



Ligand free, highly efficient synthesis of diaryl ether over copper fluorapatite as heterogeneous reusable catalyst

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ARTICLE INFO

Article history:

Received 12 December 2011

Revised 25 January 2012

Accepted 28 January 2012

Available online 4 February 2012

Keywords:

Copper fluorapatite

Ullmann coupling

Phenol

Diaryl ethers

Arylhalide

ABSTRACT

A novel ligand-free, highly efficient, and an inexpensive method has been developed by using ecofriendly, heterogeneous reusable copper fluorapatite (CuFAP) catalyst for the synthesis of diaryl ethers from the cross coupling reaction of the various substituted aryl halides (fluoride, chloride, bromide, and iodide) with the potassium salts of various substituted phenols in the presence of *N*-methyl 2-pyrrolidone (NMP) as a solvent at 120 °C. The protocol obtained the corresponding cross coupling products in good to excellent yield. The CuFAP catalyst was recovered by simple filtration from the reaction mixture and reused several times without the loss of catalytic activity.

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Diaryl ether motifs are present in the natural products and medicinally important compounds.¹ Diaryl ether molecules are not only important in biological systems but also key moieties in pharmaceutical, agricultural, polymer, industrial, and life science.² However, carbon–carbon and carbon–heteroatom bond forming reactions catalyzed by transition metals are an important fundamental transformation in synthetic chemistry.³ The most simplest and straightforward way to synthesize diaryl ethers involves the direct formation of aryl–oxygen bond from an aryl halide.⁴ The classical copper catalyzed Ullmann coupling reaction for ether synthesis has been extensively used for the formation of diaryl ether on industrial scale in polar solvents (pyridine, DMF, collidine).⁵ However, application on industrial scale synthesis has been limited due to harsh reaction conditions such as high reaction temperature (125–300 °C), longer reaction time at which many functional groups are unstable hence lower yield of the desired product. In addition, the requirement of excess or stoichiometric quantities of copper complexes leads to the problem of waste disposal.⁶

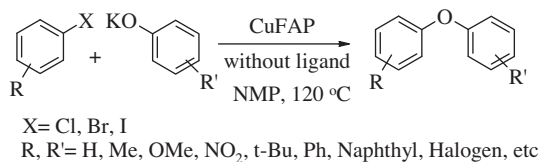
Owing to the importance of diaryl ether moieties in life sciences, pharmaceutical, agricultural, polymer, world-wide efforts have been made in the last few decades to develop various methods for the synthesis of Ullmann diaryl ethers using varieties of reagents. The catalysts in combination with the various ligands have been reported as catalytical processes,^{7–9} a palladium catalyzed coupling reaction in the presence of ligand between sodium phenoxide and electron deficient aryl bromide,¹⁰ microwave assisted Cu(0) nano

particles,^{11a} Nano Ceria,^{11b} KF/supported on natural nano-porous Zeolite,^{12a} Ullmann and Goldberg reactions,^{12b} copper^{13,14} and palladium¹⁵ complexes in the presence of ligands. Moreover, phosphine–palladium complexes are air sensitive and other complexes with palladium are expensive compared to copper or copper complexes. Even though significant improvements have been achieved, almost all these methods reported so far lack general applicability. The use of metals and/or noble metals as catalysts with highly expensive ligands along with harsh reaction conditions limits to implement their application for the commercial-scale productions. However, the development of more general and cost effective ligand-free catalysts for the O-arylation of phenol, which is equally applicable to electron-deficient, electronically neutral, and electron-rich aryl halides is still challenging and an active research area, which enable aryl ether formation under much milder, more efficient, environment friendly conditions compared to the classical Ullmann and Goldberg reactions.^{12b} Herein, we report ligand-free, highly efficient, an inexpensive, and general method for the synthesis of diaryl ethers in good to excellent yield from the cross coupling reactions of a wide range of electron-deficient, electronically neutral, and electron-rich aryl halides with the potassium salts of various substituted phenols over ecofriendly, heterogeneous reusable copper fluorapatite (CuFAP) catalyst in the presence of *N*-methyl 2-pyrrolidone (NMP) as a solvent at 120 °C (Scheme 1).

To develop the protocol for O-arylation cross coupling reaction, bromobenzene, and potassium salt of phenol catalyzed by CuFAP catalyst, prepared as per reported procedure in the literature¹⁶ was selected as a model reaction to optimize the reaction conditions.¹⁷ Initially, we studied the effect of solvent on the cross

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Scheme 1. CuFAP catalyzed Ullmann diaryl etherification of potassium salt of substituted phenol with substituted halo-arene.

coupling reaction. The reactions were carried out in various solvents at a different temperature by taking bromobenzene (1 mmole) and potassium salt of phenol (1.1 mmole) in the presence of 100 mg CuFAP catalyst, however, only NMP at 120 °C gives the cross-coupling product in a 93% isolated yield (Table 1, entry 8) whereas DMF, DMSO, and diglyme give 8%, 10% and 15% yields (Table 1, entries 5–7), respectively. The desired cross-coupling product formation was not observed during the reaction in THF, CH₃CN, toluene, and dioxane (Table 1, entries 1–4).

Results on the cross coupling product of bromobenzene and potassium salt of phenol in NMP solvent using CuFAP catalyst at optimized reaction conditions¹⁷ encourage us to investigate the application of CuFAP catalyst for Ullmann diaryl etherification. Therefore, a variety of electron-deficient, electron-rich, and electronically neutral substituted haloarenes (Fluoro, chloro, bromo, and iodo) possessing a wide range of the functional group reacted with potassium phenoxide in NMP to obtain cross-coupling product in good to excellent yield; the results are shown in Table 2. The formation of the desired cross-coupling product was not observed in the absence of CuFAP catalyst (Table 2, entry 1). The electron-deficient aryl halide such as 4-nitrochlorobenzene, 4-nitrobromobenzene, 4-nitroiodobenzene, 4-chlorobromobenzene, and 3-bromo, 4-fluoro benzaldehydeacetal reacted with potassium phenoxide to provide an excellent yield to the desired cross coupling product in the short reaction time (Table 2, entries 2–6). However, the electron-rich and electronically neutral aryl halides such as 4-bromoanisole, 3-bromotoluene, 4-iodoanisole, (Table 2, entries 7–9) and bromobenzene, iodobenzene, (Table 2, entry 12 and 13) respectively, coupled with potassium phenoxide without any difficulties to obtain the corresponding cross coupling products in moderate to good yield with longer reaction time; while chlorobenzene provides very poor yield, (Table 2, entry 11) fluorobenzene gave no coupled product (Table 2, entry 10).

To explore the scope of this methodology over CuFAP catalyst for electron-deficient, electronically neutral, and electron-rich

Table 2

Diaryl etherification of potassium phenoxide with substituted haloarenes^a (X = F, Cl, Br, I)

Entry	Aryl halide	Product	Time (h)	Yield ^b (%)
1			8	N.R. ^c
2			5	91
3			4	94
4			3	94
5			3	93
6			5	92
7			5	87
8			5	90
9			4	89
10			15	N. R.
11			15	18
12			5	93
13			4	93

^a Reaction conditions: aryl halide (1 mmol), potassium phenoxide (1.1 mmol), NMP (1 ml), CuFAP (100 mg), 120 °C.

^b Isolated yields.

^c No reaction without CuFAP catalyst.

Table 1
Effect of solvent on the Ullmann diaryl etherification^a

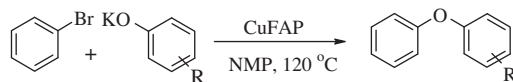
Entry	Solvent	Temperature (°C)	Yield ^b (%)
1	THF	70	N.R.
2	CH ₃ CN	80	N.R.
3	Toluene	110	N.R.
4	Dioxane	100	N.R.
5	DMF	140	8
6	DMSO	150	10
7	Diglyme	150	15
8	NMP	120	93

^a Reaction conditions: bromobenzene (1 mmol), potassium phenoxide (1.1 mmol), solvent (1 ml), CuFAP (100 mg).

^b Isolated yields.

potassium salt of various substituted phenols such as 4-methoxyphenol, 4-methylphenol, 3-methylphenol, 2-methylphenol, 4-ter-butylphenol, alpha-naphthol, beta-naphthol, 4-phenylphenol, 4-nitrophenol, 4-chlorophenol were successfully coupled with bromobenzene to give the corresponding diaryl ethers in good to excellent yield (Table 3, entries 1–10), however, poor yield was obtained in the case of potassium salt of 4-nitro phenol in long reaction time (Table 3, entry 9).

The recyclability of CuFAP catalyst for the Ullmann diaryl etherification was investigated using bromobenzene and potassium phenoxide as substrate in NMP solvent at 120 °C, the results are summarized in Table 4. The CuFAP catalyst was recovered

Table 3Ullmann diaryl etherification of bromobenzene with substituted potassium phenoxides^a

Entry	Substituted phenoxide	Product	Time (h)	Yield ^b (%)
1			4	93
2			5	92
3			6	90
4			5	87
5			5	88
6			6	89
7			6	86
8			4	87
9			16	15
10			6	82

^a Reaction conditions: bromobenzene (1 mmol), substituted potassium phenoxide (1.1 mmol), NMP (1 ml), CuFAP (100 mg), 120 °C.^b Isolated yields.

quantitatively by simple filtration and reused for several times without the loss of catalytic activity (Table 4, entries 1–5). The isolated yield obtained for cross coupling product even after the fourth recycle of CuFAP catalyst (Table 4, entries 2–5) is very much consistent with fresh CuFAP catalyst (Table 4, entry 1). The consistent catalytic activity of reused CuFAP catalyst for coupling product indicates that the reused catalyst shows excellent performance for the Ullmann diaryl etherification and no leaching and loss of copper occurred during the course of reaction, which was also confirmed by atomic absorption spectroscopy.

According to the previous research work over CuFAP catalyst for the *N*-arylation of heterocycles,¹⁶ the possible mechanism proposed in Scheme 2 for O-arylation may involve the CuFAP catalyzed nucleophilic substitution that proceeds via the formation of the complex (a) with potassium phenoxide and then subsequently onto the oxidative addition of aryl halide via the formation of another complex (b) followed by the instantly in situ reductive elimination to release the diaryl ether product (c) as well as CuFAP catalyst in its original form (to recycle again).

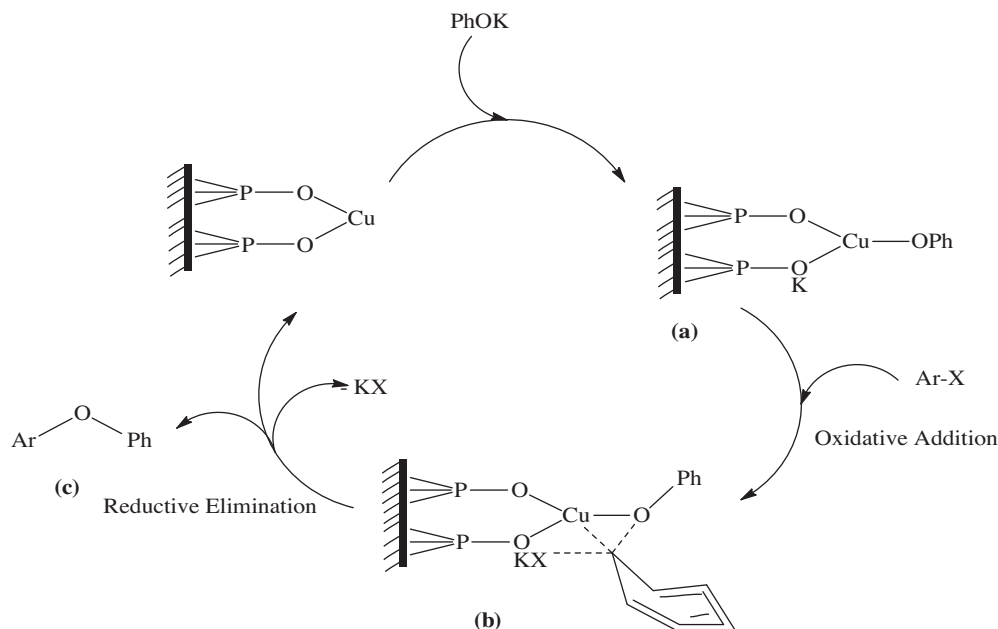
In conclusion, a novel ligand-free, highly efficient, and an inexpensive method has been developed by using ecofriendly,

heterogeneous reusable copper fluorapatite (CuFAP) catalyst for the synthesis of Ullmann diaryl ethers from the cross coupling reaction of the various substituted aryl halides with the potassium salts of various substituted phenols in the presence of *N*-methyl

Table 4Recyclability studies of CuFAP catalyst for the Ullmann diaryl etherification^a

Cycle	Yield ^b (%)
1	93
2	92
3	93
4	92
5	92

^a Reaction conditions: bromobenzene (1 mmol), potassium phenoxide (1.1 mmol), NMP (1 ml), CuFAP (100 mg), 120 °C, 5 h.^b Isolated yields



Scheme 2. Plausible mechanism for the Ullmann diaryl etherification reaction over CuFAP catalyst.

2-pyrrolidone (NMP) as a solvent at 120 °C. The protocol obtained the corresponding cross coupling products in good to excellent yield. The CuFAP catalyst was recovered by simple filtration from the reaction mixture and reused several times without the loss of catalytic activity.

Acknowledgments

SMI, MYP and SSC thank CSIR New Delhi for a SRF and JRF, respectively. The authors also thank Dr. B. D. Kulkarni, and Dr. V. V. Ranade, Chair, CE-PD for their encouragement and support.

References and notes

- (a) Evans, D. A.; DeVeres, K. M. In *Glycopeptide Antibiotics Drug and pharmaceutical sciences*; Marcel Dekker Inc.: New York, 1994; Vol. 63, p 63; (b) Deshpande, V. E.; Gokhle, N. J. *Tetrahedron Lett.* **1992**, 33, 4213; (c) Singh, S. B.; Pettit, G. R. *J. Org. Chem.* **1990**, 55, 2797; (d) Pettit, G. R.; Singh, S. B.; Niven, M. L. *J. Am. Chem. Soc.* **1985**, 107, 4909; (e) Seldon, R. A. *Chirotechnology*; Marcel Dekker Inc.: New York, 1998, pp. 62.
- (a) Thiel, F. *Angew. Chem., Int. Ed.* **1999**, 38, 2345; (b) Nicolaou, K. C.; Boddy, C. N. C. *J. Am. Chem. Soc.* **2002**, 124, 10451; (c) Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, 37, 2700; Evan, D. A.; Dinsmore, C. J.; Watson, P. S.; Wood, M. R.; Richardson, T. I.; Trotter, B. W.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, 37, 2704.
- (a) Mino, T.; Shirae, Y.; Sakamoto, M.; Fujita, T. *Synlett* **2003**, 882; (b) Jonckers, T. H. M.; Maes, B. U.; Leimere, G. L. F.; Rombouts, G.; Pieters, L.; Haemers, A.; Domisse, R. A. *Synlett* **2003**, 615; (c) Gonthier, E.; Breinbauer, R. *Synlett* **2003**, 1049; (d) Iyer, S.; Jayanthi, A. *Synlett* **2003**, 1125; (e) Nicilaou, K. C.; Christopher, N. C. B. *J. Am. Chem. Soc.* **2002**, 124, 10451; (f) Strurmer, R. *Angew. Chem., Int. Ed.* **1999**, 38, 3307; (g) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buckwald, S. L. *Acc. Chem. Res.* **1998**, 31, 805.
- For reviews, see: Sawyer, J. S. *Tetrahedron* **2000**, 56, 5045; (b) Lindley, J. *Tetrahedron* **1984**, 40, 1433; (c) Moroz, A. A.; Shvartsberg, M. S. *Russ. Chem. Rev.* **1974**, 43, 679.
- (a) Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, 111, 1063; (b) Boger, D. L.; Yhannes, D. J. *Org. Chem.* **1990**, 55, 6000; (c) Boger, D. L.; Patane, M. A.; Zhou, J. *J. Am. Chem. Soc.* **1994**, 116, 8544.
- (a) Ullmann, F. *Chem. Ber.* **1904**, 37, 853; (b) Sawyer, J. S. *Tetrahedron* **2000**, 56, 5045.
- (a) Jung, N.; Brase, S. J. *Comb. Chem.* **2009**, 11, 47; (b) Frlan, R.; KiKelji, D. *Synthesis* **2006**, 2271; (c) Jammi, S.; Satkhivel, S.; Rout, L.; Pummiamurthy, T. *J. Org. Chem.* **1971**, 2009, 74.
- (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, 248, 2337; (b) Zhang, Q.; Wang, D.; Wang, X.; Ding, K. *J. Org. Chem.* **2009**, 74, 7187; (c) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428.
- (a) Kidwai, M.; Mishra, N. K.; Bansal, V.; Kumar, A.; Mazumdar, S. *Tetrahedron Lett.* **2007**, 48, 8883; (b) Miao, T.; Wang, L. *Tetrahedron Lett.* **2007**, 48, 95; (c) Zhang, J.; Zhang, Z.; Wang, Y.; Zheng, X.; Wang, Z. *Eur. J. Org. Chem.* **2008**, 5112.
- Mann, G.; Hartwig, J. F. *Tetrahedron Lett.* **1997**, 38, 8005.
- (a) Banaskar, F.; Engels, V.; Patil, N.; Rebrov, E. V.; Schouten, J. C.; Wheatley, E. H. *Tetrahedron Lett.* **2010**, 51, 248; (b) Agawane, S. M.; Nagarkar, J. M. *Tetrahedron Lett.* **2011**, 52, 5220.
- (a) Khalilzadeh, M. A.; Hosseini, A.; Pilevar, A. *Eur. J. Org. Chem.* **2011**, 1587; (b) Ouail, A.; Spindler, J.-F.; Jutand, A.; Taillefer, M. *Adv. Synth. Catal.* **1906**, 2007, 349.
- Ullmann reaction with use of stoichiometric amount of copper: (a) Lipshutz, B. H.; Unger, J. B.; Taft, B. R. *Org. Lett.* **2007**, 9, 1089; (b) Buck, E.; Song, Z. J.; Tschae, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, 4, 1623; (c) Wipf, P.; Jung, J. K. *J. Org. Chem.* **2000**, 65, 6319; (d) Cai, Q.; Zou, B. L.; Ma, D. W. *Angew. Chem.* **2006**, 118, 1298. *Angew. Chem. Int. Ed.* **2006**, 45, 1276; (e) Cristau, H.-J.; Cellier, P. P.; Hamada, S.; Spindler, J.-F.; Taillefer, M. *Org. Lett.* **2004**, 6, 913; (f) Xu, L.-W.; Xia, C.-G.; Li, J.-W.; Hu, X.-X. *Synlett* **2003**, 2071; (g) Sofia, B.; Florian, M.; Michel, W.; Catherine, B.; Fouad, O.; Marc, T. *Green Chem.* **2009**, 11, 1121; (h) Jogdand, N. R.; Shingate, B. B.; Shingare, M. S. *Tetrahedron Lett.* **2009**, 50, 4019; (i) Chang, J. W.; Chee, S.; Mak, S.; Buranaparasertsuk, P.; Chavasiri, W.; Chan, P. W. *Tetrahedron Lett.* **2008**, 49, 2018.
- (a) Kalnin, A. V.; Bower, J. F.; Riebel, P.; Snieckus, V. *J. Org. Chem.* **1999**, 64, 2986; (b) Pellon, R. F.; Docampo, M. L. *Synth. Commun.* **2003**, 33, 921; (c) Paine, A. J. *J. Am. Chem. Soc.* **1987**, 109, 1496; (d) Luo, Y. T.; Wu, J. X.; Ren, R. X. *Synlett* **2003**, 1734; (e) Gujadhur, R.; Venkataraman, D. *Synth. Commun.* **2001**, 31, 2865; (f) Gujadhur, R. K.; Bates, C. G.; Venkataram, D. *Org. Lett.* **2001**, 3, 4315; (g) Marcoux, J. F.; Doye, S.; Buckwald, S. L. *J. Am. Chem. Soc.* **1997**, 119, 10539; Sreedhar, B.; Arundhati, R.; Linga Reddy, P.; Laxmi Kantam, M. *J. Org. Chem.* **2009**, 74, 7951.
- (a) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, 121, 3224; (b) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Buchward, S. L. *J. Am. Chem. Soc.* **1999**, 121, 4369; (c) Harkal, S.; Kumar, K.; Machalik, D.; Zapf, A.; Jackstell, R.; Rataboul, F.; Riermeier, T.; Monsees, A.; Beller, M. *Tetrahedron Lett.* **2005**, 46, 3237.
- Choudhary, B. M.; Sridhar, C.; Kantam, M. L.; Venkanna, G. T.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, 127, 9948.
- General experimental procedure for Ullmann diaryl etherification:* Arylhalide (1 mmol), potassium salts of phenol (1.1 mmol), NMP (1 ml) and CuFAP catalyst (100 mg) were taken in a 10 ml round bottomed flask and stirred in nitrogen atmosphere at 120 °C for 3–16 h (Table 2 and 3) and the progress of the reaction was monitored by TLC. After the completion of the reaction, reaction mixture was cooled to room temperature and diluted with 20 ml ethyl acetate followed by filtration to recover the catalyst. The filtrate was concentrated in vacuo to get the crude product, which was further purified by column chromatography on silica gel (hexane/ethyl acetate, 80:20) to obtain diaryl ether product.

Spectral data for diphenylether (Table 2, entry 12): Colorless liquid; Yield: 93%; IR (CHCl₃) ν 660, 725, 1240, 1498, 1610, 3021 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.32–7.24 (m, 4H), 7.08–6.93 (m, 6H). ¹³C NMR (200 MHz, CDCl₃) δ 157.21, 129.71, 123.19, 118.86.