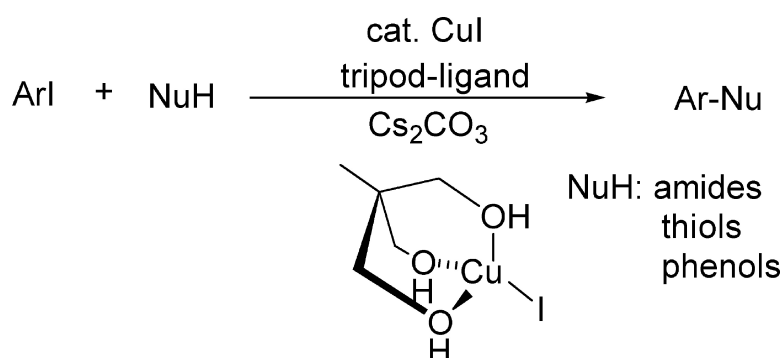


# 1,1,1-Tris(hydroxymethyl)ethane as a New, Efficient, and Versatile Tripod Ligand for Copper-Catalyzed Cross-Coupling Reactions of Aryl Iodides with Amides, Thiols, and Phenols

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# 1,1,1-Tris(hydroxymethyl)ethane as a New, Efficient, and Versatile Tripod Ligand for Copper-Catalyzed Cross-Coupling Reactions of Aryl Iodides with Amides, Thiols, and Phenols

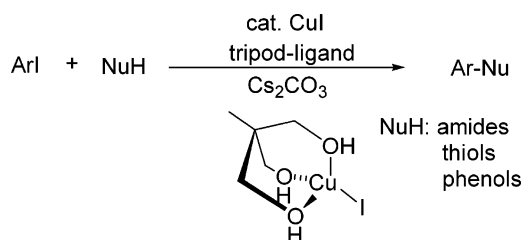
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## ABSTRACT



1,1,1-Tris(hydroxymethyl)ethane was presented as a new, efficient, and versatile tridentate O-donor ligand suitable for the copper-catalyzed formation of C–N, C–S, and C–O bonds. This inexpensive and commercially available tripod ligand has been demonstrated to facilitate the copper-catalyzed cross-coupling reactions of aryl iodides with amides, thiols, and phenols to afford the corresponding desired products in good to excellent yields.

Transition-metal-catalyzed cross-coupling reactions of aryl halides with various nucleophilic compounds are now among the most prominent synthetic methods for the formation of carbon–nitrogen, carbon–oxygen, and carbon–sulfur bonds in the preparation of numerous important products in fields of pharmaceutical, biological, and material science.<sup>1</sup> Most noteworthy among them are palladium-catalyzed N-arylation of amines/amides,<sup>2</sup> O-arylation of phenols,<sup>3</sup> and S-arylation of thiols.<sup>4</sup> Although significant improvements have been

achieved in these coupling reactions, some limitations still remain. For example, the palladium-catalyzed amidation of electron-rich or ortho-substituted aryl halides is difficult.<sup>5</sup> Moreover, the high cost and air sensitivity of Pd catalyst systems commonly limit their application to large- and

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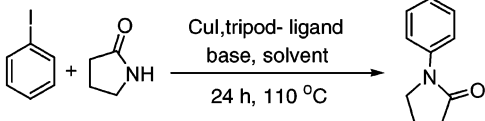
industrial-scale formation of these bonds. Recently, a growing number of papers have focused on the deliberate use of additional ligands to facilitate copper-catalyzed N-arylation of amines/amides, O-arylation of phenols, and S-arylation of thiols.<sup>6</sup> Among a variety of multidentate chelating ligands used, neutral bidentate chelators appear to be in the majority of the copper-catalyzed coupling reaction protocols. The variety of donor combinations mostly includes N,N-, O,O-, and N,O-chelators. Notably, only few examples have been reported to demonstrate that the versatility of the same ligands without any additional modification can be used in three or more kinds of copper-catalyzed cross-coupling reactions for the formation of aryl–heteroatom and/or aryl–carbon bonds, such as neocuproine (2,9-dimethyl-1,10-phenanthroline; a bidentate ligand with N,N-chelators for Ar–N, Ar–O, and Ar–S bond formations),<sup>7</sup> pyrrolidine-2-phosphonic acid phenyl monoester (a bidentate ligand with N,O-chelators for Ar–N, Ar–O, and Ar–P bond formations),<sup>8</sup> and Chxn-Py-Al (a tetradentate ligand with N,N,N,N-chelators for Ar–N, Ar–O, and Ar–C bond formations).<sup>9</sup> However, the high cost and/or the tedious preparation procedure of the ligands used in these important protocols are drawbacks. Hence, it is still essential to search other new, less costly, and versatile ligands for this copper-catalyzed protocol.

1,1,1-Tris(hydroxymethyl)ethane, an inexpensive and commercially available tripod ligand, has been used in the synthesis of some metal clusters for their magnetic studies.<sup>10</sup> Results show that this tripodal ligand can change the spin ground states of the species due to the nature of its special skeleton. On the other hand, an interesting study has been reported that complexes of the type Cu<sup>I</sup>(tripod)X [tripod =

1,1,1-tris(diphenylphosphanyl)ethane; X<sup>−</sup> = halide, thiophenolate, phenylacetylide] are phosphorescent in solution and in the solid state.<sup>11</sup> It is suggested that the emission is facilitated by the rigid tetrahedral structure, which is imposed by the tripod ligand. Nevertheless, no further reports dealing with these tripodal ligands in metal-catalyzed cross-coupling reactions have been presented to date. Finally, Buchwald and co-workers have highlighted that ethylene glycol can act as an effective bidentate O-donor ligand in the copper-catalyzed N- and S-arylation of aryl iodides with amines and thiols, respectively.<sup>12</sup> Notably, they also pointed out that amides and anilines were poor substrates in their Cu-catalyzed protocol. On the basis of these studies, we were prompted to examine whether this tripodal ligand can be presented as a new class of tridentate O-donor ligands suitable to be used in copper-catalyzed cross-coupling reactions. Herein, we report that this inexpensive and commercially available triol, 1,1,1-tris(hydroxymethyl)ethane, can be used as an efficient, versatile, and novel tripod ligand in the copper-catalyzed formation of C–N, C–O, and C–S bonds between aryl iodides and amides, phenols, and thiols, respectively.

As a model study, we first chose to study the effect of 1,1,1-tris(hydroxymethyl)ethane as a tripod ligand on the efficiency of the Cu(I)-catalyzed aryl amidation reaction of iodobenzene with 2-pyrrolidone, and the results are summarized in Table 1. When the reaction was performed with

**Table 1.** Cu(I)-Catalyzed Amidation of Iodobenzene with 2-Pyrrolidone<sup>a</sup>



entry	CuI:ligand (%)	base	solvent	yield <sup>b</sup>
1	5 : 0	K <sub>3</sub> PO <sub>4</sub>	toluene	trace <sup>c</sup>
2	5 : 5	K <sub>3</sub> PO <sub>4</sub>	toluene	56 <sup>c</sup>
3	5 : 5	K <sub>3</sub> PO <sub>4</sub>	toluene	76
4	10 : 10	K <sub>3</sub> PO <sub>4</sub>	toluene	91
5	10 : 10	K <sub>3</sub> PO <sub>4</sub>	dioxane	81
6	10 : 10	K <sub>3</sub> PO <sub>4</sub>	DMSO	83
7	10 : 10	K <sub>3</sub> PO <sub>4</sub>	DMF	97
8	10 : 10	K <sub>3</sub> PO <sub>4</sub>	mix <sup>d</sup>	98
9	10 : 10	K <sub>2</sub> CO <sub>3</sub>	mix <sup>d</sup>	4
10	10 : 10	Cs <sub>2</sub> CO <sub>3</sub>	mix <sup>d</sup>	98
11	10 : 10 <sup>e</sup>	K <sub>3</sub> PO <sub>4</sub>	mix <sup>d</sup>	63
12	10 : 10 <sup>f</sup>	K <sub>3</sub> PO <sub>4</sub>	mix <sup>d</sup>	81

<sup>a</sup> Reaction conditions: PhI (1 mmol), Cu(I) (5 or 10 mol %), tripod ligand (5 or 10 mol %), 2-pyrrolidone (1.2 mmol), and base (2.03 mmol) in solvent (0.5 M) at 110 °C for 24 h. <sup>b</sup> Isolated yield. <sup>c</sup> At 80 °C. <sup>d</sup> DMF/dioxane = 1:9. <sup>e</sup> Using neopentyl alcohol as a monodentate ligand. <sup>f</sup> Using neopentyl glycol (2,2-dimethyl-1,3-propanediol) as a bidentate ligand.

5 mol % of Cu(I) and 5 mol % of tripod ligand in the presence of K<sub>3</sub>PO<sub>4</sub> as a base in toluene at 80 °C for 24 h, the expected coupling product of 1-phenylpyrrolidin-2-one

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was afforded in 56% yield (Table 1, entry 2). For a blank test (Table 1, entry 1), only trace amounts of the product could be obtained while the same reaction condition was carried out in the absence of the tripod ligand. The result indicates that this tripod ligand must play an important role in accelerating the rate of the Cu(I)-catalyzed cross-coupling reaction. For further optimization of the reaction conditions, increasing yields of the coupling product were observed by simply increasing the reaction temperature to 110 °C (76%, Table 1, entry 3) and further by increasing the added amounts of Cu(I) (10 mol %) and tripod ligand (10 mol %) at 110 °C (91%, Table 1, entry 4). To evaluate the effect of the solvent (Table 1, entries 4–8), the results showed that toluene, dioxane, DMSO, DMF, and a mixture of DMF and dioxane (1:9) were effective solvents. Among them, DMF and a mixture of DMF and dioxane (1:9) were the most efficient. Considering the convenience of the workup procedure, the latter was used in the following experiments. For comparison on the efficiency of the base in the amidation reactions (Table 1, entries 8–10), both  $K_3PO_4$  and  $Cs_2CO_3$  were found to be highly effective whereas  $K_2CO_3$  was much less effective. Finally, to examine the effect of different dentate ligands in the copper-catalyzed amidation reactions, significant differences in yield were observed by using 1,1,1-tris(hydroxymethyl)ethane, neopentyl glycol (2,2-dimethyl-1,3-pro-

panediol), and neopentyl alcohol as the tri-, bi-, and monodentate ligand, respectively (Table 1, entries 8, 11, and 12). Among them, the results indicate that 1,1,1-tris(hydroxymethyl)ethane as a tridentate ligand was the most effective. Moreover, the ratio of Cu(I) to tripod ligand used in this study is only equal to 1:1 whereas a 1:2 ratio is usually used in most other copper-catalyzed cross-coupling reactions using other bidentate ligands. Presumably, 1,1,1-tris(hydroxymethyl)ethane acts as a tridentate O-donor ligand that might be more effective in stabilizing or solubilizing the copper complex. On the basis of these results, it is plausible to propose that 1,1,1-tris(hydroxymethyl)ethane represents not only a new class of tridentate O-donor ligands but also an efficient tripod ligand suitable to be used in copper-catalyzed cross-coupling reactions.





































Thus, the optimized reaction conditions utilized 10 mol % of Cu(I), 10 mol % of tripod ligand, and  $K_3PO_4$  or  $Cs_2CO_3$  (2.03 equiv) in a mixture of DMF and dioxane (1:9) as a solvent (0.5 M) at 110 °C under nitrogen. In the first part of this study, these reaction conditions were applied to the coupling of various functionalized aryl iodides and amides (Table 2). Keto and methoxy groups are tolerated on the aryl iodide component. No significant electronic effects were observed for para-substituted aryl iodides when  $Cs_2CO_3$  was used as a base, based on the yields of reactions obtained (Table 2, entries 2, 4, 8, and 9). *ortho*-Methoxy aryl iodide typically gave a lower yield in the reaction using  $K_3PO_4$  as a base, but it also can be more efficient in the reaction by using  $Cs_2CO_3$  as a base (Table 2, entries 5 and 6). Interestingly,  $Cs_2CO_3$  has been found to be more effective than  $K_3PO_4$  as a base in all cases, except for 2-oxazolidone (Table 2, entries 10–12).

A second portion of this work involved the application of our protocol to the Cu(I)-catalyzed S-arylation of thiols with various aryl iodides. The optimal cross-coupling conditions were found to be the same as those in the case of N-arylation of amides when  $Cs_2CO_3$  was used as a base, and the desired aryl thioether products were obtained in excellent yields (Table 3). Results revealed that our Cu-catalyzed protocol can facilitate efficiently the cross-coupling reactions of various substituted aryl iodides with various substituted thiophenols as well as with alkanethiol (Table 3, entry 8).

The final portion of this work involved the extension of our protocol to the Cu(I)-catalyzed O-arylation of phenols with various aryl iodides. The cross-coupling reactions were carried out under the optimal catalytic conditions: Ar(I) (1 mmol), Cu(I) (10 mol %), tripod ligand (10 mol %), phenols (1.2 mmol), and  $Cs_2CO_3$  (2.03 mmol) in dioxane (0.5 M) at 110 °C for 48 h. The desired diaryl ether products were given in good to very good yields (Table 4). On the basis of the rates and yields of reactions, obviously, our protocol was found to be less effective in O-arylations of phenols with aryl iodides than that in both N-arylations of amides and S-arylations of thiols.

In conclusion, we have successfully demonstrated that 1,1,1-tris(hydroxymethyl)ethane can be used as a new, efficient, and versatile tridentate ligand in the copper-catalyzed formation of C–N, C–S, and C–O bonds. Using

**Table 2.** Cu(I)-Catalyzed Amidation of Aryl Iodides with Amides<sup>a</sup>

ArI + amides $\xrightarrow[24\text{ h, } 110\text{ }^\circ\text{C}]{\substack{10\text{ mol \% CuI} \\ 10\text{ mol \% tripod-ligand} \\ Cs_2CO_3 \\ DMF:dioxane(1:9)}}$ N-arylation products					
entry	Ar-I	amide	base	product	yield <sup>b</sup>
1			$K_3PO_4$		98
2			$Cs_2CO_3$		98
3			$K_3PO_4$		83
4			$Cs_2CO_3$		96
5			$K_3PO_4$		73
6			$Cs_2CO_3$		91
7			$K_3PO_4$		84
8			$Cs_2CO_3$		86
9			$Cs_2CO_3$		92 <sup>c</sup>
10			$K_3PO_4$		83
11			$K_3PO_4$		92 <sup>d</sup>
12			$Cs_2CO_3$		33

<sup>a</sup> Reaction conditions: Ar(I) (1 mmol), Cu(I) (10 mol %), tripod ligand (10 mol %), amides (1.2 mmol), and base (2.03 mmol) in DMF/dioxane = 1:9 (0.5 M) at 110 °C for 24 h. <sup>b</sup> Isolated yield. <sup>c</sup> 48 h. <sup>d</sup> 72 h

**Table 3.** Cu(I)-Catalyzed Arylation of Thiols with Aryl Iodides<sup>a</sup>

10 mol % CuI 10 mol % tripod- ligand $\text{Cs}_2\text{CO}_3$ DMF:dioxane(1:9) 24 h, 110 °C				
entry	Ar-I	thiol	thioether	yield <sup>b</sup>
1				92
2				98
3				98
4				91
5				98
6				93
7				97
8		$\text{C}_{12}\text{H}_{25}\text{-SH}$		96

<sup>a</sup> Reaction conditions: Ar(I) (1 mmol), Cu(I) (10 mol %), tripod ligand (10 mol %), thiols (1.2 mmol), and  $\text{Cs}_2\text{CO}_3$  (2.03 mmol) in DMF/dioxane = 1:9 (0.5 M) at 110 °C for 24 h. <sup>b</sup> Isolated yield.

this inexpensive and commercially available tripodal ligand, the copper-catalyzed cross-coupling reactions of aryl iodides with amides, thiols, and phenols were readily facilitated to afford the corresponding desired products in good to excellent yields. Particularly, this catalyst system using this new class of tridentate O-donor ligands provides an excellent complement not only to the Pd-catalyzed methodology but also to the Cu-catalyzed system using ethylene glycol as a bidentate O-donor ligand in the amidation of aryl iodides. Further

**Table 4.** Cu(I)-Catalyzed Arylation of Phenols with Aryl Iodides<sup>a</sup>

10 mol % CuI 10 mol % tripod- ligand $\text{Cs}_2\text{CO}_3$ , dioxane 48 h, 110 °C				
entry	Ar-I	phenol	ether	yield <sup>b</sup>
1				87
2				84
3				81
4				83
5				87
6				84
7				82
8				82

<sup>a</sup> Reaction conditions: Ar(I) (1 mmol), Cu(I) (10 mol %), tripod ligand (10 mol %), phenols (1.2 mmol), and  $\text{Cs}_2\text{CO}_3$  (2.03 mmol) in dioxane (0.5 M) at 110 °C for 48 h. <sup>b</sup> Isolated yield.

studies of this and related copper-catalyzed cross-coupling reactions are in progress.

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**Supporting Information Available:** Experimental details and characterization for all known compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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