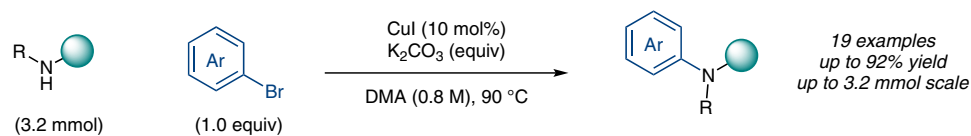


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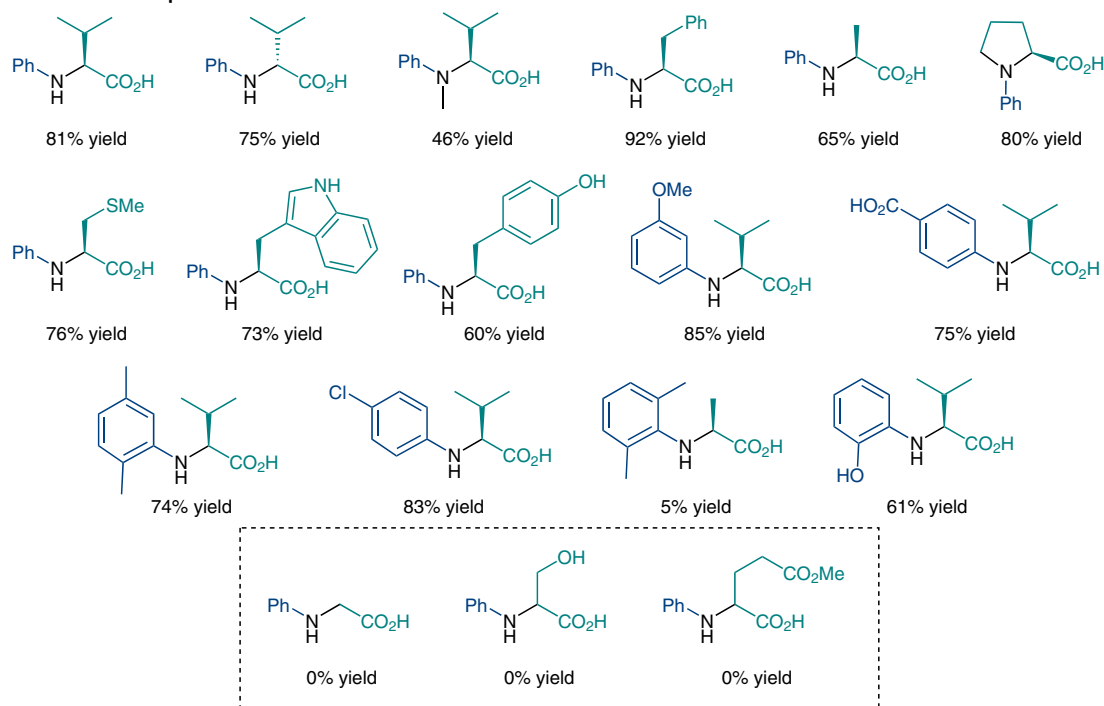
Accelerating Effect Induced by the Structure of  $\alpha$ -Amino Acid in the Copper-Catalyzed Coupling Reaction of Aryl Halides with  $\alpha$ -Amino Acids. Synthesis of Benzolactam-V8

*J. Am. Chem. Soc.* **1998**, *120*, 12459–12467, DOI: 10.1021/ja981662f.

## Amino-Acid Promoted Ullmann-Type C–N Coupling



### Selected examples:



**Significance:** Since the early 1900s, copper-catalyzed Ullmann coupling reactions between nucleophiles and aryl halides became increasingly popular. In 1998, Ma and co-workers were investigating the use of enantiomerically pure amines as coupling partners to access biologically relevant chiral N-aryl- $\alpha$ -amino acids. They discovered that the reaction with amino acids could proceed at significantly lower temperature, and tolerate traditionally difficult electron-rich aryl halides as coupling partners. Following this report, many bidentate ligands, including amino acids, have been developed to promote Ullmann-type coupling reactions.

**Comment:** Amines with larger hydrophobic substituents gave higher yields, while amines with hydrophilic groups were incompatible in the reaction. Notably, no racemization was observed in most cases. Control experiments supported the notion of an accelerating effect induced by the structure of the amino acid. The authors proposed the amino acid salt chelates to the Cu and forms a  $\pi$ -complex with the aryl halide, prior to an intramolecular nucleophilic substitution.

**Review:** D. Ma, Q. Cai *Acc. Chem. Res.* **2008**, *41*, 1450–1460.