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Oxidative Friedel−Crafts Reaction and its Application to the Total Syntheses of *Amaryllidaceae* Alkaloids

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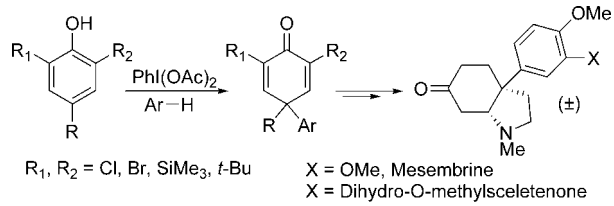

An oxidative Friedel−Crafts reaction involving different aromatic compounds mediated by a hypervalent iodine reagent has been performed, using polysubstituted phenols. The strategy fits within the concept of "aromatic ring umpolung", which opens up novel opportunities in chemical synthesis. The reaction takes place in useful yields, and allows rapid access to highly functionalized compounds containing a dienone, a quaternary carbon center, and an aromatic ring. The product's skeleton is present in numerous natural products. As an illustration of the potential of this transformation, total syntheses of compounds belonging to the *Amaryllidaceae* alkaloids family such as *O*-methyljoubertiamine, mesembrine, and its natural derivative the dihydro-*O*-methylsceletenone have been achieved in eight/nine steps. The synthetic route to these molecules features a novel and efficient transformation on the basis of a Fukuyama and Michael−retro-Michael tandem process to produce the required nitrogen-containing ring system.

Introduction

Electron-rich aromatic compounds, such as phenols and their derivatives, normally react as nucleophiles. However, oxidative activation[1,2] can transform these aromatics into very reactive electrophilic species, which may be intercepted with appropriate mild nucleophiles in synthetically useful yields. An indication of how this objective can be achieved is apparent in the work of Kita,[1] who has shown that phenols[3] may be activated under the influence of hypervalent iodine reagents such as iodobenzene diacetate (DIB), an environmentally benign and inexpensive reagent, leading to species such as **2** (Figure 1). Electrophilic species **2** tends to react at the 4-position (cf. reaction mode b), at least with heteronucleophiles. We have recently determined that in a bimolecular process more hindered carbon-based

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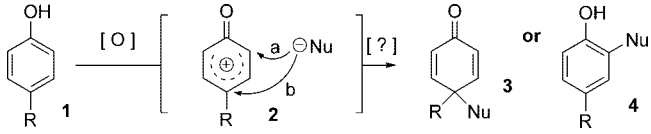

FIGURE 1. Phenol oxidative activation.

nucleophiles[3p] attack the presumed intermediate **2** at the least hindered position (pathway a), resulting in the formation of product **4**. As first demonstrated by Kita, this reaction is generally best performed in solvents such as hexafluoroisopropanol (HFIP). If one considers the behavior of the electrophilic species **2**, this reversal of reactivity may thus be thought of as involving "aromatic ring umpolung".[4]

An important aspect of this reaction is the possibility to rapidly generate C−C bonds. While similar transformations are known in the intramolecular mode,[5] broadening the scope to successfully achieve a similar intermolecular reaction would open up new opportunities in chemical synthesis. In this regard, we wished to explore the behavior of polysubstituted phenols as potential substrates for an oxidative addition with a carbon-based nucleophile, thus providing rapid access to dienones containing a quaternary carbon center. A key step to the realization of such a transformation was recently provided by Quideau and co-workers,[6] who disclosed examples of oxidative allylation of substituted 1-naphthol in aprotic solvents with phenyliodine bis-trifluoracetate (PIFA).[7] Moreover, a unique example of such an outstanding transformation has been demonstrated by the transformation of 4-methyl-2,6-di-*tert*-butylphenol into 4-methyl-4-phenylcyclohexa-2,5-dienone by treatment with chlorodiphenyl-13-iodane (Ph_2ICl).[8] Intriguingly, in this oxidative reaction, aromatic compounds are employed as both the electrophilic and nucleophilic species. In a bimolecular process, the erstwhile phenol displays electrophilic character and is trapped by an electron-rich aromatic compound in a manner consistent with the rules governing electrophilic aromatic substitution. To accomplish an intermolecular version of this transformation, we focused our attention toward the reaction of electron-rich aromatic species such as furan, veratrole, benzodioxolone, and anisole (and their derivatives) with polysubstituted phenols in an oxidative Friedel−Crafts process that would lead to products such as **3**. The selectivity observed on the electrophilic species would be controlled by choosing the appropriating protecting group at the ortho or para position (Figure 2).

Results and Discussion

The concept of "aromatic ring umpolung" provides new strategic opportunities in synthetic chemistry. In this paper, we illustrate a novel version of the Friedel−Crafts reaction that takes place via an oxidative process, and its direct application to the total syntheses of *Amaryllidaceae* alkaloids such as *O*-methyljoubertiamine,[12] mesembrine,[14−16] or 4,5-dihydro-4′-*O*-methylsceletenone.[17] As an initial investigation, we decided to test the reactivity of furan with simple polysubstituted phenols

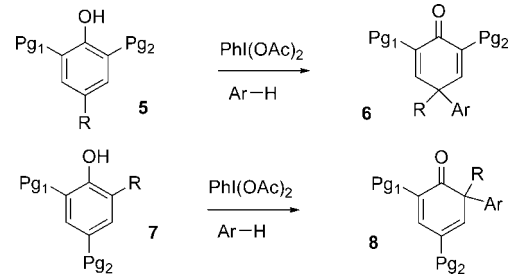

FIGURE 2. Protecting groups controlling reaction selectivity.

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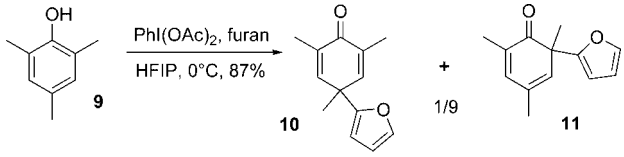
SCHEME 1



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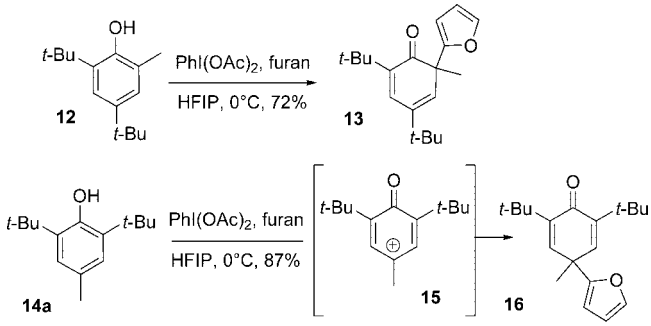

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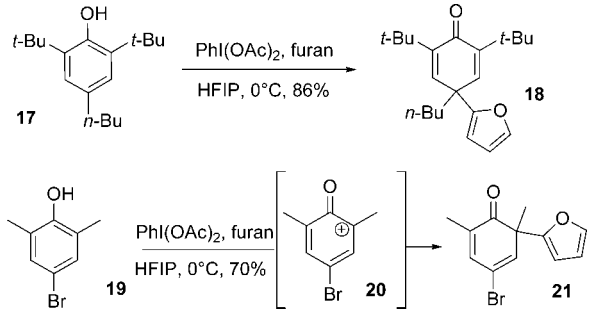


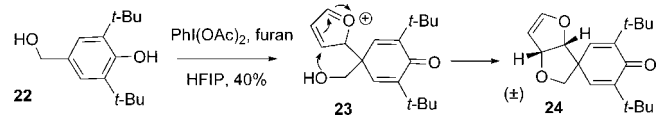
such as 2,4,6-trimethylphenol, **9**. This example allowed us to evaluate the feasibility and the regioselective outcome of the process (Scheme 1).

The reaction occurs in good yield and shows interesting selectivity (9/1) in favor of reaction at the ortho position. This reaction is performed in HFIP, and the use of trifluoroethanol (TFE) as the solvent in the reaction leads to addition of TFE on the substrate. To exercise better control of the regioselectivity, we switched to alkyl-di-*tert*-butylphenols as the electrophilic precursors. The choice of these phenols seemed reasonable as possibly allowing enhanced regiocontrol, because of the enhanced steric effect generated by the bulky *tert*-butyl groups, as shown in Scheme 2.

The presence of halide substituents could also provide interesting selectivity patterns due to their stereoelectronic effect. These atoms are efficiently introduced onto aromatic rings. In addition, bromo or iodo substituents may be useful handles to subsequently generate C−C bonds by means of palladium chemistry. The selectivity observed with alkyl substituents may be explained by considering that resonance form **20** is a weak contributor to the overall delocalized system and provides the more accessible position. In addition, alkyls are known to be electron-donor groups, whereas halides are electron-withdrawing (Scheme 3).

An interesting tricyclic product was observed upon treatment of compound **22** with furan. This transformation occurs via a formal [2+3] cycloaddition, as we have earlier reported,[9] but for the first time, the substitution occurs at the para position. A possible mechanism is described in Scheme 4.

SCHEME 4



To explore the scope and limitations of this reaction, we proceeded to study various electron-rich aromatic compounds with sufficient reactivity to trap the electrophilic species **15**. Our first attempt was on anisole, an inexpensive substrate. The reaction promoted by DIB afforded the desired compound, together with byproduct **26**, resulting from the addition of acetate on the species **15**, in a ratio (4/1) favoring **25a**.[10] The side reaction was easily eliminated by using phenyliodine bis-trifluoracetate (PIFA). Trifluoroacetic acid is a stronger acid and a weaker nucleophile than acetic acid, which explains why compound **25a** is formed exclusively (Scheme 5).

To broaden the scope of this reaction, different phenol derivatives were oxidized in the presence of anisole and 2-bromoanisole. The reaction occurs in good yield with alkyl-di-*tert*-butylphenols such as **14**. Halo-anisole and anisole display similar behavior, as shown in the Table 1 summary.

This transformation can also be performed regioselectively at the ortho position with compounds such as **12**. However, in this specific case DIB has to be used to afford **28**. Indeed, with PIFA the stronger trifluoroacetic acid released instantaneously induces a dienone−phenol rearrangement to afford the biphenyl **29** in 67% yield. It is likely that the dienone−phenol rearrangement occurs more rapidly with compounds such as **28** than with **25** due to the proximity of the carbonyl group (Figure 3).

Oxidative treatment of compound **14a** in the presence of benzodioxolone leads to the desired compound **30** in 64% yield (Scheme 6). Phenol **32**, which was identified as a byproduct, had not been present in the reaction with anisole under the same oxidative conditions and probably accounts for the difference in yield. The formation of this product can be rationalized if we consider that a quinone methide intermediate **15** is generated in the media that can then be trapped by benzodioxolone in a 1,6-Michael addition process. A similar result was observed with veratrole.

If polysubstituted phenols such as alkyl-di-*tert*-butylphenols are useful for exploring the scope of such a reaction, they are actually of low potential as starting materials for the total synthesis of natural products. Consequently, to move away from *tert*-butyl groups, we have investigated easily removable protecting groups capable of blocking selected positions on the aromatic ring. The choice of directing groups has to achieve two possible results: a steric effect similar to that of a *tert*-butyl, e.g., trimethysilyl, or an inductive effect such as that induced by an electronegative halide. An interesting choice would be the halides, which can be efficiently introduced onto an aromatic ring and are convenient handles to generate C−C bonds by means of palladium chemistry. This synthetic strategy could be useful for the total synthesis of a number of natural products. Unfortunately, oxidation of 2,6-dibromo cresol led to inextricable byproduct. A plausible explanation is that the two strong electron-withdrawing groups provide excessive destabilization of the generated electrophilic species **15**, which rapidly decomposes. To avoid this pitfall, we studied the combination of a halide and a TMS group as substituents. In this case, the umpoled intermediate is sufficiently stable to afford the desired compounds. These compounds are easily obtained from the

SCHEME 5

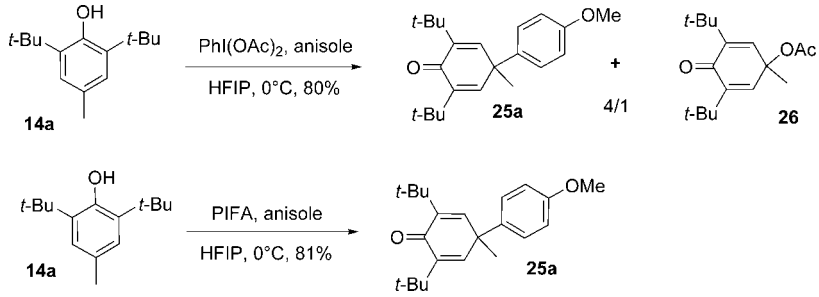
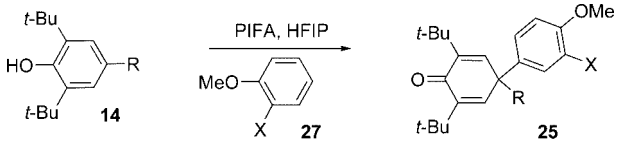


TABLE 1. Oxidative Addition with Anisole Derivatives



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b	Me	Br	82
c	Et	H	70
d	Bu	H	73

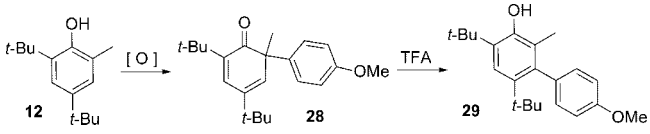
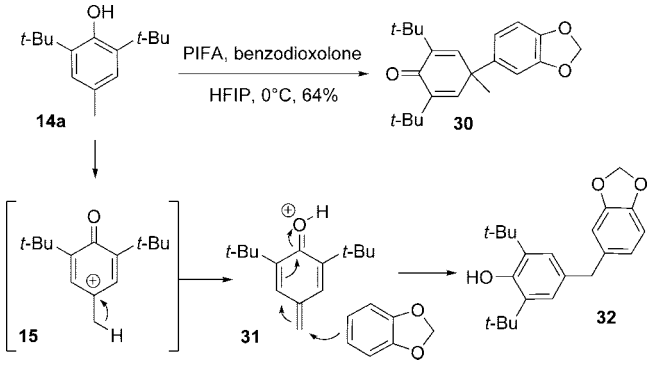


FIGURE 3. Dienone−phenol rearrangement.

SCHEME 6

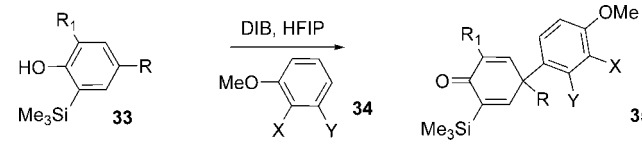


corresponding dibromophenols.[11] However, such protected phenols are not compatible with an oxidant such as PIFA, probably due to the high acidity generated in the medium, and in such cases, DIB has to be used despite the presence of a small amount of a byproduct such as **26** resulting from the addition of acetic acid on the electrophilic species (∼15%). To evaluate the scope of this reaction, different moderately nucleophilic functionalities were introduced on the side chain and different substituted anisoles were used. Numerous spectator functionalities such as alcohols, sulfonamides, and alkenes are compatible with the reaction conditions. A summary of representative experiments appears in Table 2.

This transformation takes place in the presence of these numerous functional groups, and although the efficiency of this transformation with such substituents calls for improvement [37−52%], the reaction outcome, i.e., the production of structural complex compounds containing functional groups from readily available simple starting materials, easily compensates for the moderate yields. Skeletons afforded by this transformation could lead to the highly functionalized cores found in numerous natural products such as the family of *Amaryllidaceae* alkaloids. Intriguingly, this reaction seems to occur equally with a very electron-withdrawing halide such as chloride **35b** or with **35c**. The selectivity observed with 3-bromoanisole **35c** has been verified by NMR NOE analysis. A remarkable, and useful, aspect of this transformation is the fact that the oxidation can be performed in the presence of an azide functionality (Figure 4). Indeed treatment of compound **33a** in the presence of 3-azido-anisole **36** affords compound **37** in 29% yield. The regioselectivity observed has been checked by NMR NOE analysis.

Despite the low yield observed, this example constitutes a rare example of a Friedel−Crafts reaction on a substrate containing an azide group. If this transformation is optimized, the stability of such functionality with respect to the reaction conditions could open up multiple opportunities for subsequent synthetic transformations, with potential applications in the total synthesis of natural products. Moreover, a treatment of such polysubstituted phenols with veratrole leads to the desired compound. Indeed, the oxidation of compound **33g** has gener-

TABLE 2. Oxidative Addition of Polysubstituted Phenols



entry	R	R_1	X	Y	yield
a	$CH_2CH_2OTBDPS$	Br	H	H	37
b	$CH_2CH_2OTBDPS$	Cl	H	H	38
c	$CH_2CH_2OTBDPS$	Cl	H	Br	52
d	CH_2CH_3	Br	H	H	43
e	$CH_2CH{=}CH_2$	Br	H	H	42
f	CH_2CH_2OMs	Br	H	Br	41
g	CH_2CH_2NMeNs	Br	I	H	44

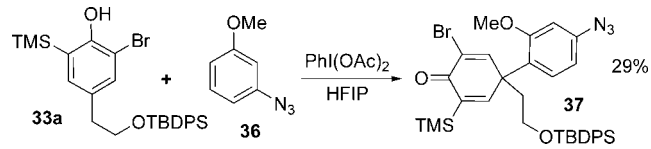
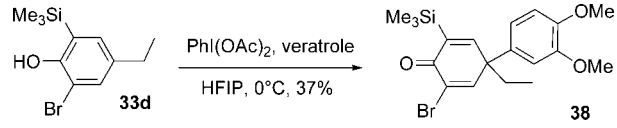


FIGURE 4. Regioselective addition of 3-azido-anisole.

SCHEME 7



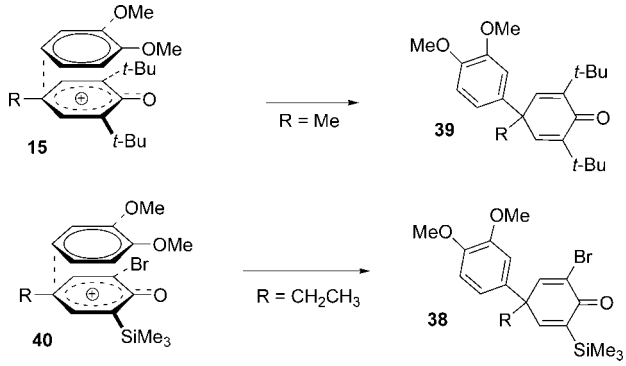


FIGURE 5. Plausible approach.

ated compound **38**, and a similar result has been observed with benzodioxolone (Scheme 7).

Mechanistically, we propose that the aromatic ring approaches the generated electrophilic species as illustrated in the next figure. We envisage that an orbital overlap due to a π-stacking interaction could explain the obtained results. In the case of the intermediate **15**, we believe that the steric crowding between the *tert*-butyl group and the second methoxy group of veratrole could perturb the approach and explain the formation of compounds such as **32** (Scheme 6). In the case of species **40**, the methoxy group may be located above the unhindered halide and the lack of this steric interaction would explain the absence of a compound such as **32**. In the case of anisole, since there are no steric interactions, only the desired reaction occurs (Figure 5).

We were interested in testing different silyl groups less fragile than a TMS in order to obtain yields close to those presented in Table 1. The corresponding polysubstituted phenols such as **43** or **45** are easily afforded by a retro-Brook rearrangement (Scheme 8). Unfortunately, these groups behave similarly to the TMS group in the reaction. The differences in yields between the di-*tert*-butyl and silyl polysubstituted phenols can be rationalized if we consider that the *tert*-butyl group is a better electron-donor group than silyl. The electron-donor effect generated by *tert*-butyl stabilizes the electrophilic species **15**, and consequently limits the formation of byproduct, but unfortunately this group is not easily removable.

However the presence of a silyl group leads to interesting opportunities for chemical transformation. Indeed, treatment of

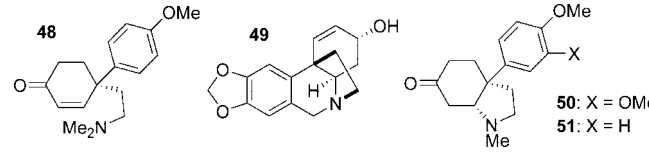


FIGURE 6. *Amaryllidaceae* alkaloids.

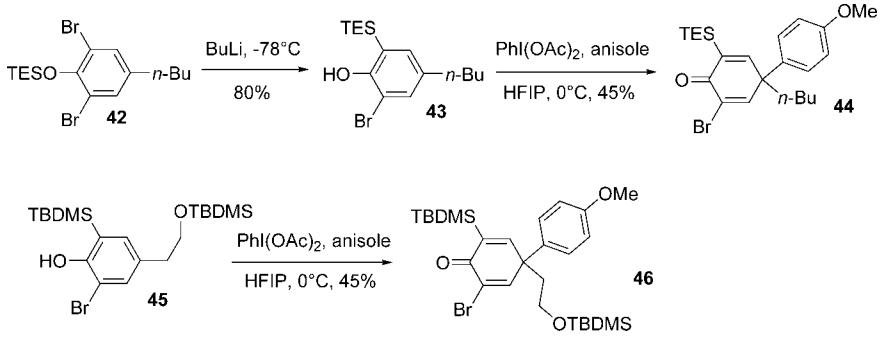
compound **35a** or **46** in the presence of TBAF leads in good yield to the bicyclic compound **47** with complete regioselectivity regarding the alkene containing the silyl group, the latter being subsequently removed under the reaction conditions (Scheme 9).

This oxidative Friedel−Crafts reaction allows rapid access to functionalized synthons containing a quaternary carbon center, a dienone, and an aromatic moiety, and different functionalities can be present on the side chain. Such an intermediate could afford some opportunity for total synthesis. Numerous natural products with such structures are known in the literature. The most well-known belong to the family of *Amaryllidaceae* alkaloids such as *O*-methyljoubertiamine,[12] **48**, crinnine,[13] **49**, mesembrine,[14−16] **50**, and its related analogues, 4,5-dihydro-4′-*O*-methylsceletenone,[17] **51** (Figure 6).

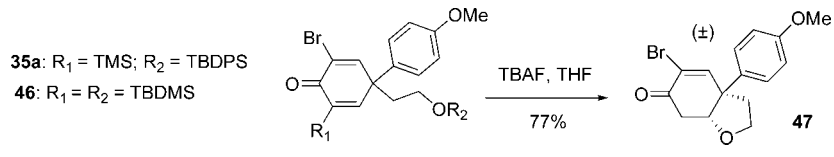
As an illustration of the potential of this method, we have synthesized two alkaloids of this family. Mesembrine and *O*-methyljoubertiamine are alkaloids present in *Sceletium tortuosum*. They have been shown to be very potent serotonin reuptake inhibitors, active at very low doses. Interest in Mesembrine alkaloids has recently been renewed with the discovery of several analogues found in various *sceletium* species. Extracts of these Southwest Africa plants are used as pharmacological drugs. The 4,5-dihydro-4′-*O*-methylsceletenone, **51**, is a simpler natural derivative of mesembrine isolated from *a. cordifolia*. Starting from the available 2-(4-hydroxyphenyl)ethanol **52**, dibromination with NBS was carried out to produce **53** in 91% yield. This latter was treated with HMDS followed by BuLi and TMSCl to give the tri-TMS product **54** in 87% yield. At this point, deprotection of the aliphatic and more nucleophilic alcohol present in the side chain was quantitatively achieved by treatment of **54** with PPTS in ethanol. The free alcohol on **55** was then transformed into a leaving group with MsCl and triethylamine to generate **56** in 92% yield (Scheme 10).

At this point, in order to introduce the necessary nitrogen moiety, an S_N2 reaction was performed between **56** and the corresponding

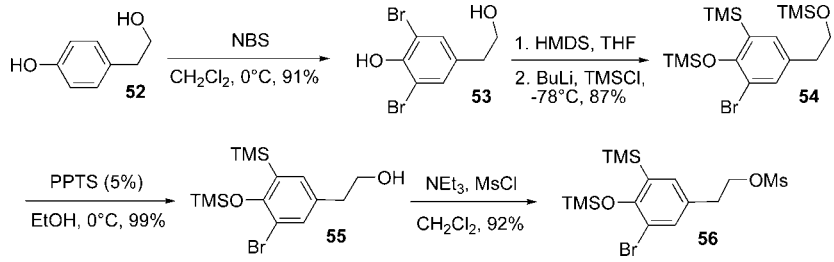
SCHEME 8



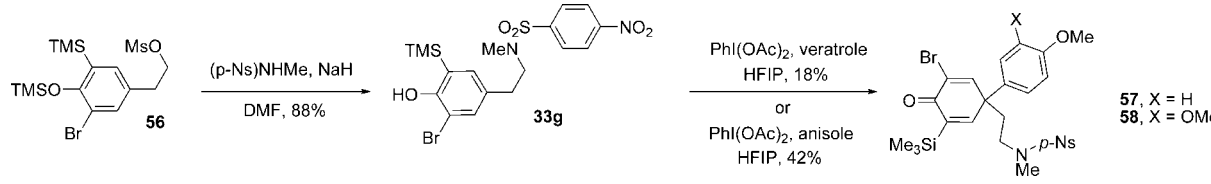
SCHEME 9



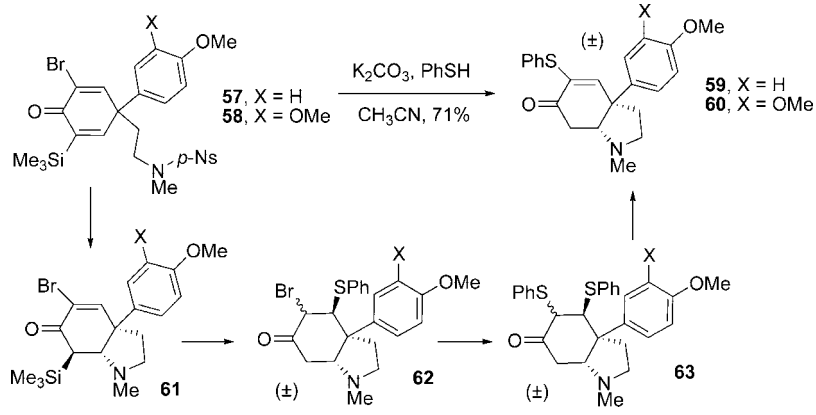
SCHEME 10



SCHEME 11



SCHEME 12

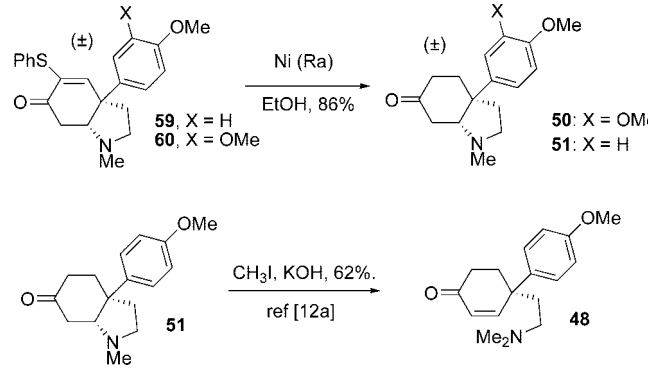


anion of *N*-methyl-*p*-nosylamide, generated in DMF with sodium hydride. This reaction proceeded in 88% yield; the phenol protecting *O*-TMS group was then removed in the same pot. Nosylamide or Fukuyama's sulfonamide[18] was chosen because it is known to be easily cleaved under mild reaction conditions. Compound **33g**, when treated with anisole or veratrole in oxidative conditions, led to the corresponding dienone **57** and **58**. While this process occurs in reasonable yield with anisole (42%), unfortunately oxidation of compound **33g** with veratrole only gave compound **58** in low yield (Scheme 11).

From these key compounds total syntheses of these natural products were efficiently accomplished via an unprecedented transformation afforded by treatment of compounds **57** or **58** with K_2CO_3 and thiophenol (Fukuyama's condition).[18] This novel transformation, occurring in good yield (71% yield), takes place via six successive distinct steps: (1) a nucleophilic aromatic substitution (S_NAr) deprotection leads to the corresponding free amine; (2) the free amine reacts via a Michael process to afford the bicyclic compound **61**; (3) desylilation followed by (4) addition of thiophenol leads to compound **62**; (5) substitution of the bromide by an S_N2 process occurs to generate **63**; and (6) a final retro-Michael reaction produces **59** (X = H) or **60** (X = OMe) (Scheme 12). This method provides rapid and efficient access to the main core of these alkaloids and may be assimilated to a Fukuyama and Michael−retro-Michael tandem process.

(18) Review: Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 105.

SCHEME 13



Total syntheses of mesembrine and 4,5-dihydro-4′-*O*-methylsceletenone were completed by treatment of compounds **59** and **60** with Raney Nickel in ethanol to reduce the alkene and remove the thio-ether, forming the desired natural product in 86% yield. These syntheses represent a first application of this new transformation and demonstrate its utility in chemical synthesis. In addition, the conversion of 4,5-dihydro-4′-*O*-methylsceletenone, **51**, into *O*-methyljoubertiamine, **48**, may be achieved by treatment with iodomethane[12a] (Scheme 13).

Conclusions

In summary, a novel transformation involving an oxidative Friedel−Crafts reaction on a variety of polysubstituted phenols

and electron-rich aromatic compounds has been carried out. The synthetic potential of this reaction has been illustrated by the synthesis of natural compounds belonging to the *Amaryllidaceae* alkaloids family. This transformation fits within the concept of "aromatic ring umpolung" and demonstrates the potential of such an approach. Further applications on more elaborate natural products based on this transformation are under study in our laboratories and will be disclosed in due course.

Experimental Section

Oxidative Process: General Procedure. To a stirred solution of phenol (0.1 mmol) in HFIP (0.5 mL) at 0 °C was added anisole or one of its derivatives (0.9 mmol, 9 equiv) or furan (0.7 mmol, 7 equiv), followed by addition of DIB or PIFA (Table 1) (0.15 mmol, 1.5 equiv) dissolved in HFIP (0.2 mL), over 20 s. The solution was stirred for another 2 min and quenched with sat. aq $NaHCO_3$ (2 mL). The aqueous phase was extracted with EtOAc (3 × 5 mL), and the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by chromatography (*n*-hexane:dichloromethane or *n*-hexane:ethylacetate as required).

***N*-{2-[3-Bromo-4-hydroxy-5-(trimethylsilyl)phenyl]ethyl}-*N*-methyl-4-nitrobenzenesulfonamide (33g).** To a solution of *N*-methyl-*p*-nosylamide (1.85 g, 8 mmol, 4 equiv) in dry DMF (7 mL) was added sodium hydride (60%, 320 mg, 8 mmol), then the solution was stirred during 30 min after the end of the gas evolution. Compound **56** (880 mg, 2 mmol) in dry THF (2 mL) was added dropwise and the resulting mixture was stirred at room temperature for 3 h. The reaction was quenched by addition of a saturated solution of NH_4Cl (10 mL) followed by the addition of ethyl acetate (30 mL). The organic layer was washed with brine (2 × 10 mL), tehn aqueous layers were combined and washed with ethyl acetate (2 × 20 mL). The combined organic layers were dried over sodium sulfate, filtered, and then concentrated. The crude mixture was purified by chromatography (SiO_2, hexanes/ethyl acetate, 83:12). A white solid was obtained, **33g** (854 mg, 1.76 mmol, 88%). Mp 161 °C; IR υ (cm^{-1}) 3496, 2941, 1529, 1347, 1244, 1161, 1077; ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, J = 8.8 Hz, 2H), 7.88 (d, J = 8.8 Hz, 2H), 7.20 (s, 1H), 7.06 (s, 1H), 5.63 (s, 1H), 3.30 (t, J = 7.0 Hz, 2H), 2.84 (s, 3H), 2.78 (t, J = 7.0 Hz, 2H), 0.30 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.9, 149.8, 144.0, 134.8, 132.8, 130.8, 128.2, 127.4, 124.2, 110.3, 51.8, 34.8, 33.5, −1.2; HRMS (ESI) calcd for $C_{18}H_{24}BrN_2O_5SSi$ $(M + H)^+$ 487.0359, found 487.0355.

***N*-{2-[3-Bromo-1-(4-methoxyphenyl)-4-oxo-5-(trimethylsilyl)-cyclohexa-2,5-dien-1-yl]ethyl}-*N*-methyl-4-nitrobenzenesulfonamide (57).** Pale yellow oil; IR υ (cm^{-1}) 2921, 1650, 1530, 1348, 1247, 1164; ^1H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, J = 8.8 Hz, 2H), 7.91 (d, J = 8.8 Hz, 2H), 7.29 (d, 1H, J = 2.3 Hz, 1H), 7.17 (d, 1H, J = 8.2 Hz, 2H), 7.03 (d, 1H, J = 2.3 Hz, 1H), 6.91 (d, J = 8.8, Hz, 2H), 3.81 (s, 3H), 2.99 (m, 1H), 2.89 (m, 1H), 2,83 (s, 3H), 2.48 (m, 2H), 0.22 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.1, 160.4, 159.3, 152.3, 150.1, 143.2, 139.7, 129.3, 128.3, 127.4, 125.2, 124.5, 114.7, 55.3, 50.7, 46.8, 35.9, 35.7, 1.5; HRMS (ESI) calcd for $C_{25}H_{30}BrN_2O_6SSi$ $(M + H)^+$ 593.0777, found 593.0781.

***N*-{2-[3-Bromo-1-(3,4-dimethoxyphenyl)-4-oxo-5-(trimethylsilyl)cyclohexa-2,5-dien-1-yl]ethyl}-*N*-methyl-4-nitrobenzenesulfonamide (58).** Pale yellow oil; IR υ (cm^{-1}) 2923, 1650, 1533, 1344, 1245; ^1H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, J = 8.8 Hz, 2H), 7.91 (d, J = 8.8 Hz, 2H), 7.29 (d, 1H, J = 2.3 Hz, 1H), 7.03 (d, 1H, J = 2.3 Hz, 1H), 6.87 (d, J = 8.8, Hz, 1H), 6.82 (d, J= 8.8 Hz, 1H), 6.71 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.98 (m, 1H), 2.89 (m, 1H), 2,83 (s, 3H), 2.48 (m, 2H), 0.22 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.0, 160.2, 152.1, 149.5, 149.0, 143.2, 139.7, 129.6, 128.3, 125.2, 124.5, 118.6, 111.6, 109.4, 55.9, 50.9, 46.9, 35.9, 29.6, −1.5; HRMS (ESI) calcd for $C_{26}H_{32}BrN_2O_7SSi$ $(M + H)^+$ 623.0883, found 623.0881.

3a-(4-Methoxyphenyl)-1-methyl-5-(phenylthio)-1,2,3,3a,7,7a-hexahydro-6*H*-indol-6-one (59). To a solution of **57** (24 mg, 0.04 mmol) in degassed acetonitrile (1 mL) was added K_2CO_3 solid (28 mg, 0.2 mmol) and thiophenol (22 mg, 0.2 mmol). The solution was stirred overnight and filtrated directly on silica (ethyl acetate−hexane−NEt_3, 49:49:2) to afford **59** (11 mg, 0.03 mmol, 71%) as a pale yellow oil. IR υ (cm^{-1}) 2920, 1603, 1506, 1248; ^1H NMR (300 MHz, acetone-d_6) δ 7.47 (d, J = 7.6 Hz, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.32 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.33 (s, 1H), 3.78 (s, 3H), 3.20 (td, J = 9.4, 2.9 Hz, 1H), 2.69 (br, 1H), 2.63 (dd, J = 15.8, 2.3 Hz, 1H), 2.56 (dd, J = 15.8, 2.3 Hz, 1H), 2.52 (t, J = 8.8 Hz, 1H), 2.36 (td, J = 8.8, 2.9 Hz, 1H), 2.27 (s, 3H), 2.02 (m, 1H); ^{13}C NMR (150 MHz, acetone-d_6) δ 194.2, 160.5, 151.5, 137.0, 135.2, 135.0, 134.4, 131.3, 129.7, 129.6, 115.8, 75.0, 57.1, 56.5, 54.4, 41.0, 40.4, 38.5. HRMS (ESI) calcd for $C_{22}H_{24}NO_2S$ $(M + H)^+$ 366.1528, found 366.1523.

3a-(3,4-Dimethoxyphenyl)-1-methyl-5-(phenylthio)-1,2,3,3a,7,7a-hexahydro-6*H*-indol-6-one (60). The same procedure was used with compound **58** (12.5 mg, 0.02 mmol) to afford **60** (5.8 mg, 0.014 mmol, 73%) as a pale yellow oil: IR υ (cm^{-1}) 2922, 1606, 1501, 1242; ^1H NMR (600 MHz, acetone-d_6) δ 7.47 (d, J = 7.6 Hz, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.33 (t, J = 7.6 Hz, 1H), 6.92 (d + s, J = 8.2 Hz, 2H), 6.88 (d, J = 8.8 Hz, 1H), 6.33 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.20 (td, J = 9.4, 2.9 Hz, 1H), 2.73 (br, 1H), 2.63 (d, J = 17.0 Hz, 1H), 2.60 (d, J = 17.0 Hz, 1H), 2.52 (t, J = 8.2 Hz, 1H), 2.39 (td, J = 8.8, 2.9 Hz, 1H), 2.27 (s, 3H), 2.02 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.3, 151.5, 151.3, 150.3, 135.2, 135.0, 134.5, 131.3, 129.7, 120.8, 113.7, 112.7, 74.8, 57.1, 57.1, 57.0, 54.7, 41.0, 40.5, 38.7; HRMS (ESI) calcd for $C_{23}H_{26}NO_3S$ $(M + H)^+$ 396.1633, found 396.1641.

Mesembrine (50). To a solution of **60** (5.5 mg, 0.014 mmol) in a melange of EtOH/ethyl acetate (1 mL, 2:1) was added a small amount of Ni (Raney) at 0 °C until the reaction was completed as indicated by TLC (SiO_2, hexanes/ethyl acetate, 1/3). The mixture was filtered, and then concentrated under vacuo. Purification of the resulting crude product by column chromatography (ether) afforded **50** (3.5 mg, 0.012 mmol, 86%) as a yellow oil identical with the natural product. IR υ (cm^{-1}) 2926, 1719, 1519, 1455, 1254; ^1H NMR (600 MHz, C_6D_6) δ 6.75 (d, J = 2.3 Hz, 1H), 6.69 (dd, J = 8.8, 2.3, 1H), 6.60 (d, J = 8.8, 1H), 3.48 (s, 3H), 3.45 (s, 3H), 2.85 (td, J = 8.2, 2.3 Hz, 1H), 2.69 (t, J = 3.5 Hz, 1H), 2.48 (d, J = 15,8, 2.9 Hz, 1H), 2.35 (m, 1H), 2.31 (dd, J = 15.8, 3.5 Hz, 1H), 2.06 (s, 3H), 2.04 (m, 2H), 1.93−1.69 (m, 4H); HRMS (ESI) calcd for $C_{17}H_{24}NO_3$ $(M + H)^+$ 290.1756, found 290.1751.

4,5-Dihydro-4′-*O*-methylsceletenone (51). The same procedure was used as with **59** (7.3 mg, 0.02 mmol) to afford **51** (4.5 mg, 0.17 mmol, 87%) as a yellow oil identical with the natural product. IR υ (cm^{-1}) 2924, 1716, 1455; ^1H NMR (600 MHz, C_6D_6) δ 7.00 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.8, 2H), 3.37 (s, 3H), 2.82 (td, J = 8.2, 2.3 Hz, 1H), 2.60 (t, J = 3.5 Hz, 1H), 2.44 (dd, J = 15.8, 2.9 Hz, 1H), 2.33 (m, 1H), 2.22 (dd, J = 15.8, 3.5 Hz, 1H), 2.04 (s, 3H), 2.00 (m, 2H), 1.90−1.66 (m, 4H); HRMS (ESI) calcd for $C_{16}H_{22}NO_2$ $(M + H)^+$ 260.1651, found 260.1645.

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Supporting Information Available: ^1H and ^{13}C NMR data for all compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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