

## Abstracts

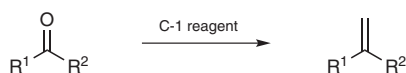
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### 2.1.1 Modern Variants of Wittig, Peterson, and Tebbe Protocols

*C. Müller, M. Cokoja, and F. E. Kühn*

The reaction of carbanions with aldehydes or ketones is the most established strategy for the preparation of alkenes via alkenation. Generally, the carbanion is stabilized by an electron-withdrawing group and, depending on its nature, these are known as Wittig, Horner–Wittig, Horner–Wadsworth–Emmons (phosphorus-based), Julia (sulfur-based), and Peterson (silicon-based) alkenation reactions. Carbonyl alkenations can also be carried out with metal carbenes, carbenoids, or *gem*-dimetal complexes, using titanium (Tebbe reagent), zinc, chromium, or zirconium.

This section discusses the introduction of C-1 units using the Wittig, Peterson, and Tebbe protocols, with a special focus on new developments.



R<sup>1</sup> = alkyl, aryl; R<sup>2</sup> = alkyl, OR<sup>3</sup>, NR<sup>3</sup><sub>2</sub>

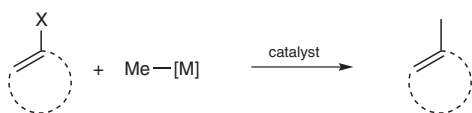
**Keywords:** methylenation • Wittig reaction • Peterson alkenation • Tebbe reagent • Petasis reagent • Takai alkenation • Nysted reagent

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### 2.2.1 Cross-Coupling Methods for Methylation

*G. A. Molander and D. Ryu*

Transition-metal-catalyzed cross-coupling reactions provide a facile way to introduce methyl groups onto aryl, hetaryl, and alkenyl halide electrophiles. This chapter outlines the various reagents that are utilized in such transformations.



**Keywords:** methylation • cross coupling • catalysis • Suzuki coupling • Negishi coupling • Stille coupling

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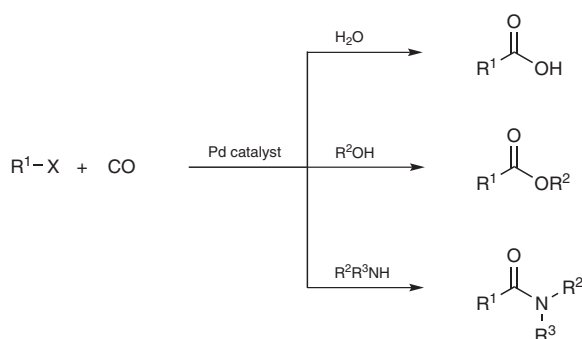
### 2.2.2 Carbonylation of Aryl and Vinyl Halides

*H. Neumann and J. Schranck*

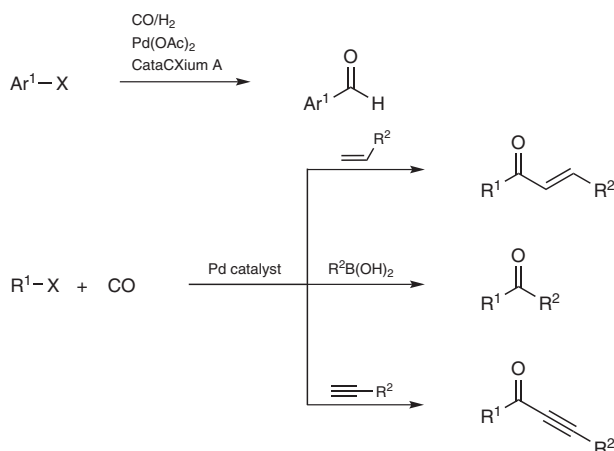
The carbonylation of aryl and vinyl halides gives arenecarboxylic acids and  $\alpha,\beta$ -unsaturated carboxylic acids, respectively. Alkoxy-carbonylation and aminocarbonylation of the same substrates give esters and amides.

Starting from aryl bromides, aromatic aldehydes can be synthesized in a palladium-catalyzed carbonylation using synthesis gas.

The well-established Heck, Suzuki, and Sonogashira C–C cross-coupling reactions can be carried out in a carbonylative manner using carbon monoxide to give  $\alpha,\beta$ -unsaturated ketones, unsymmetrical ketones, and alkynones, respectively.



R<sup>1</sup> = aryl, vinyl



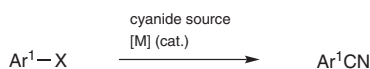
R<sup>1</sup> = aryl, vinyl

**Keywords:** aromatic carboxylic acids · esters · amides · carbon monoxide · aromatic aldehydes · synthesis gas · aryl bromides · CataCXium A ·  $\alpha,\beta$ -unsaturated ketones · unsymmetrical ketones · alkynones · carbonylative Heck reaction · carbonylative Suzuki reaction · carbonylative Sonogashira reaction

### 2.2.3 Cyanation of Aryl Halides

*A. Ouali and M. Taillefer*

The cyanation of aryl halides (iodides, bromides, and chlorides) constitutes a very useful transformation in organic chemistry. Indeed, it allows the preparation of arenecarbonitriles, which are important intermediates and targets throughout life and material sciences. The most convenient methods for the cyanation of aryl halides (Ar<sup>1</sup>X) involve a transition-metal catalyst and a cyanide source, the most common ones being alkali metal cyanides, zinc cyanide, potassium hexacyanoferrate(II), and, to a lesser extent, cyanohydrins or trimethylsilyl cyanide. The main transition metals able to promote such reactions are nickel, palladium, and copper. The choice of the metal mainly depends on the nature of the aryl halide to be converted, with the reactivity of aryl halides decreasing from aryl iodides to aryl bromides to aryl chlorides. Nickel and palladium systems are able to activate all aryl halides, including the less expensive but less reactive chlorides, while copper catalysts can be used for cyanations of aryl iodides and bromides. In this chapter, emphasis is placed on palladium- and copper-based catalysts, taking into account their better ease of execution, their better sustainability, and the high number of systems reported, compared to their nickel counterparts.



X = I, Br, Cl; M = Pd, Ni, Cu

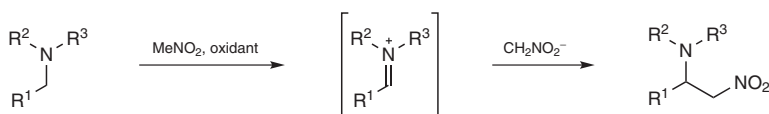
**Keywords:** cyanation · aryl halides · arenecarbonitriles · catalysis · homogeneous · cyanide · nickel · palladium · copper · ligand · potassium cyanide · sodium cyanide · zinc cyanide · potassium hexacyanoferrate(II) · cyanohydrin · trimethylsilyl cyanide · poisoning

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## 2.2.4 Oxidative Coupling of Nitromethane

R. Ballini and M. Petrini

Oxidation of tertiary amines under various conditions generates the corresponding iminium ions, which readily react with the methanenitronate anion, leading to  $\beta$ -nitro amines. Molecular oxygen, peroxides, and peracids are widely used for this purpose in transition-metal-catalyzed reactions. Conversely, organic oxidants such as (diacetoxyiodo)benzene, 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone, and 2,2,6,6-tetramethylpiperidin-1-oxyl are effective without the need for any added catalyst. Visible-light photoinduced coupling reactions are emerging as a safe and environmentally friendly alternative to the above-mentioned procedures. Oxidation is mediated by organometallic complexes of iridium and ruthenium as well as organic sensitizers (rose Bengal and eosin Y) brought into their excited states by irradiation with visible light. Utilization of nitromethyl radicals, obtained by oxidation of nitromethane with ammonium cerium(IV) nitrate, in addition reactions with electron-rich alkenes is limited to the synthesis of nitrosugar derivatives.



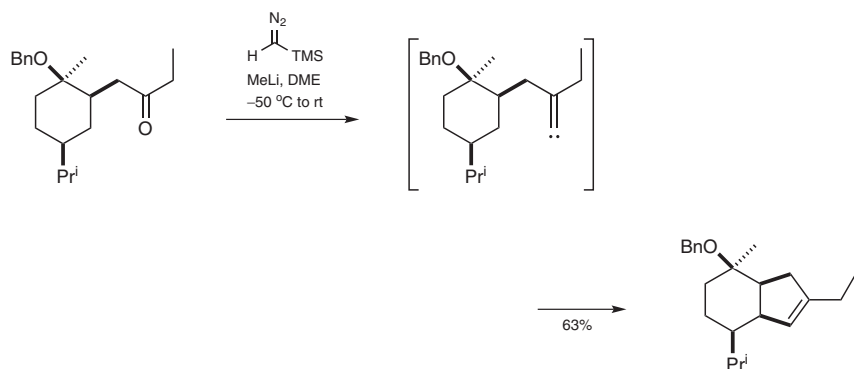
**Keywords:** amines · imines · nitromethane · metal catalysis · nucleophilic addition · organocatalysis · oxidation · photochemistry

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## 2.3.1 Carbene Insertion into C–H Bonds with C-1

M. C. Nicasio and T. R. Belderrain

Treatment of a diazo compound, i.e. a (diazomethyl)phosphonate or diazo(trimethylsilyl)methane, with a base, and subsequent alkenation of a carbonyl compound (Wittig–Hörner reaction or Peterson elimination), followed by decomposition of the resulting diazoalkene affords an alkylidene carbene. This species may undergo intramolecular C–H insertion to generate five-membered carbocyclic or heterocyclic systems. In this chapter, some applications of this methodology in organic synthesis are reviewed.

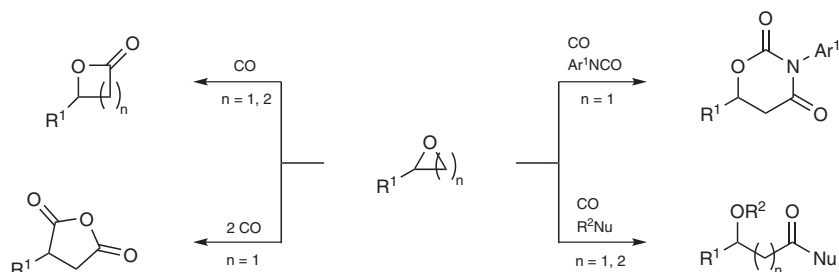


**Keywords:** diazo compounds · diazo(trimethylsilyl)methane · diethyl (diazomethyl)-phosphonate · alkylidene carbenes · C–H insertion reactions · cyclopentenes · 2,5-dihydrofurans · 2,5-dihydropyrroles

## 2.4.1 Carbon Monoxide Insertion into Epoxides and Oxetanes

*H. Ibrahim*

In this chapter, the most significant developments in the relatively unexplored but industrially relevant area of epoxide and oxetane carbonylation are reviewed. The coverage includes only catalytic procedures and excludes hydroformylation chemistry of the substrates discussed herein. Methods include the ring-expansion carbonylation and ring-opening carbonylation of epoxides and oxetanes, with a full coverage of the underdeveloped asymmetric carbonylation of epoxides. A historic and mechanistic background of the chemistry is presented in the General Introduction. The section on epoxide carbonylation begins with the ring-expansion carbonylation of epoxides to  $\beta$ -lactones and is structured according to the diverse catalytic systems reported thus far. This is followed by other carbonylative epoxide ring-expansion reactions. The ring-opening carbonylation of epoxides covers alkoxy- and aminocarbonylation, leading to  $\beta$ -hydroxy carboxylic acid derivatives. The chapter closes with an overview of the relatively few methods reported for oxetane carbonylation.

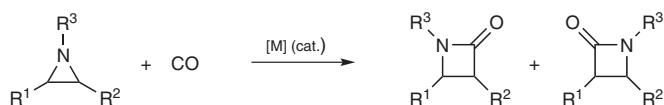


**Keywords:** epoxides ·  $\beta$ -lactones ·  $\beta$ -hydroxy esters · carbonylation · ring-expansion carbonylation · ring-opening carbonylation · octacarbonyldicobalt(0) · cobaltate salts · alkoxycarbonylation · aminocarbonylation

### 2.4.2 Carbon Monoxide Insertion into Aziridines

*H. Ibrahim*

In this chapter, the most significant developments in the area of aziridine carbonylation are reviewed. The majority of procedures deal with the ring-expansion carbonylation of aziridines to  $\beta$ -lactams catalyzed by cobalt, rhodium, or palladium complexes. In the General Introduction, an effort is made to summarize the current mechanistic understanding of these diverse carbonylation systems. The regio- and stereoselectivity of these reactions is then discussed with regard to aziridine substitution and the type of catalytic system used. The chapter closes with short sections on the ring-expansion carbonylation of methyleneaziridines,  $\alpha$ -lactams (aziridin-2-ones), and diaziridines.



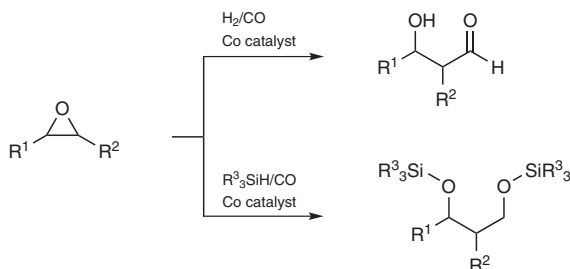
[M] = Co<sup>0</sup>, Rh<sup>I</sup>, Pd<sup>0</sup>

**Keywords:** aziridines ·  $\beta$ -lactam · ring-expansion carbonylation · octacarbonyldicobalt(0) · cobaltate salts · rhodium · palladium ·  $\alpha$ -lactams · azetidine-2,4-diones · aza- $\beta$ -lactams

### 2.5.1 Hydroformylation of Epoxides

*K. Takahashi and K. Nozaki*

The reaction of epoxides with dihydrogen and carbon monoxide catalyzed by cobalt-based complexes affords  $\beta$ -hydroxy aldehydes. This reaction is formally regarded as the hydroformylation of epoxides. Silylformylation of epoxides by the reaction of epoxides with hydrosilanes and carbon monoxide to give 1,3-disiloxyalkanes [bis(silyl ethers)] is a mechanistically related reaction and is also summarized in this chapter.



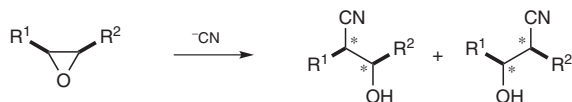
**Keywords:** oxiranes · carbonylation · aldehydes · hydroxy carbonyl compounds · cobalt catalysts · ketols · silanes · silyl ethers · hydroformylation · silylformylation · phosphorus ligands

### 2.5.2 Cyanation of Epoxides

*C. te Grotenhuis, L. Schoonen, and F. P. J. T. Rutjes*

Opening of epoxides with cyanide yields  $\beta$ -cyanoalcohols ( $\beta$ -hydroxy nitriles), which are synthetically versatile intermediates that can be readily converted into a wide array of new functional groups. During the ring-opening reaction two contiguous stereocenters are generated, which can be controlled in several ways. When the reaction is performed

without activation, terminal epoxides can be opened such that attack will take place at the least hindered carbon atom. Addition of a hard Lewis acidic catalyst will lead to activation of the epoxide, due to coordination to the epoxide oxygen atom, allowing the use of electronically and sterically more demanding substrates. Furthermore, ligands surrounding the metal of the catalyst can direct to which position of the epoxide attack will take place. If enantiopure ligands are used, *meso*-epoxides can be desymmetrized, resulting in the formation of a single enantiomer of the  $\beta$ -hydroxy nitrile product.



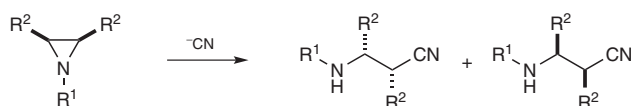
**Keywords:** epoxide · cyanide · cyanation · nucleophilic ring opening · Lewis acid activation ·  $\beta$ -hydroxy nitrile ·  $\beta$ -cyanohydrin

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### 2.5.3 Cyanation of Aziridines

*L. Schoonen, C. te Grotenhuis, and F. P. J. T. Rutjes*

Aziridines, three-membered nitrogen-containing heterocycles, are useful precursors for the synthesis of many biologically interesting molecules, such as  $\alpha$ - and  $\beta$ -amino acids and alkaloids, using ring-opening reactions. In this regard, cyanide is an interesting nucleophile because of its low cost and the synthetic versatility of the resulting  $\beta$ -amino nitriles. Non-activated aziridines, bearing a hydrogen or stabilizing electron-donating substituent, often need activation prior to nucleophilic ring opening. Therefore, only limited examples of cyanide-mediated ring opening of non-activated aziridines are known. Activated aziridines are more readily opened, due to the electron-withdrawing substituent on the nitrogen, which destabilizes the ring structure. In some cases, no additives are required for the reaction to proceed, but in most cases a Lewis acid, Lewis base, metal catalyst, or other additive is employed to achieve stereoselective ring opening.



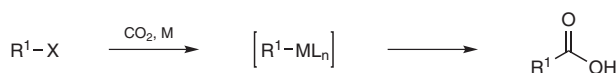
**Keywords:** aziridine · cyanide · cyanation · nucleophilic ring opening ·  $\beta$ -amino nitrile

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### 2.5.4 Carboxylation of Organometallic Reagents

*J. Takaya and N. Iwasawa*

Nucleophilic carboxylations of organometallic compounds, organic halides, and aromatic hydrocarbons with carbon dioxide are promoted by transition-metal catalysts or stoichiometric basic promoters. These reactions provide efficient methods for the synthesis of carboxylic acids and their derivatives.



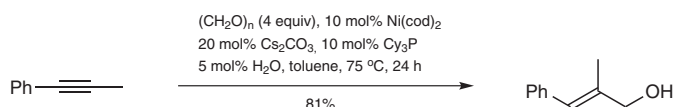
X = less reactive metal, halide, H; M = more reactive metal

**Keywords:** carbon dioxide · carboxylic acids · C–C bond formation · transition metals · nucleophilic addition · organometallic compounds

### 2.5.5 Reaction of Formaldehyde with Organometallic Reagents

*M. Kaposi, J. Witt, M. Cokoja, and F. E. Kühn*

Formaldehyde is one of the most important single-carbon electrophiles; it is inexpensive and can be used in many organic reactions and thus in natural product synthesis. However, there are scant examples of the application of formaldehyde with organometallic reagents in synthesis. This may be due to the properties of formaldehyde. Monomeric formaldehyde tends to polymerize rapidly to give poorly reactive species such as paraformaldehyde and the trimer trioxane. Paraformaldehyde and trioxane are depolymerized thermally; however, thermal cracking produces highly toxic, gaseous formaldehyde that rapidly repolymerizes. Alternatively, paraformaldehyde and trioxane can be depolymerized with Lewis acids, but this introduces new factors, such as corrosion, toxic waste disposal, and difficult handling. Formaldehyde is also available as an aqueous solution, known as formalin, but this approach is often unsuitable due to the instability of the organometallic compounds in the presence of water. This section discusses all that can be achieved despite these factors.



**Keywords:** formaldehyde · hydroxymethylation · aldol reaction · Prins reaction · carbon-yl-ene reaction · hydroformylation · hydrohydroxymethylation

### 2.5.6 Mannich-Type Reactions

*P. Merino*

The nucleophilic addition of enolizable carbonyl compounds to imines and related derivatives such as iminium salts, nitrones, oximes, and hydrazones provides direct access to  $\beta$ -amino carbonyl derivatives. This reactivity has been employed in efficient approaches to the synthesis of enantiomerically pure compounds.



X =  $^+\text{NR}^5_2$ ,  $^+\text{N}(\text{O}^-)\text{R}^5$ ,  $\text{NR}^5$ ,  $\text{NOR}^5$ ,  $\text{NNR}^5\text{R}^6$ ;  $\text{R}^1$  = alkyl, aryl, hetaryl;  
 $\text{R}^2$  = alkyl, aryl, hetaryl;  $\text{R}^3$  = alkyl, aryl, hetaryl;  $\text{R}^4$  = alkyl, aryl, hetaryl, alkoxy

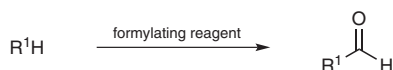
**Keywords:** carbonyl compounds · enolates · hydrazones · imines · iminium salts · Mannich bases · Mannich reaction · nitrones · oximes

### 2.5.7 Formylation and the Vilsmeier Reagent

*N. Zhang and D. Dong*

Formylation, allowing the introduction of a formyl group to an organic molecule, is a useful reaction in organic synthesis. The obtained formyl group can be readily reduced to afford alcohols or oxidized to give acids. Moreover, formylation plays a key role in biological and pharmaceutical fields. This chapter covers formylating reagents that are capable of efficiently introducing a formyl group to various organic molecules. Due to the versa-

tility, ease of operation, and tolerance of many functional groups, the Vilsmeier reaction for the formylation of organic compounds is the main focus of this chapter.



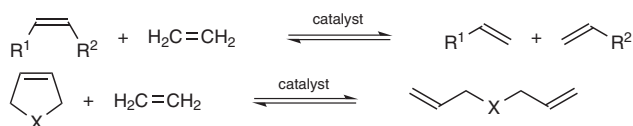
**Keywords:** formylation · magnesium methoxide · paraformaldehyde · hexamethylene-tetramine · acid · carbon monoxide · *N*-methylaniline · transition metal · Vilsmeier–Haack reaction · Vilsmeier reagent · halomethyleniminium salts · phosphoryl chloride · dimethylformamide

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### 2.5.8 Metathesis Adding a C-1 Unit

*C. Bruneau and C. Fischmeister*

This chapter introduces metal-catalyzed cross metathesis with ethene (ethenolysis) as an efficient procedure to cleave internal alkenes and introduce a C-1 unit (a CH<sub>2</sub> group) at both sides of the starting alkene, leading to two terminal alkene groups. Using this strategy, linear alkenes provide two new terminal alkenes whereas cyclic alkenes give rise to dienes.



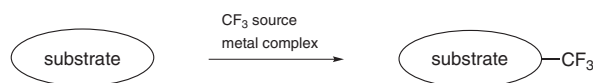
**Keywords:** alkene metathesis · alkenes · C=C bond cleavage · dienes · ethenolysis · molybdenum catalysis · rhenium catalysis · ruthenium catalysis · tungsten catalysis

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### 2.6.1 Trifluoromethylation

*A. Lishchynskiy, P. Novák, and V. V. Grushin*

Metal-catalyzed/-promoted trifluoromethylation reactions represent a powerful tool for the synthesis of a broad variety of organic compounds bearing a CF<sub>3</sub> group on sp<sup>3</sup>, sp<sup>2</sup>, or sp-hybridized carbon atoms.



**Keywords:** trifluoromethylation · fluorine compounds · coupling reactions · copper complexes · copper catalysts · palladium catalysts

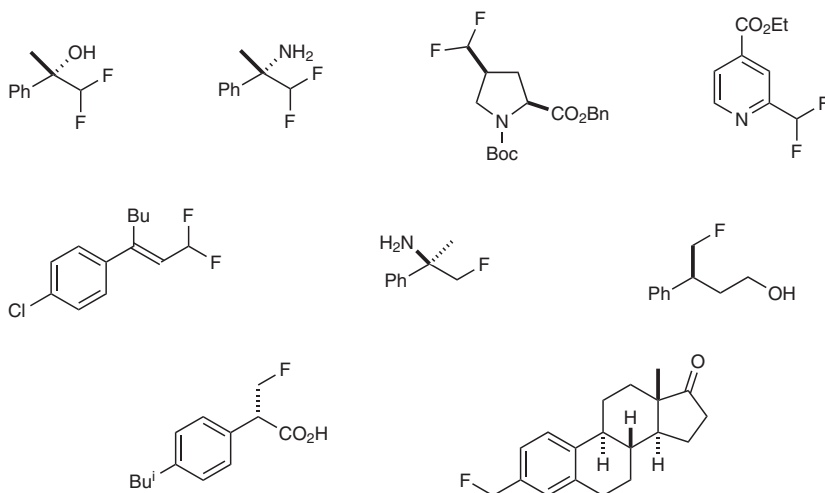
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### 2.6.2 Difluoro- and Fluoromethylation

*J. Hu and C. Ni*

This chapter summarizes the currently known synthetically useful difluoro- and fluoromethylation methods employing various fluorinated C-1 building blocks. The classical routes to difluoro- and fluoromethyl compounds are direct nucleophilic, electrophilic, and free-radical reactions, but more recent developments involving fluoroalkyl transition-metal species are also included.





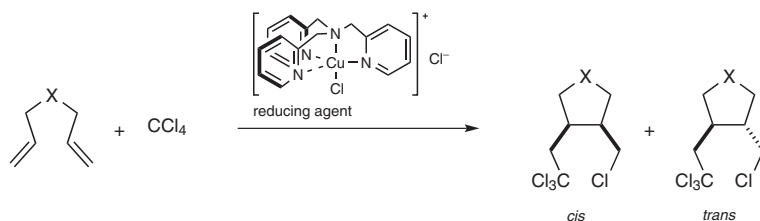
**Keywords:** difluoromethyl compounds · difluoromethylation · fluoromethyl compounds · fluoromethylation · fluoroalkylation · nucleophilic reaction · electrophilic reaction · radical reaction · cross-coupling reactions · auxiliary groups · transition metals · asymmetric synthesis · sulfones · desulfonylation · desulfanylation · dephosphorylation · dehalogenation · sulfoximides · sulfonium salts · iodonium compounds · silanes

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### 2.6.3 Kharasch Reaction (Atom-Transfer Radical Addition Reactions)

*J. M. Muñoz-Molina and T. R. Belderrain*

Since the 1990s, highly active ruthenium and copper catalysts for atom-transfer radical addition (ATRA) reactions have been described and applications of these processes in organic synthesis have been developed. In this chapter are presented some examples of homologation reactions using carbon tetrachloride or haloform polyhalogenated compounds (halogen = Cl, Br) for atom-transfer radical addition for which isolated yields have been reported.



**Keywords:** atom-transfer radical addition · Kharasch addition · transition-metal catalysis · one-carbon homologation · cyclization · polyhaloalkanes · alkenes · haloform · carbon tetrachlorides