Chapter 1 : Full text of "Organolithiums in enantioselective synthesis"

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It was originally proposed that lower aggregates such as monomers are more reactive in alkyllithiums. The mechanism of how these additives increase reactivity is still being researched. As a result, the carbon attracts most of the electron density in the bond and resembles a carbanion. Thus, organolithium reagents are strongly basic and nucleophilic. Some of the most common applications of organolithium reagents in synthesis include their use as nucleophiles, strong bases for deprotonation, initiator for polymerization, and starting material for the preparation of other organometallic compounds. Carbolithiation reactions[edit] As nucleophiles, organolithium reagents undergo carbolithiation reactions, whereby the carbon-lithium bond adds across a carbon-carbon double or triple bond, forming new organolithium species. Carbolithiation is key in anionic polymerization processes, and n-butyllithium is used as a catalyst to initiate the polymerization of styrene , butadiene, or isoprene or mixtures thereof. First, it is possible for the product cyclic organolithium species to react with electrophiles, whereas it is often difficult to trap a radical intermediate of the corresponding structure. Secondly, anionic cyclizations are often more regio- and stereospecific than radical cyclization, particularly in the case of 5-hexenyllithiums. Intramolecular carbolithiation allows addition of the alkyl-, vinyllithium to triple bonds and mono-alkyl substituted double bonds. Aryllithiums can also undergo addition if a 5-membered ring is formed. The limitations of intramolecular carbolithiation include difficulty of forming 3 or 4-membered rings, as the intermediate cyclic organolithium species often tend to undergo ring-openings. The lithium species derived from the lithium-halogen exchange cyclized to form the vinyllithium through 5-exo-trig ring closure. The vinyllithium species further reacts with electrophiles and produce functionalized cyclopentylidene compounds. They can react with aldehydes and ketones to produce alcohols. The addition proceeds mainly via polar addition, in which the nucleophilic organolithium species attacks from the equatorial direction, and produces the axial alcohol. This reaction provides ketones when the organolithium reagents is used in excess, due to chelation of the lithium ion between the N-methoxy oxygen and the carbonyl oxygen, which forms a tetrahedral intermediate that collapses upon acidic work up. First, since the 1,4 adduct is the likely to be the more thermodynamically favorable species, conjugate addition can be achieved through equilibration isomerization of the two product , especially when the lithium nucleophile is weak and 1,2 addition is reversible. Secondly, adding donor ligands to the reaction forms heteroatom-stabilized lithium species which favors 1,4 conjugate addition. In one example, addition of low-level of HMPA to the solvent favors the 1,4 addition. In the absence of donor ligand, lithium cation is closely coordinated to the oxygen atom, however, when the lithium cation is solvated by HMPA, the coordination between carbonyl oxygen and lithium ion is weakened. This method generally cannot be used to affect the regioselectivity of alkyl- and aryllithium reagents. This reactivity is widely applied in the industrial syntheses of pharmaceutical compounds. Lithium acetylide is added to a prochiral ketone to yield a chiral alcohol product. The structure of the active reaction intermediate was determined by NMR spectroscopy studies in the solution state and X-ray crystallography of the solid state to be a cubic 2: Most organolithium reagents used in a alkylations are more stabilized, less basic, and less aggregated, such as heteroatom stabilized, aryl- or allyllithium reagents. As base[edit] Organolithium reagents provide a wide range of basicity. Some commonly used lithium bases are alkyllithium species such as n-butyllithium and lithium dialkylamides LiNR2. Reagents with bulky R groups such as lithium diisopropylamide LDA and lithium bis trimethylsilyl amide LiHMDS are often sterically hindered for nucleophilic addition, and are thus more selective toward deprotonation. Lithium dialkylamides LiNR2 are widely used in enolate formation and aldol reaction. Metalation[edit] Metalation with organolithium reagents, also known as lithiation or lithium-hydrogen exchange, is achieved when an organolithium reagent, most commonly an alkyllithium, abstracts a proton and forms a new organolithium species.

Chapter 2 : Inter- and intramolecular enantioselective carbolithiation reactions

Organolithium chemistry occupies a central position in the selective construction of C-C bonds in both simple and complex molecules. Paralleling the surge of interest in methods for asymmetric synthesis, the use of organolithiums in enantioselective synthesis has witnessed spectacular advances in a little over a decade.

Additions to Epoxides and Oxetanes. To achieve high enantioselectivities, the organolithium reagent should be tightly coordinated by the chiral ligand during the enantioselective step of the CC bond formation. Competing background additions without enantiopure additives, yielding racemic products, should be avoided. In some cases good enantioselectivities are observed even with sub-stoichiometric or catalytic amounts of chiral additives. Nowadays, organolithium chemistry shows very dynamic growth, and organolithiums are well-established precious reagents for organic syntheses [14â€”16]. A catalytic variant, the Mukaiyma aldol reaction, i. In , Nozaki et al. Chiral ligands, the enantioselectivities refer to Eq. In , Seebach et al. After further systematic studies [26â€”28], Seebach et al. In Mukaiyama et al. The reaction was performed with a ratio of 24 Bernd Goldfuss protic chiral additive 4: For a ratio of 3. Alberts and Wynberg studied the addition of ethyllithium to PhCHO, mediated by the lithiated product R phenylpropanol-d1 [40]. After addition of LiCl or LiClO4 to the reaction mixtures, a decrease of enantioselectivity was observed. This was pointing to the formation of achiral mixed anionic halide aggregates, which give rise to racemic products. Structural variations of the ligands were performed to elucidate the basis for the observed enantioselectivities [45]. More equivalents of 11 e. Diethyl ether was found to give for all ligands superior enantioselectivities than THF. With less equivalents of n-BuLi 1: From these and from other experiments in organolithium chemistry it can be concluded that higher enantioselectivities in alkyllithium additions to alde- Scheme 2. Chiral complexes, enantioselectivities refer to Eq. Dimeric n-BuLi was found to be only 10 times more reactive than the tetrameric species. The more supporting coordination in the transition state rather than in the pre-complex was found to be the origin of kinetically favored directed ortho-metallations of benzene derivatives with organolithiums [51â€”54]. Ethereal solvents, low temperatures and protic ligands, which are prone to lithiation in situ and then form mixed aggregates with the organolithium reagent, are apparently the best choice for highly enantioselective aldehyde alkylations. Organozinc or organotitanium catalysts [62â€”67] were found to be more suitable to achieve high enantioselectivities in aldehyde alkylations, especially with catalytic amounts of chiral additives. Due to the central role of mixed chiral organolithiums aggregates in alkylation reactions [e. Hilmersson and Davidsson studied by means of intensive NMR investigations a mixed 1: This demonstrates the crucial role of the N-isopropyl substituent in With lithiated 16, enantioselectivities of up to Using the modular nature of these anisyl fencholates, the compositions of the mixed aggregates as well as enantioselectivities in benzaldehyde butylations can be controlled. While H as ortho-substituent X yields a 3: Similar mixed aggregates with a 2: Variations of the alkoxide: Detailed NMR spectroscopic investigations showed that butylide additions to the aldehyde are much faster than structural exchanges of the alkylating mixed aggregates and that a 2: The groups of Knochel and Carreira developed catalytic alkynylation procedures based on cesium and zinc species [83, 84]. The formation of enolates via deprotonation of a-hydrogens in the sub- 28 Bernd Goldfuss strate or reduction via b-hydrogen atoms in the organometallic are sometimes critical side reactions. The propensity for these side reactions is less pronounced for organolithiums than for Grignard reagents [86, 87]. The most prominent example of enantioselective organolithium additions to ketones is the development of the anti-AIDS drug efavirenz 23 Scheme 3 , a non-nucleoside reverse transcriptase inhibitor for a variety of HIV-1 mutant strains [88, 89]. The key step in the synthesis of 23 is the enantioselective generation of its quaternary carbon center. This can be accomplished by adding to the protected ketoaniline precursor 24 the lithium acetylide 25 [Eq. These detailed investigations provide intriguing information on the nature of reactive intermediates and the origins of enantioselectivity. Higher enantioselectivities were achieved with lithiated ephedrine derivatives with different N-substituents e. These high enantioselectivities were not observed with simple alkyllithiums and they are also sensitive to acetylide b-carbon substituents [88]. It was also observed that an excess of acetylide 25 relative to alkoxide 26 erodes

the enantioselectivity. The high temperature necessary for this conversion points to an unusually slow mixed aggregate exchange [94]. Two equivalents of acetylide 25 and alkoxide 26 are required for full conversion of one equivalent of ketoaniline Addition of ketone 24 to an equimolar alkynylation mixture of 25 and 26 1: Further ketone addition at these temperatures gives rise to IR detectable carbonyl as well as NH functions of ketone 24, but no C-H signal of a protonated acetylene from 25 could be detected. The completion of the reaction for this 1: Attempts to perform an X-ray analysis of 28 failed, instead a hexameric 4: The lower reactivity of 29 can be explained by the remote positions of acetylide from the free i. In contrast, the more reactive 2: Hence, both intriguing phenomena, the aging effect and the requirement for the 2: The computations also support a stereochemical model which correctly reproduces the sense of selectivity for the acetylide transfer within the ketone-coordinated, mixed 2: The product alcoholate of 27 was suggested to exhibit chelating abilities similar to the amino alcoholate Then 26 and lithiated 27 could block via chelation the lithiums close to the acetylide moiety and cause the observed low reactivity, which is also apparent in There is a close structural analogy between the mixed 2: As suggested to explain the lower reactivity of 29 relative to 28, the lithium ions neighbouring to the carbanionic moiety in 19 and in 29 are blocked by the chelating ligand, whereas the trans-situated lithium ion has a free coordination site in 19, or is coordinated by labile THF in In contrast, the lithiums neighbored to the carbanionic moiety are free in 20, which corresponds to the proposed structure of The development of the efavirenz synthesis illustrates very nicely the fruitful interplay between synthetic demand on the one side and helpful elucidations by NMR and X-ray structural analyses as well as computational chemistry on the other. As with aldehydes, catalytic additions to ketones are more promising with less polar organometallics and some enantioselective catalytic organozinc additions to ketones have been developed [96, 97]. Analogous Lewis base-catalyzed reactions are rare []. While organolithiums are rarely employed, applications of hetero-nucleophiles are well known in enantioselective desymmetrizations of meso-epoxides []. The group of Tomioka studied chiral ether ligands as mediators in phenyllithium additions to cyclohexene oxide [Eq. For enantioselectivities refer to Eq. They observed that addition of 1. The t-Bu group and the imino hydrogen atom in 33 were found to be essential for high enantioselectivities. The group of Harada used chiral arylboron Lewis acids for the enantioselective ring cleavage of 1,3-dioxolanes by silyl enol ethers as carbon nucleophiles [,]. Higher selectivities than with alkyllithiums were achieved with aryllithiums: With smaller amounts of sparteine, i. Sparteine 1 was found to be less satisfactory for this purpose []. Complexes between MeLi and Chiral 3-aminopyrrolidine lithium amides bearing a second asymmetric center on their lateral amino group have been studied using multinuclear low-temperature NMR spectroscopy, and a relationship between the topology of these complexes and the sense of induction in the enantioselective alkylation of aaromatic aldehydes by alkyllithiums has been proposed []. In this review, the optical purities are reported uncorrected as presented in the original publications 2. Wiley, New York 3. Huryn DM In: Pergamon Press, Oxford, p 49 4. Wiley, New York 5. Methoden org chem Houben Weyl. Snieckus V ed , Advances in carbanion chemistry, vol 1. Jai Press, Greenwich, CT 8. Goldfuss B Nachr Chem Tomioka K Synthesis Noyori R Asymmetric catalysis in organic synthesis. Wiley, New York For a review on the Mukaiyama aldol reaction, see: Carreira EM In: Sawamura M, Ito Y In: Ojima I ed , Catalytic asymmetric synthesis. Brandsma L, Verkruijsse H Preparative polar organometallic chemistry. Scheffold R ed Modern synthetic methods, vol 4. Development of new methodology for asymmetric reactions of organolithium reagents constitutes a remarkable area of fundamental progresses in recent synthetic organic chemistry. We do not describe additions which use chiral auxiliary groups in carbonyl compounds. Addition to a,b-Unsaturated Imines. Addition to Oxime Ethers. Addition to an Imine-Chiral Ligand Complex. Reaction in the Presence of an External Chiral Ligand.

Chapter 3 : Book Review: Organolithiums: Selectivity for Synthesis - Jonathan Clayden

This book is a valuable addition to the Topics in Organo-metallicChemistry series that has successfully culled a vasttopic into engaging and focused chapters through skillfuleditorship.

Pergamon Description This book, Volume 23 in the Tetrahedron Organic Chemistry series, presents organolithium chemistry from the perspective of a synthetic organic chemist, drawing from the synthetic literature to present a unified overview of how organolithiums can be used to make molecules. The development of methods for the regioselective synthesis of organolithiums has replaced their image of indiscriminate high reactivity with one of controllable and subtle selectivity. Organolithium chemistry has a central role in the selective construction of C-C bonds in both simple and complex molecules, and for example has arguably overtaken aromatic electrophilic substitution as the most powerful method for regioselective functionalisation of aromatic rings. The twin themes of reactivity and selectivity run through the book, which reviews the ways by which organolithiums may be formed and the ways in which they react. Topics include recent advances in directed metallation, reductive lithiation and organolithium cyclisation reactions, along with a discussion of organolithium stereochemistry and the role played by ligands such as - -sparteine. Editorial Review A great many reactions are possible with organolithium compounds, and an understanding of their reactivity and selectivity is the key to the utility of these reactions. The most important additives, which lead to deaggregation and exert a direct influence on the reactivity of the organyl, are mentioned in this introductory chapter. These explanations are easily understood by and are oriented toward the practicing chemist, but students with an interest in organometallics will also find "Organolithiums: Selectivity for Synthesis" quite enjoyable. The subsequent chapters on specific reactions are quite substantial and hold some surprises. By providing an abundance of quite different reaction examples that demonstrate how selectivity plays a role, which factors it depends upon, and how it can be influenced, this monograph truly lives up to its title. The literature citations are further supplemented with mechanistic commentaries. The comprehensive scope of the literature citations also justifies the use of this book as a reference work. Selectivity for Synthesis" is recommended for every chemist who wishes to become thoroughly acquainted with the potential of organolithium chemistry. Jonathan Clayden has succeeded in conveying this knowledge with succinct commentaries supported by appropriate examples. Contents Scope and overview. Regioselective Synthesis of Organolithiums by Deprotonation. Cooperation, competition and regioselectivity. Reductive lithiation of alkyl and aryl halides. Reductive lithiation of C-O bonds. Reductive lithiation of C-N bonds. Reductive lithiation of C-S bonds. Stereoselective and Stereospecific Synthesis of Organolithiums. Configurational stability of organolithiums. Stereospecific synthesis of organolithiums by X-Li exchange. Stereospecific and Stereoselective Substitution Reactions of Organolithiums. Stereospecific reactions of organolithium compounds. Stereoselective substitution in the presence of chiral ligands. Regio- and Stereoselective Addition Reactions of Organolithiums. Intramolecular addition and substitution reactions: Corydalic acid methyl ester: California Red Scale Pheromone: S Methyldodecyl acetate, a Drosophila pheromone:

Chapter 4 : Organolithiums in Enantioselective Synthesis : David M. Hodgson :

Preface Organolithiums are versatile, widely used reagents and intermediates in organic synthesis. As part of the accelerating interest in developing methods for asymmetric synthesis, the use of organolithiums in enantioselective synthesis has witnessed spectacular advances in the last dozen years.

Chapter 5 : www.nxgvision.com | Organolithiums in Enantioselective Synthesis | | Boeken

Organolithiums in Enantioselective Synthesis Organolithiums in Enantioselective Synthesis Majewski, Marek State of the Art in the Area of Stereoselectivity Control using Organolithium Reagents In the opening sentence of the preface to this book, David Hodgson says: Ã¢ Organolithiums are versatile, widely used reagents and intermediates in organic

synthesis.Ã¢ While.

Chapter 6 : Organolithium reagent - Wikipedia

Read "Organolithiums in Enantioselective Synthesis. (Series: Topics in Organometallic Chemistry, Vol. 5.). Edited by David M. Hodgson., Angewandte Chemie International Edition" on DeepDyve, the largest online rental service for scholarly research with thousands of academic publications available at your fingertips.

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