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Efficient iron(III)-catalyzed three-component coupling reaction of alkynes, CH_2Cl_2 and amines to propargylamines†

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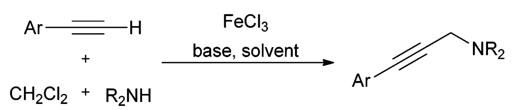
An iron(III)-catalyzed three-component coupling reaction of alkynes, CH_2Cl_2 and amines was developed for facile synthesis of propargylamines. Preliminary mechanism investigation using *in situ* FT-IR reveals that the crucial Fe-acetylide intermediate could be formed through C–H bond activation of alkynes thanks to cooperative effect of $FeCl_3$ and 1,1,3,3-tetramethylguanidine.

Propargylamines have been attracting considerable attention over the last few years due to their wide applications in drug discovery.[1] However, stoichiometric highly moisture sensitive alkynyl-metal reagents and harsh reaction conditions are generally required in conventional synthetic procedures.[2] In this aspect, a three-component coupling reaction of aldehydes, alkynes, and amines (A^3) catalyzed by various transition-metals represents a more attractive and atom-efficient approach to synthesize propargylamines.[3–11] Recently, Contel and coworkers reported that a Au-catalyzed three-component coupling reaction of alkynes, haloalkanes and amines (AHA) was smoothly performed to produce propargylamines, where new C–C and C–N bonds are constructed *via* the activation of C–H and C–halogen bonds.[12] Later, Cu(I)[13] and nano-In_2O_3[14] were also proved to be able to catalyze this kind of AHA reaction. It is worth mentioning that much cheaper and readily available haloalkanes such as dichloromethane as a reactant can be used in an AHA coupling reaction. Unfortunately, a precious transition metal such as Au or In is still needed.

In this context, iron compounds have found many applications in catalysis, presumably due to unique properties such as distinct Lewis acid character besides environmental and economic benefits.[15] In particular, iron could be an efficient catalyst for C–C bond-forming reactions through C–H bond activation.[16] As a part of our program aiming at developing iron-catalyzed organic reactions,[17] we herein would like to report the $FeCl_3$-catalyzed AHA coupling reaction of aromatic terminal alkynes, CH_2Cl_2 and secondary amines in combination with an organic base *i.e.*



Scheme 1 Iron(III)-catalyzed AHA coupling reaction of terminal alkyne, CH_2Cl_2 and secondary amine.

1,1,3,3-tetramethylguanidine (TMG) to synthesize propargylamines as depicted in Scheme 1.

Various iron salts were screened by employing phenylacetylene, dichloromethane and diethylamine as representative substrates and the influences of other reaction parameters on the reaction such as base, solvent, catalyst amount, and reaction temperature were also investigated in detail.[18] To our delight, although relatively high catalyst loading and reaction temperature were needed, good yield of the product *i.e.* *N*,*N*-diethyl-3-phenylprop-2-yn-1-amine was successfully attained with the aid of both $FeCl_3$ and TMG by using CH_3CN as a solvent at 100 °C (entry 1, Table S4 and entry 5, Table S6, ESI†). In other words, either $FeCl_3$ or TMG alone did not work well; and simultaneous presence of both $FeCl_3$ and TMG is required for the reaction. To further evaluate the role of traces of metal impurities or contaminants, we used $FeCl_3$ with the quality as high as 99.99% to carry out the reaction under identical reaction conditions (entry 1, Table 1). The results could suggest that this is a real iron-catalyzed reaction. In addition, $FeCl_3$ and CuCl showed the same activity (entry 1 *vs.* 2). Subsequently, the utility and generality of this protocol were evaluated by employing various terminal alkynes with dichloromethane and piperidine. As a result, aromatic alkynes with either electron-donating or electron-withdrawing substituents reacted smoothly to afford the corresponding propargylamine products in good to excellent yields under the optimal reaction conditions (entries 3–8, Table 1). Whereas, aliphatic alkynes, for instance 3,3-dimethyl-1-butyne and 1-hexyne, were found to be inactive (entries 9 and 10), probably being ascribed to the low activity of the aliphatic alkynyl C–H.

On the other hand, various amines were further surveyed for this AHA coupling reaction. As expected, acyclic and heterocyclic secondary aliphatic amines gave moderate to excellent yields under the given reaction conditions (entries 1, 11–14). Diisopropylamine showed relatively low activity (entry 12). Unfortunately, both aromatic primary amines like aniline and aliphatic primary amines such as *n*-butylamine failed to give the propargylamine product (entries 15 and 16).

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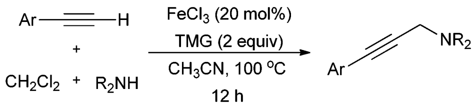
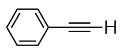
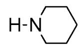
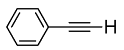
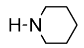
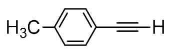
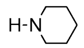
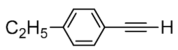
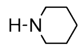
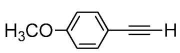
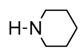
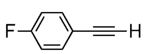
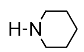
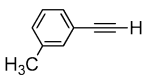
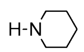
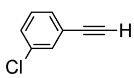
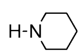
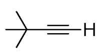
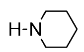
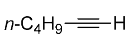
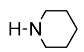
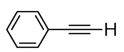
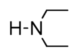
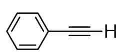
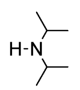
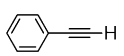
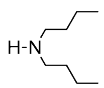
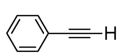
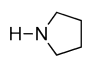
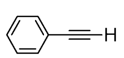
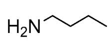
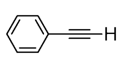
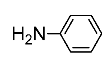
† Electronic supplementary information (ESI) available: General experimental methods and procedures, optimization of reaction conditions, characterization and spectra of products and other supplementary information. See DOI: 10.1039/c2cc17616e

Table 1 $FeCl_3$-catalyzed AHA coupling reaction[a]



Entry	Alkyne (A1)	Dihalomethane (H)	Amine (A2)	Yield[b] (%)
1[c]		CH_2Cl_2		95
2[d]		CH_2Cl_2		94
3		CH_2Cl_2		78
4		CH_2Cl_2		64
5		CH_2Cl_2		86
6		CH_2Cl_2		81
7		CH_2Cl_2		88
8[e]		CH_2Cl_2		84
9		CH_2Cl_2		0
10		CH_2Cl_2		0
11		CH_2Cl_2		67
12		CH_2Cl_2		37
13[f]		CH_2Cl_2		72
14[f]		CH_2Cl_2		50
15		CH_2Cl_2		0
16		CH_2Cl_2		0

[a] Reaction conditions: alkyne (1.0 mmol); dichloromethane (2.0 mmol, 128 μL); amine (2.0 mmol); TMG (2.0 mmol, 230.4 mg); $FeCl_3$ (20 mol%, 32.4 mg, purchased from Aladdin with >99% purity, Cu content was determined to be 0.026% w/w by using an ICP method); CH_3CN, 0.5 mL; 100 °C; 12 h. [b] Determined by ^1H NMR using $MeNO_2$ as the internal standard. [c] Two kinds of $FeCl_3$ from Sigma-Aldrich with 99.99% purity and Aladdin with >99% purity gave the same result. [d] CuCl was used instead of $FeCl_3$. [e] 24 h. [f] Phenylacetylene (2.0 mmol); amine (1.0 mmol).

As for alkyne participated nucleophilic reaction, complexation of a terminal alkyne with a transition metal could generate a π-complex,[19] whereby the terminal alkynyl C–H bond can be further deprotonated by a weak base like amine with the formation of the metal-acetylide, which could be active nucleophilic species for the reaction. In this context, an *in situ* IR spectroscopic study was undertaken to gain insight into the reaction mechanism. As shown in Fig. 1(a), the alkynyl C–H stretch signal of a solution of phenylacetylene in acetonitrile was observed at 3277 cm^{-1}. After addition of 1.1 equiv. of TMG, a decrease in the absorbance intensity of the C–H stretch was observed, which could be attributed to the dilution effect. Accordingly, the deprotonation only induced by TMG itself can be reasonably excluded. However, subsequent addition of 1.0 equiv. of $FeCl_3$ in batches led to complete disappearance of alkynyl C–H bond absorption within 3 h as the temperature was increased from 30 to 100 °C. These results imply that $FeCl_3$ could activate the alkynyl C–H bond and simultaneously a base *i.e.* TMG could easily make phenylacetylene deprotonated, with eventual generation of the Fe-acetylide intermediate.

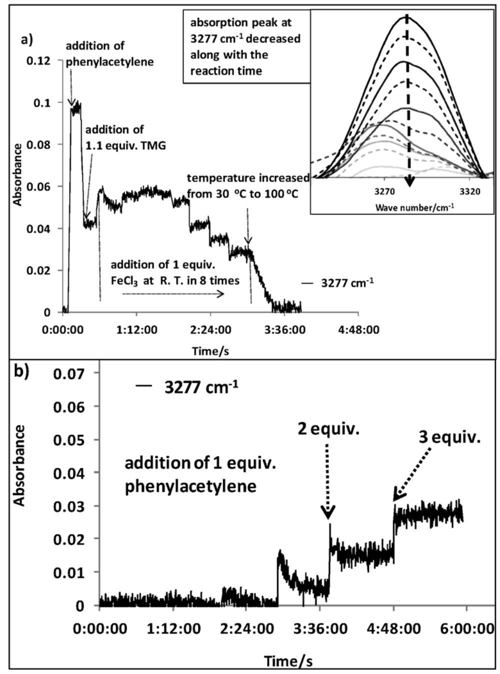
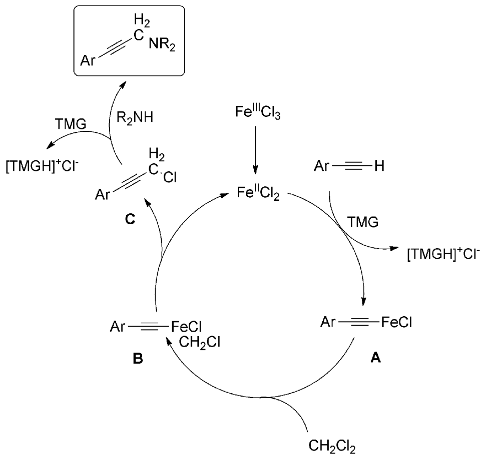


Fig. 1 ReactIR spectra indicating the change in the acetylenic C–H stretch band: (a) disappearance of the acetylenic C–H stretch resonance at 3277 cm^{-1} due to deprotonation of phenylacetylene by $FeCl_3$ and TMG and (b) time course of the successive addition of up to 3 equiv. of phenylacetylene to a mixture of $FeCl_3$ (1 equiv.) and TMG (2 equiv.) in CH_3CN.

C–H activation of the terminal alkyne upon synergistic effect of both $FeCl_3$ and a base (TMG) can be further supported by the results obtained from Fig. 1(b). The background was measured in the presence of $FeCl_3$ and 2 equiv. of TMG in CH_3CN. A signal at 3277 cm^{-1} corresponding to the terminal alkynyl C–H bond absorption was observed when 1 equiv. of phenylacetylene was added and this signal disappeared within 50 min. On the other hand, when additional phenylacetylene was introduced up to 3 equiv., the absorbance intensity of the terminal alkynyl C–H bond increased with each addition.

Based on the *in situ* FT-IR exploration in this study and the literature results,[4,12,13] the reaction mechanism was proposed as shown in Scheme 2. The precatalyst $FeCl_3$ would presumably be initially reduced to a low-valent Fe^{II} state in the presence of amine and/or TMG, producing the Fe^{II} alkynylate complexes,[20] being also identified by the XPS analytic results.[21] As a result,



Scheme 2 Proposed reaction mechanism for the AHA coupling reaction.

this $FeCl_3$ catalyzed AHA reaction could be a homogeneous catalytic process. The catalytic cycle could start *via* the activation of the terminal alkyne C–H bond promoted by $FeCl_2$ in conjunction with TMG with the generation of a Fe-acetylide intermediate **A**, which is considered to be the active nucleophilic species. Then, the intermediate **A** reacts with CH_2Cl_2 to form the iron(III) species **B** which further goes through a reductive elimination to afford the propargylchloride **C** and regenerate $FeCl_2$. Finally, the reaction of **C** with a secondary amine in the presence of TMG could furnish the propargylamine product. As a result, a base like TMG would play a dual role including co-activation of alkynyl C–H through deprotonation and trapping the formed HCl to promote the reaction.

In conclusion, we have developed an economical and practical protocol for facile synthesis of propargylic amines through an iron(III)-catalyzed three-component coupling reaction of aromatic terminal alkynes, CH_2Cl_2 and aliphatic secondary amines. Notably, *in situ* IR spectroscopic investigation strongly suggests that $FeCl_3$ could activate the alkynyl C–H bond in combination with TMG as a base. The study of the reactive iron-acetylide intermediate would be of vital importance for the continuing evolution of iron catalyzed reactions for direct C–C bond formation through C–H bond activation.

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