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# Easy access to benzylic esters directly from alkyl benzenes under metal-free conditions<sup>†‡</sup>

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An efficient metal free protocol has been developed for the synthesis of benzylic esters *via* a cross dehydrogenative coupling (CDC) involving alkylbenzene(s) as a self- or as a cross-coupling partner(s) *via* the intermediacy of Ar–COOH and the benzylic carbocation obtained from the other half of the alkylbenzene; both symmetrical as well as unsymmetrical esters can be prepared using Bu<sub>4</sub>NI and TBHP.

The selective oxidative cleavage of the sp<sup>3</sup> C–H bond is of paramount interest to both academic and industrial research.<sup>1</sup> The two most common strategies adopted for the C–H bond activation processes rely on the concept of chelation assisted C–H bond functionalization<sup>2</sup> and cross dehydrogenative coupling (CDC).<sup>3</sup> CDC based methodologies are highly appreciable because it does not require substrate prefunctionalisation. Besides being atom and step economic, these reactions are often air and moisture insensitive, and thereby can be performed in an aqueous environment or an air atmosphere.<sup>4</sup> The CDC approach has been mainly exploited towards the C–C bond formations,<sup>3a,5</sup> but of late the number of C–O bond forming reactions are also increasing.<sup>3e,6</sup>

The CDC based protocols in the construction of a C–O bond have been achieved using transition metal catalysts such as Cu, Fe, Ru, Rh, Ir, and Pd in combination with various oxidants.<sup>7</sup> However, the disadvantages associated with these methodologies, owing to the use of expensive metal catalysts, elevated reaction temperature, and the problems associated with the removal of metal residues limit their practical applicability. Therefore, increasing interest has been focused on metal free catalysts, particularly towards the formation of a C–O bond.<sup>6*a*–*c*,8</sup>

Selective to the C–O bond formation, the ester functionalities, particularly the benzylic esters, are common target because of their applications in synthetic organic and medicinal chemistry.<sup>9</sup> Besides the traditional esterification reactions involving alcohols and acids (or their equivalents) (path I, Scheme S1, ESI‡),<sup>10</sup> several elegant

protocols have been developed lately. Catalysts such as Ru, Rh, Ir, Pd and V have been employed for the cross dehydrogenative coupling (CDC) between aldehydes or the *in situ* generated aldehydes and alcohols (paths II and III, Scheme S1, ESI‡) for the synthesis of benzylic esters.<sup>11</sup> Most of these processes rely on the concept of either hydrogen borrowing<sup>12</sup> or a hydrogen auto transfer process.<sup>13</sup> Recently, a CDC based approach has been developed by our group for the synthesis of benzylic esters from aryl aldehydes and alkylbenzenes using Cu( $\pi$ ) as the catalyst and *tert*-butyl hydroperoxide (TBHP) as the oxidant (path IV, Scheme S1, ESI‡).<sup>6e</sup> Efficient coupling of carboxylic acids or the *in situ* generated carboxylic acids and alkylbenzenes has also been reported under metal free conditions using tetra *n*-butylammonium iodide (Bu<sub>4</sub>NI) as the catalyst and TBHP as the oxidant (path V, Scheme S1, ESI‡).<sup>8c-d</sup>

During the course of our investigations on CDC coupling between benzaldehyde and *p*-methoxytoluene, the formation of benzoic acid and *p*-methoxybenzyl alcohol originating respectively from benzaldehyde and *p*-methoxytoluene was observed. The *in situ* generated *p*-methoxybenzyl alcohol can be further converted to its aldehyde and subsequently to carboxylic acid under the oxidative reaction conditions. Thus, the *in situ* formed aldehyde or acid can in turn couple with the unreacted alkylbenzene in the medium to give an ester *via* a CDC approach (Scheme S1, ESI,‡ paths IV and V).<sup>6e,8c-d</sup> Hence, we envisaged a self-coupling of an alkylbenzene or a crosscoupling between two different alkylbenzenes to obtain a symmetrical or an unsymmetrical ester (Scheme S1, ESI,‡ path VI).

In pursuit of the above objective when toluene (a) was treated with  $Cu(OAc)_2 \cdot 2H_2O$  (0.1 equiv.) and TBHP (4 equiv.), a condition similar to our previous report, only a trace (<3%) of benzylbenzoate (aa) was formed (entry 1, Table S1, see ESI‡) along with substantial formation of benzoic acid.<sup>6e</sup> In spite of the presence of significant amount of benzoic acid in the medium, the amount of ester (aa) formed was negligible as the Cu(n)/TBHP condition is perhaps not conducive for the coupling between an acid and an alkylbenzene.<sup>6e</sup> Traces of the ester (aa) formed is possibly due to the less concentration of benzaldehyde and benzyl alcohol present in the medium, while most of the benzaldehyde gets rapidly oxidised to benzoic acid.<sup>6e</sup> Metal free catalyst  $Bu_4NI$  in combination with oxidant TBHP is not only an efficient reagent for the oxidation of alkylbenzenes to

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 $<sup>\</sup>dagger$  We would like to dedicate this manuscript to Prof. Dr. Fritz Eckstein on the occasion of his 80th birthday.

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acids but is also equally effective towards cross dehydrogenative coupling between acids and alkylbenzenes.<sup>8*c*-*d*</sup> With this inspiration, further optimisation was undertaken towards a metal free sp<sup>3</sup> C–H bond oxidative esterification using toluene (**a**) as the self-coupling partner. Toluene (**a**) (1 mL) was treated with 10 mol% of Bu<sub>4</sub>NI and TBHP (5–6 M in decane) (4 equiv.) at room temperature, which afforded benzylbenzoate (**aa**) in 30% isolated yield (entry 2, Table S1, see ESI‡). Here the alkylbenzene (toluene) acts as reactant(s) *i.e.* self-coupling partner(s) as well as a solvent.

Taking cues from the literature and the controlled experiments carried out, a mechanism similar to the one proposed by Yu et al.<sup>8c</sup> and Wan et al.<sup>8d</sup> could be suggested for this transformation as well. The oxidant TBHP is known to oxidize the catalyst  $Bu_4 N^+I^-$  to either  $[Bu_4N^+][IO]^-$  or  $[Bu_4N^+][IO_2]^{-14}$ . However, we have observed the formation of [IO]<sup>-</sup> *i.e.* [Bu<sub>4</sub>N<sup>+</sup>][IO]<sup>-</sup> by ESI mass analysis of the reaction mixture. This active hypoiodite [Bu<sub>4</sub>N<sup>+</sup>][IO]<sup>-</sup> species would initiate a homolytic cleavage at the benzylic C-H bond of the toluene to give a benzyl radical (I).<sup>8c-d,15</sup> Formation of a benzyl radical (I) could be the rate determining step in the entire reaction. The benzylic radical (I) is further oxidised by the hypoiodite species  $[Bu_4N^+][IO]^-$  to a benzyl cation (II). Alternatively, some of the alkylbenzene could be converted to its alcohol via a radical oxidation path and subsequently to corresponding acid (III) via an aldehyde intermediate (see Scheme S2, ESI<sup>‡</sup>). After the formation of the acid (III), the oxygen atom of the hypoiodite species [IO]<sup>-</sup> removes the acidic proton from the benzoic acid, giving a benzoate ion (IV). Finally, the coupling between the *in situ* generated benzoate ion (IV) and the benzyl cation  $(\mathbf{II})$  would give the desired ester as shown in Scheme S2 (ESI<sup>‡</sup>). As per the mechanism, four equivalents of the oxidant (TBHP) get consumed, forming an equivalent of the benzoate ion (IV) and further two equivalents are required for the formation of the benzyl cation  $(\mathbf{II})$  from alkylbenzene. Thus, a total of six equivalents of TBHP is essential for the coupling of two equivalents of alkylbenzene, giving an equivalent of ester.

Moving further onto the optimization, when the same reaction was performed using 6 equivalents of TBHP at 80 °C the yield improved upto 90% (entry 3, Table S1, see ESI<sup>‡</sup>). Gratifyingly, the use of aqueous TBHP (70%) instead of a decane solution of TBHP (5–6 M) improved the yield upto 95% (entry 4, Table S1, see ESI<sup>‡</sup>). Upon increasing the reaction temperature to 100 °C or increasing the catalyst quantity to 20 mol%, no further improvement in the yield was observed (entries 5-6, Table S1, ESI‡). However a decrease in the catalyst loading (5 mol%) and oxidant quantity (5 equiv.) reduced the product yield (entries 7–8, Table S1, ESI<sup>‡</sup>). No desired product could be obtained when oxidants H<sub>2</sub>O<sub>2</sub>, DDQ,  $PhI(OAc)_2$  (entries 9–11, Table S1, ESI<sup>‡</sup>) were used instead of TBHP. Other halogen species such as Bu<sub>4</sub>NBr, KI and I<sub>2</sub> (entries 12-14, Table S1, ESI<sup>‡</sup>) were found to be completely ineffective. Control experiments carried out in the absence of either the catalyst ( $Bu_4N^+I^-$ ) or the oxidant (TBHP) failed to bring about the desired transformation, suggesting the requirement of this particular combination.

It may be mentioned here that recently Luque *et al.* have reported a Au–Pd system for the selective oxidation of alkylbenzenes to esters.<sup>16</sup> The method mentioned not only uses expensive catalyst but also gives multitudes of other products and hence is of little industrial significance.

In light of these novel observations the optimised conditions were subsequently applied to *m*-methoxy (b), *p*-methoxy (c), p-chloro (d), p-bromo (e), and p-nitro (f) toluenes towards selfoxidative esterification. It was observed that, under the present conditions, toluene with electron-donating substituents (b and c), the reactions proceeded smoothly to afford the desired selfcoupled benzylic esters (bb, cc) in excellent yields (Scheme 1). For toluenes possessing electron-withdrawing substituents (d, e), the reaction provided the desired benzylic esters (dd, ee) in good yields but the reactions were a bit sluggish (Scheme 1). The sluggishness was quite pronounced with the substrate bearing strongly electron withdrawing  $-NO_2$  (f) in toluene under the present reaction conditions, giving a poor yield of 25% of the desired ester (ff). For such a deactivated substrate, an improved vield (80%) was obtained when the reaction was performed at 110 °C (Scheme 1). These results imply that the electronic effects of the substituents in the methyl benzene affect the reaction rates and the product yields.

The synthetic utility of this approach was then applied to various di-alkylatedbenzenes such as *o*-xylene ( $\mathbf{g}$ ), *m*-xylene ( $\mathbf{h}$ ), and *p*-xylene ( $\mathbf{i}$ ), all of which gave self-coupled monoesters ( $\mathbf{gg}$ ), ( $\mathbf{hh}$ ), and ( $\mathbf{ii}$ ) in excellent yields (Scheme 1). Only monoesters were obtained in these cases and no traces of diesters were detected. Symmetrical trialkylatedbenzene such as mesitylene ( $\mathbf{j}$ ) yielded the corresponding self-coupled monoester ( $\mathbf{jj}$ ) (Scheme 1).



**Scheme 1** Substrate scope for the synthesis of benzylic esters *via* metal free C–H functionalization. <sup>a</sup>*Reaction conditions*: alkylbenzene (1 mL), Bu<sub>4</sub>N<sup>+</sup>I<sup>-</sup> (0.1 mmol), TBHP (6 mmol), 80 °C, time 6 h. <sup>b</sup>Reactions were monitored by TLC, confirmed by spectroscopic analysis. Yield of the isolated pure product reported.

As depicted in the mechanism (Scheme S2, ESI<sup>‡</sup>), during the formation of a symmetrical ester, one half of the alkylbenzene is transformed to acid, which couples with the *in situ* generated benzyl cation derived from the other half of the alkylbenzene. Ethylbenzene is expected to form a more stable carbocation than the methylbenzene and the latter is more susceptible to oxidation, giving acid. Thus, if an equimolar mixture of ethyl and methylbenzene is treated under the present reaction conditions, synthesis of unsymmetrical esters could be feasible.

With this motivation, the present methodology was next sought towards the cross dehydrogenative coupling (CDC) between ethylbenzene (k) and various substituted toluenes bearing electron-neutral (a), electron-donating (b-c) and electronwithdrawing substituents (d-f). In all their reactions, the corresponding benzylic esters (ak-fk) were obtained in moderate to high yields via a selective C-O bond formation at the more stable 2° benzylic carbon of the ethylbenzene as has been envisaged earlier (Scheme 1). This methodology was also equally successful towards the reactions of di- and tri-alkylatedbenzenes (g-j) with ethylbenzene (k) as shown in Scheme 1. Herein as well the monoester formations (gk-jk) took place selectively as have been observed during the self-coupling of (g-j). However trace amounts (2-5%) of self-coupled esters (aa-jj) were also obtained in the entire cross-coupling cases along with the predominant formation of cross-coupled esters (ak-jk). This methodology is also equally successful for CDC between isopropylbenzene (I) and alkyl benzenes such as toluene (a) and p-chlorotoluene (d), giving modest yield of unsymmetrical esters (al) and (dl) respectively. However the yield obtained was lower than expected, which could be due to the steric factor imparted by the isopropyl group.

In conclusion, for the first time benzylic esters have been prepared from alkylbenzenes as the only precursor *via* a cross dehydrogenative coupling (CDC) under metal free conditions involving four sp<sup>3</sup> C–H bond activations. This method gives a self-coupled product for mono or poly methylatedbenzenes. The cross-coupled product can be prepared from ethylbenzene and methylbenzene where the acid part is derived from methylbenzene and the benzyl cation is derived from ethylbenzene. Various functional groups are tolerated under the present reaction conditions. Thus this approach has great academic and industrial significance.

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