Nitroarenes as electrophilic coupling partners in cross-coupling reactions

The arylamine moiety represents a prevalent motif in a variety of pharmaceuticals and functional materials.

Aryl halides, which may cause undesirable halogen-based contamination.

Various aryl pseudohalides, including aryl sulfonates such as aryl triflates, tosylates, ethers, esters, sulfamates, and carbamates have been introduced as electrophilic coupling partners as surrogates for the aryl halides.

Nitroarenes can be directly obtained from the nitration of the parent arenes, which is generally highly selective toward monofunctionalization, while the halogenation of arenes sometimes affords a mixture of mono- and dihalogenated arenes.

The Suzuki−Miyaura Coupling of Nitroarenes

***J. Am. Chem. Soc*., 2017, *139*, 9423**

Buchwald–Hartwig Amination of Nitroarenes

***Angew. Chem. Int. Ed*., 2017, *56*, 13307**

Prof. Yoshiaki Nakao

Employment

2014-present	JST-CREST team leader
2014–present	Professor, Kyoto University
2012–2014	Associate Professor, Kyoto University
2011–present	JST–PRESTO researcher
2010–2012	Senior Lecturer, Kyoto University
2002–2010	Assistant Professor, Kyoto University

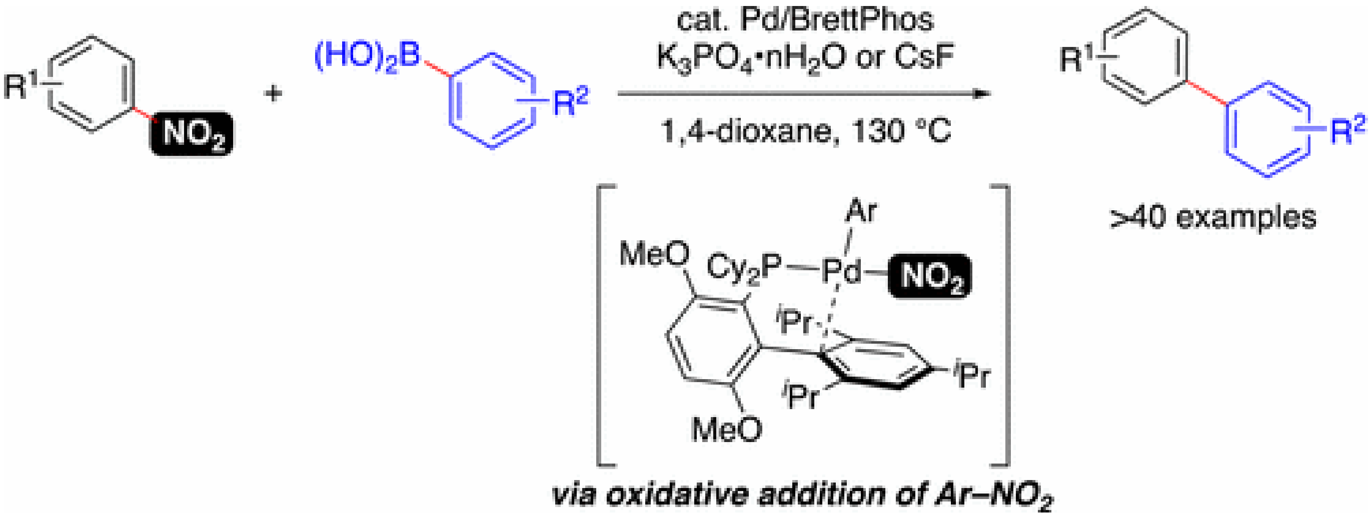
Education

2008	Max-Planck-Institut für Kohlenforschung (visiting scholar, work with Prof. Manfred T. Reetz)
2005	Ph. D., Graduate School of Engineering, Kyoto University
2001	Department of Chemistry, Yale University (visiting student, work with Prof. John F. Hartwig)
2000–2002	Department of Material Chemistry, Graduate School of Engineering Kyoto University (work with Profs. Tamejiro Hiyama and Eiji Shirakawa)
1998–2000	M. S., Department of Material Chemistry, Graduate School of Engineering, Kyoto University (work with Profs. Tamejiro Hiyama and Eiji Shirakawa)
1997–1998	B. S., Department of Industrial Chemistry, Faculty of Engineering Kyoto University

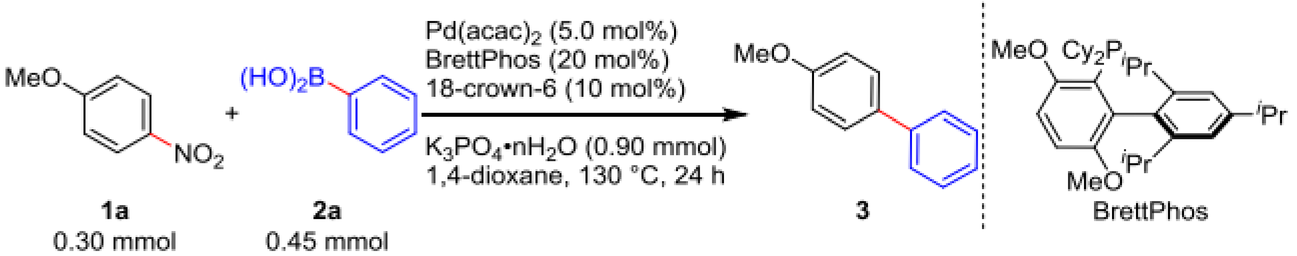
Research Interest

New Organometallic Reagents and Reactions for Selective Organic Synthesis

The Suzuki−Miyaura Coupling of Nitroarenes

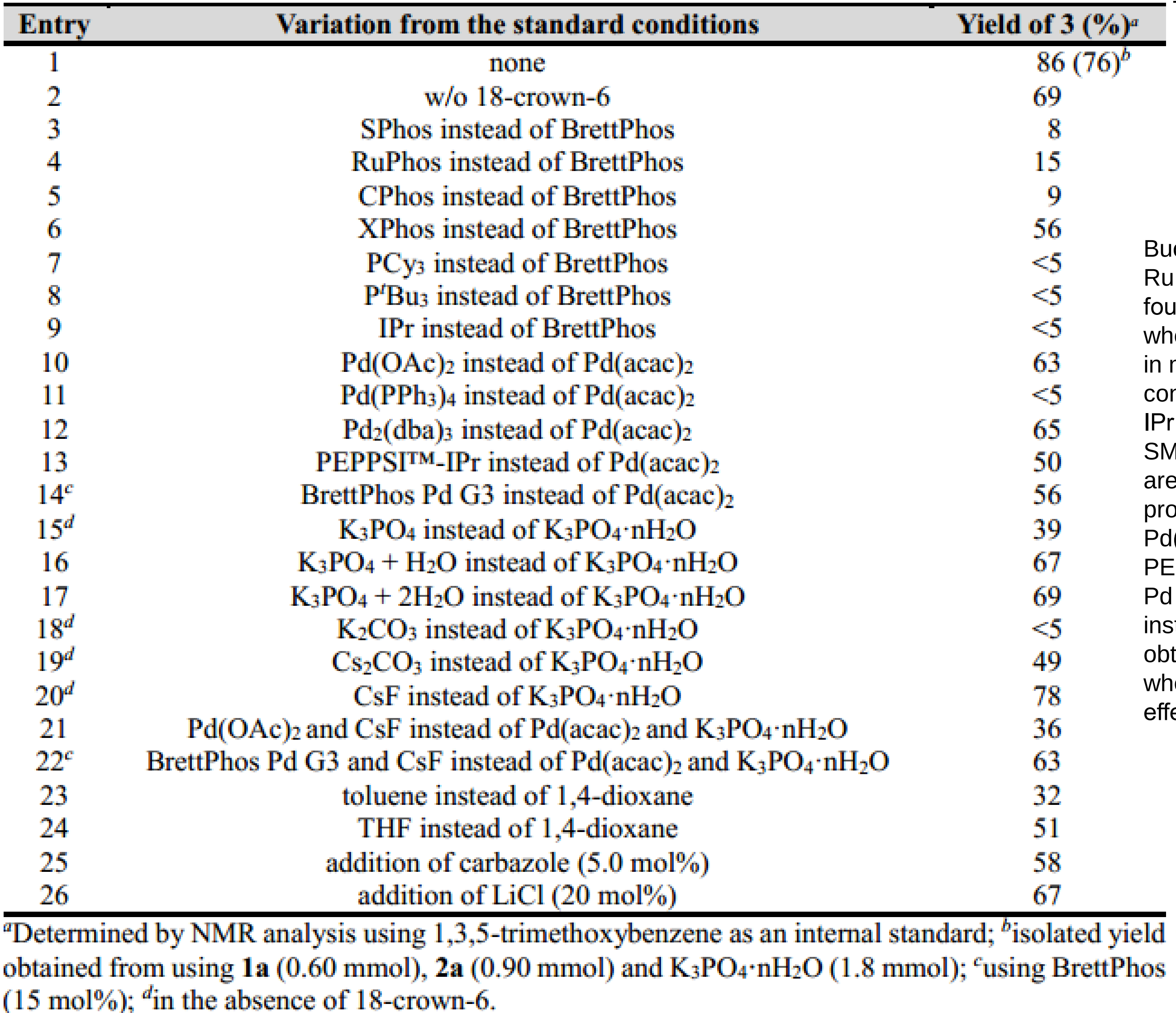


J. Am. Chem. Soc., 2017, *139*, 9423



$Pd(acac)_2$ (5.0 mol%)
BrettPhos (20 mol%)
18-crown-6 (10 mol%)
$K_3PO_4 \cdot nH_2O$ (0.90 mmol)
1,4-dioxane, 130 °C, 24 h

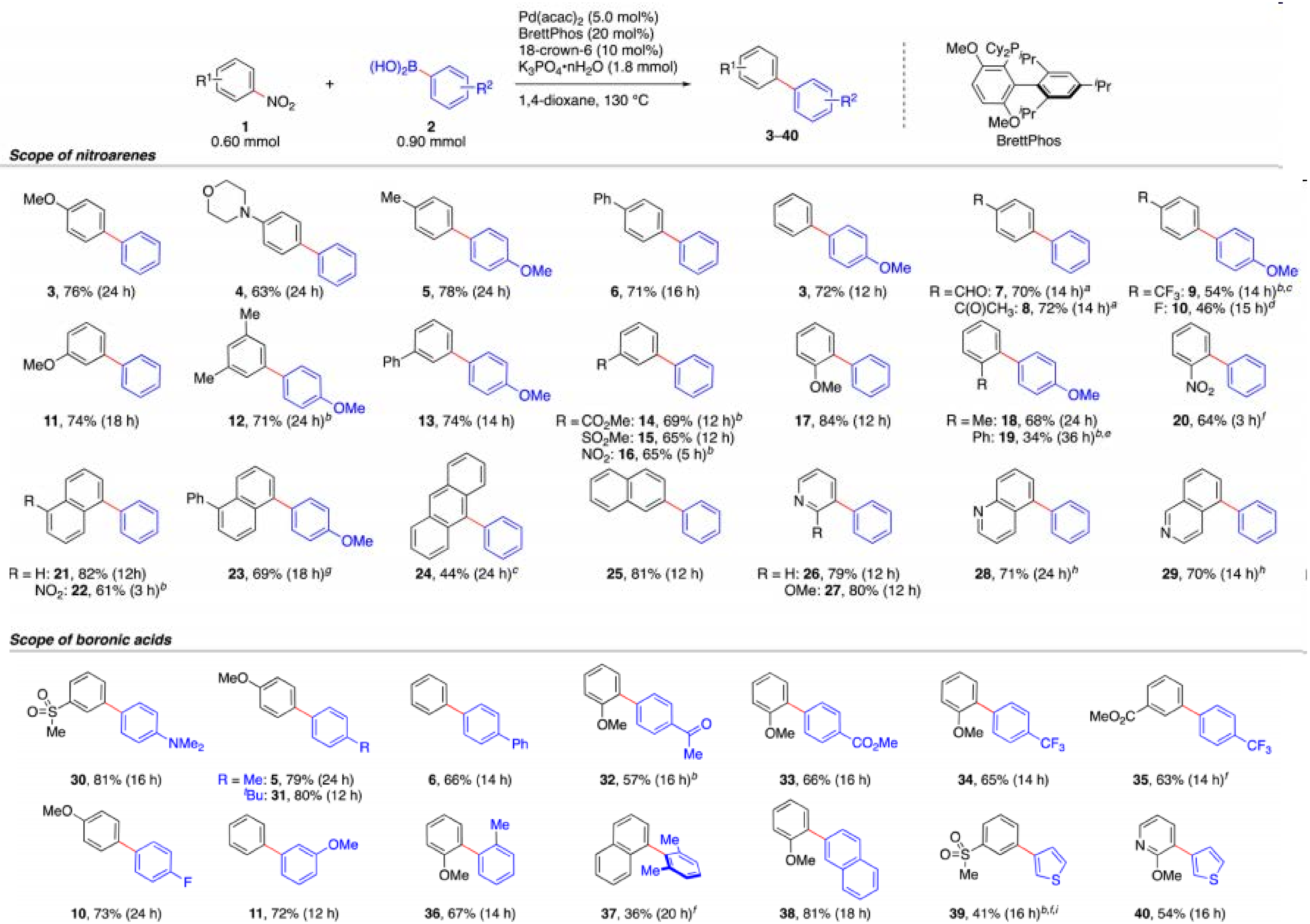
1a 0.30 mmol
2a 0.45 mmol
3



Entry	Variation from the standard conditions	Yield of 3 (%)[a]
1	none	86 (76)[b]
2	w/o 18-crown-6	69
3	SPhos instead of BrettPhos	8
4	RuPhos instead of BrettPhos	15
5	CPhos instead of BrettPhos	9
6	XPhos instead of BrettPhos	56
7	PCy_3 instead of BrettPhos	<5
8	P^tBu_3 instead of BrettPhos	<5
9	IPr instead of BrettPhos	<5
10	$Pd(OAc)_2$ instead of $Pd(acac)_2$	63
11	$Pd(PPh_3)_4$ instead of $Pd(acac)_2$	<5
12	$Pd_2(dba)_3$ instead of $Pd(acac)_2$	65
13	PEPPSI™-IPr instead of $Pd(acac)_2$	50
14[c]	BrettPhos Pd G3 instead of $Pd(acac)_2$	56
15[d]	K_3PO_4 instead of $K_3PO_4 \cdot nH_2O$	39
16	$K_3PO_4 + H_2O$ instead of $K_3PO_4 \cdot nH_2O$	67
17	$K_3PO_4 + 2H_2O$ instead of $K_3PO_4 \cdot nH_2O$	69
18[d]	K_2CO_3 instead of $K_3PO_4 \cdot nH_2O$	<5
19[d]	Cs_2CO_3 instead of $K_3PO_4 \cdot nH_2O$	49
20[d]	CsF instead of $K_3PO_4 \cdot nH_2O$	78
21	$Pd(OAc)_2$ and CsF instead of $Pd(acac)_2$ and $K_3PO_4 \cdot nH_2O$	36
22[c]	BrettPhos Pd G3 and CsF instead of $Pd(acac)_2$ and $K_3PO_4 \cdot nH_2O$	63
23	toluene instead of 1,4-dioxane	32
24	THF instead of 1,4-dioxane	51
25	addition of carbazole (5.0 mol%)	58
26	addition of LiCl (20 mol%)	67

[a]Determined by NMR analysis using 1,3,5-trimethoxybenzene as an internal standard; [b]isolated yield obtained from using **1a** (0.60 mmol), **2a** (0.90 mmol) and $K_3PO_4 \cdot nH_2O$ (1.8 mmol); [c]using BrettPhos (15 mol%); [d]in the absence of 18-crown-6.

Buchwald's ligands SPhos, RuPhos, and CPhos were found to be ineffective, whereas XPhos provided 3 in moderate yield. In contrast, PCy3 , PtBu3 , and IPr, which are effective for SMC of aryl halides and arene sulfonates, did not provide any 3. When Pd(OAc)2 , Pd2 (dba)3 , PEPPSI-IPr, or BrettPhos Pd G3 were employed instead of Pd(acac)2 , **3** was obtained in moderate yield, whereas Pd(PPh3)4 was not effective.



Scope of nitroarenes

3, 76% (24 h)
4, 63% (24 h)
5, 78% (24 h)
6, 71% (16 h)
3, 72% (12 h)
R = CHO: **7**, 70% (14 h)[a]
C(O)CH$_3$: **8**, 72% (14 h)[a]
R = CF$_3$: **9**, 54% (14 h)[b,c]
F: **10**, 46% (15 h)[d]
11, 74% (18 h)
12, 71% (24 h)[b]
13, 74% (14 h)
R = CO$_2$Me: **14**, 69% (12 h)[b]
SO$_2$Me: **15**, 65% (12 h)
NO$_2$: **16**, 65% (5 h)[b]
17, 84% (12 h)
R = Me: **18**, 68% (24 h)
Ph: **19**, 34% (36 h)[b,e]
20, 64% (3 h)[f]
R = H: **21**, 82% (12h)
NO$_2$: **22**, 61% (3 h)[b]
23, 69% (18 h)[g]
24, 44% (24 h)[c]
25, 81% (12 h)
R = H: **26**, 79% (12 h)
OMe: **27**, 80% (12 h)
28, 71% (24 h)[h]
29, 70% (14 h)[h]

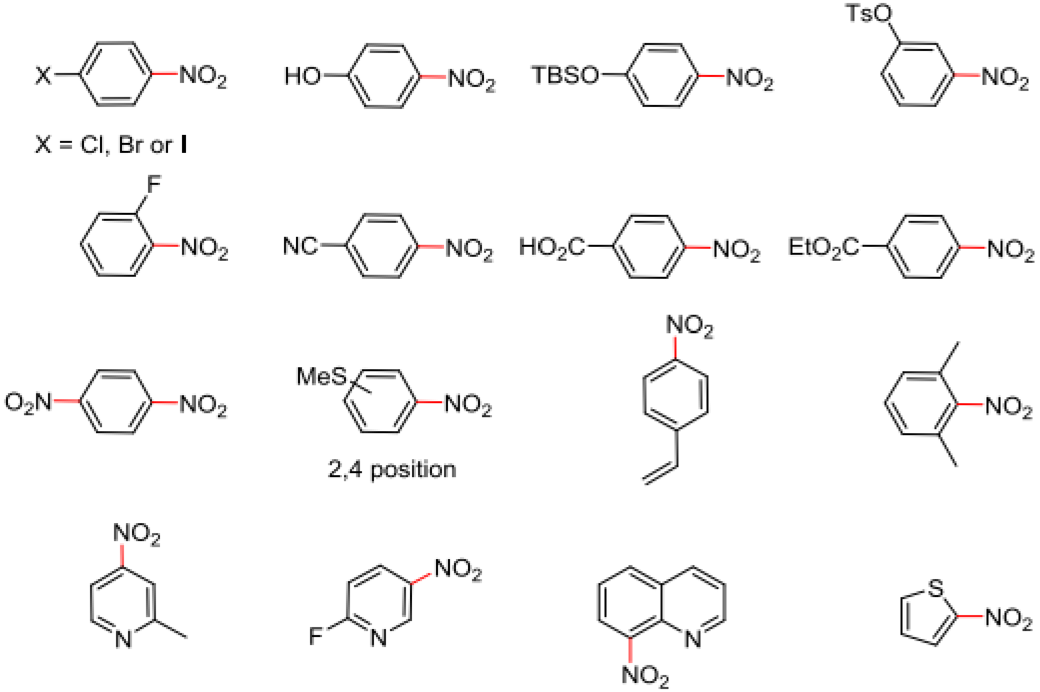
Scope of boronic acids

30, 81% (16 h)
R = Me: **5**, 79% (24 h)
^{t}Bu: **31**, 80% (12 h)
6, 66% (14 h)
32, 57% (16 h)[b]
33, 66% (16 h)
34, 65% (14 h)
35, 63% (14 h)[f]
10, 73% (24 h)
11, 72% (12 h)
36, 67% (14 h)
37, 36% (20 h)[f]
38, 81% (18 h)
39, 41% (16 h)[b,f,i]
40, 54% (16 h)

[a] Isolated yield after hydrolysis of the corresponding acetals. [b] Reaction with arylboronic acid (1.2 mmol). [c] Reaction with CsF (1.8 mmol) in toluene (3.0 mL). [d] Reaction with CsF (3.0 mmol) in toluene (3.0 mL). [e] Reaction with RuPhos (20 mol %) instead of BrettPhos and CsF (1.8 mmol). [f] Reaction with CsF (1.8 mmol). [g] Reaction with **22** (0.58 mmol). [h] Reaction without 18-crown-6. [i] Reaction with Pd(acac)$_2$ (10 mol %).

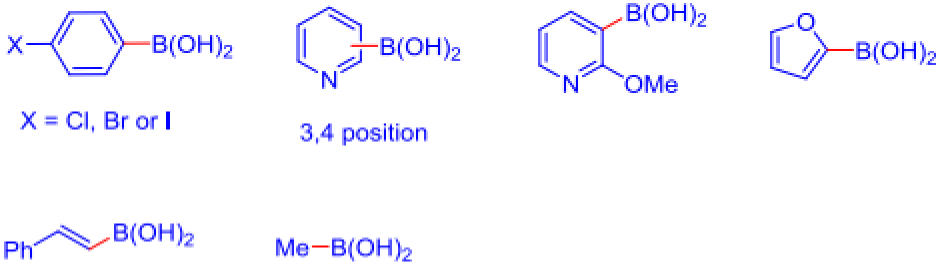
Unsuccessful substrates

Nitroarenes


X = Cl, Br or **I**

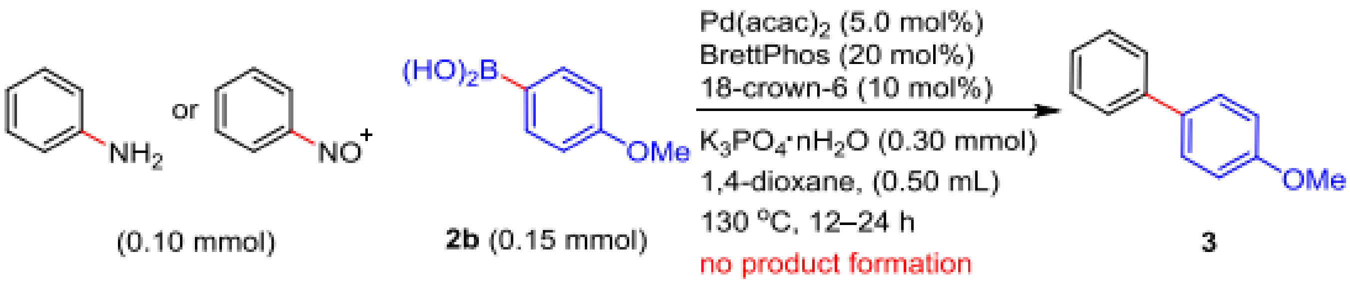
2,4 position

Boronic acids

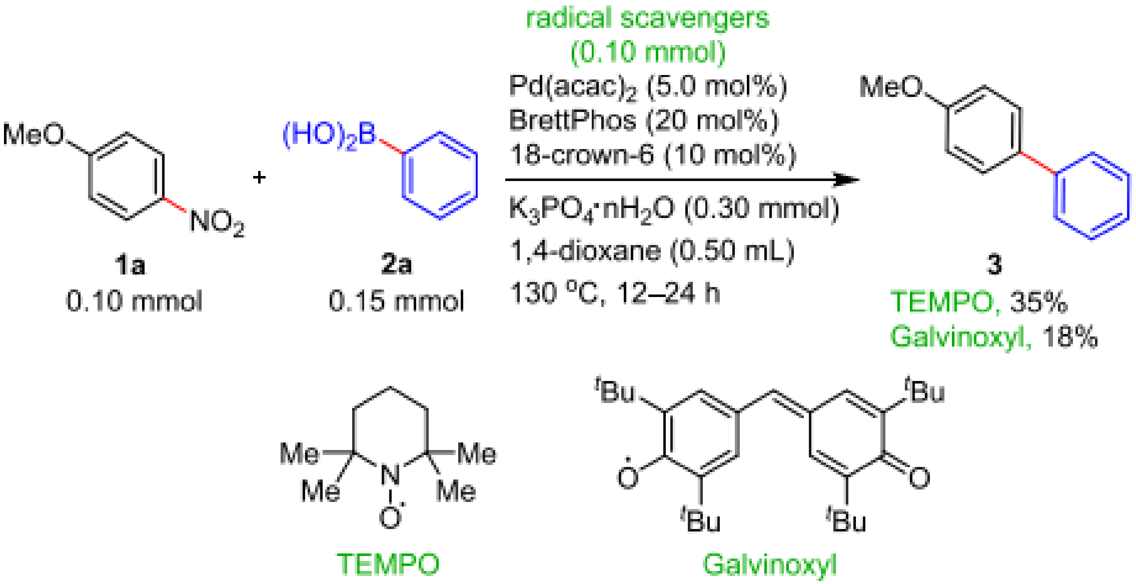

X = Cl, Br or **I**

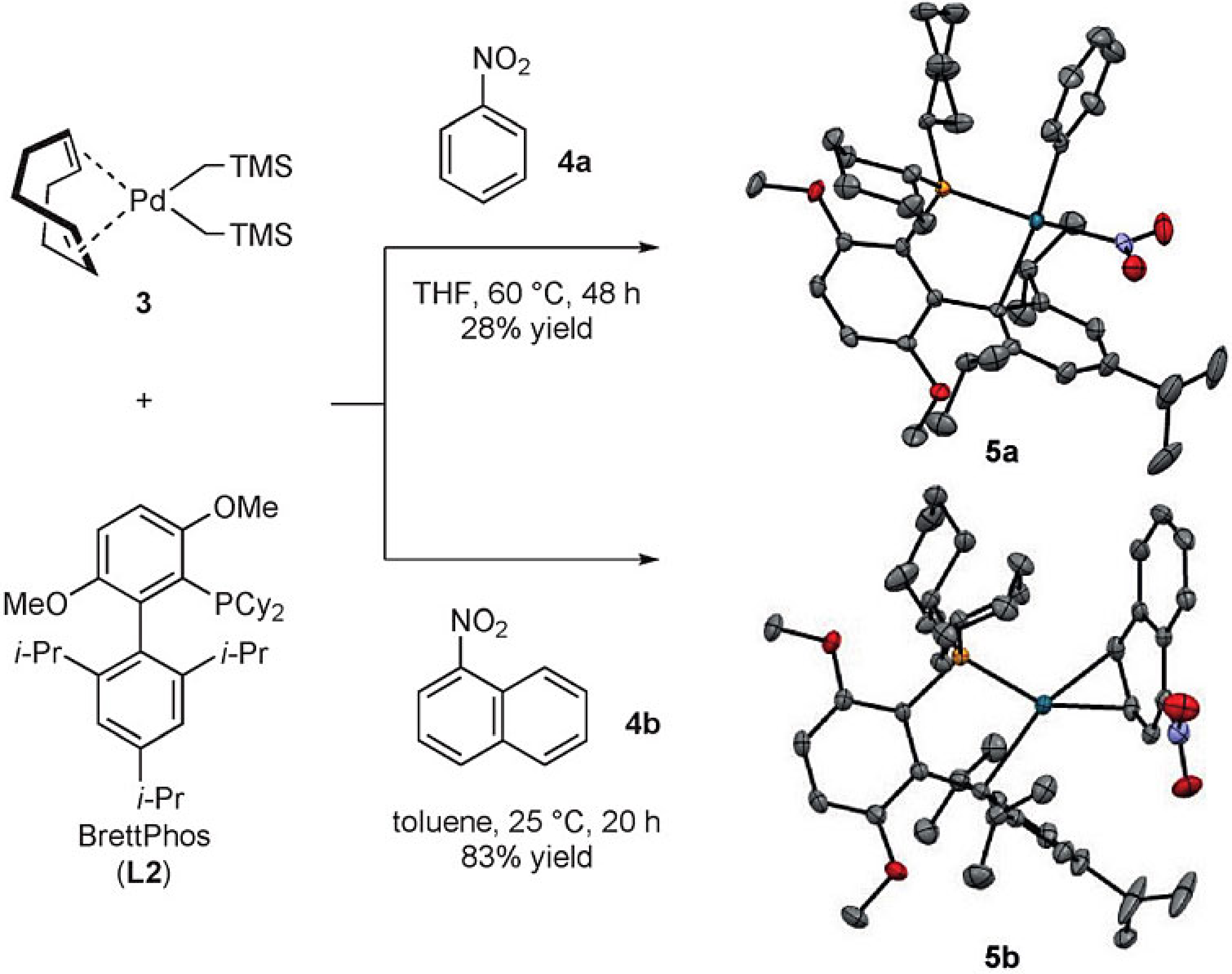
3,4 position

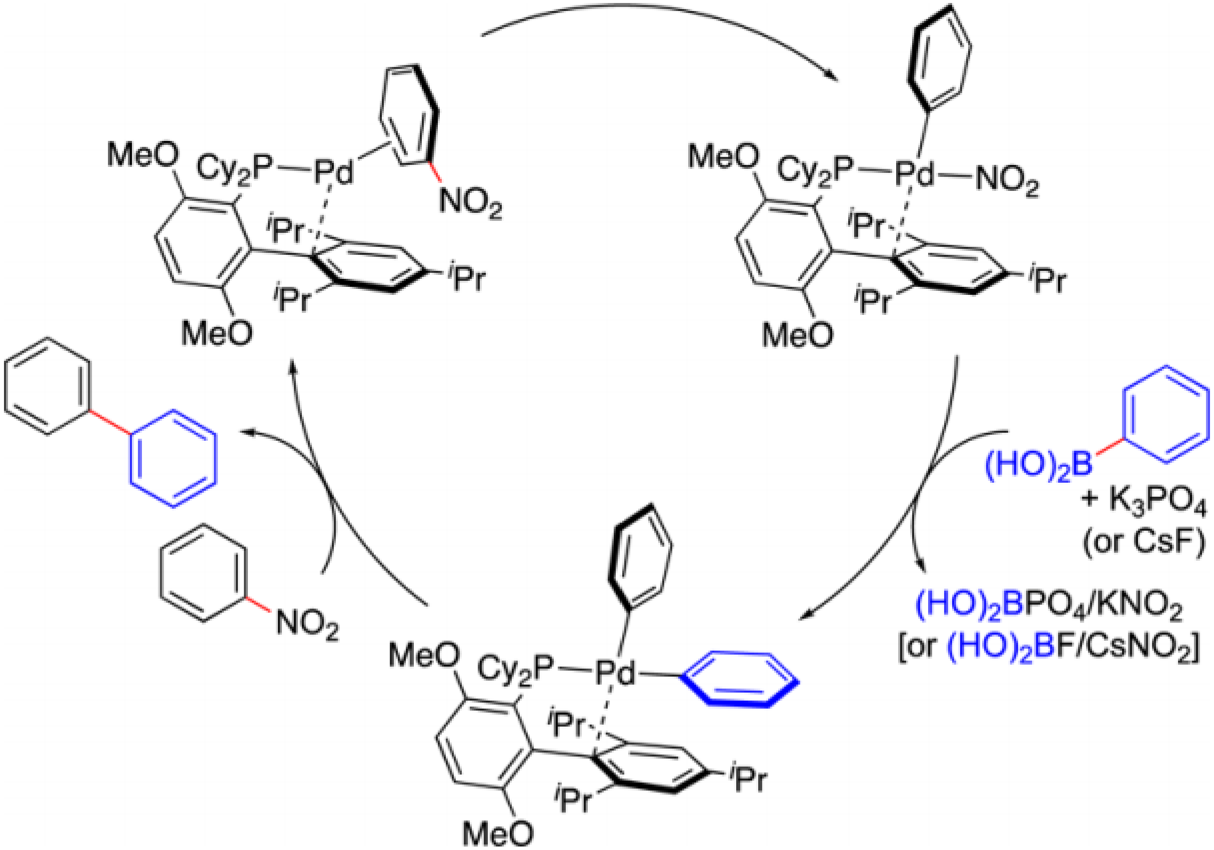
Coupling reaction of aniline or nitrosobenzne with 4-methoxyphenylboronic acid

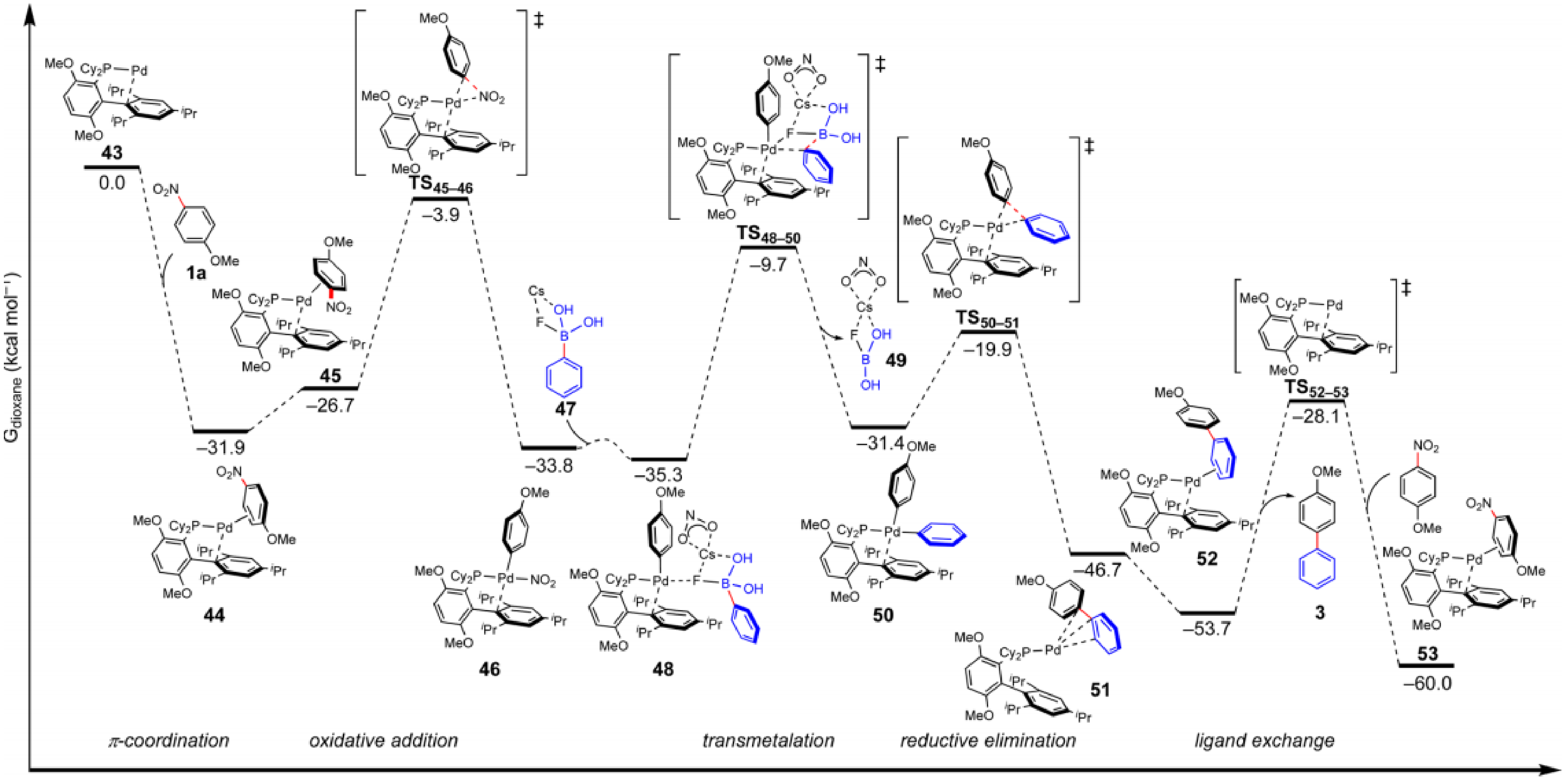


Coupling reaction in presence of radical scavengers




TMS
Pd
TMS
3
+
OMe
MeO
PCy2
i-Pr
i-Pr
i-Pr
BrettPhos
(L2)
NO2
4a
THF, 60 °C, 48 h
28% yield
NO2
4b
toluene, 25 °C, 20 h
83% yield
5a
5b


MeO
Cy2P—Pd
iPr
MeO
NO2
(HO)2B
+ K3PO4
(or CsF)
(HO)2BPO4/KNO2
[or (HO)2BF/CsNO2]



DFT-calculated geometries and Gibbs energy changes of the proposed catalytic cycle.

In summary

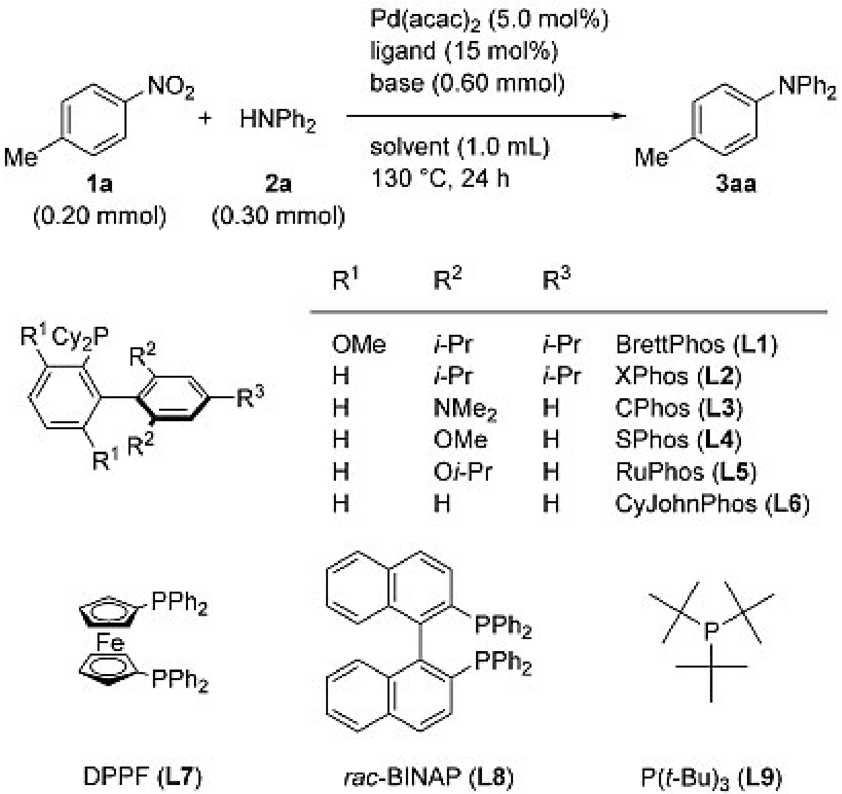
The reaction is particularly important to afford unsymmetric biaryl compounds, which are frequently encountered as core structural motifs in pharmaceuticals, agrochemicals, and organic materials.

Nitroarenes, on the other hand, are highly versatile and common aromatic building blocks in organic synthesis.

They can be directly obtained from the nitration of the parent arenes, which is generally highly selective toward monofunctionalization, while the halogenation of arenes sometimes affords a mixture of mono- and dihalogenated arenes.

Nitroarenes, particularly those bearing other electron-withdrawing groups, undergo nucleophilic substitution reactions, in which the NO2 group serves as a leaving group.

Buchwald–Hartwig Amination of Nitroarenes

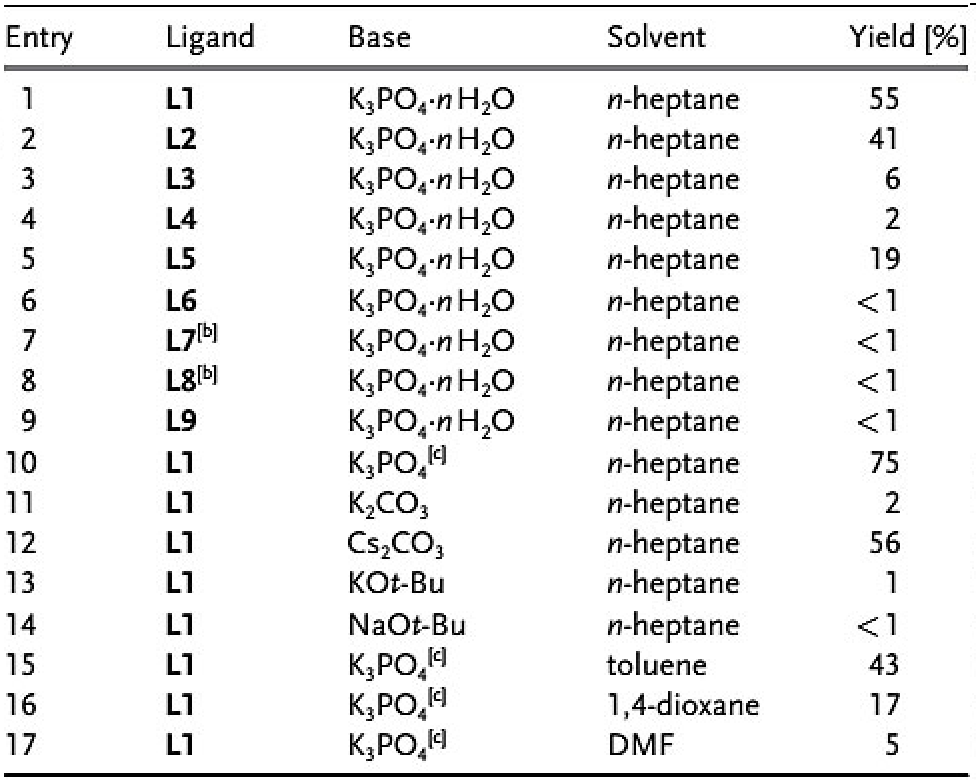


R^1	R^2	R^3	
OMe	*i*-Pr	*i*-Pr	BrettPhos (**L1**)
H	*i*-Pr	*i*-Pr	XPhos (**L2**)
H	NMe$_2$	H	CPhos (**L3**)
H	OMe	H	SPhos (**L4**)
H	O*i*-Pr	H	RuPhos (**L5**)
H	H	H	CyJohnPhos (**L6**)

DPPF (**L7**)

rac-BINAP (**L8**)

P(*t*-Bu)$_3$ (**L9**)



Entry	Ligand	Base	Solvent	Yield [%]
1	**L1**	$K_3PO_4 \cdot n\,H_2O$	*n*-heptane	55
2	**L2**	$K_3PO_4 \cdot n\,H_2O$	*n*-heptane	41
3	**L3**	$K_3PO_4 \cdot n\,H_2O$	*n*-heptane	6
4	**L4**	$K_3PO_4 \cdot n\,H_2O$	*n*-heptane	2
5	**L5**	$K_3PO_4 \cdot n\,H_2O$	*n*-heptane	19
6	**L6**	$K_3PO_4 \cdot n\,H_2O$	*n*-heptane	<1
7	**L7**[b]	$K_3PO_4 \cdot n\,H_2O$	*n*-heptane	<1
8	**L8**[b]	$K_3PO_4 \cdot n\,H_2O$	*n*-heptane	<1
9	**L9**	$K_3PO_4 \cdot n\,H_2O$	*n*-heptane	<1
10	**L1**	K_3PO_4[c]	*n*-heptane	75
11	**L1**	K_2CO_3	*n*-heptane	2
12	**L1**	Cs_2CO_3	*n*-heptane	56
13	**L1**	KO*t*-Bu	*n*-heptane	1
14	**L1**	NaO*t*-Bu	*n*-heptane	<1
15	**L1**	K_3PO_4[c]	toluene	43
16	**L1**	K_3PO_4[c]	1,4-dioxane	17
17	**L1**	K_3PO_4[c]	DMF	5

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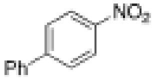
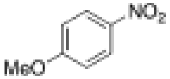
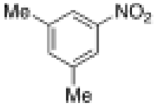
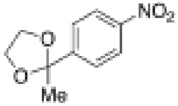
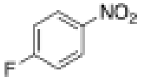
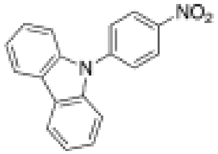
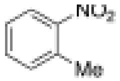
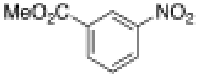
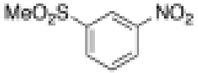
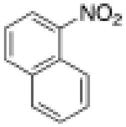
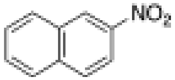
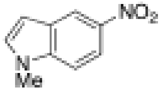
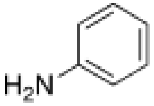
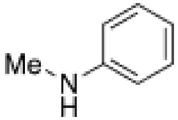
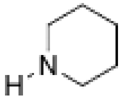
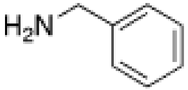
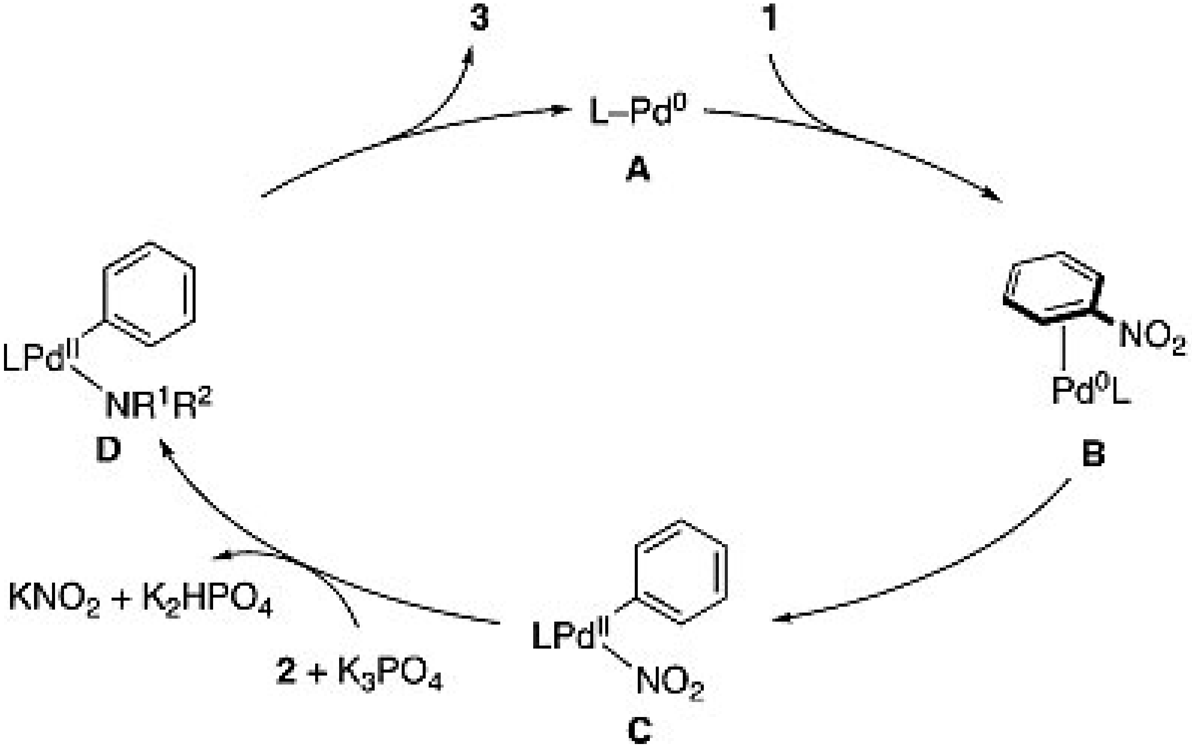
Entry	Nitroarene		Amine	Yield [%]
1		**1a**	**2a**	73 (**3aa**)
2		**1b**	**2a**	83 (**3ba**)
3[b]		**1c**	**2a**	74 (**3ca**)
4		**1d**	**2a**	66 (**3da**)
5		**1e**	**2a**	77 (**3ea**)
6		**1f**	**2a**	56 (**3fa**)
7		**1g**	**2a**	62 (**3ga**)
8[b,c,d,e]		**1h**	**2a**	57 (**3ha**)
9[d,f]		**1i**	**2a**	64 (**3ia**)
10[f]		**1j**	**2a**	78 (**3ja**)
11[b,c,g]		**1k**	**2a**	51 (**3ka**)
12[b,c,d,g]		**1l**	**2a**	50 (**3la**)
13[b]		**1m**	**2b**	74 (**3mb**)
14		**1n**	**2b**	65 (**3nb**)
15[b]		**1o**	**2a**	52 (**3oa**)

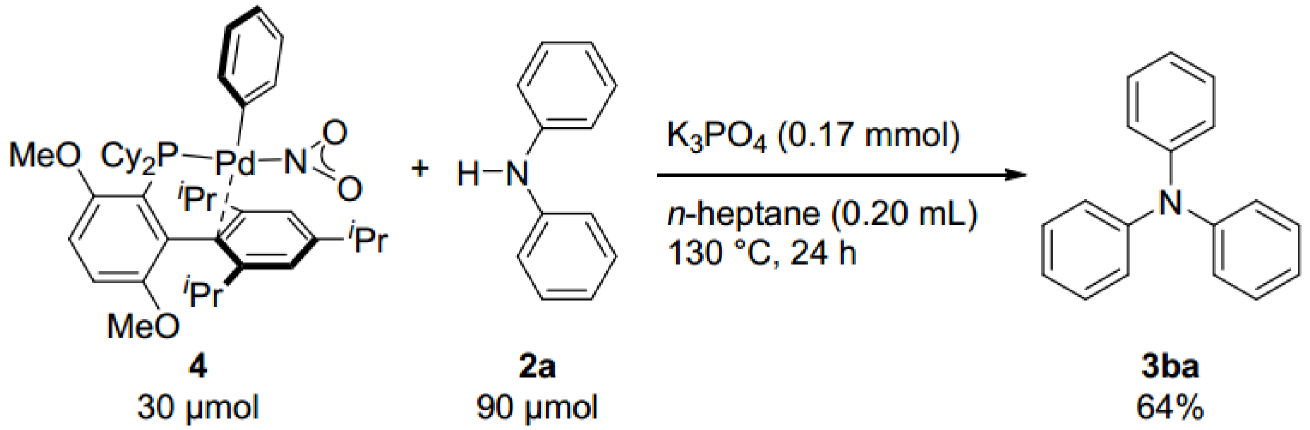
[a] Reaction conditions, unless stated otherwise: **1** (0.60 mmol, 1.0 equiv), **2** (1.5 equiv), Pd(acac)$_2$ (5 mol%), **L1** (15 mol%), dried K_3PO_4 (3 equiv), *n*-heptane (3.0 mL), 130°C, 24 h. Yields of isolated products are given. [b] Diarylamine (1.8 mmol). [c] **L3** instead of **L1**. [d] $K_3PO_4 \cdot n\,H_2O$ instead of dried K_3PO_4. [e] 1,4-Dioxane instead of *n*-heptane. [f] **L2** instead of **L1**. [g] Toluene instead of *n*-heptane. **2b**: bis(4-*tert*-butylphenyl)amine.

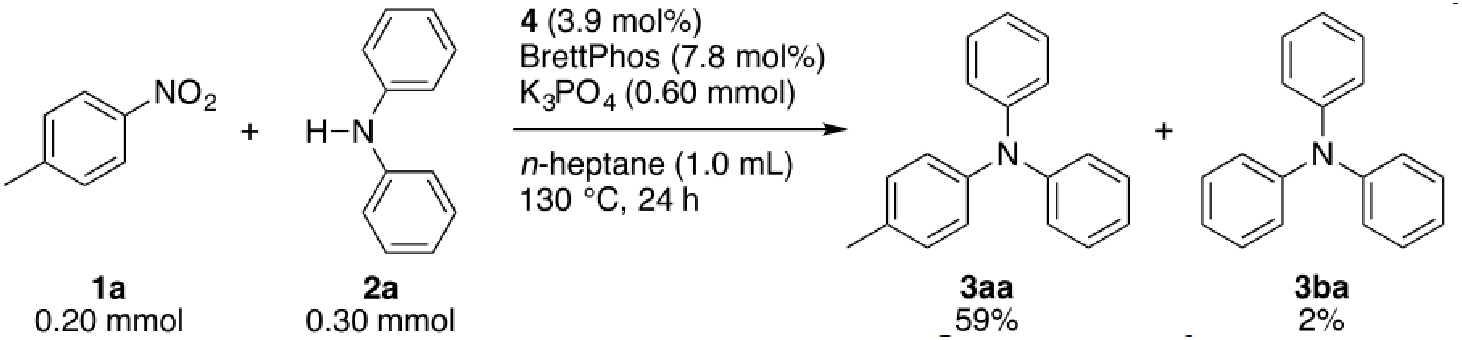
Entry	Amine		Yield [%]
1[b]		**2c**	64 (**3dc**)
2		**2d**	41 (**3dd**)
3		**2e**	61 (**3de**)
4[c]		**2f**	81 (**3ef**)
5		**2g**	72 (**3dg**)

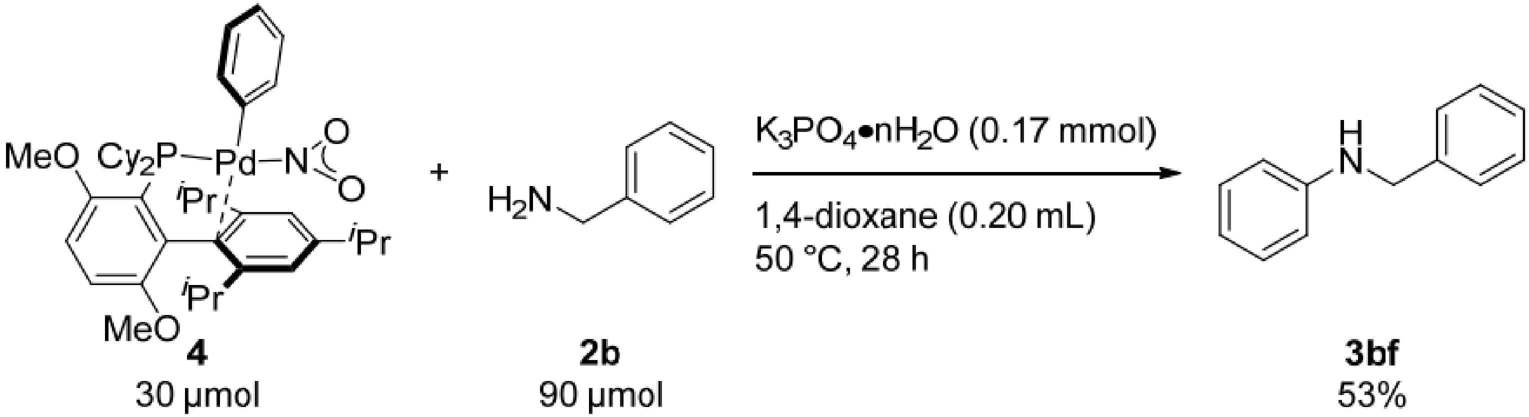
[a] Reaction conditions, unless stated otherwise: **1d** (0.60 mmol, 1.0 equiv), **2** (1.5 equiv), $Pd(acac)_2$ (5 mol%), **L1** (15 mol%), $K_3PO_4 \cdot nH_2O$ (3 equiv), 1,4-dioxane (3.0 mL), 130°C, 24 h. Yields of isolated products are given. [b] DMF instead of 1,4-dioxane. [c] **1e** instead of **1d**.

Plausible mechanism




MeO
Cy$_2$P
Pd
N
O
O
^{i}Pr
^{i}Pr
^{i}Pr
MeO
+
H–N
K$_3$PO$_4$ (0.17 mmol)
n-heptane (0.20 mL)
130 °C, 24 h
N
4
30 µmol
2a
90 µmol
3ba
64%


NO$_2$
+
H–N
4 (3.9 mol%)
BrettPhos (7.8 mol%)
K$_3$PO$_4$ (0.60 mmol)
n-heptane (1.0 mL)
130 °C, 24 h
N
+
N
1a
0.20 mmol
2a
0.30 mmol
3aa
59%
3ba
2%


MeO
Cy$_2$P
Pd
N
O
O
^{i}Pr
^{i}Pr
^{i}Pr
MeO
+
H$_2$N
K$_3$PO$_4$•nH$_2$O (0.17 mmol)
1,4-dioxane (0.20 mL)
50 °C, 28 h
H
N
4
30 µmol
2b
90 µmol
3bf
53%

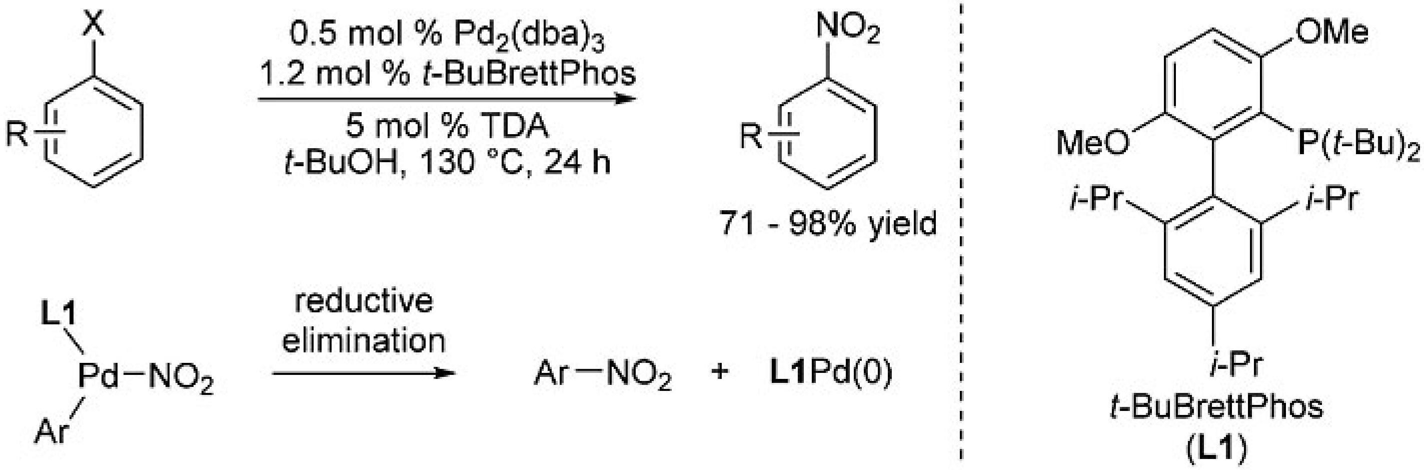
In summary

The Buchwald–Hartwig amination is a highly efficient and versatile method to access substituted arylamines.

Nitroarenes been used as electrophiles for the cross-coupling with organotin amides and amines in the presence of palladium-based catalysts to furnish arylamines.

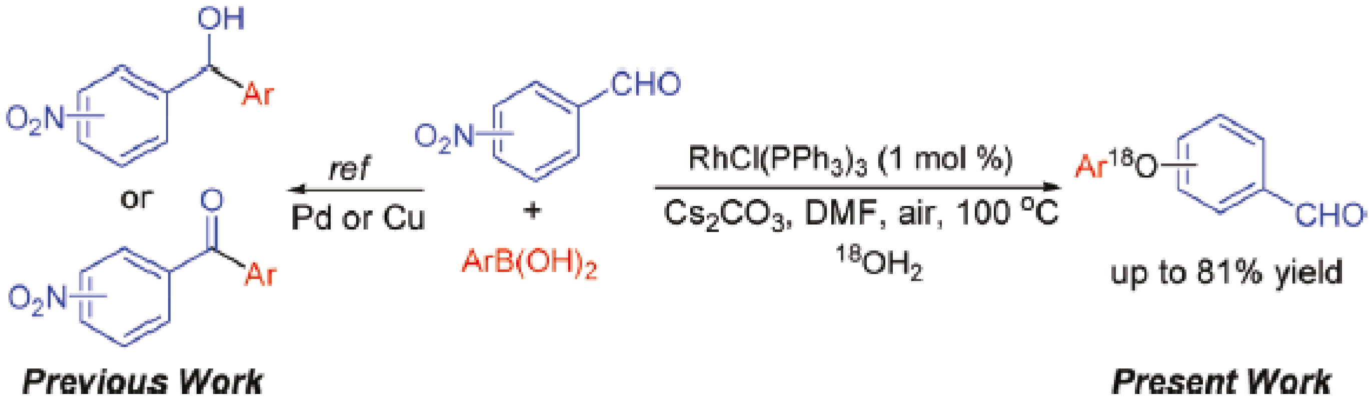
Aryl halides and various aryl pseudohalides may cause undesirable halogen-based contamination. The use of nitroarenes as pseudohalides in the Buchwald–Hartwig amination may also circumvent these problems.

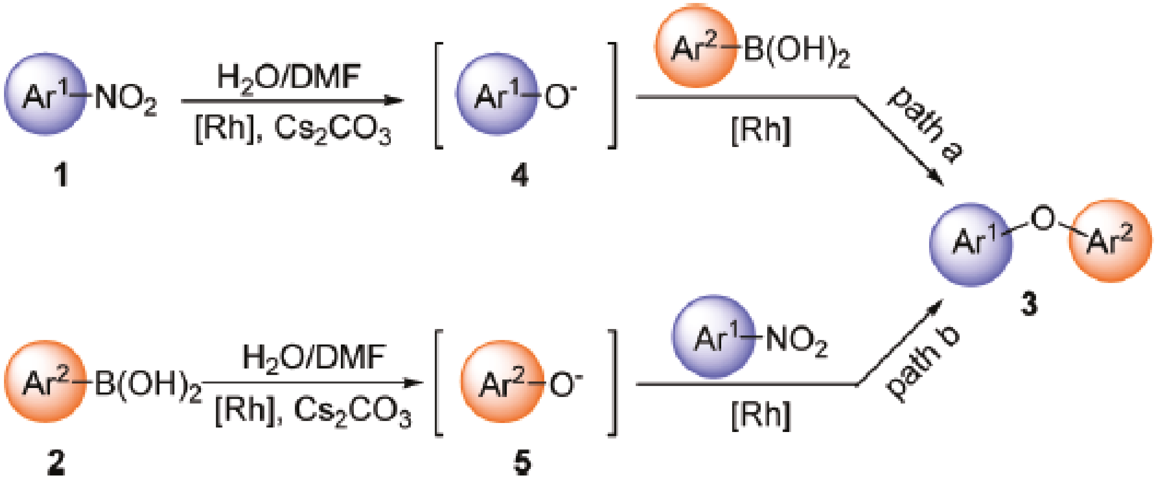
Nitroarenes are useful in an academic and industrial context as nitroarenes are readily available and serve as building blocks for functionalized arenes.



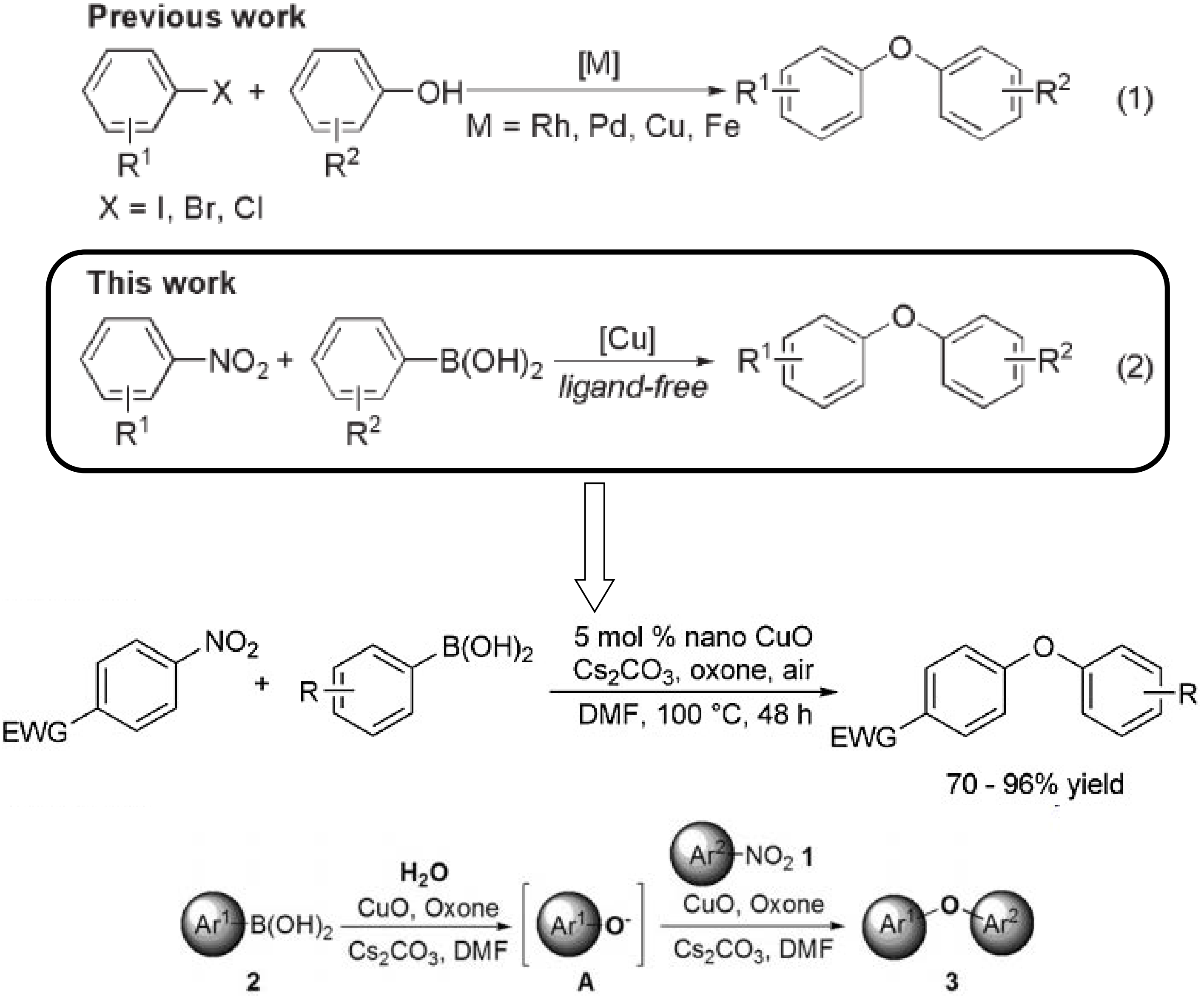
***J. Am. Chem. Soc.*, 2009, *131*, 12898**

Wu (2011)



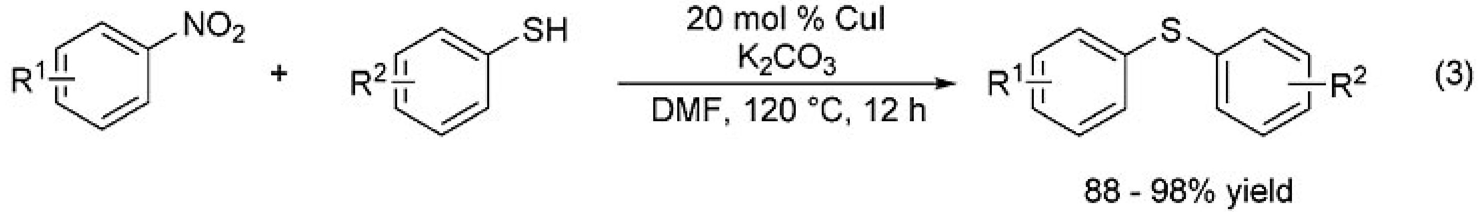


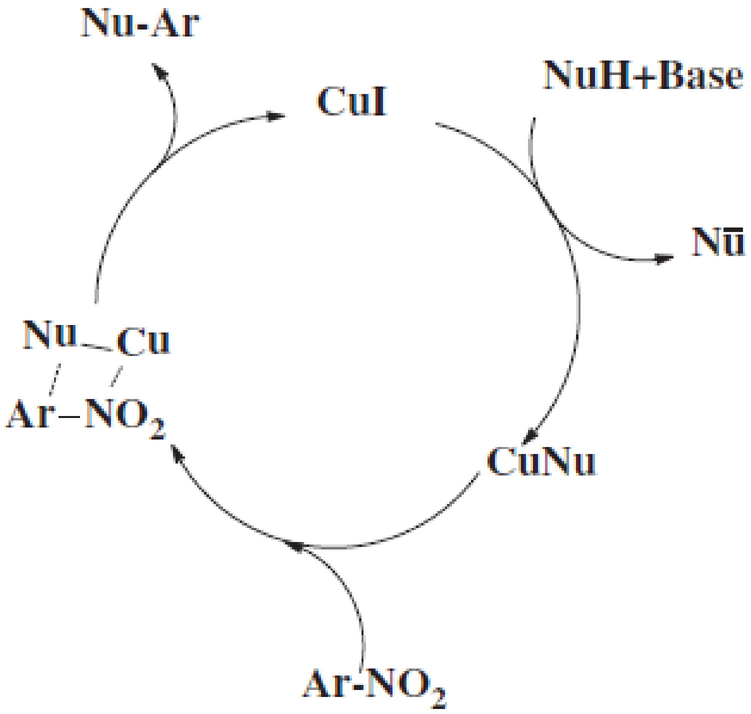
***Org. Lett.*, 2011, *13*, 1726**



***Green Chem.*, 2012, *14*, 912**

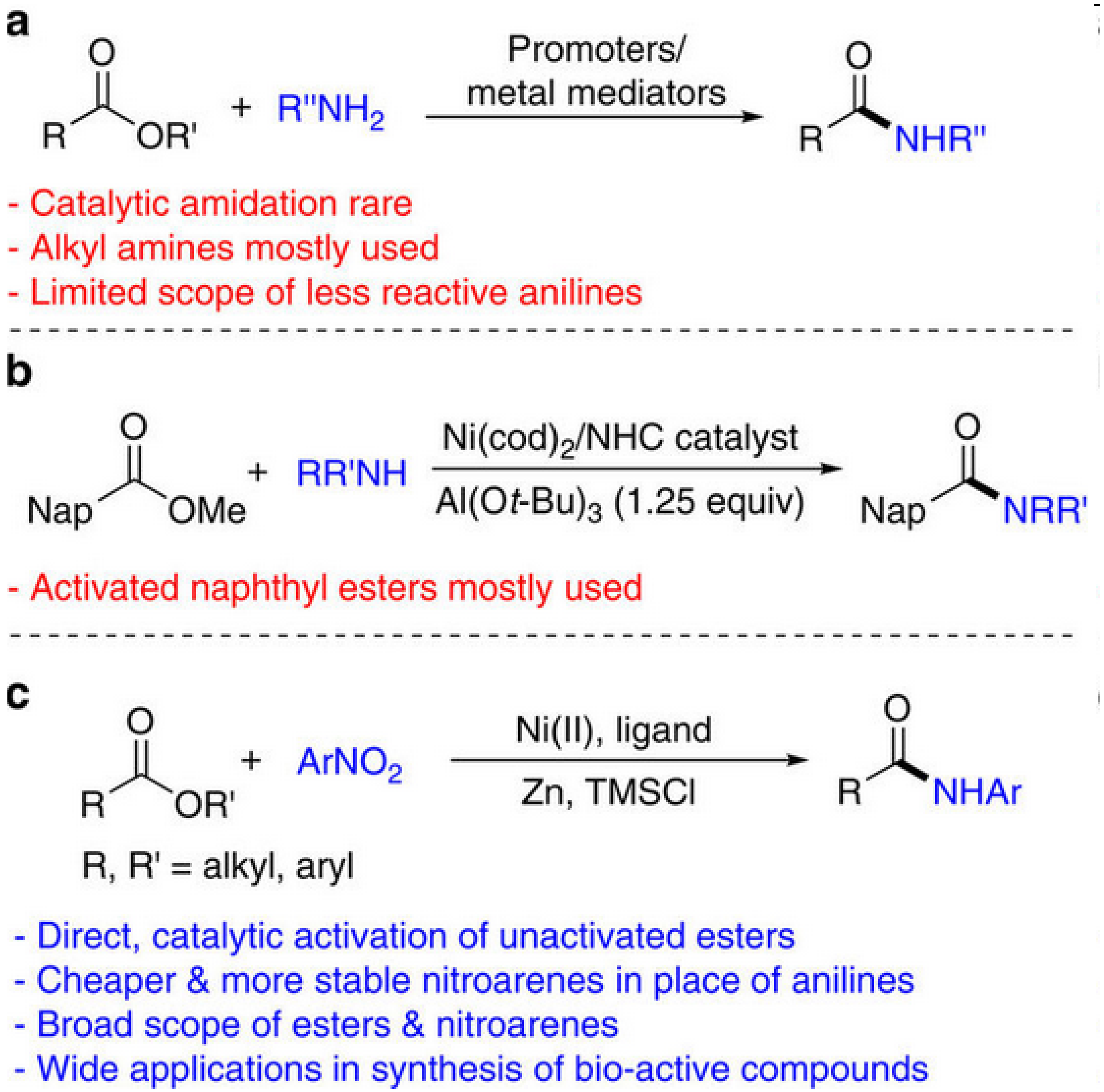
Shinde (2013)





Catal. Commun., 2013, *41*, 123

Different approaches for amidation of esters.



- Catalytic amidation rare
- Alkyl amines mostly used
- Limited scope of less reactive anilines

- Activated naphthyl esters mostly used

- Direct, catalytic activation of unactivated esters
- Cheaper & more stable nitroarenes in place of anilines
- Broad scope of esters & nitroarenes
- Wide applications in synthesis of bio-active compounds

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