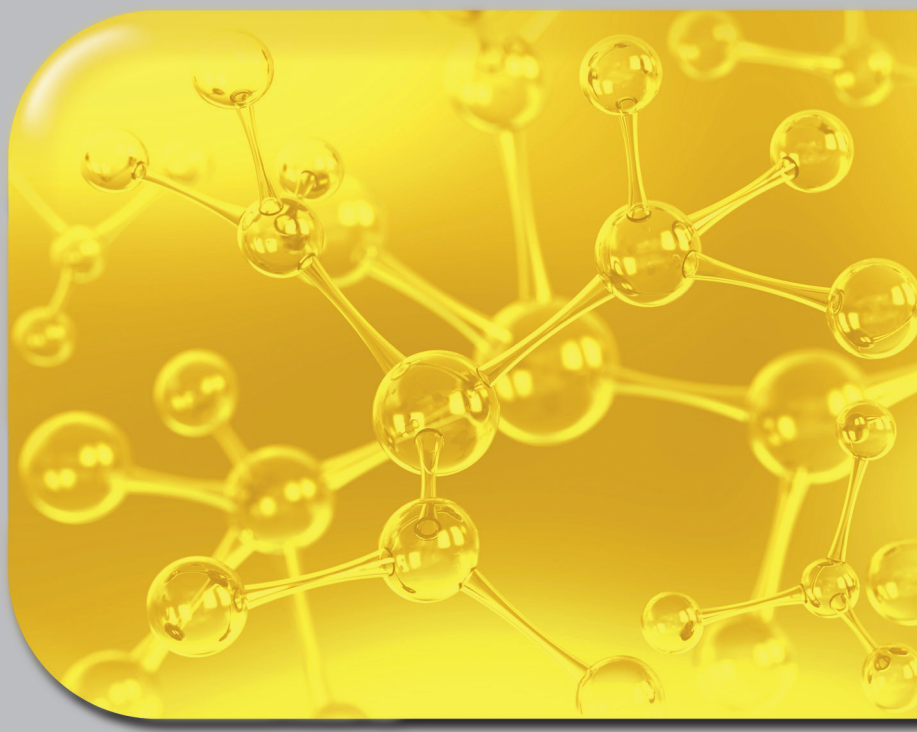
Science of Synthesis

Knowledge Updates 2025/2

Volume Editors
J. J. Li
R. Luisi
Q. Wan



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- Background information and detailed experimental procedures
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Science of Synthesis

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J. J. Li (Vols. 16 and 17)
R. Luisi (Vol. 8)
Q. Wan (Vol. 29)

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Preface

As the pace and breadth of research intensifies, organic synthesis is playing an increasingly central role in the discovery process within all imaginable areas of science: from pharmaceuticals, agrochemicals, and materials science to areas of biology and physics, the most impactful investigations are becoming more and more molecular. As an enabling science, synthetic organic chemistry is uniquely poised to provide access to compounds with exciting and valuable new properties. Organic molecules of extreme complexity can, given expert knowledge, be prepared with exquisite efficiency and selectivity, allowing virtually any phenomenon to be probed at levels never before imagined. With ready access to materials of remarkable structural diversity, critical studies can be conducted that reveal the intimate workings of chemical, biological, or physical processes with stunning detail.

The sheer variety of chemical structural space required for these investigations and the design elements necessary to assemble molecular targets of increasing intricacy place extraordinary demands on the individual synthetic methods used. They must be robust and provide reliably high yields on both small and large scales, have broad applicability, and exhibit high selectivity. Increasingly, synthetic approaches to organic molecules must take into account environmental sustainability. Thus, atom economy and the overall environmental impact of the transformations are taking on increased importance.

The need to provide a dependable source of information on evaluated synthetic methods in organic chemistry embracing these characteristics was first acknowledged over 100 years ago, when the highly regarded reference source **Houben–Weyl Methoden der Organischen Chemie** was first introduced. Recognizing the necessity to provide a modernized, comprehensive, and critical assessment of synthetic organic chemistry, in 2000 Thieme launched **Science of Synthesis, Houben–Weyl Methods of Molecular Transformations**. This effort, assembled by almost 1000 leading experts from both industry and academia, provides a balanced and critical analysis of the entire literature from the early 1800s until the year of publication. The accompanying online version of **Science of Synthesis** provides text, structure, substructure, and reaction searching capabilities by a powerful, yet easy-to-use, intuitive interface.

From 2010 onward, **Science of Synthesis** is being updated quarterly with high-quality content via **Science of Synthesis Knowledge Updates**. The goal of the **Science of Synthesis Knowledge Updates** is to provide a continuous review of the field of synthetic organic chemistry, with an eye toward evaluating and analyzing significant new developments in synthetic methods. A list of stringent criteria for inclusion of each synthetic transformation ensures that only the best and most reliable synthetic methods are incorporated. These efforts guarantee that **Science of Synthesis** will continue to be the most up-to-date electronic database available for the documentation of validated synthetic methods.

Also from 2010, **Science of Synthesis** includes the **Science of Synthesis Reference Library**, comprising volumes covering special topics of organic chemistry in a modular fashion, with six main classifications: (1) Classical, (2) Advances, (3) Transformations, (4) Applications, (5) Structures, and (6) Techniques. Titles will include *Stereoselective Synthesis*, *Water in Organic Synthesis*, and *Asymmetric Organocatalysis*, among others. With expert-evaluated content focusing on subjects of particular current interest, the **Science of Synthesis Reference Library** complements the **Science of Synthesis Knowledge Updates**, to make **Science of Synthesis** the complete information source for the modern synthetic chemist.

The overarching goal of the **Science of Synthesis** Editorial Board is to make the suite of **Science of Synthesis** resources the first and foremost focal point for critically evaluated information on chemical transformations for those individuals involved in the design and construction of organic molecules.

Throughout the years, the chemical community has benefited tremendously from the outstanding contribution of hundreds of highly dedicated expert authors who have devoted their energies and intellectual capital to these projects. We thank all of these individuals for the heroic efforts they have made throughout the entire publication process to make **Science of Synthesis** a reference work of the highest integrity and quality.

The Editorial Board June 2025

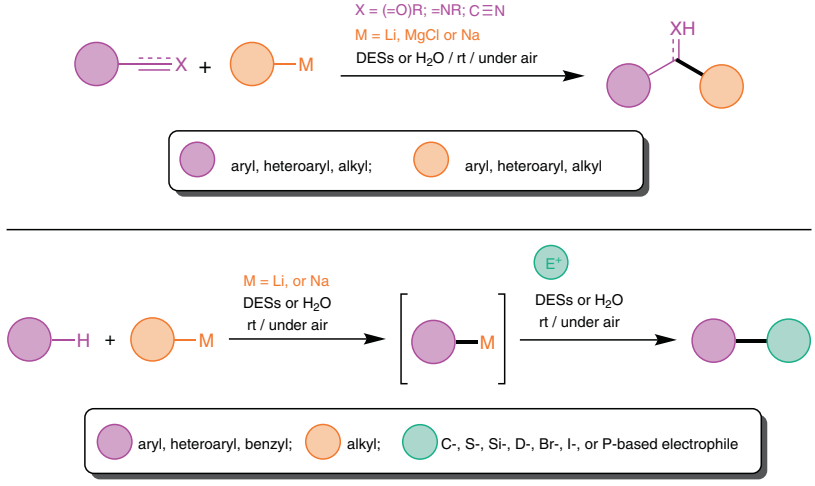
Abstracts

New p 1

8.1.36 **Organolithium Compounds and Related Reagents in Unconventional Reaction Media**

S. E. García-Garrido, A. Presa Soto, and J. García-Álvarez

Challenging the conventional need for inert atmospheres, dry solvents, and strict temperature control when using s-block organometallic reagents (such as Grignard reagents or organolithium/sodium compounds), this *Science of Synthesis* review highlights recent advances that enable their operation under air, at room temperature, and in the presence of moisture. Success has been driven by using sustainable protic solvents, such as water and deep eutectic solvents (DESs). These protocols have proven versatile for key organic transformations, including nucleophilic additions to unsaturated molecules, *ortho*- and lateral lithiation of aromatics, and palladium-catalyzed cross-couplings. Additionally, the development of one-pot tandem hybrid transformations is presented, where these polar s-block organometallic species are effectively integrated with organo-, transition-metal, or biocatalysis.



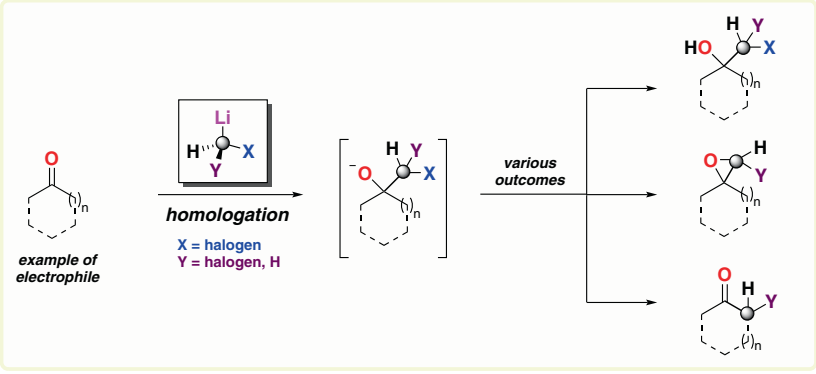
Keywords: organolithium reagents · Grignard reagents · organosodium reagents · water · deep eutectic solvents · green chemistry · alcohols · amines · direct *ortho*-metalation · lateral lithiation · one-pot tandem hybrid transformations

New p 39

8.1.37 **Lithium Halocarbenoids in Modern Synthesis**

L. Ielo and V. Pace

Mono- and dihalo lithium carbenoids have been extensively used in synthesis as homologating agents for introducing C1-units into organic arrays. Although in principle they exhibit both nucleophilic and electrophilic behavior, the former is predominantly observed. Herein, an overview of their reactivity towards carbon electrophiles is presented, together with some recent advancements on modified versions of the (aza- and oxa-) Matteson homologation. Detailed information on the preparation of these agents, as well as the use of emergent technologies (microfluidic techniques) is also discussed. Particular emphasis is given to hitherto elusive fluorinated methyllithiums as a consequence of the impact they could have for introducing CH_2F groups in medicinally relevant structures.



Keywords: carbenoids · nucleophilic addition · nucleophilic substitution · halogen chemistry · fluorine · rearrangements · C1-building blocks · Grignard reaction

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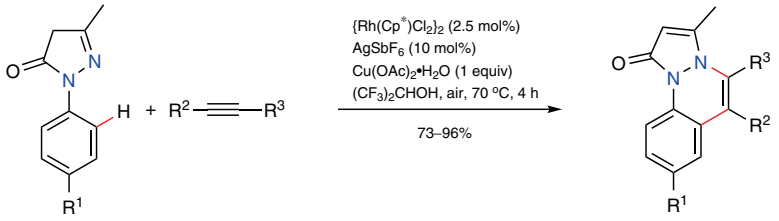
16.9.6 **Cinnolines**

J. J. Li

Cinnoline, also known as 1,2-benzodiazine, is isosteric to traditional all-carbon naphthalene systems. Some synthetic cinnoline-containing compounds have shown biological activity for a diverse collection of targets. In addition to von Richter synthesis, Borsche synthesis, and traditional conditions, more and more transition-metal-catalyzed methods have been developed to prepare cinnolines and functionalize cinnoline-containing compounds. It is also noteworthy that several electrochemical methods have been reported for the synthesis of cinnoline derivatives.



Keywords: cinnolines · aromaticity · bicyclic compounds · von Richter synthesis · Borsche synthesis · cyclization · heterocycles · diazonium ions · sulfoxonium ylides · pyrazole-fused cinnolines · rhodium(III)-catalyzed synthesis · electrochemistry · transition-metal-catalyzed reactions

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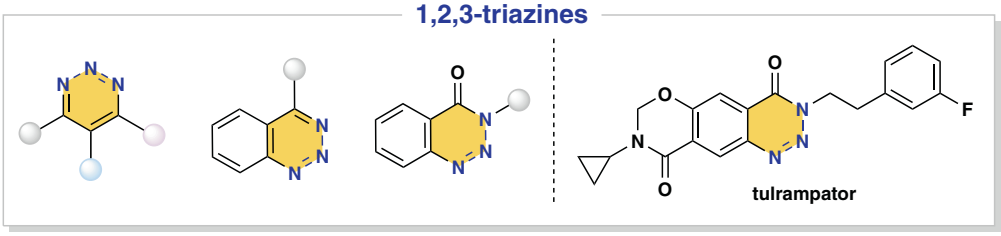
17.2.1.10 **1,2,3-Triazines**

F.-G. Zhang and J.-A. Ma

1,2,3-Triazines, also sometimes known as *v*-triazines, are characterized by three contiguous nitrogen atoms in the six-membered ring. Benzo[1,2,3]triazines and heteroarene-fused 1,2,3-triazine derivatives have found applications in drug development (tulrampator). The reactions of 1,2,3-triazines with primary amines, secondary amines, and thiols make them useful labeling molecules within biological systems. This update covers synthetic methods for the preparation 1,2,3-triazines published between 2013 and 2024.



Keywords: triazines · diazo compounds · azide compounds · cross-coupling reactions · cyclization reactions · heterocycles

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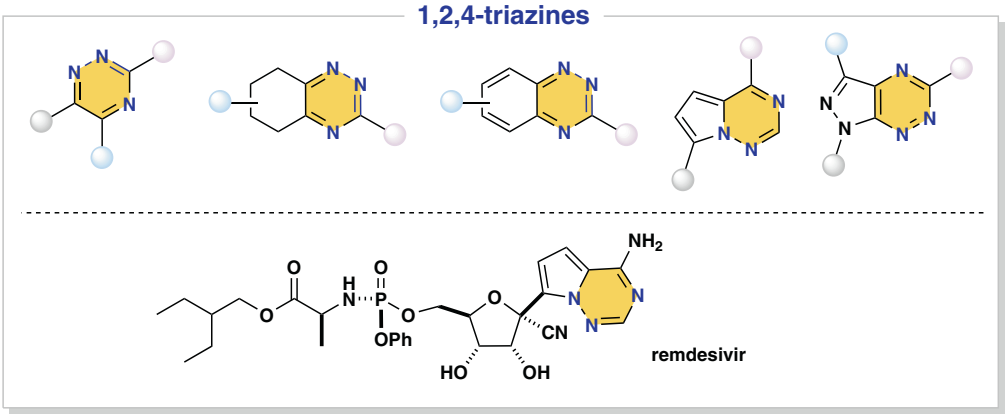
17.2.2.4 **1,2,4-Triazines**

F.-G. Zhang and J.-A. Ma

1,2,4-Triazines, also known as α-triazines, are a type of unsymmetrical six-membered heterocycle bearing three nitrogen atoms. A series of 1,2,4-triazine frameworks are emerging as core structures in an increasing number of bioactive small molecules such as remdesivir. The application of 1,2,4-triazines as cyclic aza-dienes in inverse-electron-demand Diels–Alder (IEDDA) cycloaddition reactions has been established as a useful method in N-heterocycle synthesis, natural product preparation, and bioorthogonal chemistry. This update covers synthetic methods for the preparation 1,2,4-triazines published between 2013 and 2024.



Keywords: triazines · tetrazines · diazo compounds · hydrazines · amidrazones · cyclization reactions · heterocycles

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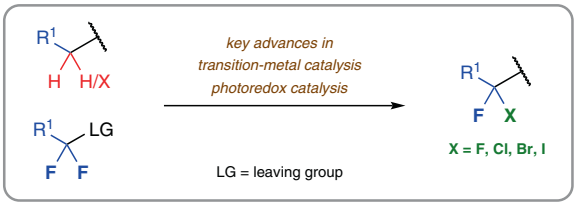
29.1.5 **F/Hal Acetals**

Q. Cheng and X. Shen

This is an update to the 2007 *Science of Synthesis* contribution on F/Hal acetals, and focuses on advances for the synthesis of these compounds that were reported between 2008 and 2023. Such functional units are frequently represented in drugs and materials, and several significant approaches for the synthesis of such compounds that were not covered in the previous chapter have been developed accordingly. Because difluoroalkyl compounds are of particular interest for pharmaceuticals and materials, the advancement of synthetic methods for preparing F/F acetals is occurring more rapidly, and accounts for the major part of this review.



Keywords: F/Hal acetals · difluoroalkylating reagents · fluorination · fluoroalkylation · defluorinative functionalization · transition-metal catalysis · photoredox catalysis · halogenation

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8.1.36 Organolithium Compounds and Related Reagents in Unconventional Reaction Media

S. E. García-Garrido, A. Presa Soto, and J. García-Álvarez

General Introduction

The use of highly polar main-group organometallic reagents derived from the metals of the alkaline group of the periodic table (R^1Li, R^1Na, R^1K, R^1Rb, and R^1Cs) in unconventional solvents [such as water, glycerol, or deep eutectic solvents (DESs)], as a general tool for the synthesis of different products (ranging from alcohols to amines or highly functionalized aromatic products), has not been systematically reviewed from a synthetic organic viewpoint. However, several overviews of this field with a strong organometallic profile have been previously reported.[1–4]

These s^1-group organometallic reagents (mainly R^1Li compounds) are considered as key instruments in the toolbox of synthetic organic chemists, basically due to their high reactivity as a consequence of the large polarity of their metal—carbon bonds.[5] In order to control their inherent high reactivity (with the concomitant desired increase in selectivity), the use of these polar reagents has been traditionally circumscribed to Schlenk-type techniques: inert-atmosphere conditions and carefully dried organic solvents are commonly needed, requiring moreover the employment of very low reaction temperatures (−78 °C).[5–7] However, by using polar unconventional reaction media (e.g., water, glycerol, and deep eutectic solvents), these synthetic organic protocols promoted by organolithium reagents can now take place under aerobic ambient conditions, and under safe conditions (for both human beings and the environment).

Note that DESs are mixtures of Lewis or Brønsted acids and bases that are strongly associated with each other, exhibiting a significant depression of freezing points far below that of ideal mixtures (each component has a higher melting point than the mixture). For a recent review in this field, see ref[8].

SAFETY: The vast majority of the reported examples compiled in this review describe the use of relatively small quantities (0.5–2 mmol) of polar organometallic alkaline reagents, which allows their handling under bench-type conditions using the standard precautions generally taken with other potentially hazardous substances found in a modern chemical laboratory. However, due to the high reactivity of these reagents, large-scale protocols should be handled with extreme care (potentially pyrophoric and explosive compounds). Conversely, Hevia and co-workers have recently reported the possibility to implement the use of alkaline-metal-based organometallic reagents (R^1Li) under continuous, stable, and safe reaction conditions in flow and at room temperature assisted by deep eutectic solvents.[9]

8.1.36.1 Addition of Highly Polar Organometallic Reagents to Unsaturated Organic Electrophiles in Unconventional Solvents

8.1.36.1.1 Synthesis of Tertiary Alcohols via Addition of Organolithium Reagents to Ketones in Deep Eutectic Solvents

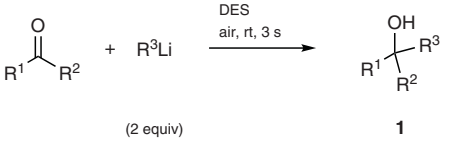
As mentioned in the introduction of this review (Section 8.1.36), the use of polar organolithium reagents is considerably limited by their usual requirements of low temperatures (in order to avoid possible undesired side reactions) as well as the need for an inert atmo-

for references see p 36

sphere and dry organic solvents (the so-called Schlenk-type protocols) to prevent their fast decomposition.[6,7] However, a pioneering study by García-Álvarez, Hevia, and co-workers[10] paved the way to the possibility to employ these readily available organometallic reagents in organic synthesis, under more environmentally friendly conditions, just by using choline chloride (ChCl) based deep eutectic solvents (DESs) as green alternative media to carry out their chemoselective and fast addition to ketones, under air and at room temperature. A comparison of the reactivity of organolithium reagents (R^1Li) in choline chloride based DESs with that observed in pure water suggested that kinetic activation of the organolithium reagents is taking place, favoring nucleophilic addition over both the competitive enolization or hydrolysis side reactions. These experimental observations were rationalized by the authors through possible formation of halide-rich lithiate species of the type $[LiCl_2R^1]^{2-}$.

This study (Scheme 1) revealed that butyllithium can be added instantaneously to 2-methoxyacetophenone to give rise to the tertiary alcohol **1** (R^1 = 2-$MeOC_6H_4$; R^2 = Me; R^3 = Bu) in good yield (60–82%) and with excellent chemoselectivity in three different choline chloride (ChCl) based DESs (water, ethylene glycol, and glycerol were used as hydrogen-bond donors in the studied DESs), in very short reaction times (3 s) under air/moisture at room temperature. Moreover, ketone substrates bearing two aryl substituents (benzophenone) or two alkyl substituents (pentan-2-one) also undergo this chemoselective butylation when using the eutectic mixtures choline chloride/water (1:2) or choline chloride/glycerol (1:2) as unconventional solvent, under the optimized conditions (rt under air). Not only aliphatic (BuLi) but also aromatic lithium reagents (e.g., PhLi) can be efficiently added to the aforementioned ketones, giving rise to the corresponding tertiary alcohols with total chemoselectivity and good yield. At this point, it is important to mention that commercially available solid lithium acetylide–ethylenediamine complex (without any volatile organic solvent) can be also added efficiently to pentan-2-one in the eutectic mixture choline chloride/water (1:2), at room temperature and under air/moisture, to produce the corresponding propargylic alcohol in almost quantitative conversion, thereby providing corroboration that the addition of organolithiums can be also performed in the absence of any volatile organic solvents (i.e., in pure eutectic mixtures).

Scheme 1 Preparation of Tertiary Alcohols by Addition of Organolithium Reagents to Ketones in Choline Chloride Based Deep Eutectic Solvents, under Air and at Room Temperature[10]



R^1	R^2	R^3	DES	Yield (%)	Ref
2-$MeOC_6H_4$	Me	Bu	ChCl/glycerol (1:2)	71	[10]
2-$MeOC_6H_4$	Me	Bu	ChCl/H_2O (1:2)	82	[10]
2-$MeOC_6H_4$	Me	Bu	ChCl/ethylene glycol (1:2)	60	[10]
Ph	Ph	Bu	ChCl/glycerol (1:2)	75	[10]
Ph	Ph	Bu	ChCl/H_2O (1:2)	68	[10]
Pr	Me	Bu	ChCl/glycerol (1:2)	73	[10]
Pr	Me	Bu	ChCl/H_2O (1:2)	85	[10]
2-$MeOC_6H_4$	Me	Ph	ChCl/glycerol (1:2)	80	[10]