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Strategies for the Preparation of Differentially Protected *ortho*-Prenylated Phenols

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Abstract

A new process for *ortho*-prenylation of phenols is presented within the context of known methods. All of the processes are briefly assessed with regards to the substitution patterns and accompanying functional groups tolerated by each strategy. The conclusion reached is that a new procedure using *ortho*-quinone methides, for which an experimental protocol is provided, offers the greatest generality and flexibility in the preparation of *ortho*-prenylated phenol derivatives.

Keywords

prenylation; phenols; *ortho*-alkylation; *ortho*-methide

1 Introduction

ortho-Prenylated phenols play an important role in mediating many biological processes. Prenylated ubiquinones are essential in cellular respiration.[1] Prenylated napthaquinones, such as shikonin, are potent anti-bacterial agents.[2] Arnebinol, an *ansa ortho*-prenylated phenol, inhibits the biosynthesis of prostaglandin.[3] Other prenylated phenols exhibit anti-fungal,[4] anti-tumor,[5] anti-HIV[6] and anti-Alzheimer activity.[7] Derivatives of *ortho*-prenylated phenols, such as the corresponding dimethyl benzopyrans, exhibit an even broader range of interesting physiological effects.[8] Clearly, such an important structural motif needs a general strategy for its preparation, particularly for systems in which other aromatic hydroxyl residues are differentiated, as is often the case with therapeutic natural products containing this pharmacophore. However, until recently no single method readily encompassed preparations of differentially protected dihydroxy aromatics such as **1b–e** (Figure 1).[9] In this document, attributes and admonitions are presented regarding the procedures for synthesizing *ortho*-prenylated phenols. In addition, a new strategy involving *ortho*-quinone methides is presented which increases access to these systems.

2 Desymmetrization of Dihydroxy Aromatics

Distinguishing functional groups in the same chemical, electronic, and structural environments can be a difficult task. In chiral systems such a challenge is referred to as *meso*-desymmetrization often requiring the use of enzymes or chiral catalysts. If a desymmetrized starting material is unavailable, substantial material is lost in order to distinguish the groups. This problem must be solved in order to construct derivatives of **1b–e**. Commercially available desymmetrized dihydroxyphenols are shown in Figure 2 to inform the readers of the approximate cost and availability of potential starting materials.

3 Directed *ortho*-Metalation (D*o*M) and Alkylation

Directed *ortho*-metalation (D*o*M) is thought by most to be the best strategy for site-specific functionalization of aromatic compounds (Scheme 1).[10] The procedure works well for the *ortho*-prenylation of symmetric phenol derivatives as well as derivatives that have already been desymmetrized and contain two or fewer oxygen substituents. Aromatic compounds displaying two or more oxygen substituents, however, can prove difficult to deprotonate. Often times, a proton transfer from a neighboring group such as −OBn or −OMOM quenches the aryl anion. Acetal [P=−CH(R)OMe] and carbamate [P=−C(O)NR_2] protecting groups avoid this potential complication. However, these *ortho* directing groups are not without their own limitations. For example, a carbamate might migrate to the *ortho*-lithiated aryl carbon atom at temperatures above −60 °C affording the corresponding salicylicamide.[10b] Furthermore, carbamate deprotection requires harsh conditions such as reduction with $LiAlH_4$. Snieckus reports that an *N*-cumyl *N*-methyl benzene-*O*carbamate undergoes cleavage under milder conditions.[10c] Substituted acetals display their own peculiarities. The 1-ethoxylethyl ether (OEE) often complicates ^{1}H NMR data interpretation by virtue of its chirality and these types of ethers are surprisingly unstable towards acidic conditions, often hydrolyzing upon chromatography. On the other hand, MOM protected phenols are robust and often require very harsh conditions for deprotection. But, as previously mentioned, a proton exchange can decrease the effectiveness of MOM ethers in D*o*M processes.[10d] Some methyl ethers have proven effective in D*o*M protocols, however, cleavage of an aryl methyl ether requires extremely harsh conditions, such as BBr_3, or refluxing MeMgI.[11] Specific examples of D*o*M processes in regards to prenylation are shown in Scheme 1a–Scheme 1d.

Phenol (**5**) smoothly couples with the carbamyl chloride to afford the carbamate **6** (Scheme 1a). Deprotonation of **6** is carried out at −78 °C with *sec*-butyllithium. Subsequent addition of prenyl bromide to the aryl anion affords the prenylated material **7** in 75% yield. Reduction of the carbamate moiety with $LiAlH_4$ produces the *o*-prenylated phenol **1a** in yields ranging from 54–64% from **5**.[10]

Despite the availability of the differentially protected hydroquinones **3a** and **3b**, application of these materials in the construction of **1b** has not been reported. However, 1,4-dimethoxybenzene (**8**) has been prenylated utilizing the D*o*M protocol to produce **9** in 69% yield (Scheme 1b).[12] The addition of catalytic CuI improves the yield of **9** to 71%. Cleavage of a single methyl ether residue in **9** to produce **10** would be a difficult transformation and to our knowledge is unknown.

Application of the D*o*M sequence becomes problematic (Scheme 1c) with the resorcinol nucleus.[13] Desymmetrization of resorcinol (**11**) is a non-trivial affair. Mono-protection affords **12** in 27% yield. The subsequent etherification with MOMCl proceeds without difficulty and the oxygen substituents cooperate in the deprotonation of **13** with butyllithium. Subsequent addition of prenyl bromide occurs exclusively at the 2-position affording **14** in 69% yield. Selective cleavage of the MOM and benzyl moieties is achieved with PPTS and Na/NH_3, respectively, affording **15** and **16** in 89% and 88% yield. However, because desymmetrization of **11** proves so inefficient the overall yield in either of these sequences is only 11%.

Desymmetrization of **17** has been accomplished with DHP in 30% yield to produce the *mono*-ether **18** (Scheme 1d).[14] Methylation of the remaining hydroxyl residue affords **19**. The D*o*M protocol proceeds smoothly resulting in an *ortho*-prenylated THP ether. Subsequent deprotection of the THP residue affords the differentially protected catechol **20** in 84% yield, a 23% overall yield from **17**.

4 Metal-Halogen Exchange and Metal-Mediated Coupling

In metal-halogen exchange (MHE) mediated transformations, the issue of regiocontrol is reassigned to the preparation of the *ortho*-halogenated material. Regioselective halogenation remains challenging and follows different trends than the D*o*M alkylation strategy. If a halogenated phenol is readily available, two processes can be used (*options a* and *b* shown in Scheme 2). In *option a*, an electrophile is added after oxidative insertion with lithium, magnesium or zinc. In *option b*, a nucleophilic prenylated metal species is added after oxidative insertion with transition metals such as Ni(0) or Pd(0). The former strategy suffers from many of the earlier discussed problems; namely, the complications arising with attendant functional groups under highly basic conditions. The transition metal mediated process tolerates a wider variety of functional groups, including alcohols. However, these couplings proceed better with protected hydroxyl groups. In addition, transition metal mediated couplings can prove challenging with electron rich aryl halides. Furthermore, most prenyl metal species favor reverse prenylation rather than direct prenylation. Examples of these two related strategies are shown in Scheme 2a–Scheme 2e.

As previously explained in regards to the D*o*M strategy, 1,3-oxygen substituents direct deprotonation at the 2-position. Therefore, the D*o*M protocol is not applicable to the construction of the 6-prenylated resorcinol **1c**. However, *option a* of the MHE strategy allows access to these types of materials (Scheme 2a).[13a] The mono-*O*-benzylated resorcinol **12**, available from resorcinol as shown in Scheme 1c, undergoes bromination with NBS to produce **21** in 50% yield. Etherification of the free phenol with MOMCl affords **22**. At this juncture, lithium-halogen exchange and subsequent addition to prenyl bromide produces **23** in 58% yield. This material can be selectively deprotected as shown earlier (Scheme 1c) yielding **24** in 6.3% overall yield from resorcinol.

Option b of the MHE process is shown in Scheme 2b. Bromination of **25** with NBS in CH_2Cl_2 proceeds at the vinyl site to afford the aryl bromide **26** in 93% yield. A palladium mediated Stille coupling between aryl bromide **26** and stannane **27** affords **28** in 88% yield.[15] Some have speculated that *ortho* substituent(s) aid(s) this coupling process by facilitating reductive elimination. Interestingly, reverse prenylation is not observed with the stannane species **27**. However, this metal species is difficult to procure.[15b] Considering the challenge of procuring **27** and poor selective cleavage of a methyl ether in **33**, this process loses its utility.

Because metal species, such as **27**, are relatively inaccessible and in most cases favor reverse prenylation, several fragments have been developed to serve as masked prenyl derivatives. For example, the Sonogashira coupling of iodophenol **29** and alkyne **30** mediated by Pd(0) produces alkyne **31** in 90% yield (Scheme 2c).[16] Subsequent Raney nickel reduction of **31** in methanol affords the tertiary alcohol **32** in nearly quantitative yield. *para*-Toluenesulfonic acid prompts elimination of the tertiary alcohol and affords a 9:1 mixture of **33** and **34**. The undesired isomer **34** can be recycled to the tertiary alcohol **32** by addition of Hg(II) and H_2O.

The Heck-type coupling reaction in Scheme 2d also uses a masked prenyl group.[17] Coupling of the aryl bromide **35** and methyl vinyl ketone (MVK) affords enone **36**. Subsequent 1,2-addition of methyl lithium produces the tertiary alcohol **37**. After per-silylation, treatment with Li/NH_3 affords anion **38** by sequential single electron transfers and elimination. This intermediate undergoes protonation to produce **39** in 43%.

An example of reverse prenylation using the MHE sequence involving copper and resulting in *ortho*-prenylation is shown in Scheme 2e.[18] O-Prenylation of the commercially available *ortho*-bromophenol (**40**) affords ether **41**. It has been postulated that treatment with 2 equivalents of *t*-BuLi and 0.5 equivalents of CuCN results in a π-allyl complex **42** followed by migration to afford product **1a**.

5 Phenoxide *ortho*-C-Alkylation

A favored strategy for preparing *ortho*-prenylated phenols under mild basic conditions is shown in Scheme 3. After phenols are deprotonated, the resulting phenoxide resembles an enolate. These phenoxides react at the adjacent carbon with prenyl bromide to yield the corresponding *ortho*-prenylated phenols.[19] Because of competing side reactions such as *para*-prenylation, bis-prenylation, and oxygen-prenylation, the yields for this procedure are moderate (30–50%).[19e] When the *para* position is blocked (Y H) the reaction is synthetically useful. Electron rich phenols, which work poorly in previously discussed metalation procedures, are the best substrates in these types of processes. The [Na^+] favors C-alkylation; whereas [K^+] and [Li^+] favor O-prenylation and bis-prenylation.[19c] A modified process using BaO/Al_2O_3 has been shown to work well.[19h] Applications of *ortho*-C-alkylations are shown in Scheme 3a,Scheme 3b.

An example of this strategy is illustrated in Scheme 3a. Sodium metal is used to form the phenoxide in the differentially protected hydroquinone **3a** and resorcinol (**11**). The phenoxide of **3a** refluxed with prenyl bromide affords the prenylated phenol **10** smoothly in 85% yield.[12] This reaction proves less successful for resorcinol (**11**). A mixture of **43a** and **43b** emerges in 16% and 27% yields, respectively, along with several other byproducts.[19g].

Addition of $ZnCl_2$ in MHE reactions improves *ortho* control even when the *para* site remains unsubstituted. It is quite remarkable that phenoxide **44** undergoes addition to either prenyl bromide or 3-bromo-3-methyl-1-butene in the presence of catalytic $ZnCl_2$ to provide only the *ortho*-functionalized isomer **1a** in 65% yield (Scheme 3b).[19i] In the absence of $ZnCl_2$, **1a** emerges from **44** in less than 25% yield. This technique is reminiscent boron mediated *ortho*-alkylations of phenols previously reported by Sugasawa.[19j,k]

6 Claisen Rearrangement

Another *ortho*-prenylation strategy involves the Claisen rearrangement of a reverse prenyl aryl ether (Scheme 4).[20] Although the process is mild and tolerates various substitution patterns, the formation of a reverse prenyl aryl ether requires several manipulations. Moreover, in the case of dihydroxylated aromatic compounds the hydroxy residues must be distinguished prior to etherification. Examples of this strategy are shown in Scheme 4a,Scheme 4b.

Reverse prenyl aryl ethers have been constructed using one of two processes (Scheme 4a). In one method, phenol (**5**) undergoes coupling as its corresponding potassium salt with 3-chloro-3-methylbutyne (**46**) mediated by potassium iodide and copper iodide to produce the alkynyl ether **47**.[20b,c] The allenyl intermediate is presumed to be formed from **46** and undergoes addition-elimination to produce alkyne **47**. Subsequent partial reduction of the alkyne using Lindlar's conditions affords the reverse prenyl ether **50**. In the alternative method, the phenoxide of **5** is coupled with the *ortho*-bromoaldehyde (**48**) to generate aldehyde **49** in good yield. This material undergoes a subsequent Wittig olefination to afford the identical reverse prenyl aryl ether **50**.[20f] Compound **50** smoothly undergoes a [3,3]-sigmatropic rearrangement upon heating (130 °C) to produce **1a**, delivering the prenyl residue to the most accessible *ortho* site thereby producing phenol **1a**.

A related strategy avoids the rather cumbersome formation of the reverse prenyl aryl ether (Scheme 4b).[21] O-Allylation readily proceeds by combination of allyl bromide and the potassium phenoxide of **51** to produce the allyl ether **52**. This material undergoes rearrangement at temperatures >180 °C and affords **53** upon subsequent methylation of the phenol. Oxidative cleavage of the olefin side-chain in **53** affords an aldehyde followed by Wittig reaction of the dimethyl phosphonium ylide to yield **54**. In the case of **1b–e**, application of this strategy would require differentially protected phenols such as **2–4**.

7 Friedel–Crafts-like Prenylations

Another method to produce *ortho*-prenylated phenols utilizes a Friedel–Crafts (FC) type reaction shown in Scheme 5. The reaction generally occurs at the less substituted carbon of the prenyl cation and the most nucleophilic site of the aromatic compound.[22] However, success mandates that the phenol substrate bear multiple electron donating substituents and the process proceeds with only moderate regiocontrol. Furthermore, these types of processes are difficult to stop after a single substitution since the addition of a prenyl residue makes the aromatic system more electron rich and hence more inclined to undergo a second addition. For these reasons, the reaction is unsuccessful with resorcinol and catechol nuclei, but works well in other instances. It is most useful when prenylating a symmetric electron rich phenol in which the *para* position is substituted. Examples are shown in Scheme 5a–Scheme 5e.

In weakly acidic media, simple phenols prove unreactive. However, more electron rich phenols such as hydroquinone (**55**) undergo prenylation with cation **56**, produced by the addition of acid to the prenyl alcohol shown, to produce **57** in 30% yield (Scheme 5a).[22a,b] Significant amounts of **55** are recovered along with the chroman **58** that results by cyclization between the phenol residue in **57** and the prenyl residue. To discourage the formation of **58** the transformation can also be carried out with nonprotic Lewis acids such as BF_3•OEt_2.[22c,d]

Acidic clays are thought to work in the same manner. For example, refluxing phenol **3a** with butadiene **59** in the presence of clay zeolites affords the hydroquinone derivative **10** in 36% yield (Scheme 5b).[22e] A similar reaction with anisole leads to a mixture of *para*- and *ortho*-prenylation products.

The (η^3-allyl)$Fe(CO)_4$ cation metal complex **61** is significantly more stable than cation **56** and often proves better behaved. Complex **61**, however, is unreactive towards phenol and hydroquinone. Electron rich ring systems, such as **60**, undergo mono-prenylation in modest yields (Scheme 5c).[22f]

Another strategy that can be loosely classified as a FC reaction involves Pt(II) and butadiene **59** or Pd(II) and allene **64** (Scheme 5d).[22g,h] Hydroquinone **3a** undergoes reaction under the Pd(II) protocol to afford **10** and **65** in 5% and 7% yields, respectively. The Pt(II) protocol applied to **3a** affords **10** and **65** in 14% and 20% yields, respectively. The resorcinol derivative **2** on the other hand undergoes reaction in the palladium protocol to produce **66** and **67** in 23% and 17% yields, respectively, while the platinum procedure affords **66** and **67** in 52% and 2% yields, respectively.

Another FC related strategy starts with prenyl ether **68**, which upon treatment with 3 equivalents of a 1:1 mixture of $TiCl_4$/$Ti(O\text{-}i\text{Pr})_4$ proceeds to the ion pair **70** and ultimately phenols **1a** and **71** in 25% and 27% yields, respectively (Scheme 5e).[22i] The imine **69** serves as a HCl scavenger and prevents formation of the chroman adduct from **1a**. Montmorillonite clay is reported to catalyze a similar transformation in O-prenylated ethers in yields ranging from 35–53%.[22j,k]

8 Birch Reduction of 2,2-Dimethyl-2*H*chromenes

The Birch strategy for the preparation of *ortho*-prenylated phenols entails reductively opening 2,2-dimethyl-2*H*chromenes by a series of single electron transfers (Scheme 6).[23,24] Examples are shown in Scheme 6a.

The chromene **99** can be constructed in a regioselective manner by several processes (Scheme 6a). In one, propargylation of phenol **2** is effected by conditions described earlier in Scheme 4a. Subsequent thermal treatment of propargyl ether **72** affords chromene **99** by cyclization.

In another procedure, an aldol-like reaction is employed, followed by heat. Treatment of phenol **2** with $PhB(OH)_2$ and 3,3-dimethylacrylaldehyde (**73**) affords the cyclic borate **74**.[23a,b] Warming this material leads to elimination, resulting in an *ortho*-quinone methide which undergoes subsequent electrocyclization to produce chromene **99**. In yet another protocol, a $-C(O)NEt_2$ protected phenol is *ortho*-lithiated and added to 3,3-dimethyl acrolein. Subsequent treament of the benzyl alcohol with acid is speculated to afford an allyl cation that undergoes cyclization with the freed phenol to afford the corresponding chromene.[24c] All of these methods confront the questions of *ortho/para* regioselectivity and multiple additions, provided that the starting phenol can be obtained with differentially protected hydroxy groups. Chromene **99** can then be opened via a series of single electron transfers using Birch reduction conditions to afford the *ortho*-prenylated phenol **66**. One or more of these methods could be applied in the synthesis of *ortho*-prenylated materials **1a,b,d,e**.

9 Net Conjugate Addition to para-Quinone

Although applicable only to the hydroquinone nucleus, a net 1,4-conjugate addition of a prenyl organometallic reagent to *para*-quinone would in principle provide a straightforward route to a prenylated hydroquinone (Scheme 7). Specific examples of this strategy are shown in Scheme 7a.

The propensity of most prenyl metal species to favor reverse prenylation is utilized in the following method. A 1,2-prenylation of the carbonyl followed by an oxy-Cope- [3,3]-rearrangement constitutes a net conjugate addition of a prenyl residue to quinone. Several metal species have been found to undergo this process (Scheme 7a).[25–28] For example, treatment of 1,4-benzoquinone (**75**) with trifluoro-(3-methyl-2-butenyl)-silane (**77**) and TBAF affords the intermediate cyclohexadienone alcohol **76**, which undergoes a subsequent rearrangement to restore aromaticity and generate the prenylated hydroquinone **57** in a respectable 87% yield.[25] The corresponding species of stannane (**27**),[26a–d] indium (**78**),[27] and nickel (**79**)[28] have all been employed in similar processes.

10 Benzylic Couplings

An alternative disconnection strategy avoids the issue of regioselectivity by coupling a vinyl metal species at the benzylic position of the appropriately protected phenol (Scheme 8). Because many of these benzylic derivatives are procured from the corresponding salicylaldehyde, access to differentially protected systems are easily accommodated. Examples of these processes are shown in Scheme 8a,b.

The highly reactive benzyl chloride **80**, available in 78% yield from **25**, undergoes Pd(0) or Ni (0) mediated coupling with the aluminum species **81** to afford CoQ_{10} (**82**) in 88% yield (Scheme 8a).[29] While only the application of the vinyl aluminum reagent has been reported, the coupling is amendable to zirconium, stannyl, and magnesium vinyl species.

A milder variant of this strategy, which avoids preparation and purification of the highly reactive benzyl chloride intermediate **80**, is shown in Scheme 8b.[30] The appropriate salicylaldehydes **83**–**87**[31] are converted by protection and reduction into the corresponding *o*-OBOC alcohols **89**– **93**. Addition of a benzyl alcohol to an excess of Grignard compound **88** results in deprotonation of the alcohol, migration of the BOC group, and elimination yielding a *ortho*-quinone methide intermediate. Subsequent 1,4-addition of **88** to this intermediate affords the desired *ortho*-prenylated phenol in respectable yields (**94**–**98**, 25–67% from the starting aldehydes **83**–**87**).[32] Inverse addition was found to be crucial in order to prevent formation of a chroman cycloadduct side product that arises by a [4+2] reaction of the hydrido form of **88** with the *ortho*-quinone methide.

11 Conclusions

We hope this discussion has illuminated the difficulties associated with the preparation of *ortho*-prenylated phenols. In dihydroxylated aromatic derivatives the problem is far more challenging than it would first seem. The only strategy examined that provides application to all of the differentially protected dihydroxylated nuclei (**1b–e**) in a mild manner is shown in Scheme 8b. The *ortho*-quinone methide strategy is exceptionally diverse considering it is such a synthetic challenge. We hope synthetic groups find the discussion useful and the *ortho*-quinone process applicable in their future preparations of natural products that contain an *ortho*-prenylated phenol.[30c]

General Protocol for Construction of 1a–e

Procedure for Acylation and Reduction of Salicylaldehydes 83–87—To a dry, nitrogen flushed, 10 mL round-bottom flask, equipped with a magnetic stir bar, charged with salicylaldehyde (93 mg, 0.673 mmol) in anhyd THF (3.4 mL, 0.2 M) was added di-*tert*-butyl dicarbonate (297 mg, 1.36 mmol). *N*,*N*-Diisopropylethylamine (59 μL, 0.337 mmol) and DMAP (2.5 mg, 0.02 mmol) were added to the reaction mixture which was stirred for 10 h at r.t. The reaction mixture was concentrated in vacuo and purified by flash silica gel chromatography (EtOAc–petroleum ether, 95:5).

To a dry, nitrogen flushed, 10 mL round-bottom flask, charged with di-BOC protected salicylaldehyde (16.2 mg, 0.4788 mmol) in anhyd THF (0.5 mL, 0.1 M) was added lithium tri-*tert*-butoxyaluminohydride until completion (5 min, monitored by TLC analysis). The reaction mixture was quenched with 0.1 M HCl (0.5 mL) and extracted with Et_2O (3 × 2 mL). The combined organic fractions were washed with brine (2 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash silica gel chromatography (EtOAc–petroleum ether, 85:15) to afford the corresponding benzyl alcohol.

Special Notes (1–5) associated with the preparation of alcohols **89**–**93**, distinguishable because of hydrogen bonding:

1) Preparation of **89** required the addition of 5 equiv of lithium tri-*tert*- butoxyaluminohydride as solid at a reaction temperature of 0 °C, then the reaction was allowed to warm up to r.t. for 15 min before quenching with 0.1 M citric acid.

2) Preparation of **90** required 1 equiv of lithium tri-*tert*-butoxyaluminohydride for reaction completion.

3) Preparation of **91** is done in dry Et_2O at 0 °C and required the solution to warm up to r.t. for 20 min after addition of 1.5 equiv of lithium tri-*tert*-butoxyaluminohydride for reaction completion.

4) Preparation of **92** required a reaction temperature of 0 °C and 5 equiv of lithium tri-*tert*-butoxyaluminohydride for reaction completion. The migration of the BOC group to the benzylic alcohol was observed and purification through flash chromatography was avoided because of the resulting cleavage of the BOC group.[32]

5) Preparation **93** required 1.2 equiv of lithium tri-*tert*-butoxyaluminohydride for reaction completion.

Preparation of [$(CH_3)_2C$=CHMgBr]—Commercially available **88** contains significant amounts of $Mg(OH)_2$ which greatly impedes the efficiency of the reaction. For this reason, **88** was freshly prepared before each use. To a dry, nitrogen flushed, 10 mL round-bottom flask,

charged with magnesium powder (356 mg, 14.6 mmol) and covered with anhyd THF (4 mL), 2-methyl-1-propenylbromide was added neat (1 mL, 9.8 mmol) at r.t. Dibromoethane (0.168 mL, 2.0 mmol) was added and the reaction mixture was heated to 40 °C. After completion (1 h) the reaction was cooled to r.t. and diluted to a 0.2 M solution.

General Procedure for Addition of the Organomagnesium Compound to ortho-OBOC Alcohol—A dry, nitrogen flushed, 10 mL round-bottom flask, equipped with a magnetic stir bar was charged with **88** (3.8 mL, 0.2 M in THF, 0.8 mmol) and cooled to 0 °C. The benzylic alcohol (51.6 mg, 0.2 M in THF, 0.15 mmol) was added dropwise by a cannula. The reaction was allowed to warm to r.t. over 10 min. The reaction was quenched with 0.1 M HCl (1.5 mL) and extracted with EtOAc (3 × 5 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 (EtOAc–petroleum ether) to yield the prenylated phenols **94**–**98**.

Special Notes (1–6) associated with the preparation of **94**–**98** resulting from the addition of RMgX to alcohols **89**–**93**:

1) DA adduct arises upon non-inverse addition of 88 to 90: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.92 (dd, *J* = 2.8, 8.6 Hz, 1 H), 6.86 (d, *J* = 2.6 Hz, 1 H), 6.80 (d, *J* = 8.8 Hz, 1 H), 5.04 (d, *J* = 8.0 Hz, 1 H), 2.95 (d, *J* = 3.8 Hz, 1 H), 2.83 (d, *J* = 16.3 Hz, 1 H), 2.40 (d, *J* = 16.3 Hz, 1 H), 1.56 (s, 9 H), 1.08 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.6, 148.5, 144.9, 122.6, 122.1, 120.3, 117.4, 98.6, 83.5, 35.1, 32.4, 32.9, 24.3, 24.0.

2) Compound 94: (petroleum ether–EtOAc, 80:20), 69% isolated yield: The benzylic alcohol (0.2 M in Et_2O) was added dropwise via syringe. The reaction was kept at 0 °C for 20 min before quenching with NH_4Cl (0.1 M) to reduce the BOC cleavage observed under acidic conditions. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06–6.77 (m, 3 H), 5.60 (s, OH), 5.25 (t, *J* = 7.22 Hz, 1 H), 3.27 (d, *J* = 7.22 Hz, 2 H), 1.74 (s, 3 H), 1.71 (s, 3 H), 1.57 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.3, 142.2, 135.3, 127.6, 122.0, 121.7, 120.8, 113.5, 94.6, 27.9, 26.0, 18.1.

Compound 95: (petroleum ether–EtOAc, 95:5), 68% isolated yield: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07 (d, *J* = 2.4 Hz, 1 H), 6.68 (dd, *J* = 8.3, 2.4, 1 H), 6.64 (d, *J* = 2.4, 1 H), 5.33 (s, OH), 5.29 (m, 1 H), 3.32 (d, *J* = 6.9 Hz, 2 H), 1.77 (s, 6 H), 1.56 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 152.2, 150.4, 135.3, 130.4, 124.7, 121.7, 113.5, 109.3, 83.7, 29.5, 27.9, 26.0, 18.1.

Compound 96: (petroleum ether–EtOAc, 95:5), 65% isolated yield: ^{1}H NMR (400 MHz, CDCl3): δ = 6.92–6.89 (m, 2 H), 6.78–6.76 (m, 1 H), 5.32–5.30 (m, 1 H), 5.08 (s, OH), 3.33 (d, *J* = 7.3 Hz, 1 H), 1.78–1.77(m, 6 H), 1.56 (s, 9 H), 3.32 (d, *J* = 6.9 Hz, 2 H), 1.77 (s, 6 H), 1.56 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.1, 144.7, 135.6, 128.0, 122.6, 121.3, 120.2, 116.3, 94.6, 83.5, 27.9, 26.0, 18.1.

Compound 97: [32]***:*** (petroleum ether–EtOAc, 80:20), 25% isolated yield: The benzylic alcohol (0.05 M in Et_2O) was added dropwise via a syringe. The reaction was kept at 0 °C for 20 min before quenching with 0.1 M HCl. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (t, *J* = 8.1 Hz, 1 H), 6.73 (d, *J* = 8.3 Hz, 2 H), 5.36 (s, OH), 5.22 (t, *J* = 7.1 Hz, 1 H), 3.34 (d, *J* = 7.1 Hz, 2 H), 1.81 (s, 3 H), 1.74 (s, 3 H), 1.55 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 152.2, 149.9, 135.3, 127.4, 121.1, 120.0, 114.6, 113.9, 83.6, 29.9, 27.9, 26.0, 23.5, 18.1.

Compound 98: (petroleum ether–EtOAc, 97:3), 63% isolated yield: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15–7.11 (m, 2 H), 6.89 (td, *J* = 1.2, 2.4, 8.6 Hz, 1 H), 6.82 (dd, *J* = 1.1, 8.3 Hz,

1 H), 5.36–5.34 (m, 1 H), 5.17 (s, OH), 3.38 (d, *J* = 7.22, 1 H), 1.80 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.48, 134.99, 130.15, 127.72, 127.01, 121.98, 120.94, 115.88, 30.00, 26.00, 18.07.

Acknowledgment

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31. The 2,6-dihydroxybenzaldehyde **88** was prepared from the demethylation of 2,6-dimethoxybenzaldehyde in 58% following reported literature procedureBoulos Z, Attardo G, Barriault N, Penney C. J. Chem. Soc., Perkin Trans. 1 1997:2925.
32. The lability of the remaining OBOC residue in **92** and our inability to purify this substance is believed to be responsible for the reduced yield of **97** when compared with the overall yields of **95**, **96** and **98**

Biographies

Christophe Hoarau was born in Marseille France in 1972. In 1995 he graduated from the Université de Luminy with a B.S. in biochemistry. In 1995 he moved to America and obtained a M.S. from San Francisco State University under the direction of Dr. Ihsan Erden. In 1999 he began working towards his PhD in the research group of Dr. Pettus.

Thomas R. R. Pettus was born in Richmond Virginia in 1967. After a false start at his father's alma mater, he eventually graduated from Longwood College summa cume laude with honors in Chemistry. After research with Professors Tomás Hudlicky, Richard Schlessinger and Samuel Danishefsky as an undergraduate, graduate and Postdoc, respectively, he began work at the University of California at Santa Barbara in 1998.

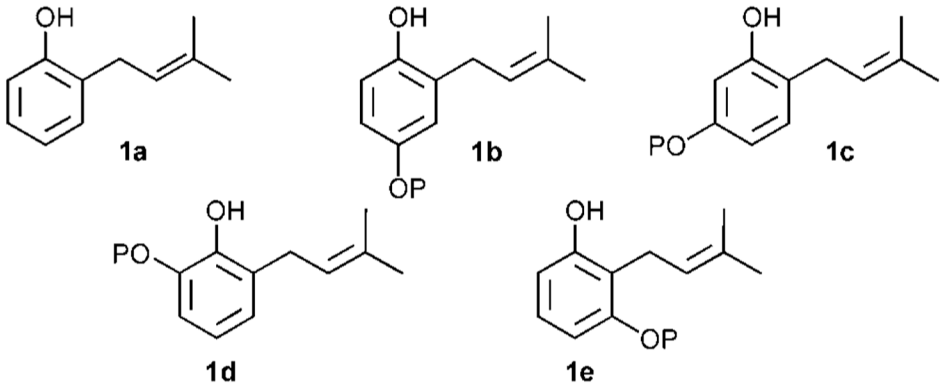
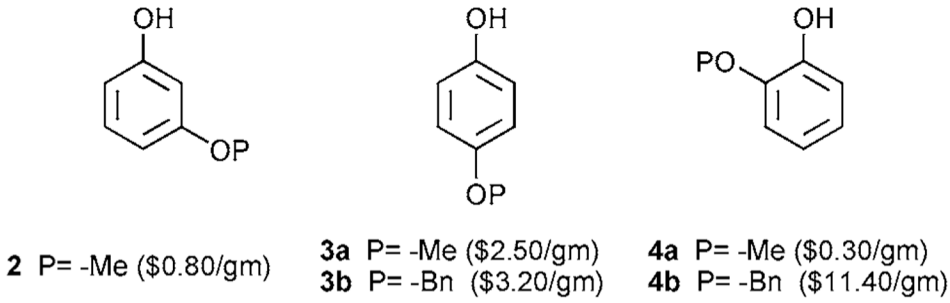


Figure 1.
All of the analogs of differentially protected *ortho*-prenylated dihydroxyphenol nuclei (PH).

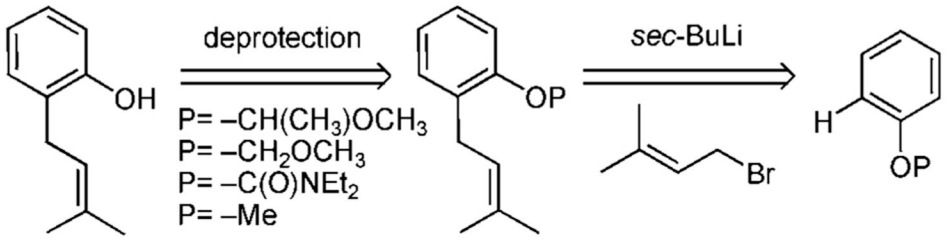


2 P= -Me ($0.80/gm)

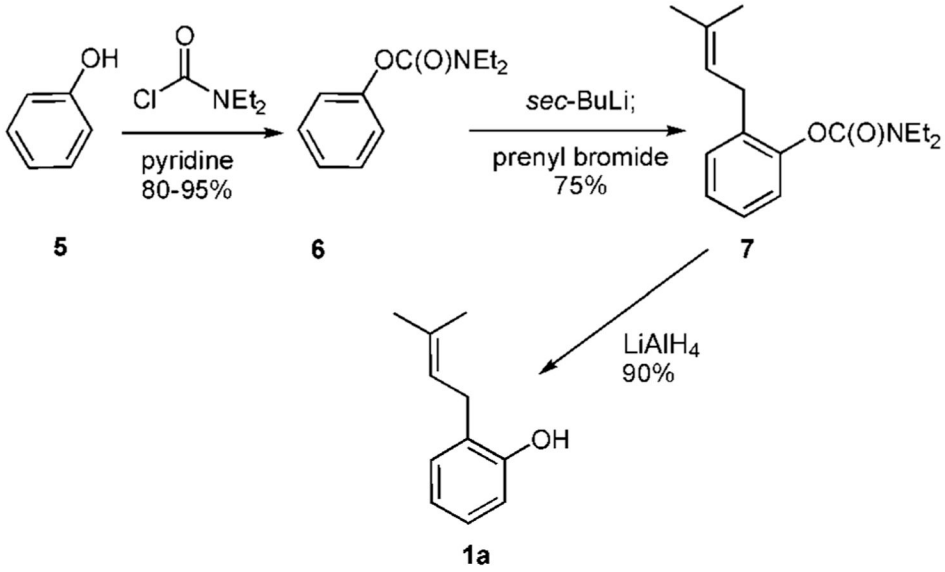
3a P= -Me ($2.50/gm)
3b P= -Bn ($3.20/gm)

4a P= -Me ($0.30/gm)
4b P= -Bn ($11.40/gm)

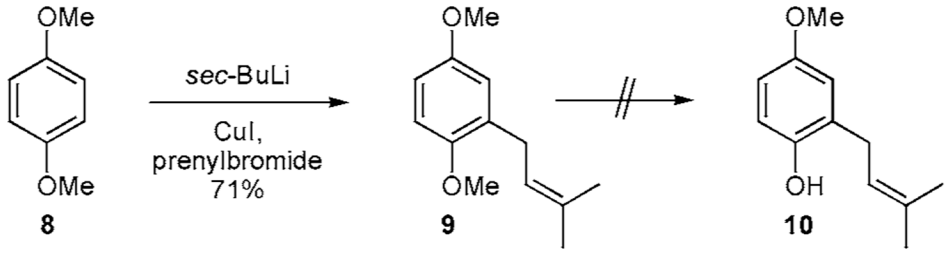
Figure 2.
Differentially protected dihydroxyphenols that are commercially available.



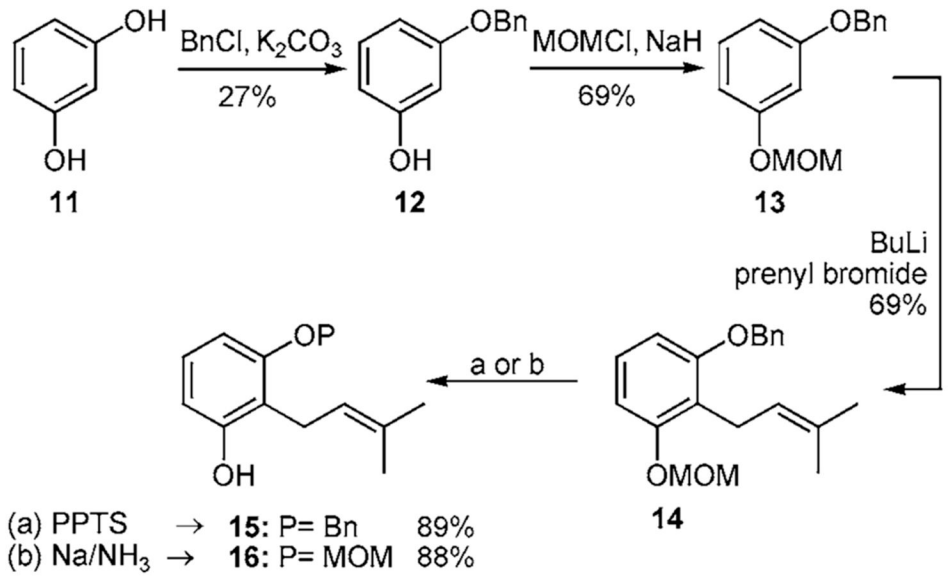
Scheme 1.
The general D*o*M strategy



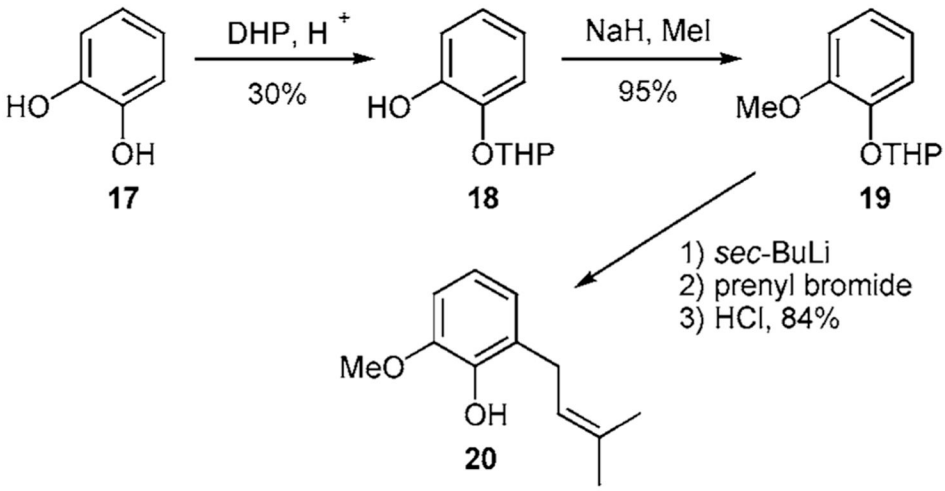
Scheme 1a.



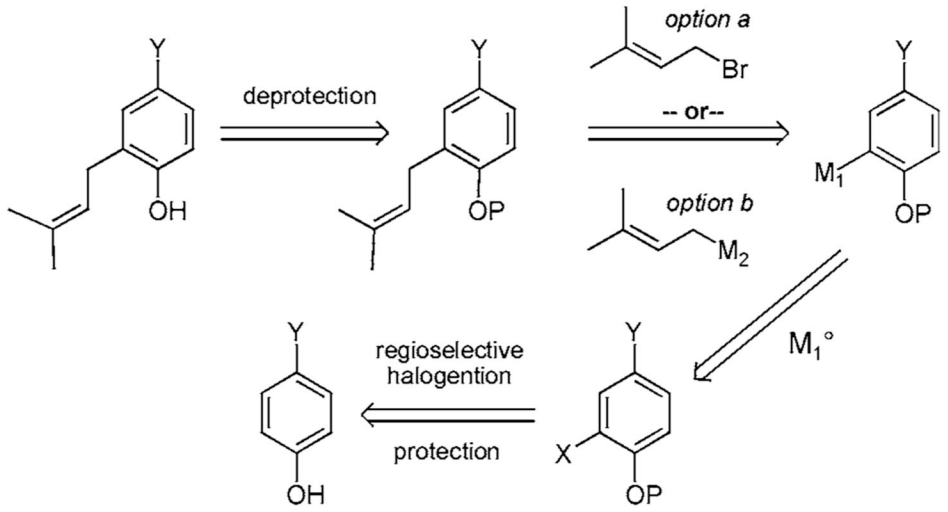
Scheme 1b.



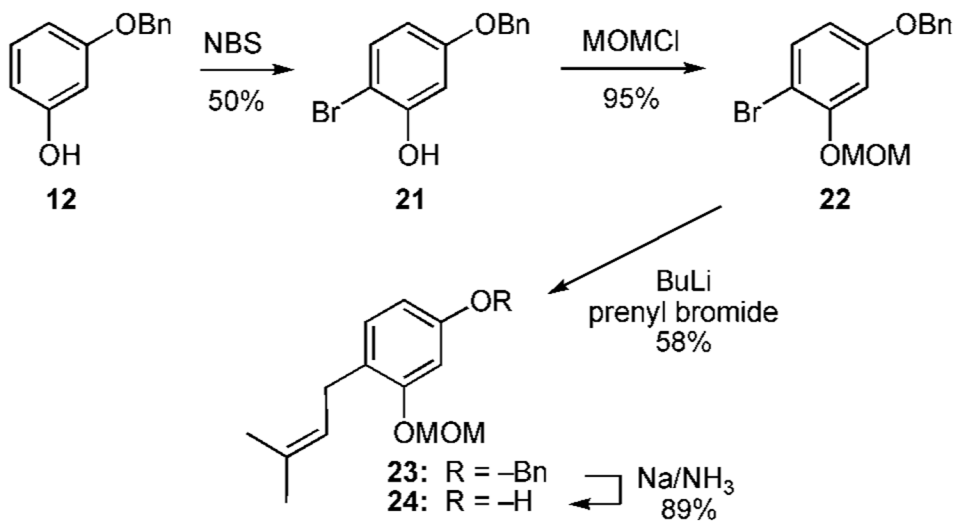
Scheme 1c.



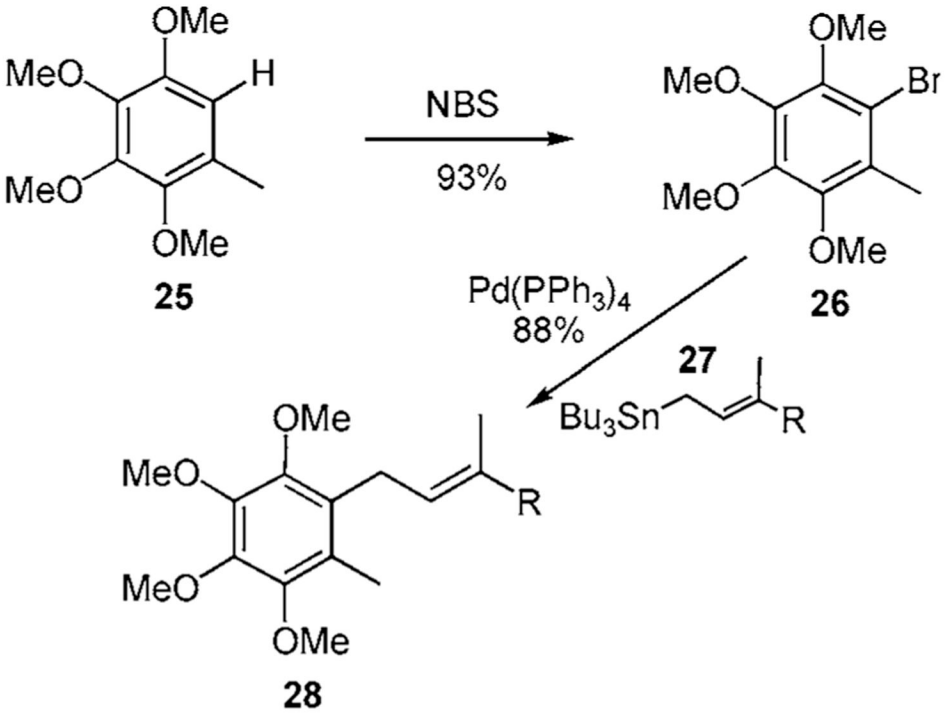
Scheme 1d.



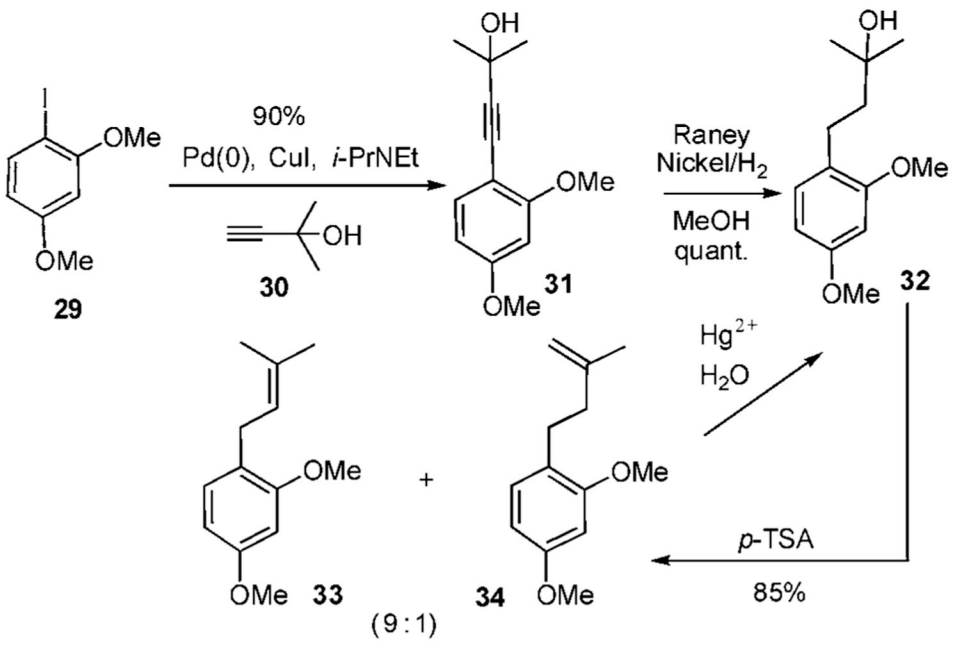
Scheme 2.
General metal exchange strategies for prenylation



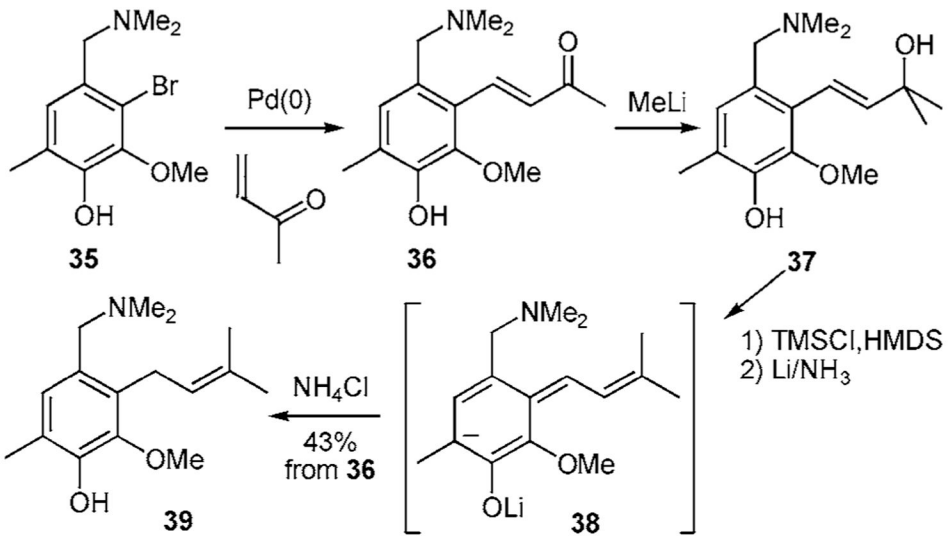
Scheme 2a.



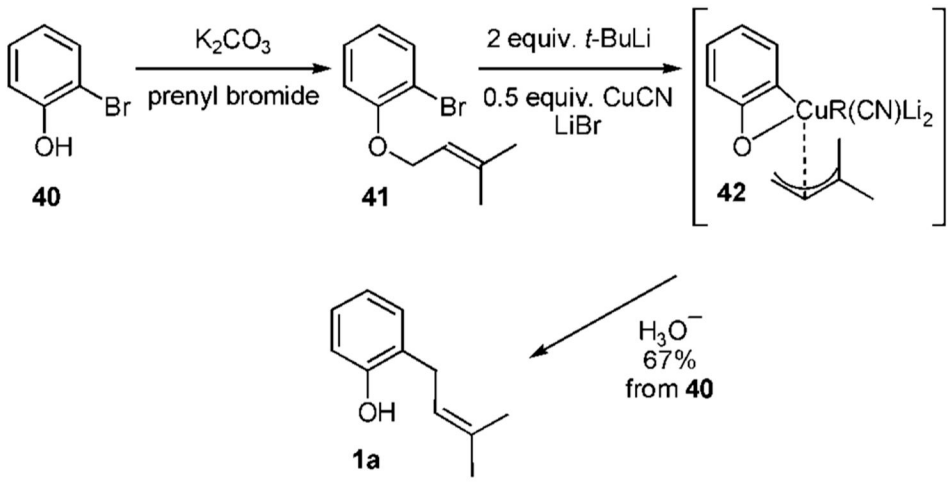
Scheme 2b.



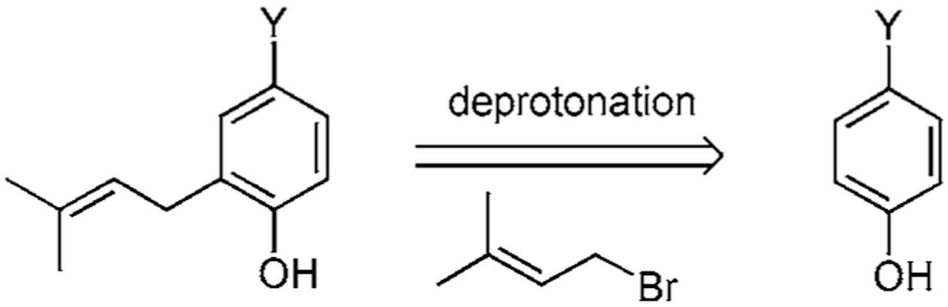
Scheme 2c.



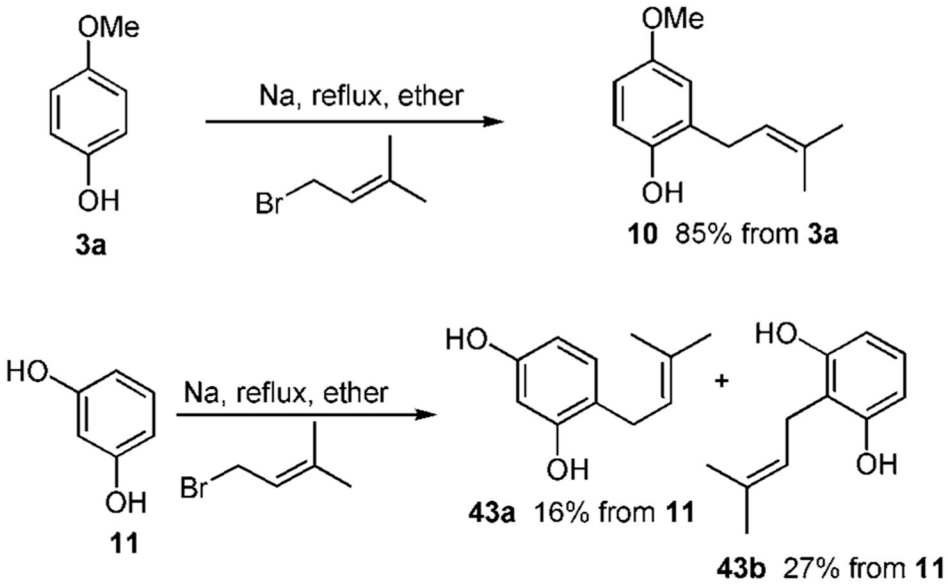
Scheme 2d.



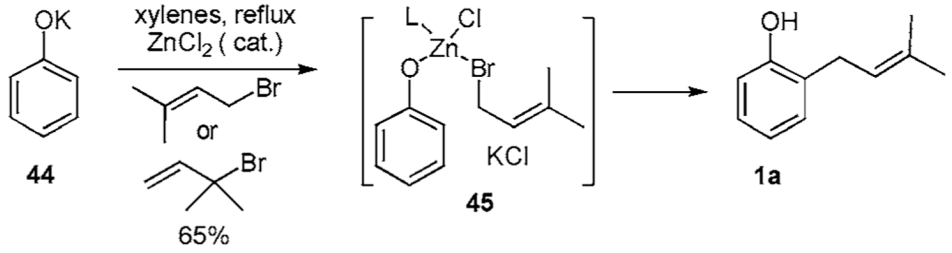
Scheme 2e.



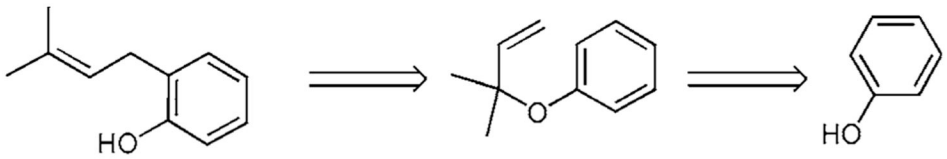
Scheme 3.
General phenoxide C-prenylation strategy



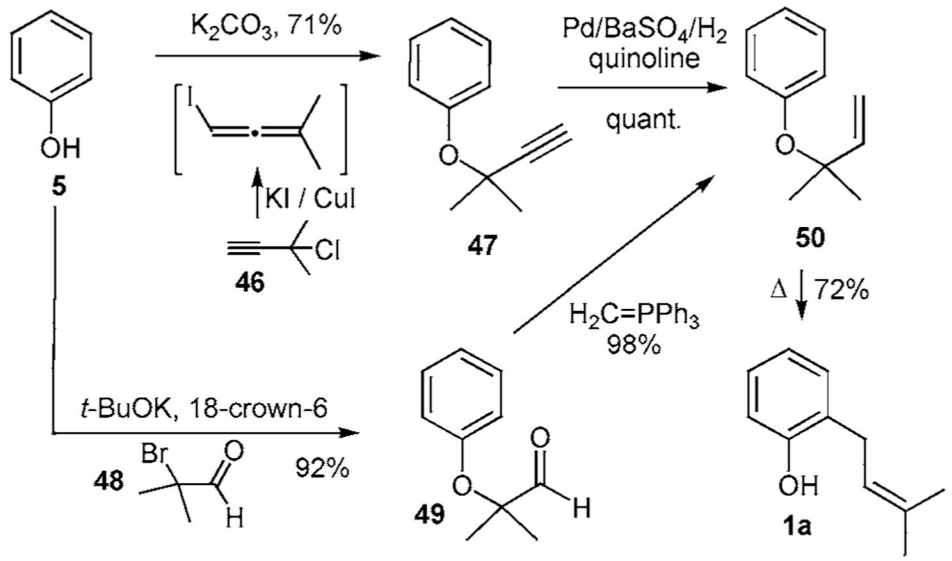
Scheme 3a.



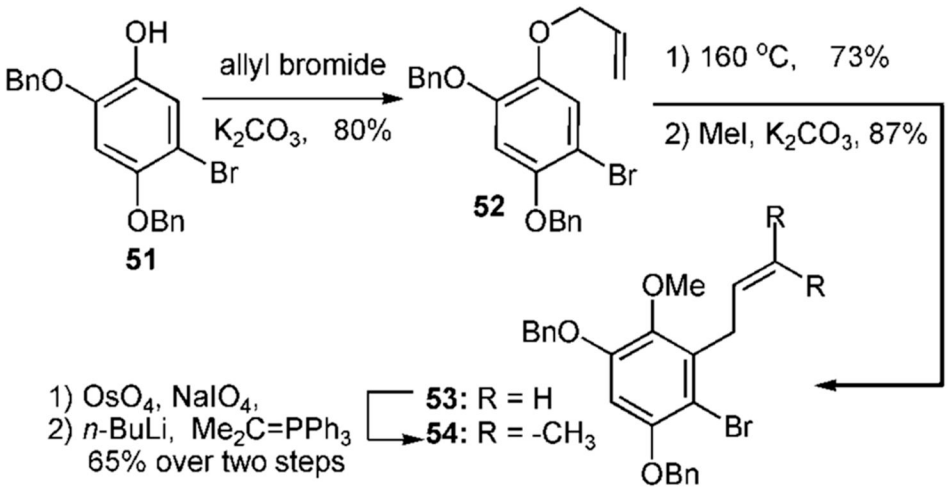
Scheme 3b.



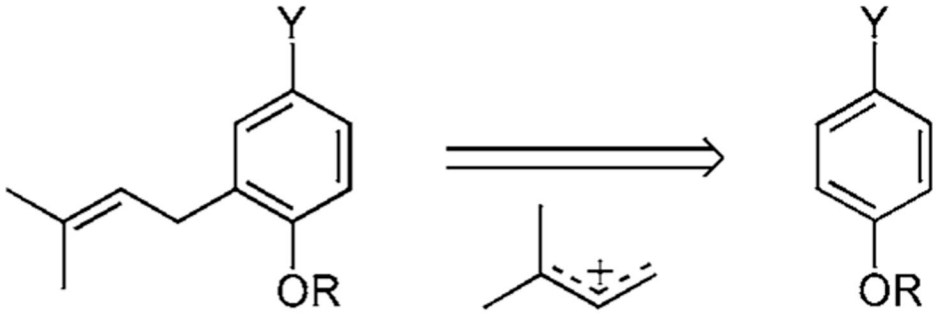
Scheme 4.
The general Claisen rearrangement strategy



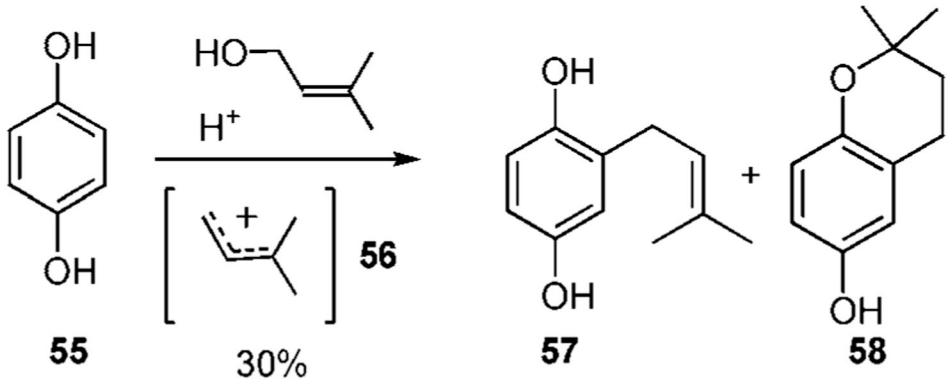
Scheme 4a.



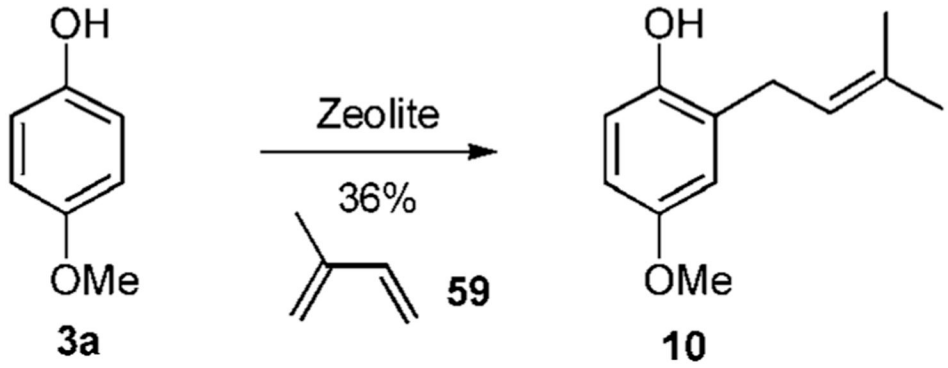
Scheme 4b.



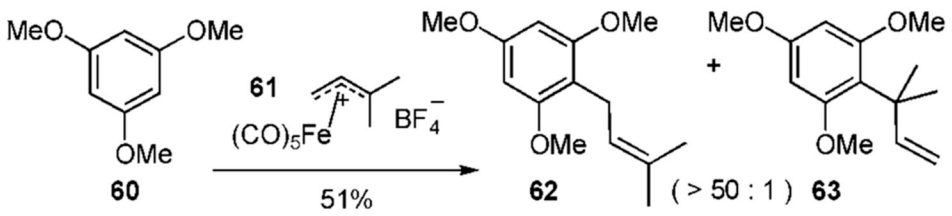
Scheme 5.
General Friedel–Crafts prenylation strategy



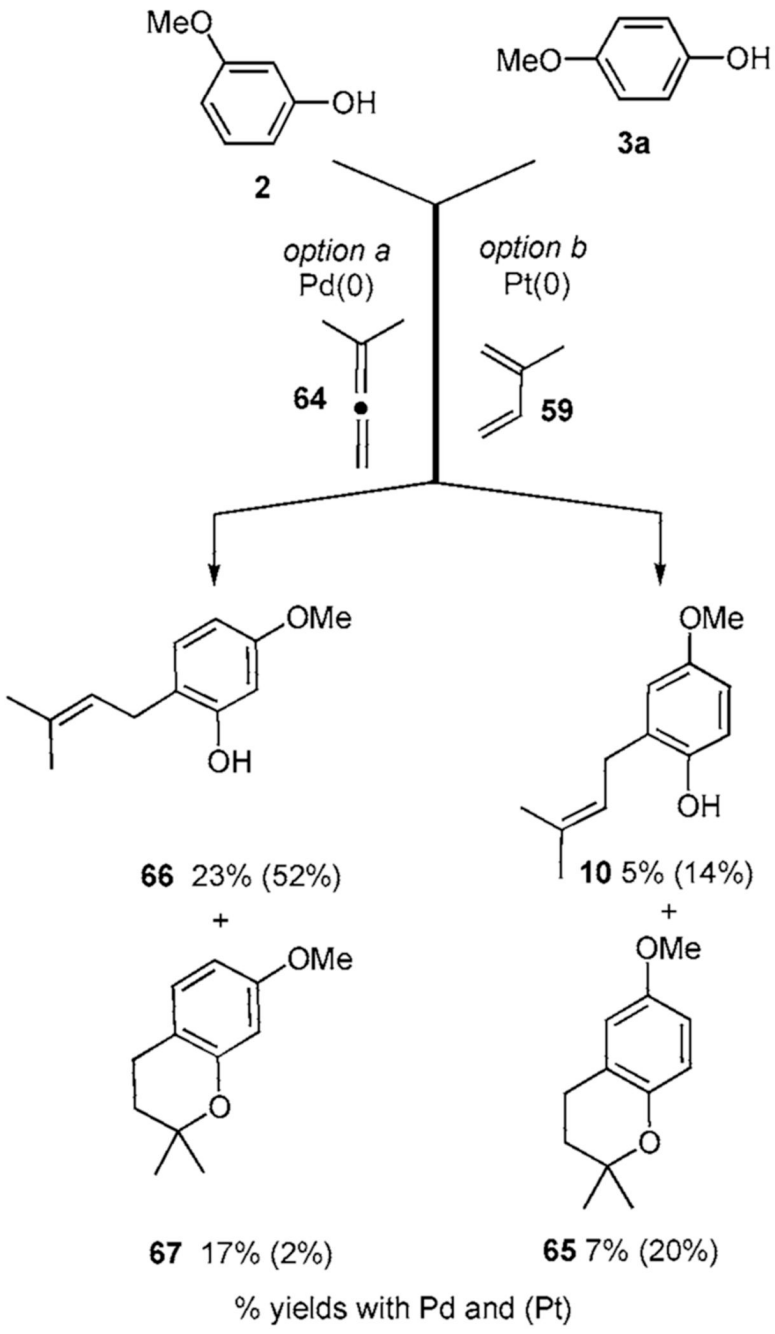
Scheme 5a.



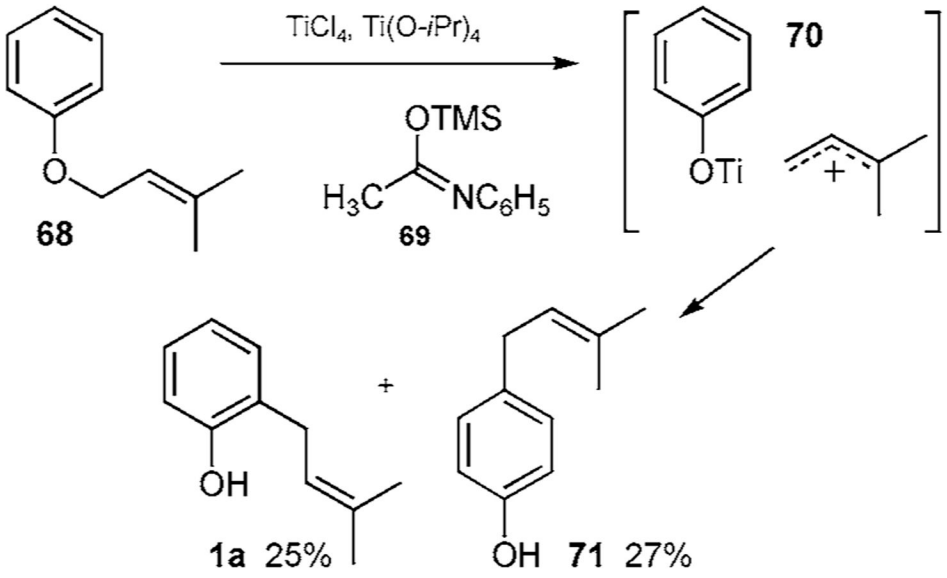
Scheme 5b.



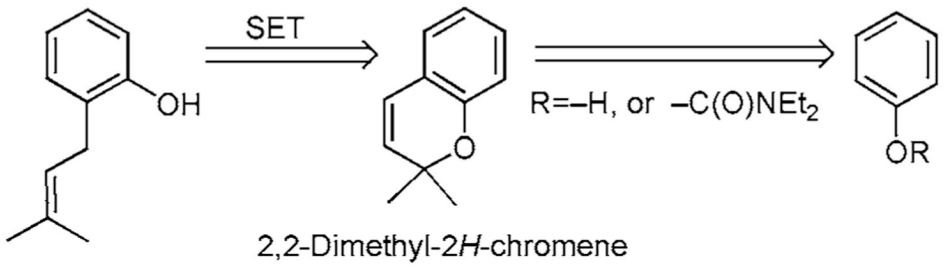
Scheme 5c.



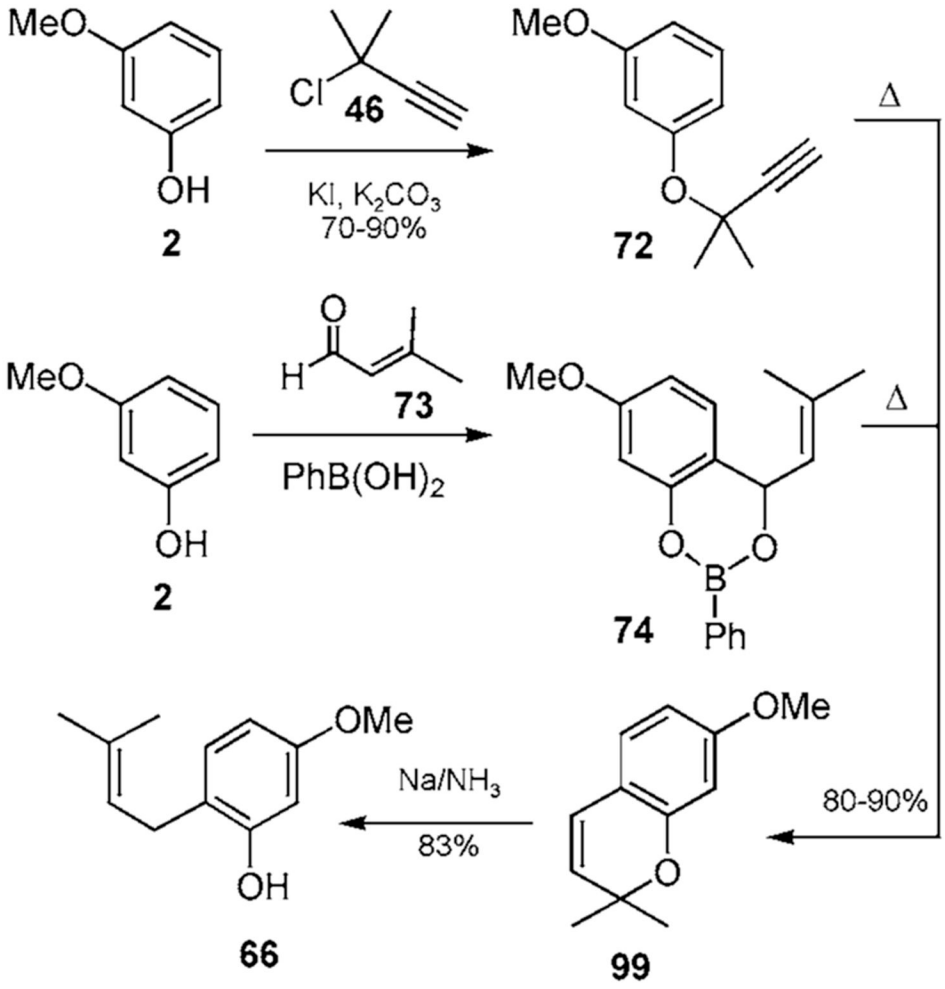
Scheme 5d.



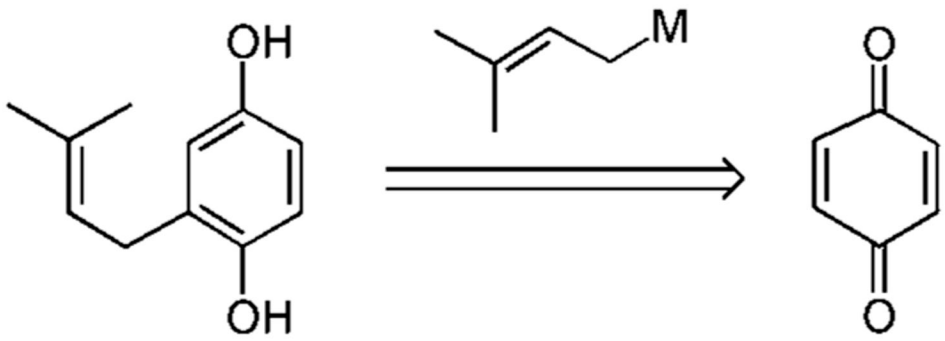
Scheme 5e.



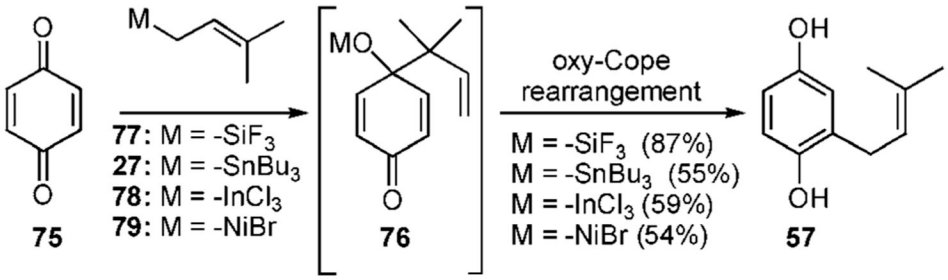
Scheme 6.
General Birch reductions strategy



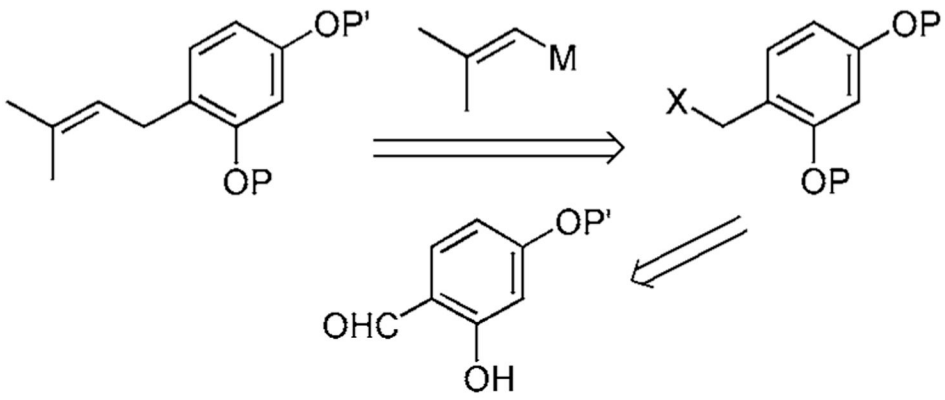
Scheme 6a.



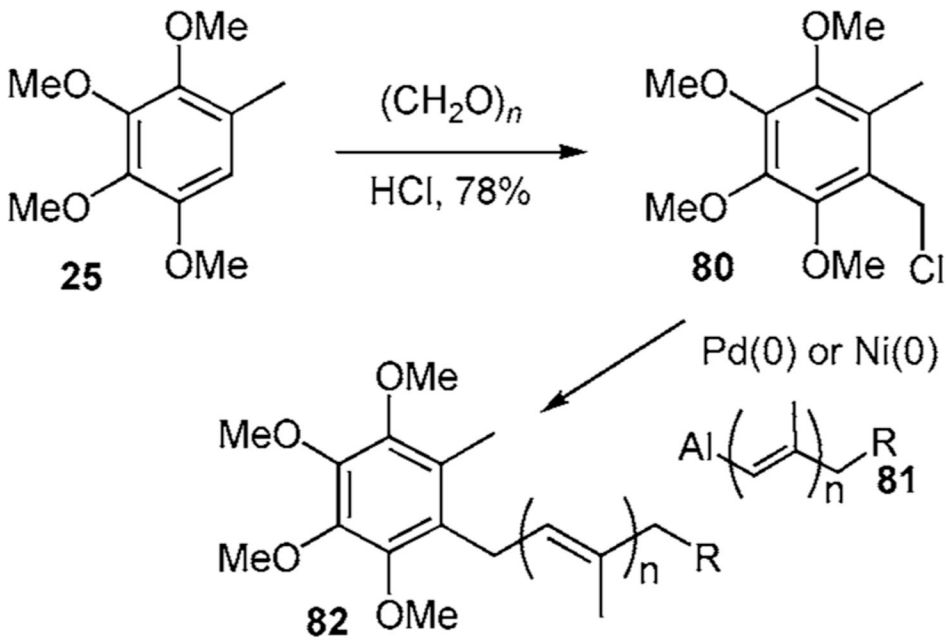
Scheme 7.
1,4-Conjugate addition strategy



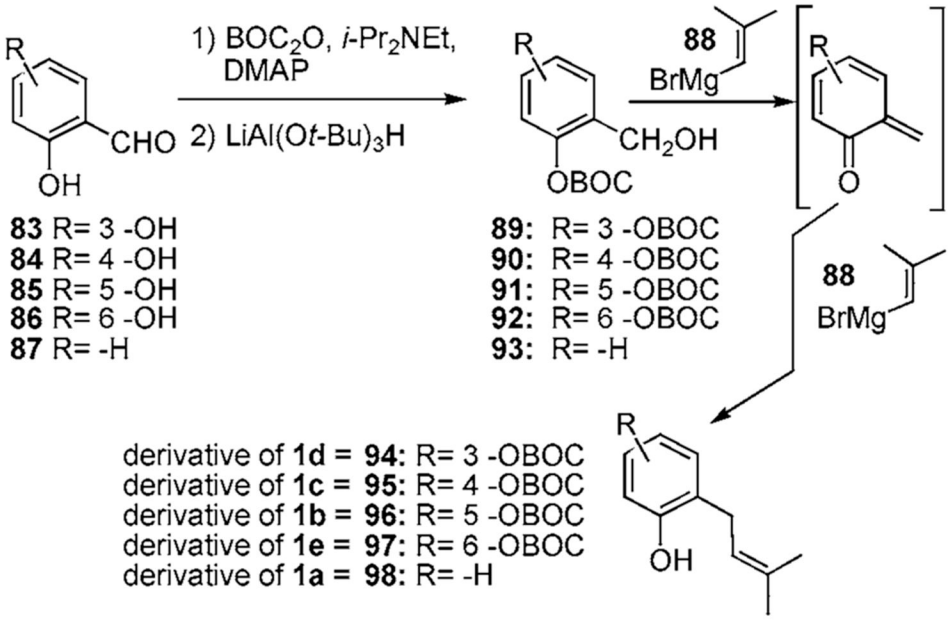
Scheme 7a.



Scheme 8.
General benzylic coupling strategy



Scheme 8a.



Scheme 8b.