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Oxidized Arenol Intermediates in Intermolecular Carbon–Carbon Bond Formation. Naphthoid Cyclohexa-2,4-dienones via Oxidative Nucleophilic Substitution

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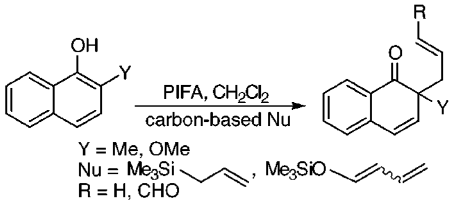
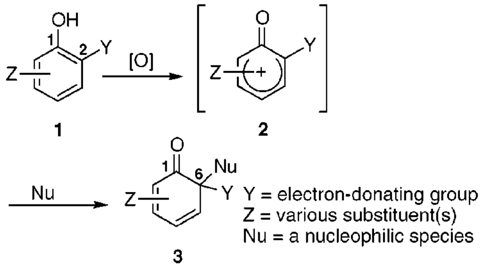
ABSTRACT



Dearomatization of arenes is a powerful strategy for the preparation of functionalized cyclic olefins. Phenol oxidation can be exploited as a dearomatization tactic to produce cyclohexa-2,4-dienones. Iodine(III)-mediated oxidation of 2-alkyl- and 2-alkoxynaphthols was accomplished in the presence of an allylsilane or a silyl enol ether carbon-based nucleophile to furnish cyclohexa-2,4-dienone derivatives in moderate to good yields. This intermolecular carbon–carbon bond-forming reaction is particularly promising for the preparation of synthetically valuable naphthoid orthoquinols.

Dearomatization of phenolic compounds (arenols) into cyclohexadienone derivatives can be accomplished by two-electron oxidation processes followed by trapping of the oxidized arenol intermediates with nucleophilic species (i.e., oxidative nucleophilic substitution).[1d,e] For example, oxidation of 2-alkyl- or 2-alkoxyphenols such as **1** in the presence of oxygen-based nucleophiles is a well-known reaction that leads to the formation of orthoquinols or orthoquinone monoketals (i.e., 6-alkyl-6-oxo- or 6-alkoxy-6-oxocyclohexa-2,4-dienones such as **3** (Scheme 1).[1] The electron-donating effect of the ortho-positioned substituent is arguably responsible for directing the introduction of the nucleophile toward the substituted carbon center of a phenoxonium ion such as

Scheme 1



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[1] (a) Swenton, J. S. In *The Chemistry of Quinonoid Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley: New York, 1988; Vol. 2, Part 2, pp 899−962. (b) Wessely, F.; Swoboda, J.; Guth, V. *Monatsh. Chem.* **1964**, *95*, 649−670 and previous papers in the same series. (c) Andersson, G. *Acta Chem. Scand. B* **1976**, *30*, 403−406 and previous papers in the same series. (d) Arzeno, H.; Barton, D. H. R.; Bergé-Lurion, R.-M.; Lusinchi, X.; Pinto, B. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2069−2076. (e) Barton, D. H. R.; Bergé-Lurion, R.-M.; Lusinchi, X.; Pinto, B. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2077−2080.

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2 or its synthetic equivalent.[2] Various oxidizing systems based on heavy metals,[3] polyvalent iodine,[1c,4] and organic oxidants such as DDQ,[1d] as well as electrochemical processes,[5] have been utilized over the years to mediate this type of transformation. Today, hypervalent iodine(III) reagents have certainly emerged as the most frequently used alternatives because of their good oxidation performances, operational facility, and low toxicity.[4a−c]

Preparation and utilization of cyclohexa-2,4-dienones in organic synthesis are not trivial matters, notably because these conjugated π-systems present both dienic and dienophilic characters that render them particularly prone to Diels−Alder dimerization, as opposed to their 2,5-dienones counterparts.[1] They are also susceptible to facile reduction and rearrangement processes that often lead to adventitious rearomatization events.[1a,9b] Nevertheless, such cyclohexadienones have found useful synthetic applications.[6,9]

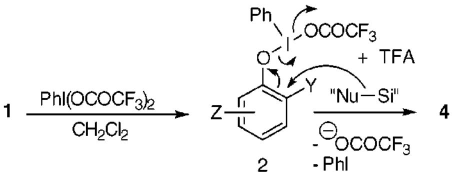
In contrast to oxygen-based nucleophiles, carbon nucleophiles have seldom been utilized to prepare cyclohexa-2,4-dienone derivatives from arenols via oxidative nucleophilic substitution, even though such reactions comprise potentially useful entries to quaternary carbon−carbon centers and synthetically valuable orthoquinol synthons.

Intermolecular versions of this carbon−carbon bond-forming reaction known to furnish isolable cyclohexa-2,4-dienone species are rare and low-yielding.[7] Reactions between olefins and oxidized phenol intermediates have been reported to give rise to transient cyclohexa-2,4-dienone species, but they efficiently rearomatized to dihydrobenzofurans.[8a,b] Similar reactions in the apparently more stable 2,5-dienone series are not very common either.[8] Notwithstanding, it should be possible to exploit the presence of suitable substituents on the arenol substrates to help in controlling the regiochemistry of carbon introduction in a manner analogous to that of oxygen introduction (Scheme 1).

Our interest in the utilization of orthoquinone ketals and orthoquinols in natural products synthesis[9] led us to explore this avenue of carbon−carbon bond formation. We here report our preliminary results on an unprecendented *intermolecular* carbon−carbon bond-forming reaction that enables the rapid preparation of highly functionalized naphthoid cyclohexa-2,4-dienone derivatives in good yields.

To examine the possibilities of introducing carbon-based nucleophiles into arenols in a regiochemically controlled manner, substrates bearing an electron-releasing group (Y = Me or OMe) in their ortho position(s) were oxidized with phenyliodine(III) bis(trifluoroacetoxy) (PIFA)[4a−d] in the presence of carbanion equivalents such as allylsilanes and silyl enol ethers. The choice of PIFA was based on the relatively weak nucleophilicity of its trifluoroacetoxy units in order to minimize competition when trapping oxidized arenols. Special care was taken to ensure anhydrous reaction conditions since iodine(III) reagents are efficient mediators of paraquinone formation in the presence of water.[4e,f] The use of silyl enol ether nucleophiles was undoubtedly optimistic for these species can be easily oxidized by iodine(III) reagents to furnish carbon−carbon self-coupled or α-oxygenated carbonyl products.[10] Nevertheless, these silicon-masked carbonyl compounds, if used under carefully timed conditions, could combine with oxidized arenol intermediates to furnish cyclohexa-2,4-dienones ideally tethered for further synthetic elaboration.[11] Moreover, we anticipated that the reactivity of these nucleophiles could be unveiled by trifluoroacetic acid (TFA)-induced cleavage of their oxygen− or carbon−silicon bonds. Since TFA would be released during the PIFA-mediated oxidation step, this process would lead to the rapid formation of highly functionalized cyclohexa-2,4-dienones in situ (Schemes 1 and 2).

Scheme 2



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(2) (a) Swenton, J. S.; Carpenter, K.; Chen, Y.; Kerns, M. L.; Morrow, G. W. *J. Org. Chem.* **1993**, *58*, 3308−3316. (b) Rieker, A.; Beisswenger, R.; Regier, K. *Tetrahedron* **1991**, *47*, 645−654. (c) Bodajla, M.; Jones, G. R.; Ramsden, C. A. *Tetrahedron Lett.* **1997**, *38*, 2573−2576. (d) Endo, Y.; Shudo, K.; Okamoto, T. *J. Am. Chem. Soc.* **1982**, *104*, 6393−6397.

(3) (a) Bubb, W. A.; Sternhell, S. *Tetrahedron Lett.* **1970**, *51*, 4499−4502. (b) McKillop, A.; Perry, D. H.; Edwards, M.; Antus, S.; Farkas, L.; Nógrádi, M.; Taylor, E. C. *J. Org. Chem.* **1976**, *41*, 282−287. (c) Hewitt, D. G. *J. Chem. Soc. C* **1971**, 2967−2973.

(4) (a) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, 1997. (b) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123−1178. (c) Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem.* **1991**, *56*, 435−438. (d) Koser, G. F. In *The Chemistry of Functional Groups, Supplement D*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1983; pp 721−811. (e) Barret, R.; Daudon, M. *Tetrahedron Lett.* **1990**, *31*, 4871−4872. (f) Pelter, A.; Elgendy, S. M. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1891−1896.

(5) (a) Swenton, J. S. *Acc. Chem. Res.* **1983**, *16*, 74−81. (b) Torii, S. *Electroorganic Syntheses: Methods and Applications*; VCH: Tokyo, 1984. (c) Rieker, A.; Beisswenger, R.; Regier, K. *Tetrahedron* **1991**, *47*, 645−654.

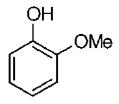
(6) For examples of recent utilizations of orthoquinone monoketals in natural products synthesis, see: (a) Haseltine, J. N.; Cabal, M. P.; Mantlo, N. B.; Iwasawa, N.; Yamashita, D. S.; Coleman, R. S.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1991**, *113*, 3850−3866. (b) Churcher, I.; Hallet, D.; Magnus, P. *J. Am. Chem. Soc.* **1998**, *120*, 10350−10358. (c) Coleman, R. S.; Grant, E. B. *J. Am. Chem. Soc.* **1995**, *117*, 10889−10904. (d) Banwell, M. G.; Ireland, N. K. *J. Chem. Soc., Chem. Commun.* **1994**, 591−592. (e) Liao, C.-C.; Chu, C.-S.; Lee, T.-H.; Rao, P. D.; Ko, S.; Song, L.-D.; Shiao, H.-C. *J. Org. Chem.* **1999**, *64*, 4102−4110. (f) Singh, V. *Acc. Chem. Res.* **1999**, *32*, 324−333. (g) Carlini, R.; Higgs, K.; Rodrigo, R.; Taylor, N. *Chem. Commun.* **1998**, 65−66.

(7) (a) Yamamura, S.; Shizuri, Y.; Shigemori, H.; Okuno, Y.; Ohkubo, M. *Tetrahedron* **1991**, *47*, 635−644. (b) Büchi, G.; Mak, C.-P. *J. Am. Chem. Soc.* **1977**, *99*, 8073−8075.

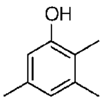
(8) (a) Kerns, M. L.; Conroy, S. M.; Swenton, J. S. *Tetrahedron Lett.* **1994**, *35*, 7529−7532. (b) Gates, B. D.; Dalidowicz, P.; Tebben, A.; Wang, S.; Swenton, J. S. *J. Org. Chem.* **1992**, *57*, 2135−2143. (c) Swenton, J. S.; Callinan, A.; Chen, Y.; Rohde, J. J.; Kerns, M. L.; Morrow, G. W. *J. Org. Chem.* **1996**, *61*, 1267−1274 and references therein. (d) Rama Krishna, K. V.; Sujatha, K.; Kapil, R. S. *Tetrahedron Lett.* **1990**, *31*, 1351−1352. (e) Szántay, C.; Blaskó, G.; Bárczai-Beke, M.; Péchy, P.; Dörnyei, G. *Tetrahedron Lett.* **1980**, *21*, 3509−3512. (f) Kita, Y.; Takada, T.; Ibaraki, M.; Gyoten, M.; Mihara, S.; Fujita, S.; Tohma, H. *J. Org. Chem.* **1996**, *61*, 223−227. (g) Kita, Y.; Arisawa, M.; Gyoten, M.; Nakajima, M.; Hamada, R.; Tohma, H.; Takada, T. *J. Org. Chem.* **1998**, *63*, 6625−6633. (h) Ward, R. S.; Pelter, A.; Abd-El-Ghani, A. *Tetrahedron* **1996**, *52*, 1303−1336. (i) Speiser, B. Doctoral Thesis, University of Tübingen, Germany, 1981.

(9) (a) Quideau, S.; Pouységu, L.; Looney, M. A. *J. Org. Chem.* **1998**, *63*, 9597−9600. (b) Quideau, S.; Looney, M. A.; Pouységu, L.; Ham, S.; Birney, D. M. *Tetrahedron Lett.* **1999**, *40*, 615−618.

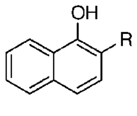
To test the feasibility of this reaction cascade proposal, we first utilized 2-alkoxyphenol guaiacol (**1a**) which can be viewed as an inappropriate susbtrate since the substitution pattern of the ring is unlikely to block Diels−Alder reactions.[1c] Thus, **1a** was treated with PIFA (1 equiv) in an anhydrous $CH_3CN-CH_2Cl_2$ solvent mixture at −41 °C for 30 min after which time the silyl enol ether **3a** (1 equiv) was added to furnish a complex mixture from which **4a** could be separated in low yield as the sole identifiable compound (see Table 1 and Supporting Information). In this minor product, at least, the methoxy group did not act as an efficient regioselector and the nucleophilic addition occurred at the unsubstituted para position of **1a**; prototropic rearrangement then led to the rearomatized substitution product **4a**. Its regiochemical assignment is based on examination of the coupling pattern in its ^{1}H NMR spectrum (see Supporting Information).



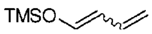
1a



1b



1c: R = OMe
1d: R = Me

3a :


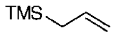
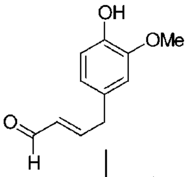
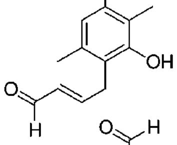
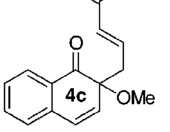
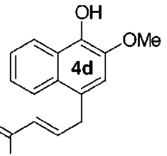
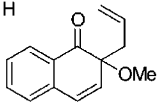
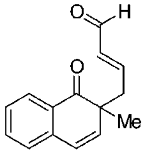
3b :


Table 1. Oxidized Arenol Intermediates in Intermolecular Carbon−Carbon Bond Formation

entry	phenol	nucleophile	product(s)	isolated yield (%)
1	**1a**	**3a**		**4a**: 10
2	**1b**	**3a**		**4b**: 44
3	**1c**	**3a**		**4c**: 22 (26) [a]
4	**1c**	**3a**		**4c**: 55 → 74 **4d**: 27 → 4
5	**1c**	**3b**		**4e**: 69
6	**1d**	**3a**		**4f**: 47 (70) [a]

[a] conversion yields

The formation of **4a** nevertheless demonstrated that two critical events of the desired reaction cascade had occurred: (1) the oxygen−silicon bond in **3a** had been broken and (2) a carbon−carbon bond to the starting phenol had been made. The latter event was not too surprising since iodine(III) reagents are known to activate arenes toward substitution by allylmetal compounds,[10] but suitable substrates and adequate experimental conditions favoring additions onto substituted centers had yet to be found.

Clearly, the experimental approach initially followed with **1a** in which the nucleophilic reagent is added to a TFA-containing solution of preoxidized phenol seemed a logical basic design to control the sequence of bond breaking and making events of this reaction. For example, premature oxidation of the silyl enol ether reagent should hence be minimized. The 2-alkylphenol-2,3,5-trimethylphenol (**1b**) was also tested to gauge the regioselecting effect of a methyl group in a sterically hindered substrate. Treatment of a solution of PIFA-oxidized **1b** in CH_2Cl_2 with an excess of **3a** (2.8 equiv) in CH_2Cl_2 at −78 °C produced a tetrasubstituted phenol in 44% yield as the sole identifiable compound (Table 1, entry 2). Steric crowding may have prevented the development of a tetrahedral center at the 2-position of **1b**. The structure **4b** has not yet been confirmed by spectroscopic means, but substitution at the 6-position of **1b** is proposed here on the basis of the higher steric impediment that can block its 4-position. Thus, no cyclohexa-2,4-dienones could be detected in these initial tests with phenols **1a** and **1b**; products **4a** and **4b** simply reflect the possibility of oxidatively adding carbon substituents to phenols.[8b,c]

Despite these observations with simple phenols, reactions were carried out with 2-substituted naphthols which constitute our choice starting materials for the synthesis of natural polyoxygenated benz[*a*]anthracenes via naphthoid cyclohexa-2,4-dienones.[12] Furthermore, we surmised than naphthols have a better potential to give rise to stable cyclohexa-2,4-dienone derivatives than phenols since their 2,3-double bond is part of an aromatic ring.[1a]

Treatment of 2-methoxy-1-naphthol **1c** with **3a** in the presence of PIFA under the same conditions as for converting **1a** into **4a** furnished the desired naphthoid keto aldehyde **4c** in a moderate but nonetheless remarkable 22% isolated yield (Table 1, entry 3), together with 15% of recovered starting naphthol **1a** (i.e., 26% conversion). This result was particularly encouraging because similar synthetic intermediates thus

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(10) Moriarty, R. M.; Vaid, R. K. *Synthesis* **1990**, 431−447.

(11) For examples of similar carbon−carbon bond-forming reactions between silyl enol ethers and alkenes, see: Zhdankin, V. V.; Mullikin, M.; Tykwinski, R.; Berglund, B.; Caple, R.; Zefirov, N. S.; Koz'min, A. S. *J. Org. Chem.* **1989**, *54*, 2605−2608.

(12) (a) Rohr, J.; Thiericke, R. *Nat. Prod. Rep.* **1992**, *9*, 103−137. (b) Kraus, G. A.; Wan, Z. *Tetrahedron Lett.* **1997**, *38*, 6509−6512.

tethered with a functionalized four-carbon chain could serve to access valuable angularly oxygenated benz[*a*]anthracene systems.[12] Effort was then focused on optimizing this reaction. By adding a solution of PIFA-oxidized **1c** in CH_2Cl_2 to a solution of an excess of **3a** (2.8 equiv) in CH_2Cl_2 at room temperature, **4c** was first obtained in 55% yield, together with 27% of the 4-substituted naphthol **4d**. A slow dropwise addition step advantageously controlled the regioselectivity of the nucleophilic attack to furnish **4c** in 74% and the undesired naphthol **4d** in only 4%. All expectations concerning the originally planned reaction cascade have thus been met in this run.

The allylsilane **3b** also gave rise to the desired cyclohexa-2,4-dienone derivative **4e** in good yield (69%, entry 5). In this case, **3b**, probably less sensitive to oxidizing conditions than **3a**, could alternatively be placed in the presence of the starting naphthol **1c** before adding the oxidizing agent at room temperature. It must be noted that this protocol was detrimental for the preparation of **4c** in any respectable yield.

Finally, the influence of a naphthol 2-alkyl substituent on the outcome of the reaction was examined by adding a solution of PIFA-oxidized 2-methylnaphthol **1d** in CH_2Cl_2 to a solution of **3a** (2.8 equiv) in CH_2Cl_2. The best yield of keto aldehyde **4f** (47%) was obtained when the reaction was performed at −78 °C. The starting naphthol **1d** was recovered in 34% yield, which corresponds to a corrected conversion yield of 70%.

In conclusion, highly functionalized carbon chain-tethered naphthoid cyclohexa-2,4-dienones have been synthesized in a concise and preparatively useful manner from naphthols via an oxidative nucleophilic substitution. Although studies are still needed to identify the key experimental factors to modulate for optimizing further this remarkable carbon−carbon bond-forming reaction, the preliminary results reported here are already quite gratifying. We are currently focusing on exploring variations aimed at the preparation of anthranoid analogues for future applications in the total synthesis of natural benz[*a*]anthracene products. This work will be reported in due course.

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Supporting Information Available: Experimental details, characterization data, and ^1H and ^{13}C NMR spectra for **4a−f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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