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One-Pot Enantioselective Synthesis of 1,4-Naphthoquinone-Derived Polycycles through Oxidative Dearomatization and Aminocatalysis

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A synthetic process merging oxidative dearomatization and asymmetric aminocatalysis in a single vessel is reported. The $PhI(OAc)_2$-mediated oxidation of 1,4-dihydroxynaphthalene is followed by a trienamine-mediated Diels–Alder cycloaddition/aldol reaction or a trienamine-mediated Diels–Alder cycloaddition/oxidation sequence depending on the dienal substitution pattern. The polycyclic compounds are obtained in good yields with enantiomeric excesses up to 99 %. Additionally, these polycyclic architectures can be synthesized with similar enantioselectivities through an unprecedented one-pot marriage of bodipy-photocatalyzed oxidative dearomatization of 1-naphthol and asymmetric aminocatalysis. A catalytic cycle is suggested to explain the reaction outcome.

Introduction

The straightforward access to enantioenriched sp^3-rich polycyclic architectures is a focal point for extensive research efforts in both academic and industrial settings. These structures are exceptionally interesting because an increase in saturation, as measured by the fraction of sp^3 carbon atoms, and a high number of asymmetric centers in the molecular structures, tend to correlate with clinical success.[1] In terms of making natural products, synthetic strategies based on the formation of nonaromatic chiral polycycles from simple building blocks has been harnessed by several research groups.[2] In particular, the marriage of oxidative dearomatization and asymmetric catalysis in a single vessel has emerged as an attractive strategy to increase molecular complexity from simple and readily-introduced functionalities.[3] Within this context, the successful synthesis of densely functionalized sp^3-rich cyclic molecules has mainly involved the combination of oxidative dearomatization and asymmetric metal-catalyzed functionalization. Comparatively, the tactics, which involve loss of aromaticity followed by in-situ asymmetric organocatalyzed desymmetrization processes, have received less attention thus far.[4] As a striking example within this field, Gaunt and coworkers described in 2008 the one-pot oxidative dearomatization of phenols followed by a desymmetrizing amine-catalyzed asymmetric Michael addition to form bicyclic carbocycles with excellent selectivities.[5] Among other examples, the groups of You[6] and Jørgensen[7] have reported asymmetric transformations dealing with one-pot oxidative dearomatization and asymmetric organocatalytic functionalizations.[8] Most of these dearomatization processes have been combined with an organocatalytic intramolecular functionalization; this dramatically limits access to a vast array of diverse and complex cyclic optically active structures. To overcome this challenge, our group has recently reported the implementation of a new one-pot strategy that directly converts hydroquinone derivatives into enantioenriched tricyclic architectures by merging $PhI(OAc)_2$-mediated dearomatization and aminocatalysis.[9] The synthetic sequence proceeds through a trienamine-mediated asymmetric Diels–Alder cycloaddition with benzoquinone derivatives generated in situ, followed by an intramolecular Michael addition to form the tricyclic architectures (Scheme 1). To prevent intramolecular C–C bond formation through Michael addition, we reasoned that 1,4-dihydronaphthalene **2a** might be a suitable partner in the oxidative dearomatization/trienamine-mediated Diels–Alder cycloaddition.[10]

In this article, we report a selective process that directly converts 1,4-dihydroxynaphthalene **2a** by reaction with dienal **1** into enantioenriched 1,4-naphthoquinone-derived polycycles **3** or **4** depending on the dienal **1** substitution pattern. The reaction proceeds through a $PhI(OAc)_2$-mediated oxidation of 1,4-dihydroxynaphthalene **2a** to produce corresponding 1,4-naphthoquinone which further reacts with dienals by aminocatalysis to produce products **3** or **4**. In addition, we describe herein an unprecedented strategy merging organic-dye photocatalytic oxidative dearomatization and asymmetric aminocatalysis in a single vessel in order to prepare optically active compounds **3** from dienal **1** and 1-naphthol **2b**.

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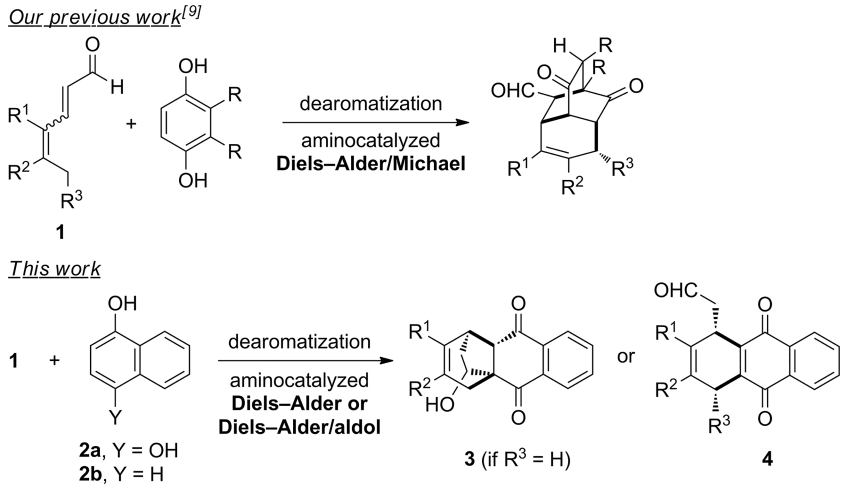
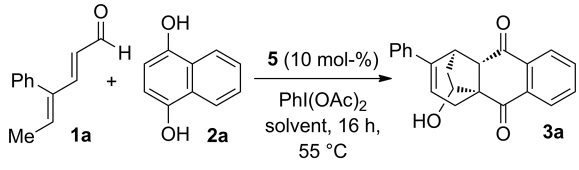


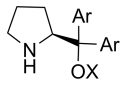
Scheme 1. Dearomatization and dienal chemistry.

Results and Discussion

We started our investigations by reacting **1a**, as a model substrate, with commercially available 1,4-dihydroxynaphthalene **2a** in the presence of $PhI(OAc)_2$ and various aminocatalysts. The results are depicted in Table 1.

Table 1. Optimization of reaction conditions.[a]





5a: X = TMS, Ar = 3,5-$(CF_3)_2C_6H_3$
5b: X = H, Ar = 3,5-$(CF_3)_2C_6H_3$
5c: X = TMS, Ar = Ph
5d: X= TBS, Ar = Ph

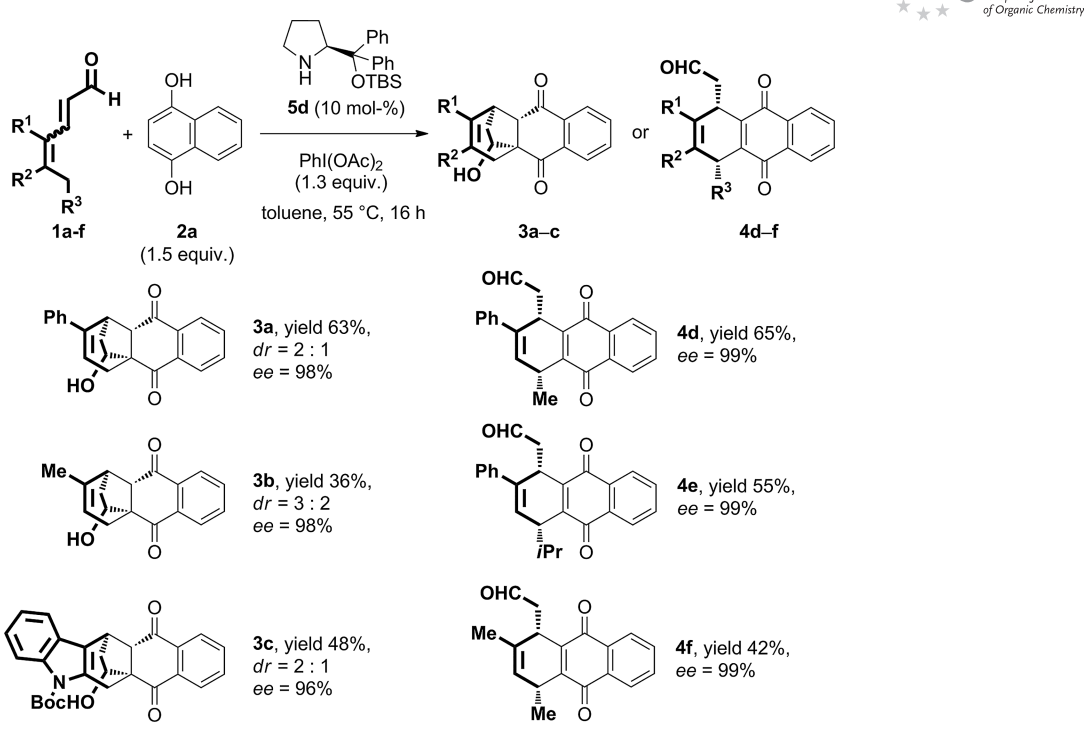
Entry	Catalyst	Solvent	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	L-Proline	$CHCl_3$	n.r.	n.d.	n.d.
2	**5a**	$CHCl_3$	n.r.	n.d.	n.d.
3	**5b**	$CHCl_3$	n.r.	n.d.	n.d.
4	**5c**	$CHCl_3$	38	2:1	96
5	**5d**	$CHCl_3$	36	2:1	98
6	**5d**	DMF	n.r.	n.d.	n.d.
7	**5d**	MeCN	31	1:1	94
8	**5d**	toluene	63	2:1	98
9[e]	**5d**	toluene	30	2:1	n.d.

[a] Reaction conditions: the reactions were performed on 0.5 mmol scale using 1 equiv. of **1a**, 1.5 equiv. of **2a**, 1.3 equiv. of $PhI(OAc)_2$ and 10 mol-% of the catalyst for 16 h at 55 °C in 2 mL of solvent unless otherwise noted; n.r.: no reaction, n.d.: not determined. [b] Isolated yields of the non-separable diastereomers. The structure of **3a** has been determined in light of our previous work (see ref.[9]) and by comparison with literature data, see experimentals. [c] Diastereomeric ratios were determined by ^1H NMR analysis of the crude product mixture. [d] Enantiomeric excesses were measured by chiral HPLC on pure analytical fractions of each diastereomer. [e] 3 mol-% of **5d** was used.

The use of L-Proline or catalysts **5a** and **5b** shut down the reaction and the formation of the polycyclic compound **3a** could not be detected (Table 1, Entries 1–3). The reaction of **1a** with **2a**, in the presence of the aminocatalyst **5c**, furnished optically active polycyclic compound **3a** in 38% yield as a mixture of diastereomers (Table 1, Entry 4). Enantiomeric excesses of 96% were obtained for both diastereomers of **3a**. Replacement of the TMS group with a bulkier TBS moiety led to interesting results by producing **4a** in 36% yield as a 2:1 mixture of diastereomers with 98% *ee* (Table 1, Entry 5). Among the solvent systems tested in the model reaction, toluene gave the best results by enabling production of **3a** in 63% yield as a 2:1 mixture of diastereomers in 98% *ee* for each diastereomer (Table 1, Entries 6–8). Lowering the catalyst loading from the initial 10 mol-% to 3 mol-% of **5d** led to a substantial decrease in yield (Table 1, Entry 9).

Having identified optimal reaction conditions (Table 1, Entry 8), we set out to explore the substrate scope of this chemistry with respect to other dienal substrates (Scheme 2).

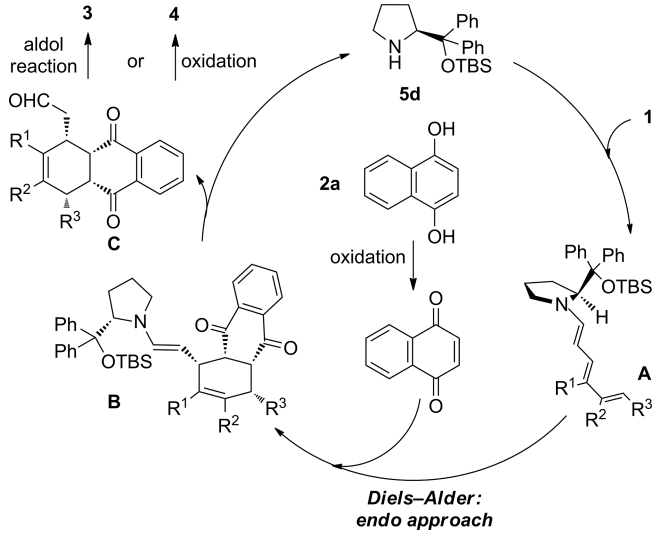
The reaction of 1,4-dihydroxynaphthalene **2a** with dienals **1a–c** bearing hydrogen as the R^3 substituent gave rise selectively to products **3a–c** by a trienamine-mediated Diels–Alder/aldol reaction sequence. For instance, compounds **3a** and **3b** were obtained in 63% and 36% yield respectively as a non-separable mixture of diastereomers with excellent enantioselectivities (*ee* = 98%). The indole-derived dienal provided **3c** in 42% yield as a 2:1 mixture of diastereomers with 96% *ee* for each diastereomer. The dearomatization/asymmetric functionalization process starting from dienals **1d–f** led to a different reaction outcome by producing tricyclic products **4d–f** whereas compounds of scaffold **3** were not detected in the crude reaction mixture. Therefore, the presence of substituents R^3 other than hydrogen in dienals **1d–f** appears to prevent the aldol reaction and only aldehydic products **4d–f** are formed after subsequent oxidation of the initial [4 + 2] cycloadducts. Substrates **1d–f** behaved similarly and enabled fair yields (42–65%) and excellent enantioselectivities (99% *ee*) for preparation of products **4d–f**. In addition, the preparation of **4d** was amenable to gram-scale production. Starting



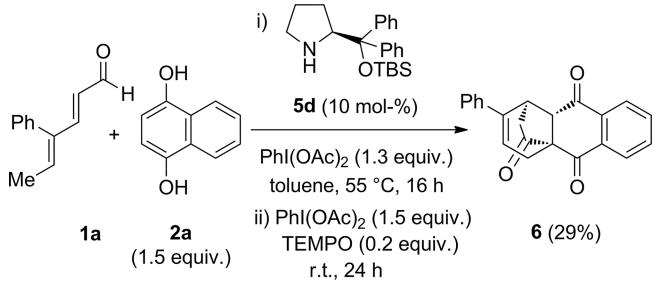
Scheme 2. Substrate scope.

from 5 mmol of **1d**, tricyclic compound **4d** (1.31 g) was isolated in 76% yield and with 98% *ee*. It is worth noting that the described one-pot sequence merging $PhI(OAc)_2$-mediated dearomatization and Diels–Alder reaction with **5d** as the catalyst produced cycloadducts **4** with higher enantioselectivities than previously reported by Jørgensen and coworkers for their reaction of dienals with 1,4-naphthoquinone promoted by aminocatalysts bearing H-bond-directing groups.[10] In the course of further studies, dienals **1** lacking substituents R^1 and/or R^2 were investigated. Nevertheless, (2*E*,4*E*)-hexadienal ($R^1 = R^2 = R^3 = H$), (2*E*,4*E*)-heptanedienal ($R^1 = R^2 = H$, $R^3 = Me$) and (*E*)-5-methyl-2,4-hexadienal ($R^1 = R^3 = H$, $R^2 = Me$) turned out to be inert under the reaction conditions. This lack of reactivity for such substrates has been previously observed by our group during studies of the trienamine-mediated reaction of dienals **1** with benzoquinone derivatives.[9] A postulated catalytic cycle explaining the selective formation of polycyclic compounds **3** or **4** is outlined in Scheme 3.

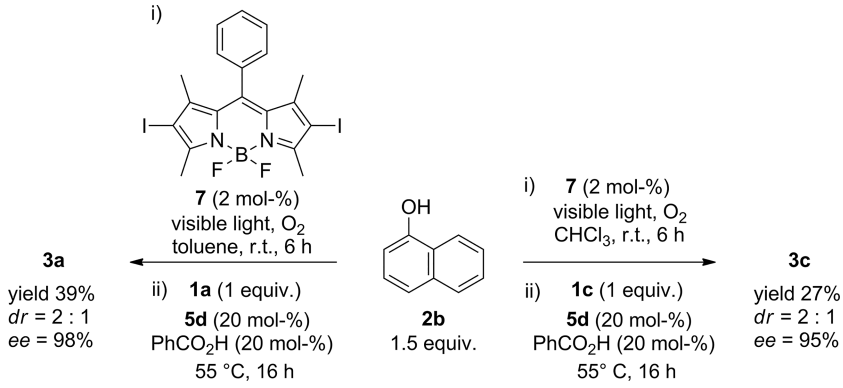
The catalytic cycle starts with condensation of aminocatalyst **5d** and dienal **1** to produce trienamine intermediate **A** which further reacts with the in-situ formed benzoquinone using an *endo* approach. Hydrolysis of enamine **B** then affords enantioenriched aldehydic compound **C**. If $R^3 = H$, further cyclization affords products **3** through an aldol reaction which is favoured due to a lower steric hindrance; compounds bearing the **4** scaffold are obtained by oxidation. The 1,4-naphthoquinone tricyclic derivatives **3** might be amenable to oxidation and as a result, a one-pot sequence involving trienamine-mediated Diels–Alder cycloaddition/aldol reaction followed by in-situ oxidation has also been developed (Scheme 4).



Scheme 3. Hypothesized catalytic cycle explaining generation of **3** and **4**.



Scheme 4. One-pot Diels Alder cycloaddition/aldol reaction/oxidation sequence.



Scheme 5. Merging of photocatalysis and aminocatalysis.

$PhI(OAc)_2$ is the central reagent for the one-pot transformation and compound **6** is synthesized in 29% yield from dienal **1a** and **2a**. During the course of further studies, we envisaged that 1-naphthol **2b** could be a suitable starting material for a new synthetic route merging photocatalytic oxidative dearomatization and asymmetric organocatalyzed functionalization process. In recent years, the combination of photoredox catalysis and asymmetric organocatalysis has spawned the development of new reactions by providing access to unprecedented retrosynthetic disconnections.[11] However, despite enormous achievements within this field, to the best of our knowledge the marriage of a photocatalytic oxidative dearomatization and asymmetric organocatalyzed functionalization in a single vessel has never been reported. For the dearomatization step, metal-free iodo-BODIPY **7** was chosen as a photosensitizer due to its ease of synthesis, strong visible light absorption and ability of oxidize phenol derivatives under aerobic conditions.[12] An intensive screening of reaction conditions involving the nature of solvents, photosensitizers, additives, reaction time and oxygen sources has been carried out (see the Supporting Information) and the best results are depicted herein (Scheme 5).

Under an oxygen rich atmosphere, the mixing of 1-naphthol **2b** in toluene for 6 h in the presence of 2 mol-% of iodo-BODIPY **7** gave rise to corresponding 1,4-naphthoquinone. The addition of dienal **1a** and the catalytic system (aminocatalyst **5d**/$PhCO_2H$) afforded polycycle **3a** in 39% yield (*dr*: 2:1, *ee* = 98%) through a one-pot sequential multicatalytic photooxygenation/Diels–Alder/aldol reaction. Under similar conditions, indole-derived polycycle **3c** was obtained in 27% yield as a 2:1 mixture of diastereomers with 95% *ee* by using $CHCl_3$ as the solvent. Unfortunately, all attempts to extend the methodology to other naphthols failed.[13]

Conclusions

In conclusion, we have developed an enantioselective process merging oxidative dearomatization and asymmetric aminocatalysis. Hypervalent iodine-mediated oxidation of 1,4-dihydroxynaphthalene or photooxygenation of 1-naphthol enabled in-situ formation of 1,4-naphthoquinone which underwent a [4 + 2] cycloaddition with a range of dienals. Depending on precise dienal substitution, the Diels–Alder reaction was followed by either an oxidative process leading to 1,4-naphthoquinone-derived aldehydic products or an intramolecular aldol reaction to form the corresponding alcohols as a mixture of diastereomers. Regardless of the sequence, high enantiomeric excesses for the polycyclic compounds are obtained and a catalytic cycle is readily envisioned that rationalizes the observed stereoselectivities.

Experimental Section

General Methods: ^1H NMR (200 or 300 MHz) and ^{13}C (50 or 75 MHz) spectra were recorded with Bruker Avance 200 or 300 MHz spectrometers using tetramethylsilane as an internal standard. Chemical shifts (δ) are given in parts per million and coupling constants are given as absolute values expressed in Hertz. Electrospray ionization (ESI) mass spectra were collected using a Q-TOF instrument supplied by WATERS. Samples (solubilized in ACN at 1 mg/mL and then diluted by 1000) were introduced into the MS via an UPLC system whilst a Leucine Enkephalin solution was co-injected via a micro pump. Infrared spectra were recorded with a Nicolet iS10 Infrared FT ATR spectrometer. Optical rotation values were measured at room temperature with a Perkin–Elmer 241 polarimeter. Thin-layer chromatography (TLC) was carried out on aluminium sheets precoated with silica gel 60 F254 (Merck). Column chromatography separations were performed using Merck Kieselgel 60 (0.040–0.060 mm). HPLC analyses were performed with a JASCO machine equipped with a UV/Vis detector at 30 °C employing chiral OD-H, AD or OJ-H columns. HPLC grade heptane and isopropyl alcohol were used as the eluting solvents (90:10, heptane/isopropyl alcohol; 1 mL/min). HPLC traces were compared to racemic samples prepared by mixture of two enantiomeric final products obtained using (S) and (R) catalysts. Toluene was dried immediately before use by distillation from standard drying agents while non-distilled chloroform was used for the one-pot reactions. For the bodipy-photocatalyzed oxidative dearomatization step, the reaction mixture was irradiated with 35-W Xe lamp (0.72 mol L^{-1} $NaNO_2$ solution was used as filter so that light with wavelength < 385 nm was blocked). Dienals **1**[14] and the bodipy photosensitizer **7**[12] were prepared according to literature procedures.

$PhI(OAc)_2$-Mediated Dearomatization/Aminocatalysis. General Procedure A: To a solution of 1,4-dihydroxynaphthalene (**2a**) (120 mg, 0.75 mmol, 1.5 equiv.) in toluene (1 mL) was added $PhI(OAc)_2$ (210 mg, 0.65 mmol, 1.3 equiv.), under heavy stirring. The dienal **1** (0.5 mmol, 1 equiv.) and catalyst **5d** (18 mg, 0.05 mmol, 0.1 equiv.) were then dissolved in toluene (0.5 mL each) and added to the previous solution, in that order. The reaction was left to stir at 55 °C for 16 h. The reaction mixture was washed with water. The aqueous phase was extracted with DCM and the organic phases were combined, dried on anhydrous $MgSO_4$, filtered and concentrated under vacuum. The diastereomeric ratio was determined by ^1H NMR at this stage. The crude product was passed through column chromatography (PE/EtOAc, 9:1) and then on a preparative TLC (PE/EtOAc, 8:2) to afford corresponding tricyclic compounds **3** or **4**.

Photooxidative Dearomatization/Aminocatalysis. General Procedure B: Bodipy **7** (2.5 mg, 0.04 mmol, 0.02 equiv.) was dissolved in toluene (2.5 mL) and added to 1-naphthol **2b** (36 mg, 0.25 mmol, 1.5 equiv.). After O_2 was left bubbling into the solution for 5 min, the reaction was left to stir for 6 h under white light irradiation under O_2 atmosphere. The solution was left to cool and excess O_2 was removed by bubbling argon into the solution. dienal **1a** or **1c** (0.15 mmol, 1 equiv.), benzoic acid (3.7 mg, 0.03 mmol, 0.2 equiv.) and catalyst **5d** (11 mg, 0.030 mmol, 0.2 equiv.) were added to the solution, in that order. The reaction was left to stir at 55 °C for 16 h. The crude was concentrated and directly passed through a column chromatography (PE/EtOAc, 8:2) to afford corresponding tricyclic compound **3a** or **3c**.

Polycyclic Compound 3a: (2*E*,4*Z*)-4-Phenylhexa-2,4-dienal (**1a**) (86.1 mg) reacted following the general procedure A (for the procedure B, 25.8 mg of **1a** was used), and was isolated as an orange oil (102.5 mg, 63% yield, mixture of diastereomers A + B); *dr*: A/B, 2:1; *ee*: 98%; TLC (PE/EtOAc, 8:2): R_f = 0.24; 0.27. ^1H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 8.11–8.03 (m, 4 H, Ar*H*, A + B), 7.80–7.73 (m, 2 H, Ar*H*, B), 7.73–7.66 (m, 2 H, Ar*H*, A), 7.45–7.25 (m, 10 H, Ar*H*, A + B), 5.98 (app t, *J* = 3.5 Hz, 1 H, C=C*H*, B), 5.82 (app t, *J* = 3.5 Hz, 1 H, C=C*H*, A), 4.49 (m, 2 H, C*H*, A + B), 3.93 (d, *J* = 6.3 Hz, 1 H, C*H*, A), 3.71 (d, *J* = 6.5 Hz, 1 H, C*H*, B), 3.40 (s, 1 H, C*H*, B), 3.30 (dd, *J* = 19.1, 4.2 Hz, 1 H, CH_2, B), 3.22 (s, 1 H, C*H*, A), 2.90 (dd, *J* = 19.1, 3.2 Hz, 1 H, *C*H_2, A), 2.80 (dd, *J* = 19.1, 4.0 Hz, 1 H, CH_2, A), 2.71–2.54 (m, 3 H, CH_2 [A] & CH_2 [B]), 2.20 (s, 2 H, O*H*, A + B), 2.05 (ddd, *J* = 13.5, 6.5, 4.2 Hz, 1 H, CH_2, A), 1.83 (dt, *J* = 13.7, 2.8 Hz, 1 H, CH_2, B) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 199.0 (2 C, A + B), 196.6 (A), 196.1 (B), 144.7 (B), 144.4 (A), 139.5 (2 C, A + B), 136.8 (A or B), 136.5 (A or B), 134.7 (B), 134.6 (B), 134.5 (B), 134.1 (A), 133.8 (2 C, A), 133.7 (A), 128.6 (A or B), 128.5 (A or B), 127.5 (A or B), 127.4 (A or B), 127.3 (A or B), 126.9 (A or B), 126.5 (A or B), 126.4 (2 C, A or B), 125.2 (4 C, A + B), 120.9 (B), 119.3 (A), 82.7 (A), 77.3 (B), 59.2 (B), 59.1 (B), 58.8 (B), 57.0 (A), 46.0 (A), 42.2 (B), 38.4 (A), 38.1 (B), 36.5 (A), 29.7 (B) ppm. IR: $\tilde{\nu}$ = 3435, 3057, 2931, 1670, 1591, 1063 cm^{-1}. HRMS (ESI) Calcd for $C_{22}H_{19}O_3$ [M + H]$^+$: 331.1334, found 331.1333. Enantiomeric excesses have been determined on analytical fractions of diastereomers A and B by HPLC analyses employing a chiral OJ-H column (heptane/2-propanol, 90:10, 1.0 mL/min), t_{rA} = 29.59 min for the minor enantiomer and t_{rA} = 47.02 min for the major enantiomer. t_{rB} = 28.40 min for the minor enantiomer and t_{rB} = 45.84 min for the major enantiomer.

Polycyclic Compound 3b: (2*E*,4*E*)-4-Methylhexa-2,4-dienal (**1b**) (55 mg) reacted following the general procedure A and was isolated as a colorless oil (48 mg, 36% yield, mixture of diastereomers A + B); *dr*: A/B, 3:2, *ee* = 98% (determined after oxidation of the alcohol function), TLC (PE/EtOAc, 8:2): R_f = 0.37. ^1H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 8.18–8.03 (m, 4 H, Ar*H*, A + B), 7.81–7.77 (m, 2 H, Ar*H*, A), 7.75–7.70 (m, 2 H, Ar*H*, B), 5.34 (br. s, 1 H, C=C*H*, A), 5.13 (br. s, 1 H, C=C*H*, B), 4.44–4.38 (m, 2 H, C*H*, A + B), 3.32 (br. s, 1 H, C*H*, A), 3.16 (d, *J* = 6.1 Hz, 1 H, C*H*, B), 3.12 (s, 1 H, C*H*, B), 3.05 (m, 1 H, CH_2, A), 2.96 (d, *J* = 6.2 Hz, 1 H, C*H*, A), 2.75–2.35 (m, 5 H, CH_2, A + B), 1.87 (ddd, *J* = 13.4, 6.1, 4.4 Hz, 1 H, CH_2, B), 1.80 (d, *J* = 1.8 Hz, 3 H, CH_3, A), 1.78 (d, *J* = 1.7 Hz, 3 H, CH_3, B), 1.68 (dt, *J* = 14.1, 2.9 Hz, 1 H, CH_2, A), 1.66 (br. s, 2 H, OH, A + B) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 199.1 (A), 199.0 (A), 197.0 (B), 196.4 (B), 142.1 (A or B), 141.6 (A or B), 136.7 (A or B), 136.6 (A or B), 134.6 (A), 134.5 (A), 134.4 (A), 134.0 (B), 133.9 (B), 133.8 (B), 127.4 (A or B), 126.7 (A or B), 126.4 (2 C, A + B), 117.6 (A), 116.2 (B), 82.3 (B), 77.3 (A), 77.2 (B), 58.8 (A), 58.7 (A), 58.3 (A), 56.6 (B), 44.7 (B), 41.4 (A), 40.3 (A), 36.1 (A), 29.3 (B), 22.0 (2 C, A + B) ppm. IR: $\tilde{\nu}$ = 3482, 3371, 2958, 2931, 2850, 1674, 1592, 1442, 1318, 1268, 1037 cm^{-1}. HRMS (ESI) Calcd for $C_{17}H_{17}O_3$ [M + H]$^+$: 269.1178, found 269.1176. Enantiomeric excess was determined on product **3b**, which underwent alcohol oxidation, by HPLC analysis employing a chiral OD-H column (heptane/2-propanol, 90:10, 1.0 mL/min), t_r = 10.51 min for the major enantiomer and t_r = 12.00 min for the minor enantiomer.

Polycyclic Compound 3c: *tert*-Butyl 2-methyl-3-(3-oxoprop-1-enyl)-1*H*-indole-1-carboxylate (**1c**) (147 mg) reacted following the general procedure A (for the procedure B, 49 mg of **1c** was used) and was isolated as a yellow oil (108.0 mg, 48% yield, mixture of diastereomers A + B); *dr*: A/B, 2:1; *ee* = 96%; TLC (PE/EtOAc, 8:2): R_f = 0.23. ^1H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 8.22–8.09 (m, 6 H, Ar*H*, A + B), 7.85–7.81 (m, 2 H, Ar*H*, B), 7.80–7.72 (m, 2 H, Ar*H*, A), 7.56–7.51 (m, 2 H, Ar*H*, A + B), 7.33–7.25 (m, 4 H, Ar*H*, A + B), 4.54 (dd, *J* = 9.8, 2.4 Hz, 1 H, C*H*, B), 4.49 (dd, *J* = 6.8, 1.5 Hz, 1 H, C*H*, A), 4.24 (d, *J* = 5.5 Hz, 1 H, C*H*, A), 4.09 (d, *J* = 19.0 Hz, 1 H, CH_2, B), 4.06 (d, *J* = 4.9 Hz, 1 H, C*H*, B), 3.76 (d, *J* = 18.6 Hz, 1 H, CH_2, A), 3.51 (d, *J* = 18.6 Hz, 1 H, CH_2, A), 3.45 (s, 1 H, C*H*, B), 3.42 (d, *J* = 19.0 Hz, 1 H, CH_2, B), 3.28 (s, 1 H, C*H*, A), 2.62 (m, 1 H, CH_2, B), 2.54 (m, 1 H, CH_2, A), 2.11–2.02 (m, 2 H, CH_2, A + B), 1.92 (br. s, 2 H, OH, A + B), 1.72 (s, 9 H, *tBu*, B), 1.71 (s, 9 H, *tBu*, A) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 198.4 (A), 198.3 (B), 196.3 (A), 195.8 (B), 150.3 (B), 150.2 (A), 136.6 (2 C, A + B), 136.3 (A), 136.2 (B), 136.1 (2 C, A + B), 134.9 (B), 134.6 (B), 134.3 (B), 134.2 (A), 134.1 (A), 133.9 (B), 132.2 (B), 130.8 (2 C, A + B), 127.6 (2 C, A + B), 127.0 (B), 126.9 (A), 126.8 (2 C, A + B), 126.7 (A), 126.6 (B), 124.1 (A), 123.9 (B), 123.1 (B), 123.0 (A), 122.9 (A), 122.8 (B), 117.6 (A), 117.5 (B), 115.6 (2 C, A + B), 84.0 (A), 83.9 (B), 82.3 (A), 77.3 (A), 76.8 (B), 59.6 (2 C, A + B), 57.3 (A), 46.8 (A), 42.4 (B), 37.2 (A), 32.8 (A), 29.9 (B), 28.3 (2 C, A + B) ppm. IR: $\tilde{\nu}$ = 3473, 2974, 2932, 1726, 1680, 1592, 1454, 1359, 1270, 1249, 1153, 1134 cm^{-1}. HRMS (ESI) Calcd for $C_{27}H_{25}NO_5Na$ [M + H]$^+$: 466.1630, found 466.1635. Enantiomeric excesses have been determined on a 3:2 mixture of diastereomers A and B by HPLC analysis employing a chiral AD column (heptane/2-propanol, 90:10, 1.0 mL/min), t_{rA} = 10.82 min for the minor enantiomer and t_{rA} = 18.19 min for the major enantiomer. t_{rB} = 12.52 min for the minor enantiomer and t_{rB} = 15.50 min for the major enantiomer.

Tricyclic Compound 4d: (2*E*,4*Z*)-4-phenylhepta-2,4-dienal (**1d**) (93 mg) reacted following the general procedure A and was isolated as a yellow oil (112 mg, 65% yield); *ee* = 99%; TLC (PE/EtOAc, 9:1): R_f = 0.32. ^1H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 9.54 (app t, *J* = 3.1 Hz, 1 H, C*H*O), 8.07–8.00 (m, 2 H, Ar*H*), 7.70–7.63 (m, 2 H, Ar*H*), 7.40–7.23 (m, 5 H, Ph*H*), 6.06 (d, *J* = 5.0 Hz, 1 H,

C=C*H*), 4.62 (dt, *J* = 6.1, 3.3 Hz, 1 H, C*H*), 3.82–3.72 (m, 1 H, C*H*), 2.57 (ddd, *J* = 15.2, 5.5, 2.7 Hz, 1 H, CH_2), 2.46 (ddd, *J* = 15.2, 6.4, 3.3 Hz, 1 H, CH_2), 1.32 (d, *J* = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 200.3, 184.4, 183.8, 147.7, 143.5, 138.9, 137.1, 133.9, 133.8, 132.2, 132.0, 128.9 (2 C), 128.6, 128.1, 126.6 (2 C), 126.5 (2 C), 49.2, 32.7, 32.1, 22.0 ppm. IR: $\tilde{\nu}$ = 2933, 2890, 2830, 2736, 1721, 1654, 1621, 1590, 1289 cm^{-1}. HRMS (ESI) Calcd for $C_{23}H_{19}O_3$ [M + H]$^+$: 343.1334, found 343.1327. $[\alpha]_D^{20}$ = –26.5 (*c* = 0.34, $CHCl_3$). Enantiomeric excess has been determined by HPLC analysis employing a chiral OJ-H column (heptane/2-propanol, 90:10, 1.0 mL/min), t_r = 16.45 min for the minor enantiomer and t_r = 25.47 min for the major enantiomer. NMR analyses were in complete agreement with the reported ones.[10]

Tricyclic Compound 4e: (2*E*,4*Z*)-7-methyl-4-phenylocta-2,4-dienal (**1e**) (110 mg) reacted following the general procedure A and was isolated as a yellow oil (98 mg, 55% yield); *ee* = 99%; TLC (PE/EtOAc, 9:1): R_f = 0.33. ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 9.68 (t, *J* = 2.6 Hz, 1 H, C*H*O), 8.15–8.08 (m, 2 H, Ar*H*), 7.78–7.72 (m, 2 H, Ar*H*), 7.50–7.32 (m, 5 H, Ph*H*), 6.12 (d, *J* = 4.8 Hz, 1 H, C=C*H*), 4.78 (dt, *J* = 5.7, 4.1 Hz, 1 H, C*H*), 3.86 (q, *J* = 4.4 Hz, 1 H, C*H*), 2.56 (dd, *J* = 5.7, 2.6 Hz, 2 H, CH_2), 2.34–2.23 (m, 1 H, C*H*), 1.21 (d, *J* = 6.9 Hz, 3 H, CH_3), 0.89 (d, *J* = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 199.7, 184.5, 184.1, 146.3, 144.8, 139.7, 139.4, 133.9, 133.8, 132.2, 132.0, 128.8 (2 C), 128.2, 126.8 (2 C), 126.5 (2 C), 123.9, 50.2, 42.0, 32.9, 32.1, 21.8, 18.9 ppm. IR: $\tilde{\nu}$ = 3059, 2955, 2928, 2868, 2730, 1721, 1655, 1618, 1592, 1284 cm^{-1}. HRMS (ESI) Calcd for $C_{25}H_{23}O_3$ [M + H]$^+$: 371.1647, found 371.1654. $[\alpha]_D^{20}$ = –44 (*c* = 1, $CHCl_3$). Enantiomeric excess has been determined by HPLC analysis employing a chiral OJ-H column (heptane/2-propanol, 90:10, 1.0 mL/min), t_r = 11.34 min for the minor enantiomer and t_r = 15.65 min for the major enantiomer.

Tricyclic Compound 4f: (2*E*,4*E*)-4-methylhepta-2,4-dienal (**1f**) (65 mg) reacted following the general procedure A and was isolated as an orange oil (60 mg, 42% yield); *ee* = 99%; TLC (PE/EtOAc, 9:1): R_f = 0.30. ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 9.84 (t, *J* = 2.7 Hz, 1 H, C*H*O), 8.11–8.03 (m, 2 H, Ar*H*), 7.74–7.68 (m, 2 H, Ar*H*), 5.65 (br. d, *J* = 4.8 Hz, 1 H, C=C*H*), 3.95 (dt, *J* = 5.8, 3.3 Hz, 1 H, C*H*), 3.64–3.55 (m, 1 H, C*H*), 2.68 (ddd, *J* = 15.7, 5.8, 2.7 Hz, 1 H, CH_2), 2.59 (ddd, *J* = 15.7, 5.8, 2.7 Hz, 1 H, CH_2), 1.84 (s, 3 H, CH_3), 1.25 (d, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 200.9, 184.4, 183.9, 148.1, 143.9, 133.8, 133.7, 132.5, 132.2, 132.0, 126.7, 126.4 (2 C), 48.9, 34.0, 30.7, 22.1, 21.1 ppm. IR: $\tilde{\nu}$ = 2967, 2930, 2873, 2730, 1720, 1656, 1621, 1592, 1326, 1288 cm^{-1}. HRMS (ESI) Calcd for $C_{18}H_{17}O_3$ [M + H]$^+$: 281.1178, found 281.1175. $[\alpha]_D^{20}$ = +13 (*c* = 1, $CHCl_3$). Enantiomeric excess has been determined by HPLC analysis employing a chiral OJ-H column (heptane/2-propanol, 90:10, 1.0 mL/min), t_r = 10.24 min for the major enantiomer and t_r = 12.41 min for the minor enantiomer. NMR analyses were in complete agreement with the reported ones.[10]

Polycyclic Compound 6: To a solution of 1,4-dihydroxynaphthalene (120 mg, 0.75 mmol, 1.5 equiv.) in toluene (1 mL) was added $PhI(OAc)_2$ (210 mg, 0.65 mmol, 1.3 equiv.), under heavy stirring. The dienal **1a** (86.1 mg, 0.5 mmol, 1 equiv.) and catalyst **5d** (18 mg, 0.05 mmol, 0.1 equiv.) were then dissolved in toluene (0.5 mL each) and added to the previous solution, in that order. The reaction was left to stir at 55 °C for 16 h. The reaction was cooled down to room temperature. Additional $PhI(OAc)_2$ (245 mg, 0.76 mmol, 1.5 equiv.) and TEMPO (16 mg, 0.1 mmol, 0.2 equiv.) were added to the solution. The reaction was left to stir at room temperature for 24 h. The mixture was washed with saturated $Na_2S_2O_3$ (aq). The aqueous phase was extracted with DCM and the organic phases were combined, washed with saturated $NaHCO_3$ (aq) and then brine, dried on anhydrous $MgSO_4$, filtered and concentrated under vacuum. The crude product was passed through column chromatography (PE/EtOAc, 9:1) and then on a preparative TLC (PE/EtOAc, 8:2) to afford corresponding product **6** 57 mg, 29% yield, *ee*: 98%. TLC (PE/EtOAc, 9:1): R_f = 0.20. ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 8.18 (dt, *J* = 13.9, 4.1 Hz, 2 H, Ar*H*), 7.80 (t, *J* = 4.4 Hz, 2 H, Ar*H*), 7.46–7.32 (m, 5 H, Ph*H*), 6.02 (t, *J* = 3.2 Hz, 1 H, C=C*H*), 4.20 (d, *J* = 5.3 Hz, 1 H, C*H*), 3.66 (s, 1 H, C*H*), 3.10 (dd, *J* = 19.2, 4.0 Hz, 1 H, CH_2), 2.95 (dd, *J* = 19.2, 2.7 Hz, 1 H, CH_2), 2.71–2.55 (m, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 209.9, 195.0, 191.3, 143.5, 138.8, 135.6, 135.1 (2 C), 134.5, 128.7 (2 C), 127.9, 127.5, 127.3, 125.3, 120.4, 77.3, 63.7, 56.8, 47.1, 36.7, 35.0 ppm. IR: $\tilde{\nu}$ = 3059, 3030, 2971, 2900, 1750, 1683, 1589, 1270 cm^{-1}. HRMS (ESI) Calcd for $C_{22}H_{17}O_3$ [M + H]$^+$: 329.1178, found 329.1176. $[\alpha]_D^{20}$ = +14 (*c* = 1, $CHCl_3$).

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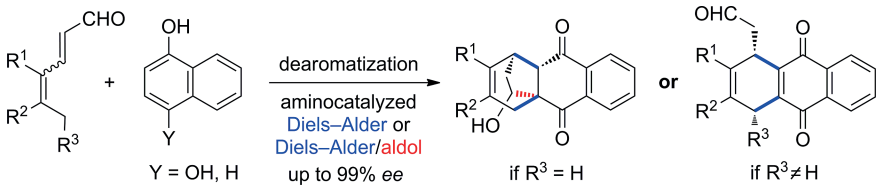

The asymmetric synthesis of diversely substituted 1,4-naphthoquinone-derived polycycles is described by merging dearomatization and aminocatalysis in a single vessel. The dearomatization step is promoted by $PhI(OAc)_2$ or oxygen in the presence of a bodipy photosensitizer and two products are selectively isolated depending on the dienal substitution.

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One-Pot Enantioselective Synthesis of 1,4-Naphthoquinone-Derived Polycycles through Oxidative Dearomatization and Aminocatalysis

Keywords: Asymmetric synthesis / Organocatalysis / Dearomatization / Cycloaddition / Photooxidation / Polycycles

