Magnetically Recoverable $CuFe_2O_4$ Nanoparticles as Highly Active Catalysts for Csp^3–Csp and Csp^3–Csp^3 Oxidative Cross-Dehydrogenative Coupling

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Abstract: This study probes the versatility of [metal] ferrite {$[M]Fe_2O_4$} nanoparticles as an effective catalyst platform for oxidative cross-dehydrogenative coupling (CDC) by comparing the reactivity of simple magnetite (Fe_3O_4) with that of the copper-substituted analogue, copper ferrite ($CuFe_2O_4$). In either case, the iron within the lattice enables magnetic recovery of the nanoparticles, simplifying the process of catalyst recycling. Both iron and copper effectively catalyze the CDC of two sp^3 carbons, while copper provides reactivity that iron cannot: activation of sp-hybridized carbons for coupling to sp^3 centers.

Key words: ferrite, magnetic nanoparticles, oxygen, cross-coupling, C–C bond formation

Efforts to both develop more direct chemical syntheses and to use simple, easily recoverable heterogeneous catalysts[1] to afford the necessary transformations represent two influential thrusts of the sustainable chemistry movement.[2]

Iron-based nanoparticles fit the bill as easily recoverable heterogeneous catalysts because their magnetic nature enables recovery and recycling by simple application of an external magnet.[3] Most schemes for this type of catalyst recovery take advantage of the magnetic particle (Fe, Fe_3O_4, Fe_2O_3, etc.) only as a support for which to anchor another catalytically active metal. Catalyst preparation becomes lengthy and complicated when this second metal[4] or organo catalyst[5] is anchored via a linker to the nanoparticle directly or instead to a protective polymer[6] or silica[7] coating. In an effort to move toward more simple schemes, several groups have devolved a series of bare magnetic nanoparticles as purely heterogeneous catalysts for organic transformations (Figure 1).

Simple iron[8] or iron–iron oxide core-shell nanoparticles can catalyze olefin hydrogenation,[9] dehydrogenation of ammonia borane[10] for release of stored hydrogen, and the coupling of aryl Grignard reagents with alkyl halides.[11]

With the understanding that iron bestows only a limited catalytic scope, a bimetalic scheme also emerged.[12] Introduction of a metal salt to a dispersion of iron–iron oxide core shell nanoparticles generates by galvanic reduction an iron-based nanoparticle decorated with nanoparticles of a more catalytically relevant metal. Introduction of pal-

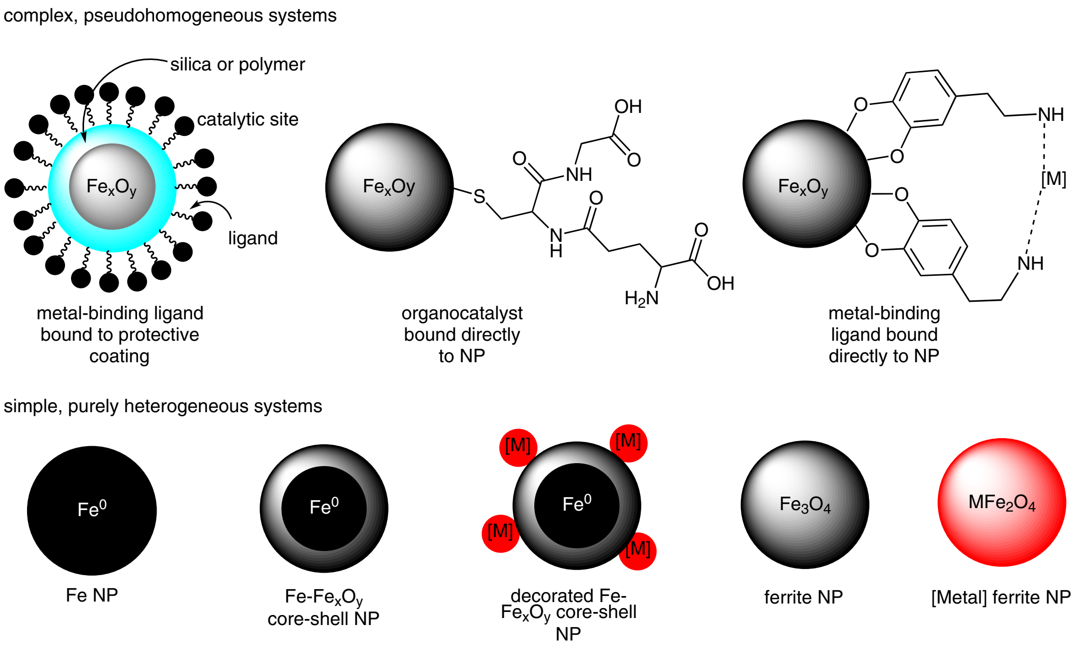

Figure 1 Various types of magnetically recoverable nanoparticle catalysts

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ladium into such a scheme enables Suzuki–Miyaura coupling,[12a] while copper facilitates the Huigsen 1,3-dipolar cycloaddition.[12b]

Catalysts that rely on a reduced iron core will always be susceptible to oxidative degradation over time. To overcome this limitation, the exploration of oxidized ferrite nanoparticles[13] and their metal-substituted analogues[14] (again to overcome the limited catalytic scope of iron alone) have been explored to facilitate numerous organic transformations. For example, Fe_3O_4 can catalyze the oxidation of olefins and alcohols,[13b] as well as A^3 coupling[13c] and similar reactions.[13a] Introduction of another catalytically active metal into the ferrite lattice can expand the scope of accessible reactions.[14c,e,g] Cobalt ferrite nanoparticles can catalyze the Knoevenagel reaction,[14h] while copper ferrite can catalyze C–O,[14l,o] C–C,[15] and C–N[14g] coupling reactions as well as the Biginelli condensation,[14m] and azide–alkyne 'click' reaction.[14n] This study examines for the first time a comparative analysis of a simple (Fe_3O_4) vs. a substituted ferrite (MFe_2O_4) for the catalysis of one class of reactions – in this case the oxidative CDC of Csp^3 carbons with other Csp^3 or Csp carbons (Scheme 1).

$$\begin{array}{c} Csp^3\text{–}H + Csp^3\text{–}H \\ \text{or} \\ Csp^3\text{–}H + Csp\text{–}H \end{array} \xrightarrow[\text{[O]}]{\text{[M]ferrite nanoparticles}} \begin{array}{c} Csp^3\text{–}Csp^3 \\ \text{or} \\ Csp^3\text{–}Csp \end{array} + H_2O$$

Scheme 1 Oxidative CDC with Fe_3O_4 and $CuFe_2O_4$ nanoparticles

The oxidative CDC represents a unique synthetic challenge whereby two C–H bonds are coupled to form a new C–C bond.[16] Most schemes for C–H bond formation require prefunctionalization. By circumventing functionalization steps, CDC reactions effectively shorten synthetic routes. Such transformations have been carried out with various catalysts including copper[16d] or iron[17] and a range of oxidants from hydrogen peroxide,[18] O_2,[19] *tert*-butylhydroperoxide (TBHP),[20] 2,3-dichloro-5,6-dicyanobenzoquinone[21] (DDQ) or even in the absence[22] of an oxidant.

Since both iron and copper represent effective catalysts for CDC reactions, we sought to compare the established reactivity of Fe_3O_4[15] with that of the copper-substituted analogue ($CuFe_2O_4$) in hopes that the latter would both increase yields and open new catalytic avenues, specifically $Csp\text{–}Csp^3$ coupling. The direct and exhaustive comparison of the activity of magnetite (Fe_3O_4) vs. copper ferrite nanoparticles for this reaction is unique to this study.

To compare the catalytic efficiency of Fe_3O_4 and $CuFe_2O_4$ nanoparticles for CDC reactivity,[23] N-arylated analogues of tetrahydroisoquinoline (a common natural product substructure) were coupled with various aromatic alkynes or nitroalkanes (Table 1). Both displayed excellent yields coupling to nitroalkanes, but only copper ferrite afforded the alkynylated product. This second result is not surprising given the ability of copper to activate alkyne species. This disparity in yield between $CuFe_2O_4$ and Fe_3O_4 toward $Csp\text{–}Csp^3$ coupling and marginal yield increase for $CuFe_2O_4$-nanoparticle-catalyzed Csp–Csp coupling validates our approach of comprehensively comparing these two catalyst systems.

In order to establish the reusability of the catalyst and its operation under a heterogeneous mechanism, we performed several additional tests on the model reaction of copper ferrite catalyzed coupling of 2-phenyl-1,2,3,4-tetrahydroisoquinoline with nitromethane. After being subjected to catalytic conditions, the nanoparticles were magnetically recovered, the supernatant decanted and filtered through Celite to remove any remaining particulate matter. This process was carried out immediately after removing the reaction vessel from the heat source in order to disfavor any equilibrium shifts that may occur if the solution were allowed to cool to room temperature. This supernatant was then used for a second round of catalysis, affording only a 40% yield. This value is in accordance with the uncatalyzed yield (41%), suggesting that no leached species are leaving the nanoparticle to conduct homogeneous catalysis. To further corroborate this claim, ICP analysis was performed on the supernatant, indicating that less than 0.39 ppm of dissolved copper was present in solution. These results strongly suggest a heterogeneous mechanism. Furthermore, the nanoparticles could be easily recovered (Figure 2), washed with ethyl acetate, and recycled up to ten times with little appreciable decrease in yield (Figure 3). Additionally, TEM images of the nanoparticles indicate no discernable change in size, shape, or morphology from before the reaction to after ten cycles of catalysis (see the Supporting Information). Before catalysis the average particle size was 34 ± 11.6 nm, while after ten cycles they measured at 31 ± 12.6 nm.

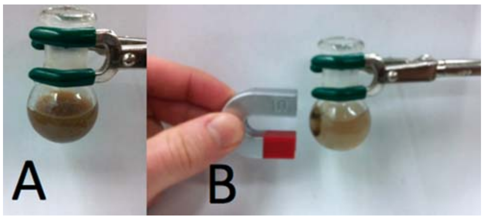


Figure 2 (A) Photograph of reaction mixture with active stirring; (B) photograph of $CuFe_2O_4$ nanoparticles adsorbed to the stir bar and attracted to an external magnet.

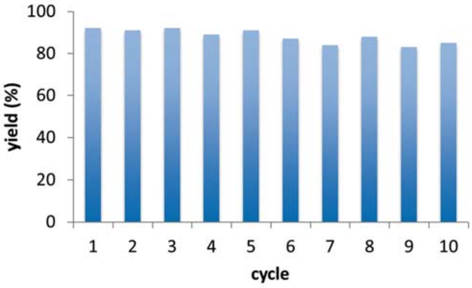
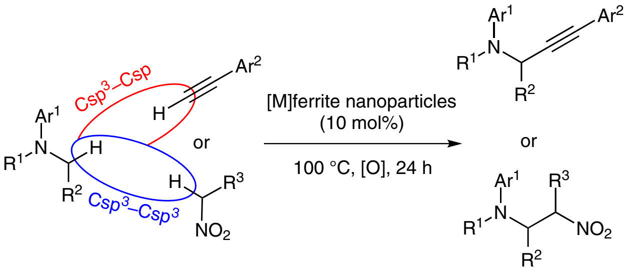


Figure 3 Recycling of $CuFe_2O_4$ nanoparticles (0.02 mmol) for the coupling of nitromethane (0.5 mL) with 2-phenyl-1,2,3,4-tetrahydroisoquinoline (0.2 mmol) with O_2 (1 atm) at 100 °C for 24 h

Table 1 Comparison of Csp^3–Csp^3 and Csp^3–Csp CDC Reaction Catalyzed by Fe$_3$O$_4$ and CuFe$_2$O$_4$ Nanoparticles[a]



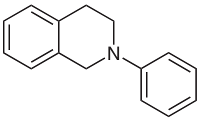
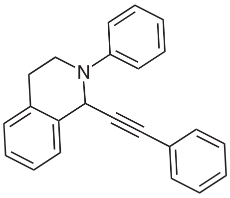
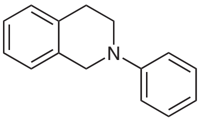
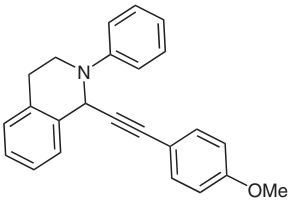
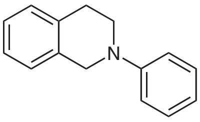
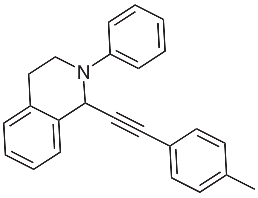
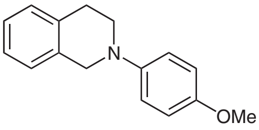
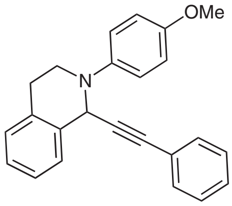
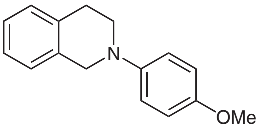
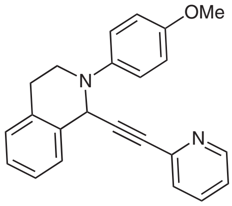
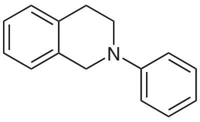
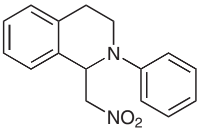
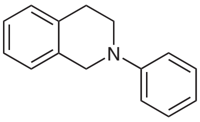
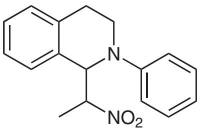
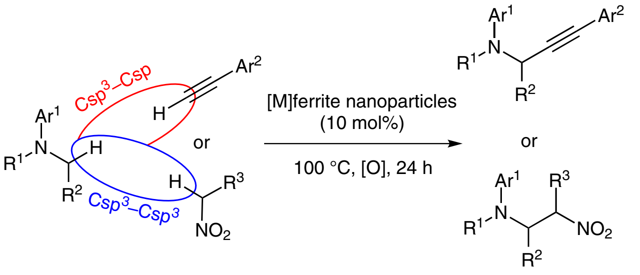
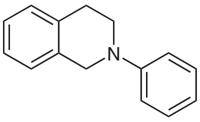
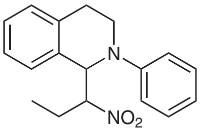
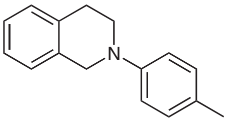
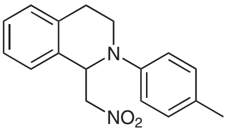
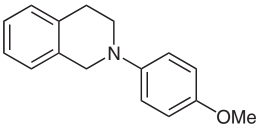
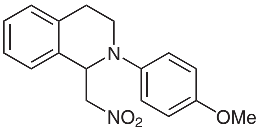
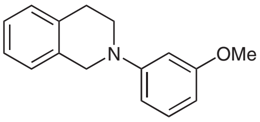
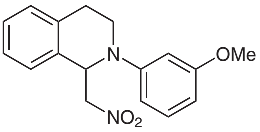
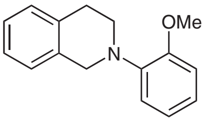
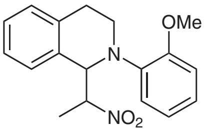
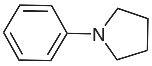
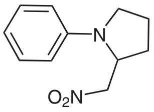
Entry	Substrate	Product	Yield of Fe$_3$O$_4$ (%)[b]	Yield of CuFe$_2$O$_4$ (%)[b]
1c			trace	68
2c			trace	71
3c			trace	61
4c			trace	69
5c			trace	53
6[d]			90e	92
7[d]			69e	76

Table 1 Comparison of Csp^3–Csp^3 and Csp^3–Csp CDC Reaction Catalyzed by Fe_3O_4 and $CuFe_2O_4$ Nanoparticles[a] (continued)



Entry	Substrate	Product	Yield of Fe_3O_4 (%)[b]	Yield of $CuFe_2O_4$ (%)[b]
8[d]			59e	73
9[d]			72e	87
10[d]			91e	91
11[d]			93e	92
12[d]			79	88
13[d]			32	41

[a] Tertiary amine (0.2 mmol), [M]ferrite nanoparticles (10 mol%), 100 °C, 24 h.

[b] Isolated yield.

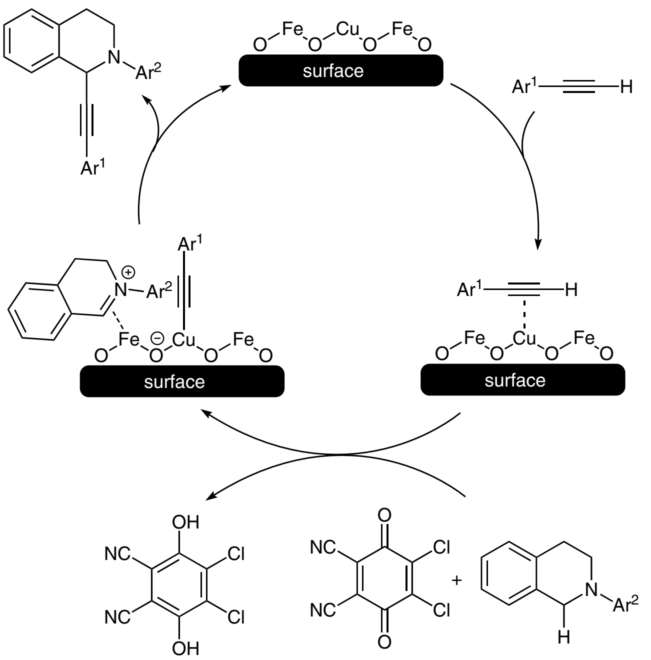
[c] Aromatic alkyne (0.22 mmol), decane (0.5 ml), [O] = DDQ (0.2 mmol).

[d] Nitroalkane (0.5 mL), [O] = O_2 (1 atm).

[e] Csp^3–Csp^3 for Fe_3O_4-nanoparticle-catalyzed CDC reactions were previously reported[15] by our group, verified in this study and reproduced herein for comparison.

A mechanism has already been proposed for the Fe_3O_4-nanoparticle-catalyzed CDC reaction of nitroalkanes to tertiary amines.[15] Herein we propose a similar mechanism for $CuFe_2O_4$-nanoparticle-catalyzed coupling of aromatic alkynes to tertiary amines (Scheme 2). The notable difference is that we propose that copper must activate the alkyne while the iminium cation generated from the tertiary amine can coordinate to a neighboring iron or copper atom within the ferrite lattice, before the two are ultimately coupled. The proposed route of coupling through an sp^2-hybridized intermediate suggests that this coupling could also be referred to as pseudo sp^2.

Both iron and copper are effective catalysts for the CDC of two Csp^3–H bonds. The ability of both $CuFe_2O_4$ and Fe_3O_4 to catalyze these reactions is therefore not surprising. Copper, however, offers the unique benefit of alkyne activation, which means $CuFe_2O_4$ nanoparticles expand the scope of [metal] ferrite nanoparticles beyond that of simple unsubstituted Fe_3O_4 nanoparticles. This finding then implies that the ferrite lattice is a versatile catalyst platform into which various metals can be substituted to afford different reactivities. No matter the metal substitution, the iron within the lattice imparts a magnetic nature, which offers an easy and environmentally benign means for catalyst recovery and recycling.



Scheme 2 Proposed mechanism for CuFe$_2$O$_4$ nanoparticle catalyzed Csp^3–Csp CDC

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(23) **Experimental Procedure**
$CuFe_2O_3$ (<50 nm particle size), Fe_2O_4 (<50 nm particle size) and other reagents were purchased from Sigma-Aldrich and used as received. 2-Aryl-1,2,3,4-tetrahydroisoquinolines were prepared by a previously reported method. For coupling with nitroalkanes, $CuFe_2O_3$ nanoparticles (0.02 mmol), nitroalkane (0.5 mL), 2-aryl-1,2,3,4-tetrahydroisoquinolines (0.2 mmol), and a magnetic stir bar were added to a reaction vessel to which a refluxing condenser was connected and a balloon of O_2 sealed the top and reacted at 100 °C for 24 h. For coupling with aromatic alkynes, $CuFe_2O_3$ nanoaprticles (0.02 mmol), aromatic alkyne (0.22 mmol), 2-aryl-1,2,3,4-tetrahydroisoquinolines (0.2 mmol), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.2 mmol), decane (0.5 mL), and a magnetic stir bar were added to a reaction vessel, sealed, and reacted at 100 °C for 24 h. The nanoparticles were magnetically recovered, washed with EtOAc, air-dried, and reused without further modification (only for the recycling tests). The reaction supernatant was filtered through Celite, and any volatile compounds were removed under vacuum. The residue was purified by flash column chromatography on silica gel (eluent: hexane–EtOAc, 5:1).