Highly Reactive, General and Long-Lived Catalysts for Palladium-Catalyzed Amination of Heteroaryl and Aryl Chlorides, Bromides, and Iodides: Scope and Structure-Activity Relationships

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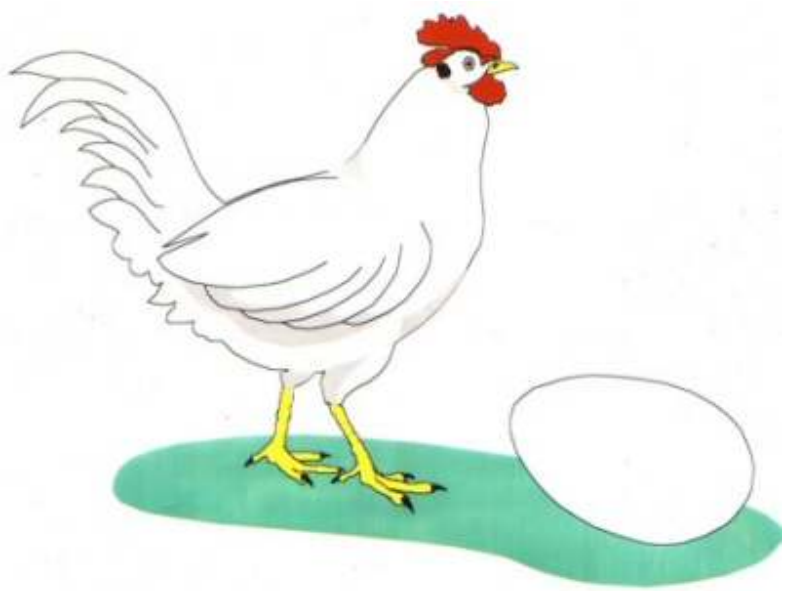
Current Literature

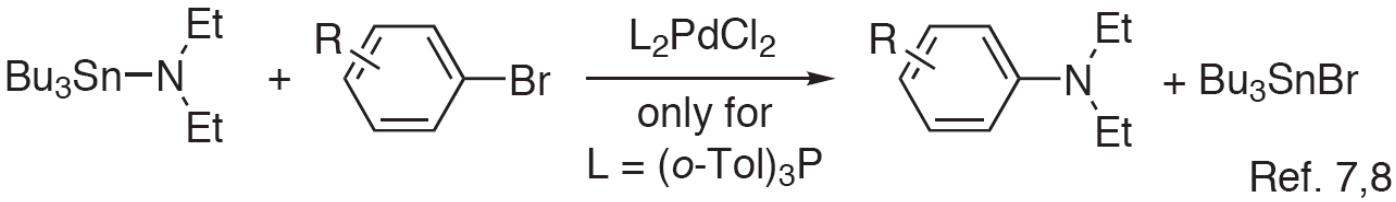
Bryan Wakefield

5/30/08

A Brief History:
Who came first the Buchwald or the Hartwig?

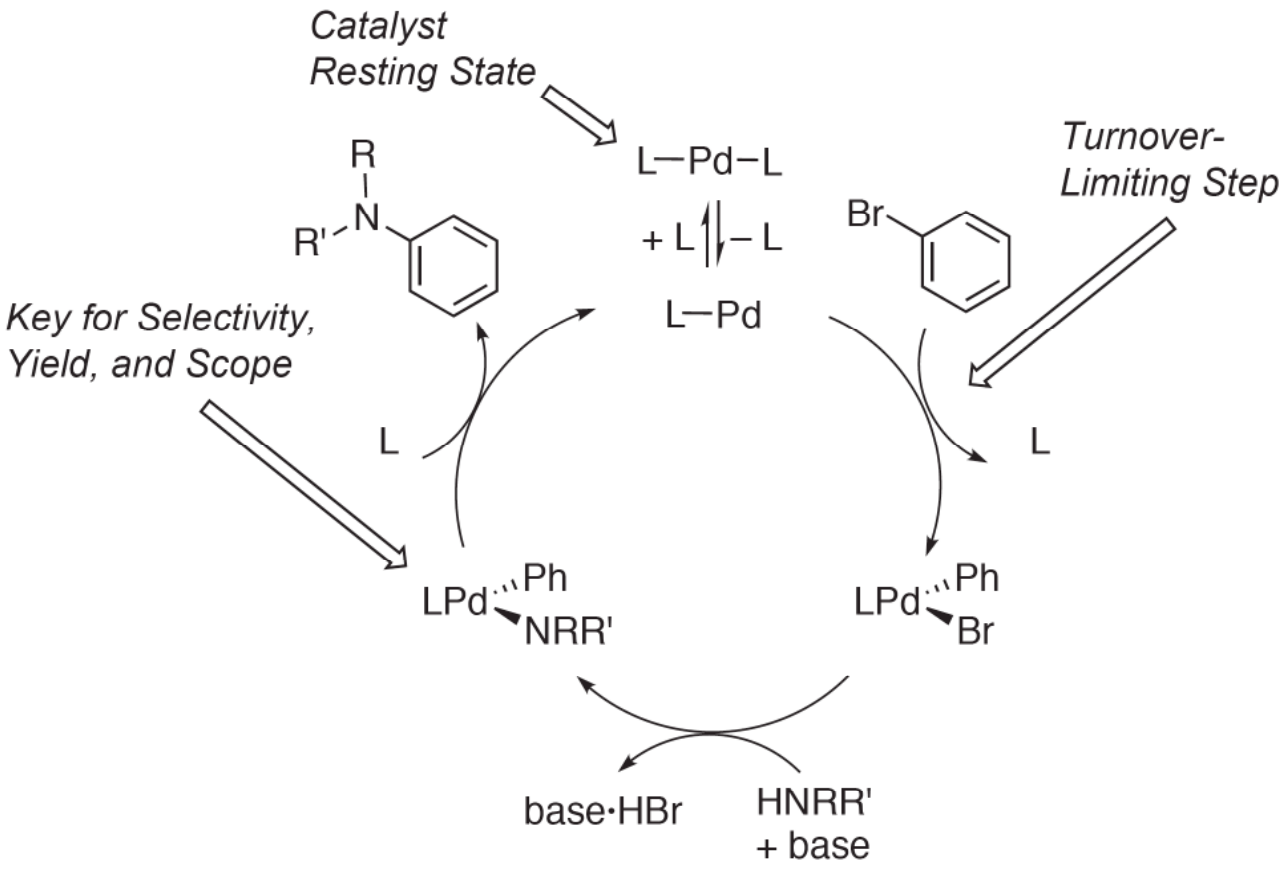


Neither was first, the original report that inspired both Hartwig and Buchwald was made by Kameyama, Kosugi, And Migita in the early 1980's

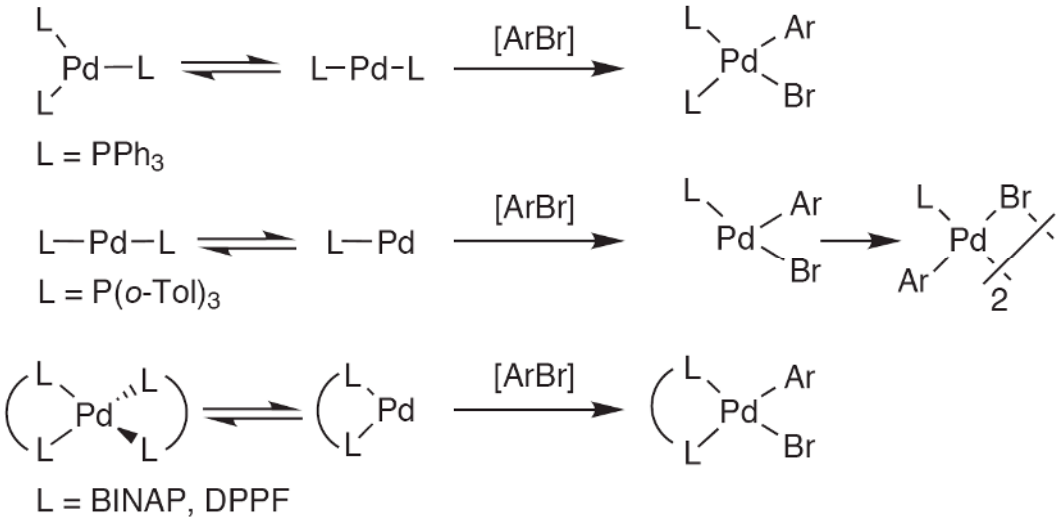


Hartwig, J. F. *Synlett*, **2006**, 1283

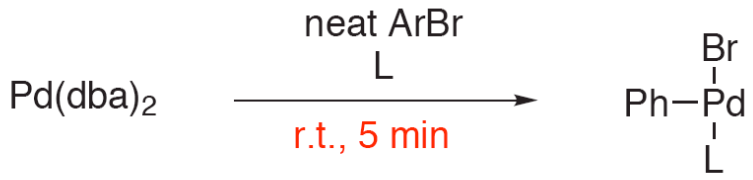
Mechanism of the Buchwald-Hartwig Coupling



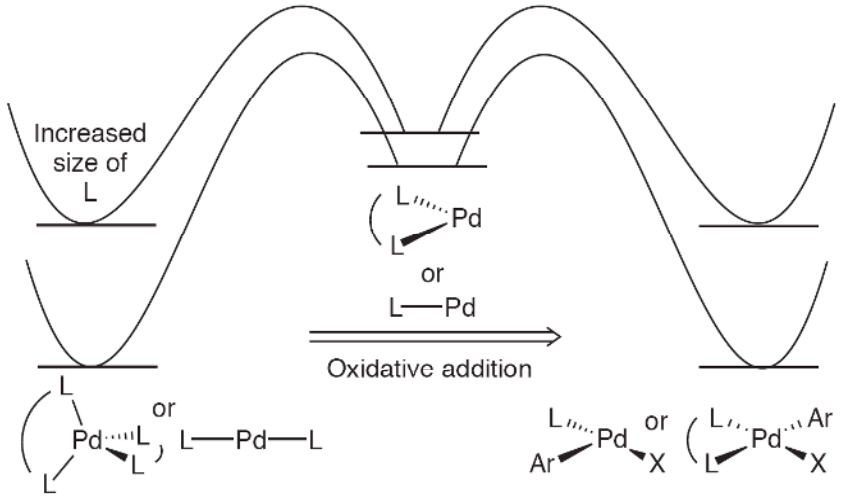
Mechanism of Oxidative Insertion



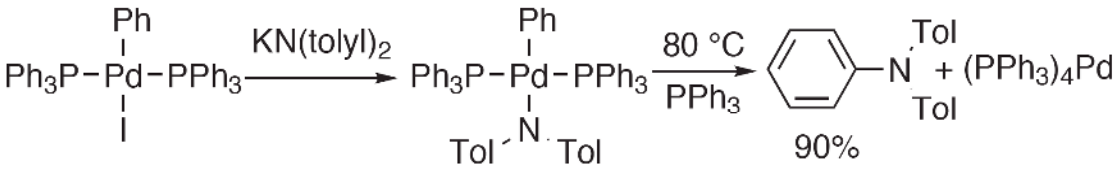
Sterically hindered phosphine ligands lead to coordinatively unsaturated palladium complexes which readily undergo oxidative insertion



L = P(*t*-Bu)$_3$, P(1-Ad)(*t*-Bu)$_2$, or Q-phos

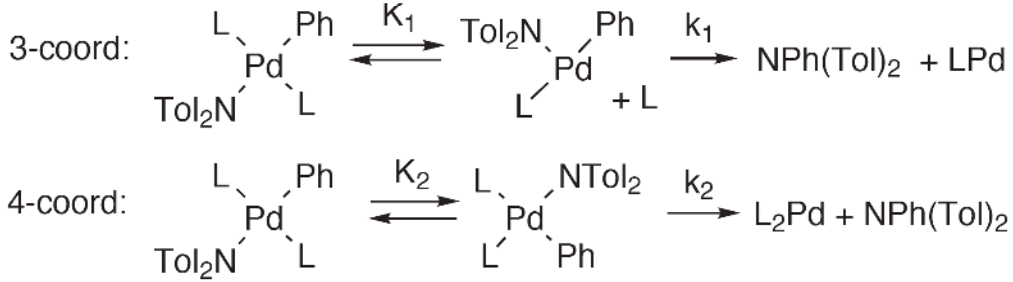


Reductive Elimination of Amines

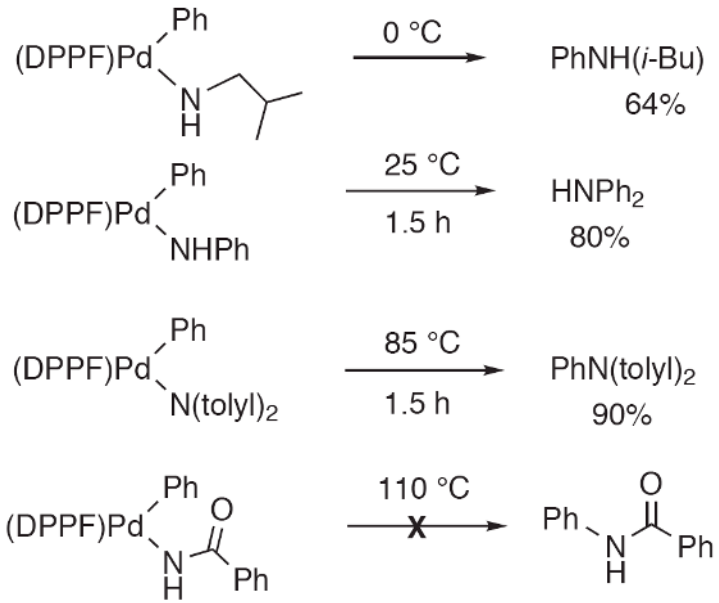


Reductive elimination
Occurs most quickly
From 3-coord. Pd-complex

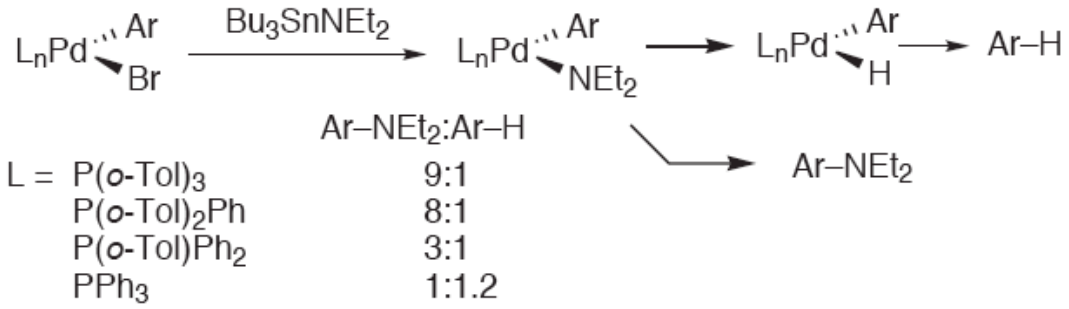
Kinetic Studies Show Two Concurrent Mechanisms



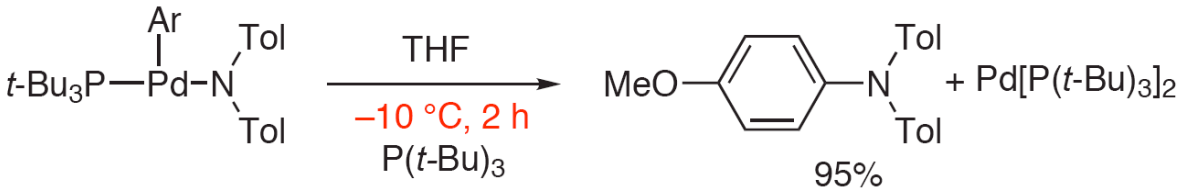
Reductive elimination occurs most quickly when electron rich amines in Pd complexes with electron withdrawing ligands



Reductive Elimination of Amines

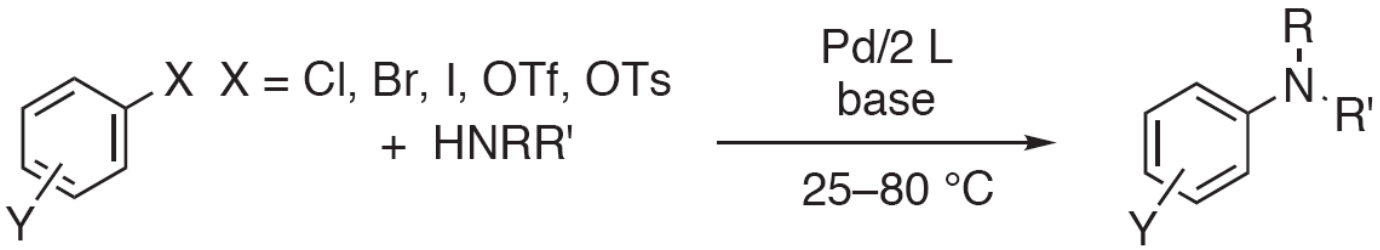


Sterically hindered ligands reduce the amount of β-hydride elimination.



compare to 80 °C, 2 h for DPPF complexes

General Scope of Buchwald-Hartwig Amination



L = hindered monodentate ligands

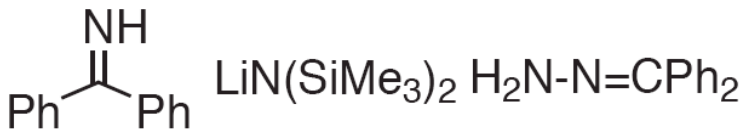
$P(o\text{-Tol})_3$, $P(t\text{-Bu})_3$, $Ph_5FcP(t\text{-Bu})_2$ (Q-phos), heterocyclic carbenes, (Biaryl)PR_2, $^{-}OP(t\text{-Bu})_2$, Solvias metallacycle, Verkade's phosphatranes

or chelating bidentate ligands

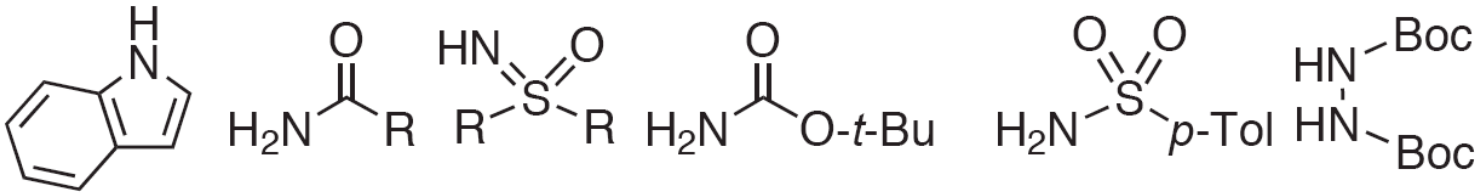
DPPF, BINAP, Josiphos ligands, Xantphos

Broad scope:

cyclic secondary, acyclic secondary, primary aliphatic, aromatic amines

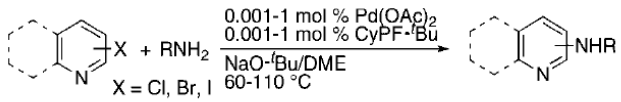


Narrower scope:



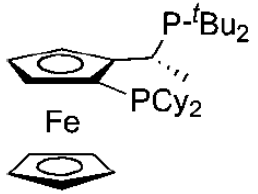
Current Work: Coupling to Heteroaryl Halides

Table 1. Coupling of Heteroaryl Halides with Primary Alkylamines Catalyzed by $Pd(OAc)_2$ and CyPF-^{t}Bu (1:1)[a]



entry	Ar	X	R	cat. (%)	conditions	yield (%)[b]
1	2-Py	Cl	octyl	0.001	100 °C, 48 h	86
2		Br	octyl	0.0005	110 °C, 12 h	84
3		I	octyl	0.005	110 °C, 12 h	96
4		Cl	Bn	0.001	100 °C, 10 h	85
5		Br	Bn	0.0005	110 °C, 12 h	83
6		Cl	cyclohexyl	0.01	70 °C, 12 h	98
7		Br	cyclohexyl	0.005	60 °C, 12 h	96
8		I	^{s}Bu	0.05	110 °C, 12 h	98
9[d]		Cl	1- methylbenzyl[f]	0.05	100 °C, 24 h	99
10	3-Me-2-Py	Cl	octyl	0.005	90 °C, 24 h	96
11	3-Py	Cl	octyl	0.005	90 °C, 24 h	93
12[c]		Cl	octyl	0.005	100 °C, 24 h	99
13		Br	octyl	0.005	100 °C, 36 h	99
14		Cl	Bn	0.01	100 °C, 24 h	95
15		Br	Bn	0.005	100 °C, 48 h	99
16		Br	^{s}Bu	0.005	100 °C, 48 h	93
17		I	^{t}Bu	0.05	100 °C, 12 h	96
18		Cl	cyclohexyl	0.01	100 °C, 48 h	79
19		I	cyclohexyl	0.05	100 °C, 12 h	78
20		Cl	^{t}Bu	1.0	70 °C, 16 h	67
21[d]		Cl	1- methylbenzyl[g]	0.05	100 °C, 24 h	91
22	4-Py	Cl	octyl	0.01	90 °C, 24 h	83
23		Br	octyl	0.005	100 °C, 36 h	93
24		I	octyl	0.05	100 °C, 48 h	80
25		Cl	PhC(O)-	1.0	70 °C, 10 h	75
26	2-pyrazinyl	Cl	octyl	0.005	100 °C, 16 h	82
27		I	octyl	0.05	100 °C, 36 h	83
28[e]	1,3-pyrimidyl-5-	Br	cyclohexyl	1.0	100 °C, 48 h	80
29	3-quinolinyl	Cl	cyclohexyl	0.01	100 °C, 48 h	60
30	1-*iso*-quinolinyl	Cl	octyl	0.005	90 °C, 15 h	91
31	4-*iso*-quinolinyl	Br	octyl	0.005	100 °C, 36 h	93

[a] Reactions conducted with a 1:1 ratio of metal to ligand, 1 mmol aryl halide, 1.2 equiv amine, and 1.4 equiv NaO-^{t}Bu in 1 mL DME. [b] Isolated yield. [c] Reaction performed without using a drybox. [d] from phenethylamine that is stated to be 99% ee. [e] Using K_3PO_4 as the base. [f] 96% ee. [g] 95% ee.

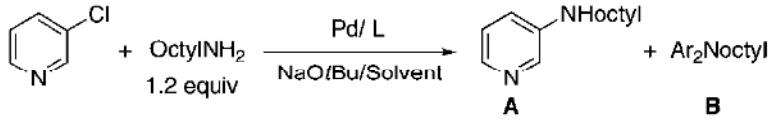


CyPF-^{t}Bu 1

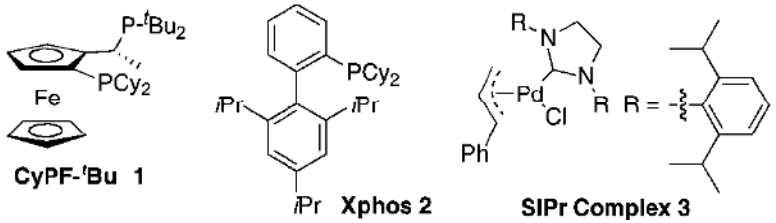
- Catalysts generated from $Pd(dba)_2$ or $PdCl_2(PhCN)_2$ were not effective
- The relative rate of amidation of aryl halides: Br>Cl>I.

Comparision of Ligands commonly used for Amination

Table 2. Comparison of the Activity of CyPF-^{t}Bu, Xphos, and SIPr for the Reactions of a Heteroaryl Chloride with a Primary Alkylamine[a]



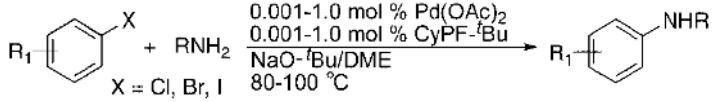
entry	catalyst	loading	solvent	T [°C][b]	t [h]	conversion[c] (%)	A/B
1	Pd(OAc)$_2$/**1**	0.005	DME	90	24	100(92)	100:0
2	Pd(OAc)$_2$/**2**	0.05	toluene	90	24	40	5.4:1
3	Pd(OAc)$_2$/**2**	0.1	toluene	90	24	85(80)	2.4:1
4	Pd(OAc)$_2$/**2**	0.1	DME	90	24	14	–
5	Pd(dba)$_2$/**2**	0.1	toluene	90	24	47	4.8/1
6	Pd(OAc)$_2$/**2**	0.5	toluene	90	12	88(81)	2.6:1
7	Pd(OAc)$_2$/**2**	0.5	DME	90	24	74	4.1:1
8	Pd(dba)$_2$/**2**	0.5	toluene	90	12	83	3.0/1
9	**3**	0.005	DME	110	24	<10	–
10	**3**	0.05	DME	110	48	58	>25:1
11	**3**	0.5	DME	110	12	100(71)	7.6:1



[a] The experiments were conducted with a 1:1 ratio of Pd/CyFP-^{t}Bu or 1:2 ratio of Pd/Xphos, 1 mmol 3-chloropyridine and 1.2 equiv of 1-octylamine, and 1.4 equiv base in 1.0 mL of solvent. [b] Bath temperature. [c] Determined by ^{1}H NMR analysis of the crude product. Isolated yields are indicated in parentheses.

Amination of Aryl Halides

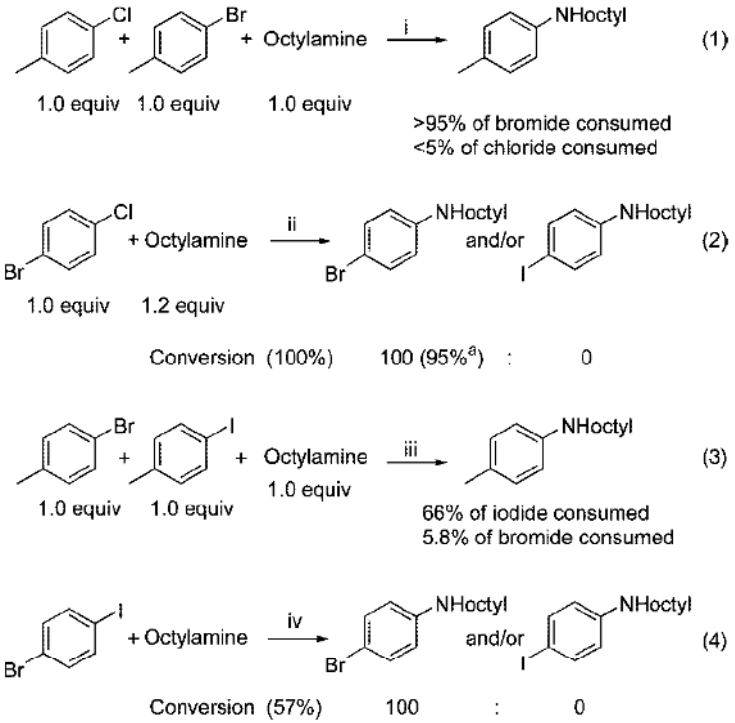
Table 3. Coupling of Aryl Halides with Primary Alkylamines Catalyzed by $Pd(OAc)_2$ and CyPF-^{t}Bu (1:1)[a]



entry	R_1	X	R	cat. (%)	conditions	yield (%[b]
1	H	Cl	cyclohexyl	0.05	100 °C, 36 h	99
2		Br	cyclohexyl	0.01	100 °C, 24 h	96
3		Cl	Bn	0.005	100 °C, 48 h	99
4		Br	Bn	0.001	100 °C, 36 h	97
5	2-Me	Cl	octyl	0.01	100 °C, 48 h	98
6		Br	octyl	0.005	100 °C, 36 h	99
7		I	octyl	0.05	100 °C, 8 h	96
8	2-MeO	Br	cyclohexyl	0.05	100 °C, 24 h	94
9	4-Me	Cl	^{i}Bu	0.1	100 °C, 48 h	83
10[c]		Br	^{i}Bu	0.05	100 °C, 24 h	90
11		I	^{i}Bu	0.05	100 °C, 18 h	75
12[d]		I	^{i}Bu	0.02	100 °C, 36 h	81
13		Br	^{s}Bu	0.05	100 °C, 24 h	87
14		I	^{s}Bu	0.5	100 °C, 24 h	82
15	4-MeO	Cl	octyl	0.1	100 °C, 48 h	92
16		I	octyl	1.0	100 °C, 36 h	67
17	4-cyano	Cl	^{i}Bu	0.005	80 °C, 24 h	99
18		Br	cyclohexyl	0.005	80 °C, 48 h	92
19	3-MeO	Cl	Bn	0.005	80 °C, 48 h	98
20		I	Bn	0.005	100 °C, 48 h	99
21		Br	cyclohexyl	0.01	100 °C, 36 h	99
22		I	cyclohexyl	0.05	100 °C, 18 h	94
23	naphathyl	I	octyl	0.05	100 °C, 8 h	97
24	2-^{i}Pr	Br	^{i}Bu	0.05	100 °C, 48 h	95
25	2,6-Di-Me	Cl	octyl	0.1	100 °C, 36 h	97
26		Br	octyl	0.05	100 °C, 48 h	98
27		Br	^{s}Bu	0.5	100 °C, 24 h	97

[a] Reactions conducted with a 1:1 ratio of metal to ligand 1 mmol ArX (X = Cl, Br, I), 1.2 equiv amine and 1.4 equiv NaO-^{t}Bu in 1 mL DME. [b] Isolated yields. [c] 3.0 equiv of octylamine used. [d] Reaction with 5.5 g of 4-iodotoluene (25.0 mmol).

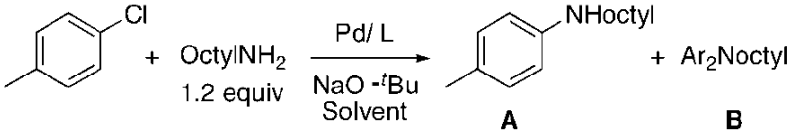
Scheme 1. Comparison of the Reactivity of Aryl Chlorides vs Aryl Bromides and Aryl Bromides vs Aryl Iodides in the Presence of $Pd(OAc)_2$ and CyPF-^{t}Bu (1:1)[a]



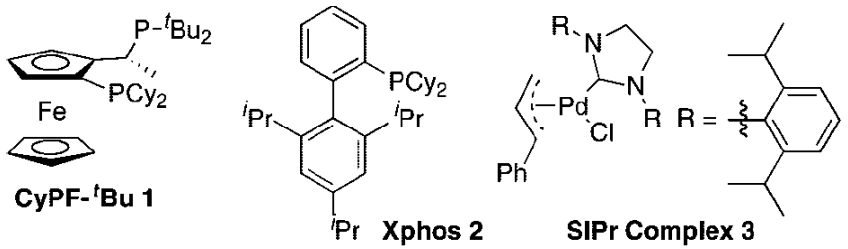
[a] Reagents and conditions: [a] Isolated yield. i. 0.01 mol % $Pd(OAc)_2$, 0.01 mol % CyPF-^{t}Bu, 1.4 equiv. NaO-^{t}Bu, DME, 100 °C, 10 h; ii. 0.005 mol % $Pd(OAc)_2$, 0.005 mol % CyPF-^{t}Bu, 1.4 equiv. NaO-^{t}Bu, DME, 100 °C, 20 h; iii. 0.05 mol % $Pd(OAc)_2$, 0.05 mol % CyPF-^{t}Bu, 1.4 equiv. NaO-^{t}Bu, DME, 100 °C, 20 h; 0.5 mol % $Pd(OAc)_2$, 0.5 mol % CyPF-^{t}Bu, 1.4 equiv NaO-^{t}Bu, DME, 100 °C, 20 h.

Comparision of Ligands commonly used for Amination

Table 4. Comparison of the Activity of CyPF-^{t}Bu, Xphos, and SiPr for the Reactions of 4-Chlorotoluene with a Primary Alkylamine[a]



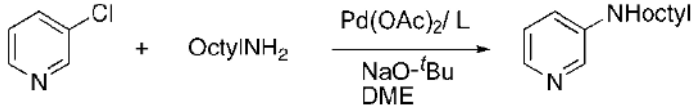
entry	catalyst	loading	solvent	T [°C][b]	t [h]	conversion (%)[c]	A:B
1	$Pd(OAc)_2$/**1**	0.01	DME	100	48	100(95)	100:0
2	$Pd(OAc)_2$/**2**	0.05	toluene	100	48	13	18:1
3	$Pd(dba)_2$/**2**	0.1	toluene	100	48	25	10:1
4	$Pd(OAc)_2$/**2**	0.1	toluene	100	48	16	39:1
5	$Pd(OAc)_2$/**2**	0.5	toluene	100	12	96(91)	2.7:1
6	$Pd(dba)_2$/**2**	0.5	toluene	100	12	100(93)	2.3:1
7	**3**	0.005	toluene	110	48	40	>50:1
8	**3**	0.05	toluene	110	48	76	15.3:1
9	**3**	0.5	toluene	110	12	100	4.3:1



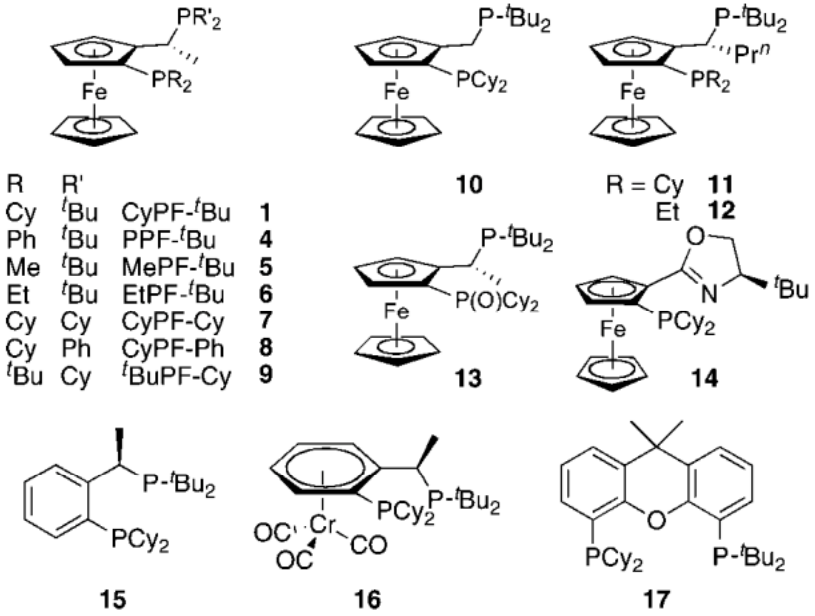
[a] The experiments were conducted with a 1:1 ratio of Pd/CyFP-^{t}Bu or 1:2 ratio of Pd/Xphos, 1 mmol of 4-chlorotoluene and 1.2 equiv 1-octylamine, and 1.4 equiv base in 1.0 mL solvent. [b] Bath temperature. [c] Determined by ^{1}H NMR analysis of the crude product. Isolated yields are indicated in parentheses.

Catalyst SAR

Table 10. Comparison of the Activity of Josiphos CyPF-^{t}Bu Analogs for the Coupling of Heteroaryl Chloride with Primary Alkylamine



entry	ligand	loading	temp. (°C)	time (h)	yield (%)
1	CyPF-^{t}Bu **1**	0.005	90	24	93
2	PPF-^{t}Bu **4**	1.0	90	24	67
3	MePF-^{t}Bu **5**	0.005	90	24	<5
4	EtPF-^{t}Bu **6**	0.005	90	24	<5
5	CyPF-Cy **7**	1.0	90	24	46
6	CyPF-Ph **8**	1.0	90	24	48
7	^{t}BuPF-Cy **9**	0.005	90	24	62
8	**10**	0.005	90	24	50
9	**11**	0.001	100	48	16
10	**11**	0.005	90	24	93
11	**12**	0.005	90	24	<5
12	**13**	0.005	90	24	<5
13	**14**	0.005	90	24	<5
14	**15**	0.005	90	24	<5
15	**16**	0.005	90	24	<5
16	**17**	0.005	90	24	<5



Why is this ligand good?

- The rigid backbone of the ligand allows for tight binding of palladium that prevents displacement by primary amines and basic heterocycles.
- The ligand is strongly electron donating, which promotes oxidative addition to less reactive haloarenes.
- The ligand's steric bulk disfavors diarylation, facilitates the generation of the (chelate)Pd(0) intermediate, and promotes reductive elimination.

Conclusion

- This work describes the use of very low loadings of Pd in combination with the CyPF-*t*Bu ligand to achieve amination of heteroaryl and aryl halides.
- These low loadings could increase the use of this method in industry by lowering cost and easing the removal of Pd from the final product.
- The catalysts using the CyPF-*t*Bu ligand were shown to have higher Turnover numbers and selectivity than those with the commonly used Xphos.
- Systematic variation of the ligand structure showed which features are necessary.