



Review

Advances in metal-assisted non-electrophilic fluoroalkylation reactions of organic compounds



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Abbreviations: BHT, butylated hydroxytoluene; Boc, butoxycarbonyl; Boc₂O, butoxycarbonyl anhydride; Bpin, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane; Bpy, 2,2'-bipyridine; *t*-BuXPhos, 2-di-*t*-butylphosphino-2',4',6'-triisopropylbiphenyl; CF₃TMS, trimethylsilyltrifluoromethane; Dabco, 1,4-diazabicyclo[2.2.2]octane; DAST, diethylaminosulfur trifluoride; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCE, dichloroethane; DCM, dichloromethane; DME, dimethoxyethane; DMF, *N,N*-dimethylformamide; DMI, dimethylimidazole; DMSO, dimethylsulfoxide; DPEphos, (bis-[2-(diphenylphosphino)phenyl]ether); dtbbpy, 4,4'-dit-butyl-2,2'-bipyridine; ET, electron transfer; HMPA, hexamethylphosphoramide; HR ESI-MS, high resolution electrospray ionization mass spectrometry; NMP, *N*-methyl pyrrolidone; Phen, 9,10-phenanthroline; phenCu(R_f), phenanthroline-copper-R_f complex; ppy, 2-phenylpyridine; PT, proton transfer; r.t., room temperature; R_fX, perfluoroalkyl halide; RuPhos, 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl; SET, single electron transfer; S_NAr, aromatic nucleophilic substitution; S_AH, homolytic aromatic substitution; S_{RN}1, unimolecular radical nucleophilic substitution; TBHP, *t*-butylhydroperoxide; TESCf₃, triethylsilyl trifluoromethane; TFA, 2,2,2-trifluoroacetic acid; TIPS, triisopropyl silane; TMEDA, tetramethyl ethylene diamine; TMP, tetramethylpiperidine; TMS, trimethylsilyl; TMSCF₂H, trimethylsilyldifluoromethane; T_fO, triflate; TPGS-750-M, DL-α-tocopherol methoxypolyethylene glycol succinate solution; Xantphos, 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene; *p*TSA, *para*-toluenesulfonic acid.

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ARTICLE INFO

Article history:

Received 2 October 2014

Accepted 19 November 2014

Available online 27 November 2014

Keywords:

Metal-assisted trifluoromethylation

Fluoroalkylation of aromatics

Trifluoromethylation by metal–organic species

ABSTRACT

Metal-assisted trifluoromethylation and perfluoroalkylation reactions are probably one of the first approaches employed to achieve fluoroalkyl-group substitutions of organic substrates through the use of metals such as copper. Fluoroalkylation reactions of both aromatic and aliphatic substrates involving the employment of perfluoroalkyl halides R_fX in conjunction with metallic species, and nucleophilic fluoroalkylating reagents in the presence of metals or organometallic species will be studied. Fluoroalkylation reactions utilizing electrophilic fluoroalkylating reagents in the presence of transition metals or trifluoromethylthiolation reactions will not be the subject of this article. Recently emerging literature (2011–present), with special emphasis on updates from previous review articles on the metal-mediated fluoroalkylation of aromatic substrates will be dealt with.

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1. Introduction

Introduction of fluoroalkyl groups into organic substrates is an important transformation on account of the changes that these groups impart to molecules, such as an increase in lipophilicity, resistance to oxidation, bioavailability, increase in bioactivity, water repellent properties, etc. Recently, the introduction of trifluoromethyl and perfluoroalkyl groups into aromatic or heteroaromatic substrates has been reinvigorated, as evidenced by the large volume of papers published in the last five years [1–4].

The catalytic aspects of coupling and radical reactions for selective aryl trifluoromethylation and perfluoroalkylation functionalization employing Pd, Ru, Ag, Cu, and Zn organo-catalysts or metals alone is a topic of constant research. The radical nature of some of these metal-assisted transformations has been revisited in recent review articles [5].

The review by Grushin and collaborators [1] summarizes all metal complex-mediated reactions for synthesizing trifluoromethylated and perfluoroalkyl-substituted arenes, with a large variety of Pd(II) trifluoromethyl complexes and Cu-promoted (Cu(I)) trifluoromethyl group *ipso* substitution of haloarenes. Also, the trifluoromethylation of haloarenes in organic solvents catalyzed by Ni was used for the aromatic carbon-halogen bond activation and has been summarized as well [5–8].

Although the involvement of transition metals to effect perfluoroalkylation reactions has relied in the past on the employment of costly organocatalysts and/or harsh reaction conditions, alternative metal-mediated perfluoroalkylation strategies of organic substrates have been sought after.

To this end, the contributions by Baran et al. [9] with the fluoroalkyl sulfinate zinc salts, those from Ritter with the Ni [4,10] and other metals [11] have augmented the repertoire for accomplishing fluorination reactions on organic substrates.

This review intends to be an update of previously published accounts [5], where new approaches and examples on perfluoroalkylation reactions performed through the aid of metals are illustrated, exploring the benefits and advantages of transition metals in polar and radical perfluoroalkylation reactions. These reactions exclude the utilization of electrophilic fluoroalkylating species which encompass an emerging class of reagents that effect both addition and substitution reactions on a large array of organic substrates which have been the subject of a recent review article [12]. The account will make special emphasis on the different classes of organic substrates that can be substituted with trifluoromethyl or perfluoroalkyl moieties with the intervention of metals or metallic organocatalysts rather than the use of a particular metallic species [5].

2. Metal-mediated trifluoromethylation and fluoroalkylation reactions of arenes and heteroarenes

Trifluoromethylated aromatic substrates are widely used as active components of numerous modern pharmaceuticals and agrochemicals (Scheme 1), this being the reason for the continuous search for more and improved protocols into the incorporation of the CF_3 functionality at the last stages of a synthetic approach.

There exists a comprehensive review article on the trifluoromethylation of aromatic compounds with metal complexes by Tomanshenko and Grushin [1] in 2011. Consequently, discussion on these types of substrates will be limited to developments in this expanding area published thereafter. Updates on copper-mediated trifluoromethylation of aromatic compounds have also recently been introduced [13,14].

In the following sections, recent developments on the fluoroalkylation reactions of functionalized arenes such as haloarenes, arylboronic acids, diazobenzenes, and the $C_{aryl}-H$ fluoroalkylation reactions assisted by metals shall be described.

2.1. Fluoroalkylation of aromatic halides [15]

Palladium-catalyzed transmetalation processes afford trifluoromethyl-substituted aromatic substrates from functionalized substituted haloarenes and the nucleophilic CF_3SiMe_3 source [5,16,17a].

2.1.1. Fluoroalkylation of aryl iodides [17b]

The vast majority of previously reported Cu-mediated/catalyzed trifluoromethylation reactions of aromatic electrophiles occurs efficiently only in the presence of a specifically added ligand, preferentially phenanthroline and a iodoarene [18].

In contrast, Grushin and colleagues have presented a fluoroform-derived $CuCF_3$ [19,20] as being reactive toward iodoarenes in the absence of any added ligands. These and other authors [20–22] have very recently accomplished the trifluoromethylation of aryl and heteroaryl halides through the use of a fluoroform-derived CF_3 -copper compound, according to Scheme 2.

The generation of the $CuCF_3$ complex had previously been carried out employing $MeS(O)CH_2K$, and CuI , which upon decomposition renders the trifluoromethyl cuprate, according to Scheme 3.

However, this methodology (Scheme 3) of generating $CuCF_3$, provides unwanted side products in the trifluoromethylation reaction of aryl iodides, and the stabilization of $CuCF_3$ cannot be attained.

The new method reported by Grushin et al. [20,23] (Scheme 4) is based on a novel *ate* complex reagent, $[K(DMF)][(t-BuO)_2Cu]$, that

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