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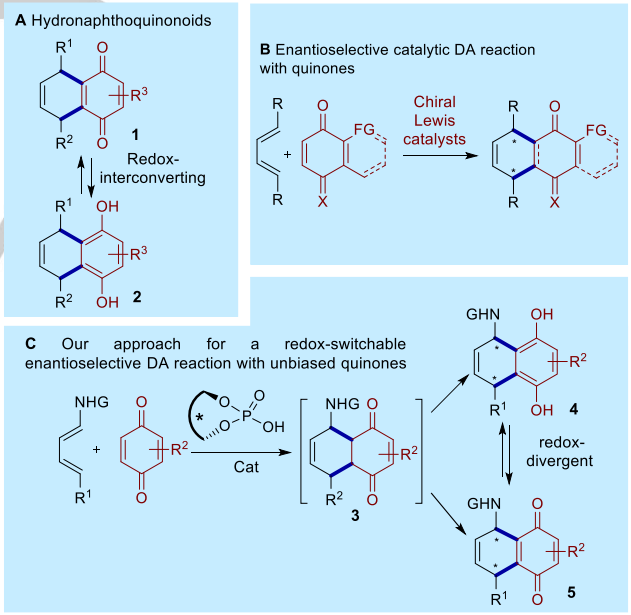
Abstract: An efficient enantioselective construction of tetrahydronaphthalene-1,4-diones as well as dihydronaphthalene-1,4-diols *via* a chiral phosphoric acid catalyzed quinone Diels–Alder reaction with dienecarbamate was reported. The nature of the protected group on diene was key to the success showing a remarkable influence for achieving high enantioselectivity. The divergent "redox" selectivity is controlled by adequate amount of quinones used. Reversible redox switching without erosion of enantioselectivity was possible from individual redox isomers.

Quinones have been recognized as important units because of their rich and important reactivity.[1] Indeed, the reversible redox properties[2] of the couple benzoquinone/hydroquinone play a central role in a number of biological systems.[3,4a] Among these, the two redox isomers dihydronaphthalene-1,4-diol **1** and tetrahydronaphthalene-1,4-dione **2** (Scheme 1, A), are valuable structural units found in various natural products.[4]

In 1928, Diels and Alder uncovered an easy transformation allowing to build hydronaphthoquinonoids,[4b,5] and since then the [4+2] cycloaddition involving quinones has continuously been an active research area.[4b,6] Early on, it has been recognized as a valuable tool for the synthesis of natural products, as first demonstrated by Woodward during the total synthesis of steroids.[7] However, in spite of a long history, catalytic quinone centered enantioselective [4+2] cycloaddition remains underdeveloped.[8] Moreover, as far as we are aware, there is still no example of enantioselective process targeting selectively at will both, the reduced or oxidized form of the naphthoquinone through Diels-Alder (DA) reaction.

Efficient asymmetric quinone DA reactions are known (Scheme 1, B),[1a,b,9] but essentially rely on the use of biased or suitably designed quinones (masked ones,[10] bearing an additional activation site[11] or substituted with sterically and electronically demanding groups).[12] Indeed, reaction with unbiased benzoquinones, remains a significant challenge, as the presence of two potential carbonyl binding sites for the catalyst and two reacting C=C bonds in the quinone render the enantiocontrol rather difficult. Only very few efficient enantioselective DA reactions with simple quinones have been developed so far. The first example was reported in 2001 by White et al. using a (S)-Bi-2,2-naphthotitanium dichloride complex as catalyst for the enantioselective synthesis of (-)-ibogamine.[13] In 2005, Jacobsen et *al.* described a highly enantioselective quinone DA reaction catalyzed by a monomeric tridentate [(Schiff base)Cr^{III}] complex.[14] However it should be noticed that a single example using benzoquinone was documented and a moderate enantiomeric excess value was obtained. More recently, Coeffard, Greck et *al.* reported an elegant enantioselective organocatalytic sequential oxidative quinone DA reaction / Michael reaction sequence.[15] Despite these notable achievements, general and broadly applicable catalytic enantioselective DA reaction, moreover leading selectively to the quinone or hydroquinone form, is still unprecedented. Therefore, the development of a not only highly stereocontrolled, but also a divergent process to reach both redox isomers, would be significantly rewarding.



Scheme 1. Quinone DA reaction.

Our interest in catalytic, enantioselective cycloaddition extends back over several years.[16] We originally reported an enantioselective (3+2) cycloaddition of benzoquinones and enecarbamates using chiral phosphoric acids as catalysts.[16e] Inspired by this work and our recent success in the development of a variety of cycloadditions with dienecarbamates,[12d,g,j,16] we envisaged an enantioselective switchable process[18] to access hydronaphthoquinonoids.[19] Redox-selective phosphoric acid-catalyzed asymmetric DA reaction of dienecarbamates and

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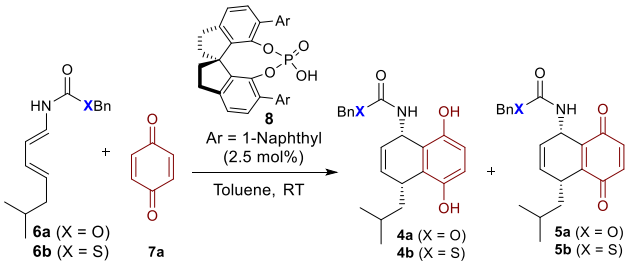
unbiased quinones should lead to both enantioenriched dihydronaphthalene-1,4-diols **4** and tetrahydronaphthalene-1,4-diones **5** according to a judicious choice of the experimental conditions. In addition, considering access to both redox isomers, allows to envisage the reversible redox interconversion between **4** and **5**. We report herein the first enantioselective redox-divergent quinone DA reaction leading to tetrahydronaphthalene-1,4-diones and/or dihydronaphthalene-1,4-diols in high yields with excellent regio-, diastereo-, and enantioselectivities (Scheme 1, C). In addition, conditions allowing fully reversible switching between both isolated redox isomers were established. Finally, versatile post transformations increased the accessible molecular diversity from individual isomers.

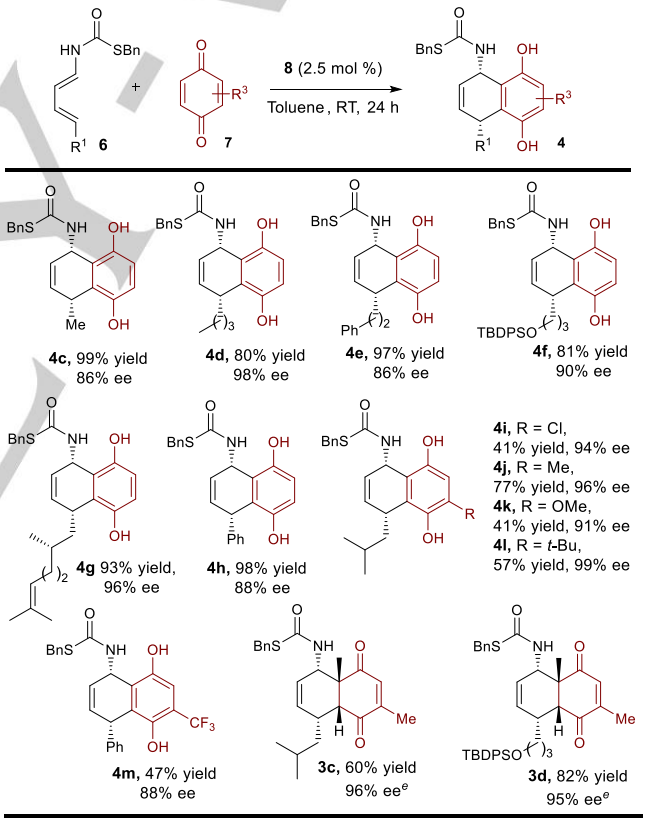
Table 1. Survey of Reaction Conditions for Enantioselective [4+2] Cycloaddition[a]



Entry	Ratio 6:7 (Y:Z)	**4** Yield [%][b]	**4** ee [%][c]	**5** Yield [%][b]	**5** ee [%][c]
1	1:1	59 [**4a**]	46 [**4a**]	17 [**5a**]	49 [**5a**]
2	1:0.8	93 [**4a**]	49 [**4a**]	-	-
3[d]	1:3	ND	ND	96 [**5a**]	60 [**5a**]
4	1:1	92 [**4b**]	92 [**4b**]	< 5 [**5b**]	92 [**5b**]
5	1:0.8	99 [**4b**]	93 [**4b**]	-	-
6	1:3	-	-	90 [**5b**]	90 [**5b**]
7[d]	1:3	-	-	87 [**5b**]	94 [**5b**]
8[e]	1:0.8	98 [**4a**]	-	-	-
9[e]	1:0.8	34 [**4b**]	-	34 [**5b**]	-
10[f]	1:0.8	94 [**4b**]	93 (4b)	-	-
11[d,f]	1:3	-	-	93 [**5b**]	92 [**5b**]

[a] Reaction conditions: **7a** (Y time 0.05 mmol), **6** (Z time 0.05 mmol) and **8** (0.00125 mmol) in 1.0 mL of toluene for 24 h. [b] Yields refer to chromatographically pure all *cis*-isomer **4** determined to be higher than 98/2 by ^{1}H NMR. [c] ee values were determined by HPLC with a chiral stationary phase. [d] at 0°C. [e] Without catalyst. [f] With 1 mmol of **6b**.

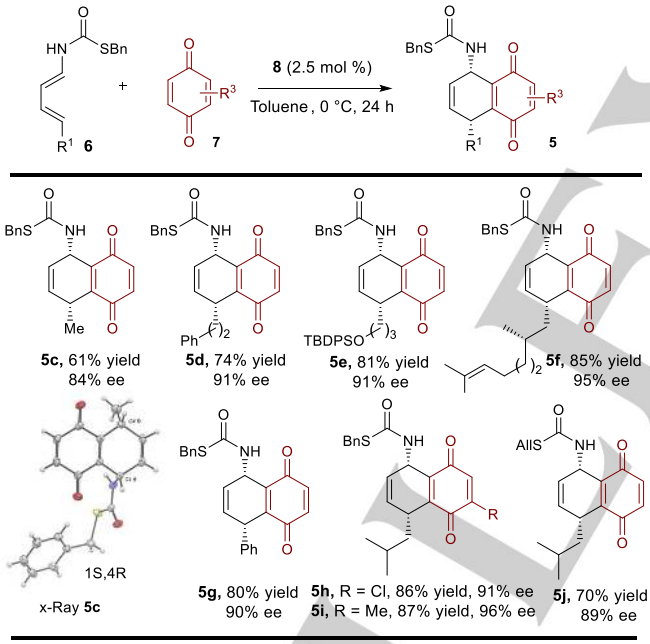
As a model reaction, we investigated the reactivity of benzyl (penta-1,3-dien-1-yl) carbamate **6a** with *p*-benzoquinone **7a** in the presence of 2.5 mol % of (S)-6,6'-bis(1-naphthyl)-SPINOL phosphoric acid **8**. While hexahydronaphthalene-1,4-dione **3a** was not isolated after purification, we identified the *cis*-tetrahydronaphthalene-1,4-dione **4a** (49% yield) along with *cis*-dihydronaphthalene-1,4-diol **5a** (17% yield). However, the enantioselectivity for both **4a** and **5a** did not exceed 50% *ee*. This preliminary result encouraged us to investigate different conditions in an attempt to improve enantioselectivity and redox-selectivity. Unfortunately, no better result was achieved in further screening of catalysts and solvents (Cf Tables S1 and S2 in Supporting Information). However, changing the *N*-protecting group of **6** from carbamate to (S)-thiocarbamate gave rise to a dramatic increase in enantioselectivity (**4b**: 92% ee and **5b**: 92% *ee*, entry 4). Additionally, the redox-selectivity was enhanced but not satisfactory yet. To address this issue, we reasoned that since the tetrahydronaphthalene-1,4-dione **5** probably resulted from the oxidation of **4** by the unreacted quinone **7a**, it should be possible to control its formation according to the amount of quinone used.[20] Indeed, with 0.8 equiv. of **6a**, the dihydronaphthalene-1,4-diol product **4b** was obtained almost exclusively and isolated in excellent yield (99%, entry 5). It should be noted that such hydroquinone form is sensitive to autooxidation and often requires further functionalization to be isolable,[21] which was not required in our case. In contrast, as already noted by others,[12j] when an excess amount of quinone (3 equiv.) was used in the reaction mixture, the targeted tetrahydronaphthalene-1,4-dione **5b** was exclusively produced at RT (entry 6) with highest enantiocontrol at 0 °C (entry 7).



Scheme 2. Scope of the enantioselective synthesis of dihydronaphthalene-1,4-diols **4**.[a,b,c,d] [a] General reaction conditions: **6** (0.06 mmol), **7** (0.05 mmol) and **8** (0.00125 mmol) in toluene at RT for 24 h [b] Yield of isolated pure product after column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. [e] The relative configuration was assigned based on NOESY spectroscopy (Cf. Supporting Information)

Having established the optimized conditions, the scope of enantioselective synthesis of dihydronaphthalene-1,4-diol **4** using a slight deficit of benzoquinones was explored (Scheme 2). In general, good yields and excellent regio-, diastereo-, and enantioselectivities (up to 98% *ee*) were obtained in this asymmetric [4+2] cycloaddition/aromatization sequence

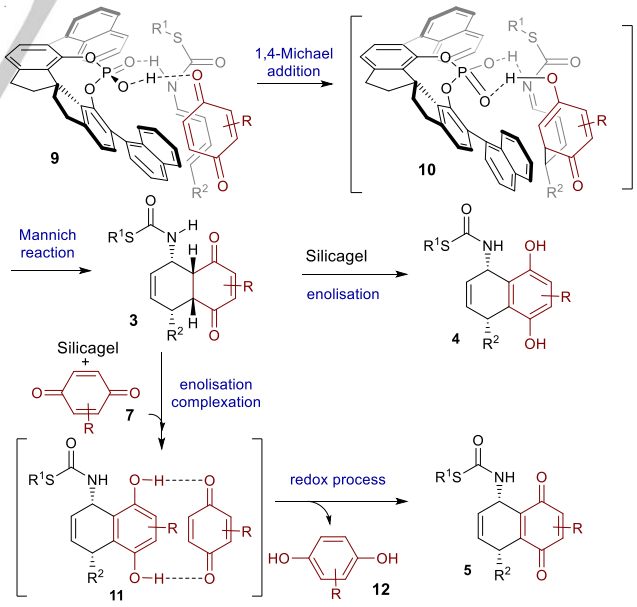
regardless of the substituents at the γ position of **6**. For instance, diene-thiocarbamates bearing different linear alkyl groups were converted to the corresponding cycloadducts **4b-4e** with excellent yields and enantioselectivities. Additional functional groups (such as silyl ether, **4f**) could also be introduced into **4** without any influence on the results. Noteworthy is that the diene (S)-thiocarbamate derived from (S)-citronellol gave **4g** as a single diastereomer in an excellent yield and enantioselectivity. In a similar manner, the diene γ-substituted by phenyl led to product **4h** in 98% yield with 88% *ee*. Pleasingly, other benzoquinones reacted smoothly to give the corresponding dihydronaphthalene-1,4-diols **4i-4m** with excellent regio- and enantioselectivities. The electronic property of the quinone ring did not affect much the enantioselectivity, but did impact the yield. For instance, quinones bearing weak electron-donating substituents produced the corresponding products in good yields (**4j** and **4l**), although electron poor (**4i** and **4m**) and strongly electron-rich (MeO group, **4k)** substituents showed lower yields. Sterically demanding substituted quinones (*t*-Bu substituted one, **4l**) were also well tolerated. Challenging symmetrical disubstituted *p*-benzoquinones such as 2,5-dimethylquinone provided the corresponding hexahydronaphthalene-1,4-dione **3c** and **3d** with a complete control of configuration at all four stereocenters (96% *ee*).



Scheme 3. Scope of the enantioselective synthesis of tetrahydronaphthalene-1,4-diones **5**.[a,b,c,d,e] [a] General reaction conditions: **6** (0.06 mmol), **7** (0.15 mmol) and **8** (0.00125 mmol) in toluene at 0 °C for 24 h [b] Yield of isolated pure product after column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. [e] The absolute configuration (1*S*,4*R*) was assigned by X-ray single crystal structure analysis of enantioenriched **5c** (see Supporting Information.

We next turned our attention to the scope of enantioselective DA reaction/oxidation sequence (Scheme 3). A variety of selected thioenecarbamates **6** reacted with similar diastereo- and enantioselectivities in comparison to the model reaction. As previously, the reaction conditions tolerate various substituent patterns on the *p*-benzoquinones **7** such as methyl and chloride providing the tetrahydronaphthalene-1,4-diones **5h** and **5i** in 86% and 87% yields, respectively, with total regio- and diastereoselectivity and excellent enantiomeric excesses (up to 96% *ee*). Interestingly, use of allyl thiocarbamate diene instead of benzyl analogue also yielded to cycloadduct **5j** in good yield and enantioselectivity. It can be noted that *cis*-tetrahydronaphthalene-1,4-diones **5** were generally obtained with slightly higher enantiomeric excess when compared to analogous dihydronaphthalene-1,4-diols **4**; difference in reaction temperature (0° C *vs* rt) can account for this increase.

Relatively few mechanistic studies on quinones centered [4+2] cycloaddition have been conducted but a concerted mechanism[22] rather than a stepwise[23] mechanism has been often suggested. However, based on a recent theoretical study, a stepwise ionic mechanism has been proposed. [12m] In this context, to determine whether the cycloaddition proceeds through a stepwise or concerted mechanism, we evaluated the effect of substituents on the quinone ring. Correlations between the Hammett parameters (σ) of quinone substituents and the corresponding conversions obtained after 5 min (Cf Supporting Information) have shown a drop in yields in the presence of substituents with σ values inferior or superior to 0. The concave downward deviation indicates a maintained mechanism, but a change in rate determining step;[24] in other world, they are at least two steps, which excludes a concerted mechanism.[25] In addition, when the reaction was carried out with 1,4-benzoquinone and trifluoromethylated-one and diene **6b** in toluene-d_8 as solvent under standard conditions, an imine intermediate **10** was observed by ^{1}H-NMR (Cf Supporting Information). Further characterization of the imine **10** could not be achieved, as **10** gradually evolves to cycloadduct **3** (Cf Supporting Information).[26] These findings fully support that the reaction operates in a stepwise fashion which involves 1,4-Michael addition and intramolecular Mannich reaction (Scheme 4, **9** to **3**).



Scheme 4. Activation models and possible reaction mechanism.

Subsequently, additional experiments were undertaken to gain more insight into the redox-switch. Firstly, the cycloadditions between **6b** and **7a** were carried out under both conditions (0.8 and 3 equiv. of **7a**) and monitored by ^{1}H NMR spectroscopy. In

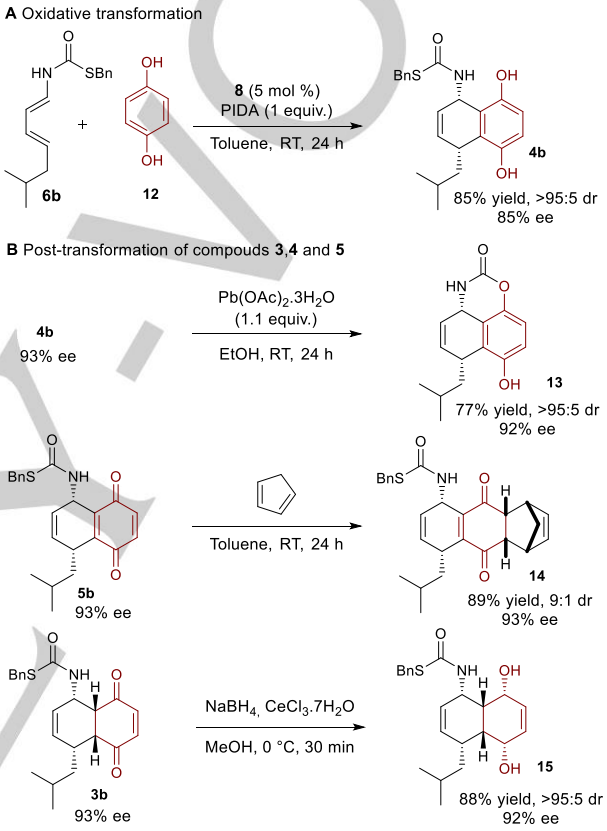
both cases, the 1H NMR and NOESY spectra showed the exclusive formation of *trans*-hexahydronaphthalene-1,4-dione intermediate **3b** (Cf Supporting Information). It can be highlighted that in absence of silicagel, excess of quinone is not able to oxidize compound **3** to compound **5**. However, TLC or purification on silica showed only the formation of **4b** or **5b** according to the condition used.

Several control experiments were performed to uncover the role of the thiocarbamate on the enantioselectivity in the cycloaddition. First, the uncatalyzed reaction of dienecarbamate **6a** or dienethiocarbamate **6b** with **7a** was followed by ^{1}H NMR and we found that the reaction rate was higher with **6a**. After 24h, the corresponding cycloadducts **4a** and a mixture of **4b** and **5b** were obtained in 98% and 68% (**4b**+**5b** yield) respectively (entries 8 and 9, Table 1, and Figure S8 in Supporting Information). Second, the cross-reaction of two different dienes **6a** and **6b** with **7a** (0.8 equiv) in presence of catalyst **8** gave the cycloadducts **4a** and **5b** in ratio 3:2 in favor of **5b** (Cf Supporting Information). These results indicate that both the stronger background reaction with **6a** and a better activation of diene-thiocarbamate **6b** (than **6a)** by the phosphoric acid **8** might explain the low enantioselectivity with **6a**.

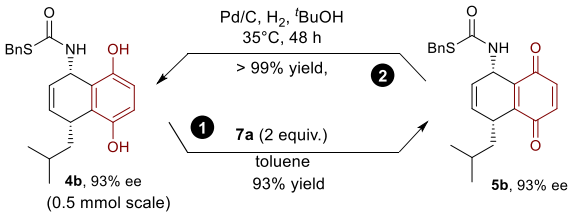
On the basis of the above results as well as other reports,[4b,12m,16,22,23,27] a plausible reaction mechanism is depicted in Scheme 4. According to the dual activation model, the two substrates involved in the reaction are activated simultaneously by bifunctional catalyst. Disruption of this activation using protic solvent (EtOH, Cf Supporting Information), almost shut down the enantioselectivity. Exact chiral environment of the complex is currently not completely understood but π-π interactions between the ancillary naphthyl groups with both, the quinone core and diene moiety, might be involved. Indeed, as observed early in the work, phenyl substituted Binol derived catalysts furnished higher enantioselectivity when compared to triisopropyl phenyl one (see table S1, entries 2-3). Overall based on the chiral space organization, and following a two-step process, a formal endo approach of the diene to the *Si* face of the quinone would lead to the (*R*)-isomer of cycloadduct **3** with high enantioselectivity. In a subsequent step, compound **3** aromatized on silica through enolization to deliver compound **4.** The latter, in presence of excess of quinone **7** undergoes an oxidation through a quinhydrone complex[28] **11** to produce **5**.

To demonstrate the synthetic utility of this redox divergent enantioselective process, 1 mmol scale synthesis of **4** and **5** was performed under the standard reaction conditions. To our delight, the reactions proceeded smoothly to afford corresponding product **4b** and **5b** without significant erosion of diastereoselectivity, enantioselectivity, and yield (Table 1, entries 10 and 11). The versatility of the enantioselective cycloaddition was further increased by developing an oxidative enantioselective process using readily available hydroquinone as starting material. Based on our previous work,[16e] $PhI(OAc)_2$ was identified as a viable oxidant and the corresponding cycloadduct **4b** was exclusively isolated in good yield and enantioselectivity in the presence of 5 mol% of chiral catalyst **8** (Scheme 5, A). Using 1 equiv of oxidant that rapidly convert hydroquinone to quinone avoid over oxidation of **4** to **5** and explain the resulting selectivity. With more than 1 equiv of $PhI(OAc)_2$, the remaining oxidant will react faster with diene **6** than cycloadduct formation, thereby reducing the yield of product **4**.

Furthermore, some representative transformations of cycloadducts **3, 4** and **5** were exhibited. For example, a regioselective protection of hydroxyl group at 8-position was achieved through *trans*-carbomylation of phenol with the (S)-thiocarbamate (Scheme 5, B). Remarkably, cycloadduct **5b** can undergo a second [4+2] cycloaddition with cyclopentadiene to form **14** with excellent diastereoselectivity. We next evaluated the potential of intermediate **3** in being used as template to generate more diverse class of cyclic compounds. Direct reduction of the crude **3b** with $NaBH_4$ and $CeCl_3$ gave **15** bearing six contiguous stereocenters in 88 % yield without any chirality erosion.



Scheme 5. Practicability and synthetic transformation of **3**, **4** and **5.**



Scheme 6. Redox-Reversible Interconversion.

Finally, with access to both, dihydronaphthalene-1,4-diol **4** and tetrahydronaphthalene-1,4-dione **5**, we turned our attention to their possible redox reversible interconversion (Scheme 6). The reaction of dihydronaphthalene-1,4-diol **4b** with *p*-benzoquinone **7a** (2 equiv.) resulted in a fast and clean conversion into the expected enantioenriched tetrahydronaphthalene-1,4-dione **5b** in excellent yield with no loss of enantioselectivity. Pleasingly, the resulting enriched product under reductive hydrogenation conditions was readily converted to **4b** without notable erosion of

yield and *ee*. Interestingly, the reversible redox- interconversion between **4** and **5** can be carried out in 0.5 mmol scale demonstrating process robustness. As such this couple represent an interesting chiral molecular switch.[29]

In conclusion, we have developed an efficient organocatalytic enantioselective Diels-Alder reaction of unbiased quinones with thiodienecarbamates using a SPINOL chiral phosphoric acid catalyst. Importantly, individual redox stereoisomers are directly accessed in high enantiomeric excesses by simply changing the amount of quinones used in the cycloaddition reaction. This redox switching is reversible employing an excess of quinone, delivering dihydronaphthalene-1,4-diols or tetrahydronaphthalene-1,4-diones smoothly with good enantio- and diastereoselectivity.

Acknowledgements ((optional))

We thank ICSN and CNRS for financial support; T. V. and C. G. thank Saclay University for the doctoral fellowships.

Keywords: [4+2] cycloaddition• chiral phosphoric acid • quinone • Diels-Alder reaction • hydrogen bonding

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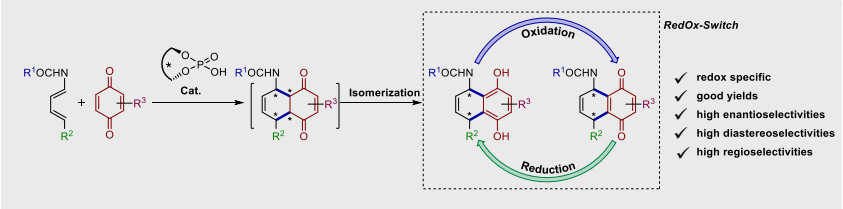

"One way or another, I'm gonna get ya". Chiral phosphoric acid catalysed stoichiometry driven redox divergent synthesis of enantioenriched dihydronaphthalene-1,4-diol or tetrahydronaphthalene-1,4-dione (by Diels-Alder reaction).

*Thomas Varlet, Coralie Gelis, Pascal Retailleau, Guillaume Bernadat, Luc Neuville and Géraldine Masson**

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Redox-Divergent Chiral Phosphoric Acid-Catalyzed Enantioselective Formal Quinone Diels–Alder Reactions