

Cu-Catalyzed Cross-Coupling Reactions ~from Pd to Cu~

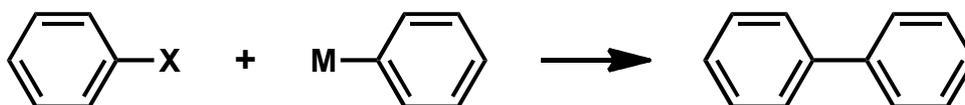
12th/May/2012 Ozawa Jun (M1)

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1. Introduction
 2. Sonogashira-type reactions
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1. Introduction

The discovery of a cross-coupling reaction is one of the most striking breakthrough in organic chemistry and it has brought us a lot of benefit:

- (i) it has expanded the scope for what we can synthesize and
- (ii) it has changed the methodology for the retrosynthesis, enabling us to shorten the synthetic procedures.



easily accessible to biaryl structures!

Cu-catalyzed coupling reactions have longer history than Pd-catalyzed ones: for example, Glaser coupling was reported in 1869, almost 100 years before Mizorogi-Heck reaction was reported in 1971, 1972.



C. Glaser *Ber. Dtsch. Chem. Ges.* **1869**, 2, 422

After the discovery of Pd-catalyzed couplings in 1970s, Pd chemistry has developed drastically:

1971, 1972 Mizorogi-Heck (alkene)
1972 Kumada-Tamao-Corriu (R-MgX')
1975 Sonogashira-Hagihara (terminal alkyne)
1977 Negishi (R-ZnX')
1977, 1978 Migita-Kosugi-Stille (R'-SnY₃)
1979 Suzuki-Miyaura (R-BY₂)
1988 Hiyama (R'-SiY₃)
1994 Buchwald-Hartwig (R-NHR' or R-OH)

The Pd reactions above achieve
(i) **catalytic** amount of Pd loading,
(ii) **low** reaction temperature, and
(iii) **high yields**.

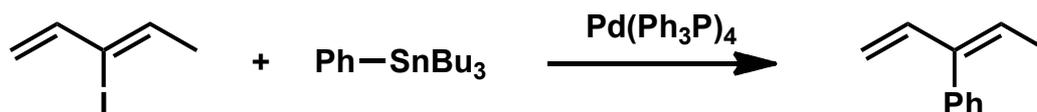
Whereas,

the pioneering Cu reactions required **non-catalytic** amount of Cu source and **very high reaction temperature** (~ 200 deg. or more).

Then, Cu chemistry gradually got neglected.

In these days, however, Cu is again attracting the attention of researchers around the world as an alternative of Pd in coupling reactions, because Pd is a precious metal and the reserve is much less than Cu, so it will cost more to use Pd.

♣ Recently "oxidative" coupling reactions have been studied actively because they are benign to earth; no need for preparing organometallics and halides, which results in reducing wastes. But it is still difficult in oxidative couplings to control reaction sites; therefore, they are hardly applicable to the syntheses in industry or laboratories. So usual non-oxidative coupling reactions are still in demand.

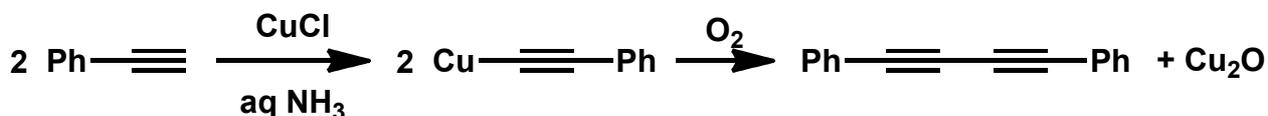


The coupling reaction like this is difficult to conduct in an oxidative coupling manner.

2. Sonogashira-type reactions

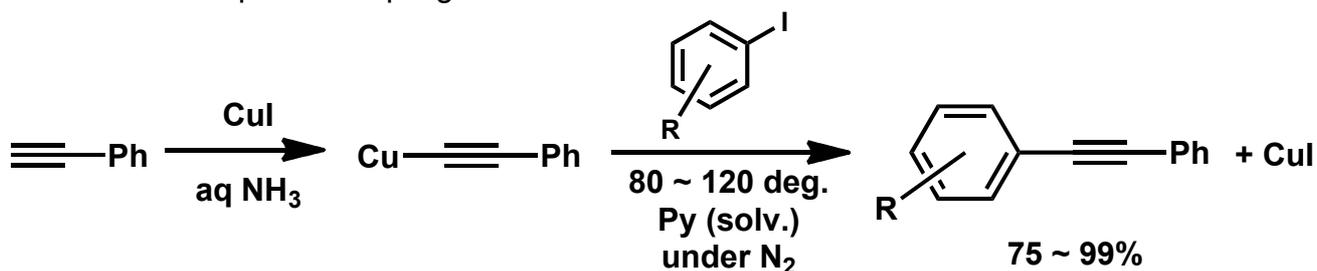
- Pioneering work of alkyne couplings using Cu

Glaser coupling



C. Glaser *Ber. Dtsch. Chem. Ges.* **1869**, 2, 422

Castro-Stephens coupling

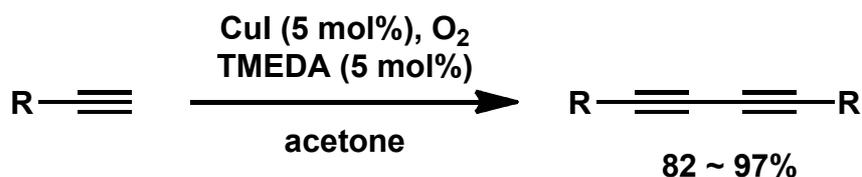


R. D. Stephens and C. E. Castro *JOC*, **1963**, 28, 3313

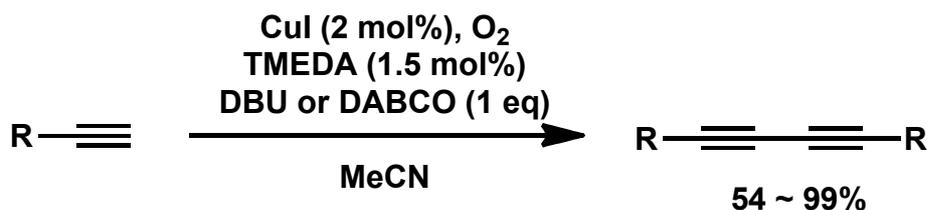
Both reactions are the 2-step conversion and require stoichiometric amount of Cu(I), that is, copper acetylides are isolated and they react with another reagent in the next step.

The reactions below achieve to conduct the coupling with a catalytic amount of Cu.

- homocoupling of alkynes

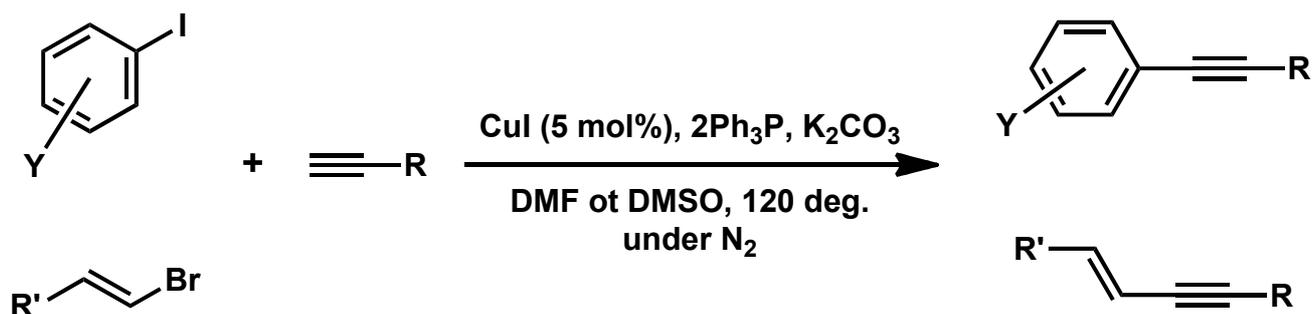


A. S. Hay *JOC* **1962**, 27, 3320

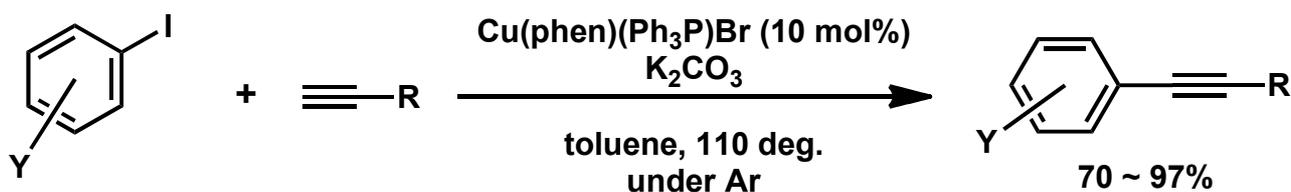


U. Beifuss *JOC* **2009**, 74, 5648

• heterocoupling of alkynes



M. Miura *JOC* 1993, 58, 4716



D. Venkataraman *OL* 2001, 26, 4315

substrate scope of Miura's case

Table III. Reaction of 1a with Several Terminal Alkynes 2b-g^a

2	time (h)	yield of 3 ^b (%)	recov of 1a ^b (%)
2b ^c	45	3b (48)	(51)
2b ^{c,d}	45	3b (90)	(8)
2b	26	3b, 96	(2)
2c	36	3c	(80)
2d ^e	24	3d, 87	0
2e ^e	24	3e, 90	(10)
2f	26	3f, 37	(14)
2g ^e	48	3g, 44	(26)

^a The reaction of 1a (1.0–5.0 mmol) with 2a (1.0–5.0 mmol) was carried out in DMSO (3–10 mL) at 120 °C under N₂ unless otherwise noted; [1a]:[2]:[CuI]:[PPh₃]:[K₂CO₃] = 1:1:0.05:0.1:1.5. ^b Isolated yield. Value in parentheses is GLC yield. ^c Reaction in DMF. ^d dppb (1,4-bis(diphenylphosphino)butane) in place of PPh₃ was used. ^e [CuI] = 0.1.

Table IV. Reaction of Aryl Halides 1b-j with Alkynes 2a or 2b^a

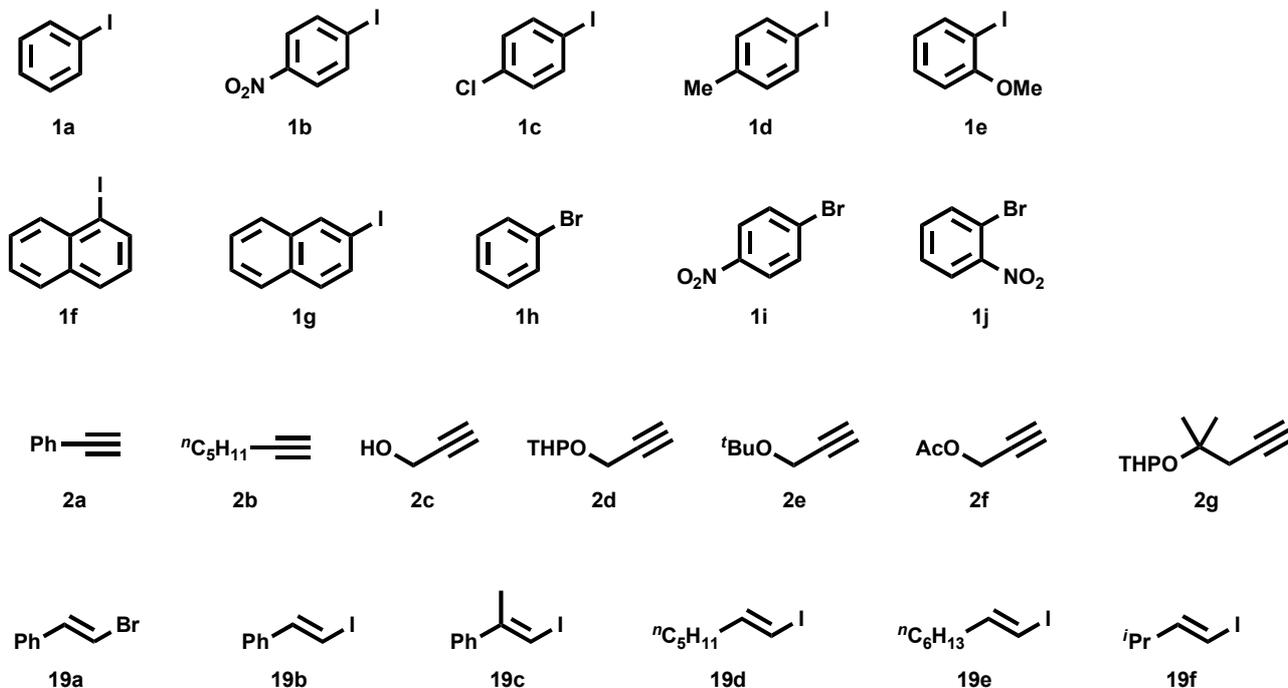
1	2	time (h)	product, % yield
1b ^b	2a	16	5, 95
1c ^b	2a	24	6, 92
1c	2b	18	7, 96
1d ^b	2a	24	8, 95
1d	2b	46	9, 21 ^c
1d ^d	2b	24	9, 75 ^e
1e	2a	18	10, 84
1f	2a	24	11, 84
1g	2a	17	12, 92
1h	2a	48	3a, 8
1i	2a	22	5, 5
1j ^{b,f}	2a	24	13, 23 ^g

^a The reaction of 1a (1.0–5.0 mmol) with 2a was carried out in DMF (with 2a) or DMSO (with 2b) at 120 °C under N₂ unless otherwise noted; [1]:[2]:[CuI]:[PPh₃]:[K₂CO₃] = 1:1:0.1:0.1:1.5. ^b [CuI] = 0.05. ^c 1d (75%) was recovered. ^d CoCl₂ was added. [CoCl₂] = 0.05. ^e 1d (21%) was recovered. ^f Reaction in DMSO. ^g Nitrobenzene (21%) and 4 (16%) were formed as byproducts.

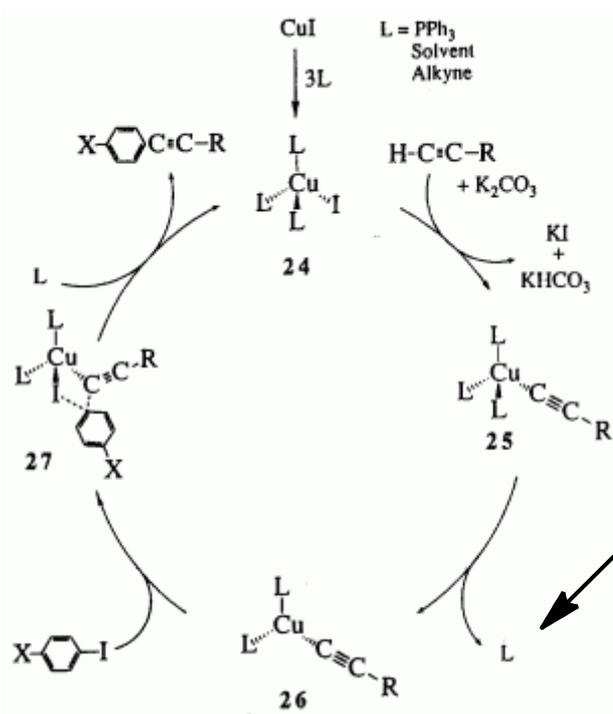
Table VI. Reaction of Vinyl Halides 19a-f with Alkynes 2a-e^a

vinyl halide 19 (E/Z)	alkyne 2	time (h)	yield (%)	E/Z
PhCH=CHBr (19a, >99/1)	2a	24	20a, 88	>99/1
	2b ^b	24	20b, 85	
	2d ^b	24	20c, 65	
	2e ^b	24	20d, 89	
	2a ^c	28	20a, 72	
Ph(CH ₃)C=CHI (19c, 98/2)	2a ^b	20	20e, 93	99/1
	2b	16	20f, 86	
<i>n</i> -C ₈ H ₁₁ CH=CHI (19d, 96/4)	2a	5	20g, 92	98/2
	2a	7	20g, 82	
<i>n</i> -C ₈ H ₁₃ CH=CHI (19e, 84/16)	2a ^c	10	20h, 96	84/16
	2b	5	20i, 86	
<i>i</i> -C ₃ H ₇ CH=CHI (19f, 97/3)	2a	14	20j, 73	97/3

^a The reaction of 19 (1.0–3.0 mmol) with 2 (1.0–3.0 mmol) was carried out in DMF (with 2a) or DMSO (with 2b) at 120 °C under N₂ unless otherwise noted; [19]:[2]:[CuI]:[PPh₃]:[K₂CO₃] = 1:1:0.05:0.1:1.5. ^b [CuI] = 0.1. ^c Reaction at 80 °C.



Copper acetylides are polymeric by nature and are almost insoluble in many organic solvents; they don't dissolve even in DMF completely without ligands. By adding some appropriate ligands in advance, copper acetylides make complexes with them and become monomeric species that are soluble in organic solvents, resulting in these "catalytic" reactions.



In the step **25** to **26**, one ligand must leave from **25**, so excess equivalent of ligands or more electron-donating ligands are ineffective; 2 eq of Ph_3P is the best for Miura's conditions.

* Do Cu(III) species generate from Cu(I) like Ar-L₂Pd(II)-(alkyne) in Pd-catalyzed cross-coupling?

→ The fact is verified that the oxidative addition and reductive elimination of Cu(I) can occur in the presence of ArX, so it is possible that Cu(I) undergoes the steps similar to Pd(0) in cross-coupling reactions.

S. S. Stahl and X. Ribas *Chem. Sci.* **2010**, *1*, 326

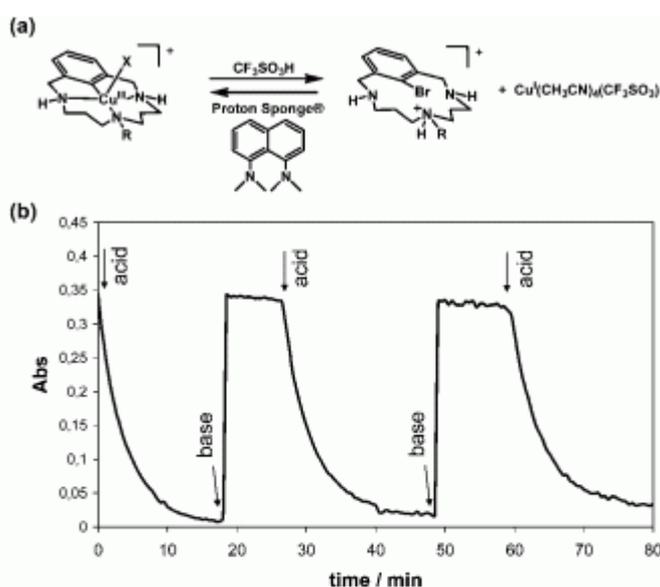
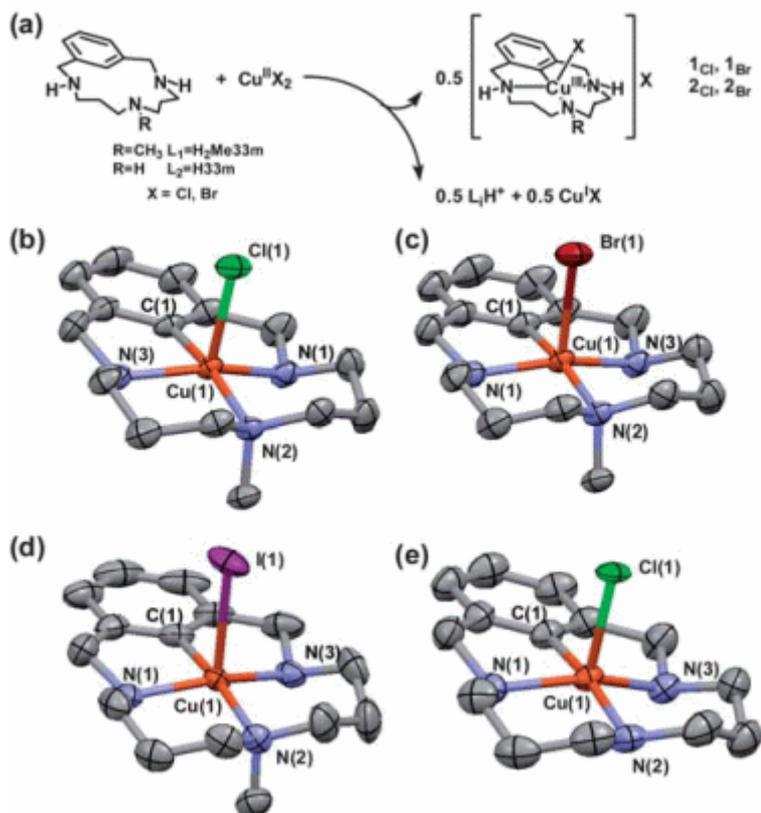
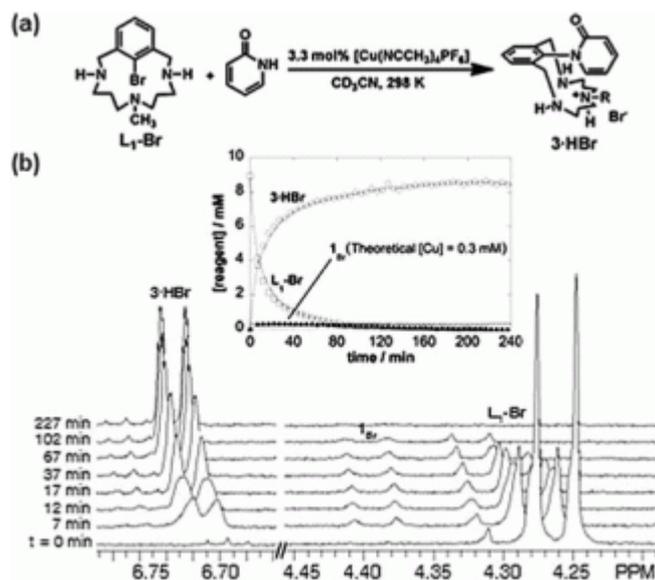
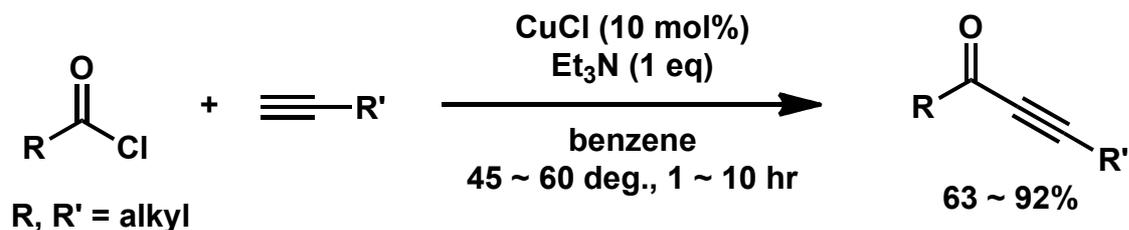


Fig. 3 (a) Reversible reductive elimination/oxidative addition induced by the presence of acid or base. (b) Monitoring of **1_{Br}** by UV-visible spectroscopy at 400 nm upon successive acid and base additions (initial conditions: [**1_{Br}**] = 0.3 mM, addition of 2 equiv. of triflic acid and Proton Sponge® in the respective additions, CH₃CN, 297 K).

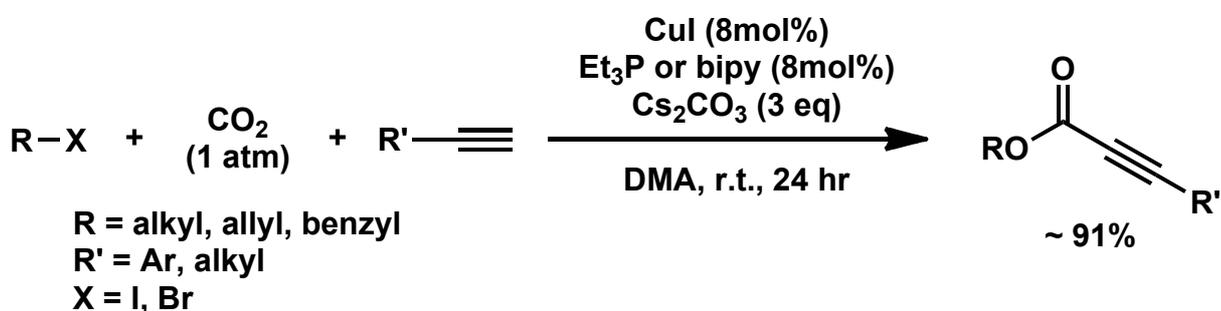


N-Arylation of pyridone occurs with ArBr and catalytic amount of [Cu(MeCN)₄PF₆]

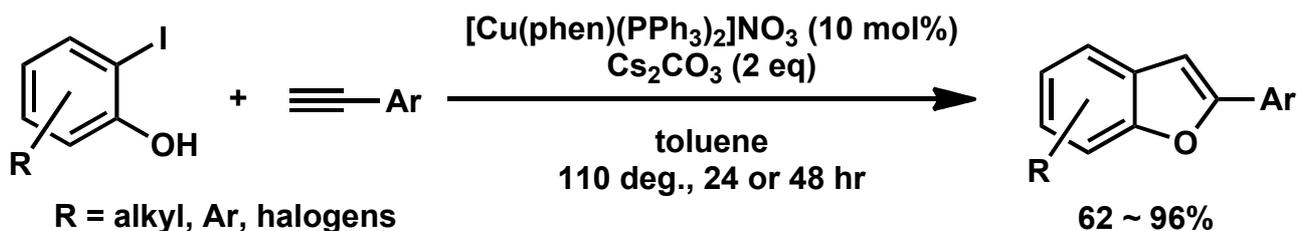
* other examples



A. S. Zanina *Mendeleev Communications* **1994**, 4, 207



K. Inamoto and Y. Kondo *Org. Biomol. Chem.* **2012**, 10, 1514



D. Venkataraman *OL*. **2002**, 4, 4727

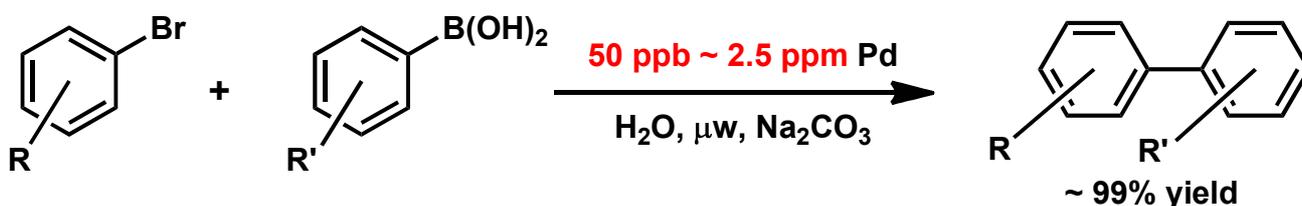
5. Perspectives

Cross-coupling reactions catalyzed by Cu have been growing steadily, but there're still some disadvantages:

(i) large catalyst loading

The Cu-catalyzed couplings usually require 1 ~ 10 mol% of Cu source; on the other hand, the Pd-catalyzed couplings need 0.01 ~ 5 mol% of Pd source. Even though Cu itself is cheaper than Pd ($\text{Pd}(\text{OAc})_2$: 47500 yen/10 g, $\text{Cu}(\text{OAc})_2$: 27700 yen/100 g at Sigma Ald.), large catalyst loading offsets the merit of lower price of Cu.

♣ Pd catalyst is outstanding...



N. E. Leadbeater *JOC*, **2003**, 68, 5660

N. E. Leadbeater *JOC*, **2005**, 70, 161

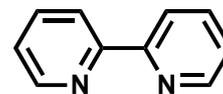
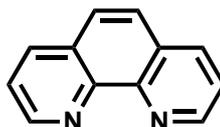
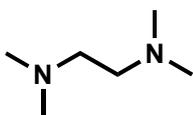
The Pd loading is **0.0000008 mol%** and turnover number is **1250000!**

(ii) lack of understanding of the ligand effect

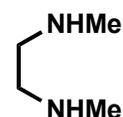
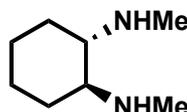
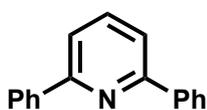
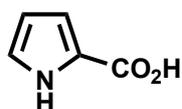
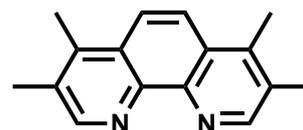
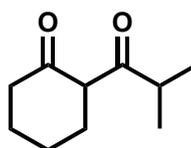
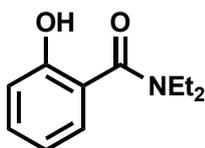
The catalytic systems are usually developed by random tryals because it is still in a black box what we should take care about when tuning the system.

• the ligands shown in this paper

Ph₃P



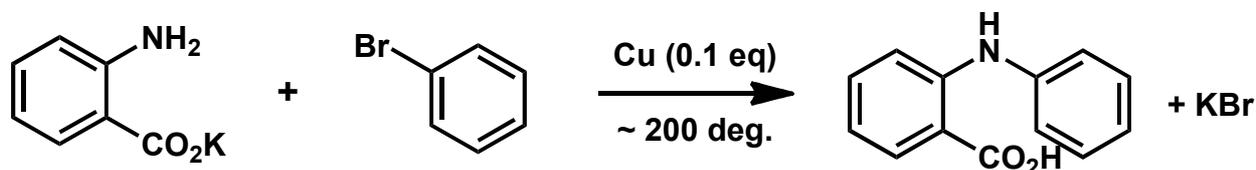
Et₃P



4. Buchwald-Hartwig-type reactions

- Pioneering work using Cu

Ullmann condensation



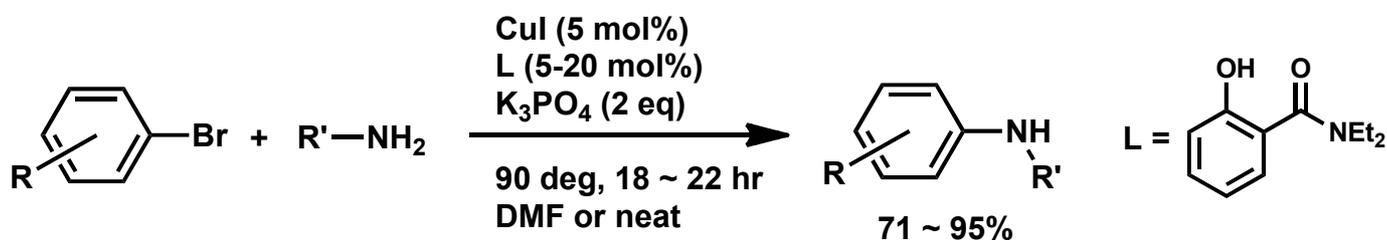
F. Ullmann *Ber. Dtsch. Chem. Ges.* **1903**, 36, 2382 (amination)
 F. Ullmann *Chem. Ber.* **1905**, 38, 2211 (etherification)
 I. Goldberg *Chem. Ber.* **1906**, 39, 1691 (amination, amidation)

This Ullmann-Goldberg condensation has been used until most recently, 1994, among other Cu-promoted couplings, to obtain diaryl- or triamines because there was no other practical method. But the reactions also require harsh prolonged heating at 200 deg. or higher, so its application is limited.

Many bidentate ligands have been recently reported as efficient ligands for the amination reactions and those systems are overcoming such limitations.

- Arylation of alkyl amines

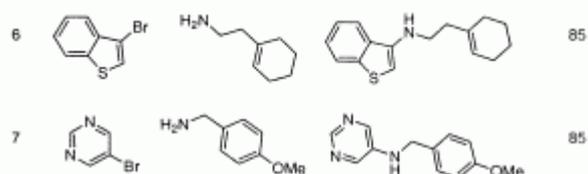
Primary and cyclic secondary amines can be arylated, but secondary non-cyclic amines shows low reactivity, most likely due to steric reasons.



L. S. Buchwald *OL* **2003**, 5, 793

substrate scope

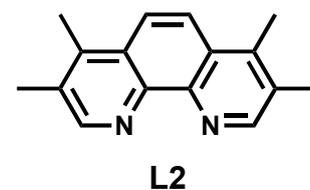
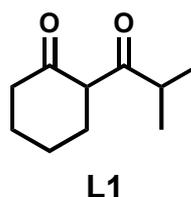
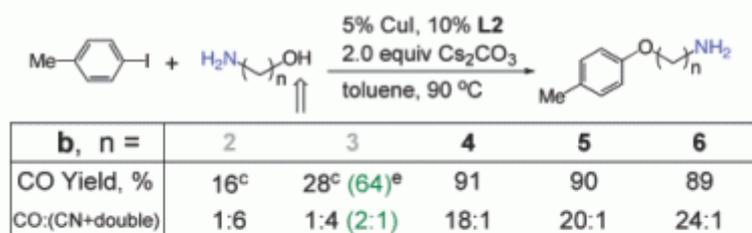
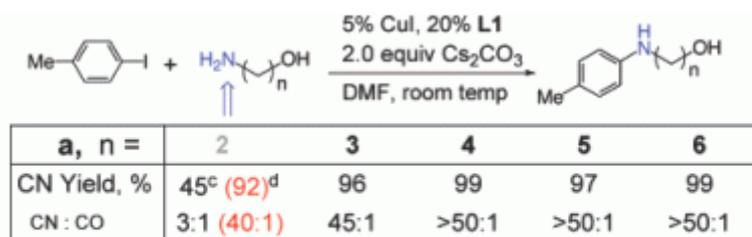
entry	ArBr	amine	product	% yield ^b
1 ^c				88
2				81
3 ^c				79
4				92
5				91



^a Reaction conditions: CuI (0.05 mmol, 5 mol %), *N,N*-diethylsalicylamide (0.2 mmol, 20 mol %), ArBr (1.0 mmol), amine (1.5 mmol), and K₃PO₄ (2.0 mmol) in DMF at 90 °C under argon. ^b Isolated yield (average of two experiments). ^c Reaction temperature: 100 °C.

N-arylation occurs in the presence of OH (entry 2).

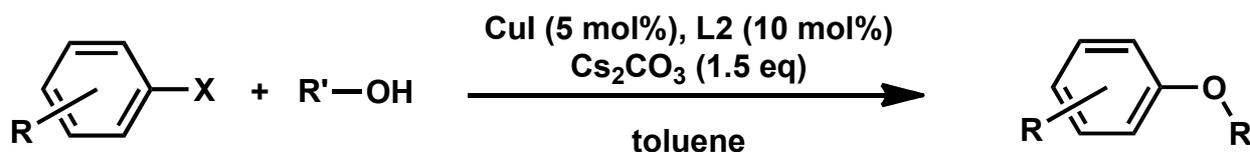
♣ *N*- vs *O*-arylation (S. L. Buchwald *JACS* **2007**, *129*, 3490)



Other non-linear aminoalcohols with more than 4 atoms between N and O can be also arylated selectively (C-N: up to > 50 :1; C-O: up to 20: 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.

L2 is used for various *O*-arylation of alkyl alcohols. (S. L. Buchwald *JOC* **2008**, *73*, 284)



entry	product	X =	temperature (°C)	time (h)	yield (%)
1		I	80	20	87 ^b
2		I	110	24	99 ^{b,c}
3		I	110	12	95 ^b
4		R = Me	110	24	83
5		OMe	110	30	94
6		Cl	110	24	80
7		I	80	20	82
8		I	80	24	72 ^d
9		I	80	16	75
10		I	80	20	74
11		I	80	16	81

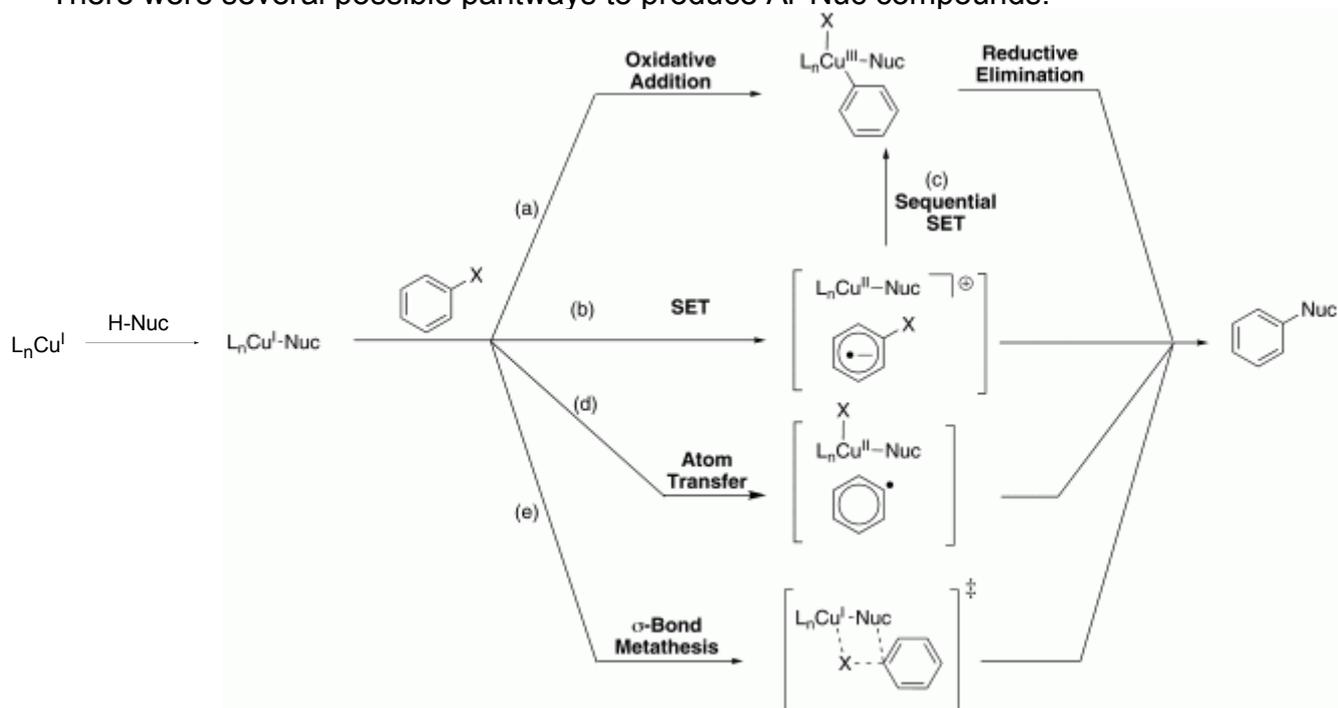
This system is not efficient for secondary non-cyclic alcohols.

^a Reaction conditions: 1.0 mmol of ArX, 1.5 of mmol alcohol, 0.050 of mmol CuI (5%), 0.10 mmol of Me₄Phen (10%), 1.5 mmol of Cs₂CO₃, and 0.50 mL of toluene under an Ar atmosphere. The isolated yields reported are averages of two or more runs of material judged to be >95% pure by ¹H NMR and/or elemental analysis. ^b GC yield reported. ^c 2% CuI, 4% Me₄Phen. ^d GC analysis: 14:1 mixture of I- to Br-substituted products which were separated by column chromatography. ^e Inseparable 7:1 mixture of depicted product and *n*-hexyl 4-(hexyloxy)benzoate. ^f 200 mg of 4 Å mol sieves added to reaction mixture. ^g One regioisomer detected by GCMS and ¹H NMR. ^h 10% CuI, 20% Me₄Phen. ⁱ 130 °C, 0.50 mL of *n*-hexanol used as solvent.

* What brings these N/O selectivities?

→ Computational study was conducted by Buchwald (S. L. Buchwald *JACS* **2010**, *132*, 6205).

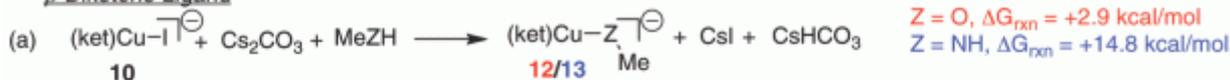
There were several possible pathways to produce Ar-Nuc compounds.



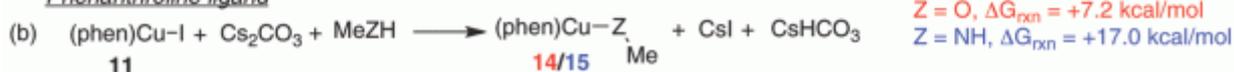
The free energy of each pathway was calculated.

* the coordination step

β-Diketone Ligand



Phenanthroline ligand



The coordination of an alcohol is much more favorable than that of an amine in each case.
 → This step is not selectivity-determining.

* the steps, (a), (b), (d), (e)

		(a)	(e)	(d)	(b)	
	Cu(ZMe) formation	TSOA	TSSig	IAT	SET	product formation
(ket)Cu Complexes						
MeO-bound (12)	2.9	64.6	57.1	32.9	27.2	-41.3
MeNH-bound (13)	14.8	55.0 ^a	65.6	41.1	26.2	-48.0
(phen)Cu Complexes						
MeO-bound (14)	7.2	43.2	43.4	34.0	43.6	-47.1
MeNH-bound (15)	17.0	53.7	50.9	39.6	35.1	-52.6

^a Energy of the oxidative addition complex (see the text for details).

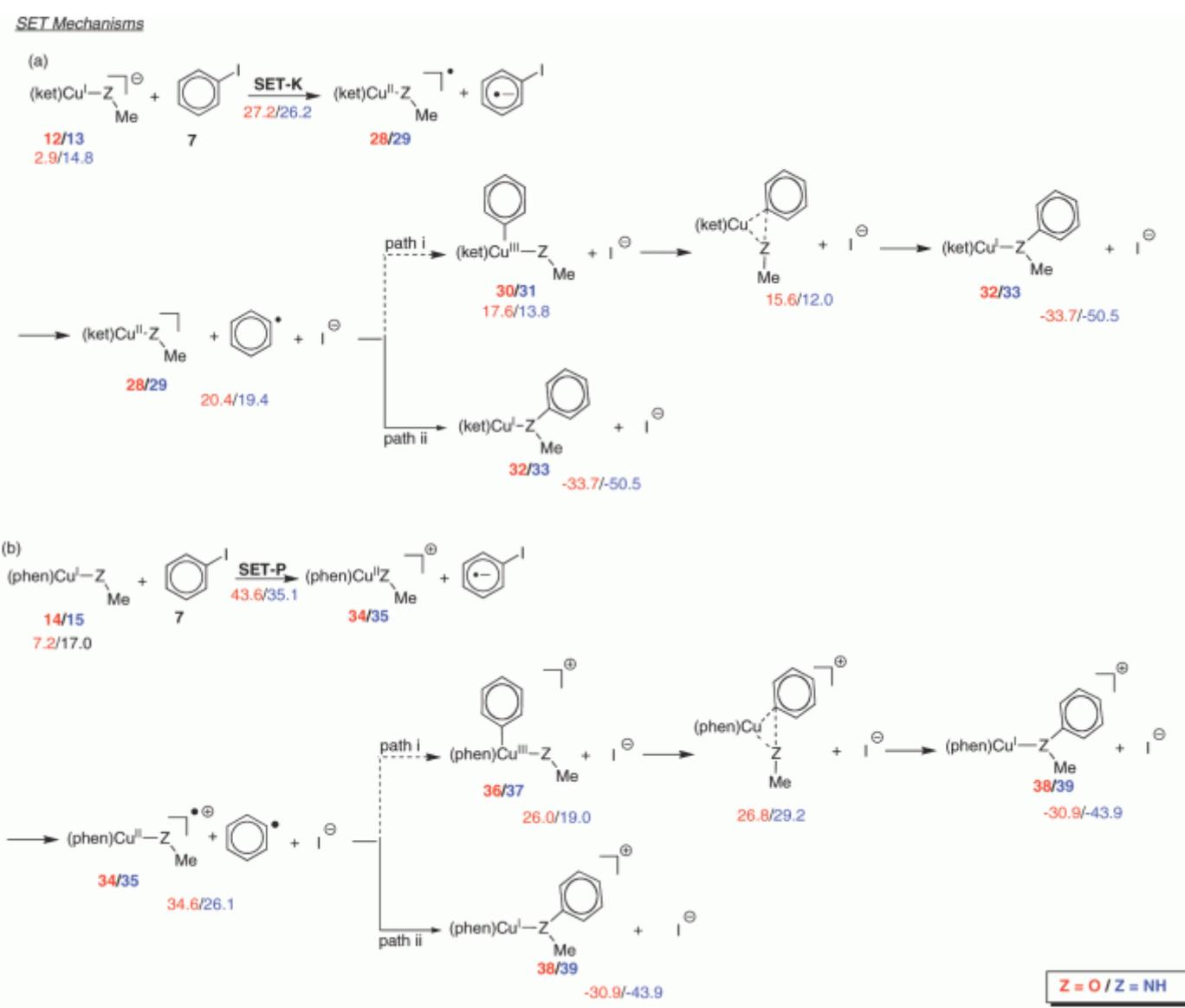
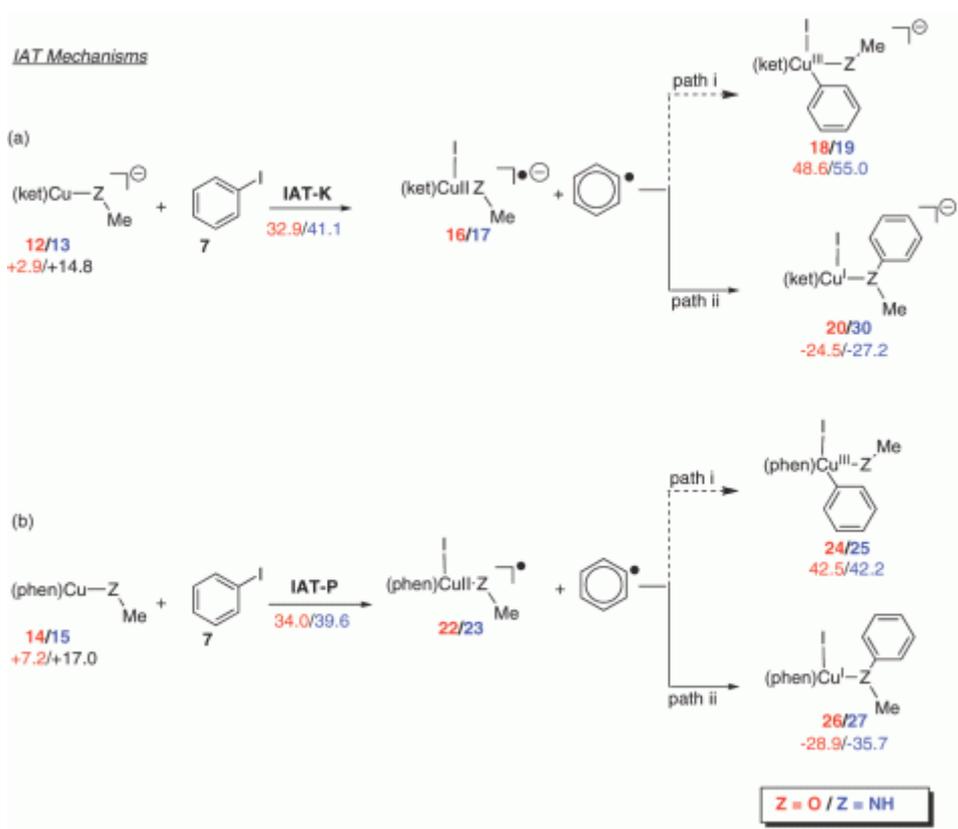
The energies of TSOA and TSSig are much higher than IAT or SET, so IAT or SET is more favorable than the other 2 pathways.

In the case of (ket)Cu complexes, SET is preferred both when Z is O and Z is NH; (phen)Cu complexes also favor SET when Z is NH, but don't when Z is O and then IAT is preferable.

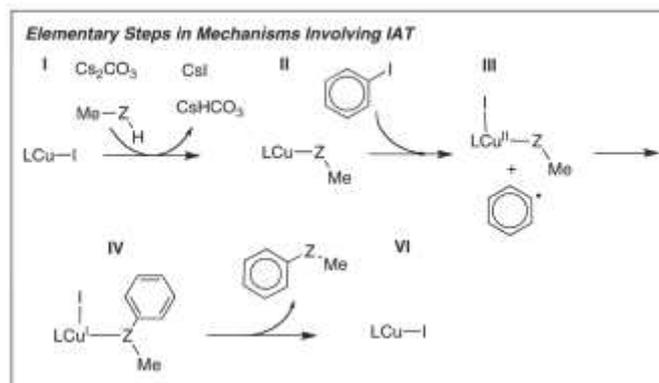
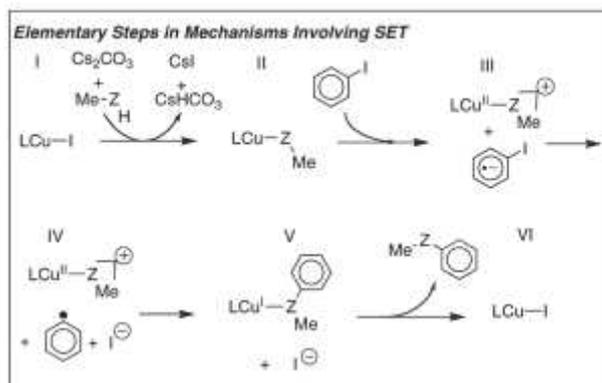
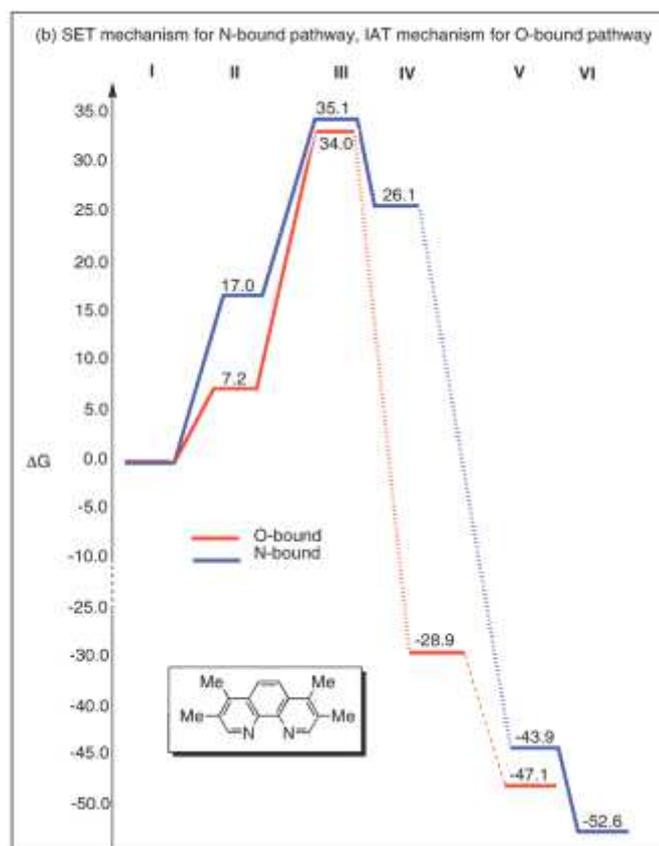
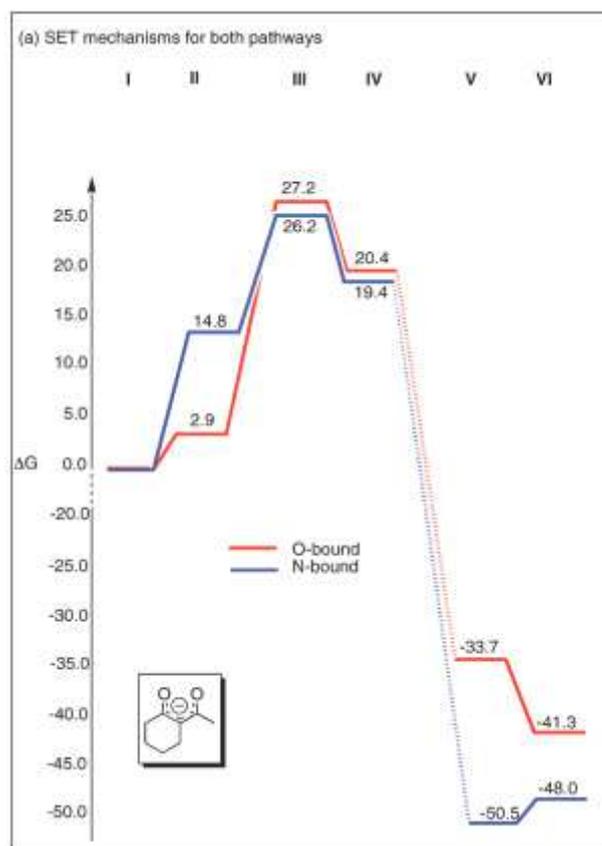
*IAT: Iodine Atom Transfer

* The energies of the steps after IAT or SET.

In all the pathways, the generation of C(III) species is not desirable and instead Cu(I)/Cu(II) mediated pathways are preferred.



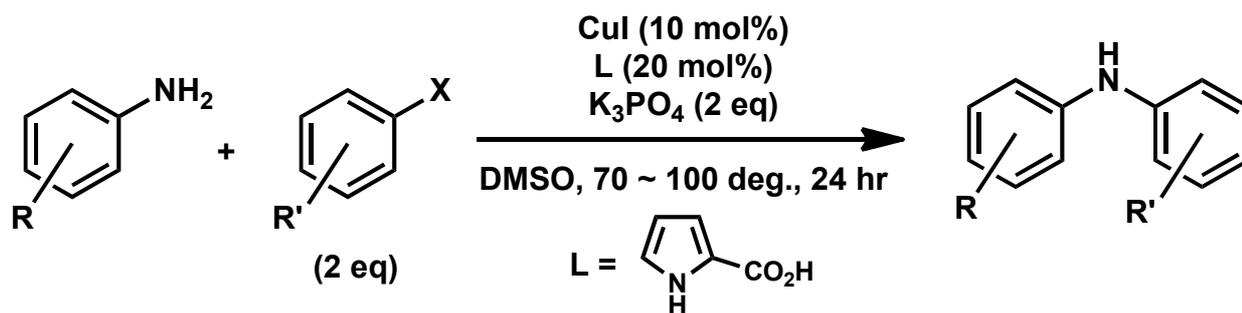
* Summarized free-energy profiles



- Electron-rich ligands promote SET mechanism, where e^- is transferred from the Cu(I)-Nuc complex. N-bound Cu(I) complexes are rather e^- rich and undergo SET pathway even if the ligand is phen or similar ones; O-bound complexes undergo IAT pathway when the ligand is not-so-electron-donating, because alkoxides are worse electron donor than amides.
- The pathways via Cu(III) species are unfavorable surely because Cu(III) is unstable, so Cu(II) intermediate returns to rather stable Cu(I) instead.
- Toluene, the solvent used for O-arylation (IAT, non-anionic/cationic pathway), may slow down N-arylation (SET, anionic/cationic pathway) relatively.

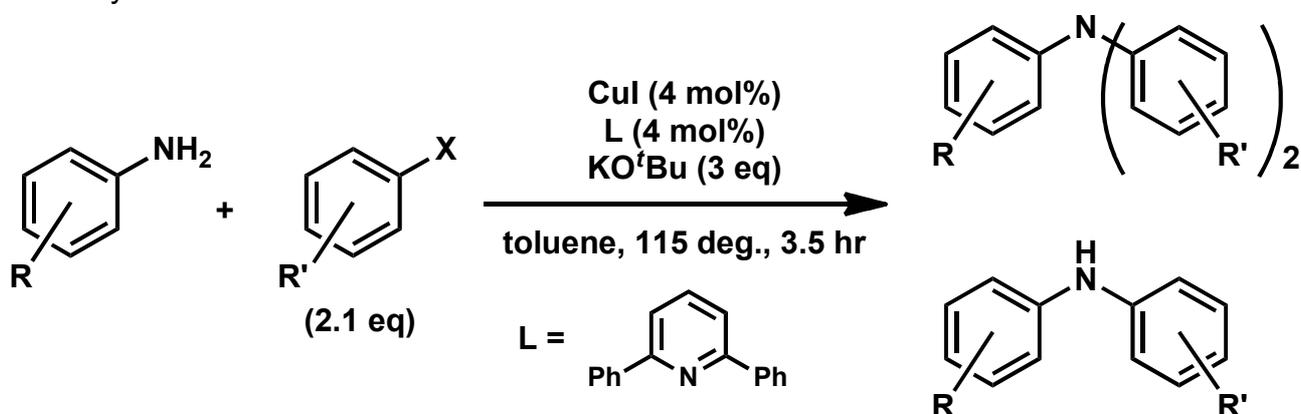
- * other *N*-arylation
- Arylation of arylamines

diarylamines



S. L. Buchwald *JOC*, **2008**, 73, 5167

triarylamines



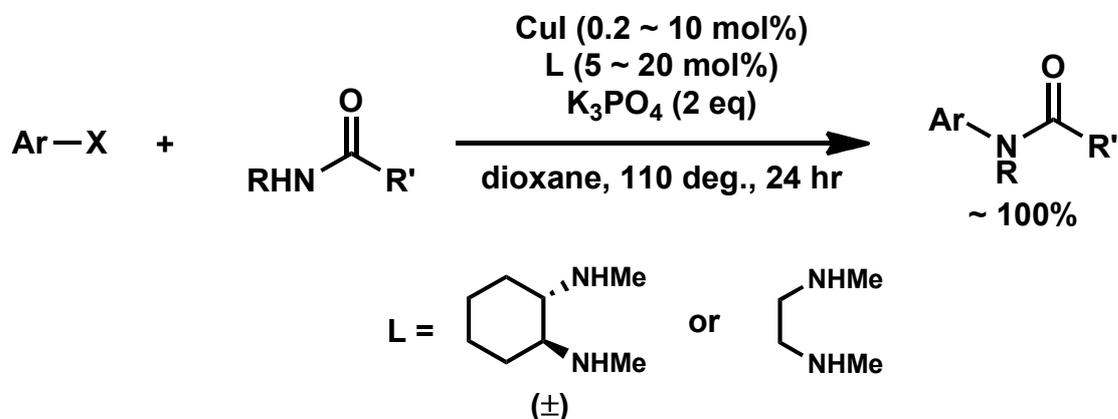
triaryl/diaryl ratios are up to 95/2

R. V. Chaudhari *TL* **2002**, 43, 7143

R. V. Chaudhari *J. Mol. Catal. A: Chem.* **2004**, 223, 45

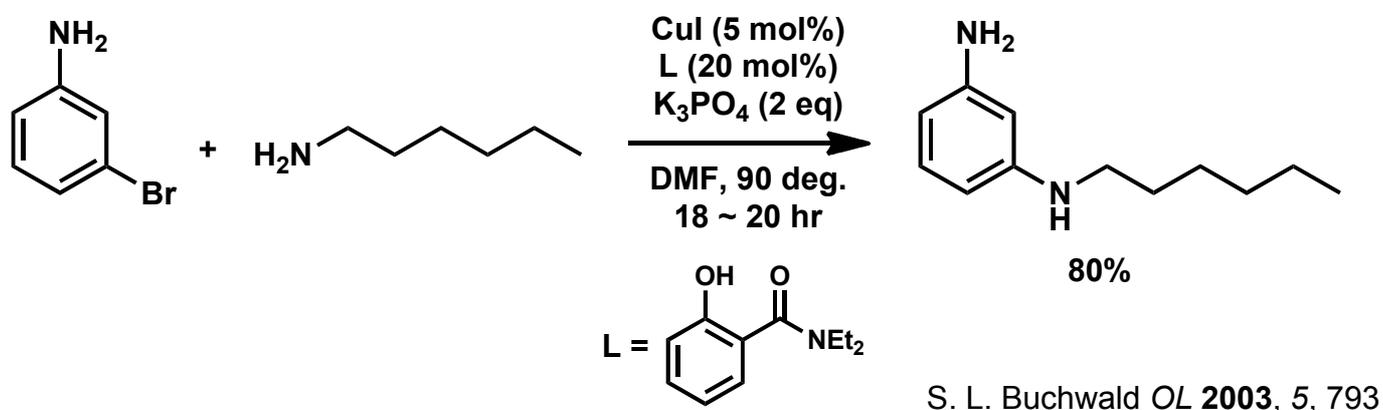
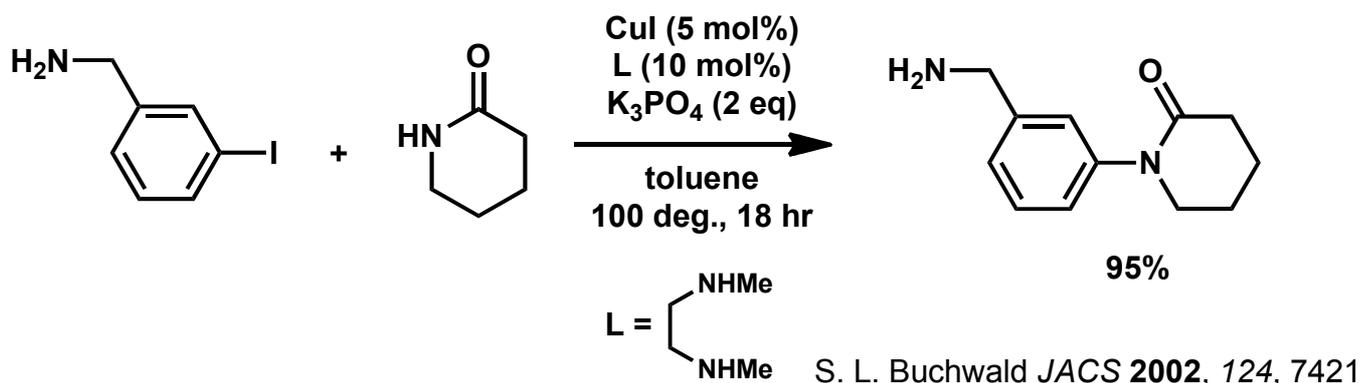
The authors don't mention in the papers about what results in the selectivity, di- or triarylation.

- Arylation of amides



S. L. Buchwald *JACS* **2002**, 124, 7421

* The rates of *N*-arylation differ as the type of amines differ: normal amines, aniline derivatives, and amides



after all, **aniline derivatives < normal amines < amides**

This is probably due to the difference of pK_a s and nucleophilicities of $\text{RR}'\text{NH}$.

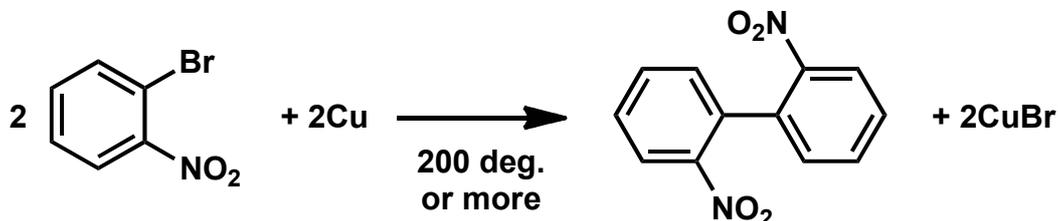
Amides are the worst nucleophiles but show the lowest pK_a ; in contrast, normal amines are the best nucleophile but show the highest pK_a , which may result in the order of the *N*-arylation rates.

	R-C(=O)-NH_2	Ph-NH_2	$\text{H}_2\text{N-H}$
pK_a	17	27	35
nucleophilicity	low	middle	high
rate	fast	slow	middle

3. Stille-type reactions

- Pioneering work to obtain biaryl compounds using Cu

Ullmann coupling

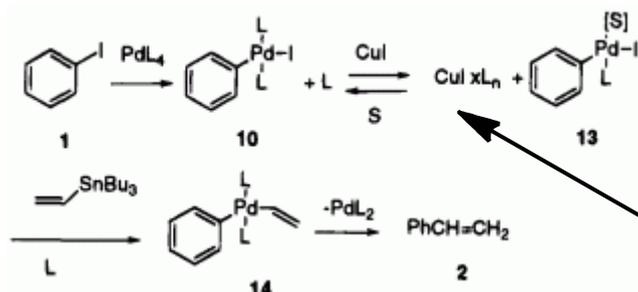


F. Ullmann *Chem. Ber.* **1901**, 34, 2174

Biaryl compounds can be synthesized using Cu, but the reaction requires stoichiometric amount of Cu and very high reaction temperature, and is not applicable to heterocoupling, say, Aryl1-Aryl2, or Aryl-vinyl coupling.

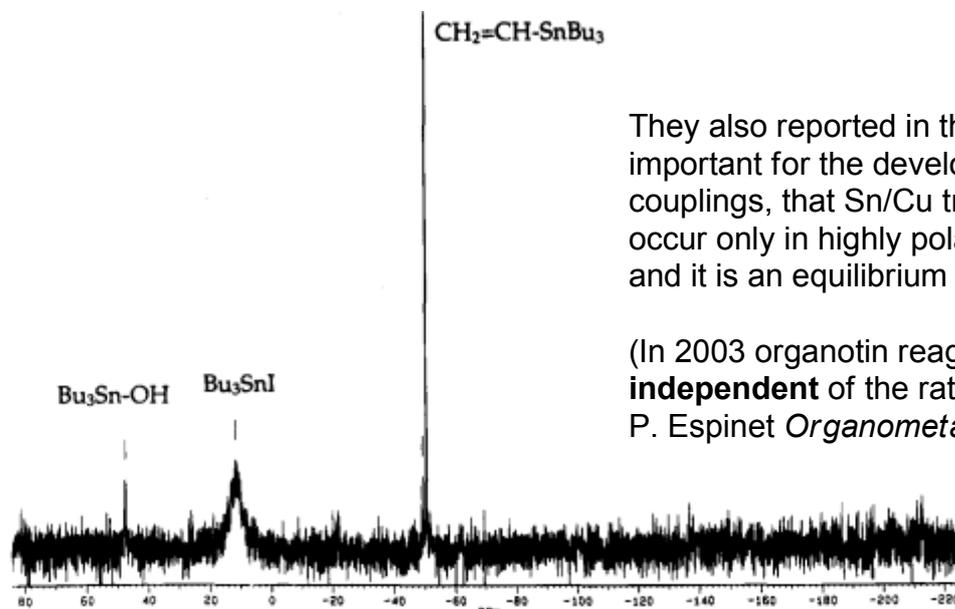
In Stille coupling, additional Cu(I) is known to accelerate the reaction:

V. Farina and L. S. Liebeskind reported in 1994 that Cu(I) scavenges ligands of Pd and accelerates the rate-determining transmetalation.



V. Farina and L. S. Liebeskind
JOC **1994**, 59, 5905

One of the ligand must be dissociated so that the transmetalation can occur, and CuI helps the step.



They also reported in the paper, this is more important for the development of Cu-catalyzed couplings, that Sn/Cu transmetalation does occur only in highly polar solvents like NMP, and it is an equilibrium reaction.

(In 2003 organotin reagents are revealed to be **independent** of the rate enhancement:
P. Espinet *Organometallics* **2003**, 22, 1305.)

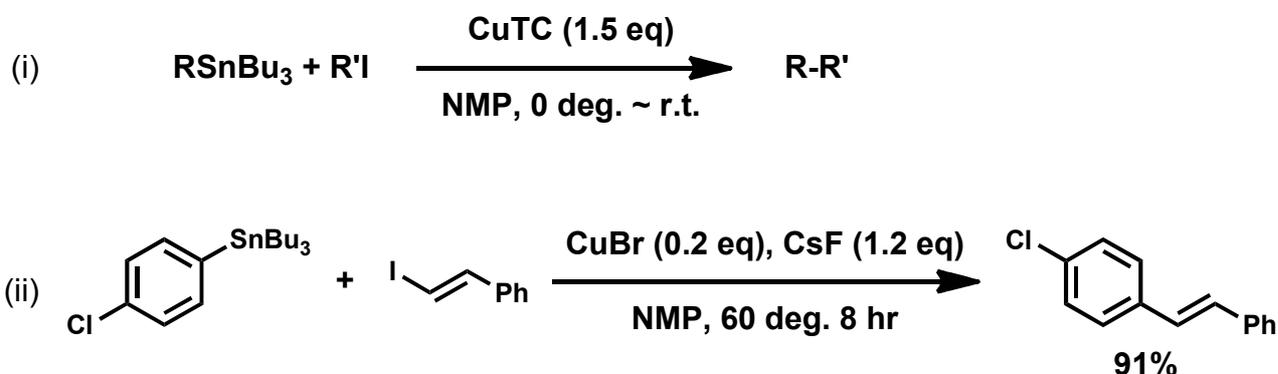
$^{119}\text{Sn-NMR}$. Experiment 1: 0.18 M CuI in dry NMP + 1 equiv of vinyltributyltin, rt, 16 h.

To enhance the transmetalation in Cu-catalyzed coupling, there're 2 choices:

(i) using an excess of CuX to drive the transmetalation or

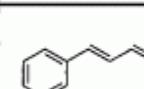
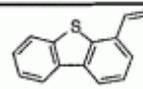
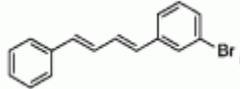
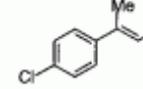
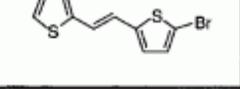
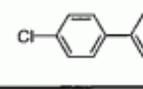
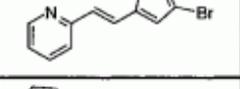
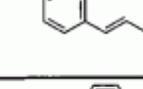
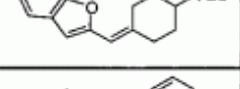
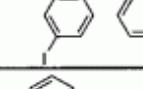
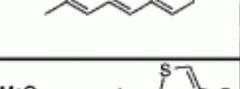
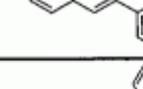
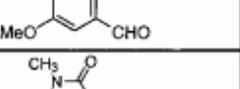
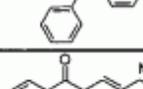
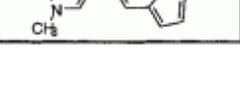
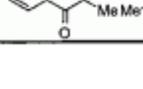
(ii) adding some reagent(s) that scavenge Bu_3SnX .

Both cases were tried by L. S. Liebeskind.



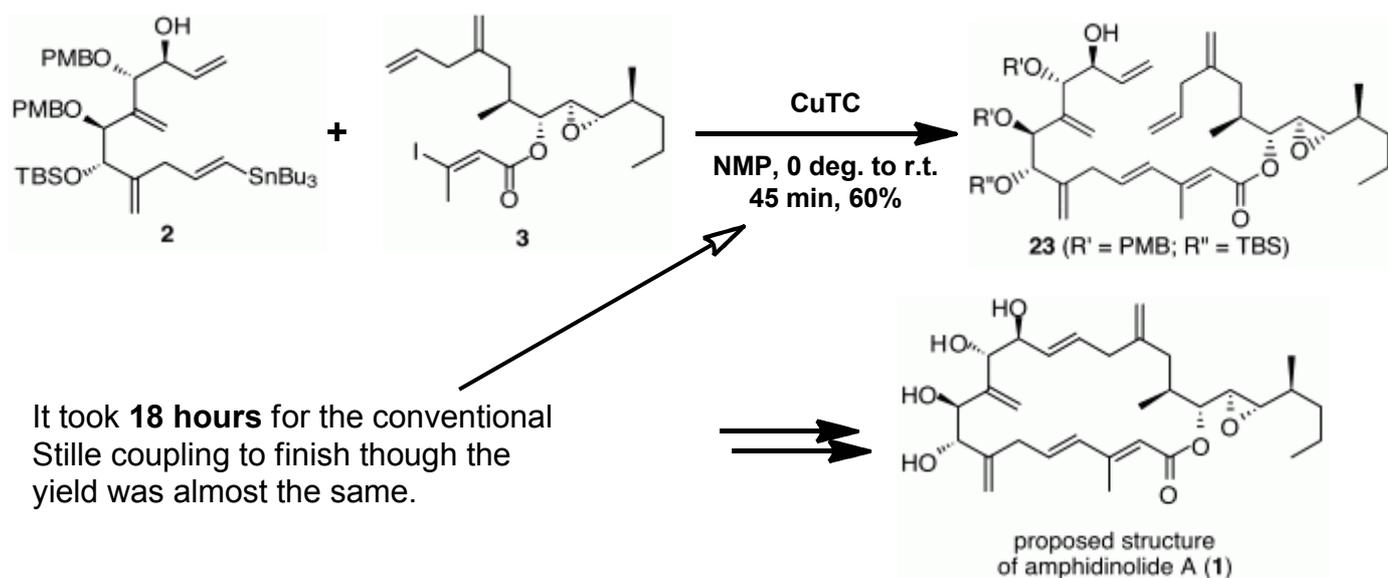
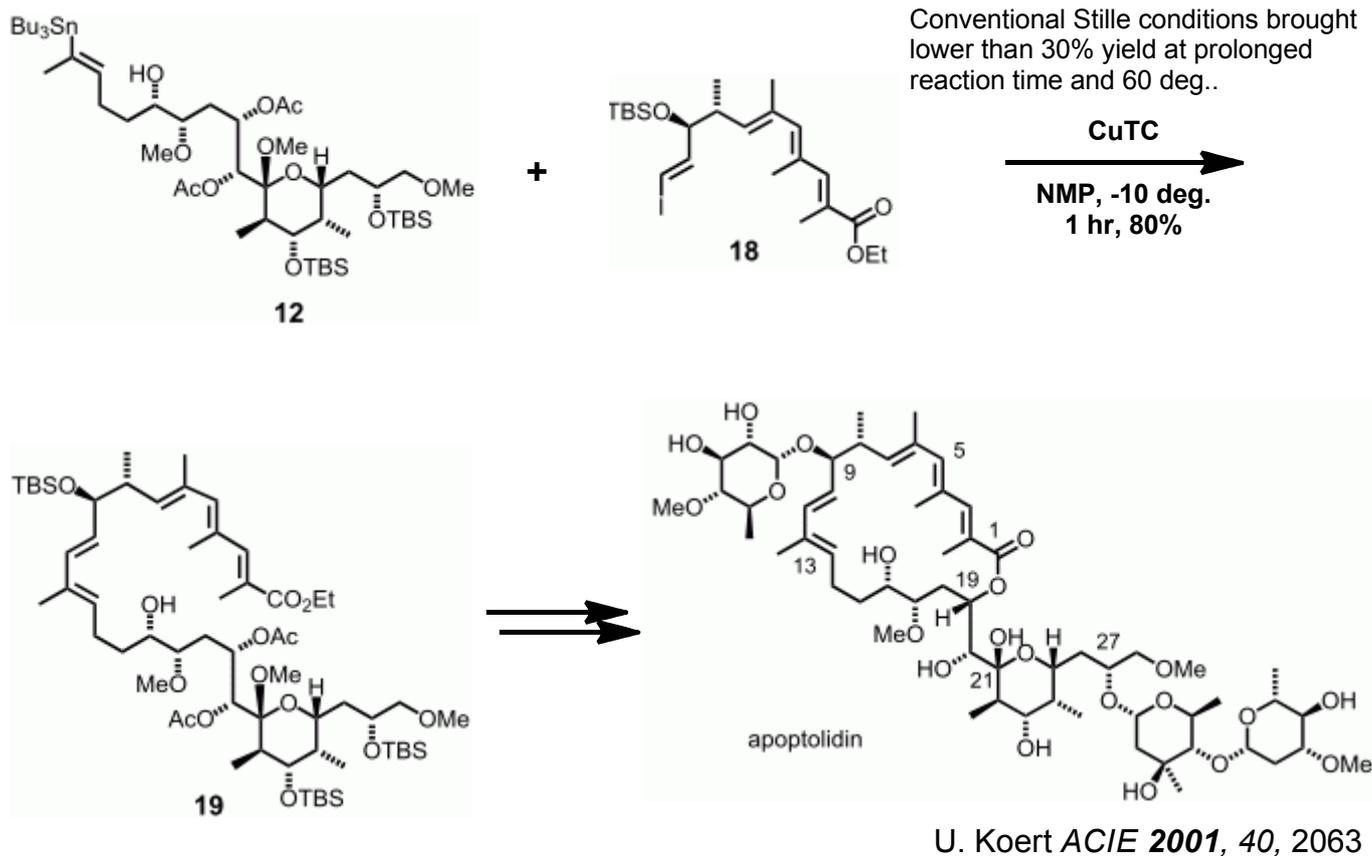
L. S. Liebeskind *JACS* **1996**, *118*, 2748

substrate scope of (i)

Entry	RSnBu_3 R'I	Product	Temp Time Yield	Entry	RSnBu_3 R'I	Product	Temp Time Yield
1	(E)- β -(<i>n</i> -Bu ₃ Sn)styrene (E)- β -iodostyrene		0 °C 5 min 89%	9	1-(<i>n</i> -Bu ₃ Sn)dibenzothiophene ethyl (Z)- β -iodoacrylate		23 °C 5 min 71%
2	(E)- β -(<i>n</i> -Bu ₃ Sn)styrene (E)-3-bromo- β -iodostyrene		0 °C 5 min 93%	10	4-chlorophenyl- <i>n</i> -Bu ₃ Sn (E)-4-iodo-3-pentene-2-one		23 °C 15 min 89%
3	2-(<i>n</i> -Bu ₃ Sn)thiophene (E)-2-(2-iodovinyl)-5-bromothiophene		0 °C 5 min 89%	11	4-chlorophenyl- <i>n</i> -Bu ₃ Sn 5,5-dimethyl-3-iodocyclohex-2-enone		23 °C 30 min 81%
4	2-(<i>n</i> -Bu ₃ Sn)pyridine (E)-2-(2-iodovinyl)-4-bromothiophene		0 °C 5 min 83%	12	4-iodophenyl- <i>n</i> -Bu ₃ Sn (E)- β -iodostyrene		23 °C 5 min 97%
5	2-(<i>n</i> -Bu ₃ Sn)benzofuran 4- <i>t</i> -butyl-1-iodomethylenecyclohexane		23 °C 30 min 77%	13	4-iodophenyl- <i>n</i> -Bu ₃ Sn (Z)- β -iodostyrene		23 °C 5 min 95%
6	2-Me-1-(<i>n</i> -Bu ₃ Sn)-1-propene (E)- β -iodostyrene		23 °C 15 min 80%	14	(E)- β -(<i>n</i> -Bu ₃ Sn)styrene <i>o</i> -iodonitrobenzene		23 °C 30 min 74%
7	2-(<i>n</i> -Bu ₃ Sn)-4,5-dimethoxybenzaldehyde (E)-2-(2-iodovinyl)-4-bromothiophene		23 °C 5 min 78%	15	(Z)- β -(<i>n</i> -Bu ₃ Sn)styrene (Z)- β -iodostyrene		0 °C 5 min 94%
8	5-(<i>n</i> -Bu ₃ Sn)-1,3-dimethyluracil (E)-2-(2-iodovinyl)-5-bromothiophene		23 °C 5 min 75%	16	2-Me-3-(<i>n</i> -Bu ₃ Sn)-1,4-naphthoquinone (E)-1-iodo-3-(2,6,6-tri-Me-2-cyclohexenyl)-1-propene		23 °C 15 min 93%

- The reactions finish within minutes under low temperatures with high yields.
- Carbonyl groups and ArX, even Aryl iodides (except *o*-iodonitrobenzene, entry **14**), are tolerated in this reaction, which results in the chemoselectivity that is not achieved under typical Stille reaction conditions.
- The reactions are excellently stereoretentive, precluding a radical chain mechanism (entries **1**, **15** and **12**, **13**).

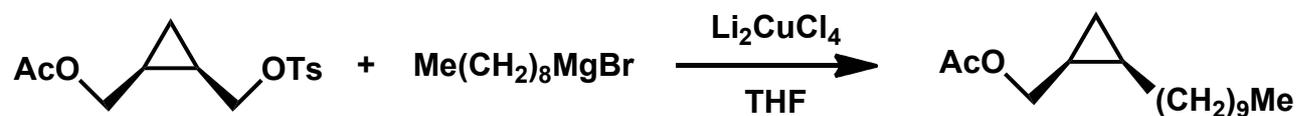
♣ The CuTC-catalyzed coupling was employed in some total syntheses.



R. E. Maleczka, Jr. *OL* **2002**, 4, 2841

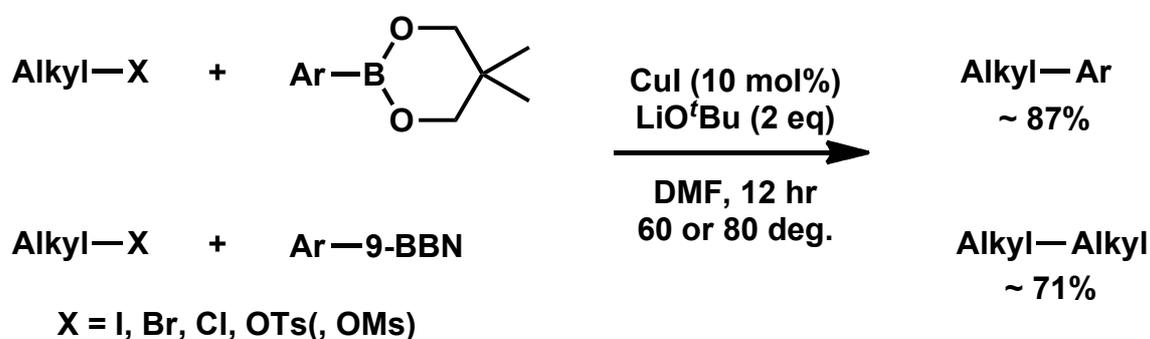
* The cross-coupling reactions using other organometallics are also developed.

Kumada-Tamao-Corriu-type



K. Mori *Eur. J. Org. Chem.* **2001**, 3797

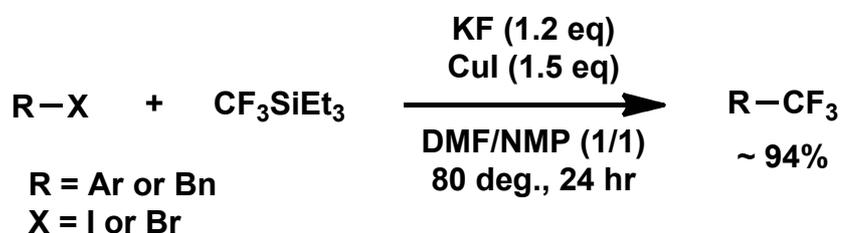
Suzuki-Miyaura-type



L. Liu *ACIE* **2011**, 50, 3904

This reactions don't proceed when CuI is replaced with $\text{Pd}(\text{OAc})_2$!

Hiyama-type



T. Fuchikami *TL*, **1991**, 32, 91