Dearomative Dihydroxylation with Arenophiles

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Aromatic hydrocarbons are some of the most elementary feedstock chemicals, produced annually on a million metric ton scale, and are used in the production of polymers, paints, agrochemicals, and pharmaceuticals. Dearomatization reactions convert simple, readily available arenes into more complex molecules with broader potential utility; however, despite substantial progress and achievements in this field, there are relatively few methods for the dearomatization of simple arenes that also selectively introduce functionality. Here, we describe a new dearomatization process that involves visible-light activation of small, heteroatom-containing organic molecules – arenophiles – resulting in their *para*-cycloaddition with a variety of aromatic compounds. The approach uses *N*–*N* arenophiles to enable dearomative dihydroxylation and diaminodihydroxylation of simple arenes. This strategy provides direct and selective access to highly-functionalized cyclohexenes and cyclohexadienes and is orthogonal to existing chemical and biological dearomatization processes. Finally, we demonstrate the synthetic utility of this strategy with the concise synthesis of several biologically active compounds and natural products.

The dearomatization of aromatic compounds is a fundamental synthetic strategy, providing direct and efficient access to a wide range of valuable intermediates from simple and abundant sources of hydrocarbons[1–5]. Numerous bioactive compounds, natural products, and drugs, such as the analgesic morphine[6–8], the broad-spectrum antibiotic doxycycline[9], and the antiviral drug oseltamivir (Tamiflu™)[10–12], have been synthesized utilizing dearomatization as a key step. Despite their strategic and widespread use, most dearomative strategies do not result in the introduction of additional functionality. Indeed, the venerable dissolving metal reduction (Birch reduction)[13], oxidative dearomatization of phenols[14], and arene-alkene photocycloadditions[15] are exceptionally powerful synthetic transformations; however, most of the dearomatized products have to be subjected to further

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manipulations to install the desired level of functionalization. To date, only certain stoichiometric reactions of transition metal complexes based on Os, Ru, Re, Cr, and Mn can enable more elaborate functionalizations of the corresponding metal-bound arenes (Fig. 1a, left)[2,16–19]. Both η^2- and η^6-coordination modes greatly reduce the aromatic character of arene ligands and, as a consequence, activate them towards reaction with electrophiles or nucleophiles. After additional functionalization, oxidative decomplexation liberates the dearomatized products. While these methods provide rapid access to compounds which otherwise require long and tedious manipulations, the toxicity and cost of the above-mentioned metal complexes have been significant deterrents to their widespread synthetic use. In addition to stoichiometric methods, a catalytic dearomative polyhydroxylation of benzene is known and proceeds through photoinduced charge-transfer osmylation[20].

In addition to chemical processes, microbial arene oxidation converts arenes into the corresponding *cis*-1,2-dihydroxy-cyclohexa-3,5-dienes (2,3-dihydrodiols, Fig. 1a, right) with high levels of enantioselectivity[21]. While exceptionally powerful and synthetically useful[22], this biotransformation often involves the use of specific bacterial strains or recombinant organisms to effect substrate-specific transformations, and these can usually be obtained only from the laboratories in which they were first cultured.

The development of dearomative functionalization strategies for arenes is intrinsically challenging and remains a largely unsolved synthetic problem. The high resonance energy makes aromatic compounds particularly unreactive starting materials, and reagents that can overcome this chemical inertness will preferentially react with the more reactive, unsaturated dearomatized products. Ultimately, this problem leads to overreaction and decomposition of the starting material. We envisioned dearomative functionalization as a two-stage process, thus avoiding restrictive reactivity differences between starting arenes and partially unsaturated products. Key to the successful execution of this plan was the use of visible-light photoactivable 2π components, for which we introduce the term ‘arenophiles’, in analogy with thermal cycloaddition processes. Specifically, using heteroatom-containing arenophiles

that could formally react in a [4+2] fashion would significantly expand the toolbox of dearomative chemistry, as they would simultaneously induce dearomatization, introduce functionality, create stereogenic centers, and enable further functionalization. Subsequent retrocycloaddition or fragmentation of the arenophile moiety would then provide selective access to the corresponding dearomatized products. Herein, we report the realization of this concept in the development of a method for the dearomative dihydroxylation and diaminodihydroxylation of simple arenes (Fig. 1a, bottom). By using an *N–N*-arenophile and osmium-catalyzed dihydroxylation, a variety of hydrocarbon aromatic compounds were selectively transformed to the corresponding 3,4-dihydrodiols or diaminodihydrodiols. The synthetic value of this method has been demonstrated through the synthesis of several highly-functionalized small organic molecules from readily available staring arenes (Fig. 1b).

Results and discussion

Design of arenophiles and reaction development. Cycloaddition reactions involving arenes encompass an important group of dearomatization strategies[23]. Aromatic compounds, known for their stability in the ground state, become exceptionally reactive upon photoexcitation and can undergo cycloaddition with a variety of alkenes[15]. For these processes, high-energy UV light is usually required to access the relatively high π,π*-singlet state of the aromatic nucleus to enable reactivity. The resulting *meta*-photocycloaddition is well documented in the literature and has been used many times in organic synthesis[24,25], while the *ortho*- and particularly the *para*-photocycloadditions have not received much attention, since both types rarely occur with olefins, and typically are low-yielding side reactions[24].

A conceptually distinct approach toward dearomative cycloaddition involves photoexcitation of the other cycloaddent to engage the arene in the ground state during the reaction (Fig. 2a). Ideally, this alternative activation mode would provide complimentary periselectivity as well as enable cycloaddition with partners other than alkenes. In this context, we were intrigued by a report by Hamrock and Sheridan[26], indicating the existence of arenophile-type reactivity with benzene; however, due to its transient nature, the corresponding *para*-cycloadduct has never been isolated or chemically explored.

Furthermore, arene-arenophile photocycloadditions are still mechanistically ambiguous and could occur *via* multiple reaction trajectories, including photo-induced electron- or charge-transfer complexes between the arene and the excited arenophile[23]. Nevertheless, the energy provided by visible light is sufficient to electronically excite only the arenophile, due to its much lower-lying and narrower HOMO-LUMO gap compared to that of an arene (Fig. 2a, inset).

A crucial electronic requirement for the photoreactivity of an arenophile is that both the HOMO and LUMO energies are within the range of the HOMO of the arene. In order to evaluate the viability of potential *N*–*N*-arenophiles for the photocycloaddition chemistry, we performed a computational frontier molecular orbital analysis[27] of several small organic molecules using benzene (**1a**) (HOMO = –9.9 eV) and naphthalene (**2a**) (HOMO = –8.4 eV) as benchmarks (Fig. 2b). Thus, a number of different 1,2,4-triazoline-3,5-diones **A1** (HOMO = –11.2 eV, LUMO = –9.7 eV), **A2** (HOMO = –10.8 eV, LUMO = –9.7 eV), **A4** (HOMO = –10.8 eV, LUMO = –9.3 eV), and **A5** (HOMO = –10.4 eV, LUMO = –8.9 eV), and certain symmetric, cyclic (*Z*)-diazo-containing compounds connected to electron deficient groups, such as **A3** (HOMO = –10.9 eV, LUMO = –9.5 eV) and **A6** (HOMO = –9.9 eV, LUMO = –8.8 eV) were found to meet the electronic criteria to react with benzene (for the complete list of compounds, see Supplementary Information, page 67). Next, upon the visible-light irradiation of dichloromethane solutions containing potential arenophiles (**A1**-**A6**) in the presence of benzene, we detected formation of *para*-cycloadducts in three different cases. While **A1**, **A2**, and **A4** all showed the desired reactivity, we decided to continue our investigations with 4-methyl-1,2,4-triazoline-3,5-dione (**A2**, MTAD) due to the ease of its preparation and its stability.

We commenced our studies on dearomative dihydroxylation by evaluating optimal reaction parameters for formation of the cycloadduct of benzene with MTAD and its *in situ* trapping with osmium tetroxide. Although cycloaddition occurred readily at –78 °C under the influence of visible light, as evidenced by complete disappearance of the characteristic magenta color of MTAD (Fig. 2c) and monitoring by ^{1}H–NMR, the corresponding cycloadduct proved to be rather thermally unstable. We

noticed cycloreversion occurring slowly at temperatures above –50 °C and rapidly above –10 °C. Furthermore, we found that a 10:1 molar ratio of arene to MTAD proved optimal, though ratios as low as 2:1 often gave similar yields, albeit at the expense of longer reaction times. In view of the low thermal stability of the intermediate product, the development of reaction conditions for cold-temperature dihydroxylation proved necessary. As a result, two different catalytic conditions were identified for *in situ* dihydroxylation of MTAD cycloadducts with mononuclear arenes. Under the first set of conditions (Table 1, conditions A), the cycloaddition reaction was run in acetone, and subsequent addition of osmium(VIII) oxide and a solution of 4-methylmorpholine *N*-oxide (NMO), water, and *p*-toluenesulfonamide (*p*-$TsNH_2$) delivered dihydroxylated benzene cycloadduct **3a** in 56% yield. The addition of *p*-$TsNH_2$ proved to be crucial for higher yields as it facilitated hydrolysis of the intermediate osmate ester[28]. The second dihydroxylation process (conditions B), based on a modified Narasaka–Sharpless method[29], was performed using dichloromethane as the solvent. Thus, after disappearance of magenta color, addition of osmium(VIII) oxide, NMO, and *n*-butylboronic acid afforded cyclic boronate ester **4a** in 65% yield.

Reaction generality. With the optimal conditions in hand, we began an exploration of the scope of this dearomative tetrafunctionalization by examining simple, mononuclear arenes (Table 1). In addition to benzene (**1a**), a variety of monosubstituted derivatives proved to be suitable photocycloaddition partners. The tolerance of halogens (**1k**, **1l**, **1m**) and benzylic heteroatom substituents (**1e**, **1f**, **1h**, **1i**, **1l**) is noteworthy, as these type of substrates are not generally compatible with chemical-based dearomatizations. Traditionally, the use of UV irradiation in arene cycloaddition chemistry does not permit broader functional group incorporation[15,23]. In contrast, even benzyl chloride (**1l**) and bromobenzene (**1m**) underwent *para*-cycloaddition with MTAD. This dearomative protocol can be conducted on a larger scale, exemplified with a multigram conversion of benzene (**1a**) and bromobenzene (**1m**) without significant erosions in yields (see Supplementary Information, pages 7 and 21). In addition to cycloaddition, we also observed that abstraction of benzylic C–H bonds by photoexcited MTAD was a competitive process with certain substrates, giving formal C–H amidation products (for limitations of the

method, see Supplementary Information, page 22)[30]. For example, amidation proved to be a major reaction pathway with toluene (not shown), and minor side process with cumene (**1b**). Importantly, all substrates reacted in a highly stereo- and regioselective manner; the resulting products were consistently obtained as a single constitutional and diastereoisomer (for an X-ray structure of acetonide protected **3a** see Supplementary Information, page 162). At present, there is not a conclusive explanation for the high observed regioselectivity of the cycloaddition process; however, computational studies are currently ongoing to elucidate the origins of this selectivity. Finally, at the current level of development, polysubstituted mononuclear arenes are not suitable substrates for the dearomatization reaction we describe (see Supplementary Information, page 23).

With dihydroxylated bicyclic adducts prepared, we turned our attention to cycloreversion of the arenophile moiety, to liberate the desired dihydrodiols. Although similar unsaturated bicyclic urazoles are known to undergo thermal cycloreversion[31], no reaction was observed upon heating cycloadducts **3** or **4** to temperatures up to 250 °C. Therefore, we decided to examine a one-pot urazole hydrolysis/bicyclic hydrazine oxidation sequence that would generate dihydrodiols *via* the extrusion of molecular dinitrogen. Although the hydrolysis and oxidation sequence was expected to be reasonably straightforward, the lability of such dihydrodiols was potentially troublesome[21,32]. Indeed, this turned out to be the case, as we observed significant amounts of phenol formation during the oxidation step. However, upon examination of a range of protecting groups and conditions, we eventually found that using the corresponding acetonides **5** in combination with neat hydrazine or KOH in 2-propanol[33], followed by $CuCl_2$-mediated oxidation successfully generated protected dihydrodiols **6** as stable compounds. This one-pot sequence proved to be highly efficient, as the corresponding diene diol products were prepared in high yields (Table 2, left side). Most of the functional groups tested proved resistant to urazole hydrolysis and hydrazine oxidation, with the exception that esters were converted to the corresponding carboxylic acids (**6j**) and alcohols (**6e**, **6f**, **6g**). Importantly, under the reaction conditions described, no potentially competitive re-aromatization process was observed and all acetonide protected dihydrodiols were stable

to standard purification methods. Finally, all substituted dihydrodiols were complementary constitutional isomers to those obtained by microbial arene oxidation[21].

Next, we sought to investigate arenophile fragmentation to further extend the functional scope and utility of this method (Table 2, right side). This manipulation was achieved in two steps using hydrolysis of the urazole moiety under above-mentioned conditions, followed by benzoylation and reductive cleavage of the *N–N* bond with samarium diiodide[34]. A range of substituted cycloadducts were transformed into the respective unsaturated diaminodiols **7**. Moreover, vinyl bromide (**7m**) survived under these reductive conditions; only benzyl chloride derived cycloadduct **5l** was converted to the corresponding amide **7l** during this reaction sequence. Importantly, this synthetic sequence provides direct and selective access to highly-functionalized small molecules that are characterized by four contiguous heteroatom-containing stereogenic centers. The arenophile-mediated dihydroxylation with subsequent fragmentation was also applicable to site-selective dearomatization of polynuclear arenes (Table 3)[35–38]. Thus, using a two-step protocol involving MTAD cycloaddition/dihydroxylation and urazole hydrolysis/catalytic hydrogenation, a series of naphthalene derivatives were successfully converted to the corresponding diaminodiols. In addition to halogens (**2b**–**2d**), amide (**2e**), and benzylic ketal (**2f**) substituents survived under the reaction conditions.

Moreover, this strategy proved suitable for trinuclear arenes, such as phenyl- and pyridine-containing naphthalenes (**2g** and **2h**) and phenanthrene (**2j**). In case of **2g** and **2h**, the observed site-selectivity of dearomatization could be explained by the higher ionization potentials of phenyl and pyridine as compared to naphthalene[39]. In all cases, a single constutional and diastereoisomer was obtained (for an X-ray structure of **8a** and tetra-acetylated **Ac-9a**, see Supplementary Information, page 163 and S164).

Applications of dearomative dihydroxylation. This dearomative dihydroxylation strategy can enable rapid access to small, highly-functionalized organic molecules; three illustrative cases are demonstrated in Figure 3. For example, conduramine A[40] (**11**) was prepared from the corresponding MTAD-benzene

cycloadduct **5a** through a modified hydrolysis-oxidation sequence that installed additional 1,4-*syn*-aminohydroxy functionality. Accordingly, one pot successive urazole hydrolysis, hydrazine/oxamic acid oxidation,[41] and subsequent hetero Diels–Alder reaction delivered bicyclic product **10** in 83% yield. Concurrent *N–O* cleavage and deprotection of the Troc group under reductive conditions, followed by acid-mediated deprotection of the acetonide, furnished conduramine A (**11**). Next, highly oxygenated cyclohexene herbicidal natural product MK7607 (**13**)[42] was expediently synthesized in three steps from benzyl alcohol derived dihydrodiol **6e** *via* protection, dihydroxylation (**6e→12**) and subsequent double deprotection. Similarly, bromodihydro-3,4-diol **6m** was concisely converted to the 3-*O*-desmethylated analog of the potent herbicidal agent phomentrioloxin (**16**)[43] through a stereoselective dihydroxylation, followed by Sonogashira coupling between the resulting vinyl bromide **14** and acetylene **15**, and deprotection[44].

Conclusion

In summary, we have disclosed a dearomative functionalization of simple arenes that provides access to dihydrodiols and diaminodihydrodiols. Notable features of this strategy include visible light activation of the arenophile, *in situ* dihydroxylation of the corresponding arene-arenophile cycloadduct, and subsequent arenophile cycloreversion or fragmentation. This method permits the use of substrates that are normally not suitable for chemical-based dearomatizations, such as halogen- and benzylic heteroatom-containing arenes, and provides products that are not obtained by microbial oxidation. In addition to engaging a broad range of monosubstituted benzene derivatives, this system was also found to be applicable to the site-selective dearomative diaminodihydroxylation of polynuclear arenes. Finally, we have showcased the utility of arenophile-based dihydroxylation as a starting point in the expedient preparation of highly-functionalized, small organic molecules. The study and expansion of the arenophile dearomative platform to other areas, including the application of different functionalization reactions and natural product synthesis, is currently underway and will be reported in due course.

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Author contributions

E.H.S., J.P., J.F., and D.R.H. conducted the experiments, analysed the data and prepared the supporting information. E.H.S., J.P., and D.S. conceived and designed the project, analysed the data and wrote the manuscript.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Crystallographic data for this paper have been deposited at the Cambridge Crystallographic Data Centre under deposition numbers CCDC 1455841–1455843. These data can be obtained free of charge from www.ccdc.cam.ac.uk/data_request/cif. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to D.S.

Competing financial interests

The authors declare no competing financial interests.

Figure captions associated with this text:

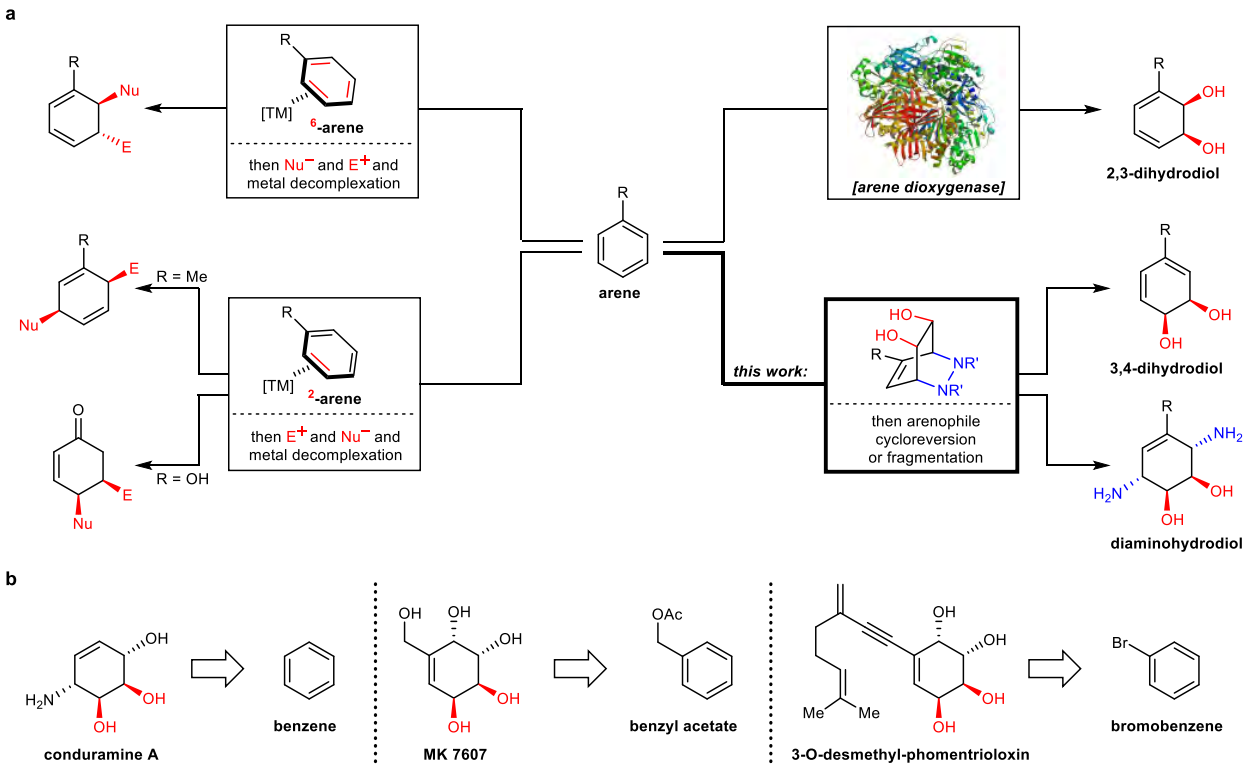

Figure 1| Current strategies in dearomative functionalization of arenes, including this work. a, (left) Transition metal complexation to arenes results in in significant distortions of the of the π–electron density and enables dearomative functionalization. (top right) Arene dioxygenase is a key enzyme in microbial arene oxidation that converts monosubstituted, mononuclear arenes to the corresponding optically pure 2,3-dihydrodiols. (bottom right) Visible-light activation of small organic molecules – arenophiles – with *in situ* dihydroxylation provides tetrafunctionalized bicyclic compounds (this work). Subsequent retrocycloaddition or fragmentation delivers racemic 3,4-dihydrodiols or diaminodihydrodiols, respectively. **b**, Small, highly-functionalized molecules prepared using arenophile-based dihydroxylation. Conduramine synthesis was achieved *via* nitroso Diels–Alder cycloaddition and deprotection from the benzene-derived dihydrodiol. MK7607 synthesis was accomplished *via* dihydroxylation and deprotection of the corresponding dihydrodiol derivative of benzyl acetate. Synthesis of 3-*O*-desmethyl phomentrioloxin was completed *via* dihydroxylation and Sonogashira coupling of the bromobenzene-derived dihydrodiol. TM, transition metal; Nu, nucleophile; E, electrophile.

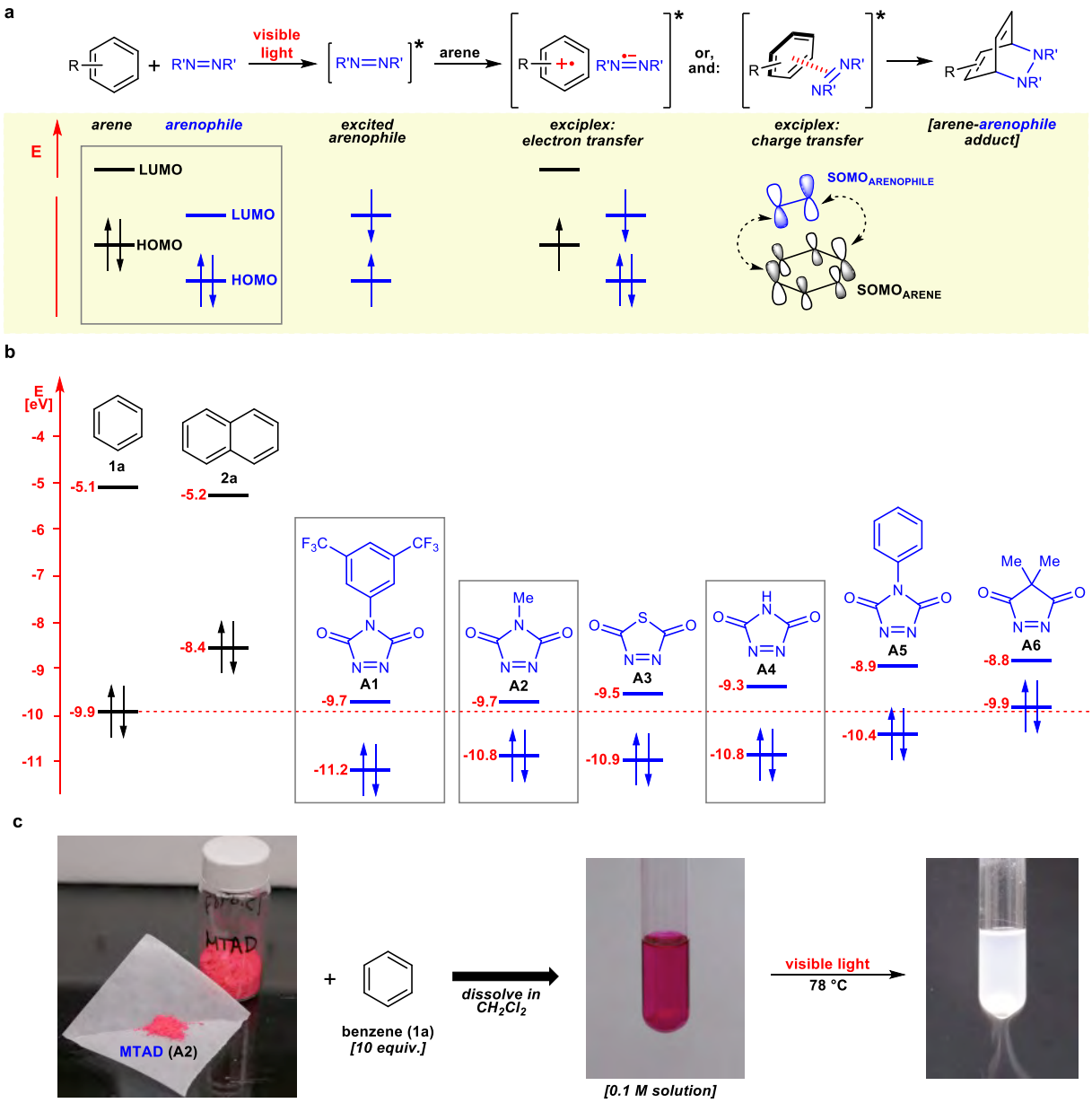

Figure 2| Mechanistic considerations and necessary criteria for arenophile reactivity. a, Mechanistic rationale for visible-light activation of arenophile in the presence of an arene. The excited state of the arenophile is capable of forming an electron- and/or charge-transfer derived exciplex with the ground state arene. The resulting exciplex subsequently collapses to form an arene-arenophile cycloadduct. **b**, Mechanism-guided, computational [B3LYP/6-311+G(d,p)] discovery of potential arenophiles, based on benzene (**1a**) and naphthalene (**2a**) as archetypical arenes. The requirements for arenophile reactivity are: 1) the HOMO-LUMO gap of the arene is narrow enough to permit visible light excitation, and 2) the HOMO of the arene is within the HOMO-LUMO gap of the arenophile. Three arenophiles (insets) showed desired reactivity with benzene. **c**, Magenta color of solution of MTAD (**A2**) and benzene (**1a**, 10 equiv.) in dichloromethane before and after visible light-mediated photocycloaddition.

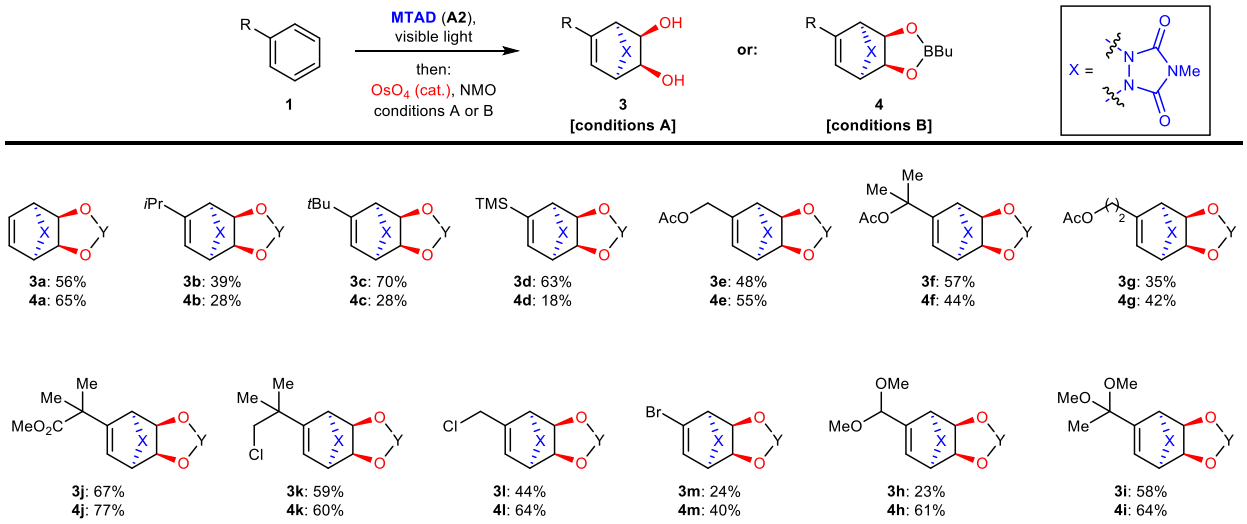

Table 1| Substrate scope of mononuclear arenes.

Conditions A: arene (**1**, 10 equiv.), MTAD (**A2**, 1.0 equiv.), visible light LEDs, CH_2Cl_2, - 78 °C, 4h; then OsO_4 (5 mol%), NMO (1.2 equiv.) $TsNH_2$ (1.2 eq.), H_2O (20 equiv.), acetone (0.1M based on MTAD), –78 °C to 0 °C. **Conditions B:** arene (**1**, 10 equiv.), MTAD (**A2**, 1.0 equiv.), visible light LEDs, CH_2Cl_2 (0.1M based on MTAD), - 78 °C, 4h; then OsO_4 (5 mol%), NMO (1.2 equiv.) $BuB(OH)_2$ (1.2 equiv.), CH_2Cl_2, –78 °C to 0 °C. Isolated yields of purified material based on MTAD. Pr, propyl; Bu, butyl; TMS, trimethylsilyl; Ac, acetyl; MTAD, 4-Methyl-1,2,4-triazoline-3,5-dione.

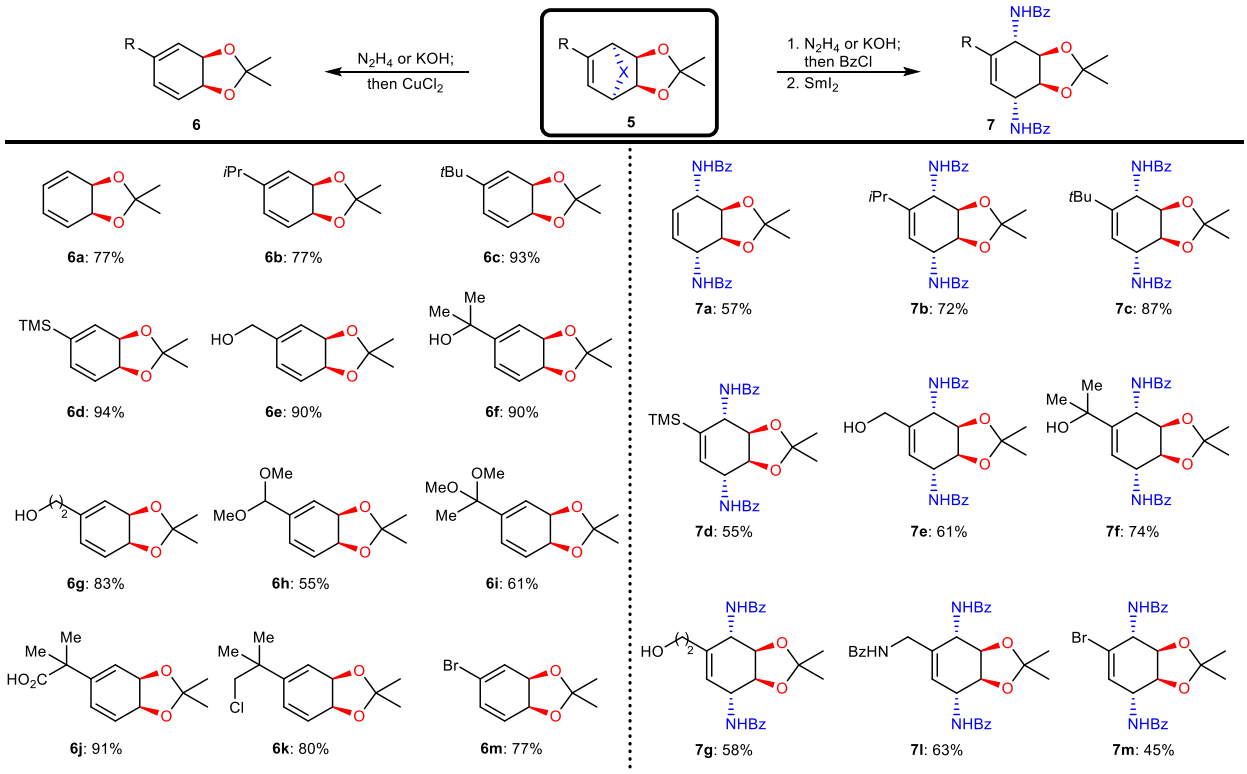

Table 2| Cycloreversion or fragmentation of arenophile moiety.

Conditions for preparation of 6: N_2H_4 (10 equiv.), 100 °C, 12 h; or KOH (10 equiv.) *i*PrOH (0.1 M), 100 °C, 12 h; then pH 7, $CuCl_2$ (1.0 equiv.), NH_3, 25 °C, 1 h. **Conditions for preparation of 7:** N_2H_4 (10 equiv.), 100 °C, 12 h; or KOH (10 equiv.) *i*PrOH (0.1 M), 100 °C, 12 h; then PhCOCl (5.0 equiv.). SmI_2 (3.0 equiv.), MeOH, 25 °C, 1 h. Isolated yields of purified material based on MTAD-arene cycloadduct **5**. Bz, benzoyl.

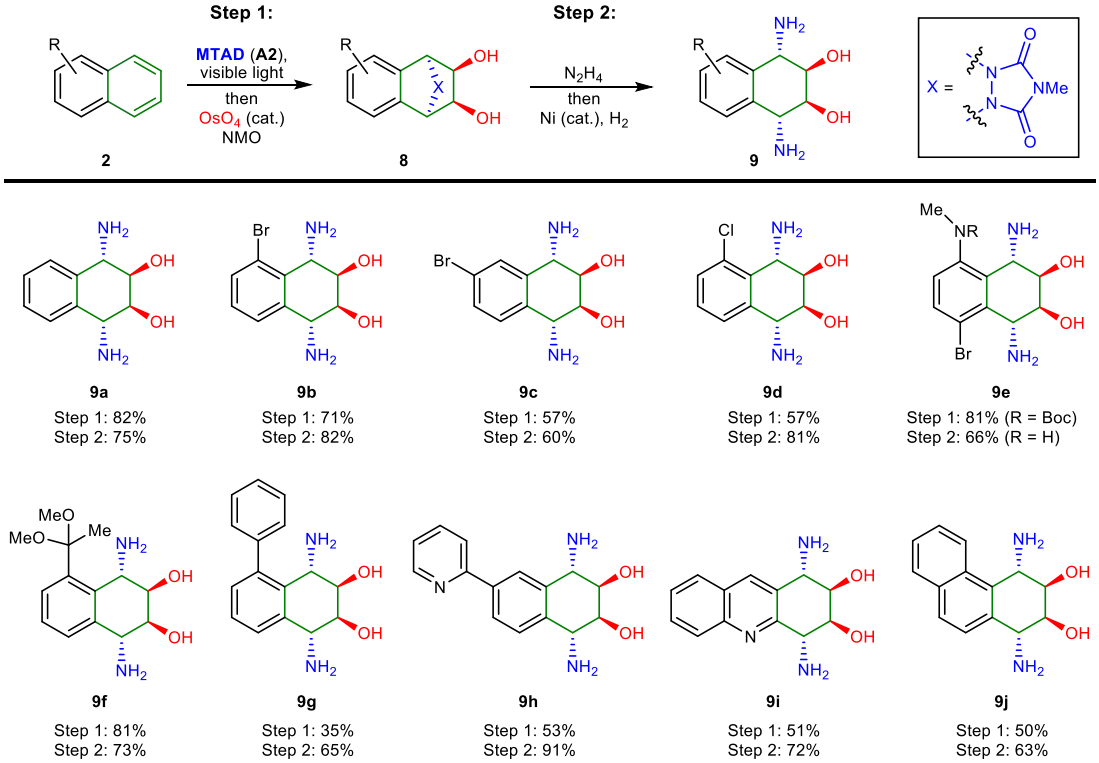

Table 3| Site-selective dearomative diaminodihydroxylation of polynuclear arenes.

Conditions for step 1: arene (**2**, 1.5 equiv.), MTAD (**A2**, 1.0 equiv.), visible light LEDs, acetone, –78 °C, 3 h; then OsO_4 (5 mol%), NMO (1.2 equiv.) $TsNH_2$ (1.2 eq.), H_2O (20 equiv.), acetone (0.1M based on MTAD), –78 °C to 0 °C. **Conditions for step 2:** N_2H_4 (10 equiv.), 100 °C, 12 h; then Raney-Ni (0.5 equiv.), H_2, EtOH, 50 °C, 12 h. Isolated yields of purified material. Boc, *t*-butoxycarbonyl.

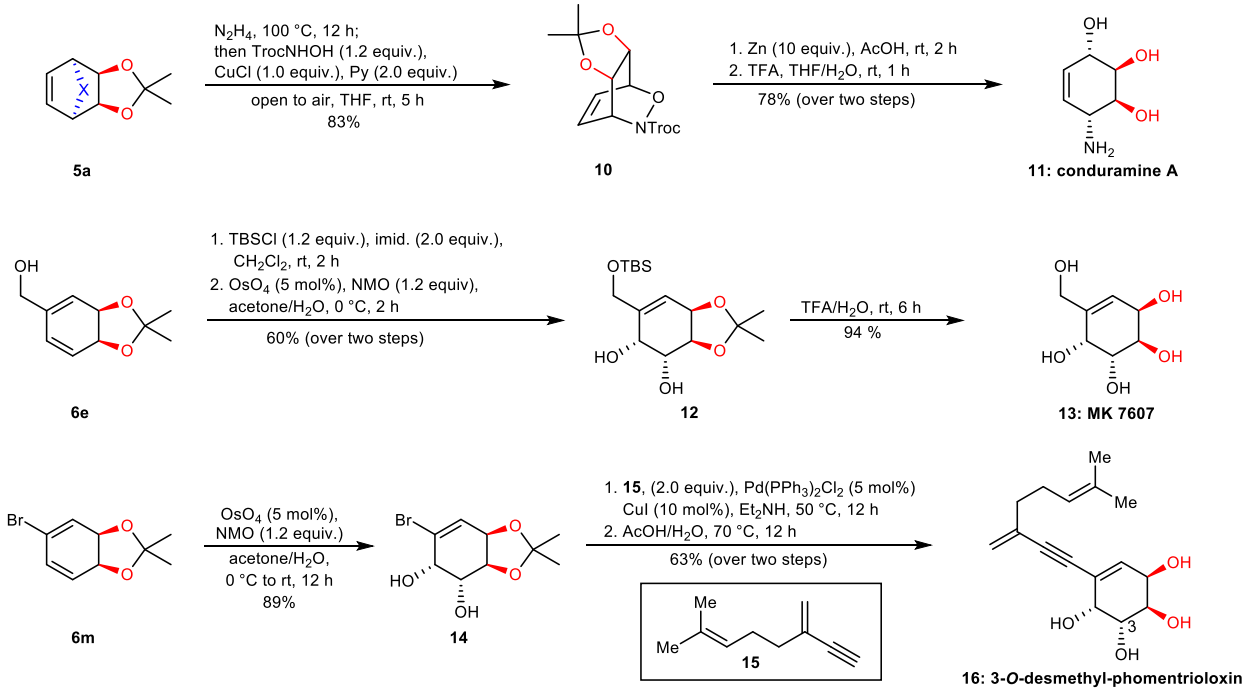

Figure 3| Synthetic applications of dearomative dihydroxylation. Further functionalization of dihydroxylated MTAD-benzene cycloadduct (**6a**), benzyl alcohol-, and bromobenzene-derived 3,4-dihydrodiols (**6e** and **6m**) provides rapid access to conduramine A (**11**), MK 7607 (**13**), and 3-*O*-desmethyl-phomentrioloxin (**16**). Troc, trichloroethoxycarbonyl; Py, pyridine; TBS, *t*-butyldimethylsilyl; imid., imidazole; NMO, *N*-methylmorpholine *N*-oxide; TFA, trifluoroacetic acid; Ph, phenyl; Et, ethyl.

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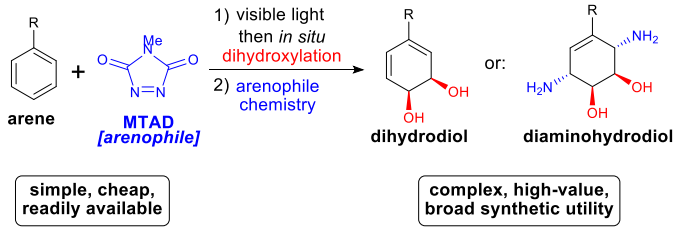

Dearomatization reactions that can simultaneously introduce functionality are valuable transformations that are largely underdeveloped. A synthetic strategy based on the combination of arenophiles with catalytic dihydroxylation reactions now enables rapid and controlled access to synthetically useful cyclohexene and cyclohexadiene derivatives from readily available arene starting materials.