Professor Stephen L. Buchwald – This is your (research) life

Literature Review

Bobby Brooks
Dr Ed Anderson Group

21/06/13

Professor Buchwald – Academic history

- 1955 – Born in Bloomington, Indiana
- 1977 – Sc.B. Brown University
  - Worked a summer with Prof. Gilbert Stork at Columbia University
- 1982 – Ph.D. Harvard University: Studying the mechanism of phosphoryl transfer reactions in chemistry and biochemistry under Prof. Jeremy R. Knowles
- 1982 to 1984 – Myron A. Bantrell postdoctoral fellow at Caltech with Prof. Robert H. Grubbs: Studying titanocene methylenes as reagents in organic synthesis
- 1984 – Assistant Professor in Chemistry at MIT
- 1989 – Associate Professor in Chemistry
- 1993 – Professor in Chemistry
- 1997 – Camille Dreyfus Professor of Chemistry
- >350 papers and >50 patents

Professor Buchwald and Group – Awards

- **2000**
  - Award in Organometallic Chemistry from the American Chemical Society
  - Fellow of the American Academy of Arts and Sciences
- **2005**
  - Bristol-Myers Squibb Distinguished Achievement Award
  - CAS Science Spotlight Award
- **2006**
  - American Chemical Society's Award for Creative Work in Synthetic Organic Chemistry
  - Siegfried Medal Award in Chemical Methods which Impact Process Chemistry
- **2008**
  - Elected as a member of the National Academy of Science
- **2010**
  - Gustavus J. Esselen Award for Chemistry in the Public Interest
- **2013**
  - Arthur C. Cope Award from the American Chemical Society
- Harold Edgerton Faculty Achievement Award of MIT
- Arthur C. Cope Scholar Award
- MERIT award from the National Institutes of Health
- Associate editor of Advanced Synthesis and Catalysis and Chemical Science

Presentation Summary

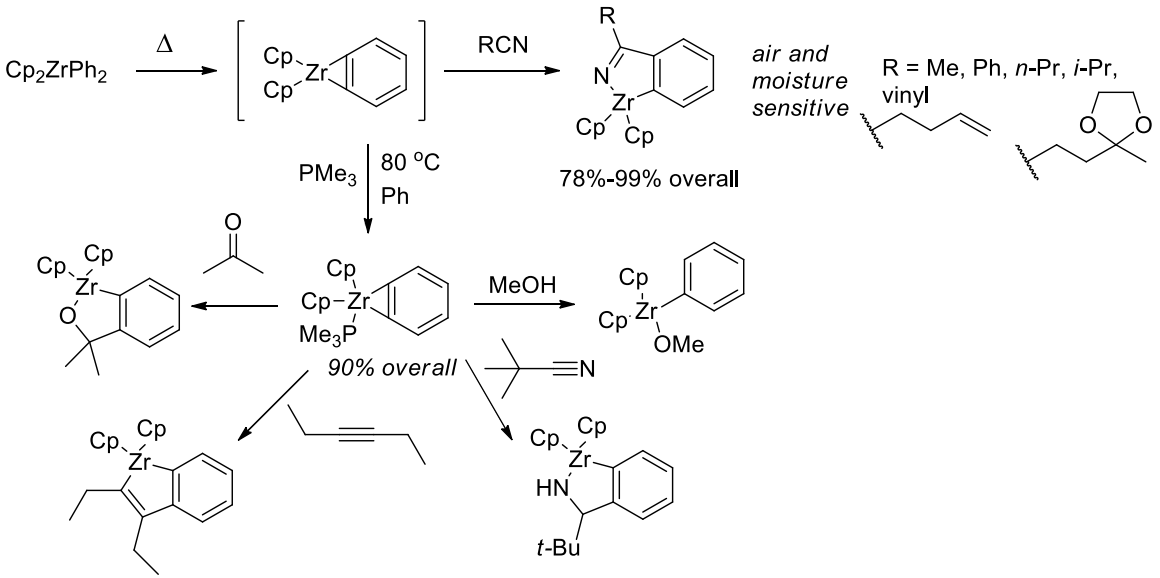
- Zirconocene chemistry
- Titanocene chemistry
- Palladium cross coupling chemistry
- Recent work
- Summary

Presentation Summary

- **Zirconocene chemistry**
  - Complexes with benzyne
  - Complexes with cyclohexyne
  - Syntheses and functionalisations
  - Case studies in organic synthesis
  - Quirks
- Titanocene chemistry
- Palladium cross coupling chemistry
- Recent work
- Summary

Zirconocenes

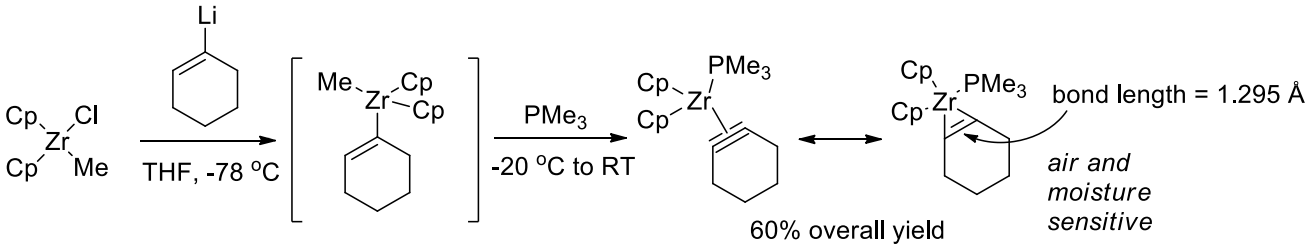
- Transition metals have the ability to stabilise high energy organic species
- Also make them more susceptible to attack by a variety of reagents
- Followed on from Erker's work[1] with zirconocene complex of benzyne, interested in feasibility of coupling other functional groups
- Initially nitriles were the only group that showed any success[2]



1. Erker, G.; Kropp, K. *J. Am. Chem. Soc.* **1979**, *101*, 3659
2. Buchwald, S. L.; Sayers, A.; watson, B. T.; Dewan, J. C. *Tet. Lett.* **1987**, *28*, 3245

Zirconocene: Cycloalkyne

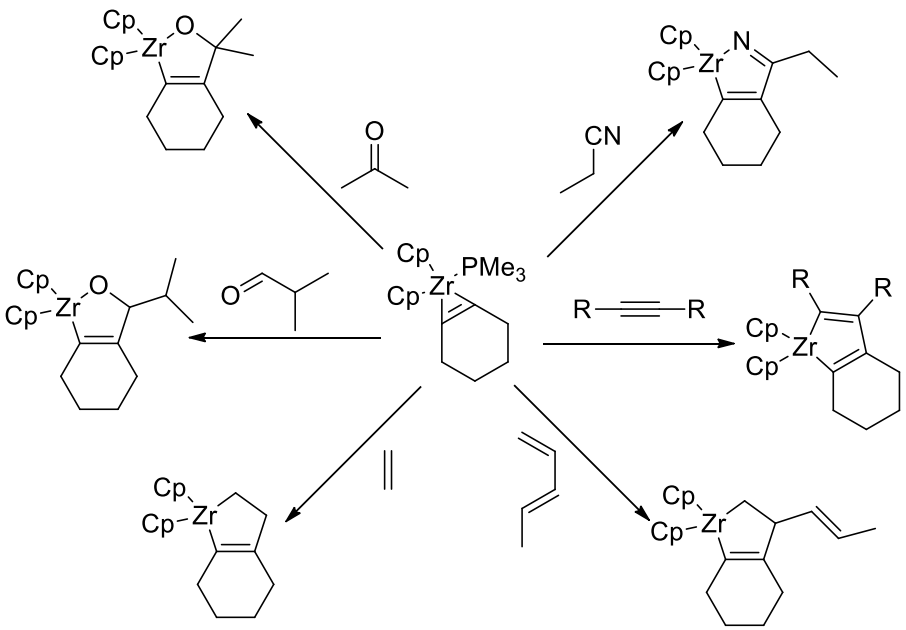
- Difficult to isolate cycloalkynes as they are too strained
- Cycloheptyne had previously been trapped out with bis(triphenylphosphine)platinum[1]
- Reported in 1986,[2] the first example of transition metal-small ring cycloalkyne complexes – this cyclohexyne example isolated as the trimethyl phosphine adduct



1. Krebs, A.; Wilke, J. *Top. Curr. Chem.* **1983**, *109*, 189.
2. Buchwald, S. L.; Lum, R. T.; Dewan, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 7441

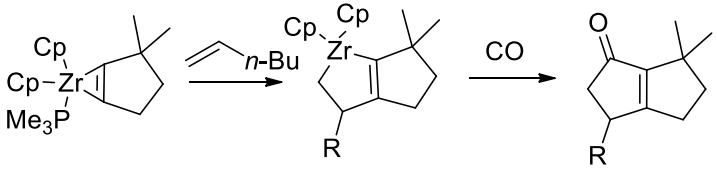
Zirconocene chemistry

- Discovered that the product could be converted into a wide range of substrates

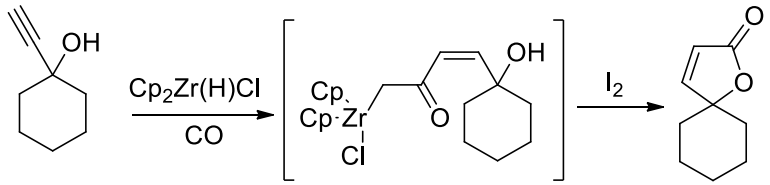


Zirconocene

- Cyclopentenone synthesis[1]



- Butenolide synthesis[2]



- Functionalisation of cyclic olefins[3]

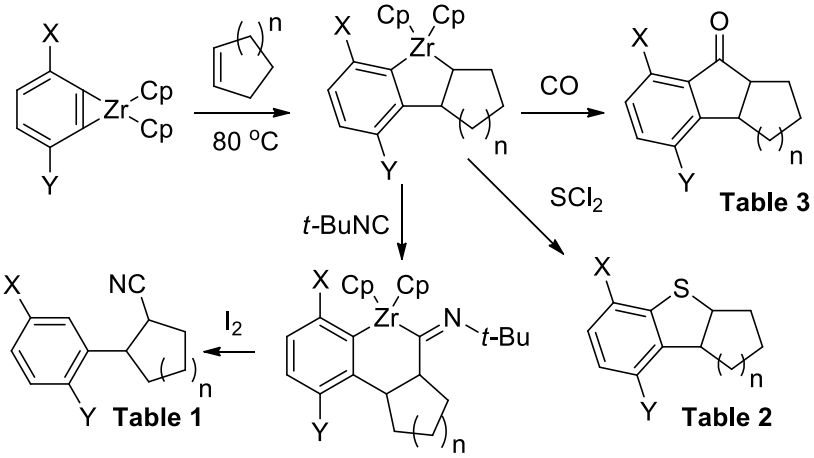


Table 1

aryllithium	*n*	product (yield, %)
X = OMe, Y = H	1	5 (41)
X = OMe, Y = H	3	9 (41)
X = OMe, Y = OMe	1	10 (41)

Table 2

aryllithium	*n*	product (yield, %)
X = OMe, Y = H	1	11 (47)
X = OMe, Y = OMe	1	12 (40)
X = OMe, Y = H	3	7 (56)
X = $N(Me)_2$, Y = H	1	13 (25)

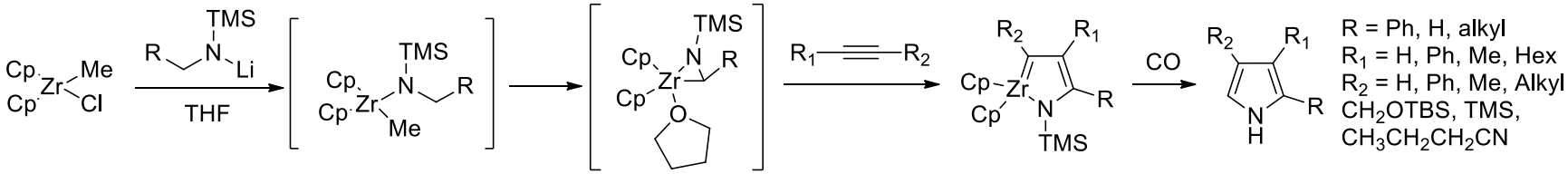
Table 3

aryllithium	*n*	product (yield, %)
X = OMe, Y = H	1	14 (52)
X = OMe, Y = OMe	1	15 (47)
X = Me, Y = H	3	16 (48)
X = OMe, Y = H	3	8 (50)
X = $N(Me)_2$, Y = H	1	17 (41)
X = Me, Y = H	1	18 (28)

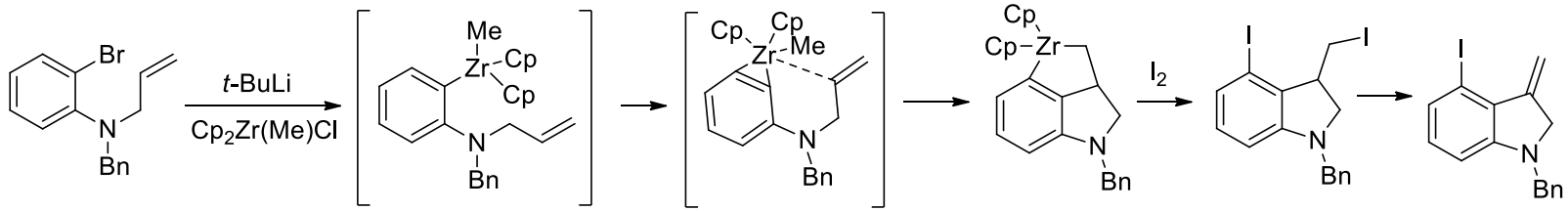
1. Buchwald, S. L.; Lum, R. T.; Fisher, R. A.; Davis, W. M. *J. Am. Chem. Soc.* **1989**, *111*, 9113
2. Buchwald, S. L.; Fan, Q.; King, S. M. *Tet. Lett.* **1988**, *29*, 3445
3. Cuny, G. D.; Gutierrez, A.; Buchwald, S. L. *Organometallics.* **1991**, *10*, 537

Zirconocene

- Extended this chemistry to a number of systems
  - Pyrrole Synthesis[1]

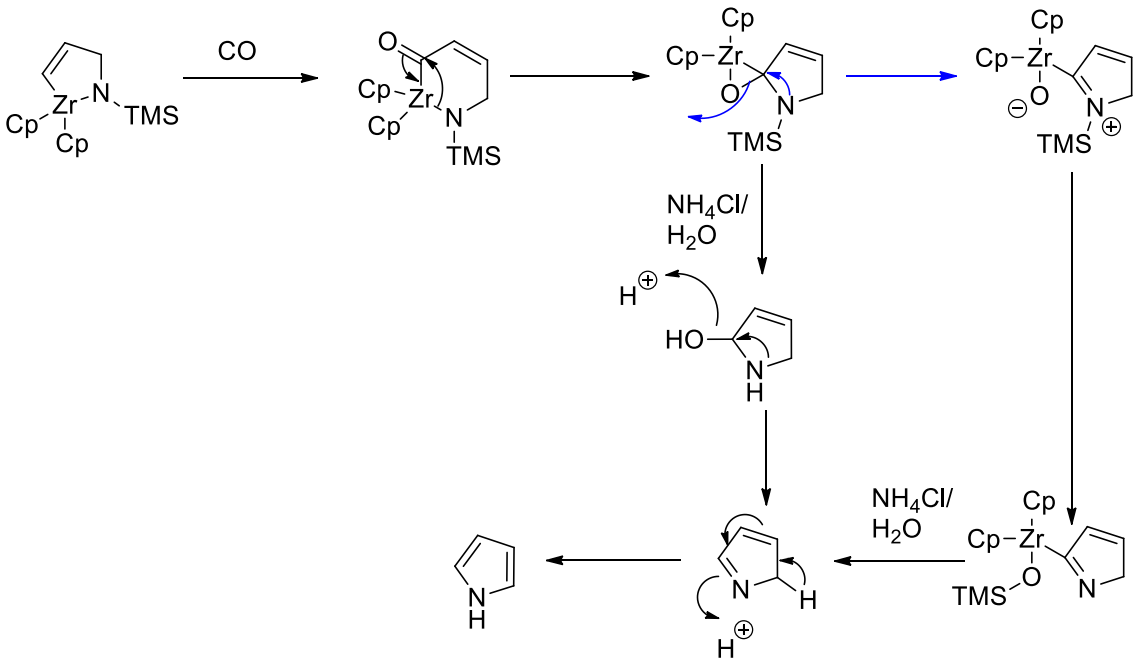


  - Indole synthesis[2]



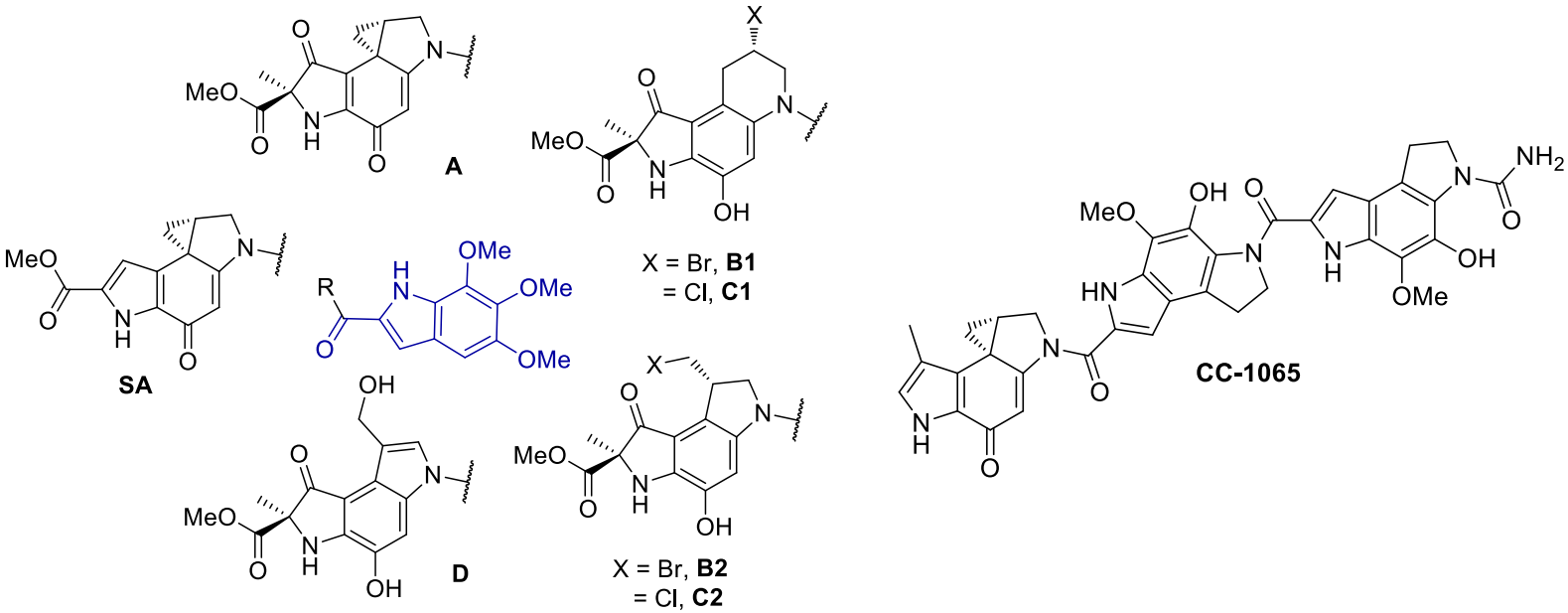
1. Buchwald, S. L.; Wannamaker, M. W.; Watson, B. T. *J. Am. Chem. Soc.* **1989**, *111*, 776
2. Tidwell, J. H.; Senn, D. R.; Buchwald, S. L. *J. Am. Chem. Soc,* **1991**, *113*, 4685; Tidwell, J. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11797

Zirconocene: pyrrole synthesis



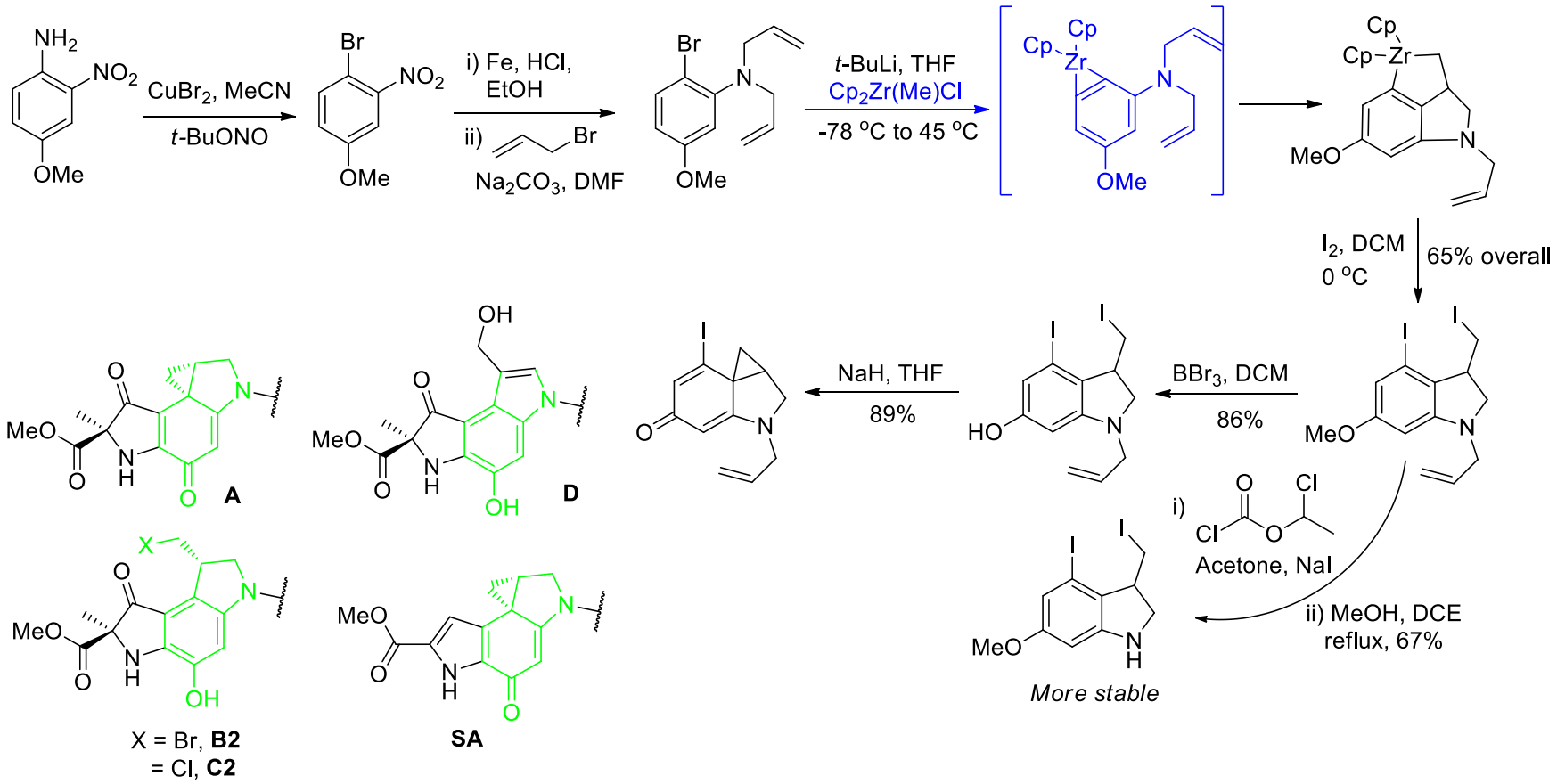
Organic synthesis case study: Duocarmycin pharmacore

- Duocarmycin family isolated in 1988 by Nakano and co-workers[1]
- Show potent antitumour properties[2]
- Buchwald proposed a methodology utilising zirconocene chemistry[3]



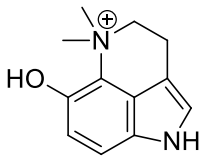
1. Takahashi, I.; Takahashi, K.; Ichimura, M.; Morimoto, M.; Asano, K.; Kawamoto, I.; Tomita, F.; Nakano, H. *J. Antibio.* **1988**, *41*, 3728.
2. Boger, D. L. *Chemtracts: Organic Chemistry*. **1991**, *4*, 329.
3. Tidwell, J. H.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 6380.

Use in organic synthesis: Duocarmycin pharmacore

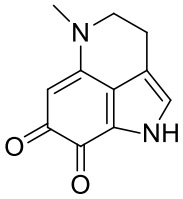


Use in organic synthesis: Tetrahydropyrroloquinolines

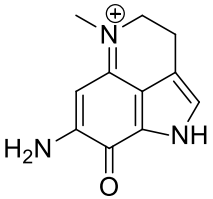
- Important motif in many natural products such as



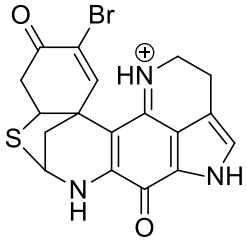
Dehydrobufotenine 1



Damirone B



Makaluvamine C

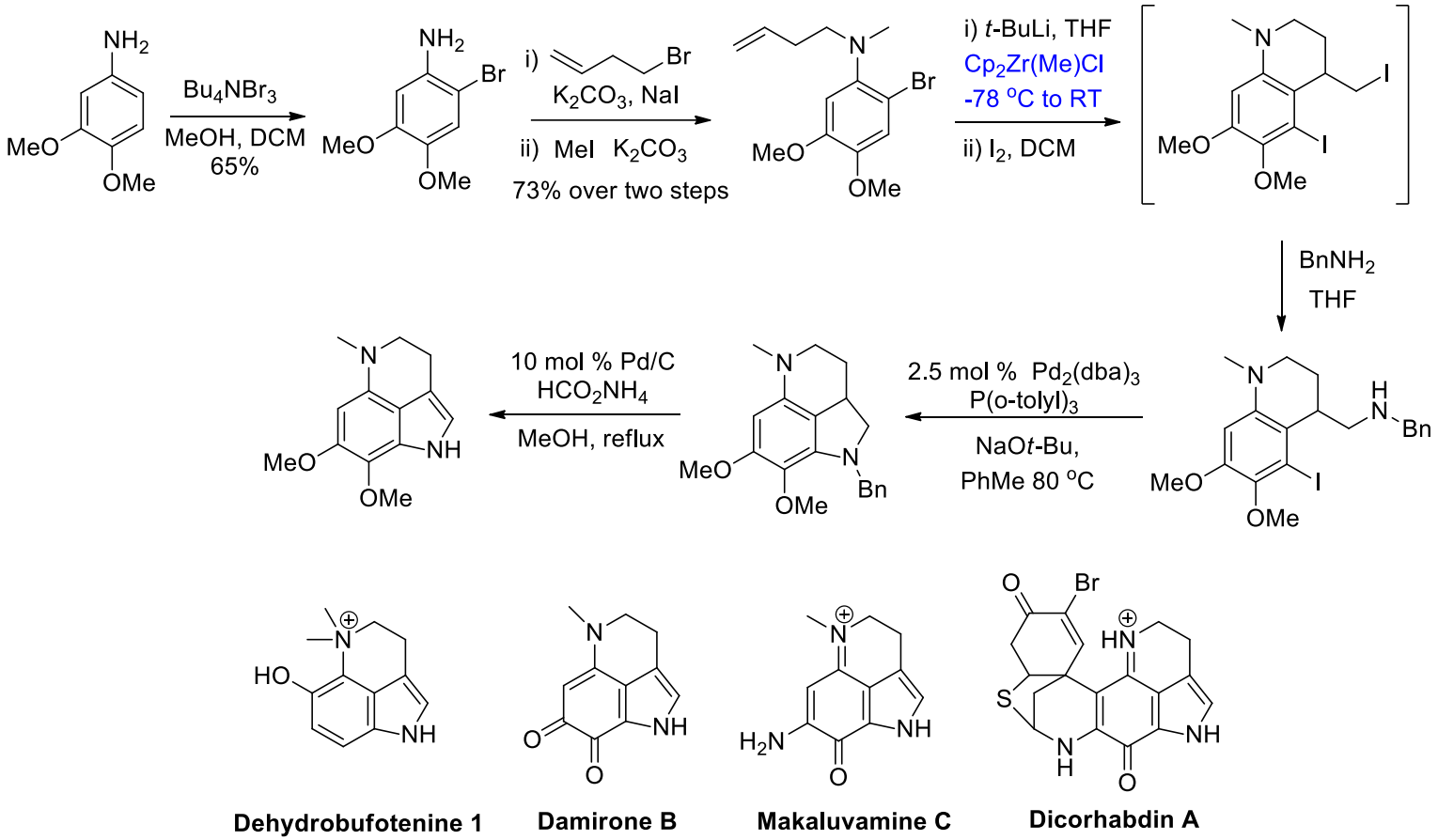


Dicorhabdin A

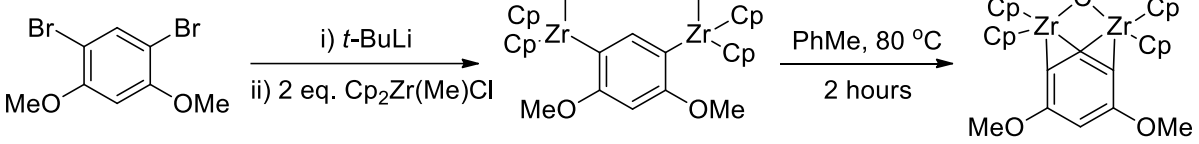
- Previously received attention due to some (such as the makaluvamines[3]) exhibiting *in vitro* cytotoxicity against tumour cell lines

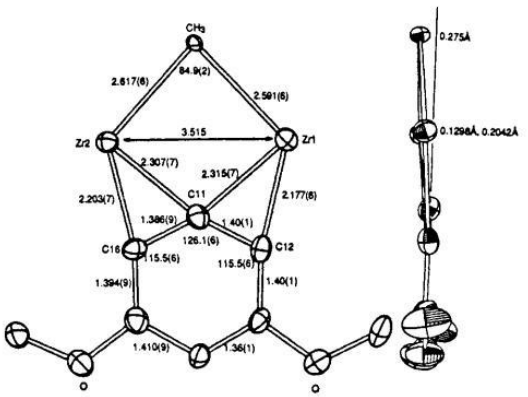
1. Marki, F.; Robertson, A. V.; Witkop, B. J. *J. Am. Chem. Soc.* **1961**, *83*, 3341
2. Stierle, D. B.; Faulkner, D. J. *J. Nat. Prod*. **1991**, *54*, 1131.
3. Radisky, D. C.; Radisky, E. S.; Barrows, L. R.; Copp, B. R.; Kramer, R. A.; Ireland, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 1632.
4. Perry, N. B.; Blunt, J. W.; McCombs, J. D.; Munro, M. H. G. *J. Org. Chem.* **1986**, *51*, 5476. Perry, N. B.; Blunt, J. W.; Munro, M. H. G. *Tet.* **1988**, *44*, 1727. Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Higa, T.; Sakai, R. *J. Org. Chem.* **1988**, *53*, 4127.

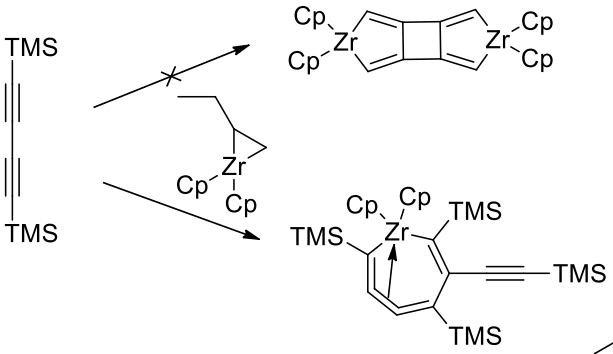
Use in organic synthesis: Tetrahydropyrroloquinolines

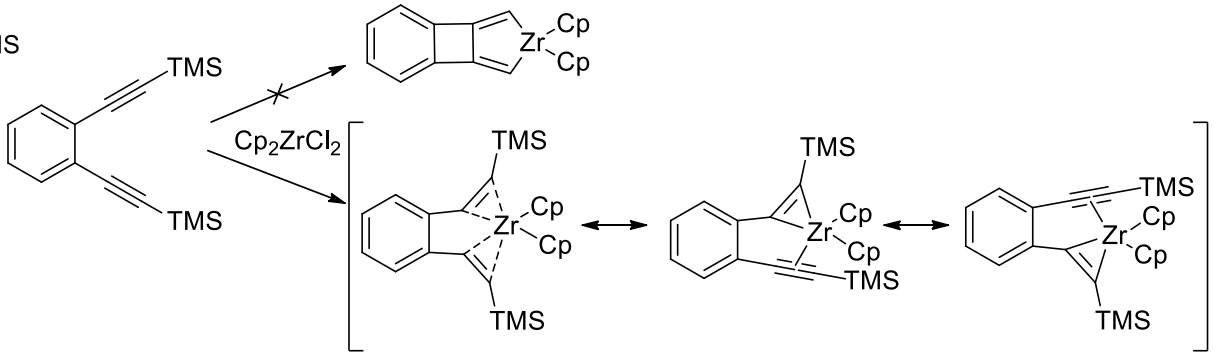


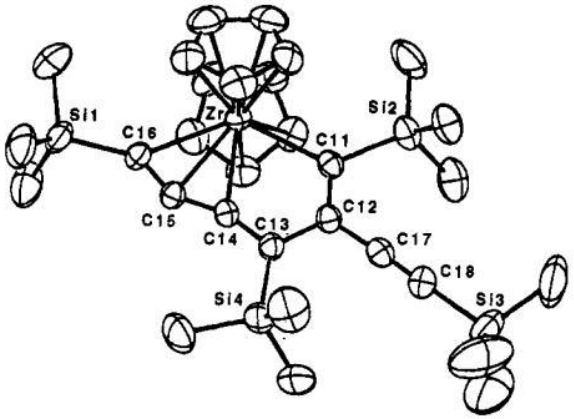
Zirconocenes: Quirky structures











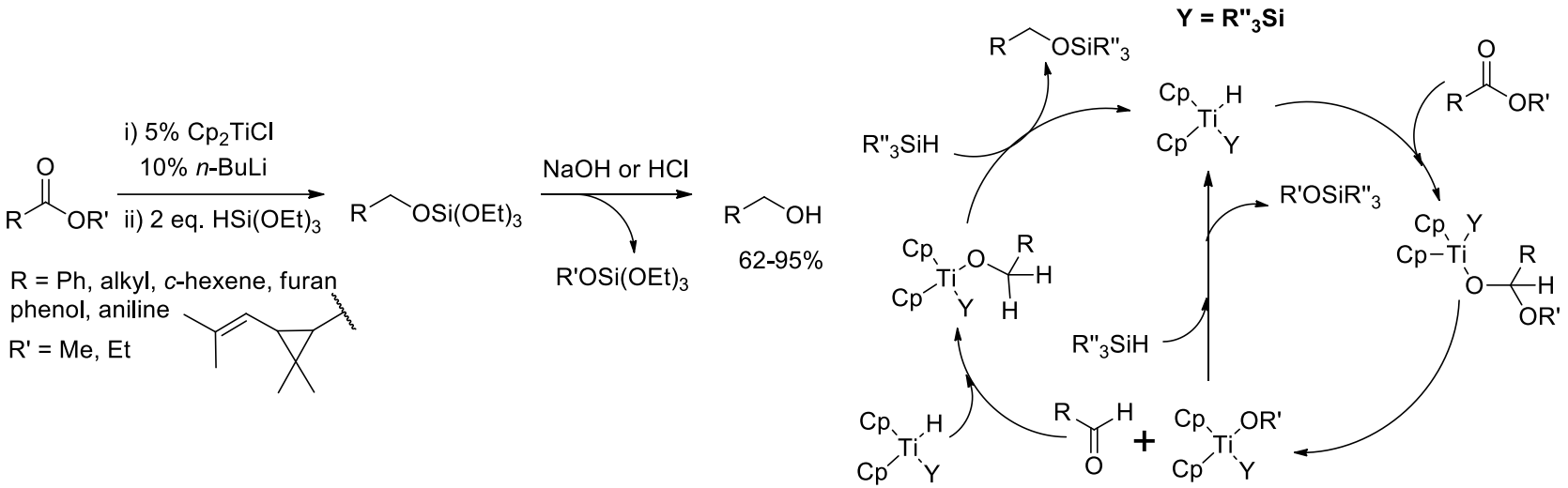
1. Buchwald, S. L.; Lucas, E. A.; Davis, W. M. *J. Am. Chem. Soc.* **1989**, *111*, 397.
2. Hsu, D. P.; Davis, W. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993,** *115*, 10394
3. Warner, B. P.; Davis, W. M.; Buchwald, S. L. *J. Am. Chem. Soc*. **1994**, *116*, 5471

Presentation Summary

- Zirconocene chemistry
- **Titanocene chemistry**
  - Hydrogenations
  - Cycloisomerisations and cyclisations
    - Pauson-Khand
- Palladium cross coupling chemistry
- Recent work
- Summary

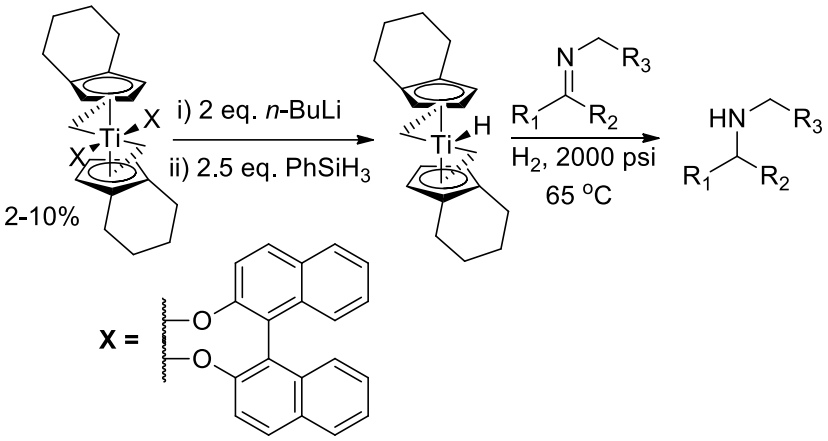
Titanocenes: Hydrogenation

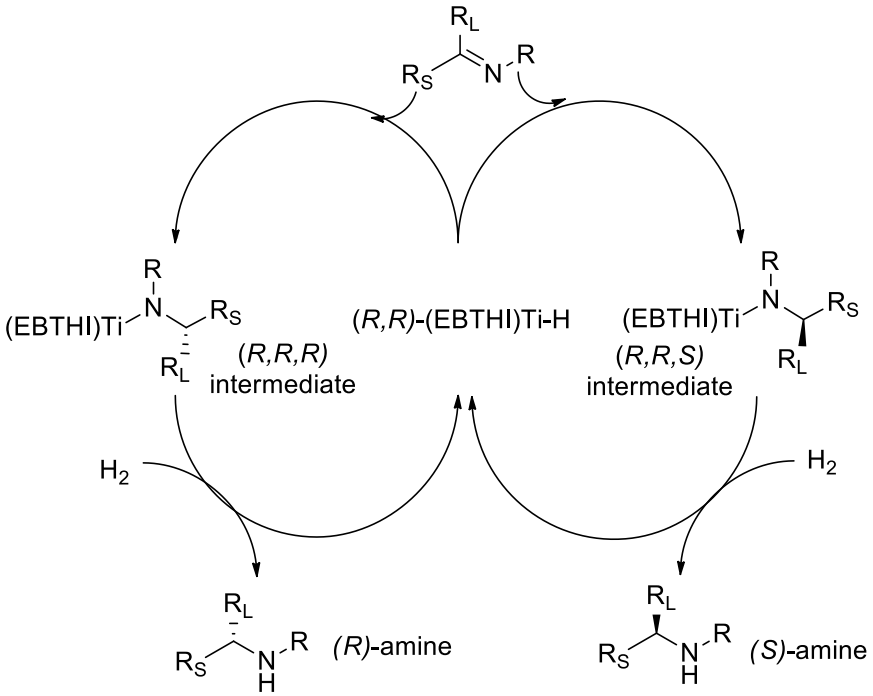
- Catalytic reduction of esters to alcohols (racemic)



Berk, S. C.; Kreutzer, K. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **1991**, *113*, 5093; Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 3751

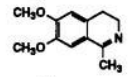
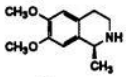
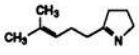
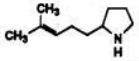
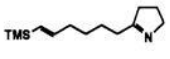
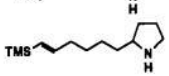
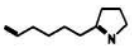
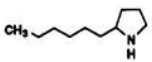
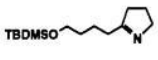
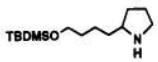
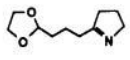
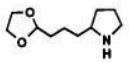
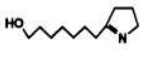
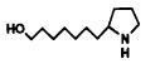
Titanocenes: Imine hydrogenation

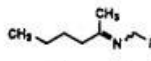
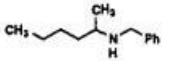
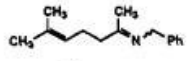
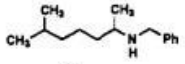
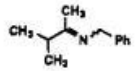
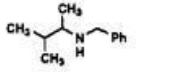
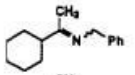
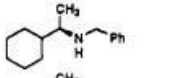
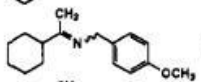
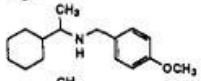
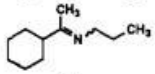
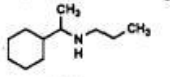
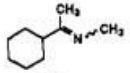
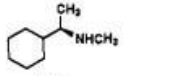
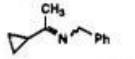
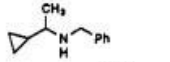
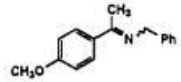
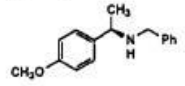




Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 7562; Willoughby, C. A.; Buchwald, S. L. *J. Org. Chem.* **1993**, *58*, 7627; Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc* **1994**, *116*, 8952; Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **1994**, *116*, 11703.

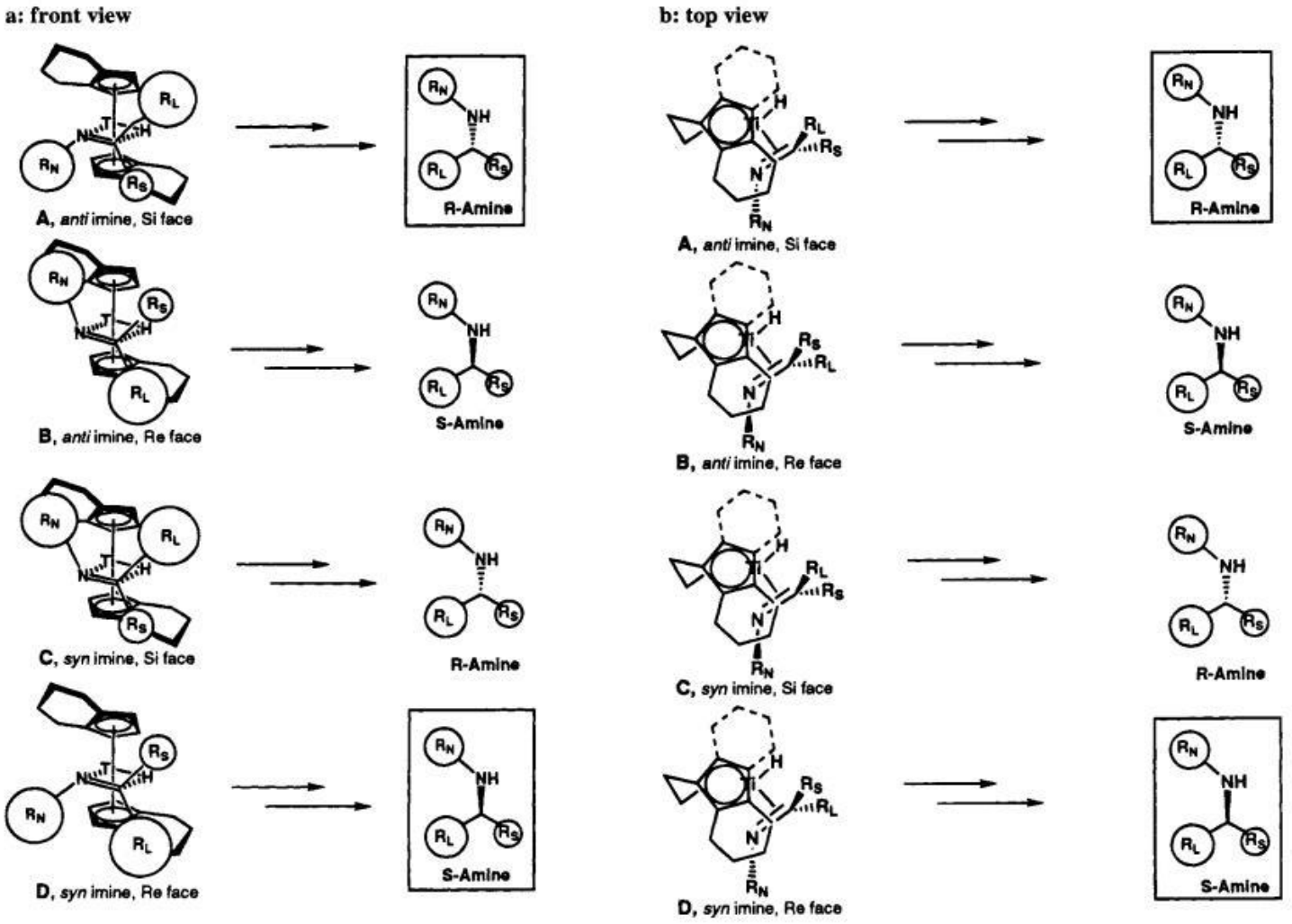
Titanocenes: Imine hydrogenation

entry	imine	amine	time (h)	pressure (psig)	T (°C)	yield (%)	ee (%)
1			24	500	21	86	99
			7	80	65	84	99
			42	80	65	83	99[b]
			8	80	65	80	99[c]
2			24	500	65	78	98
3			24	500	45	71	98
			30	80	65	74	97
4			50	80	65	79	95
5			24	500	23	83	99
			6	80	65	72	99
6			23	80	50	79	99
7			27	80	50	73[d]	99
8			23	80	45	72	99
9			10	80	65	82	99
10			16	80	65	82	99
11			8	80[e]	65	84	99

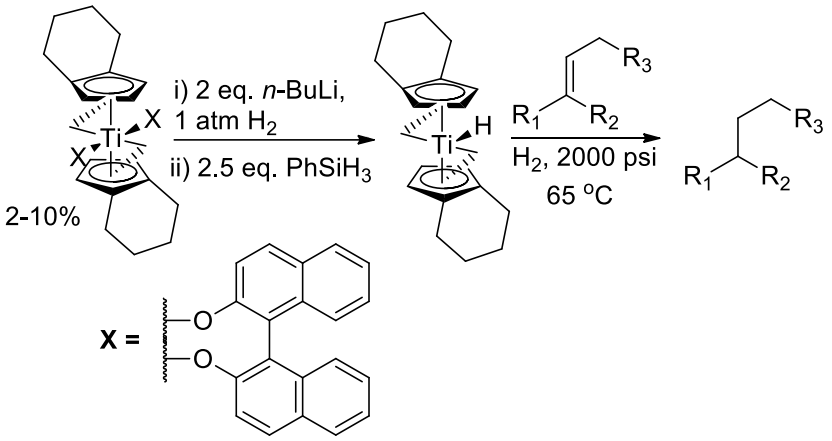
Entry	Imine	(anti / syn)	Amine	Pressure (psig)	Yield (%)	ee (%)	(±)
1		(3.3:1)		2000	68	58[b]	(-)
2		(3:1)		2000	64	62[b]	(-)
3		(13:1)		2000	66	76[b]	(-)
4		(11:1)		2000	93	76	(-)
				500	85	43	(-)
5		(14:1)		2000	92	78	(-)
				500	81	62	(-)
6		(9:1)		2000	70	79[c]	(-)
				80	65	4	(+)
7		(11:1)		500	85	92	(-)
				80	62	92	(-)
8		(7.5:1)		2000	91	61	(-)
9		(17:1)		2000	86	86	(+)
10		(17:1)		2000	81	77[d]	(+)
				2000	93	85[e]	(+)
11		(10:1)		2000	70	53	(+)
12		(44:1)		2000	82	70	(+)

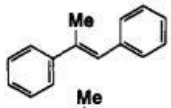
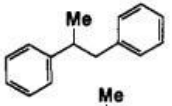
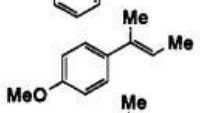
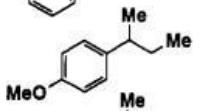
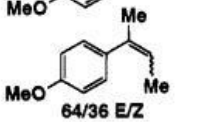
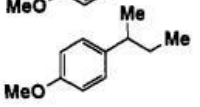
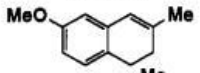
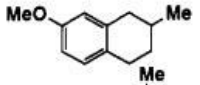
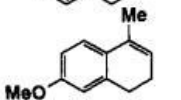
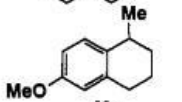
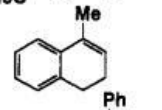
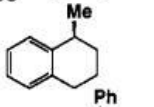
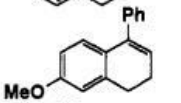
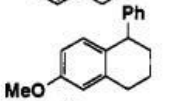
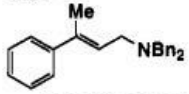
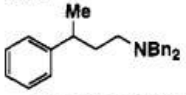
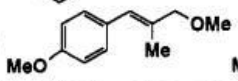
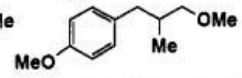
Titanocenes: Imine hydrogenation

Rationale for enantioselectivity with an *(R,R)* catalyst



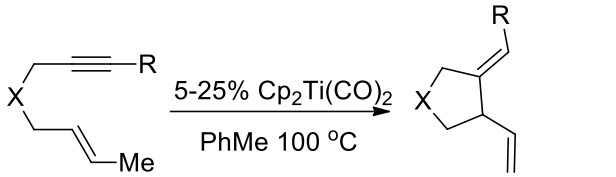
Titanocenes: Hydrogenation of unfunctionalised trisubstituted alkenes



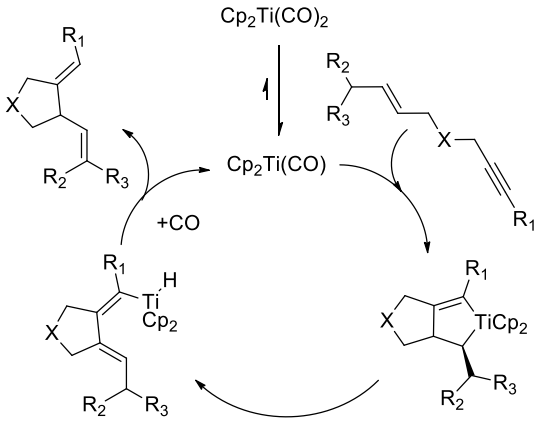
Entry	Starting Material	Product	ee (%)	Time (h)	Yield (%)
1			>99[c] >99[d] >99	48[e] 9 14[f]	91 94 80
2			95[d]	48	79
3	 64/36 E/Z		31	146	80
4[b]			92	44	77
5			93	132[g]	70
6			83[h]	184	70
7			83	169[i]	87% Conversion
8			95	43	75
9			94 93	48	86 80

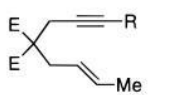
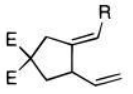
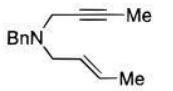
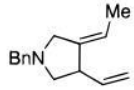
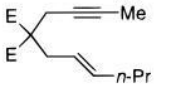
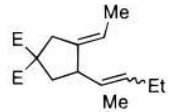
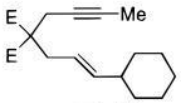
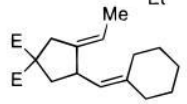
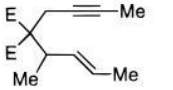
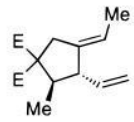
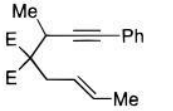
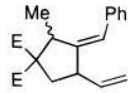
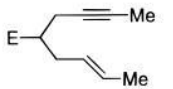
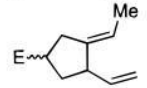
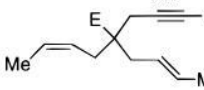
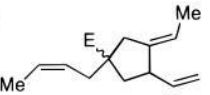
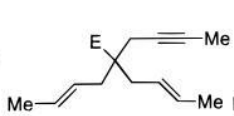
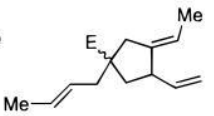
Broene, R. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12569

Titanocene: Enyne Cycloisomerisations



X = $(EtO_2C)_2C$, R = Me, R_1 = H, 54%
X = $(t\text{-}BuO_2C)_2C$, R = Me, R_1 = H, 44%
X = $(CO_2Et)_2$, R = Me, R_1 = Me, N.R.

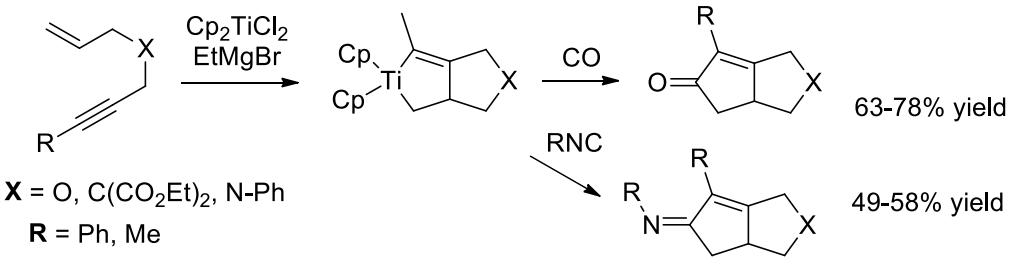


Entry	Substrate[a]	Product	Mol % (1)[b]	Yield (%)[16] (isomer ratio)
1			R = Me 10[c]	97
2			R = *n*-Pr 10[c]	82
			5	82
3			R = Ph 10	79
4			5[c]	85
5			15[c]	87 (1 : 3.5)
6			25	79
7			10	89 (1 isomer)
8			20[c]	85 (1 : 1.3)
9			10	87 (1 : 1)
10			5	88 (1 : 1)
11			5	85 (1 : 1)

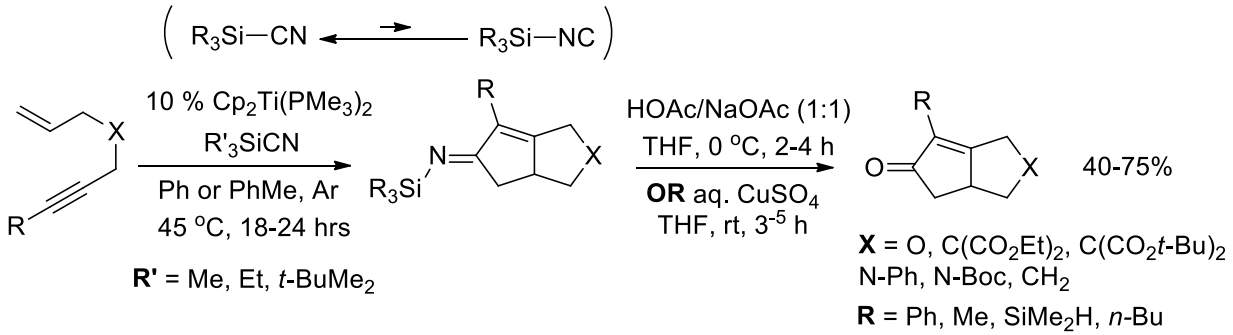
Sturla, S. J.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 1976

Titanocene: Enyne cyclisation

- Initial cyclisations with practical titanocene reagent[1]

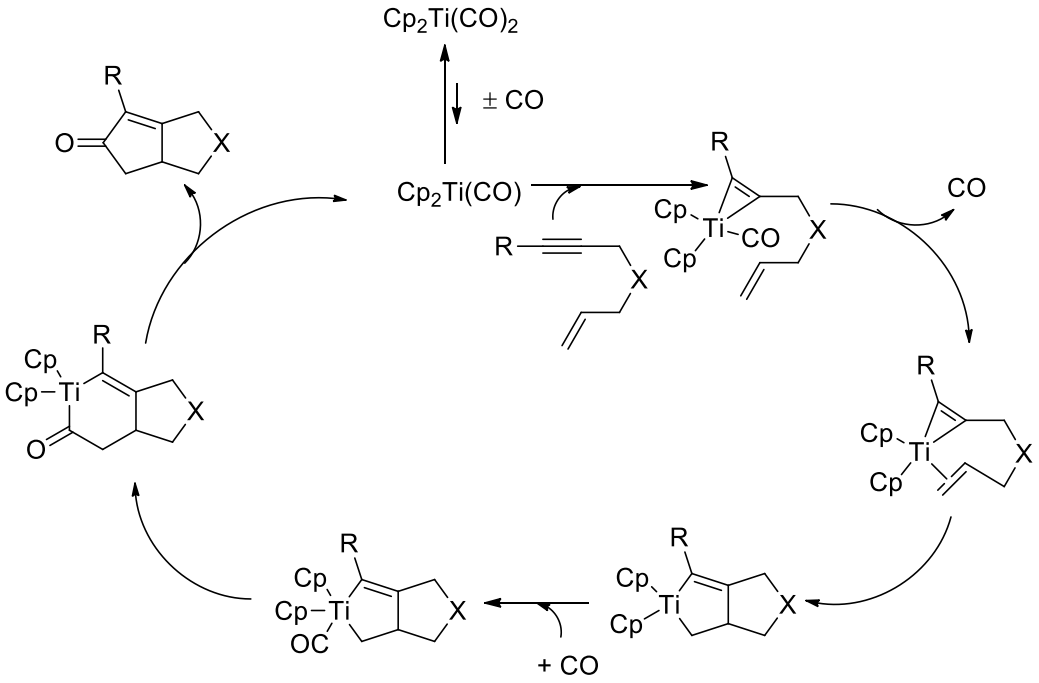


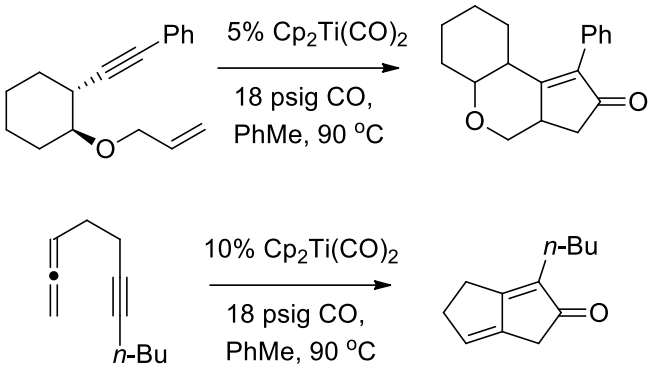
- Found that the cyanide would react with the titanocene, utilised a silyl-cyanide that was less reactive towards the catalyst[2]



1. Grossman, R. B.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 5803; Hicks, F. A.; Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 2713; Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 9450; Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 5881.
2. Berk, S. C.; Grossman, R. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 4912; Berk, S. C.; Grossman, R. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, 8593.

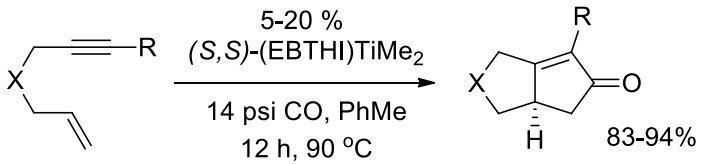
Titanocene: Enyne cyclisation

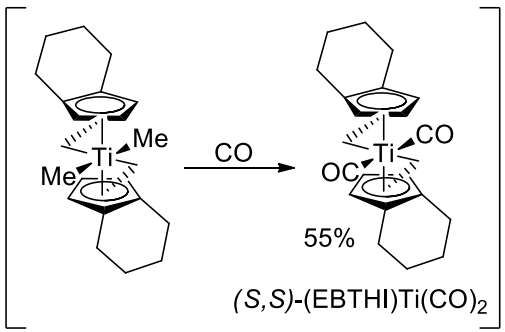


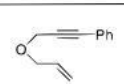
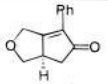
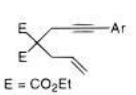
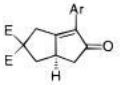
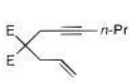
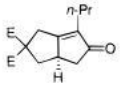
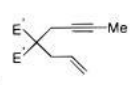
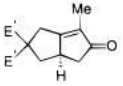
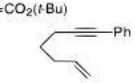
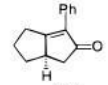
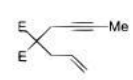
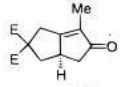
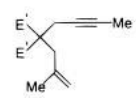
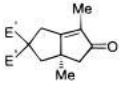
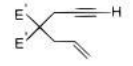
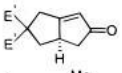
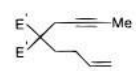
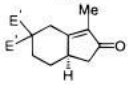


Titanocene mediated asymmetric Pauson-Khand

- A continuation from the previous work is the analysis of a Pauson-Khand type cycloisomerisation





Entry	Substrate	Product	Mol% (S,S) Cat	ee (%)	Yield (%)
1			20	96	85
			2 Ar = Ph, 7.5	94	92
			3 Ar = *p*-MeOC$_6$H$_4$, 7.5	92	89
2 - 6			4 Ar = *p*-ClC$_6$H$_4$, 10	90	82
			5 Ar = *p*EC$_6$H$_4$, 10	87	84
			6 Ar = *p*CF$_3$C$_6$H$_4$, 10	93	88
7			5	89	94
8			5	89	88
9			20	87	70
10			5	87	90
11			20	72	90
12			20	50	87
13			20	47	77

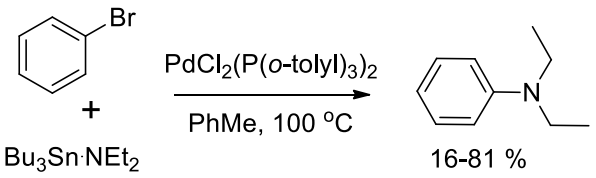
Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **1996**, *118*, 11688.; Sturla, S. J.; Buchwald, S. L. *J. Org. Chem*. **1999**, *64*, 5547; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **1999**, *121*, 7026

Presentation Summary

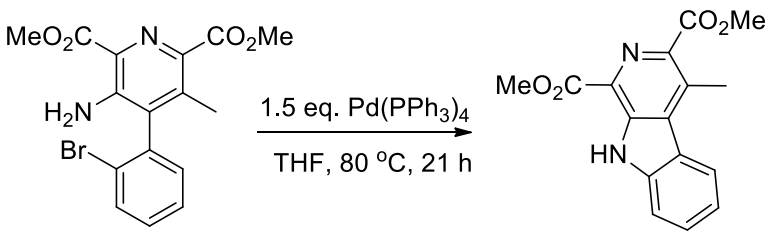
- Zirconocene chemistry
- Titanocene chemistry
- **Palladium cross coupling chemistry**
  - *C-N bond formation (Buchwald-Hartwig amination)*
  - C-O bond formation
  - C-C bond formation
- Recent work
- Summary

Previous Pd-mediated aminations

- First example – Migita[1]



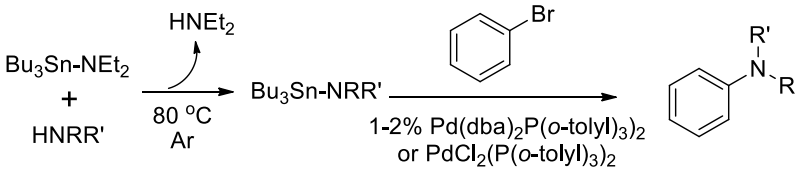
- Boger and Panek also showed C-N bond formation in their synthesis of Lavendamycin[2]



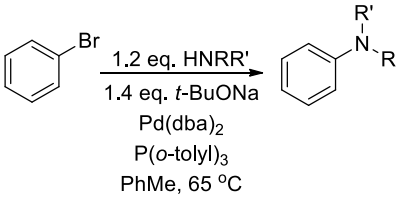
1. Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Let.* **1983**, *12*, 927
2. Boger, D. L.; Panek, J. S. *Tet. Lett.* **1984**, *25*, 3175
3. Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc*. **1994**, *116*, 5969

Pd cross coupling: C-N bond formation

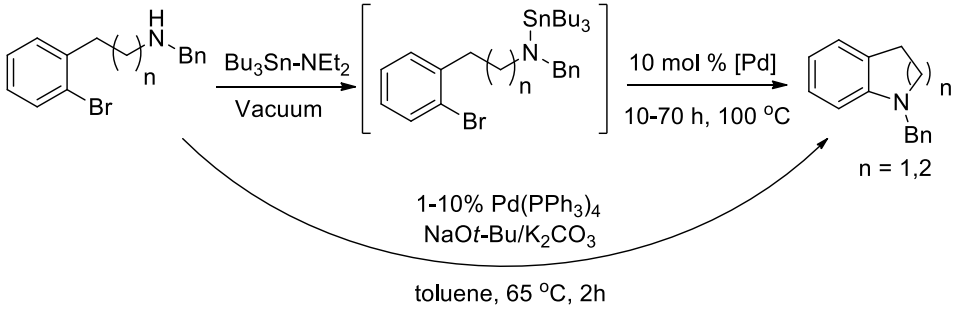
- Buchwald's initial work:[1]

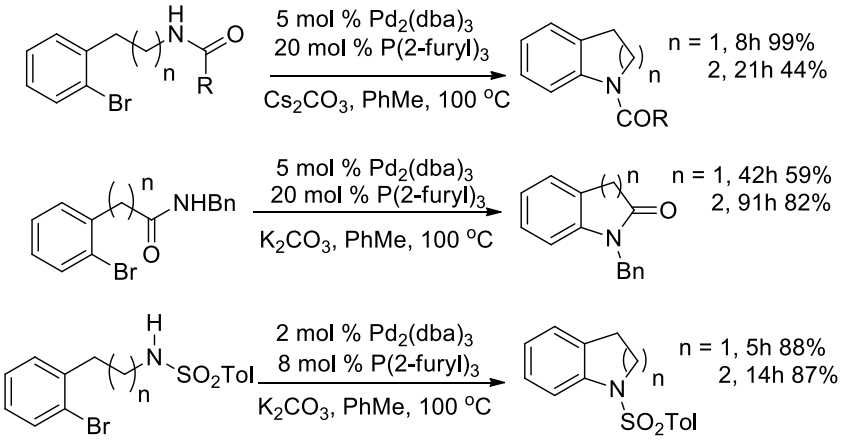


- Tin free amination:[2]



- Intermolecular aminohalide cyclisation[3]





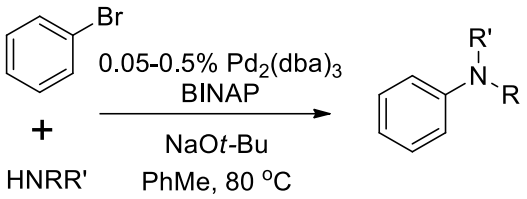
1. Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901

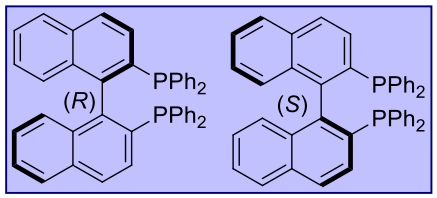
2. Guram, A. S; Rennels, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1995**, *34*, 1348; Wolfe, J. P; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133 (aryl iodides)

3. Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tet.* **1996**, *52*, 7525

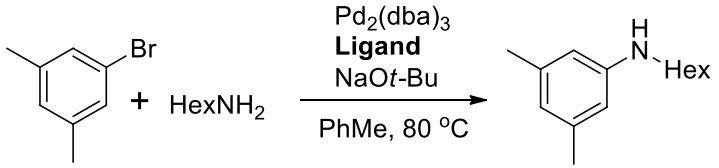
Pd cross coupling: Buchwald-Hartwig amination

- Improved catalytic system with BINAP ligand ('second generation')[1]
- Allowed for milder conditions, better conversion and an increased substrate scope (including primary amines)
- Blocks β-hydride elimination





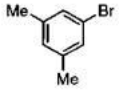
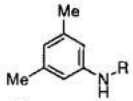
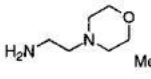
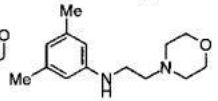
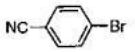
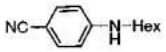
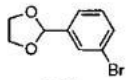
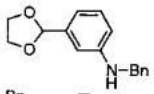
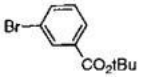
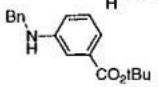
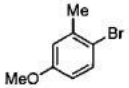
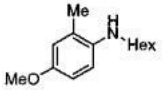
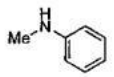
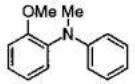
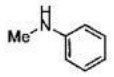
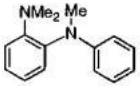
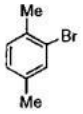
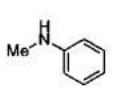
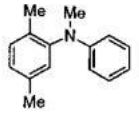
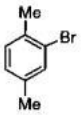
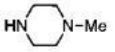
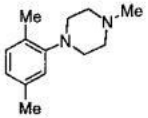
- **Ligand effects**



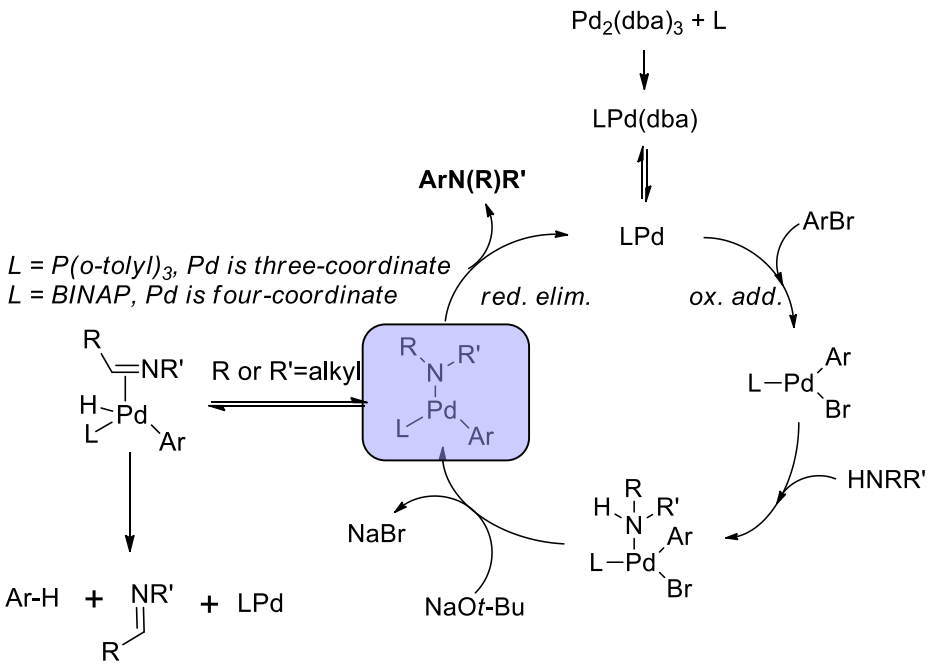
Ligand	% Conversion	Time	% yield
BINAP	100%	2 h	88%
P(*o*-tolyl)$_3$	22%	22 h	35%
DPPB	18%	3 h	-
DPPF	100%	3 h	-
DPPE	7%	6 h	-
DPPP	2%	6 h	-

Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc*, **1996**, *118*, 7215

Pd cross coupling: Buchwald-Hartwig amination

Halide	Amine	Product		Catalyst Loading (mol % Pd)	Rxn Time (h)	Isolated Yield (%)
	RNH_2		R= *n*-Hexyl	0.5	2	88 (35)[a]
			R=Bn	0.5	4	79
				0.05	7	79
			R= Cyclohexyl	0.5	18	83
				0.5	20	84
	$nHexNH_2$			0.5	<1	98[b]
				0.05	1.5	97
	H_2NBn			0.5	2	81
	H_2NBn			0.5	3.5	71
	$nHexNH_2$			0.5	6	95
				0.5[c]	29	75
				2.0	14	61 (0)
				1.0[c]	39	66
				2.0	36	65 (0)
				0.5[c]	36	94
				2.0	4	79 (5)
				0.5[c]	4	98
				2.0	15	98 (47)
				0.05[c]	6	94

Buchwald-Hartwig amination mechanism[1]



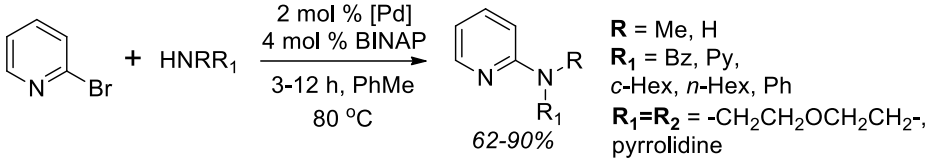
- Reductive elimination can occur from both three-coordinate monophosphine and four-coordinate biphosphine complexes
- Reductive elimination from three-coordinate is faster
- However, β-hydride elimination can occur quickly from the monophosphine tri-coordinated Pd complex
- β-hydride elimination occurs more slowly for four-coordinate diphosphines, allowing for greater proportion of reductive elimination[2]

1. Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 4708. Hartwig, J. F.; Richards, S.; Baranaño, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626. Widenhoefer, R. A.; Buchwald, S. L. *Organometallics*. **1996**, *15*, 2755.

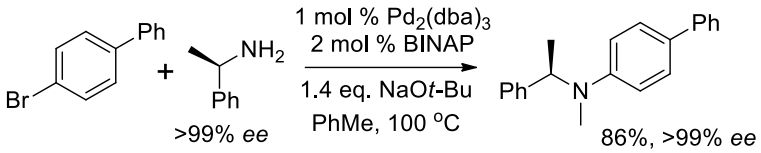
2. Hartwig, J. F. *Pure App. Chem.* **1999**, *71*, 1416

Buchwald-Hartwig amination

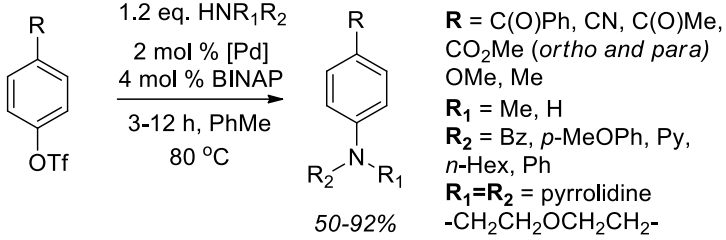
- Can be extended to a wide variety of systems:
- Pyridyl bromides[1]



- Optically active amines[3]



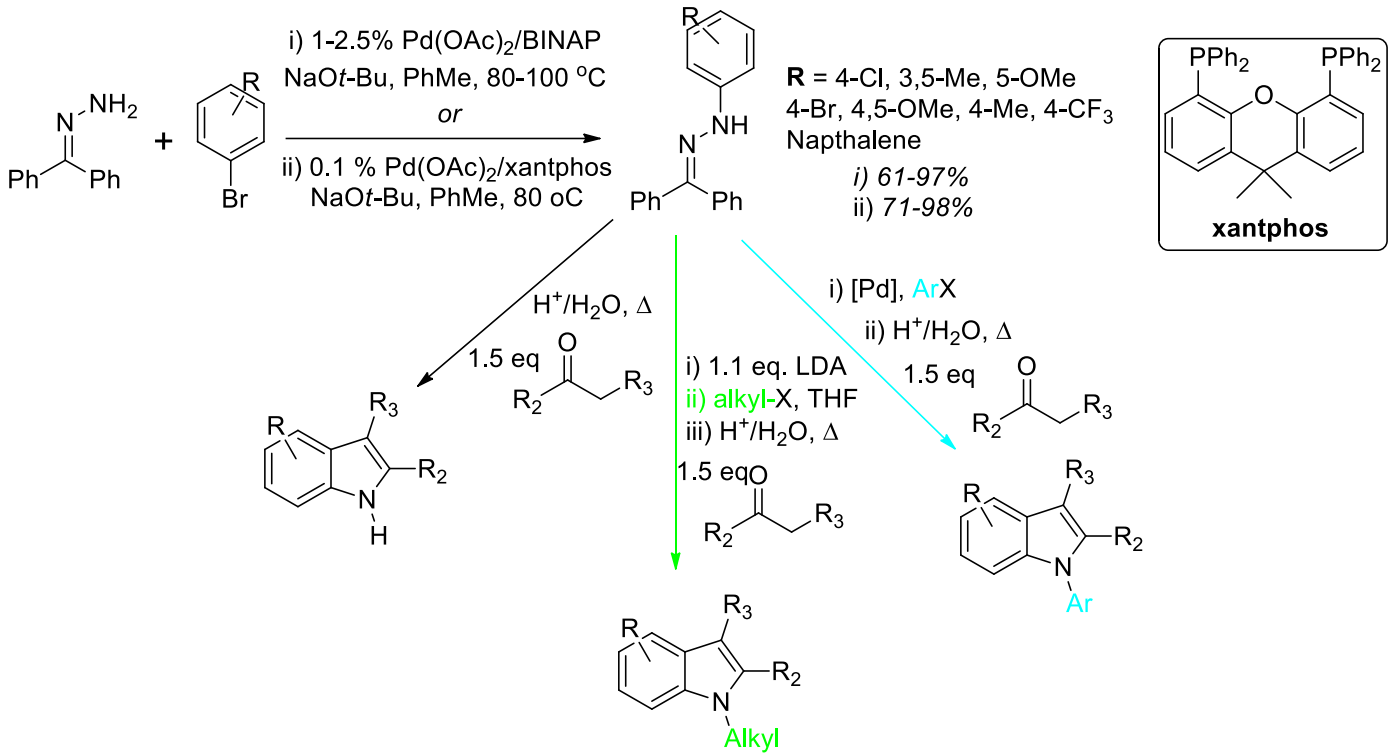
- Aryl triflates[2]



1. Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240
2. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264. Åhman, J.; Buchwald, S. L. *Tet. Lett.* **1997**, *38*, 6363
3. Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451

B-H amination: Fischer indole synthesis

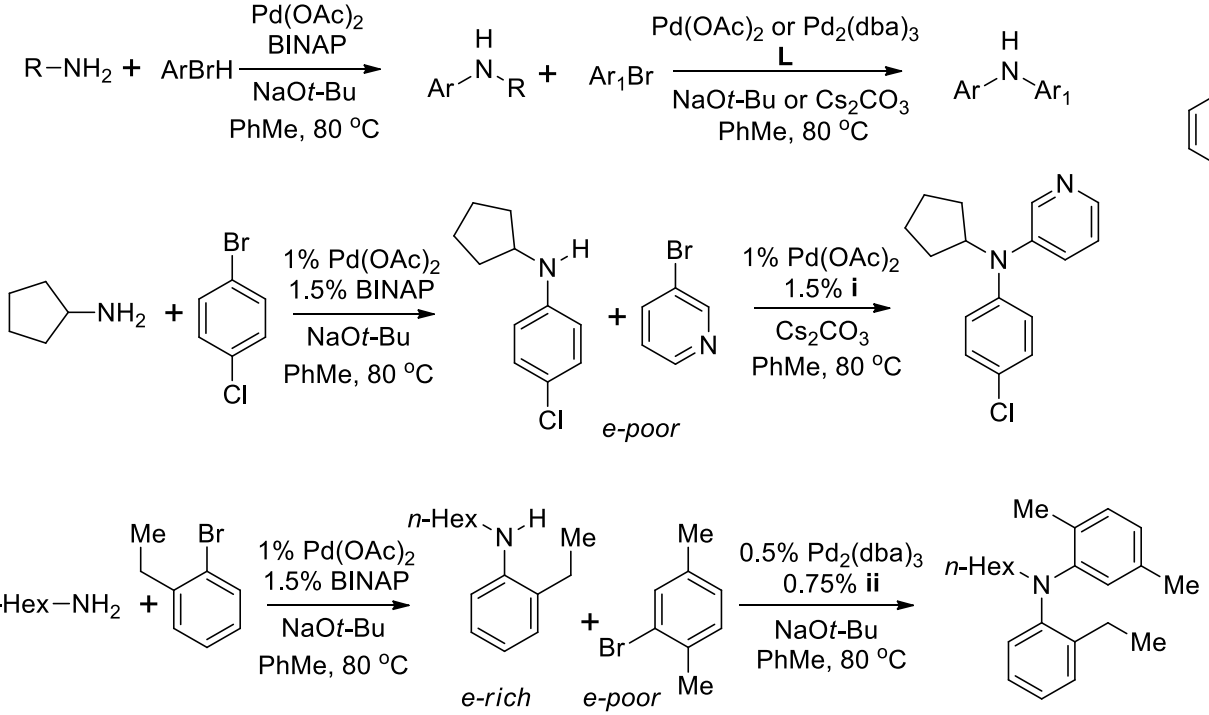
- Can form a Fischer-type enolisable aryl hydrazone

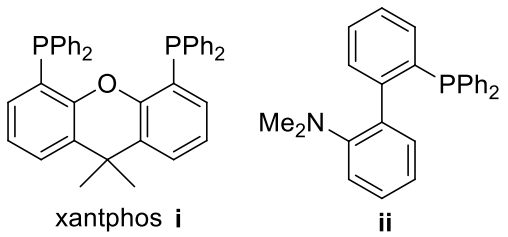


Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6621.; Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251

B-H amination: Double amination

- Coupling two different aryl groups to an amine





	Ar(R)NH	
Ar_1Br	e-poor	e-rich
e-poor	**i**	**ii**
e-rich	-	**ii**

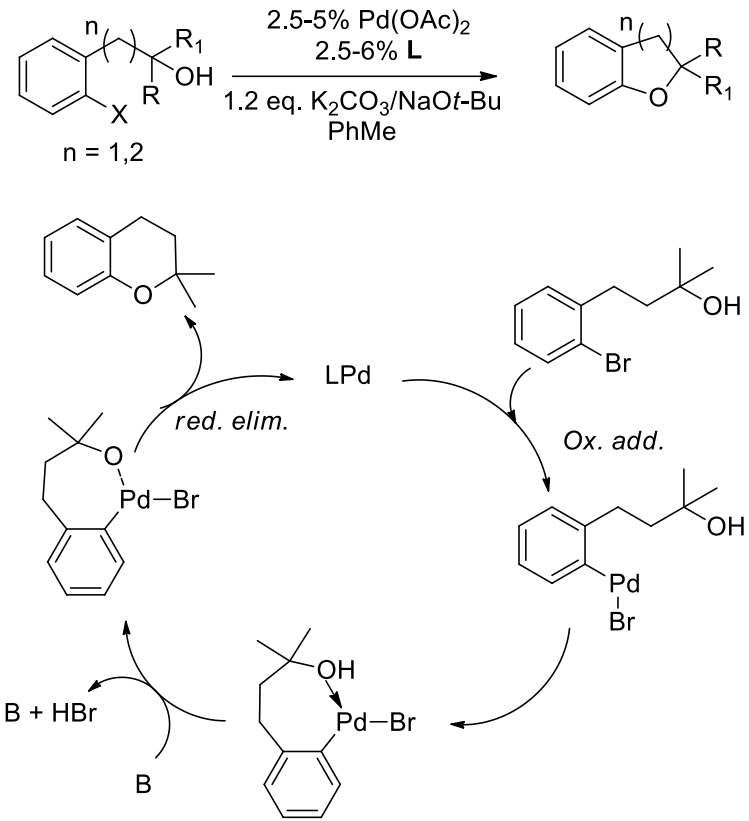
Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem.* **1999**, *38*, 6019

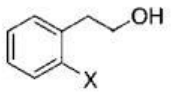
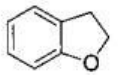
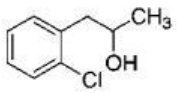
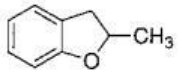
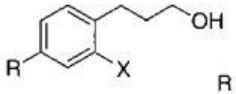
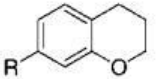
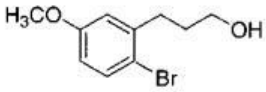
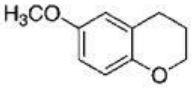
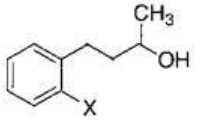
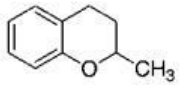
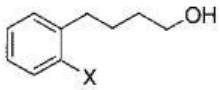
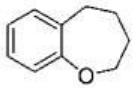
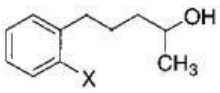
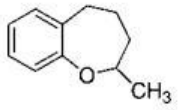
Presentation Summary

- Zirconocene chemistry
- Titanocene chemistry
- **Palladium cross coupling chemistry**
  - C-N bond formation (Buchwald-Hartwig amination)
  - *C-O bond formation*
  - C-C bond formation
- Recent work
- Summary

Pd mediated C-O bond formation

- Intramolecular bond formation

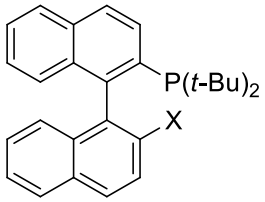


Entry	Substrate		mol% Pd[a]	T (°C), t (h)	Product	Yield (%)[b]
1		X = Br	2	50, 26		85 (82)
2		X = Cl	2	50,23		71
3			3	60, 26		71 (75)
4		R = H, X = Br	2	50, 21		85 (72)
5		R = H, X = Cl	2	65, 21		85
6		R = CH_3, X = Br	2	50, 24		83
7			2	50, 24		71
8		X = Br	3	65, 25		79 (83)
9		X = Cl	3	80, 24		78 (82)
10		X = Br	2	70, 23		73
11		X = Cl	2	70, 23		74
12		X = Br	3	80, 28		71
13		X = Cl	3	80, 28		65

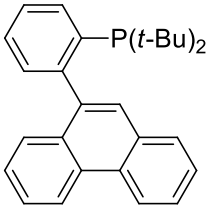
Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333.

Pd mediated C-O bond formation

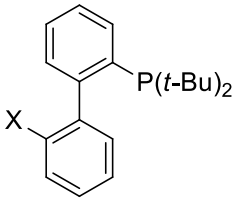
- Enantioretentive bond formation



1: X=H
2: X=N(CH$_3$)$_2$

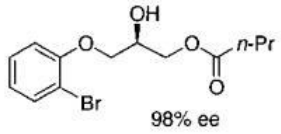
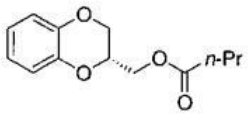
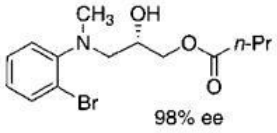
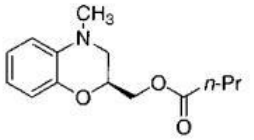
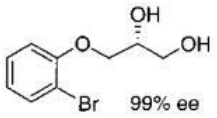
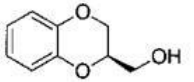
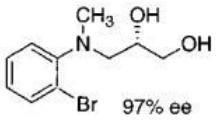
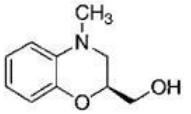
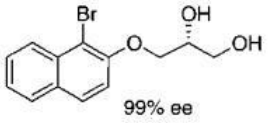
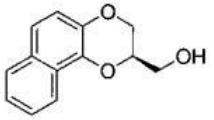
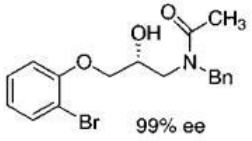
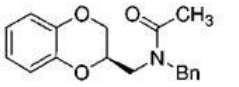
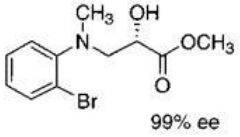
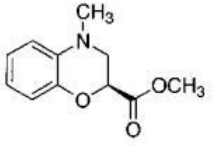


3



4: X=H
5: X=N(Me)2
6: X=*i*-Pr

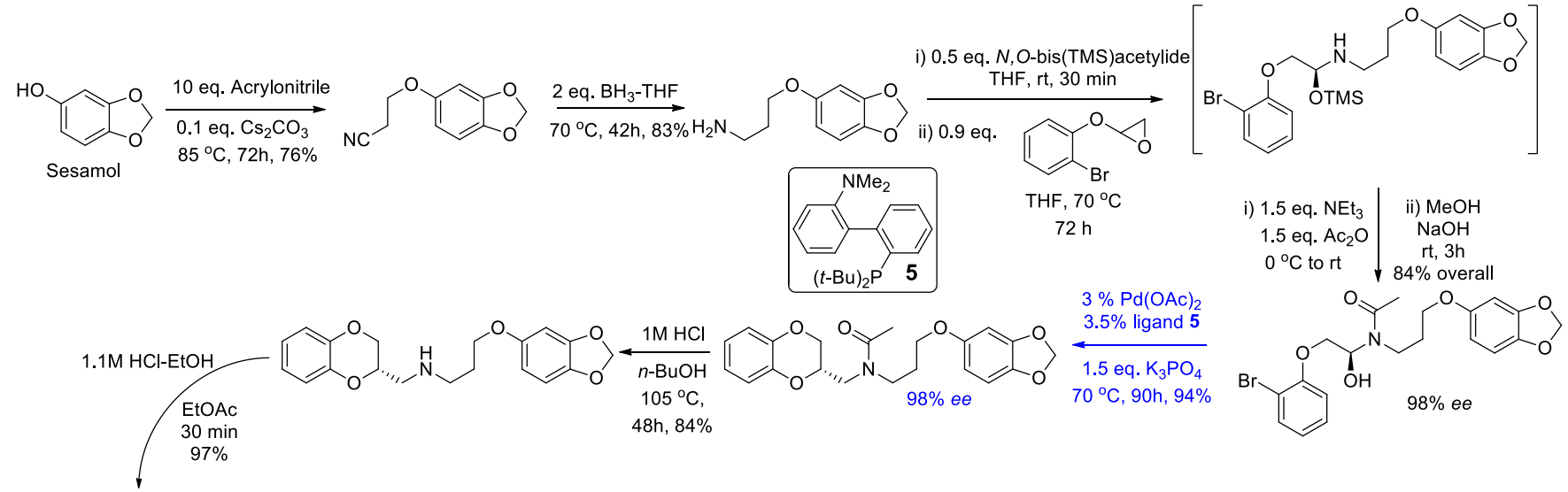
entry	ee (%)[a]	Pd precursor	L	base	*T* (°C), *t* (h)	yield (%)	ee (%)[b]
1[c]	96	$Pd(OAc)_2$	**1**	Cs_2CO_3	70, 48	66	94
2[c]	96	$Pd(OAc)_2$	**3**	Cs_2CO_3	70, 48	48	
3[c]	96	$Pd(OAc)_2$	**5**	Cs_2CO_3	70, 20	80	95
4[d]	90	$Pd_2(dba)_3$	**1**	*t*-BuONa	50, 24	89	90
5[d]	90	$Pd_2(dba)_3$	**5**	*t*-BuONa	50, 20	95	90
6[d]	90	$Pd_2(dba)_3$	**5**	*t*-BuOK	50, 20	33	
7[e]	90	$Pd_2(dba)_3$	**5**	Cs_2CO_3	70, 40	93	90

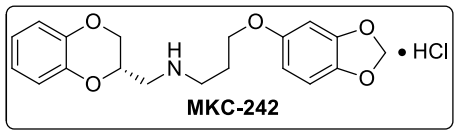
Entry	Substrate	L	T (°C), t (h)	Product	Yield (%)	ee (%)
1		**1**	70, 44		84	98
2		**4**	50, 44		86	98
3		**1**	70, 72		72	99
4		**4**	70, 44		80	97
5		**1**	70, 44		86	99
6		**1**	70, 24		83	99
7		**1**	70, 48		80	99

Kuwabe, S.-I.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc*, **2001**, *123*, 12202

Use in organic synthesis: MKC-242

- Antidepressant in phase II trials





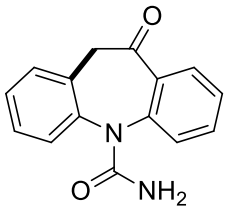
- Overall 7 steps, 40% yield
- Retention of Stereochemistry in cyclisation step
- Long timeframe – Almost two weeks for the entire synthesis!

Presentation Summary

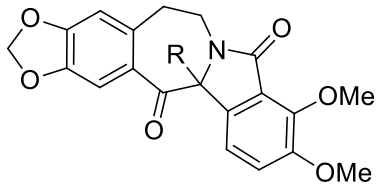
- Titanocene chemistry
- Zirconocene chemistry
- **Palladium cross coupling chemistry**
  - C-N bond formation (Buchwald-Hartwig amination)
  - C-O bond formation
  - *C-C bond formation*
- Recent work
- Summary

Pd mediated C-C bond formation

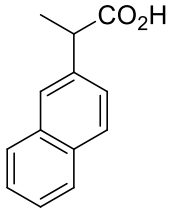
- α-arylation of carbonyls
- γ-arylation of ketones and enones
- Comprise a wide range of natural products



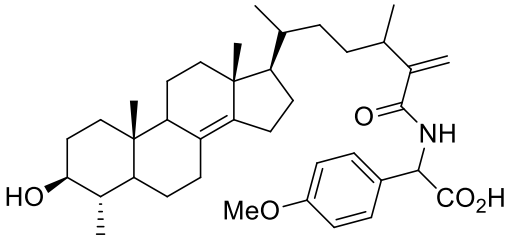
Trileptal
anticonvulsant



R = H = **Deoxychenine**
R = OH = **Chenine**

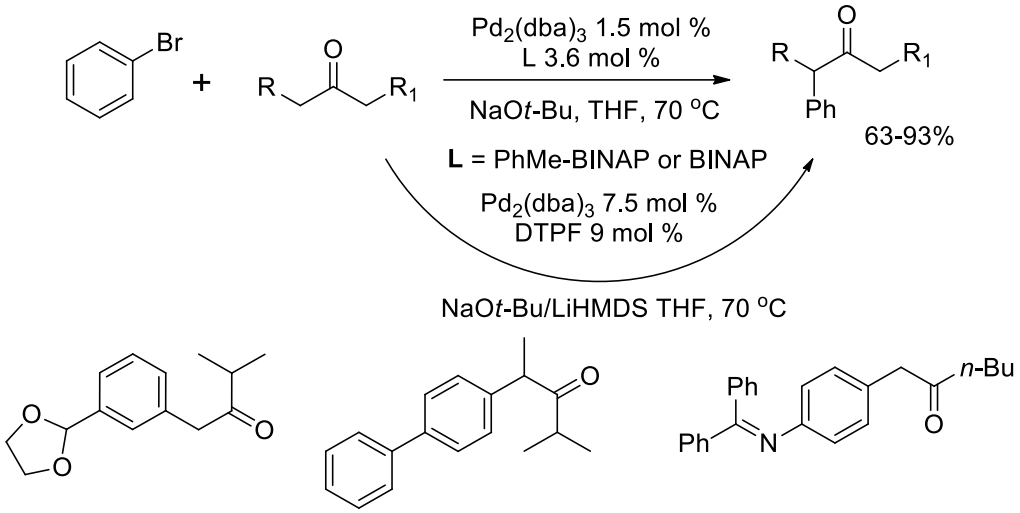


Naproxen
NSAID



Polimastamide

α-arylated carbonyls

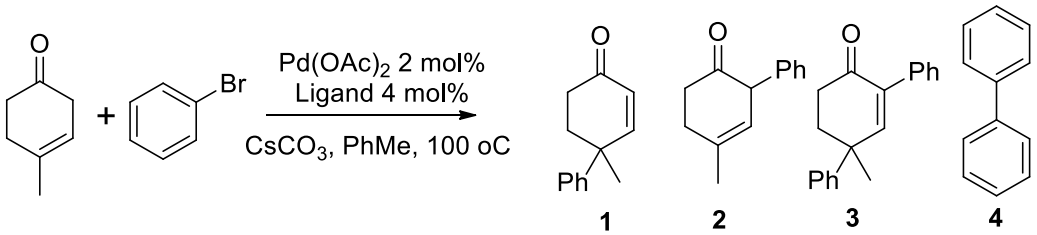


- Buchwald observed selective arylation at least hindered site
- Both groups noted lack of β-hydride elimination
  - Biphosphine ligands render Pd square planar with no open coordination site
- Hartwig observed:
  - e^- rich/e^- neutral aryl substrates selective for LiHMDS
  - e^- poor substrates selective for NaO*t*-Bu

Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108.; Hamann, B. C.; artwig, J. F. *J. Am. Chem. Soc*, **1997**, *119*, 12382

γ-arylation of ketones and enones

- Arylation of α,β and β,γ unsaturated ketones: ligand screen

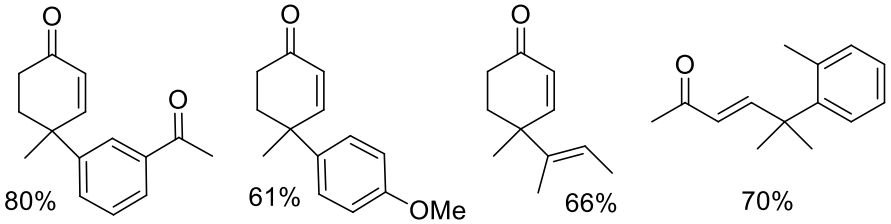


Ligand	1	2	3	4
P(*o*-tol)$_3$	35%	-	23%	26%
Xantphos	11%	125	49%	-
CyJohnPhos	41%	7%	17%	14%
XPhos	-	4%	50%	-
Dppe	**84%**	**-**	**-**	**-**
Dppp	56%	-	-	5%
Dppb	50%	2%	7%	-
BINAP	50%	7%	32%	-
Dppf	28%	25%	53%	-
P(*t*Bu)$_3$	7%	0	27%	-

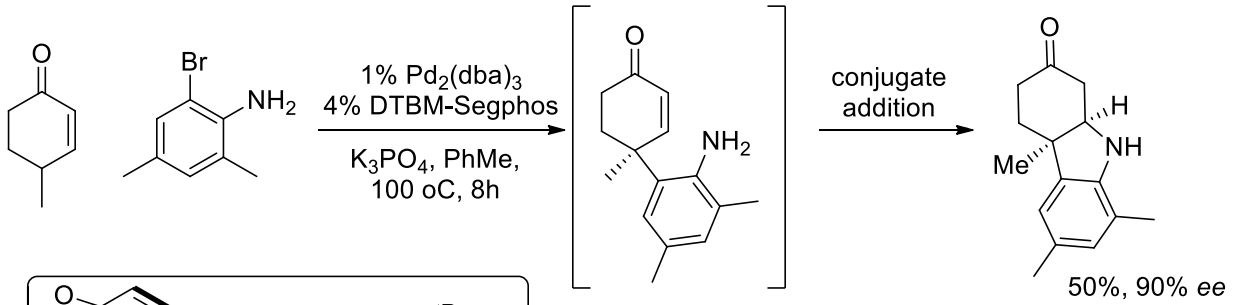
Hyde, A. M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 177

γ-arylation of ketones and enones

- Reaction scope

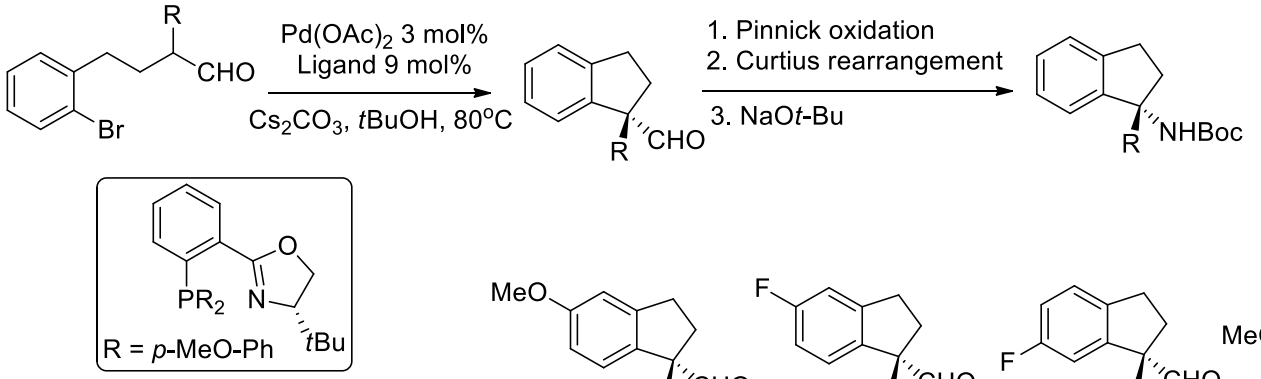


- One pot asymmetric domino reaction to ketoindoline



Intramolecular arylation of aldehydes

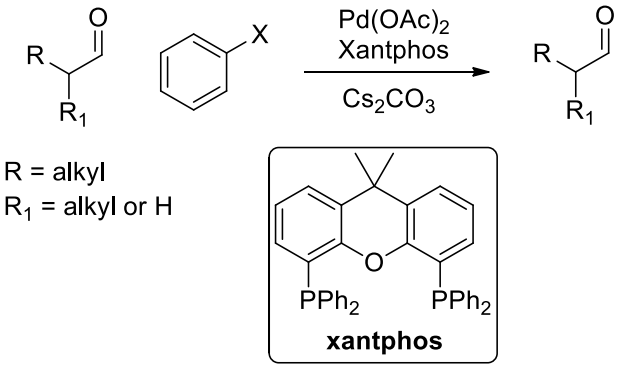
- Previous issues with aldehyde arylation
  - Under basic conditions, can get aldol condensation
- Buchwald developed asymmetric method

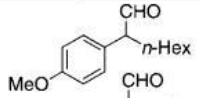
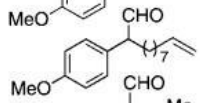
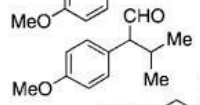
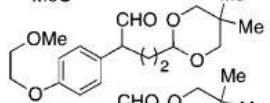
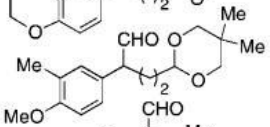
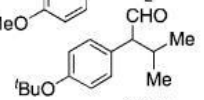
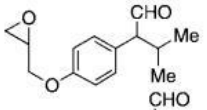
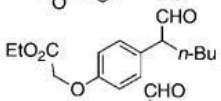
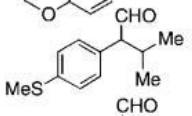
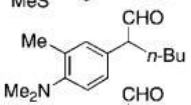
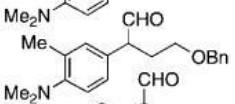
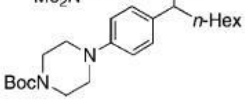


Garcia-Fortanet, J.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 8108

Intramolecular arylation of aldehydes: H_2O mediated pre-activation

- Pre-generate LPd^0 by heating $Pd(OAc)_2$ (1 mol%), H_2O (4 mol%) and L (3 mol%) for 1 min at 80 °C in dioxane



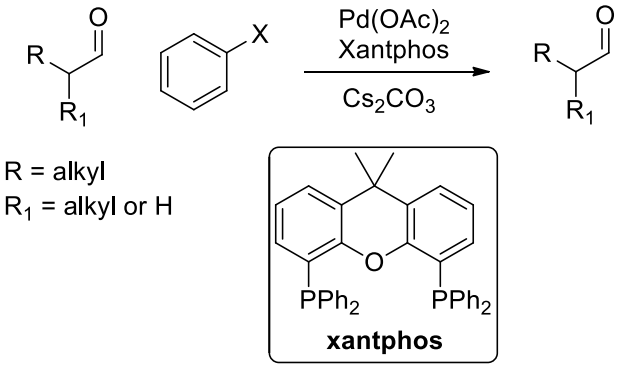
entry	product	X[a]	yield (%)[b]
1		Br	70[c]
		Cl	65
2		Br	73[c]
		Cl	58
3		Br	64[d]
		Cl	51
4		Br	66[e]
		Cl	60
5		Br	74[e]
		Cl	58
6		Br	65[d]
		Cl	61
7		Br	56[d]
		Cl	51
8		Br	65[c]
		Cl	45
9		Br	58[d]
		Cl	50
10		Br	84[d]
		Cl	62
11		Br	73[d]
		Cl	57
12		Br	56[e]
		Cl	50

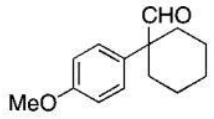
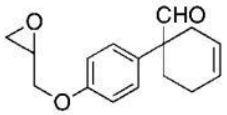
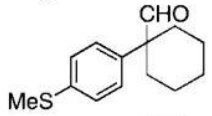
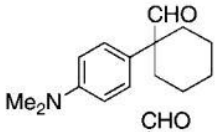
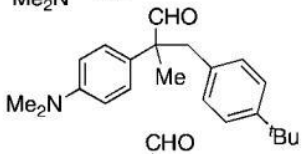
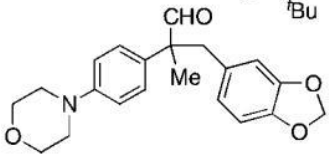
Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505

Martin, R.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 4561

Intramolecular arylation of aldehydes: H_2O mediated pre-activation

- Pre-generate LPd^0 by heating $Pd(OAc)_2$ (1 mol%), H_2O (4 mol%) and L (3 mol%) for 1 min at 80 °C in dioxane



entry	product	X[a]	yield (%)[b]
1		Br Cl	63 60
2		Br Cl	54 51
3		Br Cl	65 54
4		Br Cl	67 59
5		Br Cl	68 55
6		Br Cl	56 52

Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505

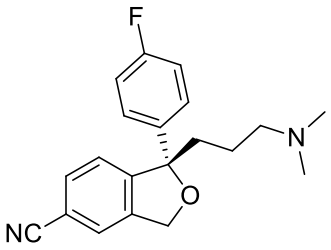
Martin, R.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 4561

Presentation Summary

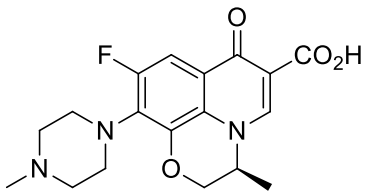
- Titanocene chemistry
- Zirconocene chemistry
- Palladium cross coupling chemistry
- **Recent work**
  - Conversion of aryl triflates to aryl fluorides
- Summary

Recent work: Conversion of aryl triflates to aryl fluorides

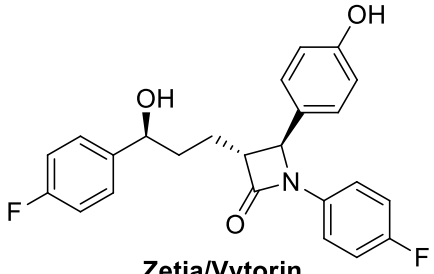
- Increasingly large number of pharmaceutical and agricultural chemicals contain Ar-F groups
- Fluorination enhances bioavailablity
- Radioactive ^{18}F also used in medical screening (VG group)



Lexapro
Antidepressant



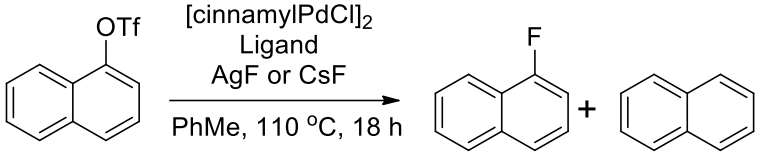
Levaquin
Antibiotic

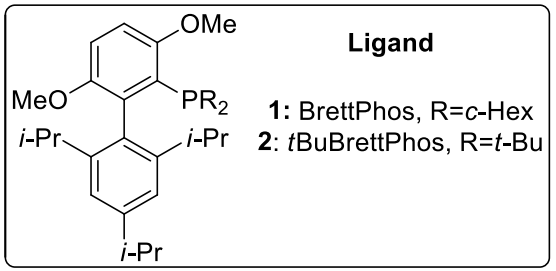


Zetia/Vytorin
Inhibit cholesterol absorption

Conversion of aryl triflates to aryl fluorides

- Optimisation

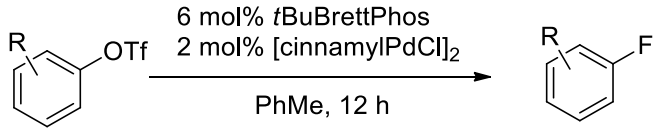


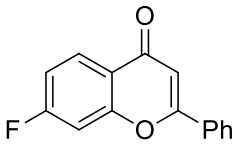


Pd (mol%)	Ligand (mol %)	F⁻ source (eq.)	Conversion	Fluorinated product	Napthalene
10	**1** (10)	AgF (1.5)	-	Trace	-
10	**1** (10)	CsF (1.5)	90%	30%	5%
10	**2** (10)	CsF (1.5)	100%	71%	1%
2	**2** (3)	CsF (2.0)	100%	79%	1%

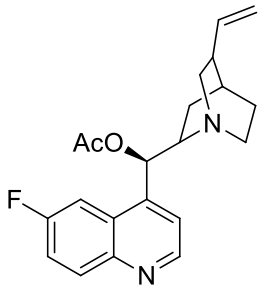
Watson, D.A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science*. **2009**, *325*, 1661.

Conversion of aryl triflates to aryl fluorides

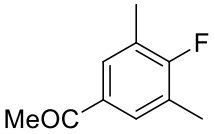




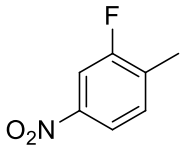
63%, 80 °C



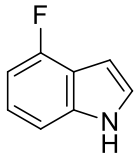
70%, 10 mol% [Pd], 110 °C



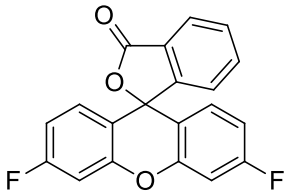
83%, 110 °C



83%, 110 °C



63%, 80 °C



73%, 8 mol% [Pd], 110 °C

Watson, D.A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science*. **2009**, *325*, 1661.

Presentation Summary

- Zirconocene chemistry
- Titanocene chemistry
- Palladium cross coupling chemistry
- Recent work
- **Summary**

Summary

- Buchwald's work has led to many new methods for synthetic transformations, some asymmetric
- His work on C-N bond formation led to the Buchwald-Hartwig amination; transforming Ar-X into Ar-NRR' with wide substrate scope in good yields and the ability to retain stereochemistry if neccessary
- His in-house developed arylphosphine ligands show remarkable selectivity in enantioselective reactions, and are available commercially through Sigma-Aldrich[1]
- All in all, a fascinating chemist who has worked in several areas throughout his career and has added significant knowledge and expertise to the field of organic chemistry

Mauger, C. C.; Mignani, G. A. *Ald. Acta.*,**2006**, *1*, 17.; Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599

Availability online: http://www.sigmaaldrich.com/chemistry/chemical-synthesis/technology-spotlights/buchwald-ligands.html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