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Enaminone ligand-assisted homo- and cross-coupling of terminal alkynes under mild conditions

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ABSTRACT

Copper-catalyzed oxidative coupling reactions of terminal alkynes have been performed at room temperature by using enaminone as effective ligand. Both symmetrical and unsymmetrical 1,3-diynes bearing various functional groups have been synthesized in moderate to excellent yields via homo- and crosscoupling reactions.

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Conjugated 1,3-diynes are widely employed starting materials in organic synthesis, including the synthesis of natural product,¹⁻³ polymer materials,⁴⁻⁶ pharmaceuticals,^{7,8} and many other functional organic molecules.^{9,10} The dimerization coupling of two terminal alkynes is the most straightforward method for the synthesis of 1,3-diynes.¹¹⁻¹⁴ Numerous efforts have been devoted to discovering facile and simple catalyst systems for this kind of reactions since the reports by Glaser¹⁵ and Hay.¹⁶ A general feature of most reports on this oxidative coupling transformation is the utilization of transition metal catalyst or co-catalysts such as Pd/Cu,¹⁷⁻²¹ Ag/ Cu,²² Ni/Cu,^{23,24} and Cu/Ti,²⁵ and most of these reported catalytic systems provide target diyne products with satisfactory results.

Among the efforts made for establishing economical approaches of 1,3-diyne, reaction with copper as the only catalyst has drawn considerable attention owing to the low cost of copper catalysts and excellent reaction efficiency from these catalyzed reactions.²⁶⁻³⁴ Most of the copper-catalyzed coupling protocols are performed either at high temperature without ligand or under mild reaction conditions with the assistance of a ligand. In several cases, stoichiometric amount of copper was required. Therefore, development of more efficient and atom economical approaches via searching easily available and highly effective ligand remains as desirable work. Enaminone derivatives that contain flexible *N*-and *O*-chelating sites have been demonstrated as excellent ligands in transition metal-catalyzed coupling reactions by this and other groups, including Ullmann-type C–N coupling reaction,³⁵ C–S

0040-4039/\$ - see front matter @ 2013 Elsevier Ltd. All rights reserved. http://dx.doi.org/10.1016/j.tetlet.2013.05.063 coupling reaction,^{36,37} C–O coupling^{38,39} reaction, and Suzuki coupling reaction.⁴⁰ Based on our ongoing interests in the topic of enaminone-type ligands promoted, transition metal-catalyzed C–C bond formation reactions,⁴¹ we report herein the copper-catalyzed, enaminone ligand-assisted homo- and cross-coupling reactions of terminal alkynes under mild conditions.

Initially, the homo-coupling of phenylacetylene **1a** yielding 1,4diphenylbuta-1,3-divne 2a was selected as a model reaction. The first entry was performed using CuBr₂ as catalyst and enaminone L1 as ligand in DMSO in the presence of 2 equiv of K₂CO₃, and corresponding product 2a was obtained in 12% yield. After screening different inorganic and organic bases, we were pleased to find that the entry using pyrrolidine exhibited significantly higher yield than other bases (entries 1–8, Table 1). During the following experiments, it has been found that the yield could be further improved when dichloromethane was employed as solvent, while other solvents such as toluene, DMF, ethyl lactate gave inferior results (entries 9-12, Table 1). Interestingly, even though ligand L1 has been found as generally efficient ligand in enaminone promoted coupling reactions reported previously,^{35–39} *p*-nitrophenyl funtionalized enaminone **L2** was better ligand than **L1**, **L3**, **L4**^{42,43} and other classical ligands such as L-proline L5 and 8-hydroxylquinoline L6 (entries 12–17, Table 1) in this reaction. Finally, other copper catalysts such as CuBr, CuI, and Cu(OAc)₂ were also respectively employed and displayed no better effect than CuBr₂ (entries 18–20, Table 1).

With the optimized conditions, we then investigated the homocoupling transformation using different terminal alkynes to demonstrate the application scope of the present protocol.⁴⁴ Results obtained from entries using different alkyne substrates were

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Table 1

Optimization of the reaction conditions for homo-coupling of phenylacetylene^a



Entry	Ligand	Solvent	Catalyst	Base	Yield ^b (%)
1	L1	DMSO	CuBr ₂	K ₂ CO ₃	12
2	L1	DMSO	CuBr ₂	NaHCO ₃	13
3	L1	DMSO	CuBr ₂	Cs ₂ CO ₃	8
4	L1	DMSO	CuBr ₂	Na ₂ CO ₃	7
5	L1	DMSO	CuBr ₂	Et ₃ N	7
6	L1	DMSO	CuBr ₂	DMAP	5
7	L1	DMSO	CuBr ₂	КОН	10
8	L1	DMSO	CuBr ₂	Pyrrolidine	64
9	L1	DMF	CuBr ₂	Pyrrolidine	74
10	L1	Toluene	CuBr ₂	Pyrrolidine	71
11	L1	EL ^c	CuBr ₂	Pyrrolidine	26
12	L1	CH_2Cl_2	CuBr ₂	Pyrrolidine	91
13	L2	CH_2Cl_2	CuBr ₂	Pyrrolidine	99
14	L3	CH_2Cl_2	CuBr ₂	Pyrrolidine	91
15	L4	CH_2Cl_2	CuBr ₂	Pyrrolidine	89
16	L5	CH_2Cl_2	CuBr ₂	Pyrrolidine	61
17	L6	CH_2Cl_2	CuBr ₂	Pyrrolidine	87
18	L2	CH ₂ Cl ₂	CuBr	Pyrrolidine	94
19	L2	CH ₂ Cl ₂	CuI	Pyrrolidine	93
20	L2	CH ₂ Cl ₂	$Cu(OAc)_2 \cdot H_2O$	Pyrrolidine	95
O OH L1 O HN ^{Ph}		$ \begin{array}{c} $	N I	$CI \rightarrow L3$	V

^a General reaction conditions: a mixture of 0.6 mmol **1a**, 20 mol % copper catalyst 20 mol % ligand, and 2 equiv base in 1 mL solvent was stirred at room temperature for 12 h.

^b Yields of isolated products.

^c EL, ethyl lactate.

outlined in Table 2. Various terminal alkynes were investigated under the optimized conditions. A variety of different symmetrical diynes have been efficiently synthesized by coupling of either aryl or alkyl terminal alkynes. Generally, diynes were obtained with good to excellent yields, while an exception was the reaction of 4-bromophenylacetylene which gave corresponding diyne **2e** in 21% yield (entry 4, Table 2), which is probably because of the poor solubility of the product.²³ Electronic property of substitutions in the phenyl ring did not show evident impact on the reaction result. It is noteworthy that volatile alkyl alkynes were also efficiently transformed to corresponding diynes in good to excellent yield in the standard catalytic system (entries 8–10, Table 2).

Encouraged by the good results of homo-coupling of terminal alkynes, we then explored cross-coupling reactions between two different terminal alkynes. To our delight, the cross-coupling reactions proceeded well in the standard conditions. Results given by cross-coupling reactions of different aryl and alkyl alkynes were shown in Table 3. According to the results obtained from this section, different functional groups such as alkyl, alkoxyl, and halides were tolerated well to the cross-coupling conditions. Corresponding unsymmetrical diyne products **3** were afforded with fair to excellent yields. Successful synthesis of these unsymmetrical diynes further illustrated the broad application scope of this enaminone ligand assisted reaction system.

According to known literature as well as results obtained in our work, a general mechanism on this enaminone ligand assisted,

Table 2

Homo-coupling reactions of terminal alkynes^a

2 R-== 1	$\frac{\text{CuBr}_2/\text{L2/pyrroli}}{\text{CH}_2\text{Cl}_2, \text{ rt}}$	dine → R-==- 2	——————————————————————————————————————
Entry	R	Product	Yield ^b (%)
1	4-EtC ₆ H ₄	2b	77
2	4-PrC ₆ H ₄	2c	92
3	$4-FC_6H_4$	2d	80
4	4-BrC ₆ H ₄	2e	21
5	4-MeOC ₆ H ₄	2f	67
6	3-BrC ₆ H ₄	2g	76
7	3-NH ₂ C ₆ H ₄	2h	85
8	n-Butyl	2i	67
9	n-Hexyl	2j	99
10	Cyclopropyl	2k	97
11	2-ClC ₆ H ₄	21	87

^a General conditions: 0.6 mmol **1**, 20 mol % CuBr₂, 20 mol % **L2**, and 0.6 mmol pyrrolidine in 1 mL CH₂Cl₂, stirred at room temperature for 12 h. ^b Yields of isolated products.

copper-catalyzed coupling reactions of terminal alkynes is postulated as shown in Scheme 1. The $CuBr_2$ catalyst was first incorporated by enaminone ligand to provide intermediate **4**. The activated copper complex displaced the terminal hydrogen to generate alkynyl copper intermediate **5** via transition state I. Finally, Y. Liu et al./Tetrahedron Letters xxx (2013) xxx-xxx

Table 3

Cross-coupling reactions of terminal alkynes^a

R-===	+ <u>=</u> R' -	CuBr ₂ / L2 /pyrrolic CH ₂ Cl ₂ , rt	dine → R-==	≡————————————————————————————————————
Entry	R	R′	Product	Yield ^b (%)
1	Ph	4-EtC ₆ H ₄	3a	96
2	Ph	4-BrC ₆ H ₄	3b	73
3	4-EtC ₆ H ₄	4-PrC ₆ H ₄	3c	78
4	4-MeOC ₆ H ₄	Cyclopropyl	3d	33
5	4-MeOC ₆ H ₄	4-EtC ₆ H ₄	3e	72
6	4-MeOC ₆ H ₄	4-FC ₆ H ₄	3f	44
7	Ph	4-PrC ₆ H ₄	3g	81
8	4-MeOC ₆ H ₄	$4-PrC_6H_4$	3h	56

^a General conditions: two different alkynes in 0.3 mmol, respectively, 20 mol % CuBr₂, 20 mol % L2, and 0.6 mmol pyrrolidine in 1 mL CH₂Cl₂, stirred at room temperature for 12 h.

^b Yields of isolated products.



Scheme 1. Postulated mechanism for enaminone assisted coupling reactions of terminal alkynes.

the corporation of two molecules of 5 led to the production of divne products via the other transition state II.

In conclusion, we have developed a mild and facile copper-catalyzed approach for the synthesis of various diynes via the dehydrogenative couplings of two terminal alkynes with the assistance of an enaminone ligand. The protocol tolerated a broad range of functional groups for the synthesis of both symmetrical and unsymmetrical diynes in the form of homo- and cross-coupling, respectively. The present method will be reasonably useful as complementary option for the synthesis of diynes owing to its atom economics, mild conditions as well as high yields.

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Supplementary data

Supplementary data (general experimental details, characterization data as well as ¹H and ¹³C NMR spectra for products **2a-1**, **3a-h**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.063.

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- 44. General procedure for the synthesis of diyne products 2a-k and 3a-f. To a 10 mL round bottom flask were employed terminal alkynes 0.6 mmol (for homo-coupling) or two different terminal alkynes 0.3 mmol each (for crosscoupling), 0.06 mmol CuBr2, 0.06 mmol L2 and 0.6 mmol pyrrolidine. Then dichloromethane (1 mL) was added and the resulting mixture was stirred at room temperature (25 °C) for 12 h (TLC). The solvent was removed at reduced pressure and water (8 mL) was added, and the resulting mixture was extracted with ethyl acetate (8 mL \times 3). The organic phases were combined and dried with anhydrous Na2SO4. After removing solvent at reduced pressure, the residue was subjected to column chromatography or preparative TLC with petroleum ether as eluent to provide pure product. 1-Ethyl-4-(phenylbuta-1,3diynyl)benzene (**3a**). Pale yellow solid; ¹H NMR (CDCl₃, 400 MHz) δ 7.52–7.49 (m, 2H), 7.42 (dd, 2H, J1 = 8.0 Hz, J2 = 6.0 Hz), 7.34–7.20 (m, 3H), 7.13 (d, 2H, J = 8.0 Hz), 2.62 (q, 2H, J = 8.0 Hz), 1.21 (t, 3H, J = 8.0 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 145.9, 145.8, 132.6, 129.2, 128.5, 128.1, 122.0, 119.0, 82.0, 81.3, 74.2, 73.4, 29.0, 15.3.

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