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Catalytic Enantioselective Desymmetrization of Norbornenoquinones via C(sp^2)−H Alkylation

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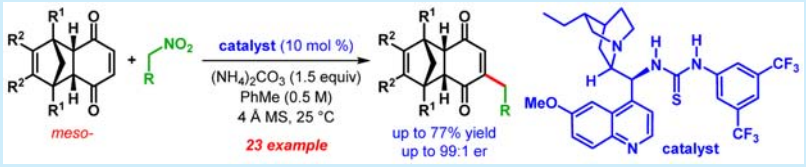
Supporting Information



ABSTRACT: The enantioselective Diels−Alder (DA) reaction with monosubstituted *p*-benzoquinones is an unmet challenge. A new approach for the enantioselective synthesis of monosubstituted quinone-DA adducts is presented based on C(sp^2)−H alkylative desymmetrization of *meso*-DA adducts. Catalyzed by a tertiary amino-thiourea derivative, this reaction utilizes nitroalkanes as the alkylating agents and generates densely functionalized products bearing at least four contiguous stereogenic centers remote from the reaction site with excellent enantioselectivities.

Norbornenoquinones, obtained from a Diels−Alder (DA) reaction between cyclopentadiene (CP) and *p*-benzoquinones, are not only important historically[1] but also because of the presence of this core structure in various natural products and biologically active compounds (Figure 1).[2] In addition, they have

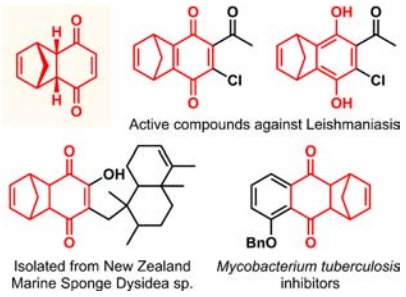
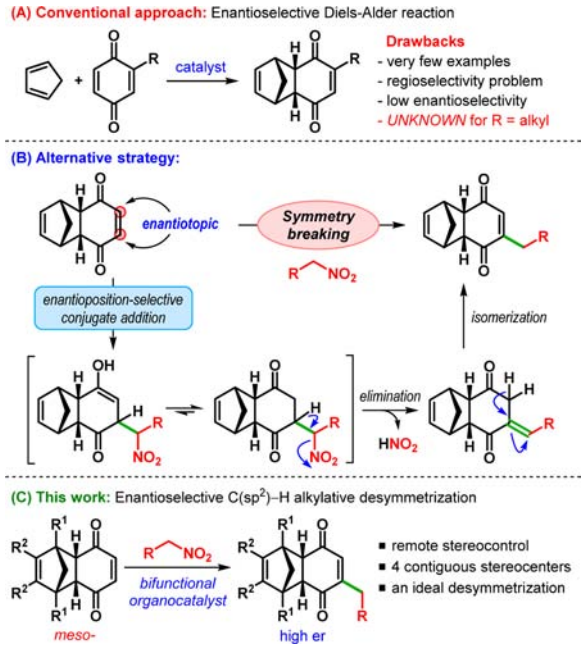


Figure 1. Norbornenoquinone and examples of natural products and bioactive compounds containing this scaffold.

been used as building blocks for the synthesis of several quinonoid natural products, such as epoxyquinones, jesterone, phyllostine, ambuic acid, cycloepoxydone, etc.[3] The importance of norbornenoquinone scaffold makes their enantioselective synthesis highly desirable.

Even though quinones are considered to be a very reactive class of dienophiles, enantioselective quinone−DA reactions are rather limited.[2e,4] In fact, enantioselective DA reactions between CP and monosubstituted *p*-benzoquinones remain elusive (Scheme 1A).[5] Inspired by the synthetic value of enantiopure norbornenoquinones and dearth of useful methods for the enantioselective synthesis of monosubstituted norbornenoquinones, we sought an alternative strategy for their enantioselective synthesis. We recognized that any symmetry-breaking operation on *meso*-norbornenoquinone would generate chiral norbornenoquinones

Scheme 1. Catalytic Enantioselective Synthesis of Monosubstituted Norbornenoquinones



(Scheme 1B). Enantioselective desymmetrization of this type is a powerful strategy, a unique advantage of which is the possibility of creating stereogenic centers remote from the reaction site.[6]

We recently developed an organocatalytic enantioselective alkylation of olefinic C(sp^2)−H bonds using inexpensive and air-stable nitroalkanes as the alkylating agents.[7] We envisioned that a

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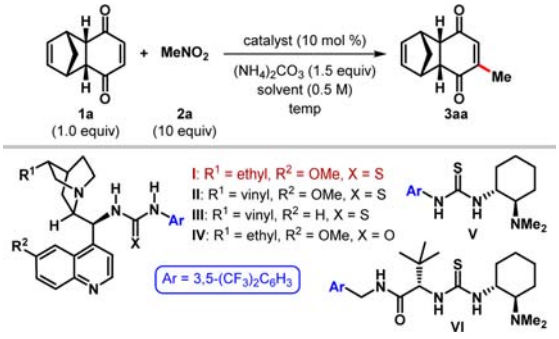
similar C(sp^2)−H alkylative desymmetrization of *meso*-norbornenoquinones would circumvent the limitations associated with the direct enantioselective synthesis of monosubstituted norbornenoquinones. Herein, we present a distinct method for the catalytic enantioselective synthesis of monosubstituted norbornenoquinones, which proceeds via C(sp^2)−H alkylation of *meso*-norbornenoquinones (Scheme 1C).

As in our previous report,[7a] an enantioposition-selective conjugate addition of nitroalkanes to the electron-deficient olefin of *meso*-norbornenoquinones was reasoned to be the key to the success of this approach (Scheme 1B). Accordingly, tertiary amino-(thio)urea-based bifunctional compounds[8] were once again selected as the catalyst candidate.

We chose *endo*-norbornenoquinone **1a** as the model substrate and nitromethane **2a** as the alkylating agent (Table 1).

Table 1. Catalyst Screening and Reaction Optimization[a]



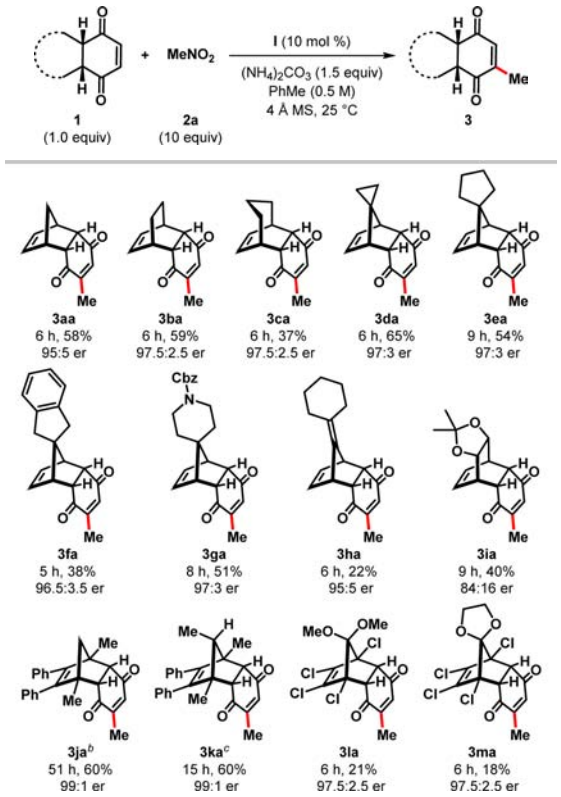
entry	cat.	solvent	temp (°C)	t (h)	yield (%)[b]	er[c]
1	–	$PhCF_3$	25	12	n.d.	–
2	**I**	$PhCF_3$	25	6	33	91.5:8.5
3	**I**	CH_2Cl_2	25	8	26	91:9
4	**I**	$CHCl_3$	25	8	37	91.5:8.5
5	**I**	PhF	25	6	32	91:9
6	**I**	PhMe	25	6	42	94.5:5.5
7[d]	**I**	PhMe	25	6	58	95:5
8[d]	**I**	PhMe	0	6	41	96:4
9[d]	**I**	PhMe	50	6	53	94.5:5.5
10[d]	**II**	PhMe	25	6	57	94.5:5.5
11[d]	**III**	PhMe	25	6	37	83:17
12[d]	**IV**	PhMe	25	6	45	93:7
13[d]	**V**	PhMe	25	6	37	9:91
14[d]	**VI**	PhMe	25	6	32	13.5:86.5

[a]Reactions were carried out on a 0.1 mmol scale. [b]Yields correspond to the isolated yield; n.d. = not determined. [c]Enantiomeric ratio (er) was determined by HPLC analysis on a chiral stationary phase. [d]4 Å MS (50 mg) was used as an additive.

Identification of a suitable terminal base incapable of catalyzing the conjugate addition was crucial before undertaking the catalyst optimization. After screening several bases,[9] $(NH_4)_2CO_3$ turned out to be the optimum as no product formation was observed when the reaction was carried out in the absence of any catalyst in trifluorotoluene at 25 °C (Table 1, entry 1). When 10 mol % of dihydroquinine-derived thiourea **I** was used as the catalyst under the same reaction conditions, the desired monosubstituted norbornenoquinone **3aa** was formed in 33% yield after 6 h with a promising er of 91.5:8.5 (entry 2). A solvent screening[9] at this point revealed toluene as the optimal solvent both in terms of reaction efficiency and enantioselectivity (entries 3−6). The product yield could be improved by using 4 Å MS as an additive (entry 7). Variation in reaction temperature failed to offer any beneficial effect on either yield or enantioselectivity (entries 8−9). A number of other bifunctional (thio)ureas (**II**−**VI**) derived from either cinchona alkaloids or *trans*-1,2-diaminocyclohexane were also tested as catalyst under the same reaction conditions (entries 10−14). However, thiourea derivative **I** emerged as the catalyst of choice.

The catalyst and the reaction conditions optimized for *endo*-norbornenoquinone **1a** (Table 1, entry 7) were then applied to other *meso*-DA adducts (**1b**−**m**) toward C(sp^2)−H methylation with nitromethane. As illustrated in Table 2, this protocol is

Table 2. Scope of the Desymmetrization with Regard to *meso*-Diels−Alder Adducts[a]



[a]Reactions were carried out on a 0.1 mmol scale. Yields correspond to the isolated yield. Er was determined by HPLC analysis on a chiral stationary phase. [b]After 48 h, reaction mixture was passed through Celite, concentrated, and treated with KOAc/18-crown-6 in THF for 3 h. [c]After 12 h, reaction mixture was passed through Celite, concentrated, and treated with KOAc/18-crown-6 in THF for 3 h.

applicable to DA adducts derived from *p*-benzoquinone and a variety of dienes including those having different ring sizes (**1a**−**c**), spiro-fused dienes (**1d**−**g**), fulvene (**1h**), and highly substituted cyclopentadienes (**1j**−**m**). The corresponding methylated products (**3aa**−**am**) were obtained generally with good to excellent enantioselectivities. Both the tetra- and penta-substituted norbornenoquinones **1j** and **1k**, under the optimum reaction conditions, resulted in a mixture of desired C−H alkylated product and the corresponding Michael adduct (see Scheme 3). When these mixtures in each case were treated with KOAc (1.2 equiv) and 18-crown-6 (1.2 equiv) in THF for 3 h, the desired products (**3ja** and **3ka**) containing two all-carbon quaternary stereocenters were formed with 60% yield and 99:1 er. The yields of the reactions are modest in most cases due to the innate instability of both the quinone-DA adducts and the

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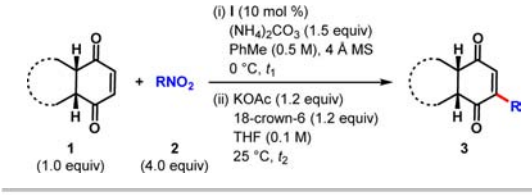
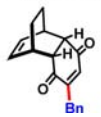
methylated products. The desymmetrized products obtained from fulvene and tetrachloro cyclopentadienone-ketals derived DA adducts (**3ha** and **3la**–**ma**, respectively) are particularly unstable and formed with poor yield, albeit with high er.

We next examined the scope of this C(sp^2)–H alkylative desymmetrization with regard to other nitroalkanes (Table 3).

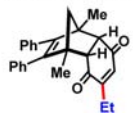
Table 3. Scope of the Desymmetrization with Respect to Nitroalkane[a]



R	t_1, h	t_2, h	yield (%)	er
Et (**3ab**)	72	0.5	40	95:5
Bn (**3ac**)	72	3	34	92.5:7.5
CH_2(4-MeC_6H_4) (**3ad**)	72	3	18	90.5:9.5
CH_2(*c*-Hex) (**3ae**)	72	5	30	99:1
 (**3af**)	72	5	22	95:5
CH_2CO_2Et (**3ag**)[b]	9	-	77	82:18
CH_2COMe (**3ah**)[b]	15	-	61	76:24
CH_2COPh (**3ai**)[b]	6	-	48	73.5:26.5



3bc
t_1 = 72 h, t_2 = 2 h
25%, 94.5:5.5 er



3jb
t_1 = 72 h, t_2 = 3 h
42%, 98:2 er

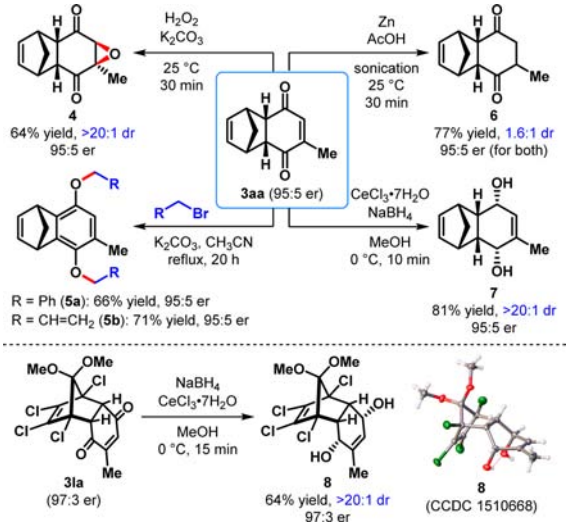
[a]Reactions were carried out on a 0.1 mmol scale. Yields correspond to the isolated yield. Er was determined by HPLC analysis on a chiral stationary phase. [b]Reaction was conducted at 25 °C using the one-step protocol as in Table 2.

Surprisingly, when **1a** was subjected to alkylation with nitroethane (**2b**) under our standard reaction conditions, formation of a complex mixture was observed instead of the desired product. To our relief, conducting the reaction at 0 °C using 4.0 equiv of nitroethane resulted the Michael adduct, which could be converted to the desired product **3ab** on treatment with KOAc/18-crown-6 in 40% yield with 95:5 er. This modified two-step protocol was then followed for alkylation with other nitroalkanes. *endo*-Norbornenoquinone **1a** could be alkylated with a number of nitroalkanes, furnishing the alkylated products (**3ab**–**ai**) in moderate to decent yields with up to 99:1 er. In the case of ester- or keto-functionalized nitroalkanes (**2g**–**i**), the products were obtained in moderate to good yields under the one-step protocol, albeit with significantly reduced er. Cyclohexadiene and tetrasubstituted cyclopentadiene-derived DA adducts (**1b** and **1j**) were also alkylated with phenylnitromethane (**2c**) and nitroethane (**2b**), respectively, with good to excellent enantioselectivities.

It must be noted that, for majority of these products, this is the first example of their enantioselective synthesis.

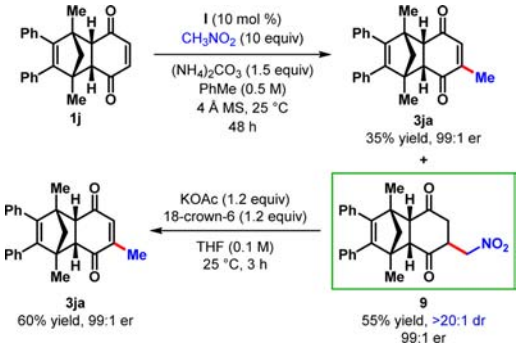
The enantioenriched products obtained in these newly developed C(sp^2)–H alkylative desymmetrization reactions are densely functionalized and can be further transformed into potentially useful building blocks. For example, Weitz–Scheffer-type epoxidation[10] of **3aa** provided the epoxynorbornenoquinone **4** as a single diastereomer with 64% yield (Scheme 2). The *exo*-epoxide **4** and its prenyl analogue have been utilized for the synthesis of the core structure of bioactive kinamycin natural products[3a] and antifungal natural product jesterone,[3j] respectively. Treatment of **3aa** with benzyl or allyl bromide in the presence of K_2CO_3 under reflux furnished the chiral dihydroquinone derivatives **5a**–**b** in high yields. Selective reduction of the electron deficient olefin of **3aa** was possible using Zn/AcOH. However, the product (**6**) was obtained with poor diastereoselectivity (1.6:1 dr). Reduction of **3aa** and **3la** under Luche conditions[11] was found to be completely regio- and diastereoselective and furnished the corresponding diols **7** and **8**, respectively, in high yields.[12] The relative and absolute stereochemistry of **8** was established from its single crystal X-ray diffraction analysis.[13] The absolute configurations of **7** and the desymmetrized products (**3**, Tables 2 and 3) were inferred in analogy with **8**. The *endo*,*endo*-*cis*-diol **7** found its application in the synthesis of the carbocyclic core of bioactive natural products antroquinonols.[3b] In all these cases, the reactions proceeded without any erosion of enantioselectivity.

Scheme 2. Synthetic Elaboration of the Desymmetrized Products



While exploring the scope of the reaction, *endo*-norbornenoquinone derivative **1j** under the optimized reaction conditions delivered, along with the desired methylated analogue **3ja**, the Michael adduct **9** as a single diastereomer in 55% yield with 99:1 er (Scheme 3). Exposure of **9** to KOAc/18-crown-6 generated **3ja** with identical er as that of **9** and **3ja** obtained directly from **1j**. These results provide direct evidence in support of the intermediacy of **9** in this C(sp^2)–H alkylation reaction. This experiment also suggests that the conjugate addition of nitroalkanes (**2**) to *endo*-norbornenoquinone derivatives (**1**) is

Scheme 3. Identification and Isolation of the Intermediate



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the enantiodetermining step of the reaction, as conceived at the outset of this study (Scheme 1B).

Notwithstanding the tremendous progress in catalytic asymmetric Diels–Alder reactions during the past several decades, enantioselective synthesis of DA adducts from monosubstituted *p*-benzoquinones remains elusive. Here we have offered an alternative solution to this problem, more specifically for the enantioselective synthesis of monosubstituted *endo*-norbornenoquinones and related polycyclic compounds. Our approach is based on the C(sp^2)–H alkylative desymmetrization of *meso*-norbornenoquinones and related polycyclic compounds using inexpensive and air-stable nitroalkanes as the alkylating agents. These reactions are catalyzed by a dihydroquinine-based tertiary amino-thiourea derivative and deliver highly functionalized quinone-DA adducts bearing at least four contiguous stereocenters remote from the reaction site in moderate to good yields with excellent enantioselectivities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03168.

Experimental details (PDF)
Characterization data (PDF)
Crystallographic data for **8** (CIF)

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Notes

The authors declare no competing financial interest.

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(13) CCDC 1510668 contains the crystallographic data for **8**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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