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Ligand-free Fe–Cu Cocatalyzed Cross-coupling of Terminal Alkynes with Aryl Halides

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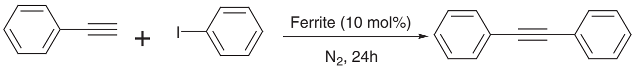
Copper ferrite-nanoparticle-mediated cross-coupling of terminal alkynes with aryl halides under ligand-free conditions was demonstrated. The magnetic nature of the copper ferrite nanoparticles was exploited for easy and quantitative separation of the catalyst. Leaching of Fe and Cu to the reaction medium was found to be within permissible limit and the activity of the catalyst was almost unaltered up to three consecutive cycles.

Transition-metal-catalyzed cross-coupling of alkynes with aryl halides has emerged as a robust method in organic synthesis to achieve a number of natural and nonnatural products of biological significance.[1] Although the activation of terminal alkyne C–H bonds by a quantitative amount of copper iodide (CuI) was reported earlier by Stephens and Castro,[2] the catalytic version was popularized as the Sonogashira coupling.[3] The latter reaction has been routinely performed using a palladium-based catalyst (e.g., $[Pd(PPh_3)_4]$) and a copper(I) salt as cocatalyst to access aryl alkynes. However, toxicity and high cost of Pd catalysts restrict their use on industrial scale.[4] Thus, researchers have turned their attention toward the use of less expensive, less toxic, and more efficient metals to replace Pd. Meanwhile, ligand-assisted copper-catalyzed cross-coupling reactions of alkynes with aryl halides have gained significant attention due to the low cost and relatively lower toxicity. Various ligands including diamines, amino acids, β-ketoesters, 1,10-phenanthroline derivatives, poly(ethylene glycol), ninhydrin, and other nitrogen- and/or oxygen-containing ligands which chelate copper have been used for cross-coupling reactions.[5–12] Recently, copper/iron cocatalytic systems were also successfully used for the cross-coupling reactions under homogeneous conditions considering the cheap and environment-friendly behavior of iron.[13] In contrast, development of a reusable heterogeneous catalytic system for cross-coupling of alkynes has received less attention. To our knowledge, only three heterogeneous catalytic systems have been developed so far. Namely, reusable Cu-nanoclusters were employed by Rothenberg et al.[14] for cross-coupling of phenylacetylene and aryl iodide. Heterogeneous copper catalyst (CuO/Al) developed by Biffis et al.[15] shows interesting activity, but the high degree of copper leaching restricts its reusability. Later, silica-anchored proline–copper(I) complex was reported by Wang et al.[16] for carbon–carbon (C–C) bond formation and was found to be reusable. Though these results are encouraging, still there is scope for the development of a cheap, environment-friendly, and reusable heterogeneous catalytic protocol for efficient alkynylation reactions.

In recent years, due to large surface area and reactive morphology, nanoparticles exhibit attractive catalytic activity in various reactions.[17] However, the small size of nanoparticles often makes their separation and recycling difficult, which impedes their use in large scale.[18] In order to circumvent such problems, superparamagnetic nanoparticles, whose flocculation and dispersion can be controlled reversibly by application of a magnetic field, were employed successfully.[19] As part of our ongoing research, recently, we reported the magnetic copper ferrite-mediated N-arylation of heterocycles with aryl halides in the presence of base.[20] As a continuation, here we report the catalytic activity of copper ferrite nanoparticles for the cross-coupling of alkynes with aryl halides under "ligand-free" conditions. The magnetic nature of the catalyst was further exploited for easy and quantitative removal of the catalyst for further use.

In the present article, the reaction between phenylacetylene and iodobenzene in the presence of ferrite catalyst was tested as a model reaction for the C–C cross-coupling (Scheme 1).

Initially, Fe_3O_4 and different substituted ferrite nanoparticles, MFe_2O_4 ($M = Cu^{II}$, Co^{II}, and Ni^{II}), were synthesized following the standard protocol and subsequently screened. We observed that Fe_3O_4, $CoFe_2O_4$, and $NiFe_2O_4$ nanoparticles were inactive, whereas $CuFe_2O_4$ nanoparticles[21] catalyzed the alkynylation reaction (70% yield) in 1,4-dioxane at 110 °C in the presence of two equiv of Cs_2CO_3 (Table 1). In order to realize



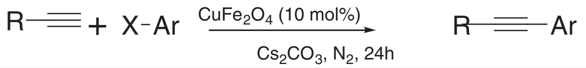
Scheme 1.

Table 1. Alkynylation of phenylacetylene with iodobenzene in various solvents and bases in the presence of different ferrites

Entry	Catalyst	Solvent	Base	Yield/%[a]
1	$CuFe_2O_4$	1,4-Dioxane	Cs_2CO_3	70
2	$CuFe_2O_4$	DMF	K_2CO_3	≤5
3	$CuFe_2O_4$	DMF	NaOAc	≤5
4	$CuFe_2O_4$	DMF	Cs_2CO_3	35
5	$CuFe_2O_4$	DMF	$NaHCO_3$	≤5
6	$CuFe_2O_4$	DMF	*t*-BuOK	38
7	$CuFe_2O_4$	1,4-Dioxane	*t*-BuOK	25
8	$CuFe_2O_4$	DMSO	*t*-BuOK	25
9	$CuFe_2O_4$	CH_3CN	*t*-BuOK	38
10	$CuFe_2O_4$	*t*-BuOH	*t*-BuOK	0
11	$CuFe_2O_4$	Toluene	*t*-BuOK	15
12	$CuFe_2O_4$	THF	*t*-BuOK	≤5
13	$CuFe_2O_4$	DMF	Pyridine	≤5
14	$CuFe_2O_4$	1,4-Dioxane	Et_3N	≤5
15	Fe_3O_4	DMF	*t*-BuOK	0
16	$CoFe_2O_4$	DMF	*t*-BuOK	0
17	$NiFe_2O_4$	DMF	*t*-BuOK	8
18	CuO	1,4-Dioxane	Cs_2CO_3	25

[a] Reaction conditions: 1.02 mmol of phenylacetylene, 1.52 mmol of iodobenzene, 10 mol % of catalyst, 2.0 equiv of base, 5 mL of solvent, 24 h reflux under N_2 atmosphere.

Table 2. $CuFe_2O_4$-catalyzed C–C cross-coupling of terminal alkynes with aryl halides



Entry	R	X	Ar	Product	Yield/%[a]
1	Ph	I	C_6H_5	**1**	70[a]
2	Ph	I	4-COMe-C_6H_4	**2**	48[a]
3	Ph	I	4-OMe-C_6H_4	**3**	51[a]
4	Ph	Br	C_6H_5	**1**	58[b]
5	Ph	Br	4-COMe-C_6H_4	**2**	35[b]
6	Ph	Br	4-CO_2Et-C_6H_4	**4**	42[b]
7	Ph	Br	4-OMe-C_6H_4	**3**	48[b]
8	Ph	Cl	C_6H_5	**1**	20[b]
9	Ph	Cl	4-COMe-C_6H_4	**2**	25[b]
10	Ph	Cl	4-OMe-C_6H_4	**3**	25[b]
11	n-C_6H_{13}	I	C_6H_5	**5**	65[a]
12	n-C_6H_{13}	I	4-OMe-C_6H_4	**6**	55[a]
13	Ph	I	C_7H_4NS	**7**	51[a]
14	Ph	I	C_5H_4N	**8**	58[a]

[a]Reaction conditions: 1.02 mmol of phenylacetylene, 1.52 mmol of aryl halide, 10 mol % of $CuFe_2O_4$ nanoparticles, 2.0 equiv of Cs_2CO_3, 5 mL of 1,4-dioxane, 24 h reflux under N_2 atmosphere. [b]Reaction conditions: 1.02 mmol of phenylacetylene, 1.52 mmol of aryl halide, 10 mol % of $CuFe_2O_4$ nanoparticles, 2.0 equiv of Cs_2CO_3, 1.52 mmol KI, 5 mL of 1,4-dioxane, 24 h reflux under N_2 atmosphere.

the role of Fe in catalyst, the reaction was carried out in the presence of CuO nanoparticles, but poor isolated yield (25%) of diphenylacetylene was obtained. Thus, it may be concluded that the synergistic effects of Fe and Cu in $CuFe_2O_4$ nanoparticles cocatalyze the alkynylation reaction and are in line with other earlier articles.[13] The magnetic nature of the copper ferrite nanoparticles facilitates their easy and quantitative removal from the reaction medium in the presence of an external magnetic field for further use.

The reaction conditions were then optimized with different combinations of solvents and bases. As summarized in Table 1, the cross-coupling reactions were carried out in different solvents such as DMF, DMSO, THF, acetonitrile, *tert*-butanol (*t*-BuOH), toluene, and 1,4-dioxane in the presence of commonly used bases (*t*-BuOK, Cs_2CO_3, K_2CO_3, Et_3N, pyridine, $NaHCO_3$, and NaOAc). However, 1,4-dioxane and Cs_2CO_3 served as the best choice for higher yield of the cross-coupled product. It may be noted that for this cross-coupling the right choice of solvent/base pair is important. A decrease in the catalyst loading from 10 to 5 to 1 mol % also afforded the product in lower yield. Thus, optimum yield of diphenylacetylene was obtained when phenylacetylene, iodobenzene, and 10 mol % of copper ferrite nanoparticles were heated in 1,4-dioxane at 110 °C in the presence of Cs_2CO_3.

After determining the optimized conditions,[22] we then investigated the scope of the magnetic catalyst for the C–C cross-coupling reactions of differently substituted aryl halides with phenylacetylene (Table 2).[23] We found that only the aryl iodides gave the cross-coupled product. However, aryl chlorides and bromides gave the cross-coupled product only when an equivalent amount of KI was added to the reaction mixture.

Table 3. Reusability of $CuFe_2O_4$ nanoparticles and leaching of Cu and Fe in multicycle alkynylation reactions

Cycle	Recovered $CuFe_2O_4$/%	Product yield /%[a]	Cu leakage (in ppm)	Fe leakage (in ppm)
1	—	70	0.35	0.06
2	97	68	0.3	0.02
3	95	68	0.2	0.02

[a]Reaction conditions: 1.02 mmol of phenylacetylene, 1.52 mmol of iodobenzene, 10 mol % of $CuFe_2O_4$ nanoparticles (for cycle 1 and the remaining recovered amount of the catalyst was used for subsequent cycles), 2.0 equiv of Cs_2CO_3, 5 mL of 1,4-dioxane, 24 h reflux under N_2 atmosphere.

More interestingly, substituted aryl halides as well as heteroaryl iodides (e.g. 2-iodobenzo[*d*]thiazole and 2-iodopyridine; Entries 13 and 14) also underwent cross-coupling with appreciable yield.

Then, we turned our attention toward the coupling of alkylalkynes with aryl iodides. Thus, when reactions were carried out in the presence of 10 mol % of catalyst under optimized conditions, 55–65% of the cross-coupled products were isolated (Table 2, Entries 11 and 12).[23]

Next, we studied the reusability of a heterogeneous $CuFe_2O_4$ catalyst in C–C coupling reactions (Table 3). After completion of the reaction, the catalyst was recovered by the application of an external magnet, was washed with ethyl acetate and then acetone, and was dried in a hot air oven at 120 °C for 2 h. The recovered catalyst was reused under similar conditions for the next run, and the catalytic behavior of the $CuFe_2O_4$ nanoparticles was found to be unaltered (yield, 68%), even up to three consecutive cycles.

Then, the possibility of Fe and Cu leakage from $CuFe_2O_4$ to the medium during the reaction was investigated. After completion of the reaction, the supernatant was collected and tested for Fe and Cu by atomic absorption spectroscopy (AAS). The leaching of Cu and Fe in three consecutive cycles was found to be $\leq$0.5 ppm (Table 3), which is well below the permissible level.[24]

In conclusion, for the first time, we have demonstrated a ligand-free heterogeneous magnetic catalytic system for the C–C cross-coupling of terminal alkynes with aryl halides. The synergistic effects of iron and copper in copper ferrite nanoparticles for the alkynylation reaction were exploited. The catalyst can be recovered quantitatively in presence of external magnet for further use. The negligible leaching of Cu and Fe make the catalytic process environment benign. Further investigations on the catalytic activity of $CuFe_2O_4$ nanoparticles in C–O and C–S cross-coupling reactions are under progress.

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21 $CuFe_2O_4$ nanoparticles of size 15–25 nm (mean average size 15.5 ± 1 nm) were prepared and characterized by following the procedure reported in ref. 20.

22 *General procedure for alkynylation reaction*: To a solution of phenylacetylene (1 equiv), iodobenzene (1.52 equiv), and Cs_2CO_3 (2 equiv) in dry 1,4-dioxane, $CuFe_2O_4$ (10 mol %) was added and heated at reflux for 24 h. After cooling to room temperature, the mixture was diluted with ethyl acetate and catalyst was separated by magnetic separator. The catalyst was washed with ethyl acetate. The combined ethyl acetate layer was washed with water (thrice), dried over anhydrous Na_2SO_4, and concentrated to yield the crude product, which was further purified by silica gel column chromatography using petroleum ether/ethyl acetate to yield desired product.

23 Analytical data for compounds **2**–**6**. Compound **2**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.59 (s, 3H), 7.32–7.40 (m, 3H), 7.50–7.56 (m, 2H), 7.60 (d, $J = 8.4$ Hz, 2H), 7.92 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.7, 88.7, 92.9, 122.8, 128.3, 128.4, 128.6, 129.0, 131.8, 131.9, 136.3, 197.4. Compound **3**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 3H), 6.80–6.95 (m, 2H), 7.30–7.40 (m, 3H), 7.45–7.58 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 88.0, 89.3, 114.0, 115.3, 123.5, 127.9, 128.3, 131.4, 133.0, 159.6. Compound **4**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (t, 3H, $J = 7.2$ Hz), 4.39 (q, 2H, $J = 7.2$ Hz), 7.32–7.38 (m, 3H), 7.51–7.60 (m, 4H), 7.90–8.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 60.8, 88.4, 92.0, 122.6, 127.5, 128.1, 128.4, 129.1, 129.5, 131.1, 131.4, 165.7. Compound **5**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, 3H, $J = 6.8$ Hz), 1.30–1.41 (m, 4H), 1.42–1.54 (m, 2H), 1.56–1.68 (m, 2H), 2.43 (t, 2H, $J = 7.2$ Hz), 7.26–7.35 (m, 3H), 7.38–7.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (q), 19.4 (t), 22.6 (t), 28.6 (t), 28.7 (t), 31.4 (t), 80.5 (s), 90.5 (s), 124.1 (s), 127.4 (d), 128.1 (d), 131.5 (d). Compound **6**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, 3H, $J = 6.8$ Hz), 1.25–1.38 (m, 4H), 1.40–1.52 (m, 2H), 1.58–1.70 (m, 2H), 2.40 (t, 2H, $J = 7.2$ Hz), 3.81 (s, 3H), 6.80–6.86 (m, 2H), 7.30–7.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (q), 19.4 (t), 22.5 (t), 28.6 (t), 28.8 (t), 31.3 (t), 55.2 (q), 80.2 (s), 88.8 (s), 113.7 (d), 116.3 (s), 132.8 (d), 159.1 (s).

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