The Synthesis and Reactivity of Naphthoquinonynes\*\*

Renato L. de Carvalho,[a][b]+ James M. Wood,[c][d]+ Renata G. Almeida,[a] Neil G. Berry,[b] Eufrânio N. da Silva Júnior\*[a] and John F. Bower\*[b][c]

[a] Dr. R. L. de Carvalho, Dr. R. G. Almeida, Prof. Dr. E. N. da Silva Júnior
Instituto de Ciências Exatas, Departamento de Química
Universidade Federal de Minas Gerais - UFMG
31270-901, Belo Horizonte – MG, Brazil
E-mail: eufranio@ufmg.br

[b] Dr. R. L. de Carvalho, Prof. N. G. Berry, Prof. J. F. Bower
Department of Chemistry
University of Liverpool
Crown Street, Liverpool, L69 7ZD, United Kingdom

E-mail: john.bower@liverpool.ac.uk

[c] Dr. J. M. Wood, Prof. J. F. Bower
School of Chemistry,

 University of Bristol,

 Cantock’s Close, Bristol, BS8 1TS, United Kingdom

[d] Dr. J. M. Wood

 The Ferrier Research Institute,

 Victoria University of Wellington

 Wellington, 6012, New Zealand

+ These authors contributed equally to this work

[\*\*] Supporting information for this article is given via a link at the end of the document.

**Abstract:** The first systematic exploration of the synthesis and reactivity of naphthoquinonynes is described. Routes to two regiosomeric Kobayashi-type naphthoquinonyne precursors have been developed, and the reactivity of the ensuing 6,7- and 5,6-aryne intermediates has been investigated. Remarkably, these studies have revealed that a broad range of cycloadditions, nucleophile additions and difunctionalizations can be achieved *while maintaining the integrity of the highly sensitive quinone unit*. The methodologies offer a powerful diversity oriented approach to C6 and C7 functionalized naphthoquinones, which are typically challenging to access. From a reactivity viewpoint, the study is significant because it demonstrates that aryne-based functionalizations can be utilized strategically in the presence of highly reactive and directly competing functionality.

Introduction

Quinones and the Diels-Alder reaction share a rich history, from the reaction between quinone and cyclopentadiene, first reported by Diels and Alder in 1928,1 to the many landmark total syntheses featuring [4+2] cycloadditions of quinones (Scheme 1A, top equation).2 Indeed, the reactivity of quinones in cycloadditions has been extensively documented, and this process is also invoked in the biosynthesis of numerous natural products.3 The electrophilic nature of the quinone ring also renders it amenable to the 1,4-addition of polar nucleophiles,4 or Giese reactions with radical species.5 These rich chemistries have found extensive application because of the high value of quinoidal targets; for example, they feature as bioactive type II polyketides,6 as coenzymes in electron transport and blood coagulation,7 and have found application in drug development,8 as photosensitizers,9 and in energy storage.10 Our group has a longstanding interest in quinoidal compounds as antiparasitic agents to target *T. cruzi*11 or *Leishmania,*12 which are responsible for Chagas and leishmaniasis disease, respectively.13



**Scheme 1**. Methods to functionalize naphthoquinones, and considerations for accessing and harnessing naphthoquinonynes.

As part of our ongoing medicinal chemistry efforts, we have sought methods for the selective functionalization of naphthoquinones. While the chemistry outlined above allows easy derivatization of the highly reactive quinoidal B-ring, selective functionalization of the strongly deactivated benzenoid A-ring poses a significant challenge that has yet to be adequately addressed. In certain cases, carbonyl-directed, metal-catalyzed C−H functionalization can introduce substituents at C5 (Scheme 1A, bottom equation);14 however, distal functionalization at C6 and C7 is a largely unmet issue that instead typically requires *de novo* syntheses15 or indirect methods.16 Within this context, we were intrigued by the possibility of generating aryne intermediates (**Int-I** and **Int-II**) on the benzenoid A-ring (Scheme 1B).17 If successful, this approach would allow the diversity oriented introduction of up to two different substituents in a single operation. Although arynes have been generated on protected hydroquinone scaffolds,18 we are unaware of any examples involving quinoidal systems. This is unsurprising because the high reactivity of the quinone unit would be expected to compromise any aryne-based protocol. While synthetically enabling methodologies have emerged that involve the generation of arynes on “core functionalized” and more reactive ring systems (e.g. pyridynes and indolynes, Scheme 1C),19 to the best of our knowledge there are no aryne-based protocols that even approach the seemingly naïve chemoselectivity demands required for Scheme 1B.Nevertheless, as described below, we have found that such processes can indeed be executed. Our study encompasses the first systematic exploration of the synthesis and reactivity of naphthoquinonynes and, in broader terms, demonstrates that aryne-based functionalizations can be utilized strategically in the presence of highly reactive and directly competing functionality.

Results and Discussion

To access **Int-1** and **Int-II** we targeted Kobayashi-type aryne precursors because these have found wide applicability in other contexts, and aryne generation using fluoride was deemed potentially compatible with the presence of the sensitive quinone unit.17,20,21 To this end, regiosomeric *ortho*-silyl triflates and nonaflates **6a,b** and **12a,b** were targeted so as we could access the respective C6-C7 and C5-C6 arynes **Int-I** and **Int-II**. The synthesis of naphthoquinones **6a,b** proved to be straightforward (Scheme 2A). Iridium catalyzed C–H borylation-oxidation at C6 of dimethoxynaphthalene **1** gave naphthol **2** in quantitative yield and with complete regioselectivity.16 This process could be performed on decagram scale using just 0.5 mol% of the iridium catalyst. Advancement of **2** to carbamate **3** then allowed introduction of the C7 trimethylsilyl unit via directed lithiation.22 Upon completion of this process, LiAlH4 was added to effect reductive removal of the carbamate and provide **4** in 90% yield for the one pot process. Reaction of **4** with Tf2O or NfF provided **5a** and **5b**, which were oxidized (CAN) to generate the target naphthoquinones **6a** and **6b**. These species were unstable upon prolonged storage and so were synthesized as required from bench-stable precursors **5a** and **5b**.



**Scheme 2.** Synthesis of (A) 6,7-aryne (**6**) and (B) 5,6-aryne precursors (**12**).

Access to C5-C6 aryne precursors **12a** and **12b** was more challenging (Scheme 2B). Treatment of bromide **7** with LDA generated dimethoxybenzyne, which underwent cycloaddition with furan and subsequent acid-catalyzed rearrangement to afford naphthol **8** in 69% yield (two steps).23 *Ortho*-selective bromination and *O*-silylation provided **9**, which was targeted to allow installation of the C6-silyl group via a retro-Brook rearrangement. Indeed, halogen-lithium exchange from **9** triggered O→C silyl migration to provide naphthol **10** in 90% yield. Unfortunately, despite extensive efforts, we were unable to convert **10** to **11a**.24 Attempts to telescope the rearrangement and triflation processes were more promising and we were able to access *ortho*-silyl triflate **11a**, but in only 17% yield. Pleasingly, the telescoped protocol was efficient for accessing nonaflate **11b**, which was generated in 72% yield. CAN promoted oxidation of **11a** and **11b** provided target quinones **12a** and **12b** in good yield.

To investigate the viability of generating the putative naphthoquinoidal aryne **Int-I**, we explored initially its cycloaddition with furan (Table 1). Pleasingly, when naphthoquinone **6a** and furan (5.0 equiv.) were exposed to a variety of fluoride sources (CsF, KF/18-crown-6 or TBAF), cycloaddition product **13b** was observed in modest yields (Entries 1-4). Further investigations used 2,5-dimethylfuran, and reaction of this with **6a** using KF/18-crown-6 at room temperature provided **13a** in 48% yield (Entry 5). Here, marginal improvements to efficiency were observed by slow addition of naphthoquinone **6a** to the reaction mixture at 50 oC. In these reactions, a major side product was sulfone **13’**, which likely forms via competitive anionic thia-Fries rearrangement.Related O→C transfers of -SO2CF3 have been studied for aryl lithium species,25 and these processes were found to be particularly facile for substrates bearing electron-withdrawing substituents. This side reaction is generally not observed as a major process in Kobayashi fragmentation reactions;26 however, it has been observed as the predominant pathway in specific systems.26b To circumvent this issue, nonaflate **6b** was selected for further optimization because we reasoned that the more sterically shielded S-center of this system should suppress thia-Fries rearrangement. Although nonaflates have been used previously for Kobayashi-type aryne precursors,27 we are unaware of examples where this was done specifically to suppress thia-Fries rearrangement. Pleasingly, nonaflate **6b** gave improved yields of cycloadduct **13a**, with comparable results obtained using either KF/18-crown-6 or tetrabutylammonium difluorotriphenylsilicate (TBAT) (Entries 6 and 7). Ultimately, optimal results were obtained by setting up the reaction in a glovebox with reagents that had been rigorously dried. Using these precautions, cycloadduct **13a** was obtained in 70% yield at room temperature and without the need for slow addition of **6b** (Entry 8).

**Table 1.** Selected aryne generation optimization results.[a,b]



[a] See the SI for full details of reaction optimization. [b] Standard conditions: Naphthoquinone (0.2 mmol), furan (5.0 eq.), fluoride source, solvent, 3 h. [c] Naphthoquinone was added dropwise over 1.5 h. [d] Side product **13'** was observed in 24% yield. [e] The reaction was set up in a glove box, and the yield refers to isolated material. [f] Yields were determined by 1H NMR analysis using 1,4-dinitrobenzene as an internal standard.

With efficient 6,7-aryne generation conditions established, the scope of the protocol was examined. Various furan cycloadducts were successfully prepared in 45–94% yield (Table 2). Notably, furan arynophiles with electron-donating substituents afforded cycloadducts in high yield (e.g. **13e** and **13f**), whereas arynophiles with electron-withdrawing substituents were less efficient (e.g. **13d** and **13g**). These results are consistent with the idea that the aryne LUMO(aryne)-HOMO(arynophile) interaction is predominant in these [4+2] cycloadditions. In all cases, possible competitive cycloaddition with the quinone unit of **6b** or the products was not observed. Selected limitations are outlined at the bottom of Table 2, and, unsurprisingly, include an inverse-electron demand 1,2-diazine.

**Table 2.** Generation and utility of a 6,7-naphthoquinoidal aryne.[a]



[a] Standard conditions: **6b** (0.2 mmol), arynophile (5.0 eq), KF (2.1 eq), 18-crown-6 (2.1 eq), THF (0.07 M), 3 h, Ar, reaction set up in a glovebox.

In addition to [4+2] furan cycloadducts, the aryne capture procedure was also performed using 6,6-dimethylfulvene as an arynophile, from which compound **14a** was obtained in 71% yield (Table 3).28 Beyond [4+2] cycloadditions, aryne capture with 3-methylbut-2-enal afforded chromene **14b** in 67% yield, which is an isomer of the antivascular natural product dehydro-α-lapachone.29 This reaction likely proceeds via [2+2] cycloaddition with the aldehyde to form a strained 4-membered cyclic intermediate, followed by rearrangement.30 Dihalogenated or dichalcogenated products **14c** and **14d** were obtained by capture of the aryne with iodine31 and diphenyldiselenide, respectively. Use of phenol as the arynophile unexpectedly provided **14e** in 30% yield. This process presumably involves initial nucleophilic attack of THF onto the aryne to generate an oxonium species, which is then opened by phenol phenol, as previously outlined by Biju and co-workers.32 [3+2] cycloaddition between the aryne and pyridine-*N*-oxide was followed by rearrangement to give *ortho*-pyridin-3-yl naphthol **14f** in 50% yield.32b The 6,7-aryne could also be trapped with various nucleophilic amines, including 1,2-pyrazole and bulky diisopropylamine, to give adducts **14g** and **14i** in 67% and 57% yield, respectively. Remarkably, in all of these processes the quinone unit remained intact, which demonstrates the higher reactivity of the aryne (a) in cycloadditions, (b) with electrophiles, and (c) with nucleophiles.

**Table 3.** Further utility of a 6,7-naphthoquinoidal aryne.[a]



[a] Standard conditions: **6b** (0.2 mmol), arynophile (5.0 eq), KF (2.1 eq), 18-crown-6 (2.1 eq), THF (0.07 M), 3 h, Ar, reaction set up in a glovebox. [b] **6b** (0.4 mmol), aniline (0.2 mmol).

The reactivity of 5,6-aryne precursor **12b** was investigated next, with this system offering the opportunity to probe the regioselectivity of different aryne capture protocols (Table 4). Cycloadditions with 2,5-dimethylfuran and furan proceeded efficiently to give cycloadducts **15a** and **15b** in 50% and 70% yield, respectively (Entries 1 and 2). Interestingly, the use of 2-alkylated furans marginally favored the contrasteric products **15c-1** and **15d-1** (Entries 3 and 4). These results mirror a study by Buszek, Cramer, and co-workers on the reaction of 6,7-indolynes with 2-substituted furans.34 Here, the observed contrasteric regioselectivity was rationalized by invoking a highly asynchronous concerted reaction pathway, wherein the C5-center of the furan engaged with the more electrophilic C-center of the aryne, resulting in a buildup of oxocarbenium character, which was stabilized by the C2-substituent. We have modelled the structure of the putative benzoquinoidal aryne (**Int-II**) using the same approach as Garg, Houk and co-workers (see the SI for details).35 This revealed a relative flattening of the bond angle at C6 versus C5 (*θ*CCC = 128.08° vs 125.95°, see Table 4, top), indicating that the former position is marginally more electrophilic because bond formation at this position involves less ring distortion in the transition state. Although the bond angle differences are small, this analysis is consistent with the regioselectivities observed for Entries 3 and 4, and also

**Table 4.** Generation and utility of a 5,6-naphthoquinoidal aryne.[a]



[a] Standard conditions: **12b** (0.2 mmol), arynophile (5.0 eq), KF (2.1 eq), 18-crown-6 (2.1 eq), THF (0.07 M), 3 h, Ar, reaction set up in a glovebox. [b] Ratio determined by 1H NMR analysis of the crude mixture. [c] Only traces (<5%) of the regioisomeric product were observed.

rationalizes the C6 selectivities observed for heteroatom-based nucleophiles to give **14e-14k** (Entries 6-8). Using *i*-PrNH2, complete C6 selectivity was observed to give **14i**, whereas PhNHMe offered more marginal regioselectivity for **14k** (3:1 **14k:15k**). These outcomes suggest that potentially modest regioselectivities in the aryne capture process can be enhanced by employing sterically demanding nucleophiles.

As highlighted in the Introduction, the method described here is of synthetic interest because it allows the diversity oriented introduction of substituents to the less accessible C6 and C7 centers of naphthoquinoidal cores. It is important to recognize that this can then setup systems for further functionalization. To demonstrate this, we have validated N-directed C–H functionalizations of product **14g** under Pd-catalyzed conditions (Scheme 3). Using NFSI as the oxidant and fluorine source, C5-selective conversion of **14g** to fluorinated derivative **16a** was readily achieved by adaption of Hierso and co-workers’ protocol.36,37 Alternatively, use of PhB(OH)2 provided **16b-1** and **16b-2** in a 1:1 ratio, thereby demonstrating the possibility of installing C–C bonds.38 Although we have previously demonstrated that the weakly directing carbonyl units of naphthoquinone can function as intrinsic directing-groups for C–H functionalizations (see Scheme 1A),14 both processes in Scheme 3 require the pyrazole unit, thereby implicating an N-directed pathway (as in **Int-III**).



**Scheme 3.** Palladium-catalyzed C–H functionalizations of **14g**.

Conclusions

In summary, we have outlined a diversity oriented approach to challenging C6 and C7 functionalized naphthoquinones by exploiting the intermediacy of 6,7- and 5,6-naphthoquinonynes. Our study represents the first systematic exploration of the synthesis and reactivity of these species, and selected points of interest include: (a) efficient routes to Kobayashi-type precursors, (b) the use of nonaflates to suppress thia-Fries rearrangement during aryne generation and (c) the elucidation of regioselectivity trends associated with reactions involving the 5,6-naphthoquinonyne (**Int-II**). More significantly, the aryne intermediates can be engaged in cycloadditions, nucleophile additions and difunctionalizations *while maintaining the integrity of the highly sensitive quinone unit*. As outlined in Scheme 1C, the recent renaissance in aryne chemistry has resulted in a growing number of processes that involve “core functionalized” and more reactive ring systems, and these methods have proved to be enabling for complex molecule synthesis.19 We suggest that our study is unique because aryne-based functionalizations are achieved in the presence of highly reactive and directly competing functionality. Going forward, the methods described here may streamline access to naphthoquinoidal natural product targets; for example, ploiariquinone A39 (see Scheme 1C) shares the same core framework as naphthoquinonyne derivative **14b**. Our efforts towards applied objectives of this type are ongoing and will be reported in due course.

Author contributions

Conceptualization: J.M.W, E.N.S.J. and J.F.B.; Project administration: E.N.S.J. and J.F.B.; Formal analysis: R.L.C., J.M.W., E.N.S.J. and J.F.B.; Data curation, Investigation and Methodology: R.L.C., J.M.W. and R.G.A.; Computation: N. G. B.; Resources, Supervision, Validation and Visualization: E.N.S.J. and J.F.B.; Writing – original draft: R.L.C., J.M.W. and E.N.S.J.; Writing – reviewing and editing: E.N.S.J. and J.F.B.; All authors revised and agreed with the present form of the paper.

**Supporting Information**

The authors have cited additional references within the Supporting Information.40-44

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Conflict of interest

The authors declare no conflict of interest.

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The first systematic exploration of the synthesis and reactivity of naphthoquinonynes is described. Routes to two regiosomeric Kobayashi-type naphthoquinonyne precursors have been developed, and the reactivity of the ensuing aryne intermediates has been investigated. A broad range of cycloadditions, nucleophile additions and difunctionalizations can be achieved while maintaining the integrity of the highly sensitive quinone unit.