Titrating Soluble RM, R_2NM and ROM Reagents

A wide variety of methods for the titration of organometallic reagents are available.

Organolithium reagent titration methods can be grouped into 4 categories:

(1) Coordination of organometallic reagents to polycyclic aromatic bases (bipy, phen) to form coloured charge-transfer complexes. These are then titrated with a standard solution of sBuOH.

(2) Single deprotonation of an organic compound to afford a coloured anion which is then titrated with a standard solution of $PhCO_2H$ or *s*BuOH.

(3) Double deprotonation of an organic reagent to form a colourless monoanion followed by a highly coloured dianion.

(4) Deprotonation of a known amount of an alcohol in the presence of a polycyclic aromatic base (bipy, phen). Once the alcohol has been monodeprotonated, the RM reagent is available to form a highly coloured charge-transfer complex

(5) Unsymmetrical cleavage of bright red Te_2Ph_2 or brown I_2 to form much less intensely coloured products (Te_2Ph_2 + RM → RTePh + MTePh or I_2 + RM → RI + MI).

The first two categories are perhaps less straightforward since they require the use of a stock solution (e.g. of *s*BuOH) in addition to an indicator. However, they do typically allow the titration of only weakly basic reagents (e.g. Grignards and MHMDS)

The 3rd category is typically most effective and straightforward for the titration of strongly basic RLi reagents. It is only suitable for the titration of more weakly basic RC≡CLi, RMgX or R_2NM reagents when the indicator is especially prone to double deprotonation.

The 4th category is suitable for the titration of only weakly basic reagents.

The 5th category has also been shown to be effective for the titration of weakly basic grignard reagents (Te_2Ph_2), and is also reported to be effective for the titration of alkyl zincs (I_2). The use of Te_2Ph_2 is not always desirable due to toxicity and the foul smell of some RTePh compounds that may be produced (depending on the nature of R).

An overview of the most common colourimetric single-titration methods is given in the tables below:

Titrations involving the use of a single reagent (only starred authors shown in author list)

Indicator (conditions)	Organometallics to be titrated	End-point colour change	Reference
I_2 in THF saturated with LiCl (~0.5M) at 0 °C *(no interaction with MOR and not suitable for s- or tBuLi due to HI elim)*	Primary RLi , RMgX, MgR_2 (alkyl, aryl, vinyl), RZnX, ZnR_2 *(almost no details given)*	brown → colourless	Knochel, *Synthesis-Stuttgart*, **2006**, 5, 890
9-methylfluorene	**RLi (*n*BuLi, *s*BuLi, *t*BuLi, MeLi, PhLi), LDA, NaHMDS, $NaCH_2S(O)Me$, $LiCH_2SO_2Ph$**	**colourless → red (THF) colourless → yellow (OEt_2)**	Mash, *J. Org. Chem.* **2002**, 9087
salicylaldehyde phenylhydrazone	**RLi (*n*BuLi, *s*BuLi, *t*BuLi, MeLi), RMgX (R = Me, nPr, iPr, nBu, tBu, Ph), LAH, RedAl**	**yellow → bright orange**	Love, *J. Org. Chem.* **1999**, 3755
N-benzylbenzamide (THF) temperature depends on RLi *(not useful for grignard or NaHMDS)*	***n*BuLi, *s*BuLi, *t*BuLi (-40 °C) MeLi (-20 °C), PhLi, Li_2MeBr, LDA (0 °C)**	**colourless → blue**	Chong, *JOMC*, **1997**, *542*, 281
1-pyreneacetic acid (1-pyrenemethanol)	RLi (*n*BuLi, *s*BuLi, *t*BuLi, *n*BuC≡CLi), MeMgI, LDA	colourless → red (colourless → olive)	Hase, *J. Org. Chem.* **1991**, 6950
Te_2Ph_2 *(no reaction with ROM)*	RLi (*n*BuLi, *t*BuLi, MeLi, PhLi PhC≡CLi), RMgX (R = *n*Bu, Me, Ph, vinyl), LDA	red → pale yellow	Ogura, *J. Org. Chem.* **1989**, 5627
N-pivaloyl-*o*-toluidine (or *N*-pivaloyl-*o*-benzylaniline)	RLi (*n*BuLi, *s*BuLi, *t*BuLi, PhLi, MeLi)	colourless → yellow (colourless → orange)	Suffert, *J. Org. Chem.* **1989**, 509
4-biphenylmethanol (or 4-biphenyl-acetic acid or 4-biphenylmethanol/$HCPh_3$)	RLi (*n*BuLi, *s*BuLi, *t*BuLi, MeLi)	colourless → orange (yellow or red)	Juaristi, *J. Org. Chem.* **1983**, 2603
2,5-dimethoxybenzylalcohol (benzene or THF)	RLi (*n*BuLi, *s*BuLi, *t*BuLi, PhLi)	colourless → red	Ronald, *Chem. Commun.* **1980**, 87
1,3-diphenyl-2-propanone-*p*-tosylhydrazone	RLi (*n*BuLi, *t*BuLi, MeLi PhLi)	Colourless → orange	Lipton, *JOMC*, **1980**, *186*, 155
2,2-diphenylacetic acid (THF, RT)	RLi (*n*BuLi, MeLi)	colourless → yellow	Kofron, *J. Org. Chem.* **1976**, 1879
Menthol / 2,2'-bipyridine (THF, RT)	RLi	colourless → red	Lin, Paquette, *Synth. Commun.*, **1994**, *24*, 2503

Titrations involving the use of a stock solution of *s*BuOH in addition to an indicator

(1) XS 1',4'-dihydro-2,3'-biquinolyl (THF, RT). (2) sBuOH in xylene	RLi (*n*BuLi, *s*BuLi, PhLi), $LiNEt_2$, MHMDS (M = Li, Na, K), $NaCH_2S(O)Me$,	pale yellow → red → pale yellow	Aksenov, Magedov, *J. Chem. Res.-Synopses*, **1994**, *10*, 402
(1) XS 4-phenylbenzylidene benzylamine (2) *s*BuOH	RLi (*n*BuLi, *t*BuLi, PhLi, MeLi), MHMDS (M = Na, K)	Colourless → deep blue → pale yellow (via red)	Duhamel, *JOMC*, **1993**, *448*, 1
(1) XS *N*-phenyl-1-naphthylamine (2) *s*BuOH	RLi (*n*BuLi, *t*BuLi), RMgX (R = Me, *n*Oct, *s*Bu, Ph), sBu_2Mg	colourless → yellow-orange → colourless	Bergbreiter, *J. Org. Chem.* **1981**, 219
(1) XS *N*-benzylbenzamine in THF, OEt_2, benzene or hexanes (2) addition of *s*BuOH in xylene	RLi (*n*BuLi, *s*BuLi, *t*BuLi, PhLi)	colourless → red-purple → colourless	Duhamel, *J. Org. Chem.* **1979**, 3404
(1) XS 1,10-phenanthroline (2,2'-biquinoline also mentioned) (2) *s*BuOH	RLi (*n*BuLi, *s*BuLi, *t*BuLi), RMgX (R = *n*Bu, Ph), sBu_2Mg, *i*BuMgMe	colourless → violet → colourless	Watson, Eastham, *JOMC*, **1967**, *9*, 165

Titrating metal hydride reagents

9-fluorenone	LAH in OEt_2 or THF	yellow → colourless	Brown, Lézé, Touet, *Tet. Lett.*, **1991**, *32*, 4309
(1) 1,10-phenanthroline in THF, (2) PhMgBr solution, (3) $PhCH_2OH$ in tol, (4) $LiAlH_4$ solution, (5) $PhCH_2OH$ in tol	LAH solution in OEt_2	colourless → violet-pink → yellowish → violet → yellow-orange	Villieras, Mambaud, Kirschleger, *JOMC*, **1983**, *249*, 315
I_2 (benzene)	LAH solution	red-brown → colourless	Felkin, *Bull. Soc. Chim. Fr.*, **1951**, 347

Standard procedure for the use of N-benzylbenzamide for the titration of alkyl lithium reagents

- Fit an oven dried 10 mL three neck flask equipped with a nitrogen inlet adapter, a stirring bar and a rubber septum.
- Charge the flask with exactly 100 mg of N-benzylbenzamide.
- Add 5 ml of THF, and then cool to -45 ^{o}C (dry ice-acetonitrile bath, better for ^{n}BuLi, essential for ^{t}BuLi), -20 ^{o}C (for MeLi) or 0 ^{o}C (for LDA) under N_2.

- To the resulting colourless solution, added the alkyl lithium solution dropwise via a 0.5 mL syringe (graduated in 0.01 mL increments). During addition, a blue colouration will appear in solution, but will disperse rapidly. At the endpoint, the intense blue coloration will become obviously persistent in the solution. The colour is royal blue for the titration of *n*BuLi, but is more of a greenish-blue for the titration of *t*BuLi.

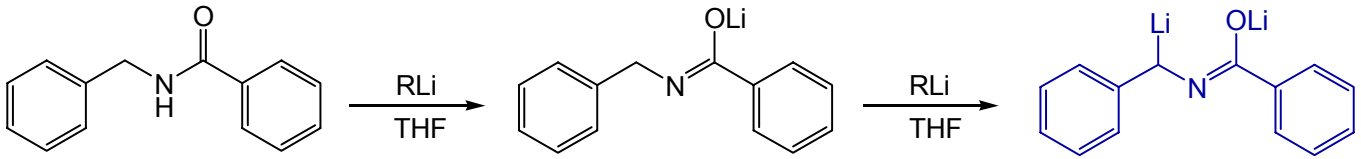
- Calculate the molarity of the RLi solution using the volume of RLi solution added and the exact mass of NBB used.
  For quick determination:

100 mg N-benzylbenzamide = 0.4733 mmol

For a 1.6M solution of RLi, 0.30mL will be required to reach the end-point.

$$\textbf{Molarity of Solution} = \frac{\textbf{Mass of NBB (in mg)}}{\textbf{211.26 gmol}^{-1}\textbf{ x Vol of RLi solution added (in ml)}}$$

The chemical reaction occurring during the titration is:



Colourless Colourless Deep Blue