Journal of Organometallic Chemistry 747 (2013) 43–50

Contents lists available at SciVerse ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Review

N-Heterocyclic carbenes in organofluorine chemistry

V. Prakash Reddy[a,*], Avinash Vadapalli[a], Ekkehard Sinn[b], Narayan Hosmane[c]

[a] Department of Chemistry, Missouri University of Science and Technology, Rolla, MO 65409, USA
[b] Department of Chemistry, Western Michigan University, Kalamazoo, MI 49008, USA
[c] Department of Chemistry, Northern Illinois University, DeKalb, IL 60115, USA

ARTICLE INFO

Article history:
Received 22 March 2013
Received in revised form
26 April 2013
Accepted 29 April 2013

Keywords:
N-Heterocyclic carbene
Trifluoromethylation
Enantioselective synthesis
Organofluorine chemistry
Catalysis

ABSTRACT

This short review summarizes the recent progress in organofluorinations catalyzed by N-heterocyclic carbene (NHC)-transition metal ion complexes. NHC-metal ion complexes are increasingly used in a variety of organic transformations, and they have opened up new opportunities, especially in the synthesis of organofluorine compounds. New advances in olefin metathesis, trifluoromethylations, Heck and Suzuki coupling, selective hydrodefluorination, and enantioselective synthesis of organofluorine compounds have been achieved through catalysis by NHC and their metal ion complexes. In this review, synthetic methods for various NHC-metal ion complexes and their applications in the synthesis of organofluorine compounds are comprehensively outlined.

Contents

1. Introduction

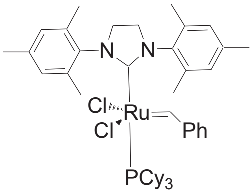
Organofluorine compounds have unique physicochemical properties, and high metabolic stabilities owing to their remarkably strong C–F bonds. The van der Waals radius of fluorine (1.47 Å) is similar to that of oxygen (1.52 Å), and only slightly larger than that of hydrogen (1.20 Å). Further, the C–F bond is isopolar and isosteric with C–OH, and therefore substitution of the fluorine for a hydroxyl group in biologically relevant compounds does not significantly alter their steric or electronic properties, while at the same time these fluorinated compounds show an increased lipophilicity and have higher metabolic stabilities. Similarly, the fluoro-olefin moiety ψ[CF = C] is isosteric and isopolar with peptide amide bonds, and the corresponding peptide isosteres show improved bioavailability and stability. Due to the combination of these unique characteristics, organofluorine compounds have found wide applications as pharmaceuticals, agrochemicals, refrigerants, and specialty chemicals [1–6]. Due to the growing importance of the organofluorine compounds, there has been a recent surge in the development of synthetic methodologies for these compounds. More recently, a variety of transition

---

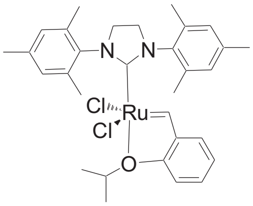
[*] Corresponding author. Tel.: +1 573 341 4768.
E-mail address: preddy@mst.edu (V.P. Reddy).

0022-328X/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jorganchem.2013.04.051

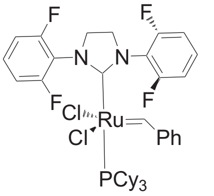
metal derived catalysts have been developed for the incorporation of fluorine into organic compounds [7–11]. N-heterocyclic carbene (NHC)-transition metal complexes, especially those derived from imidazolinylidenes or their saturated analogs, the imdazolidinylidenes, have been widely used as catalysts for various reactions, such as Heck, Sonogashira, and Suzuki reactions, alkene metathesis, hydrogenation, and cyclopropanation [12–17]



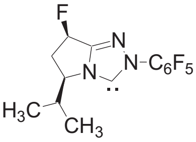
1 (Cy = cyclohexyl)



2



3 (Cy = cyclohexyl)



4

The widely used Grubbs' second generation (**1**) and Grubbs–Hoveyda (**2**) olefin metathesis catalysts are synthesized by substituting one of the phosphine ligands in the original first generation catalysts by the sterically crowded 1,3-dimesityl-4,5-dihydroimidazolidinylidene carbene ligand. These carbene complexes, and their various structurally related analogs, are usually prepared by the *in situ* deprotonation of the imidazolidinium salts with a base (e.g., Ag_2O) in the presence of the benzylidenebis(-tricyclohexylphosphine)-dichlororuthenium, a Grubbs' first generation catalyst [18,19]. The NHC-derived second generation catalysts have superior efficiency over the first generation catalysts in olefin metathesis reactions, and their catalytic activity can be fine-tuned by varying the substituents on the aryl rings. For example, the fluorinated version of the Grubbs's second generation catalyst, **3**, is a relatively more efficient olefin metathesis catalyst than the second generation complex **1** [18]. Structural and computational investigations revealed involvement of fluorine–ruthenium interactions which are responsible for the improved catalytic activity [18,20,21]. Similarly, the fluorinated triazolium-based carbene (**4**)-catalyzed asymmetric Stetter reactions of aryl and heterocyclic aldehydes with nitroalkenes proceed under mild conditions, and in high enantioselectivity [22,23].

Although numerous synthetic methodologies have been developed using NHC catalysis, in this review, we will focus on application of NHC and their metal ion complexes to the synthesis of organofluorine compounds.

2. Nucleophilic trifluoromethylation of carbonyl compounds

Song and coworkers have reported a convenient procedure for the nucleophilic trifluoromethylation of carbonyl compounds using the Ruppert–Prakash (CF_3TMS) reagent [24,25] and a commercially available sterically hindered NHC, 1,3-diadamantyl-1H-imidazolin-2-ylidene (**5**) [26]. This NHC, **5**, was originally synthesized and isolated by Arduengo and coworkers as the first stable crystalline carbene by the deprotonation of the 1,3-di(1-adamantyl)imidazolium chloride with NaH [27]. The NHC **5** serves as a σ-donating weak base to catalyze the trifluoromethylation reactions. A variety of aromatic aldehydes and ketones, and aliphatic aldehydes and ketones, and α-ketoesters could be trifluoromethylated under these mild reaction conditions. Loading as low as 0.5 mol% of the catalyst **5** is sufficient for achieving the trifluoromethylations. Use of other convenient solvents such as THF, however, require the use of about 10 mol% of the catalyst for optimal yields [26]. A reasonable mechanism for the catalytic effect of this NHC in trifluoromethylations is given below. This mechanism is in accord with those of other Lewis base