

Ullmann-Ma reaction

20200804

王馨

Brief Introduction



Fritz Ullmann

1875-1939 German chemist
1905 PhD in University of Geneva
Carl Gräbe

Ullmann reaction, Ullmann condensation
Graebe-Ullmann synthesis,
Jordan-Ullmann-Goldberg synthesis.



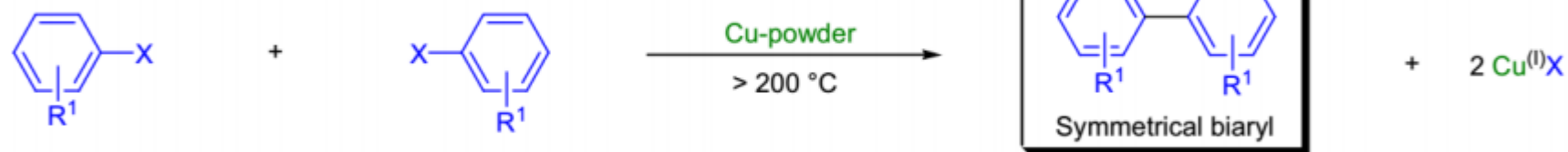
Ma Dawei

Born in 1963, Henan Province
1984 BS from Shandong University
1989 PhD from SIOC, Lu Xiyan
1993 Postdoctoral research at the University of
Pittsburgh and Mayo Clinic in the United States
1994 –present SIOC

2019 Member of the Chinese Academy of Sciences

Ullmann Reactions

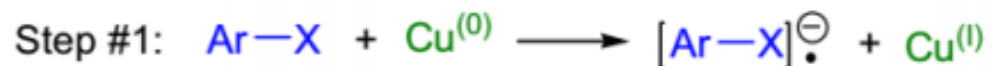
Synthesis of symmetrical biaryls (Ullmann, 1901):



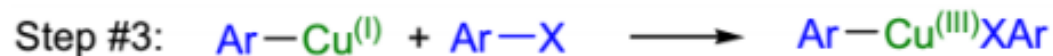
$R^1, R^2 = \text{H, CN, NO}_2, \text{CO}_2\text{R, I, Br, Cl}$; $\text{X} = \text{I, Br, Cl, SCN}$; solvent: DMF, pyridine, quinoline, nitrobenzene, *p*-nitro toluene

Mechanism:

Pathway involving aryl radicals:



Pathway involving arylcopper intermediates:



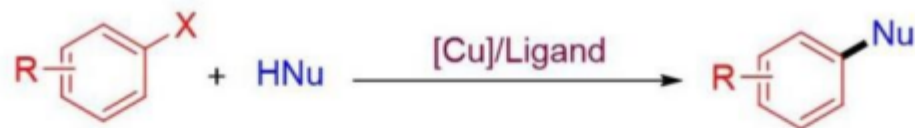
Drawbacks of traditional Ullmann reactions

Drawbacks

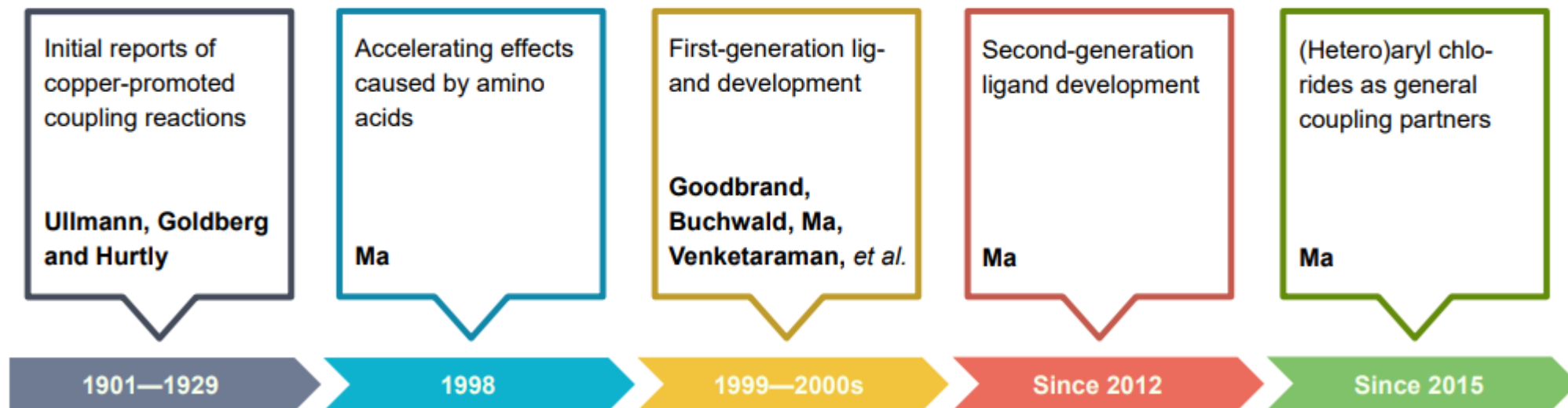
narrow substrate scope

harsh reaction conditions (high temperatures, strong bases)

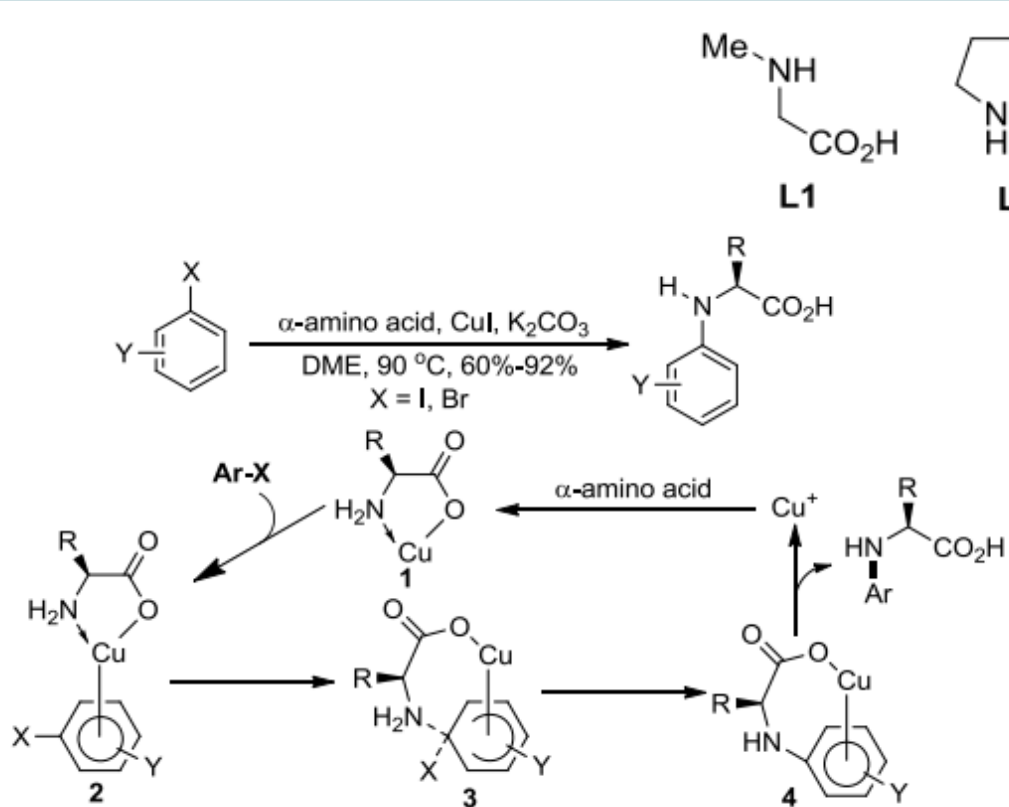
the requirement of stoichiometric amounts of copper reagents



Ligand: Amino Acids; Oxalic Diamides and Related Amides

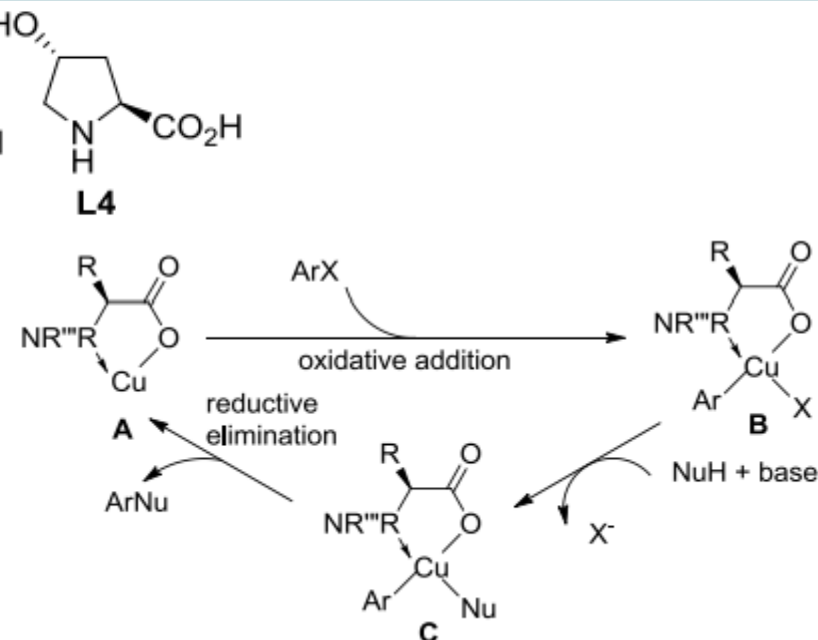


Amino Acids: First-Generation Ligands for Ullmann-Ma Reaction

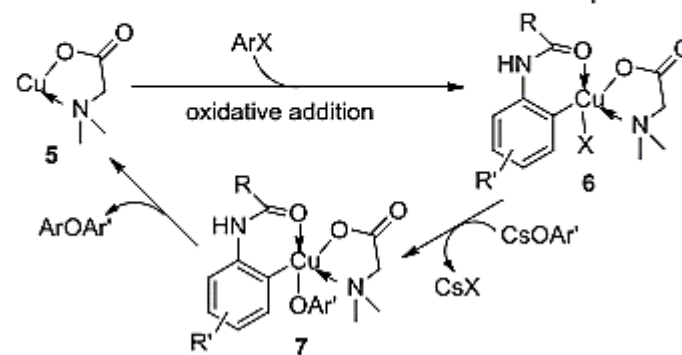
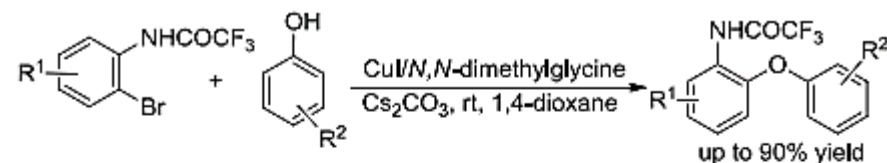


Picture 1 CuI-catalyzed coupling reaction of aryl halides with α -amino acids and proposed mechanism

Ortho-substituent effect of amido group:
efficiency order, CF₃CO > CH₃CO > PhCO:

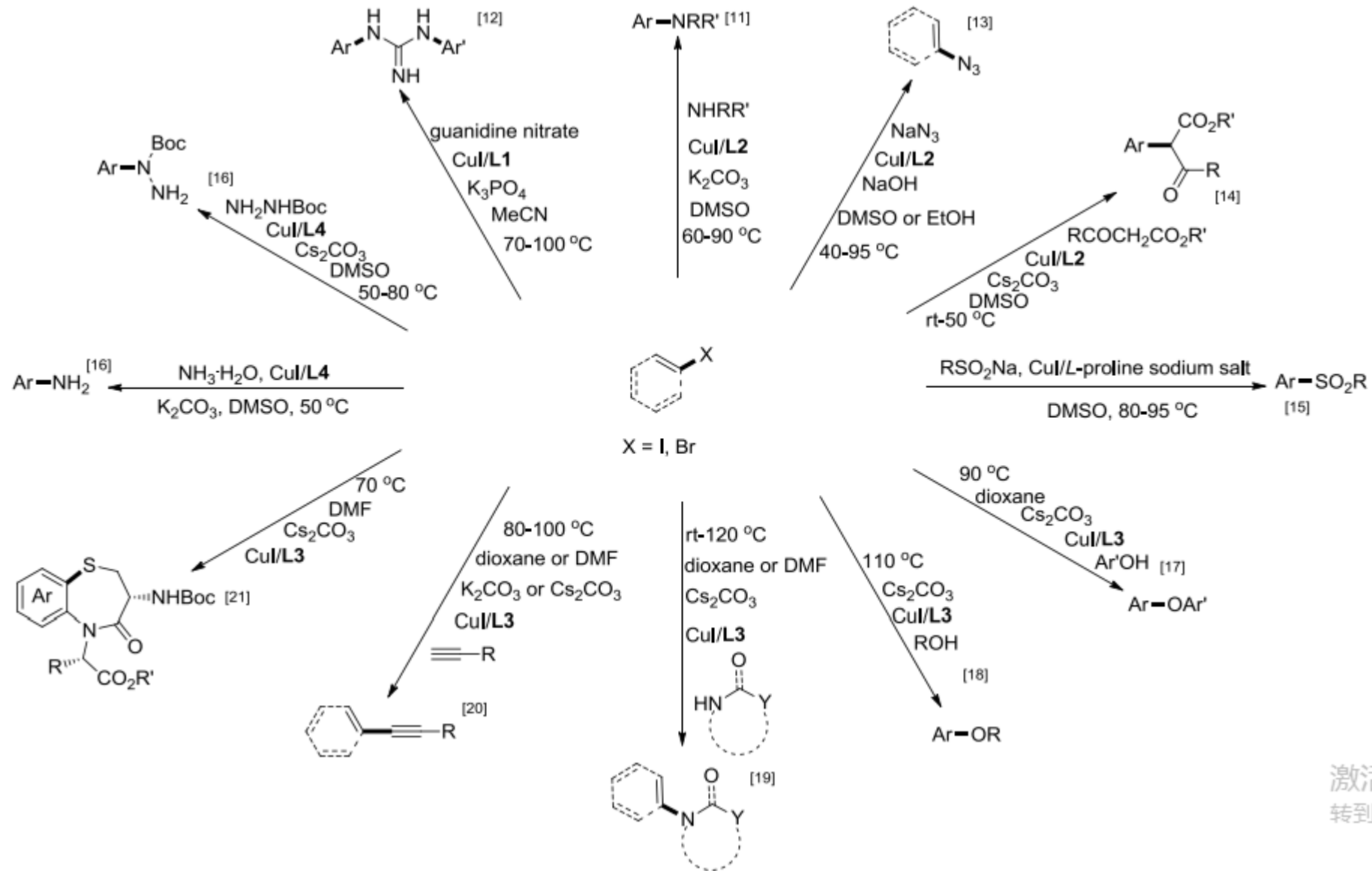


Picture 2 Proposed catalytic cycle



Picture 3 Room-temperature biaryl ether formation

Amino Acids: First-Generation Ligands for Ullmann-Ma Reaction

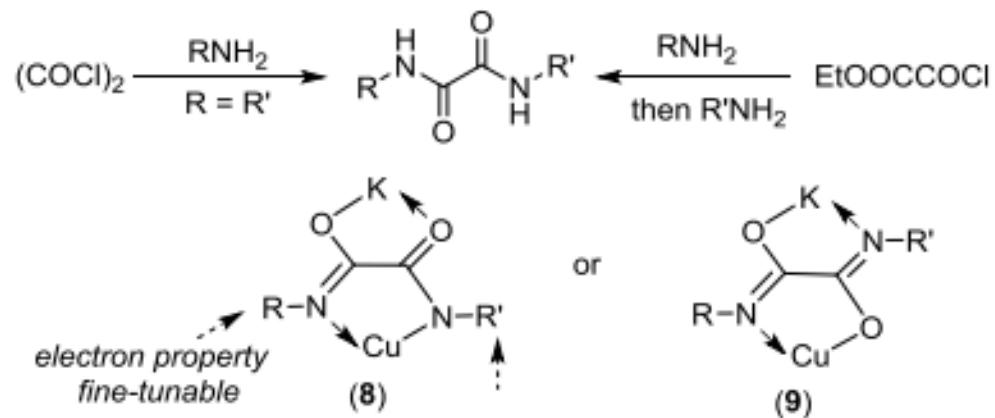


激活
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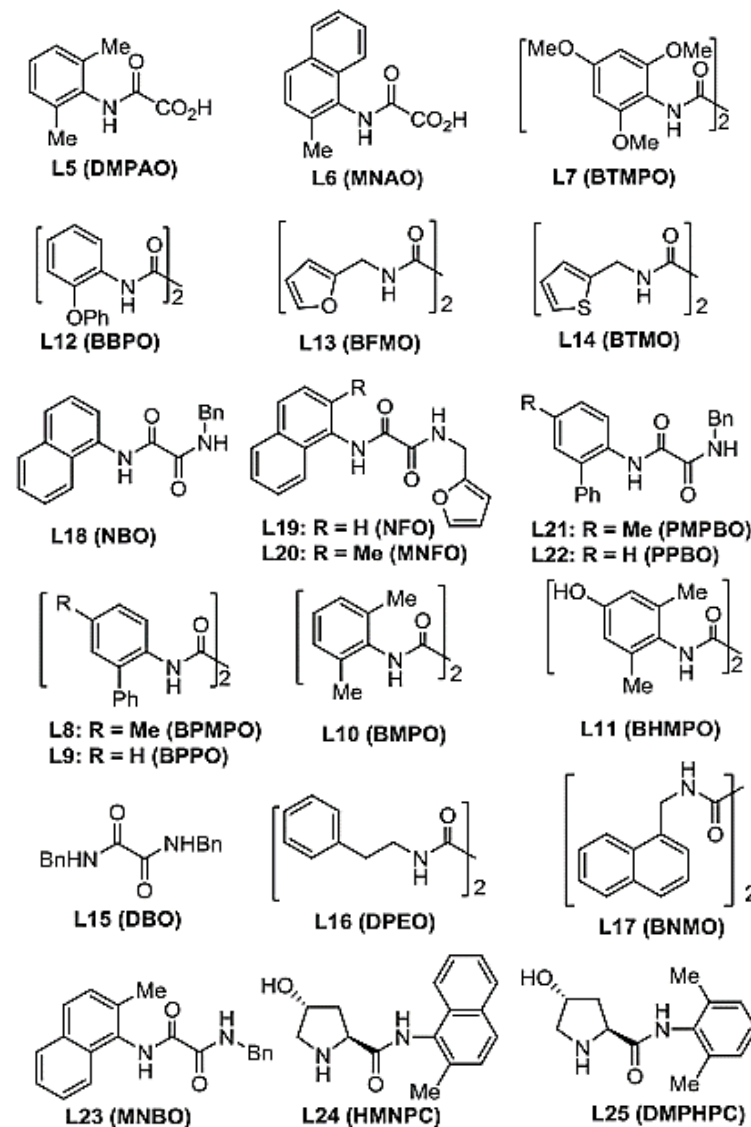
Picture 4 CuI/amino acids-catalyzed coupling reactions of aryl halides and vinyl halides with nucleophiles

Oxalic Diamides and Related Amides: Second-Generation Ligands for Ullmann-Ma Reaction

Deficiencies after development of first generation of ligand: substrate scope, efficiency and activity

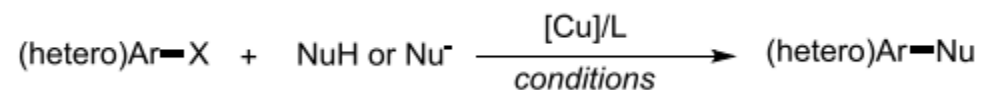


Picture 5 The synthesis of oxalic diamides and the working model



Picture 6 Representative second-generation ligands

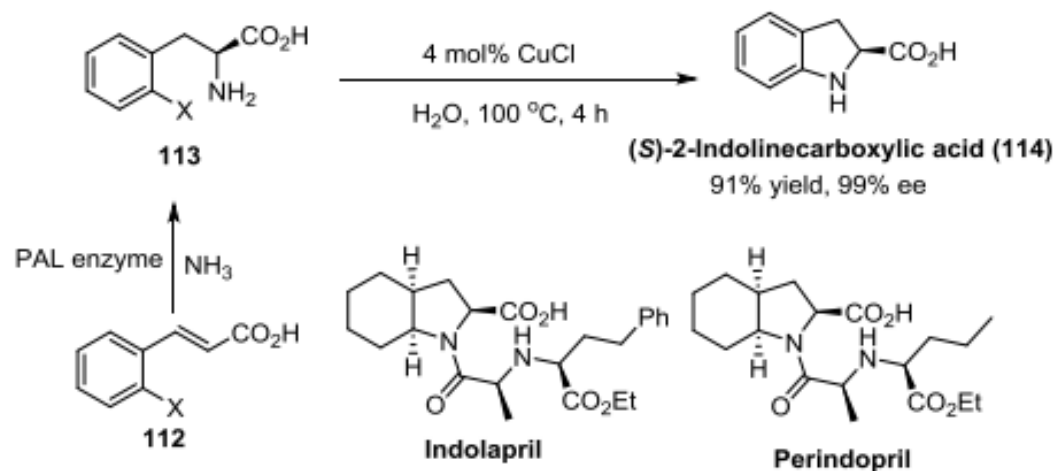
Oxalic Diamides and Related Amides: Second-Generation Ligands for Ullmann-Ma Reaction



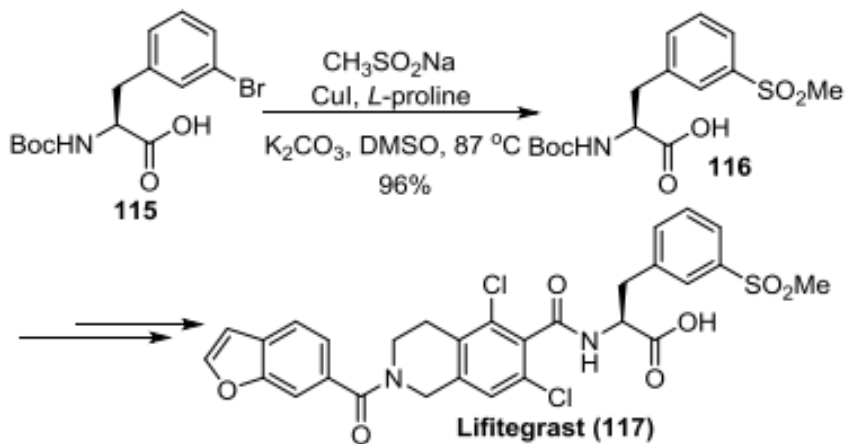
Entry	NuH or Nu-	Conditions	(Het)Ar-Nu Yield	Ref	
1	cyclic & acyclic secondary amines	X = Br, I: 1–10 mol% CuI & 2–20 mol% L5 K ₃ PO ₄ , DMSO, 60–110 °C	(Het)Ar-NRR' up to 100%	[33]	→ Aliphatic acyclic secondary amines
2	KOCN/ROH	X = Br, I: 20 mol% CuI & L5, K ₃ PO ₄ , 100–110 °C X = I, Br, Cl: 3–10 mol% CuI & L6, K ₃ PO ₄ , 100–130 °C	(Het)Ar-NHCOOR 40%–92%	[34]	
3	KOCN, NHRR'	X = Br: 20 mol% CuI & 40 mol% L5, K ₃ PO ₄ , MeCN, 110 °C	(Het)Ar-NHCONRR' 60%–95%	[35]	
4	NHRR'	X = Cl: 2–10 mol% CuI & L7, K ₃ PO ₄ , DMSO, 120 °C X = Br: 1 mol% CuI & L7 or L13, K ₃ PO ₄ , EtOH, 60–80 °C	(Het)Ar-NRR' 50%–97%	[36,37]	→ First time for (hetero)aryl chloride
5	NH ₃ aqueous or gaseous	X = Cl: 2–20 mol% CuI & L8, K ₃ PO ₄ , DMSO, 110–120 °C	(hetero)aryl-NH ₂ 43%–95%	[38]	
6	NH ₃ ·H ₂ O	X = Br: 0.1 mol% Cu ₂ O & L20, 80 °C X = I: 0.1 mol% Cu ₂ O & L19, 60 °C, KOH, EtOH	(hetero)aryl-NH ₂ 64%–98%	[39a]	→ Low catalyst loadings
7	RNH ₂ , ArNH ₂ cyclic secondary amines	X = Br, I: 0.01–0.5 mol% Cu ₂ O & L23, KOH, EtOH, 50–80 °C	(hetero)aryl-NRR' up to 98%	[39a]	
8	N ₂ H ₄ ·H ₂ O	X = I, Br: 2 mol% CuI & L10, 2–4 mol% of CTAB, K ₃ PO ₄ , H ₂ O, 80 °C; then HCl	Ar-NHNH ₂ ·HCl 40%–90%	[39b]	

Picture 7 The conditions and scope of Ullmann-Ma reactions under the catalysis of copper and second-generation ligands

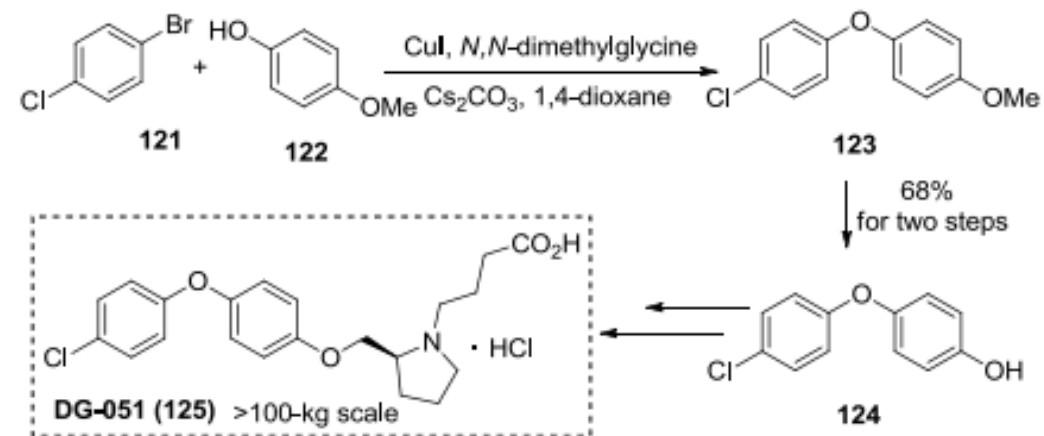
Applications



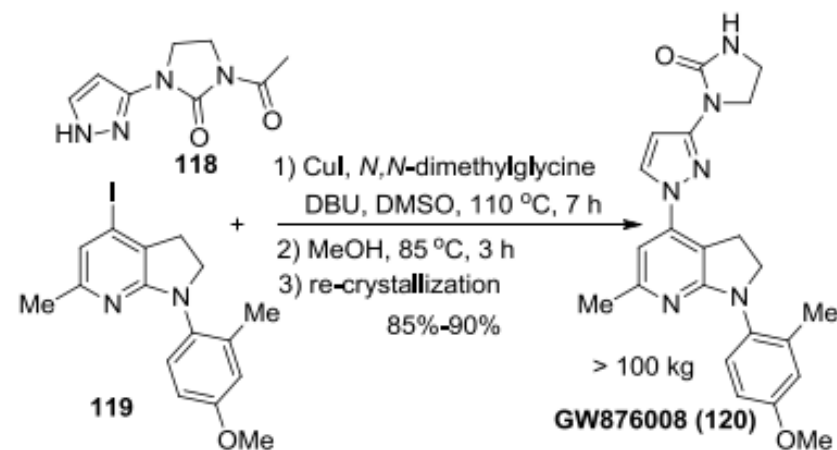
Picture 8 Ton-scale preparation of (S)-2-indolinecarboxylic acid



Picture 10 Ton-scale preparation of Lifitegrast



Picture 9 100-kg scale synthesis of DG-051 with Ullmann-Ma reaction as key step



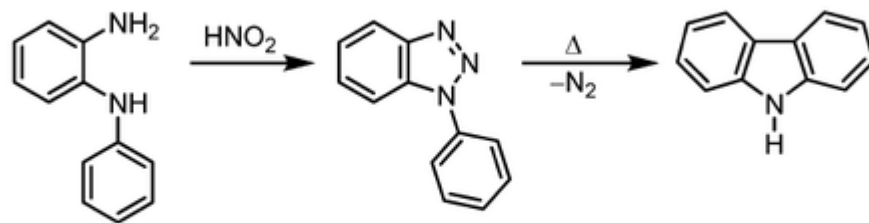
Picture 11 100-Kg scale manufacturing route to GW876008 through Ullmann-Ma reaction

Limitations still exist and further efforts

- highly desirable to develop more general, reactive and milder catalytic systems for practical use
- C—C coupling reactions is far behind that of Pd
- Copper catalyzed asymmetric coupling reactions remain as great challenges

Thanks for listening

A third method for the synthesis of carbazole is the Graebe–Ullmann reaction.



In the first step, an *N*-phenyl-1,2-diaminobenzene (*N*-phenyl-*o*-phenylenediamine) is converted into a diazonium salt which instantaneously forms a 1,2,3-triazole. The triazole is unstable and at elevated temperatures, nitrogen is set free and the carbazole is formed.^{[7][8]}



Born in 1955, American chemist
1977 BS from Brown University
1982 PhD from Harvard University, Jeremy R. Knowles
Postdoctoral fellow at Caltech with Robert H. Grubbs
1984-present MIT

Stephen L. Buchwald



Born in 1964, American chemist
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1990 PhD from University of California, Berkeley
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Postdoctoral at MA American Cancer Society
2011-present University of California, Berkeley

John F. Hartwig