JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

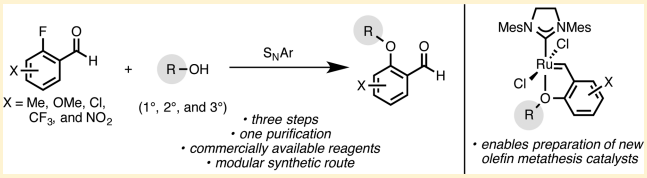
An S_NAr Approach to Sterically Hindered *ortho*-Alkoxybenzaldehydes for the Synthesis of Olefin Metathesis Catalysts

Keary M. Engle, Shao-Xiong Luo, and Robert H. Grubbs*

Arnold and Mabel Beckman Laboratory of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

Supporting Information

ABSTRACT: A three-step procedure has been developed for preparing *ortho*-alkoxybenzaldehydes from *ortho*-fluorobenzaldehydes that tolerates the use of sterically hindered sodium alkoxide nucleophiles. The protocol is modular and operationally convenient. The *ortho*-alkoxybenzaldehyde products can be converted in one additional step to *ortho*-alkoxystyrenes by a Wittig reaction. These styrenes are precursors to the chelating benzylidene moiety in a proposed series of novel ruthenium complexes for use in olefin metathesis. Chelation with three representative styrenes has been demonstrated.



The discovery and development of catalysts with novel reactivity and selectivity has continued to propel the field of olefin metathesis over the past three decades (e.g., **1**–**7**, Figure 1).[1,2] In 1999, Hoveyda and co-workers made an important advance in this respect with the synthesis of ruthenium catalyst **3**, containing a chelating *ortho*-isopropoxybenzylidene.[3] The Hoveyda and Blechert groups later used this benzylidene in preparing second-generation catalyst **4**.[4] Since that time, several research groups, including our own, have used the Hoveyda-type chelating benzylidene in combination with different phosphines and *N*-heterocyclic carbene L-type ligands (e.g., **3**–**7**).[1,5,6] Generally speaking, the Hoveyda chelate imparts a high level of stability in the catalyst, particularly with respect to air and moisture, which makes these catalyst valuable tools in organic synthesis.[1] Moreover, by virtue of not having a labile phosphine ligand, Hoveyda-type catalysts are not susceptible to certain phosphine-mediated catalyst decomposition pathways.[1e]

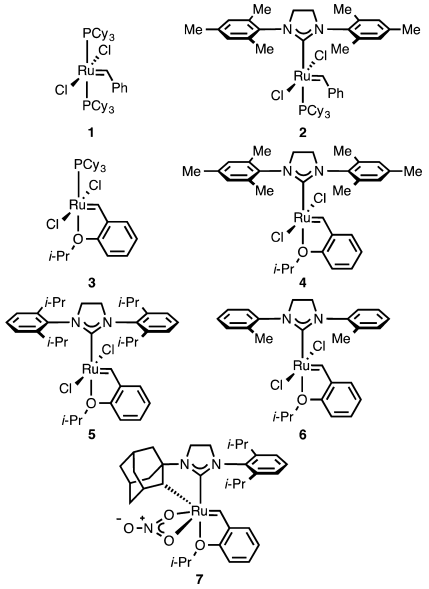


Figure 1. Representative ruthenium olefin metathesis catalysts (**1**–**7**).

In addition to variation of the L- and X-type ligands, a wide variety of chelating alkylidene and benzylidene moieties have been examined, and it has been found that the structure of this group dramatically affects catalyst initiation.[6−15] In the case of Hoveyda-type catalysts, initiation takes place when the chelated catalyst reacts with an olefin-containing substrate to release the chelating benzylidene as an *ortho*-alkoxystyrene derivative, generating the propagating ruthenium alkylidene species. Broadly speaking, being able to tune the catalyst initiation rate in a predictable manner for specific applications is highly desirable.[1,6] *ortho*-Isopropoxybenzylidene-containing catalysts generally initiate slowly, which can be disadvantageous in some contexts because there is a comparatively low concentration of active catalyst at any given time, particularly at the beginning of the reaction. To overcome this issue, several fast-initiating variants have been developed (e.g., **8**–**10**, Figure 2).[7,8,14]

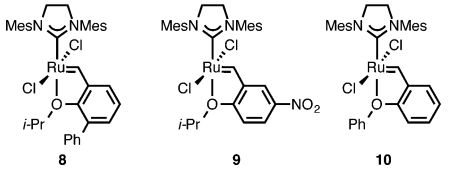


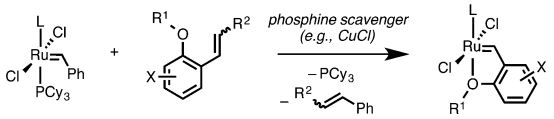
Figure 2. Representative fast-initiating ruthenium olefin metathesis catalysts containing chelating benzylidenes (**8**–**10**).

Received: March 12, 2015

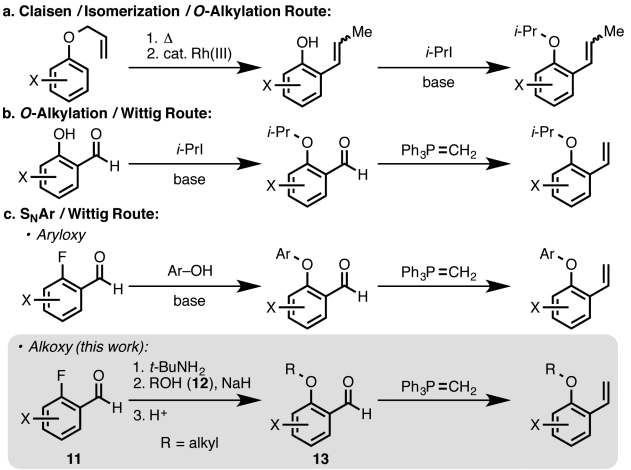
DOI: 10.1021/acs.joc.5b00563
J. Org. Chem. XXXX, XXX, XXX−XXX

Catalysts **3**–**10** are typically prepared by combining a phosphine-containing precursor (e.g., **1** or **2**) with the corresponding 2-alkoxystyrene or 1-alkoxy-2-(prop-1-en-1-yl)-benzene in the presence of a phosphine scavenger (Scheme 1).[4,16] These benzylidene precursor compounds, in turn, are prepared according to the routes shown in Scheme 2.[3,4,8−10,13]

Scheme 1. General Synthesis of Ruthenium Olefin Metathesis Catalysts Containing Chelating Benzylidenes



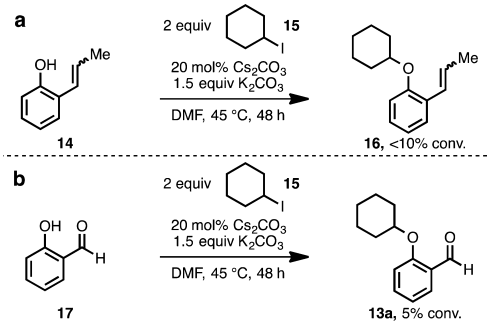
Scheme 2. General Synthetic Approaches for Accessing Benzylidene Precursors



The two most common approaches rely of *O*-alkylation, in which the alkoxy group is formed by treating an aryloxide nucleophile with an alkyl halide electrophile, typically 2-iodopropane (Scheme 2a and b).[3,4,8,9,13] Recently, Plenio prepared a series of ruthenium catalysts containing chelating aryloxy benzylidenes; the corresponding styrenes were synthesized via nucleophilic aromatic substitution (S_NAr) between 2-fluorobenzaldehyde and various aryloxide nucleophiles, followed by Wittig olefination (Scheme 2c, top).[14] These synthetic strategies allow efficient access to benzylidenes with different functional groups on the aryl ring (and in the case of Plenio's catalysts, on the aryloxy group). As such, the effect of benzylidene aryl modification on initiation rate has been extensively studied.[7−13] On the other hand, comparatively little is known regarding the effect of alkoxy group modification on initiation,[4a,13,14,17] as the vast majority of examples contain an isopropoxy group. To probe this question, a reliable method to synthesize benzylidene precursors with varied alkoxy groups was required. In this paper, a modular route to *ortho*-alkoxybenzaldehydes through S_NAr chemistry is presented (Scheme 2c, bottom).

While *O*-alkylation is effective for installing simple primary and secondary alkyl groups, it was anticipated that sterically bulky secondary and tertiary alkyl halides would be problematic. Indeed, in two pilot experiments with iodocyclohexane (**15**), *O*-alkylation of 2-propenylphenol (**14**) and salicylaldehyde (**17**) was ineffective (Scheme 3).

Scheme 3. Unsuccessful Attempts to Prepare Representative *ortho*-Alkoxybenzylidene Precursors via *O*-alkylation[a]

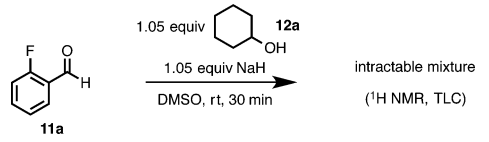


[a]Conversion determined by ^{1}H NMR analysis of the crude reaction mixture.

At the outset, we were attracted to S_NAr chemistry because a diverse collection of alcohols and *ortho*-fluorobenzaldehydes are commercially available. However, sterically bulky alkoxides are strong Brønsted bases and relatively weak nucleophiles and are thus challenging to use as reaction partners in S_NAr chemistry.[18] Similarly, despite some recent encouraging progress,[19] metal-catalyzed cross-coupling with bulky alkoxide nucleophiles is also generally challenging. For the purposes of this study, we elected to focus on S_NAr chemistry.

In an initial experiment, 2-fluorobenzaldehyde was treated with sodium cyclohexanoxide in DMSO at room temperature (Scheme 4). A reaction immediately took place, generating an

Scheme 4. Unsuccessful Attempt at Direct S_NAr with 2-Fluorobenzaldehyde (11a)

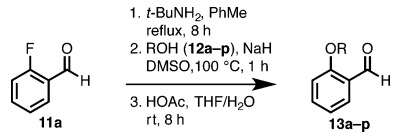


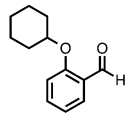
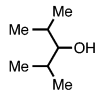
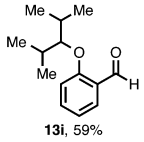
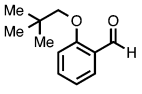
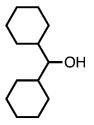
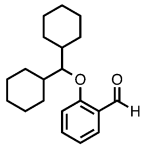
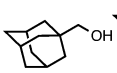
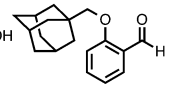
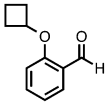
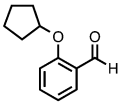
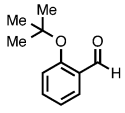
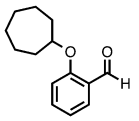
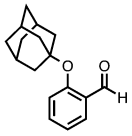
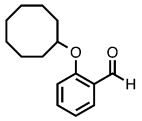
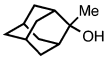
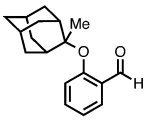
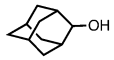
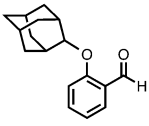
intractable mixture of products. We reasoned that the aldehyde moiety reacted indiscriminately with sodium cyclohexanoxide. To circumvent this issue, the aldehyde was first converted to the corresponding *N*-*tert*-butyl imine.[20] Treating this masked aldehyde with sodium cyclohexanoxide, followed by acidic hydrolysis, yielded 45% of the desired product **13a** over three steps (Table 1, entry 1).

With this three-step protocol, the scope of alkoxide nucleophiles was evaluated using the *N*-*tert*-butyl imine derived from 2-fluorobenzaldehyde (**11a**) as the electrophile (Table 1). Briefly, the procedure for this sequence was as follows. Reactions were performed on a 10 mmol scale. The *N*-*tert*-butyl imine was first prepared by condensing *tert*-butylamine with the desired *ortho*-fluorobenzaldehyde in toluene at vigorous reflux for 8 h using a Dean–Stark trap to remove water. The solvent was evaporated, and the crude *N*-*tert*-butyl imine was used in the S_NAr step without further purification. The sodium alkoxide nucleophile was preformed by adding the alcohol of choice to a solution of NaH in DMSO at room temperature. A solution of the *N*-*tert*-butyl imine in DMSO was added, and the reaction mixture was allowed to stir at 100 °C for 1 h. Lastly, after aqueous workup, the crude product was exposed to acidic hydrolysis conditions (HOAc in THF/H_2O) at room temperature for 8 h. Following extraction, a single silica

DOI: 10.1021/acs.joc.5b00563
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 1. Scope of Sodium Alkoxide Nucleophiles[a,b]



entry	alcohol	product	entry	alcohol	product
1[c]	 **12a**	 **13a**, 45%	9	 **12i**	 **13i**, 59%
2	 **12b**	 **13b**, 76%	10	 **12j**	 **13j**, 57%
3	 **12c**	 **13c**, 52%	11[d]	 **12k**	---
4	 **12d**	 **13d**, 42%	12[d]	 **12l**	---
5	 **12e**	 **13e**, 55%	13[e]	 **12m**	 **13m**, 26%
6	 **12f**	 **13f**, 50%	14	 **12n**	 **13n**, 24%
7	 **12g**	 **13g**, 51%	15	 **12o**	 **13o**, 8%
8	 **12h**	 **13h**, 40%	16[d]	 **12p**	---

[a]General procedure. Step 1: *ortho*-fluorobenzaldehyde (10.0 mmol), *tert*-butylamine (1.00 equiv), toluene, reflux (140−150 °C, Dean−Stark apparatus), 8 h. Step 2: crude product from Step 1 (assumed to be 10.0 mmol), NaH (1.05 equiv), alcohol (1.05 equiv), DMSO, 100 °C, 1 h. Step 3: crude product from Step 2 (assumed to be 10.0 mmol) 50:15:1 H_2O:THF:HOAc, room temp (20−22 °C), 8 h. [b]Isolated yield over three steps. [c]Under otherwise identical conditions, <10% conversion was observed after 24 h in Step 2 when the *N*-*tert*-butyl imine derived from 2-chlorobenzaldehyde was used as the electrophile. [d]After 1 h, only the unreacted *N*-*tert*-butyl imine starting material was observed in the crude reaction mixture. There was no evidence for formation of the desired product. [e]Commercially available sodium *tert*-butoxide was used as the nucleophile.

gel column chromatographic purification at the end of the sequence delivered the desired *ortho*-alkoxybenzaldehyde.

We elected to focus on alkoxy groups that would be difficult to introduce by *O*-alkylation. Consistent with the expected order of reactivity, primary sodium alkoxide nucleophiles, such as those prepared from neopentanol (**12b**) and (1-adamantyl)-methanol (**12c**), gave among the highest isolated yields of the desired products **13b** and **13c** (Table 1, entries 2 and 3). A range of different cyclic and acyclic secondary alkoxide nucleophiles were competent reaction partners, consistently delivering isolated yields between 40% and 60% (entries 1 and 4−10). Tertiary sodium alkoxide nucleophiles were lower yielding (entries 13−15). The sodium alkoxide salts of *tert*-butanol (**12m**), 1-adamantanol (**12n**), and 2-methyl-2-adamantanol (**12o**) produced yields of 26, 24, and 8%, respectively. Three sodium alkoxide salts were unreactive (entries 11, 12, and 16). In the case of sodium 1,1,1,3,3,3-hexafluoroisopropoxide (from **12k**), electron-withdrawing fluoride substituents presumably attenuate nucleophilicity, whereas, with sodium triphenylmethoxide (from **12p**), enhanced steric hindrance is likely at fault. The origin of the lack of reactivity with penta-1,4-dien-3-ol (**12l**) is unclear. For comparison, the *N*-*tert*-butyl imine derived from 2-chlorobenzaldehyde was also treated with sodium cyclohexanoxide, and as expected, it was far less reactive (<10% conversion after 24 h).

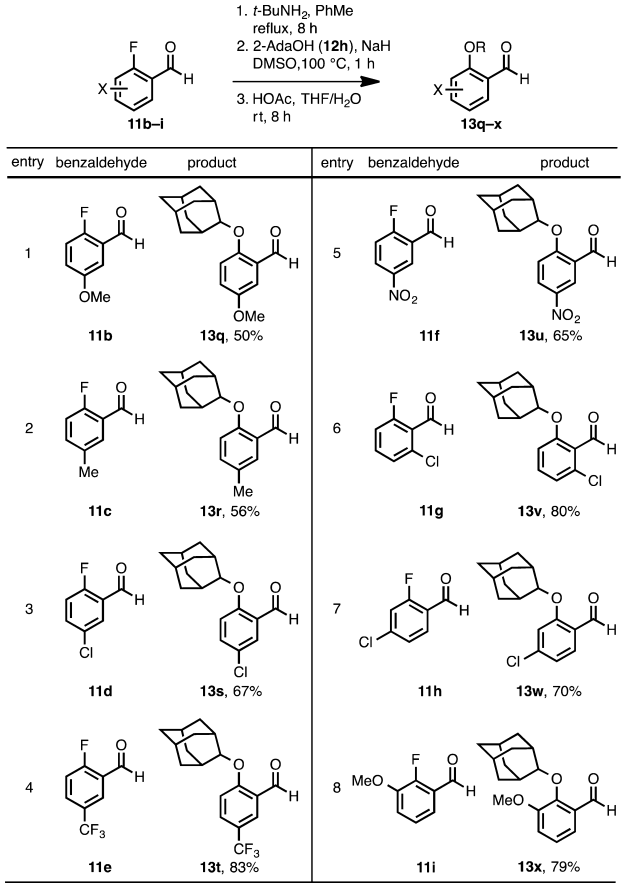
Though the focus of this study was determining how the steric properties of the alkoxy group influence initiation,[17,21] varying the electronic properties of the benzylidene is also an established means of enhancing initiation.[8−13] Thus, it was envisioned that combining these two effects in a single chelating benzylidene could be a fruitful approach. To this end, the scope of 2-fluorobenzaldehydes was next examined. A representative secondary alkoxide nucleophile, sodium 2-adamantyloxide (from **12h**), was thus reacted with a series of 2-fluorobenzaldehyde-derived *N*-*tert*-butyl imines (Table 2). First, the effect of electronic variation at the position *para* to the fluoride leaving group was systematically studied (entries 1−5). As anticipated, the presence of electron-withdrawing substituents, such as chloro, trifluoromethyl, and nitro groups, resulted in improved yields (entries 3−5). Electron-donating substituents, such as methyl and methoxy groups, on the other hand, led to comparatively lower yields (entries 1 and 2). A chloride group was also tolerated at the 4- and 6-positions (entries 6 and 7). In the case of entry 6, the superior leaving group ability of fluoride compared to chloride in *ipso*-S_NAr reactions leads to exclusive formation of product **13v**. Notably, substrate **11i**, in which the site of substitution is highly sterically congested, was also reactive (entry 8).

Interestingly, it was observed that all substituted benzaldehydes were higher yielding than the unsubstituted substrate (40%, Table 1, entry 8), suggesting that more functionalized aromatic rings suppress one or more decomposition pathways, such as deprotonation to form benzyne intermediates or unselective nucleophilic addition to other aryl ring positions. In all cases, the conversion in the S_NAr step was >95% by ^1H NMR analysis of the crude reaction mixture. The reaction generally appeared to be clean by ^1H NMR and TLC, meaning that the low material balance could be due to the formation of insoluble oligomers or polymers.

Lastly, to demonstrate that the *ortho*-alkoxybenzaldehydes in this paper can indeed be transformed into new metathesis-active ruthenium catalysts, benzaldehydes **13b**, **13h**, and **13n** were converted by routine Wittig olefination to styrenes **18**−

DOI: 10.1021/acs.joc.5b00563
J. Org. Chem. XXXX, XXX, XXX−XXX

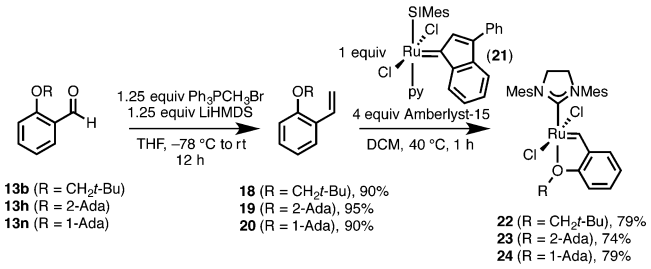
Table 2. Scope of 2-Fluorobenzaldehyde Electrophiles[a,b]



[a]The general procedure from Table 1 was followed. [b]Isolated yield over three steps.

20. These styrenes were treated with **21** in the presence of Amberlyst-15 resin[14,16b] to yield catalysts **22**–**24**, as was recently reported by our group (Scheme 5).[21] All three catalysts

Scheme 5. Preparation of New Catalysts 22–24[a,21]



[a]py = pyridine.

were found to exhibit enhanced initiation efficiency compared to the isopropxy control (**3**), and 2-adamantyloxy catalyst **23** was observed to be among the fastest initiating Hoveyda-type catalysts reported to date.

In summary, we report a three-step procedure to access sterically hindered *ortho*-alkoxybenzaldehydes. The sequence requires only a single chromatographic purification event, and the products are generally obtained in moderate to good yields. A wide range of 2-fluorobenzaldehyde electrophiles and alcohol nucleophiles are commercially available, making this route highly modular.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all materials were used as received from commercial sources without further purification. In air- or moisture-sensitive reactions, anhydrous, degassed solvents were used. THF and DCM were purified by passage through solvent purification columns. Anhydrous DMSO was purchased from a commercial supplier. NMR spectra were recorded on 500 MHz (^{1}H: 500 MHz and ^{13}C: 125 MHz) or 300 MHz (^{19}F: 282 MHz) instruments. Spectra were internally referenced to $SiMe_4$ or residual solvent signals. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, and m = multiplet. Accurate mass measurements were made either by electron ionization (EI) with a direct insertion probe (DIP) or by fast atom bombardment (FAB) using a double-focusing, high-resolution, magnetic sector mass spectrometer.

General Three-Step S_NAr Procedure. *General Imine Condensation Procedure.*[22] To a 100 mL round-bottom flask equipped with a Teflon-coated magnetic stir bar were added *tert*-butylamine (1.04 mL, 10.0 mmol), the appropriate *ortho*-fluorobenzaldehyde (10.0 mmol), and toluene (50 mL). The flask was equipped with a Dean–Stark apparatus wrapped in aluminum foil and a reflux condenser. The reaction was allowed to stir at vigorous reflux (140–150 °C) for 8 h. During the course of the reaction, water accumulated at the bottom of the Dean–Stark apparatus. The reaction mixture was allowed to cool to room temperature. A small aliquot was taken, concentrated *in vacuo*, and analyzed by ^{1}H NMR to monitor the reaction progress. (The *ortho*-fluorobenzaldehyde starting materials possess a characteristic ^{1}H NMR peak at 10.2–10.5 ppm (s) in $CDCl_3$, and the product possesses a characteristic ^{1}H NMR peak at 8.3–8.6 ppm (s). Comparison of these two peaks provides a convenient means of monitoring the reaction progress.) In cases where the reaction had not proceeded to >95% conversion, an additional portion of *tert*-butylamine commensurate with the amount of remaining starting material was added, and the reaction was heated for an additional 2–4 h. Upon completion, the reaction mixture was allowed to cool to room temperature, and the solvent was removed *in vacuo*. The crude imine product was obtained as a colorless or yellow oil and was used in the subsequent step without further purification.

General S_NAr Procedure.[20c] To a 100 mL Schlenk flask equipped with a Teflon-coated magnetic stir bar under Ar were added dry NaH (252 mg, 10.5 mmol), DMSO (20 mL), and the appropriate alcohol (10.5 mmol). Upon addition of the alcohol, vigorous bubbling was observed. The solution was allowed to stir at room temperature for 1 h, during which time the reaction mixture became a white suspension. A solution of the crude *ortho*-fluoro imine from the previous step (assumed to be 10.0 mmol) in DMSO (10 mL) was added. The reaction mixture was heated to 100 °C for 1 h, during which time it changed color from yellow to red to brown. After 1 h, a small aliquot of the reaction mixture was removed with a syringe and quenched with H_2O. The resulting mixture was extracted with Et_2O, and the organic phase was concentrated *in vacuo* and examined by ^{1}H NMR spectroscopy to monitor the reaction progress. (The starting material has a characteristic ^{1}H NMR peak at 8.4–8.6 ppm (s) in $CDCl_3$, and the product has a characteristic ^{1}H NMR peak at 8.7–8.9 ppm. Comparison of these two peaks provides a convenient means of monitoring the reaction progress.) In instances where the reaction had not proceeded to completion (i.e., >95% conversion), an additional portion of NaH and alcohol commensurate with the amount of remaining starting material was added, and the reaction mixture was heated at 100 °C for an additional 1 h. Upon completion of the reaction, the flask was allowed to cool to room temperature. The reaction mixture was carefully poured into a separatory funnel containing 100 mL of H_2O to quench residual base. The mixture was extracted with Et_2O (3 × 100 mL). The organic layers were combined and concentrated *in vacuo*. The crude product was obtained as a pink oil or off-white solid and was used in the next step without further purification.

DOI: 10.1021/acs.joc.5b00563
J. Org. Chem. XXXX, XXX, XXX–XXX

General Acidic Hydrolysis Procedure.[20c] To a 500 mL round-bottom flask equipped with a Teflon-coated magnetic stir bar was added the crude *ortho*-alkoxy imine from the previous step (assumed to be 10.0 mmol). A 50:15:1 H_2O:THF:HOAc solution (132 mL) was added, and the reaction was stirred at room temperature for 8 h. THF was removed *in vacuo*, and the resulting aqueous solution was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel column chromatography using the specified eluent provided the final *ortho*-alkoxy benzaldehyde product. The yield was calculated for the combined three steps.

General Wittig Olefination Procedure.[23] To a flame-dried 100 mL Schlenk flask equipped with a magnetic stir bar under Ar were added methyltriphenylphosphonium bromide (1.34 g, 3.75 mmol) and anhydrous THF (20 mL). LiHMDS solution (1.0 M in THF) (3.75 mL, 3.75 mmol) was added at 0 °C. The resulting yellow solution was allowed to warm to room temperature and stirred until it became homogeneous (approximately 1 h). The solution was cooled to −78 °C in a dry ice/acetone bath, and the appropriate *ortho*-alkoxybenzaldehyde (3.0 mmol) was added. The solution was allowed to warm to room temperature and stirred overnight (approximately 12 h). Et_2O (30 mL) was added, and the resulting heterogeneous solution was cooled to −20 °C for 30 min. The solution was filtered through a pad of Celite to remove the triphenylphosphine oxide precipitate, and the Celite was washed twice with Et_2O that had been cooled to 0 °C. The filtrate was concentrated *in vacuo*, and the resulting yellow oil was purified by silica gel column chromatography using a gradient solvent system (100:1 hexane:Et_2O → 40:1 hexane:Et_2O) as the eluent. The pure product was thus obtained as a white solid or colorless oil. To prevent polymerization during prolonged storage, all styrenes were kept under an Ar atmosphere at −20 °C.

General Chelation Procedure with Amberyst-15 Resin.[14,16b] To a flame-dried 20 mL Schlenk flask equipped with a magnetic stir bar under Ar were added Umicore M31 (**21**) (152 mg, 0.2 mmol), dry Amberlyst-15 hydrogen form (4.7 mmol H^+/g) (170 mg, 0.8 mmol H^+), the appropriate styrene (0.2 mmol), and DCM (5 mL). The reaction was stirred at 40 °C for 1 h, during which time a color change from maroon to brown or green was observed. The reaction vessel was allowed to cool to room temperature, and the reaction mixture was filtered through a pad of cotton in a glass pipet to remove the Amberlyst-15 resin. The resulting filtrate was concentrated *in vacuo* to give a brown residue. Pentane (10 mL) was added, and the resulting suspension was sonicated for 1 min, during which time the pentane phase became dark brown, and a green precipitate was observed. The suspension was filtered through a fritted Buchner filter funnel. The green precipitate was washed sequentially with methanol (2 × 5 mL) and pentane (2 × 5 mL) and then dried under high vacuum to give the analytically pure product as a green solid.

Characterization of New Compounds. Data for *ortho*-alkoxybenzaldehyde products **13a−13x** are included below. Original NMR spectra can be found in the Supporting Information. Analytical data for compounds **18−20** and **22−24** have been reported elsewhere.[21]

*2-(Cyclohexyloxy)benzaldehyde (**13a**).* The title compound was prepared from 2-fluorobenzaldehyde (1.05 mL, 10.0 mmol) and cyclohexanol (1.10 mL, 10.5 mmol) according to the general three-step procedure. Purification by silica gel column chromatography (40:1 hexane:Et_2O → 10:1 hexane:Et_2O) provided the product as a colorless oil (910 mg, 45% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.52 (d, J = 0.8 Hz, 1H), 7.81 (dd, J_1 = 7.7 Hz, J_2 = 1.9 Hz, 1H), 7.49 (ddd, J_1 = 8.5 Hz, J_2 = 7.3 Hz, J_3 = 1.9 Hz, 1H), 7.01−6.92 (m, 2H), 4.41 (tt, J_1 = 8.1 Hz, J_2 = 3.6 Hz, 1H), 1.99−1.92 (m, 2H), 1.82−1.74 (m, 2H), 1.68−1.59 (m, 2H), 1.58−1.51 (m, 1H), 1.45−1.34 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.1, 160.7, 135.7, 128.4, 126.1, 120.5, 114.4, 76.2, 31.6, 25.6, 23.5; **HRMS** (FAB+) m/z Calcd for $C_{13}H_{17}O_2$ $[M + H]^+$ 205.1229, found 205.1219.

*2-(Neopentyloxy)benzaldehyde (**13b**).* The title compound was prepared from 2-fluorobenzaldehyde (1.05 mL, 10.0 mmol) and neopentyl alcohol (926 mg, 10.5 mmol) according to the general three-step procedure. Purification by silica gel column chromatography (40:1 hexane:Et_2O → 20:1 hexane:Et_2O) provided the product as a colorless oil (1.46 g, 76% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.59 (d, J = 0.8 Hz, 1H), 7.84 (dd, J_1 = 7.7 Hz, J_2 = 1.8 Hz, 1H), 7.53 (ddd, J_1 = 8.4 Hz, J_2 = 7.3 Hz, J_3 = 1.9 Hz, 1H), 7.03−6.99 (m, 1H), 6.98−6.95 (m, 1H), 3.72 (s, 2H), 1.08 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 189.7, 162.0, 136.0, 128.3, 125.2, 120.6, 112.6, 78.5, 32.3, 26.8; **HRMS** (FAB+) m/z Calcd for $C_{12}H_{17}O_2$ $[M + H]^+$ 193.1229, found 193.1252.

*2-(((3r,5r,7r)-Adamantan-1-yl)methoxy)benzaldehyde (**13c**).* The title compound was prepared from 2-fluorobenzaldehyde (1.05 mL, 10.0 mmol) and 1-adamantanemethanol (1.75 g, 10.5 mmol) according to the general three-step procedure. Purification by silica gel column chromatography (20:1 hexane:Et_2O → 10:1 hexane:Et_2O) provided the product as a white solid (1.40 g, 52% yield). **mp** = 89−91 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.59 (d, J = 0.8 Hz, 1H), 7.83 (dd, J_1 = 7.7 Hz, J_2 = 1.8 Hz, 1H), 7.52 (ddd, J_1 = 8.4 Hz, J_2 = 7.3 Hz, J_3 = 1.9 Hz, 1H), 6.99 (tt, J_1 = 7.6 Hz, J_2 = 0.9 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 3.61 (s, 2H), 2.06−2.01 (m, 3H), 1.81−1.75 (m, 3H), 1.73−1.67 (m, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 189.9, 162.2, 136.0, 128.3, 125.4, 120.5, 112.7, 78.9, 39.8, 37.2, 34.2, 28.3; **HRMS** (FAB+) m/z Calcd for $C_{18}H_{23}O_2$ $[M + H]^+$ 271.1698, found 271.1704.

*2-Cyclobutoxybenzaldehyde (**13d**).* The title compound was prepared from 2-fluorobenzaldehyde (1.05 mL, 10.0 mmol) and cyclobutanol (0.82 mL, 10.5 mmol) according to the general three-step procedure. Purification by silica gel column chromatography (20:1 hexane:Et_2O → 10:1 hexane:Et_2O) provided the product as a colorless oil (740 mg, 42% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.50 (d, J = 0.8 Hz, 1H), 7.82 (dd, J_1 = 7.7 Hz, J_2 = 1.8 Hz, 1H), 7.49 (ddd, J_1 = 8.4 Hz, J_2 = 7.3 Hz, J_3 = 1.9 Hz, 1H); 7.01−6.97 (m, 1H), 6.81 (d, J = 6.7 Hz, 1H), 4.75 (quint, J = 7.5 Hz, 1H), 2.53−2.47 (m, 2H), 2.29−2.21 (m, 2H), 1.95−1.88 (m, 1H), 1.78−1.69 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.2, 160.2, 135.9, 128.5, 125.0, 120.7, 113.5, 72.3, 30.7, 13.4; **HRMS** (EI+) m/z Calcd for $C_{11}H_{12}O_2$ $[M]^+$ 176.0837, found 176.0830.

*2-(Cyclopentyloxy)benzaldehyde (**13e**).* The title compound was prepared from 2-fluorobenzaldehyde (1.05 mL, 10.0 mmol) and cyclopentanol (0.95 mL, 10.5 mmol) according to the general three-step procedure. Purification by silica gel column chromatography (40:1 hexane:Et_2O → 20:1 hexane:Et_2O) provided the product as a yellow oil (1.05 g, 55% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.46 (d, J = 0.9 Hz, 1H), 7.82 (dd, J_1 = 7.9 Hz, J_2 = 1.8 Hz, 1H), 7.51 (ddd, J_1 = 8.5 Hz, J_2 = 7.3 Hz, J_3 = 1.8 Hz, 1H), 7.00−6.95 (m, 2H), 4.91−4.88 (m, 1H), 1.98−1.89 (m, 4H), 1.87−1.77 (m, 2H), 1.72−1.62 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.3, 160.8, 135.8, 128.4, 125.5, 120.3, 114.0, 80.3, 33.0, 24.1; **HRMS** (EI+) m/z Calcd for $C_{12}H_{14}O_2$ $[M]^+$ 190.0994, found 190.1015.

*2-(Cycloheptyloxy)benzaldehyde (**13f**).* The title compound was prepared from 2-fluorobenzaldehyde (1.05 mL, 10.0 mmol) and cycloheptanol (1.28 mL, 10.5 mmol) according to the general three-step procedure. After the first chromatographic purification on silica gel (100:1 hexane:Et_2O → 20:1 hexane:Et_2O), the product still contained unidentifiable impurities. A second purification by silica gel column chromatography (10:1 hexane:DCM → 1:1 hexane:DCM) provided the product as a colorless oil (1.01 g, 50% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.52 (d, J = 0.8 Hz, 1H), 7.83 (dd, J_1 = 7.7 Hz, J_2 = 1.8 Hz, 1H), 7.51 (ddd, J_1 = 8.5 Hz, J_2 = 7.3 Hz, J_3 = 1.9 Hz, 1H), 7.00−6.96 (m, 1H), 6.95 (d, J = 8.5 Hz, 1H), 4.59 (tt, J_1 = 8.0 Hz, J_2 = 4.2 Hz, 1H), 2.09−2.02 (m, 2H), 1.93−1.85 (m, 2H), 1.80−1.72 (m, 2H), 1.68−1.59 (m, 4H), 1.55−1.46 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.4, 160.7, 135.9, 128.5, 125.9, 120.4, 114.2, 78.8, 33.8, 28.5, 23.0; **HRMS** (FAB+) m/z Calcd for $C_{14}H_{19}O_2$ $[M + H]^+$ 219.1385, found 219.1386.

*2-(Cyclooctyloxy)benzaldehyde (**13g**).* The title compound was prepared from 2-fluorobenzaldehyde (1.05 mL, 10.0 mmol) and cyclooctanol (1.39 mL, 10.5 mmol) according to the general three-step procedure. Purification by silica gel column chromatography (40:1 hexane:Et_2O → 20:1 hexane:Et_2O) provided the product as a colorless oil (1.18 g, 51% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.49 (d, J = 0.8 Hz, 1H), 7.82 (dd, J_1 = 7.7 Hz, J_2 = 1.9 Hz, 1H), 7.50 (ddd, J_1 = 8.7

DOI: 10.1021/acs.joc.5b00563
J. Org. Chem. XXXX, XXX, XXX−XXX

Hz, J_2 = 7.3 Hz, J_3 = 1.8 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 8.5 Hz, 1H), 4.56 (tt, J_1 = 8.0 Hz, J_2 = 4.0 Hz, 1H), 2.07−1.87 (m, 4H), 1.83−1.76 (m, 2H), 1.74−1.47 (m, 8H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.4, 160.6, 135.9, 128.4, 125.8, 120.3, 114.2, 78.9, 31.5, 27.2, 25.7, 23.0; **HRMS** (FAB+) m/z Calcd for $C_{15}H_{21}O_2$ $[M + H]^+$ 233.1542, found 233.1541.

*2-(((1r,3r,5r,7r)-Adamantan-2-yl)oxy)benzaldehyde (**13h**).* The title compound was prepared from 2-fluorobenzaldehyde (1.05 mL, 10.0 mmol) and 2-adamantanol (1.59 g, 10.5 mmol) according to the general three-step procedure. Purification by silica gel column chromatography (20:1 hexane:Et_2O → 10:1 hexane:Et_2O) provided the product as a white solid (1.01 g, 40% yield). **mp** = 69−71 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.63 (d, J = 0.8 Hz, 1H), 7.84 (dd, J_1 = 7.9 Hz, J_2 = 1.9 Hz, 1H), 7.49 (ddd, J_1 = 8.5 Hz, J_2 = 7.3 Hz, J_3 = 1.9 Hz, 1H), 6.99−6.95 (m, 2H), 4.58 (t, J = 3.2 Hz, 1H), 2.25−2.19 (m, 2H), 2.16−2.10 (m, 2H), 1.97−1.86 (m, 4H), 1.83−1.75 (m, 4H), 1.62−1.57 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.2, 160.4, 135.8, 128.5, 125.9, 120.3, 114.0, 80.2, 37.4, 36.4, 31.8, 31.7, 27.3, 27.2; **HRMS** (EI+) m/z Calcd for $C_{17}H_{20}O_2$ $[M]^+$ 256.1463, found 256.1453.

*2-((2,4-Dimethylpentan-3-yl)oxy)benzaldehyde (**13i**).* The title compound was prepared from 2-fluorobenzaldehyde (1.05 mL, 10.0 mmol) and 2,4-dimethyl-3-pentanol (1.47 mL, 10.5 mmol) according to the general three-step procedure. Purification by silica gel column chromatography (40:1 hexane:Et_2O) provided the product as a yellow oil (1.31 g, 59% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.59 (d, J = 0.8 Hz, 1H), 7.81 (dd, J_1 = 7.7 Hz, J_2 = 1.9 Hz, 1H), 7.47 (ddd, J_1 = 8.5 Hz, J_2 = 7.2 Hz, J_3 =1.9 Hz, 1H), 7.02 (d, J = 8.6 Hz, 1H), 6.93 (ddt, J_1 = 8.0 Hz, J_2 = 7.3 Hz, J_3 = 0.9 Hz, 1H), 4.09 (t, J = 5.7 Hz, 1H), 2.15−2.01 (m, 2H), 0.98 (d, J = 6.7 Hz, 6H), 0.95 (d, J = 6.8 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.3, 163.5, 135.9, 128.5, 125.1, 112.0, 113.6, 88.2, 30.8, 20.2, 17.9; **HRMS** (FAB+) m/z Calcd for $C_{14}H_{21}O_2$ $[M + H]^+$ 221.1542, found 221.1530.

*2-(Dicyclohexylmethoxy)benzaldehyde (**13j**).* The title compound was prepared from 2-fluorobenzaldehyde (1.05 mL, 10.0 mmol) and dicyclohexylmethanol (2.06 g, 10.5 mmol) according to the general three-step procedure. Purification by silica gel column chromatography (40:1 hexane:Et_2O) provided the product as a colorless oil (1.72 g, 57% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.58 (d, J = 0.8 Hz, 1H), 7.81 (dd, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.46 (ddd, J_1 = 8.6 Hz, J_2 = 7.2 Hz, J_3 = 1.9 Hz, 1H), 7.00 (d, J = 8.7 Hz, 2H), 6.92 (ddt, J_1 = 8.0 Hz, J_2 = 7.3 Hz, J_3 = 0.9 Hz, 1H), 4.11 (t, J = 5.6 Hz, 1H), 1.86−1.69 (m, 8H), 1.69−1.60 (m, 4H), 1.31−1.05 (m, 10H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.4, 163.7, 135.9, 128.5, 125.0, 119.9, 113.6, 87.1, 40.0, 30.6, 28.3, 26.53, 26.48, 26.3; **HRMS** (FAB+) m/z Calcd for $C_{20}H_{29}O_2$ $[M + H]^+$ 301.2168, found 301.2179.

*2-(tert-Butoxy)benzaldehyde (**13m**).* The title compound was prepared from 2-fluorobenzaldehyde (1.05 mL, 10.0 mmol) and sodium *tert*-butoxide (1.01 g, 10.5 mmol) according to the general three-step procedure. Purification by silica gel column chromatography (40:1 hexane:Et_2O → 20:1 hexane:Et_2O) provided the product as a colorless oil (465 mg, 26% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.45 (d, J = 0.8 Hz, 1H), 7.84 (ddd, J_1 = 7.7 Hz, J_2 = 1.9 Hz, J_3 = 0.5 Hz, 1H), 7.50 (ddd, J_1 = 8.3 Hz, J_2 = 7.2 Hz, J_3 = 1.9 Hz, 1H), 7.16−7.08 (m, 2H), 1.44 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 191.0, 159.2, 135.0, 130.2, 128.1, 122.94, 122.91, 80.8, 29.1; **HRMS** (EI+) m/z Calcd for $C_{11}H_{14}O_2$ $[M]^+$ 178.0994, found 178.0954.

*2-(((1s,3s)-Adamantan-1-yl)oxy)benzaldehyde (**13n**).* The title compound was prepared from 2-fluorobenzaldehyde (1.05 mL, 10.0 mmol) and 1-adamantanol (1.59 g, 10.5 mmol) according to the general three-step procedure. Purification by silica gel column chromatography (40:1 hexane:Et_2O) provided the product as an off-white solid (609 mg, 24% yield). **mp** = 90−93 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.49 (d, J = 0.8 Hz, 1H), 7.84 (dd, J_1 = 7.7 Hz, J_2 =1.9 Hz, 1H), 7.50 (ddd, J_1 = 8.2 Hz, J_2 = 7.3 Hz, J_3 = 1.9 Hz, 1H), 7.18−7.12 (m, 2H), 2.23−2.18 (m, 3H), 1.96−1.91 (m, 3H), 1.69−1.58 (m, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 191.2, 158.2, 134.9, 131.2, 127.9, 125.1, 123.6, 80.6, 43.0, 36.1, 31.1; **HRMS** (FAB+) m/z Calcd for $C_{17}H_{19}O_2$ $[(M + H) - H_2]^+$ 255.1385, found 255.1376.

*2-(((1r,3r,5r,7r)-2-Methyladamantan-2-yl)oxy)benzaldehyde (**13o**).* The title compound was prepared from 2-fluorobenzaldehyde (1.05 mL, 10.0 mmol) and 2-methyl-2-adamantanol (1.75 g, 10.5 mmol) according to the general three-step procedure. After the first chromatographic purification on silica gel (100:1 hexane:Et_2O → 20:1 hexane:Et_2O), the product still contained unidentifiable impurities. A second purification by silica gel column chromatography (10:1 hexane:DCM → 1:1 hexane:DCM) provided the product as a pale-yellow solid (229 mg, 8% yield). **mp** = 38−40 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.52 (d, J = 0.8 Hz, 1H), 7.84 (dd, J_1 = 7.7 Hz, J_2 = 1.9 Hz, 1H), 7.44 (ddd, J_1 = 8.4 Hz, J_2 = 7.2 Hz, J_3 = 1.9 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 7.02 (ddt, J_1 = 8.0 Hz, J_2 = 7.3 Hz, J_3 = 0.9 Hz, 1H), 2.36−2.30 (m, 2H), 2.26−2.21 (m, 2H), 1.95−1.81 (m, 6H), 1.77−1.73 (m, 2H), 1.65−1.59 (m, 2H), 1.45 (s, 3H); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ 191.1, 160.1, 135.5, 129.2, 128.5, 121.7, 120.6, 86.8, 38.68, 38.66, 35.5, 33.5, 28.0, 27.5, 23.0; **HRMS** (FAB+) m/z Calcd for $C_{18}H_{23}O_2$ $[M + H]^+$ 271.1698, found 271.1687.

*2-(((1r,3r,5r,7r)-Adamantan-2-yl)oxy)-5-methoxybenzaldehyde (**13q**).* The title compound was prepared from 2-fluoro-5-methoxybenzaldehyde (1.24 mL, 10.0 mmol) and 2-adamantanol (1.59 g, 10.5 mmol) according to the general three-step procedure. Purification by silica gel column chromatography (10:1 hexane:Et_2O → 4:1 hexane:Et_2O) provided the product as a white solid (1.44 g, 50% yield). **mp** = 123−125 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.58 (s, 1H), 7.32 (d, J = 3.0 Hz, 1H), 7.09 (dd, J_1 = 9.0 Hz, J_2 = 3.0 Hz, 1H), 6.93 (d, J = 9.0 Hz, 1H), 4.48 (t, J = 3.3 Hz, 1H), 3.79 (s, 3H), 2.21−2.16 (m, 2H), 2.14−2.08 (m, 2H), 1.95−1.85 (m, 4H), 1.80−1.73 (m, 4H), 1.62−1.55 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 189.8, 155.3, 153.6, 126.4, 123.8, 116.3, 110.2, 81.2, 55.9, 37.5, 36.5, 31.9, 31.8, 27.4, 27.3; **HRMS** (FAB+) m/z Calcd for $C_{18}H_{22}O_3$ $[M]^+$ 286.1569, found 286.1570.

*2-(((1r,3r,5r,7r)-Adamantan-2-yl)oxy)-5-methylbenzaldehyde (**13r**).* The title compound was prepared from 2-fluoro-5-methylbenzaldehyde (1.22 mL, 10.0 mmol) and 2-adamantanol (1.59 g, 10.5 mmol) according to the general three-step procedure. Purification by silica gel column chromatography (20:1 hexane:Et_2O → 10:1 hexane:Et_2O) provided the product as a white solid (1.52 g, 56% yield). **mp** = 90−93 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.59 (s, 1H), 7.63 (d, J = 2.2 Hz, 1H), 7.29 (ddd, J_1 = 8.5 Hz, J_2 = 2.4 Hz, J_3 = 0.8 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 4.53 (t, J = 3.4 Hz, 1H), 2.29 (s, 3H), 2.23−2.17 (m, 2H), 2.14−2.09 (m, 2H), 1.95−1.84 (m, 4H), 1.81−1.74 (m, 4H), 1.60−1.53 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.2, 158.5, 136.5, 129.8, 128.4, 125.7, 114.2, 80.4, 37.5, 36.5, 31.79, 31.77, 27.34, 27.27, 20.3; **HRMS** (FAB+) m/z Calcd for $C_{18}H_{23}O_2$ $[M + H]^+$ 271.1698, found 271.1694.

*2-(((1r,3r,5r,7r)-Adamantan-2-yl)oxy)-5-chlorobenzaldehyde (**13s**).* The title compound was prepared from 5-chloro-2-fluorobenzaldehyde (1.59 g, 10.0 mmol) and 2-adamantanol (1.59 g, 10.5 mmol) according to the general three-step procedure. Purification by silica gel column chromatography (10:1 hexane:Et_2O) provided the product as a pale-yellow solid (1.96 g, 67% yield). **mp** = 136−139 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.54 (s, 1H), 7.78 (d, J = 2.8 Hz, 1H), 7.43 (dd, J_1 = 8.9 Hz, J_2 = 2.8 Hz, 1H), 6.93 (d, J = 9.0 Hz, 1H), 4.55 (t, J = 3.5 Hz, 1H), 2.24−2.17 (m, 2H), 2.12−2.06 (m, 2H), 1.97−1.86 (m, 4H), 1.82−1.75 (m, 4H), 1.63−1.56 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 188.7, 158.9, 135.3, 128.2, 126.9, 126.1, 115.8, 81.1, 37.4, 36.5, 31.80, 31.76, 27.3, 27.2; **HRMS** (FAB+) m/z Calcd for $C_{17}H_{20}ClO_2$ $[M + H]^+$ 291.1152, found 291.1140.

*2-(((1r,3r,5r,7r)-Adamantan-2-yl)oxy)-5-(trifluoromethyl)-benzaldehyde (**13t**).* The title compound was prepared from 2-fluoro-5-(trifluoromethyl)benzaldehyde (1.41 mL, 10.0 mmol) and 2-adamantanol (1.59 g, 10.5 mmol) according to the general three-step procedure. Purification by silica gel column chromatography (50:1 hexane:Et_2O → 25:1 hexane:Et_2O) provided the product as a pale-yellow solid (2.67 g, 83% yield). **mp** = 118−120 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.58 (s, 1H), 8.07 (d, J = 2.3 Hz, 1H), 7.69 (dd, J_1 = 8.9 Hz, J_2 = 2.3 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H), 4.64 (t, J = 3.5 Hz, 1H), 2.23−2.18 (m, 2H), 2.08 (d, J = 12.3 Hz, 2H), 1.96−1.84 (m, 4H), 1.82−1.73 (m, 4H), 1.60 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 188.5, 162.4, 132.2 (q, J_{C-F} = 3.5 Hz), 126.1 (q, J_{C-F} = 3.9

DOI: 10.1021/acs.joc.5b00563
J. Org. Chem. XXXX, XXX, XXX−XXX

Hz), 125.6, 124.0 (q, J_{C-F} = 270.0 Hz), 122.8 (q, J_{C-F} = 33.4 Hz), 114.3, 81.3, 37.3, 36.3, 31.71, 31.69, 27.2, 27.1; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −62.11 (s, 9F); **HRMS** (FAB+) *m/z* Calcd for $C_{18}H_{18}O_2F_3$ $[(M + H) - H_2]^+$ 323.1259, found 323.1261.

*2-(((1r,3r,5r,7r)-Adamantan-2-yl)oxy)-5-nitrobenzaldehyde (**13u**).* The title compound was prepared from 2-fluoro-5-nitrobenzaldehyde (1.69 g, 10.0 mmol) and 2-adamantanol (1.59 g, 10.5 mmol) according to the general three-step procedure. Purification by silica gel column chromatography (2:1 hexane:DCM) provided the product as a pale-yellow solid (1.97 g, 65% yield). **mp** = 142−145 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.53 (s, 1H), 8.62 (d, *J* = 2.9 Hz, 1H), 7.08−7.06 (m, 1H), 8.33 (dd, J_1 = 9.3 Hz, J_2 = 3.0 Hz, 1H), 7.09 (d, *J* = 9.3 Hz, 1H), 4.73 (t, *J* = 3.4 Hz, 1H), 2.27−2.20 (m, 2H), 2.10−2.02 (m, 2H), 1.99−1.86 (m, 4H), 1.85−1.74 (m, 4H), 1.65−1.58 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 187.7, 164.3, 141.1, 130.4, 125.3, 124.7, 114.1, 82.0, 37.1, 36.2, 31.63, 31.61, 27.0, 26.9; **HRMS** (FAB+) *m/z* Calcd for $C_{17}H_{20}O_4N$ $[M + H]^+$ 302.1392, found 302.1402.

*2-(((1r,3r,5r,7r)-Adamantan-2-yl)oxy)-6-chlorobenzaldehyde (**13v**).* The title compound was prepared from 2-chloro-6-fluorobenzaldehyde (1.59 g, 10.0 mmol) and 2-adamantanol (1.59 g, 10.5 mmol) according to the general three-step procedure. Purification by silica gel column chromatography (10:1 hexane:Et_2O → 4:1 hexane:Et_2O) provided the product as an off-white solid (2.32 g, 80% yield). **mp** = 107−110 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.60 (s, 1H), 7.33 (t, *J* = 8.3 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 4.55 (t, *J* = 3.1 Hz, 1H), 2.20−2.16 (m, 2H), 2.14−2.07 (m, 2H), 1.95−1.84 (m, 4H), 1.80−1.73 (m, 4H), 1.60−1.54 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 189.2, 160.9, 135.8, 134.3, 123.6, 122.9, 112.6, 81.3, 37.4, 36.5, 31.72, 31.71, 27.3, 27.2; **HRMS** (FAB+) *m/z* Calcd for $C_{17}H_{20}O_2Cl$ $[M + H]^+$ 291.1152, found 291.1161.

*2-(((1r,3r,5r,7r)-Adamantan-2-yl)oxy)-4-chlorobenzaldehyde (**13w**).* The title compound was prepared from 4-chloro-2-fluorobenzaldehyde (1.58 g, 10.0 mmol) and 2-adamantanol (1.59 g, 10.5 mmol) according to the general three-step procedure. Purification by silica gel column chromatography (8:1 hexane:Et_2O) provided the product as a pale-yellow solid (2.03 g, 70% yield). **mp** = 128−131 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.53 (d, *J* = 0.7 Hz, 1H), 7.79−7.75 (m, 1H), 6.99−6.93 (m, 2H), 4.55 (t, *J* = 3.3 Hz, 1H), 2.24−2.19 (m, 2H), 2.13−2.06 (m, 2H), 1.99−1.87 (m, 4H), 1.84−1.76 (m, 4H), 1.63−1.59 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 188.9, 160.8, 141.9, 129.7, 124.5, 121.0, 114.5, 81.1, 37.4, 36.4, 31.8, 31.7, 27.3, 27.2; **HRMS** (FAB+) *m/z* Calcd for $C_{17}H_{20}ClO_2$ $[M + H]^+$ 291.1152, found 291.1159.

*2-(((1r,3r,5r,7r)-Adamantan-2-yl)oxy)-3-methoxybenzaldehyde (**13x**).* The title compound was prepared from 2-fluoro-3-methoxybenzaldehyde (1.54 g, 10.0 mmol) and 2-adamantanol (1.59 g, 10.5 mmol) according to the general three-step procedure. Purification by silica gel column chromatography (10:1 hexane:Et_2O) provided the product as a white solid (2.27 g, 79% yield). **mp** = 69−71 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.53 (d, *J* = 0.9 Hz, 1H), 7.39 (dd, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.09 (dd, J_1 = 8.1 Hz, J_2 = 1.7 Hz, 1H), 7.03 (td, J_1 = 7.9 Hz, J_2 = 0.9 Hz, 1H), 4.38 (t, *J* = 3.3 Hz, 1H), 3.83 (s, 3H), 2.23−2.15 (m, 4H), 1.90−1.77 (m, 4H), 1.74−1.69 (m, 2H), 1.67−1.62 (m, 2H), 1.60−1.55 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.8, 153.0, 151.7, 130.3, 123.1, 119.2, 118.3, 87.4, 56.1, 37.5, 36.8, 32.6, 31.8, 27.4, 27.2; **HRMS** (FAB+) *m/z* Calcd for $C_{18}H_{23}O_3$ $[M + H]^+$ 287.1647, found 287.1657.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rhg@caltech.edu (R.H.G.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The research described in this paper was supported financially by the Office of Naval Research (Award Number N00014-12-1-0596) and the National Institutes of Health NIGMS (Award Number F32GM108145; postdoctoral fellowship to K.M.E.). Prof. Jeffrey S. Cannon (Occidental College) and Dr. Sarah M. Bronner (Genentech) are gratefully acknowledged for helpful discussions. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Office of Naval Research or the National Institutes of Health.

■ REFERENCES

(1) For reviews, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (c) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592−4633. (d) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490−4527. (e) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746−1787. (f) Schrock, R. R. *Chem. Rev.* **2009**, *109*, 3211−3226. (g) Samojłowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev.* **2009**, *109*, 3708−3742. (h) Hoveyda, A. H. *J. Org. Chem.* **2014**, *79*, 4763−4792. (i) Nelson, D. J.; Manzini, S.; Urbina-Blanco, C. A.; Nolan, S. P. *Chem. Commun.* **2014**, *50*, 10355−10375.

(2) For early reports on the development of well-defined ruthenium-based olefin metathesis catalysts, see: (a) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974−3975. (b) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858−9859. For the first disclosure of catalysts **1** and **2**, see: (c) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1995**, *34*, 2039−2041. (d) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(3) (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791−799. For a review, see: (b) Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8−23.

(4) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179. (b) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973−9976.

(5) (a) Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441−444. (b) Courchay, F. C.; Sworen, J. C.; Wagener, K. B. *Macromolecules* **2003**, *36*, 8231−8239. (c) Rosebrugh, L. E.; Herbert, M. B.; Marx, V. M.; Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2013**, *135*, 1276−1279.

(6) For a review on ruthenium olefin metathesis catalysts containing chelating benzylidenes, see: Vidavsky, Y.; Anaby, A.; Lemcoff, N. G. *Dalton Trans.* **2012**, *41*, 32−43.

(7) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2403−2405.

(8) Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4038−4040.

(9) Dunne, A. M.; Mix, S.; Blechert, S. *Tetrahedron Lett.* **2003**, *44*, 2733−2736.

(10) Bujok, R.; Bieniek, M.; Masnyk, M.; Michrowska, A.; Sarosiek, A.; Stępowska, H.; Arlt, D.; Grela, K. *J. Org. Chem.* **2004**, *69*, 6894−6896.

(11) Zhan, Z.-Y. J. *Recyclable ruthenium catalysts for metathesis reactions*. U.S. Patent US20070043180 A1, February 22, 2007.

(12) Rix, D.; Caijo, F.; Laurent, I.; Boeda, F.; Clavier, H.; Nolan, S. P.; Mauduit, M. *J. Org. Chem.* **2008**, *73*, 4225−4228.

(13) Thiel, V.; Hendann, M.; Wannowius, K.-J.; Plenio, H. *J. Am. Chem. Soc.* **2012**, *134*, 1104−1114.

DOI: 10.1021/acs.joc.5b00563
J. Org. Chem. XXXX, XXX, XXX−XXX

(14) Kos, P.; Savka, R.; Plenio, H. *Adv. Synth. Catal.* **2013**, *355*, 439−447.
(15) Nelson, D. J.; Queval, P.; Rouen, M.; Magrez, M.; Toupet, L.; Caijo, F.; Borré, E.; Laurent, I.; Crévisy, C.; Baslé, O.; Mauduit, M.; Percy, J. M. *ACS Catal.* **2013**, *3*, 259−264.
(16) (a) Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502−12508. (b) Monsaert, S. F.; Verpoort F. W. C. (Umicore AG & Co. KG and Ghent University). *Process for preparation of ruthenium-based carbene catalysts with chelating alkylidene ligands*. World Patent WO2011091980 A1, August 4, 2011.
(17) (a) Barbasiewicz, M.; Bieniek, M.; Michrowska, A.; Szadkowska, A.; Makal, A.; Woźniak, K.; Grela, K. *Adv. Synth. Catal.* **2007**, *349*, 193−203. (b) Hejl, A. Ph.D. Thesis, California Institute of Technology, Pasadena, CA, 2007. (c) Bornand, M.; Torker, S.; Chen, P. *Organometallics* **2007**, *26*, 3585−3596.
(18) Woiwode, T. F.; Rose, C.; Wandless, T. J. *J. Org. Chem.* **1998**, *63*, 9594−9596.
(19) For representative recent reports, see: (a) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395−3396. (b) Mann, G.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 5413−5418. (c) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224−3225. (d) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2498−2500. (e) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973−976. For representative early reports, see: (f) Bacon, R. G. R.; Rennison, S. C. *J. Chem. Soc. C* **1969**, 308−312. (g) Bacon, R. G. R.; Rennison, S. C. *J. Chem. Soc. C* **1969**, 312−315. (h) Whitesides, G. M.; Sadowski, J. S.; Lilburn, J. *J. Am. Chem. Soc.* **1974**, *96*, 2829−2835. (i) Aalten, H. L.; van Koten, G.; Grove, D. M.; Kuilman, T.; Piekstra, O. G.; Hulshof, L. A.; Sheldon, R. A. *Tetrahedron* **1989**, *45*, 5565−5578. (j) Keegstra, M. A.; Peters, T. H. A.; Brandsma, L. *Tetrahedron* **1992**, *48*, 3633−3652. For a review of early contributions, see: (k) Lindley, J. *Tetrahedron* **1984**, *40*, 1433−1456.
(20) (a) Heath, P. C.; Ratz, A. M.; Weigel, L. O. (Eli Lilly and Co.). *Stereospecific Method for Preparing Tomoexetine and Intermediates Thereof*. World Patent WO2000058262 A1, October 5, 2000. (b) Kiankarimi, M.; Hudson, S.; Dwight, W. J.; Wade, W. S. (Neurocrine Biosciences, Inc.). *Monoamine Re-Uptake Inhibitors and Methods Relating Thereto*. U.S. Patent US20060252818 A1, November 9, 2006. (c) Forrest, A. K.; Jarvest, R. L.; Sheppard, R. J. (GlaxoSmithKline PLC). *Novel Compounds*. World Patent WO2007017267 A2, February 15, 2007. (d) Caprathe, B. W.; Gogliotti, R. D.; Jennings, R. A.; Simons, L. J. (Pfizer, Inc.). *Piperidine Derivatives*. World Patent WO2008023258 A1, February 28, 2008. (e) Hudson, S.; Kiankarimi, M.; Eccles, W.; Mostofi, Y. S.; Genicot, M. J.; Dwight, W.; Fleck, B. A.; Gogas, K.; Wade, W. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4495−4498. (f) Carruthers, N. I.; Shireman, B. T.; Tran, V. T.; Jablonowski, J. A. (Janssen Pharmaceutica). *Modulators of Serotonin Receptor*. World Patent WO2010059390 A1, May 27, 2010.
(21) Engle, K. M.; Lu, G.; Luo, S.-X.; Henling, L. M.; Takase, M. K.; Liu, P.; Houk, K. N.; Grubbs, R. H. *J. Am. Chem. Soc.* **2015**, DOI: 10.1021/jacs.5b01144.
(22) Franchi, P.; Casati, C.; Mezzina, E.; Lucarini, M. *Org. Biomol. Chem.* **2011**, *9*, 6396−6401.
(23) Yao, Q. *Angew. Chem., Int. Ed.* **2000**, *39*, 3896−3898.

DOI: 10.1021/acs.joc.5b00563
J. Org. Chem. XXXX, XXX, XXX−XXX