



# A frank synthesis of alkyl–aryl ethers from 2-halobenzaldehydes and aromatic olefins without transition metal co-catalyst and ligand



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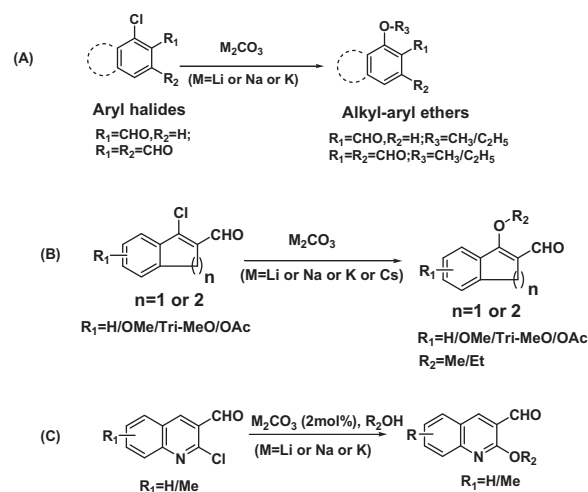
## ABSTRACT

An efficient synthesis of alkyl ethers has been developed for *o*-deactivated aryl halides and 1-halotetralenes. The method shows good regioselectivity towards *ortho* substituted halides. Alkali metal carbonates ( $\text{Li}_2\text{CO}_3/\text{Na}_2\text{CO}_3/\text{K}_2\text{CO}_3/\text{Cs}_2\text{CO}_3$ ) have been used without a transition metal co-catalyst and ligand. The method is simple, straight-forward and proceeds to afford products in good isolated yields. The method holds potential for future applications in organic synthesis.

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Alkyl–aryl ethers are an important class of compounds possessing diverse biological and physical properties.<sup>1–3</sup> Generally, these are prepared through etherification of aryl halides, which is an important reaction in synthetic chemistry.<sup>4–6</sup> A variety of strong nucleophiles including  $\text{OH}^-$ ,  $\text{OR}^-$ ,  $\text{NH}_2^-$ ,  $\text{RS}^-$  and some cases neutral nucleophiles like  $\text{NH}_3$  and  $\text{RNH}_2$  undergo this reaction. The formation of aryl–oxygen bond via cross coupling reactions is an important aspect to prepare pharmaceutically important drugs or other biologically important compounds. Aryl–alkyl ethers have many applications ranging from pharmaceuticals, cosmetics, solvents, paints and varnishes, etc.<sup>1–3</sup>

Previously, several methods were developed to prepare alkyl–aryl ethers of aryl halides using  $\text{Cs}_2\text{CO}_3\text{-CuI}$ ,  $\text{Cs}_2\text{CO}_3\text{-Pd(OAc)}_2$ ,  $\text{Cu(OAc)}_2$ , *t*-BuOLi, *t*-BuONa, *t*-BuOK–CuI, NaOMe–CuBr,  $\text{Ag}_2\text{SO}_4\text{-BaF}_2$ ,  $\text{AgF-AgO}_3\text{ScF}_3$ , CuBr–NMP, Zinc salts, etc.<sup>7</sup> Copper catalysed Ullmann coupling is one of the most powerful coupling reactions to achieve this bonding.<sup>8,9</sup> But, harsh reaction conditions, insolubility problem with copper salts, long reaction times, stoichiometric amount of Cu salts and unsuitability to up-scale are some of the drawbacks of this reaction.<sup>9</sup> However, use of suitable ligands–Cu complexes have resolved insolubility problem to a great extent.<sup>8,9</sup> Now, a few ligand free copper catalysed reactions have also been reported with moderate to good yields of ethers.<sup>10</sup> Use of palladium catalysts is another approach to prepare aryl–alkyl-ethers

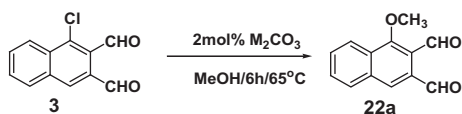


**Scheme 1.** Etherification of aryl chlorides, indenes, tetralenes and heterocyclic system in the presence of metal carbonates.

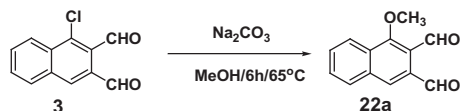
through Buchwald–Hartwig coupling reaction.<sup>1,2,11–16</sup> All these methods are involved with tedious reaction conditions, expensive catalysts, low yields of products and requirement of ligands. There is continued effort to achieve simpler and economic synthesis of alkyl–aryl ethers. Present Letter describes a simpler, straight-forward and economic etherification process for aryl halides

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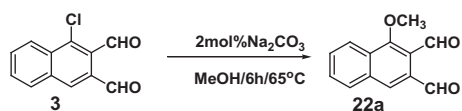
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**Table 1**  
Suitability of reagent (metal carbonate)

Entry	Metal carbonate (alkali carbonate)	Solubility	Yield <sup>a</sup> (%)
1	Li <sub>2</sub> CO <sub>3</sub>	Cloudiness	52
2	Na <sub>2</sub> CO <sub>3</sub>	Partially soluble	89
3	K <sub>2</sub> CO <sub>3</sub>	Fully soluble	84
4	Cs <sub>2</sub> CO <sub>3</sub>	Fully soluble	81

<sup>a</sup> Isolated yield of **22a**.**Table 2**  
Optimization of molar ratio of the reagent

Entry	% Mol of Na <sub>2</sub> CO <sub>3</sub>	Yield (%)
1	No	Not detected
2	0.4	42
3	1	53
4	2	89

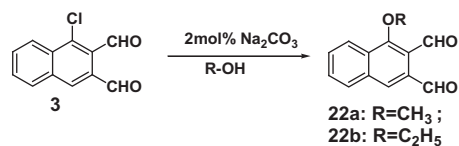
**Table 3**  
Optimization of reaction time

Entry	Time (h)	Yield
1	1	29
2	2	42
3	4	57
4	6	89
5	12	91

without the use of any co-catalyst. This is the first Letter of preparation of alkyl-aryl ethers in the presence of alkali metal carbonates (Li<sub>2</sub>CO<sub>3</sub>/Na<sub>2</sub>CO<sub>3</sub>/K<sub>2</sub>CO<sub>3</sub>/Cs<sub>2</sub>CO<sub>3</sub>) without the use of any co-catalyst and ligand (see Scheme 1).

Initially, 2-formyl-aryl chlorides were treated with various alcohols in the presence of Na<sub>2</sub>CO<sub>3</sub> to obtain 1-alkoxy-aryl aldehydes. Methanol was treated with 1-chloro-2,3-diformylnaphthalene (**3**, Table 5 entry 4) in 2 mol % of sodium carbonate at 65 °C. The reaction was complete in 6 h giving 1-methoxy-2,3-diformylnaphthalene as the exclusive product (**22a**, Table 5 entry 4) in 89% yield. However, the yield of 1-ethoxy-2,3-diformylnaphthalene (**22b**, Table 5 entry 5) was relatively low (52%).

The detailed optimization of the reaction conditions for etherification of 1-chloro-2,3-diformylnaphthalene (**3**) as model substrate varying from type of alcohol, metal carbonate (Table 1),

**Table 4**  
Reaction with various alcohols

Entry	Alcohol/phenol	Reaction time (h)	Yield (%)
1	MeOH	6	89
2	EtOH	6	52
3	<i>n</i> -PrOH	6	3
4	<i>n</i> -BuOH	8	2

mol % of reagent (Table 2) and reaction time (Table 3) is shown. The optimization study with various alkali metal carbonates (Li<sub>2</sub>CO<sub>3</sub>/Na<sub>2</sub>CO<sub>3</sub>/K<sub>2</sub>CO<sub>3</sub>/Cs<sub>2</sub>CO<sub>3</sub>) from table 1, the etherification of 1-chloro-2,3-diformylnaphthalene (**3**) with sodium carbonate (2 mol %) gave the best results. Reaction did not proceed in the absence of alkali carbonate.

The optimum mol % of sodium carbonate was found to be 2 mol % (Table 2). Lower mol % gave reduced yields while higher mol % did not improve the yield. The reaction was run up to 12 h and there was no significant improvement in the yield of the ether product (**22a**). Hence, 6 h time was optimum for this reaction (Table 3). We tried to extend this reaction with various alcohols but the reaction goes well with methanol and ethanol only (Table 4). With *n*-propanol and *n*-butanol yields were very poor.

After optimizing reaction conditions various aryl halides (Table 5, entries 1–6), tetralenes (Table 5, entries 14–21), indenes (Table 5, entries 23–25) and some heterocyclic compounds (Table 5, entries 12, 13 and 22), were used as substrates to generalize the reaction.<sup>17,18</sup> A few diverse substrates were used to know the limitations of this simple and convenient etherification reaction.

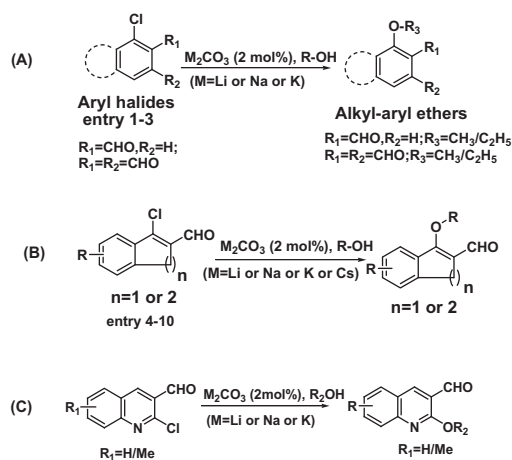
It is clearly evident that the reaction proceeded only for *o*-halo products (X = Cl/Br) with at least an aldehyde group in the ring and did not occur in case of *p*- or *m*-substituted halogens (Table 5, entries 1, 7 and 8) thus, gives regioselective product. The presence of a second aldehyde in the aromatic ring enhanced the yield of the product in the aromatic system. The reaction did not proceed in the absence of aldehyde (Table 5, entry 9) or when the aldehyde was replaced with other withdrawing groups like nitro or cyanide (Table 5, entries 10 and 11). The reaction proceeds better in the case of methanol and the yields were relatively low in case of ethanol. The etherification of olefinic compounds was more favourable than the aryl halides by this method.

Alkylation of haloalkenes or aryl halides is an important reaction to get alkyl ethers. There are several methods previously reported but their usage is limited due to the use of co-catalysts and ligands, tedious reaction conditions, expensive reagents and poor yields. The present method provides a straight-forward etherification method with simple reaction conditions. However, in case of aryl halides aldehyde group should be present *ortho* to halide group.

In summary, we have discovered a simple, straight-forward and efficient etherification method to achieve methyl or ethyl ethers from 1-chloro/bromo-2-aldehydes of aromatic and olefinic systems. Various aryl halides and olefinic halides have been explored for this etherification. The regioselectivity in case of dihalo systems, cheap reagent (Na<sub>2</sub>CO<sub>3</sub>), mild reaction conditions and operational simplicity make this process acceptable in synthetic chemistry.

**Table 5**

Etherification of various alkyl halides and indenenes and tetralenes with alcohols



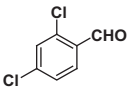
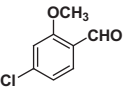
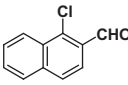
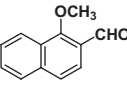
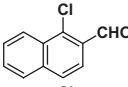
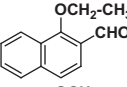
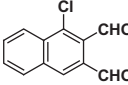
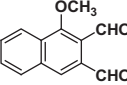
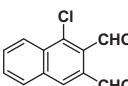
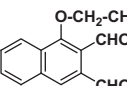
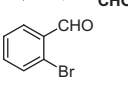
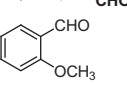
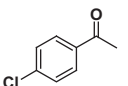
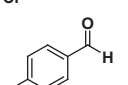
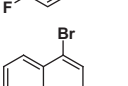
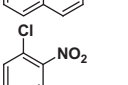
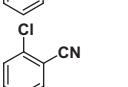
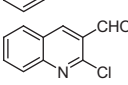
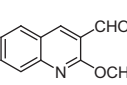
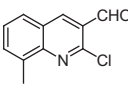
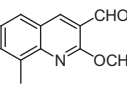
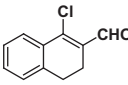
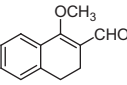
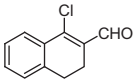
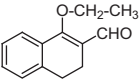
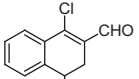
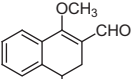
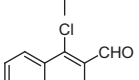
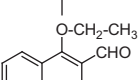
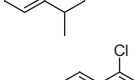
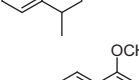
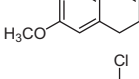
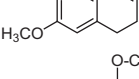
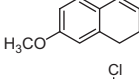
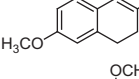
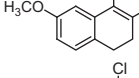
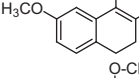
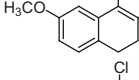
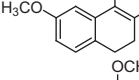
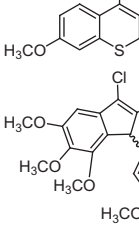
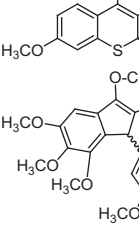
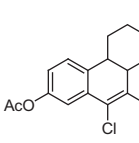
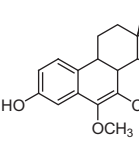
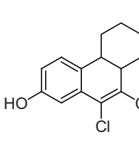
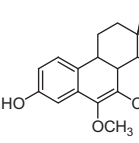
Entry	Substrate	Compd code	Alcohol	Product	Product code	Temperature (°C)	Time (h)	Yield (%)
1		<b>1</b>	MeOH		<b>20</b>	65	3	51
2		<b>2</b>	MeOH		<b>21a</b>	65	4	56
3		<b>2</b>	EtOH		<b>21b</b>	78	6	Traces*
4		<b>3</b>	MeOH		<b>22a</b>	65	6	89
5		<b>3</b>	EtOH		<b>22b</b>	78	6	52
6		<b>4</b>	MeOH		<b>23</b>	65	6	53
7		<b>5</b>	MeOH/EtOH	No reaction	—	65/78	8	0
8		<b>6</b>	MeOH/EtOH	No reaction	—	65/78	8	0
9		<b>7</b>	MeOH/EtOH	No reaction	—	65/78	8	0
10		<b>8</b>	MeOH/EtOH	No reaction	—	65/78	8	0
11		<b>9</b>	MeOH/EtOH	No reaction	—	65/78	8	0
12		<b>10</b>	MeOH		<b>24</b>	65	4	70
13		<b>11</b>	MeOH		<b>25</b>	65	6	46
14		<b>12</b>	MeOH		<b>26a</b>	65	8	94

Table 5 (continued)

Entry	Substrate	Compd code	Alcohol	Product	Product code	Temperature (°C)	Time (h)	Yield (%)
15		<b>12</b>	EtOH		<b>26b</b>	78	5	42
16		<b>13</b>	MeOH		<b>27a</b>	65	4	92
17		<b>13</b>	EtOH		<b>27b</b>	78	6	51
18		<b>14</b>	MeOH		<b>28a</b>	65	6	84
19		<b>14</b>	EtOH		<b>28b</b>	78	8	51
20		<b>15</b>	MeOH		<b>29a</b>	65	3	84
21		<b>15</b>	EtOH		<b>29b</b>	78	6	43
22		<b>16</b>	MeOH		<b>30</b>	65	5	93
23		<b>17</b>	EtOH		<b>31</b>	78	6	Traces*
24		<b>18</b>	MeOH		<b>32</b>	65	6	Traces*
25		<b>19</b>	MeOH		<b>32</b>	65	6	Traces*

\* &lt;2%.

## Acknowledgements

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2015.03.086>.

## References and notes

- Hartwig, J. F. *Angew. Chem.* **1998**, *110*, 2154–2177.
- Kraft, P.; Bajgrowicz, J. A.; Denis, C.; Frater, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046–2067.
- Evano, G.; Blanchard, N. M.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054–3131.
- Yi, C. S.; Yun, S. Y. *Org. Lett.* **2005**, *7*, 2181–2183.
- Oi, S.; Sakai, K.; Inoue, Y. *Org. Lett.* **2005**, *7*, 4009–4011.
- Hartwig, J. F. In *Handbook of Organo-palladium chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley InterScience: New York, 2002. add few more.
- (a) Suzuki, H.; Abe, A.; Osuka, A. *Chem. Lett.* **1981**, 151; (b) Osuka, A.; Ohmasa, N.; Suzuki, H. *Synthesis* **1982**, 857–858; (c) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109–13110; (d) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *JACS* **1997**, *119*, 3395–3396; (e) King, A.; Brunold, T.; Stahl, S. J. *Am. Chem. Soc.* **2009**, *131*, 5044–5045; (f) Huang, J.; Chen, Y.; Chan, J.; Ronk, M. L.; Larsen, R. D.; Faul, M. M. *Synlett* **2011**, 1419–1422; (g) Ghosh, R.; Lindstedt, E.; Jalalian, N.; Olofsson, B. *Chem. Open* **2014**, *3*, 54–57; (h) Keegstra, M. A.; Peters, T. H. A.; Brandsma, L. *Tetrahedron* **1992**, *48*, 3633–3652.

8. Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469.
9. Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449.
10. Basu, B.; Das, S.; Mandal, B. *Ind. J. Chem.* **2008**, *47B*, 1701–1706.
11. Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 10718–10719.
12. Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818.
13. Yang, B. Y.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125–146.
14. Baranano, D.; Mann, G.; Hartwig, J. F. *Curr. Org. Chem.* **1997**, *1*, 287–305.
15. Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., de Meijere, A., Eds.; John Wiley & Sons: New York, 2002; Vol. 1, pp 1051–1096.
16. Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131–209.
17. *Typical experimental procedure*: To a stirred solution of substrate (1 mmol, aryl halide/olefinic halide) in suitable alcohol (MeOH/EtOH, 10 mL), sodium carbonate (1.06 g, 2 mol %) was added and the reaction mixture was refluxed (MeOH = 65 °C/EtOH = 78 °C) for specified time. On completion, the reaction mixture was filtered, washed with methanol and dried in vacuo. The residue was taken in ethyl acetate (20 mL) and washed with water. Organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo. The residue thus obtained was purified through Flash chromatography using ethyl acetate–hexane system. All the compounds were characterized and confirmed by comparison of their spectral data and physical properties with reported literature.
18. See [Supporting information](#).