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Toward a Catalytic Atroposelective Synthesis of Diaryl Ethers Through C(sp²)–H Alkylation with Nitroalkanes

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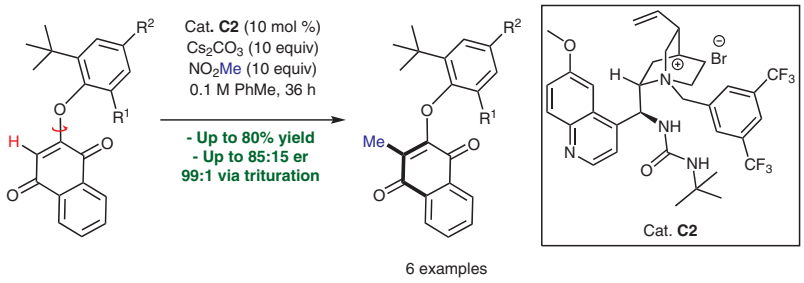

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Abstract We report studies toward a small-molecule-catalytic approach to access atropisomeric diaryl ethers that proceeds through a C(sp²)–H alkylation using nitroalkanes as the alkyl source. A quaternary ammonium salt derived from quinine, containing a sterically hindered urea at the C-9 position, was found to effect atroposelective C(sp²)–H alkylation with moderate to good enantioselectivities across several naphthoquinone-containing diaryl ethers. Products could then be isolated in >95:5 er after one round of trituration. For several substrates that were evaluated, we obtained nitroethylated products in similar yields and selectivities.

Key words atropisomerism, alkylation, phase-transfer catalysis, asymmetric catalysis, chirality

Atropisomerism is a type of chirality that occurs when there is hindered rotation about a bond, typically between two sp² atoms, wherein the rotational isomers are enantiomeric.[1–5] Although molecules that do not possess adequate barriers to rotation are not considered atropisomeric,[6] they possess the potential to be atropisomeric when engaging a chiral receptor (e.g., in protein binding or when interacting with a chiral catalyst).[7–12]

Previous work from our group and others has demonstrated that atropisomer conformation can be leveraged to improve various properties of biologically active small molecules.[13–16] This work, in part, serves as a call to action for the development of new synthetic methods toward atropisomeric compounds. Whereas there have been several excellent examples of atroposelective catalysis over the past few decades,[17–20] the vast majority of examples have involved biaryl scaffolds. Examples of atroposelective catalysis on nonbiaryl atropisomers have largely focused on benzamides and anilides.[2,8,9]

Diaryl ethers are a type of atropisomer that have been largely overlooked by the enantioselective catalysis community, despite the prevalence of these functional groups in natural products as exemplified by the macrocyclic diaryl ether moieties present in vancomycin. Furthermore, atropisomerically unstable diaryl ethers are common motifs in drug discovery (Figure 1). To date, the literature involving diaryl ethers is highlighted by some elegant diastereoselective examples en route to vancomycin[21] and by several excellent studies by Clayden and co-workers[22–26] wherein they characterized the stereochemical stabilities of variously substituted diaryl ethers and developed diastereoselective routes to atropisomeric diaryl ethers. Notably, in collaboration with Turner, they disclosed the only catalytic atroposelective route towards diaryl ethers currently in the literature; this route employs oxidase or reductase enzymes to desymmetrize prochiral diaryl ethers (Scheme 1A).

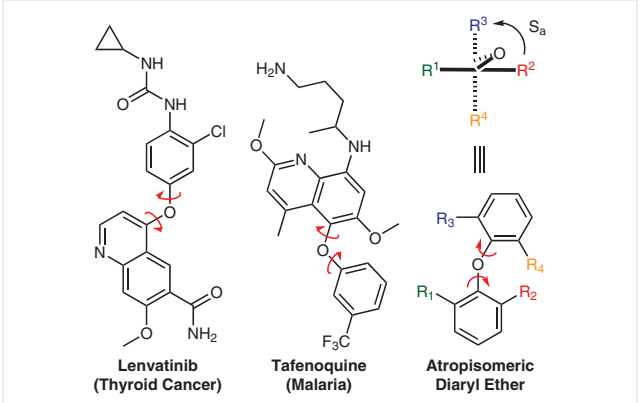
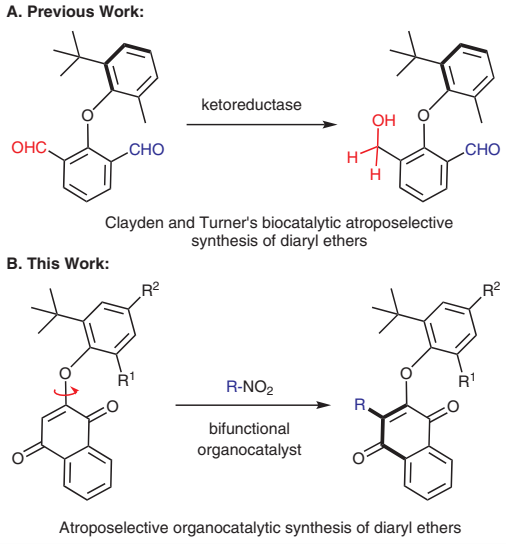


Figure 1 Illustrative examples of diaryl ethers



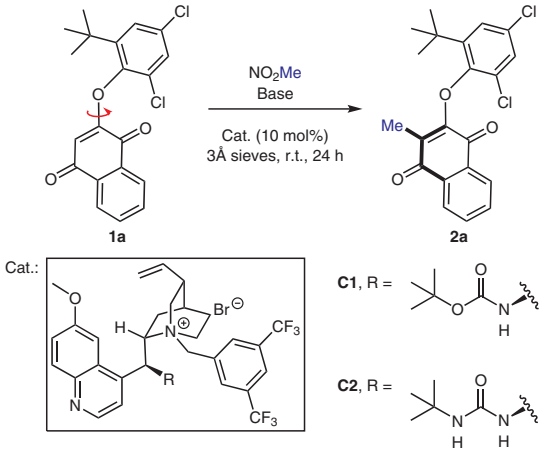
Scheme 1 (A) Previous catalytic atroposelective route towards diaryl ethers. (B) Proposed atroposelective alkylation of diaryl ethers.

Other than these groundbreaking examples, work on the catalytic atroposelective synthesis of diaryl ethers has been scarce. Perhaps the major reason for this is that diaryl ethers possess two axes (Figure 1), which can complicate reaction development, analysis, and, in some cases, result in racemization at a lower-than-expected energy through a concerted gearing mechanism.[23,27] When defining the chirality of diaryl ethers, Clayden and others have made an analogy to atropisomeric biaryl systems, defining chirality based on the orientation of the substituents across both aryl planes when the molecule is viewed along one aryl ether axis (see Figure 1; the priority in the example is assigned according to the R group number).

Recent work from our group has focused on the atroposelective synthesis of naphthoquinone-based biaryls by rigidification of a rapidly interconverting axis through a 1,4-nucleophilic addition to the quinone.[28] As there was a lack of enantioselective routes towards atropisomeric diaryl ethers, we decided to test whether this approach could be extended to this scaffold (Scheme 1B). We chose to evaluate naphthoquinones such as **1a**, in which the aryl group bears a large *tert*-butyl group and a second smaller substituent *ortho* to the ether axis, as Clayden has shown that the presence of one large quaternary substituent is often a prerequisite for the formation of stereochemically stable diaryl ethers.

While evaluating nucleophiles for the addition into **1a**, we observed that the use of nitromethane in the presence of excess Cs_2CO_3 and tetrabutylammonium bromide (TBAB) resulted in the isolation of the C(sp^2)–H methylated product **2a** (Table 1, entry 1), in line with seminal work reported by Mukherjee and co-workers.[29,30] Quinine-derived quaternary amines with hydroxy substitution at the cinchona alkaloid C-9 position gave almost no observable selectivities [see Supporting Information (SI) for details]. On the other hand, catalyst **C1**, which has a C-9 stereochemically inverted Boc-protected amine (Table 1, entry 2), gave reasonable levels of enantioselectivity, albeit with low conversions into **2a**. The selectivity could be further improved to an enantiomeric ratio (er) of 85:15 when the *tert*-butyl urea-containing catalyst **C2** was used.

Table 1 Optimization of C(sp^2)–H Methylation of **1a**[a]



Entry	Solvent	Catalyst	Base	MS	Yield (%)	er[b]
1	toluene	TBAB	Cs_2CO_3	–	18	-
2	toluene	**C1**	Cs_2CO_3	–	18	62:38
3	toluene	**C2**	Cs_2CO_3	–	17	85:15
4	toluene–H_2O	**C2**	Cs_2CO_3	–	40	50:50
5	toluene	**C2**	Na_2CO_3	–	20	60:40
6	toluene	**C2**	K_2CO_3	–	15	65:35
7	toluene	**C2**	K_3PO_4	–	60	80:20
8	toluene	**C2**	K_3PO_4	4 Å	51	75:25
9	toluene	**C1**	K_3PO_4	4 Å	36	64:36
10	toluene	**C2**	K_3PO_4	3 Å	68	81:19
11	CH_2Cl_2	**C2**	K_3PO_4	3 Å	38	68:32
12	MTBE	**C2**	K_3PO_4	3 Å	71	73:27

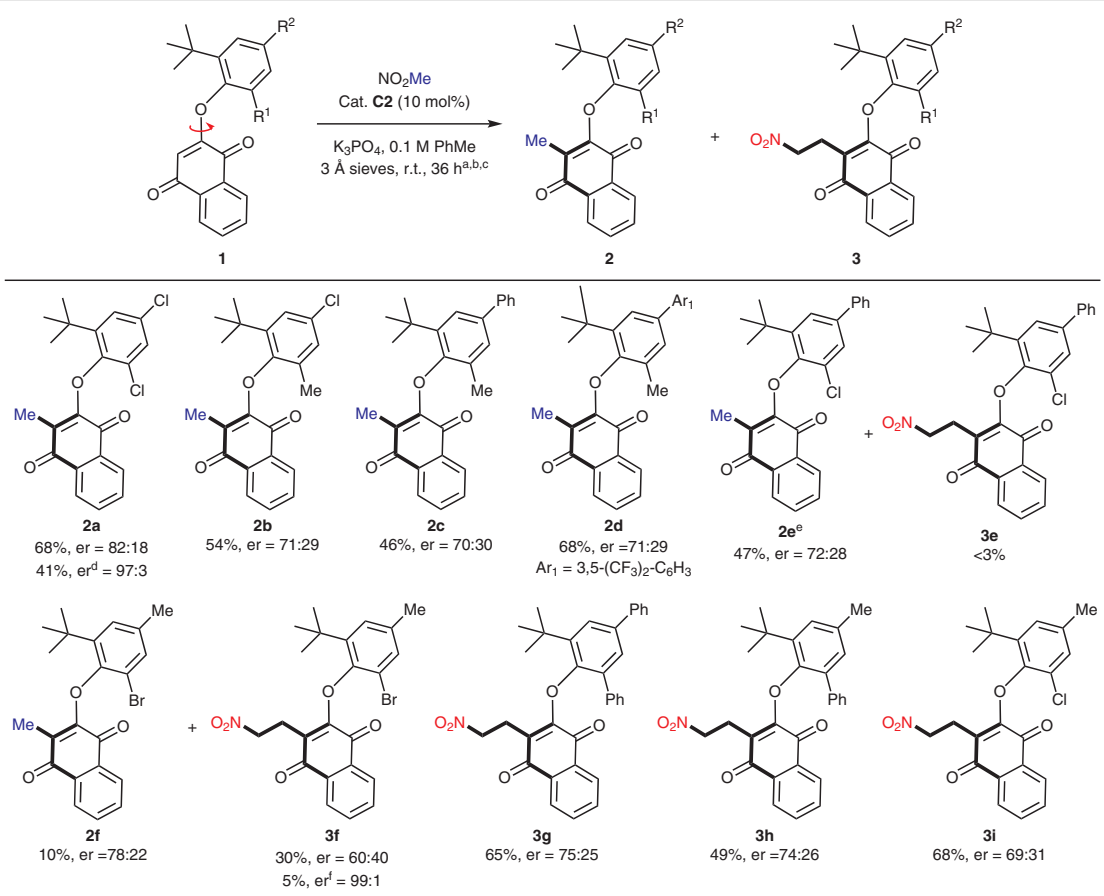
[a]Reactions were performed on a 0.028 mmol scale with 10 equiv of both base and nitromethane in 0.1 M solvent.
[b] Calculated by HPLC; the results are reported as an average from at least two trials. See the SI for more details.

The addition of water, or the use of other carbonate bases, resulted in a loss in selectivity with a minimal increase in yield (Table 1, entries 4–6); however, the use of tribasic potassium phosphate (Table 1, entry 7) resulted in an increase in yield to 60% with only a slight drop in selectivity (er 80:20) when compared with Cs_2CO_3. Finally, in line with Mukherjee's work, we found that the addition of 3 Å molecular sieves (MS) resulted in yields of **2a** that

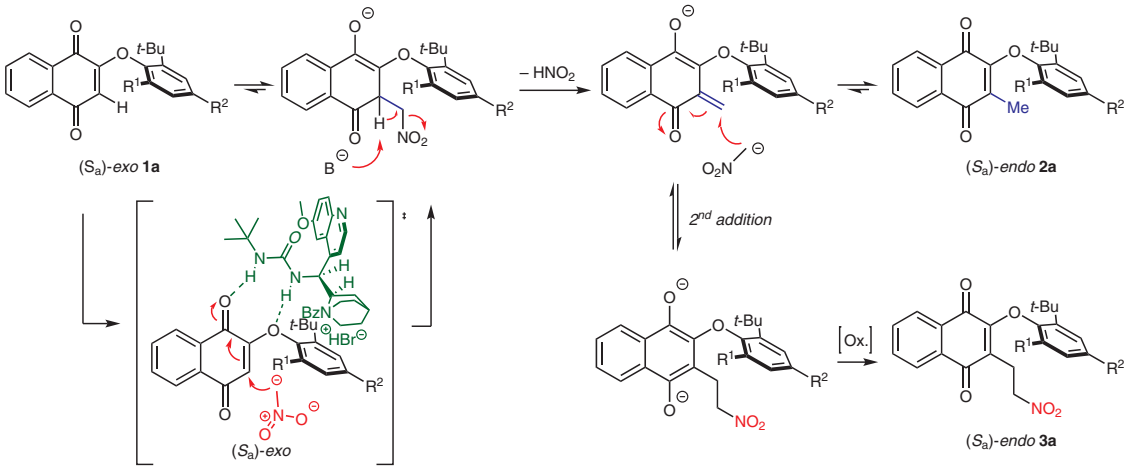
approached 70% with a small increase in selectivity to 81:19 er (Table 1, entry 10). Whereas these selectivities can be considered moderate, **1a** was further enantioenriched through trituration with isopropanol to provide **2a** in greater than 97:3 er. Product **2a** proved to be moderately stable, with an experimentally determined barrier to rotation at 65 °C of 26.6 kcal/mol, likely resulting in what LaPlante refers to as a 'Type-II atropisomer" that would be expected to display significant racemization at room temperature over the course of a few weeks.

Extensive experimentation failed to achieve an increase in er. Nonetheless, we decided to evaluate the conditions in Table 1, entry 10 across several variously substituted substrate analogues (Scheme 2).[31–33] Substrate **1b**, in which the aryl group bore a 6-methyl substituent, resulted in a decrease in yield and enantioselectivity in the isolated product **2b** to 54% yield with 71:29 er. Substrate **1c**, which contained 4-phenyl and 6-methyl substituents, gave **2c** with similar selectivities. These results can be explained by an increase in electron density on the ether, reducing the electrophilicity of the quinone. Diaryl ether **1d**, which possesses an electron-deficient *para*-aryl ring, reinforced this hypothesis, as its reaction proceeded with a significant increase in the yield of **2d**, while retaining moderate enantioselectivity (er 71:29).

Substrate **1e**, which contained 4-phenyl and 2-chloro substituents on the aryl ring, also gave moderate selectivities and yields of **2e** (47% yield; 72:28 er); however, we also obtained small amounts of the nitroethylated product **3e** (see below). Substrate **1f**, which contained a 6-bromo substituent, gave a 1:3 mixture of methylated **2f** (10% yield) to nitroethylated **3f** (30% yield). Interestingly, whereas **2f** was obtained in 78:22 er, **3f** was obtained in only 60:40 er. Surprisingly, one round of trituration with hexanes permitted the isolation of **3f** in 99:1 er, albeit in low overall yield. Substrate **1g**, which possesses 4,6-diphenyl substitution, gave the nitroethylated product **3g** exclusively with a 75:25 er. We observed similar results with **1h** and **1i,** which gave nitroethylated **3h** and **3i** with similar yields and selectivities.



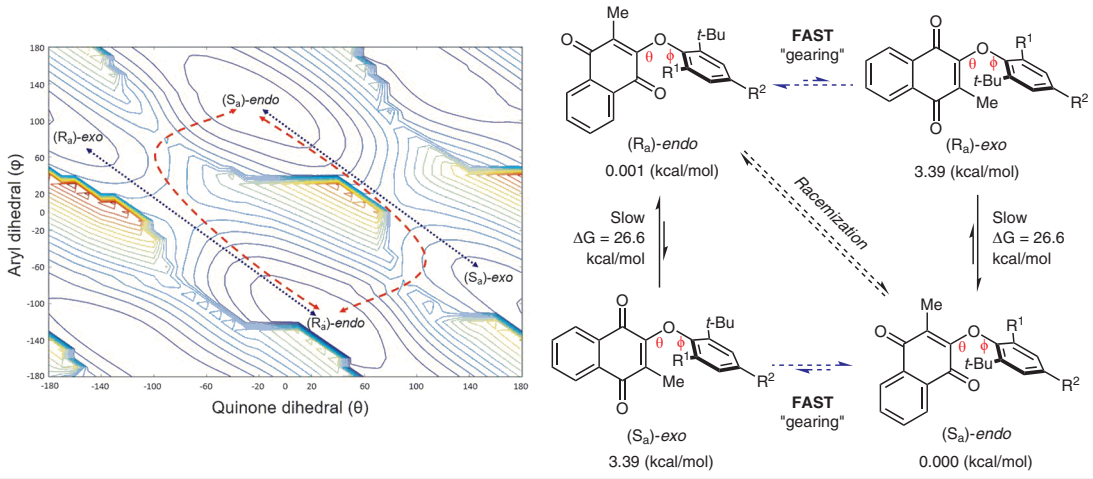
Scheme 2 [a] Reactions were performed on a 0.028 mmol scale with 10 equiv of both base and nitromethane in 0.1M toluene. [b] The formation of both products was observed for substrates **1a–i**. The major product is shown above together with its yield and er. More information about product ratios can be found in the SI. [c] The er was determined by HPLC from at least two trials. [d] **2a** was triturated with HPLC-grade isopropanol. [e] A mixture of the methylated and 'nitroethylated' products was detected by mass spectroscopy; only the methylated product **2e** was isolated and characterized. [f] **3f** was triturated with HPLC-grade hexanes. See SI for more details.



Scheme 3 Proposed mechanism for nucleophilic methylation. The key intermediate involves a quinone methide that is heavily affected by electronic effects of the aryl ring. Stabilization of the intermediate can induce subsequent addition of nitromethane, forming the nitroethylated product. We hypothesize that the urea catalyst interacts with both the diaryl ether and the carbonyl oxygen of the substrate, thereby locking the substrate into an (S_a)-*exo* conformation. Subsequent tautomerization or second addition of nitronate, followed by oxidation, provides the diaryl ether products **2a** and **3a**, respectively.

Referring back to Mukherjee's hypothesized mechanism of C(sp^2)–H alkylation with nitroalkanes, we postulate that our diaryl ether substrates react via a quinone methide intermediate.[29] If this intermediate is sufficiently long-lived, then another equivalent of nitronate anion can add in a 1,4-fashion to the quinone methide to give the nitroethylated product (Scheme 3). Although the exact mechanism of quinone methide stabilization is unknown, we suspect that it is due to a subtle electronic effect, as nitroethylation is only observed with substrates that possess electron-neutral or electron-donating substituents *para* to the ether group.

We next sought to define the stereochemical induction of this reaction. As we were unable to obtain suitable crystals, we compared experimental and computational circular dichroism (CD) spectra, a method that is gaining acceptance in the stereochemical community.[34–36] We obtained a CD spectrum of highly enantioenriched **2a** (er > 97:3) and we compared this to computed CD spectra of **2a** in all possible stable conformations about both ether axes (Scheme 4). This analysis suggests that the major product is in the S_a configuration with the proximal quinone carbonyl *endo* to the aryl ring, (S_a)-*endo*.



Scheme 4 A dihedral-angle contour diagram, generated through a force-field molecular model, conveys an energetically favorable pathway towards racemization via a concerted gearing mechanism (see SI for more details). Substrate–catalyst interactions can induce a high energy *exo*-conformation, followed by immediate gearing to the respective *endo*-enantiomer.

When we generated these conformations for the computational CD studies, we observed striking differences in their predicted energies (Scheme 4). For example, the (S_a)-*endo*-conformation of **2a** is predicted to be significantly more stable than the (S_a)-*exo*-conformation. Interestingly, we observed the opposite trend for the starting material **1a**, with the *exo*-conformation being the more stable (see SI for more details).

To investigate this further, we generated contour energy maps of the rotational landscape about both axes of the diaryl ether (Scheme 4). In a manner consistent with results from Clayden and co-workers,[23] these maps demonstrate that there is a low-energy pathway for interconversion between the *exo*- and *endo*-conformations of a given enantiomer that proceeds through a concerted gearing mechanism. It is therefore likely that the *exo*-conformation of the starting material is more stable and is likely to be the conformation that interacts with the catalyst. However, addition of the methyl leads to an immediate conformational gear shift to the *endo*-enantiomer.

Our working model for stereoinduction is shown in the proposed transition state shown in Scheme 3, in which we propose that the urea moiety of the catalyst forms a hydrogen bond with both the ether oxygen and one of the quinone carbonyls of the lower-energy *exo*-diaryl ether conformation. From here, the diaryl ether is preorganized into the (S_a)-atropisomer to avoid steric interactions between the *tert*-butyl group and the quinuclidinium that would be present in the (R_a) atropisomer/catalyst complex. We postulate that the hydrogen bonding activates the diaryl ether toward nucleophilic attack by the nitronate anion and that the molecule subsequently undergoes HNO_2 elimination followed by tautomerism to give the alkylated quinone, or subsequent attack by nitronate followed by oxidation to give the nitroethylated byproduct. At this point, it is likely that both products will rapidly relax to the *endo*-conformation, perhaps providing a release mechanism from the catalyst.

In conclusion, we have disclosed the first example of a small molecule catalytic synthesis of diaryl ethers. Although our selectivities were moderate to good, highly enantioenriched ethers can be accessed through trituration. We also discuss several mechanistic aspects of this work. We hope that these studies will serve as a starting point for future efforts towards the enantioselective syntheses of diaryl ethers and related atropisomers.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609581.

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(31) **Substituted Diaryl Ether Naphthoquinones 2; General Procedure**
A scintillation vial was charged with 3 Å powdered MS (10 mg) and an oven-dried stirrer bar. The sieves were activated, and toluene was syringed into the vial (0.1 M). The appropriate diaryl ether naphthoquinone **1** (0.026 mmol, 1 equiv), K_3PO_4 (0.26 mmol, 10 equiv), quaternary ammonium salt catalyst **C2** (.0026 mmol, 0.1 equiv), and NO_2Me (0.26 mmol, 10 equiv) were added sequentially. The mixture was stirred at r.t. for 36 h then then diluted with toluene and filtered through Celite to remove excess base and MS. Purification by flash column chromatography [silica gel, hexanes–CH_2Cl_2 (100:0 to 80:20)] gave the desired methylated and nitroethylated products. (~3–68% yield).
(32) **2-[2-*tert*-Butyl-4,6-dichlorophenoxy]-3-methylnaphthoquinone (2a)**
Bright-yellow solid; yield: 6.8 mg (68%); mp 123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (dd, *J* = 7.7, 1.3 Hz, 1 H), 7.91 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.72 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.66 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.32 (d, *J* = 2.5 Hz, 1 H), 7.18 (d, *J* = 2.5 Hz, 1 H), 2.26 (s, 3 H), 1.38 (s, 9 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 185.01, 178.23, 154.23, 150.33, 142.76, 134.01, 133.37, 131.95, 130.49, 129.17, 128.39, 127.62, 126.47, 126.40, 126.29, 125.23, 35.85, 29.99, 9.73. MS (APCI): *m/z* [M + H]$^+$ calcd for $C_{21}H_{18}Cl_2O_3$: 390.3; found: 390.3.
(33) **2-(2-Bromo-6-*tert*-butyl-4-methylphenoxy)-3-(2-nitroethyl)naphthoquinone (3f)**
Orange solid; yield: 3.8 mg (30%); mp 135 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13 (dd, *J* = 7.6, 1.3 Hz, 1 H), 7.93 (dd, *J* = 7.7, 1.3 Hz, 1 H), 7.75 (td, *J* = 7.6, 1.4 Hz, 1 H), 7.68 (td, *J* = 7.5, 1.4 Hz, 1 H), 7.21 (d, *J* = 2.0 Hz, 1 H), 7.17 (d, *J* = 2.2 Hz, 1 H), 4.80–4.68 (m, 2 H), 3.59 (ddd, *J* = 13.2, 9.0, 6.9 Hz, 1 H), 3.43 (ddd, *J* = 13.2, 8.8, 6.0 Hz, 1 H), 2.35 (s, 3 H), 1.37 (s, 9 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 184.16, 177.98, 155.80, 149.75, 135.52, 134.29, 133.68, 131.66, 130.66, 128.41, 127.85, 127.48, 126.70, 126.41, 124.44, 71.98, 35.54, 30.32, 29.70, 22.44, 20.94. MS (APCI): *m/z* [M + H]$^+$ calcd for $C_{23}H_{22}BrNO_5$: 473.3; found: 473.3.
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