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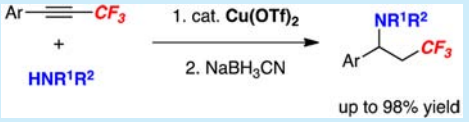
Copper-Catalyzed Intermolecular Hydroamination of Internal Alkynes with Anilines and Amines

Tomoki Ishikawa, Taro Sonehara, Maki Minakawa, and Motoi Kawatsura*

Department of Chemistry, College of Humanities & Sciences, Nihon University, Sakurajosui, Setagaya-ku, Tokyo 156-8550, Japan

Supporting Information

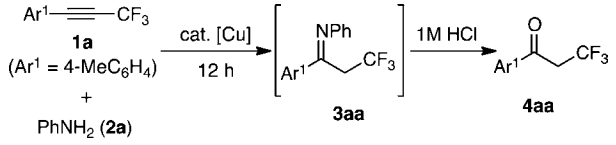
ABSTRACT: The copper-catalyzed regioselective intermolecular hydroamination of the aryl and trifluoromethyl group or electron-withdrawing group substituted internal alkynes with amines has been accomplished. The reaction was effectively catalyzed by the ligand-free $Cu(OTf)_2$ and afforded the intended amine derivatives in good yields after treatment of $NaBH_3CN$.



The addition of amines to alkynes is known as the hydroamination reaction, which is one of the most efficient reactions to construct amine derivatives, and several metal catalysts are employed for this reaction.[1] While there are some reports about the intermolecular hydroamination of alkynes using several transition-metal catalysts, most of them were successful in the reaction of terminal alkynes,[2−10] while there are only limited examples of the internal alkynes.[11−16] For example, it is well-known that the early transition metal or lanthanide complexes catalyze the intermolecular hydroamination of internal alkynes,[11] but there are a few examples of the late-transition-metal-catalyzed reaction of internal alkynes.[12−16] To the best of our knowledge, some late transition-metal catalysts, such as ruthenium,[2] rhodium,[3] iridium,[4] palladium,[5] platinum,[6] silver,[7] gold,[8] and zinc,[9] exhibit a catalyst activity for the reaction of terminal alkynes, but there are only limited examples of the reaction for the internal alkynes with amines. For example, rhodium,[12] nickel,[13] palladium,[14] silver,[15] and gold[16] are known to exhibit a catalyst activity for the reaction of internal alkynes with amines. Furthermore, a rare copper-catalyzed intermolecular hydroamination of terminal alkynes with amines[17] has also been reported, but copper-catalyzed intermolecular hydroamination of internal alkynes with amines is a more difficult process,[18,19] and to realize such a reaction is a challenging topic in synthetic organic chemistry. On the other hand, fluorine-containing organic compounds have attracted much interest in the field of medicinal chemistry and material science,[20] and discovering their new transformation methods is also an important topic in the field of organic synthesis. Based on this background, we recently studied several types of transition-metal-catalyzed reactions of fluorine-containing organic compounds[21] including the aryl and trifluoromethyl group substituted internal alkynes,[22] and during the course of these studies, we found that the intermolecular hydroamination of internal alkynes with amines is effectively catalyzed by a ligand-free copper catalyst.

To realize the intermolecular hydroamination of the aryl and trifluoromethyl group substituted internal alkyne[23] with an amine by a copper catalyst, we examined the reaction of an aryl and trifluoromethyl group substituted alkyne **1a** with aniline (**2a**). As shown in Table 1, the reaction without a catalyst did not give any products (Table 1, entry 1), but we confirmed that some copper salts without any additional ligand exhibited catalytic

Table 1. Copper-Catalyzed Hydroamination of 1a with Aniline (2a)[a]



entry	[Cu] (mol %)	solvent	temp (°C)	yield[b] of **4aa** (%)
1		dioxane	80	0
2	$CuCl_2$ (5)	dioxane	80	76
3	CuCl (5)	dioxane	80	82
4	$CuBr_2$ (5)	dioxane	80	19
5	CuBr (5)	dioxane	80	50
6	CuI (5)	dioxane	80	<2
7	CuF_2 (5)	dioxane	80	22
8	$Cu(OAc)_2$ (5)	dioxane	80	14
9	$Cu(acac)_2$ (5)	dioxane	80	<2
10	CuOTf (5)	dioxane	80	>98
11	$Cu(OTf)_2$ (5)	dioxane	80	>98
12[c]	CuOTf (5)	dioxane	80	42
13[c]	$Cu(OTf)_2$ (5)	dioxane	80	95
14	$Cu(OTf)_2$ (5)	dioxane	40	>98
15	$Cu(OTf)_2$ (10)	THF	40	>98
16	$Cu(OTf)_2$ (10)	THF	25	78
17[d]		THF	40	0
18	$Cu(OTf)_2$ (10)	CH_3CN	40	21
19	$Cu(OTf)_2$ (10)	toluene	40	13

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (1.2 equiv), and [Cu] (5 or 10 mol %) in solvent (0.2 mL, 0.5 M) at the indicated temperature for 12 h, 1 mL of 1 N HCl was added at room temperature, and the mixture was stirred for 15 min. [b]Yields are determined by ^1H and/or ^{19}F NMR analysis of crude materials using an internal standard (trioxane or $C_6H_5CF_3$). [c]Reaction time: 1 h. [d]1 or 10 mol % of TfOH was used without copper salts.

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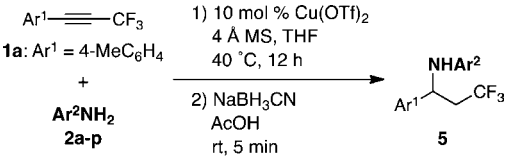
activities and provided the intended aminated product **3aa**.[24] After the initial experimental trials, we confirmed that the imine **3aa** was slightly unstable during the workup process and gradually hydrolyzed to **4aa**; therefore, we treated the reaction mixture with aqueous HCl to convert **3aa** to the ketone **4aa**. The screening with the aim of finding an effective copper catalyst for the intended hydroamination reaction was performed using several copper salts. As the result, several copper salts were found to catalyze the desired reaction to give **4aa** (entries 2−11). In particular, Cu(OTf) and $Cu(OTf)_2$ exhibited high catalyst activities providing a quantitative yield of **4aa** (entries 10 and 11). To compare the catalyst activity of Cu(OTf) and $Cu(OTf)_2$, we examined these reactions for a shortened reaction time (1 h) and confirmed that the $Cu(OTf)_2$ produced a higher yield (entries 12 and 13). We further conducted the Cu(OTf)-catalyzed reaction at a lower temperature (40 °C) by increasing the amount of Cu(OTf) to 10 mol % in dioxane or THF and succeeded in obtaining the product **4aa** without any reduced yield (entries 14 and 15). Unfortunately, the reaction at room temperature resulted in a lower yield (78%) (entry 16), and this result indicated that the reaction requires 40 °C to provide quantitative yields in 12 h. To avoid the possibility that TfOH, which might be produced from Cu(OTf) in situ, catalyzed the hydroamination reaction,[25] we carried out the reaction of **1a** with **2a** in the presence of a catalytic amount of TfOH (1 or 10 mol %) and confirmed that not even a trace amount of the product was formed (entry 17). Furthermore, we examined the $Cu(OTf)_2$-catalyzed reaction in other solvents, such as CH_3CN or toluene, and concluded that THF is the best solvent for this hydroamination reaction (entries 18 and 19).

With the optimal reaction conditions (10 mol % of $Cu(OTf)_2$ in THF at 40 °C for 12 h) in hand, we examined the reaction of **1a** with several aniline derivatives **2a−q**. To prevent the formation of ketones **4** by the hydrolysis of **3** with trace amount of residual H_2O in the reaction mixture and obtain secondary amine derivatives **5**[26] as products, we conducted the copper-catalyzed reaction in the presence of molecular sieves 4 Å, and the reaction mixture was treated with $NaBH_3CN$ in AcOH after 12 h. For example, the reaction of **1a** with **2a** provided the trifluoromethyl group possessing a secondary amine **5aa** in 95% isolated yield (Table 2, entry 1). The reaction with several aniline derivatives, which contained electron-donating or electron-withdrawing groups at the para position on the aromatic ring, smoothly proceeded and gave the desired secondary amines **5ab−ah** in the range of 75−97% yield (entries 2−8). Aniline derivatives **2i** and **2j**, which have a substituent at the *meta* position in the aromatic ring, also gave desired products **5ai** and **5aj** in good yields (entries 9 and 10). We further succeeded in the reactions with **2k−n**, which might be sterically hindered aniline analogues, and obtained the intended products **5ak−an** (entries 11−14). The reaction with 2,6-diisopropylaniline (**2o**) also afforded an aminated product **5ao**, but the isolated yield was slightly low even at 60 °C (entry 15). Unfortunately, the reaction with 2-aminopyridine (**2p**) did not occur which resulted in almost no reaction (entry 16).

We next investigated the $Cu(OTf)_2$-catalyzed hydroamination of several types of aryl group substituted trifluoromethyl groups containing internal alkynes **1b−q** with aniline (**2a**), and the results are summarized in Table 3. All of the reactions of **1b−q** provided the intended amines **5ba−pa** in good yields (80−98%) (Table 2, entries 1−15). We further succeeded in obtaining the 2-thienyl group substituted secondary amine **5qa** in 86% yield (entry 16). These results clearly indicated that this copper

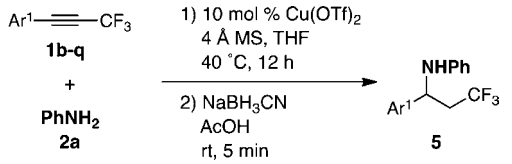
Table 2. $Cu(OTf)_2$-Catalyzed Hydroamination of 1a with Anilines 2a−p[a]



entry	2	time (h)	yield[b] of 5 (%)
1	**2a**: Ar^2 = Ph	12	95 (**5aa**)
2	**2b**: Ar^2 = 4-MeC_6H_4	12	97 (**5ab**)
3	**2c**: Ar^2 = 4-$MeOC_6H_4$	12	94 (**5ac**)
4	**2d**: Ar^2 = 4-HOC_6H_4	12	92 (**5ad**)
5	**2e**: Ar^2 = 4-ClC_6H_4	24	93 (**5ae**)
6	**2f**: Ar^2 = 4-BrC_6H_4	24	89 (**5af**)
7	**2g**: Ar^2 = 4-IC_6H_4	24	82 (**5ag**)
8	**2h**: Ar^2 = 4-$F_3CC_6H_4$	24	75 (**5ah**)
9	**2i**: Ar^2 = 3-$MeOC_6H_4$	12	89 (**5ai**)
10	**2j**: Ar^2 = 3-FC_6H_4	24	93 (**5aj**)
11	**2k**: Ar^2 = 2-$MeOC_6H_4$	12	92 (**5ak**)
12	**2l**: Ar^2 = 2-FC_6H_4	48	84 (**5al**)
13	**2m**: Ar^2 = 1-naphthyl	24	85 (**5am**)
14	**2n**: Ar^2 = mesityl	48	82 (**5an**)
15[c]	**2o**: Ar^2 = 2,6-$^i Pr_2C_6H_3$	24	43 (**5ao**)
16	**2p**: Ar^2 = 2-pyridyl	24	< 2 (**5ap**)

[a]Reaction conditions: **1a** (0.3 mmol), **2** (1.2 equiv), and $Cu(OTf)_2$ (10 mol %) in THF (0.6 mL, 0.5 M) at 40 °C for 12 h, $NaBH_3CN$ (1.5 equiv) in MeOH solution and AcOH (1.5 equiv) were added, and the mixture was stirred at room temperature for 5 min. [b]Yields are isolated products by silica gel chromatography. [c]Reaction was conducted at 60 °C.

Table 3. $Cu(OTf)_2$-Catalyzed Hydroamination of 1a−q with Aniline (2a)[a]



entry	1	yield[b] of 5 (%)
1	**1b**: Ar^1 = Ph	80 (**5ba**)
2	**1c**: Ar^1 = 4-PhC_6H_4	95 (**5ca**)
3	**1d**: Ar^1 = 4-$MeOC_6H_4$	98 (**5da**)
4	**1e**: Ar^1 = 4-FC_6H_4	88 (**5ea**)
5	**1f**: Ar^1 = 4-ClC_6H_4	96 (**5fa**)
6	**1g**: Ar^1 = 4-BrC_6H_4	96 (**5ga**)
7	**1h**: Ar^1 = 4-$F_3CC_6H_4$	91 (**5ha**)
8	**1i**: Ar^1 = 4-$EtO_2CC_6H_4$	87 (**5ia**)
9	**1j**: Ar^1 = 3,5-$Me_2C_6H_3$	88 (**5ja**)
10	**1k**: Ar^1 = 3-MeC_6H_4	88 (**5ka**)
11	**1l**: Ar^1 = 3-Cl-4-MeC_6H_3	92 (**5la**)
12	**1m**: Ar^1 = 3,4-$Cl_2C_6H_3$	95 (**5ma**)
13	**1n**: Ar^1 = 2-$MeOC_6H_4$	95 (**5na**)
14	**1o**: Ar^1 = 2-ClC_6H_4	85 (**5oa**)
15[c]	**1p**: Ar^1 = 1-naphthyl	83 (**5pa**)
16	**1q**: Ar^1 = 2-thienyl	86 (**5qa**)

[a]Reaction conditions: **1** (0.3 mmol), **2a** (1.2 equiv), and $Cu(OTf)_2$ (10 mol %) in THF (0.6 mL, 0.5 M) at 40 °C for 12 h, $NaBH_3CN$ (1.5 equiv) in MeOH solution and AcOH (1.5 equiv) were added, and the mixture was stirred at room temperature for 5 min. [b]Yields are isolated products by silica gel chromatography. [c]Reaction time: 36 h.

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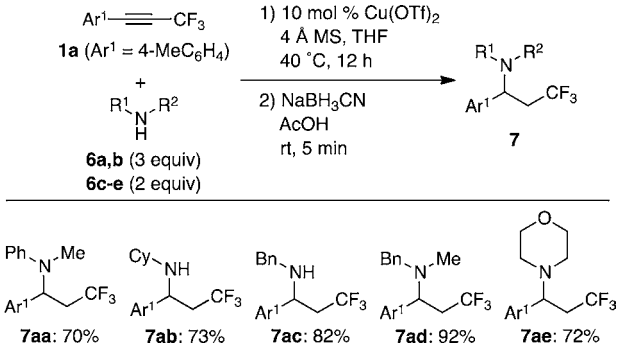
catalyst effectively works for the variety of aryl and trifluoromethyl group substituted unsymmetrical internal alkynes.

We further demonstrated the hydroamination of **1a** with other types of amines (Scheme 1). Although these reactions required

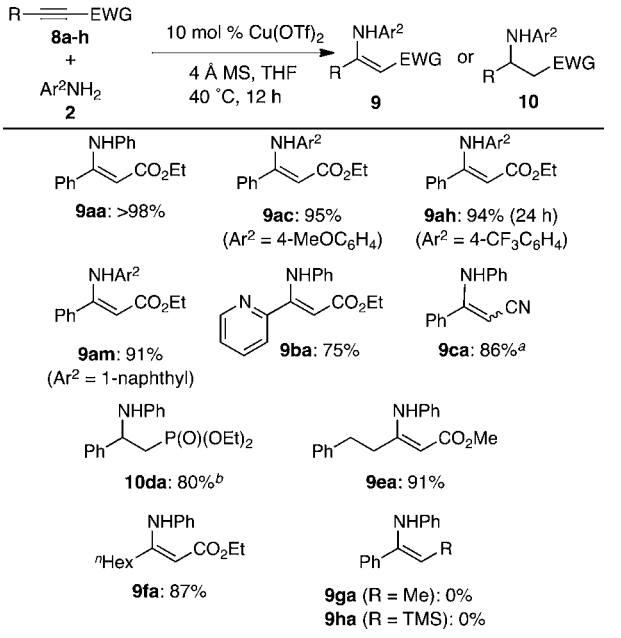
Scheme 1. $Cu(OTf)_2$-Catalyzed Hydroamination of 1a with Aliphatic Amines



an increased amine amount, the expected reaction with *N*-methylaniline (**6a**) proceeded and gave **7aa** in an acceptable yield (70%). Reactions with an aliphatic primary amine, such as **6b** and **6c**, also provided the intended products in 73% and 82% yield, respectively. Furthermore, we examined the reaction of **1a** with an aliphatic secondary amine and succeeded in obtaining the tertiary amines **7ad** (92%) and **7ae** (72%).

We also tried the reaction of other internal alkynes bearing different electron-withdrawing groups than the trifluoromethyl group with aniline analogues, and these results are summarized in Scheme 2. The reaction of ethyl 3-propiolate (**8a**) with aniline

Scheme 2. $Cu(OTf)_2$-Catalyzed Hydroamination of Electoron-Withdrawing Group Substituted Internal Alkynes 8a−h with Anilines



[a]Product was obtained as a mixture of *E*/*Z* stereoisomers (*E*/*Z* = 1/1.25). [b]Product **10da** was obtained after treatment with $NaBH_3CN$/AcOH as the initial product was gradually hydrolyzed to ketone during the workup process.

(**2a**) smoothly proceeded using the $Cu(OTf)_2$ catalyst and afforded the enamine **9aa** in high yield (>98%). The reactions of **8a** with other anilines (**2c**, **2h**, or **2n**) also provided desired product in over 91% yield, and this catalyst system effectively worked for the reaction of the 2-pyridyl group substituted alkyne **8b**, and gave a desired enamine **9ba** in 75% yield. Furthermore, we investigated the reaction of cyano or diethyl phosphonate group substituted internal alkynes (**8c** and **8d**) or alkyl group substituted alkynes (**8e** and **8f**) and confirmed that these reactions proceeded in good yields. However, the reaction of **8g** and **8h**, which possess the methyl or TMS group instead of electron-withdrawing groups, did not provide any products.

In conclusion, we have demonstrated the $Cu(OTf)_2$-catalyzed intermolecular hydroamination of aryl and trifluoromethyl group substituted internal alkynes with amines and succeeded in obtaining the desired amine derivatives after treatment with $NaBH_3CN$. The reaction proceeded with several types of amines and provided the desired product in good yield. Furthermore, we confirmed that $Cu(OTf)_2$ also catalyzed the reaction of other internal alkynes, which have an electron-withdrawing group instead of the trifluoromethyl group, and provided enamines in good to high yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00352.

Experimental procedures and spectral data for the products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kawatsur@chs.nihon-u.ac.jp.

Notes

The authors declare no competing financial interest.

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