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Iron-Catalyzed Ligand-Free Three-Component Coupling Reactions of Aldehydes, Terminal Alkynes, and Amines

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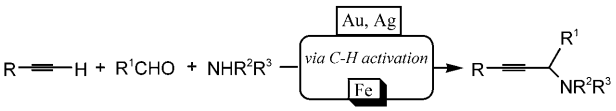
Over the past few years, iron salts as effective, alternative, and promising transition-metal catalysts have received much more attention because of their less expensive, readily available, and environmentally benign properties. Since the pioneering research work of Tamura and Kochi,[1] iron-catalyzed oxidation,[2] hydrogenation,[3] hydrosilylation,[4] rearrangement,[5] Michael addition,[6] and carbon–carbon bond forming reactions have been intensively investigated.[7–9] Most recently, iron-catalyzed *S*-arylation of thiols (C–S bond formation),[10] *N*-arylation of nitrogen nucleophiles (C–N bond formation),[11] and *O*-arylation of phenols (C–O bond formation)[12] with aryl halides, and classic Sonogashira reactions have been developed.[13] There is a keen interest from both the academia and industry to expand the application scope of iron catalysts in organic transformations because of their unique and significant advantages.

One-pot multicomponent coupling reactions, which introduce several elements of diversity into a molecule in a single step, are efficient methods for the preparation of complex molecules starting from readily available raw materials in organic synthesis.[14] Three-component coupling of aldehydes, alkynes, and amines is one of the best examples of such a process and has received much attention in recent years.[15] The resultant propargylamines obtained from the reactions are frequent skeletons[16] and synthetically versatile key intermediates[17] in the preparation of many nitrogen-containing biologically active compounds such as β-lactams, oxotremorine analogues, conformationally restricted peptides, isosteres, natural products, and therapeutic drug molecules.[16b,18] Within the past few years, there have been several noble transition-metal salts or their bimetallic systems, such as Ag^{I} salts,[19] Au^{I}/Au^{III} salts,[15,20] Au^{III}–salen complexes,[21] Cu^{I} salts,[22] Ir complexes,[23] Hg_2Cl_2,[24] and Cu/Ru^{II} bimetallic systems,[25] which can catalyze this atom-economical three-component coupling reaction by C–H activation of terminal alkynes under homogeneous reaction conditions, for which water is the only theoretical by-product. But all of these transformations suffer from the loss of precious or hazardous catalysts at the end of the reaction. Au^{I}, Ag^{I}, and Cu^{I} in ionic liquids, supported Au^{III}, Ag^{I}, Cu^{II}, and Cu^{I} were successfully used to catalyze the three-component coupling reactions under heterogeneous reaction conditions with recyclability and reusability of the transition-metal catalysts,[26] however, iron-catalyzed three-component coupling reactions of aldehydes, terminal alkynes, and amines have not so far been described. Herein, we report our results on the three-component coupling reactions of aldehydes, terminal alkynes, and amines catalyzed by highly efficient $FeCl_3$ in the absence of any ligand (Scheme 1).



Scheme 1.

Our initial investigation focused on the effect of iron sources on the three-component coupling reactions of aldehydes, terminal alkynes, and amines. Several iron sources were screened in a model reaction of phenylacetylene (**1**), isobutyraldehyde (**2**), and dibenzylamine (**3**), and the results are summarized in Table 1. The three-component coupling reaction could be catalyzed by Fe^{III} salts, Fe^{III} oxide, or Fe^{II} salts, such as $FeCl_3{\cdot}6H_2O$, $Fe(NO_3)_3{\cdot}9H_2O$, $Fe_2(SO_4)_3$, Fe_2O_3, $Fe(acac)_3$, $FeCl_3$, and $FeCl_2$, in the absence of any ligand in toluene. It is evident that $FeCl_3$ (anhydrous) was the most effective catalyst for the reaction (Table 1, entries 1–7). But, more stable Fe^{II} complexes and Fe^{0}, such as $FeCp_2$, and Fe^{0}

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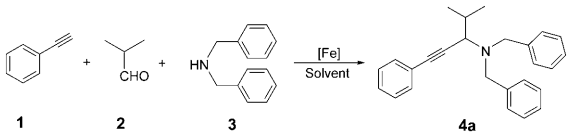
Table 1. Screening of catalysts, ligands, and solvents for the iron-catalyzed three-component coupling reactions of phenylacetylene (**1**), isobutyraldehyde (**2**), and dibenzylamie (**3**).[a]



1 2 3 4a

Entry	Fe source	Ligand[b]	Solvent[c]	**4a** [%][d]
1	$FeCl_3 \cdot 6H_2O$	none	toluene	26
2	$Fe(NO_3)_3 \cdot 9H_2O$	none	toluene	21
3	$Fe_2(SO_4)_3$	none	toluene	29
4	Fe_2O_3	none	toluene	34
5	$Fe(acac)_3$	none	toluene	64
6	$FeCl_3$	none	toluene	79
7	$FeCl_2$	none	toluene	74
8	$FeCp_2$	none	toluene	0
9	Fe powder (100 nm)	none	toluene	0
10	$FeCl_3$	none	benzene	70
11	$FeCl_3$	none	DCE	44
12	$FeCl_3$	none	C_2H_5OH	40
13	$FeCl_3$	none	CH_3CN	48
14	$FeCl_3$	none	dioxane	39
15	$FeCl_3$	none	DMSO	0
16	$FeCl_3$	none	DMF	0
17	$FeCl_3$	none	DMA	0
18	$FeCl_3$	DMEDA	toluene	0
19	$FeCl_3$	1,10-phenanthroline	toluene	0
20	$FeCl_3$	DCH	toluene	48
21	$FeCl_3$	TMHD	toluene	42
22	$FeCl_3$	$(C_6H_5)_3P$	toluene	82
23	$FeCl_3$	$(C_6H_{11})_3P$	toluene	83
24	$FeCl_3$	DPPF	toluene	87
25[e]	$FeCl_3$	none	toluene	95
26[e]	$FeCl_3$	DPPF	toluene	96

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.0 equiv), **3** (1.0 equiv), Fe source (0.1 equiv), ligand (0.1 equiv), solvent (1.0 mL mmol^{-1}), sealed tube, 120 °C, under argon, 24 h. [b] Cp = cyclopentadienyl, acac = acetylacetonate, DMEDA = *N,N′*-dimethylethylenediamine, DCH = (*dl*)-*trans*-1,2-diaminocyclohexane, TMHD = 2,2,6,6-tetramethyl-3,5-heptadione, DPPF = 1,1′-bis(diphenylphosphino)ferrocene. [c] DMF = *N,N*-dimethylformamide, DMA = *N,N*-dimethylacetamide, DMSO = dimethyl sulfoxide, DCE = 1,2-dichloroethane. [d] Yields of isolated products after flash chromatography. [e] In the presence of 4 A molecular sieves (100 mg).

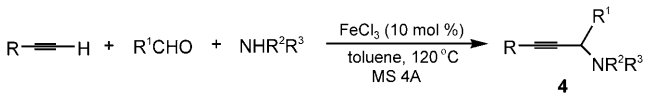
powder (100 nm), failed to catalyze the reaction (Table 1, entries 8 and 9). The effect of solvent on the reaction by using $FeCl_3$ as catalyst was also surveyed (Table 1, entries 6, 10–17). Among the solvents tested, toluene and benzene were the most suitable reaction media for this three-component coupling reaction. 1,2-Dichloroethane, ethanol, acetonitrile, and dioxane were inferior and generated **4a** in 44, 40, 48, and 39 % yields, respectively (Table 1, entries 11–14). Unfortunately, no desired product was isolated when the reactions were carried out in dimethyl sulfoxide (DMSO), *N,N*-dimethylformamide (DMF), or *N,N*-dimethylacetamide (DMA) (Table 1, entries 15–17). In general, iron-catalyzed carbon–carbon and carbon–heteroatom bond formation reactions could be enhanced by a suitable ligand containing nitrogen or oxygen atoms.[7–9] However, N-ligands, such as 1,10-phenanthroline, (*dl*)-*trans*-1,2-diaminocyclohexane, and *N,N′*-dimethylethylenediamine (DMEDA), and O-ligand, 2,2,6,6-tetramethyl-3,5-heptadione, did not assist the iron-catalyzed three-component coupling reactions of aldehydes, terminal alkynes, and amines, and conversely, restrained the reactivity of the catalyst (Table 1, entries 18–21). It should be noted that no corresponding product was obtained when 1,10-phenanthroline or DMEDA was added to the reaction and starting materials were recovered. Fortunately, when a P-ligand such as $(C_6H_5)_3P$, $(C_6H_{11})_3P$, or 1,1′-bis(diphenylphosphino)ferrocene (DPPF) was added to the reaction systems, we found that especially DPPF accelerates the reaction to give **4a** in 87 % yield (Table 1, entries 22–24). It is noteworthy that the isolated yield of **4a** increased up to 95 % when 4 A molecular sieves were added to the reaction system even in the absence of DFFP (Table 1, entry 25). However, additional DPPF did not improve the yield of **4a** in the presence of 4 A molecular sieves (Table 1, entry 26). During the course of our further optimization of the reaction conditions, the reaction was generally completed within 24 h when it was performed at 120 °C by using 10 mol % of $FeCl_3$ in the presence of 4 A molecular sieves (100 mg mmol^{-1}) in toluene without additional DPPF.

To examine the scope of this three-component coupling reaction, we extended our studies to different combinations of aldehydes, amines, and alkynes. The results are listed in Table 2. At the beginning of the search for the suitable alkynes, isobutyraldehyde and dibenzylamine were used as model substrates and a variety of alkynes were examined for the coupling reactions (Table 2, entries 1–7). As can be seen from Table 2, aromatic alkynes were much more reactive than aliphatic ones. Aromatic alkynes, such as phenylacetylene, *p*-methylphenylacetylene, *p*-chlorophenylacetylene, *p*-fluorophenylacetylene, and diphenylacetylene, reacted with dibenzylamine and isobutyraldehyde smoothly and generated the corresponding products in excellent yields (Table 2, entries 1–5). Fortunately, the reactions involving aliphatic alkynes also gave both higher conversions and isolated yields, leading to the corresponding propargylamines in good yields (Table 2, entries 6 and 7).

To expand the scope of aldehyde substrates, a combination of phenylacetylene-dibenzylamine-aldehydes was chosen and various aldehydes were surveyed. The aliphatic aldehydes, cyclic or acyclic, such as *n*-butyraldehyde, isobutyraldehyde, isovaleraldehyde, *para*-formaldehyde, and cyclohexanecarboxaldehyde, displayed high reactivity under the present reaction conditions, and high yields of the desired three-component coupling products were obtained (Table 2, entries 1, and 8–11). Fortunately, aromatic aldehydes with both electron-donating and electron-withdrawing functionalities, such as methoxy, methyl, and chloro groups, afforded the corresponding propargylamines in good yields (Table 2, entries 12–16).

Subsequently, a variety of amines was also examined and the results listed in Table 2 indicated that cyclic, heterocyclic, and acyclic secondary aliphatic amines, such as dibenzylamine, piperidine, and morpholine, gave high yields of products under the optimized reaction conditions (Table 2, entries 1, 13, 17, and 18). However, aromatic secondary amines, such as *N*-benzylaniline and *N*-methylaniline, were

Table 2. Iron-catalyzed three-component coupling reactions of aldehydes, terminal alkynes, and amines.[a]



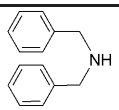
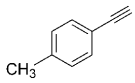
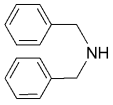
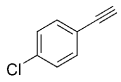
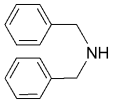
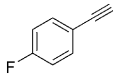
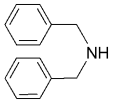
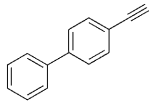
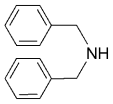
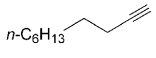
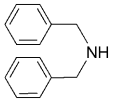
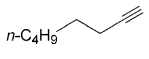
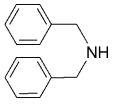
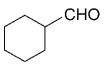
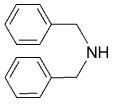
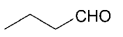
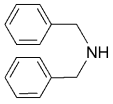
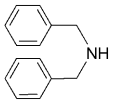
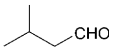
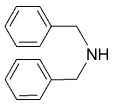
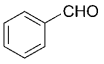
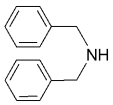
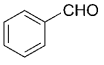
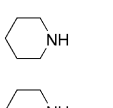
Entry	Alkyne	Aldehyde	Amine	**4** [%][b]
1				95
2				94
3				96
4				97
5				90
6				85
7				78
8				98
9				79
10		$(CH_2O)_n$		70
11				90
12				84
13				91
14				92
15				78
16				75

Table 2. (Continued)

Entry	Alkyne	Aldehyde	Amine	**4** [%][b]
17				84
18				82

[a] Reaction conditions: aldehyde (1.0 mmol), amine (1.0 mmol), alkyne (1.0 mmol), $FeCl_3$ (0.1 mmol), 4 A molecular sieves (100 mg), toluene (1.0 mL), sealed tube, 120 °C, under argon, 24 h. [b] Yields of isolated products after flash chromatography.

less reactive in reactions with phenylacetylene and isobutyraldehyde, and only trace amounts of the desired products were isolated.

A possible mechanism of the iron-catalyzed one-pot three-component coupling of aldehyde, alkyne, and amine is shown in Scheme 2. The precatalyst $FeCl_3$, a trivalent iron

Scheme 2. Possible mechanism of iron-catalyzed three-component coupling of aldehyde, alkyne, and amine.

salt, would presumably be initially reduced to a low-valent Fe^{II} state, which probably possesses only one alkynyl group given the notable stability of Fe^{II} alkynylate complexes, compared to Fe^0 and Fe^{III} analogues.[27] When $FeCl_2$ was used instead of $FeCl_3$ under the optimized reaction conditions, **4a** was isolated in 91 % yield and comparable catalytic activity of Fe^{II} and Fe^{III} was observed. However, Fe^0 powder (freshly prepared, 100 nm) failed to catalyze the reaction. On the other hand, we hypothesize that the generated HCl accelerates the formation of the immonium salt from the aldehyde and the secondary amine,[28] and that $FeCl_3$, as a Lewis acid, plays a role in increasing the electrophilic character of the starting aldehyde and stabilizing the immonium salt by the coordination of the oxygen or nitrogen lone electron pair with $FeCl_3$.[29] The resulting Fe^{II} alkynylate complex subsequently reacted with the immonium salt generated in situ to give the corresponding propargylamine and regenerate the Fe^{II} catalyst for further reactions.

In summary, we have successfully developed a novel, economical, environmentally friendly, and practical iron-catalyzed ligand-free one-pot three-component coupling reaction of aldehydes, alkynes, and amines. The reactions were

carried out in the presence of catalytic amounts of $FeCl_3$ and in conjunction with 4 A molecular sieves without any ligand, and generated the corresponding propargylamines in good to excellent yields. The reactions were also applicable to aromatic and aliphatic aldehydes, alkynes, and aliphatic secondary amines. In addition, the novel $FeCl_3$-catalyzed ligand-free one-pot three-component coupling reaction should expand the application scope of iron catalysts as a versatile tool in organic synthesis. Further investigations on the application of this kind of catalyst in asymmetric catalysis are underway in our laboratory.

Experimental Section

General procedure for the iron-catalyzed ligand-free three-component coupling reactions of aldehydes, alkynes, and amines: Under an argon atmosphere, a sealable reaction tube equipped with a magnetic stir bar was charged with aldehyde (1.0 mmol), amine (1.0 mmol), alkyne (1.0 mmol), $FeCl_3$ (0.1 mmol), 4 A molecular sieves (100 mg), and toluene (1.0 mL). The rubber septum was then replaced by a Teflon-coated screw cap, and the reaction vessel placed in an oil bath at 120 °C. After the mixture had been stirred at this temperature for 24 h, it was cooled to room temperature and diluted with dichloromethane. The resulting solution was directly filtered through a pad of silica gel using a sintered glass funnel, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluant: hexane/ethyl acetate = 3:1, v/v) to give the desired three-component coupling product. The identity and purity of known products was confirmed by ^1H and ^{13}C NMR spectroscopy, and new products were fully characterized. See the Supporting Information for full details.

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Keywords: alkynes · coupling reactions · iron · multicomponent reactions · synthetic methods

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