



Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient zinc-catalyzed cross-coupling reaction of aryl iodides with terminal aromatic alkynes

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ARTICLE INFO

Article history:

Received 15 July 2015

Revised 10 August 2015

Accepted 11 August 2015

Available online xxxx

Keywords:

Zinc-catalyst

Cross-coupling reactions

Terminal acetylenes

Transition metal catalysts

C–C bond formations

Sonogashira type coupling

ABSTRACT

The first Zn-catalyzed protocol for C(sp²)-C(sp) cross-coupling reactions for the synthesis of disubstituted alkynes is described. A broad spectrum of functional groups is tolerated during the catalysis and successfully afforded a variety of diaryl substituted acetylenes.

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Transition metal catalyzed cross coupling reactions¹ are one of the predominant strategies for the formation of conjugated systems which possess wide applications in the synthesis of natural products, heterocycles, pharmaceuticals, polymers, dyes, sensors, guest-host systems, electronics, and electroopticals.² Due to the vast importance of acetylenic moieties, numerous methodologies have been introduced for their synthesis. Among these methods, Sonogashira coupling reactions of terminal acetylenes with aryl halides are the most popular ones. The Sonogashira cross-coupling reactions have been initiated independently by the seminal works of Castro,³ Cassar,⁴ Heck,⁵ and Sonogashira.⁶

The typical Sonogashira reactions are performed with palladium(0) catalyst and copper(I) co-catalyst in organic solvents using a suitable base.⁷ Development of competent catalysts and reduction during the homocoupling of alkynes are the challenges faced by Sonogashira (C(sp²)-C(sp)) cross-coupling reactions. Despite all the challenges, significant modifications have been introduced in Sonogashira coupling reactions over the last few years. Among these, the Sonogashira type cross-coupling reaction under copper-free conditions⁸ and the same under palladium-free conditions⁹ serve the two promising protocols. Of great importance are the recent modifications such as using aqueous solvents,¹⁰ aerobic atmosphere,¹¹ room temperature,¹² and solvent free conditions^{8h} as well as the use of certain other transition metals for catalysis.¹³ Moore and co-workers reported a palladium-

catalyzed zinc chloride promoted coupling of terminal alkynes with aryl bromides in 2009.¹⁴ However, to the best of our knowledge, C(sp²)-C(sp) cross-coupling reactions of terminal alkynes with aryl halides catalyzed by Zn(II) systems have not yet been reported. Herein, we disclose the first efficient zinc-catalyzed Sonogashira type cross-coupling reaction of alkynes with aryl iodides in the absence of added Pd and Cu sources.

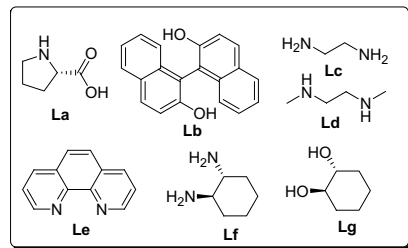
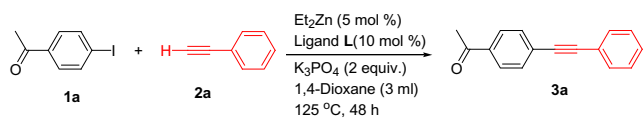
On the basis of our recent study on zinc-proline catalytic system for carbon-sulfur bond-formation reactions,¹⁵ we anticipated that the same catalytic system would be successful for C(sp²)-C(sp) cross-coupling reaction. In this context, we tried diethyl zinc in the presence of proline **La** and other commonly available ligands **Lb-Lg** for screening. We initiated our studies on zinc-catalyzed C(sp²)-C(sp) cross-coupling reaction using phenylacetylene and 4-iodoacetophenone as reactants under various catalytic conditions. The reactions were carried out in a previously dried sealed tube in the presence of K₃PO₄ in 1,4-dioxane at 125 °C under nitrogen atmosphere (Table 1).

Thus the reaction of 4-iodoacetophenone **1a** with phenylacetylene **2a** in the presence of proline **La**, 1,1'-bi-2-naphthol **Lb**, or ethylenediamine **Lc** and K₃PO₄ in 1,4-dioxane at 125 °C afforded very small quantity of the product **3a** (Table 1, entries 1–3). However, to our delight, when the reaction of **1a** with **2a** was conducted in the presence of *N,N*-dimethylethylenediamine **Ld** (DMEDA) and K₃PO₄ in 1,4-dioxane at 125 °C, the coupled product **3a** was formed in promising yield of 75% along with the dimerized product of phenylacetylene (Table 1, entry 4). The structure of the product **3a** was confirmed by NMR and mass spectrometric

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Table 1
Ligand screening for zinc-catalyzed C(sp²)-C(sp) cross-coupling reactions^a



Entry	Ligand	Yield ^b (%)
1	La	8
2	Lb	nd ^c
3	Lc	12
4	Ld	75
5	Le	23
6	Lf	66
7	Lg	nd

The bold is used to indicate ligand names and Entry 4 in bold corresponds to the optimized ligand.

^a Reaction conditions: phenylacetylene (1 mmol), 4-iodoacetophenone (1.1 mmol), K₃PO₄ (2 equiv), Et₂Zn (5 mol %), ligand (10 mol %), 1,4-dioxane (3 ml), 125 °C.

^b Isolated yield.

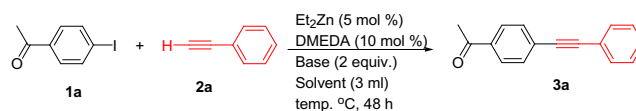
^c Not detected.

analyses. In view of the pleasing result, we decided to conduct optimization studies in detail (Table 2).

Screening of bases revealed that K₃PO₄ is the optimal base and with this base the required product **3a** was generated in 75% yield (Table 2, entry 1). The K₂CO₃ is also a suitable base for this reaction, but the yield was slightly less compared to that of K₃PO₄. After finding the suitable base, we examined the effect of various solvents in this cross-coupling reaction. The solvent effect analysis revealed that the preferred solvent is 1,4-dioxane. Lower yields were observed when DME and THF were used as solvents (Table 2, entries 9 and 12). Solvents such as DMF, DMSO, and NMP were found to be ineffective for the zinc-catalyzed C(sp²)-C(sp) cross-coupling reaction (Table 2, entries 24–32). Attempts to find out the influence of reaction temperature disclosed that a lower yield of **3a** was found as the temperature decreased (Table 2, entry 33). No product was observed in the absence of base or catalytic system (Table 2, entry 34, 37). Lower yield of the product was found both in the absence of Et₂Zn (Table 2, entry 35) and in the absence of DMEDA (Table 2, entry 36). Lower catalytic activity was observed with 1:1 combination of Et₂Zn and DMEDA (Table 2, entry 38). Decreasing the amount of K₃PO₄ led to a reduction in the yield of **3a** (Table 2, entry 39). Carrying out the reaction in the absence of inert atmosphere afforded only a trace amount of the desired cross-coupled product along with the dimerized product of phenylacetylene (Table 2, entry 40). Running the reaction with lower catalyst loading also decreased the yield of the required product **3a** (Table 2, entry 41). Thus, the optimum reaction condition for the desired zinc-catalyzed C(sp²)-C(sp) cross-coupling reaction was found to be 5 mol % of Et₂Zn, 10 mol % of DMEDA, and 2 equiv of K₃PO₄ at 125 °C in 1,4-dioxane (Table 2, entry 1).

To explore the generality and functional group compatibility of this zinc-catalyzed C(sp²)-C(sp) coupling reaction, we carried out the reaction of electronically and structurally diverse aryl iodides and alkynes under optimum reaction conditions. Aryl iodides with both electron-withdrawing and electron-releasing substituents on

Table 2
Optimization of reaction conditions^a



Entry	Base	Solvent (3 ml)	Yield ^b (%)
1	K₃PO₄	1,4-Dioxane	75
2	K ₂ CO ₃	1,4-Dioxane	60
3	CS ₂ CO ₃	1,4-Dioxane	35
4	Et ₃ N	1,4-Dioxane	Trace
5	NaO ^t Bu	1,4-Dioxane	nd ^c
6	KO ^t Bu	1,4-Dioxane	nd
7	NaOH	1,4-Dioxane	nd
8	KOH	1,4-Dioxane	nd
9	K ₃ PO ₄	DME	44
10	K ₂ CO ₃	DME	nd
11	CS ₂ CO ₃	DME	25
12	K ₃ PO ₄	THF	38
13	K ₂ CO ₃	THF	31
14	CS ₂ CO ₃	THF	Trace
15	K ₃ PO ₄	Toluene	Trace
16	K ₂ CO ₃	Toluene	25
17	CS ₂ CO ₃	Toluene	20
18	K ₃ PO ₄	^t BuOH	30
19	K ₂ CO ₃	^t BuOH	20
20	CS ₂ CO ₃	^t BuOH	Trace
21	K ₃ PO ₄	CH ₃ CN	20
22	K ₂ CO ₃	CH ₃ CN	Trace
23	CS ₂ CO ₃	CH ₃ CN	Trace
24	K ₃ PO ₄	DMF	nd
25	K ₂ CO ₃	DMF	nd
26	CS ₂ CO ₃	DMF	nd
27	K ₃ PO ₄	DMSO	nd
28	K ₂ CO ₃	DMSO	nd
29	CS ₂ CO ₃	DMSO	nd
30	K ₃ PO ₄	NMP	nd
31	K ₂ CO ₃	NMP	nd
32	CS ₂ CO ₃	NMP	nd
33 ^d	K ₃ PO ₄	1,4-Dioxane	40
34	—	1,4-Dioxane	nd
35 ^e	K ₃ PO ₄	1,4-Dioxane	34
36 ^f	K ₃ PO ₄	1,4-Dioxane	18
37 ^g	K ₃ PO ₄	1,4-Dioxane	nd
38 ^h	K ₃ PO ₄	1,4-Dioxane	28
39 ⁱ	K ₃ PO ₄	1,4-Dioxane	52
40 ^j	K ₃ PO ₄	1,4-Dioxane	Trace
41 ^k	K ₃ PO ₄	1,4-Dioxane	43

The bold is used to indicate the optimized reaction condition.

^a Reaction conditions: phenyl acetylene (1 mmol), 4-iodoacetophenone (1.1 mmol), K₃PO₄ (2 equiv), Et₂Zn (5 mol %), DMEDA (10 mol %), 1,4-dioxane (3 ml), 125 °C.

^b Isolated yield.

^c Not detected.

^d Reaction temperature is 80 °C.

^e Absence of DMEDA.

^f Absence of Et₂Zn.

^g Absence of both DMEDA and Et₂Zn.

^h 1:1 ratio of DMEDA and Et₂Zn.

ⁱ 1 equiv of K₃PO₄.

^j Absence of N₂ atmosphere.

^k 2 mol % of Et₂Zn.

reaction with phenylacetylene afforded moderate to good yield of the required product indicating the absence of electronic effects in these reactions (Table 3, entries 1, 3, and 5–7). Apart from substituted aryl iodides and alkynes, we also examined unsubstituted aryl iodide and phenylacetylene, which also underwent smooth coupling affording the required product in good yield (Table 3, entry 4). It is noteworthy that the present zinc-catalyzed Sonogashira type cross-coupling reaction proceeds well in the case of heterocyclic iodides also (Table 3, entry 10). Interestingly the phenylacetylene derivatives bearing –CH₃ and –OCH₃ substituents

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