UC Santa Barbara
UC Santa Barbara Previously Published Works

Title

Strategies for ortho - tert -Butylation of Phenols and their Analogues

Authors

Chan, Kazaf KC

Pettus, Thomas RR

Peer reviewed

www.thieme.com

SYNLETT
Accounts and Rapid Communications in Chemical Synthesis
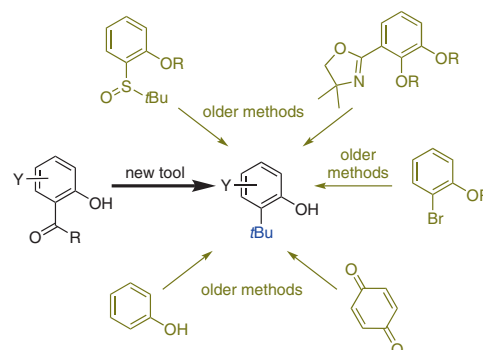
Thieme

Strategies for *ortho-tert*-Butylation of Phenols and their Analogues

Kazaf KC Chan
Thomas R. R. Pettus*

Department of Chemistry and Biochemistry, University of California at Santa Barbara, Santa Barbara, California, 93106, USA
pettus@chem.ucsb.edu

Abstract A new general process for constructing *ortho-tert*-butyl phenols is presented within the context of other known methods. All are briefly evaluated with regards to regioselectivity, efficiency, and functional group tolerance. In addition, we present an assortment of *tert*-butyl substrates accessed through *o*-QM chemistry. Our conclusion is that the *o*-QM process provides greater yields, flexibility, and generality than most other known methods for delivering *ortho-tert*-buytlated phenols and their derivatives.

1   Introduction
2   Friedel–Crafts Alkylation
3   Addition of *t*-Bu⁻ or *t*-Bu• to Carbonyl Compounds
4   *ipso*-S_NAr Reactions of Aryl Methoxy and *tert*-Butylsulfoxide Moieties
5   Metal-Mediated Coupling of Aryl Bromides
6   Applications of *o*-Quinone Methides (*o*-QMs)
7   Conclusion

Thomas R. R. Pettus was born in Virginia (USA) in 1967. He graduated *summa cum laude* from Longwood University with honors in chemistry. After years with Professors Tomás Hudlicky, Richard Schlessinger, and Samuel Danishefsky, as an undergraduate, graduate and Postdoc researcher respectively, he began his academic career at the University of California Santa Barbara in 1998.

Kazaf KC Chan was born in China in 1990 and immigrated to the United States in 2010 and recently became a U.S. citizen in 2021. She graduated from Kingsborough Community College with honors in physics and Smith College *cum laude* with honors in chemistry. After research with Prof. Gorin as an undergraduate, she began her graduate research career with Prof. Pettus at University of California Santa Barbara in 2016.

1   Introduction

Often an aromatic compound displaying a methyl residue is identified from a high-throughput screen of its biological potency (Figure 1). However, when a methyl substituent is positioned *ortho* with an oxygen substituent, as in compound **1**, it renders the methyl residue oxidatively vulnerable. One plausible solution replaces the simple methyl residue with a more oxidatively sturdy *tert*-butyl residue.[1] Instances abound amongst many pharmaceutical agents. Compound **2**, disclosed as a potent NS5B polymerase inhibitor for example, has been explored as a treatment for HVC

by AbbVie.[2] Similar *tert*-butyl phenolic skeletons have been studied by Roche for numerous therapeutic applications.[3a] BMS has further investigated this motif, reporting compound **3** as an antithrombotic and P2Y₁ inhibitor.[3b] Thus, important *ortho-tert*-butyl phenols need efficient and robust strategies for their construction. However, it was not until Vertex adopted our method to deliver ivacaftor (**4**) and its deuterated counterpart on kilogram scale that we became fully enlightened as to the challenges presented by this venerable motif and the utility that *o*-QM chemistry
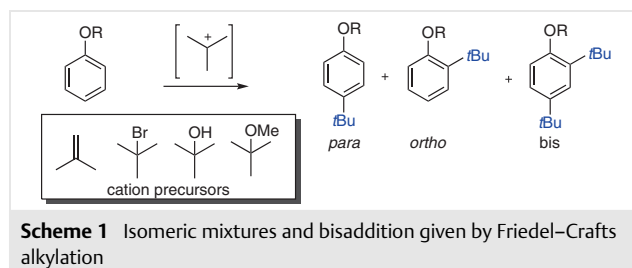
K. K. Chan, T. R. Pettus

Figure 1 Examples of some *tert*-butyl-phenolic therapeutic derivatives
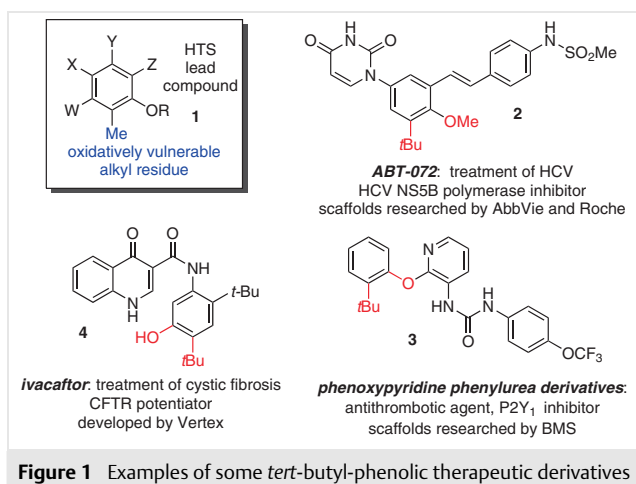
provides to solve this long-standing problem.[4] We therefore wish to share our analysis of existing *tert*-butylation tactics, along with their respective strengths and shortcomings, and conclude with some additional *o*-QM examples.
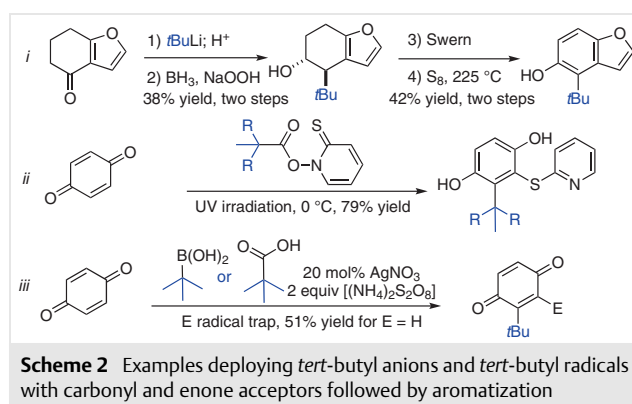
2 Friedel–Crafts Alkylation

Friedel–Crafts alkylation has been a mainstay for the introduction of *tert*-butyl groups onto various anisole derivatives (Scheme 1). However, this strategy provides poor *ortho* regiocontrol. Introduction of additional electron-donating groups only further complicates matters. In attempt to address these issues, researchers have investigated a number of *tert*-butyl cation precursors in conjunction with various Lewis acid promoters. Sharma found Amberlyst-15 provided the greatest amount of the corresponding *para* product (97:3:0), performing better than either *p*-toluene sulfonic acid, aluminum trichloride, or many other Lewis acids investigated.[5a] Hojo has reported the highest *ortho*-yielding examples by using *tert*-butyl bromide impregnated onto silica gel. The reaction results in a 41% overall conversion with a distribution of 32% (*ortho*), 58% (*para*) and 10% (*bis*) amongst products.[5c] Application of the Lewis acid *tert*-butyl dimethylsilyltrifluoromethane sulfonate has been reported to produce *ortho-tert*-butylated phenols and naphthols, but again with poor regiocontrol.[5d,e] More recently, *ortho-tert*-butylation of aryl methyl ethers have been studied by deploying Keggin tungstophosphoric acid ($H_3PW_2O_{40}$) or Santa Barbara Amorphous clay (SBA-15) in conjunction with similar *tert*-butyl cation precursors, and all have illuminated similar regiocontrol problems.[5f] Given these and many other studies, it should be apparent to all that cationic alkylation regimes fail to provide much synthetic utility. However, if the *para* site is blocked with a deactivating group, such as a bromo substituent, then a combination of isobutylene and sulfuric acid has been shown to

smoothly afford the corresponding mono-*ortho-tert*-butylated *para*-bromo phenol, whereupon the bromide atom can be reductively removed by Raney nickel as shown by Hart.[5b] However, such strategies require regioselective access to the desired precursor, which can prove problematic as well.

Scheme 1 Isomeric mixtures and bisaddition given by Friedel–Crafts alkylation

3 Addition of *t*-Bu⁻ or *t*-Bu˙ to Carbonyl Compounds

Scheme 2 Examples deploying *tert*-butyl anions and *tert*-butyl radicals with carbonyl and enone acceptors followed by aromatization

Both radical and anionic formation of a carbon–carbon bond containing a *tert*-butyl group is a challenging problem. Nevertheless, there are several examples where this strategy has proven effective to arrive at *ortho*-functionalized phenols from carbonyl and alkene substrates. For example, Hammond deployed a four-step sequence to produce the desired 4-*tert*-buytl-5-hydroxy-benzofuran (Scheme 2, i).[6] Remarkably, he observed that a *tert*-butyl lithium anionic nucleophile participated in the desired 1,2-reaction with a vinylogous ester carbonyl, whereupon an acidic workup promoted the elimination of the corresponding tertiary alcohol. Further oxidative hydroboration of the intermediate cyclohexene afforded the secondary alcohol shown. Swern oxidation of this material, followed by both enolization and a sulfur-prompted dehydrogenation produced the desired *tert*-butylated hydroxy benzofuran in 16% overall yield.[6] Barton reported that pivylate esters, outfitted as *N*-hydroxy-3-thiopyridinones, participated in a 1,4-conjugate radical addition with 1,4-quinones under UV light resulting in the hydroquinone shown (Scheme 2, ii).[7] In a related strategy, Baran reported that silver nitrate had prompted cross-coupling of an assortment of alkyl boronic

K. K. Chan, T. R. Pettus

acids with *para*-quinones mediated by ammonium persulfate as a co-oxidant (Scheme 2, *iii*).[8a] However, low yields were observed amongst *tert*-butyl examples. Baxter subsequently described a slightly modified procedure that led to a similar *tert*-butylated quinone in a 51% yield,[8b] and extended this reaction to the direct use of carboxylic acids, including pivalic acid.[8b,c] While these Scheme 2 strategies are not particularly high yielding for the introduction *tert*-butyl residues, they have proven exceedingly effective for incorporation of less congested alkyl groups onto *p*-quinone precursors.

4 *ipso*-S$_N$Ar Reactions of Aryl Methoxy and *tert*-Butylsulfoxide Moieties

ipso-S$_N$Ar reactions have also been extensively studied for *tert*-butylation (Scheme 3, *i–iii*). In the 1940's Richtzenhain described the addition of various Grignard reagents to 2,3-dimethoxy benzonitriles. However, the reaction was lower yielding for Grignard reagents and nearly failed for *tert*-butyl lithium (Scheme 3, i).[9] In the 1970's Myers explored using an aryl oxazoline as a surrogate to the earlier nitrile system (Scheme 3, *ii.*) The reaction proved very useful for less congested aliphatic and aryl nucleophiles. However, the introduction of *tert*-butyl residue only proceeded if a *meta*-methoxy oxazoline was present (43% yield), and it failed altogether when not (R = H, 0% yield).[10a,b] Myers also investigated other leaving groups and found that fluoride could be used in place of the *ortho*-methoxy residue. However, these substrates failed altogether to provide *tert*-butyl products.[10c] More recently, Clayden has shown that aryl *tert*-butyl sulfoxides undergo *ipso*-S$_N$Ar reactions with anionic nucleophiles (Scheme 3, *iii*).[11] Remarkably, these reactions proceed with neighboring electron-withdrawing groups (R), such as an oxazoline or an amide, or with electron-donating groups, such as a methoxy residue. Examples outfitted with electron-withdrawing groups afforded greater overall yields across the two steps. Indeed, the 75% yield in the methyl anisole example is extraordinary (Scheme 3,
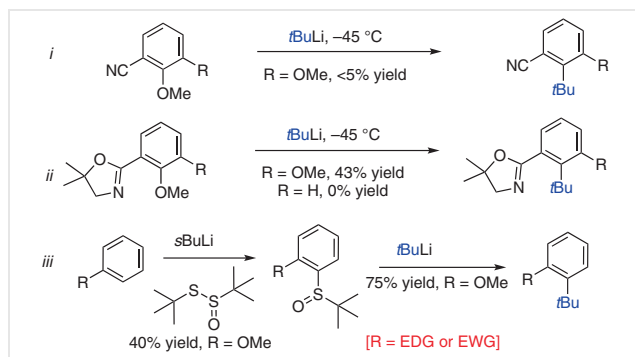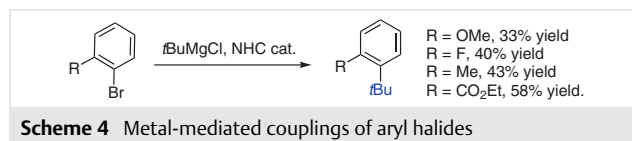
iii). Nevertheless, construction of the respective sulfoxide precursors proves cumbersome (<40%) and leads to an inefficient overall process.

5 Metal-Mediated Coupling of Aryl Bromides

Metal-mediated cross-couplings have also been investigated for producing *tert*-butylated aromatics (Scheme 4). The reaction has been shown to proceed moderately well, despite the risk of β-elimination with *ortho* OR substituents.[12] However, there are two obstacles one must consider before implementing this strategy. First, halogenated materials with *ortho*-donating substituents (R = OH, OMe, etc.) often prove resistant to oxidative insertion.[13,14] Second, regioselective *ortho* bromination of phenols[15] and particularly anisoles can prove very challenging in its own regards. However, if the desired halogenated material can be procured, then copper, nickel, zinc, and even chromium species have proven to be effective in arbitrating couplings with various *tert*-butyl nucleophiles. For example, Glorius has recently achieved moderate yields (33%) by combining *ortho*-bromo anisole with *tert*-butyl magnesium chloride in the presence of a NHC catalyst. However, similar reactions of nonanisole derivatives provided greater yields.[13]


R—[phenyl ring with Br] →(*t*BuMgCl, NHC cat.)→ R—[phenyl ring with *t*Bu]

R = OMe, 33% yield
R = F, 40% yield
R = Me, 43% yield
R = CO$_2$Et, 58% yield.

Scheme 4 Metal-mediated couplings of aryl halides

6 Application of *o*-Quinone Methides

In 2000, we published a communication describing a general method to access *o*-quinone methide intermediates under basic conditions. It was a disruptive process, because for the first time it enabled *o*-QM to form and engage anionic carbon nucleophiles at low temperatures (Scheme 5, i).[16a] While the construction of *ortho*-*tert*-butyl phenols was not our focus, a solitary example delivering the phenol **9** from the *ortho*-OBoc acetophenone **5** (*p*-OBoc) was included. In our early study, three important conclusions were made. First, from screening acyl residues, which enabled a controlled *o*-quinone methide formation, we determined *tert*-butyloxycarbonate (Boc) to be superior in both formation and subsequent reactions from among methoxycarbonate, acetyl, and pivalate alternatives. Second, from screening several solvents, we determined that dilute solution of diethyl ether provided superior yields to tetrahydrofuran, benzene, and toluene; possibly owing to subtle changes in the Schlenk equilibrium. Third, application of an organomagnesium reagent proved indispensable in delivering the *tert*-butylated product(s) **B**, as the corresponding

Scheme 3 S$_N$Ar reactions of aryl rings with methoxy and sulfoxide moieties

Synlett 2022, *33*, 575–580

organolithium led to the corresponding styrene product **A**; presumably by a 1,5-sigmatropic shift. Expanding upon this earlier work, in 2001 we investigated acetophenones **7** and **8** resulting in the *tert*-butyl compounds **10** and **11**.[16b] These compounds were accessed from both their corresponding *o*-OBoc acetophenones **5–8** as well as their *ortho*-OBoc methyl esters **12–14**. In both cases, these one-pot transformations were demonstrated in diethyl ether with the requisite 2 or 3 equivalents of methyl magnesium chloride.[16b] However, methyl benzoate examples were noted to afford undesired methyl benzylic ethers **15** in about 20% yield

along with the desired *tert*-butyl adducts (**9b–11b**) in a similarly decreased yield. Some years later, while perusing curcuphenol (**17**) from the benzaldehyde **16**, we explored a slight modification to our original protocol, whereby two equivalents of methyl lithium were deployed to cause both phenol deprotonation and methyl addition, followed by introduction of Boc₂O, whereupon addition of the organomagnesium reagent caused *o*-QM formation and incorporation of the desired side chain.[16c] However, this modification, in so far as *tert*-butyl formation, was never investigated.[16d]
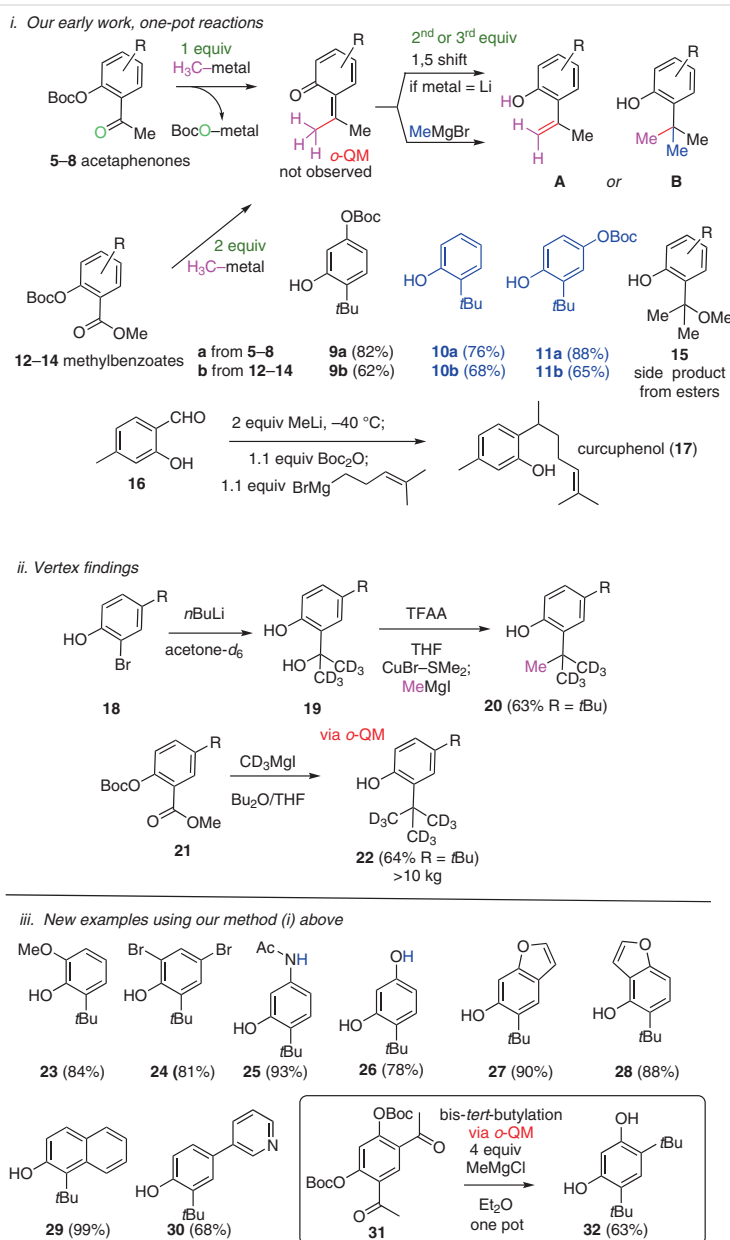
Scheme 5 *o*-QM reactions furnishing *ortho-tert*-butyl phenols

In 2017, Vertex informed us that due of the pitfalls of other *tert*-butylation methods, they were testing our *o*-QM method for preparation of ivacaftor (**4**). In 2020, they reported some of their findings in regard to deuterated derivatives (Scheme 5, *ii*).[17] Their tactics closely mirror our earlier work. However, their evaluations were more thorough and exhaustive, resulting in some additional observations and refinements. First, after preparing the diol **19** from the aryl bromide **18**, they surveyed several additional acylation reagents, including PivCl, and BzCl, and reported trifluoroacetic anhydride (TFAA) to be equal, if not superior to our original selection of Boc$_2$O for the conversion of the diol **19** into derivative **20**. Moreover, their entire sequence beginning from the aryl bromide **18** could be carried out in a single pot, if so desired. Second, they indicated that a solvent mixture comprised of *n*-butyl ether and THF to be slightly better than our original choice of diethyl ether. They implemented this change with the ester **21** to arrive at the perdeuterated *tert*-butyl derivative **22** in 64% (>10 kg). Third, they indicated that organomagnesium iodides, which are easier to prepare on industrial scale, performed marginally better than other organomagnesium halides, and they further postulated that this was perhaps due to perturbations in the Schlenk equilibrium. Lastly, they indicated that some metal additives, particularly CuBr–SMe$_2$, in small quantities improved overall yields.

Given the importance of this motif, we decided to examine a few additional cases to better demarcate our method's scope. Because our yields with acetophenones were usually better than those the corresponding methyl benzoates, we focused our attention upon these starting materials. The *tert*-butyl-*ortho*-phenols **23–30** and **32** were all prepared following our traditional protocol from their corresponding *ortho*-OBoc methyl ketone derivatives. Toleration of several new functional groups was demonstrated to include methoxy, halogen, unprotected phenol, and amide residues, as well as reactions upon naphthalene and benzofuran cores. Relative higher yields amongst the various products likely reflect an *o*-QM intermediate of greater stability in our opinion. Of special note, we found that the reaction proceeds with an unprotected NH-amide and phenol functionality yielding compounds **25** and **26**, respectively; an additional equivalent of methyl magnesium chloride is added to deprotonate their acidic Ar–X–H functionality In addition, we found that when the starting compound was the bis-*ortho*-OBoc acetophenone **31**, our method delivered four methyl residues arriving at the bis-*ortho-tert*-butyl resorcinol **32** in a 63% yield.

7   Conclusion

We hope our review of *o*-phenolic *tert*-butylation methods has illuminated the difficulties surrounding the construction of this medically relevant functionality as well as

offered a potential solution. We find, when an *o*-OBoc acetophenone[18,19] is deployed in this *o*-QM generation and consumption method by action of methyl Grignard, the reaction often provides the corresponding *ortho-tert*-butyl phenol with good substrate scope and in high efficiency; thereby it constitutes a new tool for synthetic chemists.

Conflict of Interest

The authors declare no conflict of interest.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1719875.

References and Notes

(1) Barnes-Seeman, D.; Jain, M.; Bell, L.; Ferreira, S.; Cohen, S.; Chen, X.-H.; Amin, J.; Snodgrass, B.; Hatsis, P. *ACS Med. Chem. Lett.* **2013**, *4*, 514.

(2) Randolph, J. T.; Krueger, A. C.; Donner, P. L.; Pratt, J. K.; Liu, D.; Motter, C. E.; Rockway, T. W.; Tufano, M. D.; Wagner, R.; Lim, H. B.; Beyer, J. M.; Mondal, R.; Panchal, N. S.; Colletti, L.; Liu, Y.; Koev, G.; Kati, W. M.; Hernandez, L. E.; Beno, D. W. A.; Longenecker, K. L.; Stewart, K. D.; Dumas, E. O.; Molla, A.; Maring, C. J. *J. Med. Chem.* **2018**, *61*, 1153.

(3) (a) Talamas, F. X.; Abbot, S. C.; Anand, S.; Brameld, K. A.; Carter, D. S.; Chen, J.; Davis, D.; de Vincent, J.; Fung, A. D.; Gong, L.; Harris, S. F.; Inbar, P.; Labadie, S. S.; Lee, E. K.; Lemoine, R.; Le Pogam, S.; Leveque, V.; Li, J.; McIntosh, J.; Nájera, I.; Park, J.; Railkar, A.; Rajyaguru, S.; Sangi, M.; Schoenfeld, R. C.; Staben, L. R.; Tan, Y.; Taygerly, J. P.; Villaseñor, A. G.; Weller, P. E. *J. Med. Chem.* **2014**, *57*, 1914. (b) Pi, Z.; Sutton, J.; Lloyd, J.; Hua, J.; Price, L.; Wu, Q.; Chang, M.; Zheng, J.; Rehfuss, R.; Huang, C. S.; Wexler, R. R.; Lam, P. Y. S. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4206.

(4) Hadia, S.; Van Goor, F.; Zhou, J.; Arumugam, V.; McCartney, J.; Hazlewood, A.; Decker, C.; Negulescu, P.; Grootenhuis, P. D. J. *J. Med. Chem.* **2014**, *57*, 9776.

(5) (a) Chaudhuri, B.; Sharma, M. M. *Ind. Eng. Chem. Res.* **1991**, *30*, 227. (b) Hart, H. *J. Am. Chem. Soc.* **1949**, *71*, 1966. (c) Kamitori, Y.; Hojo, M.; Masuda, R.; Izumi, T.; Tsukamoto, S. *J. Org. Chem.* **1984**, *49*, 4161. (d) Gagea, B. C.; Parvulescu, A. N.; Parvulescu, V. I.; Auroux, A.; Grange, P.; Poncelet, G. *Catal. Lett.* **2003**, *91*, 141. (e) Gagea, B. C.; Pârvulescu, A. N.; Poncelet, G.; Pârvulescu, V. I. *Catal. Lett.* **2005**, *105*, 219. (f) Pezzotta, C.; Fleury, G.; Soetens, M.; Van der Perre, S.; Denayer, J. F. M.; Riant, O.; Gaigneaux, E. M. *J. Catal.* **2018**, *359*, 198.

(6) Zambia, R. A.; Caldwell, C. G.; Kopka, I. E.; Hammond, M. L. *J. Org. Chem.* **1988**, *53*, 4135.

(7) Barton, D. H. R.; Sas, W. *Tetrahedron* **1990**, *46*, 3419.

(8) (a) Fujiwara, Y.; Domingo, V.; Seiple, I. B.; Gianatassio, R.; Del Bel, M.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 3292. (b) Hamsath, A.; Galloway, J. D.; Baxter, R. D. *Synthesis* **2018**, *50*, 2915. (c) Galloway, J. D.; Mai, D. N.; Baxter, R. D. *Org. Lett.* **2017**, *19*, 5772.

(9) Richtzenhain, H.; Nippus, P. *Chem. Ber.* **1949**, *82*, 408; and references cited therein.

(10) (a) Meyers, A. I.; Mihelich, E. D. *J. Am. Chem. Soc.* **1975**, *97*, 7383. (b) Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372. (c) Meyers, A. I.; Williams, B. E. *Tetrahedron Lett.* **1978**, *3*, 223.

(11) Clayden, J.; Stimson, C. C.; Keenan, M. *Chem. Commun.* **2006**, 1393.

(12) (a) Rudolph, A.; Lautens, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 2656. (b) Glorius, F. *Angew. Chem. Int. Ed.* **2008**, *47*, 8347. (c) Terao, J.; Naitoh, Y.; Kuniyasu, H.; Kambe, N. *Chem. Commun.* **2007**, 825. (d) Frisch, A. C.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 674. (e) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222. (f) Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646. (g) Vechorkin, O.; Proust, V.; Hu, X. *J. Am. Chem. Soc.* **2009**, *131*, 9756. For organozinc reagents, see: (h) Cahiez, G.; Foulgoc, L.; Moyeux, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 2969. For organocopper reagents, see: (i) Langlois, J.-B.; Alexakis, A. *Chem. Commun.* **2009**, 3868. For organomagnesium reagents, see: (j) Hayashi, T.; Konishi, M.; Yokota, K.; Kumada, M. *Chem. Lett.* **1980**, 767. (k) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199. (l) Bell, T. W.; Hu, L.-Y.; Patel, S. V. *J. Org. Chem.* **1987**, *52*, 3847. (m) Hintermann, L.; Xiao, L.; Labonne, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 8246. (n) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245. For chromium, see: (o) Liu, P.; Chen, C.; Cong, X.; Tang, J.; Zheng, X. *Nat. Commun.* **2018**, *9*, 4637.

(13) Lohre, C.; Dröge, T.; Wang, C.; Glorius, F. *Chem. Eur. J.* **2011**, *17*, 6052.

(14) Ando, S.; Mawatari, M.; Matsunaga, H.; Ishizuka, T. *Tetrahedron Lett.* **2016**, *57*, 3287.

(15) For *ortho* bromination of a phenol, see: Pearson, D. E.; Wysong, R. D.; Breder, C. V. *J. Org. Chem.* **1967**, *32*, 2358.

(16) (a) Van De Water, R. W.; Magdziak, D.; Chau, J. N.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2000**, *122*, 6502. (b) Jones, R. M.; Van De Water, R. W.; Lindsey, C. C.; Hoarau, C.; Ung, T.; Pettus, T. R. R. *J. Org. Chem.* **2001**, *66*, 3435. (c) Green, J. C.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2011**, *133*, 1603. (d) Bai, W.-J.; David, J. G.; Feng, Z.-G.; Weaver, M. G.; Wu, K.-L.; Pettus, T. R. R. *Acc. Chem. Res.* **2014**, *47*, 3655.

(17) Looker, A. R.; Wilde, N.; Ryan, M. P.; Roeper, S.; Ye, Z.; Lewandowski, B. L. *J. Org. Chem.* **2020**, *85*, 501.

(18) **Representative Procedure**
To dry nitrogen-flushed 10 mL Schlenk flask, equipped with a magnetic stir bar, was charged with **SI-1** (100 mg) in dry Et_2O (3.8 mL, 0.1 M) and MeMgCl (0.42 mL, 2.69 M, 1.13 mmol, 3.0 equivalent) was added dropwise at –78 °C. The reaction was allowed to slowly warm to room temperature overnight. The reaction was quenched with 1 M aq. NH_4Cl (3 mL) and extracted with Et_2O (4 × 1 mL). The combined organic fractions were washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography (ethyl acetate–hexane, 1:9) to yield the *tert*-butylated phenol **23** (56.9 mg, 84% isolated yield). ^1H NMR (500 MHz, $CDCl_3$): δ = 6.91 (dd, *J* = 6.7, 2.8 Hz, 1H), 6.82–6.74 (m, 2 H), 6.01 (s, OH), 3.89 (s, 3 H), 1.42 (s, 9 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 146.82, 144.43, 135.75, 119.19, 118.81, 108.58, 56.28, 34.78, 29.54. HRMS (EI+): *m/z* calcd for $C_{11}H_{16}O_2$ [M$^+$]: 180.1150; found: 180.1149.

(19) Preparations of the acetophenones are all fully described in the Supporting Information.