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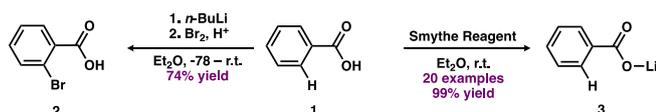
The Smythe Reagent: ~1.6 M LiOH in Hexane

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Abstract: The Smythe reagent is an approximately 1.6 M suspension of LiOH in hexane, and is ubiquitous in synthetic chemistry laboratories worldwide. While commercially available, it is more frequently prepared from *n*-butyllithium, usually by accident. We describe a range of applications for this reagent, such as the *O*-lithiation of carboxylic acids, hydrolysis of ethyl esters and chlorophosphines, racemisation of alpha-stereocenters and poly-Claisen condensations.

On a rainy Friday afternoon in 1963, Schwarz Smythe left a bottle of *n*-butyllithium open on his bench. That night the Smythe reagent was born. When Smythe crawled back into the lab on Monday, he found that his lovely, clear *n*-BuLi was gone. In its place was a milky yellow soup. Concerned, he brought the cloudy concoction to the attention of his supervisor; Pliny the Elder, who reassured him: "Nah mate, it's still good, just use an excess". Smythe shrugged and proceeded with the day's experiments. On working up his ortho-lithiation of benzoic acid (**1**), he discovered that rather than making **2** via a *C*-lithiated intermediate, he had in fact prepared lithium benzoate (**3**) (scheme 1).

Smythe, 1963



Scheme 1. The divergent reactivity of *n*-BuLi and the Smythe Reagent.

Smythe and Pliny immediately recognised the significance of their discovery. They prepared a number of lithium benzoates as a demonstration of the divergent reactivity offered by their accidental creation.¹

The Smythe reagent typically appears as an off-white suspension, reminiscent of a snow-globe (figure 1). Its composition is variable, but most preparations constitute a suspension of LiOH in hexane, with traces of Li₂CO₃, lithium pentanoate, butene and *n*-butylhydroperoxide stabilised by dissolved Parafilm.² Its concentration is dependant on how hard one shakes it, but as an excess is always used, this is rarely a setback. Chemical vendors such as Smegma-Aldrich supply the Smythe reagent,³ but given its facile preparation it is more commonly synthesised in-house (see experimental section).



Figure 1. Flasks of *n*-butyllithium (left) and Smythe Reagent (right).

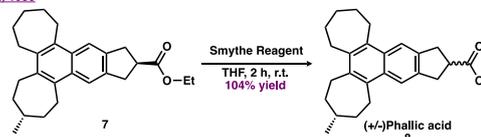
The contrasting reactivity of the Smythe Reagent was further demonstrated by Cluckwald in 1975 (scheme 2).⁴ During their synthesis of the now-ubiquitous Cluckwald-Birchtwig ligands, the eponymous chemists observed that while *n*-BuLi lithiated **4** to produce the desired product (**5**), the Smythe Reagent reacted directly with chlorodicyclohexylphosphine to form dicyclohexylphosphine oxide (**6**).

The Smythe Reagent was employed by R. B. Woodward in 1986, to cleave an ethyl ester (**7**) in the final step of his seminal synthesis of *rac*-phallic acid (**8**).⁵ This supernatural product, a potent vasodilator, was prepared in four steps from charcoal, with the elegance and brevity typical of Woodward's work.

Cluckwald, 1975



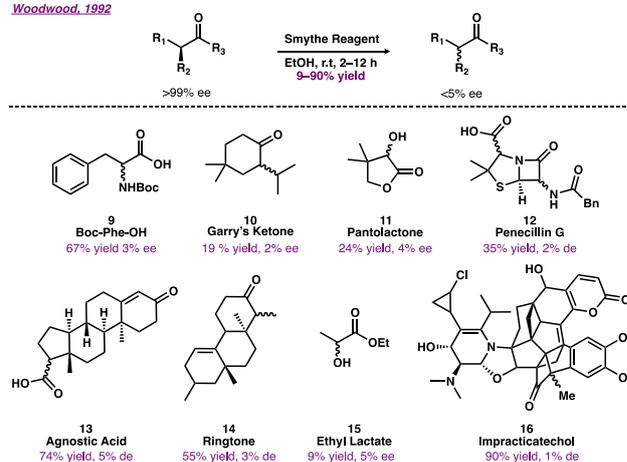
Woodward, 1986



Scheme 2. Hydrolysis of a chlorophosphine and ethyl phallate.

In the course of this work, Woodward noted that while a single diastereomer of ethyl phallate was employed, a racemic mixture of phallic acids were obtained. It transpired that Woodward had inadvertently discovered another facet of the reagent's reactivity: a capacity to racemise stereocenters.

Woodward, 1992

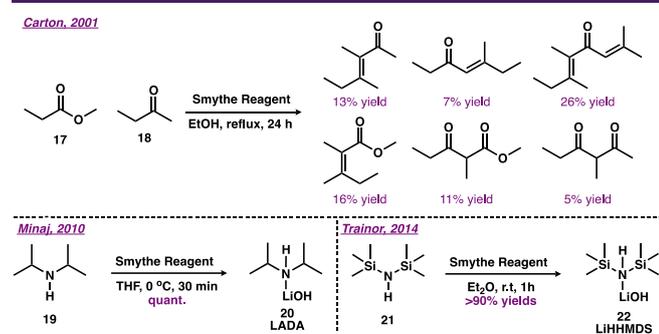


Scheme 3 Racemisation of stereocenters with the Smythe reagent.



Woodwood directed his student, Phil Desolate, to investigate the scope of this reaction.⁶ Beginning with simple substrates containing acidic α -hydrogens, Desolate demonstrated that N-Boc-phenylalanine (**9**) could be racemised without loss of the carbamate protecting group. Ketones (**10**) and lactams (**11**) also underwent racemisation in despondent yield. Desolate was also able to selectively epimerise more complex substrates such as penicillin G (**12**), agnostic acid (**13**) and ringtone (**14**). Making ethyl lactate (**15**) proved to be challenging with this methodology, while the supernatural product impracticatatechol⁷ (**16**) was racemised in exultant yield. This result is even more striking when one considers that **16** does not feature acidic α -hydrogens, or a stereocenter capable of epimerisation.

Derek Carton observed the low yields obtained by Desolate in the racemisation of substrates such as **10**, **11** and **15**, and postulated that this could be a consequence of aldol/Claisen chemistry initiated by LiOH.⁸ Carton demonstrated the validity of this theory by exposing a mixture of methyl propionate (**17**) and methyl-ethyl ketone (**18**) to the Smythe reagent. From the fuming brown tar that resulted, Carton isolated a number of unsaturated ketones and β -keto-esters (scheme 4).



Scheme 4. Death by aldol, and LiOH-amine complexes.

The Smythe reagent is frequently used to prepare other bases. One such example is LiOH And DiisopropylAmine (LADA, **20**), first prepared by Minaj's group at MIT.⁹ This reagent consists of a THF solution of LiOH complexed with diisopropylamine (**19**). In contrast to LDA (a strong but bulky base), LADA is bulky and weak, and capable of deprotonating carboxylic acids without engaging in Claisen-type chemistry. Lithium HexamethylDiSilazine (LiHHMDS, **22**) was prepared by Trainor and co-workers in an analogous procedure in 2014.¹⁰ LiHHMDS is such a weak base that only mineral acids are capable of protonating it.

Experimental

A standard preparation of LiOH/Hexane¹¹

An Unsureal[®] bottle of *n*-butyllithium (1.6 M, 800 mL) was punctured approximately 50 times with a blunt needle. Parafilm (2.3 g, 0.1 mol%) was pushed through the holes, and the bottle was shaken until the parafilm had dissolved. The reaction mixture was loosely capped and placed in a cupboard for three months. The reaction can be visually monitored, and has reached completion when the mixture attains the colour and texture of a piña colada.

Alternative preparations

Alternative methods of preparing the smith reagent include storing a solution of *n*-BuLi in an ungreased ground-glass flask for a week, or in a beaker in a fume hood overnight. For a facile

preparation, one can give a fresh Schlenk of *n*-BuLi to a masters student, and let nature take its course.

Conclusions

Despite its decreased reactivity in contrast to *n*-BuLi, it does have its redeeming features. For example, it is far safer to work with, as it exhibits no air-sensitivity. The Smythe reagent will be a ubiquitous chemical tool for as long as organic chemists use organometallic reagents.

About the Authors

Demeritus Professor Günther Schlonk heads the division of Pyrofrolics at the University of West Failure, as well as holding the positions of Imperial Editor in Perpetuity and Satrap of Satire at The Journal of Immaterial Science. He likes the colour purple, walks on the beach and the music of Urethra Franklin.

Conflicts of Interest

G. S. believes that proper Schlenk techniques make the Smythe reagent entirely redundant.

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Notes and references

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