A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: A Catalytic Oxidative Quinone Heterofunctionalization Method - Synthesis of Strongylophorine-26

Authors: Wanwan Yu, Per Hjerrild, Kristian Jacobsen, Henriette Tobiesen, Line Clemmensen, and Thomas Bjørnskov Poulsen

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201805580
Angew. Chem. 10.1002/ange.201805580

Link to VoR: http://dx.doi.org/10.1002/anie.201805580
http://dx.doi.org/10.1002/ange.201805580

WILEY-VCH

10.1002/anie.201805580

WILEY-VCH

COMMUNICATION

A Catalytic Oxidative Quinone Heterofunctionalization Method – Synthesis of Strongylophorine-26

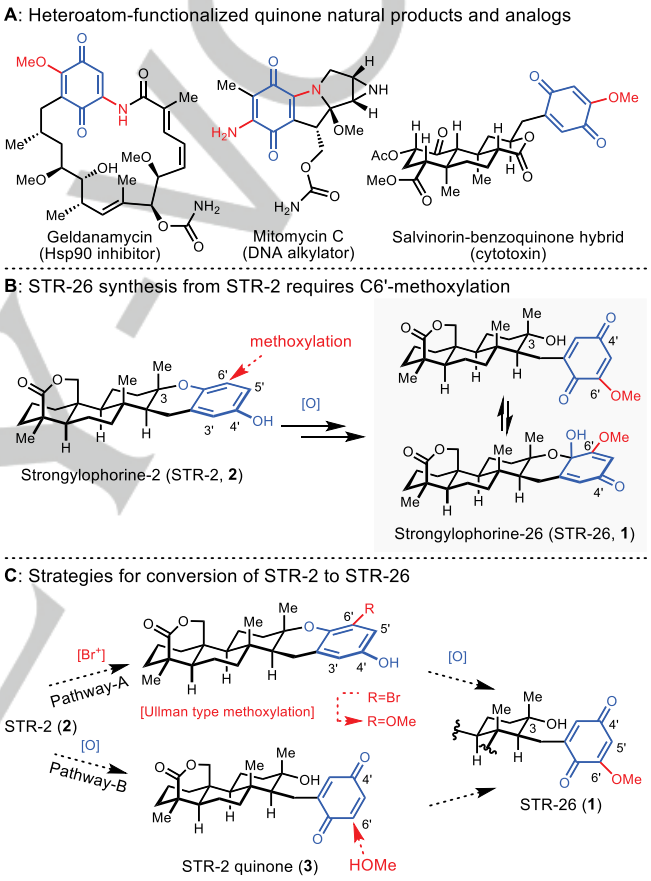
Wanwan Yu[+], Per Hjerrild[+], Kristian M. Jacobsen, Henriette N. Tobiesen, Line Clemmensen, Thomas B. Poulsen*[a]

Abstract: The preparation of heteroatom-substituted *p*-quinones is ideally performed by direct addition of a nucleophile followed by *in situ* reoxidation. Albeit an appealing strategy, the reactivity of the *p*-quinone moiety is not easily tamed and no broadly applicable method for heteroatom functionalization exists. Here, we show that $Co(OAc)_2$ and $Mn(OAc)_3{\bullet}2H_2O$ act as powerful catalysts for oxidative *p*-quinone functionalization with a collection of O, N, and S-nucleophiles using oxygen as the terminal oxidant. Preliminary mechanistic observations and the first synthesis of the cytotoxic natural product strongylophorine-26 is presented.

Quinones have a strong propensity for undergoing proton-coupled electron-transfer reactions,[1] which has spurred numerous applications within materials/polymer science[2] and chemical biology.[3] While redox cycling of quinones has been harnessed for powerful oxidative transformations,[4] the redox characteristics of unprotected quinones limit their utility as chemical reactants. The introduction of heteroatoms onto the quinone ring affords increased stability and these groups are prevalent in bioactive natural products (Scheme 1A),[5] underscoring the value of efficient synthetic methods. Here, we report a novel and broadly applicable quinone-heterofunctionalization reaction, which we have employed in the first synthesis of the cytotoxic meroterpenoid strongylophorine-26 (STR-26, **1**).

We earlier achieved the first synthesis of strongylophorine-2 (STR-2, **2**, Scheme 1B)[6] – a potential synthetic precursor to other STR natural products. In this respect, STR-26 (**1**, Scheme 1B) is of particular interest as **1** has been reported to depolarize cancer cells by actin-remodeling.[7,8] These effects likely underlie the potent cytotoxicity of **1**, but the detailed mechanism is unknown. In solution, STR-26 (**1**) exists in an equilibrium between the 6´-methoxy-quinone and two diastereomeric hemiketals involving the C3-hydroxyl group (Scheme 1B).[7] To prepare **1** from **2**, oxidative opening of the 4'-phenoxychromane ring and installation of the methoxy substituent are required. We initially aimed for functionalization of the chromane moiety prior to oxidative opening (Scheme 1C, Pathway-A), but despite considerable efforts this strategy could not be realized (see Table S1 and Scheme S1, Supporting Information).

Next, we considered direct methoxylation of *p*-benzoquinone **3**, which can be generated by $NaIO_4$-oxidation of **2**.[6] While ostensibly an attractive option (Scheme 1C, Pathway-B), the advantage of applying this approach had not been exploited. Indeed, a literature survey revealed the lack of a general method for *p*-benzoquinone alkoxylation.



Scheme 1. Heteroatom-functionalized quinone natural products and strategies for constructing STR-26 from STR-2.

Recently, the Lumb lab reported an excellent method for the aerobic coupling of phenols to *o*-quinones, but this system was unable to functionalize *p*-quinones.[9] In fact, the evaluation of the methods known to us[10] in a simple quinone test system (**4**) was not encouraging (Figure 1), as we observed either no reactivity, or complex mixtures containing only small quantities of mono-methoxyquinone **6a**.

These discouraging results likely reflect the propensity of *p*-benzoquinones to dimerize and oligomerize under both acidic and basic conditions.[11] Interestingly, a control experiment revealed that simply heating **4** in MeOH under oxygen was superior to all other conditions that we had tested at this point affording **6a** in mediocre yield at full conversion of **4** (Figure 1). While somewhat encouraging, this reactivity is not general.[12] We hypothesized

[a] Dr. W. Yu,[+] P. Hjerrild,[+] K. M. Jacobsen, H. N. Tobiesen, L. Clemmensen, Prof. Dr. T. B. Poulsen
Department of Chemistry, Aarhus University
Langelandsgade 140, 8000 Aarhus C (Denmark)
*E-mail: thpou@chem.au.dk.

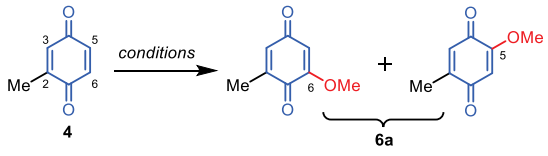
[+] The authors contributed equally to this work

Supporting information and the ORCID identification number(s) for the author(s) are given via a link at the end of the document.

10.1002/anie.201805580

WILEY-VCH

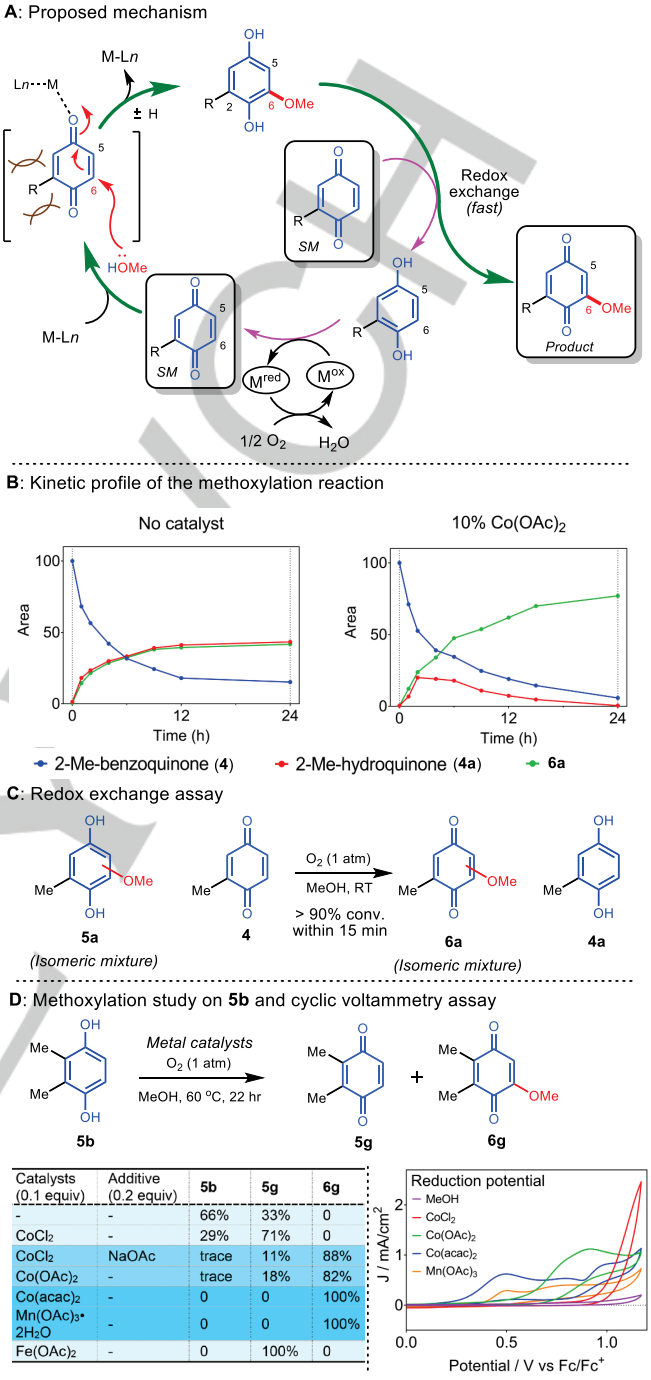
that an additive could be identified which would accelerate both nucleophilic addition and reoxidation of a putative hydroquinone intermediate, leading us to perform a broad screen of metal salts for promoting mono-methoxylation of **4** (representative results in Figure 1 – complete data in Table S2, Supporting Information).[12] This led to the discovery that $Mn(OAc)_3$•$2H_2O$ and in particular $Co(OAc)_2$ afford good to excellent yields of **6a** as a mixture of regioisomers.[13] Other metal-salts displayed disparate effects, most prominently $Fe(OAc)_2$, which completely blocked conversion of **4**. Catalytic quantities of the respective metal salts were sufficient to enhance or suppress reactivity.



Known Methods (Yield of **6a** [ratio: C6/C5])			
I_2/KOH[a]	30% [1.2/1]	NaOMe	complex mixture
I_2/$Cu(OAc)_2$	<10% conv.	30% aq. NH_4OH	complex mixture
I_2/$CeCl_3$	<10% conv.	MeOH/THF	complex mixture
I_2/$HgCl_2$	complex mixture	O_2, MeOH	44% [1.1/1]
$Fe_2(SO_4)_3$/H_2SO_4	complex mixutre		
Screening of Metal Catalysts[b] (Yield of 6a [ratio: C6/C5])			
$Cu(OAc)_2$ (1 equiv)	13% [1.4/1]	$Co(OAc)_2$ (1 equiv)	80%[c] [1.3/1]
AgOAc (1 equiv)	28% [1.4/1]	$Co(OAc)_2$ (0.1 equiv)	81%[c] [1.3/1]
$Zn(OAc)_2$ (1 equiv)	32% [1/1]	$Fe(OAc)_2$ (1 equiv)	<10% conv.
$Mn(OAc)_3$•$2H_2O$ (1 equiv)	68%[c] [1.1/1]	$Fe(OAc)_2$ (0.1 equiv)	<10% conv.
$Mn(OAc)_3$•$2H_2O$ (0.1 equiv)	66%[c] [1.1/1]	$Ni(OAc)_2$•$4H_2O$ (1 equiv)	39% [1.5/1]

Figure 1. Methoxylation of 2-methyl-*p*-benzoquinone. Yield and isomer ratio determined by ^{1}H NMR of the reaction mixture. [a] 4% of C3-isomer observed. [b] Conditions: O_2 (1 bar), MeOH, 60 °C, 22 h. [c] Isolated yield.

To probe the mechanism, we investigated the kinetic profiles of methoxylation of **4** (Figure 2A, 2B). With no catalyst, the reaction affords a mixture of **6a** and **4a** in a ratio that is clearly correlated, suggesting involvement of **4** as the kinetically favoured oxidant of a hydroquinone intermediate (**5a**). Catalytic amounts of $Co(OAc)_2$ facilitates reoxidation of **4a** and ultimately allows productive funnelling to the product **6a**. In accord, the hydroquinone intermediate **5a** undergoes spontaneous redox exchange with **4** at ambient temperature (Figure 2C). The disubstituted quinone **5g,** generated upon oxidation of hydroquinone **5b**, does not undergo spontaneous methoxylation in methanol at 60 ºC and thus can test the ability of the catalysts to facilitate both nucleophilic addition and hydroquinone reoxidation (Figure 2D). Partial oxidation of hydroquinone **5b** to quinone **5g** was evident by ^{1}H-NMR analysis of the crude reaction mixtures, however, catalytic $Co(OAc)_2$, $Co(acac)_2$, or $Mn(OAc)_3$•$2H_2O$ were required for formation of product **6g**. Thus, the metal is needed for quinone activation. The nature of the counterion is decisive in tuning the properties as $CoCl_2$, $Co(OAc)_2$ and $Co(acac)_2$ afford differing reactivity in this system. Combined addition of $CoCl_2$ and NaOAc effectively mimics the reactivity of the corresponding $Co(OAc)_2$ reaction. Catalytic amount of $Fe(OAc)_2$ provided quantitative oxidation of **5b** however without the formation of **6g,** further substantiating a specific interaction



Catalysts (0.1 equiv)	Additive (0.2 equiv)	5b	5g	6g
-	-	66%	33%	0
$CoCl_2$	-	29%	71%	0
$CoCl_2$	NaOAc	trace	11%	88%
$Co(OAc)_2$	-	trace	18%	82%
$Co(acac)_2$	-	0	0	100%
$Mn(OAc)_3$•$2H_2O$	-	0	0	100%
$Fe(OAc)_2$	-	0	100%	0

Figure 2. Proposed mechanism and mechanistic elaboration.

between the quinoid compounds and $Fe(OAc)_2$. Cyclic voltammetry measurements of the metal salts in methanolic solution indicate a correlation between the oxidation potential and the catalytic activity of the corresponding metal salt (Figure 2D).

The generality of the catalytic system was probed (Figure 3). Methoxylation and ethoxylation are generally possible and in sterically biased systems high regiocontrol is observed (**6b** and **6c**). Addition of isopropanol was possible (**6d**) but *tert*-butanol and phenol did not couple. Highly efficient 2,5-dialkoxylation was

10.1002/anie.201805580

WILEY-VCH

COMMUNICATION

performed on *p*-benzoquinone (**6e** and **6f**) and 2-Ph-*p*-benzoquinone (**6m**). In general, reactions can also be initiated from the corresponding hydroquinone (**6g** and **6h**) as discussed above. Methoxylation of chlorinated quinones was challenging due to competing vinylic substitution (**6i** and **6j**), however the presence of $Co(OAc)_2$ was required for reactivity. *p*-Naphthoquinone underwent alkoxylation in good yields (**6k** and **6l**) and naturally occurring quinone compounds or analogs (**6n, 6o**) may be produced.

We investigated the addition of amine-nucleophiles to *p*-benzoquinones. Prior studies have reported similar transformations,[14] but the use of catalytic $Co(OAc)_2$ provided excellent outcomes for the majority of applied substrates (Supporting Information, Scheme S2 displays examples (**7a-h, 7m-q**) of mono-addition of amines). Notably, the method delivered 2,5-diamino-*p*-benzoquinones (**7i**, **7j**) or mixed 2,5-aminoalkyl-methoxy-*p*-benzoquinones (**7k**, **7l**) with very high regioselectivities (Figure 3). As a further application, we prepared 2,5-diaminoalkyl-*p*-benzoquinone **7p** in excellent yield (Figure 3). Ring-closing metathesis afforded atropisomeric macrocycle **12a** in nearly quantitative yield.[15]

Thiol-addition was also facile as exemplified with the thioethylation of *p*-naphthoquinone (**8a**). Selective bis-thioethylation proceeded albeit in low yield (**8b**) and tri-substituted

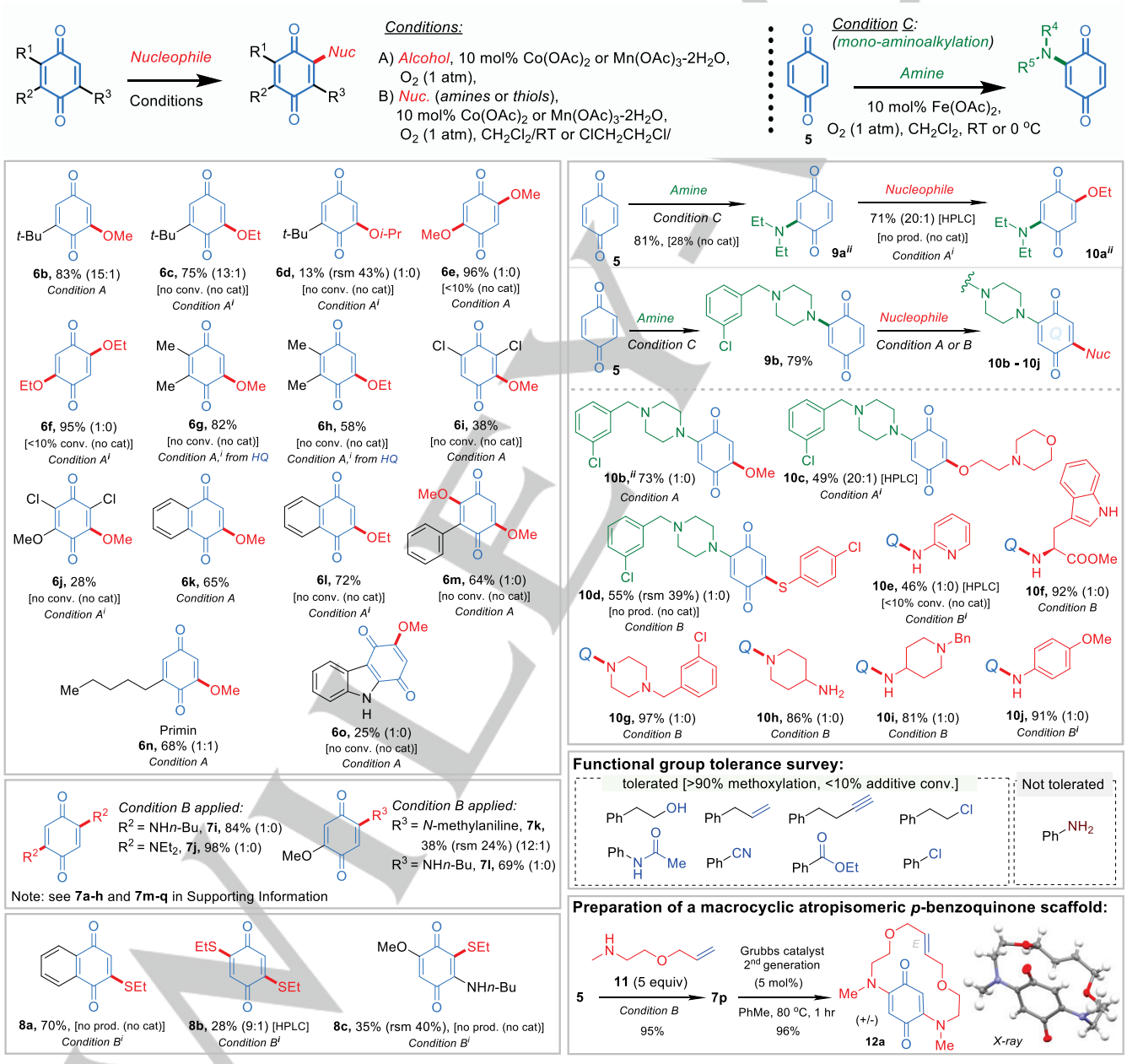


Figure 3. Scope of the quinone heterofunctionalization conditions. [i] $Mn(OAc)_3 \cdot 2H_2O$ was applied; [ii] decomposition was observed during purification. Abbreviations: no cat = no catalyst was applied; no conv. = no conversion was observed by TLC analysis; no prod. = no product formation was observed by TLC analysis; rsm = recovered starting materials; [HPLC] = preparative HPLC purification was applied; from HQ = the corresponding hydroquinone was used as the substrate.

10.1002/anie.201805580

compounds such as **8c** could also be prepared.[16]

Finally, we explored the preparation of unsymmetric benzoquinones based on mono-aminated starting materials **9a** and **9b**, which we serendipitously found can be accessed efficiently using catalytic $Fe(OAc)_2$. This enabled construction of a series of 2,5-disubstituted quinone derivatives (**10a-j**) with excellent regiocontrol. The unanimous tendency for 2,5-substitution found in compounds with two heteroatom substituents (**6e-f**, **m**,**o**; **7i-l**; **8b**; **10a-j**) is indicative of a Lewis acid activation mode through chelate-coordination of the mono-functionalized quinone.

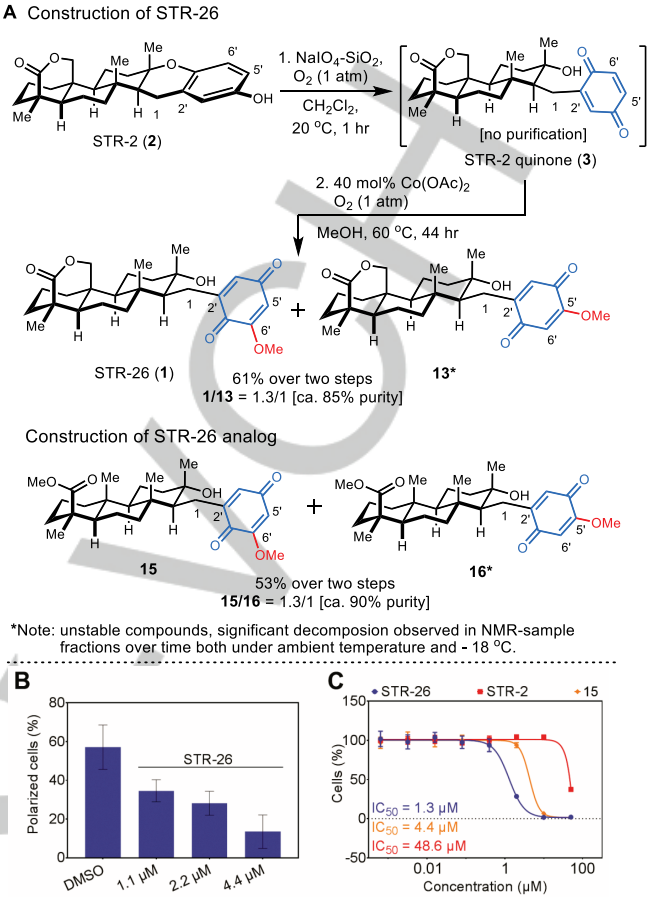
We evaluated the robustness of the methoxylation reaction of **5b** in the presence of nine stoichiometric additives (Figure 3).[17] A functional group was deemed tolerated if the methoxylation proceeded in 90% in comparison to the standard reaction, with conversion of the additive being below 10%. Aniline, being itself a substrate (**7q**, Scheme S2), was not tolerated but all other functional group sampled were compatible (Figure 3).

We now returned to the initial synthetic target – STR-26 (**1**). Chromane-oxidation of **2** using $NaIO_4$•SiO_2 afforded quinone **3**. We did not attempt purification of this rather unstable species, but immediately subjected it to the methoxylation-conditions using $Co(OAc)_2$ in methanol at reflux for 44 h. We used 40 mol% $Co(OAc)_2$ to facilitate conversion, as the amount of **2** disallowed mimicking the substrate concentration previously utilized. Gratifyingly, this afforded a mixture of **1** and the tentative 5'-regioisomer (**13**) in 61% yield (ca. 85% purity) over two steps (Scheme 2A). Further purification by preparative HPLC afforded **1**, however **13** could not be obtained cleanly. The spectroscopic data for synthetic **1** matched the data reported for STR-26 isolated from the natural source (Table S3,4, Supporting Information).[7]

We also conducted the methoxylation on a non-lactone analog (see Supporting Information) to generate a mixture of methoxy-quinones **15** and **16** (53% yield, ca. 90% purity) (Scheme 2A). Again, only the 6´-isomer (**15**) could be obtained cleanly following HPLC purification, and NMR analysis revealed that this analog also equilibrates to the hemiketal. We validated the previously reported ability of **1** to depolarize cancer cells and to kill MDA-MB-231 breast cancer cells at low micromolar concentrations (Scheme 2B).

Comparison of the cytotoxicity of **1** with **2** and analog **15** demonstrates that both the *δ*-lactone and the methoxyquinone functionalities of **1** are needed for potency (Scheme 2C). Preliminary evaluation of additives for ability to modulate toxicity of **1** and **2** was performed (Figure S7, Supporting Information).

In conclusion, we have developed a simple and broadly applicable method for functionalization of *p*-quinones with a variety of heteroatom nucleophiles under aerobic catalytic conditions. Mechanistic features have been evaluated in an effort to understand the intricacies of the reaction. For many substrates, the reaction proceeds in good yields and high selectivities and application in a late-stage setting was demonstrated. The method does not translate directly to *o*-quinones and more studies will be required to understand this limitation. With access to STR-26, as well as unnatural analogs, further biological studies are now possible.



Scheme 2. A. Synthetic route to STR-26 (**1**) and analog (**15**). **B.** Cell polarization was assessed in MDA-MB-231 cells by visual inspection ($N > 300$ for each condition). **C.** Viability of MDA-MB-231 cells. Curves from a representative experiment are shown.

Acknowledgements

We thank the Lundbeckfoundation, the Danish Research Foundation, and the Carlsberg Foundation for financial support. Jacob Overgaard is acknowledged for X-Ray analysis of **12a**. Access to the 950 MHz NMR spectrometer at the Danish Center for Ultrahigh-Field NMR Spectroscopy (Ministry of Higher Education and Science grant AU-2010-612-181) is acknowledged. The K. A. Jørgensen group is acknowledged for technical assistance. The Collins Pine Company of Chester, California is acknowledged for supplying Pinus Ponderosa bark.

Keywords: Quinones • Catalysis • Oxygen • Oxidative coupling • Natural Products

[1] N. Song, C. J. Gagliardi, R. A. Binstead, M.-T. Zhang, H. Thorp, T. Meyer, *J. Am. Chem. Soc.* **2012**, *134*, 18538-18541.

[2] W. Ma, Y.-T. Long, *Chem. Soc. Rev.* **2014**, *43*, 30-41.

[3] a) D. P. Walton, D. A. Dougherty, *J. Am. Chem. Soc,* **2017**, *139*, 4655-4658; b) M. N. Levine, R. T. Raines, *Chem. Sci.* **2012**, *3*, 2412-2420.

[4] For a review, see: a) A. E. Wendlandt, S. S. Stahl, *Angew. Chem. Int. Ed.* **2015**, *54*, 14638-14658; Recent examples: b) X. Chen, J.-J. Li, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 78-79; c) K. L.

Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, 129, 11904-11905; d) C. C. Pattillo, I. I. Strambeanu, P. Calleja, N. A. Vermeulen, T. Mizuno, M. C. White, *J. Am. Chem. Soc.* **2016**, *138*, 1265-1272; e) S. H. Hong, D. P. Sanders, C. W. Lee, R. H. Grubbs, *J. Am. Chem. Soc.* **2005**, *127*, 17160-17161.

[5] For a review, see: a) S. N. Sunassee, M. T. Davies-Coleman, *Nat. Prod. Rep.* **2012**, *29*, 513-535; recent examples: b) C. Xing, J. P. LaPorte, J. K. Barbay, A. G. Myers, *Proc. Natl. Acad. Sci. USA*, **2004**, *101*, 5862-5866; c) M. T. Hoyt, R. Palchaudhuri, P. J. Hergenrother, *Invest. New Drugs*, **2011**, *29*, 562-573.

[6] W. Yu, P. Hjerrild, J. Overgaard, T. B. Poulsen, *Angew. Chem. Int. Ed.* **2016**, *55*, 8294-8298.

[7] K. Warabi, L. M. McHardy, L. Matainaho, R. Van Soest, C. D. Roskelley, M. Roberge, R. J. Andersen, *J. Nat. Prod.* **2004**, *67*, 1387-1389.

[8] a) L. M. McHardy, K. Warabi, R. J. Andersen, C. D. Roskelley, M. Roberge, *Mol. Cancer Ther.* **2005**, *4*, 772-778; b) K. Warabi, B. O. Patrick, P. Austin, C. D. Roskelley, M. Roberge, R. J. Andersen, *J. Nat. Prod.* **2007**, *70*, 736-740.

[9] a) Z. Huang, J.-P. Lumb, *Angew. Chem. Int. Ed.* **2016**, *55*, 11543-11547; see also: b) K. V. N. Esguerra, Y. Fall, L. Petitjean, J.-P. Lumb, *J. Am. Chem. Soc.* **2014**, *136*, 7662-7668; c) Z. Hunag, M. S. Askari, K. N. Esguerra, T.-Y. Dai, O. Kwon, X. Ottenwaelder, J.-P. Lumb, *Chem. Sci.* **2016**, *7*, 358-369. For alkylation and arylation of quinones, see: d) D. Dixon, J. W. Lockner, Q. Zhou, P. S. Baran, *J. Am. Chem. Soc.* **2012**, *134*, 8432-8435; e) X.-L. Xu, Z. Li, *Angew. Chem. Int. Ed.* **2017**, *56,* 8196-8200; f) Á. Gutiérrez-Bonet, C. Remeur, J. K. Matsui, G. A. Molander, *J. Am. Chem. Soc.* **2017**, *139*, 12251-12258.

[10] a) G. A. Kraus, I. Kim, *J. Org. Chem.* **2003**, *68*, 4517-4518; b) M. Kidwai, P. Kumar, S. J. Kohli, *Chem. Res.* **1997**, 24-25; c) Z.-E. Yan, Y. Xiao, L. Zhang, *Angew. Chem. Int. Ed*. **2012**, *51*, 8624-8627; d) D. R. Milić, M. J. Gašić, W. Muster, J. J. Csanádi, B. A. Šolaja, *Tetrahedron* **1997**, *53*, 14073-14084; e) L. Garuti, M. Roberti, D. Pizzirani, A. Pession, E. Leoncini, V. Cenci, S. Hrelia, *Farmaco* **2004**, *59*, 663-668; f) T. Ling, E. Poupon, E. J. Rueden, S. H. Kim, E. A. Theodorakis, *J. Am. Chem. Soc.* **2002**, *124*, 12261-12267; For alkoxylations of 2-acyl quinones, see e.g.: g) F. Farina, J. Valderrama, *Synthesis*, **1971**, 315-316; h) P. Capdeville, M. Maumy, *Tetrahedron*, **2001**, *57*, 379-384.

[11] a) P. Jacob III, P. S. Callery, A. T. Shulgin, N. Castagnoli Jr., *J. Org. Chem.* **1976**, *41*, 3627-3629; b) S. I. Sadykh-Zade, A. V. Ragimov, S. S. Suleimanova, V. I. Liogon'kii, *Polym. Sci. (USSR) (Engl. Transl.),* **1972**, *14*, 1395-1403.

[12] Alkoxylation of mono-alkyl quinones under neutral conditions was observed previously: a) J. M. Singh, A. B. Turner, *J. Chem. Soc., Perkin Trans. 1* **1974**, 2556-2559. In these studies Zn(II) was also tested as a Lewis acid, with limited advantage over the uncatalyzed reaction. This is in accord with our observation that $Zn(OAc)_2$ is not able to facilitate methoxylation of **4**. For even earlier studies, see: b) Knoevenagel, E.; Bückel, C. *Chem. Ber.* **1901**, *34*, 3993-3998.

[13] Anhydrous and hydrate-forms of $Mn(OAc)_3$ and $Co(OAc)_2$ afforded similar outcomes.

[14] See e.g.: a) C. J. Cavallto, A. E. Soria, J. O. Hoppe, *J. Am. Chem. Soc.* **1950**, *72*, 2661-2665; b) A. H. Crosby, R. E. Lutz, *J. Am. Chem. Soc.* **1956**, *78*, 1233-1235; c) H. Zhang, L. Liu, Y. Chen, D. Wang, C. Li, *Adv. Synth. Catal.* **2006**, *348*, 229-235.

[15] CCDC 1548695 (**12a**) contains the supplementary crystallographic data. The data are provided free of charge by The Cambridge Crystallographic Data Centre.

[16] Thiophenol derivatives did not couple to **5b** under standard conditions.

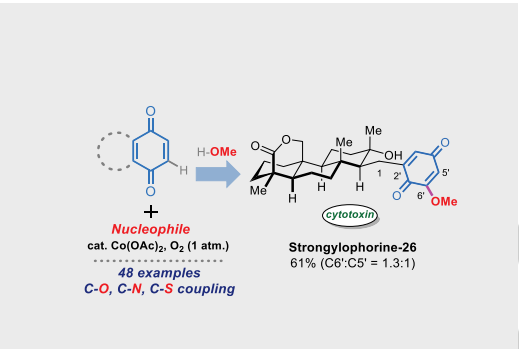
[17] K. D. Collins, F. Glorius, *Nat. Chem.* **2013**, *5*, 597-601.

10.1002/anie.201805580

WILEY-VCH

COMMUNICATION

Sine qua non: Heteroatom-functionalized *p*-quinones are important within the chemical sciences and recurring elements of bioactive natural products. A powerful catalytic method employing transition metal salts and molecular oxygen as terminal oxidant for direct coupling of *p*-quinones to O, N, S-nucleophiles is reported. The value of the method is demonstrated by the first preparation of the terpenoid strongylophorine-26.



*Wanwan Yu[+], Per Hjerrild[+], Kristian Mark Jacobsen, Henriette N. Tobiesen, Line Clemmensen, Thomas B. Poulsen**

Page No. – Page No.

A Catalytic Oxidative Quinone Heterofunctionalization Method – Synthesis of Strongylophorine-26