ORGANIC LETTERS

2013
Vol. 15, No. 12
3010–3013

1,4-Naphthoquinones in H-Bond-Directed Trienamine-Mediated Strategies

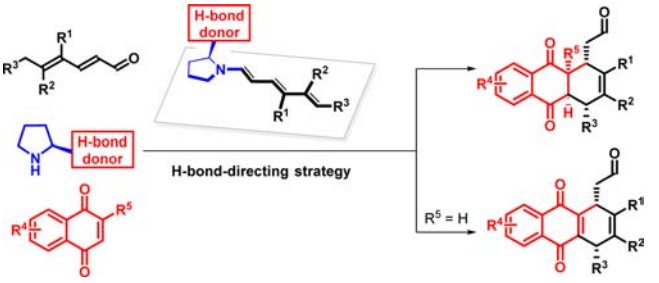
Łukasz Albrecht, Clarisa Villegas Gómez, Christian Borch Jacobsen, and Karl Anker Jørgensen*

Center for Catalysis, Department of Chemistry, Aarhus University, 8000 Aarhus C, Denmark

kaj@chem.au.dk

Received April 29, 2013

ABSTRACT



The synthesis of optically active, carboannulated dihydronaphthoquinone and naphthoquinone derivatives with up to four stereogenic centers is demonstrated by H-bond-directed, trienamine-mediated [4 + 2]-cycloadditions. The outcome of the reaction between 2,4-dienals and 1,4-naphthoquinones is controlled by the substituent in the 2-position of the 1,4-naphthoquinone. In the case of sterically demanding 2-substituted derivatives, dihydronaphthoquinones are obtained. However, when a hydrogen atom is present in the 2-position, a subsequent oxidation of the initially formed cycloadducts occurs yielding naphthoquinones.

The carboannulated naphthoquinone and dihydronaphthoquinone structural motif is an important carbocyclic scaffold present in various compounds relevant for life science.[1] Selected examples of natural products containing such a framework are shown in Figure 1. Zeylanone and juglorescein have been isolated from the shrub *Plumbago zeylanica* and from *Streptomyces* strains GW4184 and 815, respectively.[2] Zeylanone is known for its antifungal and antibacterial activities as well as cytotoxicity.[2b] Owing to the broad availability from natural sources and intriguing biological properties, interest in compounds containing the carboannulated naphthoquinone and dihydronaphthoquinone structural motif is growing. As a consequence, the development of stereoselective methods for their preparation is important.

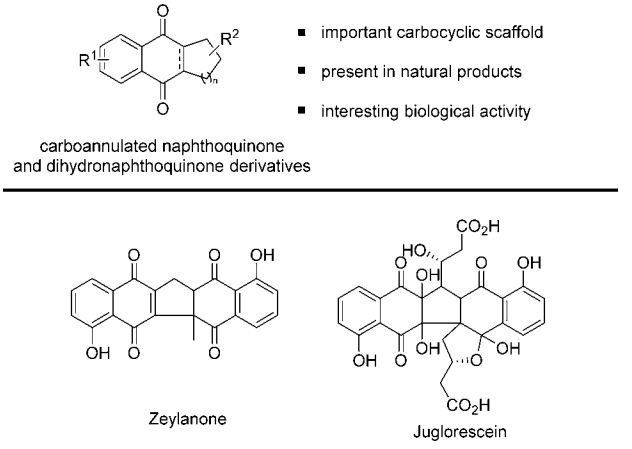


Figure 1. Carboannulated naphthoquinone and dihydronaphthoquinone motif and important derivatives.

(1) (a) *The Chemistry of the Quinonoid Compounds*, Vol. 2, Parts 1 and 2; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1988. (b) Thomson, R. H. In *Naturally Occurring Quinones IV*; Blackie Academic: London, 1997. (c) Lumb, J.-P. G.*Progress in the Chemistry of Quinoidal Natural Products*; ProQuest: 2008. (d) Powis, G. *Pharmac. Ther.* **1987**, *35*, 57.

(2) (a) Sankaram, A. V. B.; Rao, A. S. *Tetrahedron* **1979**, *35*, 1777. (b) Gu, J.-Q.; Graf, T. N.; Lee, D.; Chai, H.-B.; Mi, Q.; Kardono, L. B. S.; Setyowati, F. M.; Ismail, R.; Riswan, S.; Farnsworth, N. R.; Cordell, G. A.; Pezzuto, J. M.; Swanson, S. M.; Kroll, D. J.; Falkinham, J. O., III.; Wall, M. E.; Wani, M. C.; Kinghorn, A. D.; Oberlies, N. H. *J. Nat. Prod.* **2004**, *67*, 1156. (c) Lessmann, H.; Maskey, R. P.; Fotso, S.; Lackner, H.; Laatsch, H. *Z. Naturforsch., B: J. Chem. Sci.* **2005**, *60*, 189.

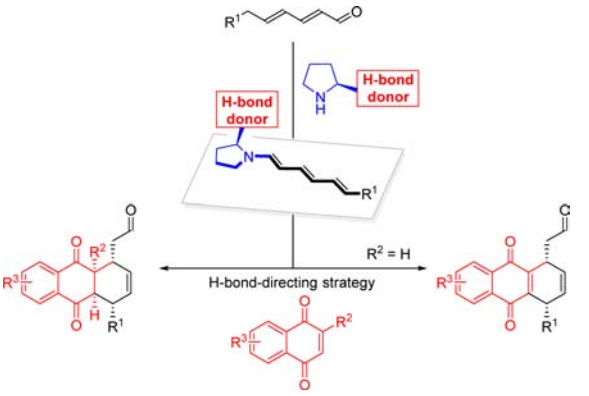
10.1021/ol401204a
Published on Web 06/03/2013

In recent years, 1,4-benzoquinones and 1,4-naphthoquinones have received considerable attention in asymmetric organocatalysis.[3] Most strategies applying these compounds take advantage of the fact that these systems are powerful Michael acceptors easily undergoing subsequent rearomatization or reoxidation.[3,4] In contrast, enantioselective transformations involving application of these compounds in cycloaddition reactions are rare.[5]

Among different activation strategies allowing for cycloaddition reactions, the application of vinylogous and hyper-vinylogous, enamine-based nucleophiles is an important topic.[6] In most cases, the stereochemical outcome of dienamine- or trienamine-mediated reactions is governed by the steric shielding effect exerted by the bulky substituent present in the aminocatalyst, with silyl protected diarylprolinols being the most potent group of catalysts.[6] Recently, an alternative strategy has been devised utilizing H-bond-directing aminocatalysis.[7] In this approach, the corresponding aminocatalyst serves a triple purpose. First, it activates the starting enal or 2,4-dienal via dienamine or trienamine formation, respectively. Second, it independently activates the electrophilic counterpart via H-bonding interactions. Finally, it positions the reactive species correctly in space allowing for facile and smooth remote functionalizations.

Surprisingly, to the best of our knowledge, simple 1,4-naphthoquinones and their derivatives have never before been employed as electrophilic reagents in trienamine chemistry. We envisioned that application of these systems in such a stereodifferentiating process might open access to various important and interesting carboannulated products (Scheme 1). Notably, depending on the substitution pattern of the starting 1,4-naphthoquinones various reactivities might take place. It was anticipated that when 2-substituted naphthoquinones were employed in organocatalytic reactions with 2,4-dienals, via a trienamine intermediate, a classical [4 + 2]-Diels–Alder-cycloaddition could occur leading to the stereoselective formation of dihydronaphthoquinones. It should be noted that 2-substituted naphthoquinones are challenging substrates due to the fact that Michael additions to sterically demanding acceptors are usually relatively slow and highly reversible. A different reactivity pattern can be assumed when simple 1,4-naphthoquinones that do not contain the 2-substituent are considered. For such systems, subsequent oxidation of the originally formed cycloadduct to give naphthoquinones could be expected.[3a,c,f,g] However, in this case further challenges related to aromatization of the products or originally formed cycloadducts had to be taken into consideration.[3b,d,e,4]

Scheme 1. Trienamine-Mediated H-Bond Directed Synthesis of Carboannulated Naphthoquinones and Dihydronaphthoquinones



Despite the potential problems related to the reactivity and chemo- and stereoselectivity of the devised strategies, studies on the application of substituted 1,4-naphthoquinones **2** in trienamine-mediated Diels–Alder reactions using 2,4-dienals **1** were undertaken. In the first part of the studies, the possibility to employ 2-substituted-1,4-naphthoquinones **2** was evaluated (Scheme 2). Initial screening demonstrated that the aminocatalyst **3** with a H-bond-directing group incorporated was performing better than the classical TMS-protected diphenylprolinol catalyst in the reaction (see Supporting Information for details). Furthermore, employment of 1,2-dichloroethane as a solvent and performing the reaction at elevated temperature proved beneficial for the reaction outcome. Notably, the presence of *N*,*N*-diethylacetamide (DEA) was important for the catalytic activity of the system. Under these conditions various 2-substituted-1,4-naphthoquinones **2** could be successfully employed opening access to different carboannulated dihydronaphthoquinones **4a–e** containing a quaternary stereogenic center. Both aromatic and aliphatic substituents could be present in the 2-position

(3) For examples, see: (a) Alemán, J.; Richter, B.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5515. (b) Alemán, J.; Cabrera, S.; Maerten, E.; Overgaard, J.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5520. (c) Alemán, J.; Jacobsen, C. B.; Frisch, K.; Overgaad, J.; Jørgensen, K. A. *Chem. Commun.* **2008**, 632. (d) Wang, C.; Chen, X. H.; Zhou, S. M; Gong, L. Z. *Chem. Commun.* **2010**, 1275. (e) Jensen, K. L.; Franke, P. T.; Nielsen, L. T.; Daasbjerg, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 129. (f) Siau, W.-Y.; Li, W. J.; Xue, F.; Ren, Q.; Wu, M. H.; Sun, S. F.; Guo, H.; Jiang, X. F.; Wang, J. *Chem.—Eur. J.* **2012**, *18*, 9491. (g) Yu, J.-S.; Zhou, F.; Liu, Y.-L.; Zhou, J. *Beilstein J. Org. Chem.* **2012**, *8*, 1360.

(4) For a recent example, see: He, Z.; Liu, T.; Tao, H.; Wang, C.-J. *Org. Lett.* **2012**, *14*, 6230.

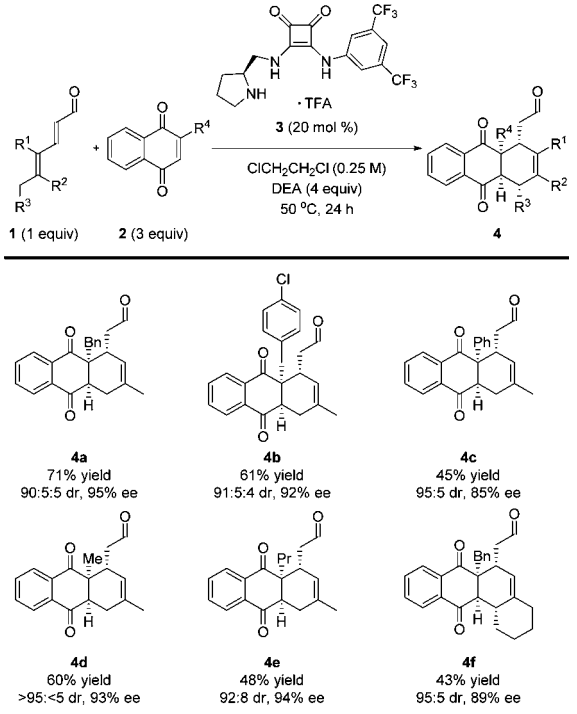
(5) For a review on asymmetric, organocatalytic cycloadditions, see: Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703. For examples of nonorganocatalytic enantioselective approaches, see: (b) Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10162. (c) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388. (d) Han, Z.-Y.; Chen, D.-F.; Wang, Y.-Y.; Guo, R.; Wang, P.-S.; Wang, C.; Gong, L.-Z. *J. Am. Chem. Soc.* **2012**, *134*, 6532.

(6) For recent reviews, see: (a) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248. (b) Li, J.-L.; Liu, T.-Y.; Chen, Y.-C. *Acc. Chem. Res.* **2012**, *45*, 1491. (c) Arceo, E.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 5290. (d) Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865. (e) Kumar, I.; Ramaraju, P.; Mir, N. A. *Org. Biomol. Chem.* **2013**, *11*, 709. (f) Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Chem. Sci.* **2013**, *4*, 2287. (g) Jurberg, I. D.; Chatterjee, I.; Tannert, R.; Melchiorre, P. *Chem. Commun.* **2013**, *49*, 4869.

(7) (a) Albrecht, Ł.; Dickmeiss, G.; Cruz Acosta, F.; Rodríguez-Escrich, C.; Davis, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 2543. (b) Albrecht, Ł.; Cruz Acosta, F.; Fraile, A.; Albrecht, A.; Christensen, J.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 9088. (c) Albrecht, Ł.; Dickmeiss, G.; Weise, C. F.; Rodríguez-Escrich, C.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 13109. (d) Jiang, H.; Rodriguez-Escrich, C.; Johansen, T. K.; Davis, R. L.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 10271.

of **2** without significant influence on the reaction outcome. All of the reactions proceeded in a highly enantio- and diastereoselective fashion providing **4a**–**e** in moderate to good yields. Furthermore, the reactions were fully regioselective as products were formed as a single regioisomer. Notably, other 2,4-dienals **1** could also be successfully employed as demonstrated for the cyclohexyl-derived substrate providing **4f** in moderate yield and high diastereo- and enantioselectivity. Interestingly, 2-substituted benzoquinones proved unreactive under the conditions employed.

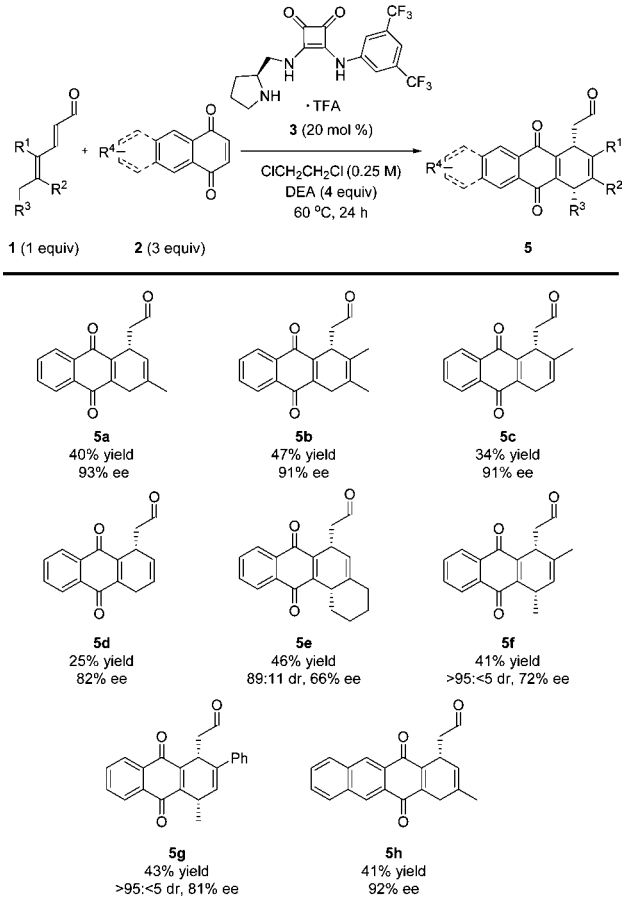
Scheme 2. Scope in Trienamine-Mediated Diels–Alder Reactions between 2,4-Dienals **1** and Substituted 1,4-Naphthoquinones **2** for the Formation of Dihydronaphthoquionones **4**[a]



[a] All reactions performed on a 0.2 mmol scale (see Supporting Information for details). Isolated yields are given. Diastereomeric ratio (dr) determined by ^{1}H NMR spectroscopy. Enantiomeric excess (ee) determined by chiral stationary phase UPC[2] (see Supporting Information for details). For compounds **4d,e**, the enantiomeric excess was determined after the transformation into corresponding **7a,b**.

In the course of further studies, 1,4-naphthoquinones that did not contain the substituent in the 2-position were examined. Interestingly, when the optimized reaction conditions were employed, the reaction proceeded with concomitant oxidation of the initially formed cycloadduct. The excess of the unsubstituted 1,4-naphthoquinone served as the oxidant in this reaction as the consecutive formation of 1,4-dihydroxynaphthalene was observed in the ^{1}H NMR spectra of the crude reaction mixtures.[8] Importantly, other 2,4-dienals **1** proved to be valid substrates in the developed cascade involving [4 + 2]-cycloaddition followed by oxidation as demonstrated in the synthesis of naphthoquinones **5**. Interestingly, reactions with different 2,4-dienals, allowing for the introduction of an additional stereogenic center in the products **5e**–**g**, proceeded only with moderate enantioselectivity (Scheme 3). Disappointingly, all attempts to extend the developed strategy to simple benzoquinones failed. In contrast, employment of 1,4-anthraquinone possessing an extended fused aromatic system in the reaction sequence proved possible yielding **5h** with comparable results. Utilization of unsymmetrical 1,4-naphthoquinones with a substituent on the aromatic part of **2** led to mixtures of isomers due to low regioselectivity.

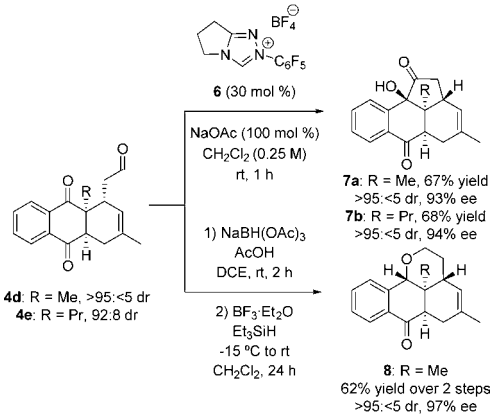
Scheme 3. Scope in Trienamine-Mediated Diels–Alder-Oxidation Cascade in the Reaction between 2,4-Dienals **1** and 1,4-Naphthoquinones **2** for the Formation of Optically Active Naphthoquinones **5**[a]



[a] All reactions performed on a 0.2 mmol scale (see Supporting Information for details). Isolated yields are given. Diastereomeric ratio (dr) determined by ^{1}H NMR spectroscopy. Enantiomeric excess (ee) determined by chiral stationary phase UPC[2] (see Supporting Information for details).

The synthetic potential of the cycloadducts obtained was demonstrated in different stereoselective transformations (Scheme 4). Initially, cycloadducts **4d,e** were subjected to NHC-catalyzed intramolecular benzoin condensation for the construction of the cyclopentanone ring. To our delight, NHC-precatalyst **6** was an efficient promoter of the transformation, as tetracyclic compounds **7** were formed in

Scheme 4. Diastereoselective Transformations of Cycloadducts **4**



good yields. Furthermore, stereochemical information introduced in the first organocatalytic step was preserved in the reaction yielding products **7a**,**b** in a highly stereoselective fashion. Subsequently, the introduction of a tetrahydropyrane motif into the products was attempted. For this reason, dihydronaphthoquinone **4d** was subjected to a sequence of reactions involving chemoselective reduction of an aldehyde moiety followed by reductive etherification yielding **8** in good overall yield as a single diastereoisomer.

The absolute and relative configuration of products **4** and **5** was assigned by analogy to the previous work on *exo*-selective trienamine-mediated reactions.[9,10] It is assumed that the carbonyl group of the corresponding 1,4-naphthoquinone **2** is involved in the recognition process with the H-bonding site of the catalyst **3**. Hereby, *exo*-approach of the dienophile to trienamine reacting in the (C2−C3)-*s*-*trans*-(C4−C5)-*s*-*cis* conformation is postulated to occur.

In conclusion, a stereoselective approach to enantiomerically enriched carboannulated dihydronaphthoquinones and naphthoquinones has been developed. The strategy was based on a trienamine-mediated H-bond directed [4 + 2]-cycloaddition reaction utilizing 2,4-dienals and 1,4-naphthoquinones as reactants. The reaction outcome was possible to control by the choice of the substituent in the 2-position of the naphthoquinone counterpart. While unsubstituted derivatives underwent a subsequent oxidation reaction yielding naphthoquinone derivatives as the final product, 2-substituted-1,4-naphthoquinones led to the formation of dihydronaphthoquinones bearing a quaternary stereogenic center. Importantly, reactions proceeded in moderate to good yields, and the stereoselectivities were in most cases high. Moreover, the potential of the cycloadducts obtained was demonstrated in various stereoselective transformations leading to polycyclic frameworks with high stereochemical complexity.

Acknowledgment. This work was made possible by grants from Aarhus University, FNU, and the Carlsberg Foundation.

Supporting Information Available. Detailed experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

(8) If less than 3 equiv of **2f** is employed, a mixture of oxidized and nonoxidized products was obtained. Optimization studies on reaction involving solvent, temperature, and reactant ratio screening did not lead to overall yield improvement.

(9) For examples of *exo*-selective trienamine-mediated Diels−Alder reactions, see: (a) Jia, Z.-J.; Zhou, Q.; Zhou, Q.-Q.; Chen, P.-Q.; Chen, Y. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 8638. (b) Ma, C.; Jia, Z.-J.; Liu, J.-X.; Zhou, Q.-Q.; Dong, L.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2013**, *52*, 948.

(10) All attempts to obtain crystals suitable for X-ray analysis failed.

The authors declare no competing financial interest.