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Cobalt-catalyzed alkyne-dihalomethane-amine coupling: an efficient route for propargylamines

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ABSTRACT

A cobalt-catalyzed three-component coupling of terminal alkynes, dihalomethanes, and amines was developed. This method offers an efficient way for propargylamines via the dual activation of C–H and C–halogen bond. The reaction uses cheap CoBr₂ as catalyst and is phosphine ligand-free. A wide range of functional groups were found to tolerate the reaction conditions.

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Transition-metal-catalyzed methods for the direct activation of C-H bonds have emerged as powerful alternatives to more traditional reactions that rely heavily on stoichiometric substrate preactivation.¹ In this context, the three-component coupling of an aldehyde, an alkyne, and an amine (A³ coupling) reaction has received considerable attention in which the terminal alkyne is used as a carbon nucleophilic source via C–H activation.² This excellent reaction also provided an attractive and atom-efficient approach for the synthesis of propargylamines, which are useful building blocks as well as important skeletons of biologically active compounds and synthetic intermediates.³ Recently, Contel and Urriolabeitia reported an efficient gold-catalyzed three-component coupling of alkynes, dihaloalkanes, and amines (AHA coupling), which offered an alternative way for propargylamines via the activation of C-H and C-halogen bond.⁴ In addition, significant progress has been documented for AHA coupling catalyzed by copper,⁵ nano-In₂O₃,⁶ and FeCl₃.⁷ However, comparing to various transition-metal-catalyzed A³ coupling, the catalyst employed for AHA coupling is still limited.

Cobalt-based systems as catalysts for the reactions involving alkynes such as Pauson–Khand reaction,⁸ Vollhardt [2+2+2] cyclization,⁹ and Nicholas reaction¹⁰ have been well studied. Cobalt complexes were also proved to be efficient catalysts for the C–C bond formation via C–H activation.¹¹ However, all these reactions are based on the η^2 interaction between the triple bond of alkynes

* Corresponding author. *E-mail address:* zhoul39@mail.sysu.edu.cn (L. Zhou). with cobalt, the example for the cobalt-catalyzed reaction of terminal alkynyl C–H bond is rare.¹² As a catalytic Grignard type reaction for the transformation of alkynyl C–H bond, herein we disclose an alkyne-dihalomethane–amine coupling with simple CoBr₂ as the catalyst, which affords a series of propargylamines in good yields under mild conditions.

At the outset of this investigation, we employed phenylacetylene, dichloromethane, and diethylamine as substrates by using 10 mol % of CoCl₂ as catalyst in MeCN at 40 °C for 24 h, and the desired propargylamine 4a was generated in 16% yield (Table 1, entry 1). Increasing the reaction temperature increased the yield, giving 55% and 74% yields when the reaction was carried out at 60 °C and 80 °C, respectively (Table 1, entries 2 and 3). Among the various cobalt salts examined, CoBr₂ gave the best results (Table 1, entries 3-6). However decreased yields were observed when $CoBr_2(PPh_3)_2$, CoBr₂(dppe), CoBr₂(dppm), CoBr₂(dppb), and CoCl₂(PPh₃)₂ complexes were employed as the catalysts (Table 1, entries 7-11). Further inspection of the reaction conditions revealed that this reaction proceeded more efficiently in the presence of organic bases such as DBACO and TEA (Table 1, entries 12 and 13), whereas inorganic bases K₂CO₃, NaOAc, and K₃PO₄ were found to be unfavorable (Table 1, entries 14-16). MeCN appeared to be the best choice among the common solvents such as CH₂Cl₂, THF, toluene, DMF, and DMSO (Table 1, entries 17-21).

With the optimized condition in hand, we then tested the scope and limitation of this cobalt-catalyzed three-component coupling of alkynes, dihalomethanes, and amines reaction. As shown in Table 2, dichloromethane, dibromomethane, and diiodomethane





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Table 1Optimization of reaction conditions^a

			Co(II) 10 mol%	/	
Ph-===	+ CH_2Cl_2 +	HNEt ₂	solvent, base, T°C	Ph′	
1a	2a	3a			4a
Entry	Catalyst	Base	Solvent	T/°C	Yield ^b %
1	CoCl ₂	DBU ^c	MeCN	40	16
2	CoCl ₂	DBU	MeCN	60	55
3	CoCl ₂	DBU	MeCN	80	74
4	CoBr ₂	DBU	MeCN	80	90
5	CoI ₂	DBU	MeCN	80	68
6	$Co(OAc)_2$	DBU	MeCN	80	36
7	$CoBr_2(PPh_3)_2$	DBU	MeCN	80	51
8	CoBr ₂ (dppe)	DBU	MeCN	80	44
9	CoBr ₂ (dppm)	DBU	MeCN	80	61
10	CoBr ₂ (dppb)	DBU	MeCN	80	52
11	$CoCl_2(PPh_3)_2$	DBU	MeCN	80	40
12	CoBr ₂	DABCO	O ^d MeCN	80	82
13	CoBr ₂	TEA ^e	MeCN	80	75
14	CoBr ₂	K_2CO_3	MeCN	80	47
15	CoBr ₂	NaOAd	: MeCN	80	40
16	CoBr ₂	K ₃ PO ₄	MeCN	80	25
17	CoBr ₂	DBU	CH ₂ Cl ₂	80	88
18	CoBr ₂	DBU	THF	80	45
19	CoBr ₂	DBU	toluene	80	48
20	CoBr ₂	DBU	DMF	80	60
21	CoBr ₂	DBU	DMSO	80	74

^a All the reactions were conducted by using phenylacetylene **1a** (0.3 mmol), dichloromethane **2a** (0.9 mmol), diethylamine **3a** (0.9 mmol), base (2 equiv) in 2 mL of solvent

^b Yields were determined by ¹H NMR by using MeNO₂ as the internal standard.

^c DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene.

^d DABCO: 1,4-Diazabicyclo[2.2.2]octane.

^e TAE: Triethylamine.

are all good coupling partners for the reaction with phenylacetylene and diethylamine under the present cobalt-catalyzed system (Table 2, entries 1–3). Aromatic alkynes such as 4-ethynyl toluene,



Scheme 1. The reaction of 3-chloro-1-phenyl-1-propyne 5 with piperdine.

4-methoxyphenylacetylene, and 4-fluorophenylacetylene underwent coupling with dichloromethane and diethylamine smoothly to afford propargylamines **4b-d** in good yields (Table 2, entries 4-6). It is worth mentioning that the alkyl terminal alkynes 4-phenyl-1-butyne and 1-hexyne were also suitable substrates for the reaction, generated the propargylamines 4e and 4f in the yields of 74% and 61%, respectively (Table 2, entries 7 and 8). For the three-component coupling of aromatic alkynes, dichloromethane, and piperdine, various functional groups including halogens, ester, methyl, and methoxyl groups present in alkynes were well tolerated during the course of the reaction (Table 2, entries 9-14). Besides. 1-ethynyl naphthalene was also suitable for the reaction. vielding the desired product **4m** in 88% (Table 2, entry 15). We were pleased to find that both cyclic and acyclic secondary amines such as 4-methyl piperdine, pyrrolidine, morpholine, and diisopropylamine were efficiently converted into the corresponding AHA coupling products in moderate to good yields (Table 2, entries 16-19). However, in the cases of primary amines and diphenylamine, no coupling product was identified.

To understand the mechanism of the reaction, 3-chloro-1-phenyl-1-propyne **5** was prepared and reacted with piperdine in the presence of DBU in MeCN at 80 °C, the reaction gave propargylamines **4g** in 91% isolated yield (Scheme 1).

Based on this observation and the literature reports,^{4–7,12,13} a plausible mechanism involving Co(I)-Co(III)-Co(I) catalytic cycle was proposed as shown in Scheme 2. Initially, Co(I) catalyst was generated in situ from Co(II), which might be reduced by alkynes or bases. The insertion of the C–H bond of the terminal alkyne by Co(I) species gave alkynyl-cobalt complex **A**. Oxidative addition

Table 2

Cobalt-catalyzed three-component coupling of alkynes, dihaloalkanes, and amines. ^{a,14}



Entry	Alkyne R	Dihalo methane	Amine	Product	Yield ^b %
1	Ph	CH ₂ Cl ₂	Et ₂ NH	4 a	85
2	Ph	CH_2Br_2	Et ₂ NH	4a	87
3	Ph	CH ₂ I ₂	Et ₂ NH	4a	88
4	p-MeC ₆ H ₄	CH_2Cl_2	Et ₂ NH	4b	88
5	p-MeOC ₆ H ₄	CH_2Cl_2	Et ₂ NH	4c	80
6	$p-FC_6H_4$	CH_2Cl_2	Et ₂ NH	4d	75
7 ^c	PhCH ₂ CH ₂	CH_2Cl_2	Et ₂ NH	4e	74
8 ^d	C ₄ H ₉	CH_2Cl_2	Et ₂ NH	4f	61
9	Ph	CH_2Cl_2	Piperdine	4g	92
10	p-MeOC ₆ H ₄	CH_2Cl_2	Piperdine	4h	87
11	$p-FC_6H_4$	CH ₂ Cl ₂	Piperdine	4i	71
12	$p-ClC_6H_4$	CH_2Cl_2	Piperdine	4j	80
13	p-MeO ₂ CC ₆ H ₄	CH_2Cl_2	Piperdine	4k	77
14	m-MeC ₆ H ₄	CH_2Cl_2	Piperdine	41	89
15	1-Naphthyl	CH_2Cl_2	Piperdine	4m	88
16	Ph	CH_2Cl_2	4-Methyl piperdine	4n	94
17	Ph	CH ₂ Cl ₂	Pyrrolidine	40	60
18	Ph	CH ₂ Cl ₂	Morpholine	4p	68
19	Ph	CH ₂ Cl ₂	ⁱ Pr ₂ NH	4q	42

^a All the reactions were carried out by using 0.5 mmol of terminal alkynes, 3 equiv of dihalomethanes, 3 equiv of amines, and 2 equiv of DBU in the presence of 10 mol % of CoBr₂ in MeCN at 80 °C for 24 h.

^b Isolated vield.

^c Reaction time: 30 h.

 $^{\rm d}\,$ The reaction was performed at 60 $^\circ C$ for 40 h.



Scheme 2. Mechanistic Rationale.

of CH_2Cl_2 to intermediate **A** formed Co(III) species **B**, which subsequently underwent reductive elimination to afford propargylchloride **C** and regenerate the Co(I) catalyst. The reaction of propargylchloride with an amine would give the corresponding propargylamines **4**.

In conclusion, we have developed a method for the synthesis of propargylamines via cobalt-catalyzed three-component coupling of alkynes, dihalomethanes, and amines. A wide range of functional groups were found to tolerate the reaction conditions. Moreover, this reaction uses cheap CoBr₂ as catalyst and is phosphine ligand-free, thus having significant economic advantages and potential application for large scale synthesis.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08. 136.

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- Representative experimental procedure for cobalt-catalyzed three-component coupling of alkynes, dihaloalkanes, and amines. Synthesis of 4a: CoBr₂ (10.9 mg, 10 mol %) and DBU (152 mg, 1 mmol) were suspended in CH3CN (2 mL) in a 5 mL schlenk tube under nitrogen. And then phenylacetylene (51 mg, (126 mg, dichloromethane 1.5 mmol). and diethylamine 0.5 mmol). (109.5 mg, 1.5 mmol) were added via syringe. The resulting solution was stirred at 80 °C for 24 h. After cooling to room temperature, the resulting mixture was filtered through a short path of silica gel, eluting with dichloromethane. The volatile compounds were removed in vacuo and the residue was purified by column chromatography (SiO2, hexane/ethyl acetate = 10:1) to give **4a** as a colourless oil (79.5 mg, 85%).¹H NMR (300 MHz, CDCl₃) δ 7.43 -7.40 (m, 2H), 7.30-7.25 (m, 3H), 3.68 (s, 2H), 2.68 (q, J = 7.2 Hz, 4H), 1.16 (t, J = 7.2 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃): δ = 131.8, 128.3, 128.0, 123.5, 85.3, 84.5, 47.6, 41.8, 12.9 ppm.