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Cascade Claisen and Meinwald Rearrangement for One-Pot Divergent Synthesis of Benzofurans and 2*H*-Chromenes

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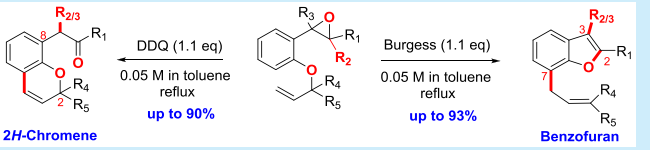
ABSTRACT: A new cascade approach has been developed for the one-pot four-step divergent synthesis of polysubstituted benzofurans and 2*H*-chromenes, featuring a novel cascade aromatic Claisen rearrangement/Meinwald rearrangement/dehydrative or oxidative cyclization. This new method was demonstrated with 39 examples tolerating different substitutions at an epoxide, allylic ether, and aromatic ring, and we showcased its utility with the first total synthesis of natural product liparacid A in seven steps.



Benzofurans and 2*H*-chromenes (2*H*-1-benzopyrans) are two classes of heteroarenes of pharmaceutical importance and regarded as privileged scaffolds in medicinal chemistry due to their unique physicochemical properties.[1] Selected examples are presented in Figure 1, which shows that benzofurans and

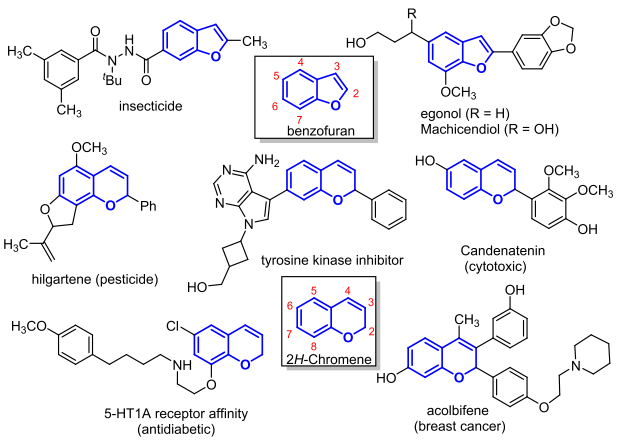


Figure 1. Selected examples of benzofurans and 2*H*-chromenes with biological activity.

2*H*-chromenes have a wide range of applications including insecticides, pesticides, antidiabetics, and antibacterial and anticancer drugs.[2] In addition, 2*H*-chromenes are a core structural framework of many bioactive natural products.[3] The medicinal importance of benzofurans and 2*H*-chromenes has aroused great interest from the synthetic community in developing new and improved synthetic methods,[4] which have tremendously advanced the development of benzofuran- and 2*H*-chromene-containing drugs. Nevertheless, the efficient synthesis of polyfunctionalized benzofurans and 2*H*-chromenes continues to be important and remains challenging, in particular for substitution at the benzene ring. Herein, we report the development of a new cascade process that allows for expedite access to not only 7-allyl benzofurans but also 8-(*β*-keto)alkyl 2*H*-chromenes.

Recently, we developed a new cascade reaction for the synthesis of 2*H*-chromenes.[5] The key cascade process was believed to involve aromatic Claisen rearrangement, *in situ* generation of *ortho*-quinone methides (*o*-QM) via 1,6-elimination of HOAc, and 6*π*-electrocyclization (Scheme 1a). We hypothesized that if an epoxide group was preinstalled to the benzylic position (Scheme 1b), a new cascade involving aromatic Claisen rearrangement[6]/Meinwald rearrangement[7] with R_2 migration would deliver the flanked substituted phenol intermediate that might undergo either dehydrative (Burgess[8]) or oxidative (DDQ[9]) cyclization to 7-allyl benzofurans and 8-(*β*-keto)alkyl 2*H*-chromenes, respectively. Notably, such site substitution has rarely been addressed by prior synthetic methodologies.

Our study began with examination of the heating conditions (Table 1) to initiate the proposed cascade process using compound **1a** as the model substrate (the synthesis of **1a** was provided in the Supporting Information (SI)). A survey of different solvents was first conducted, and both toluene and xylene were found to be suitable (entries 2−3) to give the key intermediate **2a**, probably owing to their high boiling points required for the thermo-promoted Claisen−Meinwald rearrangement. Lower temperature cannot initiate the desired reaction (entry 1), and higher temperature would slightly

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Scheme 1. Our Previous Synthesis of 2*H*-Chromenes and This Work

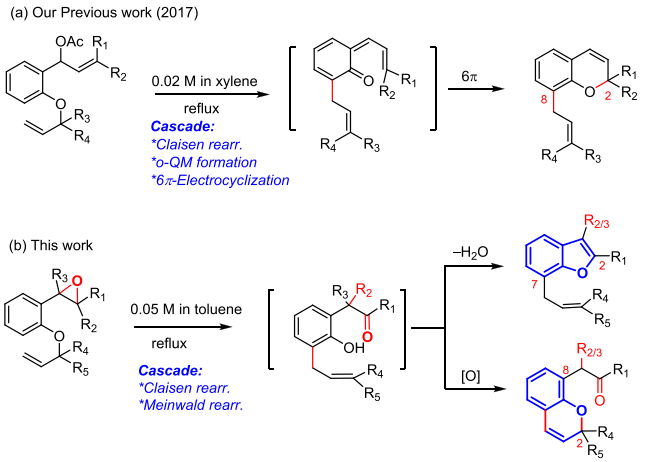
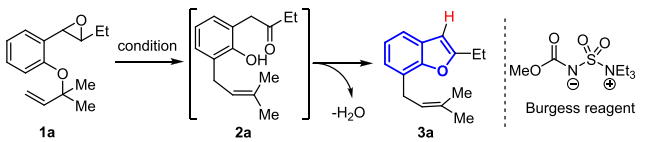


Table 1. Selected Conditions for the One-Pot Claisen Rearrangement/Meinwald Rearrangement/Dehydrative Cyclization



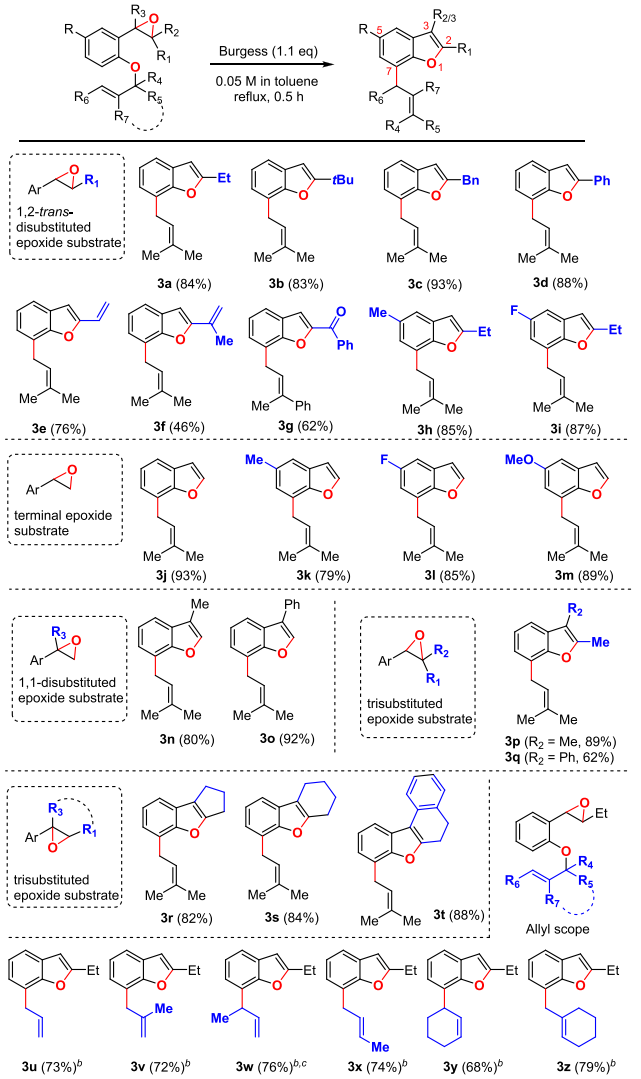
entry[a]	solvent	temp (°C, time)	additive	Yield[b] (%, 2a/3a)
1	PhH	80 (30 min)	–	<5 (1/0)
2	PhMe	110 (30 min)	–	80 (1/0)
3	xylene	140 (30 min)	–	78 (1/0)
4	DCB	180 (30 min)	–	71 (1/0)
5	DCB	180 (2 h)	–	38 (1/2)
6[c]	PhMe	110 (30 min)	H_3PO_4	0
7[c]	PhMe	110 (30 min)	HCl	0
8[c]	PhMe	110 (30 min)	TFA	0
9[c]	PhMe	110 (30 min)	TsOH	23 (0/1)
10[c]	PhMe	110 (30 min)	A-15	32 (0/1)
11[d]	PhMe	110 (30 min)	MsCl/DBU	54 (0/1)
12[e]	PhMe	110 (30 min)	Burgess	79 (0/1)
13[f]	PhMe	110 (30 min)	Burgess	84 (0/1)

[a]Condition: **1a** (0.2 mmol), solvent (4 mL), nitrogen atmosphere, reflux, 30 min. [b]Isolated yields. [c]Cooled to rt, 0.2 equiv of acid was added. [d]Cooled to rt, 1.2 equiv of DBU and 1.1 equiv of MsCl were added. [e]Cooled to rt, 1.1 equiv of Burgess reagent was added and heated to reflux for 30 min. [f]Burgess reagent was added prior to the cascade reaction. DCB: 1,2-dichlorobenzene. DBU: 1,8-diazabicyclo-[5.4.0]undec-7-ene. A-15: Amberlyst 15 hydrogen form (polystyrene-based ion-exchange resin with strongly acidic sulfonic group).

erode the yield (entry 4). We found that extended time at elevated temperature would result in partial dehydration to benzofuran **3a**, though the overall yield was not satisfactory (entry 5). After the cascade Claisen and Meinwald rearrangement was completed, we attempted to add an acid to activate the carbonyl group for the well-established ketalization–dehydration sequence[10] (entries 6–10). Unfortunately, no dehydration was observed at room temperature when 0.2 equiv of H_3PO_4, HCl, or CF_3CO_2H was used (entries 6–8), while *p*-toluenesulfonic acid or amberlyst-15 gave only low yields (23–32%, entries 9–10). This "unexpected" difficulty may be attributed to the presence of the acid-labile prenyl group that involved acid-catalyzed reactions and resulted in a mixture of unknown products. We then tried to use MsCl/DBU to trap the cyclic hemiketal that was believed to be in equilibrium with the keto-ol form (**2a**). It was very encouraging with 54% yield of **3a** (entry 11). Finally, we found Burgess reagent[8] was better for dehydration (79%yield, entry 12) and could be added before heating (84%, entry 13). This greatly simplified the operation (a mixture of epoxide substrate and Burgess reagent in toluene was heated to reflux for 30 min) and constitutes a new, unique one-pot four-step reaction.

With the optimized conditions in hand, the substrate scope was then examined and presented in Scheme 2. A series of substrates (**1a–1z**) were prepared by using the modified literature protocols (see SI for details). As depicted in Scheme 2, C2- (and C5-) substituted benzofurans (**3a–3i**) could be efficiently prepared by using the one-pot cascade reaction from 1,2-*trans*-disubstituted epoxide substrates (**1a–1i**) bearing

Scheme 2. Substrate Scope[a]



[a]Condition: epoxide (0.2 mmol), Burgess reagent (0.22 mmol), toluene (4 mL), nitrogen atmosphere, reflux, 30 min. Isolated yields are shown. [b]1,2-Dichlorobenzene as the solvent. Remove solvent, toluene (4 mL), Burgess reagent (0.22 mmol), nitrogen atmosphere, reflux, 30 min. Isolated yields are shown. [c]Containing inseparable impurities.

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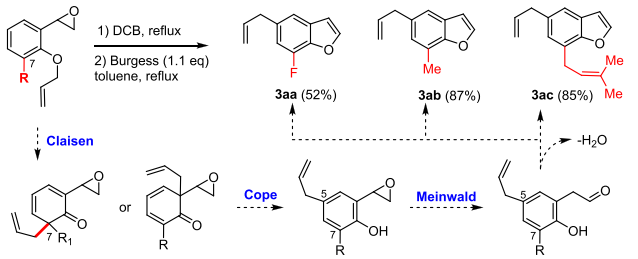
different substituents (R_1) on the epoxide in 46−93% yields. Alkyl or phenyl substituents (R_1) would result in good to excellent yields (**3a**−**3d**), and the electron-rich and electron-withdrawing substituents (R) on the aromatic ring had little effect on the reaction yields (**3h**−**3i**). However, alkenyl or benzoyl substituents (R_1) would lead to slightly lower yields (**3e**−**3g**). The sharp contrast of yields between **3e** and **3f**, whose chemical structures are similar, did exist and might be due to the increased steric effect on the carbonyl group during the subsequent cyclization. The cascade reaction of terminal epoxide substrates (**1j**−**1m**) afforded the corresponding benzofurans (**3j**−**3m**) in good to excellent yields. The electron-rich and electron-withdrawing substituents (R) on the aromatic ring did not seem to greatly influence the reaction yields. The 1,1-disubstituted epoxide substrates (**1n**−**1o**) delivered the C3-substituted benzofurans in good to excellent yields (**3n**−**3o**). Then we examined the trisubstituted epoxide substrates. It was notable that R_2 (methyl or phenyl) migrated to the benzylic position to provide the C2- and C3-disubstituted benzofurans (**3p**−**3q**). Interestingly, the phenyl group, not the methyl group, was found to involve the migration in the Meinwald rearrangement. Importantly, these two examples substantiated the Meinwald rearrangemnt and excluded the possible 1,5-H/alkyl migration in our system. When the cyclic epoxides (**1r**−**1t**) were used, the cascade one-pot four-step reaction furnished polycyclic benzofurans (**3r**−**3t**) in excellent yields.

Next, we came to examine the allyl scope of substrates (Scheme 2). The R_4−R_7 substitution on the allyl groups did not significantly erode the yields of cascade reactions (**3a**, **3u**−**3x**, **3z**). However, a lower yield was observed when R_6 was not hydrogen (**3y**), which might be due to the negative steric effect on the Claisen rearrangement. The alkene geometry of **3x** was determined by the large coupling constant of the *trans*-alkene protons. Note that ca. 8% unidentified impurities could not be separated from **3w**, although many efforts had been made.

In order to further expand the substrate scope and provide expedited access to aromatic C5 substituted benzofurans, we envisioned that if there was a non-hydrogen substituent at C7, the *para* Claisen rearrangement (or Claisen−Cope rearrangement[11]) might occur and the subsequent Meinwald rearrangement would generate the requisite intermediate for the cyclization−dehyration sequence, providing otherwise poorly accessible benzofurans with substitutions at both C5 and C7. To test this idea, we synthesized a small series of substrates (**3aa**−**3ac**) with C7 substitution and examine the cascade process (Scheme 3). It was found that the nature of the C7 substituent would have a significant influence on the reaction. For example, the cascade reaction of compound **1aa** with fluoride at C7 gave **3aa** in 52% yield, while substrates (**1ab**−**1ac**) with the carbon-based substituents (methyl, prenyl) at C7 smoothly underwent the cascade reaction to furnish benzofurans (**3ab**−**3ac**) in excellent yields. Notably, **3ac** exhibited abnormal chemoselectivity, because the allyl group, not the preinstalled prenyl group at C7, participated in the second Cope rearrangement. This observation was consistent with our previous report.[5]

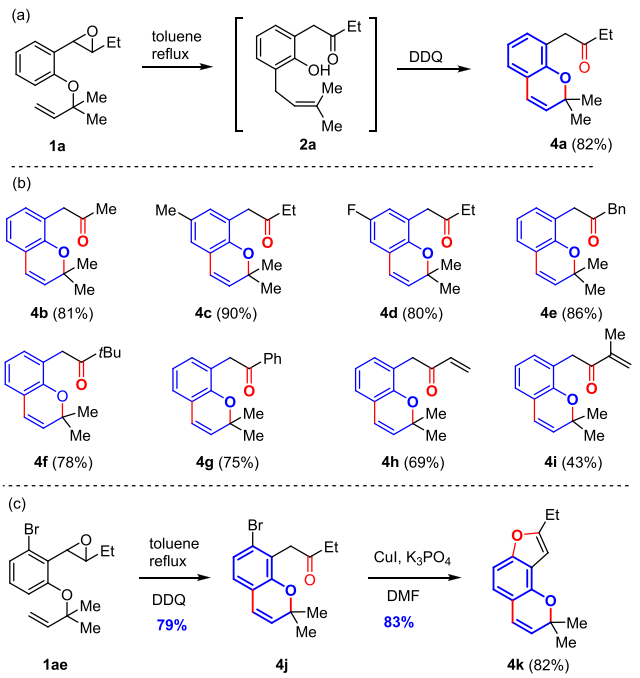
To further exploit highly functionalized intermediate **2a** from the new cascade Claisen and Meinwald rearrangement, we conceived that **2a** might undergo oxidative oxa-6π-electrocyclization to deliver 2*H*-chromenes if an appropriate oxidant could be identified to generate the *ortho*-quinone methide (*o*-QM)[12] (Scheme 4). This would considerably

Scheme 3. Cascade Claisen Rearrangement/Cope Rearrangement/Meinwald Rearrangement/Dehydration to Benzofurans[a]



[a]Condition: epoxide (0.2 mmol), 1,2-dichlorobenzene (4.0 mL), nitrogen atmosphere, reflux, 30 min. Remove solvent, toluene (4.0 mL), Burgess reagent (0.22 mmol), nitrogen atmosphere, reflux, 30 min. Isolated yields are shown.

Scheme 4. Cascade Claisen Rearrangement/Meinwald Rearrangement/Oxidative Oxa-6π-electrocyclization to 2*H*-Chromenes[a]



[a]Condition: epoxide (0.2 mmol), DDQ (0.22 mmol), toluene (4 mL), nitrogen atmosphere, reflux, 30 min. Isolated yields are shown.

expand the utility of the newly discovered cascade Claisen−Meinwald rearrangement to access polyfunctionalized 2*H*-chromenes. To our delight, the mixture of substrate **1a** and DDQ[9] in toluene under reflux conditions afforded the desired 2*H*-chromene **4a** in excellent yield (Scheme 4a) and DDQ did not seem to negatively affect the cascade Claisen rearrangement/Meinwald rearrangement. The substrate scope was examined briefly and presented in Scheme 4b. Alkyl or phenyl substituents (R_1) were well tolerated, and the corresponding substituted 2*H*-chromenes were isolated in good to excellent yield (**4a**−**4b**, **4e**−**4g**), while alkenyl substituents (R_1) would erode the reaction yields (**4h**−**4i**). The presence of the methyl group in **4i** showed a negative steric effect and lowered the reaction yield. The electronegativity or the position of substituents on the aromatic ring had little effect on the

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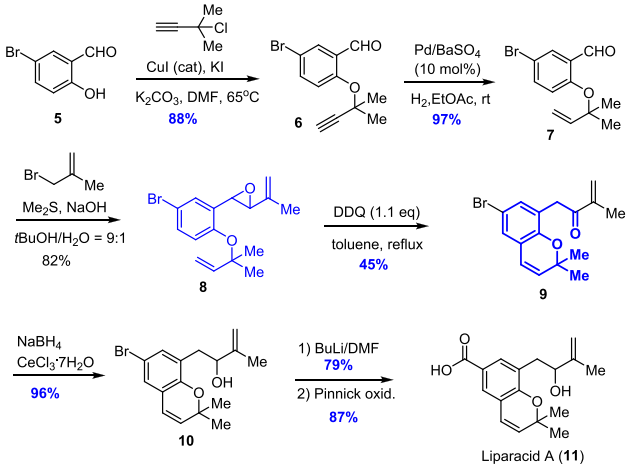
reaction yields (**4c**−**4d**, **4j**). Notably, CuI-catalyzed Ullmann-type C−O bond formation[13] could be used to elaborate 2*H*-chromene **4j** to the tricyclic hybrid benzofuran-2*H*-chromene **4k** (Scheme 4c).

Finally, we showcased the utility of this new cascade process by the first total synthesis of the scarce natural product liparacid A (**11**). Liparacid A[14] was isolated in 2007 from the rhizoma of *Liparis nakaharai*, which has been used in Chinese folk medicine for the treatment of cancer. As depicted in Scheme 5, our synthesis commenced with synthesis of aryl

Scheme 5. Total Synthesis of Liparacid A



propargyl ether **6** by CuI-catalyzed etherification[15] of 4-bromosalicylaldehyde (**5**) in 88% yield. Lindlar reduction[16] of **6** (97% yield) and subsequent Corey−Chaykovsky reaction[17] provided the epoxide **8** in 80% yield over two steps. The desired 2*H*-chromene core system **9** was obtained from **8** via our new cascade approach on a 2.0 mmol scale with a 45% overall yield. A conventional three-step sequence involving Luche reduction[18] of ketone **9** (96%), formylation (79%), and Kraus−Pinnick oxidation (87%)[19] furnished Liparacid A (**11**). All spectroscopic data for our synthetic sample were well in agreement with those reported for the natural Liparacid A.

In summary, we have developed a new cascade strategy for the one-pot four-step divergent syntheses of otherwise more difficult to access substituted benzofurans and 2*H*-chromenes with high efficiency. The new cascade processes involved either aromatic Claisen rearrangement−Meinwald rearrangement−cycloketalization−dehydration or aromatic Claisen rearrangement−Meinwald rearrangement−*o*-quinone methide formation−oxa-6π-electrocyclization. The new cascades were illustrated with 39 examples and employed as the key strategy for the first total synthesis of natural product liparacid A (seven steps). We believe that this new synthetic approach is complementary to the prior synthetic methods and will find wide application for the synthesis of polysubstituted benzofurans and 2*H*-chromenes, in particular with substituents at C7 or C8.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00770.

Experimental details, procedures, and characterization of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) *Handbook of Heterocyclic Chemistry*, 3rd ed.; Katritzky, A. R., Ramsden, C. A., Joule, J. A., Zhdankin, V. V., Eds.; *Elsevier: Oxford*, 2010; pp 815−822. (b) Brimble, M. A.; Gibson, J. S.; Sperry, J. Pyrans and their Benzo Derivatives: Synthesis. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier Ltd.: Oxford, 2008; Vol. 7, pp 419−699.

https://dx.doi.org/10.1021/acs.orglett.0c00770
Org. Lett. XXXX, XXX, XXX−XXX

(2) (a) Miao, Y.-H.; Hu, Y.-H.; Yang, J.; Liu, T.; Sun, J.; Wang, X.-J. Natural Source, bioactivity and synthesis of benzofuran derivatives. *RSC Adv.* **2019**, *9*, 27510−27540. (b) Costa, M.; Dias, T. A.; Brito, A.; Proenca, F. Biological importance of structurally diversified chromenes. *Eur. J. Med. Chem.* **2016**, *123*, 487−507.

(3) (a) Pratap, R.; Ram, V. J. Natural and Synthetic Chromenes, Fused Chromenes, and Versatility of Dihydrobenzo[h]chromenes in Organic Synthesis. *Chem. Rev.* **2014**, *114*, 10476−10526. (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. Natural Product-like Combinatorial Libraries Based on Privileged Structures. 1. General Principles and Solid-Phase Synthesis of Benzopyrans. *J. Am. Chem. Soc.* **2000**, *122*, 9939−9953.

(4) For leading reviews on synthesis of benzofurans and 2*H*-chromenes, see: (a) Agasti, S.; Dey, A.; Maiti, D. Palladium-catalyzed benzofuran and indole synthesis by multiple C-H functionalizations. *Chem. Commun.* **2017**, *53*, 6544−6556. (b) Zeni, G.; Larock, R. C. Synthesis of Heterocycles via Palladium-Catalyzed Oxidative Addition. *Chem. Rev.* **2006**, *106*, 4644−4680. (c) Majumdar, N.; Paul, N. D.; Mandal, S.; de Bruin, B.; Wulff, W. D. Catalytic Synthesis of 2*H*-Chromenes. *ACS Catal.* **2015**, *5*, 2329−2366. For selected most recent methods, see: (d) Zhang, L.; Cao, T.; Jiang, H.; Zhu, S. *Angew. Chem., Int. Ed.* **2020**, *59*, 2−9. (e) Bu, H.-Z.; Li, H.-H.; Luo, W.-F.; Luo, C.; Qian, P.-C.; Ye, L.-W. Synthesis of 2*H*-Chromenes via Unexpected [4 + 2] Annulation of Alkynyl Thioethers with *o*-Hydroxybenzyl Alcohols. *Org. Lett.* **2020**, *22*, 648−652. (f) Yang, P.; Xu, W.; Wang, R.; Zhang, M.; Xie, C.; Zeng, X.; Wang, M. Potassium *tert*-Butoxide-Mediated Condensation Cascade Reaction: Transition Metal-Free Synthesis of Multisubstituted Aryl Indoles and Benzofurans. *Org. Lett.* **2019**, *21*, 3658−3662. (g) Harish, B.; Subbireddy, M.; Obulesu, O.; Suresh, S. One-Pot Allylation-Intramolecular Vinylogous Michael Addition-Isomerization Cascade of *o*-Hydroxycinnamates and Congeners: Synthesis of Substituted Benzofuran Derivatives. *Org. Lett.* **2019**, *21*, 1823−1827. (h) Fernández-Canelas, P.; Rubio, E.; González, J. M. Oxyacylation of Iodoalkynes: Gold(I)-Catalyzed Expeditious Access to Benzofurans. *Org. Lett.* **2019**, *21*, 6566−6569. (i) An, C.; Li, C.-Y.; Huang, X.-B.; Gao, W.-X.; Zhou, Y.-B.; Liu, M.-C.; Wu, H.-Y. Selenium Radical Mediated Cascade Cyclization: Concise Synthesis of Selenated Benzofurans (Benzothiophenes). *Org. Lett.* **2019**, *21*, 6710−6714. (j) Ohno, S.; Qiu, J.; Miyazaki, R.; Aoyama, H.; Murai, K.; Hasegawa, J.-y.; Arisawa, M. Ni-Catalyzed Cycloisomerization between 3-Phenoxy Acrylic Acid Derivatives and Alkynes via Intramolecular Cleavage and Formation of the C-O Bond to Give 2,3-Disubstituted Benzofurans. *Org. Lett.* **2019**, *21*, 8400−8403. (k) Liou, Y.-C.; Karanam, P.; Jang, Y.-J.; Lin, W. Synthesis of Functionalized Benzofurans from *para*-Quinone Methides via Phospha-1,6-Addition/O-Acylation/Wittig Pathway. *Org. Lett.* **2019**, *21*, 8008−8012. (l) Rong, M.; Qin, T.-Z.; Zi, W. Rhenium-Catalyzed Intramolecular Carboalkoxylation and Carboamination of Alkynes for the Synthesis of C3-Substituted Benzofurans and Indoles. *Org. Lett.* **2019**, *21*, 5421−5425. (m) Fernández-Canelas, P.; Rubio, E.; González, J. M. Oxyacylation of Iodoalkynes: Gold(I)-Catalyzed Expeditious Access to Benzofurans. *Org. Lett.* **2019**, *21*, 6566−6569. (n) Khan, F.; Fatima, M.; Shirzaei, M.; Vo, Y.; Amarasiri, M.; Banwell, M. G.; Ma, C.; Ward, J. S.; Gardiner, M. G. Tandem Ullmann-Goldberg Cross-Coupling/CyclopalladationReductive Elimination Reactions and Related Sequences Leading to Polyfunctionalized Benzofurans, Indoles, and Phthalanes. *Org. Lett.* **2019**, *21*, 6342−6346. (o) Iqbal, N.; Iqbal, N.; Maiti, D.; Cho, E. J. Access to Multifunctionalized Benzofurans by Aryl Nickelation of Alkynes: Efficient Synthesis of the Anti-Arrhythmic Drug Amiodarone. *Angew. Chem., Int. Ed.* **2019**, *58*, 15808−15812. (p) Deng, G.; Li, M.; Yu, K.; Liu, C.; Liu, Z.; Duan, S.; Chen, W.; Yang, X.; Zhang, H.; Walsh, P. J. Synthesis of Benzofurans Derivatives through Cascade Radical Cyclization/Intermolecular Coupling of 2-Azaallyls. *Angew. Chem., Int. Ed.* **2019**, *58*, 2826−2830. (q) Zhang, Y.; Jermaks, J.; MacMillan, S. N.; Lambert, T. H. Synthesis of 2*H*-Chromenes via Hydrazine-Catalyzed Ring-Closing Carbonyl-Olefin Metathesis. *ACS Catal.* **2019**, *9*, 9259−9264. (r) Faβbender, S. I.; Metternich, J. B.; Gilmour, R. Spatiotemporal Control of Pre-existing Alkene Geometry: A Bio-Inspired Route to 4-Trifluoromethyl-2*H*-chromenes. *Org. Lett.* **2018**, *20*, 724−727. (s) Porcu, S.; Demuro, S.; Luridiana, A.; Cocco, A.; Frongia, A.; Aitken, D. J.; Charnay-Pouget, F.; Guillot, R.; Sarais, G.; Secci, F. Brønsted Acid Mediated Cascade Reaction To Access 3-(2-Bromoethyl)benzofurans. *Org. Lett.* **2018**, *20*, 7699−7702. (t) Zhou, Z.; Bian, M.; Zhao, L.; Gao, H.; Huang, J.; Liu, X.; Yu, X.; Li, X.; Yi, W. 2*H*-Chromene-3-carboxylic Acid Synthesis via Solvent-Controlled and Rhodium(III)-Catalyzed Redox-Neutral C-H Activation/[3 + 3] Annulation Cascade. *Org. Lett.* **2018**, *20*, 3892−3896. (u) Song, X.; Gao, C.; Zhang, X.; Fan, X. Synthesis of Diversely Functionalized 2*H*-Chromenes through Pd-Catalyzed Cascade Reactions of 1,1-Dibromoloefin Derivatives with Arylboronic Acids. *J. Org. Chem.* **2018**, *83*, 15256−15267. (v) Fu, R.; Li, Z. Direct Synthesis of 2-Methylbenzofurans from Calcium Carbide and Salicylaldehyde *p*-Tosylhydrazones. *Org. Lett.* **2018**, *20*, 2342−2345. (w) Yang, K.; Pulis, A. P.; Perry, G. J. P.; Procter, D. J. Transition-Metal-Free Synthesis of C3-Arylated Benzofurans from Benzothiophenes and Phenols. *Org. Lett.* **2018**, *20*, 7498−7503. (x) Hu, W.; Li, M.; Jiang, G.; Wu, W.; Jiang, H. Synthesis of 2,3-Difunctionalized Benzofuran Derivatives through Palladium-Catalyzed Double Isocyanide Insertion Reaction. *Org. Lett.* **2018**, *20*, 3500−3503. (y) Zheng, H.-X.; Shan, X.-H.; Qu, J.-P.; Kang, Y.-B. Strategy for Overcoming Full Reversibility of Intermolecular Radical Addition to Aldehydes: Tandem C-H and C-O Bonds Cleaving Cyclization of (Phenoxymethyl)arenes with Carbonyls to Benzofurans. *Org. Lett.* **2018**, *20*, 3310−3313. (z) Paul, N. D.; Mandal, S.; Otte, M.; Cui, X.; Zhang, X. P.; de Bruin, B. Metalloradical Approach to 2*H*-Chromenes. *J. Am. Chem. Soc.* **2014**, *136*, 1090−1096. (aa) Majumdar, N.; Korthals, K. A.; Wulff, W. D. Simultaneous Synthesis of Both Rings of Chromenes via a Benzannulation/o-Quinone Methide Formation/Electrocyclization Cascade. *J. Am. Chem. Soc.* **2012**, *134*, 1357−1362.

(5) (a) Song, L.; Huang, F.; Guo, L.; Ouyang, M.-A.; Tong, R. A cascade Claisen rearrangement/*o*-quinone methide formation/electrocyclization approach to 2*H*-chromenes. *Chem. Commun.* **2017**, *53*, 6021−6024. (b) Song, L.; Yao, H.; Tong, R. Biomimetic Asymmetric Total Syntheses of Spirooliganones A and B. *Org. Lett.* **2014**, *16*, 3740−3743.

(6) Castro, A. M. M. Claisen Rearrangement over the Past Nine Decades. *Chem. Rev.* **2004**, *104*, 2939−3002.

(7) (a) Meinwald, J.; Labana, S. S.; Chadha, M. S. Peracid reactions. III. The Oxidation of Bicyclo[2.2.1]heptadiene. *J. Am. Chem. Soc.* **1963**, *85*, 582−585. (b) Wu, H.; Wang, Q.; Zhu, J. Catalytic Enantioselective Pinacol and Meinwald Rearrangements for the Construction of Quaternary Stereocenters. *J. Am. Chem. Soc.* **2019**, *141*, 11372−11377.

(8) (a) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. Thermal reactions of alkyl N-carbomethoxysulfamate esters. *J. Org. Chem.* **1973**, *38*, 26−31. (b) Santra, S. Burgess Reagent: From Oblivion to Renaissance in Organic Synthesis. *Synlett* **2009**, *2009*, 328−329. For a recent example from our lab, see: (c) Cheng, H.; Zhang, Z.; Yao, H.; Zhang, W.; Yu, J.; Tong, R. Unified Asymmetric Total Syntheses of (−)-Alotaketals A-D and (−)-Phorbaketal A. *Angew. Chem., Int. Ed.* **2017**, *56*, 9096−9100.

(9) (a) Saimoto, H.; Ueda, J.; Sashiwa, H.; Shigemasa, Y.; Hiyama, T. A General Approach for the Synthesis of Phenolin Natural Products. Facile Syntheses of Grifolin and Colletochlorins B and D. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1178−1185. (b) Tsukayama, M.; Kikuchi, M.; Kawamura, Y. Regioselective Prenylation of Phenols by Palladium Catalyst: Syntheses of Prenylphenols and Chromans. *Heterocycles* **1994**, *38*, 1487−1490.

(10) Song, L.; Yao, H.; Zhu, L.; Tong, R. Asymmetric Total Syntheses of (−)-Penicipyrone and (−)-Tenuipyrone via Biomimetic Cascade Intermolecular Michael Addition/Cycloketalization. *Org. Lett.* **2013**, *15*, 6−9.

(11) (a) Schmidt, B.; Riemer, M.; Schilde, U. Tandem Claisen Rearrangement/6-*endo* Cyclization Approach to Allylated and Prenylated Chromones. *Eur. J. Org. Chem.* **2015**, *2015*, 7602−7611. (b) Patre, R. E.; Shet, J. B.; Parameswaran, P. S.; Tilve, S. Cascade Wittig reaction-double Claisen and Cope rearrangements: one-pot

https://dx.doi.org/10.1021/acs.orglett.0c00770
Org. Lett. XXXX, XXX, XXX−XXX

synthesis of diprenylated coumarins gravelliferone, balsamiferone, and 6,8-diprenylumbelliferone. *Tetrahedron Lett.* **2009**, *50*, 6488−6490.
(12) For a review, see: (a) Ferreira, S.; da Silva, F. D. C.; Pinto, A. C.; Gonzaga, D. T. G.; Ferreira, V. F. Syntheses of chromenes and chromanes via o-quinone methide intermediates. *J. Heterocycl. Chem.* **2009**, *46*, 1080−1097. For a representative example, see: (b) Majumdar, N.; Korthals, K. A.; Wulff, W. D. Simultaneous Synthesis of Both Rings of Chromenes via a Benzannulation/*o*-Quinone Methids Formation/Electrocyclization Cascade. *J. Am. Chem. Soc.* **2012**, *134*, 1357−1362. (c) Parker, K. A.; Mindt, T. L. Electrocyclic Ring Closure of the Enols of Vinyl Quinones. A 2*H*-Chromene Synthesis. *Org. Lett.* **2001**, *3*, 3875−3878.
(13) Chen, C.-y.; Dormer, P. G. Synthesis of Benzo[*b*]furans via CuI-Catalyzed Ring Closure. *J. Org. Chem.* **2005**, *70*, 6964−6967.
(14) Kuo, W.-L.; Huang, Y.-L.; Shen, C.-C.; Shieh, B.-J.; Chen, C.-C. Prenylated Benzoic Acids and Phenanthrenes from *Liparis nakaharai*. *J. Chin. Chem. Soc.* **2007**, *54*, 1359−1362.
(15) Bell, D.; Davies, M. R.; Geen, G. R.; Mann, I. S. Copper(I) Iodide: A Catalyst for the Improved Synthesis of Aryl Propargyl Ethers. *Synthesis* **1995**, *1995*, 707−712.
(16) Wang, X.; Lu, N.; Yang, Q.; Gong, D.; Lin, C.; Zhang, S.; Xi, M.; Gao, Y.; Wei, L.; Guo, Q.; You, Q. Studies on chemical modification and biology of a natural product, gambogic acid (III): Determination of the essential pharmacophore for biological activity. *Eur. J. Med. Chem.* **2011**, *46*, 1280−1290.
(17) Parisotto, S.; Deagostino, A. Synthesis of High Functionalized Allyl Alcohols from Vinyl Oxiranes and *N*-Tosylhydrazones via a Tsuji-Trost-Like "Palladium-Iodide" Catalyzed Coupling. *Org. Lett.* **2018**, *20*, 6891−6895.
(18) Gemal, A. L.; Luche, J. L. Lanthanoids in organic synthesis. 6. Reduction of α-enones by sodium borohydride in the presence of lanthanoid chlorides: synthetic and mechanistic aspects. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459.
(19) (a) Kraus, G. A.; Taschner, M. J. Model Studies for the Synthesis of Quassinoids. 1. Construction of the BCE Ring System. *J. Org. Chem.* **1980**, *45*, 1175−1176. (b) Kraus, G. A.; Roth, B. Synthetic Studies toward Verrucarol. 2. Synthesis of the AB Ring System. *J. Org. Chem.* **1980**, *45*, 4825−4830. (c) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. Oxidation of α,β-Unsaturated Aldehydes. *Tetrahedron* **1981**, *37*, 2091−2096.

https://dx.doi.org/10.1021/acs.orglett.0c00770
Org. Lett. XXXX, XXX, XXX−XXX