# Organophotocatalytic Reduction of Benzenes to Cyclohexenes

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**ABSTRACT:** The reduction of abundant benzene rings to scarce C($sp^3$)-rich motifs is invaluable for drug design as C($sp^3$) content is known to correlate with clinical success. Cyclohexenes are attractive targets as they can be rapidly elaborated into large product libraries and are stable against rearomatization. However, partial reduction reactions of benzenes to cyclohexenes are rare and have a very narrow scope. Herein, we report a broadly applicable method that converts electron-poor benzenes to cyclohexenes and tolerates Lewis-basic functional groups like triazoles and thioethers, as well as reducible groups like cyanides, alkynes, and sulfones. The reaction utilizes an organic donor that induces mild arene reduction by pre-association to a photoexcitable electron-donor-acceptor (EDA) complex and mild isomerization of redox-inert 1,4-cyclohexadienes to reducible 1,3-cyclohexadienes without a strong base in its oxidized thioquinone methide form.

Medicinal chemists identified an overreliance on arenes as a challenge in drug design that limits the number of drug targets and leads to poor pharmacokinetic profiles.[1–3] Dearomatization reactions can mitigate this bias by converting readily accessible arenes into scarce C($sp^3$)-rich motifs.[4–6] Benzene rings are the natural targets for dearomatization, as they make up over 50% of monocyclic rings in drugs[7] and methods amenable to their reduction at a late stage in either drug candidates or complex precursors are particularly desired as they streamline synthetic routes to C($sp^3$)-rich derivatives.[8] The impact of this strategy is enhanced by partial reduction reactions as they provide modular access to C($sp^3$)-rich compound libraries via elaboration of alkenes and allylic C–H bonds (Figure 1, A).[9] While cyclohexadienes are the most versatile motifs, many examples are unstable as the weak C–H bonds in both isomers render them susceptible to rearomatization.[10] Cyclohexenes have slightly stronger allylic C–H bonds balancing synthetic versatility via four new exit vectors with a $10^5$ times higher resistance against rearomatization making them ideal products.[10]

However, a Scifinder™ search on the tolerance of the most common functional groups[11] and heteroarenes[7] in drugs shows that partial reductions of benzenes to cyclohexenes have a particularly low functional group tolerance making their application to drug design impossible (Figure 1, B, see supporting information (SI) for a list of investigated motifs). While improved catalysts have led to mild hydrogenation reactions to cyclohexanes,[4,12–18] and innovations in solvent design, and electro-, photo-, as well as mechano-chemistry have improved practicability and scope of Birch reductions to 1,4-cyclohexadienes,[19–26] cyclohexenes are challenging to access via both hydrogenation and single electron transfer (SET) pathways. The high reactivity of alkenes towards hydrogenation restricts partial hydrogenations to isolated examples like the Asahi cyclohexene process[27] and methods via SET require a strong base to isomerize redox-inert 1,4-cyclohexadienes to reducible 1,3-cyclohexadienes.[28,29] These Benkeser conditions lead to defunctionalization and overreduction making them unsuitable for even minimally functionalized molecules.

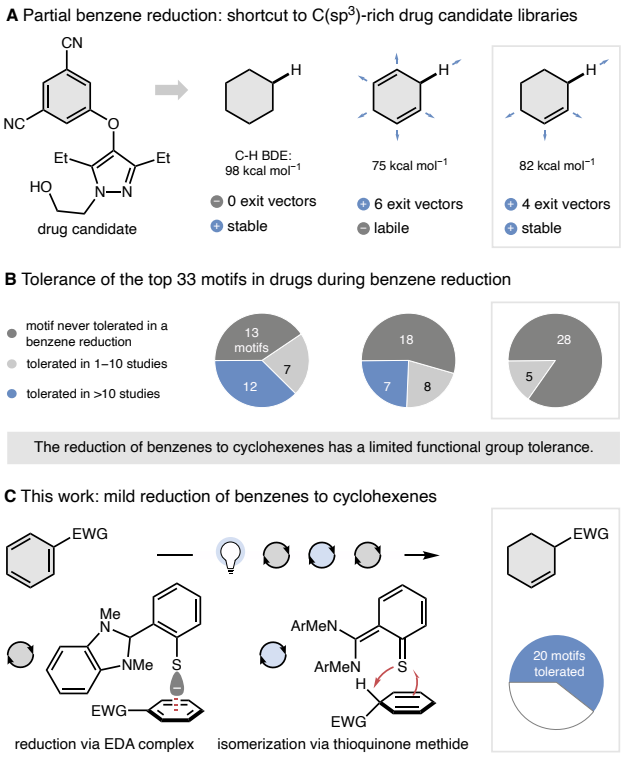


**Figure 1. Concept. A** The reduction of benzenes to cyclohexenes enables direct access to C($sp^3$)-rich drug libraries. **B** A Scifinder™ search reveals that almost none of the 33 most common functional groups and heteroarenes are tolerated during partial reduction to cyclohexenes. Only examples with >50% yield are counted (see supporting information for a complete list). **C** This work: mild partial reduction of benzenes to cyclohexenes by excitation of EDA complexes and thioquinone methide-mediated isomerization. Et, ethyl; BDE, bond dissociation energy; EWG, electron-withdrawing group; Me, methyl; SET, single electron transfer; EDA, electron-donor-acceptor; Ar, aryl.

Inspired by unusual dearomatization mechanisms,[30] especially those via exciplexes,[31–33] we aimed to utilize

photomediated single electron-transfer (SET) via electron-donor-acceptor (EDA) complexes to achieve a mild reduction of benzenes to cyclohexenes (Figure 1, C). We anticipated that pre-association to EDA complexes would enable chemoselective reductions by steric matching[34] and simplify the reaction design by eliminating the need for either arene or electron donor to independently absorb visible light. However, the rapid back electron transfer (BET) within radical pairs usually requires a fragmentable leaving group on the acceptor to ensure product formation, as cationic leaving groups on the donor are severely underexplored.[35] Although this strategy is impossible for the desired arene reduction, we surmised that the creation of an acidic C–H bond upon oxidation of the donor and a basic radical anion upon reduction of the arene acceptor (pKa (1,4-cyclohexadiene) = 28 in DMSO, (calculated)[36]) primes this system to undergo in-cage proton transfer to prevent BET. We reasoned that a dihydro benzimidazol (DHBI) thiophenolate would be the ideal donor since thiophenolates are common donors in EDA complexes[37] and because the oxidized thiophenoxyl radical acidifies benzylic bonds.[38] This effect would be enhanced by the radical-stabilizing DHBI unit,[39] which is used in strong terminal reductants in photoredox catalysis,[40–44] and as proton/H-atom donors in naphthol-based photoredox catalysts for desulfonation and iodination reactions by the Hasegawa group.[45,46] Based on reports of isomerization reactions in quinone-mediated oxidations,[47,48] we anticipated that the oxidized *ortho*-thioquinone methide would catalyze isomerization of 1,4-cyclohexadienes to more stable and reducible 1,3-cyclohexadienes via a cyclohexadienyl radical. Herein, we report the realization of this design, enabling reduction of benzenes to cyclohexenes while tolerating >60% of the 33 most common functional groups and (hetero-) arenes in drugs.[7,11]

Our detailed design plan starts with the excitation of EDA complex **5** leading to contact radical pair **6** (Figure 2, A). Proton transfer would form stabilized benzylic bis(α-amine) radical **7** and cyclohexadienyl radical **8**. The high reducing power of **7** [half-wave reduction potential $E_{1/2}^{red}$ (**7**/**9**) < –2.3 V vs saturated calomel electrode (SCE) in $CH_3CN$][39] resulting from cation stabilization by the nitrogen-centered lone pairs and the strongly electron-donating *ortho*-sulfide ($\sigma_p(S^-)$= –1.2)[49] should enable reduction of the cyclohexadienyl radical **8** to anion **11**, which would easily be protonated to form closed-shell cyclohexadiene **2** along with the oxidized donor **9**. This species should have both zwitterion and thioquinone methide character (**9**) and could be reduced to dihydro benzimidazole **10** by a terminal reductant. Thioquinone methide **9** could also undergo light-induced excitation to **12** empowering it to abstract the weak doubly allylic C–H bond in 1,4-cyclohexadiene **2** (BDE 1,4-cyclohexadiene: 75 kcal $mol^{-1}$)[50] catalyzing isomerization to the more stable 1,3-diene **3** (BDE 1,3-cyclohexadiene: 79 kcal $mol^{-1}$). Diene **3** contains an electron-poor alkene that is easily reduced to cyclohexene **4** thus completing the envisioned catalytic cycle.

The optimization revealed Rongalite – an inexpensive commodity chemical with few synthetic applications[51] – as uniquely well-suited for matching the rates of both catalytic

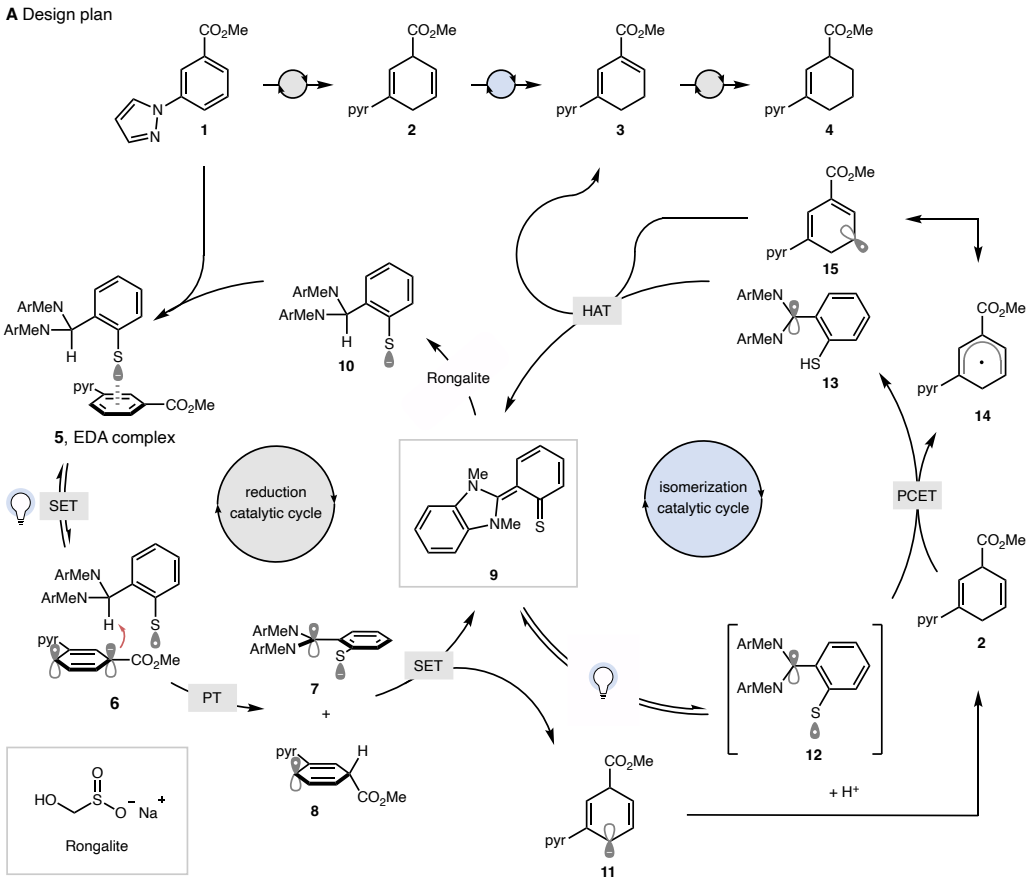


**Figure 2**. Reaction development. **A** Design plan. The counterion ($Na^+$ or $DBUH^+$) was omitted for clarity. **B** Selected optimization experiments show the unique suitability of Rongalite as terminal reductant and of thioquinone methide **9** as donor precursor. Me, methyl; pyr, 1*H*-pyrazol-1-yl; Ar, aryl; SET, single electron transfer; PT, proton transfer, PCET, proton-coupled electron transfer; Ph, phenyl; EDA, electron-donor-acceptor; DBU, 8-diazabicyclo[5.4.0]undec-7-ene.

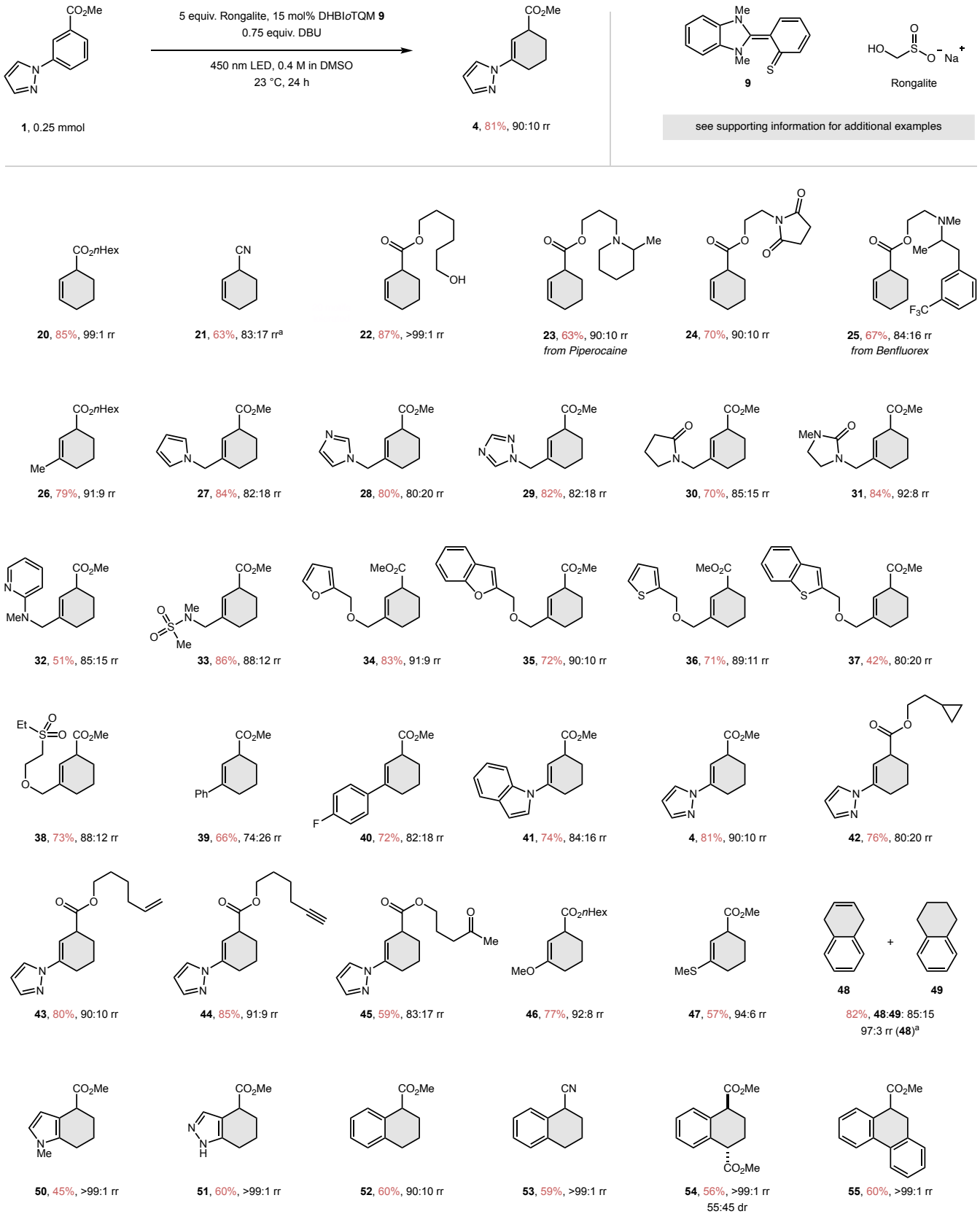


**Figure 3.** Scope. Isolated yields averaged over two experiments are reported. rr and dr values were obtained by GC-FID analysis prior to isolation. A value of >99:1 is noted if only a single isomer could be detected. [a]Analytical yield as an average of 5 experiments on 0.1 mmol scale. Me, methyl; equiv., equivalents; DHBI, dihydrobenzimidazole; *o*TQM, *ortho*-thioquinone methide; DBU, 8-diazabicyclo[5.4.0]undec-7-ene; LED, light-emitting diode; DMSO, dimethyl sulfoxide; rr, regioisomeric ratio; Hex, hexyl; Et, ethyl; dr, diastereomeric ratio; GC, gas chromatography; FID, flame ionization detector.

cycles (Figure 2, B, and Table S2). Moreover, among the precursors tested, only **9**, which contains both a thiophenolate and DHBI unit in the active donor (**10**), provided significant amounts of cyclohexene **4**, which is received in 97% yield and 96:4 regioisomeric ratio (rr) under the optimized conditions (Table S10).

The facile accessibility of oxidized donor **9** in just two high-yielding steps from commercial materials, storability, and stability under ambient conditions enabled convenient exploration of the reaction's scope (Figure 3). Esters were selected as electron-withdrawing directing group for EDA complex formation since they are broadly commercially available (Scifinder$^{TM}$ lists > 2 million commercial benzoic esters), among the most common motifs in drug design making them native functionalities,[11] and may act as versatile linchpin for further functionalization. The similarly abundant and versatile nitriles (**21**, **53**) act as an alternative directing group also providing the reduced products in high yields and regioisomeric ratios. Naphthalene [$E_{1/2}^{red}$ = –2.7 V vs SCE (–3.1 V vs ferrocene) in tetrahydrofuran][52] was reduced even without an activating group delivering 1,4 dihydronaphthalene (**48**) as major product. Notably, the reduction reaction regioselectively provides 2-cyclohexene carboxylates (**4**, **20**, **22**–**47**) whereas the overwhelming majority of Diels Alder reactions provide 3-cyclohexene carboxylates starting from a functionalized 1,3- diene and an acrylate (see SM). Inverse electron-demand Diels-Alder reactions are significantly less explored and would in the case of terminal cyclohexene rings also require ethylene as dienophile making Diels-Alder reactions to such 2-cyclohexene carboxylates inconvenient for standard laboratory syntheses. This explains why only a single synthesized cyclohexene product had previously been described in the literature despite their straightforward nature and demonstrates that the reaction provides access to new building blocks. Terminal as well as 3-substituted arenes are both suitable substrates with 2-substituted arenes showing lower reactivity (33% for hexyl-2-toluene carboxylate) and 4-substituted arenes being poorly reactive (10% for hexyl-4-toluene carboxylate, see Figure S6 for a list of unsuccessful substrates) despite near-identical redox potentials. We explain this finding with either a sterically controlled preferential EDA complex formation or a more rapid proton transfer. Annulated arenes, like an indole (**50**), an indazole (**51**), naphthalenes (**48**, **49**, **52**–**54**), and a phenanthrene (**55**) are less prone to steric effects, reduced in high yields, and generally exhibit complete reduction of the least electron-rich aromatic ring (**50**–**55**). This regioselectivity stands in contrast to catalytic hydrogenation reactions which generally reduce the least aromatic and

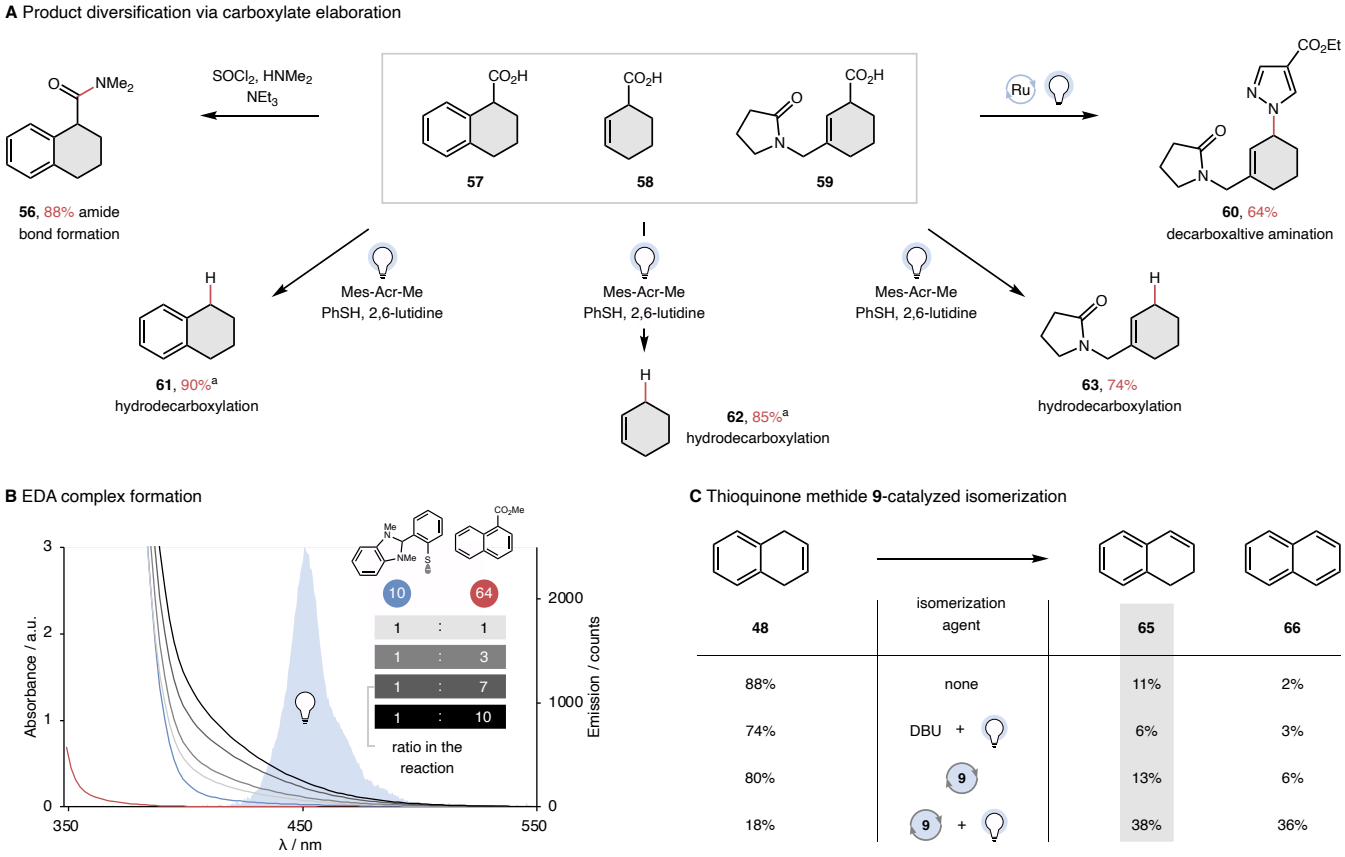


**Figure 4. Synthetic versatility of the reaction products and mechanistic studies. A** Product diversification via amide bond formation and decarboxylative amination, and removal of the carboxylate by photocatalyzed decarboxylation. Hydrodecarboxylation enables the esters to act as traceless and native directing groups for arene reduction. Isolated yields are reported. The carboxylic acids were accessed by a high-yielding saponification. **B** A red-shifted absorption in the UV/Vis spectrum, which enables overlap with the emission spectrum of the LED, suggests that EDA complex formation is responsible for the reactivity. Analogous experiments with thiophenolate and dihydrobenzimidazole suggest that the former moiety acts as donor (see Figure S9, 10). **C** Control experiments confirm that the isomerization is mediated by the oxidized donor **9**. [a]Analytical yield as an average of 5 experiments on 0.1 mmol scale. dr, diasteromeric ratio; Me, methyl; Et, ethyl; Mes-Acr-Me, 9-Mesityl-10-methylacridinium tetrafluoroborate; Ph, phenyl; *i*Pr, *iso*-propyl; rr, regioisomer ratio; EDA, electron-donor-acceptor. a.u., arbitrary unit; DBU, 8-diazabicyclo[5.4.0]undec-7-ene.

sterically hindered ring,[4] (see SI for a Scifinder™ search on indole hydrogenation). Perhaps most notably, the reaction tolerates a wide number of medicinally and synthetically relevant motifs. Functional groups with active hydrogens like alcohols (**22**) and free indazoles (**51**) are equally well-tolerated as Lewis-basic groups like imidazoles (**28**), triazoles (**29**), aminopyridines (**32**), pyrazoles (**4**, **42**–**45**), and thioethers (**47**). Most interesting to us is the broad tolerance of reducible functional groups like cyanides (**21**, **53**), sulfones (**38**), or alkynes (**44**) since our Scifinder™ search indicates that neither of these motifs have previously been tolerated in any reduction of a benzene ring, regardless of whether the product is a 1,4-cyclohexadiene, cyclohexene or -hexane (see SM, for details). Nevertheless, it should be noted that groups that have significantly higher redox potentials than benzoic esters are reduced in preference over the arene. Finally, the developed method was successfully applied to the reduction of a terminal benzene ring in the active pharmaceutical ingredients (APIs) Piperocaine (**23**) and Benfluorex (**25**).

The ability of the carboxylate functionality to act as adaptive functional group[54,55] for product elaboration into functional molecules was demonstrated with an amide bond formation (to **56**) and a decarboxylative amination (to **60**)[56] starting from the free carboxylic acids (**57, 59**) obtained by a high-yielding saponification (Figure 4, A see SI for details). Moreover the application of a modified decarboxylation protocol developed by the Nicewicz group[53] converted naphthalene (**57**) as well as terminal (**58**) and 3-substituted cyclohexene (**59**) carboxylic acids into their decarboxylated products (**61**–**63**) in high yields. This effectively makes the ester a native traceless directing group that enables chemoselective hydrogenation of a particular target arene to its cyclohexene counterpart.

Preliminary mechanistic experiments focused on verifying the key mechanistic proposals of EDA complex formation and thioquinone methide-mediated isomerization. UV/Vis absorption studies demonstrated the formation of an EDA complex between in situ-prepared thiophenolate **10** and methyl naphthalene-1-carboxylate (**64**) (Figure 4, C). Analogous experiments were conducted by replacing naphthalene-1-carboxylate with model substrate **1**, and by replacing the donor with thiophenol and phenyl dihydrobenzimidazole, respectively (Figure S7–10). These experiments suggest that EDA complex formation is a general mechanism for this transformation and that the thiophenolate rather than the DHBI moiety acts as donor. Isomerization studies conducted for commercially available 1,4-dihydronaphthalene **48** confirm that the thioquinone methide **9** and light are both required eliminating the possibility of a base-mediated isomerization (Figure 4, D). The generation of reoxidized naphthalene in this experiment and the quantitative generation of benzene in an analogous experiment for 1,4-cyclohexadiene demonstrates the importance of controlling the ratio between reduced (**10**) and oxidized donor (**9**). The exact mechanism of the isomerization remains unclear since hydride transfer, hydrogen atom transfer, oxidation/elimination and non-concerted proton-coupled electron transfer (PCET) have all been invoked for quinone-mediated oxidation reactions.[48] Based on the polarity-mismatched hydride and H-atom abstraction from the α-ester C–H bond, we currently favor a PCET mechanism for the generation of a cyclohexadienyl radical as key step for the isomerization.

In conclusion, we have developed a method for the conversion of benzoic esters and nitriles into the corresponding cyclohexenes using a newly designed organic donor that transfers electrons to arenes via EDA complex formation and isomerizes 1,4-cyclohexadienes to 1,3-cyclohexadienes in its oxidized thioquinone methide form. The reaction delivers orthogonal regioisomers compared to the Diels-Alder reaction, exhibits broad tolerance of Lewis-basic and reducible functional groups like triazoles, nitriles, sulfones, and alkynes, and can be paired with a saponification and decarboxylation to yield free cyclohexenes. Moreover, the ester group offers a convenient synthetic handle for further functionalization via decarboxylative cross-coupling.

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