1,2-Addition of Phenylacetylene to Aldimines Catalyzed by $InCl_3$/CuCl in Water under Barbier Conditions

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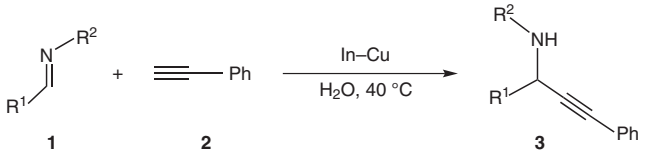
Abstract: A new and efficient method for the preparation of various propargylamines has been achieved by the simple Barbier–Grignard-type reaction of phenylacetylene with a variety of aldimines under aqueous conditions, catalyzed by a bimetallic In–Cu system.

Key words: aldimines, water, indium chloride, copper chloride, propargylamines

There has been growing interest in the use of reactions of metallic elements in aqueous media,[1] as they offer significant advantages over conventional reactions in dry organic solvents. The development of such reactions also offer the possibility of obtaining environmentally benign reaction conditions.[2] The study and application of Barbier–Grignard type reactions[3] is still in its infancy. Since their history is only a decade old, the full synthetic potential of such reactions is still waiting to be explored.[4] The use of water as solvent could reduce or eliminate environmental damage by organic wastes.[5]

Furthermore, the addition of terminal alkynes to imines or carbonyl compounds, is of great interest because of the versatility of the corresponding propargylic amines or alcohols.[6] While several catalytic methods are known to promote the addition of acetylenes to aldehydes in very high yields,[7] only very recently a limited number of organometallic systems has been reported to afford propargylamines.[8] Stoichiometric amounts of strong bases such as organolithium, organomagnesium, or dialkylzinc[9] reagents are widely used for this type of reaction. Intrinsic drawbacks, however, such as the use of stoichiometric amounts of metal reagents and a separate step for metal acetylide preparation make it difficult to achieve an atom-economical process with high total efficiency. The in situ catalytic generation of metal nucleophiles and their use in carbon–carbon bond-forming reactons[10,11] is currently a major interest in organic synthesis. Thus, the development of an alkynylation of various imines using a catalytic amount of metal is in high demand. However, the addition of organometallic reagents to the C=N double bond of imines has been severely restricted both by the poor electrophilicity of the azomethine carbon and by the tendency of enolizable imines to undergo deprotonation rather than addition.[12] To circumvent these problems, several methods have been explored, for example, activation of the C=N bond either by N-substitution with electron-withdrawing group or by N-coordination to a Lewis acid.[13] Hoveyda and co-workers[14] used a Zr(IV) complex, Li developed a Cu(I) complex of pyridyl-bisoxazoline[15] that was able to promote the direct alkyne-imine addition in toluene and in water. Knochel and co-workers[16] described the addition of functionalized alkynes to enamines catalyzed by Cu(I)–Quinap. Finally, Jiang and Si[17] reported the zinc acetylide addition to reactive ketoimines in the presence of a chiral amino alcohol under mild reaction conditions.[18]

Following our interest in organometallic reactions,[19] we have focused on developing metal-catalyzed practical C–C bond-formation reactions. As such, we report herein an indium-copper bimetallic catalytic system for effective 1,2-addition of phenylacetylene to a variety of aldimines in aquous medium. Initially, we examined the addition reaction of phenylacetylene with 4-methoxybenzylidene-4-methylaniline derived from 4-methoxy benzaldehyde and *p*-toluidine. However, when we reacted 1 equivalent each of phenylacetylene and imine with 0.5 equivalent of indium(III) chloride and copper(I) chloride in water at room temperature, we did not observe the desired addition reaction due to the poor electrophilicity of the azomethine carbon.



Scheme 1

It was found that after addition of 1.2 mol% of $InCl_3$ and 12 mol% of CuCl, the reaction improved dramatically. So, the addition of a terminal alkyne to an imine could proceed smoothly to give the desired propargylamine in excellent yields when 1.2 mol% of $InCl_3$ and 12 mol% of CuCl were used in the reaction mixture (Scheme 1). The reactions proceeded in high yields at room temperature without formation of any side products. However, when the reaction was carried out at an elevated temperature

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Table 1 In–Cu-Catalyzed Addition of Phenylacetylene to Aldimines in Water

Entry	Imine **1**		Propargylamines **3**	Time (h)[a]	Yield (%)[b]
1	**1a**	R^1 = 4-MeOC$_6$H$_4$ R^2 = 4-MeC$_6$H$_4$	**3a**	4	85[25a]
2	**1b**	R^1 = 4-MeC$_6$H$_4$ R^2 = Ph	**3b**	3.5	82[25a]
3	**1c**	R^1 = 4-MeC$_6$H$_4$ R^2 = 4-MeC$_6$H$_4$	**3c**	4	80[25b]
4	**1d**	R^1 = 4-ClC$_6$H$_4$ R^2 = 4-MeC$_6$H$_4$	**3d**	4	78[25a]
5	**1e**	R^1 = 4-ClC$_6$H$_4$ R^2 = 4-MeOC$_6$H$_4$	**3e**	3.5	81[25c]
6	**1f**	R^1 = Ph R^2 = Ph	**3f**	4.5	80[25a]
7	**1g**	R^1 = Ph R^2 = 4-MeOC$_6$H$_5$	**3g**	4	83[25b]
8	**1h**	R^1 = 4-ClC$_6$H$_4$ R^2 = Ph	**3h**	4	80[25a,b]
9	**1i**	R^1 = 4-O$_2$NC$_6$H$_4$ R^2 = Ph	**3i**	3.5	75[25b]
10	**1j**	R^1 = 4-MeC$_6$H$_4$ R^2 = 4-MeC$_6$H$_4$SO$_2$	**3j**	5	65
11	**1k**	R^1 = Ph R^2 = 4-MeC$_6$H$_4$SO$_2$	**3k**	5	60

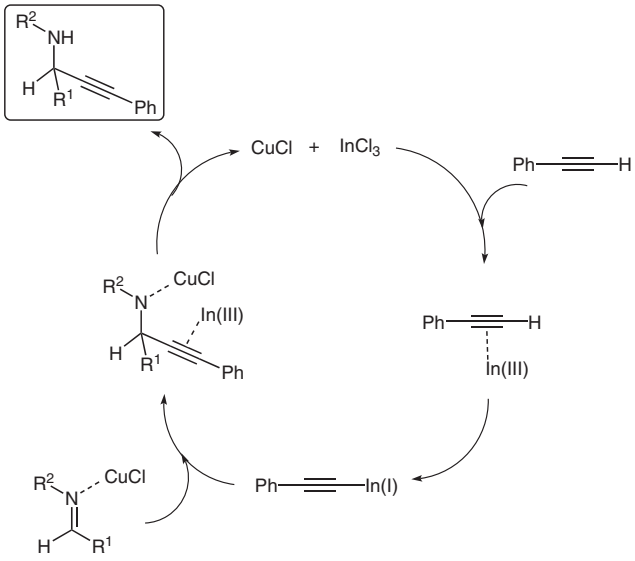
[a] When carried out at r.t., reactions took 9–12 h to reach completion.
[b] Yield refers to pure isolated products, fully characterized by ^{1}H NMR and IR spectroscopy and by comparison with authentic samples.

(40 °C), the reaction time reduced to a great extent without affecting the yield.[20]

This is in contrast to an earlier report,[21] where the indium-mediated alkynylation of aldehydes under thermal conditions gave benzylic alcohols as byproducts along with the homoalkynyl alcohols. During our investigation, it was found that CuCl alone also provided the desired product, albeit in low conversions, whilst addition of 1.2 mol% $InCl_3$ promotes this reaction. The use of 1.2 mol% $InCl_3$ as co-catalyst was necessary for the reaction to go to completion. The conversion was decreased when a smaller amount of CuCl was used. When $PdCl_2$ or $AlCl_3$ was used in place of $InCl_3$ for activation, the reaction did not proceed effectively. Among various bicatalytic systems, it was found that the desired addition product was formed by using $InCl_3$–CuCl in water and without the addition of any base. The reaction was generalized by employing various aldimines, and the results obtained are summarized in Table 1.

When a ketimine derived from acetophenone and aniline was used in the reaction, alkynylation of the aldimine with phenyl acetylene did not occur even after 16 hours of stirring at room temperature. Elevating the temperature to 60 °C and increasing the reaction time further gave no significant improvement and resulted in decomposition of the starting materials. It is relevant to note that, during allylations in aqueous media, many imines are hydrolyzed to the corresponding carbonyl compounds before allylation occurs, thus giving the homoallylic alcohols.[2] Also, it is notable that indium promotes[21] the homocoupling of imines in aqueous media to give the corresponding 1,2-diamines. However, with the In–Cu bimetallic combination, we observed neither the formation of hydrolyzed products nor 1,2-diamines. The results in Table 1 reveal the generality of this methodology in terms of structural variations of the aldimine. In each case, homoalkynylic products were isolated in high yields. Furthermore, electron-donating or -withdrawing groups on the aromatic ring did not seem to affect the reaction significantly, either in the yield of the product or the rate of the reaction. Moreover, a nitro function was not reduced under the reaction conditions. Thus, *p*-nitrobenzaldehyde imine **1i** was successfully propargylated. Usually, a nitro group is sensitive to reduction by metals and is not tolerated under Barbier conditions.[22] Remarkably, the reaction with imines bearing an electron-withdrawing group on the nitrogen atom such as *N*-tosylimines is not so effective, and the corresponding *N*-sulfonyl propargylic amines were obtained in 60–65% yields, but superior to the 43% yield reported by Carreira et al.[23] These experiments demonstrate that the combination of a catalytic amount of indium chloride and a catalytic amount of copper chloride showed catalytic activity, and the best yield of the desired product was obtained without the use of any base.

Although the route for addition of alkynes to imines has not been established experimentally, it is believed that both the metal salts play a crucial role in the transformation. A probable pathway is shown in Scheme 2. It is proposed that an indium alkynylide is formed from phenylacetylene and indium chloride,[24] and this then at-



Scheme 2

tacks the CuCl-activated electrophilic carbon atom of the aldimine. The proposed mechanism is also in agreement with the fact that the reaction is sluggish in the absence of the indium catalyst and also when the amount of CuCl is decreased.

In conclusion, the In–Cu-catalyzed Barbier–Grignard-type reaction of phenylacetylene with aldimines with C–H activation has been developed under aqueous conditions and in excellent yields. This bimetallic catalyzed one-pot synthesis of various propargylamines is simple, high yielding, and environment friendly and will constitute a useful alternative to the commonly accepted procedures. The scope, mechanism, and synthetic application of this reaction is under investigation.

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(20) **General Experimental Procedure for the Addition of Alkynes 1 to Aldimines 2**
Aldimine **1a** (0.225 g, 1 mmol) in a round-bottomed flask was treated with $InCl_3$ (0.0026 g, 1.2 mol%), CuCl (0.120 g, 12 mol%), phenyl acetylene (0.12 g, 1.2 mmol), and H_2O (2 mL). The mixture was then stirred at r.t. for 20 min and then at 40 °C for 4 h. Stirring was continued until no further increase of the reaction product as monitored by ^1H NMR. After completion, the product was extracted with Et_2O or EtOAc (3 × 30 mL). The combined organic layers were washed with H_2O and dried over anhyd Na_2SO_4. Evaporation of the solvent gave a crude product which was subjected to column chromatography on silica gel with EtOAc–hexane (1:6) as eluent to afford exclusively the corresponding propargylamine **3a** in 85% yield.
Conpound **3b**: IR (liquid film): ν_{max} = 3410, 2230, 1615, 1510, 1325, 1185 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.20 (s, 3 H), 4.12 (br, 1 H), 5.21 (s, 1 H), 6.84–7.01 (m, 3 H), 7.18–7.36 (m, 7 H), 7.40–7.48 (m, 2 H), 7.62 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 50.6, 85.2, 89.0, 115.1, 119.2, 123.1, 127.5, 128.3, 128.5, 129.3, 129.6, 132.1, 137.2, 138.2, 146.8. MS: *m/z* = 297 [M^+].

Compound **3h**: mp 185–86 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 3 H), 4.83 (br, 1 H), 5.48 (d, 1 H), 7.18–7.24 (m, 2 H), 7.32–7.48 (m, 8 H), 7.59–7.65 (m, 2 H), 7.76 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 50.1, 85.6, 87.2, 120.0, 127.2, 127.6, 128.2, 128.6, 128.8, 129.0, 129.6, 131.5, 137.4, 137.8, 144.5. MS: *m/z* = 361 [M^+].
Compound **3j**: mp 192–193 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3 H), 2.34 (s, 3 H), 4.82 (br, 1 H), 5.42 (d, 1 H), 7.10–7.31 (m, 9 H), 7.38 (d, *J* = 8.5 Hz, 2 H), 7.68 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 21.7, 50.2, 85.6, 87.0, 121.3, 127.1, 127.8, 128.4, 129.0, 129.2, 129.8, 130.2, 132.0, 136.2, 137.4, 138.6, 145.8. MS: *m/z* = 375 [M^+].
Compound **3k**: mp 197–199 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3 H), 4.80 (br, 1 H), 5.50 (d, 1 H), 7.19–7.42 (m, 10 H), 7.55 (d, *J* = 8.5 Hz, 2 H), 7.70 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 49.8, 85.6, 87.0, 121.2, 127.0, 127.8, 128.4, 128.6, 129.1, 129.2, 129.8, 130.2, 132.1, 136.2, 137.3, 138.6, 145.8. MS: *m/z* = 361 [M^+].

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