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Three Different Reactions, One Catalyst: A Cu(I) PNP Pincer Complex as Catalyst for C−C and C−N Cross-Couplings

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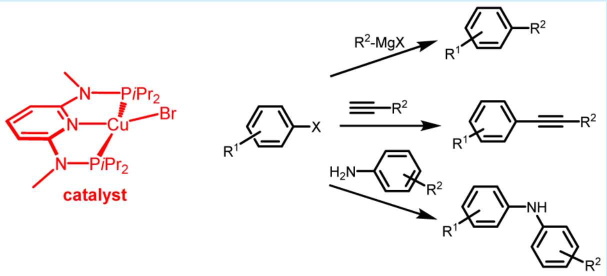
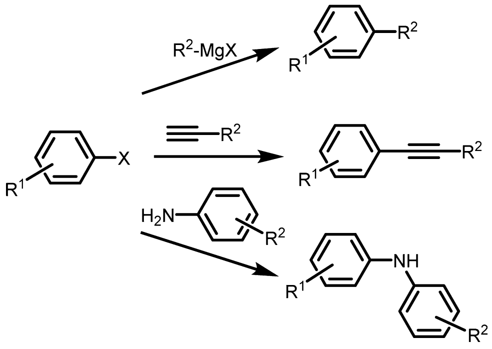
Ⓢ *Supporting Information*

ABSTRACT: An air-stable, thermally robust, and well-defined Cu(I) PNP pincer complex based on the 2,6-diaminopyridine scaffold is described. This complex is an active catalyst for the cross-couplings of a range of aryl and heteroaryl (including benzoxazole, thiazole, pyridine, and thiophene) halides with different organomagnesium reagents, alkynes, and aryl-amines giving excellent to good isolated yields.

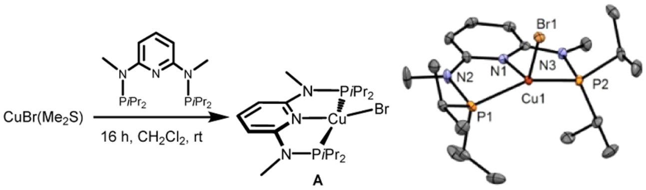


Cross-coupling reactions have become one of the most important and prevalent methods for the construction of C−C and C−heteroatom bonds in synthetic organic chemistry. They comprise a wide array of synthetic targets, ranging from manufacturing of materials and pharmaceuticals to the synthesis of building blocks and natural products. Although palladium cross coupling catalysts still dominate the field,[1] copper was actually the first metal used for C−C and C−N coupling reactions known as Glaser,[2] Goldberg,[3] Ullmann,[4] Cadiot−Chodkiewicz,[5] and Castro−Stephens[6] reactions. In fact, the Glaser reaction, a copper-promoted homocoupling of metallic acetylides, was described as early as 1869.[2] In terms of sustainability and economic viability, copper is more abundant, less expensive, and less toxic as compared to palladium, and the use of copper catalysts for cross coupling reactions is thus rapidly growing.[7,8] In fact, copper catalyst are highly efficient for the formation of C−C and C−heteroatom bonds and deal with a wide range of halides and pseudo halides (mesylates, tosylates, triflates, and pivalates).[7,8]

Scheme 1. Cross-Coupling Reactions Catalyzed by the Cu(I) PNP Complex [Cu(PNP^{Me}-*i*Pr)Br]·(A)



Scheme 2. Synthesis of [Cu(PNP^{Me}-*i*Pr)Br]·(A) and Structural View of [Cu(PNP^{Me}-*i*Pr)Br]·$C_4H_8O_2$ (A·$C_4H_8O_2$) Showing 50% Thermal Ellipsoids (H Atoms Omitted for Clarity)[a]



[a]Selected bond lengths (Å) and angles (deg): Cu1−Br1 2.4492(3), Cu1−P1 2.2693(6), Cu1−P2 2.2635(6), Cu1−N1 2.102(2), Br1−Cu1−N1 118.02(4), P1−Cu1−P2 141.88(2), P1−Cu1−N1 80.64(5), P2−Cu1−N1 81.87(4).

In this letter, we report on an air-stable and well-defined Cu(I) PNP pincer complexes based on the 2,6-diaminopyridine scaffold, which is an efficient catalyst for the coupling of several aromatic and aliphatic halides and triflates with different organomagnesium reagents, alkynes, and aromatic amines (Scheme 1). This type of PNP ligand was recently also successfully used in combination with the nonprecious metals Mn, Fe, and Ni as catalysts for dehydrogenations and C−C and C−N coupling reactions.[9] It has to be noted that PNP pincer complexes have been rarely used in copper chemistry and catalysis.[10,11]

The neutral Cu(I) PNP complex [Cu(PNP^{Me}-*i*Pr)Br]·(**A**) was obtained by treatment of CuBr(Me_2S) with the ligand PNP^{Me}-*i*Pr in 93% isolated yield (Scheme 2). The molecular structure of **A** was determined by single-crystal X-ray

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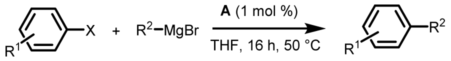
Table 1. Cu(I) Catalyzed Cross-Couplings of Aryl Halides and Alkyl Triflates with Phenyl- and Alkynyl Magnesium Bromides



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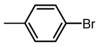
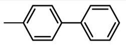
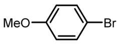
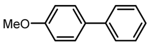
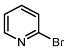
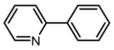
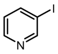
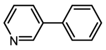
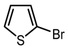
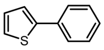
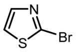
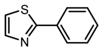
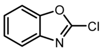
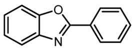
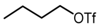
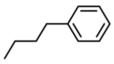
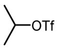
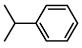
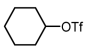
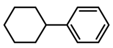
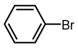
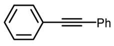
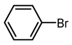
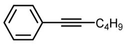
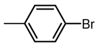
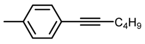
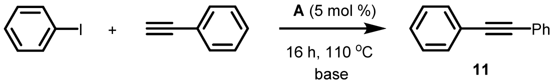
1		PhMgBr	 **1**	84
2		PhMgBr	 **2**	81
3		PhMgBr	 **3**	70
4		PhMgBr	 **4**	87
5		PhMgBr	 **5**	81
6		PhMgBr	 **6**	89
7		PhMgBr	 **7**	92
8		PhMgBr	 **8**	58
9		PhMgBr	 **9**	47
10		PhMgBr	 **10**	78
11[b]		Ph—≡—MgBr	 **11**	94
12[b]		C_4H_9—≡—MgBr	 **12**	91
13[b]		C_4H_9—≡—MgBr	 **13**	93

[a] Isolated yields after purification with silica column chromatography. [b] Alkyne mixed with *i*-PrMgBr.

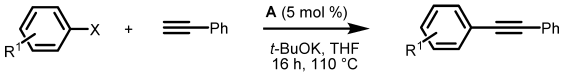
Table 2. Efficiency of Aryl-Alkyne Cross-Couplings

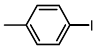
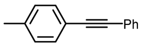
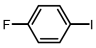
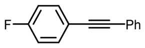
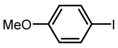
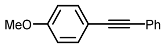
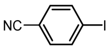
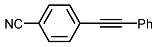
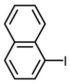
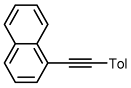
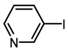
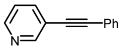
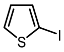
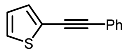
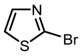
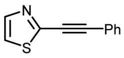
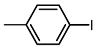
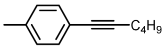
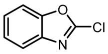
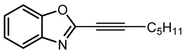


entry	solvent	base	yield[a] [%]
1	toluene	*t*-BuOK	traces
2	THF	*t*-BuOK	89
3	DMF	*t*-BuOK	0
3	DME	*t*-BuOK	81
4	dioxane	*t*-BuOK	69
5	THF	Cs_2CO_3	62
6	THF	TEA	traces
7	THF	DIPA	traces
8[b]	THF	*t*-BuOK	traces

[a] Isolated yields after purification with silica column chromatography. [b] $CuBr(Me_2S)$ as catalyst.

Table 3. Cu(I) Catalyzed Aryl-Alkyne Cross-Couplings



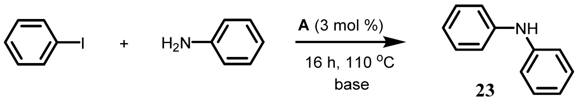
entry	R-X	product	yield [%][a]
1		 **14**	93
2		 **15**	84
3		 **16**	87
4[b]		 **17**	86
5		 **18**	91
6		 **19**	89
7		 **20**	85
8		 **21**	83
9		 **13**	81
10		 **22**	86

[a] Isolated yields after purification with silica column chromatography. [b] Cs_2CO_3 was used as base at 130 °C.

diffraction. A structural view is depicted in Scheme 2 with selected bond distances given in the caption.

The first reactions we investigated were Kumada–Corriu[1] and Castro–Stephens type[6] cross-couplings of aryl halides and alkyl triflates with phenyl- and alkynyl magnesium bromides. For the latter, *i*-PrMgCl was added to prepare the organomagnesium compound *in situ*. All reactions were performed in THF with 1 mol % of the catalyst at 50 °C for 16 h without further optimizations. The results of these coupling reactions are summarized in Table 1. In general, good to excellent isolated yields were observed for all substrates. Also heteroaryl halides (based on benzoxazole, thiazole, pyridine, and thiophene) afforded good yields (Table 1, entries 3–7). Moreover, we tested the reactivity of nonactivated primary and secondary aliphatic triflates for the cross coupling with

Table 4. Efficiency of Aryl-Amine Cross-Couplings



entry	solvent	base	yield[a] [%]
1	toluene	*t*-BuOK	20
2	THF	*t*-BuOK	91
3	THF	*t*-BuONa	93
4	THF	K_2CO_3	44
5	THF	Cs_2CO_3	87
6	DME	*t*-BuOK	78
7[b]	THF	*t*-BuOK	traces

[a] Isolated yields after purification with silica column chromatography. [b] $CuBr(Me_2S)$ as catalyst.

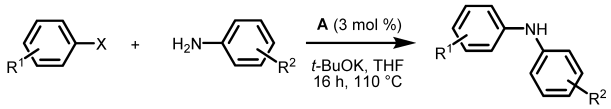
PhMgBr (Table 3, entries 8−10). These reactions proceeded in good to excellent isolated yields (47−94%). It has to be noted that $CuBr(Me_2S)$ itself was catalytically poorly active. Under identical reaction conditions the coupling of 4-bromotoluene with PhMgBr afforded **1** in only 11% isolated yield as compared to 84% with catalyst **A** (Table 1, entry 1).

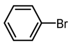
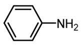
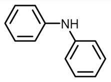
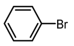
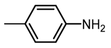
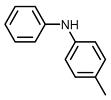
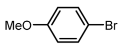
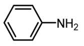
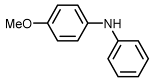
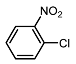
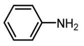
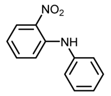
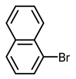
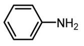
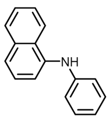
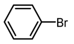
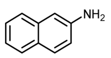
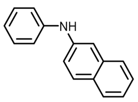
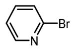
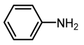
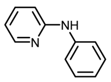
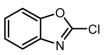
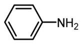
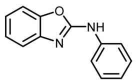
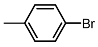
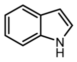
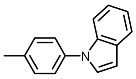
Next we investigated the reaction of aromatic halides with phenyl acetylene. Coupling reactions between alkynes and sp^2 systems are well-known as Sonogashira reaction with copper as additive, while palladium-free reactions are described less commonly in the literature.[12] The reaction of iodobenzene and phenyl acetylene was chosen to identify the optimal reaction conditions for this process (Table 2). The best results were achieved in THF at 110 °C for 16 h with *t*-BuOK (1.2. equiv) as base and a catalyst loading of 5 mol %. $CuBr(Me_2S)$ was catalytically inactive (Table 2, entry 8). To explore the scope of catalyst A we evaluated the coupling of various aryl and heteroaryl halides with phenyl acetylene. The results of the couplings are given in Table 3. Both aryl heteroaryl halides (based on pyridine, thiophene, and thiazole) afforded good to excellent yields. In the case 4-iodobenzonitrile, the reaction temperature was 130 °C, and Cs_2CO_3 (1.2. equiv) was used as base in order to obtain a high isolated yield (Table 3, entry 4).

Finally, we tested the reactivity of catalyst **A** for the coupling of aromatic halides with anilines (Ullman, Goldberg, and Buchwald-Hartwig[13] type reactions). The reaction of iodobenzene and phenyl aniline was investigated to identify the most efficient conditions for the aryl-amine coupling as depicted in Table 4. The best results were again obtained in THF at 110 °C with *t*-BuOK (1.2. equiv) as base for 16 h and 3 mol % of catalyst. $CuBr(Me_2S)$ again was catalytically inactive (Table 4, entry 7). The scope of catalyst **A** was studied for the coupling of various aryl and heteroaryl halides with anilines. These results are summarized in Table 5. In all cases good to excellent isolated yields were observed. In the case of 1-chloro-2-nitrobenzene, Cs_2CO_3 (1.2. equiv) was used as base (Table 5, entry 4). With 2-chlorobenzoxazole, the reaction time could be reduced to 3 h (Table 5, entry 8). Unactivated chloro compounds did not react under these conditions.

In conclusion, we described the synthesis and catalytic applications of a thermally robust and well-defined Cu(I) PNP pincer complex based on the 2,6-diaminopyridine scaffold. We have developed different protocols for the coupling of aryl and heteroaryl halides with a wide range of aryl amines, alkynes, and organomagnesium reagents. The catalyst works well with a wide variety of substrate, and in most cases, high yields of isolated products are obtained. This is particularly interesting in the case of heterocycles due their coordinating properties. This palladium-free application of a Cu(I) catalyst constitutes an environmentally benign processes and is an excellent alternative for various sp, sp^2, and sp^3 coupling reactions revealing a broad functional group tolerance.

Table 5. Cu(I) PNP Catalyzed Aryl-Amine Cross-Coupling



entry	R-X	R-NH2	product	yield[a] [%]
1			 **23**	84
2			 **24**	87
3			 **25**	82
4[b]			 **26**	76
5			 **27**	91
6			 **28**	86
7			 **29**	73
8[c]			 **30**	93
9			 **31**	86

[a] Isolated yields after purification with silica column chromatography. [b] Cs_2CO_3 was used as base at 130 °C. [c] Reaction time 3 h.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00857.

Crystallographic data for **A** (CCDC entry 1522968) (CIF)

Synthetic procedures, ^{1}H, $^{13}C\{^{1}H\}$, and $^{31}P\{^{1}H\}$ NMR spectra of **A** and all organic products (PDF)

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Notes

The authors declare no competing financial interest.

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