Cross-Coupling of Two Different tert-Alkyl Radicals for Highly Congested Unnatural α-Amino Acid Synthesis

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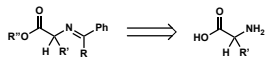
Introduction

Amino Acid Schiff bases for Unnatural α-Amino Acids Synthesis

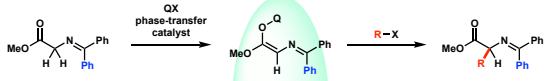


Amino acid Schiff base

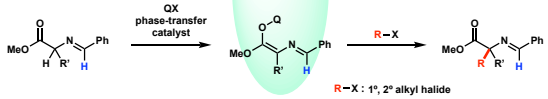
O'Donnell, M. J. *Tetrahedron* 2019, *75*, 3667.

Previous Work: 2e⁻ Reaction

- Glycinate Schiff base (ketoimine)



- Amino acid Schiff base (aldimine)

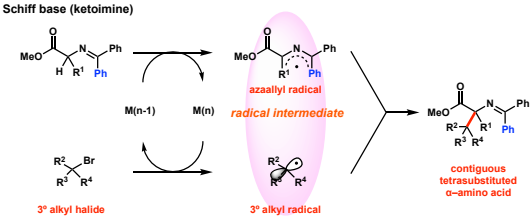


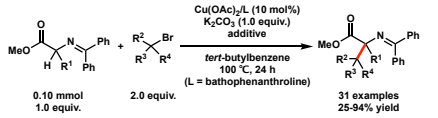
R−X : 1°, 2° alkyl halide

Maruoka, K. *et al. Chem. Rev.* 2007, *107*, 5656.

This Work: 1e⁻ Reaction

- Amino acid Schiff base (ketoimine)



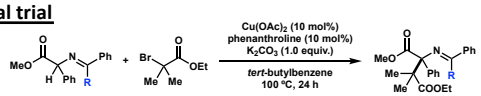


- Construction of contiguous tetrasubstituted carbon centers
- Successive β-functionalization and oxidation
- Three-components cross-coupling reaction

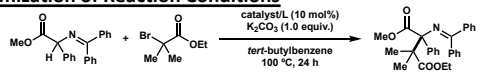
Matsumoto, Sawamura, Murata, Nishikata, Yazaki, Ohshima (*J. Am. Chem. Soc.* 2020, *142*, 8498).

Results and Discussion

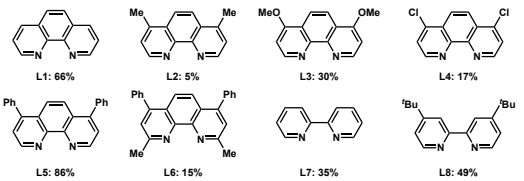
Initial trial



Optimization of Reaction Conditions



▪ Ligand optimization with $Cu(OAc)_2$

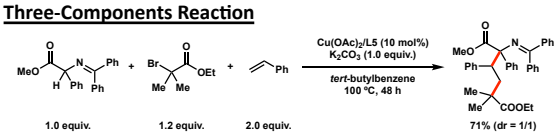


▪ Catalyst optimization with L5

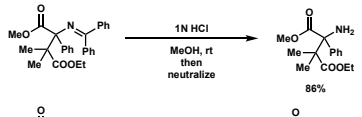
$Cu(OAc)_2$	$Cu(OTf)_2$	$CuCl_2$	$CuBr_2$	CuOAc
86%	11%	9%	42%	22%
$(CuOTf)_2$•benzene[a]	CuCl	CuBr	$Fe(OAc)_2$	$NiBr_2$•diglyme
11%	18%	9%	0%	0%

Yields were determined by ^1H NMR analysis. [a]5 mol% of $(CuOTf)_2$-benzene complex was used.

Three-Components Reaction

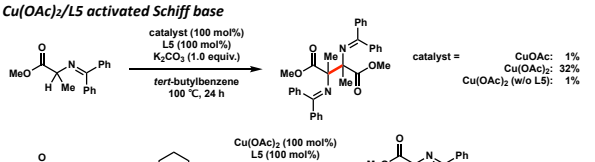


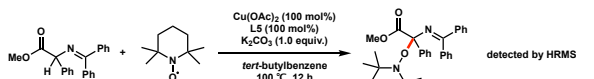
Transformation of the Products

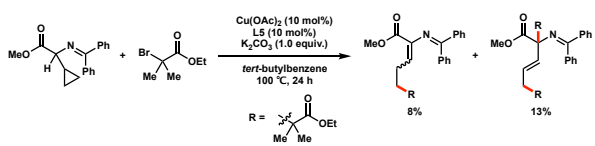


Control Experiments

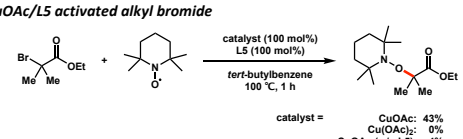
$Cu(OAc)_2$/L5 activated Schiff base



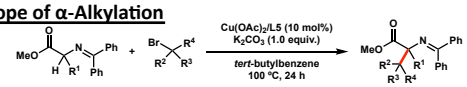




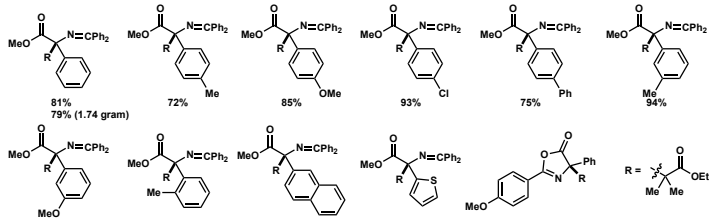
CuOAc/L5 activated alkyl bromide



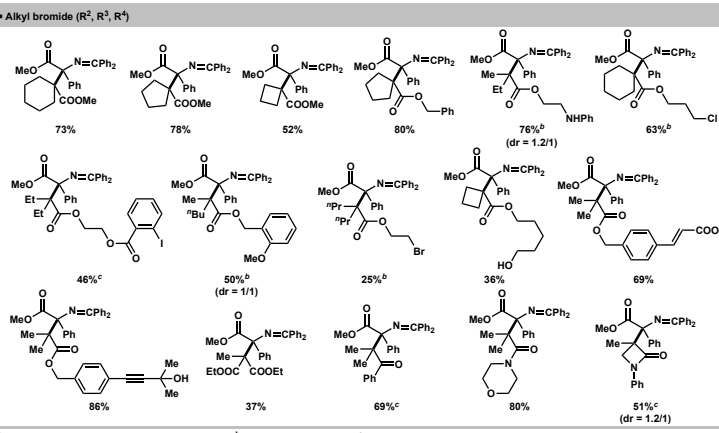
Substrate Scope of α-Alkylation



▪ Amino acid Schiff base (R^1)

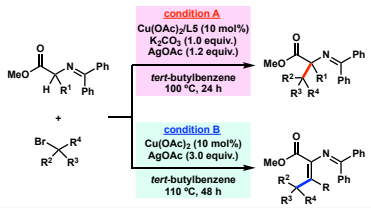


▪ Alkyl bromide (R^2, R^3, R^4)

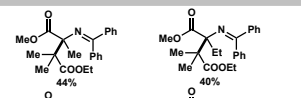


[a]Regioisomer ratio of C4/C2 of azlactone = 4.2/1. [b]Reaction time was 72 h. [c]Reaction time was 48 h.

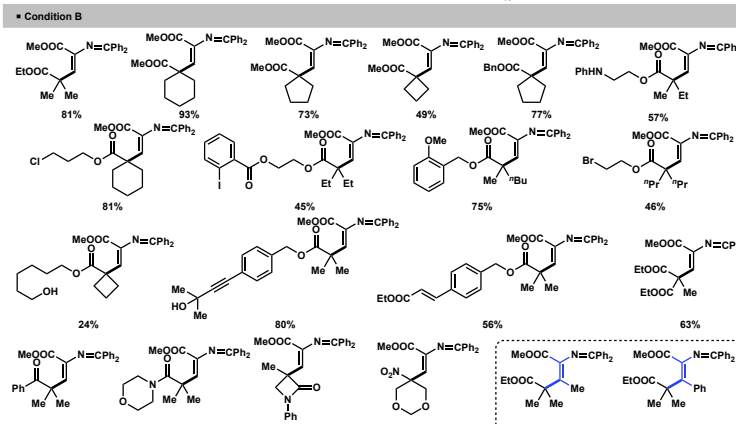
Substrate Scope of Chemoselective Alkylation



▪ Condition A



▪ Condition B



[a]Reaction temperature was 130 °C.