Towards a Paradigm Shift in Main Group Polar Organometallic Chemistry

Eva Hevia

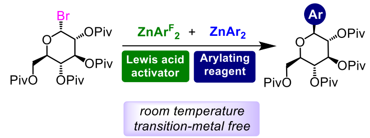
IASOC 18
Naples, 22nd-25th September

University of Strathclyde
Science

Research in the Hevia Group

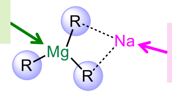
Cooperative effects in Main Group Organometallics

Bond Forming Strategies



ACIE, **2018**, *57*, 187
ACIE, **2017**, *56*, 9566
ACIE, **2016**, *55*, 13147
Chem.Comm., **2017**, *53*, 3653
Chem. Sci. **2014**, *5*, 3552

s-Block Cooperative Catalysis

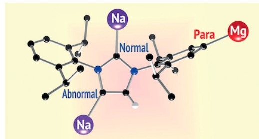


(Lewis acid/ Lewis base)

ACIE, **2018**, *57*, *early view*
Chem. Comm. **2018**, *54*, 1223
Chem. Eur. J. **2016**, 22, 17646
Chem. Comm. **2013**, *49*, 8659

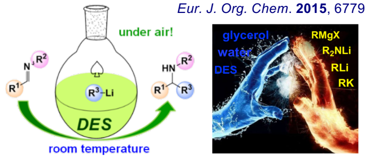
NHCs/Small Molecule Activation

Chem. Eur. J. **2018**, early view
ACIE, **2017**, *56*, 6632
ACIE, **2015**, *54*, 14075
Chem. Sci. **2015**, *6*, 5719



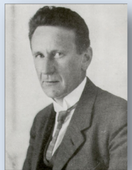
Green Chemistry

ACIE, **2016**, *53*, 16145
Chem. Eur. J. **2018**, 24, 1720
ACIE, **2014**, *53*, 5969
ACIE, **2014**, *53*, 2706
Eur. J. Org. Chem. **2015**, 6779

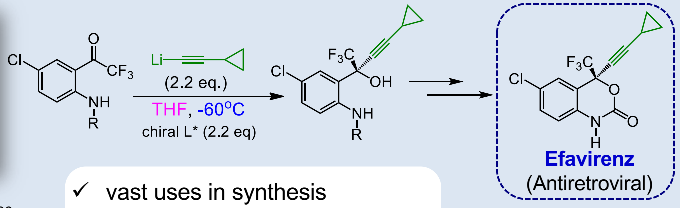


Polar organometallic reagents

Organolithium Reagents



W. Schlenk,
Ber. Dtsch. Chem. Ges.
1917, *50*, 262



- ✓ vast uses in synthesis
- ✓ high reactivity
- ✓ soluble in hydrocarbon solvents

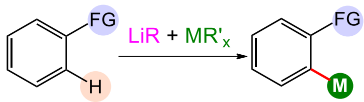
Top 20 best-selling drugs
(€3.11 billion per year)

Key Drawbacks

- low selectivity
- poor FG tolerance
- extremely low T (-78°C)
- air and moisture sensitive

How can we overcome these drawbacks?

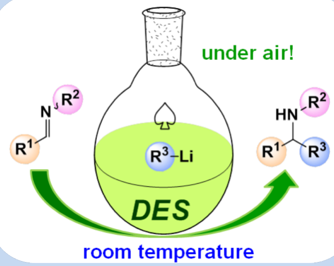
Multicomponent Reagents for Metallation



Li/ M cooperation

- ✓ **Regioselective**
- ✓ **Good FG tolerance**
- ✓ **Room temperature**

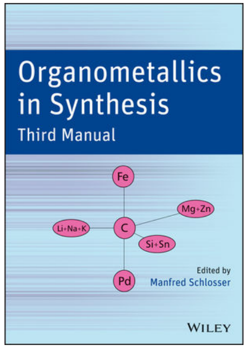
Polar Organometallic Reagents in Deep Eutectic Solvents



M. Schlosser in "Organometallics in Synthesis"

University of Strathclyde Glasgow

*"no difference in the reactivity pattern of given organometallic reagents can be rationalised unless the **metal** and its specific **interactions** with the accompanying **carbon backbone**, the surrounding **solvent** and the **substrate** of the reaction are explicitly taken into account"*



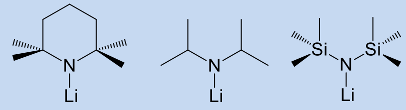
Deprotonative metallation

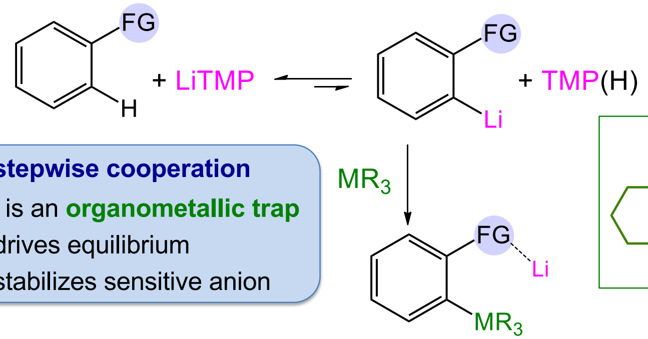
Ar-C-H **inert**

↓

Ar-C-metal **reactive**

Lithium Amides: Utility bases in Synthesis

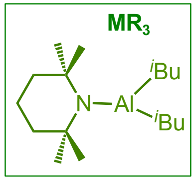




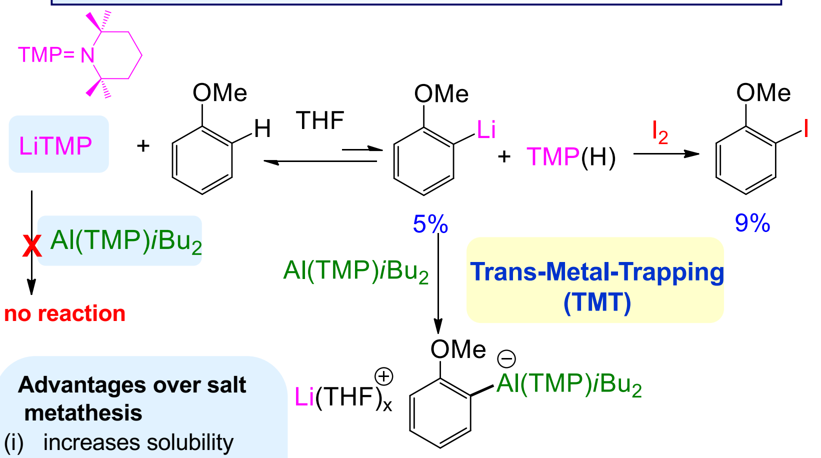
stepwise cooperation

MR_3 is an **organometallic trap**

- drives equilibrium
- stabilizes sensitive anion



Stepwise Synergy: Introducing Trans-Metal-Trapping



Advantages over salt metathesis

(i) increases solubility
(ii) faster reactions
(iii) high selectivity
(iv) drives equilibrium to products

Why not $AlCl_3$?

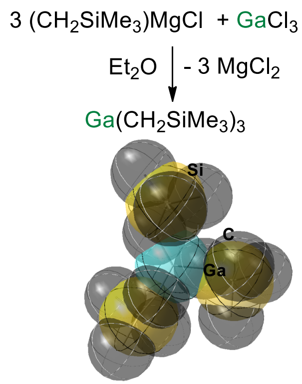
Chem. Sci. **2014**, *5*, 3031

Donna Ramsay

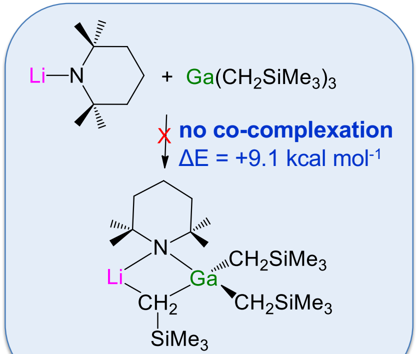
Extending TMT to Gallium Chemistry

GaR_3
($R = CH_2SiMe_3$)

- Ga has similar size to Al, but is more electronegative
- forms more covalent (less polar) M-C bonds
- greater potential to stabilize sensitive carbanions
- hardly been used in metalation chemistry

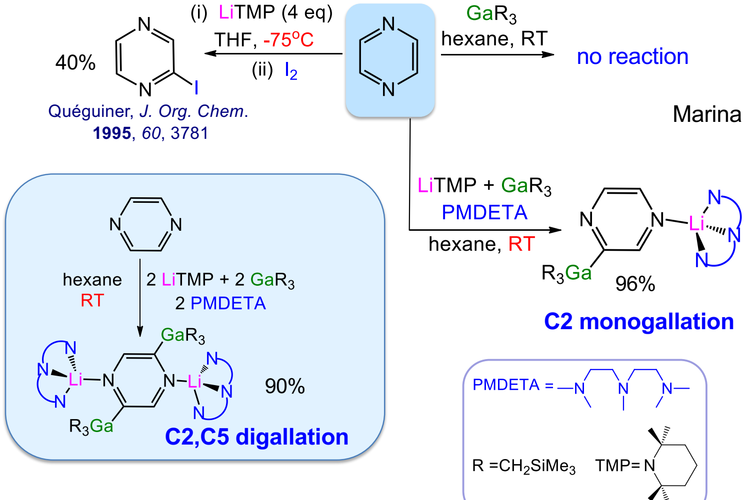


Okuda et al, *Eur. J. Inorg. Chem.* **2007**, 665



Inorg. Chem. **2017**, *56*, 8615

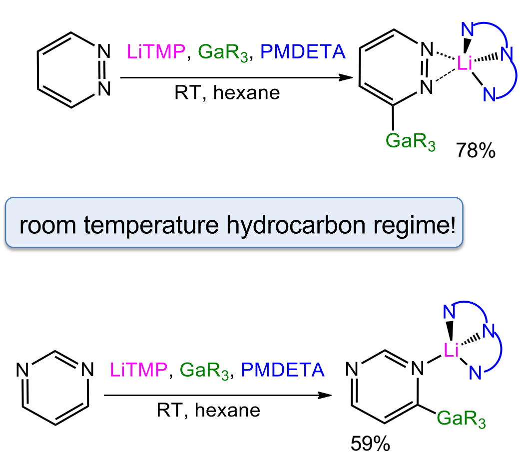
Applying TMT for functionalisation of diazines



Marina Uzelac

Angew. Chem. Int. Ed. **2016**, *55*, 13147

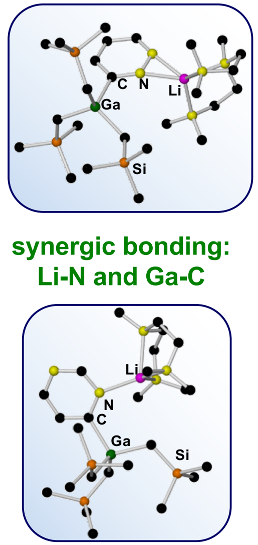
Applying TMT for functionalisation of diazines



room temperature hydrocarbon regime!

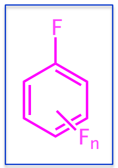
Angew. Chem. Int. Ed. **2016**, *55*, 13147

Marina Uzelac

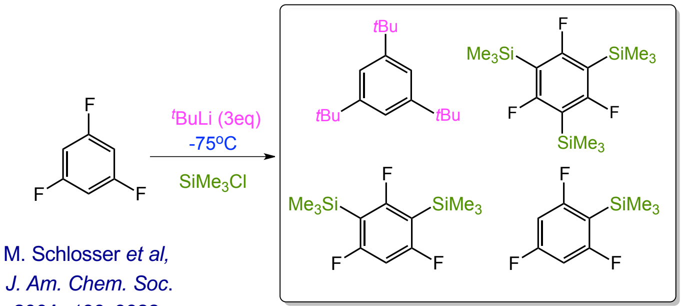


synergic bonding: Li-N and Ga-C

Metallation of fluoroaromatics



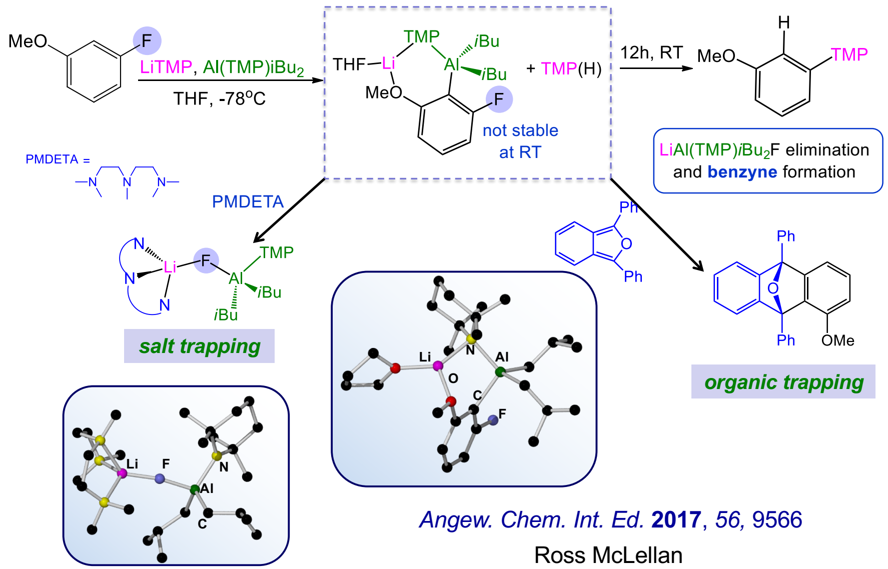
- Unique chemical and biological properties
- Wide applications in industry
- Rare naturally occurrence
- Challenging to functionalized (benzyne formation, autometallation, cascade processes)



M. Schlosser *et al*, *J. Am. Chem. Soc.* **2001**, *123*, 3822

Metallation of fluoroaromatics: Al vs Ga

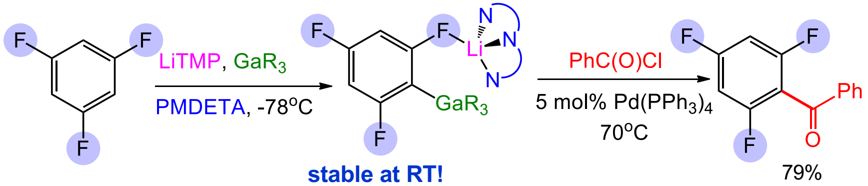
University of Strathclyde Glasgow

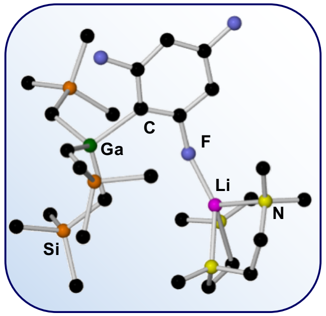


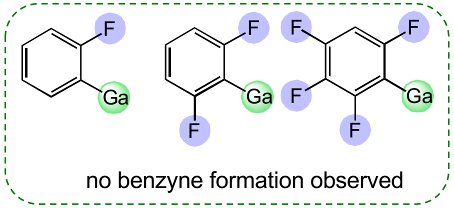
Angew. Chem. Int. Ed. **2017**, *56*, 9566

Ross McLellan

Metallation of fluoroaromatics



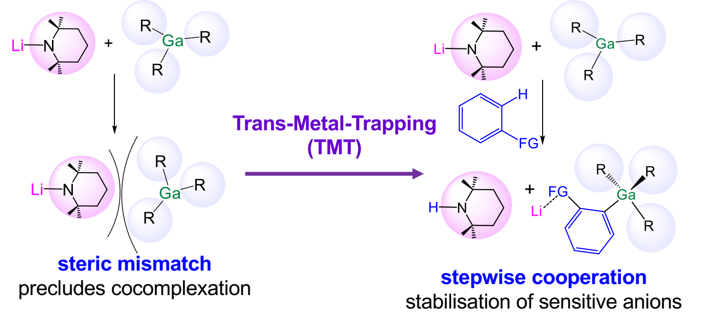


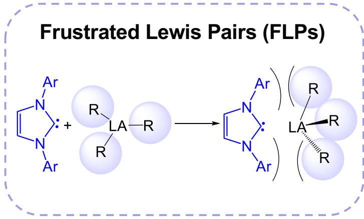


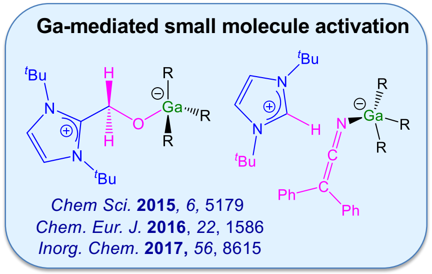
Marina Uzelac, Ross McLellan

Angew. Chem. Int. Ed. **2017**, *56*, 9566

Merging TMT with FLP chemistry

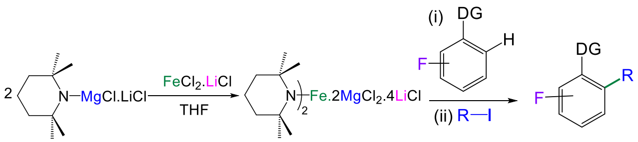






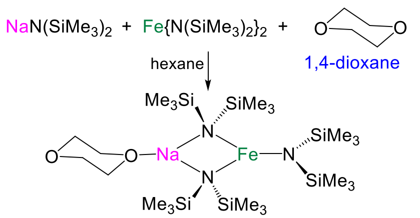
Synchronised Cooperation: Direct ferration of fluoroarenes

University of Strathclyde Glasgow

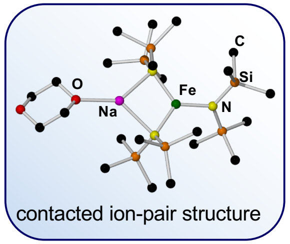


Knochel et al, *Angew. Chem. Int. Ed.* **2009**, *48*, 9717

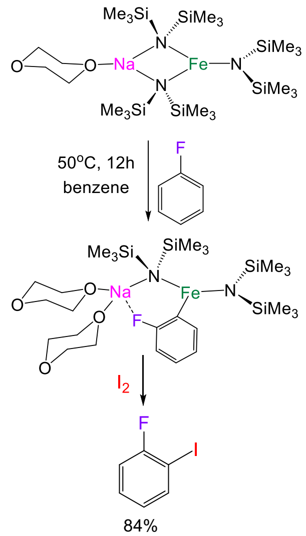
Interlocking co-complexation approach



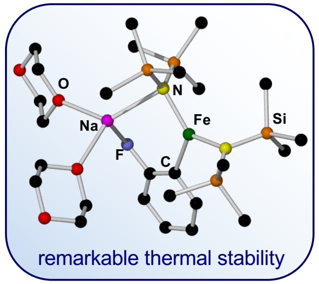
Lewis Maddock



Alkali-metal mediated ferration (AMM*Fe*) of fluorobenzene



Angew. Chem. Int. Ed. **2018**, *57*, 187

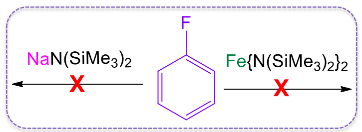


Alkali-metal mediated ferration (AMM*Fe*):

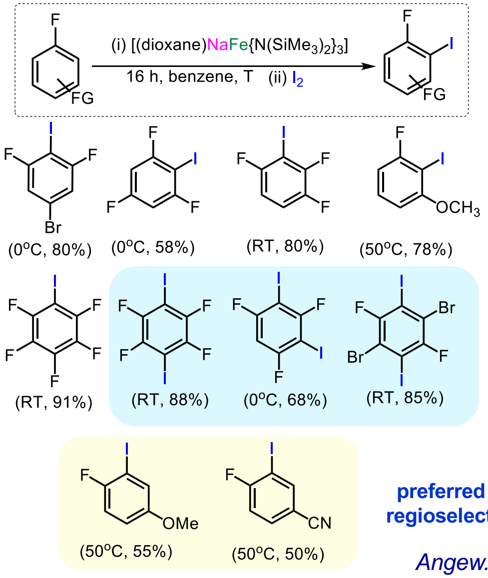
synchronised cooperation

Na: activates substrate by coordination

$Fe(NR_2)_3^-$: anionic activation Fe-N bonds



AMMFe of fluoroarenes



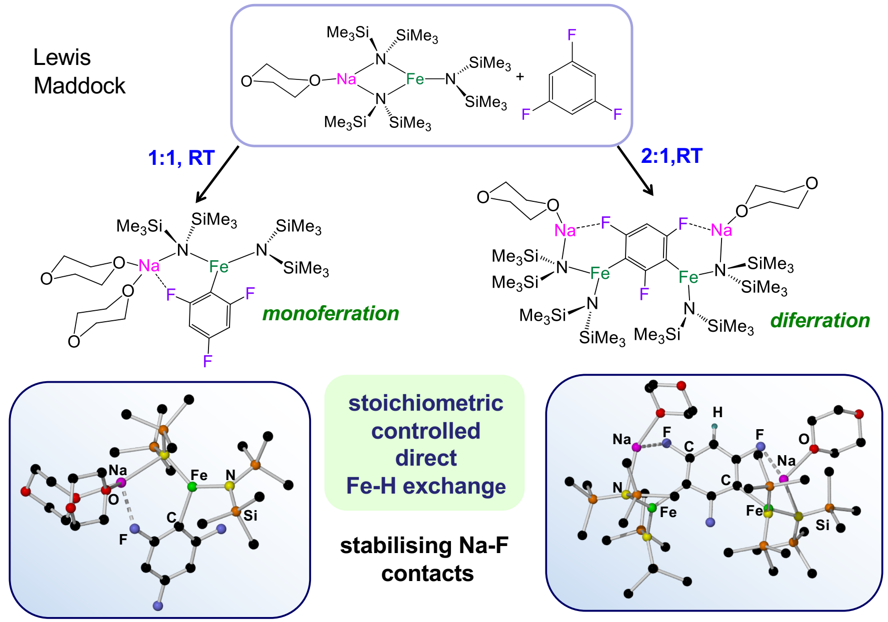
14 examples
yields **50-91%**
regioselective control
no benzyne formation at RT!

RT regioselective differation
(using 2 eq of base)

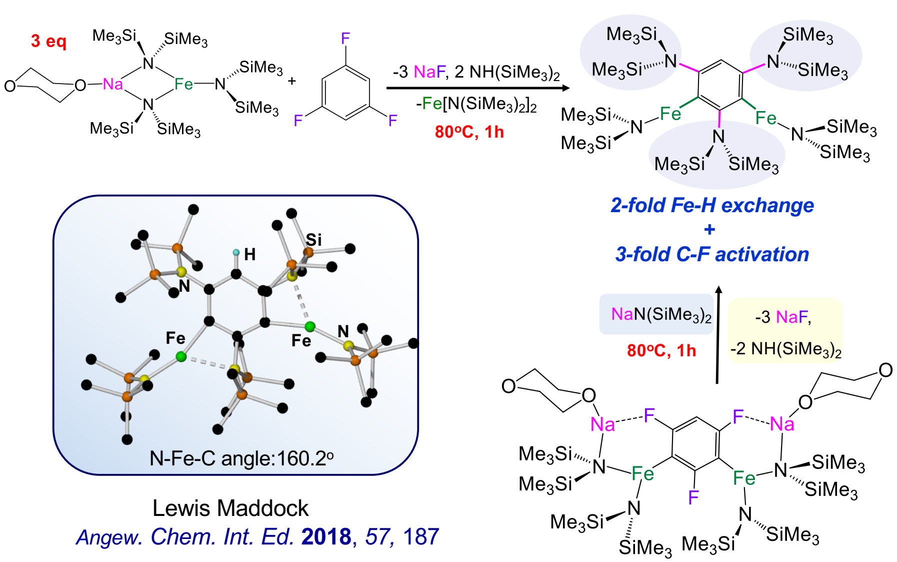
preferred *o*-F regioselectivity

Angew. Chem. Int. Ed. **2018**, *57*, 187

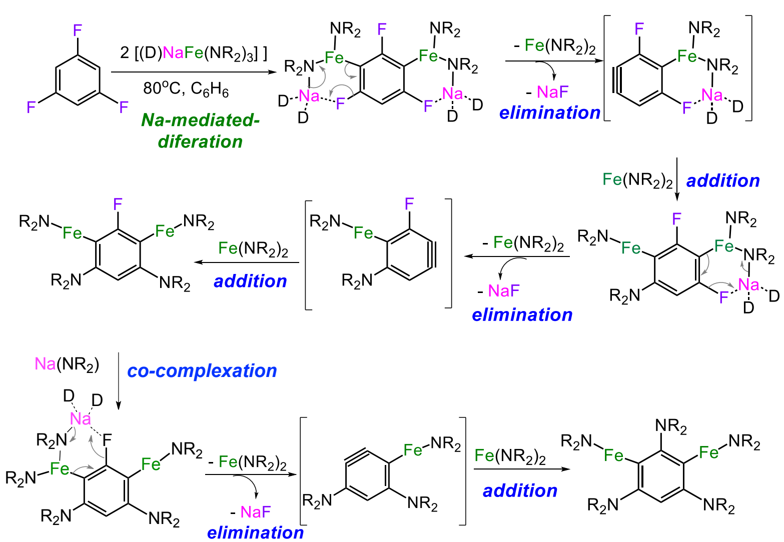
AMM*Fe* of 1,3,5-trifluorobenzene: Stoichiometric control



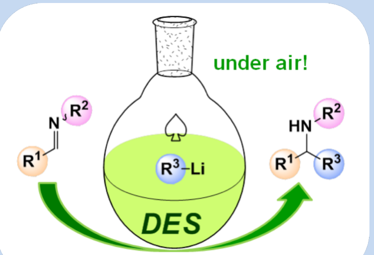
Fe-H exchange/C-F activation



Possible Rationale: Cascade Activation Process



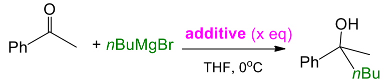
Polar Organometallic Reagents in Deep Eutectic Solvents



Joaquin Garcia-Alvarez,
Universidad de Oviedo, Spain

Mixed Ammonium-Magnesiate Salts

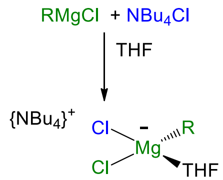
Addition of ammonium salts can greatly enhance the reactivity of Grignard reagents



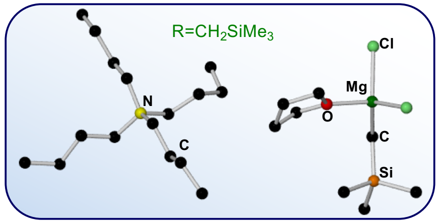
additive	yield(%)
none	49
NBu_4Cl (1eq)	91
NBu_4Cl (0.1 eq)	89

activating effect remains unclear!

L. Song *et al*, *J. Org. Chem.* **2012**, *77*, 4645



ammonium magnesiate



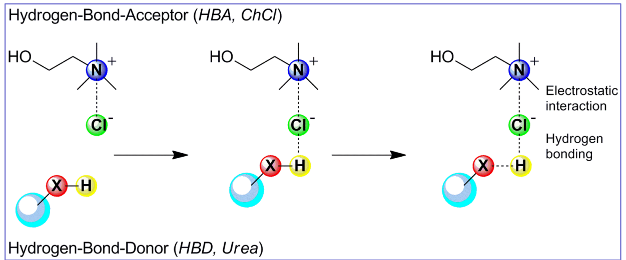
^1H DOSY NMR
structure retained in THF solutions

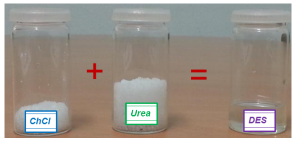
Ate formation = kinetic activation
enhanced Nu power over neutral RMgX's
better regioselectivity control

Alberto Hernan-Gomez

Deep Eutectic Solvents (DESs)

Combination of two components:
H-bond donor (urea, gly, H_2O) and H-bond acceptor (ammonium salt)





133°C (mp)	302 °C (mp)	1ChCl/2Urea 12 °C (mp)

- ❖ cheap ❖ renewable components
- ❖ non-toxic ❖ wealth of applications
- ❖ biodegradable ❖ non-conventional solvents

A. P. Abbott et al, *Chem. Commun.*, **2003**, 70

Deep Eutectic Solvents (DESs) in organic chemistry

ChemPubSoc Europe DOI: 10.1002/ejoc.201501197 EurJOC Microreview

Sustainable Chemistry

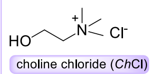
Deep Eutectic Solvents: The Organic Reaction Medium of the Century

Diego A. Alonso*[a] Alejandro Baeza*[a] Rafael Chinchilla*[a] Gabriela Guillena*[a] Isidro M. Pastor*[a] and Diego J. Ramón*[a]

Eur. J. Org. Chem. **2016**, 612

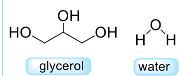
Key advantages
low volatility, non-flammable, non toxic
high availability
recycling capabilities

Hydrogen bond acceptor (**HBA**)



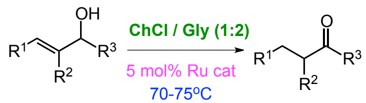
non-toxic quaternary ammonium salt

Hydrogen bond donor (**HBD**)



safe and renewable hydrogen donors

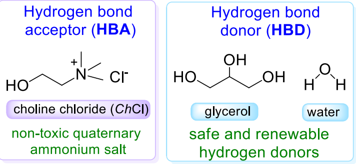
Köning et al. *Green Chem.* **2009**, *11*, 848



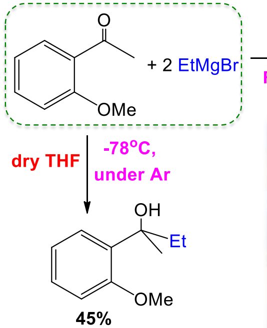
Garcia-Alvarez et al *Chem. Commun.* **2014**, 12927

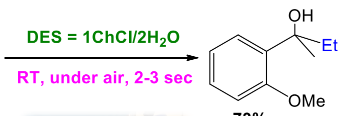
Introducing DES's to Polar Organometallic Chemistry

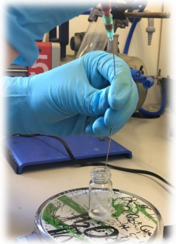
RMgX in Deep Eutectic Solvents (DESs)



Nucleophilic additions to ketones







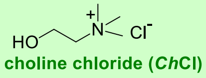
neat H_2O
hydrolysis of EtMgBr, yields **below 10%**

- **addition** favored over competing **hydrolysis**
- kinetic activation of EtMgBr
- DES plays a major role

Angew. Chem. Int. Ed. **2014,** *53*, 5969

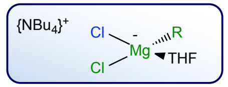
Introducing DES's to Polar Organometallic Chemistry

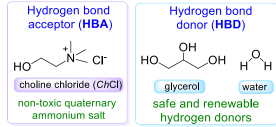
Working Rationale: Formation of more nucleophilic ammonium-magnesiates



dual role of ChCl
component of DES mixture
Cl^- source of ate alkylating reagent

Substrate activation
H-bonding between ketone and H_2O or Gly





Entry	R^1	R^2	R^3	DES	Yield (%)
1	o(MeO)C_6H_4	Me	vinyl	1*ChCl*/2Gly	**78**
2	o(MeO)C_6H_4	Me	Et	1*ChCl*/$2H_2O$	**73**
3	Ph	Ph	vinyl	1*ChCl*/2Gly	**69**
4	*n*Pr	Me	vinyl	1*ChCl*/2Gly	**79**
5	*n*Pr	Me	vinyl	1*ChCl*/$2H_2O$	**87**
6	o(MeO)C_6H_4	Me	ethynyl	1*ChCl*/2Gly	**77**
7	o(MeO)C_6H_4	Me	ethynyl	1*ChCl*/$2H_2O$	**72**

DES controls competing Nu addition over hydrolysis

enables

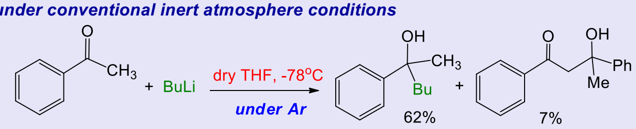
RMgX reaction under air, at RT in the presence of H_2O

Angew. Chem. Int. Ed. **2014,** *53*, 5969

Introducing DES's to Organolithium Chemistry

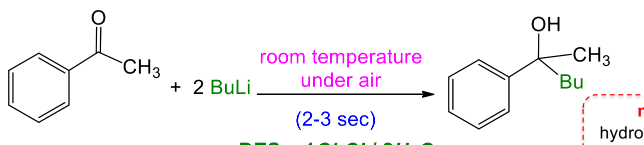
Highly polar RLi reagents : more reactive but less selective , low T required

under conventional inert atmosphere conditions



Ishihara, *Org. Lett.* **2005**, *7*, 573

our approach



neat H_2O
hydrolysis of BuLi, yields **below 8%**

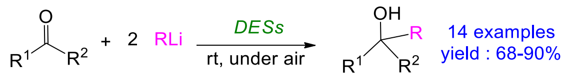
kinetic activation of **RLi**
enhanced Nu power

greater control of **chemoselectivity** of RLi

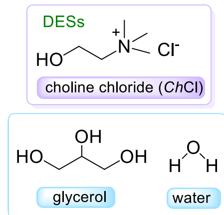
Angew. Chem. Int. Ed. **2014,** *53*, 5969

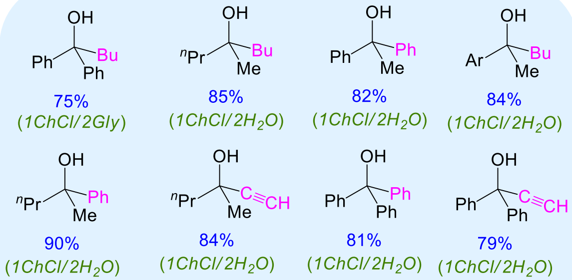
Introducing DES's to Organolithium Chemistry

University of Strathclyde Glasgow



14 examples
yield : 68-90%





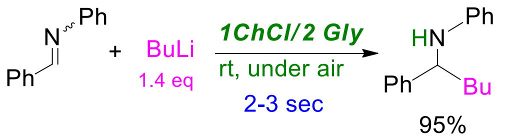
Angew. Chem. Int. Ed. **2014,** *53*, 5969
Eur. J. Org. Chem. **2015**, 6779

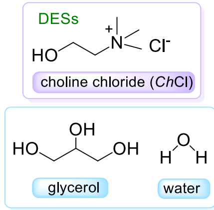
DES controls competing Nu addition over hydrolysis

enables

reactions under air, at RT in the presence of H_2O

Chemoselective Control: Ultrafast Addition of RLi to Imines

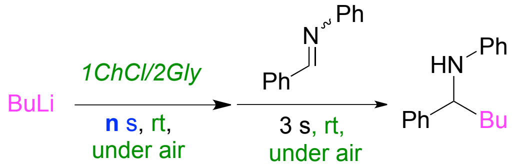




does not work with BuMgCl 8%

important effect of the H-bond donor of DES

1ChCl/ 2H_2O 54%; *1ChCl/ 2 Urea* 38%

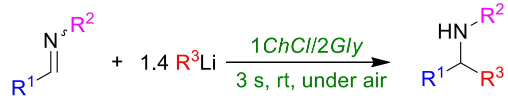


t (s)	Yield (%)
3	89
15	89
60	63
120	42
210	2

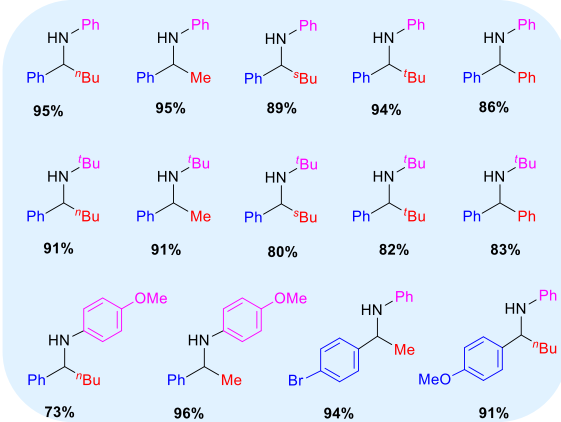
remarkable kinetic stability of RLi in DESs !

Angew. Chem. Int. Ed. **2016,** *55*, 16145; *Chem. Eur. J.* **2018**, *24*, 1720

Ultrafast Addition of RLi to Imines: Substrate Scope



20 examples
Yield: 73-96%

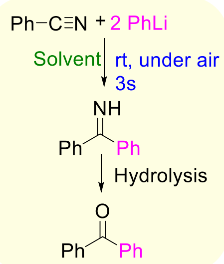


overcomes some key limitations of RLi chemistry

- air and moisture compatible
- RT chemoselective control
- avoid dry organic solvents
- good FG tolerance: (Br, OMe)
- works well for a wide range of RLi and non-activated imines

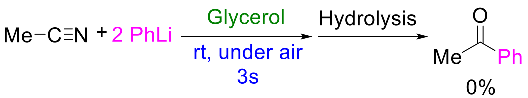
Angew. Chem. Int. Ed. **2016,** *55*, 16145

Gly as a sustainable medium in RLi chemistry: Additions of ArLi to Nitriles at RT under air

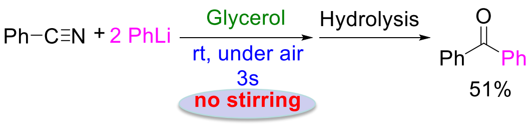


Solvent	Yield (%)
1ChCl/ Gly	71
Gly	83
H_2O	79
EG	53
MeOH	8

"on glycerol" conditions: nitrile is insoluble in Gly



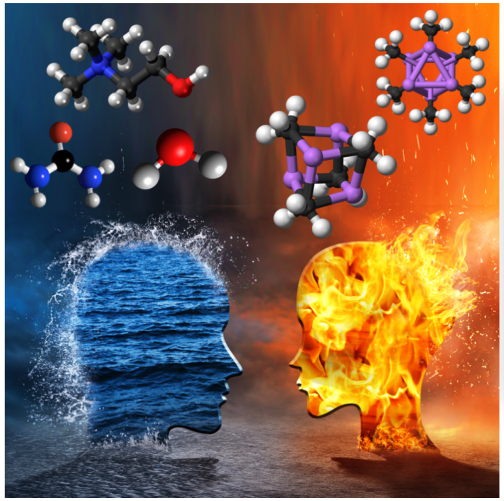
MeCN is soluble in Gly



reaction thought to occur in the **organic/gly liquid interphase**

; *Chem. Eur. J.* **2018**, *24*, 1720

The Future of Polar Organometallic Chemistry Written in Bio-Based Solvents



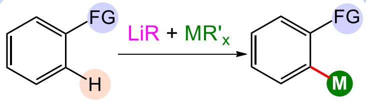
Once upon a time….

*according to a Japanese legend, the **God of Water** and the **Goddess of Fire** lived as one before being turned against each other by the **Lord of Winds...***

Chem. Eur. J. **2018**, *24*, early view *(Concept Article)*

Conclusions

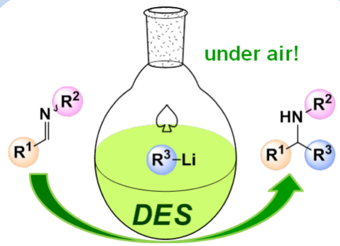
Multicomponent Reagents for Metallation



Li/ M cooperation

- ✓ Regioselective
- ✓ Good FG tolerance
- ✓ Room temperature

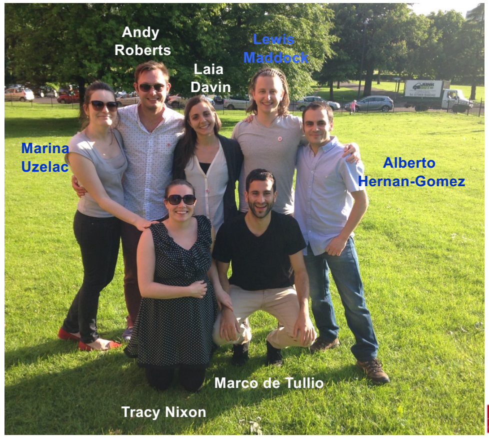
Polar Organometallic Reagents in Deep Eutectic Solvents



room temperature

Acknowledgments

EH group



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Royal Society of Chemistry · The Royal Society (Celebrating 350 Years) · WestCHEM · The Nuffield Foundation · Janssen · EPSRC Engineering and Physical Sciences Research Council · erc European Research Council