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

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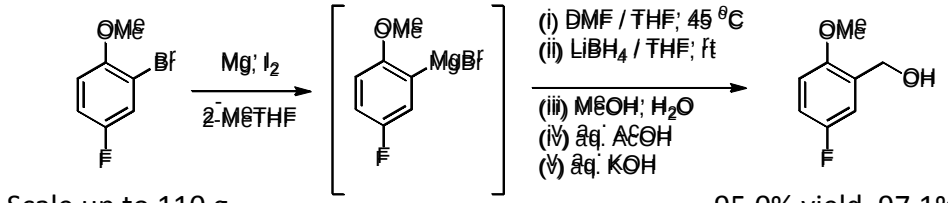
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TOC graphic



Scale up to 110 g

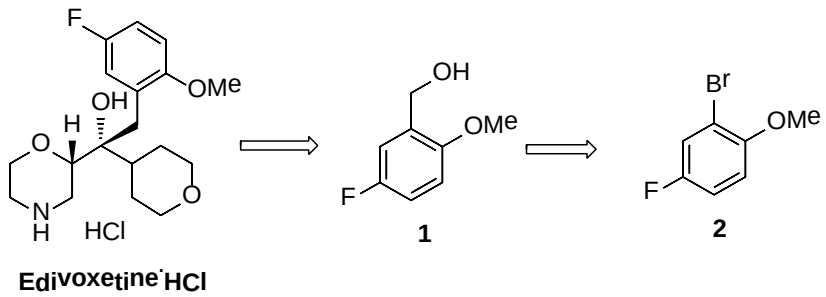
95.0% yield, 97.1% purity

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 optimised using a rational, mechanistic-based approach. This approach enabled telescoping of the two steps into a single efficient process, readily amenable to scale-up.

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 Company 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.

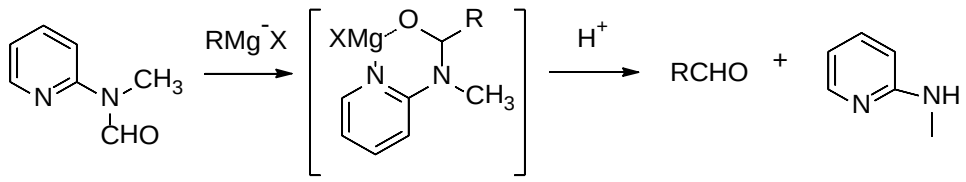


Edivoxetine·HCl

Scheme 1. Edivoxetine·HCl Retrosynthesis.

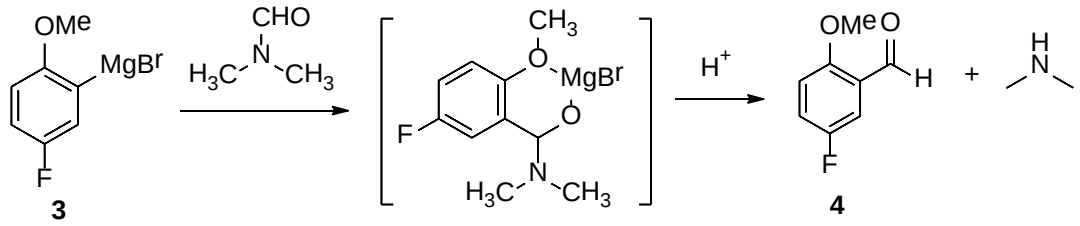
The most common hydroxylation approach is reaction of a Grignard reagent directly with formaldehyde or paraformaldehyde to produce the desired hydroxymethyl alcohol.[2] This can be accomplished by "cracking" paraformaldehyde or addition of solid paraformaldehyde to a pre-formed Grignard reagent. However, the generation of anhydrous formaldehyde is often extremely hazardous as thermal runaway reactions can occur as 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 bischloromethyl ether which is a highly dangerous by-product 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*-methylformyl-aminopyridine[5] as an efficient formylating reagent which has been hypothesized to form a tight chelate preventing release of the aldehyde during 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 α-methoxy group under Bouveault conditions would afford similar benefits as 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]



Scheme 3. Proposed Synthesis of Aldehyde **4**.

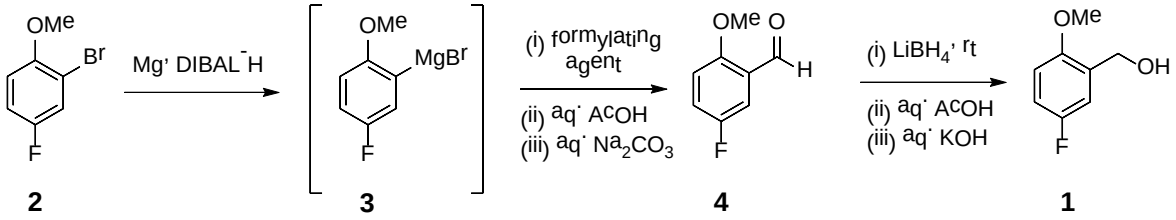
In addition, Meyers further extended the acylation methodology by demonstrating that Grignard aldehydic intermediates could be trapped in controlled fashion with a second nucleophile to produce tertiary alcohols.[7] Meyer's methodology was of interest as we sought to produce the greenest possible synthesis of **1**, which may require production of several multi-ton quantities in the future. Herein we report the results of our studies towards 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 work-up (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.

Table 1. Two-Step Synthesis of **1.**



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

entry	solvent	formylating agent	formylation temp.	**4** crude yield (%)[a]	**4** purity (%)[b]	**1** crude yield (%)[c]	**1** purity (%)[b]
1	2-MeTHF	DMF	45 °C	100.6	89.8	97.8	92.2
2	THF	DMF	45 °C	92.4	96.0	78.8	98.8
3	CPME	DMF	45 °C	95.1	94.4	96.4	91.2
4	2-MeTHF	*N*-formylmorpholine	45 °C	91.4	86.8	–	–
5	THF	*N*-formylmorpholine	45 °C	87.3	82.5	81.7	89.3

6	CPME	*N*-formylmorpholine	45 °C	73.7	62.6	–	–
7	2-MeTHF	*N*-formylpiperidine	45 °C	92.3	93.8	–	–
8	THF	*N*-formylpiperidine	45 °C	75.7	83.2	73.4	90.3
9	2-MeTHF	DMF	rt	105.4	85.8	–	–
10	THF	DMF	rt	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**.

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 when compared 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 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 removing excess *N*-formylpiperidine from the reaction mixture.

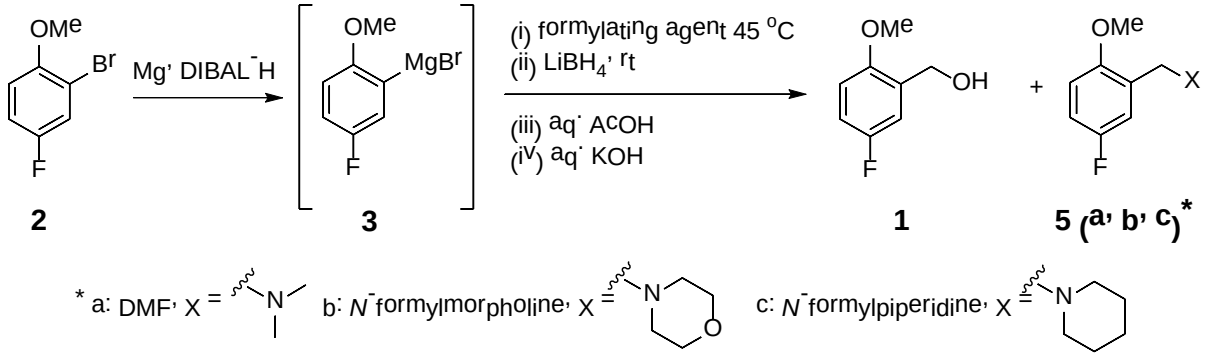
In a previous report by Olah and co-workers investigating the preparation of aldehydes and ketones from *N*,*N*-dialkylamides and Grignard reagents,[10] it had been found that reactions must be conducted at low temperatures (0–20 °C) to avoid the occurrence of competing secondary reactions. In order 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 scale-up 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 work-up. 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) yield 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 by-product (**5a**) was observed.

Table 2. Tandem Acylation/Reduction Strategy.



entry	solvent	formylating agent	quench[a]	crude yield (%)[b]	purity **1** (%)[c]	impurity (%)
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 1 h or immediately after addition of $LiBH_4$.

[b] Mass yield recovered after work-up procedures.

[c] As determined by GC-MS analysis.

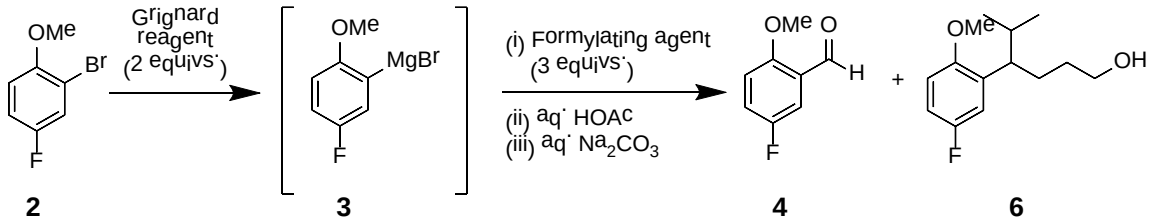
The telescoped process was subsequently trialled with *N*-formylmorpholine and *N*-formylpiperidine as formylating agents in THF (Table 2, entries 3 and 4).[11] Once again, successful formation of **1** was recorded in good yield, however, a decrease in product purity was observed with enrichment of reductive amination by-products **5b** and **5c**. The impurities **5a**, **5b** and **5c** appear to form mainly during the quench by reaction of the liberated secondary amine by-product with the forming aldehyde. For the DMF system, the dimethylamine by-product 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 by-products are not volatile, hence formation of the reductive amination by-products is not prevented and **5b** and **5c** 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 minimises the propensity for runaway reactions. Knochel and co-worker discovered that the use of 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 exchange were explored.

Table 3. Grignard Exchange Synthesis of **4**.



2 **3** **4** **6**

entry	Grignard reagent	solvent	temp.	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 °C	4	DMF	93.2	98.8	0.4
7	*i*-PrMgCl	THF	30 °C	4	DMF[f]	96.0	96.7	0.7
8	*i*-PrMgCl	THF	30 °C	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 three equivalents of formylating agent unless otherwise stated.

[c] Mass yield recovered after work-up procedures.

[d] As determined by GC-MS analysis.

[e] Isolated product contains 13.1% 2-bromo-4-fluoroanisole **2**. Experiments were conducted examining increased equivalents of *i*-PrMgCl in 2-MeTHF and longer reflux periods, however, for all reactions trialled conversion to Grignard **3** was found to stall at ~90%.

[f] Formylation was conducted at 30 °C.

[g] Two equivalents of DMF were used.

Initial studies in this area focused on 2-MeTHF as reaction solvent. At the outset low temperature (–10 °C and rt) 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 work-up 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. Favourably, 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 utilised (Table 3, entry 1) and thus a Grignard based reaction incorporating ring opened THF with addition of the *iso*-propyl moiety has been postulated for its formation. This side reaction is likely radical based and is precedented based on 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 optimise 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), three equivalents of DMF were employed in line with literature procedures, however the use of just two equivalents 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 the 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 by-product **8**, the phenol by-product **9** and the *bis*-addition by-product **10**. The phenolic by-product **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 exchange reactions. By-product **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 analysed by our GC-MS method to confirm the retention times of these impurities. Compounds **5a**, **5b**, **5c**, **6**, **8**, **10** and **11** were

isolated from the crude product mixtures by flash chromatography and characterised to assign their structure.

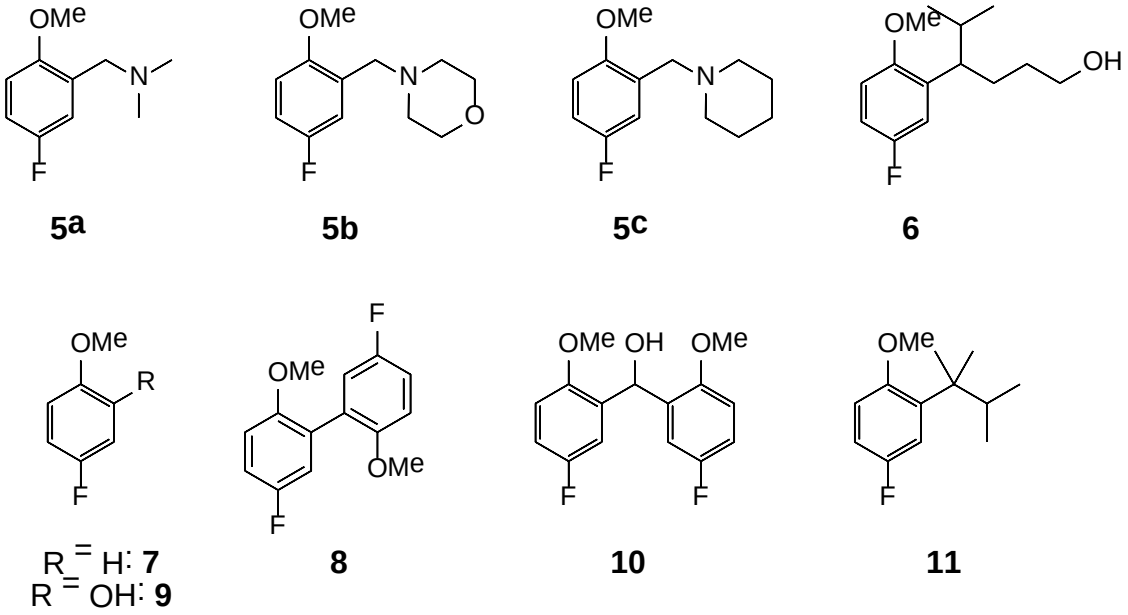


Figure 1. Impurities identified in the preparation of **1.**

Scale-Up of 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 work-up 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% yield, 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 work-up steps, thus minimising 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 purity of ≥98.9% achieved following crystallisation (see Figure 2 for impurities in crude product mixture).

Scale-up 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 work-up step in *method b*, thus minimising product loss to the aqueous layer.[16]

The scaled-up two-step synthesis of alcohol **1** employing Grignard exchange chemistry for the formation of **3** was conducted using two equivalents *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 crystallisation (Table 4, entry 4, see Figure 2 for impurities in crude product mixture).

Table 4. Large-Scale Experiments.

entry	procedure	crude		after crystallisation	
		yield (%)[a]	purity **1** (%)[b]	purity **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 work-up procedures.

[b] As determined by GC-MS analysis.

[c] 2-MeTHF was added to the reaction mixture during work-up procedures to minimise product loss to the aqueous layer.

[d] Successful crystallisation not achieved due to presence of suspected borohydride-derived byproducts.[16]

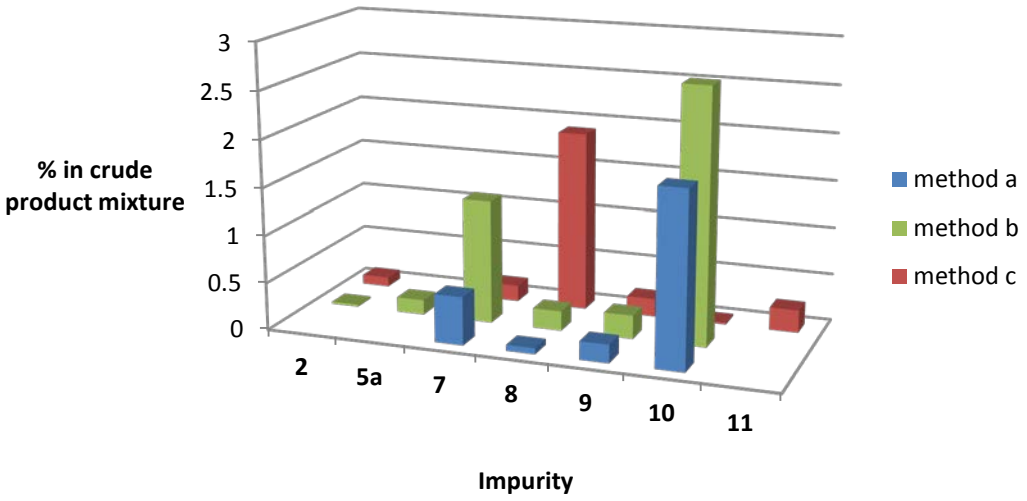
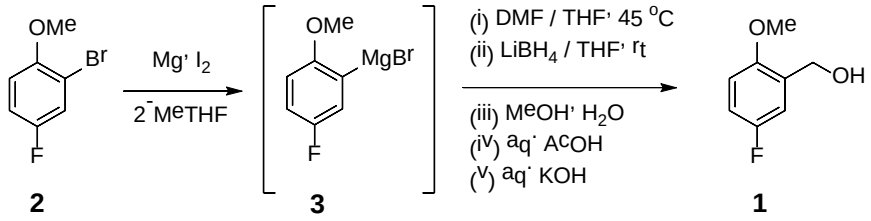


Figure 2. Comparison of GC-MS impurities in the crude product mixture for reactions conducted using *method a*, *method b* and *method c*.

Further Optimisation 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 (revised procedure is *method d*). Firstly, 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 work-up 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 by-product **5a**. As shown in Table 5, the optimised 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. Optimisation of One-Pot Procedure.



2 **3** **1**

entry	Procedure	**2** (g)	yield (%)[a]	**1** (%)[b]	**5a** (%)[b]	**9** (%)[b]	**10** (%) [b]
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 work-up procedures.

[b] As determined by GC-MS analysis.

[c] For process safety data for *method e* see 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 campaign two additional changes were implemented to address issues of process safety at the increased scale and impurity levels, respectively. The changes were: 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 equivalents 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 scale-up.[17] As previously described (Table 4), the purity of the isolated product **1** was increased to >99% following crystallisation with toluene/heptane (overall yield = 88.0%).

CONCLUSIONS

The synthetic route to benzyl alcohol **1** leading to introduction of the hydroxymethyl group *via* combination of the Bouveault formylation and hydride reduction has been optimised 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 work-up 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 for the synthesis of other useful pharmaceutical, fine chemical and agricultural product intermediates.

EXPERIMENTAL SECTION

General. 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 MHz, 400 MHz 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 x 0.25 mm id x 0.25 µm film) column under the following conditions: oven temperature program from 45 °C 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; ionisation 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 x 4.6 mm x 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 and temperature ambient.

Two-Step Synthesis (Method a).

Magnesium (2.10 g, 86.0 mmol) was suspended in THF (36.0 mL) and diisobutylaluminum hydride (1M 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 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 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 and lithium borohydride (4M solution in THF, 9.15 mL, 36.6 mmol) was added dropwise and the mixture 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), 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 crystallisation in toluene/heptane as follows: The crude alcohol **1** (9.60 g) was dissolved in toluene (12.4 mL) and the solution cooled to 0 °C. Heptane (15.7 mL) was added dropwise to the stirring solution and after addition of 3 mL

of heptane the product **1** started to crystallise without seeding. The remaining heptane was added over 20 min. Additional heptane (56.0 mL) was added slowly over 45 min and the mixture 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 (1M 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 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 and lithium borohydride (4M solution in THF, 9.15 mL, 36.6 mmol) was added dropwise and the mixture 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 then the phases were separated. The organic phase was washed with aqueous potassium hydroxide (10 wt%, 100 mL), 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).

iso-Propylmagnesium chloride (2M 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 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 and lithium borohydride (4M solution in THF, 9.15 mL, 36.6 mmol) was added dropwise and the mixture 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 then the phases were separated. The organic phase was washed with aqueous potassium hydroxide (10 wt%, 100 mL), 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 crystallisation 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 and 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 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 and lithium borohydride (4M solution in THF, 9.15 mL, 36.6 mmol) was added dropwise and the mixture 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 and the mixture stirred for 0.5 h then the phases were separated. The organic phase was once washed with aqueous potassium hydroxide (10 wt%, 100 mL), then 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 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 non-distilled commercial 2-MeTHF (220 mL) then iodine (1.36 g, 0.0054 mol) was added, and the mixture 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) 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 non-distilled commercial THF (110 mL) were charged and the temperature 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 stirring at 45–50 °C. (Note 2: During the Grignard reagent feed a light suspension forms which re-dissolves after addition of ~75% of the Grignard reagent feed). After the feed was completed 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. then cooled to 20 °C. Lithium borohydride (2M solution in THF, 268 mL, 0.536 mol) was added and the mixture stirred for 0.5 h at 20 °C. GC-MS analysis (MeOH quenched sample) reveals <1% aldehyde **4**. To a 3 L jacketed vessel was charged water (330 mL) and methanol (220 mL) then the contents temperature 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 transferred to the quench vessel. Acetic acid (112.8 g, 1.88 mol) was dissolved in water (330 ml) then the aqueous acetic acid solution added to the quench mixture. After stirring 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 x 550 mL NaOH (0.5 N) and the aqueous rinsings discarded. (Note 3: The second base wash was stirred for 1 h to assure full hydrolysis of any remaining boronate ester. The pH of the first base was ~6; the second base wash ~13). The organic layer was then washed with water (550 ml) and the aqueous layer (pH ~10) separated and discarded. The organic layer was concentrated and displaced with toluene/ 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 crystallisation 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 x 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 x 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, $^{2}J_{CF}$ 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 calculated 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 x CH_2), 3.52 (2H, s, CH_2N), 3.70–3.75 (4H, sym m, 2 x 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} 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 x CH_2), 111.3 (CH, d, $^{3}J_{CF}$ 8.2, aromatic CH), 113.7 (CH, d, $^{2}J_{CF}$ 23.0, aromatic CH), 116.6 (CH, d, $^{2}J_{CF}$ 23.6, aromatic CH), 128.1 (C, d, $^{3}J_{CF}$ 6.9, aromatic C), 153.8 (C, d, $^{4}J_{CF}$ 2.2, aromatic C), 157.1 (C, d, $^{1}J_{CF}$ 237.9, aromatic C); δ_F(400 MHz) –124.1; HRMS (ES^+): Exact mass calculated 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 x CH_2), 2.42 (4H, t, *J* 4.7, 2 x CH_2), 3.48 (2H, s, C*H*$_2$N), 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 x CH_2), 55.9 (OCH_3), 56.4 (CH_2N), 111.1 (CH, d, $^{3}J_{CF}$ 8.1, aromatic CH), 113.2 (CH, d, $^{2}J_{CF}$ 23.0, aromatic CH), 116.6 (CH, d, $^{2}J_{CF}$ 23.0, aromatic CH), 129.0 (C, d, $^{3}J_{CF}$ 6.9, aromatic C), 153.7 (C, d, $^{4}J_{CF}$ 2.0, aromatic C), 157.2 (C, d, $^{1}J_{CF}$ 237.5, aromatic C); δ_F(400 MHz) –124.3; HRMS (ES^+): Exact mass calculated 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, C*H* and one of CH_2), 2.82–2.89 (1H, bm, CH), 3.56 (2H, t, *J* 6.6, C*H*$_2$OH), 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 (O*C*H_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 calculated 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 calculated 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 x 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 x OCH_3), 66.8 (CH), 111.4 (CH, d, $^3J_{CF}$ 8.1, 2 x aromatic CH), 114.4 (CH, d, $^2J_{CF}$ 23.1, 2 x aromatic CH), 114.8 (CH, d, $^2J_{CF}$ 24.5, 2 x aromatic CH), 132.2 (C, d, $^3J_{CF}$ 6.6, 2 x aromatic C), 152.8 (C, d, $^4J_{CF}$ 2.1, 2 x aromatic C), 157.2 (C, d, $^1J_{CF}$ 238.6, 2 x aromatic C); δ_F(400 MHz) –123.3; HRMS (ES^+): Exact mass calculated 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 x CH_3), 1.24 (6H, s, 2 x 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 x CH_3), 32.4 (CH), 41.4 (C), 55.7 (O*C*H_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 calculated for $C_{13}H_{20}FO$ $(M+H)^+$, 211.1498. Found 211.1495.

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SUPPORTING INFORMATION

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

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(9) The Grignard reagent formation is highly exothermic with a reaction enthalpy of –291 KJ / mol with T_{Ad} = 141 ^{o}C. For this reason it is critical that 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 scale-up an additional impurity was observed by ^{1}H NMR analysis which was not identified in the previous small-scale studies. This impurity appears to be due to 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: 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.