Investigating the Influence of Various Migratory Allyl Ethers on the Regioselectivity of the Aromatic Claisen Rearrangement

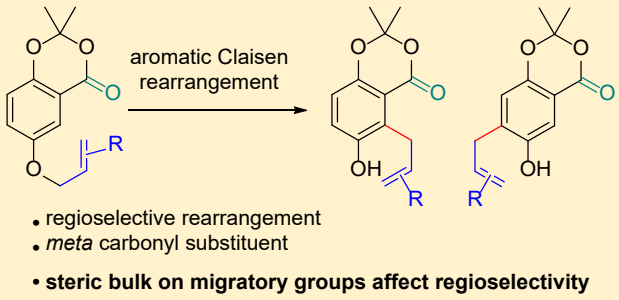
Logan E. Brown [1], Mitchell P. Croatt [1*]

1. University of North Carolina at Greensboro, Department of Chemistry and Biochemistry

Submitted: April 24th, 2023.

KEY WORDS: aromatic Claisen rearrangement, aryl allyl ether, benzopyran, regioselectivity

ABSTRACT: We report an investigation into the regioselectivity of the aromatic Claisen rearrangement within a novel asymmetric substrate that possesses an internal base *meta* to the aryl allyl ether position. We utilize various migratory aryl allyl ethers and aryl propargyl ethers to study how steric bulk influences the regioselectivity. Our results show that steric bulk does influence the regioselectivity of the aromatic Claisen rearrangement.



INTRODUCTION

The aromatic Claisen rearrangement was first described by German chemist Rainer Ludwig Claisen (1851-1930) in 1912.[1] The aromatic Claisen rearrangement is a 3,3-sigmatropic rearrangement that involves the isomerization of the allyl side chain of an allyl aryl ether to a γ,δ-unsaturated carbonyl, a non-aromatic product. The compound then undergoes tautomerization to rearomatize the ring with the final product being an *ortho*-substituted phenol (**Figure 1**).[1]

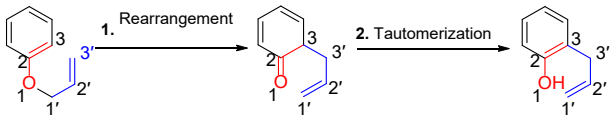


Figure 1: The Aromatic Claisen Rearrangement

The aromatic Claisen rearrangement has been studied extensively in organic synthesis as a useful tool to access γ,δ-unsaturated aldehydes, ketones, and highly functionalized phenolic systems.[2-5] In the Croatt lab, we are working with an asymmetric substrate that undergoes a regioselective rearrangement to the more sterically hindered position. The substrate is unique because it features a neighboring carbonyl that we hypothesize influences the regioselectivity of the rearrangement (**Figure 2**). The current hypothesis is that the neighboring carbonyl acts as an intramolecular base for tautomerization, promoting isomerization to the more sterically hindered ring position. There are many things that we believe will affect this regioselectivity: the electronics of the ring system, the identity of the base, and the steric bulk of the migratory group. Herein, we report our results into the investigation of various migratory allyl ethers and their effects on the regioselectivity of the Aromatic Claisen Rearrangement.

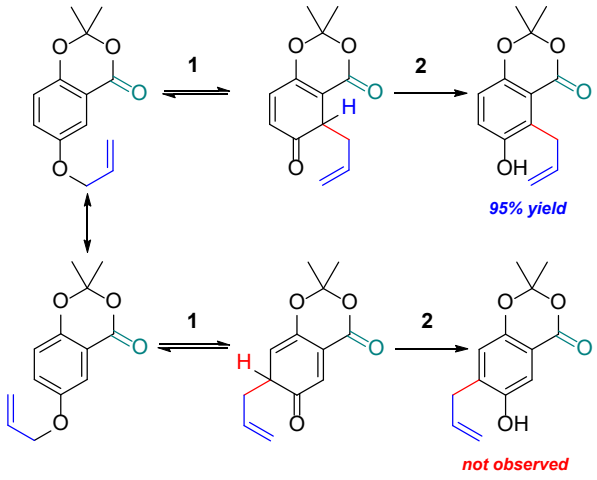


Figure 2: Regioselective Aromatic Claisen Rearrangement

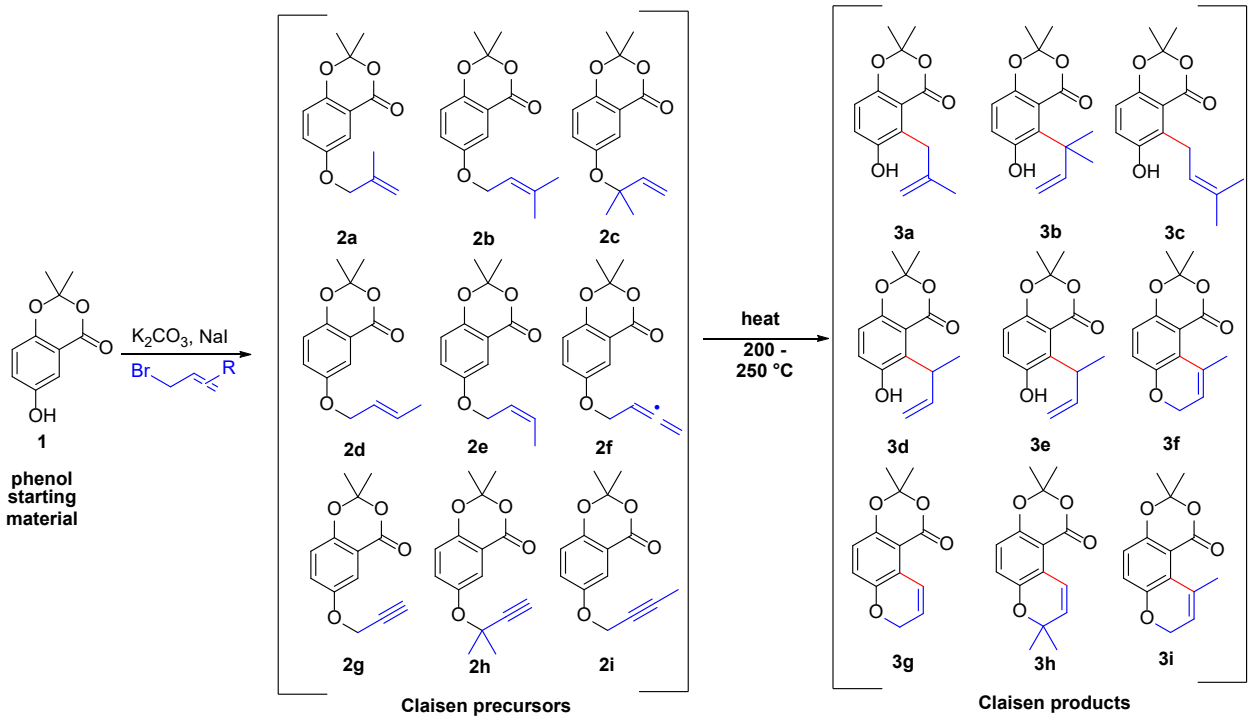
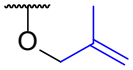
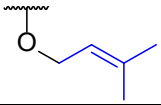
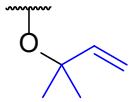
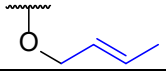
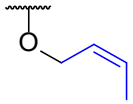
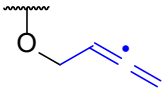
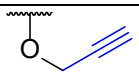
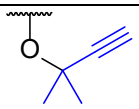
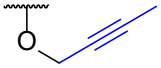


Figure 3: Our Substrate Scope for Mechanistic Analysis

Figure 3 shows the substrate scope utilized for the mechanistic analysis of the aromatic Claisen rearrangement. Substituents were specifically chosen to test how introducing steric bulk to various positions along the allyl migratory group would affect the regioselectivity. There are three such positions that steric bulk can be added along the allyl migratory group: the methylene carbon, the internal vinyl carbon, and the terminal vinyl carbon. Compound **2a** has a methyl substituent on the internal vinyl carbon. Compounds **2b**, **2d**, and **2e** have methyl substituents on the terminal vinyl carbon while **2i** has a methyl substituent on the terminal propargylic carbon. Compounds **2c** and **2h** have methyl substituents on the methylene position along the allyl migratory group. Compounds **2g-2i** are propargylic systems. Being propargylic, and therefore linear, the distance between the pi-system and the aromatic ring has increased. Compound **2f** explores the possibilities of an allene substituent. Our project has two specific aims, to synthesize the Claisen precursors, and to run each precursor through the Claisen rearrangement and quantify the regioselectivity of the various migratory groups. (**Figure 3**)

RESULTS AND DISCUSSION

Entry	Compound	Migratory Allyl Ether	Isomeric Ratio* (Hindered:Unhindered)	Yield
1	**2a**		3:1	20%
2	**2b**		0:1 *(hindered not observed)*	14%
3	**2c**		1:0	94%**
4	**2d**†		1:1	33%
5	**2e**††		1:9	11%
6	**2f**		1:0 *(hindered not observed)*	3%
7	**2g**		1:0 *(unhindered not observed)*	73%
8	**2h**		3:1	19%
9	**2i**		1:0 *(unhindered not observed)*	5%

*= Hindered product refers to the product where the migratory group has rearranged *ortho* to the lactone carbonyl. Unhindered refers to the product where the migratory group has rearranged *para* to the lactone carbonyl.

**= Crude Yield. The crude mixture was not purified.

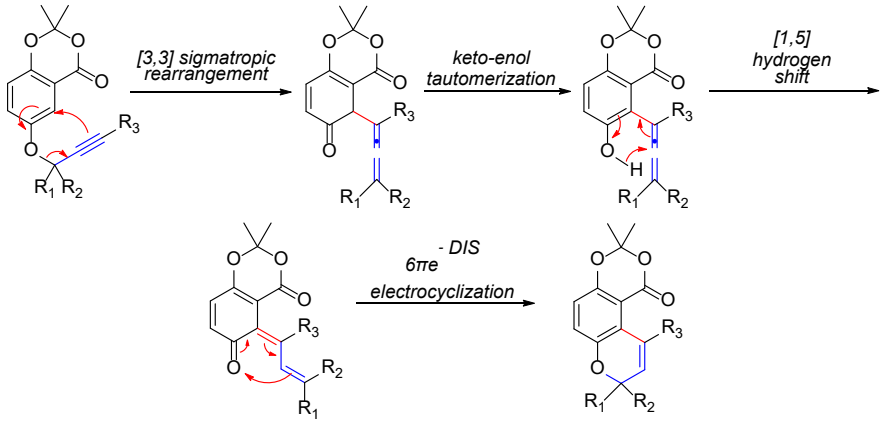
†= Due to the nature of the commercially available materials, synthesis of compound **2d** produced an inseparable mixture of *trans* and *cis* products in a 3:1 ratio, respectively. The *cis/trans* mixture was still utilized in the Claisen rearrangement.

††= Due to the nature of Lindlar's Hydrogenation, synthesis of compound **2e** produced an inseparable mixture of *cis* and *trans* products in a 22:1 ratio, respectively. Similar to above, the *cis/trans* mixture was still utilized in the Claisen rearrangement.

Figure 4: Regioselectivity of the Aromatic Claisen Rearrangement

Figure 4 details the results of the study on how steric bulk on different positions along the allyl group affect the regioselectivity of the aromatic Claisen rearrangement. As stated above, the different migratory groups were used because of the varying substituent placements. The model allyl system (**Figure 2**) had complete regioselectivity to the hindered side of the molecule. However, when substituting the internal vinyl hydrogen with a methyl group, as seen in compound **2a**, the regioselectivity drops as a 3:1 mixture was produced (**Figure 4**, entry 1). When substituting one of the terminal vinyl hydrogens with a methyl group, regardless of if the substituent is *cis* or *trans* to the phenolic scaffold, the regioselectivity also decreases (**Figure 4**, entries 4 and 5). When both terminal vinylic hydrogens are substituted with methyl groups, it is now completely regioselective to the unhindered side of the molecule (**Figure 4**, entry 2). This elucidates

a trend where substituents on the terminal vinyl position reduce the regioselectivity 3-fold more than substituents on the internal vinyl position for alkenyl systems.



Compound **2g** R_1, R_2, R_3 = H
Compound **2h** R_1, R_2 = Me, R_3 = H
Compound **2i** R_1, R_2, = H, R_3 = Me

Figure 5: Proposed Mechanistic Pathway for the Conversion of Aryl Propargyl Ethers into Benzopyrans[6]

Propargylic systems differ due to the hybridization of the carbons. In alkenes, carbons are sp^2 hybridized. Their preferred bond angles are 120° as they are trigonal planar. However, alkynyl carbons are *sp* hybridized, and their preferred bond angles are 180°, making them linear. Due to this, the distance between the aromatic ring and the reacting pi-system of the migratory group is increased. Propargylic systems also produce benzopyran structures, as shown in **Figure 3**. The mechanism of formation of these benzopyran products was described by Houk et al in 2021. (**Figure 5**).[6] Also, due to the nature of alkynyl systems, only two positions can be modified: the methylene position, and the terminal propargyl position. A simple propargyl system, exemplified by compound **2g**, maintains the regioselectivity of the model allyl system, exclusively migrating to the more hindered side of the system. However, modifications made to the methylene carbon reduce regioselectivity, as shown in the Claisen of compound **2h** (**Figure 4**, entry 8). Modifications made to the terminal propargyl carbon does not reduce the regioselectivity, as only formation of the more hindered product is observed (**Figure 4**, entry 9). This trend differs from alkenyl systems which lost regioselectivity when methyl groups were substituted in for the terminal vinyl hydrogens (**Figure 4**).

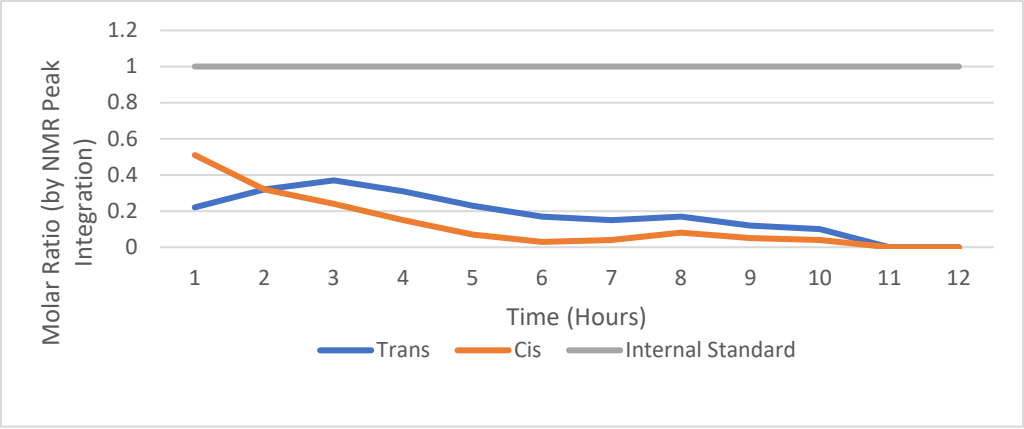


Figure 6: Molar Ratio of Cis and Trans Isomers over the Course of the Claisen Rearrangement

Figure 6 shows evidence of the equilibrium between the γ,δ-unsaturated carbonyl intermediate and the starting aryl allyl ether. Compounds **2e** and **2d** were subject to the Claisen as a 22:1 mixture, respectively. As the rearrangement proceeds, there is a notable increase in concentration of the trans alkene isomer during hours 1-3 of the reaction because trans alkenes are thermodynamically favored over cis alkenes. This equilibrium is important as our hypothesis depends on this equilibrium being present for regioselectivity to favor the more sterically hindered product formation.

CONCLUSION

The aromatic Claisen rearrangement has been studied heavily in synthetic chemistry. Our asymmetric system has a lactone carbonyl *meta* to the migratory allyl ether. We hypothesize that it influences this regioselectivity by rapidly speeding up the tautomerization step after rearrangement to the more hindered position (**Figure 2**). Here, we also proved that the γ,δ-unsaturated carbonyl intermediate is in equilibrium with the aryl allyl ether starting material (**Figure 6**). Due to the increased rate of tautomerization of the γ,δ-unsaturated carbonyl, products of this aromatic Claisen rearrangement tend to favor migration to the more sterically hindered side of the molecule. In this project, we explored the effects of migratory groups with varying steric bulk at different positions on this regioselectivity first by synthesizing these aryl allyl ethers and subjecting them to common Claisen conditions. As steric bulk increased on these migratory groups, regioselectivity for the more sterically hindered position decreased. Although this does not directly support the hypothesis in regard to the *meta* carbonyl, it clearly shows a correlation between steric bulk on the migratory groups and regioselectivity of the aromatic Claisen rearrangement. However, this is only a small piece of the puzzle as there are multiple other lines of investigation being performed within the Croatt Research Group. We are confident that we will elucidate the importance of the tautomerization step within the aromatic Claisen rearrangement.

ACKNOWLEDGMENTS

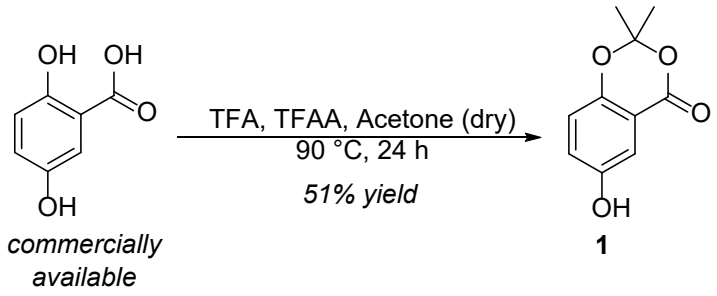
The author is grateful for the funding provided by the University of North Carolina at Greensboro MARC-U-STAR Program, NIH: T34GM113860. Thank you to Dr. Mitchell P. Croatt*† for project advising, Dr. Franklin Moy† for assistance with NMR, Dr. Tian Li† for helping with mass spectroscopy, Abe "the Cardinal" Ustoyev† and Dr. Khyarul "Fahim" Alam† for in-lab mentorship, Emily J. Ramirez† and Emily J. Guin† for in lab assistance, and the other Claisen Project members: Tangela C. "the Cardinal" Johnson†, David K. "the Cardinal" Tanas†, Harris H. Khan†, Runzi "Didi" Li†, and Gurjant Sekhon†.

† = Affiliated with the University of North Carolina at Greensboro, Department of Chemistry and Biochemistry

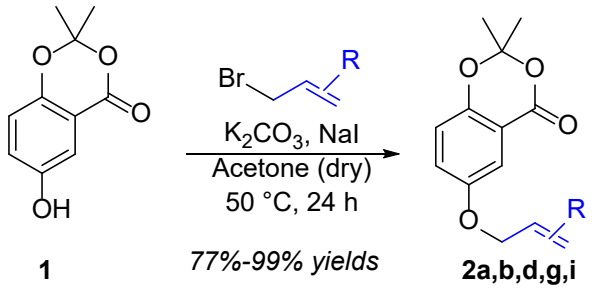
ANALYTICAL METHODS

^{1}H Nuclear Magnetic Resonance was used to quantify regioselectivity through the integration of the signals that correlate to the protons along the allyl groups and comparing them with the signals of aromatic protons. Because the splitting pattern of each isomer produced is different, they can be compared easily to obtain an isomeric ratio used to quantify the regioselectivity of each compound. 400 MHz and 500 MHz machines were utilized in this study. Crude NMR spectra was studied to avoid data variation due to the fact that material is always inevitably lost during flash column chromatography. However, if regioselectivity could not be quantified through this method, then purification took place before quantifying the regioselectivity.

EXPERIMENTAL SYNTHETIC METHODS

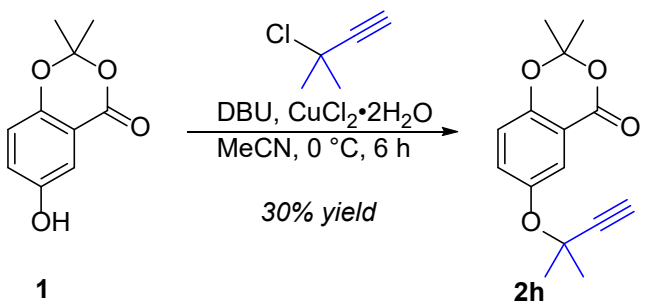


Synthesis of 6-hydroxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one: To a stirred ice-cold suspension of 2,5-dihydroxybenzoic acid (5 g, 32.44 mmol) in trifluoroacetic acid (0.79 M), trifluoroacetic anhydride (31.6 mL, 227.08 mmol) was added dropwise followed by addition of dry acetone (16.9 mL, 227.08 mmol). The reaction mixture was stirred at 90 °C under reflux for 24 hours before it was allowed to cool to room temperature and subsequently concentrated under reduced pressure. The resulting crude mixture was dissolved in ethyl acetate, extracted with DI water (x3) and saturated sodium bicarbonate (x2) and subsequently dried with brine and anhydrous sodium sulfate. The mixture was separated via vacuum filtration and concentrated under reduced pressure. The mixture was subsequently dissolved into silica gel and purified using automated silica gel chromatography (40 g HP Silica Column, CV = 58.9 mL, gradient of 5% from 0-35% EA:hexanes). The product eluted at 25% to yield the title compound (6-hydroxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one, 3.21 g, 16.54 mmol, 51% yield) as an orange crystalline solid.

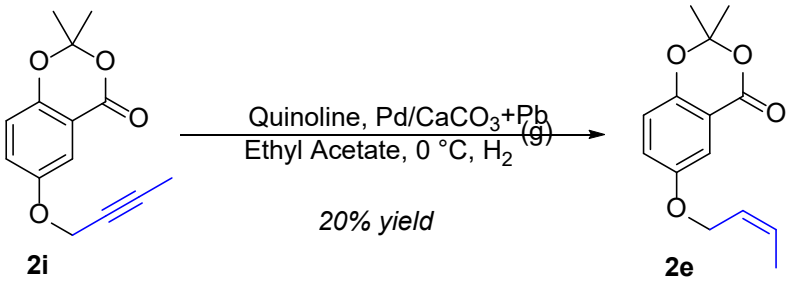


General Procedure for the Synthesis of Aryl Allyl Ethers[7]: Anhydrous potassium carbonate (4.0 eq) was added to a flask with a magnetic stir bar and 6-hydroxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (1.0 eq) followed by the addition of sodium iodide (catalytic, 10-40 mol%*). The resulting powder mixture was dissolved in dry acetone (0.5 M) before addition of the allylic bromide (2.5 eq). The reaction mixture was brought to 50 °C and left to stir until completion, as monitored by thin layer chromatography. The crude mixture was filtered via vacuum filtration and washed with ethyl acetate. The filtrate was collected and washed twice with DI water, before subsequent drying with brine and anhydrous sodium sulfate. The mixture was concentrated via reduced pressure and purified via silica gel column chromatography to yield the aryl allyl ethers.

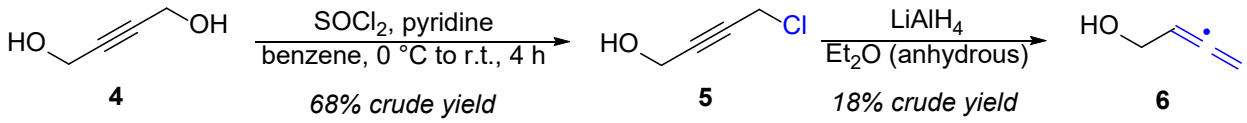
*= Increase in catalyst amount shortened reaction time to completion without a detriment to yields.



Synthesis of 2,2-dimethyl-6-((2-methylbut-3-yn-2-yl)oxy)-4*H*-benzo[*d*][1,3]dioxin-4-one[8]: To a solution of 6-hydroxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (4000 mg, 20.60 mmol) and copper(II) chloride (69.90 mg, 0.41 mmol) in anhydrous acetonitrile (40 mL, 0.52 M) under an argon atmosphere at 0 °C, 1,8-diazabicyclo[5.4.0]undec-7-ene (3997.05 µL, 4076.99 mg, 26.78 mmol) was added dropwise followed by dropwise addition of propargyl chloride (3-chloro-3-methylbut-1-yne, 2082.65 µL, 1901.46 mg, 18.54 mmol) over 5 h. The reaction was allowed to stir at 0 °C until completion monitored by thin layer chromatography. The crude mixture was concentrated under reduced pressure and extracted with toluene and water. The organic extract was washed with 2 M hydrochloric acid (3 times, 60 mL), saturated sodium bicarbonate (3 times, 60 mL) before it was dried with brine and anhydrous sodium sulfate. The organic extract was filtered, concentrated under reduced pressure, and purified via silica gel column chromatography (isocratic 15% ether:pentane, CV = 204 mL, product elutes at 2.47 CV) to yield 2,2-dimethyl-6-((2-methylbut-3-yn-2-yl)oxy)-4*H*-benzo[*d*][1,3]dioxin-4-one (1591.4 mg, 6.11 mmol, 30% yield) as a yellow oil.

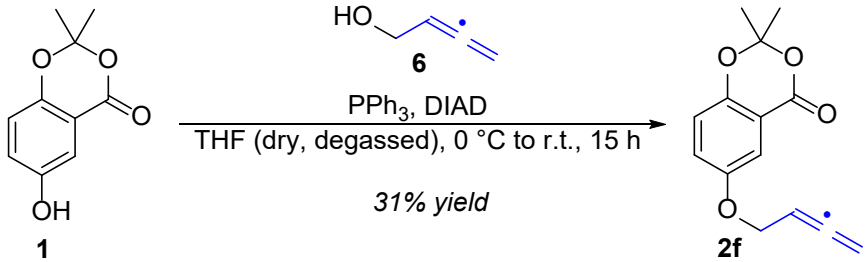


Synthesis of (*Z*)-6-(but-2-en-1-yloxy)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one[9]: Quinoline (5.67 µL, 5.1 mg, 0.04 mmol) was added to a round bottom flask containing a suspension of palladium on calcium carbonate poisoned with lead (5% weight, 15.8 mg, 0.026 mmol) in ethyl acetate (6 mL). The flask was evacuated and back filled with H_2 gas three times before addition of a solution of 6-(but-2-yn-1-yloxy)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (125 mg, 0.51 mmol) in ethyl acetate (5 mL) via syringe. The reaction mixture was stirred at 0 °C under an H_2 atmosphere (balloon pressure) until full consumption of starting material was observed via thin layer chromatography. The mixture was then filtered through a pad of celite and washed with ethyl acetate. The resulting filtrate was concentrated under reduced pressure and purified via column chromatography (gradient of 2% from 10-16%, product eluted at 12%) to yield a mixture of (*Z*)-6-(but-2-en-1-yloxy)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one and (*E*)-6-(but-2-en-1-yloxy)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one in a 22 to 1 ratio (25.3 mg, 0.10 mmol, combined yields), respectively, as a yellow oil.

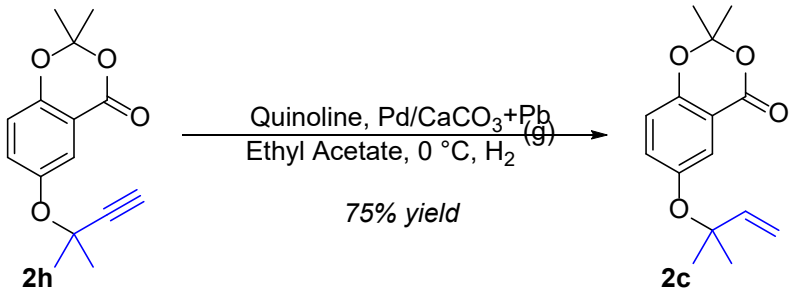


Synthesis of 4-chlorobut-2-yn-1-ol[10]: A three-necked flash equipped with a dropping funnel was charged with 1,4-butynediol (5000 mg, 58.08 mmol) and benzene (25 mL, 2.5 M) before pyridine (5.17 mL, 5052.91 mg, 63.88 mmol) was added in one portion. The resulting was cooled to 0 °C before the dropwise addition of thionyl chloride (4.63 mL, 7599.16 mg, 63.88 mmol) via the dropping funnel over a period of 10 minutes. After evolution of hydrochloride gas ceased, the mixture was further stirred at room temperature overnight. The mixture was then quenched by pouring onto ice DI water followed by an extraction with ether (x2). The organic layers were washed with DI water (x1), neutralized by the addition of sodium bicarbonate and sodium carbonate, dried over sodium sulfate, and concentrated under reduced pressure. The crude was taken to the next step without purification.

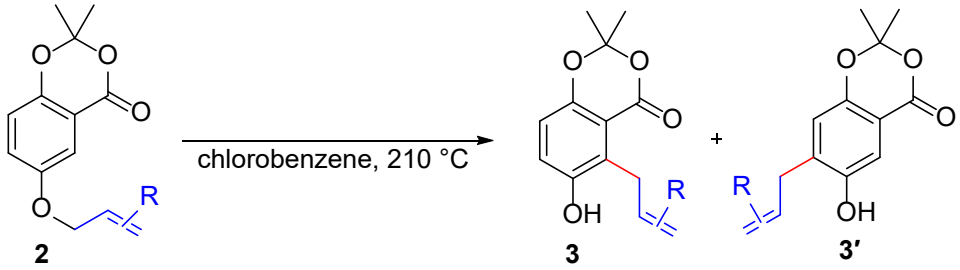
Synthesis of buta-2,3-dien-1-ol[10]: Lithium aluminum hydride (3630 mg, 95.67 mmol) was added portion-wise to a flask of 4-chlorobut-2-yn-1-ol (1000 mg, 9.57 mmol) dissolved in anhydrous ether (5.5 mL, 0.45 M) at 0 °C. After addition was complete, the mixture was allowed to warm to room temperature and stirred for an additional 30 minutes before it was cooled to 0 °C again and quenched by the addition of solid sodium sulfate decahydrate (very slow!) until no more smoke was produced followed by the addition of a saturated aqueous solution of potassium sodium tartrate tetrahydrate (Rochelle's Salt). The resulting slurry was left to stir overnight. The crude mixture was filtered through a pad of celite and rinsed with ether before being concentrated under reduced pressure. The concentrated filtrate containing buta-2,3-dien-1-ol was carried on to the next step without purification.



Synthesis of 6-(buta-2,3-dien-1-yloxy)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one[11]: To a flame dried flask equipped with a stir bar, solid triphenylphosphine (456.3 mg, 1.74 mmol, 1.5 eq) was added followed by subsequent addition of 6-hydroxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (225.3 mg, 1.16 mmol, 1.0 eq) and buta-2,3-dien-1-ol (122.6 mg, 1.75 mmol, 1.5 eq) dissolved in dry and degassed tetrahydrofuran (3.31 mL, 0.35 M). The flask was sealed and flushed with N_2 before being cooled to 0 °C, and diisopropyl azodicarboxylate (351.84 mg, 341.59 µL, 1.74 mmol, 1.5 eq) was added dropwise. The resulting reaction mixture was allowed to warm to room temperature and left to stir overnight. Once the reaction was complete, as monitored by thin layer chromatography, the crude was concentrated and redissolved in ethyl acetate, washed with sodium hydroxide (2x, 2 M), DI water (2x), then dried with brine and sodium sulfate. The product was purified via column chromatography (10% isocratic EA/Hex, CV = 60 mL, product elutes after 2 CV) to yield 6-(buta-2,3-dien-1-yloxy)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (87.3 mg, 0.35 mmol, 31% yield) as a clear oil.



Synthesis of 2,2-dimethyl-6-((2-methylbut-3-en-2-yl)oxy)-4*H*-benzo[*d*][1,3]dioxin-4-one[9]: Quinoline (5.67 µL, 5.1 mg, 0.04 mmol) was added to a round bottom flask containing a suspension of palladium on calcium carbonate poisoned with lead (5% weight, 15.8 mg, 0.026 mmol) in ethyl acetate (6 mL). The flask was evacuated and back filled with H_2 gas three times before addition of a solution of 2,2-dimethyl-6-((2-methylbut-3-yn-2-yl)oxy)-4*H*-benzo[*d*][1,3]dioxin-4-one (125 mg, 0.51 mmol) in ethyl acetate (5 mL) via syringe. The reaction mixture was stirred at 0 °C under an H_2 atmosphere (balloon pressure) until full consumption of starting material was observed via thin layer chromatography. The mixture was then filtered through a pad of celite and washed with ethyl acetate. The resulting filtrate was concentrated under reduced pressure and purified via column chromatography (isocratic 10%, product eluted after 2.26 CV) to yield 2,2-dimethyl-6-((2-methylbut-3-en-2-yl)oxy)-4*H*-benzo[*d*][1,3]dioxin-4-one (1.13 g, 4.31 mmol, inseparable impurity exists at a 0.13:1 molar ratio by NMR) as a yellow oil.



General Procedure for the Claisen Rearrangement: A solution of aryl allyl (or propargyl) ether dissolved in chlorobenzene (5 mL) was subjected to 210 °C in a microwave reactor (300 W) until complete conversion of starting material was observed via thin layer chromatography. The resulting crude mixture was dried under N_2 and further dried via reduced pressure to ensure complete removal of chlorobenzene. The mixture was purified via column chromatography to yield the *ortho*-substituted phenol or benzopyran products.

REFERENCES

1. Claisen, L. Über Umlagerung von Phenol-Allyläthern in C-Allyl-Phenole. *Ber. Dtsch. Chem. Ges.* **1912**, *45* (3), 3157–3166.
2. Chiu, C. K.-F.; Berliner, M. A.; Li, Z. B. 2.13 - Alkenyl and Aryl Chalcogenides: Oxygen-Based Functional Groups. *In Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier: Oxford, **2005**; pp 595–658.
3. Handa, S. 3.01 - Aldehydes: Alkyl Aldehydes. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier: Oxford, **2005**; pp 1–58.

4. Parkes, K. E. B.; Richardson, S. K. 3.04 - Ketones: Dialkyl Ketones. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Elsevier Science: Oxford, **1995**; pp 111–204.
5. Kotha, S.; Gunta, R. A New Synthetic Strategy to 2,3-Diallyl-1,4-Quinones via One-Pot Double Claisen Rearrangement and Retro Diels–Alder Reaction. *Tetrahedron Lett*. **2016**, *57* (27), 3021–3023.
6. Ramirez, M.; Vece, V.; Hanessian, S.; Houk, K. N. Computation and Further Experimental Explorations of the Competing Cascades Following Claisen Rearrangements of Aryl Propargyl Ethers: Substituent Effects on Reactivity and Regioselectivity. *J. Org. Chem.* **2021**, *86*, 17955-17964.
7. Williamson, A. XLV. Theory of Ætherification. *Philos. Mag. (1798-1977)***. 1850**, *37* (251), 350–356.
8. Lucas, C. L.; Lygo, B.; Blake, A. J.; Lewis, W.; Moody, C. J. Regioselectivity of the Claisen Rearrangement in meta-Allyloxy Aryl Ketones: An Experimental and Computational Study, and Application in the Synthesis of (R)-(−)-Pestalotheol D. *Chem. - Eur. J.* **2011**, *17* (6), 1972-1978.
9. Liu, J.; Miotto, R. J.; Segard, J.; Erb, A. M.; Aponick, A. Catalytic Dehydrative Lactonization of Allylic Alcohols. *Org. Lett.* **2018**, *20* (10), 3034-3038.
10. Grugel, C. P.; Breit, B. Rhodium-Catalyzed Diastereo- and Enantioselective Tandem Spirocyclization/ Reduction of 3-Allenylindoles: Access to Functionalized Vinylic Spiroindolines. *Org. Lett.* **2019**, *21* (23), 9672-9676.
11. Mitsunobu, O.; Yamada, M. Preparation of Esters of Carboxylic and Phosphoric Acid via Quaternary Phosphonium Salts. *Bull. Chem. Soc. Jpn.* **1967**, *40* (10), 2380–2382.