2.6.2 Difluoro- and Fluoromethylation

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General Introduction

Among many methods for the preparation of difluoro- and fluoromethyl compounds, the selective introduction of a difluoro- or a fluoromethyl group represents the most streamlined method, which is especially useful for late-stage modification of complex molecules.[1,2] Compared to trifluoromethylation chemistry, the systematic exploration of difluoro- and fluoromethylation has only emerged more recently.[3] Selective difluoro- and fluoromethylation are generally accomplished by two strategies: one is the direct transfer of a difluoromethyl or fluoromethyl group into organic molecules, and the other is the transfer of a fluorinated C-1 moiety with removable auxiliary groups (such as CF_2R^1, $CHFR^1$, or CFR^1R^2), followed by removal of the auxiliary groups to give a difluoromethyl or fluoromethyl group.[1,2]

Although the direct transfer of a difluoromethyl or fluoromethyl group is of high atom economy, the available reagents, including (difluoromethyl)silanes, (difluoromethyl)stannanes, difluoro- and fluoromethanesulfinates, difluoro(halo)methanes (CHF_2X; X = F, Cl, Br, I), fluoro(halo)methanes (CH_2FX; X = Cl, Br, I), *S*-(difluoromethyl) sulfoximides, *S*-[bromo(difluoro)methyl]sulfonium salts, *S*-(fluoromethyl)sulfonium salts, and *N*-(difluoromethyl)ammonium salts, suffer from limitations such as harsh reaction conditions, lack of general applicability, and/or longer reaction times. The introduction of removable auxiliary groups onto the fluorine-bearing carbons of the difluoro- and fluoromethylation reagents not only facilitates the generation of the reactive species, but also tunes their reactivity in fluoroalkylation reactions. Among the fluoroalkylation reagents assisted by removable auxiliary groups such as sulfonyl, sulfonimidoyl, sulfanyl, selanyl, dialkoxyphosphoryl, alkoxycarbonyl, and halides, fluorinated sulfones have been widely used both in difluoromethylation and in fluoromethylation.[1–5] A comprehensive review on selective difluoro- and fluoromethylation reactions was published in 2009.[2] Other related reviews covering this topic are also available.[1,3–5]

SAFETY: All preparations can be carried out using the standard precautions generally taken with other hazardous chemicals found in a modern chemical laboratory. Some fluoromethyl compounds such as ω-fluorocarboxylic acids with an even number of carbon atoms are known to have high toxicity.[6] In general, however, most difluoro- and fluoromethyl compounds have low acute toxicity, although care should be taken to avoid inhalation and skin contact.

2.6.2.1 Difluoromethylation

According to the reactivity of the difluorinated reactive species involved in the formation of the C—C bond, difluoromethylation reactions are classified into four types: nucleophilic, electrophilic, and free-radical reactions, and difluoromethylation reactions involving transition-metal complexes.

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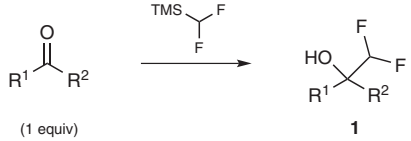
2.6.2.1.1 Nucleophilic Difluoromethylation

Nucleophilic difluoromethylation typically features the transfer of a difluoromethyl group (CHF_2) or its equivalent (CF_2R^1) to an electrophile. The synthetically useful nucleophilic difluoromethylation reagents are (difluoromethyl)trimethylsilanes, difluoromethyl phenyl sulfone, [difluoro(phenylsulfonyl)methyl]trimethylsilane, [difluoro(phenylsulfanyl)methyl]trimethylsilane, (difluoromethyl)phosphonates and their derivatives, *S*-(difluoromethyl)sulfoximides, trimethyl(trifluoromethyl)silane, and some difluoromethylenation reagents.

2.6.2.1.1.1 Using (Difluoromethyl)trimethylsilane

(Difluoromethyl)silanes are ideal reagents for direct difluoromethylation, although their synthetic utility has been largely unexploited. The nucleophilic activation of the silicon center with Lewis base initiators such as potassium fluoride, cesium fluoride, potassium *tert*-butoxide, or tetrabutylammonium triphenyldifluorosilicate allows transfer of the difluoromethyl moiety to electrophiles such as aldehydes, ketones, and aldimines.[7,8] In 1995, Hagiwara and Fuchikami reported the direct nucleophilic difluoromethylation of carbonyl compounds using (difluoromethyl)dimethyl(phenyl)silane and potassium fluoride at high temperature (100 °C), but the reaction only worked well for some aldehydes.[7] (Difluoromethyl)trimethylsilane, a more readily available reagent than (difluoromethyl)-dimethyl(phenyl)silane,[9] can be prepared by magnesium-mediated difluoromethylation of chlorotrimethylsilane with difluoromethyl phenyl sulfone,[10] or hydrodefluorination of (trifluoromethyl)trimethylsilane (also known as the Ruppert–Prakash reagent) with sodium borohydride.[11–13] In 2011, Hu and co-workers found that when Lewis bases such as potassium *tert*-butoxide and cesium fluoride are used, (difluoromethyl)trimethylsilane can react with both non-enolizable and enolizable aldehydes and ketones to give the corresponding difluoromethylated products **1** in satisfactory yields (Scheme 1).[8]

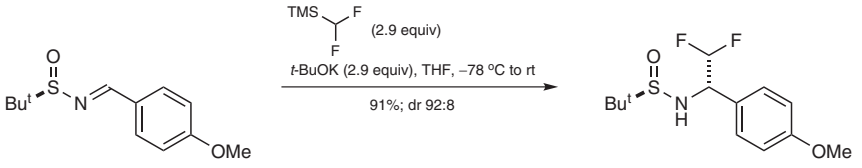
Scheme 1 Nucleophilic Difluoromethylation of Aldehydes and Non-enolizable Ketones Using (Difluoromethyl)trimethylsilane[8]



R^1	R^2	Equiv of $TMSCHF_2$	Conditions	Yield (%)	Ref
4-$MeOC_6H_4$	H	2.0	CsF (13 mol%), DMF, rt, 9 h, then TBAF, rt, 1 h	91	[8]
$(CH_2)_2Ph$	H	2.0	CsF (13 mol%), DMF, rt, 9 h, then TBAF, rt, 1 h	53	[8]
4-ClC_6H_4	4-ClC_6H_4	2.9	*t*-BuOK (2.9 equiv), THF, −78 °C to rt	97	[8]

The direct difluoromethylation of *N*-(*tert*-butylsulfinyl)imines derived from non-enolizable aldehydes using (difluoromethyl)trimethylsilane under the action of a stoichiometric amount of potassium *tert*-butoxide gives the corresponding addition products in good to excellent yields with good diastereoselectivity (Scheme 2).[8] This reaction is useful for the synthesis of enantioenriched α-difluoromethyl amines after the removal of the *tert*-butylsulfinyl group.

Scheme 2 Nucleophilic Difluoromethylation of an *N*-(*tert*-Butylsulfinyl)imine Derived from a Non-enolizable Aldehyde Using (Difluoromethyl)trimethylsilane[8]



2,2-Difluoro-1-(4-methoxyphenyl)ethanol (1, R^1 = 4-$MeOC_6H_4$; R^2 = H); Typical Procedure:[8] CsF (10 mg, 0.07 mmol) was added to a soln of 4-methoxybenzaldehyde (68 mg, 0.50 mmol) and $TMSCHF_2$ (124 mg, 1.0 mmol) in DMF (2 mL) at rt under N_2. After the mixture had been stirred at the same temperature for 9 h, a 1 M soln of TBAF in THF (1.0 mL, 1.0 mmol) was added and the mixture was stirred at rt for 1 h. After extraction of the mixture with Et_2O and H_2O, the Et_2O extract was washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel) to give the product as a colorless oil; yield: 85 mg (91%).

2.6.2.1.1.2 Using Difluoromethyl Phenyl Sulfone

Difluoromethyl phenyl sulfone is a powerful nucleophilic difluoromethylation reagent due to the high reactivity of the sulfonyl-stabilized difluoromethyl anion toward many electrophiles including carbonyl compounds,[14–21] imines,[22–24] alkyl halides,[25] and cyclic sulfates and sulfamidates,[26] although a further reductive desulfonylation is required to obtain the target difluoromethyl compounds. In the nucleophilic reaction step, depending on the substrate structure, strong bases, such as potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide, lithium hexamethyldisilazanide, sodium hexamethyldisilazanide, and potassium hexamethyldisilazanide, are used to generate the nucleophilic difluoro(phenylsulfonyl)methyl anion in situ, and many solvents such as dichloromethane, dimethylformamide, tetrahydrofuran, and toluene can be used. Sometimes, the use of hexamethylphosphoric triamide as an additive is necessary to improve the reaction.[16–19] In the desulfonylation step, sodium/mercury amalgam and magnesium are the commonly used reducing reagents.

As a nucleophilic difluoromethylation reagent, difluoromethyl phenyl sulfone was first reported to react with some aldehydes using sodium hydroxide as the base under phase-transfer conditions; however, the reaction is only applicable for aromatic aldehydes and sterically hindered aliphatic aldehydes such as 2-methylpropanal, and the desulfonylation with sodium gives the difluoromethyl-substituted alcohols in low yields.[14] A modified procedure using lithium hexamethyldisilazanide as a base and hexamethylphosphoric triamide as an additive works well for various ketones and non-enolizable aldehydes, affording the difluoro(phenylsulfonyl)methyl alcohols in good to excellent yields. As for enolizable aldehydes such as heptanal, only moderate yields are obtained albeit using two equivalents of aldehyde.[18] Moreover, the diastereoselectivity of nucleophilic difluoro(phenylsulfonyl)methylation varies depending on the substrate. For example, the difluoro(phenylsulfonyl)methylation of pregnenolone acetate (**2**) followed by desulfonylation and deacetylation using sodium/mercury amalgam in methanol gives 20-(difluoromethyl)pregn-5-ene-3,20-diol (**3**) in high yield with excellent diastereoselectivity (Scheme 3).[18] Furthermore, magnesium/acetic acid/sodium acetate in dimethylformamide can also be used as an environmentally benign system for desulfonylation with high efficiency.[27]

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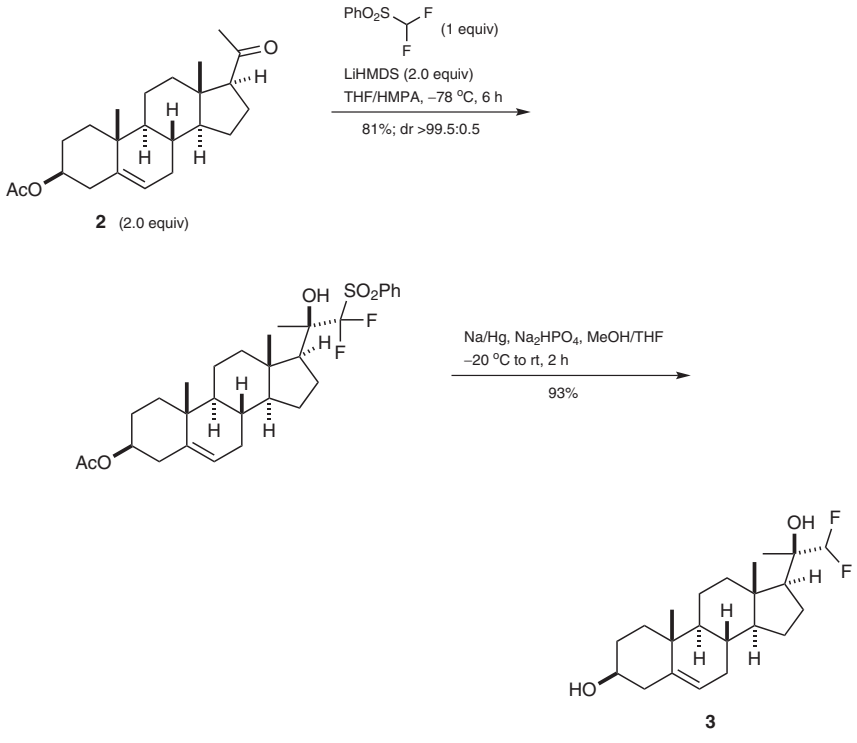
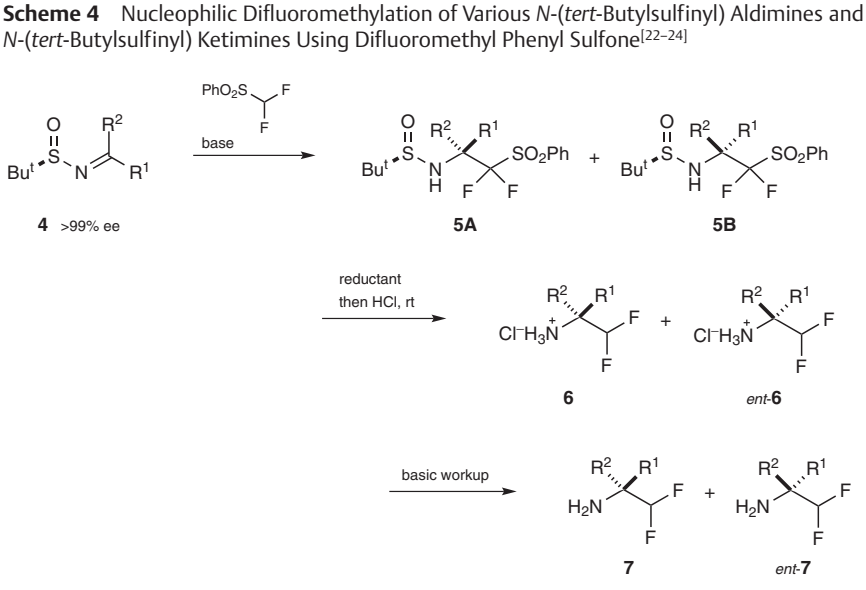
Scheme 3 Nucleophilic Difluoromethylation of Pregnenolone Acetate Using Difluoromethyl Phenyl Sulfone[18]



The diastereoselective addition of difluoromethyl phenyl sulfone to *N*-(*tert*-butylsulfinyl)-imines **4** using a sterically hindered base is one of the most effective protocols for the synthesis of enantioenriched α-difluoromethyl amines or their ammonium salts (e.g., **7** and **6**, respectively). The substrate scope is wide; not only various aldimines, but also ketimines work well in this difluoromethylation reaction (Scheme 4).[22–24]

Scheme 4 Nucleophilic Difluoromethylation of Various *N*-(*tert*-Butylsulfinyl) Aldimines and *N*-(*tert*-Butylsulfinyl) Ketimines Using Difluoromethyl Phenyl Sulfone[22–24]



R^1	R^2	Equiv[a] of **4**	Conditions (Step 1)	Ratio[b] (**5A**/**5B**)	Reductant (Step 2)	Yield[c] (%)	Ref
Ph	H	1.05	LiHMDS (1.2 equiv), THF, −78 °C, 10–20 min	>99:1	Na/Hg	79[d]	[22]
Et	H	1.05	LiHMDS (1.2 equiv), THF, −78 °C, 10–20 min	>99:1	Na/Hg	66[d]	[22]
(*S*)-CH(NBn_2)Bn	H	1.1	NaHMDS (1.4 equiv), THF, −78 °C, 3–5 h	>99:1	Mg	65[e]	[23]
Ph	Me	1.2	KHMDS (1.3 equiv), toluene, −78 °C, 2 h	1:99	Mg	69	[24]
Ph	Et	1.2	KHMDS (1.3 equiv), toluene, −78 °C, 2 h	3:97	Mg	70	[24]
iPr	Me	1.2	KHMDS (1.3 equiv), toluene, −78 °C, 2 h	1:99	Mg	87[f]	[24]
Ph	(*E*)-CH=CHPh	1.2	KHMDS (1.1 equiv), THF, −78 °C, 4 h	5:95	Mg	85	[24]
Ph	C≡CPh	1.2	NaHMDS (1.2 equiv), THF, −78 °C, 2 h	2:98	Mg	87	[24]
Ph	C≡CTIPS	1.2	NaHMDS (1.2 equiv), THF, −78 °C, 2 h	1:99	Mg	77	[24]

[a] Relative to $PhSO_2CHF_2$.
[b] Determined by ^{19}F NMR analysis of the crude products.
[c] Yield (%) of *ent*-**7** unless otherwise stated.
[d] Yield of **6** starting from **4**.
[e] Yield of the free amine **7**.
[f] Yield of **5B**.

The nucleophilic substitution reaction using difluoromethyl phenyl sulfone takes place only at primary carbon centers.[25,26,28] Difluoro(phenylsulfonyl)methylation of primary alkyl iodides under the action of a base such as potassium *tert*-butoxide affords (difluoromethyl)alkanes in moderate yields after reductive desulfonylation (Scheme 5).[25] However, in the substitution step, formation of *gem*-difluoroalkenes via β-elimination promoted by strong bases is a possible side reaction.[28] Nucleophilic difluoro(phenylsulfonyl)methylation of 1,2-cyclic sulfamidates followed by reductive desulfonylation affords β-difluoromethyl amines (e.g., **8**) in good yields (Scheme 6).[26] Similarly, 1,2-cyclic sulfates can be transformed into β-difluoromethyl alcohols.[26]

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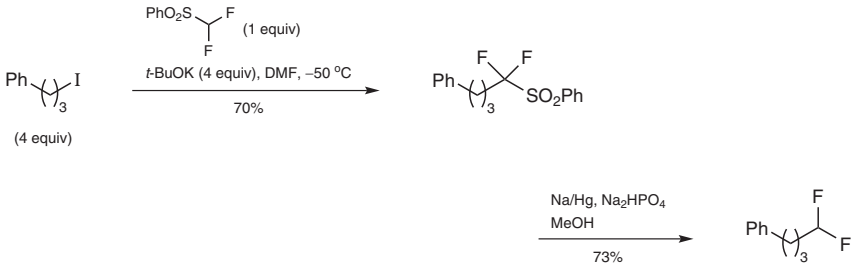
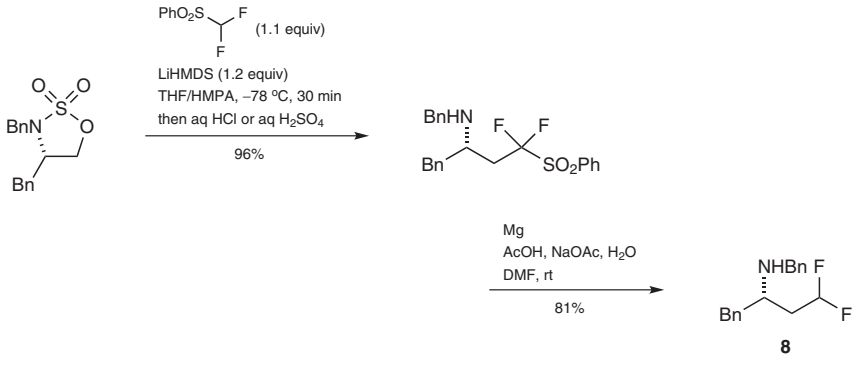
Scheme 5 Nucleophilic Difluoromethylation of Primary Alkyl Iodides Using Difluoromethyl Phenyl Sulfone[25]



Scheme 6 Nucleophilic Difluoromethylation of 1,2-Cyclic Sulfamidates Using Difluoromethyl Phenyl Sulfone[26]



(*R*)-*N*-[(*S*)-2,2-Difluoro-1-phenyl-2-(phenylsulfonyl)ethyl]-2-methylpropane-2-sulfinamide (5A, R^1 = Ph; R^2 = H); Typical Procedure:[22]

A 1.06 M soln of LiHMDS in THF (2.2 mL, 2.4 mmol) was added at −78 °C under N_2 to a 20-mL Schlenk flask containing *N*-(*tert*-butylsulfinyl)imine **4** (R^1 = Ph; R^2 = H; 440 mg, 2.1 mmol) and difluoromethyl phenyl sulfone (385 mg, 2.0 mmol) in THF (10 mL). The mixture was then stirred at −78 °C for 20 min, followed by addition of sat. brine (10 mL) at this temperature. The mixture was extracted with EtOAc (3 × 25 mL), and the combined organic phases were dried ($MgSO_4$). The ratio of diastereomers was determined by ^{19}F NMR analysis of this soln. After removal of the solvents under reduced pressure, the crude product was further purified by column chromatography (silica gel) to give the major isomer **5A** (R^1 = Ph; R^2 = H) as a white solid; yield: 763 mg (95%); ratio (**5A**/**5B**) >99:1; mp 144–146 °C; $[\alpha]_D^{20}$ −27.4 (*c* 0.8, $CHCl_3$).

(*S*)-2,2-Difluoro-1-phenylethanamine Hydrochloride (6, R^1 = Ph; R^2 = H); Typical Procedure:[22]

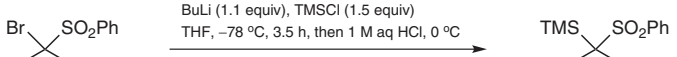
10% Na/Hg (ca. 3.6 mmol Na) was added under N_2 to a 10-mL flask containing **5A** (R^1 = Ph; R^2 = H; 180 mg, 0.45 mmol) and Na_2HPO_4 (510 mg, 3.6 mmol) in anhyd MeOH (5 mL) at −20 °C. The mixture was stirred at −20 to −10 °C for 1 h and then the liquid phase was decanted, and most of the organic phase was removed under reduced pressure. Brine (20 mL) was added and the mixture was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$), and the solvent was removed to give the intermediate product without further purification. The intermediate product was redissolved in anhyd MeOH (5 mL) and a 4 M soln of HCl in 1,4-dioxane (1 mL) was added. After the mixture had been stirred at rt for 30 min, it was concentrated to near dryness, and Et_2O was added to precipitate out the

amine hydrochloride. The precipitate was collected by filtration and washed with Et_2O to provide pure amine hydrochloride **6** (R^1 = Ph; R^2 = H) as a white solid; yield: 72 mg [83% (79% from **4**)]; $[\alpha]_D^{25}$ +25.4 (*c* 1.0, MeOH). The reductive desulfonylation can also be performed using magnesium (see Section 2.6.2.1.1.3).

2.6.2.1.1.3 Using [Difluoro(phenylsulfonyl)methyl]trimethylsilane

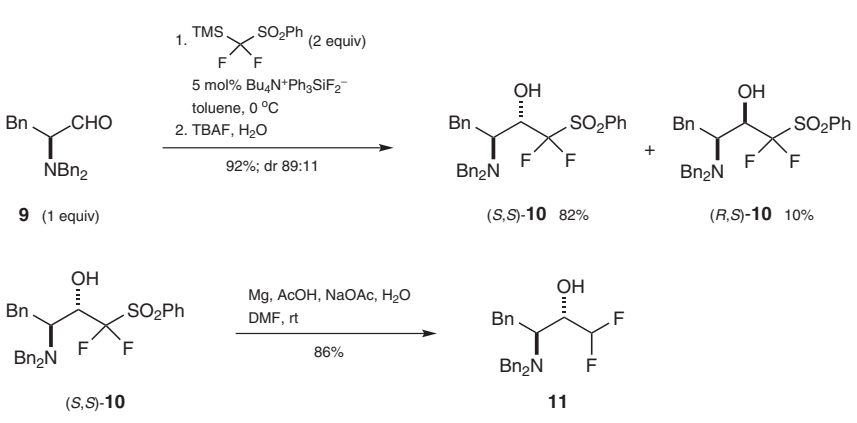
[Difluoro(phenylsulfonyl)methyl]trimethylsilane, which is prepared in good yield from bromodifluoromethyl phenyl sulfone by bromo–lithium exchange followed by reaction with chlorotrimethylsilane (Scheme 7),[29] is a much milder difluoro(phenylsulfonyl)methylation reagent than difluoromethyl phenyl sulfone. Under the action of Lewis bases such as tetrabutylammonium triphenyldifluorosilicate, potassium fluoride, potassium hydrogen difluoride, and potassium carbonate, the difluoro(phenylsulfonyl)methyl group can be transferred to carbonyl compounds,[27,29] alkyl halides,[30] and nonactivated imines.[31–33]

Scheme 7 Preparation of [Difluoro(phenylsulfonyl)methyl]trimethylsilane[29]



The nucleophilic difluoromethylation of carbonyl compounds using [difluoro(phenylsulfonyl)methyl]trimethylsilane avoids the use of an excess of the carbonyl compound, and is thus rather effective for enolizable aldehydes. Diastereoselective difluoromethylation of α-amino aldehydes such as **9** can be achieved using this protocol to give difluoro(phenylsulfonyl)methyl-substituted 1,2-amino alcohols (e.g., **10**), which are otherwise difficult to prepare from difluoromethyl phenyl sulfone. The corresponding difluoromethyl 1,2-amino alcohols (e.g., **11**) are obtained by desulfonylation with magnesium (Scheme 8).[29]

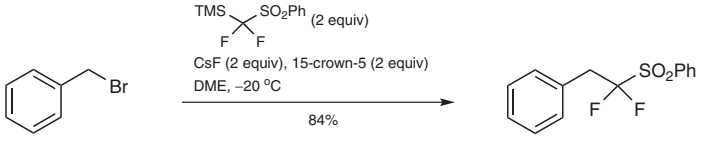
Scheme 8 Nucleophilic Difluoromethylation of an Enolizable Aldehyde Using [Difluoro(phenylsulfonyl)methyl]trimethylsilane[29]



Nucleophilic difluoro(phenylsulfonyl)methylation of primary alkyl iodides and bromides, can be accomplished without the formation of *gem*-difluoroalkenes by using cesium fluoride/15-crown-5 as an initiating system in 1,2-dimethoxyethane. The amount of 15-crown-5 is critical to the yield of the product (Scheme 9).[30]

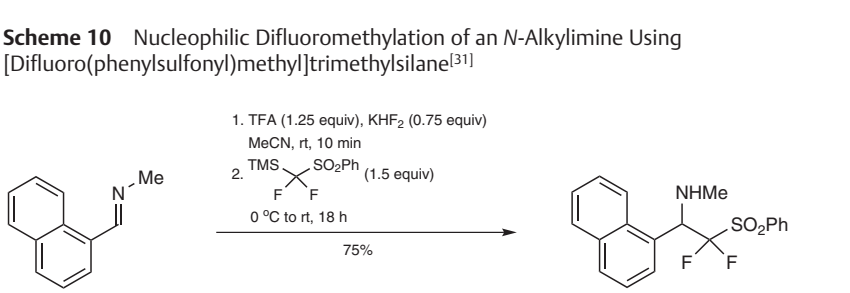
for references see p 455

Scheme 9 Nucleophilic Difluoro(phenylsulfonyl)methylation of a Primary Alkyl Halide Using [Difluoro(phenylsulfonyl)methyl]trimethylsilane[30]



N-Alkylimines, *N*,*N*-dialkyl enamines, *N*,*N*-acetals, and heterocycles, such as dihydroisoquinolines, quinolines, and pyridines, are unreactive toward nucleophilic fluoroalkylation reagents under conventional Lewis basic conditions. After being activated with a Brønsted acid such as trifluoroacetic acid[31,33] or alkylating agents such as methyl trifluoromethanesulfonate,[32] their reaction with [difluoro(phenylsulfonyl)methyl]trimethylsilane under the activation of a Lewis base affords the addition products in good yields.[31–33] For example, the difluoro(phenylsulfonyl)methylation of *N*-(naphthalen-1-ylmethylene)-methanamine (**12**) followed by desulfonylation gives α-difluoromethyl amine **13** in 65% overall yield (Scheme 10).[31]

Scheme 10 Nucleophilic Difluoromethylation of an *N*-Alkylimine Using [Difluoro(phenylsulfonyl)methyl]trimethylsilane[31]



(2*S*,3*S*)- and (2*R*,3*S*)-3-(Dibenzylamino)-1,1-difluoro-4-phenyl-1-(phenylsulfonyl)butan-2-ol [(*S*,*S*)- and (*R*,*S*)-10]; Typical Procedure:[29]

A soln of [difluoro(phenylsulfonyl)methyl]trimethylsilane (265 mg, 1.0 mmol) in toluene (4 mL) was added to a soln of (2*S*)-2-(dibenzylamino)-3-phenylpropanal (**9**; 165 mg, 0.5 mmol) and tetrabutylammonium triphenyldifluorosilicate (14 mg, 0.025 mmol) in toluene (6 mL) at 0 °C under N_2. The mixture was then stirred at 0 °C for about 10 h. Subsequently, TBAF (1.0 mmol) was added, and the mixture was stirred at rt for 1 h. The reaction was quenched by addition of sat. brine (10 mL). After the mixture had been warmed to rt, it was extracted with Et_2O (3 × 25 mL), and the combined organic phase was washed with brine and dried ($MgSO_4$). The solvents were removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, petroleum ether/EtOAc 12:1) to give as white solids (*S*,*S*)-**10**; yield: 212 mg (82%); mp 42–44 °C; $[\alpha]_D^{25}$ +20.50 (*c* 0.93, $CHCl_3$); and (*R*,*S*)-**10**; yield: 27 mg (10%); mp 136–138 °C; $[\alpha]_D^{25}$ +25.68 (*c* 1.07, $CHCl_3$).

(2*S*,3*S*)-3-(Dibenzylamino)-1,1-difluoro-4-phenylbutan-2-ol (11); Typical Procedure:[29]

Into a 100-mL Schlenk flask containing (*S*,*S*)-**10** (522 mg, 1.0 mmol) in DMF (10 mL) at rt was added AcOH/NaOAc (1:1) buffer soln (8 mol/L; 6 mL). Mg turnings (360 mg, 15 mmol) were added in portions, and the mixture was stirred at rt for 3 h followed by addition of

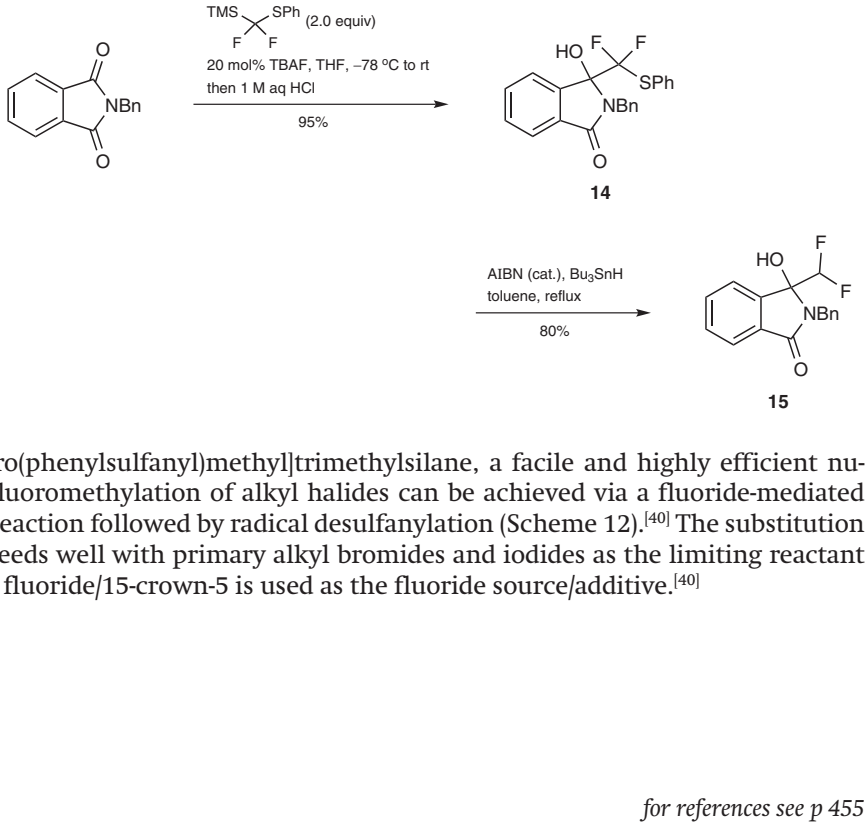
H_2O (30 mL). The mixture was extracted with Et_2O (3 × 20 mL), and the combined organic phases were washed with sat. aq $NaHCO_3$ and brine, and dried ($MgSO_4$). After removal of Et_2O, the crude product was purified by column chromatography (silica gel, petroleum ether/EtOAc 15:1) to give the product as a colorless liquid; yield: 328 mg (86%); $[\alpha]_D^{24}$ +3.95 (*c* 1.08, $CHCl_3$).

2.6.2.1.1.4 Using [Difluoro(phenylsulfanyl)methyl]trimethylsilane

Nucleophilic difluoro(phenylsulfanyl)methylation is another effective method for the introduction of difluoromethyl groups into carbonyl compounds,[34–38] imines,[32,39] enamines,[31] and alkyl halides;[40] however, unpleasant-smelling, toxic tributylstannane has to be used to remove the phenylsulfanyl group. Under radical conditions, the difluoro(phenylsulfanyl)methyl compounds containing vinyl functional groups may form five- or six-membered rings via intramolecular cyclization rather than the desired difluoromethyl compounds.[37,38]

[Difluoro(phenylsulfanyl)methyl]trimethylsilane, which is readily prepared from bromodifluoromethyl phenyl sulfide, magnesium, and chlorotrimethylsilane in dimethylformamide via a Barbier coupling process,[10] can serve as an efficient difluoro(phenylsulfanyl)methylation reagent. Not only a variety of simple aldehydes and ketones[35] but also functionalized carbonyl compounds such as α- and γ-oxo esters[36] and cyclic imides can be difluoro(phenylsulfanyl)methylated in high yields under the activation of a catalytic amount of a Lewis base.[37] For example, using this protocol, 2-benzyl-3-(difluoromethyl)-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one (**15**) is synthesized in good yield from *N*-benzylphthalimide via 2-benzyl-3-[difluoro(phenylsulfanyl)methyl]-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one (**14**) (Scheme 11).[37]

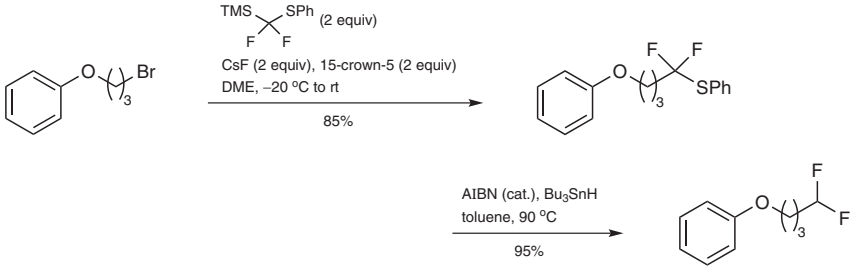
Scheme 11 Nucleophilic Difluoromethylation of a Phthalimide Using [Difluoro(phenylsulfanyl)methyl]trimethylsilane[37]



Using [difluoro(phenylsulfanyl)methyl]trimethylsilane, a facile and highly efficient nucleophilic difluoromethylation of alkyl halides can be achieved via a fluoride-mediated substitution reaction followed by radical desulfanylation (Scheme 12).[40] The substitution reaction proceeds well with primary alkyl bromides and iodides as the limiting reactant when cesium fluoride/15-crown-5 is used as the fluoride source/additive.[40]

for references see p 455

Scheme 12 Nucleophilic Difluoromethylation of a Primary Alkyl Halide Using [Difluoro(phenylsulfanyl)methyl]trimethylsilane[40]



2-Benzyl-3-[difluoro(phenylsulfanyl)methyl]-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one (14); Typical Procedure:[37]

To a mixture of $TMSCF_2SPh$ (0.928 g, 4 mmol) and *N*-benzylphthalimide (0.470 g, 2 mmol) in THF (5 mL) was added a 1 M soln of TBAF in THF (0.4 mL, 0.4 mmol). The mixture was stirred at −78 °C followed by slowly warming up to rt overnight. The soln was quenched with 1 M aq HCl (3 mL), and the mixture was extracted with EtOAc (3 × 25 mL). The organic phase was washed successively with H_2O and brine, dried (Na_2SO_4), and the solvent was removed under reduced pressure. Purification of the residue by radial chromatography (silica gel, hexanes/EtOAc 9:1 to 4:1) afforded the product as white crystals; yield: 0.753 g (95%); mp 142–144 °C.

2-Benzyl-3-(difluoromethyl)-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one (15); Typical Procedure:[37]

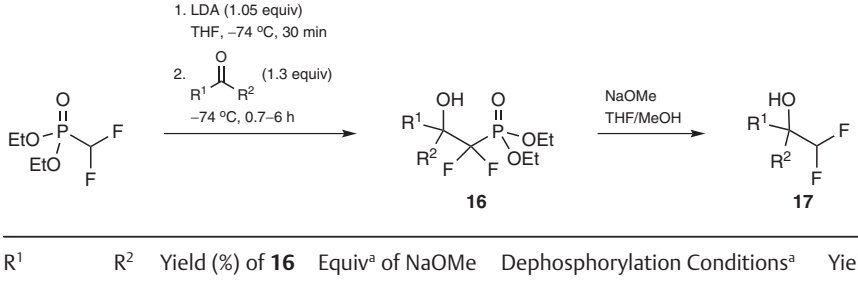
Argon was bubbled through a soln of **14** (0.397 g, 1 mmol) in toluene (5 mL) for 30 min and Bu_3SnH (0.47 mL, 1.75 mmol) was added. Deoxygenation was continued for 5 min. AIBN (25 mg, 0.15 mmol) was added and the soln was refluxed for 5 h. Volatiles were removed and the residue was dissolved in EtOAc (5 mL). The soln was stirred overnight with KF/H_2O (30 mg/0.3 mL), and extracted with EtOAc (3 × 20 mL). The organic phase was washed successively with H_2O and brine, dried (Na_2SO_4), and the solvent was removed under reduced pressure. Purification of the residue by radial chromatography (silica gel, hexanes/EtOAc 100:0 to 4:1) afforded the product as a white solid; yield: 0.232 g [80% (76% from *N*-benzylphthalimide)]; mp 123–126 °C.

2.6.2.1.1.5 Using (Difluoromethyl)phosphonates and Their Derivatives

Similar to difluoromethyl phenyl sulfone and its derivatives, (difluoromethyl)phosphonates and their derivatives can also function as nucleophilic difluoromethylation reagents. (Dialkoxyphosphoryl)difluoromethyl anions, which are more stable than the difluoro(phenylsulfonyl)methyl anion, can be pregenerated at −78 °C, and thus facilitate the difluoromethylation of base-sensitive electrophiles such as enolizable aldehydes. Diethyl (difluoromethyl)phosphonate/lithium diisopropylamide,[41–46] diethyl [bromo(difluoro)methyl]phosphonate/Grignard reagent,[47] and diisopropyl [difluoro(methylsulfanyl)methyl]phosphonate/*tert*-butyllithium[48] are commonly used to generate (dialkoxyphosphoryl)difluoromethyl anions. Furthermore, diethyl difluoro(trimethylsilyl)methylphosphonate is also well-recognized in the nucleophilic (diethoxyphosphoryl)difluoromethylation of aldehydes and ketones under the action of Lewis bases such as tetrabutylammonium fluoride.[49] A comprehensive review on fluorinated phosphonates covers the synthesis of α,α-difluorinated phosphonates using various (dialkoxyphosphoryl)difluoromethyl anions.[50]

Nucleophilic (diethoxyphosphoryl)difluoromethylation has been most often used for the synthesis of biologically important α,α-difluorinated phosphoric acids,[50] whereas its application in the synthesis of difluoromethyl compounds via dephosphorylation is rare. The seminal reaction is the rearrangement of intermediate lithium 1-aryl-2-(diethoxyphosphoryl)-2,2-difluoroethanolate adducts derived from aromatic aldehydes to 1-aryl-2,2-difluoroethyl diethyl phosphates;[41] however, in most cases, the Wadsworth–Horner–Emmons alkenation is the main reaction. Later, an effective rearrangement of various (diethoxyphosphoryl)difluoromethyl alcohols to difluoromethyl-containing phosphates was developed using potassium carbonate as the base.[42] When sodium methoxide is used as the dephosphorylation reagent, the fluoroalkylation of various aldehydes and ketones affords difluoromethylated alcohols **17** via β-hydroxy-substituted phosphonates **16** in moderate to good overall yields (Scheme 13).[43]

Scheme 13 Nucleophilic Difluoromethylation of Various Aldehydes and Ketones Using Diethyl (Difluoromethyl)phosphonate[43]



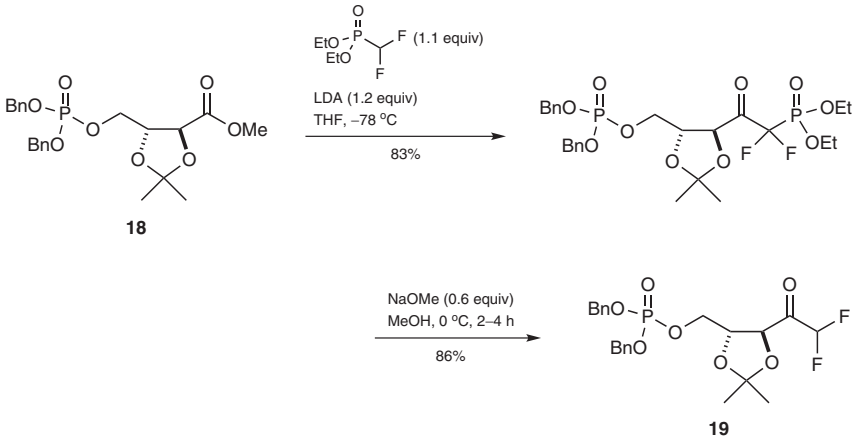
R^1	R^2	Yield (%) of **16**	Equiv[a] of NaOMe	Dephosphorylation Conditions[a]	Yield[a] (%) of **17**	Ref
Ph	H	93	1.5	rt, 1 h	83	[43]
$(CH_2)_2Ph$	H	81	2	30 °C, 2 h	90	[43]
Ph	Ph	60	2	rt, 1 h	86	[43]
Ph	Me	76	4	40 °C, 1 h	82	[43]
Me	Me	80	n.r.	n.r.	n.r.	[43]

[a] n.r. = not reported.

Dephosphorylation of (diethoxyphosphoryl)difluoromethyl ketones, prepared by oxidation of secondary difluoro(phosphoryl)methyl alcohols or difluoro(phosphoryl)methylation of acyclic methyl esters, is an effective method for the synthesis of difluoromethyl ketones.[44–46] For example, 1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-xylulose dibenzyl phosphate (**19**) can be prepared in 71% yield from the corresponding methyl ester **18** using a similar procedure to that used for the preparation of difluoromethyl-substituted alcohols (Scheme 14).[46]

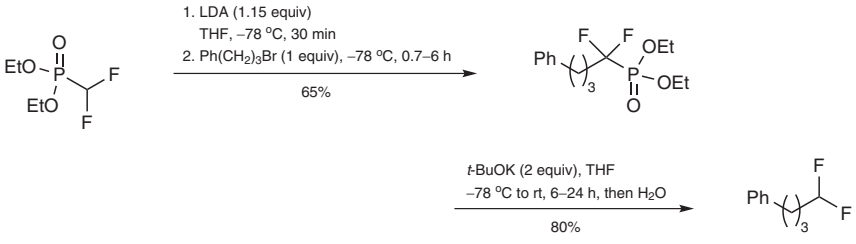
for references see p 455

Scheme 14 Nucleophilic Difluoromethylation of an Ester Using Diethyl (Difluoromethyl)phosphonate[46]



Nucleophilic substitution of primary alkyl bromides followed by hydrodephosphorylation with potassium *tert*-butoxide can afford 1,1-difluoroalkanes (Scheme 15).[42] Although only three examples are available, this transformation sets up the possibility for the dephosphorylation of many other simple difluoro(phosphoryl)methyl compounds such as difluoro(phosphoryl)methyl-substituted aromatic compounds.

Scheme 15 Nucleophilic Difluoromethylation of a Primary Alkyl Bromide Using Diethyl (Difluoromethyl)phosphonate[42]



Diethyl (1,1-Difluoro-2-hydroxy-2-phenylethyl)phosphonate (16, **R^1 = Ph; R^2 = H); Typical Procedure:**[43]

A 1.5 M soln of BuLi in cyclohexane (8.6 mL, 12.84 mmol) was added dropwise to a stirred soln of iPr_2NH (1.80 mL, 12.84 mmol) in THF (30 mL) cooled to 0 °C. The mixture was stirred at 0 °C for 20 min and then cooled to −74 °C. A soln of diethyl (difluoromethyl)phosphonate (2.3 g, 12.23 mmol) in THF (8 mL) was added dropwise, followed by stirring at this temperature for 30 min. A soln of PhCHO (1.69 g, 15.9 mmol) in THF (5 mL) was added, and the mixture was stirred for 2 h at −74 °C before it was warmed up to 0 °C over 10 min. Sat. aq NH_4Cl (20 mL) was added. The product was extracted into EtOAc or Et_2O (4 × 40 mL). The combined organic extracts were washed with sat. brine (10 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. Purification of the residue by column chromatography (silica gel, EtOAc/hexanes 35:65 to 50:50) afforded the product as a white solid; yield: 3.35 g (93%); mp 74–75 °C.

2,2-Difluoro-1-phenylethanol (17, **R^1 = Ph; R^2 = H); Typical Procedure:**[43]

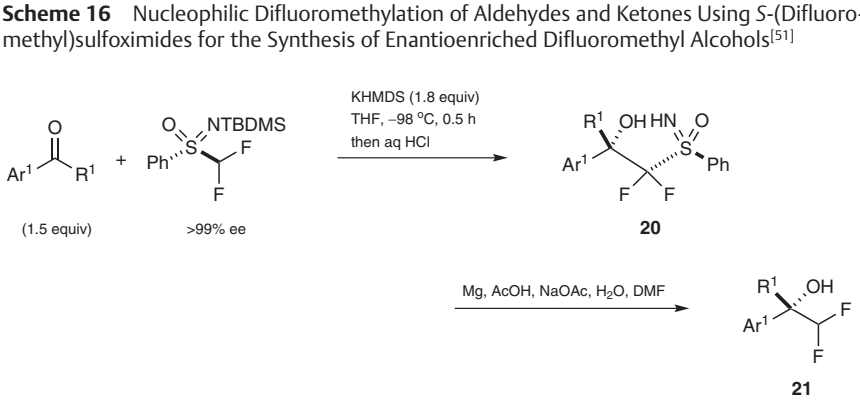
A 4 M soln of NaOMe in MeOH (0.19 mL, 0.75 mmol) was added to a soln of phosphonate **16** (R^1 = Ph; R^2 = H; 148 mg, 0.5 mmol) in THF (8 mL). The mixture was stirred at rt for 1 h

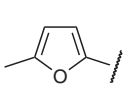
followed by the addition of sat. NH_4Cl (10 mL). The product was extracted into EtOAc (4 × 15 mL). The combined organic extracts were washed with sat. brine (6 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. Purification of the residue by column chromatography (silica gel, Et_2O/hexanes 15:85) afforded the product as a colorless oil; yield: 66 mg (83%).

2.6.2.1.1.6 Using *S*-(Difluoromethyl)sulfoximides

Diastereoselective nucleophilic difluoromethylation can be realized using chiral reagents such as *S*-(difluoromethyl)sulfoximides. Among various N-substituted *S*-(difluoromethyl)-sulfoximides, *N*-(*tert*-butyldimethylsilyl)-*S*-(difluoromethyl)-*S*-phenylsulfoximide is a good nucleophilic difluoromethylation reagent for electrophiles such as aldehydes and ketones.[51] Using the (*R*)-isomer of the sulfoximide as the limiting reagent, difluoro(phenylsulfonimidoyl)methylation of 1.5 equivalents of the carbonyl compound leads to adducts **20** in high yields with moderate to good diastereoselectivity (Scheme 16).[51] After separation of the major diastereomers and reductive desulfonimidoylation with magnesium, difluoromethyl alcohols **21** are obtained with high enantiopurity.[51] This method is useful for the synthesis of enantioenriched difluoromethyl alcohols, especially the tertiary alcohols.

Scheme 16 Nucleophilic Difluoromethylation of Aldehydes and Ketones Using *S*-(Difluoromethyl)sulfoximides for the Synthesis of Enantioenriched Difluoromethyl Alcohols[51]



Ar^1	R^1	dr[a]	Yield[b] (%)		Ref
			20	**21**	
Ph	Me	93:7	88	77[c]	[51]
Ph	Pr	93:7	86	83	[51]
3-$MeOC_6H_4$	Me	93:7	70	90	[51]
	Me	87:13	62	84	[51]
4-BrC_6H_4	H	80:20	65	68	[51]

[a] Determined by ^{19}F NMR analysis of the crude products.
[b] Isolated yield of the major diastereomer.
[c] >99% ee.

(R_S,2*S*)-1,1-Difluoro-2-phenyl-1-(*S*-phenylsulfonimidoyl)propan-2-ol (20, Ar^1 = Ph; R^1 = Me); Typical Procedure:[51]

A 1.0 M soln of KHMDS in THF (1.8 mL, 1.8 mmol) was added slowly to a soln of acetophenone (180 mg, 1.5 mmol) and (*R*)-*N*-(*tert*-butyldimethylsilyl)-*S*-(difluoromethyl)-*S*-phenyl-

for references see p 455

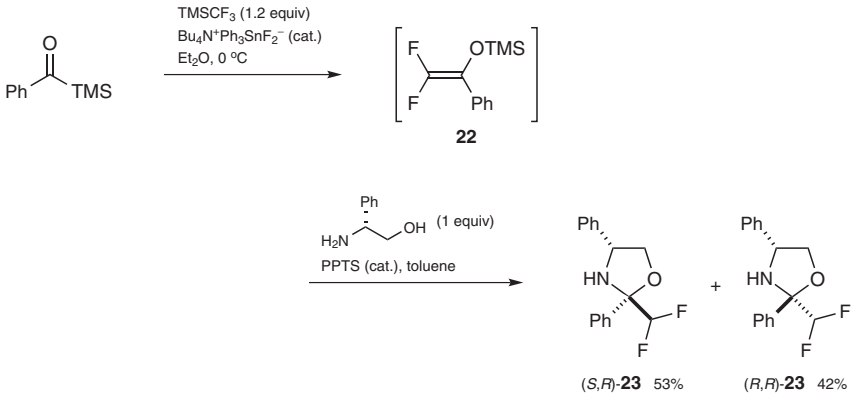
sulfoximide (>99% ee; 305 mg, 1 mmol) in THF (6 mL) at −98 °C under N_2. After 30 min, 12 M aq HCl (1.5 mL, 18 mmol) was added to quench the reaction. After the mixture had been stirred at rt for 30 min, it was neutralized with 20% aq NaOH. The mixture was extracted with EtOAc and the organic phase was washed with brine, dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel, petroleum ether/EtOAc 8:1) to give the major diastereomer as a white solid; yield: 273 mg (88%); mp 168–170 °C; $[\alpha]_D^{28}$ −37.1 (*c* 0.52, $CHCl_3$).

(2*S*)-1,1-Difluoro-2-phenylpropan-2-ol (21, Ar[1] = Ph; R[1] = Me); Typical Procedure:[51]
Mg turnings (180 mg, 7.5 mmol) were added to a soln of alcohol **20** (Ar^1 = Ph; R^1 = Me; 155 mg, 0.5 mmol) in DMF (5 mL) and NaOAc/AcOH/H_2O buffer soln (8 M; 3.6 mL) at rt in several portions. The mixture was stirred overnight and the reaction was quenched with sat. aq NH_4Cl (20 mL). The mixture was extracted with EtOAc (3 × 20 mL) and the collected organic phases were washed with brine, dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc 20:1) to give the product as a colorless oil; yield: 66 mg (77%); $[\alpha]_D^{21}$ −13.0 (*c* 1.0, $CHCl_3$).

2.6.2.1.1.7 Using Trimethyl(trifluoromethyl)silane

The reaction between acylsilanes and trimethyl(trifluoromethyl)silane under the activation of tetrabutylammonium difluoro(triphenyl)stannate provides silyl difluoroenol ethers in good to excellent yields.[52,53] Both aryl silyl ketones and alkyl silyl ketones are suitable substrates. The reaction involves a domino sequence of nucleophilic trifluoromethylation–Brook rearrangement–fluoride elimination. The silyl enol ethers can be readily converted into difluoromethyl ketones by a fluoride-mediated desilylative hydrolysis.[52,54] The silyl enol ethers can also be used as difluoromethyl ketone equivalents to undergo further transformation. For example, the reaction of silyl enol ether **22** with (*R*)-phenylglycinol gives 2-(difluoromethyl)oxazolidine **23** as two diastereomers in excellent yield (Scheme 17).[53]

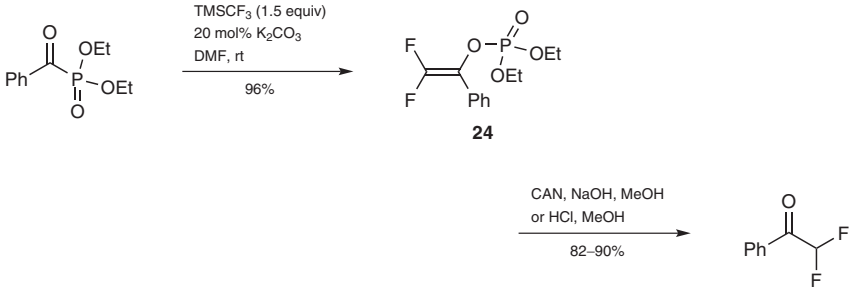
Scheme 17 Nucleophilic Difluoromethylation of a Silyl Ketone Using Trimethyl(trifluoromethyl)silane[53]



Similar to acylsilanes, the trifluoromethylation of various benzoylphosphonates with trimethyl(trifluoromethyl)silane under the activation of potassium carbonate affords 2,2-difluorovinyl phosphates such as **24** in excellent yields after rearrangement and fluoride elimination (Scheme 18); further conversion using hydrogen chloride hydrolysis or am-

monium cerium(IV) nitrate mediated oxidation gives aryl difluoromethyl ketones in high yields.[55]

Scheme 18 Nucleophilic Difluoromethylation of a Benzoylphosphonate Using Trimethyl(trifluoromethyl)silane[55]



(2*S*,4*R*)- and (2*R*,4*R*)-2-Difluoromethyl-2,4-diphenyloxazolidine [(*S*,*R*)- and (*R*,*R*)-23]; Typical Procedure:[53]

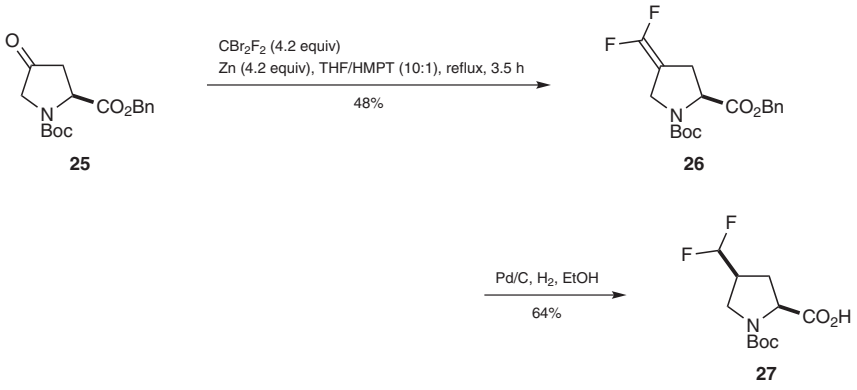
To a stirred soln of benzoyltrimethylsilane (1.07 g, 6.0 mmol) in Et_2O (15 mL) at 0 °C were added $TMSCF_3$ (1.05 g, 7.4 mmol) and tetrabutylammonium difluoro(triphenyl)stannate (34 mg, 0.054 mmol). After complete conversion, as determined by GC, the resulting mixture was filtered and the filtrate was concentrated to afford [(2,2-difluoro-1-phenylvinyl)oxy]trimethylsilane (**22**; 1.37 g), which was dissolved in toluene (40 mL). (*R*)-Phenylglycinol (0.83 g, 6.0 mmol) and PPTS (0.15 g, 0.60 mmol) were added, and the mixture was heated to reflux using a Dean–Stark apparatus for 24 h under argon and then cooled to 0 °C with an ice bath. The resulting mixture was filtered on Celite, and the toluene was removed under reduced pressure. Separation by flash column chromatography (silica gel, petroleum ether/EtOAc 19:1) afforded as yellow oils (*S*,*R*)-**23**; yield: 0.87 g (53%); $[\alpha]_D^{20}$ +14.7 (*c* 0.74, $CHCl_3$); and (*R*,*R*)-**23**; yield: 0.70 g (42%); $[\alpha]_D^{20}$ −86.8 (*c* 0.84, $CHCl_3$).

2.6.2.1.1.8 Using Difluoromethylenation Reagents

The reductive hydrogenation of *gem*-difluoroalkenes is a useful method for constructing difluoromethyl-bearing tertiary carbon centers. A full summary of the synthesis of *gem*-difluoroalkenes is reported in a review published in 2012.[56] The difluoromethylenation of ketones followed by hydrogenation has found application in the synthesis of complex molecules.[57–59] For example, treatment of 4-oxopyrrolidine-2-carboxylate **25** with dibromo(difluoro)methane/zinc/hexamethylphosphorous triamide gives 4-(difluoromethylene)pyrrolidine-2-carboxylate **26** in 48% yield, and pyrrolidine **26** can be further hydrogenated to give 4-(difluoromethyl)pyrrolidine-2-carboxylic acid **27** in 64% yield (Scheme 19).[57]

for references see p 455

Scheme 19 Difluoromethylation of a Ketone Using Nucleophilic Difluoromethylenation Followed by Hydrogenation[57]



Benzyl (2*S*)-1-(*tert*-Butoxycarbonyl)-4-(difluoromethylene)pyrrolidine-2-carboxylate (26); Typical Procedure:[57]

CBr_2F_2 (0.30 mL, 3.06 mmol) and HMPT (0.54 mL, 3.06 mmol) were added to a soln of benzyl (2*S*)-1-(*tert*-butoxycarbonyl)-4-oxopyrrolidine-2-carboxylate (**25**; 229 mg, 0.72 mmol) in THF (7 mL) at 0 °C. The mixture was allowed to warm to rt, and Zn dust (200 mg, 3.06 mmol) and HMPT (40 μL) were added. After the mixture had been refluxed for 3.5 h, H_2O (20 mL) and Et_2O (20 mL) were added, and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with sat. aq $CuSO_4$, H_2O, and brine, and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc 30:1) to give the product as a colorless oil; yield: 122 mg (48%); $[\alpha]_D^{20}$ −25.1 (*c* 1.96, $CHCl_3$).

(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-(difluoromethyl)pyrrolidine-2-carboxylic Acid (27); Typical Procedure:[57]

To a soln of pyrrolidine-2-carboxylate **26** (321 mg, 0.91 mmol) in EtOH (20 mL) was added 10% Pd/C (520 mg) and the mixture was hydrogenated at rt overnight. After filtration and removal of EtOH under reduced pressure, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc 1:1) to give the product as a white solid; yield: 155 mg (64%); mp 96.5–98.5 °C; $[\alpha]_D^{20}$ −77.6 (*c* 0.56, $CHCl_3$).

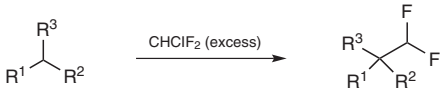
2.6.2.1.2 Electrophilic Difluoromethylation

It has been proposed that difluoromethylation of carbon nucleophiles with chloro(difluoro)methane,[2,60] bromo(difluoro)methane,[2] *S*-(difluoromethyl)sulfoximides,[61] tributyl(difluoromethyl)ammonium salts,[62] and *S*-[bromo(difluoro)methyl]sulfonium salts,[63] involves the transfer of a difluorocarbene to the nucleophile. Difluoromethylation of enolates with trifluoromethane[64] and trifluoro(iodo)methane[65] is proposed to proceed by direct electrophilic attack of the enolate on the fluorinated carbon. 3,3-Dimethyl-1-[difluoro(phenylsulfonyl)methyl]-1,2-benziodoxole is known to be an electrophilic difluoro(phenylsulfonyl)methylation reagent.[66,67] Therefore, all of the above-mentioned carbon difluoromethylation reactions are classified as electrophilic difluoromethylations.

2.6.2.1.2.1 Using Chloro(difluoro)methane and Bromo(difluoro)methane

Chloro(difluoro)methane is the most frequently used difluorocarbene reagent for the direct incorporation of a difluoromethyl group into various nucleophiles.[2] However, difluoromethylation of carbon nucleophiles is generally more difficult than difluoromethylation of oxygen, nitrogen, and sulfur nucleophiles, and it has been found that the CH acidity of the carbon nucleophile plays an important role in the carbon difluoromethylation reaction.[2] Some activated carbon acids **28** are difluoromethylated in moderate yields using an excess of chloro(difluoro)methane under the action of a base (Scheme 20).[68–74] The so-obtained difluoromethyl compounds **29** are useful for the synthesis of bioactive α-difluoromethyl amino acids.[68–70,74]

Scheme 20 Electrophilic Difluoromethylation of Various Carbon Acids Using Chloro(difluoro)methane[68–74]

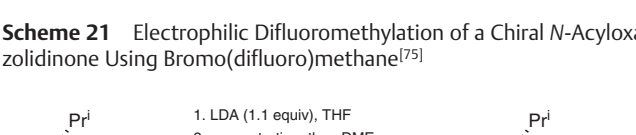


28 **29**

R^1	R^2	R^3	Conditions	Yield (%)	Ref
$(CH_2)_2CH{=}CH_2$	CO_2Me	N=CHPh	NaH (1.05 equiv), THF, 50 °C	69	[68,69]
$(CH_2)_3NC$	CO_2Me	NC	NaH (2 equiv), DMF, 10 °C to rt, 4 d	40	[70]
CO_2Et	CO_2Et	SMe	*t*-BuOK, THF, 10 °C	42	[71,72]
Ph	Ph	CN	50% aq NaOH (3 equiv), TEBAC (5 mol%), benzene, rt, 6 h	43	[73]
CO_2Me	CO_2Me	NHAc	$(Et_2N)_3P{=}NMe$ (4 equiv), CH_2Cl_2, −35 °C to rt	69	[74]

When a chiral auxiliary is attached to the carbonyl group, the difluoromethylation can proceed diastereoselectively. For example, difluoromethylation of the lithium enolate derived from *N*-acyloxazolidinone **30** using bromo(difluoro)methane affords α-difluoromethyl amide **31** as the major diastereomer (Scheme 21).[75]

Scheme 21 Electrophilic Difluoromethylation of a Chiral *N*-Acyloxazolidinone Using Bromo(difluoro)methane[75]

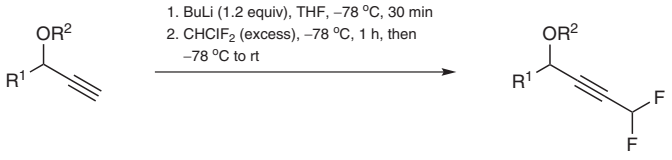


30 **31**

Terminal alkynes can also be difluoromethylated by carbene reagents. The reaction of chloro(difluoro)methane with various acetylides derived from the corresponding propargylic ethers (Scheme 22) or phenylacetylene proceeds smoothly to afford difluoromethyl compounds (e.g., **32**) in high yields without detectable byproducts. The use of other acetylenes such as dec-1-yne results in a mixture of the difluoromethylated acetylene and unknown byproducts.[76]

for references see p 455

Scheme 22 Electrophilic Difluoromethylation of Terminal Alkynes Using Chloro(difluoro)methane[76]



32

R^1	R^2	Yield (%)	Ref
H	Bn	72	[76]
CH_2OBn	TBDMS	98	[76]
$(CH_2)_4Me$	TBDMS	94	[76]

Methyl 2-[(*E*)-(Benzylideneamino)]-2-(difluoromethyl)hex-5-enoate [29, $R^1 = (CH_2)_2CH{=}CH_2$; $R^2 = CO_2Me$; $R^3 = N{=}CHPh$]; Typical Procedure:[68]

A soln of **28** [$R^1 = (CH_2)_2CH{=}CH_2$; $R^2 = CO_2Me$; $R^3 = N{=}CHPh$; 11.10 g, 0.048 mol] in THF (20 mL) was added to a suspension of NaH (45% dispersion in oil; 2.66 g, 0.050 mol; washed three times with pentane) in THF (80 mL) under N_2. After the mixture had been heated at 50 °C for 2.5 h, a stream of $CHClF_2$ was rapidly bubbled through the soln maintained at 50 °C. H_2O was added and the solvent was removed under reduced pressure, yielding an oil, which was dissolved in Et_2O. The organic layer was washed with H_2O and brine, and dried ($MgSO_4$). Concentration under reduced pressure and distillation gave the product as a colorless oil; yield: 9.35 g (69%); bp 155 °C/0.075 Torr (Kugelrohr).

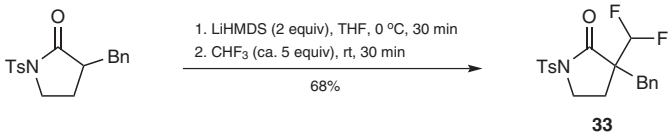
Benzyl 4,4-Difluorobut-2-ynyl Ether (32, $R^1 = H$; $R^2 = Bn$); Typical Procedure:[76]

To a soln of 3-(benzyloxy)prop-1-yne (146 mg, 1 mmol) in THF (1 mL) was added BuLi (1.2 mmol) at −78 °C. The mixture was then stirred at that temperature for 30 min. After an excess of $CHClF_2$ was added, the mixture was stirred for 1 h at −78 °C and then gradually warmed to rt. After the reaction had been quenched with sat. aq NH_4Cl, the organic material was extracted with Et_2O. The extract was washed with H_2O and sat. aq NH_4Cl, dried ($MgSO_4$), concentrated, and purified by chromatography (silica gel); yield: 141 mg (72%).

2.6.2.1.2.2 Using Trifluoromethane

The direct difluoromethylation of lithium enolates derived from ketones, esters, and amides using trifluoromethane gives α-difluoromethyl products (e.g., **33**) in moderate to good yields.[64] Among various bases used for the generation of the enolates, only lithium hexamethyldisilazanide works for this α-difluoromethylation. Moreover, the amount of the base used is crucial for the reaction; two equivalents (relative to esters and amides) gives the highest yields (Scheme 23).[64]

Scheme 23 Electrophilic Difluoromethylation of an Amide Using Trifluoromethane[64]



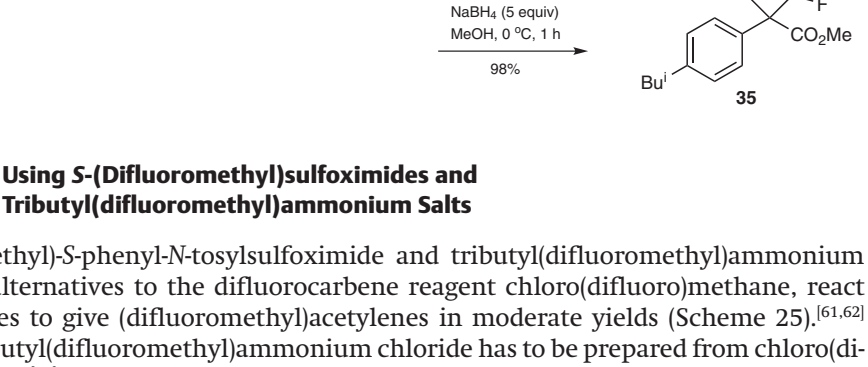
33

3-Benzyl-3-(difluoromethyl)-1-tosylpyrrolidin-2-one (33); Typical Procedure:[64]
To a 1.0 M soln of LiHMDS in THF (0.3 mL, 0.3 mmol) was added 3-benzyl-1-tosylpyrrolidin-2-one (50 mg, 0.15 mmol) in THF (0.3 mL) at −78 °C under argon. The mixture was then stirred at 0 °C for 30 min. To the mixture was added CHF_3 (ca. 1.5 mmol) at −95 °C. After the mixture had been stirred at rt for 30 min, it was poured into a mixture of H_2O and EtOAc. The aqueous layer was extracted with EtOAc, the combined organic layers were washed with H_2O and brine, dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification of the residue by column chromatography (silica gel, EtOAc/hexane 1:19) afforded the product; yield: 39 mg (68%).

2.6.2.1.2.3 Using Trifluoro(iodo)methane

Trifluoro(iodo)methane can undergo C—F bond cleavage to serve as a difluoro(iodo)methylation reagent. The reaction between trifluoro(iodo)methane and lithium enolates derived from ketones, esters, and *N*-tosyl amides under the action of lithium hexamethyldisilazanide or butyllithium gives difluoro(iodo)methyl products in moderate to good yields. The hydrodeiodination of difluoro(iodo)methyl compounds such as **34** gives the difluoromethyl compounds such as **35** in high yield (Scheme 24).[65] The nature of the secondary amine derived from the lithium amide source affects the reactivity of the lithium enolates: for example, diisopropylamine significantly retards the α-difluoro(iodo)methylation and, in contrast, hexamethyldisilazane does not affect the yield in this α-difluoromethylation at all.[65]

Scheme 24 Electrophilic Difluoromethylation of an Ester Using Trifluoro(iodo)methane[65]

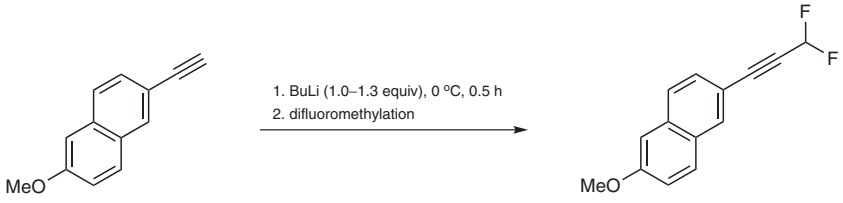


2.6.2.1.2.4 Using *S*-(Difluoromethyl)sulfoximides and Tributyl(difluoromethyl)ammonium Salts

S-(Difluoromethyl)-*S*-phenyl-*N*-tosylsulfoximide and tributyl(difluoromethyl)ammonium chloride, as alternatives to the difluorocarbene reagent chloro(difluoro)methane, react with acetylides to give (difluoromethyl)acetylenes in moderate yields (Scheme 25).[61,62] However, tributyl(difluoromethyl)ammonium chloride has to be prepared from chloro(difluoro)methane.[62]

for references see p 455

Scheme 25 Electrophilic Difluoromethylation of an Acetylene Using an *S*-(Difluoromethyl)sulfoximide and a Tributyl(difluoromethyl)ammonium Salt[61,62]

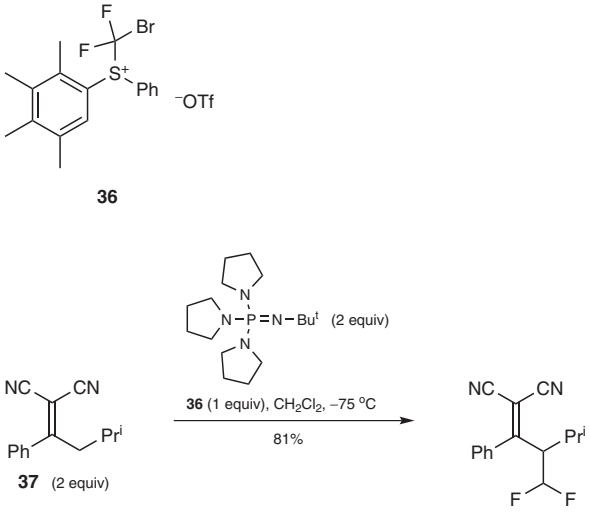


Difluoromethylation Conditions	Yield (%)	Ref
$PhS(O)(NTs)CHF_2$ (0.5 equiv), −78 to 0 °C, 6 h	78	[61]
$(Bu_3NCHF_2)^+Cl^-$ (1.2 equiv), −78 °C to rt, 8 h	40	[62]

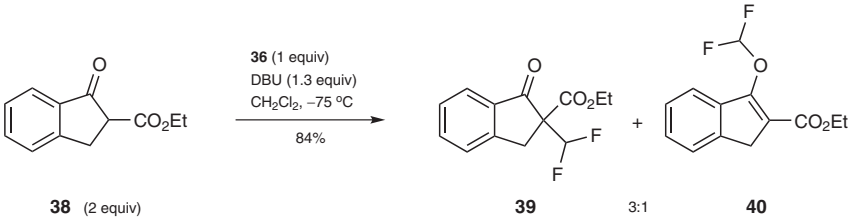
2.6.2.1.2.5 Using *S*-[Bromo(difluoro)methyl]sulfonium Salts

S-[Bromo(difluoro)methyl]sulfonium salts such as *S*-[bromo(difluoro)methyl]-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium trifluoromethanesulfonate (**36**)[63] can be used for the direct difluoromethylation of sp^3-carbon acids. The reaction between 2-alkylidenemalononitriles such as **37** and sulfonium salt **36** gives 2-[2-(difluoromethyl)alkylidene]-malononitriles in good yields without the formation of any C—H bromination product (Scheme 26),[63] whereas the difluoromethylation of oxo esters such as **38** gives a mixture of difluoromethylation products **39** and **40** at carbon and oxygen, respectively, with the formation of α-bromo-β-oxo esters as major byproducts (Scheme 27).[63]

Scheme 26 Electrophilic Difluoromethylation of a 2-Alkylidenemalononitrile Using an *S*-[Bromo(difluoro)methyl]sulfonium Salt[63]



Scheme 27 Electrophilic Difluoromethylation of an Oxo Ester Using an *S*-[Bromo(difluoro)methyl]sulfonium Salt[63]



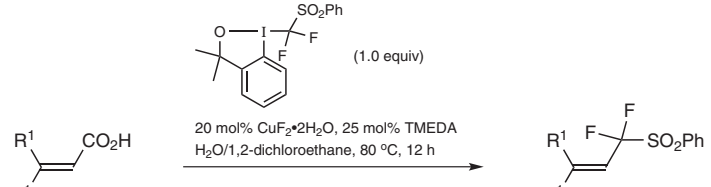
38 (2 equiv) **39** 3:1 **40**

2.6.2.1.2.6 Using Difluoro(phenylsulfonyl)methyl Hypercovalent Iodine Compounds

Copper(II)-catalyzed decarboxylative difluoro(phenylsulfonyl)methylation of alk-2-enoic and alk-3-enoic acids with the electrophilic fluoroalkylation reagent 3,3-dimethyl-1-[difluoro(phenylsulfonyl)methyl]-1,2-benziodoxole[66,67,77] followed by reductive desulfonylation can afford vinylic and allylic difluoromethylation products (Schemes 28–30).[78,77] Although an excess of alkenoic acid (2–3 equiv) is required to trap the difluoro(phenylsulfonyl)methyl group efficiently, the excess alkenoic acid can be recovered in high yield.

The vinylic difluoro(phenylsulfonyl)methylation is performed in a mixed solvent system of water/1,2-dichloroethane using copper(II) fluoride/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine as the catalyst at 80 °C (Scheme 28).[67] Both electron-rich and electron-deficient 3-aryl-substituted alk-2-enoic acids can smoothly undergo the reaction. Furthermore, 3-hetaryl- and 3,3-dialkyl-substituted alk-2-enoic acids are also viable substrates in the same reaction, giving the corresponding alkenes in moderate to good yields. Notably, the reactions are highly stereoselective, with only the *E*-isomer of the product being observed.[67]

Scheme 28 Decarboxylative Difluoro(phenylsulfonyl)methylation of Alk-2-enoic Acids Using 3,3-Dimethyl-1-[difluoro(phenylsulfonyl)methyl]-1,2-benziodoxole[67]



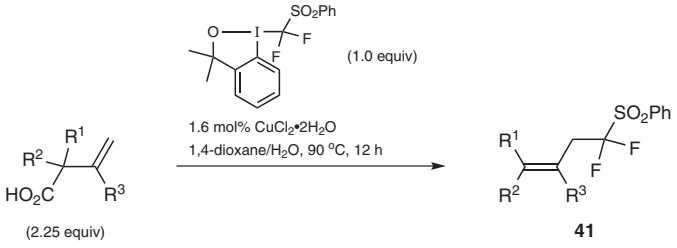
R^1	Ar^1	Yield (%)	Ref
Me	2-$MeOC_6H_4$	88	[67]
Me	3-pyridyl	60	[67]
H	2-Tol	73	[67]

The allylic difluoro(phenylsulfonyl)methylation is conducted in a mixed solvent system of water/1,4-dioxane using copper(II) chloride as the catalyst at 90 °C (Scheme 29).[77] The electron-rich 3-aryl-substituted alk-3-enoic acids undergo the reaction giving allylic fluoroalkylation products **41** in higher yields than the electron-deficient ones. Many synthetically important functional groups, including bromo, hydroxy, alkynyl, formyl, and ester groups, are well tolerated in the reaction. Moreover, 2,2-dialkyl-substituted alk-3-enoic acids, cyclic alk-3-enoic acids, and alka-3,4-dienoic acids are also suitable substrates.[77] A

for references see p 455

representative example of reductive desulfonylation, of the allylic difluoro(phenylsulfonyl)methylation product 1-bromo-4-[2-(4-bromobenzyl)-5,5-difluoro-3-methyl-5-(phenylsulfonyl)pent-2-enyl]benzene to give 1-bromo-4-[2-(4-bromobenzyl)-5,5-difluoro-3-methylpent-2-enyl]benzene (**42**), is presented in Scheme 30.[77]

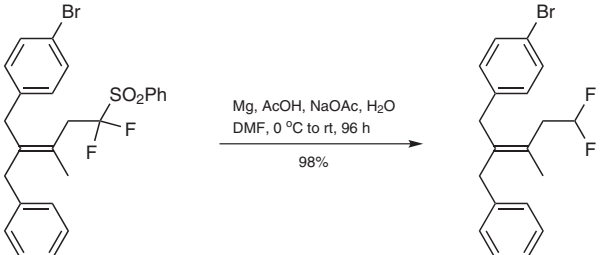
Scheme 29 Decarboxylative Difluoro(phenylsulfonyl)methylation of Alk-3-enoic Acids Using 3,3-Dimethyl-1-[difluoro(phenylsulfonyl)methyl]-1,2-benziodoxole[77]



41

R^1	R^2	R^3	Yield (%)	Ref
H	H	2,5-$(MeO)_2C_6H_3$	92	[77]
H	H	3-BrC_6H_4	50	[77]
H	H	4-$(HOCH_2)C_6H_4$	83	[77]
4-$BrC_6H_4CH_2$	4-$BrC_6H_4CH_2$	Me	75	[77]

Scheme 30 Reductive Desulfonylation of the Product of an Allylic Difluoro(phenylsulfonyl)methylation Reaction[77]



42

1-Bromo-4-[2-(4-bromobenzyl)-5,5-difluoro-3-methyl-5-(phenylsulfonyl)pent-2-enyl]benzene (41, $R^1 = R^2 = 4\text{-}BrC_6H_4CH_2$; R^3 = Me); Typical Procedure:[77]

CAUTION: *Hypercovalent iodine compounds are potentially explosive and thus should be handled in small amounts with special care.*

To a reaction flask equipped with a magnetic stirrer bar and a reflux condenser containing 3,3-dimethyl-1-[difluoro(phenylsulfonyl)methyl]-1,2-benziodoxole (362 mg, 0.8 mmol), 2,2-bis(4-bromobenzyl)-3-methylbut-3-enoic acid (788 mg, 1.8 mmol), and $CuCl_2•2H_2O$ (2.0 mg, 0.0125 mmol) were added 1,4-dioxane (4 mL) and H_2O (1 mL). After the mixture had been heated at 90 °C for 12 h with stirring, it was extracted with Et_2O (3 × 15 mL), the combined extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc 20:1); yield: 350 mg (75%).

1-Bromo-4-[2-(4-bromobenzyl)-5,5-difluoro-3-methylpent-2-enyl]benzene (42); Typical Procedure:[77]

To a 50-mL Schlenk flask containing 1-bromo-4-[2-(4-bromobenzyl)-5,5-difluoro-3-methyl-5-(phenylsulfonyl)pent-2-enyl]benzene (166 mg, 0.285 mmol) in DMF (4 mL) at rt was added an AcOH/NaOAc (1:1) buffer soln (8 mol/L; 4 mL). Mg turnings (288 mg, 12 mmol) were then added in portions at 0 °C. The mixture was stirred at rt for 96 h, and then H_2O (30 mL) was added. The mixture was extracted with Et_2O (3 × 20 mL), and the extracts were washed with sat. aq $NaHCO_3$ and brine, dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc 30:1); yield: 124 mg (98%).

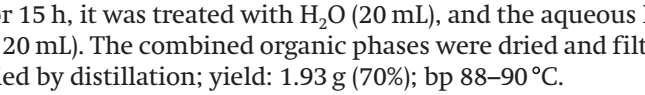
2.6.2.1.3 Free-Radical Difluoromethylation

Free-radical difluoromethylation typically features the transfer of a fluoroalkyl radical (CHF_2 or CF_2R^1) to a π-system such as alkynes, alkenes (including enol ethers, enolates, and enamines), and (hetero)aromatics. The synthetically useful radical difluoromethylation reagents currently known are difluoro(iodo)methane, zinc(II) difluoromethanesulfinate, dibromo(difluoro)methane, bromo(chloro)difluoromethane, and difluoro(iodo)methyl phenyl sulfone.

2.6.2.1.3.1 Using Difluoro(iodo)methane

Difluoro(iodo)methane is prepared in good yield by heating difluorocarbene precursors such as 2,2-difluoro-2-(fluorosulfonyl)acetic acid and potassium chloro(difluoro)acetate with potassium iodide.[79] Difluoro(iodo)methane can be used as a free-radical difluoromethylation reagent for alkenes and alkynes. When sodium dithionite is used as a free-radical initiator, the addition products (e.g., **43**) are formed in high yields under very mild conditions (Scheme 31).[79]

Scheme 31 Free-Radical Difluoromethylation of Hept-1-ene Using Difluoro(iodo)methane[79]



43

1,1-Difluoro-3-iodooctane (43); Typical Procedure:[79]

Hept-1-ene (0.98 g, 10 mmol), $Na_2S_2O_4$ (3.48 g, 20 mmol), $NaHCO_3$ (1.68 g, 20 mmol), MeCN (6 mL), H_2O (7 mL), and CHF_2I (1.78 g, 10 mmol) were placed in a 100-mL, two-necked flask equipped with a magnetic stirrer bar and a thermometer. After the mixture had been stirred at rt for 15 h, it was treated with H_2O (20 mL), and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic phases were dried and filtered, and the product was purified by distillation; yield: 1.93 g (70%); bp 88–90 °C.

2.6.2.1.3.2 Using Zinc(II) Difluoromethanesulfinate

Zinc(II) difluoromethanesulfinate is a radical difluoromethylation reagent under the action of an oxidant such as *tert*-butyl hydroperoxide (Scheme 32).[80,81] Many heteroaromatics, such as pyridines, pyrazines, pyrimidines, pyrroles, imidazoles, and thiadiazoles, show good reactivity in a dichloromethane/water solvent system.[80] The reaction is tolerant of several potentially sensitive functional groups such as acyl groups and halogens. In most cases, heteroaromatics with multiple potential reaction sites exhibit high levels of

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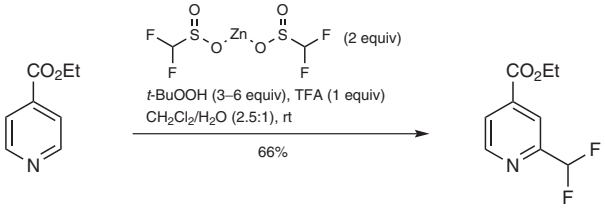
regioselectivity, commonly producing only one observable regioisomer with C—H difluoromethylation occurring at electron-deficient positions. Moreover, cyclic α,β-enones such as cyclohex-2-enone can also be difluoromethylated in a Michael addition manner, albeit in only moderate yields.[80] As a representative example, the preparation of ethyl 2-(difluoromethyl)pyridine-4-carboxylate (**44**) is shown in Scheme 32.

Scheme 32 Free-Radical Difluoromethylation of a Hetarene Using Zinc(II) Difluoromethanesulfinate[80]



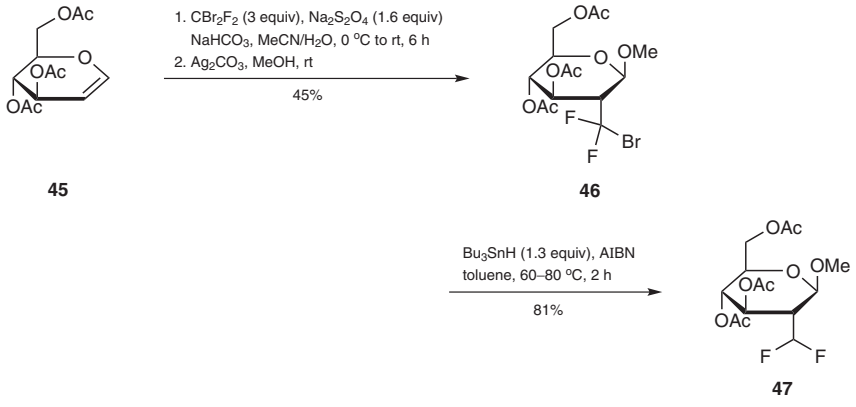
44

Ethyl 2-(Difluoromethyl)pyridine-4-carboxylate (44); Typical Procedure:[80]
To a mixture of ethyl pyridine-4-carboxylate (38 mg, 0.25 mmol), $(HCF_2SO_2)_2Zn$ (150 mg, 0.50 mmol) in CH_2Cl_2 (1.0 mL), and H_2O (0.4 mL) at rt was added TFA (20 μL, 0.25 mmol) followed by slow addition of 70% aq *t*-BuOOH (0.17 mL, 1.25 mmol, 5.0 equiv) with vigorous stirring. For reactions which do not go to completion in 24 h, a second addition of $(HCF_2SO_2)_2Zn$ (2.7 equiv) and *t*-BuOOH (5.0 equiv) may be performed to drive the reaction further. Upon consumption of the starting material, the mixture was partitioned between CH_2Cl_2 (2.0 mL) and sat. aq $NaHCO_3$ (2.0 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 2.0 mL). The organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, CH_2Cl_2/hexanes) to provide the product as a colorless oil; yield: 33 mg (66%).

2.6.2.1.3.3 Using Dibromo(difluoro)methane

Free-radical addition of dibromo(difluoro)methane to alkenes followed by reductive debromination can afford difluoromethylated products. The radical addition can be initiated by sodium dithionite,[82] Rongalite,[82] thiourea dioxide,[82] or transition-metal species such as copper(I) chloride,[83] chromium(III) chloride/iron,[84] tetrakis(triphenylphosphine)palladium(0),[85] ruthenium(II)/light,[86] and iridium(III)/light[86] in moderate to excellent yields. For example, under the initiation of sodium dithionite, free-radical bromo(difluoro)methylation of glucal **45** with dibromo(difluoro)methane followed by debromination of the bromo(difluoro)methyl-substituted compound **46** with tributylstannane gives the difluoromethylated product **47** in moderate yield (Scheme 33).[87]

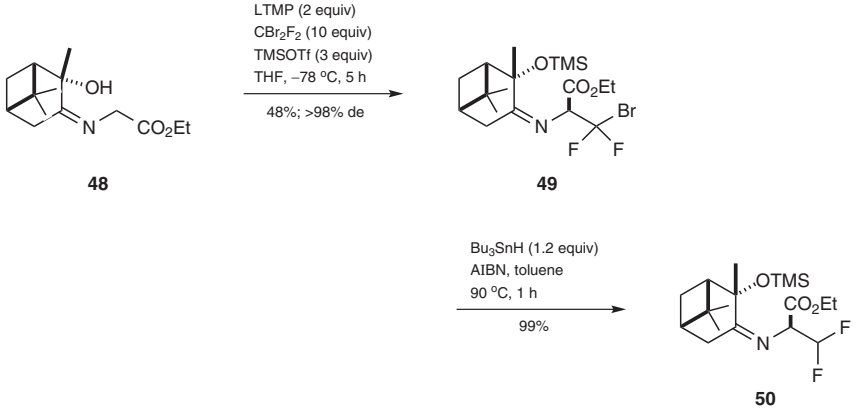
Scheme 33 Free-Radical Difluoromethylation of an Alkene Using Dibromo(difluoro)methane[87]



45 **46** **47**

The bromo(difluoro)methylation of resonance-stabilized carbon nucleophiles such as esters,[88,89] amides,[89] aldehydes,[90] and ketones[89] using dibromo(difluoro)methane can proceed via addition of the bromo(difluoro)methyl radical to the corresponding silyl enol ethers or enamines. However, the bromo(difluoro)methylation of lithium, sodium, and potassium enolates[75,91] and non-resonance-stabilized carbon nucleophiles such as acetylides[92] may proceed via difluorocarbene.[60] For instance, the bromo(difluoro)methylation of Schiff base **48** under the action of lithium 2,2,6,6-tetramethylpiperidide and trimethylsilyl trifluoromethanesulfonate gives the bromo(difluoro)methylated product **49** in moderate yield but with excellent diastereoselectivity (Scheme 34).[88] Reductive debromination of **49** with tributylstannane affords the α-difluoroalanine precursor **50** quantitatively.[88]

Scheme 34 Diastereoselective Free-Radical Difluoromethylation of an Ester Using Dibromo(difluoro)methane[88]



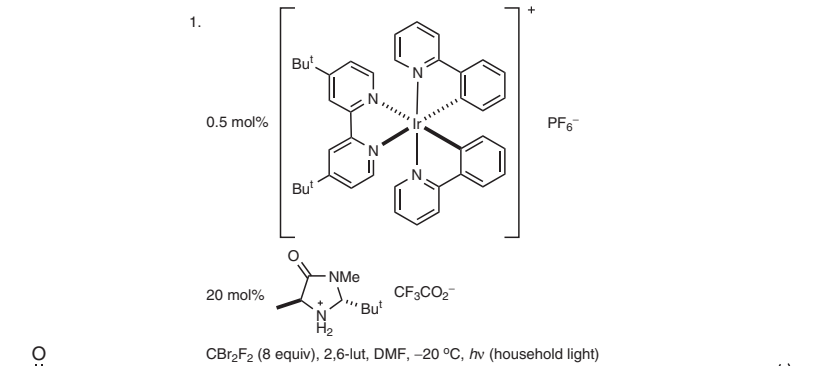
48 **49** **50**

The bromo(difluoro)methylation of octanal via photoredox organocatalysis using an iridium photocatalyst and an imidazolidinone catalyst gives 2-[bromo(difluoro)methyl]octan-1-ol (after reduction with sodium borohydride) with excellent enantioselectivity (Scheme 35).[90] Considering that this methodology has been used for the trifluoromethylation of a

for references see p 455

series of aliphatic aldehydes with trifluoro(iodo)methane,[90] this similar bromo(difluoro)-methylation is believed to be general for aliphatic aldehydes and is expected to find application in the synthesis of optically active difluoromethyl compounds.

Scheme 35 Enantioselective Free-Radical Bromo(difluoro)methylation of an Aliphatic Aldehyde Using Dibromo(difluoro)methane[90]



Methyl 3,4,6-Tri-*O*-acetyl-2-[bromo(difluoro)methyl]-2-deoxy-β-D-glucopyranoside (46); Typical Procedure:[87]

CBr_2F_2 (1.3 g, 6.0 mmol) was added at 0 °C to a vigorously stirred soln of 3,4,6-tri-*O*-acetyl-D-glucal (**45**; 0.54 g, 2.0 mmol), $Na_2S_2O_4$ (0.56 g, 3.2 mmol), and $NaHCO_3$ (0.6 g, 7.2 mmol) in MeCN (5 mL)/H_2O (3 mL) in an argon-flushed Schlenk flask. Under stirring, the mixture was allowed slowly to warm to rt over 2 h and stirring was continued for a further 4 h. Subsequently, Et_2O (40 mL) was added and the mixture was washed with sat. brine (20 mL) and H_2O. The separated Et_2O phase was then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. After the Et_2O phase had been dried under reduced pressure (<40 °C), the syrupy residue was dissolved in anhyd MeOH (15 mL) followed by addition of Drierite (0.5 g). The mixture was stirred for 1 h and, during this time, Ag_2CO_3 (0.45 g, 1.6 mmol) was added in small portions. After filtration, the solvent was removed and the residue was purified by column chromatography (silica gel, heptane/EtOAc 7:3) giving the product which still contained small amounts of impurities. The pure product was obtained after recrystallization (MeOH containing some H_2O); yield: 0.39 g (45%); mp 91–92 °C; $[\alpha]_D^{20}$ +123.73 (*c* 1.13, $CHCl_3$).

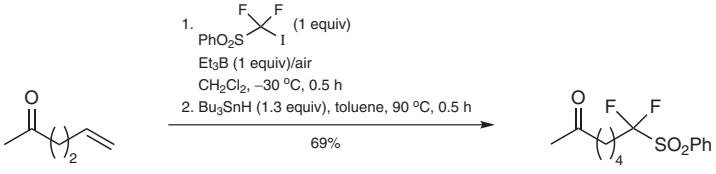
Methyl 3,4,6-Tri-*O*-acetyl-2-(difluoromethyl)-2-deoxy-β-D-glucopyranoside (47); Typical Procedure:[87]

To a soln of glucopyranoside **46** (0.43 g, 1.0 mmol) in anhyd toluene (5 mL) were added Bu_3SnH (0.38 g, 1.3 mmol) and AIBN (2–5 mg) under an inert gas atmosphere. After the mixture had been stirred for 2 h at 70 °C, it was diluted with Et_2O (50 mL) and washed with aq KF (10 mL) and H_2O. The organic layer was dried (Na_2SO_4) and concentrated, and the residue was purified by column chromatography (silica gel, heptane/EtOAc 7:3); yield: 0.29 g (81%); mp 54–56 °C (MeOH); $[\alpha]_D^{20}$ +2.34 (*c* 1.37, $CHCl_3$).

2.6.2.1.3.4 Using Difluoro(iodo)methyl Phenyl Sulfone

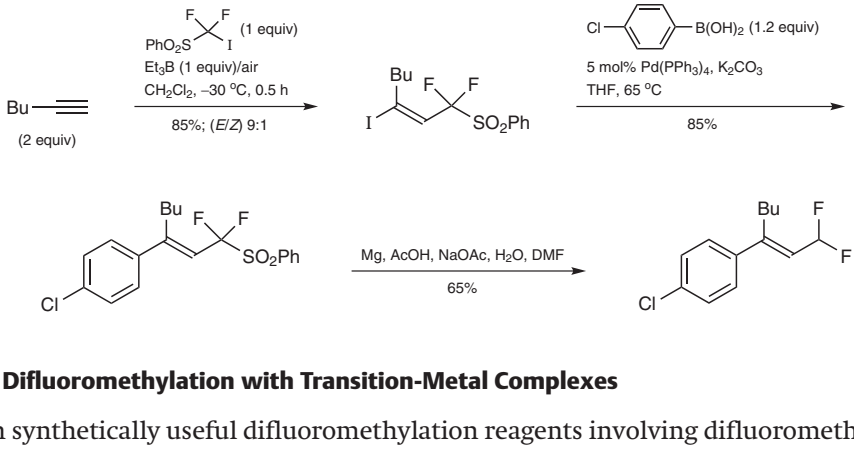
Since the difluoro(phenylsulfonyl)methyl group can be readily converted into the difluoromethyl group by reductive desulfonylation, free-radical addition of difluoro(iodo)methyl phenyl sulfone to alkenes and alkynes initiated by triethylborane/air[93,94] or arenediazonium salt/titanium(III) chloride[95] has been developed for the synthesis of difluoro(phenylsulfonyl)methylated alkanes and alkenes. The reaction is compatible with various functionalities such as carbonyl, ester, and ether groups. For example, the radical addition of difluoro(iodo)methyl phenyl sulfone to hex-5-en-2-one followed by deiodination with tributylstannane gives 7,7-difluoro-7-(phenylsulfonyl)heptan-2-one in 69% yield (Scheme 36).[93]

Scheme 36 Free-Radical Difluoro(phenylsulfonyl)methylation of Hex-5-en-2-one Using Difluoro(iodo)methyl Phenyl Sulfone[93]



The reaction between terminal alkynes and difluoro(iodo)methyl phenyl sulfone gives difluoro(phenylsulfonyl)methyl-substituted iodoalkenes with high stereoselectivity. The iodoalkenes can undergo cross coupling with arylboronic acids to afford trisubstituted alkenes (Scheme 37).[94]

Scheme 37 Free-Radical Difluoro(phenylsulfonyl)methylation of a Terminal Alkyne Using Difluoro(iodo)methyl Phenyl Sulfone and Further Transformation[94]



2.6.2.1.4 Difluoromethylation with Transition-Metal Complexes

All the known synthetically useful difluoromethylation reagents involving difluoromethyl–transition-metal complexes are mediated or catalyzed by copper(I) iodide. Useful difluoromethylation reagents for coupling reactions are (difluoromethyl)trimethylsilane, tributyl(difluoromethyl)stannane, ethyl 2,2-difluoro-2-(trimethylsilyl)acetate, and [difluoro(phenylsulfonyl)methyl]trimethylsilane.

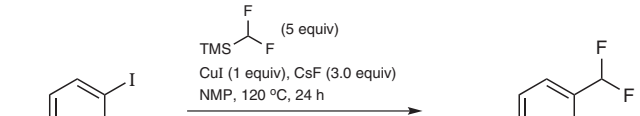
for references see p 455

2.6.2.1.4.1 Using (Difluoromethyl)trimethylsilane and Tributyl(difluoromethyl)stannane

(Difluoromethyl)copper(I) has been prepared by a metathesis reaction between bis(difluoromethyl)cadmium(II) and copper(I) bromide in dimethylformamide.[96,97] Unlike perfluoroalkylcopper reagents, the (difluoromethyl)copper(I) reagent is found to be relatively unstable. At temperatures above −30 °C, rapid decomposition takes place to give 1,1,2,2-tetrafluoroethane and (*Z*)-1,2-difluoroethene.[97] Although the preformed (difluoromethyl)copper(I) species reacts readily with allylic and propargylic halides, 1-iodoalkynes, chloromethyl ethyl ether, and benzyl bromide,[97] its thermal instability hampers its practical application.

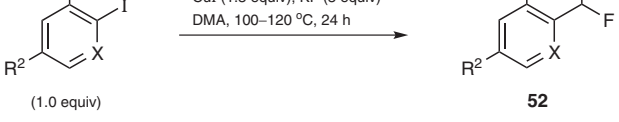
However, (difluoromethyl)trimethylsilane and tributyl(difluoromethyl)stannane can be used for the in situ generation of (difluoromethyl)copper(I) in the presence of a fluoride salt and a stoichiometric amount of copper(I) iodide at 100–120 °C in an polar aprotic solvent. The (difluoromethyl)copper(I) species thus formed undergoes cross-coupling reactions with various vinyl and aryl halides through an oxidative addition and reductive elimination pathway.[12,98] The difluoromethylation reaction using (difluoromethyl)trimethylsilane to give, for example, 1-butyl-4-(difluoromethyl)benzene (**51**) (Scheme 38) tolerates amine, ether, amide, ester, aromatic bromide, and protected alcohol functionalities in the aryl iodides and proceeds in high yield and with high stereoselectivity with vinyl iodides (Scheme 40); however, the reaction does not work for electron-deficient aryl iodides.[12] In contrast, the difluoromethylation reaction using tributyl(difluoromethyl)stannane to give (difluoromethyl)arenes **52** not only works well for electron-deficient aryl and hetaryl iodides in moderate to good yields, but also for electron-neutral and electron-rich aryl iodides in moderate yields (Scheme 39).[98]

Scheme 38 Copper-Mediated Difluoromethylation of an Aryl Iodide Using (Difluoromethyl)trimethylsilane[12]



(1 equiv) **51**

Scheme 39 Copper-Mediated Difluoromethylation of Hetaryl and Aryl Iodides Using Tributyl(difluoromethyl)stannane[98]



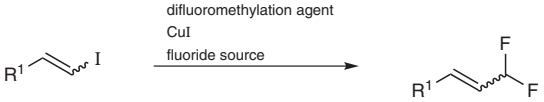
(1.0 equiv) **52**

R^1	R^2	X	Equiv of Bu_3SnCHF_2	Temp (°C)	Yield (%)	Ref
Ac	H	CH	2	100	74[a]	[98]
H	Br	N	2	100	75[b]	[98]
H	Ph	CH	3	120	44[a]	[98]
H	CF_3	CH	3	120	78[b]	[98]

[a] Isolated yield.
[b] Yield determined by ^{19}F NMR spectroscopy.

Moreover, the difluoromethylation of vinyl iodides using either (difluoromethyl)trimethylsilane or tributyl(difluoromethyl)stannane proceeds stereospecifically giving only the *Z*- or *E*-isomer in moderate to good yields. No isomerization of the double bond was observed during the reaction (Scheme 40).[12,98]

Scheme 40 Copper-Mediated Difluoromethylation of Vinyl Iodides Using (Difluoromethyl)trimethylsilane and Tributyl(difluoromethyl)stannane[12,98]



R^1	Config[a]	Conditions	Yield (%)	Ref
4-*t*-BuC_6H_4	*E*	$TMSCHF_2$ (5.0 equiv), CuI (1.0 equiv), CsF (3.0 equiv), NMP, 120 °C, 24 h	80	[12]
$(CH_2)_5Me$	*E*	$TMSCHF_2$ (5.0 equiv), CuI (1.0 equiv), CsF (3.0 equiv), NMP, 120 °C, 24 h	91	[12]
$(CH_2)_5Me$	*Z*	$TMSCHF_2$ (5.0 equiv), CuI (1.0 equiv), CsF (3.0 equiv), NMP, 120 °C, 24 h	42	[12]
Ph	*E*	Bu_3SnCHF_2 (2.0 equiv), CuI (1.3 equiv), KF (3.0 equiv), DMA, 100 °C, 24 h	85	[98]
4-BrC_6H_4	*E*	Bu_3SnCHF_2 (2.0 equiv), CuI (1.3 equiv), KF (3.0 equiv), DMA, 100 °C, 24 h	72	[98]
4-BrC_6H_4	*Z*	Bu_3SnCHF_2 (2.0 equiv), CuI (1.3 equiv), KF (3.0 equiv), DMA, 100 °C, 24 h	68	[98]

[a] Reaction is stereospecific: stereochemistry of starting material is maintained in product.

1-Butyl-4-(difluoromethyl)benzene (51); Typical Procedure:[12]

CAUTION: *The pressure increases during the reaction due to the formation of volatile fluorotrimethylsilane as a stoichiometric product!*

In a N_2-filled glovebox, anhyd NMP (2.5 mL) was added to a mixture of 1-butyl-4-iodobenzene (89 μL, 0.5 mmol), CuI (95 mg, 0.5 mmol), and CsF (228 mg, 1.5 mmol) in a 20-mL vial, followed by $TMSCHF_2$ (310 mg, 2.5 mmol). The mixture was heated in a sealed vessel at 120 °C for 24 h. The dark red soln was allowed to cool to rt and diluted with Et_2O (15 mL). The mixture was filtered over Celite, which was then washed with Et_2O (20 mL). The combined filtrate was washed with H_2O (5 × 20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, pentane/Et_2O 100:0 to 90:10); yield: 83 mg (90%).

1-[2-(Difluoromethyl)phenyl]ethanone (52, R^1 = Ac; R^2 = H; X = CH); Typical Procedure:[98]
To a 20-mL microwave vial equipped with a magnetic stirrer bar were added anhyd KF (0.087 g, 1.5 mmol), CuI (0.124 g, 0.65 mmol), 1-(2-iodophenyl)ethanone (123 mg, 0.5 mmol), and Bu_3SnCHF_2 (0.341 g, 1 mmol) in that order under N_2 in a glovebox. DMA (4 mL) was added and the mixture was heated to 100 °C in an oil bath protected from light for 24 h. After the mixture had been allowed to cool to rt, it was filtered and the residue was washed with CH_2Cl_2 (20 mL). The resulting combined filtrate was mixed with

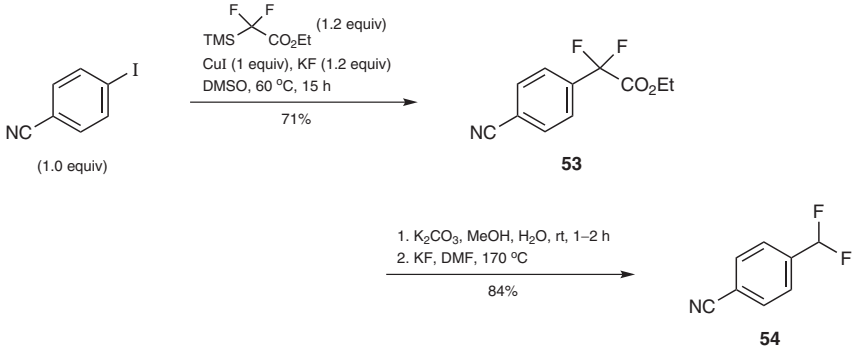
for references see p 455

H_2O and extracted with CH_2Cl_2. The combined organic phase was washed with H_2O (5 × 10 mL), dried ($MgSO_4$), and concentrated, and the residue was purified by column chromatography (silica gel); yield: 63 mg (74%).

2.6.2.1.4.2 Using Ethyl 2,2-Difluoro-2-(trimethylsilyl)acetate

The copper-mediated cross-coupling reaction of aryl iodides with readily available ethyl 2,2-difluoro-2-(trimethylsilyl)acetate in combination with hydrolysis–decarboxylation affords difluoromethylated arenes (e.g., **54**) in moderate yields via the corresponding 2,2-difluoroacetate **53** (Scheme 41).[99,100] The decarboxylation is performed in dimethylformamide at 170 °C or in 1-methylpyrrolidin-2-one at 200 °C in the presence of fluoride salts such as potassium and cesium fluoride.[99] This cross-coupling–hydrolysis–decarboxylation sequence is also effective for heteroaromatics such as bromopyridines and iodopyridines;[100] however, the sequence is ineffective for electron-rich aryl iodides.[99]

Scheme 41 Copper-Mediated Difluoromethylation of an Electron-Deficient Aryl Iodide Using Ethyl 2,2-Difluoro-2-(trimethylsilyl)acetate[99]



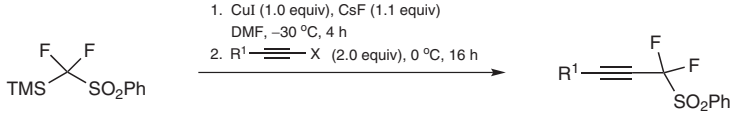
Ethyl 2-(4-Cyanophenyl)-2,2-difluoroacetate (53); Typical Procedure:[99]
Ethyl 2,2-difluoro-2-(trimethylsilyl)acetate (70.7 mg, 0.36 mmol) was added to a mixture of CuI (57.1 mg, 0.30 mmol), KF (20.9 mg, 0.36 mmol), 4-iodobenzonitrile (68.7 mg, 0.30 mmol), and DMSO (0.6 mL) at rt. The mixture was stirred at 60 °C under N_2 for 15 h and then quenched with H_2O. The aqueous layer was extracted with EtOAc and the combined organic phases were washed with H_2O and dried (Na_2SO_4). After concentration, purification of the residue by column chromatography (silica gel, hexane/EtOAc 50:1) gave the product as a colorless oil; yield: 48.3 mg (71%).

4-(Difluoromethyl)benzonitrile (54); Typical Procedure:[99]
To a soln of 2,2-difluoroacetate **53** (450.4 mg, 2.0 mmol) in MeOH (6.0 mL) was added 2 M aq K_2CO_3 (6.0 mL) at rt. The mixture was stirred at 25 °C for 2 h, poured into 5% aq HCl, and successively extracted with EtOAc. The combined organic phases were washed with brine and dried (Na_2SO_4). After removal of the solvents under reduced pressure, the residue and KF (581.1 mg, 10.0 mmol) were dissolved in DMF (8.0 mL), and the mixture was stirred at 170 °C under N_2 for 2 h. After the mixture had been allowed to cool to rt, H_2O (3.0 mL) was added. The mixture was extracted with EtOAc (3 ×) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, hexane/EtOAc 50:1) gave the product as a pale yellow oil; yield: 256.6 mg (84%).

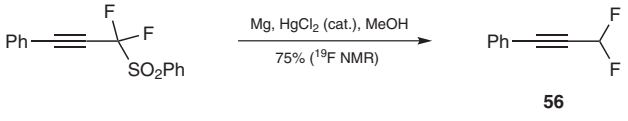
2.6.2.1.4.3 Using [Difluoro(phenylsulfonyl)methyl]trimethylsilane

[Difluoro(phenylsulfonyl)methyl]copper(I) species can be prepared by a reaction between [difluoro(phenylsulfonyl)methyl]trimethylsilane and copper(I) iodide in the presence of cesium fluoride.[101] Alkynyl halides react smoothly with the copper reagent giving cross-coupling products **55** in moderate to good yields (Scheme 42).[101] The phenylsulfonyl group in **55** can be removed using a magnesium/mercury(II) chloride system, e.g. to give (3,3-difluoroprop-1-ynyl)benzene (**56**).[101] However, unlike (trifluoromethyl)copper(I) species, [difluoro(phenylsulfonyl)methyl]copper(I) species possess lower thermal stability, and decompose even at room temperature.

Scheme 42 Copper-Mediated Difluoromethylation of Alkynyl Iodides and Bromides Using [Difluoro(phenylsulfonyl)methyl]trimethylsilane[101]



R^1	X	Yield (%)	Ref
Ph	I	79	[101]
Ph	Br	69	[101]
Bu	I	82	[101]
CH_2OBn	I	45	[101]



2.6.2.2 Fluoromethylation

According to the reactivity of the monofluorinated species involved in the formation of the C—C bonds, fluoromethylation reactions are also classified into four types: nucleophilic, electrophilic, free-radical, and reactions involving difluoromethyl–transition-metal complexes. With the exception of fluoromethylation with fluorinated sulfones, which has been studied extensively, other methods for carbon fluoromethylation using *S*-(fluoromethyl)sulfoximides, fluoro(halo)methanes (CH_2FX; X = Cl, Br, I), *S*-(fluoromethyl)sulfonium salts, and zinc(II) fluoromethanesulfinate are less exploited and only some sporadic examples are documented. Fluoro(dihalo)methylation followed by hydrodehalogenation is a potentially useful fluoromethylation method.[102] For the preparation of fluoro(dihalo)methyl compounds (R^1CFXY; X, Y = Cl, Br) using C-1 building blocks see *Science of Synthesis*, Vol. 22 [Three Carbon—Heteroatom Bonds: Thio-, Seleno- and Tellurocarboxylic Acids and Derivatives; Imidic Acids and Derivatives; Ortho Acid Derivatives (Sections 22.7.1.1.5.2, 22.7.1.1.5.3, 22.7.1.1.5.6, and 22.7.1.1.6.3)].

for references see p 455

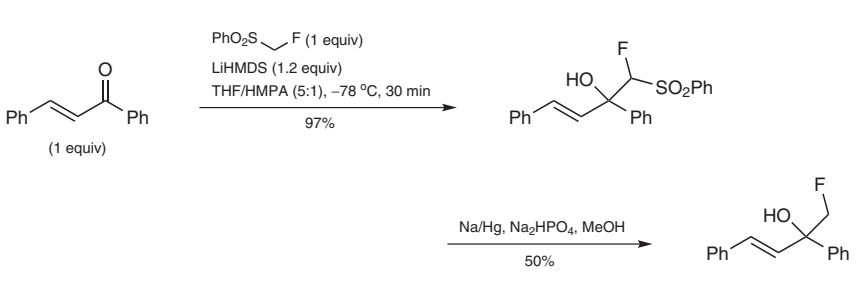
2.6.2.2.1 Nucleophilic Fluoromethylation

Nucleophilic fluoromethylation typically features the transfer of a fluoromethyl equivalent ($CHFR^1$ or CFR^1R^2) to an electrophile. The synthetically useful nucleophilic fluoromethylation reagents are fluoromethyl phenyl sulfone, *S*-(fluoromethyl)sulfoximides, and fluorobis(phenylsulfonyl)methane.

2.6.2.2.1.1 Using Fluoromethyl Phenyl Sulfone

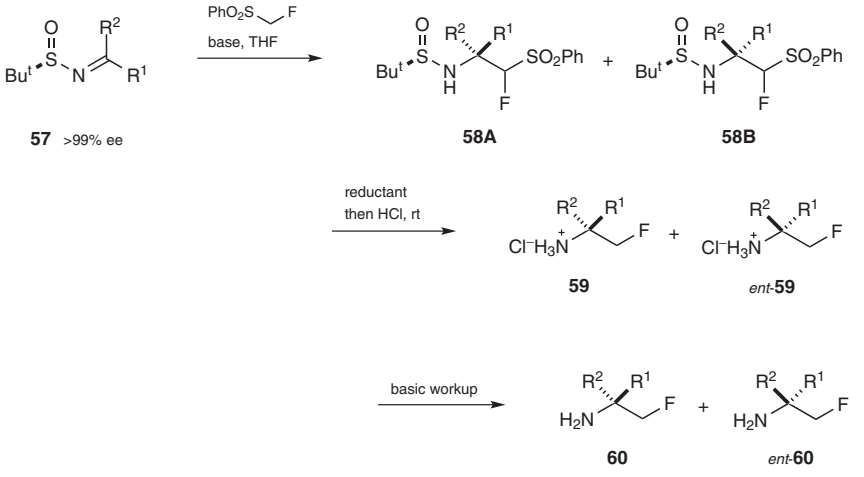
Early reports on the synthetic application of fluoromethyl phenyl sulfone focus on the preparation of monofluorinated alkenes from carbonyls via a nucleophilic addition–acylation–elimination–desulfonylation sequence;[103] the synthetic application of fluoromethyl phenyl sulfone as a fluoromethyl equivalent has been developed very recently.[19,23,104,105] The reductive desulfonylation of the addition products with sodium/mercury amalgam affords fluoromethylated alcohols in moderate yields (Scheme 43);[19] sometimes, the formation of monofluorinated alkenes as the minor products is observed.[106] α-(Fluoromethyl) alcohols are usually prepared by ring opening of terminal epoxides with hydrogen fluoride derivatives such as tetrabutylammonium hydrogen difluoride.[107]

Scheme 43 Nucleophilic Fluoromethylation of a Ketone Using Fluoromethyl Phenyl Sulfone[19]



The diastereoselective addition of fluoromethyl phenyl sulfone to *N*-(*tert*-butylsulfinyl)-imines **57** under the action of a base is an effective protocol for the synthesis of enantioenriched α-(fluoromethyl) amines or ammonium salts (e.g., **60** and **59**, respectively) (Scheme 44).[23,104,105] For aldimines **57** (R^2 = H), the addition reaction readily takes place using the in situ generated fluoro(phenylsulfonyl)methyl anion;[23,104] however, the fluoroalkylation of ketimines **57** (R^2 = Me) requires pregeneration of the fluoro(phenylsulfonyl)methyl anion.[105]

Scheme 44 Nucleophilic Fluoromethylation of Various *N*-(*tert*-Butylsulfinyl)imines Using Fluoromethyl Phenyl Sulfone[23,104,105]



R^1	R^2	Equiv[a] of $PhSO_2CH_2F$	Conditions (Step 1)	Ratio[b] (**58A**/**58B**)	Reductant (Step 2)	Yield[c] (%) of **59**	Ref
Ph	H	1	LiHMDS (1.05 equiv), −78 °C, 15 min	99:1	Na/Hg	77	[104]
2-furyl	H	1	LiHMDS (1.05 equiv), −78 °C, 15 min	99:1	Na/Hg	71	[104]
Pr	H	1	LiHMDS (1.05 equiv), −78 °C, 15 min	99:1	Na/Hg	70	[104]
(*S*)-CH(NBn_2)Bn	H	0.95	NaHMDS (2 equiv), −78 °C, 2–3 h	>99:1	Mg	58	[23]
4-$MeOC_6H_4$	Me	1.2	BuLi (1.3 equiv), −78 °C, 30 min, then **57** (1 equiv), −78 °C, 1 h	4:96	Mg	68[d]	[105]
4-$MeOC_6H_4$	Me	2.0	KHMDS (2.2 equiv), −78 °C, 30 min, then **57** (1 equiv), −78 °C, 2 h	1:99	Mg	62[e]	[105]

[a] Relative to **57**.
[b] Determined by ^{19}F NMR analysis of the crude products.
[c] Yield of the major isomer **59** starting from **57** unless otherwise stated.
[d] Yield of the major isomer *ent*-**60** starting from **57**.
[e] Yield of **58B**.

(*R*)-*N*-[(2*R*)-1-Fluoro-2-(4-methoxyphenyl)-1-(phenylsulfonyl)propan-2-yl]-2-methylpropane-2-sulfinamide (58B, **R^1 = 4-$MeOC_6H_4$; R^2 = Me); Typical Procedure:**[105]

Under N_2, a 2.5 M soln of BuLi in hexane (0.52 mL, 1.3 mmol) was added dropwise to a soln of $PhSO_2CH_2F$ (209 mg, 1.2 mmol) in THF (8 mL) at −78 °C. After the mixture had been stirred at −78 °C for 30 min, *N*-(*tert*-butylsulfinyl)imine **57** (R^1 = 4-$MeOC_6H_4$; R^2 = Me; 253 mg, 1.0 mmol) in THF (2 mL) was added slowly. The mixture was stirred vigorously at

for references see p 455

−78 °C for 1 h, followed by the addition of sat. brine (10 mL). The mixture was extracted with Et_2O (3 × 10 mL) and the combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (silica gel) to give the product as a pair of diastereomers; yield: 363 mg (85%); ratio (**58A**/**58B**) 4:96.

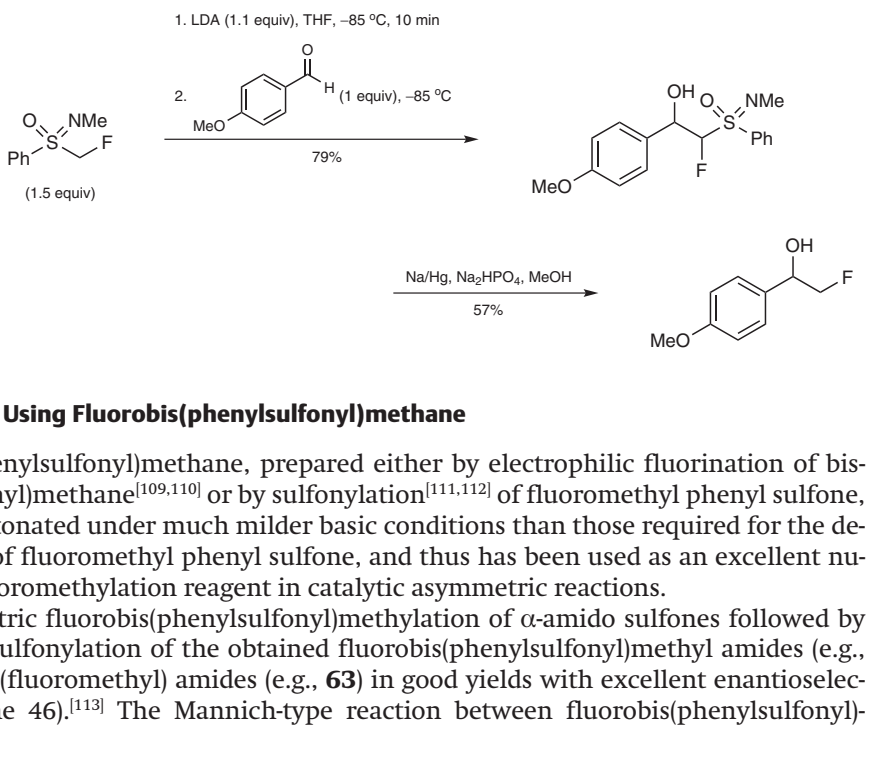
(*R*)-1-Fluoro-2-(4-methoxyphenyl)propan-2-amine (*ent*-60, R^1 = 4-$MeOC_6H_4$; R^2 = Me); Typical Procedure:[105]

Into a 50-mL Schlenk flask containing (*R*)-*N*-[(2*R*)-1-fluoro-2-(4-methoxyphenyl)-1-(phenylsulfonyl)propan-2-yl]-2-methylpropane-2-sulfinamide (**58B**, R^1 = 4-$MeOC_6H_4$; R^2 = Me; 222 mg, 0.52 mmol) in DMF (5 mL) at rt was added AcOH/NaOAc (1:1) buffer soln (8 mol/L; 3 mL). Mg turnings (183 mg, 7.5 mmol) were added in portions and the mixture was stirred at rt for 8 h. H_2O (10 mL) was added and the mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with sat. aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. This residue was dissolved in MeOH (5 mL), 4 M HCl in dioxane (0.5 mL, 2.0 mmol) was added, and the mixture was stirred at rt for 30 min. After removal of the solvents under reduced pressure, sat. aq $NaHCO_3$ (10 mL) was added. The mixture was extracted with Et_2O and the extract was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (silica gel); yield: 76 mg (80%; 68% from **57**).

2.6.2.2.1.2 Using *S*-(Fluoromethyl)sulfoximides

S-(Fluoromethyl)-*N*-methyl-*S*-phenylsulfoximide is a nucleophilic fluoromethylation reagent for aldehydes and ketones.[108] Using the pregenerated anion of the racemic sulfoximide, fluoro(phenylsulfonimidoyl)methylation of carbonyl compounds affords the adducts in good to excellent yields; subsequent reductive desulfoximination with sodium/mercury amalgam gives fluoromethyl alcohols in moderate yields (Scheme 45).[108]

Scheme 45 Nucleophilic Fluoromethylation of an Aldehyde Using *S*-(Fluoromethyl)-*N*-methyl-*S*-phenylsulfoximide[108]



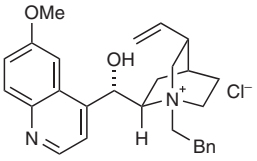
2.6.2.2.1.3 Using Fluorobis(phenylsulfonyl)methane

Fluorobis(phenylsulfonyl)methane, prepared either by electrophilic fluorination of bis(phenylsulfonyl)methane[109,110] or by sulfonylation[111,112] of fluoromethyl phenyl sulfone, can be deprotonated under much milder basic conditions than those required for the deprotonation of fluoromethyl phenyl sulfone, and thus has been used as an excellent nucleophilic fluoromethylation reagent in catalytic asymmetric reactions.

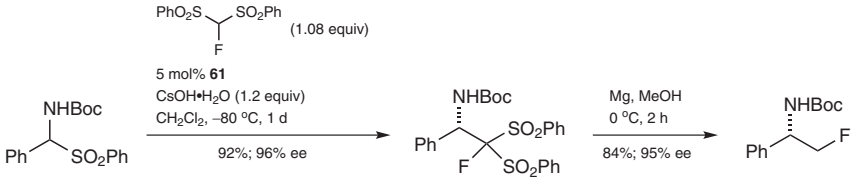
Asymmetric fluorobis(phenylsulfonyl)methylation of α-amido sulfones followed by reductive desulfonylation of the obtained fluorobis(phenylsulfonyl)methyl amides (e.g., **62**) affords α-(fluoromethyl) amides (e.g., **63**) in good yields with excellent enantioselectivity (Scheme 46).[113] The Mannich-type reaction between fluorobis(phenylsulfonyl)-

methane and the in situ generated aldimines (from both aromatic and aliphatic α-amido sulfones) proceeds smoothly at −80 °C in dichloromethane by using solid cesium hydroxide as a base and *N*-benzylquinidinium chloride (**61**) as the chiral phase-transfer catalyst.[113]

Scheme 46 Enantioselective Nucleophilic Fluoromethylation of an α-Amido Sulfone Using Fluorobis(phenylsulfonyl)methane[113]

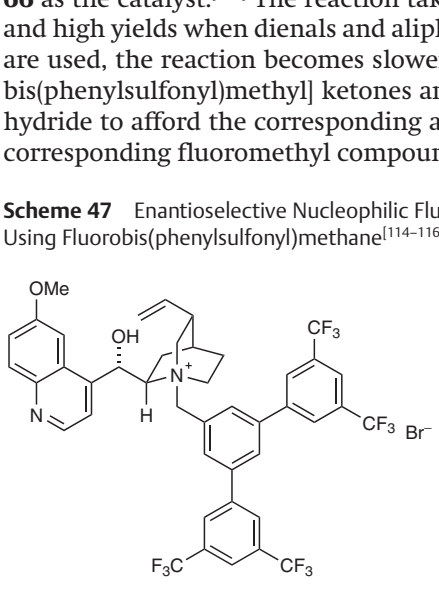


61

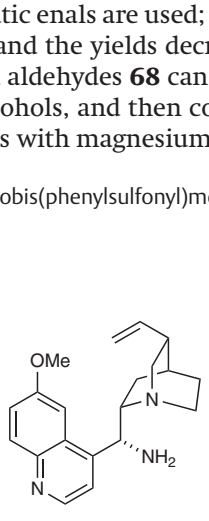


Enantioselective Michael addition of fluorobis(phenylsulfonyl)methane to α,β-enones or enals can be realized by using chiral ammonium salts (e.g., **64**) or chiral amines (e.g., **65** and **66**) as the catalyst (Scheme 47). The reaction with α,β-enones, such as (2*E*)-1,3-diphenylprop-2-en-1-one (**67**, $R^1 = R^2 = Ph$), proceeds smoothly under the action of cesium carbonate using quinidinium salt **64** bearing a sterically demanding benzyl substituent.[114] The reaction with α,β-enones, such as (3*E*)-4-phenylbut-3-en-2-one (**67**, $R^1 = Me$; $R^2 = Ph$), occurs under neutral conditions using 9-amino-9-deoxyepiquinine (**65**) as the catalyst.[115] The reaction with α,β-enals can also proceed under neutral conditions using chiral pyrrolidine **66** as the catalyst.[116] The reaction takes place with excellent levels of enantioselectivity and high yields when dienals and aliphatic enals are used; however, when aromatic enals are used, the reaction becomes slower and the yields decrease slightly.[116] The β-[fluorobis(phenylsulfonyl)methyl] ketones and aldehydes **68** can be reduced with sodium borohydride to afford the corresponding alcohols, and then conveniently converted into the corresponding fluoromethyl compounds with magnesium in ethanol (Scheme 48).[115]

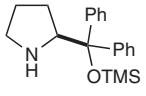
Scheme 47 Enantioselective Nucleophilic Fluorobis(phenylsulfonyl)methylation of α,β-Enones and Enals Using Fluorobis(phenylsulfonyl)methane[114–116]



64

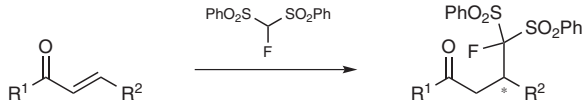


65



66

for references see p 455

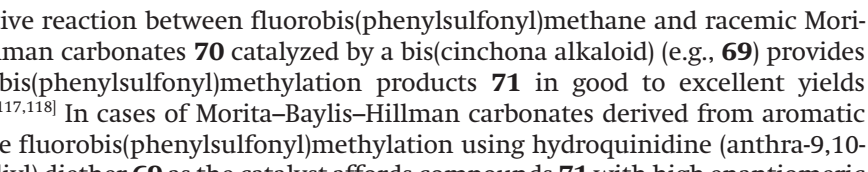


67 **68**

R^1	R^2	Equiv[a] of **67**	Conditions	Config[b]	ee (%)	Yield (%)	Ref
Ph	Ph	1.1	Cs_2CO_3 (3 equiv), **64** (5 mol%), CH_2Cl_2, −40 °C, 1 d	*S*	97	80	[114]
Ph	Me	1.1	Cs_2CO_3 (3 equiv), **64** (5 mol%), CH_2Cl_2, −40 °C, 1–2 d	*R*	85	91	[114]
Me	Ph	0.83	**65** (10 mol%), *t*-BuOMe, rt, 5 d	n.r.	91	87	[115]
Me	Et	0.83	**65** (10 mol%), *t*-BuOMe, rt, 5 d	n.r.	80	85	[115]
$(CH_2)_4$		0.83	**65** (10 mol%), *t*-BuOMe, rt, 5 d	n.r.	89	93	[115]
H	Ph	1.5	**66** (20 mol%), toluene, 4 °C, 1–4 d	*S*	96	63	[116]
H	Et	1.5	**66** (20 mol%), toluene, 4 °C, 1–4 d	*R*	94	87	[116]
H	(*E*)-CH=CHMe	1.5	**66** (20 mol%), toluene, 4 °C, 1–4 d	*S*	96	90	[116]

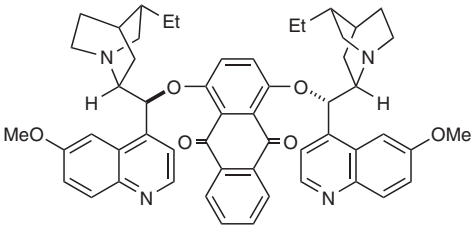
[a] Relative to $(PhSO_2)_2CHF$.
[b] n.r. = not reported.

Scheme 48 Transformation of a β-[Fluorobis(phenylsulfonyl)methyl] Ketone[115]

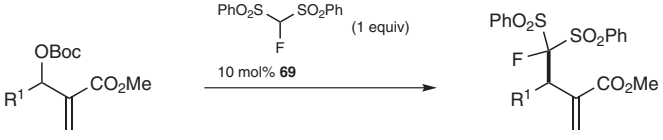


Enantioselective reaction between fluorobis(phenylsulfonyl)methane and racemic Morita–Baylis–Hillman carbonates **70** catalyzed by a bis(cinchona alkaloid) (e.g., **69**) provides allylic fluorobis(phenylsulfonyl)methylation products **71** in good to excellent yields (Scheme 49).[117,118] In cases of Morita–Baylis–Hillman carbonates derived from aromatic aldehydes, the fluorobis(phenylsulfonyl)methylation using hydroquinidine (anthra-9,10-quinone-1,4-diyl) diether **69** as the catalyst affords compounds **71** with high enantiomeric excesses of 84–97%. Cooperative catalysis using **69** and a Lewis acid, particularly iron(II) chloride, is more effective for this transformation and using this cooperative system the products **71** are furnished with over 90% enantiomeric excess for all aryl-substituted substrates.[117] When toluene is used as the solvent, the enantiopure products can be obtained in good yields after a simple filtration.[118] However, Morita–Baylis–Hillman carbonates derived from aliphatic aldehydes give the products **71** with only low enantioselectivity.[117] The β-[fluorobis(phenylsulfonyl)methyl] esters **71** obtained can be efficiently converted into β-(fluoromethylated) esters without any loss of enantiomeric purity (Scheme 50).[117]

Scheme 49 Enantioselective Nucleophilic Fluoromethylation of Morita–Baylis–Hillman Carbonates Using Fluorobis(phenylsulfonyl)methane[117,118]



69

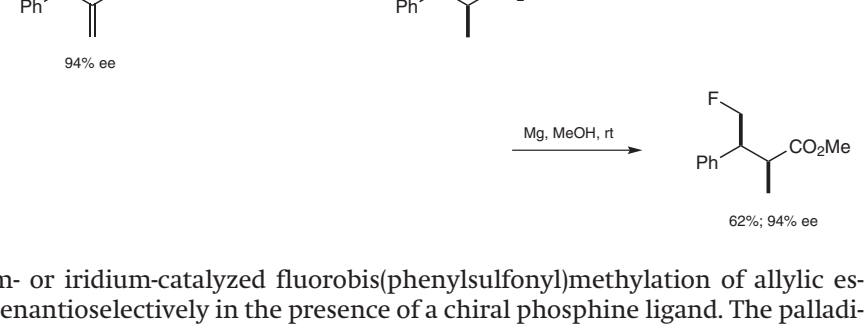


70 (1.1 equiv) **71**

R^1	Conditions	ee (%)	Yield (%)	Ref
Ph	$PhCF_3$, 40 °C, 3–4 d	94	93	[117]
2-ClC_6H_4	$PhCF_3$, 40 °C, 3–4 d	87	80	[117]
Me	$PhCF_3$, 40 °C, 3–4 d	22	66	[117]
2-ClC_6H_4	$FeCl_2$ (10 mol%), $PhCF_3$, 40 °C, 3–4 d	95	80	[117]
2-ClC_6H_4	toluene, 50 °C, 48 h, then filtration	>99.9	72[a]	[118]

[a] 1.5 equiv of **70** was used.

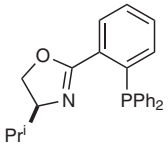
Scheme 50 Transformation of an Allylic Fluorobis(phenylsulfonyl)methylation Product via Desulfonylation[117]



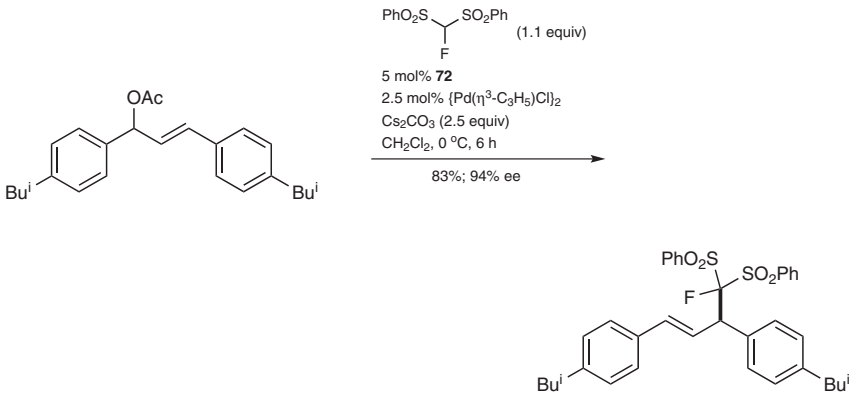
The palladium- or iridium-catalyzed fluorobis(phenylsulfonyl)methylation of allylic esters proceeds enantioselectively in the presence of a chiral phosphine ligand. The palladium-catalyzed reaction between 1,3-disubstituted allylic acetates and fluorobis(phenylsulfonyl)methane using a chiral phosphine ligand gives the fluorobis(phenylsulfonyl)methylated products (e.g., **73**) with high enantioselectivities.[110] The choice of chiral ligand is dependent on the structure of the allylic acetate: (4*S*)-2-[2-(diphenylphosphino)phenyl]-4-isopropyl-4,5-dihydrooxazole (**72**) is best for 1,3-diaryl-substituted allylic acetates (Scheme 51),[110] whereas *N*,*N*′-[(1*R*,2*R*)-cyclohexane-1,2-diyl]bis[2-(diphenylphosphino)-benzamide] is best for cyclic allylic acetates.[110]

for references see p 455

Scheme 51 Palladium-Catalyzed Enantioselective Nucleophilic Fluorobis(phenylsulfonyl)-methylation of an Allylic Acetate Using Fluorobis(phenylsulfonyl)methane[110]



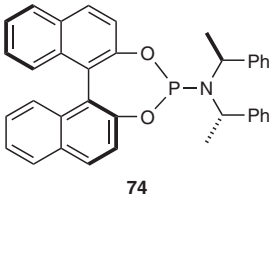
72



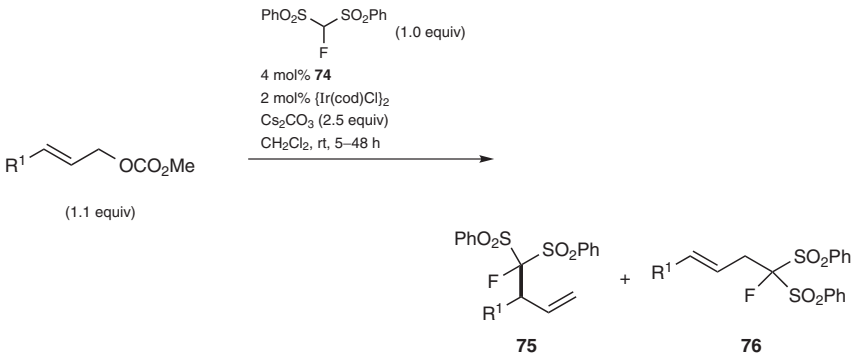
73

When monosubstituted allyl methyl carbonates are used, the iridium-catalyzed fluorobis-(phenylsulfonyl)methylation using chloro(cycloocta-1,5-diene)iridium(I) dimer {[Ir(-cod)Cl]$_2$} and a phosphoramidite ligand such as **74** gives predominantly the branched products **75** with high enantioselectivities (Scheme 52).[119] Both aromatic allylic carbonates and aliphatic allylic carbonates are suitable substrates, although the latter give slightly lower enantiomeric excesses.[119]

Scheme 52 Iridium-Catalyzed Enantioselective Nucleophilic Fluorobis(phenylsulfonyl)-methylation of Allyl Carbonates Using Fluorobis(phenylsulfonyl)methane[119]



74

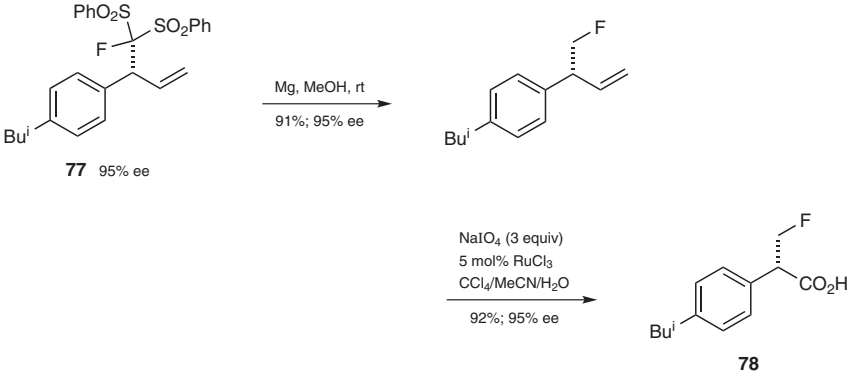


R^1	Ratio[a] (**75**/**76**)	ee (%)	Yield (%) of **75**	Ref
4-iBuC_6H_4	97:3	95	96	[119]
3-$MeOC_6H_4$	95:5	91	91	[119]
4-BrC_6H_4	99:1	92	66	[119]
4-BrC_6H_4	99:1	>99[b]	54[b]	[119]
(*E*)-CH=CHMe	84:16	75	52	[119]
Me	87:13	89	92	[119]

[a] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture.
[b] After recrystallization.

The phenylsulfonyl groups in the fluorobis(phenylsulfonyl)methylated products can be removed either directly (for terminal alkenes such as **77**)[119] or after further transformation (for conjugated alkenes such as **73**).[110] For example, the reductive desulfonylation of **77** with activated magnesium in methanol followed by oxidation catalyzed by ruthenium(III) chloride gives monofluorinated ibuprofen analogue **78** in 84% overall yield without loss of enantiomeric purity (Scheme 53).[119]

Scheme 53 Transformation of an Allylic Fluorobis(phenylsulfonyl)methylation Product via Desulfonylation–Oxidation[119]

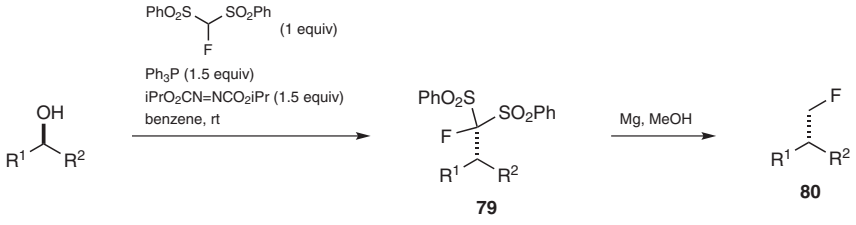


Stereoselective nucleophilic substitution between chiral alcohols and fluorobis(phenylsulfonyl)methane under Mitsunobu conditions gives the fluorobis(phenylsulfonyl)methylated products **79** with full inversion of the configuration.[120] The reaction is performed under mild conditions and is amenable to primary, secondary, allylic, benzylic, and alicy-

for references see p 455

clic alcohols (Scheme 54).[120] Although alkyl halides can also be used as the electrophiles, the direct reaction with secondary alkyl halides is less efficient than this Mitsunobu reaction with secondary alcohols.[121]

Scheme 54 Stereoselective Nucleophilic Fluoromethylation of Alcohols Using Fluorobis(phenylsulfonyl)methane under Mitsunobu Conditions[120]

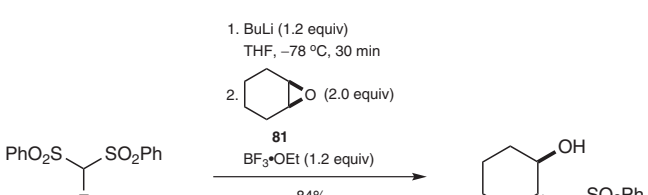


R^1	R^2	Yield[a] (%)		Ref
		79	**80**	
4-Tol	H	90	n.r.	[120]
(*E*)-CH=CHPh	H	80	74	[120]
Ph	Bn	67[b]	76	[120]
Ph	Me	81	n.r.	[120]
$(CH_2)_5$		60	n.r.	[120]

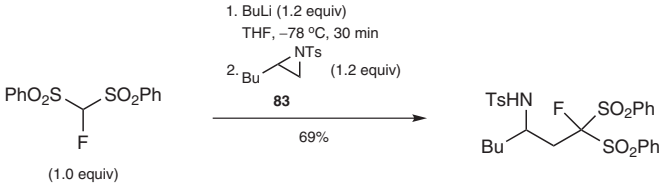
[a] n.r. = not reported.
[b] The racemic alcohol was used.

Furthermore, nucleophilic substitution of epoxides (e.g., **81**) and aziridines (e.g., **83**) with fluorobis(phenylsulfonyl)methane gives the precursors (e.g., **82**) of β-fluoromethylated alcohols and amines in high yields (Schemes 55 and 56). This protocol is more efficient than the nucleophilic reaction with fluoromethyl phenyl sulfone.[109]

Scheme 55 Nucleophilic Fluorobis(phenylsulfonyl)methylation of an Epoxide Using Fluorobis(phenylsulfonyl)methane[109]



Scheme 56 Nucleophilic Fluorobis(phenylsulfonyl)methylation of an Aziridine Using Fluorobis(phenylsulfonyl)methane[109]



***tert*-Butyl [(1*S*)-2-Fluoro-1-phenyl-2,2-bis(phenylsulfonyl)ethyl]carbamate (62); Typical Procedure:**[113]

$(PhSO_2)_2CHF$ (118.5 mg, 0.38 mmol) was added in one portion to a mixture of *tert*-butyl [phenyl(phenylsulfonyl)methyl]carbamate (121.6 mg, 0.35 mmol), *N*-benzylquinidinium chloride (**61**; 7.9 mg, 0.018 mmol), and $CsOH•H_2O$ (70.5 mg, 0.42 mmol) in CH_2Cl_2 (1.0 mL) at −80 °C. The mixture was then vigorously stirred at the same temperature. After 1 d, the reaction was quenched with sat. aq NH_4Cl and the mixture was extracted with EtOAc (2 × 5 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated, and the residue was purified by column chromatography (silica gel, acetone/hexane 1:5) to afford the product as a white solid; yield: 92%; 96% ee; $[\alpha]_D^{25}$ 39.6 (*c* 1.0, $CHCl_3$).

***tert*-Butyl [(1*S*)-2-Fluoro-1-phenylethyl]carbamate (63); Typical Procedure:**[113]

Under N_2, a flask containing Mg (145.8 mg, 6.0 mmol) was heated to dry it. The flask was cooled to 0 °C, and then MeOH (0.28 mL) and *tert*-butyl [(1*S*)-2-fluoro-1-phenyl-2,2-bis(phenylsulfonyl)ethyl]carbamate (**62**; 96% ee; 103.7 mg, 0.20 mmol) were added. After the mixture had been stirred at 0 °C for 2 h, the reaction was quenched with sat. aq NH_4Cl and the mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated, and the residue was purified by column chromatography (silica gel, EtOAc/hexane 1:10) to afford the product as a white solid; yield: 40.2 mg (84%; 77% for 2 steps); 95% ee; $[\alpha]_D^{25}$ +43.1 (*c* 0.40, $CHCl_3$).

(3*S*)-4-Fluoro-1,3-diphenyl-4,4-bis(phenylsulfonyl)butan-1-one (68, $R^1 = R^2 = Ph$); Typical Procedure:[114]

(*E*)-1,3-Diphenylprop-2-en-1-one (**67**, $R^1 = R^2 = Ph$; 80.3 mg, 0.385 mmol) was added in one portion to a mixture of $(PhSO_2)_2CHF$ (110.0 mg, 0.350 mmol), *N*-{3,5-bis[3,5-bis(trifluoromethyl)phenyl]benzyl}quinidinium bromide (**64**; 16.1 mg, 0.018 mmol), and Cs_2CO_3 (342.1 mg, 1.05 mmol) in CH_2Cl_2 (0.7 mL) at −40 °C. After the mixture had been stirred at −40 °C for 1 d, the reaction was quenched with sat. aq NH_4Cl. Then, the mixture was extracted with CH_2Cl_2, and the extract was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (silica gel, acetone/hexane 1:4) to give the product as a white solid; yield: 145.7 mg (80%); 97% ee; $[\alpha]_D^{25}$ −226.4 (*c* 1.0, $CHCl_3$).

β-[Fluorobis(phenylsulfonyl)methyl] Ketones 68; General Procedure Using 9-Amino-9-deoxyepiquinine (65) as Catalyst:[115]

The α,β-enone **67** (0.3 mmol) was added to a stirred mixture of $(PhSO_2)_2CHF$ (113.1 mg, 0.36 mmol) and 9-amino-9-deoxyepiquinine (**65**; 9.7 mg, 0.03 mmol) in *t*-BuOMe (0.6 mL) at rt. After the mixture had been stirred at rt for 5 d, the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel).

for references see p 455

Methyl (3*R*)-4-Fluoro-2-methylene-3-phenyl-4,4-bis(phenylsulfonyl)butanoate (71, R^1 = Ph); Typical Procedure:[117]

A mixture of Morita–Baylis–Hillman carbonate **70** (R^1 = Ph; 32.2 mg, 0.110 mmol), $(PhSO_2)_2CHF$ (31.4 mg, 0.100 mmol), and bis(cinchona alkaloid) **69** (8.6 mg, 0.010 mmol) was dissolved in anhyd $PhCF_3$ (1.0 mL), and the mixture was warmed at 40 °C. After the mixture had been stirred at 40 °C for 3 d, the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane/CH_2Cl_2 1:4) to give the product as a white solid; yield: 45.4 mg (93%); 94% ee; $[\alpha]_D^{25}$ −57.8 (*c* 0.54, $CHCl_3$).

2-Substituted (2*S*)-1-Fluoro-1,1-bis(phenylsulfonyl)but-3-enes 75**; General Procedure:**[119]

Into a dry Schlenk tube filled with argon were added $\{Ir(cod)Cl\}_2$ (2.7 mg, 0.004 mmol), phosphoramidite ligand **74** (4.3 mg, 0.008 mmol), THF (0.5 mL), and $PrNH_2$ (0.3 mL). The mixture was heated at 50 °C for 30 min and then the volatile solvents were removed under reduced pressure to give a yellow solid. After that, allylic carbonate (0.22 mmol), $(PhSO_2)_2CHF$ (62.8 mg, 0.20 mmol), Cs_2CO_3 (163 mg, 0.50 mmol), and CH_2Cl_2 (2.0 mL) were added. The reaction was stirred at rt until the carbonate had been fully consumed, as monitored by TLC or ^1H NMR spectroscopy. Then, the crude mixture was filtered over Celite and the solvent was removed under reduced pressure. The ratio of regioisomers was determined by ^1H NMR spectroscopy of the crude mixture. The crude residue was purified by flash column chromatography (silica gel, petroleum ether/EtOAc).

1-[2-Fluoro-2,2-bis(phenylsulfonyl)ethyl]-4-methylbenzene (79, R^1 = 4-Tol; R^2 = H); Typical Procedure:[120]

A soln of diisopropyl azodicarboxylate (0.29 mL, 1.5 mmol) in benzene (**CAUTION:** *carcinogen*) was added under argon to a Schlenk flask containing a mixture of $(PhSO_2)_2CHF$ (314 mg, 1.0 mmol), (4-tolyl)methanol (134 mg, 1.1 mmol), and Ph_3P (393 mg, 1.5 mmol) in anhyd benzene (5 mL). The mixture was stirred at rt and, after completion of the reaction as monitored by ^{19}F NMR spectroscopy, H_2O was added. The mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. Purification of the residue by column chromatography (silica gel, hexane/CH_2Cl_2 gradient) gave the product as a white powder; yield: 379 mg (90%).

(1*R,2*R**)-2-[Fluorobis(phenylsulfonyl)methyl]cyclohexanol (82); Typical Procedure:**[109]

To a soln of $(PhSO_2)_2CHF$ (157 mg, 0.5 mmol) in THF (5 mL) at −78 °C was added a 2.5 M soln of BuLi in hexane (0.24 mL, 0.6 mmol). After the mixture had been stirred at that temperature for 30 min, $BF_3{\bullet}OEt_2$ (0.6 mmol) was added followed by the addition of cyclohexene oxide (**81**; 98 mg, 1.0 mmol). After the mixture had been stirred at temperatures ranging from −78 °C to rt for 2 h, the reaction was quenched with sat. aq $NaHCO_3$ (5 mL). The mixture was extracted with EtOAc (3 × 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, petroleum ether/EtOAc 2.5:1) afforded the product as a white solid; yield: 173 mg (84%); mp 143–145 °C.

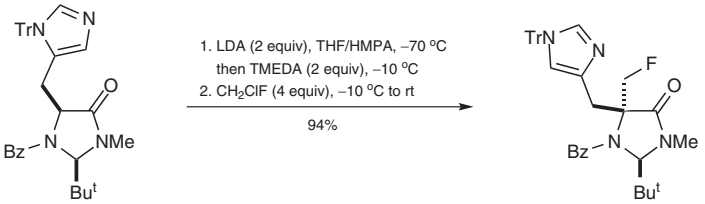
2.6.2.2.2 Electrophilic Fluoromethylation

Electrophilic fluoromethylation is rare; however, some carbon acids have been fluoromethylated using chloro(fluoro)methane, bromo(fluoro)methane, and *S*-(fluoromethyl)-sulfonium salts.

2.6.2.2.1 Using Chloro(fluoro)methane and Bromo(fluoro)methane

Although chloro(fluoro)methane is a frequently used reagent for the fluoromethylation of oxygen, nitrogen, and sulfur nucleophiles,[122] its use in the fluoromethylation of carbon acids is rare. One reported example is the electrophilic fluoromethylation of α-amido amide **84** under the action of a base giving fluoromethylated product **85** in excellent yield (Scheme 57).[123] Similarly, bromo(fluoro)methane has been used for the fluoromethylation of 2-amidomalonates in moderate yields.[74] However, these reagents are not applicable for the fluoromethylation of activated C—H bonds in simple amides, ketones, and α-oxo esters.[122]

Scheme 57 Electrophilic Fluoromethylation of an α-Amido Amide Using Chloro(fluoro)methane[123]

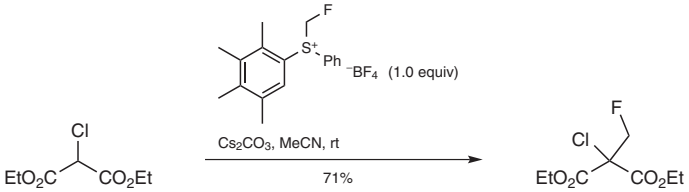


84 **85**

2.6.2.2.2 Using *S*-(Fluoromethyl)sulfonium Salts

S-(Fluoromethyl)-*S*-phenyl-*S*-(2,3,4,5-tetramethylphenyl)sulfonium tetrafluoroborate can be used for the electrophilic fluoromethylation of some carbon acids.[124] For example, fluoromethylation of diethyl 2-chloromalonate under the action of cesium carbonate gives the fluoromethylated compound in 71% yield (Scheme 58).[124] However, only trisubstituted carbon acids with at least two electron-withdrawing groups are suitable precursors for this reaction.

Scheme 58 Electrophilic Fluoromethylation of a Trisubstituted Carbon Acid Using an *S*-(Fluoromethyl)sulfonium Salt[124]



(1.0 equiv)

2.6.2.3 Free-Radical Fluoromethylation

Unlike free-radical trifluoromethylation and difluoromethylation, free-radical fluoromethylation is rare; very recently, zinc(II) fluoromethanesulfinate has been developed as a synthetically useful free-radical fluoromethylation reagent.

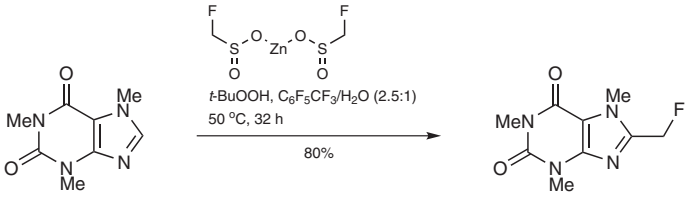
2.6.2.3.1 Using Zinc(II) Fluoromethanesulfinate

Zinc(II) fluoromethanesulfinate is a radical fluoromethylation reagent under the action of *tert*-butyl hydroperoxide.[81] Some heteroaromatics including caffeine and its derivatives, 2-methylquinoxaline, 3-acetyl-1-methyl-1*H*-pyrrole, and ethyl pyridine-4-carboxylate are

for references see p 455

fluoromethylated in moderate to good yields. For example, the fluoromethylation of caffeine in a perfluorotoluene/water solvent system gives the fluoromethylated compound in 80% yield (Scheme 59).[81] For reactions that do not go to completion in 12–24 hours, a second portion of zinc(II) fluoromethanesulfinate (2–3 equiv overall) and *tert*-butyl hydroperoxide (3–5 equiv overall) may be added to drive the reaction further.[81]

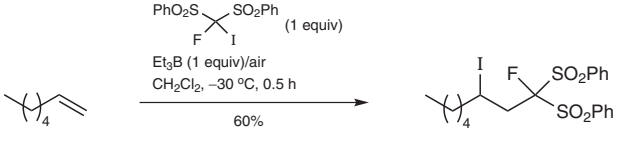
Scheme 59 Free-Radical Fluoromethylation of a Hetarene Using Zinc(II) Fluoromethanesulfinate[81]



2.6.2.2.3.2 Using Fluoro(iodo)bis(phenylsulfonyl)methane

Fluoro(iodo)bis(phenylsulfonyl)methane can undergo a radical addition reaction with terminal alkenes under similar conditions to those used for difluoro(iodo)(phenylsulfonyl)methane.[125] For example, fluoro(iodo)bis(phenylsulfonyl)methylation of hept-1-ene initiated by triethylborane/air affords 1-fluoro-3-iodo-1,1-bis(phenylsulfonyl)octane in 60% yield (Scheme 60).[125] However, the further conversion of fluorobis(phenylsulfonyl)methyl compounds obtained by this method into fluoromethyl compounds is not reported.

Scheme 60 Free-Radical Fluorobis(phenylsulfonyl)methylation of an Alkene Using Fluoro(iodo)bis(phenylsulfonyl)methane[125]



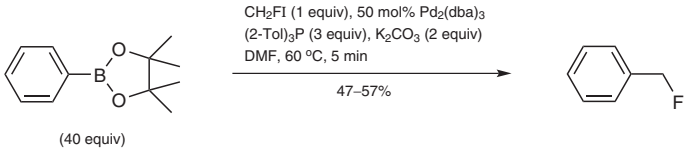
2.6.2.2.4 Fluoromethylation with Transition-Metal Complexes

Coupling reactions involving fluoromethyl–transition-metal complexes are still underdeveloped; however, it has been reported that some fluoromethylated (hetero)aromatics can be prepared by palladium-mediated fluoromethylation of arylboronates using fluoro(iodo)methane, and copper-mediated or -catalyzed fluoromethylation of hetaryl and aryl iodides using fluoro(iodo)methyl 2-pyridyl sulfone.

2.6.2.2.4.1 Using Fluoro(iodo)methane

The only reported example is the coupling reaction of fluoro(iodo)methane and pinacol phenylboronate mediated by a palladium(0)–phosphine complex to give (fluoromethyl)benzene in up to 57% yield (Scheme 61).[126] (Fluoromethyl)benzene is proposed to be formed by reductive elimination from a (fluoromethyl)palladium(II) complex.[126] Although a large excess of the arylboronate is required, this methodology is potentially useful for quick access to ^{18}F-labeled (fluoromethyl)arenes from ^{18}F-labeled fluoro(iodo)methane.[126]

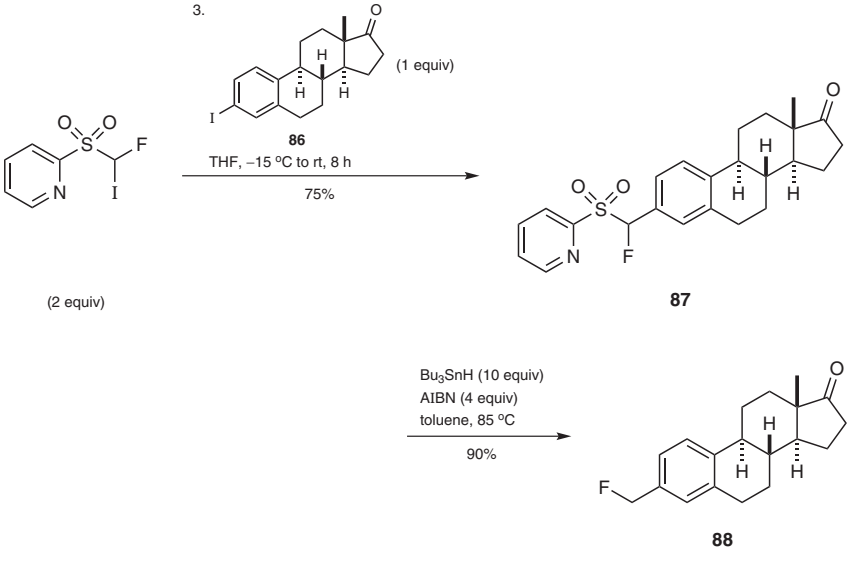
Scheme 61 Palladium-Mediated Fluoromethylation of an Arylboronate Using Fluoro(iodo)methane[126]



2.6.2.2.4.2 Using Fluoro(iodo)methyl 2-Pyridyl Sulfone

The copper-mediated or -catalyzed cross-coupling reaction of hetaryl and aryl iodides with fluoro(iodo)methyl 2-pyridyl sulfone under the action of diethylzinc can be used for the synthesis of fluoromethylated (hetero)aromatics.[127] The [fluoro(2-pyridylsulfonyl)methyl]copper(I) species involved in the reaction is generated by zinc–iodine exchange between fluoro(iodo)methyl 2-pyridyl sulfone and diethylzinc followed by transmetalation with copper(I) iodide.[127] When a stoichiometric amount of copper(I) iodide is used, the coupling reaction proceeds smoothly at room temperature affording fluoro(2-pyridylsulfonyl)methylated aromatics in good to excellent yields. The coupling reaction can also proceed catalytically with 30 mol% of copper(I) iodide; however, an elevated temperature (usually 60 °C) is required and slightly lower yields are obtained.[127] The reaction tolerates several reactive functionalities on the aromatic ring, such as hydroxy groups, aldehydes, and ketones. Bromo- and chloro-substituted iodoarenes react selectively at the aryl—iodine bond. The method is amenable to the late-stage fluoromethylation of biologically active molecules. For example, the coupling reaction between 3-iodo-3-deoxyestrone (**86**) and fluoro(iodo)methyl 2-pyridyl sulfone mediated by stoichiometric amounts of diethylzinc and copper(I) iodide to give compound **87**, followed by radical hydrodesulfonylation, affords 3-(fluoromethyl)-3-deoxyestrone (**88**) in 68% overall yield (Scheme 62).[127]

Scheme 62 Copper-Mediated Fluoromethylation of an Aryl Iodide Using Fluoro(iodo)methyl 2-Pyridyl Sulfone[127]



for references see p 455

3-Fluoro(2-pyridylsulfonyl)methyl-3-deoxyestrone (87); Typical Procedure:[127]
Under argon, a 1.0 M soln of Et_2Zn in hexane (0.3 mmol) was added to a soln of fluoro(iodo)methyl 2-pyridyl sulfone (150 mg, 0.50 mmol) in DMF (2 mL) at −30 °C. The mixture was warmed to −25 °C over 5 min, and then CuI (95 mg, 0.50 mmol) was added. After the mixture had been warmed to −15 °C and all CuI had dissolved (within 15 min), 3-iodo-3-deoxyestrone (**86**; 95 mg, 0.25 mmol) in THF (2 mL) was added. After the mixture had been stirred at rt for 8 h, H_2O was added and the mixture was extracted with EtOAc (3 ×). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel); yield: 80 mg (75%).

3-(Fluoromethyl)-3-deoxyestrone (88); Typical Procedure:[127]
Argon was bubbled through a soln of 3-fluoro(2-pyridylsulfonyl)methyl-3-deoxyestrone (**87**; 33 mg, 0.077 mmol) in toluene (3 mL) for 30 min, and Bu_3SnH (40 μL, 0.15 mmol) was added. After argon had been bubbled through the mixture for 5 min, AIBN (10 mg, 0.06 mmol) was added, and the soln was heated at 85 °C. Additional Bu_3SnH (4 × 40 μL, 0.6 mmol) and AIBN (4 × 10 mg, 0.24 mmol) were added after 2 h, 4 h, 10 h, and 16 h. After completion of the reaction as monitored by ^{19}F NMR spectroscopy, the mixture was concentrated and the residue was purified by column chromatography (silica gel); yield: 20 mg (90%; 68% from **86**); mp 158–160 °C.

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