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Chapter 1 : [Full text] Recent advances in green fluorine chemistry | ROC

The Journal of Fluorine Chemistry contains reviews, original papers and short communications. The journal covers all aspects of pure and applied research on the chemistry as well as on the applications of fluorine, and of compounds or materials where fluorine exercises significant effects.

Editor who approved publication: Fluorinated compounds are intriguing for the development of pharmaceuticals, agrochemicals, and materials, and thus, much effort has been exerted to develop more general and efficient approaches for introducing fluorine atom s or fluoroalkyl group s into organic molecules. Although many traditional methods usually cannot satisfy the simplicity and cost efficiency for industrial production and laboratorial synthesis, significant progress in green fluorine chemistry has been made in recent years, allowing efficient incorporation of fluorine into complex organic molecules. The main purpose of this review is to describe recent advances in organofluorine chemistry, with an emphasis on generality, selectivity, and environmental friendliness of related methods. Balzâ€"Schiemann reaction and the halex reaction are used for aromatic fluorination. Balzâ€"Schiemann reaction, which was first reported in the late s, 5 represents one of the most general methods for the introduction of a single fluorine into an aromatic ring Equation 1. Despite most of the commercially available aryl fluorides are synthesized by this approach, the explosive nature of aryl diazonium salts and the requirement of high reaction temperatures retard its application in laboratory. The halex reaction Equation 2 , 6 which typically proceeds via an SNAr pathway, is usually carried out at an elevated temperature and limited to electron-deficient aromatic substrates. Swarts reaction and Simons electrochemical fluorination are applicable for aliphatic fluorination. Swarts reaction was first reported by Belgium chemist Swarts in However, both SbF3 and HF are hazardous reagents and during this transformation, a large amount of HCl is generated as by-product. Simons electrofluorination, an application of electrosynthesis in organofluorine chemistry, is another foundational method for the preparation of organofluorine compounds Equation 4. The Simons process, which can be regarded as an improvement in fluorination with dangerous fluorine gas, was developed by Simons in the s but published in However, compared with fluorination with fluorine gas, this cost-effective process may result in low yields. From this perspective, the generation and use of toxic materials should be avoided. In the last 5 years, much effort has been directed toward finding new synthetic approaches to fluorine-containing molecules. These new methods use unactivated substrates and safe, environmentally benign reagents and can readily access desired molecules that are otherwise difficult to synthesize with traditional approaches. This review aims to describe recent advances in the efficient fluorination and fluoroalkylation methods, with an emphasis on the green reactions possessing high generality, selectivity, and environmental friendliness. Advances in fluorination Câ€"F bond formation for the synthesis of aryl fluorides In , Hull et al reported the first palladium-catalyzed fluorination of Câ€"H bonds Figure 1. The presence of PdIVâ€"F complex was confirmed in the subsequent mechanistic studies. It was believed that this ligand not only promotes reductive elimination of Arâ€"F because of its large size but also prevents the formation of dimeric complexes [LPdAr F]2. It is worth noting that regioisomeric products were formed in a few cases, which indicates that aryne intermediates may be involved in a competing pathway. Temp, temperature; h, hours. The 18F-labeled molecules could be synthesized by either electrophilic or nucleophilic fluorination reactions. However, electrophilic fluorination reagents, such as 18F2 and [18F]-N-F reagents, are produced in lower specific activity than [18F]-fluoride. In , Lee et al reported a new late-stage electrophilic fluorination reagent for PET imaging Figure 3. It should be noted that during this transformation, a net [18F]-fluoride umpolung is realized. Additionally, this fluorination reagent is stable at room temperature and can be manipulated briefly in air. Thus, it can be prepared on a large scale, stored, and used when needed. Figure 3 Palladium-mediated late-stage fluorination for PET imaging. Although the method mentioned above is the first oxidative fluorination using fluoride as the fluorine source, this protocol has some drawbacks for 18F-labeled synthesis: Moreover, the fluoride must be dry, which makes the reaction procedure not user friendly. To overcome these inherent limitations of the palladium chemistry, Lee et al developed a nickel-mediated oxidative fluorination reaction using the similar [18F]-fluoride umpolung

protocol. This reaction proceeds in less than 1 minute and is not only successful for the synthesis of both electron-rich and electron-poor, highly functionalized aryl fluorides but also applicable for the synthesis of alkenyl fluorides. Furthermore, the nickel complexes are moisture- and air-stable solids and can be stored under air. Figure 4 Nickel-mediated oxidative fluorination for PET imaging. In , Mazzotti et al developed palladiumIII-catalyzed fluorination of aryl boronic acids Figure 5. First, the PdII complex is oxidized by Selectfluor through an SET pathway to give PdIII intermediate and Selectfluor radical cation, which undergoes fluorine atom transfer with aryl trifluoroborate to form the Câ€”F bond and generate a delocalized aryl radical. The Pd-catalyzed fluorination reaction proceeds under mild conditions and is tolerant with moisture. However, this method is ineffective for fluorination of heterocycles. Furthermore, substrates bearing electron-withdrawing groups are likely to give constitutional isomers which are difficult to separate from the desired products. Figure 5 Palladium III -catalyzed fluorination of aryl boronic acids. Câ€”F bond reductive elimination from high-valence metal center is not restricted to palladium and nickel. In , Furuya et al described the silver-catalyzed electrophilic fluorination of aryl stannanes Figure 6 , left. The proposed mechanism is distinct from conventional cross-coupling reactions and features a multinuclear high-valent aryl silver fluoride complex. It was suggested that, compared with mononuclear complexes, the AgIIâ€”AgII redox interactions may reduce the energy barrier of Câ€”F reductive elimination. Figure 6 Silver-mediated fluorination of aryl stannanes and aryl boronic acids. Considering that organotin compounds are expensive and toxic, Furuya and Ritter developed a new protocol, 23 namely using readily available, nontoxic aryl boronic acids instead of aryl stannanes as aryl sources Figure 6 , right. However, transmetallation from boron to silver is too fast to develop a catalytic cycle; thus, in this case, stoichiometric silver triflate is needed to prepare aryl silver in situ. Copper has also been introduced in fluorination reactions. In , a CuII-promoted fluorination of arene was reported Figure 7 , 24 in which CuF2 served as an electrophilic fluorination reagent and is converted into Cu 0 and HF. However, due to its harsh conditions, only structurally simple aryl fluorides, such as fluorobenzenes, fluorotoluenes, and difluorobenzenes, can be synthesized, and the regioselectivity is low. Figure 7 Copper II fluoride-mediated fluorination of arenes. In , Fier and Hartwig described a copper-mediated fluorination of aryl iodides Figure 8 , left. Furthermore, it is difficult to separate the desired fluorination products from the protonated byproducts. After preliminary mechanistic studies, pathways involving radical intermediates and aryne intermediates were ruled out. Figure 8 Copper-mediated fluorination of aryl iodides and aryl boronate esters. Only 1 year later, Fier et al reported another copper-mediated fluorination reaction, that is, copper-mediated electrophilic fluorination of aryl boronate esters Figure 8 , right. Substrates containing ester, ketone, aldehyde, amide, nitrile, halide, and heterocycle functionalities undergo fluorination in moderate-to-good yield. The major side reaction is protodeborylation, which forms the corresponding arenes. Deuterium-labeling experiments suggest that the proton comes from the adventitious water in the reaction system. After extensively studying the reaction mechanism, the authors concluded that fluorination does not occur via the formation of ArCu I species. Instead, a cationic Cu III fluoride intermediate is in situ generated and reacts with the combination of AgF and aryl boronate esters. Shortly after, Ye and Sanford published a similar protocol for copper-mediated fluorination of aryl stannanes and aryl trifluoroborates Figure 9. Furthermore, the reactions proceed under very mild conditions at room temperature in many cases. Figure 9 Copper-mediated fluorination of aryl stannanes and aryl trifluoroborates. Although electrophilic fluorination reagents are widely used as both excellent oxidants and fluorine sources in many transition-metal-promoted fluorination reactions, these reagents do have limitations as they are too expensive for large-scale applications and not suitable for PET imaging applications. Ye et al reasoned that the combination of an additional oxidant and a nucleophilic fluorine source could also enable the copper-promoted fluorination of aryl boron derivatives Figure Pyridine derivatives also undergo fluorination, albeit in low yields. However, substrates containing chloride, bromide, and iodide on the aromatic ring are susceptible to undergo competing halodeboronation under the reaction conditions. In this reaction, Cu OTf 2 is both a transition-metal promoter and an oxidant for Câ€”F bond formation. Besides late transition metals, main group metals such as magnesium can also be used in fluorination reactions. In , Yamada et al reported an efficient electrophilic fluorination of functionalized aryl and heteroaryl Grignard reagents Figure The authors found that direct

fluorination of Grignard reagents is inefficient. It is believed that the formation of the protonated arene as a side product can be attributed to the formation of a radical intermediate, which abstracts a hydrogen atom from the solvent. Thus, when the original solvent tetrahydrofuran was replaced by other solvents with poor hydrogen atom-donating ability, a dramatic improvement in reaction yield was observed. Figure 11 Electrophilic fluorination of aryl magnesium reagents. Phenols are also good substrates for deoxyfluorination. In , Tang et al developed a new deoxyfluorination reagent, Phenfluor, for one-step fluorination of phenols Figure Both electron-rich and electron-deficient functional groups are tolerant. However, strong hydrogen-bond donors such as alcohols are not tolerated. Mechanistic studies showed that there is a hydrogen bond between one hydrogen atom of the imidazolium heterocycle and bifluoride counteranion in the crystal structure of reaction intermediate. It is suggested that the hydrogen bonding renders the uronium a better nucleofuge and thus facilitates fluorination reactions. Figure 12 Deoxyfluorination of phenols and alcohols. Although Phenfluor was developed for deoxyfluorination of phenols, after appropriate modification of the reaction conditions, this reagent can also be used in late-stage deoxyfluorination of alcohols. The fluorination process is highly chemoselective, and thus, tertiary alcohols and hydroxyl groups engaging in hydrogen bonding are not reactive. Although, in , Bienvenu et al had established the 19F version of this oxidative fluorination, 33 the potential use of this fluorination in 18F radiochemistry had not been examined before. In this method, the tert-butyl group is essential because a good electrofuge is needed in acid-catalyzed aromatization. Figure 13 Metal-free oxidative fluorination of phenols with [18F]-fluoride. Fluorinated heterocycles such as 2-fluoropyridines are prevalent in pharmaceuticals, agrochemicals, and materials. Traditional approaches to these compounds require pre-functionalized substrates, are limited in scope, and can be hazardous. In , Hartwig et al reported a silver II fluoride-mediated selective Câ€”H fluorination reaction for vicinal position of pyridines and diazines Figure Further mechanistic studies revealed that AgF2 serves not only as a fluorination reagent but also as an oxidant. Synthesis of alkyl fluorides Early methods for fluorination mainly focused on activated substrates containing sp3Câ€”H bond, such as carbonyl derivatives, sulfones, and phosphate esters Figure One attractive strategy for alkyl fluoride synthesis is vicinal fluorocyclization of alkenes. Both electrophilic and nucleophilic fluorine sources can be employed in this strategy. In general, these fluorocyclization reactions are divided into two categories: Figure 16 Fluorocyclization of alkenes. One representative example for the fluorinationâ€”cyclization comes from Kong et al Figure

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Advances in the field of fluorine chemistry have been applied extensively to the syntheses of 18 F-labelled organic compounds and radiopharmaceuticals. However, 18 F has sparely been used as a tool to explore inorganic chemistry and can be viewed as a research area worthy of further development.

Chapter 5 : Journal of Fluorine Chemistry - Elsevier

Introduction: Fluorine Chemistry Past advances in research and modern chemistry have advanced understanding of

how the distinctive place of ï¬,uorine in the.

Chapter 6 : Recent advances in green fluorine chemistry | ROC

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