**SYNLETT Spotlight 393**

**$n$-Butyllithium**

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Dedicated to my research supervisor Dr. Pinaki S. Bhadury

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**Introduction**

$n$-Butyllithium ($n$-BuLi) is one of the most prominent organolithium reagents in the whole of synthetic chemistry,\(^1\)\(^-\)\(^3\) and available as solutions in alkanes such as pentane, hexane, or heptane, which is usually encountered as a pale yellow solution. It is unstable towards air or moisture but stable in an atmosphere of nitrogen. It has been widely used in organic reactions, such as regioselective lithiation reaction,\(^4\) reversible metathesis reaction,\(^5\) Claisen rearrangement,\(^6\) phospho-Fries rearrangement,\(^7\) coupling reaction,\(^8\) asymmetric deprotonation–electrophilic trapping reaction,\(^9\) enantioselective hydroxyalkylation,\(^10\) etc. In general, $n$-butyllithium is commercially available and can also be prepared readily by the reaction of 1-bromobutane or 1-chlorobutane with Li metal (Scheme 1).\(^11\) An overview of the usage of $n$-BuLi in organic synthesis is presented below.

![Scheme 1](image)

(A) Fort and co-workers described an efficient method for the synthesis of polysubstituted fur[2,3-c]pyridines via successive regioselective lithiations, using $n$-BuLi or [$n$-BuLi/LiDMAE] as base. For each step the products were obtained in moderate to excellent yields.\(^4\)

(B) Bailey et al. reported mild and highly efficient experimental conditions for the reversible metathesis reaction known as the lithium–halogen exchange. The reaction products of 1-bromo-4-tert-butylbenzene with $n$-BuLi at 0 °C are obtained quantitative in heptane containing a small quantity of THF. Particularly, nettlesome side reactions, including coupling of aryllithium with the co-generated alkyl halide and formation of a benzyne intermediate via ortho-metallation of the aryl halide, are effectively avoided.\(^5\)

(C) Upon treatment with $n$-BuLi, a variety of allyl 1,1-dichlorovinyl ethers undergo rearrangement to furnish high yields of $\gamma,\delta$-unsaturated esters after alcohol addition. A potential advantage of this method over other variants of the Claisen rearrangement is the ability to add a variety of alcohol nucleophiles to the proposed ketene intermediate, allowing the one-pot preparation of diverse esters of $\gamma,\delta$-unsaturated carboxylic acids with high stereoselectivity.\(^6\)
(D) $n$-BuLi together with $i$-Pr$_2$NH has been used in the preparation of bifunctional BINOL ligands bearing phosphine oxides [P(=O)R$_2$], phosphonates [P(=O)(OR)$_2$], or phosphoramides [P(=O)(NR)$_2$] at the 3,3'-positions via a phospho-Fries rearrangement as key step. This method has an advantage with regard to yield and purification in comparison with a coupling method that uses halide compounds, expensive diphenylphosphine oxide [Ph$_2$P(=O)H], and palladium or nickel catalysts.7

(E) Tarselli and Micalizio described a successful procedure for the coupling of aliphatic imines with allylic and allenic alkoxides enabled by a unique reactivity profile of Ti(IV) isopropoxide/$n$-BuLi compared to well-known Ti(IV) isopropoxide/RMgX systems. This coupling proceeds with moderate to excellent yields.8

(F) An enantioselective hydroxyalkylation of $o$-tolualdehyde and 3-aminotetrahydrofurans (or 3-aminopyrrolidines, 3-aminotetrahydrothiophens) in the presence of $n$-BuLi and lithium amides gives the target product $1-o$-tolylpentan-1-ol in good yield and moderate ee.10

(G) The highly pyramidalized alkene pentacyclo[4.3.0.0$^{2,4}$,0$^{3,8}$,0$^{5,7}$]non-4-ene was successfully synthesized with $n$-BuLi via dehalogenation of vicinal dihalides. The method has proven to be reliable for the synthesis of a variety of strained alkenes.12

(H) Luliński et al. found that lithiated benzonitriles can be generated in high yields from reactions of bromobenzonitriles with $n$-BuLi in THF under standard cryogenic conditions (ca. –70 °C, even up to –60 °C). The reverse addition mode is employed to reduce significantly side reactions.13

References