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Selectfluor-Mediated Stereoselective [1 + 1 + 4 + 4] Dimerization of Styrylnaphthols

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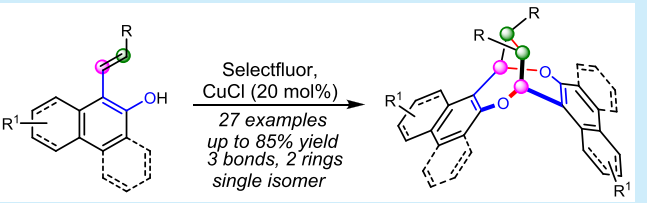
Supporting Information

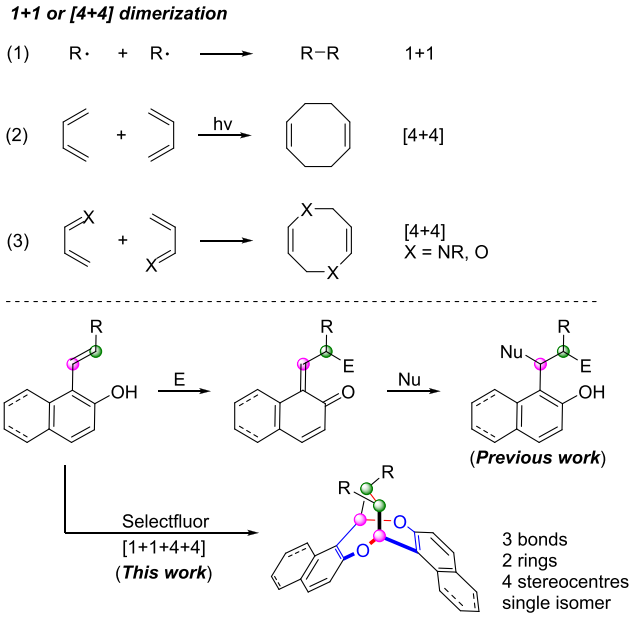
ABSTRACT: Stereoselective [1 + 1 + 4 + 4] dimerization of 1-styrylnaphthols has been developed by using Selectfluor as the oxidant for the first time. The reaction was compatible with various functional groups, giving a class of ethanodinaphtho[b,f][1,5]dioxocines with novel 3D skeletons. DFT calculations indicate that this method merges an intriguing stereoselective intermolecular 1 + 1 radical coupling to construct a bridged C−C bond and then an intramolecular [4 + 4] formal cycloaddition of the in situ generated *o*-quinone methide intermediate.



Dimerization reactions represent a synthetically powerful strategy for the rapid construction of molecular complexity in organic chemistry. Many dimerization reactions have been developed for the synthesis of natural and unnatural compounds containing symmetric moieties.[1] Elegant approaches including 1 + 1 radical dimerization reactions[2] and [4 + 4] cycloaddition reactions[3−5] have emerged as powerful tools for the construction of C−C and C−X bonds. Various compounds such as resveratrol,[6] oxindoles,[1p,2b,i] isatins,[2l] as well as alkynes[1e,k−m,2j,k] and other bioactive compounds[2n] were employed as substrates for 1 + 1 radical dimerization to generate one C−C bond by using oxidative or reductive strategies (Scheme 1, eq 1). The [4 + 4] cycloaddition reaction is very significant for the construction of annulated eight-membered rings, including the photocycloaddition of 1,3-dienes (Scheme 1, eq 2)[3] and formal cycloaddition of unsaturated imines[4] or aldehyde/ketone[5] with two new bonds formed (Scheme 1, eq 3). Although the thermal process is forbidden for the [4 + 4] cycloaddition of 1,3-dienes, it is allowed for the hetero-[4 + 4] cycloaddition.[5] However, compared with various tandem reaction methods developed for efficient formation of complex molecules, current dimerization reactions mostly focuses on one *m* + *m* reaction. Only a few examples of a tandem strategy including dimerization reactions are available.[1n,2n]

Tandem dimerization and cyclization of stilbene derived monomers (e.g., resveratrol) is proposed as biosynthetic route in nature and also realized in the lab by enzymatic catalysis or oxidative conditions. A series of resveratrol dimerization reactions have been developed,[6] which appears to proceed via the coupling of oxidatively generated phenoxyl radicals. Recently, Stephenson and co-workers developed an efficient synthetic route to reseveratrol dimers by using oxidative 1 + 1 radical dimerization and Friedel−Crafts reactions.[6o] Despite the prominence of dimerization reaction in organic synthesis,

Scheme 1. 1 + 1 and [4 + 4] Dimerization Reactions



from the synthetic point of view, the combination of *m* + *m* and [*n* + *n*] dimerization reactions in a single step may allow efficient creation of multicyclic ring skeletons.

Stereoselective construction of multiple rings in a single step is a fascinating and synthetically useful strategy for rapid assembly of polycyclic molecules. Numerous intramolecular Diels−Alder reactions and tandem reactions have been developed for the synthesis of bridged bicyclic ring systems

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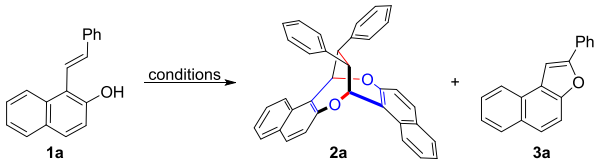
Table 1. Optimization of the Reaction Conditions[a]



entry	oxidant (equiv)	additive	solvent	t (h)	yield (%)[b] 2a	yield (%)[b] 3a
1	DDQ (1.2)		THF	8	40	55
2	MnO_2 (1.2)		THF	48	trace	23
3	Selectfluor (1.2)		THF	48	50	5
4	NBS (1.2)		THF	48		73
5	Selectfluor (1.2)		toluene	48		trace
6	Selectfluor (1.2)		DCM	48		trace
7	Selectfluor (1.2)		EtOAc	48	56	15
8	Selectfluor (1.2)	$Sc(OTf)_3$	EtOAc	48	34	41
9	Selectfluor (1.2)	$Cu(OTf)_2$	EtOAc	36	60	10
10	Selectfluor (1.2)	CuBr	EtOAc	36	58	21
11	Selectfluor (1.2)	CuCl	EtOAc	24	77	16
12[c]	Selectfluor (1.2)	CuCl	EtOAc	12	65	18
13	Selectfluor (1.0)	CuCl	EtOAc	12	80	9
14	Selectfluor (0.8)	CuCl	EtOAc	12	85	8
15	Selectfluor (0.6)	CuCl	EtOAc	12	74	9
16	Selectfluor (1.5)	CuCl	EtOAc	12	70	8

[a]Reactions were carried out with **1a** (0.20 mmol), additive (0.04 mmol), and oxidant (0.24 mmol) in solvent (2.0 mL) under N_2 at 40 °C. [b]Isolated yield. [c]The reaction temperature is 50 °C.

containing the cyclohexene motif.[7] Nonetheless, creation of medium-sized multicyclic rings by other cycloaddition reactions has lagged far behind, and there are only a few examples describing the formation of eight-membered ring systems.[8] At the same time, the bridged structure of a dioxabicyclo[3.3.1] nonane unit commonly occurs in natural products and drug molecules, such as cyanomaclurin and cyanomaclurin analogue.[8b] The design and synthesis of compounds with novel bridged structures is a significant and ongoing challenge within molecular science. Therefore, developing new methods to realize tandem dimerization for the construction of polycyclic molecules is highly desirable.

Recently, our group has been interested in the chemistry of vinylphenol by taking advantage of its unique reactivity.[9] Motivated by our research program on efficiently accessing benzofuran[9a] and benzoindole skeletons[9b] by [3 + 2] cycloaddition reactions and previous work on the resveratrol dimerization, we envisioned that (*E*)-1-styrylnaphthols bearing an ortho hydroxyl group could dimerize to generate *o*-quinone methide intermediates via a oxidative radical dimerization strategy. Subsequent intramolecular [4 + 4] cycloaddition would then generate a bridged bicyclic ring system. Herein, we report a concise construction of ethanodinaphtho[b,f][1,5]-dioxocine with novel 3D skeletons from (*E*)-1-styrylnaphthol by using Selectfluor as the oxidant in a one-pot fashion for the first time (Scheme 1). Intriguingly, multiple events occurred in this reaction: (1) A tandem stereoselective intermolecular 1 + 1 radical coupling and an intramolecular [4 + 4] cyclization occurred. (2) One bridged C−C single bond and two C−O single bonds were formed. (3) A bridged bicyclic seven-membered ring was obtained in one step. (4) The diastereoselectivity was excellent—only one isomer was observed.

We commenced our investigations with the model reaction shown in Table 1. To our delight, the desired product **2a** was obtained in 40% yield when the (*E*)-1-styrylnaphthol **1a** was treated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in THF at 40 °C for 8 h (Table 1, entry 1). The structure of **2a** was determined unambiguously by X-ray crystallographic analysis. Meanwhile, the benzofuran **3a** was also isolated as a side product in 55% yield. Encouraged by the result, several other oxidants were investigated. When MnO_2 was used as the oxidant, almost no desired product was formed (Table 1, entry 2). Compared with DDQ, Selectfluor was found to be more effective for this transformation (Table 1, entry 3 vs entry 1). In contrast, the reaction afforded **3a** exclusively when *N*-bromosuccinimide (NBS) was used as the oxidant (Table 1, entry 4). Next, various solvents were screened, and EtOAc gave the best results (Table 1, entries 5−7). To further improve its synthetic efficiency, a range of additives such as $Sc(OTf)_3$, $Cu(OTf)_2$, CuBr, and CuCl were evaluated (Table 1, entries 8−11). Fortunately, a significant improvement was obtained (77% yield) when CuCl (0.2 equiv) was used as an additive, and it was also found that the starting material **1a** was totally consumed (Table 1, entry 11). In addition, a further increase of the reaction temperature could not improve the efficiency of the reaction (Table 1, entry 12 vs entry 11). Finally, decreasing the amount of Selectfluor to 1.0 equiv or 0.8 equiv has a positive effect on the reaction conversion (Table 1, entries 13 and 14). However, further reducing the amount of Selectfluor to 0.6 equiv resulted in a decrease in the yield of **2a** (Table 1, entry 15). On the other hand, an increase in the Selectfluor loading (from 1.2 equiv to 1.5 equiv) had no significant influence on the reaction efficiency (Table 1, entry 16).

With the optimized conditions established (Table 1, entry 14), the substrate scope of the reaction was explored. As shown

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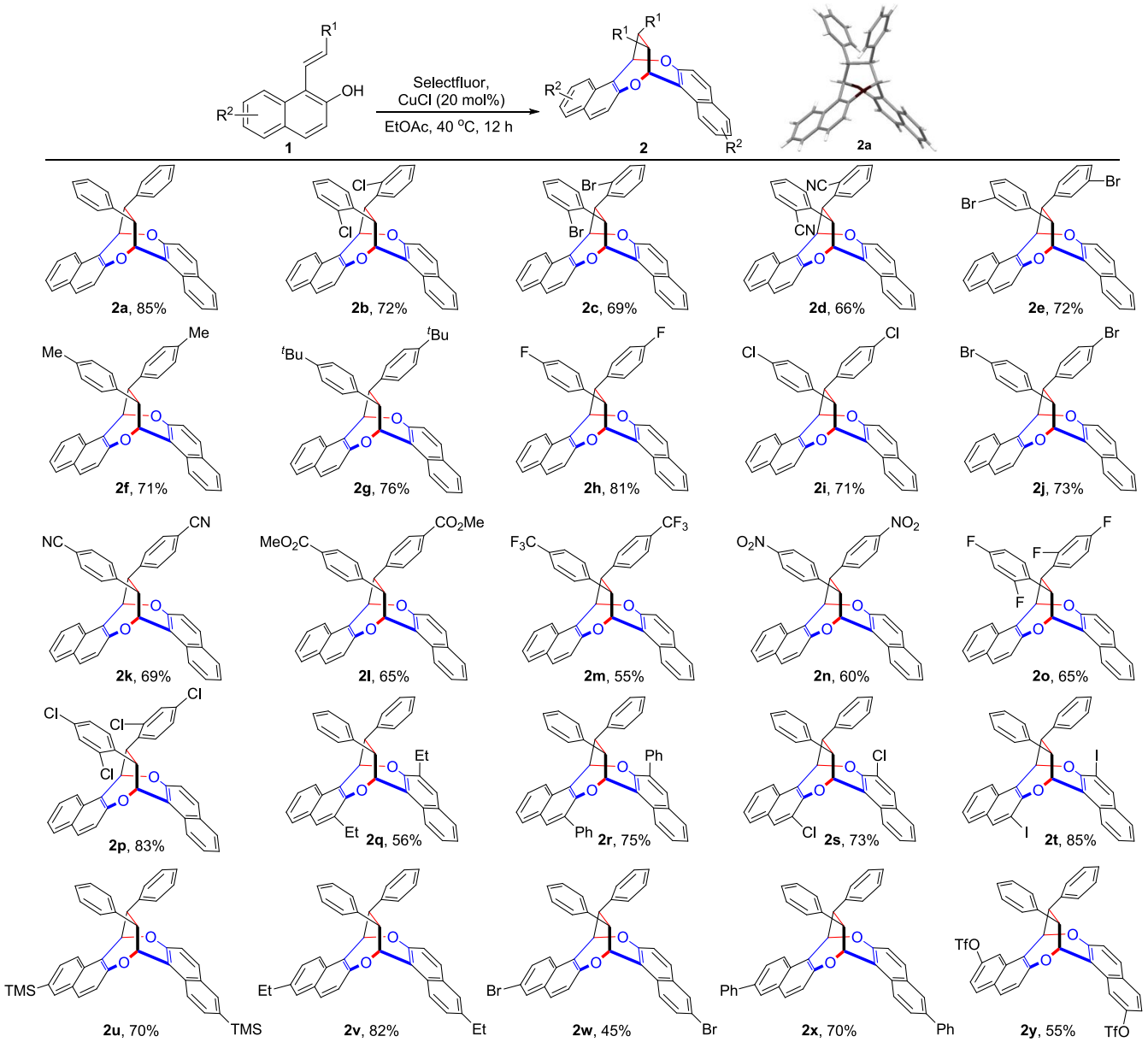
Scheme 2. Substrate Scope of (*E*)-1-Styrylnaphthols[a]



[a]Reactions were carried out with **1** (0.2 mmol), Selectfluor (0.16 mmol), and CuCl (0.04 mmol) in EtOAc (2.0 mL) at 40 °C under N_2. The yields shown are for isolated products.

in Scheme 2, various substituted (*E*)-1-styrylnaphthols were surveyed. We were pleased to find that substituents at the *ortho*-position of the phenyl ring, such as Cl, Br, and CN, all could afford the desired products in good yields (Scheme 2, **2b**−**d**). In addition, product **2e** with a 3-Br substituent phenyl was obtained in 72% yield. Furthermore, substrates with different substituents at the *para*-position of the phenyl ring were well tolerated under the identical conditions, all proceeding in moderate to excellent yields (Scheme 2, **2f**−**n**). As a result, substrates with electron-donating or -withdrawing substituents at the *para*-position of the phenyl ring could give the corresponding products in good yields. Nonetheless, strong electron-withdrawing substituents returned measurably lower yields (Scheme 2, **2k**−**n**). The reason may be that the electron-withdrawing substituents decreased the electron density of the substrates; thus, the stability of the corresponding radical intermediates was reduced. Further investigation demonstrated that disubstituted substrates could also provide the corresponding products in good yields (Scheme 2, **2o**−**p**).

In addition, we surveyed the substrate scope with regard to the naphthol moiety. Substrates with substituents at the 3-position of the naphthol could be well tolerated, wherein the corresponding products **2q**−**2t** were delivered in moderate to excellent yields ranging form 56% to 85%. Additionally, substrates with different substituents bearing TMS, Et, Br, or Ph at the 6-position of the naphthol were transformed effectively (**2u**−**x**). Finally, product **2y** with an OTf substituent at the 7-position of the naphthol was obtained in good yield. Notably, the tolerance of the halogens and OTf provided great potential to produce more complex structures through cross-coupling reactions.

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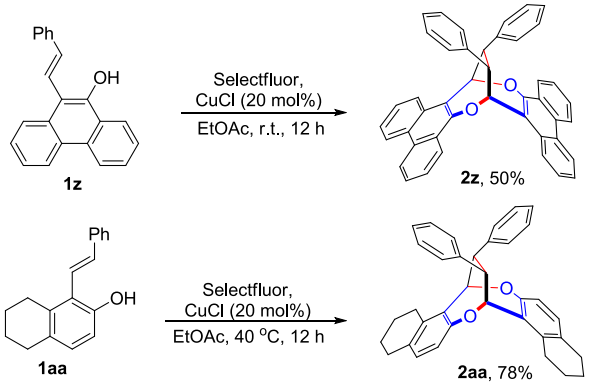
Interestingly, the strategy was also applicable for 10-styrylphenanthren **1z**; the corresponding saddle-shaped product **2z** could be readily achieved (Scheme 3). To further

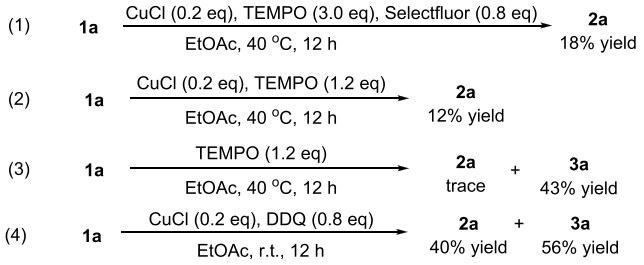
Scheme 3. Reaction of 1z and 1aa with Selectfluor



demonstrate the utility of this method, (*E*)-2-styrylphenol **1aa** was treated under the standard reaction conditions, and the desired product **2aa** was obtained smoothly in high yield.

To elucidate the reaction mechanism, some control experiments were conducted. As shown in Scheme 4, it was

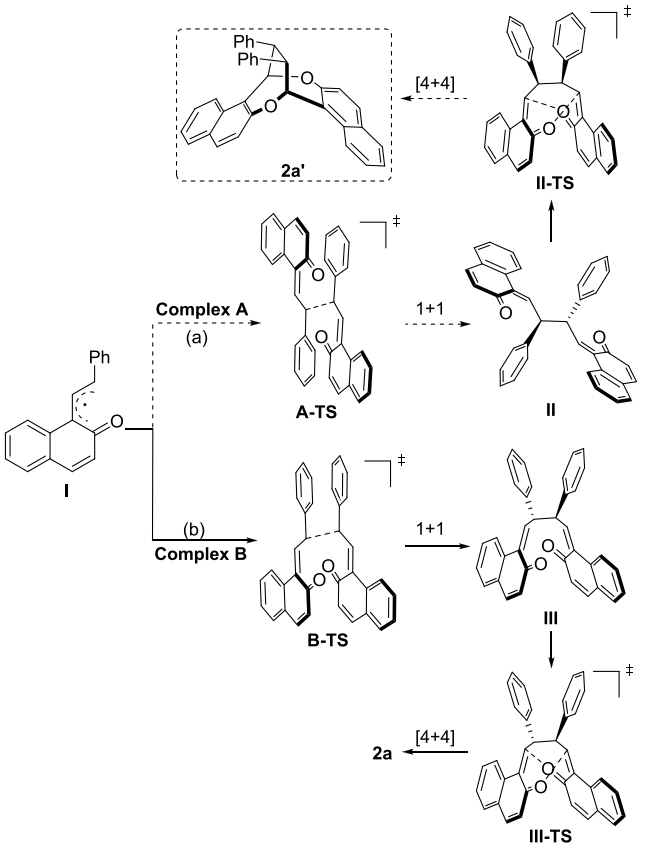
Scheme 4. Control Experiments



found that the desired product could be obtained in only 18% yield when TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) was added, indicating that the reaction may proceed via a radical pathway (Scheme 4, eq 1 vs Table 1, entry 14). At the same time, the desired product **2a** was still obtained when Selectfluor was absent (eq 2), because compound **1a** can be oxidized by TEMPO directly (eq 3). Moreover, reaction of **1a** with DDQ in the presence of CuCl gave a result similar to that in the absence of CuCl (Scheme 4, eq 4 vs Table 1, entry 1), while clear improvement was observed when CuCl was used together with Selectfluor (Table 1, entry 7 vs entry 11). These results suggested that CuCl plays a role in the Selectfluor oxidation process. Indeed, Ritter and co-workers reported an unusual SET/fluoride transfer/SET mechanism by which a Pd(IV)-complex captures fluoride and subsequently transfers it to nucleophiles.[10a] Lectka and co-workers explored the supposed SET chemistry between copper and Selectfluor, including outter-sphere or inner-sphere electron transfer mechanisms.[10b]

On the basis of the above results and previous studies, we propose a plausible reaction mechanism for this transformation (Scheme 5). First, (*E*)-1-styrylnaphthol **1a** was oxidized by Selectfluor or a Cu(II) species to form the oxygen radical intermediate,[11] which underwent a radical dearomatization to generate *o*-quinone methide radical intermediate **I**. Next, a radical−radical coupling reaction of the intermediate **I** would

Scheme 5. Plausible Reaction Mechanism



generate two possible intermediates **II** or **III**. The reason why the diastereoisomer **III** was produced predominantly may be due to the $\pi-\pi$ stacking interaction between both phenyl and naphthalene rings in the transition state **B-TS**. Additionally, the corresponding tertiary radical coupling product was not observed probably because of the steric reason. Next, the substrate-controlled stereoselective intramolecular [4 + 4] cycloaddition reaction of **III** would form the desired product **2a**. The side-product **3a** was formed possibly via an intramolecular radical cyclization process from intermediate **I** or a cationic cyclization process from a carbocation intermediate generated by further oxidization of intermediate **I**.[10,12]

We next conducted DFT studies to gain insight into the reaction mechanism and the origin of the high levels of stereoselectivity observed. All calculations were performed with Gaussian 09. The geometries of all intermediates and transition states were optimized at the B3LYP-D3/6-1G(d) level, and energies were calculated at the M06-2X/6-311G* level with the solvation effect (Figure 1). Indeed, the potential energy of the transition state **B-TS** was found to be lower than that of the transition state **A-TS** by 8.7 kcal/mol.[11] Further intramolecular [4 + 4] cycloaddition reaction of **III** gave the desired product **2a** through a moderate barrier (**III-TS**, 13.7 kcal/mol), whereas a higher barrier of **II-TS** (18.9 kcal/mol) was observed.

In conclusion, we have developed a novel and practical dimeration of (*E*)-1-styrylnaphthols by using Selectfluor as the oxidant under mild reaction conditions, leading efficiently to interesting bridged ethanodinaphtho[b,f][1,5]dioxocine scaffolds. This reaction underwent a formation of bridged C−C

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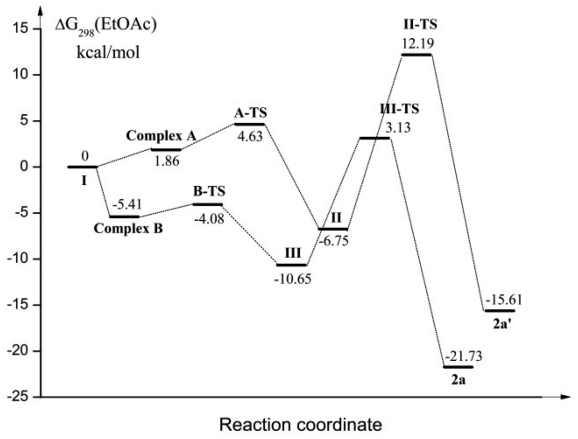

Figure 1. Energy profile of dimerization of styrylnaphthols.

bond by intermolecular 1 + 1 radical coupling and an intramolecular [4 + 4] cycloaddition of *o*-quinone methides. This work provides a novel combination of 1 + 1 and [4 + 4] dimerization reactions in a single reaction step. The applications of such a strategy for other dimerization reactions are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03587.

Experimental details and spectroscopic and analytical data for new compounds (PDF)

Accession Codes

CCDC 1882505 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Kim, J.; Movassaghi, M. General Approach to Epipolythiodiketopiperazine Alkaloids: Total Synthesis of (+)-Chaetocins A and C and (+)-12,12′-Dideoxychetracin A. *J. Am. Chem. Soc.* **2010**, *132*, 14376−14378. (b) Constantin, M.-A.; Conrad, J.; Merişor, E.; Koschorreck, K.; Urlacher, V. B.; Beifuss, U. Oxidative Dimerization of (*E*)- and (*Z*)-2-Propenylsesamol with O_2 in the Presence and Absence of Laccases and Other Catalysts: Selective Formation of Carpanones and Benzopyrans under Different Reaction Conditions. *J. Org. Chem.* **2012**, *77*, 4528−4543. (c) Hong, F.-J.; Low, Y.-Y.; Chong, K.-W.; Thomas, N. F.; Kam, T.-S. Biomimetic Oxidative Dimerization of Anodically Generated Stilbene Radical Cations: Effect of Aromatic Substitution on Product Distribution and Reaction Pathways. *J. Org. Chem.* **2014**, *79*, 4528−4543. (d) Wendinger, D.; Januszewski, J. A.; Hampel, F.; Tykwinski, R. R. Thermal dimerization of [n]cumulenes (n = 5, 7, 9). *Chem. Commun.* **2015**, *51*, 14877−14880. (e) Álvarez-Pérez, M.; Frutos, M.; Viso, A.; Fernández de la Pradilla, R.; de la Torre, M. C.; Sierra, M. A.; Gornitzka, H.; Hemmert, C. Gold(I)-Catalyzed Cycloisomerization−Dimerization Cascade of Benzene-Tethered 1,6-Enynes. *J. Org. Chem.* **2017**, *82*, 7546−7554. (f) Chen, Y.-F.; Chen, J.; Lin, L.-J.; Chuang, G. J. Synthesis of Azoxybenzenes by Reductive Dimerization of Nitrosobenzene. *J. Org. Chem.* **2017**, *82*, 11626−11630. (g) Cho, B. S.; Chung, Y. K. Palladium(II)-Catalyzed Transformation of 3-Alkylbenzofurans to [2,3′-Bibenzofuran]-2′(3′H)-ones: Oxidative Dimerization of 3-Alkylbenzofurans. *J. Org. Chem.* **2017**, *82*, 2237−2242. (h) Chong, K.-W.; Hong, F.-J.; Thomas, N. F.; Low, Y.-Y.; Kam, T.-S. Electrochemically Mediated Oxidative Transformations of Substituted 4-Methoxystilbenes: Effect of Ortho-Substituted Nucleophilic Groups. *J. Org. Chem.* **2017**, *82*, 6172−6191. (i) Garcia-Borràs, M.; Konishi, A.; Waterloo, A.; Liang, Y.; Cao, Y.; Hetzer, C.; Lehnherr, D.; Hampel, F.; Houk, K. N.; Tykwinski, R. R. Tautomerization and Dimerization of 6,13-Disubstituted Derivatives of Pentacene. *Chem. - Eur. J.* **2017**, *23*, 6111−6117. (j) Sib, A.; Gulder, T. A. M. Stereoselective Total Synthesis of Bisorbicillinoid Natural Products by Enzymatic Oxidative Dearomatization/Dimerization. *Angew. Chem., Int. Ed.* **2017**, *56*, 12888−12891. (k) Wang, D.; Liu, S.; Lan, X.-C.; Paniagua, A.; Hao, W.-J.; Li, G.; Tu, S.-J.; Jiang, B. Tunable Dimerization and Trimerization of *β*-Alkynyl Ketones via Silver Catalysis for Accessing Spiro and Dispiro Compounds Containing 1H-Isochromene. *Adv. Synth. Catal.* **2017**, *359*, 3186−3193. (l) Żak, P.; Bołt, M.; Lorkowski, J.; Kubicki, M.; Pietraszuk, C. Platinum Complexes Bearing Bulky N-Heterocyclic Carbene Ligands as Efficient Catalysts for the Fully Selective Dimerization of Terminal Alkynes. *ChemCatChem* **2017**, *9*, 3627−3631. (m) Claus, V.; Schukin, M.; Harrer, S.; Rudolph, M.; Rominger, F.; Asiri, A. M.; Xie, J.; Hashmi, A. S. K. Gold-Catalyzed Dimerization of Diarylalkynes: Direct Access to Azulenes. *Angew. Chem., Int. Ed.* **2018**, *57*, 12966−12970. (n) Green, N. J.; Connolly, C. A.; Rietdijk, K. P. W.; Nichol, G. S.; Duarte, F.; Lawrence, A. L. Bio-inspired Domino oxa-Michael/Diels−Alder/oxa-Michael Dimerization of para-Quinols. *Angew. Chem., Int. Ed.* **2018**, *57*, 6198−6202. (o) Paris, E.; Bigi, F.; Cauzzi, D.; Maggi, R.; Maestri, G. Oxidative dimerization of anilines with heterogeneous sulfonic acid catalysts. *Green Chem.* **2018**, *20*, 382−386. (p) Yao, X.; Wang, T.; Zhang, Z. Gold(I)-Catalyzed Dimerization of 3-Diazooxindoles towards Isoindigos. *Eur. J. Org. Chem.* **2018**, *2018*, 4475−4478. (q) Breit, B.; Steib, P. Concise Total Synthesis of (−)-Vermiculine through a Rhodium-Catalyzed C2-symmetric Dimerization Strategy. *Chem. - Eur. J.* **2019**, *25*, 3532−3535. (r) Kurpil, B.; Markushyna, Y.; Savateev, A. Visible-Light-Driven Reductive (Cyclo)Dimerization of Chalcones over Heterogeneous Carbon Nitride Photocatalyst. *ACS Catal.* **2019**, *9*, 1531−1538. (s) Peng, C.; Kusakabe, T.; Kikkawa, S.; Mochida, T.; Azumaya, I.; Dhage, Y. D.; Takahashi, K.; Sasai, H.; Kato, K. Asymmetric Cyclizative Dimerization of (ortho-Alkynyl Phenyl) (Methoxymethyl) Sulfides with Palladium(II) Bisoxazoline Catalyst. *Chem. - Eur. J.* **2019**, *25*, 733−737.

(2) (a) Becker, H. D.; Langer, V. Photochemical dimerization modes of 9-methoxyanthracenes and 9-(2-hydroxy-2-propyl)anthracene. *J. Org. Chem.* **1993**, *58*, 4703−4708. (b) Fang, C.-L.; Horne, S.; Taylor, N.; Rodrigo, R. Dimerization of a 3-Substituted Oxindole at C-3 and Its Application to the Synthesis of (±)-Folicanthine. *J. Am. Chem. Soc.* **1994**, *116*, 9480−9486. (c) Fry, A. J.; Porter, J. M.; Fry, P. F.

DOI: 10.1021/acs.orglett.9b03587
Org. Lett. XXXX, XXX, XXX−XXX

Electrochemical Formation and Dimerization of α-Substituted Benzyl Radicals. Steric Effects on Dimerization. *J. Org. Chem.* **1996**, *61*, 3191−3194. (d) Bryant, J. R.; Mayer, J. M. Oxidation of C−H Bonds by $[(bpy)_2(py)RuIVO]^{2+}$ Occurs by Hydrogen Atom Abstraction. *J. Am. Chem. Soc.* **2003**, *125*, 10351−10361. (e) Li, W.-D. Z.; Ma, B.-C. A Simple Biomimetic Synthesis of dl-Chamaejasmine, a Unique 3,3′-Biflavanone. *Org. Lett.* **2005**, *7*, 271−274. (f) Beer, L.; Reed, R. W.; Robertson, C. M.; Oakley, R. T.; Tham, F. S.; Haddon, R. C. Tetrathiophenalenyl Radical and its Disulfide-Bridged Dimer. *Org. Lett.* **2008**, *10*, 3121−3123. (g) Melikyan, G. G.; Sepanian, R.; Spencer, R.; Rowe, A.; Toure, P. Cobalt-Complexed Propargyl Cations: Generation under Neutral Conditions and Spontaneous, High-Temperature Conversion to Propargyl Radicals. *Organometallics* **2009**, *28*, 5541−5549. (h) Du, Y.; Wang, Y.; Li, X.; Shao, Y.; Li, G.; Webster, R. D.; Chi, Y. R. N-Heterocyclic Carbene Organocatalytic Reductive β,β-Coupling Reactions of Nitroalkenes via Radical Intermediates. *Org. Lett.* **2014**, *16*, 5678−5681. (i) Ghosh, S.; Chaudhuri, S.; Bisai, A. Oxidative Dimerization of 2-Oxindoles Promoted by KO^{t}Bu-I_2: Total Synthesis of (±)-Folicanthine. *Org. Lett.* **2015**, *17*, 1373−1376. (j) Melikyan, G. G.; Davis, R.; Anker, B.; Meron, D.; Duncan, K. Acquiring a Prognostic Power in $Co_2(CO)_6$-Mediated, Cobaltocene-Induced Radical Dimerizations of Propargyl Triflates. *Organometallics* **2016**, *35*, 4060−4070. (k) Qiu, S.; Zhang, Y.; Huang, X.; Bao, L.; Hong, Y.; Zeng, Z.; Wu, J. 9-Ethynylfluoroenyl Radicals: Regioselective Dimerization and Post Ring-Cyclization Reactions. *Org. Lett.* **2016**, *18*, 6018−6021. (l) Wang, C.-M.; Xia, P.-J.; Xiao, J.-A.; Li, J.; Xiang, H.-Y.; Chen, X.-Q.; Yang, H. Photoredox-Catalyzed Reductive Dimerization of Isatins and Isatin-Derived Ketimines: Diastereoselective Construction of 3,3′-Disubstituted Bisoxindoles. *J. Org. Chem.* **2017**, *82*, 3895−3900. (m) Wojcik, L.; Michaud, F.; Gauthier, S.; Cabon, N.; Le Poul, P.; Gloaguen, F.; Le Poul, N. Reversible Redox Switching of Chromophoric Phenylmethylenepyrans by Carbon−Carbon Bond Making/Breaking. *J. Org. Chem.* **2017**, *82*, 12395−12405. (n) Abeyawardhane, D. L.; Fernández, R. D.; Heitger, D. R.; Crozier, M. K.; Wolver, J. C.; Lucas, H. R. Copper Induced Radical Dimerization of α-Synuclein Requires Histidine. *J. Am. Chem. Soc.* **2018**, *140*, 17086−17094. (o) Kawamata, T.; Yamaguchi, A.; Nagatomo, M.; Inoue, M. Convergent Total Synthesis of Asimicin via Decarbonylative Radical Dimerization. *Chem. - Eur. J.* **2018**, *24*, 18907−18912. (p) Romero, K. J.; Galliher, M. S.; Pratt, D. A.; Stephenson, C. R. J. Radicals in natural product synthesis. *Chem. Soc. Rev.* **2018**, *47*, 7851−7866.

(3) (a) Sieburth, S. M.; Chen, J. L. A photochemical [4 + 4] method for the construction of annulated eight-membered rings. *J. Am. Chem. Soc.* **1991**, *113*, 8163−8164. (b) Sieburth, S. M.; Chen, J.; Ravindran, K.; Chen, J.-l. A 2-Pyridone Photo-[4 + 4] Approach to the Taxanes. *J. Am. Chem. Soc.* **1996**, *118*, 10803−10810. (c) Bearpark, M. J.; Deumal, M.; Robb, M. A.; Vreven, T.; Yamamoto, N.; Olivucci, M.; Bernardi, F. Modeling Photochemical [4 + 4] Cycloadditions: Conical Intersections Located with CASSCF for Butadiene + Butadiene. *J. Am. Chem. Soc.* **1997**, *119*, 709−718. (d) Deumal, M.; Bearpark, M. J.; Smith, B. R.; Olivucci, M.; Bernardi, F.; Robb, M. A. Product Distributions from Molecular Mechanics−Valence Bond Dynamics: Modeling Photochemical [4 + 4] Cycloadditions. *J. Org. Chem.* **1998**, *63*, 4594−4600. (e) Lee, Y.-g.; McGee, K. F.; Chen, J.; Rucando, D.; Sieburth, S. M. A [4 + 4] 2-Pyridone Approach to Taxol. 3. Stereocontrol during Elaboration of the Cyclooctane. *J. Org. Chem.* **2000**, *65*, 6676−6681. (f) Sieburth, S. M.; Madsen-Duggan, C. B.; Zhang, F. Diastereoselectivity during 2-pyridone photo-[4 + 4] cycloaddition. The tribenzylsilyl protecting group. *Tetrahedron Lett.* **2001**, *42*, 5155−5157. (g) Wang, R.; Yuan, L.; Macartney, D. H. Cucurbit[7]uril Mediates the Stereoselective [4 + 4] Photodimerization of 2-Aminopyridine Hydrochloride in Aqueous Solution. *J. Org. Chem.* **2006**, *71*, 1237−1239. (h) Yang, C.; Nakamura, A.; Fukuhara, G.; Origane, Y.; Mori, T.; Wada, T.; Inoue, Y. Pressure and Temperature-Controlled Enantiodifferentiating [4 + 4] Photocyclodimerization of 2-Anthracenecarboxylate Mediated by Secondary Face- and Skeleton-Modified γ-Cyclodextrins. *J. Org. Chem.* **2006**, *71*, 3126−3136. (i) Khatri, B. B.; Vrubliauskas, D.; Sieburth, S. M. Photo-[4 + 4]-cycloaddition (para) of meta-substituted benzenes with 2-pyridones. *Tetrahedron Lett.* **2015**, *56*, 4520−4522. (j) Maturi, M. M.; Fukuhara, G.; Tanaka, K.; Kawanami, Y.; Mori, T.; Inoue, Y.; Bach, T. Enantioselective [4 + 4] photodimerization of anthracene-2,6-dicarboxylic acid mediated by a C_2-symmetric chiral template. *Chem. Commun.* **2016**, *52*, 1032−1035. (k) Kulyk, S.; Khatri, B. B.; Sieburth, S. M. Enyne [4 + 4] Cycloaddition/Oxidation: Ring Contraction via Cyclopropanones and Their Anionic Ring-Opening Reactions. *Angew. Chem., Int. Ed.* **2017**, *56*, 319−323. (l) Wang, R.; Liu, H.; Li, J.; Tian, J.; Li, Z.; Zhao, Y. Solid-State Photodimerization of Azaanthracene Derivative Based on a [4 + 4] Cycloaddition. *Asian J. Org. Chem.* **2018**, *7*, 906−909. (m) Hsu, T.-G.; Chou, H.-C.; Liang, M.-J.; Lai, Y.-Y.; Cheng, Y.-J. Regio- and stereo-selective [4 + 4] photodimerization of angular-shaped dialkyltetracenedithiophene. *Chem. Commun.* **2019**, *55*, 381−384.

(4) (a) Tanaka, K.; Siwu, E. R. O.; Hirosaki, S.; Iwata, T.; Matsumoto, R.; Kitagawa, Y.; Pradipta, A. R.; Okumura, M.; Fukase, K. Efficient synthesis of 2,6,9-triazabicyclo[3.3.1]nonanes through amine-mediated formal [4 + 4] reaction of unsaturated imines. *Tetrahedron Lett.* **2012**, *53*, 5899−5902. (b) Tsutsui, A.; Tanaka, K. 2,6,9-Triazabicyclo[3.3.1]nonanes as overlooked amino-modification products by acrolein. *Org. Biomol. Chem.* **2013**, *11*, 7208−7211. (c) Ni, H.; Tang, X.; Zheng, W.; Yao, W.; Ullah, N.; Lu, Y. Enantioselective Phosphine-Catalyzed Formal [4 + 4] Annulation of α,β-Unsaturated Imines and Allene Ketones: Construction of Eight-Membered Rings. *Angew. Chem., Int. Ed.* **2017**, *56*, 14222−14226.

(5) (a) Arnold, Z.; Budesinsky, M. 2,6,9-Trioxabicyclo[3.3.1]nona-3,7-diene-4,8-dicarbaldehyde, a dissymmetric propeller-like molecule. The structure and chirality proof. *J. Org. Chem.* **1988**, *53*, 5352−5353. (b) Osyanin, V. A.; Popova, Y. V.; Klimochkin, Y. N. Synthesis of 6,12-di(adamantane-2′-spiro)-6H,12H-dibenzo[b,f][1,5]dioxocine. *Russ. J. Org. Chem.* **2010**, *46*, 302−303.

(6) (a) Li, X.-M.; Huang, K.-S.; Lin, M.; Zhou, L.-X. Studies on formic acid-catalyzed dimerization of isorhapontigenin and of resveratrol to tetralins. *Tetrahedron* **2003**, *59*, 4405−4413. (b) Li, W.; Li, H.; Li, Y.; Hou, Z. Total Synthesis of (±)-Quadrangularin A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7609−7611. (c) Panzella, L.; De Lucia, M.; Amalfitano, C.; Pezzella, A.; Evidente, A.; Napolitano, A.; d'Ischia, M. Acid-Promoted Reaction of the Stilbene Antioxidant Resveratrol with Nitrite Ions: Mild Phenolic Oxidation at the 4′-Hydroxystiryl Sector Triggering Nitration, Dimerization, and Aldehyde-Forming Routes. *J. Org. Chem.* **2006**, *71*, 4246−4254. (d) Ponzoni, C.; Beneventi, E.; Cramarossa, M. R.; Raimondi, S.; Trevisi, G.; Pagnoni, U. M.; Riva, S.; Forti, L. Laccase-Catalyzed Dimerization of Hydroxystilbenes. *Adv. Synth. Catal.* **2007**, *349*, 1497−1506. (e) Li, W.; Li, H.; Luo, Y.; Yang, Y.; Wang, N. Biosynthesis of Resveratrol Dimers by Regioselective Oxidative Coupling Reaction. *Synlett* **2010**, *2010*, 1247−1250. (f) Davis, M. C.; Groshens, T. J. Dimerization of resveratrol trimethyl ether by phosphotungstic acid, structure confirmation of resformicol A and B. *Tetrahedron Lett.* **2012**, *53*, 3521−3523. (g) Li, C.; Lu, J.; Xu, X.; Hu, R.; Pan, Y. pH-switched HRP-catalyzed dimerization of resveratrol: a selective biomimetic synthesis. *Green Chem.* **2012**, *14*, 3281−3284. (h) Zhong, C.; Liu, X.-H.; Chang, J.; Yu, J.-M.; Sun, X. Inhibitory effect of resveratrol dimerized derivatives on nitric oxide production in lipopolysaccharide-induced RAW 264.7 cells. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4413−4418. (i) Keylor, M. H.; Matsuura, B. S.; Stephenson, C. R. J. Chemistry and Biology of Resveratrol-Derived Natural Products. *Chem. Rev.* **2015**, *115*, 8976−9027. (j) Matsuura, B. S.; Keylor, M. H.; Li, B.; Lin, Y.; Allison, S.; Pratt, D. A.; Stephenson, C. R. J. A Scalable Biomimetic Synthesis of Resveratrol Dimers and Systematic Evaluation of their Antioxidant Activities. *Angew. Chem., Int. Ed.* **2015**, *54*, 3754−3757. (k) Xie, J.-S.; Wen, J.; Wang, X.-F.; Zhang, J.-Q.; Zhang, J.-F.; Kang, Y.-L.; Hui, Y.-W.; Zheng, W.-S.; Yao, C.-S. Potassium Hexacyanoferrate (III)-Catalyzed Dimerization of Hydroxystilbene: Biomimetic Synthesis of Indane Stilbene Dimers. *Molecules* **2015**, *20*, 22662−22673. (l) Keylor, M. H.; Matsuura, B. S.; Griesser, M.; Chauvin, J.-P. R.; Harding, R. A.; Kirillova, M. S.; Zhu, X.; Fischer, O. J.; Pratt, D. A.; Stephenson, C. R. J. Synthesis of

DOI: 10.1021/acs.orglett.9b03587
Org. Lett. XXXX, XXX, XXX−XXX

resveratrol tetramers via a stereoconvergent radical equilibrium. *Science* **2016**, *354*, 1260−1265. (m) Li, W.; Dong, T.; Chen, P.; Liu, X.; Liu, M.; Han, X. Concise synthesis of several oligostilbenes from the enzyme-promoted oxidation of brominated resveratrol. *Tetrahedron* **2017**, *73*, 3056−3065. (n) Liu, M.; Dong, T.; Guan, X.; Shao, Z.; Li, W. Regioselective biomimetic oxidation of halogenated resveratrol for the synthesis of (±)-ε-viniferin and its analogues. *Tetrahedron* **2018**, *74*, 4013−4019. (o) Romero, K. J.; Galliher, M. S.; Raycroft, M. A. R.; Chauvin, J.-P. R.; Bosque, I.; Pratt, D. A.; Stephenson, C. R. J. Electrochemical Dimerization of Phenylpropenoids and the Surprising Antioxidant Activity of the Resultant Quinone Methide Dimers. *Angew. Chem., Int. Ed.* **2018**, *57*, 17125−17129.

(7) (a) Bear, B. R.; Sparks, S. M.; Shea, K. J. The Type 2 Intramolecular Diels−Alder Reaction: Synthesis and Chemistry of Bridgehead Alkenes. *Angew. Chem., Int. Ed.* **2001**, *40*, 820−849. (b) Iwasawa, N.; Inaba, K.; Nakayama, S.; Aoki, M. Complexation-Initiated Intramolecular [4 + 2] Cycloaddition: Construction of Bridged-Type Cycloadducts. *Angew. Chem., Int. Ed.* **2005**, *44*, 7447−7450. (c) Lauchli, R.; Whitney, J. M.; Zhu, L.; Shea, K. J. Synthesis and Chemistry of Bridgehead Allylsilanes. Stereoselective Reactions with Aldehydes. *Org. Lett.* **2005**, *7*, 3913−3916. (d) Brailsford, J. A.; Zhu, L.; Loo, M.; Shea, K. J. Enantioselective Synthesis of Bridged Bicyclic Ring Systems. *J. Org. Chem.* **2007**, *72*, 9402−9405. (e) Ko, H. M.; Dong, G. Cooperative activation of cyclobutanones and olefins leads to bridged ring systems by a catalytic [4 + 2] coupling. *Nat. Chem.* **2014**, *6*, 739−744. (f) Feng, H.-X.; Wang, Y.-Y.; Chen, J.; Zhou, L. A Dehydrogenative Diels−Alder Reaction of Prenyl Derivatives with 2,3-Dichloro-5,6-dicyanobenzoquinone. *Adv. Synth. Catal.* **2015**, *357*, 940−944. (g) Kron, K. J.; Kosich, M.; Cave, R. J.; Vosburg, D. A. Divergent Diels−Alder Reactions in the Biosynthesis and Synthesis of Endiandric-Type Tetracycles: A Computational Study. *J. Org. Chem.* **2018**, *83*, 10941−10947. (h) Xu, W.-L.; Zhang, H.; Hu, Y.-L.; Yang, H.; Chen, J.; Zhou, L. Metal-Free Dehydrogenative Diels−Alder Reactions of Prenyl Derivatives with Dienophiles via a Thermal Reversible Process. *Org. Lett.* **2018**, *20*, 5774−5778. (i) Xu, W.-L.; Tang, L.; Ge, C.-Y.; Chen, J.; Zhou, L. Synthesis of Tetrahydroisoindolinones via a Metal-Free Dehydrogenative Diels-Alder Reaction. *Adv. Synth. Catal.* **2019**, *361*, 2268−2273.

(8) (a) Liu, H.; Wang, Y.; Guo, X.; Huo, L.; Xu, Z.; Zhang, W.; Qiu, S.; Yang, B.; Tan, H. A Bioinspired Cascade Sequence Enables Facile Assembly of Methanodibenzo[b,f][1,5]dioxocin Flavonoid Scaffold. *Org. Lett.* **2018**, *20*, 546−549. (b) Du, J.-Y.; Ma, Y.-H.; Meng, F.-X.; Chen, B.-L.; Zhang, S.-L.; Li, Q.-L.; Gong, S.-W.; Wang, D.-Q.; Ma, C.-L. Lewis Acid Catalyzed Tandem 1,4-Conjugate Addition/Cyclization of in Situ Generated Alkynyl *o*-Quinone Methides and Electron-Rich Phenols: Synthesis of Dioxabicyclo[3.3.1]nonane Skeletons. *Org. Lett.* **2018**, *20*, 4371−4374.

(9) (a) Feng, W.; Yang, H.; Wang, Z.; Gou, B.-B.; Chen, J.; Zhou, L. Enantioselective [3 + 2] Formal Cycloaddition of 1-Styrylnaphthols with Quinones Catalyzed by a Chiral Phosphoric Acid. *Org. Lett.* **2018**, *20*, 2929−2933. (b) Hu, Y.-L.; Wang, Z.; Yang, H.; Chen, J.; Wu, Z.-B.; Lei, Y.; Zhou, L. Conversion of two stereocenters to one or two chiral axes: atroposelective synthesis of 2,3-diarylbenzoindoles. *Chem. Sci.* **2019**, *10*, 6777−6784. (c) Sun, H.-R.; Zhao, Q.; Yang, H.; Yang, S.; Gou, B.-B.; Chen, J.; Zhou, L. Chiral Phosphoric-Acid-Catalyzed Cascade Prins Cyclization. *Org. Lett.* **2019**, *21*, 7143−7148.

(10) (a) Brandt, J. R.; Lee, E.; Boursalian, G. B.; Ritter, T. Mechanism of electrophilic fluorination with Pd(IV): fluoride capture and subsequent oxidative fluoride transfer. *Chem. Sci.* **2014**, *5*, 169−179. (b) Pitts, C. R.; Bloom, S.; Woltornist, R.; Auvenshine, D. J.; Ryzhkov, L. R.; Siegler, M. A.; Lectka, T. Direct, Catalytic Monofluorination of sp^3 C−H Bonds: A Radical-Based Mechanism with Ionic Selectivity. *J. Am. Chem. Soc.* **2014**, *136*, 9780−9791.

(11) See the Supporting Information for details.

(12) Pan, C.; Yu, J.; Zhou, Y.; Wang, Z.; Zhou, M.-M. An Efficient Method to Synthesize Benzofurans and Naphthofurans. *Synlett* **2006**, *2006*, 1657−1662.

DOI: 10.1021/acs.orglett.9b03587
Org. Lett. XXXX, XXX, XXX−XXX