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# Threefold and chemoselective couplings of triarylbismuths with benzylic chlorides and iodides using palladium catalysis†

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This paper describes the palladium-catalyzed studies on threefold coupling of triarylbismuth reagents with benzylic chlorides and iodides. The optimized protocol conditions are operationally simple, delivering threefold coupling of a variety of triarylbismuths in combination with benzylic chlorides and iodides. The two optimized protocols allowed the synthesis of a diverse range of unsymmetrical diarylmethanes in an efficient manner. As part of this study, chemoselective transformation of benzylic chlorides and iodides was also achieved.

## Introduction

Bismuth compounds are user friendly reagents with high reactivity and selectivity for various transformations in organic synthesis.[1,2] The emphasis and utilization of bismuth reagents in organic synthesis is highly beneficial, as bismuth compounds are non-toxic and are used in medicinal and other applications.[3] Our focussed efforts in the utilization of triarylbismuths as threefold coupling reagents is conceptually novel and synthetically useful as this approach allows threefold coupling in one-pot operation with 1/3 loading of aryl organometallic nuclephiles.[4] As part of these efforts, we recently demonstrated the facile coupling reactivity of triarylbismuth reagents with benzylic bromides under Pd-catalyzed conditions.[5]

Importance of benzylic couplings originates from the fact that diarylmethanes are significant skeletons of biological and medicinal importance. For example, sergliflozin, dapagliflozin and tofogliflozin (Fig. 1) are recently investigated for Selective Sodium Glucose Cotransporter 2 (SGLT2) inhibition studies for type 2 diabetes applications.[6]

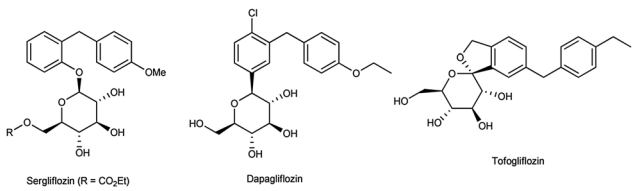


Fig. 1 A few examples of SGLT2 inhibitors.

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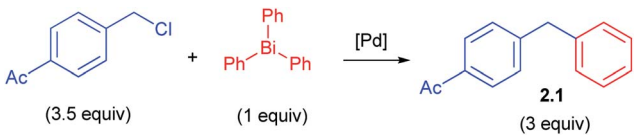
† Electronic supplementary information (ESI) available: Spectra for all the literature unknown products (including $^{1}H$ NMR, $^{13}C$ NMR and mass spectra). See DOI: 10.1039/c3ra46672h

Thus, new ways of synthesizing diarylmethane skeletons through simple and more adaptive means are highly useful. This gives an additional advantage when one of the reactants offers multi-fold couplings in one-pot operation with additional, functional group tolerance and chemoselectivity. To the best of our knowledge, the coupling studies of triarylbismuths in combination with benzylic chlorides and iodides are not reported so far.[5,7] In continuation, we report here our studies on the couplings of triarylbismuth reagents with benzylic chlorides and iodides using palladium-catalyzed conditions.

## Results and discussion

To start the process, the cross-coupling reactivity study of benzylic chloride and $BiPh_3$ was checked under our earlier conditions developed for benzylic bromides[5] (Table 1). This study with 4-acetylbenzyl chloride utilizing $Pd(PPh_3)_4$ catalyst using *N*,*N*-dimethylacetamide (DMA) solvent in the presence of $K_3PO_4$ base provided 57% yield of the cross-coupled product **2.1** in one hour reaction time (entry 1). Increasing the reaction time to two hours did not provide high product yield (entry 2). Evaluation of different solvents such as *N*,*N*-dimethylformamide (DMF) and *N*-methyl-2-pyrrolidone (NMP) offered 69% and 53% yields (entries 3 and 4). Different bases in DMF solvent also proved to be beneficial, in particular $K_2CO_3$ and $Na_2CO_3$ delivered 91% and 93% yields (entries 6 and 7); while $Cs_2CO_3$ gave **2.1** in 41% yield (entry 5). Other palladium precursors such as $PdCl_2(PPh_3)_2$ and $Pd_2(dba)_3$ proved to be ineffective with low cross-coupled yields (entries 8 and 9). Further checks to find the optimum amount required for threefold coupling gave mixed results with varied amounts of base (entries 10–15). The cross-coupling was ineffective without base (entry 15), while reactions with increasing amounts of base furnished improved yields between 40 and 84% (entries 10–14) and a high outcome was achieved with 6 equiv. of base giving 93% yield (entry 7). The

Table 1 Screening for benzylic chloride couplings[a,b,c]




| Entry | Catalyst (equiv.) | Base (equiv.) | Solvent | Yield[b] [%] |
|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ | $K_3PO_4$ (6) | DMA | 57[d] |
| 2 | $Pd(PPh_3)_4$ | $K_3PO_4$ (6) | DMA | 60 |
| 3 | $Pd(PPh_3)_4$ | $K_3PO_4$ (6) | DMF | 69 |
| 4 | $Pd(PPh_3)_4$ | $K_3PO_4$ (6) | NMP | 53 |
| 5 | $Pd(PPh_3)_4$ | $Cs_2CO_3$ (6) | DMF | 41 |
| 6 | $Pd(PPh_3)_4$ | $K_2CO_3$ (6) | DMF | 91 |
| 7 | $Pd(PPh_3)_4$ | $Na_2CO_3$ (6) | DMF | 93 |
| 8 | $PdCl_2(PPh_3)_2$ | $Na_2CO_3$ (6) | DMF | 7 |
| 9 | $Pd_2(dba)_3$ | $Na_2CO_3$ (6) | DMF | 33 |
| 10 | $Pd(PPh_3)_4$ | $Na_2CO_3$ (5) | DMF | 84 |
| 11 | $Pd(PPh_3)_4$ | $Na_2CO_3$ (4) | DMF | 82 |
| 12 | $Pd(PPh_3)_4$ | $Na_2CO_3$ (3) | DMF | 64 |
| 13 | $Pd(PPh_3)_4$ | $Na_2CO_3$ (2) | DMF | 40 |
| 14 | $Pd(PPh_3)_4$ | $Na_2CO_3$ (1) | DMF | 44 |
| 15 | $Pd(PPh_3)_4$ | No base | DMF | — |
| 16 | $Pd(PPh_3)_4$ | $Na_2CO_3$ (6) | DMF | 50[e] |
| 17 | $Pd(PPh_3)_4$ | $Na_2CO_3$ (6) | DMF | 59[f] |
| 18 | $Pd(PPh_3)_4$ | $Na_2CO_3$ (6) | DMF | —[g] |
| 19 | $Pd(PPh_3)_4$ | $Na_2CO_3$ (6) | DMF | 52[h] |
| 20 | $Pd(PPh_3)_4$ | $Na_2CO_3$ (6) | DMF | 55[i] |
| 21 | No catalyst | $Na_2CO_3$ (6) | DMF | — |

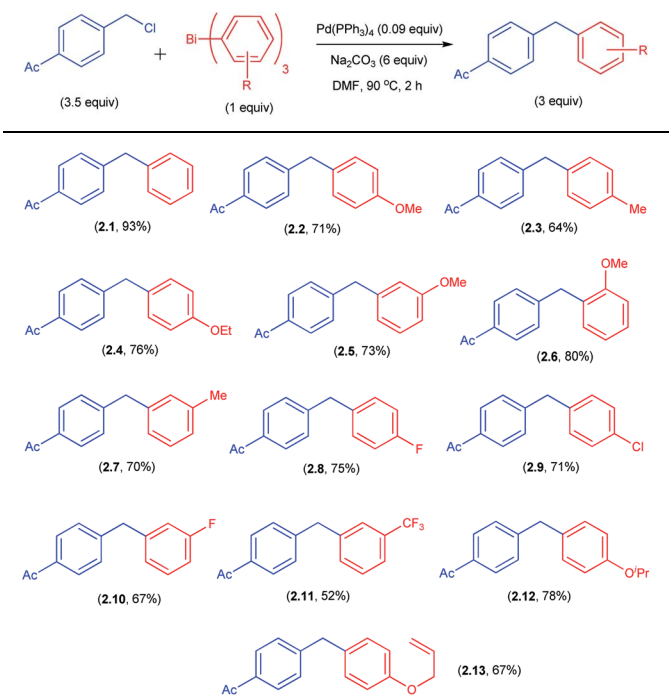
[a] Conditions: 4-acetylbenzyl chloride (0.875 mmol, 3.5 equiv.), $BiPh_3$ (0.25 mmol, 1 equiv.), Pd-catalyst (0.0225 mmol, 0.09 equiv.), base (1.5 mmol, 6 equiv.), solvent (3 mL), 90 °C, 2 h. [b] Isolated yields reported. [c] Homo-coupled biphenyl formed in minor amounts. [d] For 1 h. [e] At 80 °C. [f] At 60 °C. [g] At 40 °C. [h] With 0.06 equiv. of catalyst. [i] With 0.03 equiv. of catalyst.

couplings conducted at different temperature conditions were informative. For example, reactions at 80 °C or 60 °C provided moderate yields (entries 16 and 17) and found to be ineffective at 40 °C (entry 18). Screenings with lowered amounts of catalysts provided moderate yields (entries 19 and 20) and the desired coupling did not occur in the absence of catalyst (entry 21). As is known in these couplings,[2] invariably homo-coupled biphenyl was formed in varied amounts during screening reactions. However, it was easy to separate it from the desired cross-coupling product during chromatographic separation. After this investigation, it was clear that the cross-coupling is high yielding with the protocol consisting of $Pd(PPh_3)_4$ (0.09 equiv.) and $Na_2CO_3$ (6 equiv.) in DMF solvent at 90 °C for 2 hours (entry 7); and it was considered as our optimum condition. It should be mentioned that the optimized palladium protocol is effective with the delivery of threefold coupling of triphenylbismuth in reactions with three equivalents of functionalized benzyl chloride for 2 hours reaction time. This is very fast and appreciable reactivity of this coupling method.

To demonstrate the generality, various bismuth reagents were tested in threefold coupling with 4-acetylbenzyl chloride under the optimized conditions. For this, electronically different aryl bismuth reagents were employed (Table 2) substituted with *p*-methyl, *p*-methoxy, *m*-methoxy, *o*-methoxy, *m*-methyl, *p*-fluoro, *p*-chloro, *m*-trifluoromethyl, *p*-isopropoxy and *p*-allyloxy groups. In this evaluation, the general coupling ability was proved to be effective and the desired unsymmetrical diarylmethanes (**2.1–2.13**) were formed in 52–93% yields. Simultaneously, this has also demonstrated the facile threefold coupling nature of numerous aryl bismuth reagents in one-pot operation. This study also indicated the effective functional group tolerance in the formation of diverse unsymmetrical diarylmethanes in a short reaction time.

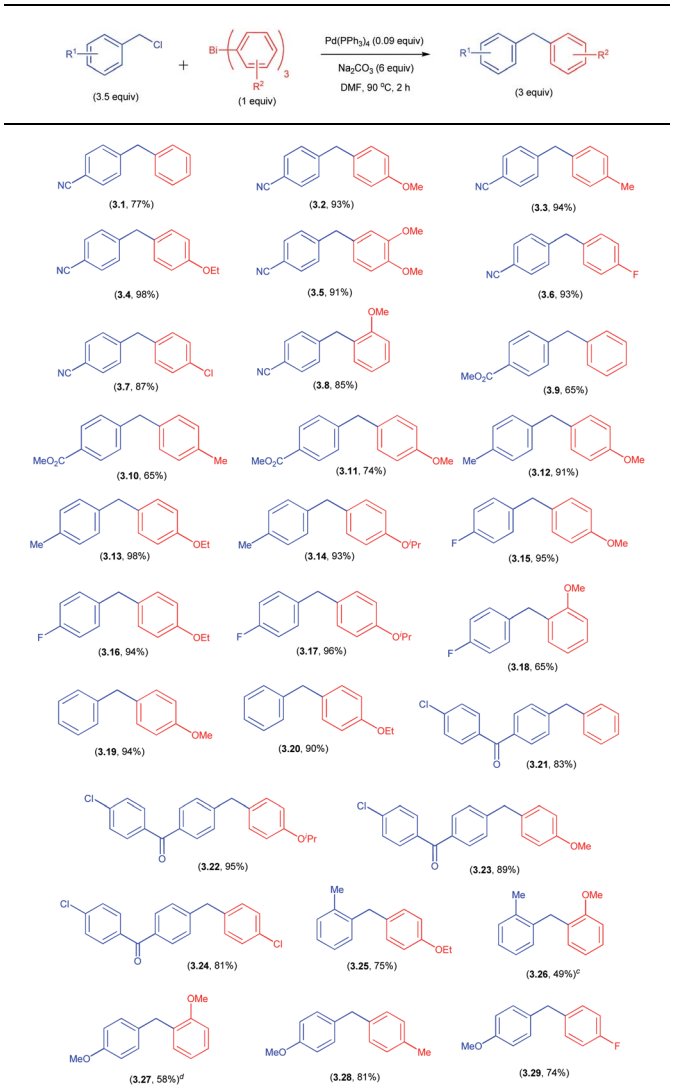
Further investigation under the optimized protocol conditions proved to be capable of efficient couplings with diverse benzylic chlorides (Table 3). This was achieved with benzyl chlorides comprising electronically different functional groups and in conjunction with a variety of triarylbismuth reagents. It was interesting to note that electron-rich or -poor benzyl chlorides in general furnished excellent yields indicating the synthetic efficiency of these couplings. Functional group tolerance that was observed further demonstrates the general coupling ability and compatibility of our protocol conditions. This elegance of aryl bismuth reagents with threefold coupling in combination with electronically different benzyl chlorides provided a diverse range of unsymmetrical diarylmethanes under simple protocol conditions. This is a novel and facile reactivity and the corresponding products were isolated between 49 and 98% yields (**3.1–3.29**). Notably, sterically

Table 2 Couplings with different $BiAr_3$ reagents[a,b]




[a] Reaction conditions: 4-acetylbenzyl chloride (0.875 mmol, 3.5 equiv.), $BiAr_3$ (0.25 mmol, 1 equiv.), $Pd(PPh_3)_4$ (0.0225 mmol, 0.09 equiv.), $Na_2CO_3$ (1.5 mmol, 6 equiv.), DMF (3 mL), 90 °C, 2 h. Isolated yields reported. [b] Homo-coupled biaryls formed in minor amounts.

Table 3 Couplings with different benzylic chlorides[a,b]




[a] Reaction conditions: benzylic chloride (0.875 mmol, 3.5 equiv.), $BiAr_3$ (0.25 mmol, 1 equiv.), $Pd(PPh_3)_4$ (0.0225 mmol, 0.09 equiv.), $Na_2CO_3$ (1.5 mmol, 6 equiv.), DMF (3 mL), 90 °C, 2 h. Isolated yields reported. [b] Homo-coupled biaryls formed in minor amounts. [c] 5 hours. [d] 4 hours.

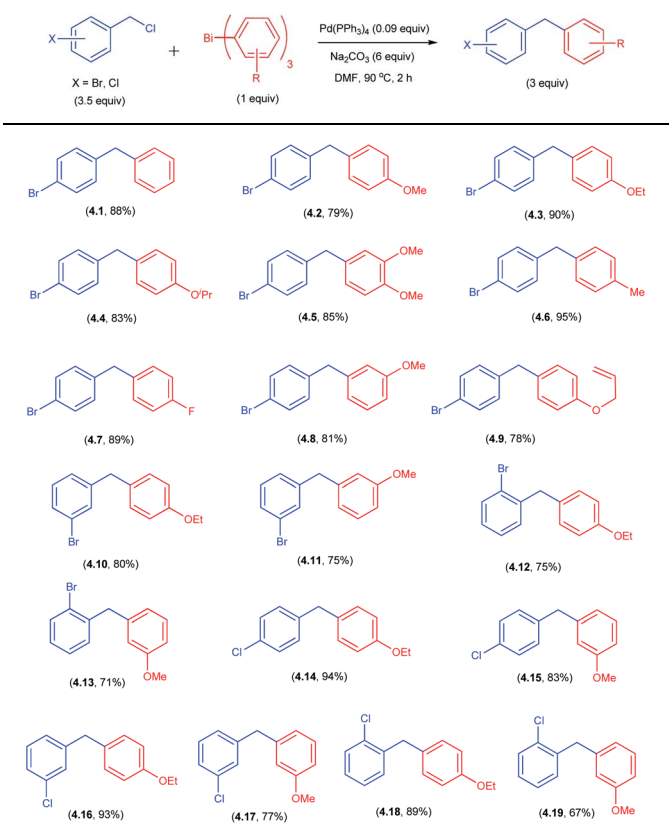
congested *ortho* substituted triarylbismuth reagent and benzyl chlorides provided moderate to high yields of diarylmethanes (**3.8**, **3.18**, **3.25–3.27**) under the established conditions. In some of the cases where moderate yields are given, unreacted benzyl halide and its conversion to diarylethanes or benzyl alcohol in minor amounts were observed along with the usual formation of biaryl from triarylbismuth in minor amounts. Formation of these side products is well known under metal-catalyzed conditions.

Next, our investigation was focussed on chemoselective couplings of functionalized benzylic chlorides with bismuth reagents (Table 4). It was amazing to see that the relatively more labile bromide did not participate in aryl couplings[8] thus furnishing chemoselective benzylic reactivity under the present protocol conditions.

The comprehensive couplings carried out with *p*-bromo, *m*-bromo, and *o*-bromo benzyl chlorides underwent selective benzylic couplings and delivered the corresponding bromo substituted unsymmetrical diarylmethanes (**4.1–4.13**) in 71–95% yields. Similar couplings with *p*-chloro, *m*-chloro, and *o*-chloro benzyl chlorides also furnished chemoselective couplings and the respective chloro diarylmethanes (**4.14–4.19**) were obtained in 67–94% yields. Thus, this protocol allowed the synthesis of regio-isomerically substituted bromo or chloro derivatives of diarylmethanes in good to high yields. More importantly, the presence of reactive bromide and chloride groups in diarylmethane core products is synthetically useful for further modifications under metal catalyzed conditions.

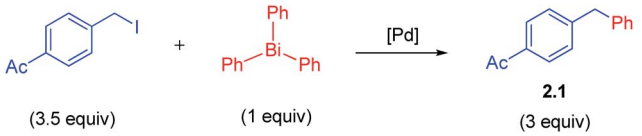
At this stage of study, we considered the couplings with benzylic iodides as they are expected to be more reactive under metal catalysis. This led us to test the couplings of 4-acetylbenzyl iodide as given in Table 5. The initial screening of the model reaction with our benzylic bromide condition[5] employing $Pd(PPh_3)_4$ and $K_3PO_4$ base in *N*,*N*-dimethylacetamide (DMA) at 90 °C furnished **2.1** in 42% yield (entry 1). This reaction with the condition established above for chloride couplings showed poor reactivity with 17% yield (entry 2).

Table 4 Chemoselective benzylic chloride couplings[a,b]




[a] Reaction conditions: benzylic chloride (0.875 mmol, 3.5 equiv.), $BiAr_3$ (0.25 mmol, 1 equiv.), $Pd(PPh_3)_4$ (0.0225 mmol, 0.09 equiv.), $Na_2CO_3$ (1.5 mmol, 6 equiv.), DMF (3 mL), 90 °C, 2 h. Isolated yields reported. [b] Homo-coupled biaryls formed in minor amounts.

Table 5 Screening for benzylic iodide couplings[a,b,c]




| Entry | Base (equiv.) | Solvent | Temp (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | $K_3PO_4$ (6) | DMA | 90 | 1 | 42 |
| 2 | $Na_2CO_3$ (6) | DMF | 90 | 2 | 17 |
| 3 | $K_3PO_4$ (6) | DMF | 90 | 1 | 15 |
| 4 | $K_3PO_4$ (6) | NMP | 90 | 1 | 32 |
| 5 | $K_3PO_4$ (6) | 1,4-Dioxane | 90 | 1 | 88 |
| 6 | $Cs_2CO_3$ (6) | DME | 90 | 1 | 36 |
| 7 | $K_2CO_3$ (6) | THF | 90 | 1 | 33 |
| 8 | $K_3PO_4$ (5) | 1,4-Dioxane | 90 | 1 | 79 |
| 9 | $K_3PO_4$ (4) | 1,4-Dioxane | 90 | 1 | 79 |
| 10 | $K_3PO_4$ (3) | 1,4-Dioxane | 90 | 1 | 58 |
| 11 | $K_3PO_4$ (6) | 1,4-Dioxane | 60 | 1 | 49 |
| 12 | $K_3PO_4$ (6) | 1,4-Dioxane | 40 | 1 | 35 |
| 13 | $K_3PO_4$ (6) | 1,4-Dioxane | 90 | 0.5 | 84 |
| 14 | $K_3PO_4$ (6) | 1,4-Dioxane | 90 | 0.5 | 85[d] |
| 15 | $K_3PO_4$ (6) | 1,4-Dioxane | 90 | 0.5 | 66[e] |
| 16 | No base | 1,4-Dioxane | 90 | 0.5 | — |
| 17 | $K_3PO_4$ (6) | 1,4-Dioxane | 90 | 0.5 | —[f] |

[a] Conditions: 4-acetylbenzyl iodide (0.875 mmol, 3.5 equiv.), $BiPh_3$ (0.25 mmol, 1 equiv.), $Pd(PPh_3)_4$ (0.0225 mmol, 0.09 equiv.), base (1.5 mmol, 6 equiv.), solvent (3 mL). [b] Isolated yields reported. [c] Homo-coupled biphenyl formed in minor amounts. [d] With 0.06 equiv. of $Pd(PPh_3)_4$. [e] With 0.03 equiv. of $Pd(PPh_3)_4$. [f] Without catalyst.

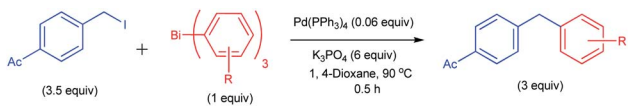
To circumvent this, further screening was continued to find the right condition for iodide couplings. Initially, different solvents and bases were tested to check their suitability and this gave mixed results (entries 3–7). This study revealed that 1,4-dioxane in combination with $K_3PO_4$ was a more suitable combination with 88% yield (entry 5). *N*,*N*-dimethylformamide (DMF), *N*-methyl-2-pyrrolidone (NMP), 1,2-dimethoxyethane (DME) and tetrahydrofuran (THF) solvents furnished yields in the range of 15–36% with different base combinations. Further checks carried out with $K_3PO_4$ base in 3–5 equivalents (entries 8–10) revealed that 6 equiv. was the most suitable to provide a high yield (entry 5). Couplings at different temperature conditions also indicated that the desired coupling is more effective at 90 °C (entry 5) while reactions under 40–60 °C conditions gave 35–49% yields (entries 11 and 12). Further optimization with 0.5 hour reaction time furnished 84% yield (entry 13). Screening with catalyst loading of 0.06 equiv. also furnished **2.1** in 85% yield (entry 14) whereas, 0.03 equiv. delivered only 66% yield (entry 15). Coupling reactions without base or catalyst proved to be ineffective (entries 16 and 17). Overall, this search thus furnished the condition with $Pd(PPh_3)_4$ (0.06 equiv.) and $K_3PO_4$ (6 equiv.) in 1,4-dioxane at 90 °C in 0.5 hour reaction time as the optimum condition for efficient coupling with benzylic iodide substrate (entry 14).

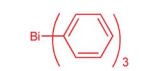
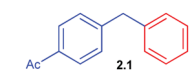
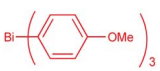
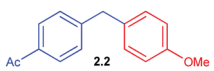
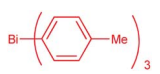
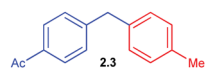
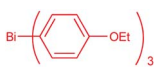
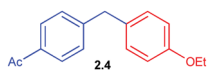
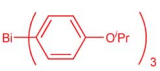
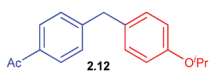
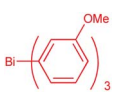
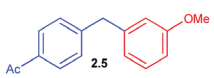
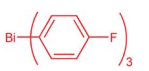
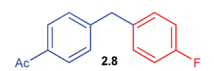
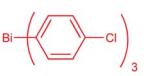
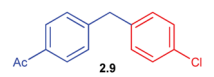
Having established the optimum conditions for benzyl iodide couplings with triphenylbismuth, various other bismuth reagents were subjected to this protocol with 4-acetylbenzyl iodide (Table 6). This effort gave a significant general reactivity of triarylbismuths in benzylic iodide couplings furnishing good to high cross-coupled yields. This also revealed the minimum dependence on electronic impact of aryl bismuth reagents in threefold coupling with benzylic iodides under the established protocol. This has provided various unsymmetrical diarylmethanes in 55–85% yields (**2.1–2.9**).

Further evaluation of the established protocol was carried out with different benzylic iodides and bismuth reagents (Table 7). In these couplings, a variety of functional benzylic iodides fared well in effective couplings with aryl bismuth reagents. In these cases, the corresponding unsymmetrical diarylmethanes were formed in 51–83% yields.

To further investigate, chemoselective couplings were carried out with functionalized benzylic iodides as given in Table 8. These reactions with bromo and chloro substituted benzyl iodides demonstrated preferential couplings at the benzylic terminus furnishing the corresponding chemoselective products in 55–70% yields. The reactivity of various benzylic iodides were fast and are effective in threefold coupling with bismuth reagents even with low catalyst loadings (0.06 equiv.)

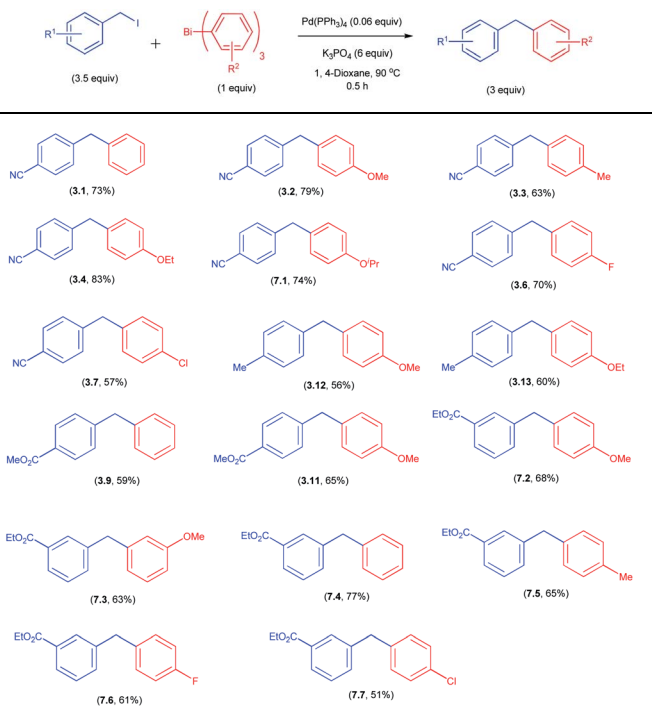
Table 6 Couplings with different $BiAr_3$ reagents[a,b]




| Entry | $BiAr_3$ | Diarylmethanes | Yield (%) |
|---|---|---|---|
| 1 |  |  | 85 |
| 2 |  |  | 83 |
| 3 |  |  | 72 |
| 4 |  |  | 85 |
| 5 |  |  | 78 |
| 6 |  |  | 55 |
| 7 |  |  | 76 |
| 8 |  |  | 81 |

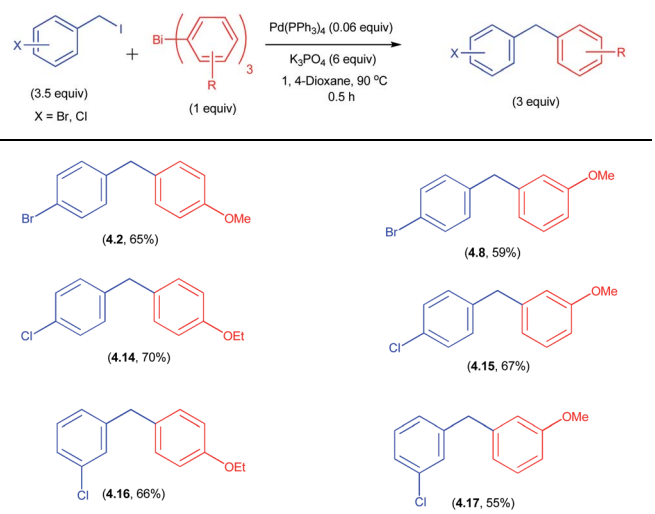
[a] Conditions: 4-acetylbenzyl iodide (0.875 mmol, 3.5 equiv.), $BiAr_3$ (0.25 mmol, 1 equiv.), $Pd(PPh_3)_4$ (0.015 mmol, 0.06 equiv.), $K_3PO_4$ (1.5 mmol, 6 equiv.), 1,4-dioxane (3 mL), 90 °C, 0.5 h. Isolated yields reported. [b] Homo-coupled biaryls formed in minor amounts.

Table 7 Couplings with different benzylic iodides[a,b]




[a] Conditions: benzylic iodide (0.875 mmol, 3.5 equiv.), $BiAr_3$ (0.25 mmol, 1 equiv.), $Pd(PPh_3)_4$ (0.015 mmol, 0.06 equiv.), $K_3PO_4$ (1.5 mmol, 6 equiv.), 1,4-dioxane (3 mL), 90 °C, 0.5 h. Isolated yields reported. [b] Homo-coupled biaryls formed in minor amounts.

Table 8 Chemoselective benzylic iodide couplings[a,b]



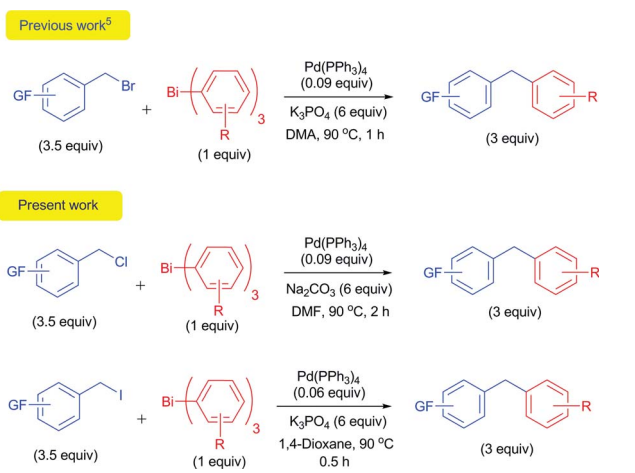

[a] Conditions: benzylic iodide (0.875 mmol, 3.5 equiv.), $BiAr_3$ (0.25 mmol, 1 equiv.), $Pd(PPh_3)_4$ (0.015 mmol, 0.06 equiv.), $K_3PO_4$ (1.5 mmol, 6 equiv.), 1,4-dioxane (3 mL), 90 °C, 0.5 h. Isolated yields reported. [b] Homo-coupled biaryls formed in minor amounts.

and short reaction time in comparison to the couplings given above with benzylic chlorides involving 2 hours or earlier results with benzylic bromides using 1 hour reaction conditions.[5]

It is to be highlighted that these chemoselective benzylic couplings are useful for further structural elaborations.[5,9] The present chemoselective study has clearly demonstrated the amenable reactivity of various halo substituted benzylic systems in reaction with triarylbismuth reagents under simple palladium protocol conditions.

The overall threefold coupling reactivity of triarylbismuth reagents with benzylic halides is given in Scheme 1. As stated, we have earlier demonstrated the coupling reactivity with benzylic bromides under palladium conditions.[5] The present study dealt with the couplings of benzyl chlorides and iodides. It is evident that this investigation revealed the exemplary reactivity of these substrates with functional group (FG) tolerance and chemoselectivity. For general reactivity comparison, benzylic iodides reacted with low catalyst loadings and 0.5 hour short reaction time condition. Benzylic chlorides needed 2 hours while our earlier benzylic bromide couplings required 1 hour time to obtain high yields. Thus, the present investigation shed light on the relative reactivity of various benzylic halides in couplings with triarylbismuth reagents (Scheme 1).

The versatile couplings of various functionalized benzylic chlorides and iodides, in addition to chemoselective investigation carried out here hence expanded the scope and generality of triarylbismuth reagents as threefold coupling reagents in benzylic couplings. In comparison, the three palladium protocol conditions indicated that base and solvent have crucial roles in reactions with different benzylic halides. In fact, the change of base and solvent evolved through systematic screening and has delivered facile coupling reactivity with different benzylic bromides, chlorides, and iodides (Scheme 1). An additional advantage of the present study is that benzylic chlorides, that are otherwise supposed to be less reactive, showed excellent coupling reactivity in tune with that of benzylic bromides.[5] Reactions with electronically rich benzyl chlorides also showed better couplings under our coupling conditions. This was not the case with literature known examples using other organometallic reagents.[7d] The couplings with benzylic iodides using bismuth reagents is notable as these



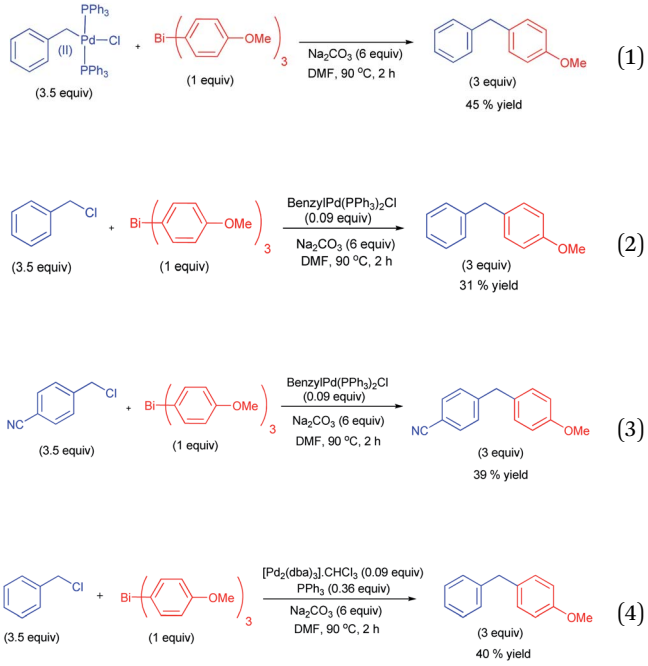

Scheme 1 Benzylic halide couplings with $BiAr_3$ reagents.

substrates are not popularly studied in a similar manner[7h] and this could be partly due to stability related issues known with these compounds. This demonstration of versatile, general and chemoselective reactivity of benzyl chlorides and iodides as electrophilic coupling partners is a first time elaboration with triarylbismuth reagents. Importantly, this was achieved using routinely used palladium catalyzed conditions. As similar comprehensive investigations are not available with bismuth reagents in benzylic couplings,[5,10,11] the present study is a notable contribution.

Some methods are known in the literature using benzylic halides as coupling partners with other organometallic reagents.[7] For example, the known benzyl chloride coupling with aryltrifluoroborate utilizes dppf ligand under palladium conditions with longer reaction times delivering one C–C coupling.[7a] Similar reactions with aryl boronic acids employing specialized phosphine[7d] or pincer[7b] ligands in the palladium protocol need a longer reaction course or higher reaction temperature delivering one C–C coupling. The corresponding benzylic iodide couplings are scarcely studied in the literature.[7h] In that context, this study reveals a new scope of these couplings with triarylbismuth reagents with efficient reactivity, selectivity, short reaction times and good to high yields involving threefold couplings from bismuth reagents in one-pot operation. Of note is that in the literature not many organometallic reagents are known which can serve as threefold coupling partners for similar coupling reactions.[10] The structural importance of diarylmethanes in synthetic, medicinal, biological and other applications adds further credence to the importance of this method in the synthesis of various functionalized unsymmetrical diarylmethanes.

The mechanistic aspect of benzylic couplings under metal catalyzed couplings with organometallic nucleophiles is well documented in the literature. The oxidative addition of benzylic halide to palladium(0) to give **2a** (ref. 13) and its involvement in transmetallation with organometallic reagent to give **2b** was proposed earlier.[12] The reductive elimination of **2b** further generates benzyl coupled diarylmethane product as proposed in catalytic cycle (Fig. 2).

To check this, we carried out a few investigations as outlined below. Firstly, the coupling reaction of *in situ* generated benzylpalladium(II) chloride was performed with tri(*p*-anisyl) bismuth under standardized conditions (eqn (1)).




In this attempt, the benzylpalladium(II) chloride prepared using benzyl chloride with $Pd_2(dba)_3/PPh_3$ was directly used for couplings after removing the solvent under vacuum[13] and with the addition of DMF solvent and other reagents (eqn (1)). This reaction gave the cross-coupled diarylmethane product namely, 1-benzyl-4-methoxybenzene in 45% yield. This utilization of preformed Pd(II) intermediate (**2a**) and its reactivity is in tune with the proposed oxidative addition step and its subsequent involvement in the catalytic cycle (Fig. 2). Further investigations using the above prepared benzylpalladium(II) chloride precatalyst in coupling reactions with different benzyl chlorides furnished 31% and 39% yields, respectively (eqn (2) and (3)). This additionally supports the facile participation and catalytic reactivity of the preformed Pd(II) intermediate. Further couplings with the direct use of $Pd_2(dba)_3/PPh_3$ replacing $Pd(PPh_3)_4$ in the standardized protocol also delivered the cross-coupled 1-benzyl-4-methoxybenzene in 40% yield (eqn (4)). It should also be noted that the GC-MS analyses of the crude reaction mixtures indicated the formation of biaryl homocoupling product from bismuth reagent in eqn (1)–(4) along with unreacted benzyl chloride in eqn (2)–(4). Based on these investigations, it is most likely that the cross-coupling follows the proposed catalytic cycle to deliver the diarylmethane product. The threefold coupling reactivity of triarylbismuth reagents can also be envisaged through the repetitive participation of aryl bismuth species[4c] in the catalytic cycle as the high yields of coupled yields were seen usually under standardized conditions.

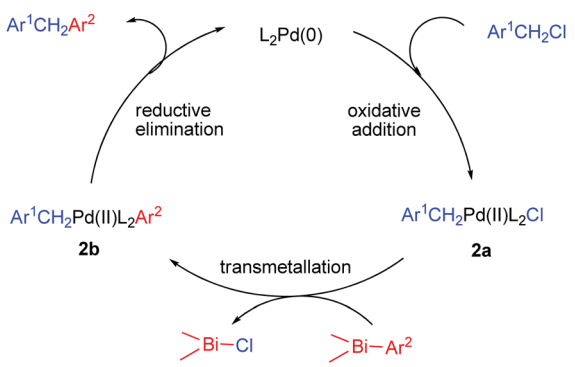



Fig. 2 Proposed catalytic cycle.

## Conclusions

In conclusion, a diverse range of functionalized unsymmetrical diarylmethane compounds have been synthesized using cross-

coupling methodology involving the first time couplings of benzylic chlorides and iodides with triarylbismuths as threefold coupling partners. The two palladium protocol conditions established in this study involve routinely used palladium catalysts under convenient reaction conditions. This study also delivered the functionalized unsymmetrical diarylmethanes in high product yields. The optimized protocols also delivered chemoselective couplings both with benzyl chlorides and iodides.

# Experimental

### General

All reactions were performed according to standard procedures in a oven-dried Schlenk tube under inert nitrogen atmosphere. Triarylbismuths were prepared using the literature procedures.[2] Benzylic chlorides and benzylic iodides were prepared using the known methods.[14,15] JEOL-Lambda (500 MHz and 400 MHz) spectrometers was used for NMR measurements using $CDCl_3$ as solvent. Waters CAB155 GCT Premier analyzer was used for HRMS spectral measurements.

### Representative coupling procedure for 4-acetylbenzyl chloride

To an oven dried Schlenk tube, 4-acetylbenzyl chloride (0.875 mmol, 0.147.5 g), triphenylbismuth (0.25 mmol, 0.11 g), $Na_2CO_3$ (1.5 mmol, 0.159 g), $Pd(PPh_3)_4$ (0.0225 mmol, 0.026 g) and dry DMF (3 mL) were added in the order specified under nitrogen atmosphere. The contents were stirred at 90 °C for 2 h using an oil bath. After the specified time, the reaction mixture was quenched with water and extracted with ethyl acetate (2 × 20 mL). The organic extract after treating with brine was dried over anhydrous $MgSO_4$ and concentrated using a rotatory evaporator. The crude product was subjected to silica gel column chromatography (1% EtOAc–hexane) to obtain 1-(4-benzylphenyl)ethanone as a colourless oil (0.146 g, 93%). The yield was calculated considering 0.75 mmol of the product as 100%.

*Note*: in the case of products **3.27–3.29**, *p*-methoxybenzyl chloride was added after addition of the solvent with a slight change in the representative procedure. This was done as a vigorous color change, heat generation and decomposition were observed when *p*-methoxybenzyl chloride was added to the solid mixture before addition of the solvent.

### Coupling conditions for benzylic iodide couplings

The above procedure was also used for benzylic iodide couplings with the following conditions. Benzyl iodide (0.875 mmol, 3.5 equiv.), $BiAr_3$ (0.25 mmol, 1 equiv.), $K_3PO_4$ (1.5 mmol, 6 equiv.), $Pd(PPh_3)_4$ (0.015 mmol, 0.06 equiv.), dry 1,4-dioxane (3 mL), 90 °C, 0.5 h. The yield was calculated considering 0.75 mmol of the product as 100%.

All the products were identified by spectroscopic means and in comparison with the literature data wherever available.

### 1-(4-(2-Methoxybenzyl)phenyl)ethanone (2.6)

Colorless liquid (145 mg, 80%), $R_f$ (5% EtOAc–hexane) 0.22; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.85–7.84 (m, 2H), 7.29–7.21 (m, 3H), 7.07 (d, $J$ = 7.45 Hz, 1H), 6.90–6.85 (m, 2H), 4.01 (s, 2H), 3.79 (s, 3H), 2.55 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 197.88, 157.28, 146.98, 134.96, 130.34, 128.99, 128.74, 128.41, 127.82, 120.53, 110.48, 55.29, 36.07, 26.53. IR (neat, cm$^{-1}$): 3002, 2937, 2836, 1681, 1606, 1493, 1463, 1438, 1357, 1267, 1245. EI (*m*/*z*) calcd for $C_{16}H_{16}O_2$ $[M]^+$ 240.1150; found 240.1154.

### 1-(4-(3-Fluorobenzyl)phenyl)ethanone (2.10)

Colorless liquid (114 mg, 67%), $R_f$ (5% EtOAc–hexane) 0.32; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.88 (d, $J$ = 8.3 Hz, 2H), 7.26–7.23 (m, 3H), 6.94 (d, $J$ = 7.45 Hz, 1H), 6.90 (dt, $J$ = 8.9, 2.3 Hz, 1H), 6.84 (d, $J$ = 9.75, 1H), 4.00 (s, 2H), 2.56 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 197.82, 163.75 (d, $J_{C-F}$ = 245.61 Hz), 145.96, 135.56, 130.14 (d, $J_{C-F}$ = 8.35 Hz), 129.20, 128.82, 124.65, 115.90 (d, $J_{C-F}$ = 21.46 Hz), 113.53, 113.37, 41.63, 26.66. IR (neat, cm$^{-1}$): 2925, 1682, 1589, 1486, 1358, 1267, 785. EI (*m*/*z*) calcd for $C_{15}H_{13}FO$ $[M]^+$ 228.0950; found 228.0950.

### 1-(4-(4-Isopropoxybenzyl)phenyl)ethanone (2.12)

Pale brown liquid (with benzyl chloride or iodide, 157 mg, 78%), $R_f$ (5% EtOAc–hexane) 0.25; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.87 (d, $J$ = 8 Hz, 2H), 7.26 (d, $J$ = 8 Hz, 2H), 7.06 (d, $J$ = 8.3 Hz, 2H), 6.81 (d, $J$ = 8.6 Hz, 2H), 4.52–4.47 (m, 1H), 3.95 (s, 2H), 2.56 (s, 3H), 1.31 (d, $J$ = 6.3 Hz, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta_C$ = 197.85, 156.40, 147.32, 135.08, 131.88, 129.85, 128.97, 128.58, 115.93, 69.81, 40.98, 26.57, 22.03. IR (neat, cm$^{-1}$): 2980, 2926, 1511, 1681, 1607, 1510, 1412, 1358, 1267, 1245, 1077, 1115. HRMS (ES$^+$): calcd for $C_{18}H_{21}O_2$ $[M + H]^+$ 269.1542; found 269.1542.

### 1-(4-(4-(Allyloxy)benzyl)phenyl)ethanone (2.13)

Colorless liquid (133 mg, 67%), $R_f$ (5% EtOAc–hexane) 0.28; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.86 (d, $J$ = 8.3 Hz, 2H), 7.25 (d, $J$ = 8.35 Hz, 2H), 7.06 (d, $J$ = 8.9 Hz, 2H), 6.84 (d, $J$ = 8.6 Hz, 2H), 6.07–5.99 (m, 1H), 5.39 (dd, $J$ = 1.45 Hz, 17.4 Hz, 1H), 5.26 (dd, $J$ = 1.45 Hz, 10.6 Hz, 1H), 4.50 (d, $J$ = 5.45 Hz, 2H), 3.95 (s, 2H), 2.56 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 197.81, 157.16, 147.24, 135.13, 133.28, 132.27, 129.84, 128.96, 128.59, 117.62, 114.82, 68.80, 40.98, 26.55. IR (neat, cm$^{-1}$): 2980, 2926, 1511, 1681, 1607, 1510, 1412, 1358, 1267, 1245, 1077, 1115, 1047, 810, 680, 602. HRMS (ES$^+$): calcd for $C_{18}H_{19}O_2$ $[M + H]^+$ 267.1385; found 267.1382.

### 4-(3,4-Dimethoxybenzyl)benzonitrile (3.5)

White solid (172 mg, 91%); m.p. 58–60 °C, $R_f$ (5% EtOAc–hexane) 0.35. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.56 (d, $J$ = 8.0 Hz, 2H), 7.27 (d, $J$ = 8.0 Hz, 2H), 6.81 (d, $J$ = 8.30 Hz, 1H), 6.69 (d, $J$ = 8.05 Hz, 1H), 6.65 (s, 1H), 3.97 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 149.11, 147.81, 147.00, 132.24, 131.75, 129.45, 121.01, 118.96, 112.13, 111.32, 109.96, 55.88, 55.82, 41.48. IR (KBr, cm$^{-1}$): 3037, 2834, 2225, 1603, 1517, 1260, 1240, 1171, 1158, 1027, 811, 561. HRMS (ES$^+$): calcd for $C_{16}H_{16}NO_2$ $[M + H]^+$ 254.1181; found 254.1188.

**4-(4-Chlorobenzyl)benzonitrile (3.7)**

White solid (with benzyl chloride, 149 mg, 87%; with benzyl iodide, 99 mg, 57%), m.p. 53–55 °C, $R_f$ (5% EtOAc–hexane) 0.59; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.57 (d, $J$ = 8.05 Hz, 2H), 7.27–7.24 (m, 4H), 7.07 (d, $J$ = 8.3 Hz, 2H), 3.98 (s, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 146.07, 137.74, 132.56, 132.37, 130.26, 129.54, 128.87, 118.83, 110.28, 41.22. IR (KBr, cm$^{-1}$): 2223, 1603, 1488, 1405, 1176, 1088, 1014, 870, 819, 795. HRMS (ES$^+$): calcd for $C_{14}H_{11}ClN$ $[M + H]^+$ 228.0580; found 228.0584.

**4-(2-Methoxybenzyl)benzonitrile (3.8)**[7e]

Colorless liquid (142 mg, 85%), $R_f$ (5% EtOAc–hexane) 0.45; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.53 (d, $J$ = 8.35 Hz, 2H), 7.29 (d, $J$ = 8.30 Hz, 2H), 7.26–7.22 (m, 1H), 7.09 (d, $J$ = 5.7 Hz, 1H), 6.92–6.87 (m, 2H), 4.00 (s, 2H), 3.79 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 157.23, 146.90, 132.03, 130.40, 129.49, 128.13, 127.82, 120.60, 119.20, 110.55, 109.54, 55.27, 36.32. IR (neat, cm$^{-1}$): 2838, 2216, 1612, 1511, 1300, 1247, 1117, 1110. EI ($m/z$) calcd for $C_{15}H_{13}NO$ $[M]^+$ 223.0997; found 223.0999.

**Methyl 4-benzylbenzoate (3.9)**[16]

Colorless liquid (with benzyl chloride or iodide, 110 mg, 65%), $R_f$ (5% EtOAc–hexane) 0.55; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.95 (d, $J$ = 8.3 Hz, 2H), 7.30–7.20 (m, 5H), 7.17 (d, $J$ = 7.15 Hz, 2H), 4.02 (s, 2H), 3.89 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 167.05, 146.49, 140.09, 129.79, 128.92, 128.58, 128.05, 126.35, 52.00, 41.88. IR (neat, cm$^{-1}$): 2950, 1610, 1721, 1611, 1452, 1281, 1178, 1108, 805, 742. HRMS (ES$^+$): calcd for $C_{15}H_{15}O_2$ $[M]^+$ 227.1072; found 227.1071.

**Methyl 4-(4-methylbenzyl)benzoate (3.10)**[7i]

White solid (117 mg, 65%), m.p. 59–62 °C $R_f$ (5% EtOAc–hexane) 0.59; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.94 (d, $J$ = 8.3 Hz, 2H), 7.24 (d, $J$ = 8.3 Hz, 2H), 7.10 (d, $J$ = 8 Hz, 2H), 7.05 (d, $J$ = 8 Hz, 2H), 3.98 (s, 2H), 3.88 (s, 3H), 2.31 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 167.07, 146.82, 137.04, 135.89, 129.77, 129.27, 128.85, 128.80, 127.96, 51.98, 41.47, 20.99. IR (KBr, cm$^{-1}$): 2950, 1721, 1610, 1513, 1434, 1280, 1177, 1109, 1020, 819, 739. HRMS (ES$^+$): calcd for $C_{16}H_{17}O_2$ $[M + H]^+$ 241.1229; found 241.1227.

**Methyl 4-(4-methoxybenzyl)benzoate (3.11)**[17]

Colorless liquid (with benzyl chloride, 142 mg, 74%; with benzyl iodide, 125 mg, 65%), $R_f$ (5% EtOAc–hexane) 0.43; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.94 (d, $J$ = 8.3 Hz, 2H), 7.23 (d, $J$ = 8 Hz, 2H), 7.08 (d, $J$ = 8.3 Hz, 2H), 6.83 (d, $J$ = 8.55 Hz, 2H), 3.96 (s, 2H), 3.88 (s, 3H), 3.77 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 167.07, 158.12, 147.00, 132.18, 129.88, 129.77, 128.79, 127.95, 113.97, 55.23, 51.99, 40.99. IR (neat, cm$^{-1}$): 2951, 1720, 1611, 1511, 1435, 1282, 1247, 1178, 1109, 1035. HRMS (ES$^+$): calcd for $C_{16}H_{17}O_3$ $[M + H]^+$ 257.1178; found 257.1177.

**1-Ethoxy-4-(4-methylbenzyl)benzene (3.13)**

White solid (with benzyl chloride, 167 mg, 98%; with benzyl iodide, 101 mg, 60%), m.p. 68–70 °C, $R_f$ (hexane) 0.65; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.10–7.05 (m, 6H), 6.81 (d, $J$ = 8.55 Hz, 2H), 4.99 (q, $J$ = 7.15 Hz, 2H), 3.88 (s, 2H), 2.31 (s, 3H), 1.39 (t, $J$ = 6.85 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 157.21, 138.54, 135.39, 133.38, 129.74, 129.07, 128.66, 114.39, 63.36, 40.57, 20.98, 14.87. IR (KBr, cm$^{-1}$): 2836, 2226, 1610, 1511, 1301, 1247, 1117, 1110, 1034, 810, 761, 572. HRMS (ES$^+$): calcd for $C_{16}H_{18}ONa$ $[M + Na]^+$ 249.1255; found 249.1253.

**1-Isopropoxy-4-(4-methylbenzyl)benzene (3.14)**

Colorless liquid (169 mg, 93%), $R_f$ (hexane) 0.67; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.11–7.07 (m, 6H), 6.81 (d, $J$ = 8.6 Hz, 2H), 4.52–4.47 (m, 1H), 3.88 (s, 2H), 2.32 (s, 3H), 1.32 (d, $J$ = 6.3 Hz, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 156.12, 138.53, 135.38, 133.35, 129.74, 129.06, 128.68, 115.84, 69.81, 40.58, 22.06, 20.09. IR (neat, cm$^{-1}$): 2836, 2226, 1610, 1511, 1301, 1247, 1117, 1110, 1034, 810, 761, 572. HRMS (ES$^+$): calcd for $C_{17}H_{19}O$ $[M - H]^+$ 239.1436; found 239.1431.

**1-Methoxy-4-(4-fluorobenzyl)benzene (3.15)**[7h]

Colorless liquid (154 mg, 95%), $R_f$ (hexane) 0.65; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.12–7.06 (m, 4H), 6.95 (t, $J$ = 8.75 Hz, 2H), 6.83 (d, $J$ = 8.55 Hz, 2H), 3.88 (s, 2H), 3.77 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 161.33 (d, $J_{C-F}$ = 242.02 Hz), 158.00, 137.21, 133.03, 130.11 (d, $J_{C-F}$ = 8.33 Hz), 129.74, 115.13 (d, $J_{C-F}$ = 21.42 Hz), 113.90, 55.23, 40.14. IR (KBr, cm$^{-1}$): EI ($m/z$) calcd for $C_{14}H_{13}FO$ $[M]^+$ 216.0950; found 216.0950.

**1-Ethoxy-4-(4-fluorobenzyl)benzene (3.16)**

Colorless liquid (162 mg, 94%), $R_f$ (hexane) 0.67; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.12–7.10 (m, 2H), 7.06 (d, $J$ = 8.85 Hz, 2H), 6.94 (t, $J$ = 8.72 Hz, 2H), 6.82 (d, $J$ = 8.6 Hz, 2H), 4.00 (q, $J$ = 6.85 Hz, 2H), 3.88 (s, 2H), 1.39 (t, $J$ = 6.85 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 161.32 (d, $J_{C-F}$ = 243.22 Hz), 157.37, 137.23, 132.88, 130.12 (d, $J_{C-F}$ = 8.35 Hz), 129.72, 115.11 (d, $J_{C-F}$ = 21.46 Hz), 114.48, 63.38, 40.16, 14.85. IR (neat, cm$^{-1}$): 2980, 1609, 1509, 1245, 1048, 816. EI ($m/z$) calcd for $C_{15}H_{15}FO$ $[M]^+$ 230.1107; found 230.1108.

**1-Isopropoxy-4-(4-fluorobenzyl)benzene (3.17)**

Colorless liquid (175 mg, 96%), $R_f$ (hexane) 0.69; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.13–7.10 (m, 2H), 7.04 (d, $J$ = 8.55 Hz, 2H), 6.95 (t, $J$ = 8.9 Hz, 2H), 6.80 (d, $J$ = 8.6 Hz, 2H), 4.51–4.47 (m, 1H), 3.87 (s, 2H), 1.30 (d, $J$ = 6 Hz, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 161.33 (d, $J_{C-F}$ = 242.02 Hz), 156.30, 137.21, 132.85, 130.14 (d, $J_{C-F}$ = 7.16 Hz), 129.73, 115.91, 115.11 (d, $J_{C-F}$ = 21.46 Hz), 69.87, 40.17, 22.06. IR (neat, cm$^{-1}$): 2977, 1608, 1507, 1241, 1119, 956, 811. HRMS (ES$^+$): calcd for $C_{16}H_{16}FO$ $[M - H]^+$ 243.1185; found 243.1182.

**1-(4-Fluorobenzyl)-2-methoxybenzene (3.18)**

Colorless liquid (105 mg, 65%), $R_f$ (hexane) 0.65; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.22–7.14 (m, 3H), 7.05 (d, $J$ = 7.45 Hz, 1H), 6.96–6.92 (m, 2H), 6.90–6.86 (m, 2H), 3.93 (s, 2H), 3.81 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 161.22 (d, $J_{C-F}$ = 242.36 Hz), 157.22, 136.61, 130.20 (d, $J_{C-F}$ = 8.38 Hz), 129.46, 127.54, 120.48,

114.92 (d, $J_{C-F}$ = 21.60 Hz), 110.40, 55.30, 35.12. IR (neat, $cm^{-1}$): 3005, 2900, 2841, 1589, 1500, 1439, 1222, 1177. EI (*m*/*z*) calcd for $C_{14}H_{13}FO$ $[M]^+$ 216.0950; found 216.0957.

**1-Benzyl-4-methoxybenzene (3.19)[18]**

Colorless liquid (140 mg, 94%), $R_f$ (hexane) 0.65; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 7.29–7.25 (m, 2H), 7.19–7.17 (m, 3H), 7.12–7.09 (m, 2H), 6.84–6.82 (m, 2H), 3.93 (s, 2H), 3.78 (s, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 157.94, 141.56, 133.23, 129.84, 128.79, 128.41, 125.95, 113.84, 55.23, 41.01. IR (neat, $cm^{-1}$): 3026, 2906, 2834, 1610, 1511, 1493, 1453, 1300, 1246, 1116, 1035. EI (*m*/*z*) calcd for $C_{14}H_{14}O$ $[M]^+$ 198.1045; found 198.1042.

**(4-Chlorophenyl)(4-(4-chlorobenzyl)phenyl)methanone (3.24)**

White solid (207 mg, 81%), m.p. 90–91 °C $R_f$ (5% EtOAc–hexane) 0.25; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 7.73 (d, $J$ = 8.55 Hz, 2H), 7.70 (d, $J$ = 7.95 Hz, 2H), 7.44 (d, $J$ = 8.55 Hz, 2H), 7.27–7.25 (m, 4H), 7.12 (d, $J$ = 8.55 Hz, 2H), 4.01 (s, 2H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 195.06, 145.79, 138.77, 138.42, 135.92, 135.32, 132.31, 131.35, 130.39, 130.29, 128.85, 128.76, 128.59, 41.20. IR (KBr, $cm^{-1}$): 2909, 1647, 1604, 1310, 1280, 1112, 1088, 1012, 929, 792, 766, 737, 500, 471. EI (*m*/*z*) calcd for $C_{20}H_{14}Cl_2O$ $[M]^+$ 340.0422; found 340.0421.

**1-(4-Ethoxybenzyl)-2-methylbenzene (3.25)**

Colorless liquid (126 mg, 74%), $R_f$ (hexane) 0.35; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.17–7.15 (m, 3H), 7.11 (d, $J$ = 4.85 Hz, 1H), 7.05 (d, $J$ = 8.72 Hz, 2H), 6.83 (d, $J$ = 8.24 Hz, 2H), 4.02 (q, $J$ = 7.32 Hz, 2H), 3.94 (s, 2H), 2.26 (s, 3H), 1.42 (t, $J$ = 6.88 Hz, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 157.14, 139.35, 136.53, 132.22, 130.19, 129.73, 129.60, 126.29, 125.90, 114.33, 63.33, 38.52, 19.61, 14.86. EI (*m*/*z*) calcd for $C_{16}H_{18}O$ $[M]^+$ 226.1358; found 226.1353.

**1-Methoxy-2-(2-methylbenzyl)benzene (3.26)[19]**

Colorless liquid (78 mg, 49%), $R_f$ (hexane) 0.35; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.23–7.13 (m, 4H), 7.06 (d, $J$ = 6.4 Hz, 1H), 6.89 (d, $J$ = 8.24 Hz, 1H), 6.85 (d, $J$ = 4.6 Hz, 1H), 3.96 (s, 2H), 3.85 (s, 3H), 2.27 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 157.32, 138.65, 136.77, 130.00, 129.74, 129.61, 128.74, 127.12, 126.11, 125.85, 120.38, 109.99, 55.29, 33.01, 19.49. EI (*m*/*z*) calcd for $C_{15}H_{16}O$ $[M]^+$ 212.1201; found 212.1201.

**1-Methoxy-2-(4-methoxybenzyl)benzene (3.27)**

Colorless liquid (100 mg, 58%), $R_f$ (2.5% EtOAc–hexane) 0.50; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.21–7.17 (m, 1H), 7.14 (d, $J$ = 8.24 Hz, 2H), 7.05 (d, $J$ = 7.32 Hz, 1H), 6.89–6.86 (m, 2H), 6.82 (d, $J$ = 8.68 Hz, 2H), 3.92 (s, 2H), 3.82 (s, 3H), 3.78 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 157.71, 157.23, 133.04, 130.11, 130.07, 129.84, 127.25, 120.41, 113.65, 110.32, 55.31, 55.20, 34.90. EI (*m*/*z*) calcd for $C_{15}H_{16}O_2$ $[M]^+$ 228.1150; found 228.1156.

**4-(4-Bromobenzyl)-1,2-dimethoxybenzene (4.5)**

Brown liquid (195 mg, 85%), $R_f$ (hexane) 0.45; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 7.39 (d, $J$ = 8.3 Hz, 2H), 7.04 (d, $J$ = 8.6 Hz, 2H), 6.78 (d, $J$ = 8.30 Hz, 1H), 6.69–6.67 (m, 1H), 6.65 (d, $J$ = 2 Hz, 1H), 3.86 (s, 2H), 3.84 (s, 3H), 3.81 (s, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 148.96, 147.52, 140.34, 132.92, 131.46, 130.49, 120.83, 119.85, 112.05, 111.17, 55.88, 55.79, 40.82. IR (neat, $cm^{-1}$): 2950, 1721, 1610, 1513, 1434, 1280, 1177, 1109, 1020, 819, 739. HRMS ($ES^+$): calcd for $C_{15}H_{16}BrO_2$ $[M + H]^+$ 307.0334; found 307.0339.

**1-(Allyloxy)-4-(4-bromobenzyl)benzene (4.9)**

Colorless liquid (177 mg, 78%), $R_f$ (hexane) 0.25; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 7.38 (d, $J$ = 8.3 Hz, 2H), 7.06–7.02 (m, 4H), 6.83 (d, $J$ = 8.6 Hz, 2H), 6.07–6.0 (m, 1H), 5.39 (dd, $J$ = 17.45 Hz, 1.45 Hz, 1H), 5.27 (dd, $J$ = 10.6 Hz, 1.45 Hz, 1H), 4.50 (d, $J$ = 5.45 Hz, 2H), 3.85 (s, 2H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 157.11, 140.50, 133.33, 132.70, 131.44, 130.53, 129.77, 119.79, 117.61, 114.78, 68.82, 40.38. IR (neat, $cm^{-1}$): 2980, 2926, 1511, 1681, 1607, 1510, 1412, 1358, 1267, 1245, 1077, 1115, 1047, 810, 680, 602. HRMS ($ES^+$): calcd for $C_{16}H_{16}BrO$ $[M + H]^+$ 302.0306; found 302.0301.

**1-Bromo-3-(3-methoxybenzyl)benzene (4.11)**

Colorless liquid (155 mg, 75%), $R_f$ (hexane) 0.50. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 7.33–7.32 (m, 2H), 7.22 (t, $J$ = 7.95 Hz, 1H), 7.16–7.10 (m, 2H), 6.77–6.76 (m, 2H), 6.71 (s, 1H), 3.91 (s, 2H), 3.78 (s, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 159.74, 143.22, 141.70, 131.86, 129.97, 129.55, 129.23, 127.52, 122.51, 121.30, 114.80, 111.48, 55.14, 41.51 ppm. IR (neat, $cm^{-1}$): 3001, 2934, 2834, 1593, 1567, 1488, 1475, 1454, 1258, 1050. EI (*m*/*z*) calcd for $C_{14}H_{13}BrO$ $[M]^+$ 276.0150; found 276.0157.

**1-Bromo-2-(4-ethoxybenzyl)benzene (4.12)**

Colorless liquid (163 mg, 75%), $R_f$ (hexane) 0.55. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.55 (d, $J$ = 6.75 Hz, 1H), 7.23–7.20 (m, 1H), 7.12–7.05 (m, 4H), 6.82 (d, $J$ = 8.55 Hz, 2H), 4.04 (s, 2H), 3.99 (q, $J$ = 7.05 Hz, 2H), 1.39 (t, $J$ = 7.05 Hz, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 157.40, 140.81, 132.78, 131.35, 130.93, 129.93, 127.74, 127.41, 124.78, 114.43, 63.36, 40.87, 14.86 ppm. IR (neat, $cm^{-1}$): 3031, 2979, 2925, 1612, 1592, 1567, 1510, 1425, 1392, 1245, 1176, 1070. EI (*m*/*z*) calcd for $C_{15}H_{15}BrO$ $[M]^+$ 290.0306; found 290.0307.

**1-Bromo-2-(3-methoxybenzyl)benzene (4.13)**

Colorless liquid (147 mg, 71%), $R_f$ (hexane) 0.55. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 7.56 (d, $J$ = 7.95 Hz, 1H), 7.23–7.19 (m, 2H), 7.14–7.13 (m, 1H), 7.09–7.06 (m, 1H), 6.79–6.74 (m, 3H), 4.09 (s, 2H), 3.77 (s, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 159.69, 141.07, 140.16, 132.81, 131.05, 129.39, 127.90, 127.46, 124.84, 121.40, 114.85, 111.44, 55.12, 41.70 ppm. IR (neat, $cm^{-1}$): 3001, 2934, 2834, 1593, 1567, 1488, 1475, 1454. EI (*m*/*z*) calcd for $C_{14}H_{13}BrO$ $[M]^+$ 276.0150; found 276.0151.

**1-Chloro-4-(4-ethoxybenzyl)benzene (4.14)**

White solid (with benzyl chloride, 174 mg, 94%; with benzyl iodide, 129 mg, 70%), m.p. 47–49 °C, $R_f$ (hexane) 0.59; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.24–7.23 (m, 2H), 7.09 (d, $J$ = 8.55 Hz, 2H), 7.06 (d, $J$ = 8.85 Hz, 2H), 6.83–6.81 (m, 2H), 4.00 (q, $J$ = 6.70 Hz, 2H), 3.88 (s, 2H), 1.40 (t, $J$ = 6.70 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 157.44, 140.08, 132.49, 131.73, 130.11, 129.77, 128.48, 114.53, 63.40, 40.33, 14.84. IR (KBr, cm$^{-1}$): 3030, 2979, 2908, 1612, 1582, 1510, 1489, 1477, 1244, 1175. EI ($m/z$) calcd for $C_{15}H_{15}ClO$ $[M]^+$ 246.0811; found 246.0810.

**1-(4-Chlorobenzyl)-3-methoxybenzene (4.15)**

Colorless liquid (with benzyl chloride, 145 mg, 83%; with benzyl iodide, 117 mg, 67%), $R_f$ (hexane) 0.55; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.25–7.19 (m, 3H), 7.12 (d, $J$ = 8.55 Hz, 2H), 6.76–6.74 (m, 2H), 6.70 (s, 1H), 3.91 (s, 2H), 3.77 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 159.75, 142.10, 139.36, 131.87, 130.22, 129.51, 128.53, 121.25, 114.75, 111.43, 55.13, 41.22. IR (neat, cm$^{-1}$): 3001, 2935, 2835, 1599, 1584, 1489, 1454, 1436, 1406, 1257, 1149. EI ($m/z$) calcd for $C_{14}H_{13}ClO$ $[M]^+$ 232.0655; found 232.0658.

**1-Chloro-3-(4-ethoxybenzyl)benzene (4.16)**

Colorless liquid (with benzyl chloride, 172 mg, 93%, with benzyl iodide, 124 mg, 66%), $R_f$ (hexane) 0.55. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.21–7.15 (m, 3H), 7.08–7.04 (m, 3H), 6.83 (d, $J$ = 8.85 Hz, 2H), 4.01 (q, $J$ = 7.05 Hz, 2H), 3.88 (s, 2H), 1.40 (t, $J$ = 7.0 Hz, 3H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 157.50, 143.66, 134.17, 132.11, 129.85, 129.62, 128.87, 126.96, 126.15, 114.55, 63.39, 40.65, 14.85 ppm. IR (neat, cm$^{-1}$): 3032, 2980, 2925, 1613, 1596, 1583, 1572, 1511, 1475, 1245, 1176. EI ($m/z$) calcd for $C_{15}H_{15}ClO$ $[M]^+$ 246.0811; found 246.0813.

**1-Chloro-3-(3-methoxybenzyl)benzene (4.17)**

Colorless liquid (with benzyl chloride, 135 mg, 77%; with benzyl iodide, 97 mg, 55%), $R_f$ (hexane) 0.57. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.23–7.16 (m, 4H), 7.07 (d, $J$ = 7.35 Hz, 1H), 6.77–6.75 (m, 2H), 6.71 (s, 1H), 3.92 (s, 2H), 3.78 (s, 3H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 159.75, 142.92, 141.73, 134.20, 129.65, 129.55, 128.96, 127.06, 126.31, 121.31, 114.81, 111.49, 55.14, 41.55 ppm. IR (neat, cm$^{-1}$): 3001, 2935, 2835, 1595, 1585, 1573, 1488, 1454, 1434, 1258, 1163, 1050. EI ($m/z$) calcd for $C_{14}H_{13}ClO$ $[M]^+$ 232.0655; found 232.0658.

**1-Chloro-2-(3-methoxybenzyl)benzene (4.19)**

Colorless liquid (117 mg, 67%), $R_f$ (hexane) 0.55. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.38–7.36 (m, 1H), 7.23–7.20 (m, 1H), 7.18–7.14 (m, 3H), 6.80–6.75 (m, 3H), 4.08 (s, 2H), 3.77 (s, 3H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 159.66, 141.09, 138.46, 134.17, 130.98, 129.49, 129.39, 127.66, 126.81, 121.34, 114.79, 111.39, 55.11, 39.14 ppm. IR (neat, cm$^{-1}$): 2935, 2834, 1600, 1584, 1488, 1469, 1453, 1441, 1256, 1051. EI ($m/z$) calcd for $C_{14}H_{13}ClO$ $[M]^+$ 232.0655; found 232.0650.

**Ethyl 3-(4-methoxybenzyl)benzoate (7.2)[20]**

Colorless liquid (136 mg, 68%), $R_f$ (5% EtOAc–hexane) 0.52; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.89 (s, 2H), 7.35–7.33 (m, 2H), 7.10 (d, $J$ = 8.55 Hz, 2H), 6.83 (d, $J$ = 8.55 Hz, 2H), 4.36 (q, $J$ = 7.20 Hz, 2H), 3.96 (s, 2H), 3.78 (s, 3H), 1.38 (t, $J$ = 7.30 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 166.70, 158.07, 141.83, 133.30, 132.64, 130.62, 129.86, 129.80, 128.44, 127.28, 113.95, 60.92, 55.23, 40.80, 14.32. IR (neat, cm$^{-1}$): 2981, 2933, 2835, 1717, 1611, 1585, 1160, 1246, 1104, 1034. EI ($m/z$) calcd for $C_{17}H_{18}O_3$ $[M]^+$ 270.1256; found 270.1254.

**Ethyl 3-(3-methoxybenzyl)benzoate (7.3)**

Colorless liquid (127 mg, 63%), $R_f$ (5% EtOAc–hexane) 0.48; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.90–7.87 (m, 2H), 7.37–7.32 (m, 2H), 7.21–7.18 (m, 1H), 6.78–6.71 (m, 3H), 4.35 (q, $J$ = 7.30 Hz, 2H), 3.99 (s, 2H), 3.76 (s, 3H), 1.38 (t, $J$ = 7.0 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 166.67, 159.75, 142.08, 141.16, 133.41, 130.66, 129.98, 129.51, 128.47, 127.42, 121.27, 114.75, 111.44, 60.93, 55.13, 41.70, 14.32. IR (neat, cm$^{-1}$): 2980, 2935, 2836, 1717, 1599, 1585, 1465, 1454, 1439, 1279, 1194, 1105. EI ($m/z$) calcd for $C_{17}H_{18}O_3$ $[M]^+$ 270.1256; found 270.1255.

**Ethyl 3-benzylbenzoate (7.4)[11c]**

Colorless liquid (139 mg, 77%), $R_f$ (5% EtOAc–hexane) 0.59; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.91–7.88 (m, 2H), 7.38–7.33 (m, 2H), 7.30–7.26 (m, 2H), 7.22–7.17 (m, 2H), 4.36 (q, $J$ = 7.05 Hz, 2H) 4.03 (s, 2H), 1.38 (t, $J$ = 7.35 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 166.68, 141.35, 133.43, 133.10, 130.64, 129.98, 128.85, 128.54, 128.47, 127.37, 126.25, 60.94, 41.68, 14.32. IR (neat, cm$^{-1}$): 2982, 1615, 1366, 1277, 1177, 1104, 1021. EI ($m/z$) calcd for $C_{16}H_{16}O_2$ $[M]^+$ 240.1150; found 240.1155.

**Ethyl 3-(4-methylbenzyl)benzoate (7.5)**

Colorless liquid (124 mg, 65%), $R_f$ (5% EtOAc–hexane) 0.65; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.90–7.87 (m, 2H), 7.35–7.33 (m, 2H), 7.11–7.06 (m, 4H), 4.36 (q, $J$ = 7.05 Hz, 2H), 3.98 (s, 2H), 2.31 (s, 3H), 1.38 (t, $J$ = 7.0 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 166.70, 141.66, 137.48, 135.76, 133.37, 130.60, 129.92, 129.23, 128.71, 128.44, 127.28, 60.91, 41.27, 20.99, 14.32. IR (neat, cm$^{-1}$): 2981, 1610, 1513, 1276, 1176, 1106, 1021, 739. EI ($m/z$) calcd for $C_{17}H_{18}O_2$ $[M]^+$ 254.1307; found 254.1306.

**Ethyl 3-(4-fluorobenzyl)benzoate (7.6)**

Colorless liquid (117 mg, 61%), $R_f$ (5% EtOAc–hexane) 0.62; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.89 (d, $J$ = 8.85 Hz, 2H), 7.37–7.32 (m, 2H), 7.14–7.12 (m, 2H), 6.99–6.95 (m, 2H), 4.36 (q, $J$ = 7.0 Hz, 2H), 3.99 (s, 2H), 1.38 (t, $J$ = 7.05 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 166.60, 161.5 (d, $J_{C-F}$ = 242.37 Hz), 141.20, 136.18, 133.28, 130.78, 130.45 (d, $J_{C-F}$ = 8.38 Hz), 129.88, 128.56, 127.49, 115.33 (d, $J_{C-F}$ = 21.6 Hz), 60.97, 40.84, 14.32. IR (neat, cm$^{-1}$): 2987, 1718, 1619, 1509, 1277, 1105, 1021, 781. EI ($m/z$) calcd for $C_{16}H_{15}FO_2$ $[M]^+$ 258.1056; found 258.1058.

**Ethyl 3-(4-chlorobenzyl)benzoate (7.7)**

Colorless liquid (102 mg, 51%), $R_f$ (5% EtOAc–hexane) 0.58; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.90–7.87 (m, 2H), 7.37–7.32 (m, 2H), 7.26–7.24 (m, 2H), 7.10 (d, $J$ = 8.25 Hz, 2H), 4.36 (q, $J$ = 7.0 Hz, 2H), 3.99 (s, 2H), 1.38 (t, $J$ = 7.0 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 166.57, 140.81, 138.96, 133.31, 132.10, 130.77, 130.18, 129.90, 128.66, 128.60, 127.57, 61.00, 40.98, 14.32. IR (neat, cm$^{-1}$): 3033, 1716, 1610, 1491, 1277, 1177, 1105, 1016. EI ($m/z$) calcd for $C_{16}H_{15}ClO_2$ $[M]^+$ 274.0761; found 274.0763.

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