

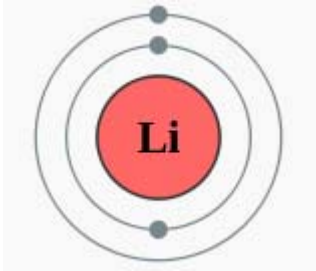
Lithium in Organic Chemistry

Reporter: Pan Hu

Date: 2014.5.5

- Introduction of lithium
- Stable lithium complex with organic ligand
- Organolithium in organic reactions
- Summary

Lithium



Discovered in 1817 in Sweden.

0.0065% in Earth.

Isotopes: ${}^6\text{Li}$ (7.42%) , ${}^7\text{Li}$ (92.58%).

Lightest Metal.

Natural Lithium Minerals:



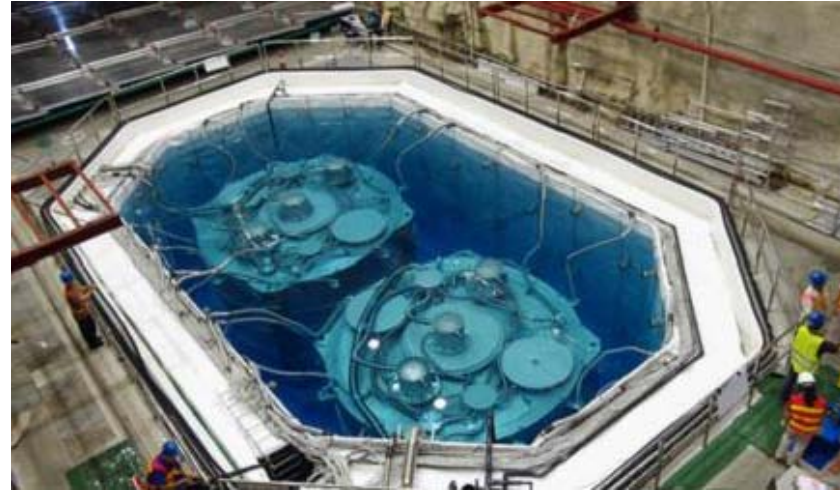
Consumption of Lithium



Lithium Bromide:
an alternative of
freon.



Lithium Battery



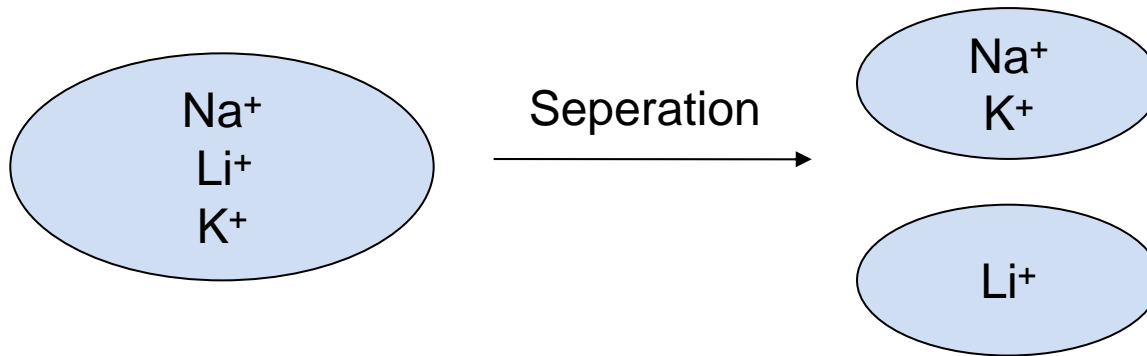
Nuclear Reactor

Since 2004, lithium consumption raises 25% annual. It is possible that lithium consumption will reach to 260,000 ton.

Production of Lithium

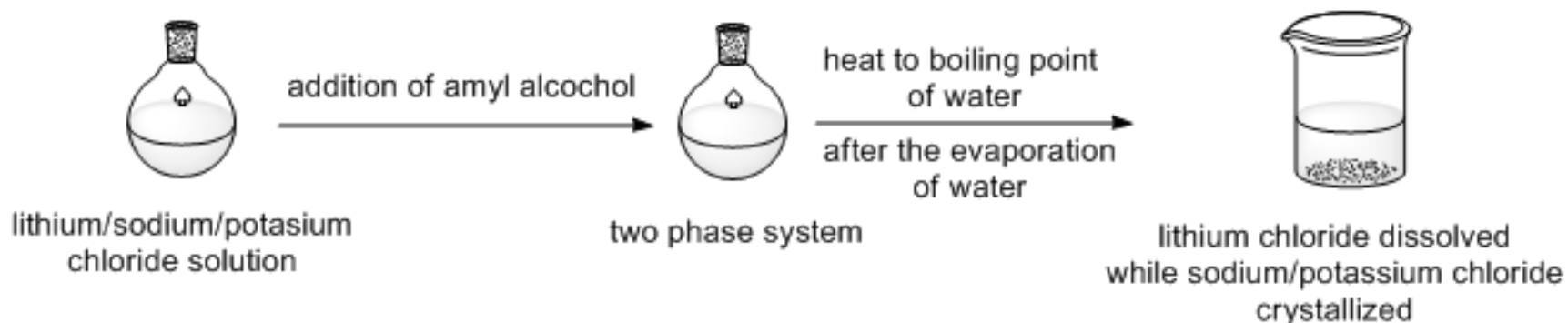
- Challenges:

Majority of lithium resource exist in salt lakes not minerals.



Lithium Complex with Organic Ligand

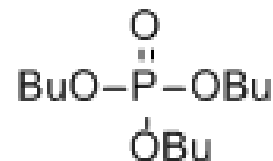
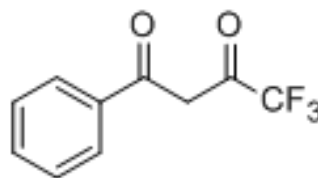
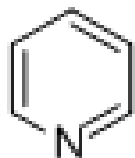
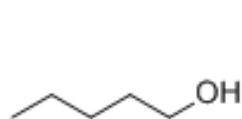
- In 1887, F.A.Gooch sought to effect the separation of lithium chloride from the chlorides of sodium and potassium by means of amyl alcohol (pentanol).



J. Am. Chem. Soc., 1908, 30 (7), 1104–1115.

Lithium Extraction Process

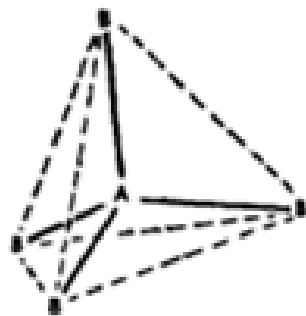
- After over 100 years development, people have discovered many kinds of organic ligands with lithium selectivity.



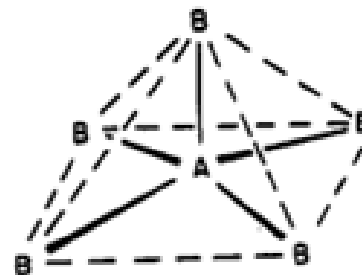
- All these organic ligands are used to the extraction process of lithium.

Lithium Complex

Lithium ion compounds exhibit coordination numbers varying from 2-8. But the most selective Li^+ ionophores exhibit 4-fold tetrahedral coordination and 5-fold square pyramidal coordination.



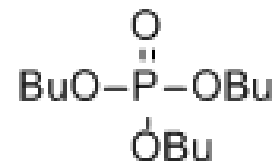
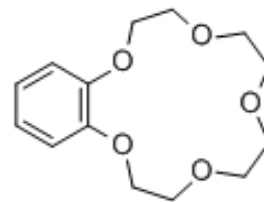
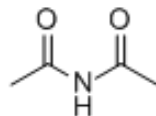
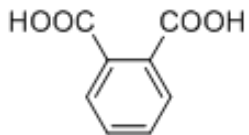
4-fold tetrahedral



5-fold square pyramidal

Organic Ligands

- 1 carboxylic acid
- 2 amines
- 3 ethers, ketones, alcohols
- 4 phosphates (shortest Li-Ligand distance)
- 5 watercarboxylic acid



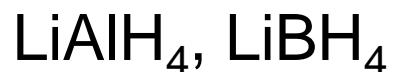
Organolithium in Organic Reactions

- 1 Strong Base

It is well known that organolithium compounds can be used as strong organic base such as n-BuLi, LDA, LiHMDS...



- 2 Counterion of Reduction reagent



Unlike organomagnesium reagent, organolithium reagent is not introduced into product because of its poor nucleophilicity.

Cross Coupling reactions of Organolithium

well established methods:



X=halide or sulfonate

M=Sn, Mg, Zn, B, Si



Sometimes organolithium is much easier to produce.



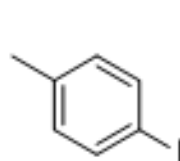
- Challenges:

rapid lithium–halogen exchange

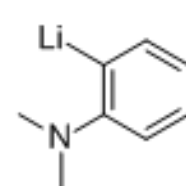
Homocoupling.

Poor nucleophilicity of organolithium reagents.

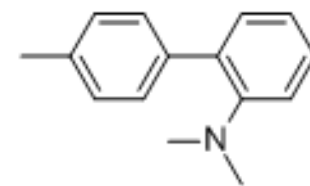
In 1979, Murahashi reported a cross coupling reaction of alkenyl halide and alkyl lithium. But reflux temperature (benzene) was required.



+



→

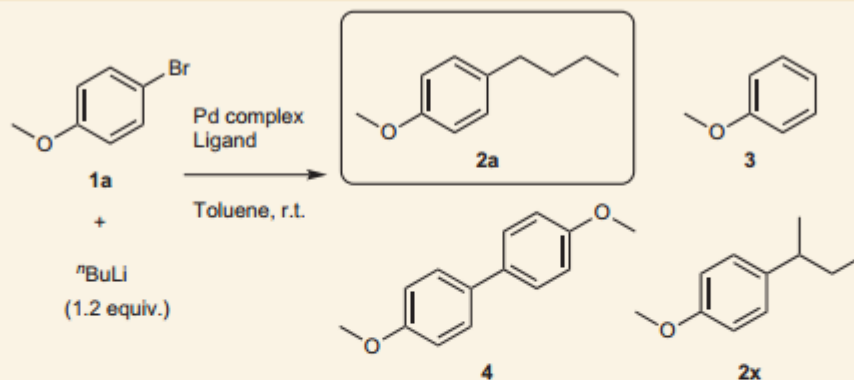


J. Org. Chem. 44,2408–2417 (1979).



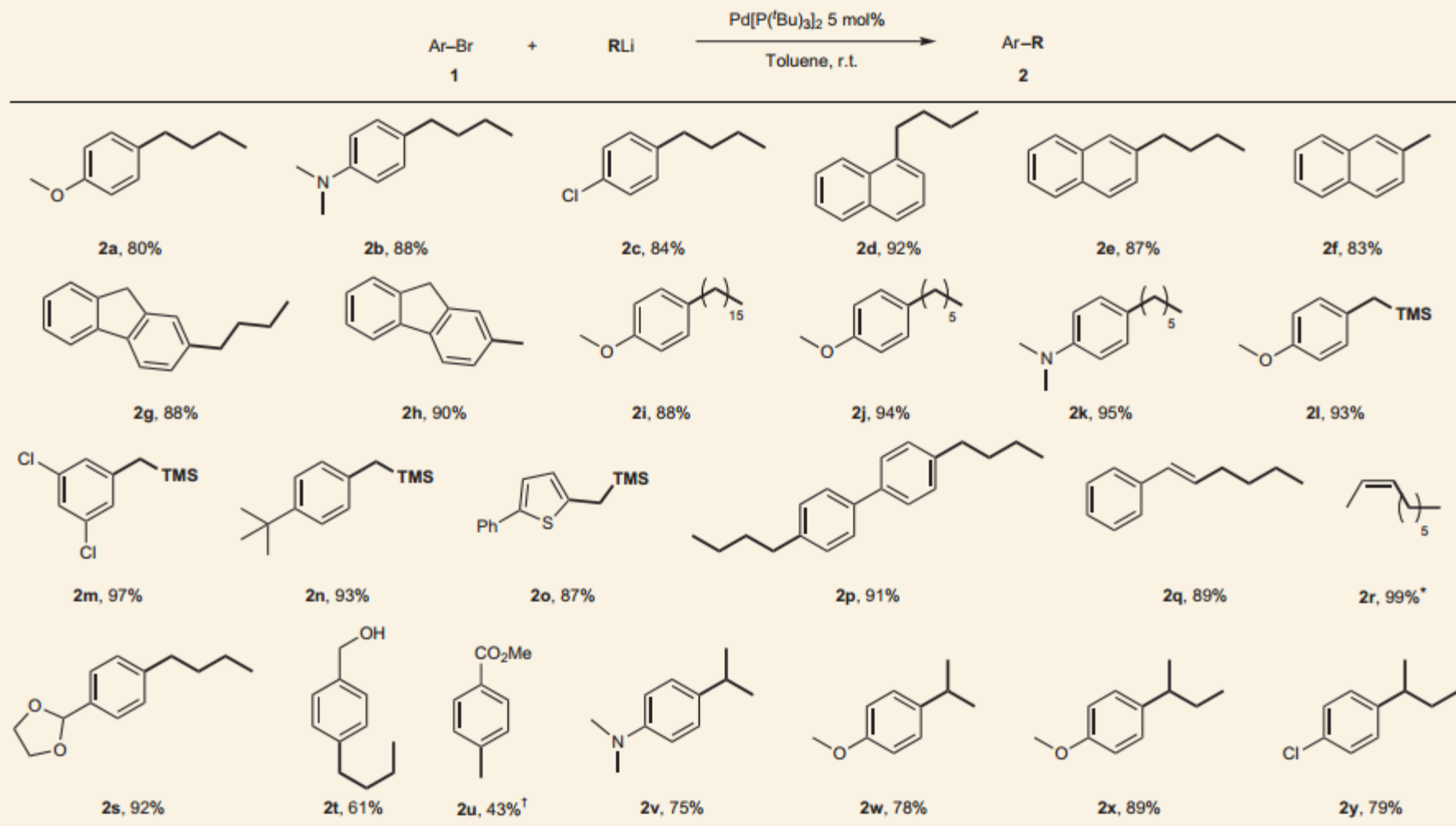
Recently, Ben L. Feringa's group reported a Direct catalytic cross-coupling of organolithium compounds.

Table 1 | Cross-coupling of *n*-BuLi and 4-methoxy-bromobenzene.



Entry	Pd complex	Ligand	Reaction time (h)	Conversion (%)	2a:3:4:2x*
1	Pd ₂ (dba) ₃ , 2.5 mol%	XPhos, 10 mol%	3	Full	80:5:10:5
2	-	-	3	25	-: >95: -: -
3	Pd ₂ (dba) ₃ , 2.5 mol%	-	3	22	23:48:29: -
4	Pd ₂ (dba) ₃ , 2.5 mol%	SPhos, 10 mol%	1	Full	89:5:6: -
5	Pd ₂ (dba) ₃ , 2.5 mol%	P(<i>t</i> -Bu) ₃ , 6 mol%	1	Full	90:6:4: -
6	Pd[P(<i>t</i> -Bu) ₃] ₂ , 5 mol%	-	1	Full	96:4: -: -
7	Pd[P(<i>t</i> -Bu) ₃] ₂ , 1 mol%	-	1	Full	95:4:1: -

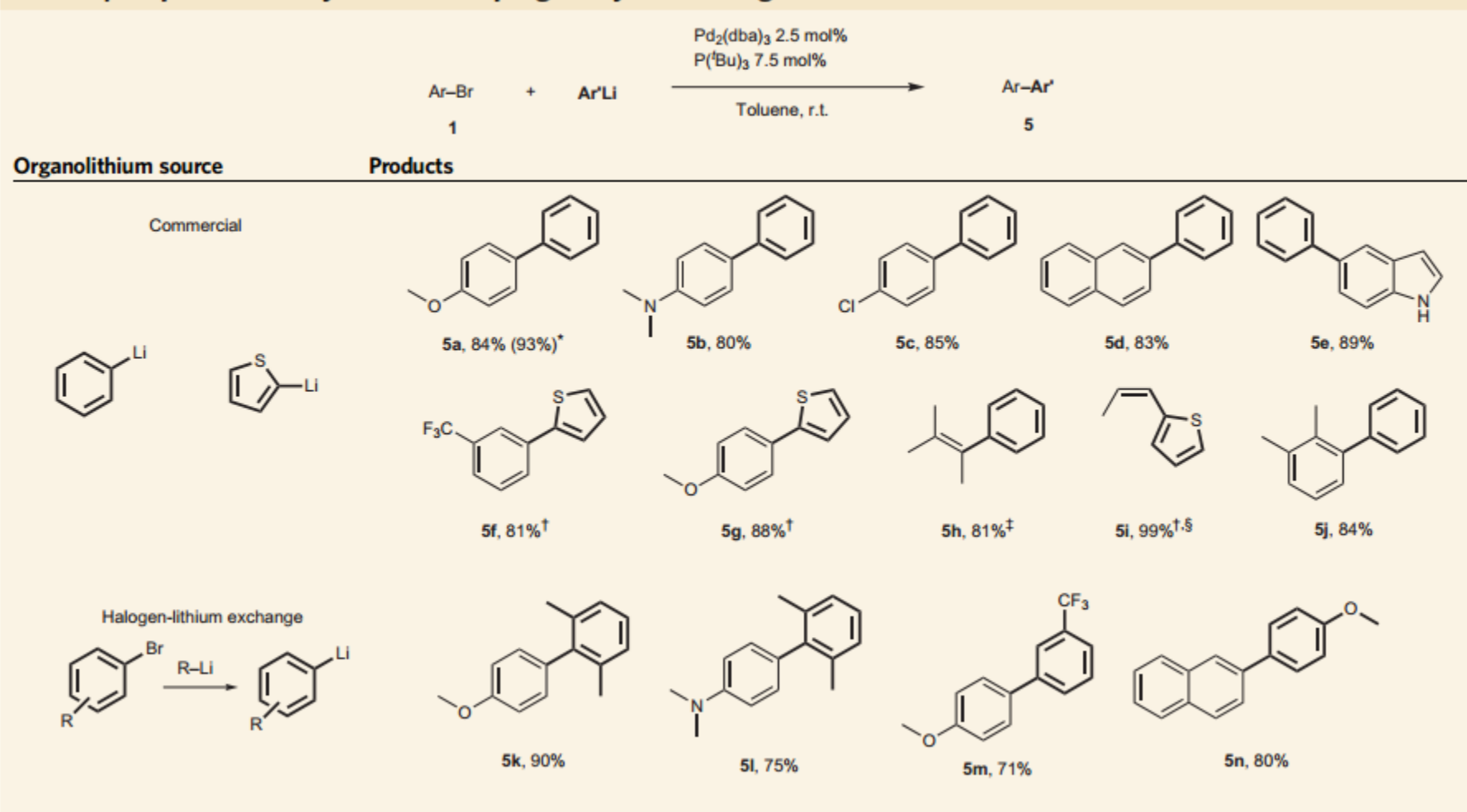
He use Pd[P(*t*-Bu)₃]₂ instead of Pd(PPh₃)₄, toluene instead of benzene. The reaction occurs at room temperature.

Table 2 | Scope of Pd-catalysed cross-coupling of alkyllithium reagents.

And good functional group tolerance, even unprotected alcohol could give moderate yield.



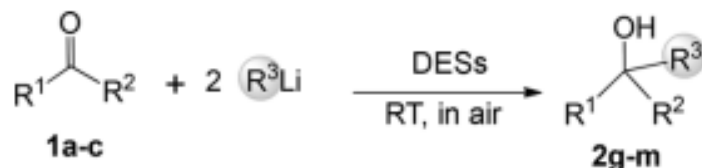
Table 3 | Scope of Pd-catalysed cross-coupling of aryllithium reagents.



Nature Chemistry, 2013, 5(8): 667-672.

Addition to Ketones

Table 3: Addition of organolithium (RLi) reagents to ketones **1a–1c** in ChCl-based eutectic mixtures.^[a]

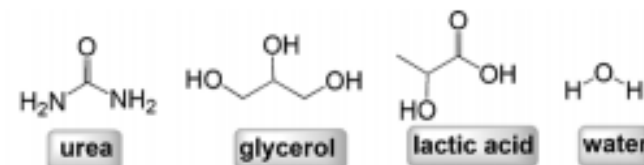


entry	R ¹	R ²	R ³	DES	Yield [%] of 2 ^[b]
1	<i>o</i> -(MeO)C ₆ H ₄	Me	Bu	1ChCl/2Gly	2g 71 ^[c]
2	<i>o</i> -(MeO)C ₆ H ₄	Me	Bu	1ChCl/2H ₂ O	2g 82
3	<i>o</i> -(MeO)C ₆ H ₄	Me	Bu	1ChCl/2EG	2g 60
4 ^[c]	Ph	Ph	Bu	1ChCl/2Gly	2h 75 (12)
5 ^[c]	Ph	Ph	Bu	1ChCl/2H ₂ O	2h 68 (9)
6	CH ₃ (CH ₂) ₂	Me	Bu	1ChCl/2Gly	2i 73
7	CH ₃ (CH ₂) ₂	Me	Bu	1ChCl/2H ₂ O	2i 85
8	<i>o</i> -(MeO)C ₆ H ₄	Me	Ph	1ChCl/2Gly	2j 80
9	<i>o</i> -(MeO)C ₆ H ₄	Me	Ph	1ChCl/2H ₂ O	2j 82
10	Ph	Ph	Ph	1ChCl/2Gly	2k 81
11	Ph	Ph	Ph	1ChCl/2H ₂ O	2k 85
12	CH ₃ (CH ₂) ₂	Me	Ph	1ChCl/2Gly	2l 72
13	CH ₃ (CH ₂) ₂	Me	Ph	1ChCl/2H ₂ O	2l 90
14 ^d	CH ₃ (CH ₂) ₂	Me	ethynyl	1ChCl/2H ₂ O	2m 84



choline chloride

(nontoxic quaternary ammonium salt)



(safe and renewable hydrogen donor)

Future Works...

- Control the reactivity of organolithium reagents.

all those cross coupling reactions require very slow addition of organolithium reagent(1ml--1h).

- Suppress the rapid halogen-lithium exchange.

The mechanism of halogen-lithium exchange reaction remains unknown. ("ate complex"?)

SUMMARY

- Lithium will become more and more important because of its application in energy.
- Organic ligand will play an important role in lithium production.
- Organolithium reagent is a potential nucleophilic reagent for cross coupling reactions.

THANK YOU