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A REVIEW ON DIFLUOROMETHYLATION OF ARYL AND HETEROARYL COMPOUNDS

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ABSTRACT:

The difluoro methylated aryl andheteroaryl compounds are of immense importance in agrochemical and pharmaceutical industry owing to the various properties of difluoro methyl group (CF_2H) like weakly acidic nature and capability of hydrogen-bonding interactions that improve the binding selectivity of biologically active compounds and it can act as a more-lipophilic isostere of carbinol, thiol, hydroxamic acid or amide groups.The transition metals in difluoro methylation reactions play various roles, including stabilizing the difluoro methyl anion (as difluoro methyl carriers), promoting the formation of difluoro methyl free radicals (such as transition-metal photo redox catalysts) and facilitating the formation of HF_2C-C and HF_2C-X bonds (through the reductive elimination of difluoro methyl-metal complexes).This review paper discuss about the various methods that have been reported for difluoro methylation reactions using various transition metals like, copper, palladium, palladium/silver (bimetallic catalyst system), silver, nickel, palladium with platinum, Iridium photo catalyst etc.

Keywords: Difluoromethylation, difluoromethylated aryl compounds, difluoromethylatedheteroaryl compounds, difluoromethyl group.

INTRODUCTION

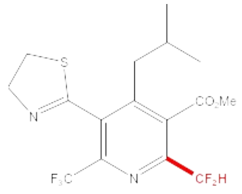
Introduction of fluorine or fluorinated moieties into biologically active compounds can increase their membrane permeability, metabolic stability and bioavailability due to enhancement of lipophilicity and resistance towards oxidation. This is due to unique intrinsic properties of fluorine, like high electronegativity and small atomic radius.

Among the various fluorinated groups, the difluoro methyl group (CF_2H) is of great importance because it can act as a more-lipophilic isostere of carbinol, thiol, hydroxamic acid, or amide groups. The CF_2H group is weakly acidic and is capable of hydrogen-bonding interactions to improve the binding selectivity of biologically active compounds.

On the other hand, in general, the heteroaryl moiety is regarded as one of the most common fragments in the majority of marketed drugs.

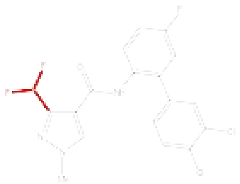
So logically, difluoro methylated aryl andheteroaryl compounds that combines beneficial properties from both units could be conceived as a promising family of pharmacores that are able to modulate the lipophilicity, polarity, and hydrogen bonding capacity of the target molecules, and consequently the physiochemical and pharmacokinetics of the drugs.

There are various examples of fungicide, herbicide and pharmaceutical medicines that containsdifluoro methyl (CF_2H) group attached to aryl andheteroaryl compounds.

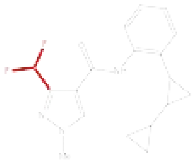


Thiazopyr

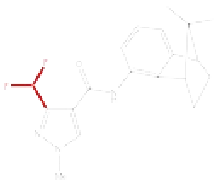
1.1 Example of Herbicide that contains difluoromethyl (CF_2H) group attached to heteroaryl compound



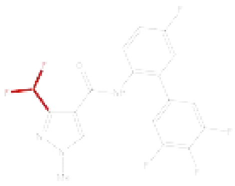
BIXAFEN



SEDAXANE

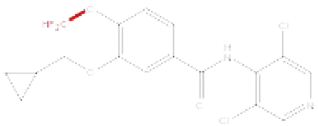


ISOPYRAZAM

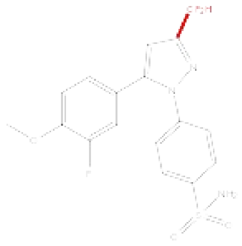


FLUXAPYROXAD

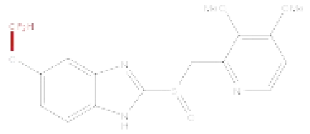
1.2 Examples of some Fungicides that contains difluoromethyl (CF_2H) groupattached to heteroaryl compound



Roflumilast



Deracoxib



Pantoprazole

1.3 Examples of Pharmaceutical medicines that contains difluoromethyl (CF_2H) group attached with aryl andheteroaryl compound.

REVIEW METHOD

We used keywords such as difluoromethylation, difluoromethylated aryl compounds, difluoromethylatedheteroaryl compounds, difluoromethylgroup.Then, the literature that matched such key words was reviewed thoroughly and their outcomes were properly noted.

SYNTHESIS OF DIFLUOROMETHYLATED (CF_2H) ARYL AND HETEROARYL COMPOUNDS

Knowing about the great importance of difluoro methyl (CF_2H) group in enhancing the biological activity of the compounds, the study of various synthetic approaches for introducing difluoro methyl group to an aryl orheteroaryl compound is of immense importance for agrochemical and pharmaceutical researchers in recent decade.

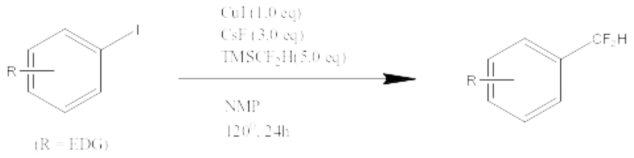
Various synthetic methods have been developed in the past decade for describing difluoro methylation of aryl andheteroaryl compounds.

All these discussed methods use different source of difluoro methyl (CF_2H) group including bromodifluoro methane ($BrCHF_2$), organosilicon reagent like –trimethylsilyldifluoromethane ($TMSCF_2H$), organozinc reagent like – $(DMPU)_2Zn\ (CF_2H)_2$, difluoro methyl zinc reagent bearing a diamine TMEDA i.e. $(TMEDA)Zn\ (CF_2H)_2$, selectfluor and bromodifluoro acetate ($BrCF_2CO_2Et$) etc.

The discussed methods are metal-mediated reactions using mostly transition metals like copper, palladium, palladium/silver (bimetallic catalyst system), silver, nickel, palladium with platinum, Iridium photo catalyst etc.

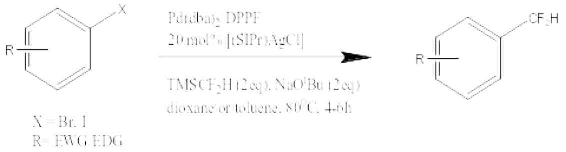
3.1 Synthesis of difluoromethylatedarenes by difluoro methylation of aromatic halides

Fier P. S. &Hartwig J. F. (2012) first time described one-step regioselectivedifluoro methylation of aryl iodides and vinyl iodides mediated by copper catalyst having stochiometric amount of CuI and CsF, by using an organosilicon reagent, trimethylsilyldifluoromethane ($TMSCF_2H$) as the source of the CF_2H group.



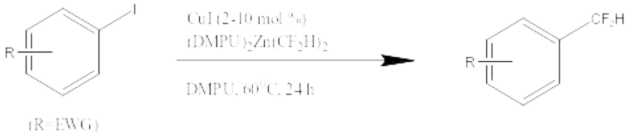
Copper mediated Difluromethylation of aryl iodides using $TMSCF_2H$

Gu Y., Leng X., &Shen Q. (2014) described the method of direct difluoro methylation of aryl bromide/iodide by using dual palladium/silver bimetallic catalyst system with readily available organosilicon reagent, trimethylsilyldifluoromethane (TMSCF2H) as the source of the CF_2H group along with stichiometric quantity of NaO^tBu under mild conditions.



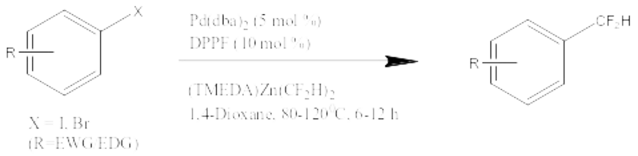
Direct diflurometylation of aryl bromides/iodides using $TMSCF_2H$ and dual palladium/silver catalyst

Serizawa H., Ishii K., Aikawa K. &Mikami K. (2016) described the copper catalyseddifluoro methylation of aryl iodides with organozinc reagent $(DMPU)_2Zn\ (CF_2H)_2$ to afford difluoro methylated arenes.



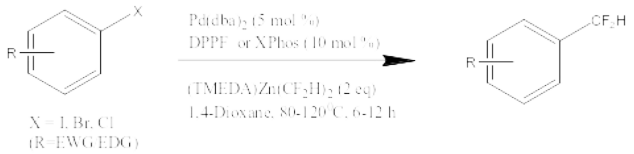
Copper-Catalyzed Difluoromethylation of Aryl Iodides with (Difluoromethyl)zinc Reagent

Aikawa K., Serizawa H., Ishii K. &Mikami K. (2016) disclosed a method of palladium-catalysedNegishi cross-coupling reaction of aryl iodides and bromides with (difluoro methyl) zinc reagent bearing a diamine such as TMEDA to provide the difluoro methylated aromatic compounds in good to excellent yields.



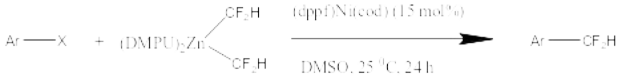
Palladium-Catalyzed Negishi Cross-Coupling Reaction of Aryl Halides with (Difluoromethyl)zinc Reagent

Mikami K. et al (2016) reported an efficient palladium-catalysedNegishi cross-coupling of aryl halides with the (difluoro methyl) zinc reagent (TMEDA)Zn (CF2H)2 to afford a wide range of difluoro methylated aromatic compounds in good to excellent yields



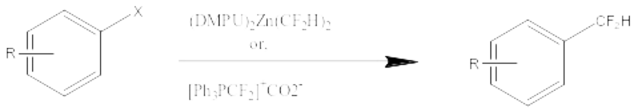
Catalytic Difluoromethylation of Aryl Halogenides

XuL. and Vicic D. A. (2016) reported the preparation of a stable and isolable difluoro methyl zinc reagent that can be used for the difluoro methylation of aryl bromides, iodides, and triflates using a nickel catalyst at room temperature.



Direct Difluoromethylation of Aryl Halides via Base Metal Catalysis at Room Temperature

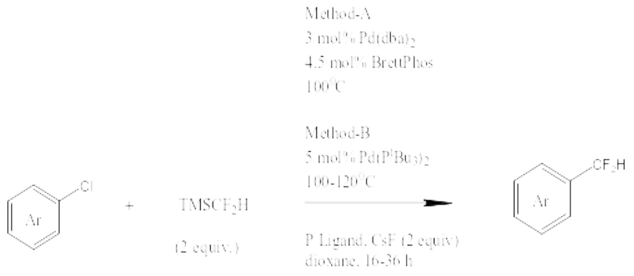
Yerien D. E., Barata-Vallejo S. &Postigo A. (2017) discussed various works related to difluoro methylation reaction of organic compounds which includes difluoro methylation of aryl halides by various metal catalysed reactions.



Rong J., Ni C. & Hu J. (2017) discussed about the various works related to the direct difluoro methylation reactions that use transition metals in both stoichiometric and catalytic amounts. They discussed work of **Hartwig et al (2012), Shen Q et al (2014), Vicic et al (2016) and Mikami et al (2016)** which has been already described in this literature review.

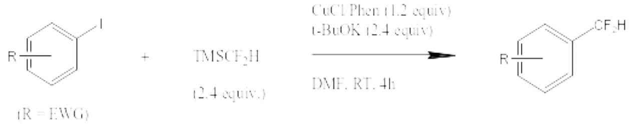
They also explained how transition metals in difluoro methylation reactions play various roles, including stabilizing the difluoro methyl anion (as difluoro methyl carriers), promoting the formation of difluoro methyl free radicals (such as transition-metal photo redox catalysts), and facilitating the formation of HF_2C-C and HF_2CX bonds (through the reductive elimination of difluoro methyl-metal complexes). The discussion is focused on recent developments in metal-catalysed direct difluoro methylation reactions, that is, reactions that involve the direct transfer of a CF_2H group.

Ferguson D. M., Malapit C. A., Bour J. R. & Sanford M. S. (2019) described Palladium-CatalysedDifluoro-methylation of Aryl Chlorides and Bromides with $TMSCF_2H$. They targeted a new difluoro-methylation method that both obviates the need for stoichiometric organozinc/silver reagents and enables the use of readily available aryl chlorides and bromides as substrates. They identified two different catalyst systems with similar efficacy. The first (Method A) involves the use of 3 mol % of Pd(dba)2 and 4.5 mol % of BrettPhos at 100 °C and (Method B) involves the use of 5 mol % of Pd (Pt Bu3)2 at 120 °C.



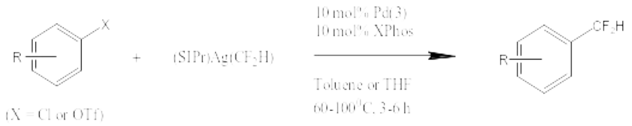
Pd-Catalyzed Difluoromethylation of Aryl Chlorides and Bromides

Jiang X.-L., Chen Z.-H., Xu X.-H.& Qing F.-L. (2014) reported a convenient method for one step introduction of the difluoro methyl group into electron-poor aryl iodides by employing copper-mediated direct difluoro methylation using $TMSCF_2H$ at room temperature. The mild reaction conditions make this method attractive for the synthesis of a series of difluoro methylated compounds. This work was an important complement to **Hartwig et al (2012)** method.



Copper-mediated direct difluoromethylation with TMSCF2H

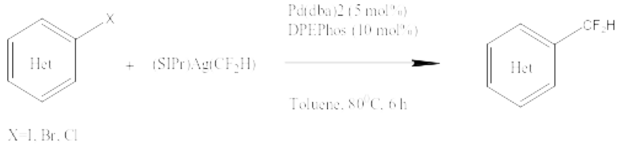
Lu C., Lu H., Wu J., Shen H. C., Hu T., GuY.&Shen Q. (2018) described a palladium-catalyseddifluoro methylation of a series of aryl chlorides and triflates under mild conditions. A variety of common functional groups were tolerated.



Palladium-Catalyzed Difluoromethylation of Aryl Chlorides or Triflates

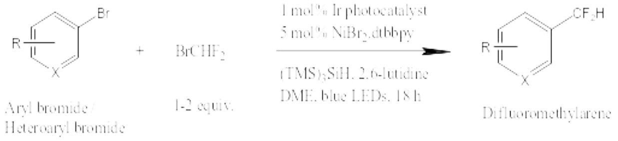
3.2 Synthesis of difluoro methylated arenes by difluoro methylation of heteroaryl halides

Lu C., Gu Y., Wu J., GuY.&Shen Q. (2017) described a palladium-catalyseddifluoro methylation of a series of heteroaryl chlorides, bromides and iodides under mild conditions. They detailed the development of an efficient palladium-catalyst that is capable of direct difluoro methylation of a vast range of different bromo- or iodo-substituted heteroarenes such as pyridine, pyrimidine, pyrrole, furan, thiophene, quinoline, carbazole, dibenzo[b,d]thiophene, pyrazine, thiazole, oxazole, pyrazole and activated heteroaryl chlorides.



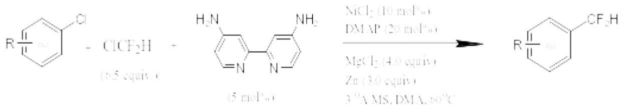
Palladium-Catalyzed Difluoromethylation of Heteroaryl haides

Bacauanu V., Cardinal S., Yamauchi M., Kondo M., Fernández D. F., Remy R. & MacMillan D. W. C. (2018) reported a convenient and broadly applicable strategy for the difluoro methylation of aryl bromides via metalophotoredox catalysis. Bromodifluoromethane, a simple and commercial alkyl halide, is harnessed as an effective source of difluoro methyl radical via silyl radical-mediated halogen abstraction. The merger of this fluoroalkyl electrophile activation pathway with a dual nickel/photo redox catalytic platform enables the difluoro methylation of a diverse array of aryl and heteroaryl bromides under mild conditions.



Metallaphotoredox Difluoromethylation of Aryl Bromides

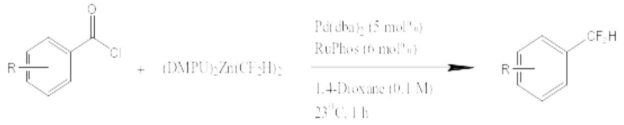
Xu C., Guo W.-H., He X., Guo Y.-L., Zhang X.-Y.& Zhang X. (2018) describe a strategy for difluoro-methylation of aromatics through nickel-catalysed cross-coupling of $ClCF_2H$ with readily accessible (hetero)aryl chlorides and bromides.



Difluoromethylation of (hetero)aryl chlorides with chlorodifluoromethane catalyzed by nickel

3.3 Synthesis of difluoro methylated arenes by difluoro methylation of aromatic acid halides

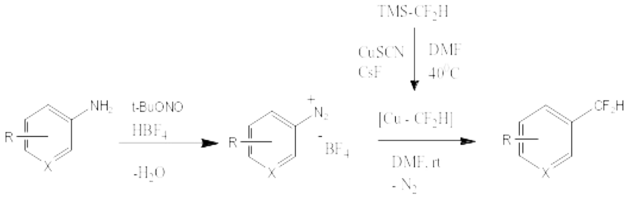
Pan F., Boursalian G. B. & Ritter T. (2018) described Palladium-catalyseddecarbonylative cross-coupling reaction of acid chlorides with a difluoro methyl zinc reagent to prepare difluoro methylated compounds from a wide range of aromatic carboxylic acid at Room Temperature.



Palladium-Catalyzed Decarbonylative Difluoromethylation of Acid Chlorides at Room Temperature

3.4 Synthesis of difluoro methylated arenes by sandmeyerdifluoro methylation of hetero arenedizonium salts

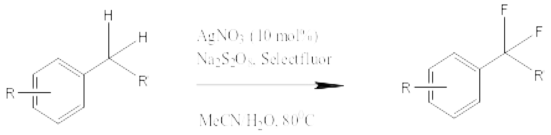
Matheis C., Jouvin K. &Goossen L. J. (2014) described a Sandmeyer-type difluoro methylation process that allows the straightforward conversion of (hetero-)arenediazonium salts into the corresponding difluoro methyl (hetero-)arenes under mild conditions. The actual difluoromethylating reagent, a difluoromethyl-copper complex, is formed in situ from copper thiocyanate and TMS−CF_2H. The diazonium salts are either preformed or generated in situ from broadly available aromatic amines.



Sandmeyer-type difluoro methylation of hetero arene diazonium salt

3.5 Synthesis of difluoro methylated arenes by silver-catalyzed oxidative activation of benzylic c-h bonds

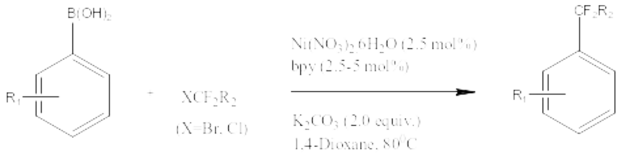
Xu P., Guo S., Wang L. & Tang P. (2014) presented the first example to form difluoro methylated arenes, by a silver catalysed oxidative activation of a benzylic C-H bond, utilizing AgNO3 as the catalyst. Various arenes with diverse functional groups undergo activation/fluorination of benzylic C-H bonds with commercially available Selectfluor reagent as a source of fluorine in aqueous solution.



Silver-catalyzed activation of benzylic C–H bonds for the synthesis of difluoromethylated arenes

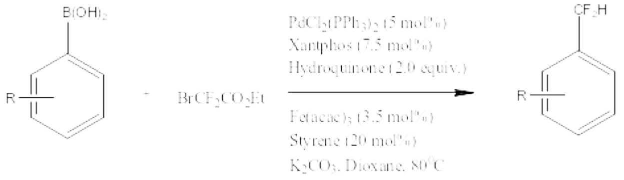
3.6 Synthesis of difluoro methylated arenes by difluoromethylation of aryl / hetero-aryl boronic acids

Xiao Y.-L., Guo W.-H., He G.-Z., Pan Q., & Zhang X. (2014) described the first successful example of nickel-catalyseddifluoro alkylation of aryl boronic acids. The reaction allows access to a variety of functionalized difluoro-methyl bromides and chlorides, and paves the way to highly cost-efficient synthesis of a wide range of difluoro-alkylated arenes.



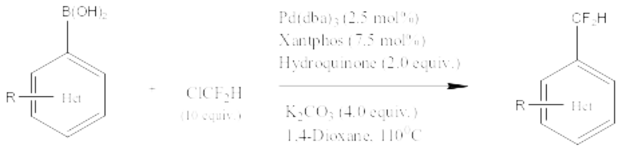
Nickel-catalyzed difluoroalkylation of organoboronic acids with functionalized difluoromethyl bromides and chlorides

Feng Z., Min Q. Q. & Zhang X. (2016) described an unprecedented example of Pd-catalyseddifluoro methylation of aryl boronic acids with bromodifluoro acetate. The protocol reveals that reaction proceeds under mild reaction conditions with hydroquinone and Fe(acac)$_3$ as additives. Preliminary mechanistic studies reveal that a difluorocarbene pathway is involved in the reaction, which is unusual compared to the most traditional approaches.



Pd-Catalyzed Difluoromethylation of Arylboronic Acids with Bromodifluoroacetate

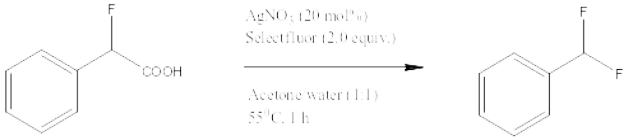
Feng Z., Min Q.-Q., Fu X.-P., An L., & Zhang X. (2017) described a direct palladium-catalyseddifluoro methylation method for coupling ClCF$_2$H with aryl boronic acids and esters to generate difluoro methylated arenes with high efficiency. The reaction exhibits a remarkably broad substrate scope, including hetero aryl boronic acids. Preliminary mechanistic studies revealed that a palladium difluorocarbene intermediate is involved in the reaction.



Pd-catalysed cross-coupling of ClCF2H with arylboronic and heteroarylboronic acids

3.7 Synthesis of difluoro methylated arenes by catalytic decarboxylativeflruorination

Mizuta S., Stenhagen I. S. R., O'Duill M., Wolstenhulme J., Kirjavainen A. K., Forsback S. J., Tredwell M., Sandford G., Moore P. R., Huiban M., Luthra S. K., Passchier J., Solin O., &Gouverneur V. (2013) reported that R, R-difluoro aryl acetic acids respond to silver-catalysedfluoro-decarboxylation in the presence of Selectfluor under Ag(I) catalysis. This approach to tri- and difluoro-methyl arenes distinguishes itself from classical methods relying on trifluoromethylating reagents.



Synthesis of Difluoromethylated arenes by fluorination of R-Fluoroaryl Acetic Acids

As discussed above, various synthetic methods were described for difluoro methylation of aryl / heteroaryl compounds.

Compared to the highly developed methods for trifluoromethylation, difluoro methylation is still underdeveloped, probably owing to the lack of efficient sources of the difluoro methyl group and stable difluoro methyl-metal complexes.

Following are the observed limitations for the reactions involving introduction of difluoro methyl group to aryl / heteroaryl compounds.

Use of metals:

Most of the discussed methods are metal-mediated reactions using mostly transition metals like copper, palladium, palladium/silver (bimetallic catalyst system), silver, nickel, palladium with platinum, Iridium photo catalyst etc. Use of other transition metals and their applicability to the difluoro methylation reactions is unexplored.

Lack of efficient photo catalysis method:

Efficient photo catalysis reactions are not well explored for difluoro methylation reactions.

No metal free reaction reported:

All the discussed literatures use metal / transition metal. No literature reported for metal free reaction strategy for difluoro methylation reactions.

High reaction temperatures:

Most of the reported literature uses moderate to high reaction temperatures for difluoro methylation reactions, only few of them are reported for room temperature and none of them reported favourable conditions at temperature lower than room temperature.

CONCLUSIONS

The difluoro methylated aryl andheteroaryl compounds are of immense importance in agrochemical and pharmaceutical industry owing to the various properties of difluoro methyl group (CF_2H) like weakly acidic nature and capability of hydrogen-bonding interactions that improve the binding selectivity of biologically active compounds and it can act as a more-lipophilic isostere of carbinol, thiol, hydroxamic acid or amide groups.

The transition metals in difluoro methylation reactions play various roles, including stabilizing the difluoro methyl anion (as difluoro methyl carriers), promoting the formation of difluoro methyl free radicals (such as transition-metal photo redox catalysts), and facilitating the formation of HF_2C-C and HF_2C-X bonds (through the reductive elimination of difluoro methyl-metal complexes).

Various methods have been reported for difluoro methylation reactions using various transition metals like, copper, palladium, palladium/silver (bimetallic catalyst system), silver, nickel, palladium with platinum, Iridium photo catalyst etc.

There is a scope of the development of [Metal-CF_2H] complexes of other metals, such as iron, rhodium, and gold.There is further scope for the development of more-efficient difluoro methyl sources and difluoro methyl-metal complexes with tunable reactivity.Additionally there is scope in the areas of photo catalysis, especially in transition-metal-free strategies involving organic dyes and other metal-free organic compounds aimed at producing the CF_2 radical species. This is of particular concern in the pharmaceutical industry to avoid the use of transition metals. In this particular area, there is scope of further method development for photo catalyticdifluoro methylation reactions of non-activated arenes.

Most of reported procedures uses moderate to high temperatures for reactions, so there is scope of developing the low temperature for reactionconditions to avoid the altering of other functional groups present in molecules or to avoid formation of other degradation by products during the reactions.Another area which deserves particular attention, in terms of difluoromethylating strategies, is the application of flow systems to achieve CF_2H substitutions in high yields and minimal reaction times. The flow systems, has received particular attention for trifluoromethylation, perfluoro alkylation and fluorination reactions, however, no report of a difluoro methylation flow system has been presented.

CONFLICT OF INTEREST

The author affirms that there is no conflict of interest regarding this paper.

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