Electrochemical Generation of Catalysts using Batch and Flow Technology

Charlotte Willans

Dial-a-Molecule Annual Meeting: Enabling Synthesis

10th July 2018

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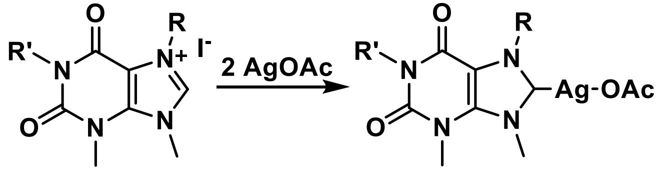
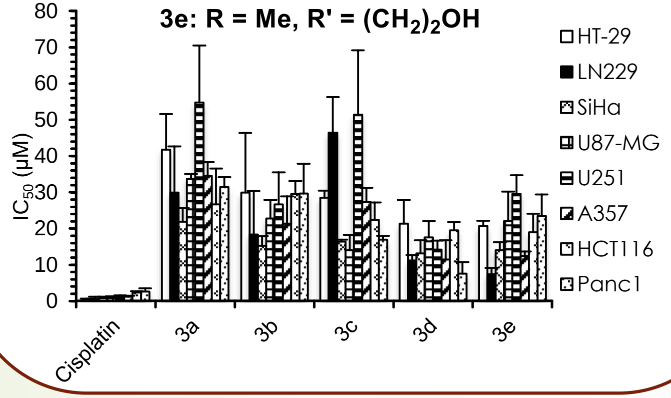
Metal-N-Heterocyclic Carbenes (NHCs)

Cancer Therapeutics

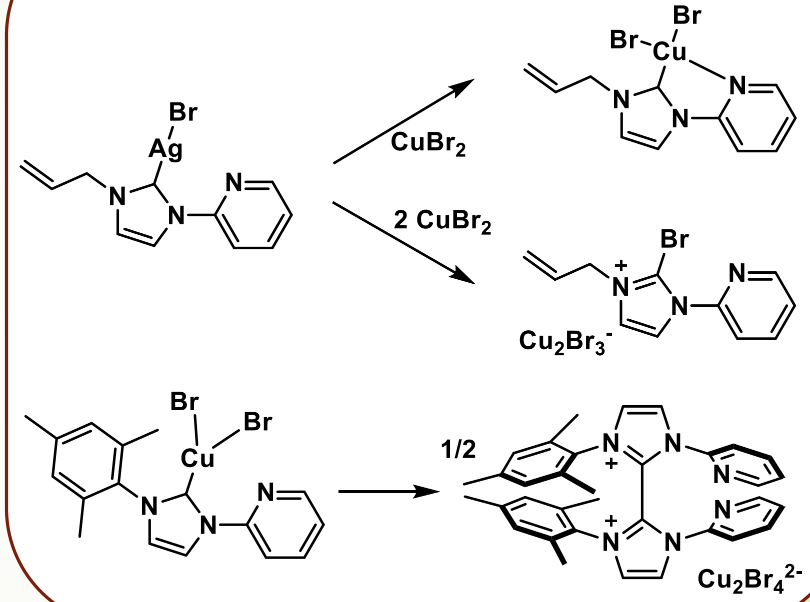


3a: R = Me, R' = Me, 3b: R = Bn, R' = Me
3c: R = ^{n}Bu, R' = Me, 3d: R = Ph, R' = Me
3e: R = Me, R' = $(CH_2)_2OH$



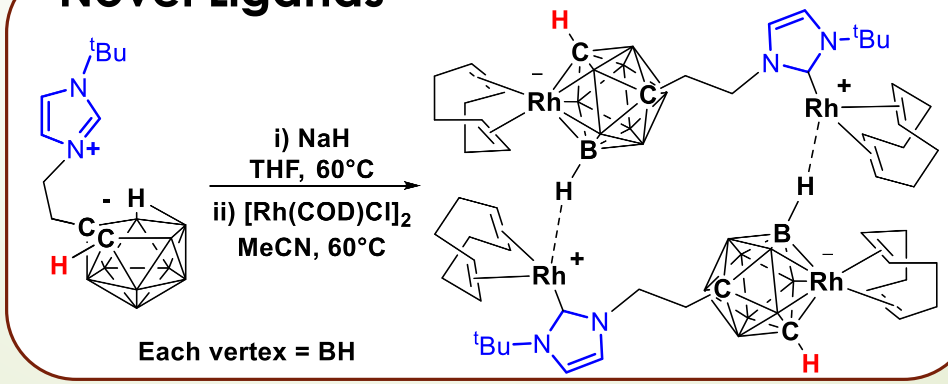
RSC Advances **2018** *8*, 10474. *Cancer Lett*. **2017** *403*, 98. *Dalton Trans*. **2015** *44*, 7563. *Dalton Trans*. **2012** *41*, 3720

Catalysis (and Deactivation)



Chem. Sci. **2017** *8*, 7203. *Chem. Commun*. **2016** *52*, 5057. *Organometallics* **2015** *34*, 3497. *JACS* **2015** *137*, 4151. *Chem. Eur. J*. **2014** *20*, 12729.

Novel Ligands



Chem. Commun. **2016** *52*, 6443. *Dalton Trans*. **2016**, *45*, 15818.

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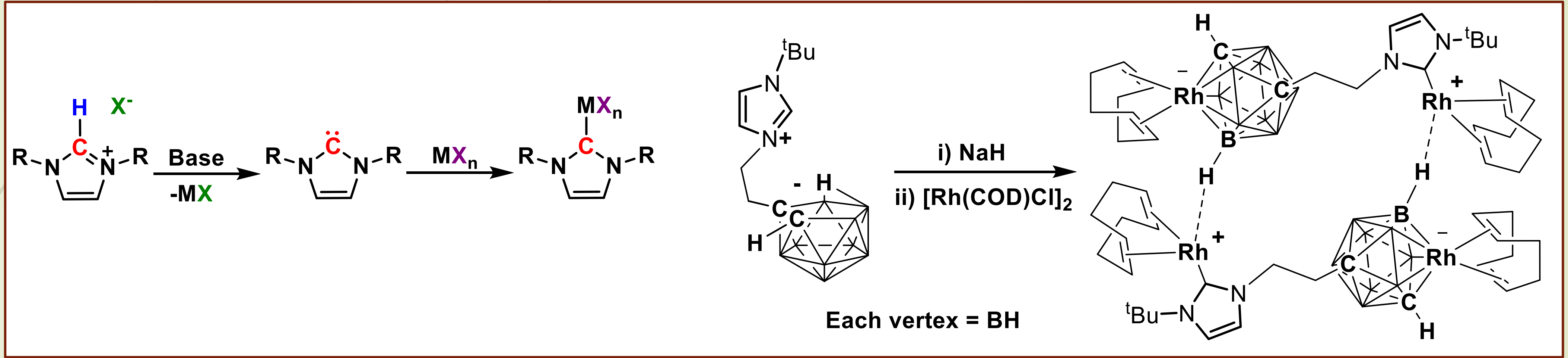
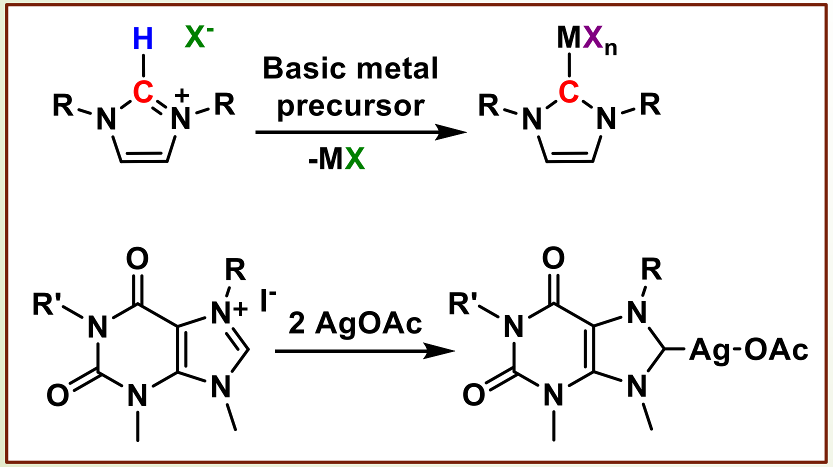
Metal-NHC Synthesis

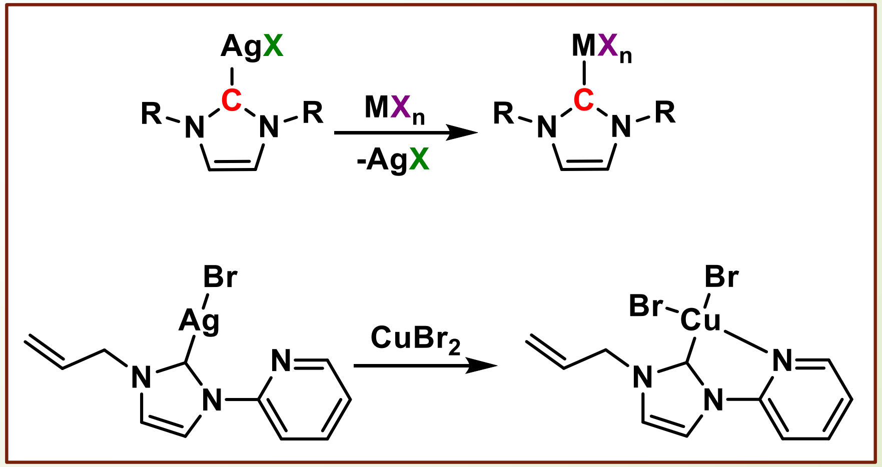
Base deprotonation and (*in situ*) coordination



Basic metal precursor



Transmetallation



- Atom efficiency
- Metal salt by-products
- Compatibility with *N*-substituents

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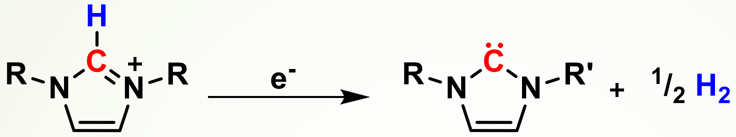
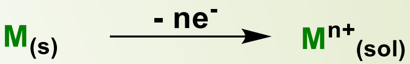
Electrochemical Synthesis of Metal-NHCs

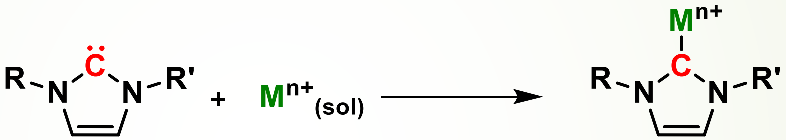
Cathode

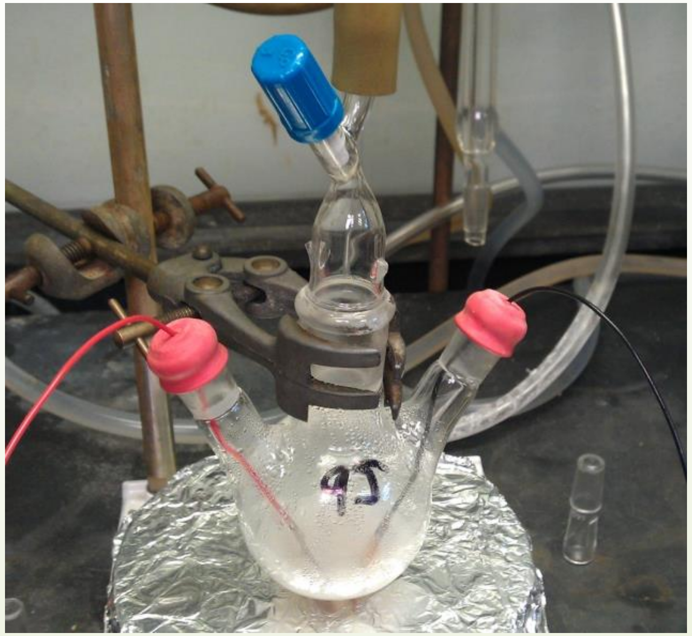


Anode



Solution





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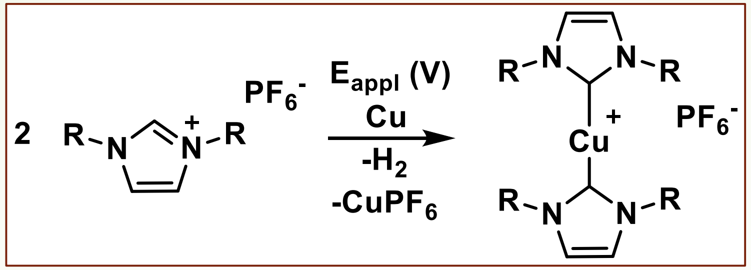
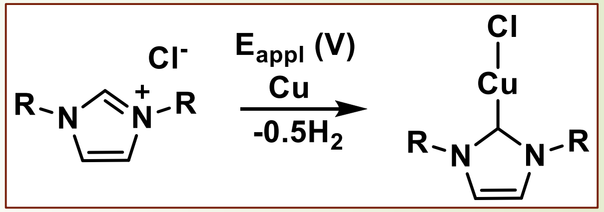
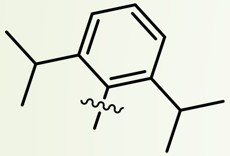
Electrochemical Synthesis of Copper-NHCs

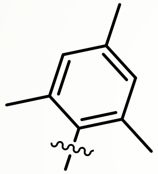




1: R = R' =

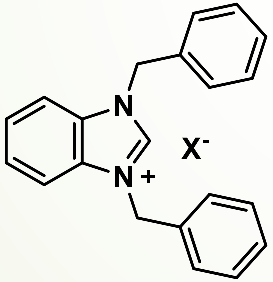


2: R = R' =

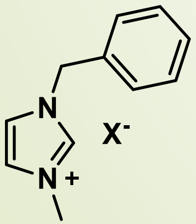


3: R = CH_3, R' = CH_2CH_3

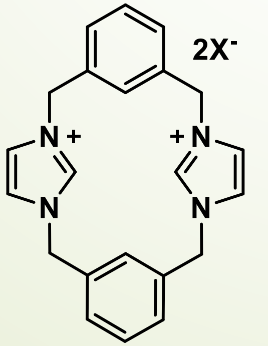
4:



5:



6:



Ligand	Time (mins)	Charge (Q)	Current (mA)	Yield (%)
1 X=Cl	80	3	60	62
2 X=Cl	19	1	50	59
3 X=Cl	60	2	60	#
4 X=Cl	45	1.5	50	68
5 X=Cl	60	2	50	67
1 X=PF_6	300	10	50	42
2 X=PF_6	220	14	100	74
4 X=PF_6	330	11	50	64
5 X=PF_6	150	5	50	58
6 X=PF_6	880	5.5	10	72

Q: Number of times more charge than theoretical value. Yield = isolated pure product. #: Due to the air sensitive and sticky nature of the product an accurate yield was not obtained.

Ben Lake, *Chem. Commun.* **2012**, *48*, 4887

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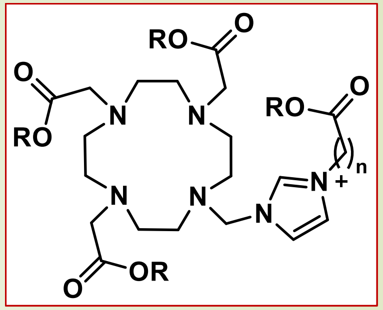
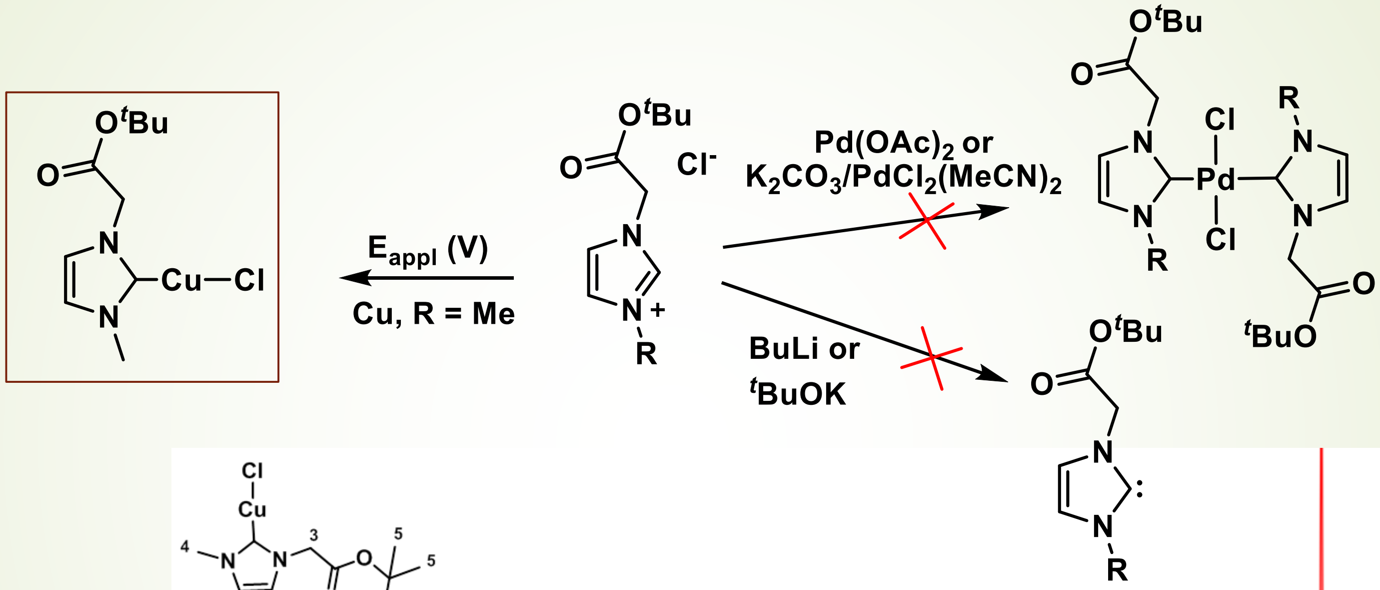
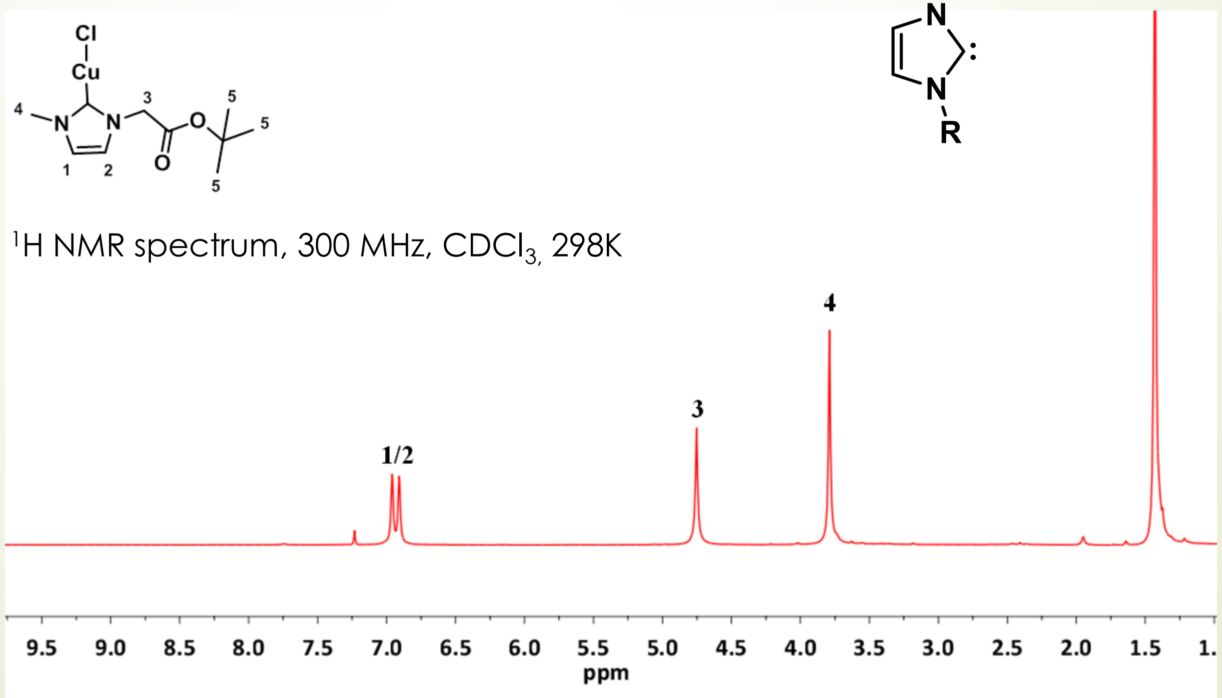
Base-Sensitive *N*-Substituents

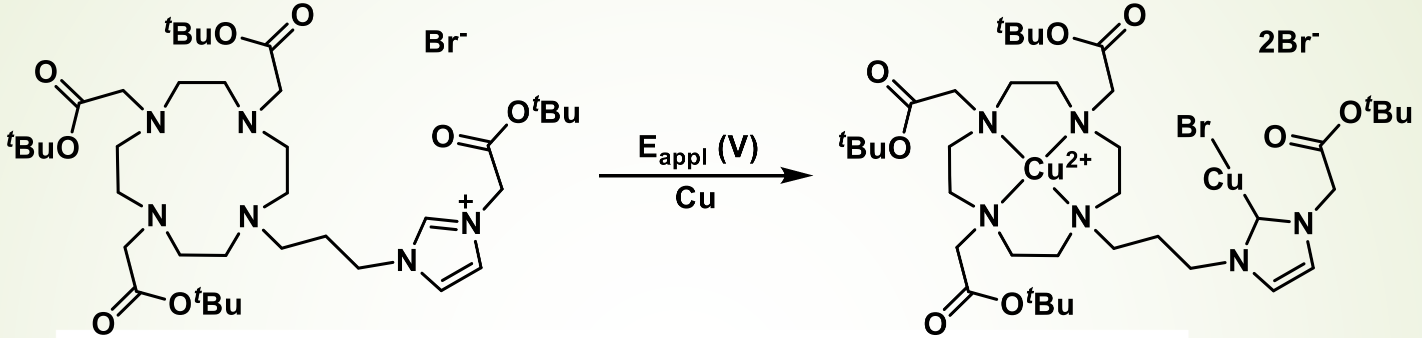


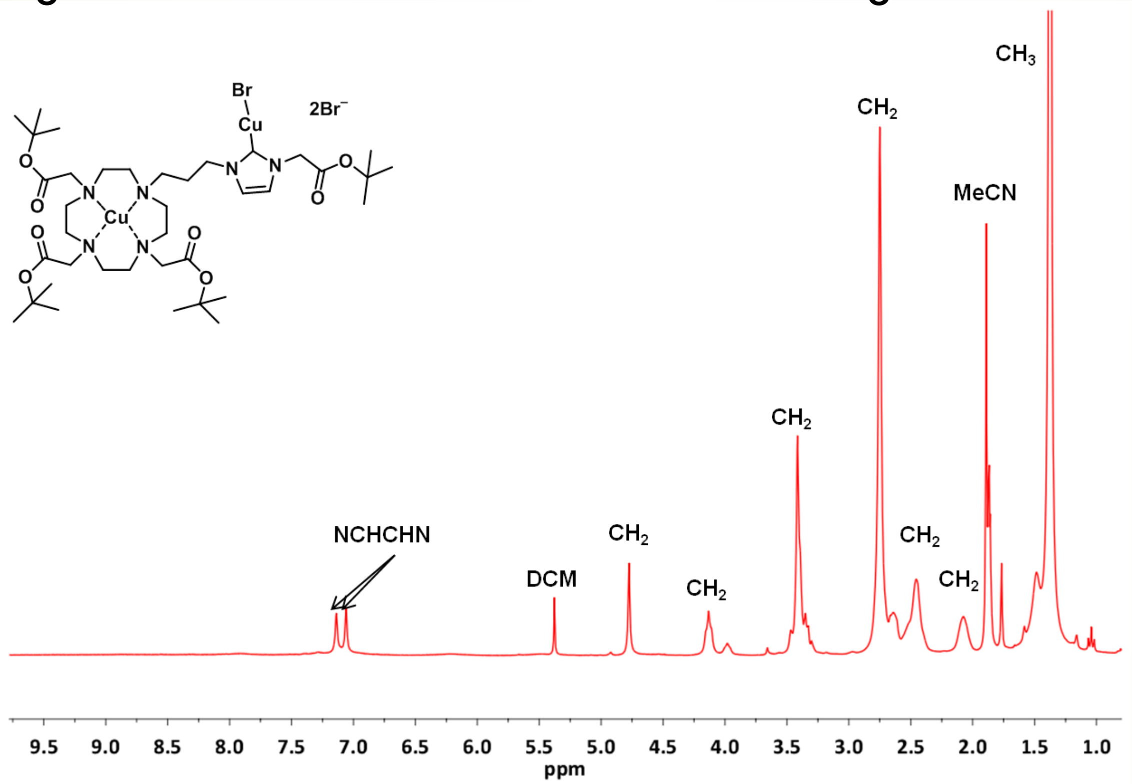




Ben Lake, *Chem. Commun.* **2012**, *48*, 4887

Base-Sensitive *N*-Substituents





- *m/z* (ESI+): 1024.2 [M-Br]$^+$
- EPR confirms presence of Cu(II)

^{1}H NMR spectrum, 500MHz, CD_3CN, 298K

Emma Bullough, *Unpublished results*

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Faradaic Efficiency

Ligand	Time (mins)	Time (Q)	Current (mA)	Yield (%)
1 X=Cl	80	3	60	62
2 X=Cl	19	1	50	59
3 X=Cl	60	2	60	#
4 X=Cl	45	1.5	50	68
5 X=Cl	60	2	50	67
1 X=PF_6	300	10	50	42
2 X=PF_6	220	14	100	74
4 X=PF_6	330	11	50	64
5 X=PF_6	150	5	50	58
6 X=PF_6	880	5.5	10	72

Q: Number of times more charge than theoretical value. Yield = isolated pure product. #: Due to the air sensitive and sticky nature of the product an accurate yield was not obtained.

Batch Synthesis	Flow Synthesis
Size of reactor determines scale	Length of reaction determines scale
Isolation and reactor clean-up	Continual flow, often multi-step
Mixing can be problematic	More efficient mixing
Inefficient mass transfer	Designed for efficient mass transfer
Large overpotential, low Faradaic efficiency	Appropriate potential, Faradaic efficiency Q=1?

Chemistry iPRD Chemical Engineering

Institute of Process Research and Development

Electrochemical flow reactor for the efficient synthesis of metal complexes under mild conditions.

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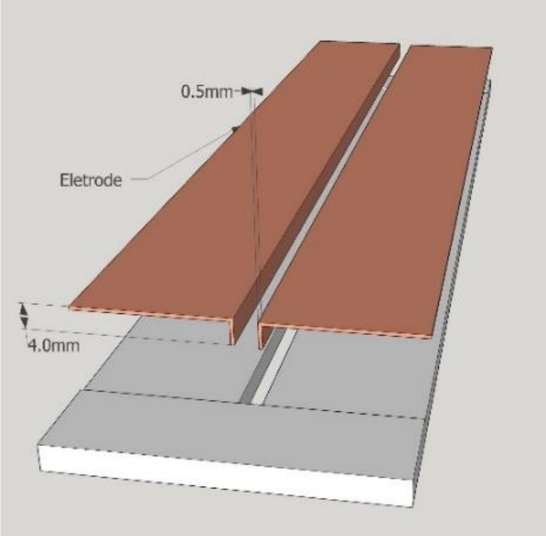
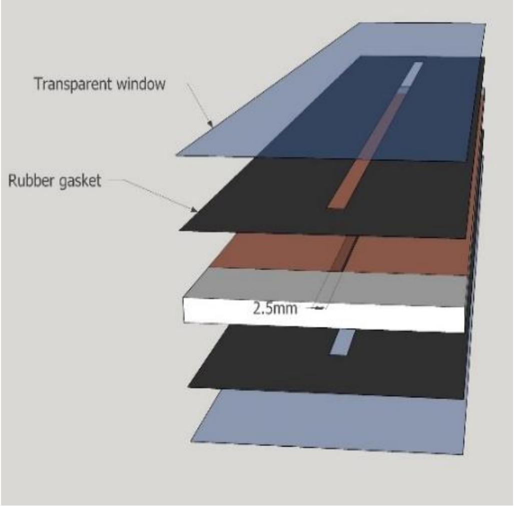
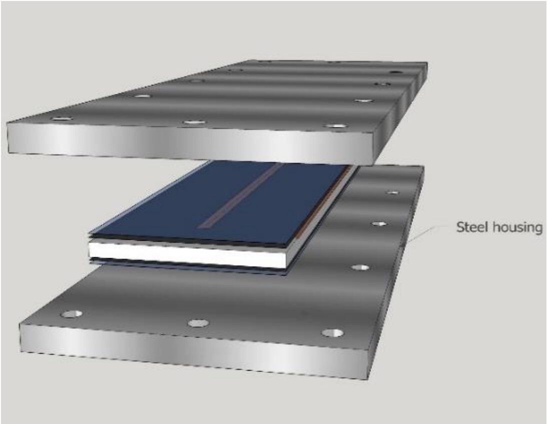
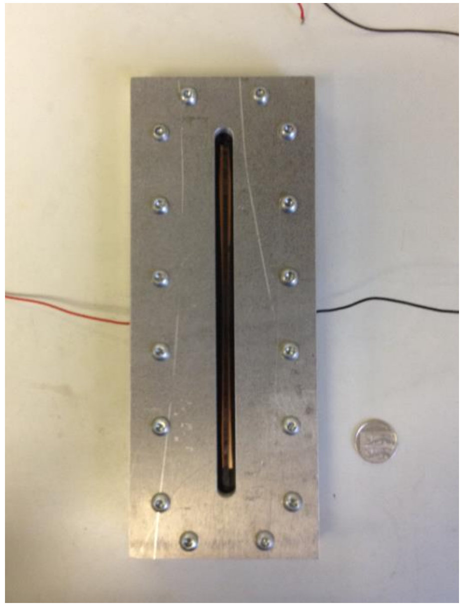
First-Generation Flow Reactor

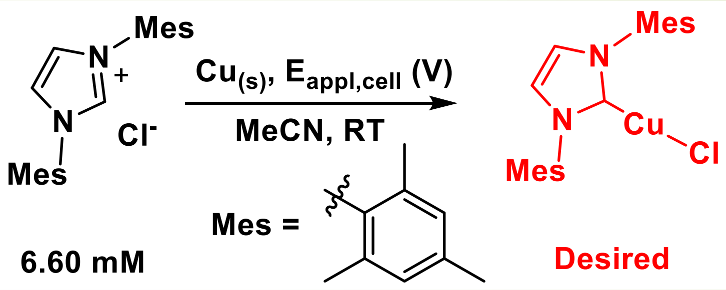


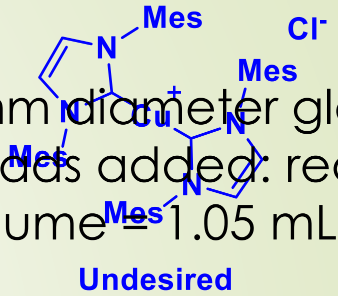






- Inter-electrodes: 2.5 mm
- Reactor volume: 1.9 mL
- Interfacial area: 15.2 cm^2

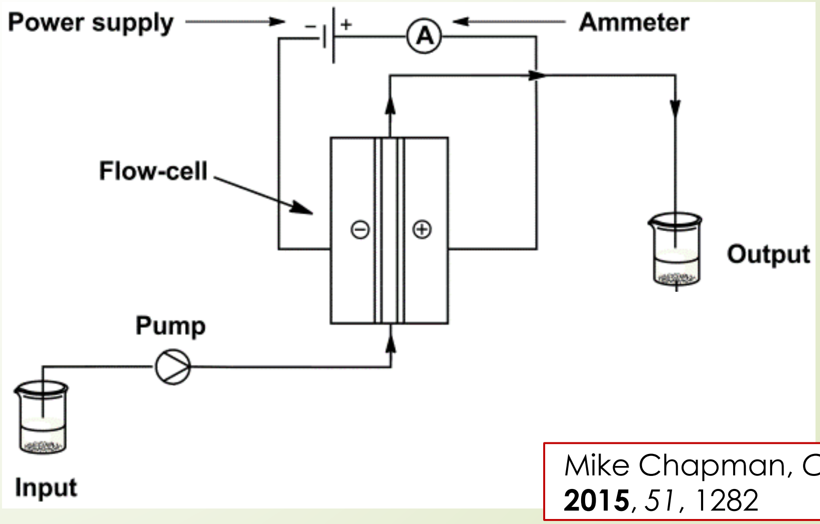




2mm diameter glass beads added: reactor volume = 1.05 mL

Single pass conditions:
- Applied potential: 2.5 V
- Flow rate: 0.50 mLmin^{-1}
- Conversion: 36 %
- Voltaic efficiency: 70 %

Recirculatory conditions:
- Applied potential: 2.5 V
- Flow rate: 0.50 mLmin^{-1}
- Process time: 80 min
- Conversion: 92 %



Mike Chapman, *Chem. Commun.* **2015**, *51*, 1282

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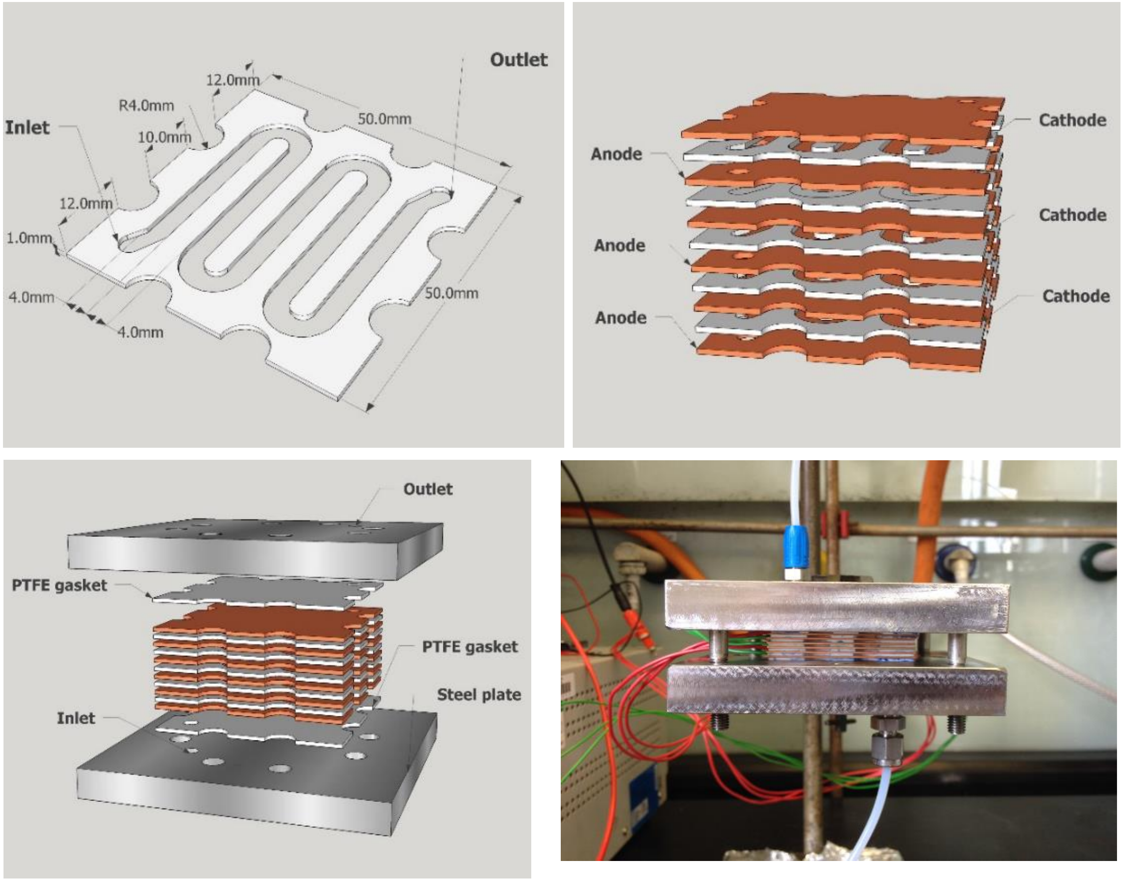
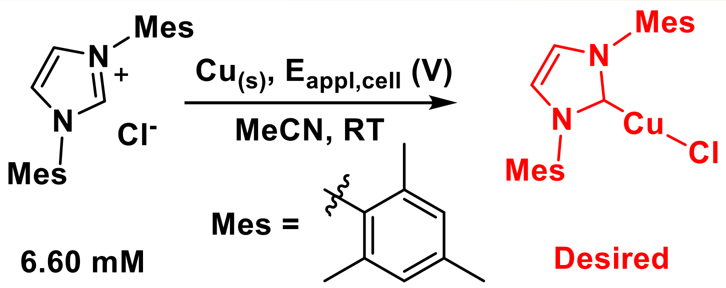
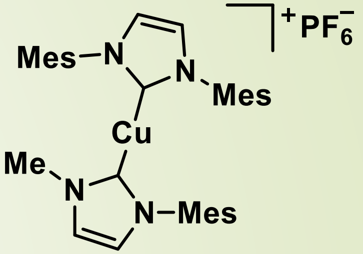
Second-Generation Flow Reactor



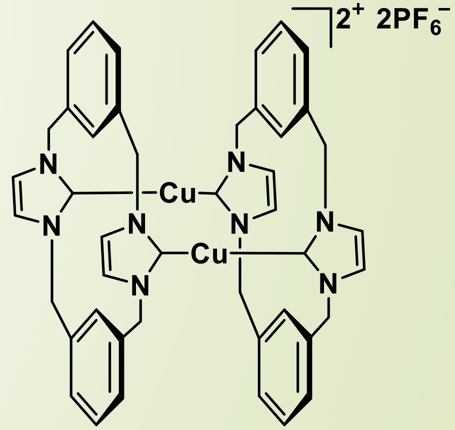
- Consecutive parallel-plate reactors
- Inter-electrodes: 1 mm
- Reactor volume: 4 mL
- Interfacial area: 125 cm^2



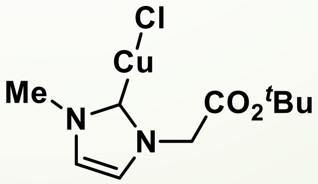
Single pass:
- Applied potential: 1.94 V
- Flow rate: 0.50 mLmin^{-1}
- Residence time: 6.0 min
- Conversion: 97 %
- Voltaic efficiency: 93 %



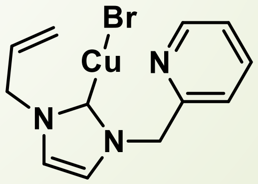
E = 2.54V, τ_R = 20 min
93%



E = 4.90V, τ_R = 300 min
95%



E = 2.40V, τ_R = 13 min
95%

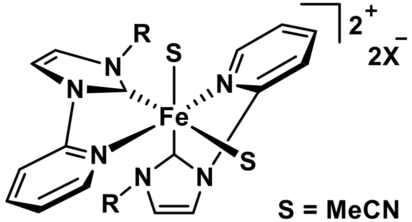


E = 2.20V, τ_R = 6 min
91%

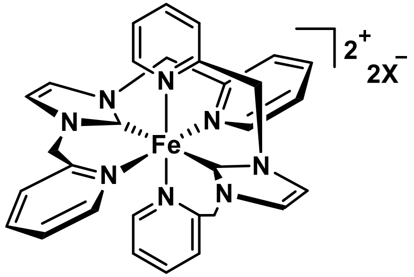
Mike Chapman, *Chem. Commun.* **2015**, *51*, 1282

Alternative Metals and Ligands

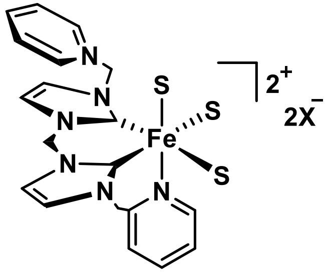
- NHCs: Cu, Ag, Au, Fe
- Salen: Zn, Cu, Ni, Fe, Mn



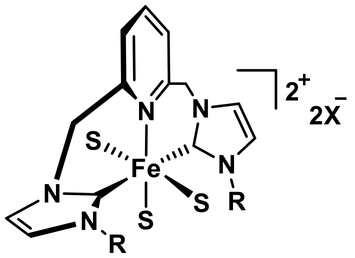
R = Mes, X = PF_6 (74%)
R = pyridyl, X = PF_6 (82%)



X = PF_6 (85%)

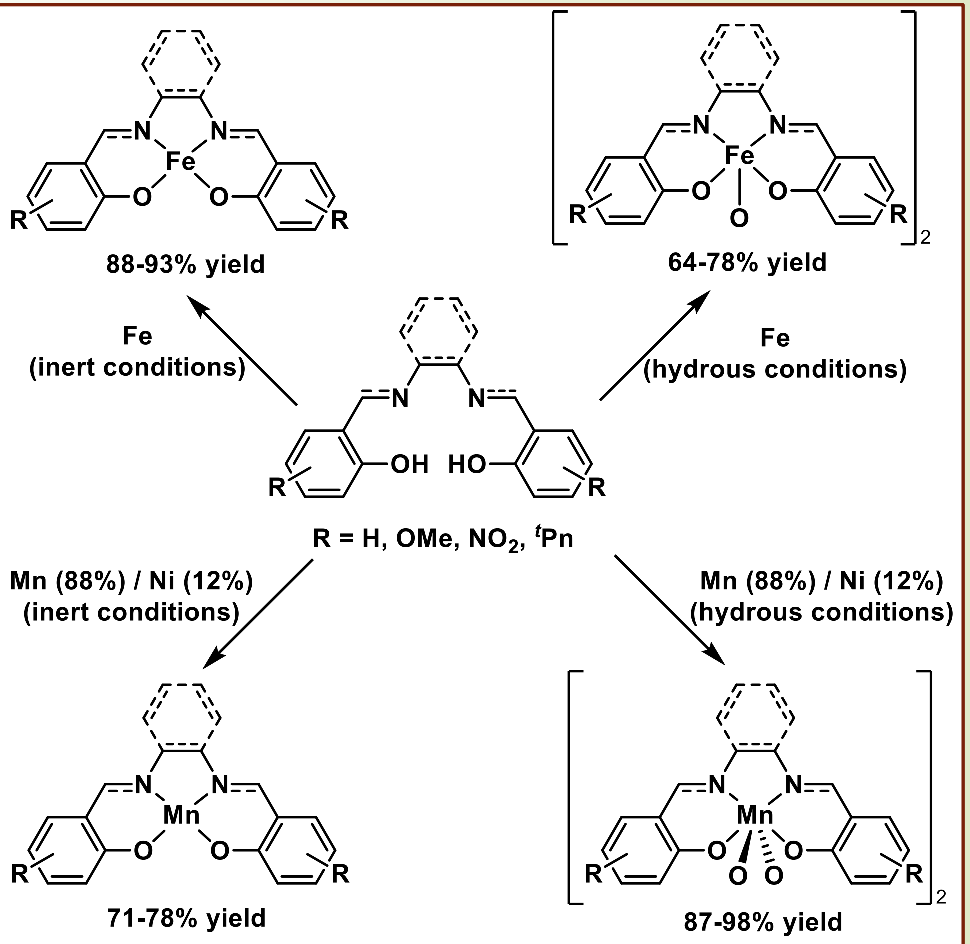


X = PF_6 (91%)



R = Me, X = PF_6 (91%)

Cf. $Fe[N(SiMe_3)_2]_2$



$Mn^{2+} + 2e^-$	$\rightleftharpoons$	$Mn_{(s)}$	-1.185
$Ni^{2+} + 2e^-$	$\rightleftharpoons$	$Ni_{(s)}$	-0.25

Mike Chapman, *ChemistryOpen* **2016**, *5*, 351

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Conclusions and Ongoing Studies

- Electrochemical synthesis enables clean, atom efficient synthesis of a range of metal complexes, including the use of base-sensitive ligands.
- Electrochemical flow-reactor overcomes challenges with mass transfer and low faradaic efficiency, with potential scalability.
- No necessary requirement for isolation/purification – catalyst screening.

(‘Multifunctional Electrochemical Flow Platform for High-Throughput Synthesis & Optimisation of Catalysts’ EP/R009406/1)

- Triazolium ring-opening mechanism being probed.
- Electrochemical batch methodology may

be standardised using an IKA ElectraSyn.

- Electrochemical generation of Fe-NH_3:
  - Source of ‘N’ and ‘H’?
  - Catalytic?

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Acknowledgements

Group

- Dr Ben Lake
- Dr Mike Chapman
- Dr Emma Bullough
- Frances Singer

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- Prof Andrew Smith (St Andrews)

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- BP
- University of Leeds
- AstraZeneca
- EPSRC

THE ROYAL SOCIETY

bp

iPRD

AstraZeneca

EPSRC Engineering and Physical Sciences Research Council

Advion Mass Spectrometry for Chemists

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Conclusions and Ongoing Studies

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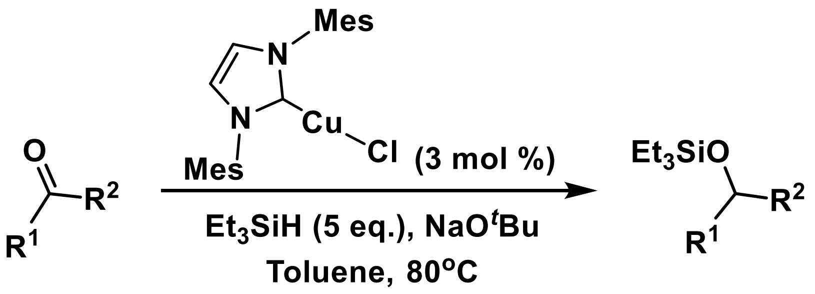

R^1	R^2	Time (h)	Yield (%)	Time (h)	Yield (%)
Cyclohexyl	Cyclohexyl	2	97	2	98
2-Furyl	Methyl	6	95	6	94
2-Thiophenyl	Methyl	6	97	6	97
2-Pyridyl	Methyl	6	94	6.5	90
2-Chlorophenyl	Methyl	5	97	6	98

[a]Electrochemically derived catalyst, [b]Purified catalyst

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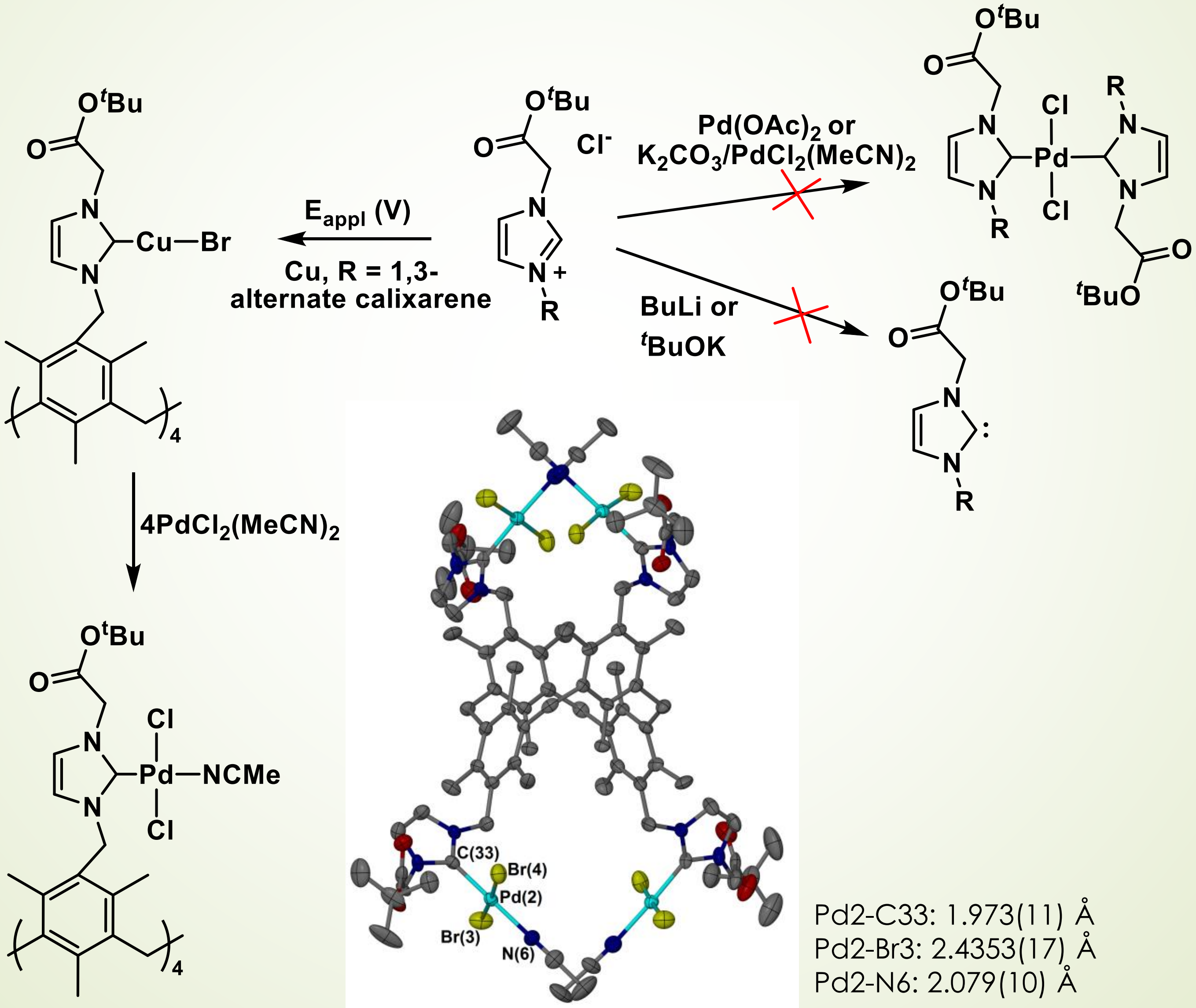
Base-Sensitive *N*-Substituents



Pd2-C33: 1.973(11) Å
Pd2-Br3: 2.4353(17) Å
Pd2-N6: 2.079(10) Å

Emma Bullough, *Organometallics* **2013**, *32*, 570