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N- versus O-Arylation of Aminoalcohols: Orthogonal Selectivity in Copper-Based Catalysts

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In 2002, we disclosed a set of complementary procedures for the copper-catalyzed N- and O-arylation of β-aminoalcohols.[1] While no added ligand was required for these Ullmann-type couplings, attempts to expand the scope to other types of aminoalcohols resulted in low levels of chemoselectivity. We reasoned that since a 1,2-aminoalcohol itself can assist in the reaction by acting as a supporting ligand an additional ligand might be required for nonchelating substrates. Therefore, ligand-assisted Ullmann coupling of aminoalcohols was investigated; the preliminary findings of this study are disclosed in this report.

Recently, a number of ligands were shown to expedite Ullmann arylation of aliphatic amines.[2−4] We began by examining the coupling of 5-amino-1-pentanol with 3-iodobromobenzene using 5% CuI and 20% of diketone **L1** (Scheme 1).[4] After only 7 h at room temperature, the desired N-arylated product **1a** was isolated in 97% yield, with none of the O-arylated regioisomer detectable.

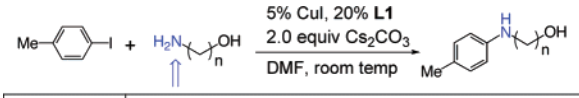
Our previous work on copper-catalyzed C−O coupling using phenanthroline or the more soluble tetramethylphenanthroline (**L2**)[5] prompted us to see if a switch to this type of ligand might alter the observed chemoselectivity. Indeed, the coupling of 3-iodobromobenzene with 5-amino-1-pentanol in the presence of 5% CuI and 10% **L2** at 90 °C was complete after 16 h, affording the O-arylated product **1b** in 86% yield (Scheme 2).[6]

Together, the protocols shown in Schemes 1 and 2 represent a complementary set of conditions for copper-catalyzed N- and O-arylation of 5-amino-1-pentanol. To test the generality of these processes, arylation of a series of linear (C_2−C_6) aminoalcohols was performed. As shown in Table 1, the catalyst based on **L1** was highly effective for substrates with $n \geq 3$, affording the N-arylated products **3a**−**6a** in excellent yields and chemoselectivity. Only the reaction of ethanolamine led to a sluggish reaction and a sizable fraction of the O-arylated product. It is likely that the formation by ethanolamine of stable *five-membered* chelate rings[7] might interfere with the normal functioning of the catalyst. Interestingly, in the absence of added ligand, the N-arylated ethanolamine (**2a**) was obtained selectively in 92% yield (40:1) after only 14 h at room temperature.

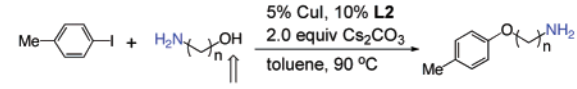
In a related series of experiments, an OH−NH_2 separation of at least four methylene units was found to be necessary to ensure selective (>15:1) O-arylation using ligand **L2**. Although only traces of the N-arylated isomer were detected for these substrates, some (2−4%) of the N-, O-diarylated byproduct was observed, along with some reduced ArH. The reasons for N,O-diarylation in the presence of excess aminoalcohol are currently under investigation. The coupling of aminoalcohols with fewer methylene groups (n = 2, 3) gave rise to a mixture of N-, O-, and double-arylation products. Although some success with O-arylation was achieved under ligand-free conditions, an efficient O-selective method for these is yet to be realized.

The data presented in Table 1 suggest that the selectivity in ligand-assisted reactions is only achieved for nonchelating aminoalcohols and that 1-amino-3-propanol represents a "borderline"

Table 1. Effect of Spacer Length of N- and O-Arylation Reactions[a,b]



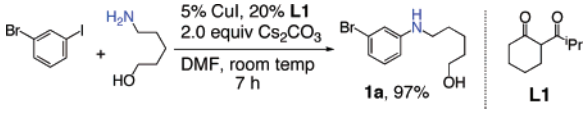
a, n =	2	3	4	5	6
CN Yield, %	45[c] (92)[d]	96	99	97	99
CN : CO	3:1 (40:1)	45:1	>50:1	>50:1	>50:1



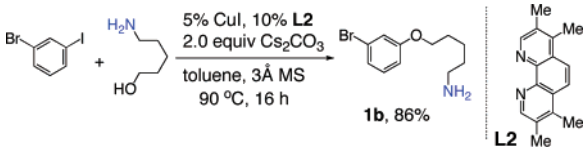
b, n =	2	3	4	5	6
CO Yield, %	16[c]	28[c] (64)[e]	91	90	89
CO:(CN+double)	1:6	1:4 (2:1)	18:1	20:1	24:1

[a] Using 1.5−2.0 equiv of aminoalcohol. [b] Isolated yields, average of two runs. [c] GC yield. [d,e] Ligand-free conditions; see Supporting Information.

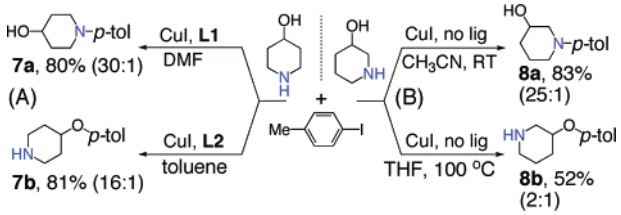
Scheme 1. N-Arylation of 5-Amino-1-pentanol



Scheme 2. O-Arylation of 5-Amino-1-pentanol



Scheme 3. N- and O-Arylation of 4- and 3-Piperidinols



case. This hypothesis was put to the test in the arylation of 3- and 4-piperidinols. Despite being structurally related, the two differ significantly in their metal-chelating abilities. As expected, the coupling of the nonchelating 4-piperidinol employing ligands **L1** and **L2** led to the selective formation of both the N-arylated **7a** (80%, 30:1) and the O-arylated **7b** (81%, 16:1) (Scheme 3A). Under the same reaction conditions, the potentially chelating 3-piperidinol gave rise to a mixture of products. On the other hand, submitting a mixture of 3-piperidinol and 4-iodotoluene to the "ligand-free" protocol developed for N-arylation of ethanolamine afforded the

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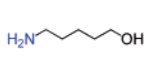
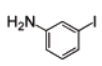
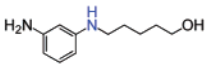
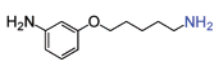
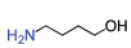
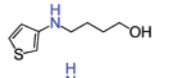
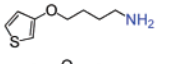
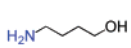
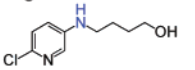
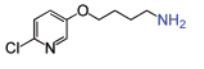
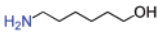
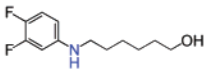
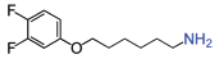
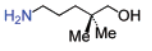
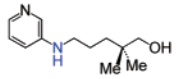
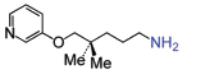
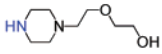
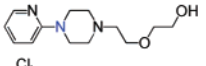
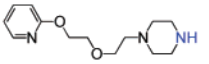
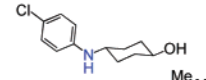
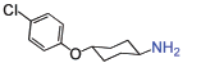
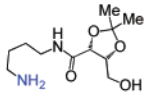
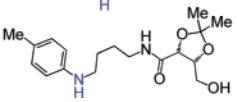
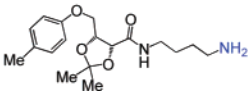
Table 2. Copper-Catalyzed N- and O-Arylation of Aminoalcohols[a]

entry	aminoalcohol	ArI	C-N product	C-N, %[b,c] (N:O)	C-O product	C-O, %[d,e,f] (N:O)
1				**9a**, 84 (>50:1)		**9b**, 79 (16:1)
2				**10a**, 85 (>50:1)		**10b**, 80 (20:1)
3				**11a**, 84 (25:1)		**11b**, 78 (16:1)
4				**12a**, 93 (>50:1)		**12b**, 79 (18:1)
5				**13a**, 83 (20:1)		**13b**, 80 (15:1)
6				**14a**, 83 (18:1)		**14b**, 81 (15:1)
7				**15a**, 80 (20:1)		**15b**, 80 (18:1)
8				**16a**, 85 (20:1)		**16b**, 81 (16:1)

[a] Isolated yields, average of two runs. [b] With **L1**. [c] Selectivity: %CN:%CO. [d] With **L2**. [e] Selectivity: %CO:(%CN + % double). [f] Balance: ArH (from ArI) and Ar_2O.

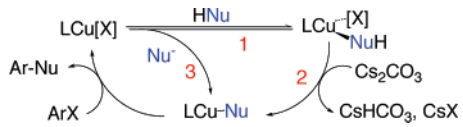
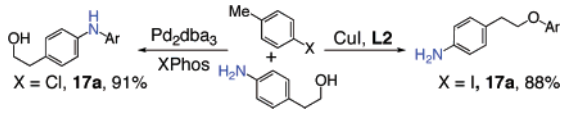


Figure 1. A working hypothesis of the mechanistic cycle.

Scheme 4. N- and O-Arylation of 4-Aminophenethyl Alcohol (Ar = *p*-tolyl)[a]



[a] See Supporting Information for details.

N-arylated product **8a** smoothly in 83% yield (25:1, Scheme 3B). It was also possible to achieve a moderately selective ligand-free O-arylation of 3-piperidinol.

With this set of two orthogonal catalysts, the targeting of either the N- or the O-terminus in several molecules was investigated. As shown in Table 2, electron-rich and electron-deficient as well as heteroaryl iodides underwent both N- and O-arylation with good to excellent chemoselectivities.

Our current hypothesis is that the two initial steps, coordination (1) and deprotonation (2) (Figure 1), are responsible for the observed selectivities. These events are interdependent since the pK_a of Cu-bound nucleophiles is significantly lower than that of the free species. For anionic **L1**, the lowered electrophilicity of the Cu(I) center might disfavor the binding of alcohol and allow the high affinity of amine to Cu(I) to dictate the outcome.[8] The more Lewis acidic (**L2**)Cu(I) species may lead to non-negligible concentration of the copper-bound alcohol; facile deprotonation of such species would favor O-selectivity. Alternatively, the (**L2**)Cu(I) catalyst may require a pre-deprotonated nucleophile (3), favoring once again the more acidic alcohol.

Unlike the efficient coupling of aliphatic amines, N-arylation of the less acidic aromatic amines proved to be more challenging. Thus, while copper-catalyzed O-arylation of 4-aminophenethyl alcohol using **L2** afforded the expected **17b** in 88% yield (Scheme 4), attempts to perform N-arylation using **L1** were not successful. In this case, switching to a palladium catalyst afforded the N-arylated **17a** in 91% yield.[9]

In summary, we have disclosed two complementary copper-based methods for the selective N- and O-arylation of aminoalcohols. Work is currently underway to understand the exact role of ligands and to expand the scope of these methods.

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Supporting Information Available: Detailed experimental procedures and characterization of products. The material is available free of charge via the Internet at http://pubs.acs.org.

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(6) The use of activated 3 Å MS suppressed the formation of biaryl ethers.
(7) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th ed.; John Wiley & Sons: New York, 1988.
(8) Preliminary calculations (DFT) revealed that, for the neutral β-diketonate−Cu(I) complex, coordination of ethylamine is favored by a factor of 1.7 × 10^9 over the coordination of ethanol.
(9) For examples of Pd-catalyzed C−N coupling of aminoalcohols, see: (a) Harris, M. C.; Huang, X. H.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 2885−2888. (b) Shen, Q. L.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1371−1375.

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