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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b03048 • Publication Date (Web): 15 Jan 2019

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Metal-Free Regioselective Cross Dehydrogenative Coupling of Cyclic Ethers and Aryl carbonyls

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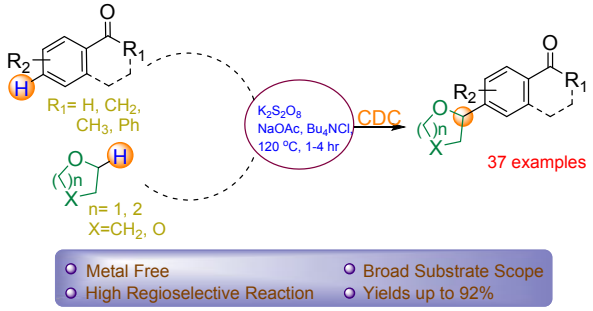
KEYWORDS: Metal- free • Regioselective • CDC • DFT



ABSTRACT: A highly regioselective, efficient and metal free oxidative cross dehydrogenative coupling (CDC) of aryl carbonyls with cyclic ethers has been developed. This method offers easy access to substituted α-arylated cyclic ethers with high functional group tolerance in good to excellent yields. The regioselectivity of this CDC reaction was confirmed by density functional theory (DFT) based calculations.

INTRODUCTION

Functionalized cyclic ethers are important scaffolds that are found in a variety of natural products and pharmaceutical ingredients.[1] Generally, tetrahydrofuran (THF), 1,4-dioxane and tetrahydropyrans (THP) are the examples of cyclic ethers. These compounds show a broad spectrum of biological activity, including antibacterial, [2a] anti-inflammatory, [2b] anticancer, [2c-e], and antidiabetic.[2f-g] They have also been employed in the synthesis of agricultural pesticide **1**(figure 1).[3]

Lignin's are the class of natural compounds that exclusively contain substituted THF as a core unit.[5] Examples of lignin's includes sesamin **2** and galbacin **3** (figure.1).These compounds are known to exhibit anticancer, [4a] antioxidant, [4b] anti-inflammatory, [4c] and antiobesity [4d] properties. Strebluslignanol F **4**, a natural product, contains 1, 4-dioxane as core unit and shows potent anti-hepatitis B virus activity.[5a] On the other hand, omaragliptin **5** is an oral antidiabetic drug with substituted THP as the core moiety.[5b]

The formation of the C-C bond *via* C-H bond activation of sp^3, sp^2 hybridised carbons as cross-coupling participants has generated renewed attention over the last few decades.[6a-b] However, sp^3 C–H bond activation is a challenging task due to their inertness, gained from high bond energy and high p*K*a values. Hence, CDC reactions have attracted the attention of organic chemists for the preparation of C-C bonds under metal and metal-free conditions in academic as well as industrial research.[6c-f]

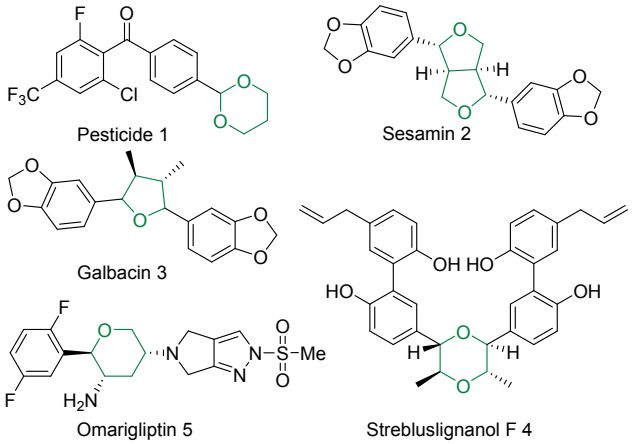
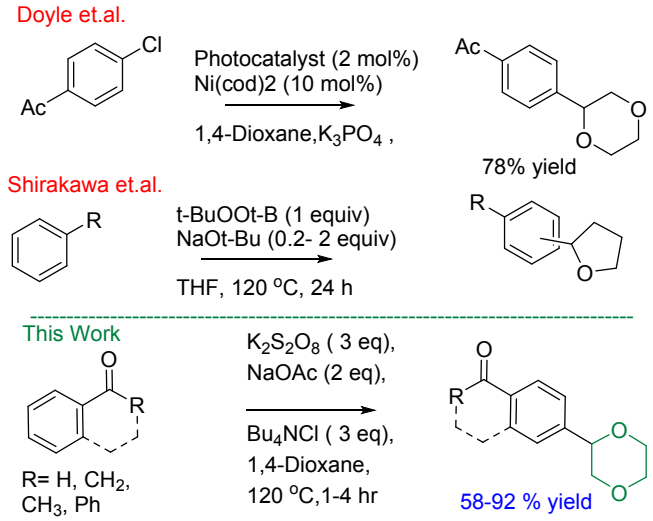


Figure 1: Biologically Active Cyclic Ethers

After a careful survey of the literature, we realised that both metal and metal-free approaches have been employed for the oxidative cross dehydrogenative coupling of cyclic ethers with arenes and heteroarenes. Some of these important methods include the use of transition metals such as Cu (I) catalysed cross coupling between substituted 1, 1'-diarylethenes and cyclic ethers, [7] Cu (II) catalysed addition of α-oxyalkyl radical to isoquinolinium salts [8] and Fe (II) catalysed α-arylation of cyclic and acyclic ethers with azoles.[9] Also, Doyle and co-workers have achieved α-arylation of cyclic ethers through Ni (II) catalysed photoredox coupling between aryl halide and cyclic ethers, as shown in Scheme 1.[10]

Various electron deficient heterocyclic arenes were sub-jected for α-arylation of cyclic and acyclic ethers under oxidative metal-free conditions using a variety of oxidants such as DTBP, TBHP, BPO and $K_2S_2O_8$. These heterocycles contain substituted pyridines,[11] thiophenes,[12] indoles,[13] quinines,[14] azoles[15] and chromanes.[16] Although these methods are efficient towards yielding the CDC product, they are limited to activated heterocyclic systems. Recently, Shirakawa et al. reported base promoted oxidative dehydrogenative coupling between a substituted benzene derivative and cyclic ethers, as well as amides, in the presence of DTBP oxidant and NaOt-Bu, base.[17] Despite some advantages, the reaction suffers from certain limitation's such as, poor yields and poor regioselectivity when electron withdrawing substituent's were present on the aryl rings.



Scheme 1: Strategies for the α-Arylation of Cyclic Ethers

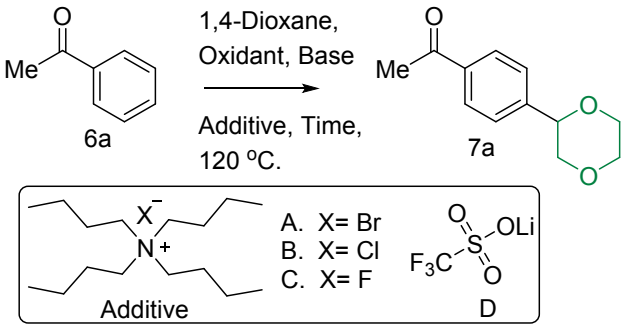
To overcome these shortcomings and inspired by metal free approaches, [18] our motive has been to develop a synthetic method for the α-functionalisation of cyclic ethers with better yields and regioselectivity (Scheme 1). Thus, we have described the metal free CDC reaction via Csp3–Csp2 coupling between various cyclic ethers and aromatic carbonyls to generate a wide range of α-arylated cyclic ethers. The key features of this reaction are: short reaction time, good to excellent yields and high regioselectivity.

RESULTS AND DISCUSSION

We have started our investigation, by taking acetophenone as a model substrate and 1,4-dioxane as a coupling partner as well as solvent. The results are summarised in **Table 1**.

Initially, when acetophenone **6a** (1 equiv) and 1,4-dioxane (30 equiv, also acts as solvent) are reacted at 120 °C in the presence of oxidant $K_2S_2O_8$ (3 equiv), tetra butyl ammonium bromide (A) (2 equiv) as an additive and NaOAc (2 equiv), to our delight we got the expected product **7a** in 51% yield within 4 h of reaction time (Table1, entry 1). When the reaction time was increased from 4 h to 12 h, the yield of **7a** was reduced to 45%, as a result of decomposition of the obtained product (Table1, entry 2). With increased equivalence of tetra butyl ammonium bromide (A) from 2 to 3 and refluxing at 120 °C, we obtained 57% yield of the desired product (Table1, entry 3). When terta butyl ammonium chloride (B) was used instead of tetra butyl ammonium bromide (A) as an additive and the mixture refluxed for 4 h, we got the expected product in 81% yield, which was a significant improvement (Table1, entry 4) in comparison to the first 3 entries (Table1, entry 1 to 3). It was also observed that the reaction did not proceed in the absence of additive as well as base (Table1, entry 5 & 6) and resulted in the recovery of the starting material. By increasing the additive tetra butyl ammonium chloride (B) from 3 to 4 equiv, we observed increase in yields only by 4% (Table1, entry 7). Keeping the tetra butyl ammonium chloride (B) (3 equiv), $K_2S_2O_8$ (3 equiv) constant

Table 1. Optimisation Conditions for Cross Dehydro-genative Coupling



Entry	Oxidant (3 equiv)	Addtive (equiv)	Base (equiv)	Time (h)	Yield (%)[a]
1	$K_2S_2O_8$	A (2)	NaOAc (2)	4	51
2	$K_2S_2O_8$	A (2)	NaOAc (2)	12	45
3	$K_2S_2O_8$	A (3)	NaOAc (2)	4	57
4[b]	$K_2S_2O_8$	B (3)	NaOAc (2)	4	81
5	$K_2S_2O_8$	B (3)	-	4	N.R.
6	$K_2S_2O_8$	-	NaOAc (2)	12	N.R.
7	$K_2S_2O_8$	B (4)	NaOAc (2)	4	85
8	$K_2S_2O_8$	B (3)	NaOAc (4)	4	79
9	$Na_2S_2O_8$	B (3)	NaOAc (2)	12	31
10	$(NH_4)_2S_2O_8$	B (3)	NaOAc (2)	12	N.R.
11[c]	$K_2S_2O_8$	B (3)	NaOAc (2)	12	N.R.
12[d]	$K_2S_2O_8$	C (3)	NaOAc (2)	4	67
13	$K_2S_2O_8$	B (3)	K_2CO_3 (2)	4	N.R.
14	$K_2S_2O_8$	B (3)	NaOEt (2)	4	70
15	$K_2S_2O_8$	B (3)	Cs_2CO_3 (2)	4	N.R.
16	$K_2S_2O_8$	B (3)	NaO^{t}Bu(2)	4	N.R.
17	$K_2S_2O_8$	-	Bu_4NOH	4	N.R.
18	$K_2S_2O_8$	D (2)	NaOAc (2)	12	55
19	$K_2S_2O_8$	D (2)	-	12	N.R.
20	Oxone	B (3)	NaOAc (2)	4	17
21	TBHP	B (3)	NaOAc (2)	4	N.R.
22	DTBP	B (3)	NaOAc (2)	4	Trace
23	BPO	B (3)	NaOAc (2)	4	N.R.

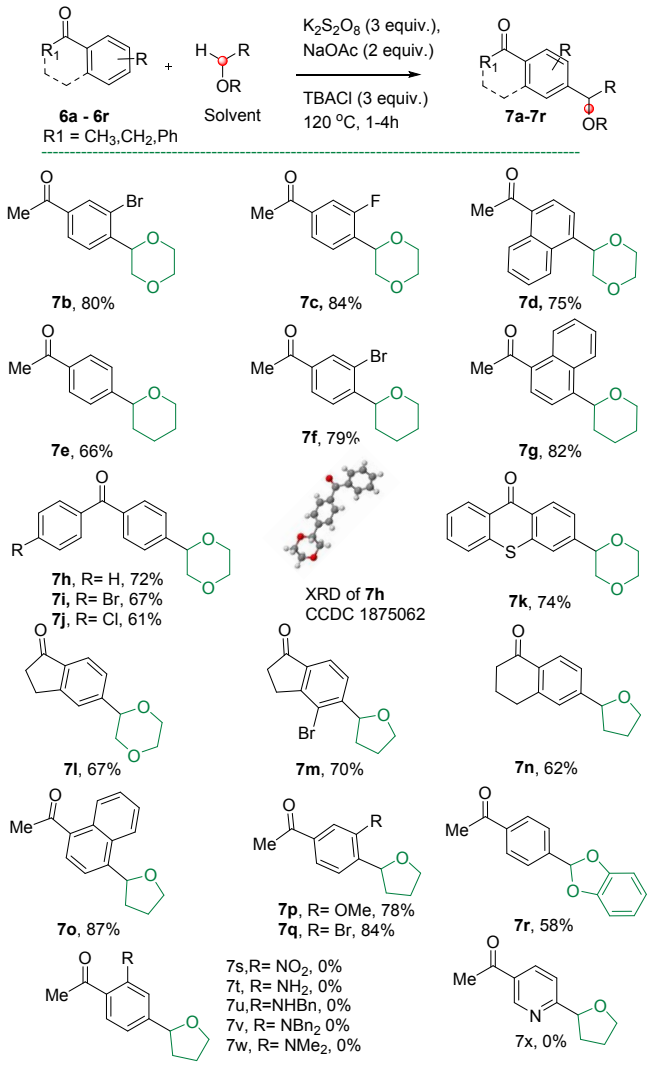
[b] TBACl in 50% aq. solution. [c] Temp. 80 °C. [d] $Bu_4NF.3H_2O$. N.R. = No Reaction.

and increasing the stoichiometry of NaOAc (2 to 4 equiv) lead to 79 % yield for the CDC product (Table 1, entry 8). In continuation, the oxidant $Na_2S_2O_8$ offers only 31% yield of the desired product (Table 1, entry 9). No conversion was observed using $(NH_4)_2S_2O_8$ (Table 1, entry 10). However, no significant improvement was observed with the use of different combinations of additives and bases. Instead, most of

the attempts were not fruitful (Table 1, entry 11-23). However, changing the bases didn't lead to enhancement in the yields. In order to examine the effect of atmospheric oxygen, the reaction was conducted under inert atmosphere, which did not affect the yield. In addition to this, the effect of the solvent was also studied (**see SI**). Therefore, the best regioselectivity and the highest yield of isolated product were achieved by using $K_2S_2O_8$ (3 equiv), terta butyl ammonium chloride (B) (3 Equiv) and NaOAc (2 equiv) for the reaction at 120 °C for 4 h (Table1, entry 4).

With these optimized reaction conditions in hand (Table 1, entry 4), the substrate scope of this unique transformation and limitations of the CDC reaction were studied by evaluating a variety of aryl carbonyls in order to investigate the generality of this reaction.

Scheme 2: CDC Reaction between Aromatic Ketones and Cyclic Ethers

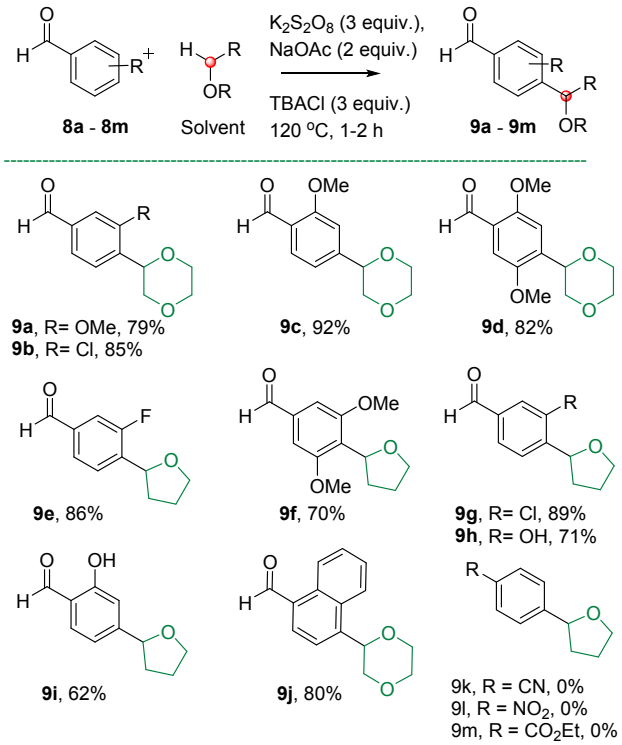


Reaction condition: 6a (0.83 mmol), $K_2S_2O_8$ (2.5 mmol), TBACl (2.5 mmol 50% aq. solution), NaOAc (1.66 mmol), 1,4-Dioxane (3 ml) and Temp. 120 °C.

As shown in scheme 2, the CDC reaction proceeds without any difficulty for a wide range of substrates bearing various substituents at different positions on the aryl ketones, providing the coupling products in moderate to good yields. When the electron withdrawing and electron donating groups were present at the position meta to the acetyl group and the reaction done under optimised conditions, the desired products were obtained in excellent yields (**7b**,**7c**,**7f**). The unsubstituted acetophenone was subjected to the standard reaction conditions with THP as a coupling ether, and gave the desired product **7e** in 66% yield. 1-Acetonaphthone also gave the expected α-arylated products of different cyclic ethers with excellent yields (**7d**, **7g**, **7o**). On the other hand, substituted cyclic ketones such as indanone and tetralone resulted in moderate yields of the products (**7l-7n**). It is noteworthy that thioxanthone successively yielded CDC product **7k** under oxidation conditions without any adverse effect of the sulphur. When acetophenone subjected under the standardized reaction conditions using 1,3-benzodioxole as a solvent, the corresponding product **7r** was formed in 58 % yield. Also, acyclic ethers as coupling partners led to undesired polymerisation. Unfortunately this approach failed to yield the expected CDC products (**7s-7x**) when the reaction was carried out on N-substituted aryl carbonyls and heterocyclic aryl ketones.

Next, we examined the efficiency of substituted aldehydes as coupling partners under the optimized experimental conditions. Notably, it was observed that the rate of the CDC reaction between benzaldehydes and cyclic ethers was faster than for the aryl ketones.

Scheme 3: CDC Reaction between Aromatic Aldehydes and Cyclic Ethers



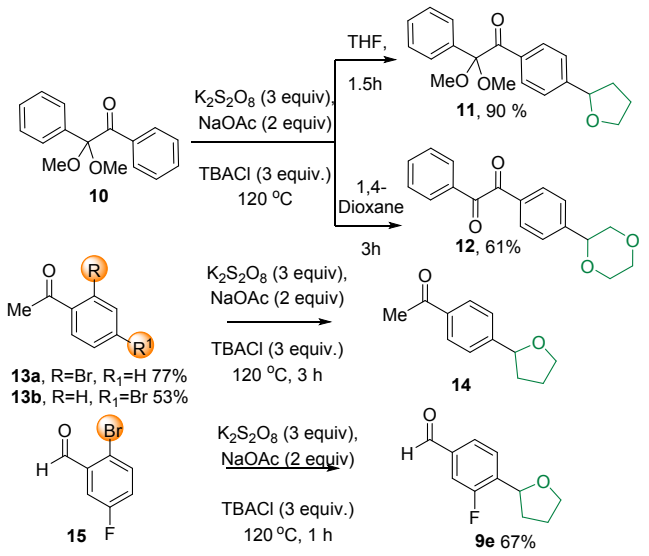
Reaction condition: 8a (0.73 mmol), $K_2S_2O_8$ (2.20 mmol), TBACl (2.20 mmol 50% aq. solution), NaOAc (1.47 mmol), 1,4-Dioxane (3 ml) at 120 °C.

Various substrates having electron-withdrawing substituents, such as Cl, Br, and F groups on the aromatic ring of the

aldehydes were efficiently reacted to produce the substituted para-alkylated benzalehydes with excellent yields (Scheme 3, entries **9b**, **9e** and **9g**). Surprisingly, hydroxy substituted benaldehydes also offer good yields of alkylated aryl carbonyls under oxidative conditions (**9h** and **9i**). Benzaldehydes with different elec-tron donating substituents also led to the corresponding product with good to excellent yields. (**9c**, **9d** & **9f**). A reaction performed with 2,5-dimethoxy benzaldehyde on a 6 mmol scale provided **9d** in 79% yield. Cyano, nitro and carboxylate substituted aryl derivatives were unable to give the desired product with our optimized reaction conditions. (**9k-m**).

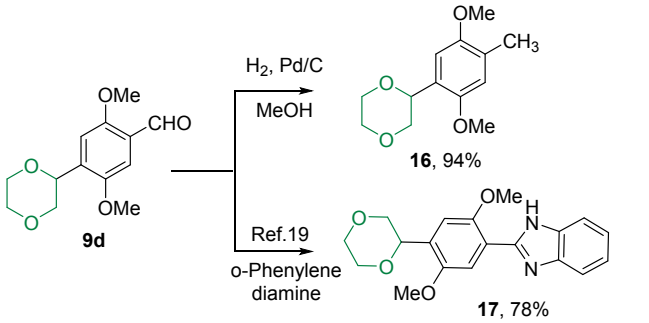
When benzil, α, α'-dimethyl acetal was subjected to the reaction under standard reaction condition, it gave unexpected products. In THF, the acetal group remained unaffected, whereas in 1,4-dioxane, it got deprotected to ketone (Scheme 4). An uncommon phenomenon that has been observed is that the presence of bromine on the *ortho* or *para* position to the aryl carbonyls delivers unexpected debrominated products, i.e. **14** and **9e**, as shown in Scheme 4.

Scheme 4: Some Unexpected Result of CDC Reaction



To show the utility of the reaction, the para-alkylated aryl carbonyl derivatives were further functionalized under various reaction conditions, as shown in scheme 5. The compound **9d** was subjected for the hydrogenation reaction using Pd/C; the aldehyde group of **9d** got reduced to methyl to give the toluene

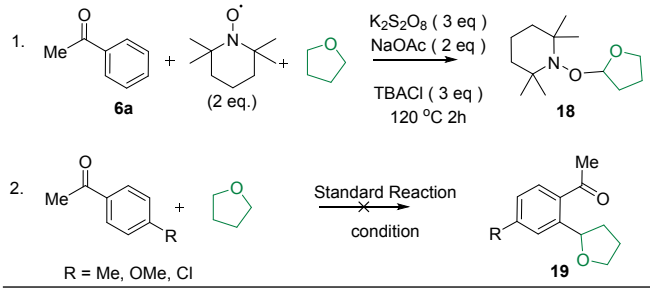
Scheme 5: Synthetic Transformations of the Products



derivative **16** in quantitative yield. Subsequently, the same compound **9d** was converted into its 1,2-benzimidazole derivative under the known protocol.[19]

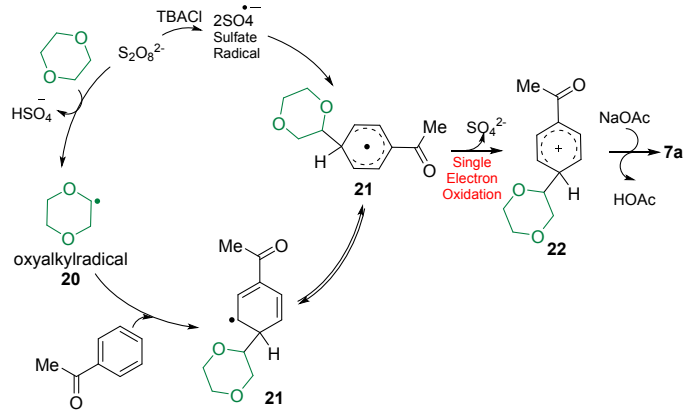
In order to understand the mechanism of this CDC reaction, we carried out control experiments (Scheme 6), where two equivalents of TEMPO (2,2,6,6-tetramethyl piperidine-N-oxide) were added into the reaction system under optimized reaction conditions. It was observed that the THF radical coupled with TEMPO to from a TEMPO-THF adduct **18**, instead of the expected product **7a**. This indicates that the reaction might be proceeding via the radical pathway. In the second control experiment, when the reaction was performed with p-substituted aryl ketone, we did not obtain the expected ortho alkylated product **19**.

Scheme 6: Control Experiments



This indicates that the reaction regioselectively goes only to the para position. Based on the above control experiments and the reported literature, [20, 21] the possible catalytic cycle was then initially proposed in scheme 7, as the α-oxyalkyl radical

Scheme 7: Expected Reaction Mechanism of Dehydro-genative Coupling



20 was generated via hydrogen atom abstraction from 1,4-dioxane by persulfate.[20] Then, this α-oxyalkyl radical **20** reacted with acetophenone **6a** to generate the aryl radical species **21**. This was followed by single electron oxidation to form the aryl cation species **22**. [21] The aryl cationic species further underwent aromatization to form the desired product **7a**.

In order to elucidate the reasons behind the *para* product being formed exclusively, quantum chemical calculations have been done using density functional theory (DFT). (see SI for more details, Fig. S1 and S2).

CONCLUSION

In conclusion, we have developed the first efficient and metal free CDC reaction of aromatic carbonyls with inactive cyclic ethers to give the desired p-alkylated aryl aldehydes and ketones in good to excellent yields with high regioselectivity. In addition, this reaction tolerates various functional groups under oxidative conditions and can be applied to obtain a wide range of substituted aromatic carbonyls. The utility of the products of CDC were shown by converting them to benzimidazole heterocycles and the toluene derivative.

Experimental Section

General Information:

Solvents were purified and dried using standard procedures before use. All air and moisture sensitive reactions were carried out in flame dried glassware under a positive pressure of dry argon using standard techniques. Commercially available chemicals were used without further purification unless otherwise mentioned. For moisture sensitive reactions, tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were dried using standard solvent purification system. The following dry solvents are commercially available and were used without further purification:

Acetonitrile: Acros Organics, 99.9% extra dry, over molecular sieves. Ethanol: Acros Organics, 99.5% extra dry. Methanol: Acros Organics, 99.8% extra dry, over molecular sieves. Technical solvents for column chromatography were used after simple distillation. The reactions were monitored by TLC visualized by UV (254 nm) and/or with iodine. The purification was done using column chromatography on silica 60 (Merck, 230-400 mesh) with the indicated eluent mixtures (v/v).

Nuclear Magnetic Resonance Spectra were recorded at room temperature on a Bruker AVHD-200, AVHD-400, AVHD-500 spectrometers in appropriate solvents using TMS as internal standard or the solvent signals as secondary standards and the chemical shifts are shown in δ scales. Coupling constants are given in hertz (Hz) and the classical abbreviations are used to describe the signal multiplicities. 1H NMR spectra were calibrated to the residual proton signal of chloroform-d1 (δ = 7.27 ppm), 13C NMR spectra were referenced to the 13C triplet of CDCl3 (δ = 77.16 ppm). Apparent multiplets which occur as a result of coupling constant equality between magnetically non-equivalent protons are marked as virtual (virt.). Following abbreviations for single multiplicities were used: br – broad, s – singlet, d – doublet, t – triplet, q – quartet, m – multiplet. High Resolution Mass Spectra (HRMS) for all new compounds were recorded on a ESI+ method and ORBITRAP mass analyzer (Thermo Scientific Q-Exactive, Accela 1250 pump). All chemicals are purchased from Sigma-Aldrich and used without further purification.

Typical Experimental Procedure for the Synthesis of 1-(4-(1,4-dioxan-2-yl) phenyl) ethan-1-one (7a):

To a 25 mL round-bottom flask acetophenone **6a** (0.833 mmol, 100 mg), $K_2S_2O_8$ (2.5 mmol, 676 mg), tetrabutylammonium chloride (TBACl, 2.5 mmol, 1.4 ml) and NaOAc (1.66 mmol, 136 mg) was taken in 1,4-dioxane (3 ml). The round-bottom flask was equipped with a condenser and the resulting reaction mixture was refluxed to 120 °C for 4 h, and the progress of the reaction was monitored by TLC. Upon completion of the reaction, the reaction mixture was dried under vacuum. Then the crude reaction mixture was diluted with ethyl acetate (10 mL) and washed with brine. Eluted with EtOAc (25 mL * 2). The organics was evaporated and the crude residue was preadsorbed on silica gel and purified by column chromatography (100-200 mesh silica Using 80/20 petroleum ether/ethyl acetate as the eluent to afford the corresponding compound **7a** in 81% yield.

1-(4-(1,4-dioxan-2-yl)phenyl)ethan-1-one (7a): white solid. Yield: 81% (139 mg); M.P.: 91-93 °C. ^{1}H NMR (500MHz , $CDCl_3$): δ 7.99 - 7.87 (m, J = 8.4 Hz, 2H), 7.54 - 7.39 (m, J = 8.0 Hz, 2H), 4.68 (dd, J = 2.3, 9.9 Hz, 1H), 3.98 - 3.94 (m, 1H), 3.92 (dd, J = 2.3, 11.1 Hz, 1H), 3.89 - 3.86 (m, 1H), 3.83 - 3.79 (m, 1H), 3.74 (dd, J = 3.1, 11.4 Hz, 1H), 3.41 (t, J = 10.9 Hz, 1H), 2.59 (s, 3H)). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 197.6, 143.4, 136.7, 128.4, 126.2, 77.3, 72.1, 66.9, 66.2, 26.5; HRMS (ESI) m/z calculated for $C_{12}H_{15}O_3$ [(M+H)$^+$] 207.1016, found 207.1019.

1-(3-bromo-4-(1,4-dioxan-2-yl)phenyl)ethan-1-one (7b): white solid. Yield: 80% (114 mg); M.P.: 87-89 °C. ^{1}H NMR (500MHz , $CDCl_3$): δ 8.02 (d, J = 1.5 Hz, 1H), 7.83 (dd, J = 1.5, 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 4.92 (dd, J = 2.5, 9.7 Hz, 1H), 4.01 (dd, J = 2.5, 11.6 Hz, 1H), 3.91 (s, 1H), 3.90 - 3.88 (m, 1H), 3.77 - 3.74 (m, 1H), 3.69 - 3.63 (m, 1H), 3.15 (dd, J = 9.7, 11.6 Hz, 1H), 2.51 (s, 3H)). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 196.3, 142.6, 137.8, 132.4, 128.2, 127.4, 122.0, 77.0, 70.5, 67.1, 66.3, 26.6; HRMS (ESI) m/z calculated for $C_{12}H_{14}O_3Br$ [(M+H)$^+$] 285.0121, found 285.0127.

1-(4-(1,4-dioxan-2-yl)-3-fluorophenyl)ethan-1-one (7c): white solid. Yield: 84% (136 mg); M.P.: 116-118 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 - 7.78 (m, 1H), 7.57 - 7.66 (m, 2H), 4.97 (dd, J = 9.9, 2.3 Hz, 1H), 3.91 - 4.00 (m, 3H), 3.80 - 3.84 (m, 1H), 3.70 - 3.77 (m, 1H), 3.36 (dd, J = 11.4, 9.9 Hz, 1H), 2.59 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 196.4 , 160.4-158.4 (d, J_{F-C} = 247.96 Hz), 138.4-138.3 (d, J_{F-C} = 6.68 Hz), 130.8-130.7 (d, J_{F-C} = 14.31 Hz), 128.04-128.01 (d, J_{F-C} = 3.81 Hz), 124.4, 114.8-114.6 (d, J_{F-C} = 22.89 Hz), 71.9 , 70.9, 67.2 , 66.3, 26.6 ; HRMS (ESI) m/z calculated for $C_{12}H_{14}O_3F$ [(M+H)$^+$] 225.0921, found 225.0928.

1-(4-(1,4-dioxan-2-yl)naphthalen-1-yl)ethan-1-one (7d): gummy liquid. Yield: 75% (113 mg). ^{1}H NMR (200MHz , $CDCl_3$): δ 8.87 - 8.64 (m, 1H), 8.15 - 8.05 (m, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.66 - 7.51 (m, 2H), 5.43 (dd, J = 2.4, 9.7 Hz, 1H), 4.18 - 4.04 (m, 3H), 3.95 - 3.76 (m, 2H), 3.50 (dd, J = 10.0, 11.9 Hz, 1H), 2.75 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 201.7, 138.7, 135.5, 130.4, 129.9, 127.7, 127.3, 126.6, 126.5, 122.5, 122.1, 74.7, 71.9, 67.2, 66.4, 29.8; HRMS (ESI) m/z calculated for $C_{16}H_{17}O_3$ [(M+H)$^+$] 257.1172, found 257.1171.

1-(4-(tetrahydro-2H-pyran-2-yl)phenyl)ethan-1one (7e)): whitish semisolid. Yield: 66% (112 mg). ^{1}H NMR (200MHz , $CDCl_3$): δ 7.97 - 7.86 (m, J = 8.3 Hz, 2H), 7.49 - 7.38 (m, J = 8.2 Hz, 2H), 4.39 (d, J = 10.6 Hz, 1H), 4.17 (dd, J = 2.9, 10.9 Hz, 1H), 3.71 - 3.56 (m, 1H), 2.60 (s, 3H), 1.86 (d, J = 12.3 Hz, 1H), 1.75 - 1.47 (m, 5H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 197.9, 148.7, 136.1, 128.4, 125.8, 79.5, 68.9, 34.1, 26.6, 25.7, 23.9; HRMS (ESI) m/z calculated for $C_{13}H_{17}O_2$ [(M+H)$^+$] 205.1223, found 205.1222.

1-(3-bromo-4-(tetrahydro-2H-pyran-2-yl)phenyl)ethan-1-one (7f): Clear oil. Yield: 79% (113 mg). ^{1}H NMR (500MHz , $CDCl_3$): δ 8.08 (s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 4.65 (d, J = 10.7 Hz, 1H), 4.16 (d, J = 11.1 Hz, 1H), 3.65 (t, J = 10.7 Hz, 1H), 2.57 (s, 3H), 2.03 (d, J = 13.4 Hz, 1H), 1.93 (br. s., 1H), 1.74 - 1.65 (m, 2H), 1.60 (d, J = 8.4 Hz, 1H), 1.31 - 1.24 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 196.4, 147.7, 137.1, 132.3, 127.5, 127.4, 121.5, 78.9, 69.0, 32.6, 26.5, 25.7, 23.7; HRMS (ESI) m/z calculated for $C_{13}H_{16}O_2Br$ [(M+H)$^+$] 283.0328, found 283.0333.

1-(4-(tetrahydro-2H-pyran-2-yl)naphthalen-1-yl)ethan-1-one (7g): Gummy oil. Yield: 82% (123 mg). ^{1}H NMR (400MHz , $CDCl_3$): δ 8.78 (d, J = 7.9 Hz, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 7.3 Hz, 1H), 7.62 - 7.51 (m, 2H), 5.09 (d, J = 11.0 Hz, 1H), 4.31 - 4.22 (m, 1H), 3.85 - 3.73 (m, 1H), 2.74 (s, 3H), 2.11 - 1.99 (m, 2H), 1.86 - 1.78 (m, 2H), 1.72 - 1.64 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 201.6, 143.8, 134.5, 130.2, 130.0, 128.0, 126.9, 126.3, 125.9,

122.9, 121.0, 76.6, 69.0, 33.2, 29.7, 25.6, 23.8; HRMS (ESI) m/z calculated for $C_{17}H_{19}O_2$ [(M+H)$^+$] 255.1380, found 255.1378

(4-(1,4-dioxan-2-yl)phenyl)(Phenyl)methanone(7h*):* White solid. Yield: 72% (106 mg); M.P.: 70-72 ^{o}C. ^{1}H NMR (200MHz , $CDCl_3$): δ 7.84 - 7.77 (m, 4H), 7.65 - 7.55 (m, 1H), 7.54 - 7.44 (m, 4H), 4.73 (dd, J = 2.7, 10.2 Hz, 1H), 4.01 - 3.93 (m, 2H), 3.92 - 3.85 (m, 1H), 3.85 - 3.69 (m, 2H), 3.48 (dd, J = 10.2, 11.5 Hz, 1H)). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 195.6, 142.5, 137.3, 137.0, 132.0, 129.9, 129.7, 128.0, 126.3, 125.6, 125.1, 77.1, 72.0, 66.7, 66.0; HRMS (ESI) m/z calculated for $C_{17}H_{17}O_3$ [(M+H)$^+$] 269.1172, found 269.1174.

(4-(1,4-dioxan-2-yl)phenyl)(4-bromophenyl)methanone (7i): White solid. Yield: 67% (89 mg); M.P.: 88-90 ^{o}C. ^{1}H NMR (200MHz , $CDCl_3$): δ 7.81 - 7.74 (m, J = 8.3 Hz, 2H), 7.71 - 7.60 (m, 4H), 7.54 - 7.43 (m, J = 8.1 Hz, 2H), 4.73 (dd, J = 2.6, 10.0 Hz, 1H), 4.01 - 3.92 (m, 2H), 3.89 (d, J = 2.7 Hz, 1H), 3.84 - 3.69 (m, 2H), 3.46 (dd, J = 10.2, 11.6 Hz, 1H). ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$): δ 194.5, 142.4, 136.1, 135.6, 131.0, 130.8, 129.4, 127.6, 126.9, 126.6, 125.5, 76.7, 71.6, 66.3, 65.7; HRMS (ESI) m/z calculated for $C_{17}H_{16}O_3Br$ [(M+H)$^+$] 347.0277, found 347.0285.

(4-(1,4-dioxan-2-yl)phenyl)(4-chlorophenyl)methanone (7j): White solid. Yield: 61% (85 mg); M.P.: 90-92 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.0 Hz, 2H), 7.48 (dd, J = 9.9, 8.4 Hz, 4H), 4.73 (dd, J = 10.3, 2.7 Hz, 1H), 3.97 - 4.00 (m, 1H), 3.90 - 3.95 (m, 2H), 3.82 - 3.86 (m, 1H), 3.76 (td, J = 11.3, 3.2 Hz, 1H), 3.47 (dd, J = 11.4, 10.3 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 194.7, 142.7, 138.6, 136.5, 135.5, 131.1, 129.8, 128.3, 125.8, 77.1, 71.9, 66.7, 66.0; HRMS (ESI) m/z calculated for $C_{17}H_{16}O_3Cl$ [(M+H)$^+$] 303.0782, found 303.0789.

3-(1,4-dioxan-2-yl)-9H-thioxanthen-9-one (7k): White solid. Yield: 74% (104 mg); M.P.: 163-165 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 - 8.66 (m, 2H), 7.56 - 7.66 (m, 3H), 7.46 - 7.53 (m, 1H), 7.42 (dd, J = 8.2, 1.8 Hz, 1H), 4.76 (dd, J = 10.1, 2.7 Hz, 1H), 3.91 - 4.05 (m, 3H), 3.85 (dd, J = 11.4, 2.7 Hz, 1H), 3.76 (td, J = 11.3, 3.4 Hz, 1H), 3.46 (dd, J = 11.9, 10.1 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ179.7, 142.9, 137.6, 137.2, 132.3, 130.0, 129.8, 129.2, 128.8, 126.4, 126.0, 124.1, 123.2, 72.1, 67.0, 66.3; HRMS (ESI) m/z calculated for $C_{17}H_{15}O_3S$ [(M+H)$^+$] 299.0736, found 299.0733.

5-(1,4-dioxan-2-yl)-2,3-dihydro-1H-inden-1-one (7l): White solid. Yield: 67% (110 mg); M.P.: 128-130 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 - 7.70 (m, 2H), 7.39 (d, J = 6.7 Hz, 1H), 5.68 (d, J = 9.2 Hz, 1H), 3.92 - 4.08 (m, 3H), 3.82 (d, J = 11.0 Hz, 1H), 3.72 (td, J = 11.0, 3.7 Hz, 1H), 3.22 (t, J = 10.4 Hz, 1H), 3.05 - 3.17 (m, 2H), 2.58 - 2.83 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 207.0, 155.7, 138.5, 134.6, 132.6, 125.9, 124.6, 73.2, 71.7, 67.0, 66.3, 36.6, 25.6; HRMS (ESI) m/z calculated for $C_{13}H_{15}O_3$ [(M+H)$^+$] 219.1016, found 219.1018.

4-bromo-5-(tetrahydrofuran-2-yl)-2,3-dihydro-1H-inden-1-one (7m): off white solid. Yield: 70% (93 mg); M.P.: 116-118 ^{o}C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.62 (d, J = 8.2 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 5.64 (t, J = 6.9 Hz, 1H), 4.06 (q, J = 7.1 Hz, 1H), 3.79 - 3.97 (m, 1H), 2.92 - 3.06 (m, 2H), 2.43 - 2.69 (m, 3H), 1.72 - 2.06 (m, 2H), 1.34 - 1.55 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 206.5, 155.1, 144.2, 137.1, 134.5, 125.2, 120.1, 76.4, 69.1, 36.4, 34.0, 26.9, 25.8; HRMS (ESI) m/z calculated for $C_{13}H_{14}O_2Br$ [(M+H)$^+$] 281.0172, found 281.0170.

6-(tetrahydrofuran-2-yl)-3,4-dihydronaphthalen-1(2H)-one (7n): Clear oil. Yield: 62% (91 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 8.5 Hz, 1H), 7.13 - 7.24 (m, 2H), 4.85 (d, J = 6.7 Hz, 1H), 4.04 (d, J = 7.9 Hz, 1H), 3.89 (d, J = 7.3 Hz, 1H), 2.85 - 2.97 (m, 2H), 2.52 - 2.64 (m, 2H), 2.21 - 2.36 (m, 1H), 2.01 - 2.13 (m, 2H), 1.91 - 2.00 (m, 2H), 1.65 - 1.79 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, CDCl3): δ 197.9, 149.1, 144.4, 131.3, 127.0, 125.2, 123.6, 79.9, 68.6, 38.8, 34.3, 29.5, 29.4, 25.7, 23.0; HRMS (ESI) m/z calculated for $C_{14}H_{17}O_2$ [(M+H)$^+$] 217.1223, found 217.1222.

1-(4-(tetrahydrofuran-2-yl)naphthalen-1-yl)ethan-1-one (7o): White solid. Yield: 87% (123 mg); M.P.: 65-67 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, J = 8.5 Hz, 1H), 7.94 (d, J = 7.3 Hz, 1H), 7.98 (d, J = 7.9 Hz, 1H), 7.70 (d, J = 7.3 Hz, 1H), 7.52 - 7.65 (m, 2H), 5.61 - 5.76 (m, 1H), 4.20 - 4.37 (m, 1H), 4.06 (q, J = 7.7 Hz, 1H), 2.75 (s, 3H), 2.54 - 2.70 (m, 1H), 1.96 - 2.13 (m, 2H), 1.87 (dt, J = 12.5, 6.6 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 201.8, 144.9, 134.7, 130.6, 130.4, 128.5, 127.4, 126.8, 126.3, 123.4, 120.2, 77.7, 68.9, 34.0, 30.0, 25.9; HRMS (ESI) m/z calculated for $C_{16}H_{17}O_2$ [(M+H)$^+$] 241.1223, found 241.1226.

1-(3-methoxy-4-(tetrahydrofuran-2-yl)phenyl)ethan-1-one (7p): Clear oil. Yield: 78% (114 mg). ^{1}H NMR (400MHz , $CDCl_3$): δ 7.48 - 7.43 (m, 2H), 7.38 (s, 1H), 5.09 (t, J = 7.0 Hz, 1H), 4.10 - 4.00 (m, 1H), 3.90 - 3.85 (m, 1H), 3.84 - 3.80 (m, 3H), 2.52 (s, 3H), 2.36 (dd, J = 6.7, 12.8 Hz, 1H), 1.88 (qd, J = 6.9, 14.2 Hz, 2H), 1.62 - 1.55 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 197.8, 156.2, 138.4, 137.0, 125.3, 121.6, 108.6, 75.8, 68.6, 55.4, 33.0, 26.5, 25.8; HRMS (ESI) m/z calculated for $C_{13}H_{17}O_3$ [(M+H)$^+$] 221.1172, found 221.1177.

1-(3-bromo-4-(tetrahydrofuran-2-yl)phenyl)ethan-1-one (7q): Clear oil. Yield: 84% (113 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 1.5 Hz, 1H), 7.86 (dd, J = 8.0, 1.5 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 5.15 (t, J = 7.1 Hz, 1H), 4.17 (td, J = 7.6, 6.1 Hz, 1H), 3.97 (q, J = 7.2 Hz, 1H), 2.51 - 2.64 (m, 4H), 1.98 (td, J = 14.0, 7.1 Hz, 2H), 1.65 (dd, J = 12.6, 7.6 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz,$CDCl_3$): δ 196.4, 148.5, 137.2, 132.4, 127.3, 126.6, 121.5, 79.7, 69.2, 33.2, 26.5, 25.7; HRMS (ESI) m/z calculated for $C_{12}H_{14}O_2Br$ [(M+H)$^+$] 269.0172, found 269.0178.

1-(4-(benzo[d][1,3]dioxol-2-yl)phenyl)ethan-1-one (7r): white solid. Yield: 58% (116 mg); M.P.: 70-72 ^{o}C. ^{1}H NMR (500MHz, $CDCl_3$): δ 8.04 (s, 1H), 8.02 (s, 1H), 7.70 (s, 1H), 7.68 (s, 1H), 7.01 (s, 1H), 6.89 (s, 4H), 2.63 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 197.5, 147.2, 140.9, 138.4, 128.6, 126.6, 121.9, 108.8, 108.7, 26.7; HRMS (ESI) m/z calculated for $C_{15}H_{13}O_3$ [(M+H)$^+$] 241.0859, found 241.0864.

Typical Experimental Procedure for the Synthesis of 4-(1,4-dioxan-2-yl)-3-methoxybenzaldehyde (9a):

To a 25 mL round-bottom flask 3-methoxybenzaldehyde **8a** (0.73 mmol), $K_2S_2O_8$ (2.20 mmol, 594 mg), tetrabutylammonium chloride (TBACl, 2.20 mmol, 1.2 ml) and NaOAc (1.47 mmol, 121 mg) was taken in 1,4-dioxane (3 ml). The round-bottom flask was equipped with a condenser and the resulting reaction mixture was refluxed to 120 °C for 1.5 h, and the progress of the reaction was monitored by TLC. Upon completion of the reaction, the reaction mixture was dried under vacuum. Then the crude reaction mixture was diluted with ethyl acetate (10 mL) and washed with brine. Eluted with EtOAc (20 mL * 2). The organics was evaporated and the crude residue was preadsorbed on silica gel and purified by column chromatography (100-200 mesh silica Using 85/15 petroleum ether/ethyl acetate as the eluent to afford the corresponding compound **9a** in 79% yield.

4-(1,4-dioxan-2-yl)-3-methoxybenzaldehyde (9a): Clear oil. Yield: 79% (128 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.97 (s, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.46 - 7.52 (m, 1H), 7.33 - 7.39 (m, 1H), 5.03 (dd, J = 9.7, 2.5 Hz, 1H), 4.02 (dd, J = 11.4, 2.7 Hz, 1H), 3.92 - 4.00 (m, 2H), 3.90 (s, 3H), 3.79 - 3.84 (m, 1H), 3.69 - 3.76 (m, 1H), 3.26 (dd, J = 11.3, 9.7 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 191.6, 156.2, 136.7, 133.8, 127.0, 124.4, 107.9, 72.6, 70.7, 67.1, 66.2, 55.3; HRMS (ESI) m/z calculated for $C_{12}H_{15}O_4$ [(M+H)$^+$] 223.0965, found 223.0964.

3-chloro-4-(1,4-dioxan-2-yl)benzaldehyde (9b): Pale yellow solid. Yield: 85% (137 mg); M.P.: 72-74 ^{o}C. ^{1}H NMR

(400MHz , $CDCl_3$): 9.96 (s, 1H), 8.04 - 7.75 (m, 3H), 5.18 - 5.00 (m, 1H), 4.08 (d, J = 11.6 Hz, 1H), 4.04 - 3.93 (m, 2H), 3.84 (d, J = 12.2 Hz, 1H), 3.75 (dd, J = 4.0, 10.1 Hz, 1H), 3.36 - 3.17 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 190.1, 142.1, 136.5, 132.4, 129.6, 128.1, 127.9, 74.5, 70.1, 66.8, 66.0; HRMS (ESI) m/z calculated for $C_{11}H_{12}O_3Cl$ $[(M+H)^+]$ 227.0469, found 227.0467.

4-(1,4-dioxan-2-yl)-2-methoxybenzaldehyde (9c): Clear oil. Yield: 92% (150 mg). ^1H NMR (500MHz , $CDCl_3$): δ 10.43 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.04 (s, 1H), 6.95 (d, J = 8.0 Hz, 1H), 4.66 (dd, J = 2.7, 10.3 Hz, 1H), 3.98 - 3.93 (m, 4H), 3.91 (t, J = 3.4 Hz, 1H), 3.89 - 3.87 (m, 1H), 3.83 - 3.79 (m, 1H), 3.76 - 3.72 (m, 1H), 3.41 (dd, J = 10.3, 11.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 189.1, 161.7, 146.5, 128.3, 124.0, 117.9, 108.8, 77.1, 71.8, 66.6, 66.0, 55.4; HRMS (ESI) m/z calculated for $C_{12}H_{15}O_4$ $[(M+H)^+]$ 223.0965, found 223.0963.

4-(1,4-dioxan-2-yl)-2,5-dimethoxybenzaldehyde (9d): Yellow solid. Yield: 82% (124 mg); M.P.: 118-120 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 10.43 (s, 1H), 7.27 (s, 1H), 7.19 (s, 1H), 4.98 (dd, J = 9.5, 2.3 Hz, 1H), 4.04 (dd, J = 11.3, 2.5 Hz, 1H), 3.96 - 3.99 (m, 1H), 3.92 - 3.96 (m, 4H), 3.82 (s, 3H), 3.79 - 3.81 (m, 1H), 3.69 - 3.76 (m, 1H), 3.22 (dd, J = 11.1, 9.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 189.2, 156.9, 149.9, 135.5, 123.8, 110.8, 108.1, 73.1, 70.9, 67.3, 66.4, 56.2, 55.7; HRMS (ESI) m/z calculated for $C_{13}H_{17}O_5$ $[(M+H)^+]$ 253.1071, found 253.1069.

3-fluoro-4-(tetrahydrofuran-2-yl) benzaldehyde (9e): Clear oil. Yield: 86% (135 mg) & 67% (105 mg). ^1H NMR (200MHz , $CDCl_3$): 9.96 (s, 1H), 7.72 - 7.61 (m, 2H), 7.52 (d, J = 9.9 Hz, 1H), 5.16 (t, J = 7.1 Hz, 1H), 4.12 (q, J = 6.8 Hz, 1H), 4.03 - 3.87 (m, 1H), 2.59 - 2.39 (m, 1H), 2.09 - 1.93 (m, 2H), 1.75 (dd, J = 7.6, 12.1 Hz, 1H). $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ 190.7 , 162.3-157.3 (d, J = 248.82 Hz), 138.4-138.1 (d, J = 14.27 Hz), 137.0-136.9 (d, J = 6.22 Hz,), 127.4-127.3 (d, J = 4.39 Hz), 126.3-126.2 (d, J = 2.93 Hz,), 115.0-114.6 (d, J = 22.32 Hz), 74.9-74.8 (d, J = 1.83 Hz), 68.8 , 33.4 , 25.9; HRMS (ESI) m/z calculated for $C_{11}H_{12}O_2F$ $[(M+H)^+]$ 195.0816, found 195.0815.

3,5-dimethoxy-4-(tetrahydrofuran-2-yl)benzaldehydes (9f): Clear oil. Yield: 70% (99 mg). ^1HNMR (500MHz , $CDCl_3$): 10.43 (s, 1H), 7.27 (s, 1H), 7.19 (s, 1H), 4.98 (dd, J = 2.3, 9.5 Hz, 1H), 4.04 (dd, J = 2.5, 11.3 Hz, 1H), 3.99 - 3.97 (m, 1H), 3.96 - 3.91 (m, 4H), 3.82 (s, 3H), 3.81 - 3.79 (m, 1H), 3.75 - 3.70 (m, 1H), 3.22 (dd, J = 9.9, 11.1 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 191.4, 158.8, 136.2, 124.5, 104.9, 71.8, 68.7, 55.6, 29.9, 27.4; HRMS (ESI) m/z calculated for $C_{13}H_{17}O_4$ $[(M+H)^+]$ 237.1121, found 237.1119.

3-chloro-4-(tetrahydrofuran-2-yl)benzaldehydes (9g): Clear oil. Yield: 89% (134 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 7.75 (d, J=1.5 Hz, 1H), 7.60 - 7.70 (m, 2H), 5.14 (t, J=7.1 Hz, 1H), 4.03 - 4.17 (m, 1H), 3.90 (q, J=7.3 Hz, 1H), 2.50 (dd, J=12.5, 6.4 Hz, 1H), 1.83 - 2.02 (m, 2H), 1.51 - 1.65 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 190.3, 148.2, 135.9, 132.0, 129.6, 127.9, 126.6, 77.4, 68.8, 32.7, 25; HRMS (ESI) m/z calculated for $C_{11}H_{12}O_2Cl$ $[(M+H)^+]$ 211.0520, found 211.0519

3-hydroxy-4-(tetrahydrofuran-2-yl)benzaldehydes (9h): Yellow oil. Yield: 71% (111 mg). ^1H NMR (200 MHz, $CDCl_3$): δ 9.98 (s, 1H), 9.80 (s, 1H), 7.20 - 7.46 (m, 2H), 7.10 (dd, J = 7.5, 1.8 Hz, 1H), 5.89 (dd, J = 9.6, 6.2 Hz, 1H), 4.09 - 4.35 (m, 1H), 3.77 - 4.04 (m, 1H), 2.49 - 2.70 (m, 1H), 1.96 - 2.23 (m, 2H), 1.63 - 1.84 (m, 1H). $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ 193.3, 157.2, 134.0, 128.5, 127.8, 124.7, 123.5, 80.2, 68.6, 32.9, 25.6; HRMS (ESI) m/z calculated for $C_{11}H_{11}O_3$ $[(M-H)^+]$ 191.0703, found 191.0702

2-hydroxy-4-(tetrahydrofuran-2-yl)benzaldehydes (9i): Clear oil. Yield: 62% (98 mg). ^1H NMR (200 MHz, $CDCl_3$): δ 11.07 (s, 1H), 9.86 (s, 1H), 7.52 (d, J = 8.5 Hz, 1H), 6.89 - 7.07 (m, 2H), 4.92 (t, J = 7.1 Hz, 1H), 3.90 - 4.16 (m, 2H), 2.37 (dd, J = 11.9, 6.3 Hz, 1H), 1.93 - 2.07 (m, 2H), 1.70 - 1.87 (m, 1H). $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ 195.3, 161.1, 153.7, 133.1, 119.0, 116.4, 113.5, 79.3, 68.4, 33.9, 25.2; HRMS (ESI) m/z calculated for $C_{11}H_{12}O_3$ $[(M+H)^+]$ 193.0859, found : 193.0858.

4-(1,4-dioxan-2-yl)-1-naphthaldehyde (9j): Clear oil. Yield: 80% (131 mg). ^1H NMR (200 MHz, $CDCl_3$): δ 10.29 (s, 1H), 9.17 - 9.35 (m, 1H), 8.01 - 8.10 (m, 1H), 7.93 (d, J = 7.5 Hz, 1H), 7.82 (d, J = 7.5 Hz, 1H), 7.50 - 7.68 (m, 2H), 5.37 (dd, J = 9.9, 2.3 Hz, 1H), 3.98 - 4.11 (m, 3H), 3.73 - 3.84 (m, 2H), 3.41 (dd, J = 11.9, 9.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ 192.7, 141.0, 135.7, 130.4, 130.0, 129.7, 128.0, 126.6, 125.1, 122.3, 122.2, 74.4, 71.5, 66.8, 66.0; HRMS (ESI) m/z calculated for $C_{15}H_{14}O_3Na$ $[(M+Na)^+]$ 265.0835, found 265.0832.

2,2-dimethoxy-2-phenyl-1-(4-(tetrahydrofuran-2-yl) phenyl)ethan-1-one (11): White semisolid. Yield: 90% (114 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 7.9 Hz, 2H), 7.61 (d, J = 7.3 Hz, 2H), 7.20 - 7.46 (m, 5H), 4.74 - 4.98 (m, 1H), 4.00 - 4.12 (m, 1H), 3.81 - 3.98 (m, 1H), 3.21 (s, 6H), 2.21 - 2.40 (m, 1H), 1.90 - 2.07 (m, 2H), 1.72 (dt, J = 12.4, 7.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ 194.6, 148.8, 136.9, 133.0, 130.2, 128.8, 128.4, 126.9, 125.2 , 103.5, 80.1, 68.8, 50.0, 34.4, 25.9; HRMS (ESI) m/z calculated for $C_{20}H_{22}O_4Na$ $[(M+Na)^+]$ 349.1410, found 349.1406.

1-(4-(1,4-dioxan-2-yl)phenyl)-2-phenylethane-1,2-dione (12): Yellow oil. Yield: 61% (70 mg). ^1H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, J = 7.6 Hz, 4H), 7.61 - 7.73 (m, 1H), 7.43 - 7.58 (m, 4H), 4.61 - 4.81 (m, 1H), 3.86 - 4.00 (m, 3H), 3.82 (d, J = 10.7 Hz, 1H), 3.73 (td, J = 11.3, 2.9 Hz, 1H), 3.40 (t, J = 10.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ 194.4, 194.0, 145.5, 134.9, 132.9, 132.5, 130.0, 129.9, 129.0, 126.6, 77.2, 72.1, 66.9, 66.3; HRMS (ESI) m/z calculated for $C_{18}H_{16}O_4Na$ $[(M+Na)^+]$ 319.0941, found 319.0936.

1-(4-(tetrahydrofuran-2-yl)phenyl)ethan-1-one(14): Clear oil Yield 77% (121 mg) & 53% (83 mg). ^1H NMR (400MHz , $CDCl_3$): 7.93 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 4.95 (t, J = 7.3 Hz, 1H), 4.14 - 4.07 (m, 1H), 3.97 (q, J = 7.3 Hz, 1H), 2.60 (s, 3H), 2.37 (dd, J = 6.4, 12.5 Hz, 1H), 2.02 (td, J = 7.0, 14.0 Hz, 2H), 1.81 - 1.74 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 197.8, 149.2, 136.1, 128.4, 125.6, 80.1, 68.9, 34.7, 26.6, 25.9. HRMS (ESI) m/z calculated for $C_{12}H_{14}O_2$ $[(M+H)^+]$ 191.1067, found 191.1062.

Experimental Procedure for the synthesis of 2-(2,5-dimethoxy-4-methylphenyl)-1,4-dioxane (16: Degassed methanol (4.0 ml) was added to the mixture of Pd/C (10 wt %) and **9d** (0.3 mmol,76 mg). After stirring under 1 atm pressure of hydrogen for 12 h at room temperature, the reaction mixture was filtered, and then evaporated under reduced pressure. The crude product was then purified by flash column chromatography (eluent: 90/10 pet.ether/ethyl acetate) to give hydrogenated product **16** (67 mg) as a clear oil.

2-(2,5-dimethoxy-4-methylphenyl)-1,4-dioxane (16): clear oil yield: 94% (71 mg). ^1H NMR (400MHz, $CDCl_3$): 6.89 (s, 1H), 6.59 (s, 1H), 4.95 - 4.82 (m, 1H), 3.92 - 3.83 (m, 3H), 3.75 (s, 3H), 3.72 - 3.62 (m, 5H), 3.22 (t, J = 10.4 Hz, 1H), 2.14 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 151.6, 149.2, 126.1, 124.1, 113.2, 108.8, 72.5, 71.2, 67.1, 66.1, 55.7, 55.6, 15.9; HRMS (ESI) m/z calculated for $C_{13}H_{18}O_4Na$ $[(M+Na)^+]$ 261.1097, found 261.1093.

Experimental Procedure for the synthesis of 2-(4-(1,4-dioxan-2-yl)-2,5-dimethoxyphenyl)-1H-benzo[d]imidazole (17): To a 25 mL round-bottom flask 4-(1,4-dioxan-2-yl)-2,5-dimethoxybenzaldehyde (0.396 mmol,100

mg), *o*-phenylenediamine (0.396 mmol,42 mg), 30% H_2O_2 in water (94 mg, 0.82 ml) and HCl 37% in water (50.5 mg, 0.15 ml) was taken in acetonitrile (3 ml). After stirring for 1 h at rt the reaction mixture was evaporated under reduced pressure, Then the crude reaction mixture was diluted with ethyl acetate (10 mL) and washed with brine. Eluted with EtOAc (15 mL * 2). The organics was evaporated and the crude residue was preadsorbed on silica gel and purified by column chromatography (100-200 mesh silica Using 70/30 petroleum ether/ethyl acetate as the eluent to afford the corresponding compound **17** in 78% yield as a white solid.

2-(4-(1,4-dioxan-2-yl)-2,5-dimethoxyphenyl)-1H-benzo[d]imidazole (17): White solid. Yield: 78% (159 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.80 (br. s., 1H), 8.08 (s, 1H), 7.84 (br. s., 1H), 7.52 (br. s., 1H), 7.13 - 7.35 (m, 3H), 5.05 (dd, J = 9.7, 2.5 Hz, 1H), 4.07 - 4.13 (m, 4H), 3.96 - 4.05 (m, 2H), 3.95 (s, 3H), 3.82 - 3.87 (m, 1H), 3.74 - 3.81 (m, 1H), 3.31 (dd, J = 11.1, 10.3 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 151.1, 150.2, 149.6, 129.7, 122.6, 122.1, 118.9, 116.9, 110.7, 110.5, 110.3, 72.7, 71.0, 67.1, 66.2, 56.3, 55.8; HRMS (ESI) m/z calculated for $C_{19}H_{21}O_4N_2$ [$(M+H)^+$] 341.1496, found 341.1502.

ASSOCIATED CONTENT

Supporting Information:

Analytical Data (^{1}H, ^{13}C, crystallographic data for compound **7h** and DFT Calculation Studies)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

(KDM and AM thank CSIR-New Delhi and UGC respectively for providing fellowship. We acknowledge the Department of Science and Technology DST for providing funds. We thank Dr Rajesh Gonnade, CSIR-NCL, for providing the single crystal X-ray dif-fraction data. K.V. is grateful to DST (EMR/2014/000013) for providing financial assistance

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