JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

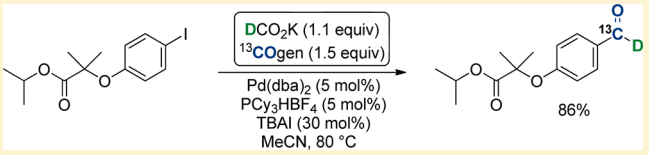
# Reductive Carbonylation of Aryl Halides Employing a Two-Chamber Reactor: A Protocol for the Synthesis of Aryl Aldehydes Including $^{13}$C- and D-Isotope Labeling

Signe Korsager, Rolf H. Taaning,* Anders T. Lindhardt, and Troels Skrydstrup*

Center for Insoluble Protein Structures (InSPIN), the Interdisciplinary Nanoscience Center (iNANO), Department of Chemistry, Aarhus University, Gustav Wieds Vej 14, 8000 Aarhus C, Denmark

Supporting Information

**ABSTRACT:** A protocol has been developed for conducting the palladium-catalyzed reductive carbonylation of aryl iodides and bromides using 9-methylfluorene-9-carbonyl chloride (COgen) as a source of externally delivered carbon monoxide in a sealed two-chamber system (COware), and potassium formate as the in situ hydride source. The method is tolerant to a wide number of functional groups positioned on the aromatic ring, and it can be exploited for the isotope labeling of the aldehyde group. Hence, reductive carbonylations run with $^{13}$COgen provide a facile access to $^{13}$C-labeled aromatic aldehydes, whereas with $DCO_2K$, the aldehyde is specifically labeled with deuterium. Two examples of double isotopic labeling are also demonstrated. Finally, the method was applied to the specific carbon-13 labeling of the $\beta$-amyloid binding compound, florbetaben.




## INTRODUCTION

The importance of the aldehyde group is clearly demonstrated by its presence as a key functional group in a diverse array of named reactions, such as the Wolff−Kishner reduction, pinacol coupling, Wittig, Corey−Fuchs, Ohira−Bestmann or Seyferth−Gilbert homologation, and the Friedländer reaction, some of which lead directly to heterocyclic scaffolds.[1] Due to the high usefulness of aldehydes as a platform for further synthetic transformation, the synthesis of aromatic aldehydes has been thoroughly investigated, and access to such compounds includes oxidation of alcohols, electrophilic formylation reactions, transition metal-catalyzed reductive carbonylations of aryl halides, and hydroformylation of alkenes, as well as other routes.[2]

In spite of the importance of aldehydes as reactive intermediates in medicinal chemistry and other advanced organic synthesis disciplines, the selective $^{13}$C- or D-isotope labeling of this functional group using modern synthetic methods has received only sporadic attention, and to date, no single method exists, which allows for the mild introduction of the double isotopically labeled aromatic aldehyde bearing a carbon-13 and deuterium at this functionality.[3] Stable isotope labeling is a widespread tool in a variety of disciplines, including reaction mechanism elucidation, isotope dilution mass spectrometry (IDMS), structural elucidation, etc. Furthermore, hydrogen to deuterium replacement at metabolically labile positions of potential pharmaceuticals has recently received considerable attention as an approach for improving the metabolic stability of such compounds.[4]

The classical route to isotopically labeled aromatic aldehydes involves a three-step synthesis from the corresponding aryl halide and utilizes strongly basic aryl metal species and harsh reducing agents, such as $LiAlH_4$.[3b] Recent work by Georg and co-workers, demonstrated that zirconium-deuteride reagents effectively transform amides into deuterated aldehydes in a single and mild synthetic step. However, $^{13}$C-labeling of this position was not addressed.[5]

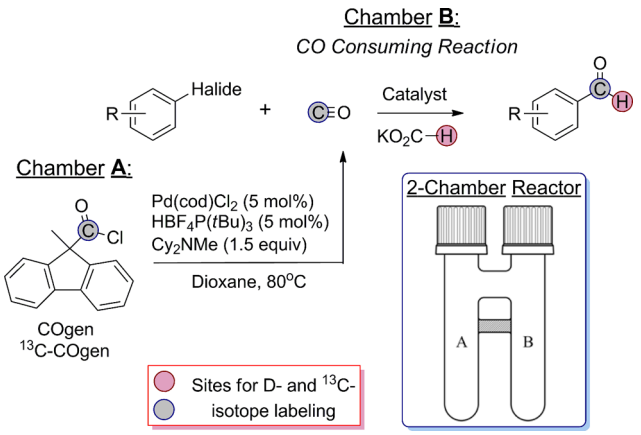
The palladium(0)-catalyzed reductive carbonylation of aryl halides with carbon monoxide and hydrogen is a powerful method for obtaining aromatic aldehydes, and industrial applications of this transformation have been achieved.[6] Nevertheless, the use of these gaseous reagents under elevated pressures makes this reaction unsuitable for performing isotopic labeling. On the other hand, formate salts have been shown to be efficient hydride donors for this reaction.[7] We therefore envisaged that this hydride source could be combined with our recent work on the use of solid sources of carbon monoxide in palladium-catalyzed carbonylation reactions applying only stoichiometric amounts of CO in a two-chamber system.[8] This would allow access to a simple method for the carbon-13 and deuterium-labeling of aromatic aldehydes (Scheme 1).

In this contribution, we report a protocol for conducting reductive carbonylation of aryl bromides and iodides using nongaseous precursors, which allows for the direct and efficient isotopic labeling of aromatic aldehydes with both carbon-13 and deuterium. The protocol takes advantage of 9-methylfluorene-9-carbonyl chloride (COgen) as a source of externally delivered carbon monoxide in a sealed two-chamber system (COware),[8a] and potassium formate as the in situ hydride

**Received:** April 12, 2013
**Published:** May 22, 2013

   dx.doi.org/10.1021/jo400741t | J. Org. Chem. 2013, 78, 6112−6120

**Scheme 1. Approach to the Synthesis of Isotopically Labeled Aryl Aldehydes**



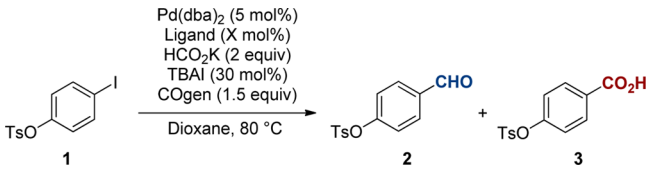

source. $^{13}$COgen provides easy access to $^{13}$C-labeled aromatic aldehydes, whereas the use of $DCO_2K$ makes this protocol suitable for specific deuterium labeling of aldehydes.

## RESULTS AND DISCUSSION

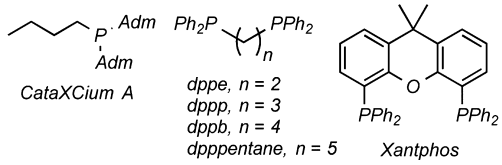
Preliminary experiments were conducted with aryl iodide **1** using a two-chamber reactor, employing COgen as the stoichiometric CO precursor, in order to identify appropriate catalytic conditions for the selective transformation of aryl halides to the corresponding aldehyde. As in our earlier work (see also Experimental Procedures), the CO release from COgen was initiated using a combination of $Pd(dba)_2$ (5 mol %), $P(tBu)_3HBF_4$ (5 mol %), and $Cy_2NMe$ (1.5 equiv). All initial optimizations for the reductive carbonylation were run in dioxane using $Pd(dba)_2$, a ligand, and potassium formate as the hydride donor. Use of the latter reagent required the addition of tetra-*n*-butyl ammonium iodide as a phase transfer catalyst, as its absence led to low turnovers for aldehyde formation. From the ligand screening, it was immediately seen that the use of less sterically demanding monodentate ligands such as $PCy_3$ or its $HBF_4$ salt (entries 3 and 4) and CataCXium A[6e] (entry 5) afforded aldehyde **2** with good selectivity. On the other hand and as previously published,[9] the bulky monodentate phosphine ligands, such as $P(tBu)_3$ (entry 6), or bidentate phosphine ligands, including dppe, dppp, dppb, dpppentane, and Xantphos (entries 7–11) provided either high preference for the carboxylic acid **3** or no selectivity at all. From the experiment with $PCy_3HBF_4$ (entry 3), aldehyde **2** could then be isolated in a good 84% yield.

The conditions reported in Table 1, entry 4, were unfortunately found to be limited to electron-rich aryl iodides, whereas electron-deficient aryl iodides either exhibited a poor conversion of starting material (4-iodoacetophenone) or a poor selectivity between the formation of the aldehyde and the reductive dehalogenation (4-iodobenzonitrile).[10] In order to include electron-deficient aryl iodides as viable substrates for the reductive carbonylation with stoichiometric CO, further optimization was undertaken, whereby different solvents were tested with 4-iodobenzonitrile **4** as the substrate (Table 2). DMF is the most frequently used solvent in the reductive carbonylation reactions, but in our hands, this solvent only provided a conversion of 50% into a 1:1 ratio of the aldehyde **5** and carboxylic acid **6** (entry 4).[11] Acetonitrile proved superior to DMF in the reductive carbonylation, providing a 75%

**Table 1. Screening Ligands for the Reductive Carbonylation of Aryl Iodide 1**[a]




| Entry | Ligand | Conversion [b] (%) | **2**:**3** [b] (%) [c] |
|---|---|---|---|
| 1 | $PPh_3$ | > 95 | 61:39 |
| 2 | $P(o\text{Tol})_3$ | > 95 | 88:12 |
| 3 | $PCy_3$ | > 95 | > 99:1 |
| 4 | $PCy_3HBF_4$ | > 95 | > 99:1 (84) |
| 5 | CataXCium A | > 95 | 98:2 |
| 6 | $P(t\text{Bu})_3$ | > 95 | 4:96 |
| 7 | Dppe | 33 | 45:55 |
| 8 | Dppp | 15 | 40:60 |
| 9 | Dppb | 55 | 18:82 |
| 10 | dpppentane | 13 | > 99:1 |
| 11 | Xantphos | > 95 | 89:11 |



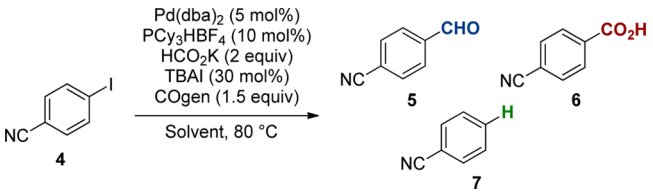

[a]Chamber 1: **1** (0.5 mmol), $Pd(dba)_2$ (5 mol %), ligand (monodentate: 10 mol %, bidentate: 5 mol %), $HCO_2K$ (1 mmol), TBAI (0.15 mmol), dioxane (3 mL). Chamber 2: COgen (0.75 mmol), $Cy_2NMe$ (1.5 mmol), $Pd(cod)Cl_2$ (5 mol %), $P(t\text{Bu})_3HBF_4$ (5 mol %), dioxane (3 mL) at 80 °C for 18 h. [b]Based on $^1$H NMR analysis on the crude reaction mixture. [c]Isolated yields in parentheses.

conversion with improved selectivity (entry 7). Dimethyl carbonate also gave a good selectivity for the aldehyde **5**, albeit at the expense of the conversion (entry 6). Heck and co-workers have shown that increasing the concentration of $PPh_3$ in the carbonylation of ArPdX complexes resulted in a decreased rate of formation of the corresponding ArCOPdX complexes.[12] Decreasing the ligand load from 10 to 5 mol % significantly improved the selectivity of aldehyde **5** to carboxylic acid **6** from a ratio of 75:25 to 89:10 and enabled the isolation of **5** in a 89% yield (Table 3, entry 8). This also correlates well with the palladium dimer complex proposed by Beller and co-workers as an intermediate in the catalytic cycle of the reductive carbonylation using syngas. The proposed palladium dimer complex displays a 1:1 ratio between Pd and phosphine ligand with trialkylphosphine ligands, such as $PCy_3$ and CataXCium A.[6e]

With this protocol in hand, we next turned to investigate the scope of the reaction with a number of aryl iodides (Scheme 2). In most cases, the reaction afforded a high selectivity toward


dx.doi.org/10.1021/jo400741t | J. Org. Chem. 2013, 78, 6112–6120

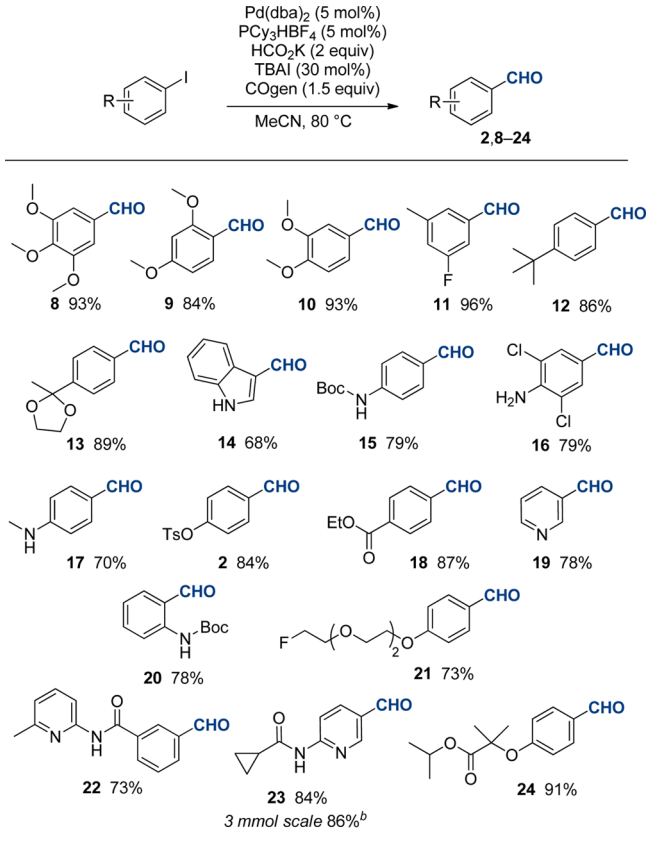
**Table 2. Solvent Studies in the Reductive Carbonylation of the Electron-Deficient Aryl Iodide 4[a]**




| entry | solvent | conversion[b] (%) | 5:6:7[b] (%)[c] |
|---|---|---|---|
| 1 | dioxane | >95 | 42:0:68 |
| 2 | toluene | 46 | 45:0:55 |
| 3 | anisole | <5 | – |
| 4 | DMF | 50 | 43:57:0 |
| 5 | isopropylacetate | 26 | 38:8:54 |
| 6 | dimethyl carbonate | 73 | 90:10:0 |
| 7 | MeCN | >95 | 75:0:25 |
| 8[d] | MeCN | >95 | 89:1:10 (89%) |

[a]Chamber 1: **4** (0.5 mmol), $Pd(dba)_2$ (5 mol %), $PCy_3HBF_4$ (10 mol %), $HCO_2K$ (1 mmol), TBAI (0.15 mmol), solvent (3 mL). Chamber 2: COgen (0.75 mmol), $Cy_2NMe$ (1.5 mmol), $Pd(cod)Cl_2$ (5 mol %), $P(tBu)_3HBF_4$ (5 mol %), solvent (3 mL) at 80 °C for 18 h. [b]Based on $^1H$ NMR analysis on the crude reaction mixture. [c]Isolated yield of aldehyde **5** in parentheses. [d]$PCy_3HBF_4$ (5 mol %).

**Scheme 2. Reductive Carbonylation of Aryl Iodides[a]**




[a]Chamber 1: Aryl iodide (0.5 mmol), $Pd(dba)_2$ (5 mol %), $PCy_3HBF_4$ (5 mol %), $HCO_2K$ (1 mmol), TBAI (30 mol %), MeCN (3 mL). Chamber 2: COgen (0.75 mmol), $Cy_2NMe$ (1.5 mmol), $Pd[COD]Cl_2$ (5 mol %), $P(tBu)_3HBF_4$ (5 mol %), MeCN (3 mL) at 80 °C for 18 h. [b] 1 mol % of $Pd[COD]Cl_2$ and $P(tBu)_3HBF_4$ in the CO-producing chamber.

the aldehyde and proved compatible with functional groups such as anilines with and without protecting groups (**15**–**17** and **20**) and amides (**22** and **23**). 4-Iodoacetophenone continued to pose a problem, and undesired dehalogenation dominated the reaction. Protecting the acetyl functionality as the corresponding ketal allowed for the reductive carbonylation to proceed smoothly, resulting in a satisfying 89% isolated yield of aldehyde **13**. In addition, use of 3-iodoindole and two different iodopyridines resulted in high isolated yields of the corresponding aldehydes with the applied reaction conditions, as illustrated by compounds **14**, **19**, and **23**. For compound **14**, the nitrogen of the starting 3-iodoindole was initially protected as its Cbz-carbamate. Upon reductive carbonylation, simultaneous deprotection under the reaction conditions led to indole aldehyde in a 68% isolated yield.

A scale-up from the standard 0.5 mmol scale of the aryl iodide to 3 mmol was attempted on a 3-iodopyridine, and gratifyingly, a similar high yield of **23** was obtained. More importantly, at the 3 mmol scale, the catalyst loadings of the CO-producing chamber was reduced to 1 mol %, and the reaction was performed without the use of glovebox techniques, flushing the system with argon prior to heating of the reaction mixture (see Experimental Procedures).

The conditions developed for aryl iodides proved inefficient for the transformation of aryl bromides to the corresponding aldehydes. However, the reactivity was reinstated by a simple increase of the reaction temperature to 100 °C. Nevertheless, this required the use of a higher-boiling solvent, and acetonitrile (bp 82 °C) was simply replaced with butyronitrile (bp 115–117 °C).[13] At the same time, the role of the phase transfer catalyst was examined. Changing the additive from TBAI to TBAB results in a lower conversion of the aryl bromide, while the omission of the ammonium salt halts the reaction entirely. This could signify that TBAI plays a dual role in the catalytic cycle, besides acting as a phase transfer catalyst for the formate ion. It is not entirely sure what the explanation for this halide effect is, but if the exchange is generating a more electrophilic palladium(II) species, the migratory insertion of CO can be facilitated.[14]

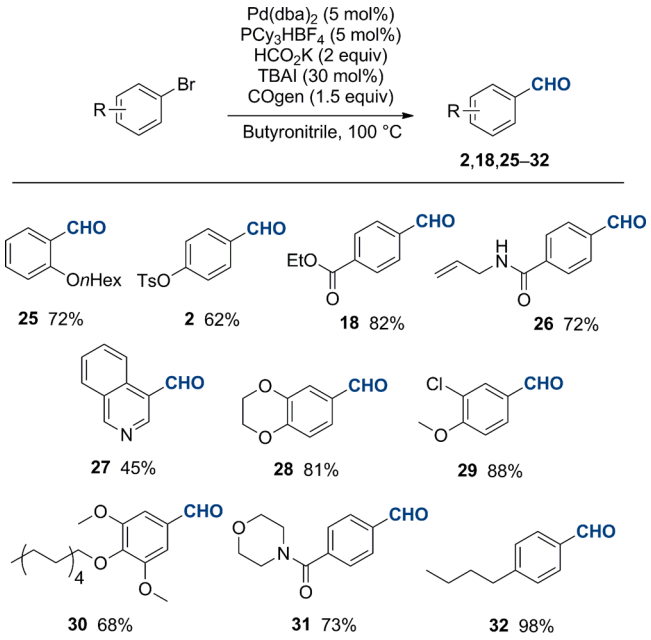
The transformation of aryl bromides to their corresponding aldehydes with stoichiometric CO was probed, and in general, the trend observed was the same as that for the aryl iodides (Scheme 3), whereby both electron-rich and electron-deficient aromatic bromides performed well. Functional groups susceptible to reduction such as a tosylate (**2**), ester (**18**), chloride (**29**), and amides (**26** and **31**) were also well tolerated.

Our next goal was then to examine the use of this chemistry for the specific isotope labeling of aromatic aldehydes with deuterium and carbon-13. $DCO_2K$ was readily prepared from deuterated formic acid by treatment with $K_2CO_3$. Submitting aryl iodides to the conditions for reductive carbonylation using only 1.1 equiv of $DCO_2K$ afforded the corresponding monodeuterated benzaldehydes D-**2**, D-**18**, and D-**24** in isolated yields of 79%, 82%, and 83%, respectively (Scheme 4). A reductive carbonylation reaction using $^{13}$COgen proved the potency of this protocol as a way to introduce specific labeling at the carbonyl carbon, providing $^{13}$C-**17** and $^{13}$C-**20** in good isolated yields. Furthermore, $DCO_2K$ and $^{13}$COgen could be combined in the reductive carbonylation to produce the double isotopically labeled aryl aldehydes $^{13}$C,D-**2** and $^{13}$C,D-**24**.

In our continued effort to study and understand the binding of small molecules to protein fibrils, such as *β*-amyloid

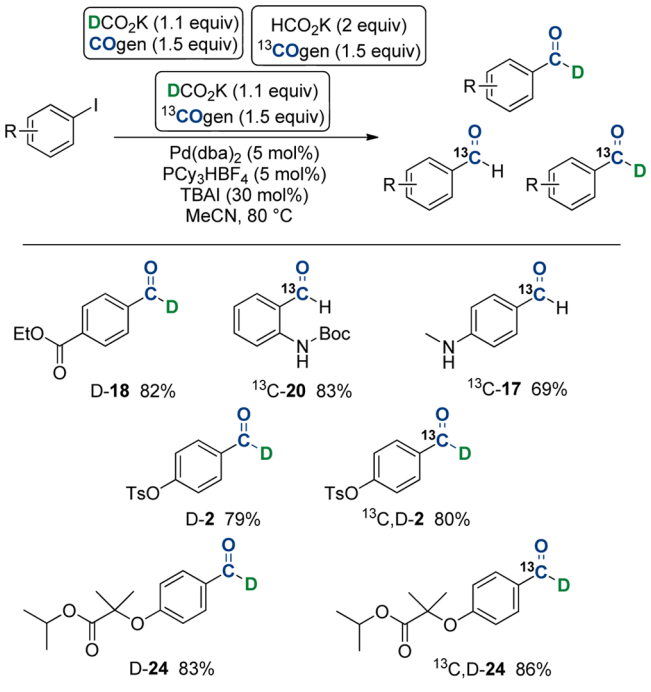

dx.doi.org/10.1021/jo400741t | J. Org. Chem. 2013, 78, 6112–6120

**Scheme 3. Reductive Carbonylation of Aryl Bromides**[a]




[a]Chamber 1: Aryl bromide (0.5 mmol), $Pd(dba)_2$ (5 mol %), $PCy_3HBF_4$ (5 mol %), $HCO_2K$ (1 mmol), TBAI (0.15 mmol), butyronitrile (3 mL). Chamber 2: COgen (0.75 mmol), $Cy_2NMe$ (1.5 mmol), $Pd[COD]Cl_2$ (5 mol %), $P(tBu)_3HBF_4$ (5 mol %), butyronitrile (3 mL) at 100 °C for 18 h.

**Scheme 4. Specific Isotope Labeling of Aromatic Aldehydes**[a]




[a]Chamber 1: Aryl iodide (0.5 mmol), $Pd(dba)_2$ (5 mol %), $PCy_3HBF_4$ (5 mol %), $HCO_2K$ (1 mmol) or $DCO_2K$ (0.55 mmol), TBAI (0.15 mmol), dioxane or MeCN (3 mL). Chamber 2: COgen or $^{13}$COgen (0.75 mmol), $Cy_2NMe$ (1.5 mmol), $Pd[COD]Cl_2$ (5 mol %), $P(tBu)_3HBF_4$ (5 mol %), dioxane or MeCN (3 mL) at 80 °C for 18 h.

fibrils,[8i,15] we set out to specifically carbon-13 label the β-amyloid binding compound, florbetaben, with the goal of measuring $^{13}C-^{13}C$ distance measurements between the core of florbetaben and $^{13}$C-labeled Aβ with solid-state NMR experiments.[16,17] The construction of florbetaben with a specific $^{13}$C-carbon in the styryl core was envisioned as possible in a single step using a Horner–Wadsworth–Emmons reaction from a $^{13}$C-labeled aldehyde and a benzylic phosphonate ester.

The synthesis of the phosphonate ester **33** from *p*-cresol was easily achieved in five synthetic steps in an overall yield of 48%.[18] $^{13}$C-Florbetaben **34** was effectively prepared from the reaction of the benzylic phosphonate ester **33** and the previously formed *p*-methylamino-$^{13}$C-benzaldehyde $^{13}$C-**17** in a 66% isolated yield (Scheme 5).

## CONCLUSION

In conclusion, we have developed a convenient method for the synthesis of aryl aldehydes via the reductive carbonylation of aryl iodides and bromides using only stoichiometric and externally generated carbon monoxide. This could be achieved by the use of the two-chamber reactor, COware, and the carbon monoxide precursor, COgen. The reaction conditions are tolerant toward many functional groups and a number of benzaldehydes with reasonable molecular complexity have been synthesized. In particular, we have been able to adapt the protocol to the isotope labeling of the aldehyde functionality with deuterium and carbon-13, and an example for the specific isotope labeling of the β-amyloid binding compound, florbetaben was achieved.

## EXPERIMENTAL PROCEDURES

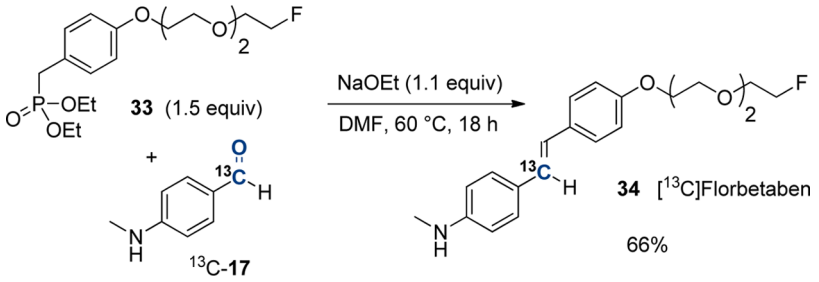
**General Methods.** All purchased chemicals were used as received without further purification. Solvents were dried according to standard procedures, and flash chromatography was carried out on silica gel 60 (230–400 mesh). The chemical shifts are reported in ppm relative to the solvent residual peak. The $^1$H NMR spectra were recorded at 400 MHz, $^{13}$C NMR spectra at 100 MHz, $^{19}$F NMR spectra at 367 MHz, and $^{31}$P NMR spectra at 162 MHz. MS spectra were recorded on a LC TOF (ES) apparatus. The reactions were performed in a previously reported two-chamber system (see the graphic on page 2 of the Supporting Information) under an argon atmosphere, and a glovebox was employed for weighing out the reagents. 9-Methylfluorene-9-carbonyl chloride (COgen), and its $^{13}$C-isotope-labeled version ($^{13}$COgen) were prepared as previously reported.[8a,19]

**$DCO_2K$.** To $DCO_2D$ (Formic-*d* 99$^+$ atom % D, acid-*d* 90$^+$ atom % D) (2.5 mL, 0.063 mmol) was added $K_2CO_3$ (6.75 g, 0.049 mmol), and the mixture was stirred 3 h at 100 °C in an argon atmosphere. The mixture was concentrated in vacuo to yield 4.1 g (98%) of the corresponding $DCO_2K$ as a colorless solid.

**General Procedure for Reductive Carbonylation of Aryl and Heteroaryl Iodides.** *Chamber 1*: $Pd(dba)_2$ (14.4 mg, 0.0250 mmol), $PCy_3HBF_4$ (10.8 mg, 0.0250 mmol), $KHCO_2$ (83 mg, 1.0 mmol), TBAI (55 mg, 0.15 mmol), and the aryl iodide (0.500 mmol) were weighed out and added to chamber 1 of the two-chamber system. Acetonitrile (3 mL) was then added, and the chamber was sealed with a screwcap fitted with a silicone/PTFE seal. *Chamber 2*: To chamber 2 of the two-chamber system, the following reagents and solvent were added in the order as indicated: $P(tBu)_3HBF_4$ (10.9 mg, 0.0375 mmol), $Pd[COD]Cl_2$ (10.7 mg, 0.0375 mmol), 9-methylfluorene-9-carbonyl chloride (COgen) (182 mg, 0.75 mmol), acetonitrile (3 mL), and $Cy_2NMe$ (320 μL, 1.5 mmol). The chamber was sealed with a screwcap fitted with a silicone/PTFEseal. The loaded two-chamber system was removed from the glovebox and heated to 80 °C for 18 h. Upon concentration of chamber 2 in vacuo the crude product was purified by column chromatography.


dx.doi.org/10.1021/jo400741t | J. Org. Chem. 2013, 78, 6112–6120

**Scheme 5. Specific Isotope Labeling of Aromatic Aldehydes**




**4-Hydroxybenzaldehyde 4-Methylbenzenesulfonate Ester (2).**[20] Flash chromatography using pentane/EtOAc 5:1 as eluent resulted in 116 mg (84% yield) of the title product obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 9.96 (s, 1H), 7.82 (d, 2H, $J$ = 8.8 Hz), 7.71 (d, 2H, $J$ = 8.5 Hz), 7.32 (t, 2H, $J$ = 8.8 Hz), 7.17 (t, 1H, $J$ = 8.5 Hz), 2.44 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 190.6, 153.8, 145.9, 134.8 (2C), 132.0, 131.2, 129.9 (2C), 128.4 (2C), 123.1 (2C), 21.7. HRMS $C_{14}H_{12}O_4S$ [M + $Na^+$]; calculated 299.0354, found 299.0351.

**[D]-4-Hydroxybenzaldehyde 4-Methylbenzenesulfonate Ester ([D]-2).** Dioxane was used as the solvent in the reductive carbonylation reaction. Flash chromatography using pentane/EtOAc 5:1 as eluent resulted in 109 mg (79% yield) of the title product obtained as a colorless solid with a 2% proton incorporation (determined by $^1$H NMR). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.82 (d, 2H, $J$ = 8.8 Hz), 7.71 (d, 2H, $J$ = 8.5 Hz), 7.32 (t, 2H, $J$ = 8.8 Hz), 7.17 (t, 1H, $J$ = 8.5 Hz), 2.44 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 190.6 (t, $J$ = 30.4 Hz), 153.8, 145.9, 134.8 (2C), 132.0, 131.2, 129.9 (2C), 128.4 (2C), 123.1 (2C), 21.7. HRMS $C_{14}H_{11}DO_4S$ [M + $Na^+$]; calculated 300.0417, found 300.0410.

**[D,$^{13}$C]-4-Hydroxybenzaldehyde 4-Methylbenzenesulfonate Ester ([D,$^{13}$C-2].** Dioxane was used as solvent in the reductive carbonylation reaction. Flash chromatography using pentane/EtOAc 5:1 as eluent resulted in 111 mg (80% yield) of the title product obtained as a colorless solid with a 2% proton incorporation (determined by $^1$H NMR). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.82 (dd, 2H, $J$ = 8.8, 2.3 Hz), 7.71 (d, 2H, $J$ = 8.5 Hz), 7.32 (t, 2H, $J$ = 8.8 Hz), 7.17 (t, 1H, $J$ = 8.5 Hz), 2.44 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 190.6 (d, $J$ = 30.4 Hz, $^{13}$C-enriched), 153.8, 145.9, 134.8 (2C), 132.0, 131.2, 129.9 (2C), 128.4 (2C), 123.1 (2C), 21.7. HRMS $^{13}CC_{14}H_{12}DO_4S$ [M + $Na^+$]; calculated 301.0450, found 301.0446.

**4-Formylbenzonitrile (5).**[21] Flash chromatography using pentane/EtOAc 20:1 as eluent resulted in 58 mg (89% yield) of the title product obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 10.09 (s, 1H), 7.99 (d, 2H, $J$ = 8.7 Hz), 7.84 (d, 2H, $J$ = 8.7 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 190.6, 138.7, 132.9, 129.9, 117.7, 117.6. HRMS $C_8H_5NO$ [M + $Na^+$]; calculated 154.0269, found 154.0263.

**3,4,5-Trimethoxybenzaldehyde (8).**[22] Flash chromatography using pentane/EtOAc 20:1 as eluent resulted in 91 mg (93% yield) of the title product obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 9.85 (s, 1H), 7.11 (s, 2H), 3.92 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 191.0, 153.6 (2C), 143.5, 131.7, 106.6 (2C), 61.0, 56.2 (2C). HRMS $C_{10}H_{12}O_4$ [M + $H^+$]; calculated 197.0814, found 197.0808.

**2,4-Dimethoxybenzaldehyde (9).**[23] Flash chromatography using pentane/EtOAc 20:1 → 5:1 as eluent resulted in 70 mg (84% yield) of the title product obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 10.27 (s, 1H), 7.79 (d, 1H, $J$ = 8.6 Hz), 6.53 (dd, 1H, $J$ = 2.1; 8.6 Hz), 6.43 (d, 1H, $J$ = 2.1 Hz), 3.88 (s, 3H), 3.86 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 188.3, 166.2, 163.6, 130.7, 119.0, 105.7, 97.9, 55.59, 55.57. HRMS $C_9H_{10}O_3$ [M + $Na^+$]; calculated 189.0528, found 189.0525.

**3,4-Dimethoxybenzaldehyde (10).**[24] Flash chromatography using pentane/EtOAc 10:1 as eluent resulted in 80 mg (96% yield) of the title product obtained as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 9.86 (s, 1H), 7.46 (dd, 2H, $J$ = 2.9, 8.3 Hz), 7.41 (d, 2H, $J$ = 2.9 Hz), 6.91 (t, 2H, $J$ = 8.3 Hz), 3.98 (s, 3H), 3.94 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 190.8, 154.4, 149.6, 130.1, 126.8, 110.4, 108.9, 56.1, 55.9. HRMS $C_9H_{10}O_3$ [M + $H^+$]; calculated 167.0708, found 167.0700.

**3-Fluoro-5-methylbenzaldehyde (11).** Flash chromatography using pentane/EtOAc 30:1 as eluent resulted in 66 mg (96% yield) of the title product obtained as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 9.93 (s, 1H), 7.47 (s, 1H), 7.35 (d, 2H, $J$ = 8.6 Hz), 7.13 (d, 2H, $J$ = 8.6 Hz), 2.40 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 191.0 (d, $J$ = 2.5 Hz), 163.0 (d, $J$ = 249.2 Hz), 141.5 (d, $J$ = 7.7 Hz), 138.2 (d, $J$ = 6.8 Hz), 127.0 (d, $J$ = 2.5 Hz), 122.1 (d, $J$ = 22.0 Hz), 112.6 (d, $J$ = 21.6 Hz), 21.1. $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ (ppm) −112.6 (t, $J$ = 8.8 Hz). HRMS $C_8H_7FO$ [M + $H^+$]; calculated 139.0559, found 139.0551.

**4-(*tert*-Butyl)benzaldehyde (12).**[25] Flash chromatography using pentane/EtOAc 20:1 as eluent resulted in 70 mg (86% yield) of the title product obtained as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 9.97 (s, 1H), 7.82 (d, $J$ = 8.7 Hz, 2H), 7.55 (d, $J$ = 8.7 Hz, 2H), 1.35 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 192.1, 158.4, 134.0, 129.7 (2C), 126.0 (2C), 35.3, 31.1 (3C). HRMS $C_{11}H_{14}O$ [M + $H^+$]; calculated 163.1123, found 163.1116.

**4-(2-Methyl-1,3-dioxolan-2-yl)benzaldehyde (13).**[26] Flash chromatography using pentane/EtOAc 20:1 as eluent resulted in 86 mg (89% yield) of the title product obtained as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 10.02 (s, 1H), 7.86 (d, 2H, $J$ = 8.7 Hz), 7.66 (d, 2H, $J$ = 8.7 Hz), 4.11−4.02 (m, 2H), 3.81−3.73 (m, 2H), 1.66 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 191.9, 150.0, 136.0, 129.8 (2C), 126.0 (2C), 108.4, 64.6 (2C), 27.4. HRMS $C_{11}H_{12}O_3$ [M + $H^+$]; calculated 193.0865, found 193.0872.

**1*H*-Indole-3-carbaldehyde (14).**[27] Flash chromatography using pentane/EtOAc 5:1 as eluent resulted in 49 mg (68% yield) of the title product obtained as a colorless solid. $^1$H NMR (400 MHz, DMSO) $\delta$ (ppm) 12.10 (br s, 1H), 9.92 (s, 1H), 8.26 (d, 1H, $J$ = 3.14 Hz), 8.07 (d, 1H, $J$ = 7.39 Hz), 7.49 (d, 1H, $J$ = 7.69 Hz), 7.26−7.18 (m, 2H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ (ppm) 185.4, 138.9, 137.5, 124.6, 123.9, 122.6, 121.3, 118.6, 112.9; HRMS $C_9H_8NO$ [M + $H^+$]; calculated 146.0606, found 146.0602.

***tert*-Butyl (4-Formylphenyl)carbamate (15).**[28] Flash chromatography using pentane/EtOAc 20:1 as eluent resulted in 88 mg (79% yield) of the title product obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 9.88 (s, 1H), 7.81 (d, 2H, $J$ = 8.7 Hz), 7.53 (d, 2H, $J$ = 8.7 Hz), 6.88 (br s, 1H), 1.52 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 191.0, 152.0, 144.2, 131.3, 131.2 (2C), 117.8 (2C), 81.5, 28.2. HRMS $C_{12}H_{15}NO_3$ [M + $Na^+$]; calculated 244.0950, found 244.0947.

**4-Amino-3,5-dichlorobenzaldehyde (16).** Flash chromatography using pentane/EtOAc 10:1 as eluent resulted in 76 mg (79% yield) of the title product obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 9.69 (s, 1H), 7.71 (s, 2H), 5.02 (br s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 188.3, 145.3, 129.6, 128.9, 128.4, 127.1, 119.2. HRMS $C_7H_5Cl_2NO$ [M + $Na^+$]; calculated 211.9646, found 211.9643.

**4-Methylamino-benzaldehyde (17).**[29] Flash chromatography using pentane/EtOAc 2:1 as eluent resulted in 47 mg (70% yield) of the title product obtained as a yellow solid. $^1$H NMR (400 MHz,


dx.doi.org/10.1021/jo400741t | J. Org. Chem. 2013, 78, 6112−6120

$CDCl_3$) $\delta$ (ppm) 9.79 (s, 1H), 7.70 (d, 2H, $J$ = 8.6 Hz), 6.70 (d, 2H, $J$ = 8.6 Hz), 4.45 (br s, 1H), 2.92 (d, 3H, $J$ = 4.9 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 190.3, 154.3, 132.3, 129.6, 126.3, 122.4, 111.5, 30.0. HRMS $C_8H_9NO$ [M + $Na^+$]; calculated 158.0582, found 158.0579.

**[$^{13}$C]-4-Methylamino-benzaldehyde ($^{13}$C-17).** Flash chromatography using pentane/EtOAc 3:1 as eluent resulted in 47 mg (69% yield) of the title product obtained as a yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 9.71 (d, 1H, $J$ = 170.4 Hz), 7.69 (dd, 2H, $J$ = 8.5, 4.9 Hz), 6.60 (d, 2H, $J$ = 8.5), 4.57 (br s, 1H), 2.90 (d, 3H, $J$ = 4.9 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 190.4 ($^{13}$C-enriched). HRMS $C_7{}^{13}CH_9NO$ [M + $Na^+$]; calculated 159.0615, found 159.0621.

**Ethyl 4-Formylbenzoate (18).**[30] Flash chromatography using pentane/$CH_2Cl_2$/EtOAc 10:2:1 as eluent resulted in 73 mg (82% yield) of the title product obtained as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 10.10 (s, 1H), 8.20 (d, 1H, $J$ = 8.0 Hz), 7.95 (d, 1H, $J$ = 8.0 Hz), 4.42 (q, 2H, $J$ = 7.2 Hz), 1.42 (t, 3H, $J$ = 7.2 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 191.6, 165.5, 139.0, 135.4, 130.1 (2C), 129.5 (2C), 61.6, 14.3. HRMS $C_{10}H_{10}O_3$ [M + $H^+$]; calculated 179.0708, found 179.0712.

**[D]-Ethyl 4-Formylbenzoate ([D]-18).** Flash chromatography using pentane/$CH_2Cl_2$/EtOAc 10:2:1 as eluent resulted in 73 mg (82% yield) of the title product obtained as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 8.20 (d, 1H, $J$ = 8.0 Hz), 7.95 (d, 1H, $J$ = 8.0 Hz), 4.42 (q, 2H, $J$ = 7.2 Hz), 1.42 (t, 3H, $J$ = 7.2 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 191.4 (t, $J$ = 27.7 Hz), 165.5, 143.3, 135.4, 130.1 (2C), 129.4 (2C), 61.6, 14.2. HRMS $C_{10}H_{10}DO_3$ [M + $H^+$]; calculated 180.0771, found 180.0778.

**Nicotinaldehyde (19).**[31] Flash chromatography using pentane/EtOAc 1:1 as eluent resulted in 42 mg (78% yield) of the title product obtained as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 10.13 (s, 1H), 9.09 (d, 1H, $J$ = 2.1 Hz), 8.86 (dd, 1H, $J$ = 4.6, 2.1 Hz), 8.18 (dt, 1H, $J$ = 7.9, 2.0 Hz), 7.5 (dd, 1H, $J$ = 4.6, 7.9 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 190.7, 154.6, 151.9, 135.8, 131.4, 124.6. HRMS $C_6H_5NO$ [M + $H^+$]; calculated 108.0449, found 108.0441.

***tert*-Butyl (2-Formylphenyl)carbamate (20).**[32] Flash chromatography using $CH_2Cl_2$/pentane 3:2 as eluent resulted in 86 mg (78% yield) of the title product obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 10.39 (br s, 1H), 9.89 (s, 1H), 8.45 (d, 1H, $J$ = 8.5 Hz), 7.62 (d, 1H, $J$ = 7.5 Hz), 7.56 (t, 1H, $J$ = 7.5 Hz), 7.13 (t, 1H, $J$ = 7.5 Hz), 1.53 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 195.0, 152.8, 141.8, 136.0, 135.9, 121.5, 121.2, 118.2, 80.9, 28.3 (3C). HRMS $C_{12}H_{15}NO_3$ [M + $Na^+$]; calculated 244.0950, found 244.0946.

**[$^{13}$C]-*tert*-Butyl (2-Formylphenyl)carbamate ($^{13}$C-20).** Flash chromatography using $CH_2Cl_2$/pentane 3:2 as eluent resulted in 92 mg (83% yield) of the title product obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 10.39 (br s, 1H), 9.89 (d, 2H, $J$ = 175.9 Hz), 8.45 (d, 1H, $J$ = 8.7 Hz), 7.62 (t, 1H, $J$ = 7.5 Hz), 7.55 (t, 1H, $J$ = 7.5 Hz), 7.13 (t, 1H, $J$ = 7.5 Hz), 1.53 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 195.0 ($^{13}$C-enriched). HRMS $C_{11}{}^{13}CH_{15}NO_3$ [M + $Na^+$]; calculated 245.0983, found 245.0976.

**4-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)benzaldehyde (21).**[33] Flash chromatography using pentane/EtOAc 2:1 as eluent resulted in 89 mg (73% yield) of the title product obtained as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 9.84 (s, 1H), 7.78 (d, 2H, $J$ = 8.7 Hz), 6.98 (d, 2H, $J$ = 8.7 Hz), 4.57 (dd, 1H, $J$ = 4.2; 3.2 Hz), 4.46 (dd, 1H, $J$ = 4.2; 3.2 Hz), 4.18 (dd, 2H, $J$ = 5.9; 4.7 Hz), 3.86 (dd, 2H, $J$ = 5.9; 4.7 Hz), 3.73−3.66 (m, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 190.8, 154.4, 149.6, 130.1, 126.8, 110.4, 108.9, 56.1, 55.9. $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ (ppm) 7.89 (tt, $J$ = 28.7, 47.8 Hz). HRMS $C_{13}H_{17}FO_4$ [M + $Na^+$]; calculated 279.1009, found 279.1019.

**3-Formyl-*N*-(6-methylpyridin-2-yl)benzamide (22).** Flash chromatography using pentane/EtOAc 5:1 as eluent resulted in 88 mg (73% yield) of the title product obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 10.10 (s, 1H), 8.59 (br s, 1H), 8.42 (s, 1H), 8.21 (d, 1H, $J$ = 7.9 Hz), 8.17 (d, 1H, $J$ = 8.3 Hz), 8.08 (d, 1H, $J$ = 7.8 Hz), 7.71−7.65 (m, 2H), 6.96 (d, 1H, $J$ = 7.1 Hz), 2.48 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 191.2, 164.3, 157.0, 150.5, 138.8, 136.7, 135.4, 133.0, 132.7, 129.7, 128.3, 119.8, 111.0, 23.9. HRMS $C_{14}H_{12}N_2O_2$ [M + $H^+$]; calculated 241.0977, found 241.0976.

***N*-(5-Formylpyridin-2-yl)cyclopropanecarboxamide (23).** Flash chromatography using pentane/EtOAc 1:1 as eluent resulted in 80 mg (84% yield) of the title product obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 9.98 (s, 1H), 8.95 (br s, 1H), 8.75 (d, 1H, $J$ = 1.9 Hz), 8.37 (d, 1H, $J$ = 8.7 Hz), 8.16 (dd, 1H, $J$ = 8.7, 1.9 Hz), 1.62 (tt, 1H, $J$ = 7.8, 4.5 Hz), 1.15 (dt, 2H, $J$ = 7.8, 4.5 Hz), 0.95 (dt, 2H, $J$ = 7.8, 4.5 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 189.4, 172.8, 155.4, 151.3, 138.9, 128.1, 113.7, 16.1, 9.1 (2C). HRMS $C_{10}H_{10}N_2O_2$ [M + $H^+$]; calculated 191.0821, found 191.0814.

**Synthesis of 23 by Reductive Carbonylation: 3 mmol Scale.** *Chamber 1*: To chamber 1 of the two-chamber system was added $Pd(dba)_2$ (85.8 mg, 0.15 mmol), $HBF_4{\cdot}PCy_3$ (64.8 mg, 0.15 mmol), $KHCO_2$ (0.498 g, 6.0 mmol), TBAI (0.33 g, 0.9 mmol), and *N*-(5-iodopyridin-2-yl)cyclopropanecarboxamide (0.865 g, 3 mmol) in that order. The chamber was flushed with argon and sealed with a screwcap fitted with a Teflon seal, and acetonitrile (18 mL) was added. *Chamber 2*: To chamber 2 of the two-chamber system was added $HBF_4{\cdot}P(t\text{Bu})_3$ (13.1 mg, 0.045 mmol), Pd[COD]$Cl_2$ (12.8 mg, 0.045 mmol), and 9-methyl-9*H*-fluorene-9-carbonyl chloride (1.09 g, 4.5 mmol). The chamber was flushed with argon and sealed with a screwcap fitted with a Teflon seal, and acetonitrile (18 mL) and $Cy_2NMe$ (1.9 mL, 9 mmol) were added. The loaded two-chamber system was heated to 80 °C for 18 h. Upon concentration of chamber 2 in vacuo the crude product was purified by column chromatography and using pentane/EtOAc 1:1 as eluent resulted in 489 mg (86% yield) of the title product obtained as a colorless solid.

**Isopropyl 2-(4-Formylphenoxy)-2-methylpropanoate (24).** Flash chromatography using pentane/EtOAc 20:1 as eluent resulted in 113 mg (91% yield) of the title product obtained as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 9.87 (s, 1H), 7.7 (d, 2H, $J$ = 8.8 Hz), 6.89 (d, 2H, $J$ = 8.8 Hz), 5.07 (sept., 1H, $J$ = 6.4 Hz), 1.65 (s, 6H), 1.18 (s, 3H), 1.17 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 190.7, 172.9, 161.0, 131.4 (2C), 130.2, 117.6 (2C), 79.5, 69.4, 25.3 (2C), 21.5 (2C). HRMS $C_{14}H_{18}O_4$ [M + $Na^+$]; calculated 273.1103, found 273.1117.

**[D]-Isopropyl 2-(4-formylphenoxy)-2-methylpropanoate ([D]-24).** Flash chromatography using pentane/EtOAc 20:1 as eluent resulted in 104 mg (83% yield) of the title product obtained as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.7 (d, 2H, $J$ = 8.8 Hz), 6.89 (d, 2H, $J$ = 8.8 Hz), 5.07 (sept., 1H, $J$ = 6.4 Hz), 1.65 (s, 6H), 1.18 (s, 3H), 1.17 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 190.7 (t, $J$ = 25.7 Hz), 172.9, 161.0, 131.4 (2C), 130.2, 117.6 (2C), 79.5, 69.4, 25.3 (2C), 21.5 (2C). HRMS $C_{14}H_{17}DO_4$ [M + $Na^+$]; calculated 274.1166, found 274.1172.

**[D-$^{13}$C]-Isopropyl 2-(4-formylphenoxy)-2-methylpropanoate ([D,$^{13}$C]-24).** Flash chromatography using pentane/EtOAc 20:1 as eluent resulted in 109 mg (86% yield) of the title product obtained as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.70 (dd, 2H, $J$ = 4.5; 8.8 Hz), 6.89 (d, 2H, $J$ = 8.8 Hz), 5.07 (sept, 1H, $J$ = 6.4 Hz), 1.65 (s, 6H), 1.18 (s, 3H), 1.17 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 190.7 (t, $J$ = 25.7 Hz), 172.9, 161.0, 131.4 (2C), 130.2, 117.6 (2C), 79.5, 69.4, 25.3 (2C), 21.5 (2C). HRMS $C_{14}H_{17}DO_4$ [M + $H^+$]; calculated 253.1380, found 253.1374.

**General Procedure for Reductive Carbonylation of Aryl and Heteroaryl Bromides.** *Chamber 1*: $Pd(dba)_2$ (14.4 mg, 0.0250 mmol), $PCy_3HBF_4$ (10.8 mg, 0.0250 mmol), $KHCO_2$ (83 mg, 1.0 mmol), TBAI (55 mg, 0.15 mmol), and the aryl bromide (0.500 mmol) were weighed out and added to chamber 1 of the two-chamber system. Butyronitrile (3 mL) was then added, and the chamber was sealed with a screw-cap fitted with a silicone/PTFE seal. *Chamber 2*: To chamber 2 of the two-chamber system, the following reagents and solvent were added in the order as indicated: $P(t\text{Bu})_3HBF_4$ (10.9 mg, 0.0375 mmol), Pd[COD]$Cl_2$ (10.7 mg, 0.0375 mmol), 9-methylfluorene-9-carbonyl chloride (182 mg, 0.75 mmol), butyronitrile (3 mL), and $Cy_2NMe$ (320 $\mu$L, 1.5 mmol). The chamber was sealed with a screwcap fitted with a silicone/PTFEseal. The loaded two-chamber system was removed from the glovebox and heated to 100 °C for 18 h.


dx.doi.org/10.1021/jo400741t | *J. Org. Chem.* 2013, 78, 6112−6120

Upon concentration of chamber 2 in vacuo the crude product was purified by column chromatography.

**2-(*n*-Hexyloxy)benzaldehyde (25).**[34] Flash chromatography using pentane/EtOAc 30:1 as eluent resulted in 75 mg (72% yield) of the title product obtained as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 10.52 (s, 1H), 7.82 (dd, 1H, $J$ = 7.9, 1.9 Hz), 7.52 (dt, 1H, 1.9 Hz, 8.6 Hz), 7.1−6.96 (m, 2H), 4.07 (t, 2H, $J$ = 6.8 Hz), 1.82−1.80 (m, 2H), 1.52−1.45 (m, 2H), 1.39−1.25 (m, 4H), 0.93−0.88 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 189.9, 161.6, 135.9, 128.2, 124.9, 120.4, 112.5, 68.5, 31.5, 29.0, 25.7, 22.6, 14.0. HRMS $C_{13}H_{18}O_2$ [M + $H^+$]; calculated 207.1385, found 207.1381.

***N*-Allyl-4-formylbenzamide (26).** Flash chromatography using pentane/EtOAc 2:1 as eluent resulted in 68 mg (72% yield) of the title product obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 9.82 (s, 1H), 7.40−7.37 (m, 2H), 6.97 (d, 2H, $J$ = 8.94), 4.34−4.27 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 190.7, 149.2, 143.9, 130.6, 124.2, 118.4, 117.8, 64.7, 64.0. HRMS $C_{11}H_{11}NO_2$ [M + $H^+$]; calculated 190.0868, found 190.0863.

**Isoquinoline-4-carbaldehyde (27).**[35] Flash chromatography using pentane/EtOAc 1:1 as eluent resulted in 35 mg (45% yield) of the title product obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 10.52 (s, 1H), 9.21 (d, 1H, $J$ = 4.3 Hz), 9.02 (dd, 1H, $J$ = 8.5; 1.5 Hz), 8.22 (d, 1H, $J$ = 8.5 Hz), 7.83 (dt, 1H, $J$ = 7.0; 1.5 Hz), 7.80 (d, 1H, $J$ = 4.3 Hz), 7.74 (dt, 1H, $J$ = 7.0; 1.5 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 192.8, 150.4, 149.2, 136.8, 130.2, 130.0, 129.4, 125.8, 124.4, 123.9. HRMS $C_{10}H_8NO$ [M + $H^+$]; calculated 158.0606, found 158.0602.

**2,3-Dihydrobenzo[*b*][1,4]dioxine-6-carbaldehyde (28).**[36] Flash chromatography using pentane/EtOAc 10:1 as eluent resulted in 65 mg (81% yield) of the title product obtained as a yellow liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 9.82 (s, 1H), 7.40−7.37 (m, 2H), 6.97 (d, 2H, $J$ = 8.94), 4.34−4.27 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 190.7, 149.2, 143.9, 130.6, 124.2, 118.4, 117.8, 64.7, 64.0. HRMS $C_9H_8O_3$ [M + $H^+$]; calculated 165.0552, found 165.0548.

**3-Chloro-4-methoxybenzaldehyde (29).**[37] Flash chromatography using pentane/EtOAc 10:1 as eluent resulted in 75 mg (88% yield) of the title product obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 9.83 (s, 1H), 7.88 (d, 1H, $J$ = 1.9 Hz), 7.75 (dd, 1H, $J$ = 8.4, 1.9 Hz), 7.02 (d, 1H, $J$ = 8.4 Hz), 3.97 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 189.7, 159.8, 131.1, 130.6, 130.2, 123.6, 111.7, 56.5. HRMS $C_8H_8ClO_2$ [M + $H^+$]; calculated 171.0213, found 171.0208.

**4-(*n*-Decyloxy)-3,5-dimethoxybenzaldehyde (30).** Flash chromatography using pentane/EtOAc 30:1 as eluent resulted in 110 mg (68% yield) of the title product obtained as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 9.84 (s, 1H), 7.10 (s, 2H), 4.05 (t, 2H, $J$ = 6.7 Hz), 3.89 (s, 6H), 1.74 (quin., 2H, $J$ = 7.2 Hz), 1.46−1.39 (m, 2H), 1.34−1.23 (m, 12 H), 0.86 (t, 3 H, $J$ = 7.6 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 191.1, 153.9 (2C), 142.0, 131.5, 106.7 (2C), 73.7, 56.2 (2C), 31.9, 30.1, 29.6, 29.5, 29.4, 29.3, 25.7, 22.7, 14.1. HRMS $C_{19}H_{30}O_4$ [M + $H^+$]; calculated 323.2222, found 323.2218.

**4-(Morpholine-4-carbonyl)benzaldehyde (31).**[38] Flash chromatography using EtOAc/pentane 2:1 as eluent resulted in 80 mg (73% yield) of the title product obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 10.02 (s, 1H), 7.92 (d, 2H, $J$ = 8.3 Hz), 7.54 (d, 2H, $J$ = 8.3 Hz), 3.77−3.37 (m, 8H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 191.4, 168.9, 140.9, 137.0, 129.9 (2C), 127.7 (2C), 66.7 (4C). HRMS $C_{12}H_{14}NO_3$ [M + $H^+$]; calculated 220.0974, found 220.0968.

**4-*n*-Butylbenzaldehyde (32).**[39] Flash chromatography using pentane/EtOAc 50:1 as eluent resulted in 79 mg (98% yield) of the title product obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 9.96 (s, 1H), 7.79 (d, 2H, $J$ = 8.3 Hz), 7.33 (d, 2H, $J$ = 8.3 Hz), 2.68 (t, 2H, $J$ = 7.8 Hz), 1.62 (quin., 2H, $J$ = 7.8 Hz), 1.36 (hex., 2H, $J$ = 7.8 Hz), 0.93 (t, 3H, $J$ = 7.8 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 191.9, 150.4, 134.4, 129.9 (2C), 129.0 (2C), 35.9, 33.2, 22.3, 13.9. HRMS $C_{11}H_{14}O$ [M + $H^+$]; calculated 163.1123, found 163.1123.

**2-(2-(2-(p-Tolyloxy)ethoxy)ethoxy)ethanol.** To *p*-cresol (2.2 g, 20 mmol) in DMF (8 mL) was added $K_2CO_3$ (5.2 g, 30 mmol), NaI (0.3 g, 2 mmol), and triethylene glycol monohydrinhydrin (4.1 g, 24 mmol), and the reaction mixture was heated to 95 °C for 18 h. The reaction mixture was cooled to rt and diluted with EtOAc. The organic phase was washed twice with water and once with brine, dried over $Na_2SO_4$, and concentrated under vacuum. Flash chromatography using pentane/EtOAc 1:1 → EtOAc as eluent resulted in 4.1 g (86% yield) of the title product obtained as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.06 (d, 2H, $J$ = 8.6 Hz), 6.81 (d, 2H, $J$ = 8.6 Hz), 4.11−4.09 (m, 2H), 3.85−3.83 (m, 2H), 3.74−3.60 (m, 8H), 2.27 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 156.6, 130.1, 129.8 (2C), 114.5 (2C), 72.5, 70.8, 70.4, 69.8, 67.4, 61.7, 20.4; HRMS $C_{13}H_{20}O_4$ [M + $Na^+$]; calculated 263.1259, found 263.1265.

**2-(2-(2-(*p*-Tolyloxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate.** To 2-(2-(2-(*p*-tolyloxy)ethoxy)ethoxy)ethanol (2.4 g, 10 mmol) in $CH_2Cl_2$ (8 mL) under cooling were added TsCl (2.3 g, 12 mmol), $Et_3N$ (7 mL, 50 mmol) and a catalytic amount of DMAP. The reaction mixture was maintained at 0 °C for 0.5 h and left at rt for 1 h. The mixture was then washed twice with water and once with brine, dried over $Na_2SO_4$, and concentrated in vacuum. Flash chromatography using pentane/EtOAc 1:1 → EtOAc as eluent resulted in 3.8 g (97% yield) of the title product obtained as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.79 (d, 2H, $J$ = 8.30 Hz), 7.32 (d, 2H, $J$ = Hz), 7.06 (d, 2H, $J$ = 8.7 Hz), 6.8 (d, 2H, $J$ = 8.7 Hz), 4.17−4.14 (m, 2H), 4.08−4.06 (m, 2H), 3.81−3.78 (m, 2H), 3.70−3.67 (m, 2H), 3.66−3.64 (m, 2H), 3.61−3.59 (m, 2H), 2.42 (s, 3H), 2.28 (2, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 156.6, 144.8, 133.0, 130.0, 129.84 (2C), 129.79 (2C), 128.0 (2C), 114.5 (2C), 70.77, 70.73, 69.9, 69.4, 68.7, 67.5, 21.6, 20.4.

**1-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)-4-methylbenzene.**[40] To a solution of 2-(2-(2-(*p*-tolyloxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (1.3 g, 3.3 mmol) in THF was added TBAF (1.0 M in THF, 9 mL). The reaction was heated in a microwave reactor at 110 °C for 0.5 h. After cooling and concentration in vacuum, the residue was purified by flash chromatography using pentane/EtOAc 5:1 as eluent to afford the title compound as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.07 (d, 2H, $J$ = 8.6 Hz), 6.81 (d, 2H, $J$ = 8.6 Hz), 4.63−4.61 (m, 1H), 4.51−4.49 (m, 1H), 4.12−4.10 (m, 2H), 3.86−3.84 (m, 2H), 3.80−3.78 (m, 1H), 3.76−3.70 (m, 5H), 2.28 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 156.6, 130.0, 129.8, 114.5, 83.2 (d, $J$ = 169 Hz), 70.8, 70.5, 70.3, 69.9, 67.5, 20.4. $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ (ppm) 7.79 (tt, $J$ = 29.5, 47.7 Hz); HRMS $C_{13}H_{19}FO_3$ [M + $Na^+$]; calculated 265.1216, found 265.1210.

**1-(Bromomethyl)-4-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)-benzene.**[40] A mixture of 1-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)-4-methylbenzene (0.72 g, 3.0 mmol), NBS (0.56 g, 3.3 mmol), and benzoyl peroxide (50 mg) in dry $CCl_4$ was heated to reflux for 4 h and cooled to rt, and the white precipitate was removed by filtration. The filtrate was concentrated under vacuum and subjected to flash chromatography to afford the product (0.72 g, 75%) as a colorless liquid. Some impurities were still evident and the compound was used without further purification.

**Diethyl 4-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)-benzylphosphonate (33).**[40] To a solution of 1-(bromomethyl)-4-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)benzene (0.51 g, 1.6 mmol) in dry $CH_2Cl_2$ were added triethyl phosphite (0.33 g, 2 mmol) and $ZnBr_2$ (0.33 mmol, 74 mg). The reaction mixture was stirred at rt for 18 h, concentrated in vacuum, and subjected to flash chromatography to afford the product (0.37 g, 61%) as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.19 (d, 2H, $J$ = 9.0 Hz), 6.84 (d, 2H, $J$ = 9.0 Hz), 4.55 (dt, 2H, $J$ = 47.5, 4.6 Hz), 4.10 (t, 2H, $J$ = 4.7 Hz), 4.03−3.93 (m, 4H), 3.84 (t, 2H, 4.7 Hz), 3.80−3.77 (m, 1H), 3.75−3.68 (m, 5H), 3.06 (d, 2H, $J$ = 21.6 Hz), 1.22 (t, 6H, $J$ = 7.2 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 157.7 (d, $J$ = 3.5 Hz), 130.7 (d, 2C, $J$ = 6.7 Hz), 123.7 (d, $J$ = 9.3 Hz), 114.7 (d, 2C, $J$ = 3.0 Hz), 83.2 (d, $J$ = 169.4 Hz), 70.8 (d, $J$ = 1.2 Hz), 70.5, 70.3, 69.8, 67.4, 62.0 (d, $J$ = 6.8 Hz), 32.8 (d, 2C, $J$ = 138.8 Hz), 16.4 (d, 2C, $J$ = 6.1 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ (ppm) 7.79 (tt, $J$ = 28.9, 48.0 Hz). $^{31}$P NMR


dx.doi.org/10.1021/jo400741t | J. Org. Chem. 2013, 78, 6112−6120

(162 MHz, $CDCl_3$) $\delta$ (ppm) 26.7. HRMS $C_{17}H_{28}FO_6P$ [M + $Na^+$]; calculated 401.1505, found 401.1498.

**(*E*)-4-(4-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)styryl)-*N*-methylaniline (34)[41] (Florbetaben).** Aldehyde **17** (27 mg, 0.2 mmol) dissolved in DMF was added dropwise at room temperature to a solution of phosphonate **33** (109 mg, 0.3 mmol) and NaOEt (20 mg, 0.3 mmol) in dry DMF, and the reaction was then heated to 60 °C overnight. The reaction mixture was diluted with $CH_2Cl_2$, washed twice with water and once with brine, dried over $MgSO_4$, and concentrated in vacuum. Flash chromatography using $CH_2Cl_2$ → $CH_2Cl_2/Et_2O$ as eluent resulted in 50 mg (69% yield) of the title product obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.39 (d, 2H, $J$ = 8.5 Hz), 7.34 (d, 2H, $J$ = 8.5 Hz), 6.90−6.87 (m, 4H), 6.63 (d, 2H, $J$ = 8.5 Hz), 4.58 (dt, 2H, $J$ = 47.7, 4.1 Hz), 4.15 (d, 2H, $J$ = 4.7 Hz), 3.87 (d, 2H, $J$ = 5.2 Hz), 3.80 (t, 1H, $J$ = 4.5 Hz), 3.77−3.71 (m, 6H), 2.86 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 157.8, 148.69, 148.65, 131.1, 127.4 (2C), 127.1 (2C), 127.0, 126.9, 124.0, 114.8 (2C), 112.5, 83.2 (d, $J$ = 168.9 Hz), 70.8 (d, $J$ = 1.5 Hz), 70.5, 70.3, 69.8, 67.4, 30.7. $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ (ppm) 7.90 (tt, $J$ = 29.4, 47.4 Hz). HRMS $C_{21}H_{26}FNO_3$ [M + $Na^+$]; calculated 382.1794, found 382.1794.

**[$^{13}$C]-(*E*)-4-(4-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)styryl)-*N*-methylaniline ($^{13}$C-34) ([$^{13}$C]-Florbetaben).** Aldehyde $^{13}$C-**17** (27 mg, 0.2 mmol) dissolved in DMF was added dropwise at room temperature to a solution of phosphonate **33** (109 mg, 0.3 mmol) and NaOEt (20 mg, 0.3 mmol) in dry DMF, and the reaction was then heated to 60 °C overnight. The reaction mixture was diluted with $CH_2Cl_2$, washed twice with water and once with brine, dried over $MgSO_4$, and concentrated in vacuum. Flash chromatography using $CH_2Cl_2$ → $CH_2Cl_2/Et_2O$ as eluent resulted in 46 mg (64% yield) of the title product obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.41 (d, 2H, $J$ = 8.3 Hz), 7.34 (d, 2H, $J$ = 8.3 Hz), 6.90−6.87 (m, 4H), 6.61 (d, 2H, $J$ = 8.3 Hz), 4.53 (dt, 2H, $J$ = 47.9, 4.3 Hz), 4.15 (d, 2H, $J$ = 4.1 Hz), 3.87 (d, 2H, $J$ = 5.2 Hz), 3.76 (t, 1H, $J$ = 4.5 Hz), 3.77−3.71 (m, 6H), 2.86 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 126.9 ($^{13}$C-enriched). $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ (ppm) 7.90 (tt, $J$ = 29.1, 47.1 Hz). HRMS $C_{20}{}^{13}CH_{26}FNO_3$ [M + $Na^+$]; calculated 383.1828, found 383.1833.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Initial optimizations toward the reductive carbonylation of aryl iodide **1**, procedures for the synthesis of phosphonate ester **33** from *p*-cresol, and copies of $^1$H NMR and $^{13}$C NMR spectra for all end products. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: rt@chem.au.dk (R.H.T.), ts@chem.au.dk (T.S.).


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We are deeply appreciative of generous financial support from the Danish National Research Foundation, the Danish Natural Science Research Council, the Carlsberg Foundation, the Lundbeck Foundation, iNANO, and Aarhus University.

## ■ REFERENCES


(1) (a) Kürti, T.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: Burlington, 2005. (b) Mundy, B. P.; Ellerd, M. G.; Favaloro, F. G., Jr. *Name Reactions and Reagents in Organic Synthesis*; John Wiley & Sons, Inc.: Hoboken, NJ, 2005.

(2) (a) Starkey, L. S., Ed. *Introduction to Strategies for Organic Synthesis*; John Wiley & Sons: Hoboken, NJ, 2012; Chapter 3.9, pp 105−114. (b) Trost, B. M., Ed. *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol *8*, pp 259−305.

(3) (a) Thompson, A. F.; Cromwell, N. H. *J. Am. Chem. Soc.* **1939**, *61*, 1374. (b) Franzen, V. V. *Liebigs Ann. Chem.* **1956**, *600*, 109. (c) Seebach, D.; Erickson, B. W.; Singh, G. *J. Org. Chem.* **1966**, *31*, 4303. (d) Bennett, D. J.; Kirby, G. W.; Moss, V. A. *J. Chem. Soc., Chem. Commun.* **1967**, 218. (e) Olofson, R. A.; Zimmerman, D. M. *J. Am. Chem. Soc.* **1967**, *89*, 5057. (f) Craig, J. C.; Kray, L. R. *J. Org. Chem.* **1968**, *33*, 871. (g) Axenrod, T. A.; Loew, L.; Pregosin, P. S. *J. Org. Chem.* **1968**, *33*, 1274. (h) Scott, C. A.; Smith, D. G.; Smith, D. J. H. *Synth. Commun.* **1976**, *6*, 135. (i) Degani, I.; Fochi, R. *Synthesis* **1976**, 759. (j) Meyers, A. I.; Nabeya, A.; Adickes, H. W.; Politzer, I. R. *J. Am. Chem. Soc.* **1969**, *91*, 763. (k) Schowen, R. L.; Burgstahler, A. W.; Walker, D. E.; Kuebrich, J. P. *J. Org. Chem.* **1972**, *37*, 1272. (l) Yamashita, M.; Miyoshi, K.; Nakazono, Y.; Suemitsu, R. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1663.

(4) (a) Northrop, D. B. *Methods Enzymol.* **1982**, *87*, 607. (b) Shao, L.; Hewitt, M. C. *Drug News Perspect.* **2010**, *23*, 398. (c) Fisher, M. B.; Henne, K. R.; Boer, J. *Curr. Opin. Drug Dev.* **2006**, *9*, 101. (d) Foster, A. B. *Advances in Drug Research*; Academic Press: London, 1985. (e) Foster, A. B. *Trends Pharmacol. Sci.* **1984**, *5*, 524.

(5) (a) Spletstoser, J. T.; White, J. M.; Georg, G. I. *Tetrahedron Lett.* **2004**, *45*, 2787. (b) Spletstoser, J. T.; White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2007**, *129*, 3408.

(6) (a) Klaus, S.; Neumann, H.; Zapf, A.; Strübing, D.; Hübner, S.; Almena, J.; Riermeier, T.; Groß, P.; Sarich, M.; Krahnert, W.-R.; Rossen, K.; Beller, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 154. (b) Brennführer, A.; Neumann, H.; Beller, M. *Synlett* **2007**, *2007*, 2537. (c) Mutin, R.; Lucas, C.; Thivolle-Cazat, J.; Dufaud, V.; Dany, F.; Basset, J. M. *J. Chem. Soc., Chem. Commun.* **1988**, 896. (d) Singh, A. S.; Bhanage, B. M.; Nagarkar, J. M. *Tetrahedron Lett.* **2011**, *52*, 2383. (e) Sergeev, A. G.; Spannenberg, A.; Beller, M. *J. Am. Chem. Soc.* **2008**, *130*, 15549.

(7) (a) Pri-Bar, I.; Buchman, O. *J. Org. Chem.* **1984**, *49*, 4009. (b) Pri-Bar, I.; Buchman, O. *J. Org. Chem.* **1988**, *53*, 624.

(8) (a) Hermange, P.; Lindhardt, A. T.; Taaning, R. H.; Bjerglund, K.; Lupp, D.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 6061. (b) Friis, S. D.; Taaning, R. H.; Lindhardt, A. T.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 18114. (c) Hermange, P.; Gøgsig, T. M.; Lindhardt, A. T.; Taaning, R. H.; Skrydstrup, T. *Org. Lett.* **2011**, *13*, 2444. (d) Nielsen, D. U.; Taaning, R. H.; Lindhardt, A. T.; Gøgsig, T. M.; Skrydstrup, T. *Org. Lett.* **2011**, *13*, 4454. (e) Xin, Z.; Gøgsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. *Org. Lett.* **2012**, *14*, 284. (f) Gøgsig, T. M.; Taaning, R. H.; Lindhardt, A. T.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 798. (g) Bjerglund, K.; Lindhardt, A. T.; Skrydstrup, T. *J. Org. Chem.* **2012**, *77*, 3793. (h) Gøgsig, T. M.; Nielsen, D. U.; Lindhardt, A. T.; Skrydstrup, T. *Org. Lett.* **2012**, *14*, 2536. (i) Burhardt, M. N.; Taaning, R.; Nielsen, N. C.; Skrydstrup, T. *J. Org. Chem.* **2012**, *77*, 5357. (j) Nielsen, D. U.; Neumann, K.; Taaning, R. H.; Lindhardt, A. T.; Modvig, A.; Skrydstrup, T. *J. Org. Chem.* **2012**, *77*, 6155. (k) *J. Labelled Compd. Radiopharm.* **2012**, *55*, 411. (l) Burhardt, M. N.; Taaning, R.; Nielsen, N. C.; Skrydstrup, T. *Org. Lett.* **2013**, *15*, 948.

(9) Korsager, S.; Taaning, R. H.; Skrydstrup, T. *J. Am. Chem. Soc.* **2013**, *135*, 2891.

(10) As the CO insertion step into the Pd−Aryl bond can be slow with aromatic ring systems possessing electron-deficient substituents, this will result in competitive reduction of the aryl halide: Ishiyama, T.; Kizaki, H.; Hayashi, T.; Suzuki, A.; Miyaura, N. *J. Org. Chem.* **1998**, *63*, 4726.

(11) Okano, T.; Harada, N.; Kiji, J. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2329.

(12) Garrou, P. E.; Heck, R. F. *J. Am. Chem. Soc.* **1976**, *98*, 4115.

(13) The optimization studies for the reductive carbonylation of 4-bromobenzonitrile can be found in the Supporting Information.

(14) (a) Cross, R. J. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. *9*, p 407. (b) Ankersmit, H. A.; Witte, P. T.; Kooijman, H.; Lakin, M. T.; Spek, A. L.; Goubitz, K.; Vrieze, K.;

Vankoten, G. *Inorg. Chem.* **1996**, *35*, 6053. (c) Stang, P. J.; Zhong, Z.; Arif, A. M. *Organometallics* **1992**, *11*, 1017. (d) Anderson, G. K.; Cross, R. J. *Acc. Chem. Res.* **1984**, *17*, 67. (e) Anderson, G. K.; Cross, R. J. *J. Chem. Soc., Dalton Trans.* **1980**, 712.
(15) (a) Pedersen, M. Ø.; Mikkelsen, K.; Behrens, M. A.; Pedersen, J. S.; Enghild, J. J.; Skrydstrup, T.; Malmendal, A.; Nielsen, N. C. *J. Phys. Chem. B* **2010**, *114*, 16003. (b) Huynh, T. H. V.; Mantel, M.; Mikkelsen, K.; Lindhardt, A. T.; Nielsen, N. C.; Otzen, D.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 999.
(16) Rule, G. S.; Hitchen, K. T. *Fundamentals of Protein NMR Spectroscopy*; Springer: Dordrecht, 2006.
(17) Florbetaben is an $^{18}$F-PET tracer recently launched by Bayer Healthcare for the early diagnosis of Alzheimers disease. Barthel, H.; Sabri, O. *J. Alzheimers Dis.* **2011**, *26*, 117.
(18) The synthesis of **33** is described in the Supporting Information.
(19) COgen, $^{13}$COgen, and COware are commercially available from Sigma-Aldrich and SyTracks.com.
(20) Hammadi, A.; Nuzillard, J. M.; Poulin, J. C.; Kagan, H. B. *Tetrahedron: Asymmetry* **1992**, *3*, 1247.
(21) Pelletier, G.; Bechara, W. S.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 12817.
(22) Li, W.; Li, J.; Wu, Y.; Fuller, N.; Markus, M. A. *J. Org. Chem.* **2010**, *75*, 1077.
(23) Rolfe, A.; Probst, D. A.; Volp, K. A.; Omar, I.; Flynn, D. L.; Hanson, P. R. *J. Org. Chem.* **2008**, *73*, 8785.
(24) Maddani, M.; Prabhu, K. R. *Tetrahedron Lett.* **2008**, *49*, 4526.
(25) Cui, L.-Q.; Liu, K.; Zhang, C. *Org. Biomol. Chem.* **2011**, *9*, 2258.
(26) Hyder, Z.; Mo, J.; Xiao, J. *Adv. Synth. Catal.* **2006**, *348*, 1699.
(27) Guillon, R.; Logé, C.; Pagniez, F.; Ferchaud-Roucher, V.; Duflos, M.; Picot, C.; Pape, P. L. *J. Enzym. Inhib. Med. Chem.* **2011**, *26*, 261.
(28) (a) Rai, R.; Katzenellenbogen, J. A. *J. Med. Chem.* **1992**, *35*, 4150. (b) Schadendorf, T.; Hoppmann, C.; Rück-Braun, K. *Tetrahedron Lett.* **2007**, *48*, 9044.
(29) Jiao, J.; Zhang, X.-R.; Chang, N.-H.; Wang, J.; Wei, J.-F.; Shi, X.-Y.; Chen, Z.-G. *J. Org. Chem.* **2011**, *76*, 1180.
(30) Shang, R.; Fu, Y.; Li, J.-B.; Zhang, S.-L.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 5738.
(31) Hossain, M. M.; Shyu, S.-G. *Adv. Synth. Catal.* **2010**, *352*, 3061.
(32) Nugent, B. M.; Williams, A. L.; Prabhakaran, E. N.; Johnston, J. N. *Tetrahedron* **2003**, *59*, 8877.
(33) Cui, M.; Ono, M.; Kimura, H.; Liu, B.; Saji, H. *J. Med. Chem.* **2011**, *54*, 2225.
(34) Robertson, L.; Hartley, R. C. *Tetrahedron* **2009**, *65*, 5284.
(35) Lipshutz, B. H.; Pfeiffer, S. S.; Chrisman, W. *Tetrahedron Lett.* **1999**, *40*, 7889.
(36) Koul, S.; Koul, J. L.; Taneja, S. C.; Dhar, K. L.; Jamwal, D. S.; Singh, K.; Reen, R. K.; Singh, J. *Bioorg. Med. Chem.* **2000**, *8*, 251.
(37) Watanabe, N.; Kabasawa, Y.; Takase, Y.; Matsukura, M.; Miyazaki, K.; Ishihara, H.; Kodama, K.; Adachi, H. *J. Med. Chem.* **1998**, *41*, 3367.
(38) Nitsche, C.; Steuer, C.; Klein, C. D. *Bioorg. Med. Chem.* **2011**, *19*, 7318.
(39) Zhou, W.-J.; Wang, K.-H.; Wang, J.-X. *J. Org. Chem.* **2009**, *74*, 5599.
(40) Shen, Q.; Wang, L.; Yu, J.; Liu, M.; Qiu, J.; Fang, L.; Guo, F.; Tang, J. *Synthesis* **2012**, *44*, 389.
(41) Chu, W.; Rothfuss, J.; Zhou, D.; Mach, R. H. *Bioorg. Med. Chem.* **2011**, *21*, 2192.