JOC The Journal of Organic Chemistry
Cite This: J. Org. Chem. XXXX, XXX, XXX−XXX
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pubs.acs.org/joc

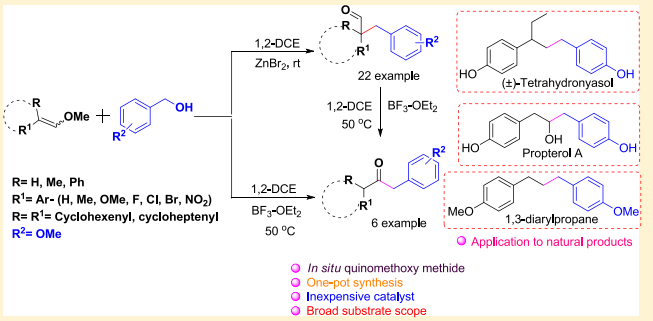
Direct α-Benzylation of Methyl Enol Ethers with Activated Benzyl Alcohols: Its Rearrangement and Access to (±)-Tetrahydronyasol, Propterol A, and 1,3-Diarylpropane

Tapan Kumar Jena and Faiz Ahmed Khan*

Department of Chemistry, Indian Institute of Technology Hyderabad, Kandi, Sangareddy, Telangana 502 285, India

Supporting Information

ABSTRACT: Herein, we report a one-pot Lewis acid mediated synthesis of bi- and triarylpropanal derivatives and their corresponding isomeric ketones from aromatic enol ethers. This transformation takes place via nucleophilic attack of enol ethers to electron-rich benzyl alcohols. The substrate scope of this indicates that it might proceed via quinomethoxy methide as a key intermediate leading to propanal derivatives, and their Wagner−Meerwein rearrangement afforded isomeric ketones. Further, this methodology was applied for the synthesis of (±)-tetrahydronyasol, propterol A, and 1,3-diarylpropane.



1,3-Biarylated carbonyl compounds are among the versatile intermediates in organic synthesis for the preparation of various biologically, naturally occurring compounds.[1] Owing to their biological properties present in several small natural products and pharmaceutical agents (Figure 1), many

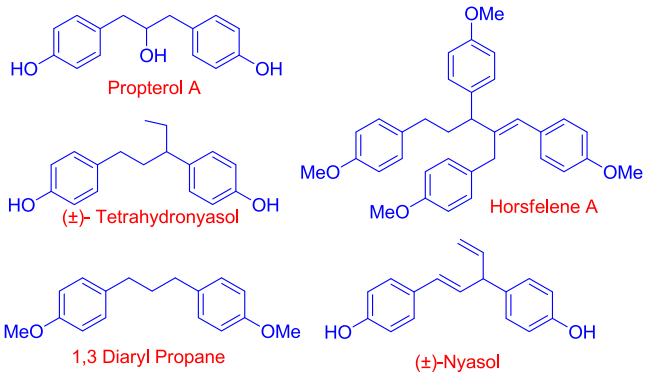


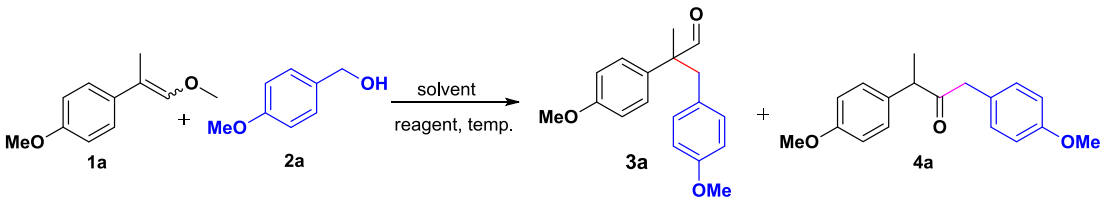
Figure 1. Biologically important natural products.

methods have been developed for their synthesis.[2−5] Carbonyl compounds with aldehyde functional groups are prone to undergo skeletal rearrangement to ketones via 1,2-group shift,[6] and strategies used for the synthesis of diarylated ketone derivatives include C−H insertion of diazoalkane,[7] Dakin−West syntheses,[8] and the carbonylative coupling of benzyl bromide.[9] However, for the direct construction of a C−C bond for preparing substituted carbonyl compounds, α-alkylation is one of the fundamental approaches in organic synthesis.[10] Moreover, they enable the access creation of stereocenters or quaternary centers at α-position of aldehydes or ketones, which are highly epidemic in natural products. Because of this, these reactions have invigorated scientific exploration in the field of organic synthesis. As alcohols are readily available, their exploitation in C−C bond-forming reactions has become one of the suggestive approaches in direct functionalization of α-C−H bonds of carbonyl compounds in place of halogenated compounds. This approach avoids the formation of stoichiometric amount of byproducts and makes reaction environmentally friendly by the formation of water as a byproduct.[11] Moreover, the widely used methods for α-alkylation of carbonyl compounds involve expensive transition-metal catalysts.[12,13] Non-metal-catalyzed methods have also been developed for the construction of a quaternary center at the α-position by means of enamine catalysis with a wide range of electrophiles.[14] In this direction, List and co-workers have reported the first amino catalyzed α-alkylation of branched aldehydes with benzyl bromide as alkylating agent.[15] Cozzi et al. used the amino organocatalyst and acid cocatalyst to activate the aldehydes via enamine intermediates and Bronsted acids for the formation of diaryl methyl cations from the corresponding diaryl methanols.[16] Mazet et al. also reported Pd-catalyzed α- and γ-benzylation of aldehydes for the formation of quaternary centers using benzyl methyl carbonates.[17] Due to the possible side reactions, α-functionalization is particularly challenging.[18] To the best of our knowledge, a direct synthesis of 1,3-bi- or tri arylated carbonyl derivatives with activated benzyl alcohol and methyl enol ether in one step remains unexplored.

Herein, we describe a one-pot synthesis of di- and triaryl propanals using a simple, zinc salt as catalyst and their

Received: July 29, 2019
Published: September 23, 2019

Table 1. Optimization of Reaction Conditions[a]



entry	reagent (equiv)	temp (°C)	yield[b] (%) of **3a**	yield[b] (%) of **4a**
1	$BF_3{\cdot}OEt_2$ (0.5)	rt	70	ND
2	$BF_3{\cdot}OEt_2$ (1.5)	50		73
3	$FeCl_3$ (1.0)	50		54
4	$ZnCl_2$ (1.0)	rt	63	ND
5	$ZnCl_2$ (2.0)	50	59	ND
6	$ZnBr_2$ (1.0)	rt	86	ND
7	$ZnBr_2$ (2.0)	50	79	ND

[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.4 mmol), 1,2-DCE (2 mL), 4–6 h. [b]Isolated yields. ND = not detected.

skeletal rearrangement to isomeric ketones via direct α-benzylation of methyl enol ethers with activated primary benzyl alcohols. Further, synthesized compounds via this methodology have been utilized for the synthesis of (±)-tetrahydronyasol, propterol A, and 1,3-diarylpropane in short synthetic routes.

To find the optimum reaction conditions for alkylation, 1-methoxy-4-(1-methoxyprop-1-en-2-yl)benzene (**1a**) and 4-methoxybenzyl alcohol (**2a**) were chosen as model substrates.

Initially, the reaction was carried out in the presence of $BF_3{\cdot}OEt_2$ as Lewis acid catalyst in 1,2-dichloroethane at room temperature, which furnished the desired product **3a** in 70% yield (entry 1, Table 1). When the reaction temperature was raised to 50 °C, a new product started to appear (TLC monitoring) with concomitant depletion of **3a**. Subsequent additions of two 0.5 equiv of $BF_3{\cdot}OEt_2$ batches at 30–40 min intervals allowed the reaction to proceed to completion with complete disappearance of **3a**. On the basis of the spectral data, the new product was assigned as ketone **4a**, a rearranged product of **3a**. When the reaction was performed with 1.0 equiv of $FeCl_3$ at 50 °C, we observed the rearranged product **4a** in 54% yield (entry 3, Table 1). Among the different Lewis acids examined, $ZnBr_2$ was found to be efficient for α-benzylation transformation to obtain the product **3a** in 86% (entry 6, Table 1). Interestingly, **4a** was not detected even at 50 °C with zinc salts (entry 5 and 7, Table 1). For the selective preparation of benzylated isomeric ketone **4a**, $BF_3{\cdot}OEt_2$ was found to give best results (73%, entry 2, Table 1).

Encouraged by these observations from the optimized condition, we have investigated the substrate scope of reaction (Table 2) using the optimum reaction condition mentioned in (entry 6 of Table 1). First, we examined different substituted derivatives of ketone and aldehyde derived enol ethers with electron-donating as well as electron-withdrawing substituents. As shown, a wide variety of ketone derived enol ether derivatives reacted with 4-methoxybenzyl alcohol to afford in all cases the expected product in one pot. Enol ethers having electron-withdrawing group such as −F, −Cl, and −Br at *para* position afforded good yields (**3g**–**3i**). Similarly, substituents with −Br at *meta* and −Cl at *ortho* position also gave good yields (**3k**–**3l**). Moreover, enol ethers **1j** and **1m** possessing an $-NO_2$ group also reacted with **2a** and delivered good yields (**3j**, **3m**). Similarly, enol ethers with electron-donating groups such as −OMe, −Me, and −H at different positions also reacted well with **2a** and provided the corresponding products (**3b**–**3f**, **3o**) in good yields. Enol ethers having both aryl groups (R and R^1 = aryl) possessing electron-donating groups also gave the expected products (**3p**, **3q**, **3r**) in good yields, while in the case of enol ether **1r**, rearranged product formation was also observed (**3r′**). We also tested aldehyde derived enol ether (**1n**), which reacted well with **2a** to give 72% yield of **3n**. Cyclic aliphatic enol ether **1s** and **1t** when reacted with **2a** gave compound **3s** and **3t** in moderate yields.

After having the aldehyde derivative **3** in hand, we became interested in exploring the direct skeletal rearrangement of biaryl propanal derivatives to its isomeric ketone products (Table 3). Employing the conditions depicted in Table 1 (entry 2), 1,3-diaryl butanone derivatives **4a** and **4b** were synthesized in good yield. The reaction works well for the preparation of symmetrical 1,3-bi- (**4c**, 52%) and triarylpropanone (**4d**, 58%), *albeit* in somewhat lower yield. When the reaction was carried out keeping R^1 as an ethyl group we observed inseparable 1,2-alkyl along with 1,2-aryl group migration with 70:30 ratio respectively (**4e**, **4e′**, Table 3). The assignment is based on comparison of ^1H and ^{13}C NMR of mixture of **4e**, **4e′** with the authentic compound **4e** synthesized from **4c** (Scheme 1, B, also see the Supporting Information).

After having 1,3-arylated carbonyl compounds from the substrate scope of enol ether, we moved to check the scope of benzyl alcohol (Table 4). Benzyl alcohols having an −OMe group in the ortho and para positions provided the corresponding products in moderate yields (Table 4). Unfortunately, when benzyl alcohol having an electron-donating group (−OMe) at the *meta* position, product formation was not observed (**3ab**, **3ac**). When 2,4,5-trimethoxybenzyl alcohol was used, we observed product formation with moderate yield after 24 h (**3aa**).

Further, we extend the synthetic utility of this methodology for the synthesis of natural products such as propterol A, (±)-tetrahydronyasol (derivative of nyasol), and 1,3-diarylpropane using **4c** as a representative example (Scheme 1). Reduction of compound **4c** followed by deprotection in the presence of BBr_3 (1.0 M in DCM) afforded compound **5** and propterol A (**6**), respectively. (±)-Tetrahydronyasol was synthesized by alkylation of **4c** with iodoethane, which led

DOI: 10.1021/acs.joc.9b02064
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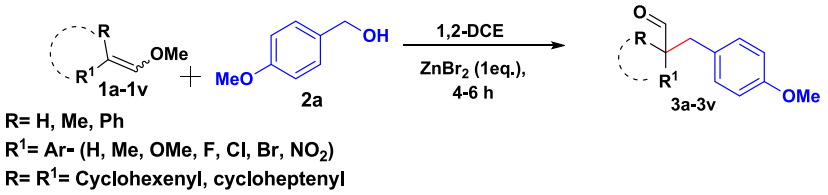
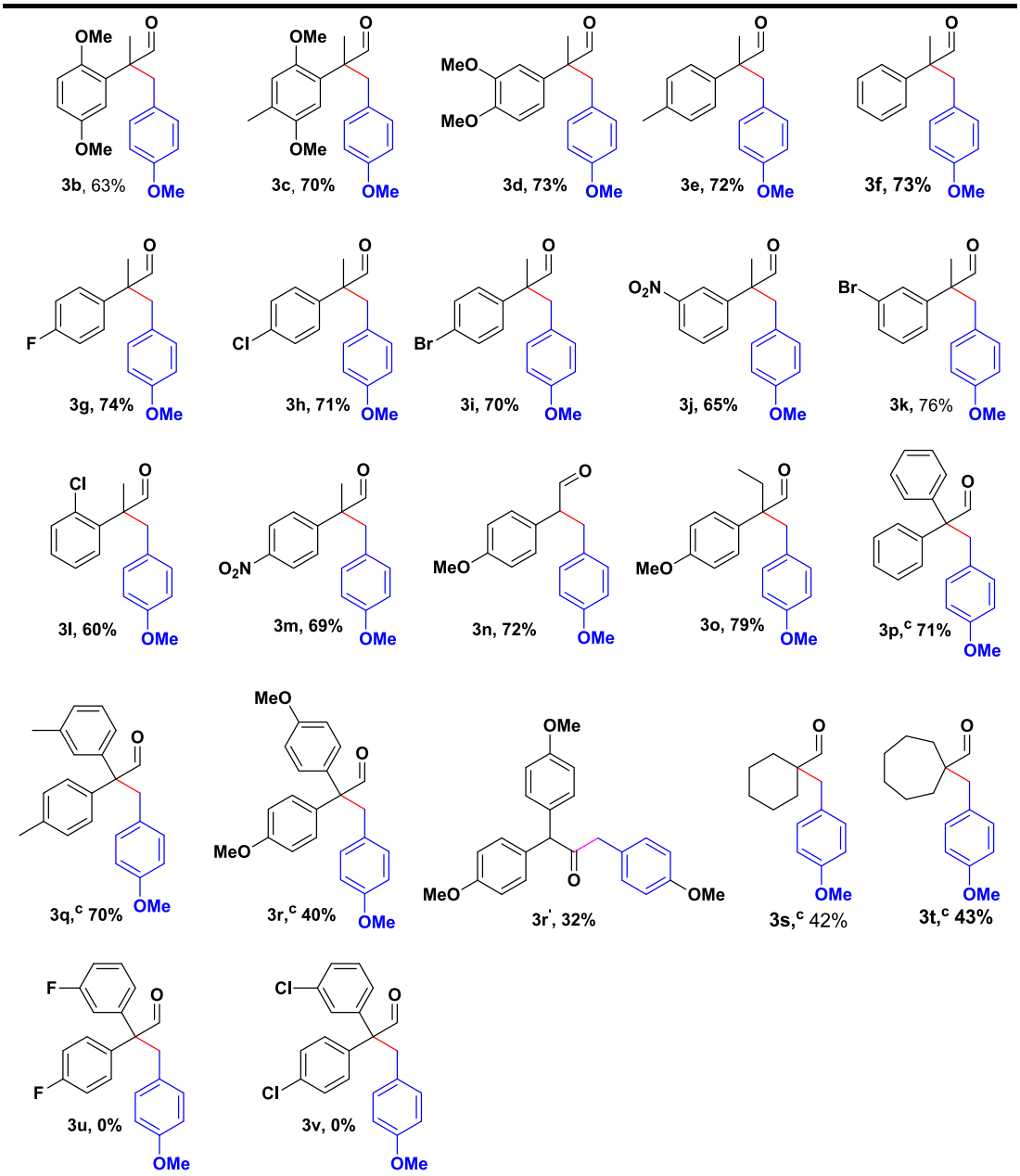
Table 2. Substrate Scope of Different Aromatic Enol Ethers[a−c]





[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.4 mmol), $ZnBr_2$ (1.0 equiv), in 1,2-DCE (2 mL), for 4−11 h. [b]Yields are reported for compounds isolated after silica gel column chromatography. [c]**2a** (0.8 mmol) was used portionwise.

to compound **4e** in 56% yield. Further reduction of the carbonyl functional group to methylene unit using triethylsilane and $BF_3{\cdot}OEt_2$ gave compound **7** in 80% yield. Finally, compound **8** was synthesized by deprotection of compound **7** in the presence of BBr_3 in 99% yield. Similarly, compound **9** (1,3-bis(4-methoxyphenyl)propane), a natural product,[19] was also synthesized by using the same conditions as were used for the synthesis of compound **7**.

After obtaining the results and careful observation of the reactivity of different substrates, we proposed a plausible reaction mechanism (for compounds **3** and **4**). Initially, nucleophilic addition of methyl enol ethers to in situ generated 1,6-quinomethoxy methide from activated benzyl alcohol **2a** in the presence of acid catalyst through the intermediate **10** would take place to form compound **11** (Scheme 2). In the next step, hydrolysis of compound **11**

DOI: 10.1021/acs.joc.9b02064
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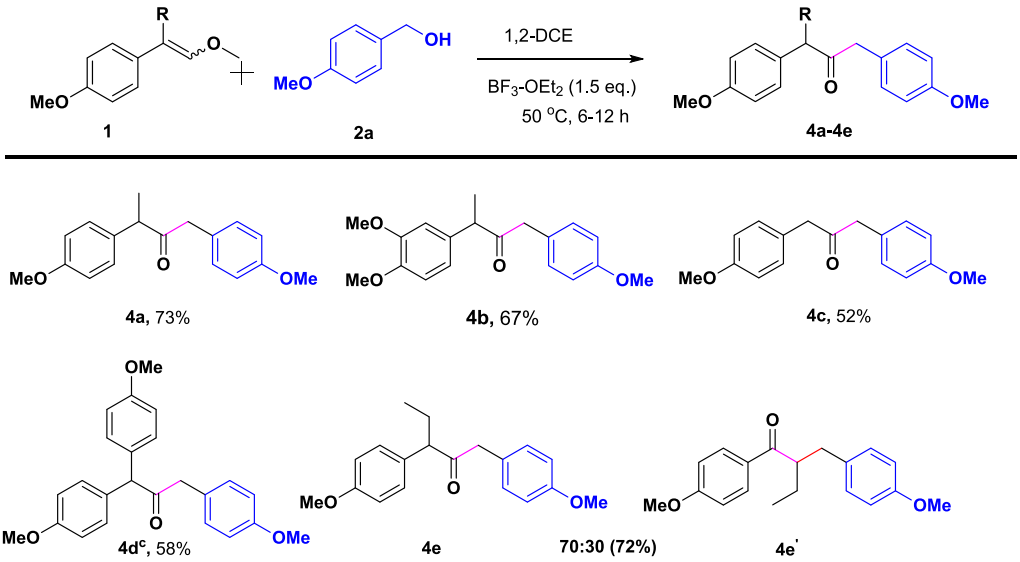
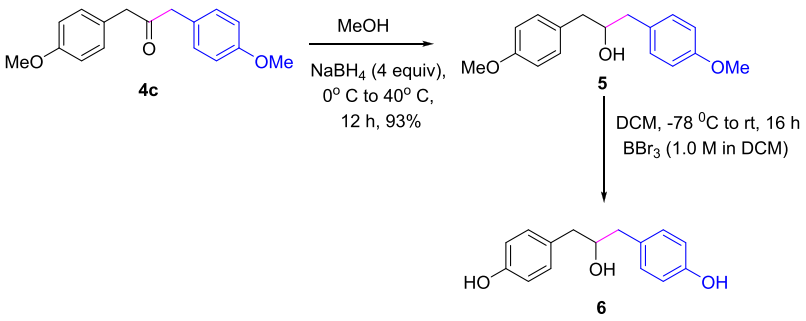
Table 3. Direct Rearrangement from Enol Ether[a−c]



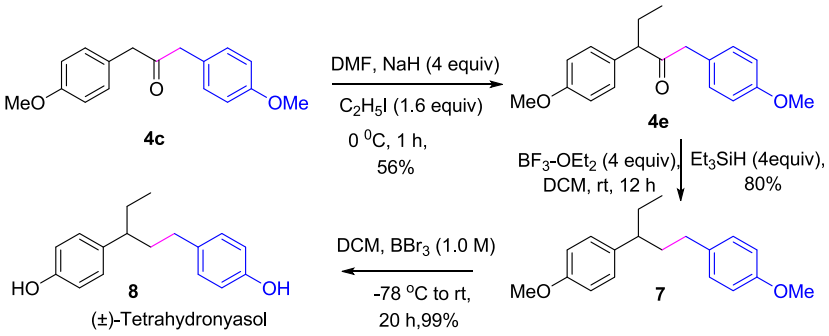
[a]Reaction conditions: **1** (0.4 mmol), **2a** (0.4 mmol), $BF_3{\cdot}OEt_2$ (1.5 equiv), in 1,2-DCE (2 mL), for 6−12 h. [b]Yields are reported for compounds isolated after silica gel column chromatography. [c]**2a** (0.8 mmol) was used portionwise.

Scheme 1. Synthetic Applications

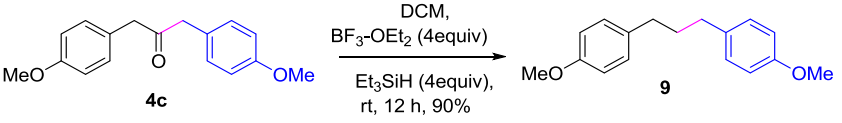
A. Synthesis of Propterol A (6)



B. Synthesis of (±)-Tetrahydronyasol



C. Synthesis of 1,3-diaryl propane



DOI: 10.1021/acs.joc.9b02064
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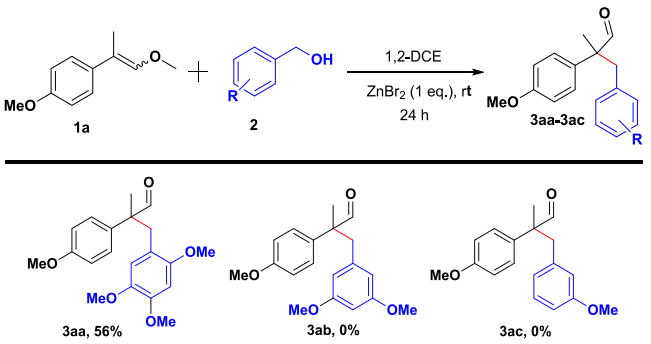
Table 4. Substrate Scope of Benzyl Alcohol



would lead to the desired product **3a**. At the same time, after formation of compound **3a** directly from enol ethers, it could undergo Wagner–Meerwein rearrangement via a stable carbocation leading to 1,2-alkyl shift with subsequent hydride ion transfer for the formation of compound **4a** (Scheme 2).

CONCLUSIONS

In summary, we have developed a one-pot direct benzylation reaction of different substituted methyl enol ethers with activated benzyl alcohol for the synthesis of biaryl, triaryl propanal, symmetrical 1,3-diarylpropanone, and also bi- and triaryl ketone derivatives via Wagner–Meerwein rearrangement in the presence of Lewis acid with moderate to good yield. Also, we applied this methodology to synthesize small natural products in short synthetic sequence. This method allows a facile alternative method for the construction of a quaternary center.

EXPERIMENTAL SECTION

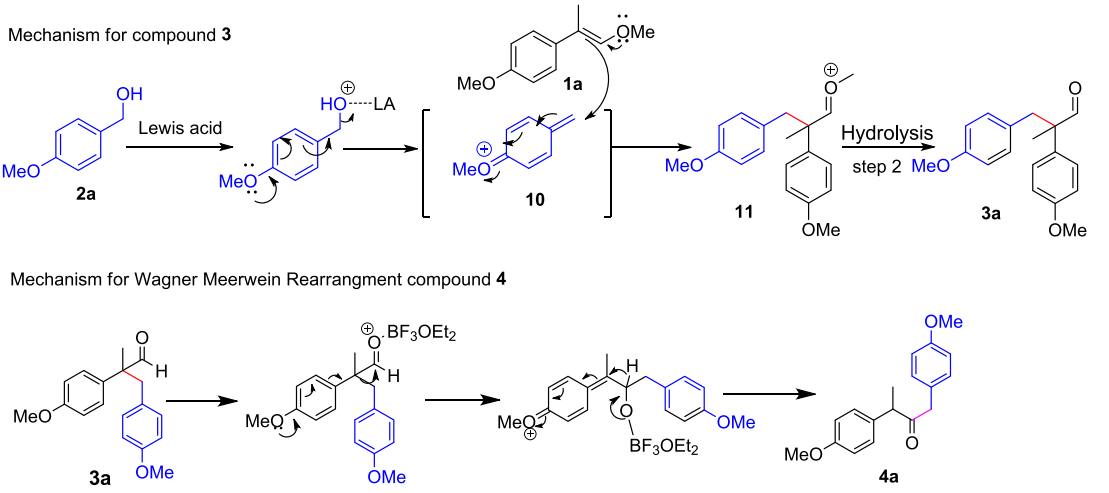
General Procedure. IR spectra were recorded on an FTIR spectrophotometer. ^{1}H NMR spectra were recorded on 400 MHz spectrometer in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) (δ_H = 0.00 ppm) or $CHCl_3$ (δ_H = 7.25 ppm). ^{13}C NMR spectra were recorded on 100 MHz spectrometer at in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [δ_C = 77.00 ppm (central line of triplet)]. In the ^{1}H NMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, dd = doublet of doublets, m = multiplet and brs = broad singlet. The assignment of signals was confirmed by ^{1}H, ^{13}C, and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded using electron spray ionization (ESI) or atmospheric chemical ionization (APCI) mode. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. Zinc bromide ($ZnBr_2$) was purchased from Alfa Aeser, and boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) was purchased from a commercial source and purified immediately before use. Tetrahydrofuran (THF) solvent was dried prior to use over sodium/benzophenone ketyl under argon. 1,4-Dioxane was distilled prior to use from sodium metal. K^{t}OBu was purchased from Avra Synthesis Pvt, Ltd. All reactions were performed in oven-dried apparatus under N_2 atmosphere. Commercial grade solvents were distilled before use. The reactions were monitored by thin-layer chromatography (TLC) on microscopic slides coated with silica gel, and visualization of spots was accomplished by exposure to iodine vapor or by UV radiation. The silica gel (100–200) column chromatography was carried for purification of compounds with a various combinations of hexane and EtOAc solvent system as eluent.

General Procedure (GP-I) for the Synthesis of Enol Ethers 1a–1t. Enol ethers **1a–1t** are known compounds except **1c** and are prepared by following the literature report.[20−24]

General Procedure for Synthesis of Enol Ether 1c. A flame-dried RBF, charged with a magnetic stir bar and the corresponding "Wittig salt" (methoxymethyl)triphenylphosphonium chloride (5.29 g, 15.463 mmol, 1.5 equiv) in THF, was cooled to 0 °C, and potassium *tert*-butoxide (1.85 g, 16.494 mmol, 1.6 equiv) was added in portions to give a dark red solution. After the solution was stirred for 40 min at room temperature, a solution of substituted ketone 1-(2,5-dimethoxy-4-methylphenyl)ethanone (2 g, 10.309 mmol, 1.0 equiv) in THF was added dropwise at 0 °C, and the mixture was then warmed to room temperature. After stirring for 8 h as monitored by TLC, the reaction mixture solvent was evaporated in rotatory evaporator and then poured into water (5 mL), and the aqueous phase was extracted with ethyl acetate (20 mL × 4). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by column chromatography using 3% ethyl acetate in petroleum ether (3/100) as an eluent on silica gel to afford the desired compound as mixtures of *E*/*Z* isomers with excellent yield.

For benzophenone the procedure was slightly modified. To a solution of (methoxymethyl)triphenylphosphonium chloride (16.483 mmol, 1.5 equiv) in dry 1,4-dioxane (20 mL) was slowly added sodium bis(trimethylsilyl)amide (21.978 mmol, 1.0 M solution in THF, 2.0 equiv) at 0 °C and stirred for 30 min at the same

Scheme 2. Plausible Reaction Mechanism



DOI: 10.1021/acs.joc.9b02064
J. Org. Chem. XXXX, XXX, XXX–XXX

temperature. A solution of benzophenone derivative (10.989 mmol, 1.0 equiv) was then slowly added at 0 °C, and the mixture was stirred at room temperature for 24 h. The reaction mixture was treated with satd aq NH_4Cl solution, and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by silica gel column chromatography using 2% ethyl acetate in petroleum ether (2/100) as an eluent to afford the desired product.

*1,4-Dimethoxy-2-(1-methoxyprop-1-en-2-yl)-5-methylbenzene (**1c**).* Colorless liquid; 2.2 g, 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.73 (s, 1 H), 6.68 (s, 2 H), 6.63 (s, 1 H), 6.22 (d, J = 1.5 Hz, 1 H), 6.02 (q, J = 1.5 Hz, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.77 (s, 3 H), 3.68 (s, 3 H), 3.54 (s, 3 H), 2.21 (s, 6 H), 1.96 (d, J = 1.5 Hz, 3 H), 1.87 (d, J = 1.5 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 151.5, 151.1, 150.5, 146.1, 143.2, 133.8, 133.6, 128.5, 126.0, 125.9, 125.3, 114.9, 114.6, 113.2, 112.5, 111.6, 59.7, 59.6, 56.5, 56.3, 56.1, 56.0, 18.7, 16.3, 16.1, 14.0. IR ν_{max} (neat): 2935, 1671, 1504, 1458, 1398, 1208, 1140, 1043, 861 cm^{-1}. HRMS (ESI-TOF) m/z: [M + NH_4]$^+$ calcd for $C_{13}H_{22}NO_3$ 240.1594, found 240.1586.

*1,2-Dimethoxy-4-(1-methoxyprop-1-en-2-yl)benzene (**1d**).*[22] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24 (s, 1 H), 7.03 (d, J = 8.3 Hz, 1 H), 6.79−6.71 (m, 4 H), 6.25 (s, 1 H), 5.99 (s, 1 H), 3.81 (s, 6 H), 3.79 (s, 6 H), 3.63 (s, 3 H), 3.60 (s, 3 H), 1.90 (s, 3 H), 1.82 (s, 3 H).

*1-Methoxy-4-(1-methoxybut-1-en-2-yl)benzene (**1o**).*[23] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44−7.40 (m, 2 H), 7.21−7.18 (m, 2 H), 6.88−6.81 (m, 4 H), 6.17 (s, 1 H), 6.02 (s, 1 H), 3.78 (s, 6 H), 3.65 (s, 3 H), 3.60 (s, 3 H), 2.49 (d, J = 7.8 Hz, 2 H), 2.29 (dd, J = 1.0, 7.3 Hz, 2 H), 0.99 (dt, J = 4.9, 7.3 Hz, 6 H).

*(Methoxymethylene)cycloheptane (**1t**).*[25] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.78−5.76 (m, 1 H), 3.54 (s, 3 H), 2.29−2.25 (m, 2 H), 2.07−2.02 (m, 2 H), 1.59−1.47 (m, 8 H).

General Procedure A for the Synthesis of Compound 3a. To a stirred solution of compounds **1a** (1-methoxy-4-(1-methoxyprop-1-en-2-yl)benzene (71 mg, 0.4 mmol, 1.0 equiv) and **2a** (55 mg, 0.4 mmol, 1.0 equiv) in 1,2-DCE (2 mL) was added $ZnBr_2$ (90 mg, 0.4 mmol, 1.0 equiv) at room temperature, and the mixture stirred until complete conversion of starting material (monitored by TLC) for 5 h. After completion of the reaction, it was diluted with water (2 mL), and the aqueous layer was extracted with dichloromethane (2 × 10 mL). All organic layers were dried over Na_2SO_4, solvent was evaporated at reduced pressure, and the product was isolated by using column chromatography 3% ethyl acetate in petroleum ether (3/100) as an eluent.

*2,3-Bis(4-methoxyphenyl)-2-methylpropanal (**3a**).* Colorless liquid (98 mg, 86%), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.58 (s, 1 H), 7.09 (d, J = 8.9 Hz, 2 H), 6.90 (d, J = 8.9 Hz, 2 H), 6.74−6.67 (m, 4 H), 3.82 (s, 3 H), 3.74 (s, 3 H), 3.15−3.06 (m, 2 H), 1.33 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 202.1, 158.8, 158.1, 131.3, 131.1, 128.9, 128.7, 114.1, 113.2, 55.2, 55.1, 54.4, 41.8, 18.3. IR ν_{max} (neat): 2935, 1606, 1508, 1457, 1246, 1176, 1037, 816 cm^{-1}. HRMS (ESI-TOF) m/z: [M + NH_4]$^+$ calcd for $C_{18}H_{24}NO_3$ 302.1751, found 302.1754.

*2-(2,5-Dimethoxyphenyl)-3-(4-methoxyphenyl)-2-methylpropanal (**3b**).* Compound **3b** was prepared according to the general procedure A by treating enol ether **1b** (83 mg, 0.4 mmol, 1.0 equiv) and **2a** (55 mg, 0.4 mmol, 1.0 equiv) in 1,2-DCE (2 mL). Purification of the crude material by silica gel column chromatography using 2% ethyl acetate in petroleum ether (2/100) as an eluent furnished the compound **3b** as a colorless liquid (89 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.59 (s, 1 H), 6.89−6.78 (m, 2 H), 6.67−6.57 (m, 4 H), 6.43 (d, J = 2.9 Hz, 1 H), 3.74 (s, 6 H), 3.68 (s, 3 H), 3.24 (d, J = 13.6 Hz, 1 H), 3.05 (d, J = 13.5 Hz, 1 H), 1.21 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 203.3, 157.9, 153.6, 150.9, 131.5, 130.9, 129.2, 115.8, 113.0, 112.5, 111.7, 55.8 (2C), 55.1, 52.8, 38.8, 19.2. IR ν_{max} (neat): 2940, 1695, 1507, 1230, 1177, 1039, 811 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{23}O_4$ 315.1591, found 315.1589.

*2-(2,5-Dimethoxy-4-methylphenyl)-3-(4-methoxyphenyl)-2-methylpropanal (**3c**).* Compound **3c** was prepared according to the general procedure A by treating enol ether **1c** (89 mg, 0.4 mmol, 1.0 equiv) and **2a** (55 mg, 0.4 mmol, 1.0 equiv) in 1,2-DCE (2 mL). Purification of the crude material by silica gel column chromatography using 2% ethyl acetate in petroleum ether (2/100) as an eluent furnished the compound **3c** as a colorless liquid (96 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.59 (s, 1 H), 6.75 (s, 1 H), 6.68−6.51 (m, 4 H), 6.28 (s, 1 H), 3.73 (s, 6 H), 3.60 (s, 3 H), 3.19 (d, J = 13.7 Hz, 1 H), 3.06 (d, J = 13.7 Hz, 1 H), 2.24 (s, 3 H), 1.20 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 203.6, 157.9, 151.7, 150.4, 131.6, 129.4, 127.3, 126.9, 114.1, 112.9, 111.9, 56.3, 55.9, 55.1, 52.7, 38.9, 19.2, 16.2. IR ν_{max} (neat): 2936, 1721, 1505, 1457, 1396, 1205, 1037, 881 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{25}O_4$ 329.1747, found 329.1754

*2-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-2-methylpropanal (**3d**).* Compound **3d** was prepared according to the general procedure A by treating enol ether **1d** (83 mg, 0.4 mmol, 1.0 equiv) and **2a** (55 mg, 0.4 mmol, 1.0 equiv) in 1,2-DCE (2 mL). Purification of the crude material by silica gel column chromatography using 2% ethyl acetate in petroleum ether (2/100) as an eluent furnished the compound **3d** as a colorless liquid (92 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.57 (s, 1 H), 6.85 (d, J = 8.3 Hz, 1 H), 6.74−6.71 (m, 3 H), 6.70−6.67 (m, 2 H), 6.61 (d, J = 2.0 Hz, 1 H), 3.88 (s, 3 H), 3.81 (s, 3 H), 3.73 (s, 3 H), 3.11 (s, 2 H), 1.34 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 202.1, 158.2, 149.0, 148.4, 131.6, 131.3, 129.9, 128.9, 120.0, 113.6, 113.3, 111.2, 111.0, 55.9, 55.9, 55.1, 54.7, 41.8, 18.4. IR ν_{max} (neat): 2934, 1597, 1511, 1456, 1255, 1028, 810 cm^{-1}. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{19}H_{22}O_4Na$ 337.1410, found 337.1408

*3-(4-Methoxyphenyl)-2-methyl-2-(p-tolyl)propanal (**3e**).* Compound **3e** was prepared according to the general procedure A by treating enol ether **1e** (65 mg, 0.4 mmol, 1.0 equiv) and **2a** (55 mg, 0.4 mmol, 1.0 equiv) in 1,2-DCE (2 mL). Purification of the crude material by silica gel column chromatography using 2% ethyl acetate in petroleum ether (2/100) as an eluent furnished the compound **3e** as a colorless liquid (81 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.58 (s, 1 H), 7.16 (d, J = 7.8 Hz, 2 H), 7.06 (d, J = 8.3 Hz, 2 H), 6.75−6.64 (m, 4 H), 3.73 (s, 3 H), 3.22−2.99 (m, 2 H), 2.34 (s, 3 H), 1.33 (s, 3 H). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 202.2, 158.2, 137.1, 136.4, 131.4, 129.5, 128.9, 127.5, 113.3, 55.1, 54.8, 41.8, 21.0, 18.3. IR ν_{max} (neat): 2928, 1609, 1509, 1456, 1245, 1177, 1032, 819 cm^{-1}. HRMS (ESI-TOF) m/z: [M + NH_4]$^+$ calcd for $C_{18}H_{24}NO_2$ 286.1802, found 286.1801.

*3-(4-Methoxyphenyl)-2-methyl-2-phenylpropanal (**3f**).* Compound **3f** was prepared according to the general procedure A by treating enol ether **1f** (59 mg, 0.4 mmol, 1.0 equiv) and **2a** (55 mg, 0.4 mmol, 1.0 equiv) in 1,2-DCE (2 mL). Purification of the crude material by silica gel column chromatography using 2% ethyl acetate in petroleum ether (2/100) as an eluent furnished the compound **3f** as a colorless liquid (74 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.62 (s, 1 H), 7.38−7.33 (m, 2 H), 7.31−7.27 (m, 1 H), 7.19−7.15 (m, 2 H), 6.79−6.55 (m, 4 H), 3.18−3.08 (m, 2 H), 1.36 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 202.2, 158.2, 139.4, 131.3, 128.7, 127.6, 127.4, 113.2, 55.1, 55.1, 41.8, 18.2. IR ν_{max} (neat): 2931, 1707, 1607, 1507, 1458, 1245, 1176, 1032, 819 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{19}O_2$ 255.1380, found 255.1383.

*2-(4-Fluorophenyl)-3-(4-methoxyphenyl)-2-methylpropanal (**3g**).* Compound **3g** was prepared according to the general procedure A by treating enol ether **1g** (66 mg, 0.4 mmol, 1.0 equiv) and **2a** (55 mg, 0.4 mmol, 1.0 equiv) in 1,2-DCE (2 mL). Purification of the crude material by silica gel column chromatography using 2% ethyl acetate in petroleum ether (2/100) as an eluent furnished the compound **3g** as white solid (80 mg, 74%). Mp = 97−98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.60 (s, 1 H), 7.15−7.09 (m, 2 H), 7.08−7.01 (m, 2 H), 6.69 (s, 4 H), 3.74 (s, 3 H), 3.16−3.04 (m, 2 H), 1.36 (s, 3 H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 201.9, 162.03 (d, J_{CF} = 245 Hz), 158.2, 135.1, 131.3, 129.28 (d, J_{CF} = 8 Hz), 128.4, 115.57 (d, J_{CF} = 21 Hz), 113.3, 55.1,

DOI: 10.1021/acs.joc.9b02064
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54.6, 42.0, 18.4. IR ν_{max} (neat): 2933, 1605, 1509, 1458, 1239, 1172, 1032, 834 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ calcd for $C_{17}H_{21}NFO_2$ 290.1551, found 290.1566.

*2-(4-Chlorophenyl)-3-(4-methoxyphenyl)-2-methylpropanal (**3h**).* Compound **3h** was prepared according to the general procedure A by treating enol ether **1h** (73 mg, 0.4 mmol, 1.0 equiv) and **2a** (55 mg, 0.4 mmol, 1.0 equiv) in 1,2-DCE (2 mL). Purification of the crude material by silica gel column chromatography using 2% ethyl acetate in petroleum ether (2/100) as an eluent furnished the compound **3h** as a colorless liquid (82 mg, 71%). ^1H NMR (400 MHz, $CDCl_3$) δ = 9.59 (s, 1 H), 7.39−7.28 (m, 2 H), 7.16−6.94 (m, 2 H), 6.69 (s, 4 H), 3.73 (s, 3 H), 3.13−3.05 (m, 2 H), 1.35 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 201.7, 158.3, 137.9, 133.4, 131.3, 129.7, 129.0, 128.9, 128.8, 128.2, 113.3, 55.1, 54.8, 41.9, 18.3. IR ν_{max} (neat): 2942, 1682, 1603, 1509, 1246, 1173, 1093, 1030, 824, 757 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ calcd for $C_{17}H_{21}NClO_2$ 306.1255, found 306.1257.

*2-(4-Bromophenyl)-3-(4-methoxyphenyl)-2-methylpropanal (**3i**).* Compound **3i** was prepared according to the general procedure A by treating enol ether **1i** (90 mg, 0.4 mmol, 1.0 equiv) and **2a** (55 mg, 0.4 mmol, 1.0 equiv) in 1,2-DCE (2 mL). Purification of the crude material by silica gel column chromatography using 2% ethyl acetate in petroleum ether (2/100) as an eluent furnished the compound **3i** as a colorless liquid (93 mg, 70%). ^1H NMR (400 MHz, $CDCl_3$) δ = 9.59 (s, 1 H), 7.51−7.43 (m, 2 H), 7.07−6.99 (m, 2 H), 6.70 (s, 4 H), 3.74 (s, 3 H), 3.13−3.05 (m, 2 H), 1.35 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 201.6, 158.3, 138.5, 131.8, 131.3, 129.3, 128.2, 121.6, 113.3, 55.1, 54.9, 41.8, 18.3. IR ν_{max} (neat): 2932, 1725, 1517, 1462, 1249, 1177, 1034, 829 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{17}BrO_2Na$ 355.0304, found 355.0309.

*3-(4-Methoxyphenyl)-2-methyl-2-(3-nitrophenyl)propanal (**3j**).* Compound **3j** was prepared according to the general procedure A by treating enol ether **1j** (77 mg, 0.4 mmol, 1.0 equiv) and **2a** (83 mg, 0.6 mmol, 1.5 equiv) in 1,2-DCE (2 mL) at 40 °C in oil bath for 11 h. Purification of the crude material by silica gel column chromatography using 3% ethyl acetate in petroleum ether (3/100) as an eluent furnished the compound **3j** as a yellow solid (78 mg, 65%). Mp = 113−115 °C. ^1H NMR (400 MHz, $CDCl_3$) δ = 9.68 (s, 1 H), 8.17 (ddd, *J* = 1.0, 2.2, 8.1 Hz, 1 H), 8.07 (t, *J* = 2.0 Hz, 1 H), 7.65−7.37 (m, 2 H), 6.76−6.54 (m, 4 H), 3.74 (s, 3 H), 3.17 (d, *J* = 1.5 Hz, 2 H), 1.48 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 201.1, 158.5, 148.4, 141.9, 134.0, 131.2, 129.5, 127.4, 122.5, 113.5, 55.2, 55.1, 42.2, 18.6. IR ν_{max} (neat): 2932, 1695, 1522, 1462, 1350, 1248, 1176, 1033, 851 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ calcd for $C_{17}H_{21}N_2O_4$ 317.1496, found 317.1499.

*2-(3-Bromophenyl)-3-(4-methoxyphenyl)-2-methylpropanal (**3k**).* Compound **3k** was prepared according to the general procedure A by treating enol ether **1k** (90 mg, 0.4 mmol, 1.0 equiv) and **2a** (55 mg, 0.4 mmol, 1.0 equiv) in 1,2-DCE (2 mL). Purification of the crude material by silica gel column chromatography using 2% ethyl acetate in petroleum ether (2/100) as an eluent furnished the compound **3k** as a colorless liquid (101 mg, 76%). ^1H NMR (400 MHz, $CDCl_3$) δ = 9.60 (s, 1 H), 7.48−7.37 (m, 1 H), 7.32 (t, *J* = 1.7 Hz, 1 H), 7.22 (t, *J* = 7.8 Hz, 1 H), 7.14−7.03 (m, 1 H), 6.79−6.62 (m, 4 H), 3.73 (s, 3 H), 3.21−2.98 (m, 2 H), 1.35 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 201.5, 158.3, 142.0, 131.6, 131.3, 130.6, 130.5, 130.1, 128.1, 126.3, 123.0, 113.4, 113.3, 55.1, 55.1, 41.9, 18.3. IR ν_{max} (neat): 2932, 1724, 1511, 1464, 1248, 1177, 1034, 827 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{17}BrO_2Na$ 355.0304, found 355.0309.

*2-(2-Chlorophenyl)-3-(4-methoxyphenyl)-2-methylpropanal (**3l**).* Compound **3l** was prepared according to the general procedure A by treating enol ether **1l** (73 mg, 0.4 mmol, 1.0 equiv) and **2a** (55 mg, 0.4 mmol, 1.0 equiv) in 1,2-DCE (2 mL). Purification of the crude material by silica gel column chromatography using 2% ethyl acetate in petroleum ether (2/100) as an eluent furnished the compound **3l** as a colorless liquid (69 mg, 60%). ^1H NMR (400 MHz, $CDCl_3$) δ = 9.82 (s, 1 H), 7.45 (dd, *J* = 1.5, 7.8 Hz, 1 H), 7.30−7.22 (m, 1 H), 7.18−7.12 (m, 1 H), 6.89 (dd, *J* = 1.5, 7.8 Hz, 1 H), 6.66−6.52 (m, 4 H), 3.72 (s, 3 H), 3.48 (d, *J* = 13.8 Hz, 1 H), 3.17 (d, *J* = 13.8 Hz, 1 H), 1.30 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 202.9, 158.1, 138.2, 133.4, 131.5, 130.6, 130.1, 129.1, 128.4, 126.9, 113.1, 55.2, 55.1, 38.2, 20.2. IR ν_{max} (neat): 2989, 1703, 1512, 1460, 1248, 1035, 823,743 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{17}ClO_2Na$ 311.0809, found 311.0825.

*3-(4-Methoxyphenyl)-2-methyl-2-(4-nitrophenyl)propanal (**3m**).* Compound **3m** was prepared according to the general procedure A by treating enol ether **1m** (77 mg, 0.4 mmol, 1.0 equiv) and **2a** (83 mg, 0.6 mmol, 1.5 equiv) in 1,2-DCE (2 mL) at 40 °C in oil bath for 12 h. Purification of the crude material by silica gel column chromatography using 4% ethyl acetate in petroleum ether (4/100) as an eluent furnished the compound **3m** as a yellow solid (82 mg, 69%). Mp = 99−100 °C. ^1H NMR (400 MHz, $CDCl_3$) δ = 9.67 (s, 1 H), 8.19 (d, *J* = 8.8 Hz, 2 H), 7.33 (d, *J* = 9.3 Hz, 2 H), 6.69 (s, 4 H), 3.73 (s, 3 H), 3.16 (s, 2 H), 1.46 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 201.0, 158.5, 147.1, 147.1, 131.2, 128.6, 127.4, 123.6, 113.5, 55.6, 55.1, 42.3, 18.6. IR ν_{max} (neat): 2932, 1725, 1605, 1515, 1459, 1346, 1250, 1032, 851, 705 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ calcd for $C_{17}H_{21}N_2O_4$ 317.1496, found 317.1495.

*2,3-Bis(4-methoxyphenyl)propanal (**3n**).* Compound **3n** was prepared according to the general procedure **A**, by treating enol ether **1n** (66 mg, 0.4 mmol, 1.0 equiv), and **2a** (83 mg, 0.6 mmol, 1.5 equiv) in 1,2-DCE (2 mL) for 6 h. Purification of the crude material by silica gel column chromatography using 4% ethyl acetate in petroleum ether (4/100) as an eluent furnished the compound **3n** as a colorless liquid (78 mg, 72%). ^1H NMR (400 MHz, $CDCl_3$) δ = 9.69 (d, *J* = 2.0 Hz, 1 H), 7.03 (d, *J* = 8.8 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 6.88−6.83 (m, 2 H), 6.74 (d, *J* = 8.8 Hz, 2 H), 3.79 (s, 1 H), 3.78 (s, 3 H), 3.73 (s, 3 H), 3.35 (dd, *J* = 14.2, 6.8 Hz, 1 H), 2.88 (dd, *J* = 14.2, 8.3 Hz, 1 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 200.1, 159.1, 158.0, 130.9, 130.1, 130.0, 129.4, 127.6, 114.4, 114.3, 113.8, 113.7, 60.3, 55.2, 55.1, 35.3. IR ν_{max} (neat): 2931, 1718, 1606, 1509, 1456, 1244, 1172, 1031, 826 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{19}O_3$ 271.1329, found 271.1327.

*2-(4-Methoxybenzyl)-2-(4-methoxyphenyl)butanal (**3o**).* Compound **3o** was prepared according to the general procedure **A**, by treating enol ether **1o** (77 mg, 0.4 mmol, 1.0 equiv), and **2a** (55 mg, 0.4 mmol, 1.0 equiv) in 1,2-DCE (2 mL) for 4 h. Purification of the crude material by silica gel column chromatography using 4% ethyl acetate in petroleum ether (4/100) as an eluent furnished the compound **3o** as a colorless liquid (94 mg, 79%). ^1H NMR (400 MHz, $CDCl_3$) δ = 9.61 (s, 1 H), 7.09−7.03 (m, 2 H), 6.97−6.86 (m, 2 H), 6.72 (s, 4 H), 3.83 (s, 3 H), 3.76 (s, 3 H), 3.22- 3.09 (m, 2 H), 1.90 (dd, *J* = 5.4, 7.3 Hz, 2 H), 0.94 (t, *J* = 7.3 Hz, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 202.8, 158.7, 158.1, 131.1, 130.4, 129.1, 128.7, 114.0, 113.3, 58.4, 55.2, 55.1, 37.8, 23.9, 8.6. IR ν_{max} (neat): 2948, 1718, 1607, 1509, 1454, 1245, 1180, 1031, 827 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{23}O_3$ 299.1642, found 299.1635.

*3-(4-Methoxyphenyl)-2,2-diphenylpropanal (**3p**).* Compound **3p** was prepared according to the general procedure A by treating enol ether **1p** (84 mg, 0.4 mmol, 1.0 equiv) and **2a** portionwise (110 mg, 0.8 mmol, 2.0 equiv) in 1,2-DCE (2 mL) for 5 h. Purification of the crude material by silica gel column chromatography using 2% ethyl acetate in petroleum ether (2/100) as an eluent furnished the compound **3p** as a colorless liquid (90 mg, 71%). ^1H NMR (400 MHz, $CDCl_3$) δ = 9.83 (s, 1 H), 7.42−7.20 (m, 6 H), 7.09 (dd, *J* = 1.7, 8.1 Hz, 4 H), 6.68−6.49 (m, 4 H), 3.78−3.73 (m, 1 H), 3.70 (s, 3 H), 3.63 (s, 2 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.1, 157.9, 140.0, 131.8, 129.4, 128.8, 128.4, 127.3, 112.9, 65.3, 55.1, 39.7. IR ν_{max} (neat): 2984, 1724, 1603, 1508, 1446, 1258, 1177, 1038, 815 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ calcd for $C_{22}H_{24}NO_2$ 334.1802, found 334.1807.

*3-(4-Methoxyphenyl)-2,2-di-p-tolylpropanal (**3q**).* Compound **3q** was prepared according to the general procedure A by treating enol ether **1q** (95 mg, 0.4 mmol, 1.0 equiv) and **2a** portionwise (110 mg,

DOI: 10.1021/acs.joc.9b02064
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0.8 mmol, 2.0 equiv) in 1,2-DCE (2 mL) for 5 h. Purification of the crude material by silica gel column chromatography using 2% ethyl acetate in petroleum ether (2/100) as an eluent furnished the compound **3q** as a colorless solid (96 mg, 70%). Mp = 94−95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.77 (s, 1 H), 7.09 (d, J = 7.8 Hz, 4 H), 6.96 (d, J = 7.8 Hz, 4 H), 6.66−6.44 (m, 4 H), 3.71 (s, 3 H), 3.58 (s, 2 H), 2.33 (s, 6 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.3, 157.8, 137.05, 136.9, 131.9, 130.2, 129.3, 129.1, 128.9, 112.8, 64.7, 55.1, 39.7, 21.0. IR ν_{max} (neat): 2934, 1720, 1609, 1510, 1454, 1244, 1179, 1033, 815 cm^{-1}. HRMS (ESI-TOF) m/z: [M + NH_4]$^+$ calcd for $C_{24}H_{28}NO_2$ 362.2115, found 362.2115.

*2,2,3-Tris(4-methoxyphenyl)propanal (**3r**).* Compound **3r** was prepared according to the general procedure A by treating enol ether **1r** (108 mg, 0.4 mmol, 1.0 equiv) and **2a** portionwise (110 mg, 0.8 mmol, 2.0 equiv) in 1,2-DCE (2 mL) for 5 h. Purification of the crude material by silica gel column chromatography using 2% ethyl acetate in petroleum ether (2/100) as an eluent furnished the compound **3r** as a colorless liquid (60 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.73 (s, 1 H), 6.99 (d, J = 8.3 Hz, 4 H), 6.82 (d, J = 8.8 Hz, 4 H), 6.64−6.56 (m, 4 H), 3.79 (s, 6 H), 3.71 (s, 3 H), 3.56 (s, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.0, 158.7, 157.9, 131.9, 131.8, 130.5, 129.1, 128.6, 113.8, 113.2, 112.9, 64.0, 55.2, 55.2, 55.1, 40.0. IR ν_{max} (neat): 2927, 1719, 1607, 1508, 1458, 1296, 1246, 1178, 1032, 827 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{24}H_{25}O_4$ 377.1747, found 377.1749.

*1,1,3-Tris(4-methoxyphenyl)propan-2-one (**3r′**).* Colorless liquid (48 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06−7.03 (m, 6H), 6.85−6.82 (m, 6H), 5.10 (s, 1H), 3.79 (s, 3H), 3.77 (s, 6H), 3.70 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 206.7, 158.7, 130.5, 130.0, 126.2, 114.1, 114.0, 113.7, 113.6, 60.9, 55.2, 48.5. IR ν_{max} (neat): 2942, 1710, 1606, 1510, 1459, 1249, 1175, 1032, 822 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{24}H_{25}O_4$ 377.1747, found 377.1755.

*1-(4-Methoxybenzyl)cyclohexanecarbaldehyde (**3s**).* Compound **3s** was prepared according to the general procedure A by treating enol ether **1s** (44 mg, 0.4 mmol, 1.0 equiv) and **2a** portionwise (110 mg, 0.8 mmol, 2.0 equiv) in 1,2-DCE (2 mL) for 5 h. Purification of the crude material by silica gel column chromatography using petroleum ether as an eluent furnished the compound **3s** as a colorless liquid (39 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.53 (s, 1 H), 7.04−6.93 (m, 2 H), 6.89−6.67 (m, 2 H), 3.79 (s, 3 H), 2.69 (s, 2 H), 2.00−1.87 (m, 2 H), 1.64 (d, J = 3.9 Hz, 3 H), 1.38−1.20 (m, 5 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 207.5, 158.3, 131.1, 128.2, 113.5, 55.1, 50.7, 42.6, 31.1, 25.6, 22.7. IR ν_{max} (neat): 2928, 1697, 1607, 1508, 1452, 1245, 1179, 1034, 824 cm^{-1}. HRMS (ESI-TOF) m/z: [M + NH_4]$^+$ calcd for $C_{15}H_{24}NO_2$ 250.1802, found 250.1807.

*1-(4-Methoxybenzyl)cycloheptanecarbaldehyde (**3t**).* Compound **3t** was prepared according to the general procedure A by treating enol ether **1t** (50 mg, 0.4 mmol, 1.0 equiv) and **2a** portionwise (110 mg, 0.8 mmol, 2.0 equiv) in 1,2-DCE (2 mL) for 5 h. Purification of the crude material by silica gel column chromatography using petroleum ether as an eluent furnished the compound **3t** as a colorless liquid (42 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.55 (s, 1 H), 7.10−6.89 (m, 2 H), 6.89−6.70 (m, 2 H), 3.79 (s, 3 H), 2.73 (s, 2 H), 1.95−1.83 (m, 2 H), 1.61−1.41 (m, 10 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 206.5, 158.2, 131.1, 128.9, 113.5, 55.1, 53.8, 42.8, 32.6, 30.4, 22.8. IR ν_{max} (neat): 2925, 1702, 1612, 1512, 1452, 1246, 1034, 828 cm^{-1}. HRMS (ESI-TOF) m/z: [M + NH_4]$^+$ calcd for $C_{16}H_{26}NO_2$ 264.1958, found 264.1944.

General Procedure B for the Synthesis of Compound 4. To a stirred solution of compound **1** (0.4 mmol, 1.0 equiv) and **2** (0.4 mmol, 1.0 equiv) in 1,2-DCE (2 mL) was added BF_3·OEt_2 (0.6 mmol, 1.5 equiv) at room temperature and stirred at 50 °C in an oil bath until complete conversion of starting material (monitored by TLC) for 6−12 h. After completion of the reaction, it was diluted with saturated aqueous $NaHCO_3$ (2 mL), and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The organic layers were dried over Na_2SO_4, solvent was evaporated at reduced pressure, and the product was isolated by using column chromatography (ethyl acetate in petroleum ether).

*1,3-Bis(4-methoxyphenyl)butan-2-one (**4a**).* Compound **4a** was prepared according to the general procedure B by treating enol ether **1a** (71 mg, 0.4 mmol, 1.0 equiv) and **2a** (55 mg, 0.4 mmol, 1.0 equiv) in 1,2-DCE (2 mL) for 6 h. Purification of the crude material by silica gel column chromatography using 4% ethyl acetate in petroleum ether (4/100) as an eluent furnished the compound **4a** as a colorless liquid (83 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.11 (d, J = 8.8 Hz, 2 H), 6.97 (d, J = 8.8 Hz, 2 H), 6.88 (d, J = 8.8 Hz, 2 H), 6.82 (d, J = 8.8 Hz, 2 H), 3.81 (s, 3 H), 3.79−3.74 (m, 4 H), 3.56 (s, 2 H), 1.33 (d, J = 6.8 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 208.7, 158.7, 158.5, 132.4, 130.4, 129.0, 126.5, 114.3, 114.0, 55.3, 55.2, 50.9, 46.9, 17.7. IR ν_{max} (neat): 2933, 1711, 1607, 1510, 1459, 1247, 1176, 1032, 830 cm^{-1}. HRMS (ESI-TOF) m/z: [M + NH_4]$^+$ calcd for $C_{18}H_{24}NO_3$ 302.1751, found 302.1749.

*3-(3,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)butan-2-one (**4b**).* Compound **4b** was prepared according to the general procedure B by treating enol ether **1d** (83 mg, 0.4 mmol, 1.0 equiv) and **2a** (55 mg, 0.4 mmol, 1.0 equiv) in 1,2-DCE (2 mL) for 7 h. Purification of the crude material by silica gel column chromatography using 4% ethyl acetate in petroleum ether (4/100) as an eluent furnished the compound **4b** as a colorless liquid (84 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.98−6.94 (m, 2 H), 6.85−6.79 (m, 3 H), 6.77−6.74 (m, 1 H), 6.61 (d, J = 2.0 Hz, 1 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.77 (s, 1 H), 3.57 (s, 2 H), 1.34 (d, J = 6.9 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 208.6, 158.5, 149.3, 148.2, 132.9, 130.4, 126.5, 120.3, 114.0, 111.5, 110.9, 55.9, 55.8, 55.2, 51.4, 47.0, 17.6. IR ν_{max} (neat): 2942, 1710, 1600, 1513, 1454, 1252, 1159, 1029, 816 cm^{-1}. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{19}H_{22}O_4Na$ 337.1410, found 337.1401.

*1,3-Bis(4-methoxyphenyl)propan-2-one (**4c**).* Compound **4c** was prepared according to the general procedure B by treating enol ether **1n** (500 mg, 3.048 mmol, 1.0 equiv) and **2a** (631 mg, 4.572 mmol, 1.5 equiv) in 1,2-DCE (15 mL) for 12 h. Purification of the crude material by silica gel column chromatography using 10% ethyl acetate in petroleum ether (10/100) as an eluent furnished the compound **4c** as a light yellow solid (440 mg, 53%). Mp = 84−86 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07−7.04 (m, 4H), 6.86−6.84 (m, 4H), 3.79 (s, 6H), 3.64 (s, 4H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 206.5, 158.6, 130.5, 126.1, 114.1, 55.2, 48.0. IR ν_{max} (neat): 2937, 1707, 1610, 1511, 1250, 1176, 1033, 826, 730 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{19}O_3$ 271.1329, found 271.1330.

*1,3-Bis(4-methoxyphenyl)pentan-2-one and 2-(4-Methoxybenzyl)-1-(4-methoxyphenyl)butan-1-one (**4e** and **4e′**).* Compounds **4e** and **4e′** were prepared according to the general procedure B by treating enol ether **1o** (77 mg, 0.4 mmol, 1.0 equiv) and **2a** (55 mg, 0.4 mmol, 1.0 equiv) in 1,2-DCE (2 mL) for 7 h. Purification of the crude material by silica gel column chromatography using 4% ethyl acetate in petroleum ether (4/100) as an eluent furnished the compound **4e** and **4e′** as a colorless liquid (86 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.11−7.07 (m, 4 H), 6.99−6.93 (m, 4 H), 6.87−6.78 (m, 7 H), 6.73 (d, J = 8.8 Hz, 1 H), 3.79 (s, 4 H), 3.77 (s, 6 H), 3.74 (s, 2 H), 3.57−3.52 (m, 4 H), 3.32 (dd, J = 7.8, 13.7 Hz, 1 H), 2.82 (dd, J = 7.1, 13.9 Hz, 1 H), 2.39 (dd, J = 7.3, 18.1 Hz, 1 H), 2.21 (dd, J = 7.3, 17.6 Hz, 1 H), 1.98 (dd, J = 6.8, 14.2 Hz, 1 H), 1.64 (td, J = 7.5, 13.8 Hz, 1 H), 0.89 (t, J = 7.1 Hz, 3 H), 0.74 (t, J = 7.3 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 210.9,208.2, 158.8, 158.7, 158.5, 157.9, 131.9, 130.8, 130.8, 130.5, 129.9, 129.5, 129.3, 126.3, 114.2, 114.2, 114.0, 113.6, 59.9, 58.6, 55.2, 55.2, 55.1, 47.8, 37.9, 35.5, 25.3, 11.9, 7.8. IR ν_{max} (neat): 2960, 1704, 1512, 1258, 1177, 1136, 895, 826 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{23}O_3$ 299.1642, found 299.1649.

*(2-(4-Methoxyphenyl)-2-methyl-3-(2,4,5-trimethoxyphenyl)-propanal (**3aa**).* Compound **3aa** was prepared according to the general procedure A by treating enol ether **1a** (71 mg, 0.4 mmol, 1.0

DOI: 10.1021/acs.joc.9b02064
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equiv) and **2aa** (79 mg, 0.4 mmol, 1.0 equiv) in 1,2-DCE (2 mL) for 24 h. Purification of the crude material by silica gel column chromatography using 4% ethyl acetate in petroleum ether (4/100) as an eluent furnished the compound **3aa** as a colorless liquid (77 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.58 (s, 1 H), 7.16 (d, J = 8.8 Hz, 2 H), 6.90 (d, J = 8.8 Hz, 2 H), 6.45 (s, 1 H), 6.19 (s, 1 H), 3.85 (s, 3 H), 3.79 (s, 3 H), 3.69 (s, 3 H), 3.60 (s, 3 H), 3.42 (s, 3 H), 3.44 (d, J = 13.6 Hz, 1 H), 2.87 (d, J = 13.6 Hz, 1 H), 1.30 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 202.0, 158.7, 151.8, 148.2, 142.2, 132.2, 128.6, 116.6, 115.8, 114.0, 97.1, 56.2, 56.0, 55.9, 55.3, 54.5, 35.7, 18.2. IR ν_{max} (neat): 2934, 1714, 1514, 1504, 1211, 1034, 864 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{25}O_5$ 345.1697, found 345.1696.

Synthesis of Propterol A. *Step 1. 1,3-Bis(4-methoxyphenyl)-propan-2-ol (**5**).* To a solution of compound **4c** (100 mg, 0.370 mmol) in dry MeOH was added $NaBH_4$ (42 mg, 1.110 mmol) portionwise at 0 °C, and the resulting reaction mixture was stirred at 40 °C in an oil bath for 12 h. After complete conversion of starting material (monitored by TLC), the reaction mixture solvent was evaporated under reduced pressure and diluted with cold water, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography. White solid (94 mg, 93%), mp = 57−59 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.14 (d, J = 8.8 Hz, 4 H), 6.85 (d, J = 8.8 Hz, 4 H), 4.00−3.89 (m, 1 H), 3.79 (s, 6 H), 2.79 (dd, J = 4.9, 13.7 Hz, 2 H), 2.68 (dd, J = 8.1, 13.9 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.3, 130.5, 130.4, 114.0, 73.8, 55.3, 42.4.

*Step 2 (**6**).* Propterol A was obtained by demethylation of the compound **5** (94 mg, 0.3455 mmol, 1.0 equiv) by using a 1.0 M solution of BBr_3 (1.4 mL, 1.382 mmol, 4.0 equiv) in CH_2Cl_2 at −78 °C to room temperature for 16 h. Colorless needle-like prisms (40 mg, 47%), mp = 170−172 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.29 (br. s., 2 H), 7.05 (d, J = 8.4 Hz, 4 H), 6.71 (d, J = 8.4 Hz, 4 H), 4.50−4.41 (m, 1 H), 3.13 (dd, J = 4.9, 14.7 Hz, 2 H), 2.93 (dd, J = 8.6, 14.4 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 155.3, 130.1, 129.7, 114.8, 72.8, 42.2. HRMS (ESI-TOF) m/z: [M + NH_4]$^+$ calcd for $C_{15}H_{20}NO_3$ 262.1438, found 262.1430. Data reported here is identical with literature reported data.[1c]

Procedure for Synthesis of (±)-Tetrahydronyasol. *Step 1. 1,3-Bis(4-methoxyphenyl)pentan-2-one (**4e**).* To a stirred solution of compound **4c** (100 mg, 0.370 mmol, 1.0 equiv) in DMF was added NaH (35 mg, 1.481 mmol, 4.0 equiv) at 0 °C, followed by dropwise addition of iodoethane (92 mg, 0.592 mmol, 1.6 equiv). The solution was stirred for 1 h, and the reaction mixture was quenched with saturated aqueous NH_4Cl. The aqueous solution was extracted with 2 × 10 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude material by silica gel column chromatography using 4% ethyl acetate in petroleum ether (4/100) as an eluent furnished the desired compound as a colorless liquid (62 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.11−7.07 (m, 2 H), 6.98−6.95 (m, 2 H), 6.88−6.79 (m, 4 H), 3.79 (s, 6 H), 3.57−3.53 (m, 3 H), 1.98 (dd, J = 6.8, 14.2 Hz, 1 H), 1.64 (td, J = 7.5, 13.8 Hz, 1 H), 0.74 (t, J = 7.3 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 208.3, 158.8, 158.5, 130.8, 130.5, 129.5, 126.4, 114.3, 114.0, 58.6, 55.3, 55.2, 47.8, 25.3, 12.0. IR ν_{max} (neat): 2924, 1697, 1603, 1511, 1252, 1174, 1032, 826 cm^{-1}. HR-MS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{19}H_{22}O_3Na$ 321.1461, found 321.1457.

*Step 2. Synthesis of Compound 4,4′-(Pentane-1,3-diyl)bis-(methoxybenzene) (**7**).* To a solution of compound **4e** (30 mg, 0.1 mmol, 1.0 equiv) in dichloromethane were added $BF_3{\cdot}OEt_2$ (57 mg, 0.4 mmol, 4.0 equiv) and triethylsilane (46 mg, 0.4 mmol, 4.0 equiv) at room temperature and the mixture stirred for 12 h. After complete conversion of the reaction, as monitored by TLC, the crude mixture was directly loaded in column chromatography for further purification using 2% ethyl acetate in petroleum ether (2/100) as an eluent to furnish the compound **7** as a colorless liquid (23 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.07 (d, J = 8.3 Hz, 2 H), 7.01 (d, J = 8.8 Hz, 2 H), 6.85 (d, J = 8.8 Hz, 2 H), 6.79 (d, J = 8.8 Hz, 2 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 2.42−2.31 (m, 3 H), 1.96−1.87 (m, 1 H), 1.85−1.75 (m, 1 H), 1.68−1.60 (m, 1 H), 1.56−1.47 (m, 1 H), 0.74 (t, J = 7.3 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.8, 137.5, 134.8, 130.0, 129.2, 128.7, 113.7, 113.6, 113.5, 55.3, 55.2, 55.2, 46.4, 38.6, 32.9, 30.0, 12.1. IR ν_{max} (neat): 2926, 1510, 1245, 1176, 1036, 824 cm^{-1}. HRMS (ESI-TOF) m/z: [M + NH_4]$^+$ calcd for $C_{19}H_{28}NO_2$ 302.2115, found 302.2105

*Step 3. Synthesis of (±)-Tetrahydronyasol (**8**).* Demethylation of compound **7** was done by following the known literature method.[3a] A 1.0 M solution of BBr_3 in dichloromethane was added dropwise to a solution of compound **8** (20 mg, 0.07 mmol) in dichloromethane at −78 °C to room temperature for 20 h. White solid (18 mg, 99%), mp = 103−105 °C (lit.[3a] mp 102−103 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.96 (d, J = 8.3 Hz, 2 H), 6.90 (d, J = 8.3 Hz, 2 H), 6.78 (d, J = 8.3 Hz, 2 H), 6.72 (d, J = 8.3 Hz, 2 H), 6.31 (br. s., 2 H), 2.35−2.26 (m, 3 H), 1.91−1.80 (m, 1 H), 1.78−1.68 (m, 1 H), 1.67−1.60 (m, 1 H), 1.52−1.39 (m, 1 H), 0.70 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.6, 153.4, 137.7, 135.0, 130.2, 129.4, 128.9, 115.2, 115.1, 115.1, 46.4, 38.5, 32.9, 30.0, 12.1. IR ν_{max} (neat): 3310, 2923, 1605, 1508, 1449, 1336, 1224, 825 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{21}O_2$ 257.1536, found 257.1525.

1,3-Bis(4-methoxyphenyl)propane (9). Compound **9** was prepared according to the procedure for **7** using compound **4c** (20 mg, 0.074 mmol, 1.0 equiv) in dichloromethane, $BF_3{\cdot}OEt_2$ (42 mg, 0.296 mmol, 4.0 equiv) and triethylsilane (34 mg, 0.296 mmol, 4.0 equiv) were added at room temperature, and the mixture was stirred for 12 h. After complete conversion of the reaction, as monitored by TLC, the crude mixture was directly loaded in column chromatography for further purification using 2% ethyl acetate in petroleum ether (2/100) as an eluent furnished the compound **9** as a colorless solid (17 mg, 90%). Mp = 41−43 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16−7.00 (m, 4 H), 6.90−6.68 (m, 4 H), 3.78 (s, 6 H), 2.70−2.50 (m, 4 H), 1.88 (t, J = 7.6 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.7, 134.5, 129.3, 113.7, 55.3, 34.5, 33.4. IR ν_{max} (neat): 2929, 1610, 1510, 1456, 1243, 1177, 1036, 822 cm^{-1}. HRMS (ESI-TOF) m/z: [M + NH_4]$^+$ calcd for $C_{17}H_{24}NO_2$ 274.1802, found 274.1797.

Gram-Scale Synthesis of the Product (3o). To a stirred solution of compounds **1o** (1.0 g, 5.181 mmol, 1.0 equiv) and **2a** (0.715 g, 5.181 mmol, 1.0 equiv) in 1,2-DCE (20 mL) was added $ZnBr_2$ (1.165 g, 5.181 mmol, 1.0 equiv) at room temperature and the mixture stirred for 6 h. After the reaction completed, it was diluted with water and the aqueous layer was extracted with dichloromethane. All organic layers were dried over Na_2SO_4, solvent was evaporated at reduced pressure, and the product was isolated by using column chromatography 4% ethyl acetate in petroleum ether (4/100) as an eluent to give **3o** as a colorless liquid (998 mg, 65%).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b02064.

Copies NMR spectra for all synthesized compounds (**1c**, **3a**−**3t**, **3aa**, **4a**−**4e**, **5**, **6**, **7**, **8**, **9**) (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: faiz@iith.ac.in. Tel: (040) 2301 6084.

ORCID

Faiz Ahmed Khan: 0000-0001-8057-8117

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.joc.9b02064
J. Org. Chem. XXXX, XXX, XXX−XXX

■ ACKNOWLEDGMENTS

We gratefully acknowledge the Department of Science and Technology, Science and Engineering Research Board (SERB), India, for financial support. T.K.J. thanks MHRD, India, for the award of a research fellowship.

■ REFERENCES

(1) (a) Rao, A. V. S.; Mathew, J.; Sankaram, A. V. B. Propterol: A 1,3-Diarylpropan-2-ol from Pterocarpus Marsupium. *Phytochemistry* **1984**, *23*, 897. (b) Kijjoa, A.; Giesbrecht, A. M.; Gottlieb, O. R.; Gottlieb, H. E. 1,3-Diaryl-propanes and Propan-2-ols from Virola Species. *Phytochemistry* **1981**, *20*, 1385. (c) Maurya, R.; Ray, A. B.; Chattopadhyay, S. K.; Duah, F. K.; Lin, M. C.; Slatkin, D. J.; Schiff, P. L., Jr The Synthesis of Propterol, A Novel 1,3-Diarylpropan-2-ol from Pterocarpus Marsupium. *J. Nat. Prod.* **1985**, *48*, 313.

(2) Fang, Y.; Park, H. Practical Synthesis of (±) Nysol. *Synth. Commun.* **2015**, *45*, 137.

(3) (a) Quan, W. G.; Yu, B. X.; Zhang, J. Y.; Liang, Q. R.; Sun, Y. Q.; She, X. G.; Pan, X. F. A Facile Approach to Synthesis of Di-*O*-Methyl Ethers of (−)-Agatharesinol, (−)-Sugiresinol, (+)-Nyasol and (+)-Tetrahydronyasol. *Chin. J. Chem.* **2007**, *25*, 688. (b) Marini-Bettolo, G. B.; Nicoletti, M.; Messana, I.; Galeffi, C.; Msonthi, J. D.; Chapya, W. A. Glucosides of Hypoxis Nyasica Bax. The Structure of Nyasoside, a New Glucoside Biologically Related to Hypoxoside. *Tetrahedron* **1985**, *41*, 665.

(4) Lassen, P. R.; Skytte, D. M.; Hemmingsen, L.; Nielsen, S. F.; Freedman, T. B.; Nafie, L. A.; Christensen, S. B. Structure and Absolute Configuration of Nyasol and Hinokiresinol Via Synthesis and Vibrational Circular Dichroism Spectroscopy. *J. Nat. Prod.* **2005**, *68*, 1603.

(5) Wang, P. S.; Zhou, X. L.; Gong, L. Z. An Organocatalytic Asymmetric Allylic Alkylation Allows Enantioselective Total Synthesis of Hydroxymetasequirin-A and Metasequirin-B Tetramethyl Ether Diacetates. *Org. Lett.* **2014**, *16*, 976.

(6) (a) Gutierrez-Bonet, A.; Flores-Gaspar, A.; Martin, R. Fe-catalyzed Regiodivergent [1,2]-Shift of α-Aryl Aldehydes. *J. Am. Chem. Soc.* **2013**, *135*, 12576. (b) Olah, G. A.; Mathew, T.; Marinez, E. R.; Esteves, P. M.; Etzkkorn, M.; Rasul, G.; Prakash, G. K. S. Acid-Catalyzed Isomerization of Pivalaldehyde to Methyl Isopropyl Ketone via a Reactive Protosolvated Carboxonium Ion Intermediate. *J. Am. Chem. Soc.* **2001**, *123*, 11556. (c) Prakash, G. K. S.; Mathew, T.; Marinez, E. R.; Esteves, P. M.; Rasul, G.; Olah, G. A. $BF_3.2CF_3CH_2OH$ (BF_3.2TFE), an Efficient Superacidic Catalyst for Some Organic Synthetic Transformations. *J. Org. Chem.* **2006**, *71*, 3952. (d) Davies, H. M. L.; Dai, X. Lewis Acid Induced Tandem Diels-Alder Reaction/Ring Expansion as an Equivalent of a [4 + 3] Cycloaddition. *J. Am. Chem. Soc.* **2004**, *126*, 2692.

(7) Wommack, A. J.; Kingsbury, J. S. Synthesis of Acyclic Ketones by Catalytic, Bidirectional Homologation of Formaldehyde with Nonstabilized Diazoalkanes. Application of a Chiral Diazomethyl-(pyrrolidine) in Total Syntheses of Erythroxylon Alkaloids. *J. Org. Chem.* **2013**, *78*, 10573.

(8) Tran, K.-V.; Bickar, D. Dakin-West Synthesis of α-Aryl Ketones. *J. Org. Chem.* **2006**, *71*, 6640.

(9) Potter, R. G.; Hughes, T. S. Synthesis of Heterosubstituted Hexaarylbenzenes via Asymmetric Carbonylative Couplings of Benzyl Halides. *Org. Lett.* **2007**, *9*, 1187.

(10) (a) Su, W.; Raders, S.; Verkade, J. G.; Liao, X.; Hartwig, J. F. Pd-Catalyzed α-Arylation of Trimethylsilyl Enol Ethers with Aryl Bromides and Chlorides: A Synergistic Effect of Two Metal Fluorides as Additives. *Angew. Chem., Int. Ed.* **2006**, *45*, 5852. (b) Reetz, M. T. Lewis Acid Induced α-Alkylation of Carbonyl Compounds. *Angew. Chem.* **1982**, *94*, 97; *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 96. (c) Nishimoto, Y.; Onishi, Y.; Yasuda, M.; Baba, A. α-Alkylation of Carbonyl Compounds by Direct Addition of Alcohols to Enol Acetates. *Angew. Chem., Int. Ed.* **2009**, *48*, 9131. (d) Xing, C.; Sun, H.; Zhang, J.; Li, G.; Chi, Y. R. Bronsted Acid Catalyzed α-Alkylation of Aldehydes with Diaryl Methyl Alcohols. *Chem. - Eur. J.* **2011**, *17*, 12272. (e) Rubenbauer, P.; Bach, T. Chemo- and Diastereoselective $Bi(OTf)_3$-Catalyzed Benzylation of Silyl Nucleophiles. *Tetrahedron Lett.* **2008**, *49*, 1305.

(11) (a) Kumar, R.; Van Der Eycken, E. V. Recent Approaches for C−C bond Formation via Direct Dehydrative Coupling Strategies. *Chem. Soc. Rev.* **2013**, *42*, 1121. Recent α-alkylation on ketones: (b) Charvieux, A.; Giorgi, J. B.; Duguet, N.; Metay, E. Solvent-Free Direct α-Alkylation of Ketones by Alcohols Catalyzed by Nickel Supported on Silica−Alumina. *Green Chem.* **2018**, *20*, 4210. (c) Das, J.; Vellakkaran, M.; Banerjee, D. Nickel- Catalyzed Alkylation of Ketone Enolates: Synthesis of Monoselective Linear Ketones. *J. Org. Chem.* **2019**, *84*, 769. (d) Genc, S.; Gunnaz, S.; Cetinkaya, B.; Gulcemal, S.; Gulcemal, D. Iridium(I)-Catalyzed Alkylation Reactions to Form α-Alkylated Ketones. *J. Org. Chem.* **2018**, *83*, 2875. (e) Chakraborty, S.; Daw, P.; David, Y. B.; Milstein, D. Manganese-Catalyzed α-Alkylation of Ketones, Esters, and Amides Using Alcohols. *ACS Catal.* **2018**, *8*, 10300. (f) Gawali, S. S.; Pandia, B. K.; Gunanathan, C. Manganese(I)-Catalyzed α-Alkenylation of Ketones Using Primary Alcohols. *Org. Lett.* **2019**, *21*, 3842.

(12) Selected references on α-arylation of ketones: (a) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. Highly Active and Selective Catalysts for the Formation of α-Aryl Ketones. *J. Am. Chem. Soc.* **2000**, *122*, 1360. (b) Kawatsura, M.; Hartwig, J. F. Simple, Highly Active Palladium Catalysts for Ketone and Malonate Arylation: Dissecting the Importance of Chelation and Steric Hindrance. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (c) Johansson, C. C. C.; Colacot, T. J. Metal-Catalyzed α-Arylation of Carbonyl and Related Molecules: Novel Trends in C-C Bond Formation by C-H Bond Functionalization. *Angew. Chem., Int. Ed.* **2010**, *49*, 676.

(13) Enantioselective protocols: (a) Spielvogel, D. J.; Buchwald, S. L. Nickel-BINAP Catalyzed Enantioselective α-Arylation of α-Substituted γ-Butyrolactones. *J. Am. Chem. Soc.* **2002**, *124*, 3500. (b) Hamada, T.; Chieffi, A.; Ahman, J.; Buchwald, S. L. An Improved Catalyst for the Asymmetric Arylation of Ketone Enolates. *J. Am. Chem. Soc.* **2002**, *124*, 1261. (c) Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. Asymmetric Arylation of Ketone Enolates. *J. Am. Chem. Soc.* **1998**, *120*, 1918.

(14) For reviews on enamine catalysis, see: (a) List, B. The Ying and Yang of Asymmetric Aminocatalysis. *Chem. Commun.* **2006**, *0*, 819. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. Asymmetric Enamine Catalysis. *Chem. Rev.* **2007**, *107*, 5471. (c) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. Asymmetric Aminocatalysis-Gold Rush in Organic Chemistry. *Angew. Chem.* **2008**, *120*, 6232; *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (d) Xu, L. W.; Luo, J.; Lu, Y. Asymmetric Catalysis with Chiral Primary Amine-Based Organocatalysts. *Chem. Commun.* **2009**, 1807.

(15) List, B.; Coric, I.; Grygorenko, O. O.; Kaib, P. S. J.; Komarov, I.; Lee, A.; Leutzsch, M.; Pan, S. C.; Tymtsunik, A. V.; Gemmeren, M. V. The Catalytic Asymmetric α-Benzylation of Aldehydes. *Angew. Chem., Int. Ed.* **2014**, *53*, 282.

(16) Cozzi, P. G.; Benfatti, F.; Zoli, L. Organocatalytic Asymmetric Alkylation of Aldehydes by S_N1-type Reaction of Alcohols. *Angew. Chem.* **2009**, *121*, 1339; *Angew. Chem., Int. Ed.* **2009**, *48*, 1313.

(17) Franzoni, I.; Guenee, L.; Mazet, C. A general Pd-Catalyzed α- and γ-Benzylation of Aldehydes for the Formation of Quaternary Centers. *Org. Biomol. Chem.* **2015**, *13*, 6338.

(18) Hodgson, D. M.; Charlton, A. Methods for Direct Generation of α-Alkyl-Substituted Aldehydes. *Tetrahedron* **2014**, *70*, 2207.

(19) Du, S. Z.; Kuang, F.; Liu, Y.; Chen, Y. G.; Zhan, R. A New Dimeric DiarylPropane from Horsfieldia Tetratepala. *Nat. Prod. Res.* **2018**, *32*, 162.

(20) Lippincott, D. J.; Trejo-Soto, P. J.; Gallou, F.; Lipshutz, B. H. Copper-Catalyzed Oxidative Cleavage of Electron-Rich Olefins in Water at Room Temperature. *Org. Lett.* **2018**, *20*, 5094.

(21) Sorensen, U. S.; Bleisch, T. J.; Kingston, A. E.; Wright, R. A.; Johnson, B. G.; Schoepp, D. D.; Ornstein, P. L. Synthesis and Structure-Activity Relationship Studies of Novel 2-Diarylethyl Substituted (2-Carboxycycloprop-1-yl)glycines as High-Affinity

DOI: 10.1021/acs.joc.9b02064
J. Org. Chem. XXXX, XXX, XXX−XXX

Group II Metabotropic Glutamate Receptor Ligands. *Bioorg. Med. Chem.* **2003**, *11*, 197.
(22) Tian, G.; Fedoseev, P.; Van der Eycken, E. V. Hypervalent Iodine(III)-Mediated Cascade Cyclization of Propargylguanidines and Total Syntheses of Kealiinine B and C. *Chem. - Eur. J.* **2017**, *23*, 5224.
(23) Hoffmann, S.; Nicoletti, M.; List, B. Catalytic Asymmetric Reductive Amination of Aldehydes via Dynamic Kinetic Resolution. *J. Am. Chem. Soc.* **2006**, *128*, 13074.
(24) Chepiga, K. M.; Feng, Y.; Brunelli, N. A.; Jones, C. W.; Davies, H. M. L. Silica-Immobilized Chiral Dirhodium(II) Catalyst for Enantioselective Carbenoid Reactions. *Org. Lett.* **2013**, *15*, 6136.
(25) Reichardt, C.; Ferwanah, A. R.; Pressler, W.; Yun, K. Y. Syntheses with Aliphatic Dialdehydes, XXXVIII- Synthesis and Properties of Cycloalkylmalonaldehydes. *Liebigs Ann. Chem.* **1984**, .649

DOI: 10.1021/acs.joc.9b02064
J. Org. Chem. XXXX, XXX, XXX−XXX