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ALDRICHIMICA ACTA

Greener and Sustainable Applications of Phosphorus and Sulfur Ylides

Trimethylsilyldiazomethane ($TMSCHN_2$) in Carbon–Carbon and Carbon–Heteroatom Bond-Forming Reactions

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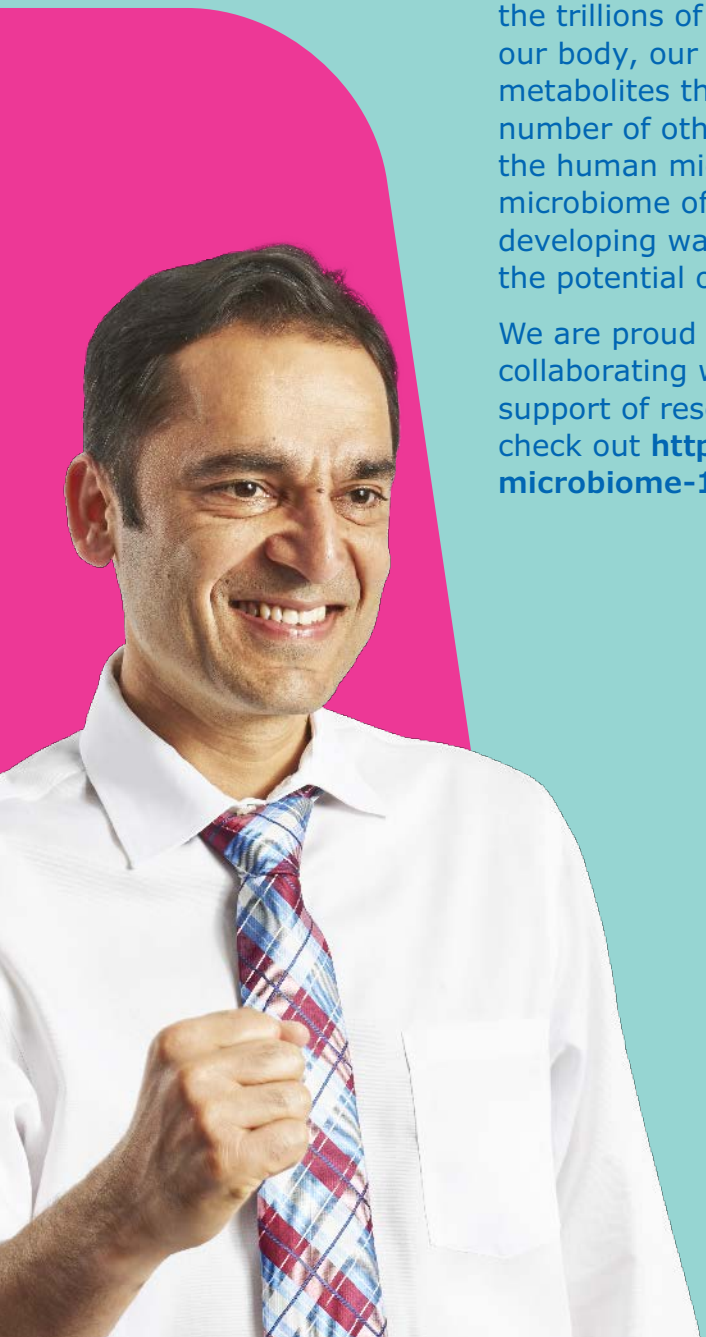

Sincerely yours,

Udit Batra, Ph.D.
CEO, Life Science

Member of the Executive Board,
Merck KGaA, Darmstadt, Germany

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Professor Keary M. Engle of the Department of Chemistry at The Scripps Research Institute kindly suggested that we offer three new nucleophilic fluorinating reagents that are complementary to TBAF hydrate: TBAF(pTol$_3$COH)$_2$ (**809578**), TBAF(9-Ph-9-fluorenol)$_3$ (**900016**), and TBAF(pin)$_2$ (**900021**). These fluoride–alcohol complexes, first described by Professor Véronique Gouverneur of the Chemistry Research Laboratory at the University of Oxford, are more stable and less hygroscopic than TBAF and are more convenient to handle. By attenuating fluoride nucleophilicity through hydrogen bonding, the complexes allow the controlled release of fluoride in solution, making them highly useful in organic synthesis.

Engle, K. M.; Pfeifer, L.; Pidgeon, G. W.; Giuffredi, G. T.; Thompson, A. L.; Paton, R. S.; Brown, J. M.; Gouverneur, V. *Chem. Sci.* **2015**, *6*, 5293.

$(n\text{-Bu})_4N^+ F^-$ [(4-MeC$_6$H$_4$)$_3$COH]$_2$	$(n\text{-Bu})_4N^+ F^-$ (9-Ph-9-fluorenol)$_3$	$(n\text{-Bu})_4N^+ F^-$ [Me$_2$C(OH)C(OH)Me$_2$]$_2$
809578 TBAF(pTol$_3$COH)$_2$	**900016** TBAF(9-Ph-9-fluorenol)$_3$	**900021** TBAF(pin)$_2$

809578	TBAF(pTol$_3$COH)$_2$	1 g
900016	TBAF(9-Ph-9-fluorenol)$_3$	1 g
900021	TBAF(pin)$_2$	1 g

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ABOUT OUR COVER

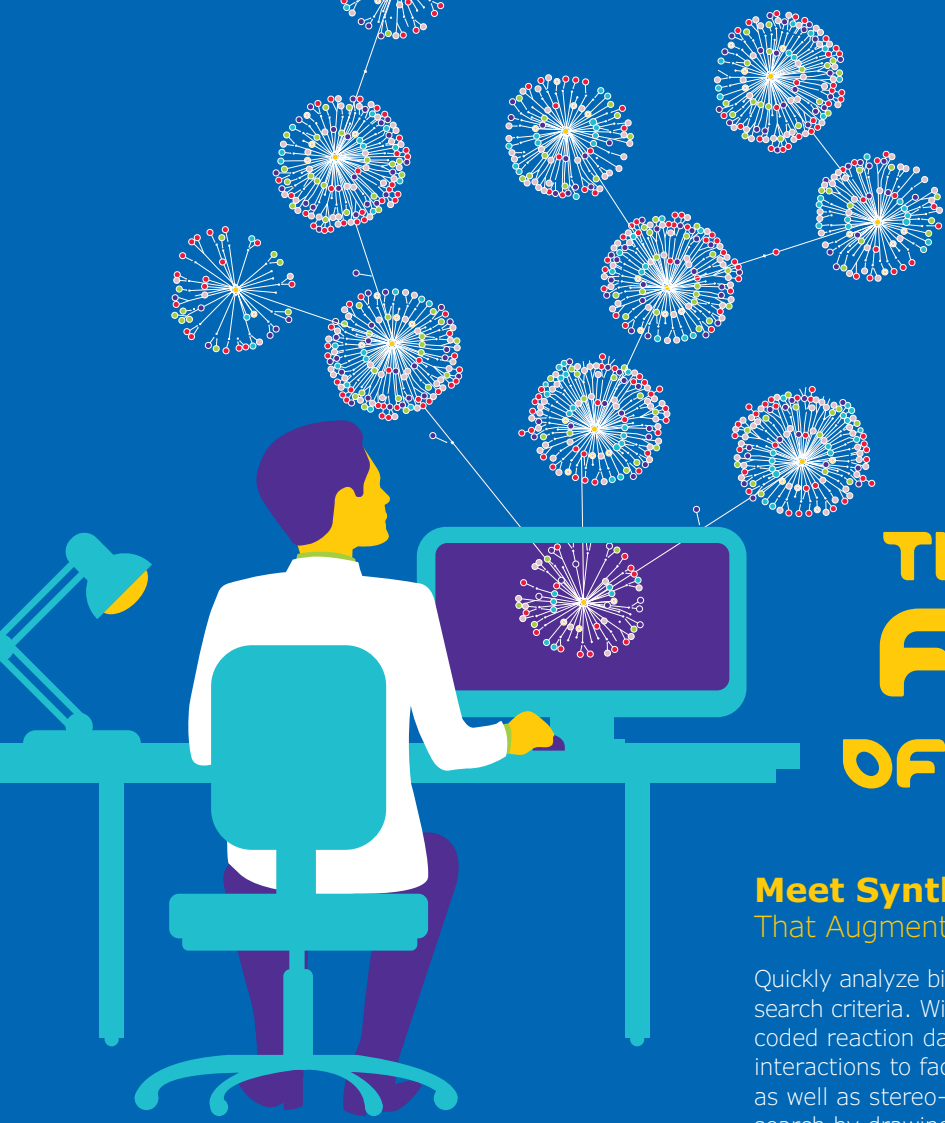
On Their Way to Camp (oil on board, 48.9 x 75.2 cm) was painted in 1873 by the famed American painter (Jonathan) Eastman Johnson (1824–1906). Born and raised in Maine, he received his early apprenticeship in Boston and his rigorous multi-year artistic training in Europe (Düsseldorf, The Hague, and Paris), where he was influenced by, among others, Emanuel Gottlieb Leutze and the works of seventeenth-century Flemish and Dutch masters. In the U.S., he acquired a favorable reputation at an early age, had wealthy and influential patrons, and was able to fetch high prices for his compositions. While he painted in several locales (Augusta, Washington DC, Northern Wisconsin, and Cincinnati) he created most of his work while residing in Manhattan and Nantucket. He exhibited widely and was in much demand during his lifetime.

Detail from ***On Their Way to Camp***. Photo courtesy National Gallery of Art, Washington, DC.

He is best-known as a portraitist and a meticulous painter of realistic scenes of ordinary people carrying on their everyday activities in simple, often outdoor, settings. ***On Their Way to Camp*** is one charming, fully finished, and particularly important example of the latter genre and was born out of sketches he made on his many trips to maple sugar camps in New England. His legacy endures today, not only through his well-known sketches and paintings, but also through his other important contributions to the art world.*

Paul Mellon Fund and Gift of Jo Ann and Julian Ganz, Jr., National Gallery of Art, Washington, DC.

** To find out more about Eastman Johnson's enduring legacy to the art world, visit **SigmaAldrich.com/Acta***



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Greener and Sustainable Applications of Phosphorus and Sulfur Ylides


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Keywords. phosphorus ylides; sulfur ylides; green synthesis; CO_2 activation; Wittig olefination; carbene precursor; C^1 synthon.

Abstract. The present review highlights relevant recent examples (2013–2018) of sustainable synthetic reactions involving phosphorus and sulfur ylides. These examples include catalytic, halide- and base-free Wittig olefination reactions and P-ylides as CO_2 activators. They also include sustainable protocols for the synthesis of S-ylides and recent applications of these as C^1 synthons, carbene precursors, and in selected rearrangement reactions.

Outline

1. Introduction

Phosphorus and sulfur (sulfonium and sulfoxonium) ylides are widely utilized reagents in organic chemistry, and are traditionally employed for olefination and cyclization reactions. Although these transformations opened new pathways in organic synthesis, their environmental footprint is still a relevant issue since both of these classes of ylides are typically used in stoichiometric amounts, and the unavoidable byproducts formed (phosphine or sulfur oxides) must be separated from the reaction mixture and disposed of at the end of the process, highlighting the need for "greener" options. In this context, the present review showcases recent examples of ylide-based synthetic reactions that are characterized by an improved environmental footprint.

2. Phosphorus Ylides

2.1. Greener Wittig reactions

2.1.1. Catalytic

The Wittig reaction is rightly considered one of the most effective and versatile pathways for the synthesis of a carbon–carbon double bond starting from carbonyl compounds (e.g., aldehydes or ketones). The first example was described in 1953 by Georg Wittig,[1] who reported the formation of 1,1′-diphenylethene upon heating triphenylphosphonium ylide with benzophenone (**Scheme 1**, Part (a)).

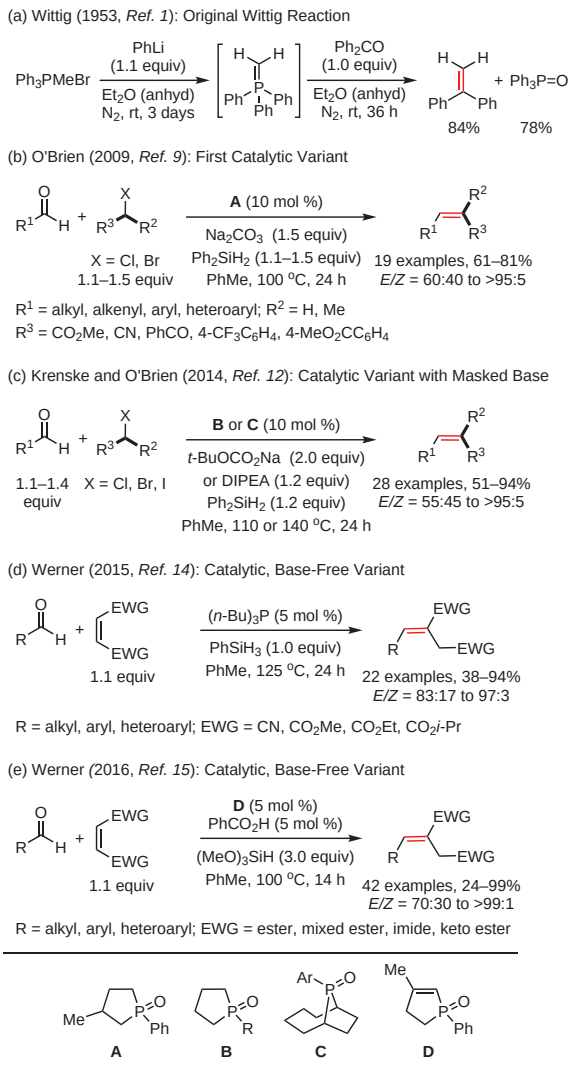
The protocol reported by Wittig required the use of a strong base in stoichiometric amounts to deprotonate the starting phosphonium salt and form the reactive ylide intermediate. The driving force for the reaction is the formation of the olefin product with a concurrent irreversible formation of an equimolar amount of triphenylphosphine oxide (Ph_3PO) as a byproduct. Despite these significant limitations with respect to sustainability and atom economy, the initial report by Wittig was a milestone in olefin synthesis and has resulted in a reliable, versatile, and widely applicable procedure with demonstrated synthetic

utility. However, the phosphine oxide byproduct still represents a waste that hampers product recovery and purification and gives rise to environmental and safety concerns because it is either incinerated or the starting phosphine regenerated at a high chemical cost (harsh conditions, use of reducing agents). Moreover, the poor atom economy associated with the classical Wittig protocol has prompted several research groups to develop catalytic alternatives in which substoichiometric amounts of the phosphine, or suitable synthetic equivalents, are utilized. In particular, research efforts have been aimed at reducing the formation of phosphorus(V) byproducts without compromising the protocol efficiency.[2] For example, a promising approach involves the use of catalytic variants, in which the phosphine oxide is reduced in situ, thus allowing phosphorus turnover and utilization of substoichiometric amounts of the phosphorus ylide (vide infra). Nevertheless, the most common reduction pathways of phosphine oxide to phosphine require the use of harsh reducing agents such as lithium aluminum hydride ($LiAlH_4$) or trichlorosilane ($HSiCl_3$), which may not be compatible with some of the reagents or the desired products.

A different approach relies on the use of alternatives to P-based ylides such as arsenic-,[3-6] tellurium-,[7] or antimony-based ones.[8] All have been successfully employed in catalytic Wittig reactions, since the respective oxides are much easier to reduce thanks to their weaker element–oxygen bond strengths. However, these protocols are not applicable on a large scale due to the high toxicity of these elements.

The first successful example of a phosphine-based, catalytic Wittig reaction protocol was proposed in 2009 by O'Brien and co-workers.[9] Diphenylsilane was found to be a suitable reducing agent, transforming selectively the precatalyst, 3-methyl-1-phenylphospholane-1-oxide (**A**, 10 mol %), into the corresponding phosphine, while keeping all of the other components unaltered. The in situ generated phosphine reacted with activated alkyl halides (containing electron-withdrawing groups) in the presence of a base, such as Na_2CO_3, to generate the corresponding stabilized phosphonium ylides. These reacted with a series of aldehydes to form the desired alkenes (61–81%, *E/Z* = 60:40 to >95:5) and regenerate the precatalyst (Scheme 1, Part (b)).[9] In 2013, O'Brien and co-workers reported an alternative protocol utilizing an organic base, *N,N*-diisopropylethylamine (DIPEA)—which is soluble in organic solvents—to replace heterogeneous sodium carbonate.[10] The same group also observed that the presence of a Brönsted acid, such as 4-nitrobenzoic acid, facilitates the reduction of phosphine oxide to the point that the reaction could be performed at room temperature. In particular, using 1-*n*-butylphospholane-1-oxide, phenylsilane as the reducing agent, and 4-nitrobenzoic acid, the first example of a room-temperature, catalytic Wittig reaction (RT-CWR) was efficiently performed.[11] Moreover, using this protocol, green solvents such as ethyl acetate and cyclopentyl methyl ether (CPME) proved to be effective alternatives to THF and toluene. RT-CWR allowed for the synthesis of 16 olefins in 61–91% isolated yields and very good *E* diastereoselectivities, with the *E/Z* ratio typically in the range of 80:20 to >95:5.

Krenske, O'Brien, and co-workers recently improved the experimental design of the catalytic Wittig reaction by extending its applicability to semi-stabilized [pK_a (DMSO) = 17–18] and unstabilized ylides [pK_a (DMSO) = 22–25]. The key to this improvement was the choice of base, which has to be sufficiently strong to abstract the ylide-forming proton of the phosphonium salt (**Scheme 2**, Step III) without compromising the rest of the CWR. Sodium *tert*-butoxycarbonate ($NaOCO_2t$-Bu), which slowly releases NaO*t*-Bu, was chosen as the masked base (Scheme 1, Part (c) and Scheme 2).[12] To further lower the pK_a of the ylide-forming proton, electron-withdrawing groups such as CF_3 were introduced into the phenyl ring of the phosphine oxide precatalyst, thus decreasing the electron density of the phosphorus center. The proposed mechanism shown in Scheme 2, however, fails to account for the fate



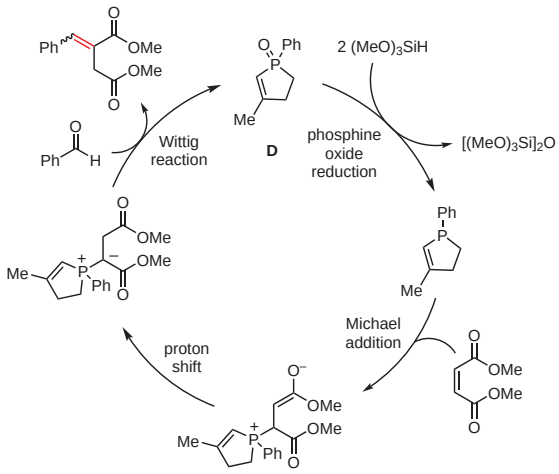
Scheme 1. Evolution of the Wittig Reaction: from Stoichiometric to Catalytic.

of the starting silane, which is bound to form an Si–O bond that represents the driving force for the reaction as well as its limitation in terms of atom economy.

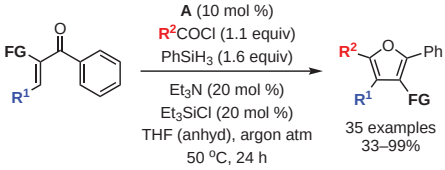
Werner and co-workers reported the first example of a catalytic enantioselective Wittig reaction[13] and described the reaction conditions for a highly efficient, catalytic, and base-free Wittig protocol (Scheme 1, Part (d)).[14] The proposed catalytic cycle consists of three steps: An initial Michael addition of $(n\text{-Bu})_3P$ to a substituted alkene acceptor (diethyl maleate) and a subsequent [1,2]-H shift lead to the corresponding ylide under base-free conditions. In the second step, the ylide formed in situ reacts with the aldehyde starting material to afford succinates and $(n\text{-Bu})_3P{=}O$. In the last step of the catalytic cycle, $(n\text{-Bu})_3P$ is regenerated in situ by reaction of $(n\text{-Bu})_3PO$ with phenyl silane ($PhSiH_3$). After protocol optimization, 22 succinate derivatives were obtained in good-to-excellent yields of up to 94%. Moreover, in the case of aromatic and heteroaromatic aldehydes, very good *E*/*Z* selectivities of up to 97:3 were obtained.

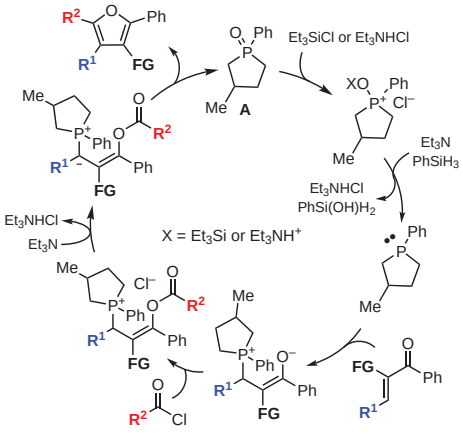
This protocol was further optimized using 3-methyl-1-phenyl-2-phospholene 1-oxide (**D**) as the precatalyst in the presence of trimethoxysilane [$(MeO)_3SiH$] as the in situ reducing agent.[15] The influence of Brönsted acid on the reduction of the phosphine oxide was also investigated. Using benzoic acid (5 mol %), nine activated olefins and 33 aldehydes (aliphatic, aromatic, and heteroaromatic) were converted into 42 highly functionalized alkenes in isolated yields of up to 99%. In all cases, good-to-excellent selectivity for the *E* isomer was observed, and the proposed scheme (**Scheme 3**)[15] parallels that proposed by Krenske and O'Brien.

The scope of the catalytic Wittig reaction has been extended by Lin and co-workers to the intramolecular synthesis of highly functionalized furans.[16] In this protocol, α-substituted chalcones react with an acyl chloride in the presence of a phosphine oxide precatalyst (10 mol %) and Et_3N (20 mol %). Phenylsilane ($PhSiH_3$) is used as a reducing agent (1.6 equiv) and Et_3SiCl (20 mol %) as a promoter of the reduction of the phosphine oxide. Moreover, the in situ generated byproduct (Et_3NHCl) was also found to accelerate the reduction of the phosphine oxide. Using the optimized reaction conditions, 35 highly functionalized furans were synthesized in 33–99% isolated yields (**Scheme 4**).[16]

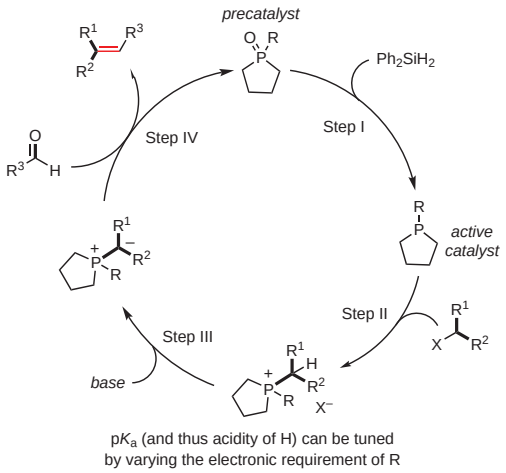


Scheme 3. Werner's Proposed Mechanism for the Base-Free, Catalytic Wittig Reaction. *(Ref. 15)*





Scheme 4. Lin's Intramolecular Catalytic Wittig Olefination Leading to Highly Functionalized Furans. *(Ref. 16)*



Scheme 2. Krenske and O'Brien's Proposed Mechanism of a Catalytic Wittig Reaction Utilizing a Masked Base. *(Ref. 12)*

All the catalytic Wittig protocols described so far constitute significant improvements on the classic Wittig reaction. Notably, for the first time, the phosphine oxide byproduct could be employed as the precatalyst in catalytic amounts. However in these CWR protocols, an equimolar amount of byproduct is always formed, since the silane reducing agent is used in stoichiometric quantities, is quantitatively oxidized, and has to be disposed of at the end of the reaction. A desirable evolution of this chemistry would thus rely on the development of catalytic reductions of the phosphine oxide.

A life cycle analysis (LCA) of the catalytic Wittig reaction developed by O'Brien versus the classic stoichiometric analogue was carried out by Huijbregts and co-workers by evaluating two quantitative measures: the global warming potential over 100 years (GWP 100a developed by the International Panel for Climate Change) expressed in CO_2 equivalents and the cumulative energy demand (CED, the total energy consumption for the life cycle inventory). The CED, in particular, is considered a proxy for the total environmental burden of a process. The process data included the quantities of all reagents and solvents necessary to produce 1 mole of olefin. The LCA followed a cradle-to-gate analysis for all materials employed, including contributions to prepare Ph_3P, silane, and aldehyde, but excluding subsequent use of the olefin and waste treatment of the chemicals produced. The comparison showed a clear advantage of the catalytic variant in reducing energy consumption, greenhouse gas (GHG) emissions, and waste generation (**Scheme 5**).[17] The authors concluded that, even though the catalytic Wittig reaction conditions require the use of additional reagents such as sodium carbonate, this contributed only marginally to its environmental impact when compared to the classic Wittig reaction. In contrast, the advantages of using silanes as sacrificial reducing agents in the catalytic reaction are clearly demonstrated by the reduction of CED and GHG emissions when compared to the use of stoichiometric quantities of triphenylphosphine in the classic reaction protocol.

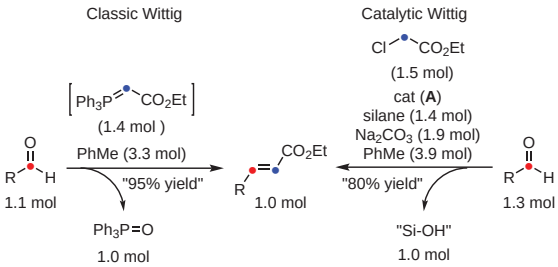
2.1.2. Halide- and Base-free

Aiming to improve the sustainability of the Wittig protocol, we reported the first example of a simple, versatile, and sustainable halide- and base-free Wittig vinylation.[18] This sustainable pathway for the synthesis of vinyl derivatives from aldehydes and ketones was performed in two steps. In the first, the Wittig vinylating agent, methyltriphenylphosphonium methylcarbonate ($[Ph_3PCH_3][CH_3OCO_2]$, **1**), was readily prepared by quaternarization of triphenylphosphine (TPP) in the presence of the nontoxic methylating agent dimethyl carbonate.[18] Remarkably, this reaction step is characterized by a 100% atom economy. The XRD crystal structure of **1** revealed a short distance between the methylcarbonate oxygen and the P-CH_3 methyl group (3.174 Å at 100 K), suggesting a significant H-bonding in the solid state. This proximity represents strong evidence of a latent ylide, which could be formed via a "counterion-mediated" deprotonation.

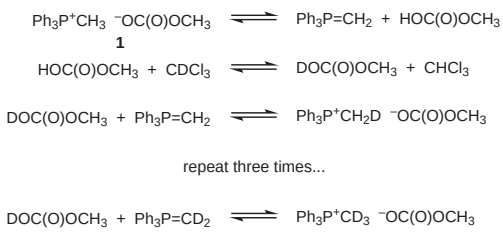
A preliminary study demonstrated that when treating **1** with a 15-fold molar excess of $CDCl_3$, a hydrogen–deuterium exchange occurs between the P-CH_3 protons (pK_a > 20) of the phosphonium salt and deuterium of $CDCl_3$ (pK_a = 25), leading to the quantitative formation of the deuterated analogue $[Ph_3PCD_3][CH_3OCO_2]$ presumably via the proposed mechanism shown in **Scheme 6**.[18]

The second step, the halide- and base-free Wittig vinylation protocol, was effected by reacting the model carbonyl substrate benzaldehyde with **1** and using the bio-derived 2-Me-THF as solvent. Styrene was quantitatively obtained after only 40 minutes at 80 °C. The reaction was optimized and its scope extended to 8 aromatic and aliphatic carbonyl compounds, leading to the corresponding alkenes in good-to-excellent yields (**eq 1**).[18]

We then carried out an evaluation of the efficiency and environmental impact of our protocol vis-à-vis three existing ones that follow the classic Wittig process (**Table 1**).[18-21] Applying three simple green chemistry metrics [atom economy (AE, %), environmental factor (EF), and mass index (MI)] to the Wittig reaction of piperonal as a model reaction, we found that the calculated AE values of the four methods are all intrinsically low due to the need for stoichiometric amounts of the phosphonium ylide and the resulting formation of stoichiometric amounts of triphenylphosphine oxide. Nonetheless the halide- and base-free protocol is still slightly more atom-efficient (29.5%), due to the absence of halides and of added bases. Sheldon's EF



Scheme 5. Huijbregts's Comparison of the Quantitative Environmental Impact of the Classic Wittig Reaction (Left) Versus the Catalytic Variant Developed by O'Brien and Co-workers (Right). *(Ref. 17)*



Scheme 6. Proposed Mechanism of the Hydrogen–Deuterium Exchange for the Wittig Vinylation Agent ($[Ph_3PCH_3][CH_3OCO_2]$, **1**). *(Ref. 18)*

appears to favor Stevenson's process due to an exceptionally high yield reported by using purely stoichiometric amounts (1.0 equiv) of phosphonium salt and BuLi. In contrast, the MI of our protocol is significantly more advantageous (9.60) than those of the other three (15.70–19.31) due to the high conversion and selectivity achieved in the presence of low amounts of solvent (methylenedioxystyrene/2-Me-THF = 0.150 g/mL) and the resulting positive effects on the reaction rate. In all cases, chromatography solvents were not included in the calculations.

2.2. Organocatalysis for CO_2 activation

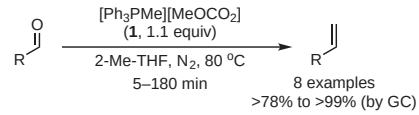
Among other applications, ylides, and in particular disyline bisphosphine adducts, have been efficiently employed for carbon dioxide (CO_2) transformation into desirable and economically competitive products. CO_2 is a thermodynamically inert molecule that is formed at the end of any carbon-based combustion process. Therefore, relatively high-energy co-reagents are often used to promote its reduction. In these processes, CO_2 activation is pivotal for its effective transformation.

The first nonmetal-mediated, direct CO_2 reduction to CO at room temperature was reported in 2011 by Kato, Baceiredo, and co-workers who utilized a bench-stable disilyne bis(phosphine) adduct (**eq 2**).[22] The adduct was characterized by a peculiar ligand effect of phosphine toward the Si^I center, whereby the phosphine ligands behave as weakly σ-donating ligands without a π-accepting character and induce a strong π donor–acceptor character in the Si^I centers. Consequently, the Si–Si fragment in the disilyne bis(phosphine) adduct exhibits some multiple-bond character. Owing to this peculiar property, the disilyne bis(phosphine) adduct showed high reactivity with CO_2, and, upon mixing with CO_2 at room temperature, it reacted with four equivalents of the latter, formally extracting three oxygen atoms and capturing one CO_2 molecule. Three molecules of CO and one molecule of the aminosilicate were generated, and the aminosilicate structure was confirmed and fully characterized by NMR analysis and XRD crystal structure determination.

It is well known that phosphorus ylides are powerful and versatile nucleophilic reagents in organic synthesis. In 1966, Matthews et al. reported the first CO_2 adduct of a P-ylide formed from the nucleophilic addition of the ylide to CO_2.[23a] More recently, Zhou, Lu, and co-workers synthetized a series of P-ylide-CO_2 adducts, and showed them to be very efficient metal- and halogen-free organocatalysts for a number of reactions that transform CO_2 into useful fine chemicals under mild conditions (**Scheme 7**).[23b] One adduct in particular (**2**; R^1 = R^2 = Me) proved to be very stable even at 80 °C.

These catalysts were tested in the cycloaddition of CO_2 with terminal epoxides leading to cyclic organic carbonates. In particular, ylide adduct **2** (R^1 = H, R^2 = *n*-Pr; 5 mol %)

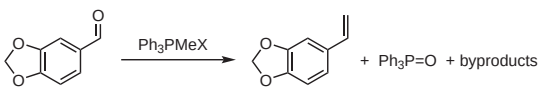
Halide- and Base-Free Wittig Vinylation Reaction
Employing the Novel Vinylation Reagent $[Ph_3PMe][MeOCO_2]$



R = *n*-C_9H_{19}, $PhCHMeCH_2$, 4-XC_6H_4 (X = H, MeO, Cl, NO_2), furan-2-yl, 1,3-benzodioxol-4-yl

eq 1 *(Ref. 18)*

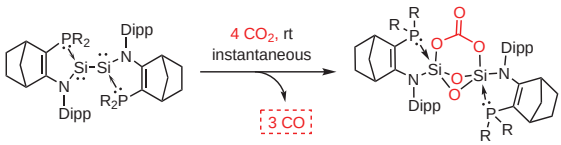
Table 1. Calculated Green Metrics for the Synthesis of 3,4-Methylenedioxystyrene by Various Wittig Reaction Protocols



Protocol By	Ref.	X	AE	EF	MI
Gaset (1982)	19	I	22.9%	4.34	15.85
Stevenson (2006)	20	Br	25.9%	2.99	15.70
Joullié (2007)	21	Br	25.9%	3.90	19.31
Perosa (2015)	18	$MeOCO_2$	29.5%	3.82	9.60

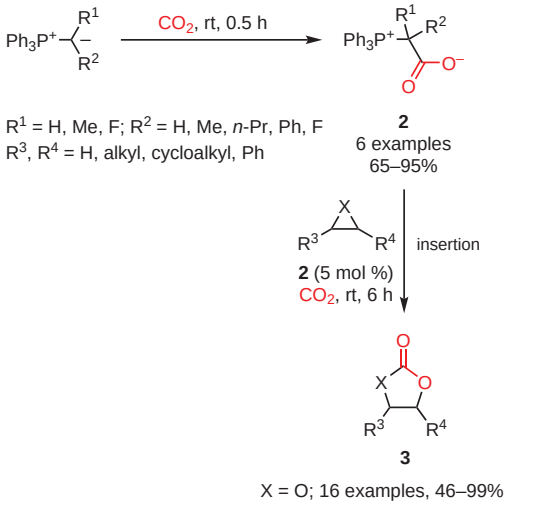
AE = atom economy; EF = environmental factor; MI = mass index

Room -Temperature Direct CO_2 Reduction to CO with a Disilyne Bis(phosphine) Adduct



R = *t*-Bu; Dipp = 2,6-(*i*-Pr)$_2$$C_6H_3$

eq 2 *(Ref. 22)*



R^1 = H, Me, F; R^2 = H, Me, *n*-Pr, Ph, F
R^3, R^4 = H, alkyl, cycloalkyl, Ph

X = O; 16 examples, 46–99%
X = N(*n*-Bu); R^3 = Ph, R^4 = H; 95%

Scheme 7. P-Ylides–CO_2 Adducts Prepared by Zhou, Lu, and Co-workers for Use as Organocatalysts for Activating CO_2 toward a Number of Useful Transformations. *(Ref. 23b)*

promoted a quantitative conversion of propylene oxide into propylene carbonate (98% yield) at room temperature after 4 h in the absence of any additional solvent. At 100 °C, 100% selectivity and 78% yield of propylene carbonate was achieved with a very low loading (0.5 mol %) of the same ylide adduct. After protocol optimization, the same organocatalyst (5 mol %) was used for the synthesis of 16 different cyclic organic carbonates in 46–99% yields (Scheme 7).[23b] The authors proposed a mechanism whereby the P-ylide activates the free CO_2 by forming a P-ylide adduct. Being less sterically hindered, the acetate fragment of this CO_2 complex is more nucleophilic than the starting P-ylide. After the epoxide starting material is activated through coordination to the central P^+ unit on the P-ylide, the activated CO_2 anion simultaneously attacks the less substituted C–O bond of the epoxide. A final intermolecular cyclization produces the cyclic carbonate and regenerates the P-ylide, which re-enters the catalytic cycle (**Scheme 8**).[23b] The P-ylides–CO_2 adducts were effective catalysts also for the insertion of CO_2 into aziridines and for the reduction of CO_2 with 9-BBN in the presence of anilines to form the corresponding *N*-methyl- and *N*-formylanilines.[23b]

3. Sulfonium and Sulfoxonium Ylides

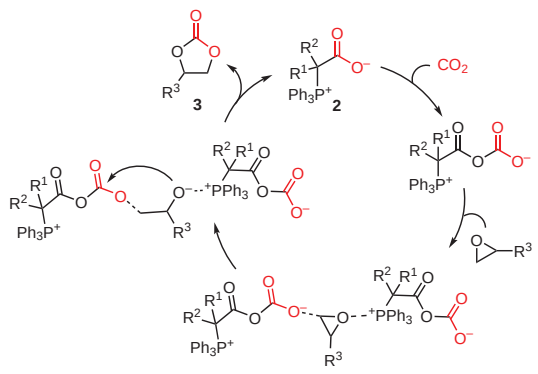
Sulfur-based ylides are among the most versatile reagents in organic synthesis, providing easy access to nucleophilic C^1 synthons. They have been successfully applied in a large number of synthetically relevant transformations, leading to the construction of small rings such as epoxides, aziridines, and cyclopropanes (**Scheme 9**); multicyclic heterocycles; or to ring expansions of lactones and lactams.[24–25] Notably, all of the above-mentioned transformations can be carried out with high levels of diastero- and/or enantioselectivity,[26–27] highlighting the importance and wide applicability of sulfur-based ylides in contemporary organic synthesis in both academia and industry.[28] Moreover, the synthetic relevance of these transformations is attested to by the number of recent review articles focusing on the various synthetic applications of sulfur-based ylides: their use as diazocarbonyl equivalents in metal-catalyzed insertion reactions;[29] the development of metal-, organo-, and photocatalytic asymmetric cyclization protocols based on sulfur ylides;[30] advances in transition-metal-catalyzed sulfonium or sulfoxonium ylide reactions;[31] synthesis and reactivity of vinyl sulfonium and vinyl sulfoxonium ylides;[32] and propargylic sulfides.[33]

Sulfur ylides are zwitterions, typically constituted by carbanions with an adjacent positive sulfur atom. Their stability depends on their molecular structure, in particular on the electronic delocalization of the negative charge of the carbanionic center and on the nature and type of substituents on the sulfur atom. For example, the presence of carbonyl groups attached to the carbanionic center—as is the case in ketosulfonium and ketosulfoxonium ylides—results in less reactive sulfur ylides, whereas the presence of a heteroatom attached to the sulfur center increases the ylide stability (Scheme 9).

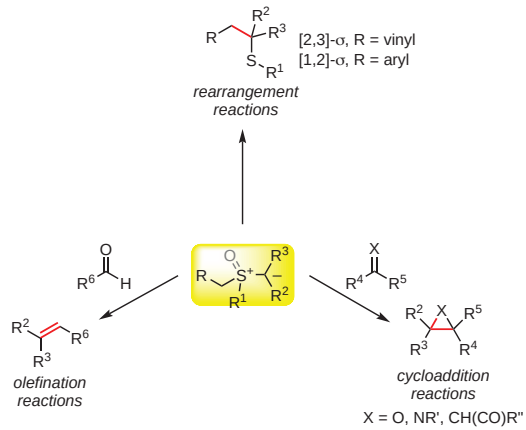
Sulfur ylides are accessed mainly through (i) hydrogen abstraction from sulfonium and sulfoxonium salts, and (ii) reaction between a sulfide or sulfoxide with a metal–carbene complex that is typically derived from a diazo compound.[29,34] The second approach is far less studied, since sulfur-based ylides are considered safer and more stable synthetic alternatives to the highly reactive diazo compounds. Thus, the development of new methods for the preparation of these ylides, especially the more stable ones (e.g., substituted ketosulfonium and ketosulfoxonium ylides), is still of great interest. Additionally, the development of truly sustainable synthetic methodologies for the preparation of sulfur ylides is still an open challenge.

3.1. Sustainable Synthesis of Sulfur Ylides: the Case of β-Keto Thioethers

The preparation of β-keto thioethers, which are biologically and agrochemically relevant S-containing compounds, can serve as an example of a sustainable application of S-ylides in



Scheme 8. Proposed Catalytic Cycle for the Insertion of CO_2 into Epoxides Promoted by P-Ylide–CO_2 Adducts. *(Ref. 23b)*



Scheme 9. The Reactivity of Sulfur Ylides.

synthesis. These compounds are bench-stable solids employed synthetically as benzothiophenes and Julia reagent precursors.[35] They are traditionally prepared via metal-catalyzed S–H insertion into diazocarbonyl compounds or via nucleophilic substitution from haloketones in the presence of thiolates. While the former methodology requires the use of highly reactive reagents (diazocarbonyl compounds), the latter consists of a multistep reaction sequence with superstoichiometric amounts of base and is characterized by poor regiochemical control. Moreover, haloketones are unstable, noncommercially available, and irritating (lachrymatory) reagents, typically prepared starting from toxic and reactive precursors (e.g., Br_2 or NBS). Dias and Burtoloso have reported a sustainable method for synthesizing β-keto thioethers starting from easily prepared keto sulfoxonium ylides and commercially available aryl thiols (**Scheme 10**, Part (a)).[36] This organocatalytic reaction involves an initial, rate-determining thiol addition to the sulfoxonium ylide formed in situ, followed by an irreversible nucleophilic displacement of DMSO and formation of the β-keto thioether product. The β-keto thioethers were synthesized with high chemoselectivity, and the protocol was applied to a diverse library of substituted aryl thiols (25 examples, yields up to 94%).[36]

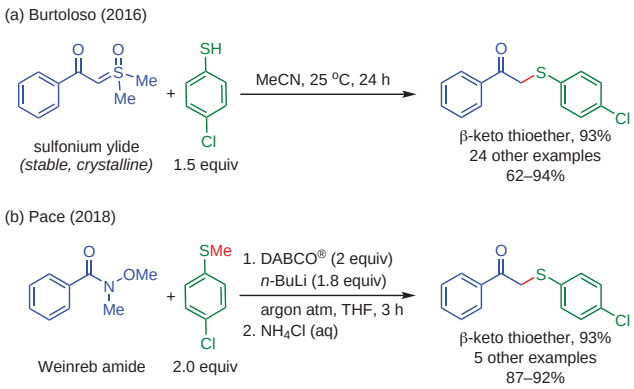
More recently, Pace and co-workers described the reaction of Weinreb amides with α-functionalized methyllithium reagents derived from thiols (carbenoid nucleophiles generated in situ), which gave rise to the corresponding β-keto thioethers in high yields and selectivity (Scheme 10, Part (b)).[37] Notably, this protocol was also applicable to the preparation of α-thioacetal-like methyl ketones.

Biju and co-workers developed a simple and sustainable methodology for the selective preparation of α-functionalized β-oxo arylthioethers (**Scheme 11**).[38] The reported procedure is mild, does not use transition metals, and works well for a broad range of substituted alkyl allyl thioether and aryne [generated from 2-(trimethylsilyl)aryl triflates] precursors. The reaction proceeds through a sulfur ylide intermediate generated from the aryne and alkyl allyl thioether, followed by an intramolecular [2,3]-sigmatropic Stevens rearrangement resulting in the formation of new carbon–sulfur and carbon–carbon bonds, respectively. Moreover, the conversion of the β-oxo arylthioethers into useful aryl heteroaryl thioethers and substituted pyridazines was demonstrated in one case by following a two-step procedure consisting of an initial ozonolysis and subsequent intramolecular condensations.

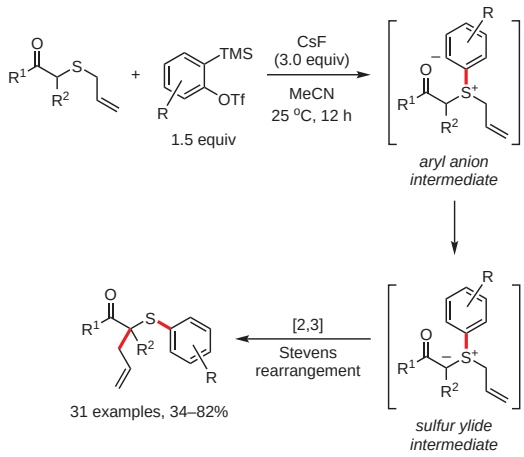
Maulide and co-workers reported an S^{IV}, transition-metal-free divergent process for the selective preparation of stabilized sulfonium ylides from active methylene compounds, indoles, or pyrroles; and for the direct α-arylation of carbonyl compounds (**Scheme 12**).[39] Selectivity toward one reaction pathway or the other is likely due to the structure of the S^{IV} ylide intermediate and counteranion basicity, with the more basic anions favoring S-alkylation and the less basic ones promoting the Lewis acid reactivity of the S^{IV} intermediate.

3.2. Sulfur Ylides as C^1 Precursors

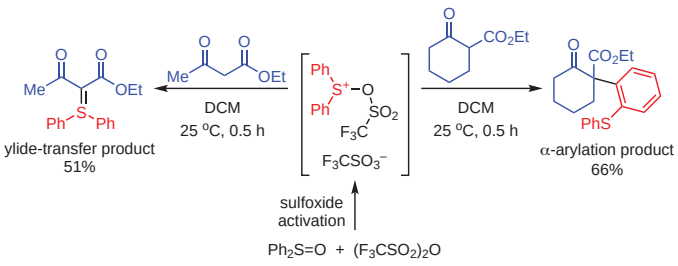
As mentioned previously, reactive sulfur-containing species, such as sulfur-based ylides, are typically generated by sulfide



Scheme 10. Representative Examples of Sustainable Syntheses of β-Keto Thioethers. *(Ref. 36,37)*



Scheme 11. Synthesis of α-Substituted β-Oxo Arylthioethers via a [2,3]-Stevens Rearrangement of Sulfur Ylide Intermediates Generated from the Reaction of Alkyl Allyl Thioethers with in Situ Generated Arynes. *(Ref. 38)*



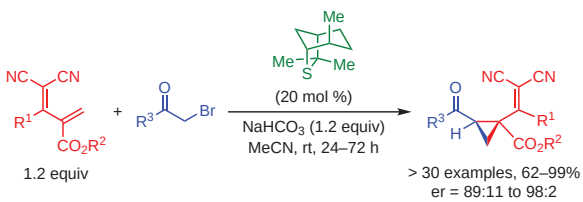
Scheme 12. Divergent Reactivity of Stabilized S-Ylides with β-Keto Esters. *(Ref. 39)*

alkylation with an alkyl halide followed by deprotonation. This sequence can be performed in situ or, for the most stable ylides, in a previous synthetic step, but it has a detrimental impact on the sustainability of the overall process in terms of step-economy, atom economy, and environmental compatibility. As a consequence, sustainable alternative protocols for this alkylation–deprotonation sequence have been developed. These require the use of base-nonsensitive Michael acceptors, thus allowing a one-pot reaction in which the sulfide is regenerated as the reaction progresses, resulting in sulfide loadings as low as 20 mol %.[40] Despite these positive developments, direct sulfide catalysis is rather underexplored, and only scattered results have been reported so far.[26,41-42] Recently, Li and co-workers reported the first example of effective, sulfide-based enantioselective organocatalysis using halide substrates bearing an electron-withdrawing group. An efficient, metal-free cyclopropanation protocol via direct sulfide catalysis was developed and applied to different electron-deficient halides including α-brominated ketones, esters, and amides. The reaction generated vinylcyclopropanes featuring a quaternary chiral center (>30 examples) with yields of up to 99% and enantiomeric ratios (er) of up to 98:2 (**eq 3**).[43] The protocol is characterized by mild operating conditions, the use of inexpensive sulfides, and by being highly regio- and diastereoselective.

A similar approach was reported by Huang and co-workers who developed a transition-metal-free Suzuki-type cross-coupling between benzyl halides and boronic acids via a 1,2-metalate shift involving a zwitterionic boron "ate" intermediate. The reaction takes place through a novel catalytic cycle using commercially available sulfides as organocatalysts and involving formation of the corresponding sulfonium salts as the rate-determining step. Rearrangement to a reactive sulfur ylide, oxidative addition of the boronic acid to form the boron "ate" complex, 1,2-metalate shift, and protodeboronation lead to the final C(sp^3)–C(sp^2) coupling product (**eq 4**).[44] This approach eliminates possible undesirable homocoupling reactions for substrates with multiple aryl halide substituents, and enables a modular synthesis of unsymmetrical, highly functionalized diarylmethanes from polyhalogenated substrates by using sequential cross-coupling steps.

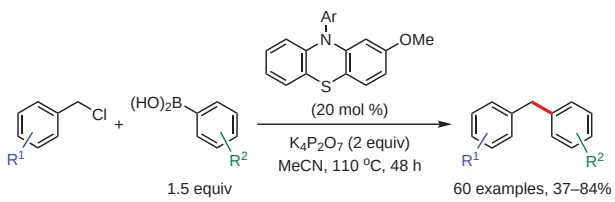
The reaction of S-ylides as nucleophiles in cycloadditions with aldehydes, ketones, and ketenes is well established[45] and has become an important synthetic tool for the stereoselective preparation of epoxides, aziridines, and cyclopropane moieties,[46] respectively. In contrast, a thorough understanding of the reactivity patterns occurring between S-based ylides and Michael acceptors is still lacking. Achieving this understanding is complicated by the fact that most Michael acceptors do not behave analogously, and require a case by case study. It has been noted, however, that in the presence of selected Michael acceptors, S-ylides undergo [4 + 1] rather than [2 + 1] cycloaddition to form the corresponding 5-membered rings. These reactions generally occur in the presence of a transition-metal Lewis acid catalyst. In 2012, Bolm and co-workers were the first to report the selective formation of enantioenriched dihydropyrazoles from the [4 + 1] cycloaddition of conjugated azoalkenes (generated in situ from the corresponding α-haloketones) and sulfoxonium ylides.[47] The protocol, however, required the use of a chiral Cu-BINAP catalyst. Later, Lu, Lan, Xiao, and co-workers reported the first example of an iron-catalyzed decarboxylative [4 + 1] cycloaddition that leads to a wide range of functionalized indoline products starting from readily available vinyl benzoxazinanones and sulfur ylides.[48] These initial observations led to the development of catalyst-free [4 + 1] cycloadditions starting from 1,2-diaza-1,3-dienes (DDs) and S-ylides. Thus, Wang, Fang, and co-workers have synthesized a small library of 5-(trifluoromethyl)pyrazolines through a catalyst-free [4 + 1] annulation of α-halo hydrazone derivatives with trifluoroethyldiphenylsulfonium triflate. In this reaction, the reactive DDs are generated in situ under mild conditions, and are readily trapped by reaction with the activated but unstable trifluoroethylidenesulfur ylide (**Scheme 13**, Part (a)).[49] The same year, Shao, Chen, and co-workers reported a substrate-controlled protocol for the selective synthesis of bicyclic 4,5-dihydropyrazoles, starting from DDs and stabilized S-ylides under mild conditions. In particular, they noted that, when the DDs include a cyclopentene ring, the corresponding trans bicyclic 4,5-dihydropyrazolones were obtained in moderate-to-good yields (Scheme 13, Part (b)). Intriguingly, when acyclic DDs were employed, the corresponding 5,6-diazaspiro[2.4]-hept-6-en-4-ones (formal [2 + 1]-cycloaddition products) were obtained selectively.[50]

Structurally similar azaoxyallyl cation intermediates are typically involved in [3 + m]-cycloaddition reactions that lead to



R^1 = H, Ph, aryl, heteroaryl; R^2 = Me, Et, *t*-Bu
R^3 = Me, Ph, aryl, heteroaryl, phenoxy, anilino, chromon-2-yl

eq 3 *(Ref. 43)*



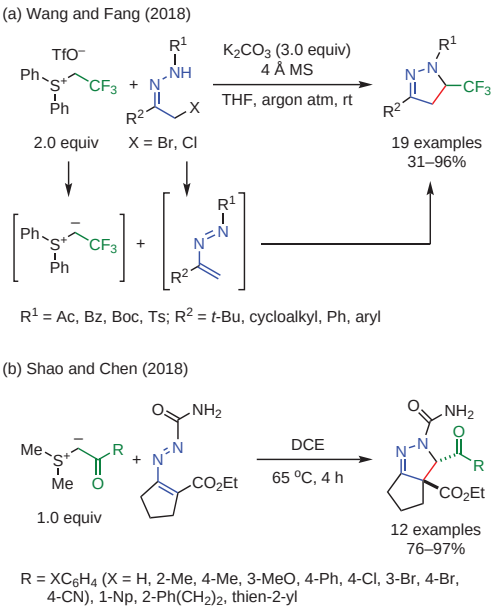
Ar = 4-MeOC$_6$H$_4$
R^1 = MeO, MeS, CF_3O, CO_2Et, CN, alkyl, Ph, aryl, halogen
R^2 = Ph_2N, MeS, alkyl, alkoxy, phenoxy, siloxy, Ph, aryl, heteroaryl, halogen

eq 4 *(Ref. 44)*

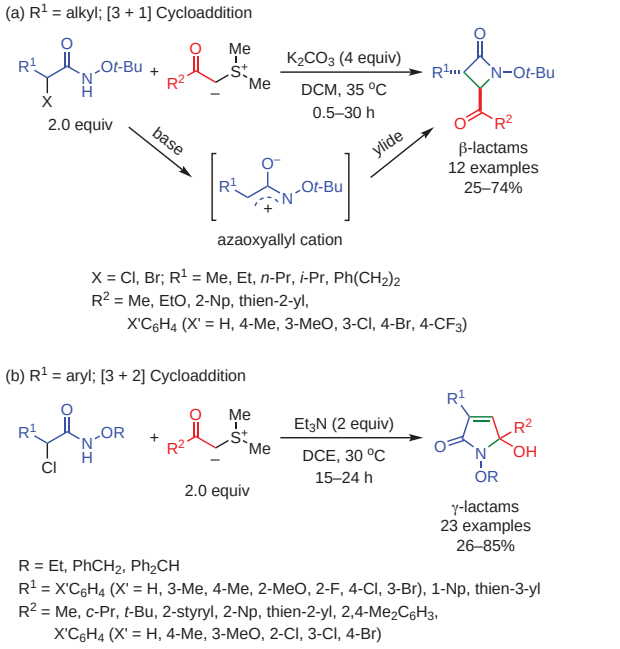
N-heterocycles.[51] The azaoxyallyl cations—generated in situ from α-halohydroxamates in the presence of base—were recently used by Liu, Chen, and co-workers as three-atom units in cycloaddition reactions with sulfur ylides.[52] The expected [3 + 1] cycloaddition products (β-lactams) were formed diasteroselectively (dr > 19:1) and in acceptable yields (up to 74%) only when starting from α-alkyl-substituted α-halohydroxamates (**Scheme 14**, Part (a)).[52] Moreover, moderate enantioselectivity was observed when chiral sulfur ylides were employed. When α-aryl-substituted α-halohydroxamates were used, an unexpected [3 + 2] cycloaddition reaction took place leading to the selective formation of γ-lactams instead (Scheme 14, Part (b)). In this case and for the first time, sulfur ylides stabilized by a vicinal ketone group acted as two-carbon cycloaddition partners.[52]

Maulide and co-workers extended the range of applications of azaoxyallyl derivatives by developing a new carbonyl olefination approach that relies on the formation of an intermediate *N*-iminylaziridine. Upon thermal decomposition, the three-membered-ring intermediate, prepared in a one-pot fashion by addition of a sulfoxonium ylide to an azine, leads to formation of the desired olefin in good-to-high yields (**Scheme 15**).[53] This procedure is applicable to a wide range of alkyl- and aryl-substituted aldehydes, enals, and alkyl-substituted sulfoxonium ylides. This methodology represents a novel carbonyl olefination approach when compared to the Wittig, Julia, Peterson, and Tebbe olefinations. It selectively delivers trans-disubstituted olefins and dienes from α,β-unsaturated carbonyls, and opens new reactivity pathways for sulfoxonium ylides. The same laboratory extended the use of stabilized S-ylides to heterocyclic targets, reporting a novel strategy for the synthesis of 2-amino-4,5-dihydrothiophenes (21 examples, yields up to 95%) upon [3 + 2] cycloaddition between nitro-olefins and thiouronium ylides. The latter compounds act as push–pull 1,3-dipoles resulting in fine-tuning of the reaction outcome based on the relative stability of the thiocarbonyl ylide: obtaining reduced yields for less stabilized ylides and observing a complete shutdown of reactivity when the ylide is "overstabilized".[54]

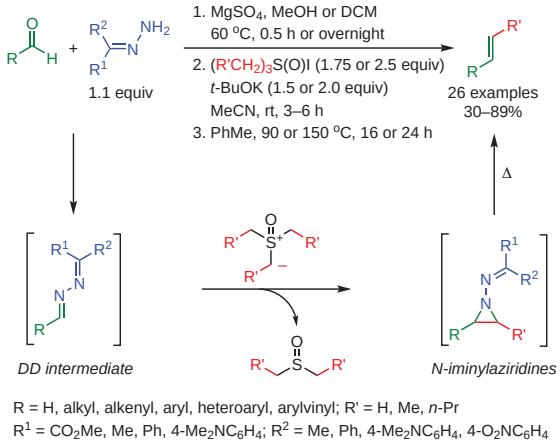
Prop-2-ynylsulfonium salts are a relatively new class of S-ylides that has shown borderline reactivity between C[1]



Scheme 13. Catalyst-free Reactivity of in Situ Generated 1,2-Diaza-1,3-dienes and S-Ylides. *(Ref. 49,50)*



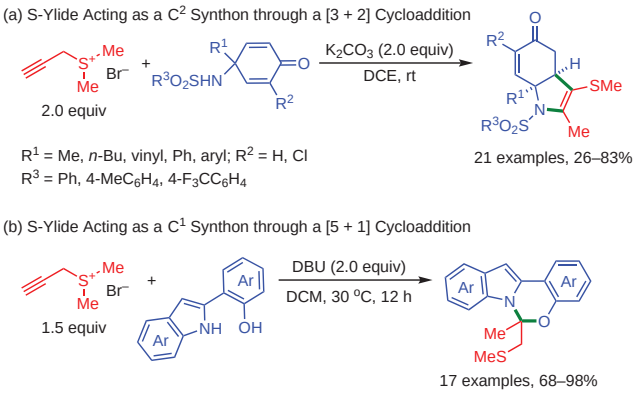
Scheme 14. Divergent Reactivity of Azaoxyallyl Halides with S-Ylides. *(Ref. 52)*



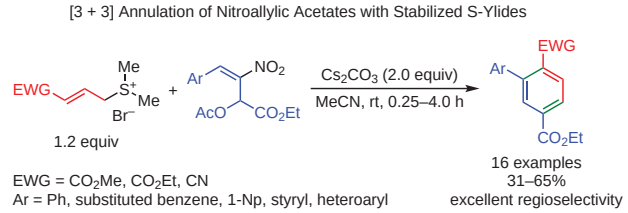
Scheme 15. Maulide's Novel Olefination of Activated Carbonyl Compounds with Sulfoxonium Ylides. *(Ref. 53)*

and C^2 synthons. For example, Huang and co-workers have reported a method to construct hydroindol-5-ones containing a methylthiogroup via [3 + 2] cycloaddition of prop-2-ynylsulfonium salts and *p*-quinamines (**Scheme 16**, Part (a)).[55] In this context, prop-2-ynylsulfonium salts isomerize into the corresponding allenic sulfonium salts acting as C^2 synthons with formation of the corresponding organosulfur bicyclic compounds. A year later, the same research laboratory reported the first formal [5 + 1]-annulation reaction between S-ylides and 2-(1*H*-indol-2-yl)-phenols, leading to a library of indole-fused 4*H*-benzo[*e*][1,3]-oxazines (Scheme 16, Part (b)).[56] In this reaction, the prop-2-ynylsulfonium salt participates with its electrophilic β-carbon atom, acting as a novel C^1 synthon and allowing for the formation under mild conditions of the corresponding polycyclic oxazolines bearing a thioether substituent in good-to-high yields.

G.-L. Wu and Q.-P. Wu have developed a metal-free domino reaction that is based on S-ylides and is selective for 4,5-disubstituted 1,2,3-(*NH*)-triazoles. The protocol involves an initial coupling between sulfur salts and aldehydes followed by the introduction of sodium azide. It is interesting to note that when the sulfur salts react with the aldehydes in the presence of L-proline, olefinic sulfur salt intermediates form instead of the expected epoxides; once formed, these intermediates undergo facile cyclization with azide ion.[57]



Scheme 16. The Reactivity of Propargyl-Substituted S-Ylides as C^1 and C^2 Synthons. *(Ref. 55,56)*



eq 5 *(Ref. 59)*

Nitroallylic derivatives are synthetically relevant reaction partners for annulation reactions, forming functional and biologically relevant derivatives.[58] When nitroallylic acetates were reacted with crotonate-derived stabilized S-ylides, Satham and Namboothiri selectively formed 2-arylterephtalates, which are formal precursors of farnesyltransferase inhibitors as well as potential monomers for polymerization reactions. The reaction occurs in a regioselective fashion through a cascade process consisting of two consecutive Michael additions (an initial intramolecular S_N2' followed by an intramolecular *6-endo-trig* cyclization) and two base-catalyzed eliminations (**eq 5**).[59]

Fan and co-workers developed a novel, highly efficient approach for the synthesis of spirocyclopentenyl *para*-dienones building blocks, relying on a base-mediated tandem spirocyclopropanation/rearrangement reaction of vinyl *para*-quinone methides (*p*-VQMs) with sulfonium salts. A series of highly functionalized spirocycles were thus prepared in good yields (up to 96%) and diastereoselectivities (up to 14:1 dr) under mild, metal-free conditions.[60]

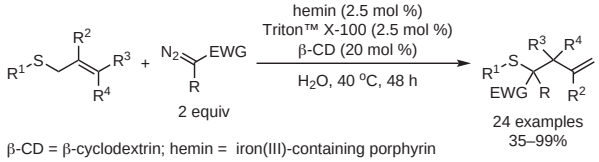
3.3. Sulfur Ylides as Carbene Precursors

Since their discovery in 1960, sulfonium and sulfoxonium ylides have been extensively employed as carbene precursors in transition-metal-catalyzed reactions, most likely because they are safer and more stable alternatives to diazo compounds.[29,31,61] The chemistry of metal carbenoids generated from diazo compounds has an established role in organic synthesis, particularly in cyclopropanations and insertion reactions into C–H and X–H (X = N, O, S, P, Se) bonds. The same chemistry can conceivably be accessed with metal carbenoids derived from sulfonium and sulfoxonium ylides. However, the generation of metal carbenoids from the ylides is much more challenging, especially because the reverse reaction—the formation of sulfonium ylides from the combination of metal carbenoids with sulfides—is facile and well-studied. In an effort to increase the sustainability of the Doyle–Kirmse reaction, one of the most commonly employed strategies to synthesize sulfonium ylides—the reaction between an allyl sulfide and a diazo reagent—was performed in aqueous solvent using hemin, a porphyrin-based catalyst. To ensure phase homogeneity, amphiphilic additives such as cyclodextrin (CD) and Triton™ X-100 were added. The protocol is characterized by high catalytic activity and broad functional-group tolerance, producing the corresponding homoallyl sulfides selectively in up to 99% yield (**eq 6**).[62]

The same protocol was extended to benzyl phenyl sulfide, observing selective formation of the [1,2]-Stevens and Sommelet–Hauser rearrangements products. Selectivity toward one type of rearrangement or another could be predicted based on the electronic properties of the substituents on the benzyl group together with solvent effects. Electron-donating or weak electron-withdrawing groups lead to the [1,2]-Stevens rearrangement, whereas strong electron-withdrawing substituents in the para position favor the Sommelet–Hauser rearrangement.[63] Fasan and co-workers reported the first example of a biocatalytic [2,3]-sigmatropic rearrangement

involving allylic sulfides and diazo reagents.[64] This variant of the Doyle–Kirmse C–C bond-forming reaction was efficiently catalyzed by engineered variants of sperm whale myoglobin. The protocol worked highly efficiently for a variety of sulfide substrates and α-diazo esters. Moreover, the reaction with propargylic sulfides led to the formation of substituted allenes. The active-site mutations increased the catalytic efficiency of the hemoprotein, modulated the enantioselectivity, and allowed the identification of Mb(L29S,H64V,V68F) as a myoglobin variant that is capable of effecting asymmetric Doyle–Kirmse reactions with enantiomeric excesses up to 71%.[64]

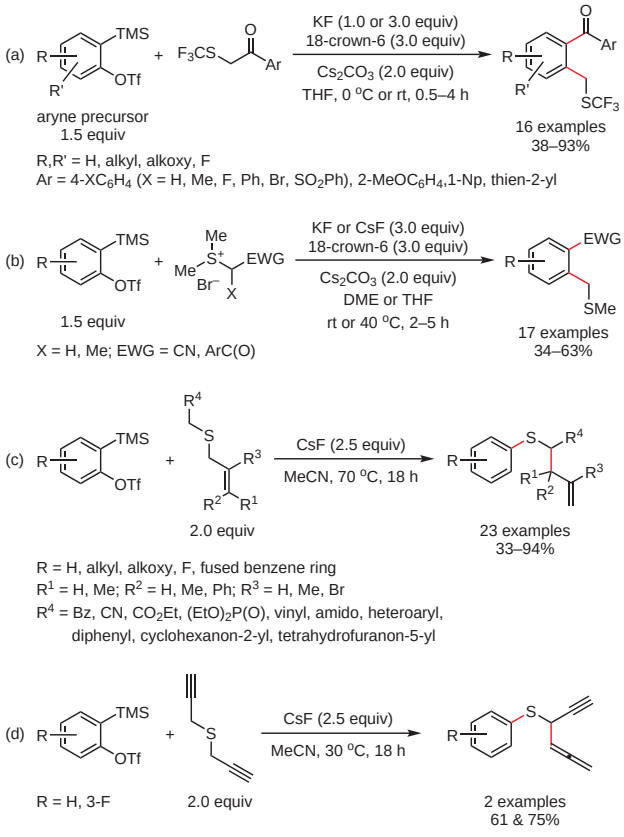
Hemin-Catalyzed Sulfonium Ylide Formation and Subsequent [2,3]-Sigmatropic Rearrangement in Aqueous Medium



β-CD = β-cyclodextrin; hemin = iron(III)-containing porphyrin

EWG = CO_2Me, CO_2Et, CO_2t-Bu, CO_2Bn, TMS
R = H, Ph, 1-Np; R^2 = H, Me; R^3 = H, Me, Ph; R^4 = H, Me
R^1 = Me, Et, *n*-Hex, Bn, 2-Pyr, 2-Np, XC_6H_4 (X = H, 3-Me, 4-Et, 4-MeO, 4-Br, 4-F, 4-NO_2)

eq 6 *(Ref. 62)*



Scheme 17. Novel Reactivity of S-Ylides with Arynes Opening the Door to Pharmaceutically Relevant Benzophenones and Sulfides. *(Ref. 65–67)*

3.4. Novel Reactivity of Sulfur-Based Ylides

Sulfur-based ylides are sources of active methylenes, thanks to their 1,2-dipolar nature, whereby the electron-rich carbon is stabilized by the adjacent electropositive sulfur atom. Compared with the classical metal-carbenoid-mediated [2,3]-sigmatropic rearrangement reactions, it is anticipated that a transition-metal-free method would provide an effective synthetic alternative. Mhaske and co-workers have reported a novel and efficient transition-metal-free reaction pathway for aryne insertion into substituted C–S bonds, resulting in ortho-difunctionalized arenes. The protocol requires mild reaction conditions and works with a broad range of aryne precursors and different S-ylides. For example, pharmaceutically relevant *ortho*-(trifluoromethylmercaptomethyl)-substituted benzophenones (16 examples, up to 93%) were prepared upon aryne insertion into α-(trifluoromethyl)thiomethyl ketones (**Scheme 17**, Part (a)).[65] With S-aryl/alkyl sulfonium salts, the same reaction led to ortho-substituted thioanisoles in good-to-moderate yields (17 examples, up to 63%; Scheme 17, Part (b)).[66] Moreover, Tan, Xu, and co-workers have reported a highly efficient aryne-induced [2,3]-sigmatropic rearrangement of allyl and propargyl thioethers, in which the S-ylide intermediate was generated in situ (Scheme 17, Parts (c) and (d)).[67] This approach had a broad substrate scope and allowed the selective synthesis of a library of highly functionalized sulfides in good yields (25 examples, up to 94%).[67]

4. Conclusion

In conclusion, and despite the healthy number of exciting research findings that have been disclosed so far, the "greening" of reactions based on phosphorus and sulfur ylides is still a research field in its infancy. The examples highlighted in the present review have demonstrated the viability of using phosphorus and sulfur ylides to discover and develop more environmentally friendly and sustainable processes, and should provide more impetus for further research in this emerging area of synthetic chemistry.

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Trimethylsilyldiazomethane ($TMSCHN_2$) in Carbon–Carbon and Carbon–Heteroatom Bond-Forming Reactions


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Keywords. trimethylsilyldiazomethane; TMSD; $TMSCHN_2$; homologation; insertion; carbene; cycloaddition.

Abstract. Trimethylsilyldiazomethane, a safe and stable substitute for diazomethane, has emerged as an indispensable modern synthetic tool that has found wide applications in a variety of synthetic transformations. This selective review provides an overview of the significant developments in chemistry that have occurred mainly over the last decade and a half, and focuses on application examples that demonstrate the novelty, value, and power of this reagent.

Outline

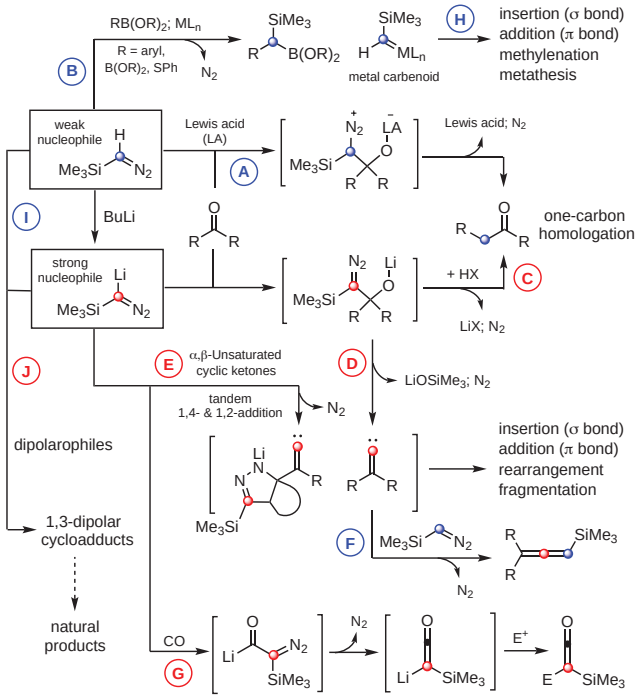
1. Introduction

Trimethylsilyldiazomethane ($TMSCHN_2$ or TMSD)[1] has been used most commonly in Lewis acid promoted one-carbon homologation reactions with various acyclic and cyclic carbonyl compounds (**Scheme 1**, Path **A**).[2] Similarly, the one-carbon insertion into C–B, B–B, and B–S bonds serves as an effective platform for installing polysubstituted sp^3-hybridized carbon centers bound to different p-block elements (Scheme 1, Path **B**). As opposed to neutral $TMSCHN_2$, the corresponding lithiated reagent, $TMSC(Li)N_2$, is a much stronger nucleophile; it thus reacts readily with a broader range of carbonyl compounds to generate, not only one-carbon insertion products (Scheme 1, Path **C**), but also alkylidene carbene intermediates (Scheme 1, Path **D**). These highly reactive unsaturated carbenes can participate in insertion reactions with N–H, O–H, O–Si, C–Si, and N–Li bonds to form hetero- or carbocycles, or in addition reactions with alkenes to form alkylidenecyclopropanes. With appropriate structural elements, alkylidene carbenes can also undergo rearrangement or fragmentation to form either terminal or internal alkynes. α,β-Unsaturated cyclic ketones react with 2 equivalents of $TMSC(Li)N_2$ in tandem 1,4- and 1,2-addition to generate an adduct (Scheme 1, Path **E**), that can subsequently follow the reaction course in Path **D**. Moreover, the insertion of an alkylidene carbene with $TMSCHN_2$ generates a silylallene (Scheme 1, Path **F**), and the insertion of $TMSC(Li)N_2$ with CO results in the formation of ketenes and their derivatives (Scheme 1, Path **G**).

Transition-metal complexes (ML_n) of Ru, Rh, Ni, and Pd react with $TMSCHN_2$ to form the corresponding carbenoids (Scheme 1, Path **H**), which participate in cycloaddition, C–H insertion, and metathesis processes. Moreover, $TMSCHN_2$ serves as a

1,3-dipole that undergoes cycloadditions with electron-deficient alkenes, alkynes, and carbon–heteroatom multiple bonds, forming structurally diverse heterocycles (Scheme 1, Paths **I** and **J**). $TMSC(Li)N_2$ is an anionically activated 1,3-dipole that displays higher reactivity toward electron-deficient dipolarophiles thus expanding the scope of the $TMSCHN_2$-based dipolar cycloaddition chemistry. The merits of $TMSCHN_2$ and $TMSC(Li)N_2$ in various C–C and C–heteroatom bond-forming reactions have been exploited for the synthesis of various natural products, including *ent*-kaurane diterpenoid steviol, scillasciloside E-1, amathaspiramides, plantensimycin, and delnudine.

Because of its higher stability and lower volatility, $TMSCHN_2$ is considered a safer alternative to diazomethane owing to the potential explosivity, flammability, and pulmonary toxicity of the latter. However, it is important to keep in mind that great caution needs to be exercised at all levels during its handling because of its potentially fatal toxicity following inhalation.[3]



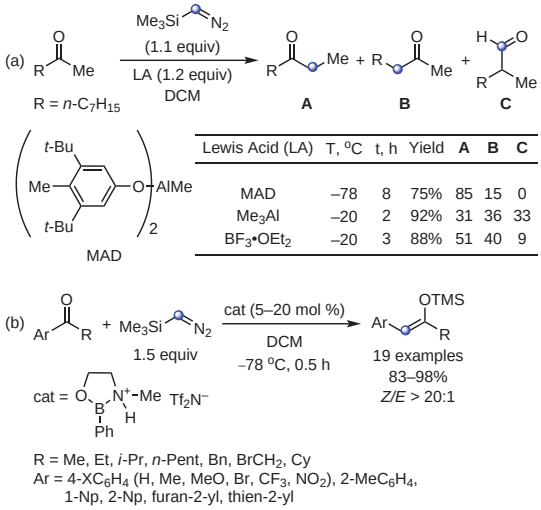
Scheme 1. Outline of Common Transformations of $TMSCHN_2$ and $TMSC(Li)N_2$.

2. Homologation Reactions

2.1. Insertion into C(O)–C and C(O)–H Bonds

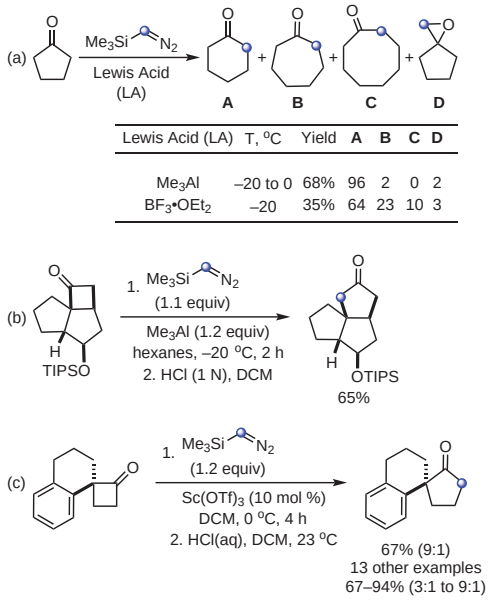
One-carbon homologations have been achieved via insertion of $TMSCHN_2$ into C(O)–C and C(O)–H bonds aided by Lewis acids. For the homologation of acyclic ketones, bulky Lewis acids such as methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide (MAD) provide improved selectivity for the homologated product (**Scheme 2**, Part (a)).[4,5] A new, highly stereoselective synthesis of monohomologated (*Z*)-silyl enol ethers has been achieved through the oxazaborolidinium ion catalyzed reaction of TMSD with alkyl aryl ketones (Scheme 2, Part (b)).[6]

The homologation of cyclopentanone is dependent on Lewis acid and reaction conditions (**Scheme 3**, Part (a)),[4] whereas the homologation of cyclobutanones consistently results in monohomologation. The regioselectivity of group migration depends on the overall environment of the cyclobutanone. For



Lewis Acid (LA)	T, °C	t, h	Yield	A	B	C
MAD	–78	8	75%	85	15	0
Me_3Al	–20	2	92%	31	36	33
BF_3•OEt_2	–20	3	88%	51	40	9

Scheme 2. Single Homologation through Trimethylsilyldiazomethane Insertion into Acyclic Ketones. *(Ref. 4–6)*



Lewis Acid (LA)	T, °C	Yield	A	B	C	D
Me_3Al	–20 to 0	68%	96	2	0	2
BF_3•OEt_2	–20	35%	64	23	10	3

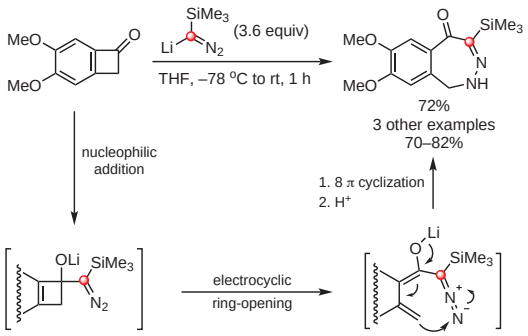
Scheme 3. Homologation of Cyclopentanone and Cyclobutanones with Trimethylsilyldiazomethane. *(Ref. 4,7a,8)*

example, in the formation of a triquinane skeleton, the migration of a more substituted carbon occurs selectively when catalyzed by $AlMe_3$ (Scheme 3, Part (b)),[7a] whereas the homologation of cyclobutanone derivatives with spiro-α,α-dibenzylic substituents provides cyclopentanone derivatives after migration of a less substituted carbon[7b] in the presence of $Sc(OTf)_3$ as catalyst (Scheme 3, Part (c)).[8]

In contrast to cyclobutanone derivatives, the ring-expansion of benzocyclobutenone takes a completely different course. This is a consequence of an extra π system, which causes the alkoxycyclobutene moiety to undergo electrocyclic ring-opening followed by 7-endo cyclization between an extended enolate and a diazo functionality, leading to 2,3-benzodiazepin-5-one (**Scheme 4**).[9]

Unlike the Lewis acid catalyzed ketone homologation with $TMSCHN_2$, which often involves insertion of more than one carbon atom, the corresponding homologation with $TMSC(Li)N_2$ generates an anionic intermediate, which, when protonated, ensures insertion of a single carbon (**Scheme 5**).[10] For example, protonation of such an intermediate with MeOH at low temperature followed by silica gel treatment provides the highest yield of ring-expanded five- to eight-membered-ring product with a minimal amount of epoxide byproduct. Unless electronically biased, unsymmetrical cyclic ketones display preferential migration of a less-substituted carbon center.

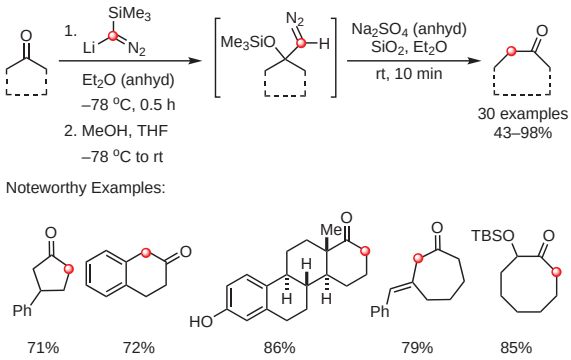
The product distribution of the one-carbon homologation of aldehydes by insertion of $TMSCHN_2$ into the C(O)–H bond is dependent on the nature of the catalyst. While the one-carbon homologation with $InCl_3$ as a Lewis acid catalyst generates the corresponding homologated α-trimethylsilyl ketones, that with $Sc(OTf)_3$ provides mainly silyl enol ethers, and a mixture of these products was obtained with other Lewis acids such as $BF_3•OEt_2$, $ZnCl_2$, and $MgBr_2$ (**Scheme 6**, Part (a)).[11] In contrast, the one-carbon homologation of cyclic β-alkoxyenals with $TMSCHN_2$ catalyzed by TMSOTf results in ring-expansion that is initiated by Mukayama-type 1,4-addition of $TMSCHN_2$ followed by migration of an sp^2-hybridized carbon and desilylation (Scheme 6, Part (b)).[12]



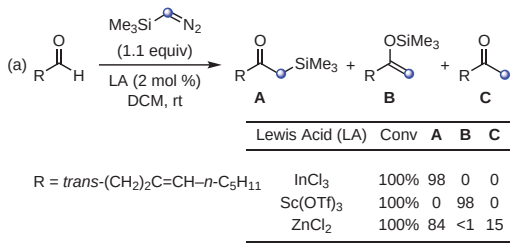
Scheme 4. $TMSC(Li)N_2$ Enabled Synthesis of 2,3-Benzodiazepines from Benzocyclobutenes. *(Ref. 9)*

2.2. Insertion into C–B, B–B, and B–S Bonds

$TMSCHN_2$ readily reacts with alkyl- and arylboronic acids and boronates to effect a one-carbon homologation via insertion into the C–B bond. This insertion reaction is the consequence of an initial interaction between the empty p orbital on the central boron atom and the weakly nucleophilic carbon center of $TMSCHN_2$ to generate a zwitterionic intermediate. For instance, an alkyl catechol boronate reacts with $TMSCHN_2$ to generate a one-carbon homologated alkyl *gem*-silyl boronate (**Scheme 7**, Part (a)).[13a] An aryl *gem*-silyl boronate was similarly obtained from the reaction of $TMSCHN_2$ with boroxines.[13b] Based on the one-carbon insertion into a C–B bond by $TMSCHN_2$, a robust and scalable synthesis of homoallylic alcohols was achieved

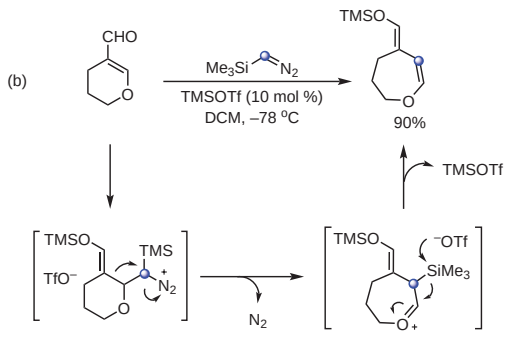


Scheme 5. New, Selective One-Carbon Homologation of Cyclic Ketones Employing a Nucleophile Activation Strategy. *(Ref. 10)*



Lewis Acid (LA)	Conv	A	B	C
$InCl_3$	100%	98	0	0
$Sc(OTf)_3$	100%	0	98	0
$ZnCl_2$	100%	84	<1	15

R = *trans*-$(CH_2)_2C{=}CH–n\text{-}C_5H_{11}$



Scheme 6. One-Carbon Homologation of Aldehydes with Trimethylsilyldiazomethane. *(Ref. 11,12)*

(Scheme 7, Part (b)).[14] Insertion of $TMSCHN_2$ into a B–B bond such as in B_2Pin_2 afforded the one-carbon-homologation product $(Bpin)_2HC(SiMe_3)$, which readily reacted with cyclohexanone upon treatment with lithium tetramethylpiperidide to provide a *gem*-silyl boronate-containing tetrasubstituted alkene (Scheme 7, Part (c)).[15] Similarly, insertion of $TMSCHN_2$ into the B–S bond of PhS–Bpin followed by deborylative alkylation with NaO*t*-Bu and alkyl halide provided the corresponding alkylated α-silyl sulfides (Scheme 7, Part (d)).[16]

2.3. Insertion into sp-Hybridized Carbons

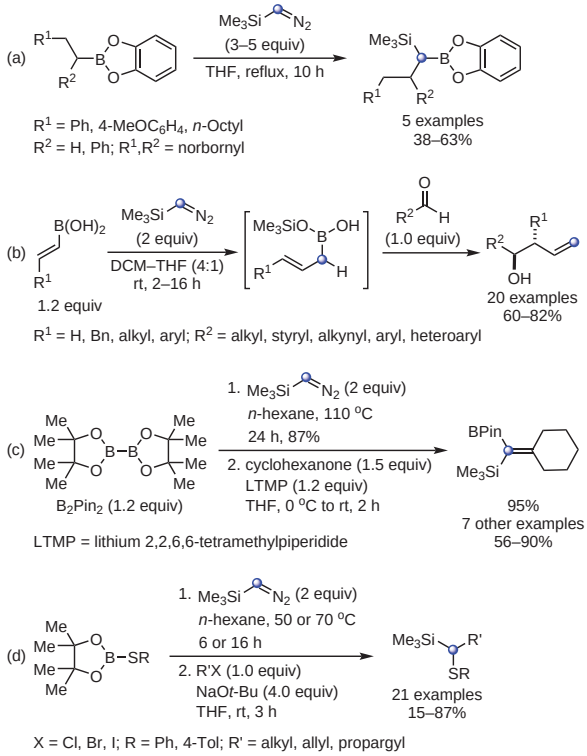
The reaction between CO and $TMSC(Li)N_2$ generates, after extrusion of N_2, lithium silylethynolate ($LiOC{\equiv}CSiMe_3$) which readily participates in the ketenylation reaction of epoxides and aziridines. The aluminum reagent generated from lithium silylethynolate and Me_3Al reacts efficiently with epoxides to provide alkoxy ketenes, which spontaneously cyclize to afford 2-trimethylsilyl-γ-lactones (**Scheme 8**, Part (a)).[17a] Similarly, the reaction of lithium silylethynolate with aziridines generates α-silyllactam enolates, which upon addition of excess aldehyde undergo a Peterson-type olefination to deliver α-alkylidene lactams in good yields (Scheme 8, Part (b)).[17b] When the reaction of $TMSC(Li)N_2$ with ^{11}CO to form ^{11}C-labeled silylethynolate was followed by reaction with 3-diazopyrazole, it provided ^{11}C-labeled pyrazolotriazine-1*H*-4-one (Scheme 8, Part (c)).[18] This ^{11}C-labeled bioactive compound could be used for positron emission tomography (PET).

In analogy to the formation of ketene from the combination of CO and $TMSC(Li)N_2$, allenes can be generated from the reaction of alkylidene carbenes and $TMSCHN_2$ (Scheme 8, Part (d)).[19] The empty p orbital of alkylidene carbenes readily reacts with the weakly nucleophilic carbon center of $TMSCHN_2$ to generate a zwitterionic intermediate that can undergo $E1_{CB}$-type elimination of N_2, generating silyl-substituted allenes.

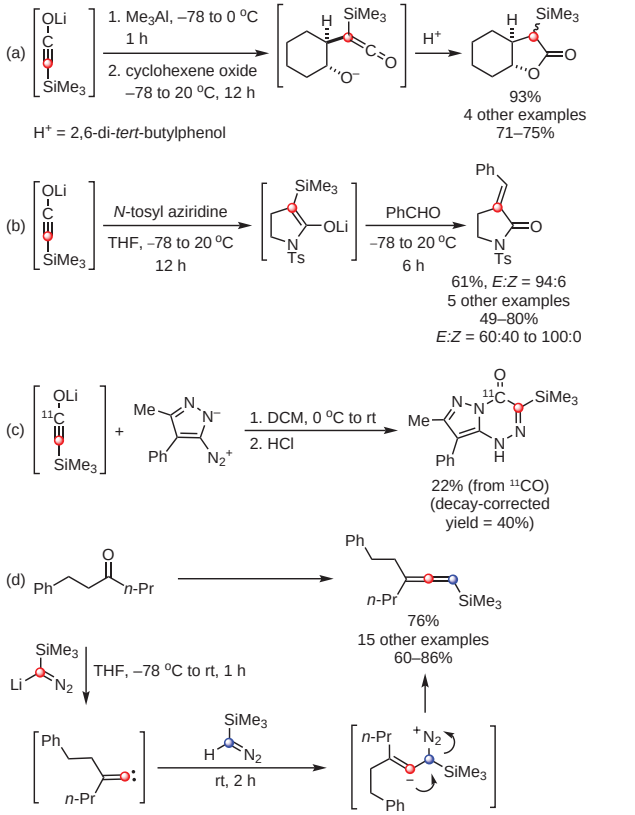
3. Reactions Involving an Alkylidene Carbene

3.1. Insertion into C–H and C–Si Bonds

An alkylidene carbene can be generated from the reaction of a ketone with $TMSC(Li)N_2$, and its highly electrophilic nature promotes an effective C–H insertion reaction to generate typically cyclopentene products. The C–H insertion into a bridgehead C–H bond constitutes a particularly versatile strategy for the construction of bridged carbocycles. In the synthesis of the tricyclic core of platensimycin, alkylidene-based C–H insertion was employed as the key step, where high selectivity for the bridgehead C–H_a bond was observed (**Scheme 9**, Part (a)).[20]



Scheme 7. One-Carbon Insertions into C–B, B–B, and B–S Bonds. *(Ref. 13–16)*



Scheme 8. Trimethylsilyldiazomethane-Enabled Ketenylation and Allenylation Reactions. *(Ref. 17–19)*

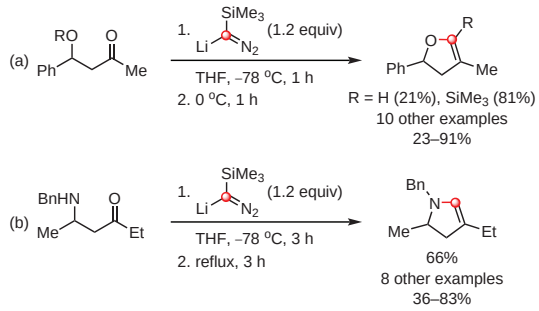
This selectivity is considered to be a consequence of the slightly deactivated nature of the C–H_b bond as compared to the C–H_a because of the high electronegativity of the geminal oxygen atom. The alkylidene-carbene-based insertion into bridgehead C–H bonds was also employed in the synthesis of the ABC ring system of delnudine (**Scheme 9**, Part (b)).[21]

The high reactivity of an alkylidene carbene can also promote the insertion reaction into C–Si bonds to generate silyl-substituted cyclopropenes. Thus, the preparation of α-silyl ketones from the $InCl_3$-catalyzed reaction of $TMSCHN_2$ and aldehydes followed by treatment of the α-silyl ketones with $TMSC(Li)N_2$ leads to the formation of alkylidene carbene intermediates, which undergo an insertion reaction preferentially with the proximal C–Si bond over the distal C–H bond or π bond to generate the silyl-substituted cyclopropenes (**Scheme 9**, Part (c)).[22]

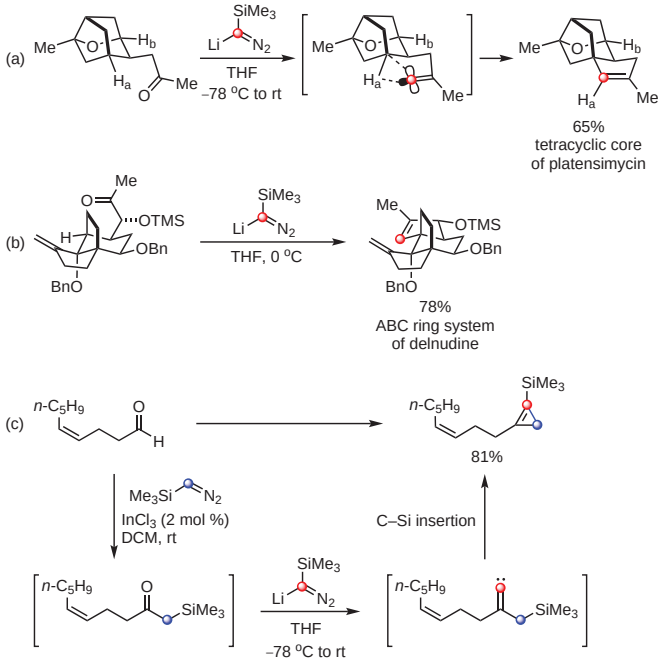
3.2. Insertion into Other σ Bonds and Fragmentation

Alkylidene carbenes generated from the reaction between ketones and $TMSC(Li)N_2$ can readily form 2,3-dihydrofuran derivatives after insertion into O–H and O–Si bonds that are positioned at the β carbon of the ketone (**Scheme 10**, Part (a)).[23] The insertion into O–Si bonds is more efficient than that into O–H bonds, and in some cases a group migration process competes with the insertion into alkynes. Similarly, alkylidene carbenes generated from β-amino ketones insert into N–H bonds to form dihydropyrroles (**Scheme 10**, Part (b)). Reactions of $TMSC(Li)N_2$ with *ortho*-acyl-*N*-substituted anilines generated either 3-substituted indoles or *ortho*-alkynyl-*N*-substituted anilines depending on the nature of the nitrogen substituent.[24,25] It was observed that *N*-Ts and *N*-Boc favored N–H bond insertion by the alkylidene carbene to form indole derivatives, whereas with the *N*-pivaloyl substituent the Colvin rearrangement outcompeted the N–H bond insertion to form the alkyne as the major product.

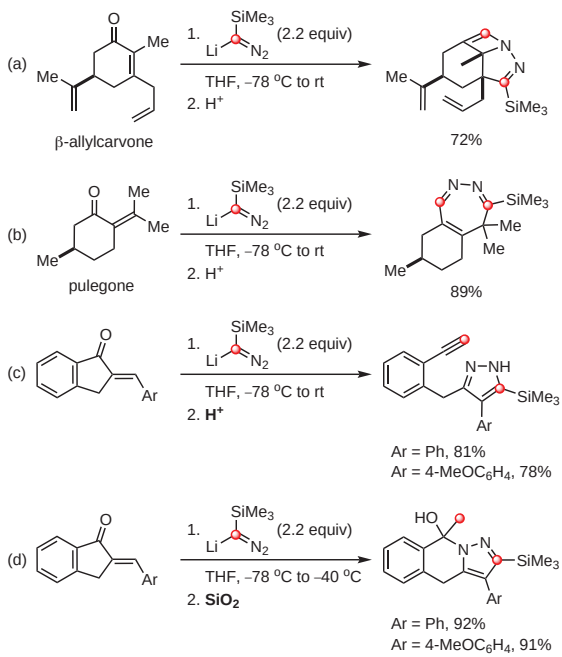
The reaction between cyclic α,β-unsaturated ketones and $TMSC(Li)N_2$ selectively engages in 1,4-addition followed by cyclization to form fused pyrazolines after protonation. Thus, β-allylcarvone underwent sequential 1,4- and 1,2-additions with 2 equivalents of $TMSC(Li)N_2$ to form a lithium pyrazolinate-fused cyclohexylidene carbene. The carbene then provided a tricyclic product via an N–Li bond insertion followed by protonation (**Scheme 11**, Part (a)).[26] A related alkylidene carbene derived



Scheme 10. Alkylidene Carbene Insertion into O–H, O–Si, and N–H Bonds. *(Ref. 23)*



Scheme 9. Applications of Alkylidene Carbene Insertions into C–H and C–Si Bonds in the Synthesis of Alkaloids and Antibacterial Agents. *(Ref. 20–22)*



Scheme 11. Alkylidene Carbene Insertion into N–Li and Grob-type C–C Bond Fragmentation. *(Ref. 26)*

from pulegone underwent an N–Li bond insertion followed by a cycloreversion to form a bicyclic 4*H*-1,2-diazepine derivative (Scheme 11, Part (b)).[26] On the other hand, a spirobicyclic lithium pyrazolinate-fused cyclopentylidene carbene derived from benzylidene indanone selectively engaged in a C–C fragmentation process to predominantly generate pyrazole derivatives containing a terminal alkyne moiety (Scheme 11, Part (c)).[26] Interception of the 1,4/1,2-bis adduct of TMSC(Li)N_2 before elimination of a lithium silanolate by quenching with SiO_2 at low temperature induced a different course of C–C bond fragmentation to generate as the major product benzo-fused bicyclic pyrazoles containing a hemiaminal moiety (Scheme 11, Part (d)).

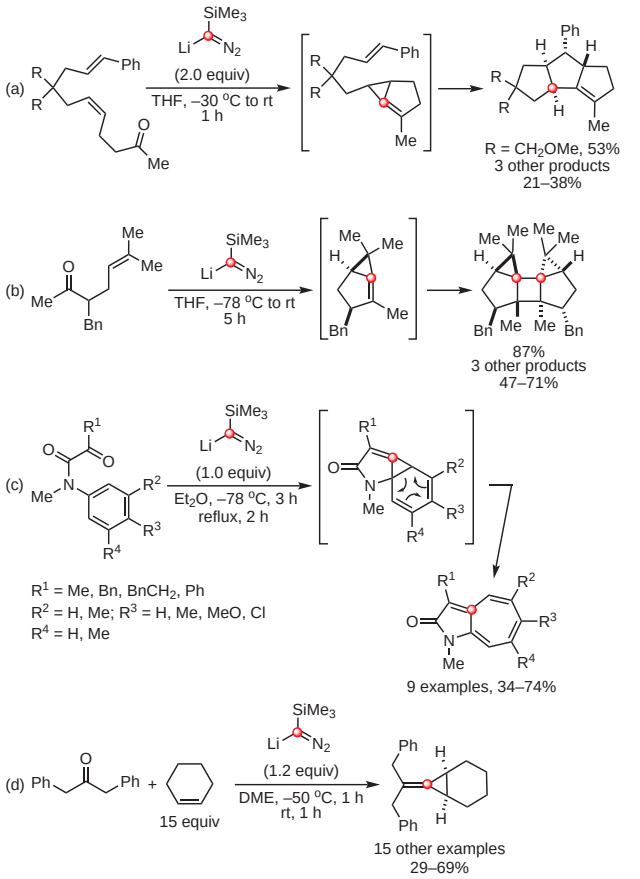
3.3. Addition to Alkenes and Formation of Alkynes

The alkylidene carbenes generated from the reaction between TMSC(Li)N_2 and ketones can undergo an intramolecular [2 + 1] cycloaddition to form a highly strained bicyclo[3.1.0]hex-1-ene intermediate. C–C bond fragmentation of the strained three-membered ring of this intermediate generates a trimethylenemethane diyl, which undergoes intramolecular [3 + 2] cycloaddition to provide a linearly fused triquinane derivative (**Scheme 12**, Part (a)).[27] In contrast, structurally simpler bicyclo[3.1.0]hex-1-enes that do not contain a tethered alkene participate in a dimerization reaction via a [2 + 2] cycloaddition (Scheme 12, Part (b)).[28] The alkylidene carbene generated from an α-ketoanilide readily undergoes a [2 + 1] cycloaddition with a proximal aromatic π system to form a norcaradiene moiety, which rearranges to form a cycloheptatriene product (Scheme 12, Part (c)).[29] Moreover, alkylidene carbenes can undergo intermolecular [2 + 1] cycloaddition with external alkenes to form cyclopropylidene derivatives (Scheme 12, Part (d)).[30]

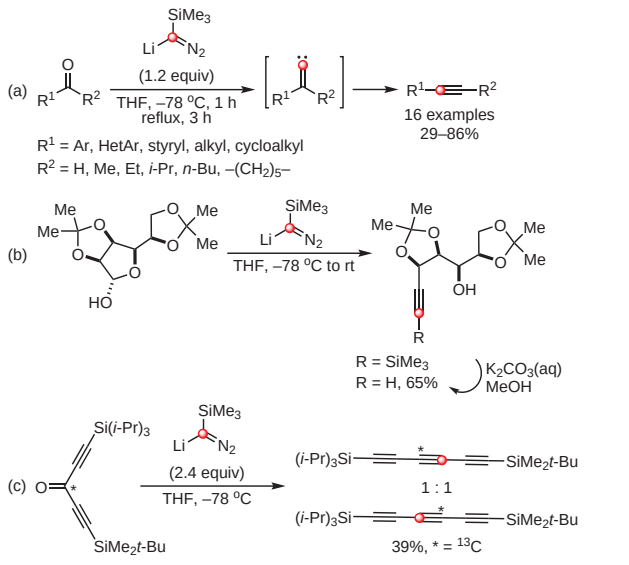
The reaction of TMSC(Li)N_2 with aldehydes and alkyl aryl/alkenyl/alkynyl ketones to generate alkynes constitutes a robust and efficient one-step method for the preparation of terminal alkynes from aldehydes and internal alkynes from ketones.[31] For example, treating alkyl aryl ketones with TMSC(Li)N_2 provides the corresponding internal alkynes (**Scheme 13**, Part (a)).[32] This transformation has been widely applied in complex-molecule synthesis such as in the synthesis of kedarcidin[33a] and of the hikizimycin core starting from sugar-based hemiacetals (Scheme 13, Part (b)).[33b] It was shown that group migration generally occurs in the order of H > sp^2-C ~ sp-C > sp^3-C, but groups of similar characteristics don't display strong selectivity in the migration. For example, a terminally differentiated, ^{13}C-labeled bisalkynyl ketone provided a mixture of two isotopomers in a 1:1 ratio upon treatment with TMSC(Li)N_2 (Scheme 13, Part (c)).[34]

4. Reactions Involving Metal-Alkylidene Formation

$TMSCHN_2$ readily reacts with various transition-metal complexes of Ni, Ru, Rh, and Cu to form the corresponding metal carbenoids that can engage in a variety of transformations.



Scheme 12. Intra- and Intermolecular Addition of Alkylidene Carbenes to π bonds. *(Ref. 27–30)*



Scheme 13. Alkyne Synthesis through the Colvin Rearrangement Enabled by Reaction of TMSC(Li)N_2 with Ketones. *(Ref. 32–34)*

4.1. With Ni and Pd Complexes

1,3-Dien-6-yne readily participated in a highly efficient [4 + 2 + 1] cycloaddition with $TMSCHN_2$ in the presence of $Ni(cod)_2$ to form a bicyclo[5.3.0]decane system in good yield and excellent diastereoselectivity (**Scheme 14**, Part (a)).[35] It was proposed that the reaction proceeds through formation of a Ni-carbenoid species in different manifolds of pathways, including a metathesis cascade initiated by an initially formed Ni-carbenoid, or an initial oxidative cyclization of the diene-yne by a Ni(0) complex followed by $TMSCHN_2$ insertion to form a Ni-carbenoid species.

Similarly, Pd(0) complexes promote the reactions of $TMSCHN_2$ with various reagent classes such as benzyl bromides to generate styrenes[36a] and vinylic halides (Scheme 14, Part (b)).[36b] With vinylic halides, the initial oxidative addition forms a vinyl-Pd(II) complex that induces insertion of $TMSCHN_2$ to form a vinyl-Pd(II)–carbenoid complex. Subsequently, vinyl group migration generates a π-allyl-Pd(II) complex, which reacts with a nucleophile such as secondary amine or the anion of malononitrile or malonate to generate the double-bond-transposed vinyl silanes.[36c] The reaction of 2-bromostyrene derivatives with $TMSCHN_2$ catalyzed by Pd(0) complexes proceeds via a formal [4 + 1] annulation to generate polycyclic aromatic compounds (Scheme 14, Part (c)).[37]

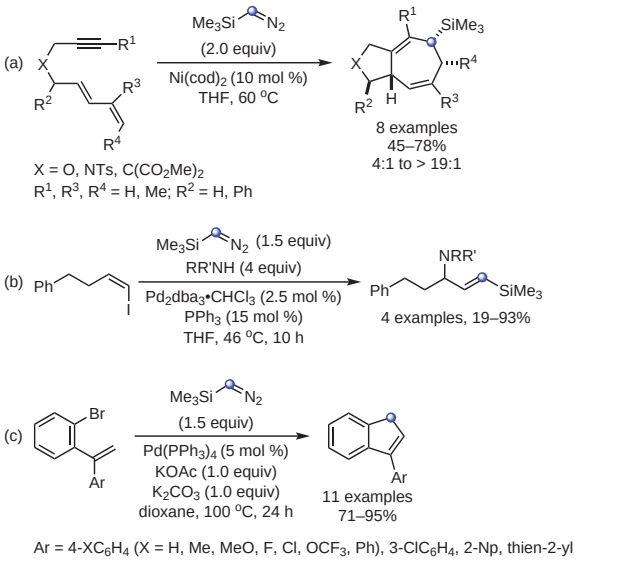
4.2. With Ru, Rh, and Cu Complexes

Ruthenium complexes such as [Cp*Ru(cod)Cl] readily react with $TMSCHN_2$ to generate Ru-alkylidenes, which undergo a metathesis reaction with alkynes to generate 1,3-dienes with good stereoselectivity (**Scheme 15**, Part (a)).[38] In contrast, under almost identical conditions, TsN-tethered 1,6-enynes are converted into bicyclo[3.1.0]hexanes, where the cyclopropane moiety probably arises from reductive elimination from the metallacyclobutane intermediate (Scheme 15, Part (b)).[39] The putative vinyl Ru-carbenoids display yet another mode of reactivity involving C–H insertion to generate cyclopentane derivatives (Scheme 15, Part (c)).[40] $[RhCl(PPh_3)_3]$ brings about efficient methylenation of aldehydes and ketones in the presence of $TMSCHN_2$, 2-propanol, and triphenylphosphine.[41] This alkenylation protocol was employed by Baran and co-workers for the conversion of an α-hydroxyketone intermediate into the corresponding allylic alcohol during the synthesis of the kaurane family natural product steviol (Scheme 15, Part (d)).[42] In the catalytic methylenation of aldehydes and ketones, copper complexes were substituted for the rhodium complex, and (IPr)CuCl was identified as one of the most effective catalysts in most cases, including the conversion of perillaldehyde into the corresponding triene (Scheme 15, Part (e)).[43]

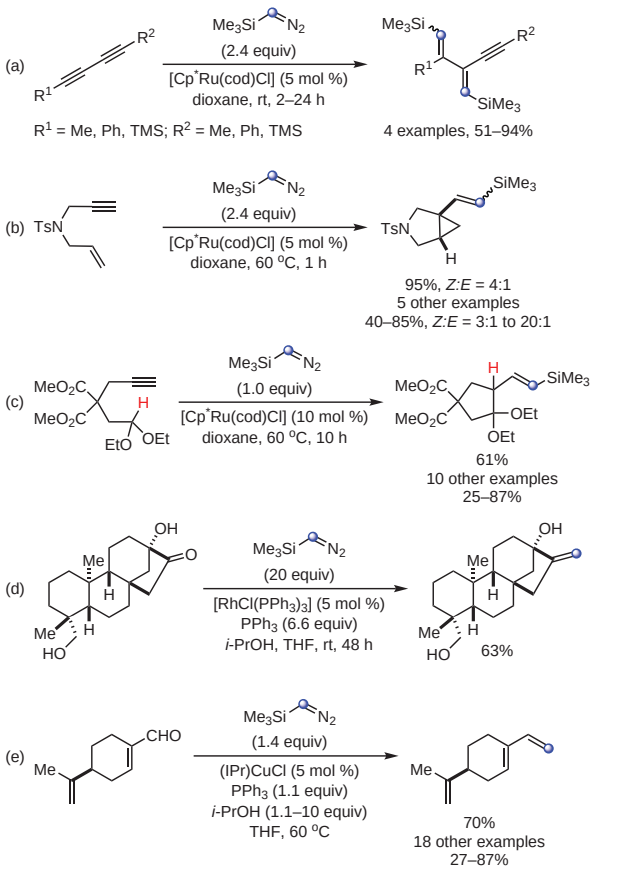
5. Addition Reactions

5.1. With Alkenes

The relatively high reactivity of the diazo group toward electron-deficient alkenes has been exploited in the auxiliary-based, Lewis acid catalyzed asymmetric [3 + 2] dipolar



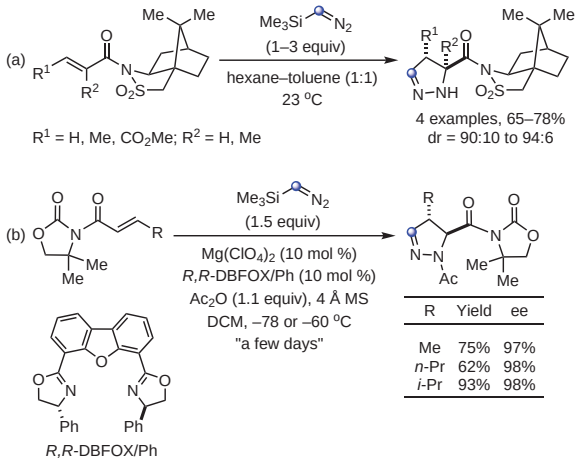
Scheme 14. Reactions Involving Ni and Pd Carbenoids. *(Ref. 35–37)*



Scheme 15. Noteworthy Applications of Ru, Rh, and Cu Carbenoids in Synthesis. *(Ref. 38–40,42,43)*

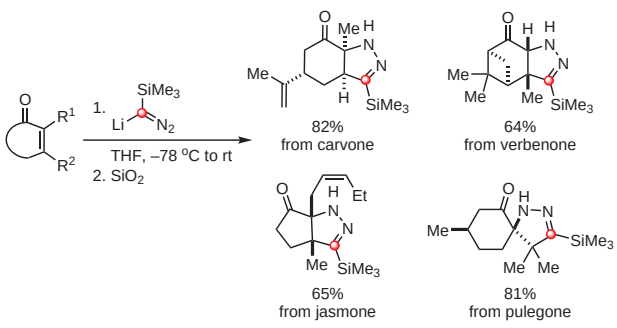
cycloaddition. The reactions of $TMSCHN_2$ with camphor sultam bound α,β-unsaturated carbonyl compounds proceeded at room temperature to generate Δ^2-pyrazolines after spontaneous loss of the trimethylsilyl group. While relatively high diastereoselectivity was observed in all cases, the α-methyl substituted substrate resulted in the highest selectivity (94:6) (**Scheme 16**, Part (a)).[44a] This dipolar cycloaddition approach to establishing a chiral C–N bond was taken advantage of in the synthesis of *ent*-stellettamide A.[44b] A chiral Lewis acid catalyzed approach was also developed for this cycloaddition, where the reaction between achiral oxazolidinone-bound α,β-unsaturated carbonyl compounds and $TMSCHN_2$ was effectively catalyzed by a chiral Mg–DBFOX complex (Scheme 16, Part (b)).[45] An unusual observation in this reaction was that the more sterically hindered substituents at the β position of the substrates provided significantly higher yields.

The reaction of $TMSC(Li)N_2$ with α,β-unsaturated cyclic ketones proceeds exclusively with 1,4-addition providing



Scheme 16. Asymmetric [3 + 2] Cycloadditions of $TMSCHN_2$ with Electron-Deficient Alkenes. *(Ref. 44,45)*

First Step in the Formal Aminocyanation of α,β-Unsaturated Cyclic Enones



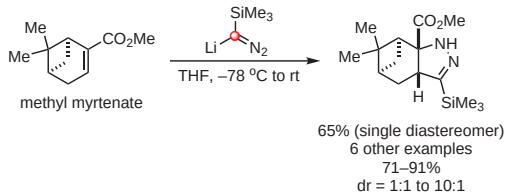
eq 1 *(Ref. 46)*

Δ^2-pyrazolines, whereas the corresponding acyclic α,β-unsaturated ketones engage in 1,2-addition to generate 1,3-enynes. The 1,4-addition appears to be a consequence of the steric interaction between the trimethylsilyl group and the cyclic framework of cyclic ketones. The reaction of $TMSC(Li)N_2$ with carvone, an α-methyl-substituted enone, affords a fused bicyclic pyrazoline in 82% yield, whereas verbenone, another trisubstituted enone containing a β-methyl substituent, leads to the corresponding pyrazoline in 64% yield. Even tetrasubstituted enones such as jasmone and pulegone provide fused and spirobicyclic pyrazolines containing vicinal quaternary carbons in 65 and 81% yields, respectively (**eq 1**).[46]

The general reactivity of α,β-unsaturated esters toward $TMSC(Li)N_2$ is similar to that of α,β-unsaturated cyclic ketones. Thus, the reaction of methyl myrtenate with $TMSC(Li)N_2$ produced the corresponding Δ^2-pyrazoline in 65% yield as a single diastereomer (**eq 2**).[47] 1,2-Addition is a more favored mode of reaction for β,β-disubstituted esters when typical methyl and ethyl esters are employed; however, β,β-disubstituted *tert*-butyl esters cleanly produce Δ^2-pyrazolines. The (*E*)-cinnamate-derived ester produced the corresponding pyrazoline as a 10:1 mixture of diastereomers, while methyl cyclopentenecarboxylate afforded a bicyclic pyrazoline in 71% yield as a single diastereomer.

On the basis of the efficient formal cycloaddition (1,4-addition–cyclization) of α,β-unsaturated esters with $TMSC(Li)N_2$, total syntheses of natural products containing an α-amino quaternary carbon such as in amathaspiramides and massadine were pursued.[47,48] For the synthesis of amathaspiramide C, a functionalized cinnamate derivative was treated with $TMSC(Li)N_2$ to directly generate a bicyclic pyrazoline. After the proton-mediated N–N bond cleavage, the cyanoester was converted into spirobicyclic Fukuyama's advanced intermediate via a three-step protocol. This route constitutes a formal synthesis of all members of the amathaspiramide family of natural products, and includes a total synthesis of amathaspiramide C.[47] Similarly, the reaction of substituted cyclopentene carboxylate with $TMSC(Li)N_2$ generated a fused bicyclic pyrazoline. Cleavage of the N–N bond in the pyrazoline led to an advanced intermediate containing all suitably functionalized carbons with the correct stereochemistry for a total synthesis of massadine, a structurally

Formal [3 + 2] Cycloaddition, the First Step in the Aminocyanation of Enoates



eq 2 *(Ref. 47)*

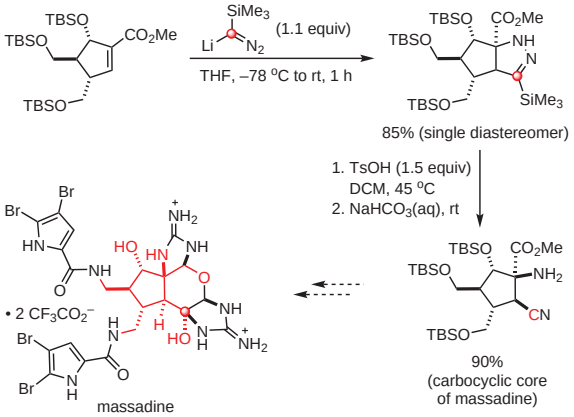
complex alkaloid which is isolated from a marine sponge and which acts as an inhibitor of geranylgeranyltransferase type I (GGTase I) (**Scheme 17**).[48]

5.2. With Alkynes

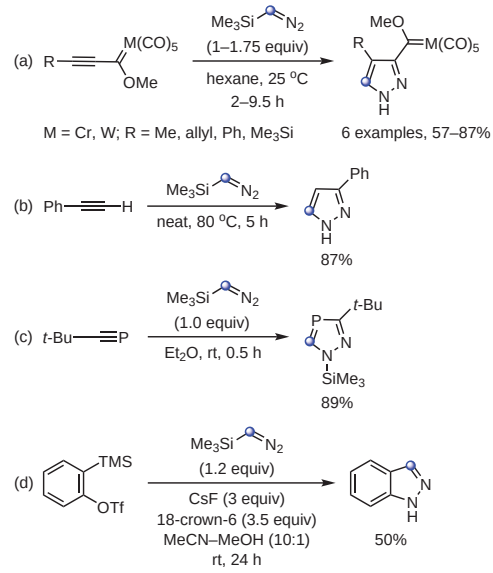
Alkynes containing a classical Fisher carbene moiety can undergo a regioselective [3 + 2] cycloaddition with $TMSCHN_2$ to provide pyrazoles, which can be oxidized to the corresponding methyl esters with cerric ammonium nitrate (CAN) (**Scheme 18**, Part (a)).[49] Electronically unactivated alkynes such as phenylacetylene still can participate in a [3 + 2] cycloaddition with $TMSCHN_2$ in the absence of solvents at relatively elevated temperatures (Scheme 18, Part (b)).[50] On the other hand, polarized heteroalkynes containing a carbon–phosphorus triple bond react with $TMSCHN_2$ at ambient temperature to form a phosphorus-containing heterocycle (Scheme 18, Part (c)).[51] Similarly, strained alkynes such as benzyne in situ generated from the Kobayashi precursor, can also readily react with $TMSCHN_2$ at room temperature to generate 1*H*-indazoles in high yields (Scheme 18, Part (d)).[52]

5.3. With sp-Carbon-Containing Multiple Bonds

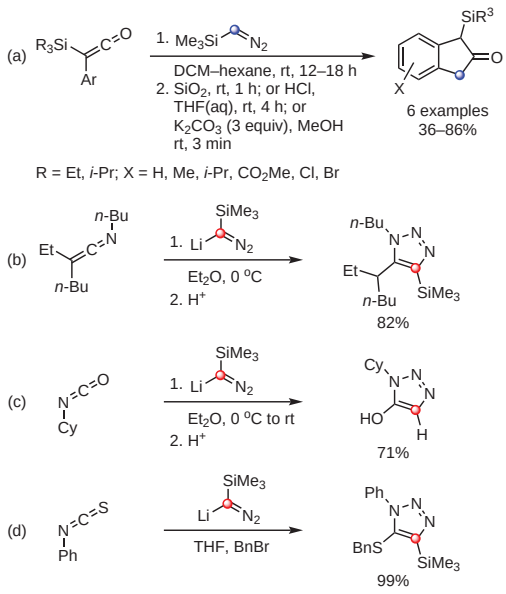
The reactivity of compounds containing an sp-hybridized carbon such as ketenes, ketenimines, isocyanates, and thioisocyanates toward nucleophiles depends mainly on the polarity of the central sp-carbon–heteroatom bond. Trialkylsilyl alkenyl ketenes are electrophilic enough to react with $TMSCHN_2$ to form zwitterionic intermediates, which undergo a Nazarov-type cyclization involving 2-oxypentadienyl cation, leading to cyclopentenones.[53] The double bond in an aromatic system also undergoes a similar annulation to generate 2-indanone derivatives from which the trimethylsilyl group can be removed by treatment with SiO_2 or dilute HCl (**Scheme 19**, Part (a)).[53] Ketenimines are less electrophilic than ketenes and require the stronger nucleophile $TMSC(Li)N_2$ for the initial bond-forming event. After forming a cyclic adduct, a series of double-bond isomerizations leads to 1,2,3-triazole products (Scheme 19, Part (b)).[54] Similarly, the reaction of isocyanate and $TMSC(Li)N_2$ generates 4-hydroxy-1,2,3-triazole after desilylation, which is the consequence of a keto-enol tautomerization (Scheme 19, Part (c)).[55] The reaction of phenyl isothiocyanate with $TMSC(Li)N_2$ affords two completely different products depending on the reaction conditions. In THF,



Scheme 17. Application of the Stereoselective Formal [3 + 2] Cycloaddition of α,β-Unsaturated Esters with $TMSC(Li)N_2$ to the Formal Total Synthesis of Massadine, an inhibitor of Geranylgeranyltransferase Type I (GGTase I). *(Ref. 48)*



Scheme 18. Cycloaddition Reactions of Trimethylsilyldiazomethane with Alkynes. *(Ref. 49–52)*



Scheme 19. Reactions with sp-Carbon-Containing Multiple Bonds. *(Ref. 53–56)*

the formation of lithio-1,2,3-triazole-5-thiolates is preferred, which can be alkylated in situ with alkyl halides to generate the final product (Scheme 19, Part (d)).[56] In contrast, in Et_2O, 2-amino-1,3,4-thiadazoles are generated in good yields. The formation of these two different classes of products is the consequence of the involvement of either the C=N bond or C=S bond of the isothiocyanate in the cycloaddition, but it is unclear whether these different kinds of products evolve from a common intermediate or two independent intermediates.

6. References

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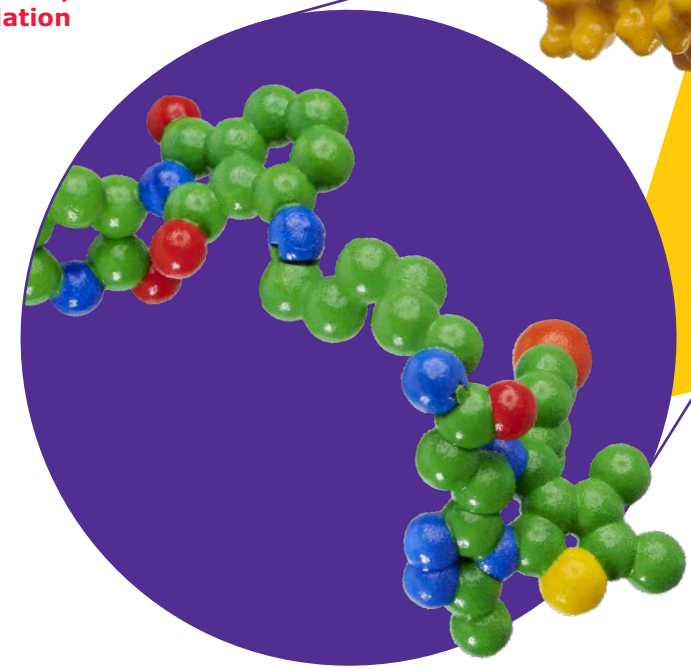

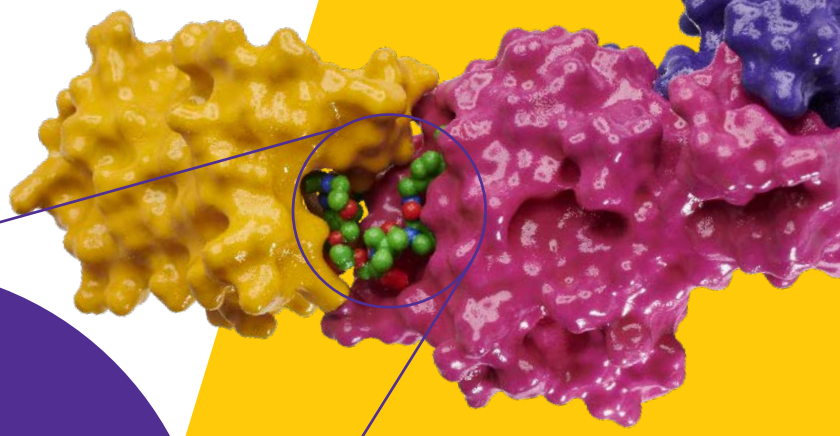

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