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The Cross-Dehydrogenative-Coupling of Alkoxybenzenes with Toluences: Copper(II) Halide Mediated Tandem Halo/Benzylation of Arenes

Thomas E. Storr, Christopher J. Teskey and Michael F. Greaney[a]

Abstract: A cross-dehydrogenative-coupling of alkoxybenzenes and toluenes with concomitant halogenation is reported. Conditions employed were the use of stoichiometric copper halide salts and dialkylperoxides to afford a range of bromoalkoxydi- and triarylmethanes. Preliminary mechanistic studies suggest that the in situ production of haloarenes (or dihalobenzenes) followed by a copper mediated coupling of a benzylic radical is operational.

Introduction

Diarylmethanes, also known as benzhydryls, are privileged structural motifs found in pharmaceuticals, supramolecular chemistry, functional molecules, polymers, ligands, catalysts and dyestuffs. A number of pharmacologically active natural products contain the diarylmethane subunit, such as the vidalos A and B; halogenated diarylmethanes recently isolated from marine algae and shown to possess a wide range of biological activities, such as inhibition of carbonic anhydrase and phospholipase A2 (Figure 1).

Figure 1. Representative pharmaceuticals and algae-derived diarylmethane natural products.

The synthesis of diarylmethanes is generally carried out using nucleophilic substitution or cross-coupling of a-(pseudo)halide bearing benzylic units. Unfortunately, these methods sometimes require the use of forcing conditions (high temperatures) or the use of expensive transition metal catalyst and ligand systems. There has been growing interest in C–H functionalization approaches to directly functionalize benzylic C(sp³)–H bonds, cutting out pre-functionalization steps and improving overall atom economy. Despite a number of recent reports disclosing the direct substitution of benzylic C(sp³)–H bonds for various functional groups, reports of the analogous arylation are rare. Early work from Miura on this transformation demonstrated that para-nitrotoluene could be effectively cross-coupled with arylhalides to generate diarylmethanes. These findings have been extended to a number of Pd-catalyzed benzylic-C(sp³)–H direct arylation, but all require significant acidification of the benzylic position through electron-withdrawing groups (Scheme 1a), along with pre-functionalized aryl components (arylhalide or arylorganometallic). Within our research group, we have a continued interest in the use of cross-dehydrogenative-coupling reactions (CDC), where two disparate C–H components can be coupled to generate a new C–C bond. This approach has limited precedent for benzhydryl synthesis; the homo-dehydrogenative-coupling (HDC) of C(sp³)–C(sp³) positions is known for simple aromes such as para-xylene and mesitylene, and the CDC of C(sp³)–H and benzylic C(sp³)–H bonds has been the subject of a small number of reports. The groups of Shi, Song and Chen have described iron catalysed di- and tri-arylmethane syntheses using DDQ as an oxidant (Scheme 1b), and Duan and Zhang/Wen have described copper catalysed CDC benzylaion of coumarins and indoles, respectively.

Scheme 1. Benzylic C(sp³)–H arylation protocols.

We were thus interested in exploring the potential of CDC coupling to access alternative benzhydryls based on electron rich arene components. During our investigations into the feasibility of a CDC protocol we uncovered an unprecedented tandem reaction; the halo-benzylation of alkoxyarennes (Scheme 1c), which is the subject of this report.

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Supporting information, including copies of NMR spectra, for this article is given via a link at the end of the document.
Results and Discussion

Reaction discovery: We began by studying the reaction of toluene derivatives with various arenes under oxidative conditions. We were surprised to find that treatment of 1,3,5-trimethoxybenzene (1a, as limiting reagent) with para-xylene (2a, as solvent and coupling partner), in the presence of stoichiometric copper(II) bromide and di-tert-butyl peroxide (DTBP), gave the brominated benzydryl compound 4 (X = Br) as the major product along with small amounts of mono- and dibrominated 1,3,5-trimethoxybenzene (5 and 6) (Table 1, entry 4; see SI for full details). These reaction conditions have brought about the formation of the desired C(sp²)–C(sp³) bond as well as concomitant formation of a C(sp³)–Br bond. The reaction also occurred, albeit in poorer yield, with copper(II) chloride (entry 5).

Both para-bromotoluene and para-chlorotoluene were found to be poor coupling partners generating 4i and 4j in 28% and 25% yields respectively (Scheme 2). Surprisingly, toluene itself could not be effectively used to generate the desired product 4k. The reason for this observed phenomenon is not yet understood. The use of saturated heterocycles and cycloalkanes as coupling partners was attempted, but to no avail (Scheme 2).

![Scheme 2: Bromo-benzylation of 1,3,5-trimethoxybenzene.](image)

Table 1. Screening of copper salts to mediate a CDC formation of diarylmethanes

<table>
<thead>
<tr>
<th>entry</th>
<th>copper salt</th>
<th>yield of 3 (%)</th>
<th>yield of 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OTf)₂</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OAc)₂</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>CuSO₄</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>CuBr₂</td>
<td>0</td>
<td>49</td>
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<tr>
<td>5</td>
<td>CuCl₂</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>CuF₂</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Cu(acac)₂</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Given the striking similarity of the benzhydryl products of this tandem reaction to a number of marine natural products and pharmaceuticals, we were interested in further investigating this process. Optimization of the reaction conditions (see SI for details) established the general method of para-xylene (25 equiv.), CuBr₂ (2.0 equiv.) and either Luperox® 101 (2.5-Bis(tert-butylperoxy)-2,5-dimethylhexane, 2.25 equiv: Conditions A) or DTBP (4.5 equiv.: Conditions B) at 110 °C for 18 hours, providing 4a in serviceable yields of 52% and 48% respectively.

Substrate scope: We began by varying the substitution pattern and functionality of the benzylic component (Scheme 2). All xylene substitution patterns were tolerated providing the respective bromodiarylmethanes 4a, 4b and 4c in moderate yields (Scheme 2). In general, Luperox 101® was found to give slightly higher yields in comparison to using di-tert-butylperoxide so this oxidant was used for the majority of the future experiments performed. Other polymethylbenzenes, including mesitylene, durene and prehenitine, were tolerated (4d, 4e and 4f) along with tert-butylmethyl benzenes (4g and 4h; Scheme 2).

Due to the high crystallinity of many of the bromodiarylmethanes produced it was possible to grow single crystals of 4a and 4f suitable for X-ray diffraction analysis (Figure 2).

![Figure 2: Ortep diagrams for compounds 4a and 4f; thermal ellipsoids shown at 50% probability.](image)

It was possible to produce a tertiary benzylic carbon center from the respective secondary benzylic coupling partner: Using Conditions A with diphenylmethane the synthesis of triphenylmethane 4m was accomplished in 40% yield; 1,4-diethylbenzene and indane generated 4n and 4o in 41% and 20% yields respectively (Scheme 3). Interestingly, when using fluorene as the coupling partner with 1,3,5-trimethoxybenzene the des-halo product 4p was obtained which is in contrast to the halo-substituted product obtained with diphenylmethane.
Using the general protocol with Luperox 101® as the oxidant, an assessment of the electron rich component was performed. A number of 1,3-di and tri-alkoxybenzenes were subjected to the tandem bromination-xylation reaction conditions, all of which generated the desired product (Scheme 4). With an increase in steric congestion of the alkyl groups a decrease in chemical yield from 52% to 20% was observed (Mes=Et=Pr). Using 3,4,5-trimethoxytoluene as the substrate, it was possible to generate the respective highly functionalised hexa-substituted aromatic product 4s in a 12% yield. 1,3-Dimethoxybenzene was also reacted to yield compound 4t in a yield of 43%. We could also access chloride 4u in 38% yield from 1,3,5-trimethoxybenzene using CuCl₂ in place of CuBr₂, demonstrating that alternative copper-ions were viable in the transformation. 2,4,6-Trimethoxybenzoic acid was productive in the reaction, giving the bromide 4a in 44% yield via copper-mediated protodecarboxylation.¹¹

Mechanistic probes: With a functioning protocol for this unusual reaction in hand, our attention was turned to experiments which would allow us to speculate on a plausible mechanism for the tandem process (Figure 3). Firstly, a number of control experiments were performed: 1) it was found that the tandem process does not function if the peroxide is omitted; 2) stoichiometric copper(II) bromide is also necessary and cannot be substituted for copper(I) bromide; 3) adventitious oxygen is also detrimental to the efficacy of the reaction. We next examined the possibility of benzyl bromide being formed in situ from the respective toluene and copper(II) bromide in a similar process to the Wohl-Ziegler bromination.¹² Mixtures of para-xylene and copper(II) bromide (at the same concentration and stoichiometry as the tandem reaction protocol) gave only small amounts (14%) of the benzyl bromide in the presence of excess peroxide (Scheme 4a). On treatment of 1,3,5-trimethoxybenzene with an equivalent of α-bromo-para-xylene in benzene at 110 °C for 18 hours, little to none of the desired product was formed (Scheme 4b), suggesting that this reaction does not proceed via a benzyl halide intermediate.

Scheme 3. Scope of α-substituted benzylic coupling partner.

As a demonstration of the applicability of this methodology, we set out to synthesize penta-O-methyl vidalol A (8), which has shown moderate carbonic anhydrase inhibitory activity, in a single step.¹³ The poly-substituted toluene 7 was prepared and used as the benzylic component under our tandem reaction conditions with 1a. In order to render the reaction more economic with respect to the benzylic component, it was found possible to reduce the stoichiometry of 7 to 5.0 equivalents using benzene as a co-solvent. Pleasingly, the target compound 8 was produced under the reaction conditions, albeit in a low yield of 19% (Scheme 6). A number of attempts at demethylation to give the natural product were performed: but, due to the apparent instability of vidalol A, we were not able to isolate a sample of the natural product.

Scheme 4. Scope of the aryl coupling partner for halobenzylaition.

During our studies, we found that not all alkoxybenzenes will undergo the tandem functionalization process, in general these are substrates which already bear an electron withdrawing substituent at the 2-position (Scheme 5). To exemplify this single C–H functionalization process, 2-Nitro-1,3,5-trimethoxybenzene gave the product 4v in a good 76% yield. 2-Fluoro- and 2-Formyl-1,3,5-trimethoxybenzene were xylylated in 18% and 20% yields respectively although a number of minor by-products were observed in these reactions. Some alkoxybenzenes were also found to only produce the des-halo product, namely 1,2,3-trimethoxybenzene, 1,2,4,5-tetramethoxybenzene, and 1,4-dimethoxybenzene (4y – 29%, 4z – 22% and 4aa – 21%).

Scheme 5. Scope of the aryl coupling partner for benzylation.

Scheme 6. Synthesis of penta-O-methyl vidalol A.
Second, we studied the bromination of 1,3,5-trimethoxybenzene as it is well known that copper(II) bromide can be used as an effective electrophilic brominating agent. Treatment of 1a with 2.0 equivalents of copper(II) bromide, with and without the peroxide oxidant, afforded the mono-(5) and di-brominated (6) products, in approximately 1:2 ratio respectively (Figure 3c). The assertion of electrophilic bromination is also supported by the observation that a flocculent white precipitate, attributed to copper(I) salts, is formed relatively rapidly during the initial stages of the reaction.

Thirdly we subjected the pre-brominated compounds, 5 and 6, individually to the reaction conditions and successfully demonstrated that they are competent substrates for the synthesis of the benzhydyl product 4a in the presence of either copper(II) bromide and copper(I) bromide, albeit in decreased yield (Figure 3d and 3e). In the absence of any copper salts no reaction product was observed, and upon using substoichiometric quantities of both copper(II) bromide and copper(I) bromide a significantly decreased yield was observed (<10%). Interestingly, it was possible to further promote C–C bond formation (Figure 3f). If the reaction was run under the standard conditions for twenty hours, then an additional one equivalent of copper(I) bromide added to the reaction vessel, followed by further heating for 24 further hours, then 43% of the expected product 4a was isolated along with a considerable quantity of di-xylylated product 10 (25%).

Fourth, it is well known that the generation of radicals is possible from DTBH and benzylic C–H groups and heating.24 With this in mind, the role of these radicals was assessed. When carrying out the benchmark reaction in the presence of 2.0 equivalents of radical trapping agents TEMPO and galvinoxyl radical, no diphenylmethane product 4a was observed (Figure 3g; only halogenated starting materials were detected). These results support the hypothesis that a benzylic radical is generated as a key intermediate during the course of the reaction.

It is important to note that there is a significant dependence upon the electronics of the substrate; an electron withdrawing group on the alkoxybenzene substrate (at the meta-position with respect to the reactive position) is almost always necessary for the benzylation reaction to proceed hence why no dehalogenated products such as 3 are observed in most cases.

**Figure 3.** Mechanistic experiments and control reactions.

With the information gained from the control reactions and mechanistic probes, a plausible mechanism for the formation of 4a in this tandem process can be proposed (Scheme 7). The primary step involves the bromination of 1a with copper(II) bromide to generate 5, and the presence of the peroxide oxidant is able to accomplish a second bromination generating 6. Di-tert-butylperoxide undergoes a thermal homolysis of the O–O bond to generate reactive radicals, which abstract a hydrogen atom from the benzylic position of para-xylene. The benzylic radical produced is then reacted with 6 under the action of copper to generate the new C(sp²)–C(sp³) bond and the product. The exact role and intermediacy of the organocopper intermediates in this final step still remains to be established, but a benzylic radical could possibly react with a copper(II) salt generating a highly reactive alkyl copper(III) species. Studies to elucidate the mechanism of this interesting tandem reaction are on-going.

**Scheme 7.** A plausible reaction mechanism.
Conclusions

In summary, a new approach to the synthesis of highly substituted halodiarylmethanes has been demonstrated. The protocol employs stoichiometric copper(II) halides and dialkyl peroxides to promote the tandem halogenation-cross-dehydrogenative benzylolation of electron rich alkoxyarenes. Despite moderate yields being observed in many cases, the protocol is operationally simple and enables the one-step production of poly-substituted diarylmethanes from bulk commodity chemicals. The facility for rapidly generating high value functionalised arenes of biological interest was demonstrated in the one-step preparation of penta-O-methoxy vindalol A (8). Initial studies have revealed that this reaction likely proceeds via primary di-halogenation followed by a copper mediated coupling of a benzylic radical. Studies to further understand the mechanism of this tandem reaction are ongoing, with the aim of further developing and exploiting this novel cascade process in synthesis.

Experimental Section

General considerations: Nuclear Magnetic Resonance (NMR) spectra were recorded on 500, 400 or 300 MHz Bruker NMR spectrometers in CDCl₃ at 300 K (unless stated otherwise). For proton NMR, samples were prepared using ca. 10 mg of compound dissolved in 1.0 mL of CDCl₃ and for carbon NMR using ca. 10 mg of compound dissolved in 1.0 mL of CDCl₃ were prepared using ca. 10 mg of compound dissolved in 1.0 mL of CDCl₃. All spectra were referenced to the residual solvent peak (δ = 77.0 ppm) for ¹H NMR and the CDCl₃ solvent peak (δ = 37.0 ppm) for ¹³C[¹H] NMR. NMR Chemical shifts (δ) are reported in ppm; coupling constants (J) are reported in Hz; splitting patterns are assigned as singlet, doublet, triplet, quartet, br = broad signal and app = the apparent multiplicity. Where possible, when mixtures of isomers were isolated, the ¹H NMR spectrum was used to assign the substitution patterns and the ratio of isomers using comparison to literature data and authentic compounds. When purified compounds had inseparable residual starting material present, ¹H NMR spectrum was used to calculate the quantity and mass of the product and is quoted in the characterization data. High resolution mass spectrometry (HRMS) was measured using electrospray ionization (ESI) or electron impact ionization (EI) using a 0.5-1.0 mMold⁻¹ solution of compound in acetonitrile. Solvents, unless otherwise stated, were purchased in reagent grade or anhydrous quality and used as received. Reagents were either purchased directly from commercial suppliers or prepared according to literature procedures. All reactions were carried out in glass microwave vials equipped with aluminum crimp caps and a round-bottomed flask and sealed with a glass stopper and heated in oil baths with a thermocouple temperature control. Flash column chromatography was performed manually on silica gel eluting with hexane/ethyl acetate under pressurized air flow. 1,3,5-triarylxylenes were synthesized from 1,3,5-trifluorobenzene and the respective alcohol according to the procedure described by Jalalian and Olhoff.⁸⁻¹ or from phenylorgocinol and 3,5-dimethoxyphenol and alkylhalides using literature protocols.²⁸

General procedure: To a 10 mL reaction tube, equipped with a magnetic stirrer bar, was added the alkoxybenzene (0.25 mmol, 1.0 eq.), vacuum dried copper(II) bromide (111.7 mg, 0.5 mmol, 2.0 eq.) and a substituted toluene (6.25 mmol, 25 eq.). The reaction vessel was then purged with N₂, Luperox® 101 (196 mL, 0.56 mmol, 2.25 eq.) or di-tert-butylperoxide (207 µL, 1.13 mmol, 4.5 eq.) was then added and the reaction vessel was immediately sealed under N₂ atmosphere with a crimp cap seal and placed into a preheated oil bath at 110 °C. The reaction was heated for 18 hours, after which time the reaction was allowed to cool, diluted with dichloromethane (ca. 10 mL), analysed by thin layer chromatography and filtered through a cotton wool plug. The reaction mixture was then adsorbed onto the minimum amount of silica gel and purified by silica gel chromatography (gradient elution with ethyl acetate:hexane 2.98 to 3.5:96.5 to 5.95 and higher for the phenols). The product containing fractions were evaporated in vacuo to yield the product.

2-Bromo-1,3,5-trimethoxy-4-(4-methoxybenzyl)benzene (4a): Using the general procedure using Luperox101® (186 µL), copper(II) bromide (111.7 mg), 1,3,5-trimethoxybenzene (42.2 mg) and para-xylene (771 µL) yielded the title compound as an off-white crystalline solid 44.4 mg (101 µmol, 51%); T₆₂ = 110–112 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.10 (d, J = 8.0, 2H), 7.03 (d, J = 8.0, 2H), 6.35 (s, 1H), 3.97 (s, 3H), 3.90 (s, 3H), 3.81 (s, 3H), 3.71 (s, 3H), 2.29 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 158.2, 156.9, 155.8, 141.2, 137.6, 129.0, 127.9, 112.9, 112.6, 112.5, 116.9, 98.1, 92.8, 61.1, 56.4, 55.9, 29.2; MS (ESI) m/z = 182.1 (trimethoxyluteolene cation, 35.7), 357.2 (M[Br⁺]+Na⁺, 18.1), 359.2 (M[Br⁺]+CH₃⁺Na⁺, 23.5), 373.0 (M[Br⁺]+Na⁺, 14.9), 375.0 (M[Br⁺]+Na⁺, 14.2); HRMS (ESI) = 373.0415 (calcld = 373.0410 C₁ₙH₁₃Br₃NaO₃).  

2-Bromo-1,3,5-trimethoxy-4-(3-methylbenzyl)benzene (4b): Using the general procedure using Luperox101® (186 µL), copper(II) bromide (111.7 mg), 1,3,5-trimethoxybenzene (42.2 mg) and meta-xylene (764 µL) yielded the title compound as a light yellow solid crystalline solid 35.5 mg (101 µmol, 40%); ¹H NMR (400 MHz, CDCl₃) δ 7.11 (t, J = 7.5, 1H), 7.02 (s, 1H), 6.99 (d, J = 7.5, 1H), 6.95 (d, J = 7.5, 1H), 6.36 (s, 1H), 3.97 (s, 2H), 3.91 (s, 3H), 3.81 (s, 3H), 3.70 (s, 3H), 2.29 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 158.2, 156.9, 155.8, 141.2, 137.6, 129.0, 127.9, 126.4, 125.3, 116.9, 98.1, 92.8, 61.1, 56.4, 55.9, 29.2, 21.0; MS (ESI) m/z = 182.1 (trimethoxyluteolone cation, 39.5), 357.2 (M[Br⁺]+CH₃⁺Na⁺, 18.1), 359.2 (M[Br⁺]+CH₃⁺Na⁺, 23.5), 373.0 (M[Br⁺]+Na⁺, 14.9), 375.0 (M[Br⁺]+Na⁺, 14.2); HRMS (ESI) = 373.0415 (calcld = 373.0410 C₁₉H₁₃Br₃NaO₃).  

2-Bromo-1,3,5-trimethoxy-4-(2-methylbenzyl)benzene (4c): Using the general procedure using Luperox101® (186 µL), copper(II) bromide (111.7 mg), 1,3,5-trimethoxybenzene (42.2 mg) and ortho-xylene (755 µL) yielded the title compound as a white crystalline solid 45.0 mg (128 µmol, 51%); ¹H NMR (400 MHz, CDCl₃) δ 7.15 (d, J = 7.4, 1H), 7.06 (d, J = 7.4, 1.6, 1H), 6.97 (dd, J = 7.4, 1.6, 1H), 6.39 (s, 1H), 3.94 (s, 2H), 3.93 (s, 3H), 3.77 (s, 3H), 3.61 (s, 3H), 2.43 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 158.4, 157.0, 155.9, 139.2, 135.9, 129.6, 127.2, 125.7, 125.5, 116.2, 98.1, 92.7, 61.0, 56.4, 55.9, 26.8, 19.8; MS (ESI) m/z = 182.1 (trimethoxyluteolene cation, 34.6), 357.2 (M[Br⁺]+CH₃⁺Na⁺, 12.7), 359.2 (M[Br⁺]+CH₃⁺Na⁺, 16.9), 373.0 (M[Br⁺]+Na⁺, 17.1), 375.0 (M[Br⁺]+Na⁺, 15.6); HRMS (ESI) = 373.0401 (calcld = 373.0410 C₁₉H₁₃Br₃NaO₃).  

2-Bromo-1,3,5-trimethoxy-4-(3,5-dimethoxybenzyl)benzene (4d): Using the general procedure using Luperox101® (186 µL), copper(II) bromide (111.7 mg), 1,3,5-trimethoxybenzene (42.2 mg) and mestyrene (869 µL) yielded the title compound as an off-white solid 38.3 mg (105 µmol, ...
3H), 3.69 (s, 3H), 2.27 (s, 3H), 1.28 (s, 9H); 13C NMR (101 MHz, CDCl3) δ 158.3, 156.9, 155.7, 150.6, 140.8, 137.1, 126.1, 123.4, 122.7, 117.3, 98.1, 92.8, 61.0, 56.4, 55.9, 34.4, 31.4, 29.8, 21.7; MS (ESI) m/z = 182.1 (trimethoxytoluene cation, 30.5); 401.1 (M[BrNa]+Na+, 47.6); 403.1 (M[BrNa]+Na+, 48.4); HRMS (ESI) = 403.0701 (calcld. = 403.0768 C7H8Br2Na2O3);

2-Bromo-3,5,5-trimethoxy-4-(2,4,6-trimethylphenyl)benzene (4g): Using the general procedure using Luperox101® (186 µL), copper(II) bromide (111.7 mg), 1,3,5-trimethylbenzene (42.2 mg) and diphenylmethane (105 mg) to produce 4g as a white solid in 41% yield.

(3)-Bromo-2,4,6-trimethoxyphenyl)methylenedibenzene (4m): Using the general procedure using Luperox101® (186 µL), copper(II) bromide (111.7 mg), 1,3,5-trimethylbenzene (42.2 mg) and diphenylmethane (105 mg) to produce 4m as a white solid in 41% yield.

2-Bromo-3,5,5-trimethoxy-4-(1,3-diethylbenzyl)benzene (4h): Using the general procedure using Luperox101® (186 µL), copper(II) bromide (111.7 mg), 1,3,5-trimethylbenzene (42.2 mg) and para-diethylbenzene (839 mg) to produce 4h as a white solid in 33% yield.

2-Bromo-3,5,5-trimethoxy-4-(4-bromobenzyl)benzene (4i): Using the general procedure using Luperox101® (186 µL), copper(II) bromide (111.7 mg), 1,3,5-trimethylbenzene (42.2 mg) and para-bromotoluene (769 µL) to produce 4i as a white solid in 32% yield.

2-Bromo-3,5,5-trimethoxy-4-(4-chlorobenzyl)benzene (4j): Using the general procedure using Luperox101® (186 µL), copper(II) bromide (111.7 mg), 1,3,5-trimethylbenzene (42.2 mg) and para-chlorotoluene (1.08 mL) to produce 4j as a white solid in 41% yield.
1-(3-Bromo-2,4,6-trimethoxyphenyl)-2,3-dihydro-1H-indene (4a): Using the general procedure using Luperox101® (186 μl), copper(II) bromide (111.7 mg), 1,3,5-trimethoxybenzene (42.2 mg) and indane (766 μl) yielded the title compound as a yellow solid 19.3 mg (53 μmol; 21%); T<sub>sub</sub> = 74 – 76 °C; 11H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.79 (d, J = 7.5 Hz, 2H), 7.34 – 7.29 (m, 2H), 7.74 – 7.17 (m, 4H), 6.31 (d, J = 2.3 Hz, 1H), 5.95 (d, J = 2.3 Hz, 1H), 5.81 (s, 1H), 3.98 (s, 3H), 3.80 (s, 3H), 2.97 (s, 3H); 13C NMR (125 MHz, CDCl<sub>3</sub>): δ 160.2, 159.9, 159.8, 148.5, 141.2, 126.2, 123.7, 119.5, 110.7, 92.0, 91.1, 56.4, 55.9, 54.3, 38.6; MS (EI) m/z = 270.1 (M<sup>+</sup>Br<sup>-</sup>), 100.4; 394.1 (M<sup>+</sup>Na<sup>+</sup>), 97; HRMS (EI) = 392.0983 (calcd. = 392.0982 C<sub>20</sub>H<sub>15</sub>BrO<sub>2</sub>Na<sup>+</sup>).

2-Bromo-1,3,5-triisopropyl-4-(4-methylbenzyl)benzene (4r): Using the general procedure using Luperox101® (186 μl), copper(II) bromide (111.7 mg), 1,3,5-triisopropylbenzene (63.5 mg) and para-xylene (771 μl) yielded the title compound as an off-white solid 32.9 mg (84 μmol, 33%); T<sub>sub</sub> = 74 – 76 °C; 11H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.12 (d, J = 7.9 Hz, 2H), 7.02 (d, J = 7.9 Hz, 2H), 6.29 (s, 1H), 4.06 (q, J = 7.0 Hz, 2H), 3.96 (q, J = 7.0 Hz, 2H), 3.94 (s, 2H), 3.86 (q, J = 7.0 Hz, 2H), 2.28 (s, 3H), 1.46 (t, J = 7.0 Hz, 3H), 1.40 (t, J = 7.0 Hz, 3H), 1.34 (t, J = 7.0 Hz, 3H); 13C NMR (101 MHz, CDCl<sub>3</sub>): δ 157.6, 156.1, 155.2, 138.8, 135.0, 128.8, 128.5, 117.9, 99.1, 95.1, 69.5, 65.3, 64.3, 26.3, 21.7, 15.9, 14.9, 14.9; MS (EI) m/z = 392.1 (M<sup>+</sup>Br<sup>-</sup>), 100.0; 394.1 (M<sup>+</sup>Na<sup>+</sup>), 97; HRMS (EI) = 392.0983 (calcd. = 392.0982 C<sub>20</sub>H<sub>15</sub>BrO<sub>2</sub>Na<sup>+</sup>).

1-Bromo-2,3,4-trimethoxy-6-methyl-5-(4-methylbenzyl)benzene (4s): Using the general procedure using Luperox101® (186 μl), copper(II) bromide (111.7 mg), 3,4,5-trimethoxylutene (45.6 mg) and para-xylene (839 μl) yielded the title compound as a yellow oil 11.0 mg (30 μmol, 12%); 11H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.06 (d, J = 7.7 Hz, 2H), 6.97 (d, J = 7.7 Hz, 2H), 4.04 (s, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.74 (s, 3H), 2.29 (s, 3H), 2.28 (s, 3H); 13C NMR (125 MHz, CDCl<sub>3</sub>): δ 151.6, 149.6, 145.2, 137.3, 135.4, 132.9, 129.6, 129.2, 118.7, 61.2, 61.0, 32.8, 21.1, 19.9; MS (EI) m/z = 349.0 (M<sup>+</sup>Br<sup>-</sup>CH<sub>3</sub>), 251.0 (M<sup>+</sup>Br<sub>2</sub>CH<sub>3</sub>), 11.0, 364.1 (M<sup>+</sup>Br<sub>3</sub>), 100; 366.1 (M<sup>+</sup>Br<sub>4</sub>), 97; HRMS (EI) = 364.0655 (calcd. = 364.0674 C<sub>20</sub>H<sub>15</sub>Br<sub>4</sub>O<sub>2</sub>).
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Keywords: Copper Catalysis • Cross-Dehydrogenative-Coupling (CDC) • Diarylmethane • Tandem Reaction • Vidalol A


A copper mediated cross-dehydrogenative-coupling of alkoxybenzenes and toluenes with concomitant halogenation is reported. A range of bromoalkoxydi- and tri-arylmethanes are synthesized and a plausible mechanism is proposed.