Current Literature
July 19, 08

Jitendra Mishra

Arylhalide-Tolerated Electrophilic Amination of Arylboronic Acids with N-Chloroamides Catalyzed by CuCl at Room Temperature

Aiwen Lei *et.al.*
College of the Chemistry andMolecular Sciences
Wuhan University
Wuhan, Hubei, 430072 (PR China)

Angew. Chemie. Int. Ed. 2008, Early view

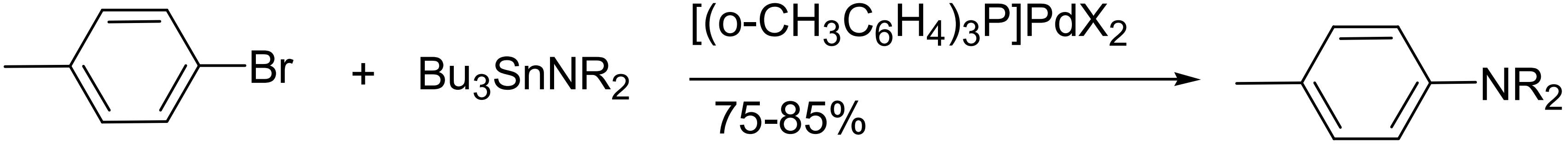
Introduction

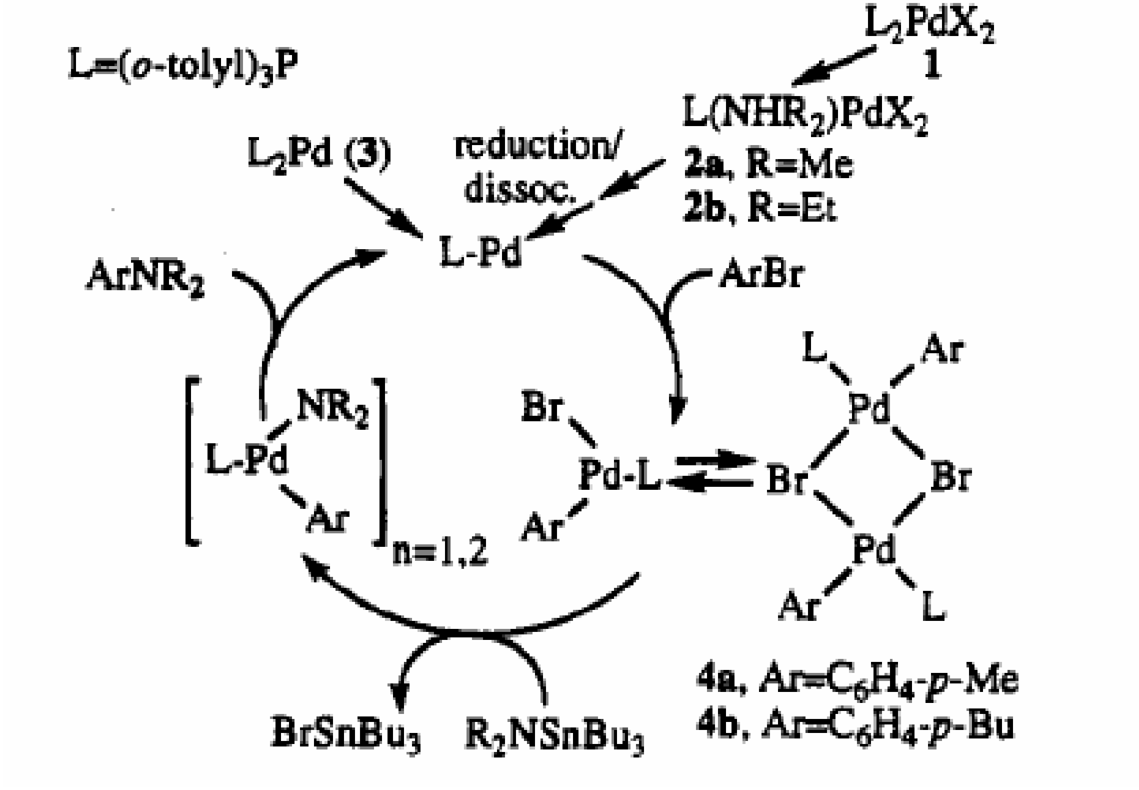
- Aryl amines are common place in chemistry.
- Arene-nitrogen or arene-oxygen linkage is included in nitrogen or oxygen heterocycles such as Indole, and benzofurans.
- Isodityrosine based natural product such as vancomycin.
- Conjugated polymers such as polyanilines.
- Readily oxidized triarylamines used in electronic applications such as such as N,N'-diphenyl-N,N'-bis(3-methylphenyl)-

1,1'-biphenyl-4,4'-diamine.

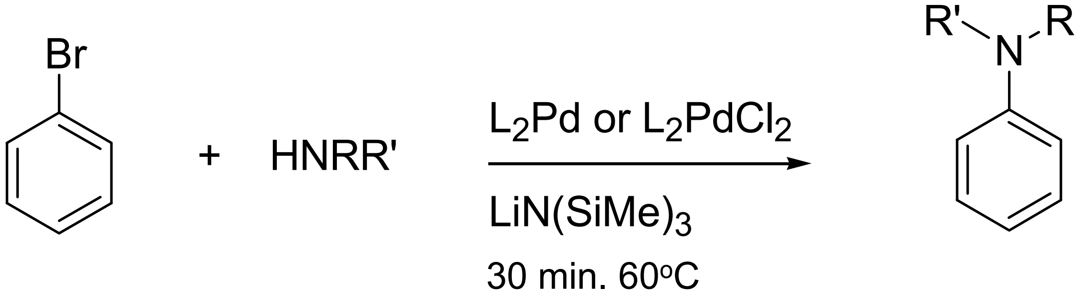
Historical Background:

The initial effort for the formation of transition metal mediated C-N bond was made by Hartwig et. al. and Buchwald group independently**.**



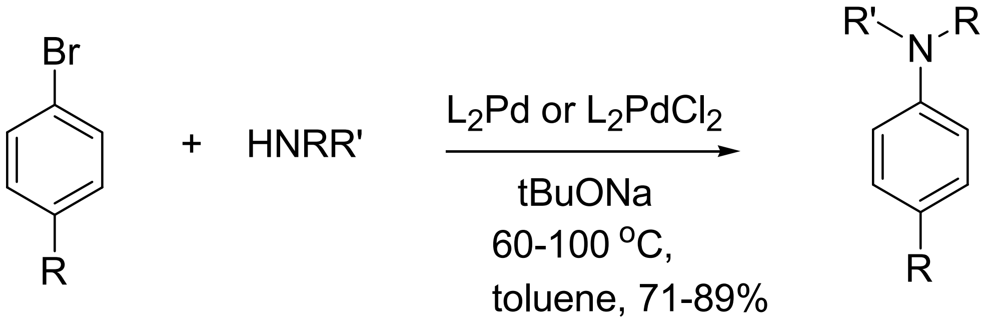


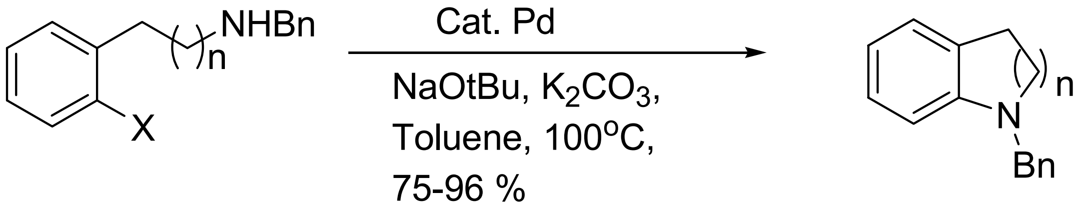
Hartwig *et. al. JACS* **1994**, 5969.



Hartwig *et. al.* TL 1995, 3609

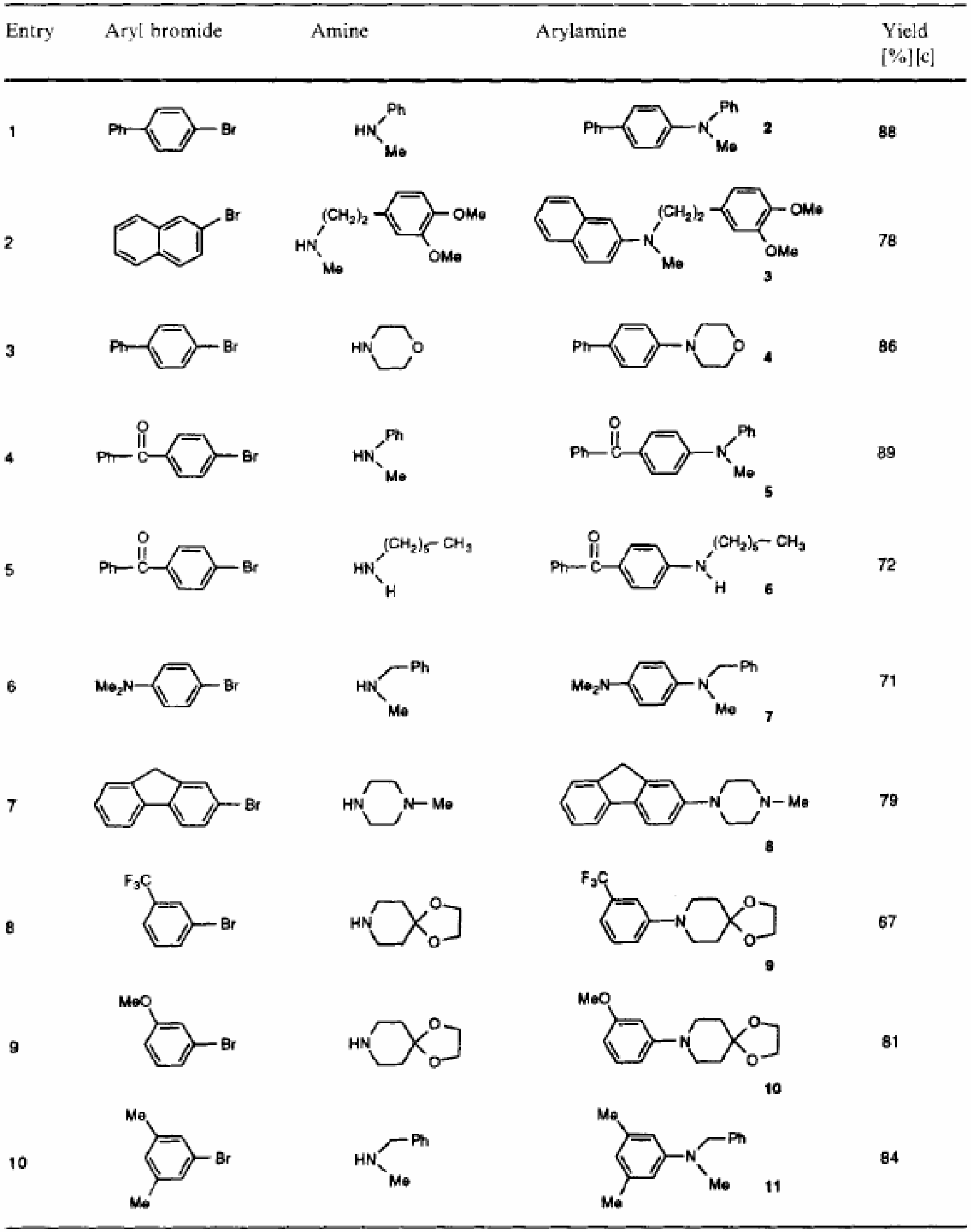
-First tin reagent free Pd catalyzed amination of aryl halide.





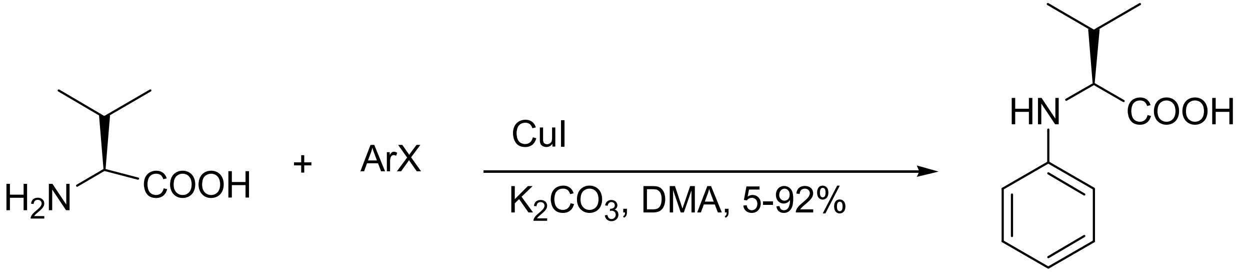
n = 1-3

Buchwald *et. al. Angew. Chem. Int. Ed.* **1995**, 1348

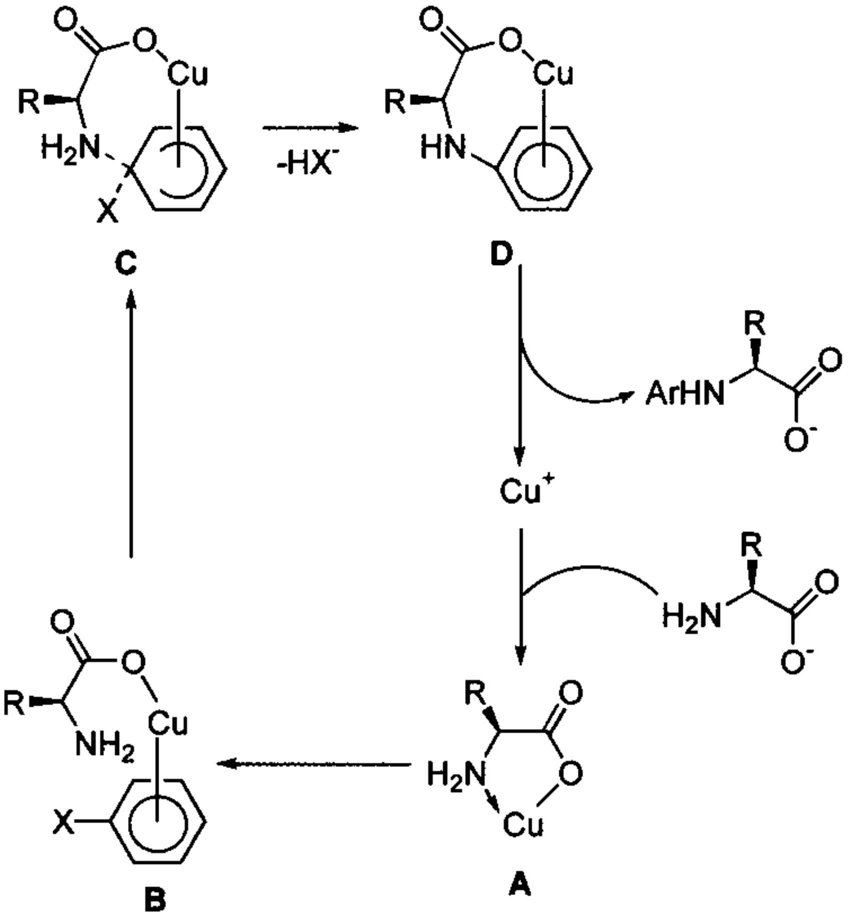


Entry	Aryl bromide	Amine	Arylamine	Yield [%][c]
1			2	88
2			3	78
3			4	86
4			5	89
5			6	72
6			7	71
7			8	79
8			9	67
9			10	81
10			11	84

[a] For entries 1 and 10, the catalyst $[Pd(dba)_2]/2\ P(o\text{-tolyl})_3$ and reaction temperature of 65 °C were employed, and for entries 2–9, the catalyst $[PdCl_2(P(o\text{-tolyl})_3)_2]$ and reaction temperature of 100 °C were employed. [b] By GC analysis using an internal standard, approximately 8, 12, 5, 6, 27, 24, 8, not determined, 12, 10% of reduced side-product was formed in entries 1–10, respectively. [c] Yields reported correspond to analytically pure, isolated compounds.

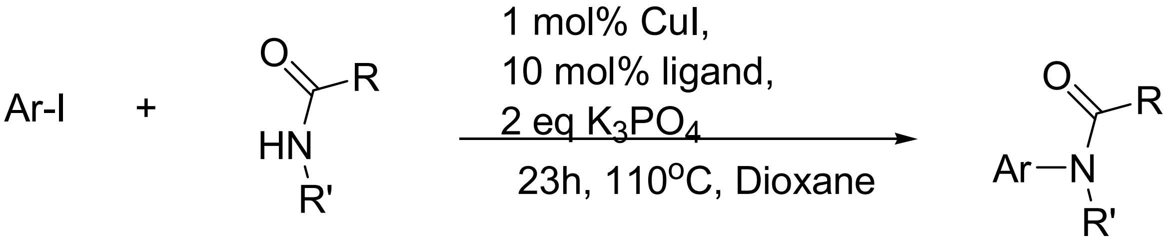


Possible catalytic cycle



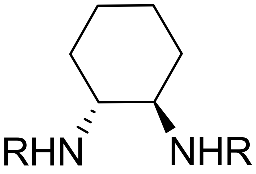
Dawai Ma *et. al.* *JACS* **1998**, 12459

- $CuSO_4$, $Cu(OAc)_2$, CuI, were used as catalysts and gave over 80% yield.
- The reaction catalyzed by CuI was faster comparision to other.
- A strong o-carboxylate accelarating effect was observed while p- has no similar effect.
- The order of halogen displacement from aromatic ring is I > Br > Cl.
- Amino acid containing larger hydrophobic group gave higher coupling yield compare to lower hydrophobic group and the amino acids with hydrophillic group yielded no coupling product at all. Cyclic amino acid gave higher yield.

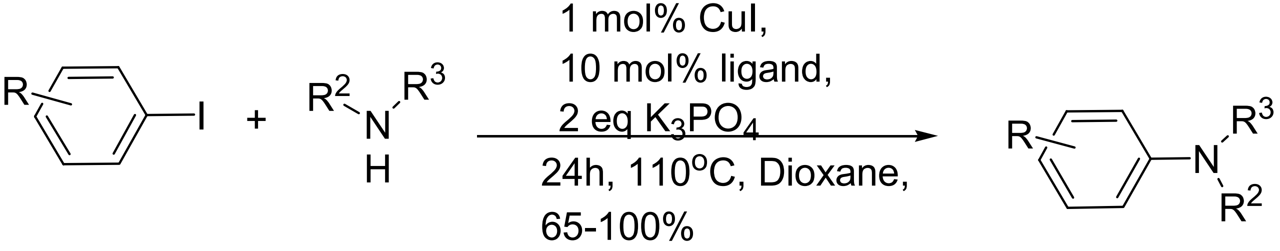


1 mol% CuI,
10 mol% ligand,
2 eq K_3PO_4
23h, 110^oC, Dioxane

Ligand



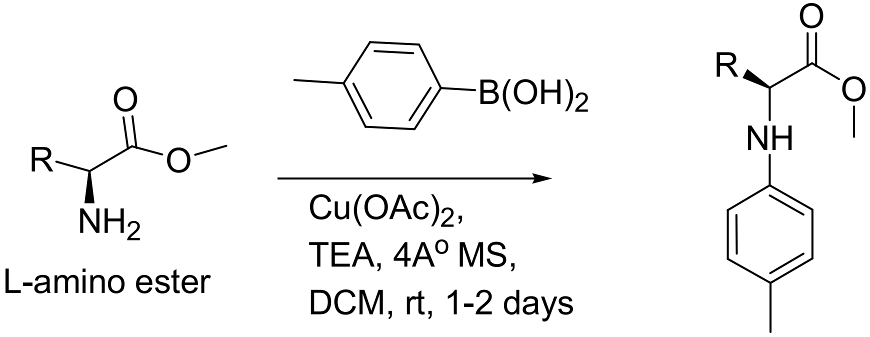
1a; R = H
1b; R = Me

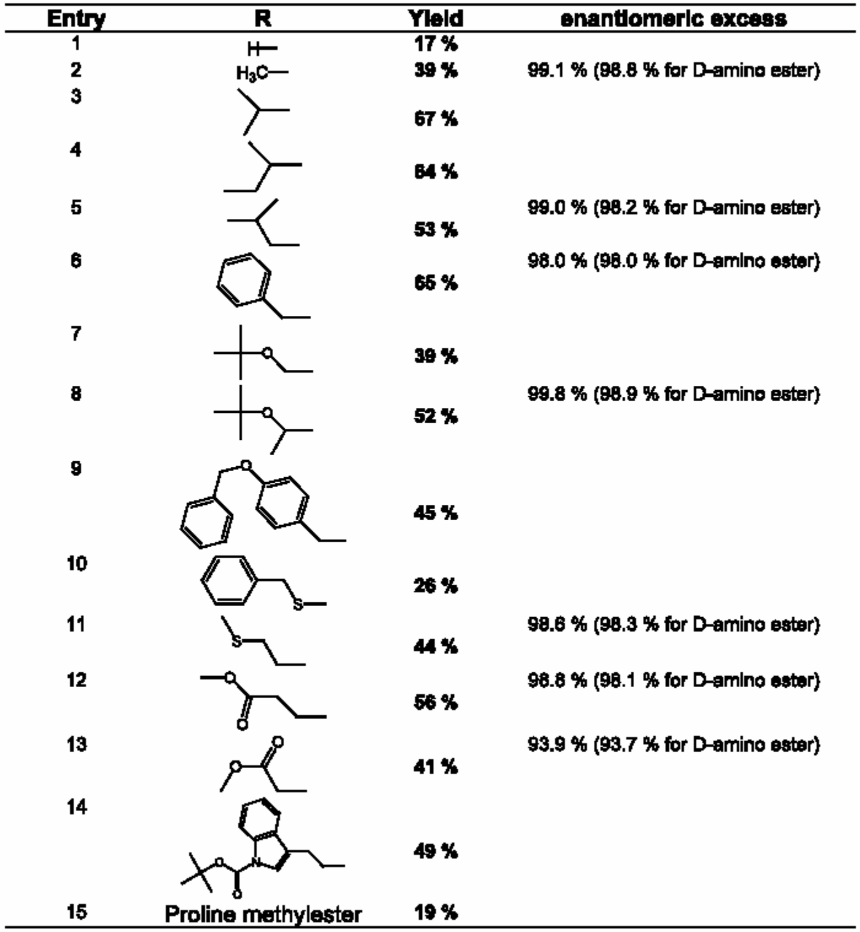


1 mol% CuI,
10 mol% ligand,
2 eq K_3PO_4
24h, 110^oC, Dioxane,
65-100%

- N-arylation of nitogen heterocycles

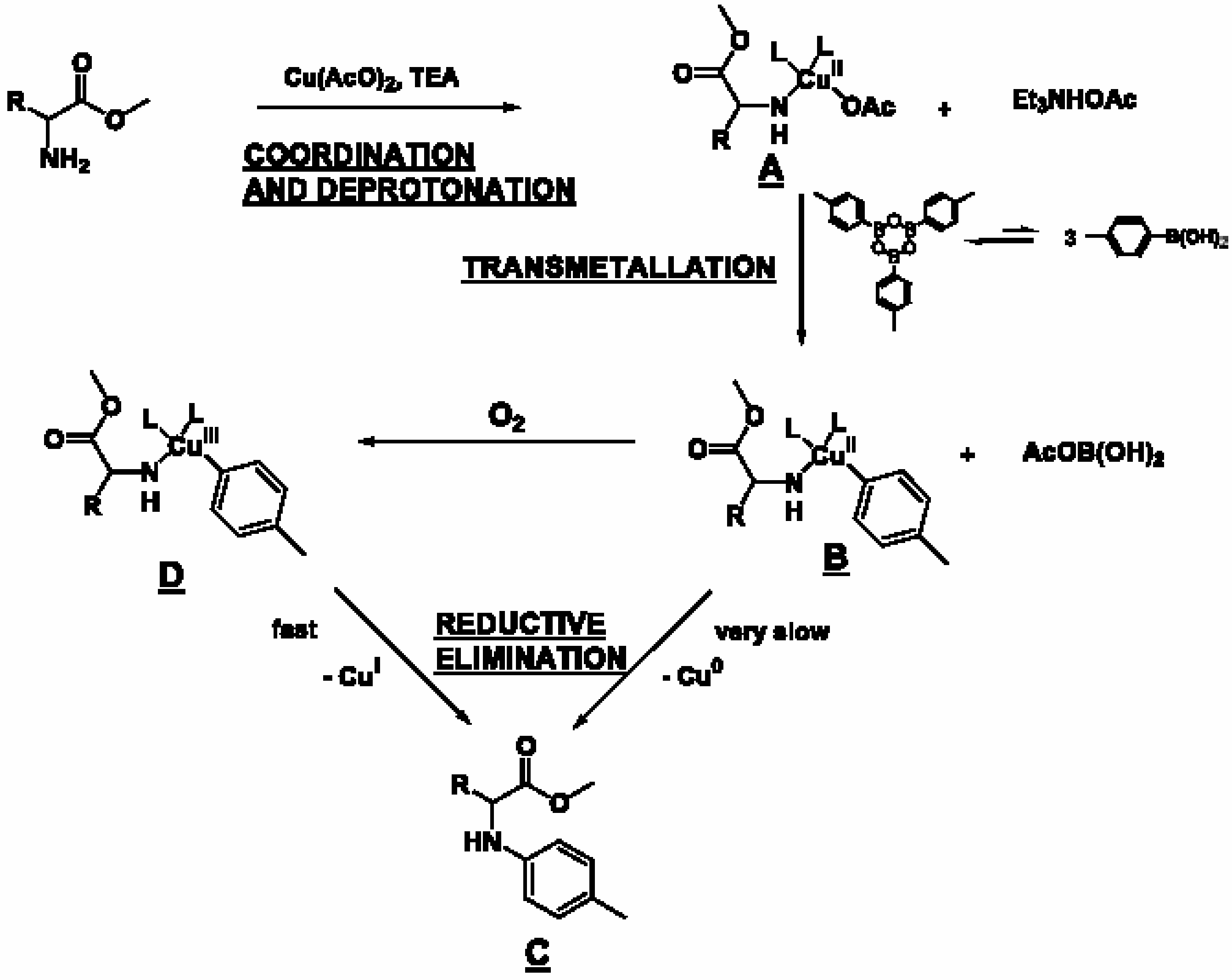
Buchwald *et. al. JACS* **2001,** 7727.

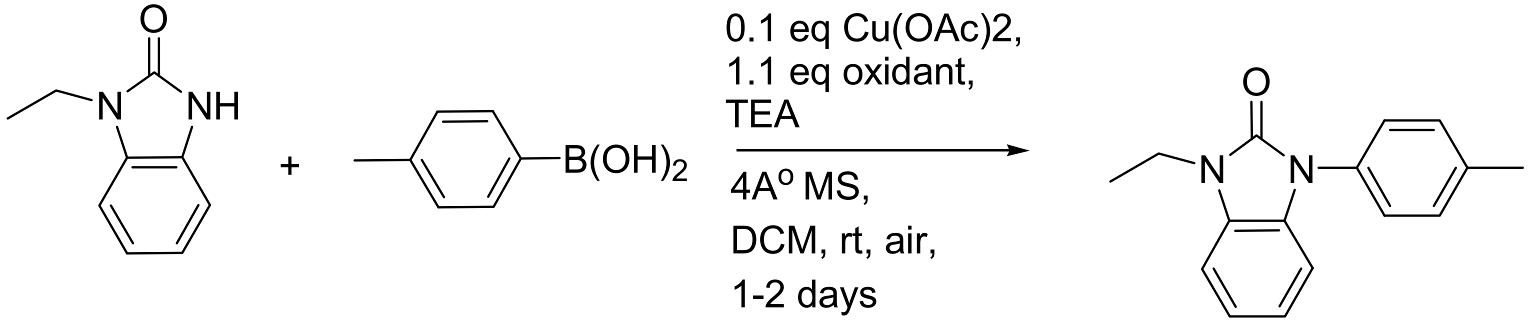




Entry	R	Yield	enantiomeric excess
1	H—	17 %	
2	H_3C—	39 %	99.1 % (98.8 % for D-amino ester)
3		67 %	
4		64 %	
5		53 %	99.0 % (98.2 % for D-amino ester)
6		65 %	98.0 % (98.0 % for D-amino ester)
7		39 %	
8		52 %	99.8 % (98.9 % for D-amino ester)
9		45 %	
10		26 %	
11		44 %	98.6 % (98.3 % for D-amino ester)
12		56 %	98.8 % (98.1 % for D-amino ester)
13		41 %	93.9 % (93.7 % for D-amino ester)
14		49 %	
15	Proline methylester	19 %	

Lam *et.al.* *TL* **2003**, 1691


Cu(AcO)2, TEA
COORDINATION AND DEPROTONATION
A
Et3NHOAc
TRANSMETALLATION
3 B(OH)2
O2
B
AcOB(OH)2
D
fast
- Cu^I
REDUCTIVE ELIMINATION
very slow
- Cu^0
C



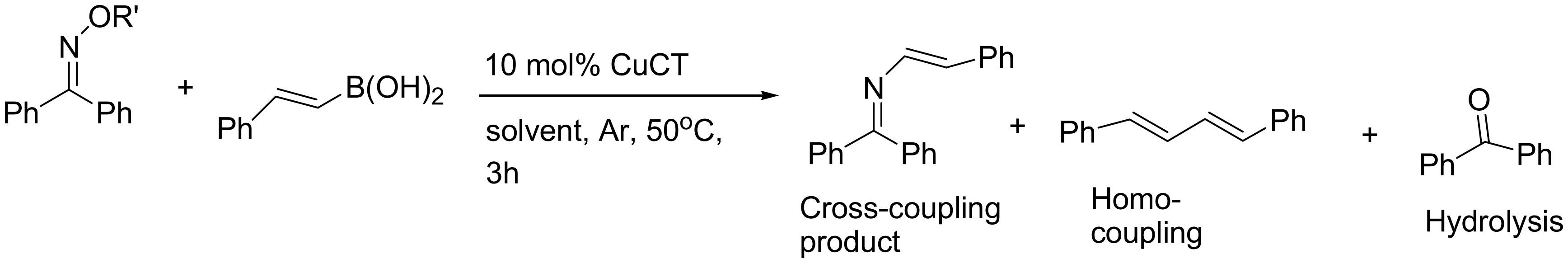
PyridineN-oxide > TEMPO > NMO > di-t-butyl nitroxide > (1*R*) (10-camphor-

69%   64%   62%   55%   48%

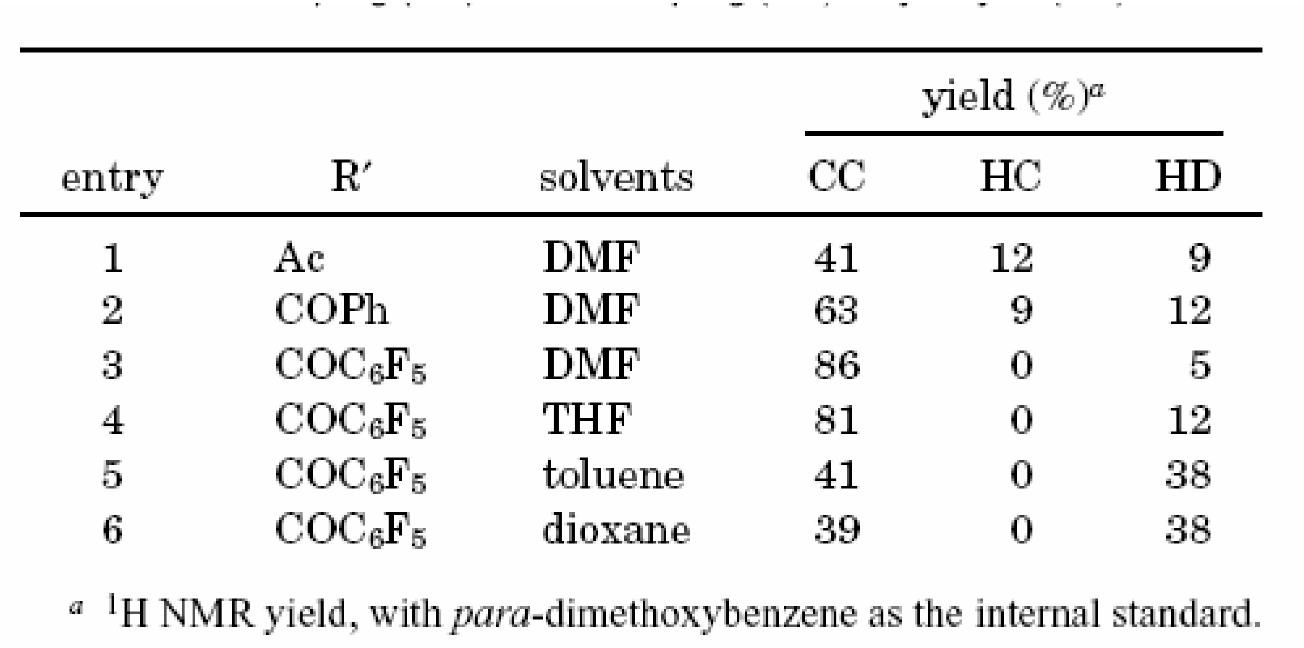
sulfonyl)oxaziridine > $NaBO_3.H_2O$, > $K_3Fe(CN)_6$ > mCPBA

31%   11%   6%

Lam *et. al. TL* **2001,** 3415



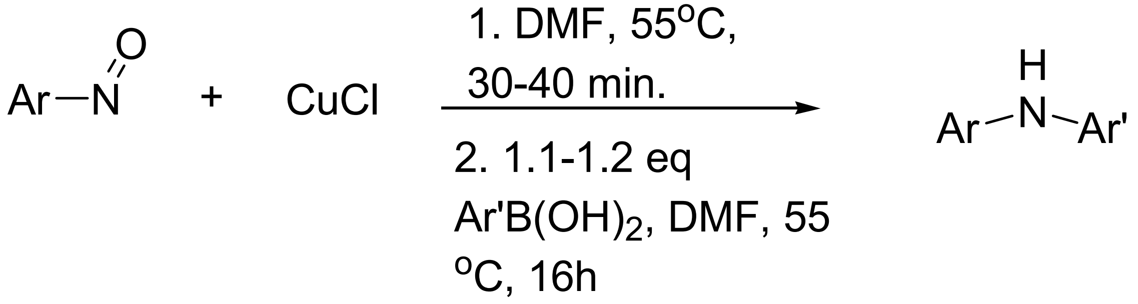
CuCT = Cu(I) thiophene-2-carboxylate



			yield (%)[a]		
entry	R′	solvents	CC	HC	HD
1	Ac	DMF	41	12	9
2	COPh	DMF	63	9	12
3	COC_6F_5	DMF	86	0	5
4	COC_6F_5	THF	81	0	12
5	COC_6F_5	toluene	41	0	38
6	COC_6F_5	dioxane	39	0	38

[a] ^{1}H NMR yield, with *para*-dimethoxybenzene as the internal standard.

Liebeskind *et.al.* **2007,** 1947.



1. DMF, 55°C, 30-40 min.

2. 1.1-1.2 eq $Ar'B(OH)_2$, DMF, 55 °C, 16h

entry	Ar	Ar′	product yield (%)[b]
1	*o*-tol	Ph	83
2	*o*-tol	4-$MeOC_6H_4$	81
3	Ph	4-$C_6H_4CF_3$	70
4	Ph	4-$C_6H_4CO_2Me$	72
5	Ph	3-C_6H_4CHO	81
6	Ph	2-C_6H_4F	61
7	Ph	4-MeO-2-C_6H_3CHO	78
8	Ph	2-dibenzofuranyl	64
9	4-Cl-*o*-tol	4-$C_6H_4CO_2Me$	70

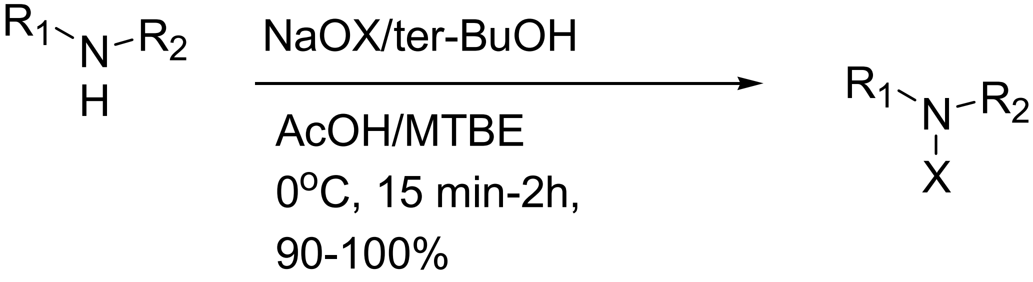
[a] Dry DMF (8 mL) was added to a reaction vessel holding a mixture of the nitroso aromatic (0.3 mmol) and CuCl (0.3 mmol), which was then heated to 55 °C for 30−40 min. The aryl boronic acid (0.33 mmol) was dissolved in 3 mL of DMF and then added, and the reaction mixture was stirred at 55 °C for another 16 h. [b] Isolated yields, average of two runs.

Liebeskind *et. al*. *OL*. **2004,** 2631

Title paper:

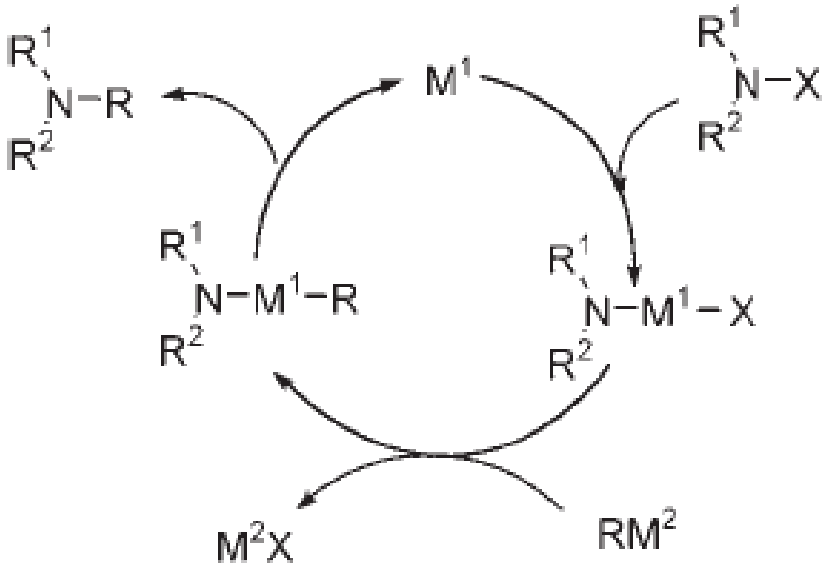
Reasons to Choose N-Chloroamides:

- Ease of preparation of N-Chloroamides.



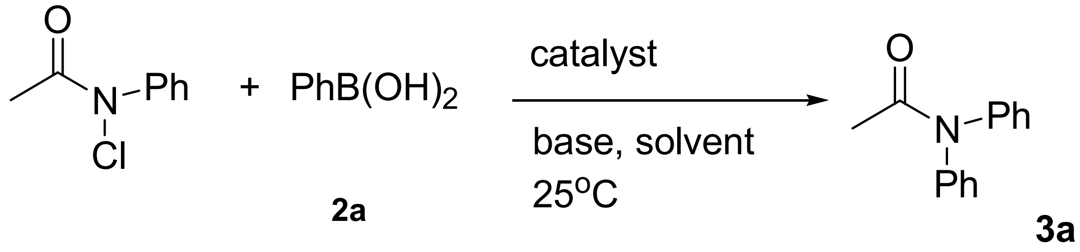
X = Br, Cl

- High activities of N-Cl bond.



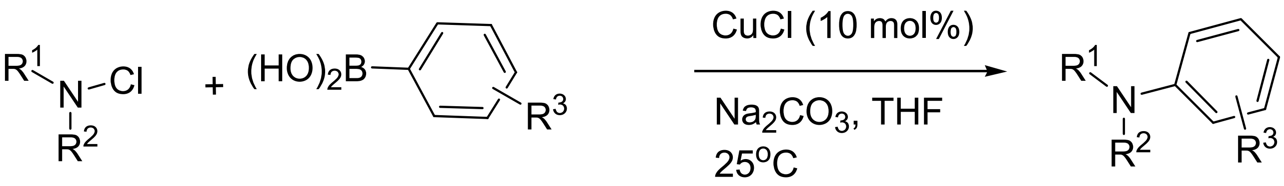
Scheme 1. Putative mechanism of transition-metal-catalyzed electrophilic amination of organometallic reagents by *N*-haloamides.

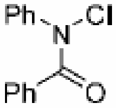
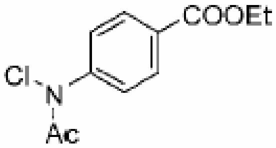
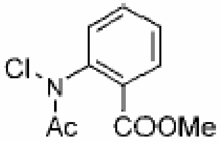
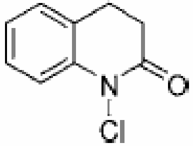
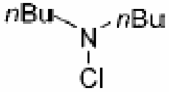
Cu Catalyzed N-Phenylation of N-chloramide



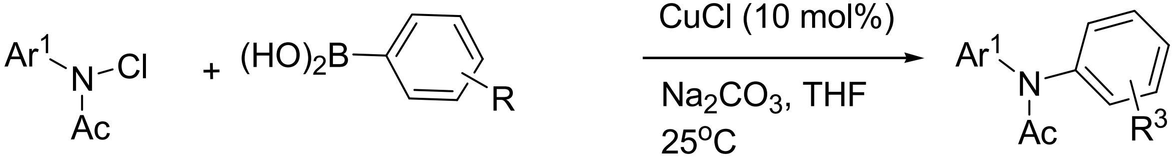
Entry	Catalyst	Base	Solvent	Yield [%][b]
1	CuCl	K_3PO_4	THF	78
2	CuBr	K_3PO_4	THF	65
3	CuI	K_3PO_4	THF	43
4	CuCN	K_3PO_4	THF	<5
5	Cu_2O	K_3PO_4	THF	<5
6	$Cu(OTf)C_6H_6$	K_3PO_4	THF	10
7	$[Cu(CH_3CN)_4]BF_4$	K_3PO_4	THF	<5
8	CuCl	K_2CO_3	THF	52
9	CuCl	Na_2CO_3	THF	99
10	CuCl	Li_2CO_3	THF	28
11	CuCl	KF	THF	22
12	CuCl	CsF	THF	57
13	CuCl	Na_2CO_3	dioxane	35
14	CuCl	Na_2CO_3	toluene	<5
15	CuCl	Na_2CO_3	acetone	<5
16	CuCl	Na_2CO_3	DMF	<5
17[c]	CuCl/TMEDA	Na_2CO_3	THF	22
18[d]	CuCl/DMEDA	Na_2CO_3	THF	53

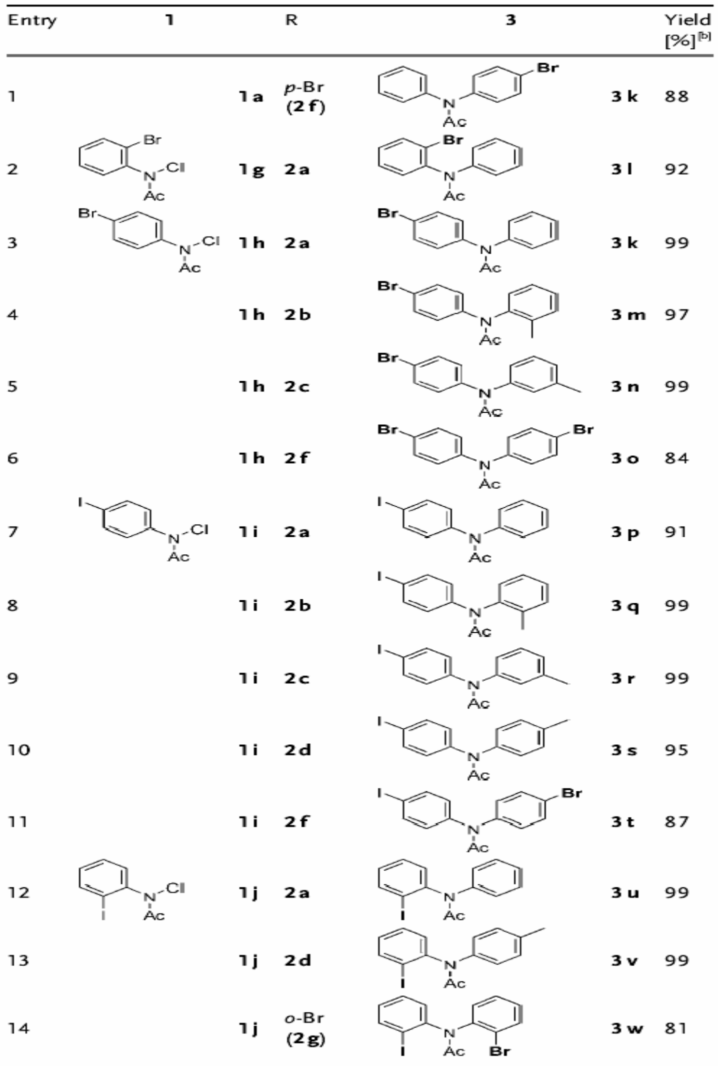
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), base (3 equiv), copper catalyst (10 mol%) in THF at 25 °C; [b] Yields determined by GC methods; [c] TMEDA (N^1,N^1,N^2,N^2-tetramethylethane-1,2-diamine) (10 mol%) was added; [d] DMEDA (N^1,N^2-dimethylethane-1,2-diamine) (10 mol%) was added.



Entry	1		R^3	Yield [%][b]
1		**1a**	*o*-Me (**2b**)	96 (**3b**)
2		**1a**	*m*-Me (**2c**)	98 (**3c**)
3		**1a**	*p*-Me (**2d**)	98 (**3d**)
4		**1a**	*p*-Cl (**2e**)	81 (**3e**)
5		**1b**	**2b**	90 (**3f**)
6		**1c**	H (**2a**)	92 (**3g**)
7		**1d**	**2a**	94 (**3h**)
8		**1e**	**2a**	83 (**3i**)
9		**1f**	**2a**	11 (**3j**)

[a] Reaction conditions: **1** (1.0 mmol), **2** (0.5 mmol), Na_2CO_3 (3 equiv), CuCl (10 mol%) in THF at 25 °C for 36 h. [b] Yields of isolated products.





Entry	1	R	3	Yield [%][b]
1	**1a**	*p*-Br (**2f**)	**3k**	88
2	**1g**	**2a**	**3l**	92
3	**1h**	**2a**	**3k**	99
4	**1h**	**2b**	**3m**	97
5	**1h**	**2c**	**3n**	99
6	**1h**	**2f**	**3o**	84
7	**1i**	**2a**	**3p**	91
8	**1i**	**2b**	**3q**	99
9	**1i**	**2c**	**3r**	99
10	**1i**	**2d**	**3s**	95
11	**1i**	**2f**	**3t**	87
12	**1j**	**2a**	**3u**	99
13	**1j**	**2d**	**3v**	99
14	**1j**	*o*-Br (**2g**)	**3w**	81

[a] Reaction conditions: **1** (1.0 mmol), **2** (0.5 mmol), Na_2CO_3 (3 equiv), CuCl (10 mol%) in THF at 25 °C for 36 h; [b] Yields of isolated products.

Conclusion

-The authors utilized easily prepared and highly reactive N-chloroamides to develop an efficient copper catalyzed electrophilic amination of arylboronic acids.

-The developed methodoly gave high yields of diarylamides and tolerated a wide variety of functional groups, including iodo, bromo, and chloro moieties, which are usually sensitive in palladium-catalyzed reactions.

-A scale up experiment was carried out to demonstrate the practicability of the method to provide biaryl amides or amines having sensitive substituents.

-The availability of various boronic acids promises highlights the potential of the methodology.

- Their preliminary mechanistic studies support the proposed mechanism and the results of additional investigations that are ongoing in their laboratory.