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

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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 dihaloarenes) followed by a copper-mediated coupling of a benzylic radical is operational.

Introduction

Diarylmethanes, also known as benzhydryls, are privileged structural motifs[1] found in pharmaceuticals,[2] supramolecular chemistry,[3] functional molecules,[4] polymers,[5] ligands,[6] catalysts[7] and dyestuffs.[8] A number of pharmacologically active natural products contain the diarylmethane subunit,[9] such as the vidalols A and B; halogenated diarylmethanes recently isolated from marine algae have been shown to possess a wide range of biological activities, such as inhibition of carbonic anhydrase and phospholipase A2 (Figure 1).[10]

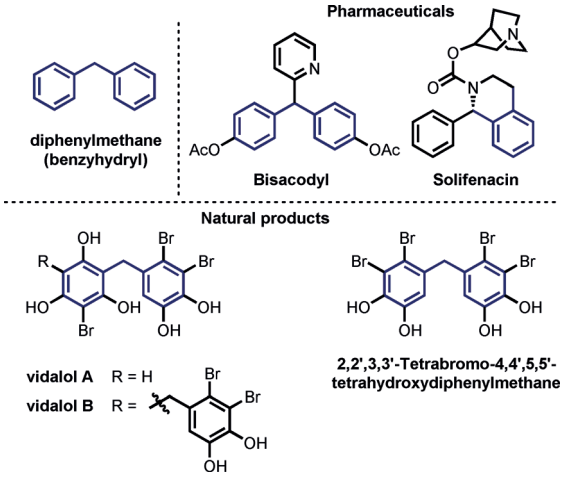

Figure 1. Representative pharmaceuticals and algae-derived diarylmethane natural products.

The synthesis of diarylmethanes is generally carried out using nucleophilic substitution or cross-coupling of an α-(pseudo)halide bearing benzylic unit.[11] Unfortunately, these methods sometimes require the use of forcing conditions (high temperatures) or the use of an expensive transition-metal catalyst and ligand systems. There has been growing interest in C–H functionalization approaches to directly functionalize benzylic C(sp^3)–H bonds, cutting out pre-functionalization steps and improving overall atom economy.[12] Despite a number of recent reports disclosing the direct substitution of benzylic C(sp^3)–H bonds for various functional groups,[13] reports of the analogous arylations are rare. Early work from Miura on this transformation demonstrated that *para*-nitrotoluenes could be effectively cross-coupled with arylhalides to generate diarylmethanes.[14] These findings have been extended to a number of Pd-catalyzed benzylic-C(sp^3)–H direct arylations, but all require significant acidification of the benzylic position through electron-withdrawing groups (Scheme 1 a),[15] 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),[16] in which two disparate C–H components can be coupled to generate a new C–C bond.[17] This approach has limited precedent for benzhydryl synthesis; the homo-dehydrogenative-coupling (HDC) of C(sp^2)–C(sp^3) positions is known for simple arenes such as *para*-xylene and mesitylene,[18] and the CDC of C(sp^2)–H and benzylic C(sp^3)–H bonds has been the subject of a small number of reports. The groups of Shi, Song and Chen have described iron-catalyzed di- and triarylmethane syntheses using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an oxidant (Scheme 1 b),[19] and Duan and Zhang/Wen have described copper-catalyzed CDC benzylation of coumarins and indoles, respectively.[20]

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

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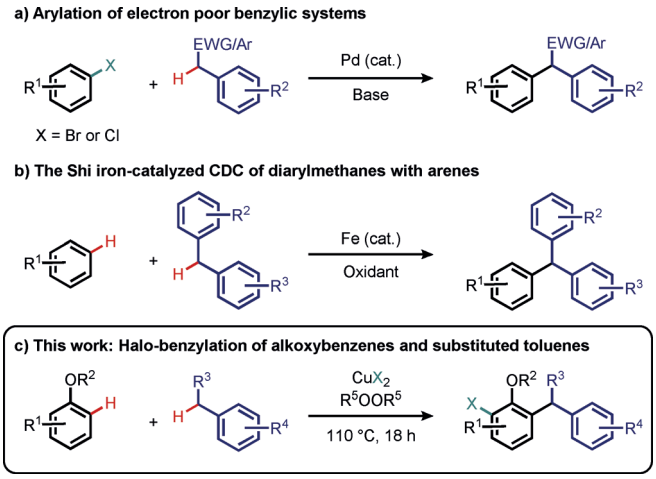


Scheme 1. Benzylic C(sp^3)–H arylation protocols.

tandem reaction, the halo-benzylation of alkoxyarenes (Scheme 1 c), which is the subject of this report.

Results and Discussion

Reaction discovery

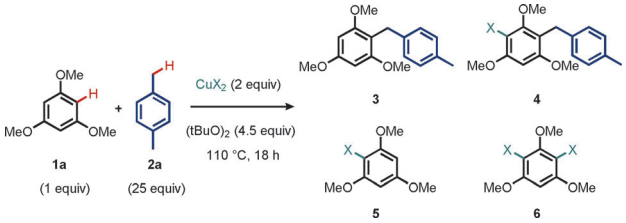
We began by studying the reaction of toluene derivatives with various arenes under oxidative conditions. We were surprised to find that treatment of 1,3,5-trimethoxybenzene (**1 a**, as a limiting reagent) with *para*-xylene (**2 a**, as the solvent and coupling partner), in the presence of stoichiometric copper(II) bromide and di-*tert*-butyl peroxide (DTBP), gave the brominated benzhydryl 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 the Supporting Information for full details). These reaction conditions have brought about the formation of the desired C(sp^2)–C(sp^3) bond as well as concomitant formation of a C(sp^2)–Br bond. The reaction also occurred, albeit in poorer yield, with copper(II) chloride (Table 1, entry 5).

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 the Supporting Information for details) established the general method of *para*-xylene (25 equiv), $CuBr_2$ (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 h, providing **4 a** in serviceable yields of 52 and 48% respectively.

Substrate scope

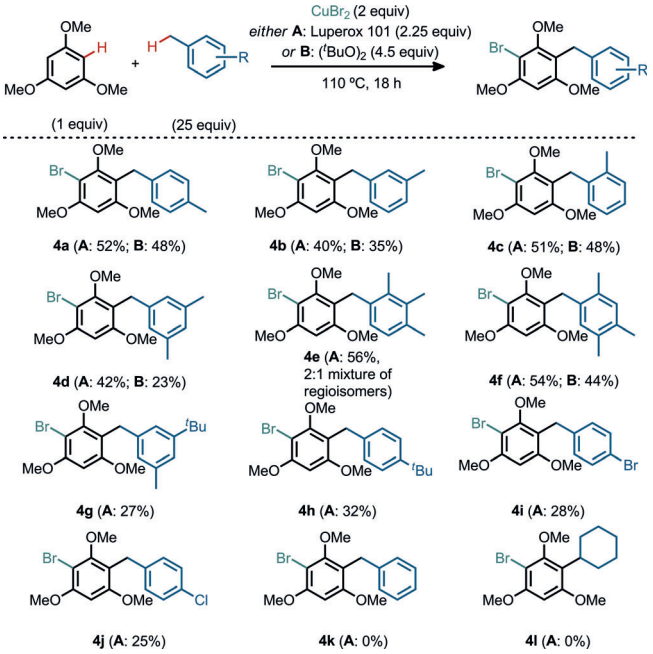
We began by varying the substitution pattern and functionality of the benzylic component (Scheme 2). All xylene substitution patterns were tolerated providing the respective bromodiarylmethanes **4 a–c** in moderate yields (Scheme 2). In general, Luperox 101® was found to give slightly higher yields 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 (**4 d–f**) along with *tert*-butylmethylbenzenes (**4 g** and **4 h**; Scheme 2). Both *para*-bromotoluene and *para*-chlorotoluene were found to be poor coupling partners generating **4 i** and **4 j** in 28 and 25% yields, respectively (Scheme 2). Surprisingly, toluene itself could not be effectively used to generate the desired product **4 k**. The reason for this observed phenomenon is not yet understood. The use of saturated heterocycles and cycloalkanes as coupling partners was attempted to no avail (Scheme 2). Due to the high crystallinity of many of the bromodiarylmethanes produced it was possible

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



Entry	Copper salt	Yield of **3** [%]	Yield of **4** [%]
1	$Cu(OTf)_2$	0	0
2	$Cu(OAc)_2$	0	0
3	$CuSO_4$	0	0
4	$CuBr_2$	0	49
5	$CuCl_2$	0	24
6	CuF_2	0	0
7	$[Cu(acac)_2]$[a]	0	0

[a] acac = acetylacetone.



Scheme 2. Bromo-benzylation of 1,3,5-trimethoxybenzene.

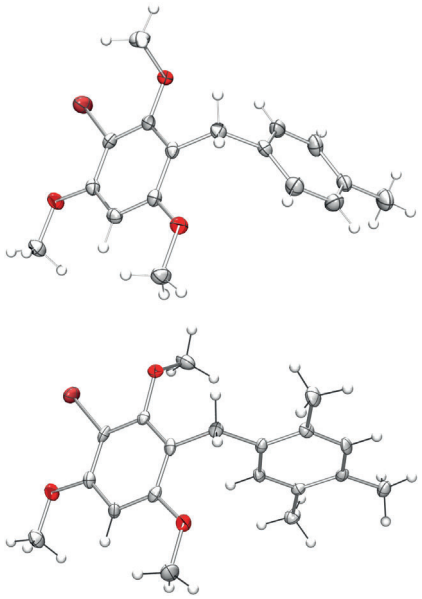
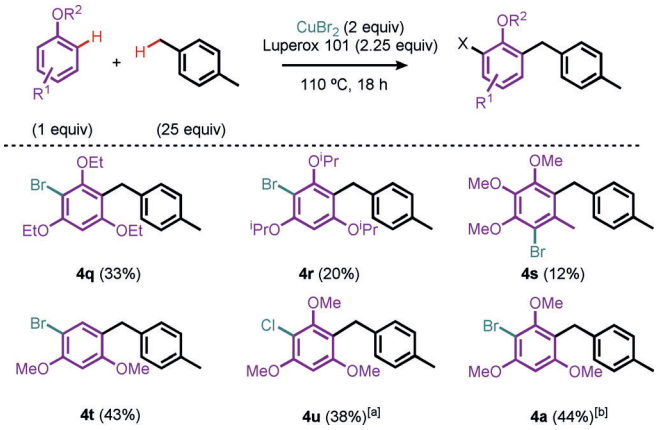


Figure 2. ORTEP diagrams for compounds **4a** (top) and **4f** (bottom); thermal ellipsoids shown at 50% probability.

to grow single crystals of **4a** and **4f** suitable for X-ray diffraction analysis (Figure 2).

It was possible to produce a tertiary benzylic carbon center from the respective secondary benzylic coupling partner: By 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.

By 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 trialkoxybenzenes were subjected to the tandem bromination–xylylation 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 (Me > Et > *i*Pr). When using 3,4,5-trimethoxytoluene as the substrate, it was possible to generate the respective highly-functionalized

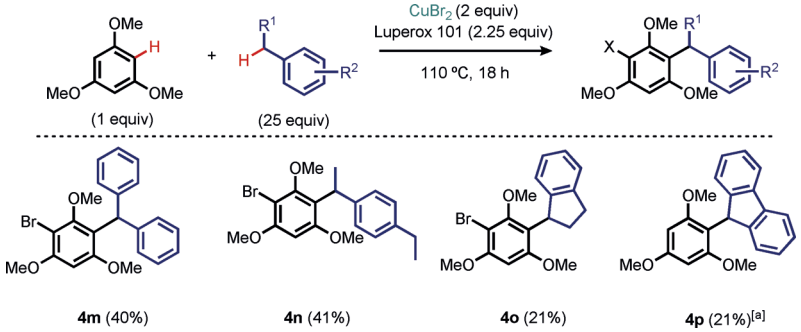


Scheme 4. Scope of the aryl coupling partner for halobenzylation. [a] $CuCl_2$ used in place of $CuBr_2$. [b] 2,4,6-Trimethoxybenzoic acid used as the substrate.

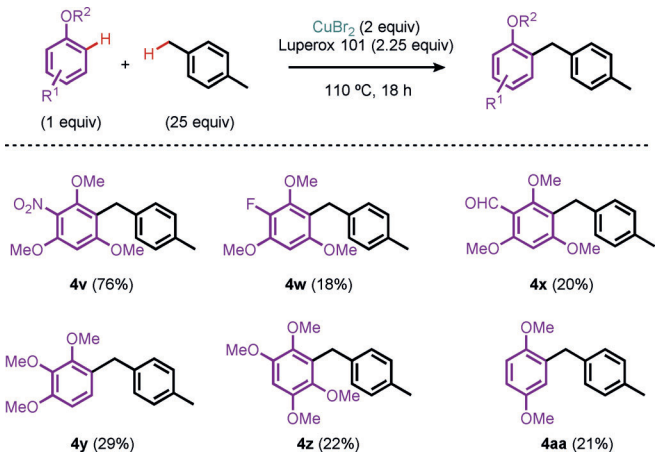
hexa-substituted aromatic product **4s** in a 12% yield. 1,3-Dimethoxybenzene was also reacted to yield compound **4t** in a yield of 43%. We could also access chloride **4u** in 38% yield from 1,3,5-trimethoxybenzene by using $CuCl_2$ in place of $CuBr_2$, demonstrating that alternative copper ions were viable in the transformation. 2,4,6-Trimethoxybenzoic acid was productive in the reaction, giving the bromide **4a** in 44% yield through copper-mediated protodecarboxylation.[21]

During our studies, we found that not all alkoxybenzenes will undergo the tandem functionalization process; in general these are substrates that 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 byproducts 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%).

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.[10i] The polysubstituted toluene **7** was prepared and used as the benzylic component under our tandem reac-

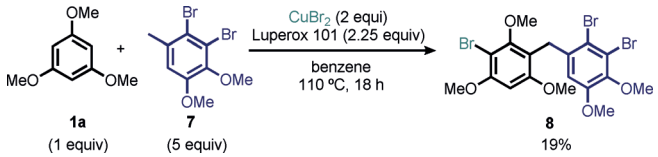


Scheme 3. Scope of an α-substituted benzyl coupling partner. [a] Reaction carried out with 15 equiv of fluorene and benzene (1 mL) as solvent.



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

tion conditions with **1a**. 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 6. Synthesis of penta-*O*-methyl vidalol A.

Mechanistic probes

With a functioning protocol for this unusual reaction in hand, our attention was turned to experiments that 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; and 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.[22] 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 (Figure 3a). On treatment of 1,3,5-trimethoxybenzene with an equivalent of α-bromo-*para*-xylene in benzene at 110 °C for 18 h, little to none of the desired product was formed (Figure 3b), which suggests that this reaction does not proceed via a benzyl halide intermediate.

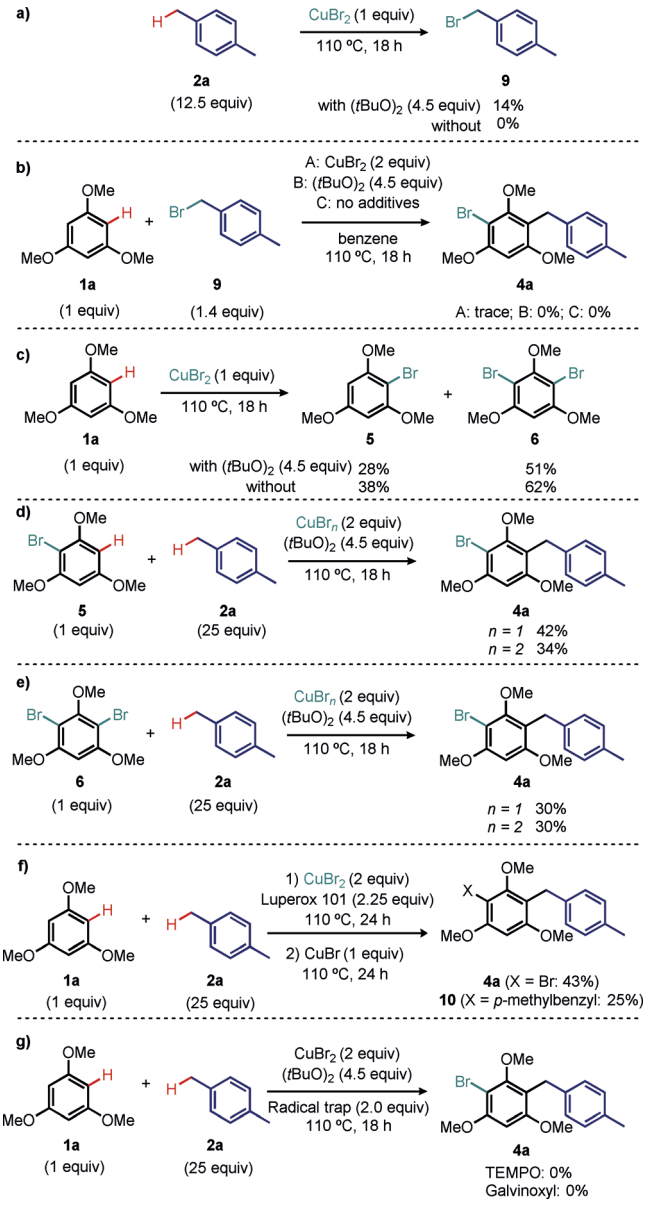


Figure 3. Mechanistic experiments and control reactions.

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.[23] Treatment of **1a** with 2.0 equivalents of copper(II) bromide, with and without the peroxide oxidant, afforded the mono- (**5**) and dibrominated (**6**) products, in an 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 or copper(I) bromide, albeit in decreased yield (Figure 3d and e). 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 3 f). If the reaction was run under the standard conditions for 20 hours, then an additional one equivalent of copper(I) bromide was added to the reaction vessel, followed by further heating for a further 24 hours, then 43% of the expected product **4a** was isolated along with a considerable quantity of dixylylated 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 3 g; 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 deshalogenated products such as **3** are observed in most cases.

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 $C(sp^2)$–$C(sp^3)$ 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.

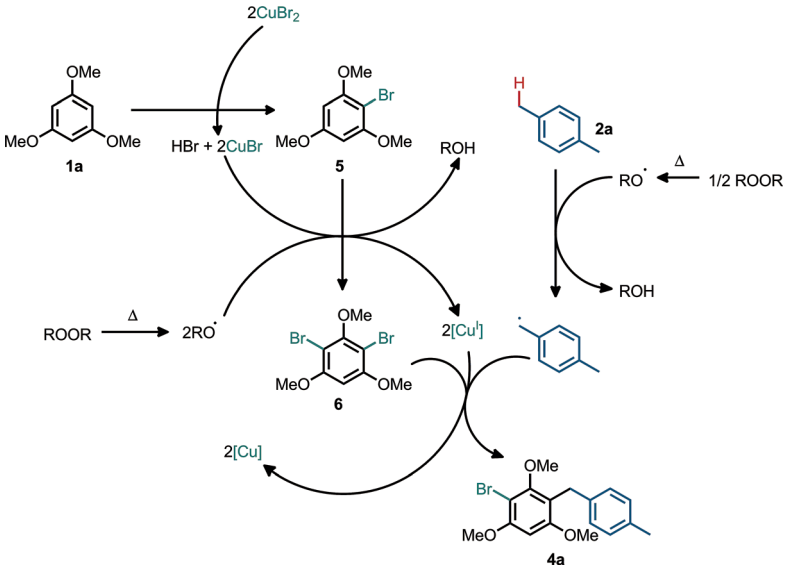
Conclusions

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 benzylation of electron-rich alkoxyarenes. Despite moderate yields being observed in many cases, the protocol is operationally simple and enables the one-step production of polysubstituted diarylmethanes from bulk commodity chemicals. The facility for rapidly generating high-value functionalized arenes of biological interest was demonstrated in the one-step preparation of penta-*O*-methoxy vidalol A (**8**). Initial studies have revealed that this reaction likely proceeds by primary dihalogenation followed by a copper-mediated coupling of a benzylic radical. Studies to further the understanding of this tandem reaction are on-going, with the aim of further developing and exploiting this novel cascade process in synthesis.

Experimental Section

General considerations

NMR spectra were recorded on 500, 400 or 300 MHz Bruker NMR spectrometers in $CDCl_3$ at 300 K (unless stated otherwise). For proton NMR, samples were prepared using ca. 10 mg of compound dissolved in 1.0 mL of $CDCl_3$ and for carbon NMR using ca. 20 mg



Scheme 7. A plausible reaction mechanism.

of compound dissolved in 1.0 mL of $CDCl_3$. All spectra were referenced to the residual solvent peak $CHCl_3$ ($\delta = 7.26$ ppm) for ^1H NMR and the $CDCl_3$ solvent peak ($\delta = 77.0$ ppm) for $^{13}C\{^1H\}$ NMR. NMR chemical shifts (δ) are reported in ppm; coupling constants (J) are reported in Hz; splitting patterns are assigned s = singlet, d = doublet, t = triplet, q = 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, the ^1H NMR spectrum was used to calculate the quantity and mass of the product and is quoted in the characterization data. HRMS was measured using electrospray ionization (ESI) or electron impact ionization (EI) using a 0.5–1.0 mMol dm^{-3} 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 aluminium crimpcaps or 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-trialkoxyarenes were synthesized from 1,3,5-trifluorobenzene and the respective alcohol according to the procedure described by Jalalian and Olofsson[25] or from phloroglucinol or 3,5-dimethoxyphenol and alkylhalides by using literature protocols.[26]

General procedure

To a 10 mL reaction tube, equipped with a magnetic stirrer bar, was added the alkoxybenzene (0.25 mmol, 1.0 equiv), vacuum-dried copper(II) bromide (111.7 mg, 0.5 mmol, 2.0 equiv) and a substituted toluene (6.25 mmol, 25 equiv). The reaction vessel was then purged with N_2, Luperox® 101 (186 μL, 0.56 mmol, 2.25 equiv) or di-*tert*-butylperoxide (207 μL, 1.13 mmol, 4.5 equiv) was added and the reaction vessel was immediately sealed under a N_2 atmosphere with a crimp cap seal and placed into a pre-heated oil bath at 110 °C. The reaction was heated for 18 h, 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-methylbenzyl)benzene (4a): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 1,3,5-trimethoxybenzene (42.2 mg) and *para*-xylene (771 μL), the title compound was obtained as an off-white crystalline solid (44.4 mg (126 μmol, 51%). $T_m = 110–112$ °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.10$ (d, $J = 8.0$, 2H), 7.03 (d, $J = 8.0$, 2H), 6.35 (s, 1H), 3.97 (s, 2H), 3.90 (s, 3H), 3.81 (s, 3H), 3.71 (s, 3H), 2.29 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 158.2$, 156.8, 155.7, 138.2, 134.9, 128.8, 128.1, 117.1, 98.1, 92.8, 61.1, 56.4, 55.9, 29.2, 21.0 ppm; MS (ESI): *m/z*: (%):182.1 [trimethoxytoluene cation] (39.5), 357.2 [$M(Br^{79})-CH_5+Na^+$] (18.1), 359.2 [$M(Br^{81})-CH_5+Na^+$] (23.5), 373.0 [$M(Br^{79})+Na^+$] (14.9), 375.0 [$M(Br^{81})+Na^+$] (14.2); HRMS (ESI): *m/z*: calcd for $C_{17}H_{19}Br^{79}NaO_3^+$: 373.0410; found: 373.0415.

2-Bromo-1,3,5-trimethoxy-4-(3-methylbenzyl)benzene (4b): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 1,3,5-trimethoxybenzene (42.2 mg) and *meta*-xylene (764 μL), the title compound was obtained as a light-yellow solid crystalline solid (35.5 mg, 101 μmol, 40%). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.11$ (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 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta =$ 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, 29.5, 21.4 ppm; MS (ESI): *m/z* (%): 182.1 [trimethoxytoluene cation] (32.5), 357.2 [$M(Br^{79})-CH_5+Na^+$] (15.1), 359.2 [$M(Br^{81})-CH_5+Na^+$] (19.6), 373.0 [$M(Br^{79})+Na^+$] (31.0), 375.0 [$M(Br^{81})+Na^+$] (31.0); HRMS (ESI): *m/z*: calcd for $C_{17}H_{19}Br^{79}NaO_3^+$: 373.0410; found: 373.0400.

2-Bromo-1,3,5-trimethoxy-4-(2-methylbenzyl)benzene (4c): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 1,3,5-trimethoxybenzene (42.2 mg) and *ortho*-xylene (755 μL), the title compound was obtained as a white crystalline solid (45.0 mg, 128 μmol, 51%). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.15$ (d, $J = 7.4$, 1H), 7.06 (td, $J = 7.4$, 1.6, 1H), 7.02 (td, $J = 7.4$, 1.6, 1H), 6.77 (dd, $J = 7.4$, 1H), 6.39 (s, 1H), 3.94 (s, 2H), 3.93 (s, 3H), 3.77 (s, 3H), 3.61 (s, 3H), 2.43 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 158.4$, 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 ppm; MS (ESI): *m/z* (%): 182.1 [trimethoxytoluene cation] (34.6), 357.2 [$M(Br^{79})-CH_5+Na^+$] (12.7), 359.2 [$M(Br^{81})-CH_5+Na^+$] (16.9), 373.0 [$M(Br^{79})+Na^+$] (17.1), 375.0 [$M(Br^{81})+Na^+$] (15.6); HRMS (ESI): *m/z*: calcd for $C_{17}H_{19}Br^{79}NaO_3^+$: 373.0410; found: 373.0401.

2-Bromo-1,3,5-trimethoxy-4-(3,5-dimethylbenzyl)benzene (4d): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 1,3,5-trimethoxybenzene (42.2 mg) and mesitylene (869 μL), the title compound was obtained as an off-white solid (38.3 mg, 105 μmol, 42%). ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.81$ (s, 2H), 6.78 (s, 1H), 6.36 (s, 1H), 3.94 (s, 2H), 3.92 (s, 3H), 3.82 (s, 3H), 3.71 (s, 3H), 2.26 ppm (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 158.3$, 156.9, 155.8, 141.2, 137.4, 127.3, 126.0, 117.1, 98.2, 92.9, 61.0, 56.4, 55.9, 29.4, 21.3 ppm; MS (ESI): *m/z* (%): 182.1 [trimethoxytoluene cation] (30.2), 387.1 [$M(Br^{79})+Na^+$] (82.3), 389.1 [$M(Br^{81})+Na^+$] (78.0); HRMS (ESI): *m/z*: calcd for $C_{18}H_{21}Br^{79}NaO_3^+$: 387.0566; found: 387.0560.

2-Bromo-1,3,5-trimethoxy-4-(2,3–4-trimethylbenzyl)benzene (4e) and 2-bromo-1,3,5-trimethoxy-4-(2,3–6-trimethylbenzyl)-benzene (4e′): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 1,3,5-trimethoxybenzene (42.2 mg) and prehenitene (932 μL), the two isomeric title compounds were obtained (in a ca. 2:1 ratio of **4e**/**4e′**) as an off-white solid (53.3 mg, 141 μmol, 56%) (samples of the isomers were isolated separately for characterization purposes). **4e**: ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.81$ (d, $J = 7.8$, 1H), 6.47 (d, $J = 7.8$, 1H), 6.38 (s, 1H), 3.94 (s, 2H), 3.93 (s, 3H), 3.76 (s, 3H), 3.61 (s, 3H), 2.34 (s, 3H), 2.24 (s, 3H), 2.22 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 158.5$, 157.1, 155.8, 136.4, 134.7, 134.3, 133.6, 126.8, 124.4, 116.4, 98.2, 92.7, 61.1, 56.5, 55.9, 27.6, 20.8, 16.0, 15.5 ppm; MS (ESI): *m/z* (%): 182.1 [trimethoxytoluene cation] (8.6), 401.1 [$M(Br^{79})+Na^+$ (100), 403.1 [$M(Br^{81})+Na^+$] (99.1); HRMS (ESI): *m/z*: calcd for $C_{19}H_{23}Br^{79}NaO_3^+$: 401.0723; found: 401.0719; **4e′**: ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.88$ (s, 2H), 6.30 (s, 1H), 4.02 (s, 2H), 3.88 (s, 3H), 3.70 (s, 3H), 3.29 (s, 3H), 2.30 (s, 3H), 2.22 (s, 3H), 2.13 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 158.2$, 157.1, 155.4, 138.2, 135.8, 135.1, 133.9, 127.2, 127.1, 117.5, 98.5, 93.1, 60.6, 56.4, 56.0,

25.1, 20.8, 20.6, 15.7 ppm; MS (ESI): *m/z* (%): 182.1 [trimethoxytoluene cation] (8.6), 401.1 [$M(Br^{79})$+Na^+] (100), 403.1 [$M(Br^{81})$+Na^+] (99.1); HRMS (ESI): *m/z*: calcd for $C_{19}H_{23}Br^{79}NaO_3^+$: 401.0723; found: 401.0719.

2-Bromo-1,3,5-trimethoxy-4-(2,4,5-trimethylbenzyl)benzene (4f): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 1,3,5-trimethoxybenzene (42.2 mg) and durene (1.00 mL), the title compound was obtained as a white crystalline solid (51.5 mg, 136 μmol, 54%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.93 (s, 1H), 6.53 (s, 1H), 6.39 (s, 1H), 3.94 (s, 3H), 3.89 (s, 2H), 3.79 (s, 3H), 3.64 (s, 3H), 2.37 (s, 3H), 2.18 (s, 3H), 2.10 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.5, 157.1, 155.8, 136.3, 133.4, 133.4, 133.0, 131.1, 128.6, 116.7, 98.2, 92.8, 61.0, 56.4, 55.9, 26.3, 19.3, 19.1, 19.1 ppm; MS (ESI): *m/z* (%): 182.1 [trimethoxytoluene cation] (30.5), 401.1 [$M(Br^{79})$+Na^+] (47.6), 403.1 [$M(Br^{81})$+Na^+] (48.4); HRMS (ESI): *m/z*: calcd for $C_{19}H_{23}Br^{79}NaO_3^+$: 401.0723; found: 401.0701.

2-Bromo-4-(3-*tert*-butyl-5-methylbenzyl)-1,3,5-trimethoxy-benzene (4g): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 1,3,5-trimethoxybenzene (42.2 mg) and 1-*tert*-butyl-3,5-dimethylbenzene (1.17 mL), the title compound was obtained as an off-white solid (27.7 mg, 68 μmol, 27%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (s, 1H), 6.97 (s, 1H), 6.80 (s, 1H), 6.35 (s, 1H), 3.96 (s, 2H), 3.91 (s, 3H), 3.81 (s, 3H), 3.69 (s, 3H), 2.27 (s, 3H), 1.28 ppm (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): 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, 61.1, 56.4, 55.9, 34.4, 31.4, 29.8, 21.7 ppm; MS (ESI): *m/z* (%): 429.1 [$M(Br^{79})$+Na^+] (8.4), 431.1 [$M(Br^{81})$+Na^+] (8.5), 475.2 [$M(Br^{79})$+ImidazoleH$^+$] (99.1), 477.2 [$M(Br^{81})$+ImidazoleH$^+$] (100); HRMS (ESI): *m/z*: calcd for $C_{21}H_{27}Br^{79}NaO_3^+$: 429.1036; found: 429.1034.

2-Bromo-1,3,5-trimethoxy-4-(4-*tert*-butylbenzyl)benzene (4h): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 1,3,5-trimethoxybenzene (42.2 mg) and *para*-*tert*-butyltoluene (1.08 mL), the title compound was obtained as an off-white solid (31.0 mg, 79 μmol, 32%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (d, J = 8.4, 2H), 7.14 (d, J = 8.4, 2H), 6.35 (s, 1H), 3.97 (s, 2H), 3.90 (s, 3H), 3.82 (s, 3H), 3.72 (s, 3H), 1.28 ppm (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.2, 156.9, 155.8, 148.3, 138.2, 127.9, 125.0, 117.2, 98.2, 92.9, 61.0, 56.5, 55.9, 34.3, 31.4, 29.1 ppm; MS (ESI): *m/z* (%): 182.1 [trimethoxytoluene cation] (9.8), 415.1 [$M(Br^{79})$+Na^+] (97.4), 403.1 [$M(Br^{81})$+Na^+] (100); HRMS (ESI): *m/z*: calcd for $C_{19}H_{23}Br^{79}NaO_3^+$: 415.0879; found: 415.0909.

2-Bromo-1,3,5-trimethoxy-4-(4-bromobenzyl)benzene (4i): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 1,3,5-trimethoxybenzene (42.2 mg) and *para*-bromotoluene (769 μL), the title compound was obtained as a mixture with 1-bromo-2,4,6-trimethoxybenzene (in a 1:2 ratio of **4i**/**5**) as a brown solid (63.1 mg; this equates to 28.8 mg of the title compound; 70 μmol, 28%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (d, J = 8.4, 2H), 7.07 (d, J = 8.4, 2H), 6.33 (s, 1H), 3.92 (s, 2H), 3.90 (s, 3H), 3.79 (s, 3H), 3.71 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.1, 156.8, 156.0, 140.4, 131.1, 130.1, 119.3, 116.3, 98.1, 92.8, 61.1, 56.5, 55.8, 29.1 ppm; MS (ESI): *m/z* (%): 182.1 [trimethoxytoluene cation] (37.2), 436.1 [$M(Br^{79}/Br^{79})$+Na^+] (22.4), 438.1 [$M(Br^{79}/Br^{81})$+Na^+] (44.5), 440.1 [$M(Br^{81}/Br^{81})$+Na^+] (22.0); HRMS (ESI): *m/z*: calcd for $C_{16}H_{16}Br^{79}{}_2NaO_3^+$: 436.9358; found: 436.9359.

2-Bromo-1,3,5-trimethoxy-4-(4-chlorobenzyl)benzene (4j): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 1,3,5-trimethoxybenzene (42.2 mg) and *para*-chlorotoluene (1.08 mL), the title compound was obtained as an off-white solid (23.0 mg; 62 μmol, 32%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, J = 8.5, 2H), 7.12 (d, J = 8.5, 2H), 6.34 (s, 1H), 3.94 (s, 2H), 3.90 (s, 3H), 3.80 (s, 3H), 3.71 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.1, 156.8, 156.0, 139.9, 131.3, 129.7, 128.2, 116.4, 98.1, 92.8, 61.1, 56.5, 55.9, 29.1 ppm; MS (ESI): *m/z* (%): 182.1 [trimethoxytoluene cation] (32.9), 392.1 [$M(Br^{79}/Cl^{35})$+Na^+] (28.2), 394.1 [$M(Br^{81}/Cl^{35}$ or $Br^{79}/Cl^{37})$+Na^+] (36.6), 396.1 [$M(Br^{81}/Cl^{37})$+Na^+] (8.2); HRMS (ESI): *m/z*: calcd for $C_{19}H_{23}Br^{79}L^3NaO_3^+$: 392.9864; found: 392.9870.

[(3-Bromo-2,4,6-trimethoxyphenyl)methylene]dibenzene (4m): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 1,3,5-trimethoxybenzene (42.2 mg) and diphenylmethane (1.05 g), the title compound obtained an off-white solid 41.2 mg (100 μmol, 40%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.23 (m, 4H), 7.22–7.11 (m, 6H), 6.34 (s, 1H), 6.06 (s, 1H), 3.90 (s, 3H), 3.51 (s, 3H), 3.44 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.5, 157.0, 156.2, 143.4, 129.1, 127.8, 125.7, 120.5, 98.6, 94.0, 91.6, 60.9, 56.3, 55.8, 46.8 ppm; MS (ESI): *m/z* (%): 182.1 [trimethoxytoluene cation] (12.0), 435.1 [$M(Br^{79})$+Na^+] (100), 437.1 [$M(Br^{81})$+Na^+] (97.7); HRMS (ESI): *m/z*: calcd: for $C_{22}H_{21}Br^{79}NaO_3^+$: 435.0566; found: 435.0560 .

2-Bromo-4-[1-(4-ethylphenyl)ethyl]-1,3,5-trimethoxybenzene (4n): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 1,3,5-trimethoxybenzene (42.2 mg) and *para*-diethylbenzene (839 μL), the title compound was obtained as a light-yellow solid (39.0 mg; 103 μmol, 41%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, J = 8.0, 2H), 7.07 (d, J = 8.0, 2H), 6.31 (s, 1H), 4.67 (q, J = 7.2, 1H), 3.88 (s, 3H), 3.67 (s, 3H), 3.59 (s, 3H), 2.59 (q, J = 7.6, 2H), 1.66 (d, J = 7.2, 3H), 1.20 ppm (t, J = 7.6, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.5, 156.6, 155.6, 142.9, 141.0, 127.2, 127.1, 122.9, 98.5, 93.7, 61.1, 56.4, 55.8, 34.1, 28.4, 18.1, 15.7 ppm; MS (ESI): *m/z* (%): 182.1 [trimethoxytoluene cation] (8.0), 401.1 [$M(Br^{79})$+Na^+] (100), 403.1 [$M(Br^{81})$+Na^+] (97.7); HRMS (ESI): *m/z*: cacld for $C_{19}H_{23}Br^{79}NaO_3^+$: 401.0723; found: 401.0725.

1-(3-Bromo-2,4,6-trimethoxyphenyl)-2,3-dihydro-1*H*-indene (4o): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 1,3,5-trimethoxybenzene (42.2 mg) and indane (766 μL), the title compound was obtained as a yellow solid (19.3 mg; 53 μmol, 21%). T_m = 110–112 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (d, J = 7.4 Hz, 1H), 7.11 (app t, J = 7.4 Hz, 1H), 7.04 (app t, J = 7.4 Hz, 1H), 6.83 (d, J = 7.4 Hz, 1H), 6.32 (s, 1H), 4.89 (app t, J = 8.1 Hz, 1H), 3.90 (s, 3H), 3.56 (br s, 6H), 3.15–3.11 (m, 1H), 3.04–2.97 (m, 1H), 2.41–2.29 ppm (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.0, 157.5, 155.9, 147.5, 143.7, 125.9, 125.8, 124.2, 123.2, 120.9, 98.6, 94.0, 56.5, 56.1, 41.8, 32.4, 31.8 ppm; MS (EI): *m/z*: 283.0 [M−Br] (48), 362.0 [$M(Br^{79})$] (100), 364.0 [$M(Br^{81})$] (99); HRMS (ESI): *m/z*: calcd for $C_{18}H_{19}Br^{79}O_3^+$: 365.0518; found: 362.0508.

9-(2,4,6-Trimethoxyphenyl)-9*H*-fluorene (4p): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 1,3,5-trimethoxybenzene (42.2 mg), fluorene (623 mg) and degassed benzene (1.0 mL) as the co-solvent, the title compound was obtained as a yellow solid (17.8 mg; 53 μmol, 21%). T_m = 98–100 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.79 (d, J = 7.5 Hz, 2H), 7.34–7.29 (m, 2H), 7.24–7.17 (m, 4H), 6.31 (d, J = 2.3 Hz, 1H),

5.95 (d, $J=2.3$ Hz, 1H), 5.61 (s, 1H), 3.98 (s, 3H), 3.80 ppm (s, 3H), 2.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=160.2$, 159.9, 159.8, 148.9, 141.2, 126.6, 126.2, 123.7, 119.5, 110.7, 92.7, 91.1, 56.4, 55.9, 55.4, 43.8 ppm; MS (EI): *m/z* (%): 165.1 [$M-C_9H_{11}O_3$] (13), 332.1 [*M*] (100); HRMS (APCI): *m/z*: calcd for $C_{22}H_{21}O_3^+$: 333.1470; found: 333.1485.

2-Bromo-1,3,5-triethoxy-4-(4-methylbenzyl)benzene (4q): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 1,3,5-triethoxybenzene (52.5 mg) and *para*-xylene (771 μL), the title compound was obtained as an off-white solid (32.9 mg; 84 μmol, 33%); $T_m=74$–$76\,^\circ$C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.12$ (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 ppm (t, $J=7.0$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=157.6$, 156.1, 155.2, 138.8, 135.0, 128.8, 128.5, 117.9, 99.1, 95.1, 69.5, 65.3, 64.3, 29.7, 21.1, 15.7, 14.9, 14.9 ppm; MS (EI): *m/z* (%): 392.1 [$M(Br^{79})$] (100), 394.1 [$M(Br^{81})$] (97); HRMS (EI): *m/z*: calcd $C_{20}H_{25}O_3{}^{79}Br^+$ for 392.0982; found: 392.0983.

2-Bromo-1,3,5-triisopropyl-4-(4-methylbenzyl)benzene (4r): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 1,3,5-triisopropylbenzene (63.0 mg) and *para*-xylene (771 μL), the title compound was obtained as a yellow oil (22.3 mg, 51 μmol, 20%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.09$ (d, $J=7.8$ Hz, 2H), 6.99 (d, $J=7.8$ Hz, 2H), 6.28 (s, 1H), 4.53 (quint, $J=6.2$ Hz, 1H), 4.45 (quint, $J=6.1$ Hz, 1H), 4.41 (quint, $J=6.0$ Hz, 1H), 3.93 (s, 2H), 2.27 (s, 3H), 1.36 (d, $J=6.1$ Hz, 6H), 1.30 (d, $J=6.2$ Hz, 6H), 1.18 ppm (d, $J=6.0$ Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=$ 156.1, 154.8, 154.2, 138.8, 134.8, 128.6, 119.9, 101.1, 98.5, 76.1, 72.9, 70.2, 30.3, 22.5, 22.3, 22.0, 21.1 ppm; MS (EI): *m/z* (%): 392.1 [$M(Br^{79})-CH_2CHCH_3$] (71), 394.1 [$M(Br^{81})-CH_2CHCH_3$] (43), 436.1 [$M(Br^{79})$] (100), 436.1 [$M(Br^{81})$] (100); HRMS (EI): *m/z*: calcd for $C_{22}H_{31}O_3{}^{79}Br^+$: 434.1451; found: 434.1447.

1-Bromo-2,3,4-trimethoxy-6-methyl-5-(4-methylbenzyl)benzene (4s): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 3,4,5-trimethoxytoluene (45.6 mg) and *para*-xylene (839 μL), the title compound was obtained as a yellow oil (11.0 mg, 30 μmol, 12%); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=$ 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 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=151.6$, 149.6, 145.2, 137.3, 135.4, 132.9, 129.6, 129.2, 128.0, 115.7, 61.2, 61.1, 61.0, 32.8, 21.1, 19.9 ppm; MS (EI) *m/z* (%): 349.0 [$M(Br^{79})-CH_3$] (13), 351.0 [$M(Br^{81})-CH_3$] (11), 364.1 [$M(Br^{79})$] (100), 366.1 [$M(Br^{81})$] (97); HRMS (EI): *m/z*: calcd for $C_{18}H_{21}O_3{}^{79}Br^+$: 364.0674; found: 364.0665.

1-Bromo-2,4-dimethoxy-5-(4-methylbenzyl)benzene (4t): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 1,3-dimethoxybenzene (32.7 μL) and *para*-xylene (771 μL), the title compound was yielded as an off-white solid (34.8 mg; 108 μmol, 43%). $T_m=81$–$83\,^\circ$C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.20$ (s, 1H), 7.08 (s, 4H), 6.47 (s, 1H), 3.89 (s, 3H), 3.83 (s, 2H), 3.82 (s, 3H), 2.31 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=157.6$, 155.2, 137.7, 135.5, 134.0, 129.2, 128.8, 123.9, 101.7, 96.8, 56.6, 55.9, 34.6, 21.2 ppm; MS (EI): *m/z* (%): 305.0 [$M(Br^{79})-CH_3$] (71), 307.0 [$M(Br^{81})-CH_3$] (43), 320.0 [$M(Br^{79})$] (100), 322.0 [$M(Br^{81})$] (97); HRMS (EI): *m/z*: calcd for $C_{16}H_{17}O_2{}^{79}Br^+$: 320.0412; found: 320.0400.

2-Chloro-1,3,5-trimethoxy-4-(4-methylbenzyl)benzene (4u): By using the general procedure with Luperox101® (186 μL), copper(II) chloride (67.2 mg), 1,3,5-trimethoxybenzene (42.2 mg) and *para*-xylene (771 μL), the title compound was yielded as a white solid (29.5 mg; 96 μmol, 38%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.10$ (d, $J=$ 7.9, 2H), 7.04 (d, $J=7.9$, 2H), 6.36 (s, 1H), 3.95 (s, 2H), 3.91 (s, 3H), 3.81 (s, 3H), 3.72 (s, 3H), 2.29 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=157.1$, 155.8, 154.8, 138.3, 135.0, 128.8, 128.1, 116.9, 108.5, 92.7, 60.9, 56.4, 55.9, 28.9, 21.0 ppm; MS (ESI): *m/z* (%): 182.1 [trimethoxytoluene cation] (4.6), 329.1 [$M(Cl^{35})+Na^+$] (100), 331.1 [$M(Cl^{37})+Na^+$] (33.7); HRMS (ESI): *m/z*: calcd for $C_{17}H_{19}Cl^{35}NaO_3{}^+$: 329.0915; found: 329.0914.

1,3,5-Trimethoxy-2-(4-methylbenzyl)-4-nitrobenzene (4v): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 2,4,6-trimethoxynitrobenzene (53.3 mg) and *para*-xylene (771 μL), the title compound was obtained as a yellow solid 60.0 mg (189 μmol, 76%); $T_m=104$–$106\,^\circ$C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.05$ (s, 4H), 6.32 (s, 1H), 3.93 (s, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 3.72 (s, 3H), 2.29 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): 160.2, 152.0, 151.5, 137.4, 135.4, 129.0, 128.1, 116.1, 91.7, 63.2, 56.6, 56.1, 28.6, 21.1 ppm; MS (EI): *m/z* (%): 270.1 [$M-OCH_3O$] (22), 317.1 [*M*] (100); HRMS (APCI): *m/z*: cacld for $C_{17}H_{19}NO_5{}^+$: 317.1258; found: 317.1246.

2-Fluoro-1,3,5-trimethoxy-4-(4-methylbenzyl)benzene (4w): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 2-fluoro1,3,5-trimethoxybenzene (46.6 mg) and *para*-xylene (771 μL), the title compound was obtained as a white solid (12.8 mg; 44 μmol, 18%) (note: a sample of 1-bromo-3-fluoro-2,4,6-trimethoxy-5-(4-methylbenzyl)benzene and 4,4′-(5-fluoro-2,4,6-trimethoxy-1,3-phenylene)bis(methylene)bis(methylbenzene) was also obtained as an inseparable mixture (11.3 mg, 7% and 4%) as determined by GCMS and ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.10$ (d, $J=7.9$ Hz, 2H), 7.03 (d, $J=7.9$ Hz, 2H), 6.29 (d, $J=6.5$ Hz, 1H), 3.90 (s, 2H), 3.88 (s, 3H), 3.81 (d, $J=$ 1.9 Hz, 3H), 3.77 (s, 3H), 2.28 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=153.3$ (d, $J=2.6$ Hz), 147.1 (d, $J=17$ Hz), 147.0 (d, $J=$ 17 Hz), 141.3 (d, $J=240$ Hz), 138.6, 135.1, 128.9, 128.4, 115.9, 93.2, 61.4 (d, $J=6.5$ Hz), 56.9, 56.3, 28.6 (d, $J=1.5$ Hz), 21.1 ppm; MS (EI): *m/z* (%): 199.1 [$M-C_7H_7$] (28), 275.1 [$M-CH_3$] (15), 290.1 [*M*] (100); HRMS (EI): *m/z*: calcd for $C_{17}H_{19}O_3F^+$: 290.1318; found: 290.1317.

2,4,6-Trimethoxy-3-(4-methylbenzyl)benzaldehyde (4x): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 2,4,6-trimethoxybenzaldehyde (49.1 mg) and *para*-xylene (771 μL), the title compound was obtained as a colorless oil 14.9 mg (50 μmol, 20%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=$ 10.33 (s, 1H), 7.09 (d, $J=7.9$ Hz, 2H), 7.03 (d, $J=7.9$ Hz, 2H), 6.27 (s, 1H), 3.92 (s, 3H), 3.91 (s, 2H), 3.88 (s, 3H), 3.71 (s, 3H), 2.28 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=188.1$, 164.3, 163.0, 162.2, 138.2, 135.2, 129.0, 128.3, 116.3, 112.4, 91.1, 63.3, 56.2, 55.9, 28.1, 21.1 ppm; MS (ESI): *m/z* (%): 105.1 [$M-C_{10}H_{11}O_4$] (100), 195.1 [$M-C_8H_9$] (65), 285.1 [$M-CH_3$] (75), 300.1 [*M*] (43); HRMS (APCI): *m/z*: calcd for $C_{18}H_{21}O_4{}^+$: 301.1434; found: 301.1422.

1,2,3-Trimethoxy-4-(4-methylbenzyl)benzene (4y): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 1,2,3-trimethoxybenzene (42.1 mg) and *para*-xylene (771 μL), the title compound was obtained as a yellow oil (19.7 mg; 72 μmol, 29%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.08$ (s, 4H), 6.78 (d, $J=8.5$ Hz, 2H), 6.60 (d, $J=8.5$ Hz, 2H), 3.88 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.75 (s, 3H), 2.31 ppm (s, 3H); ^{13}C NMR

(101 MHz, $CDCl_3$): $\delta = 152.4$, 152.0, 142.5, 138.5, 135.4, 129.1, 128.8, 127.7, 124.6, 107.2, 60.9, 60.9, 56.1, 35.3, 21.1 ppm; MS (EI): *m/z* (%): 257.1 [$M-CH_3$] (46), 272.1 [*M*] (100); HRMS (EI): *m/z*: calcd for $C_{17}H_{20}O_3^+$: 272.1412; found: 272.1408.

1,2,4,5-Tetramethoxy-3-(4-methylbenzyl)benzene (4z): By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 1,2,4,5-tetramethoxybenzene (49.6 mg) and *para*-xylene (771 μL), the title compound was obtained as an off-white solid (16.5 mg; 55 μmol, 22%). $T_m = 57–59\,^\circ C$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.14$ (d, $J = 7.6$ Hz, 2H), 7.02 (d, $J = 7.60$ Hz, 2H), 6.46 (s, 1H), 3.99 (s, 2H), 3.85 (s, 6H), 3.63 (s, 6H), 2.27 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 149.1$, 141.3, 138.5, 135.1, 129.6, 128.9, 128.6, 97.6, 60.9, 56.4, 29.9, 21.1 ppm; MS (EI): *m/z* (%): 287.1 [$M-CH_3$] (20), 302.2 [*M*] (100); HRMS (EI): *m/z*: calcd for $C_{18}H_{22}O_4^+$: 302.1513; found: 302.1512.

1,4-Dimethoxy-2-(4-methylbenzyl)benzene (4aa):[27] By using the general procedure with Luperox101® (186 μL), copper(II) bromide (111.7 mg), 1,4-dimethoxybenzene (34.5 mg) and *para*-xylene (771 μL), the title compound was obtained as an off-white solid (12.6 mg; 52 μmol, 21%). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.10$ (d, $J = 8.2$ Hz, 2H), 7.07 (d, $J = 8.2$ Hz, 2H), 6.79 (d, $J = 8.8$ Hz, 1H), 6.70 (dd, $J = 8.8$, 3.1 Hz, 1H), 6.65 (d, $J = 3.1$ Hz, 1H), 3.90 (s, 2H), 3.77 (s, 3H), 3.72 (s, 3H), 2.30 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 153.6$, 151.8, 137.7, 135.4, 131.3, 129.1, 128.9, 116.9, 111.5, 111.2, 56.2, 55.8, 35.6, 21.2 ppm; MS (EI): *m/z* (%): 227.1 [$M-CH_3$] (26), 242.1 [*M*] (100); HRMS (EI): *m/z*: calcd for $C_{16}H_{18}O_2^+$: 242.1301; found: 242.1313.

Penta-*O*-methyl vidalol A (8):[10i] To a 10 mL reaction tube, equipped with a magnetic stirrer bar, was added 1,3,5-trimethoxybenzene (55.0 mg, 0.327 mmol, 1.0 equiv), copper(II) bromide (147 mg, 0.5 mmol, 2.0 equiv) and 2,3-dibromo-4,5-dimethoxy-1-methylbenzene (507 mg, 1.64 mmol, 5.0 equiv) in degassed benzene (1.0 mL). The reaction vessel was then purged with N_2 and luperox 101 (244 μL, 0.838 mmol, 2.25 equiv) was added and the reaction vessel was immediately sealed under an N_2 atmosphere with a crimp cap seal and placed directly into a preheated oil bath at 110 °C. The reaction was heated for 18 h, after which time, the reaction was allowed to cool, diluted with dichloromethane (ca. 10 mL), analyzed by thin layer chromatography and filtered through a cotton wool plug. The reaction mixture was then purified by automated column chromatography to give the product as a yellow oil (38.4 mg, 69 μmol, 19%). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.37$ (s, 1H), 6.31 (s, 1H), 4.05 (s, 2H), 3.94 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.70 (s, 3H), 3.61 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 158.5$, 157.3, 156.5, 152.4, 145.7, 137.9, 121.6, 117.5, 114.9, 111.9, 98.2, 92.5, 61.3, 60.6, 56.6, 56.2, 56.1, 32.0 ppm; MS (ESI): *m/z* (%): 588.9 [$M(^{79}Br)+Cl^-$] (100), 590.8 [$M(^{81}Br)+Cl^-$] (90); HRMS (ESI): *m/z*: calcd (%) for $C_{18}H_{20}Br_3{}^{79}O_5^+$: 552.8855; found: 552.8857.

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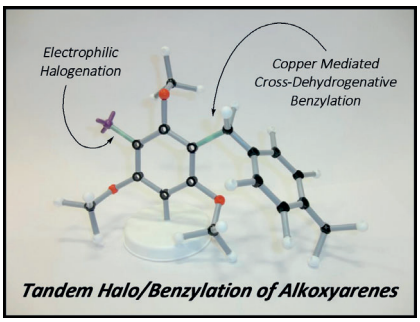
FULL PAPER

Two steps away: A copper-mediated cross-dehydrogenative-coupling of alkoxybenzenes and toluenes with concomitant halogenation is reported (see figure). A range of bromoalkoxydi- and triarylmethanes are synthesized and a plausible mechanism is proposed.



Organic Synthesis

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