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Iron-catalyzed three-component coupling of aldehyde, alkyne, and amine under neat conditions in air

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ABSTRACT

Various iron-salts (and complexes) and especially iron(III) chloride catalyzed the three-component coupling of aldehyde, alkyne, and amine to generate propargylic amines with high efficiency under neat conditions in air. The iron-catalyzed reaction is particularly effective for reactions involving aliphatic aldehydes. The reaction is not sensitive to and occurs smoothly in water and in air. No additional co-catalyst or activator is required.

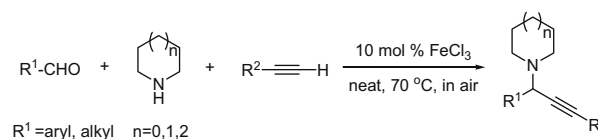
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Environmentally benign, economical, practical, and efficient processes for chemical synthesis have become increasingly important in the chemical community.¹ During the past decade, one-pot multi-component reactions to make new carbon–carbon bonds have attracted much attention and have achieved great progress.² In the past few years, we³ and others⁴ have reported various highly efficient three-component couplings of aldehyde, alkyne, and amine (A³-coupling) in water, organic media, ionic liquid, or under solvent-free condition catalyzed by copper, silver, gold, and other catalysts via catalytic C–H reaction to afford various propargylamines. A highly enantioselective addition of alkynes to imines to generate optical propargylamines in water or in organic media by using a chiral copper catalyst (AA³-coupling) has also been developed by us and others.⁵ Propargylic amines, product of the A³-coupling, are useful building blocks as well as important skeletons of biologically active compounds.⁶ Because of our continued interest in synthesizing propargylamines via activation of alkynes, we have been searching for other cheap, nontoxic, and benign catalysts for this coupling.

Iron catalysts are readily available, inexpensive, and environmental friendly with special reactivities. These features make them valuable and advantageous in synthetic processes. Many iron-catalyzed reactions such as oxidation,⁷ hydroamination,⁸ Michael addition,⁹ rearrangement,¹⁰ and other carbon–carbon bond, carbon–heteroatom bond and heteroatom–heteroatom bond forming reactions have been described recently.¹¹ During our investigation of A³-couplings several years ago, we discovered that iron could catalyze the A³ coupling in toluene.¹² However, subsequent studies showed that the reaction yields were not repeatable (changing from high yields to only trace amounts with different runs under identical conditions). To overcome this problem, we tried a variety of conditions to pin down the cause of irregularity in product yields without much success. Recently, we found and herein we wish to report that, under neat conditions and in air, FeCl₃ is an effective catalyst for the three-component coupling of aldehyde, alkyne and amine with good repeatability in reaction yields at 70 °C (Scheme 1). Furthermore, a reversal of the reactivity of aliphatic and aromatic aldehydes was observed compared to our early reported Au or Cu systems,³ in which aliphatic aldehydes were much more reactive than aromatic aldehydes (similar to the silver system).

In our initial attempt to seek a more effective and more repeatable iron catalyst for the coupling of aldehyde, alkyne, and amine, several iron salts were utilized (Table 1). When using 10 mol % of

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Scheme 1. Iron-catalyzed A³ coupling.

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Table 1

Three-component coupling of aliphatic aldehydes, amines, and alkynes catalyzed by iron in neat ^a

Entry	Catalyst (mol %)	Additive or solvent (mol %)	Yield ^b (%)
1	FeCl ₃ (10)	—	93
2	FeCl ₃ ·6H ₂ O (10)	—	84
3	Fe(acac) ₃ (10)	—	53
4	FeCl ₂ (10)	—	70
5	FeCp ₂ (10)	—	90
6	Fe ₂ (CO) ₉ (10)	—	46
7	FeF ₂ (10)	—	66
8	FeBr ₂ (10)	—	73
9	FeSO ₄ (10)	—	42
10	Iron powder (10)	—	37
11	FeCl ₃ (10) (in O ₂)	—	36
12	FeCl ₃ (10) (in N ₂)	—	74
13	FeCl ₃ (20)	—	94
14	FeCl ₃ (5)	—	90
15 ^c	FeCl ₃ (10)	—	38
16	FeCl ₃ (10)	TMEDA (20)	94
17	FeCl ₃ (10)	THF (200)	60
18	FeCl ₃ (10)	Toluene (200)	60
19	FeCl ₃ (10)	DCE (200)	21
20	FeCl ₃ (10)	H ₂ O (10)	74
21	FeCl ₃ (10)	H ₂ O (200)	38

^a All reactions were carried out with aldehyde **1** (0.5 mmol), amine **2** (0.6 mmol), and alkyne **3** (0.75 mmol) in neat and in air at 70 °C for 14 h.

^b Measured by ¹H NMR with CH₃NO₂ as the internal standard.

^c The reaction was carried out in room temperature.

the catalyst, all the Fe(III) salts, Fe(II) salts, and Fe(0) sources examined including FeCl₃, FeCl₃·6H₂O, Fe(acac)₃, FeCl₂, FeBr₂, FeF₂, FeSO₄, FeCp₂, Fe₂(CO)₉, and iron powder catalyzed the reaction of cyclohexanecarbaldehyde, piperidine, and phenylacetylene in neat and under an air atmosphere to give the corresponding propargylamine products in moderate to good yields, with FeCl₃ being the most effective and giving the three-component coupling product in 93% yield (Table 1, entries 1–10). It is worth noting that iron powder can also catalyze the reaction, albeit the yield is lower. The reaction yield decreased considerably when carried out either under a nitrogen or oxygen atmosphere (Table 1, entries 11 and 12). Almost similar yield was obtained when slightly increasing or decreasing the catalyst loading (Table 1, entries 13 and 14). The reaction could also proceed even at room temperature, although in a lower conversion (Table 1, entry 15). No significant difference was observed when a ligand such as TMEDA was presented (Table 1, entry 16). The addition of various solvents such as THF, DCE, and toluene all led to lower yields (Table 1, entries 17–19). The iron-catalyzed reaction could also proceed smoothly in the presence of a small amount of water. However, a large amount of water resulted in a lower yield (Table 1, entries 20 and 21). No desired product was obtained in the absence of FeCl₃. The optimized reaction conditions include 1.0 equiv of aldehyde, 1.2 equiv of amine, 1.5 equiv of alkyne, and 10 mol % of FeCl₃ in neat at 70 °C in air.

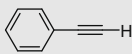
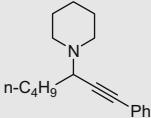
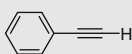
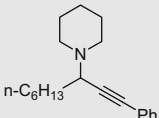
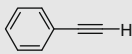
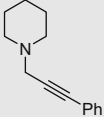
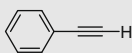
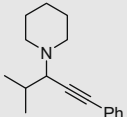
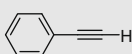
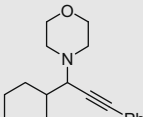
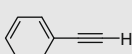
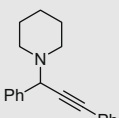
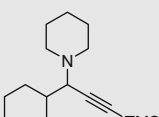
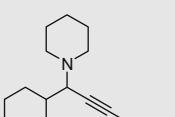
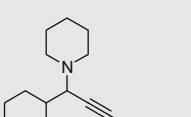
Subsequently, various aldehyde, alkyne, and amine were coupled similarly and the results are summarized in Table 2. Both aromatic and aliphatic aldehydes underwent the addition reaction to afford the corresponding three-component propargylic amines effectively. However, the reaction was found to be strongly influenced by the nature of the aldehyde, in the same manner as in the silver-catalyzed A³-coupling in water.^{3g} The use of aromatic

Table 2

Coupling of aldehyde, alkyne, and amine catalyzed by FeCl₃ in neat and in air

Entry	Aldehyde	Amine	Alkyne	Product	Yield ^{a,b} (%)
1					81 (93)
2					60 (70)
3					67 (74)
4					55 (71)
5					32 (52)

Table 2 (continued)

Entry	Aldehyde	Amine	Alkyne	Product	Yield ^{a,b} (%)
6	$n\text{-C}_4\text{H}_9\text{CHO}$				61 (72)
7	$n\text{-C}_6\text{H}_{13}\text{CHO}$				60 (71)
8	HCHO (37 wt % in H_2O)				45 (52)
9					55 (66)
10					60 (72)
11					34 (52)
12			$\text{TMS}\text{--}\text{C}\equiv\text{H}$		56 (73)
13			$n\text{-C}_4\text{H}_9\text{--}\text{C}\equiv\text{H}$		43 (58)
14			$n\text{-C}_{10}\text{H}_{21}\text{--}\text{C}\equiv\text{H}$		58 (79)

^a Isolated yields based on aldehyde were reported; carried out on a 0.5 mmol scale with aldehyde/amine/alkyne = 1:1.2:1.5 and 10 mol % FeCl_3 , 70 °C, neat, in air.

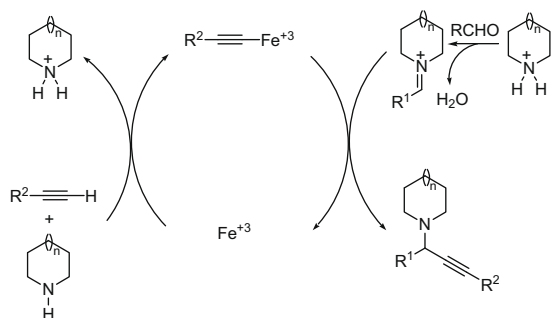
^b The data in the parentheses are the yields measured by ^1H NMR with CH_3NO_2 as the internal standard.

aldehydes gave lower conversions and lower yields. Aliphatic aldehydes, on the other hand, displayed higher reactivity and cleaner reactions. The reactions involving aliphatic aldehydes such as isobutyraldehyde, valeraldehyde, heptaldehyde, cyclohexanecarboxaldehyde, and 3-phenylpropanal all showed both higher conversions and greater yields than benzaldehyde (Table 2, entries 1, 4, 6, 7, 9, and 11). Formaldehyde (37 wt % in water) and 2-ethylbutanal afforded the desired products in moderate yields (Table 2, entries 5 and 8).

Cyclic dialkylamines such as piperidine, pyrrolidine, azepane, and morpholine reacted smoothly under these conditions to give

the propargylamines in moderate to good yields (Table 2, entries 1, 2, 3, and 10). However, acyclic dialkylamines (such as diallylamine) was less effective. Various terminal alkynes were also examined. Both aromatic alkynes and aliphatic alkynes reacted smoothly with aldehyde and amine to give the corresponding products in good yields (Table 2, entries 1, 13, and 14). Trimethylsilylacetylene also reacted smoothly in which the silyl group could tolerate the reaction conditions (Table 2, entry 12).

A tentative mechanism for the iron-catalyzed aldehyde–alkyne–amine (A^3) coupling is proposed in Scheme 2. The reaction is catalyzed most likely by Fe^{+3} ion. Reaction of Fe^{+3} with terminal



Scheme 2. Tentative mechanism for the iron-catalyzed A³ coupling.

alkyne in the presence of the amine base generated the terminal iron-acetylide, which undergoes nucleophilic addition to the iminium ion, generated in situ, to give the propargyl amine product and regenerates the Fe³⁺.

In conclusion, we have developed an effective, economical, and simple three-component coupling of aldehyde, alkyne, and amine (A³-coupling) with various iron catalysts to give a diverse range of propargylamines in moderate to high yield under mild conditions. The operation is very simple and can be carried out at a relatively low temperature, without any solvent in air. The reaction can also tolerate a small amount of water without substantially sacrificing the yield. The asymmetric version, mechanism, and synthetic application of this reaction are currently under further investigation.

General experimental procedure: To a test tube charged with FeCl₃ (8.1 mg, 0.05 mmol, 10 mol %) in air, aldehyde (0.5 mmol), amine (0.6 mmol), and alkyne (0.75 mmol) were added. The tube was then stoppered. The reaction mixture was stirred at 70 °C (oil bath temperature) for 14 h. After cooling to room temperature, the reaction mixture was filtered through Celite in a pipette eluting with ethyl acetate. The volatile was removed under vacuum and the residue was purified by flash column chromatography on silica gel (eluent:hexane/ethyl acetate = 10:1) to give the corresponding product.

Acknowledgments

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