

Efficient copper-catalyzed amination of aryl halides with amines and N–H heterocycles using *rac*-BINOL as ligand

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Received 17 February 2006; accepted 1 May 2006

Available online 6 June 2006

Abstract

A highly efficient copper-catalyzed system using commercially available racemic 1,1'-binaphthyl-2,2'-diol (*rac*-BINOL) as the ligand was developed for amination of aryl halides and heteroaryl halides with alkyl amines and N–H heterocycles. Good to high yields were obtained for aryl bromides and heteroaryl chlorides. The commercially available *rac*-BINOL ligand with excellent stability and high efficiency for aryl bromides and heteroaryl chlorides ultimately make this protocol of potentially practical utility.

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Keywords: Amination; Copper; Aryl halides; Cross-coupling; *rac*-BINOL; Ligand

1. Introduction

Transition metal catalyzed formation of carbon–nitrogen bonds via cross-coupling reactions represents a powerful means for the preparation of numerous important products in pharmaceutical and material sciences [1]. Although palladium catalyzed C–N coupling reactions have received some achievements [2], copper catalyst systems have attracted much attention, due to the cheap price and environmental friend [3]. Recently, mild copper-mediated Ullmann-type processes [4] for *N*-arylation of anilines [5,6], amides [7], amino acids [8], amino alcohols [9], hydrazides [10], sulfoximes [11,12], sulfonamide [13], oxazolidinones [14] and various N–H heterocycles [7a,15] with aryl halides as arylating reagents have been reported. However, only limited papers have contributed to *N*-arylation of aliphatic amines (not chelating substrates) [16–19], and just several ligands were found to be effective for the amination of aryl bromides or chlorides with alkyl amines [5c,15e–15g,16]. Therefore, to find more efficient and readily available ligands especially for the coupling of aryl bromides or chlorides with alkyl amines and expand the scope of the substrates are still desirable.

Our group has embarked on a program aimed at the development of ligands that are low-cost and easily prepared in few steps from readily available starting materials [17], and has reported that Cu₂O/oxime-phosphine oxide [18a] and CuBr/phosphoramidite [18b] can efficiently catalyze the coupling of aryl iodides with alkyl amines or N–H heterocycles, respectively, and found that hydroxy group was critical for the efficiency [18a]. Therefore, we suspected that bishydroxy on the aryl ring might exert an extraordinary effect on the copper-catalyzed C–N coupling reaction. Then we screened a series of bisphenols. To our delight, *rac*-BINOL was found to be highly efficient in this transformation. As is known, enantiopure BINOL has been extensively applied in various asymmetric reactions [19]. However, *rac*-BINOL has not been systematically studied in copper-mediated C–N bond formation to the best of our knowledge. Herein, we reported a highly effective copper-catalyzed system using *rac*-BINOL as the ligand for amination of aryl halides with alkyl amines and N–H heterocycles.

2. Experimental

All reactions were carried out under an argon atmosphere and monitored by thin layer chromatography (TLC). Column chromatography purifications were performed using silica gel. All solvents were dried and degassed before use. NMR spectra were measured in CDCl₃ unless otherwise stated on a Bruker DRX-

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400 NMR spectrometer (400 MHz) with TMS as an internal reference. High resolution mass spectra (HRMS) were recorded on a Mariner 5303 (Applied Biosystems, USA).

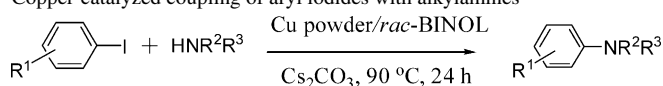
2.1. General procedure for copper-catalyzed C–N cross-coupling reaction

Cu powder or Cu powder and CuI, *rac*-BINOL, aryl halides (if solid), amines (if solid) and Cs₂CO₃ were weighed in the air and transferred into a dried Schlenk tube. The tube was evacuated and back filled with argon (three cycles). Aryl halides (if liquid, 1.0 mmol), amines (1.8 mmol) and freshly distilled DMSO (1.0 mL) or DMF (1.0 mL) were injected into the tube successively by micro-syringe at rt. The tube was sealed and stirred in an oil bath (preheated to the required temperature) for the required reaction time. The reaction mixture was cooled to rt. Ethyl ether (4 mL) and H₂O (10 mL) were added. The aqueous layer was further extracted by ethyl ether (4 × 10 mL). The combined organic layers were washed with saturated brine for two times, dried with Na₂SO₄, filtered, and concentrated to give a residue which was purified by column chromatograph on silica gel.

3. Results and discussion

To study the efficiency of a series of bisphenols, iodobenzene and morphine were used as the model substrates (Table 1).

Table 2
Copper-catalyzed coupling of aryl iodides with alkylamines^a



Entry	Arl	Amine	Product	Yield (%) ^b
1		H ₂ N- <i>n</i> -Hex		99
2		H ₂ N- <i>sec</i> -Bu		77
3		H ₂ N- <i>iso</i> -Bu		82
4		NH ₂ Bn		84 (79 ^c)
5		H ₂ N- <i>n</i> -Hex		86
6		Morpholine		84
7		Piperidine		88
8		Piperidine		75
9		Pyrrolidine		96 ^d

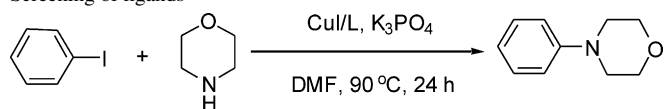
^a 1.0 mmol ArI, 1.8 mmol amine, 0.05 mmol Cu powder, 0.1 mmol *rac*-BINOL, 2.25 mmol Cs₂CO₃, 1 mL DMSO, 90 °C, 24 h.

^b Isolated yield.

^c Benzylamine was undistilled.

^d DMF as solvent.

Table 1
Screening of ligands^a



Entry	Ligand	Yield (%) ^b
1	1,2-Dihydroxybenzene	51
2	1,3-Dihydroxybenzene	11
3	1,4-Dihydroxybenzene	1
4	2,3-Dihydroxypyridine	14
5	2,2'-biphenol	35
6	<i>S</i> -BINOL	28
7	<i>R</i> -BINOL	64
8	<i>rac</i> -BINOL	64

^a Reaction conditions: 0.5 mmol PhI, 0.9 mmol morpholine, 0.05 mmol CuI, 0.1 mmol ligand, 1.13 mmol K₃PO₄, 0.5 mL DMF, 90 °C, 24 h.

^b GC yield.

Among the dihydroxybenzene, 1,2-dihydroxybenzene showed the best activity (entries 1–4). Although 35% yield was observed for 2,2'-biphenol, 64% yield was obtained for more steric hindered *rac*-BINOL (entries 5–6). Moreover, *R*-BINOL gave just the same result as *rac*-BINOL did, while *S*-BINOL gave lower result (entries 6–8).

With the best *rac*-BINOL ligand in hand, the optimal reaction conditions were subsequently screened. DMSO was proved to be the best solvent. Cs₂CO₃, K₂CO₃, K₃PO₄, and K₃PO₄·3H₂O

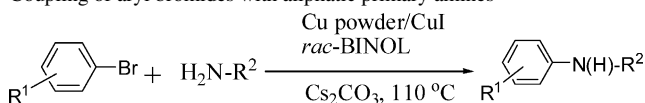
all showed effective [20], while CH_3ONa , $t\text{BuONa}$ and organic base Et_3N gave trace corresponding product. Cs_2CO_3 was the best of choice [21]. Copper powder and Cu(I) source gave similar results, of which copper powder was found to be the best copper source [22]. Under the optimal conditions, ethylene glycol [16a] gave a yield 49% lower than *rac*-BINOL gave for the model reaction.

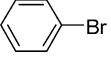
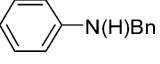
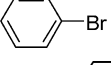
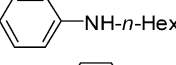
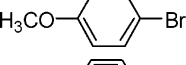
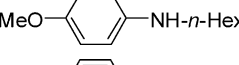
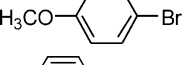
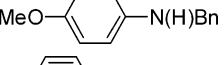
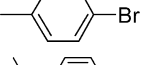
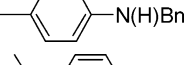
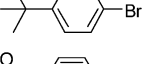
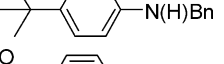
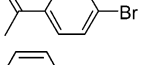
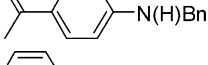
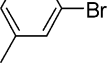
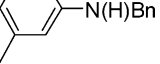
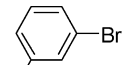
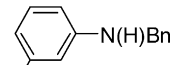


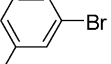
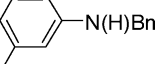
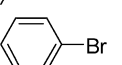
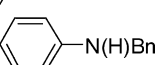
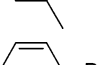
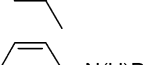
Subsequently, to explore the scope of the copper-catalyzed C–N coupling reactions, 5 mol% Cu powder/10 mol% *rac*-BINOL in DMSO with Cs_2CO_3 as the base at 90 °C were used as the general conditions to catalyze the couplings between different aryl iodides and different amines. The results were listed

in Table 2. Different primary amines including *n*-hexylamine, *sec*-butylamine, *iso*-butylamine and benzylamine were coupled successfully (entries 1–5). Good to high yields were obtained for cyclic secondary amines (entries 6–9).

Later, we used double amount of copper catalyst to catalyze the couplings between bromobenzene and primary alkyl amines. Although 59% yield was obtained for *n*-hexylamine, as for benzylamine, TLC indicated that there was only trace product produced. We suspected that there might also be the same induction period in our system as reported by Twieg [16i]. Then the efficiency of a mixture of copper powder and CuI (2:1, 1:1, 1:2) [23] was studied using bromobenzene and benzylamine as

Table 3
Coupling of aryl bromides with aliphatic primary amines^a



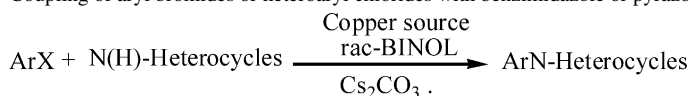
Entry	ArBr	Amine	Product	Yield (%) ^b
1		NH_2Bn		95
2		$\text{H}_2\text{N-}n\text{-Hex}$		69
3		$\text{H}_2\text{N-}n\text{-Hex}$		67
4		NH_2Bn		82 ^c
5		NH_2Bn		92
6		NH_2Bn		88 ^c
7		NH_2Bn		68 ^c
8		NH_2Bn		93
9		NH_2Bn		93
10		NH_2Bn		89
11		NH_2Bn		62 ^c
12		NH_2Bn		75
13		NH_2Bn		96 ^c

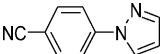
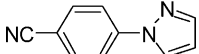
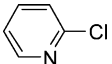
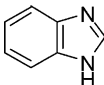
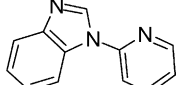
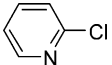
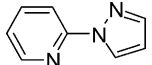
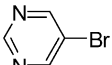
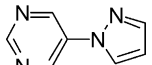
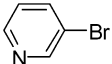
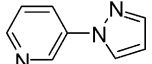
^a 1.0 mmol aryl bromides, 1.8 mmol amine, 0.05 mmol Cu powder, 0.05 mmol CuI, 0.2 mmol *rac*-BINOL, 2.3 mmol Cs_2CO_3 , 1.0 mL DMF.

^b Isolated yield.

^c 40 h.

Table 4

Coupling of aryl bromides or heteroaryl chlorides with benzimidazole or pyrazole^a

Entry	ArX	Amine	Product	Yield (%) ^b
1		Pyrazole		89 ^c
2				88 ^a
3		Pyrazole		85 ^a
4		Pyrazole		82 ^{c,d}
5		Pyrazole		98 ^c

^a 1.0 mmol ArI, 1.8 mmol amine, 0.1 mmol Cu powder, 0.2 mmol *rac*-BINOL, 2.3 mmol Cs₂CO₃, 1.0 mL DMSO, 125 °C, 48 h.^b Isolated yield.^c 1.0 mmol aryl bromides, 1.8 mmol amine, 0.05 mmol Cu powder, 0.05 mmol CuI, 0.2 mmol *rac*-BINOL, 2.3 mmol Cs₂CO₃, 1.0 mL DMF, 110 °C, 36 h.^d 40 h.

the model substrates and the ratio of 1:1 was found the best of choice. DMF showed better than DMSO, providing high yield of 95%, which was the best result reported so far (Table 3, entry 1).

The optimal reaction condition was subsequently used to examine C–N bond couplings involving functionalized aryl bromides as well (Table 3). Acetyl, carboxyl, methoxy, chloro, methyl and *t*-butyl groups were tolerated on the aryl bromide component. *n*-Hexylamine provided moderate yields (entries 2–3). For *para*-substituted aryl bromides, electron-donating substituted substrates gave better results than electron-withdrawing substituted substrates (entries 4–7). High yields were obtained for *meta*-substituted aryl bromides (entries 8–10). *ortho*-Substituted aryl bromides typically gave lower yields (entry 11). *o*-Bromobenzoic acid could be efficiently reacted to give good yield (entry 12). As for 3-bromopyridine, high yield was provided (entry 13).

Apart from the above substrates, we found that our system could also catalyze the arylation of pyrazole and benzimidazole (Table 4). Good to high yields were obtained (entries 1–5).

4. Conclusion

In conclusion, we have developed an efficient copper-catalyzed system for the amination of aryl halides and heteroaryl halides with amines and N–H heterocycles using *rac*-BINOL as the ligand. The commercially available *rac*-BINOL ligand with excellent stability and high efficiency for aryl bromides and heteroaryl chlorides ultimately make this protocol of potentially practical utility in many cases. Further studies to expand the application of this method to other catalytic reactions are currently under the way.

Acknowledgement

Financial support from the National Key Project for Basic Research (2003CB114402) is gratefully acknowledged.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2006.05.005.

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