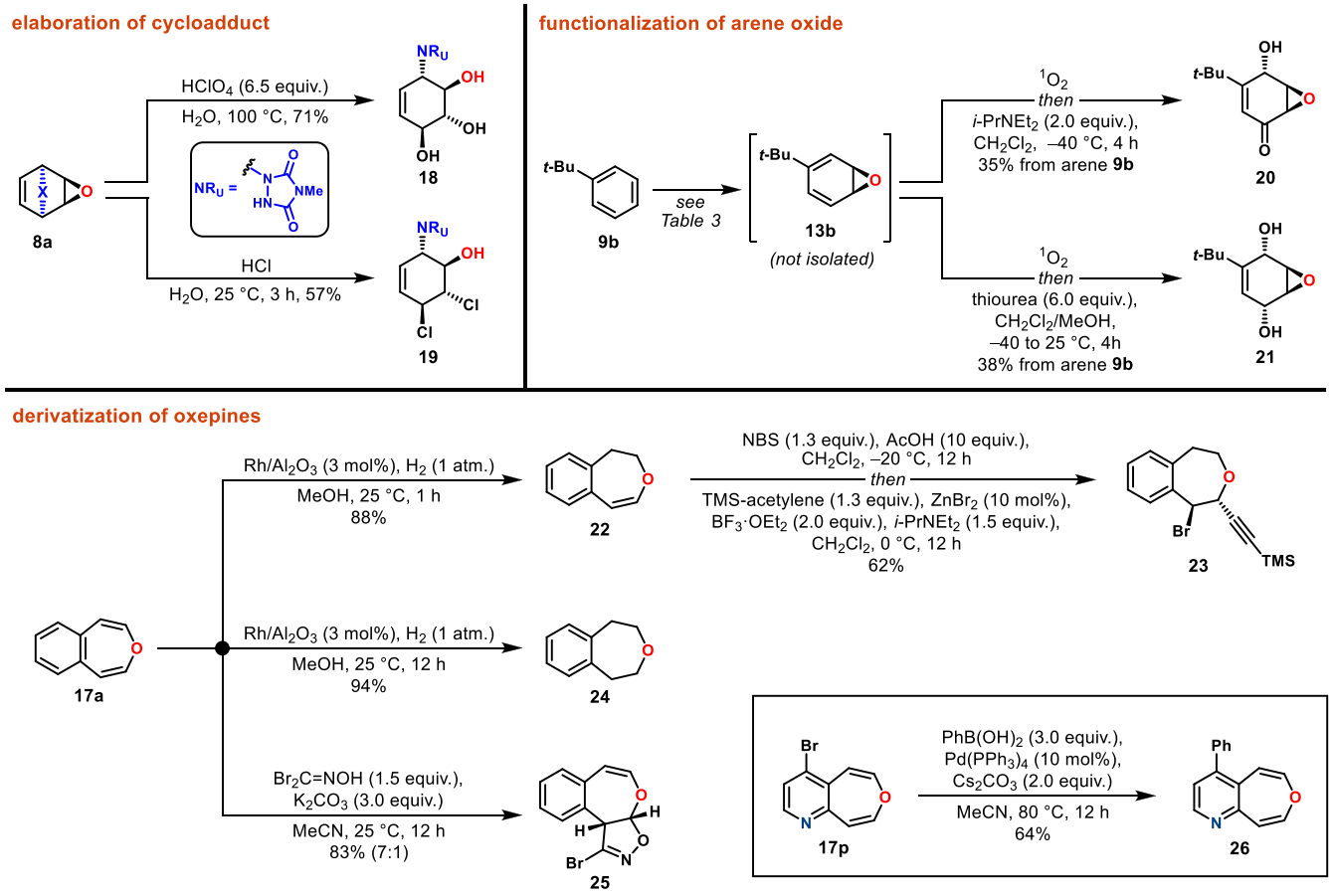

Figure 3. Diversification of products.

corresponding solutions could be immediately used for further chemistry (see below).

Synthesis of Oxepines. In addition to benzene derivatives, we questioned whether this process would be compatible with polycyclic arenes, such as naphthalenes (Table 4). Because of steric constraints and stabilization from the adjacent π-system, the initial naphthalene-2,3-oxide products should exclusively adopt the oxepine valence tautomer, which increases their stability significantly. Unfortunately, the developed epoxidation conditions (**9** → **8**) did not translate well to naphthalene (**15a**), leading only to trace product **16a**. After screening a variety of conditions (see Supporting Information, Table S2), we found that through the use of manganese(II) perchlorate and picolinic acid (5/25 mol %) as the catalyst, the corresponding epoxidized MTAD-naphthalene adduct **16a** was obtained in 84% yield from naphthalene (**15a**). Because polycyclic arene-MTAD cycloadducts are generally more thermally stable than their monocyclic congeners, the cycloaddition reactions could be conducted at −50 °C and epoxidations at −20 °C. Only with 1-substituted naphthalene derivatives and phenanthrene (**15f**−**15i**) did we observe greater thermal instability of MTAD-adducts, leading to poor yields under these conditions. Thus, a slight modification was developed, utilizing higher loadings of catalysts ($Mn(ClO_4)_2$/picolinic acid = 20/100 mol %) at −78 °C.

Cycloreversion proceeded in a similar manner as before, through the intermediacy of the semicarbazides. Gratifyingly, the pronounced stability of 3-benzoxepins permitted the use of aerobic oxidation conditions. For example, upon partial KOH-induced hydrolysis of the urazole moiety in **15a**, the semicarbazide **16a** underwent Cu-catalyzed oxidation (5 mol %) under an oxygen atmosphere, delivering 3-benzoxepine **17a** in 82% yield. We were able to obtain a crystal structure of **17a** in which a severe out-of-plane distortion relative to naphthalene was observed (Table 4, also see Supporting Information). To explore the substrate scope, a set of 1- and 2-substituted naphthalene derivatives were subjected to this process to deliver 3-benzoxepine analogs, with tolerated functionality including halogens (**17b** and **17f**), nitriles (**17c** and **17g**), and ketones (**17d** and **17h**). Moreover, phenyl-substituted naphthalene **15e** gave the desired oxepine **17e** with exclusive site selectivity for dearomative oxidation at the less-substituted ring of naphthalene. Larger polycyclic arenes could be employed with this protocol, as demonstrated with phenanthrene, which underwent a double oxidation to bis-oxepine **17i**.

In addition to arenes, we probed this dearomative oxidation strategy with heteroarenes such as benzopyridines and their derivatives, as the resulting azabenzoxepines are a largely unknown and unexplored class of heterocycles. Though at first glance they appear to be simple, containing only two fused rings and two heteroatoms, no general syntheses of such compounds have been reported to date.

Subjecting a range of quinolines to the described two-step sequence furnished the corresponding oxepino[4,5-*b*]pyridines **17j**−**17r**, without any *N*-oxide formation, and with similar efficiency that was observed for hydrocarbon arenes. In addition to quinoline (**17j**), heteroarenes with different substituents and substitution patterns were tolerated, as exemplified with alkyl (**17k**−**17m**), halogen (**17m**−**17o**),

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and trifluoromethyl (**17q**) substituted quinolines. Nevertheless, several functional groups did react under these conditions, during the basic KOH-hydrolysis/cycloreversion step, providing new functionalities. For example, the nitrile **15p** hydrolyzed to yield amide **17p** and 4-chloro-2-(trifluoromethyl)quinoline (**15q**) was sufficiently electron-deficient to undergo S_NAr with the solvent and base (EtOH/KOH) to yield compound **17q**. Also, the pivalate group in substrate **15r** underwent hydrolysis during the cycloreversion step, delivering 4-pyridone-fused oxepine **17r**. Moreover, with use of isoquinolines as substrates, this method enabled access to the complementary oxepino[4,5-*c*]pyridines **17s**−**17u**. Finally, benzo-fused heterocycles containing more than one nitrogen can be used, as exemplified with preparation of oxepino[4,5-*d*]pyrimidine (**17v**) from quinazoline. We were pleased to note that both epoxidation and cycloreversion could be performed on a gram scale, as demonstrated with compounds **16a**, **16f**, and **17a** (see Supporting Information).

Derivatization of Products. The chemistry described herein can be extended greatly through the functionalization of the obtained reactive intermediates—arene oxides and oxepines—ultimately giving access to diverse and structurally elaborated small molecules (Figure 3). For example, benzene-derived bicyclic epoxide **8a** underwent two complementary acid-mediated hydrolyses to provide aminocyclitol **18** or its dichloro derivative **19**. Moreover, arene oxide **13b** derived from *tert*-butylbenzene (**9b**, see Table 3) was directly converted to γ-hydroxyenone **20** or *syn*-1,4-diol **21** through the intermediacy of an endoperoxide.[23]

These examples demonstrate that the arenophile-based preparation of arene oxides can be applied for downstream chemistry, bypassing the highly unstable nature of these compounds. In addition, benzoxepines could serve as intermediates for further derivatization, as confirmed with substrates **17a** and **17o**. Thus, partial or full hydrogenation of benzoxepine **17a** provided **22** and **24**. The dihydrobenzoxepine **22** was further elaborated via bromohydrin chemistry to the functionalized ether **23**. Also, benzoxepine **17a** could serve as a viable cycloaddition partner, undergoing nitrile oxide mediated [3 + 2] dipolar cycloaddition[24] to give product **25** (7:1 ratio of constitutional isomers). Finally, further derivatization was also possible by conducting a Suzuki reaction on the brominated oxepinopyridine (**17o** → **26**), highlighting the ability to utilize these unexplored heterocycles as practical building blocks for medicinal chemistry.

CONCLUSION

We have developed a dearomative strategy for epoxidation of simple arenes. Our approach features an arenophile-based cycloaddition and epoxidation, followed by cycloreversion to reveal arene oxides and 3-benzoxepines. Several benzene derivatives were converted to the corresponding arene oxides with complementary chemoselectively to known methods and without any noticeable decomposition to phenols. Moreover, this protocol converted polycyclic arenes and heteroarenes into the corresponding oxepines with a broad functional group tolerability. Importantly, the described chemistry enables formal epoxidation of naphthalenes at positions 2 and 3, a biomimetic epoxidation for which no chemical equivalent exists. Given the lack of chemical methods for molecular editing of this type, as well as practical gram-scale feasibility and further options for elaboration, we anticipate the application of this dearomative strategy in the preparation of high-value intermediates.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c02724.

Full experimental procedures and characterization data for all new compounds; ^1H and ^{13}C NMR spectra and crystallographic information for **8a**, **16f**, **16q**, and **17a** (PDF)
(Crystallographic data for **8a** CIF)
(Crystallographic data for **16f** CIF)
(Crystallographic data **16q** CIF)
(Crystallographic data **17a** CIF)

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Notes

The authors declare no competing financial interest.

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