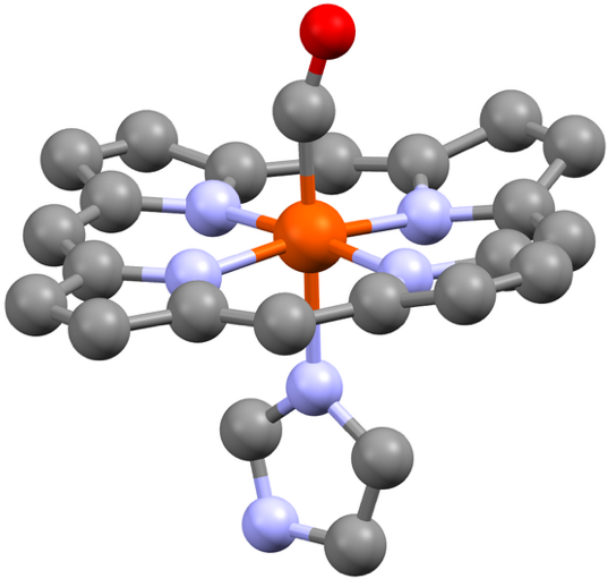
Chloroform as a Carbon Monoxide Precursor: In or Ex Situ Generation of CO for Pd-Catalyzed Aminocarbonylations

Samuel N. Gockel and Kami L. Hull

DOI: 10.1021/acs.orglett.5b01385

Current Lit 6-27-15
James Johnson
Wipf Group

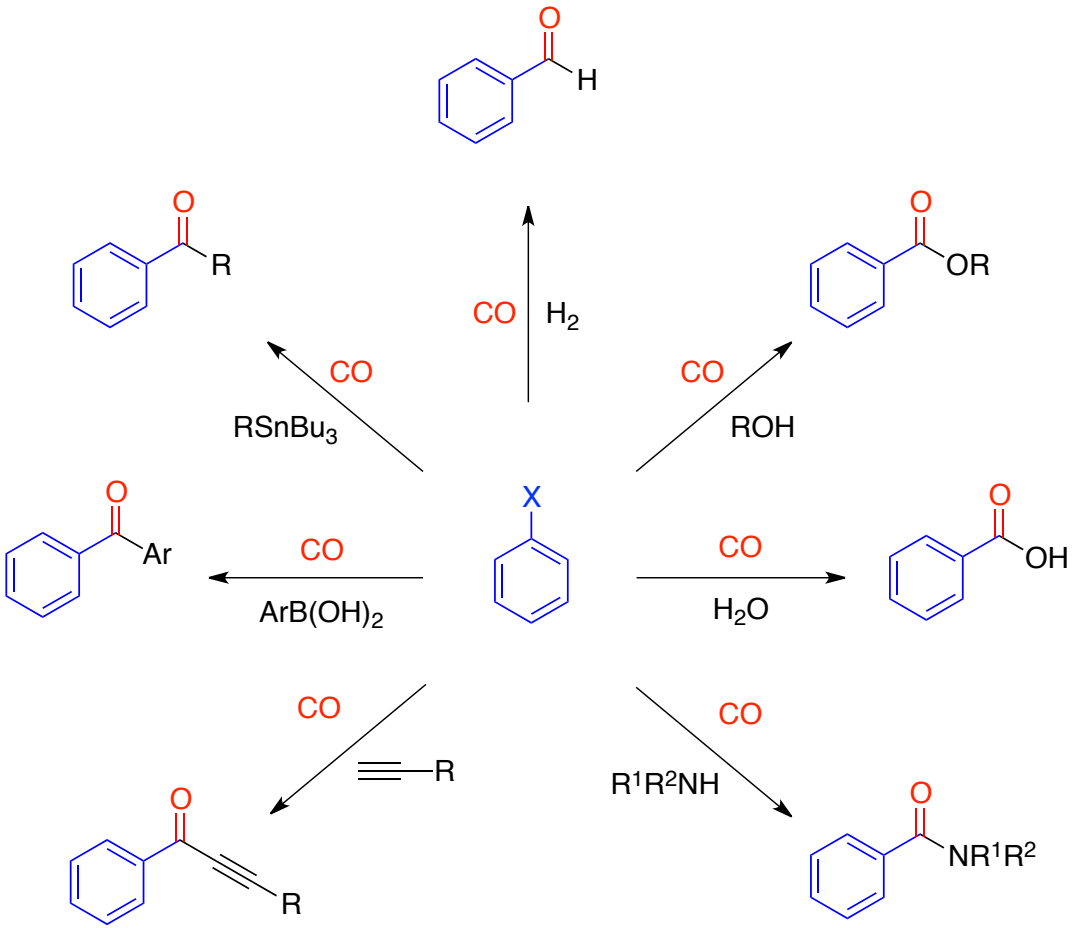
Carbon Monoxide



- CO is a colorless and odorless gas
- Isoelectronic to cyanide
- Toxic in concentrations above 35 ppm for long term exposure
- Acute toxicity above 670 ppm
- Competitive binding to hemoglobin
- Trace amounts are naturally occurring in the body
  - Used in signaling processes
- The formation of carboxyhemoglobin is a reversible process elimination half-time ranges from 2 to 6.5 h
- Inhibits the of function of CyP450

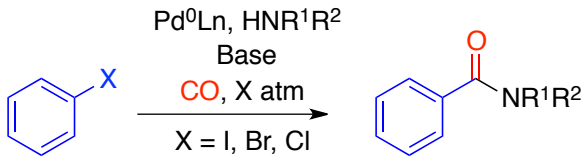
J. R. Soc. Med. 2001;94(6):270-272.

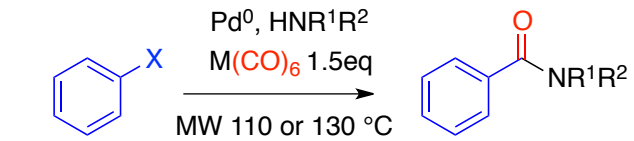
Transition metal-catalyzed carbonylations

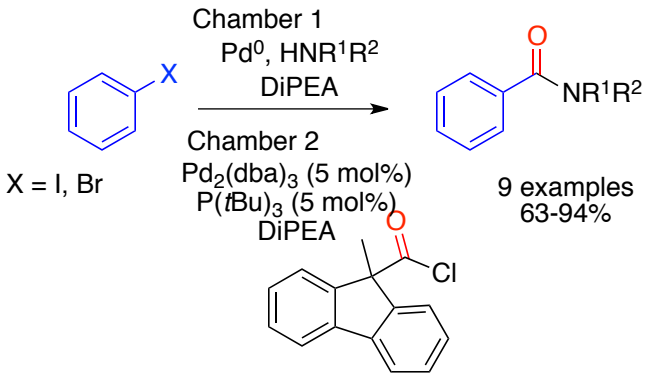


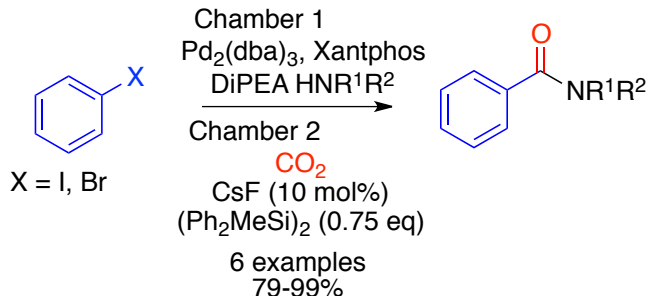
Angew. Chem. Int. Ed. 2009, 48, 4114 – 4133
RSC Adv., 2014, 4, 10367–10389

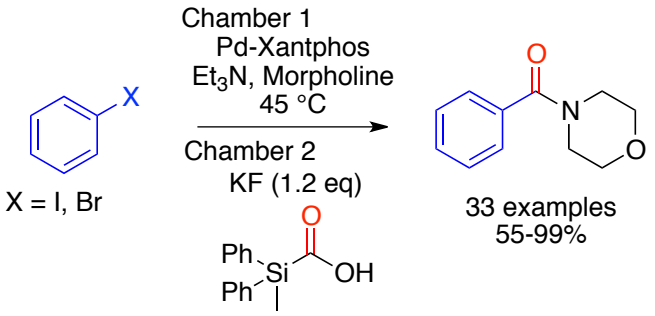
CO sources in aminocarbonylations

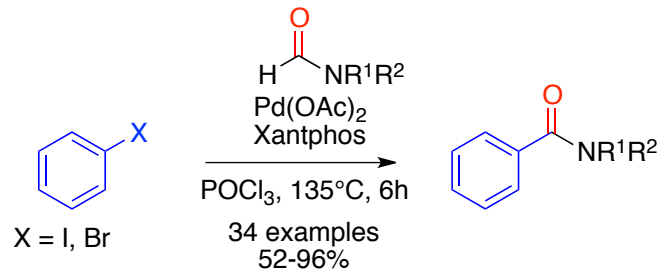


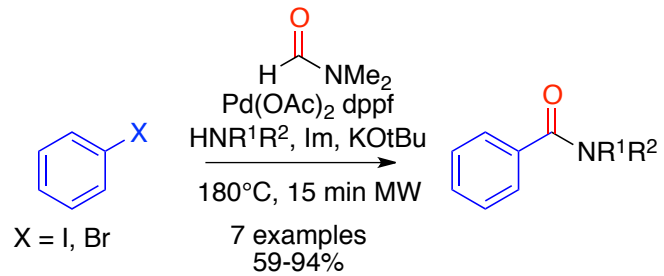












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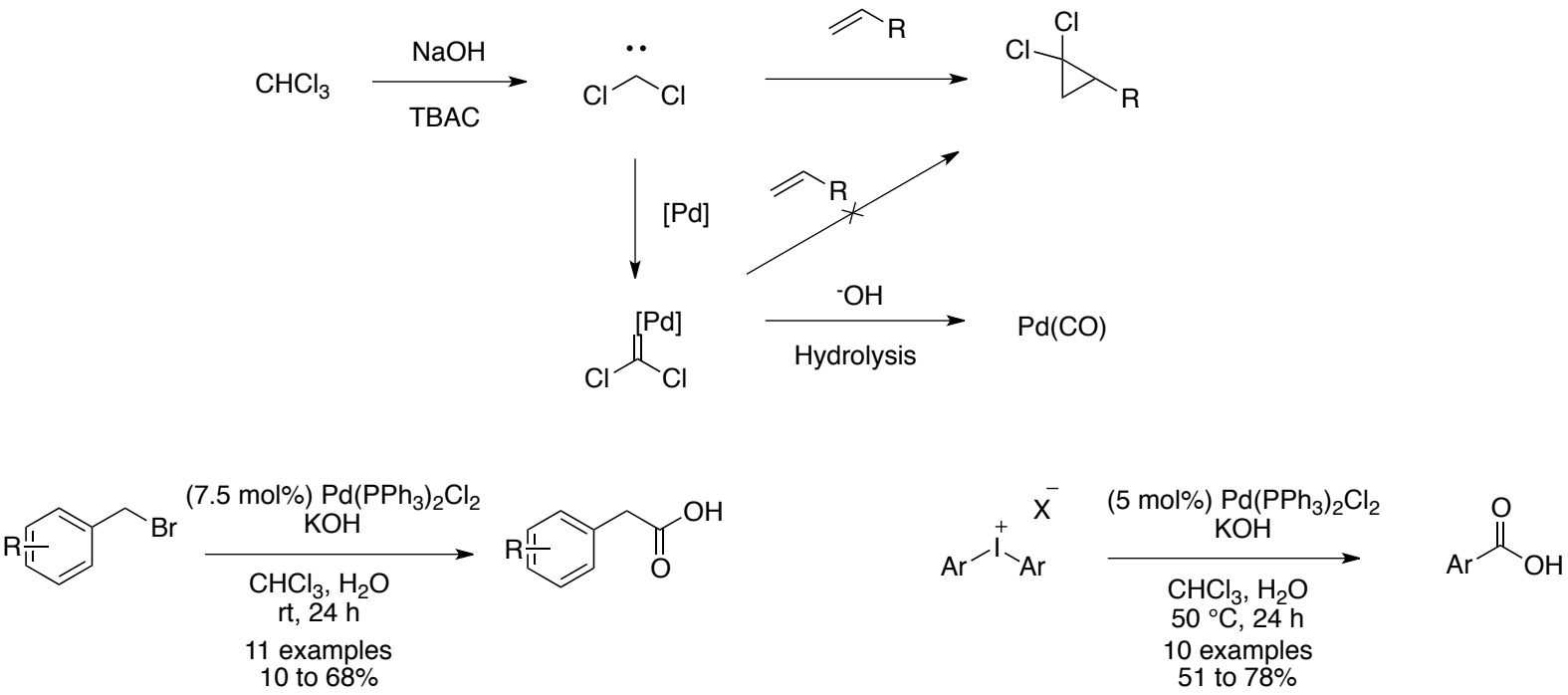
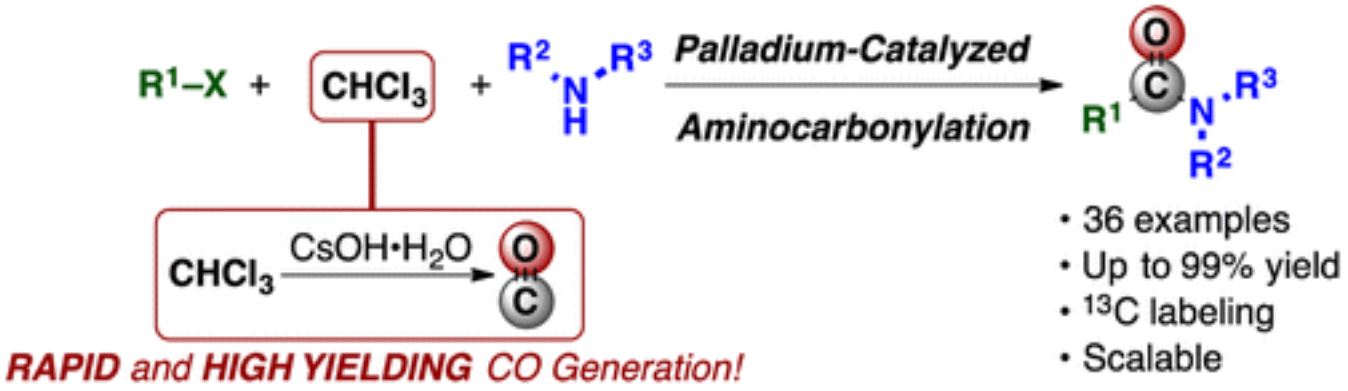
$CHCl_3$ as a source of CO



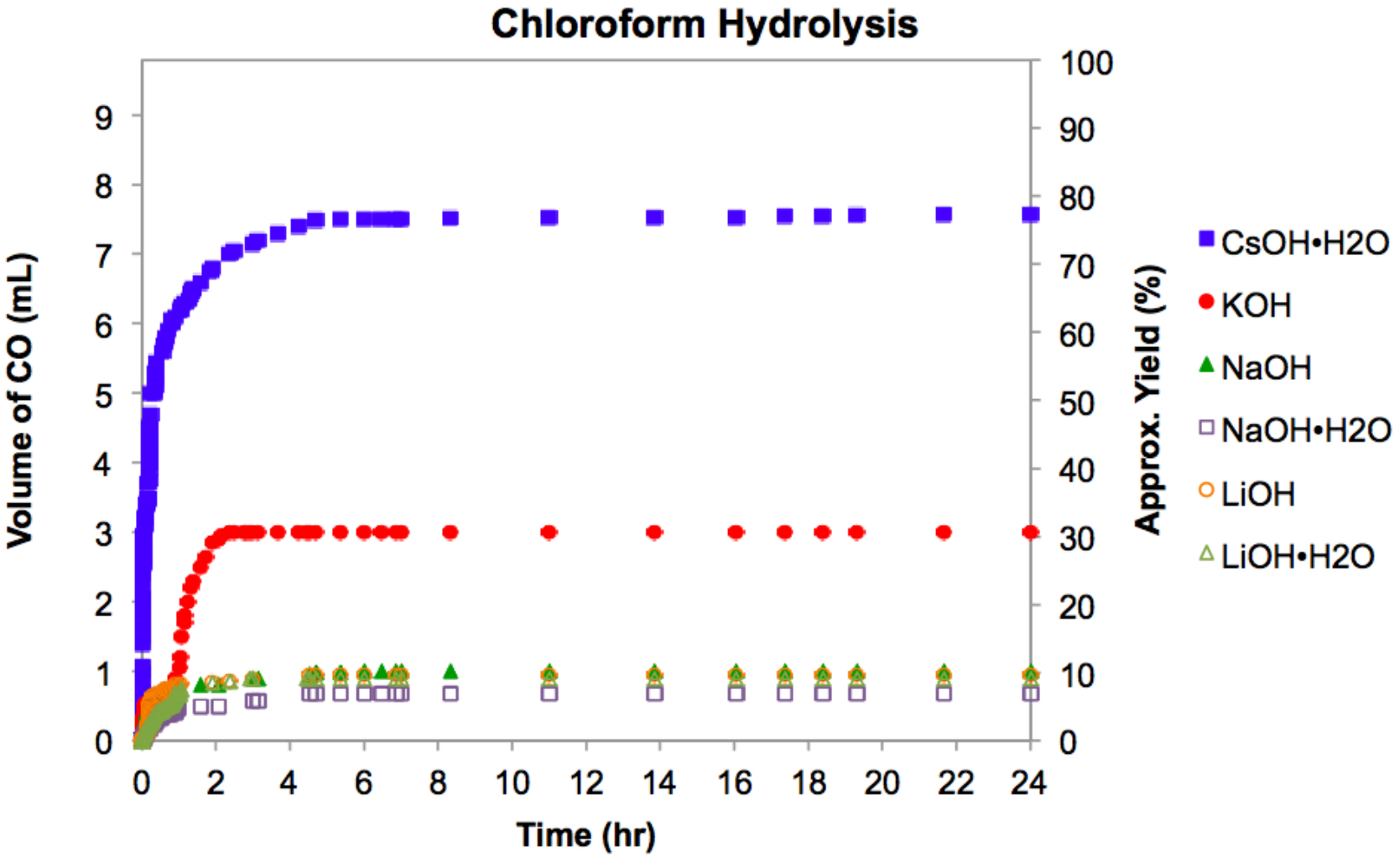
- Low overall yield of CO ca. 2.3%
- $CHCl_3$ required as solvent
- Biphasic mixture

Organometallics 1993, 12, 3846.
J. Chem. Res. (S) 1999, 328

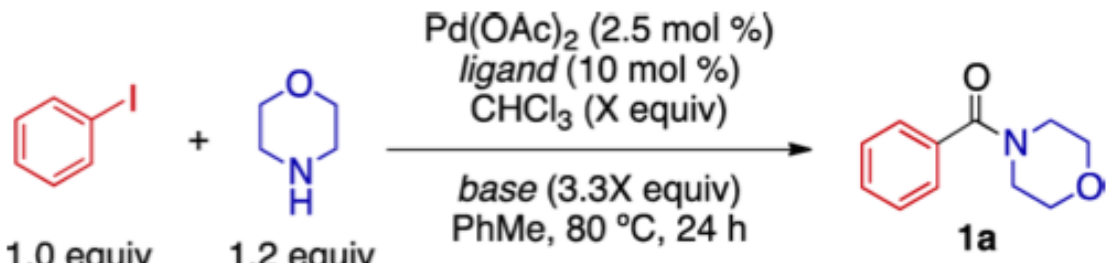
Title Paper


R1–X + CHCl3 + R2 N H R3
Palladium-Catalyzed
Aminocarbonylation
O C R1 N R2 R3
CHCl3 CsOH•H2O O C
RAPID and HIGH YIELDING CO Generation!
• 36 examples
• Up to 99% yield
• 13C labeling
• Scalable

Heterogeneous $CHCl_3$ hydrolysis

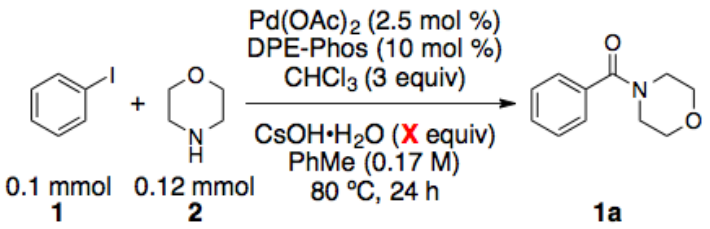


Conditions: base (1.33 mmol), $CHCl_3$ (0.40 mmol), PhMe (0.8 mL) 80 °C 24 h

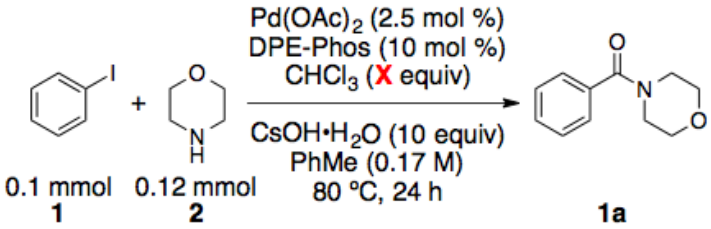


entry	ligand	base	$CHCl_3$ (equiv)	*in situ* yield (%)[b]
1	DPEphos	$CsOH{\cdot}H_2O$	1	40
2	DPEphos	$CsOH{\cdot}H_2O$	2	77
3	**DPEphos**	**$CsOH{\cdot}H_2O$**	**3**	**91**
4	PPh_3	$CsOH{\cdot}H_2O$	3	62
5	±-BINAP	$CsOH{\cdot}H_2O$	3	46
6	dppf	$CsOH{\cdot}H_2O$	3	72
7	dppp	$CsOH{\cdot}H_2O$	3	58
8	DPEphos	LiOH	3	0
9	DPEphos	NaOH	3	20
10	DPEphos	KOH	3	61
11	DPEphos	tBuOK	3	15
12	DPEphos	NaHMDS	3	0
13	DPEphos	Et_3N	3	0

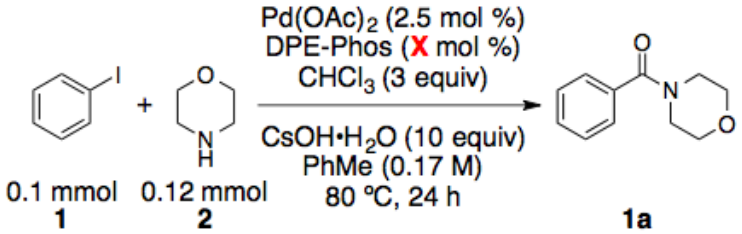
[a] $Pd(OAc)_2$ (2.5 mol %), ligand (10 mol %), base (3–10 equiv), chloroform (1–3 equiv), PhMe, 80 °C, 24 h. [b] *In situ* yield determined by gas chromatography with comparison to undecane (10 μL) as an internal standard.



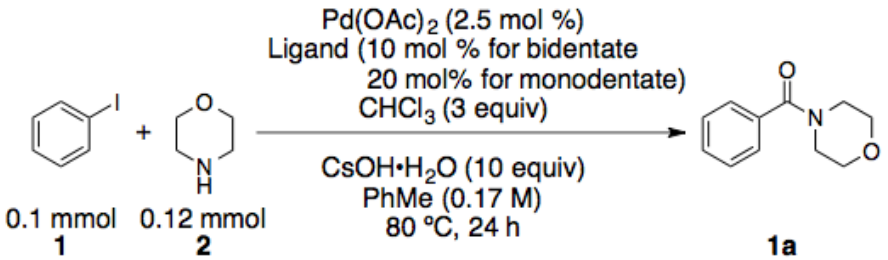
Entry	Equiv CsOH•H_2O	% yield **1a**[b]
1	3	34
2	4	37
3	5	44
4	6	57
5	8	71
6	**10**	**91**
7	20	52
8	50	50



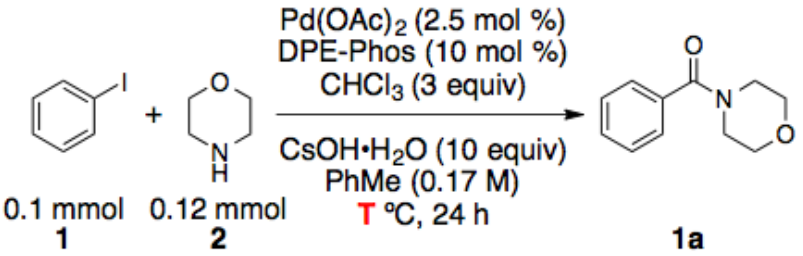
Entry	Equiv $CHCl_3$	% yield **1a**[b]
1	1	40
2	2	77
3	**3**	**91**
4	10	86
5	50	68
6	Solvent	52



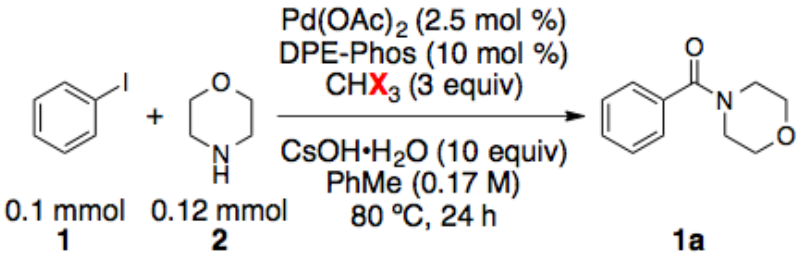
Entry	L:Pd	% yield **1a**[b]
1	0.5:1	30
2	1:1	86
3	2:1	85
4	2.5:1	87
5	**4:1**	**91**
6	5:1	84
7	6:1	82



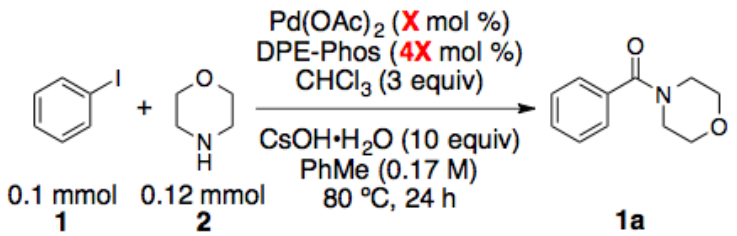
Entry	Ligand	% yield **1a**[b]
1	dppp	58
2	dppf	72
3	±-BINAP	46
4	Xantphos	91
5	**DPE-Phos**	**91**
6	Cy-DPE-Phos	80
7	PPh_3	62
8	Ph_2As-$(CH_2)_2$-PPh_2	34



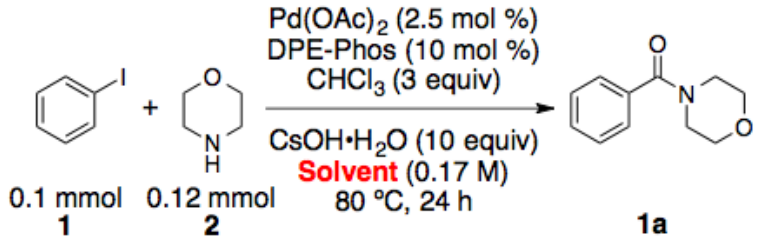
Entry	Temperature (°C)	% yield **1a**[b]
1	22	6
2	40	23
3	60	83
4	**80**	**91**
5	100	86



Entry	X	% yield **1a**[b]
1	**Cl**	**91**
2	Br	55
3	I	21
4	OMe	20
5	OEt	26

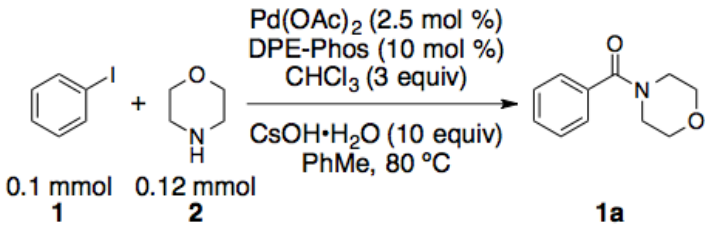


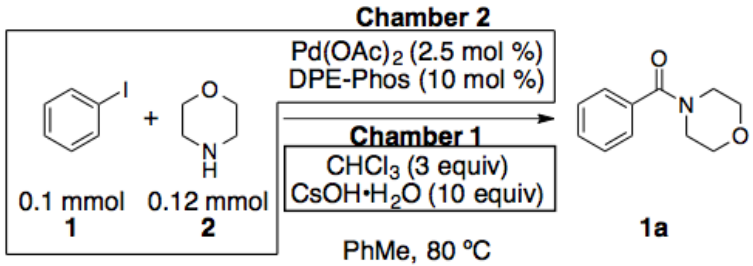
Entry	mol % Pd	% yield **1a**[b]
1	0.02	0.2
2	0.1	3
3	0.2	14
4	0.4	40
5	0.6	57
6	0.8	74
7	1.0	78
8	**2.5**	**91**

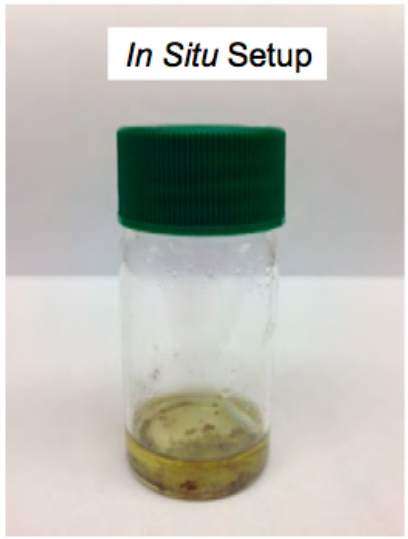


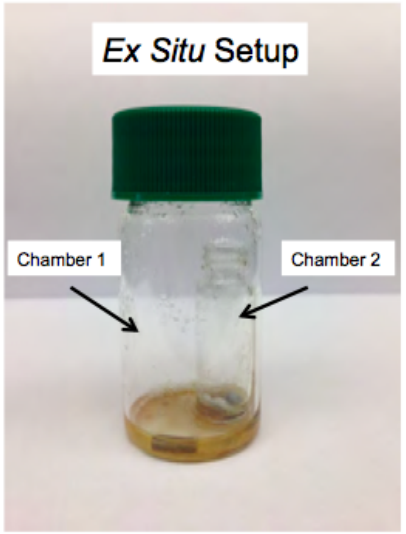
Entry	Solvent	% yield **1a**[b]
1	**Toluene**	**91**
2	Benzene	87
3	1,4-Dioxane	71
4	Acetonitrile	0
5	Tetrahydrofuran	86
6	Hexane	57

In vs *Ex* Situ

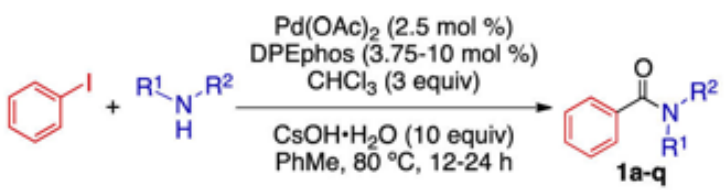




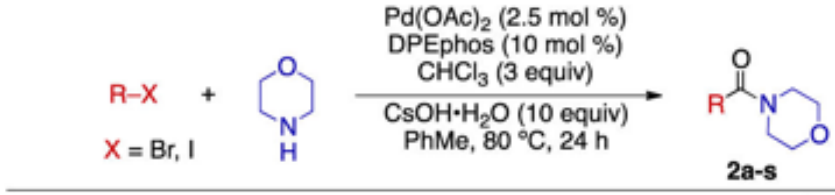




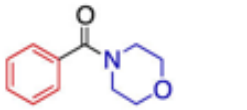
Yield	91%	85%
Initial rate	1.4 x 10^{-5} M•s^{-1}	1.3 x 10^{-5} M•s^{-1}



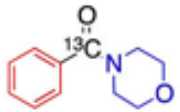
1a-q



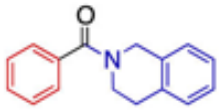
2a-s



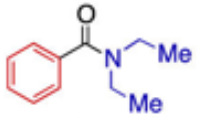
1a
81%[b], 91%[c]



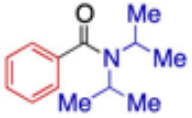
***[13]C*-1a**
96%[d], 56%[e]



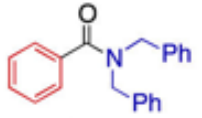
1b
84%[c]



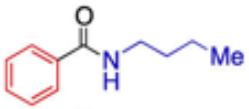
1c
74%[b], 85%[c]



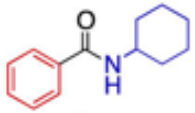
1d
20%[b], 62%[c]



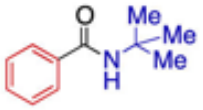
1e
67%[b], 89%[c]



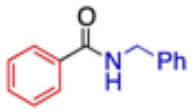
1f
87%[b,f]



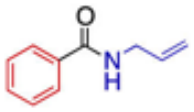
1g
89%[b,f]



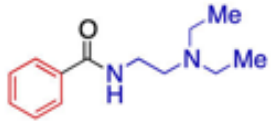
1h
87%[c]



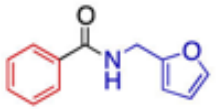
1i
85%[b,f]



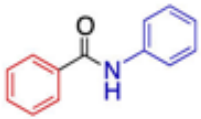
1j
82%[b,f]



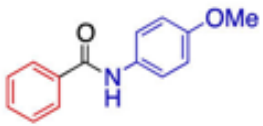
1k
86%[b,f]



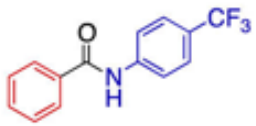
1l
94%[b,f]



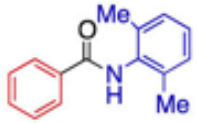
1m
80%[b]



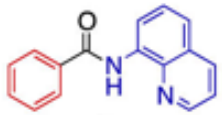
1n
96%[b]



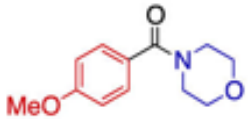
1o
59%[b], 38%[c]



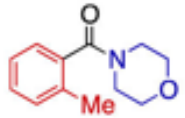
1p
58%[b], 70%[c]



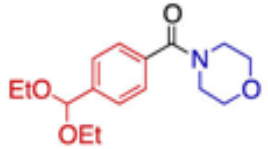
1q
73%[b]



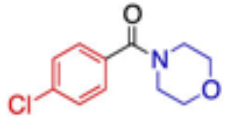
2a
99%[b]



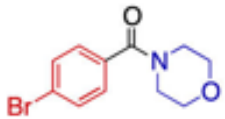
2b
78%[b]



2c
49%[c]

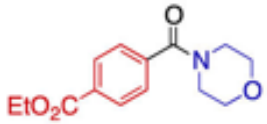


2d
97%[b]

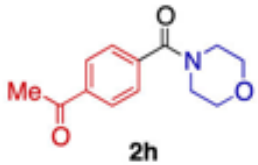


2e
89%[b]

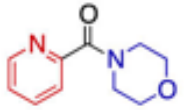
2f
19%[c]



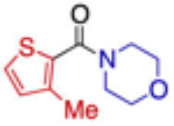
2g
94%[c]



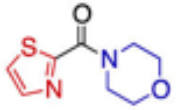
2h
92%[c]



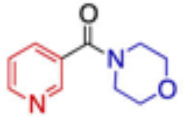
2i
73%[c]



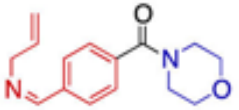
2j
72%[c]



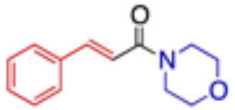
2k
79%[c]



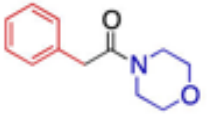
2l
80%[c]



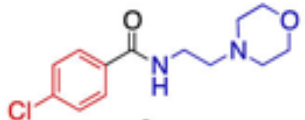
2m
88%[c,d]



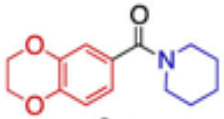
2n
95%[c]



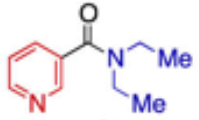
2o
65%[c]



2p
99%[b]
Moclobemide
anti-depressant



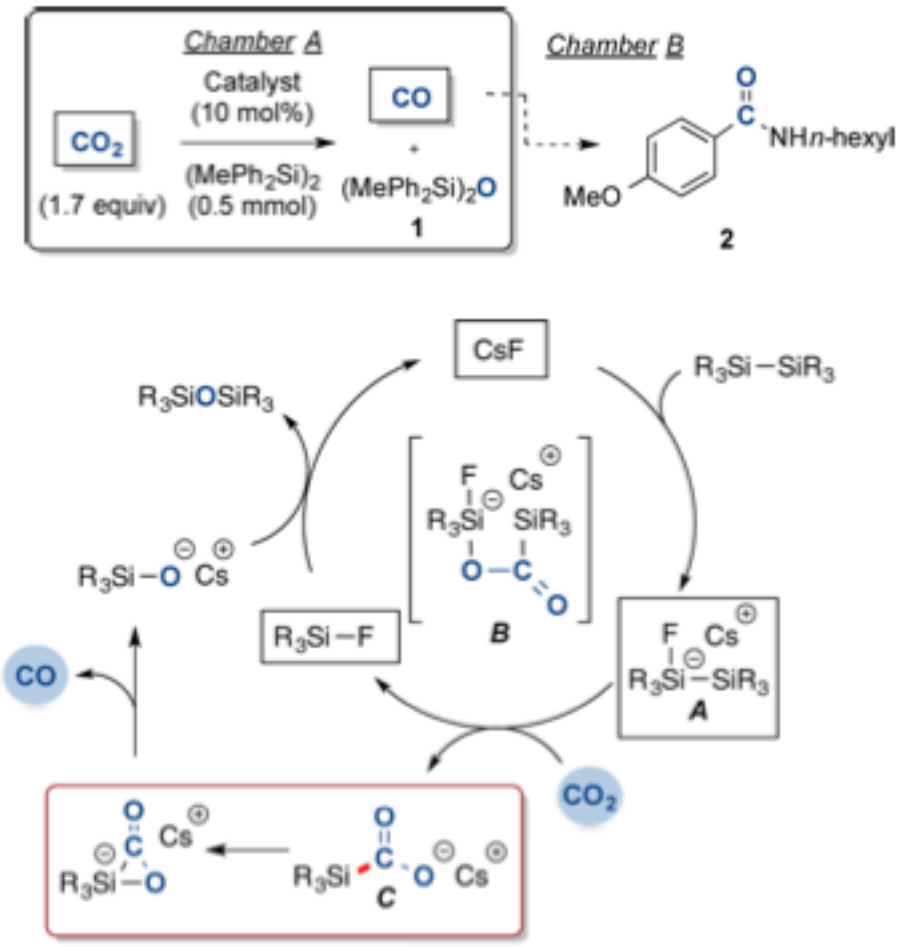
2q
99%[b]
CX-546
schizophrenia treatment

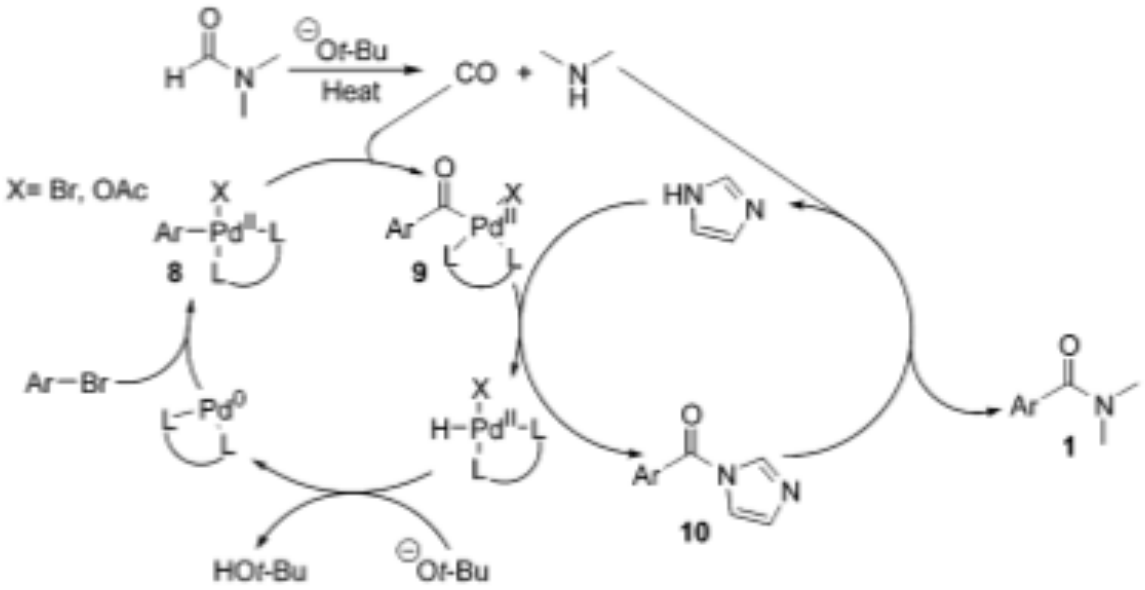


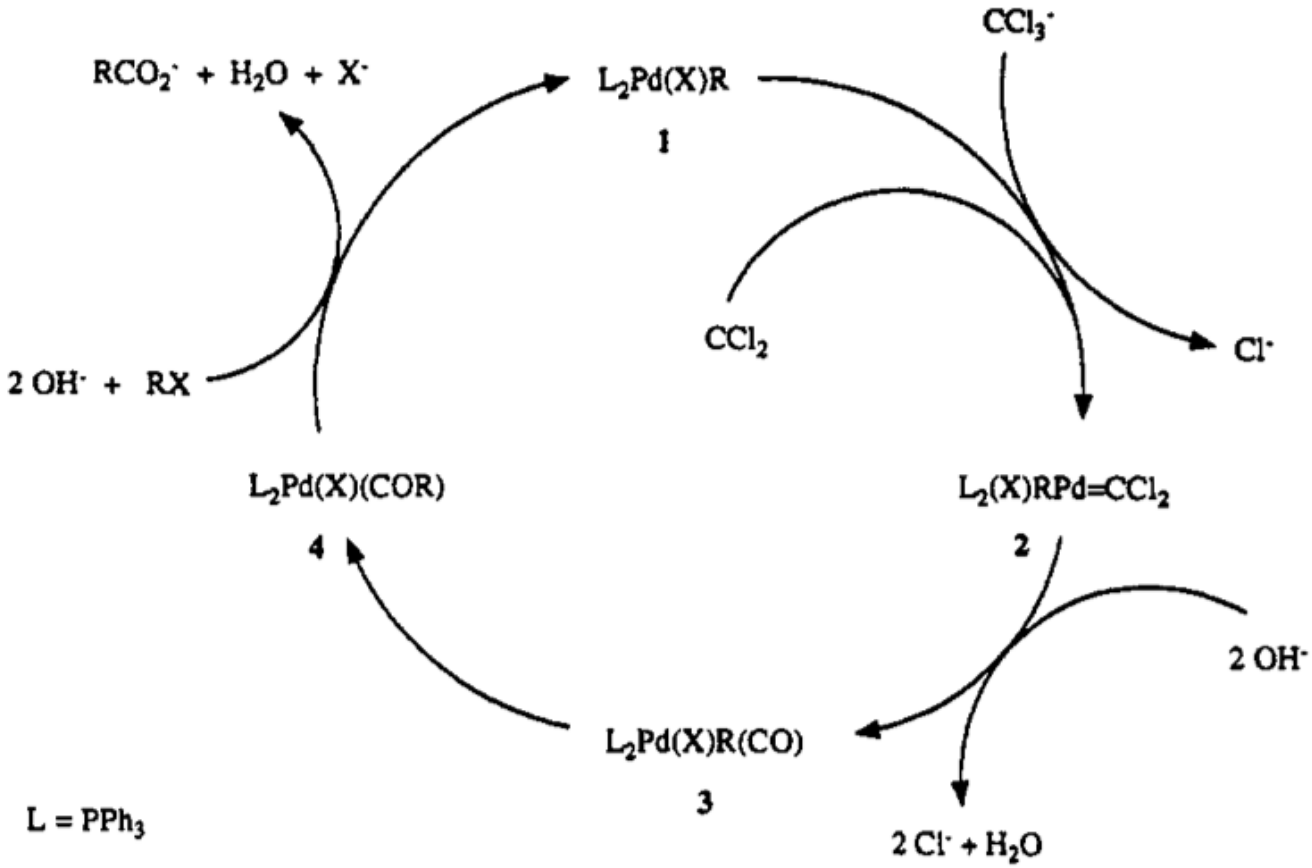
2r
79%[c]
Nikethamide
stimulant

Conclusions

- Interesting use of Chloroform
- *In* or *Ex* Situ production of CO
- Allows for isotopically labeled amides using $^{13}CHCl_3$
- Suitable for small scale/parallel synthesis
- Low cost/prep
- Future directions
  - Expand the scope to other carbonylation reactions


Chamber A
Catalyst
(10 mol%)
CO
CO2
(1.7 equiv)
(MePh2Si)2
(0.5 mmol)
(MePh2Si)2O
1
Chamber B
MeO
NHn-hexyl
2
CsF
R3Si–SiR3
R3SiOSiR3
R3Si–O Cs
R3Si–F
B
A
C
CO
CO2


Ot-Bu
Heat
CO
X= Br, OAc
8
9
10
1
Ar–Br
HOt-Bu
Ot-Bu


RCO2· + H2O + X·
L2Pd(X)R
1
CCl3·
CCl2
Cl·
2 OH· + RX
L2Pd(X)(COR)
4
L2(X)RPd=CCl2
2
2 OH·
L2Pd(X)R(CO)
3
2 Cl· + H2O
L = PPh3