Leveraging the persistent radical effect in the synthesis of *trans*-2,3-diaryl-dihydrobenzofurans

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Abstract: A simple method for accessing *trans*-2,3-diaryl-dihydrobenzofurans is reported. This approach leverages a persistent radical equilibrium between quinone methide dimers and the persistent phenoxyl radicals derived therefrom. This equilibrium is disrupted by phenols that yield transient phenoxyl radicals, leading to cross-coupling between persistent and transient radicals. The resultant quinone methides with pendant phenols rapidly cyclize to dihydrobenzofurans (DHBs). This putatively biomimetic access to dihydrobenzofurans provides superb functional group tolerance and a unified approach for the synthesis of resveratrol-based natural products.

Introduction

Resveratrol (**1**) and its oligomers, a class of stilbenoid natural products, are secondary metabolites found across multiple plant families.[1,2] This class of natural products has received heightened interest over the last 30 years in large part due to their wide range of biological properties, most notably their antioxidant activity.[1,3] Their diverse structures often include a dihydrobenzofuran (DHB) moiety, as depicted in Figure 1A. Efforts from numerous research groups have sought to develop biomimetic and *de novo* synthetic strategies towards these natural products.[3] Our longstanding goal has been to develop means to access sufficient material for rigorous characterization of the biological properties of these natural products.

The biosynthesis of resveratrol oligomers is believed to occur oxidatively, proceeding through phenoxyl radical intermediates (**1a-c**) utilizing dirigent proteins to achieve the observed regio- and stereoselectivity (Figure 1).[2] We previously reported an electrochemical dimerization of hydroxy-stilbenes for the synthesis of C8-C8' resveratrol dimers (**5**) and, through the manipulation of blocking groups, C3-C8' dimers (**6**, Figure 1B).[4] These dimers exist in equilibrium with their corresponding persistent phenoxyl radical, which can be leveraged in the synthesis of higher order resveratrol oligomers.[5] Recently, we reported a thermal isomerization of the symmetric C8-C8' quinone methide dimer (QMD) to the C3-C8' isomer, resulting in the first total synthesis of resveratrol tetramers vitisin A and vitisin D.[6] This result is in alignment with initial evaluations done by Langcake and Pryce on conditions for the biomimetic oxidative dimerization of unprotected resveratrol.[7] In their study, they isolated the C3-C8' coupling product δ-viniferin as the major product. This suggests that the natural connectivity of the

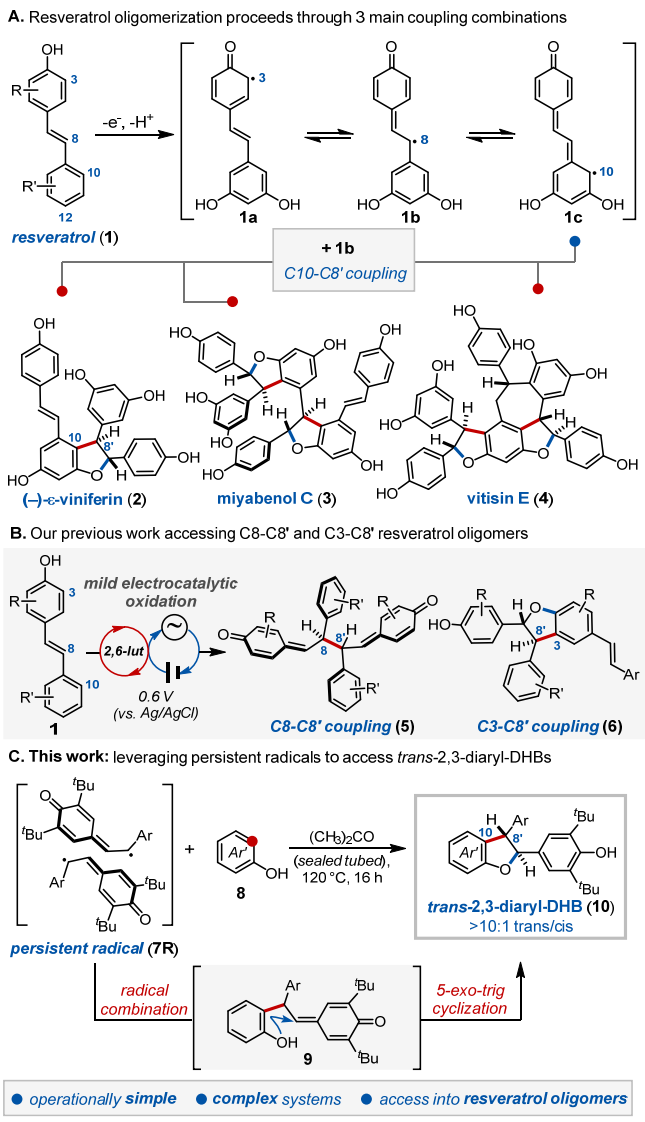

Figure 1. Inspiration for DHB formation.

single electron oxidation of resveratrol is δ-viniferin, despite that the C3-C8' connection is not broadly observed across the natural product class, instead being limited to δ-viniferin and the vitisin tetramers.[3] With a library of molecules accessed using these two strategies in hand, we conducted a number of investigations into the radical-trapping antioxidant (RTA) properties of C8-C8' and C3-C8' resveratrol natural products and QMDs, finding that QMDs[4,8] and *tert*-butylated resveratrol monomers and dimers[9] performed significantly better than their non-alkylated counterparts. However, while significant progress has been made in accessing C8-C8'[9,10] and C3-C8'[11] resveratrol oligomers, broadly useful routes towards accessing the 2,3-diaryl-DHBs that map onto the C10-C8' connection of resveratrol oligomers remain underdeveloped.[12] The C10-C8' connection exhibited in ε-viniferin (**2**) is found in the majority of higher order resveratrol oligomers such as miyabenol C (**3**) and vitisin E (**4**, Figure 1A).[3] The 2,3-diaryl-DHB motif also represents a privileged scaffold present in a variety of biologically active molecules with reported activity against multiple pathologies, including cancer, HIV, and tuberculosis.[13] For these reasons, a robust and concise method for accessing 2,3-diaryl-DHBs is desired to access not only higher order resveratrol oligomers, but also DHB scaffolds, in general.

Several reports have demonstrated innovative approaches to access 2,3-diaryl-DHBs, including transition metal-mediated C-H activation[14] and carbene-mediated C-H activation strategies[15], which have then been applied in the total synthesis of numerous natural products.[16] The homologation sequence of *ortho*-bromo phenols developed by Snyder and co-workers[17] remains a robust strategy that has resulted in the synthesis of a multitude of higher order resveratrol oligomers, including our own efforts in this area.[5,18] While the Snyder group has provided a clear blueprint for the *de novo* syntheses of these higher order natural products, we sought to develop a complimentary biomimetic synthetic strategy that relies on the QMDs highlighted above. Herein, we report on our efforts to leverage the persistent radical equilibrium between persistent phenoxyl radicals (**7R**) and their corresponding QMDs to access various *trans*-2,3-diaryl-DHBs (**10**) (Figure 1C). This allows an atom economical approach in which a single transformation can form the privileged DHB motif.

Results and Discussion

Based on our previous findings,[6] we hypothesized that the equilibrium between QMDs and their corresponding persistent phenoxyl radicals could be intercepted to form C10-C8' DHBs. Thus

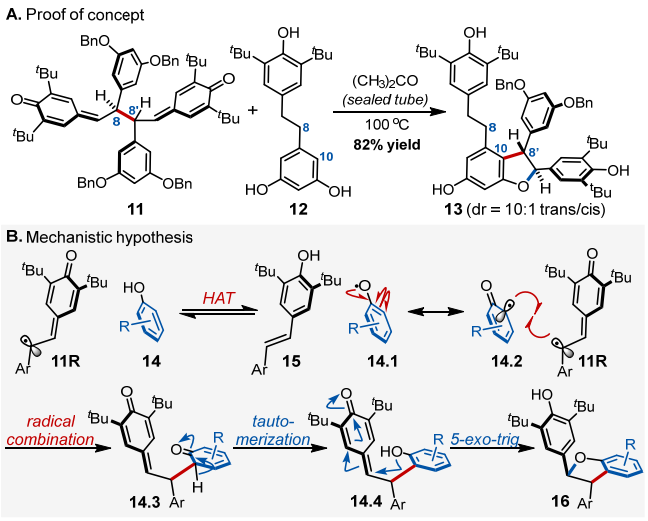

Figure 2. Proof of concept and mechanistic proposal for DHB formation

one equivalent of the persistent radical **7R** was anticipated to undergo H-atom exchange with an added phenol (**8**) to form a transient phenoxyl radical that could combine with the second equivalent of **7R** to form the C10-C8' bond in intermediate **9** (Figure 1C). Following tautormerization, 5-*exo*-trig cyclization of the phenol onto the quinone methide would forge the *trans*-diaryl-DHB (**10**) in a single transformation.

To evaluate this hypothesis, a reaction mixture containing QMD **11** and 2 equivalents of ^{t}Bu-dihydro-resveratrol (**12**) was heated in acetone in a pressure tube at 100 °C (Figure 2A). After 24 hours, complete consumption of **11** was observed, and following chromatographic purification, ^{t}Bu-dihydro-ε-viniferin (**13**) was isolated in 82% yield as a 10:1 mixture of diastereomers, favoring the *trans* configuration. In addition, the reaction yielded nearly a full equivalent of ^{t}Bu$_2$-OBn$_2$-resveratrol (from thermalized QMD).

Support for the mechanistic hypothesis was obtained using density functional theory calculations carried out at the M062X/cc-pVTZ level of theory (Figure 3).[19] Following the homolysis of **11** characterized in our earlier work,[5] one equivalent of phenoxyl radical (**11R**) can abstract a hydrogen from the phenol (**17**) in a endergonic reaction, resulting in the lesser stabilized and less

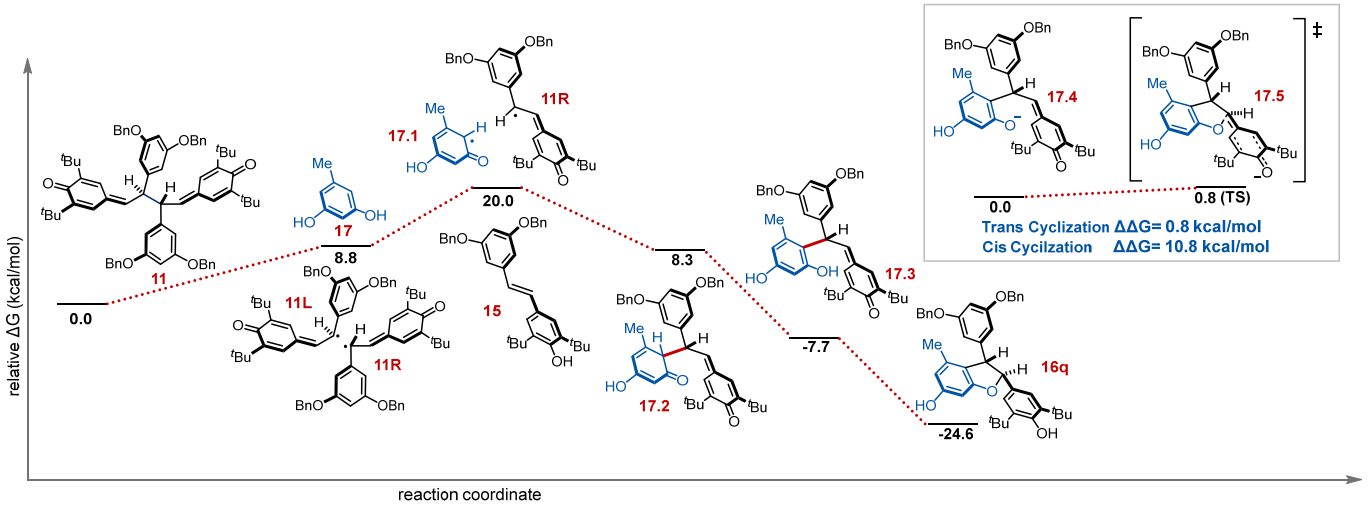

Figure 3. Calculated reaction coordinates for the DHB forming reaction. This highlights the large free energy driving force for the reaction, along with the tautomerization of 17.2 to 17.3 providing an irreversible pathway towards cyclization. These calculations were conducted using the M062X / cc-pVTZ level of theory, with acetone solvating using a conductor-like polarized continuum model (CPCM).

hindered orcinol radical (**17.1**). It is noteworthy that H-atom exchange between phenols and phenoxyls is known to be a very fast reaction.[20] The transient orcinol radical (**17.1**) can then couple with the second equivalent of persistent **11R** at C8, resulting in intermediate **17.2**. While this C-C forming step furnishes an intermediate that remains higher in energy than the starting materials, rapid tautomerization of the orcinol ring can be expected to occur resulting in **17.3**, presumably rendering the reaction irreversible under the reaction conditions. Subsequent cyclization yields the product **16q**. While a well-defined transition state between **17.3** and **16q** could not be located (presumably due to the prohibitively high energy of the resultant zwitterionic species in the gas phase), **17.4** (the conjugate base of **17.3**) is predicted to undergo an essentially barrierless cyclization to the trans-DHB **17.5**. The transition state for cyclization of **17.4** to the cis-DHB was found to have a significantly higher energy (10.8 kcal/mol), which predicts that the reaction should proceed with high diastereoselectivity.

With this initial proof of concept and a reasonable mechanism in hand, we investigated the generality of this radical cross-coupling reaction with a series of diversely substituted phenols and polyphenols (Figure 4A and Figure 5). We were gratified to see that this method allows access to a range of *trans*-2,3-diaryl-DHBs in up to 98% yield. The reaction was successful for various simple phenols and catechol-derived systems. However, lower yields were observed for phenolic systems lacking substitution (**16a**) or containing only one hydroxy substituent (**16c**, **16p**) compared to those with varying substitution patterns. When substitution was introduced at the *para* position of phenol, the yield jumped from 24% (**16a**) to 38% (**16b**). The same observation was made in resorcinol-derived substrates, where incorporating a methyl group at the 5-position of resorcinol resulted in an increase in yield from 9% (**16p**) to 60% (**16r**, Figure 5). We hypothesize that adding substitution onto the phenol slows competing homocoupling of the transient phenoxyl radical, increasing the chances of the productive cross-coupling product (Figure 4B). Sterically demanding catechol **16d**, while amenable to the reaction conditions, resulted in only a 13% yield, similar to catechol. In general, the catechol-based systems performed worse than substrates derived from phenol and resorcinol. This could be due to the strong hydrogen bonding that occurs between phenoxyl radical and the *o*-hydroxy group of catechol which, along with the electronics of the system, greatly stabilizes the *o*-semiquinone radical in solution (Figure 4B).[20, 21] This *o*-semiquinone radical has a similar stability to that of the QMD-derived radical, causing a buildup of semiquinone radicals that would enable disproportionation. Another possible deleterious side reaction would be the rapid reaction between any adventitious O_2 present and the semiquinone radical, resulting in quinone and HOO•.[22]However, switching from an *o*-hydroxy group to a *o*-methoxy group resulted in an increase in yield from 15% (**16c**) to 90% (**16f**). The lack of hydrogen-bonding in the *o*-methoxy (**16f, 16h**) and *o*-ethoxy (**16g**) phenoxyl radicals drastically reduces their radical stability and thus decreases the contribution of disproportionation. When looking at nitrogen-containing systems, 3-hydroxyindole (**16i**) and aminophenol (**16j**) performed moderately under the reaction conditions in 35% and 25% yields, respectively. While aminophenol did produce trace amounts of the hydroxy-indoline product, this product was not isolated due to purification challenges. It is unsurprising that the reaction conditions were not amenable to aminophenol since, similar to the *o*-semiquinone radical formed from catechol, the *p*-semiquinone radical formed is more stable than the QMD-derived radical (Figure 4B). This would lead to disproportionation.[22]

We then examined how reliable this DHB formation was with different quinone methide dimers (Figure 4C). These dimers can be accessed through a facile electrochemical dimerization that we've previously reported.[4] In that work, a wide variety of electron-rich and electron-poor hydroxy-stilbenes were tolerated in the

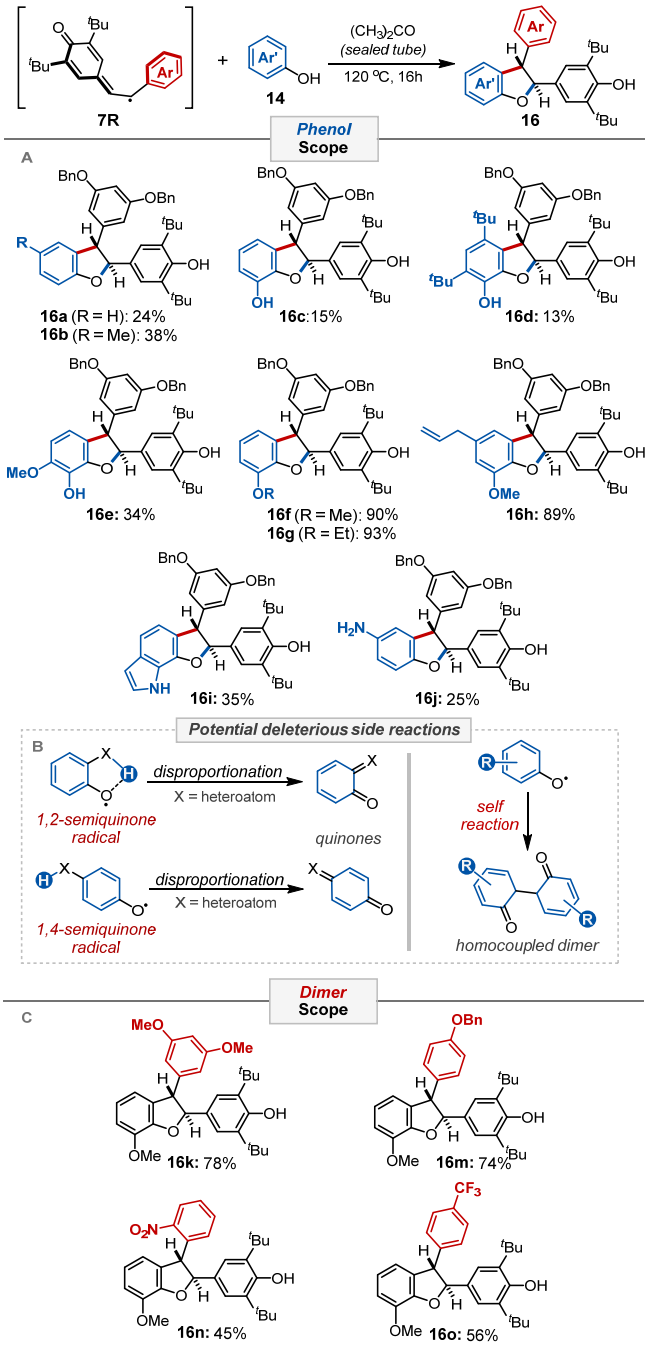

Figure 4. A) Investigation of substrate scope for *trans* 2,3-diaryl-DHB formation via intermolecular radical combinations [a]Conditions: 0.2 mmol QMD and 0.1 mmol phenol are dissolved in acetone (0.025M) that had previously been sparged for 10 min; the reaction is heated to 120 °C and left to stir for 16 h. B) Potential deleterious side reactions; C) *Dimer scope*: [b]Conditions: 0.1 mmol QMD and 0.05 mmol guaiacol are dissolved in acetone (0.025M) that had previously been sparged for 10 min; the reaction is heated to 120 °C and left to stir for 16 h

electrochemical dimerization. Guaiacol was chosen as the model phenol in this set of reactions, due to how well this substrate performed in our initial substrate scope (**16f**). As expected, electron-rich dimers **16k** and **16m** performed similarly to that of our model dimer **11**. Pleasingly, electron-deficient dimers **16n** and **16o** were able to undergo the DHB formation, albeit in slightly diminished yields.

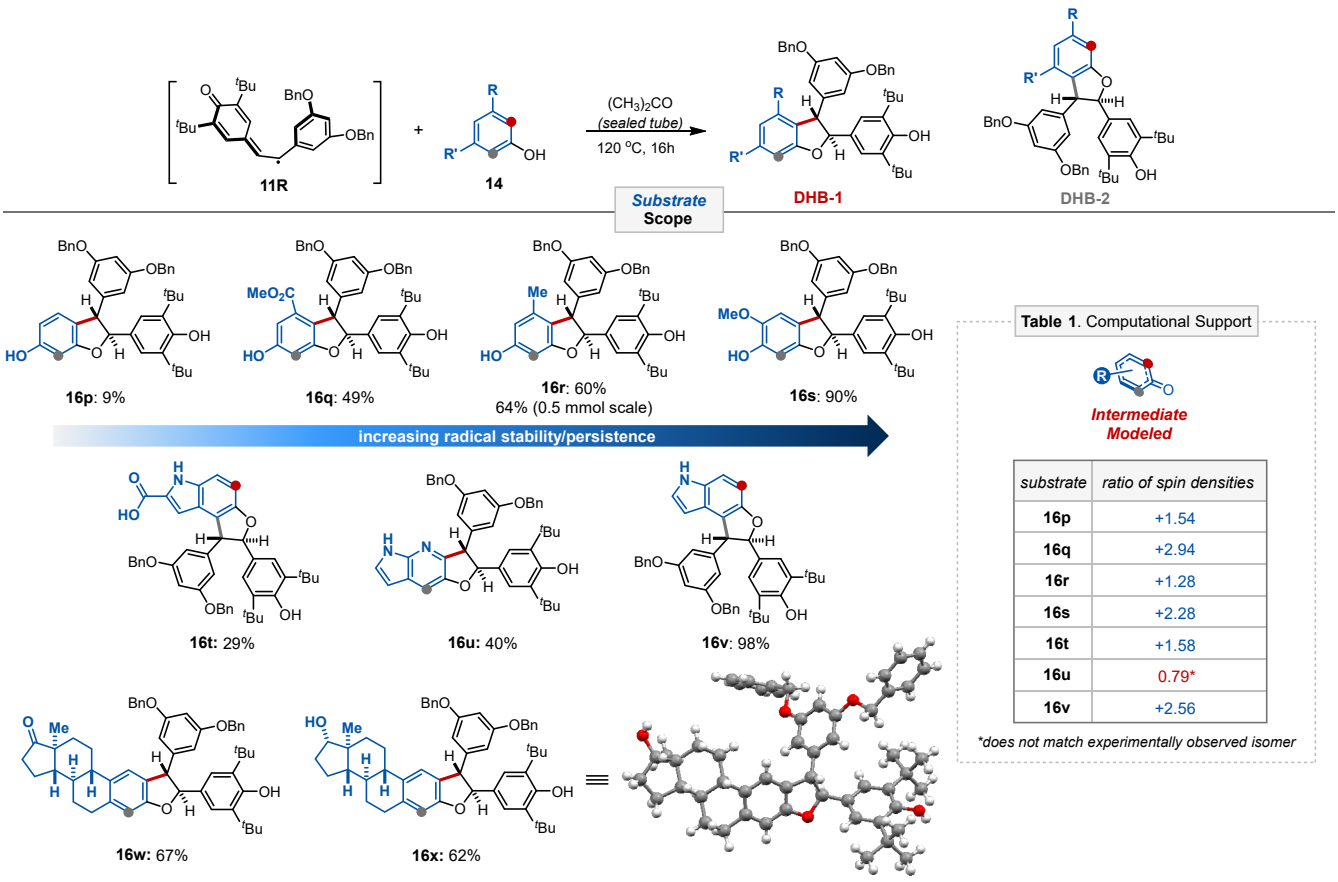

Figure 5. Investigation of substrate scope for *trans*-2,3-diaryl-DHB formation via intermolecular radical combinations [a]Conditions: 0.2 mmol QMD and 0.1 mmol phenol are dissolved in acetone (0.025M) that had previously been sparged for 10 min; the reaction is heated to 120 °C and left to stir for 16 h; **Table 1.** The electron paramagnetic resonance (EPR) coupling constant of each substrate after HAT was computed. The EPR values were then subtracted, with a blue number indicating agreement with experiment, while red does not. All computations were in alignment except for **16t**. These calculations were conducted using M062X / cc-pVTZ level of theory, with acetone solvating using a conductor-like polarized continuum model (CPCM).

Having demonstrated that this method is suitable for a range of simple phenol and catechol-based substrates, we began looking at more complex and unsymmetrical phenolic systems (Figure 5). For resorcinol substrates, **16s** resulted in a 90% yield, performing the best under the reaction conditions for this class of substrates. This is likely due to the increased stability of the phenoxyl radical that comes from the *p*-methoxy substituent. *Meta*-substituted **16q** and **16r** performed well, with 49% and 60% yields, respectively. We've also shown that the method can be scaled to 5 times the original scale while maintaining the yield (**16r**). Indole substrates **16i** and **16s-16u** showed a similar trend in terms of the relationship between radical stability and yield. Carboxylic acid-containing indole (**16t**) performed poorly, confirming that the electron-withdrawing nature of the carboxylic acid destabilizes the radical resulting in diminished yields. There were also significant differences in yield when the hydroxy group was at the 3-position (**16i**) versus the 5-position (**16v**), with 35% and 98% yields, respectively. Incorporating biologically relevant substrates into the desired DHB products proved successful with steroids estrone **16w** and estradiol **16x** leading to 62% and 67% yields, respectively.

We then sought to probe the regioselectivity of this method for unsymmetric phenolic systems that have two possible DHB regioisomers products: linear **DHB-1** and bent **DHB-2** (Figure 5). It is important to note that for all substrates highlighted in Figure 5, only one regioisomer was observed. In our initial observation of DHB formation between BQM **11** and resveratrol **12** (Figure 2A), the **DHB-1** connection was isolated as a single regioisomer, so we hypothesized that the linear DHB (**DHB-1**) would be the major regioisomer formed for all substrates. For simpler resorcinol systems with a hydrogen, ester, or methyl group at the 5-position of the resorcinol ring (**16p-16r,** respectively), **DHB-1** was the major regioisomer formed. 6-Methoxy resorcinol **16x** also gave way to the linear product. While indole substrates **16t** and **16v** formed the bent DHB, azaindole **16u** formed the linear product. For steroids **16w** and **16x**, the linear DHB was formed.

To provide insight to the observed regioselectivity, we calculated the unpaired electron spin densities at the two ortho carbons in the phenoxyl radicals **17.1** since radical coupling would be expected to occur predominantly at the sites bearing the highest spin density. The ratios, which were computed at the M062X/cc-pVTZ level of theory, are shown in Table 1. The computed ratios follow the experimental trends (where the observed DHB isomer results from cross-coupling at the carbon bearing the highest spin density) for all but one example, the 7-azaindole **16u**. Given that the 7-azaindole (**16u**) bears an electronegative nitrogen atom alpha to the labile hydrogen, tautomerization may be especially rapid, leading to a contra-thermodynamic product (the aromaticity of both rings is disrupted in the adduct leading to the observed product).

In general, there are two main factors to consider when choosing a phenolic substrate for this reaction: the thermodynamic stability (or *stability*) and the kinetic stability (or *persistence*) of the transient phenoxyl radical (Figure 6).[23] For the reaction to work well, the transient radical should be less stable than the persistent QMD radical to ensure the persistent radical effect will be operative. If the

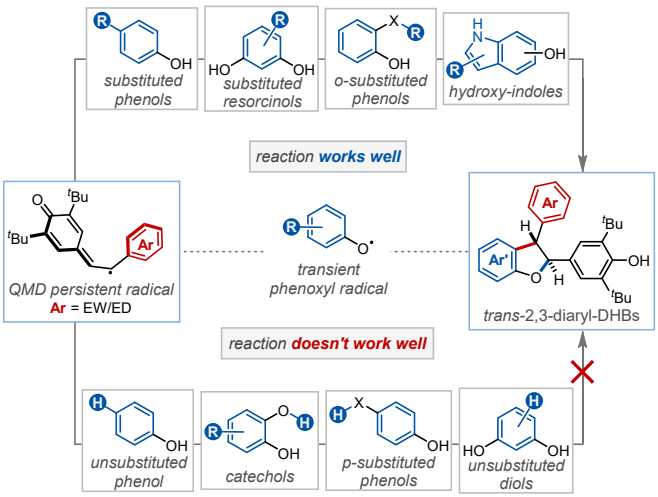

Figure 6. Summary of substrates amenable to the reaction conditions. X = heteroatom

stability of the transient radical is similar to the stability of the QMD radical, the concentration of transient radical may accumulate, leading to self-reactions, such as disproportionation (e.g., for catechol **16c** and aminophenol **16j**). At the same time, the transient phenoxyl radicals must be sufficiently persistent to enable cross-coupling with the QMD radical over competing self-reactions. As we saw with unsubstituted phenol (**16a**) and unsubstituted resorcinol (**16p**), adding a substituent or two (either electron-donating or electron-withdrawing) seems to have a significant effect on radical cross-coupling over radical homo-coupling.

Conclusion

In summary, a general and robust method for accessing *trans*-2,3-diaryl-DHBs which utilizes the persistent radical effect has been described. This approach was prompted by our prior work, wherein we leveraged the persistent radical equilibrium of quinone methide dimers in the synthesis of C8-C8' and C3-C8' resveratrol-based natural products. The approach outlined in this paper provides an operationally simple strategy for accessing 2,3-diaryl-DHBs and lays the groundwork for accessing the C10-C8' DHBs found in the majority of higher order resveratrol oligomers. The adoption of this method will result in a more streamlined approach for the synthesis of a wide range of DHB-containing natural products.

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Notes

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Keywords: resveratrol • dihydrobenzofuran • radical chemistry • quinone methides • antioxidants

[1] P. Jeandet, C. Hébrard, M.-A. Deville, S. Cordelier, S. Dorey, A. Aziz, J. Crouzet, *Molecules* **2014**, *19*, 18033-18056.

[2] S. Quideau, D. Deffieux, C. Douat-Casassus, L. Pouységu, *Angew. Chem. Int. Ed.* **2011**, *50*, 586-621.

[3] M. H. Keylor, B. S. Matsuura, C. R. J. Stephenson, *Chem. Rev.* **2015**, *115*, 8976-9027.

[4] K. J. Romero, M. S. Galliher, M. A. R. Raycroft, J.-P. R. Chauvin, I. Bosque, D. A. Pratt, C. R. J. Stephenson, *Angew. Chem. Int. Ed.* **2018**, *57*, 17125-17129.

[5] M. H. Keylor, B. S. Matsuura, M. Griesser, J.-P. R. Chauvin, R. A. Harding, M. S. Kirillova, X. Zhu, O. J. Fischer, D. A. Pratt, C. R. J. Stephenson, *Science* **2016**, *354*, 1260.

[6] K. J. Romero, M. H. Keylor, M. Griesser, X. Zhu, E. J. Strobel, D. A. Pratt, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2020**, *142*, 6499-6504.

[7] P. Langcake, R. J. Pryce, *Chem. Comm.* **1977**, 208-210.

[8] M. A. R. Raycroft, J.-P. R. Chauvin, M. S. Galliher, K. J. Romero, C. R. J. Stephenson, D. A. Pratt, *Chem. Sci.* **2020**, *11*, 5676-5689.

[9] B. S. Matsuura, M. H. Keylor, B. Li, Y. Lin, S. Allison, D. A. Pratt, C. R. J. Stephenson, *Angew. Chem. Int. Ed.* **2015**, *54*, 3754-3757.

[10] Examples of synthetic approaches towards C8-C8' resveratrol natural products: W. Li, H. Li, Y. Li, Z. Hou, *Angew. Chem. Int. Ed.* **2006**, *45*, 7609-7611; W. Li, H. Li, Y. Luo, Y. Yang, N. Wang, *Synlett* **2010**, *2010*, 1247-1250; W. Li, T. Dong, P. Chen, X. Liu, M. Liu, X. Han, *Tetrahedron* **2017**, *73*, 3056-3065; F. Klotter, A. Studer, *Angew. Chem. Int. Ed.* **2014**, *53*, 2473-2476; Y. L. Choi, B. T. Kim, J.-N. Heo, *J. Org. Chem.* **2012**, *77*, 8762-8767; S. A. Snyder, A. L. Zografos, Y. Lin, *Angew. Chem. Int. Ed.* **2007**, *46*, 8186-8191; K. J. Romero, M. S. Galliher, D. A. Pratt, C. R. J. Stephenson, *Chem. Soc. Rev.* **2018**, *47*, 7851-7866.

[11] Examples of synthetic approaches towards C3-C8' resveratrol natural products: G.-J. Fan, X.-D. Liu, Y.-P. Qian, Y.-J. Shang, X.-Z. Li, F. Dai, J.-G. Fang, X.-L. Jin, B. Zhou, *Bioorg. & Med. Chem.* **2009**, *17*, 2360-2365; Y. Takaya, K. Terashima, J. Ito, Y.-H. He, M. Tateoka, N. Yamaguchi, M. Niwa, *Tetrahedron* **2005**, *61*, 10285-10290; S. Nicotra, M. R. Cramarossa, A. Mucci, U. M. Pagnoni, S. Riva, L. Forti, *Tetrahedron* **2004**, *60*, 595-600; T. Song, B. Zhou, G.-W. Peng, Q.-B. Zhang, L.-Z. Wu, Q. Liu, Y. Wang, *Chem.* **2014**, *20*, 678-682; M. Sako, H. Hosokawa, T. Ito, M. Iinuma, *J. Org. Chem.* **2004**, *69*, 2598-2600; M. S. Galliher, B. J. Roldan, C. R. J. Stephenson, *Chem. Soc. Rev.* **2021**, *50*, 10044-10057.

[12] Examples of synthetic approaches towards oxidized and/or non-DHB-containing C10-C8' resveratrol natural products: S. A. Snyder, S. B.

Thomas, A. C. Mayer, S. P. Breazzano, *Angew. Chem. Int. Ed.* **2012**, *51*, 4080-4084; K. C. Nicolaou, T. R. Wu, Q. Kang, D. Y. K. Chen, *Angew. Chem. Int. Ed.* **2009**, *48*, 3440-3443; J. L. Jeffrey, R. Sarpong, *Org. Lett.* **2009**, *11*, 5450-5453; S. A. Snyder, N. E. Wright, J. J. Pflueger, S. P. Breazzano, *Angew. Chem. Int. Ed.)* **2011**, *50*, 8629-8633; B. H. Lee, Y. L. Choi, S. Shin, J.-N. Heo, *J. Org. Chem.* **2011**, *76*, 6611-6618; Y. Yang, D. Philips, S. Pan, *J. Org. Chem.* **2011**, *76*, 1902-1905.

[13] T. D. Sheppard, *J. Chem. Res.* **2011**, *35*, 377-385.

[14] I. Kim, J. Choi, *Org. & Biomol. Chem.* **2009**, *7*, 2788-2795.

[15] H. M. L. Davies, M. V. A. Grazini, E. Aouad, *Org. Lett.* **2001**, *3*, 1475-1477; H. Saito, H. Oishi, S. Kitagaki, S. Nakamura, M. Anada, S. Hashimoto, *Org. Lett.* **2002**, *4*, 3887-3890; C. Soldi, K. N. Lamb, R. A. Squitieri, M. González-López, M. J. Di Maso, J. T. Shaw, *J. Am. Chem. Soc.* **2014**, *136*, 15142-15145.

[16] A. E. G. Lindgren, C. T. Öberg, J. M. Hillgren, M. Elofsson, *Eur. J. Org. Chem.* **2016**, *2016*, 426-429; C. Yao, J. Zhang, J. Zhang, Y. Kang, J. Shi, *Synlett* **2016**, *27*, 1587-1591; Y. Natori, H. Tsutsui, N. Sato, S. Nakamura, H. Nambu, M. Shiro, S. Hashimoto, *J. Org. Chem.* **2009**, *74*, 4418-4421; W. Kurosawa, T. Kan, T. Fukuyama, *J. Am. Chem. Soc.* **2003**, *125*, 8112-8113.

[17] S. A. Snyder, A. Gollner, M. I. Chiriac, *Nature* **2011**, *474*, 461-466.

[18] T. H. Jepsen, S. B. Thomas, Y. Lin, C. I. Stathakis, I. de Miguel, S. A. Snyder, *Angew. Chem. Int. Ed.* **2014**, *53*, 6747-6751; N. E. Wright, S. A. Snyder, *Angew. Chem. Int. Ed.* **2014**, *53*, 3409-3413.

[19] Y. Zhao, D. G. Truhlar, *Theo. Chem. Acc.* **2008**, *120*, 215-241; T. H. Dunning, *J. Chem. Phys.* **1989**, *90*, 1007-1023.

[20] K. U. Ingold, D. A. Pratt, *Chem. Rev.* **2014**, *114*, 9022-9046.

[21] M. Lucarini, V. Mugnaini, G. F. Pedulli, *J. Org. Chem.* **2002**, *67*, 928-931.

[22] L. Valgimigli, R. Amorati, M. G. Fumo, G. A. DiLabio, G. F. Pedulli, K. U. Ingold, D. A. Pratt, *J. Org. Chem.* **2008**, *73*, 1830-1841.

[23] More on the persistent radical effect: D. Griller, K. U. Ingold, *Acc. Chem. Res.* **1976**, *9*, 13-19; D. Leifert, A. Studer, *Angew. Chem. Int. Ed.* **2020**, *59*, 74-108.