Organomagnesiums On-demand. Versatile Set-Up Designed for the Preparation of Turbo-Grignard® Reagent, Knochel-Hauser Base and Alkoxide under Continuous Flow Conditions.

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Overview

i-PrCl → *i*-PrMgCl•LiCl — Turbo Grignard

i-PrCl + TMPH → TMPMgCl•LiCl — Knochel Hauser Base

*i*PrCl → + *tert*-AmylOH → *tert*-AmylOMgCl•LiCl

Reactive
- Fresh Organomagnesium On-Demand

Soluble
- High Lithium Chloride Concentration

Scalable
- Controlled Exotherm

Versatile
- Same Column for Multiple Substrates

Practical
- Clear Solution – No Separation Needed

Fast
- 5 – 25 min Residence Time

Safe
- Flammable Gases Released Far from Heat Source

Carbon Bases: Grignard and Turbo Grignard® Reagents

Selected organobromides and chlorides were converted to Grignard reagents using the following conditions:
- Activation: 1-bromo-2-chloroethane/TMSCl/DIBALH in THF/Tol.
- Residence time: 5 min
- Column i.d.: 10 mm
- Flow rate: 0.5 mL/min
- Magnesium (20 – 230 mesh): ≥ 2 eq.
- Solvent: THF
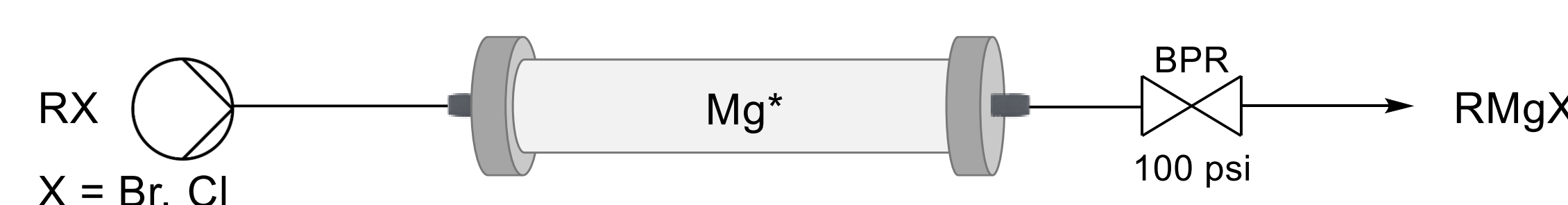
Entry	RX	T (C)	[RX] (M)[a]	[RMgX] (M)	Yield (%)
1	*i*-PrBr	25	0.9	0.75	82
2	EtBr	25	1.2	1.08	90
3	*i*-PrCl	80	2.5	2.23	89
4	*sec*-BuCl	80	2.5	2.23	89
5	*n*-BuCl	80	2.5	2.13	85
6	PhCl	100	2.5	2.24	90
7	BnCl	25	1.2	0.65	54[b]

[a] Quantitative RX conversion. [b] 1,2-Diphenylethane obtained as single by-product.

We explored the formation of Turbo Grignard® using a bicomponent column composed by magnesium and lithium chloride separated by fiber glass using the same conditions:

| Entry	RX	T (C)	[RX] (M)[a]	[RMgX•LiCl] (M)	Yield (%)
1	EtBr	25	1.5	1.30	87
2	*i*-PrCl	80	2.5	2.10	84
3	*sec*-BuCl	80	2.5	2.23	89
4	*n*-BuCl	80	2.5	2.13	85

[a] Quantitative RX conversion.

Concentration was determined by titration (duplicate) of the overall solution collected under inert at steady state:
- 2-Hydroxybenzaldehyde phenylhydrazone[5]
- Benzoic acid/4-(phenylazo)diphenylamine[6]

[RMgCl]: up to 2.2 M
n RMgCl: 10 – 100 mmol

Nitrogen Bases: Knochel-Hauser Amides

Knochel-Hauser bases were synthesized using the same setup by in-situ formation of Turbo Grignard® in presence of amine dissolved in THF/toluene (1:1):
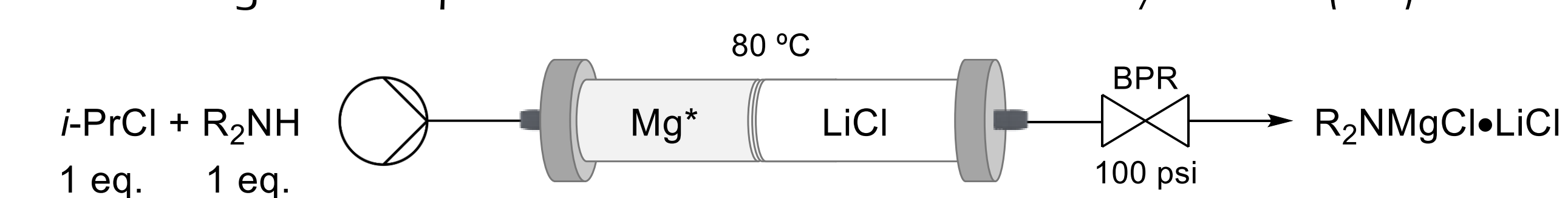
Entry	R₂NH	[R₂NH] (M)	[R₂NMgX•LiCl] (M)	Yield (%)
1	Ph₂NH	1.2	1.16	97
2	HMDS	1.2	1.15	96
3	TMPH	1.2	*i*-PrMgCl•LiCl	-

In the case of 2,2,6,6-tetramethylpiperidine (TMPH), slower reaction rate[7] required the addition of coil (10 mL) to increase residence time to 25 min.
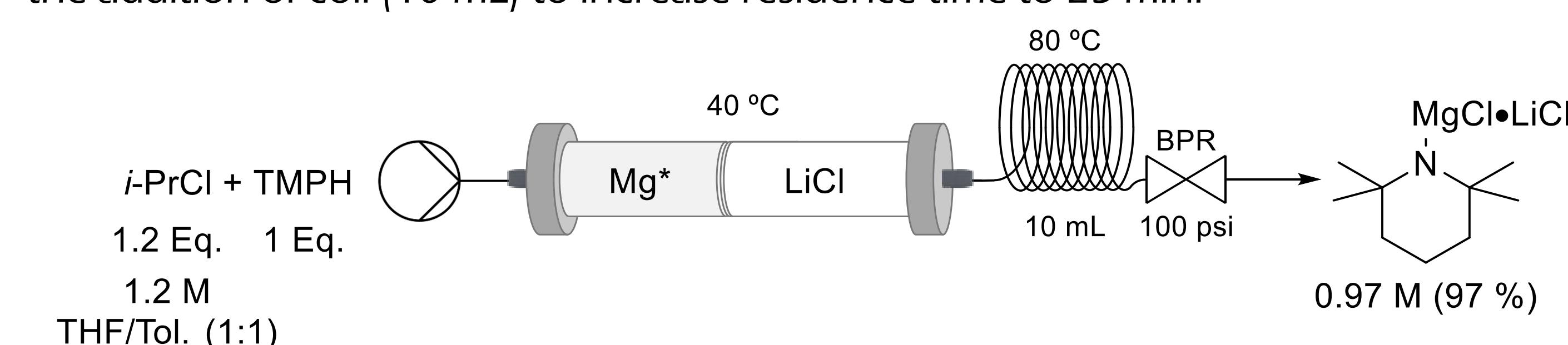
[R₂NMgCl]: up to 1.2 M
**n R₂NMgCl: 10 – 50 mmol**

Introduction

Organomagnesium compounds are strong bases as well as powerful nucleophiles widely used in organic synthesis but their preparation in batch presents several limitations:
1. Inert atmosphere needed – generation of flammable gases.
2. Exothermic reactions: metal activation and organometallic formation.
3. Difficult to scale-up due to poor heat transfer.
4. Hazardous separation of metal excess.
5. Neutralization leads to change of reactivity.
6. Low solubility.

Flow chemistry technologies and cartridges containing activated metals can overcome these limitations:
1. Metal packed bed column can be easily kept under inert condition.
2. Convenient and fast activation.
3. Efficient heat transfer provides better temperature control.
4. Metal is trapped and consumed inside the column and clear solutions are obtained.
5. Freshly prepared reagents provide reproducible results.

Knochel has demonstrated that lithium chloride (LiCl) increases reactivity and promotes solubility of organomagnesium in part due to decreasing aggregation and favoring the formation of the more nucleophilic magnesiated intermediate RMgCl₂Li⁺.[1] Despite the importance of organomagnesium synthesis only five examples under flow conditions are present in the literature,[2] and only two use a practical system with a broad range of substrates.[3] Herein, we presented a novel approach for on-demand preparation of Turbo-Grignard® reagents,[4] Knochel-Hauser bases and magnesium alkoxides using a bicomponent column composed of magnesium and LiCl. For this purpose, a ranking of the 20 most cited organomagnesium halides have been plotted using data from Scifinder and we have selected some of them to conduct our study.

The 20 Most Cited Organomagnesium Halides
Selected Organohalides
*Data from SciFinder March 26, 2019
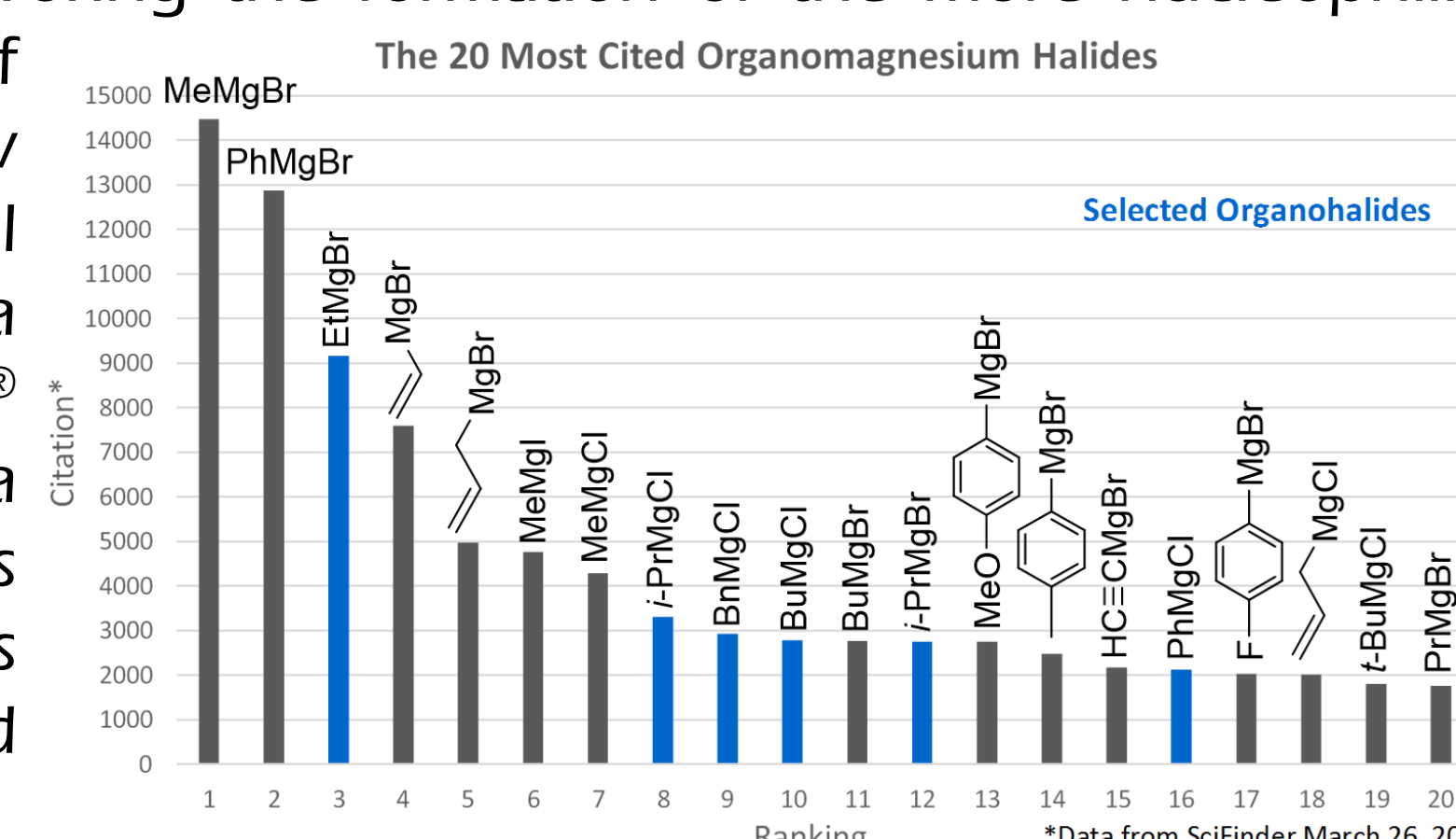
Oxygen Bases: Magnesium Alkoxides

We also investigated the formation of soluble hindered oxygen base. *tert*-Amyl magnesium alkoxide was quantitatively obtained from the corresponding alcohol and Turbo Grignard®. The alcohol was added once *i*-PrMgCl•LiCl was formed due to incompatibility between ROH and the hydride present in the activating solution.

Direct Deprotonation:
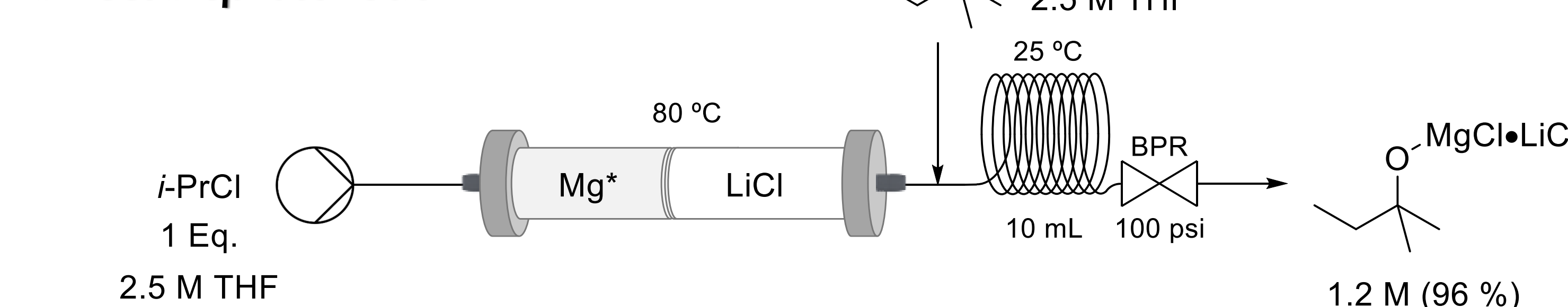
Finally, we screened conditions to form similar structures by Barbier reaction. Acetophenone was chosen to avoid enolatization pathway. Quantitative conversion was obtained but direct reduction of ketone could not be totally suppressed, generating a mixture tertiary/secondary alkoxides in 76:24 ratio.

Barbier Reaction:
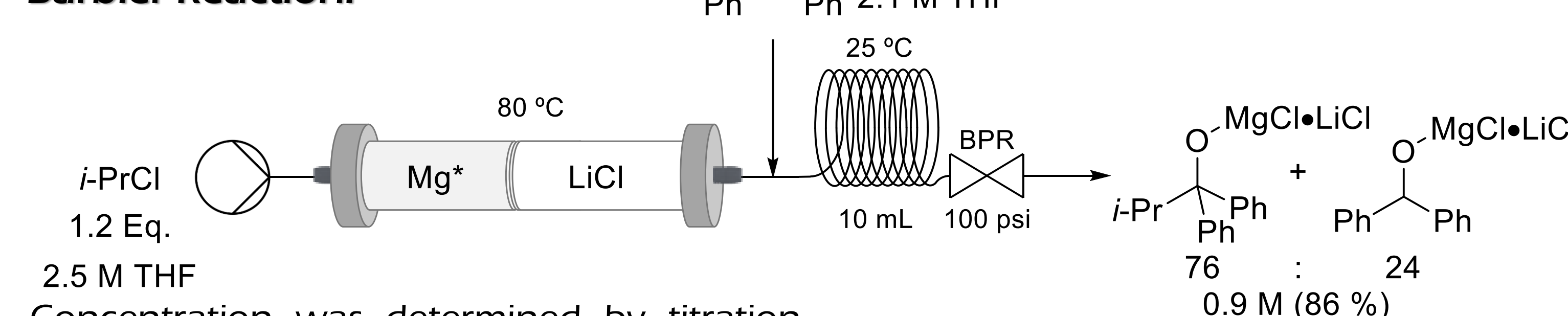
76 : 24
0.9 M (86 %)

Concentration was determined by titration (duplicate) of the overall solution collected under inert at steady state:
- Benzoic acid/thymolphthalein[8]

[ROMgCl]: up to 1.2 M
n ROMgCl: 10 – 20 mmol

Batch *versus* Flow

15x Better in Flow

i-PrMgCl • LiCl	Batch[a]	Flow
mmol of 2-chloropropane	100	100
2-Chloropropane concentration (M)	0.92	2.50
Reaction time (hour)	12	1.5
Concentration of *i*-PrMgCl • LiCl (M)	0.89	2.10[b]
Conversion of 2-chloropropane (%)	100	100
Normalized space-time yield[c]	1	15

[a] A. Krasovskiy, P. Knochel *Angew. Chem. Int. Ed.* 2006, 45, 2958; D. Göbel, N. Clamor, B. J. Nachtsheim *Org. Biomol. Chem.* 2018, 16, 4071 [b] Propene and 2,3-dimethylbutane as by-products [c] Space-time yield (mmol mL⁻¹ h⁻¹): batch = 0.065; flow = 0.980.

10x Better in Flow

TMPMgCl • LiCl	Batch[a]	Flow
mmol of 2-chloropropane	100	100
2-Chloropropane concentration (M)	1.20	1.20
TMPH concentration (M)	1.05	1.00
Reaction time (hour)	36	4
Concentration of TMPMgCl • LiCl (M)	1.03	0.97
Normalized space-time yield[b]	1	10

[a] A. Krasovskiy, V. Krasovskaya, P. Knochel *Angew. Chem. Int. Ed.* 2006, 45, 2958. [b] Space-time yield (mmol mL⁻¹ h⁻¹): batch = 0.016; flow = 0.160.

Conclusion

In summary, we have developed a versatile continuous flow method for the preparation of carbon, nitrogen and oxygen bases using a Mg – LiCl column. This setup allows the formation of useful bases on-demand with a wide range of basicity and steric hindrance. Easy and fast generation of organomagnesiums might reduce the volume of sensitive solutions wasted in laboratories worldwide. Moreover, freshly prepared reagents guarantee reproducible results.

References

[1] T. Klatt, J. T. Markiewicz, C. Sämann, P. Knochel *J. Org. Chem.* 2014, 79, 4253; D. S. Ziegler, B. Wei, P. Knochel *Chem. Eur. J.* 2019, 25, 2695. [2] A. A. Grachev, A. O. Klochkov, and V. I. Shiryaev *Russ. J. Appl. Chem.* 2012, 85, 629; P. A. Storozhenko, A. A. Grachev, A. O. Klochkov, and V. I. Shiryaev *Russ. J. Appl. Chem.* 2013, 86, 387; M. Goldbach, E. Danieli, J. Perlo, B. Kaptein, V. M. Litvinov, B. Blümich, F. Casanova, A. L. L. Duchateau *Tetrahedron Lett.* 2016, 57, 122. [3] L. Huck, A. de la Hoz, A. Díaz-Ortiz, J. Alcázar *Org. Lett.* 2017, 19, 3747; A. Herath, V. Molteni, S. Pan, J. Loren *Org. Lett.* 2018, 20, 7429. [4] R. L. Y. Bao, R. Zhao and L. Shi *Chem. Commun.* 2015, 51, 6884. [5] B. E. Love, E. G. Jones *J. Org. Chem.* 1999, 64, 3755. [6] S. Blumberg, S. F. Martin *Tetrahedron Lett.* 2015, 56, 3674. [7] A. Krasovskiy, V. Krasovskaya, P. Knochel *Angew. Chem. Int. Ed.* 2006, 45, 2958. [8] D. C. Bradley, Metal Alkoxides in Metal-Organic Compounds; Advances in Chemistry; American Chemical Society: Washington, DC, 1959, 23, 10-36.