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$Zn(OAc)_2{\cdot}2H_2O$: a versatile catalyst for the one-pot synthesis of propargylamines☆

Enugala Ramu,[a] Ravi Varala,[b] Nuvula Sreelatha[a] and Srinivas R. Adapa[a,*]

[a]*Indian Institute of Chemical Technology, Hyderabad, India*
[b]*Lab No: 202, Dept. of Quimica, Universidade Nova de Lisboa, (FCT/UNL), Caparica 2829-516, Portugal*

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Abstract—An inexpensive and readily available catalyst, $Zn(OAc)_2{\cdot}2H_2O$ is successfully evaluated for effective one-pot synthesis of propargylamines with moderate to excellent yields for most of the substrates screened, without the need of base, co-catalyst or additive in the presence of air.

Transition metal-catalyzed multi-component reactions (MCR) are a powerful synthetic tool to access complex structures from simple precursors via a one-pot procedure and exhibit high atom economy and selectivity in general.[1] For example, improved syntheses of propargylamines via the activation of a terminal alkyne C–H bond using metal-catalyzed multi-component strategies remain of continued interest to organic chemists in terms of operational simplicity and cost effectiveness. Being important building blocks and versatile synthons, propargylamines are highly featured in organic syntheses of many biologically active nitrogen containing compounds such as conformationally restricted peptide isosteres, oxotremorine analogues, allylamines, oxazoles, pyrroles and β-lactams.[2] Classical methods for the preparation of propargylamines have usually exploited the relatively high acidity of a terminal acetylenic C–H bond to form alkynyl-metal reagents by reaction with strong bases such as butyllithium,[3a] organomagnesium compounds[3b] or LDA[4] in a separate step. Unfortunately, these reagents are required in stoichiometric quantities, are highly moisture sensitive and require strictly controlled reaction conditions.

In recent years, enormous progress has been made in expanding the scope of the direct addition of alkynes to carbon–nitrogen double bonds either preformed (imines) or in one-pot (from aldehyde and amine) by employing various transition metal catalysts such as copper,[5] silver,[6] iridium,[7] gold,[8] zinc,[9] zirconium[10] and rhenium[11] for generation of metal acetylides under mild reaction conditions for propargylamine synthesis. Although several methods for construction of such units have been reported,[5–11] some required expensive Au,[8] Ag,[6] zirconium,[10] iridium[7] or rhenium[11] as catalyst, while some were limited to only one kind of aldehyde (aromatic[6] or aliphatic[8]), or an aromatic aldehyde and primary amine in the presence of $RuCl_3$ as a cocatalyst,[5b] or requirement of strictly anhydrous conditions. The other systems are limited in the addition of propargylamines to aldimines.[7,9–11]

To date, a truly efficient one-pot, three-component coupling of an aldehyde, an alkyne and an amine (A^3 coupling) using zinc salts in a catalytic amount, without any additive or base or the absence of inert conditions has not been explored.[9] The first zinc-catalyzed addition of alkynes to a C=N electrophile was reported by Carriera et al. in which they treated alkynes with nitrones[9a,c] (10 mol % $Zn(OTf)_2$, 25 mol % Hünig's base in DCM) or *N*-acyliminium ions[9g] (1.2 equiv $Zn(OTf)_2$, 1.32 equiv Et_3N, 1.32 equiv TMPDA in toluene) at room temperature under strictly anhydrous conditions. Vallee et al.[9b] employed substoichiometric amounts of Et_2Zn (0.2 equiv) for the addition of alkynes to nitrones in the absence of any base under N_2. In contrast, Jiang et al.[9f] used $ZnCl_2$ (1 mmol), Et_3N (1.2 equiv) and TMSCl (1.5 equiv) as activator for the addition of

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* Corresponding author. Tel.: +91 40 27193169; fax: +91 40 27160921; e-mail: rvarala_iict@yahoo.co.in

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phenyl acetylene to imines at 60 °C in toluene as solvent under an argon atmosphere. Kim et al.[9e] have employed $ZnBr_2$ (1 mmol) and Hünig's base (1 mmol) in acetonitrile at 50–60 °C for the addition of aryl acetylenes to *N*-tosylimines to yield the corresponding propargylic amines. Very recently, Bolm et al.[9d] reported a one-pot synthesis of *N*-aryl propargylic amines using Me_2Zn (3.5 equiv) in anhydrous toluene without any additive or base at room temperature for 2–4 days under an inert atmosphere.

In the context of the above important contributions utilizing zinc mediated chemistry[9] for the synthesis of propargylic amines, and being interested in exploring novel synthetic strategies for C–C and C-hetero bond formations,[12] herein we describe $Zn(OAc)_2{\cdot}2H_2O$ as an inexpensive, high yielding catalyst for the synthesis of propargylamines without any activator or base under aerobic conditions.

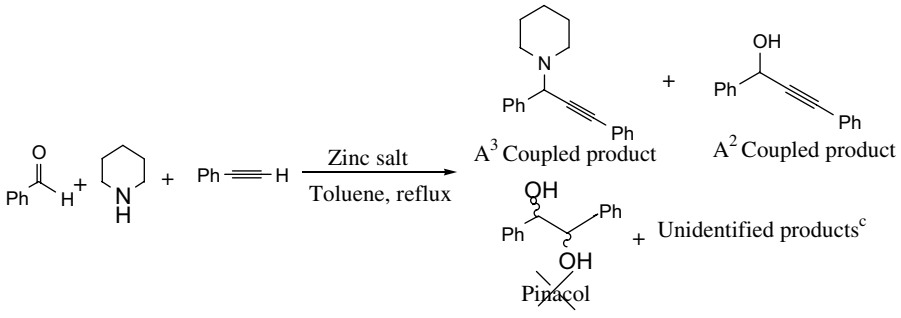
Initially, a series of zinc salts (15 mol % as standard) were examined (Table 1) in toluene for the effective A^3 coupling of benzaldehyde, piperidine and phenylacetylene in the presence and absence of Et_3N. From these studies, $Zn(OAc)_2{\cdot}2H_2O$ (entry 9) was found to be a superior catalyst.

Despite the absence of Et_3N, the corresponding A^3 coupled product was obtained with 96% conversion (almost comparable with the conversion of 98%, when Et_3N was used). The A^3 coupled product was fully characterized by IR, $^1H/^{13}C$ NMR and mass spectral analyses. $Zn(OAc)_2{\cdot}2H_2O$ alone in toluene generally does not dissolve at ambient temperature. In preheated reflux temperatures of toluene with catalyst also did not show any homogeneous reaction mixture even after stirring for several hours. Whereas, when the model reaction was kept under preheated reflux conditions with the catalyst (15 mol %) in toluene, it formed a homogeneous mixture, thereby forming the adduct in the given time.

To the best of our knowledge, this is the first example of a truly catalytic synthesis of propargylamines using zinc salts. Surprisingly, a number of the other zinc salts surveyed did not promote the reaction (entries 2–7, 10–12), and instead gave unidentified by-products. As can be seen from Table 1, entry 1 ($ZnBr_2$) and entry 8 ($Zn(OTf)_2$) gave the A^2 coupled products in the presence of Et_3N and in the absence of base resulted in the desired A^3 coupled products in 10 h (92% and 94%, respectively).

Interestingly, entry 13 (ZnO) gave the A^2 coupled product in the absence of base. When $Zn(CN)_2$ (entry 14) was employed as catalyst a mixture of A^2 and A^3 coupled products was formed in a ratio of 3:1. No pinacol coupled product was observed. In the absence of catalyst, there was no reaction at all, even after stirring for 2 days

Table 1. Comparison of various Zn salts for the A^3 coupling for the model reaction using benzaldehyde, piperidine and phenylacetylene[a]



Entry	Catalyst	Time (h)	Conversions[b] (%)	
			With Et_3N (1.2 equiv)	Without Et_3N
1	$ZnBr_2$	10	**A^2**	**A^3/92**
2[c]	$ZnCl_2$	12	0	0
3[c]	$Zn(NO_3)_2$	12	0	0
4[c]	Zn mont	12	0	0
5[c]	Zn-Hydroxyapatite	12	0	0
6[c]	Zn metal (granulated)	12	0	0
7[c]	Zn dust	12	0	0
8	$Zn(OTf)_2$	10	**A^2**	**A^3/94**
9	**$Zn(OAc)_2{\cdot}2H_2O$**	7	**A^3/98**	**A^3/96**
10[c]	$Zn(L\text{-proline})_2$	12	0	0
11[c]	$ZnSO_4$	12	0	0
12[c]	$ZnCO_3$	12	0	0
13	ZnO	12	0[c]	**A^2**
14	$Zn(CN)_2$	12	0	A^2(73):A^3(27)
15	—	48	0	0

[a] Ratio of catalyst/benzaldehyde/piperidine/phenylacetylene = 0.15:1.0:1.3:1.5 and 3 mL of toluene, reflux.
[b] Conversions were determined by ^1H NMR of the crude reaction mixture.
[c] Various unidentified products were observed.

(entry 15). Having found the most effective catalyst ($Zn(OAc)_2{\cdot}2H_2O$ in terms of yield, cost effectiveness and reaction time), we address next optimization in terms of loading and base screening (Table 2). In the optimal process, 10 mol % of $Zn(OAc)_2{\cdot}2H_2O$ generated the desired A^3 product in 96% conversion (Table 2, entry 7). Below 10 mol % of catalyst resulted in decreased conversions (entries 8 and 9).

Use of a substoichiometric (20 mol %) amount of Et_3N as additive gave only a small increase in the yield (entry 2). Replacement of Et_3N with other bases such as DIPEA, DBU, DABCO, pyridine, Na_2CO_3, K_2CO_3, Cs_2CO_3, $CsOH{\cdot}H_2O$, NaOAc and K_3PO_4 (Table 2, entries 10–19), had no influence on the process. When DIPEA (entry 10) or DABCO (entry 12) were employed, formation of the A^2 coupled product was observed.

The screening of a range of solvents (10 mol % $Zn(OAc)_2{\cdot}2H_2O$, no base, reflux) show that the solvent had a strong effect (Table 3). From Table 3, we can see that in all the solvents (entries 1–14), no desired product was obtained at room temperature even after stirring for 24 h. The reactions performed in THF (entry 5) and $CHCl_3$ (entry 10) under reflux were successful, albeit, with slightly lower yields compared to toluene (entry 4). When water was used as the solvent (entry 3), the conversion was low (10%), whereas the other solvents failed to give A^3 product. Under solvent-free conditions, heating the reaction mixture to 120 °C did not lead to the desired product.

Next, we hoped to extend the range of solvents to also polyethylene glycol and ionic liquids. Interestingly, when we performed the reaction in PEG-600 at 120 °C for 7 h, we observed formation of a significant amount of the desired product (85%). The product was extracted from the reaction mixture by the addition of ether and the recovered PEG-600 was reused without any pretreatment, at least three times with only a slight decrease in conversion (entry 13). The A^3 coupling reaction in $[Bmim][BF_4]$ gave a 78% conversion in 7 h. The recyclability of $[Bmim][BF_4]$ in the A^3 coupling reaction was examined. It is noteworthy that the catalyst exhibited comparable activity even after the third cycle as shown in Table 3 (entry 14).

Table 2. Optimization of the catalyst loading and base screening

Entry	Catalyst loading	Base	Conversion[a] (%)
1	15 mol %	Et_3N(1.2 equiv)	98
2	10 mol %	Et_3N(0.2 equiv)	98
3	1.0 equiv	No base	99
4	0.5 equiv	No base	98
5	30 mol %	No base	96
6	15 mol %	No base	96
7	**10 mol %**	**No base**	**96**
8	5 mol %	No base	89
9	2 mol %	No base	52
10[b]	10 mol %	DIPEA(1.2 equiv)	0
11	10 mol %	DBU(1.2 equiv)	0
12[b]	10 mol %	DABCO(1.2 equiv)	0
13	10 mol %	Pyridine(1.2 equiv)	0
14	10 mol %	Na_2CO_3(1.2 equiv)	0
15	10 mol %	K_2CO_3(1.2 equiv)	0
16	10 mol %	Cs_2CO_3(1.2 equiv)	0
17	10 mol %	$CsOHH_2O$(1.2 equiv)	0
18	10 mol %	NaOAc(1.2 equiv)	0
19	10 mol %	K_3PO_4(1.2 equiv)	0

[a] Determined by ^1H NMR spectroscopy prior to chromatography.
[b] A^2 coupling product.

Table 3. Solvent studies under different parameters for the model reaction catalyzed by $Zn(OAc)_2{\cdot}2H_2O$

Entry	Solvent	Time (h)/ conversion (%)[a]		Time (h)/ conversion (%)[a]
		rt[b]	Sonication[c]	Reflux
1[d]	MeOH	24/0	G[g]	12/0
2[d]	1,4-Dioxane	24/0	G	12/0
3	H_2O	24/0	G	12/10
4	Toluene	24/0	**0**	**07/96(92)**[f]**/(89)**[j]
5	THF	24/0	G	10/ 92
6[d]	DMF	24/0	G	12/0
7[d]	CH_3CN	24/0	G	12/0
8	DCM	24/0	G	12/Trace
9[d]	DMSO	24/0	G	12/0
10	$CHCl_3$	24/0	G	12/89
11[d]	AcOH	24/0	G	12/0
12	Neat	24/0	G	12/0[e]
13	PEG-600	24/0	G	07/85, 80[h]
14	$[Bmim][BF_4]$	24/0	G	07/78,74[i]

[a] Conversions based on ^1H NMR analysis.
[b] rt = Room temperature.
[c] Under sonication at 80 °C [Elmasonic S 40H].
[d] Unidentified complex mixture.
[e] Reaction run at 120 °C.
[f] Isolated yield in parentheses.
[g] G = Reaction not performed.
[h] Yield after 3rd recycle.
[i] Yield after 3rd recycle.
[j] Isolated yield in a 50 mmol scale reaction.

Intrigued by these observations, we also performed the reaction under ultrasonication in a preheated water bath at 80 °C for 30 min (entry 4), however no product formation was observed. When acetic acid (Table 3, entry 11) was employed as solvent, there was no reaction.

In order to confirm whether reflux conditions were needed for effective A^3 coupling, we carried out several parallel experiments. The reaction did not proceed at temperatures of −78 °C, 0 °C, −5 °C, 60 °C and 90 °C, even after being stirred for 12 h.

When the test reaction was conducted under inert conditions using either argon or nitrogen, the yields were comparable to those obtained under aerobic conditions. To demonstrate the scope of this protocol, the model reaction was performed on a 50 mmol scale (Table 3, entry 4). The reaction was complete in 7 h affording the corresponding product in 89% isolated yield.

After reaction establishing parameters for the model reaction, we then proceeded to apply the catalytic

Table 4. $Zn(OAc)_2{\cdot}2H_2O$-catalyzed synthesis of propargylamines

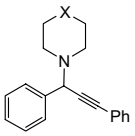
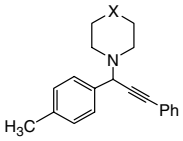
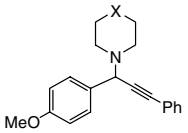
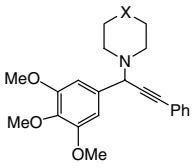
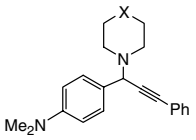
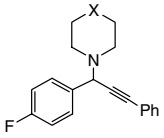
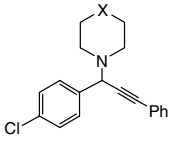
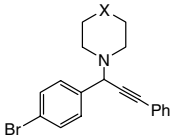
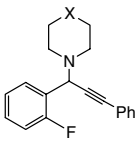
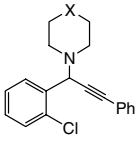
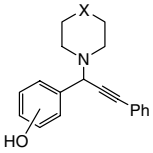
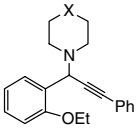
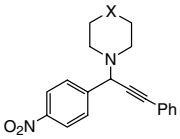
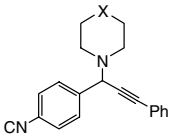
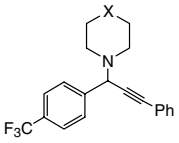
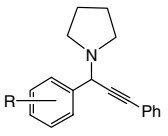
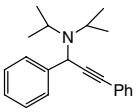
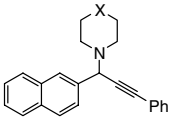
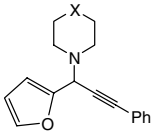
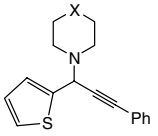
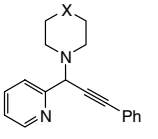
Entry[Ref.]	Product	Time (h)	Yield[a] (%)
1[5a] X = CH_2		7	92
2[5a] X = O		7	96
3 X = S		7	94
4 X = NH		7	85
5 X = N–CH_3		7	89
6 X = N–CH_2Ph		7	86
7 X = N–Pyridyl		7	80
8[6a] X = CH_2		8	88
9[5a] X = O		8	86
10[5d] X = CH_2		8	89
11[5a] X = O		8	86
12 X = N–CH_3		8	84
13 X = N–CH_2Ph		8	88
14 X = CH_2		8	86
15 X = O		8	90
16 X = CH_2		8	85
17 X = O		8	78
18 X = N–CH_2Ph		8	82
19 X = CH_2		7	96
20 X = O		7	98
21[5d] X = CH_2		7	98
22[5a] X = O		7	96
23 X = N–CH_2Ph		7	89
24[5d] X = CH_2		10	96
25[5a] X = O		14	88
26 X = N–CH_3		14	85
27 X = N–CH_2Ph		14	84
28 X = CH_2		7	94
29[5a] X = O		7	92
30 X = CH_2		7	92
31[5a] X = O		7	98

Table 4 (*continued*)

Entry[Ref.]	Product	Time (h)	Yield[a] (%)
32 *o*-OH, X = CH_2		9	76
33 *m*-OH, X = O		9	72
34 *o*-OH, X = N–CH_2Ph		9	69
35 *m*-OH, X = N–CH_2Ph		9	89
36 X = CH_2		7	93
37 X = O		7	91
38 X = CH_2		12	56
39[5a] X = O		12	72
40 X = CH_2		12	88
41 X = O		12	93
42[8b] X = CH_2		12	85
43 X = O		12	88
44[5a] R = H		7	92
45 R = *p*-CH_3		7	95
46 R = *p*-OCH_3		7	98
47 R = 3,4,5-tri-OMe		7	88
48 R = *p*-Cl		7	96
49 R = *p*-F		7	98
50 R = *p*-Br		7	88
51 R = *p*-CF_3		7	82
52 R = *o*-OH		7	85
53 Naphthyl		7	90
54[5a]		8	92
55[5d] X = CH_2		10	89
56[5a] X = O		12	94
57 X = CH_2		12	84
58[5a] X = O		12	87
59 X = CH_2		12	92
60[5d] X = O		12	96
61 X = CH_2		24	0
62 X = O		24	0

(*continued on next page*)

Table 4 (*continued*)

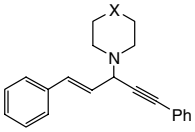
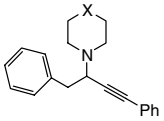
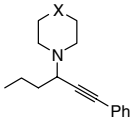
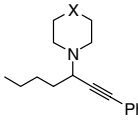
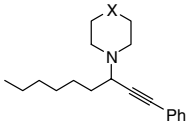
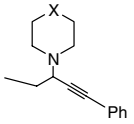
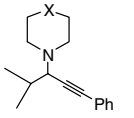
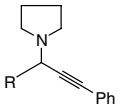
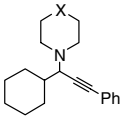
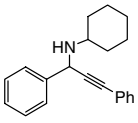
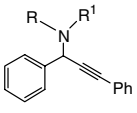
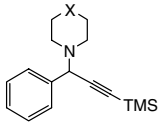
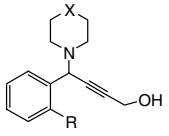
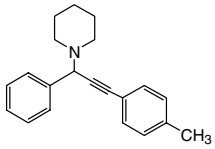
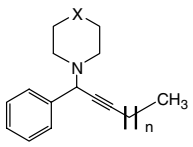
Entry[Ref.]	Product	Time (h)	Yield[a] (%)
63 X = CH_2		12	82
64 X = O		12	90
65 X = CH_2		12	62
66 X = O		12	65
67 X = CH_2		7	98
68[5a] X = O		7	99
69 X = S		7	95
70 X = NH		7	92
71 X = N–CH_3		7	89
72 X = NCH_2Ph		7	86
73 X = *N*,*N*-Diisopropyl		7	98
74 X = CH_2		7	95
75 X = O		7	98
76 X = N–CH_3		7	92
77[5d] X = CH_2		8	95
78 X = O		8	92
79 X = CH_2		8	84
80 X = O		8	82
81 X = CH_2		8	88
82 X = O		8	82
83 R = *n*-butyl		7	98
84 R = *n*-pentyl		7	92
85 R = *n*-heptyl		7	95
86 R = *n*-propyl		7	89
87 R = *i*-butyl		7	91
88 R = cyclohexyl		7	98
89[6a] X = CH_2		7	99
90[5a] X = O		7	95
91		12	68
92 R = R^1 = allyl		12	0
93 R = CH_2Ph; R^1 = H		12	0
94 R = R^1 = CH_2Ph		12	0
95 R = R^1 = CH_3		12	0
96 R = H; R^1 = Ph		12	0

Table 4 (*continued*)

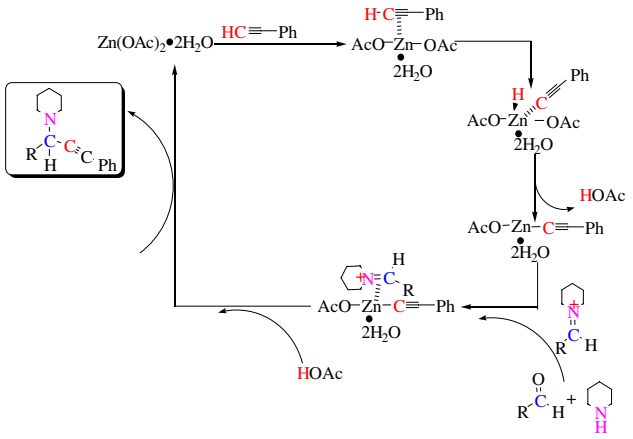
Entry[Ref.]	Product	Time (h)	Yield[a] (%)
97 X = CH_2		8	86
98[5a] X = O		9	82
99 X = CH_2; R = H		8	90
100 X = O; R = H		8	88
101 X = CH_2; R = OH		8	84
102		7	92
103[5d] *n* = 4; X = CH_2		7	89
104[5a] *n* = 4; X = O		7	90
105 *n* = 7; X = O		7	78
106 *n* = 7; X = CH_2		7	85
107 *n* = 5; X = CH_2		7	94
108 *n* = 5; X = O		7	95

[a] Isolated yields.

system (10 mol %, toluene under reflux) for the reaction of various secondary amines, aldehydes and phenylacetylene as shown in Table 4 (See Supplementary data).[13] A wide range of structurally diverse functionalized piperazines tolerated the reaction conditions (entries 1–7). The electronic nature of the substituents on the aryl aldehydes had a pronounced effect on the overall efficiency of the process.

Substrates bearing electron-rich substitutents (entries 8–37) all gave good conversions, whereas aryl aldehydes possessing electron-withdrawing groups (entries 38–43) required longer times. Halogenated substituted aldehydes (entries 19–31) gave the corresponding A^3 coupled products in almost quantitative yields.

2- and 3-Hydroxy benzaldehydes also furnished the corresponding A^3 coupled products under the optimized conditions, whereas earlier literature reported failures (entries 32–35). 2-Naphthaldehyde also produced corresponding addition products in good yields (entries 53, 55–56). Heteroaromatic aldehydes such as furfuraldehyde and thiophene 2-carboxaldehyde gave the corresponding A^3 products in good yields (entries 57–60). Interestingly, pyridine 2-carboxaldehyde did not give the addition product (entries 61–62). We have also successfully employed different aliphatic aldehydes in



Scheme 1.

our catalytic system (entries 67–90). Trimerization of aldehydes was never observed using $Zn(OAc)_2{\cdot}2H_2O$ as catalyst, while it was a major limitation of the A^3 coupling using Au[8] and Cu[5]. Diisopropylamine and cyclohexylamine were also tolerated (entries 54, 73 and 91) under the present conditions. Diallylamine, benzylamine, dibenzylamine, dimethylamine and aniline (entries 92–96) were not tolerated under the optimized conditions. Other acetylenic substrates such as trimethylsilyl acetylene, propargyl alcohol and simple aliphatic alkynes also underwent the reaction (entries 97–108). This indicates that the $Zn(OAc)_2{\cdot}2H_2O$ is also compatible with both aromatic and aliphatic alkynes as well.

A tentative mechanism is proposed involving the Lewis acid (Zn(II)) assisted proton transfer with the alkyne to form the corresponding zinc acetylide (Scheme 1). The zinc acetylide intermediate thus generated reacts with the iminium ion generated in situ from an aldehyde and secondary amine to give the corresponding propargylamine and regenerate the Zn(II) catalyst for further reaction.

In conclusion, we have successfully developed an efficient protocol using $Zn(OAc)_2{\cdot}2H_2O$ as catalyst for the one-pot synthesis of diverse propargylamines for the first time in moderate to excellent yields. Notable features of the protocol are: clean and simple reaction conditions; use of a readily available and inexpensive catalyst; tolerability of various functional groups and aerobic conditions. We believe that this protocol will be a valuable addition to modern synthetic methodologies for one-pot syntheses of propargylamines. An asymmetric version of the same transformation is currently under investigation in our lab.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.196.

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13. General procedure. A stirred solution of alkyne (1.5 mmol), $Zn(OAc)_2{\cdot}2H_2O$ (0.1 mmol), aldehyde (1.0 mmol) and amine (1.3 mmol) in toluene (3 mL) was taken in a round-bottomed flask and inserted into a preheated oil bath (120 °C bath temperature). After completion of the reaction (as monitored by TLC), the reaction mixture was diluted with aq NH_4Cl (2×5 mL) and stirred for 5 min. The aqueous layers were extracted with diethyl ether (2×10 mL), dried over Na_2SO_4 and concentrated to give the crude product which was further purified by column chromatography on silica gel (ethyl acetate/hexane = 1:6) to afford the corresponding pure propargylamine. Representative examples. Table 4, entry 1: IR (KBr): 3055, 2930, 2747, 1598, 1486, 1443, 1318, 1152, 757, 693 cm^{-1}: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.38$–1.50 (m, 2H), 1.52–1.66 (m, 4H), 2.52–2.62 (m, 4H), 4.80 (s, 1H), 7.26–7.38 (m, 6H), 7.48–7.54 (m, 2H), 7.60–7.64 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 24.3$, 26.1, 50.6, 62.3, 86.0, 87.8, 123.2, 127.3, 127.9, 128.2, 128.4, 131.7, 138.5; MS (EI) $m/z = 275$, 274, 198, 191, 115.Table 4, entry 89: IR (Neat): 3054, 2930, 2852, 2751, 1598, 1489, 1443, 1318, 1156, 1103, 890, 755, 691; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$–1.10 (m, 2H), 1.11–1.34 (m, 3H), 1.36–1.49 (m, 2H), 1.49–1.69 (m, 6H), 1.71–1.82 (m, 2H), 1.98–2.15 (m, 2H), 2.32–2.44 (m, 2H), 2.58–2.66 (m, 2H), 3.11 (d, $J = 9.8$ Hz, 1H), 7.25–7.31 (m, 3H), 7.41–7.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 24.9$, 26.3, 26.5, 27.0, 30.6, 31.6, 39.8, 64.6, 86.3, 88.0, 124.0, 127.8, 128.4, 132.0; MS (FAB) $m/z = 280$ (M^++H), 241, 198, 141, 115.