



Tris-(2-aminoethyl) amine as a novel and efficient tripod ligand for a copper(I)-catalyzed C–O coupling reaction

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ABSTRACT

We have introduced a novel, efficient, commercially available and economically attractive N-donor tripod ligand, tris-(2-aminoethyl)amine for copper-catalyzed Ullmann diaryl ether synthesis. This catalyst system is highly active for both aryl iodides and aryl bromides. Various substituted diaryl ethers have been synthesized in good to excellent yields.

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Diaryl ethers are ubiquitous in numerous fields of chemistry. They have been highlighted by their occurrence in a myriad of natural products and wide applications in pharmaceutical chemistry.¹ This structural unit is prevalent in commercially relevant polypropylene polymers and numerous pesticides.² They are extremely versatile intermediates of medicinally active compounds such as Vancomycin, Piperazinomycin (antifungal), K-13 (ACE inhibitor) and others.³

Conventionally, diaryl ethers are produced by Ullmann condensation⁴ of aryl halides and phenols with copper in the form of a metal salt. The major drawback of this method is the use of copper in stoichiometric amounts which makes the process difficult to scale-up and environmentally unfriendly due to the production of large quantities of waste. The applicability of the protocol is also limited due to the high reaction temperatures (120–200 °C) which make the substitution on the aryl halides susceptible to the harsh conditions. Recently, much emphasis has been laid on the development of Ullmann conditions and significant improvements have been achieved. Palladium has been the metal of choice for diaryl etherification, but its use as a catalyst is unpopular as it permits only the use of electron-deficient aryl bromides.⁵ Moreover, the palladium catalysis has the disadvantage of high metal and ligand costs, air-sensitivity of the phosphine ligands and the involvement of a multistep process towards the synthesis of variously substituted phosphine ligands.

Recently, several catalytic methods have been developed to improve the efficacy of the copper salt used and the ligand associated with it. To the best of our knowledge, the ligands that have been

found to promote Cu-catalyzed aryl-oxygen coupling reactions include copper salt and bulky phosphine ligands,⁶ β -keto ester,⁷ 1,10-phenanthroline,⁸ Cu(OTf)₂·PhH and ethyl acetate⁹, 1-butyl imidazole,¹⁰ silica-supported Cu(II),¹¹ 2,2,6,6-tetramethylheptane-3,5-dione,¹² BINAM-Cu(II)¹³ and 8-hydroxy quinoline.¹⁴ Though recent reports¹⁵ promise the development of a novel method, viable, inexpensive and commercially available ready to use ligands for the synthesis of diaryl ethers are still highly desirable.

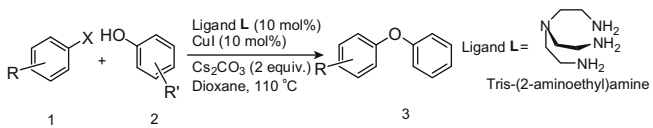
Recent thermodynamic and spectroscopic studies of tris-(2-aminoethyl) amine-lanthanide complexes¹⁶ and the use of similar polyamine-CuBr complexes in polymerization reactions¹⁷ show the significance of the tripod ligand. Very recently Chen et al. demonstrated for the first time that 1,1,1-tris-(hydroxymethyl)ethane can be used as a O-donor tridentate-tripod ligand for Cu-catalyzed carbon-heteroatom bond formation.¹⁸ Despite its versatility, the protocol requires a longer reaction time and has no mention of its applicability on aryl bromides. Keeping this in view, we have initiated a study on the application of tris-(2-aminoethyl)amine (L) as a N-donor tridentate-tripod ligand for a Cu-catalyzed diaryl etherification reaction. In this Letter, we wish to report our results concerning the tris-(2-aminoethyl)amine-Cu(I)-catalyzed O-arylation reaction. The reaction tolerates a wide range of functional groups giving isolated purified products in high yields. Moreover, it was observed that the protocol is efficiently viable with both aryl iodides and aryl bromides.

In the initial stages of the experiment, we emphasized the coupling between phenol and iodobenzene using tris-(2-aminoethyl)amine as the ligand. We initiated our study with the screening of the copper source (Table 1). It was observed that CuI is the copper salt of preference (Table 1, entry 4) as compared to

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Table 1
Screening of Cu catalyst, base and solvent



Entry	Cu source (mol %)	Base	Solvent (temperature, °C).	Yield ^a (%)
1	CuCl (10)	Cs ₂ CO ₃	1,4-Dioxane (110)	65
2	CuBr (10)	Cs ₂ CO ₃	1,4-Dioxane (110)	68
3	CuI (5)	Cs ₂ CO ₃	1,4-Dioxane (110)	72
4	CuI (10)	Cs ₂ CO ₃	1,4-Dioxane (110)	86
5	CuI (15)	Cs ₂ CO ₃	1,4-Dioxane (110)	84
6	CuI (20)	Cs ₂ CO ₃	1,4-Dioxane (110)	84
7	CuI (10)	K ₂ CO ₃	1,4-Dioxane (110)	53
8	CuI (10)	K ₃ PO ₄	1,4-Dioxane (110)	61
9	CuI (10)	KOt-Bu	1,4-Dioxane (110)	55
10	CuI (10)	Triethylamine	1,4-Dioxane (110)	31
11	CuI (10)	Cs ₂ CO ₃	Tetrahydrofuran (66)	43
12	CuI (10)	Cs ₂ CO ₃	Toluene (110)	56
13	CuI (10)	Cs ₂ CO ₃	Acetonitrile (82)	38
14	CuI (10)	Cs ₂ CO ₃	DMSO (130)	68
15	CuI (10)	Cs ₂ CO ₃	DMF (110)	57
16	CuI (10)	Cs ₂ CO ₃	DME (85)	47
17	CuI (10)	Cs ₂ CO ₃	1,4-Dioxane (110)	No reaction ^a
18	CuI (10)	Cs ₂ CO ₃	1,4-Dioxane (110)	58 ^b
19	CuI (10)	Cs ₂ CO ₃	1,4-Dioxane (110)	Trace ^c
20	CuI (10)	No base	1,4-Dioxane (110)	Trace ^d

Reaction conditions: Phenol (1 mmol), iodobenzene (1 mmol), ligand **L**, CuI, Cs₂CO₃, solvent at the respective temperatures.

^a Using 2-methylpropan-2-amine as a monodentate ligand.

^b Using *N*-(2-aminoethyl)ethane-1,2-diamine as a bidentate ligand.

^c In the absence of tris-(2-aminoethyl)amine.

^d In the absence of base.

^e Isolated yields.

CuCl and CuBr (Table 1, entries 1 and 2). When the reaction was carried out with different ratios of ligand and copper salt, it was found that 10 mol % of ligand-Cu salt forms the best combination for diaryl etherification. The ratio of 15 and 20 mol % (Table 1, entries 5 and 6) did not show any considerable effect as a catalytic combination on diaryl ether formation, whereas the use of no ligand showed products only in negligible quantities (Table 1, entry 19). Therefore, we found the air-stable and inexpensive CuI in 10 mol % ratios with ligand as the best catalytic system. The examination of the effect of various dentate ligands in the Ullmann diaryl ether synthesis shows a considerable difference in the yields of the product. The use of 2-methylpropan-2-amine as a monodentate ligand afforded no product (Table 1, entry 17), whereas the use of *N*-(2-aminoethyl)ethane-1,2-diamine as a bidentate ligand (Table 1, entry 18) proceeded with 58% yields. These results suggest that tris-(2-aminoethyl)amine has a very significant role to play as a tripodal ligand.

During the screening of bases, we found that Cs₂CO₃ is the base of choice (Table 1, entry 4) for the O-arylation of phenols. In addition to Cs₂CO₃, we also tested the feasibility of other bases such as K₂CO₃, K₃PO₄, KOt-Bu and triethylamine (Table 1, entries 7–10) only to find that these gave inferior yields compared to Cs₂CO₃. Also, a reaction in the absence of a base (Table 1, entry 20) afforded trace amounts of an O-arylated product.

A careful study of the choice of solvent for the coupling reaction suggested the use of dioxane as the best solvent (Table 1, entry 4) since it yielded diaryl ether in 86% yields. The low boiling solvents like tetrahydrofuran, acetonitrile and DME (Table 1, entries 11, 13 and 16) resulted in marginal yields of the product suggesting the choice of a high boiling solvent. However, the use of toluene, DMSO and DMF (Table 1, entries 12, 14 and 15) resulted in relatively low

Table 2
Coupling of aryl halides with phenols in the presence of a tris-(2-aminoethyl) amine-CuI catalyst

Entry	Aryl halide	Phenol	Time (h)	Product	Yield ^a (%)
1			22		86
2			22		85
3			23		80
4			23		81
5			22		83
6			24		82
7			25		80
8			21		88
9			19		89
10			30		No reaction
11			24		83
12			28		80
13			29		82
14			30		83
15			30		78

^a Isolated yields after column chromatography.

yields as compared to 1,4-dioxane. Hence, dioxane as a solvent in combination with Cs_2CO_3 as a base works well for this coupling protocol.

Table 2 shows that the reaction is equally facile with both electron-donating and electron-withdrawing substituents present on the aryl ring of aryl halide resulting in good yields of diaryl ethers. *ortho*-Substituted iodides (Table 2, entries 3–5) reacted smoothly with the respective phenols to give isolated diaryl ethers in 80%, 81% and 83% yields, respectively. The electron-withdrawing substrates on the part of aryl halides (Table 2, entries 8 and 9) facilitated diaryl ether formation in 88% and 89% yields, respectively. The strong electron-donating substrates also afforded the desired product in 82%,¹⁹ 80% and 83% (Table 2, entries 6, 7 and 11) yields, respectively. Unfortunately, the electron-withdrawing substrate on the part of phenol (Table 2, entry 10) was not found to afford diaryl ether with aryl iodide.

In addition to aryl iodides, we were delighted to note that aryl bromides could also be used as efficient substrates under the present diaryl etherification protocol (Table 2, entries 12–15). Moreover, aryl bromide that bears an electron-withdrawing group (Table 2, entry 14) is an equally viable substrate without much rise in the reaction time and temperature. Electron-donating substrates however, show a marginal decline in the yields (Table 2, entry 15). Hence, it is quite evident that the present protocol is viable enough for the O-arylation of phenols using otherwise less reactive aryl bromides.¹³ The products obtained by this method have been well characterized by physical and spectroscopic data.

In summary, we have demonstrated that tris-(2-aminoethyl) amine is a novel, efficient and commercially available ready to use tripodal ligand that can be used for diaryl etherification in combination with an air-stable and inexpensive CuI salt. Notably, we have demonstrated that the present protocol is equally facile with aryl bromides and tolerant of a range of functional groups. Further studies to investigate the applications of tris-(2-aminoethyl) amine as a ligand are in progress.

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- Representative procedure: Coupling of 1-iodo-4-methoxy benzene and phenol** (Table 2, entry 6): Into a 25 ml capacity one neck round-bottomed flask was charged dioxane (3 ml) followed by ligand L (0.085 mmol), CuI (0.085 mmol), 1-iodo-4-methoxy benzene (0.85 mmol), phenol (1.02 mmol) and Cs_2CO_3 (2.04 mmol). The reaction mixture was stirred with a magnetic stir bar and heated to 110 °C in an oil bath for 24 h. The completion of the reaction was monitored by TLC. After the consumption of 1-iodo-4-methoxybenzene is complete, the reaction mixture was cooled to room temperature and water (~15 ml) was added. The crude mixture was extracted with ethyl acetate and purified by column chromatography on silica gel to afford 4-methoxy-diphenyl ether (0.140 g, 82%) as colourless oil; R_f 0.68 (in hexane). ^1H NMR (CDCl_3 , 200 MHz) δ 7.29–7.41 (m, 2H), 6.90–7.11 (m, 7H) and (3.82 (s, 3H)); ^{13}C NMR (CDCl_3 , 50 MHz) δ 158.6, 156.0, 150.2, 129.7, 122.5, 120.9, 117.7, 115.0, 55.7. The spectroscopic data are in full agreement with those described in the literature.^{15d,e}