Masked Bisketenes as Diels–Alder Dienes

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ABSTRACT: 2,5-Bis(*tert*-butyldimethylsilyloxy)furans are established as masked vicinal bisketenes for application as dienes in the Diels–Alder reaction. Cycloaddition with olefinic dienophiles, under exceptionally mild conditions, enables convergent access to highly substituted *para*-hydroquinones in unprotected form via a one-pot Diels–Alder/ring-opening/tautomerization sequence. The synthesis of *para*-benzoquinones from acetylenic dienophiles, including benzynes, is also demonstrated, and 2,5-bis(*tert*-butyldimethylsilyloxy)pyrroles are established as competent dienes for the synthesis of *para*-iminoquinones. Application in natural product synthesis enables gram-scale access to the neuroprotective agent (±)-indanostatin.

The *para*-hydroquinone (*p*-HQ) motif is embedded within a diverse array of pharmaceuticals,[1] natural products,[2,3] synthetic reagents,[4] and ligand families[5] (**Figure 1a**). Traditional approaches towards the synthesis of highly substituted derivatives typically involve multi-step functionalization sequences, initiated from either an aromatic in a lower oxidation state, or a simple protected *p*-HQ (**Figure 1b**).[6] Selective redox state adjustment[7,8] or protecting group removal[9] can be challenging to achieve in these contexts, highlighting the need for more convergent, non-oxidative strategies that deliver *p*-HQs in unprotected form. Although a small number of such strategies have been developed, most notably the Hauser–Kraus reaction of annulated furanones,[10] and Moore rearrangement of γ-hydroxy-cyclobutenones,[11] the harsh conditions necessary for substrate preparation and/or cyclization limits generality (e.g. strong base, organolithium nucleophiles, high temperatures).

p-HQs can be retrosynthetically disconnected via a Diels–Alder (DA) transform through their bis-keto tautomer to reveal vicinal bisketenes as synthons (**Figure 1c**). The pronounced instability of this motif,[12] coupled with the propensity of ketenes to undergo [2+2] cycloadditions with olefins,[13] necessitates the development of a masked equivalent to realize the proposed strategy. We hypothesized that an appropriately 2,5-difunctionalized furan may enable direct access to *p*-HQs under redox-neutral conditions via a DA/ring-opening/tautomerization sequence.[14] The feasibility of such an approach was demonstrated by Chan and coworkers in 1980 though DA reactions of simple 2,5-bis(trimethylsilyloxy)furans, followed by NaF promoted aromatization.[15] The authors described 2,5-bis(trimethylsilyloxy)furans as "*very sensitive to moisture and air*", noting that the rate of autoxidation increased with additional substitution on the furan backbone.[16] Consequently it appears the challenges associated with substrate stability, combined with a proclivity for users to employ strong acids to promote cycloadduct unmasking,[17] have discouraged efforts to further develop this strategy.[18,19]

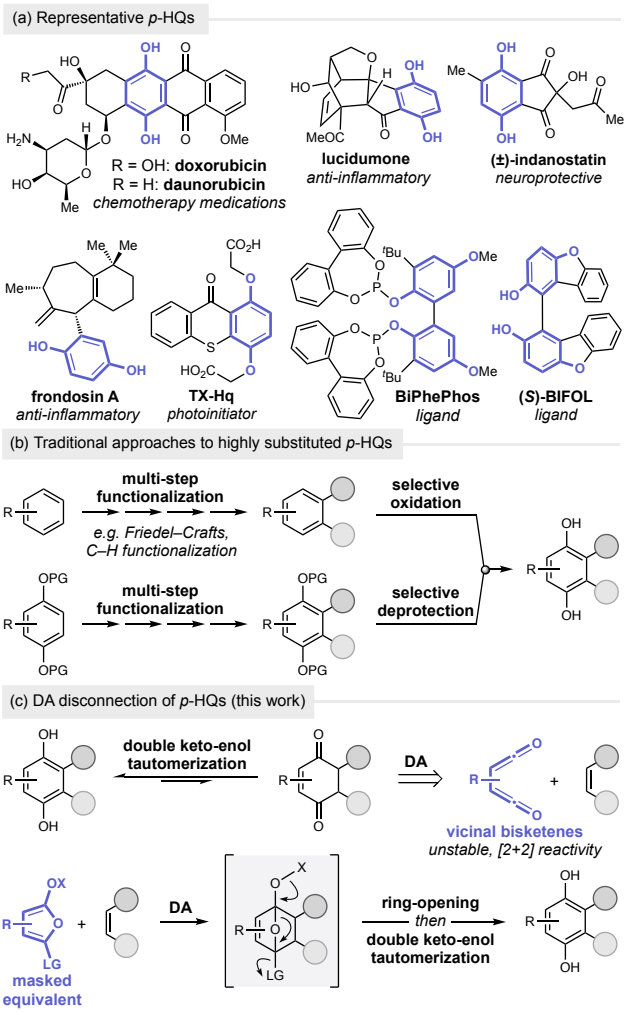


Figure 1. Motivation for reaction development. PG = protecting group, LG = leaving group.

In an attempt to address these limitations we initiated reaction development with a systematic stability study[20] of pertinent 2,5-difunctionalized furans (**Figure 2a**; see Supporting Information for additional details). In alignment with the findings of Chan, 2,5-bis(trimethylsilyloxy)furan (**1**) rapidly decomposed when employing standard handling techniques. Assessment of related candidates revealed diene stability scales with silyl group size (compare **1**–**3**), arriving at 2,5-bis(*tert*-butyldimethylsilyloxy)furan (**3**) as a robust and conveniently accessed candidate. Introduction of alternate leaving groups were also explored. Methoxy-derivative **4**, prepared in 3 steps from commercial materials, exhibited a comparable stability profile relative to **3**. Finally, introduction of bromine (**5**) proved beneficial, resulting in the most stable of all substrates prepared.

The DA reactivities of furans **1**–**5** were benchmarked in PhMe using *N*-methylmaleimide (NMM) as dienophile

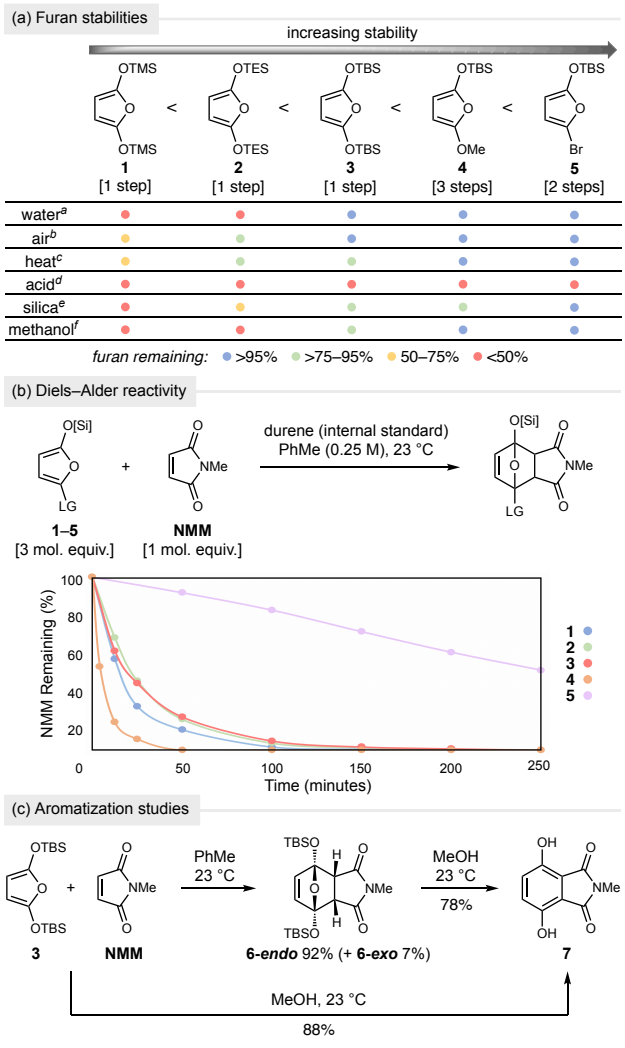


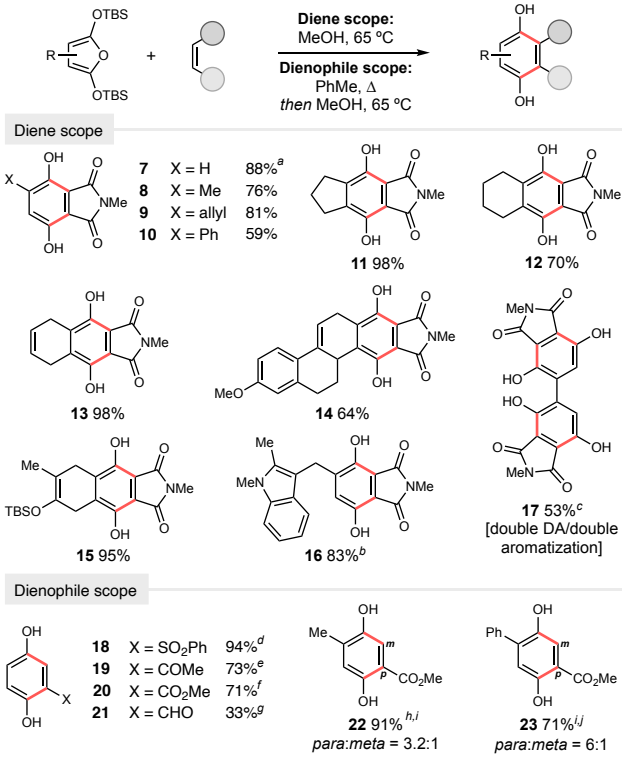
Figure 2. Development of a convenient vicinal bisketene equivalent. LG = leaving group. [a]0.025M $(CD_3)_2CO/D_2O$ mixture (9:1) stirred for 1 h. [b]Compressed air bubbled through a 0.025M $CDCl_3$ solution for 10 minutes. [c]Dilute C_6D_6 solution heated at 120 °C in a microwave reactor for 2 h. [d]0.10M TFA solution in $CDCl_3$ stirred for 1 minute. [e]1.0 mL of a 0.025M $CDCl_3$ solution stirred with untreated silica (250 mg) for 2 h. [f]0.20M $CDCl_3/CD_3OD$ mixture (1:4) stirred for 1 h.

(**Figure 2b**). Bis(silyloxy)furans **1**, **2** and **3** all reached completion within ~150 minutes, exhibiting only a small rate retardation with increased silyl group size. Methoxy-derivative **4** proved slightly more reactive, whereas bromide **5** performed the worst, with less than 50% conversion observed after 250 minutes. Overall, bis(*tert*-butyldimethylsilyloxy)furan (**3**) strikes the best balance between ease of synthesis, stability, and DA reactivity, and as such we elected to focus exclusively on its continued development.

Studies into the ring opening/tautomerization of DA adducts **6-*endo*** and **6-*exo*** revealed that simply stirring in MeOH promotes the desired aromatization event, avoiding the need for addition of an acid, or fluoride source (**Figure 2c**). Moreover, conducting the DA reaction in MeOH enabled the synthesis of *p*-HQ **7** in 88% isolated yield, directly from furan **3**, via a one-pot DA/ring-opening/tautomerization cascade.

Having identified a suitable masked vicinal bisketene motif we investigated the scope of *p*-HQ formation (**Table 1**). With respect to diene structure the reaction appears general, and a library of furans (prepared directly from the corresponding cyclic anhydrides, see Supporting Information) were readily converted into *p*-HQs upon reaction with NMM in MeOH at 65 °C. In the case of mono-functionalized derivatives, methyl (**8**), allyl (**9**), and phenyl (**10**) functionality was well tolerated. More highly substituted 5 and 6-membered fused bicyclic furans also reacted smoothly (**11**–**15**), including steroid-inspired pentacyclic derivative **14**. The chemoselectivity of desilylation was highlighted through preparation of silyl enol

Table 1. Scope of *p*-HQ formation



[a]DA at 23 °C. [b]Aromatization achieved by addition of TFA at 23 °C. [c]DA in PhMe at 23 °C, aromatization achieved by addition of H_2SO_4 at 23 °C. [d]80 °C. [e]60 °C. [f]111 °C. [g]50 °C. [h]DA neat at 23 °C. [i]Combined yield of isomers. [j]DA neat at 55 °C.

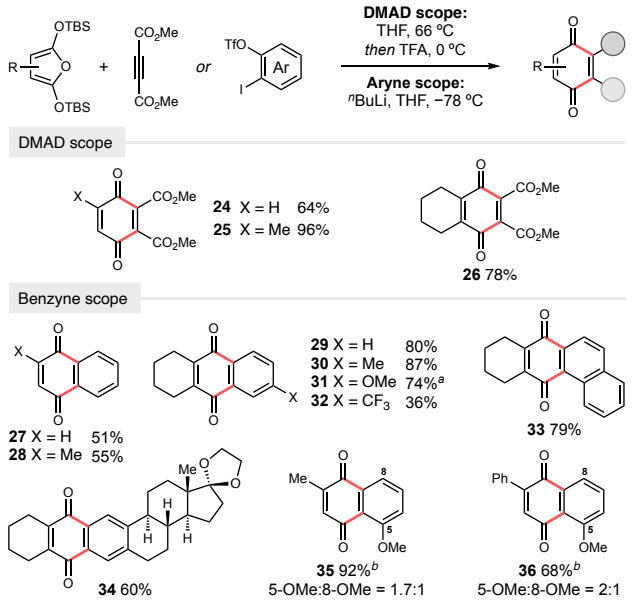
ether **15** in 95% yield, and notably, no evidence for olefin migration was observed for all substrates screened. With more sterically demanding silylated intermediates, such as for indole **16** and biaryl **17**, the rate of MeOH promoted aromatization drops significantly. In these cases *p*-HQ formation can be expedited through addition of an acid additive. Extension to a one-pot double DA/double aromatization strategy provided the BiPhePhos ligand scaffold[5a] in 53% yield (**17**), creating opportunities for a highly convergent approach to a library of ligand derivatives. With less reactive dienophiles the DA reaction is best conducted in an aprotic solvent (or neat) followed by addition of MeOH. Under these conditions, sulfone (**18**), ketone (**19**), ester (**20**) and aldehyde (**21**) activating groups were all tolerated. Finally, orientational selectivity of the cycloaddition event was demonstrated through coupling of unsymmetrical mono-functionalized dienes with methyl acrylate (**22** and **23**, up to 6:1 in favor of the expected *para*-isomer).

Exploratory studies from Chan and coworkers toward the synthesis of *para*-benzoquinones (*p*-BQ) from 2,5-bis(trimethylsilyloxy)furans were hampered by competitive *p*-HQ formation.[15] Optimistic that the 2,5-bis(*tert*-butyldimethylsilyloxy)furan motif may be more well suited to *p*-BQ formation we probed reactivity with acetylenic dienophiles (**Table 2**). Indeed, cycloaddition of several representative derivatives with dimethyl acetylenedicarboxylate (DMAD), followed by addition of TFA, provided *p*-BQs **24**–**26** in good to excellent yields (without any evidence for *p*-HQ formation). Encouraged by these results we evaluated benzynes as coupling partners. *ortho*-Iodotriflates were identified as suitable precursors, enabling low temperature benzyne generation in the presence of our furans. In contrast to the DMAD-derived cycloadducts, TFA addition is unnecessary, and intermediate unmasking can be achieved via a simple acidic workup. A brief diene screen revealed that increased steric bulk on the furan backbone resulted in improved yields (**27**–**29**). With respect to benzyne substitution, electron rich substrates react exceptionally well (**30** and **31**), however a significant reduction in yield was observed with incorporation of trifluoromethyl functionality (**32**). 1-Naphthyne is also a competent dienophile (**33**), as too are more complex steroid-derived benzynes (**34**). Although orientational selectivity[21] of the cycloaddition is not especially high in the case of **35** and **36** (up to 2:1), isomer separation can be achieved via standard flash chromatography, allowing ready access to the methoxy-naphthalene-1,4-dione fragment present in both doxo- and daunorubicin.[1]

The generality of our approach is highlighted through extension to 2,5-bis(*tert*-butyldimethylsilyloxy)pyrroles as synthetic equivalents of vicinal ketenimine-ketenes (**Figure 3a**). While these pyrrole derivatives are less stable than their corresponding furan congeners (see Supporting Information), they exhibit comparable reactivity with arynes.[22] Thus, reaction of aryl- and alkylated pyrroles **37** and **38** with benzyne provided *para*-iminoquinones (*p*-IQs) **39** and **40**, both in 61% yield. Notably, *p*-IQs feature within natural products,[23] and derivatives have been demonstrated as versatile intermediates for the synthesis of complex alkaloids,[24] and BINOL derivatives.[25] Moreover, they serve as convenient precursors to the biologically relevant *para*-aminophenol motif (e.g. paracetamol)[26] via sodium dithionite promoted reduction (**41** and **42**). Further experiments demonstrated regioselective ring opening of unsymmetrical cycloadducts can be achieved (**Figure 3b**). In this example, a two-step reductive coupling of pyrrole **37** with 1-naphthyne (generated from *ortho*-iodotriflate **43**) provided phenanthrene **44** in 75% yield.

We became interested in the development of a cross-conjugated extension to further expand the synthetic potential of our methodology (**Figure 4a**).[27] In principle the simplest candidate, vinylfuran **45**, would enable a diene-transmissive double DA sequence, which if conducted with two different dienophiles leads to even more highly functionalized aromatics. The success of such a strategy is reliant upon both the inherent diene site-selectivity of **45** (cyclic versus semi-cyclic), as well as the relative rates of the first and second cycloadditions, both of which are difficult to infer from the

Table 2. Scope of *p*-BQ formation



[a]Determined by ^{1}H NMR. [b]Combined yield of isomers.

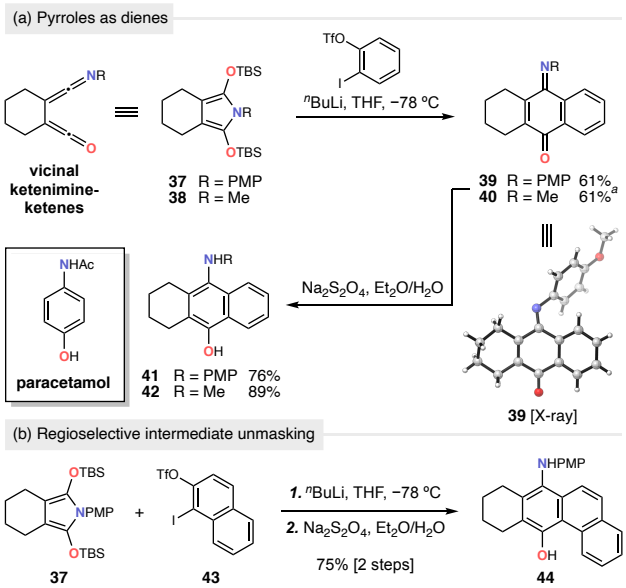


Figure 3. Bis(*tert*-butyldimethylsilyloxy)pyrroles as masked vicinal ketenimine-ketenes. PMP = *para*-methoxyphenyl. [a]Determined by ^{1}H NMR.

diverging reactivity reported for related cross-conjugated furans.[28] Fortuitously, NMM reacted with complete selectivity for the (desired) cyclic diene site of **45**.[29] Moreover, the second DA reaction is markedly slower than the first, allowing not only a change in dienophile, but bifurcation of reactivity: addition of MeOH promoted aromatization to generate vinyl-substituted *p*-HQ **46**, whereas addition of 4-phenyl-1,2,4-triazole-3,5-dione (PTAD) enabled a hetero-Diels–Alder reaction. Although subsequent deprotection and aromatization can be achieved in excellent yield via in situ addition of TFA, in this particular case purification is simplified by a stepwise approach, yielding tetracyclic *p*-HQ **47** in 80% yield over two-steps from **45**.

Finally, to demonstrate scalability of *p*-HQ formation, as well as the applicability of our methodology in natural product synthesis, we pursued the total synthesis of the neuroprotective agent (±)-indanostatin[3b] (**Figure 4b**). The marked base sensitivity of our envisioned dienophile, 1,3-cyclopentenedione (**49**), has precluded its application as a coupling partner in conceptually related anionic (formal) DA strategies towards *p*-HQs.[30] Pleasingly, methylfuran **48** (synthesized in one step from methylsuccinic anhydride) reacted smoothly with **49** in MeOH at room temperature, providing gram-scale quantities of *p*-HQ **50** in 93% yield, and without the need for chromatographic purification. A subsequent one-pot oxidation/alkylation procedure (via the intermediate trione hydrate) yielded over one gram of (±)-indanostatin in only three steps total (cf. 9 steps for the previous total synthesis[30]).

In conclusion, we have established the 2,5-bis(*tert*-butyldimethylsilyloxy)furan motif as a general vicinal bisketene equivalent for application as a diene in the DA reaction. A mild, user-friendly protocol provides access to a variety of highly substituted *p*-HQs by reaction with olefinic dienophiles. In turn, employing acetylenic dienophiles provides efficient access to *p*-BQs, or *p*-IQs when 2,5-bis(*tert*-butyldimethylsilyloxy)pyrroles are utilized as dienes. While one can imagine employing more robust silyloxy substituents in attempts to further tweak furan stability, and indeed we anticipate in some cases this may provide improved results, generally speaking it appears the *tert*-butyldimethylsilyl functionality strikes an excellent balance between diene stabilization and ease of intermediate unmasking. In essence, the methodology disclosed herein represents a transform-based strategy[31] in which two C–C bonds of several *para*-quinone ring systems are made simultaneously via a cycloaddition event. This approach avoids the need for lengthy sequences of redox manipulations and/or functional group interconversions, both of which are commonplace in more classical structure-goal strategies.[31] As such, we believe the methodology developed herein has the potential to permit more step-economic syntheses of *para*-quinones, and a proof-of-principle application has been demonstrated through a gram-scale three-step total synthesis of (±)-indanostatin.

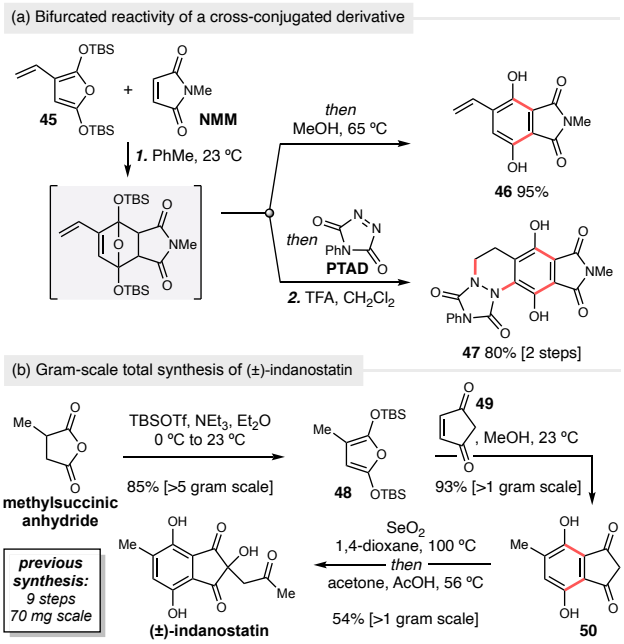


Figure 4. (a) Extension to a cross-conjugated derivative, and (b) application of *p*-HQ formation in natural product synthesis.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Minotti, G.; Menna, P.; Salvatorelli, E.; Cairo, G.; Gianni, L., Anthracyclines: Molecular Advances and Pharmacologic Developments in Antitumor Activity and Cardiotoxicity. *Pharmacol. Rev.* **2004**, *56*, 185.

(2) (a) Select reviews: Marcos, I. S.; Conde, A.; Moro, R. F.; Basabe, P.; Diez, D.; Urones, J. G., Quinone/Hydroquinone Sesquiterpenes. *Mini-Rev. Org. Chem.* **2010**, *7*, 230. (b) Sunassee, S. N.; Davies-Coleman, M. T., Cytotoxic and antioxidant marine prenylated quinones and hydroquinones. *Nat. Prod. Rep.* **2012**, *29*, 1480.

(3) (a) Representative examples: Yan, Y.-M.; Zhang, H.-X.; Liu, H.; Wang, Y.; Wu, J.-B.; Li, Y.-P.; Cheng, Y.-X., (+/−)-Lucidumone, a COX-2 Inhibitory Caged Fungal Meroterpenoid from *Ganoderma Lucidum*. *Org. Lett.* **2019**, *21*, 8523. (b) Hayakawa, Y.; Kobayashi, T.; Izawa, M., Indanostatin, a New Neuroprotective Compound from *Streptomyces* sp. *J. Antibiot.* **2013**, *66*, 731. (c) Patil,

A. D.; Freyer, A. J.; Killmer, L.; Offen, P.; Carte, B.; Jurewicz, A. J.; Johnson, R. K., Frondosins, Five New Sesquiterpene Hydroquinone Derivatives with Novel Skeletons from the Sponge *Dysidea Frondosa*: Inhibitors of Interleukin-8 Receptors. *Tetrahedron* **1997**, *53*, 5047.

(4) Karasu, F.; Arsu, N.; Jockusch, S.; Turro, N. J., Thioxanthone Hydroquinone-*O*,*O*′-diacetic Acid: Photoinitiator or Photostabilizer? *J. Org. Chem.* **2013**, *78*, 9161.

(5) (a) Billig, E.; Abatjoglou, A. G.; Bryant, D. R. Homogeneous Rhodium Carbonyl Compound-Phosphite Ligand Catalysts and Process for Olefin Hydroformylation. U.S. Patent 4,769,498, Sep. 6, 1988. (b) Sollewijn Gelpke, A. E.; Fraanje, J.; Goubitz, K.; Schenk, H.; Hiemstra, H., Resolution and Some Properties of (1,1′)-Bi(dibenzofuranyl)-2,2′-diol (BIFOL). *Tetrahedron* **1997**, *53*, 5899.

(6) (a) Select reviews: Akai, S.; Kita, Y., Recent Progress in the Synthesis of *p*-Quinones and *p*-Dihydroquinones Through Oxidation of Phenol Derivatives. A Review. *Org. Prep. Proced. Int.* **1998**, *30*, 603. (b) Weaver, M. G.; Pettus, T. R. R., Synthesis of *para*- and *ortho*-Quinones. In *Comprehensive Organic Synthesis II*, Second ed.; Knochel, P., Ed. Elsevier: 2014; Vol. 7, pp 373.

(7) (a) Behrman, E. J., The Persulfate Oxidation of Phenols and Arylamines (The Elbs and the Boyland–Sims Oxidations). In *Organic Reactions*, 1988; pp 421. (b) Behrman, E. J., The Elbs and Boyland-Sims peroxydisulfate oxidations. *Beilstein J. Org. Chem.* **2006**, *2*, doi: 10.1186/1860.

(8) (a) Representative examples: Evans, J. C.; Klix, R. C.; Bach, R. D., Diels-Alder Approaches to Model Compounds Related to Fredericamycin A. *J. Org. Chem.* **1988**, *53*, 5519. (b) Lindsey, C. C.; Wu, K. L.; Pettus, T. R. R., Synthesis of Electron Deficient 5,6-Aryloxy Spiroketals. *Org. Lett.* **2006**, *8*, 2365. (c) Wu, A.-H.; Hau, C.-K.; Wong, H. N. C., Synthesis of Enantiopure (*S*,*R*,*S*)- and (*R*,*S*,*R*)-1,4,5,8,9,16-Hexahydroxytetraphenylenes. *Adv. Synth. Catal.* **2007**, *349*, 601. (d) Gurung, S. K.; Kim, H. P.; Park, H., Inhibition of Prostaglandin E_2 Production by Synthetic Wogonin Analogs. *Arch. Pharmacal Res.* **2009**, *32*, 1503.

(9) (a) Representative examples: Gerencsér, J.; Keserü, G. M.; Macsári, I.; Nógrádi, M.; Kajtár-Peredy, M.; Szöllösy, Á., Synthesis of Isoplagiochin A. *J. Org. Chem.* **1997**, *62*, 3666. (b) Noda, Y.; Yasuda, M., Enantioselective Synthesis of (−)-(*R*)-Cordiachromene and (−)-(*R*)-Dictyochromenol Utilizing Intramolecular S_NAr Reaction. *Helv. Chim. Acta* **2012**, *95*, 1946. (c) Trost, B. M.; Hu, Y.; Horne, D. B., Total Synthesis of (+)-Frondosin A. Application of the Ru-Catalyzed [5+2] Cycloaddition. *J. Am. Chem. Soc.* **2007**, *129*, 11781.

(10) (a) Hauser, F. M.; Rhee, R. P., New Synthetic Methods for the Regioselective Annelation of Aromatic Rings: 1-Hydroxy-2,3-Disubstituted Naphthalenes and 1,4-Dihydroxy-2,3-Disubstituted Naphthalenes. *J. Org. Chem.* **1978**, *43*, 178. (b) Kraus, G. A.; Sugimoto, H., An annelation route to quionones. *Tetrahedron Lett.* **1978**, *19*, 2263. (c) Mal, D.; Pahari, P., Recent Advances in the Hauser Annulation. *Chem. Rev.* **2007**, *107*, 1892.

(11) (a) Karlsson, J. O.; Nghi, V. N.; Foland, L. D.; Moore, H. W., (2-Alkynylethenyl)ketenes: A New Benzoquinone Synthesis. *J. Am. Chem. Soc.* **1985**, *107*, 3392. (b) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W., Synthesis of Benzoquinones and Annulated Derivatives from Conjugated Ketenes. *J. Org. Chem.* **1986**, *51*, 3067. (c) Moore, H. W.; Decker, O. H. W., Conjugated Ketenes: New Aspects of Their Synthesis and Selected Utility for the Synthesis of Phenols, Hydroquinones, and Quinones. *Chem. Rev.* **1986**, *86*, 821. (d) Nguyen, T. V., Convenient Access to Hydroquinone and Quinone Derivatives from Cyclobutenedione Units. *Aust. J. Chem.* **2010**, *63*, 1309.

(12) (a) Allen, A. D.; Ma, J.; McAllister, M. A.; Tidwell, T. T.; Zhao, D.-C., New Tricks from an Old Dog: Bisketenes after 90 Years. *Acc. Chem. Res* **1995**, *28*, 265. (b) Tidwell, T. T., Ketene Chemistry after 100 Years: Ready for a New Century. *Eur. J. Org. Chem.* **2006**, 563.

(13) (a) Hyatt, J. A.; Raynolds, P. W., Ketene Cycloadditions. In *Organic Reactions*, Paquette, L. A., Ed. John Wiley and Sons, Inc.: New York: 1994; Vol. 45, pp 159. (b) Mackay, E. G.; Newton, C. G., Masked Ketenes as Dienophiles in the Diels–Alder Reaction. *Aust. J. Chem.* **2016**, *69*, 1365.

(14) Review on the DA chemistry of substituted furans: Bur, S.; Padwa, A., [4+2] Cycloaddition Chemistry of Substituted Furans. In *Methods and Applications of Cycloaddition Reactions in Organic Syntheses*, Nishiwaki, N., Ed. John Wiley & Sons, Inc: 2014; pp 355.

(15) Brownbridge, P.; Chan, T. H., Chemistry of 2,5-Bis(trimethylsiloxy) Furans. I: Preparation and Diels-Alder Reactions. *Tetrahedron Lett.* **1980**, *21*, 3423.

(16) Chan reports that in the presence of water, 2,5-bis(trimethylsilyloxy)furans hydrolyze to the corresponding succinic acid, and in the presence of oxygen they form the corresponding bis(trimethylsilyl) maleate.

(17) Le Vézouët, R.; White, A. J. P.; Burrows, J. N.; Barrett, A. G. M., Synthetic studies on the CDEF ring system of lactonamycin. *Tetrahedron* **2006**, *62*, 12252.

(18) (a) Simple derivatives of 2,5-bis(trimethylsilyloxy)furans have been applied in a handful of DA reactions. For a comprehensive list, see: Troll, T.; Schmid, K., Darstellung und reaktionen von 1,3-bis-(trimethylsiloxy)-isobenzofuranen. *Tetrahedron Lett.* **1984**, *25*, 2981. (b) Seitz, G.; van Gemmern, R., [4 + 2] Cycloaddition of trimethylsilyloxy-substituted furans with tetrachlorocyclopropenes, a new preparation of cycloheptadienediones. *Chem. Ztg.* **1987**, *111*, 209. (c) Taguchi, T.; Hosoda, A.; Tomizawa, G.; Kawara, A.; Masuo, T.; Suda, Y.; Nakajima, M.; Kobayashi, Y., The Diels-Alder Reaction of 1-Phenylsulfonyl-3,3,3-trifluoropropene. *Chemical & Pharmaceutical Bulletin* **1987**, *35*, 909. (d) Samoilova, R. I.; van Liemt, W.; Steggerda, W. F.; Lugtenburg, J.; Hoff, A. J.; Spoyalov, A. P.; Tyryshkin, A. M.; Gritzan, N. P.; Tsvetkov, Y. D., ENDOR and EPR Studies of Highly Isotopically ^{13}C-Enriched Ubiquinone Radicals *J. Chem. Soc., Perkin Trans. 2* **1994**, 609. (e) Boullais, C.; Breton, J.; Nabedryk, E.; Mioskowski, C., Synthesis of Ubiquinones-3 Specifically Labelled with ^{13}C at C(5)- or C(6)- Positions. *Tetrahedron* **1997**, *53*, 2505. (f) Falcou, A.; Boullais, C., Synthesis of [2,3-$^{13}C_2$-2,5-cyclohexadienyl] Ubiquinone 3. *J. Label. Compd. Radiopharm.* **1998**, *41*, 657. (g) van Liemt, W. B. S.; Steggerda, W. F.; Esmeijer, R.; Lugtenburg, J., Synthesis and Spectroscopic Characterisation of ^{13}C-Labelled Ubiquinone-0 and Ubiquinone-10 *Recl. Trav. Chim. Pays-Bas* **2010**, *113*, 153.

(19) (a) For a comprehensive list of 2,5-bis(trimethylsilyloxy)furans being applied in non-DA settings, see: Brownbridge, P.; Chan, T.-H., Chemistry of 2,5-Bis(trimethylsiloxy)furans. II: Reactions with Carbonyl Compounds and the Synthesis of 2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octane-4,8-diones. *Tetrahedron Lett.* **1980**, *21*, 3427. (b) Brownbridge, P.; Chan, T.-H., Chemistry of 2,5-Bis(trimethylsiloxy)furans. III: Synthesis of γ-Hydroxybutenolides. *Tetrahedron Lett.* **1980**, *21*, 3431. (c) Frick, U.; Simchen, G., Reaktionen der Trialkylsilyl-trifluormethansulfonate, VIII. Synthese von *O*-(Trimethylsilyl)keten-O,N-acetalen, 2,5-Bis(trimethylsiloxy)pyrrolen, -furanen und -thiophenen. *Liebigs Ann.* **1987**, *1987*, 839. (d) Kates, M. J.; Schauble, J. H., Facile Conversion of Succinic to Maleic-Type Anhydrides, Thioanhydrides, and Imides. *J. Org. Chem.* **1995**, *60*, 6676. (e) Pohmakotr, M.; Yotapan, N.; Tuchinda, P.; Kuhakarn, C.; Reutrakul, V., Highly Diastereoselective Synthesis of β-Carboxy-γ-lactams and Their Ethyl Esters via $Sc(OTf)_3$-Catalyzed Imino Mukaiyama-Aldol Type Reaction of 2,5-Bis(trimethylsilyloxy)furan with Imines. *J. Org. Chem.* **2007**, *72*, 5016. (f) Laws, S. W.; Howard, S. Y.; Mato, R.; Meng, S.; Fettinger, J. C.; Shaw, J. T., Organocatalytic Mukaiyama Mannich Reactions of 2,5-Bis(trimethylsilyloxy)furan. *Org. Lett.* **2019**, *21*, 5073.

(20) Stability studies adapted from those originally disclosed by Sherburn and coworkers: Horvath, K. L.; Magann, N. L.; Sowden, M. J.; Gardiner, M. G.; Sherburn, M. S., Unlocking Acyclic π-Bond Rich Structure Space with Tetraethynylethylene–Tetravinylethylene Hybrids. *J. Am. Chem. Soc.* **2019**, *141*, 19746.

(21) For a leading reference on the regio- and orientational selectivity of arynes, see: Medina, J. M.; Mackey, J. L.; Garg, N. K.; Houk, K. N., The Role of Aryne Distortions, Steric Effects, and Charges in Regioselectivities of Aryne Reactions. *J. Am. Chem. Soc.* **2014**, *136*, 15798.

(22) Attempts to employ olefinic dienophiles have so far been unsuccessful.

(23) (a) Sun, H. H.; Sakemi, S.; Burres, N.; McCarthy, P., Isobatzellines A, B, C, and D. Cytotoxic and antifungal pyrroloquinoline alkaloids from the marine sponge *Batzella* sp. *J. Org. Chem.* **1990**, *55*, 4964. (b) Chang, L. C.; Otero-Quintero, S.; Hooper, J. N. A.; Bewley, C. A., Batzelline D and Isobatzelline E from the Indopacific Sponge *Zyzzya fuliginosa*. *J. Nat. Prod.* **2002**, *65*, 776.

(24) (a) Chuang, K. V.; Navarroa, R.; Reisman, S. E., Benzoquinone-derived sulfinylimines as versatile intermediates for alkaloid synthesis: Total synthesis of (–)-3-demethoxyerythratidinone. *Chem. Sci.* **2011**, *2*, 1086. (b) Chuang, K. V.; Navarro, R.; Reisman, S. E., Short, Enantioselective Total Syntheses of (−)-8-Demethoxyrunanine and (−)-Cepharatines A, C, and D. *Angew. Chem. Int. Ed.* **2011**, *50*, 9447.

(25) Wang, J.-Z.; Zhou, J.; Xu, C.; Sun, H.; Kürti, L.; Xu, Q.-L., Symmetry in Cascade Chirality-Transfer Processes: A Catalytic Atroposelective Direct Arylation Approach to BINOL Derivatives. *J. Am. Chem. Soc.* **2016**, *138*, 5202.

(26) Bessems, J. G. M.; Vermeulen, N. P. E., Paracetamol (Acetaminophen)-Induced Toxicity: Molecular and Biochemical Mechanisms, Analogues and Protective Approaches. *Crit. Rev. Toxicol.* **2001**, *31*, 55.

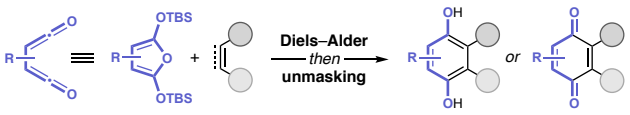
(27) (a) Hopf, H.; Sherburn, M. S., Dendralenes Branch Out: Cross-Conjugated Oligoenes Allow the Rapid Generation of Molecular Complexity. *Angew. Chem. Int. Ed.* **2012**, *51*, 2298. (b) Newton, C. G.; Sherburn, M. S., Cross-Conjugation in Synthesis. In *Cross Conjugation: Modern Dendralene, Radialene and Fulvene Chemistry*, Hopf, H.; Sherburn, M. S., Eds. Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim: 2016; pp 413.

(28) (a) Mcnamara, J. M.; Kishi, Y., Practical asymmetric synthesis of aklavinone. *Tetrahedron* **1984**, *40*, 4685. (b) Eberbach, W.; Fritz, H.; Laber, N., A Simple Route to Furo[3,4-*b*]furans, Compounds with a New Diheteropentalene System. *Angew. Chem. Int. Ed.* **1988**, *27*, 568. (c) Fallon, T.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S., Furanodendralenes. *J. Org. Chem.* **2014**, *79*, 3185.

(29) Presumably the vinyl group of **45** prefers to adopt an unreactive *s-trans* conformation (as drawn), as a result of the bulky proximal *tert*-butyldimethylsilyl substituent.

(30) Wang, S.; Kraus, G., Annulations of 5-Phenylthiobutenolides and First Synthesis of (±)-Indanostatin. *Synlett* **2019**, *30*, 353.

(31) Corey, E. J.; Cheng, X.-M., *The Logic of Chemical Synthesis*. Wiley: 1995.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