Green Chemistry: Recent Advances in Developing Catalytic Processes in Environmentally-Benign Solvent Systems

Frontiers of Chemistry Presentation
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2/2/2008

What is green chemistry?

- *Green chemistry is the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and applications of chemical products.*

- *The ideology of Green Chemistry calls for the development of new chemical reactivities and reaction conditions that can potentially provide benefits for chemical syntheses in terms of resource efficiency, energy efficiency, product selectivity, operational simplicity, and health and environmental safety.*

- Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, 1998.

Outline: Catalysis in Green Solvent Systems

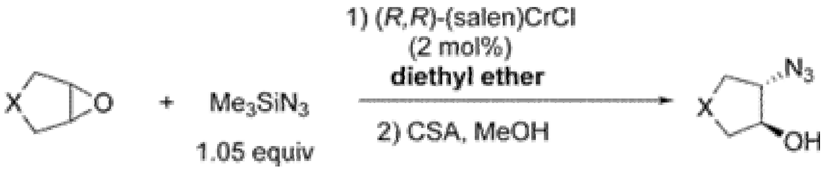
- Asymmetric Catalysis in Solvent-Free and Highly Concentrated Reactions
- Catalyzed Reactions in Ionic Liquids
- Catalyzed Reactions in Supercritical Fluids
- Catalyzed Reactions in Water

Part I: Asymmetric Catalysis in Solvent-Free and Highly Concentrated Reactions

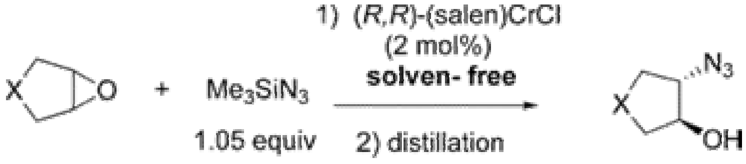
Challenges for Developing Asymmetric Catalysis under Solvent-Free Conditions

- Solvent greatly affects catalyst efficiency and enantioselectivity.
- Enantioselectivities are often dependent on catalyst concentration.
- The impact on catalyst as the reaction medium changes from reactants and substrates to products is unpredictable.

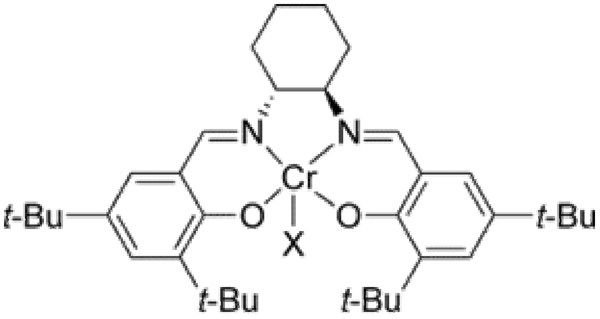
Asymmetric Epoxide Opening



entry	X	time (h)	isolated yield (%)	ee (%)
1	CH_2CH_2	18	80	88
2	CH_2	18	80	94
3	CH=CH	46	72	81



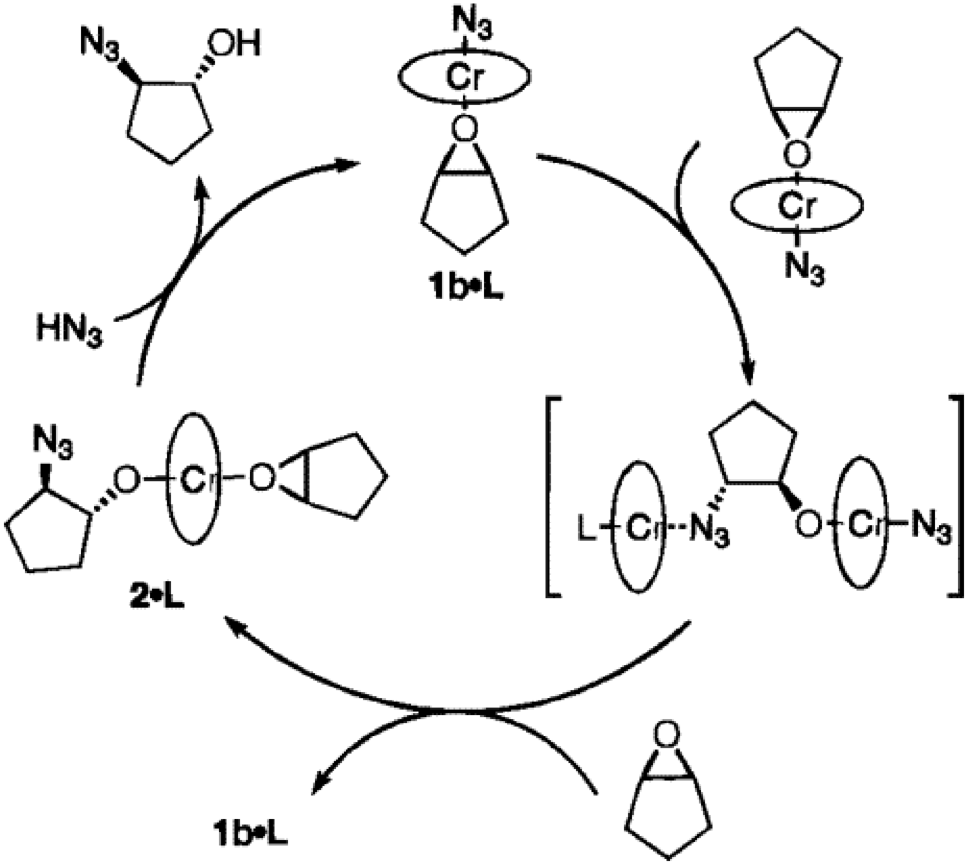
cycle	X	time (h)	isolated yield (%)	ee (%)
1	CH_2CH_2	18	86	84
2	CH_2CH_2	21	88	87
3	CH_2CH_2	20	91	88
4	CH_2	4	81	94
5	CH=CH	18	75	83



X = Cl
X = N_3

Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897.

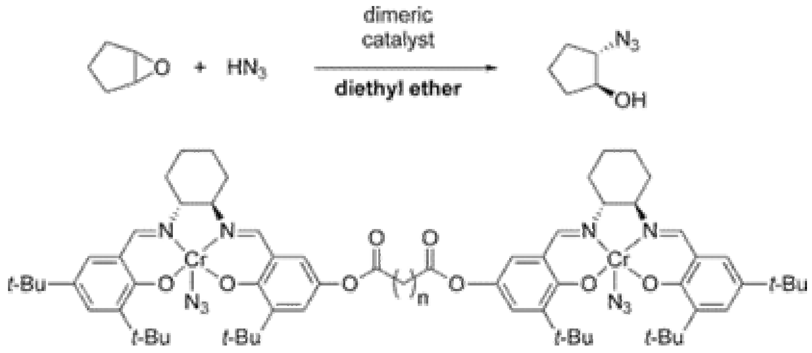
Mechanism of Action



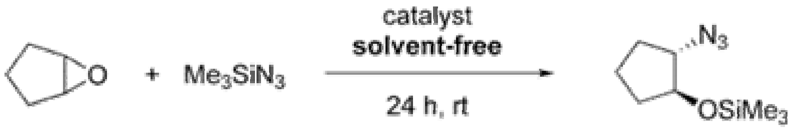
$r = k[\mathrm{cat}]^2[\mathrm{TMSN_3}]^0/[\mathrm{epoxide}]$

Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924.

Dimeric Catalyst for Enhanced Efficiency



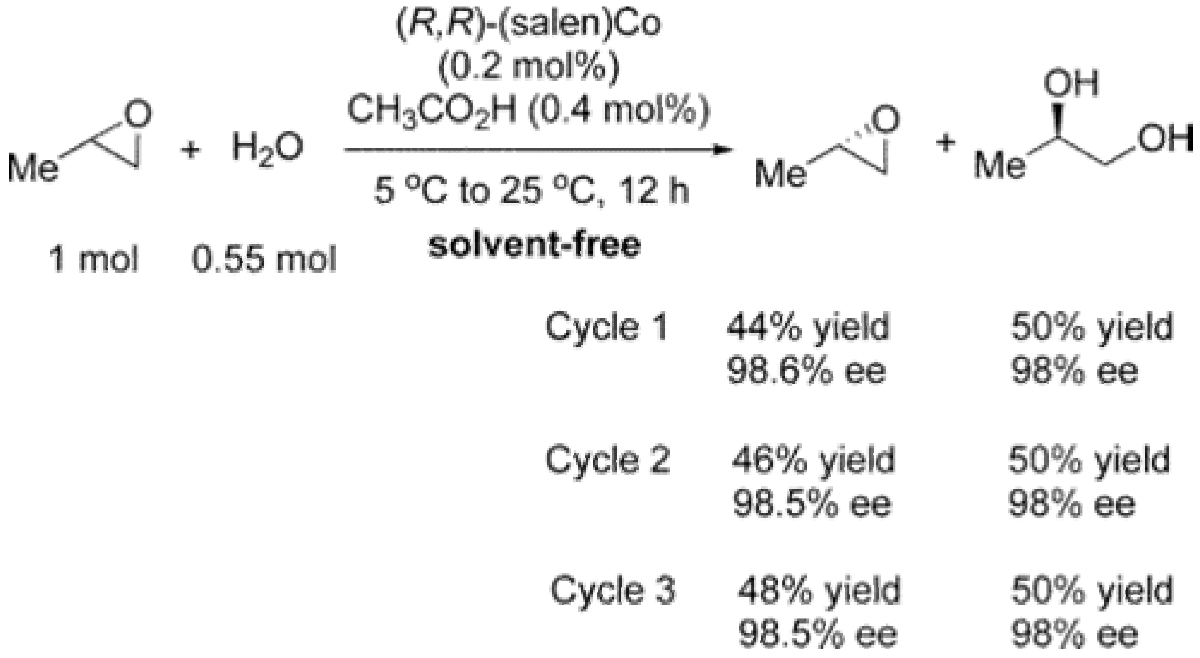
n	ee (%)	$k_{intra}{}^{a}$ (min^{-1} × 10^{-2})	k_{inter} (M^{-1} min^{-1})
2	90	4.4	15.7
4	90	5.4	15.1
5	93	42.9	27.4
6	93	31.7	15.8
7	93	20.9	7.9
8	94	14.7	10.5
10	92	3.8	4.4



catalyst loading for complete conversion in 24 h	
monomeric (salen)CrN$_3$	1 mol%
dimeric (n = 5) (salen)CrN$_3$	0.05 mol%

Konsler, R. G.; Karl, J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 10780.

Hydrolytic Kinetic Resolution of Epoxides

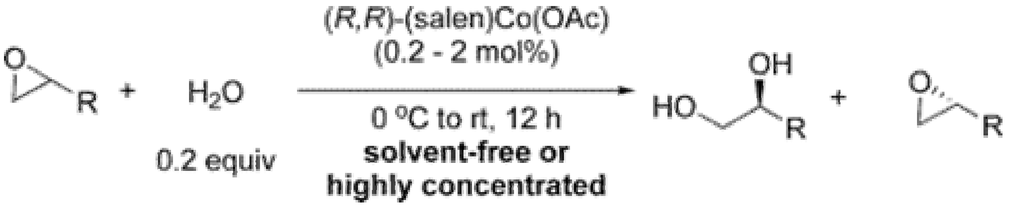


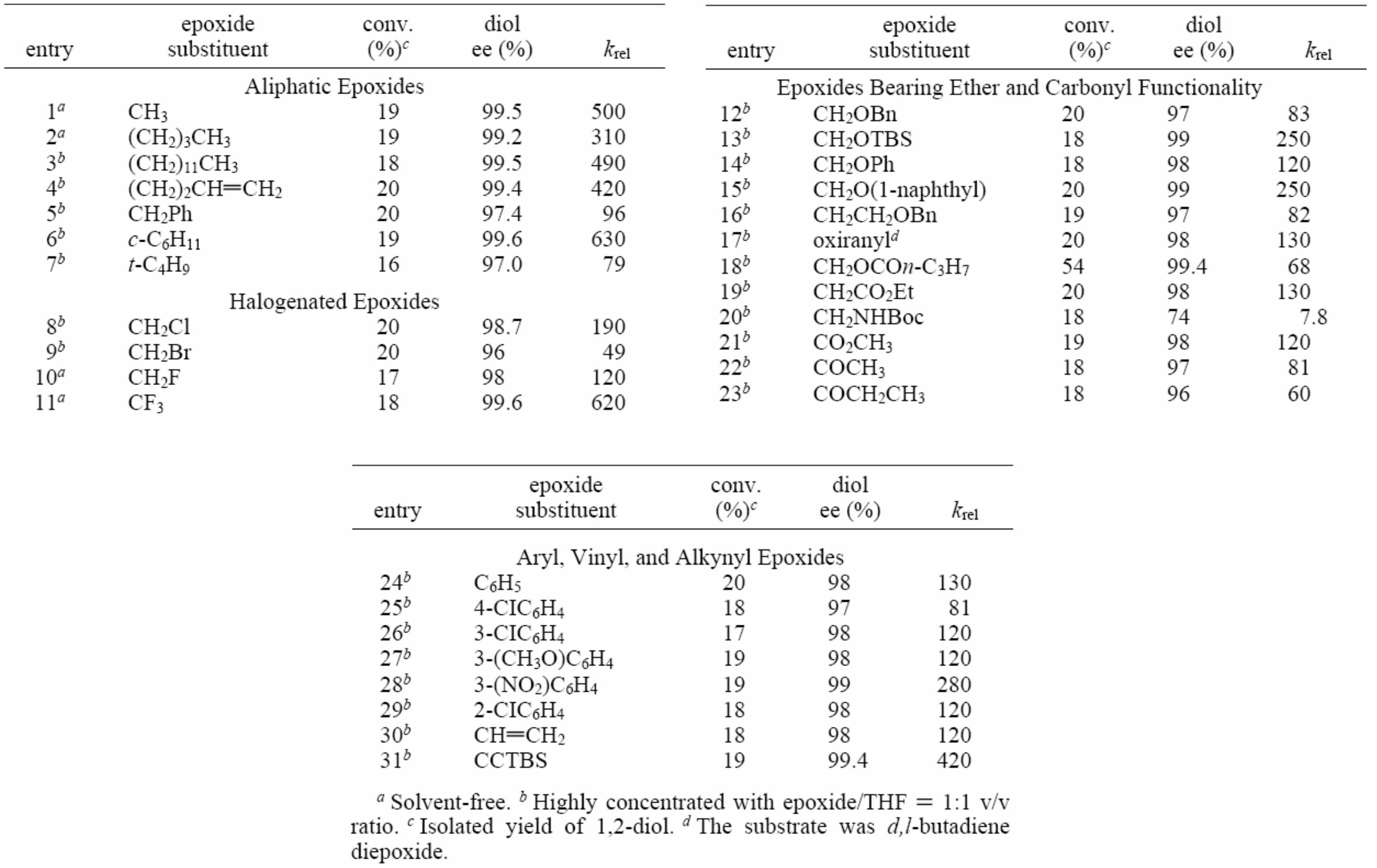
Cycle 1	44% yield 98.6% ee	50% yield 98% ee
Cycle 2	46% yield 98.5% ee	50% yield 98% ee
Cycle 3	48% yield 98.5% ee	50% yield 98% ee

reaction performed on >200 kg scale!

Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

Reaction Scope





entry	epoxide substituent	conv. (%)^c	diol ee (%)	k_{rel}
	Aliphatic Epoxides			
1^a	CH_3	19	99.5	500
2^a	$(CH_2)_3CH_3$	19	99.2	310
3^b	$(CH_2)_{11}CH_3$	18	99.5	490
4^b	$(CH_2)_2CH{=}CH_2$	20	99.4	420
5^b	CH_2Ph	20	97.4	96
6^b	c-C_6H_{11}	19	99.6	630
7^b	t-C_4H_9	16	97.0	79
	Halogenated Epoxides			
8^b	CH_2Cl	20	98.7	190
9^b	CH_2Br	20	96	49
10^a	CH_2F	17	98	120
11^a	CF_3	18	99.6	620

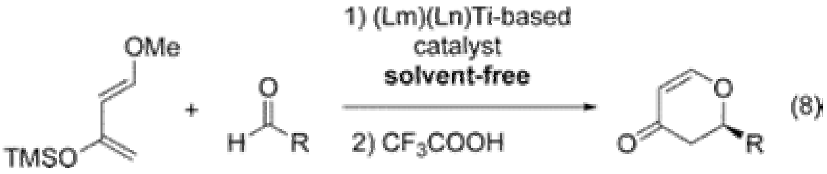
entry	epoxide substituent	conv. (%)^c	diol ee (%)	k_{rel}
	Epoxides Bearing Ether and Carbonyl Functionality			
12^b	CH_2OBn	20	97	83
13^b	CH_2OTBS	18	99	250
14^b	CH_2OPh	18	98	120
15^b	CH_2O(1-naphthyl)	20	99	250
16^b	CH_2CH_2OBn	19	97	82
17^b	oxiranyl^d	20	98	130
18^b	$CH_2OCO$$n$-$C_3H_7$	54	99.4	68
19^b	CH_2CO_2Et	20	98	130
20^b	CH_2NHBoc	18	74	7.8
21^b	CO_2CH_3	19	98	120
22^b	$COCH_3$	18	97	81
23^b	$COCH_2CH_3$	18	96	60

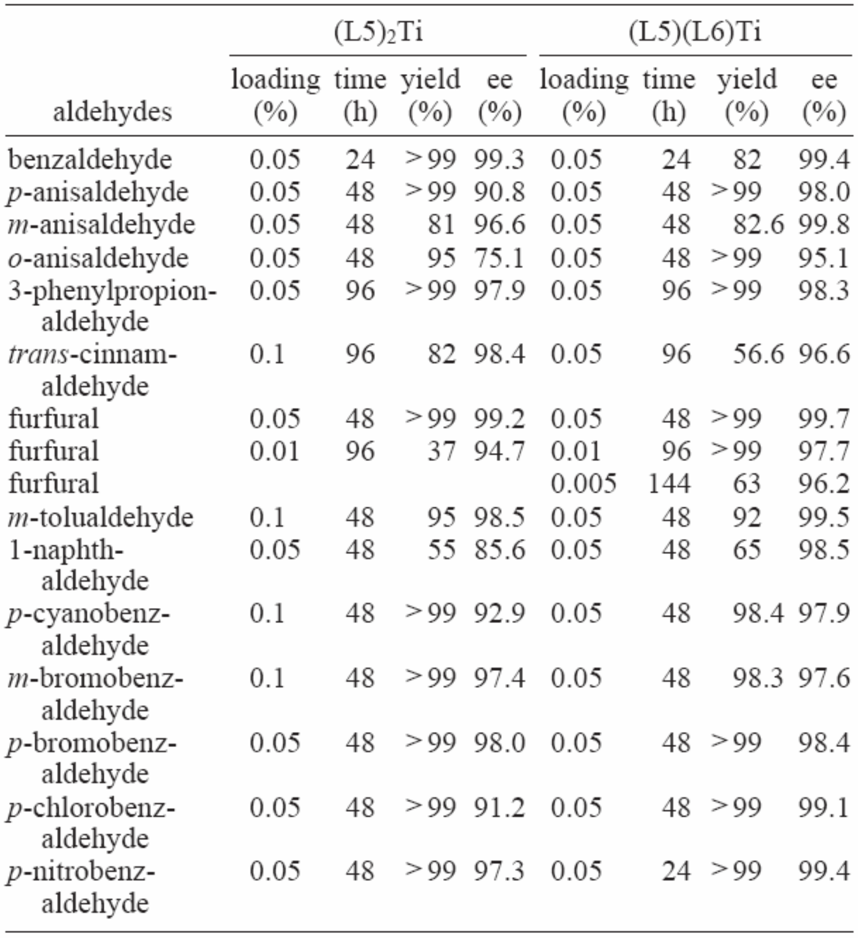
entry	epoxide substituent	conv. (%)^c	diol ee (%)	k_{rel}
	Aryl, Vinyl, and Alkynyl Epoxides			
24^b	C_6H_5	20	98	130
25^b	4-ClC_6H_4	18	97	81
26^b	3-ClC_6H_4	17	98	120
27^b	3-$(CH_3O)C_6H_4$	19	98	120
28^b	3-$(NO_2)C_6H_4$	19	99	280
29^b	2-ClC_6H_4	18	98	120
30^b	$CH{=}CH_2$	18	98	120
31^b	CCTBS	19	99.4	420

[a] Solvent-free. [b] Highly concentrated with epoxide/THF = 1:1 v/v ratio. [c] Isolated yield of 1,2-diol. [d] The substrate was *d,l*-butadiene diepoxide.

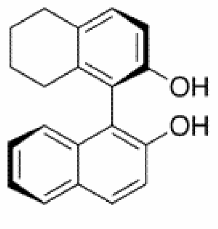
Schaus, S. E. et al. *J. Am. Chem. Soc.* **2002**, *124*, 1307

Asymmetric Hetero-Diels-Alder Reaction

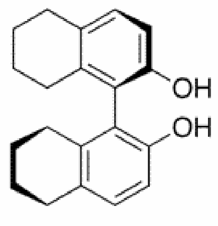




aldehydes	(L5)$_2$Ti loading (%)	(L5)$_2$Ti time (h)	(L5)$_2$Ti yield (%)	(L5)$_2$Ti ee (%)	(L5)(L6)Ti loading (%)	(L5)(L6)Ti time (h)	(L5)(L6)Ti yield (%)	(L5)(L6)Ti ee (%)
benzaldehyde	0.05	24	>99	99.3	0.05	24	82	99.4
p-anisaldehyde	0.05	48	>99	90.8	0.05	48	>99	98.0
m-anisaldehyde	0.05	48	81	96.6	0.05	48	82.6	99.8
o-anisaldehyde	0.05	48	95	75.1	0.05	48	>99	95.1
3-phenylpropionaldehyde	0.05	96	>99	97.9	0.05	96	>99	98.3
trans-cinnamaldehyde	0.1	96	82	98.4	0.05	96	56.6	96.6
furfural	0.05	48	>99	99.2	0.05	48	>99	99.7
furfural	0.01	96	37	94.7	0.01	96	>99	97.7
furfural					0.005	144	63	96.2
m-tolualdehyde	0.1	48	95	98.5	0.05	48	92	99.5
1-naphthaldehyde	0.05	48	55	85.6	0.05	48	65	98.5
p-cyanobenzaldehyde	0.1	48	>99	92.9	0.05	48	98.4	97.9
m-bromobenzaldehyde	0.1	48	>99	97.4	0.05	48	98.3	97.6
p-bromobenzaldehyde	0.05	48	>99	98.0	0.05	48	>99	98.4
p-chlorobenzaldehyde	0.05	48	>99	91.2	0.05	48	>99	99.1
p-nitrobenzaldehyde	0.05	48	>99	97.3	0.05	24	>99	99.4



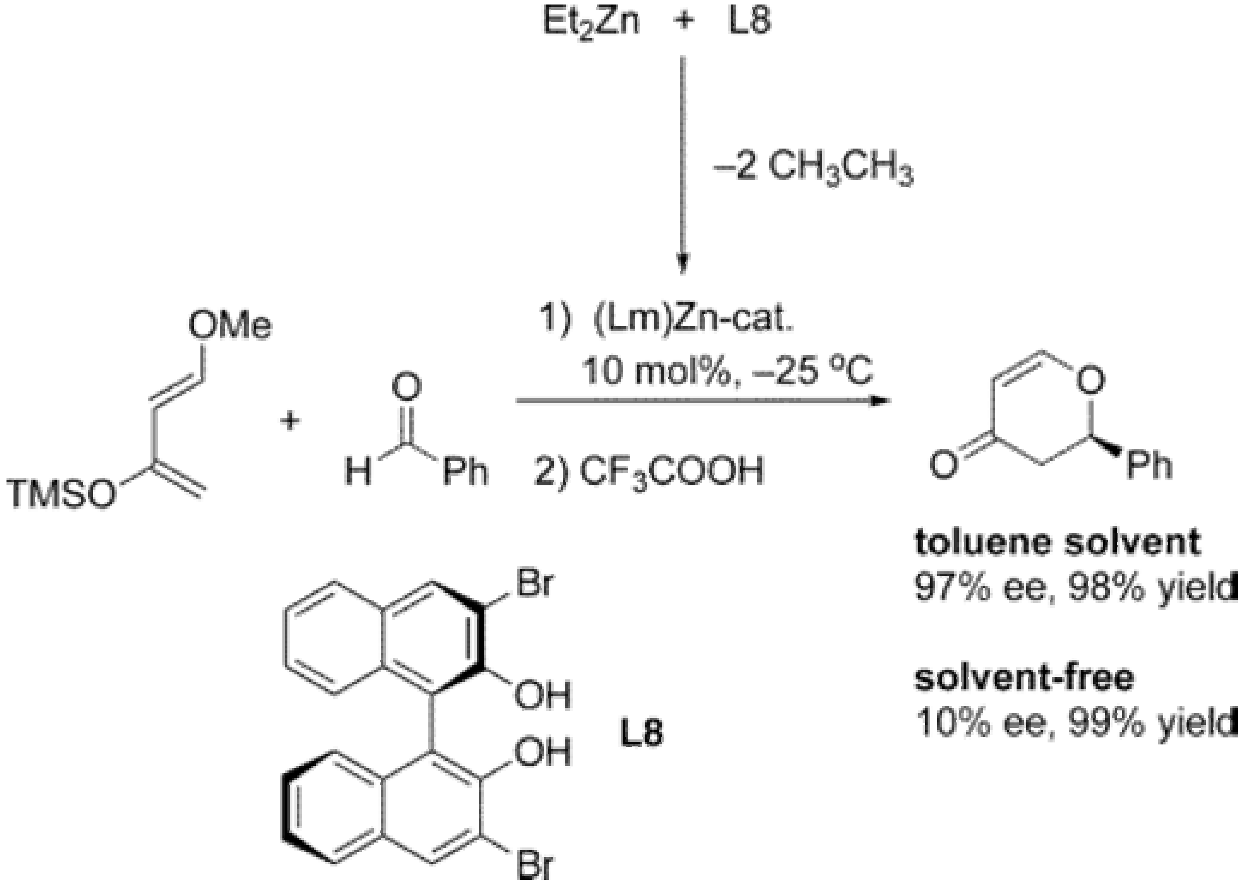
L5



L6

Long, J.; Hu, J. Y.; Shen, X. Q.; Ji, B. M.; Ding, K. L. *J. Am. Chem. Soc.* **2002**, *124*, 10.

Solvent Effect



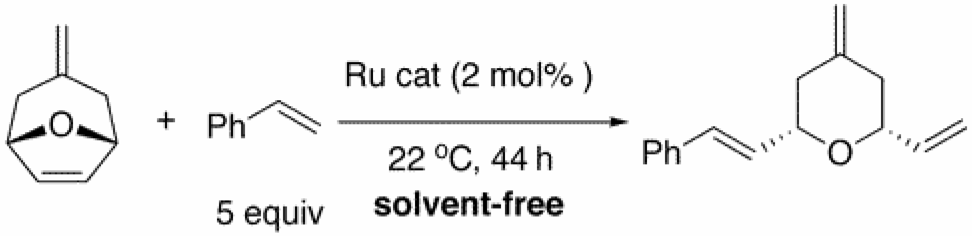
L8

toluene solvent
97% ee, 98% yield

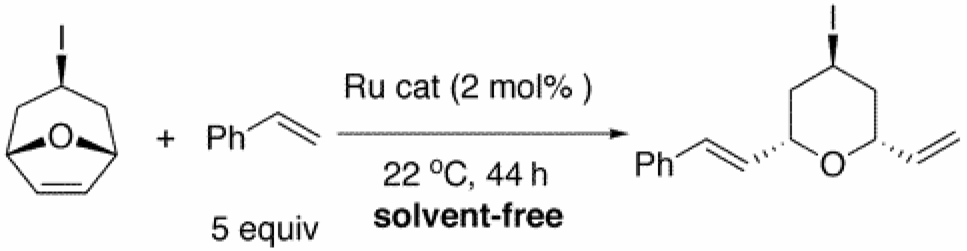
solvent-free
10% ee, 99% yield

Du, H.; Long, J.; Hu, J.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 4349.

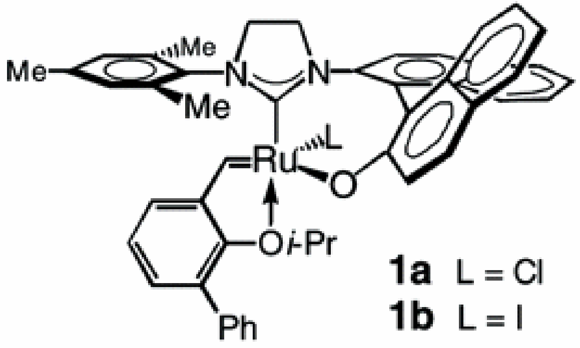
Asymmetric Ring-Opening Metathesis



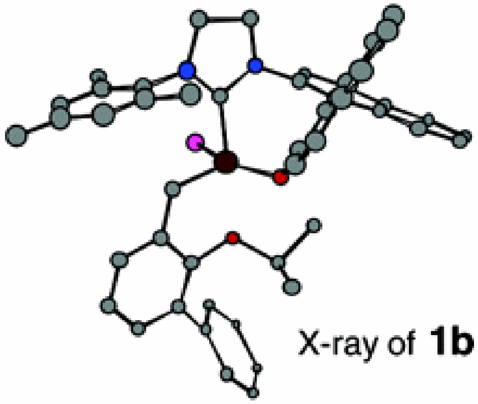
catalyst	ee (%)	yield (%)	time (h)
X = Cl	80	73	1.5
X = I	94	50	36



catalyst	ee (%)	yield (%)	time (h)
X = Cl	80	73	0.5
X = I	93	65	4



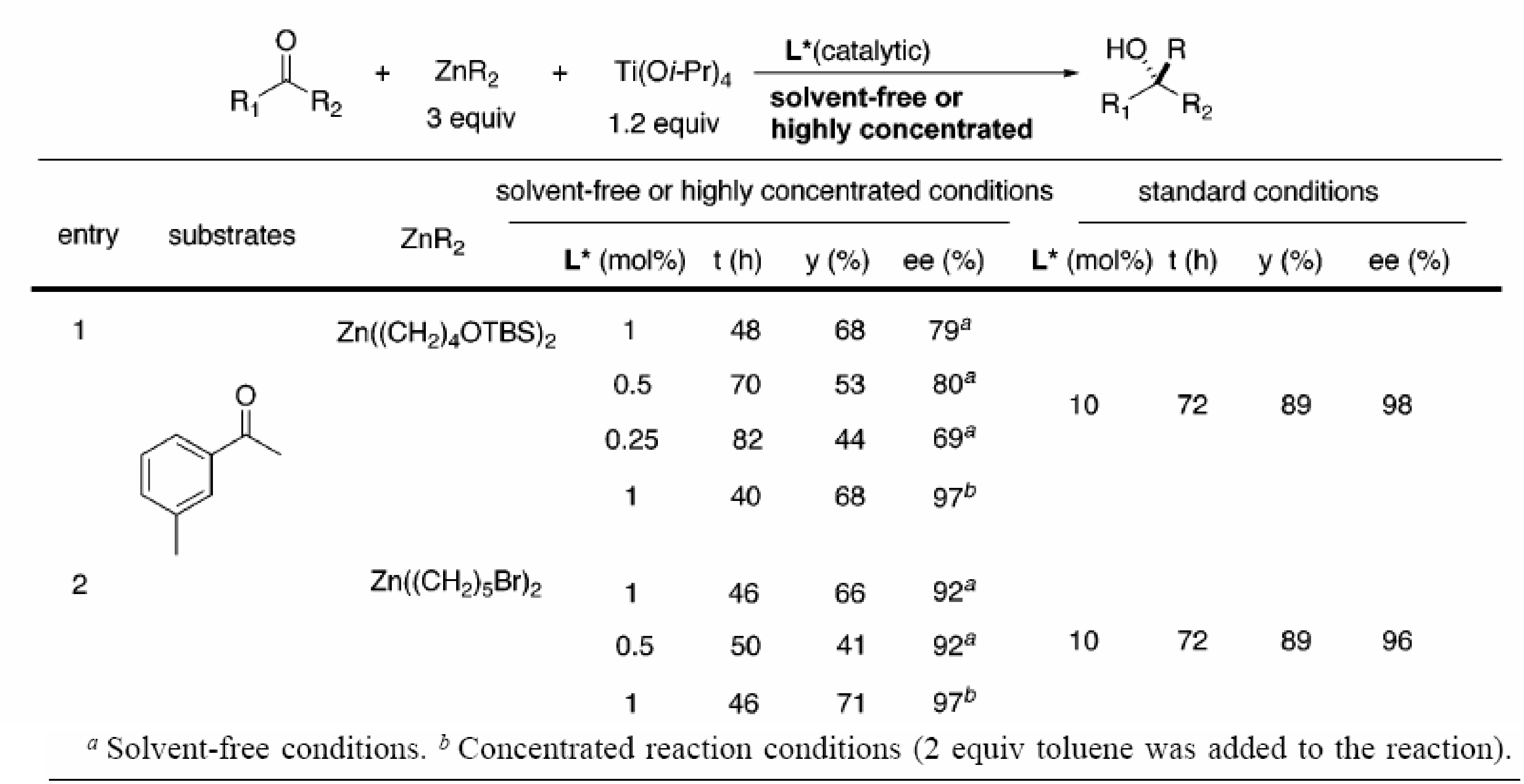
1a L = Cl
1b L = I



X-ray of **1b**

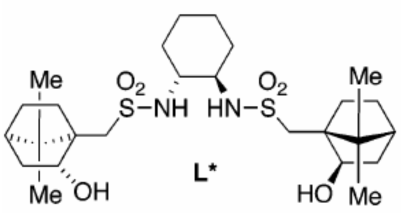
Gillingham, D. G.; Kataoka, O.; Garber, S. B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 12288

Asymmetric Addition of Organozinc Reagents to Ketones



			solvent-free or highly concentrated conditions				standard conditions			
entry	substrates	ZnR_2	L* (mol%)	t (h)	y (%)	ee (%)	L* (mol%)	t (h)	y (%)	ee (%)
1		$Zn((CH_2)_4OTBS)_2$	1	48	68	79[a]	10	72	89	98
			0.5	70	53	80[a]				
			0.25	82	44	69[a]				
			1	40	68	97[b]				
2		$Zn((CH_2)_5Br)_2$	1	46	66	92[a]	10	72	89	96
			0.5	50	41	92[a]				
			1	46	71	97[b]				

[a] Solvent-free conditions. [b] Concentrated reaction conditions (2 equiv toluene was added to the reaction).



Jeon, S.-J.; Li, H.; García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Org. Chem.* **2005**, *70*, 448.

Part I: Summary

- Asymmetric catalyst under solvent-free or highly concentrated conditions could result in stereoselectivity that rivals or even surpass what is obtained with reactions in organic solvents.

- Sometimes the presence of organic solvent is necessary to achieve high enantioselectivity/diastereoselectivity, and a screening should be performed to find the minimal amount of solvent in need, or a switch to the “green” solvent should be explored.

- Reactions conducted in the absence of solvent can rapidly generate heat, and precautions should be observed especially with large-scale reactions.

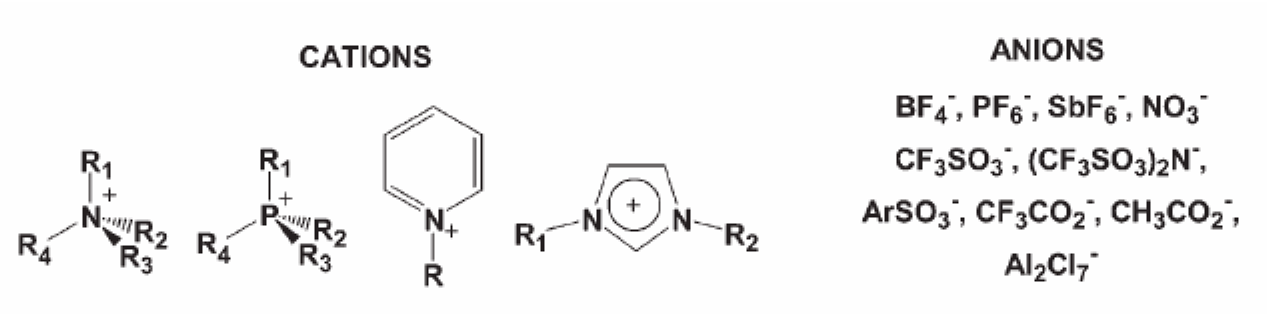
Part II: Ionic Liquid as A Solvent for Catalyzed Reactions

- Ionic liquids are substances that are completely composed of ions and are liquid at or close to room temperature.

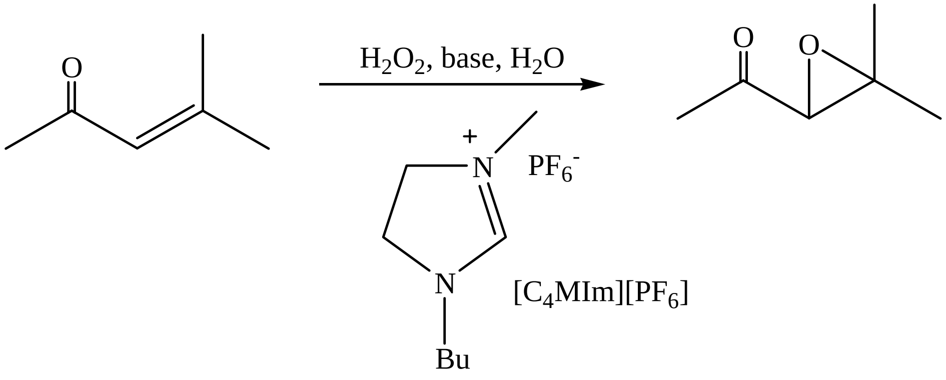
- Ionic liquids are nonvolatile and thermally stable, and their polarity, hydrophobicity, and solvent miscibility behavior could easily be tuned through appropriate modification of the cation and the anion.

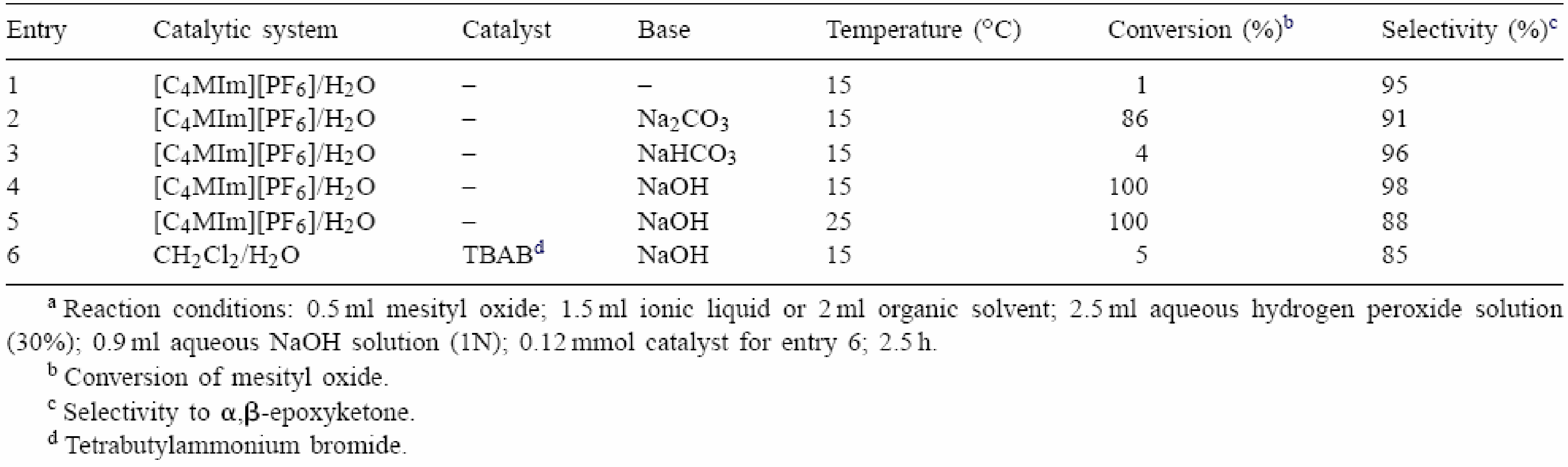
- The reaction product can generally be separated either through extraction or distillation from the ionic media, enabling recycling of the ionic liquids.

- Unique reactivities might be observed in ionic media.



Epoxidation Reactions





Entry	Catalytic system	Catalyst	Base	Temperature (°C)	Conversion (%)[b]	Selectivity (%)[c]
1	$[C_4MIm][PF_6]/H_2O$	–	–	15	1	95
2	$[C_4MIm][PF_6]/H_2O$	–	Na_2CO_3	15	86	91
3	$[C_4MIm][PF_6]/H_2O$	–	$NaHCO_3$	15	4	96
4	$[C_4MIm][PF_6]/H_2O$	–	NaOH	15	100	98
5	$[C_4MIm][PF_6]/H_2O$	–	NaOH	25	100	88
6	CH_2Cl_2/H_2O	TBAB[d]	NaOH	15	5	85

[a] Reaction conditions: 0.5 ml mesityl oxide; 1.5 ml ionic liquid or 2 ml organic solvent; 2.5 ml aqueous hydrogen peroxide solution (30%); 0.9 ml aqueous NaOH solution (1N); 0.12 mmol catalyst for entry 6; 2.5 h.

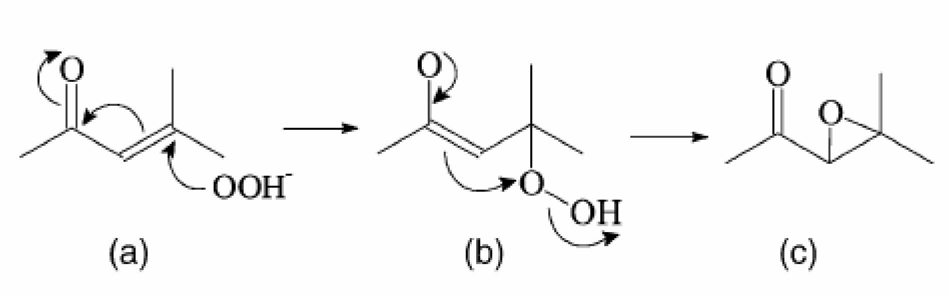
[b] Conversion of mesityl oxide.

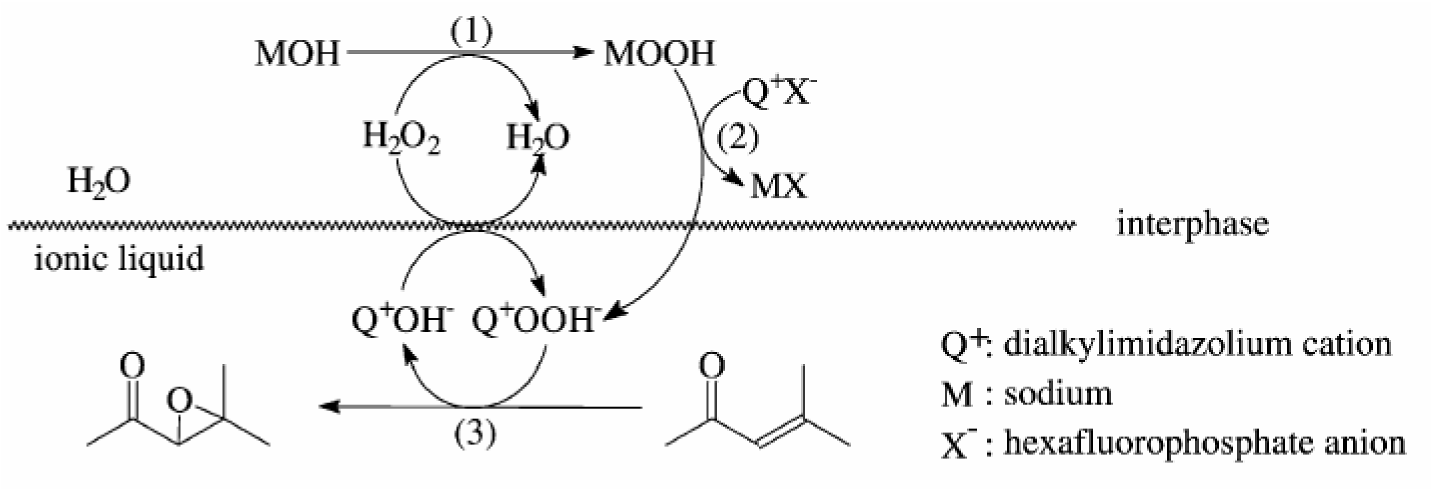
[c] Selectivity to α,β-epoxyketone.

[d] Tetrabutylammonium bromide.

Wang, B.; Kang, Y.-R.; Yang, L.-M.; Suo, J.-S. *J. Mol. Catal. A: Chem.* **2003**, *203*, 29.

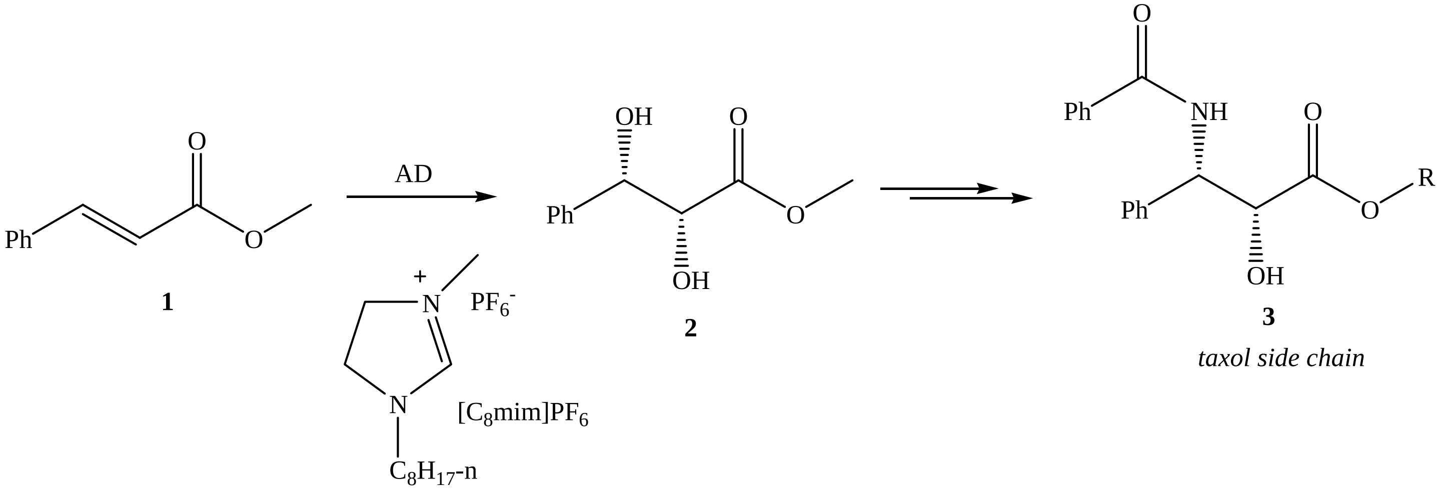
Biphasic Reaction Model





Wang, B.; Kang, Y.-R.; Yang, L.-M.; Suo, J.-S. *J. Mol. Catal. A: Chem.* **2003**, *203*, 29.

Sharpless Asymmetric Epoxidation



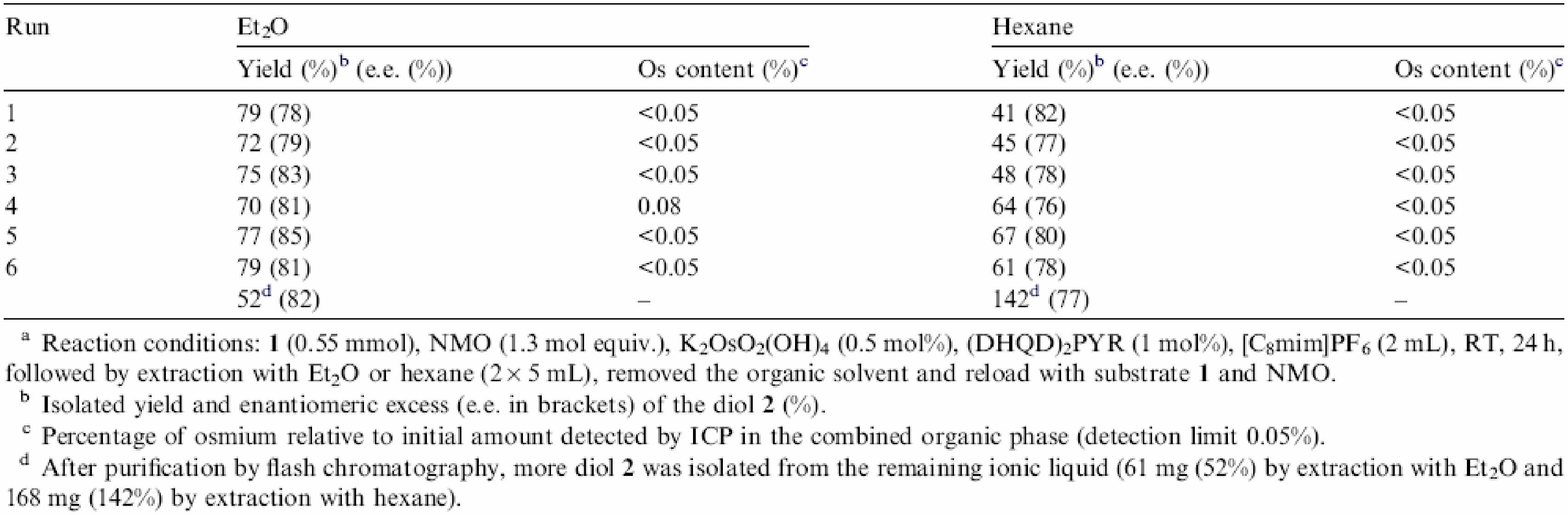
1

2

3

taxol side chain

[C_8mim]PF_6



Run	Et_2O		Hexane	
	Yield (%)[b] (e.e. (%))	Os content (%)[c]	Yield (%)[b] (e.e. (%))	Os content (%)[c]
1	79 (78)	<0.05	41 (82)	<0.05
2	72 (79)	<0.05	45 (77)	<0.05
3	75 (83)	<0.05	48 (78)	<0.05
4	70 (81)	0.08	64 (76)	<0.05
5	77 (85)	<0.05	67 (80)	<0.05
6	79 (81)	<0.05	61 (78)	<0.05
	52[d] (82)	–	142[d] (77)	–

[a] Reaction conditions: **1** (0.55 mmol), NMO (1.3 mol equiv.), $K_2OsO_2(OH)_4$ (0.5 mol%), $(DHQD)_2PYR$ (1 mol%), [C_8mim]PF_6 (2 mL), RT, 24 h, followed by extraction with Et_2O or hexane (2 × 5 mL), removed the organic solvent and reload with substrate **1** and NMO.

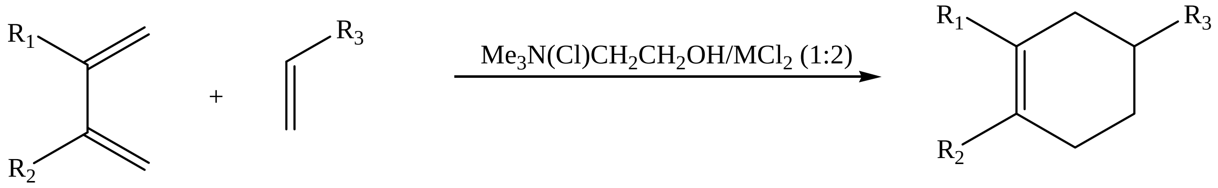
[b] Isolated yield and enantiomeric excess (e.e. in brackets) of the diol **2** (%).

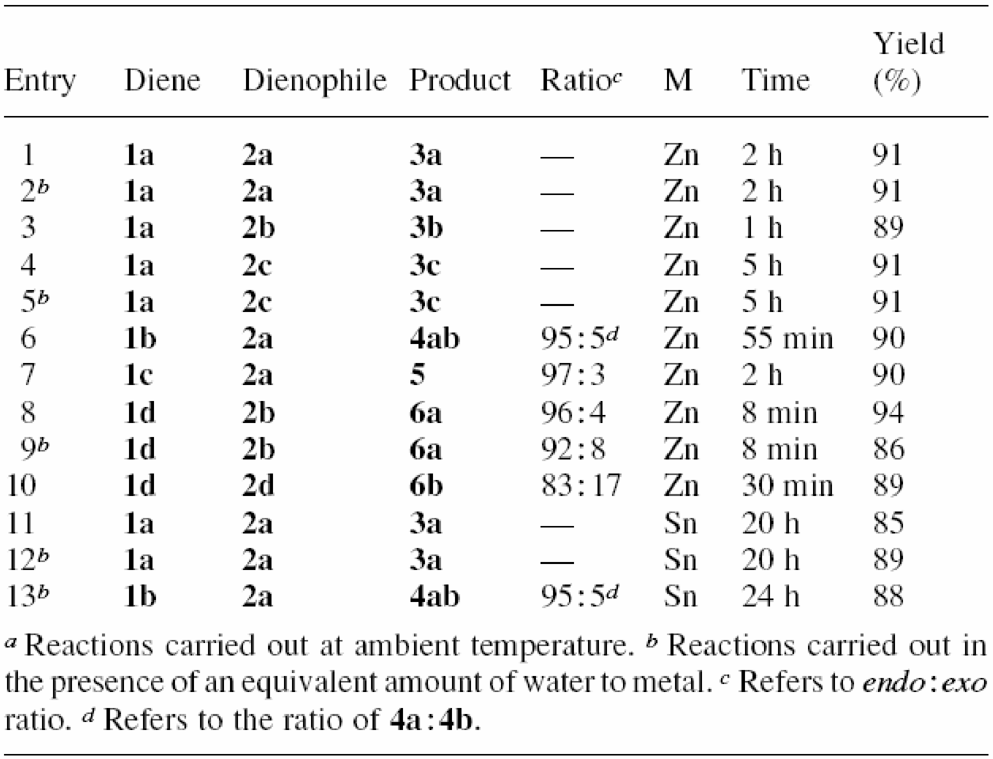
[c] Percentage of osmium relative to initial amount detected by ICP in the combined organic phase (detection limit 0.05%).

[d] After purification by flash chromatography, more diol **2** was isolated from the remaining ionic liquid (61 mg (52%) by extraction with Et_2O and 168 mg (142%) by extraction with hexane).

Serbanovic, A.; Branco, L. C.; da Ponte, M. N.; Afonso, C. A. M. *J. Organomet. Chem.* **2005**, *690*, 3600.

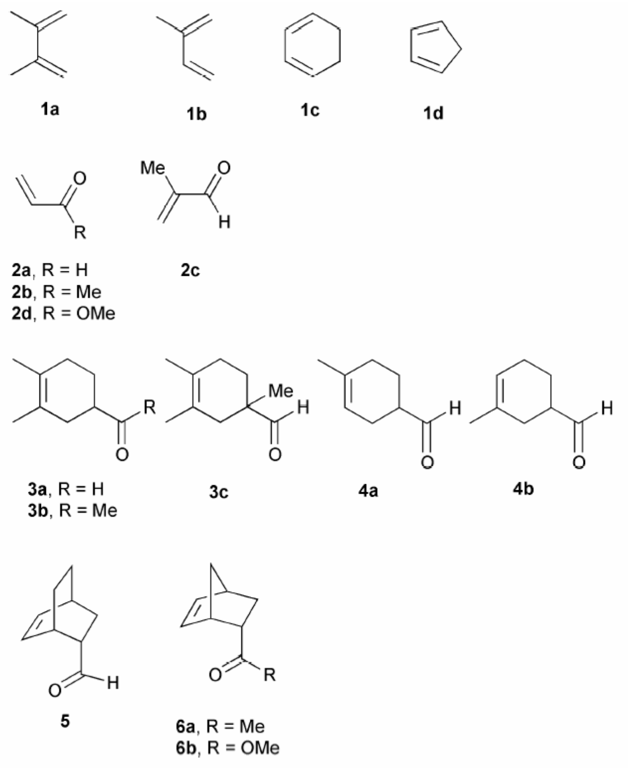
Diels-Alder Reaction





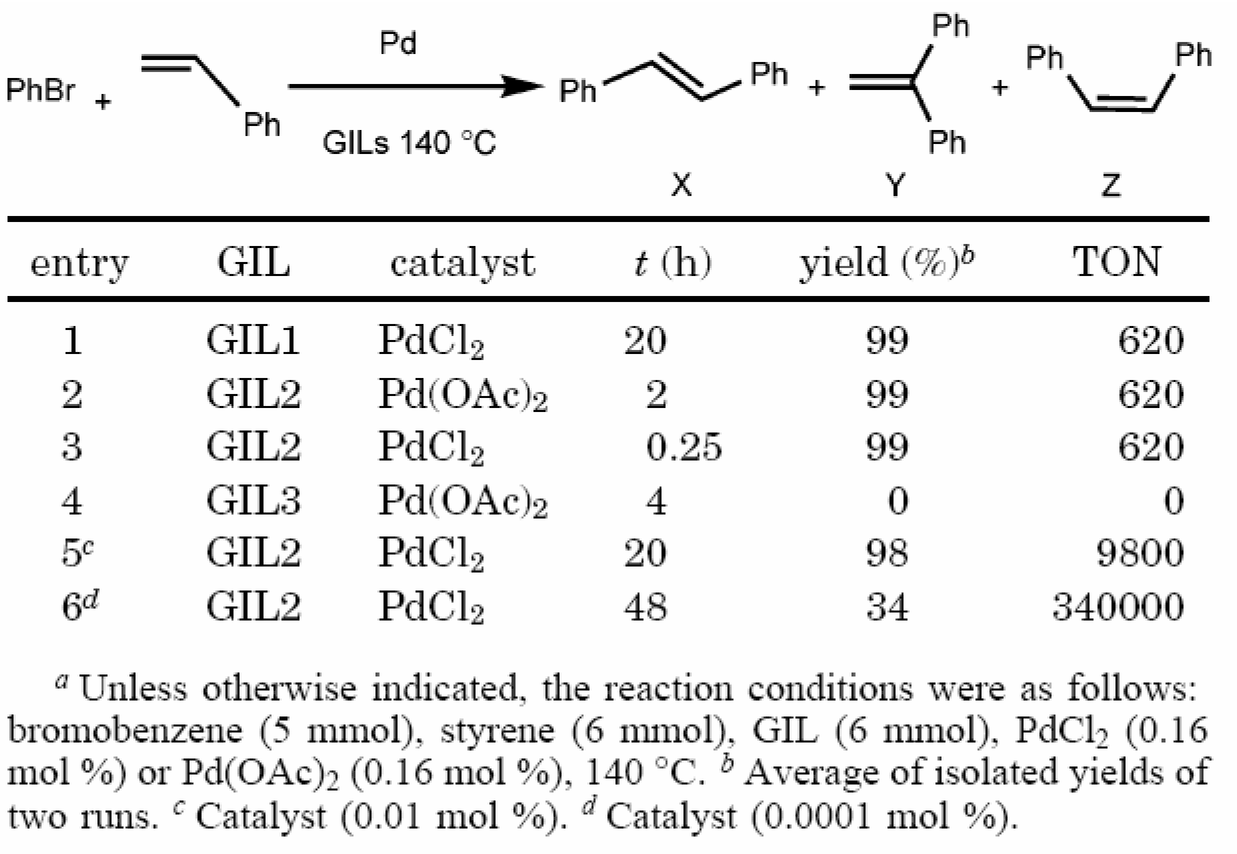
Entry	Diene	Dienophile	Product	Ratio[c]	M	Time	Yield (%)
1	**1a**	**2a**	**3a**	—	Zn	2 h	91
2[b]	**1a**	**2a**	**3a**	—	Zn	2 h	91
3	**1a**	**2b**	**3b**	—	Zn	1 h	89
4	**1a**	**2c**	**3c**	—	Zn	5 h	91
5[b]	**1a**	**2c**	**3c**	—	Zn	5 h	91
6	**1b**	**2a**	**4ab**	95:5[d]	Zn	55 min	90
7	**1c**	**2a**	**5**	97:3	Zn	2 h	90
8	**1d**	**2b**	**6a**	96:4	Zn	8 min	94
9[b]	**1d**	**2b**	**6a**	92:8	Zn	8 min	86
10	**1d**	**2d**	**6b**	83:17	Zn	30 min	89
11	**1a**	**2a**	**3a**	—	Sn	20 h	85
12[b]	**1a**	**2a**	**3a**	—	Sn	20 h	89
13[b]	**1b**	**2a**	**4ab**	95:5[d]	Sn	24 h	88

[a] Reactions carried out at ambient temperature. [b] Reactions carried out in the presence of an equivalent amount of water to metal. [c] Refers to *endo*:*exo* ratio. [d] Refers to the ratio of **4a**:**4b**.



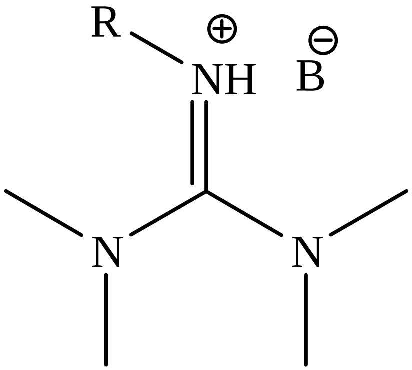
Abbott, A. P.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. *Green Chem.* **2002**, *4*, 24.

Heck Reaction



entry	GIL	catalyst	t (h)	yield (%)[b]	TON
1	GIL1	$PdCl_2$	20	99	620
2	GIL2	$Pd(OAc)_2$	2	99	620
3	GIL2	$PdCl_2$	0.25	99	620
4	GIL3	$Pd(OAc)_2$	4	0	0
5[c]	GIL2	$PdCl_2$	20	98	9800
6[d]	GIL2	$PdCl_2$	48	34	340000

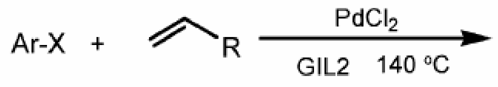
[a] Unless otherwise indicated, the reaction conditions were as follows: bromobenzene (5 mmol), styrene (6 mmol), GIL (6 mmol), $PdCl_2$ (0.16 mol %) or $Pd(OAc)_2$ (0.16 mol %), 140 °C. [b] Average of isolated yields of two runs. [c] Catalyst (0.01 mol %). [d] Catalyst (0.0001 mol %).

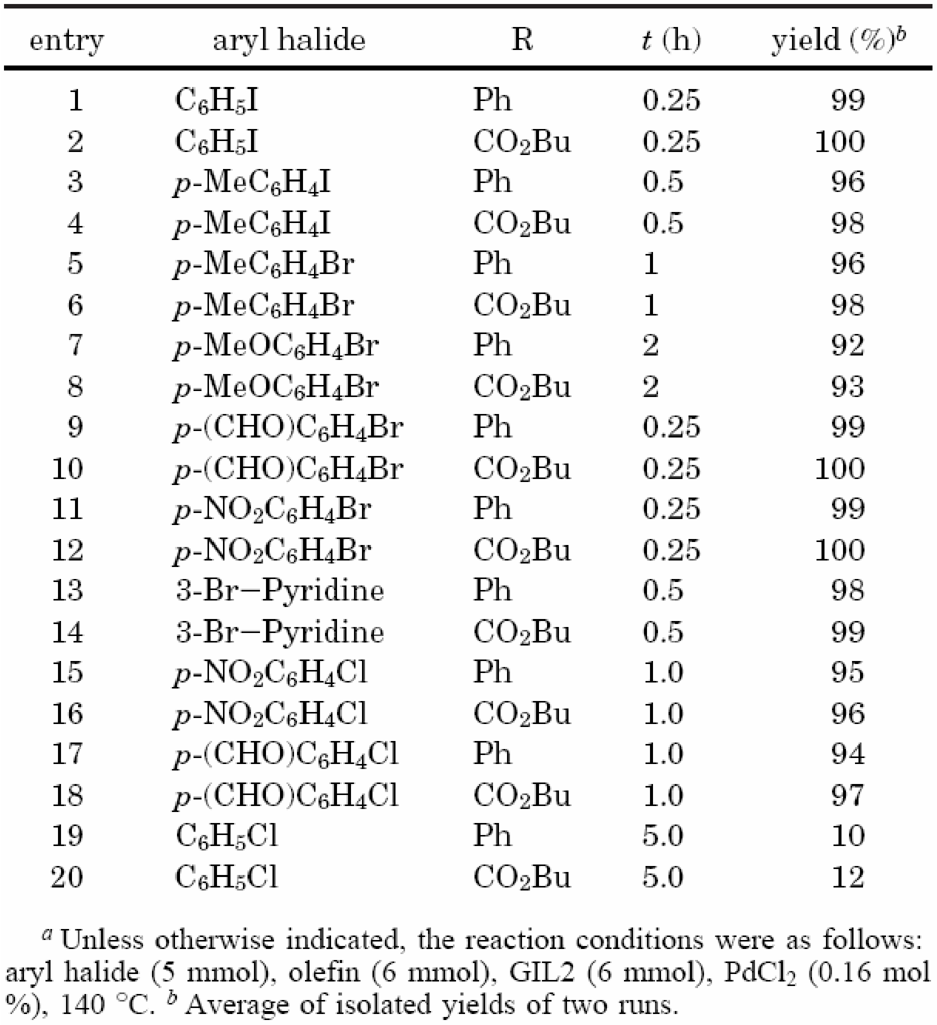


GIL 1: R = H, B = OAc
GIL 2: R = n-butyl, B = OAc
GIL 3: R = n-butyl, B = PF_6

Li, S.; Lin, Y.; Xie, H.; Zhang, S.; Xu, J. *Org. Lett.* **2006**, *8*, 391

Reaction Scope



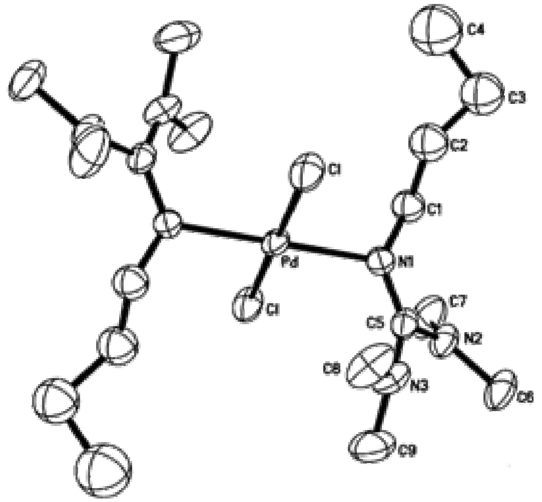


entry	aryl halide	R	t (h)	yield (%)[b]
1	C_6H_5I	Ph	0.25	99
2	C_6H_5I	CO_2Bu	0.25	100
3	p-MeC_6H_4I	Ph	0.5	96
4	p-MeC_6H_4I	CO_2Bu	0.5	98
5	p-MeC_6H_4Br	Ph	1	96
6	p-MeC_6H_4Br	CO_2Bu	1	98
7	p-$MeOC_6H_4Br$	Ph	2	92
8	p-$MeOC_6H_4Br$	CO_2Bu	2	93
9	p-$(CHO)C_6H_4Br$	Ph	0.25	99
10	p-$(CHO)C_6H_4Br$	CO_2Bu	0.25	100
11	p-$NO_2C_6H_4Br$	Ph	0.25	99
12	p-$NO_2C_6H_4Br$	CO_2Bu	0.25	100
13	3-Br−Pyridine	Ph	0.5	98
14	3-Br−Pyridine	CO_2Bu	0.5	99
15	p-$NO_2C_6H_4Cl$	Ph	1.0	95
16	p-$NO_2C_6H_4Cl$	CO_2Bu	1.0	96
17	p-$(CHO)C_6H_4Cl$	Ph	1.0	94
18	p-$(CHO)C_6H_4Cl$	CO_2Bu	1.0	97
19	C_6H_5Cl	Ph	5.0	10
20	C_6H_5Cl	CO_2Bu	5.0	12

[a] Unless otherwise indicated, the reaction conditions were as follows: aryl halide (5 mmol), olefin (6 mmol), GIL2 (6 mmol), $PdCl_2$ (0.16 mol %), 140 °C. [b] Average of isolated yields of two runs.

GIL2 functions as:

- a highly polar solvent to increase the reaction rate;
- a ligand to stabilize the activated Pd(0) during the reaction.



Li, S.; Lin, Y.; Xie, H.; Zhang, S.; Xu, J. *Org. Lett.* **2006**, *8*, 391.

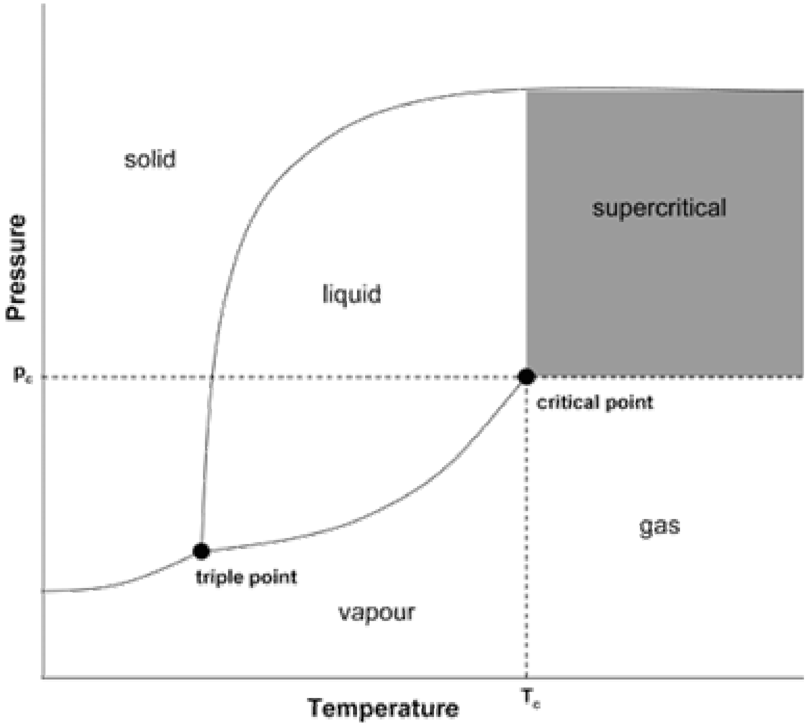
Part II: Summary

- Ionic liquids are greener substitutes for the common volatile and hazardous organic solvents.

- Separation of product is generally done by biphasic extraction or by distillation. The catalyst and ionic liquid can be recycled for usage.

- A screening is usually needed to find the optimal ionic liquid for the reaction, and multi-step synthesis is sometimes needed to prepare the ionic liquid.

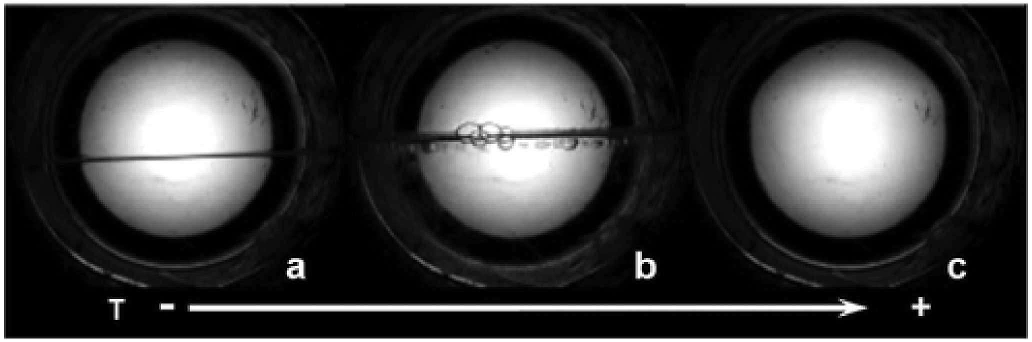
Part III: Supercritical Fluids



- A SCF is defined as the state of a compound or element above its critical temperature (*T*c) and critical pressure (*P*c) but below the pressure required to condense it into a solid.

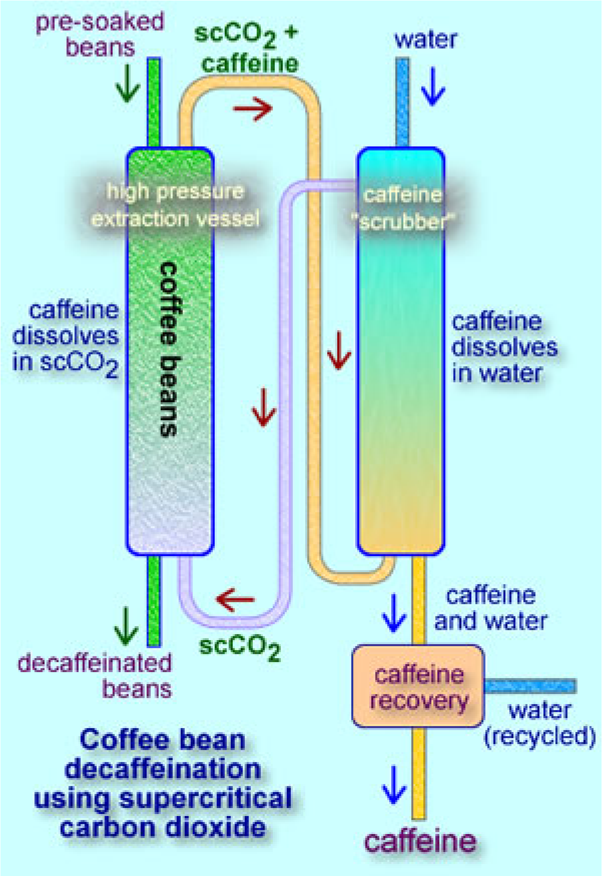
- The SCF possesses both gaseous and liquid properties. Whereas gas-like diffusivities and low viscosity coefficients allow the fluid to permeate through porous solids more quickly than a pure liquid could, liquid-like densities and dissolving powers allow the SCF to function as an effective reaction solvent.

- Small changes in temperature or pressure, particularly near the critical point, can result in dramatic changes in physical properties of the SCF.

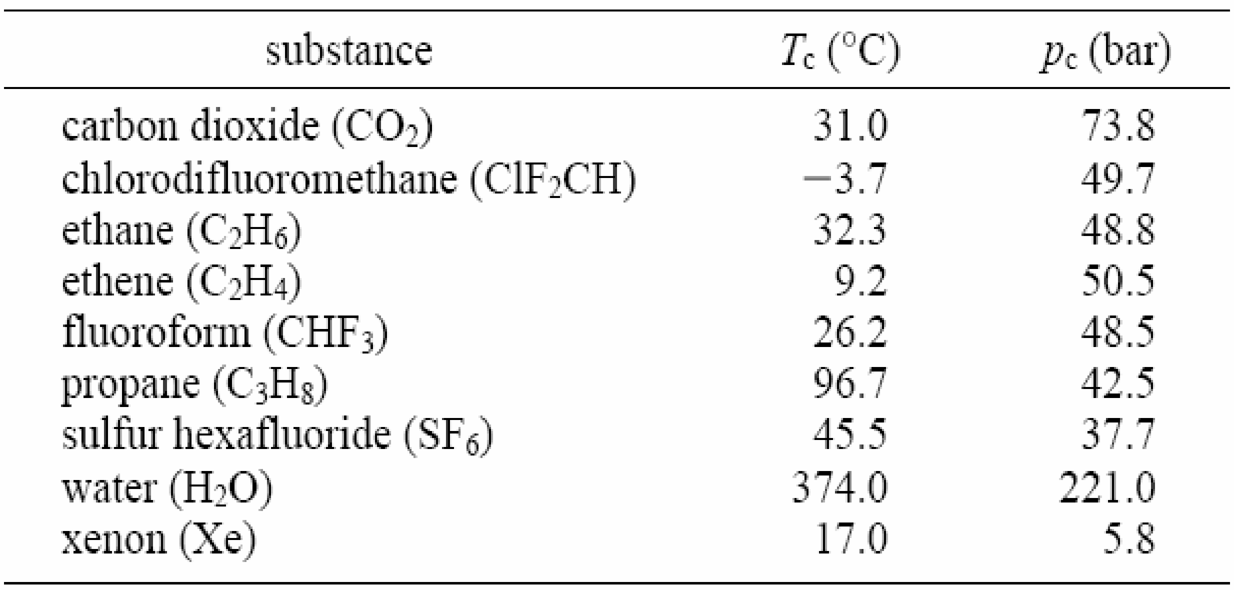


Licence, P.; Litchfield, D.; Dellar, M. P.; Poliakoff, M. *Green Chem.* **2004**, *6*, 352.

Commonly Utilized SCFs

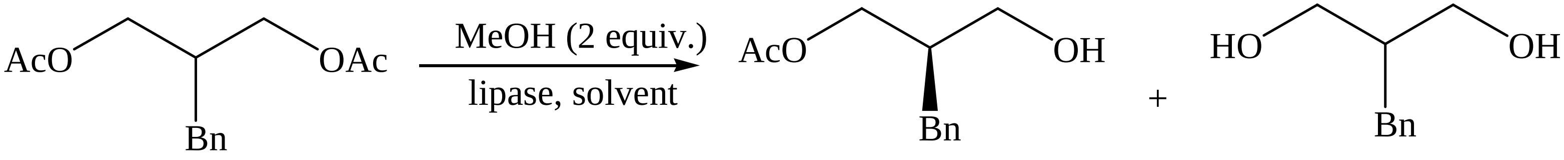


Coffee bean decaffeination using supercritical carbon dioxide

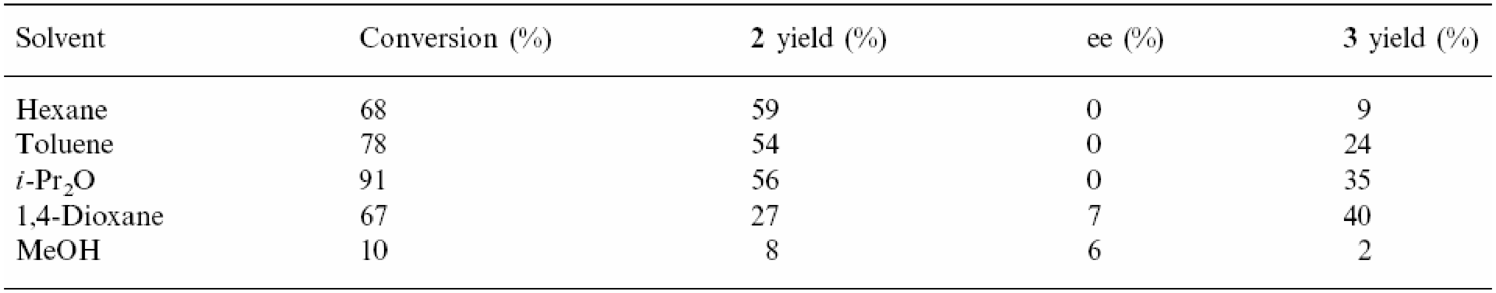


substance	T_c (°C)	p_c (bar)
carbon dioxide (CO_2)	31.0	73.8
chlorodifluoromethane (ClF_2CH)	−3.7	49.7
ethane (C_2H_6)	32.3	48.8
ethene (C_2H_4)	9.2	50.5
fluoroform (CHF_3)	26.2	48.5
propane (C_3H_8)	96.7	42.5
sulfur hexafluoride (SF_6)	45.5	37.7
water (H_2O)	374.0	221.0
xenon (Xe)	17.0	5.8

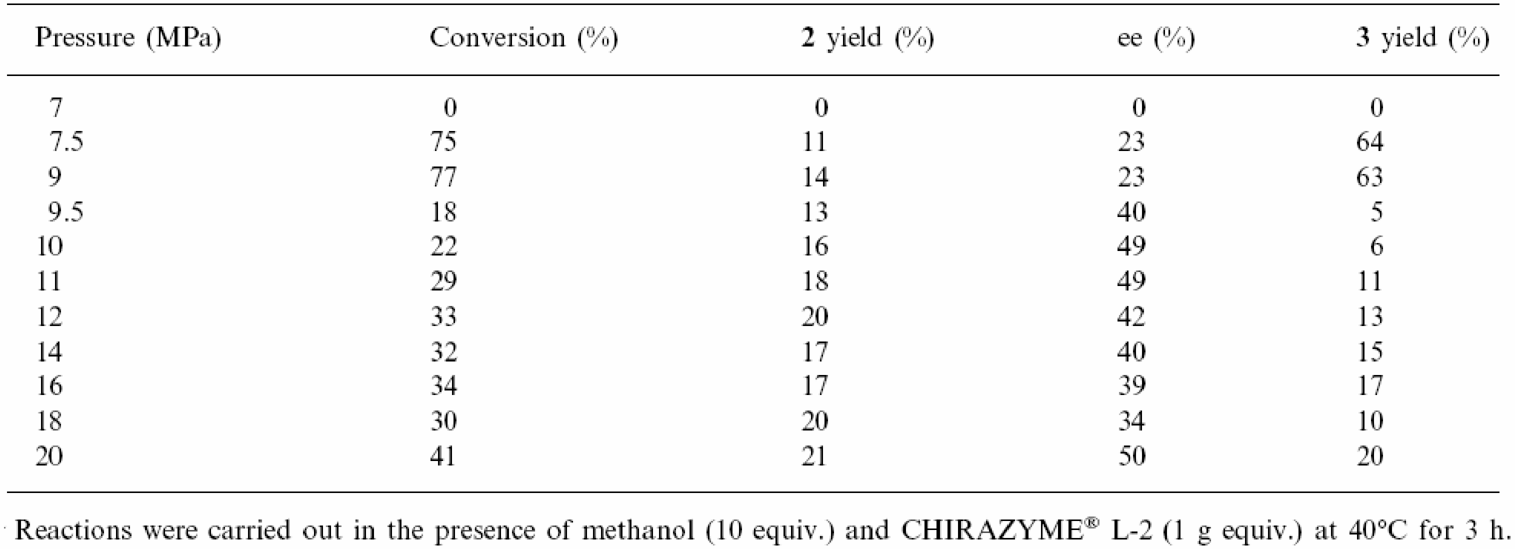
Enzymes in SCF



1 **(*R*)-2** **3**



Solvent	Conversion (%)	**2** yield (%)	ee (%)	**3** yield (%)
Hexane	68	59	0	9
Toluene	78	54	0	24
i-Pr_2O	91	56	0	35
1,4-Dioxane	67	27	7	40
MeOH	10	8	6	2

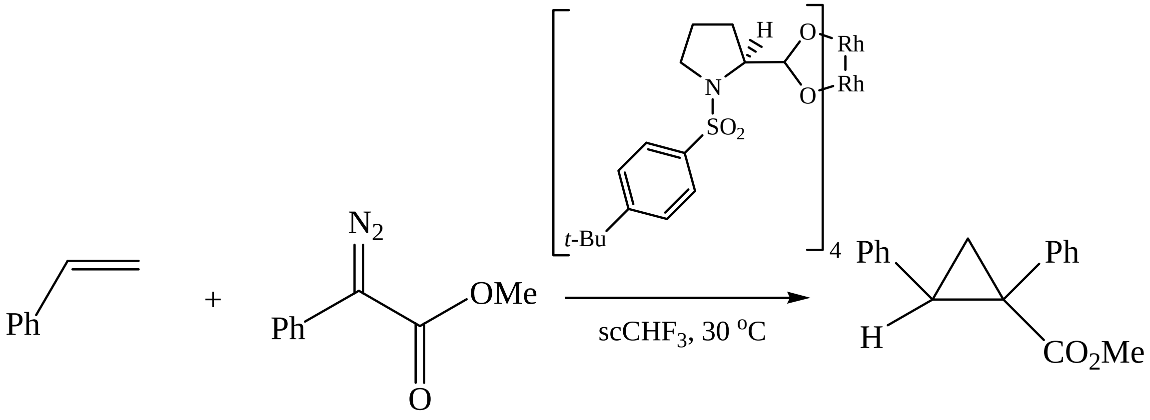


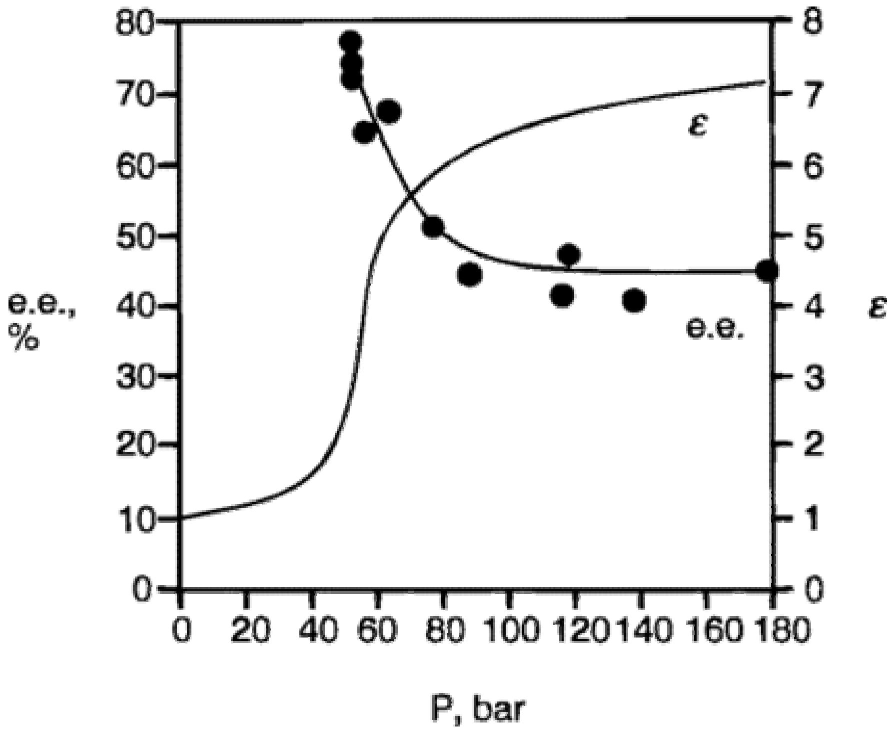
Pressure (MPa)	Conversion (%)	**2** yield (%)	ee (%)	**3** yield (%)
7	0	0	0	0
7.5	75	11	23	64
9	77	14	23	63
9.5	18	13	40	5
10	22	16	49	6
11	29	18	49	11
12	33	20	42	13
14	32	17	40	15
16	34	17	39	17
18	30	20	34	10
20	41	21	50	20

Reactions were carried out in the presence of methanol (10 equiv.) and CHIRAZYME® L-2 (1 g equiv.) at 40°C for 3 h.

Mase, N.; Sako, T.; Horikawa, Y.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 5175.

Effect of Pressure Change

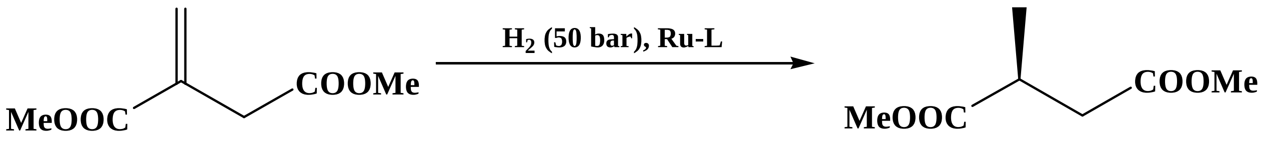


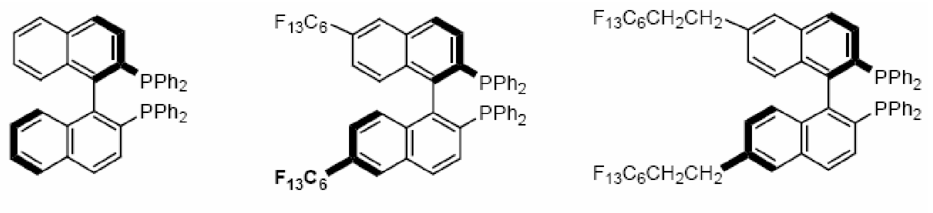


- The dependence of the dielectric constant of a SCF upon pressure can cause the enantioselectivity of homogeneous catalysis to be pressure dependent.

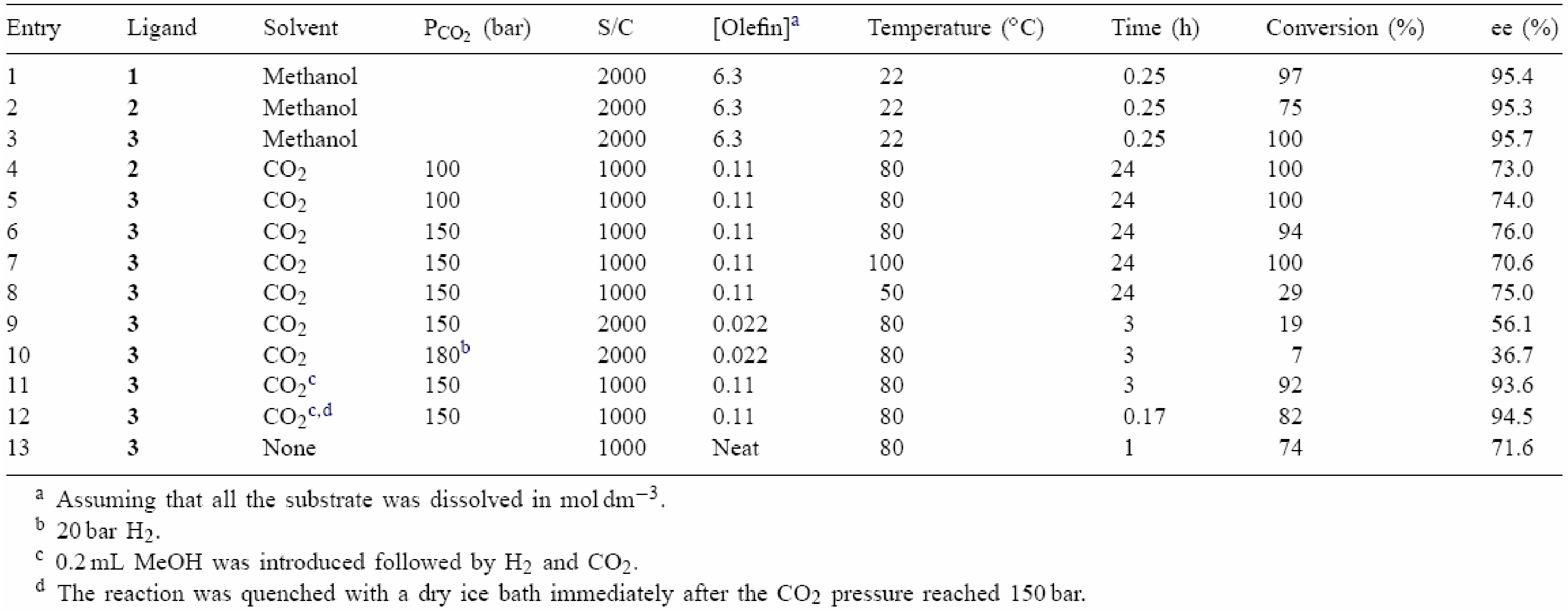
Wynne, D. C.; Olmstead, M. M.; Jessop, P. G. *J. Am. Chem. Soc.* **2000,** *122*, 7638-7647.

Asymmetric Hydrogenation





1 **2** **3**



Entry	Ligand	Solvent	P_{CO_2} (bar)	S/C	[Olefin][a]	Temperature (°C)	Time (h)	Conversion (%)	ee (%)
1	**1**	Methanol		2000	6.3	22	0.25	97	95.4
2	**2**	Methanol		2000	6.3	22	0.25	75	95.3
3	**3**	Methanol		2000	6.3	22	0.25	100	95.7
4	**2**	CO_2	100	1000	0.11	80	24	100	73.0
5	**3**	CO_2	100	1000	0.11	80	24	100	74.0
6	**3**	CO_2	150	1000	0.11	80	24	94	76.0
7	**3**	CO_2	150	1000	0.11	100	24	100	70.6
8	**3**	CO_2	150	1000	0.11	50	24	29	75.0
9	**3**	CO_2	150	2000	0.022	80	3	19	56.1
10	**3**	CO_2	180[b]	2000	0.022	80	3	7	36.7
11	**3**	CO_2[c]	150	1000	0.11	80	3	92	93.6
12	**3**	CO_2[c,d]	150	1000	0.11	80	0.17	82	94.5
13	**3**	None		1000	Neat	80	1	74	71.6

[a] Assuming that all the substrate was dissolved in mol dm^{-3}.

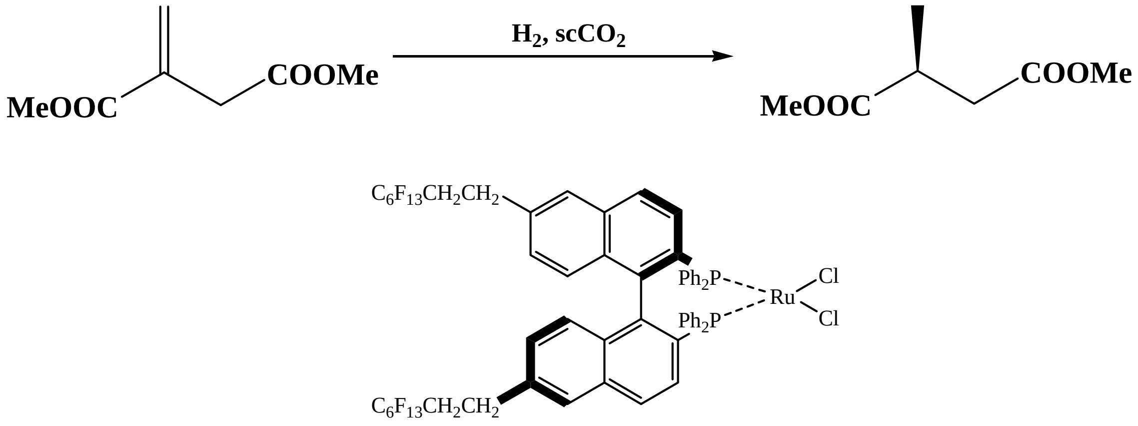
[b] 20 bar H_2.

[c] 0.2 mL MeOH was introduced followed by H_2 and CO_2.

[d] The reaction was quenched with a dry ice bath immediately after the CO_2 pressure reached 150 bar.

Hu, Y. L.; Birdsall, D. J.; Stuart, A. M.; Hope, E. G.; Xiao, J. L. *J. Mol. Catal. A: Chem.* **2004**, *219*, 57.

$scCO_2$ Not An Optimal Solvent



Entry	P_{H_2} (bar)	P_{CO_2} (bar)	Temperature (°C)	CH_3OH (mL)	Time (h)	Conversion (%)	ee (%)
1	50	10	80	0.20	1	100	95.2
2	50	20	80	0.20	1	100	96.2
3	50	40	80	0.20	1	100	92.0
4	50	60	80	0.20	1	95	79.8
5	50	100	80	0.20	1	65	84.6
6	50	150	80	0.24[b]	3	13	73.6

[a] Methanol was introduced at room temperature before hydrogenation took place. Two hundred milligram (1.3 mmol) substrate was used with S/C = 2000.

[b] Methanol was introduced under $scCO_2$ conditions via a sample loop.

- ➢ Reduced polarity from methanol to $scCO_2$ caused lower catalyst activity and enantioselectivity.

Hu, Y. L.; Birdsall, D. J.; Stuart, A. M.; Hope, E. G.; Xiao, J. L. *J. Mol. Catal. A: Chem.* **2004**, *219*, 57.

Part III: Summary

- Enzyme-catalyzed reactions in $scCO_2$ generally provides superior results to those obtained in conventional organic solvents or solvent-free systems.

- For organometallic-catalyzed reactions that are facilitated in polar solvent, SCFs are likely not the optimal solvents due their relatively low polarity. Thus new catalysts still need to be developed for efficient catalytic processes in SCFs.

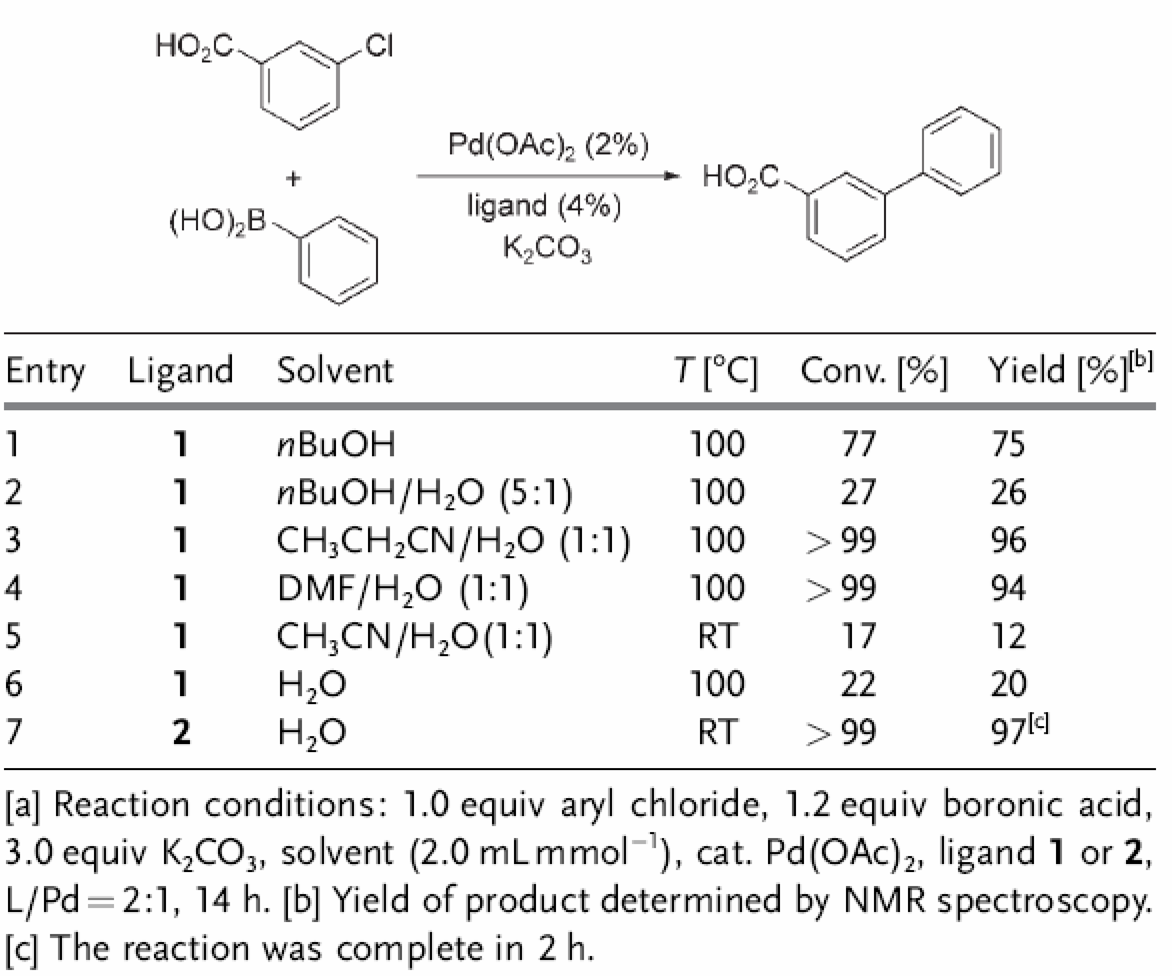
- As compared to traditional organic solvent, $scCO_2$ is superior for extraction purposes.

Part IV: Catalyzed Reactions in Water

Water: the *Greenest* Solvent of All

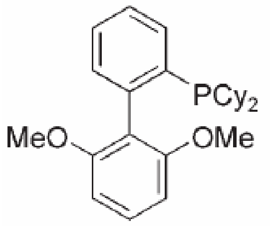
- The most abundantly existing liquid solvent
- Nontoxic, nonflammable and environmentally benign
- Unique reactivity and selectivity might result from the hydrophobic effects.

Suzuki-Miyaura Coupling



Entry	Ligand	Solvent	T [°C]	Conv. [%]	Yield [%][b]
1	**1**	nBuOH	100	77	75
2	**1**	nBuOH/H_2O (5:1)	100	27	26
3	**1**	CH_3CH_2CN/H_2O (1:1)	100	>99	96
4	**1**	DMF/H_2O (1:1)	100	>99	94
5	**1**	CH_3CN/H_2O(1:1)	RT	17	12
6	**1**	H_2O	100	22	20
7	**2**	H_2O	RT	>99	97[c]

[a] Reaction conditions: 1.0 equiv aryl chloride, 1.2 equiv boronic acid, 3.0 equiv K_2CO_3, solvent (2.0 mL mmol^{-1}), cat. Pd(OAc)$_2$, ligand **1** or **2**, L/Pd = 2:1, 14 h. [b] Yield of product determined by NMR spectroscopy. [c] The reaction was complete in 2 h.



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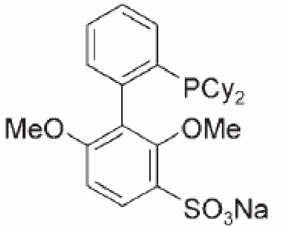
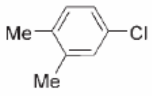
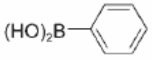
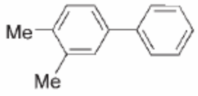
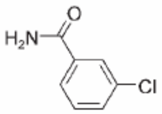
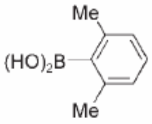
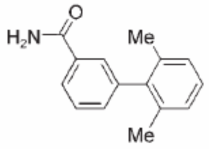
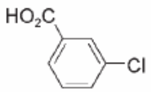
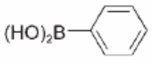
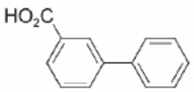
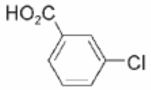
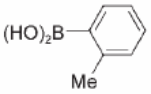
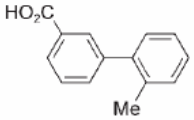
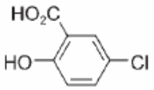
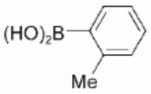
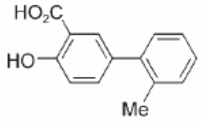
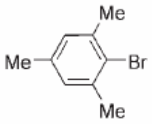
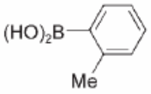
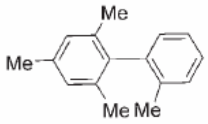
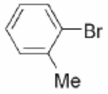
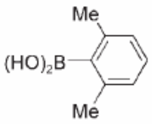
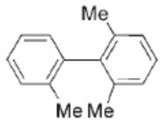
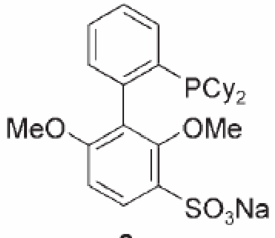


2

Anderson, K. W.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **2005**, *44*, 6173.

Reaction Scope

Entry	Halide	Boronic acid	Product	Pd [mol%]	Conditions	Yield [%][b]
1				2	RT, 10 h	99
2				1 1	100 °C, 8 h 150 °C, 10 min	99 94[c]
3				2 0.5 0.1 0.1	RT, 2 h RT, 8 h 100 °C, 5 h 150 °C, 10 min	96 97 97 98[c]
4				0.5 0.1	RT, 8 h 100 °C, 6 h	95 96
5				2 0.1	RT, 12 h 100 °C, 12 h	99[d] 96[d]
6				2	RT, 22 h	94
7				2	RT, 22 h	97

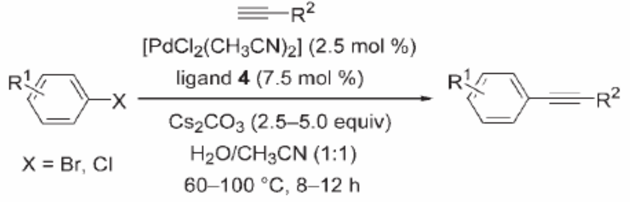


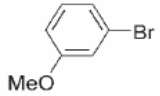
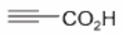
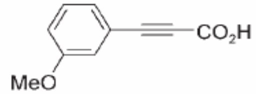
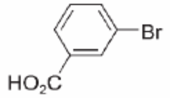
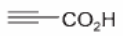
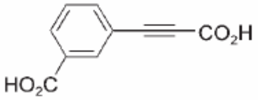
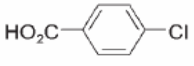
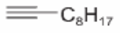
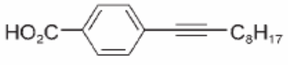
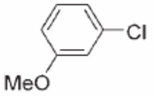
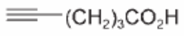
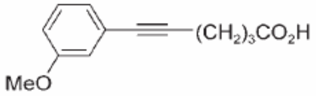
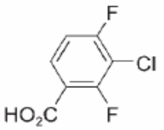
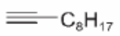
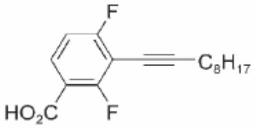
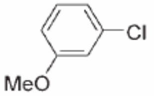
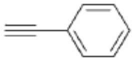
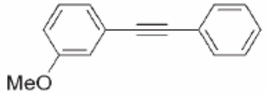
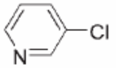
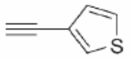
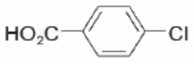
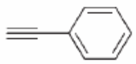
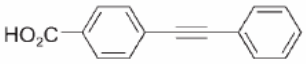
2

[a] Reaction conditions: 1.0 equiv aryl chloride, 1.2 equiv boronic acid, 3.0 equiv K_2CO_3, degassed water (1.5 mL mmol^{-1}), cat. $Pd(OAc)_2$, ligand **2**, L/Pd = 2:1. [b] Yield of isolated product (average of two runs). [c] Conducted using microwave irradiation with cooling. [d] 4.0 equiv K_2CO_3 was used.

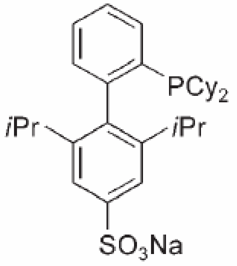
Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed*. **2005**, *44*, 6173.

Sonogashira Coupling in Water



Entry	Halide	Alkyne	Product	Yield [%][b]
1				70[c,d]
2				69[c,d]
3				86
4				85[d]
5				71
6				88
7				93
8				96[d]

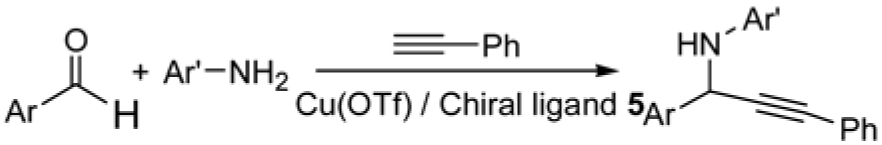
[a] Reaction conditions: 1.0 equiv aryl halide, 1.3–1.5 equiv terminal alkyne, 2.5–5.0 equiv Cs_2CO_3, degassed water (2.0 mL mmol^{-1}), CH_3CN (2.0 mL mmol^{-1}), [$PdCl_2(CH_3CN)_2$] (2.5 mol%), ligand **4** (7.5 mol%), 100 °C, 8–12 h. Reaction times were not optimized. [b] Yield of isolated product (average of two runs). [c] The alkyne was added to the reaction at 0 °C and the mixture was heated to 60 °C. [d] To ease in purification, the product was converted to the methyl ester using trimethylsilyldiazomethane.



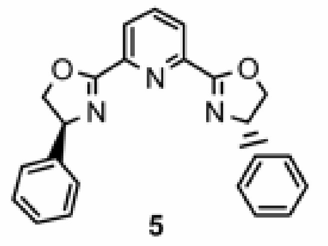
4

Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173.

Asymmetric Addition to Imines in Toluene



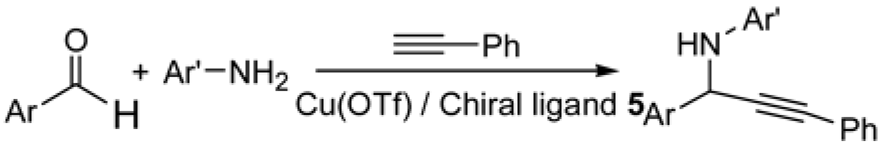
Entry	Aldehyde	Aniline	Temperature, °C/ time, days	Yield, %	OR/ ee %
1	PhCHO	$PhNH_2$	22/4	78	(+) 96
2	PhCHO	$PhNH_2$	35/2	83	(+) 93
3	$4\text{-}CH_3C_6H_4CHO$	$PhNH_2$	35/2	85	(+) 92
4	$4\text{-}C_2H_5C_6H_4CHO$	$PhNH_2$	22/4	70	(+) 96
5	$4\text{-}C_2H_5C_6H_4CHO$	$PhNH_2$	35/2	73	(+) 95
6	$4\text{-}ClC_6H_4CHO$	$PhNH_2$	22/4	85	(+) 94
7	$4\text{-}ClC_6H_4CHO$	$PhNH_2$	35/2	90	(+) 92
8	$4\text{-}BrC_6H_4CHO$	$PhNH_2$	22/4	87	(+) 94
9	$4\text{-}BrC_6H_4CHO$	$PhNH_2$	35/2	90	(+) 92
10	$3\text{-}BrC_6H_4CHO$	$PhNH_2$	22/4	85	(+) 95
11	$3\text{-}BrC_6H_4CHO$	$PhNH_2$	35/2	88	(+) 92
12	$4\text{-}PhC_6H_4CHO$	$PhNH_2$	22/4	81	(+) 94
13	$4\text{-}PhC_6H_4CHO$	$PhNH_2$	35/2	85	(+) 90
14	2-NaphCHO	$PhNH_2$	22/4	63	(+) 88
15	2-NaphCHO	$PhNH_2$	35/2	67	(+) 82
16	$4\text{-}CF_3C_6H_4CHO$	$PhNH_2$	22/4	71	(+) 93
17	PhCHO	$4\text{-}BrC_6H_4NH_2$	35/2	93	(+) 91
18	PhCHO	$4\text{-}ClC_6H_4NH_2$	35/2	92	(+) 91
19	PhCHO	$4\text{-}CH_3C_6H_4NH_2$	35/2	93	(+) 94

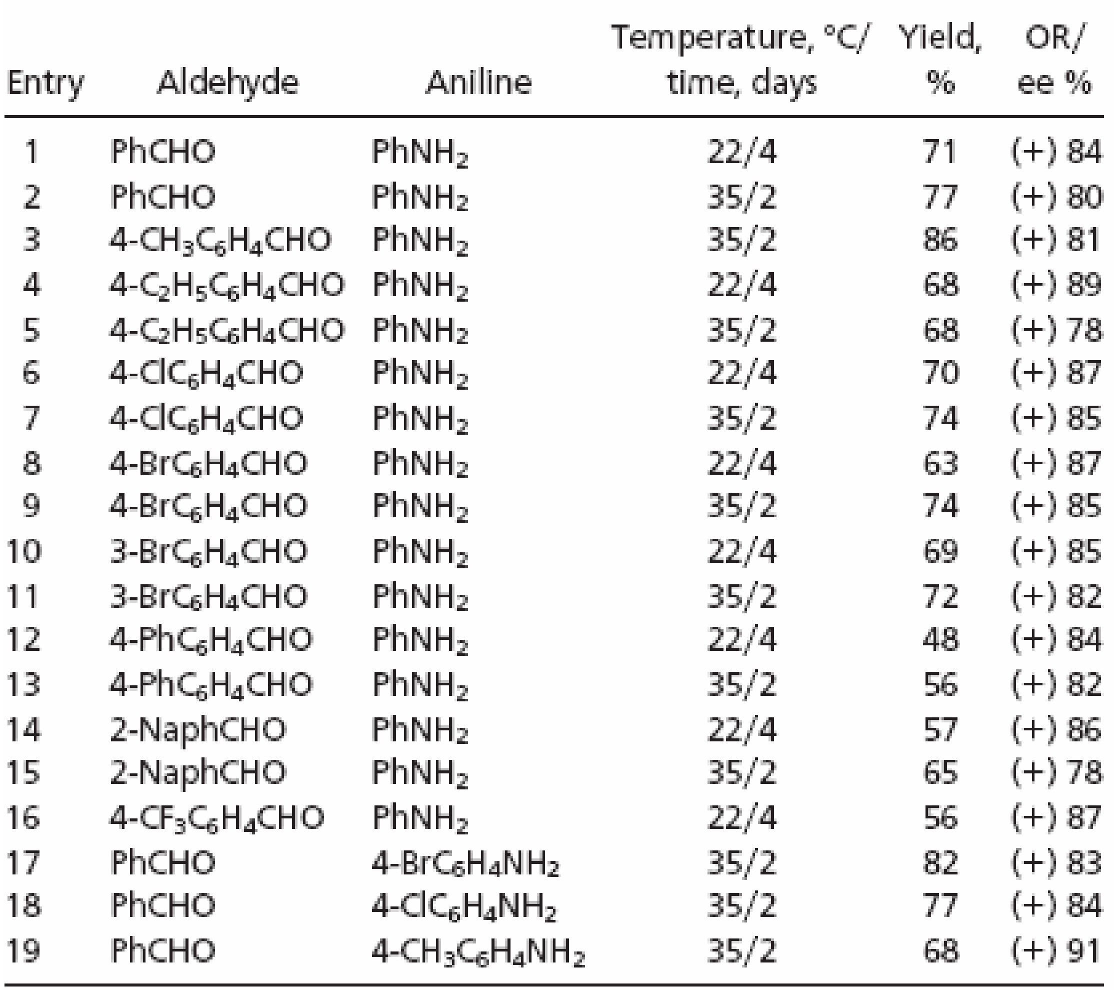


5

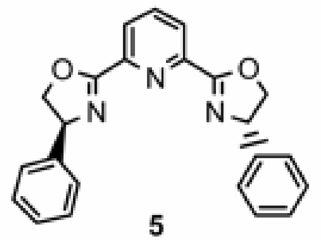
Wei, C.; Mague, J. T.; Li, C.-J. *Proc. Nat. Aca. Sci.* **2004**, *101*,5749**.**

Asymmetric Addition to Imines in Water





Entry	Aldehyde	Aniline	Temperature, °C/ time, days	Yield, %	OR/ ee %
1	PhCHO	$PhNH_2$	22/4	71	(+) 84
2	PhCHO	$PhNH_2$	35/2	77	(+) 80
3	$4\text{-}CH_3C_6H_4CHO$	$PhNH_2$	35/2	86	(+) 81
4	$4\text{-}C_2H_5C_6H_4CHO$	$PhNH_2$	22/4	68	(+) 89
5	$4\text{-}C_2H_5C_6H_4CHO$	$PhNH_2$	35/2	68	(+) 78
6	$4\text{-}ClC_6H_4CHO$	$PhNH_2$	22/4	70	(+) 87
7	$4\text{-}ClC_6H_4CHO$	$PhNH_2$	35/2	74	(+) 85
8	$4\text{-}BrC_6H_4CHO$	$PhNH_2$	22/4	63	(+) 87
9	$4\text{-}BrC_6H_4CHO$	$PhNH_2$	35/2	74	(+) 85
10	$3\text{-}BrC_6H_4CHO$	$PhNH_2$	22/4	69	(+) 85
11	$3\text{-}BrC_6H_4CHO$	$PhNH_2$	35/2	72	(+) 82
12	$4\text{-}PhC_6H_4CHO$	$PhNH_2$	22/4	48	(+) 84
13	$4\text{-}PhC_6H_4CHO$	$PhNH_2$	35/2	56	(+) 82
14	2-NaphCHO	$PhNH_2$	22/4	57	(+) 86
15	2-NaphCHO	$PhNH_2$	35/2	65	(+) 78
16	$4\text{-}CF_3C_6H_4CHO$	$PhNH_2$	22/4	56	(+) 87
17	PhCHO	$4\text{-}BrC_6H_4NH_2$	35/2	82	(+) 83
18	PhCHO	$4\text{-}ClC_6H_4NH_2$	35/2	77	(+) 84
19	PhCHO	$4\text{-}CH_3C_6H_4NH_2$	35/2	68	(+) 91



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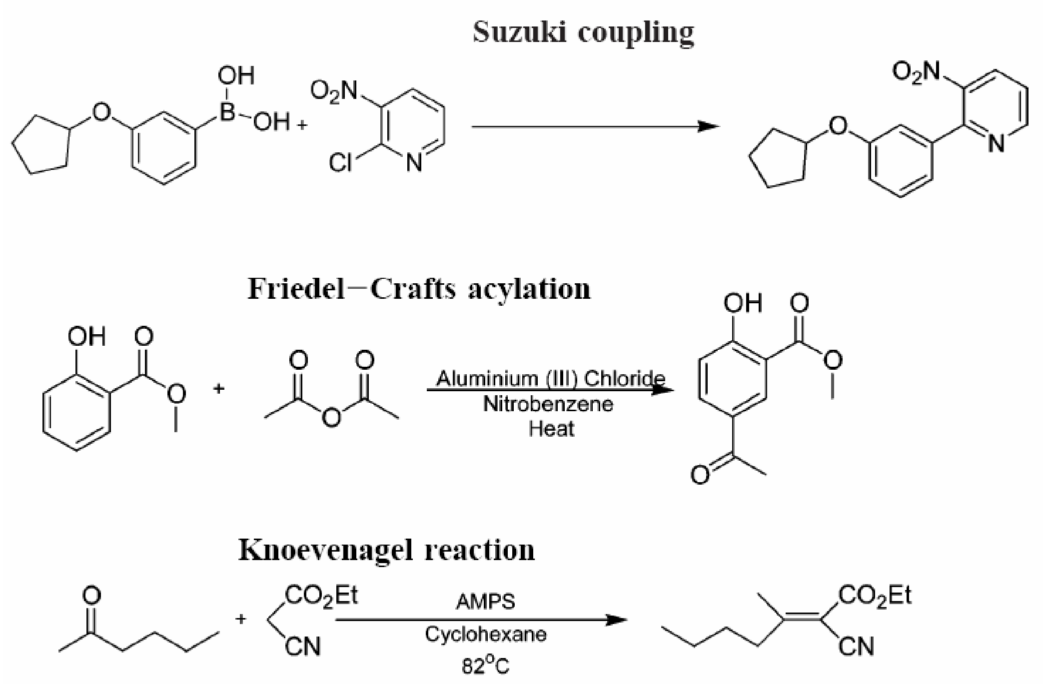
Wei, C.; Mague, J. T.; Li, C.-J. *Proc. Nat. Aca. Sci.* **2004**, *101*,5749**.**

Microwave-Assisted Reactions in Water

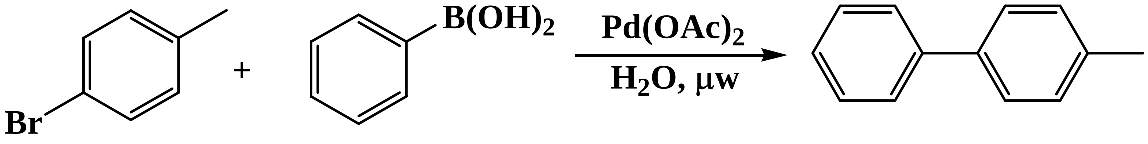


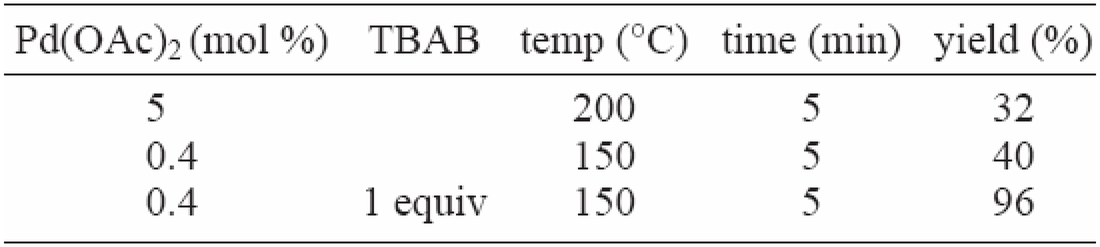
reaction	thermal yield[a]/ energy[b]	microwave yield[a]/ energy[b]	E(thermal)/ E(microwave)
heterogeneous Suzuki[c]	28.6/120700	77.4/1448	83.3:1
Friedel-Crafts acylation[c]	100/13.6	100/9.7	1.4:1
Knoevenagel[d]	68.2/132	18.2/37	3.6:1

[a] % yield.[b] kW/mol.[c] GC yield.[d] GC yield corrected by R_f.

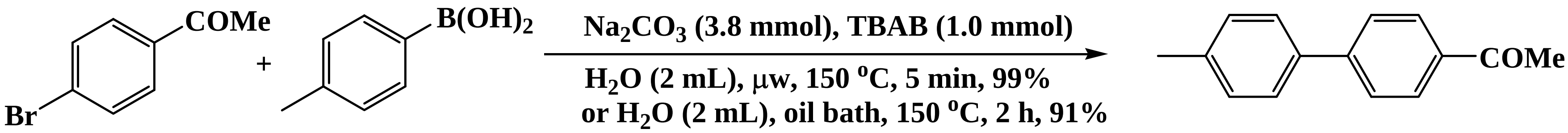
Gronnow, M. J.; White, R. J.; Clark, J. H.; Macquarrie, D. J. *Org. Process Res. Dev.* **2005**, *9*, 516.

Ligand-Free Suzuki Coupling in Water





$Pd(OAc)_2$ (mol %)	TBAB	temp (°C)	time (min)	yield (%)
5		200	5	32
0.4		150	5	40
0.4	1 equiv	150	5	96



Na_2CO_3 (3.8 mmol), TBAB (1.0 mmol)

H_2O (2 mL), µw, 150 °C, 5 min, 99%

or H_2O (2 mL), oil bath, 150 °C, 2 h, 91%

1 mmol

1.3 mmol

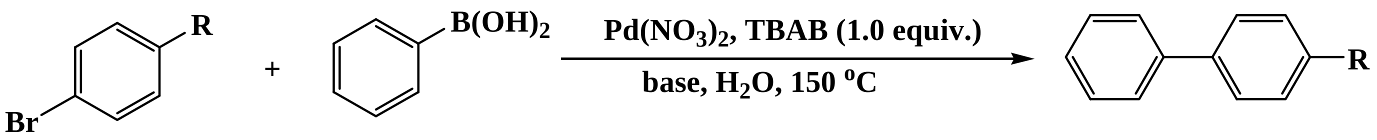
Transition Metal-Free Catalysis?

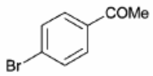
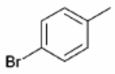
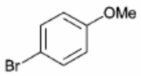
"To show that the reaction is indeed transition-metal free, we used new glassware, apparatus, reagents (not only were new bottles of reagents used but also a range of suppliers' reagents were screened in the reaction and all found to lead to the same yields of biaryl formation), and spatula and analyzed the entire crude product mixture from a reaction for palladium content. We found that there was no palladium in the mixture down to the level of detection of the analytical apparatus (less than 0.1 ppm)."

Leadbeater, N. E.; Marco, M. *Org. Lett.* **2002**, *4*, 2973.
Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 5660.

Pd Is Ubiquitous

- A careful reanalysis revealed 20-50 ppb of Pd in commercially available *ultrapure* Na_2CO_3.

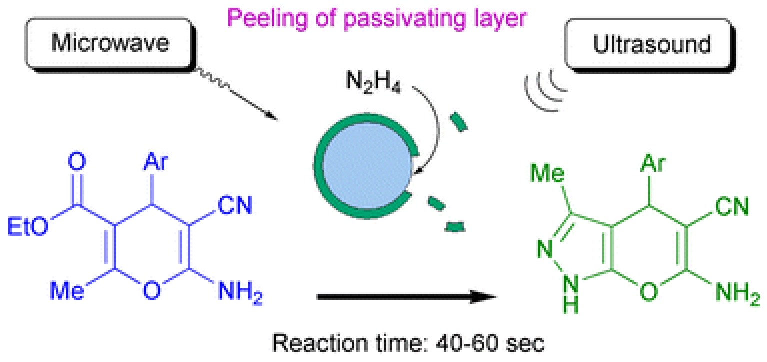


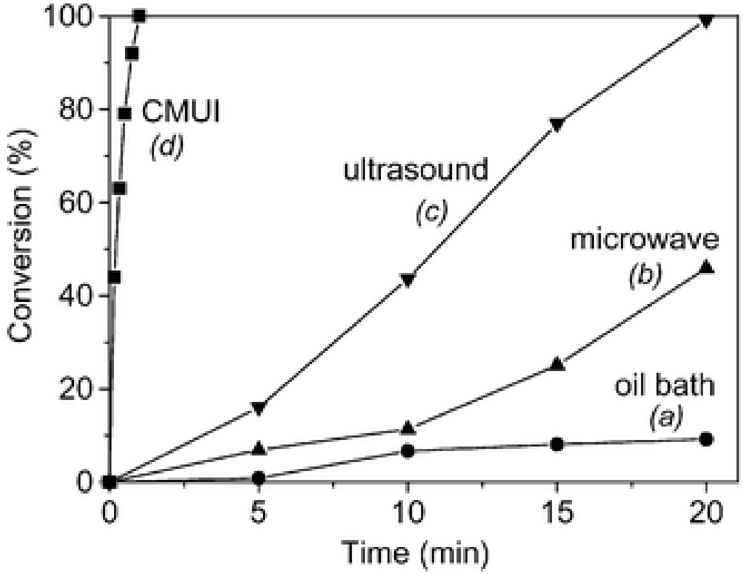
entry	reaction conditions			product yield %		
	Pd loading	base	heating method			
1	100 ppb	Na_2CO_3	μw[a]	56	3	3
2	250 ppb	Na_2CO_3	μw[a]	94	41	60
3	2.5 ppm	Na_2CO_3	μw[a]	99	92	81
4	100 ppb	Na_2CO_3	conventional[b]	8	0	0
5	250 ppb	Na_2CO_3	conventional[b]	70	60	0
6	2.5 ppm	Na_2CO_3	conventional[b]	81	70	64
7	100 ppb	K_2CO_3	μw[a]	5	4	2
8	250 ppb	K_2CO_3	μw[a]	57	14	36
9	2.5 ppm	K_2CO_3	μw[a]	89	81	79
10	2.5 ppm	K_2CO_3	conventional[b]	95	50	75

[a] Reactions run on 1 mmol scale. $Pd(NO_3)_2$ used as catalyst. Microwave irradiation of 150 W used. Temperature ramped from rt to 150 °C and held for 5 min. [b] Reactions run on 1 mmol scale. $Pd(OAc)_2$ used as catalyst. Reaction mixture placed into an oil bath preheated to 150 °C and held there for 7 min before being removed.

Arvela, R. K. et al. *J. Org. Chem.* **2005**, *70*, 161.

Combined Microwave and Ultrasound Irradiation (CMUI)





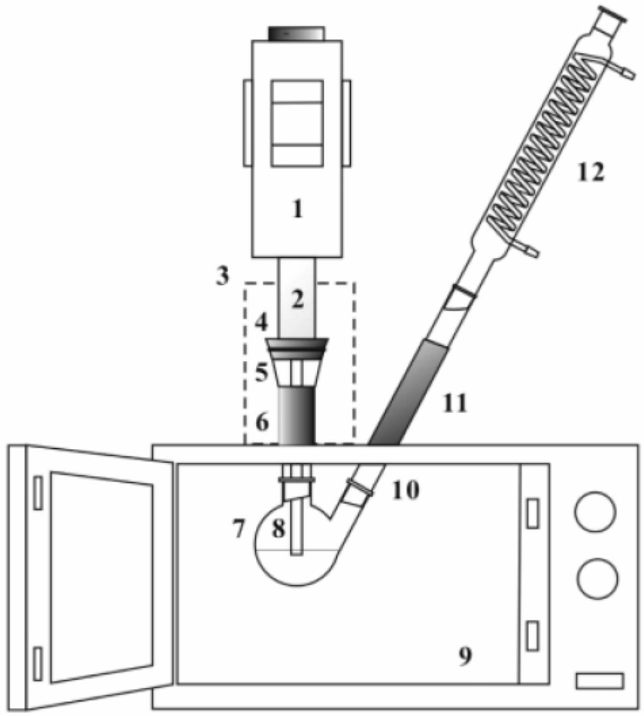
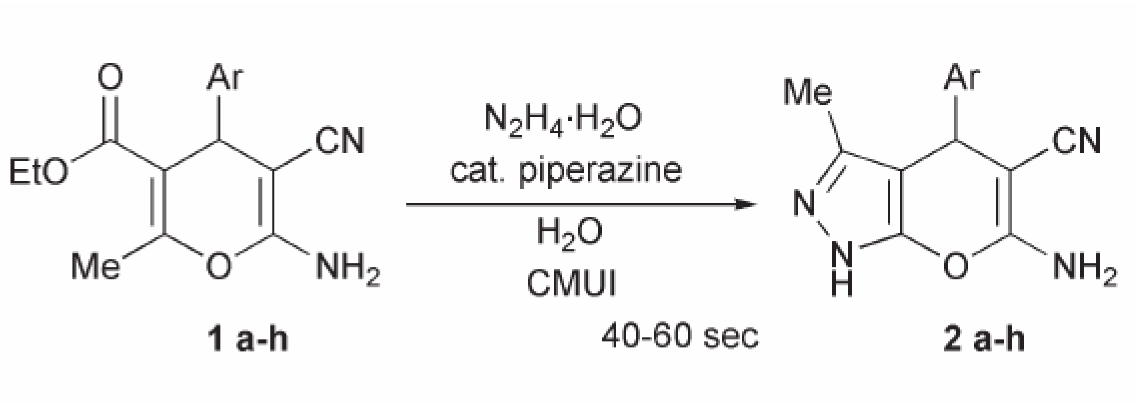


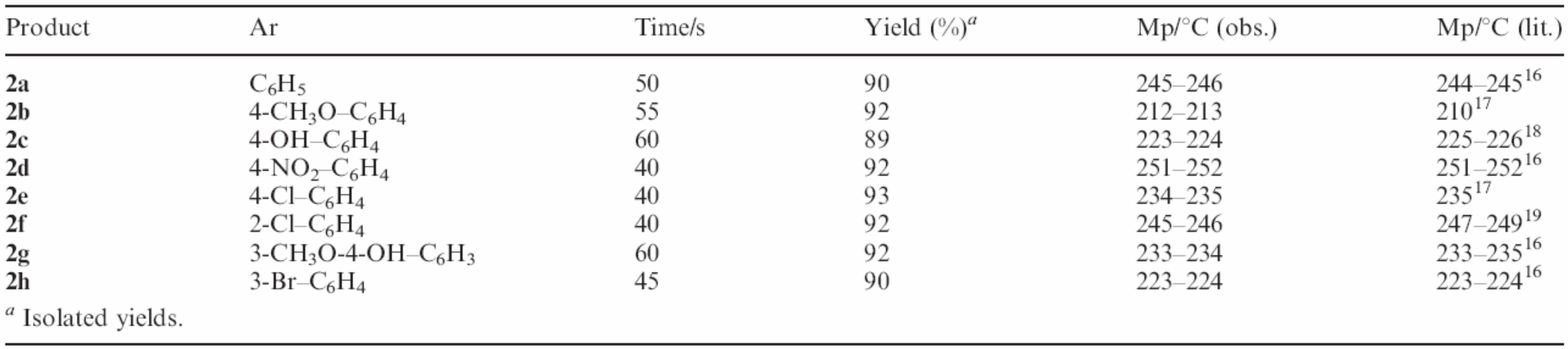
Fig. 1 Apparatus for microwave–ultrasound combined reactions: 1, transducer housing; 2, upper horn; 3, copper mesh screen; 4, rubber stopper; 5, adaptor; 6, port; 7, two-necked Pyrex flask; 8, detachable horn; 9, multimode cavity; 10, adaptor; 11, chock; 12, condenser.

- ***The rate-determining step is likely the mass transfer process at the interface of heterogeneous phases.***

Peng, Y.; Song, G. *Green Chem.* **2001**, *3*, 302.
Peng, Y.; Song, G.; Dou, R. *Green Chem.* **2006**, *8*, 573.

Scope for Heterocycle Generation





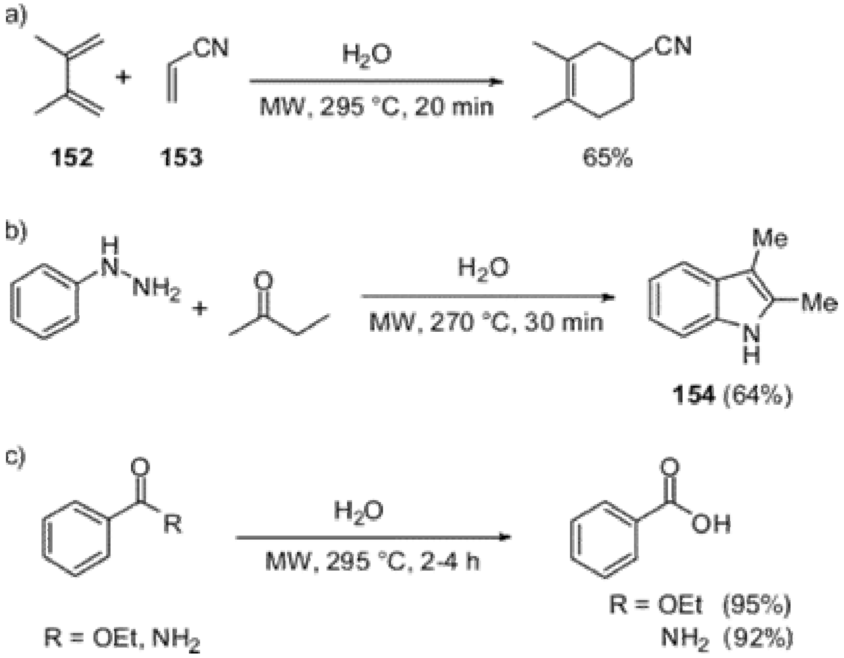
Product	Ar	Time/s	Yield (%)[a]	Mp/°C (obs.)	Mp/°C (lit.)
2a	C_6H_5	50	90	245–246	244–245[16]
2b	4-CH_3O–C_6H_4	55	92	212–213	210[17]
2c	4-OH–C_6H_4	60	89	223–224	225–226[18]
2d	4-NO_2–C_6H_4	40	92	251–252	251–252[16]
2e	4-Cl–C_6H_4	40	93	234–235	235[17]
2f	2-Cl–C_6H_4	40	92	245–246	247–249[19]
2g	3-CH_3O-4-OH–C_6H_3	60	92	233–234	233–235[16]
2h	3-Br–C_6H_4	45	90	223–224	223–224[16]

[a] Isolated yields.

Peng, Y.; Song, G.; Dou, R. *Green Chem.* **2006**, *8*, 573.

Reactions in Near-Critical Water

fluid	ordinary water ($T < 150$ °C, $p < 4$ bar)	near-critical water (NCW) ($T = 150-350$ °C, $p = 4-200$ bar)	supercritical water (SCW) ($T > 374$ °C, $p > 221$ bar)
temp (°C)	25	250	400
pressure (bar)	1	50	250
density ($\mathrm{g\ cm^{-3}}$)	1	0.8	0.17
dielectric constant, ϵ'	78.5	27.1	5.9
$\mathrm{p}K_\mathrm{W}$	14	11.2	19.4



Kremsner, J. M.; Kappe, C. O. *Eur. J. Org. Chem.* **2005**, 3672.

Part IV: Summary

- Reactions in water generally suffer from low solubility of either the reactants and reagents or the products. This could be solved by new technologies such as combined microwave and ultrasound irradiation.

- Microwave-promoted reactions in water is a relative new area for developing novel green chemistry. Short reaction time, high energy efficiency, and convenience of handling are among its advantages. Development of large microwave reactors, however, is needed for the technology to be truly practical.

- Near-critical and supercritical water have physical properties very different from ordinary water, and chemistry in such media is still largely unexplored due to the difficulty in accessing them.