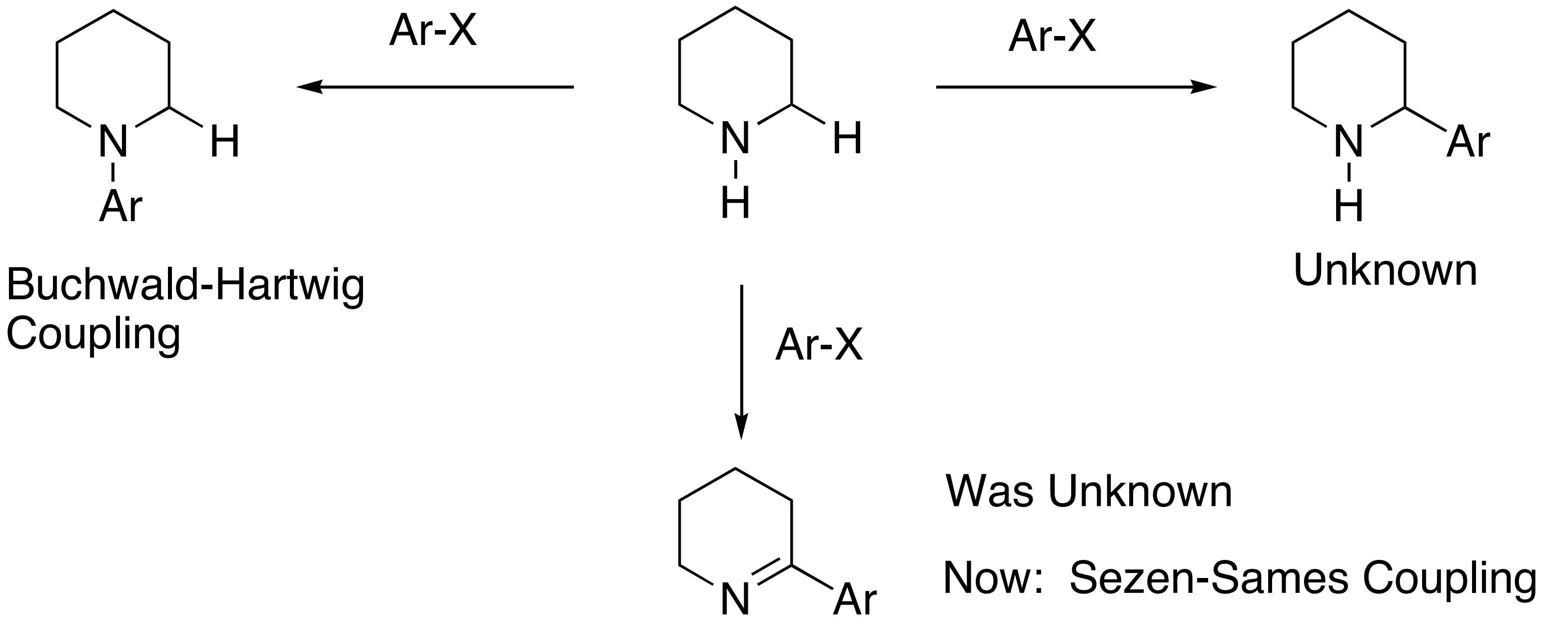
Oxidative C-Arylation of Free (NH)-Heterocycles Via Direct (sp^3) C-H Bond Functionalization

Bengu Sezen and Dalibor Sames

J. Am. Chem. Soc., **2004**, *126*, 13244



Buchwald-Hartwig
Coupling

Unknown

Was Unknown

Now: Sezen-Sames Coupling

Buchwald-Hartwig Coupling

2° Amines

Buchwald *Angew* **1995**, *34*, 1348.
Hartwig *Tet Lett.*, **1995**, 3609

$$\text{Ar-X} \quad + \quad \text{HNR}^1\text{R}^2 \quad \xrightarrow[\text{toluene, }100^\circ]{\substack{\text{2-5 mol \% PdCl}_2\text{(P(}o\text{-tolyl)}_3\text{)}_2 \\ \text{NaOBu-}t\text{ or LiN(SiMe}_3\text{)}_2}} \quad \text{Ar}-\text{NR}^1\text{R}^2$$

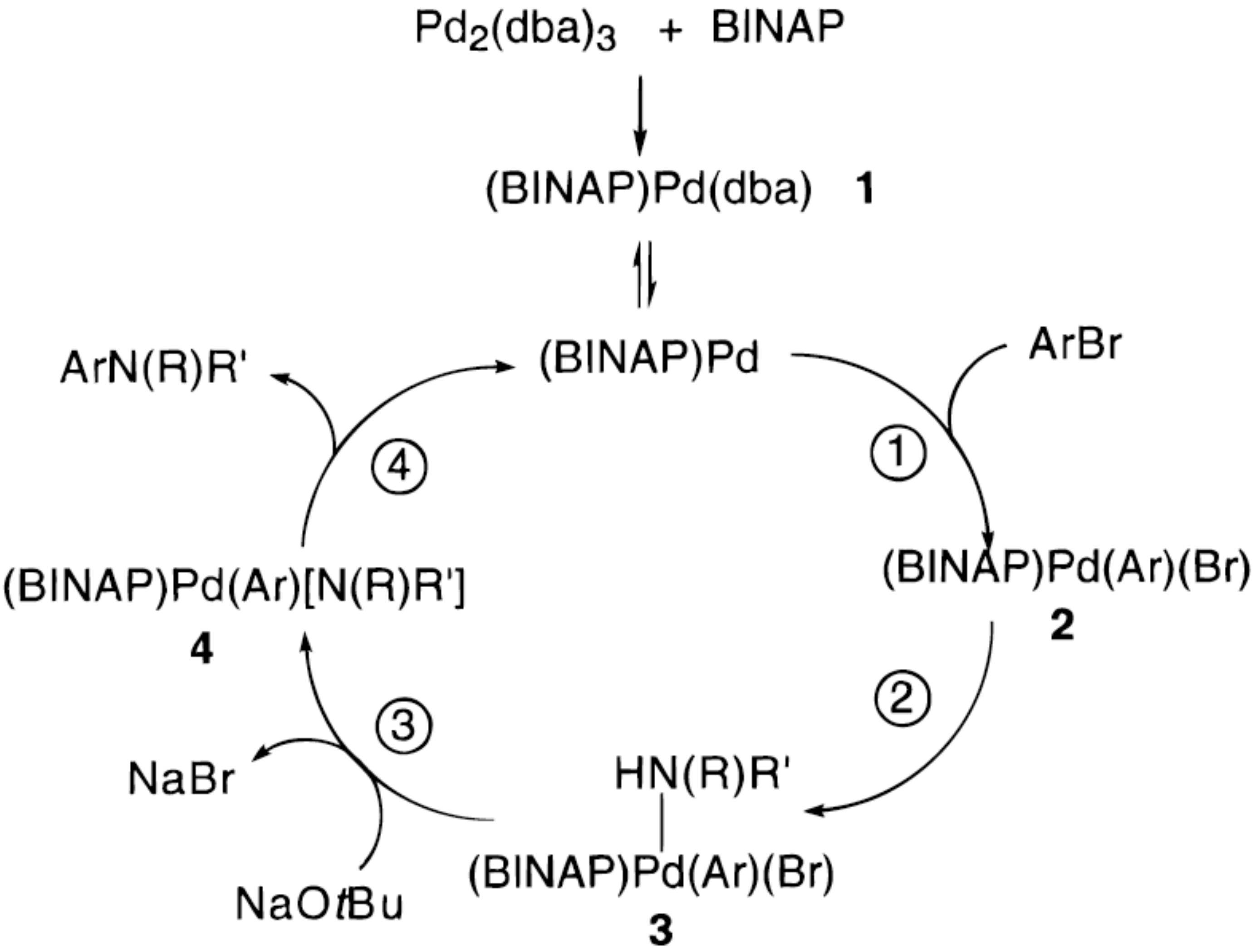
1° Amines

Buchwald *J. Am. Chem. Soc.*, **1996**, *118*, 7215.
Hartwig *J. Am. Chem. Soc.*, **1996**, *118*, 7217

$$\text{Ar-X} \quad + \quad \text{H}_2\text{NR}^2 \quad \xrightarrow[\text{THF or Toluene, 80-100}^\circ]{\substack{\text{0.5 - 5 mol \% Catalyst} \\ \text{NaOBu-}t}} \quad \text{Ar}-\text{NHR}^2$$

$\text{Pd}_2(\text{dba})_3$ + BINAP (Buchwald) $(\text{DPPF})\text{PdCl}_2$ + DPPF (Hartwig)

Scheme 1. Proposed Catalytic Cycle



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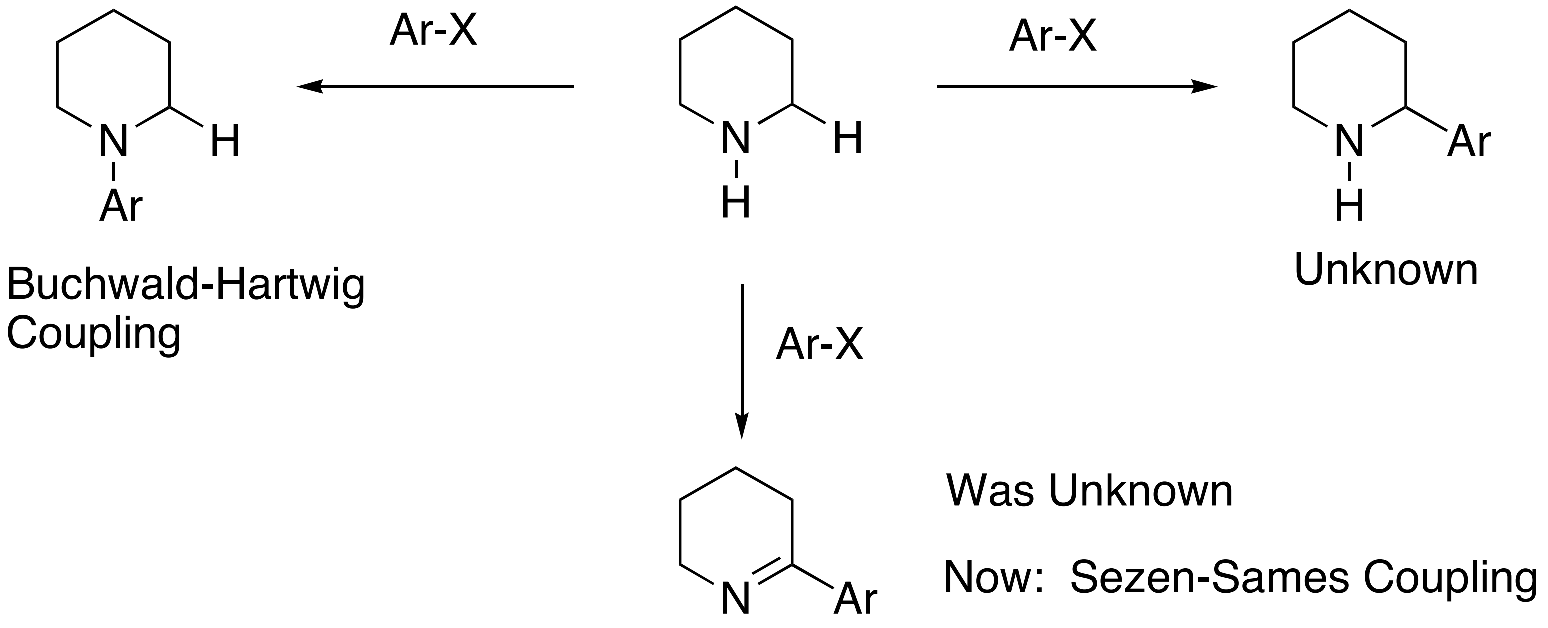


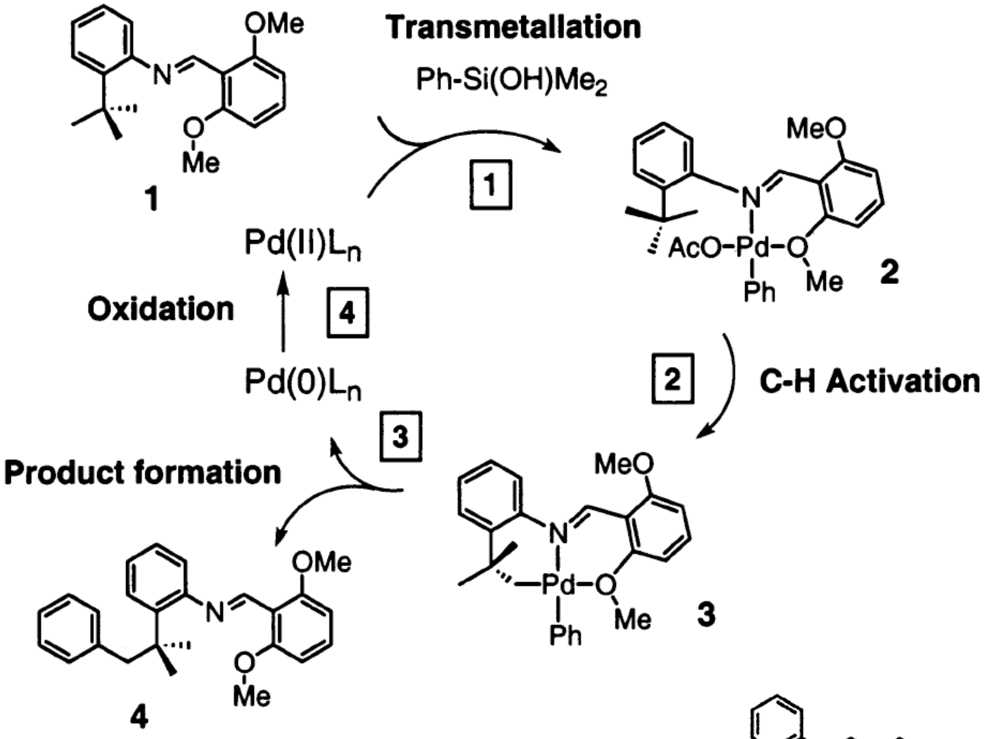
Buchwald-Hartwig Coupling

Unknown

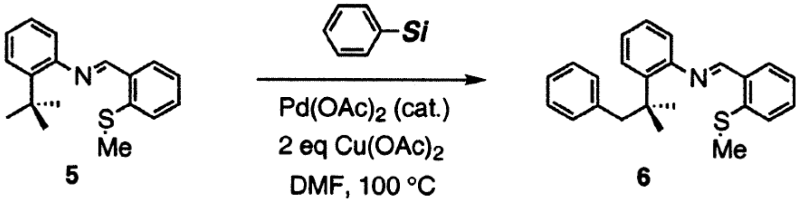
Was Unknown

Now: Sezen-Sames Coupling

Figure 1. Catalytic arylation/alkenylation of alkane segments in complex substrates via metallacycle intermediates.

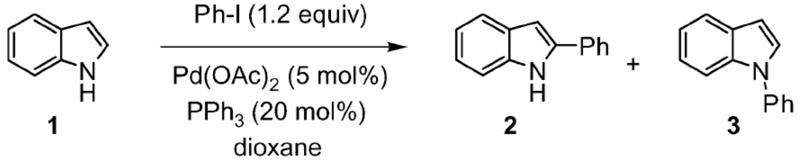


Sezen, Franz, Sames
J. Am. Chem. Soc., **2002**, *124*, 13372

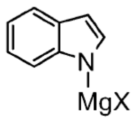


silanol	Pd(OAc)$_2$ mol %	yield %	TON	Ph-Ph (%)	PhOAc (%)
PhSi(OH)Me$_2$	2.5	33	13	5	5
Ph$_2$Si(OH)Me	**2.5**	**51**	**20**	**<1**	**<1**
PhSi(OH)$_2$Me	2.5	20	8	8	4
PhSi(OMe)$_3$	2.5	31	12	4	<1

Arylation of sp^2 C-H Bonds in Heteroaromatics



1 **2** **3**

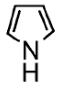
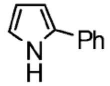
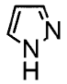
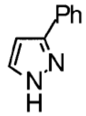
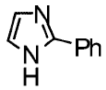
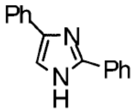
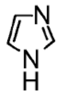
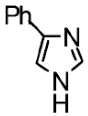
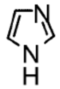
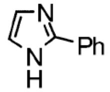
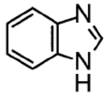
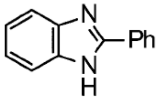
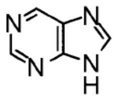
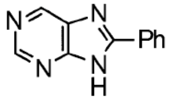


4, X=Br
5, X=OH

BASE (1.2 equiv)	isolated yield (**2** / **3**)
LiOH or NaOMe	0 / 0 %
K_3PO_4 or KOAc	0 / 0 %
Cs_2CO_3	0 / 5%
MgO	**53 / 0%**
EtMgBr[a]	**65 / 0%**
ZnO	44 / 0%

[a] Conditions: 150 °C, 15 h. (a) Indolyl Grignard salt **4** was prepared prior to the arylation reaction.

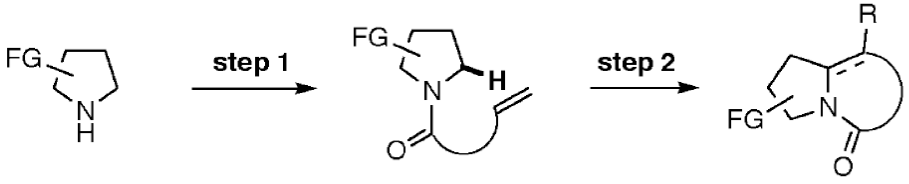
Table 2. Highly Selective C-Arylation of Free (NH)-Azoles[a]

entry	substrate	condition	product	yield
1		$\xrightarrow[\text{a}]{\text{Ph-I (1.2 equiv)}}$		86%
2		$\xrightarrow[\text{a}]{}$		81%
3		$\xrightarrow[\text{a}]{}$		81%
4		$\xrightarrow[\text{a}]{}$		72%
5		$\xrightarrow[\text{a + CuI (2 equiv)}]{}$		83%
6		$\xrightarrow[\text{a + CuI (0.2 equiv)}]{}$		90%
7		$\xrightarrow[\text{a + CuI (0.2 equiv)}]{}$		78%

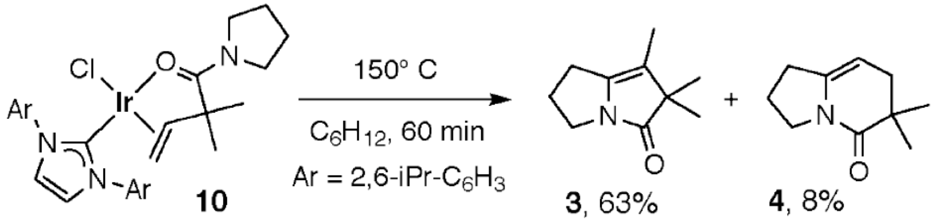
[a] Conditions: (a) PhI (1.2 equiv), Pd(OAc)$_2$ (5 mol %), PPh$_3$ (20 mol %), MgO (1.2 equiv), dioxane, 150 °C, 12−15 h. PhBr afforded 52−60% yield of the corresponding products.

Sezen, Sames, *J. Am. Chem. Soc.*, **2003**, *125*, 5274

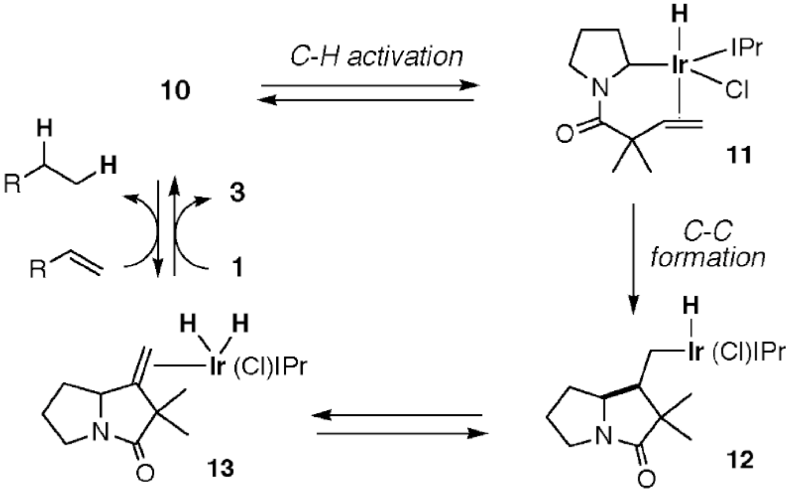
Cross-Coupling of sp^3 C-H Bonds and Alkenes



Scheme 1. Stoichiometric Reaction



Scheme 2. Proposed Catalytic Cycle



DeBoef, Pastine, Sames, *J. Am. Chem. Soc.*, **2004**, *126*, 6556

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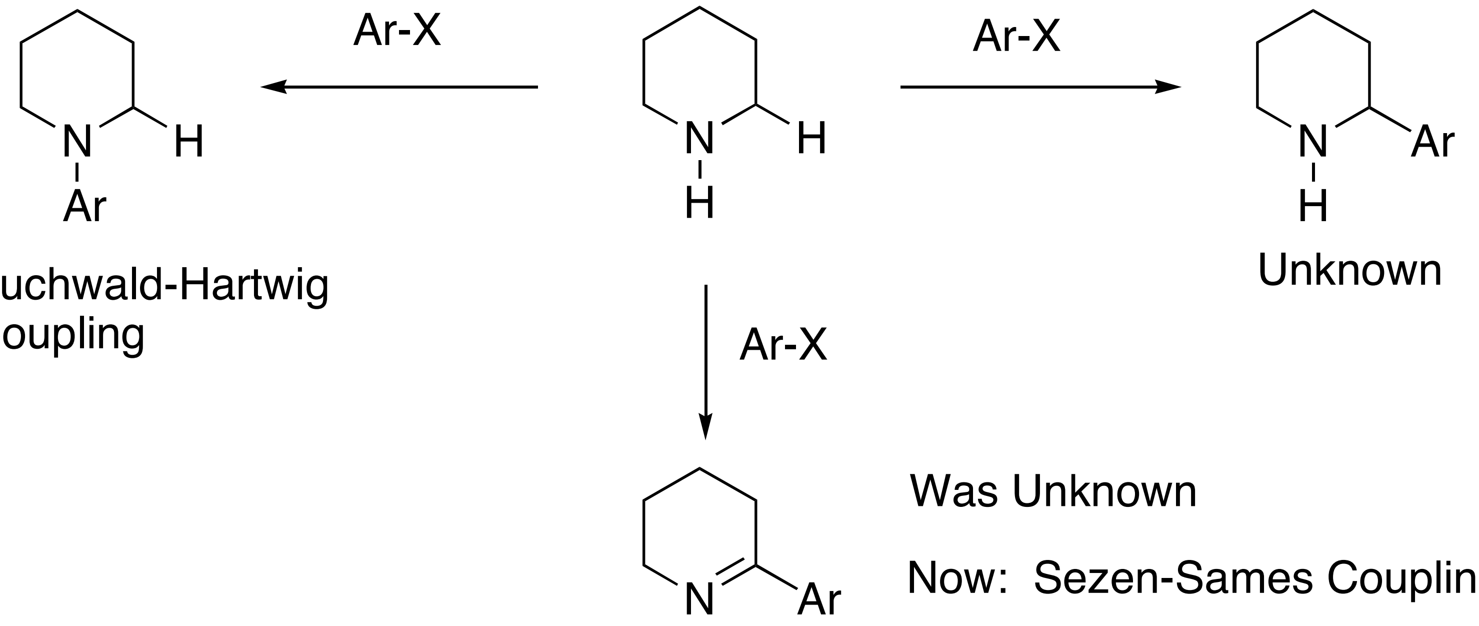
Bengu Sezen and Dalibor Sames

J. Am. Chem. Soc., **2004**, *126*, 13244



Buchwald-Hartwig Coupling

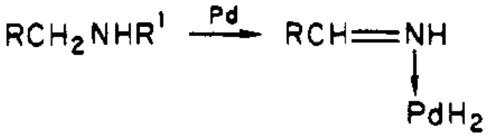
Unknown

Was Unknown

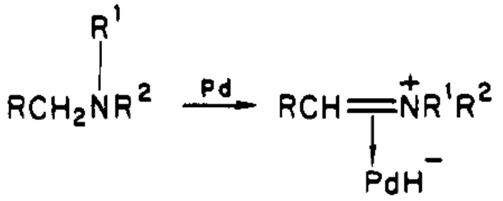
Now: Sezen-Sames Coupling

Alkyl Group Exchange in Amines

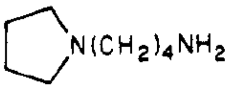
$$R^1R^2CHNHR^3 + R^4R^5NH \xrightarrow{Pd} R^1R^2CHNR^4R^5 + R^3NH_2 \qquad (1)$$



$$RCH_2NHR^1 \xrightarrow{Pd} \underset{\downarrow \atop PdH_2}{RCH{=}NH} \qquad (2)$$



$$RCH_2\overset{\displaystyle R^1 \atop |}{N}R^2 \xrightarrow{Pd} \underset{\downarrow \atop PdH^-}{RCH{=}\overset{+}{N}R^1R^2} \qquad (3)$$



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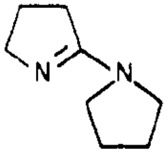

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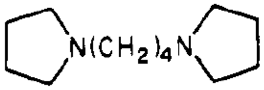
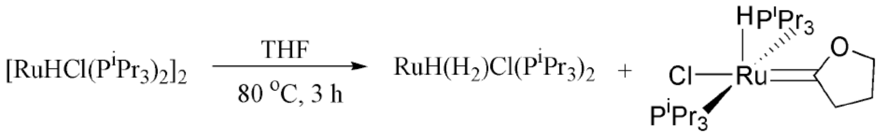


5

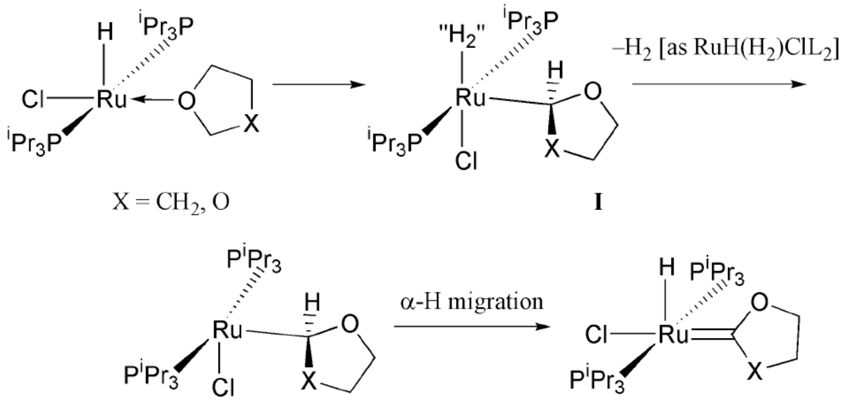
ladium at 150 °C. Noticeable is that the products from the reaction of pyrrolidine depends upon the reaction temperature.[8] The palladium-catalyzed reaction of pyrrolidine at 80 °C gave pyrrolidino-2Δ^1-pyrroline **4**, (65%) and **3** (24%), while at 200 °C 1,5-dipyrrolidinobutane (**5**) was obtained in 56% yield.

Murahashi, Yoshimura, Tsumiyama, Kojima, *J. Am. Chem. Soc.*, **1983**, *105*, 5002

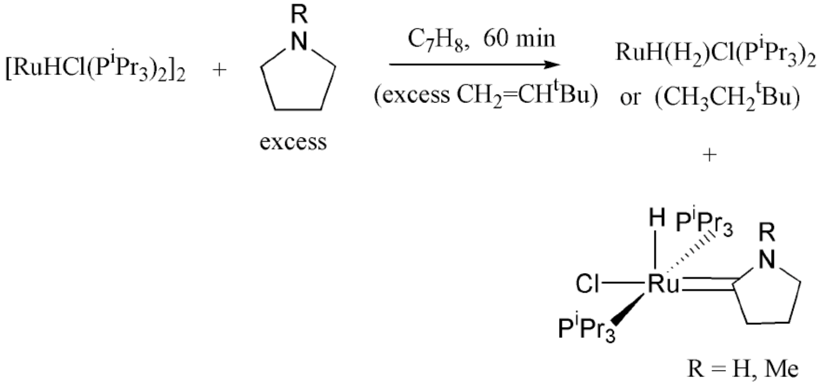
Alpha C-H Insertion



(3)



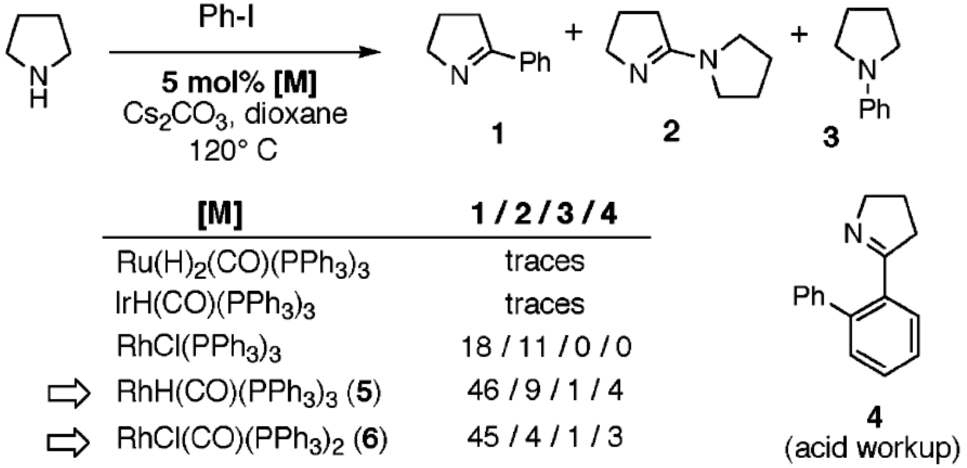
Scheme 1



(5)

Ferrando-Miquel, Coalter, Gerard Huffman, Eisenstein, Caulton, *New. J. Chem.*, **2002**, *26*, 687.

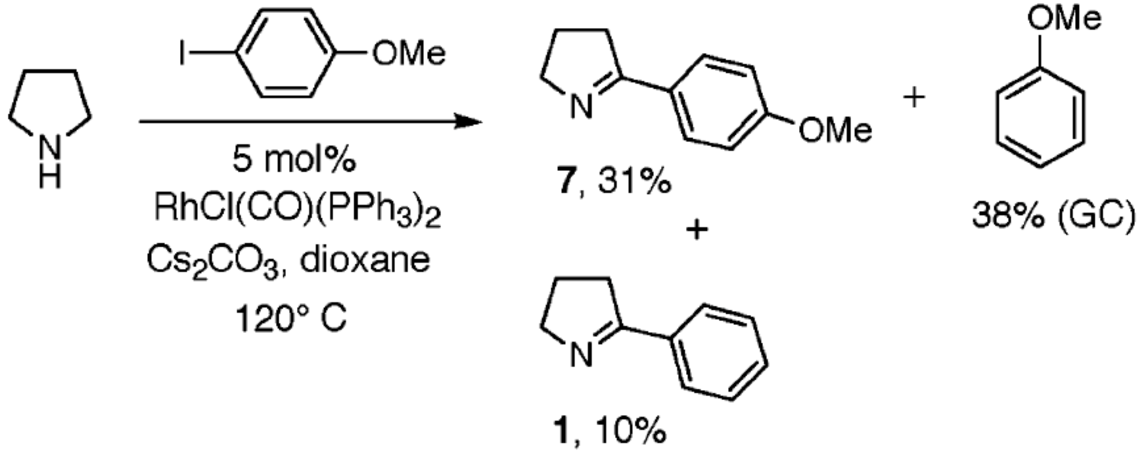
Scheme 1. Lead Identification



	[M]	**1 / 2 / 3 / 4**
	$Ru(H)_2(CO)(PPh_3)_3$	traces
	$IrH(CO)(PPh_3)_3$	traces
	$RhCl(PPh_3)_3$	18 / 11 / 0 / 0
⇨	$RhH(CO)(PPh_3)_3$ (**5**)	46 / 9 / 1 / 4
⇨	$RhCl(CO)(PPh_3)_2$ (**6**)	45 / 4 / 1 / 3

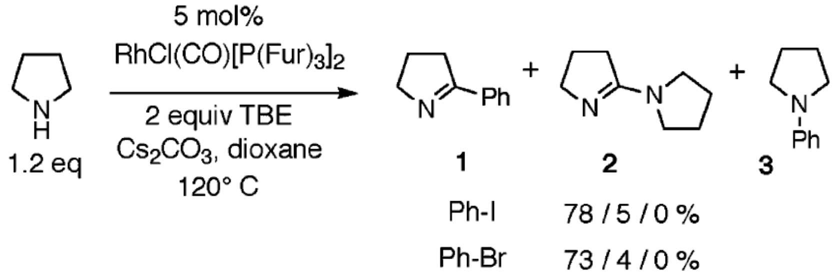
Sezen, Sames, *J. Am. Chem. Soc.*, **2004**, *126*, 13244

Scheme 2. Ligand Degradation and Dehalogenation

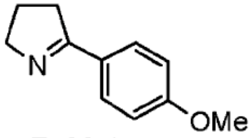


Sezen, Sames, *J. Am. Chem. Soc.*, **2004**, *126*, 13244

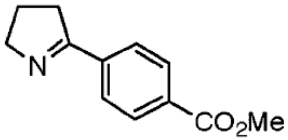
Scheme 3. Optimized Conditions[a]



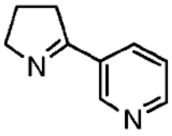
[a] P(Fur)$_3$ = tri-(2-furyl)phosphine, TBE = *tert*-butylethylene. Conditions: pyrrolidine (1.2 equiv), PhX (1 equiv), RhCl(CO)[P(Fur)$_3$]$_2$ (5 mol %), TBE (2 equiv), Cs$_2$CO$_3$ (1.2 equiv), dioxane, 120 °C, 10 h. 10−15% dehalogenation occurred. Compound **4** was also formed, <4%. The given yields are the averages of three runs with a deviation of 2−3%. Purification of reagents and anhydrous conditions are required (see Supporting Information for details).



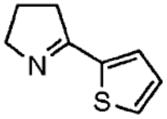
7, 62%



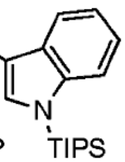
9, 56%



10, 39%



11, 44%



12, 31%

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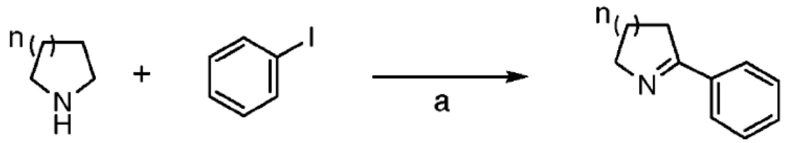
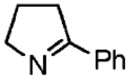
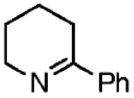
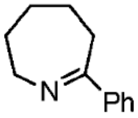
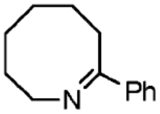
Table 2. (NH)-Heterocycle Substrate Scope[a]

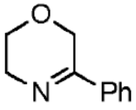


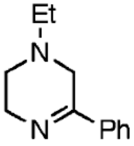

1, 78%

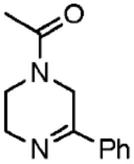

13, 65%


14, 51%


15, 52%


16, 62%

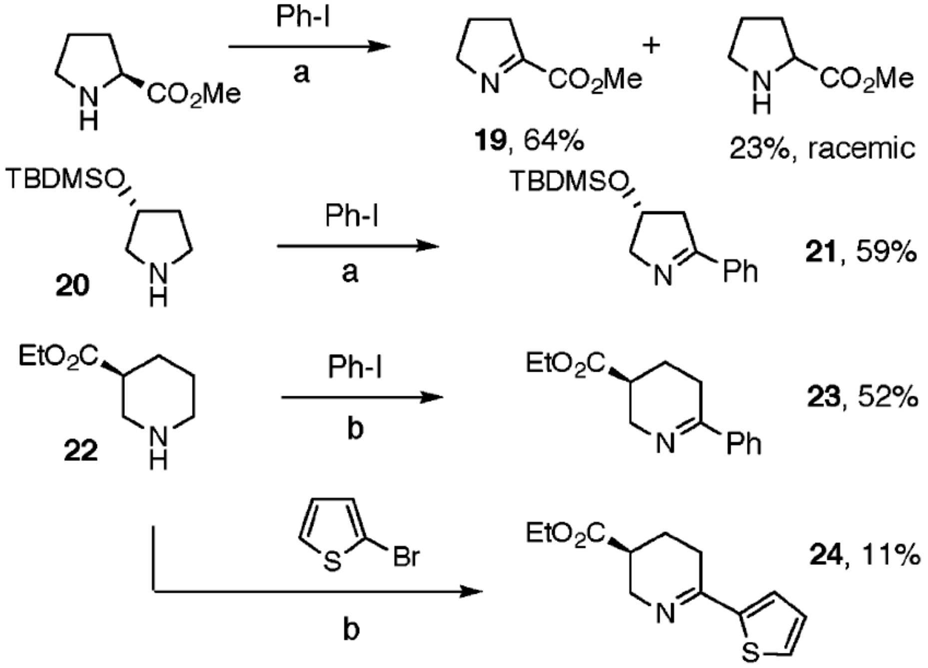

17, 53%


18, 56%

[a] Conditions: heterocycle (1.2 equiv), PhI (1 equiv), RhCl(CO)[P(Fur)$_3$]$_2$ (5 mol %), TBE (2 equiv), Cs$_2$CO$_3$ (1.2 equiv), dioxane. Reaction was performed at 120 °C for **1**. Reactions were performed at 150 °C for **13**−**18**.

Sezen, Sames, *J. Am. Chem. Soc.*, **2004**, *126*, 13244

Arylation of Substituted Heterocycles



[a] Conditions: (a) heterocycle (1.2 equiv), PhI (1 equiv), RhCl(CO)[P(Fur)$_3$]$_2$ (5 mol %), TBE (2 equiv), Cs_2CO_3 (1.2 equiv), dioxane, 120 °C, 15 h; (b) heterocycle (1.2 equiv), (Het)Ar-X (1 equiv), RhCl(CO)[P(Fur)$_3$]$_2$ (5 mol %), TBE (2 equiv), Cs_2CO_3 (1.2 equiv), dioxane, 150 °C, 16 h.

Sezen, Sames, *J. Am. Chem. Soc.*, **2004**, *126*, 13244

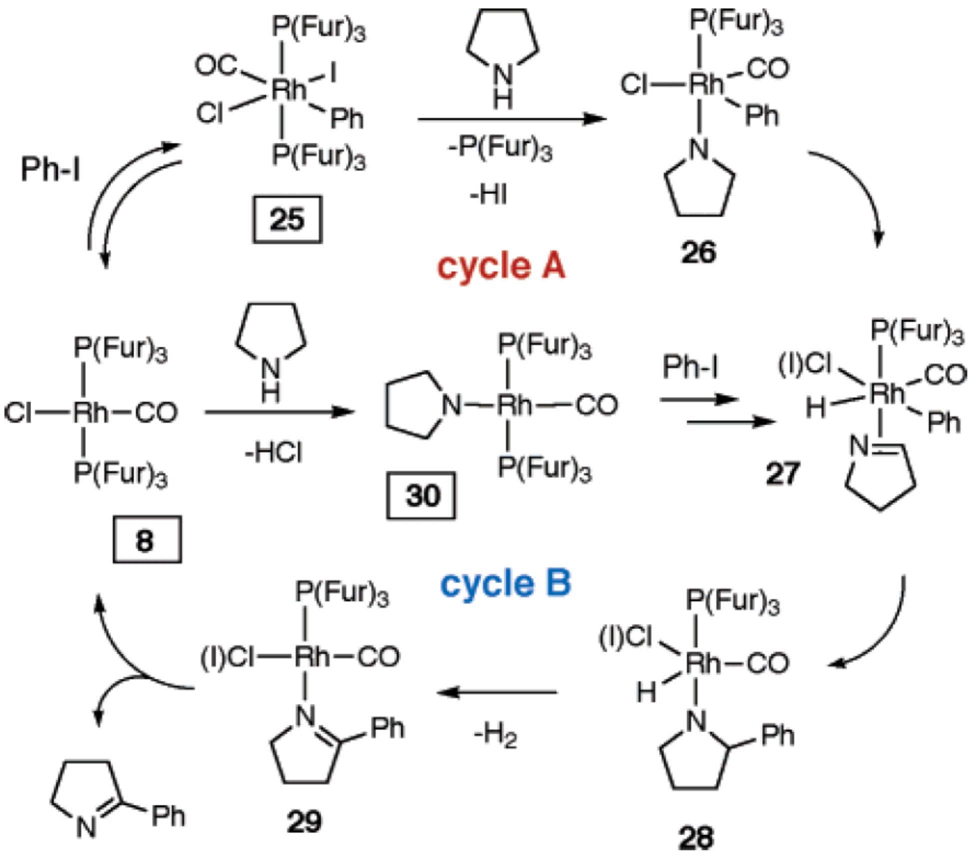


Figure 2. Proposed mechanistic rationale. Cycle A, fast and more productive cycle. Cycle B, slow and less productive cycle. Compounds **8**, **25**, and **30** were prepared and characterized.

Sezen, Sames, *J. Am. Chem. Soc.*, **2004**, *126*, 13244