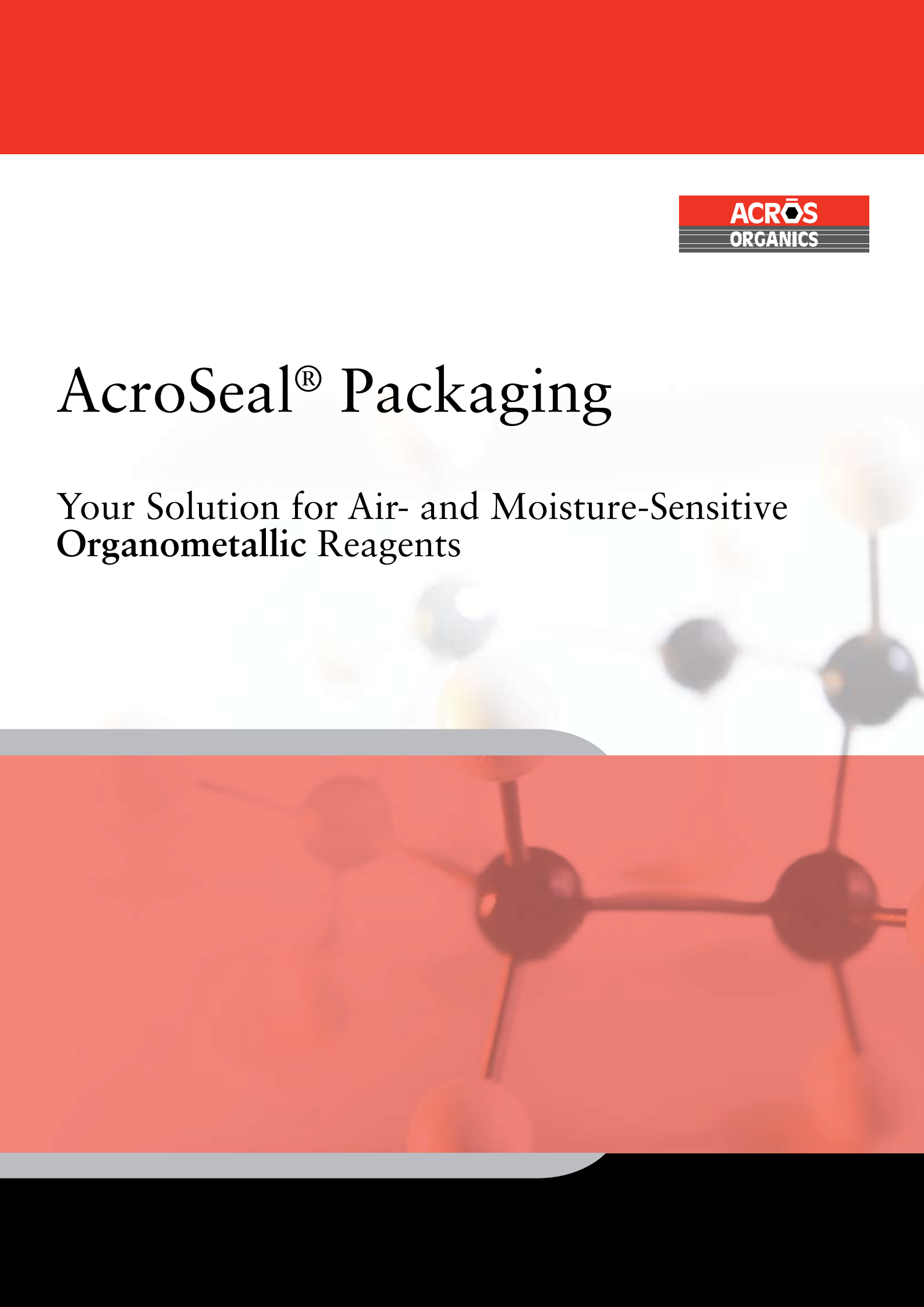
ACROS ORGANICS

AcroSeal® Packaging

Your Solution for Air- and Moisture-Sensitive **Organometallic** Reagents



AcroSeal Packaging
Your Solution for Air- and Moisture-Sensitive Organometallic Reagents

Introduction

Organometallic reagents are widely used in organic synthesis. Typical applications include their use as strong bases, as nucleophiles, in metal exchange reactions and as reducing agents. Examples of such reagents include Grignard reagents, organolithiums, organozincs and lithium amide bases. All of these reagents react readily with moisture, oxygen or both so they must be protected under an inert atmosphere.

Historically, researchers who require organometallic reagents for synthetic purposes have chosen to freshly prepare these reagents, often *in-situ*, and use them immediately. However, safety concerns due to the highly reactive nature of these reagents, as well as a continuous push to reduce time-to-market, have led researchers to purchase commercially available organometallic reagents.

For commercially available organometallic reagents, a key concern for researchers, buyers and stockroom managers alike is how long the reagent can be stored without significant decomposition. Since these reagents are generally consumed over a period of time, the packaging system becomes even more critical.

AcroSeal packaging is specifically designed to maintain the integrity of air- and moisture-sensitive reagents while providing a convenient, easy-to-use and safe means of storing and dispensing research quantities.

Key Features of AcroSeal Packaging

Septum

AcroSeal packaging uses specially designed multi-layer septa. The AcroSeal septum used for organometallic reagents consists of a double sandwich—an inner PTFE layer that is in contact with the reagent and an outer butyl rubber layer.

The thickness of the septum is double that of typical competitor brand packaging, providing improved mechanical performance during needle puncture. The inner PTFE layer is inert to the reagent and ensures that the reagent is uncontaminated with the septum material. The thick outer butylated rubber layer allows for excellent re-sealing around needle punctures.

Repeated punctures to a septum in the same spot over time increase the risk of deformation and the likelihood that the septum will not re-seal. With competing brand packaging, it is very difficult to avoid repeated punctures in the same spot due to the very limited septum surface area. The AcroSeal septum provides more than 15 times this surface area, allowing broader spread for needle punctures, leading to better re-sealing over a longer time period.

Bottle Closure System

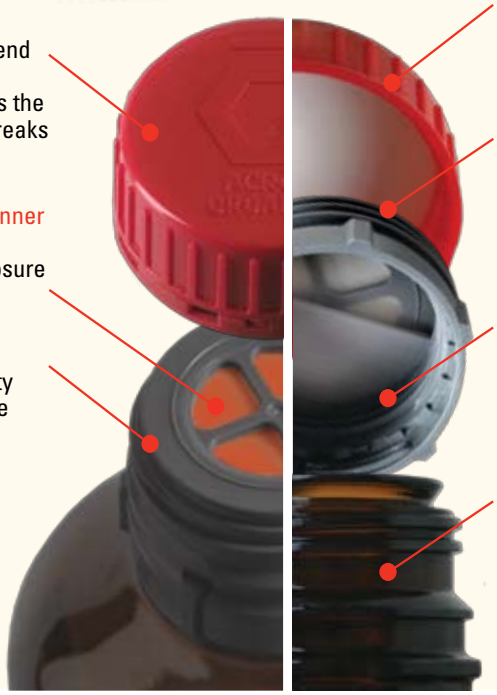
The AcroSeal closure system features a quadrant-style cap design that holds the septum in place, reducing the risk of bulging or deformation. A cushioned liner in the external cap presses against the septum and quadrant cap on closure, thus creating a secondary seal which prevents ingress of moisture and oxygen from the atmosphere. The tamper-evident seal, which breaks with the first opening of the cap, is used as a visible indicator of an unopened bottle.

The AcroSeal screw closure not only allows syringe withdrawal of the reagent through the septum, but provides the added convenience of permitting the top to be unscrewed and larger volumes to be poured from the bottle, which may then be closed by screwing the lid back onto the bottle.

Tamper-evident break ring at the lower end of the protective red cap.
Foolproof guarantee that the customer is the first to open the bottle. The lower ring breaks off with the first opening of the red cap.

Extra thick durable rubber septum with inner PTFE resin coating.
Better chemical compatibility and re-closure of any puncture hole.

Quadrant cap surface.
The quadrant cap promotes the durability of the septum because punctures can be spread over the large septum surface.



Cushioning liner in outer protective cap.
Re-seals perfectly even after the septum has been punctured multiple times.

Rim design at the inner surface of the septum holding quadrant cap will hold and stretch the septum.
Reduces the risk of bulging or deformation of the septum.

Three-plus windings in the septum holding cap for extra security.
Large contact surface prevents infiltration of air and moisture through the screw neck.

Special rim design inside the septum holding cap fits snugly over the glass rim of the bottle neck.

No risk of accidentally unscrewing the septum holding quadrant cap.

Performance

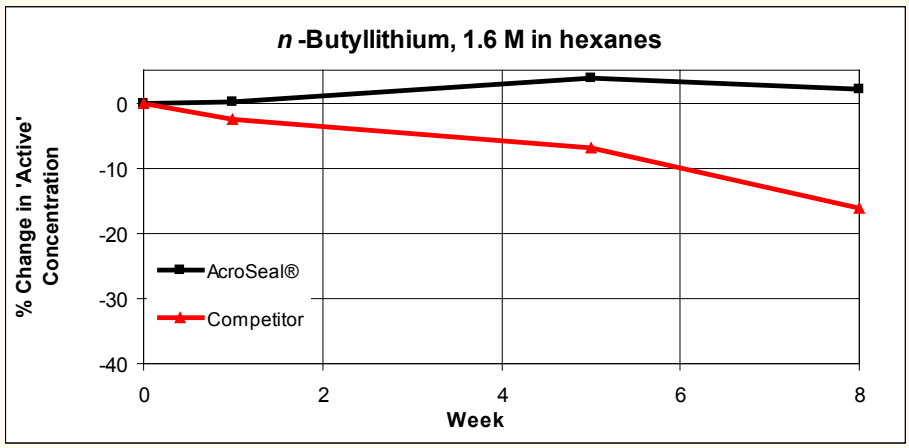
Customers often question how well AcroSeal packaging maintains the integrity of a range of organometallics compared to the packaging utilized by other brands on the market. To address this concern, we examined the percent change in 'active' concentration of a range of organometallics stored in AcroSeal packaging and in competing brand packaging.

Test Results and Discussion

An eight-week study of 'active' concentration of four organometallic reagents was conducted to determine the effectiveness of the AcroSeal packaging system and a competitor's packaging in maintaining the integrity of the organometallic reagent under normal laboratory usage.

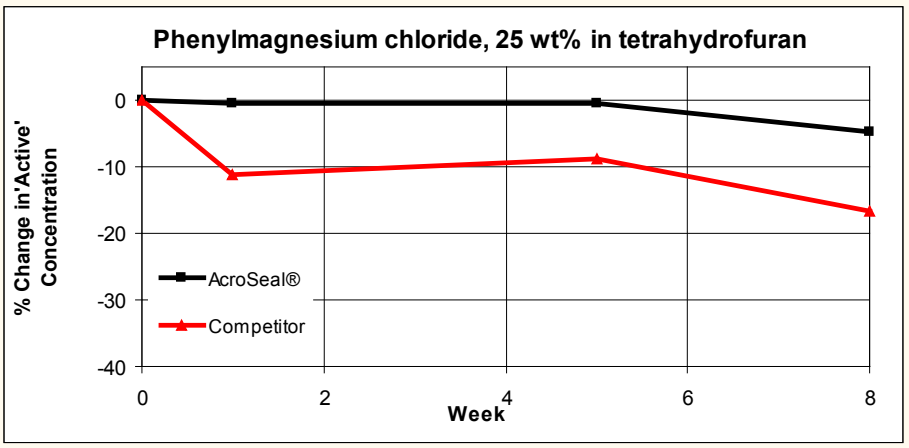
_n_-Butyllithium, 1.6M in hexanes

Over an eight-week period, the change in concentration of _n_-Butyllithium in hexanes in the AcroSeal packaging was negligible within the experimental error. Over the same time frame, _n_-Butyllithium stored in the competitor's packaging showed more than a 15% drop in 'active' concentration.



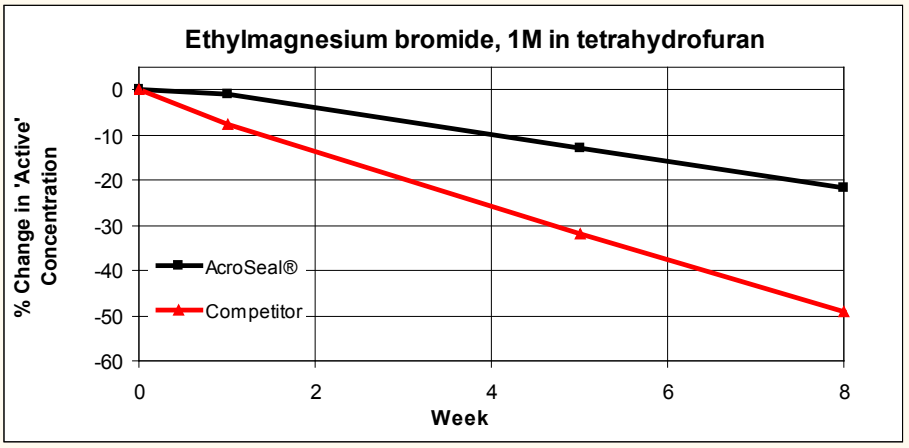
Phenylmagnesium chloride, 2M in tetrahydrofuran

Up until week 5, the 'active' concentration of Phenylmagnesium chloride, 25 wt% (2M) in tetrahydrofuran, stored in AcroSeal packaging remained constant (within experimental error), with a less than 5% drop by week 8. The 'active' concentration in the competitor product dropped rapidly by around 10% after the first week and lost more than 15% activity by week 8.



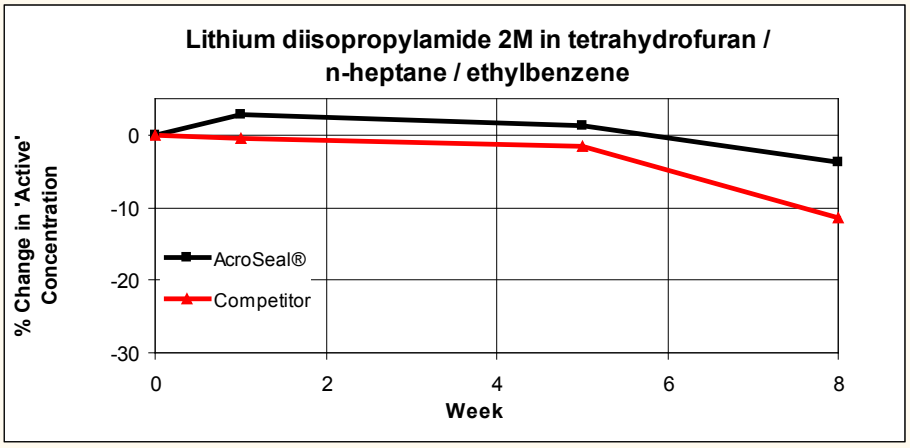
Ethylmagnesium bromide, 1M in tetrahydrofuran

For Ethylmagnesium bromide, 1M in tetrahydrofuran, the rate of loss of active organometallic was found to be twice as fast with the competitor's packaging than with AcroSeal. After eight weeks, the active level decreased by 50% in the competitor's packaging.



LDA, 2M in tetrahydrofuran/*n*-heptane/ ethylbenzene

Lithium diisopropylamide, 2M in tetrahydrofuran/*n*-heptane/ethylbenzene was relatively stable in both AcroSeal and competitor packaging over a five-week period. After eight weeks the 'active' concentration dropped by 4% in the AcroSeal packaging and 11% in the competitor packaging.



Conclusions

This study has shown that AcroSeal packaging is suitable for a wide variety of organometallics dissolved in a range of solvents:

- ***n*-Butyllithium, 1.6M in hexanes**
- **Phenylmagnesium chloride, 25 wt% (2M) in tetrahydrofuran**
- **Ethylmagnesium bromide, 1M in tetrahydrofuran**
- **Lithium diisopropylamide, 2M in tetrahydrofuran/*n*-heptane/ethylbenzene**

In all cases, the AcroSeal packaging maintained the integrity of these organometallic reagents handled under normal laboratory conditions over several weeks better than the competitor packaging.

For a complete list of reagents available in AcroSeal packaging, please visit our website at **www.acros.com.**

Experimental Section

Introduction

Solutions of organometallic reagents in inert solvents inevitably contain some metal oxides, hydroxides, alkoxides (or aroxides) and even carbonates, which result from reaction with oxygen, moisture and atmospheric carbon dioxide. If a septum fails to re-seal properly over time, the concentration of the 'active' organometallic species decreases, while the concentration of the inorganic basic by-products increases. In these studies, 'active' concentration refers to the concentration of the organometallic species.

The 'active' concentration of *n*-butyllithium in hexanes was measured using the Gilman double titration method[1], while the Watson-Eastham method was used for the other reagents[2].

Samples were taken over eight weeks, in duplicate, from 100mL bottles. The initial measurement is designated as week zero. Two bottles of each reagent with identical batch numbers were analyzed and the four results were averaged. Using 21-gauge needles, each bottle received five new punctures per septum, per week of the study. At the end of each test, the caps were firmly secured by hand. The organometallic reagents were stored and analyzed at ambient temperature.

Packaging performance was compared by examining the percent change in 'active' concentration over time. The initial 'active' concentration was subtracted from successive testing values to normalize the concentration over time. Division by the initial value and multiplication by 100 gives the percent change in 'active' concentration.

General Handling

50 mL round-bottom flasks, magnetic stirrer bars and B19 rubber septa were dried overnight in an oven at 110°C. They were removed and the flask, containing a stirrer bar, was sealed with the B19 septum. The flask was evacuated under vacuum and filled three times with nitrogen gas via a manifold.

Disposable syringes and needles used during the procedures were flushed with nitrogen several times immediately prior to use.

During dispensing of the reagent, a nitrogen line from the manifold was attached to each bottle via a syringe needle to replace the volume of reagent drawn up in the syringe.

References

[1]Gilman, H.; Haubein, A. H.; *J. Am. Chem. Soc.,* **1944**, *66*, 1515
[2]Watson, S. C.; Eastham, J. F.; *J. Organometallic Chem.,* **1967**, *9*, 165

Double Gilman Titration Method

Determination of the total base content:

A nitrogen-flushed syringe was filled with approximately 5mL of the *n*-butyllithium in hexane solution and weighed (W1). The reagent was injected into a round-bottom flask containing anhydrous hexanes (20mL) under a nitrogen atmosphere. The empty syringe was then weighed (W2). Water (20mL, HPLC grade) was added and the mixture was stirred for 10 minutes. Phenolphthalein indicator (2 drops) was added and the mixture was titrated against 1.0M hydrochloric acid (HCl) until complete disappearance of the pink color.

Calculation: Percent total base = $\frac{(VxC)}{([W1-W2]/D)}$

Where V = titer of HCl added (mL)

C = concentration of HCl (M)

W1 = weight of syringe containing *n*-butyllithium (grams)

W2 = weight of syringe after *n*-Butyllithium addition (grams)

D = density of the *n*-Butyllithium solution (0.68g/mL 25°C)

Determination of the free base content:

A nitrogen-flushed syringe was filled with approximately 5mL of the *n*-butyllithium in hexane solution, and weighed (W1). The reagent was injected into a round-bottom flask containing anhydrous hexanes (20mL) under a nitrogen atmosphere, followed by the addition of anhydrous diethyl ether (0.2mL). The empty syringe was then weighed (W2). Freshly distilled benzyl chloride (5mL) was added dropwise and the mixture was stirred for 15 minutes to ensure complete reaction with the 'active' organometallic. Water (25mL, HPLC grade) was added and the mixture was stirred for 10 minutes. Phenolphthalein indicator (2 drops) was added and the mixture was titrated against 0.1M HCl until complete disappearance of the pink color.

Calculation: Percent free base = $\frac{(VxC)}{([W1-W2]/D)}$

Calculation of the 'Active' base content:

Percent 'active' base = Total base – Free base

Watson-Eastham Method

A nitrogen-flushed syringe was filled with approximately 5mL of the organometallic reagent solution and weighed (W1). This was injected into a round-bottom flask containing anhydrous toluene (20mL) and approximately 8mg of the appropriate indicator under a nitrogen atmosphere. The empty syringe was then weighed (W2).

1,10-Phenanthroline was used as an indicator for the Grignard solutions. The mixture was titrated against freshly prepared and standardized approximately 0.1M *sec*-butanol solution in anhydrous toluene until disappearance of the pink color.

2,2´-Biquinoline was used as an indicator for the lithium diisopropylamide solution. The mixture was titrated against freshly prepared and standardized approximately 0.1M *sec*-butanol solution in anhydrous toluene until disappearance of the red color.

Calculation of the 'active' base content:

Calculation: % 'Active' base = $\frac{(VxC)}{([W1-W2]/D)}$

Where V = titer of *sec*-butanol added (mL)

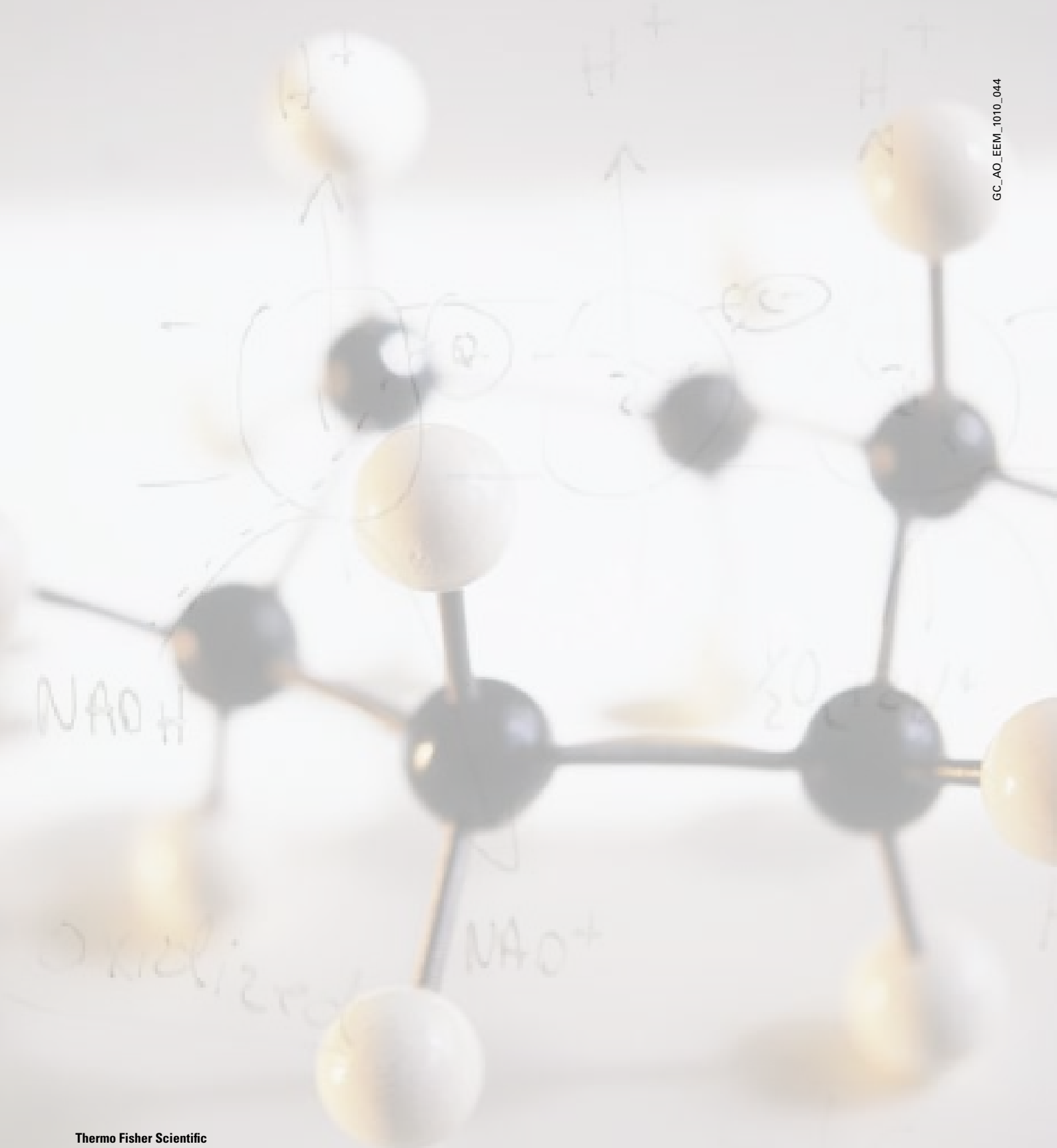
C = concentration of *sec*-butanol (M)

W1 = weight of syringe containing the organometallic reagent (grams)

W2 = weight of syringe after organometallic reagent addition (grams)

D = density of the organometallic solution (g/mL, 25°C)

Densities of the organometallic reagents:
Phenylmagnesium chloride, 25 wt% (2M) in tetrahydrofuran (d=1.042g/mL, 25°C)
Ethylmagnesium bromide, 1M in tetrahydrofuran (d=1.02g/mL, 25°C)
Lithium diisopropylamide, 2M in tetrahydrofuran/*n*-heptane/ethylbenzene (d=0.812 g/mL, 25°C)



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