Recent Advances in the Synthesis of Difluoromethylated Arenes

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Received: 16.07.2014
Accepted: 24.07.2014
Published online: 21.08.2014

Abstract The growing importance of fluorinated compounds in pharmaceuticals, agrochemicals, and materials has triggered the development of new methods for the introduction of fluorine into small molecules. Although it is a challenge to prepare fluorinated compounds, new developed reactions are addressing this challenge and facilitating the synthesis of difluoromethylated arenes. In this article, we highlight recently important developments in the synthesis of difluoromethylated arenes.

1 Introduction

The difluoromethyl group has received a great deal of attention in medicinal chemistry because it is isosteric and isopolar with the hydroxyl group and is found in various biologically active compounds (Figure 1). Generally, methods for the synthesis of difluoromethylated arenes through deoxyfluorination of aldehydes or ketones suffer from poor functional-group compatibility and require the use of expensive and toxic fluorinated reagents. Recent developments in organo- and transition-metal catalysis have allowed new methods to prepare difluoromethylated arenes. Herein we highlight recent progress in the synthesis of difluoromethylated arenes.

Figure 1 Representative drug and drug candidate containing CF2H functional group

Peng Xu (left) was born in Jiangsu Province, P. R. of China in 1990. He obtained his BSc degree from Jiangnan University in 2012 and then joined Professor Pingping Tang’s research group in Nankai University to pursue his PhD degree. His current research interests focus on fluorine chemistry.

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2 Cross-Coupling with Copper

Recently, Amii and co-workers reported a copper-catalyzed cross-coupling and decarboxylation from aryl iodides to prepare difluoromethylated arenes (Scheme 1, a).4 Although cross-coupling with α-silyldifluoroacetates was achieved under mild conditions, the decarboxylation step is limited to electron-deficient aryl iodides and requires high temperature (>170 °C). The copper-catalyzed cross-coupling of ethyl ortho-iodobenzoates with bromozinc-difluorophosphonates was reported by Zhang and co-workers.5 The benzoate ester directing group plays important roles, and the features of this reaction are the high reaction efficiency, excellent functional-group compatibility, and operational simplicity. Hartwig and co-workers presented a one-step copper-mediated cross-coupling between iodoarenes and TMSCF2H (Scheme 1, b).6 Although the reaction proceeds in high yields with good functional-group compatibility, the reaction requires a large excess amount of TMSCF2H (5 equiv) and is limited to electron-rich and electron-neutral iodoarenes. These problems were addressed successfully by Surya Prakash with n-Bu3SnCF2H as the difluoromethyl pronucleophile (Scheme 1, c).7 The disadvantages of the method are that the reaction requires high temperature and n-Bu3SnCF2H is toxic. Shen and Lu developed a copper-mediated ligandless aerobic fluoroalkylation of arylboronic acids under mild conditions to prepare difluoromethylated arenes.8 The reaction tolerates a wide range of functional groups and can be easily scaled up. Recently, Qing’s group reported a copper-mediated direct difluoroalkylation of electron-deficient aryl iodides using 2.4 equivalents of TMSCF2H at room temperature (Scheme 1, d).9 The mild reaction conditions make this method attractive for the synthesis of difluoromethylated arenes.

3 Cross-Coupling with Palladium

Early this year, Zhang and co-workers described a palladium-catalyzed difluoroallylation of aryl boronic acid using 3-bromo-3,3-difluoropropene (Scheme 2, a).10 The reaction proceeds with low catalyst loading, high regioselectivity, and excellent functional-group compatibility. At the same time, the authors also reported another palladium-catalyzed difluoroalkylation of aryl boronic acid with bromodifluoroalkylphosphonate, bromodifluoroacetate, and further derivatives, which provides a facile and useful access to a series of functionalized difluoromethylated arenes.11 Qing and co-workers reported a palladium-catalyzed directed α-arylation of α,α-difluoro ketones with aryl bromides.12 The method provides an efficient and straightforward access to a variety of difluoromethylated arenes with broad substrate scope. The disadvantage of the method is that the reaction required high temperature and high catalyst loading. This problem was addressed successfully by Hartwig and co-workers with an air- and moisture-stable palladacyclic complex as a catalyst, a broad range of electronically varied aryl bromides and chlorides was used to provide difluoromethylated arenes in high yields with low catalyst loading and lower temperature (Scheme 2, b).13
4 Cross-Coupling with Other Metals

In 2012, Li and co-workers reported a silver-catalyzed decarboxylative fluorination of aliphatic carboxylic acids with Selectfluor under mild conditions. Using Li’s method, the transformation of α-fluorocarboxylic acids into difluoromethylated arenes was achieved by Gouverneur and co-workers (Scheme 3, a). This method allows for the preparation of [18F]-labeled difluoromethylarenes using [18F]-Selectfluor bistriflate. Inoue and co-workers reported a cobalt-catalyzed cross-coupling reaction of arylzinc reagents with ethyl bromodifluoroacetate to form difluoromethylated arenes (Scheme 3, b). The reaction proceeds under mild conditions and is applicable to various arylzinc reagents to afford the corresponding ethyl aryl difluoroacetates.

Scheme 3 Formation of difluoromethylated arenes with other metals

5 C(sp³)–H Activation

Recently, directed ethoxycarbonyldifluoromethylation of aromatic compounds with BrCF₂CO₂Et was reported using Cp₂Fe by Testu Yamakawa and co-workers. Moreover, the one-pot synthesis of 3,3-difluoro-2,3-dihydroindole-2-one derivatives was achieved with para-substituted aniline derivatives using this method. Baran and co-workers reported a directed difluoromethylation of C–H bonds in heteroarenes with benchtop-stable Zn(SO₂CF₂H)₂ (Scheme 4, a). Shortly after, the authors developed other reagents, such as sodium difluoroethylsulfinate, for the synthesis of fluorinated heteroarenes. Early this year, Wang and co-workers developed a new method for visible-light photoredox difluoromethylation of electron-rich heteroarenes under mild conditions (Scheme 4, b). Mechanistic investigation indicated that the reaction proceeds through an electrophilic radical-type pathway.

Scheme 4 Formation of difluoromethylated arenes via C(sp³)–H activation

6 C(sp³)–H Activation

In 2013, Chen and co-workers reported a visible-light-promoted metal-free C–H activation for the synthesis of difluoromethylated arenes (Scheme 5, a). This is the first report of selective C–H gem-difluorination. Shortly after, we reported a silver-catalyzed oxidative activation of benzylic C–H bonds to synthesize difluoromethylated arenes (Scheme 5, b). With AgNO₃ as the catalyst, the reaction of a variety of methylated arenes with Selectfluor and Na₂S₂O₈ in acetonitrile–water (v/v = 1:1) at 80 °C under nitrogen atmosphere led to the formation of the corresponding difluoromethylated arenes in 42–93% isolated yield.

Scheme 5 Formation of difluoromethylated arenes via C(sp³)–H activation

Some representative examples are shown in Scheme 6. The mild reaction conditions generally tolerate diverse functional groups on the aryl rings. Notably, the reaction is amenable to gram-scale synthesis, proving the practicality of our method. The preliminary mechanism studies indicate that a radical-chain mechanism or single-electron transfer (SET) may be involved in this transformation.
7 Conclusion

To summarize, significant advances have been made in the synthesis of difluoromethylated arenes. Particularly, recent advances have allowed innovative approaches for benzylic C–H fluorination to prepare difluoromethylated arenes. However, some challenges still remain. Such as directed C–H activation is still not efficient. New metal catalysts such as iron are still required. These challenges are expected to stimulate further development in the synthesis of difluoromethylated arenes.

Acknowledgment

We gratefully thank the State Key Laboratory of Elemento-Organic Chemistry for generous start-up financial support. This work was supported by the '1000 Youth Talents Plan', and the Natural Science Foundation of Tianjin (Grant No. 13JCJLYC35000).

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