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Multicomponent Reactions

Identifying a Highly Active Copper Catalyst for KA^2 Reaction of Aromatic Ketones

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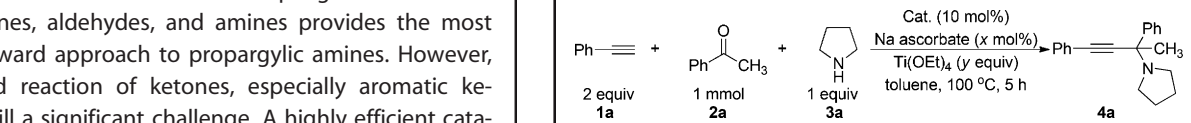
Abstract: The well-established A^3 coupling reaction of terminal alkynes, aldehydes, and amines provides the most straightforward approach to propargylic amines. However, the related reaction of ketones, especially aromatic ketones, is still a significant challenge. A highly efficient catalytic protocol has been developed for the coupling of aromatic ketones with amines and terminal alkynes, in which Cu^I, generated in situ from the reduction of $CuBr_2$ with sodium ascorbate, has been identified as the highly efficient catalyst. Since propargylic amines are versatile synthetic intermediates and important units in pharmaceutical products, such an advance will greatly stimulate research interest involving the previously unavailable propargylic amines.

Propargylic amines are a very important class of compounds in organic and medicinal chemistry. The direct aldehyde–amine–alkyne (A^3) coupling is a well-established means to form secondary propargylic amines.[1–19] However, in contrast, such three-component couplings involving ketones, amines and alkynes (KA^2 reaction) are far from being well developed because of the extremely low reactivity observed for ketones.[20–27] Recently, Larsen and co-workers utilized $CuCl_2$ and $Ti(OEt)_4$ as the catalyst to address the problem for the reaction with alkyl ketones.[28] However, such reactions with aromatic ketones remain a fundamental challenge.[29] Herein, we report a highly efficient Cu^I catalyst, generated in situ from the reduction of $CuBr_2$ with sodium ascorbate, for the coupling of aromatic ketones, amines, and alkynes to form propargylic amines in good to excellent yields with a very broad scope.

Our initial work began with phenylacetylene **1a**, acetophenone **2a**, and pyrrolidine **3a** under the catalysis of CuBr in the presence of 4 Å MS in toluene at 100 °C. Propargylic amine **4a** was afforded only in 52% yield with 48% of **2a** recovered (Table 1, entry 1). When $CuBr_2$ was used as the catalyst, the yield dropped to 39% with 61% of **2a** recovered (Table 1, entry 2). When we used a copper(I) species that was generated in situ from $CuBr_2$ and sodium ascorbate,[30] the yield was improved to 70% with 30% of **2a** recovered (Table 1, entry 3). The yield was further improved to 96% in the presence of sodium ascorbate and $Ti(OEt)_4$ (Table 1, entry 4). Increasing the loading of pyrrolidine improved the yield to 98% (Table 1, entry 5). Reducing the amount of terminal alkyne **1a** led to a lower yield (Table 1, entry 6). When we conducted the reaction at a lower concentration of 0.2 M for **2a**, a quantative yield was obtained (Table 1, entry 7). Thus, **1a** (2 equiv), **2a** (1 equiv), **3a** (1.1 equiv), $CuBr_2$ (10 mol%), sodium ascorbate (20 mol%), and $Ti(OEt)_4$ (2 equiv) in toluene at 100 °C under argon were defined as the optimized reaction conditions for further study.

Table 1. Optimization of the reaction conditions.[a]



Entry	Cat.	x [mol%]	y [equiv]	Yield of **4a** [%][b]	Recovery of **2a** [%][b]
1[c,d]	CuBr	–	–	52	48
2	$CuBr_2$	–	–	39	61
3[c]	$CuBr_2$	20	–	70	30
4	$CuBr_2$	20	2	96	4
5[e]	$CuBr_2$	20	2	98	2
6[e,f]	$CuBr_2$	20	2	89	5
7[e,g]	$CuBr_2$	20	2	quant.	–

[a] Reaction conditions (unless otherwise stated): alkyne (2.0 mmol), ketone (1.0 mmol) and amine (1.0 mmol) at 100 °C in toluene (1 mL); [b] determined by ^{1}H NMR analysis with mesitylene as the internal standard; [c] 4 Å MS (300 mg) was used and the reaction time was 12 h; [d] 5 equivalents of alkyne were used; [e] 1.1 mmol of pyrrolidine were used; [f] 1.5 mmol alkyne were used; [g] the reaction concentration for **2a** was 0.2 M.

With the optimized reaction conditions in hand, we then investigated the scope of the reaction. Firstly, different aromatic ketones were examined (Table 2). Acetophenone **2a** and propiophenone **2b** afforded excellent yields of the propargylic amines **4a** and **4b** (Table 2, entries 1 and 2). Long-chain alkyl aromatic ketone **3c** was also suitable for this reaction, with a yield of 94% (Table 2, entry 3). The cyclohexyl phenyl ketone **2d**, with a larger steric hindrance, also formed propargylic amine **4d** successfully in 95% yield (Table 2, entry 4).

Acetophenone analogues with *p*-Cl, *p*-Ph, *p*-MeO, *m*-Br, *m*-Cl or *o*-Cl substituents all afforded good to excellent yields of the corresponding products (Table 2, entries 5–10). The reaction

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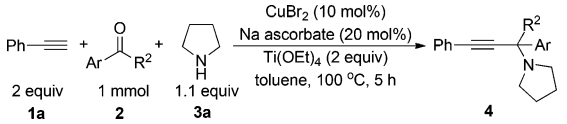
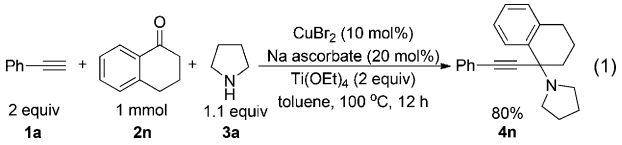
Table 2. The scope of aromatic ketones.[a]



Entry	Ar	R^2	Yield [%][b]
1	Ph	Me	92 (**4a**)
2	Ph	Et	96 (**4b**)
3[c]	Ph	$(CH_2)_{10}Me$	94 (**4c**)
4[c]	Ph	Cy	95 (**4d**)
5	4-ClC_6H_4	Me	91 (**4e**)
6	4-PhC_6H_4	Me	89 (**4f**)
7	4-$MeOC_6H_4$	Me	83 (**4g**)
8	3-BrC_6H_4	Me	82 (**4h**)
9	3-ClC_6H_4	Me	83 (**4i**)
10	2-ClC_6H_4	Me	57 (**4j**)
11	4-NCC_6H_4	Me	86 (**4k**)
12	4-$O_2NC_6H_4$	Me	78 (**4l**)
13[d]	4-$EtO_2CC_6H_4$	Me	77 (**4m**)

[a] Reaction conditions (unless otherwise stated): alkyne (2.0 mmol), ketone (1.0 mmol), amine (1.1 mmol), $CuBr_2$ (10 mol%), Na-ascorbate (20 mol%) and $Ti(OEt)_4$ (2.0 mmol) at 100 °C in toluene (5 mL) for 5 h; [b] isolated product; [c] the reaction time was 8 h; [d] the reaction was conducted at 130 °C for 7 h.

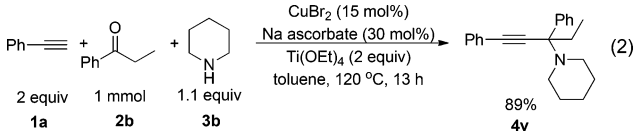
also worked well with cyano, nitro, and ester groups on aromatic ketones (Table 2, entries 11–13). Moreover, cyclic aromatic ketone 1-tetralone **2n** also yielded the corresponding product **4n** in 80% [Eq. (1)].



(1)

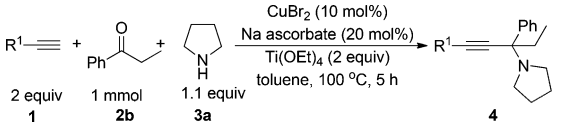
Various differently substituted terminal alkynes **1** were tested in this reaction with acetophenone **2a** (Table 3). Analogues of phenylacetylene **1a** substituted with *p*-Br, *m*-Br and *o*-Cl groups all afforded excellent yields of the corresponding products (Table 3, entries 1–3). The terminal alkyl-substituted alkyne, 1-heptyne **1e**, was also suitable for this reaction, proceeding in 62% yield (Table 3, entry 4). However, alkynes with cyano or nitro groups did not work very well, forming product **4s** in 46% yield (Table 3, entry 5) and product **4t** in 27% yield (Table 3, entry 6), respectively. In addition, ethyl 4-ethynylbenzoate **1h** afforded moderate yield of product **4u** (Table 3, entry 7).

Other cyclic amines, such as piperidine **3b**, can also be applied in this reaction to afford the propargylic amine **4v** in 89% yield [Eq. (2)]. However, acyclic secondary amines, such as dibutylamine, and primary amines, such as *n*-butylamine, were not suitable for this reaction.



(2)

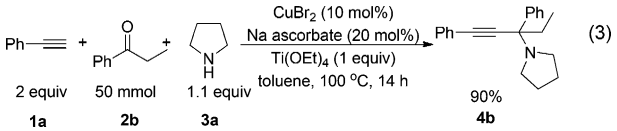
Table 3. The scope of terminal alkynes.[a]



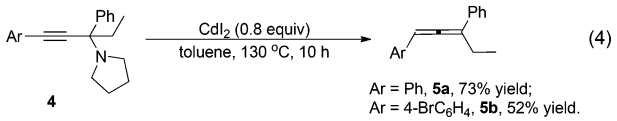
Entry	R^1	Yield [%][b]
1	4-BrC_6H_4 (**1b**)	93 (**4o**)
2	3-BrC_6H_4 (**1c**)	94 (**4p**)
3	2-ClC_6H_4 (**1d**)	92 (**4q**)
4[c]	*n*-C_5H_{11} (**1e**)	85 (**4r**)
5	3-$H_2NC_6H_4$ (**1f**)	46 (**4s**)
6	4-$O_2NC_6H_4$ (**1g**)	27 (**4t**)
7[d]	4-$EtO_2CC_6H_4$ (**1h**)	74 (**4u**)

[a] Reaction conditions (unless otherwise stated): alkyne (2.0 mmol), ketone (1.0 mmol), amine (1.1 mmol), $CuBr_2$ (10 mol%), Na-ascorbate (20 mol%) and $Ti(OEt)_4$ (2.0 mmol) at 100 °C in toluene (5 mL) for 5 h; [b] isolated product; [c] the reaction time was 12 h; [d] the reaction was conducted at 130 °C for 7 h.

The reaction was easily scaled up to 50 mmol scale, affording the propargylic amine **4b** in 90% yield with only 1 equivalent of $Ti(OEt)_4$ required [Eq. (3)]. Furthermore, the propargylic amines could also be easily converted into trisubstituted allenes in the presence of CdI_2 [Eq. (4)].[31]



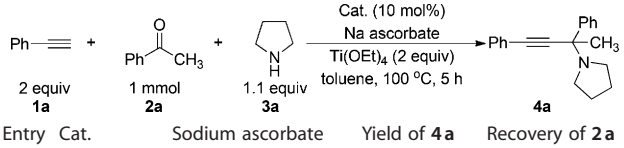
(3)



(4)

We noted that Cu^I that was generated in situ from $CuBr_2$ and sodium ascorbate[30] gave a quantitative yield in the reaction of (Table 4, entry 1). As a comparison, if we used CuBr directly, the propargylic amine **4a** was obtained in only 88%

Table 4. The effect of different copper sources.[a]

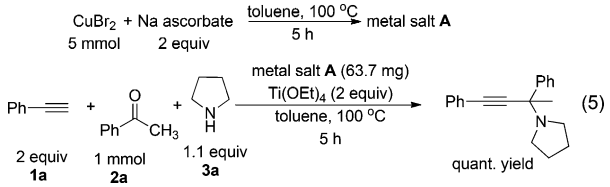


Entry	Cat. (10 mol%)	Sodium ascorbate [mol%]	Yield of **4a** [%][b]	Recovery of **2a** [%][b]
1	$CuBr_2$	20	quant.	–
2	CuBr	–	88	2
3	CuBr	20	98	2.5

[a] Reaction conditions: alkyne (2.0 mmol), ketone (1.0 mmol), amine (1.1 mmol), Na ascorbate (20 mol%) and $Ti(OEt)_4$ (2.0 mmol) at 100 °C in toluene (5 mL); [b] determined by ^1H NMR analysis with mesitylene as the internal standard.

yield (Table 4, entry 2). The yield was improved to 98% with the addition of sodium ascorbate to CuBr, indicating a unique, albeit unidentified, role of sodium ascorbate for this reaction (Table 4, entry 3).

To investigate the nature of the real catalyst in this reaction, we treated 5 mmol of $CuBr_2$ with10 mmol sodium ascorbate in toluene at 100 °C for 5 h. The resulting metal salt **A** was then applied under the standard reaction conditions, affording the corresponding propargylic amine **4a** in quantitative yield [Eq. (5)].



The oxidation state of Cu in metal salt **A** was then studied by X-ray photoelectron spectroscopy (XPS). The XPS detected the Cu $2p_{3/2}$ and Cu $2p_{1/2}$ at 931.4 and 951.6 eV respectively,[32–34] which is in agreement with Cu^{I} or Cu^{0}. The characteristic satellite peak associated with Cu^{II} at 942 eV was not observed (Figure 1 a),[32] excluding the role of Cu^{II}. To further establish the oxidation state of the highly active Cu catalyst, Cu KLL X-ray Auger electron spectroscopy (XAES) was carried out: The characteristic peak of Cu^{I} at a kinetic energy (KE) of 916 eV was detected, indicating that the actual Cu oxidation state in **A** is Cu^{I}, not Cu^{0} (Figure 1 b).[32–34]

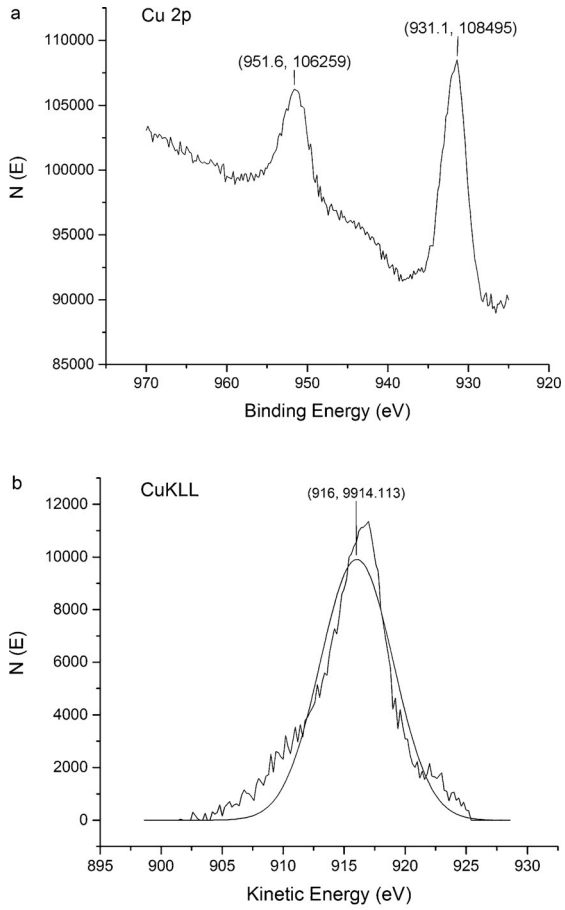


Figure 1. Cu 2p XPS (a) and Cu KLL XAES (b) studies.

In conclusion, we have developed a highly efficient $CuBr_2$/sodium ascorbate-catalyzed coupling of aromatic ketones, amines, and alkynes to form propargylic amines with a very broad scope. This unique protocol has addressed the issue that aromatic ketones cannot easily be applied in KA^2 reactions. Our investigations indicated that $CuBr_2$ was reduced in situ to Cu^{I}, which efficiently catalyzed the reaction. Sodium ascorbate is not only a reducing reagent but also works with the in situ-generated Cu^{I} to catalyze the reaction, although the precise mechanism by which this occurs remains unidentified. The broad substrate scope and high efficiency of the reaction show the potential synthetic utility of this method. Further studies, including an asymmetric version of this reaction, are being conducted in our laboratory.

Experimental Section

Preparation of 1-(2,4-diphenylbut-3-yn-2-yl)pyrrolidine 4a (Table 2, entry 1): To a dried Schlenk tube were added $CuBr_2$ (23.5 mg, 0.1 mmol), sodium ascorbate (39.8 mg, 0.2 mmol), $Ti(OEt)_4$ (456.3 mg, 2 mmol) in toluene (1 mL), **1a** (204.5 mg, 2 mmol)/toluene (2 mL), **2a** (121.7 mg, 1 mmol) in toluene (2 mL), and **3a** (92.0 μL, $d = 0.852\ g\,mL^{-1}$, 78.2 mg, 1.1 mmol) sequentially under Ar atmosphere. The Schlenk tube was then placed in a pre-heated oil bath at 100 °C with stirring for 5 h and the reaction monitored by TLC. After cooling to room temperature, the crude reaction mixture was filtered through a short pad of aluminum oxide (basic, 200–300 mesh) with a sand-core funnel eluted with acetone (20 mL). After evaporation of the solvent, mesitylene (70 μL) was added to the residue for ^1H NMR analysis and the residue was then purified by column chromatography on aluminum oxide (basic, 200–300 mesh; eluent: petroleum ether/ethyl acetate = 500:1 to 300:1) to afford **4a** (254.0 mg, 92%) as an oil: ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.84–7.72$ (m, 2H, Ar–H), 7.57–7.45 (m, 2H, Ar–H), 7.38–7.21 (m, 6H, Ar–H), 2.82–2.71 (m, 2H, NCH_2), 2.67–2.55 (m, 2H, NCH_2), 1.83–1.69 ppm (m, 7H, $2\times CH_2 + CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 145.7$, 131.8, 128.2, 128.0, 127.9, 127.0, 126.4, 123.4, 89.4, 87.2, 62.5, 48.4, 32.4, 23.8 ppm; IR (neat): $\tilde{\nu} = 2964$, 2932, 2873, 2810, 1598, 1488, 1444, 1365, 1261, 1223, 1136, 1105, 1070, 1027, 1000 cm^{-1}; MS (ESI): *m/z*: 276 [$M+H^+$], 205 [$M+H^+$ − pyrrolidine].

Preparation of 1,3-diphenylpenta-1,2-diene 5a [Eq. (4)]: To a dried Schlenk tube was added CdI_2 (293.5 mg, 0.8 mmol) inside a glove box. The Schlenk tube was then taken out and dried under vacuum with a heating gun until the white CdI_2 turned to yellow-green. **4b** (289.8 mg, 1 mmol) and toluene (5 mL) were then added under Ar atmosphere. The Schlenk tube was then equipped with a condenser and placed in a pre-heated oil bath at 130 °C with stirring for 10 h and the reaction monitored by TLC. After cooling to room temperature, the crude reaction mixture was filtered through a short pad of silica gel eluted with ether (20 mL). After evaporation of the solvent, the residue was purified by column chromatography on silica gel (eluent: petroleum ether) to afford **5a**[35] (160.1 mg, 73%) as a liquid: ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.47–7.41$ (m, 2H, Ar-H), 7.36–7.25 (m, 6H, Ar-H), 7.24–7.14 (m, 2H, Ar-

H), 6.56 (t, $J=3.2$ Hz, 1H, CH=), 2.67–2.48 (m, 2H, CH_2), 1.19 ppm (t, $J=7.6$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta=206.2$, 136.2, 134.7, 128.7, 128.4, 126.99, 126.96, 126.7, 126.0, 111.6, 98.6, 23.1, 12.5 ppm; IR (neat): $\tilde{\nu}=3082$, 3059, 3027, 2967, 2933, 2876, 1934, 1747, 1688, 1597, 1492, 1448, 1378, 1317, 1265, 1220, 1180, 1156, 1073, 1029 cm^{-1}; MS (EI) *m/z* (%): 220 (48.51) [M^+], 191 (100).

Acknowledgements

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Keywords: copper · homogeneous catalysis · propargylic amines · synthetic methods · multicomponent reactions

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