

# Synthesis of Highly Substituted Phenols and Benzenes with Complete Regiochemical Control

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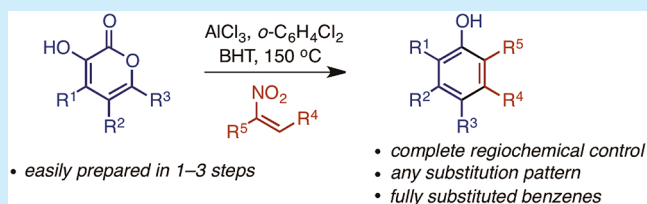


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**ABSTRACT:** Substituted phenols are requisite molecules for human health, agriculture, and diverse synthetic materials. We report a chemical synthesis of phenols, including penta-substituted phenols, that accommodates programmable substitution at any position. This method uses a one-step conversion of readily available hydroxypyrrone and nitroalkene starting materials to give phenols with complete regiochemical control and in high chemical yield. Additionally, the phenols can be converted into highly and even fully substituted benzenes.



Phenols are indispensable molecules. Substituted phenols represent essential pharmaceuticals, such as the analgesic morphine, the leukemia drug ecteinascidin, and the hormonal birth control estrogen (Figure 1).<sup>1</sup> Substituted phenols are also

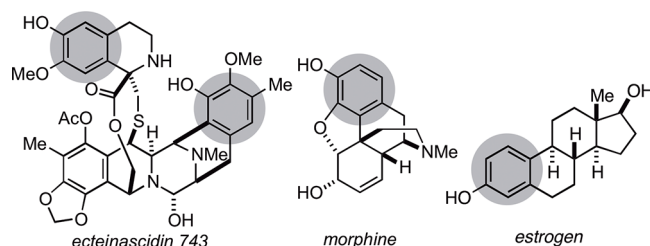


Figure 1. Pharmaceutical phenols.

common agrochemicals (e.g., the citrus fungicide 2-phenyl-phenol and the food additive butylated hydroxytoluene); many are important substructures of biological polymers (e.g., lignin, tyrosine) and are used in human-made polymers such as the ubiquitous phenolic resin plastics.<sup>2</sup> The properties of phenolic molecules are substantially influenced by the substitution on the phenolic ring.<sup>3</sup> For these reasons, the synthesis of phenols with control of substituent regiochemistry is of paramount interest to organic, medicinal, and polymer chemists.

The chemical synthesis of phenols with complex substitution patterns is an enduring challenge, and multiple strategies have emerged for this task. However, current methods have substantial limitations. For example, classic alkylations (e.g., Friedel–Crafts alkylations) of unprotected phenols give phenyl ethers, rather than substituted phenols.<sup>4</sup> Substitution of phenyl ethers gives multiple products as a result of limited regioselectivity (*ortho*- vs *para*-substitution) accompanied by overalkylation products.<sup>4</sup>

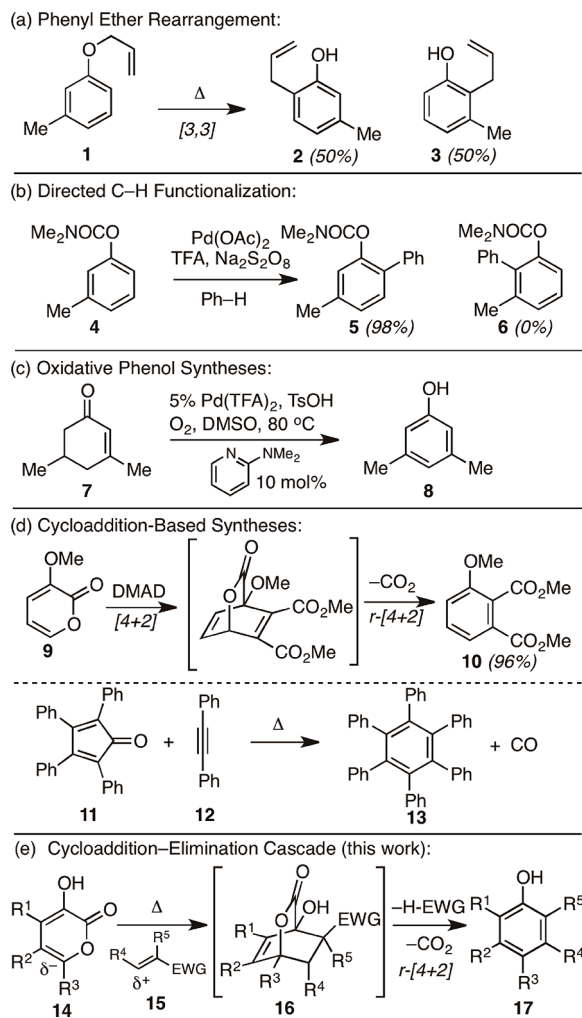
When regioselective phenol synthesis is required, a common strategy features rearrangement of *O*-bound groups to the adjacent *ortho*-position. In a classic example, allyl phenyl ethers (1) undergo Claisen rearrangements to reliably give *ortho*-substituted products 2 and 3 (Scheme 1a). When both *ortho*-positions are unsubstituted, selectivities (2 vs 3) tend to be low.<sup>5</sup> Other classic reactions (e.g., the Fries rearrangement) also follow this trend.<sup>6</sup>

There has been a flurry of recent activity directed at C–H bond functionalization of phenol derivatives.<sup>7</sup> As one example, phenol derivative 4 contains a suitable directing group, which facilitates Pd-catalyzed bond formation at the *ortho*-position (Scheme 1b).<sup>8</sup> In substrates such as 4 with two available *ortho*-positions, the contra-steric product 5 is obtained, and the product of vicinal substitution (6) is not observed. To summarize decades of work on substitution of phenol derivatives: such reactions produce limited regiochemical outcomes that disfavor vicinal substitution, making highly substituted phenols inaccessible by these routes.

Limitations associated with substitution-based strategies for phenol syntheses have spawned a variety of alternatives. One strategy is to oxidize a corresponding six-membered carbocycle to a phenol. For example, Stahl reported that cyclohexenone 7 undergoes oxidative aromatization to give substituted phenol 8 (Scheme 1c).<sup>9</sup> The challenge of preparing the substituted phenol now becomes a challenge of preparing the substituted starting material, and very few phenols with vicinal substitution

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## Scheme 1. Synthesis of Substituted Phenols



have been reported using this method. Siegel also discovered that substituted benzenes can be oxidized to phenols by direct oxidation;<sup>10</sup> however, oxidation regiochemistry is based on C–H bond strength, and regioselectivities can be moderate. These oxidative methods provide useful access to phenol products from the corresponding benzene; however, the above methods have not resulted in a phenol synthesis that produces highly substituted (i.e., penta-substituted) phenols with control of substitution patterns.

A final strategy is to use a cycloaddition cascade to prepare the phenol. The Diels–Alder reaction is commonly featured in such cascades. A substituted diene, such as pyrone **9** (Scheme 1d), or other weakly aromatic heterocycle, reacts with a dienophile, most often an alkyne, to give the phenyl ether **10**.<sup>11</sup> This reaction proceeds by a Diels–Alder–retro-Diels–Alder sequence. Nonsymmetric internal alkynes are not particularly polarized, and low regioselectivities are observed in the initial Diels–Alder event. Regioselectivities aside, these reactions are predominantly used to prepare simple mono- and disubstituted phenols.

Diels–Alder reactions of highly reactive dienes are well-known to undergo cycloaddition with alkynes to give benzenes with high levels of substitution,<sup>12</sup> including hexa-substituted benzenes. For example, heating 2,3,4,5-tetraphenyl cyclopentadiene (**11**) with diphenylacetylene (**12**) gives hexaphenyl benzene (**13**, Scheme 1d).<sup>13</sup> The limitation with these

reactions is the lack of regioselectivity; both the diene and dienophile lack strong electronic polarization, and the reaction gives either symmetric products or regiochemical mixtures that require tedious separations.<sup>12</sup> Nonetheless, these cycloadditions display tantalizing reactivity: they represent single-step transformations that bring together highly substituted coupling partners to deliver benzenes with substitution at all six carbons.

We sought to address the long-standing gap in the controlled synthesis of highly substituted phenols. Our research in this area is directed at identifying a strategy for substituted phenol and benzene synthesis that overcomes the inherent regiochemical limitations associated with substitution strategies and delivers multiple substituents on the product benzenoid ring (Scheme 1e).

We hypothesized that the reactivity and regioselectivity limitations of the Diels–Alder-based strategies discussed above could be overcome if both coupling partners are electronically polarized. Specifically, starting materials **14** and **15** would show both enhanced reactivity and give programmable regioselectivity in the products. An alkyne-equivalent<sup>14–16</sup> dienophile (**15**) would need to be identified that facilitates the initial Diels–Alder cycloaddition at lower temperatures and provides regioselectivity in the cycloaddition giving **16**. The activating group would have to double as a leaving group, undergoing elimination, prior to the final retro-cycloaddition that liberates CO<sub>2</sub> and delivers the product **17**.

Initial experimentation focused on combining a hydroxypyryone diene **18** with a vinyl sulfone dienophile (**29**, Table 1).<sup>17</sup>

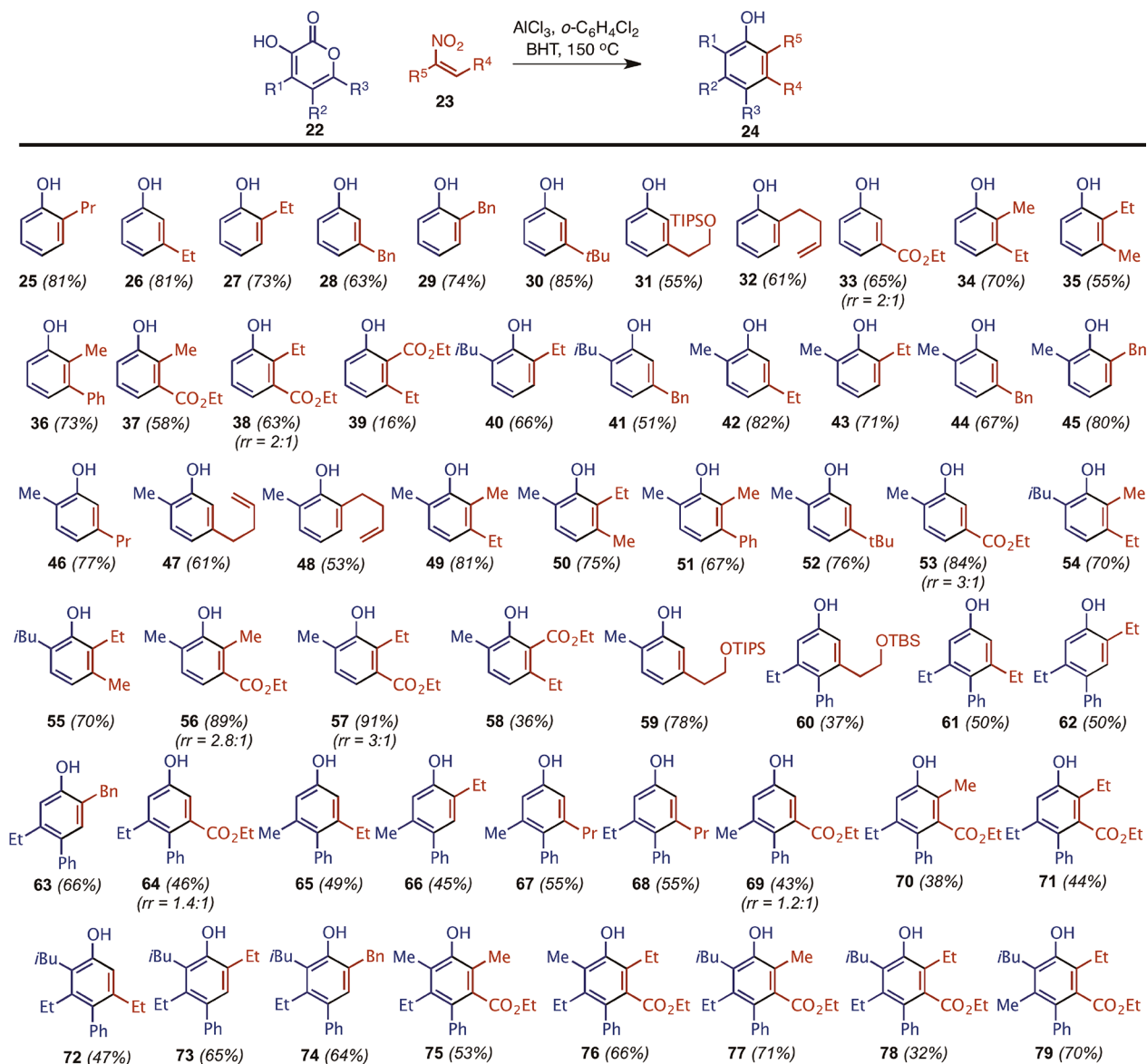
Table 1. Development of the Phenol Synthesis

entry	alkene	reagent	temp (°C)	yield (%)
1	<b>19</b>	none	170	7
2	<b>21</b>	none	150	56
3	<b>21</b>	LiClO <sub>4</sub> (1 equiv)	80	35
4	<b>21</b>	SiO <sub>2</sub> (1 equiv)	150	65
5	<b>21</b>	FeCl <sub>3</sub> (10 mol %)	150	65
6	<b>21</b>	ZnCl <sub>2</sub> (10 mol %)	150	54
7	<b>21</b>	Zn(OTf) <sub>2</sub> (10 mol %)	150	52
8	<b>21</b>	1-phenyl-3-(2-pyridyl)urea (10 mol %)	150	27
9	<b>21</b>	quinidine (1 equiv)	150	0
10	<b>21</b>	AlCl <sub>3</sub> (10 mol %)	150	76
11	<b>21</b>	AlCl <sub>3</sub> (10 mol %), BHT (10 mol %)	150	85

Both coupling partners are suitably polarized such that single regioisomeric phenol **20** is formed. However, initial experiments revealed that successful cycloadditions required high temperatures, and substantial decomposition of the reactants was observed. The requirement of forcing conditions was attributed to sluggish reactivity of the vinyl sulfone, and we sought a more reactive dienophile.

Nitroalkenes are potent dienophiles,<sup>18,19</sup> and we investigated the cycloaddition cascade with nitroalkene **21** (Table 1, entry 2).<sup>20</sup> Gratifyingly, the cycloaddition cascade was successful, and it occurred at relatively mild temperatures. Phenol **20** was observed as the major product as a single regioisomer, albeit in

Scheme 2. Substituted Phenol Synthesis



moderate yield. To the best of our knowledge this represents the first reaction of a pyrone and a nitroalkene to give a benzene product.

Diels–Alder reactions can be accelerated through catalysis.<sup>21</sup> One common paradigm involves Lewis acid (LUMO lowering) activation of the dienophile. Conditions known to activate nitroalkenes gave little rate acceleration (Table 1, entries 3–8). Alternatively, Diels–Alder reactions of hydroxypyrylone dienes can also be accelerated by activation of the diene. Partial or full deprotonation of the hydroxyl group increases the reactivity of the diene, possibly through an alkoxide anion or by promoting a stepwise Diels–Alder process.<sup>22</sup> For example, cinchona-based alkaloids, such as quinidine, are known to catalyze hydroxypyrylone Diels–Alder reactions.<sup>22</sup> However, little improvement in the reaction of **18** and **21** was observed in the presence of quinidine (entry 9). We surveyed additional Lewis acids that could complex and activate the hydroxypyrylone. It was discovered that  $\text{AlCl}_3$  promoted the reaction such that it occurred on useful time scales and in high yield (entry 10). Finally, the best chemical yields were obtained in the

presence of a radical inhibitor, butylated hydroxytoluene (BHT), which likely prevents decomposition of the reagents at elevated temperatures (entry 11). The reaction delivered one observable phenol isomer by NMR. Analysis by gas chromatography indicated that the regioisomer ratio (rr) was 33:1. Activation appears to involve deprotonation of the hydroxyl group, and the related dienes 3-methylpyrone, 3-methoxypyrylone, and 3-dibutylaminopyrylone did not react with **21** under identical conditions with  $\text{AlCl}_3$ .

The regioisomeric nitroalkene (**23**,  $R^4 = \text{H}$ ,  $R^5 = \text{Pr}$ ) was then subjected to our optimal reaction conditions (Scheme 2). The regioisomeric *ortho*-substituted phenol **25** was obtained as a single observable product (rr = 125:1, GC). This result demonstrated that a regiospecific synthesis of phenols could be realized through a cascade Diels–Alder/elimination/retro-Diels–Alder process.

The phenol synthesis was further investigated using an expanded set of coupling partners.<sup>23</sup> Our general reaction conditions ( $150\text{ }^\circ\text{C}$ , 16 h, 0.1 equiv of BHT) were used in most cases. Less hindered phenols were often formed with

shorter reaction times, and more hindered phenols occasionally required slightly elevated temperatures (i.e., 180 °C) or longer reaction times (e.g., 24 h). See [Supporting Information](#) for details.

Simple nitroalkenes bearing a single alkyl group readily participated in the reaction, and the same regioselectivity was observed. Isomeric nitroalkenes bearing alkyl groups gave regioisomeric pairs of products (**26** and **27**; **28** and **29**). Bulky substituents were tolerated on the nitroalkene (**30**), as well as silyl ethers (**31**), and unactivated alkenes (**32**). When the nitroalkene dienophile contains an additional electron-withdrawing group that competes for polarization of the dieneophile, the nitro group still controls the regioselectivity, but the reaction occasionally showed decreased regioselectivity (**33**, *rr* = 2:1).<sup>24</sup>

Nitroalkenes with increased substitution (**23**,  $R^4$  and  $R^5 \neq H$ ) also participated in the reaction to give 2,3-disubstituted phenols. Disubstituted phenol **34** was obtained as a single observable (NMR) isomer. As above, the reaction was regioselective, and regioisomeric phenol **35** was produced selectively. Note that such 2,3-disubstituted phenols are *not* products obtained from substitution of either 2-alkylphenols or 3-alkylphenols. Phenol **34** was previously prepared in six steps featuring a ring-closing metathesis to construct the six-membered ring,<sup>25</sup> and isomer **35** has not been prepared previously. Other nitroalkenes bearing two substituents participated in the phenol synthesis, and aromatic (**36**) and ester (**37**, **38**, and **39**) groups are well tolerated. As above, when the nitroalkene bears an ester group, the nitro functional group dictates the major regioisomer; however, when the ester competes for alkene polarization (**38**), the regioisomer ratio can be lower. When the ester and nitro groups are located on the same carbon, the regioselectivity is high (**39**); however, the dienophile was very reactive and prone to decomposition.

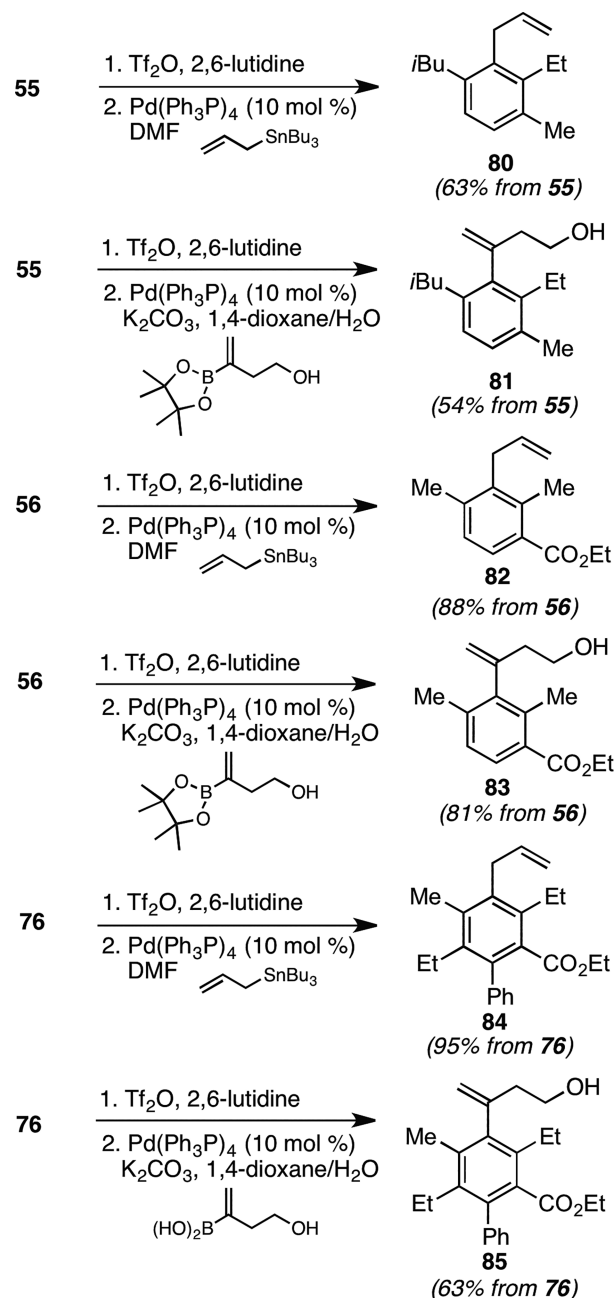
Higher substitution on the pyrone was also well tolerated. 3-Hydroxypyrene (**18**) could be regioselectively transformed to 4-alkyl-3-hydroxy-2-pyrones in two steps (**22**,  $R^1 = \text{alkyl}$ ; see [Supporting Information](#)). These substrates also underwent the pericyclic cascade reaction to give phenols in good yields (**40**–**59**). As above, the reaction was regioselective with respect to the nitroalkene dienophile and regioisomeric pairs could be prepared with nitroalkenes bearing one alkyl group (**42** and **43**; **44** and **45**; **47** and **48**), or with two alkyl groups (**49** and **50**; **54** and **55**; **57** and **58**). The reaction successfully prepared a variety of other 2,5-disubstituted, 2,6-disubstituted, and 2,5,6-trisubstituted phenols with control of substituent regiochemistry.

Matsuda's one-step Rh-catalyzed synthesis of pyrones was used to prepare 5,6-disubstituted 3-hydroxypyrones (**22**,  $R^2$  and  $R^3 \neq H$ ).<sup>26</sup> These pyrones reacted to give 3,4,5-trisubstituted or 3,4,6-trisubstituted phenols (**60**–**69**). As before the reaction gives pairs of phenols with regioselectivity (**61** and **62**; **65** and **66**) based on the choice of nitroalkene starting material. Reaction with more substituted nitroalkenes gave tetrasubstituted phenols **70** and **71**. Finally, fully substituted pyrones were prepared (**22**,  $R^1$ ,  $R^2$ , and  $R^3 \neq H$ ; see [Supporting Information](#)), and they reacted with nitroalkenes to give tetrasubstituted phenols (**72**–**74**) and pentasubstituted (i.e., fully substituted) phenols **75**–**79** with complete control of regiochemistry. This method represents a direct synthesis of substituted benzene rings with up to six different substituents with complete control of substitution

pattern. As such, this represents a major advance in the preparation of highly substituted benzenoid molecules.

A major reason for the interest in phenols is their ability to participate in bond formations using the hydroxy functional group. This allows for the conversion of phenols into substituted benzenes of interest ([Scheme 3](#)). We evaluated

**Scheme 3. Synthesis of Substituted Benzenes**



the ability of our highly substituted phenols to couple with organometallic reagents to give highly substituted benzenes. Phenol **55** underwent Stille cross-coupling<sup>27</sup> to give allyl benzene **80**, and it participated in a Suzuki–Miyaura coupling<sup>28</sup> to give **81**. The ester-containing phenol **56** also reacted under the same conditions to give high yields of benzenes **82**, and **83**, respectively. Finally, fully substituted phenol **76** was converted by Stille and Suzuki couplings to give **84** and **85**, respectively.



In conclusion, we have developed a direct synthesis of substituted phenols from 3-hydroxypyrones and nitroalkenes that is regioselective with respect to the alkene. Moreover, high levels of substitution are tolerated and fully substituted phenols are prepared by our method. Yields are synthetically useful and compare favorably with classic and modern phenol syntheses. The programmable nature of the reaction allows noncanonical substitution patterns to be constructed. Finally, conversion of the phenols to the corresponding benzenes allows synthesis of highly substituted benzenes with full control of substituent location.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.0c02157>.

Full experimental details and depicted  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for all new compounds (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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## ■ REFERENCES

- (1) Kalant, H.; Roschlau, W. H. E.; Sellers, E. M., Eds. *Principles of Medical Pharmacology*; Oxford University Press: New York, 1985.
- (2) Brydson, J. A., Ed. *Plastics Materials*; Butterworth Scientific: London, 1982.
- (3) Rappoport, Z., Ed. *The Chemistry of Phenols*; John Wiley & Sons: Hoboken, NJ, 2003.
- (4) Price, C. C. The alkylation of aromatic compounds by the Friedel–Crafts method. *Org. React.* **2011**, 3, 1–82.
- (5) Gozzo, F. C.; Fernandes, S. A.; Rodrigues, D. C.; Eberlin, M. N.; Marsaioli, A. J. Regioselectivity in aromatic Claisen rearrangements. *J. Org. Chem.* **2003**, 68, 5493–5499.
- (6) Syamala, M. S.; Rao, B. N.; Ramamurthy, V. Modification of photochemical reactivity by cyclodextrin complexation: Product selectivity in photo-Fries rearrangement. *Tetrahedron* **1988**, 44, 7234–7242.
- (7) (a) Dai, H.-X.; Li, G.; Zhang, X.-G.; Stepan, A. F.; Yu, J.-Q. Pd(II)-catalyzed *ortho*- or *meta*-C–H olefination of phenol derivatives. *J. Am. Chem. Soc.* **2013**, 135, 7567–7571. (b) Nanjo, T.; Tsukano, C.; Takemoto, Y. Palladium-Catalyzed Double C–H Functionalization of Arenes at the Positions *ortho* and *meta* to Their Directing Group: Concise Synthesis of Benzocyclobutenes. *Chem. Pharm. Bull.* **2016**, 64, 1384–1392. (c) Minami, Y.; Kodama,

T.; Hiyama, T. Dehydrogenative Carbon–Carbon Bond Formation Using Alkynyloxy Moieties as Hydrogen-Accepting Directing Groups. *Angew. Chem., Int. Ed.* **2015**, 54, 11813–11816.

(8) Zhao, X.; Yeung, C. S.; Dong, V. M. Palladium-catalyzed *ortho*-arylation of *O*-phenylcarbamates with simple arenes and sodium persulfate. *J. Am. Chem. Soc.* **2010**, 132, 5837–5844.

(9) Izawa, Y.; Pun, D.; Stahl, S. S. Palladium-catalyzed aerobic dehydrogenation of substituted cyclohexanones to phenols. *Science* **2011**, 333, 209–213.

(10) Yuan, C.; Liang, Y.; Hernandez, T.; Berriochoa, A.; Houk, K. N.; Siegel, D. Metal-free oxidation of aromatic carbon-hydrogen bonds through a reverse-rebound mechanism. *Nature* **2013**, 499, 192–196.

(11) Ziegler, T.; Layh, M.; Effenberger, F. Synthesis of highly substituted benzenes via Diels–Alder reactions with 2H-pyran-2-ones. *Chem. Ber.* **1987**, 120, 1347–1355.

(12) Suzuki, S.; Segawa, Y.; Itami, K.; Yamaguchi, J. Synthesis and characterization of hexaarylbenzenes with five or six different substituents enabled by programmed synthesis. *Nat. Chem.* **2015**, 7, 227–233.

(13) Diltz, W.; Hurtig, G. Hocharylierte aromatische Verbindungen. *Ber. Dtsch. Chem. Ges. B* **1934**, 67, 2004–2007.

(14) Kozikowski, A. P.; Floyd, W. C.; Kuniak, M. P. 1,3-Diethoxycarbonylallene: an active dienophile and ethoxycarbonylketen equivalent in the synthesis of antibiotic C-nucleosides. *J. Chem. Soc., Chem. Commun.* **1977**, 582–583.

(15) Paquette, L. A.; Moerck, R. E.; Harichian, B.; Magnus, P. D. Use of phenyl vinyl sulfone as an acetylene equivalent in Diels–Alder cycloadditions. *J. Am. Chem. Soc.* **1978**, 100, 1597–1599.

(16) Gupta, I.; Yates, P. Two methoxycarbonylketen equivalents as dienophiles in the Diels–Alder reaction. *J. Chem. Soc., Chem. Commun.* **1982**, 1227–1228.

(17) Zhao, P.; Beaudry, C. M. Enantioselective and regioselective pyrone Diels–Alder reactions of vinyl sulfones: Total synthesis of (+)-cavicularin. *Angew. Chem., Int. Ed.* **2014**, 53, 10500–10503.

(18) Holmes, H. L. The Diels–Alder reaction: Ethylenic and acetylenic dienophiles. *Org. React.* **2011**, 4, 60–173.

(19) Bartelson, K. J.; Singh, R. P.; Foxman, B. M.; Deng, L. Catalytic asymmetric [4 + 2] additions with aliphatic nitroalkenes. *Chem. Sci.* **2011**, 2, 1940–1944.

(20) Elimination of nitrous acid from nitroalkanes is well known. See: Fritzsche, K.; Beckhaus, H.-D.; Rüchardt, C. Termischer Zerfall von  $\beta$ -Phenyl- und  $\beta,\beta$ -Diphenyl-nitroalkanen. *Tetrahedron Lett.* **1988**, 29, 2805–2808.

(21) Oh, T.; Rally, M. Reagent-controlled asymmetric Diels–Alder reactions – a review. *Org. Prep. Proced. Int.* **1994**, 26, 129–158.

(22) Singh, R. P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L. Enantioselective Diels–Alder reaction of simple  $\alpha,\beta$ -unsaturated ketones with a cinchona alkaloid catalyst. *J. Am. Chem. Soc.* **2008**, 130, 2422–2423.

(23) All nitroalkenes used in this study were prepared using the Henry reaction. For review, see: Luzzio, F. A. The Henry reaction: recent examples. *Tetrahedron* **2001**, 57, 915–945.

(24) Reported yields are the combined chemical yield of both regioisomers.

(25) Yoshida, K.; Toyoshima, T.; Imamoto, T. Efficient synthetic routes to aromatic compounds using ring-closing olefin metathesis followed by dehydration, oxidation, and tautomerization. *Chem. Commun.* **2007**, 3774–3776.

(26) Matsuda, T.; Suzuki, K. Rhodium(III)-catalyzed decarbonylative coupling of maleic anhydrides with alkynes. *RSC Adv.* **2014**, 4, 37138–37141.

(27) Farino, V.; Krishnamurthy, V.; Scott, W. J. The Stille reaction. *Org. React.* **1997**, 50, 1–652.

(28) Miyaura, N.; Suzuki, A. Palladium-catalyzed cross-coupling of organoboron compounds. *Chem. Rev.* **1995**, 95, 2457–2483.