

Direct α -Arylation of Ketones

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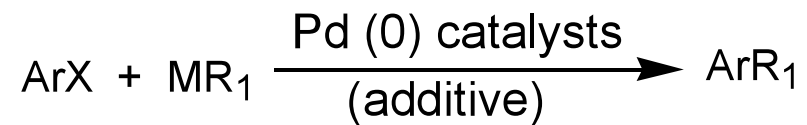
Outline

- Introduction
 - Mechanistic Study
 - Factors Influencing the Arylation of Ketone
 - ◆ Bases
 - ◆ Ligands
 - ◆ Arylation Reagents
 - Arylation Reactions of Other Stabilized Carbanions
 - Applications
 - ◆ Intramolecular Arylation Reaction
 - ◆ Asymmetric Arylation Reaction
 - Prospects
 - Conclusion
-

Outline

- Introduction
 - ◆ Coupling Reactions
 - ◆ What is direct α -arylation of ketones
 - ◆ Previous methods of ketone arylation
 - ◆ Discovery of catalytic ketone arylation reaction
 - Mechanism Study
 - Factors Influencing the arylation of ketone
 - Arylation Reactions of Other Stabilized Carbanions
 - Applications
 - Prospects
 - Conclusion
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Cross Coupling Reactions



X= Br, I, OTf, Cl

M=

Mg Kumada

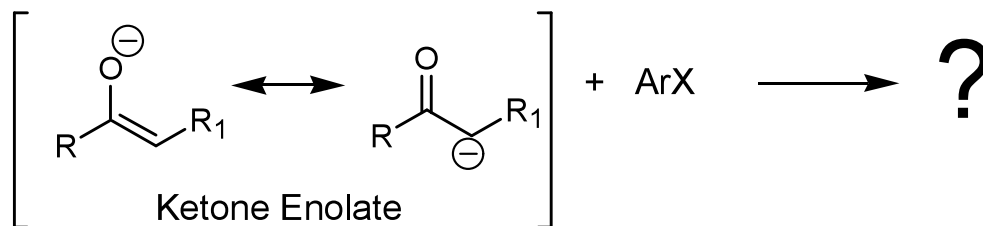
Sn Stille

B Suzuki

Si Hiyama

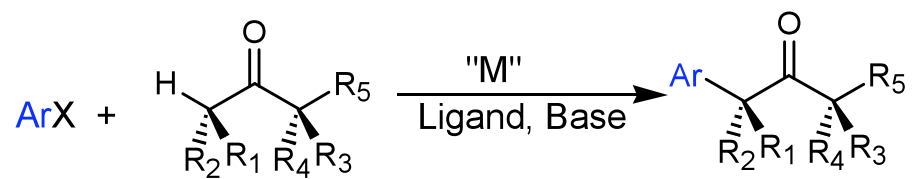
Zn Negishi

etc.



What is Direct α -Arylation of Ketone?

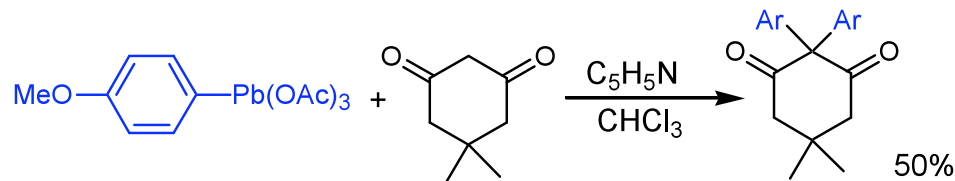
'Direct Cross Coupling of aryl halides with ketones catalyzed by transition metals'.



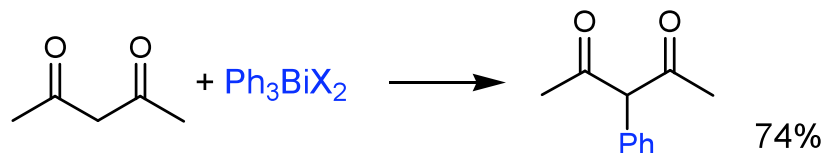
M = Metals

Drawbacks of Previous Methods of Direct α -Arylation of Ketones

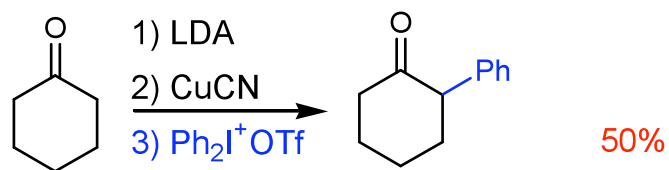
- Use of toxic main-group reagents



- Only one aryl group was transferred



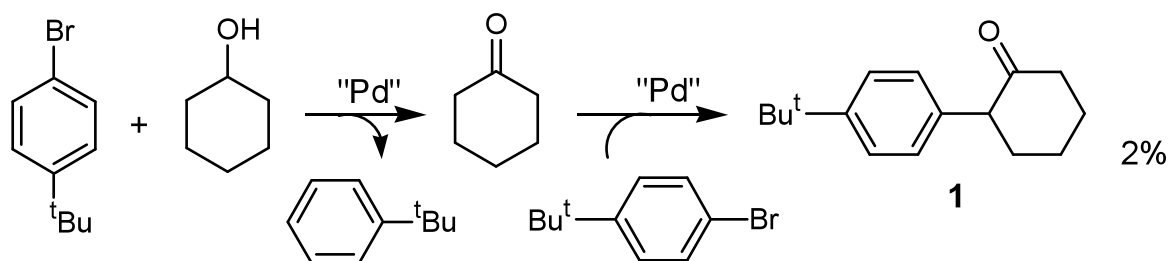
- Low product yields



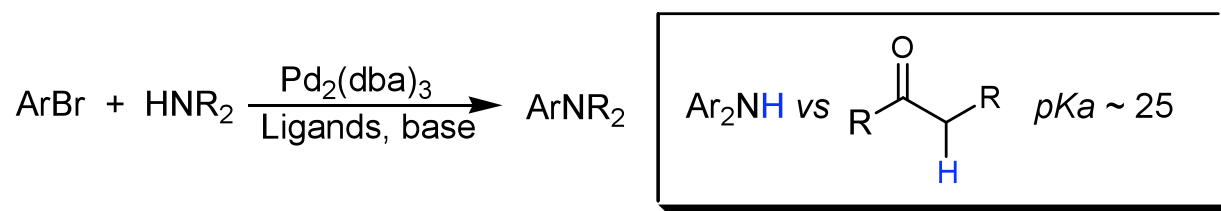
- Multiple-step preparation of stoichiometric arylation reagents
- Catalytic methods to form α -aryl ketones are less common

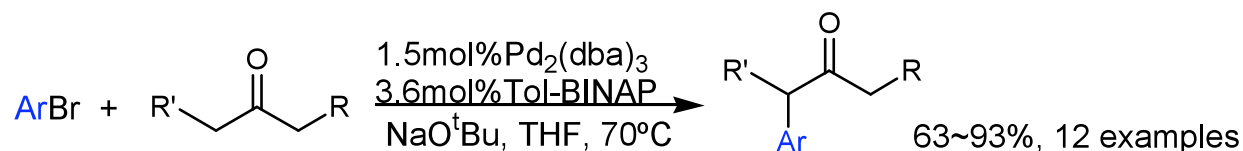
Discovery of Pd-Catalyzed α -Arylation of Ketone

- From byproduct of C-O coupling reactions by Prof. Buchwald in MIT:



- From extension of C-N coupling reactions by Prof Hartwig in Yale:

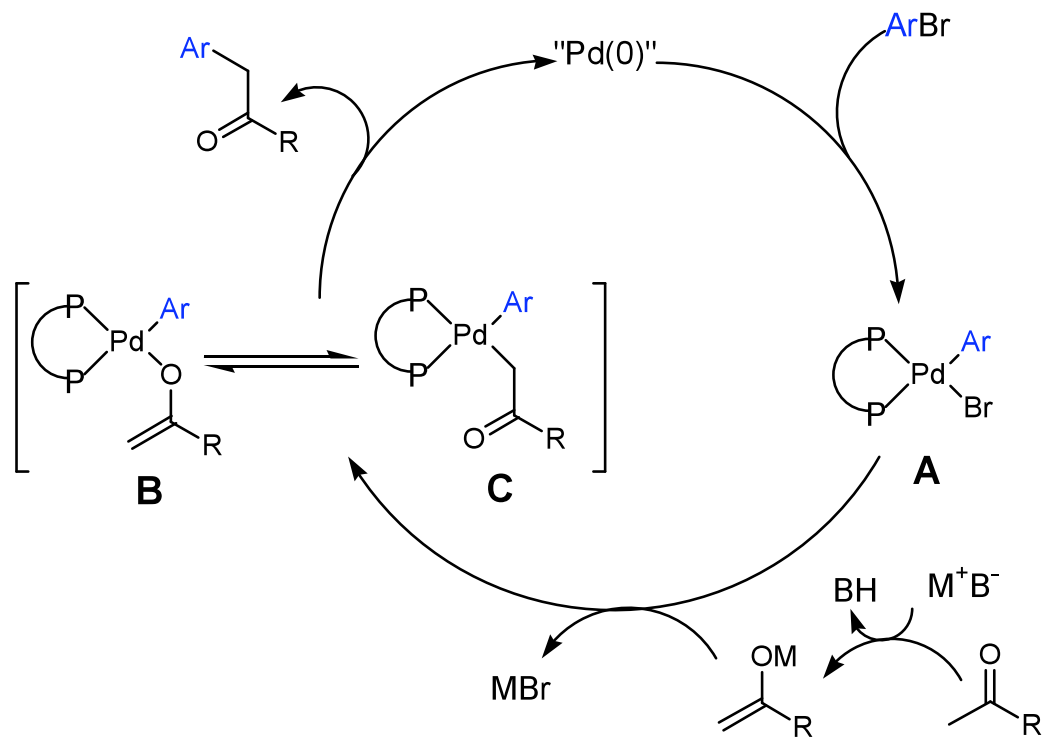


Selected Examples of Ketone α -Arylation

Entry	ArBr	Ketones	Ketone/ ArBr	Product	Mono/Di- arylation	Yield (%)
1			1.2		No Di-	93
2			1.2 2.0		30 33	67 83
3			1.2		No Di-	69
4			1.2 2.0		7 16	71 88
5			1.2		No Di-	78

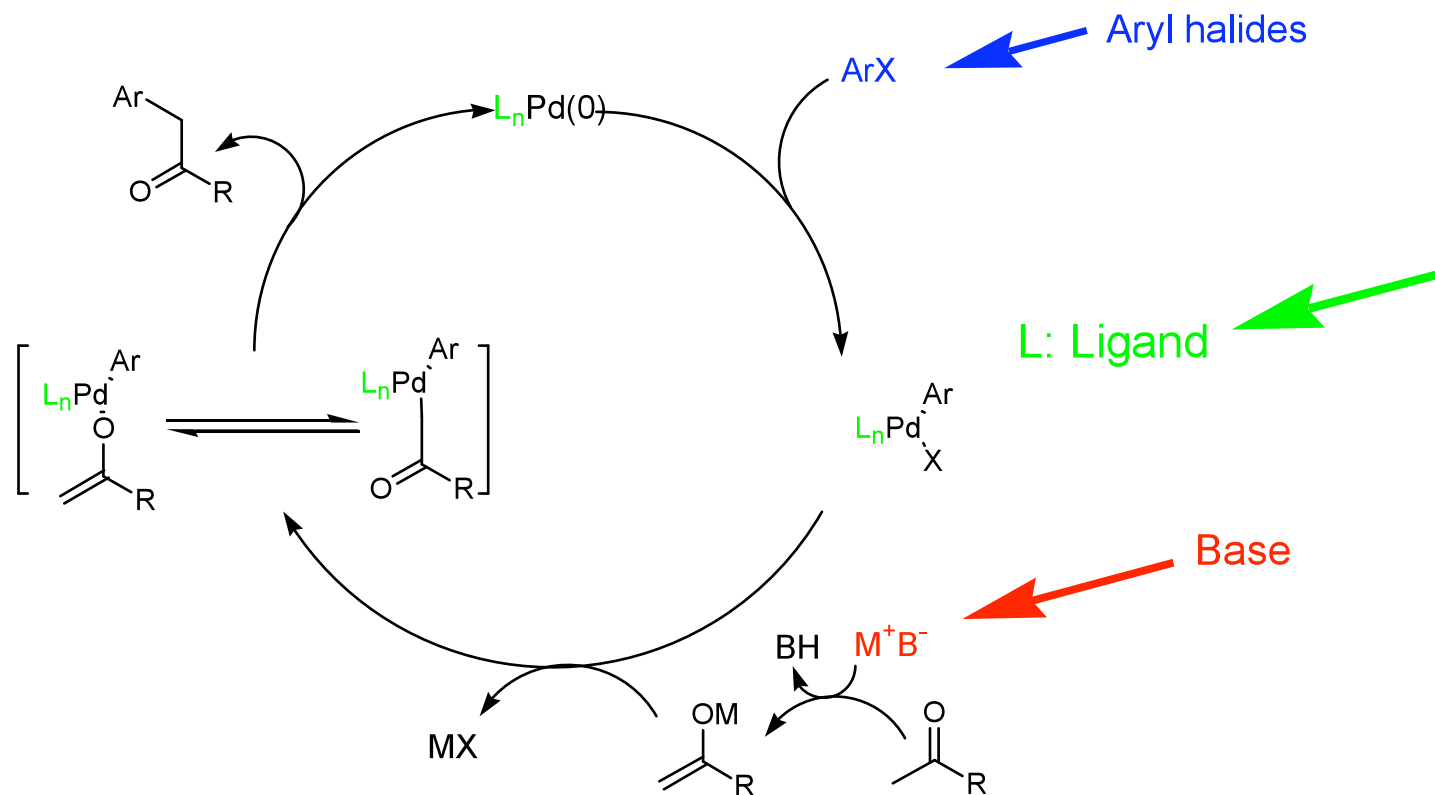
- General method for a large number of α -aryl ketones under mild conditions
- Compatible with several functional groups
- Good yield with high regioselectivity
- In most cases mono/di arylation ratios are high

Mechanism of Ketone Arylation Reaction

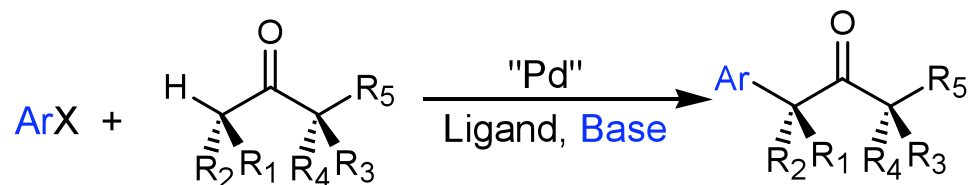


Proposed catalytic cycle of ketone arylation reaction with bidentate ligand

Main Factors Influencing the Arylation of Ketone

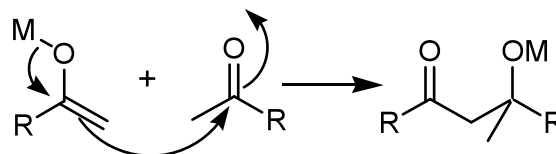


Requirement for Base

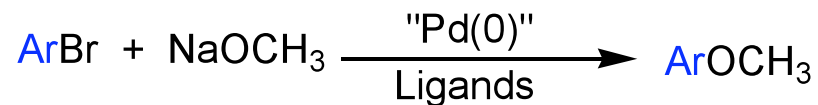


- Strong enough
- No introduction of side-reactions

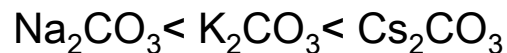
- ◆ Aldol Reaction



- ◆ C-O Coupling Reaction

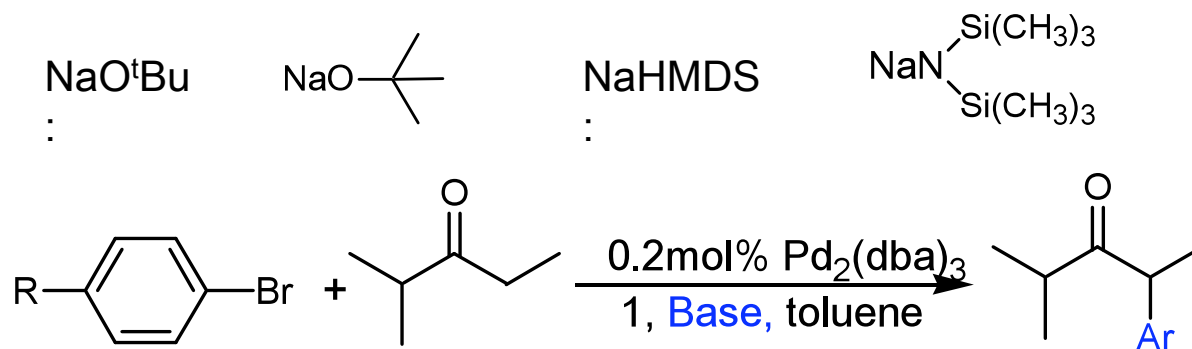


- Solubility in the solvent

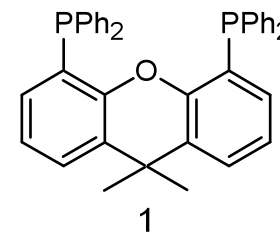


Some Bases Used in Arylation of Ketones

- Strong, bulky bases

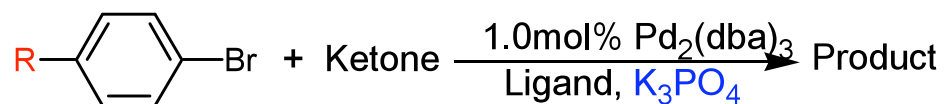


Entry	R	Base	Conditions	Yield
1	-CO ₂ ^t Bu	2 eq NaHMDS	80°C, 16h	67%
2	-CO ₂ NEt ₂	2eq NaO ^t Bu	80°C, 15h	74%

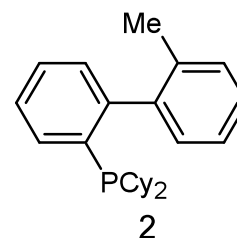
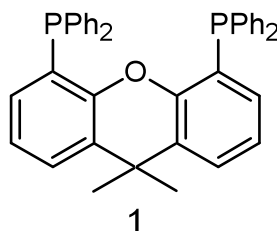


- Not compatible with several base-sensitive groups

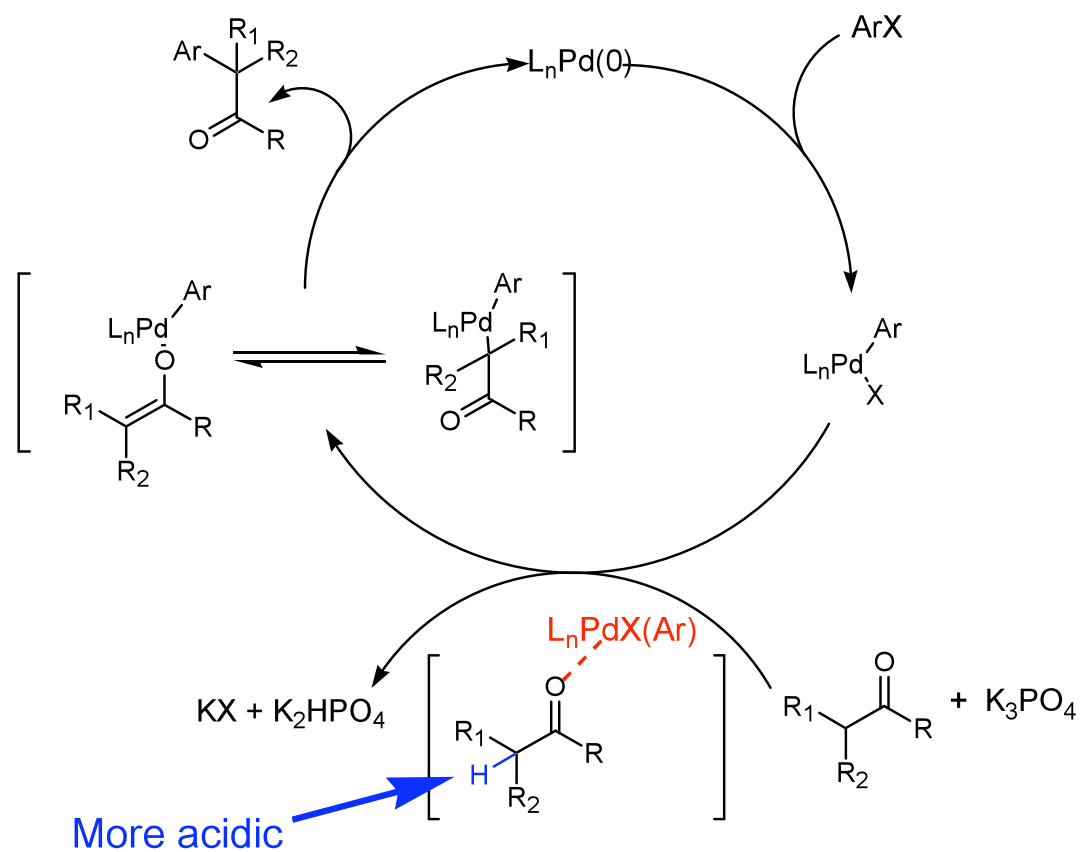
Use K_3PO_4 as Base



Entry	R	Ketone	Product	Conditions	Yield
1	-CN			THF, 80°C, 16h Ligand: 1	72%
2	-CO ₂ Et			toluene, 100°C, 23h Ligand: 2	91%
3	-CO ₂ Me			toluene, 80°C, 15h Ligand: 1	74%

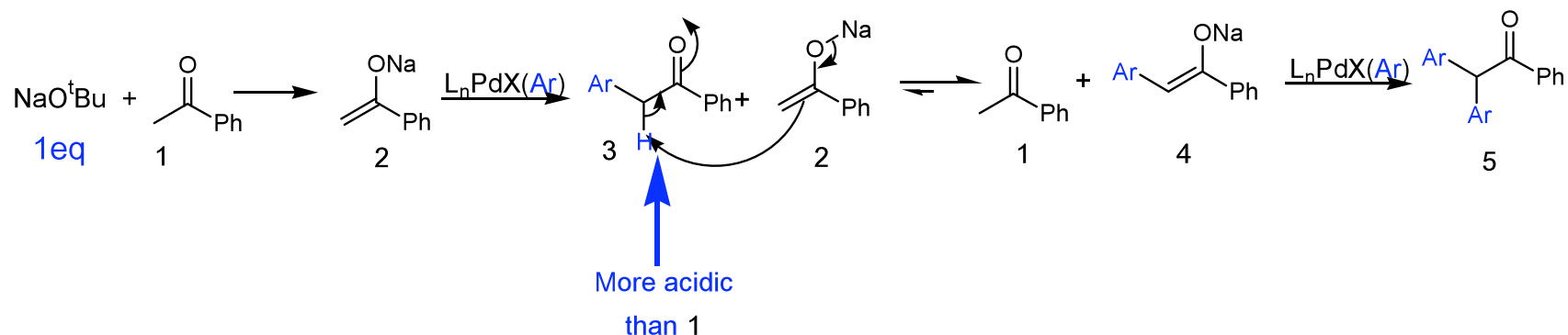


Use K_3PO_4 as Base



Excessive Base is Favored for Mono-arylated Product

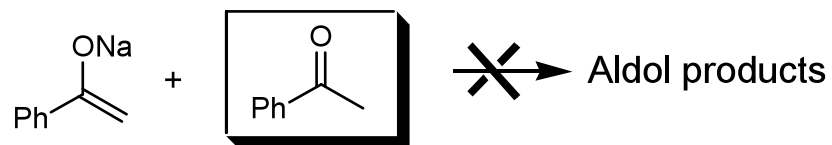
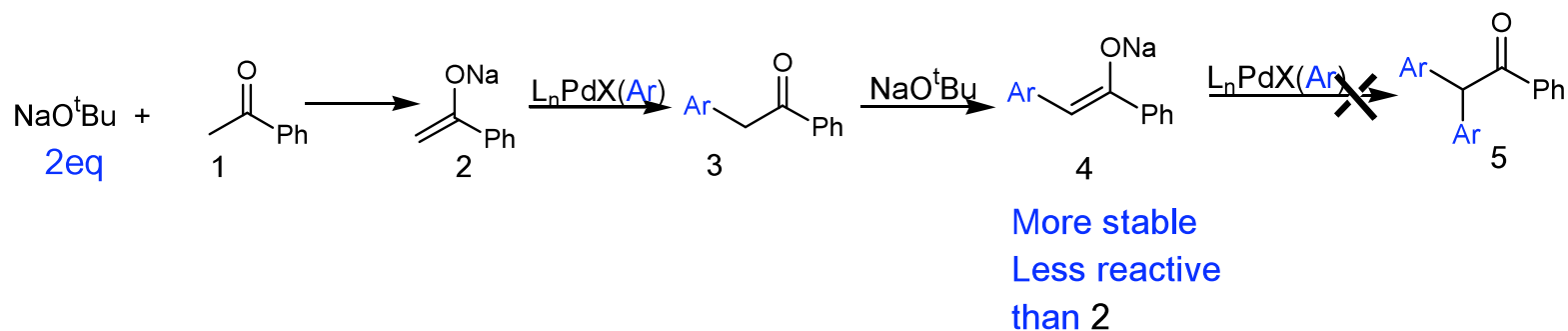
- When 1eq base is used for arylation of acetophenone



- Equilibrium between 2 and 4 will favor enolate of aryl ketone 4
- More di-arylated products would form

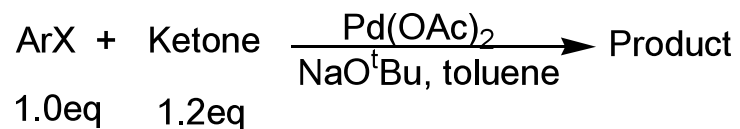
Excessive Base is Favored for Mono-arylated Product

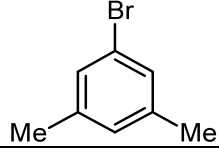
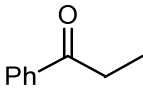
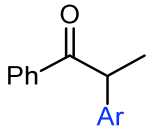
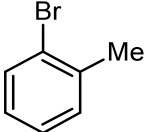
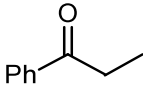
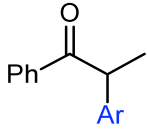
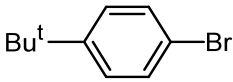
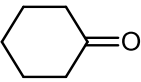
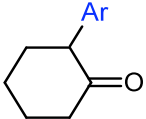
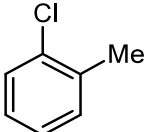
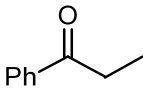
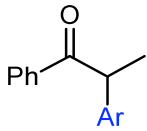
- When 2eq base is used for arylation of acetophenone



- All the ketones are in their enolate form
- High ratio of mono/ di-arylated product is expected
- Aldol reaction can be suppressed

Ligand-free Arylation of Ketones



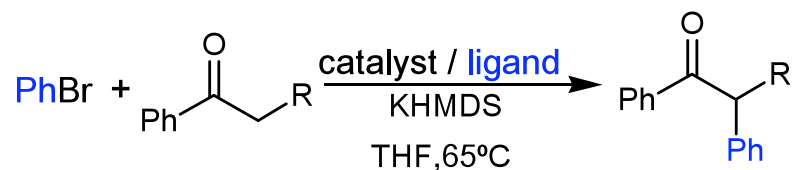
Entry	ArX	Ketone	Product	Conditions	Yield
1				80°C 23h	84%
2				80°C 14h	46%
3				70°C 14h	trace
4				80°C 24h	<1%

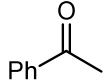
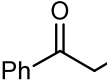
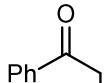
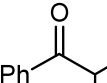
- Simple & Cheap
- Only suitable for limited substrates

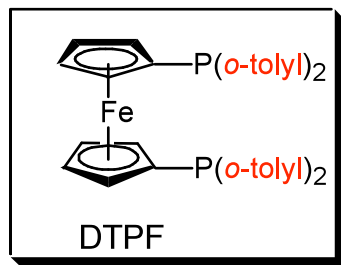
Characteristics of Phosphines Ligands

- Metal center can be stabilized by phosphine ligands
- Increase the electron density on metal center
 - ◆ The σ -donation ability to the metal:
 $\text{P}^t\text{Bu}_3 > \text{P}(\text{OR})_3 > \text{PR}_3 \approx \text{PPh}_3 > \text{PF}_3 > \text{P}(\text{OPh})_3$
- Phosphines are also electron acceptor
 - ◆ The π -acceptor ability from metals:
 $\text{P}^t\text{Bu}_3 < \text{PR}_3 < \text{PAr}_3 < \text{P}(\text{OMe})_3 < \text{P}(\text{OAr})_3 < \text{PCl}_3 < \text{PF}_3$
- Steric properties can be tuned systematically
 - ◆ The steric effect:
 $\text{P}^t\text{Bu}_3 > \text{PPh}_3 > \text{P}(\text{OPh})_3 > \text{PMe}_3 > \text{P}(\text{OR})_3 > \text{PF}_3$
- Introduction of chiral center is easy

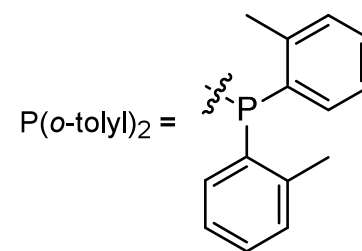
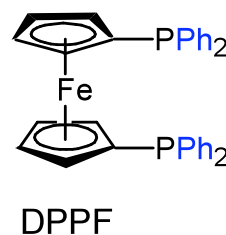
Steric Effect of Chelating Phosphine Ligands



Entry	Ketone	Catalyst	Product	Ligand	Time (h)	Yield (%)
1		7.5mol%Pd ₂ (dba) ₃ 9.0mol%Ligand		DTPF	0.75	84
				DPPF	2	76
2		7.5mol%Pd ₂ (dba) ₃ 9.0mol%Ligand		DTPF	0.75	71
				DPPF	2	47



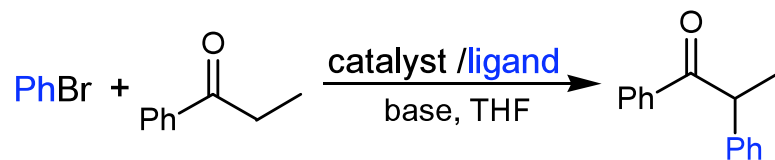
vs.



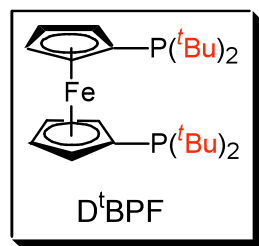
more sterically hindered

- Sterically hindered ligands can make reaction faster, afford higher yields

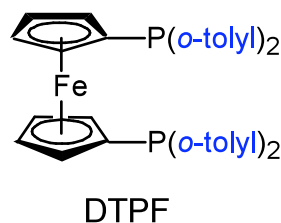
Electronic Effects of Phosphine Ligands



Entry	Catalyst	Condition	Ligand	Yield (%)
1	7.5mol%Pd ₂ (dba) ₃ 9.0mol%Ligand	65°C THF	DTPF	71
2	2mol%Pd ₂ (dba) ₃ 2.5mol%Ligand	25°C THF	D ^t BPF	99



vs.

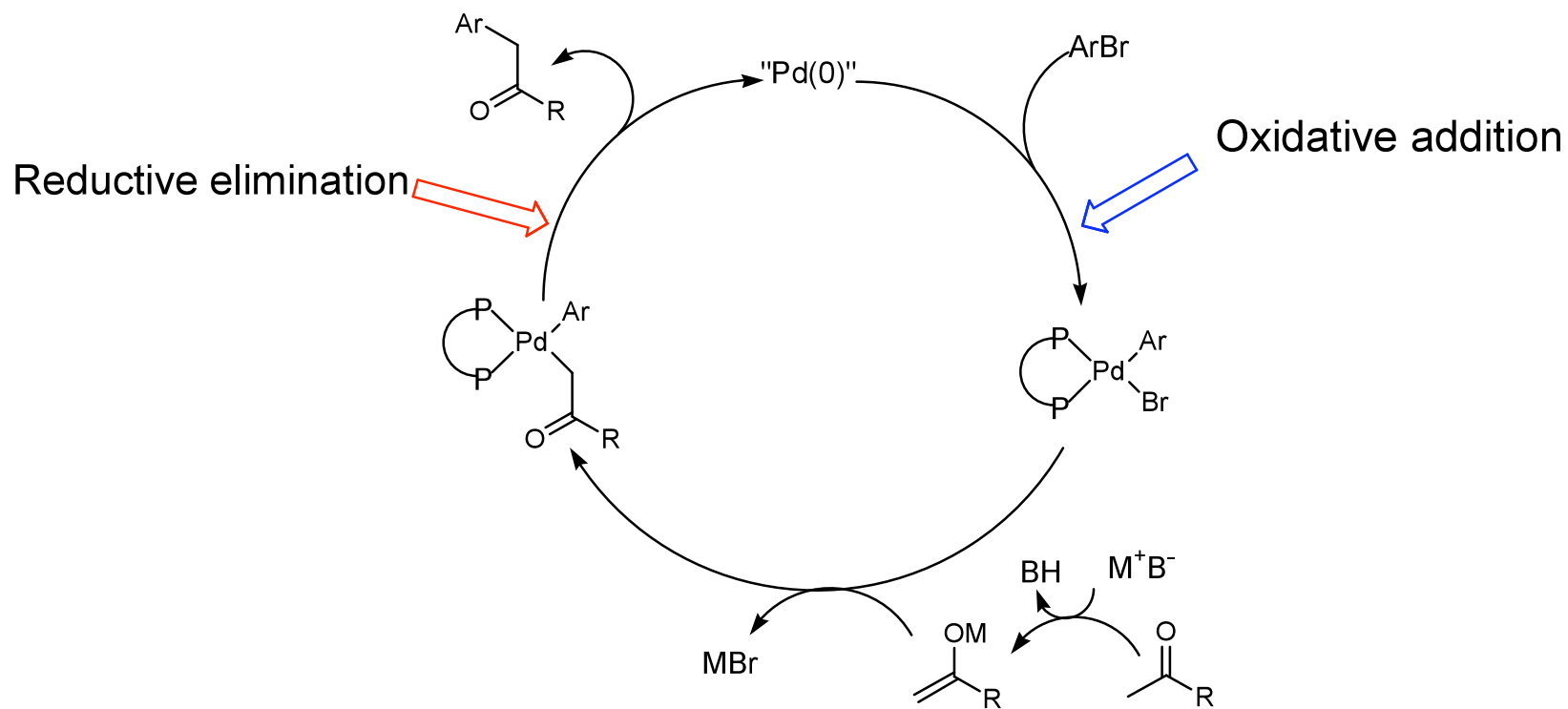


Electronically richer

- Reactions afford higher yields by using electron-rich ligands

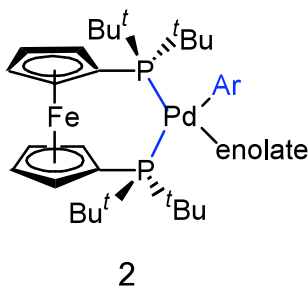
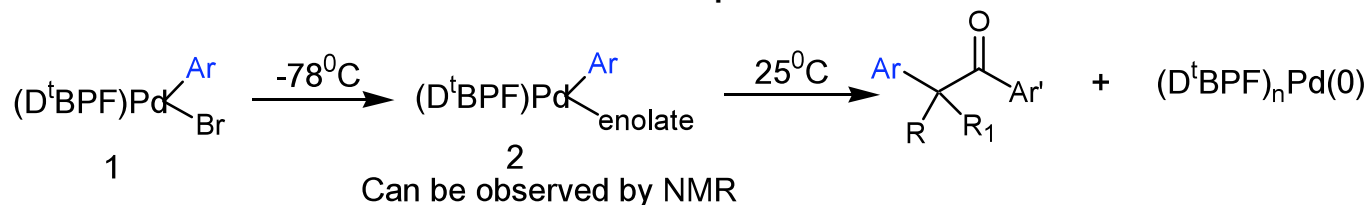
Activities of Phosphine Ligands in Ketone Arylation Reactions

- Electron-rich phosphines accelerate oxidative addition
- Sterically hindered ligands facilitate reductive elimination



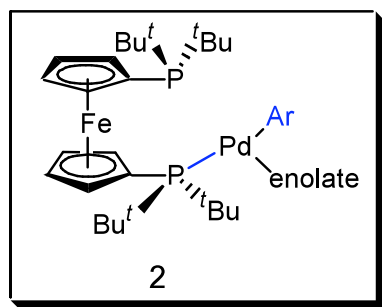
Further Discussion of Chelating Model

—low temperature ^{31}P NMR



Proposed Chelation of two phosphorous atoms

➡ Two ^{31}P singlets around 57ppm



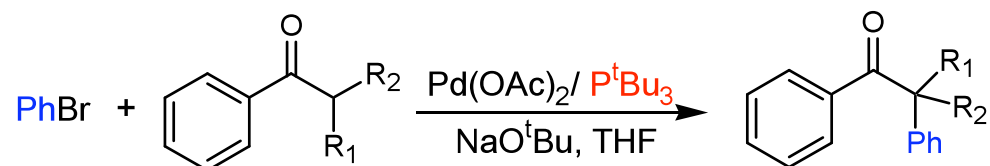
Experimentally observed:

One ^{31}P singlet at 57.2ppm, another singlet at 24.6ppm

➡ One phosphorous atom is bound to palladium center

- Sterically hindered monophosphines PR_3 may work for ketone arylation

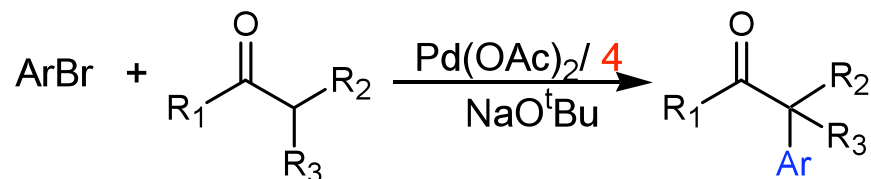
Ketone Arylation Catalyzed by Alkyl-monophosphines

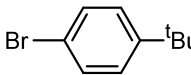
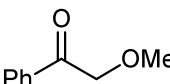
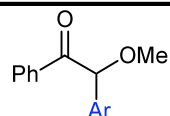
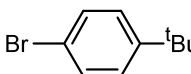
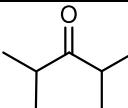
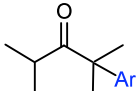
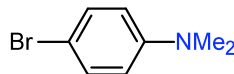
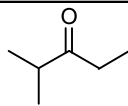
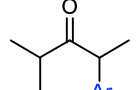
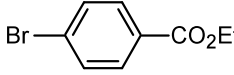
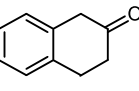
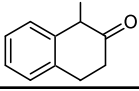
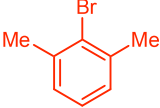
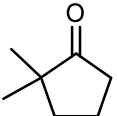
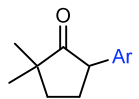


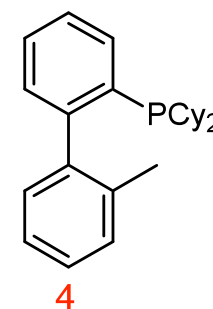
Entry	Ketones	Catalyst	Cond.	Product	Yield (%)
1		0.5mol% Pd(OAc) ₂ 0.625mol%Ligand	25°C 2h		97
2		1mol%Pd(OAc) ₂ 1.25mol%Ligand	25°C 6h		97
3		1mol%Pd(OAc) ₂ 1.25mol%Ligand	50°C 12h		82

- Alkyl-monophosphines can promote ketone arylation in high yield
- Reaction condition is mild
- Usually only work well for aromatic ketones

Ketone Arylation Catalyzed by Buchwald's Ligand 4



Entry	ArBr	Ketone	Cond.	Mol%Pd Solvent	Product	Yield (%)
1			70°C 17h	0.5 THF		83
2			85°C 24h	0.5 toluene		61
3			85°C 24h	0.5 toluene		70
4			80°C 24h	0.2 THF		85
5			70°C 23h	0.5 toluene		64



α -Arylation of Ketone with Chloroarenes

- Readily available and cheap
- Stable, easy to handle and store
- Less reactive than bromo- & iodoarenes

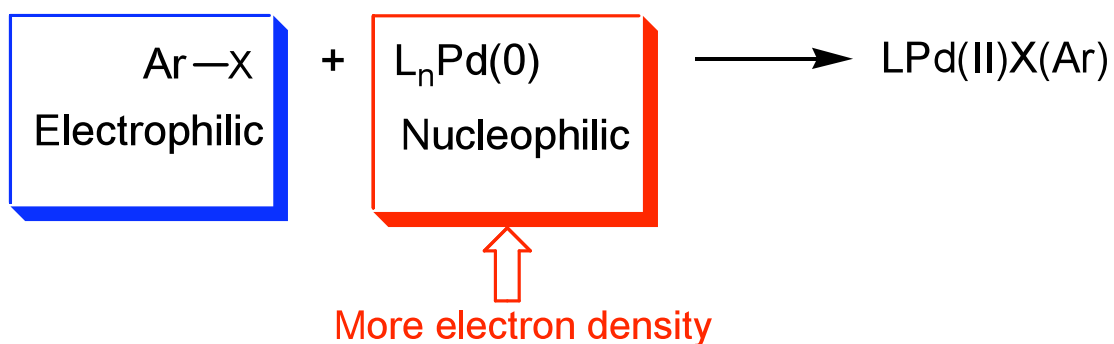
Bond dissociation energies for C-X bond in Ph-X:

C-Cl: 96 kcal/mol, C-Br: 81 kcal/mol, C-I: 65 kcal/mol

- C-Cl bond is difficult to be activated than other C-X bond

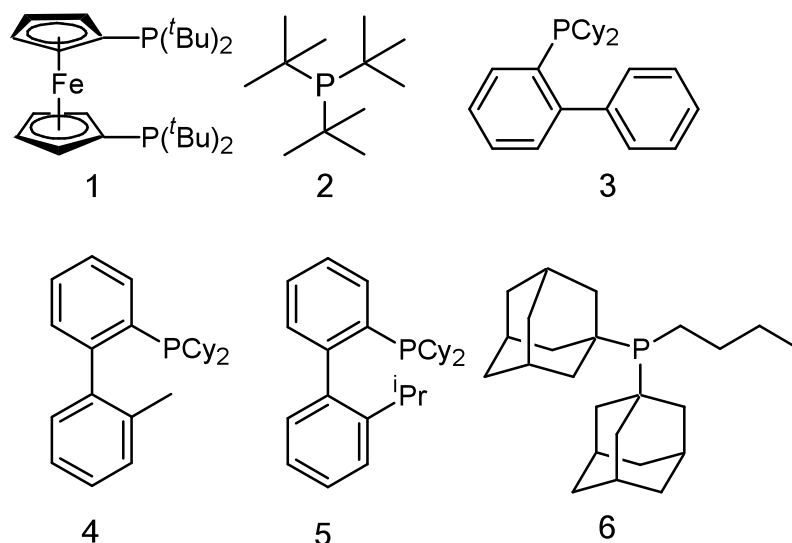
Methods to Activate Aryl Chlorides

- Oxidative addition of aryl halides:



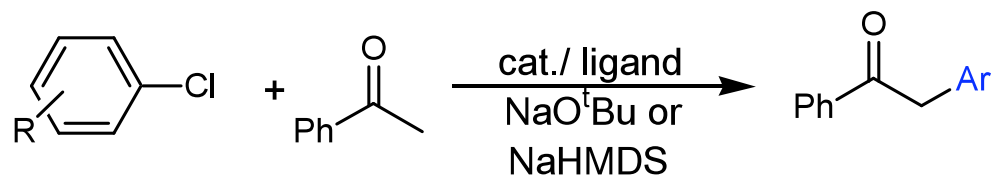
- Activate chloroarenes by electron-withdrawing groups on aromatic rings
- Increase electron density on metals by use of electron-rich ligands

Active Ligands For Aryl Chlorides

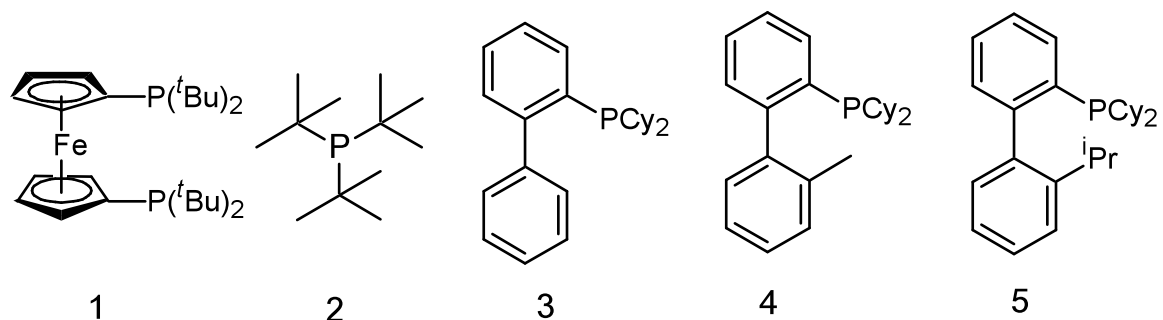


- They can facilitate oxidative addition
 - ◆ Increase electron-density on metal because of their electron richness
 - ◆ Formation of highly active $Pd(PR_3)_{2-3}$ species due to steric hindrance
- They can promote reductive elimination
 - ◆ They are highly sterically hindered ligands

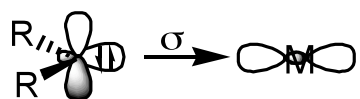
Arylation of Ketones by Aryl Chlorides



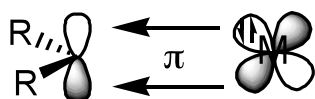
Entry	R	Catalyst	Conditions	Yield (%)
1	2-Me	Pd(dba) ₂ /1	70°C, 12h	80
2	4-OMe	Pd(OAc) ₂ /2	70°C, 12h	91
3	4-Me	Pd(OAc) ₂ /3	80°C, 12h	91
4	4-COMe	Pd(OAc) ₂ /5	80°C, 6h	76
5	4-CN	Pd(OAc) ₂ /4	80°C, 18h	78



Ketone Arylation Catalyzed by Pd-N-Heterocyclic Carbene Complex

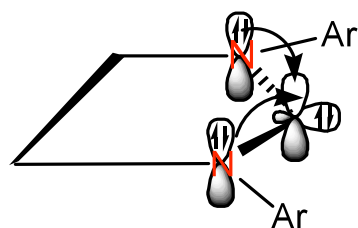
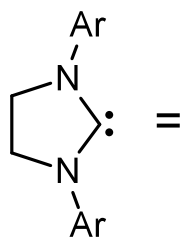


σ -Donation from carbene to metal



π -Back bonding from metal to carbene

Typical carbenes



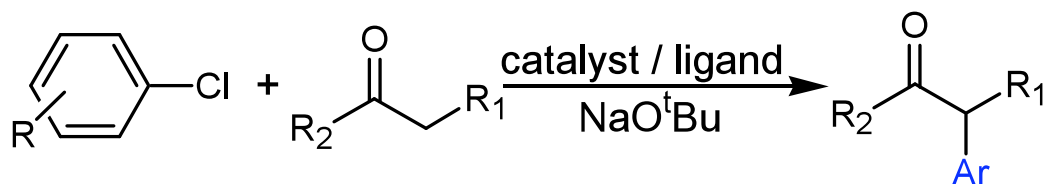
Strong donation from nitrogen to carbene center

Weak π -acceptor

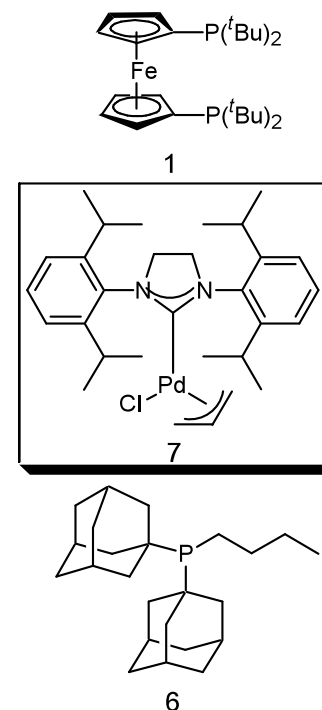
N-heterocyclic carbenes(NHC)

- Efficiently increase electron-density on metal center
- Steric effect can be tuned by aryl groups on nitrogen

Arylation of Ketones Catalyzed by Pd-NHC Complex



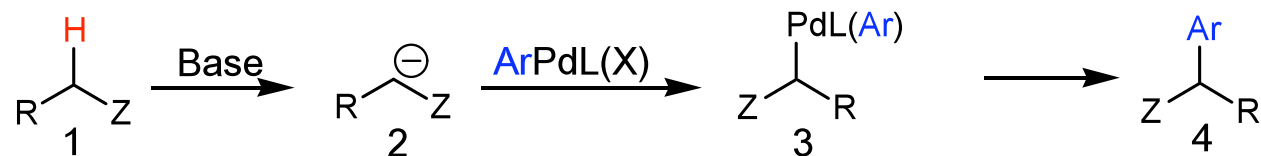
Entry	ArCl	Ketone	Catalyst	Condition	Yield (%)
1			Pd(dba) ₂ /1	70°C, 3h	86
			7	50°C, 1h	91
2			Pd(OAc) ₂ /6	100°C, 20h	25
			7	70°C, 1h	78
3			Pd(OAc) ₂ /6	100°C, 20h	59
			7	70°C, 1h	93
4			Pd(dba) ₂ /1	70°C, 12h	80
			7	60°C, 1h	87
5			7	60°C, 1h	91



- Air stable, well-defined palladium N-heterocyclic carbene complex
- Efficiently catalyze ketone arylation reaction with aryl chlorides

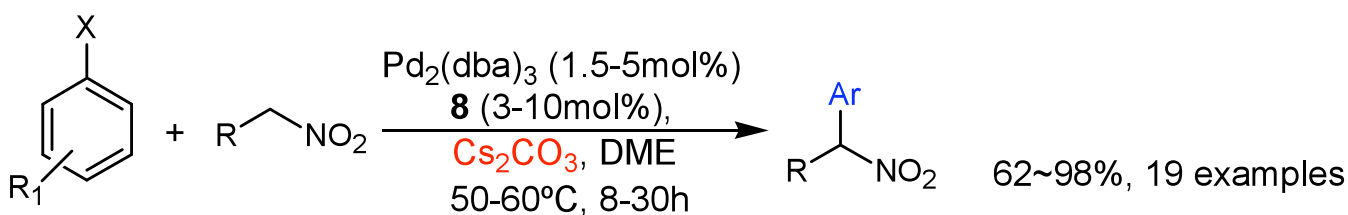
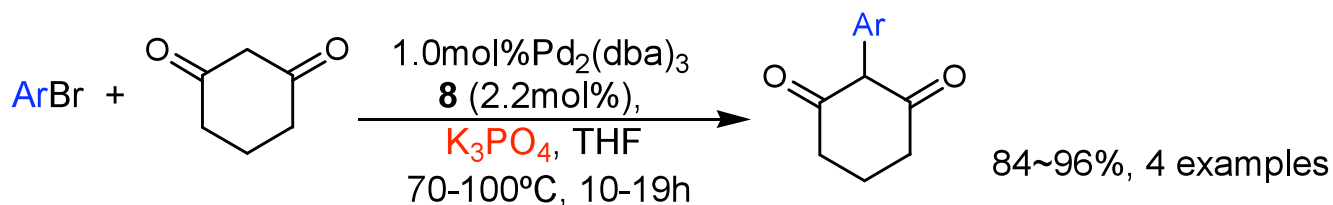
Stabilized Anions as Potential Substrates of Arylation Reaction

	Examples	Acidity constant	pKa
Diones	$\text{CH}_2(\text{COCH}_3)_2$	1.26×10^{-9}	9
Hydrocyanic acids	HCN	6.3×10^{-10}	9.2
Nitroalkanes	CH_3NO_2	6.3×10^{-11}	10.2
Malonitrile	$\text{CH}_2(\text{CN})_2$	1.0×10^{-11}	11.0
Ketoacetates	$\text{CH}_3\text{COCH}_2\text{CO}_2\text{CH}_3$	1.0×10^{-11}	11.0
Malonates	$\text{CH}_2(\text{COOEt})_2$	3.2×10^{-14}	13.5
Aldehydes	RCH_2CHO	2.0×10^{-17}	16.7
Ketones	RCOCH_3	1.0×10^{-20}	20
Esters	RCH_2COOEt	1.0×10^{-25}	25
Nitriles	RCH_2CN	1.0×10^{-25}	25
Amides	$\text{R}^1\text{CH}_2\text{CONR}_2$	1.0×10^{-35}	35



Z: Electron-withdrawing group

Arylation of Cyclo-Diketones and Nitroalkanes

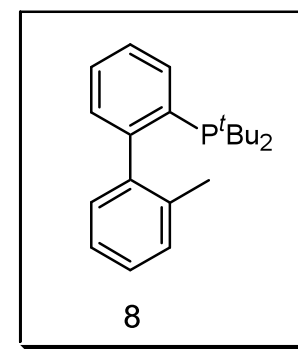


X = Br, Cl

R₁ = R, COOMe, OR, NR₂, COMe

R = Me, Et, *n*Pent., Bn

- Reaction can undergo by using mild base
- Excellent functional group tolerance for arylation of nitroalkanes

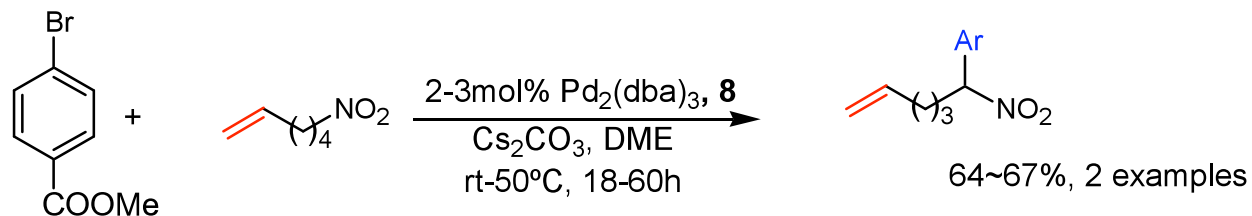


Group Tolerance in Nitroalkane Arylation Reaction

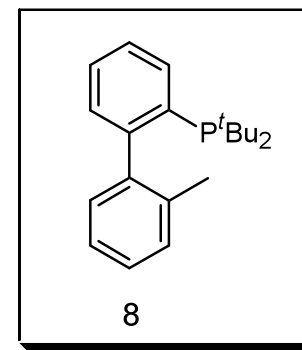


$X = \text{Br}, \text{Cl}$

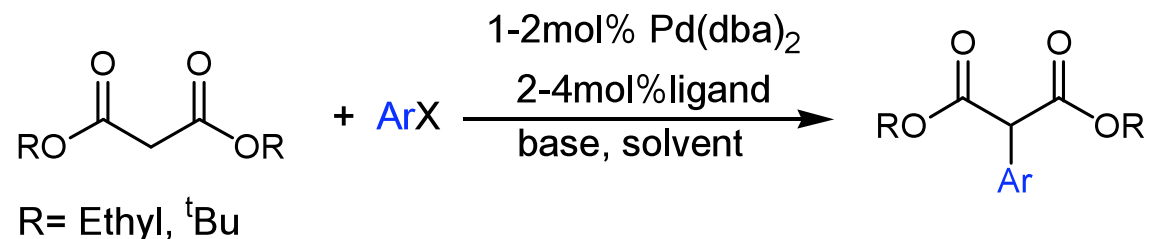
$R_1 = \text{COOMe}, \text{OMe}, \text{NMe}_2, \text{Ph}$



- Reaction condition is mild
- No di-arylated products observed
- Excellent chemoselectivity

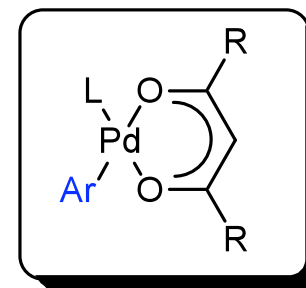
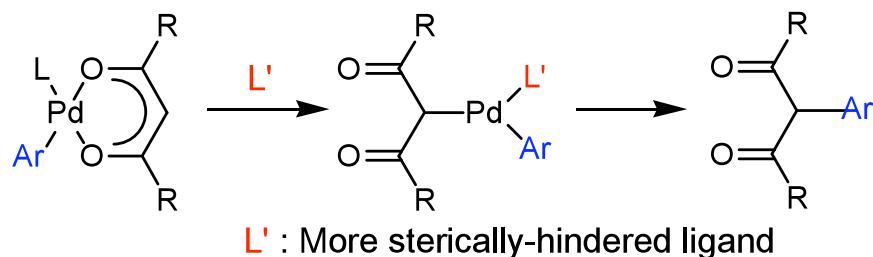


Arylation of Malonates

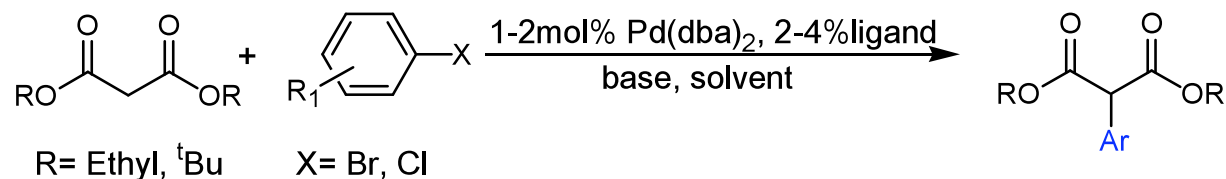


- Challenge: Low reactivity toward arylation reaction due to:
 - ◆ Stabilizing effect of two carbonyl retards the reductive elimination
 - ◆ $\eta^2\text{-O,O}$ -coordination mode of malonate anion

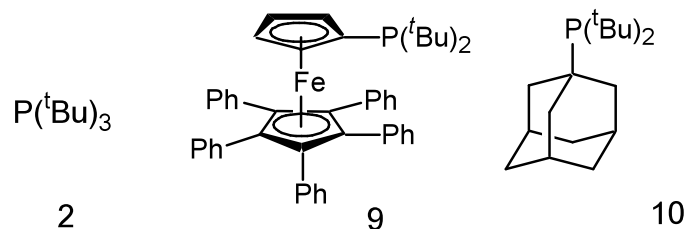
- Approach: Use of more sterically hindered ligands



Arylation of Malonates

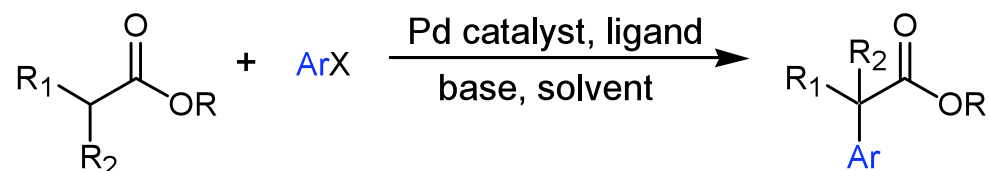


Entry	R ₁	X	Lig.	Conditions	Yield (%)
1	4-F ₃ C, OMe, CH ₃ CO	Br	2	70°C, NaH, THF	69-91
		Cl	9,10	100°C, K ₃ PO ₄ , toluene	81-90
2	4-F ₃ C, OMe, 4-Me ₂ N	Br	2	70°C, NaH, THF, 6h	85-90
		Cl	2		84-90



- Limitation: Few aryl groups such as pyridyl group can not be transferred

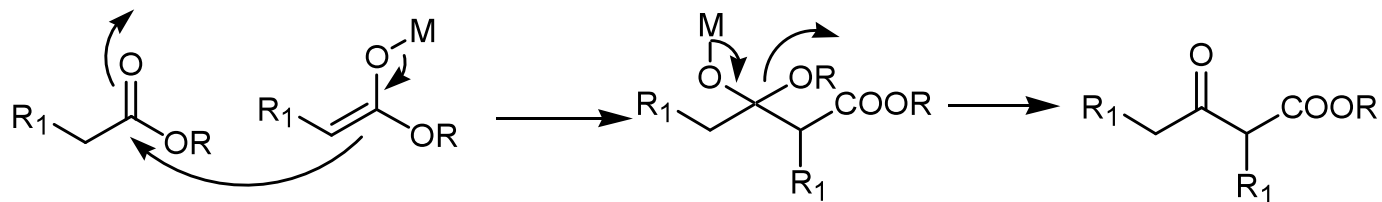
Arylation of Esters



- No regioselectivity issues to be considered

- Challenge: Lower reactivity of esters

Unstable under basic condition — Claisen reaction

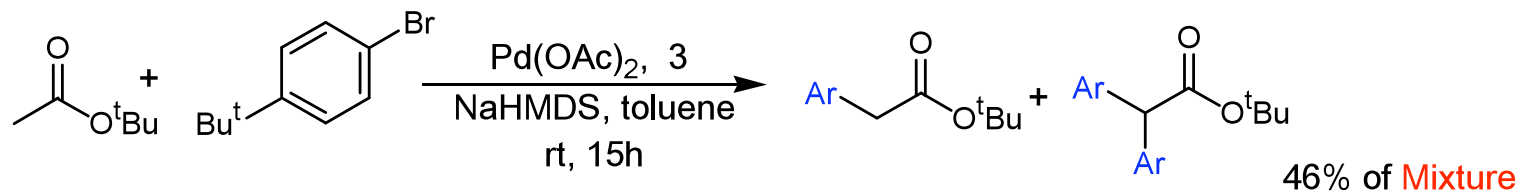


- Approach: Use of sterically hindered *tert*-butyl esters

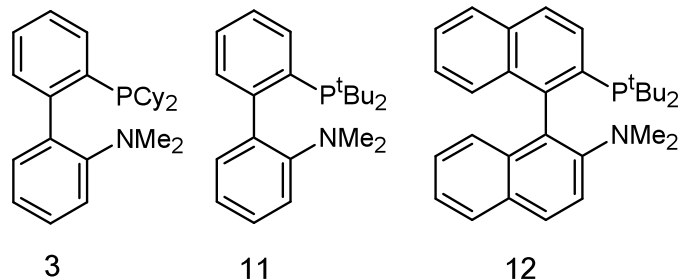
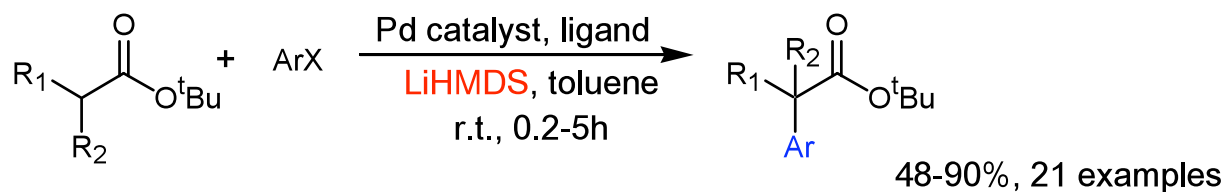


95-100% yield
Stable at room temperature

Promotion of Mono-Arylation Products of Esters

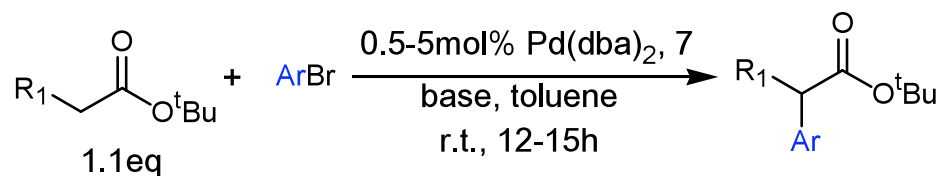


- Challenge: Double arylation of ester enolates
- Change base from NaHMDS to LiHMDS
Excessive enolates (2.3eq of *tert*-Butyl esters, 2.5eq of LiHMDS)



Promotion of Mono-Arylation Products of Esters

- Two-fold of base

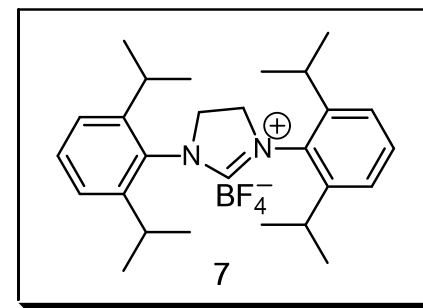


R₁ = H, **2.3eq** of LiHMDS

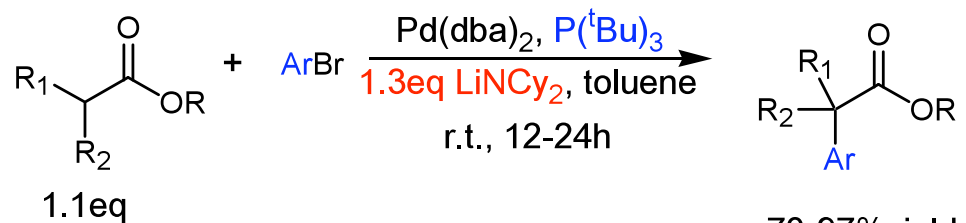
80-98% yield, 8 examples

R₁ = CH₃, **2.3eq** of NaHMDS

66-88% yield, 6 examples



- Use of stronger base



70-97% yield

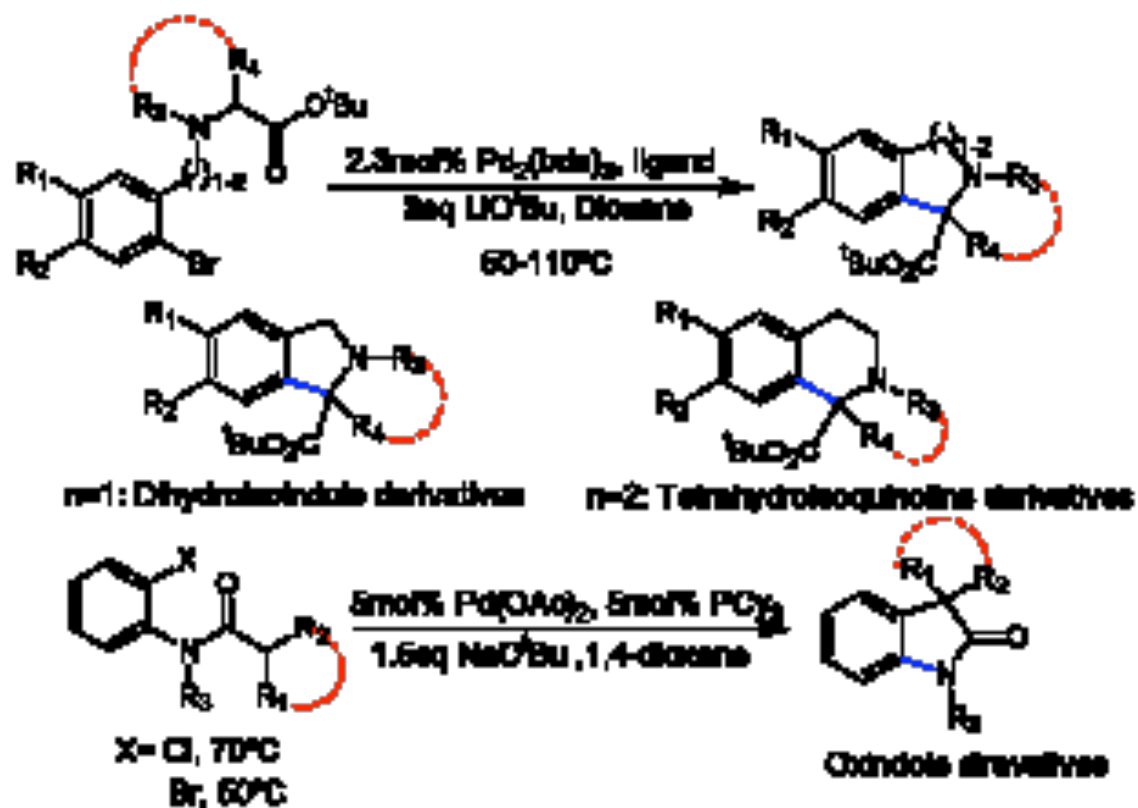
47 examples

Outline

- Introduction
 - Mechanism Study
 - Factors Influencing the Arylation of Ketone
 - Arylation Reactions of Other Stabilized Carbanions
 - **Applications**
 - ◆ Intramolecular Arylation Reaction
 - ◆ Asymmetric Arylation Reaction
 - Prospects
 - Conclusion
-

Intramolecular Arylation Reaction of Stabilized Anions

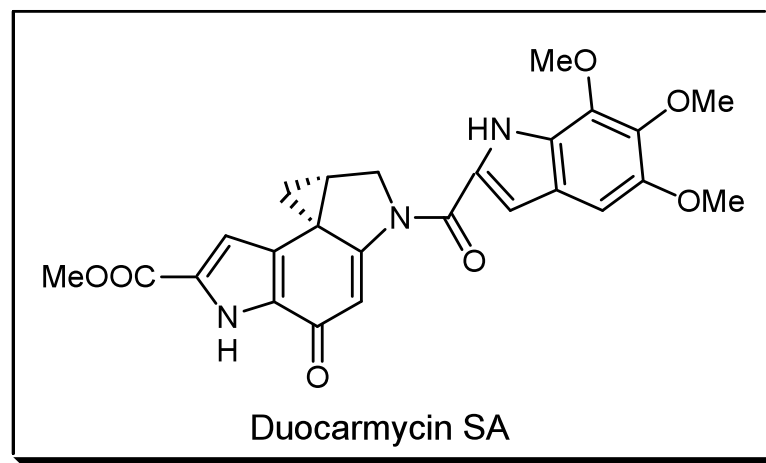
- Provide a simple way to construct many ring systems
- Represent a valuable synthetic building blocks for further reaction



Beare, Neil A.; Hartwig, J. F., *J. Org. Chem.*, 2001, 66, 3402

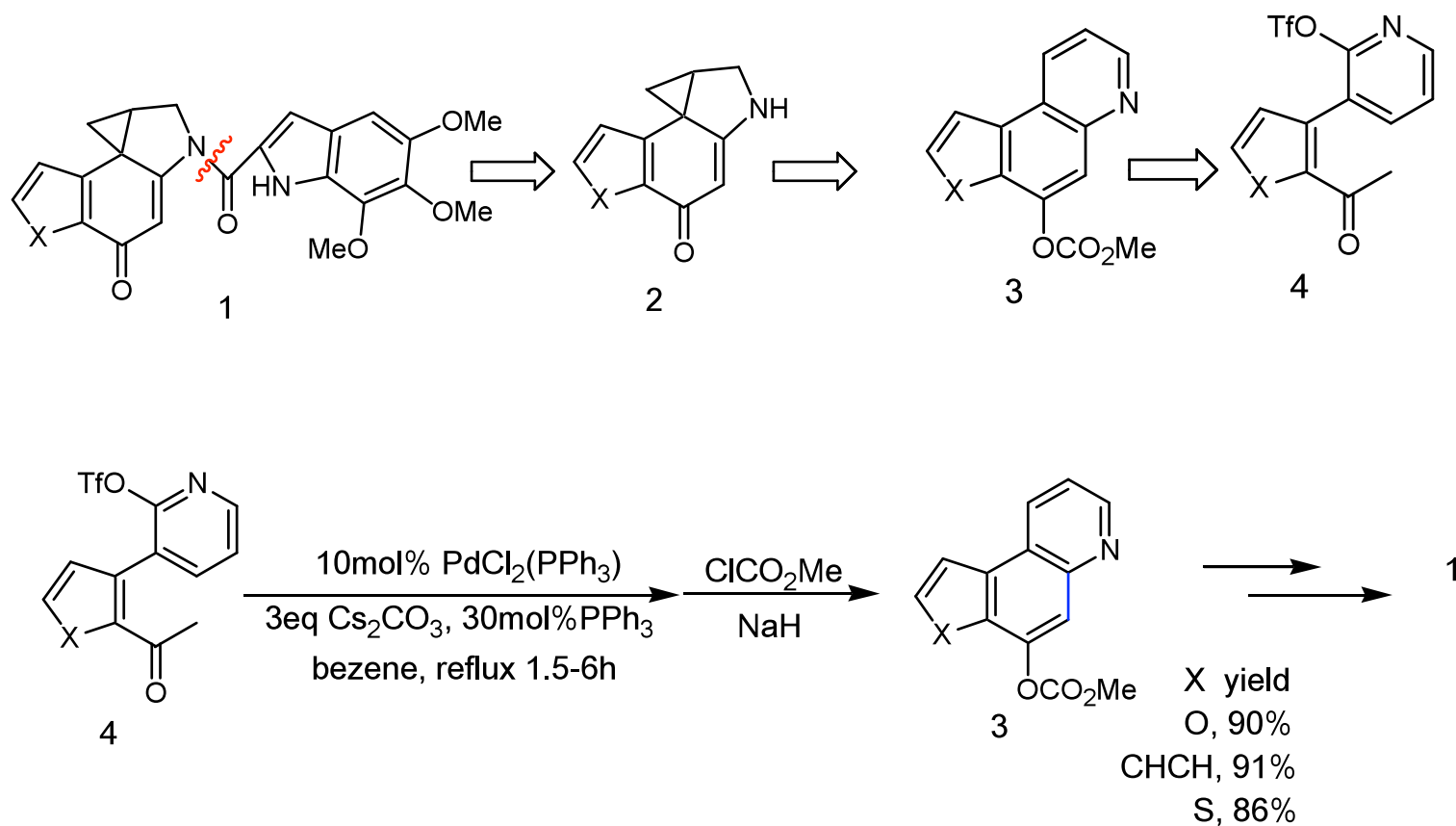
Gaertzen, Oliver and Buchwald, Stephen L. *J. Org. Chem.*, 2002, 67, 465

Synthesis of Analogs of Duocarmycin SA



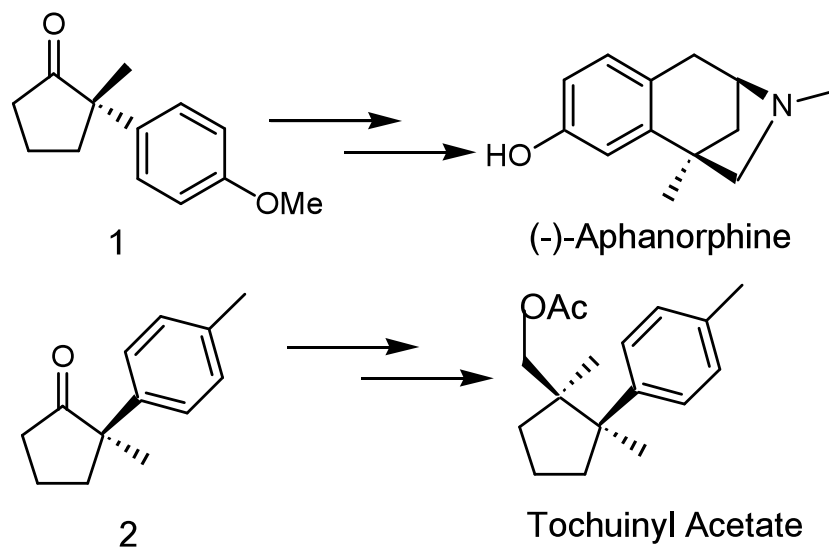
- Resource: isolated from streptomyces species in Japan.
- Bio-activities: extremely potent antitumor antibiotic

Synthesis of Analogs of Duocarmycin SA



Enantioselective Construction of Quaternary Centers

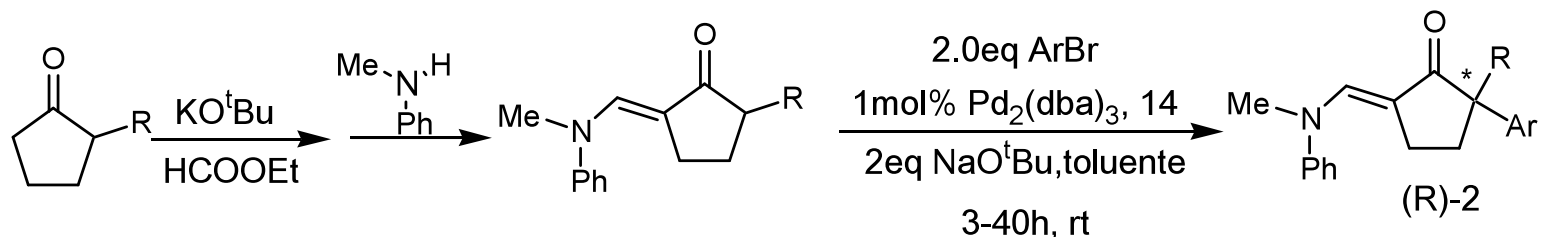
- New catalytic methods of formation of quaternary stereocenters
- Preparation of some important intermediates for natural product synthesis



Ahman, Jens; Wolfe, John, P.; Troutman, Malisa V.; Palucki, Michael; Buchwald, Stephen L.

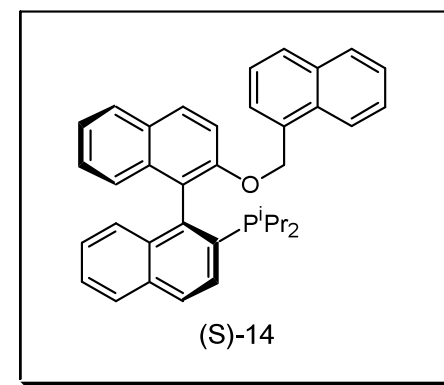
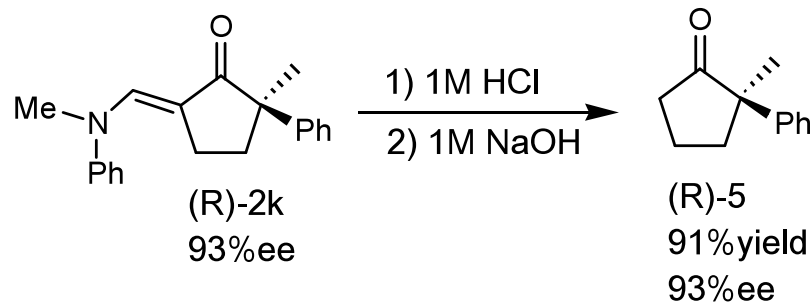
J. Am. Soc. Chem., 1998, 120, 1980

Enantioselective Construction of Quaternary Centers



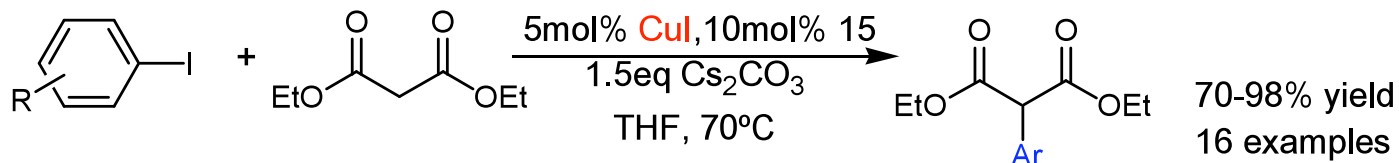
80-86% yield
88-94% ee
8 examples

- High enantioselectivity and yield
- Low catalysts loadings
- Mild conditions
- Not efficient for ortho-substituted aryl bromides



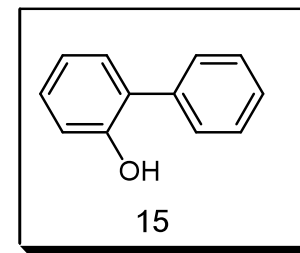
Prospects of Arylation Reactions of Stabilized Carbanions

- Arylation of malonates catalyzed by copper

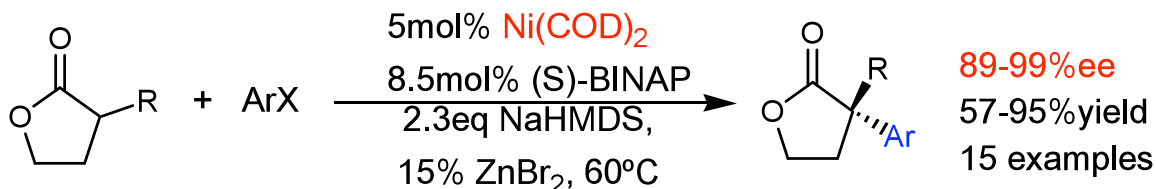


R = OMe, CF₃, NO₂, MeCO, CN
CO₂Et, OH, MeCONH, NH₂

- Cheap catalyst and ligand, excellent functional group tolerance
- Only aryl iodide is reactive



- Enantioselective arylation of γ -butyrolactones catalyzed by nickel



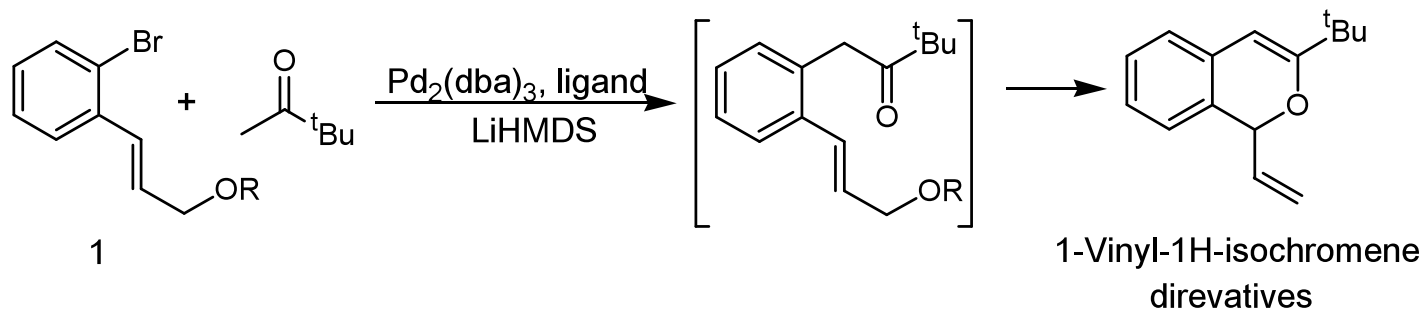
- High ee and good yield
- Not efficient for ortho-substituted aryl bromides

Hennessy, Edward; Buchwald, Stephen L.. *Org. Lett.*, 2002, 4, 269

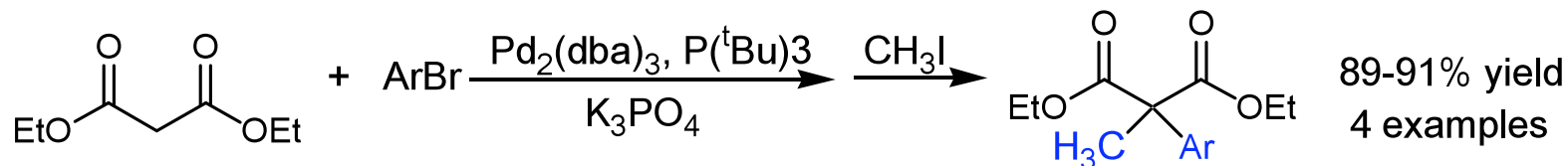
Spielvogel, Dirk J.; Buchwald, Stephen L.. *J. Am. Soc. Chem.*, 2002, 124, 3500

Tandem and One-pot Synthesis

- Tandem synthesis of 1-Vinyl-1H-isochromene derivatives



- One-pot preparation of diethyl 2-Aryl-2-methylmalonates



Conclusions

- Direct ketone arylation reaction is a general method to selectively install aryl group at α -position of ketones.
 - Ketone arylation reaction has been greatly extended to other stable carbanions
 - The intramolecular arylation reaction can furnish a number of heterocyclics.
 - Asymmetric arylation reactions have been established
 - Most recent work was briefly discussed. Their potential development is expected
-

Acknowledgement

Prof. Wulff

Prof. Borhan

Yana, Yu, Yiqian, Zhenjie, Gang, Zhiyi
and all those who helped me
