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Telescoped Approach to Aryl Hydroxymethylation in the Synthesis of a Key Pharmaceutical Intermediate

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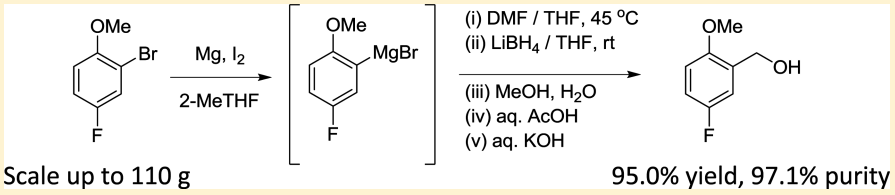
Supporting Information

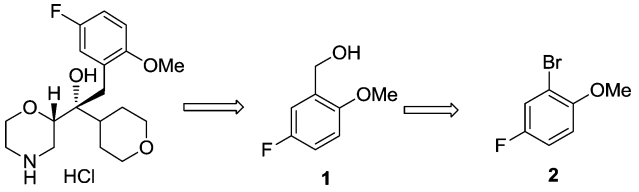


ABSTRACT: An efficient synthetic approach leading to introduction of the hydroxymethyl group to an aryl moiety via combination of the Bouveault formylation and hydride reduction has been optimized using a rational, mechanistic-based approach. This approach enabled telescoping of the two steps into a single efficient process, readily amenable to scaleup.

INTRODUCTION

Hydroxymethylation is an important transformation in organic synthesis and is often used to produce building blocks for more complex targets. Edivoxetine·HCl is a highly selective norepinephrine uptake inhibitor under development at Eli Lilly and Co. for the treatment of depression (Scheme 1).[1] An important intermediate for the synthesis of edivoxetine·HCl is (5-fluoro-2-methoxyphenyl)methanol (**1**). A key requirement in the edivoxetine·HCl synthesis is high regiochemical purity, and as such, a route to produce **1** with high isomeric purity was required.

Scheme 1. Edivoxetine·HCl Retrosynthesis



The most common hydroxylation approach is reaction of a Grignard reagent directly with formaldehyde or paraformaldehyde to produce the desired hydroxymethyl alcohol.[2] This can be accomplished by "cracking" paraformaldehyde or adding solid paraformaldehyde to a preformed Grignard reagent. However, the generation of anhydrous formaldehyde is often extremely hazardous, as thermal runaway reactions can occur; paraformaldehyde "unzipping" is very difficult to control and is highly energetic. In addition, yields for formaldehyde-based approaches are frequently very low with high impurity levels, and quenching of excess paraformaldehyde is often problematic. Hydroxymethylation can also be achieved by hydrolysis of benzyl halides produced from a halomethylation reaction.[3] A significant downside to the halomethylation approach is that benzyl halides are frequently strong lachrymators and the halomethylation step produces bis(chloromethyl) ether, which is a highly dangerous byproduct on all scales of operation. A potentially attractive approach is Bouveault formylation, where a dialkyl formamide such as DMF is reacted with a Grignard reagent followed by an immediate reduction to produce the target hydroxymethyl alcohol.[4] However, due to side reactions, the Bouveault formylation has not been generally useful on preparative scales. To avoid common formylation side reactions such as secondary nucleophilic addition, Meyers and Comins developed 2-(*N*-methylformylamino)pyridine[5] as an efficient formylating reagent, which has been hypothesized to form a

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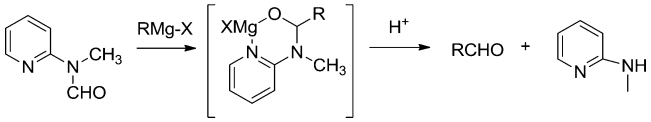
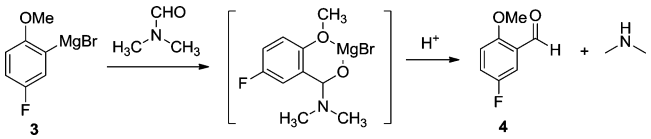
tight chelate, preventing release of the aldehyde under the reaction conditions (Scheme 2).

Scheme 2. Meyers and Bouveault Aldehyde Synthesis



We envisioned that it may be possible to directly formylate with DMF under Bouveault conditions using the Grignard reagent **3** produced from commercially available 2-bromo-4-fluoroanisole (**2**) to provide the aldehyde intermediate **4** (Scheme 3). We surmised that chelation of magnesium to the

Scheme 3. Proposed Synthesis of Aldehyde 4



α-methoxy group under Bouveault conditions would afford benefits similar to those reported by Meyers for the *N*-pyridyl system. Other formylating reagents such as *N*-formylmorpholine and *N*-formylpiperidine were also of interest, which may afford similar results for the production of **1**.[6]

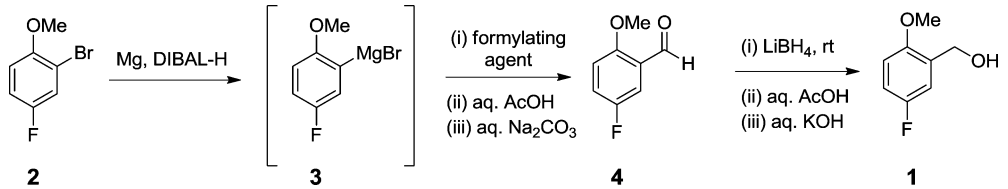
In addition, Meyers further extended the acylation methodology by demonstrating that Grignard aldehydic intermediates could be trapped in a controlled fashion with a second nucleophile to produce tertiary alcohols.[7] Meyer's methodology was of interest, as we sought to produce the greenest possible synthesis of **1**, which may require production of several multiton quantities in the future. Herein we report the results of our studies toward the synthesis of the pharmaceutical intermediate **1** employing a combination of the Bouveault formylation and hydride reduction reactions. This study includes an examination of a two-step approach for the preparation of **1**, investigation of Grignard exchange chemistry for the production of **3**, and the development of a highly efficient tandem acylation/hydride reduction amenable to use on any scale for safe production of **1**.

RESULTS AND DISCUSSION

Two-Step Synthesis of Alcohol 1. The two-step synthesis of (5-fluoro-2-methoxyphenyl)methanol (**1**) from 2-bromo-4-fluoroanisole (**2**) was initially investigated on a 5 g scale using 2-methyltetrahydrofuran (2-MeTHF), tetrahydrofuran (THF), and cyclopentyl methyl ether (CPME) as reaction solvents (Table 1, entries 1−3). THF and 2-MeTHF were of particular interest, because these solvents can be manufactured directly from the renewable resource furfural.[8] In this study, the Grignard reagent was prepared in the selected solvent system using catalytic DIBAL-H or iodine as an activator with a 12% initiation charge of substrate.[9] The acylation and reduction steps were then carried out in the same solvent systems. For each of the solvents examined, the aldehyde intermediate **4** and alcohol product **1** were produced with good purity and in generally high yields, albeit with a lower yield recorded for the reaction conducted in THF due to soluble loss of product to the aqueous layer during workup (Table 1, entry 2). While the decreased yield recorded for the reaction in THF was a concern, the purity in this case was very high and importantly, in contrast to the syntheses employing 2-MeTHF and CPME, the THF reaction proceeded without any significant solid formation during the formylation and reduction steps, which could be particularly advantageous for larger-scale reactions.

The preparation of 5-fluoro-2-methoxybenzaldehyde (**4**) using *N*-formylmorpholine and *N*-formylpiperidine in place of DMF was next examined. Reactions with *N*-formylmorpholine were conducted in 2-MeTHF, THF, and CPME (Table 1, entries 4−6). For each solvent system investigated, a reduction in yield and product purity was recorded in comparison to previous reactions employing DMF (Table 1, entries 4 vs 1, 5 vs 2, and 6 vs 3). In particular, a dramatic decrease in efficiency was recorded for the synthesis of **4** in CPME, and therefore, this solvent was not evaluated further in this study. Reduced

Table 1. Two-Step Synthesis of 1



2 **3** **4** **1**

				4		1	
entry	solvent	formylating agent	formylation temp (°C)	crude yield (%)[a]	purity (%)[b]	crude yield (%)[c]	purity (%)[b]
1	2-MeTHF	DMF	45	100.6	89.8	97.8	92.2
2	THF	DMF	45	92.4	96.0	78.8	98.8
3	CPME	DMF	45	95.1	94.4	96.4	91.2
4	2-MeTHF	*N*-formylmorpholine	45	91.4	86.8		
5	THF	*N*-formylmorpholine	45	87.3	82.5	81.7	89.3
6	CPME	*N*-formylmorpholine	45	73.7	62.6		
7	2-MeTHF	*N*-formylpiperidine	45	92.3	93.8		
8	THF	*N*-formylpiperidine	45	75.7	83.2	73.4	90.3
9	2-MeTHF	DMF	room temp	105.4	85.8		
10	THF	DMF	room temp	91.6	90.1	78.2	98.9

[a]Mass yield recovered for synthesis of aldehyde **4**. [b]As determined by GC-MS analysis. [c]Mass yield recovered for synthesis of alcohol **1**.

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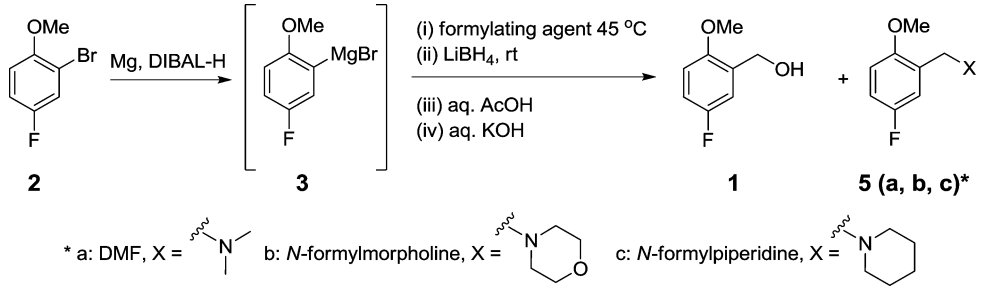
Table 2. Tandem Acylation/Reduction Strategy



entry	solvent	formylating agent	quench[a]	crude yield (%)[b]	purity of **1** (%)[c]	impurity (amt (%))
1	2-MeTHF	DMF	after 1 h	98.5	90.6	**5a** (2.9)
2	THF	DMF	after 1 h	93.1	96.8	**5a** (0.3)
3	THF	*N*-formylmorpholine	after 1 h	92.8	90.1	**5b** (4.9)
4	THF	*N*-formylpiperidine	after 1 h	95.1	89.3	**5c** (8.9)
5	THF	DMF	immediate	85.3	98.9	**5a** (0.3)
6	2-MeTHF	DMF	immediate	100.1	95.0	**5a** (0.2)

[a]Acetic acid quench performed either after 1 h or immediately after addition of $LiBH_4$. [b]Mass yield recovered after workup procedures. [c]As determined by GC-MS analysis.

purity levels and product recovery were also recorded for the reaction examining *N*-formylpiperidine in THF (Table 1, entry 8 vs 2). Interestingly, a slight increase in the purity of **4** was observed for the experiment employing *N*-formylpiperidine in 2-MeTHF (Table 1, entry 7 vs 1); however, this reaction was not further explored due to the significant amount of solid formation observed during formylation and difficulties in removing excess *N*-formylpiperidine from the reaction mixture.

In a previous report by Olah and co-workers investigating the preparation of aldehydes and ketones from *N*,*N*-dialkylamides and Grignard reagents,[10] it had been found that reactions must be conducted at low temperatures (0−20 °C) to avoid the occurrence of competing secondary reactions. In order to investigate if such a limit was also critical for product purity in our system under study, two experiments were conducted examining a reduced temperature during formylation (Table 1, entries 9 and 10). For both reactions examined a decrease in the purity of aldehyde **4** was recorded (Table 1, entries 9 vs 1 and 10 vs 2), and as a result no change to the standard 45 °C temperature for formylation was made for later scaleup studies.

Tandem Acylation/Reduction Strategy. It was subsequently surmised that we may be able to telescope the process under investigation by a tandem formylation/hydride reduction strategy. There are limited reports on such an approach, but the potential upside was large, including elimination of the problematic aldehyde workup. For these reasons we investigated the tandem addition strategy in both THF and 2-MeTHF using the standard conditions previously described for the two-step synthesis of **1**, but without isolation of the aldehyde intermediate **4**, where lithium borohydride was added to the unquenched tetrahedral intermediate.

We were pleased to discover that the proposed one-pot formylation/reduction could be successfully conducted, providing **1** in 98.5% (90.6% pure) and 93.1% (96.8% pure) yields for reactions in 2-MeTHF and THF, respectively (Table 2, entries 1 and 2). Importantly, purity levels for the isolated alcohol product **1** was in the range of those previously observed for the original two-step syntheses of **1** (Table 1, entries 1 and 2), although the formation of the reductive amination byproduct (**5a**) was observed.

The telescoped process was subsequently tested with *N*-formylmorpholine and *N*-formylpiperidine as formylating agents in THF (Table 2, entries 3 and 4).[11] Once again, successful formation of **1** was recorded in good yield; however, a decrease in product purity was observed with enrichment of reductive amination byproducts **5b**,**c**. The impurities **5a**−**c** appear to form mainly during the quench by reaction of the liberated secondary amine byproduct with the forming aldehyde. For the DMF system, the dimethylamine byproduct is volatile and can escape through the headspace at higher temperatures (45 °C). However, for the *N*-formylmorpholine and piperidine systems the corresponding morpholine and piperidine byproducts are not volatile; hence, formation of the reductive amination byproducts is not prevented and **5b**,**c** are thus observed at increased levels in the crude product mixture (Table 2, entries 3 and 4 vs entry 2).

In an effort to further probe the reaction mechanism for the one-pot process, two experiments were conducted examining an immediate quench of the reaction mixture following dropwise addition of the reducing agent (Table 2, entries 5 and 6). Interestingly, full consumption of the aldehyde intermediate **4** was again recorded under the modified reaction conditions. These observations combined with the lack of exotherm when lithium borohydride is added to the tetrahedral intermediate and no indication of hydrogen offgassing all provide compelling evidence that reduction is occurring entirely during the quench step.[20]

Grignard Exchange Chemistry. A potentially attractive Grignard processing option which has emerged over recent years is halogen−magnesium exchange chemistry, where commercially available simple Grignard reagents undergo an exchange reaction with an aryl halide to form a Grignard complex.[12] This approach has the benefit of directly avoiding handling magnesium metal and minimizes the propensity for runaway reactions. Knochel and co-worker discovered that the use of the salt additive LiCl accelerated both the rate and the efficiency of the reaction;[13] thus, in this study both commercially available *i*-PrMgCl and *i*-PrMgCl·LiCl exchanges were explored.

Initial studies in this area focused on 2-MeTHF as reaction solvent. At the outset low temperature (−10 °C and room

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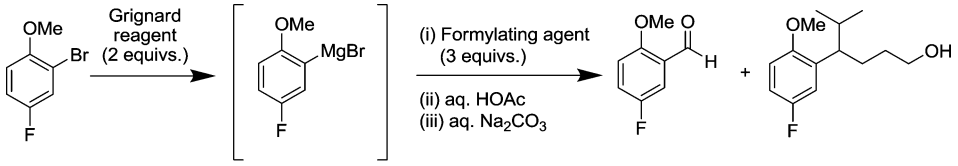
Table 3. Grignard Exchange Synthesis of 4



2 3 4 6

entry	Grignard reagent	solvent	temp (°C)	Grignard time (h)[a]	formylating agent[b]	crude yield (%)[c]	4 (%)[d]	6 (%)[d]
1	*i*-PrMgCl	2-MeTHF	reflux	2	DMF	101.4	71.6[e]	0
2	*i*-PrMgCl	THF	reflux	1	DMF	103.5	73.7	20.8
3	*i*-PrMgCl·LiCl	THF	reflux	1	DMF	102.0	78.3	18.5
4	*i*-PrMgCl	THF	reflux	1	*N*-formylmorpholine	99.8	90.2	8.2
5	*i*-PrMgCl	THF	reflux	1	*N*-formylpiperidine	84.2	76.5	19.0
6	*i*-PrMgCl	THF	30	4	DMF	93.2	98.8	0.4
7	*i*-PrMgCl	THF	30	4	DMF[f]	96.0	96.7	0.7
8	*i*-PrMgCl	THF	30	4	DMF[g]	96.7	98.5	0.2

[a]Reaction time required for >99% Grignard exchange as determined by GC-MS analysis. [b]Formylation conducted at 45 °C with 3 equiv of formylating agent unless otherwise stated. [c]Mass yield recovered after workup procedures. [d]As determined by GC-MS analysis. [e]Isolated product contains 13.1% 2-bromo-4-fluoroanisole (**2**). Experiments were conducted examining increased amounts of *i*-PrMgCl in 2-MeTHF and longer reflux periods,; however, for all reactions tested conversion to Grignard **3** was found to stall at ∼90%. [f]Formylation was conducted at 30 °C. [g]Two equivalents of DMF was used.

temperature) Grignard exchange was investigated as described by Leazer and co-workers;[14] however, no Grignard exchange was recorded, with 100% starting material **2** detected by GC-MS analysis after 1 h. Consequently, reflux conditions were implemented with successful Grignard exchange achieved after 2 h (Table 3, entry 1). As previously discussed in both the two-step and one-pot syntheses in 2-MeTHF, significant solid formation was observed upon charging DMF to the organomagnesium reagent **3**, resulting in complicated workup, and therefore this solvent was not evaluated further.

The next series of experiments employed THF as reaction solvent. Complete Grignard exchange was successfully attained with both *i*-PrMgCl and *i*-PrMgCl·LiCl after 1 h reflux (Table 3, entries 2 and 3). Negligible rate enhancement was observed with *i*-PrMgCl·LiCl, and therefore this reagent was no longer explored. Favorably, no solid formation was observed upon addition of DMF to **3** in THF; however, purity levels for the isolated aldehyde **4** were poor (73.7 and 78.2%, respectively) with high levels of impurity **6** (20.8 and 18.5%, respectively) detected by GC-MS analysis. Significantly, impurity **6** was also observed with *N*-formylmorpholine and *N*-formylpiperidine (Table 3, entries 4 and 5), albeit in lower levels for the latter formylating agent, and thus the formation of **6** was independent of the formylating agent employed. Furthermore, impurity **6** was not observed when 2-MeTHF was utilized (Table 3, entry 1), and thus a Grignard-based reaction incorporating ring-opened THF with addition of the isopropyl moiety has been postulated for its formation. This side reaction is likely radical based and is precedented on the basis of the work of Hock and co-workers.[15]

Temperature effects for the formation of impurity **6** were subsequently explored, as the higher than anticipated impurity level needed to be addressed prior to large-scale synthesis of **1** by Grignard exchange. When the halogen−magnesium exchange reaction was performed at 30 °C, dramatically reduced levels of impurity **6** (0.4%) were observed by GC-MS analysis, with excellent purity (98.8%) of the isolated aldehyde **4** (Table 3, entry 4). While a longer reaction time was required for complete Grignard exchange at 30 °C relative to reflux (4 h vs 1 h), the mild reaction conditions can be readily extended to the large-scale preparation of the Grignard reagent **3**. The effect of temperature at the formylation stage was also investigated and, as was observed for the two-step synthesis of **1**, was found to have minimal effect on product purity (Table 3, entry 7 vs 6). In an attempt to further optimize this procedure, one experiment was conducted examining a reduced loading of DMF during the formylation step. In initial Grignard exchange studies (Table 3, entries 1−7), 3 equiv of DMF was employed in line with literature procedures; however, the use of just 2 equiv of this reagent was found to be sufficient to permit full conversion to aldehyde **4** with miminal impact on purity and yield recorded (Table 3, entry 8).

Process Impurities. The principal process impurity observed was 4-fluoroanisole (**7**) (Figure 1), which was found in varying amounts in all isolated crude samples of **1**, due presumably to the presence of adventitious water in the reaction mixture or incomplete formylation. Additional common impurities also observed by GC-MS analysis included the Wurtz byproduct **8**, the phenol byproduct **9**, and the bis-addition byproduct **10**. The phenolic byproduct **9** had the highest variability and was likely produced by hydrolysis of a peroxide impurity generated from the reaction of the Grignard reagent **3** with oxygen. As already discussed, impurity **6** was observed exclusively during investigation of the Grignard

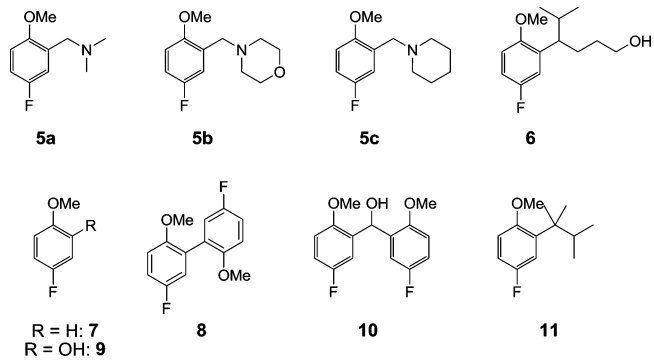


Figure 1. Impurities identified in the preparation of **1**.

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exchange reactions. Byproduct **11** was also recorded at low levels during the Grignard exchange study (≤0.3%) for Grignard reactions conducted at 30 °C. 4-Fluoroanisole (**7**) and 5-fluoro-2-methoxyphenol (**9**) were commercially available and were analyzed by our GC-MS method to confirm the retention times of these impurities. Compounds **5a**–**c**, **6**, **8**, **10**, and **11** were isolated from the crude product mixtures by flash chromatography and characterized to assign their structures.

Scaleup of the One-Pot Procedure. The synthesis of **1** was scaled to a 15 g scale of 2-bromo-4-fluoroanisole (**2**) using the optimum conditions identified for the two-step, one-pot, and Grignard exchange reactions. For this purpose, THF was employed as the reaction solvent, representing the best choice in terms of product purity and minimal solid formation; however, loss of product to the aqueous layer during workup procedures was a concern. The two-step synthesis of **1** was first examined using DMF as formylating agent and with formylation conducted at 45 °C (method a). Under these conditions, the aldehyde intermediate and alcohol product were obtained in 87.1% and 82.6% yields, respectively, giving an overall yield of 72.3% for the two-step process (Table 4, entry 1). This yield could be increased to 84.1% by addition of 2-MeTHF to the reaction mixture during the two workup steps, thus minimizing loss of both **4** and **1** to the aqueous layer (Table 4, entry 2). Significantly, the crude alcohol product was isolated in excellent purity for both large-scale experiments conducted using method a, with a purity of ≥98.9% achieved following crystallization (see Figure 2 for impurities in the crude product mixture).

Table 4. Large-Scale Experiments

		crude		after crystallization	
entry	procedure	yield (%)[a]	purity of **1** (%)[b]	purity of **1** (%)[b]	yield (%)
1	method a	72.3	97.0	98.9	56.7
2	method a[c]	84.1	98.8	99.4	72.4
3	method b	95.7	94.2	*d*	*d*
4	method c	94.4	97.3	99.4	80.5

[a]Mass yield recovered following reduction of **4** and after workup procedures. [b]As determined by GC-MS analysis. [c]2-MeTHF was added to the reaction mixture during workup procedures to minimize product loss to the aqueous layer. [d]Successful crystallization was not achieved due to the presence of suspected borohydride-derived byproducts.[16]

Scaleup of the one-pot synthesis of **1** was next examined, again using the optimal reaction conditions (method b) previously identified in the small-scale studies. The crude yield recorded in this instance was found to be significantly higher than that obtained for the alternative two-step preparation of **1** (Table 4, entry 3 vs entry 1), due presumably to the requirement for only one workup step in method b, thus minimizing product loss to the aqueous layer.[16]

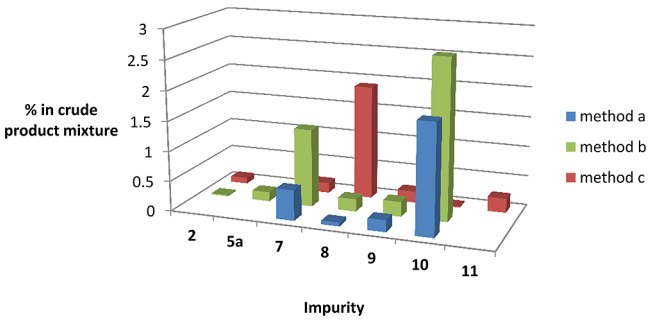
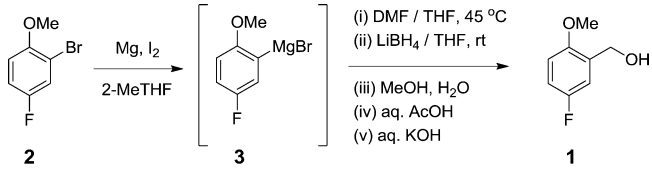


Figure 2. Comparison of GC-MS impurities in the crude product mixture for reactions conducted using methods a–c.

The scaled-up two-step synthesis of alcohol **1** employing Grignard exchange chemistry for the formation of **3** was conducted using 2 equiv of *i*-PrMgCl and DMF in THF (method c), conditions deemed optimal from our previous small-scale studies. Critically, the reaction temperature was set at 30 °C during the Grignard formation step to avoid the formation of significant quantities of byproducts **6** and **11**. Under these conditions, the desired product **1** was obtained in high yield and excellent purity, with an increase in product purity again recorded following crystallization (Table 4, entry 4, see Figure 2 for impurities in crude product mixture).

Further Optimization of the One-Pot Procedure. The long-term aim of this project was the preparation of (5-fluoro-2-methoxyphenyl)methanol (**1**) on a manufacturing scale. For this purpose, the one-pot synthesis of **1** was identified as the most suitable procedure, representing the best choice in terms of minimum reaction steps, solvent usage, and overall product yield, although notably product purity (94.2%) was slightly lower for this method. As a result, a number of changes to the original one-pot procedure (method b) were implemented prior to manufacture in an attempt to decrease impurity levels (the revised procedure is method d). First, the solvent for the Grignard formation step was changed from THF to the more environmentally benign solvent 2-MeTHF, which facilitated downstream improved aqueous phase separations. THF was still used for the formylation step, as significant solid formation was observed at this stage in previous small-scale experiments with other solvents. An altered workup procedure involving a methanol/water quench prior to addition of the acetic acid and an extended base wash period was also adopted to try to reduce the byproduct **5a**. As shown in Table 5, the optimized one-pot procedure (method d) provided the desired alcohol product **1** with a slightly increased yield and purity relative to the previous procedure (method b). There was however no decrease in the amount of **5a** present in the crude reaction mixture.

Table 5. Optimization of the One-Pot Procedure



2 **3** **1**

				amt (%)[b]			
entry	procedure	**2** (g)	yield (%)[a]	**1**	**5a**	**9**	**10**
1	method b	15	95.7	94.2	0.16	0.27	2.48
2	method d	15	96.0	94.9	0.21	0.18	1.77
3[c]	method e	110	95.0[d]	97.1	0.1	<0.1	0.2

[a]Mass yield recovered following reduction of **4** and after workup procedures. [b]As determined by GC-MS analysis. [c]For process safety data for method e, see the Supporting Information. [d]Average yield.

The Commercial Procedure (Method e). With the optimal procedure (method d) now in hand, the commercial production of (5-fluoro-2-methoxyphenyl)methanol (**1**) was next envisioned. Prior to commencement of the commercial

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campaign two additional changes were implemented to address issues of process safety at the increased scale and impurity levels, respectively. The changes were as follows. (1) The Grignard initiation was performed at 10 °C, maintaining less than 30 °C throughout the Grignard reagent formation. (2) In contrast to previous experiments (one-pot procedure), the Grignard reagent was transferred with magnesium sequestration to a one volume THF solution containing 1.2 equiv of DMF. This approach was envisioned to minimize the formation of dimer **10** and allows for the use of a magnesium heel in the Grignard formation step on a manufacturing scale. More importantly, it was anticipated that this modified process could be safely operated at all scales. As shown in Table 5, entry 3, the modified commercial procedure (method e) was successfully conducted on a 110 g scale of 2-bromo-4-fluoroanisole (**2**), providing the desired alcohol product **1** in high yield (95.0%) and importantly with high levels of purity (97.1%). Significantly, alteration of the order of addition during the formylation step resulted in a large decrease in the amount of dimer **10** present in the crude product mixture (<0.2%). Other standard process impurities were controlled well by method e; however, four additional minor process impurities were observed due to a less pure source of the 2-bromo-4-fluoroanisole raw material which was used for the scaleup.[17] As previously described (Table 4), the purity of the isolated product **1** was increased to >99% following crystallization with toluene/heptane (overall yield 88.0%).

■ CONCLUSIONS

The synthetic route to benzyl alcohol **1** leading to introduction of the hydroxymethyl group via a combination of Bouveault formylation and hydride reduction has been optimized using a rational, mechanistic-based approach. This approach enabled telescoping of the two steps into a single process, producing the target compound **1** on a commercial scale in excellent in situ yield (95%) and purity (97%). In addition, elimination of the aldehyde workup reduces the overall process mass intensity by greater than 20%. Conditions were developed which used 2-MeTHF as the primary process solvent, which may be derived from renewable resources. This approach is amenable to large-scale manufacture and affords significant process safety advantages relative to the formaldehyde and halomethylation approaches. It is anticipated that this methodology could be readily extended to the synthesis of other useful pharmaceutical, fine chemical, and agricultural product intermediates.

■ EXPERIMENTAL SECTION

General Considerations. Unless otherwise noted, tetrahydrofuran (THF) and 2-methyltetrahydrofuran (2-MeTHF) were distilled prior to use over sodium benzophenone ketyl. Cyclopentyl methyl ether (anhydrous, ≥99.9%) was used as purchased from Sigma-Aldrich. All reactions were carried out under an inert atmosphere. NMR spectra were recorded on a 300, 400, or 500 MHz NMR spectrometer. All spectra were recorded at room temperature (~20 °C) in deuterated chloroform ($CDCl_3$), unless otherwise stated, using tetramethylsilane (TMS) as an internal standard. COSY and HETCOR correlations were used to confirm the NMR peak assignments of all novel compounds. ^{19}F NMR spectra were recorded on a 400 MHz spectrometer with complete carbon decoupling and referenced using hexafluorobenzene (C_6F_6 in $CDCl_3$ δ −162.2). High-resolution mass spectrometry (HRMS) was performed on a TOF instrument in electrospray ionization (ESI) mode; samples were made up in acetonitrile. GC-MS analysis was carried out using a DB-WAX (30 m × 0.25 mm i.d. × 0.25 μm film) column under the following conditions: oven temperature program from 45 to 250 °C at 10 °C/min, and the final temperature kept for 8.5 min; injector temperature 200 °C, split injection technique (25:1 split ratio); carrier gas hydrogen, flow rate 1.0 mL/min; diluent used was toluene; ionization energy 69.9 eV, in the electronic ionization (EI) mode; ion source temperature 200 °C and scan mass range of m/z 50−500. HPLC analysis was carried out using a Zorbax SB-C8 (25 cm × 4.6 mm × 5 mm) column under the following conditions: mobile phase A, 0.1% H_3PO_4 in H_2O; mobile phase B, acetonitrile; flow rate 1.0 mL/min; gradient 0 min 10% B, 10 min 90% B, 16 min 90% B; wavelength 250 nm; ambient temperature.

Two-Step Synthesis (Method a). Magnesium (2.10 g, 86.0 mmol) was suspended in THF (36.0 mL), and diisobutylaluminum hydride (1 M solution in THF, 1.83 mL, 1.8 mmol) was added at 30 °C. 2-Bromo-4-fluoroanisole (**2**; 1.14 mL, 8.8 mmol) was added dropwise, and the resulting mixture was stirred for 0.5 h. The temperature was adjusted to 20 °C, and then 2-bromo-4-fluoroanisole (8.35 mL, 64.4 mmol) diluted with THF (36.0 mL) was added over 0.5 h, maintaining a reaction temperature of <40 °C. When addition was complete, the reaction mixture was stirred for 1 h, after which time full Grignard reagent formation was confirmed by GC-MS analysis. A solution of anhydrous DMF (6.91 mL, 89.0 mmol) in THF (36.0 mL) was added dropwise over 0.5 h to the Grignard mixture at 45 °C. The resulting mixture was stirred at 45−55 °C for 1 h and then quenched by slow addition via cannula transfer to aqueous acetic acid (20 wt %, 105 mL) at 0 °C. 2-MeTHF (50 mL) was added to the reaction mixture, and the phases were separated. The organic phase was washed with aqueous sodium carbonate (5 wt %, 183 mL). The aqueous phase was discarded, and the organic layer was concentrated by rotary evaporation to give the crude aldehyde intermediate **4** as an orange solid. A 10 wt % solution of **4** in THF was adjusted to 23 °C, lithium borohydride (4 M solution in THF, 9.15 mL, 36.6 mmol) was added dropwise, and the mixture was stirred for 1 h at this temperature. The reaction mixture was subsequently transferred via cannula to an aqueous solution of acetic acid (20 wt %, 105 mL) and stirred for 0.5 h. 2-MeTHF (50 mL) was added to the reaction mixture, and the phases were separated. The organic phase was washed with aqueous potassium hydroxide (10 wt %, 100 mL), and then the aqueous layers were separated and discarded. The solvent was removed by rotary evaporation to obtain crude (5-fluoro-2-methoxyphenyl)methanol (**1**; 9.60 g, 84.1%) as a yellow oil. The crude product was purified by crystallization in toluene/heptane as follows. The crude alcohol **1** (9.60 g) was dissolved in toluene (12.4 mL), and the solution was cooled to 0 °C. Heptane (15.7 mL) was added dropwise to the stirred solution, and after addition of 3 mL of heptane the product **1** started to crystallize without seeding. The remaining heptane was added over 20 min. Additional heptane (56.0 mL) was added slowly over 45 min, and the mixture was stirred for 1.5 h. The suspension was filtered, and the solid was washed with heptane (40.0 mL). The wet cake was dried under reduced pressure at room temperature to obtain pure 5-fluoro-2-methoxyphenyl)methanol (**1**; 8.28 g, 86.3% recovery from crude) as a white crystalline solid with >99% purity (overall yield 8.28 g, 72.4%).

One-Pot Synthesis (Method b). Magnesium (2.10 g, 86.0 mmol) was suspended in THF (36.0 mL), and diisobutylaluminum hydride (1 M solution in THF, 1.83 mL, 1.8 mmol) was added at 30 °C. 2-Bromo-4-fluoroanisole (**2**; 1.14 mL, 8.8 mmol) was added dropwise, and the resulting mixture was stirred for 0.5 h. The temperature was adjusted to 20 °C, and then 2-bromo-4-fluoroanisole (**2**; 8.35 mL, 64.4 mmol) diluted with THF (36.0 mL) was added over 0.5 h, maintaining a reaction temperature of <40 °C. When addition was complete, the reaction mixture was stirred for 1 h, after which time full Grignard reagent formation was confirmed by GC-MS analysis. A solution of anhydrous DMF (6.91 mL, 89.0 mmol) in THF (36.0 mL) was added dropwise over 0.5 h to the Grignard mixture at 45 °C. The resulting mixture was stirred at 45−55 °C for 1 h. The reaction mixture was adjusted to 23 °C, lithium borohydride (4 M solution in THF, 9.15 mL, 36.6 mmol) was added dropwise, and the mixture was stirred for 1 h at this temperature. The reaction mixture was subsequently transferred via cannula to an aqueous solution of acetic acid (20 wt %, 105 mL) and stirred for 0.5 h, and then the phases were separated.

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The organic phase was washed with aqueous potassium hydroxide (10 wt %, 100 mL), and then the aqueous layers were separated and discarded. The solvent was removed by rotary evaporation to obtain crude (5-fluoro-2-methoxyphenyl)methanol (**1**; 10.94 g, 95.7%) as a yellow oil.

Grignard Exchange Reaction (Method c). Isopropylmagnesium chloride (2 M solution in THF, 73.2 mL, 146.0 mmol) was added dropwise over 0.5 h at 30 °C to a solution of 2-bromo-4-fluoroanisole (**2**; 9.49 mL, 73.2 mmol) in THF (36.0 mL). When addition was complete, the reaction mixture was stirred for 4 h, after which time full Grignard reagent formation was confirmed by GC-MS analysis. A solution of anhydrous DMF (11.33 mL, 146.3 mmol) in THF (36.0 mL) was added dropwise over 0.5 h to the Grignard mixture at 45 °C. The resulting mixture was stirred at 45−55 °C for 1 h and then quenched by slow addition via cannula transfer to aqueous acetic acid (20 wt %, 105 mL) at 0 °C. The phases were separated, and the organic phase was washed with aqueous sodium carbonate (5 wt %, 183 mL). The aqueous phase was discarded, and the organic layer was concentrated by rotary evaporation to give the crude aldehyde intermediate **4** as an orange solid. A 10 wt % solution of **4** in THF was adjusted to 23 °C, lithium borohydride (4 M solution in THF, 9.15 mL, 36.6 mmol) was added dropwise, and the mixture was stirred for 1 h at this temperature. The reaction mixture was subsequently transferred via cannula to an aqueous solution of acetic acid (20 wt %, 105 mL) and stirred for 0.5 h, and then the phases were separated. The organic phase was washed with aqueous potassium hydroxide (10 wt %, 100 mL), and then the aqueous layers were separated and discarded. The solvent was removed by rotary evaporation to obtain crude (5-fluoro-2-methoxyphenyl)methanol (**1**; 10.78 g, 94.4%) as a yellow oil. The crude product was purified by crystallization in toluene/heptane using the method described for the two-step synthesis of **1** (method a) to produce alcohol **1** (9.20 g, 85.5% recovery from crude) as a white crystalline solid with purity >99% (overall yield 9.20 g, 80.5%).

Revised One-Pot Synthesis (Method d). Magnesium (2.10 g, 86.0 mmol) was suspended in 2-MeTHF (50.0 mL), and iodine (0.19 g, 0.73 mmol) was added. The reaction mixture was heated to 30 °C, 2-bromo-4-fluoroanisole (**2**; 1.14 mL, 8.8 mmol) was added dropwise, and the resulting mixture was stirred for 0.5 h. The temperature was adjusted to 20 °C, and then 2-bromo-4-fluoroanisole (8.35 mL, 64.4 mmol) diluted with 2-MeTHF (25.0 mL) was added over 0.5 h, maintaining a reaction temperature of <40 °C. When addition was complete, the reaction mixture was stirred for 1 h, after which time full Grignard reagent formation was confirmed by GC-MS analysis. A solution of anhydrous DMF (6.91 mL, 89.0 mmol) in THF (36.0 mL) was added dropwise over 0.5 h to the Grignard mixture at 45 °C. The resulting mixture was stirred at 45−55 °C for 1 h. The reaction mixture was adjusted to 23 °C, lithium borohydride (4 M solution in THF, 9.15 mL, 36.6 mmol) was added dropwise, and the mixture was stirred for 1 h at this temperature. The reaction mixture was subsequently transferred via cannula over 0.5 h to a solution of water (50.0 mL) and methanol (50.0 mL), maintaining a quench temperature of <30 °C. A solution of aqueous acetic acid (20 wt %, 105 mL) was added, the mixture was stirred for 0.5 h, and then the phases were separated. The organic phase was washed once with aqueous potassium hydroxide (10 wt %, 100 mL), stirred for 1 h with aqueous potassium hydroxide (10 wt %, 100 mL), and finally washed with water (100 mL). The aqueous rinsings were discarded, and the organic layer was concentrated by rotary evaporation to obtain crude (5-fluoro-2-methoxyphenyl)methanol (**1**) as a yellow oil (10.97 g, 96.0%).

Commercial Procedure (Method e). In a 1 L jacketed vessel magnesium (32.6 g, 1.34 mol) was suspended in nondistilled commercial 2-MeTHF (220 mL), iodine (1.36 g, 0.0054 mol) was then added, and the mixture was cooled to 10 °C under N_2. 2-Bromo-4-fluoroanisole (**2**; 10 g, 0.049 mol) was added, and a strong exotherm (10 °C) was observed within a couple of minutes. The exotherm quickly tailed, and once the mixture reached 10 °C, a solution containing 2-bromo-4-fluoroanisole (**2**; 100 g, 0.488 mol) and 2-MeTHF (110 mL) was added over 1.5 h, maintaining a reaction temperature of <30 °C. When the addition was complete, the temperature was adjusted to 20 °C and the mixture was stirred for an additional 1 h. HPLC analysis indicated less than 1% 2-bromo-4-fluoroanisole (**2**) starting material remaining. In a separate 1 L jacketed vessel anhydrous DMF (47.1 g, 0.64 mol, 1.2 equiv) and nondistilled commercial THF (110 mL) were charged and the temperature was adjusted to 45 °C. The Grignard reagent **3** was sequestered from the elemental magnesium and added to an addition funnel attached to the vessel containing DMF. (Note 1: the remaining magnesium heel can be reused directly at the same scale or additional magnesium added prior to the next experiment to attain the same magnesium loading.) The Grignard solution was fed over 0.5 h to the DMF solution stirred at 45−50 °C. (Note 2: during the Grignard reagent feed a light suspension formed, which redissolved after addition of ∼75% of the Grignard reagent feed.) After the feed was complete, the remaining magnesium heel was washed with 2-MeTHF (50 mL) and the rinsing added to the DMF solution. The resulting mixture was stirred at 45−55 °C for 1 h and then cooled to 20 °C. Lithium borohydride (2 M solution in THF, 268 mL, 0.536 mol) was added, and the mixture was stirred for 0.5 h at 20 °C. GC-MS analysis (MeOH quenched sample) revealed <1% aldehyde **4**. In a 3 L jacketed vessel were charged water (330 mL) and methanol (220 mL), and then the temperature of the contents was adjusted to 20 °C. The reductive reaction mixture was transferred to the quench solution over at least 0.5 h, maintaining a temperature of less than 30 °C. The reaction vessel was rinsed with 2-MeTHF (660 mL), and the rinsings were transferred to the quench vessel. Acetic acid (112.8 g, 1.88 mol) was dissolved in water (330 mL), and then the aqueous acetic acid solution was added to the quench mixture. After the mixture was stirred for 0.5 h, the phases were separated and the lower aqueous phase was removed (750 mL; pH 5). The organic phase was washed with 2 × 550 mL of NaOH (0.5 N), and the aqueous rinsings were discarded. (Note 3: the second base wash was stirred for 1 h to ensure full hydrolysis of any remaining boronate ester. The pH of the first base was ∼6 and that of the second base wash was ∼13.) The organic layer was then washed with water (550 mL), and the aqueous layer (pH ∼10) was separated and discarded. The organic layer was concentrated, taken up in toluene, and evaporated to provide an oil which was dried under high vacuum for 24 h to give the final crude compound **1** (84.8 g, 101.1%, HPLC purity 97%). Compound **1** was purified by crystallization in toluene/heptane using the method described for the two-step synthesis of **1** (method a) to produce alcohol **1** (78.0 g, 92.0% recovery from crude) as a white crystalline solid with >99% purity (overall yield 78.0 g, 93.1%).

*5-Fluoro-2-methoxybenzaldehyde (**4**):* white solid; GC-MS retention time 11.5 min; δ_H (400 MHz) 3.93 (3H, s, OCH_3), 6.96 (1H, dd, J_{HH} 9.0, J_{HF} 3.8, ArH), 7.24−7.30 (1H, m, ArH), 7.51 (1H, dd, J_{HH} 8.3, J_{HF} 3.3, ArH), 10.42 (1H, d, J 3.2, CHO); δ_F (400 MHz) −120.7. Spectral characteristics for **4** are consistent with previously reported data.[18]

*(5-Fluoro-2-methoxyphenyl)methanol (**1**):* white crystalline solid; GC-MS retention time 14.5 min; δ_H (400 MHz) 2.21 (1H, t, J 6.5, OH), 3.83 (3H, s, OCH_3), 4.66 (2H, d, J 6.5, CH_2OH), 6.78 (1H, dd, J_{HH} 8.9, J_{HF} 4.3, ArH), 6.94 (1H, td, J_{HH} 8.5, J_{HF} 3.1, ArH), 7.04 (1H, dd, J_{HH} 8.7, J_{HF} 3.1, ArH); δ_F (400 MHz) −124.3. Spectral characteristics for **1** are consistent with previously reported data.[1]

*1-(5-Fluoro-2-methoxyphenyl)-N,N-dimethylmethanamine (**5a**):* white solid: mp 64−66 °C; GC-MS retention time 9.4 min; δ_H (300 MHz) 2.44 (6H, s, 2 × CH_3), 3.73 (3H, s, OCH_3), 3.97 (2H, s, CH_2), 6.80 (1H, dd, J_{HH} 9.0, J_{HF} 4.5, ArH), 6.93−7.05 (2H, m, ArH); δ_C (75.5 MHz) 49.9 (2 × CH_3), 55.9 (OCH_3), 60.6 (CH_2), 111.9 (CH, d, $^3J_{CF}$ 8.1, aromatic CH), 117.0 (CH, d, $^2J_{CF}$ 22.8, aromatic CH), 120.8 (CH, d, $^2J_{CF}$ 22.8, aromatic CH), 154.6 (aromatic C), 155.0 (aromatic C), 157.8 (aromatic C); δ_F (400 MHz) −123.6; HRMS (ES^+) exact mass calcd for $C_{10}H_{15}FNO$ $(M + H)^+$ 184.1138, found 184.1134.

*4-(5-Fluoro-2-methoxybenzyl)morpholine (**5b**):* yellow oil; GC-MS retention time 15.4 min; δ_H (300 MHz) 2.47−2.52 (4H, sym m, 2 × CH_2), 3.52 (2H, s, CH_2N), 3.70−3.75 (4H, sym m, 2 × CH_2), 3.80 (3H, s, OCH_3), 6.77 (1H, dd, J_{HH} 8.9, J_{HF} 4.4, Ar*H*), 6.89 (1H, td, J_{HH}

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8.9, J_{HF} 3.2, Ar*H*), 7.14 (1H, dd, J_{HH} 9.2, J_{HF} 3.2, Ar*H*); δ_C (75.5 MHz) 53.7 (2 x CH_2), 56.0 (OCH_3), 56.1 (CH_2N), 67.1 (2 × CH_2), 111.3 (CH, d, $^3J_{CF}$ 8.2, aromatic CH), 113.7 (CH, d, $^2J_{CF}$ 23.0, aromatic CH), 116.6 (CH, d, $^2J_{CF}$ 23.6, aromatic CH), 128.1 (C, d, $^3J_{CF}$ 6.9, aromatic C), 153.8 (C, d, $^4J_{CF}$ 2.2, aromatic C), 157.1 (C, d, $^1J_{CF}$ 237.9, aromatic C); δ_F (400 MHz) −124.1; HRMS (ES^+) exact mass calcd for $C_{12}H_{17}FNO_2$ $(M + H)^+$ 226.1243, found 226.1233.

*1-(5-Fluoro-2-methoxybenzyl)piperidine (**5c**):* orange oil; GC-MS retention time 13.5 min; δ_H (400 MHz) 1.38−1.50 (2H, m, CH_2), 1.52−1.68 (4H, m, 2 × CH_2), 2.42 (4H, t, *J* 4.7, 2 × CH_2), 3.48 (2H, s, CH_2N), 3.79 (3H, s, OCH_3), 6.75 (1H, dd, J_{HH} 8.9, J_{HF} 4.4, Ar*H*), 6.86 (1H, td, J_{HH} 8.5, J_{HF} 2.9, Ar*H*), 7.15 (1H, dd, J_{HH} 9.3, J_{HF} 2.7, Ar*H*); δ_C (75.5 MHz) 24.3 (CH_2), 26.1 (2 x CH_2), 54.6 (2 × CH_2), 55.9 (OCH_3), 56.4 (CH_2N), 111.1 (CH, d, $^3J_{CF}$ 8.1, aromatic CH), 113.2 (CH, d, $^2J_{CF}$ 23.0, aromatic CH), 116.6 (CH, d, $^2J_{CF}$ 23.0, aromatic CH), 129.0 (C, d, $^3J_{CF}$ 6.9, aromatic C), 153.7 (C, d, $^4J_{CF}$ 2.0, aromatic C), 157.2 (C, d, $^1J_{CF}$ 237.5, aromatic C); δ_F (400 MHz) −124.3; HRMS (ES^+) exact mass calcd for $C_{13}H_{19}FNO$ $(M + H)^+$ 224.1451, found 224.1442.

*4-(5-Fluoro-2-methoxyphenyl)-5-methylhexan-1-ol (**6**):* yellow oil; GC-MS retention time 16.9 min; δ_H (400 MHz) 0.72 (3H, d, *J* 6.7, CH_3), 0.95 (3H, d, *J* 6.7, CH_3), 1.17 (1H, bs, OH), 1.29−1.36 (2H, m, CH_2), 1.48−1.58 (1H, m, one of CH_2), 1.74−1.87 (2H, m, *CH* and one of CH_2), 2.82−2.89 (1H, bm, CH), 3.56 (2H, t, *J* 6.6, CH_2OH), 3.77 (3H, s, OCH_3), 6.74−6.86 (3H, m, ArH); δ_C (75.5 MHz) 20.6 (CH_3), 20.9 (CH_3), 28.2 (CH_2), 30.8 (CH_2), 32.9 (CH), 44.0 (CH, bs), 56.1 (OCH_3), 63.1 (CH_2), 111.5 (CH, d, $^3J_{CF}$ 8.3, aromatic CH), 112.3 (CH, d, $^2J_{CF}$ 22.8, aromatic CH), 114.6 (CH, d, $^2J_{CF}$ 22.8, aromatic CH), 135.2 (C, d, $^3J_{CF}$ 6.4, aromatic C), 154.1 (C, d, $^4J_{CF}$ 2.0, aromatic C), 157.3 (C, d, $^1J_{CF}$ 237.5, aromatic C); δ_F (400 MHz) −124.0; HRMS (ES^+) exact mass calcd for $C_{14}H_{22}FO_2$ $(M + H)^+$ 241.1604, found 241.1594.

*5,5′-Difluoro-2,2′-dimethoxybiphenyl (**8**):* white solid: mp 114−117 °C; GC-MS retention time 16.6 min; δ_H (500 MHz) 3.75 (6H, s, OCH_3), 6.86−6.91 (2H, m, ArH), 6.97−7.03 (4H, m, ArH); δ_F (400 MHz) −124.4; HRMS (ES^+) exact mass calcd for $C_{14}H_{13}F_2O_2$ $(M + H)^+$ 251.0884, found 251.0879. Spectral characteristics for **8** are consistent with previously reported data.[19]

*Bis(5-fluoro-2-methoxyphenyl)methanol (**10**):* white solid: mp 105−108 °C; GC-MS retention time 22.3 min; δ_H (400 MHz) 3.47 (1H, d, *J* 5.1, OH), 3.80 (6H, s, 2 × OCH_3), 6.24 (1H, d, *J* 5.1, CH), 6.79−6.84 (2H, m, ArH), 6.91−6.99 (4H, m, ArH); δ_C (75.5 MHz) 56.0 (2 × OCH_3), 66.8 (CH), 111.4 (CH, d, $^3J_{CF}$ 8.1, 2 × aromatic CH), 114.4 (CH, d, $^2J_{CF}$ 23.1, 2 × aromatic CH), 114.8 (CH, d, $^2J_{CF}$ 24.5, 2 × aromatic CH), 132.2 (C, d, $^3J_{CF}$ 6.6, 2 × aromatic C), 152.8 (C, d, $^4J_{CF}$ 2.1, 2 × aromatic C), 157.2 (C, d, $^1J_{CF}$ 238.6, 2 × aromatic C); δ_F (400 MHz) −123.3; HRMS (ES^+) exact mass calcd for $C_{15}H_{13}O_2F_2$ $(M - OH)^+$ 263.0884, found 263.0881.

*2-(2,3-Dimethylbutan-2-yl)-4-fluoro-1-methoxybenzene (**11**):* sticky white solid; GC-MS retention time 9.5 min; δ_H (400 MHz) 0.73 (6H, d, *J* 6.9, 2 × CH_3), 1.24 (6H, s, 2 × CH_3), 2.60 (1H, qu, *J* 6.9, CH), 3.78 (3H, s, OCH_3), 6.74−6.86 (2H, m, ArH), 6.94 (1H, dd, J_{HH} 11.1, J_{HF} 3.1, ArH); δ_C (75.5 MHz) 18.1 (2 x CH_3), 23.5 (2 × CH_3), 32.4 (CH), 41.4 (C), 55.7 (OCH_3), 112.1 (CH, d, $^2J_{CF}$ 21.9, aromatic CH), 112.3 (CH, d, $^3J_{CF}$ 8.4, aromatic CH), 115.0 (CH, d, $^2J_{CF}$ 24.0, aromatic CH), 140.4 (C, d, $^3J_{CF}$ 6.0, aromatic C), 154.5 (C, d, $^4J_{CF}$ 2.1, aromatic C), 156.9 (C, d, $^1J_{CF}$ 236.5, aromatic C); δ_F (400 MHz) −124.3; HRMS (ES^+) exact mass calcd for $C_{13}H_{20}FO$ $(M + H)^+$ 211.1498, found 211.1495.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, tables, and figures giving details of the quench study, process safety data for the commercial procedure (method e) and ^1H and ^{13}C NMR, COSY, and HETCOR spectra for the novel compounds **5a−c**, **6**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) The Grignard reagent formation is highly exothermic with a reaction enthalpy of −291 kJ/mol and T_{Ad} = 141 °C. For this reason it is critical that the substrate feed is not commenced until initiation is verified. It typically takes 2−4 min to achieve a productive initiation; however, high levels of water in the system (>500 ppm) can significantly delay the onset of initiation. However, once initiation occurs, the Grignard formation is feed rate limited and the exotherm can be controlled by the substrate dosage rate.

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(16) During scaleup an additional impurity was observed by ^1H NMR analysis which was not identified in the previous small-scale studies. This impurity appears to be due to the reaction of dimethylamine with the borohydride or borohydride derived by-products, although its full structure has not been confirmed.

(17) The impurities reported according to HPLC retention time are as follows: (1) unknown, 0.68% (RRT 0.74); 5-fluoro-2-methoxy benzoic acid, 0.45% (RRT 0.95); positional isomer 1, 0.59% (RRT 1.02); positional isomer 2, 0.31% (RRT 1.05).

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(20) Further quench studies, including exploration of the sequence and relative rates of the various steps in the process, are outlined in the Supporting Information.

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